PMOD Base Functionality (PBAS)

INSTALLATION MANUAL
Version 4.4

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1 PMOD Base Functionality Introduction

This guide describes the installation of the PMOD software, the different levels of configuration, and the versatile image analysis tool which belongs to the base installation of PMOD. It supports many operations for image reviewing and scientific data analysis:

- Loading medical images in different formats, including DICOM.
- Viewing the images with different color tables and in different layouts.
- Calculating new slice images in arbitrary new orientations.
- Performing various image processing and manipulation operations.
- Displaying fusion images of matched data sets (image registration is a separate option).
- Performing volume-of-interest analyses and the calculation of time-activity curves from dynamic studies.
- Saving images in different formats, including DICOM, and directly C-STORE them to a DICOM server.
- Statistical comparison of group outcomes via a console interface to R.
- Supports data generation and preparation of the trainings sets for the PAI module. Please refer to the dedicated *PMOD Artificial Intelligence Framework (PAI)* user guide for detailed information about the learning sets preparation, prediction, classification and case studies.

Additionally, this guide explains important notions generally used in PMOD tools such as

- The image data formats, their loading and saving.
- Control of layouts and image display.
- Inter-operation of tools.

For getting started with PMOD we recommend the following approach:

1. Browse this document as it gives the foundation for all other PMOD tools.

2. Browse the **PMOD User's Guides** of the other PMOD tools you are interested in.

3. Use the training resources offered via the PMOD website including video tutorials based on the demo data provided with the installation.

For in-depth understanding of PET Kinetic Modeling we strongly recommend the PMOD users to attend one of the excellent yearly *PET Pharmacokinetics Courses.* These courses include theory as well as practical work and are organized by the the top experts in the domain. Another worthwhile course is *PET Methodology* (King's College London). An additional source of valuable information is the data analysis website of the Turku PET Centre.

2 Starting PMOD

PMOD is started using the **RunPmod** script in the Pmod4.4/Start directory. Please refer to the system-specific installation guides if adjustments are needed.

Starting with version 4.4 the PMOD default layout is the docking interface. This layout will be used for the preparation of the entire PMOD documentation. Please refer to the previous PMOD versions documentation (4.3) for the legacy layout.

The two layouts are described below

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2.1   PMOD Docked Interface

The PMOD tools are docked, reducing the number of windows used in the analysis workflows:

Licensed PMOD Modules
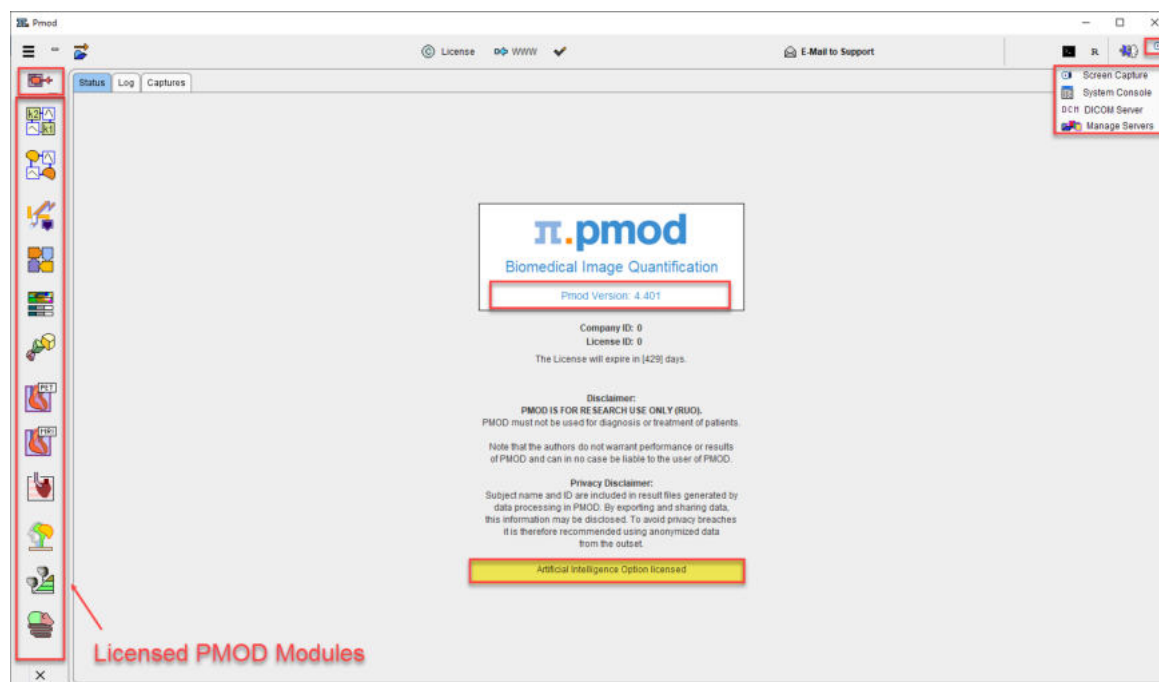
When the **Pmod Artificial Intelligence** (PAI) module has been licensed, an indication appears on the **Status** tab at the bottom of the page as highlighted in the capture above.

The PAI functionality is currently available in **PVIEW**, **PSEG**, **PCARDM** and **PNEURO.**

There are various buttons on the top line in the docking interface that are common for all modules. Their functionality is described in the table below:

☰	Allows showing/hiding the modules available for selection in the docking interface
▭ / ▢	Allows minimizing/maximizing the dock window
⇉	Allows accessing the unified data loader 28 , the new PMOD Scientific Data Management System
▪	Starts the Pipeline Batch interface.
R	Starts the PMOD R console
🗫	Allows accessing the PMOD Configuration and Users Settings
E-Mail to Support	Allows sending by email the log content and/or the screen captures to the PMOD helpdesk. The functionality is described in details in the Problem Reporting 27 section.

The selection buttons available in the upper right corner of the docking interface are related to the different PMOD functionalities.

⊡	Allows adding a capture of the entire screen (not only of the active window) to the Console Buffer

📅	Allows accessing the content of the system console.
DCM	Starts the **DICOM server** using the configuration of the current user. If it is already running, the configuration is shown. A blue background color indicates ongoing server activity, e.g. the receiving of images.
🖥️	Starts the database administration window. If the Transaction Server is already running, an information window is shown which describes the server status. A blue background color indicates ongoing server activity.

Note: The number of the tools buttons in the Dock depends on the configuration that was purchased. Only the base functionality **View** is always present.

If multiple users have been configured, one of them needs to be selected and the login 📥 button activated. Otherwise, the login procedure proceeds automatically. Note the startup window which reminds you that PMOD is a research software and shows license-related information.
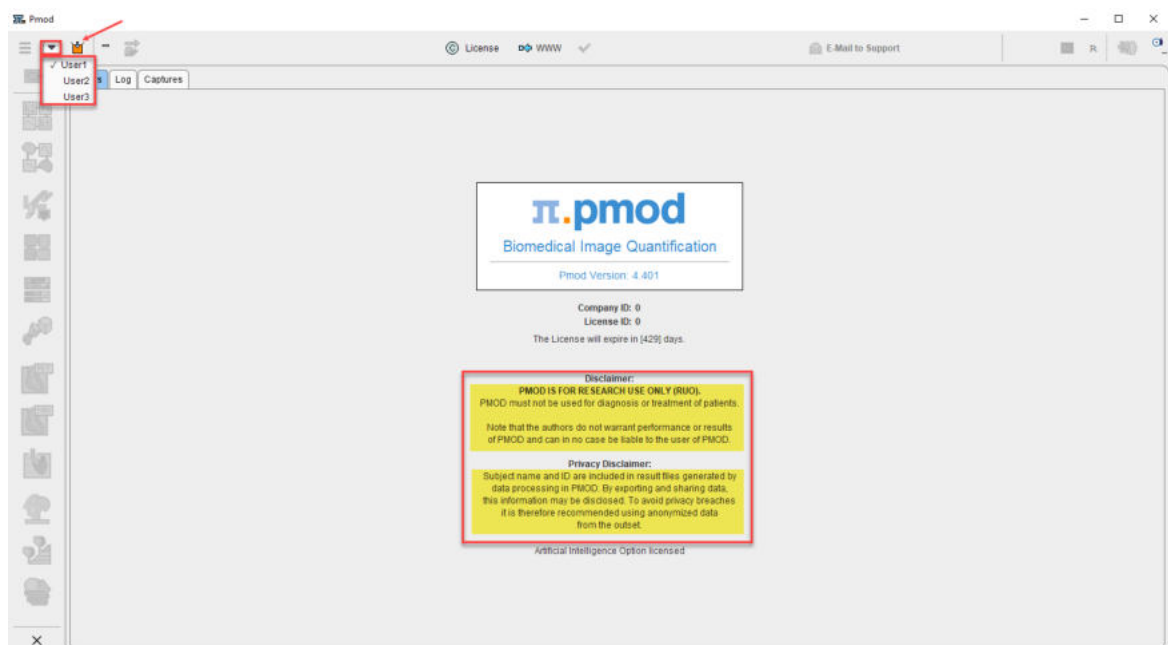
After the login, the tool buttons are active and you can start working with PMOD.
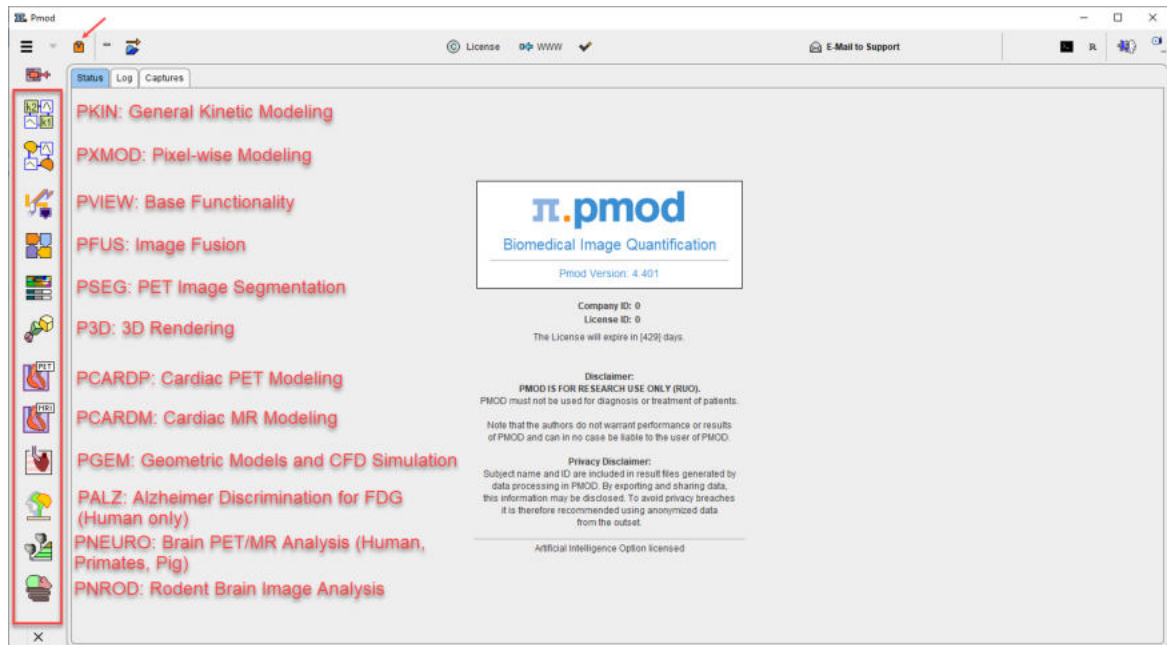
The Dock interface allows starting the different tools by activating the dedicated buttons. Alternatively, you can directly *drag* appropriate files (image files, or .km modeling files) onto the buttons.

The ⊞ button present on the top of the tools buttons allows accessing the PSAMPLE Acquisition and Correction modules used with the Twilite Blood sampling system.

Starting PMOD Tools from the Command Line with Data

In some situations it is an advantage when a single tool is started rather than first opening the ToolBox. An example is a user program such as IRW which wants to open a PMOD tool with specific data.

This can be done by adding to the system-specific startup script the name of the tool and the file names of the data to be loaded. The Windows example below

```
cd /Pmod4.4
./java/jre/bin/java       -Xmx1200M       -jar       pmod.jar   PFUS
C:/DICOM/20060815/38243299/00000210  C:/DICOM/20060815/38243299/00000888
```

starts the fusion tool (PFUS) and loads two DICOM series. The first is loaded as the reference series, the second (and following) as the reslice series. Note that it is sufficient to specify a single file even if a DICOM series consists of multiple files. The loader will find and load all images belonging to the series.

When using several users, the user to be logged in can be specified with an additional command line option **-user[n]**, where n indicates the user, numbered from 1.

PMOD Status

The icon in the top line indicated in the capture below provides status information about the state of PMOD operation. A check indicates proper operation, whereas colored bullets alert the availability of an update (green down arrow) or some malfunction (red). Activating the icon displays the status window as illustrated below.
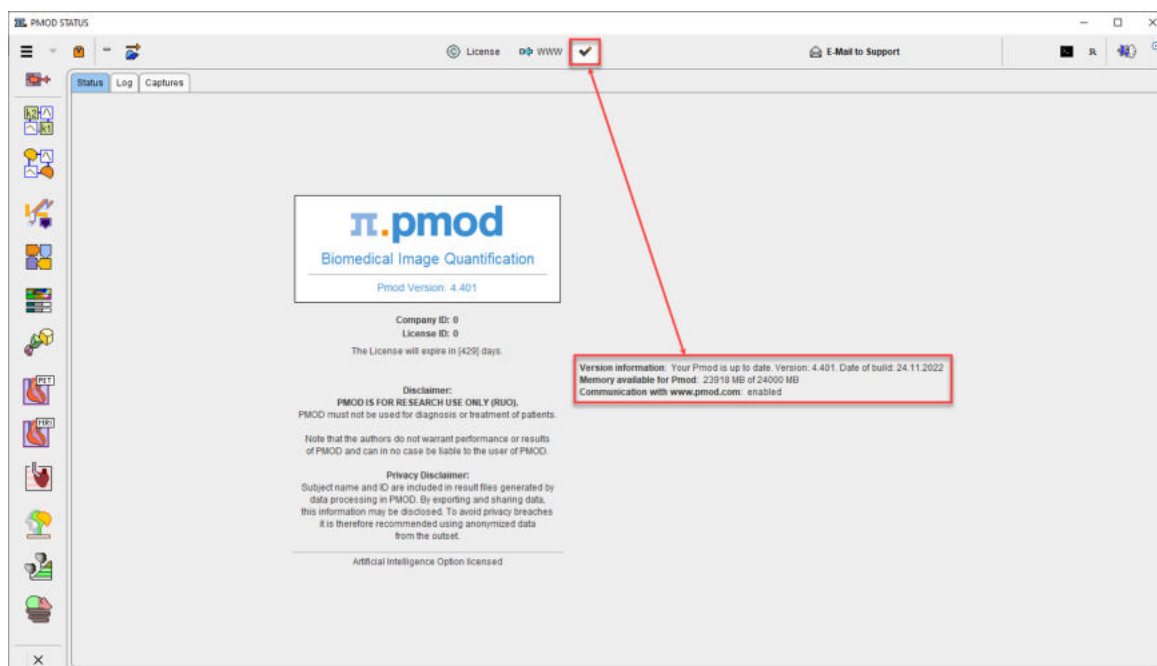
The green down arrow indicates that a new PMOD version or build is available for download. This functionality is active only when the communication with the www.pmod.com is enabled.

The customers with active maintenance agreement or customers that purchased version 4.3 are entitled to free PMOD 4.4 upgrade.

The customers who UPGRADED to version 4.3 or earlier versions are NOT entitled to free upgrade to 4.4. Purchase of 4.4 is required.

Notes:

The version checking procedure may not work properly behind institutional firewalls. In that case, it can be switched off to avoid the warning icon.

New builds of the current PMOD version are uploaded at irregular intervals, mainly to fix bugs. We therefore recommend using the latest build of a version.

All the builds within a PMOD version are freely accessible when access to the main version was purchased.

2.2   PMOD ToolBox Interface (Legacy)

Starting the Tools from the ToolBox

PMOD is started using the **RunPmod** script in the Pmod4.4/Start directory. Please refer to the system-specific installation guides if adjustments are needed. After starting, the PMOD ToolBox appears, initially with grayed tool buttons.

When the **Pmod Artificial Intelligence** (PAI) module has been licensed, a **+ AI** indication appears only next to **View** module:
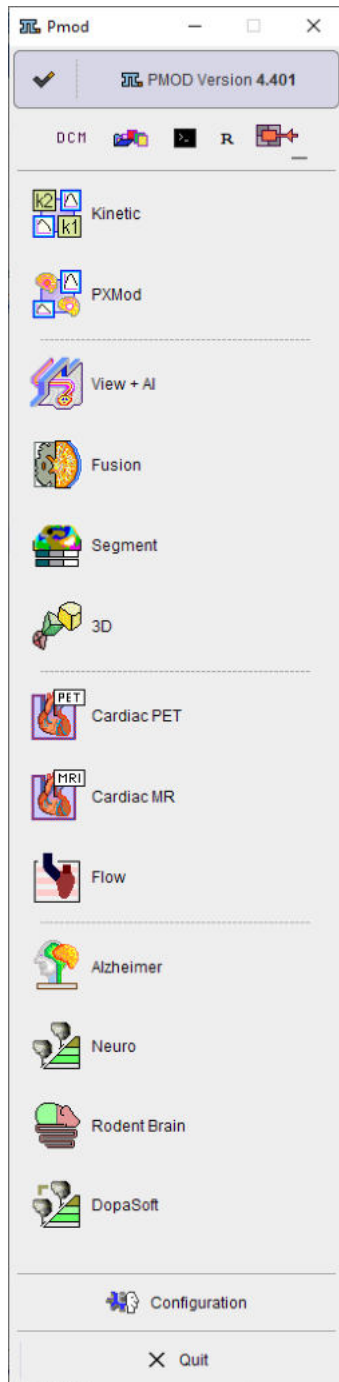
This is to emphasize that the AI training sets and data generation for trainings are supported by the **View** module. Please refer to the dedicated *PMOD Artificial Intelligence Framework (PAI)* user guide for detailed information about the learning sets preparation and data generation.

The PAI functionality is currently available in **PVIEW**, **PSEG**, **PCARDM** and **PNEURO.**

If multiple users have been configured, one of them needs to be selected and the **Log In** button activated. Otherwise, the login procedure proceeds automatically. Note the startup window which reminds you that PMOD is research software and shows license-related information.
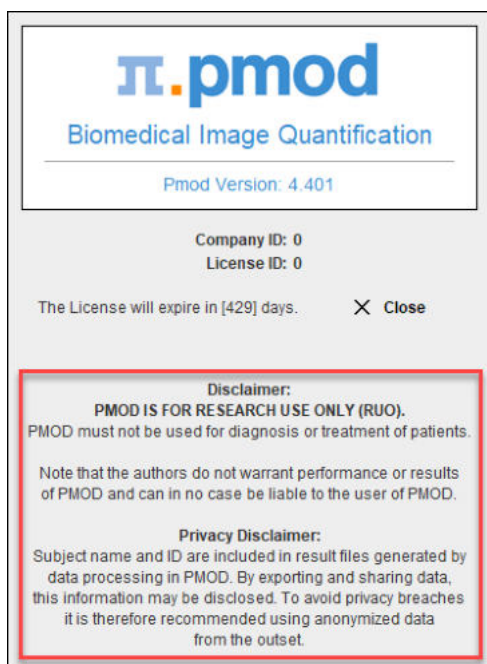
After the login, the tool buttons are active and you can start working with PMOD. The ToolBox allows starting the different tools by activating the buttons. Alternatively, you can directly *drag* appropriate files (image files, or .km modeling files) onto the buttons.

The buttons below the login section are related to the different PMOD server functionalities. They are not available for the clients of a network license setup.

DCM	Starts the **DICOM server** using the configuration of the current user. If it is already running, the configuration is shown. A blue background color indicates ongoing server activity, e.g. the receiving of images.
	Starts the **Transaction Server** for publishing a local JDBC database. If the Transaction Server is already running, an information window is shown which describes the server status. A blue background color indicates ongoing server activity.
	Starts the Pipeline Batch interface.
R	Starts the PMOD R console
	Access to the PSAMPLE Acquisition and Correction modules used with the Twilite Blood Sampling system

Note: The number of buttons in the ToolBox depends on the configuration you purchased. Only the base functionality **View** is always present.

Starting PMOD Tools from the Command Line with Data

In some situations it is an advantage when a single tool is started rather than first opening the ToolBox. An example is a user program such as IRW which wants to open a PMOD tool with specific data.

This can be done by adding to the system-specific startup script the name of the tool and the file names of the data to be loaded. The Windows example below

```
cd /Pmod4.4
./java/jre/bin/java      -Xmx1200M      -jar      pmod.jar      PFUS
C:/DICOM/20060815/38243299/00000210  C:/DICOM/20060815/38243299/00000888
```

starts the fusion tool (PFUS) and loads two DICOM series. The first is loaded as the reference series, the second (and following) as the reslice series. Note that it is sufficient to specify a single file even if a DICOM series consists of multiple files. The loader will find and load all images belonging to the series.

When using several users, the user to be logged in can be specified with an additional command line option **-user[n]**, where n indicates the user, numbered from 1.

PMOD Status

The icon in the upper left corner provides status information about the state of PMOD operation. A green check indicates proper operation, whereas colored bullets alert the availability of an update (green down arrow) or some malfunction (red). Activating the icon opens the status window illustrated below.

The green down arrow indicates that a new PMOD version or build is available for download. This functionality is active only when the communication with the www.pmod.com is enabled. The customers with active maintenance agreement or customers that purchased version 4.3 are entitled to free PMOD 4.4 upgrade.

The customers who UPGRADED to version 4.3 or earlier versions are NOT entitled to free upgrade to 4.4. Purchase of 4.4 is required.

Note:

The version checking procedure may not work properly behind institutional firewalls. In that case, it can be switched off to avoid the warning icon.

New builds of the current PMOD version are uploaded at irregular intervals, mainly to fix bugs. We therefore recommend using the latest build of a version.

All the builds within a PMOD version are freely accessible when access to the main version was purchased.

3   PMOD Basics

3.1   Directory Tree

The installation of the PMOD software results in directory tree containing the Java classes, configuration information, installers for the USB key driver, and example data for kinetic modeling data and image analysis.
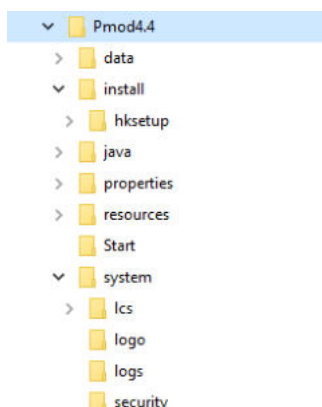
The content of the most important sub-directories is:

data	Container for data. **DATABASES** contains the tables and data of JavaDB databases, for instance of the example **Demo** database.
doc	Directory containing the PMOD html documentation as well as the pdf application guides.
install hksetup	Contains the driver installation files for the USB protection key. Each operating system has a dedicated sub-directory.
java	The **ext** sub-directory contains external Java libraries which support specific functions accessed from within PMOD. The **jre** sub-directory contains the Java Runtime Environment for running the PMOD applications.
properties	Contains the configuration of PMOD and the different tools. *properties/user1, etc:* Each PMOD user has a subdirectory containing his configuration of the different tools (*.props), the starting settings (*.ini), and the database queries (*.qry).
system	*system/lcs:* license file *pstarter.lcs.* *system/logo:* customer logo. *system/logs:* log files of PMOD program and the servers.
Start	The PMOD start scripts are located here. They are generated during the installation and take into account the installation directory and the operating system. Therefore, they can not simply be copied to another system or moved to a different directory. ▪ **RunPmod**: starts the interactive PMOD environment. ▪ **RunDbSvr**: starts the transaction server for publishing a database called **DbSvr**. Default port of the transaction server is 5100. Please edit the script for using a different port. ▪ **RunDcmSvr**: starts the DICOM server for receiving DICOM images and saving them into the **DbSvr** database. Default port of the DICOM server is 5030. ▪ **RunLcsSvr**: starts the transaction server for license serving only. This is only relevant if a network license file is contained in *system/lcs.*

3.2 Basic User Interface Elements

For efficient use of the PMOD programs it will be helpful being aware of the behavior of some user interface elements.

Option Buttons

Frequently used are option buttons. Their appearance is a button with an arrow next to it, for instance the loading button of image data
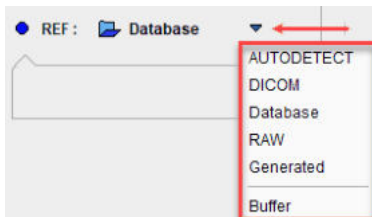
The arrow ▼ indicates that there is a selection. As soon as it is activated with the left mouse button, the different options appear as a list.
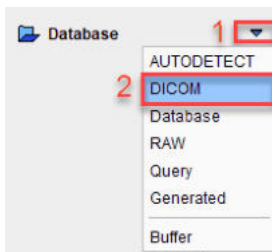
Select the appropriate option with the left mouse button, for example DICOM in the example above. The list closes, the button changes to the new option,
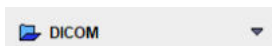
and the button operation is executed.

Sometimes, only a line below the option button is available, for instance the loading option in the lateral task bar:

The line indicates there is a selection. As soon as the loading icon is activated with the left mouse button the option list appears:
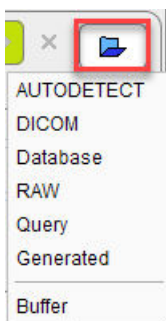
The list closes once the appropriate option is selected and the button operation is executed. In this situation the option selection is mandatory each time such option button is available.

Option buttons allow organizing related functionality with minimal space requirements, but the hidden functionality might be overlooked. Therefore it is worthwhile to initially check the hidden list wherever you see a ▼.

In some cases option buttons have also left and right arrows to quickly step through the available options, for instance through the color tables.
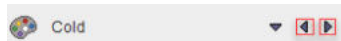
Hide/Show buttons

An interface reduction ⊙ button is located in different places to allow hiding/showing content available on a page. When it is activated it becomes a ⊙ button and some of the user interface elements are hidden to allow for more place. To show all elements, the ⊙ button needs to be activated.

Context Menus

Context menus are another way of collecting function related to a certain element. A context menu is opened by clicking the right mouse button at an element. If available, the menu opens and allows changing configurations or initiating actions. Context menus are available for image display ports (example below), curve areas, and color bars.
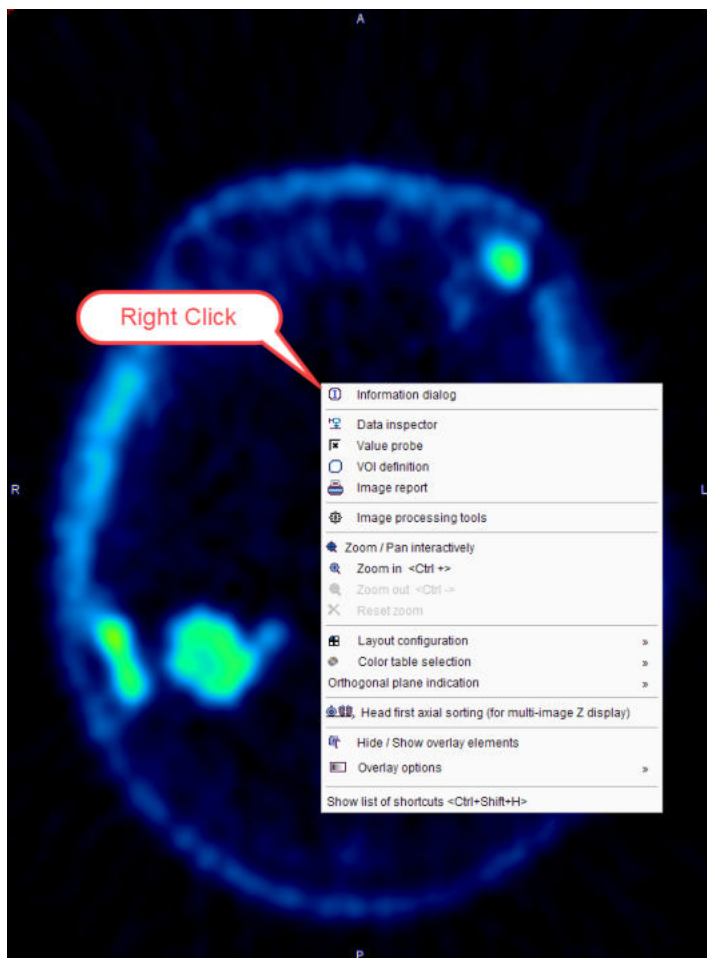
Tabbed Panes

A third way of grouping elements is through tabbed panes. Each tab shows different functions, and may also contain nested tabbed panes. The example below shows the image processing tools pane with the selected reduce **Rdc** sub-pane.
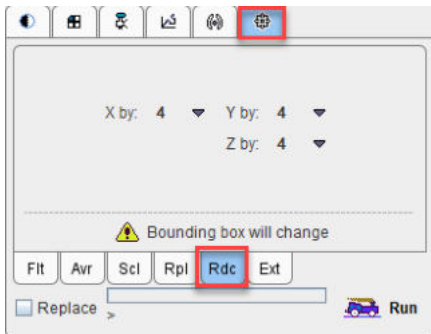
Lists

The selection of entries in a list uses the usual paradigms:

- `Ctrl+Click` adds the entry to the selection;
- `Shift+Click` adds all entries from between the selected entry and the previous selection;
- `Shift+`Drag mouse adds all touched entries to the previous selection;
- `Ctrl+A` selects all list entries.

Tooltips

Many elements of the user interface are equipped with an explanatory tooltip. If you move the cursor over the element and wait a while, the explanation pops up and may save you the effort of referring to the reference documentation. From the example below you may learn that you can use the function key `F1` for stepping through the list of color tables in the forward direction, and the combined `Ctrl` and `F1` keys in the backward direction.
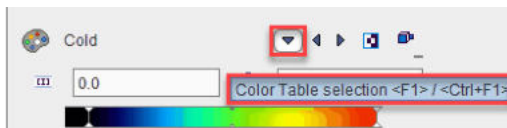
Data Loading, Example Data, Relative Paths

Loading components such as VOIs will always first bring up the database loading interface. If your data resides outside the database, use the button
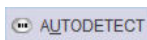
to start a file-based loader which can be pointed to a particular directory. In some situations the button is abbreviated to .

In case the user decided to install the example data with PMOD (recommended), there is a database **Demo** available which contains examples for kinetic modeling (PKIN and PXMOD), cardiac modeling (PCARD) and image fusion (PFUS). This data is installed in a sub-directory data of the PMOD installation directory. The configuration of the database shows the paths
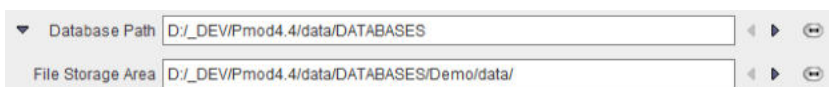
The leading part of the path **./** indicates a path which is relative to the installation directory, currently *Installation-path/Pmod4.4/data*
where *Installation-path* might be something like *C:* , */opt*, or */Applications*, depending on the operating system.

The use of relative paths has the consequence that after an upgrade to the next version the data have to be moved to the *data* directory of the new installation.

Accelerator Keys and Mouse Dragging

A substantial number of functions can be accessed using keyboard shortcuts. For instance, clicking into an image to activate it and then pressing the "Ctrl" and the "D" keyboard key (CTRL+D) will switch the layout to orthogonal planes.

Another sort of shortcuts is using modifier keys and mouse dragging. As an example, the lower and upper color table thresholds can be interactively changed by clicking into the image, then holding down the SHIFT key, and dragging the mouse left/right (lower threshold) and up/down (upper threshold) with the left mouse button pressed.

These accelerator capabilities are describe in a separate section 24 .

3.3 Keyboard Shortcuts

Many of the viewing functions can be activated and are much faster to use by keyboard shortcuts. To direct the keyboard shortcuts to the right images it is essential that they are active, indicated by the *blue color of the activator rectangle* in the upper left corner of the image display. Clicking into the image activates it. To avoid reslicing in the orthogonal viewing mode please hold down the CTRL key when clicking.

While working in PMOD the list of keyboard shortcuts can be displayed via the image context menu, which is obtained by clicking with the right mouse button onto an image shown in PMOD.
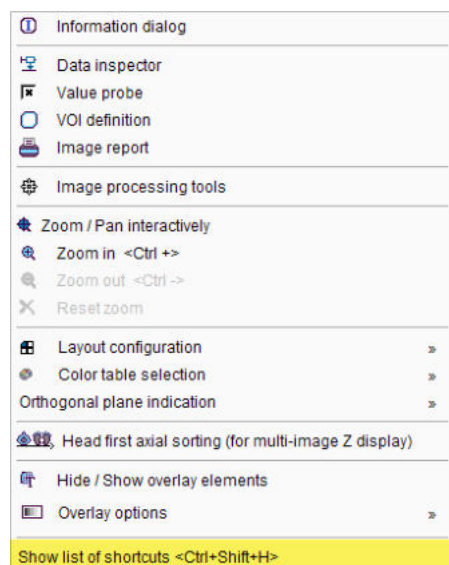
The last entry **View List of Shortcuts <Ctrl+Shift+H>** displays the window reproduced below. Note the arrow buttons to switch between pages.

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LIST of KEYBOARD SHORTCUTS: page **1 of 3**   «   »   (Focus in the viewport required)   ✕

Type	Shortcut	Effect / Test
Data Loading:	<SHIFT + L>	Load image data
	<SHIFT + Q>	Close the currently displayed study
	<Alt + Mouse_Wheel>, <Ctrl + N>	Display next study
	<Alt + Mouse_Wheel>, <Ctrl + P>	Display previous study
Layouts:	<CTRL + X,Y,Z>	Switch to x,y,z-planes (f.e.: <Ctrl+X> = x-plane (sagittal))
	<CTRL + D>	Switch to orthogonal views
	<CTRL + />	Switch to next orthogonal plane
	<CTRL + 1 .. 9>	N x M image display (f.e.: <Ctrl+2> = 2 x 2)
	<CTRL + Click>	Switch 1 x 1 and N x M image dispaly
Reslicing:	<Ctrl+ R>	Enable / disable the oblique image reslicing handles
Slice selection:	<Page Up,Down>	Replace the display by the previous / next page of slices (f.e: <Up> previous page of slices)
	<Arrows>	Increment / decrement the currently shown slices by one (f.e: <Right> next slice)
	<Home,End>	Go to first / last slice (f.e: <Home> first slice)
	<SHIFT + Page Up,Down>	Show the same slices at previous / next page of acquisition times (f.e: <SHIFT + Up> previous page of frames)
	<SHIFT + Arrows>	Show the same slices at incremented / decremented acquisition times (f.e: <SHIFT + Right> next frame)
	<SHIFT + Home,End>	For a dynamic study, go to first / last acquisition (f.e: <SHIFT + Home> first frame)
	<Mouse_Wheel>, <CTRL + Drag>	Scroll through the slices in a movie mode fashion
	<CTRL + M>	Start / Stop movie

LIST of KEYBOARD SHORTCUTS: page **2 of 3**   «   »   (Focus in the viewport required)   ✕

Type	Shortcut	Effect / Test
Zoom:	<CTRL + Mouse_Wheel,+,->	Zoom in / out (f.e: <CTRL + "+"> Zoom in)
Color Table Manipulation:	<SHIFT + Drag>	Modify color table thresholds: horizontal: left = decrease, right = increase lower threshold vertical: down = decrease, up = increase upper threshold
	<CTRL + T>	Invert color map
	<F1>	Switch to next color map
	<CTRL + F1>	Switch to previous color map
	<CTRL + S>	Apply the color table thresholds for each slice individually (slice)
	<CTRL + G>	Apply common color table thresholds over all slices of individual time (frame)
	<CTRL + A>	Apply common color table thresholds over all slices of all times (study)
	<CTRL + F>	Allows for entering absolute values for the upper and lower color table thresholds (fixed)
	<Mouse_Wheel + F>	Modify fusion balance
Contour Overlay:	<CTRL + C>	Enable / Disable showing the contour with currently defined threshold in the overlay
Volume Rendering:	<CTRL + V>	Enable / Disable the volume rendering display
		(Note that the layout is switched accordingly, as a n*m layout is not reasonable for a volume rendered display)
Reporting:	<CTRL + I>	Print image report
	<CTRL + E>	Capture Display
	<CTRL + O>	Publication Capture
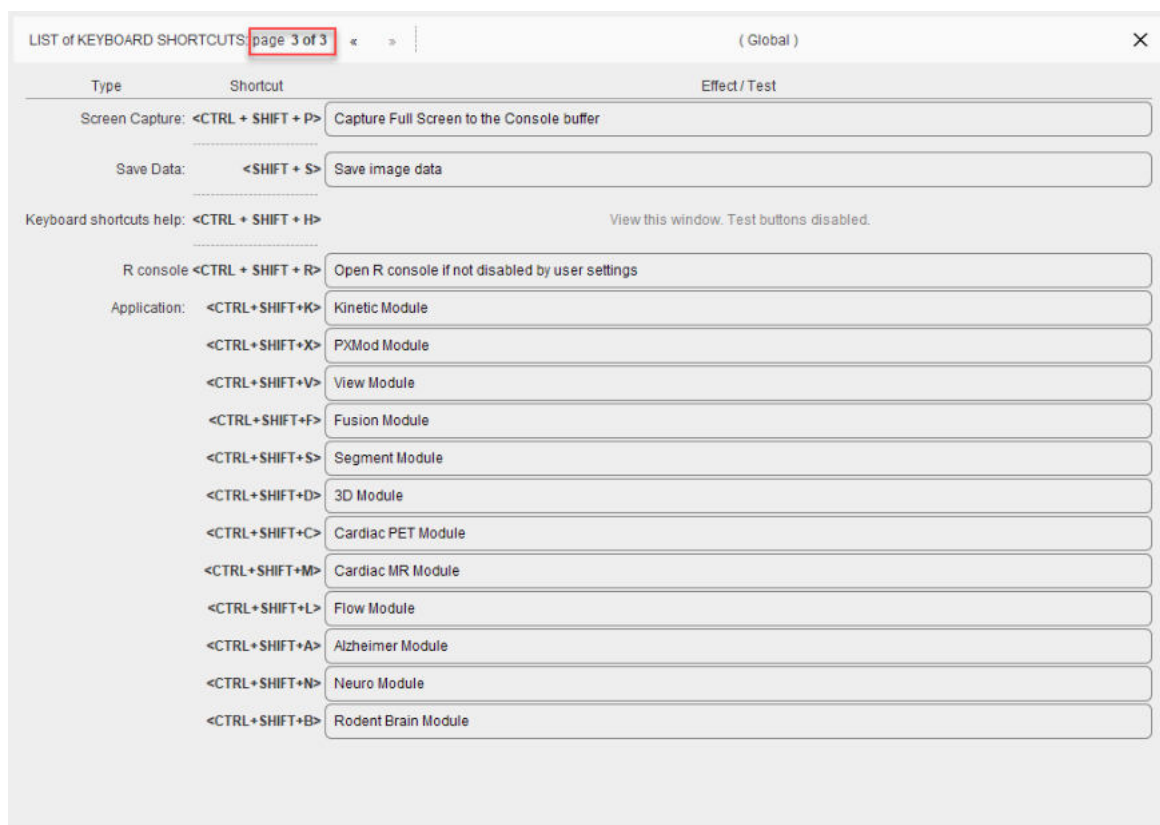
Button- and Menu-Related Shortcuts

Functionality implemented as a button or a menu item can often be activated using the keyboard. In these cases, a letter in the item text is underlined. The action item can then be activated by combining the `ALT` key with the underlined letter. In dialog windows, `ALT+C` is typically used for the **Cancel** action.
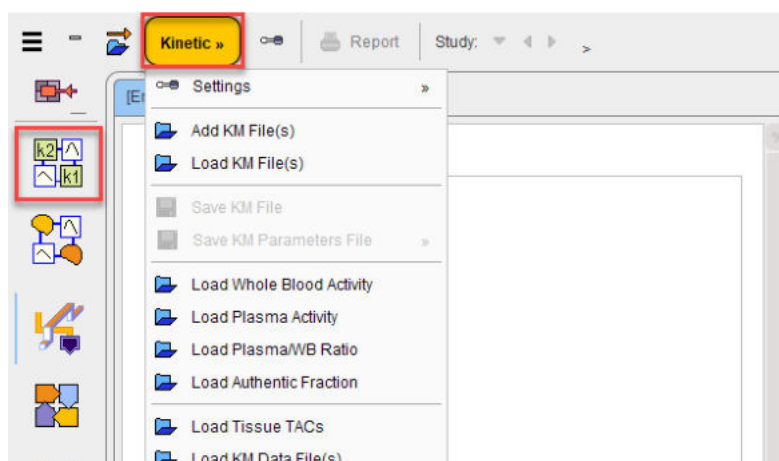
For instance, when working in PKIN, the menu **Kinetic** can be brought up quickly by `ALT+M`. Once the menu is open, an underlined letter is sufficient to activate a menu item. So `ALT+M` and then an "`L`" will quickly perform the Load KM File(s) action.

Dialog Default Action

When a dialog window is opened, the button with the most likely action is usually pre-selected. This default button can be activated with the `SPACE` keyboard key (not with the `ENTER` key). This is a Java property.

3.4 Problem Reporting

PMOD includes a functionality to directly send a problem report to the support staff of PMOD Technologies. This report can include the log output, screen captures and a problem description entered by the user.

Every PMOD tool contains dedicated selection buttons available in the upper right corner of the docking interface for creating the report. They are part of the common functionalities present in the top Menu line.

The capture button ⬛ (Ctrl+Shift+P) creates a capture of the entire screen (not only the PMOD window) and adds it to a buffer of up to 20 captures. The console button ⬛ opens the **Console** dialog window illustrated below.
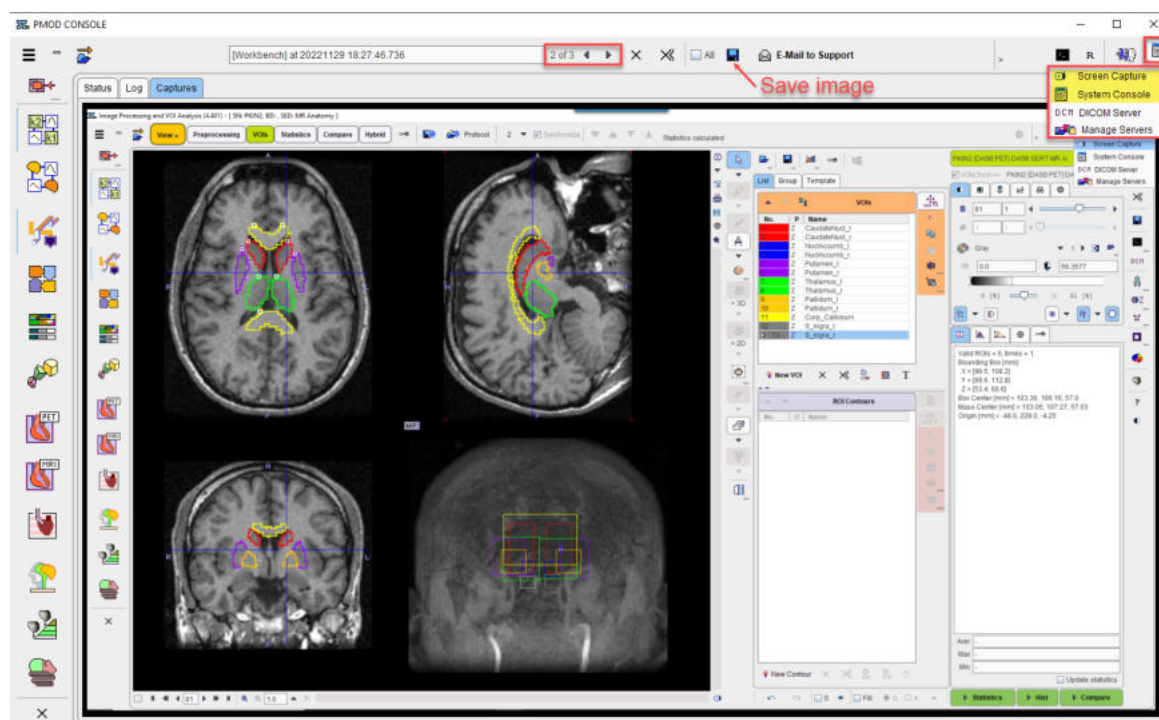
The captures can be inspected on the **Captures** pane with the left/right arrow buttons, and the current one saved in JPEG. The **Log** pane contains the log messages, if the terminal output has been configured to be saved in a file on the **On Start** tab 91 of the **Users Configuration**. Its contents can be updated by the **Refresh Log** button. Once in a while it is recommended to use **Clear Log**, to avoid excessive length of the log file.

To submit a problem description please activate the **E-mail to Support** button. It opens a dialog window,

wherein the user can select the affected **Module**, and confirm whether the **Log Output** and the **Screen Capture(s)** should be **Attach**ed. The problem description should be typed into the text field, and the user's email address into the **Your email** field. Note that multiple addresses can be specified, separated by the colon character (;). It is mandatory to enabled the **Privacy Policy** box otherwise the message will not be sent out. Finally, use the **OK** button to submit the report, or **Cancel** to cancel.

Note: Although the standard mailing port is used, corporate firewalls may prevent PMOD from submitting the e-mail. In this case a notification will be shown, and the user needs to report the problem either through his support login, or by standard e-mail to support@pmod.com.

4   PMOD Unified Data Loader

Starting with version 4.4 PMOD implements a unified data loader as the Scientific Data Management System (SDMS). It can be accessed activating the dedicate icon in the top line of the docking interface. It seamlessly integrates **DATABASE**, standalone **DICOM** data and **AUTODETECT** data loader for other formats within the same interface as illustrated below:

PMOD organizes the unified data loader functionality on different pages which can be selected by the upper tabs. They are described in detail below.

4.1   DATABASE Page

Most of the functionality is common with the database <u>Load</u> [62] page.
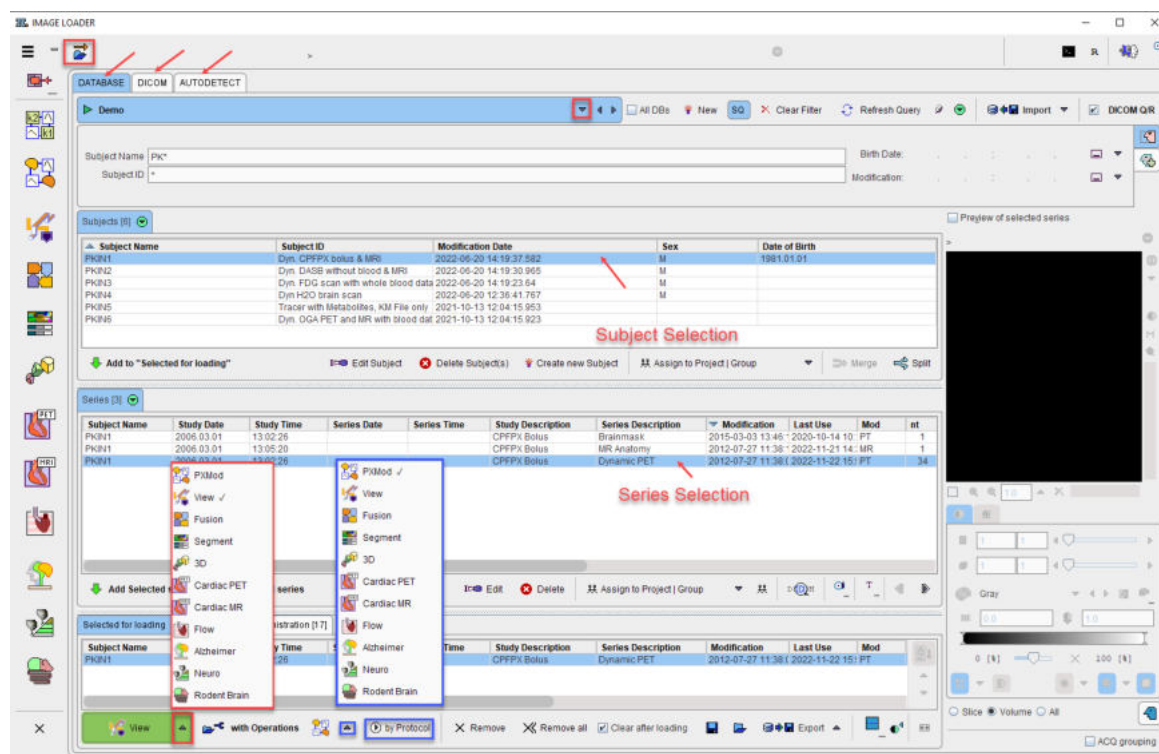
Additional functionality is added in the bottom line for the **Selected for loading** images.

1. Load the image(s) directly or **with Operation** in one of the modules available in the selection list (highlighted with red rectangle in the capture above). To load the image(s) directly, select the module with the left mouse button, for example View in the example above. The list closes, the button changes to the new option, and the button operation is executed: the image is loaded and visualized in the selected module. The **with Operation** button starts loading the image series in the module that was last used for direct loading. It opens a dialog window for specifying pre-processing options as described in <u>Image Data Transformations during Loading</u> [108].

2. Load image(s) and run **by Protocol** of the selected module (highlighted with the blue rectangle in the capture above). First select the appropriate module on the selection list. Depending on the PMOD module, the protocol may required single image (e.g. PXMOD) or multiple images(e.g. PNEURO MPA PET-MR workflow). Activate the **by Protocol** button and in the dialog window select the protocol using the left mouse button. The selected PMOD module will open displaying the protocol retrieval interface. Proceed with the protocol execution.

4.2   DICOM Page

When loading DICOM data, the directory of the last DICOM loading operation is referred to. To locate the proper directory use the **Change Folder** button and activate the 🔄 button to initiate scanning for DICOM files. If no DICOMDIR exists, all files of the directory are scanned and all valid DICOM series listed.

Most of the functionality is common with the <u>DICOM image loading</u> [105] interface as illustrated below:
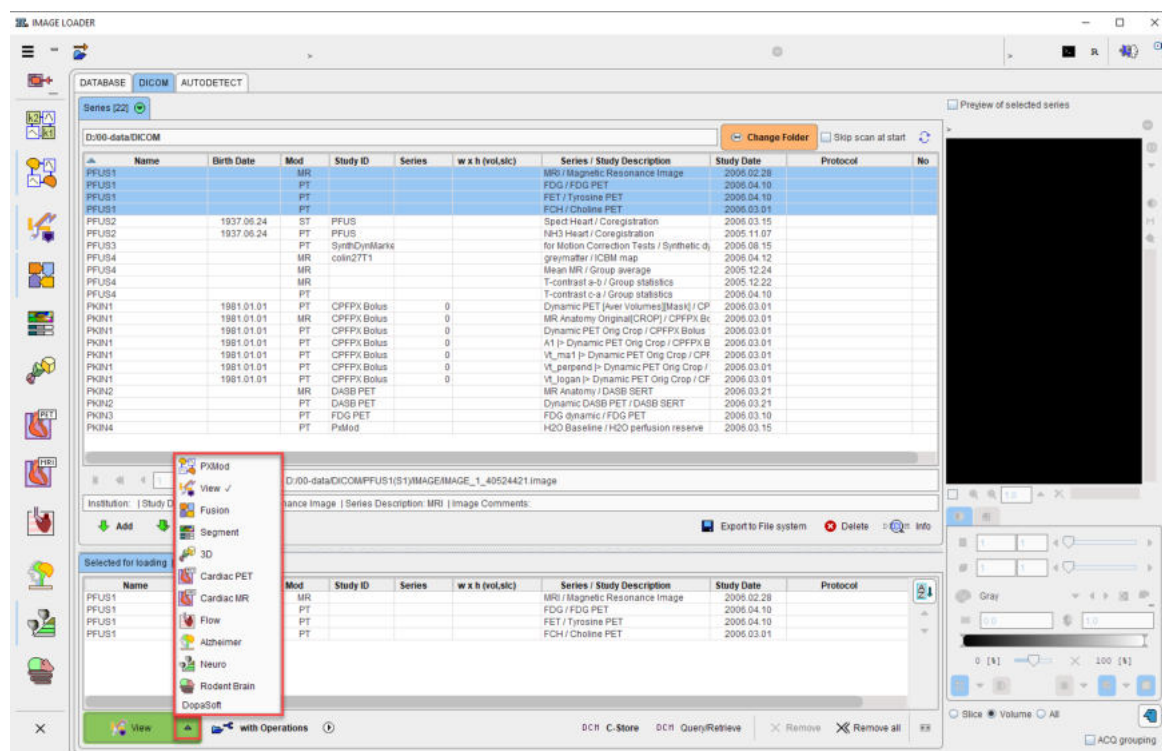
Additional functionality is added in the bottom line for the **Selected for loading** images: load the image(s) directly or **with Operation** in one of the modules available in the selection list (highlighted with red rectangle in the capture above). To load the image(s) directly, select the module with the left mouse button, for example View in the example above. The list closes, the button changes to the new option, and the button operation is executed: the image is loaded and visualized in the selected module. The **with Operation** button starts loading the image series in the module that was last used for direct loading. It opens a dialog window for specifying pre-processing options as described in <u>Image Data Transformations during Loading</u> [108]

4.3   AUTODETECT Page

For all non-DICOM type of image data the loading use the AUTODETECT loading page. The dialog looks like below.
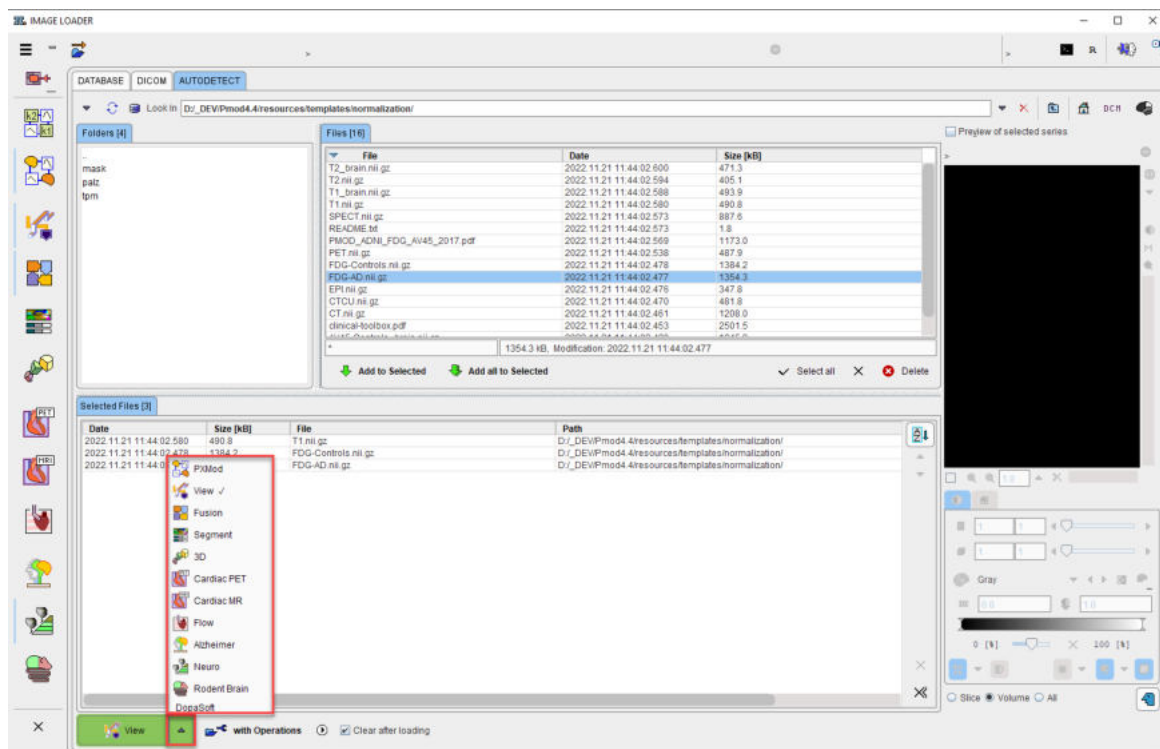
Most of the functionality is common with the [File based loading](#) 107 .

Additional functionality is added in the bottom line for the **Selected Files** images: load the image(s) directly or **with Operation** in one of the modules available in the selection list (highlighted with red rectangle in the capture above). To load the image(s) directly, select the module with the left mouse button, for example View in the example above. The list closes, the button changes to the new option, and the button operation is executed: the image is loaded and visualized in the selected module. The **with Operation** button starts loading the image series in the module that was last used for direct loading. It opens a dialog window for specifying pre-processing options as described in [Image Data Transformations during Loading](#) 108 .

5   General Configuration

The PMOD configuration utility is started with the **Configuration** button

located to the right in the top menu line. It appears with four sections accessible by the main tabs.
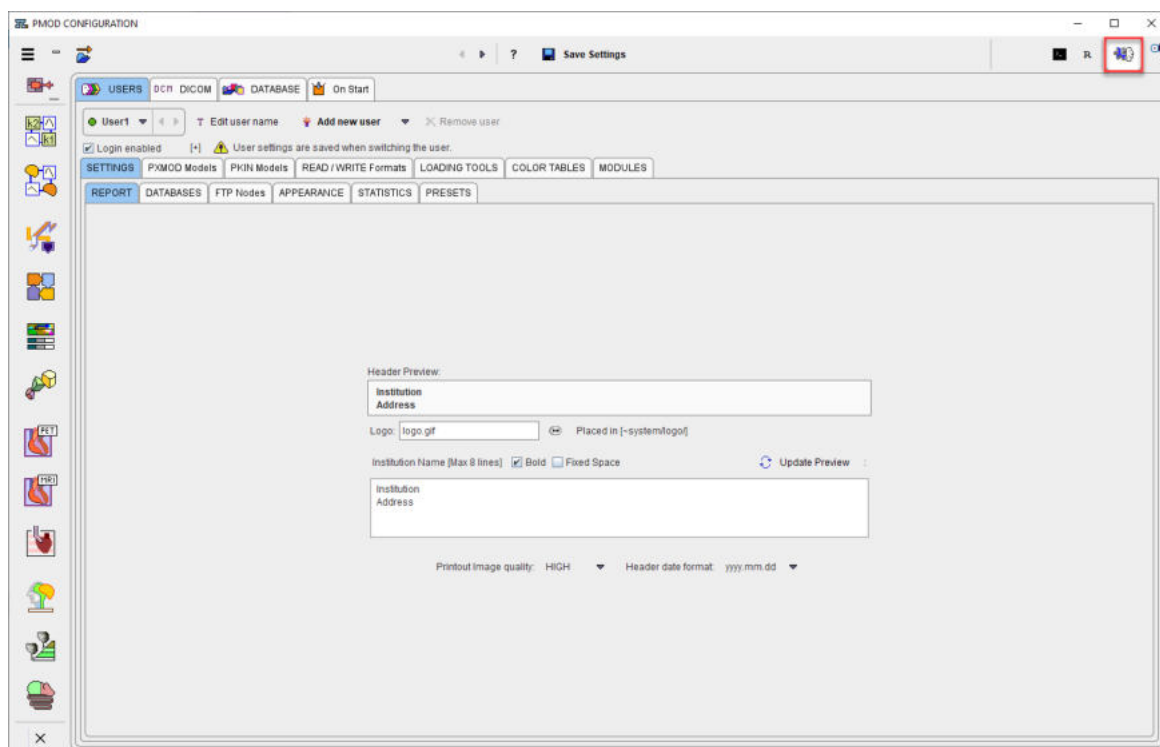
The **DCM DICOM** and **DATABASE** tabs are described in the PMOD DICOM Functionality 39 and PMOD Database Functionality 54 sections, respectively, together with the **USERS** and **On Start** tabs below.

5.1 USERS

PMOD supports the concept of different PMOD users. Each user can maintain his own preferences such as the model selection and order, user interface font size, report layout etc, and PMOD maintains for each user independent tool configurations and loading histories. The **USERS** tab of the configuration utility allows creating PMOD user accounts, and configuring their properties.

Note: For all changes of the settings it is important to *first select the affected user*, and then proceed with the configuration.

5.1.1 User Creation

New user accounts are created with the option button:
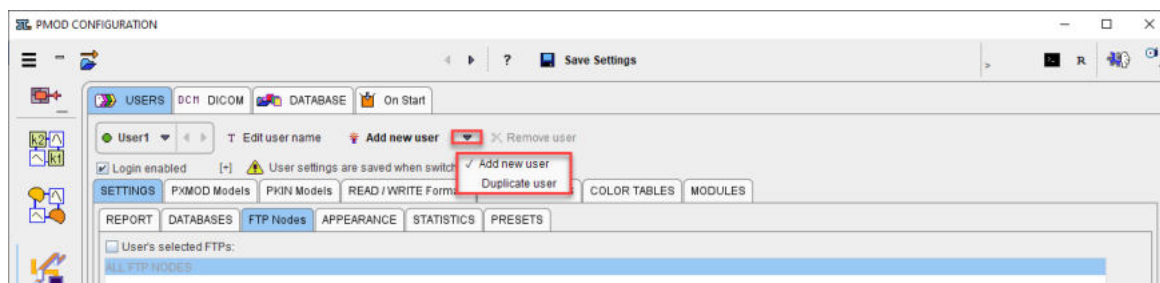
- **Add new user**: Creates a new user account with the default settings.
- **Duplicate user:** Creates a new user account using the settings of the currently selected user.
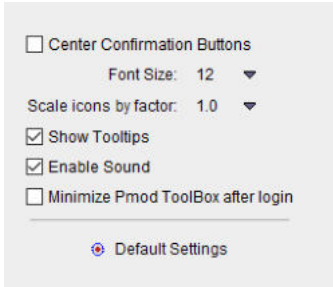
The user name needs to be specified during user creation, but can be changed later using the **Edit user name** button. This name will be attached to data saved in a database and can be used in data filtering.

Note that no user passwords are required in the standard PMOD usage, since the accounts are rather aimed at separating the processing environments for different tasks than protecting data access.

The password are enforced only in case of the ATL PMOD version which is aimed at controlled data processing.

5.1.2   USER SETTINGS

The **SETTINGS** tab houses the different settings of the currently selected user account. Their configuration panes are accessible by the sub-tabs. Since the majority of the functionality is self-explanatory, only the most important entries are briefly described below.

REPORT	Configuration of the PMOD report pages. A **Logo** can be specified (a GIF file located in the *system/logo* sub-directory) as well as the institution address in the **Institution Name** section. The address can be set to **Bold** and to use **Fixed Space** by checking the corresponding boxes. Please use the **Update Preview** button to inspect the configured layout in the **Header Preview** section. The **Printout Image quality** selection determines the resolution of the created jpeg pages and should normally be set to **HIGH** to achieve a satisfactory image and text quality. The **Header date format** allows choosing between year first/last variants.
DATABASES	Database usage profile. See <u>User-Specific Database Preferences</u> 33 .
FTP nodes	FTP nodes available to the user. See <u>DICOM Client configuration</u> 40 .
APPEARANCE	Allows changing the location of the dialog buttons, the font size, icon scaling (required for high-resolved displays), whether tooltips should be shown, notification sound when processing completes, and whether the ToolBox should be collapsed automatically after login. The **Default Settings** can be retrieved activating the dedicated button. ☐ Center Confirmation Buttons Font Size: 12 ▼ Scale icons by factor: 1.0 ▼ ☑ Show Tooltips ☑ Enable Sound ☐ Minimize Pmod ToolBox after login ⦿ Default Settings
STATISTICS	This panel allows establishing global settings that impact the statistics outcome. See <u>STATISTICS</u> 35 .
PRESETS	This panel allows establishing global layout settings. See <u>PRESETS</u> 36 .

5.1.2.1   User-Specific Database Preferences

As the database behavior can be differently configured for each user, a user must first be selected, **User1** in the example below.
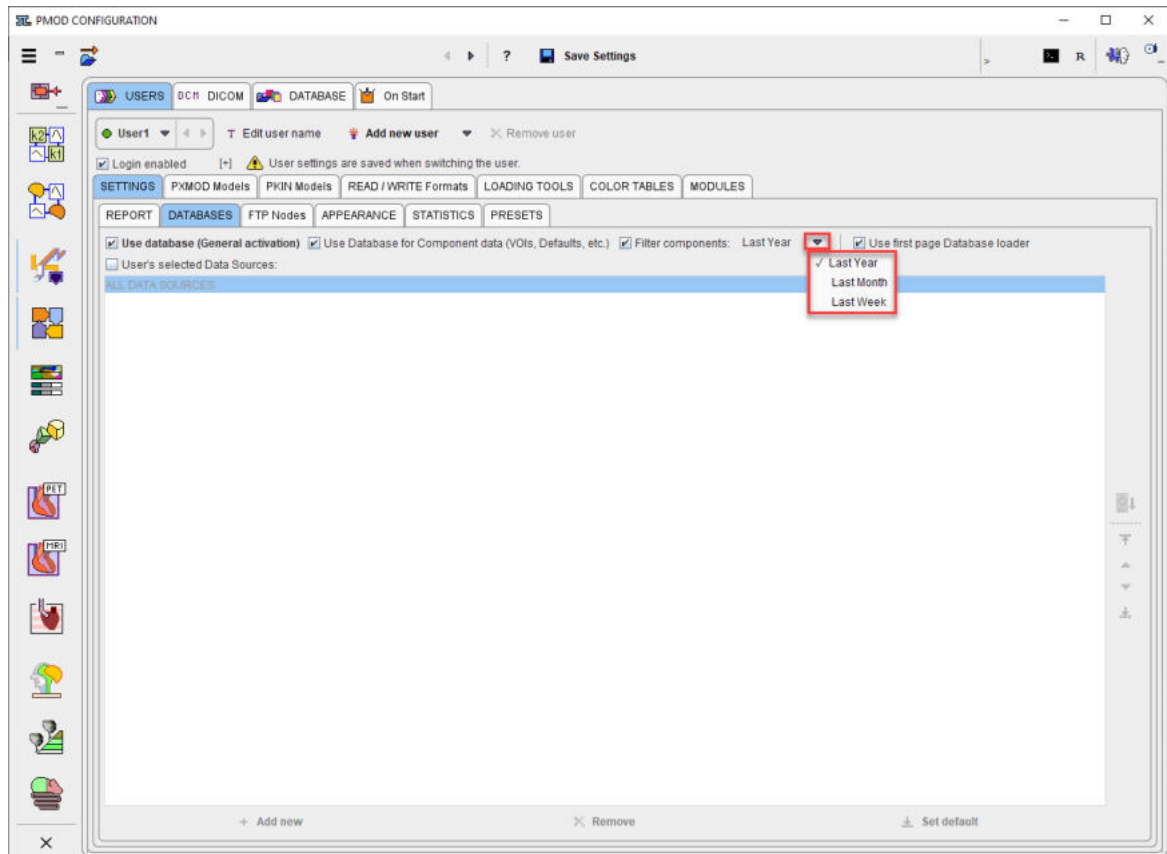
The configuration items are then available on the **DATABASE** sub-tab of the **SETTINGS** pane:

- **Use Database (General activation)**: This is the main switch. If the box is not checked, all databases are invisible for this particular user and all data loading/saving is file-based.

- **Use Database for Component data (VOIs, Defaults, etc.)**: Sometimes it is preferable to use the database only for the image data. In this case, the check can be removed from this box. Using the full database capability has the advantage that TACs and VOIs etc. are related to the image series they are derived from.

- **Filter components**: For large databases, the listing of VOIs and other components can slow done. In order to speed the listing operation up and only show recent data, a default date filter (**Last Year**, **Last Month**, **Last week**) can be enabled.

- **Use fist page Database loader**: This check box allows activating the **Load** database page for each available PMOD module.

- **User's selected Data Sources**: If there is a substantial number of different databases and a user requires only a few he can check this box, and then add the relevant ones with the **Add new** button. An additional advantage is that the user can sort the database list according to his preference.

5.1.2.2 STATISTICS
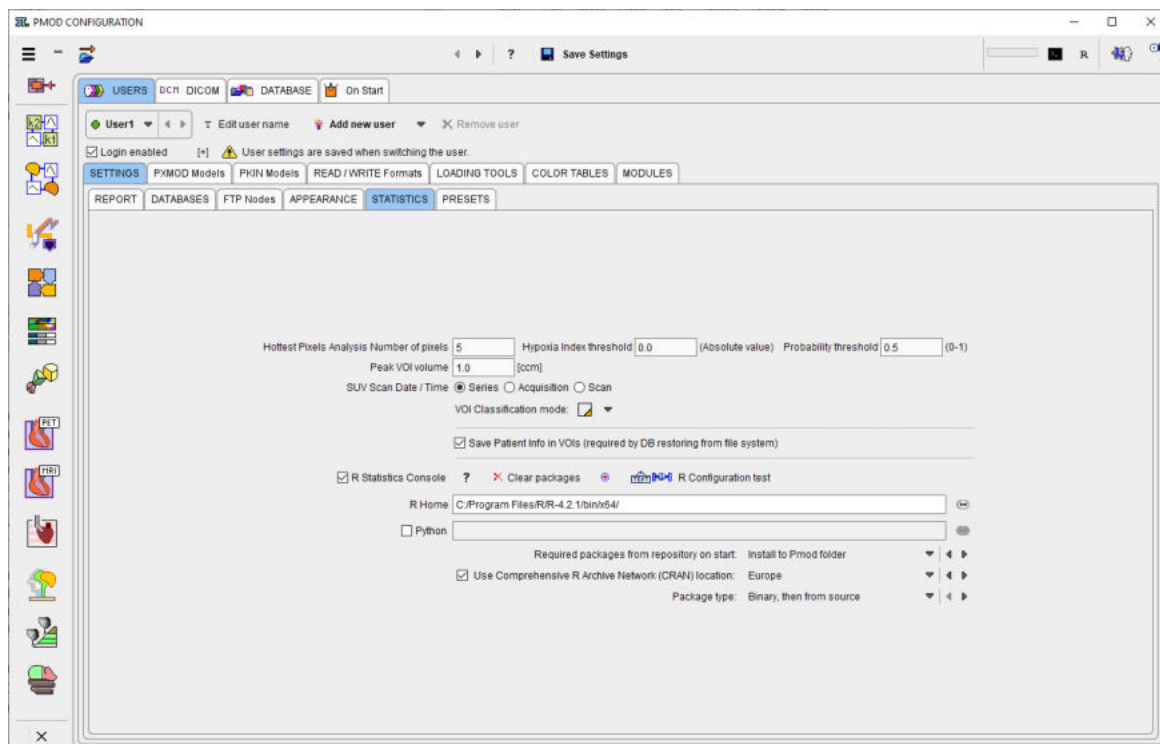
One of the VOI statistics results is the average of the highest pixel values. The **Hottest Pixel Analysis Number of Pixels** specifies the default how many pixels are included in this analysis. The **Hypoxia Index threshold** establishes a threshold for the hypoxia index calculation (hypoxia index = number of pixels in the VOI which have a value above the threshold divided by total number of pixels). **Probability threshold** defines the level which is used for converting VOI probability atlases into discrete VOIs. The **Peak VOI volume** defines the sphere volume which is used for the Sphere with Max Average (Peak VOI) 253.

The SUV 147 calculation requires information about the time the PET scan was decay corrected to. This information may be encoded in different DICOM fields, depending on the manufacturer. The **SUV Scan Date/Time** allows establishing a convenient default for the user's environment. **VOI Classification mode** sets the default Inclusion Criteria for Pixels 228.

If **Save Patient Info in VOIs** is enabled, information about the patient and the image is encoded in the VOI file. This allows reconstructing the relation between image and VOI, but may become a privacy issue when data is exchanged.

The PMOD_R console 350 provides statistical analysis via the R package. The **R Statistics Console** is configured by default and should be adjusted 350. If the user doesn't want to use this functionality, it should be disabled. The configuration of the **R Statistics Console** is mandatory for the **PAI** module.

5.1.2.3 PRESETS

The **PRESETS** contains global layout settings.
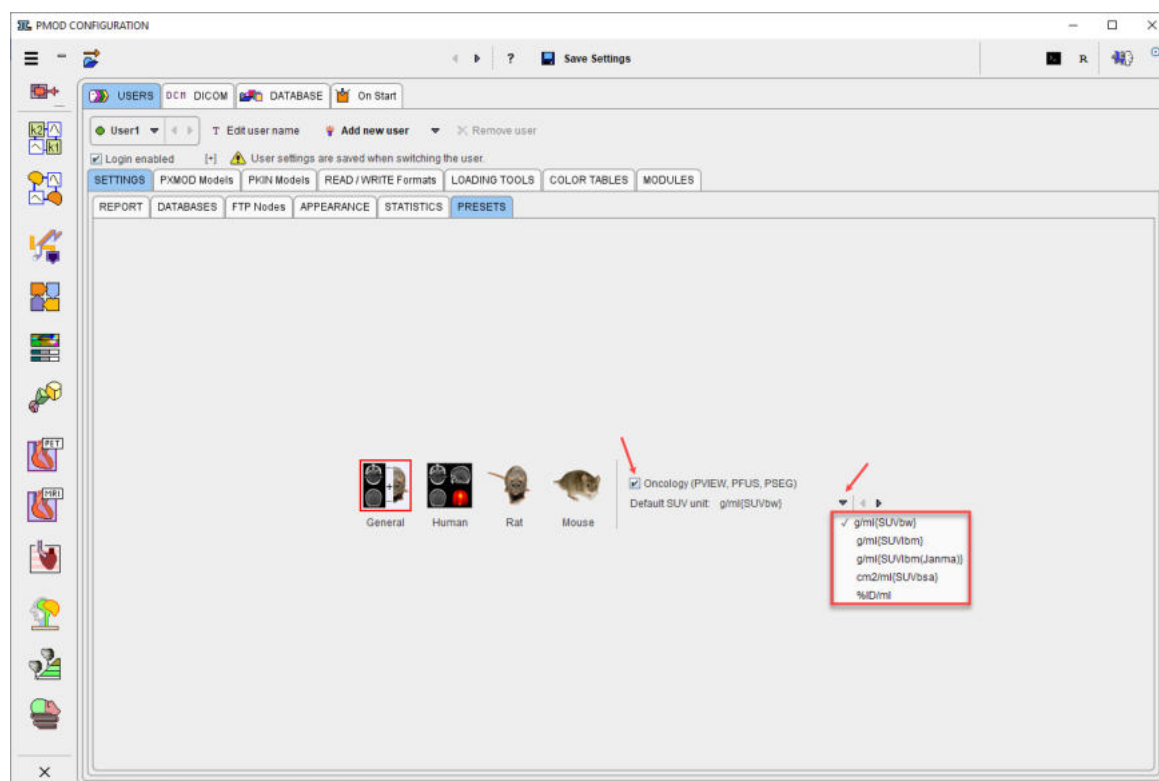
The type of the processed data may matter for some PMOD functions. For instance, animal data with small pixel sizes require also smaller default values for the sampling rates and filter sizes. If the user configures the **Human**, **Rat** or **Mouse** application domain PMOD is able to exploit appropriate presets. Otherwise, with the **General** configuration, the user can choose between the presets during data processing.

With the global **Oncology** box enabled, the functionality and usability of PMOD is tailored for the the oncology research field. It indicates to the program that hot lesion outlining and assessment is the main application purpose. Consequently:

▪ The default units for display and statistics are set to SUV, whereby the SUV type can be selected.

▪ The subject annotations (Subject Name, Subject ID) are switched on by default for the viewport.

▪ The statistics measures Volume and Total (aver*volume) are renamed to MTV (Metabolic Tumor Volume) and TLG (Total Leasion Glycolysis) respectively.

5.1.3 PXMOD, PKIN, READ/WRITE, LOADING, Color Tables Plug-ins

Many PMOD functionalities are programmed as plug-ins. Most of these plug-ins are initially installed, but they can be removed or rearranged for each user account with the different tabs. The procedure is always the same and is explained with the plug-ins (the models) of the kinetic modeling tool PKIN.

PKIN Models

When the **PKIN Models** tab is selected, the list of the currently installed model plug-ins is shown. The entries show the name in the model selection of the PKIN tool as bold and in parentheses the file names of the plug-in.

To modify the order how the models appear in the PKIN application please select an entry and move it up/down using the arrows to the right. The **?** button shows a quick model explanation.
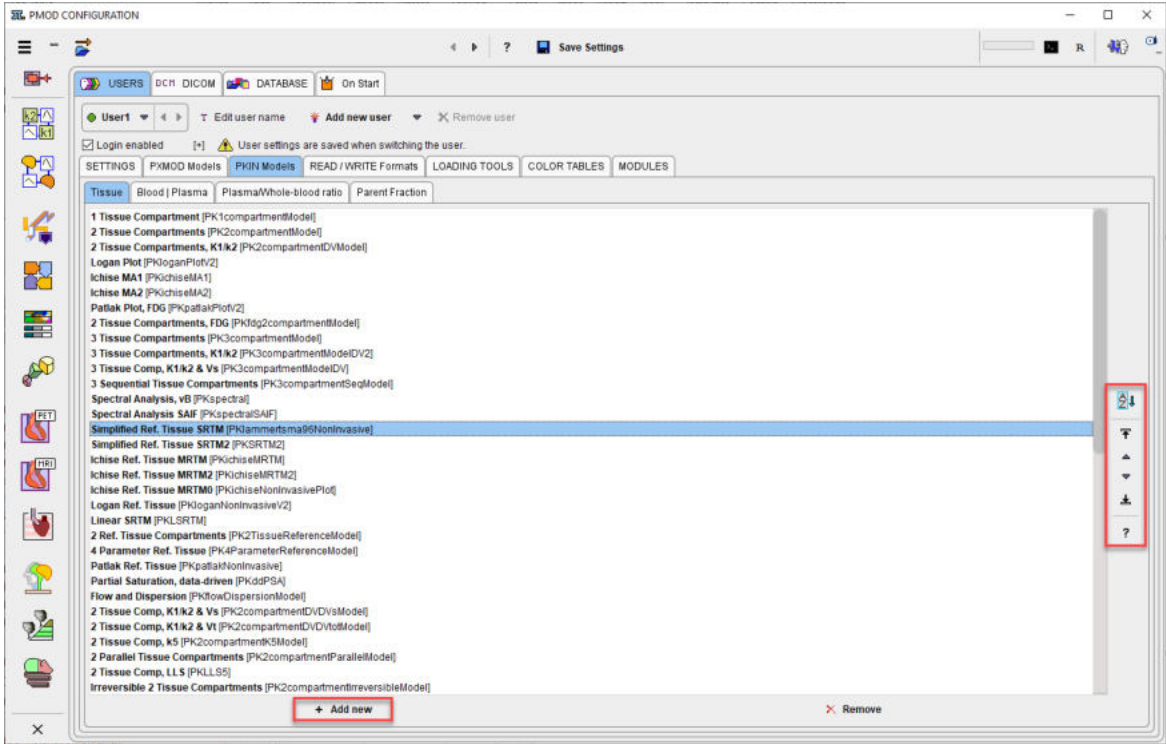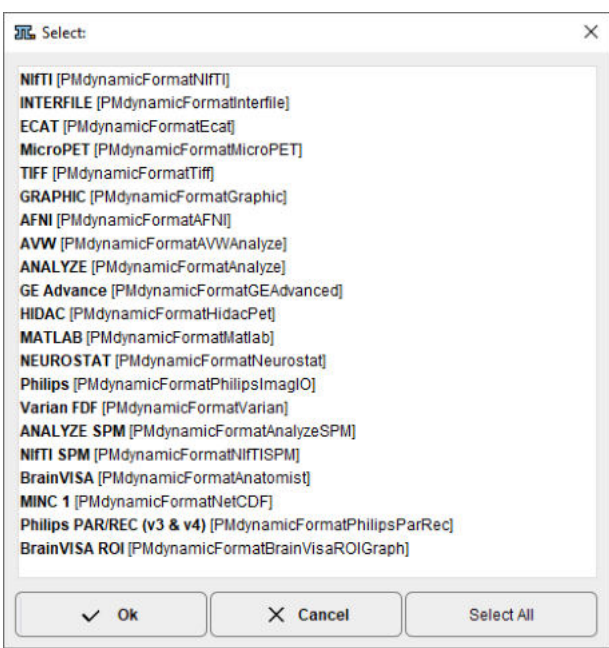
To remove a model from the list just select its list entry and activate **Remove**. To add a model back to the list use the **Add new** button. The appearing dialog window allows selecting one or more plug-in(s) and adding them by the **Ok** button.
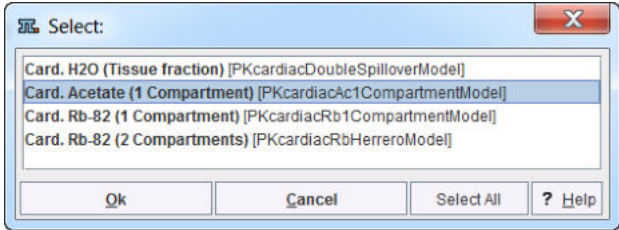
Contents of the different Plug-In Tabs

PXMOD Models	Configuration of the models which appear in the pixel-wise modeling (PXMOD) tool.
PKIN Models	Configuration of the models which appear in the modeling tool for time-activity curves (PKIN). **Tissue** contains the actual kinetic models for the tissue TACs, **Blood** the models for interpolation of the blood activity, **Plasma fraction** the models for plasma fraction activity and **Parent** the models for metabolite correction.
READ/WRITE Formats	Configuration of the image data file formats. Note that only a subset of the formats can be written.

	Select: [dialog with format list]
LOADING TOOLS	Configuration of image processing filters usable during loading.

COLOR TABLES	Configuration of user-defined color tables. These files must be
	
	▪ located in the *resources/colortables* sub-directory (see the examples there),
	
	▪ text files ending in .cltb, and
	
	▪ contain 3 columns with the RGB values (0..255) such as
	`# R G B`
	`0 0 0`
	`0 2 2`
	`0 4 4`
	etc.
	
	The filename is used as name of the color table. Care must be taken that all color table names are unique, otherwise only one of them will be shown.

The dialog in the image shows:

Select:

NIfTI [PMdynamicFormatNIfTI]
INTERFILE [PMdynamicFormatInterfile]
ECAT [PMdynamicFormatEcat]
MicroPET [PMdynamicFormatMicroPET]
TIFF [PMdynamicFormatTiff]
GRAPHIC [PMdynamicFormatGraphic]
AFNI [PMdynamicFormatAFNI]
AVW [PMdynamicFormatAVWAnalyze]
ANALYZE [PMdynamicFormatAnalyze]
GE Advance [PMdynamicFormatGEAdvanced]
HIDAC [PMdynamicFormatHidacPet]
MATLAB [PMdynamicFormatMatlab]
NEUROSTAT [PMdynamicFormatNeurostat]
Philips [PMdynamicFormatPhilipsImagIO]
Varian FDF [PMdynamicFormatVarian]
ANALYZE SPM [PMdynamicFormatAnalyzeSPM]
NIfTI SPM [PMdynamicFormatNIfTISPM]
BrainVISA [PMdynamicFormatAnatomist]
MINC 1 [PMdynamicFormatNetCDF]
Philips PAR/REC (v3 & v4) [PMdynamicFormatPhilipsParRec]
BrainVISA ROI [PMdynamicFormatBrainVisaROIGraph]

✓ Ok   ✗ Cancel   Select All

5.1.4 MODULES

The **MODULES** tab shows the PMOD tools available with the installed license file. If needed, tools can be removed from the PMOD dock interface/toolbar by un-checking the **Active** box. It is also possible to configure a favorite tool which is started as soon as the current user logs in by activating the **QStart** radio button of that tool. By activating the **Create horizontal bar** box, the modules can be grouped together in an additional horizontal bar.
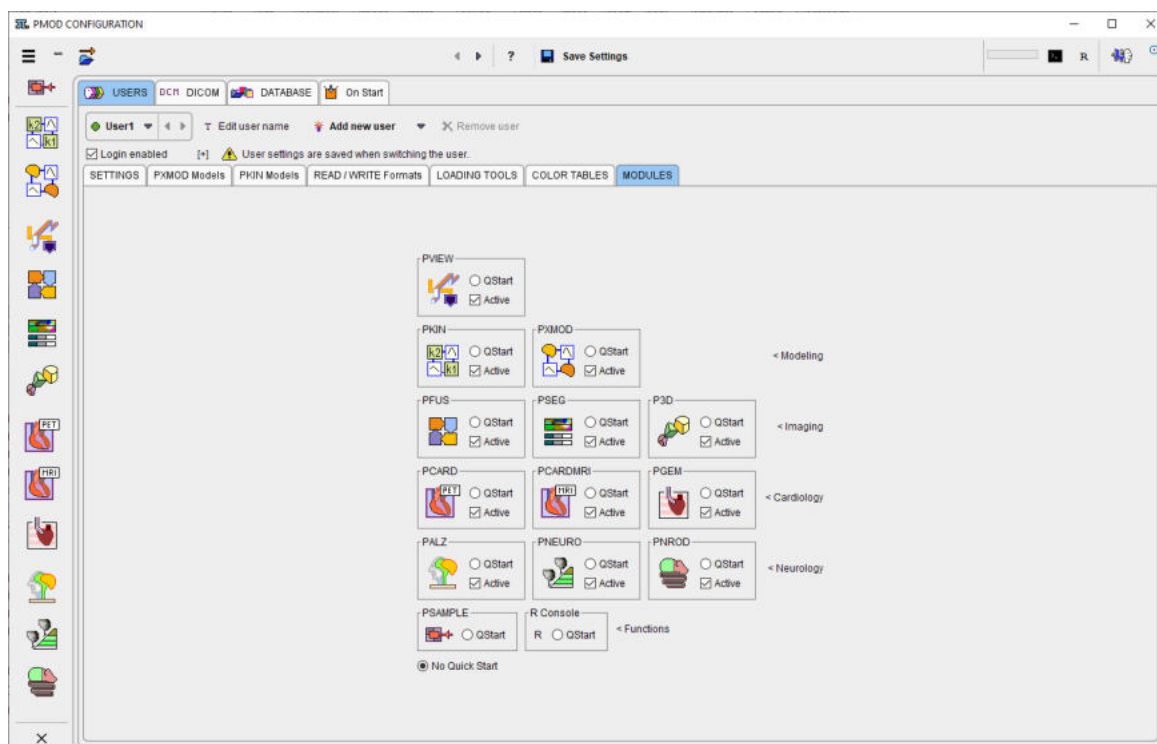
5.2 DCM DICOM Functionality

DICOM

The DICOM standard has been established to facilitate data exchange between medical systems. It defines how medical data must be encoded, and how it can be sent from an application on one computer to an application on a remote computer. DICOM basically consists of two components:

- **Information Object Definitions** (IOD): For each modality it defines a set of data fields. Some of them are mandatory, others are optional. This approach allows saving demographic and acquisition information together with the actual images.

- **Communication protocol**: DICOM has a client-server architecture. To send data from one host to the other, the sender (client) must contact the potential receiver (server) whether it is ready to accept data. The server may reject the request because it has no space left, because the client is not allowed to send data, or because it does not understand the data to be sent. Otherwise it accepts the request and sends back a proposal how the data should be transmitted. The client then sends the data and gets an acknowledgment when the data have been correctly received.

PMOD is able to act both as a DICOM client and a server.

- The PMOD DICOM server allows clients such as a PET system to push images to PMOD. Additionally, it allows a user to query remote DICOM servers (such as imaging modalities or a Picture Archiving System) and fetch studies to process them locally.

- The PMOD DICOM client allows sending image data using the C-STORE communication to any DICOM server which has been entered in the PMOD configuration.

Database for DICOM Data

The DICOM standard includes a description how DICOM data must be organized for off-line media such as CDs or DVDs. Basically, all the DICOM objects are stored in a directory tree, and a description of all stored studies must be written into a file called DICOMDIR at the root level of the directory tree. This approach is not suited for dynamically managed data, because the DICOMDIR

file must be updated each time a study is removed or added, and because reading of the DICOMDIR is slow.

To improve performance when working with DICOM images, PMOD uses SQL databases to organize DICOM data access. The most important attributes of the DICOM objects like patient information, study and image descriptions as well as the file locations are stored in database tables. When the user needs to select image data, he is shown the information from the database tables which can very efficiently be searched and retrieved. After a study is selected, the file access information is immediately available to start the loading process.

DICOM Configuration

The configuration of the PMOD DICOM functionality is a part of the general PMOD configuration. It is opened by calling the

button from the top line of the PMOD Docked Interface[13], and selecting the **DCM DICOM** tab in the appearing dialog window.

5.2.1 NODEs [C-STORE, Q/R]: DICOM Client Configuration

The **NODEs [C-STORE, Q/R]** tab allows specifying remote DICOM nodes. These nodes include DICOM servers to which PMOD can send images, and DICOM clients which are able to send images to PMOD, but not to receive.
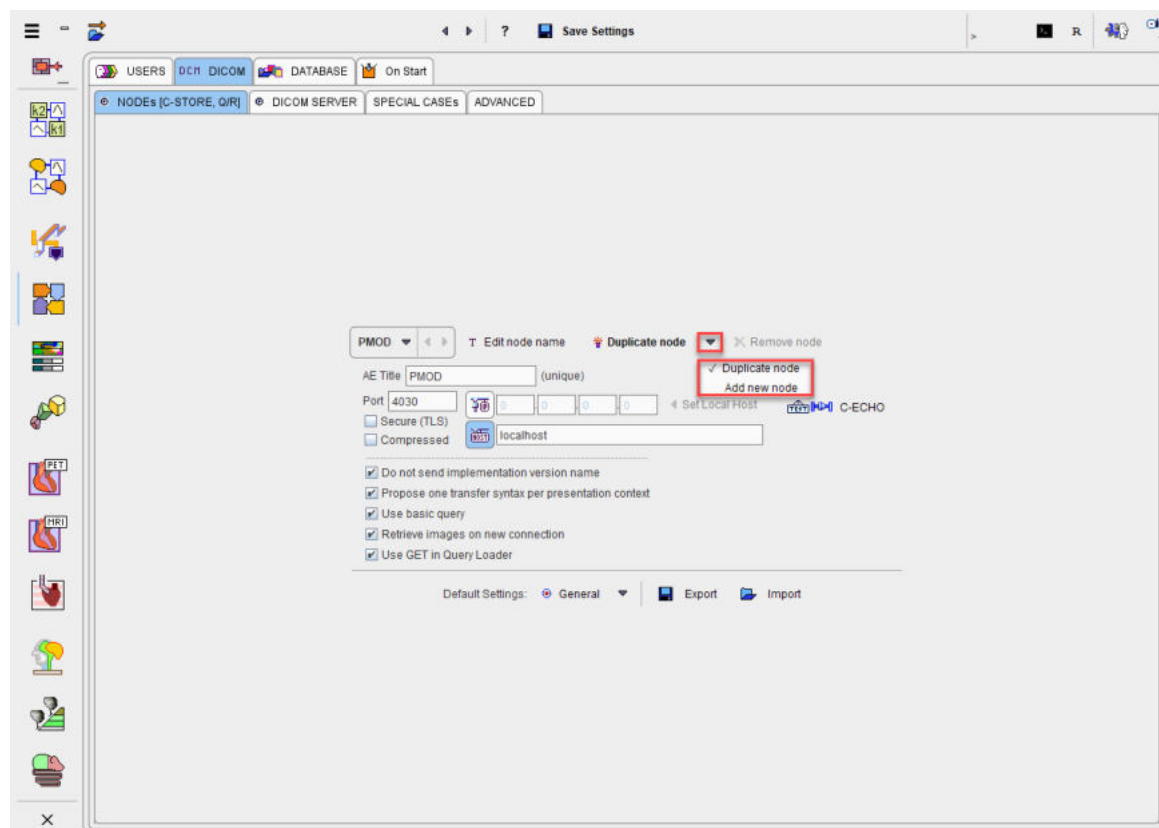
New nodes are created with the option button:

- **Add new node**: Creates a new node with the default settings.
- **Duplicate node:** Creates a new node using the settings of the currently selected node.

The node name needs to be specified during node creation, but can be changed later using the **Edit node name** button.

For each of them define its application entity title (**AE Title**), the **Port** number, and **IP** number or **host name**. The example above configures the local PMOD DICOM server as a node. As soon as the server has been started, it can be contacted and used for saving/retrieving images as any other node.

If the remote node is a PMOD DICOM server listening on a secure TLS port, please check the **Secure(TLS)** box. The **Compressed** box is the indication that the given node supports the DICOM deflated transfer syntax (1.2.840.10008.1.2.1.99). If it is checked, PMOD will propose a deflated transfer syntax, and if given a choice in the association acceptance it will choose the deflated transfer syntax with highest priority. Using compressed communication has the advantage of speeding-up communication across slow internet lines.

After configuration has been completed, the **C-ECHO** button can be used to test the connectivity. If a node is a DICOM server and running, verification should return **DICOM Verification successful**. If it is a client which just can send, verification is not applicable.

The lower part of the pane contains a list of configuration details which may need a change for some connections. Shown is the default configuration, which can be recovered by the **General** button. The option button also allows retrieving a configuration which has been proven to work with GE **Xeleris** systems.

Note the **Export** and **Import** facility for the DICOM nodes list which allows a system administrator to easily distribute a master DICOM list among PMOD installations.

5.2.2   DICOM SERVER Configuration

PMOD can run one or multiple DICOM server processes in the background which are able to receive data sent to it from modalities or a picture archiving system.

5.2.2.1   DICOM Server Properties

In general, a DICOM server is defined by three entities, the:

- IP-number (or host name) of the computer on which the DICOM server is running,
- Port number on which the server is listening,
- Application Entity Title (AE Title) which has been given to the server.

The **Port** and **AE Title** information of the PMOD DICOM server(s) is configured on the **DICOM / DICOM SERVER** pane.
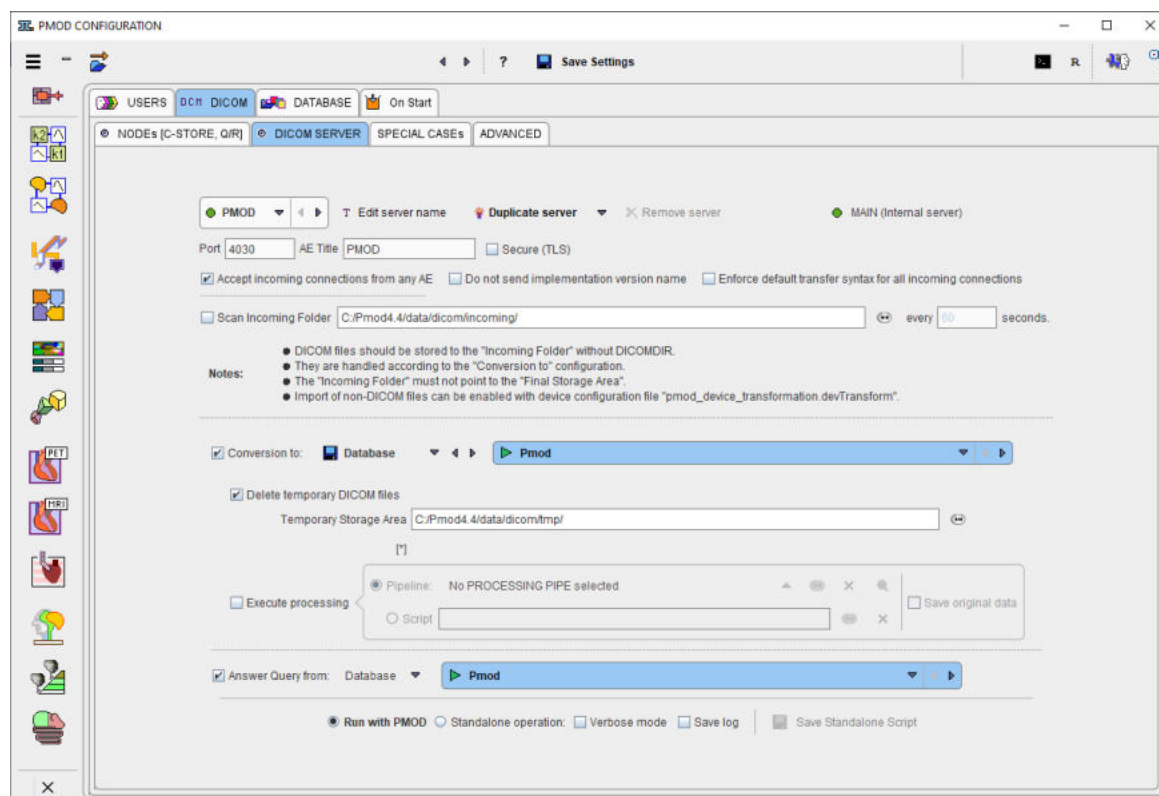
Note: On Linux systems there exist reserved ports which require special permission to allocate. If such a port is defined as the PMOD DICOM server port, the server cannot be started from a user account and issues a message *Permission denied*. Starting as root will normally succeed, but this has the disadvantage that the saved files will all belong to the root. To prevent this situation a higher port number (typically >4000) should be used on Linux, rather than the standard DICOM port 104. PMOD uses 4030 per default.

Besides the basic server information there are three checks relevant for the DICOM server operation:

- **Accept incoming connections from any AE**: If this box is not checked, the DICOM server only accepts remote systems which are configured as remote DICOM clients. If it is checked, any association request will be accepted.

- **Do not sent implementation version name (server)**: Allows switching off sending the implementation version component. This is required if a client does not handle this exchange properly and connection to the PMOD server fails.

- **Enforce default transfer syntax for all incoming connections**: Transfer syntax negotiation may fail when a client proposes only one transfer syntax which is not the DICOM default and a PMOD server prefers another. In such cases the option forces the PMOD server to always negotiate the default Little Endian Implicit transfer syntax which all DICOM applications are required to support.

Standard DICOM communication is not secure, and therefore is not recommended over public networks. To overcome this problem, a DICOM supplement was added for implementing secure connections. PMOD supports one of the proposed variants called BASIC TLS SECURE TRANSPORT CONNECTION PROFILE. Of the three optional features (entity authentication, encryption, integrity check) encryption is implemented in the current release. As a consequence, the data transferred can only be interpreted by the target DICOM server with which the communication has been established. To enable secure DICOM, check the **Secure (TLS)** box. The corresponding command line option is **-tls**.

5.2.2.2 Multiple DICOM Server Creation

New Dicom servers are created with the option button
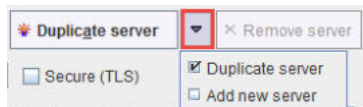
- **Duplicate server:** Creates a new server using the settings of the currently selected server.
- **Add new server**: Creates a new server with the default settings.

The server name needs to be specified during server creation, but can be changed later using the **Edit server name** button.

The default installation creates two DICOM servers: **PMOD** as **MAIN (First server)** and **PMODQ** as **AUXILIARY (Second server)**. These servers are internal DICOM server and have as default ports **4030** for **PMOD** and **5003** for **PMODQ**. They cannot be removed from the configuration.

Note that all DICOM (and Transaction) servers need unique port addresses.

5.2.2.3 What happens with received DICOM Images

There are different possibilities what the PMOD DICOM server can do with the received images:

- Save them in a directory structure and update the DICOMDIR file (DICOM part 10 conformant).
- Save them in a database as the original DICOM objects.
- Convert them to any of the supported image formats and save them as files, eg. as NiFTI files.
- Convert them to a JPEG file, and print a report page.

PMOD has the capability to configure different behaviors of the DICOM server. Example configurations are shown below, but many other conversions are also possible.

Saving the Images in a Database

The following configuration is recommended for all users who run a local database.
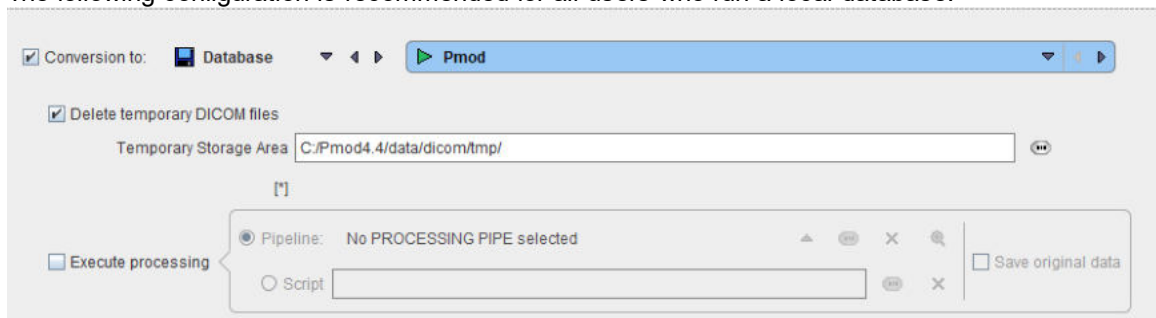
In the example the DICOM server is receiving the images in the directory *C:/Pmod4.4/data/dicom/tmp*, saves them in the database **Pmod**, and then deletes the images in the temporary directory. When a remote DICOM client queries the PMOD DICOM server for studies, it will list all the studies in the **Pmod** database.

Saving the Images as DICOM Part 10 Offline-Files

Alternatively, the received images can be saved in a DICOM Part 10 compliant manner. This behavior is configured as follows.

With this configuration, the images are stored in a directory hierarchy starting at *Pmod4.4/data/dicom/storage*. A DICOMDIR file will be maintained in the same root directory, and used to answer queries.

Note that you can use PMOD to create DICOM-compliant CDs. Just burn the DICOMDIR and the directory containing the DICOM files to a CD.

Filtering out Secondary Capture Images and Printing them

The configuration below illustrates another conversion ability.

The images are converted to JPEG (**GRAPHIC**), a report page is prepared (**Print hard copy**) and sent to the system default printer, but only if the incoming object is of type Secondary Capture (**ConvertSC objects only**). The original DICOM files are deleted, but the JPEG images are retained in the directory *Pmod4.4/data/graphic*. The additional checks allow routing the SC DICOM objects to a remote DICOM server such as a PACS, and deleting the JPEG files after printing.

Applying Processing to Received DICOM Images

It is possible to set up DICOM servers which apply an image processing pipeline to the received images. The processing steps have to be prepared and saved in the Pipeline Processing 471 interface. Naturally, in this case only the received image is processed. Beyond the processed image, results such as VOIs and VOI statistics are also saved if configured in the pipeline.

Pipeline processing of received DICOM images is configured as illustrated below for an example applying motion correction to dynamic brain PET images.

Note: This type of pipeline processing only works for DICOM servers started together with PMOD, not for DICOM servers started from script.
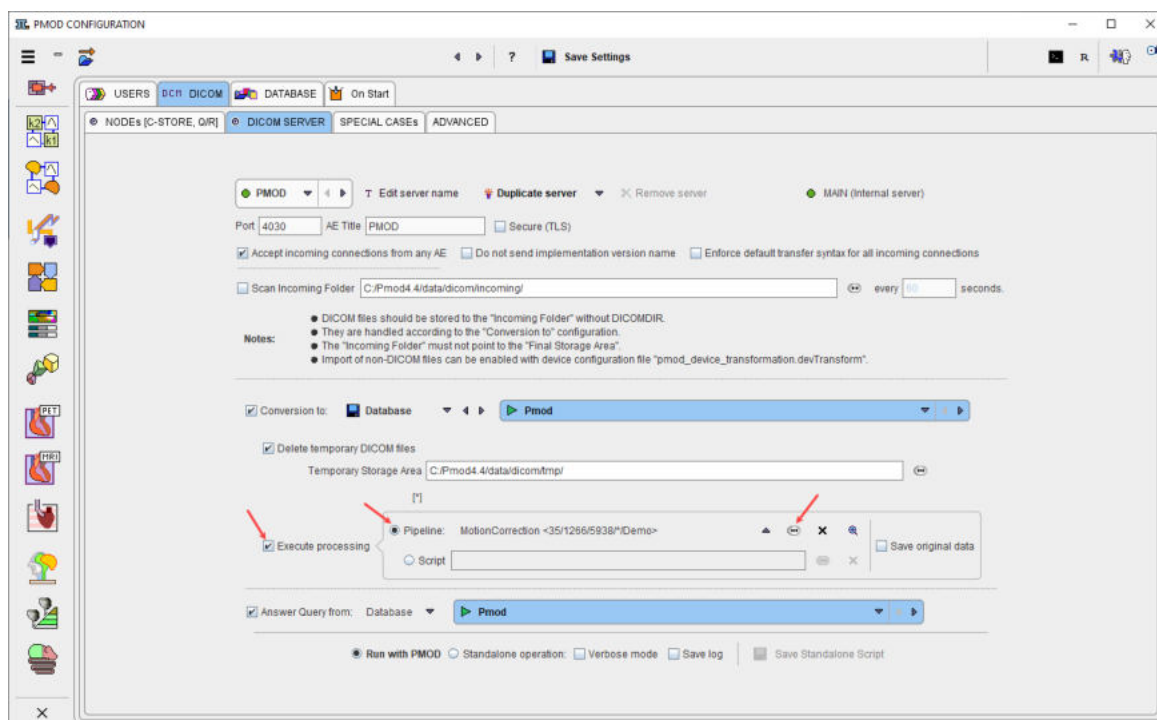
Alternatively, arrival of an image at the DICOM server can trigger execution of a script, as described in .

DICOM Server Starting with PMOD

With the **Run with PMOD** radio button enabled in the configuration the DICOM server is started together with the PMOD, and also stopped with it. With PMOD running, the DICOM server information is accessible using the DICOM Server option in the in the selection list available in the upper right corner of the PMOD docking interface:
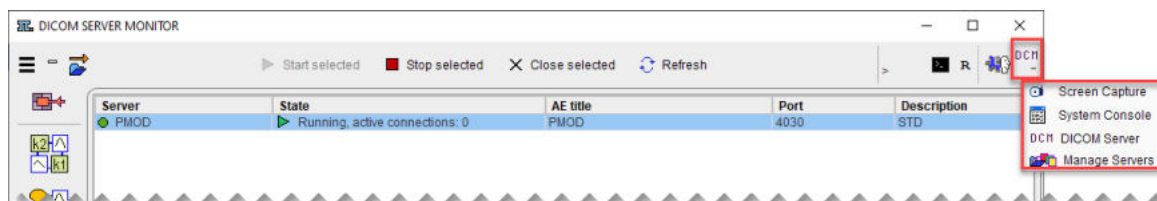
Please see for additional details.

5.2.2.4   Incoming Folder

Normally the DICOM server is receiving data over the network from DICOM clients. However, it is also possible to have the DICOM server additionally scan a directory at certain time intervals and treat found DICOM series or other image format series in the same way as if they had arrived by the network.

This functionality can be configured by the **Scan Incoming Folder** box. If it is checked, the directory to be scanned can be entered as well as a scanning interval **every ... seconds**. This import feature can be used to convert from DICOM or any other images format to any other output format, or

to add DICOM or other images format to a PMOD database. Note that after processing the images by the DICOM server they are deleted from the incoming folder.
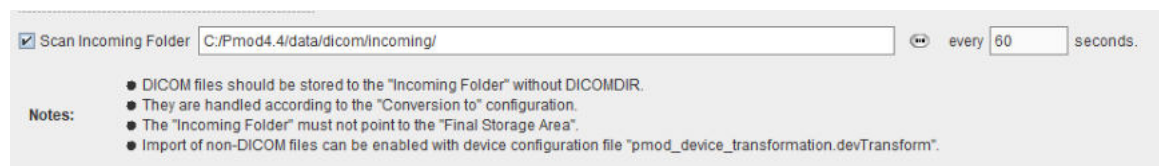
Incoming folder: Loading Format AUTODETECT

Starting with version 4.2 PMOD supports conversion of other image formats through the incoming folder, e.g Niftii, to the PMOD database using a file called *pmod_device_transformation.devTransform*. Example of such transformation device files are available in the *Pmod4.4\resources\devices\bruker*.

There are two main requirements for the incoming folder:

1. All the images belonging to one subject are stored within a folder in the incoming folder, eg. Test1

2. The *pmod_device_transformation.devTransform* file content is as illustrated below:
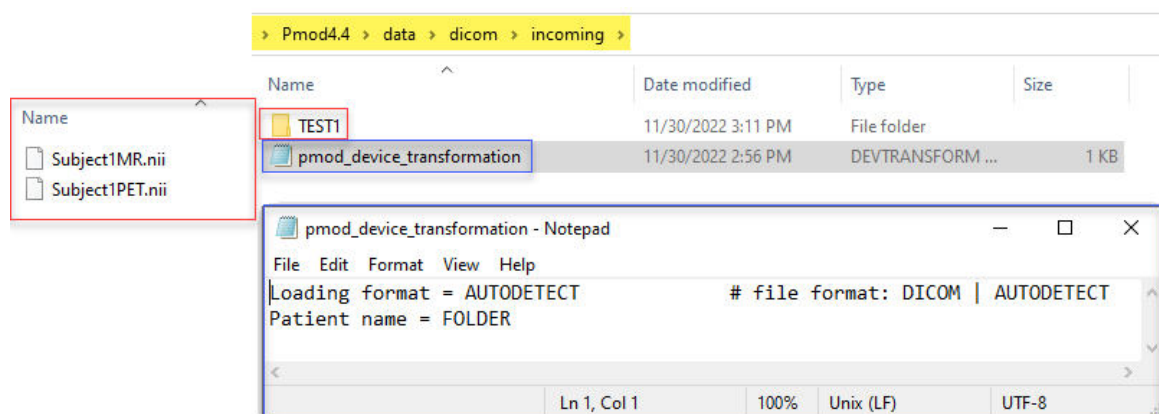
The **Loading format = AUTODETECT** indicates that image format different from DICOM are supported for the incoming folder.

The **Patient name = FOLDER** indicates that folder name will be used as **Subject name** in the PMOD database after the conversion. The files name within the folder will be used as **Series description**.

The results of the conversion is shown in the following capture:
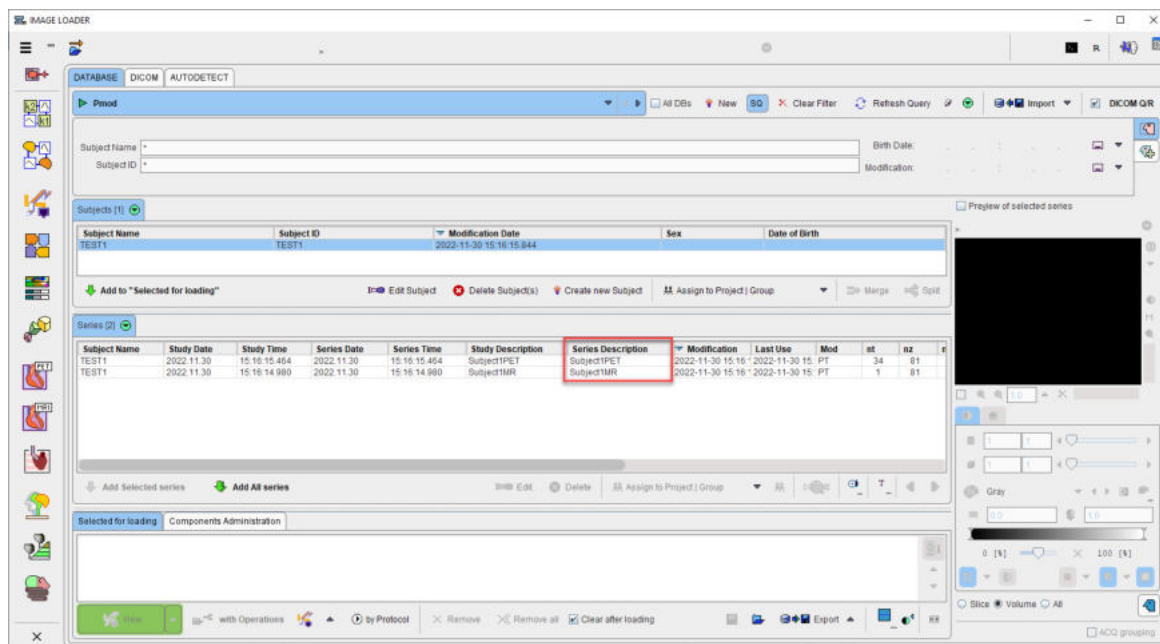
Very often image format different from DICOM are lacking subject information about the name, ID, project, diagnosis or group, age, etc. Such information need to be prepared in Excel, saved as a *.csv* file named **PMODIMPORT.csv** and copied into the incoming folder. It is an easy way to provide additional information to the imported data. This mechanism has priority over the mechanism described above to use file and folder name to set missing subject names and id and will always overwrites the information in the file.

The information in the *.csv* file is organized by the files to be imported, each file information in a single row. The first row defines the tags for the values. If the value is within " " it will be discarded.

The following column names, in the listed order, are currently recognized:

- FILENAME - the key value to match the description from the *.csv* file with the imported data. Depending on the system, the file name extension should be included in this column, e.g .nii for Niftii images. If series consists of more then one file one of those files should be selected to describe the series information. If more then one file from the same series is described in the csv file the subject and study information will be set from the first file processed (undetermined);

- PTID - indicates the subject id,

- NAME - indicates the subject name in the database ;

- AGE - indicates the subject age formatted dicom style with Y, M, W, D for years, months, weeks, and days. Years are assumed if none of the others is present;

- WEIGHT[KG] - indicates the subject weight;

- HEIGHT[CM] - indicates subject height;

- DIAGNOSIS - sets the diagnosis field in the PMOD database;

- PROJECT - sets the project field in the PMOD database;

- MODALITY - sets the modality field in the PMOD database;

- STUDYDESCRIPTION - sets the study description in the PMOD database;

- SERIESDESCRIPTION - sets the series description in the PMOD databse;

Illustrated below is an example in which a PMODIMPORT.csv file was used in the incoming folder together with the *pmod_device_transformation.devTransform* in order to import the images available in the Test1 folder:
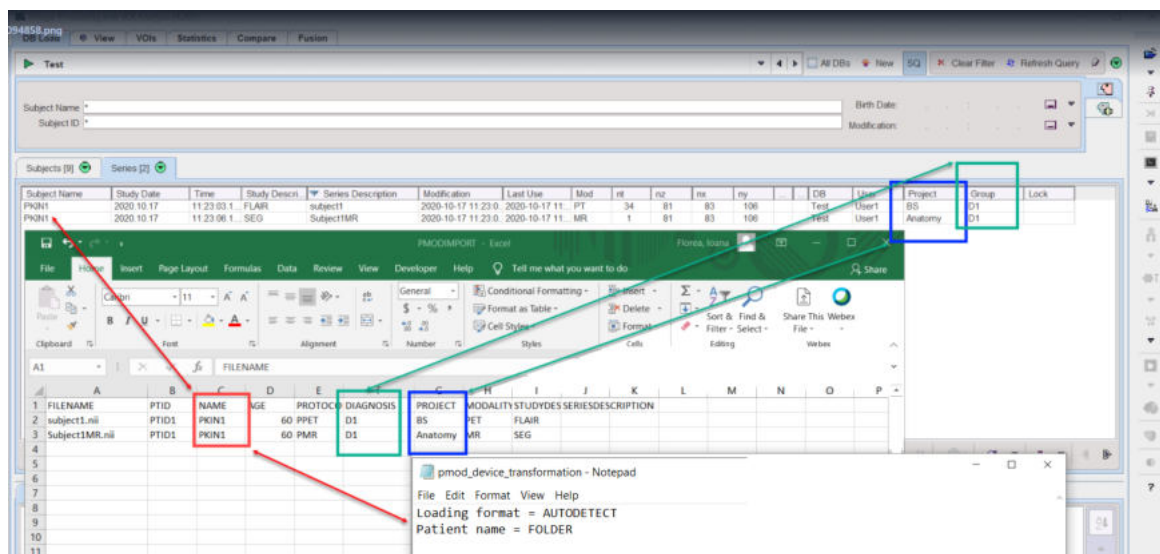
Please note that in this case the information available in the **NAME** column was used as **Subject Name** in PMOD database structure.

When additional columns are present in the **PMODIMPORT.csv** file which are not recognized by the importing algorithm, this information will be placed in the database comment of the file name import under the imported series.

Note that after processing the images by the DICOM server they are deleted from the incoming folder.

5.2.2.5 DICOM Server Starting

There are two ways of starting the DICOM server, as part of a PMOD processing session, or as a standalone process running independently. The latter has the advantage, that images can be received while PMOD is not in active use.

Starting from PMOD ToolBox

When the starting option is switched to **Start automatically**, a DICOM server is started together with PMOD, and also stopped with it. Otherwise, with the **Standalone** option, the DICOM server has to be started explicitly. With PMOD running, this can be done using the DICOM button in the ToolBox.
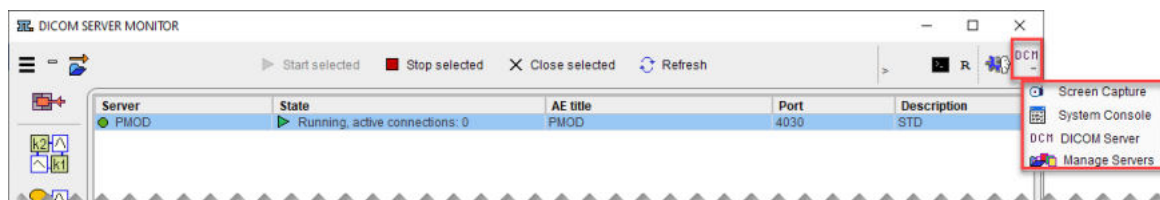
The current status is displayed in the **State** column. The status of a DICOM Server can be easily modified: initially it has to be selected in the **Server** list and then, depending on the status, the **Start selected server(s)** or **Stop/Close selected server(s)** button needs to be activated. While **Stop** will terminate the DICOM server immediately after the current job, **Close** will allow for completion of all queued jobs.

When the color of the ![DiCM] button changes to blue, a DICOM server request is being served. The color changes back after all communications have completed.

Starting using Scripts

Alternatively, the *RunDcmSvr* script in the *Start* directory can be started by double-clicking. This script is generated during the installation and represents the default DICOM server configuration. In this case the starting option should be switched to **Standalone**. If any DICOM server setting has been changed, a new script should be generated with the **Save Starting Script** button. It shows a dialog window with the contents of the script as illustrated below.
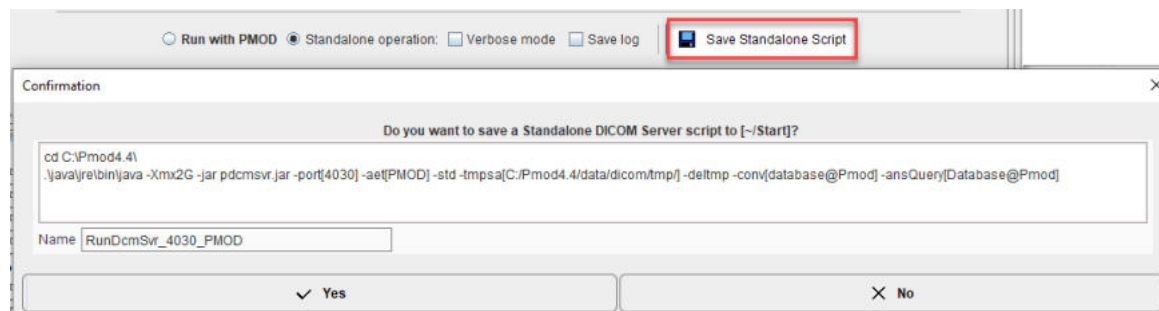
A DICOM server offers the following debug options:

- **Verbose mode**: Serves for generating detailed communication information. While it slows the operation down, it may be helpful to troubleshoot connectivity problems. The corresponding script option is **-d**. In order to obtain even finer debugging information the **-f** can be appended additionally to the script. However, this inflates the log dramatically and requires careful usage.

- **Save log**: Serves for redirecting the standalone server output to a file in *Pmod4.4/system/logs*. The corresponding script option is **-o**.

Note that there is a dedicated <u>server administration tool</u> 93 which can be used for monitoring, starting and stopping the DICOM servers for which starting scripts have been created.

5.2.2.6   Implementation of DICOM Servers on a Dedicated Machine

Note that DICOM (and <u>transaction</u> 59) servers can be operated without a PMOD license. Only the process of their configuration requires a license. Therefore, particularly in a multi-user environment, the server processes should be moved to a dedicated machine with fast disks.

To establish such a configuration, please perform a standard PMOD installation on the server machine including the USB license protection key. Use the **Configuration** facility for the database and DICOM server configuration, and generate the server starting scripts. Thereafter, the USB key can be removed and used on client machines. The server processes can be started at any time, only re-configurations will require the USB key again.

It is easy for Mac OSX and Linux to start programs like the transaction servers at system boot time and run them in the background. On Windows, this is not possible with normal programs. Rather, a command window is required which needs to stay open for the whole program duration, which is not convenient for shared server systems. A workaround is to purchase a third-party solution which wraps the DICOM servers into service processes, such as the <u>AlwaysUp</u> solution.

5.2.3   DICOM Special Cases

Sometimes the interpretation of DICOM data is unequivocal and PMOD may organize the images in an unexpected manner. To solve this situation **SPECIAL CASEs** can be defined which impose a specific interpretation of data from a certain **Manufacturer model** and **Software version**.

To create a new special case select **Add new case,** specify a name, and then select the appropriate behavior from the **Case** list. The requested information can be entered manually, but it is

easier and safer to select **Get from File**, browse to the directory where the data resides, and select the appropriate series. PMOD reads the required information from the DICOM attributes and fills it into the **Manufacturer**, the **Manufacturers model** and **Software version** fields. Note that ***** can be used to indicate applicability for all possible strings, while an empty field requires that information is also empty in the corresponding DICOM field.

To transfer these definitions between systems there is an **Export** button for saving the special cases, and **Import** button for loading them.

The **Case** selections are listed below with some example systems. However, the need and applicability of these special cases may depend on specific software versions of the originating system.
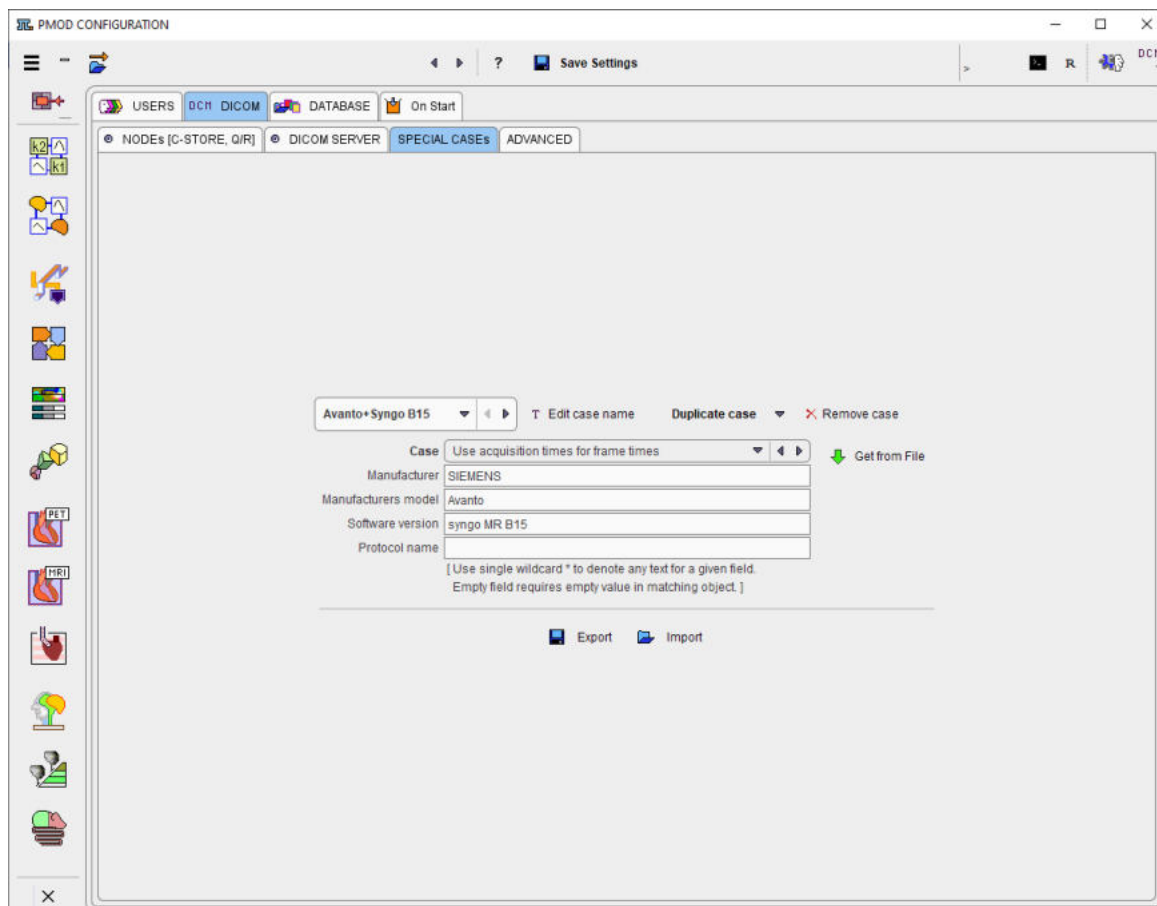
- **Non identical images times for single volume**: Select this option if the slices of a single volume are interpreted as separate frames in a dynamic series (e.g. series with no positioning information like SC).

- **Multivolume (sort by volume times)**: To be used when the time sorting of a dynamic series is wrong (Siemens Sonata, Siemens Symbia).

- **Multivolume (sort by slice position)**: Another situation where the time sorting of dynamic volume data is wrong (Siemens Evolution EBCT scanner, GE Discovery LS, GE Discovery HR, GE Signa Excite).

- **Multivolume MR (sort by trigger times)**: A third situation with wrong time sorting (GE Signa Genesis).

- **PET frame times in sec (instead of ms)**: To be applied if the acquisition times presented in PMOD for PET objects are 1000 times too small.

- **Volume SC**: For situations when a screen capture series representing a volume is displayed as a big number of separate series (GE Advantage Windows, GE Discovery HR, Siemens Somatom Emotion Duo).

- **Wrong slice spacing (use slice thickness)**: Try this case in case the slice thickness presented in PMOD differs from what you expected (some GE Xeleris versions).

- **Wrong Image Index in PET objects**: Some PET/CT systems do not construct the Image Index (0054,1330) as specified in Dicom PS3.3 paragraph C.8.9.4.1.9. As a result PET images may be sorted wrongly (GE Discovery LS via Xeleris).

- **Wrong frame reference time (use acquisition time)**: Instead of the PET specific element 0054,1300 (Frame Reference Time) the general element 0008,0032 (Acquisition Time) is used to determine frame start and end times. If the acquisition time element is present and it is filled with the frame start time this usually solves the problem. (Philips, Protocol Guardian Bod; SUINSA animal PET system).

- **Reference time at frame half (calc from duration)**: The default behavior for PMOD is to calculate frame start and end times based on frame reference time and duration assuming that the reference time points to frame start. This special case uses the assumption that the reference time is at frame mid-time. (Philips)

- **Times start not at zero (move to zero)**: This case was introduced for Philips data that had a substantial offset in the 0054,1300 Frame Reference Time. It just offsets the times so the first frame starts at 0. It does the same as **Set acquisition start time to zero** in the loading parameters dialog.

- **Wrong image class unique id**: This special case is to allow PMOD reading images that have wrong DICOM object class specified in the file.

- **Use acquisition times for frame times**: This special case instructs PMOD to use the acquisition time instead of the content time when determining the frame times for single slice objects.

Note: The DICOM server will use these case definitions when receiving the images and storing them in the database. So if series are not correctly entered into the database, please export the data and define a suitable **Case** using the **Get from file** facility. Then, delete the database entry, restart the DICOM server, and transfer the series again.

5.2.4 DICOM Advanced Options

ADVANCED options allow changing some specific conditions and parameters of the dicom communication. The default settings are illustrated below. Changing these settings means tuning of PMOD to work with systems that are not 100% conformant with Dicom 3.0.
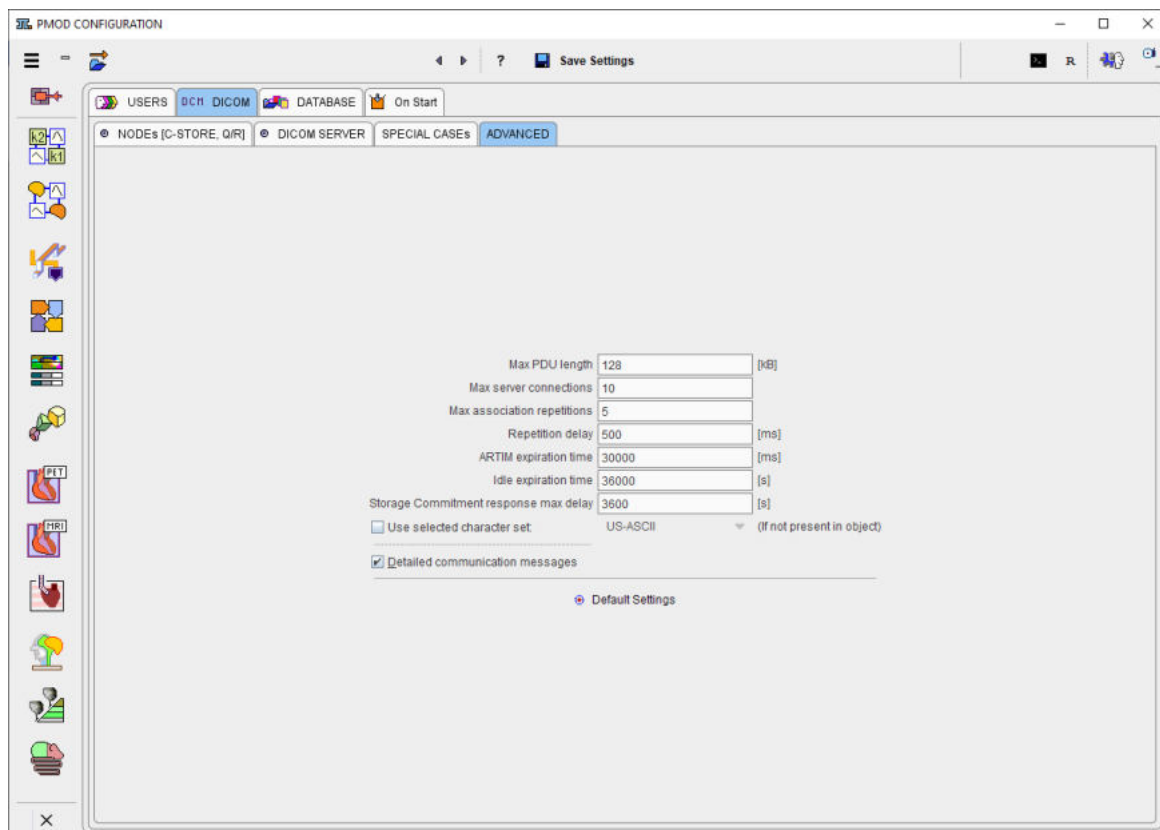
- **Max PDU length** is a PDU (Protocol Data Unit) length that PMOD will propose to other communicating nodes as well as a maximal length PMOD will accept as a PDU. The minimal value for this field is 2. A zero value (that according to the DICOM standard means accept any size) is not allowed because problems may occur with some systems.

- **Max server connections** is the maximal number of open connections handled by the PMOD server.

- **Max association repetitions** instructs PMOD how many times it will attempt an association to an other node before reporting connection failure.

- **Repetition delay** is the waiting time between association retries.

- **ARTIM Expiration Time** is the time PMOD will wait for a reply from a remote DICOM system before it will close connection and report failure.

- **Idle expiration time**: is the time after which the established DICOM connection will be closed if there is no activity (message exchange) on the connection.

- **Use selected character set ..**: DICOM allows the specification of character sets in the file. If no character set is specified, PMOD uses the operating system default character set for the interpretation of non-ASCII characters. In case non-ASCII characters are not properly displayed, the user can explicitly define the proper character set. ISO 8859-1 will be appropriate for most western european languages. Please consult the ISO 8859-x standards to choose the right one for other languages.

Note the **Default Settings** button which allows restoring the default state.

5.2.5 DICOM Query/Retrieve

A **DICOM Query/Retrieve** operation retrieves images from remote DICOM servers in order to store them locally. After the images have been received, they can be loaded and processed independently of the remote server.

Configurations for DICOM Query/Retrieve (Q/R)

There are some prerequisites for using DICOM Q/R with PMOD:

1. Locally in PMOD, the DICOM server must be configured and running because it receives the images sent from the remote system. The PMOD DICOM server configuration is explained above 41.

2. Locally in PMOD, the remote DICOM systems from which images should be retrieved must be defined. Because they will send images to the PMOD DICOM server, they are configured as DICOM client nodes as described above 40.

3. The PMOD DICOM server must be configured on the remote DICOM system by its administrator. Otherwise these systems will most likely reject the association request from PMOD, so that no images can be queried.

Retrieving Images per DICOM Query/Retrieve

The DICOM Q/R function can be called from

- the **Menu** in the PVIEW tool, or

- using the **DICOM Q/R** button on the **DATABASE** load page in any of the PMOD Tools when configured or via the unified data loader.

The dialog window shown below appears which allows the user to query and retrieve studies.
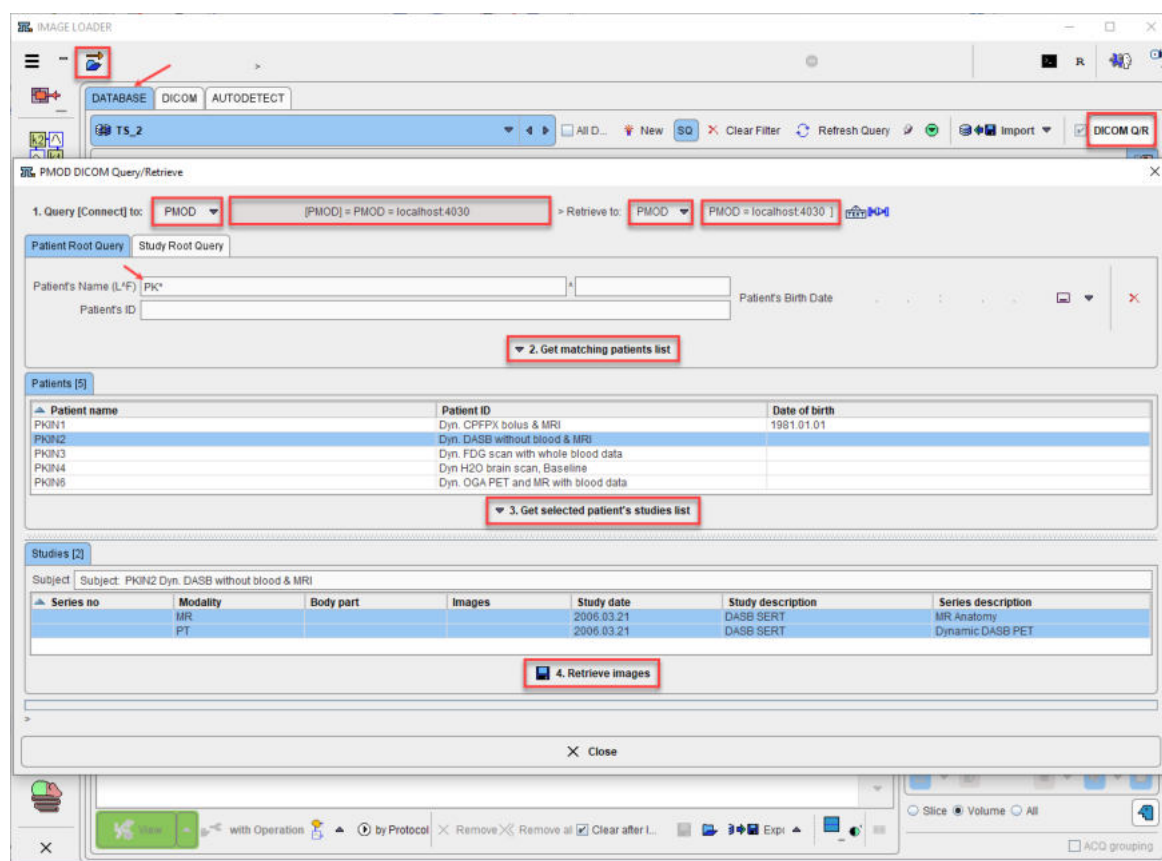
The following steps need to be performed:

1. **Query [Connect] to:** The selection lists all DICOM systems which have been configured as DICOM Clients. The connection is established as soon as the selection is activated..

2. **Retrieve to:** Typically, one would like to retrieve to the local DICOM server as shown in the example, but with **External node** it is also possible to select any of the configured DICOM clients (which must be a DICOM server) as the destination. Once the server is selected (configure, then activate), the connection can be tested with TEST.

3. Select the query mode, **Patient Root Query** or **Study Root Query** by the tab. Note that some servers may not support both modes. If the query is not supported, **Get matching patients list** remains grey.

4. **Get matching patients list:** The purpose of this step is to get a list of studies, from which the ones of interest are retrieved. To avoid excessive numbers of matches some filter fields are available. In the example above, only patients with names starting with "**P**" are queried. When **Get matching patients list** is activated, the query is sent to the remote system, the response is received and the matching patients are listed.

5. **Get selected patient's studies list:** Only studies from one patient can be retrieved at a time. Therefore a patient must be selected in the **Patients** list, and then the **Get selected patient's studies list** button activated. As a result, the remote system is asked for all studies of the selected patient, and the result is listed.

6. **Retrieve images:** To retrieve some of the studies select them in the **Studies** list (CTRL+Click), and then activate the **Retrieve images** button. A request is submitted to the remote system, which will send the requested images to the **Retrieve to** DICOM server. If the **Close after** box is checked, the dialog window will be closed while the receive process is going on in the background and will show a notification once the transfer completed. Otherwise, the dialog window remains open until the transfer completes.

> **Note:** It depends on the configuration of the receiving DICOM server, where the images are saved, and thus from where they can be loaded. The default of the local PMOD DICOM server is saving the images in the Pmod database.

5.2.6 DICOM Query Loader (Auxiliary Server)

The **Query Loader** function is a simplified **Query/Retrieve** function. Instead of first retrieving images from a remote DICOM server to the local disk and then opening them in a second step, the query loader directly displays the retrieved images. Due to the retrieve time, it may take a while until the images are shown.

A separate auxiliary DICOM server is used for this purpose, which by default is configured at installation time. The settings are shown after selecting the **PMODQ** Dicom server in the server list. Note that both the application entity title and the IP port must be different from the main DICOM server, and that this definition must also be entered on the remote DICOM servers from which images should be loaded.
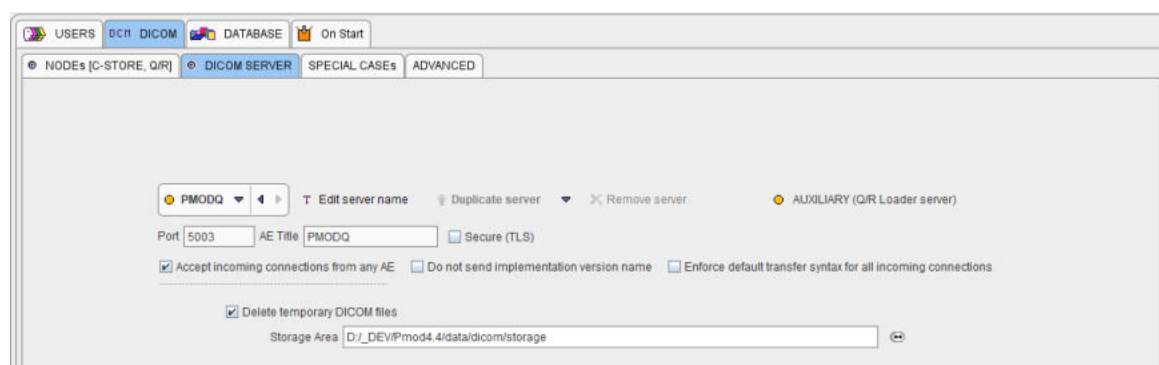
The **Query** data format is appearing as an additional format for all image loading buttons.

5.3 DATABASE Functionality

DICOM Operations using a Database

If the database is configured, PMOD can save images and all other information types such as VOIs, transformations, kinetic modeling files etc. in the same manner as described for the DICOM objects.

A **Save** operation sends a request to the database containing all relevant meta-information about the data (patient name, study, series, data type, etc) and the data itself. The database server then saves the data into a directory structure and adds the access information into its tables.
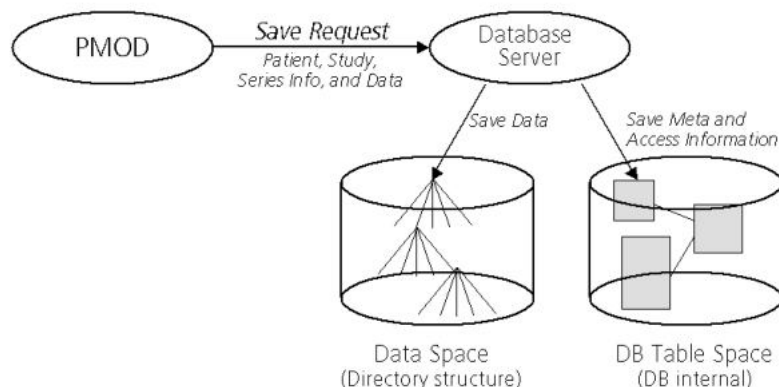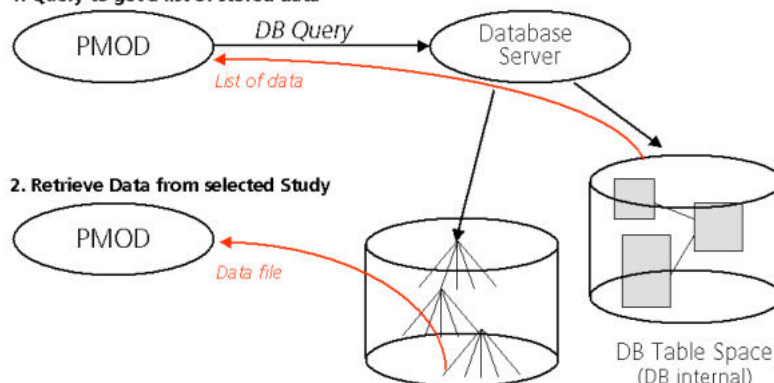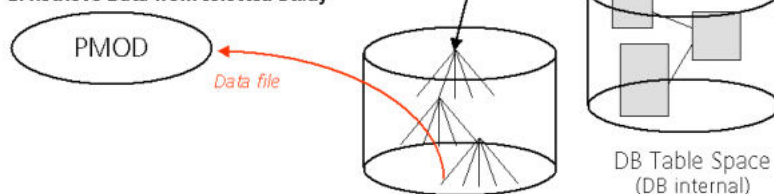

When **Load** operations are performed, this access information is presented to the user in a way which allows performing database searches, and if a data set is selected, it can be loaded into the PMOD tool using the internal access information.

Benefits of Using the Database

There are several benefits resulting from the use of the PMOD database:

- A unified user interface is shown when loading or saving all types of data.

- The searching process supports many filters and is very fast.

- Loading of the data itself, particularly the DICOM images, is fast.

- The databases can be shared over the network between different PMOD installations.

Database Engines

The PMOD database functionality is based on an external SQL database engine. Two such databases are currently supported:

- **Derby** (default), an embedded database bundled with Java which requires no installation. The use of JavaDB is encouraged, and at some time point support of mySQL might be suspended.

- **mySQL** (deprecated) is a database which runs on different platforms. Note that only mySQL server versions up to 5.0 are supported. Therefore, mySQL is only recommended for continuing legacy databases. In all other cases, JavaDB should be used.

In this section it is assumed that the database engine is working properly.

Database Access Types

There are two different types of databases in PMOD:

1. **JDBC Databases**: These are SQL databases to which PMOD communicates using the Java Data Base Connection (JDBC) interface. Typically, the JDBC Databases reside on the local machine. The user can create new JDBC databases from the PMOD configuration utility. If he wants, he can make them available to PMOD installations on different computers by a PMOD protocol called **Transaction Server** (TS, see below).

2. **Transaction Server Databases**: These are SQL databases which are not directly accessed, but indirectly through a PMOD installation usually residing on a different computer. As the transaction server databases are managed by a different PMOD installation, they cannot be created or deleted, but only used for reading and writing.

The transaction server concept is most useful in an environment of multiple PMOD installations. On one of the PMOD installations, the PMOD JDBC databases are created. On the same system, the PMOD DICOM server is started, and saves the received images in one of the databases. All other PMOD installations access the databases just through the transaction server as illustrated below.
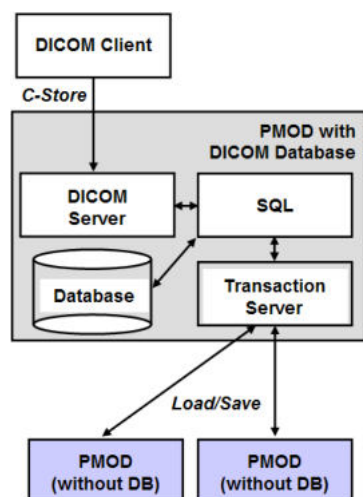
Note: After the installation of Pmod4.4, an empty **Pmod** database and a **Demo** database with various example data are available (if the example database was selected for installation). These databases reside within the PMOD installation directory. We recommend creating new databases for productive work on a separate disk which is regularly backed up, and to use transaction servers for data sharing.
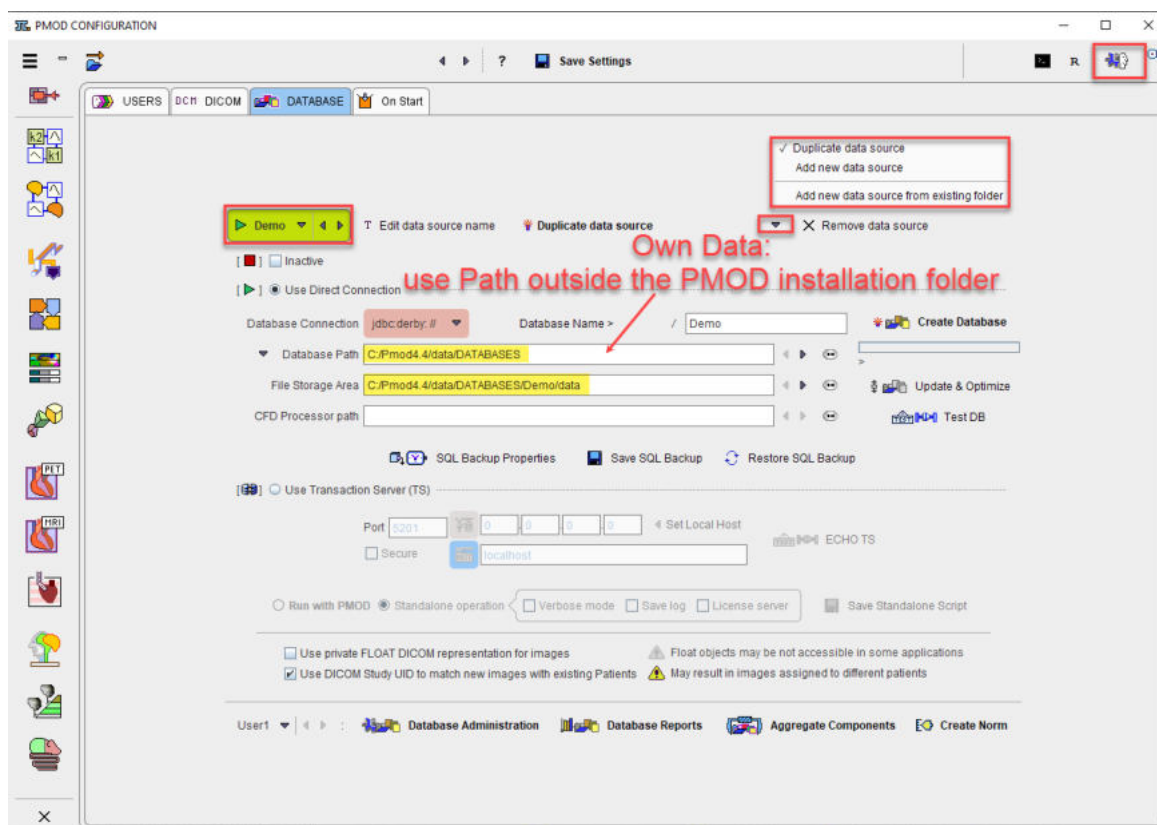
5.3.1 Creation and Configuration of Databases

The creation of databases and the configuration of remote databases is a part of the general PMOD configuration. It is opened by calling the

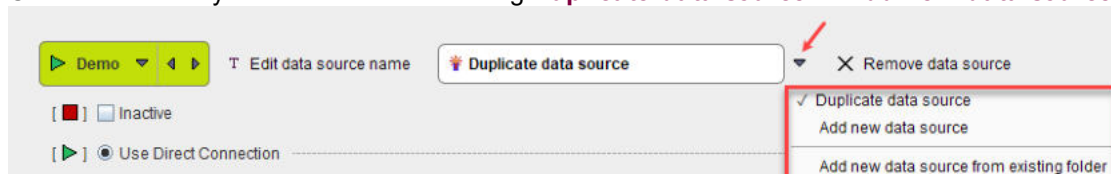
button from the PMOD ToolBox, and selecting the **DATABASE** tab in the appearing dialog window.

To create a new database please proceed as follows.

Derby JDBC Database Creation (default)

1. Create a new entry in the database list using **Duplicate data source** or **Add new data source**:

A dialog window is shown for requesting a name for the new database. The new data source is added to the list selection and must be configured in the lower section. With **Duplicate** the same settings as for the selected database are applied, otherwise the default settings. Note: Please do not change the data source name after the database has been in use.

Create a new entry in the database list using **Add new data source from existing folder**. With this selection it is mandatory to provide the same name of the data source to the new database. Define the configuration in the **Select database folder** window pointing inside the data source folder such that the **db.lck** is visible in the in the **Files** area. Activate the **Test DB** button to verify the proper connection. Note: Do NOT use the Create Database button with this option.

2. **Use Direct Connection**: Only JDBC databases can be created, so this radio button must be selected.

3. **Database Connection**: This entry defines the database access. The first part **jdbc:derby:** is the driver specification. The **Database Name** is the name by which the data source is known to the database engine. In principle the name can differ from the data source name, but this is not recommended.

4. **Database Path**: The directory where the database tables are stored (in a subdirectory named corresponding to the database name). It is highly recommended to *replace the default path by an absolute path pointing to a central location outside the PMOD installation*. This will

make it easier to perform version upgrades as well as backups. If relative path names are used starting with "**./**", the directory will be placed in *Pmod4.4/data.*

5. **File Storage Area Path**: This is the path of the root directory in which the data files will be stored. It is recommended using the indicated arrow to generate a directory within the **Database Path**.

6. **Create Data Base**: Activating this button finally creates the JDBC database. Connectivity can be tested with the **ECHO DB** button.

Note: After the installation of Pmod4.4, one or two databases are already available: an empty **Pmod** database illustrated above as an initial container for own data, and a training **Demo** database if the example database was selected for installation.

mySQL JDBC Database Creation

The only difference to the procedure for the Derby database is in step 3, **Database Connection.** Please configure as follows:

The first part is the driver **jdbc:mysql**. The second part is the host on which the mySQL server is running, in the example above the same machine PMOD is running on, thus **localhost**. The third part is the mySQL database name, **Pmod**. In principle the database name can differ from the data source name, but this is not recommended.

User:Password: Fields to specify a user who has administrator privileges in the addressed mySQL installation and his password. The standard setting of mySQl is **root** and an *empty password*. If mySQL requires to enter a non-empty password for root, please specify it in this password field.

Note: You can create different SQL databases to collect data for different projects. They must, of course, have different names and should most likely save the data files in different directories.

Configuring Transaction Server Databases

PMOD allows publishing a local database for use by other PMOD installations using a server program called **Transaction Server** 59. To address a remote transaction server database, a data source must be defined as follows:

1. **Add new data source**: Again, a new data source must be created and adequately named.

2. **Use Transaction Server**: This radio button must be selected, and the transaction server address and port entered.

In this example, PMOD is installed on a host called *localhost* where a transaction server for a particular JDBC database has been started listening on port **5200**. As the database is already existing, the initialization step is not necessary.

3. Note the **Secure** box. Please configure the communication with the properties that the transaction server is expecting (see below).

4. If the transaction server is running, connectivity can be tested with the **ECHO TS** button.

Numerical Accuracy of Images Stored in the Database

Images are stored to the database using Enhanced DICOM IODs which are selected according to the image modality setting. The accuracy of the standard IODs is limited, and if the images have a large dynamic range rounding errors can occur. In these situations PMOD may use a private IOD which supports floating numbers to avoid rounding errors. This behavior is enabled by the **Database supports FLOAT representation of image objects** box.

The float representation is an advantage if the images are used for further processing in PMOD. However, when such images are exported, PMOD converts the images to the standard IODs, whereby the rounding errors might be introduced.

Multiple Access to Derby JDBC Database

It is the nature of embedded databases such a Derby that they can only be accessed by a single process. Therefore, if you start two instances of PMOD, only the first one will be able to access the database directly. The second one will not get access and show an error message

```
Cannot connect to this database:
Database [ jdbc:derby:./DATABASES/Pmod ] may be locked by other instance of Pmod.
```

The solution for this case is to publish the database by a <u>transaction server</u> 59 and access the data through it. In this way, an arbitrary number of processes can access the database.

> **Note:** The default configuration of Pmod4.4 already includes a transaction server definition of the **Pmod** database which is called **DbSvr**. The transaction server will be automatically started with the first interactive PMOD session. Access to **Pmod** through the transaction server is configured as the **DbSvr** database.

Database Deactivation

Sometimes there is a need to temporarily deactivate a data source, e.g. because a remote system is down. In this case the box **Inactive** can be checked to avoid lengthy timeouts.

Default Database

The database which is shown in the data source list when the configuration is saved will serve as the database initially. However, once in use PMOD remembers the least recently used database.

Database Upgrading

After updating a PMOD installation there might be a need to adjust the data structure of the existing databases for using them further. To do so, select a JDBC data source and activate the **Update & Optimize** button. This operation will not only update the table structure, but also the indexes and may dramatically speed up the access to aged, large databases.
Note: Transaction server data sources must be upgraded on the site of installation.

Database Backup

It is important to regularly back up the directory of the database tables as well as the data directory. This has to be done externally by the computer system administrator using reliable mechanisms for backing up important data.

5.3.2   Setting up a Transaction Server to Publish a Database

If a PMOD installation has a JDBC database running, it can make the data available for other PMOD installations. To this end a server program - the *Transaction Server (TS)* - must be started to run in the background and wait for database access requests.

Transaction Server Configuration

Configuration of the TS is performed on the **DATABASE** panel as follows.

1. Select the local data source to be published.

2. Switch the radio button from **Use JDBC connection** to **Use Transaction Server**.

3. Set the IP **Port** for the communication. It must be a unique number not used by any other TS or other process. In the example above port address **5200** is used.

4. Get the **IP address** which should be used by the PMOD installations using TS clients for accessing the database with the **Set Local Host** button. If they are running on the same computer, **localhost** in the **HOST** field will also work.

5. The **Secure** box enables secure communication. It should be used if the communication is not confined within the institution. Otherwise it will slow down the communication speed unnecessarily.

Starting a Transaction Server

A PMOD TS is a background process which can be started as part of PMOD, or as processes running independent from the PMOD installation used for its configuration. The behavior is configured using

If **Run with PMOD** is enabled, the TS is started/stopped with PMOD, so that the published DB is not always accessible by other PMOD installations. **Standalone** indicates that a **Starting Script** is generated as described below, and the TS is executed as an independent process.

Note tat there is dedicated server administration tool 93 which can be used for monitoring, starting and stopping transaction servers for which starting scripts have been created.

Creation of Transaction Server Scripts

Save Standalone Script is a facility for generating scripts according to the configured TS properties. It becomes active when the **Standalone operation** option is enabled and generates an operating system dependent script which is shown in a dialog window. The options are:

- **Verbose commands** (**-d**): Recommended only for debugging purposes, as it slows communication down.

- **Save log** (**-o**): The TS output will be stored to a log file.

- **License Server**: Indicates that the TS is managing a network license at the same time as data sharing. If it is *not* enabled, a **-noLS** parameter is added to the command script

The example below is the result for a Windows system.

The **Yes** button saves the shown script to the *Pmod4.4/Start* directory using the specified **Name**.

Additional Transaction Server Options

An command line flag which can be added to the script in an editor is **-optimize**. If it is present, the database table indexes will be optimized before the database gets accessible. Note that this may take notable time for large databases, but it can dramatically improve speed for aging, large databases. To keep the database fast and safe, a TS started with the **-optimize** flag will backup the database tables to *data/DB_Backup/* every Sunday night at 1am and then optimize the indexes.

Another startup option is **-upgrade**. With this option, a backup of the database is copied to data/DB_Backup/upgrade/, then the database upgrade scripts are executed, a table optimization performed as with **-optimize**, and finally the TS started.

Transaction Server Status Information

All automatically started transaction servers are available for management from the PMOD ToolBox. TS management is opened by activating the button in the ToolBox:
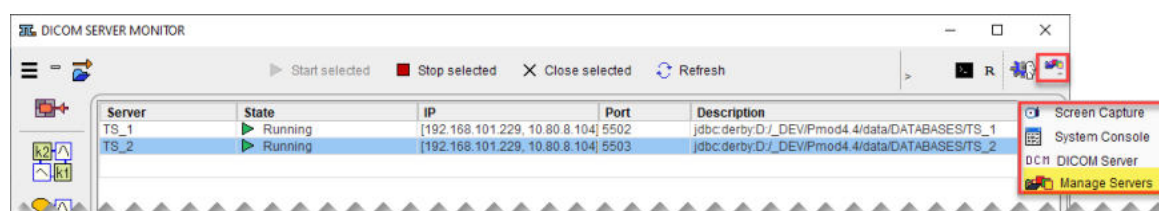
The current status is displayed in the **State** column. After selecting an entry in the list, stopped servers can be started using **Start selected server (s)**, or running servers stopped using **Stop selected server(s)**.

When the color of the button changes to blue, a TS request is being served. The color changes back after all communications have completed.

PMOD Status Information

In case of problems with the TS status the PMOD status button in the ToolBox shows a red bullet.
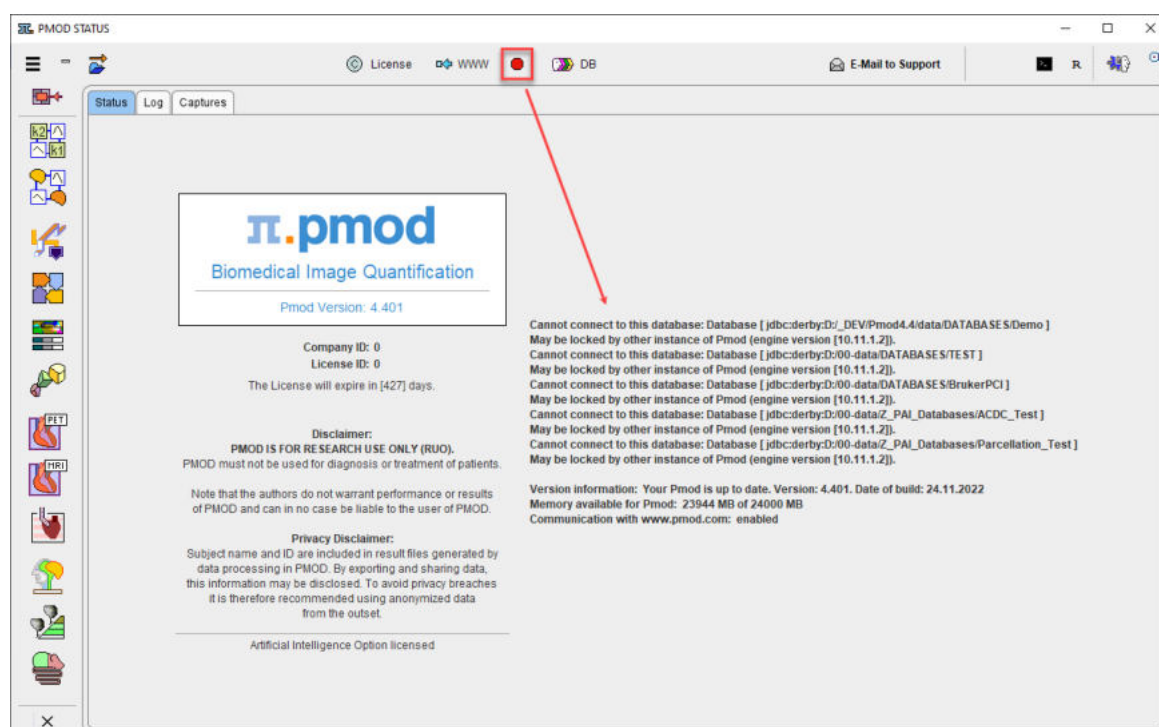
The **DB** button aside the red button is a shortcut to open the general PMOD configuration directly on the DATABASE page.

Dedicated Machine for Databases and Transaction Servers

Note that transaction servers can be started and operated without consuming a PMOD license. This allows moving them to a server machine that is continuously operating and has fast disks. On this server machine perform a standard PMOD installation, plug the USB license protection key in, and use the **Configuration** facility for the database configuration and TS script generation. Then start each of the scripts in a separate command window. In the case of a standalone license, the USB key can now be moved to the computer, where the actual data processing is performed. In the case of a network license the USB key should remain, as it is used for license serving.

It is easy for Mac OSX and Linux to start programs like the TSs at system boot time and run them in the background. On Windows, this is not possible with normal programs. Rather, a command window is required which needs to stay open for the whole program duration, which is not convenient for shared server systems. A workaround is to purchase a third-party solution which wraps the transaction servers into service processes, such as the AlwaysUp solution.

Depending on the network and server performance the speed of the load/save operations via a TS may be slower than with local loading/saving. The benefit, however, is the global availability and centralized maintenance of the data.

CAUTION: Note that the proper interaction between the transaction server and clients requires that all systems run the same PMOD version.

5.3.3 Loading Data from Databases

If the **Use first page Database** loader is enabled in the global configuration on the **USERS/SETTINGS/DATABASES**
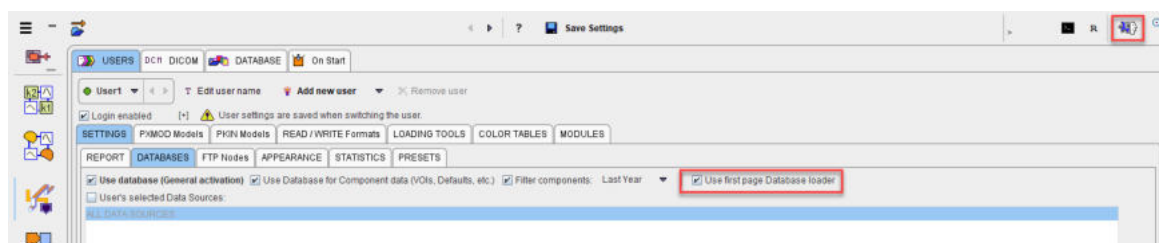
the **Load** / **Database** page becomes active in all the available modules and appears as the first module page nearby the menu button. The selected page appears highlighted as in the capture below:
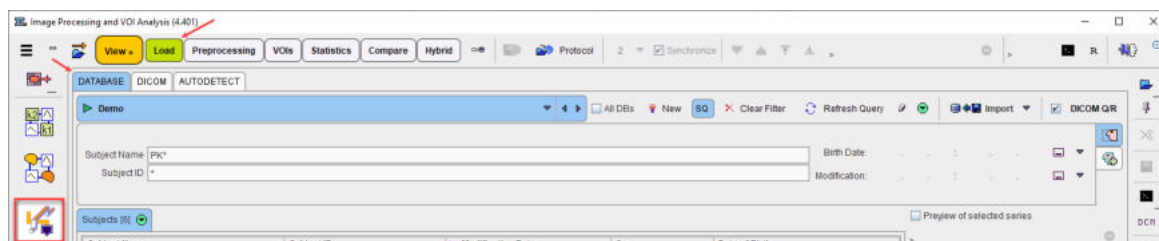
Otherwise, the unified data loader [28] DATABASE page [29] may be used when the **Use database (General activation)** is enable in the main configuration.

5.3.3.1 Image Data Loading

**Database Loading Layouts**

When loading images from the database an interface similar to the one below is shown. This example represents the vertical layout with a filter area at the top and three list areas. The first lists the subjects corresponding to the filter settings. The second lists the image series of the selected subject. The third lists the image series which will be loaded when the **Open** button is activated.
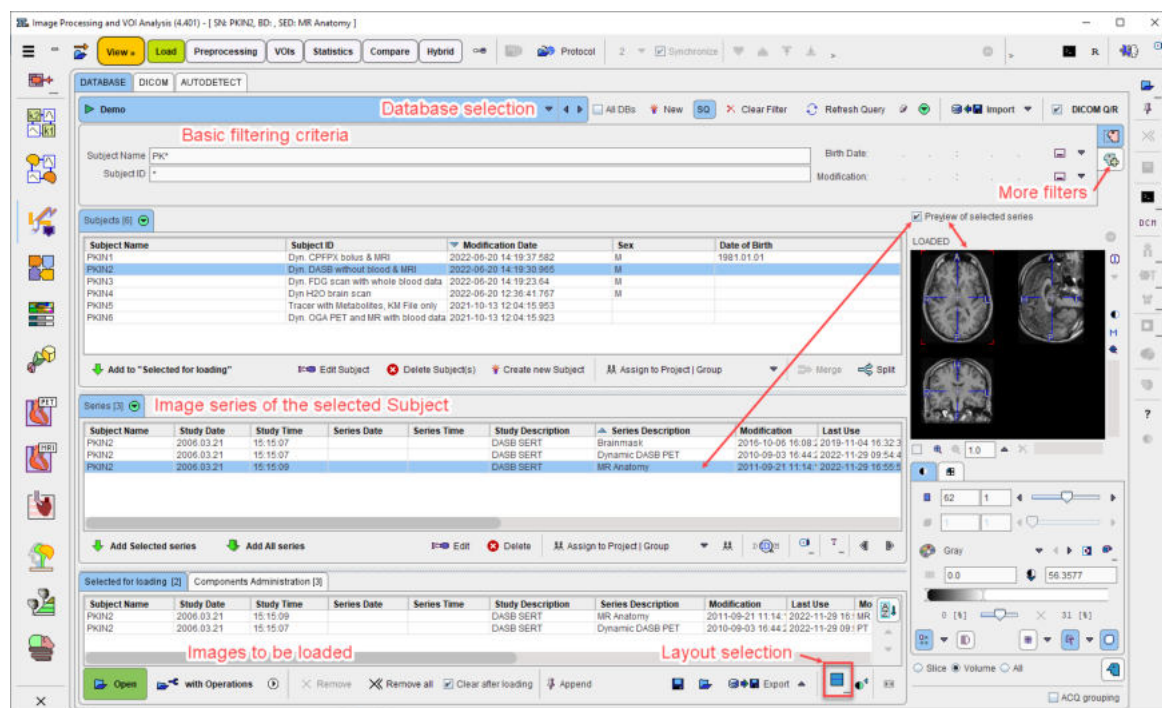

The vertical layout may not be convenient for small screen heights. In this case the layout can be switched
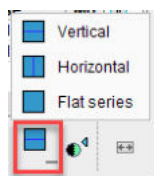
The **Horizontal** layout stacks the **Subjects** and **Series** list, to allow for more list entries. The series of the selected subject can be shown by selecting the **Series** tab, or by double-clicking the entry in the **Subjects** list.
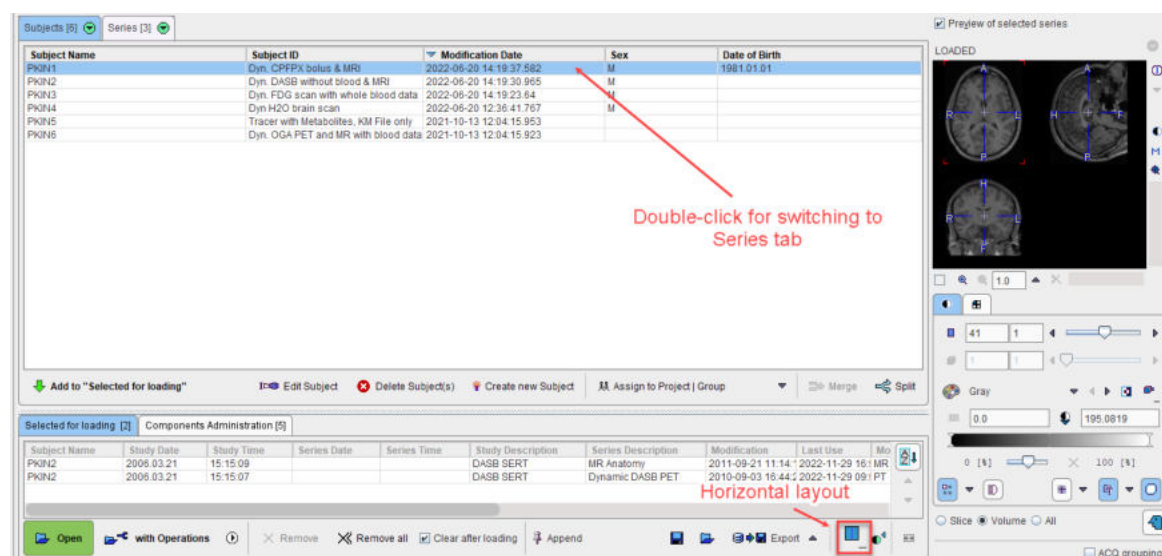
The **Flat series** layout is another arrangement which lists all image series in a single list. It allows listing series from all active databases if the **Search All** checkbox is enabled, as illustrated below. Also illustrated is the extended filtering in the upper area.
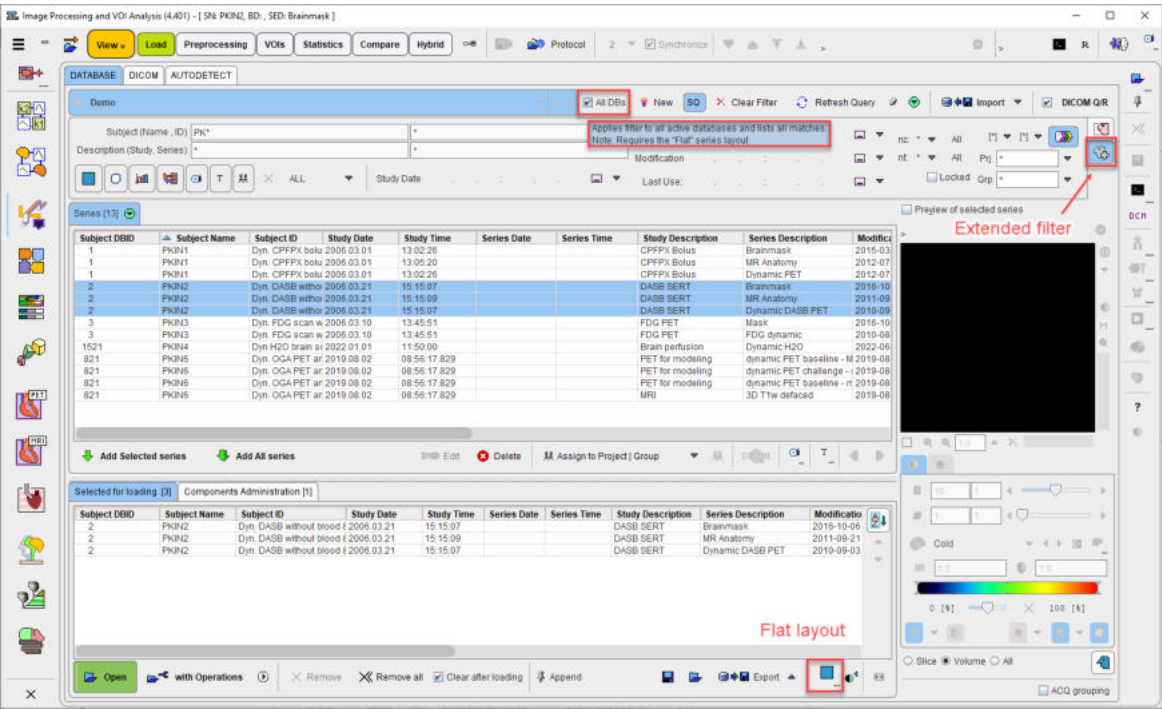
An interface reduction ⊙ button is located in different places to allow hiding/showing the patient list controls. When it is activated it becomes a ⊙ button and some of the user interface elements are hidden to allow for more list place. To show all elements, the ⊙ button needs to be activated.

Loading Overview

One or several image series can be selected and brought into the **Selected for loading** area by the **Add** button or by a double-click at the series entry. On the right side there is a preview window to verify the image contents before actually loading the whole data set. If the **Preview of selected series** box is checked, an image is displayed as soon as a series is selected.
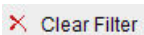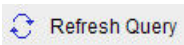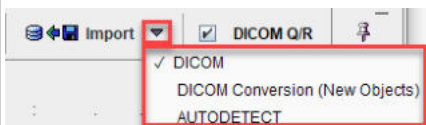
Finally, by activating the **Open** button, all series in the **Selected for loading** area are loaded into the PMOD tool. The **Append** pushpin button in the lateral task bar is important for the outcome of the loading operation: with the appending setting ⌖ the images are added, while with the overwriting setting ⌖ any already loaded images will be discarded.

Note that the availability of multi-series selection depends on the context. If only a single series is expected by the program, double-clicking at the series will immediately start image loading.

Other Loading-related Options

In the lower right corner there is a collection of loading-related functionality.

All DBs	When enabled, allows applying filters to all the active databases and lists all matched. Note that requires the **Flat** series layout.
New	Opens the global configuration tool for creating a new database
SQ	Means *Save Query*. If this button is enabled, the same filter settings will be applied when the database window is opened again.

✕ Clear Filter	This button resets the filter settings by removing all specifications.
⟳ Refresh Query	The refresh button to apply the query to the database potentially updated in the meantime, or after changing the filter and disabled automatic refreshing.
🗜, 🖉	Toggle button to enable/disable automatic refreshing after changing a filter element.
🔽/🔼	Hide/Show panel with filter settings.
Import	The **Import** functionality is a convenient way for directly importing many image series at once into the currently selected database. The **DICOM** option imports the original data, unless any information is changed in the intermediate dialog window. In contrast, **DICOM conversion** loads the images first and stores them in PMOD's own DICOM objects. When using the **AUTODETECT** import, dummy demographic information is generated if it is not available in the image headers.
DICOM Q/R	Starts the DICOM Query/Retrieve functionality in a dialog window. If the box left to **DICOM Q/R** is checked, the demographic subject information is copied to the Q/R dialog window. This convenience helps for retrieving images of the selected subject from a PACS.
DICOM (Page)	Serves for DICOM Part 10 image loading 105 from outside the database.
AUTODETECT (Page)	Serves for File-based image loading from outside the database using the AUTODETECT format. Tuser can just browse to any directory and select any type of image file. PMOD will detect its file format and load the image, if possible.

User Interface Elements for Filtering

Basic Filtering
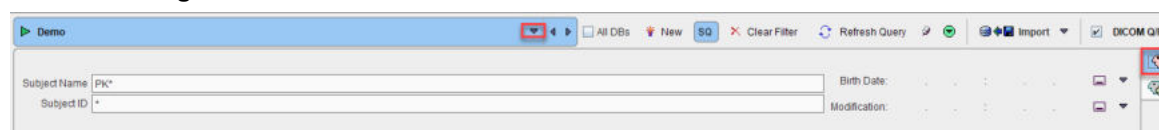
First of all the database to be searched must be selected with the selection in uppermost section, **Demo** in the example above. The basic filtering options include the following elements.

Subject Name	Subject name, starting with the last name. The wildcard * can be used as a replacement for arbitrary sub-strings.
Subject ID	The subject ID filter, also supporting wildcards.
Birth Date	The filters for the birth date include an exact date, or a date range available from the selection list.

	☐ All Dates ✓ ① Today ② Last Day ⑦ Last Week Ⓜ Last Month Ⓨ Last Year 🖭 From ... 🖽 < Between > 🖾 ... Till 🖿 One Day These specifications apply for all other filter dates.
Modification	A date/time is maintained in the database recording when the data of the subjects was modified the last time by adding an image series or by changing the subject information. For example, setting the field to **Last Week** only shows subjects modified in the last seven days.

Extended Filtering

There is an extended filtering capability available on the second sub-tab which is illustrated below.
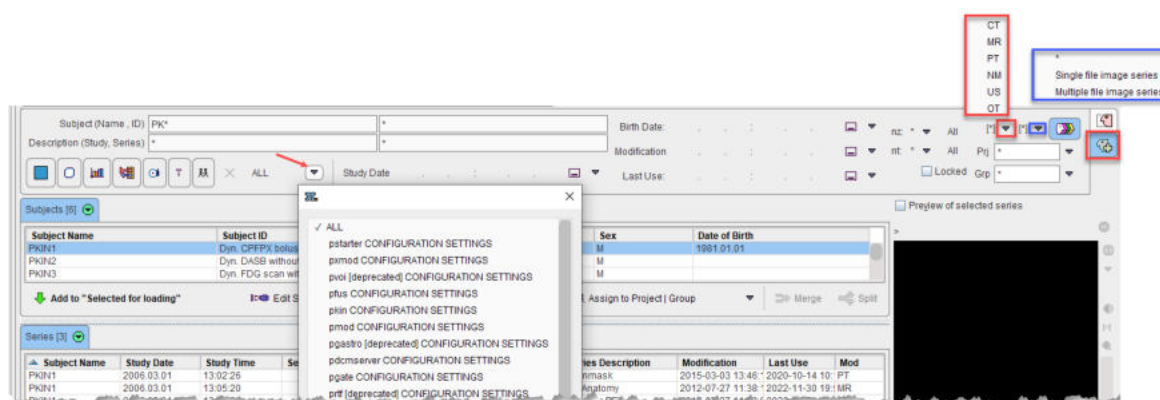
It contains several new elements:

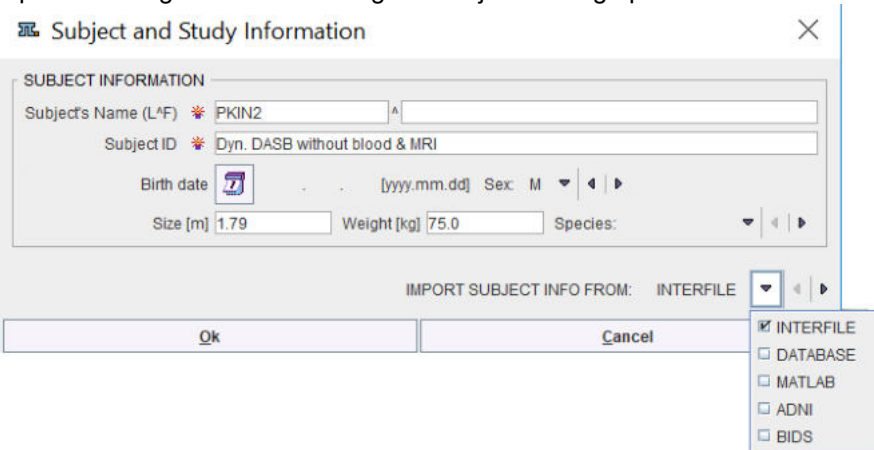|	
Study Description	Filtering of text appearing in the study description. The * wildcard is supported.
Series Description	Filtering of text appearing in the series description. The * wildcard is supported.
ALL	This selection lists all available data types in PMOD such as images, VOIs, etc. Setting this field to *VOI Templates* for example will only list patients who have a VOI definition attached to one of the image series. These shortcut buttons allow filtering for frequently used data types such as images, VOIs, statistics, kinetic modeling files, comment texts, paired series. **ALL** resets all filter setting.
Last Use	A date/time is maintained in the database when data of the subjects was accessed the last time. This information is listed for each database object. Selecting a date range allows browsing the database content based on a *least recently used* criterion.
nz	Filter to search for studies with a certain number of slices, including the criteria

	For instance, planar only studies could be looked for by setting nt = 1.
nt	Filter to search for studies with a certain number of dynamic frames. For instance nv > 1 will only list dynamic series.
Locked	If the box is checked, only subjects who have a *Locked* flag are listed.
Modality	A selection to restrict the search to a specific modality, e.g. to *PT* (PET) as in the example. Multiple modalities can be searched for at once.
Prj	Subjects can be assigned to a **Project**. The selection allows choosing from the list of available project names.
Grp	Similarly, subjects can be assigned a **Group**. The selection allows choosing from the list of available groups names.
or	Every time data is saved in the database, the PMOD name of the user who saved is recorded together with the data. This button allows restricting the search to the PMOD user currently logged in (button out), or to show data of all users (button in).
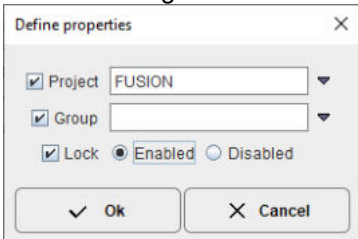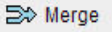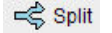
Subject Level Operations

The allows hiding/showing the Subject list controls

With , when a subject has been selected from the list, the **Subjects** list controls becomes active.

|	
Add to "Selected for loading"	Enters all series of the subject to the **Selected for loading** area.
Edit subject	Opens a dialog window for editing the subject demographic data. The **IMPORT SUBJECT INFO FROM** button allows importing this information from a file in the Interfile format, from an existing **DATABASE** subject, or from a **MATLAB, ADNI or BIDs** file. Note that the information in the DICOM object is not modified, just the database entries. However, when loading the images, the

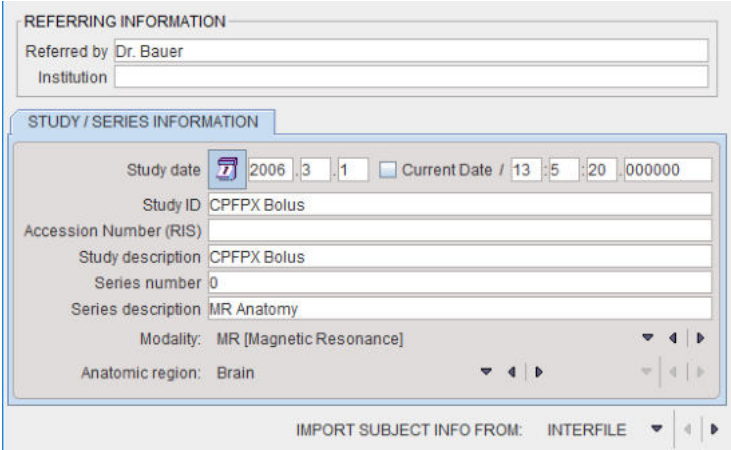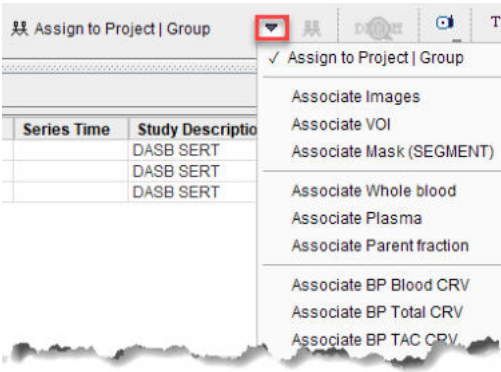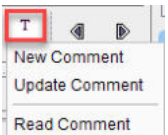|	
	information in the database overwrites the DICOM information, and when the data is saved or exported, it will contain the changed information in the file. Note that this replacement operation does not apply to weight and hight, as these properties may change due to treatment and growth.
Delete Subject(s)	Delete the subjects selected from the list and shows an option dialog which data is to be removed.
Create new Subject	Create a new subject in the database, to whom information can be attached if there is no image series in the database.
Assign to Project | Group | Lock	Allows defining three attributes for a subject: A **Project** name can be entered, or if it already exists, selected from a list. Similarly, a **Group** can be specified, and the subject can be **Lock**ed to prevent erroneous deleting.
⇻ Merge	Sometimes several entries are created for a single subject because of a mismatch in the name/ID information. To merge such entries, select all of them in the **Subjects** list (with `CTRL+Click`) and activate the **Merge** button. As a result all series end up under a single subject entry.
⇷ Split	Allows separating series listed for a single subject into different subjects. To do so, select the series, activate the **Split** button, and **Edit** the generate subject names.

Series Level Operations

The ⊙/⊙ allows hiding/showing the **Series** list controls.
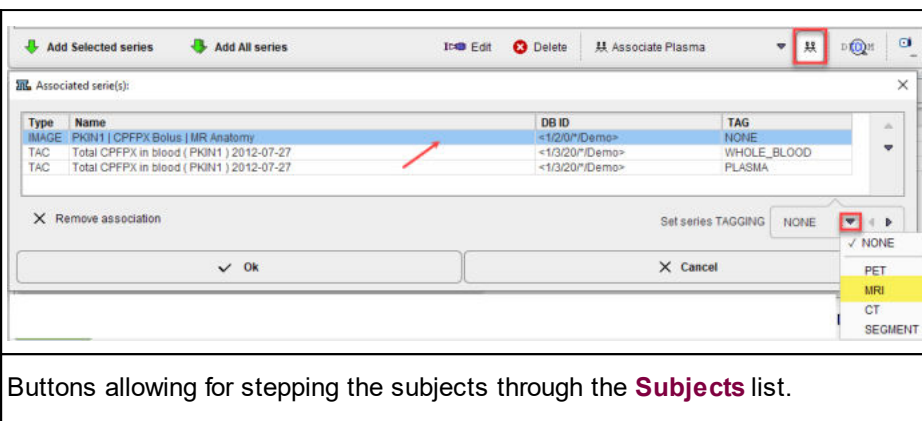
With ⊙, when a series has been selected from the list, the **Series** list controls becomes active.

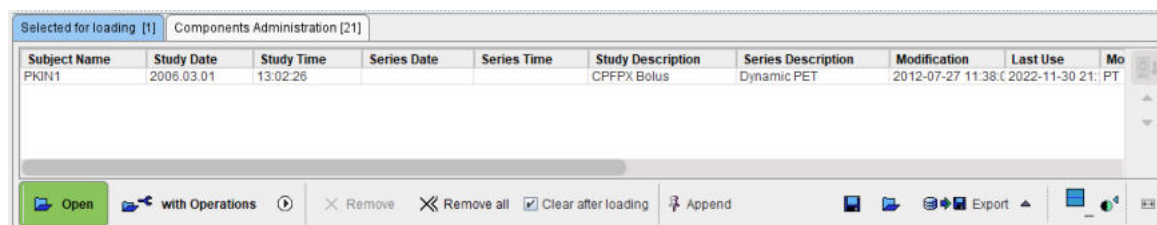|	
Add Selected series	Enters the selected series of the subject into the **Selected for loading** area.
Add All series	Enters all series of the subject into the **Selected for loading** area.
Edit	Opens a dialog window for editing the series information

Assign to Project | Group | Lock	This option button supports several functions **Assign to Project | Group** brings up the same dialog window as on the subject level to define project, diagnosis and locking on the series level. The other entries allow establishing a relation between the selected image series and a component such as a VOI or blood curves, see **Data Association** 79ᐟ.
Delete	Delete the series selected in the list.
DICOM	Inspect the attributes of the selected image series in a dialog window.
	Search JPEG or TIFF captures stored in the database. They can be opened in a viewer.
T	Option menu for comments. **New comment** opens a text editor. The created comment is added to the selected image series. **Update comment** and **Read comment** allow searching the database for comments and editing/reading tem.
	Show the components which are associated to the selected image series. In the example below an MR and two blood TACs were associated to the dynamic PET series.

◁ ▷	Buttons allowing for stepping the subjects through the **Subjects** list.
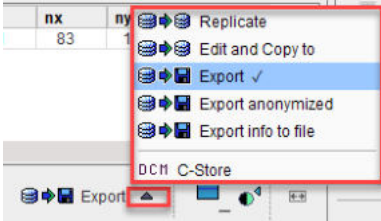
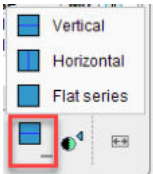**Selected for Loading Area**

In most situations more than one series (from the same or different subjects) can be added to the loading area, but there are exceptions when only a single series is allowed. The *order* in the list is relevant for the loading order. This is most important for the fusion tool because the first series will serve as the reference. To change the sorting order just click one of the column headers.

As soon as there are series in this area, the row of buttons below the list becomes active.

Open	Starts loading the image series directly. If the **Append** flag is on (🔗), the selected series will be loaded as *additional* images to the tool, otherwise the tool will be cleared before loading.
with Operations	Starts loading the image series and opens a dialog window for specifying pre-processing options as described in Image Data Transformations during Loading 108. If the **Append** flag is on (🔗), the selected series will be loaded as *additional* images to the tool, otherwise the tool will be cleared before loading.
⊙	This button serves for loading the selected data with a macro.
Remove	Removes the selected series from the selected for loading area, but does not delete from the database.
Remove All	Clears the **Selected for loading** area.
Clear after loading	If the option box is checked, the **Selected for loading** area is empty when loading the next time. Otherwise, it will show the same entries, which may be helpful when working with the same data repeatedly.
💾	Allows saving the list of the images available in the selected for loading area.
📂	Allows appending a saved list of the selected series.
Replicate	Copy the selected series including components to another database which can be selected in the appearing dialog window.

Edit and Copy to	This element shows the current entry of the option menu for exporting the selected series.
Export / Export anonymized /Export info to file	See Image Data Export 76.
DCM C-Store	This button allows sending the selected series directly to a DICOM server without first loading them into an image area. This has the advantage that *no modifications are done to the original DICOM objects*. In contrast, when loading the images and sending them to a DICOM server, some changes are applied to the DICOM attributes.
Database layout options	
◐/◑	Buttons for showing/hiding a preview of the selected series.
↕	This button enables sorting the images in **Selected for loading** by clicking into the selected column header.
▲ ▼	These buttons shift the series location in the list.
↔	This button establishes default column order and width.

The **ACQ Grouping** option, available under the image preview panel, is applicable for CT series which contain images acquired with different parameters. When opened, such data will be split into different image series.

5.3.3.2 Component Data Loading

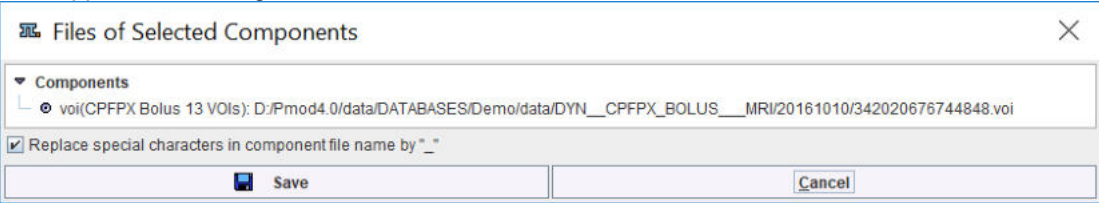Access to component data in the database is only available, if the database configuration has been set to **Use Database for Component data**.

The dialog window shown is somewhat different to the dialog window when loading images. The example below shows the dialog which appears after loading images of a patient **PKIN1** into the PVIEW tool and activating the **Load** button on the **VOI** tab.

First, the database containing the data, here **Demo**, must be selected. In the filter section similar options are available as described for image data loading. The **Subject Name** and **Subject ID** fields are normally filled in by the information of the image data which has already been loaded. The component section lists all data of proper type and matching the selection criteria.

The example patient **PKIN1** has three VOIs in the database. When a component in the list is selected, a row of action buttons below the list area becomes active.

Select all	Selects all components of the list (also `CTRL+A`).
Delete	Attention: Deletes the component data from the database and the disk!
Export	Exports the selected component data out of the database into a disk file. Multiple selections are supported. A dialog appears, and after the **Save** button has been activated the user is requested to specify the destination directory for the data export.
Rename	For changing the **component name**.
Retrieve	Starts loading the selected component.

Ca nc el	Closes dialog without loading.

The **Load from File System** button changes to file-based loading directly from the disk.

5.3.4   Saving Data to Databases

Database saving is only possible of if the database functionality is enabled.

5.3.4.1   Image Data Saving

If the database has been configured the **Database** entry is available in the list of output image formats. Image saving can be either done from the **Menu** of a PMOD tool,
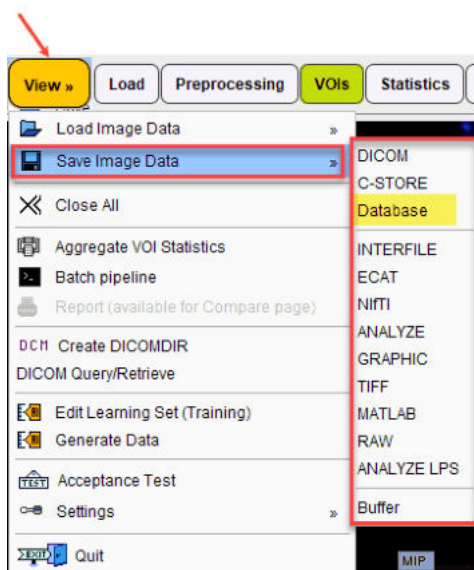
or using a **Save** button.
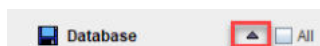
The **Save** button must be configured to the **Database** format beforehand using the arrow indicated in red.
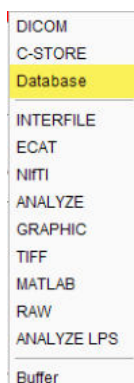
Saving to the database brings up a dialog window

which is similar to the dialog window for saving images in DICOM part 10 files or C-STORE to a DICOM server.

The images are saved to the database as the following DICOM IODs :

- CT images as Enhanced CT,
- MR images as Enhanced MR,
- all other images otherwise as Enhanced PET.

The data can be assigned to a **Project**. The selection allows choosing from the list of available project names. Similarly, the subject can be assigned to a **Group**.

For databases with enabled float storage, images with internal float representation are saved as private enhanced PMOD objects.

The **Edit Info** button can be used for adding/changing descriptive information on the patient and series level.

Activate the **Save** button to proceed with the saving or the **Cancel** button to abort the procedure.

5.3.4.2 Component Data Saving

When saving component data to the database, the principle is that it is attached to the image series it was derived from. In practice, there are two situations to consider:

1. The component data was derived from an image series loaded from the database. In this case the patient and the series are already selected in the appearing dialog. After entering a name for the component, the data is saved to the database and attached to the particular image study.

Owing to this mechanism, all derived data ends up as additional components of the images, e.g. the VOIs and the VOI statistics. If needed, the **Change Subject (Series)** button allows attaching the information to a different series.

2. When the image data was not loaded from the database pre-selection of the series is not possible.

In this case the **Attach to Subject (Series)** button must be activated to look for the subject and selecting one of his image series using the appearing database browser. If the subject is not yet defined in any of the databases, a suitable subject record with a dummy series can be created using the **Create new Subject** button of the database browser.

To save the data outside the database as a stand-alone file, activate the **Save to File System** button, browse to a specific directory, and save the component there.

Note: The saved components can be made visible and administered (exported, deleted, renamed) in the database dialog window by selecting the **Components Administration** tab.

5.3.5 Exporting Data from Databases

Any data in the database can be exported from the image loading interface as described below, or using the database administration tool 87 .

5.3.5.1 Image Data Export

To export image series (and all related data) just bring the series to the **Selected for loading** list and then use the **Export** option menu.
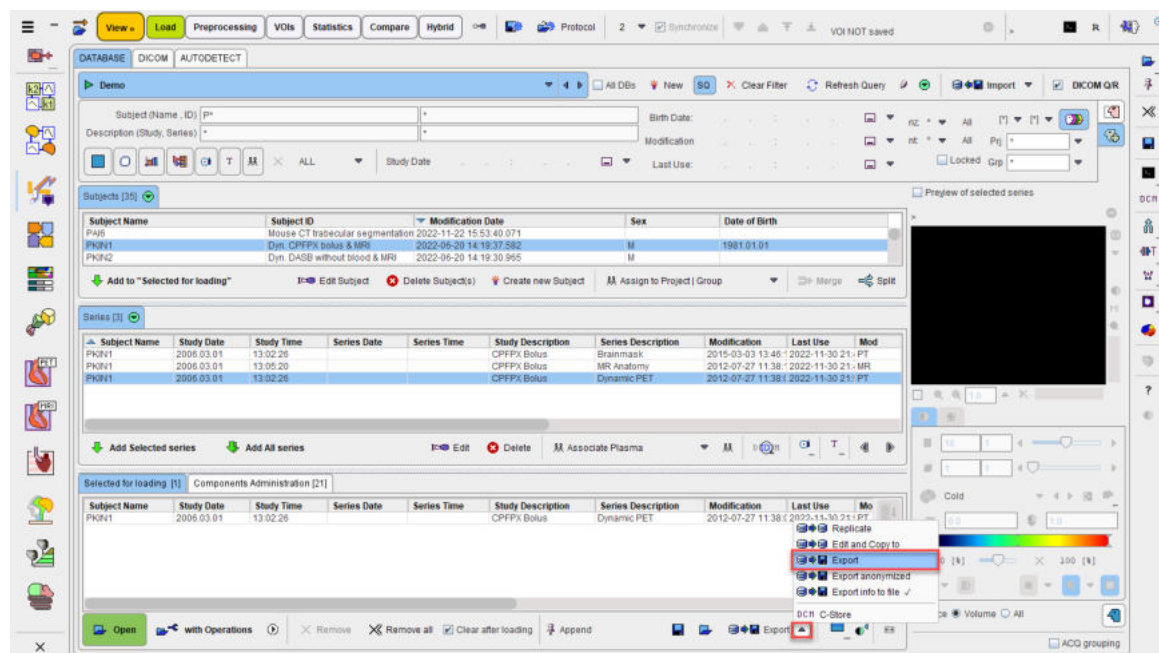
Replicate and **Edit and Copy to** allow copying the selected content to a different database, the latter after modifying demographic content. This functionality is described in Replication from one Database to Another 88 .

Standard Export

Export copies the selected contents to a directory structure. It shows a dialog window as illustrated below for configuration of the output.

SOP class	Images are stored in DICOM format in the database. The ORIGINAL STORAGE setting will export the images unchanged, whereas any other selected SOP will result in a different image encoding.
Exclude internal components	Components attached to the selected image series are also exported. Some of them are only useful within the database, but they can also be exported by unchecking the **Exclude ...** box.
Replace special characters ... by "_"	This setting is preferable to avoid the generation of unusable filenames.
Create DICOMDIR	Each image series will be stored in a dedicated sub-directoryr. **Create DICOMDIR** instructs the export to create a DICOMDIR file in the target directory of the export to facilitate subsequent image loading.
+ZIP	Compress the whole exported directory structure into a zip archive for easy and efficient copying.
DCM C-Store	Transfer the exported images to one of the configured DICOM nodes 40. No component data is transferred in this case.
Export to File system	Save the exported data in a directory to be specified. Result is a directory tree as illustrated below, with one folder per image series and a DICOMDIR on the top level. Each image directory contains a set of sub-directories, depending on the components attached to the image series. In the example below the actual image is exported into **IMAGE**, whereas the VOIs are located in **VOI**, the PXMOD protocols in **DEFPMOD**, PKIN files in **KM**, etc.
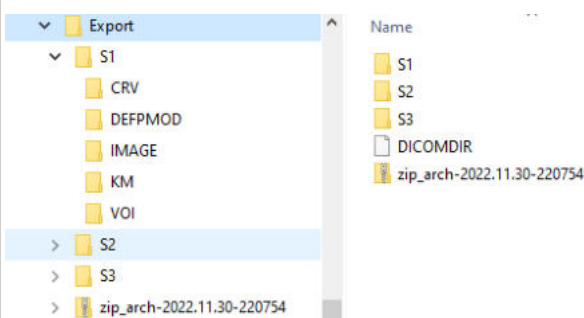
De-Identification during Data Export

Export anonymized is useful for removing subject-specific information from the images and the components (VOI files and statistics, aggregates, kinetic modeling data and parameter files, PXMOD protocols. It works in the same way as **Export**, but offers a choice between two de-identification methods.

Replace by new data is a simple option just to change subject name and ID. All other information is left intact and the result is therefore not real de-identification.

Recommended and default is the **Replace by algorithm** option which de-identifies the images according to DICOM PS3.15 Annex E. It implements the E.2 "Basic Application Level Confidentiality Profile" intended for use in Clinical Trials. It is extremely conservative and removes all information related to identity and demographics of the patient, his family, personnel and the organization. Please refer to Batch Anonymization 515 for the details of the methodology.

Generation of Information Listing

The **Export info to file** option serves for collecting administrative information from images in the database. After collecting the information it shows a dialog window which allows saving to a text file or copying to the clipboard.

Note that the **Subject age** is one of the parameters that is available for exporting. If the information is missing from the image header but the **Subject birthday** and the **Acquisition Date** are available, the age is calculated as the difference of the two dates.

DCM C-Cstore

The **DCM C-store** export option sends the selected image series to a DICOM server as described in DICOM C-STORE 121. Note that unlike the Export or Replication facilities, only the image data is transferred.

5.3.5.2   Component Data Export

When saving components such as VOIs to the database, they are attached to an the image series they were derived from (if applicable). In the database loading user interface they can be listed and exported by first selecting an image series, and then switching the panel at the lower bottom to **Components Administration**. In the example below 15 components were saved, amounting to 16 components including the **image** itself.
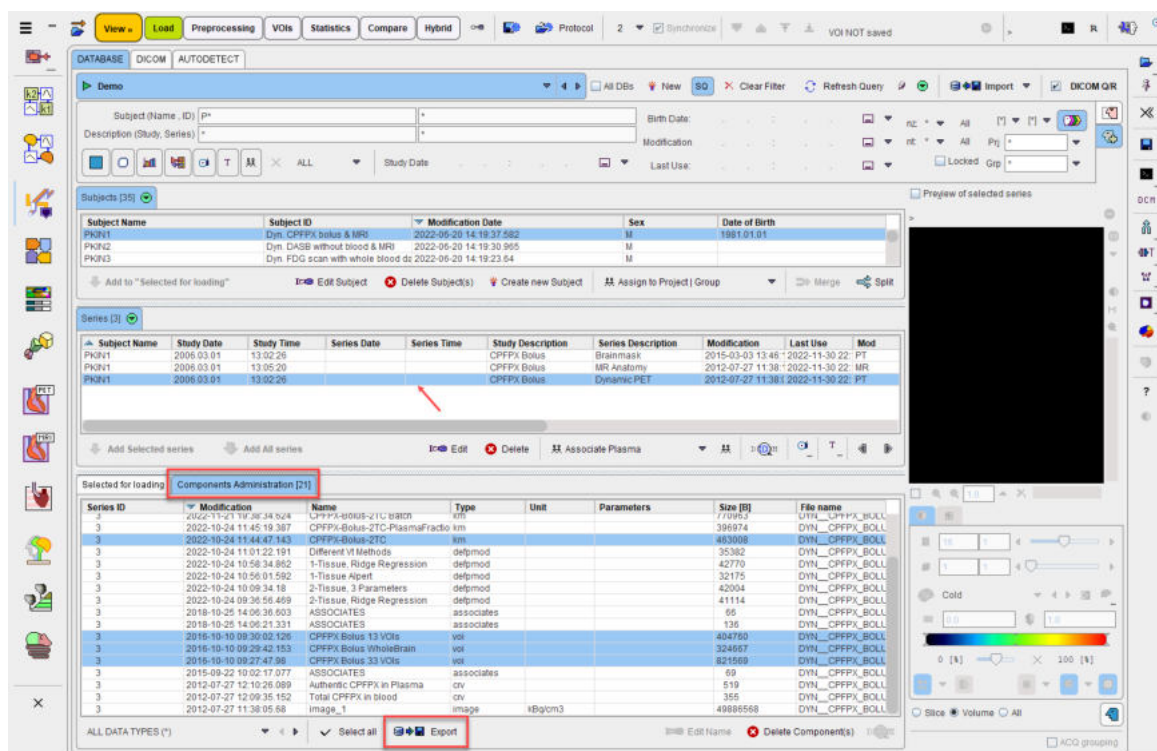
Components can be exported by simply selecting them in the **Components Administration** list and activating the **Export** button. Similar to the Image Export⎡76⎤ a dialog window is shown
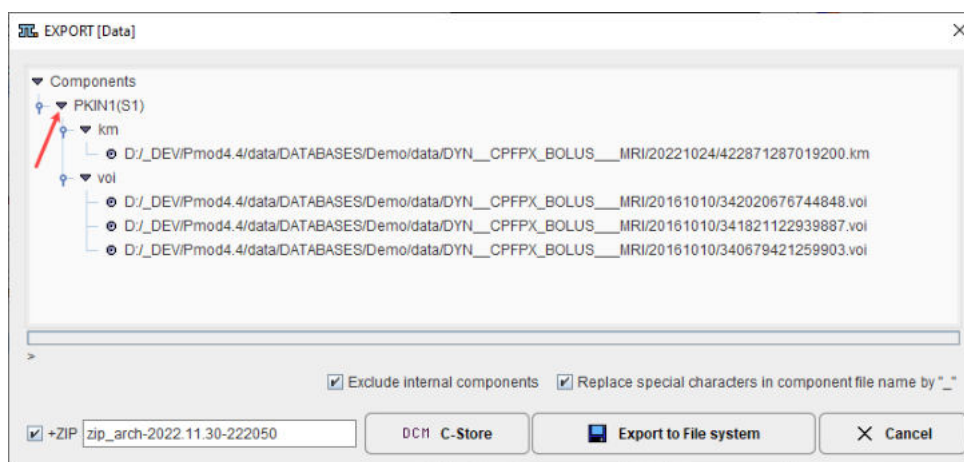
which indicates the selected information and allows saving or transferring it.

5.3.6   Data Association

The database interface allows establishing relations between stored data objects which can be accounted for in some processing tools and in pipeline processing⎡471⎤.

For instance, the tool for MR-based partial-volume correction⎡172⎤ of brain PET data requires the grey matter, white matter and CSF tissue segments, which can be calculated with an external tool⎡166⎤. When this segment image is associated to the PET image, processing is simplified because when choosing PET the corresponding tissue segments are implicit.

Another example is the absolute quantification of a dynamic PET image using a kinetic model which requires information about the tracer activity in whole blood and plasma. Such blood curves can be associated to the PET and their meaning defined by a flag, as explained below.

It is also an important feature for the [PAI Data Preparation](#) as it allows Automatic Image Association based on defined Projects.

5.3.6.1 Image Association

In order to establish a relation between two images please select them in the **Series** list.
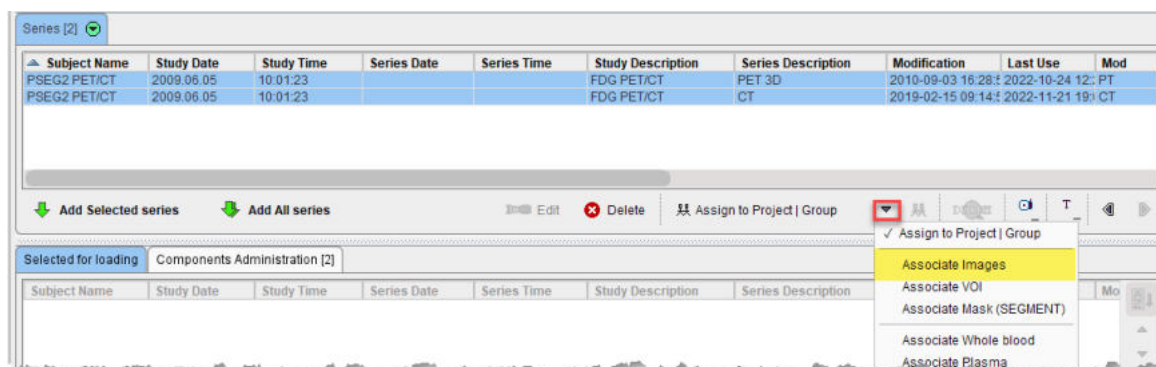
Then select the **Associate Images** entry from the **Assigned to Project | Group** list as illustrated above. The operation results in a confirmation window which can be closed.

To view the images associated with a particular image please select select the image in the **Series** list, and activate the ⚎ button.
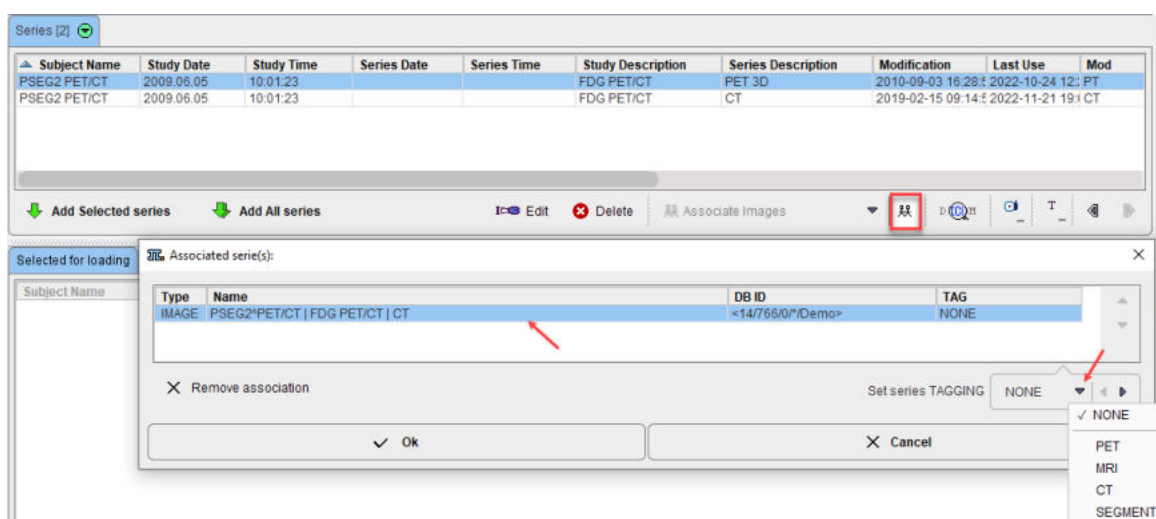
In the example above the **PET 3D** is associated to the selected **CT** series. In order to define its role in a potential processing pipeline an appropriate entry can be selected from the **Set series TAGGING** list.

5.3.6.2 VOI Association

VOI association can be used in order to establish the default VOIs for images. Select the **Dynamic PET** in the **Series** list, and open the association list as illustrated below.
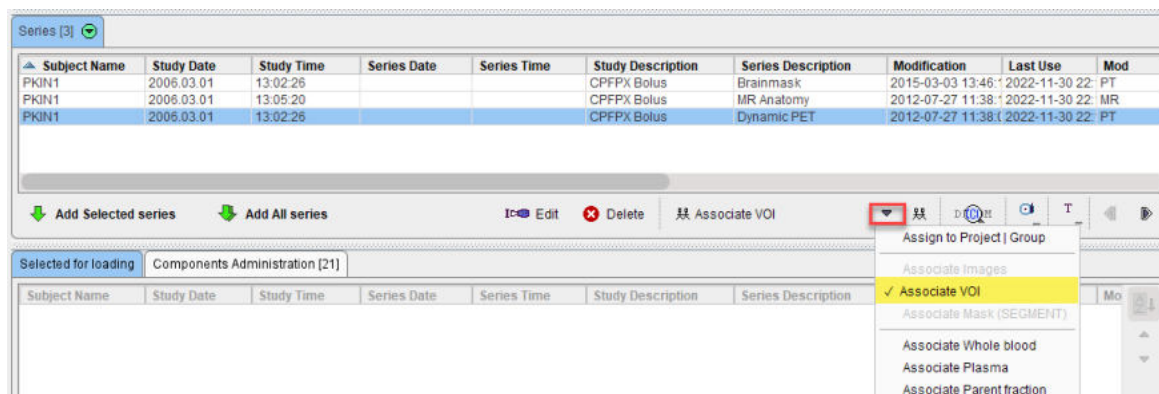
Choose **Associate VOI** to open a dialog window for selecting a VOI. Preferably it is already available in the database and can simply be selected in the **VOLUME OF INTEREST** list. Alternatively, **Set from File System** can be used to point directly to a disk file. Confirm the assignment with **Set selected**.
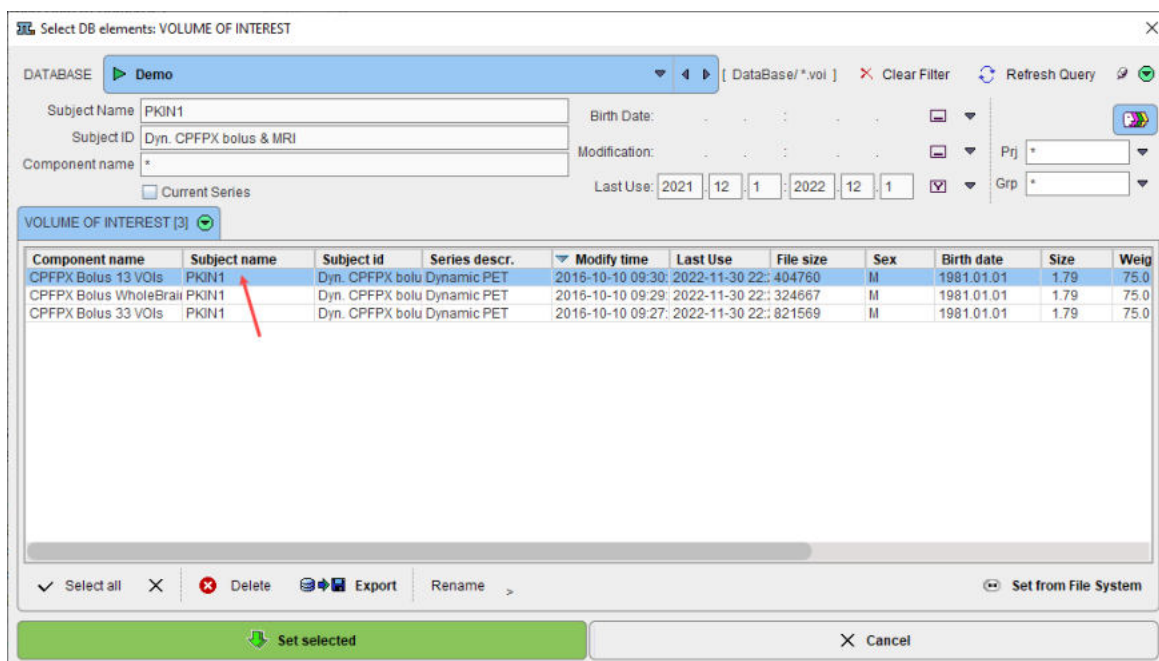
The additional VOIs association options available in the selection list are useful for PXMOD batch processing:
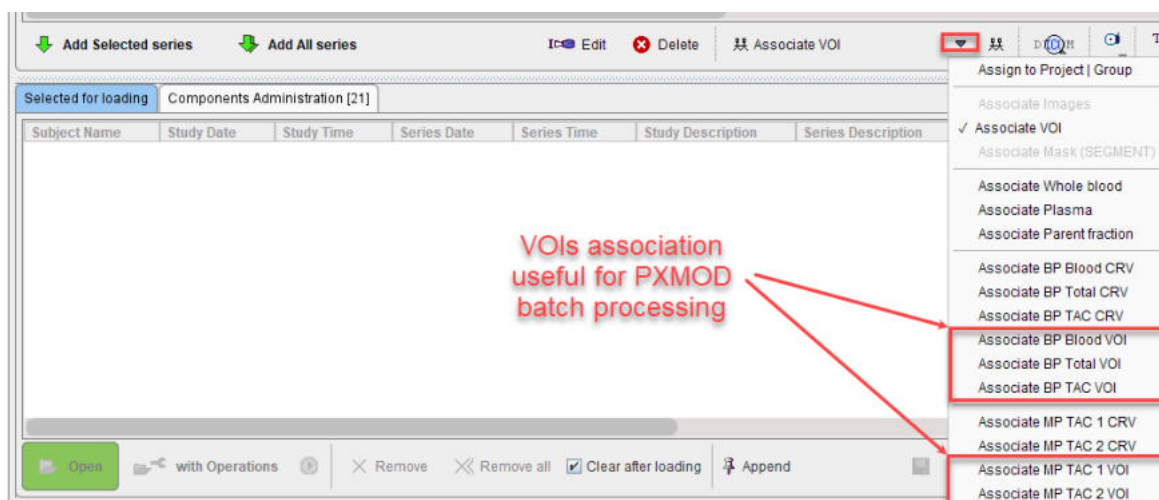
To view the association available for a particular image please select select the image in the **Series** list, and activate the button.
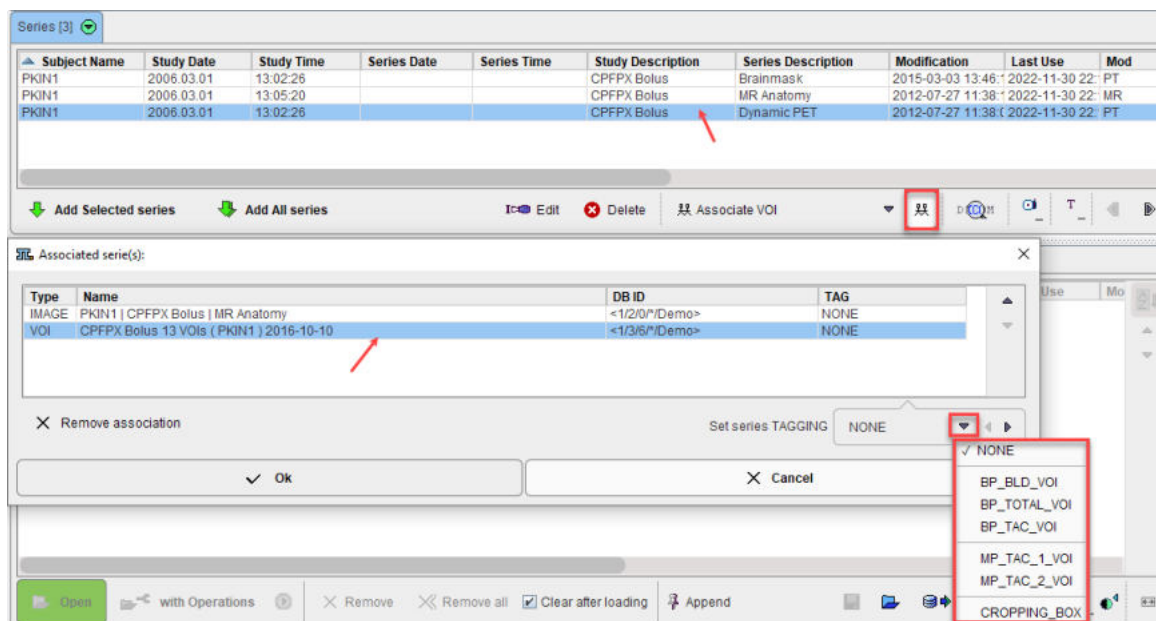
In the example above the **Dynamic PET** is associated to the selected **VOI**. In order to define its role in a potential PNEURO or PAI processing an appropriate entry can be selected from the **Set series TAGGING** list, for example CROPPING_BOX.

5.3.6.3   Curve Association

The association of curves to an image series works similarly. Select the **Dynamic PET** in the **Series** list, and open the association list as illustrated below.
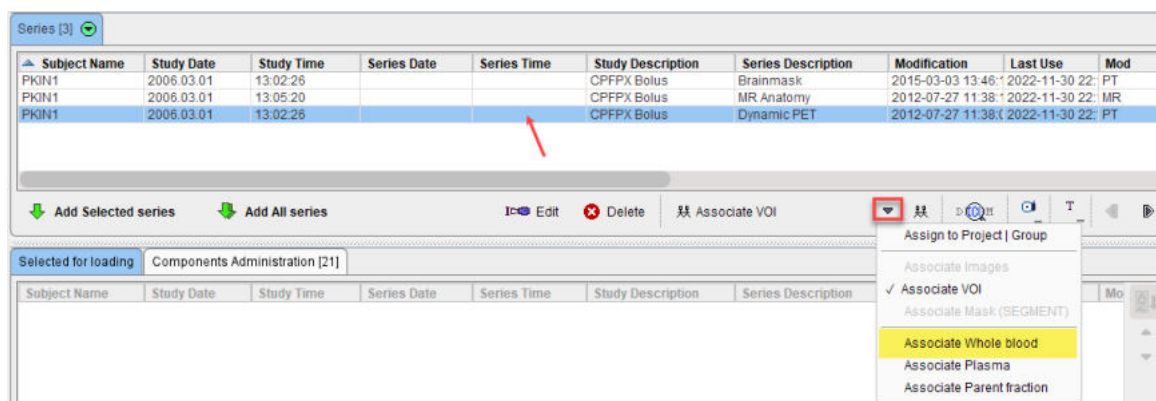
Choose **Associate Whole blood** to define a whole-blood TAC for kinetic modeling purposes. A dialog window opens for selecting a curve. Preferably it is already available in the database and can simply be selected in the **CURVE** list. Alternatively, **Set from File System** can be used to point directly to a disk file. Confirm the assignment with **Set selected**.

The additional curve association options available in the selection list are useful for PXMOD batch processing:

To view the association available for a particular image please select select the image in the **Series** list, and activate the ⚟ button.
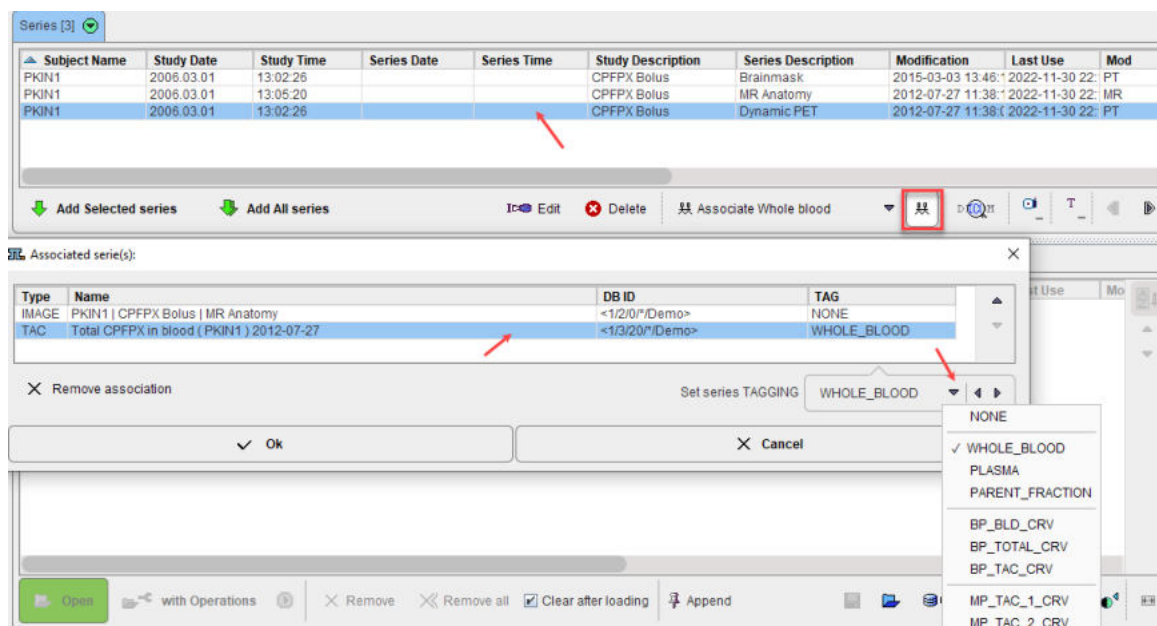
In the example above the **Dynamic PET** is associated to the selected **Whole Blood** curve.

5.3.6.4   Automatic Association

PMOD supports automatic image association using the **Project** field. The **Project** field assignment can be done manually on the **DB Load** page for each image series using the **Assign to Project | Group** option as illustrated below:
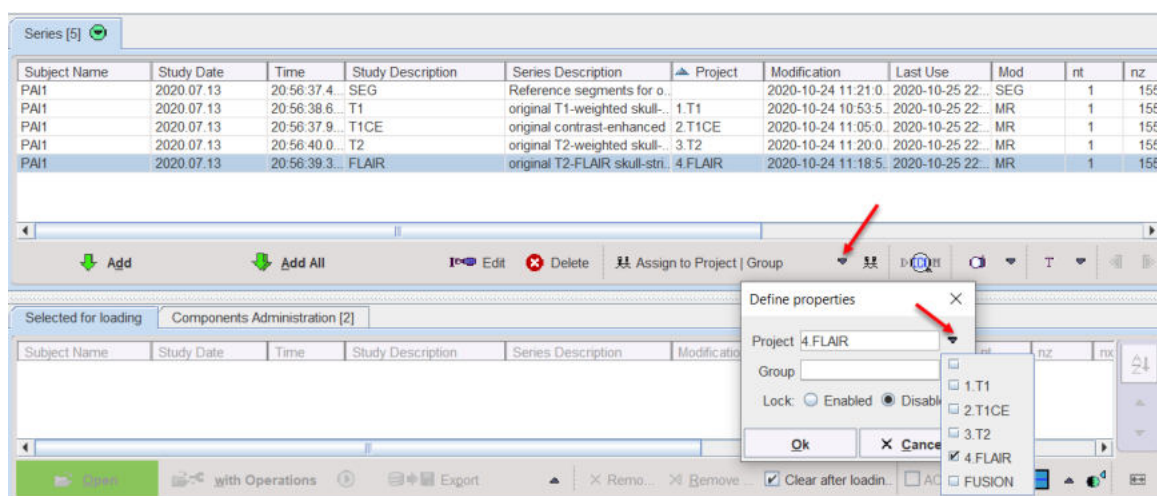
Use the **Project** text field to edit the project name or select one of the already available projects. Each time a new project name is used it will be automatically added to the selection list. Confirm the setting with the **OK** button.

PMOD support automatic project assignment when importing by Autodetect images using the incoming folder. Please refer to the dedicated section described in details <u>here</u> 45.

With all the **Project** definitions available select the entries in the subjects list and activate the **Associate Image Automatically** option available under the **Subjects** list in the **DB Load** page as illustrated below:
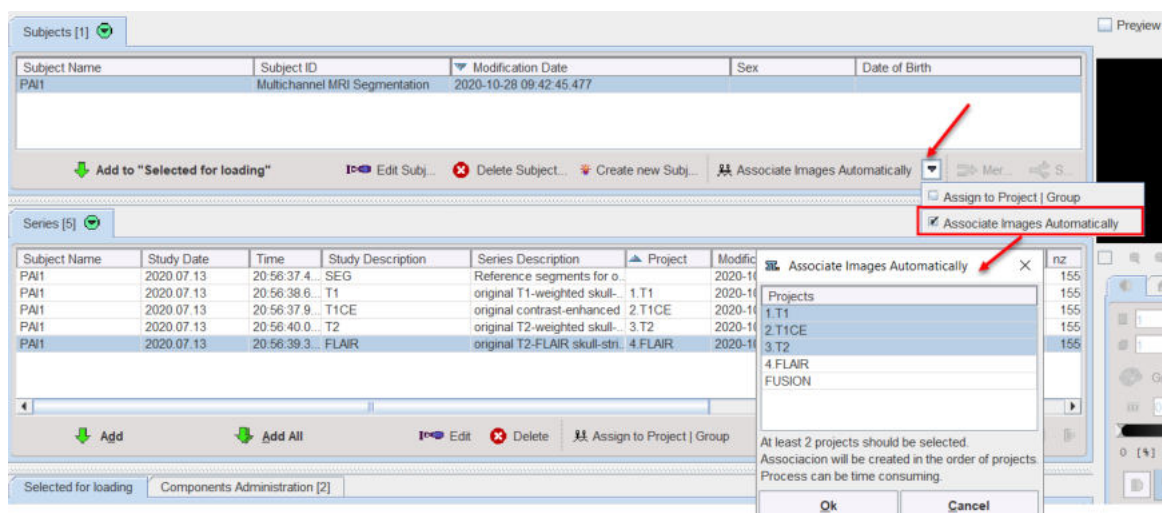
It is mandatory to select at least 2 projects. The association is generated in ascending order of the selected projects for the selected subjects. Please note that when multiple subjects are involved the process might become very time consuming. The main application is represented by the preparation of the training set for the machine learning.

5.3.6.5 Inspecting Associations

To find out which components are associated to an image series please select it in the **Series** list and activate the button indicated below.
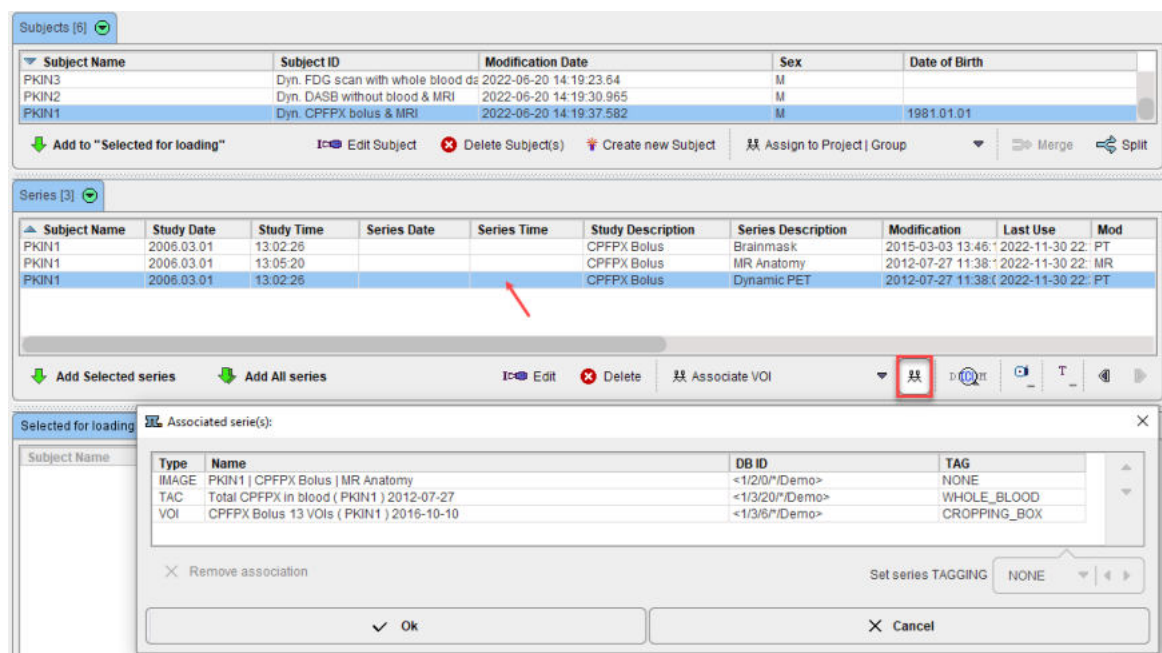
Note that if a processing refers to the associates of a series, it will used the first entry in the list if there are multiple entries with applicable definition.

5.3.7 Administrative Tools

There are four buttons on the **DATABASE** panel of the PMOD configuration page for performing administrative database tasks.

Their function briefly:

- **Data Base Administration**: Check database integrity, export data into an external directory or zip archive, replicate data between databases, modify attributes.
- **Database Reports**: Investigate the database contents, e.g. find out the number of subjects, studies, series, and list/print the subjects contained in the database, filtered using criteria such as gender, weight, etc.
- **Aggregate Components**: Export the data of certain component types, and generate tables with the VOI statistics or Kinetic Modeling results from multiple studies.
- **Create Norm**: Build normal databases from a number of healthy control subjects. There are two optional tools available, one for brain databases (PNEURO Tool), the other for cardiac databases (Cardiac PET Tool). Their creation is explained in the respective User's Guides.

5.3.7.1   Database Administration

The interface of the Data Base Administration tool is almost the same as explained in the section image loading from the database ₆₂.
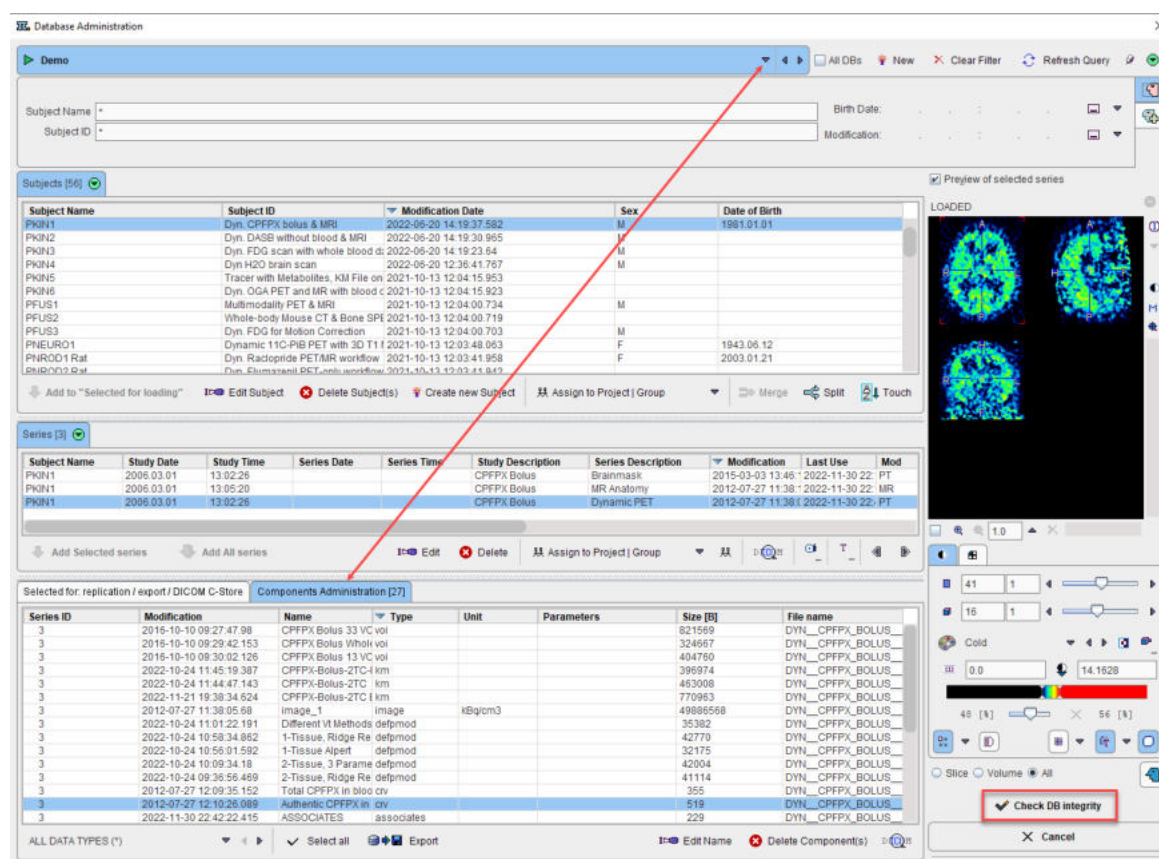
The following elements are additional:

Check DB integrity	When the button is activated the contents of the currently selected database is checked. If integrity constraints are violated, a dialog window is shown which allows fixing the problem.
Selected for: replication / export / DICOM C-Store	This tab is used for the backup of data as described below.
ALL DATA TYPES (*)	Selection to filter specific types of data, e.g. to list only VOI definitions, kinetic modeling files,

	etc. This element is not visible on the **Selected for: replication/...** tab.

> **Note:** For switching between databases the **Components Administration** tab must be selected. The reason is that only data from a single database can be used in backup procedures.

5.3.7.2 Export of Database Contents

There are different mechanisms for exporting data maintained by a PMOD database. This functionality is only visible on the **Selected for backup or replication** tab. The options can be found on the configuration button in the lower left bottom.

Replicate to	Copy data from one database to another online database.
Edit and Copy to	Allows editing and copying data from one database to another online database.
Move to	Copy data to another online database and delete the original information.
Export DICOM	Copy data to a directory.
Export anonymized DICOM	Copy anonymized data to a directory.
DCM C-Store	Sends all selected images to a DICOM server.

Export anonymized DICOM

To export images from a database using **Export anonymized DICOM** option, the following steps must be performed:

1. Select the source database from which data should be exported. The **Components Administration** tab must be selected for switching databases.

2. Activate **Selected for: replication/..** tab.

3. "Select the subjects(s) to be backed up, then activate the **Set as "Selected for Loading"** button. To incrementally add more data, select subjects/series and then activate the **Add** or **Add all** buttons. Note that image and component data are backed up with this procedure.

4. Configure the operation selection to **Export anonymized DICOM**. A dialog windows appears listing the series selected for export. A DICOMDIR can optionally be created which lists all image data, and the whole information can be packed into a zip archive.

5. Finally activate the **Export to File system** button. The selected components are exported to the selected output directory and organized in a hierarchical structure, so that all data belonging to a study end up in a common directory tree.
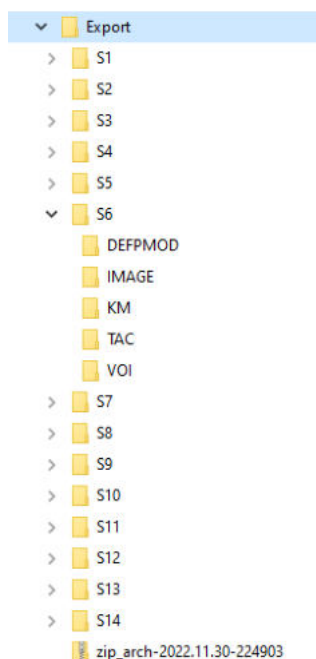
5.3.7.3 Replication from one Database to Another

Data replication is a method to copy data between two PMOD databases without any interactive loading/saving operations. The preparation steps are the same as for export DICOM data. But instead of selecting the backup option button, the **Replicate to** button is selected and the appropriate target database configured among the available ones.
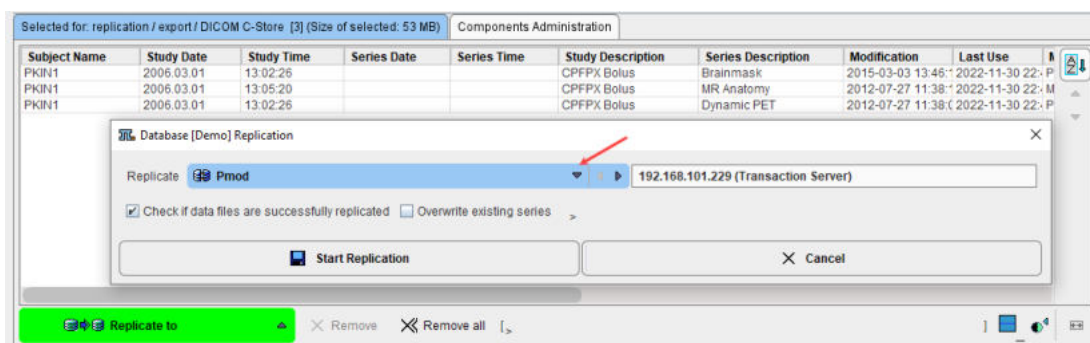
Activating **Replicate to** will then copy all selected data to the target database. For instance, data related to a single project could be copied to a newly created dedicated database, which will provide a faster response to queries than a big general database.

The **Move to** button also performs a database replication, but additionally deletes the source data after successful replication.

5.3.7.4 External Backup Procedure

For the purpose of having a backup in the case of a disaster, we propose the following simple and fast procedure:

1. **Back up of the database tables.** To this end, automatic backups can be defined in the configuration section of the data sources 56.
   Another alternative is to directly backup the relevant SQL database directory, in Windows for example:
   C:\Pmod4.4\data\DATABASES\dbname for JavaDB databases

2. **Back up of the data directory**. All data files reside under a common directory. So after the database tables have been saved, copy this directory to a different disk as a data backup.

5.3.7.5 Aggregation of Components such as VOIs and Kinetic Parameters

Over time, the database may collect a large amount of data. The **Aggregate Components** tool allows summarizing and extracting data of a specific component type such as VOI statistics, kinetic modeling parameter files etc.

The example below shows how VOI STATISTICS results can be exported. After selecting the component type **VOI STATISTICS** all corresponding results are listed.
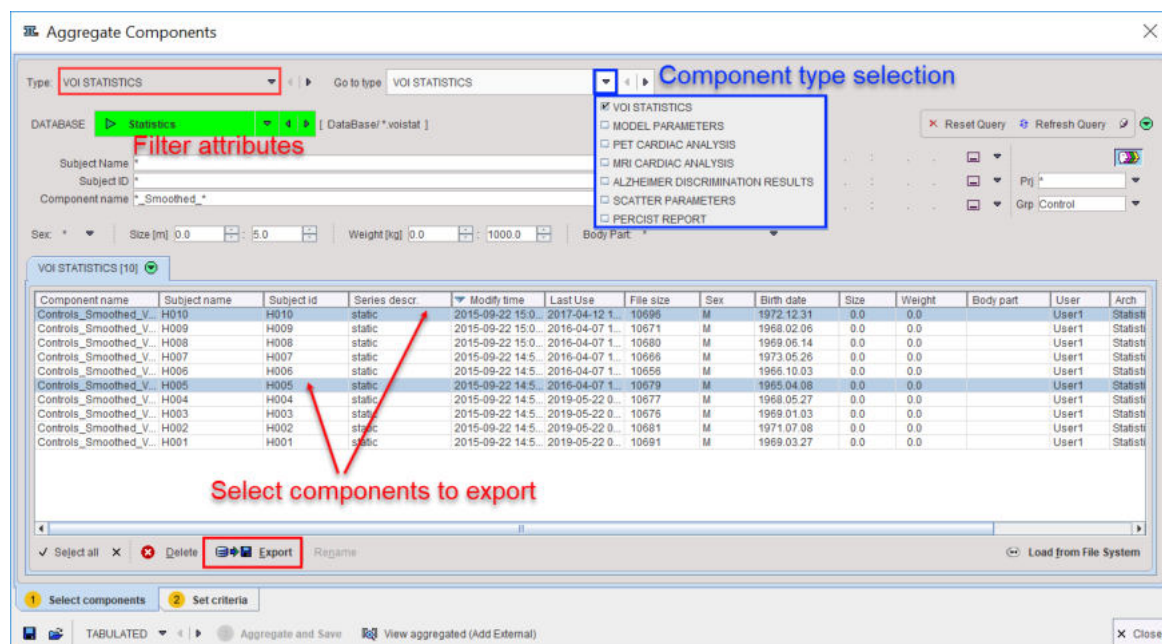
The list can further be filtered using demographic or project attributes. Then select the results to be exported (CTRL+A for *Select all*), right click on the list, and activate the appearing **Export** button. The files are then saved into a directory which can be specified. Similarly, other types of derived component data can be exported.

More sophisticated operations than a mere file export are available for *VOI statistics* (.voistat), *Model Parameters* (.kinpar), *Pet Cardiac Analysis* (.pcardRes), *MR Cardiac Analysis* (.mcardRes) and *Alzheimer Discrimination Results* (.palzRes). If either of these types is selected, the **Create** tab become active. Its purpose is to compile the results contained in multiple files into a comprehensive table (.dbTab), which can be exported for further analyses or loaded and sent directly to Pmod-R interface for statistic analysis. Note that this type of analysis is most effective if consistent naming conventions (same region names) are obeyed.

5.4   On Start

The **On Start** page contains some global layout options.
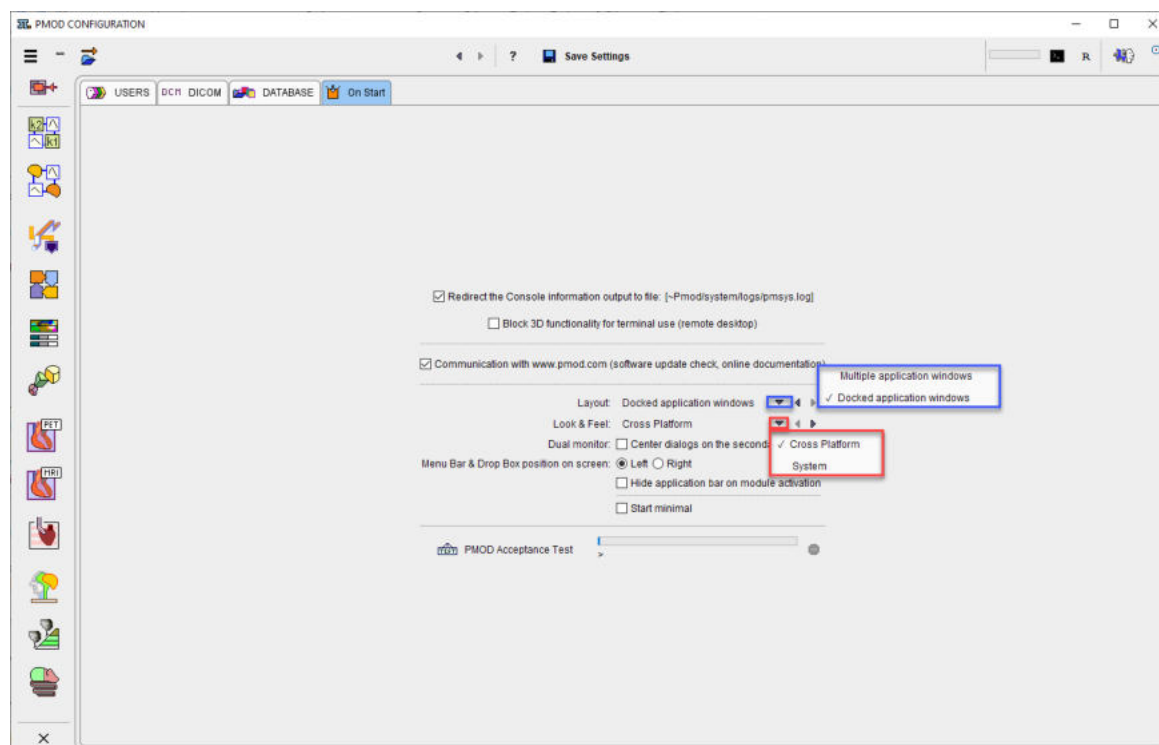
Log File

If the box **Redirect the Console information output to file** is checked, the program messages are saved in the file system/pmsys.log rather than shown in the console window. This is helpful in the case of problems because it can be submitted to the PMOD support as part of a problem report.

3D Functionality

The 3D functionality is not working when PMOD is used via remote desktop. Please enabled the the check-box **Block 3D functionality for terminal use**.

Communication with ...

This settings allows automatic notification about new build/version available. A down green arrow on the main PMOD toolbox appears and its activation shows a detailed message.

Please note that it is mandatory to have internet connection active on the PMOD installation system. When internet connection is not available it is recommended to turn off this box.

Layout

Starting with version 4.4 the the PMOD tools are docked, reducing the number of windows used in the analysis workflows. The **Docked application windows** is representing the default layout configuration at start. To switch to the legacy layout select the **Multiple application windows** option and restart PMOD

Look and Feel

The appearance of the PMOD user interface is dependent on the operating system, and on the selected **Look & Feel**. In principle, the Cross Platform and the System choices are available. However, on the latest Mac OSX systems, Cross Platform is not supported any longer by Java.

Dual Monitor

When the check box is enabled allows centering the dialogs on the second monitor.

Menu Bar ...

The **Menu bar & Drop Box position on the screen** can be set to the **Left** or **Right** side of the docking interface by selecting one of the radio buttons and restarting PMOD.

With **Hide application bar on module activation** enabled, the application bar will be hidden in the background once a PMOD module is started. Hoovering with the mouse button on the left or right side of the docking interface (according to the setting above) will activate back the menu.

Start minimal

With this box enabled PMOD will start displaying only the top line of the docking interface:
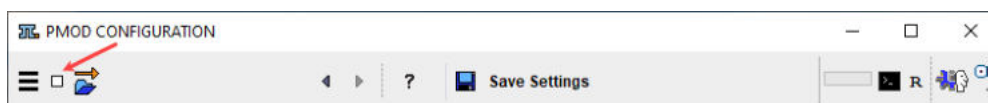
Activate the idicated Maximize button to show the full content of the docking window.

PMOD Acceptance tests

Starting with version 4.2 PMOD implements acceptance tests for all modules. They test that the functionality works properly after installation. All tests can be initiated at once from the "On Start" panel in the configuration using the dedicated button.

Activating the PMOD Acceptance Test a confirmation window appears with important information as illustrated in the capture below:
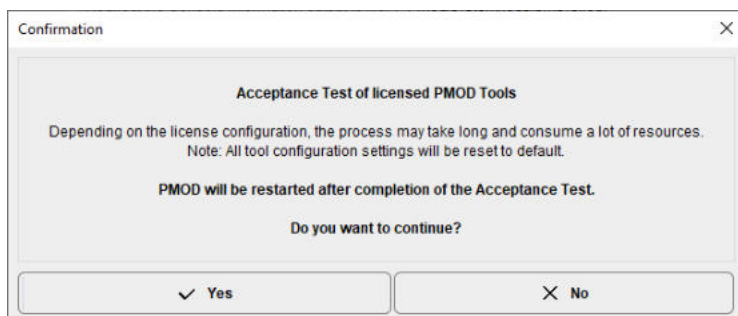
To run all the acceptance tests close the dialog window with **Yes**. Otherwise use the **No** button.

At the end of the test a report window is available showing the acceptance test results for all the available modules:
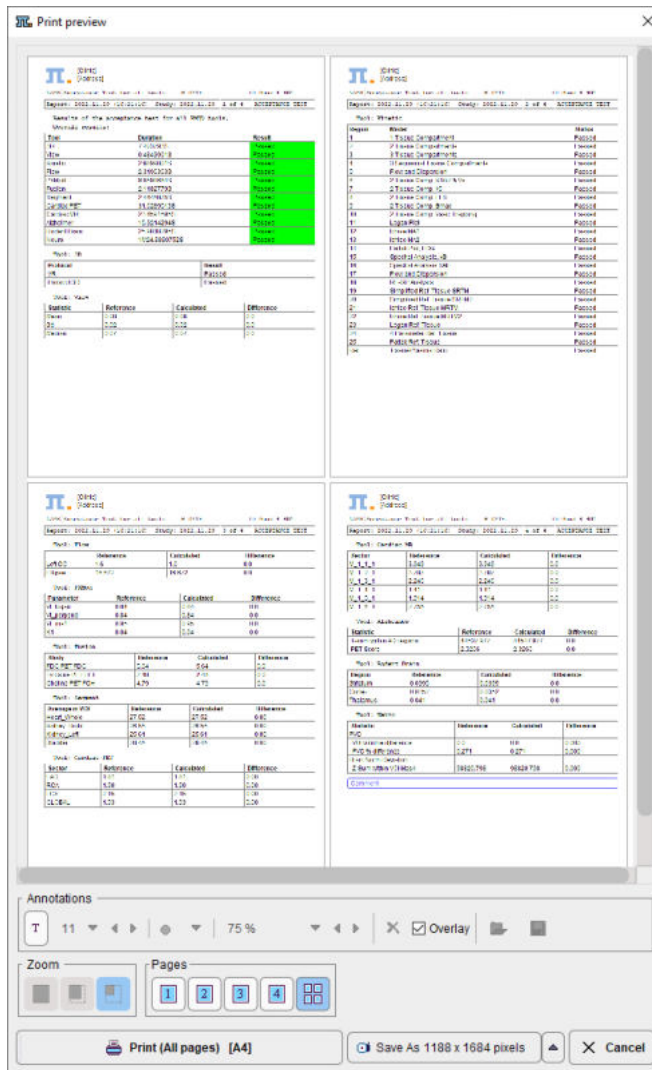
The report can be printed or saved as images.

6   PMOD Server Administration

There are three types of server processes which can be used as part of PMOD:

- <u>DICOM servers</u> 39 : They are able to receive data from external DICOM systems and store them in a PMOD database or in a directory structure.

- Database servers: These are processes that interface to actual <u>PMOD databases</u> 54 . They are called <u>transaction servers</u> 59 (TS) because they offer to PMOD clients transactions like retrieving data, saving data, moving data between databases etc.

- License servers: They are used for managing the licenses of a PMOD network installation.

For each of the server process a command script needs to be created at the time of system configuration. In production, the servers need to be started first, before using PMOD for data processing. This can either be done by executing the scripts individually from a command window or by calling them from within a system script. An alternative is to use the PMOD server administration tool described below, which offers the additional advantage to monitor the processes at runtime. It is particularly valuable when using multiple server processes.

Script for the PMOD Server Administration

The server administration tool can be called by adding the **-admin** flag to the command for calling PMOD. Most conveniently, the **RunPmod** script is copied, renamed to **RunAdmin,** and edited adding the flag. Example for the Windows platform:

```
D:
cd "D:\Pmod4.4"
.\java\jre\bin\java -Xmx16000M -jar pmod.jar -admin
```

Server Administration User Interface

When calling **RunAdmin**, a tailored ToolBox appears.
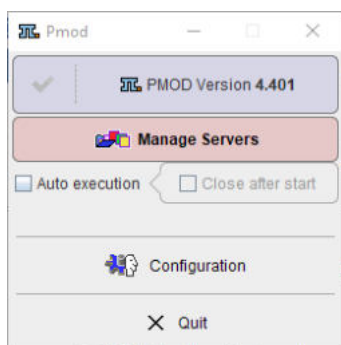
Configuration opens the standard configuration |₃₁| panel of PMOD.

Manage Servers opens the interface for the server administration illustrated below in a situation where no servers are running.
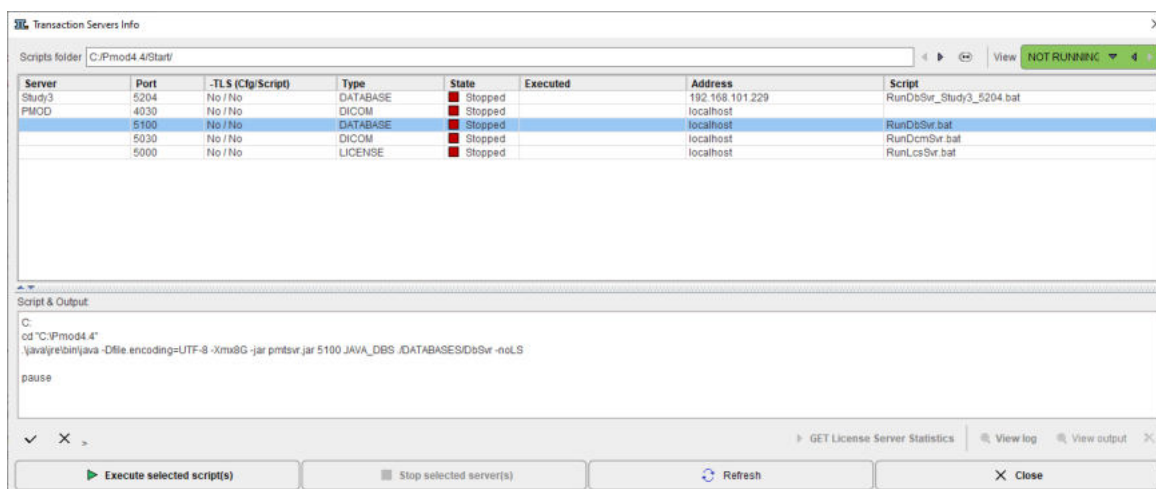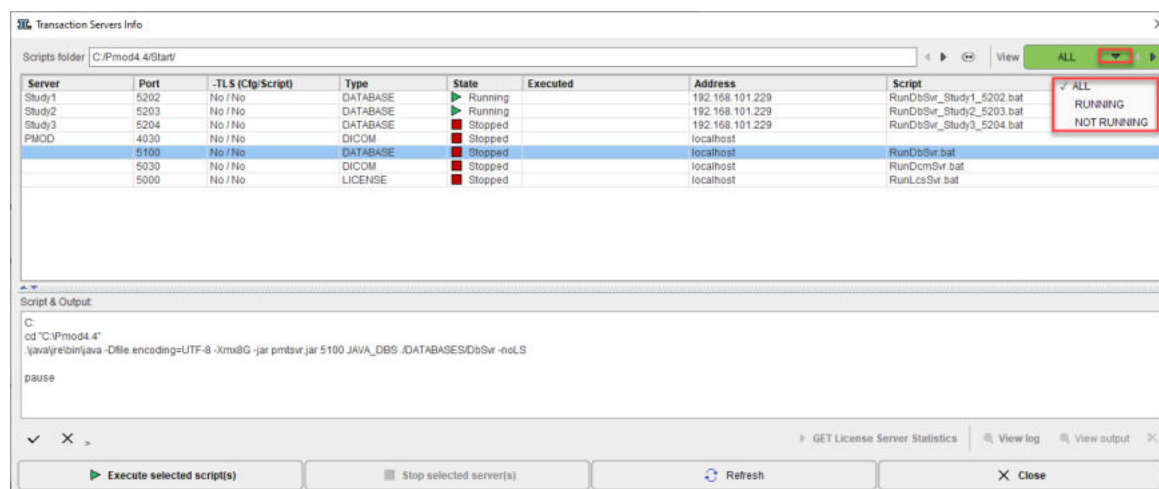
Note the **Scripts folder** which indicates to the tool where the server scripts are located. If needed, the path can be adjusted using the button. The scripts are analyzed and compared to the running processes to find out about the status of the server.

The **Server** list summarizes on each row a server process. It indicates the **port** used, whether encryption is applied (**-TLS**), the **Type** of server (**DATABASE**, **DICOM**, **LICENSE**), the state (**Stopped**, **Running**), whether the script was **Executed** from the administration tool, the **Address** (localhost, or IP number) and the name of the **Script**. The content of the selected script is shown in the **Script & Output** area.

If the **Auto execution** flag is checked, all non-running servers are immediately started when activating **Manage Servers**. With **Close after start** the user administration user interface is closed after the starting operation.

Server Starting/Stopping

To start a server process which is not running (**Stopped**) select it in the list, then activate **Execute selected script(s)**. The script contents, which is shown in the **Script & Output** section is executed, and the list updated. Illustrated below is the situation after three servers were selected and executed.

Note the **View** filter in the upper right which allows listing only servers in a specific **State**.

When selecting a **Running** server, its output during startup is shown in the **Script & Output** area.

This information can also be opened in a dialog window using the **View output** button. If the script contains the **-o** option, the server output at runtime will be directed to a log file, *pmtransvr_5204.log* in the example above. **View log** opens a window for inspecting this output conveniently, as illustrated below.
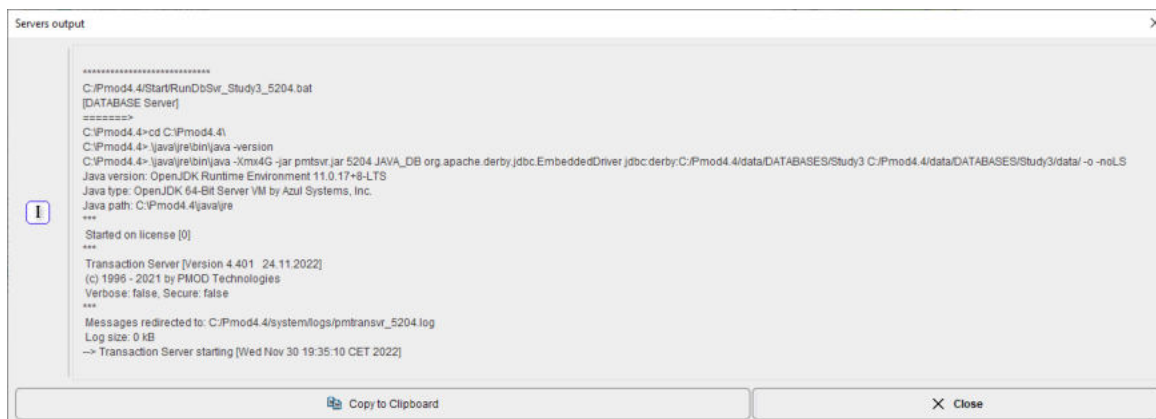
To stop a running server select it in the list and then activate **Stop selected server(s)**. It will be shut down gracefully, completing first any pending transactions.

Ending the Administration Interface

The **Close** button ends the current administration session. However, it will not shut down any server processes. They will continue running until they are explicitly stopped from the interface or from the system level. Correspondingly, they will be shown as **Running** processes the next time the server administration tool is started.

7   Tool Configurations

Each PMOD tool also has individual configuration settings which tailor it to the user's needs. These settings dialogs can be accessed by using the menu **View/Settings/Modify** entry or directly by the ⌐ button
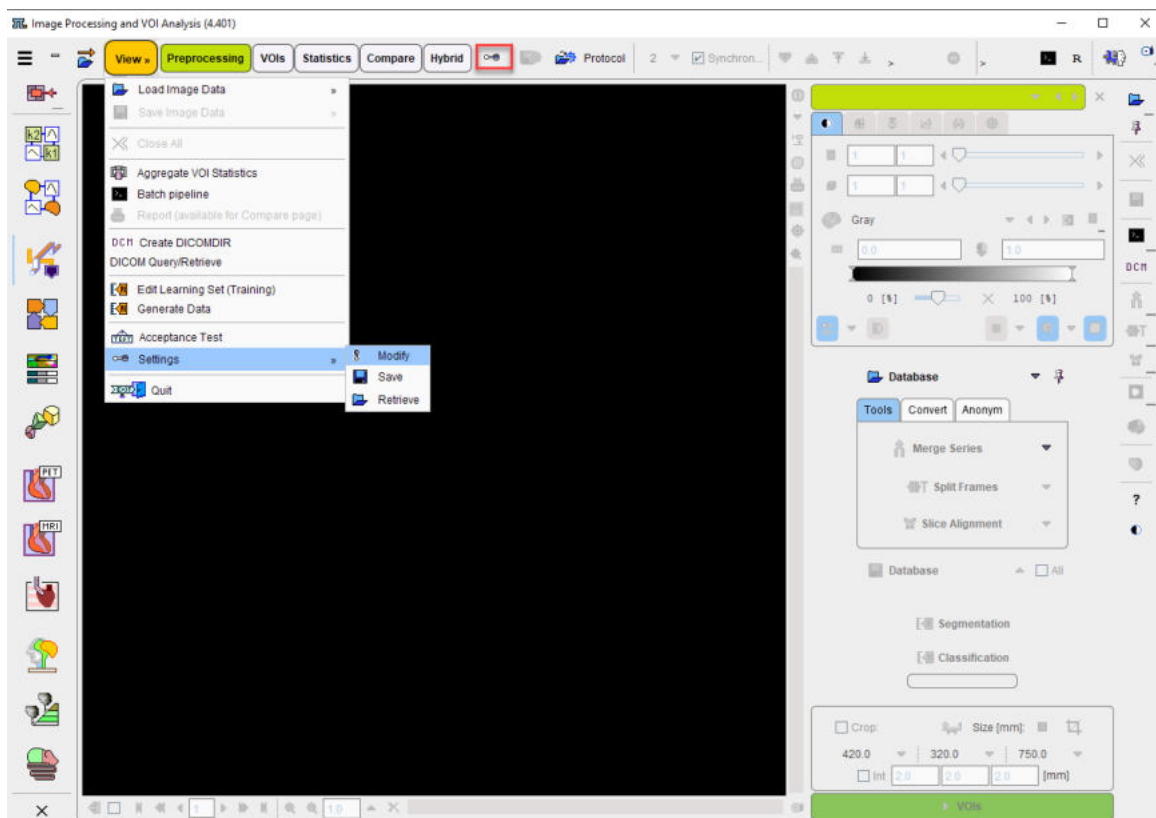
in the top line menu of the tool. The example below shows the settings dialog window of the viewing tool.
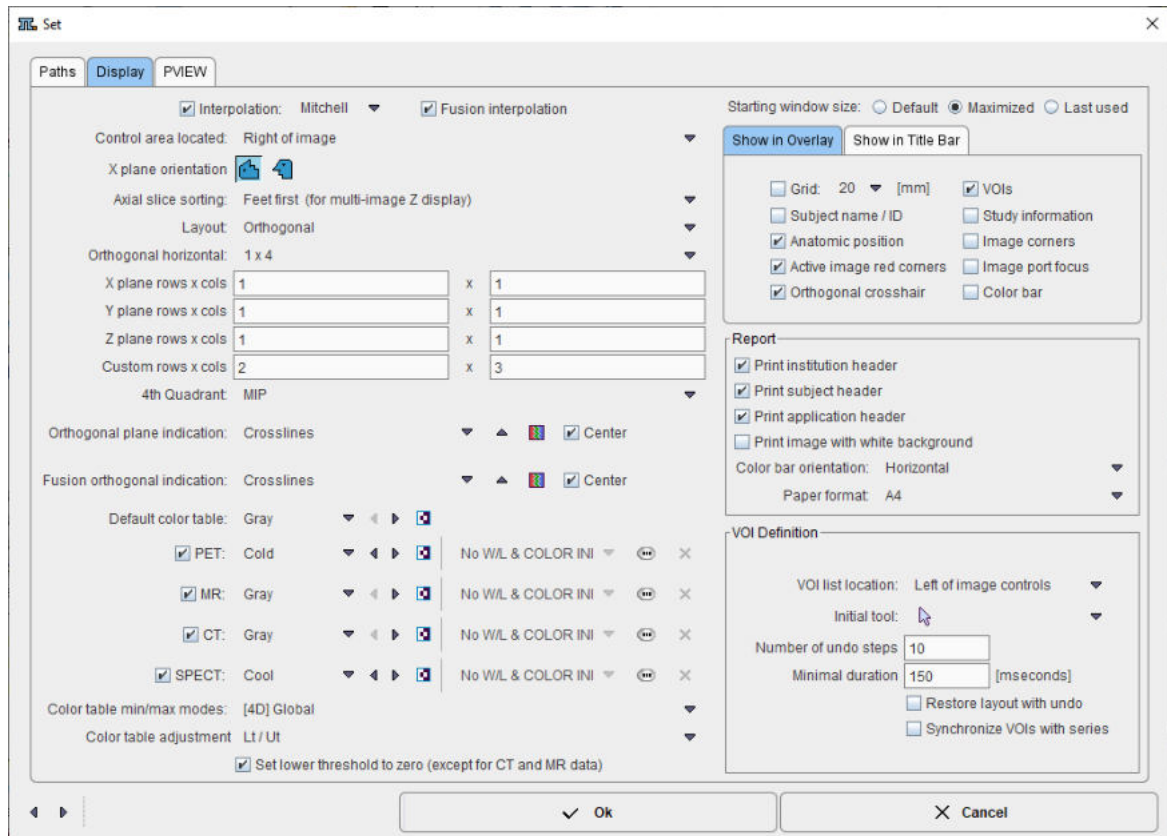
The **Paths** tab contains the default input format definition, the default output format definition, and the data paths.

The **Display** tab depends somewhat on the tool. It is mainly used for

- tailoring the initial appearance such as the size and location of the tool,
- the default image layouts and color table properties. Note that different colortable can be set for different image modalities.
- the organization of the VOI toolbars for optimal arrangement depending on the screen size, and
- configuring the contents of the report page.

The last tab, in the example above **PVIEW,** is completely tool-specific.

When the **Ok** button is activated the settings are saved and will serve as the starting configuration when the tool is opened the next time.

8 Data Loading and Saving

The PMOD tools are able to read and write different types of image data. It is important to understand that *correct data units and acquisition timing information is required* for quantitative processing steps to derive meaningful results. As an example: In quantitative PET studies a tracer is injected at time 0. At the same time a series of image acquisitions is started, and arterial blood samples are withdrawn in certain intervals. The images are needed to monitor the time-course of tracer distribution in tissue. The blood samples are analyzed to determine the unchanged tracer in plasma, the input curve during the acquisition. The tissue response and the input curve are fed into kinetic models to quantify certain properties of the tissue under investigation. For applying the model, the image and blood units must be calibrated and the times must be measured in a common time scale.

In some image formats the data units are saved with the data (eg. DICOM, Ecat). With these formats the units are automatically detected upon loading into PMOD. Otherwise the user must select the

correct units for the data and specify the acquisition timing. During loading, PMOD converts activity concentration data to its internal units, ie. kBq/cc and seconds. The appropriate scale factor is derived from the specified input units. As a result, PET images are always displayed in kBq/cc, and images are always saved with the displayed units. This has the consequence that if PET images residing in an Analyze format are loaded with units nCi/cc specified, and then again saved in Analyze, the values in the file are different, namely calibrated in kBq/cc. If this file is loaded, the units must therefore be specified as kBq/cc. These considerations do not apply if the image data are in DICOM. Therefore we highly recommend using the DICOM format, preferably in combination with the PMOD database.

Multiple transformations of the image data are supported during loading. The pre-processing capabilities include re-orientations such as orthogonal reslicing, rotations, mirroring, data processing such as smoothing or averaging over time, as well as the selection of subsets of the available slices and time frames.

Besides actual image data files PMOD is able to read and save a information needed for kinetic modeling from column-delimited text files (component data). These files may hold Volume-of-Interest definitions, kinetic modeling data, the configuration of the PMOD tools etc. They are either directly written as files into a directory, or to the database which saves the actual data into an internal directory and adds access information to the database tables. Component data reading/writing uses a unified interface which looks identical for the different component types.

It is helpful to remember that PMOD maintains three paths which are related to data loading/saving:

- DICOM path: the directory which PMOD scans in order to look for DICOM part 10 data files.
- Data path: the directory to load other image data types.
- Database path: the directory where to look for component data.

PMOD maintains a separate history for each of the three paths to rapidly switch between frequently used locations. If databases are used to manage the data, access to all types of data can be done through the database user interface.

Starting with version 4.4 PMOD implements a unified data loader [28] for the Scientific Data Management System (SDMS). It seamlessly integrates **DATABASE**, standalone **DICOM** data and **AUTODETECT** data loader for other formats within the same interface.

8.1   Image Data Formats

PMOD supports numerous image data formats in reading, and a subset also in writing. As described below the image formats have different properties. Some formats support information in addition to the image pixels such as:

- demographic subject information;
- subject positioning information which allows the derivation of the anatomical orientation in the images (anterior/posterior, left/right, head/feet);
- acquisition parameters such as the timing of a dynamic series which is essential for the modeling of the uptake;
- radiotracer information such as dose and radionuclide;
- image unit information.

8.1.1   Format Overview

The following formats are supported by PMOD. Their properties are summarized in the different columns.

Format	Read	Write	Units	Times	Write Precision	Patient Info	SUV Calculation Info
AFNI	yes	no	no	only identical duration for all frames	-	no	no
ANALYZE	yes	yes	no	only identical duration for all frames	16bit int (scaled), 32bit float	no	no
ANALYZE LPS	no	yes	Compatibility version to write images suitable for older PMOD versions				
ANALYZE SPM	yes	no	Compatibility version for reading SPM-generated images so that they are shown in HFS orientation (however, left and right are dependent on SPM settings)				
AVW	yes	no	no	no	-	no	no
BrainVISA	yes	no					
DICOM	yes	yes	yes	yes	16bit short (scaled), private objects with 32bit float precision	yes	yes, post-injection values only on private GE tags
ECAT 6	yes	no	yes	yes	-	yes	yes
ECAT 7	yes	yes	yes	yes	16bit int (scaled), 32bit float	yes	yes, during save no support for post-injection information
GE Advance	yes	no	yes	yes	-	yes	yes
Graphic	bmp, jpeg, tiff	jpeg	no	no	RGB	no	no
HIDAC	yes	no	no	yes	-	no	no
Interfile	yes	yes	yes	for dynamic study	16bit int (scaled), 32bit float	yes, some information on private tags including patient size, weight, study description, body part	yes, on save only standard elements are populated (no time values or postinjection values)
Matlab	yes	yes	yes	yes	32bit float	patient name, id	no

					and study id only	
MicroPET	yes	no	yes	yes	-	yes	yes
Neurostat	yes	no			-		
NifTI	yes	yes	PMOD Files	PMOD files, otherwise identical duration for all frames	16bit int (scaled), 32bit float	only comments supported as series description	no
MINC 1	yes	no	yes	(yes)	-	yes	yes
Philips ImageIO	yes	no	no	yes	-	yes	yes
Philips par/rec version 4	yes	no	no	yes	-	yes	no
Paravision							
Raw	yes	yes	no	no	8bit int (scaled), 16bit int (scaled), 32bit float	no	no
TIFF	yes	yes	no	no	RGB	no	no
Varian FDF	yes	no			-		

8.1.2   Format Descriptions

Autodetect (Read only)

For users working with different image formats it may be cumbersome to remember the data format of the different files, which may have similar suffixes. The **Autodetect** format makes it unnecessary to select a specific format before image loading. The user can just select the file(s) he wants to load, and PMOD will try to find out the appropriate format based on the file contents (not on the suffix) when loading.

DICOM (Read/Write)

Image data according to the **DICOM standard**. As input data, the following Information Objects have been tested: CT, Enhanced CT, MR, Enhanced MR, NM, PET, Enhanced PET, SC, SC multi-frame true color, US.

PMOD's DICOM Conformance Statement describes in detail the DICOM support implemented in PMOD. It can be downloaded from the **Support** page on the PMOD Website.

Database (Read/Write)

Data loading/saving with a PMOD database. Image data are saved based on the modality: CT as Enhanced CT IOD, MR as Enhanced MR IOD, other images as Enhanced PET IOD.

Query (Read only)

This loading "format" is a shortcut for retrieving images from a remote DICOM server and directly loading them to the image display.

Interfile (Read/Write)

Interfile is a file format developed for data in Nuclear Medicine (Todd-Pokropek A, Cradduck TD, Deconinck F, A file format for the exchange of nuclear medicine image data: a specification of Interfile version 3.3, Nucl Med Commun. 1992 Sep;13(9):673-99).

There are two basic variants of Interfile. One variant has separate header (.hdr) and image (.img) files. This variant has the advantage that the header file can be viewed and edited with a simple text editor. The other variant includes all the information in a single file (.hdr). Both variants are supported in reading and writing, restricted to the subset of data objects which are relevant for PET.

Ecat 6/7 (Read/Write)

Data format of PET data from older CTI/Siemens systems. It is a self-contained format containing all acquisition information.

When loading Ecat data an additional choice appears to explicitly define the units of the subject dose values. This facility was introduced because Ecat files without well-defined units were encountered. Experience has shown that the *Bq* unit should be selected to arrive at the correct doses, but other examples were also encountered. The dose value is important for the SUV calculation and can be checked on the SUV-related panels.
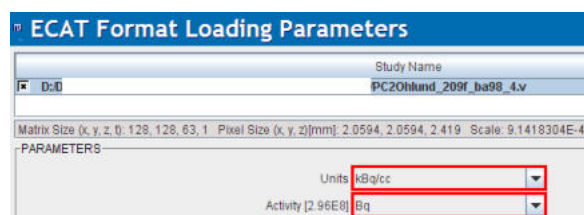
When saving data in the Ecat format, after the specification of the file name, a dialog is presented to the user with a choice of transfer syntaxes. They define the byte ordering used for saving the data. In case you want to read the images using a program other than PMOD, you are recommended to select a *big-endian (BE) encoding*.

MicroPET (Read only)

Data format of the Siemens Inveon and MicroPET **preclinical systems**. It is used both for PET and CT data.

NifTI (Read/Write)

Extended **variant** of the analyze format by the Neuroimaging Informatics Technology Initiative. Both single file (.nii) and double file (.hdr + .img) images are accepted but only in uncompressed form.

PMOD reads the following NIfTI data types:
8-bit unsigned and signed byte (DT_UINT8 and DT_INT8), 16-bit unsigned and signed short (DT_UINT16 and DT_INT16), 32-bit unsigned and signed int (DT_UINT32 and DT_INT32), 32-bit float (DT_FLOAT32), 64-bit double (DT_DOUBLE) and 24-bit RGB (DT_RGB). 64-bit double data are rounded to 32-bit float representation. Up to 4D data is supported, meaning PMOD does not accept files with the 5th dimension greater 1. Only a single value or a single RGB triplet per pixel is supported. If qform_code > 0, PMOD uses qform matrices, otherwise if sform_code > 0 sform matrices will be used. When neither is defined data orientations remain undefined in PMOD. PMOD does not support any extensions nor NIfTI statistical codes. Gzipped images must be uncompressed prior to their usage with PMOD.

NlfTI images produced by SPM require A/P mirroring (**TOP to BOTTOM** sorting) to get them into HFS position. Other NlfTI images should best be loaded with **Reorient to Standard Orientation enabled** 109.

In writing, PMOD supports the variants with two files (header information in *.hdr, image data in *.img) or a composite file (*.nii). The single file variant is required when preparing atlas template images.

Analyze (Read/Write)

Data in the **Analyze 7.5 format** consists of two files. The header file (*.hdr) contains information about dimensions, pixel representation (transfer syntax) and value scaling. The data file (*.img) contains the pixel data itself without any header offset. Value units and information about acquisition timing must be manually entered, or can be loaded from definition files.

SPM produced Analyze files are usually L/R mirrored. Such files require a 180° rotation about the z-axis s to get them into the radiological head first supine (HFS) position which is the PMOD default.

Note: Analyze has the possibility to include timing information, but only for a single frame. If a timing is specified in the file it will be applied for all frames of a dynamic study, even if a different timing was specified using Edit Times in the user interface. In such cases it is advised to load the image data, change the timing, and save the images again in a format wit better timing support (DICOM, Ecat, Interfile). PMOD writes Analyze files without timing information.

AVW (Read only)

Newer version of the Analyze format.

Raw (Read/Write)

A raw image file which holds only the pixel data. All additional information must be edited manually. Different types of number encoding (byte, signed and unsigned short integer, float) and byte orders (big/little endian) are supported.

Graphic (Read/Write)

Graphic images in **jpg**, **gif** and **bmp** can be read. When writing as a **Graphic** file, the **jpg** format is used.

TIFF (Read/Write)

The graphic tiff format is treated separately and can be read and written.

Matlab (Read/Write)

Image data can be read which has been prepared and saved in Matlab using the `save -V4` command (Note: only Matlab version 4 format is supported, thus the requirement of the `-V4` option). The following Matlab variable names/contents are expected:

- `dim[nx,ny,nz,nTime]` (number of columns, rows, slices, acquisitions)
- `vox[xSize,ySize,zSize]` (voxel sizes in mm in all 3 dimensions)
- `orig[xOrig,yOrig,zOrig]` (position of the origin measured in mm from the top left corner of the first slice)
- `time[1,...nTime]` (times when the acquisitions started)
- `timeEnd[1,...nTime]` (times when the acquisitions ended)
- a series of value vectors named `v1s1` till `v21s35` when `nTime=21` and `nz=35` (`v` denotes acquisition number and `s` slice number)
- `subjectName[]` (string with subject name)

- subjectId[] (string with subject ID)
- vUnits[] (string with value unit name)
- tUnits[] (string with time unit name)

Note that only the variables dim and v1s1 etc. are mandatory.

Neurostat (Read only)

Neurostat uses the Interfile format (.hdr, .img) to save the 8 surface projections into an image file. Please note, that this is not a volumetric data set, and therefore should be viewed in a *planar layout* such as 2x4.

AFNI (Read only)

AFNI (acronym for Analysis of Functional NeuroImages) creates two-file data (.HEAD, .BRIK).

GE Advance (Read only)

Data format of PET data exported from GE PET systems (Advance, Discovery) with the *Investigator* utility. It is a self-contained format with all acquisition information.

Philips (Read only)

Mosaic data format of PET data from Philips PET (Allegro, Gemini) and older GE Quest systems.

When PMOD recognizes more than one unit defined in the file the loading dialog window shows a choice selection for the user to choose which units will be loaded from a file, providing different range of values.

HIDAC (Read only)

Data format of the (historic) animal PET system HIDAC (Oxford Positron Systems). *To be retired.*

BrainVISA (Read only)

Format used by the **Brainvisa software**.

Varian FDF (Read only)

Flexible Image Format of Varian MR systems.

8.2   Image Data Loading

In most tools there are four different ways to load image data:

1. By **dragging** an image file from the desktop onto a tool button on the PMOD application bar. PMOD will try to recognize the data type and read the images accordingly. If it is a data format without header information the information from the last successful loading operation will be applied.

2. By using the unified data loader or the **Load** page (see here 62 for configuration) that seamlessly integrates the options to load **DATABASE**, standalone **DICOM** data and **AUTODETECT** data loader for any other formats:
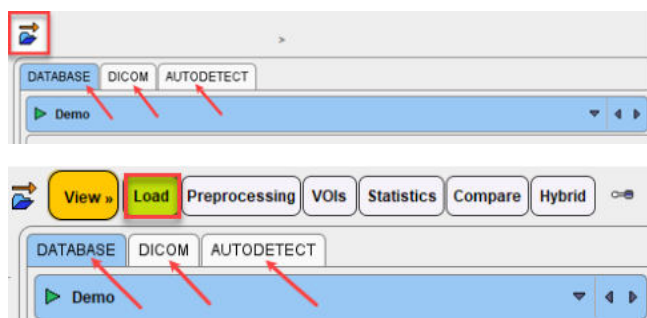
3. By selecting the appropriate format from the menu **View**/**Load Image Data**, eg
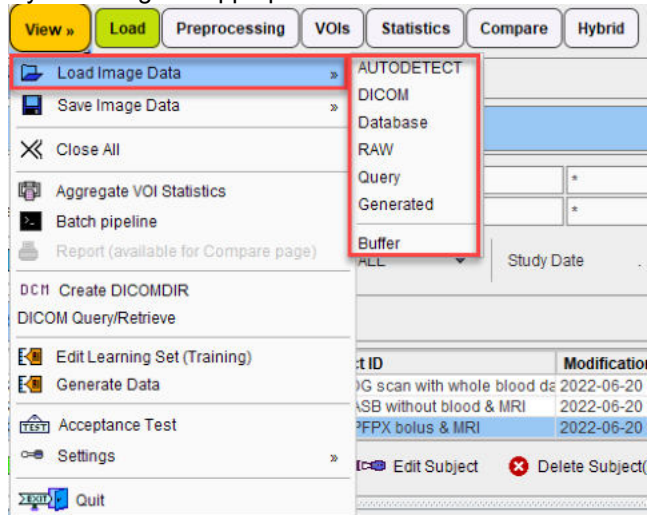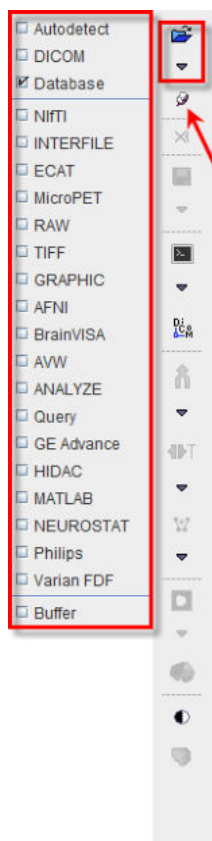

4. By configuring a multi-function **Load** button
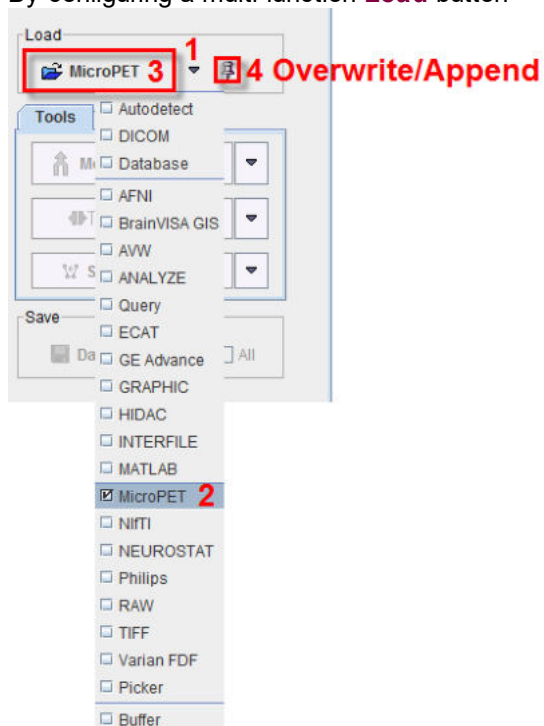
to the correct type. The loading operation will be immediately started.

5. By selecting and configuring the appropriate format in the lateral taskbar using the **Load** button

In many situations (indicated by the pin besides the format selector, 4) it is possible to load several files into a tool. In this case multiple file names can be selected in the file selection box, or multiple image series in the database loader. If images have already been loaded and the pin is fixed 🖈, the newly selected studies will be *appended* to the present one(s). Otherwise the prior studies will be overwritten.

8.2.1 Data Units

For any quantitative PET work you have to make sure that the right *input data* units are specified if the data is not read from DICOM, ECAT or the database. Activity concentration values are always converted to the internal representation of kBq/cc during a read operation. If the data is saved again, the *values after conversion will be stored.* Additionally, the acquisition times must also be specified. There is a facility for saving/retrieving timing protocols in all tools which load image data.

8.2.2 Database Loading

Database loading of images has already been described <u>above</u> 62.

8.2.3 DICOM Loading

When loading DICOM data, the directory of the last DICOM loading operation is referred to. If the **Skip scan at start** box is not checked, PMOD searches for DICOM images in the directory when the dialog windows opens. In case there are many files in a directory, the scanning process may take substantial time. This is annoying if the data to be loaded resides somewhere else. To avoid initial file scanning, the **Skip scan at start** box can be checked. The user can then locate the proper directory with the **Change Folder** button and activate the ♻ button to initiate scanning for DICOM files. If no DICOMDIR exists, all files of the directory are scanned and all valid DICOM series listed.

If a DICOMDIR file exists in the directory, it is parsed and the registered image series presented for loading. As a consequence, all non-registered DICOM files in the same directory are neglected.

The DICOM loader presents the selection of the available image series in a dialog window as illustrated below.
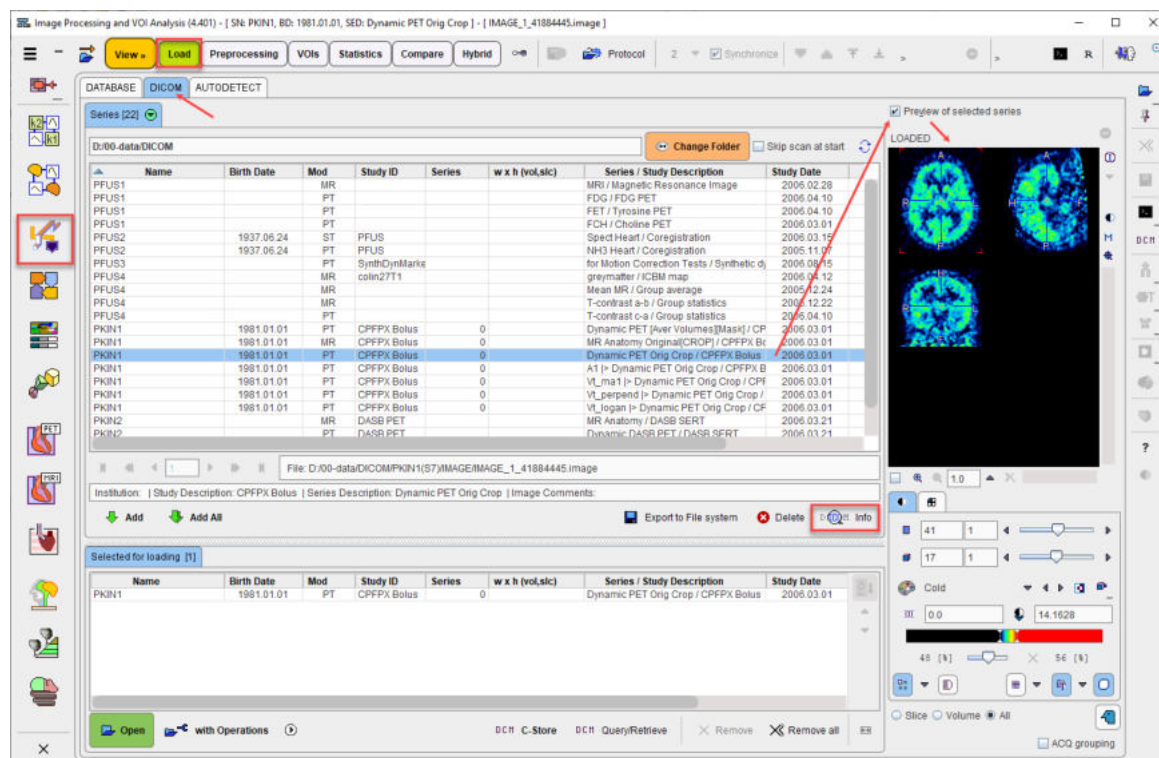
Select the series to be loaded, **Add**, and activate the **Open** button. Use **Remove** or **Remove all** to remove series from the **Selected for loading** area. Depending on the context, several series can be loaded at once, or the selection is restricted to a single series. Please note the **with Operations** button. If it is activated, the dialog window specifying loading transformations explained below is opened.

Sometimes the information shown in the list may be insufficient to identify a series unambiguously. To find out more about the selected series activate the **DICOM Info** button which opens a full DICOM data inspector. Another alternative is to use the **Image Preview** to the right: if the **Preview of the selected series** box is checked, the images are loaded as soon as a series is selected.

To modify the list order use the **Sort by selected column** button ![sort] or **Up** ![up] and **Down** ![down] buttons , or **Remove** ![x] a file. Optionally, **Remove all** using the ![xx] button allows removing all images available in the **Selected for loading** area.

The **ACQ grouping** box allows grouping the images in the selected series by the acquisition number, an optional sub-level beneath the preview panel. This is required to properly load some DICOM series, for example with CT studies which contain different reconstructions (different area/pixel) in a single series. With other series, however, acquisitions need to be displayed together, for example with whole body SPECT data covering subsequent bed positions in separate acquisitions. As there is no way for PMOD to determine the right interpretation, the user may choose between the two loading modes to solve unsatisfactory loading results.

DCM Query/Retrieve starts the dialog window for querying a remote DICOM node and pulling images from it as explained above 52 .

DCM C-Store is a utility for sending selected data sets directly to a remote DICOM server without the need to open it for viewing, and then selecting the **C-Store** saving button. Direct sending has the

advantage that the original DICOM images are transferred. Otherwise, if loaded images are sent, they contain information modified by PMOD.

Use the **Delete** button to remove all files belonging to the currently selected series from the disk.

Use the **Export to File System** to copy the selected series files to a target directory.

> **Note:** A new DICOMDIR including all DICOM studies in a directory tree can be generated using the **Create DICOMDIR** entry in the menu of the PMOD viewing tool (PVIEW).

8.2.4   File-based loading

For all non-DICOM type of image data the loading dialog looks like this example using the **AUTODETECT** format.
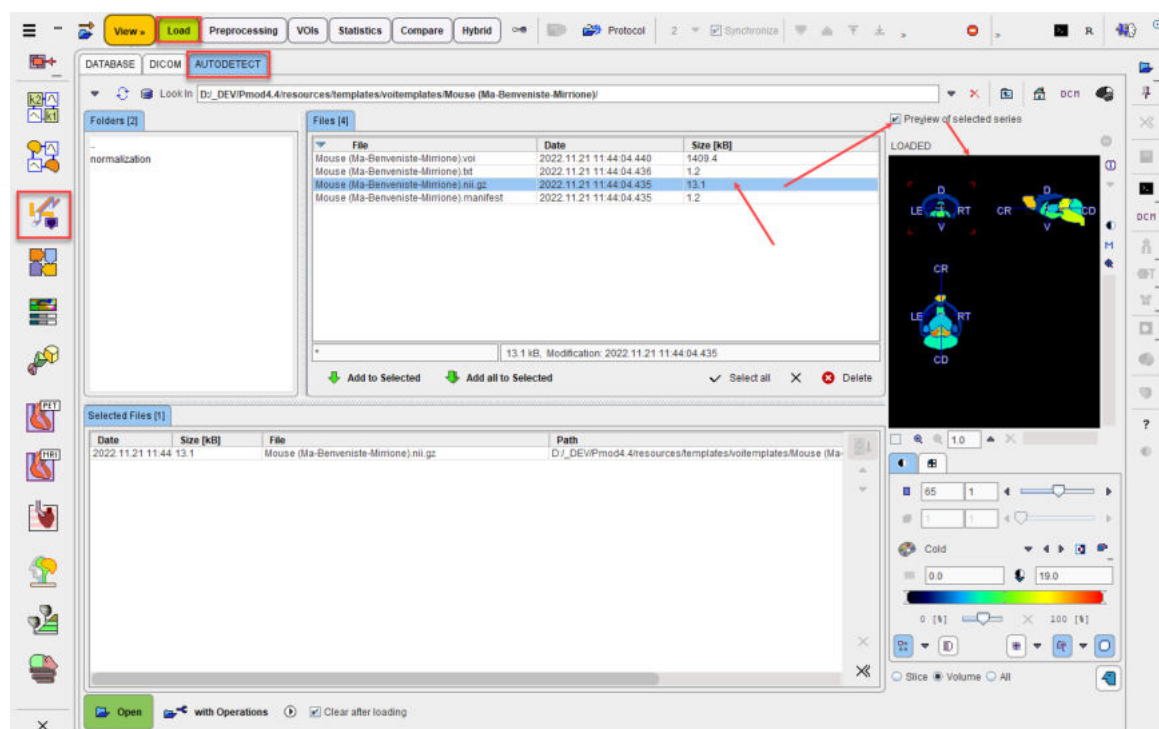
Use the navigation elements at the top to browse the directory hierarchy. The files to be viewed need to be brought to the **Selected Files** area by double-clicking, or by using the **Add to Selected** or the **Add all to Selected** button. Note that in some contexts multiple file selection may not be possible. In that case, only one file can be brought to **Selected Files.**

The images will be loaded in the order they appear on the list. This may be relevant in the fusion tool where the first image will serve as the reference, or if multiple static images are to be combined into

a dynamic study. To modify the list order use the **Sort by selected column** button $\overset{A}{Z}\downarrow$ or **Up** ▲

and **Down** ▼ buttons , or **Remove from selected** ✕ a file and add it later back to the end of the list. Optionally, **Remove all from selected** using the ✖ button allows removing all images available in the **Selected Files** area.

A preview facility allows inspecting images in the **Image Preview** to the right before loading them and continue processing. When the box **Image preview** is checked, the images are shown as soon as an item in the **Files** list is selected.

When **Open** is activated, the selected files are loaded directly. If **with Operations** button is activated, a dialog window is opened specifying loading transformations to be applied to the image as explained below.

If the **Clear after loading** option box is checked, the **Selected for loading** area is empty when loading the next time. Otherwise, it will show the same entries, which may be helpful when working with the same data repeatedly.

8.2.5 Loading Macros

Macros are applied as a data transformation during loading. To this end select one or several images for loading. Then, instead of using the **Open** button, use the ⊙ button next to it.
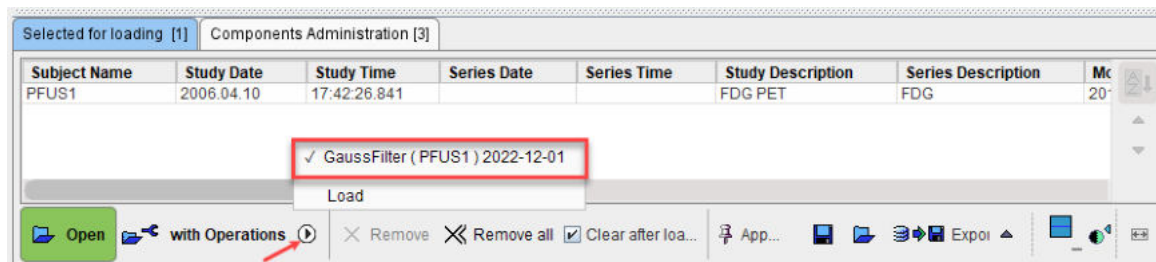
A list opens showing the currently available macros. To load a macro from a different source, use the **Load** entry. As soon as a macro is selected, the data is loaded, the processing steps applied, and finally a confirmation window **MACRO FINISHED** shown as illustrated below.
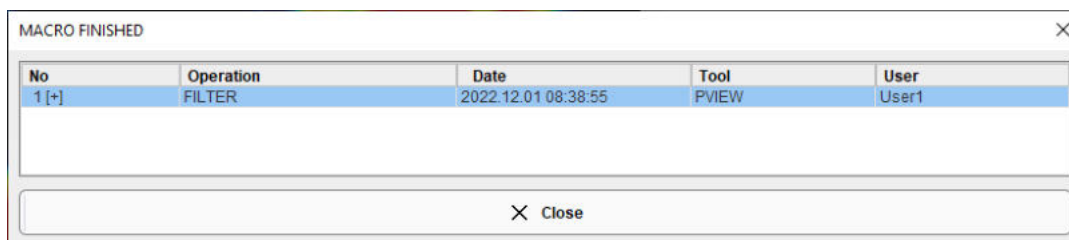
Macros can be prepared based on the image history ⌐132⌐ of a representative data processing session. The Macros can be applied in the Pipeline processing.

8.2.6 Buffer Loading

Note that to be able to load from the **Buffer**, the images need to be initially loaded in a PMOD tool and then saved to the **Buffer**. The procedure is described in the Buffer Saving ⌐121⌐ section.

8.3 Image Data Transformations during Loading

There are two basic ways how images are loaded:

1. Direct loading**:** if the **Open** ⌐ Open ⌐ button is selected on the image selection dialog; the images are immediately loaded without any data transformations.

2. If the **with Operations** ⌐ with Operations ⌐ button is selected, an intermediate dialog window is shown which allows configuring the image data properties as well as optional pre-processing steps. Initially, the *settings of the last loading* operation are shown. Activate the **Reset loading parameters** button before configuring different loading options.

The example below is an illustration of the loading dialog after three NiFTI files from the templates directory have been selected for loading using the **AUTODETECT** option.
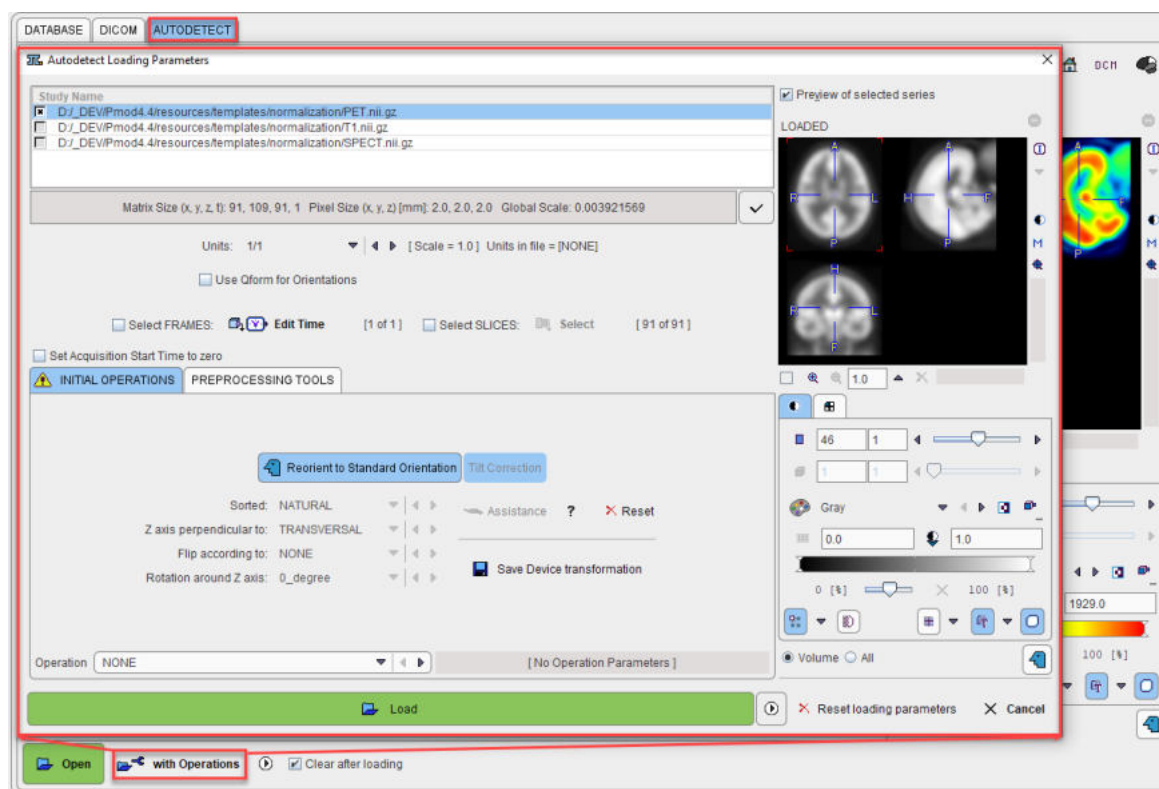
In the upper part the list of images selected for loading is shown. The rest of the dialog window allows defining the properties of the images and transformations which are to be applied to the selected image during loading.

The check boxes allow to select a subset for configuring the transformations. In this way, different transformations can be establish for the different studies. Before the actual loading with **Load**, however, all studies should be selected.

8.3.1 Changing the Image Orientation

Note that in the above SPM template example the anterior-posterior (AP) direction is opposite to the standard convention, and in fact patient right is on the right image side. This image can be brought into radiological HFS orientation by enabling the **Reorient to Standard Orientation** setting.
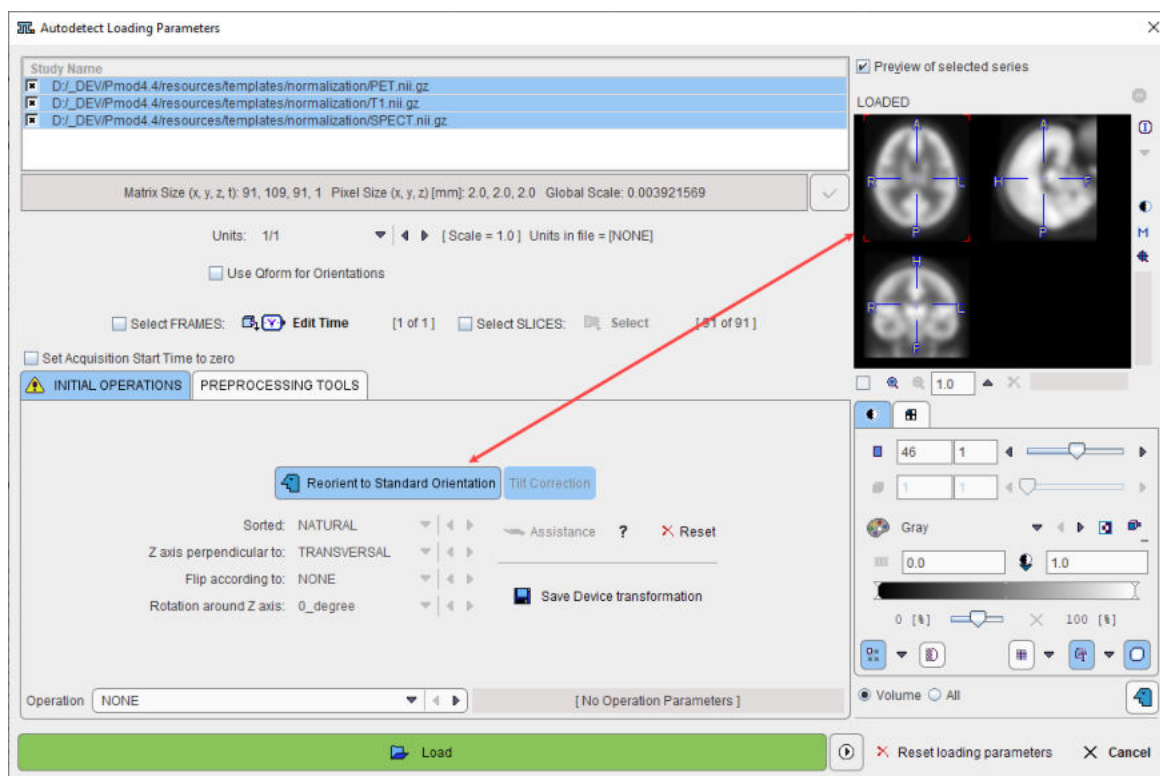
The following image re-orientations are supported

- modification of the sorting order to interchange left-right, top-bottom in the image, and front-back (slice ordering);

- rotation about the z axis;

- orthogonal sections such as coronals or sagittals.

As there are many possible combinations, activating the **Image Preview** function helps verifying how the images will look like after loading.

If data are loaded which contain consistent information about the orientation of the acquired slices (eg. DICOM, NiFTI, Ecat), the following steps allow bringing the image into standard anatomical orientation:

1. To start activate the **Assistance** button (**1**).

2. A selection window (**2**) appears allowing to choose the image type to load: **Human** or **Animal** (**3**).

3. To select the original orientation in the image file the **Down** ▾ arrow (**4**) need to be activated.

4. A dialog window pops up (**5**) allowing to select the original orientation in the image file (in the example FFP-Trans **6**).

5. To set the selection for the original orientation in the file, the selection dialog window need to be closed with **OK** (**7**).

6. The result of re-orientation is immediately reflected in the **Image Preview** section if the corresponding checkbox is enabled (**8**).
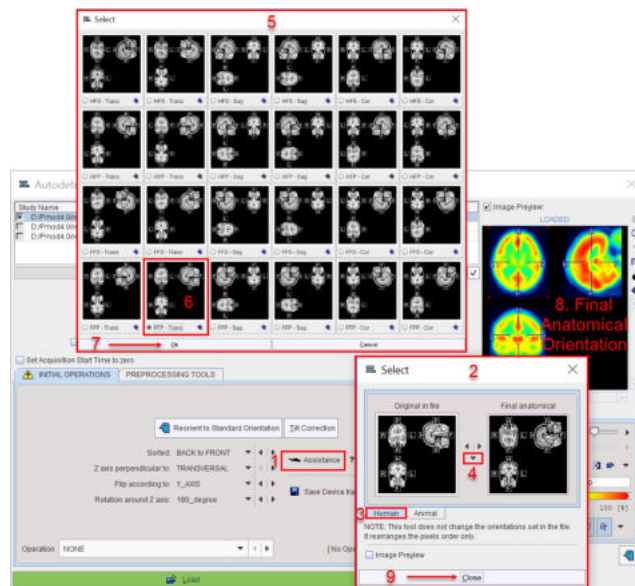
7. Finally, **Close** the orientation selection (**9**)window and load the image with the **Load** button.

More information and help about human and small animal matrix coordinates and real world coordinates are provided activating the question mark button next to the **Assistance** button.
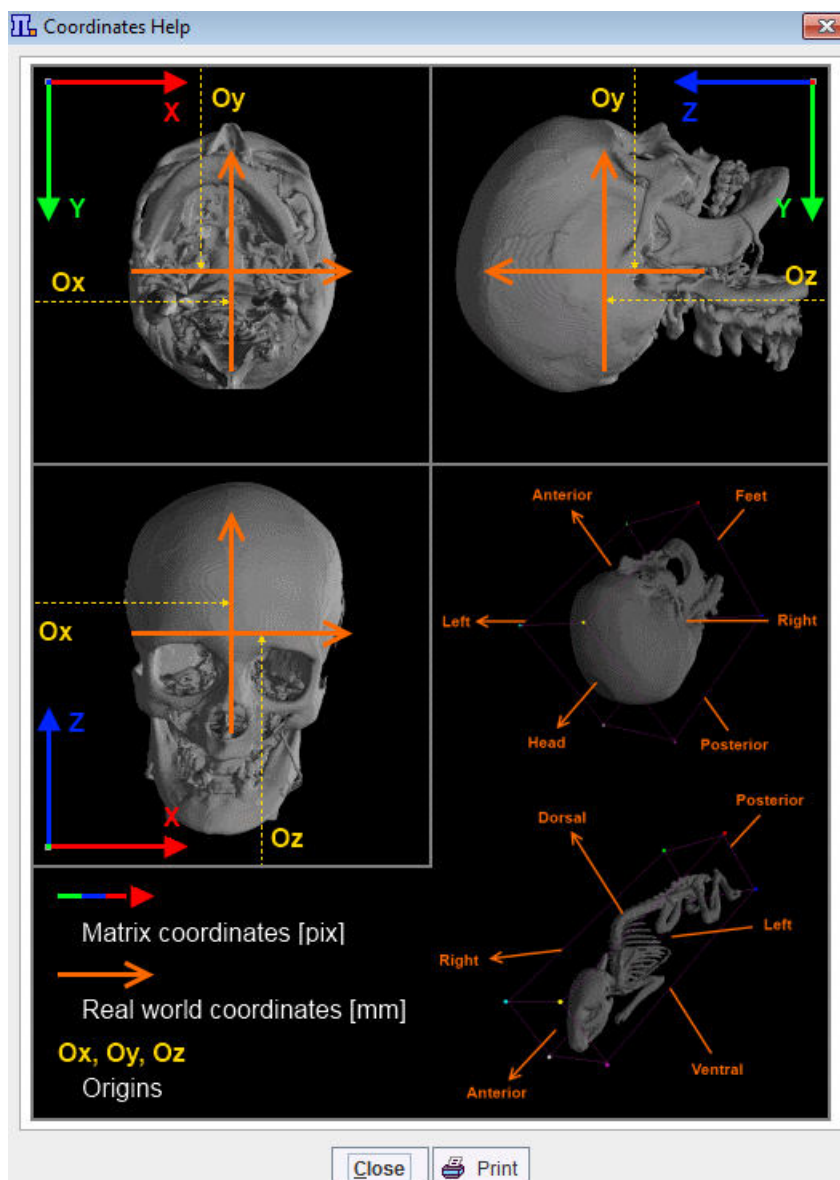
The re-orientation settings may be easily canceled activating the **Reset** button next to the **Assistance** button.

Reorient to Standard Orientation: This option will arrange the data such that the subject position is closest to the head first supine (HFS). The subject's head is directed into the display, looking up the display and left subject hand to the right side of the display. This adjustment is performed without reslicing, using only rotations by 90 degrees or multiplications of this value. It requires that enough subject positioning information is available in the image file.

Tilt Correction: If this option is selected, the corners of the slices are checked whether they are located on a line perpendicular to the slice plane. If this is not the case, as with CT data acquired with a tilted gantry, they will be resliced such that the new top left corner of the image are aligned. The default reference frame is the frame closest to the origin. If **Reorient to Standard Orientation** is active tilt correction will always be checked and performed prior to data reorientation. As a result of this correction the orthogonal planes will not show displacement artifacts.

8.3.2   Defining the Acquisition Timing

The specification of the acquisition times is important for using dynamic data in a quantification process. The times can be inspected and the definition overwritten using the **Edit Time** button, which shows the following dialog window.
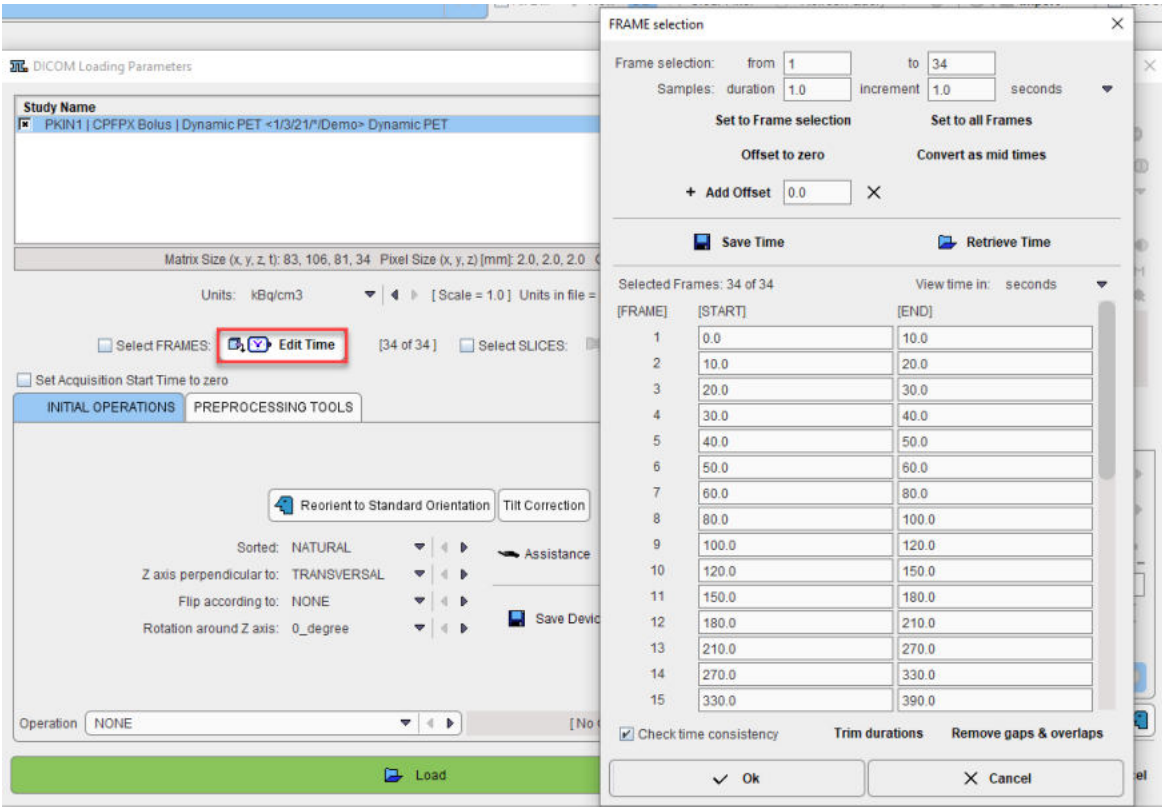
For DICOM, Ecat, MicroPET, Interfile and GE Advance data the times are read from the selected file and shown in the list. Note the **Save Time**/**Retrieve Time** buttons which allow saving/retrieving the timing of the dynamic frames to/from a file.

If the **Select FRAMES** box is checked when opening the dialog window, it is additionally possible to arbitrarily select a subset of frames for loading.

The **Trim durations** button ensures that the end times are not after the following start times.

The **Remove gaps & overlaps** button shifts start and end times in order to eliminate gaps and overlaps in the acquisition timing.

8.3.3 Initial Operations

The **INITIAL OPERATIONS** tab offers several other **Operation**s.
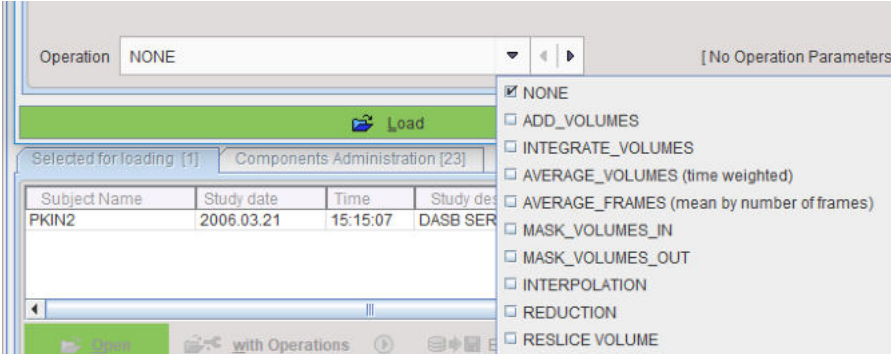
The operations are summarized in the table below

ADD_VOLUMES   Allows performing the frame summation for a dynamic acquisition.

**INTEGRATE_VOLUM   Allows calculating the area under the curve.
ES**

AVERAGE_VOLUMES **(time weighted)**	Allows performing time weighted average for a dynamic acquisition. The frame values are weighted by the relative frame duration.
AVERAGE_FRAMES **(mean by number of frames)**	Allows performing normal unweighted average.
MASK_VOLUMES_IN	Allows masking inside existing VOIs with value of 0. The values outside the VOIs remain unchanged.

The user needs to specify the *.voi* file to be used for the masking procedure:

The selection list displays only VOIs files available in the database. It is mandatory that the VOIs are in the same space as the image to be masked.

Please note that all the VOIs available in the specified *.voi* file will be masked in.

MASK_VOLUMES_OUT	Allows masking outside existing VOIs with value of 0. The values inside the VOIs remain unchanged.

The user needs to specify the *.voi* file to be used for the masking procedure.The selection list displays only VOIs files available in the database. It is mandatory that the VOIs are in the same space as the image to be masked.

Please note that all the VOIs available in the specified *.voi* file will be masked out.

|	
INTERPOLATION	Allows calculating a new image volume by specifying a new pixel size in each direction. The matrix size results from the division of the volume sized by the pixel sizes.
REDUCTION	Allows reducing the number of pixels in each direction. It is intended for situations where the number of pixels is divisible without remainder by the selected reduction factor.
RESLICE VOLUME	Allows reslicing a volume with different slice spacing. The value entered in the text field will be used as reslicing in z axis.

With the **Minimal slice thickness** box enabled the minimum value for the slice thickness can be specified in the dedicated text field. The slices with slice spacing value lower than the **Minimal slice thickness** will be resliced with the specified value.

The example below illustrates how the last seven acquisitions of a dynamic study can be averaged by selecting the frames sub-range and setting the **Operation** selection from **NONE** to **AVERAGE_VOLUMES (time weighted)**.
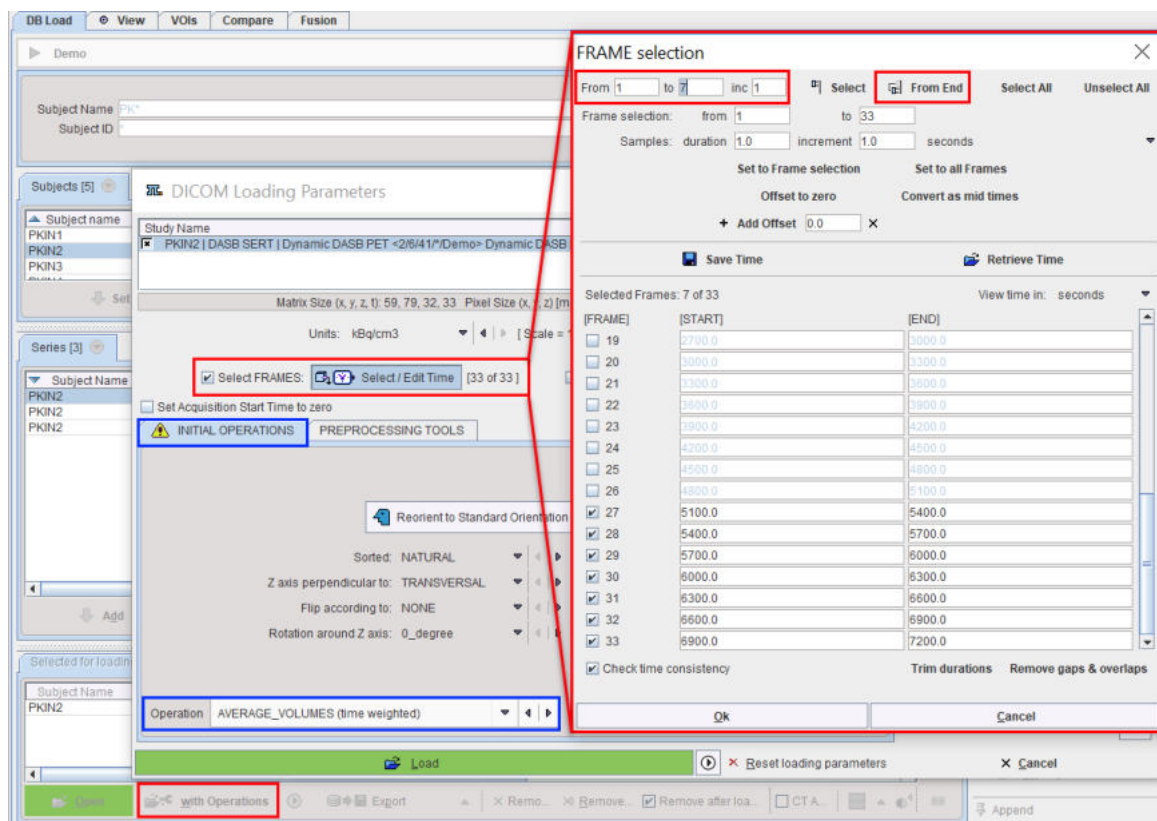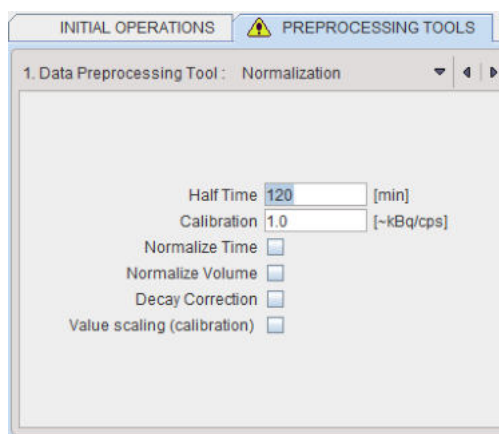
8.3.4 Enabling Pre-Processing Operations

The tab **PREPROCESSING TOOLS** makes supports the application of two successive filters to the data.
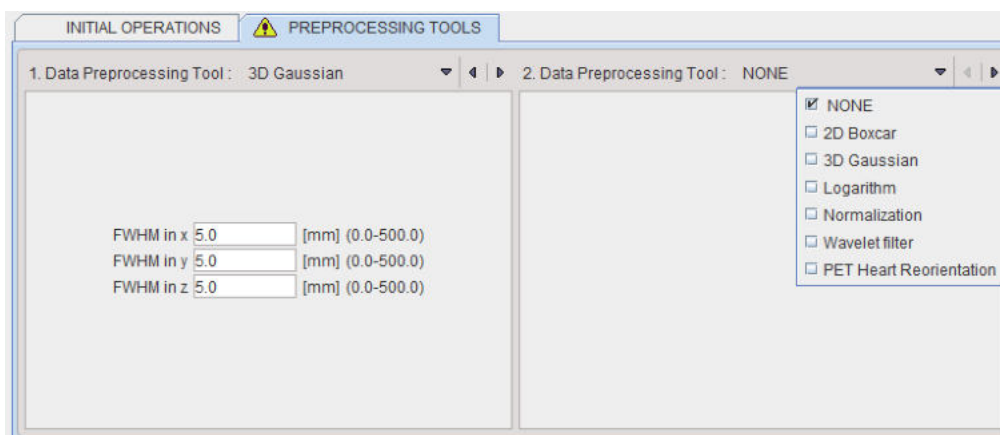
Data Normalization

Normalization is a facility for transforming reconstructed image counts into activity concentration values calibrated in kBq/cc.

The following parameters are applicable during the calibration process:

- **Half Time** is used for a correction of the physical decay to the acquisition start, if the **Decay Correction** box is enabled.

- **Calibration** is a factor for the conversion of the measured counts - which represent only a fraction of the emitted photons - into the true number of physical decays. It is applied it the **Value Scaling** flag is enabled.
  Note: The calibration factor can be determined using a phantom filled with a known, representative activity concentration. Phantom images are acquired, corrected and reconstructed using the same protocol as the research study. Then, the image values are decay corrected, time and volume normalized, resulting in images with counts per ml per second. As the next step, a homogeneous VOI is outlined and the average pixel value calculated. Finally, the calibration factor is calculated by dividing the known true phantom activity concentration by the VOI average.

- **Normalize Time** is needed, if the pixel values represent total accumulated counts during the acquisition. If the box is checked, the image values are divided by the acquisition duration.

- **Normalize Volume** is needed, if the pixel values represent activity, not activity concentration. If the box is checked, the values are divided by the image voxel size (known from the image header).

- **Decay Correction**: If the box is checked, the pixel values are decay corrected to time zero. Note that under normal circumstances the start of the first frame will correspond to time zero, so decay correction is to the acquisition start. If this is not adequate, for instance in a PET image which is to be analyzed by an autoradiographic model, the frame start/end times should be edited (e.g. set to 40min and 50min for a 10-minute scan starting 40 minutes after injection), the image saved, and then loaded again for decay correcting to the injection time.

Wavelet filter

Wavelet is a time-domain filter for dynamic data which de-noises the time vector in each pixel separately.
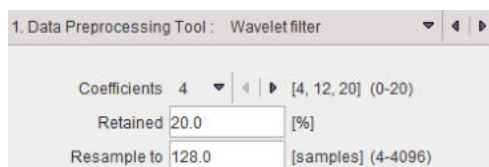
The wavelet filter uses the configured number (**4**, **12** or **20**) of Daubechies **Coefficients**.

Retained specifies the percentage of frequencies retained before applying the inverse wavelet transformation. The smaller the percentage, the smoother the result.

Wavelet filtering requires a signal length of a power of 2. Therefore, in most cases signal re-sampling has to be performed to a 2^n number specified in the **Resample to** field. Re-sampling uses linear interpolation.

Heart Reorientation

The **PET Heart Reorientation** is a facility that allows heart images re-orientation in short axis during loading. Please refer to the *Cardiac PET Tool User Guide* for the motivation of this tool.

The following parameters need to be defined:

- **Type** is representing the heart model type and can be selected from the available selection list: **HUMAN**, **RAT** or **MOUSE** according to the image to be analyzed.

- **Myocardium start frame** and **Myocardium end frame** are used to define the frames average range for creating the myocardium averaged image.

- **Blood start frame** and **Blood end frame** are used to define the frames average range for creating the blood averaged image.

- **Blood*factor**: as there may exist some activity in the cavities, a fraction of the blood volume image can be subtracted to improve the contrast. In the example above a fraction of 0.05 of the blood averaged image will be subtracted.

- **Smooth** and **FWHM**: optionally, the blood and myocardium averaged image can be smoothed with a 3D Gaussian filter with full-width half maximum value defined in the FWHM text box.

> **Note:** The preprocessing tools are plug-ins and can be configured in the main configuration dialog.

8.4   Image Data Saving

There are four types of image saving procedures:

- **File formats**: The user selects a file format and the directory wherein the image files are saved.

- **C-STORE:** The images are directly sent as DICOM objects to a DICOM server.

- **Database:** The images are saved to one of the configured databases (local or remote). To do so, they are converted to DICOM.

- **Buffer**: The images are saved to the buffer and can be loaded in any module with the **Buffer** option for loading.

The saving of image data is in analogy to the data loading operation. It can be started from the application **File** menu or from a **Save** multi-function button
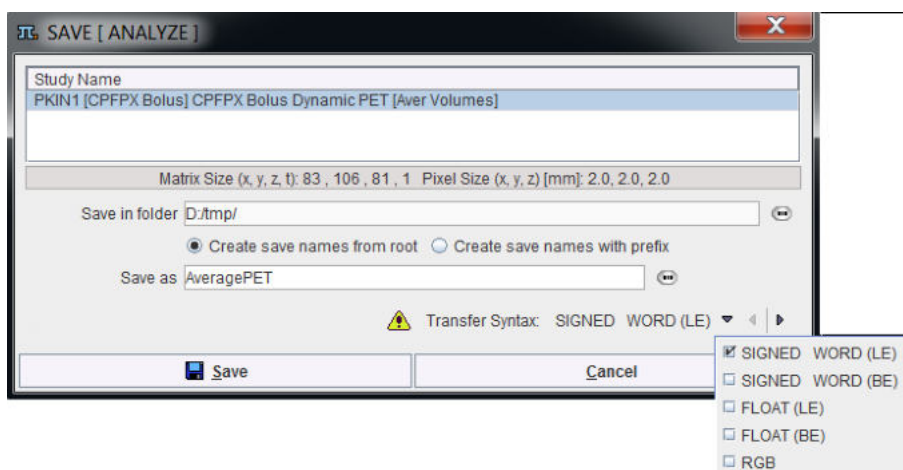

with the selections
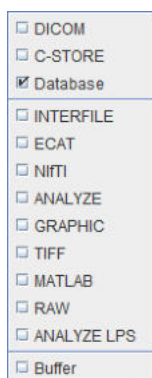
8.4.1 File-based Saving

Saving as a file involves selecting a destination directory and specifying a file name. In some cases further input is required and an additional dialog box pops up. For the **Analyze** and **Raw** formats a dialog such as

is shown and requests the definition of the number encoding in the **Transfer Syntax** selection.

The accuracy of the data representation - and the disk space requirements - increases from top to bottom. If the dynamic range in the images is large, you are recommended to use a **FLOAT** format. For PMOD the number encoding does not matter. For other programs, however, there may be preferred formats. **BE** and **LE** are related to the *byte ordering* which is different among processors (LE = little endian, on Intel and DEC Alpha processors; BE = big endian, for most other processors).

The **Transfer syntax validated** string is shown in case there is no precision loss for the selected transfer syntax. Otherwise (for the **Raw** format when saving short to byte or float to short) a warning message **Selected transfer Syntax will cause rounding error** is shown.

8.4.2 DICOM Saving

When storing the data in **DICOM** (part 10) files, a dialog window appears and allows selecting the destination directory, defining the name of the created DICOM file and the DICOM Image Information Object type into which the data will be stored.

The **Output SOP** determines compatibility with other systems that may not support all types of objects. The list contains all DICOM IODs supported by PMOD. Initially, a suitable definition is proposed, but the user may change the list selection. For RGB image data and screen captures only Secondary Capture (SC) objects are available as an **Output SOP**.

Please see our **DICOM Conformance Statement** for details.

The **Modality** type is just a descriptive string. It can be selected from the long list of modalities that are defined in the DICOM standard:

The **Create new study** box is only relevant for data originally loaded in DICOM:

- If the **Create new study** box is checked, PMOD generates new study UIDs when saving the DICOM objects.

- If the **Create new study** box is not checked, PMOD uses the study UIDs of the original data when saving the DICOM objects. In this case please do not change subject or study level information with **Edit Info**. Otherwise the receiving system may create a new study anyway.

For non-DICOM data PMOD will always generate new study UIDs.

Editing DICOM Information

DICOM has the ability to save administrative information with the image data. By activating the **Edit Info** button some of the important attributes can manually be edited:

The elements on the **SUV PARAMETERS** pane are explained in the SUV section **below** 147. The **Subject POSITION** panel allows the selection of **Subject** type: **BIPED** or **QUADRUPED**. For each type the panel displays an array of buttons which allow defining (or correcting) the subject orientation.
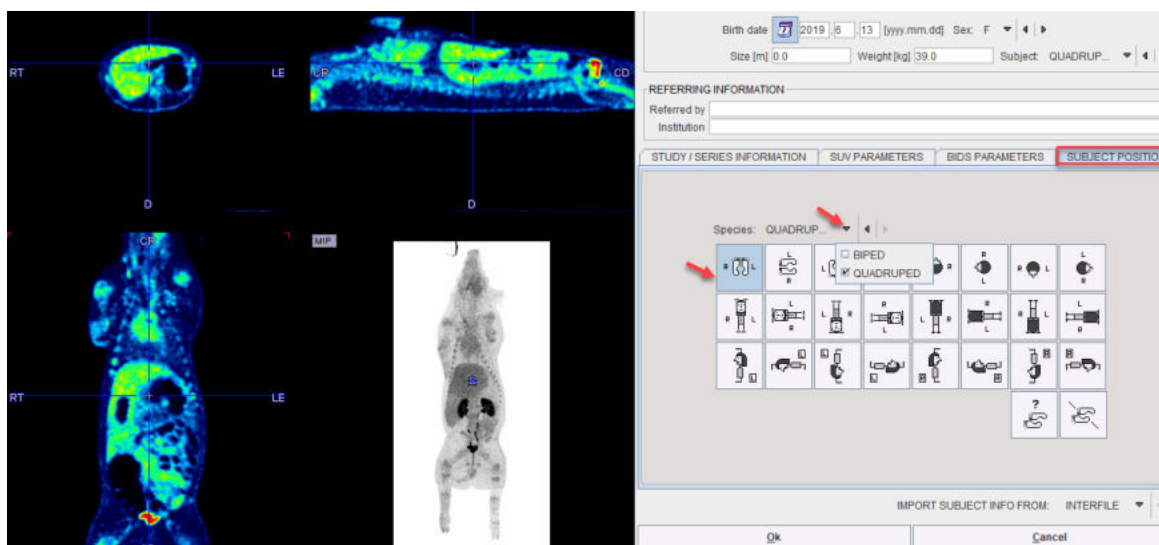
Note that after activating one of the buttons the anatomical annotations in the image overlay are adjusted. Please identify the button which generates an appropriate labeling. This information will then be saved with the data.

The buttons should only be needed for data loaded in other formats than DICOM, or if there was not enough orientation information in the loaded DICOM data. This situation is clearly indicated by the lack of anatomical annotations. If you are not sure about the anatomy, please use the **UNDEFINED Subject Position** button.

8.4.3   DICOM C-STORE

When storing the data in **C-STORE**, a similar dialog window appears as for DICOM Saving ₁₁₈, but included is also a list of DICOM servers to which the data can be sent.
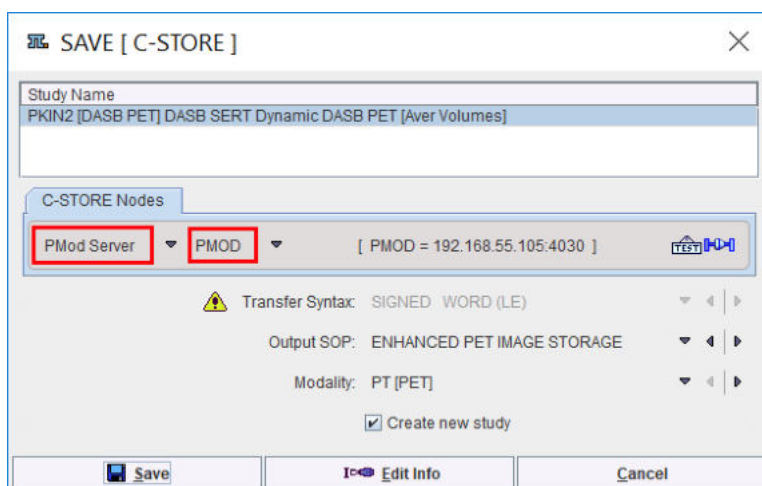
For details regarding DICOM support in PMOD please refer to the PMOD DICOM Conformance Statement.

8.4.4   Database Saving

The saving of images into a PMOD database is described above ₇₃.

8.4.5   Buffer Saving

Saving to the buffer does not involve selecting a destination directory or specifying a file name. All the images processed in, e.g., the **View** module can be saved to the **Buffer** and then loaded in a

different module with **Load** from **Buffer** option. Additionally, a new module can be opened during the loading from buffer procedure as shown below:
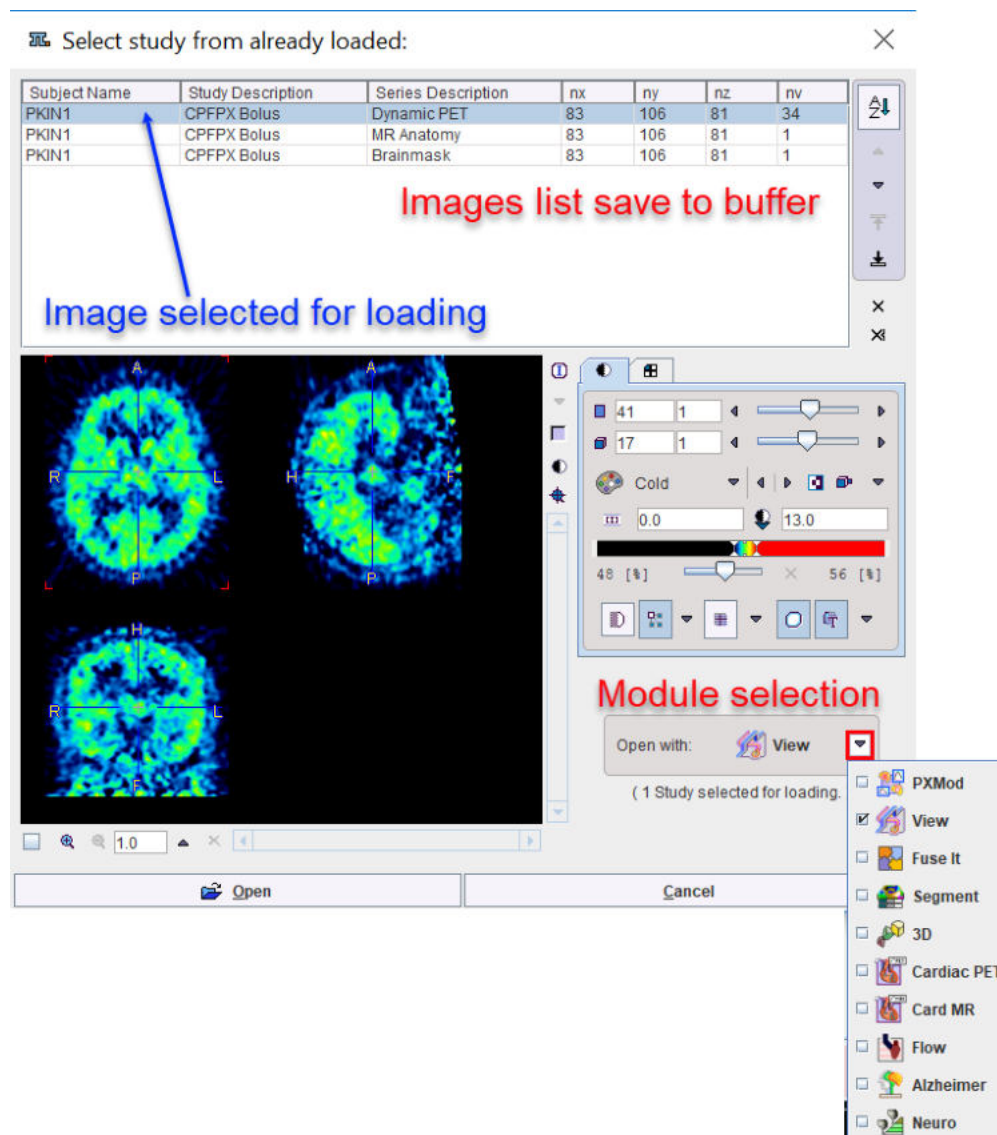
When **Load** from **Buffer** is activated a dialog window as above appers. In the uppermost part the images saved to buffer are displayed. More then one image can be selected with CTRL + click. On the right side of the image preview display, an **Open with** button allows choosing the module where the selected images are going to be loaded. Finally, click **Open** to load the images.

8.5   Component Data Loading and Saving

Component data such as pixel-wise modeling protocols (.defpmod), volume-of-interest definitions (.voi), kinetic modeling files (.km), matching transformations (.mat) etc. can be saved as disk files or

database data using the component saving buttons ⋙ in the user interface.

If the database option is active, the database loading/saving dialog always appears first.

8.5.1 Loading/Saving without Database Option

Loading

If there is no database installed or it is not enabled for component data, a dialog of the following type appears when loading component data.
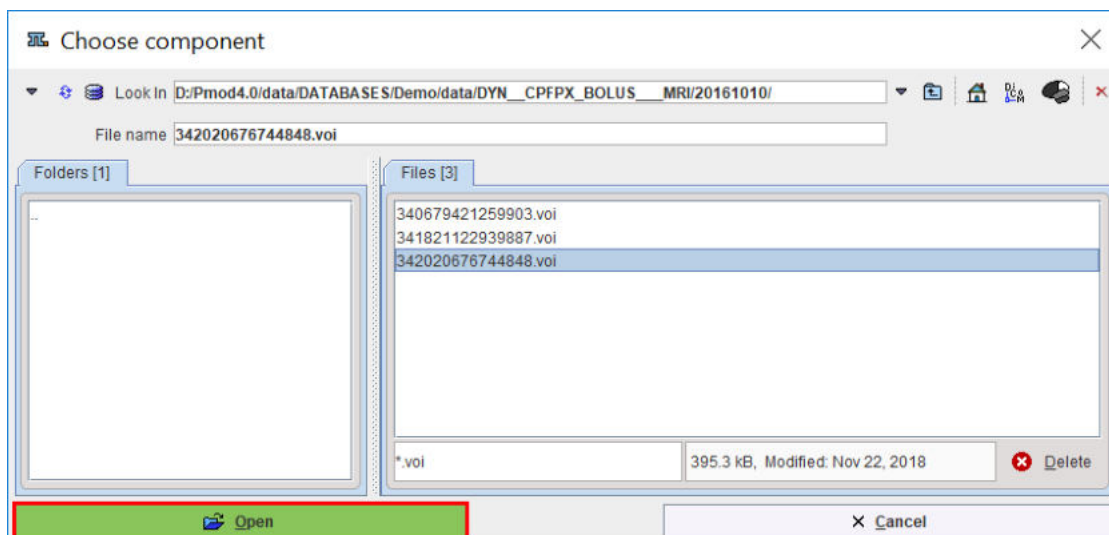
In the upper part the current search directory is indicated. Initially, it points to the directory of the last successful loading operation. To change the search directory, use the navigation buttons in the **Folders** section (**..** indicates up one level).

All files suitable for loading (having the right suffix, such as .voi for VOIs) in the search directory are listed in the **Files** section. The **Open** button starts loading the selected file, **Cancel** quits the operation, and **Delete** erases the file from the disk.

Saving

When a component is saved, a dialog appears which is very similar to the loading dialog.
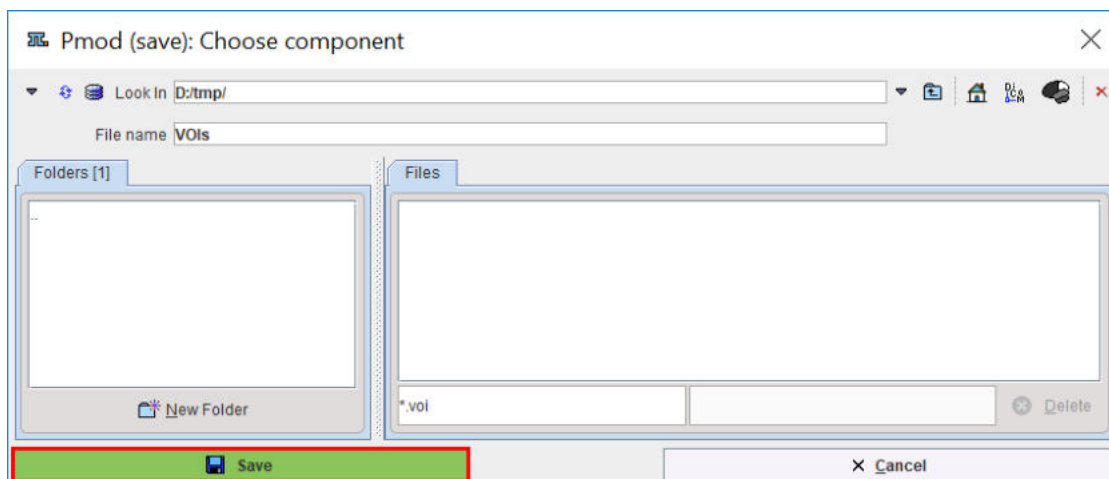
It has the same elements for changing the directory. The **File name** field allows specifying a name for the new data file, and the **Save** button will start saving.

8.5.2 Loading/Saving with Database Option

Database loading 71 and saving 74 of component data is described above.

8.5.3   Loading of Vector Data

The input of vector data is required at different places. The most important example is kinetic modeling where the plasma and the whole blood curves are time vectors. Another example is quantitative autoradiography whereby a vector contains the table to convert from optical image units to radioactivity density. Such data is expected as a two-column text file in the form below.

sample-time[time_unit]	value[value_unit]
0.0	0.0
1.0	27.0
2.0	123.1
…	…

Typical time_units are **seconds**, **minutes**, and **hours**. Typical value units are **kBq/cc** and **uCi/cc**.

Note: The *header line is required* - otherwise the values on the first line will be skipped. If valid units are found in the file header the values are converted to the internal representation [sec] and [kBq/cc]. If there are no valid units in the header line, the import procedure assumes that the data units are equal to the ones in the configuration settings of the tool.

Tabular data such as the tissue time-activity curves in kinetic modeling can be loaded from a text file with multiple columns in the form below.

start[time_unit]	end**[value_unit]**	frontal	temporal	cerebellum
0.0	10.0	0	0	0
10.0	20.0	12.3	13.5	7.8
20.0	30.0	28.6	31.9	15.5
…	…	…	…	…

Again the header line is required, and the units are considered if they are recognized. Please note that the activity units are defined *after the header of the second time column*, not after the first value header.

Such files can easily be prepared in text editors, or with MS Excel and saving as a **tab delimited text file**.

9   Image Display and Basic Processing

The same image display object is used in all PMOD tools. It consists of an image viewport, ie. the black area for the images, a set of image presentation and layout controls to the upper right of the viewport, and some tools grouped along the image.
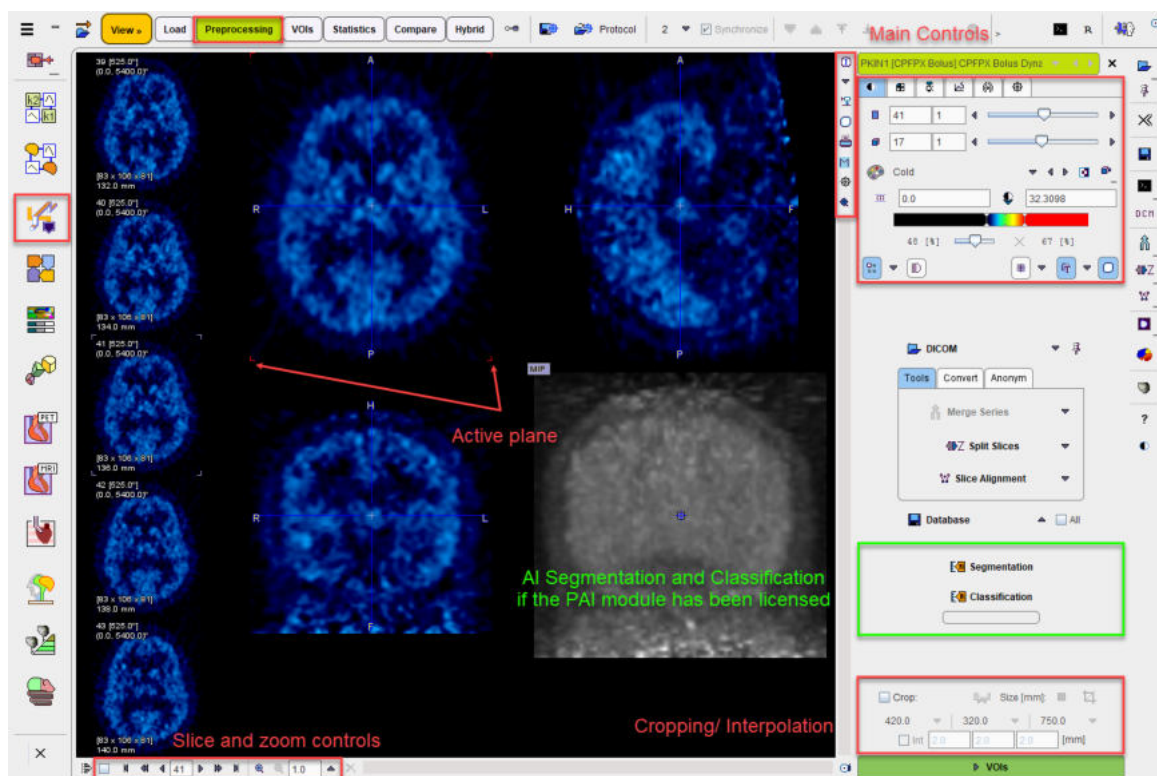
The viewport shows one or several images of a series, depending on the image layout which can be modified by use of controls. Most PMOD tools allow for loading more than one image series. The image display may then be switched between the available series with the selection at the top of the controls, eg.
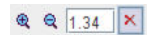

There are two arrays of buttons next to the images themselves. The vertical row in the upper right presents auxiliary tools for inspecting the image data currently displayed. Their functions are:

①	Shows information related to the displayed image series and also allows changing timing and subject/study information.
▼	Selection between the stacked image series.
🖳	Start the **Data Inspector** to examine the pixel values, time vectors of dynamic studies, the acquisition times, standard uptake values (SUV), and the origin.
◻	Start the **Volume-of-Interest** tool to outline VOIs and calculate statistics on the currently shown images.
◑	Button to **hide/show** the image controls. Hiding the controls after the images are in a suitable presentation has the advantage of a larger viewing area.
🖨	Generate a **Report** for printing or saving.
M	Allows to quickly enabling/disabling the MIP display in the orthogonal layouts.
🔧	Show the external tools list.

✴	Activate the mouse-operated **zooming** mode.

The horizontal button row in the lower left embodies the following functions (starting from the left):

◀	This toggle button enables/disables the **preview** of slices neighboring the active one along the left side of the image viewport (in 1x1 and orthogonal layouts only).
☐	This box is only functional for **dynamic** studies. In this case the user can select between stepping through the slices at a certain time (no check), or through the times for a fixed slice (check).
⏮ ◀◀ ◀ 14 ▶ ▶▶ ⏭	Buttons to step backward/forward in increments of an slice or a page (for multi-image layouts), or to jump to the begin/end. Entering a number allows positioning the display immediately. Note that slice scrolling can also be done using the mouse wheel.
⊕ ⊖ 1.34 ✕	Buttons for zooming and resetting the zoom. The sliders appearing in zoom mode below/besides the image allow positioning the zoomed images.

The image presentation can be modified in many ways by means of the control panels, which can be brought forward by clicking on the corresponding tab. Note that depending on the context some of the panels (e.g. oblique reslicing) and buttons may be missing.

Image Cropping and Interpolation

If the image field-of-view is larger than the structure of interest, the data set should be reduced in order to save RAM and optimize processing. This can be achieved by enabling the **Crop** box and defining the size of the box which appears as yellow rectangles in the image overlay. Species selection triggers pre-defined sizes for the cropping box.
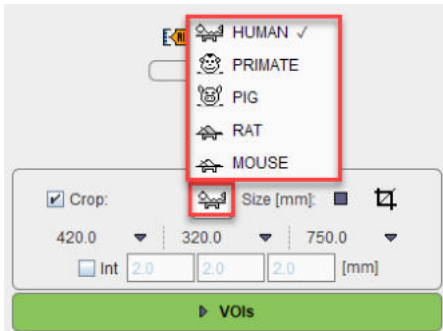
Proceed placing the yellow crop box by clicking at the center of the anatomical structure of interest. The structure of interest should be fully enclosed. If this is not the case, the edge size in **[mm]** can be adjusted for each direction by selecting the size in the corresponding list. An alternative is entering the edge sizes using the button indicated below:
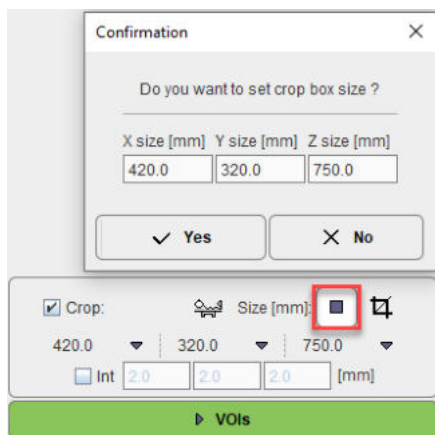
The ⊔ button initiates cropping, whereby the original data are replaced. If cropping is not activated manually, a request will be shown when proceeding to the next step with teh **VOI** red action button. Note: The cropping operation is irreversible and only allowed once.

With **All input series** box enabled the cropping is applied to all images available in the list.

To have a smoother appearance, an interpolation can be configured. To this end, activate the **Interpolate** box and specify the voxel dimensions in x,y and z in mm.

9.1 Viewing and Changing Study Information

In PMOD, each loaded image series has a set of attributes. Depending on the loaded image format they may be partly empty. Using the 🄸 button, the information can be shown in a dialog window as illustrated below, and edited.
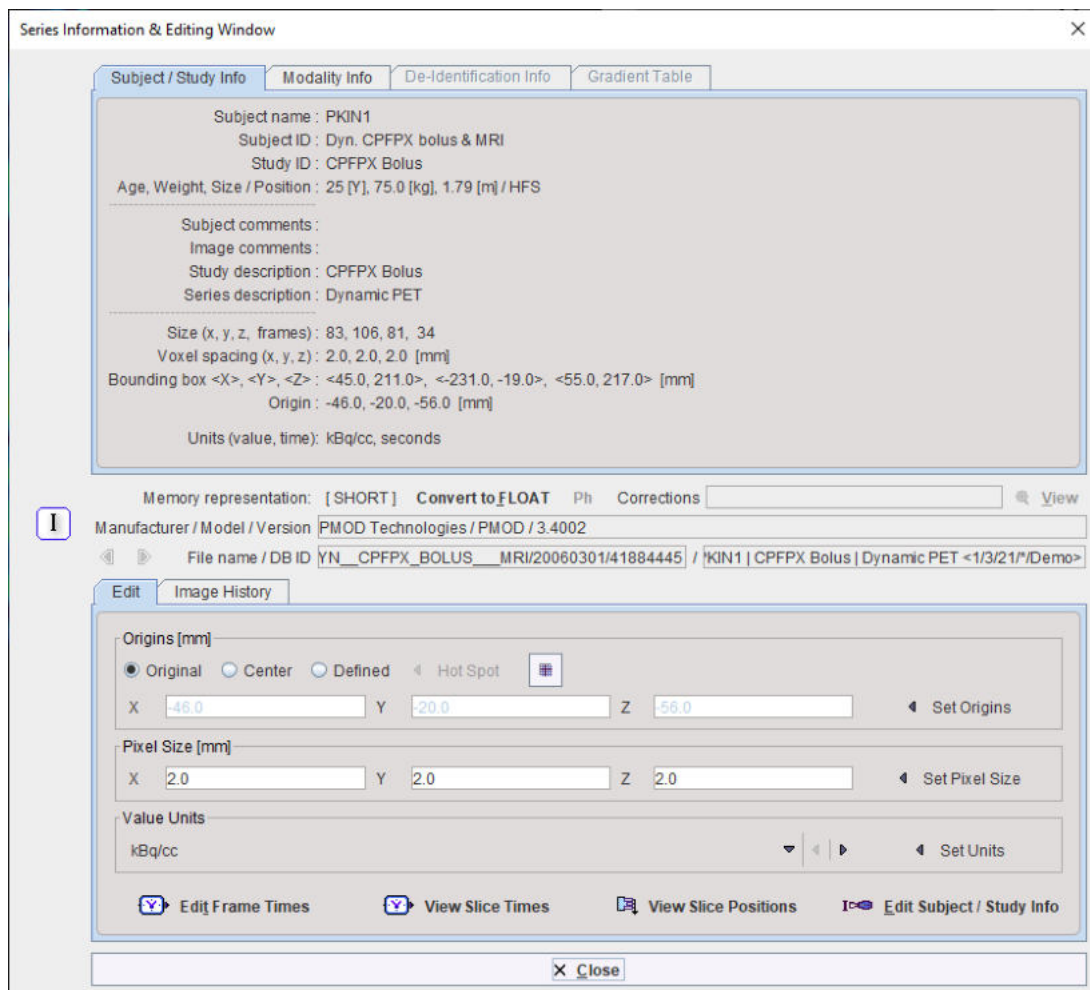
Note that after changing the information the data set needs to be saved to make the changes permanent.

9.1.1 Modality Info

The **Modality Info** tab shows information related to the acquisition and reconstruction of the data, which is very dependent on the content of the loaded image.
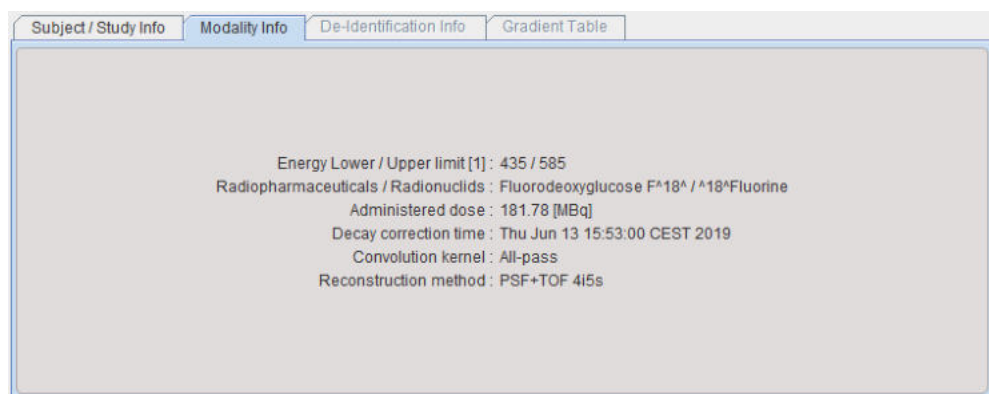
9.1.2 Image Properties

Memory Representation

π.pmod

Images with short **Memory representation** can be converted to **float** by the **Convert to Float** button. This requires more RAM, but avoids rounding problems.

Edit the Image Origin

The **Origins** area shows the coordinate of the image origin and allows setting it to a different location. The origin is relevant for the definition of volumes-of-interest, because they are defined relative to the origin. They are also relevant for image fusion. In hybrid imaging, the origin of the different modalities is set to the same anatomical location, so that the images can be aligned by simply aligning the origins. An origin of (0,0,0) indicates the upper left corner of the first slice.

The **Origins** radio button has three positions with the following meaning.

- **Original**: With this setting the origin obtained with data loading is used. This is the standard setting.

- **Center**: By selecting this button and activating **Sets Origins**, the center coordinate of the data volume is defined as the new coordinate origin.

- **Defined**: When this button is set, the origin coordinate can be entered manually into the **X**, **Y** and **Z** fields, for instance the values from an other study. As an alternative, the triangulation point can be set to the intended location of the origin, and then the button **Get from Hotspot** activated. This will transfer the triangulation coordinate to the origin to the pixel. **Sets Origins** has to be activated for making the coordinates actual.

Edit the Pixel Size
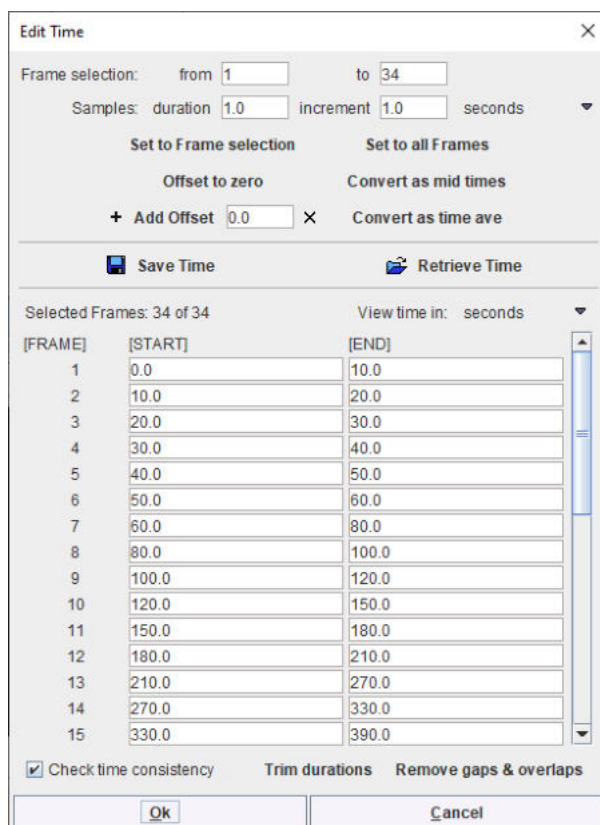
The **X**, **Y** and **Z** fields of **Pixel Size** shows the current pixel size. To change them edit the values and then activate **Set Pixel Size**.

Edit Value Units

The **Value Units** selection contains the list of supported image units. To change the units select the correct unit from the list, and then activate **Set Units**. Note that only the interpretation of the values is changed, but that there no scaling applied to the data values.

Edit Frame Times

Correct acquisition times are very important for using dynamic data in a quantification process. The times can be inspected and overwritten using the **Edit Frame Times** button, which shows the dialog window below.
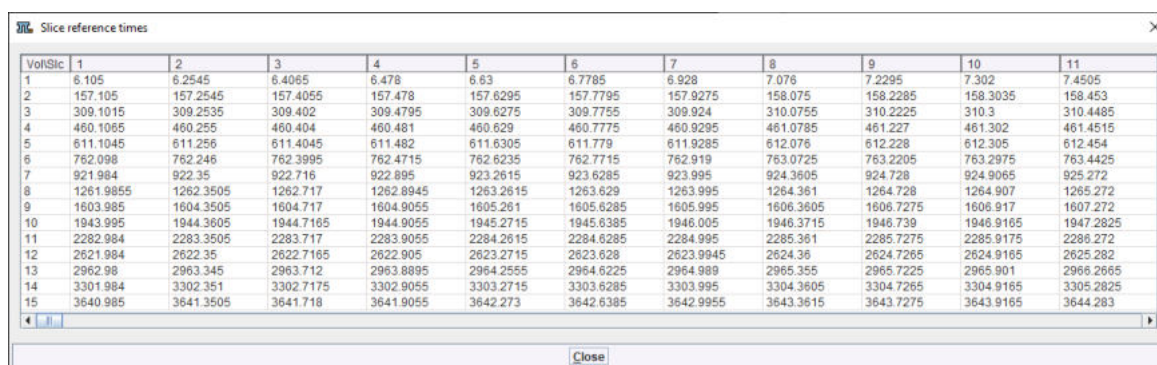
Note the **Save Time**/**Retrieve Time** buttons which allow saving/retrieving the timing of the dynamic frames to/from a file. If changes are required, the values can be overwritten and then saved with the **Ok** button.

View Slice Times

In some situations the slices in an image volume can have different timing, for instance when using a scanner with limited axial field to acquire dynamic whole-body data by multiple passes. As encoding of such timing information in the data may be vendor-dependent, the **View Slice Times** button allows inspecting the timing PMOD extracts from such data.

A dialog window is opened which lists the reference time per slice (horizontal) and frame (vertical). In the example below is apparent, how the slice reference times increases starting from slice one due to the continuous acquisition mode. The frames are separated by about several minutes representing the time between the passes.

View Slice Positions

The **View Slice Positions** button opens a viewer to inspect the slice positions. When orientation is defined in the image file, the slices orientation (the direction cosines for the image rows and columns) is available.

9.1.3 Subject, Study and SUV-related Information

To modify the study information use the **Edit Subject / Study Info** button which displays the following data editor:

Note the **SUV PARAMETERS** tab which houses the information relevant for the SUV calculation. All these fields must be completed. In the example below the decay correction was performed relative to the administration time, therefore the alert sign at the bottom.

For more information on SUV please refer to the section <u>Inspecting SUV Values</u> 147.

If the anatomical annotations are not correct, the **SUBJECT POSITION** tab can be used for correction purposes. First, the correct Species type has to be set, **BIPED** or **QUADRUPED**. Then the button representing the correct position of the subject has to be selected. The icons represent the view when looking at the transaxial images. As soon the settings are changed, the annotations in the images are adjusted for confirmation.
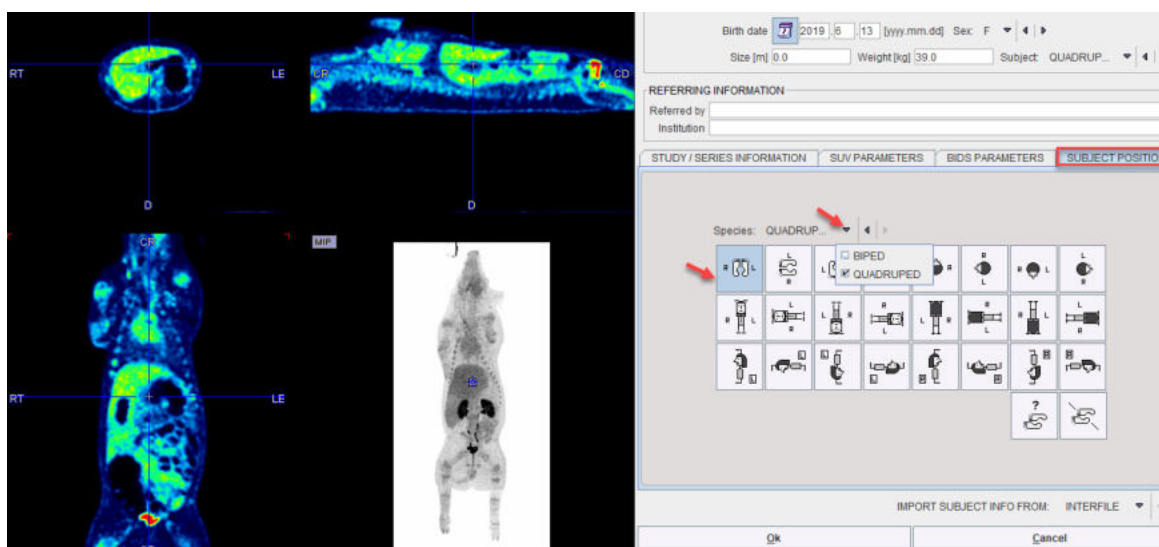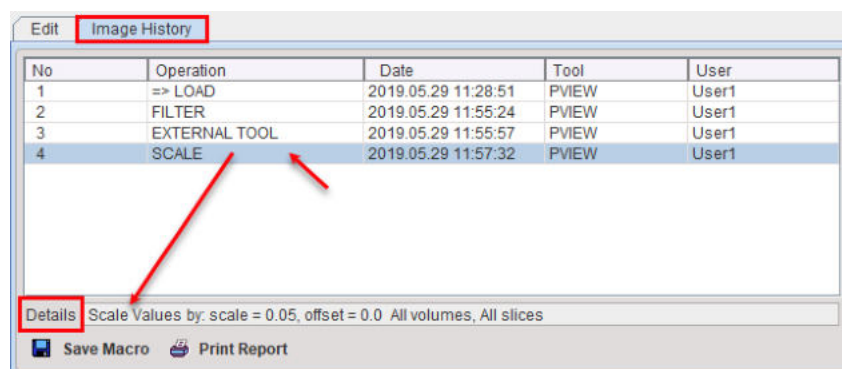

9.1.4   Image History and Macros

PMOD keeps a record for all operations applied to an image in a structure called **Image History**. The history starts with loading the data, and then a sequence of operations for which the following information are recorded:

- The **Operation** name.
- **Date** and time when the operation was applied.
- The PMOD **Tool** in which the operation was performed.
- The PMOD **User** who performed the image analysis.
- The **Details** of the operation such as filter sizes, rotation angles etc.

An example history is shown below.

The information can be printed or saved as an image using the **Print Report** button.

Macros

In some situations, the user may have to repeat the same sequence of image transformations with many data sets. In this case, he can convert the image history of a representative data processing session into a macro by saving it with the **Save Macro** button.

Macros can be applied as a data transformation during loading[108] or in Pipeline Processing[471].

9.1.5 Protocols

PMOD supports protocols in the **View** module. It is used for the acceptance test and for repeat data loading. By loading a protocol file the processing can exactly be restored at any later time. The protocol also supports VOIs saving when available.

9.2 Changing the Image Presentation

The first tab in the main controls contains most functions to modify the way how the images and the overlay information look like.
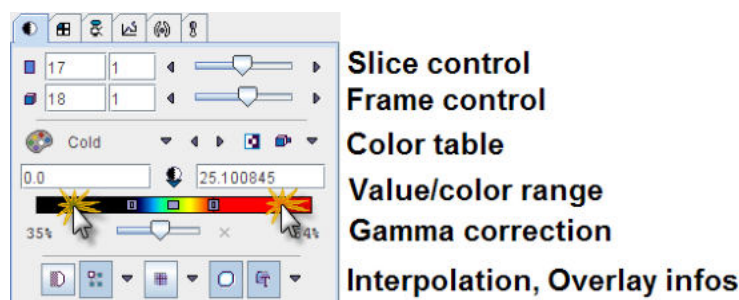
Control of Slice(s)

The slice control section allows scrolling through the images using the increment buttons, the slider, or directly by entering a slice number. The value right to the number of the active slice controls incrementing. This is particularly relevant in multi-image layouts. For example, if the increment value is set to 2, only every second image will be displayed.

Instead of selecting slices using the controls, the user can also scroll slices by dragging the left mouse button over the image holding the `CTRL` key in the `Up/Down` direction (see the summary of shortcuts below), or with the mouse wheel.

The frame control section only becomes active for dynamic studies with multiple time frames and behaves the same way as the slice control. To allow for mouse-operated scrolling over time, the time box on the left side below the image must first be checked.

> **Note:** There is a quick way for jumping to the particular slice/frame containing the maximal pixels value: just click the buttons next to the slice/frame selection.
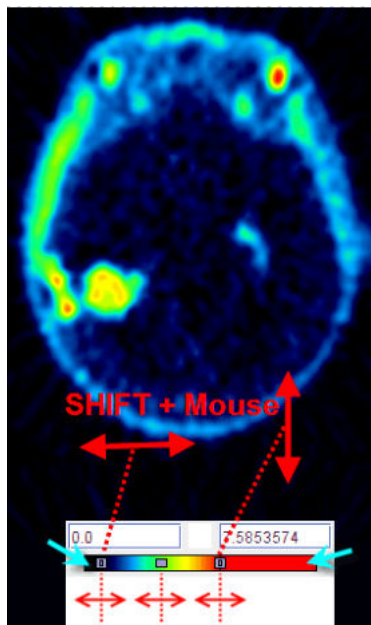
Color Tables

There is a selection of pre-defined gray and color tables which can be chosen with the list selection.
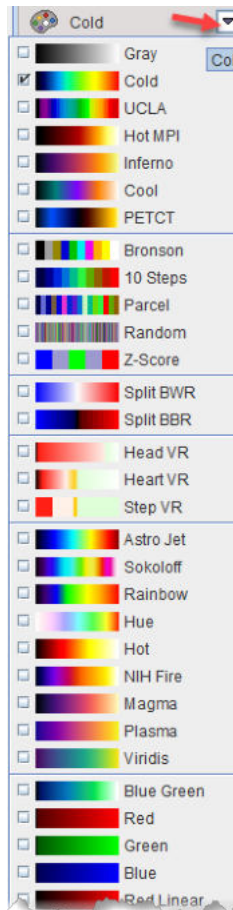
> **Note:** A new user defined color table can easily be be added. Create a 3-column text file with the RGB values and saving it to the sub-directory *resources/colortables* (see the examples there). They are appended to the lower section of the color table list such as **PETCT** in the example above.

A minimal/maximal threshold value defines the range of displayed values. The thresholds can be entered numerically, or the handles in the color bar can be dragged with the mouse. Additionally, the user can modify them by dragging the left mouse button over the image holding the SHIFT key. Left/Right movements modify the lower threshold, while Up/Down movements modify the upper window.

Note: Double-clicking into the lower end of the color bar sets the lower threshold to zero. Double-clicking into the upper end of the color bar sets the upper threshold to the maximum.

Zooming into Color Table

In some cases, the range of image values of interest only covers a small part of the color bar which makes it difficult to adjust the brightness precisely. In this situation, the user can zoom the color bar into the current sub-range of values. Clicking the right mouse button into the color bar pops up the context menu
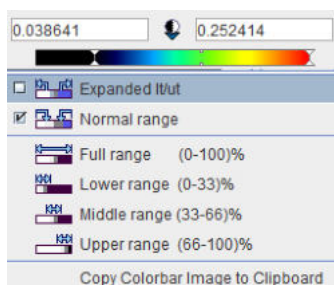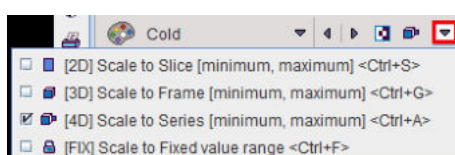

The first menu entry **Expand lt/ut** then performs the desired task and makes the color bar change to

The second entry performs the reverse operation, and the other entries are just shortcuts which may be helpful. The last option in the list allows copying the colorbar image to clipboard.

Color Table Modes

Several modes are available for the color table application. They can be selected using the option button

The different modes are:
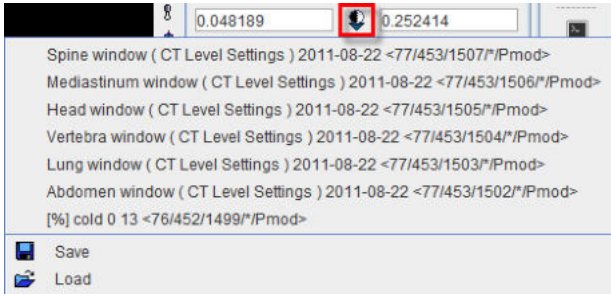
	Inversion of the color table order.
	Slice mode: The same % threshold is applied to each individual slice. Hereby the dynamic color range is fully exploited per slice. However, *the same color will represent a different value in different slices*. Therefore, this mode is not recommended in most cases.
	Frame mode: With this setting, the minimal/maximal value in an entire frame is determined, and the % threshold applied to them. As a consequence, the colors represent fixed values when inspecting the slices of a frame. However, as the absolute minimal/maximal value will vary at different times of a dynamic acquisition, the *same color will most likely represent different values when comparing different frames*. This setting is recommended for static studies.
	Study mode: With this setting, the minimal/maximal value in the entire series is determined, and the % threshold applied to them. This setting is recommended for dynamic series and movies because the same color represents the same value at all times and in all slices.
	Fixed mode: This setting allows the user entering arbitrary minimal/maximal values which need not belong to the data range.
	This button allows saving or retrieving a color table configuration. During saving a dialog windows appears allowing to choose the thresholding save option: **% Maximum-Minimum** or **Absolute values.** Finally activate **OK** to save the level settings. Different level settings can be define and saved in the database as **Absolute values** for CT images and used for CT image presentations. These settings are available on the list when the button is selected. Alternatively, the predefined color properties can be retrieved from the file system selecting the **Load** button. 0.048189 0.252414 Spine window (CT Level Settings) 2011-08-22 <77/453/1507/*/Pmod> Mediastinum window (CT Level Settings) 2011-08-22 <77/453/1506/*/Pmod> Head window (CT Level Settings) 2011-08-22 <77/453/1505/*/Pmod> Vertebra window (CT Level Settings) 2011-08-22 <77/453/1504/*/Pmod> Lung window (CT Level Settings) 2011-08-22 <77/453/1503/*/Pmod> Abdomen window (CT Level Settings) 2011-08-22 <77/453/1502/*/Pmod> [%] cold 0 13 <76/452/1499/*/Pmod> Save Load

Image Display in SUV Units

If all the relevant information is present for a data set the display units can be switched from original units to SUV [147] with the button indicated below.
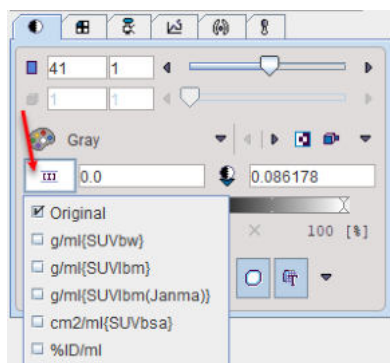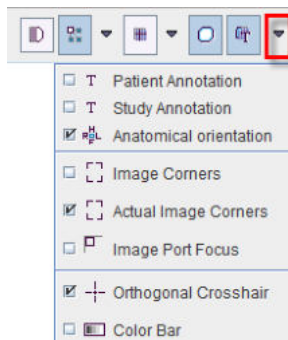
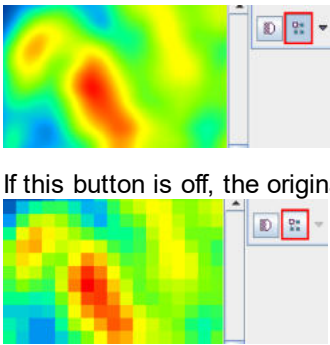The image unit symbol changes and the color bar units are converted accordingly.

Information Overlays and Image Smoothing

The lowest row contains several control buttons.

All of the buttons can be on or off, and some might have some configuration options attached. Their functionality is:

	Smoothing: Enables a temporary 9-point smoothing filter. The smoothing is only for display purposes and does not affect calculations.
	Interpolation: Enables image interpolation. Interpolation is needed because in most situations the resolution of the display viewport differs from the original image matrix. If this button is off, the original rectangular pixels are shown. The three interpolation options are **Triangle**, **BSpline**, **Mitchell** (Default). **Note:** the smoothing/interpolation functions serve only for image display enhancement. Statistical analyses are always performed with the original pixel values.
	Grid: Enables a grid centered at the origin of the data set. Bold lines indicate the location of the image origin. The grid size can be defined by the option (50,20,10,5,1mm or from 1 pixel to 10 pixels with 1 pixel increment).
	VOIs: Enables the displays of VOI contours, if there have any been defined for the current series.
	Overlay: A toggle to **switch off all overlay information at once**. Its option menu allows defining the level of information included in the overlay display as illustrated above. : This option enables Display of the anatomical annotations in the images: H - head, F - feet, A - anterior, P - posterior, R - right, L - left

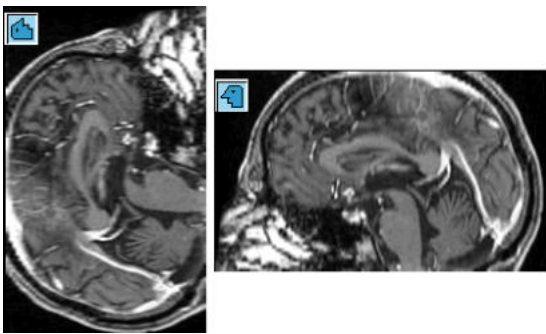|	For oblique orientations the letters are combined whereby the first letter indicates the direction closest to the current row/column direction. Allows displaying the colorbar selected for the image.

9.3   Configuring the Layout

Volumetric images can be displayed in many different ways in the PMOD tools. The layouts are accessible by the second control tab, on the first sub-tab **Layout.**
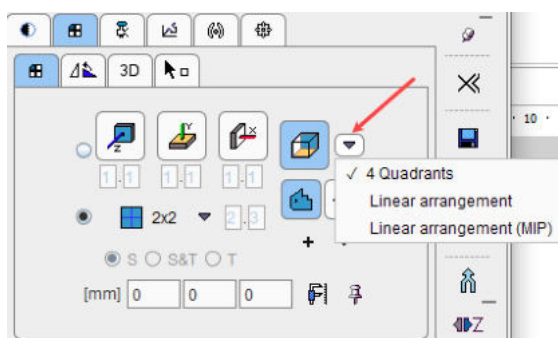
Slice Orientation

The buttons in the first row allow defining the orientation of the displayed images.

	z-Plane: Corresponding to the major slice orientation of the loaded data. Usually *axial* images. Keyboard shortcut: `CTRL+Z`.
	y-Plane: Usually the *coronal* images. Keyboard shortcut: `CTRL+Y`.
	x-Plane: Usually the *sagittal* images. Keyboard shortcut: `CTRL+X`. The x-plane image can be shown in two different ways depending on the modifier buttons.
	Orthogonal Planes: Layout showing three orthogonal slice images. The intersection point can be moved by clicking into the images. Three options are available: • **4 Quadrants**: recommended for the cubic data such as human/primates or rodent brain acquisitions • **Linear arrangements**: allows the whole-body orthogonal layout and is now available for all displays including fusion. It features better usage of the display area for non-cubic data such as human or rodent whole-body acquisitions. • **Linear arrangements (MIP)**: with this option selected the MIP image is activated together with the whole body layout.

The plane orientation can rapidly be switched by first activating an image (click into image), and then entering the keyboard shortcut.

The direction z, y or x indicates the normal to the shown plane shown. The y-, x- and orthogonal buttons are not active if the study is planar only and can thus not be resliced in an other than the original direction.
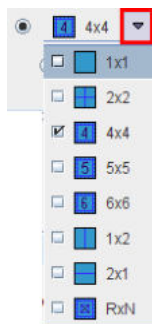
Tiling Layouts

The second and third rows allow configuring the number of images shown concurrently.

If the radio button in the second row is enabled, a dedicated row x column layout is used for the different orientations.

This is particularly helpful for a whole-body study where the coverage in z is much larger than in the other directions. The definition of the layout per plane orientation is done in the particular tool configuration Config.

Otherwise, if the radio button of the third row is enabled, the same layout is applied for all orientations and the arrangements are accessible through the selection

Keyboard shortcuts allow to quickly switch arrangements. After clicking into an image enter

- `CTRL+1` for 1x1
- `CTRL+2` for 2x2
- `CTRL+3` for 3x3
- etc.

To change from a tiling layout to 1x1 just click on the image to be enlarged holding down the `CTRL` key. To change back to the multi-image layout just `CTRL` and click once more.

The radio button in the fourth row is only applicable for image tiling with dynamic studies.

If the radio button is in the position of

- **S**: only slices acquired in a single time frame are shown in the image window.
- **T**: only the images of a single slice are shown at different acquisition times.
- **S&T**: the images are sorted by slice (vertically) and time (horizontally). Consequently each row corresponds to a slice at different times, and each column to the slices of an acquisition. An example is shown below. Note that increments >>1 have been set to cover the brain and the

acquisition duration.
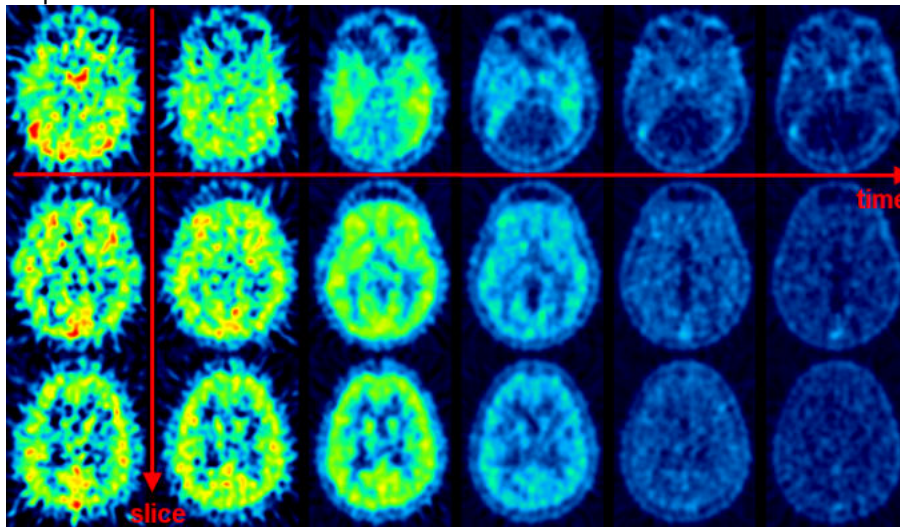
Orthogonal Layout: Regular

If the orthogonal layout is selected, three quadrants show the orthogonal slice images intersecting at the point indicated by the cross centered in the blue slice indication lines (triangulation point). As soon as the user clicks into an image, the images are updated by the slices intersecting at that new point.
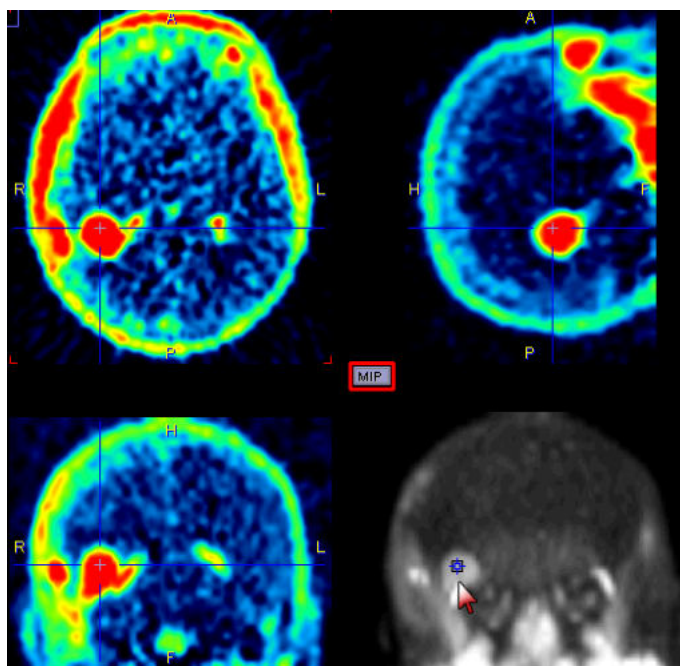
The fourth quadrant is available for different information. It can be configured by activating the button located in the upper left corner of that quadrant, indicated in red in the screen capture above. A dialog appears

π.pmod
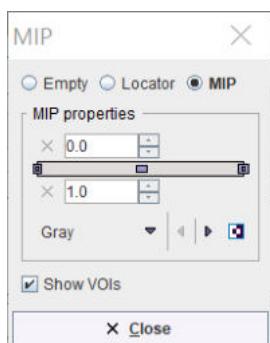
which lets choose between an **Empty** quadrant, a **Locator** display showing the slices location schematically, and a **MIP** (Maximum Intensity Projection). Note that there is a marker in the MIP image, which indicates the current slices intersection. It can be moved, and the slice images will follow. This function may be helpful to track vessels showing up highlighted in the MIP.

Use the **M** button shortcut to quickly turn ON and OFF the MIP when no configuration is needed for MIP properties.

Orthogonal Layout: Whole Body and Whole Body (MIP)

Below is an example of the **Whole Body** layout. It features better usage of the display area for non-cubic data such as human (or rodent) whole-body acquisitions.
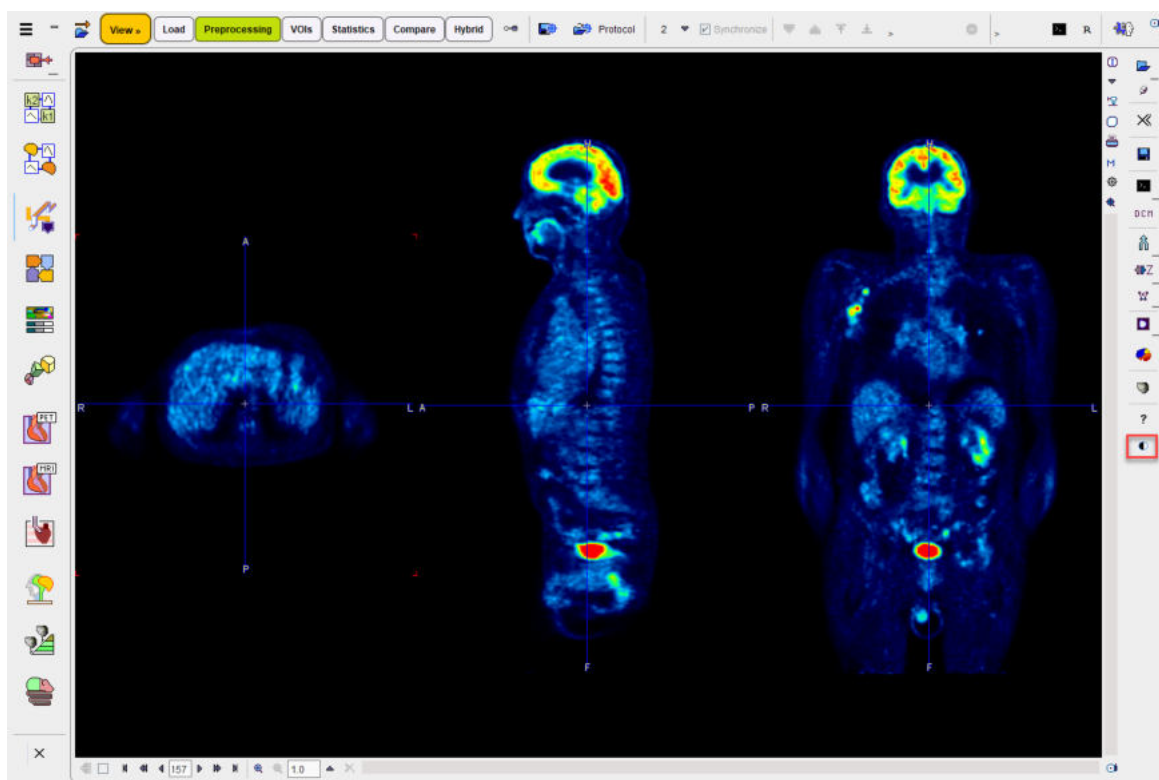
and the MIP version of it:

Positioning of Visual Slices

Several functions are available for discretely defining the slice images visible in the viewport(s). Illustrated below is the **Triangulate Center** option button for 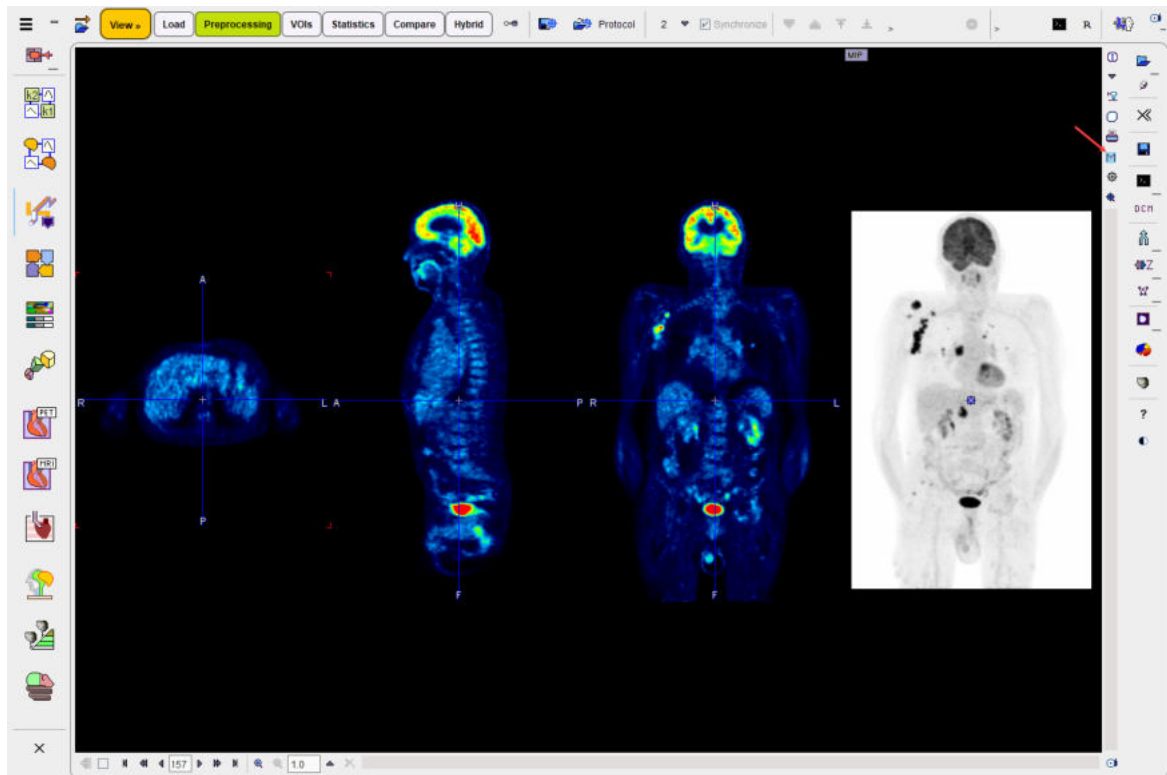positioning at the center of the image volume. Each image also has a coordinate system with an origin [128] which can be addressed with the **Triangulate Origin** button.

The box
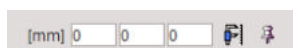
allows entering offsets in mm of the origin. The defined position is addressed with the 🔲 button. If the pushpin 📌 right to this button is set to 📌, the defined coordinate will be maintained when switching between different series which have been loaded in a viewport. This functionality is particularly useful for spatially normalized or images from a hybrid scanner.

Rotations and Mirroring

Image reorientation operations such as mirroring and rotations can be done using the buttons in the dedicated pane.
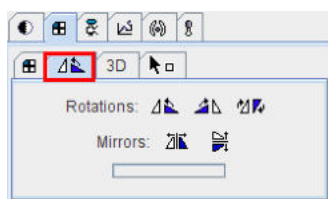
If the display is in the orthogonal viewing mode, first activate the appropriate plane by clicking onto the corresponding image (holding down the `CTRL` key avoids new reslicing), and then activate the appropriate button.

> **Note:** For data with enough information about subject positioning PMOD will keep track of subject orientation and update the annotations accordingly.

9.4   Image Zooming

Sometimes it will be helpful to zoom the shown images, for instance during VOI outlining. Image zooming can be operated in different ways

Scrollbar Zooming

Often images ports have a scrollbar area around them. Then the zoom buttons can be used for zooming/shrinking, or a zooming factor can directly be entered. ⨯ resets zooming. If the scrollbar is not visible, it can be shown by the indicated button to the image right.
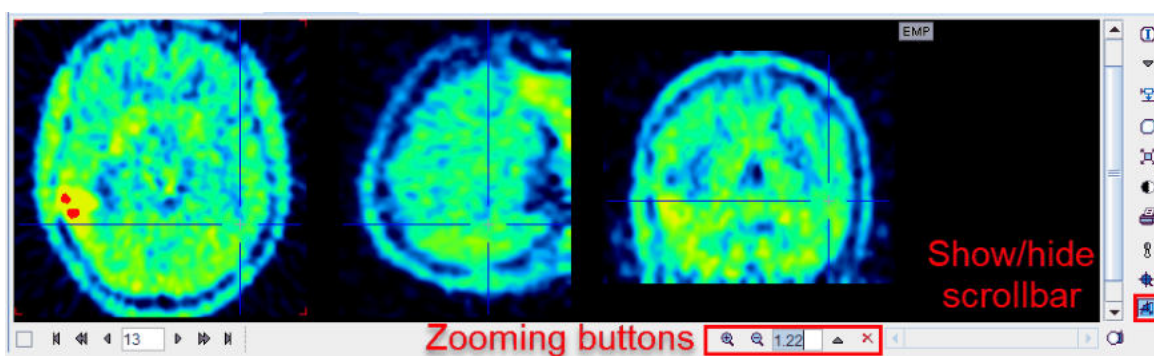
If there is no such button, the image context menu (click right mouse button in image area) can be used instead.
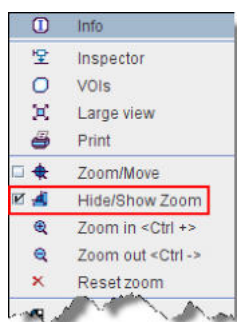
The visible part of the image can be adjusted using the scrollbars around the image which appear as soon as the full image is not visible any more.

Mouse-driven Zooming

There is also a mode for mouse-driving zooming which can be entered by the 🔸 button from the image border or the context menu.

When the cursor is moved over the image, it changes its shape:

1. In left and right border area (zooming area) it has a ⌖ shape. To zoom in/out click the left mouse button and drag up/down.

2. In the central area (panning area) it has a ⊕ shape. To adjust the visible part of the image click the left mouse button into the center of the image and drag the image around
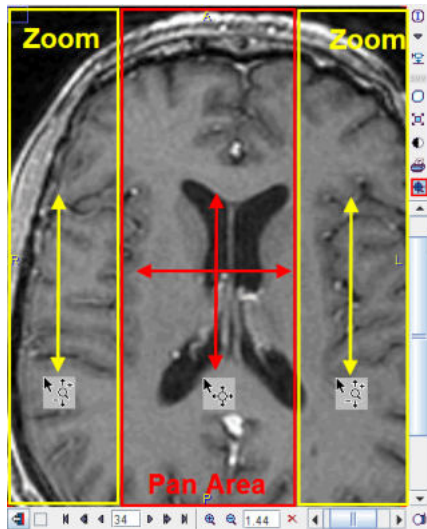
After appropriate zooming, the zoom mode should be quit by pressing 🔳 once more, because some of other mouse-operated functions might not work.

Zooming with Mouse-Wheel

Similar to the zooming mode in other programs PMOD supports zooming with the mouse wheel while holding down the CTRL key. Note that in the orthogonal mode the triangulation point will be kept within the visible area.

9.5   Data Inspector

The data inspector tool is opened using the button

🗗

and initially shows the dialog window illustrated below.
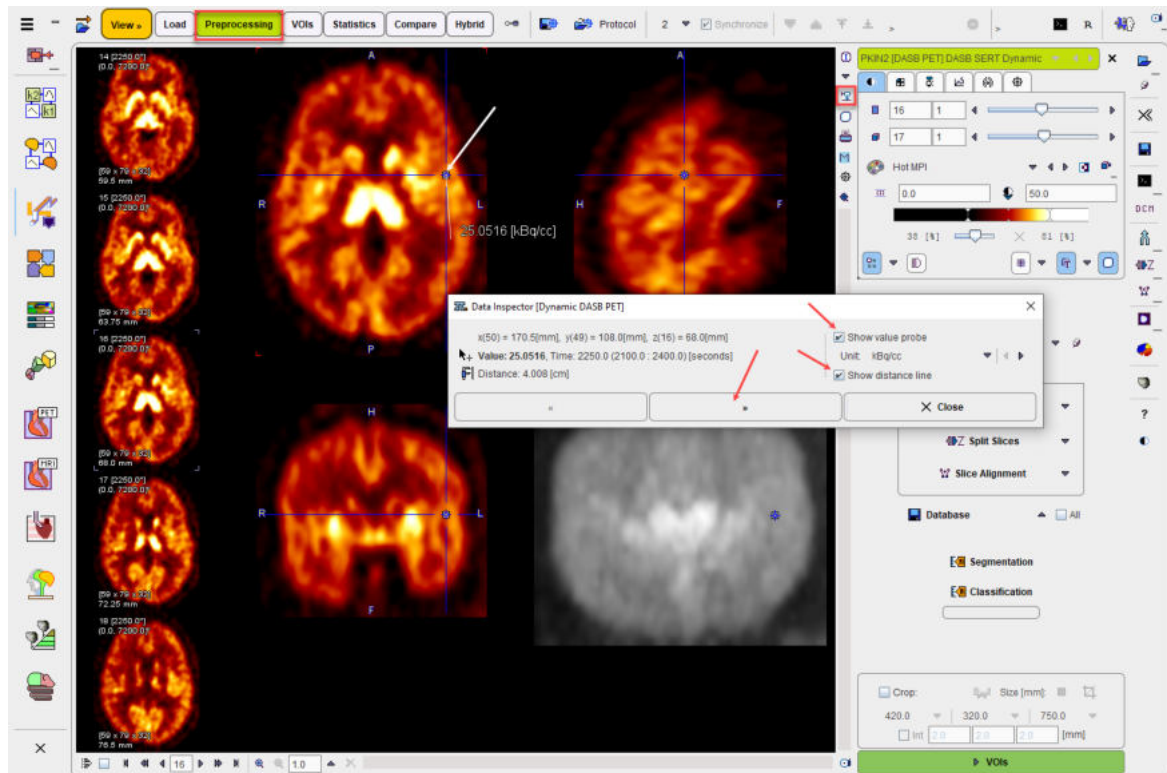
When the cursor is moved over the images, the information about the cursor location (in pixels, and mm from the coordinate system origin) and the pixel value at that location is continuously updated. A locator is shown in the image, marking the last position where the left mouse button was clicked into the image. For the dynamic images the frame start and end together with the mid frame time is displayed in the **Time** section. The distance from the locator to the current cursor position is continuously updated. If the **Show distance line** box is checked, a line indicates the measured distance. If the **Show value probe** box is checked, the pixel value is also shown close to the cursor and the units displayed. If one of the **SUV** option is selected in the **Unit** list while **Show value probe** box is enabled, the selected e.g. **g/ml{SUBbw}** is automatically calculated and displayed for each pixel. Note that in order to calculated the SUV, the subject weight and size as well as the injected dose are requested.

The **>>** button extends the dialog window to show more information
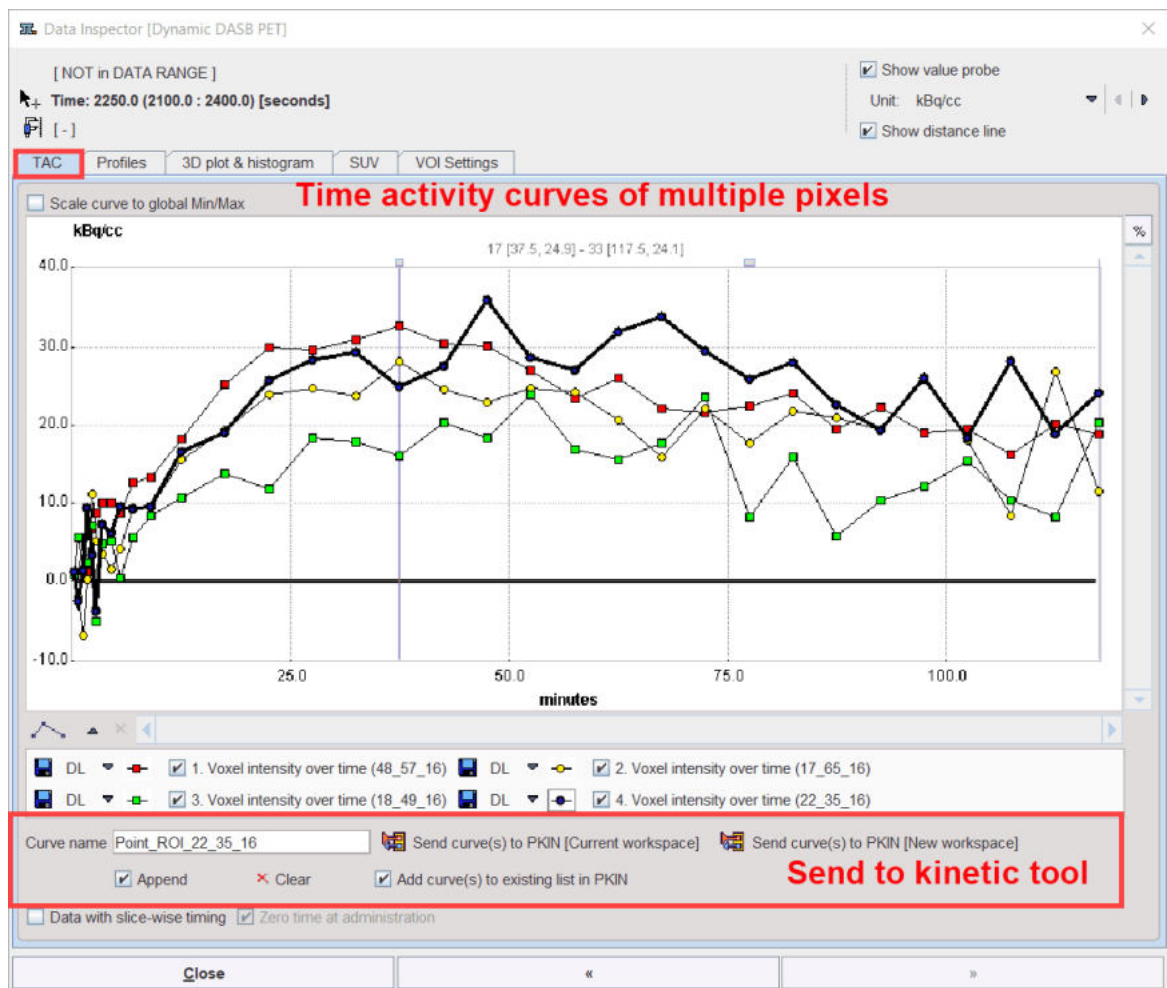
Using the **TAC** tab the time-activity curve of single pixels can be inspected (for dynamic studies only) and sent to the kinetic modeling tool. It gets updated as soon as the user clicks at a pixel. With the **Append** box enabled, each click in the image adds a new pixel time activity curve to the TAC tab. All the selected pixels TAC can be send to PKIN using one of the available buttons. With the **Data with slice-wise timing** box enabled the pixel-wise TAC uses timing of the individual slice for the TAC transfer to the kinetic tool.

The **Profiles** tab displays the horizontal and vertical profiles at the current location of the locator.
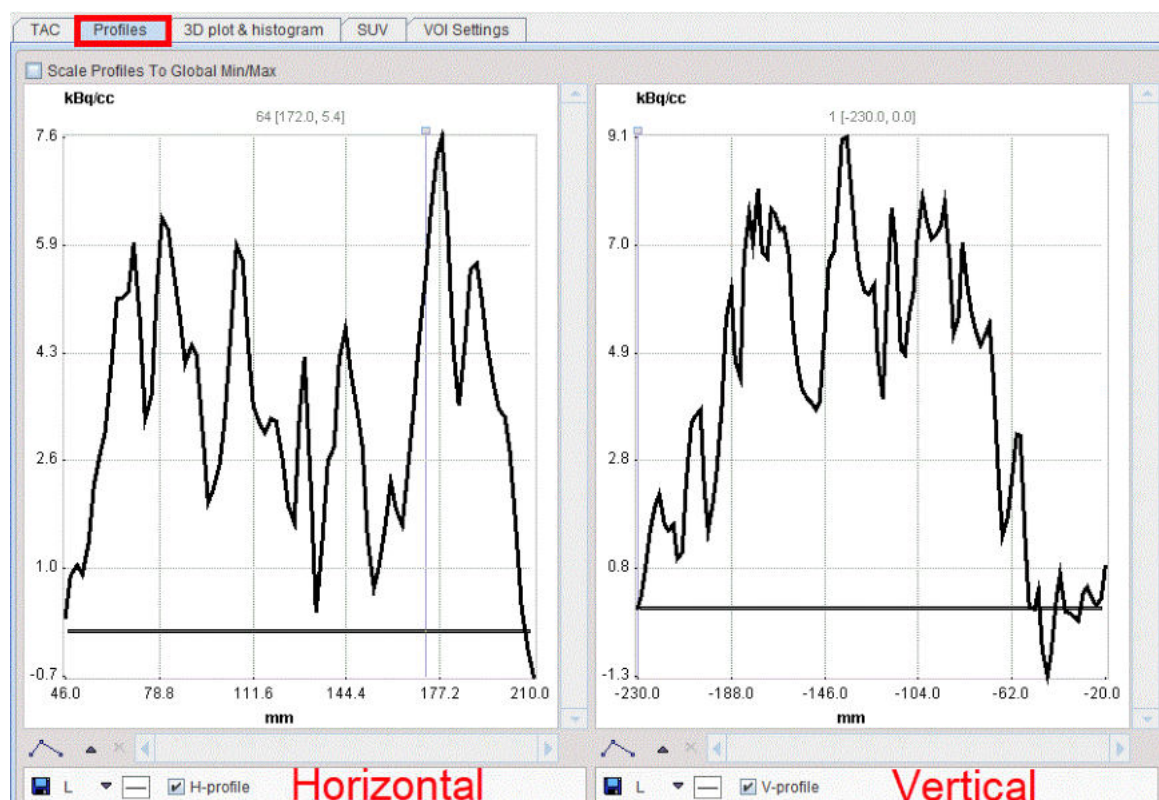
On the **3D plot & histogram** tab a 3D plot and the histogram of the slice values are shown, whereas the **SUV** tab allows inspecting the pixel values in SUV rather than kBq/cc, provided that all activity information is available. The **SUV** tab is explained in the next section.

The **VOI Settings** tab allows quick settings for the keyboard-driven definition of the Peak VOIs and isocontouring VOIs. The functionality is described in a dedicated section 258.

9.5.1   SUV Value Inspection and Statistics

Standard Uptake Values (SUV)

The information contained in PET and SPECT images is related to the physical concentration of tracer in tissue. If all images distortions are corrected by the reconstruction procedure, the value units are activity concentrations, for instance Bq/ml. The uptake in tissue is dependent on many factors, but it is directly proportional to the injected activity, and inversely related to the mass within the tracer can distribute. To calculate a measure of tracer uptake which is better comparable among subjects ("Standard Uptake Value" SUV) the measured activities are therefore divided by the injected dose and multiplied by the body mass.

SUV Calculation Methods

Different variants of the SUV calculation are used. The most straightforward directly uses the subject weight entered in the demographic subject information. Because tracer uptake in fat is typically low, normalization to lean body mass has been found to be a preferable measure. However, recently it has been found that the lean body mass calculation using the James method breaks down for obese subjects, and the Janmahasatian method should be used instead [1]. An additional variant is normalization to the body surface area. A variant used in preclinical imaging is normalization to the injected dose.

The formula applied by the PMOD SUV calculation are:

1. **SUV Body weight** [g/ml] = (A/D)*W*1000.

2. **SUV Lean Body Mass** [g/ml] James method (normal BMI range) = (A/D)*LBM*1000.
   LBM(Female) = $1.07*W-148*(W/H)^2$,
   LBM(Male) = $1.10*W-128*(W/H)^2$.

3. **SUV Lean Body Mass** [g/ml] Janmahasatian method (also for extreme BMI) = (A/D)*LBM*1000.
   LBM(Female) = $9270*W/(8780 + 244*W/L^2)$.
   LBM(Male) = $9270*W/(6680 + 216*W/L^2)$.

4. **SUV Body Surface Area** [cm^2/ml] = (A/D)*BSA*10000.
   BSA = $(W^{0.425} \times H^{0.725}) \times 0.007184$.

5. **Injected dose per ml** [%ID/ml] = A/D*100.

The variables in the formula are defined as follows:

| A	Activity concentration in the image [Bq/ml]. Note that it has to be decay corrected during reconstruction to a common time for all acquisitions of a whole-body or dynamic scan.
D	Applied dose [Bq] at the time the image is corrected to, see below.
W	subject weigth [kg]
H	subject height [cm]
L	subject height [m]

Usually, the activity of the dose to be applied is measured at a time before injection. Therefore, PMOD needs the following information for calculating the effectively injected dose at the time of image decay correction:

- the half-life of the radionuclide;
- the time when the activity was calibrated before injection;
- the activity remaining in the syringe after injection and when it was calibrated (only available in GE data);
- the time of image decay correction.

The activity remaining in the syringe will be subtracted from the calibrated activity, taking the different decay times into account.

PMOD tries to extract the information needed from the image header. For various reasons (information entered by technician, file format, manufacturer) however, it may be incomplete. In this case the information has to be entered or corrected manually before the SUV can be calculated.

SUV Value Inspection Tab
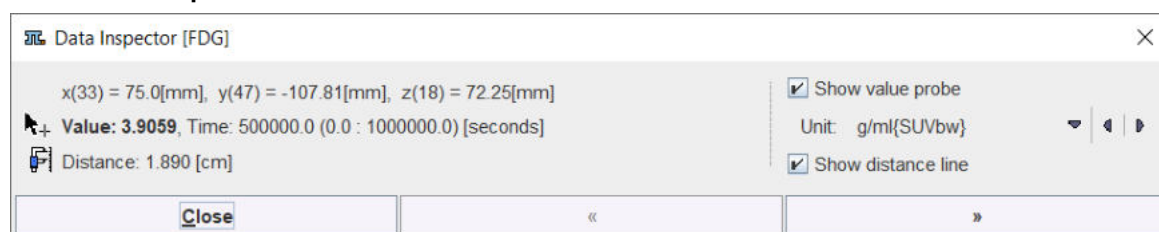
The window can be extended to show the SUV-related elements with the **>>** button. The **SUV** (Standard Uptake Value) tab content is shown below:

The upper part of the **SUV** panel shows the elements which are relevant for the SUV calculation. They should be essentially be self-explanatory. The lower part shows the different SUVs of the current pixel. The SUV values change whenever the cursor is moved over the image.

SUV Parameter Details

Unfortunately, the information regarding the time point of decay correction is unreliable in the images. In cases when it is explicitly encoded, it is shown in the **Image decay correction Date / Time** field. Otherwise, the **Date / Time** option should be specified such that the time shown represents the image decay correction time. Per default, it is set to the **Acquisition** time field of DICOM, which however is not always correct. Therefore, it is possible to alternatively select the **Series** or the **Scan** time DICOM information. As a convenience the **Copy to all** button copies the selected **Date / Time** to all other date and time fields and no correction will be applied to the specified dose.

Series Date/Time	Abstract time point which defines zero for the time vector of a dynamic series.
Acquisition Date/Time	The actual time the data acquisition started (default setting).
Scan time	Private GE field; should be used for SUV calculations with other GE fields.

Image decay correction Date/Time	May be contained in Enhanced PET objects, a copy of Administration time, calculated from decay factors in some situations, or copied from the selected **Date / Time**.
Administration Date/Time	Standard DICOM time at which radiopharmaceutical administration started. According to the DICOM standard PET images can be also decay corrected to this time point. (Please note that in this case the SUV values will change compared to previous version as an additional factor for the delay from the administration to the scan start will be calculated.)
Calibrated dose Dose calibration Date/Time	Private GE fields for SUV calculations. They are set to the standard total dose and administration time for non GE data.
Dose remaining... Remaining dose Date/Time	Private GE fields for SUV calculations. Are set to 0.0 and Administration time for non GE data.

Note: Because of the uncertainty of the SUV-related information in DICOM it is recommended to verify PMOD's SUV values with the values calculated by software of the hardware vendor.

Image Display in SUV Units

If all the information required for SUV calculation is present, the display units can be switched from the original activity concentration units to SUV values using the **button** 133 near the lower color table threshold.

SUV Statistics

The calculation of statistics in SUV units is directly supported on the original image by the **VOI functionality** 323, provided that all required information is available. Explicit SUV images can be calculated with the **SUV Image Calculation** external tool.

Reference

1. Tahari AK, Chien D, Azadi JR, Wahl RL: Optimum lean body formulation for correction of standardized uptake value in PET imaging. J Nucl Med 2014, 55(9):1481-1484. **PMC**

9.6 Handy Image Processing Tools

The processing tools pane offers a substantial range of image transformation methods.
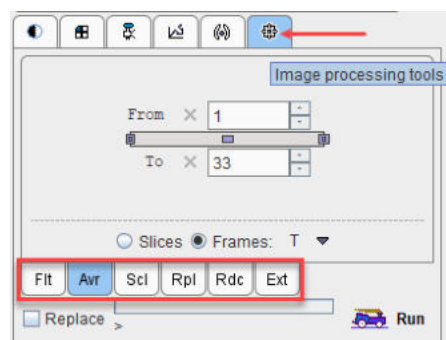
There are 5 methods which can directly used via the sub tabs, and many other image processing tools 151 via a list on the **Ext** tab. To process the current image select a sub-tab, configure the parameters of the method which appear in the pane, and then activate the **Run** button. If the

Replace box is checked, the original data is overwritten, otherwise a new image series is created and added to the list.

The directly accessible functions are:

- **Flt**: Image filtering 158 in the spatial and temporal domain.

- **Avr**: Averaging of a contiguous range of image frames or slices between the **From** and **To**.
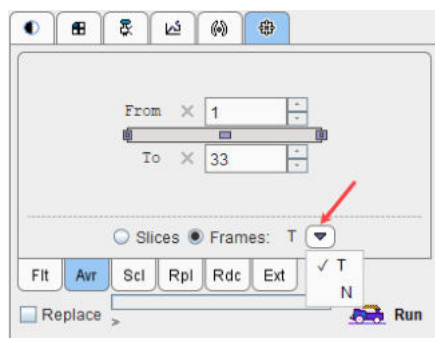

There are two variants of **Frames** averaging for dynamic series, time-weighted averaging **T**, and normal averaging **N.**

- **Scl**: Scaling 175 of the pixel values, for instance for calibration or to calculate relative uptake.

- **Rpl**: Replacing 173 of pixel values which satisfy a certain condition by a constant.

- **Rdc**: Simple function for matrix size reduction 172 .

9.7   Image Processing Tools

Image processing tools are plug-ins which take one or several images as input, and return a result image. The tools can be interactively called on individual images, or they can be used as stages in a processing pipeline 471 .

Tools Selection

The processing tools can be called interactively using the 🗕 button in the image sidebar.
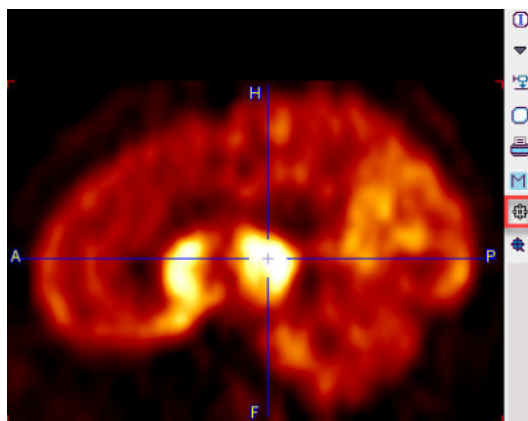
As a result, the list of available tools appears
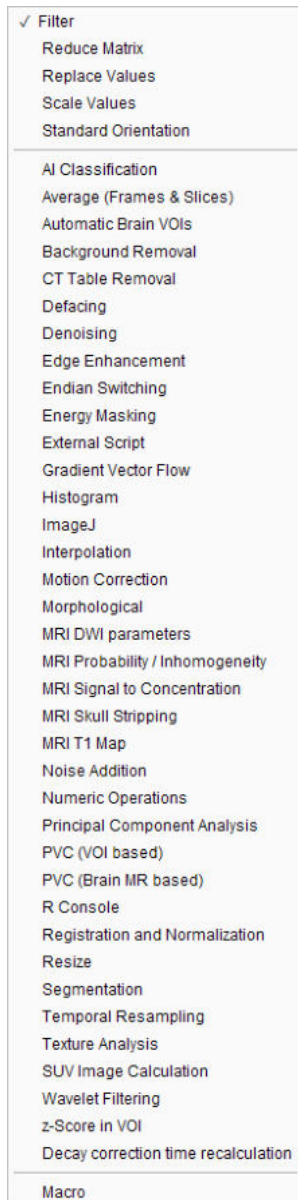
from which a tool can be selected.

Alternatively, the list can be obtained as illustrated below by the **Ext** tab in the tools section and activating the selection arrow.
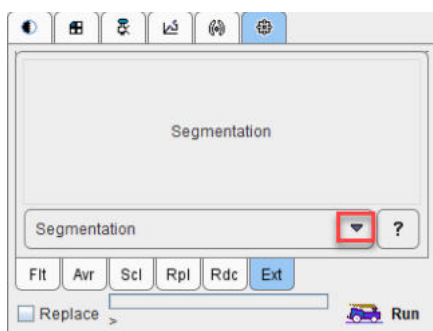
Tool Operation

After selecting a tool from the list (and activating **Run** in the tool version), a specific dialog window is opened with a short explanation and the parameters needed for processing. Shown below is the **Filter** dialog window as an example.
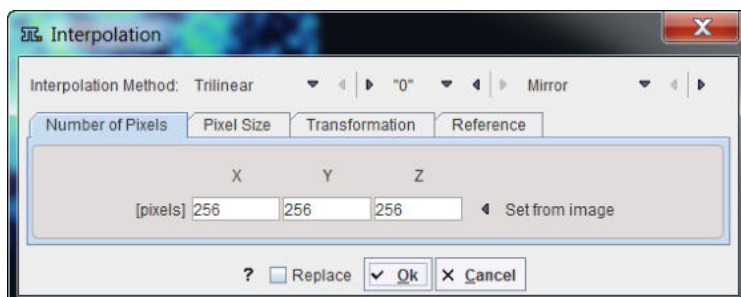
The buttons at the bottom are common to all tools. If the **Replace** box is checked, the current images are overwritten by the results. Otherwise, a new image series is created for returning the results and added to the series list. **?** provides help information of the tool functionality. **Ok** start the actual data processing.

The functionality of the external tools is described below, except for the Partial Volume Correction (PVC) 446 tools which are explained separately.

9.7.1   Average (Frames & Slices)
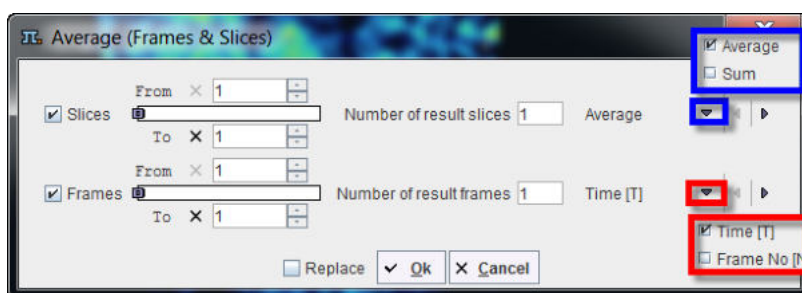
Allows simple averaging within a time range and/or within a slice range. The number of generated slices/frames can be entered numerically.

9.7.2   Automatic Brain VOIs (PFUS Option)

The tool allows generating contours VOIs in the input space according to the selected **VOI Template**. If the tool is called from pipe processing, the VOI statistics will also be evaluated and can be saved.
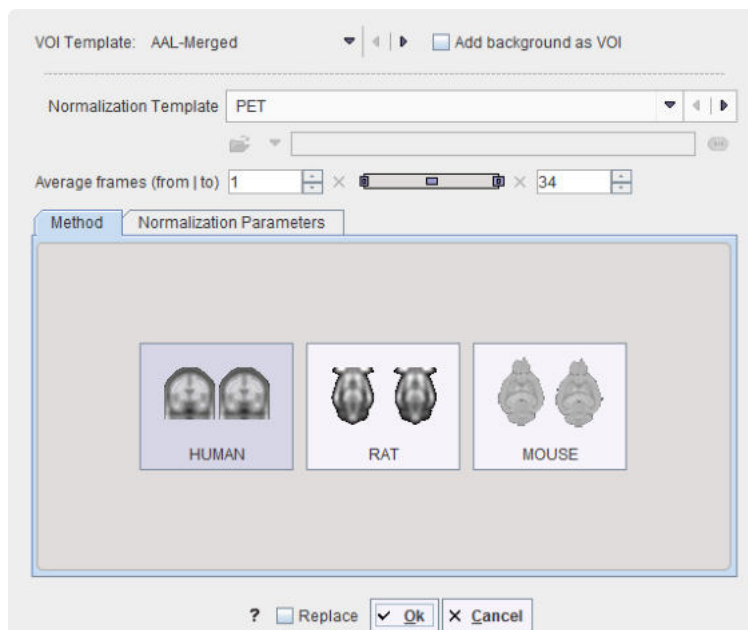
The **Method** is available for **HUMAN**, **RAT** and **MOUSE** studies. The **Input** study is normalized to the chosen **Normalization Template**. The algorithm applied is *Brain Normalization* and the inverse transformation is calculated. In case the input study is dynamic, an averaged input is created for the selected frame range **Average frames**. The selected template VOIs is transformed to the input space using the inverse transformation calculated during the normalization procedure. Finally the transformed VOIs are outlined.

Notes: This procedure is crucially dependent on a successful normalization.

9.7.3   Background Removal
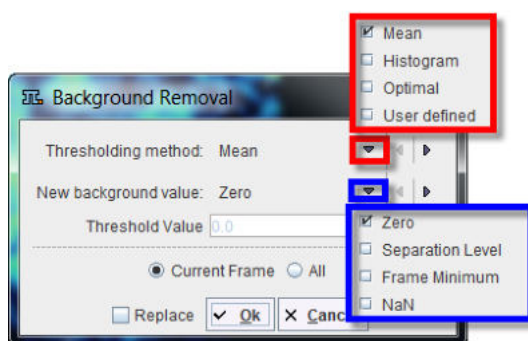
Methods to perform image background subtraction. The **Thresholding** selection contains **Mean**, **Histogram**, **Optimal**, and **User Defined**. The selected method determines a separation value, and all pixels below it will be replaced by the value specified with the **New background value**.

9.7.4   CT Table Removal

The tool allows removing the table from the CT images and organ cropping.

The tool requires as input a CT whole body image HSF oriented. The algorithm is applied to the **WHOLE BODY** or to the selected body part: **HEAD**, **LUNG** or **LIVER**. The croppin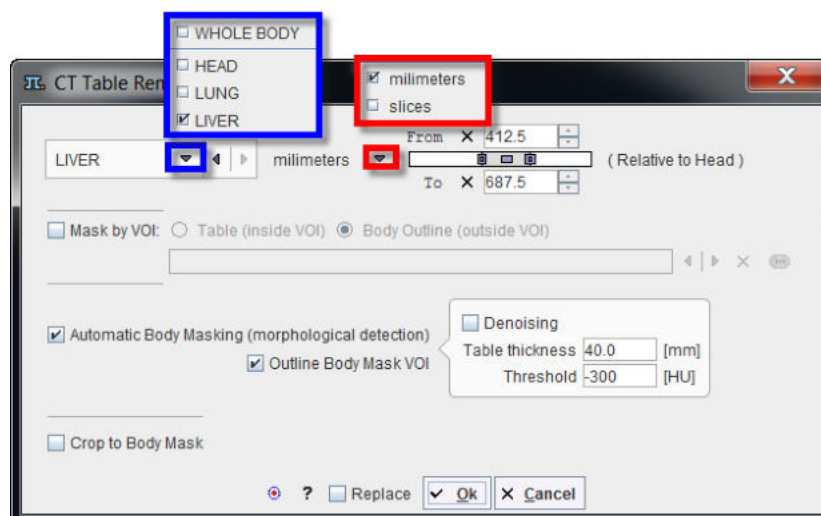g box for the selected organ is automatically defined **Relative to Head** based on the **millimeters** or the **slices** values available in the **From** and **To** fields. The values can be entered numerically, or the handles can be dragged with the mouse.

The **Mask by VOI** option allows masking the image with the specified VOI. There are two options available:

- **Table (inside VOI)**: allows removing the table form the CT study by replacing the voxels inside the VOI with the minimum value.

- **Body Outline (outside VOI)**: allows cropping the organ of interest if the **Crop to VOI** checkbox is enabled. It replaces the voxels outside the selected VOI by the minimum value.

The **Automatic Body Masking (morphological operation)** is using the **Table thickness** and the **Threshold** parameters for the automatic algorithm. Optionally, the **Denoising** can be applied. The result of the morphological operation is used to **Outline Body Mask VOI**. In addition, the **Crop to Body Mask** can be enabled.

It is recommended to use the default settings and only experiment with other parameter values if the procedure fails. The default settings are available by activating the default settings button ⊙.

9.7.5   Defacing

The tool allows removing the face voxels from human anatomical MRI and CT images. The images need to be provided in HFS orientation. It is assumed no motion is observed in case of dynamic studies.

Enable the **Define head location within image bounding box relative to image top** in **milimetres** or **slices** in the **From, to** section. Select the appropriate **Template** for the normalization procedure in the **Mask (Normalize MR/CT to Template)** panel. Initially try with the default sampling distance of 8 mm. This value can be manually edited if needed.
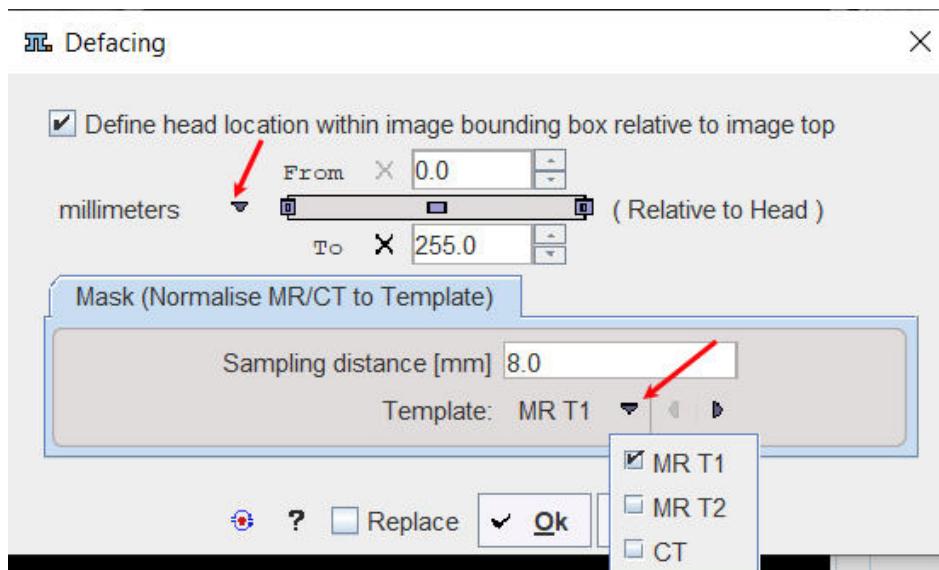
The procedure is based on the Brain Template Normalization implemented in the fusion tool. Start the defacing procedure activating the **OK** button. Initially the normalization between the input image and the selected MNI template is calculated. The inverse of the direct transformation is calculated and applied to transform the predefined faced mask in MNI space to the image space.

9.7.6   Edge Enhancement
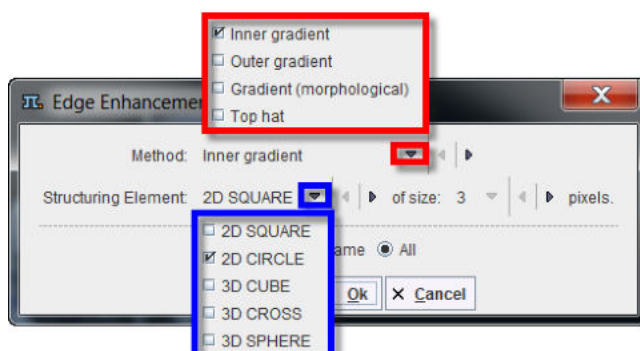
Performs an edge enhancement operation based on different **Methods**: **Inner gradient**, **Outer gradient**, **Gradient (Morphological)** and **Top hat**. **Structuring Elements** of **2D SQUARE**, **3D CUBE** and **3D CROSS** are available at the sizes of **3**, **5**, **7**, and **9** pixels.

It is a morphological contouring tool and the processing is based on voxel wise morphological operations: erosion and dilation and image subtraction. The **Methods** are summarized in the table below:

Inner gradient	the difference between the input image and its erosion using the specified structuring element
Outer gradient	the difference between the dilation and the input image using the specified structuring element
Gradient (morphological)	the difference between the dilation and the erosion using the specified structuring element
White Top hat	the difference between the input image and its opening using the specified structuring element

Black Top hat	the difference between the closing and the input image using the specified structuring element

9.7.7 Endian Switching
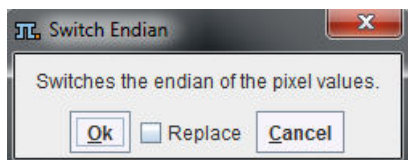
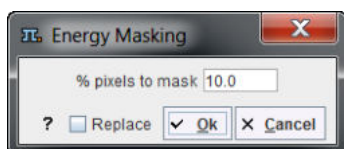Allows switching the endian encoding of the pixel values. This can be helpful if the wrong endianness was assumed during image loading.

9.7.8 Energy Masking

Performs the masking of an image series based on the signal energy.

The tool calculates the pixel-wise energy (sum of the squared signal values), determines the histogram of this energy map, and masks the specified percentage of pixels with lowest energy values based on a histogram analysis.

9.7.9 External Script
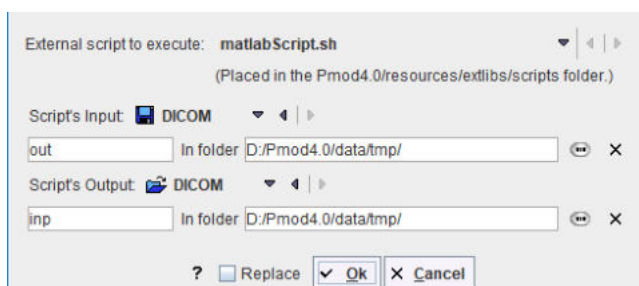
This tool allows running an external program, which needs to be placed in *Pmod4.4/resources/extlibs/scripts*. It then shows up in the **External script to execute** list as a new entry. Input to the script is an image file with the name defined in the **Script's Input** field. The script may apply any processing to the image and needs to save the resulting image under the name defined in the **Script's Output** field. Note also the image format definitions for the input and the output which must meet the file content.

When the external tool is executed, it will first save the current image with the **Script's Input** definition, call the script, and then try loading an image file with **Script's Output** definition.

Example: Execution of Matlab Script

A Matlab script example which requires Matlab's Image Processing Toolbox is available in *Pmod4.4/resources/extlibs/scripts*. It consists of two files:

- *matlabScript.sh* which starts Matlab and lets it execute the code in the mFile script. It essentially contains a system-specific matlab call:
  ```
  matlab -nosplash -r testScript
  ```

■ *mfiles/testScript.m* which contains proper the actual image processing, eg

```
% Read data from disk. Info metadata is needed to preserve
% important image features, e.g. timing.
data = dicomread('C:/Pmod4.4/data/tmp/out');
info = dicominfo('C:/Pmod4.4/data/tmp/out');
% Processing.
...
...
% Write data to disk. This will be input to PMOD.
% To save data in DICOM multiframe mode, use
% 'Create Mode' option with 'copy' value.
dicomwrite(fData,  'C:/Pmod4.4/data/tmp/inp',  info,  'CreateMode',
'copy')
quit
```

9.7.10 Filter

The **Filter** tool
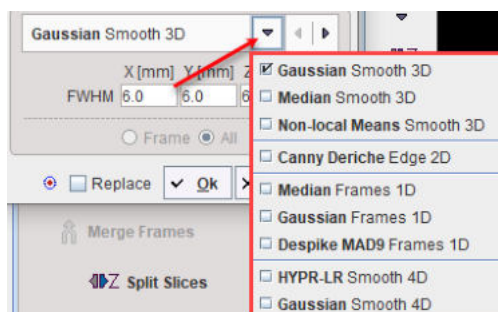
offers the following image filters:

■ **Gaussian Smooth 3D** spatial filter with a full-width at half maximum (**FWHM**) in mm;

■ **Median Smooth 3D** spatial filter with a width in mm;

■ **Non-local Means 3D** non-local means image denoising filter with **Low**, **Medium** and **Strong** settings;

■ **Canny Deriche Edge 2D** edge enhancing spatial filter;

■ **Median Frames 1D** smoothing filter in the time domain for dynamic images.

■ **Gaussian Frames 1D** smoothing filter in time domain for dynamic images.

■ **Despike MAD9 Frames 1D** despiking filter in the time domain based on 9-points neighborhood. If value differs from the median more than MAD (Median Absolute Deviation) it is replaced by the median

■ **HYPR-LR Smooth 4D** complex denoising method for the dynamic PET series.

■ **Gaussian Smooth 4D** Gaussian smoothing with kernel in spatial and temporal dimension.

9.7.11 Gradient Vector Flow

The **Gradient Vector Flow** tool allows calculating the image gradient in a specified direction [1], which is for instance used for active contours algorithms.
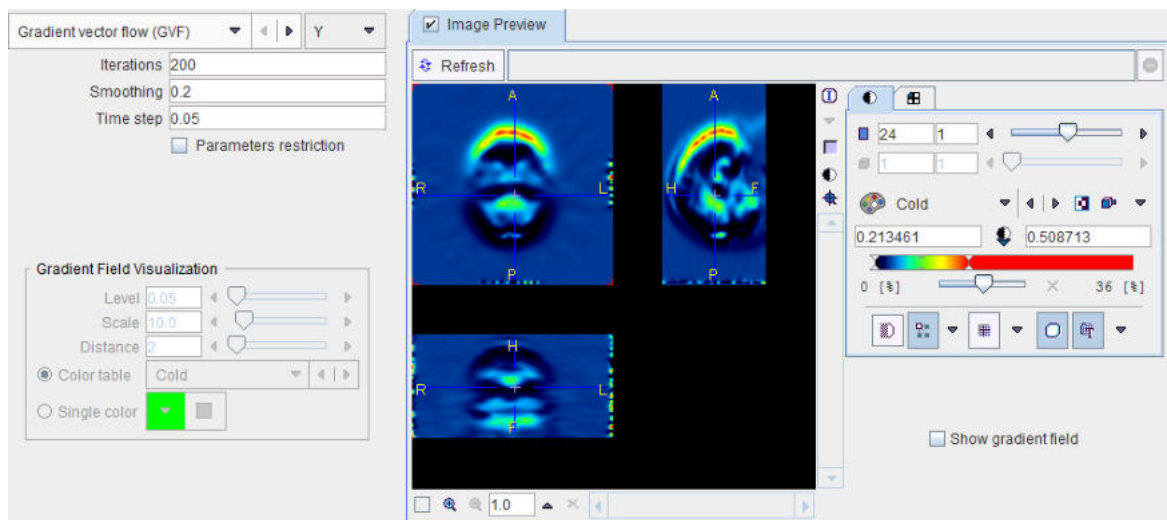
Different algorithms are supported:

- **GVF**: calculates the gradient using the gradient vector flow algorithm;

- **General GVF**: calculates the gradient using a generalized gradient vector flow algorithm;

- **Differential gradient**: calculates the gradient by subtracting values of neighbouring pixels;

- **Sobel operator**: calculates the gradient by convolving filter mask with matrix consisting of image pixels.

During the estimation procedure the following parameters can be set:

- **Gradient width**: distance (in pixels) between two points, the intensity difference which defines the gradient value;

- **Iterations**: number of iterations performed during **GVF** and **GGVF** calculation;

- Smoothing parameter (μ): regularization parameter governing the trade-off between the first and the second integral term. Smoothing parameters should be set according to the amount of noise present in the image: the higher the noise the bigger the value.

- Time step (Δ): is representing the time length for each iteration.

In order to guarantee algorithm convergence, the smoothing parameter and the time step should satisfy the following expression: $\mu < -1.36 * \Delta t + 0.22$. Therefore, the **Parameters restriction** box should be enabled.

By enabling **Image Preview** and the **Show gradient field**, the gradient vectors can be visualized.
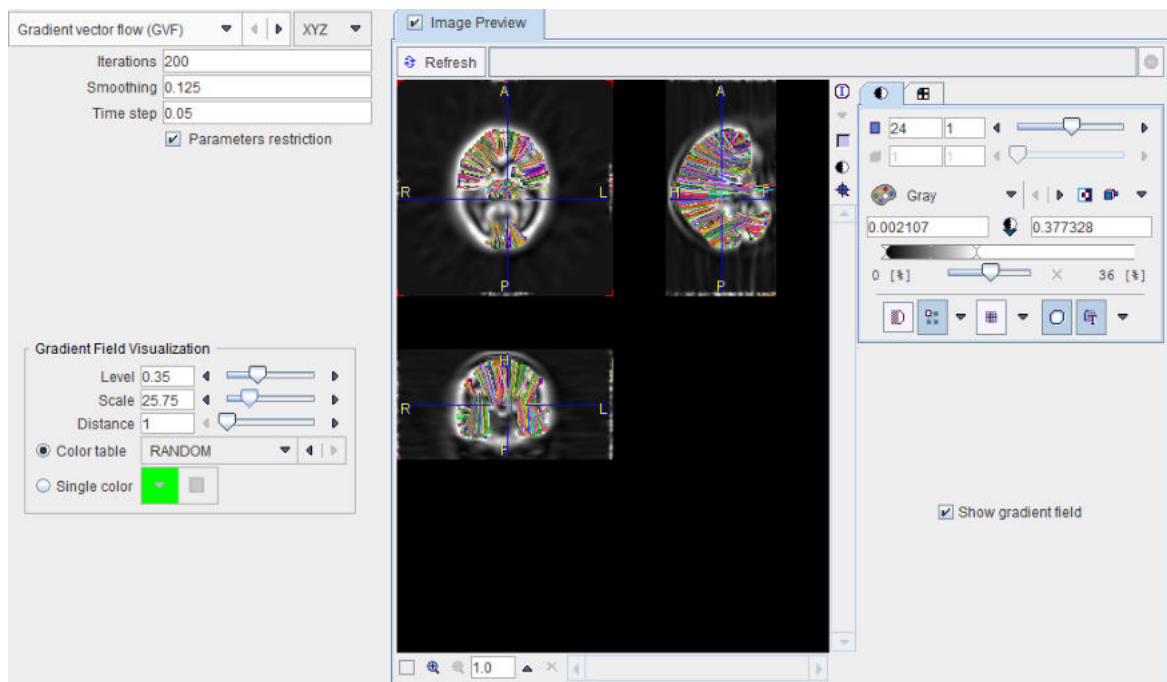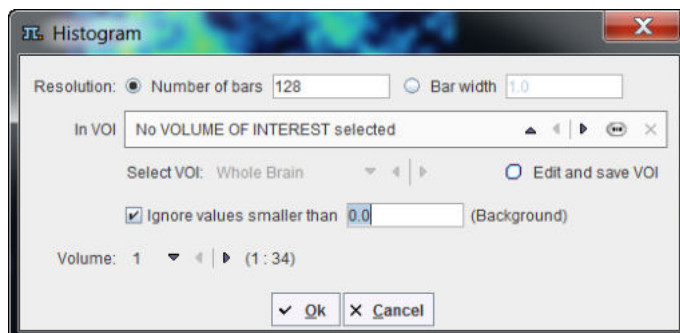
Reference

1. Chenyang Xu, Jerry L. Prince. Snakes, Shapes and Gradient Vector Flow, Transactions on Image Processing, March 1998, p. 359-369.

9.7.12 Histogram

Calculates the histogram of the pixel values in the whole **Volume** or within a VOI. An existing VOI can be selected, or created with the **Edit and save VOI** button.


If **Number of bars** is enabled, the value range is divided into the specified number of equal intervals (e.g. 128). With **Bar width**, the interval size is directly specified. Values below a **Background level** can be excluded by checking **Ignore values smaller than** and specifying the **Background** level.

The number of occurrences in each interval are counted and plotted as a curve. Additional curves (**2nd derivative**, **Cumulative**, **Smoothed Histogram**) can be enabled in the control area. Note that the numeric values of the histogram can be exported using the context menu (right mouse button in curve are, then **View Values**).
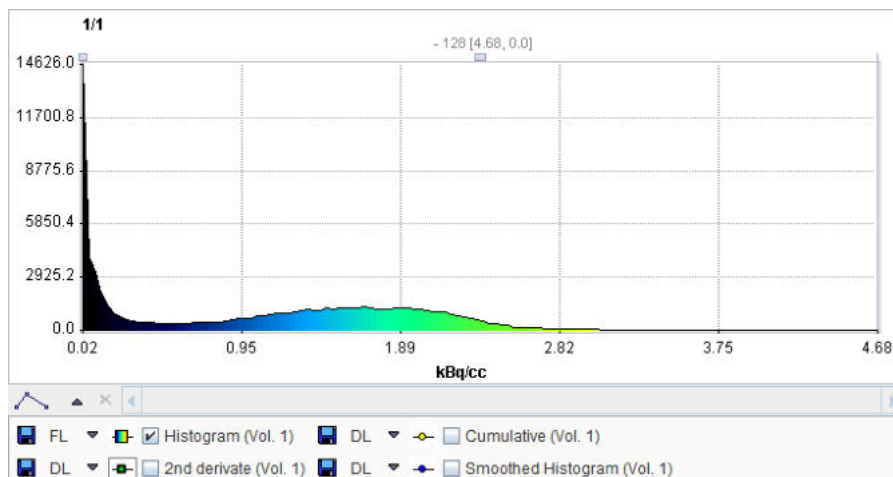
9.7.13   ImageJ
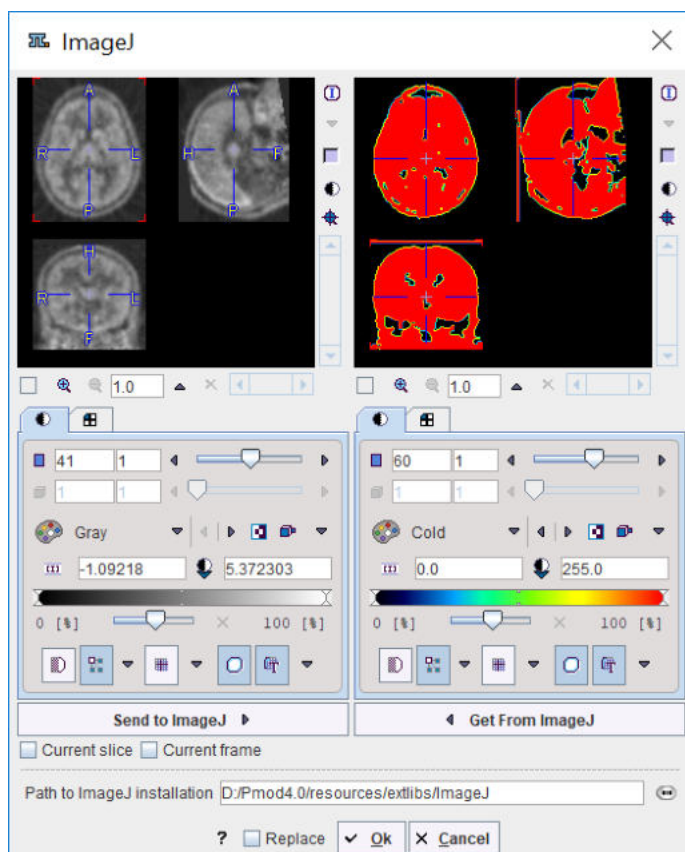
This tool allows transferring image data to ImageJ with the **Send to ImageJ** button, process the images with dedicated procedures in ImageJ, and retrieving the results with the **Get from ImageJ** button back to PMOD. Included in the distribution is a basic ImageJ version. For using a different version with dedicated plug-ins please point to your own installation using **Path to ImageJ installation**.
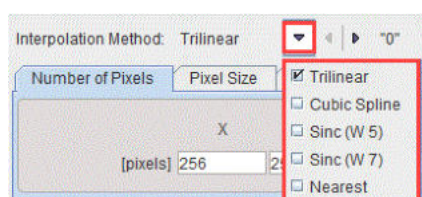
9.7.14   Interpolation

The **Interpolation** tool serves for calculating a new image volume by an interpolating values from the current image volume. It consists in three main parts:

1. The **Interpolation Method**.

2. The **Background value**.

3. The **Border sampling**.
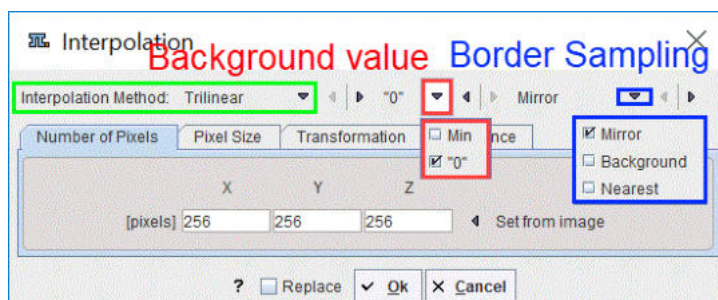
There are five choices for the **Interpolation Method** which is applied when calculating the new image.


Default is **Trilinear** which is a simple and fast interpolation using all 8 enclosing pixel values. The truncated sinc interpolations **Sinc (Window 5)** and **Sinc (Window 7)** are more accurate, but considerably slower. **Nearest** neighbor interpolation just uses the value of the closest pixel, so it is very fast but in most cases does not provide satisfactory quality. However, it is the method of choice if an object map image containing integer values needs to be resliced. The **Cubic Spline** interpolation avoids oscilations that can be introduced in high order polynomial interpolations and is continuous.

There are two options for the **Background value**: **0** or **Min**.

There are three options for the **Border sampling**: **Mirror**, **Background** and **Nearest**. The selection is not available for the **Cubic Spline** and **Nearest** interpolation methods. In case of the trilinear interpolation the selection is limited to the background or the nearest image voxel, as the mirror for the single value produces the same results as the nearest choice.
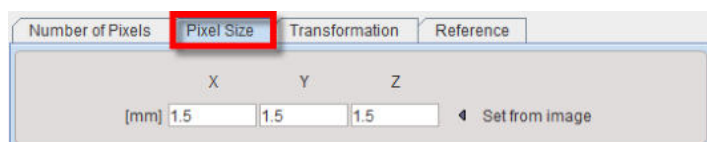
Matrix Size Specification

Using the **Number of Pixels** method
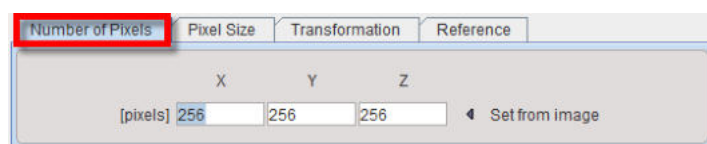
the existing image volume is sampled into a new number of pixels in each direction. The new pixel size is the result of dividing the bounding box by the new number of pixels. **Set from image** copies the current numbers into the **pixels** number fields.

Pixel Size Specification

Using the **Pixel Size** method,

a new pixel size in each direction can be specified. The matrix size results from the division of the volume sizes by the pixel sizes. Note that due to rounding the bounding box might change. **Set from image** copies the current pixel sizes into the **mm** number fields.

Spatial Transformation

Using the **Transformation** method
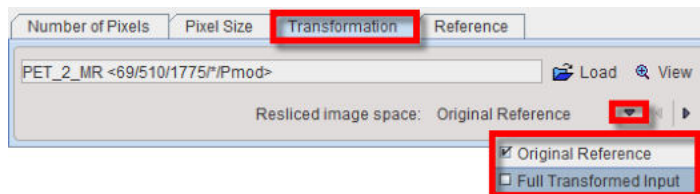
a spatial transformation matrix calculated by the fusion tool can be applied to the image. **Resliced image space** has two settings:

- **Original Reference:** The transformation is applied with the resolution of the reference image used during matching, and the result is in the bounding box of the original reference image.

- **Full Transformed Input:** The affine part of the transformation is used to calculate the space of the transformed box of the input image. The result is in the transformed space of the input image, i.e. the voxel size is that of the input image.
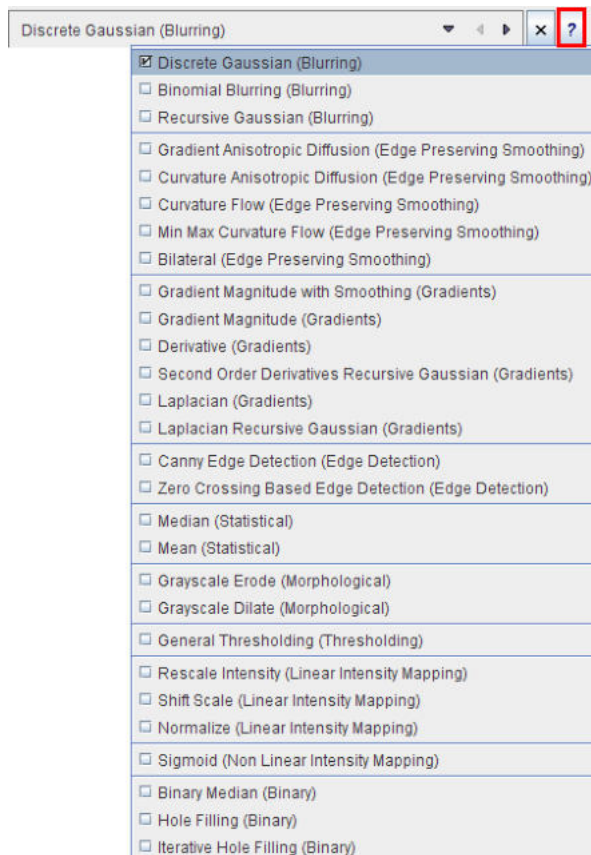
Interpolation to Reference

Using the **Reference** method
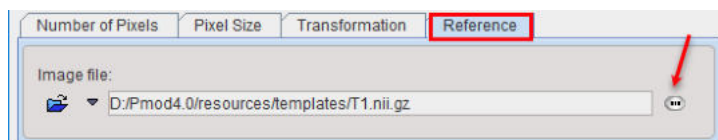
the image is interpolated to the space of the selected reference image assuming identity transformation. The resulting image will have the dimensions, pixel size, and the origins of the reference image and the pixels at zero of the real coordinates will coincide.

9.7.15   ITK Image Filters

This tool provides an interface to 28 image filters provided by the ITK (Insight Toolkit) libraries. For each filter there is a short description which can be viewed with the **?** button. The ITK is under an open-source BSD license which allows free usage. For more details please refer to the **The ITK Software Guide**.

Note: PMOD Technologies can not be held liable for permanent support of the ITK interface, nor for the performance of the provided libraries.
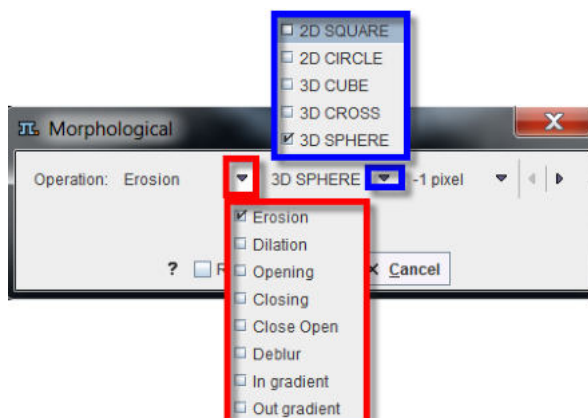
9.7.16   Motion Correction (PFUS option)

The motion correction in the external tools is mainly for the use in pipe processing. It is only available if the image fusion option is included in the PMOD license.
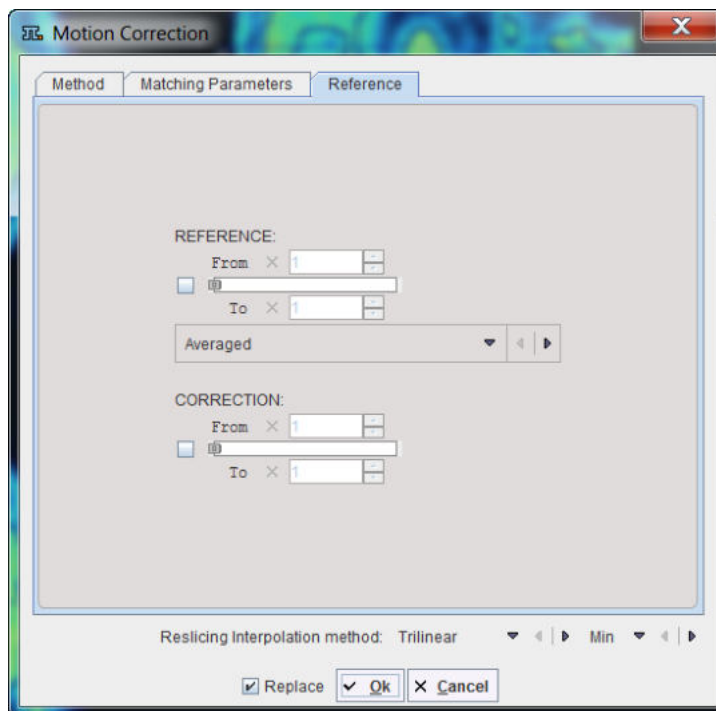
Please refer to the *PMOD Image Fusion Guide* for details about the matching options.

9.7.17 Morphological

Morphological operations process images based on shapes. It applies a structuring element defined by a shape (**2D SQUARE**, **2D CIRCLE**, **3D CUBE, 3D CROSS** and **3D SPHERE**) and a size in pixels.

Erosion removes pixels on object boundaries, darkens small bright areas, and very small bright areas like noise spikes or small spurs might be totally removed.

Dilation adds pixels to the boundaries, brightens small dark areas, and very small dark spots might be totally removed.

Opening (Erosion-Dilation) removes small objects from an image while preserving the shape and size of larger objects in the image. It darkens small bright areas, and may entirely remove very small bright spots like noise spikes.

Closing (Dilation-Erosion) brightens small dark areas, and may entirely remove very small dark spots.

**Close Open** combines the effect of an opening and a closing.

Deblur is a sharpening filter based on an erosion and a dilation.

**In gradient** uses an erosion to enhance edges in the image towards the inner.

Out gradient uses a dilation to enhance edges in the image towards the inner.

9.7.18   MRI DWI

The purpose of the **MRI DWI Parameters** tool is to load gradient vector information for diffusion weighted MR images which are not contained in the image data. This information is required for the calculation of diffusion maps and diffusion tensors. When the series is saved as a DICOM object after using the tool, the gradient information is stored together with the images.
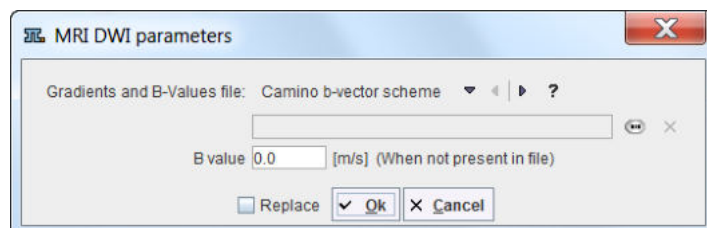
Several encoding types are supported and can be chosen from the **Gradients and B-Values file** selection:
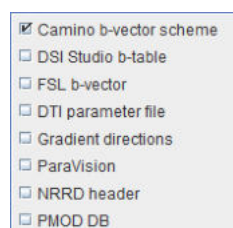
- **Camino b-vector scheme:** Text file containing four columns of data: x, y, and z coordinates of b-vectors and a b-value (last column) in s/m^2.

- **DSI Studio b-table:** Text file containing four columns of data: b-value in s/mm^2, then x, y, and z coordinates of b-vectors.

- **FSL b-vector:** Text file containing b-vector coordinates in three rows: x, y, and z values respectively. As PMOD does not support b-value files as a separate input you may add the b-values from b-value file as a fourth row in s/mm^2.

- **DTI parameter file:** Text file (.dpf) from DTI Studio containing b-vector directions and b-values.

- **Gradient directions file:** General option for text files with three to five columns. Three-column files are assumed to contain x, y, and z coordinates of b-vectors. Four-column files are assumed to have b-values in the last column. Five-column files are assumed to have gradient indexes in the first column. This option accepts gradient tables exported from the PMOD Info dialog window. B-values are in s/mm^2.

- **ParaVision:** For loading b-vectors directions and b-values from a Bruker ParaVision Parameter List file.

- **NRRD header:** For loading b-vectors directions and b-values from the DWMRI section of a NRRD format header file.

- **PMOD DB:** For loading b-vector directions and b-values from the gradient table files stored to a PMOD database. The data in the file is arranged in five columns as in **Gradient directions** file. A comment line starts with #.

9.7.19   MRI Probability / Inhomogeneity

The **MRI Probability/Inhomogeneity** tool allows applying the unified segmentation methods of SPM8 or SPM12 to the loaded T1-MR image. Depending on the **Output** setting, the Grey Matter,

White Matter, CSF probability maps are saved as frames in a dynamic series, or the MR image corrected for the spatial inhomogeneity.

Method	Two SPM-type segmentation variants are supported, the **3 Probability Maps** (SPM8) and the **6 Probability Maps** (SP12) variant. Note that the normalization transform which is obtained as part of the segmentation can be applied for the spatial normalization of the subject brain anatomy in later stages.
Denoising strength	Denoising of the MR image may improve the segmentation of gray matter, white matter and CSF. If a **Denoising strength** other than **None** is selected, a non-local means denoising algorithm is applied which preserves structure boundaries unless the strength is too high.
Sampling	Density of pixels considered in the calculation. It can be specified in **pix**el or **mm** units.
Bias regularization	Serves for compensating modulations of the image intensity across the field-of-view. Depending on the degree of the modulation, a corresponding setting can be selected from the list. The parameter to the right indicates the **FWHM [mm]** to be applied. The larger the FWHM, the smoother the variation is assumed.
Cleanup	Procedure for rectifying the segmentation along the boundaries.

It is recommended to use the default settings and only experiment with other parameter values if the segmentation fails. The default settings can be recovered by the ⊕ button.

9.7.20   MRI Signal to Concentration

The **MRI Signal to Concentration** tool was developed for converting the signal of dynamic MR sequences into concentration measurements of the contrast agent used. Three different acquisition sequences are supported

Dynamic Contrast-Enhanced MR (DCE)

The DCE method requires that in addition to the DCE data a matched T_1 map has been loaded. It is recognized by being a static series, whereas the DCE is dynamic. Note that there is the MRI T1 Map 171 tool which supports the calculation of T1 images from a sequence of gradient echo images acquired with variable flip angles q (FLASH sequence).

π.pmod

The equilibration magnetization M_0 is also required for the calculation. It is determined from the baseline average of the DCE signal before contrast arrival by

$$M_0 = S \frac{1 - \cos(\theta)E_{10}}{\sin(\theta)(1 - E_{10})}, \quad E_{10} = e^{(-TR/T_{10})}$$

where S is the steady state signal, and T_{10} the pre-contrast longitudinal relaxation time. Using M_0 and T_{10} the relaxation rate $R_1(t)$ during the DCE scan can be calculated by [1]

$$R_1(t) = -\frac{1}{TR} \ln\left(\frac{1 - (A(t) + B)}{1 - \cos(\theta)(A(t) + B)} \right), \quad A(t) = \frac{S(t) - S(0)}{M_0 \sin(\theta)}, \quad B = \frac{1 - E_{10}}{1 - \cos(\theta)E_{10}}$$

where S(t) is the DCE signal, and S(0) the baseline signal before the Gd contrast agent arrives in the tissue. Finally, using $R_1(t)$ and the relaxivity r_1 of the contrast agent used, the concentration of the contrast agent can finally be calculated by [1]

$$C(t) = \frac{1}{r_1}\left(R_1(t) - R_{10}\right)$$

where r_1 is in [L/mmol/sec] units. Carbonaro et al. [2] provide the following relaxivity values for 1.5T:

Brand Name	Acronym	R1-relaxivity [L/mmol/sec]
Magnevist	Gd-DTPA	4.1
Dotarem	Gd-DOTA	3.6
ProHance	Gd-HP-DO3A	4.1
Omniscan	Gd-DTPA-BMA	4.3
Gadovist	Gd-BTO3A	5.2
OptiMARK	Gd-DTPA-BMEA	4.7
MultiHance	Gd-BOPTA	6.7

K-t SENSE Sequence

k-t SENSE

Flip Angle	15.0	[°]
Repetition Time	0.0	[milisecs]
Prepulse delay	0.0	[milisecs]
Excitations	20	
Number of baseline points	5	(M0)

The k-t SENSE method [3] requires that in addition to the dynamic data a matched T_1 map has been loaded. The relaxivity R_1 is first calculated from the model function of the signal by an iterative fit.

For the signal intensity *SI* including readout trajectory, we have for each dynamic scan *i*:

$$SI(R_1) = M_0 \sin(\alpha) \left[\left[1 - \exp(-T_D R_1)\right] \cdot \left(\cos(\alpha)\exp(-T_R R_1)\right)^{n-1} + \left[1 - \exp(-T_R R_1)\right] \cdot \frac{1 - \left(\cos(\alpha)\exp(-T_R R_1)\right)^{n-1}}{1 - \cos(\alpha)\exp(-T_R R_1)} \right]$$

where

$SI(R_1)$	is the model for the signal intensity for each scan as a function of tissue relaxivity R_1, i.e. the current TACs
M_0	is the equilibrium magnetization (which must be guessed/evaluated from a scan)
α	is the flip angle used (DICOM field: (0018,1314): Flip Angle)
T_D	is the time from saturation prepulse to the centre of acquisition space (=*k*-space center)
	(Private DICOM field: (2001,101b))
T_R	is the repetition time (DICOM field: (0018,0080): Repetition Time)
n	is the number of excitations (readout lines) processed before *k*-space center is reached, no DICOM field exists

The R_1 obtained is then used in the equation below, which is solved for the contrast concentration C(t).

$$R_1(c(t)) = \frac{1}{T_1(c(t))} = \frac{1}{T_{1base}} + c(t) \cdot R$$

where

T_{1base} is the *T1* value without contrast (which we measure with the T1 scan)

$c(t)$ is the concentration of the contrast medium (here as fcn of time)

$R = 4.5 \left(s \frac{mmol}{L}\right)^{-1}$ is the relaxivity of the pure contrast medium

$R_1(c(t)) = \frac{1}{T_1(c(t))}$ is the relaxivity of the tissue with contrast medium applied,

which changes as contrast concentration changes with time.

Dynamic Susceptibility Contrast MR (DSC)

This tool calculates the contrast concentration for data acquired with the FLASH sequence [4].

DSC MR	▼ ◄ ▶

Echo time (TE)	150.0	[milisecs]
Number of baseline points	5	(S0)
k	1.0	(constant)

A linear relationship is assumed between the tissue contrast-agent concentration C and the change in T_2^* relaxation rate, ΔR_2^*. The concentration of the contrast agent is given by

$$C(t) = -\frac{1}{k\,TE} \ln\left(\frac{S(t)}{S_0}\right)$$

S_0 is the precontrast baseline signal, S(t) the postcontrast signal, and TE the echo time, and k a proportionality constant.

References

1. D.L. Buckley, and G.J.M. Parker. Measuring contrast agent concentration in T1-weighted dynamic contrast-enhanced MRI. in: A. Jackson, D.L. Buckley, and G.J.M. Parker, (Eds.), Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Oncology, Springer, Berlin, pp. 69-79, 2005.

2. Carbonaro LA, Pediconi F, Verardi N, Trimboli RM, Calabrese M, Sardanelli F. Breast MRI using a high-relaxivity contrast agent: an overview. AJR Am J Roentgenol. 2011;196(4):942-55.

3. Wissmann L, Niemann M, Gotschy A, Manka R, Kozerke S: Quantitative three-dimensional myocardial perfusion cardiovascular magnetic resonance with accurate two-dimensional arterial input function assessment. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance 2015, 17:108.

4. Wirestam R, Andersson L, Ostergaard L, Bolling M, Aunola JP, Lindgren A, Geijer B, Holtas S, Stahlberg F: Assessment of regional cerebral blood flow by dynamic susceptibility contrast MRI using different deconvolution techniques. Magnetic resonance in medicine 2000, 43(5):691-700. HTML

9.7.21   MRI Skull Stripping (PFUS option)

This tool serves for extracting the brain part from human anatomical MR images which need to be provided in HFS orientation.

There are three processing variants available:

1. **Mask (Normalization):** This procedure is based on the **Brain Template Normalization** method implemented in the fusion tool. Depending on the setting **Template to MR** or **MR to Template + Inverse**, the normalization between the MR and the MR MNI template is calculated, and then applied to transform the standard MNI brain mask to the MRI space. Select the **T1** or the **T2MR template**, depending on the type of input data.
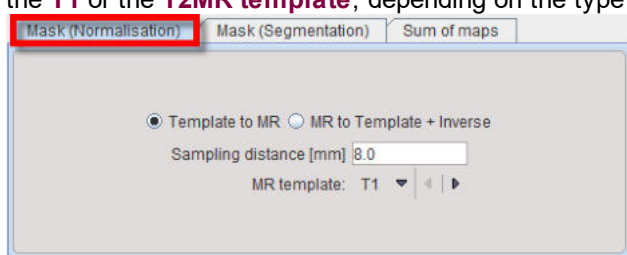
2. **Mask (Segmentation)**: The normalization between the MR and the MR MNI template is calculated based on the **3 Probability Maps** segmentation method (Unified Segmentation, SPM8). It is then applied to transform the standard MNI brain mask to the MRI space.
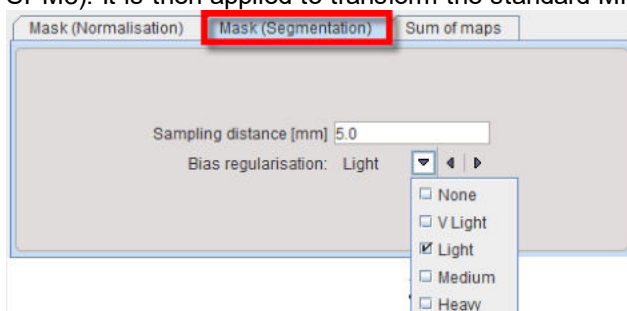
   The **Bias regularisation** serves for compensating modulations of the image intensity across the field-of-view. Depending on the degree of the modulation, a corresponding setting can be selected from the list: None, Very Light, Light, Medium, Heavy, Very Heavy. The parameter to the right indicates the FWHM [mm] to be applied. The larger the FWHM, the smoother the variation that is assumed

3. **Sum of maps:** The MR image is segmented using the **3 Probability Maps** method. The mask is created by applying a threshold at the **Binarization level** to the summed segments.
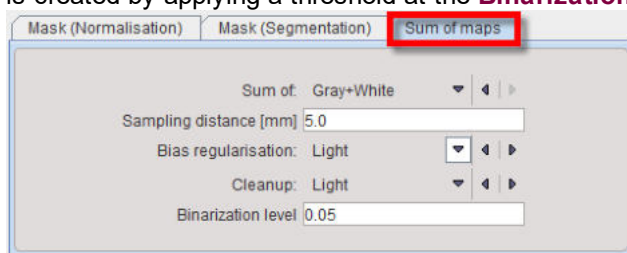
Finally, the mask is inverted and applied to the MR image for removing all non-brain pixels.

9.7.22 MRI T1 Map

This tool supports the calculation of T_1 maps from dynamic MR series acquired with two different pulse sequences. The **Lower** and **Upper limits** serve for restricting the calculated values to a physiological range.

Variable Saturation Data (FLASH)

The equation for the signal intensity using a FLASH sequence can be rearranged such that T_1 may be calculated as the slope of a linear regression fit. See Buckley et al, equation (5.7).

Inversion Recovery Data

It is assumed that the first frame contains the equilibration magnetization M_0. T_1 is then estimated using a linear regressioin as described by McVeigh et al [2], using equation (2).

References

1. D.L. Buckley, and G.J.M. Parker, Measuring contrast agent concentration in T1-weighted dynamic contrast-enhanced MRI. in: A. Jackson, D.L. Buckley, and G.J.M. Parker, (Eds.), Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Oncology, Springer, Berlin, 2005, pp. 69-79.

2. McVeigh E, Yang A, Zerhouni E. Rapid measurement of T1 with spatially selective pre-inversion pulses. Medical Physics. 1990;17(1):131-134.

9.7.23 Noise Addition

Adds Gaussian noise with zero mean and a standard deviation **Sigma** to the image.

9.7.24   Numeric Operations
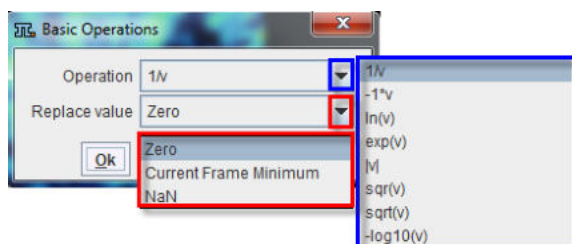
Applies the numeric function configured as **Operation** to every pixel value, and uses the defined **Replace value** if the operation is mathematically undefined.

9.7.25   Principal Component Analysis

No input is required for this function which is only applicable to *dynamic* series. The PCA performs a principal component analysis in the time domain. The generated series consists of the components sorted according to decreasing eigenvalues. The expectation is, that the PCA groups pixels with a similar uptake pattern over time in different components (representing "frames" in the generated series). The eigenvalues are written to the console.

9.7.26   PVC (VOI based)

General tool for partial-volume effect correction based on VOIs as explained in detail in a separate section 446.

9.7.27   PVC (Brain MR based)

Tool for the partial-volume effect correction of a human brain PET based on the Muller-Gartner method as described in a separate section 446.

9.7.28   R Console

Allows loading the image data displayed in the view port in the PMOD R interface for further statistic analysis.

9.7.29   Reduce Matrix

The **Reduce Matrix** tool serves for reducing the number of pixels in each direction.
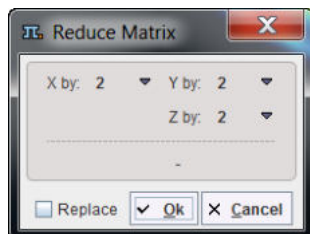
It is intended for situations where the number of pixels is divisible without remainder by the selected reduction factor. If this is not the case, a warning is shown indicating that the bounding box is changed by the operation, and the **Interpolation** function should rather be applied.

9.7.30   Registration and Normalization (PFUS Option)

The matching in the external tools is mainly for the use in pipe processing. It is only available if the image fusion option is included in the PMOD license.
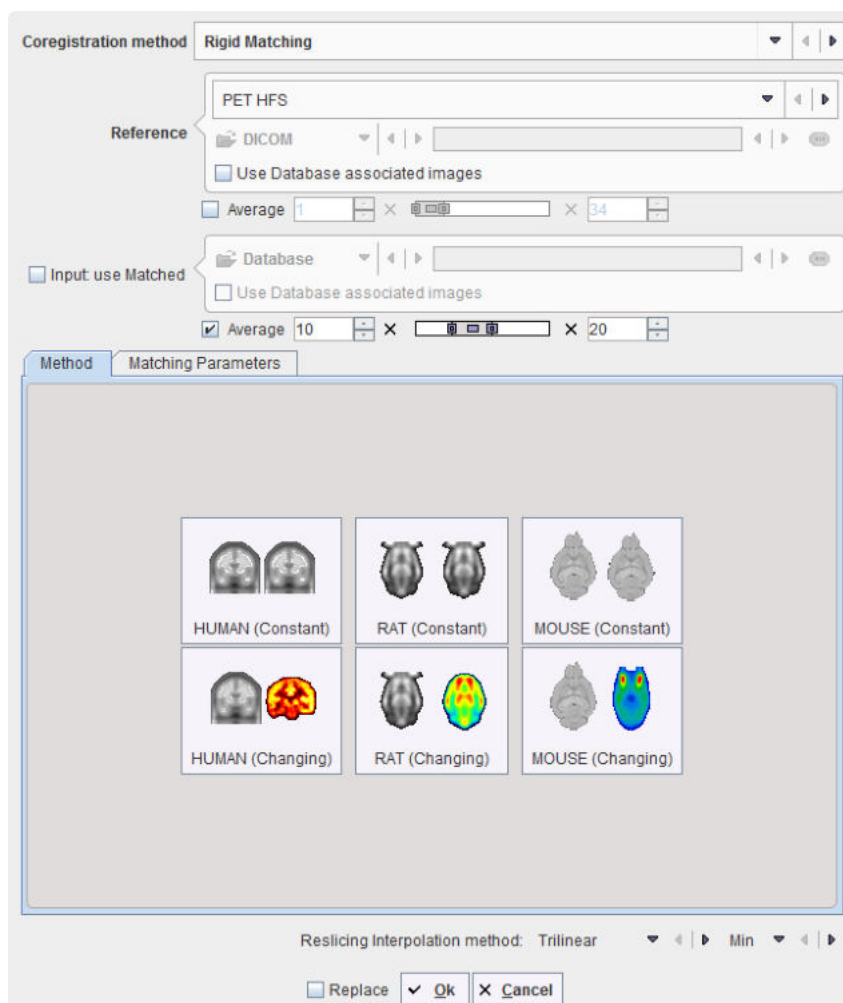
Please refer to the *PMOD Image Fusion Guide* for details about the matching options.

9.7.31 Replace Values

The **Replace Values** tool
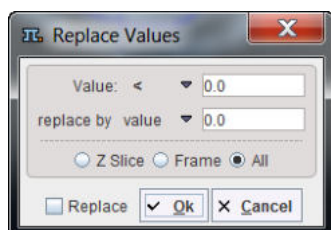
serves for replacing pixel values which satisfy a certain condition by a constant. The available criteria
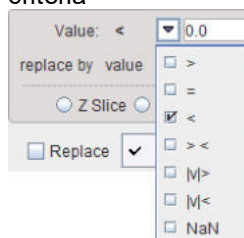
are

- larger than (**>**) the specified value;

- equal to (**=**) the specified value;

- smaller than (**<**) the specified value;

- within a value range (**> <**) `> < ▼ 0.0 0.0` specified;

- absolute value larger than (**|v|>**) the specified value;

- absolute value smaller than (**|v|<**) the specified value;

- is a NaN value (Not a Number).

9.7.32 Resize

The **Resize** tool has two tabs.
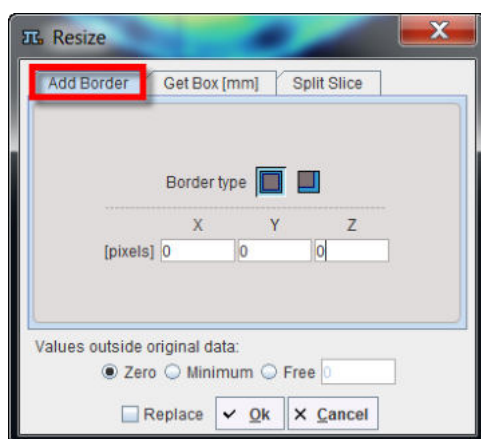
Add Border serves for padding pixels around the current series. There is a symmetrical and an unilateral variant. The number of padded pixels can be specified for each direction separately, and there are different options for the filling value.
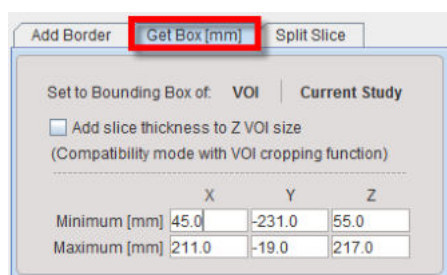
Get Box allows extracting a sub-volume of the current series (cropping). To this end, the new bounding box must be specified.

One way is to activate the **Current Study** button, which populates the **Minimum** and **Maximum** coordinates with that of the current study. Then the user can adjust the values appropriately to get a sub-volume.

Ana alternative way is to base the extraction on the bounding box of a suitable VOI, which has been defined beforehand. Using the **VOI** button a VOI can be selected, its bounding box is read from the file and applied for sub-volume extraction. Note that the same functionality is also directly available in the VOI tool. Additionally, the slice thickness can be added to the Z VOI size enabling the **Add slice thickness to Z VOI size** box.

9.7.33 Scale Values

The **Scale Values** tool
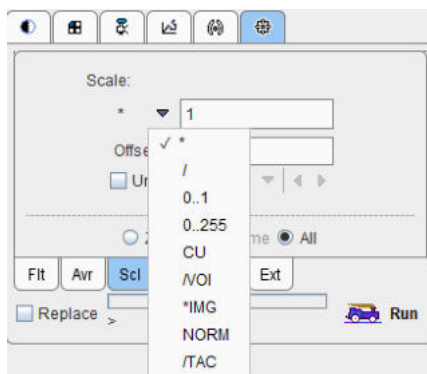
can be used for transforming the pixel values by the following operations in the **Scale** selection.
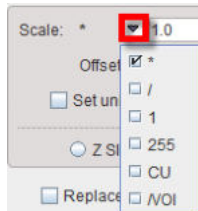
- *****: multiply with a constant and add an **Offset** which defaults to 0;
- **/**: divide by a constant and add an **Offset** which defaults to 0;
- **->1**: transform the value range to the interval [0,1];
- **->255**: transform the value range to the interval [0,255];
- **->CU**: transform the value range of CT Hounsfield numbers to the value range used in the template image of the clinical toolbox [1]. Values in [−1000..−100] are scaled to [0..900], values [−99..100] are scaled to [911…3100], values i>100 become [i+3000].
- **/VOI**: divide by a VOI average and add an **Offset** which defaults to 0; the VOI has to be saved beforehand and needs to be selected.
- ***IMG**: multiply pixelwise using data from a file
- **NORM**: divide by frame average or calculates z-score.
- **/TAC**: divide by frame average (frame to frame for dynamic data)

If **Set units** is enabled, units appropriate for the scaled image can be selected from the units list.

Reference

1. Rorden C, Bonilha L, Fridriksson J, Bender B, Karnath HO: Age-specific CT and MRI templates for spatial normalization. Neuroimage 2012, 61(4):957-965. DOI

9.7.34 Segmentation

The **Segmentation** tool is a method for simple mask creation similar to the segmentation in the 3D tool. It opens the following dialog window.
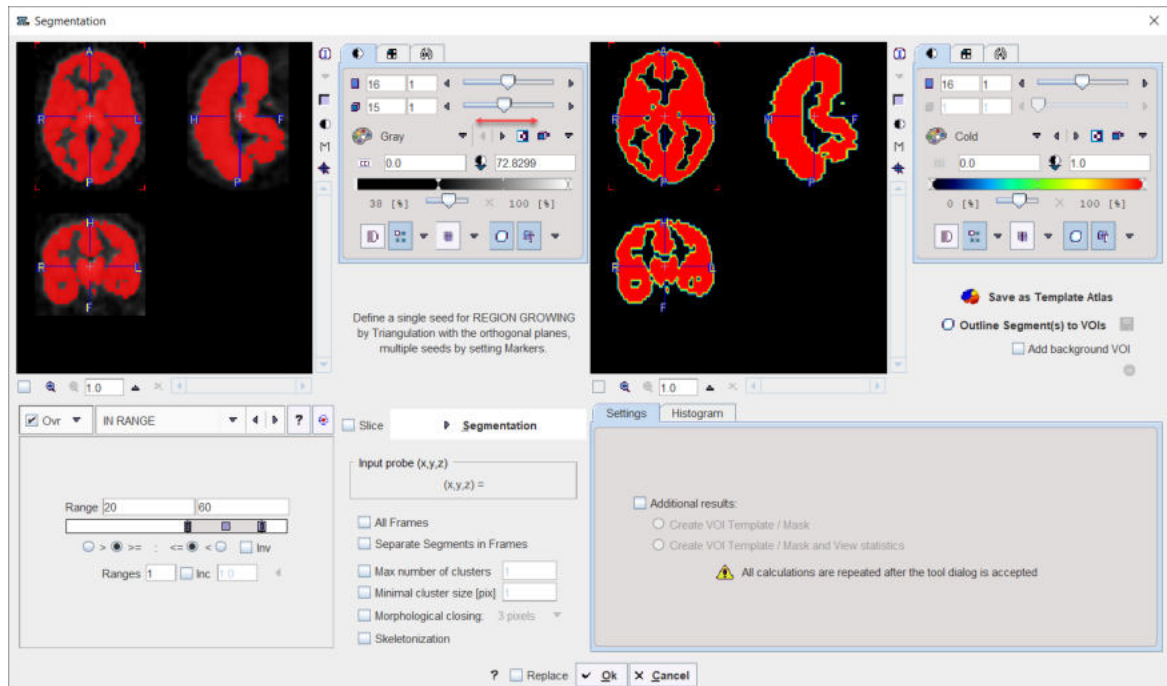
Segmentation Page Layout

The **Segmentation** interface is organized as follows:

- The input images are shown in the upper left. An overly color is used to highlight the pixels which qualify for the current segmentation settings. This segmentation preview is only approximate.

- The segmentation method is configured in the lower left by a list selection. The parameters of the selected method are updated accordingly. There are several segmentation methods for finding the object contours.

- The actual segmentation is initiated with the **Segmentation** button. It produces a binary image in the upper left with a black background and the white object (depending on the segmentation type).

- The result is shown in the right image display port. Note that if the study is dynamic, an additional box **All Frames** appears. If it is checked, segmentation will be performed for all frames separately, otherwise with the frame which is currently shown.

- useful segmentation results can be saved as Template Atlas or outlined to VOIs and saved as .voi file.

Input Probe Value

Note the **Input probe** value which displays the image value at the position of the cursor, which is useful for finding appropriate Threshold setting.
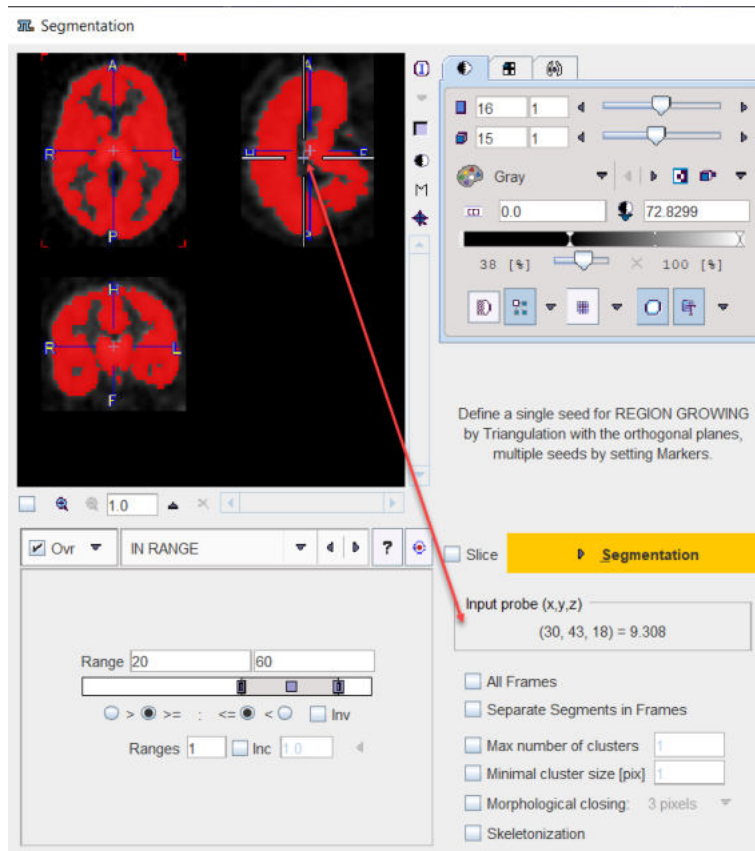
Its value can be entered manually or using the **Histogram** panel for setting the threshold value.

Additional Segmentation Settings

- **All Frames**: this additional box appears only when the study to be segmented is dynamic. When enabled, the segmentation will be performed for all frames separately, otherwise with the frame which is currently shown.

- **Segments in Separate frames**: when enabled, allows organizing multi-segments results as a dynamic image: one segment per frame.

- **Max number of clusters**: when enabled it performs a cluster analysis and limits the number of clusters per segment according to the specified value.

- **Minimal cluster size [pix]**: when enabled it performs cluster analysis and includes in the segmentation results only cluster larger than the specified size.

- **Morphological closing**: when enabled it performs a morphological closing operation per segment according with the selected option: 3, 5 or 7 pixels.

- **Skeletonization:** The skeletonization algorithm allows extracting the "center-lines" of an object and uses them to efficiently represent the object. The skeletonization algorithm is complementary to the segmentation. This particular algorithm is described in a dedicated [section] 188.

Pixel Value Distribution

The **Histogram** in the lower right panel provides an overview of the pixel value distribution in the current image volume. It may indicate a peak usable for setting a background threshold. The current threshold value is indicated by the vertical line in the histogram.
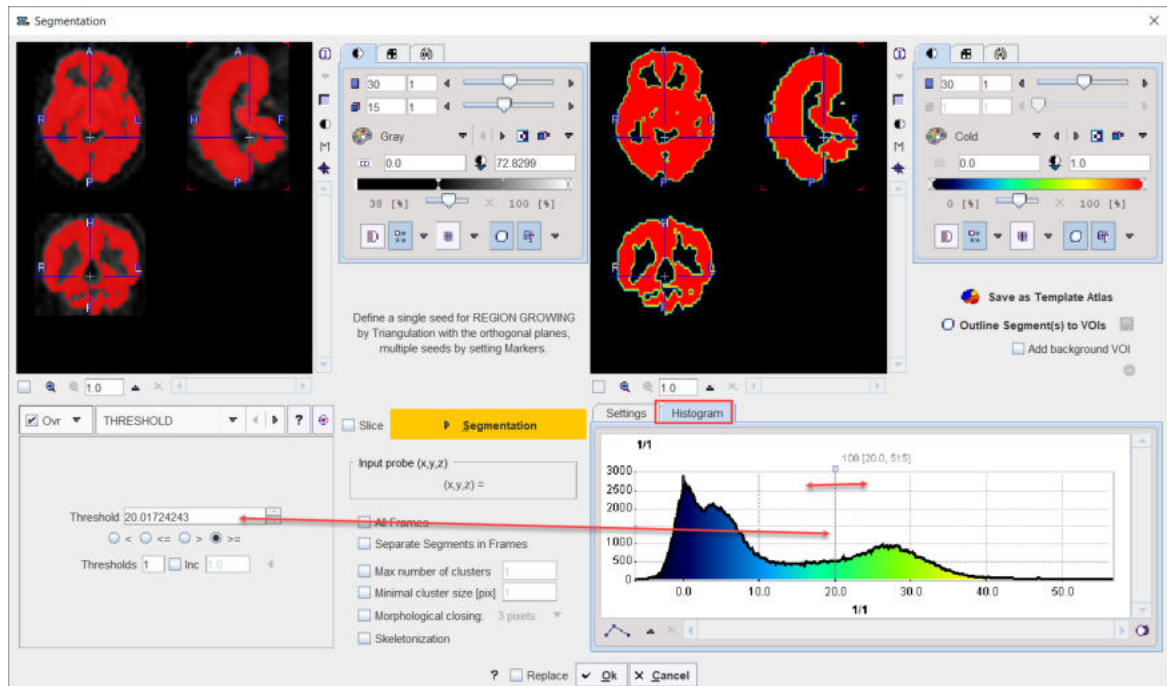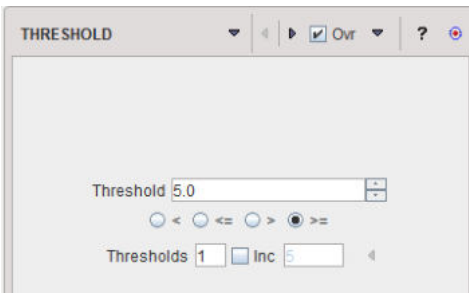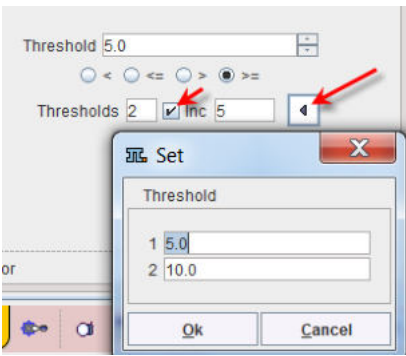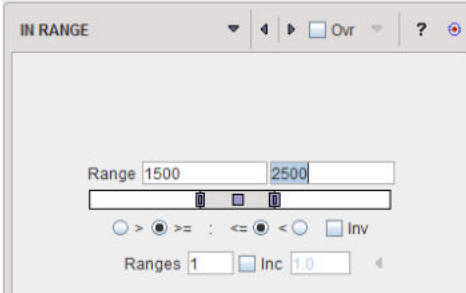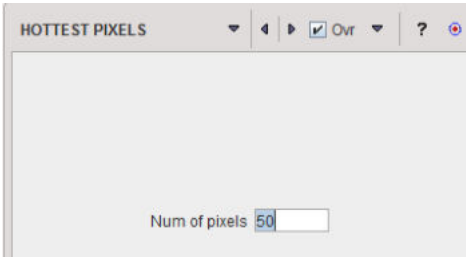
Note:
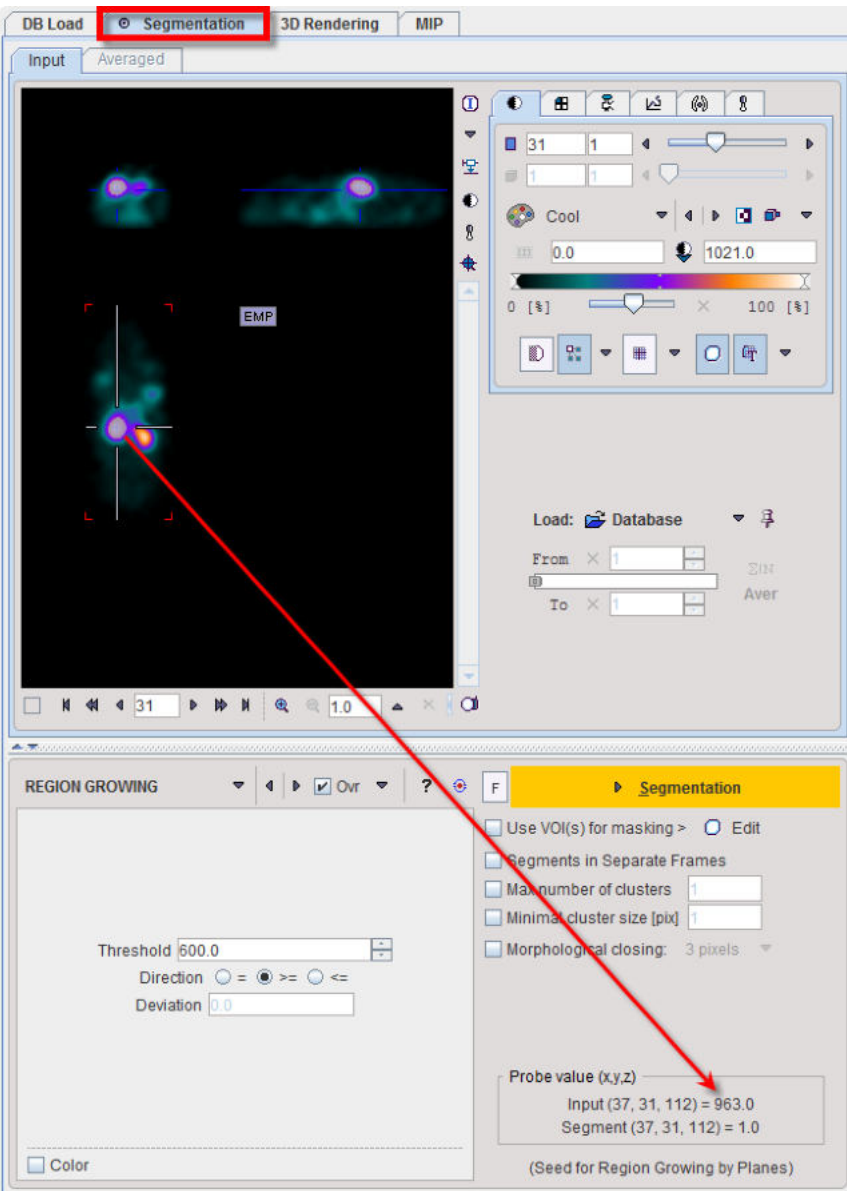
- When the study is dynamic the histogram content displays the pixel distribution of the currently selected frame. The **Histogram** panel content is updated when the frame is changed

- The histogram content is also updated when **Restrict to VOI** selection is enabled for the **Segmentation VOI** interface.
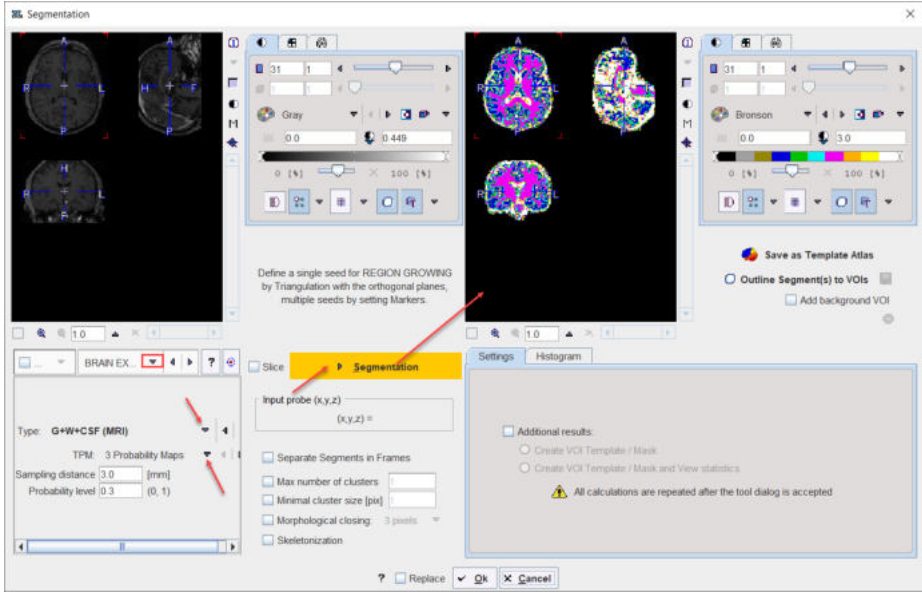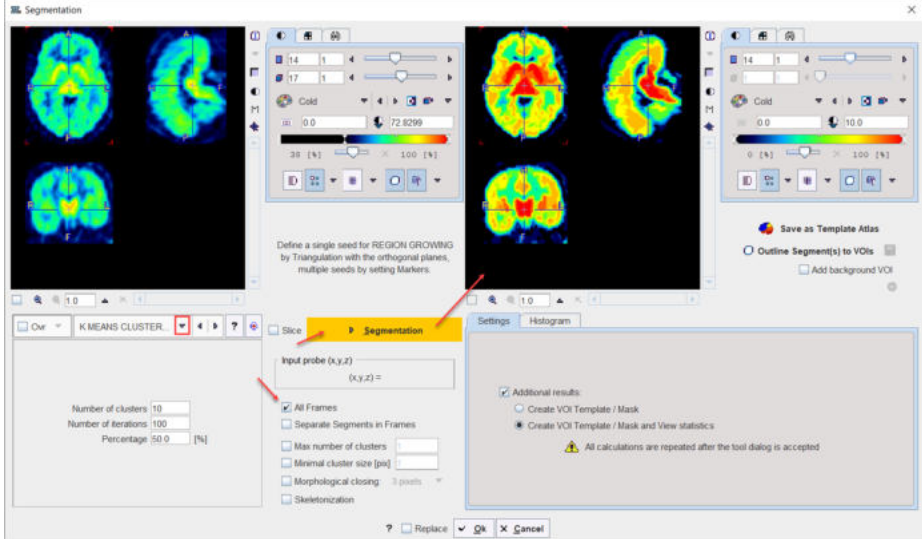
Segmentation Methods

The following segmentation methods are available.
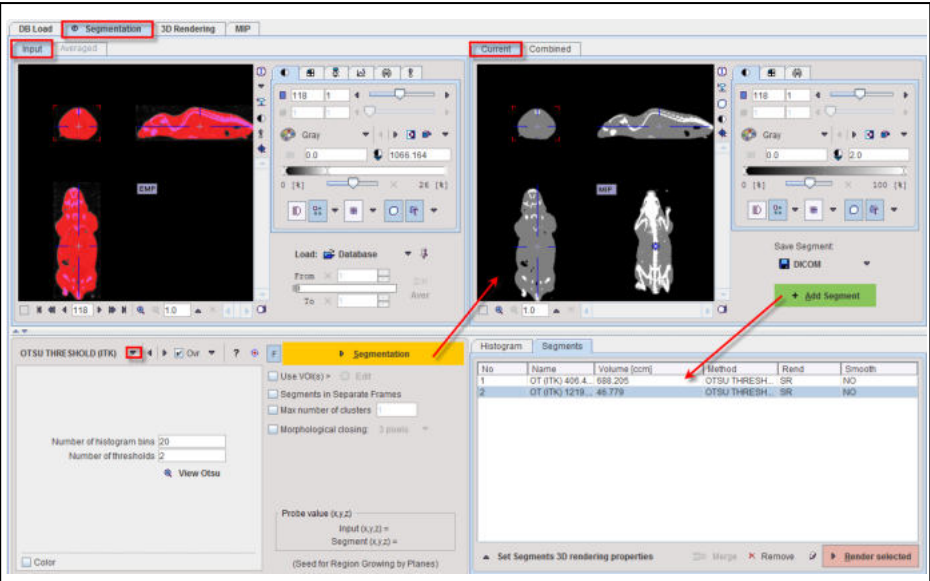
THRESHOLD	The **THRESHOLD** segmentation is conceptually simple. All pixels with value above or below the threshold are included in the segment, depending on the condition settings.
	Sometimes it is helpful to segment at several threshold levels at once. This can easily be realized by setting the number in the **Thresholds** field accordingly, and entering the threshold values in the appearing **Set** dialog window.

Multiple threshold values can be incremented with a constant value enabling the **Inc** box and specifying the step in the dedicated text box.

IN RANGE	The **IN RANGE** segmentation is similar to the **THRESHOLD** method, except that two limits are defined. The boundary values are included or excluded, depending on the radio button settings. The complementary criterion is obtained by checking the **Invert** box. Similar to the **THRESHOLD** segmentation, multiple **Ranges** can be defined and segmented at once.
HOTTEST PIXELS	The **HOTTEST PIXELS** segmentation allows obtaining the (often disconnected) pixels with the highest values. The number of included pixels can be specified in the **Num of pixels** field.
REGION GROWING	**REGION GROWING** is a method by which the user defines a starting point (seed) within the object of interest, and the algorithm tries to find all connected pixels which fulfill a certain criterion. It is required to triangulate the seed point with the orthogonal plane layout as illustrated below.

The inclusion criterion is formed by the **Threshold** value and the **Direction** specification:

- **=** include all connected pixels with a value **Threshold ± Deviation**;
- **>=** include all connected pixels above the defined **Threshold** value;
- **<=** include all connected pixels below the defined **Threshold** value.

Note the **Probe value** which displays the image value at the position of the cursor, which is useful for finding appropriate **Threshold** setting.

BRAIN EXTRACTION	This segmentation can be used for 1.the extraction of the whole brain as a unique segment from a T1 weighted brain MRI. To this end the **Brain (MRI) Type** need to be selected. 2.the classification of the pixels in a T1-weighted brain MRI into Grey Matter, White Matter and CSF when the **G+W+CSF** is selected as Type. 3.the extraction of the whole brain as a unique segment based on the Mask of the selected Template, with parameter **Sampling distance** in mm and the **Probability level** for the map discretization.

Note: The methodology variants from point 1 and 2 above is an implementation of the segmentation in SPM8 (**3 Probability Maps**) and SPM12 (**6 Probability Maps**) respectively, with parameter **Sampling distance** in mm and the **Probability level** for the map discretization.

K MEANS CLUSTERING	K-Means is a popular method which partitions N observations into K clusters. The parameters are the **Number of clusters** (=K), the **Number of iterations** of the heuristic procedure, and an assumed **Percentage** of background pixels.

The procedure can be applied to static and dynamic data. In the latter case, pixel with similar signal shapes will be clustered using the time-weighted Euclidean distance as the measurement of dissimilarity (or distance) between TACs. Note that the **All frames** box has to be enabled, because otherwise each frame of the dynamic series will be clustered separately.

The procedure for clustering based on the signal shape proceeds as follows:

1. Background pixels are removed by calculating the signal energy of the pixel-wise TACs (sum of squared TAC values), and considering only pixels above a specified percentile.

	2. K non-background pixels are randomly selected as initial cluster centroids .
	3. Each non-background pixel is assigned to the centroid with minimal distance between the TACs, thus forming K initial clusters.
	4. For each cluster a new centroid TAC is calculated as the average TAC of all pixels in the cluster.
	5. An iterative process is started which repeats the following two steps:
	(1) Each pixel TAC is compared with all centroid TACs and assigned to the cluster with minimal distance.
	(2) All centroid TACs are recalculated to reflect the updated cluster population.
	The iterations are repeated until no pixels are re-assigned to a different cluster, or a maximal number of iterations is exhausted.
SCATTER in VOI	This particular method for localizing pixels from 2D scatter plots is described in a separate section 184.
ACTIVE MODELS	Please refer to the dedicated Active Models description for details.
HOTTEST CONNECTED VOXELS	Is a segmentation method used to objectively outlined brain anatomical structure like the locus coeruleus/subcoeruleus complex in T1 weighted MRI images. Another potential application is the extraction of the image derive input function. Please refer to the dedicated Hottest Connected pixels topic for details.
OTSU THRESHOLD	The OTSU THRESHOLD method is based on the analysis of the pixel histogram and is described by The ITK Software Guide as follows: "Another criterion for classifying pixels is to minimize the error of misclassification. The goal is to find a threshold that classifies the image into two clusters such that we minimize the area under the histogram for one cluster that lies on the other cluster's side of the threshold. This is equivalent to minimizing the within class variance or equivalently maximizing the between class variance."
	The **Number of histogram bins** defines the resolution of the histogram shape, whereas the **Number of thresholds** defines the number of distinct clusters. With the mouse CT, Otsu with the settings below finds appropriate thresholds for the skeleton object and the soft tissue, as illustrated below. Note that the threshold values can be inspected only after the actual segmentation by the **View Otsu** button.

MACHINE LEARNING	If the **Pmod Artificial Intelligence (PAI)** module has been licensed, the **MACHINE LEARNING** segmentation options will be available. Please refer to the dedicated [PMOD Artificial Intelligence Framework (PAI)](#) user guide for detailed information.

Segmentation Results Saving

The segmentation result can be used in different ways:

- **Save as Template Atlas** directly saves the segmented series in an atlas format in the directory Pmod4.4/resources/templates/voitemplates. Subsequently, it can be used for statistics using the **Atlas** tab of the **Templates** pane in the VOI definition function.

- The **Outline Segment(s) to VOIs** button allows creating VOIs for each generated segment. Optionally, the background can be added as a VOI by enabling the **Add background VOI** box. The outlined VOIs can be saved as files and later used for statistics by the **Save** icon next to the **Outline** button.
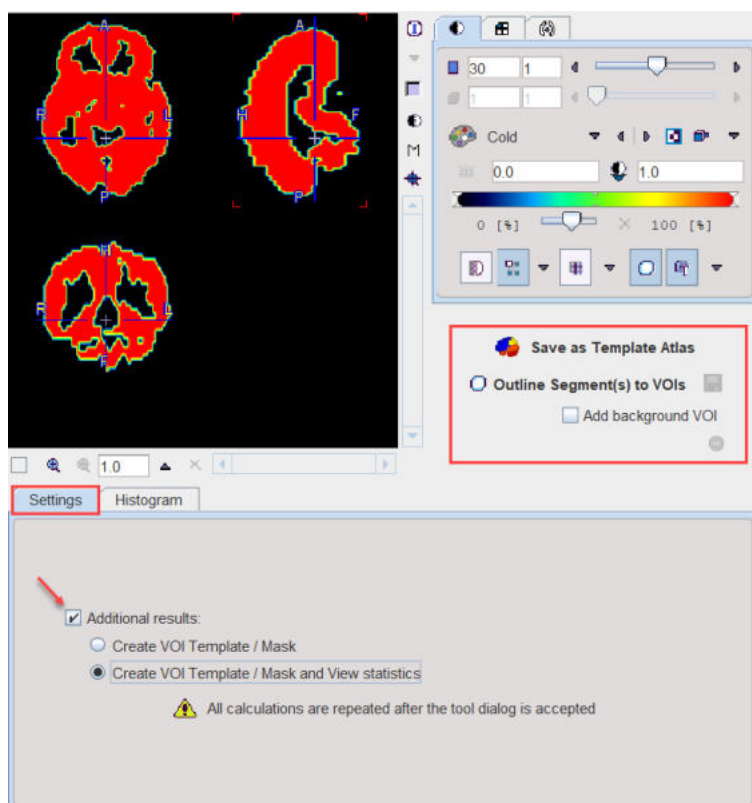
With the **Ok** button the segmentation is performed again and the resulting segment returned as an image series which is binary for a simple segmentation and an object map in the case of a clustering method. The following **Additional results** can be returned.

1. **Create VOI Template/Mask:** With this setting, the segments are also returned as a VOI template which can be activated by the **Mask** tab of the VOI **Template** function.

2. **Create VOI Template/Mask and View Statistics**: As 1), but the statistics on the current image are additionally calculated.

9.7.34.1 Mapping of Pixels from Scatter Plots

Scatter plots are a convenient method for exploring tissue function, if matched image series are available. With the brain PET example illustrated below,
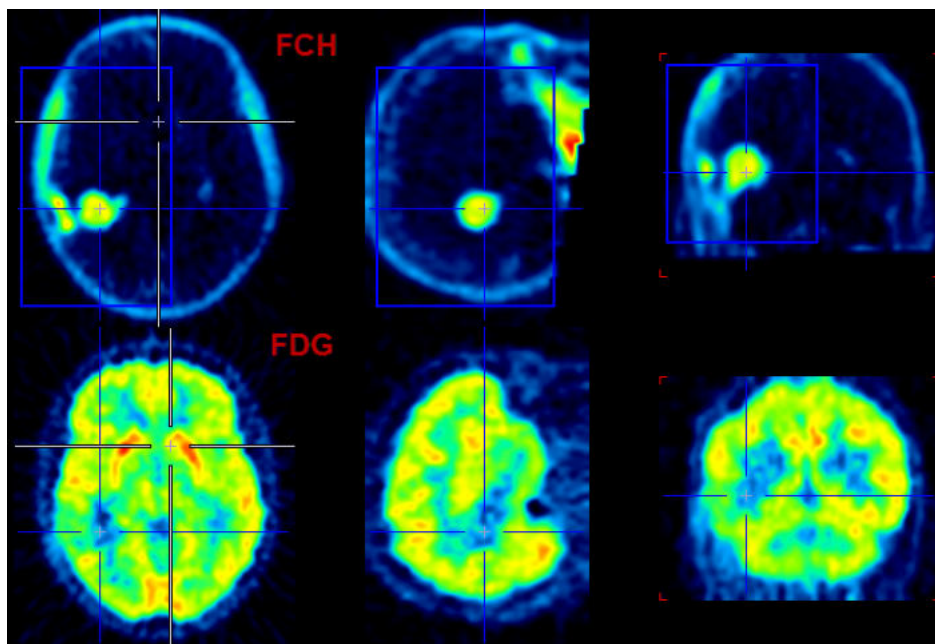
we get the following scatter plot of the pixel values in the blue VOI box.
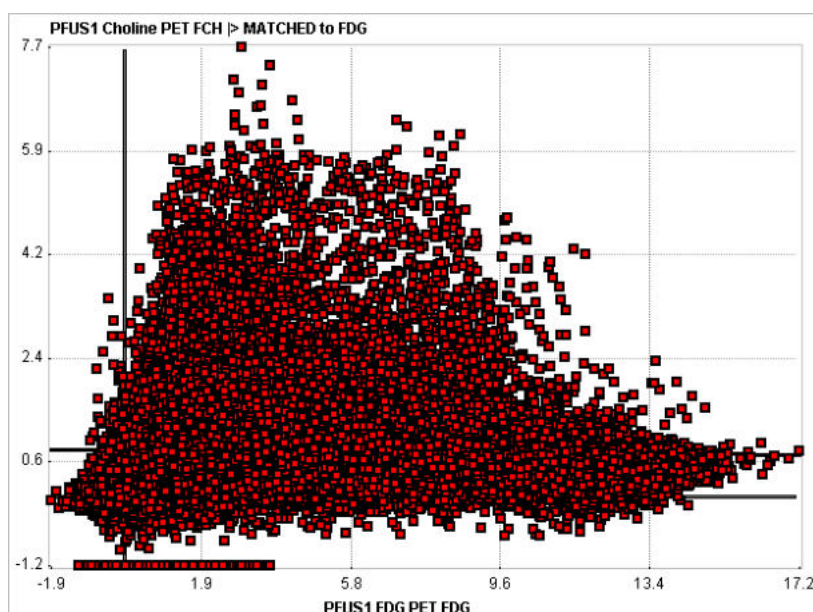
The FDG uptake of a pixel is plotted on the x-axis, and the corresponding PCH uptake on the y-axis. The **Segmentation** tool allows defining areas of interest in the scatter plot plane and mapping the enclosed pixels back to the image. The procedure converts the scatter plot to an image, in order to apply the standard PMOD VOI functionality for the area definition.

Segmentation Procedure

Please proceed as follows:

1. Load the two matched image series.

2. Define one or multiple VOIs on the first image series which enclose the tissue of interest, if needed the whole volume.

3. Select the **Segmentation** external tool, and chose the **SCATTER in VOI** method.
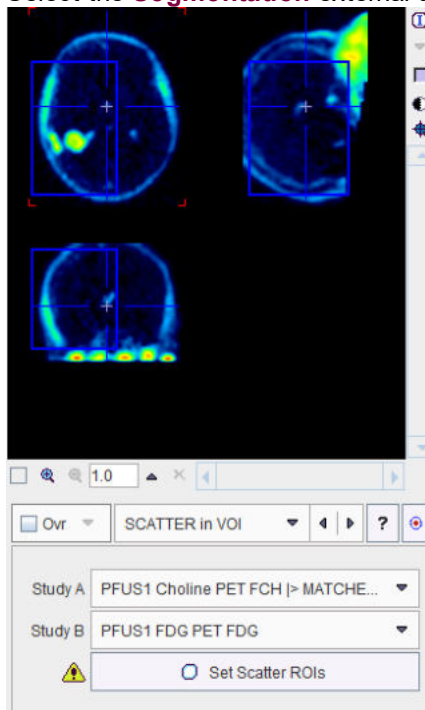
4. Using the list selection arrow, define the series with the defined VOI as **Study A**, and the other series as **Study B**.

5. Activate **Set Scatter ROIs** to create the 2D scatter plot.
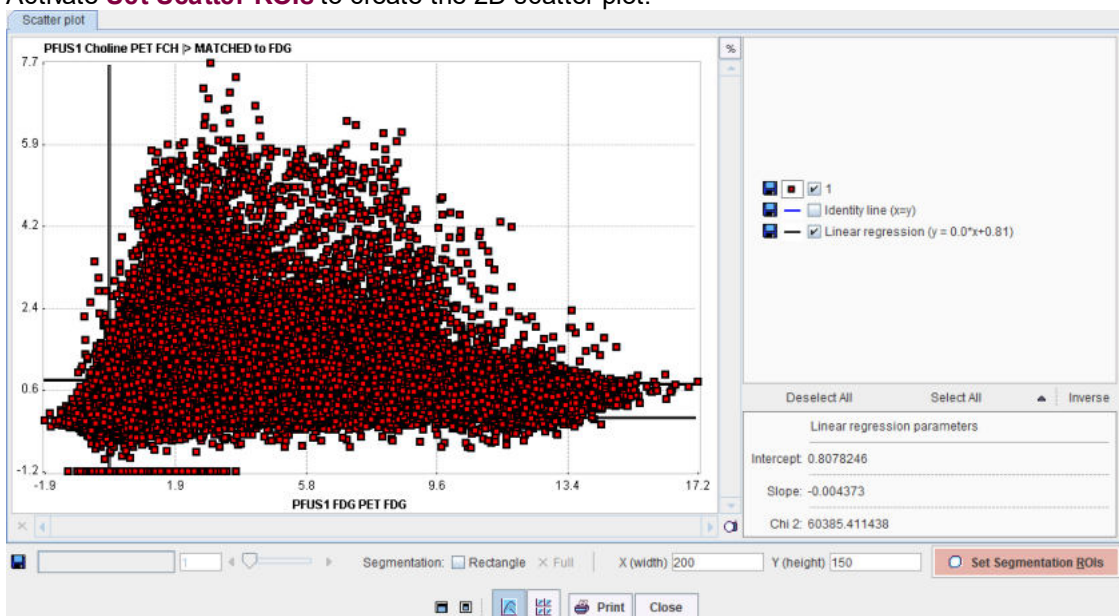
6. Convert the plot into an image by **Set Segmentation ROIs**. The **X(width)** and **Y(height)** define the number of image pixels in the two dimensions. The image value is given by the number of scatter points in the area of each image pixel.

7. A window appears showing the generated image together with the VOI definition interface. Adjust the color thresholds for localizing pixels with a specific uptake pattern and draw the ROIs.
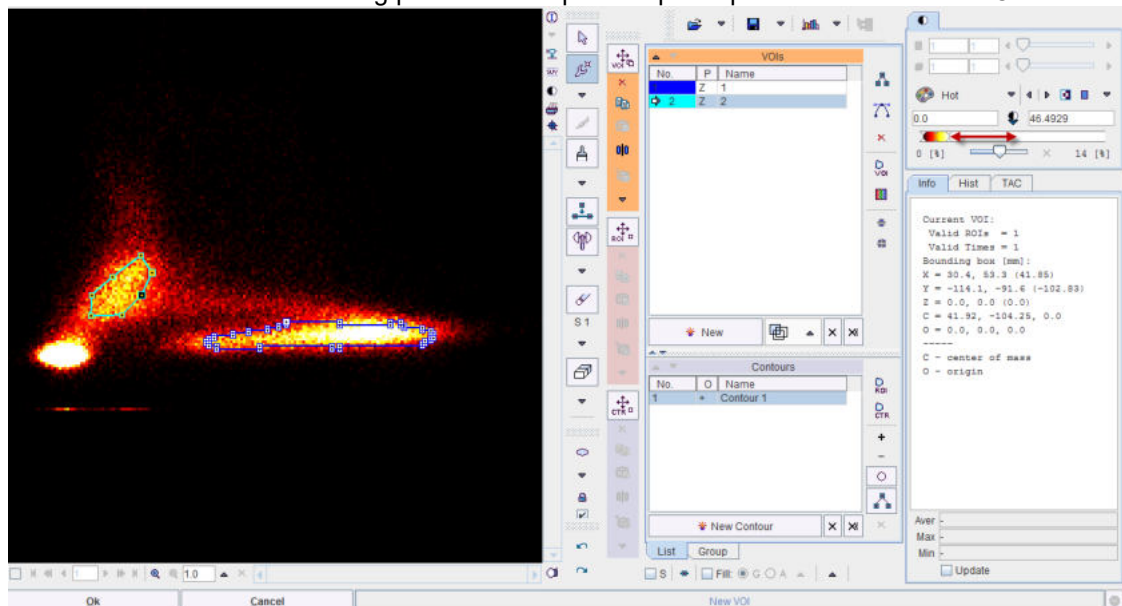
8. Closing of the VOI interface with **OK** returns to the scatter plot which now also displays the ROIs.
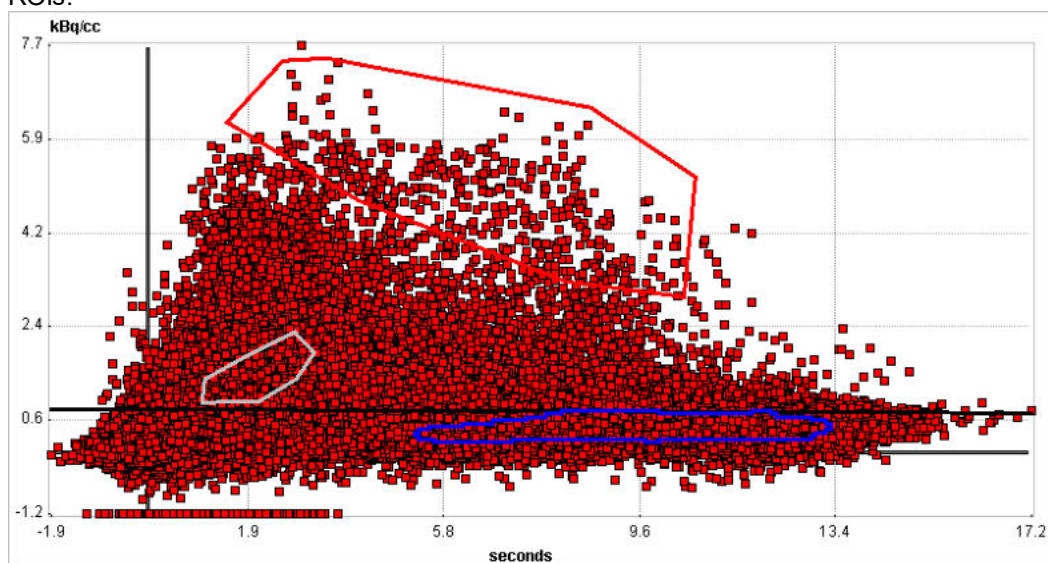
9. Complete the definition by the **Close** button to return to the **Segmentation** tool.

10. Now the scatter pixels can be mapped with the **Segmentation** button. The interpolation should be disabled to better see the generated segments. The result indicates that the tumor pixels

were well characterized by the red ROI in the scatter plot.
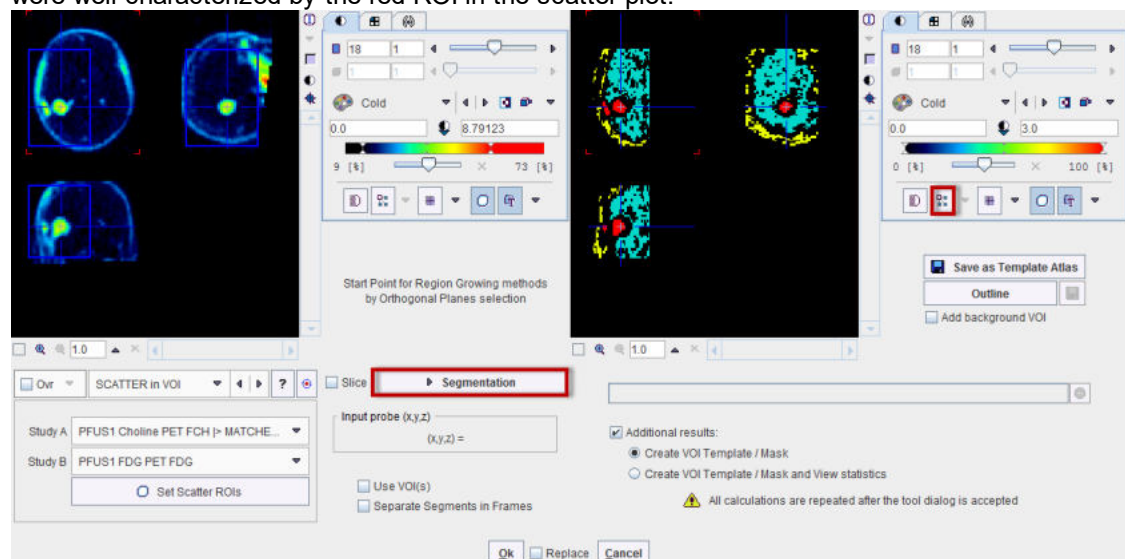
Rectangle ROI

A quick alternative to going through scatter plot rasterization and ROI outlining is to use a simple rectangular ROI. This functionality is enabled by the **Rectangle** box. A red-shaded area appears, which can be adjusted by dragging the edges. **Segmentation** will map the pixels in the defined rectangle.
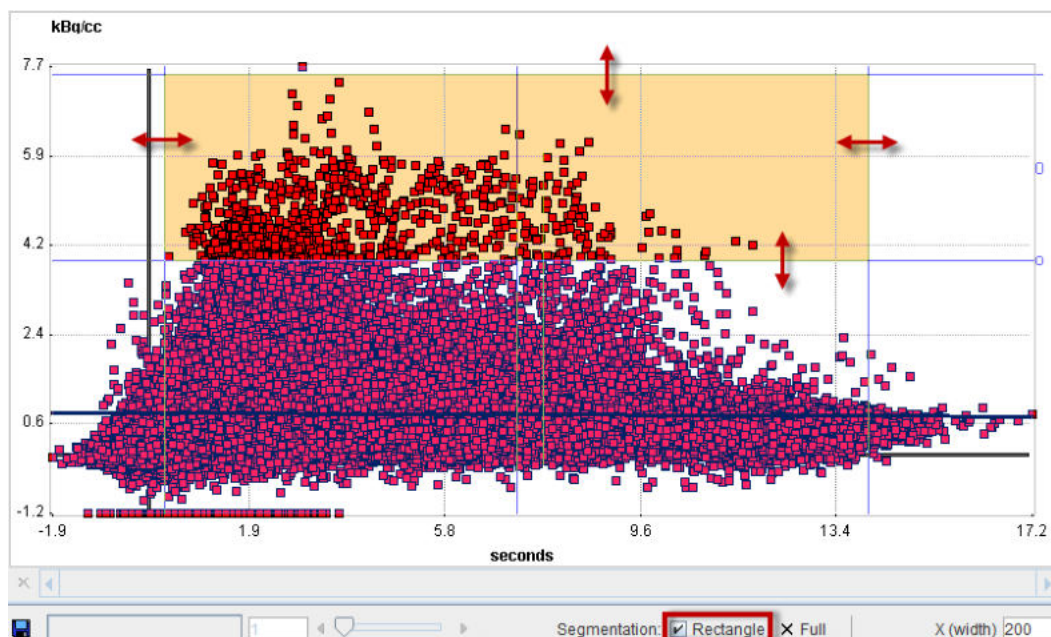
9.7.34.2 Skeletonization

PMOD implements an improved fully parallel 3D thinning algorithm [1]. It uses a 3D binary image obtained by a segmentation method and generates unit-width curve skeletons. The skeletonization algorithm extracts the "center-lines" of an object and uses them to efficiently represent the object. [2] The skeletonization algorithm is complementary to the segmentation.

The curve skeletons are well suited to describe tube-like anatomical structures, e.g. vessels, nerves, and elongated muscles [3].

The steps required to generate e.g. a skeleton for the brain vessels based on an MRI image are illustrated in the capture below:
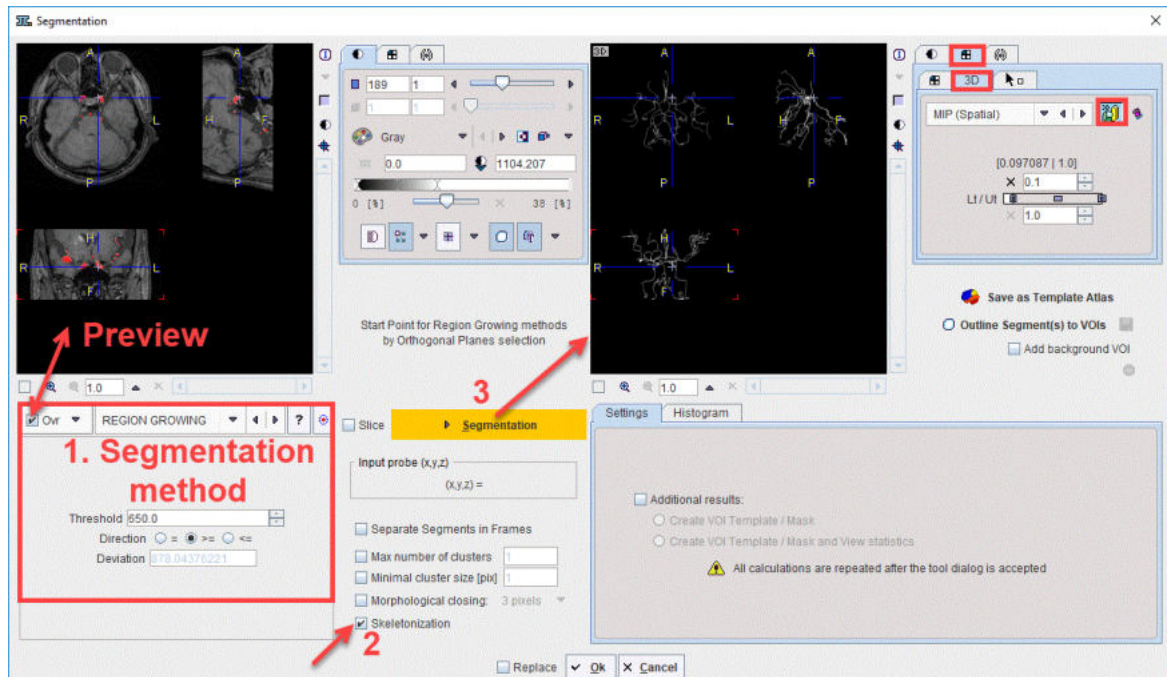
First, the segmentation method is selected in the Segmentation panel. It is recommended to enabled the **Ovr** button in order to preview the results of the segmentation algorithm in the upper left viewport. Second, the **Skeletonization** check box is enabled. Finally, the **Segmentation** button is activated to perform the actual skeletonization of the previewed 3D segment. The result is shown in the upper right viewport. It is recommended to visualize the skeletonization results using the 3D volume rendering layout.

Reference

1. Kálmán Palágyi, A 3D fully parallel surface-thinning algorithm, Theoretical Computer Science 406, October 2008, p. 119–135, DOI

2. Tao Wang, Skeletonization and Segmentation Algorithms for Object Representation and Analysis, PhD Thesis, Spring 2010, Edmonton, Alberta, University of Alberta

3. Tagliasacchi A., Delame T, Spagnuolo M., Amenta N., Telea A, 3D Skeletons: A State-of-the-Art Report, EUROGRAPHICS 2016, Volume 35 (2016), Number 2

9.7.35 Standard Orientation

Reformats the loaded images such that they are displayed in the standard radiological head first supine (HFS) position illustrated below. This function requires that correct subject positioning information is available in the image data header.
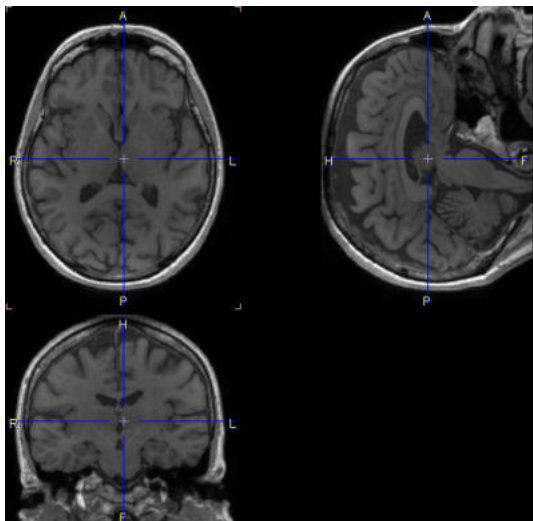
An HFS orientation of the images is mostly relevant for the automatic generation of VOIs.

9.7.36   SUV Image Calculation

Explicit SUV images can be calculated with the **Calculate SUV Image** entry of the external tools. It shows a dialog window with information related to the administration of the tracer dose explained above.

The **SUV** selection determines the SUV type to be calculated. The **Ok** button starts the calculation. A new image series with changed units ([g/ml], [cm^2/ml] or [%ID/ml]) is created if the **Replace** box is unchecked, otherwise the original series is overwritten.

Note:

For regional statistics the explicit SUV image calculation is not necessary. The statistics output [327] can be switched to SUV units, provided that all required information is available.

Using the **Copy to Study Info** button the corrected information can be saved for later use, and for saving it together with the data.

9.7.37 Temporal Resampling

Allows resampling a dynamic series according to the timings specified.
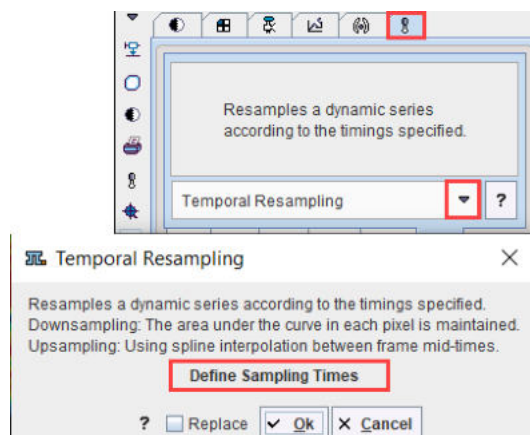
In case of down-sampling the area under the curve is maintained.

In case of up-sampling it uses spline interpolation between frames mid-time.

9.7.38 Texture Analysis

If at least one VOI has been defined 25 texture features [332] within them can be calculated using the **Texture Analysis** entry in the external tools.

9.7.39 Wavelet Filtering

The **Wavelet** tool performs de-noising of dynamic data, whereby the x and y image dimensions must be a power of 2. Note that if the z and the time domain sizes are not a power of 2, they are extended or reduced to the closest 2^n value.
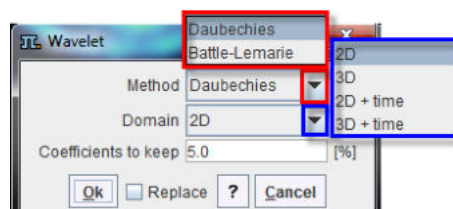
Wavelet filtering has been adapted from [1] and can be applied with two sets of coefficients:

- **Daubechies** using 20 coefficients [1];

- **Battle-Lemarie** using 71 coefficients obtained from Narayan Kowali, at that time working at Duke University.

There are four different filtering modes:

- each plane separately (**2D**),

- each frame separately (**3D**),

- each plane over time separately (**2D + time**),

- or the entire volume over time (**3D + time**).

The **coefficients to keep** determine the level of smoothing: the lower the % value entered, the smoother the image.

Reference

1. William H. Press, Saul A. Teukolsky, William T. Vetterling, and Brian P. Flannery. 1992. Numerical Recipes in C (2nd Ed.): The Art of Scientific Computing. Cambridge University Press, New York, NY, USA.

9.7.40 z-Score in VOI

This tool performs calculation of z-score values based on the average and the standard deviation of the values within a specifed VOI. When more than one VOI is available on the **VOIs** list the algorithm will consider as VOI the VOIs union selected on the **Group** tab.

The operation works frame-wise for dynamic data.
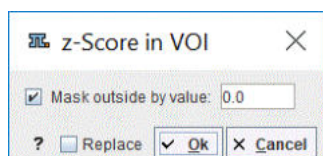
Masking outside the VOI is optional. It can be easily achieved enabling the **Mask outside by value** box. The masking value can be specified in the dedicated text field.

The **Ok** button starts the calculation. A new image series is created if the **Replace** box is unchecked, otherwise the original series is overwritten.

This preprocessing is recommended for transforming the data as input to the supervised clustering algorithm implemented in the PGEM module.

9.7.41 Macro

This tool allows applying an image macro[132] which is most useful in the context of Pipe processing[471].

9.8 Reslicing of the Images at Oblique Orientations

To calculate slices at oblique orientations or rotate images the reslicing pane must be activated. Reslicing is defined by a transformation consisting of translations in all directions, rotations about all axes, and potentially scaling along the axes. Each of these transformation components has its own sub-pane.
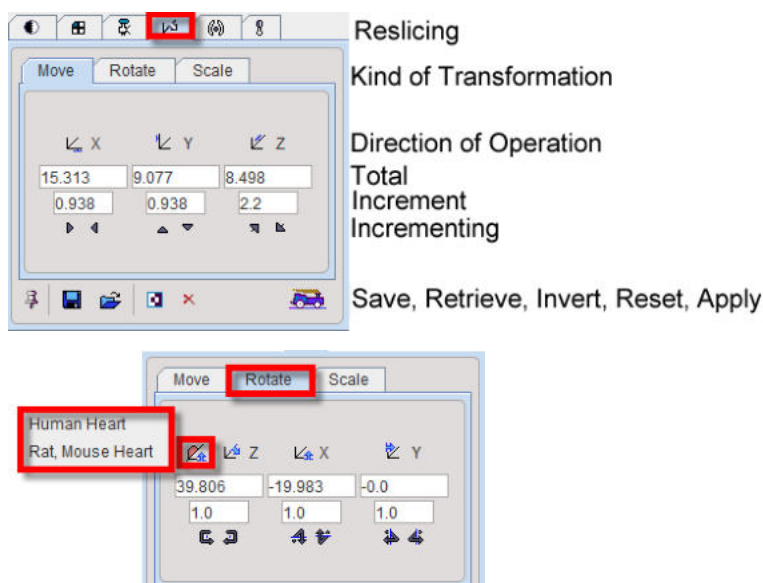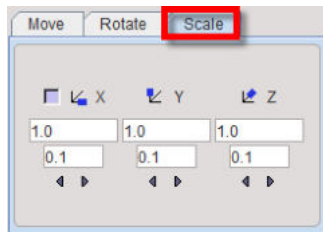
Note that **Scale** values of 1 indicate that the pixels sizes read from the image header are correct. Any other number will scale the pixel size accordingly.

The transformation parameters can be specified in different ways, on the corresponding sub-panes **Move, Rotate, Scale:**

- by entering values for the shifts or rotations in the number fields, or
- by clicking on one of the arrows to increase/decrease the values by the shown increments.

In the **Rotate** tab a help re-orientation button is available for heart studies . This option button allows re-orienting the heart data such that is closest to the short axis orientation (SA).The heart type can be selected when the button is activated. Two options are available: **Human Heart** and **Rat Mouse Heart**.

After changing the transformation, new slice images are immediately calculated and shown. However, the entire data set is only generated when needed, for instance to save the images. The button serves for enforcing the reslicing process for the whole data volume.

The button resets the transformation parameters. A transformation can be saved to disk using , and later retrieved with if needed.

Important Notes:

1. The facility buttons in the reslicing panel for **Save**, **Retrieve** and **Apply** transformation are not always available.

2. The manual transformations are not fully equivalent with the automatic rigid matching transforms of the fusion tool. Manual transformation can be used in PFUS activating the **LoadTransformation** button in the **Auto** panel available on the **Initialize/Match** page. In PFUS, the **Inverse** transformation is possible to calculate for any type of transformation activating the dedicated button .

Mouse-driven Reslicing

As soon as the reslicing pane is activated, handles appear in the image overlay. They allow for interactive, mouse-driven reslicing.
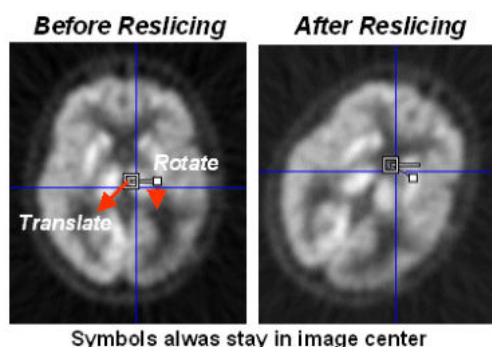
Translation: Move the mouse pointer to the open white rectangle. The cursor changes to . Click the left mouse button down, and then drag along the direction you want to move the image to.

Rotation: Move the mouse pointer to the filled small white rectangle. The cursor changes to ↖⟳. Click the left mouse button down, and then drag while the image gets rotated. To get finer control of rotation, the rectangle can first be dragged radially outward, so that the handle distance from center increases.

Per default, the reslicing handles are shown as long as the reslicing tab is selected. If another tab is selected, they disappear. To make them appear permanently in the images and enable mouse-driven reslicing at all times, the pin button 📌 can be fixed to 📌. A quick alternative to show/hide the reslicing controls in the active image is the `CTRL+R` shortcut.

9.9   Adding Iso-Contour Lines to Images

The fourth tab
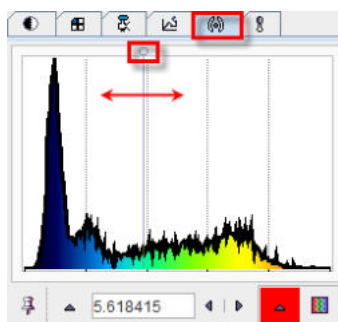
is used to overlay iso-contour lines onto the images. A histogram of the pixel values is shown, and the value at which the iso-contour lines are drawn can be adjusted by entering a numerical value, or by dragging the marker highlighted in the graphics above. The selection on the right allows choosing among several colors for the contour lines.
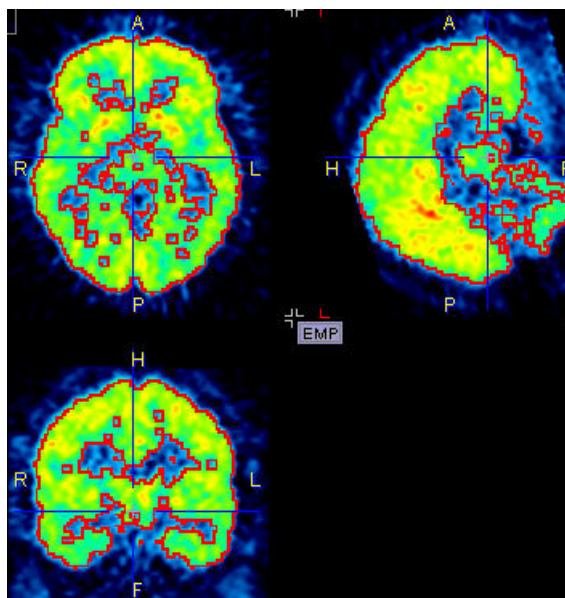
Per default, the iso-contour lines are shown as long as the iso-contour tab is selected. If another tab is selected, they disappear. To make them appear permanently in the images the pin button 📌 can be fixed to 📌.

9.10 Showing and Saving Movies

The movie player allows showing movies of slice images through the volume or through time (dynamic studies only), as well as rotating MIPs if the 3D button was selected in the layout.
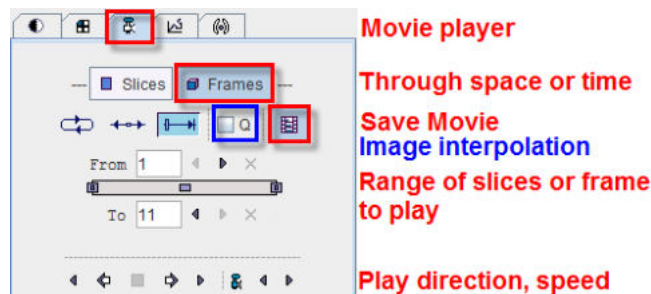
Please use the **Q** box to enable image interpolation when working with low-resolution images. If the save movie button is activated at the time the user hits the start button, a dialog window appears requesting information for movie generation.
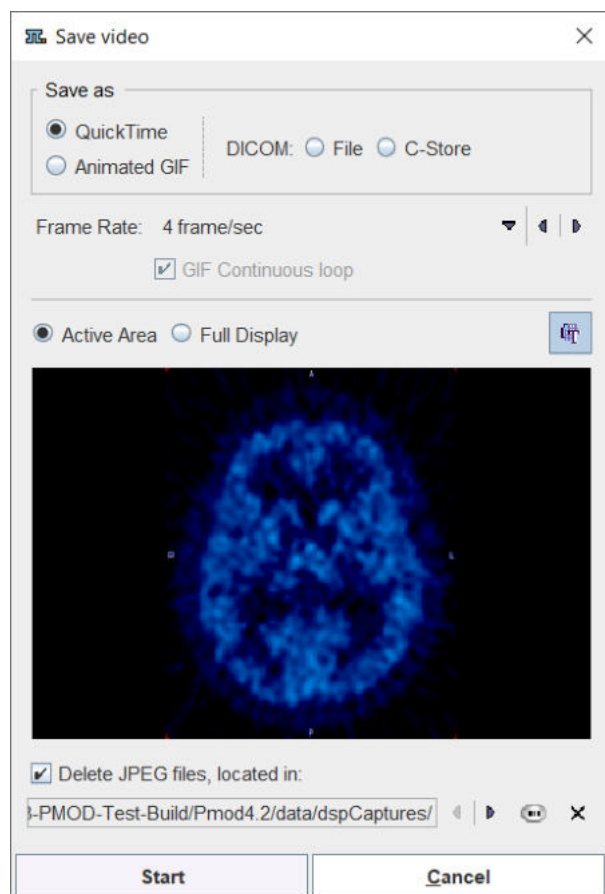
The movie formats include Quicktime or DICOM, and the active image or the entire image viewport can be captured. The movies are generated from intermediate JPEG files, which can optionally be kept for other uses.

A movie of the active image can also be started/stopped with the `CTRL+M` shortcut without the need to open the movie tab.

9.11   Image Capture

The capture button located in the lower right corner of the image viewport allows creating various types of captures:
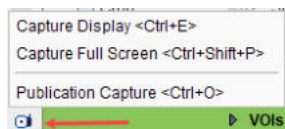
Capture Display (Ctrl+E)

The capture output is defined in the dialog window that appears.
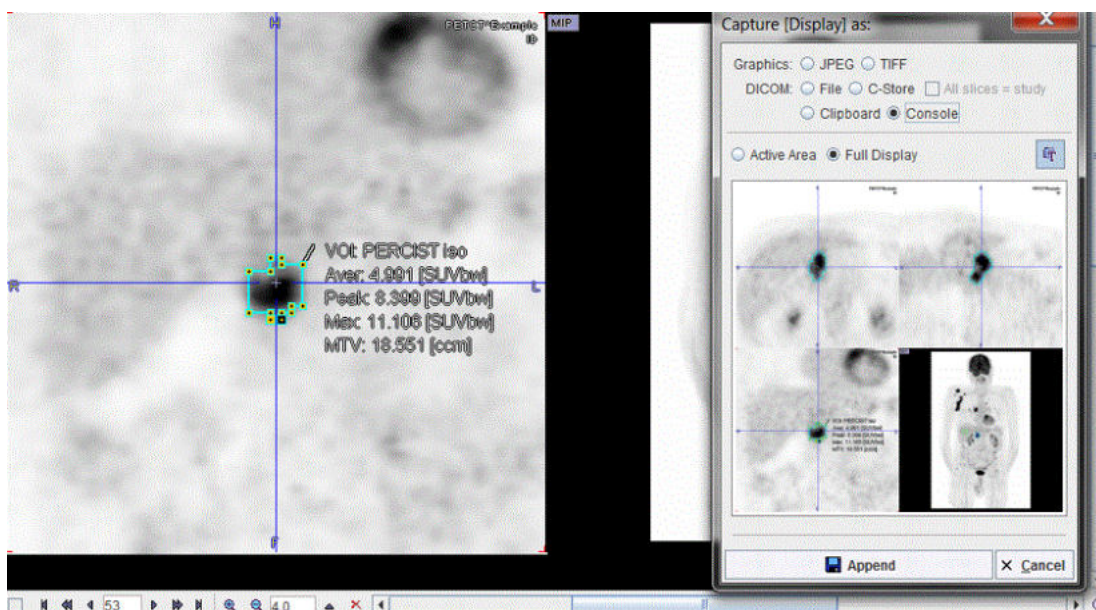
Active area only captures the content of the selected quadrant, whereas **Full Display** captures the whole image area, including MIP.

The output format is selected in the upper part: either a **DICOM** secondary capture image can be saved or directly sent to a PACS system (**C-Store**), or a graphic image file format can be specified for saving.

Note the **Console** output, which sends the capture to an image buffer in the console. When opening the console later on, the captured images can be inspected and the relevant ones saved.
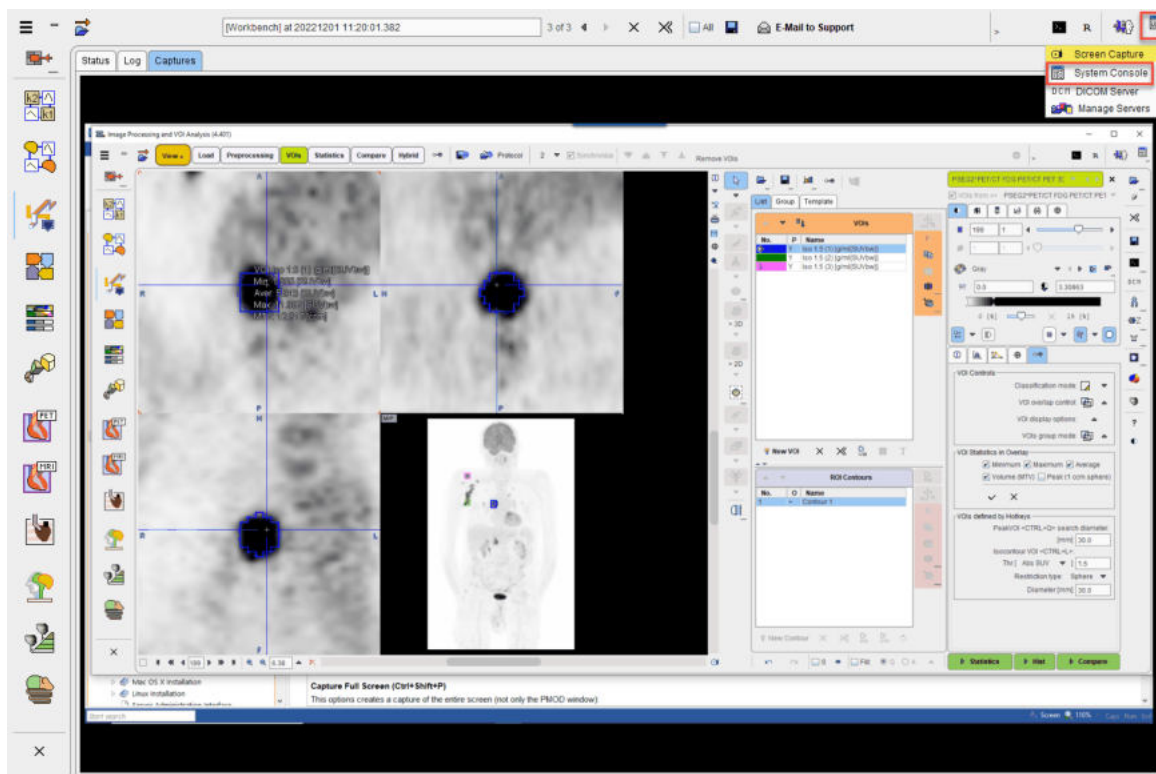
Capture Full Screen (Ctrl+Shift+P)

This options creates a capture of the entire screen (not only the PMOD window):
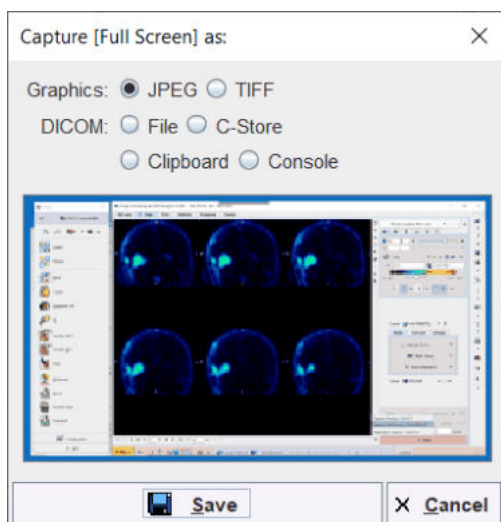
which can be saved as **JPEG**, **TIFF** or copied to **Clipboard**. The **Console** option automatically appends the capture to the buffer for problem reporting 27.

The DICOM output supports two options:

1. with the **File** the DICOM SC images are saved to disk

2. with the **C-Store** option supports direct network transfer to a DICOM server.

Publication Capture (Ctrl+O)

This option creates publication captures of predefined sizes:
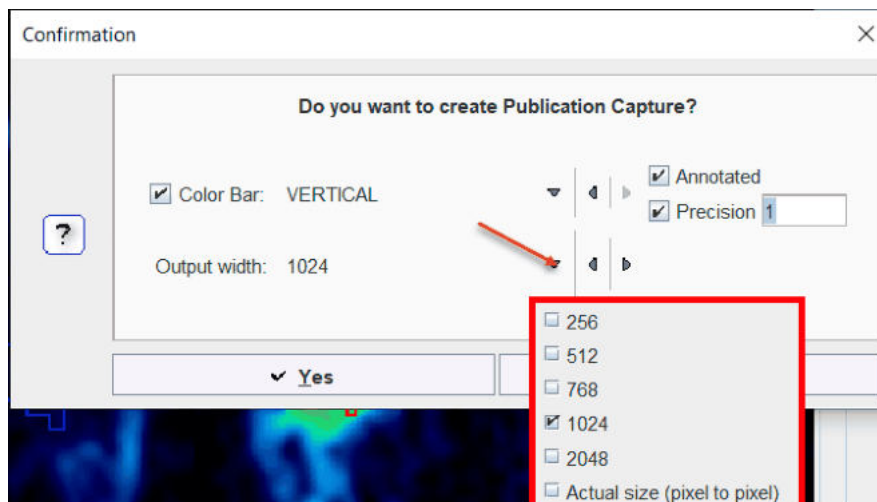
The **Output width** defines the capture size. The **Actual size** option allows obtaining exactly the same appearance in the capture like in the viewport. Optionally, annotated **Color Bar** can be added to the capture enabling the dedicated check boxes. The annotation **Precision** can be specified in the dedicated text field. Two options are available for the color bar position: **VERTICAL** and **HORIZONTAL**. The color bar annotations correspond to the lower and upper threshold set for the image display. The publication capture supports SUV units. The units are read from the display unit setting.The *Original* setting corresponds to the units stored in the image header.

The **Yes** button opens a **Scientific output** settings window as illustrated below:
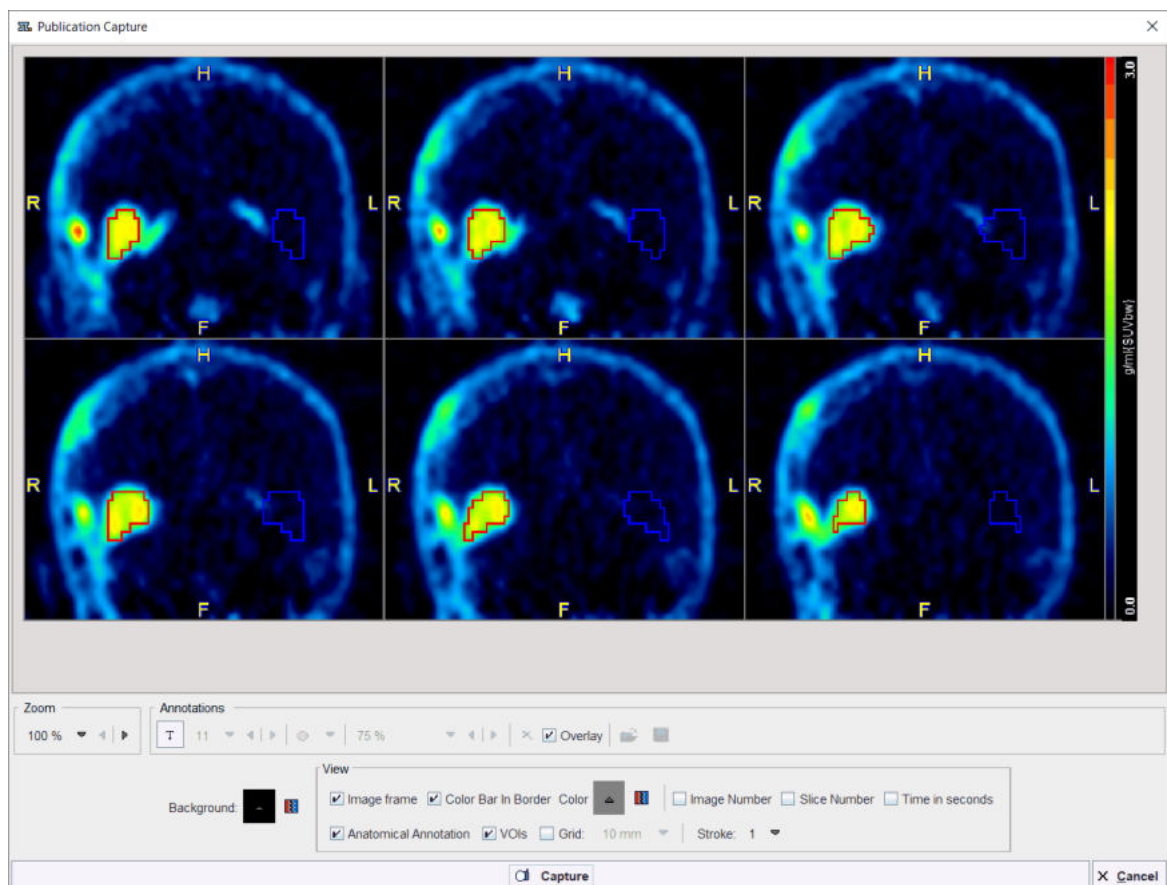
It allows adding the **Image frame**, **Slice Number**, **Anatomical Annotation**, **Grid** of predefined size, etc. Optionally, **VOIs** (if available) can be overlaid on the image. The **Capture** button allows saving the capture as **JPEG**, **TIFF** or to the **Clipboard:**
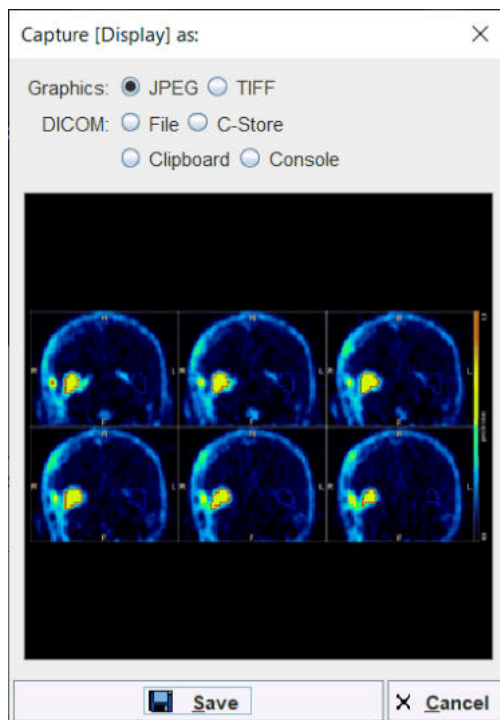
The **Console** option automatically appends the capture to the buffer for problem reporting [27]

The DICOM output supports two options:

1. with the **File** the DICOM SC images are saved to disk.

2. with the **C-Store** option supports direct network transfer to a DICOM server.

The **Save** button starts the final saving procedure.

9.12   Reports

Reports of the current configuration in a single image display can always be generated using the report button located in the top line menu. In more complex configurations such as image fusion (PFUS) or image comparison (PVIEW) a dedicated report button is available which creates a composite report.

The report button opens a dialog window consisting of a header part, the image area, a comment field, and control buttons for adding annotations, saving and printing.

The logo and the institution address of the header can be configured using the button in the PMOD top line menu. The subject demographic information is extracted from the image header. It can only be changed by changing the image information itself with the **Edit subject/Study Info** function.

The central part contains the image(s) in the layout and color as on the image viewing port(s). As long as the presentation is not fully satisfactory, the user can change it in the application and then activating the button again.
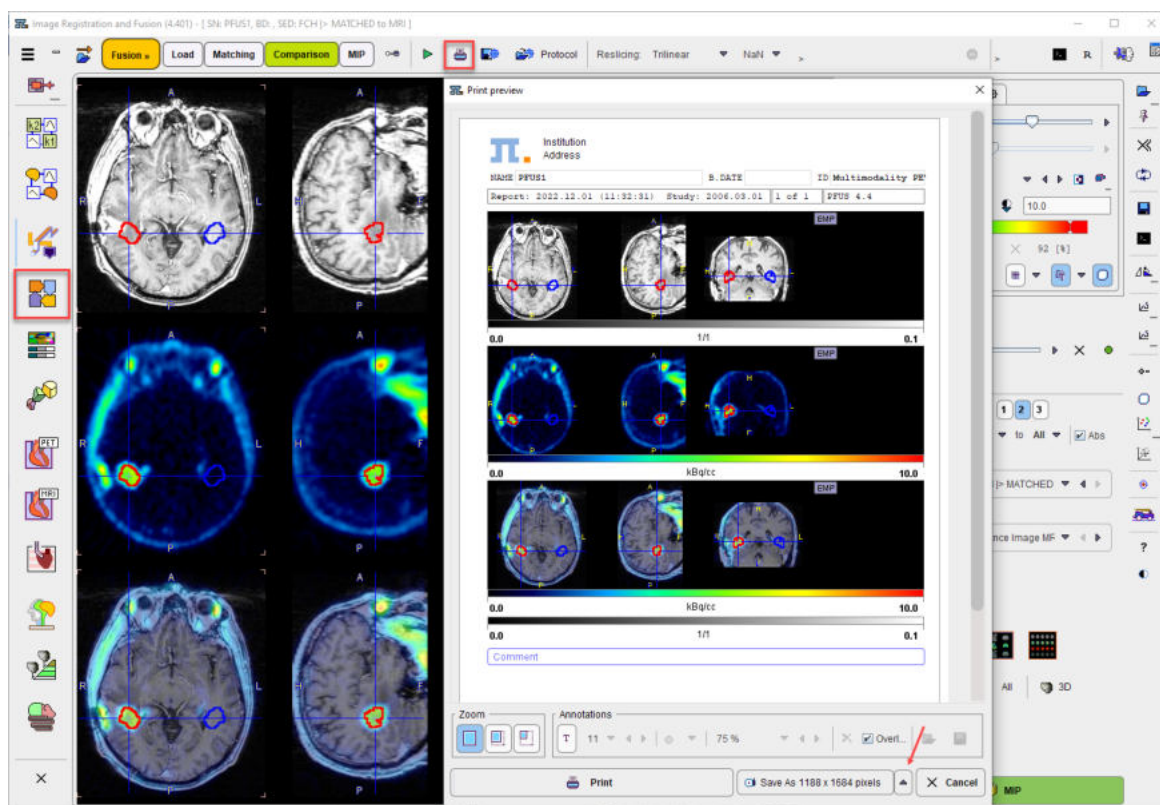
In addition to the provided content the user may add annotations. This can be achieved by enabling the T toggle button in the **Annotations** area
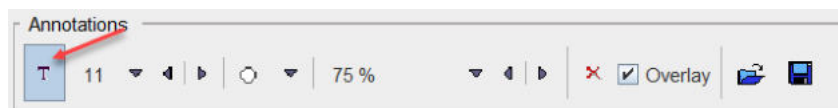
and then clicking into the report. A dialog window opens for entering a comment title and body.
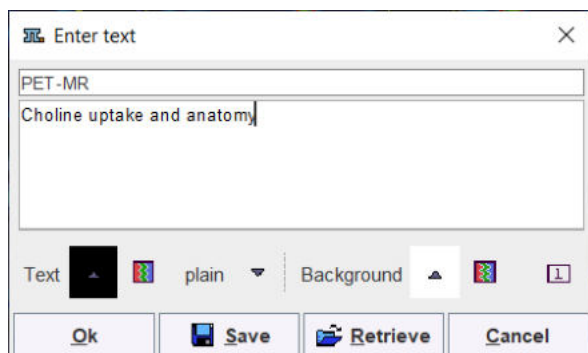
After closing with **Ok**, the comment text is shown together with a circular marker, connected by a line.
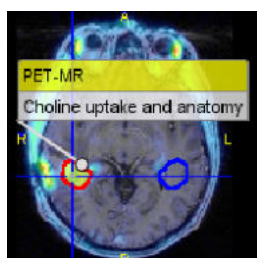
Both the text and the marker can be dragged around so as to properly label a point of interest without obstructing the view on relevant information. By changing the opacity and font size in the **Annotations** area, the comment appearance can be adjusted appropriately. To stop adding annotations, the T toggle button must be set to off by clicking it again.

When the report content is satisfactory, the page can be sent to a printer using the **Print** button. Alternatively it can be saved in different graphic formats using the **Save as** option button. Note that there are two resolutions available: **1188x1684** and **594x842**. With **1188x1684**, the generated graphic files have notable better quality (particularly the text), but are considerably larger in size.

Several saving formats are available in the appearing dialog:
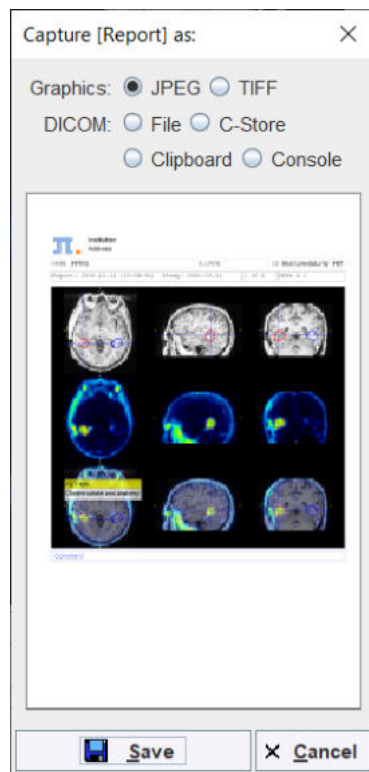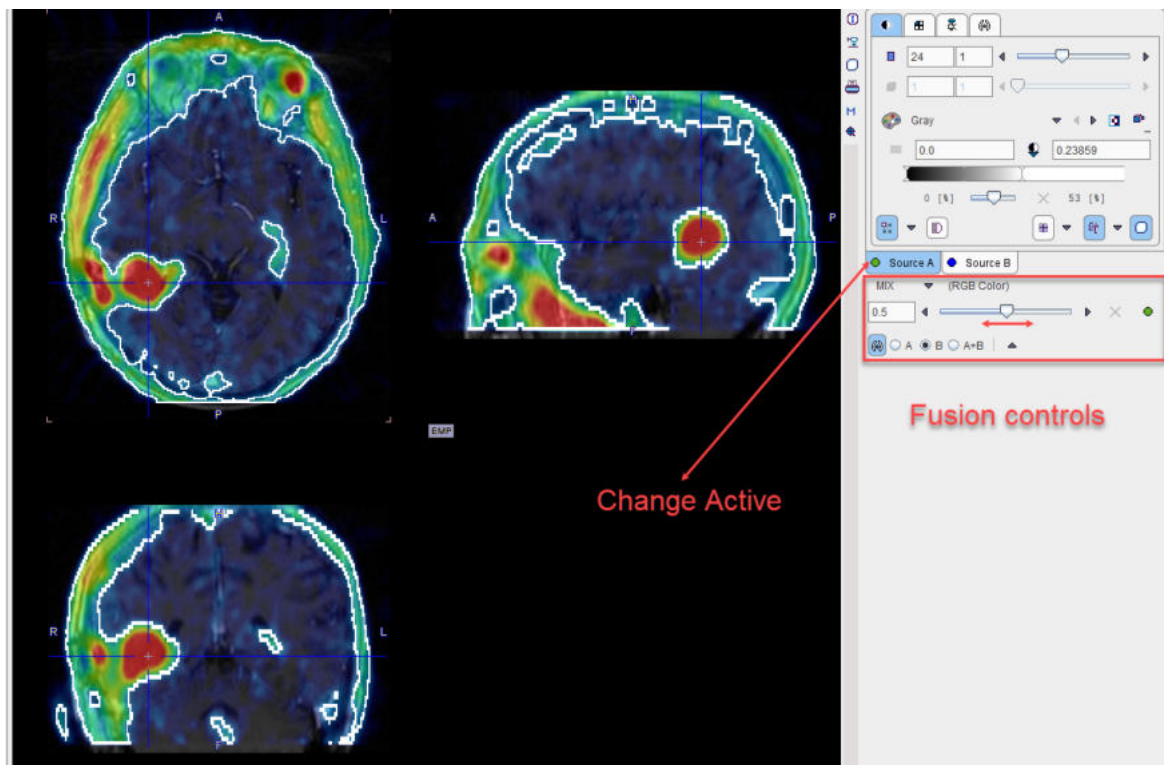
The report page can be saved as a graphic file (**JPEG** or **TIFF**) or copied to the **Clipboard** (for pasting it into a different application). Another alternative is to create a DICOM Secondary Capture object which can be can be saved to disk (**DICOM File**) or directly sent to a DICOM server (**DICOM C-Store**). The **Console** option automatically appends the capture to the buffer for <u>problem reporting</u> 27

9.13 Presentation of Fused Images

There are multiple places in PMOD where two different image sets can be combined into a fused image. Depending on the context, there are two arrangements for performing the image fusion.

Fusion Images not Visible at the same Time as the Source Images

In this layout only the fusion of two source series is shown.

To adjust the presentation of either source image, select the appropriate tab **Source A** or **Source B**, and use the image controls. During such adjustments it will sometimes be helpful to only see the image you are working on, not the fusion. This can easily be achieved by moving the balance slider to one of the end positions left or right.

Separate Source and Fusion Images

In this layout both the input images and the fusion images are visible at the same time, as in the example shown below.

π.pmod
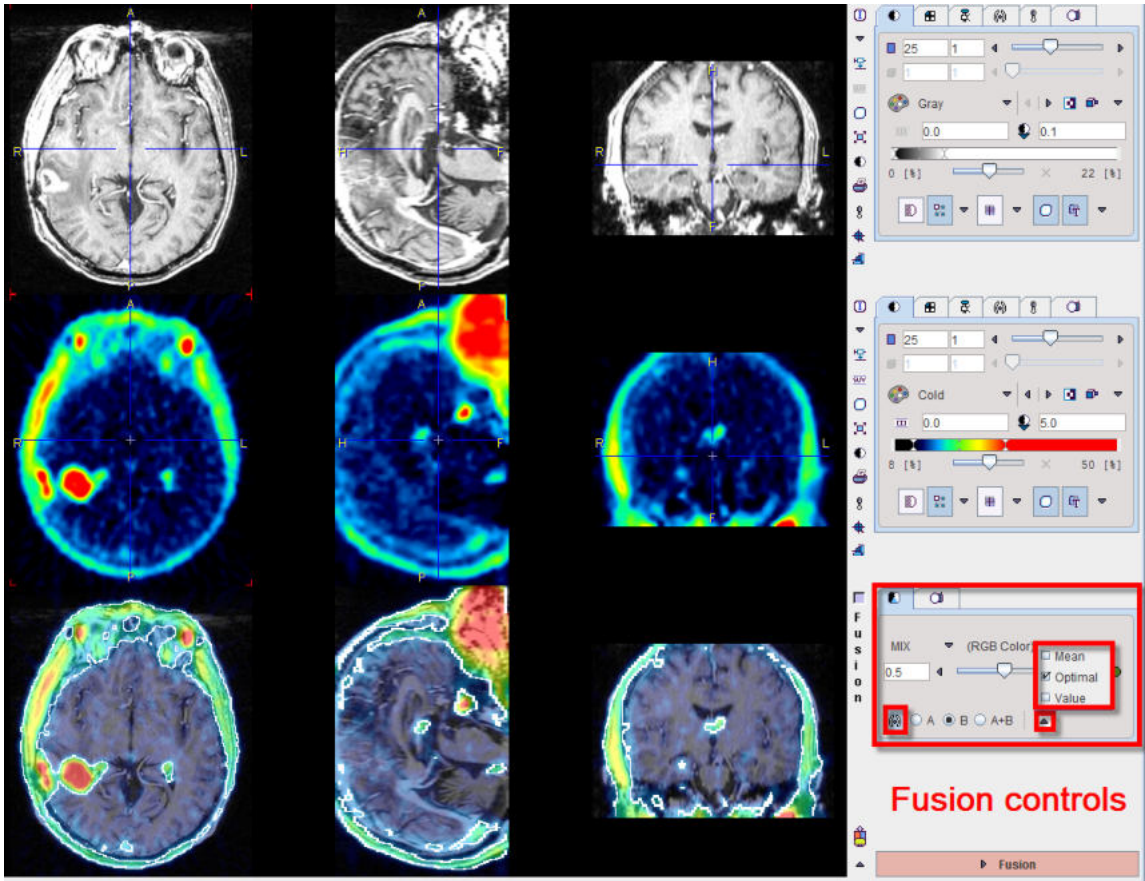
In this example the first row shows a T_1-weighted MR image, and the second a matched ^{18}F-Choline PET image with a highlighted tumor. To the right of the images the controls are available for changing the way how the images are displayed such as the color table, the thresholds, and the layouts. The third row shows the result of the fusion, depending both on the renderings of the source images, and on choice of the fusion controls located to the right.

Image Fusion Methods
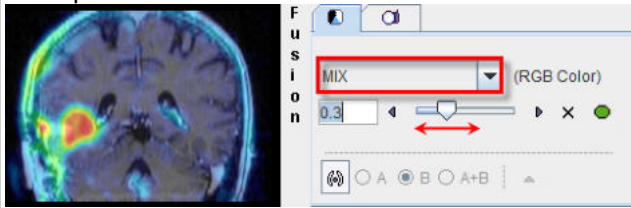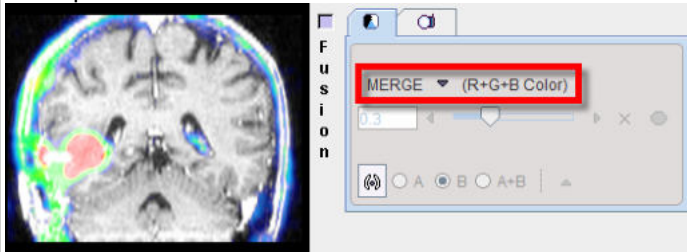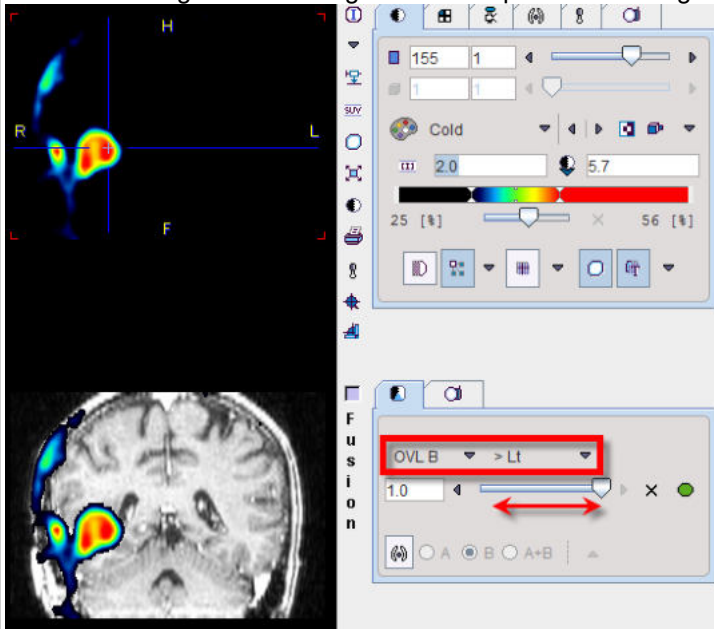
The image fusion control
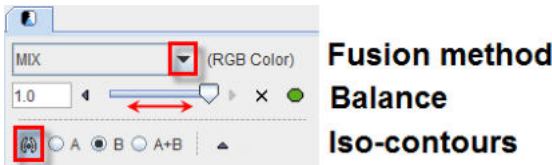
consists of three rows. The first row contains the selection(s) for choosing between the different fusion renderings, the second row allows enabling the balance to blend the contributions of the two images in the fusion, and the third row allows enabling the iso-contour overlays.

The fusion methods available are:

MIX	Alpha Blending: weighted addition of the RGB values of both source images according to $R_{fusion} = R_A*x + R_b*(1-x)$ $G_{fusion} = G_A*x + G_b*(1-x)$ $B_{fusion} = B_A*x + B_b*(1-x)$
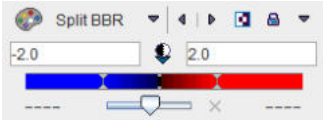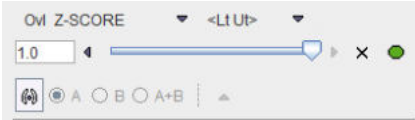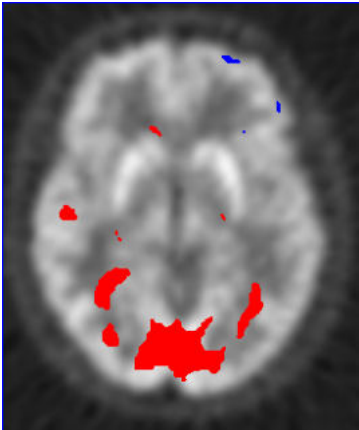
	Example: The slider allows defining the relative contributions of the source images. In the example shown image A contributes 30%, and image B 70%.
MERGE	RGB merging uses the maximal RGB value of both source images according to $R_{fusion} = Max(R_A, R_b)$ $G_{fusion} = Max(G_A, G_b)$ $B_{fusion} = Max(B_A, B_b)$ Example: This fusion mode is most adequate for data arising from RGB sources, or when encoding the images with the [R]ed, [G]reen, [B]lue color tables.
OVL B	Shows the images A as background and a part of the images B as the overlay. With the **>Lt** setting, all pixels in the PET image (B) below the lower threshold of the color table are replaced by the MR (A) values. Additionally, some transparency is added in the lesion by the balance slider. See below the description of the different threshold options.
OVL A	Is equivalent to **OVL B** except that the role of the images is reversed.
WIN A	Shows the images B (PET) as the background. When clicking into an image a rectangle appears which overlays the image A (MR).

WIN B	Shows the images A (MR) as the background. When clicking into an image a rectangle appears which overlays the image B (PET).

When the **OVL A** or **OVL B** methods are selected, different threshold settings are available in the selection to the right:

> Lt	Only the pixels (in A for **OVL A** , in B for **OVL B**) with values *above* the lower threshold are displayed. This is the most useful setting when a hot lesion is to be blended into an anatomical image (see example for **OVL B** above).
< Ut	Only the pixels (in A for **OVL A** , in B for **OVL B**) with values *below* the upper threshold are displayed.
>Lt Ut<	Only the pixels (in A for **OVL A** , in B for **OVL B**) with values *between* the lower and upper threshold are displayed.
<Lt Ut>	Only the pixels (in A for **OVL A** , in B for **OVL B**) with values *outside* the lower and upper threshold are displayed. Note that only the first and last color of the selected color table are applied in this setting. A suitable selection in this configuration is the **Split** color table.

An example of the **<Lt Ut>** method is shown below.

Image A represents normalized subject images, and image B the deviation from the normal pattern expressed as z-score values. The color table configuration of image B is	
and the fusion settings Only z-score values < -2 and > 2 are shown, without transparency. Because only the minimal	

and the maximal colors are use, the result has a binary character. Red are all pixels with an activation of more than two standard deviations, and blue all the pixels with the uptake reduced by at least two standard deviations. This is probably the most useful configuration for exploring the deviations from the standard pattern.	

Iso-contours in Image Fusion

The contours radio box allows overlaying iso-contours derived from the source images **A** or **B** or both onto the fusion result. In the example below an iso-contour circumscribes the lesion clearly delineated in the FCH PET image. The iso-contour for the image **B** can be generated automatically selecting the **Optimal** option in the list in the **Contouring** tab. Setting the radio box **B** displays this contour in the fusion, which has been set to show mainly the MR image (A) by moving the balance slider to the left end. Another helpful application of the contours is in image matching.
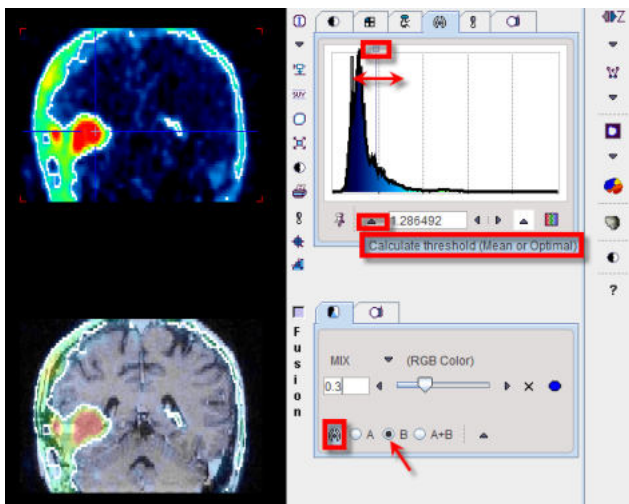
9.14 3D Volume Rendering, Rotating MIP Images

Instead of showing individual slice images, a volumetric data set can be volume rendered. Simple volume rendering can be enabled in the **3D** sub-pane
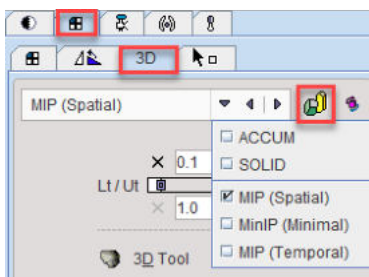
There are four methods to choose from the selection

- **ACCUM** (Accumulation of color and opacity)

- **SOLID**

- **MIP (Spatial)** Maximum Intensity Projection

- **MinIP (Minimal)** Minimal Intensity Projection (possibly useful for inverted contrasts or low-density tissue)

- **MIP (Temporal)** Maximum Intensity Projection using the maximal pixel value across time frames in a dynamic series

As soon as the rendering button indicated in red is activated (or `CTRL+V` on the image) the image display switches from slice display to volumetric display, with the projection direction orthogonal to the image plane. Three renderings of an example PET using the same color table are shown below. Note that the value range considered in the renderings is somewhat different.
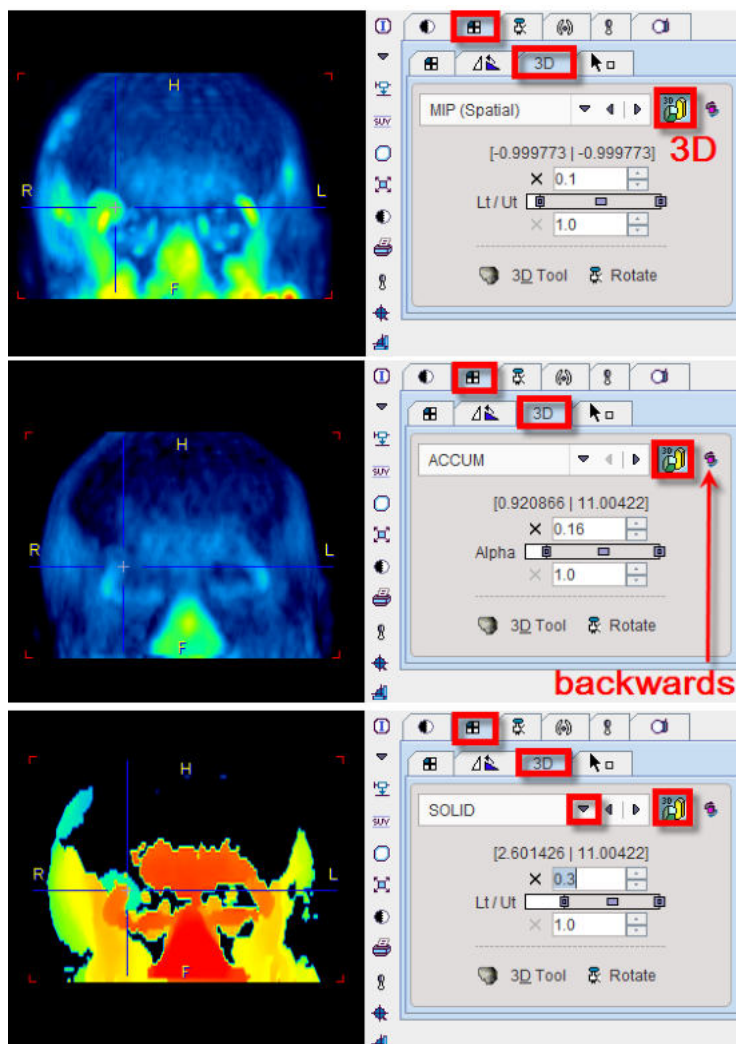
The button to the right of the 3D selection is a toggle to perform the 3D operation from backwards, which will result in a different image in the case of a depth-dependent weighting function.

> Note that image scrolling is still enabled in 3D mode. When `CTRL+Drag` the left mouse button over the image, the 3D rendering disappears and the slice images are shown until the mouse button is released.

Rotating MIP

To create a rotating coronal MIP movie please proceed as follows:

- In the **Layout** pane select the **Coronal** orientation (or `CTRL+Y` in the image).
- In the **3D** pane enable MIP and 3D, then adjust the upper/lower thresholds.
- In the **Movie** pane the number of slices has been replaced by the number of projections with a default value of 40 angles. Increase the number to get smoother rotations. Start playing.

MIP images will be calculated from different viewpoints and displayed as a rotating cine. If you would like to save a movie, enable the saving button as explained in <u>Showing and Saving Movies</u> [195].

Transfer to Full 3D Rendering

The 🌑 button in the 3D pane is only functional if the PMOD 3D option is installed. When this button is activated, the current data set together with the VOIs list (if available) are loaded into the full 3D rendering tool for advanced processing.

9.15 Markers

The **Markers** sub-pane serves for the definition of landmarks in the image.
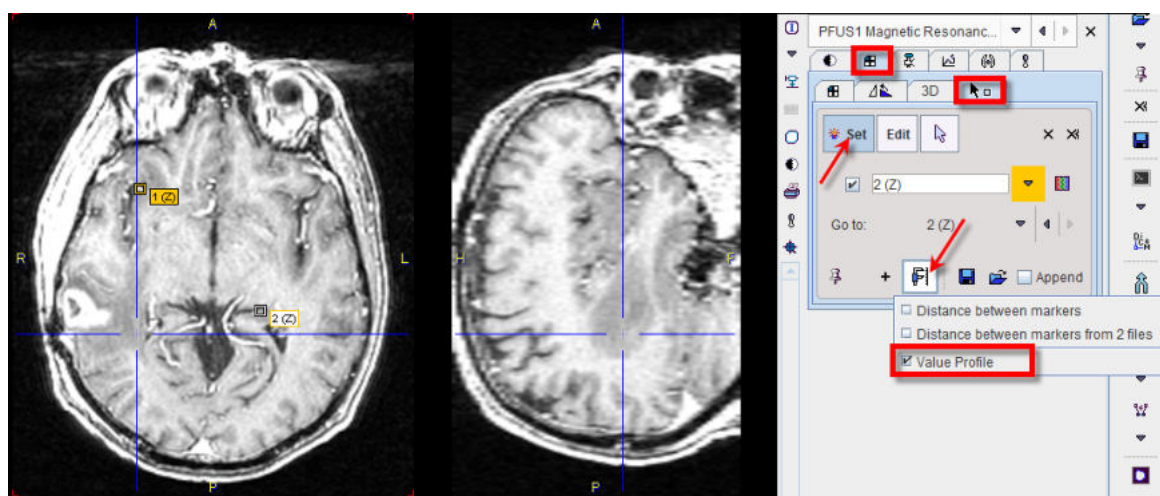
The best way to define landmarks is to operate in the orthogonal layout. If the **Set** button is active the user may click into an image to define anatomical landmarks which are shown as squares in the image. Using the **+** button, a landmark can be defined by entering its coordinates in a dialog window. To avoid marker generation, hold `CTRL+SHIFT` when clicking, or disable **Set** beforehand. The slices can be scrolled by the mouse wheel or by `CTRL+DRAG`. The spatial arrangement of landmarks can be saved for later use with 💾 .

The defined landmarks are numbered and organized in a list. The planes can be centered on a defined landmark by the **Go to** list selection. There are three types of landmark-based measurements:

▪ **Distance between markers** calculates the distances between any two landmarks and shows them in a table.

▪ **Distance between markers from two files** allows loading a second landmark set and calculating the distances between corresponding landmarks.

▪ **Value Profile** generates a plot of the values between the landmarks, connecting them them sequentially with lines.
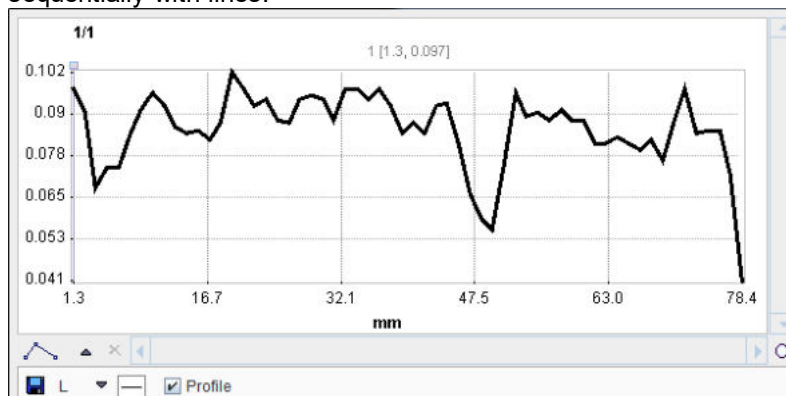
9.16 Curve Display

A common curve display object is used in all PMOD tools. It consists of a curve area and a controls area underneath.
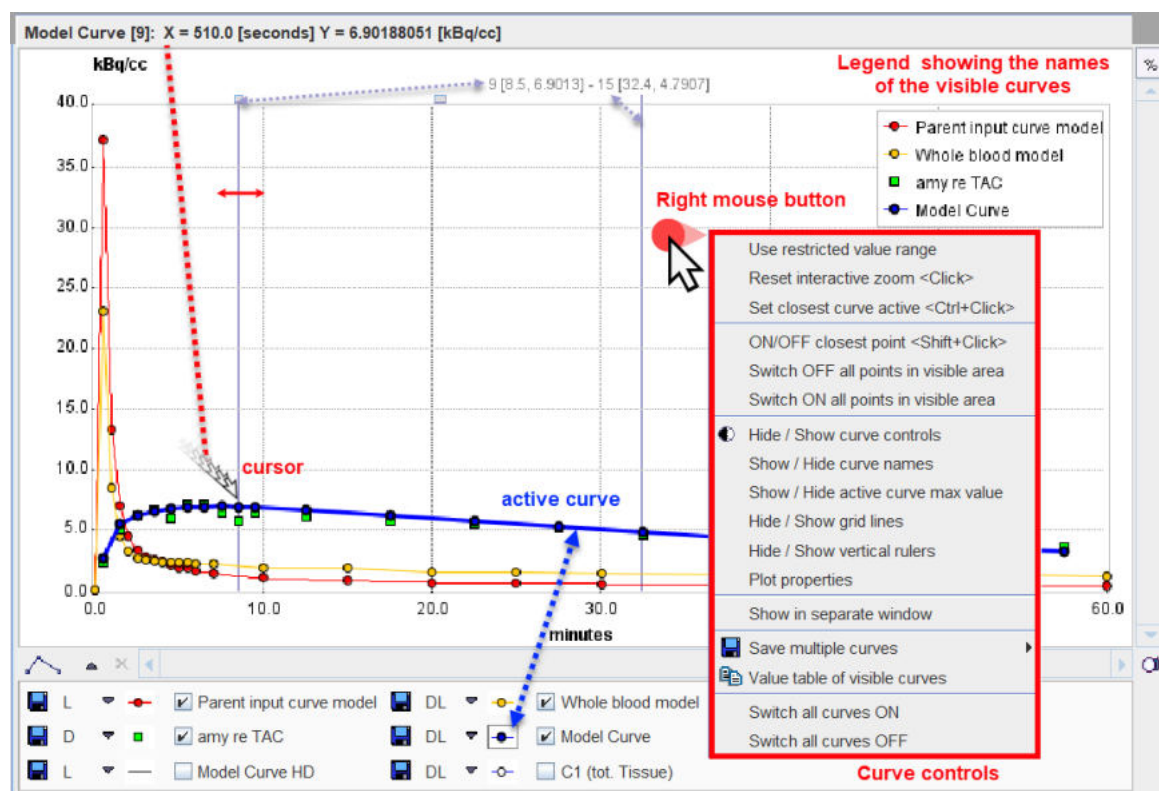
In some contexts the control area may initially be hidden. The context menu can be used to show it

Curve Area

The curve area shows the curves which are enabled for display. There is always an *active curve*, which is shown in bold. A curve can be made active by holding down the CTRL key and clicking at one of its points, or by pushing its button in the controls area as illustrated with the **Model Curve** above.

The definition of the active curve is relevant for the tools which interrogate the curve values:

▪ There are two small handles at the top of the curve area: a little rectangle to the left, and a line to the right. These are handles which can be moved left/right using the mouse, and the gray vertical

lines move with them. The values at the top center of the curve area represent the interpolated (x/y) values of the active curve at the location of the handles. To get the measurements of a different curve just `CTRL+Click` at that curve to get the values updated.

▪ Only in some curve displays: When the cursor is brought close to a point of the active curve, its x/y value pair is shown at the upper left of the curve area.

To *zoom* into an area of the curve just click the left mouse button to the corner of the area of interest and drag a rectangle. After releasing the mouse button the display is zoomed into the defined rectangle. An alternative is to define the axes **Range** in the context menu. A single mouse click into the curve area is sufficient to reset the zoom.
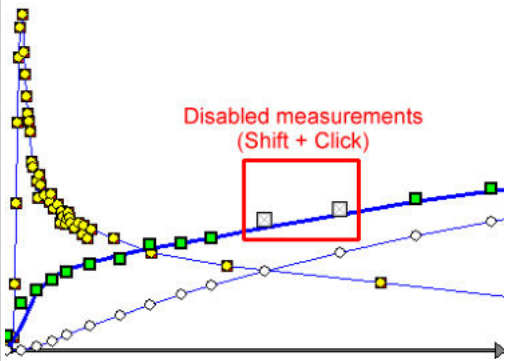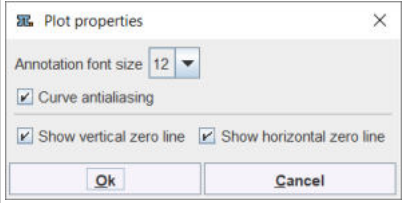
Context Menu

By clicking the right mouse button into the curve area a context menu with some additional options can be opened.
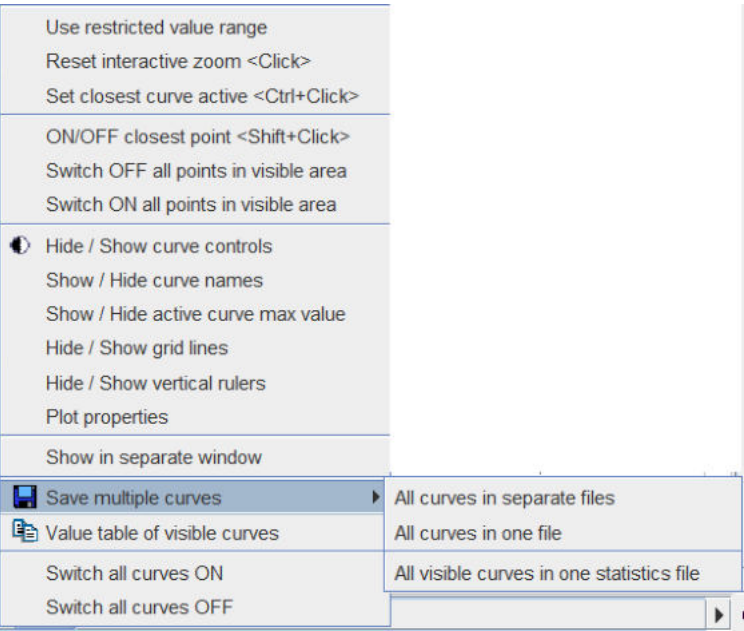
The functions are:

Use restricted value range	Set the range of the x- and y-axis by entering a numeric value. If the box is checked, the range is maintained during all manipulations. Otherwise, a single click resets the range to the default.
Reset interactive zoom <Click>	Resets the curve range to the default full range. It is grayed if the display is not zoomed or the range is fixed. Mouse operation: single `Click` into curve area.

Set closest curve active	Selects the curve nearest to the point clicked with the right mouse button to open the context menu. Mouse operation: `CTRL+Click` at a curve.
ON/OFF closest point <Shift+Click>	Disable/enables the closest point. This is reflected by setting the symbol to gray. In the context of model fitting measurements marked in gray are regarded as outliers and not considered when evaluating the cost function. Mouse operation: position the mouse close to the point and then `SHIFT+Click`.
Switch ON/OFF all points in visible area	In combination with zooming this option allows to quickly disable/enable points in the visible area.
◑ **Hide/Show curve controls**	Allows hiding the controls if the curve display area is small, and to show them again.
Show/Hide curves names	Allows showing the names of the curves in the display area, and to hide them again
Show/Hide active curve maximal value	Allows showing the maximal value of the active curve as a horizontal line, and to hide it again
Hide/Show grid lines	Controls the display of the grid lines.
Hide/Show vertical rulers	Controls whether the measurement rulers are shown.
Plot properties	With this entry a configuration dialog is opened for setting the annotation **Font size**, and for enabling curve **Antialiasing** (smooth curve appearance).It also allows enabling vertical and horizontal zero lines.
Show in separate window	With this option, the curve display can be opened in a separate, large window to closely examine the plot.

Save multiple curves	Allows saving multiple curves based on the available selection: **All curves in separate files:** Allows saving the numeric data of all curves in a separate text files. **All curves in one file:** Allows saving the numeric data of all curves in a single text file. **All visible curves in one statistics file**: Allows saving the numeric data of the visible curves in a single statistics file.
Value table of visible curves	Opens a dialog window which shows the numeric values of all visible curves in a dialog window. The window contents can be copied to the **Clipboard** and pasted to a different application.
Switch all curves ON/OFF	To quickly change the visibility of all curves.

Curve Control Area

The control area lists the curves which are available for display. There are several elements to modify the curve appearance:
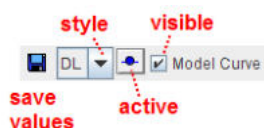
Show/Hide	To show/hide a curve check/uncheck the *visible* box.
Active curve	To set a curve to active click at the *active* button, or directly `CTRL+Click` on the curve itself. The line/symbols get bold.
Style	The list selection can be used to change the style of a curve:

Further useful interface elements:

Connections	Changes the shape of the lines defined by the measurements: Note that calculations are not based on the display representation of a curve.
💾	Saves the numeric data of a curve as a text file with two columns. These files obtain a **.crv** suffix and can easily be opened in Excel or a text editor. When working with a database the curve can be attached to a particular image using the **Attach to Subject (Series)** in the appearing dialog.

%	If this button is enabled, each curve is normalized to its own maximum and shown as percent values. This mode is helpful for comparing shapes when the dynamic range of the curves is very different.
	Allows creating a capture of the curve area or of the full screen. The captured image can be saved as a **JPEG**, **TIFF** or **DICOM** file. It can also be copied to the **Clipboard** to paste it into some office application. The **Console** option automatically appends the capture to the buffer for problem reporting 27. Capture Curve Capture Full Screen <Ctrl+Shift+P>

10   Volume-of-Interest (VOI) Analysis

The main purpose of a VOI analysis is to calculate the distribution of pixel values within delineated tissue structures. There are several VOI definitions available in PMOD which are described below.

Starting with version 4.3 the VOI algorithm was redesign in order to make iso-contouring workable for big data with more than 1300 voxels in each direction.

Starting with version 4.4 Raster VOIs were implemented to allow quick outlining and fast statistics calculation for big data.

10.1   VOI Interface

Starting a VOI Analysis

PMOD supports the access to VOI analysis in almost all situations when an image is displayed. The VOI button in the tools list next to the image
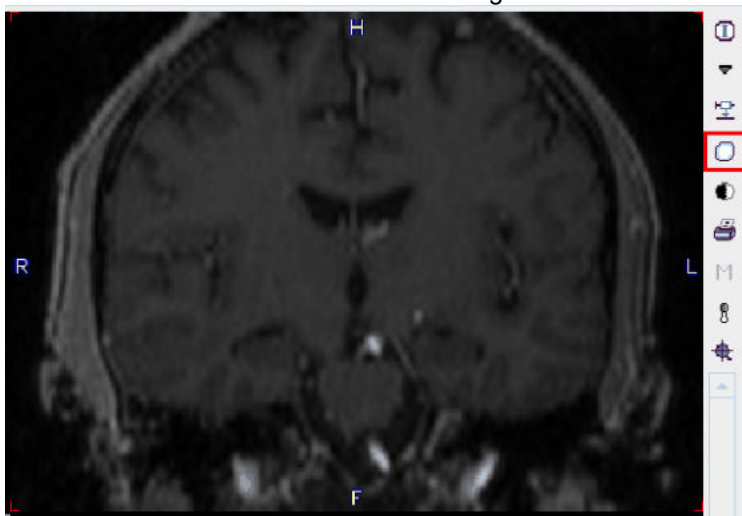
immediately switches to the VOI definition environment with the current images. In the PVIEW tool, there is a separate **VOIs** page for entering the VOI definition mode.

VOI Layout

Starting with PMOD 4.2 only the compact VOI layout is supported.

This layout uses a single vertical column for VOI definition and modification tools, with an additional configuration tab.

The location of the VOIs list can be configured in the local tool configuration:
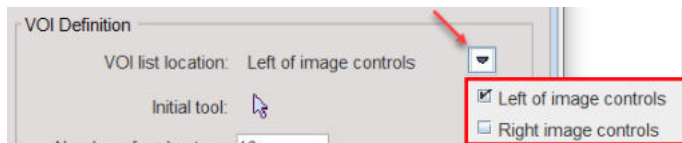
to the **Left of image controls**:
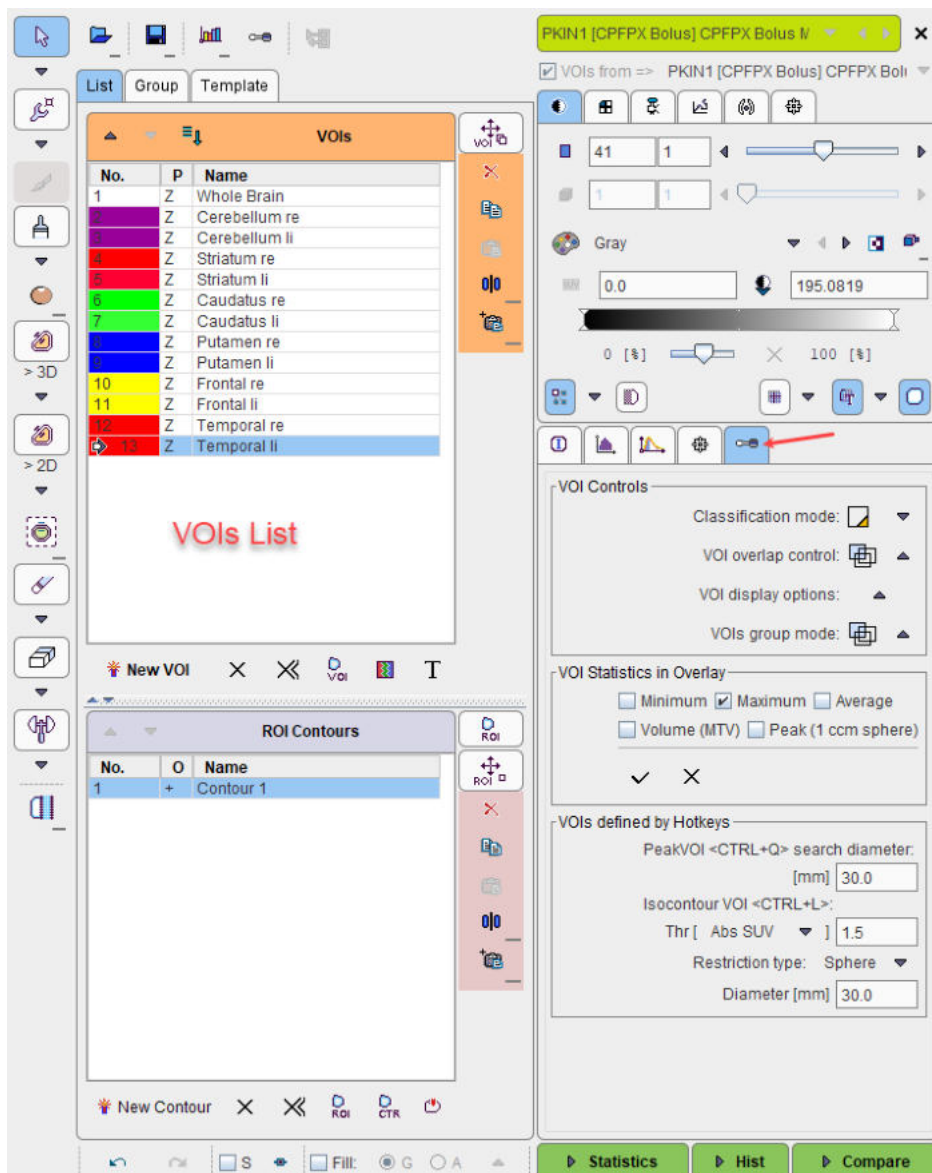
or to the **Right of image controls**:
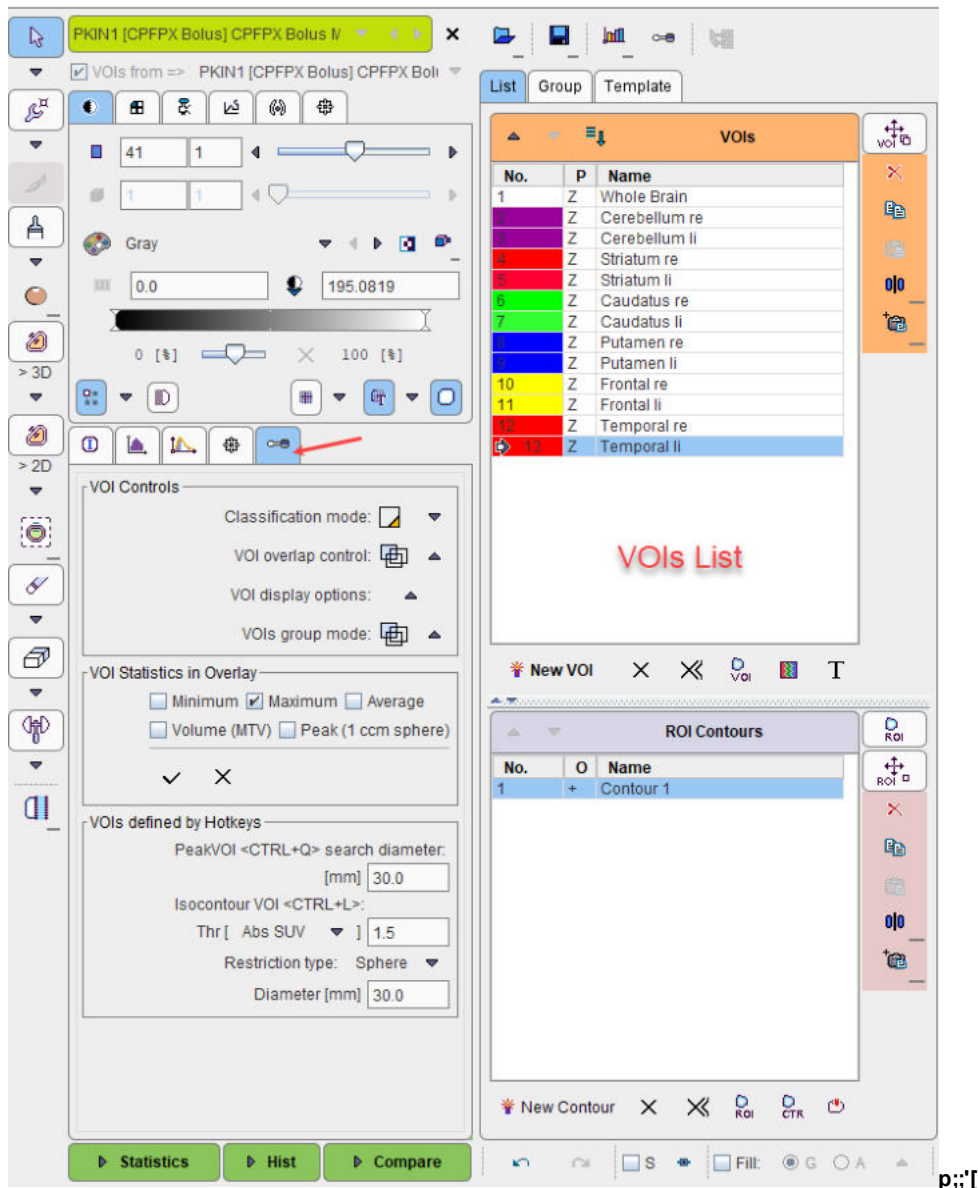
Throughout the documentation the **Left of image control** setting will be used for the **VOI list location**.

Layout Overview

Most of the interface is related to the creation and editing of contour-based VOIs. The illustration below indicates the grouping of functionality using a simple example with 13 contour VOIs. The details are described in the following sections.
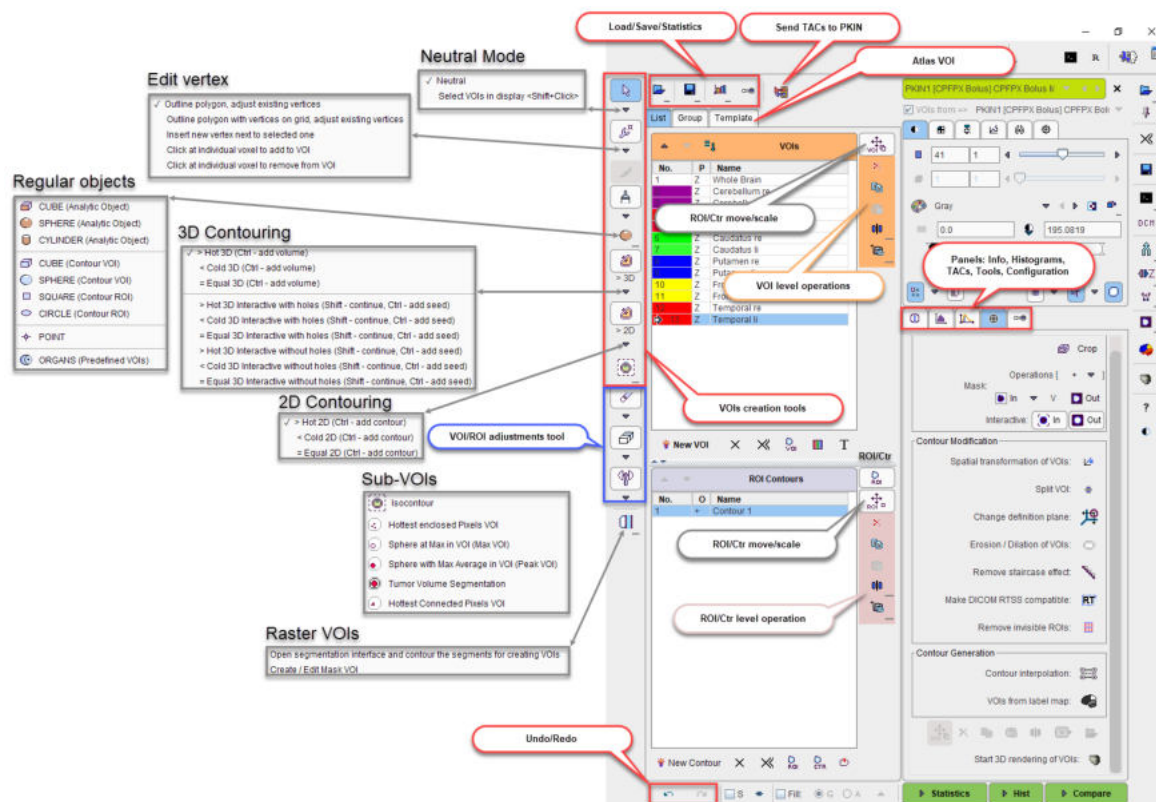
VOI Selection

When clicking at a VOI in the **VOIs** list, the lesion is triangulated in the display. If some **VOI statistics in the overlay** elements are [enabled](226), the results for the selected VOI are shown in the overlay. Double-clicking at a list entry additionally changes plane selection such that the contours can immediately be edited.

Alternative to selection in the list VOIs there is an mode for directly selecting the VOI in the image or the MIP. To this end the **Neutral** toggle has to be switched to **Select VOIs in display**.
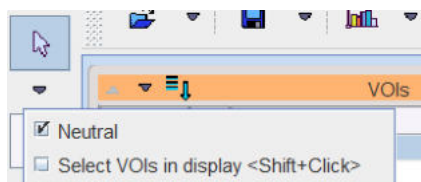
Tool Hiding Options

If during image inspection space is too much reduced by the VOI tools, there are two ways to reduce the tool area:

	Activating this button in the lateral taskbar will hide all the tools. Activating it again recovers the original layout.
	This toggle button removes the column with the VOI and contour lists. The VOI list is added as a new panel, but the contour list and VOI loading/saving/statistics are not anymore available. To return to the complete layout the button has to be activated again. This button is available only in the legacy layout.
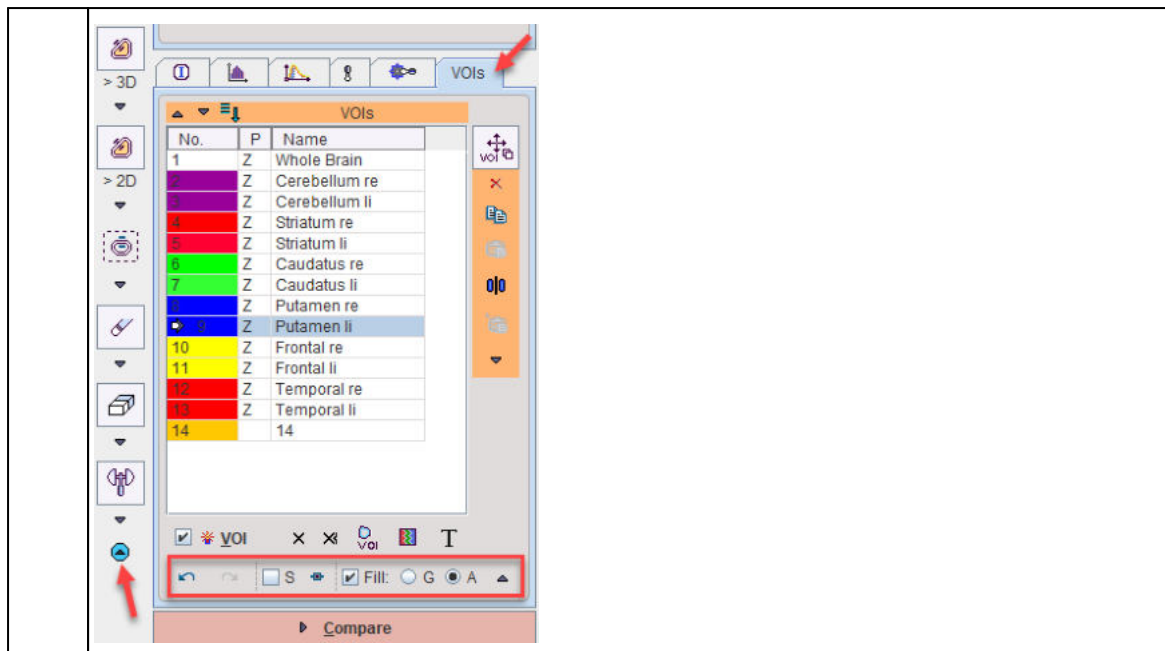
10.2   Using Contour VOIs

In PMOD a contour VOI is defined as a stack of planar, closed polygons which are named ROIs (region-of-interest). The contours are manually or semi-automatically outlined on the loaded images, and the pixels contained within the contour boundaries are considered for the VOI statistics.
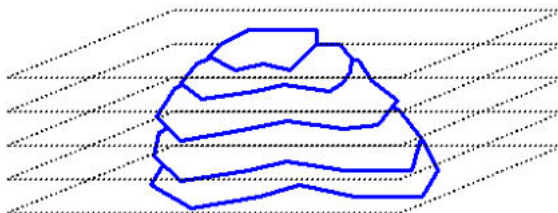
There are a few principles to bear in mind when working with contour VOIs.

- The coordinates of the contour vertexes are defined as the (x/y/z) triples. The x and y offsets are in [mm] from the image origin, whereas z represents the slice number. This makes the definition independent of the planar image resolution and the zoom factor. However, note that modification of the origin coordinate results in a shift of all VOIs defined for the image study.

- A contour VOI can be defined in each of the orthogonal directions. Naturally however, a single VOI can only consist of contours in the same direction. There exists a tool for changing the direction.

- Contour VOIs consist of one ROI per slice. This ROI can have one or multiple independent contours.

- A contour is a closed polygon which appears in PMOD as below with vertexes marked by squares and connected by straight lines.
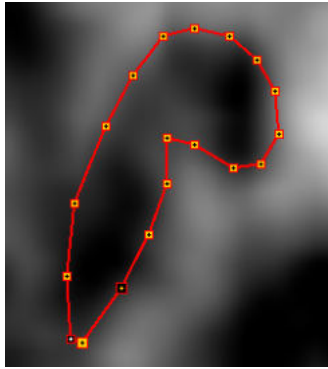
For each contour the user can define, whether the included pixels should be included into the statistics or excluded from it. By defining contours with exclusion, VOIs with hollow parts can be created.

- Single pixels are a special case of contours. They can be easily added to or removed from the contour VOI.

- For dynamic data the VOI can be extended to the temporal dimension as well. This means that the VOI may have a varying shape or location at different acquisitions over time, allowing to track moving organs over time. As long as the VOI has only been defined at one time point, it is applied equally at all times (static VOI). When defining the VOI differently at different times (dynamic VOI), care must be taken that a VOI is defined at *all* times.

- Many studies can be loaded and processed in parallel. Hereby it is possible to have individual VOIs for the different studies, but the VOIs can also be shared among spatially matched images.

10.2.1 VOI and Contour Properties

The hierarchy of three levels

1. VOI, consisting of ROIs in different slices

2. ROI, consisting of contours within a slice

3. Contour, one closed polygon

is reflected in the VOI user interface. Each level has a corresponding tool bar for object manipulations. For instance, when selecting the VOI button and shifting, the contours in all slices will be shift. When selecting the ROI button and shifting, only the contours in the current slice will be shifted.

10.2.1.1 VOI Level Properties

VOI List

The **VOIs** section on the **List** tab contains the list of defined contour VOIs, and VOIs which are in the progress of outlining.
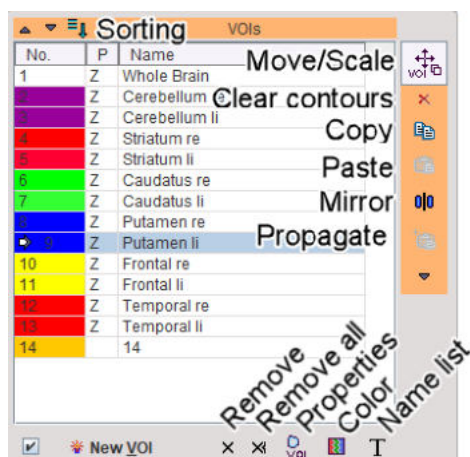
VOI Properties

VOI properties can be set while creating a **New VOI** :
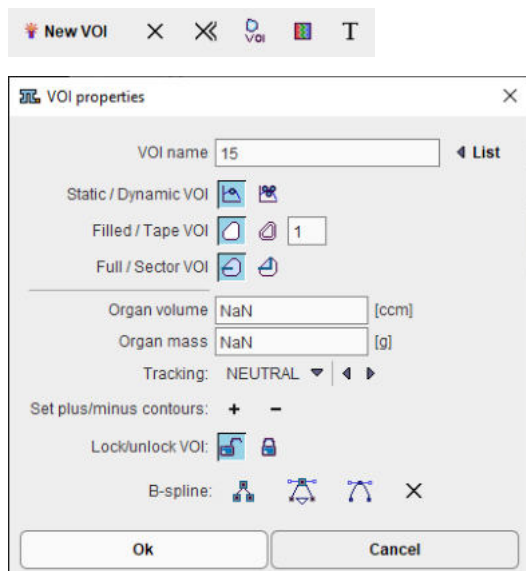
or can be changed using the button. It shows the VOI properties dialog window illustrated below.
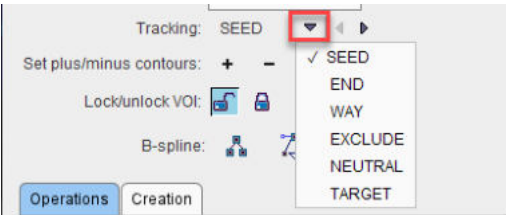
The window allows changing the properties and immediately updates the display for providing a visual feedback. The property elements have the following meaning:

VOI name	Allows assigning a name to the VOI in the list either interactively or from predefined name lists. The **List** button allows using pre-defined names stored in name lists and is described below.
Static/Dynamic VOI	This property is only relevant for dynamic series. If a VOI is defined static, the same VOI definition is applied and shown at all times. If a VOI is defined dynamic, a different VOI definition can be used at different times. Note that a dynamic VOI is only shown when viewing the images of the time frame it was defined on. As long as only one VOI is defined, statistics calculation will apply this VOI at all times as with a static VOI. However, as soon as VOIs have been defined at more than one time, it is required that VOIs are defined at *all* times. Here the VOI propagation functionality may be helpful.
Filled/Tape VOI	**Filled VOI** : All pixels enclosed by the contours belong to the VOI. **Tape VOI** : The contour is interpreted as the center line of a VOI which includes pixels inside a band along the contour. The number of pixels inside and outside can be specified. This type of VOI was introduced for myocardium VOIs.
Full/Sector VOI	**Full VOI** : Uses pixels from all directions.

	Sector VOI: Only the pixels in a defined angular sector will be considered. The sector angle can be defined in the **VOI Action** Mode using the handles at the angle corners. This type of VOI was also introduced for myocardium VOIs.
Organ volume Organ mass	Relevant for Dosimetry studies.
Tracking	Allows defining the role the VOI would have in a module which calculates tracks such as PGEM. The role of VOIs in tractography: • **SEED**: Tractography is started from the pixels in the seed VOIs, following the local vector directions. • **END**: Only tracks ending in this VOI will be used. To avoid excessive pruning of tracks, an **END** VOI should have sufficient volume. • **WAY**: Only tracks passing through the **WAY** VOI will be used. • **EXCLUDE**: Tracks passing through an **EXCLUDE** VOI will be removed. • **NEUTRAL**: Such VOIs have no impact on tractography. Setting VOIs to **NEUTRAL** allows assessing the effect of **END**, **WAY** and **EXCLUDE** VOIs without the need of removing them.
Set plus/minus Contours	The **+** and **-** buttons set all contours of the VOI to **positive** and **negative**, respectively, see ROI and Contour Level Properties 224. The main purpose of **-** is to remove parts of an enclosing VOI. This is done by merging the enclosing (positive) VOI with the enclosed (negative) VOI.
Lock/unlock VOI	Unlocked VOIs can be modified, whereas no changes are allowed for locked VOIs.
B-spline	The action buttons allow converting a polygon into a curved b-spline contour, and reverse. generates a b-spline which passes throught the original vertexes, whereas reduces the vertex number if the vertexes are very dense (e.g. generated by iso-contouring). returns the definition to polygon.
Location	X, Y and Z position of the VOI relative to the origin in [mm]. The location can be changed by entering new coordinates or using the incrementing arrow buttons.
Size	Size of the VOI bounding box in mm. The sizes can be changed and result in a proportional scaling in the corresponding direction. The sizes can be edited or incremented by the arrow buttons. Note that for contour VOIs consisting of planar ROIs the scaling is only supported within the ROI planes, not orthogonal to it. Object VOIs can be scaled in all directions.
Rotation	The VOI can be rotated in space. Note that for contour VOIs consisting of planar ROIs rotation is supported around all directions. The angles can be numerically specified in degrees, or incremented using the arrow buttons.

The illustration below illustrates the effect of the different properties on the pixels used for VOI statistics.
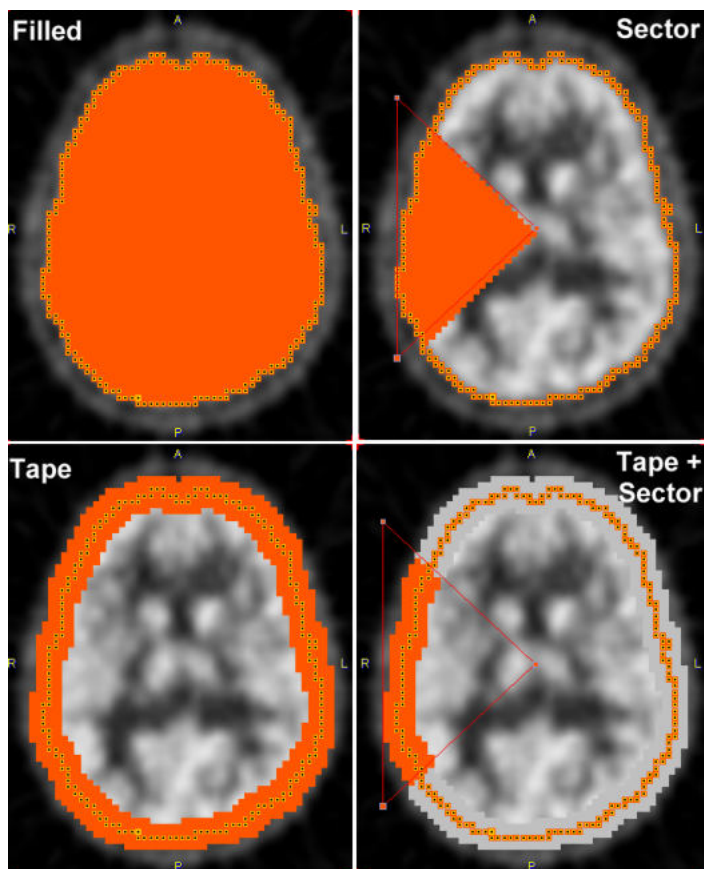

Color Definition

Colors are randomly assigned to created VOIs. To change the color, the VOI in the **VOIs** list, then activate the palette button and change the color. Note that all contours belonging to a VOI have the same color.

Use of Name List

For consistent VOI naming, the use of name lists is recommended. To use list naming, please select the VOI in the **VOIs** list, then activate . It opens the dialog window illustrated below.
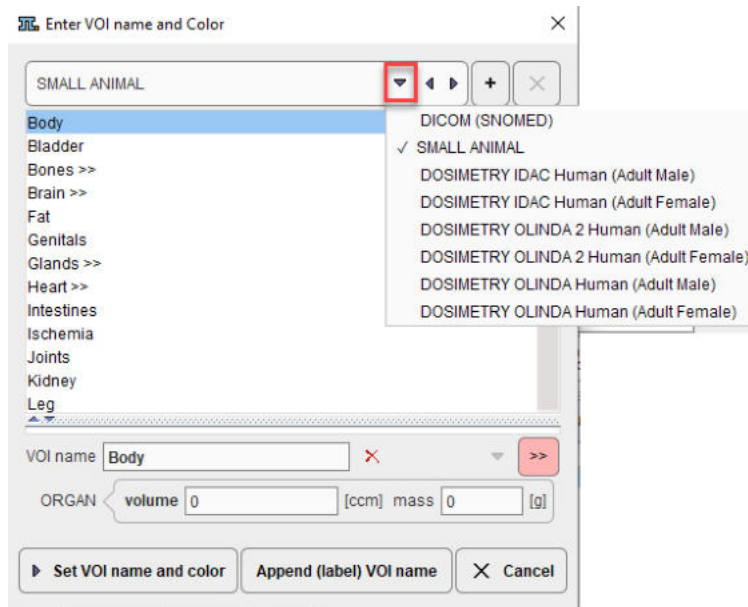
Six lists with pre-defined organ names are available: **DICOM**, **SMALL ANIMAL**, and six **DOSIMETRY** variants. Select the appropriate one in the list selection in the upper left and proceed as follows:

1. Select an organ name from the selected list.

   Note: In the **SMALL ANIMAL** list, organs with trailing **>>** such as **Tumor>>** offer a substructure list. Other organs like the **Kidneys** offer a **Laterality** choice. Select as appropriate.

1. The **VOI name** shown in the text entry field is composed from the selections, but can be edited or completely redefined.
   CAUTION: An existing VOI with exactly the same name will be overwritten. In this case please add a suffix to differentiate (e.g. CerebellumLeft in the example above)

2. The **ORGAN volume** and **mass** are relevant for dosimetry studies. There are predefined values for **DOSIMETRY** selection lists. These values can be edited if necessary for any selection.

3. Change the VOI color.

4. The **Set VOI name and color** button replaces the current VOI name, whereas **Append (label) VOI name** appends the string to it.

Custom VOI List

To create a custom VOI list please populate the **VOIs** list with a set of VOIs using the proper names. Select any of the VOIs and open the VOI properties dialog window. Activate **List** and in the appearing dialog the **+** button, to define the name of the new list.
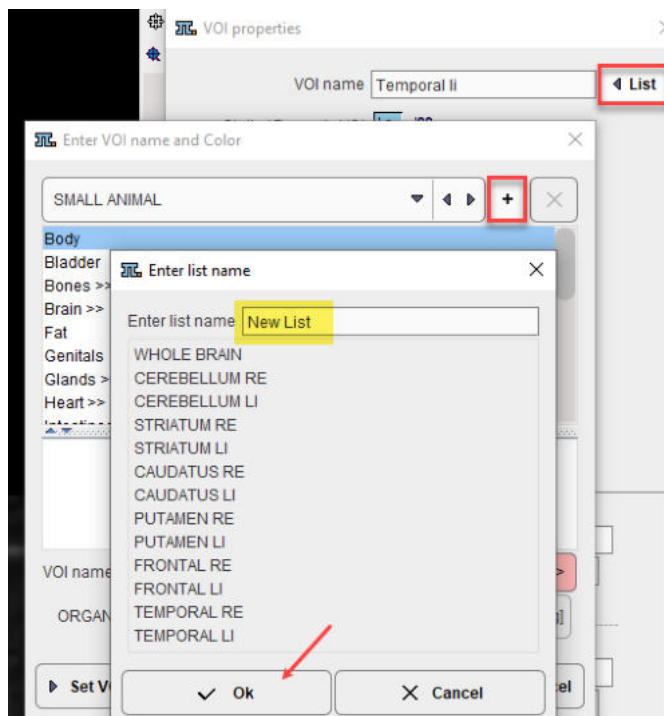
From then on, this list can be used alternatively to the pre-defined lists.

10.2.1.2 ROI and Contour Level Properties

The **Contours** section contains the list of the contours defined in the current slice of the image series for the VOI selected in the **VOIs** list. All contours belonging to a VOI in a single plane form together the planar ROI.

Changing between ROI and Contour Level

Note the vertical bar to the right, initially with a button **ROI** at the top. This indicates that operations (e.g. scaling, shifting, clearing, mirroring, etc) will be applied to all contours of the **ROI**. When the button is toggled, it is labeled as **CTR**. In this configuration, the operations will be applied only to the selected contour.
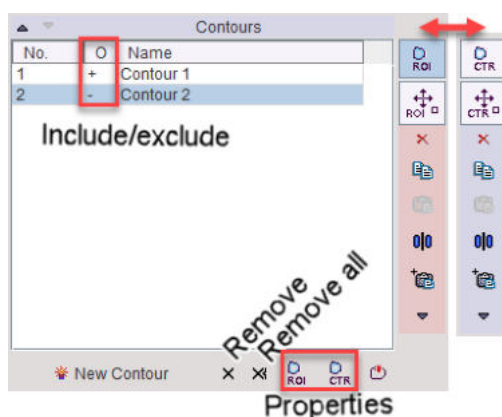
The ROIs can be scaled and rotated only on the definition plane.

Contour Properties

The ROI properties button illustrated above opens a dialog window with the following elements.
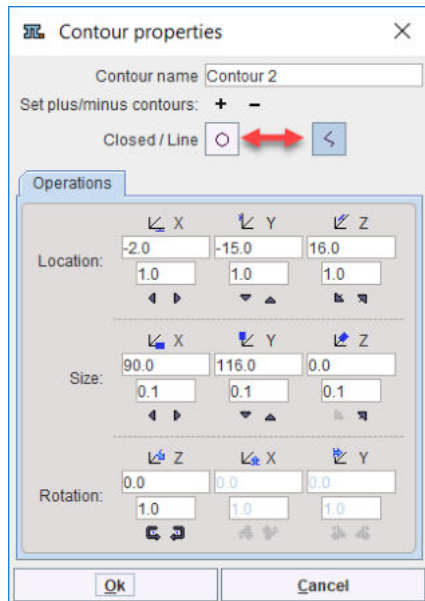
The **Set plus/minus contour** allows defining whether the contour adds to the VOI (**+** contour), or subtracts from it (**-** contour). This contour property is also reflected in the **O** column of the contours list. The **Closed/Line** button toggles between interpretation as a filled area vs. an area along the contour line.

The **Operations** panel shows the **Location** and **Size** of the selected contour. By changing the values in the text field or using the arrow buttons, the contour can be moved or scaled. Furthermore, with the **Rotation** parameter, it can be rotated within the definition plane.

ROI Properties

The ROI properties are very similar to the contour properties. However, here the **+/-** buttons will impact all contours in the list.
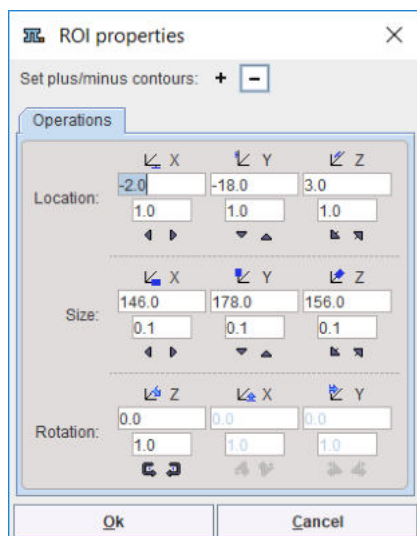
Hollow VOI

The purpose of the "minus" contours is to support VOIs with exclusions. The example below illustrates, the situation of a "plus" **Contour 1** which was obtained by hot iso-contouring. The inner **Contour 2** was obtained by the cold iso-contouring. It was then set as "minus" contour using the **-** button in the contour properties.

CAUTION: The first contour in the **Contours** list must be a "+" contour. If needed, the arrow buttons at the list top allow changing the location of the selected contour.
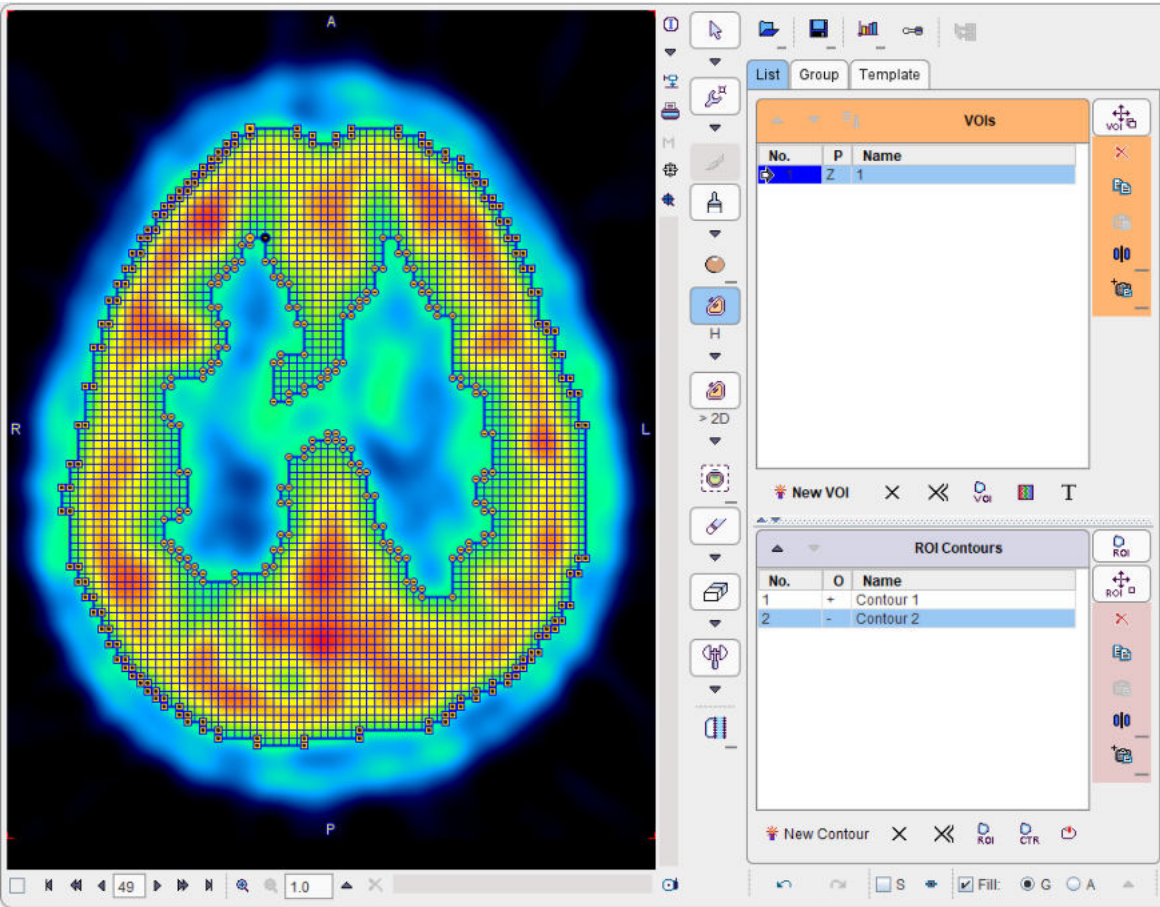
10.2.1.3 Contour Display Properties

The configuration panel houses properties defining how the VOIs are displayed in the image overlay.
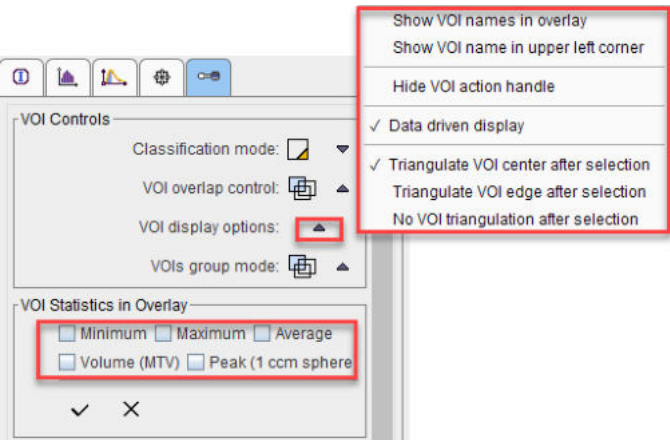
The following properties can be configured in the option menu:

Show VOI names in overlay	Shows the VOI names next to the contours in the image overlay. Note: The location of the names cannot be changed.

Show VOI name in upper left corner	Shows the names of the VOIsin the upper left corner section at the top of the image. Overlapping regions are shown as a list of names.
Hide VOI action handle	Hides the handle for moving the VOI to avoid obstructing the view with small VOIs. The VOI shifting/rotation operations have to be performed with the keyboard arrow cursors.
Data Driven Display	Determines the behavior of the image layout when switching between different series. If the box is checked, each image has its own properties such as layout, zoom, color etc. Otherwise, the images are shown with the same layout properties.
Triangulate VOI center after selection	Updates the position of the cross lines in the display at the center of the selected VOI in the list
Triangulate VOI edge after selection	Updates the position of the cross lines in the display at the edge of the selected VOI in the list
No VOI triangulation after selection	The position of the line is not updated in the

Usually contours are outlined on images displayed with interpolation, often combined with image zooming.

In such a representation the images look smooth, even if the original pixels are big as with modalities suffering from low spatial resolution relative to the structure being outlined. To make sure that the right pixels are included in the VOI it is recommended - especially for small structures - to examine the VOI pixels as follows:

1. Check the **S** box. The display shows only the contours of the currently selected VOI to avoid confusion in the presence of multiple VOIs.

2. Check the ⊞ icon. The VOIs vertexes are hidden.

3. Check the **Fill** box. The display now shows a grid with the VOI pixels (**G**). The grid can also be filled by setting the radio button to **A** (opaque filling). The degree of opacity can be change using the UP arrow ▲ right to the **A** button, whereby 100% indicates full opacity.

4. Disable image smoothing by disabling the

    button in the image control section.

5. Modify the VOI contours with the **Fill** box checked, for instance by moving a vertex. The grid is updated as soon as the changes are completed.

| ROI Fill | ROI Fill | ROI Area Fill 100% | ROI Area Fill 30% |
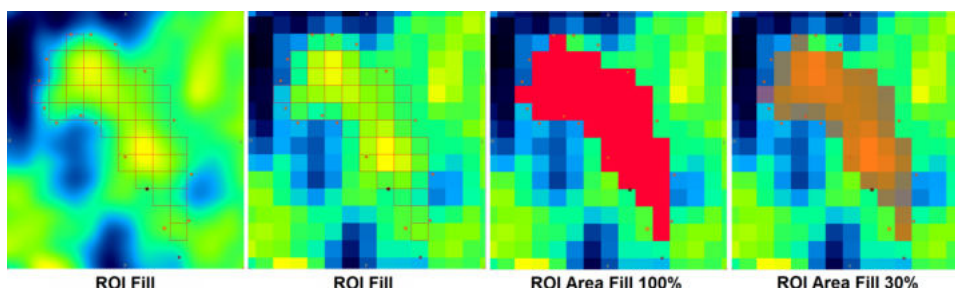
> **Note:** PMOD only considers the pixels for the statistics calculation which are visualized with the **Fill** functionality.

10.2.1.4 Inclusion Criteria for Pixels

Because the contours are defined by polygons, the contour lines may not exactly follow the edges of the image pixels, but cut across the pixel area. PMOD supports different ways of handling this situation. Consider a contour which was manually drawn in the interpolated image.
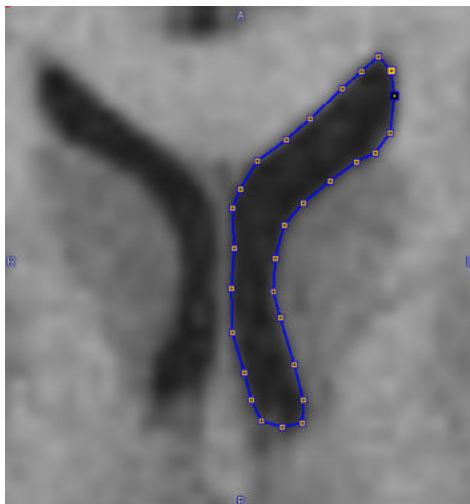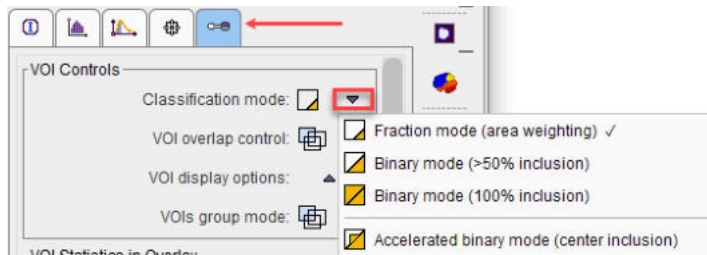

Switching interpolation off

shows how the contour lines intersect the pixel area.
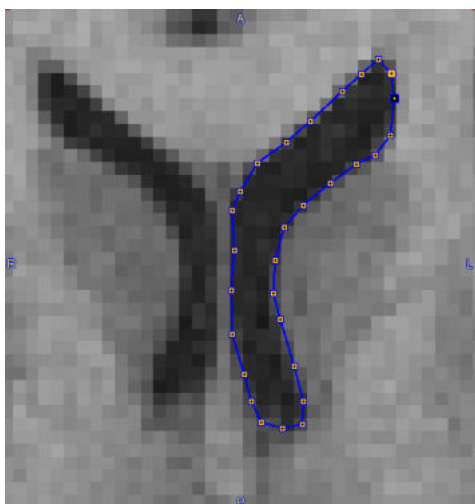
Classification Selection

The list selection illustrated below allows choosing between the different classification modes.

The **Fill** mode can be used for visualizing the classification effect.
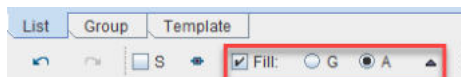
The **G** option represents the classified pixels as a grid, the **A** option as an area.

Fraction Mode (Area Weighting)
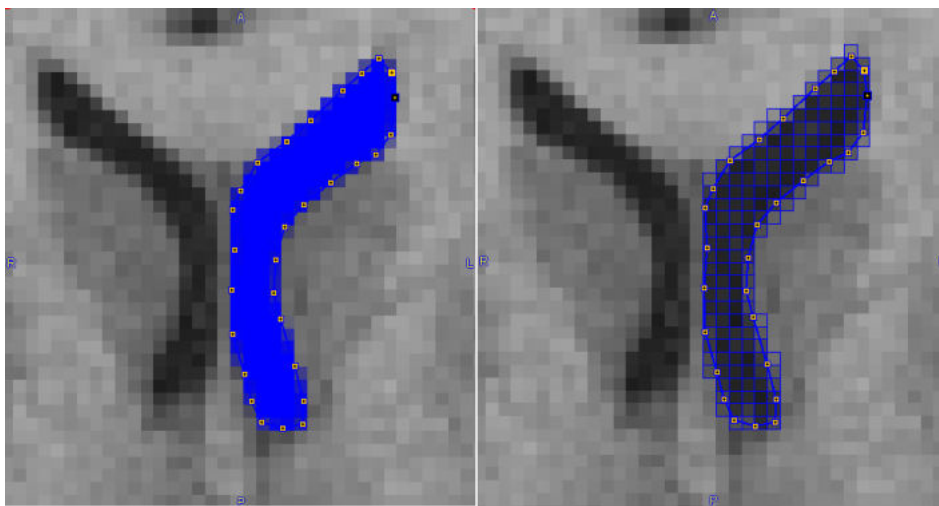
In **Fraction mode**, all pixels with any part enclosed by the contour are classified as VOI pixels. In statistics, the fractional area included is used as a weighting factor in the average [calculation](324). Note that when the **Fill A** option is activated, the color intensity of a pixel corresponds to the included fraction.

Binary Mode (>50% inclusion)
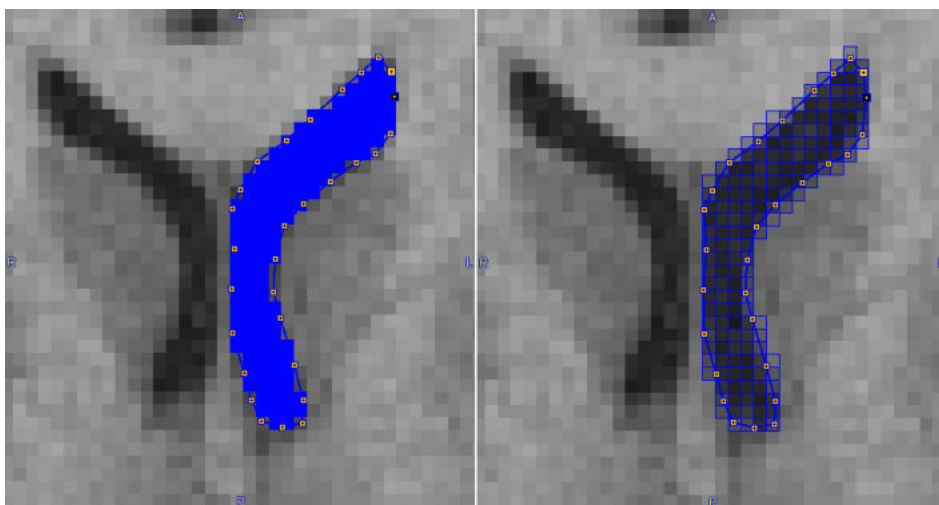
In **>50% Binary mode**, all pixels are included for which the enclosed area is >50% relative to the full pixel area. The statistics is unweighted using all classified pixels.

Binary Mode (100% inclusion)
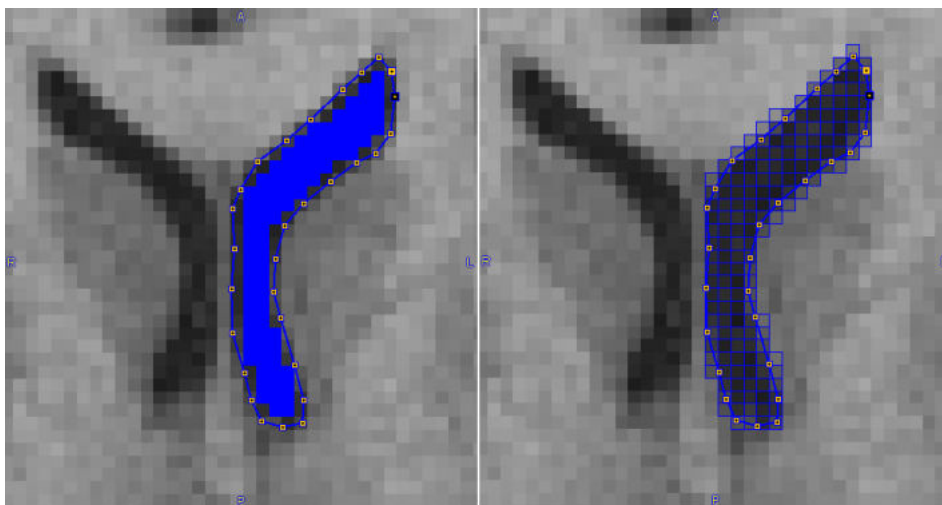
In **100% Binary mode**, only fully enclosed pixels are included. The statistics is unweighted using all classified pixels.

Accelerated Binary Mode (center inclusion)
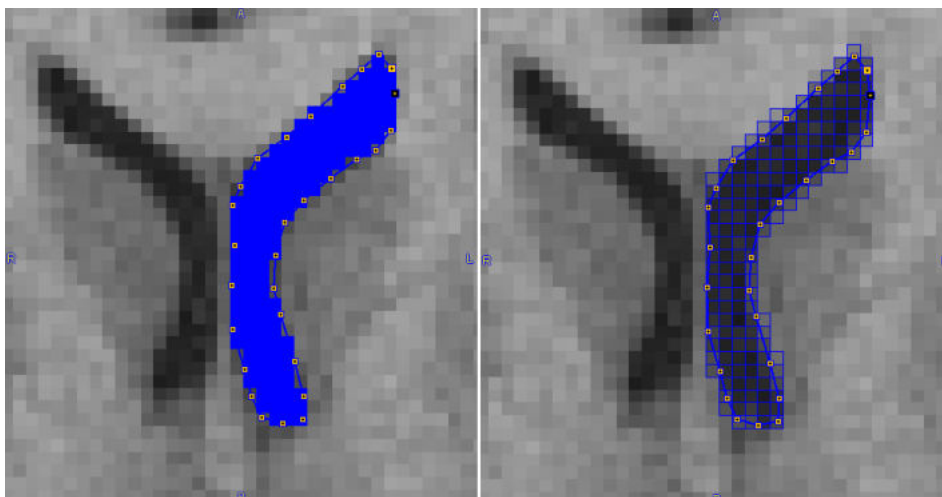
This classification variant has recently been added to improve performance for large VOIs, not only for the statistics, but also for the generating the overlays in the orthogonal layout. Classification criterion is inclusion of the pixel center in the contour. The performance gain can be several factors for large structures. Therefore, it is set as the default mode for the **PNEURO** and **PSEG** tools, which result in a big number of VOIs following the pixel edges.

Default Classification

The default **VOI Classification mode** to be used can be configured [31] for each user as illustrated below.
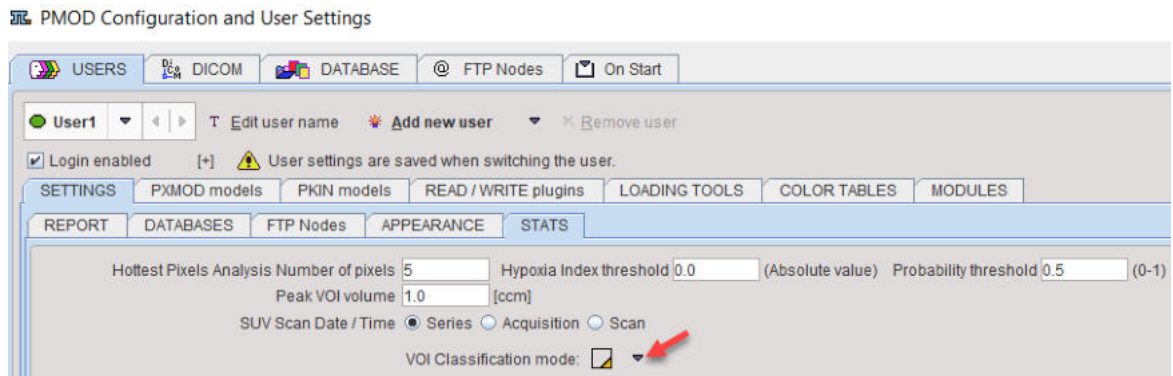
Recommendations

The following hints may be helpful for selecting an adequate classification:

- For VOIs derived by automatic methods (iso-contouring, PNEURO, PSEG) the statistics results will be the same for all classifications, because the contours follow the pixel edges. In this case use of the **Accelerated** mode is preferable.

- For small VOIs using manual outlining, use of the **Fraction** mode will provide the most accurate results, particularly in terms of volume.

10.2.1.5 Overlapping Control

When defining several VOIs, the user may want to control whether they can overlap, or not. To this end, the editing can be set to one of three different modes as illustrated below.
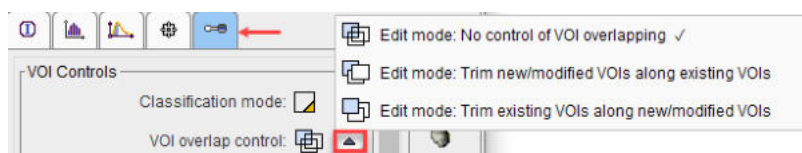
Their effect is as follows.

	No control of VOI overlapping, contours can intersect arbitrarily.
	Trim new/modified VOIs along existing VOIs. The existing VOIs have priority. The new VOI is modified by removing any intersection area with the existing VOIs.
	Trim existing VOI along new/modified VOIs. The new VOI has priority. The existing VOIs are modified by removing any intersection area with the new VOI.

The example below illustrates the effect when shifting the green ellipse left in the different control modes.
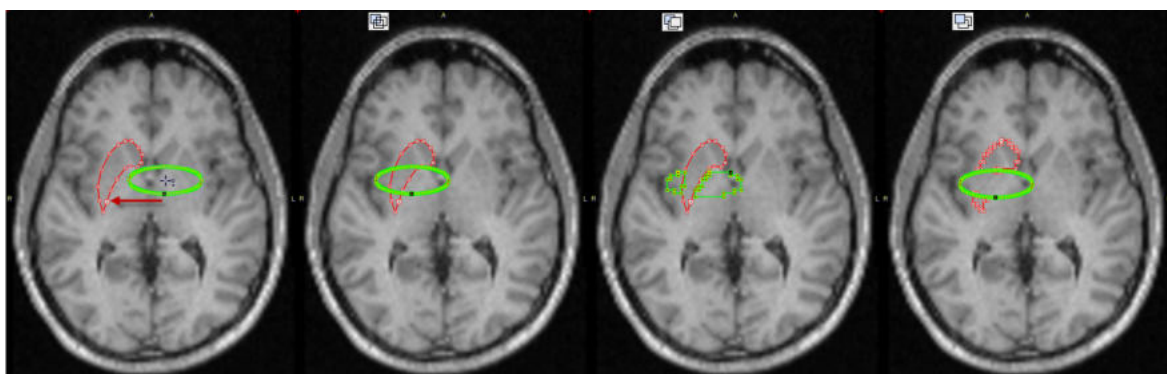
10.2.1.6 Overlay Statistics

It is possible to overlay a limited set of statistics directly in the image. This behavior can be configured in the **VOI statistics in overlay** section of the VOI configuration panel by checking the statistics of interest. Note that activating the **Peak** should be used with care, as for large VOIs it may incur visible calculation delays.
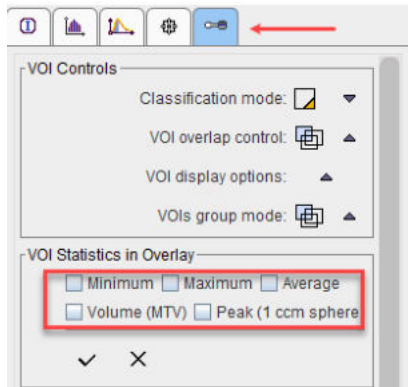
After enabling overlay statistics (illustrated below), the results are updated whenever a VOI is modified.
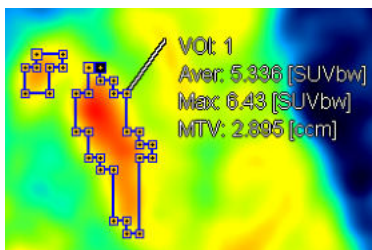
Note: Only the statistics of the VOI selected in the VOIs list is shown in the overlay to avoid cluttering of the image area.

10.2.2 Contour Definition Tools

There is a large variety of tools which generate contour VOIs and are described in the following sections.
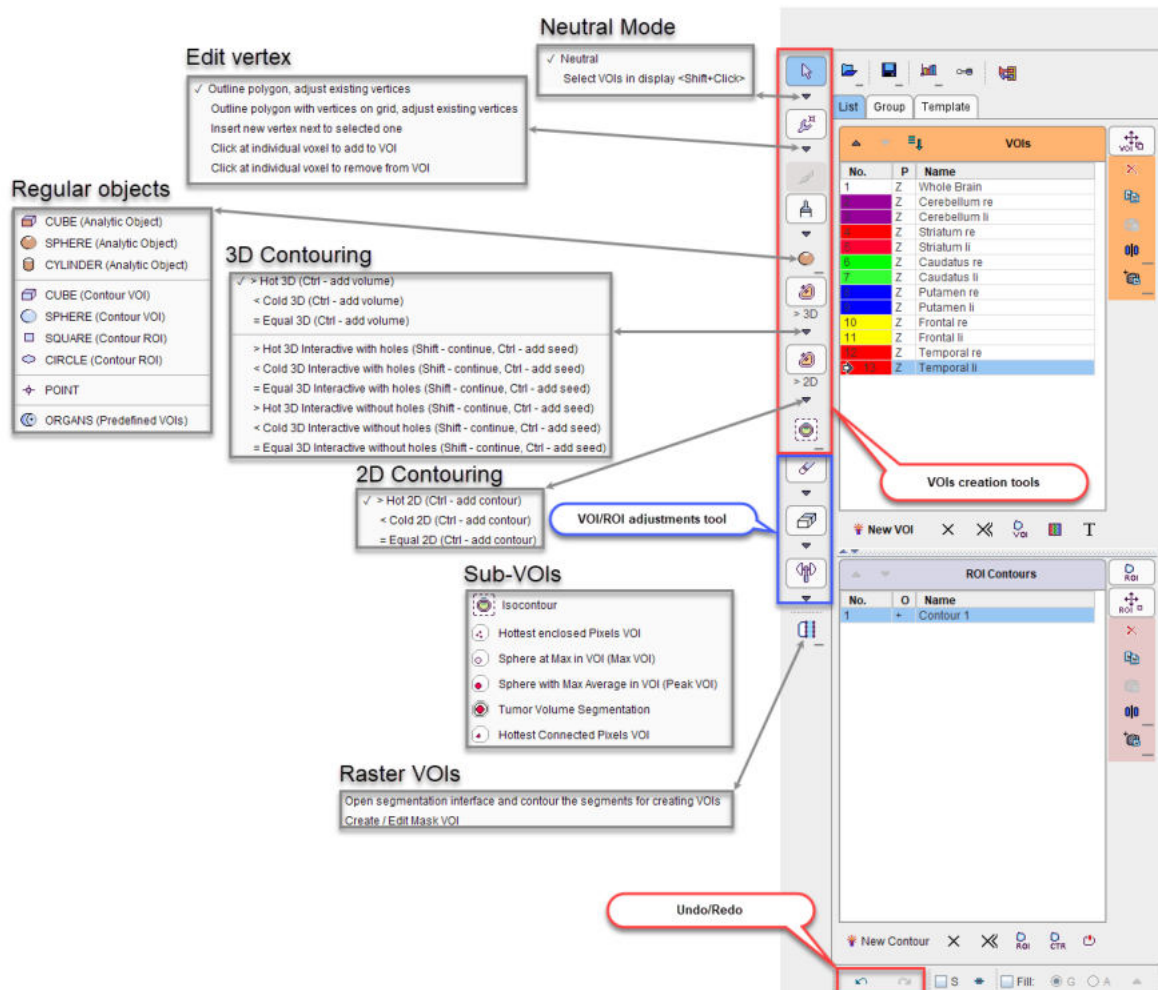
10.2.2.1 Preparations

Before starting contour definitions it is recommended to first locate the slice of interest, zoom and pan, so that the structures to be delineated are clearly seen. Also, it should be decided which of the orientations is best suited for the outlining.

VOIs for Dynamic Studies

Often the anatomical information in dynamic studies is not sufficient to delineate VOIs. In some cases, averaging of a part of the acquisitions provides a clearer picture. A quick way for time-averaging is to select the tools tab and average some frames without replacing the study.
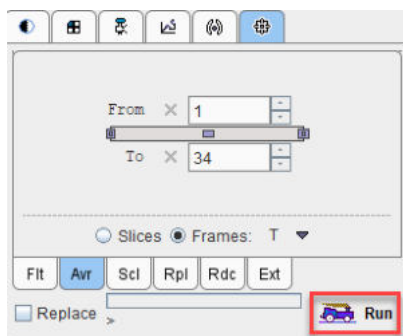
Another method is to define the VOIs using matched anatomical images of the same subject. Such a set of VOIs can then be applied to the dynamic study for calculating time-activity curves.

Using Multiple Files Simultaneously

When multiple images have been loaded (or additional ones have been created by averaging frames as shown above), each of them has its own set of VOIs. The image series and the VOIs can be switched using the selection at the top

Please note the synchronization box **VOIs from**. If it is checked, the studies and the VOIs can be selected independently from each other. If it is not checked, each study uses its own VOIs, and the VOI selection is not active.

CAUTION: If VOIs are to be defined in one study and used in another, the two studies must be matched beforehand, meaning that both of them have the image origin at exactly the same anatomical location. This type of matching can be performed with the PMOD Image Fusion tool.

10.2.2.2 Contouring Workflow

In general, the following sequence is used for defining a contour VOI:

1. Create a VOI with the **New VOI** button. It appears as a new, empty in the VOIs list.

2. Select one of the VOI definition tools. The cursor shape will change accordingly. Contours are generated by clicking into the image, whereby the behavior depends on the selected tool. If it is an automatic tool like iso-contouring, the VOI will be recreated with each click into the image. With interactive tools such a the paintbrush, the existing definition will be continued. Note that the orientation of the image which is clicked into also defines the primary plane of VOI which is inidcated in the **P** column of the **VOIs** list. Contours can only be modified in this primary plane orientation.

3. To stop contour modification when clicking into the image select the **Neutral** button.
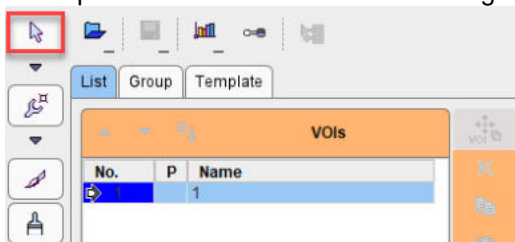
4. Activate one of the tools to continue or adjust VOI definition.

5. Continue to create new VOIs contour them as described above.

6. When selecting a VOI in the **VOIs** list with a single click, the program changes the slice position, so that the VOI can be shown in the image. When double-clicking into the list, the active slice direction is also changed, so that the contours are shown in the primary plane direction and can directly be edited.

Finally, the VOIs can be saved and the statistics created.

10.2.2.3 Neutral Mode

Browsing the image in the orthogonal layout involves clicking into the image. When VOI definition modes such as iso-contouring are active, clicks may introduce unwanted changes to the VOI definitions. This can be avoided by changing to **Neutral Mode** enabling the [cursor icon] button.

10.2.2.4 Undo/Redo

VOI definition is a tedious task, and many situations may occur where the user would like to undo a change. To this end an **Undo/redo** function for most manipulations of contour VOIs is available via the buttons.

[undo/redo buttons]
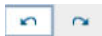
The left arrow undoes operations (goes back through history), while the right button redoes operations (goes forward through history). The number of possible undo steps saved can be configured.

Note: The **Undo** function is not applicable to changes to the image information itself.

10.2.2.5 Outline Polygon

The most basic approach for contour outlining is direct editing of a polygon.
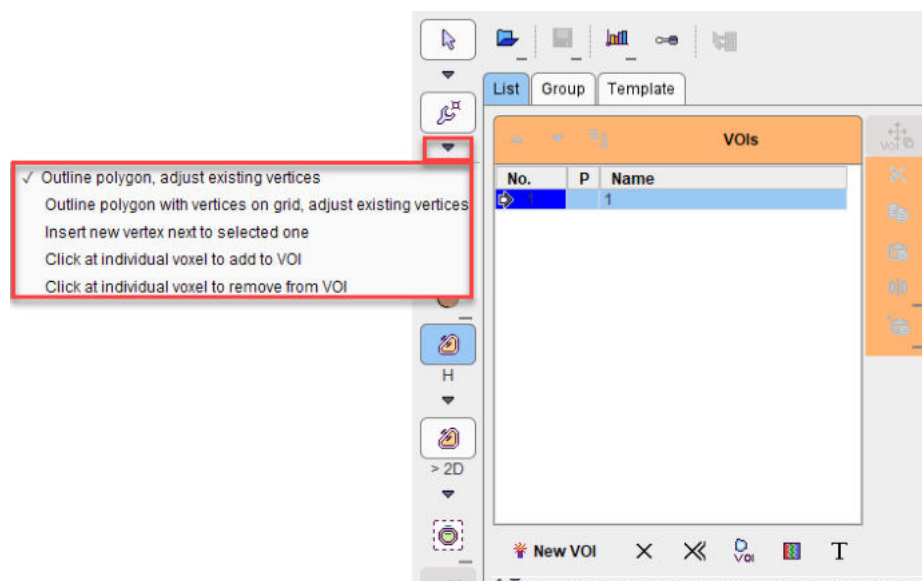
There are two variants of **Outline polygon**, one which directly connects the vertexes, the other placing the vertexes on the pixel grid and connecting them along the pixel edges.

Polygon Definition

Create an empty VOI, localize the proper plane for contour definition, and click with the left mouse button into the image. Contour definition is immediately started and the first vertex appears. Additional clicks add more vertexes to the ROI in the current plane which are connected by lines.
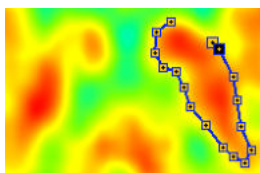
Note that while working in vertex editing mode, the VOI functionality can momentarily be disabled by holding down `CTRL+SHIFT` during clicking.

There are two possibilities to close the contour,

1. by double-clicking

2. by selecting the finish button below the **Contours** list or in the context menu (right-click into image).

Closing connects the last defined vertex with the first vertex. This operation can be undone by the unfinish button. Once a contour is closed, no vertexes can be added any more, but the existing one can be moved by clicking at them and dragging them around.

It is recommended to complete the definitions of one VOI before the next is created. To this end, the user should work through the slices containing the object: In each slice outline the required contour(s) and then step to the next slice using the mouse wheel. Alternatively, if the contours are similar in neighboring slices, the contour(s) can be propagated to the next slice and then adjusted.

With the **grid** version of polygon contouring, the vertexes and their connections follow the pixel edge grid.
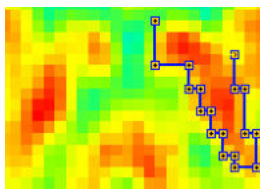
Note that in the illustration above image interpolation has been switched off to see the native image pixels.

Multiple Contours per Plane

Once the contour has been closed, polygon drawing becomes inactive. For adding another contour in the same slice, please activate the **New Contour** button. Now a polygon can be created.

10.2.2.6 Adding/Removing individual Pixels

Whenever working with contour VOIs, the user can interactively add or remove individual pixels by just clicking at them. To do so, the corresponding tool has to be selected as illustrated below.
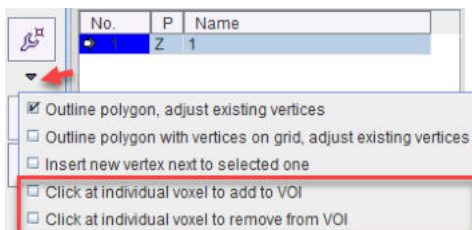
The example below illustrates the operation. A first **Contour 1** was generated using iso-contouring. Then with **Click at individual voxel to add to VOI** the pixel represented by **Contour 2** was added. Finally with **Click at individual voxel to remove from VOI** the pixel represented by the "minus" **Contour 3** was removed. The resulting ROI is the shaded area.
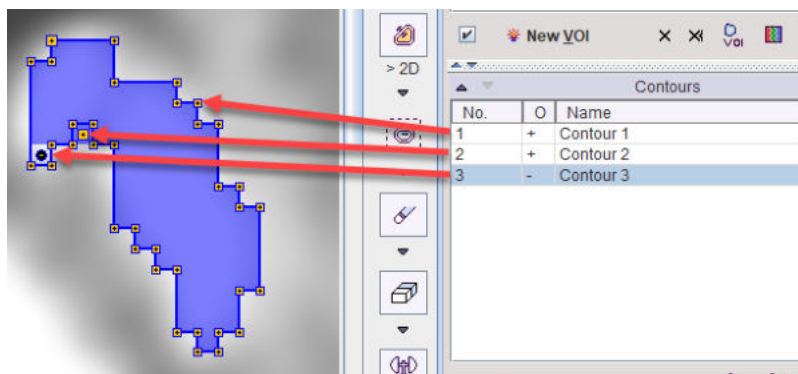
10.2.2.7 Draw Contour

Instead of clicking along a structure, the draw tool can be used.

By holding the left mouse button and dragging the cursor along the desired trajectory, a polygon with dense vertexes can be generated.
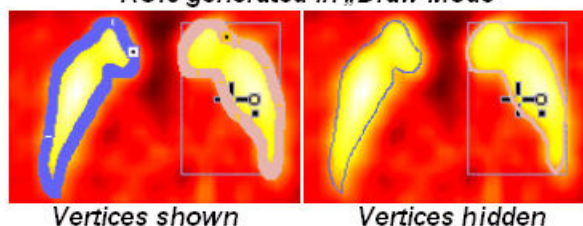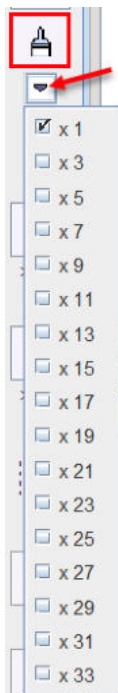

The contour is closed, as soon as the mouse button is released. This contouring mode generates many closely spaced vertexes. To view the contour more clearly, the vertexes can be hidden.

10.2.2.8 Paint ROI

The paintbrush tool consists of a circle which can have different sizes.

A ROI is generated by holding the left mouse button and dragging the brush over the desired area. The program generates as many contours as necessary for enclosing the areas covered.
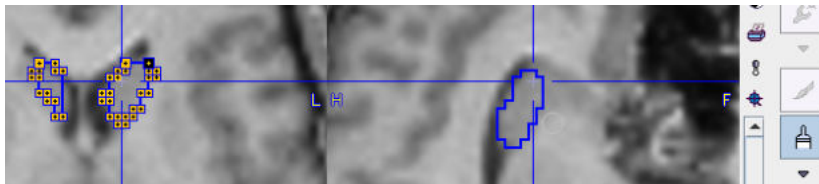
> It is noteworthy that the painting tool can be used in all plane directions, although the contours are always generated in the primary plane.

10.2.2.9 Regular VOIs

The PMOD VOI functionality supports the easy generation of regular geometric objects. They are helpful for creating bounding boxes, creating image phantoms (cylinder) and for statistics based on regular objects like spheres of a certain size rather than free-form contours.

Regular VOIs can be generated using the multi-function button illustrated below.
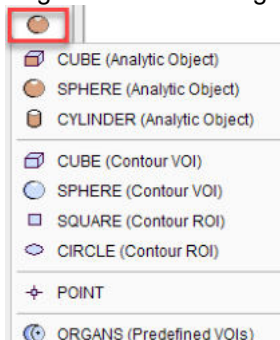
The list contains four sections:

- Analytic objects: The **CUBE (Analytic Object)** the **SPHERE (Analytic Object)** and the **CYLINDER (Analytic object)** are based on an analytical definition of the shape and the center coordinate.

- Contour VOIs: The other contour VOIs are generated from an analytical description, but the result is a set of standard outline contours.

- Point: The **POINT** base VOI allows creating regular VOI consisting of a single pixel at the specified precise location.

- Predefined VOIs: The **ORGANS (Predefined VOIs)** allows simplifying organ VOI delineation

The regular objects are defined by the center location as well as some shape-dependent parameters. These definitions can be modified in a dialog window which is shown an which also gives access to the VOI properties.

Create New VOI creates an new VOI with the defined properties in the **VOIs** list, whereas **Apply** replaces the definition of the currently selected entry in the **VOIs** list.

Analytic Object VOIs

The shapes can be scaled, so that ellipsoids of arbitrary sizes can be created from a **SPHERE (Analytic Object)**, cuboids from a **CUBE (Analytic Object)** and cylinders from a **CYLINDER (Analytic object)**. The dialog window contains **Location** and **Size** fields for the exact object specification. When the proportional box is checked, only one size field is shown for sphere and cube while for the cylinder two: one filed for the circle radius and one for the high:
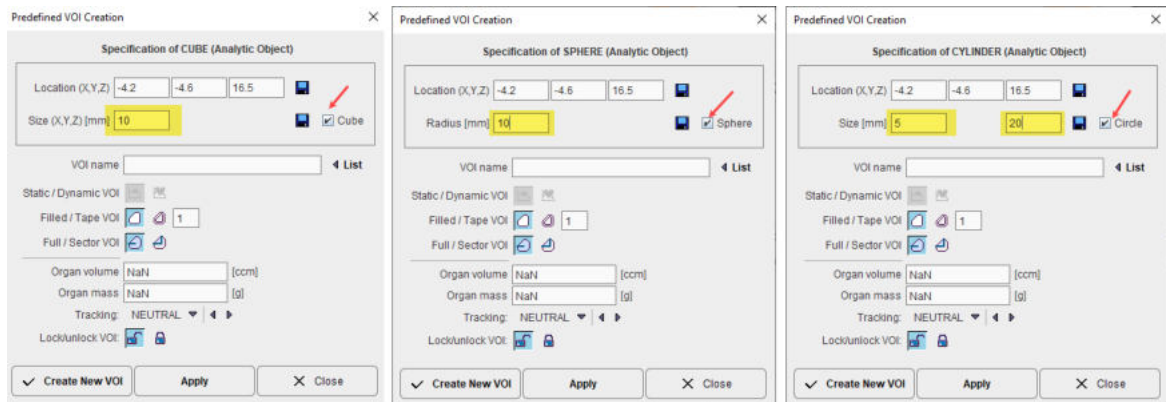
If the box for proportional is checked (**Sphere** in the illustration above), only one size field is shown. The **Create New VOI** button generates a new VOI in the list with the specified sizes, while the **Apply** button overwrites the currently selected VOI. The illustration below shows an example result with a sphere object.
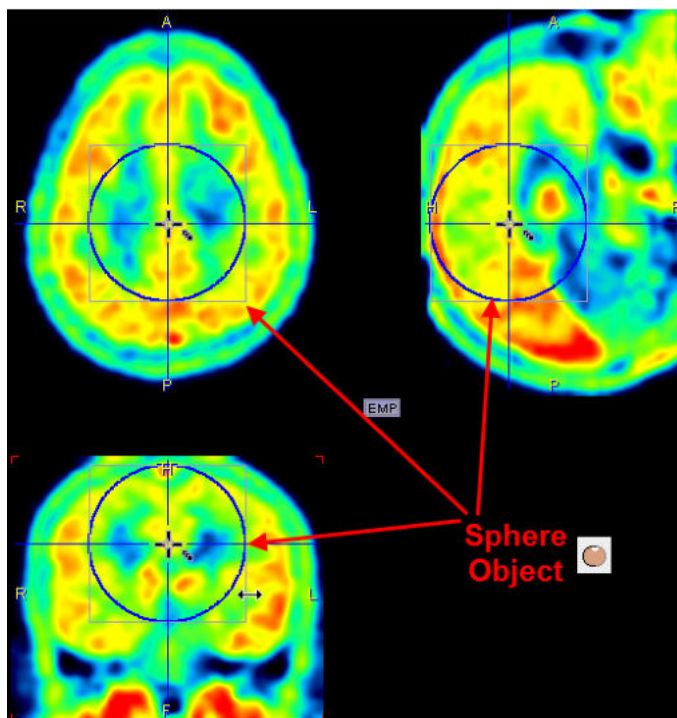
To change the location and size of the object please ensure that the **VOI Action** button is active , so that the handles for object manipulation are shown. The center of the object can then be dragged by the central handle with the left mouse button, and the shape can be scaled by dragging the sides or the corner of the bounding box in any direction. Note that holding the SHIFT key during dragging will maintain the aspect ratio in two dimensions. The result is an object with the shape of an ellipsoid.
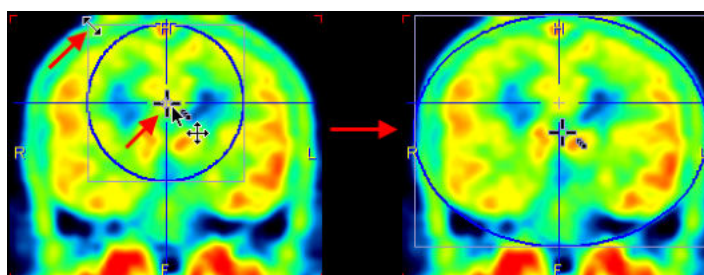
Regular Contour VOIs

The non-analytic regular VOIs are formed out of planar polygons. The example **SPHERE (Contour VOI)** illustrated below has been created with the axial plane active. Therefore circular contours were generate in the axial planes which together form a sphere. Such VOIs can be edited in the same way as normal contour VOIs. For instance they can be scaled within the definition (axial in the example) plane, but not in the other dimension.
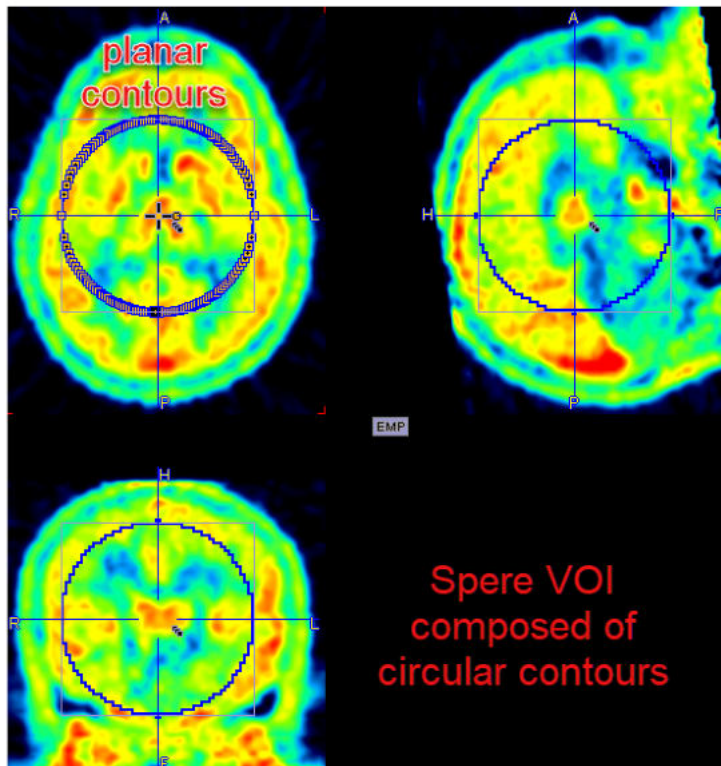
ORGANS (Predefined VOI)

PMOD supports simplified organ delineation. VOIs with typical organ shapes can easily be placed at the triangulation point and adjusted to the actual anatomy in the image by scaling and rotation in all planes. Organ VOI sets are available for humans, rats and mice.
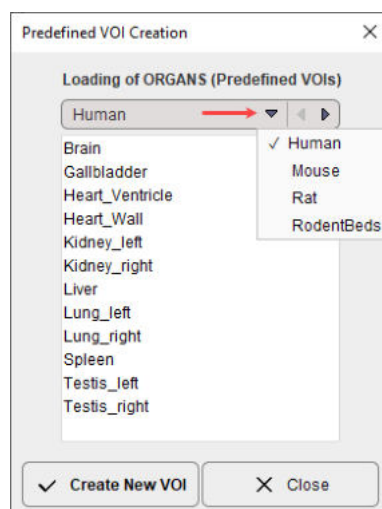
The **RodentsBeds** are aimed to facilitate the subtraction of the bed structure from the mouse images acquire with Albira and the BrukerMMPF systems:
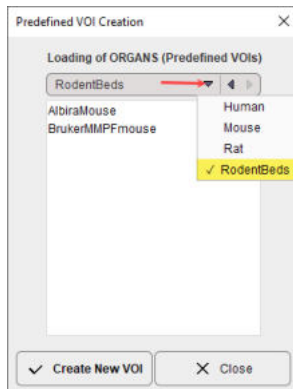
Select VOIs in the list using CTRL+click and activate **Create New VOI** to convert the organ shapes into contour VOIs. The new VOIs will apear in the VOIs list. Use the **Close** button to close the dialog window selection.
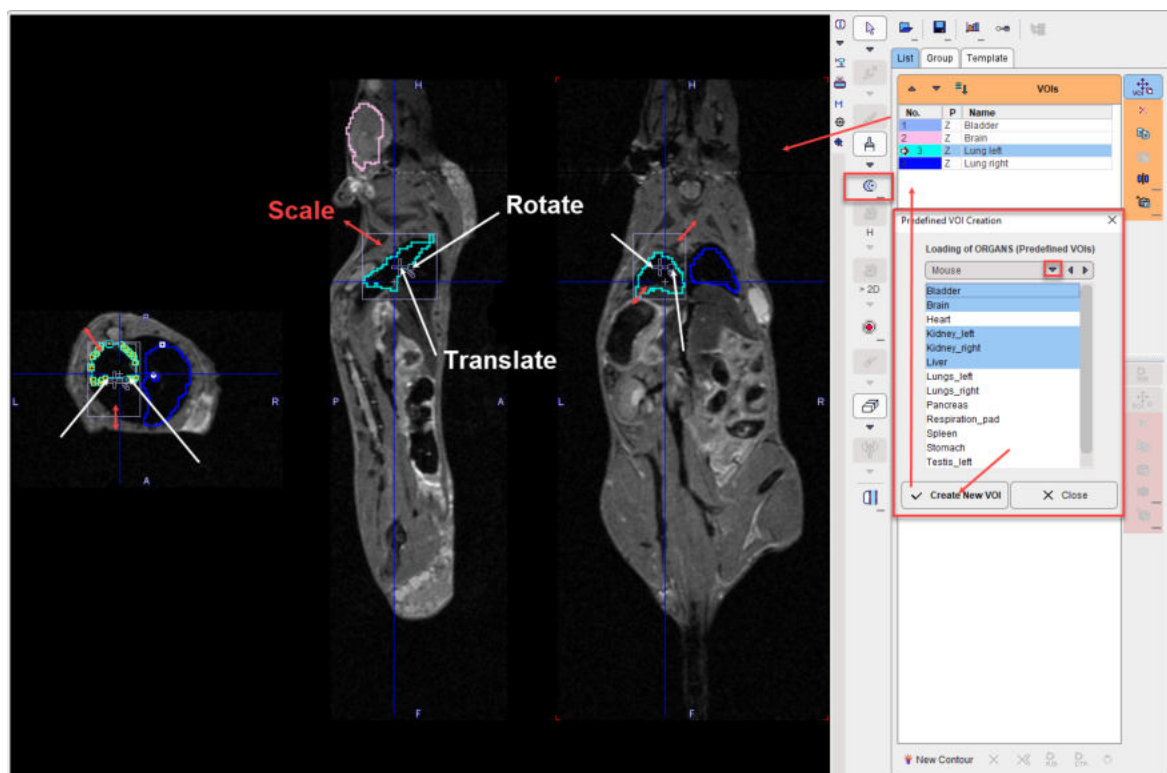
Users can create their own set of standard VOIs and copy them in a dedicated folder in the *Pmod4.4\resources\templates\organshapes*. Each VOI has to be separately saved as a VOI file. It is mandatory during the saving procedure to prefix the name of each VOI with the folder name followed by "_". In the example shown in the capture below the folder name is Mouse, while each VOIs name is prefixed with "Mouse_". The capture shows the content folder for the Mouse whole body predefined organ shapes VOIs shapes.

10.2.2.10 Interactive 3D Iso-contouring

There are different variants of 3D iso-contouring, which can be selected as illustrated below.
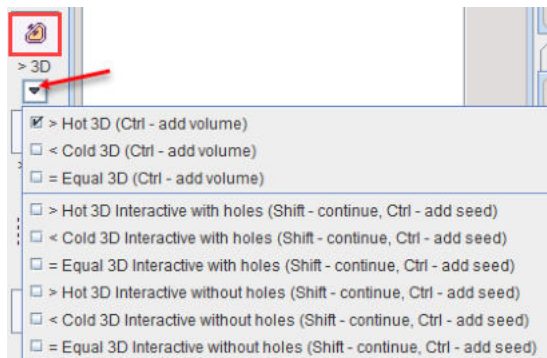
Automatic Variants

The top three entries are automatic procedures starting from the pixel, at which the user is clicking and looking for the largest connected iso-contour passing through the pixel.

- **Hot 3D**, the area with values above the clicked pixel value is enclosed

- **Cold 3D**, the area with values below the clicked pixel value is enclosed

- **Equal 3D**, the area with the clicked pixel value is enclosed (useful for label maps).

Structures are best contoured by clicking at their boundaries, as illustrated below.
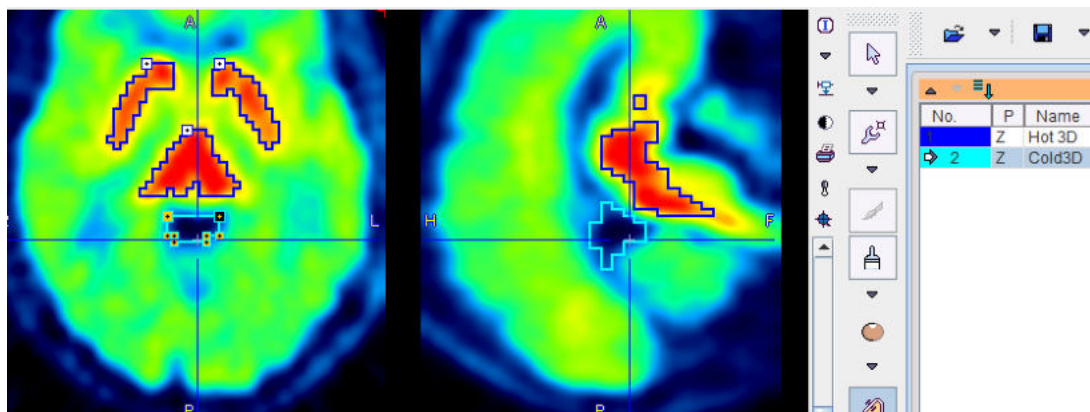
> **Note**: With each click in the image, the contour is replaced by a new iso-contour. To get an additional contour please hold down the CTRL keyboard key while clicking.

Interactive Variants

The **interactive** variants are based on region growing as long as the mouse button is hold down. As for the automatic versions, there are **Hot**, **Cold** and **Equal** variants available. The illustration below shows, how the region is growing radially from the clicking point, including pixels with values ≥ the clicked value. By repeating the interactive growing from different points while holding the `CTRL` keyboard key, multiple segments can be combined.
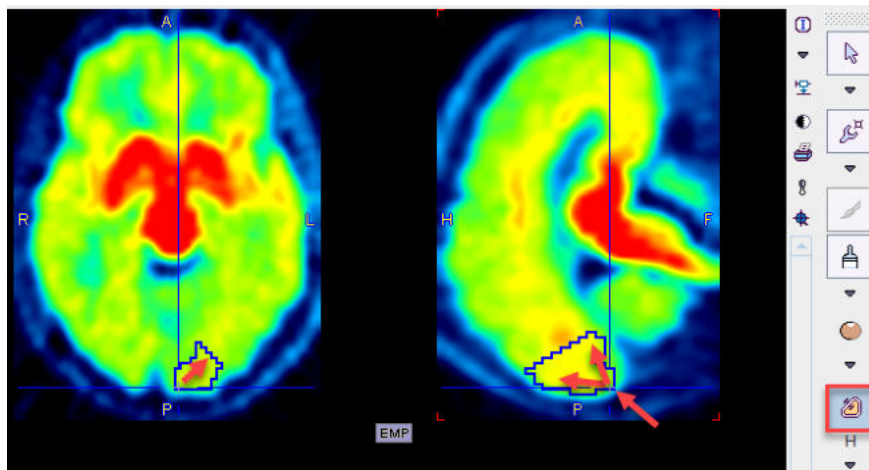
Note the variants **with holes** and **without holes**. The first one will allow cavities, while they will be filled in the second.

10.2.2.11 Interactive 2D Iso-contouring

Similar to the 3D Iso-contouring described above 243, 2D iso-contouring can be applied in individual planes. The variants for **Hot**, **Cold** or **Equal** contouring are available in a menu list.
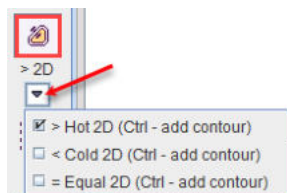
Select the appropriate tool, and clicking at the boundary of an object in an arbitrary plane.

> **Note**: With each click in the image, the contour is replaced by a new iso-contour. To get an additional contour please hold down the `Ctrl` keyboard key while clicking.

Again, while holding down **CTRL**, multiple contours can be defined. However the iso-contouring value of the different contours can not be numerically controlled and may differ.
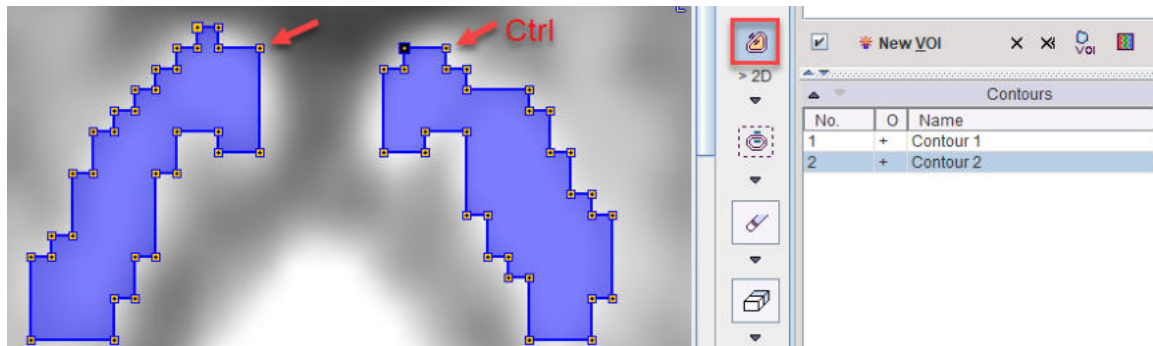
10.2.2.12 Controlled/Restricted Iso-contouring

The controlled iso-contouring tool serves for the contouring of structures based on a well-defined intensity threshold. The region-growing process can be restricted within an existing VOI, otherwise it will work on the whole image volume.
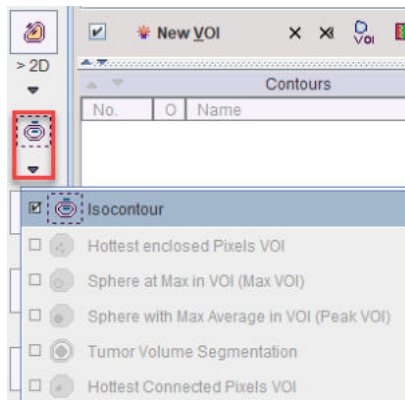
Contouring without Restriction

The whole image volume will be processed, if the **Isocontour** tool is started without selecting a non-empty VOI in the **VOIs** list. This situation is given before VOI definitions have started yet, or by creating an empty **New VOI**.

The situation below illustrates the initial situation when starting auto-iso on an FDG Brain image: One single **Hot** contour is shown at a threshold level of **50%**. without allowing **Inner holes.** The procedure operates in **2D** and defines the contours in the **Z** plane, because this plane was active at the time the tool was started.
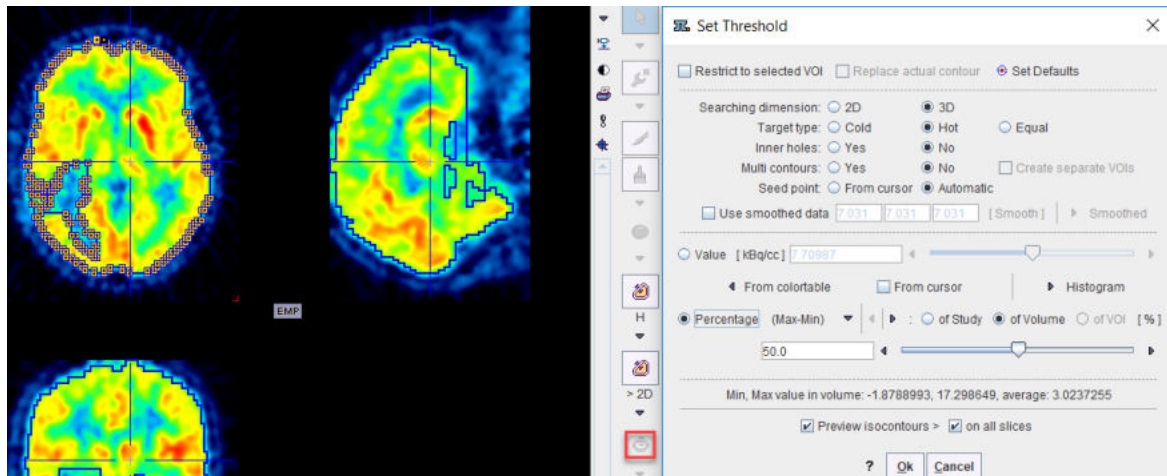
There are various parameters which change the behavior of the algorithm:

- **Threshold** options: The user can chose between various types of threshold definitions using the radio boxes. With **Value** the iso-contouring value should be entered in display units into the threshold number field. With **Percentage**, the value entered in the threshold field is interpreted as a percentage of the dynamic range (**Max-Min**) of the whole **Study**, the current **Volume**, or the enclosing **VOI**, respectively. Instead of the **Max-Min**, the percentage can also be related to the **Max** only. There are two alternatives to entering the values manually: **From colortable** copies the value of the lower threshold in the color table. With the **From cursor** check box enabled, the value is updated with the pixel value whenever one clicks into the image.

- **Searching dimension**: **2D** processes each slice individually, whereas **3D** performs the searching in all 3 dimensions.

- **Target type**: **Hot** (**Cold**, **Equal**) is including pixels above (below, equal to) the threshold value, respectively.

- **Inner holes**: In the case of **Yes**, pixels not meeting the criterion which are fully enclosed are removed from the resulting VOI. With **No**, the VOI will be completely filled.

- **Multi contours**: With **Yes**, the generation of multiple VOIs is allowed. Otherwise, only the largest VOI will be returned.

- **Seed point**: **Automatic** is starting region-growing with the aim to detect structures of maximal volume, whereas **From cursor** allows starting the search from a manually defined location. In the latter case the **From cursor** box should also be enabled.

The updated contours are shown in the image, whenever a parameter is changed. For a complete visualization, **Preview isocontours on all slices** should be enabled. To accept the VOI definition, close the dialog window with the **Ok** button.

Contouring with Restricting VOI

The process described above can be restricted to the volume of an existing VOI. To do so, select the restricting VOI in the **VOIs** list, and start the **Isocontour** tool and enable **Restrict to selected VOI**. Regular VOIs [238] are convenient restrictions as the can easily be positioned and scaled. The example below illustrates contouring in a box VOI placed on the left brain hemisphere.

π.pmod
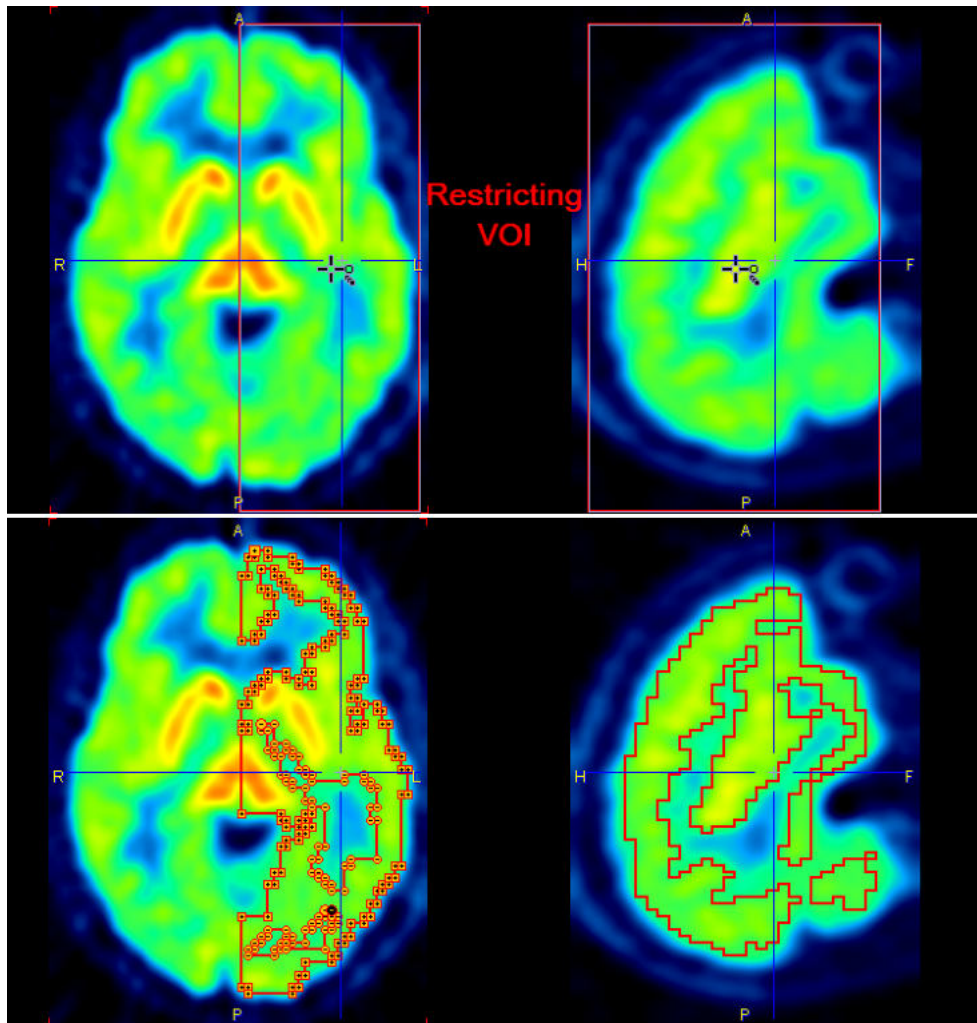
Depending on the setting of **Replace actual contour**, the bounding VOI will be overwritten, or a new VOI will be created with the contouring result.

The contouring with restriction is supported also for group of VOIs.

Contouring with Smoothing

In order to get smoother contours than the original data supports, the procedure can work on a smoothed copy of the data. This functionality is activated with the **Use smoothed data** box.If the **Smooth** button is activated, the data copy is filtered with a Gaussian function using the three numbers as the FWHM in mm along x, y and z. By adjusting the filter sizes appropriately and repeat filtering, a smooth copy and correspondingly smooth contours in the original image can be generated. The **Smoothed/Hide** toggle button can be activated to show or hide the smoothed copy.
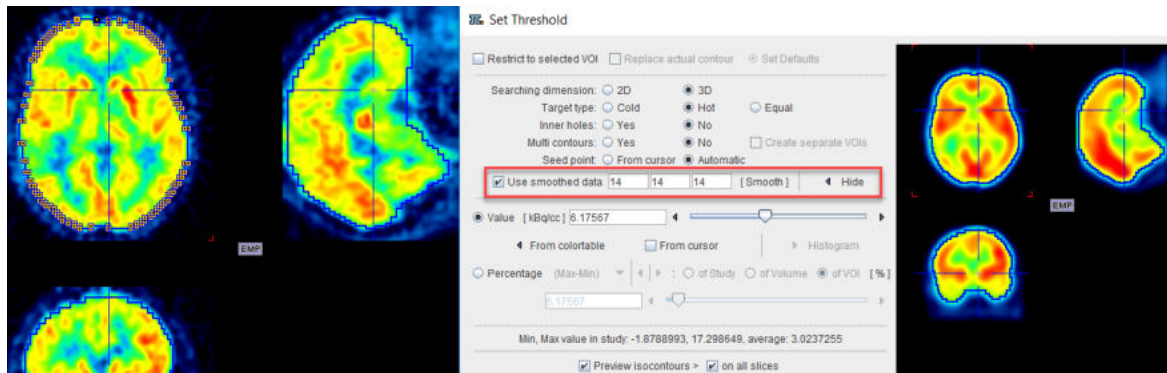
Contouring with Histogram

A histogram can be used to set the threshold **Value** for the iso-contouring. This functionality is activated with the **Histogram** button. A histogram of the pixel values is shown, and the value at which the iso-contours are drawn can be adjusted by dragging the marker highlighted in the graphics below. The threshold value is updated each time the marker position is changed and the updated contours are shown in the image. The **Hide** button collapses the histogram part of the dialog window again.
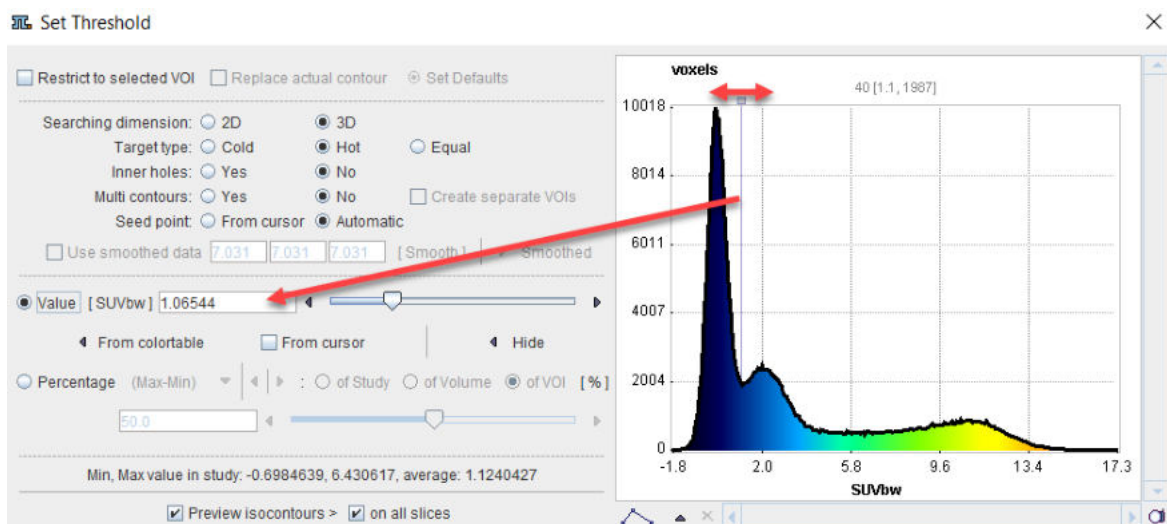
10.2.2.13 Contour Interpolation

The **Contour interpolation** tool is located in **Contour Generation** section of the VOI tools panel.
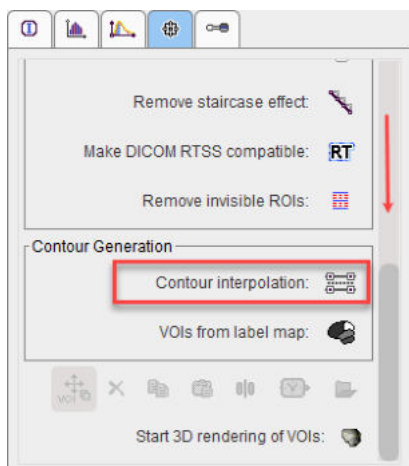
Its purpose is to allow ROI definition on a few slices and interpolate the ROIs in between.

To perform an interpolation, first select the VOI in the **VOIs** list, then activate the **Contour interpolation** tool. A dialog window opens allowing multiple choices:
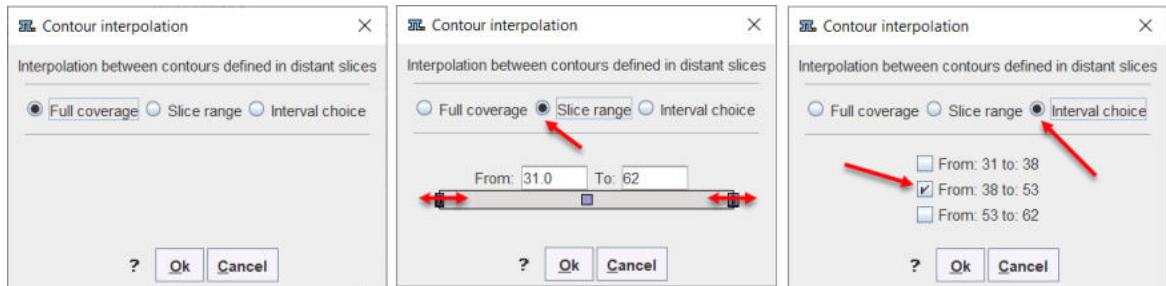
If four ROIs are drawn on axial plane on slice 31, 38, 53 and 62:

- **Full coverage**: detects the full slice range of ROI definition and interpolates the ROIs in between, from slice 31 up to slice 62 in this case:
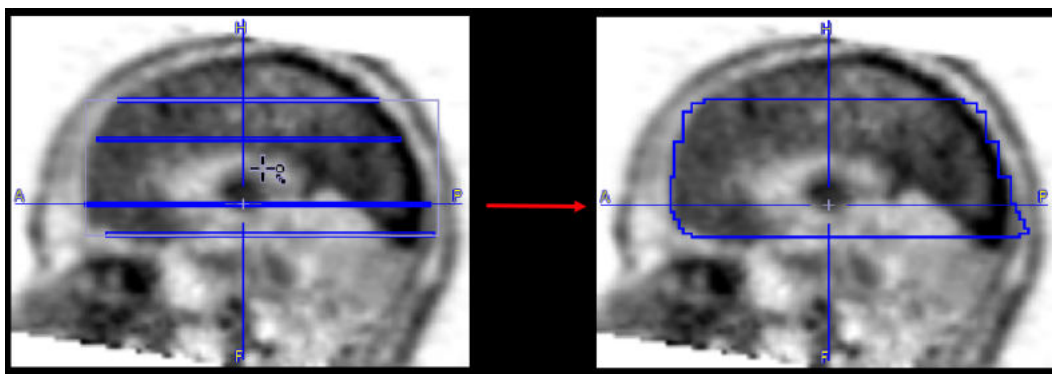
- **Slice range**: detects the full slice range of ROIs definition and allows selecting any slices within this range to perform interpolation in between. Edit the **From** and **To** text fields or use the handles to define the slice range to interpolate in between, e.g **From** slice 40 **To** 50:
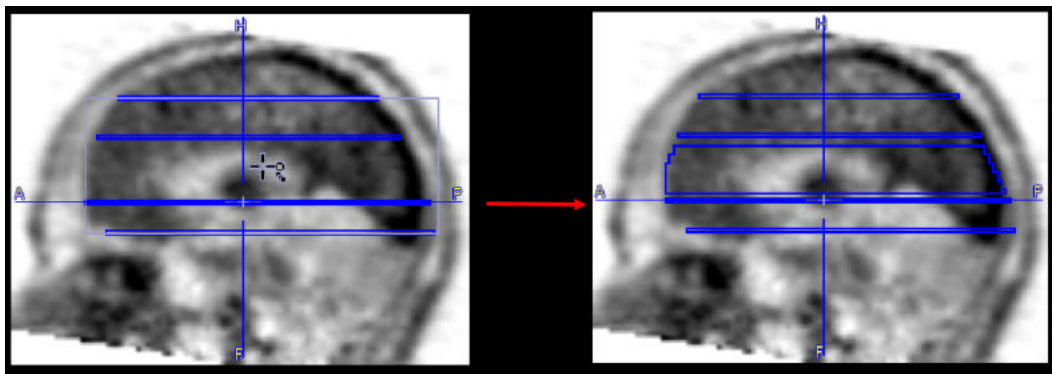
- **Interval choice**: detects the ROIs definitions slices and allows selecting fixed slice ranges to interpolate in between. The number of fixed slice ranges is representing the number of outlined ROIs minus one: e.g for 4 ROIs there will be 3 fixed slice ranges. The example illustrated below shows the interpolation in between the middle range of slice, from slice 38 to slice 53:
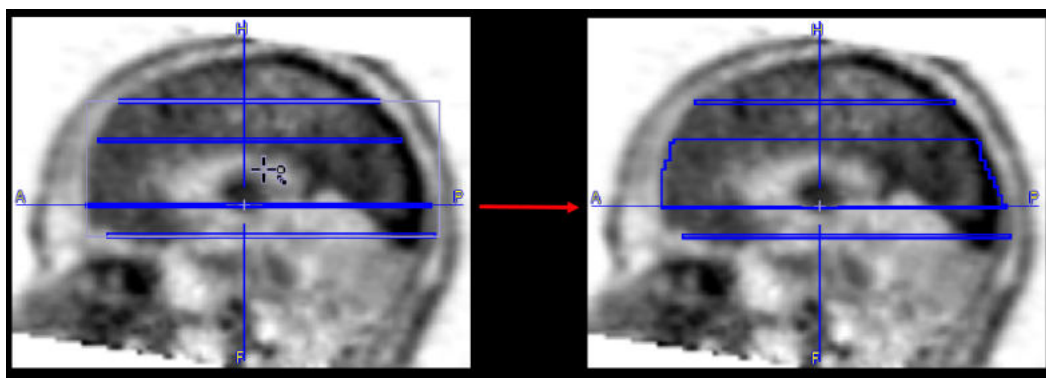
> **Note**: The interpolation only uses the contours, not the image itself.

### 10.2.2.14 VOIs from Label Maps

A map is a file which contains integer pixel values called object labels. The labels identify different objects in the image volume. Such maps are often the product of segmentation procedures.

If a label map has been loaded as image, contours of the objects can be obtained with the **VOIs from label map** button in the VOI tools panel.
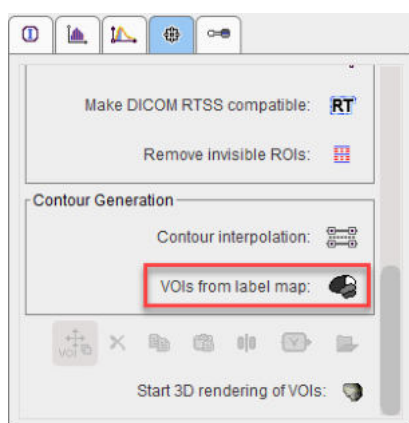
The **Step value** of 1 usually works. The file is scanned and for each label found a contour VOI is created.

Illustrated below is the example of an atlas label file after contouring. Note that in this case the names are synthetically generated and have no relation to the anatomy.
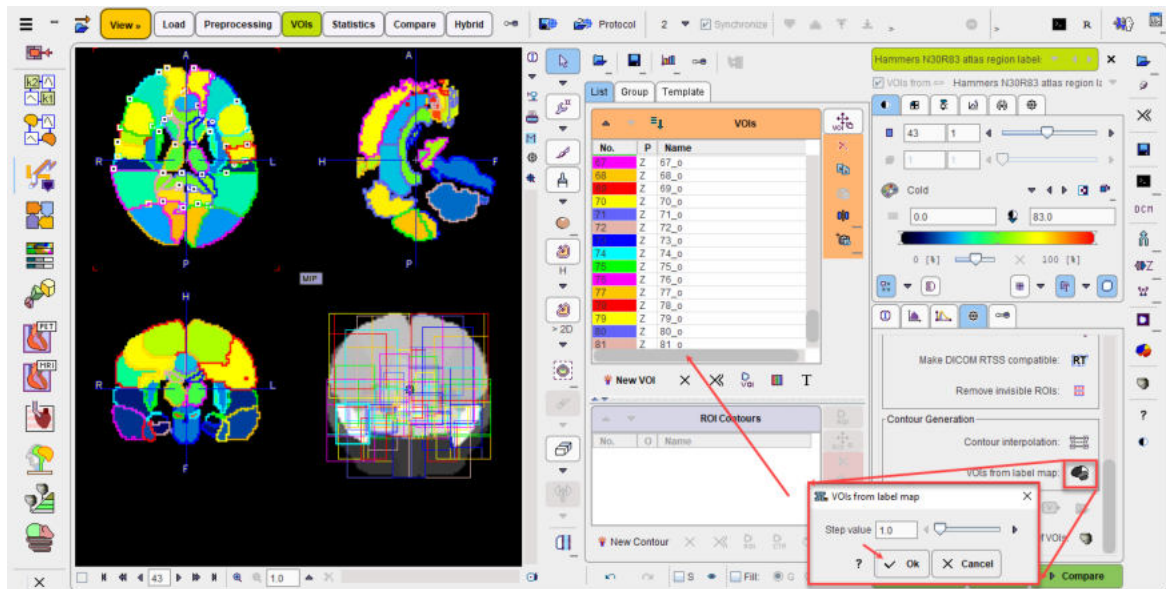
At the end of this procedure the names can be edited and the VOIs saved.

An alternative for creating the label VOIs without loading the label map as image is described in Using Label Maps Files ₃₁₉.

10.2.3 Special-purpose Sub-VOIs

Existing VOIs can be used as boundary restrictions when generating certain types of VOIs. Iso-contouring within a VOI is an example described above ₂₄₅. Five other approaches are available via the selection illustrated below.
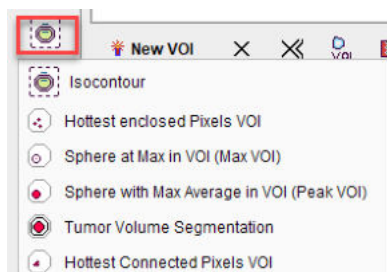
A sub-VOI is generated by first selecting the bounding VOI in the VOIs list, and thereafter one of the tools in the list. They will generate a new VOI with a name containing the bounding VOI name in brackets.
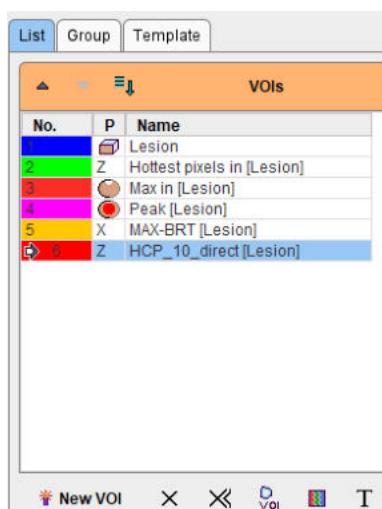
The name in brackets works as a grouping criterion on the **Group** panel.
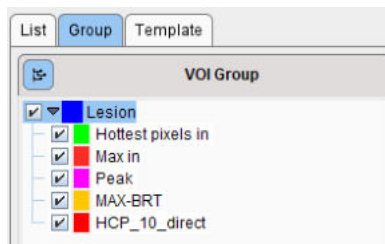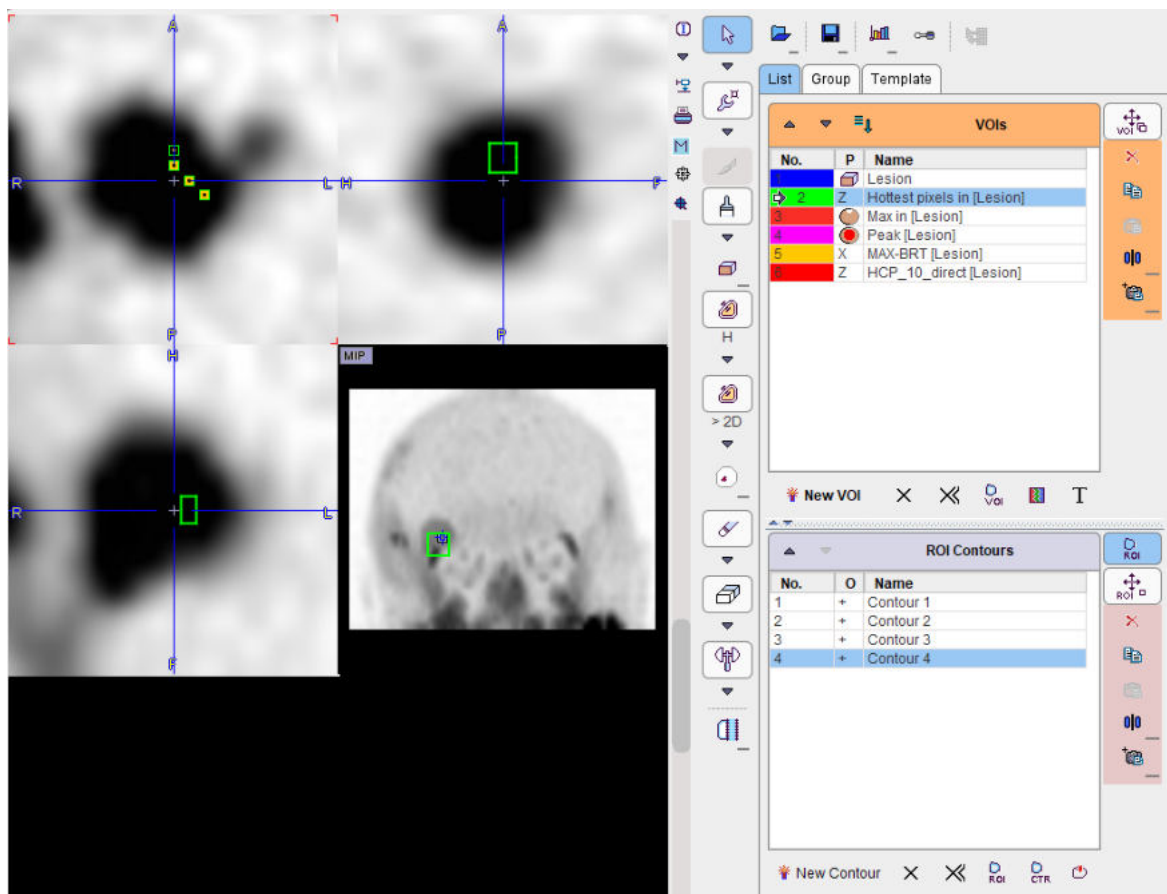

10.2.3.1 Hottest Pixels

The **Hottest enclosed Pixels VOI** function is useful for localizing the pixels with highest values in the selected VOI. The actual number of pixels can be specified in the interface window.
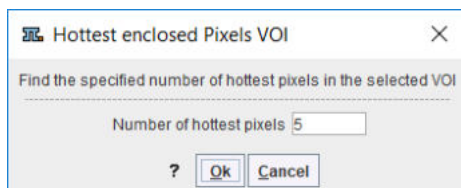

Result is a new VOI called **Hottest pixels in [enclosing-name]** with a separate contour for each of the pixels as illustrated below.
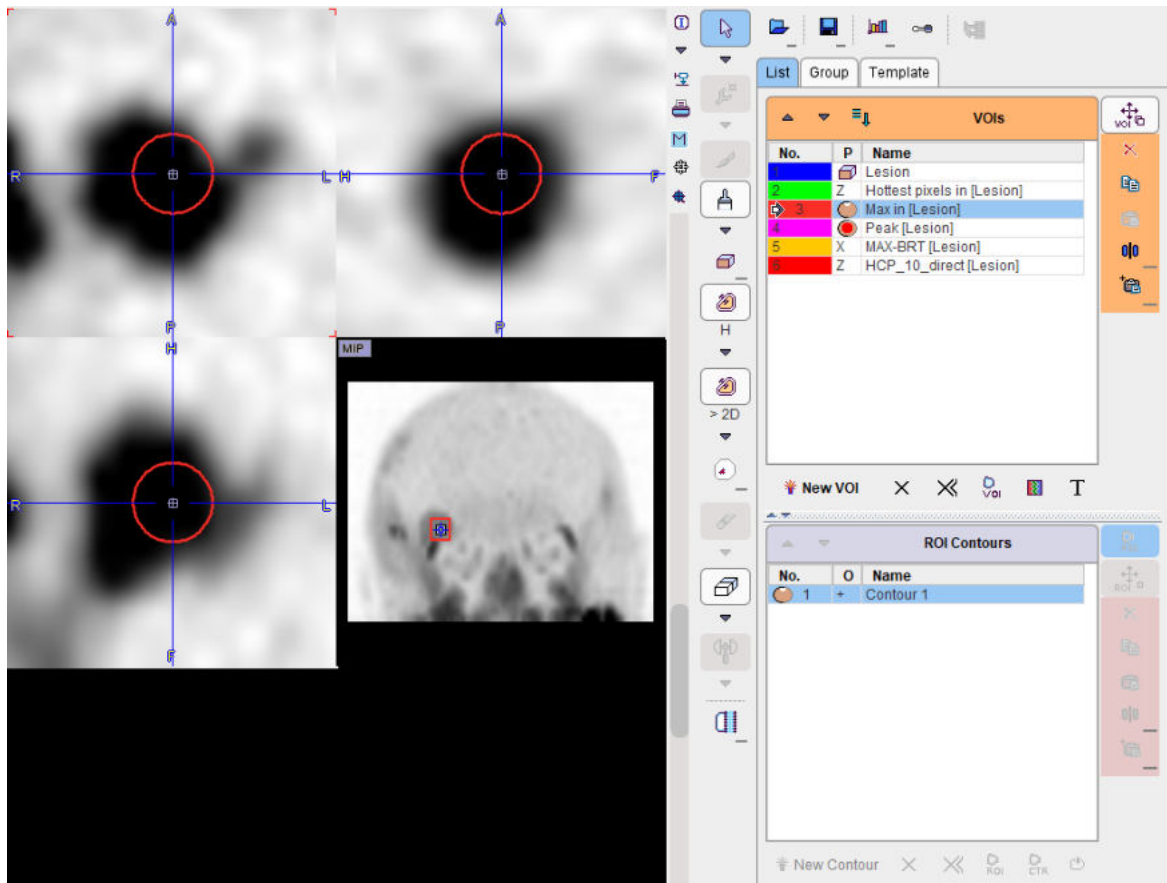

10.2.3.2 Sphere at Max

The **Sphere at Max in VOI** function creates a sphere object VOI with defined volume and centers it at the maximal pixel of the selected VOI. The actual volume can be specified in the interface window. Default is 1ccm, corresponding to the PERCIST peak value definition.
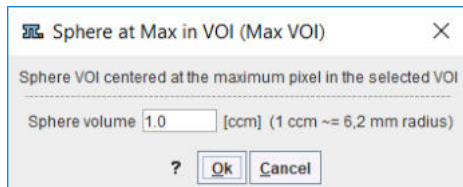
The resulting sphere is called **Max in [enclosing-name]**.

10.2.3.3 Sphere with Max Average (Peak VOI)

The **Sphere with Max Average (Peak VOI)** function creates a sphere object VOI of defined volume and places it in the bounding VOI such that the average is maximal. Beyond specification of the **Sphere volume** (default: 1ccm = PERCIST peak), the appearing dialog window offers additional options.
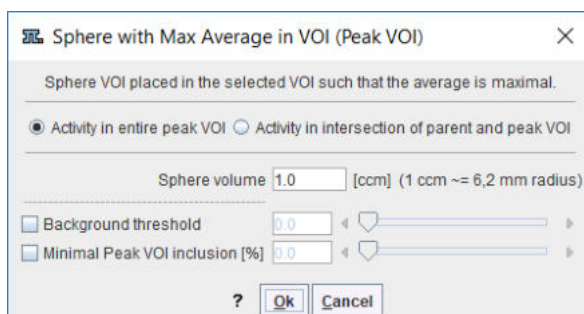

With **Activity in entire peak VOI**, the average calculation uses all the voxels intersecting the sphere. With **Activity in intersection of parent and peak VOI,** the average calculation is performed using only the voxels intersecting both parent and peak VOI. The average calculation

always uses the fraction mode which weighs the voxel value by the included fraction (see Inclusion Criteria for Pixels)[228].

With **Background threshold** enabled, the algorithm only considers spheres centered a voxels with value above the threshold. With **Minimal Peak VOI inclusion [%]** enabled, only spheres with sufficient overlap with the bounding VOI will be considered.

The resulting sphere object is called **Peak[enclosing-name]**.
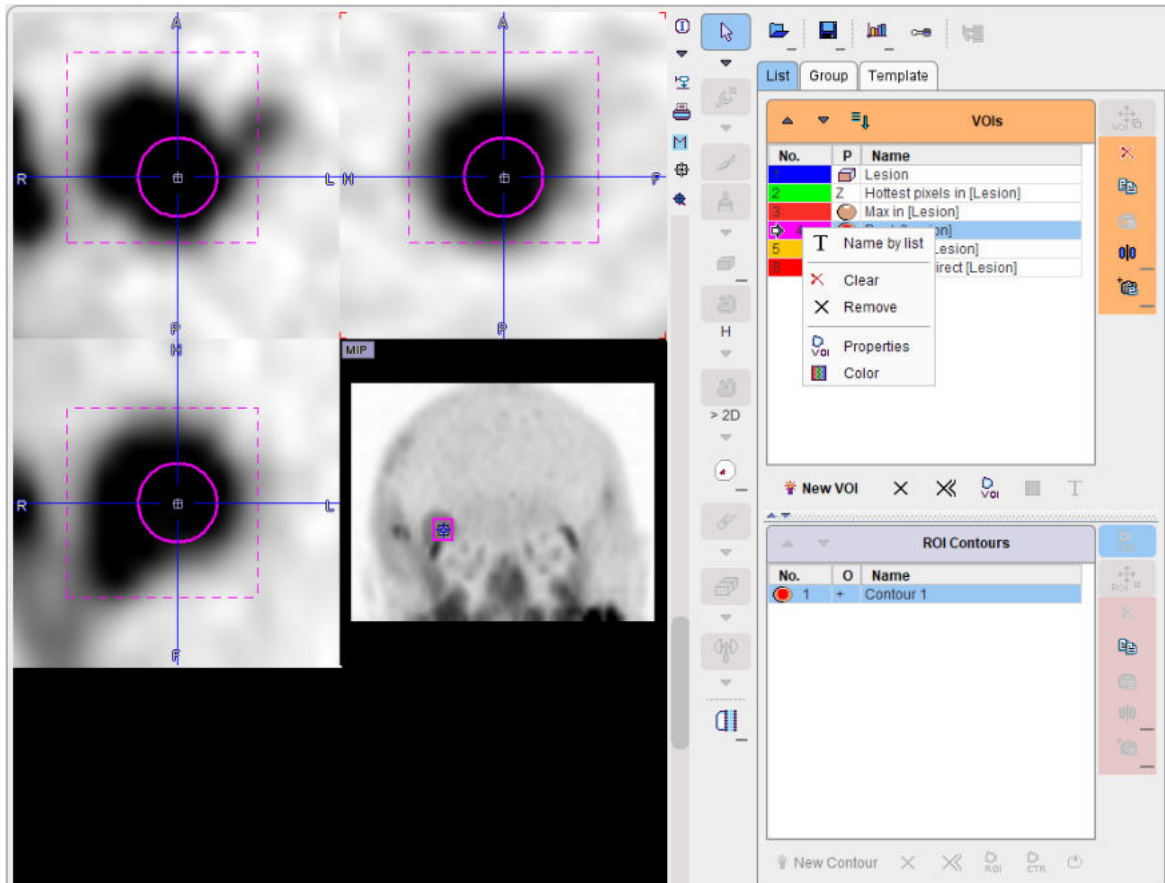
10.2.3.4 Tumor Volume Segmentation

There are various approaches for outlining a lesion in a PET image. The **PET Tumor volume segmentation** method implements an automatic model-based approach [1, 2] for determining an iso-contouring threshold which is independent of the signal-to-background ratio and provides accurate volume measurements down to the resolution of the PET scanner.

Principle

The method performs an iterative adjustment of the iso-contouring level, taking into account the scanner resolution and the background activity. In this process, the lesion geometry is approximated by a sphere and the appropriate threshold level determined by a lookup procedure which refers to a homogeneous sphere imaged at scanner resolution. During the iterations, each threshold setting results in a new tumor volume obtained by iso-contouring, which allows calculating the next threshold approximation. The process is repeated until the tumor volume becomes stable.

Required for applying this segmentation method is:

1. An initial approximation of the tumor VOI.

2. The background activity level which is subtracted.

3. The PET scanner resolution.
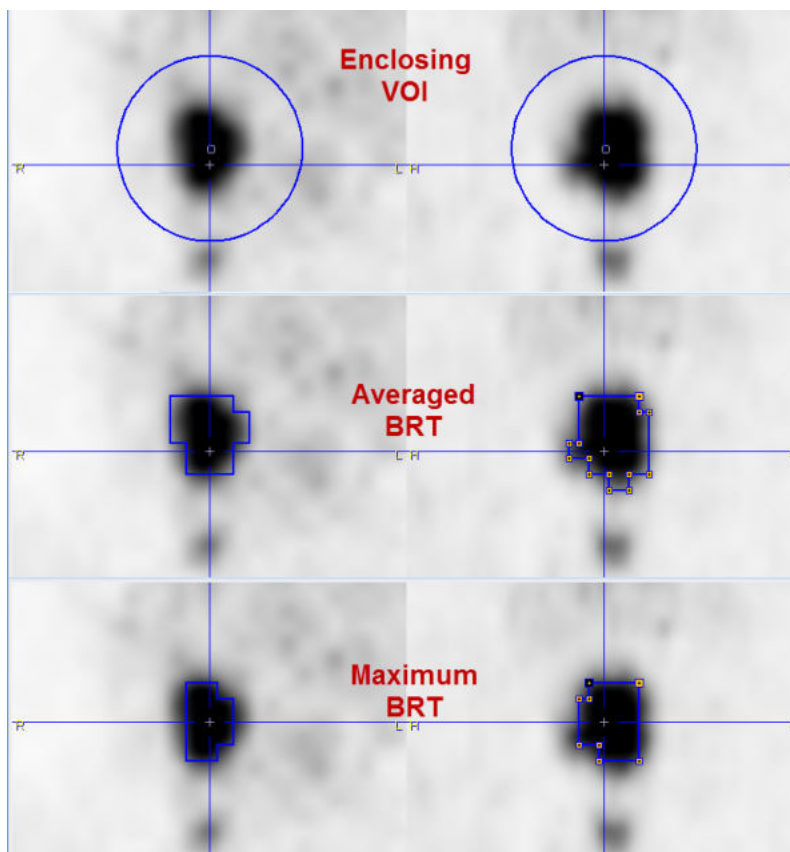
Use without Background VOI

If the tumor is isolated from the surroundings, the background can easily be obtained from the initial VOI definition. Please define a VOI enclosing the tumor, with sufficient distance to the rising edge. A sphere is used in the illustration below.

Start the **Tumor Volume Segmentation** procedure. In the appearing dialog window
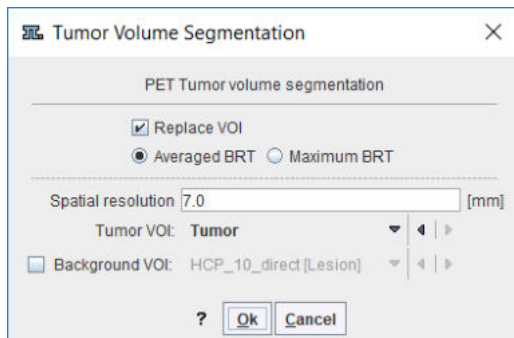

enter the **Spatial resolution** of the image. There are two different approaches implemented. With **Averaged BRT** (**B**oundary-**R**eproducing **T**hreshold) the average activity in the iteratively segmented VOI is used [1], with **Maximum BRT** the maximal activity [2]. According to Jentzen [1], the Averaged BRT is preferable for larger objects, and it is less sensitive to noise and non-uniform uptake.

Check **Replace VOI,** if the initial VOI is not used any further and start the iteration with **Ok**. The program first calculates the background activity by dilating the bounding VOI by 3 pixels and averaging the pixels along the extended contour. Then the optimal iso-contouring threshold is calculated as outlined above. The results obtained with the different criteria are illustrated below.

Use with Background VOI

If higher uptake than background is close to the tumor, the initial VOI should be close to the tumor boundaries, and an explicit background VOI should additionally be outlined. Note that the **Background VOI** box needs to be checked, and the proper VOI selected from the list next to it.
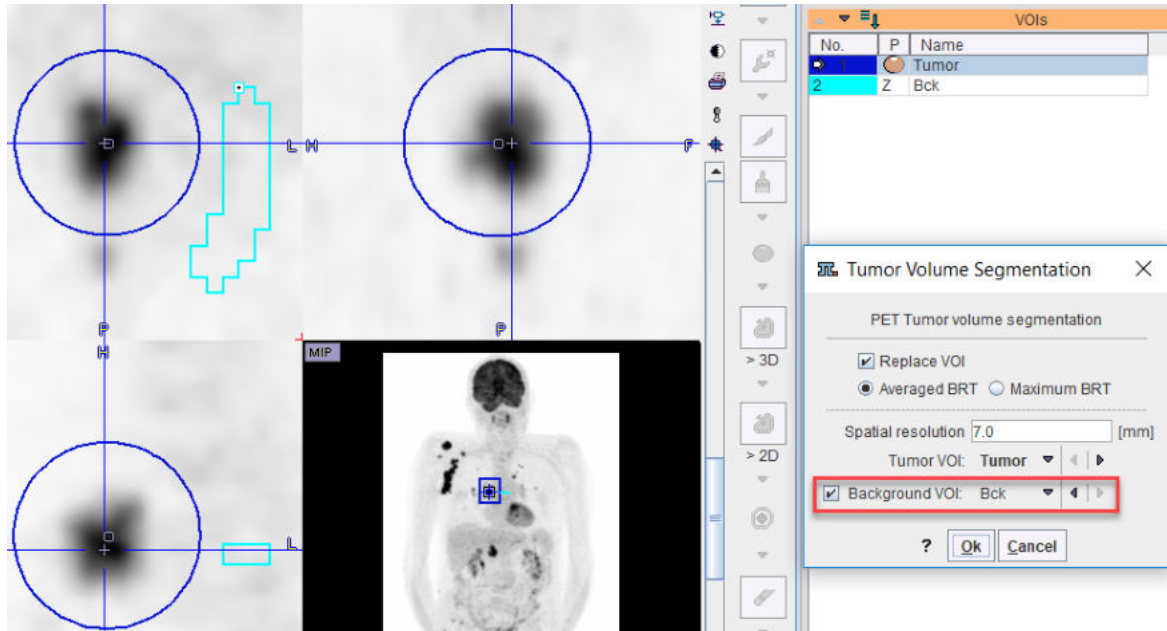
Note: The **Tumor Volume Segmentation** is called while the Group tab is active, all selected VOIs will be processed. If a background VOI is defined and named "Bck" it will be automatically considered by the algorithm.

References

1. Jentzen W.: An improved iterative thresholding method to delineate PET volumes using the delineation-averaged signal instead of the enclosed maximum signal. Journal of nuclear medicine technology 2015, 43(1):28-35. DOI

2. van Dalen JA, Hoffmann AL, Dicken V, Vogel WV, Wiering B, Ruers TJ, Karssemeijer N, Oyen WJ: A novel iterative method for lesion delineation and volumetric quantification with FDG PET. Nuclear medicine communications 2007, 28(6):485-493. DOI

10.2.3.5 Hottest Connected Pixels

The **Hottest Connected Pixels (HCP)** method has been used to outline the locus coeruleus/subcoeruleus in T_1 weighted MRI images [2]. Another potential application is the extraction of the image derive input function. The HCP method finds a specified number of connected pixels with maximal average.

With the bounding VOI selected, start the **Hottest Connected Pixels (HCP)** tool. Besides the **Number of connected pixels**, the appearing dialog window includes two definitions related to neighborhood and connectivity.
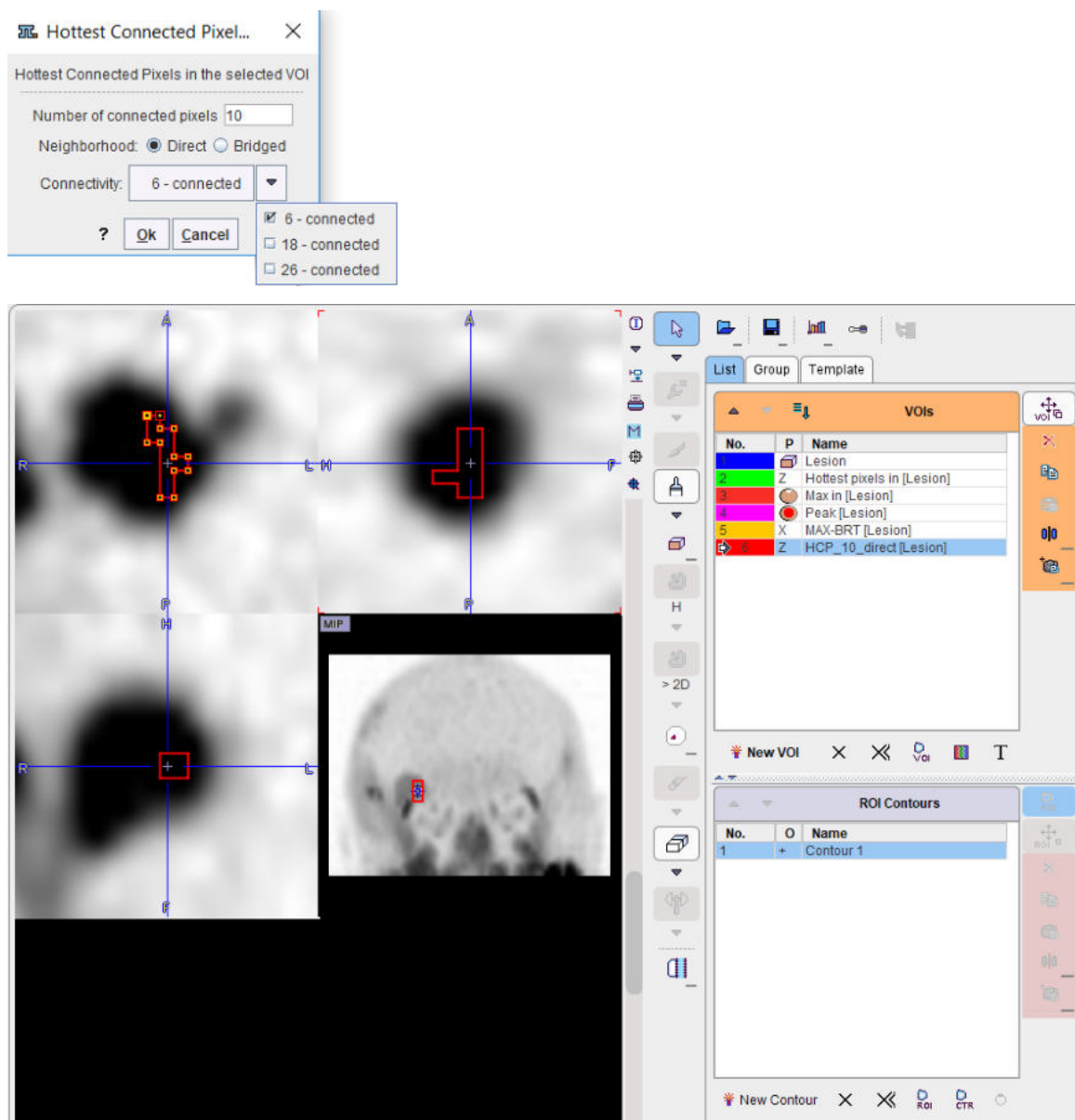
With **Direct** mode enabled, only immediate neighbors defined by the **Connectivity** setting are compared, whereas in **Bridged** mode neighbors of the immediate neighbours are also involved. The **Connectivty** options are illustrated below.
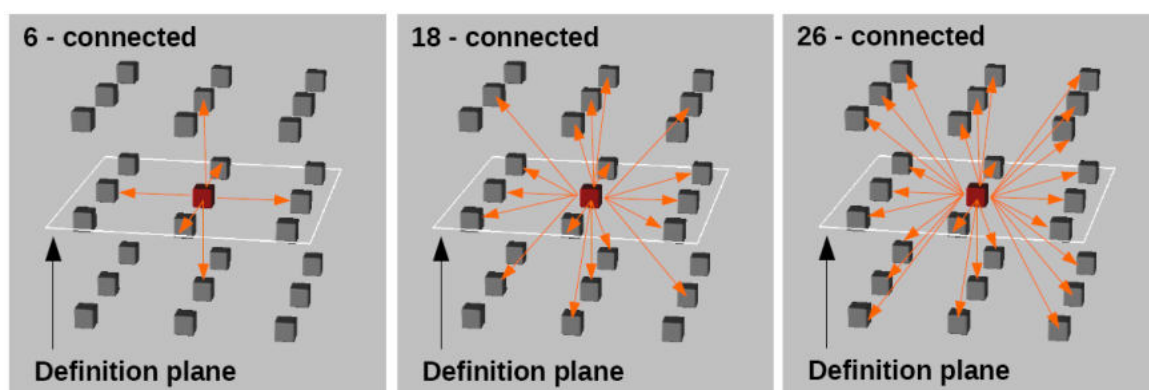

References

1. https://en.wikipedia.org/wiki/Pixel_connectivity

2. Lorenzo DG, Longo-Dos Santos C., Ewenczyk C., Leu-Semenescu S., Gallea C., Quattrocchi G.,Pita Lobo P., Poupon C.,Benali H., Arnulf I., Vidailhet M., Lehericy S.: The coeruleus/subcoeruleus complex in rapid eye movement sleep behaviour disorders in Parkinson's disease. Brain 2013, 136:2120–2129. DOI.

10.2.4 Hot-keys Based Lesion Segmentation

Three types of VOIs can be generated by pointing at the center of a hot lesion and activating a keyboard key:

1. Spherical **Peak VOI** (`Ctrl+Q`);

2. **Isocontour VOI** within a bounding space at a specified level (`Ctrl+L`);

3. PERCIST-type Iso-contouring VOI based on a reference VOI (`Ctrl+U`).

The settings for the generation of these VOIs are arranged in the VOI configuration panel as illustrated below. A similar panel is also available via the data inspector.
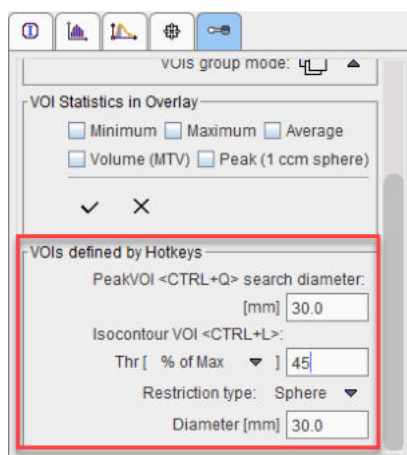
The different VOI types are described in the following sections.

Notes: The keyboard-driven definition of the VOIs is working only when the VOIs functionality is active. The generated VOIs are initially locked, as they are intended as objective measures. They can be unlocked in the VOI Level Properties 218 dialog window.

10.2.4.1 Peak VOI

The peak uptake of a lesion is defined as the average uptake in a 1ml sphere, which is positioned such that the average is maximal (see also Sphere with Max Average (Peak VOI) 253). So the peak sphere VOI requires the definition of an enclosing boundary. The hot-key peak variant uses a simplified boundary defined as a sphere with **diameter** defined in the configuration illustrated below.
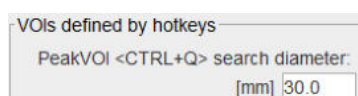

The procedure for placing a peak VOI in a lesion is as follows:

1. Activate the VOI functionality.

2. Triangulate the lesion *center* in the orthogonal layout, potentially using the MIP for fast localization.

3. Hit the `Ctrl+Q` keyboard keys. This places the enclosing sphere (VOI in dashed line) at the triangulation point and determines the location of the 1ml peak VOI with maximal average (VOI with solid line) as illustrated below.

The **search diameter** may need to be modified depending on the actual situation in the image for excluding neighboring structures.
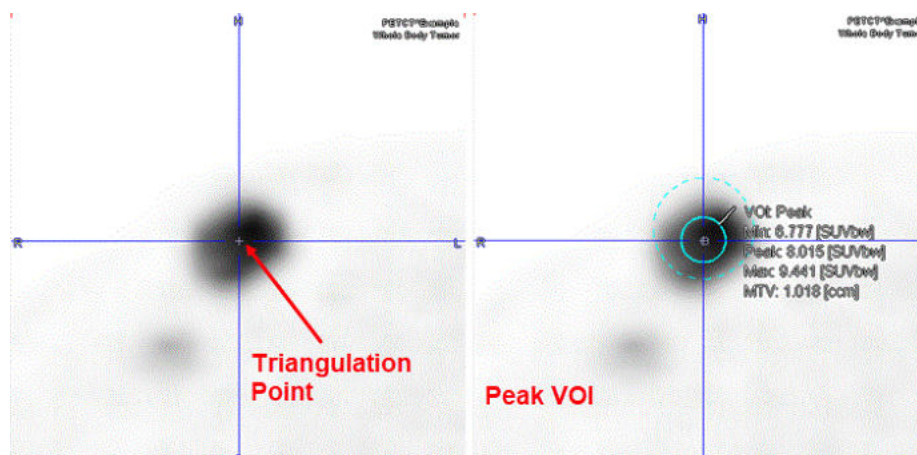
Note: The average calculation in the Peak VOI uses area-weighted statistics, corresponding to the Fraction classification mode 228 . For the peak VOI only spheres are considered with center inside the bounding sphere.

10.2.4.2 Isocontour VOI

The hot-key based **Isocontour VOI** follows the same idea of segmentation within a boundary as the Peak VOI 258 . Here a **Box** or a **Sphere** can be selected as **Restriction type**. The iso-contouring level is defined as **% of Max** or **% of Peak** within the bounding VOI, or on an absolute threshold **Abs SUV**. Note that for the latter, the values are interpreted in display units. So in order to apply iso-contouring on a defined SUV level, one of the SUV display units has to be active. An empty VOI will result if the threshold is above the maximal enclosed value.
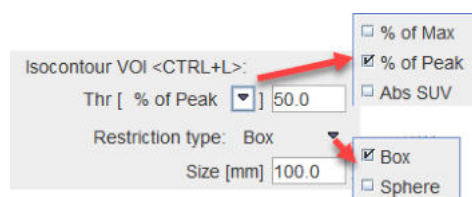

The procedure for generating an **Isocontour VOI** enclosing a lesion is as follows:

1. Activate the VOI functionality.

2. Triangulate the lesion *center* in the orthogonal layout, potentially using the MIP for fast localization.

3. Hit the `Ctrl+L` keyboard keys. First, the bounding box or sphere is generated and shown in dashed lines. If needed (for **% of Max** or **% of Peak**), the threshold is determined, and the iso-contouring is applied.

The generated isocontour VOI is added to the VOIs list with a name **Iso** followed by the threshold value and type, e.g **45% of Max.** In case of the absolute threshold the units are appended at the end of the VOI name: e.g. **Iso 2.5[g/ml{SUVbw}]**. The parent VOI does not appear in the VOIs list.

The **Size** of the enclosing **Box** or the **Diameter** for the enclosing **Sphere** may need to be modified, depending on the actual situation in the image for excluding neighboring structures.

The capture below illustrates the results of a Peak VOI within a sphere of 15 mm radius and an Isocontouring VOI with a threshold of 45% of Max within a cubic box of 40 mm for the same hot lesion.
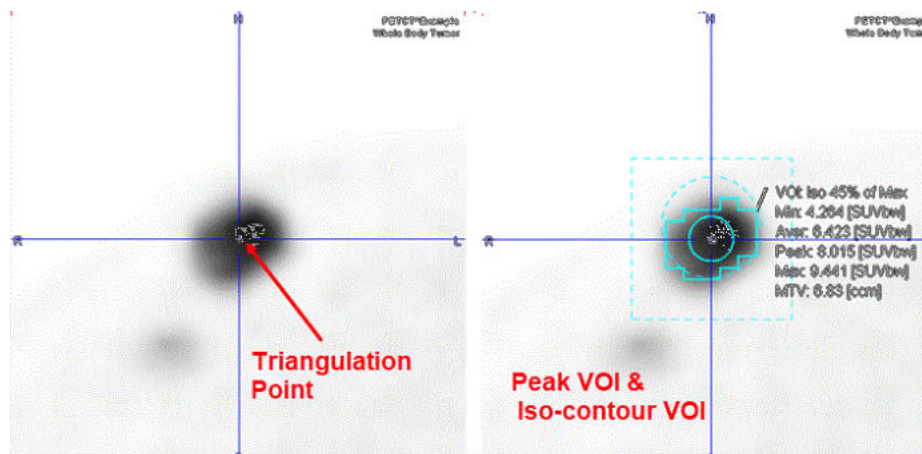

### 10.2.4.3 PERCIST-type Iso-contouring VOI based on Reference VOI

Instead of basing iso-contouring on the values in the lesion itself or an absolute SUV, the threshold can be obtained from the uptake in reference tissue. The PERCIST (PET Response Criteria in Solid Tumors) [1,2] obtains the reference activity from a 3cm diameter sphere placed in the right side of the liver, midway between the dome and inferior margin, excluding central ducts and vessels. If the liver is diseased, background is to be measured in the descending thoracic aorta (cylinder: 1cm diameter, 2cm long, avoiding wall).

The procedure for a PERCIST-conformant assessment using hot-key based VOis is as follows:

1. Activate the VOI functionality.

2. Reference sphere: Triangulate the point in the liver as described above. Use keyboard shortcut `Ctrl+Shift+U` to place the 3cm diameter reference sphere. An entry VOI named **PERCIST ref** appears in the VOIs list. The minimal level of tumor uptake is calculated as *1.5*AverageLiver+2*StandardDeviationLiver*. This value is used as iso-contouring threshold in the subsequent lesion assessment.
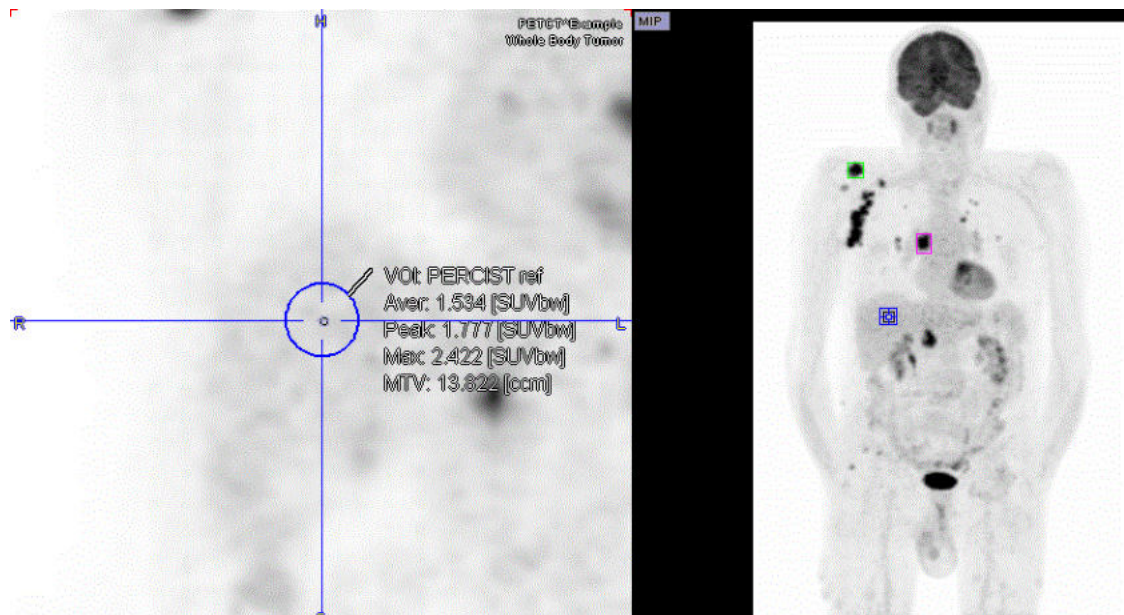
2. Lesions: For each of the lesions triangulate its center, and then use keys `Ctrl+U`. A region growing algorithm is applied and the lesion outlined on the threshold level calculated from **PERCIST ref**. If the lesion is below the minimal tumor level, no iso-contouring VOI is found. In this case the lesion is not measurable with PERCIST. Otherwise a VOI is enteredd using
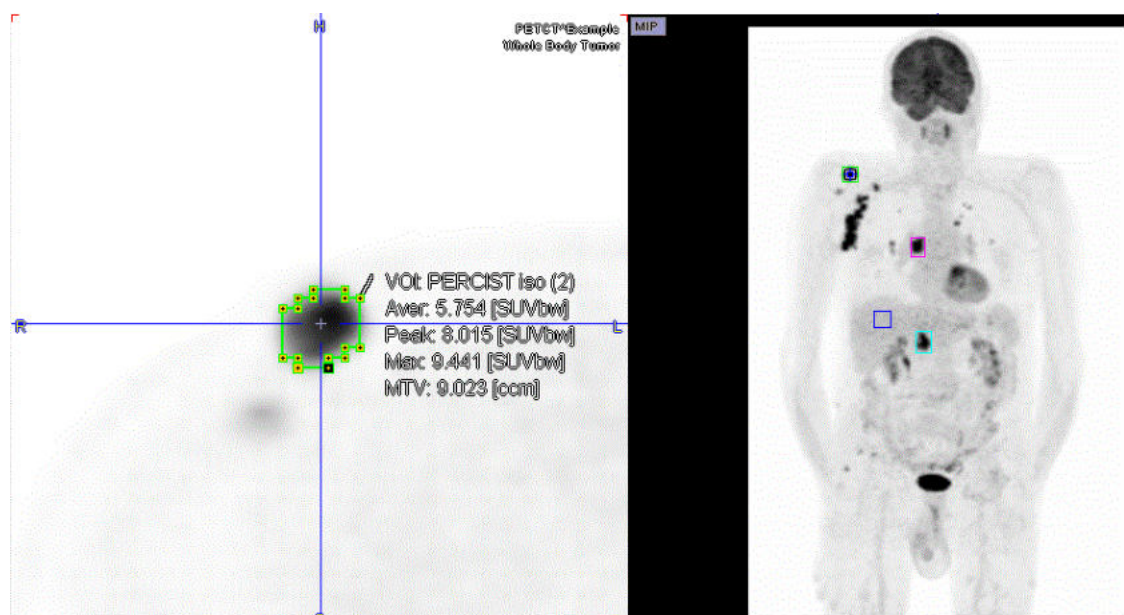
For each measurable lesion a corresponding entry will appear in the **VOIs** list named **PERCIST iso** followed by a number through round brackets, e.g. **(3)**, indicating the order of the outlining.

VOI Sorting 283 can be used for bringing the most relevant lesions to the top. For individual lesion documentation it is recommended to enable Overlay Statistics 232 and then click at the VOIs in the list and perform an Image Capture 196 with `Ctrl+E`.

References

1. Wahl RL, Jacene H, Kasamon Y, Lodge MA: From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med 2009, 50 Suppl 1:122S-150S.

2. O JH, Lodge MA, Wahl RL: Practical PERCIST: A Simplified Guide to PET Response Criteria in Solid Tumors 1.0. Radiology 2016, 280(2):576-584

10.2.5 Adjustment Tools for Contour VOIs

Once a VOI has been defined, several tools are available for its modification. The tools operate on the different definition levels:

- Operations on the entire VOI level like scaling change all contours in all slices at once.

- Operations on the ROI level change all contours in one slice at once.

- Operations on the contour level only change the selected contour in the current slice.

For each of the levels there is a toolbar illustrated below. Note that the **ROI** and **CTR** toolbars need to be toggled as they share the same location. To switch them please activate the indicated button at the top.
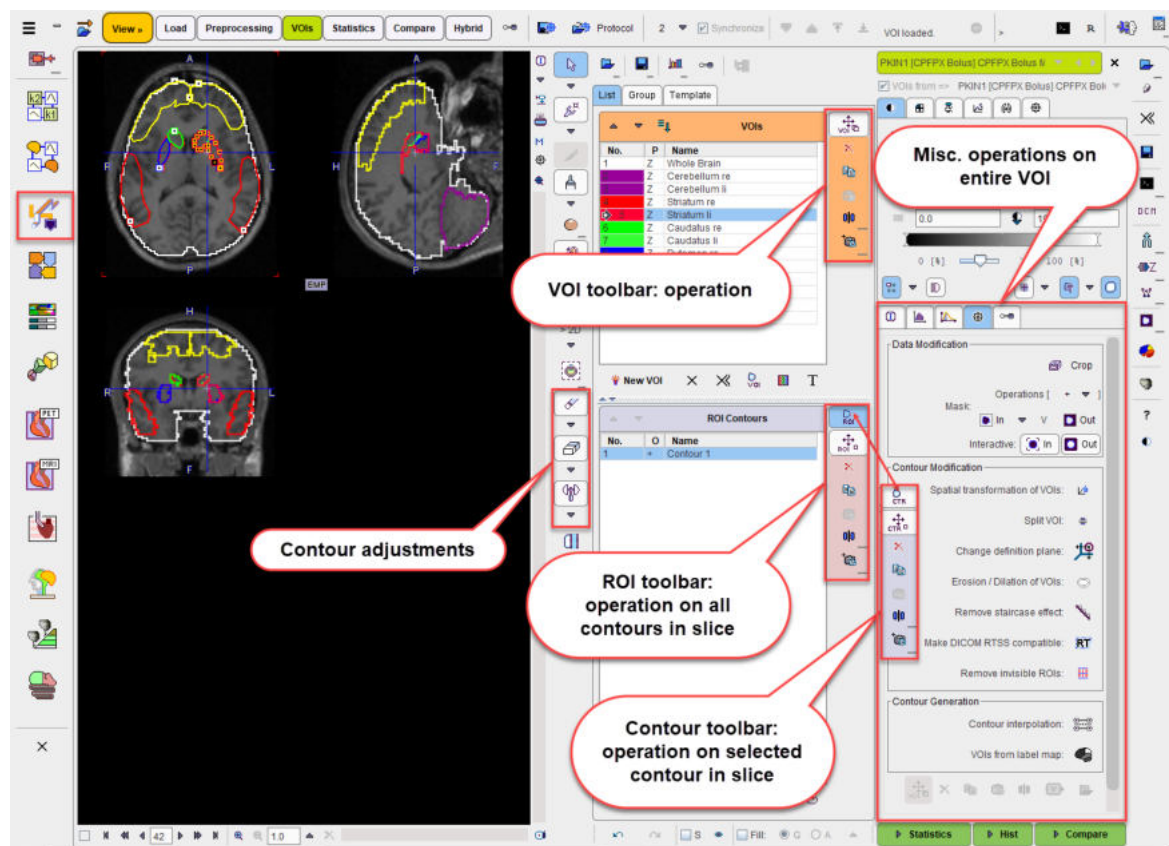
Contour VOIs are formed from a stack of planar ROIs, which themselves consist of a set of contours per slice. On each of these three levels a set of similar operations are supported via the toolbar:

- Scaling: The shape can be adjusted by dragging the edges of the object bounding box.

- Clearing: The contents of the object is cleared, but the object continues to exist and can be used again for a new definition.

- Copy/Paste: An object can be copied to the clipboard, and then pasted into an empty object on the same hierarchy level.

- Mirroring: An object can be mirrored with respect to the central axes of the image volume.

- Propagation: The aim of propagating an object is to easily get a copy of an existing object in a neighboring slice or frame. Propagation can work in both directions.

10.2.5.1 Editing Contour Shapes

The following tools are available for adjusting the shape of completed contours.

Moving Individual Vertices

When the Contour Drawing Mode 237 is active, the user can click at individual contour vertices and then drag them to more appropriate positions. Clicking at contours from different VOIs will automatically select the corresponding VOI in the **VOIs** list.
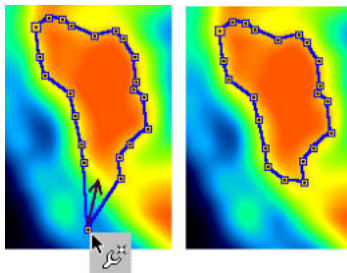

Deleting Vertices

The vertex eraser can have different shapes and sizes which may be selected from the option list below the eraser button.
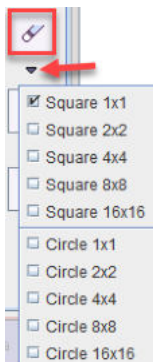
To delete vertexes from a contour VOI:

1. Select the VOI in the **VOIs** list and the contour to be edited in the **Contours** list. In the usual case of a single contour per slice it is automatically selected

2. Activate the eraser button.

3. Drag the vertex eraser shape against the contour vertexes. As soon as a vertex is crossed, it is removed and the neighbouring vertexes connected by a line.
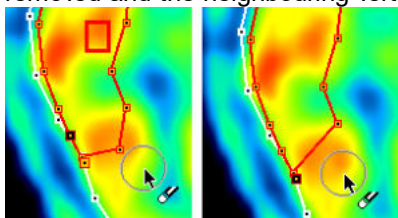
Erase Pixels from VOI

The pixel eraser works like an "pencil eraser". When moved across pixels included in a VOI, all crossed pixels are removed from the VOI. The eraser has two modes, as can be seen from its option menu.
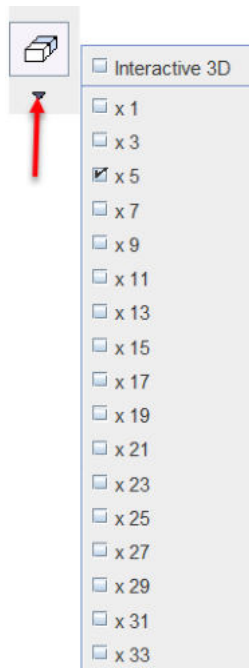
In **2D** mode, a circle size can be defined depending on the adjustment needed. The illustration below shows the effect when dragging such a circle across a contour.
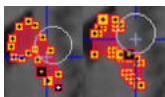
With the **Interactive 3D** selection, pixel removal is based on a sphere region growing algorithm. Click into a corner of the area *within the contour* to be deleted. Hold the mouse button while the 'growing' sphere deletes the targeted pixels. This operation can be repeated for incremental deletion of VOI parts.

Note that the eraser works in any plane direction, not only in the primary direction where the contours were defined.

Inserting Vertexes

It is also possible to insert vertexes at any location into contours. The vertex insertion tool can be selected from the outlining list as illustrated below.
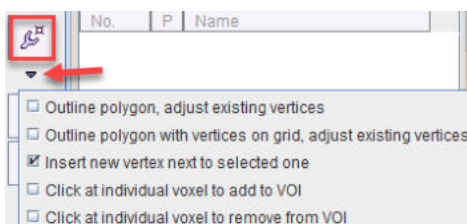
The contour to be edited can be selected in the **Contours** list or directly at the vertex where the insertion shall be performed. The connection to be divided is indicated by the emphasized vertexes at both ends. When moving the cursor, the prospective two new segments are indicated by two faint lines. When the user clicks, the vertex is placed and the two new segments added. This procedure will continue for one of the created segments. To modify a different part of the contour please click at one of the vertexes there. Note that the vertex locations cannot be changed in the insertion mode.

π.pmod
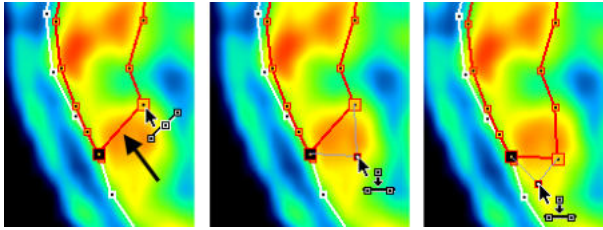
Contour Shape Deformations

For the shape adjustment of densely populated contours arising from iso-contouring or drawing, a dedicated "hammer" tool is available. Similar to the eraser tool it is a circle and can be configured for different sizes.
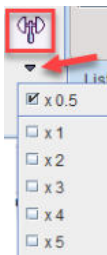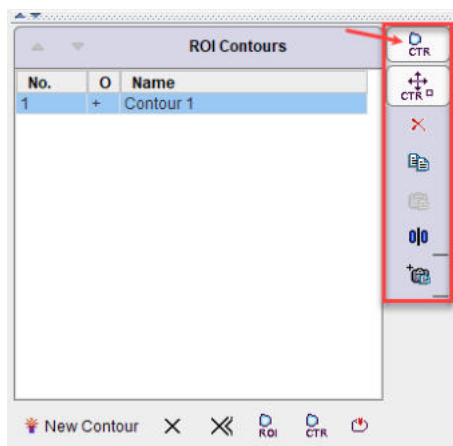

To change the contour shape with the hammer tool:

1. Select the affected contour by selection in the **Contours** list.

2. Activate the hammer tool.

3. Drag the circular towards the contour vertexes which are pushed radially away.
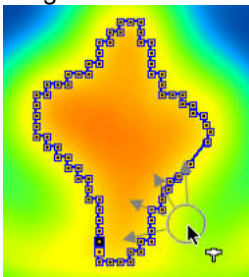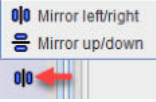

10.2.5.2 CTR Toolbar

The contour toolbar

facilitates the operations related to entire contours. It is sharing the space right to the **Contours** list with the ROI Toolbar 267. The two toolbars can be switched using the indicated button at the to.

Note that only all selected contours are affected, whereas the others remain untouched.

⊕CTR⊕	**CTR Action**. If this button is selected, contours can be selected and then moved or scaled as described below.
✕	**Clear**. Clears the selected contours of the selected VOI in the current plane. The contour remains in the list, but has no defined polygon associated.
📑	**Copy**. Copies the selected contours to the clipboard.
📋	**Paste**. Pastes the contours from the clipboard into the current contour (which must be empty, e.g. created by **New contour**).
0|0	**Mirror**. Opens a sub-menu for mirroring the selected contours in the current slice relative to the vertical or horizontal center line.
⁺📋	**Propagate** option button. Propagation copies the selected contours of the current VOI and pastes it to a neighboring slice. Note that *all* existing contours in the target slice are *overwritten*. The different propagation variants are described below.

CTR Action

In the **CTR Action** mode an entire contour can be translated, rotated or scaled within the plane. If a VOI has multiple contours, select the target contours in the **Contours** list. As illustrated below, the operations can be performed using mouse dragging. The handle in the center of the contour allows translations and rotations. When dragging the edges of the bounding box, the contour is scaled.
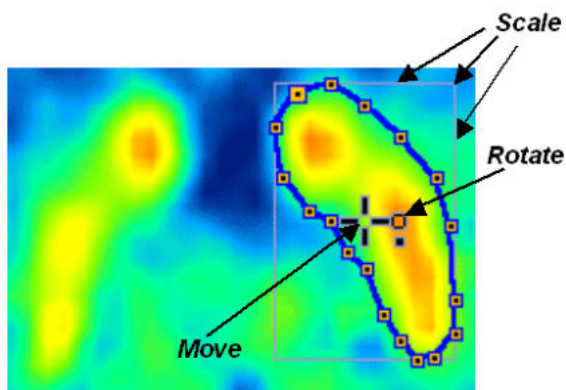
Alternatively the keyboard cursor arrows can be employed:

ARROW UP, DOWN, LEFT, RIGHT	Move contour accordingly
CTRL + ARROW UP, DOWN, LEFT, RIGHT	Scale the contour
SHIFT + ARROW UP, DOWN, LEFT, RIGHT	Rotate the contour
ALT + one of the above	Perform the operation 5 times faster

Individual vertices cannot be moved in CTR action mode.

**CTR Propagation**

The following propagation options are available:

Contour Propagate -	Pastes to the next slice in one direction (depending on the plane sorting order).
Contour Propagate +	Pastes to the next slice in the other direction.
Contour ApplyToAll	Pastes to all slices of the series.
Contour SmartApply	Pastes to all neighbouring slices which have no defined contours.
Contour Follow Max -	Pastes to the next slice in one direction and centers the contour at the maximal value in the slice (eg to follow a vessel).
Contour Follow Max +	Pastes centered at the maximum in the other direction.

Contour propagation may have advantages in the following situations:

- if it is easier to adjust the propagated contour than to outline it from scratch, and
- to create a bounding VOI which roughly encloses a structure, and then using the iso-contouring tool.

## 10.2.5.3 ROI Toolbar

The ROI toolbar
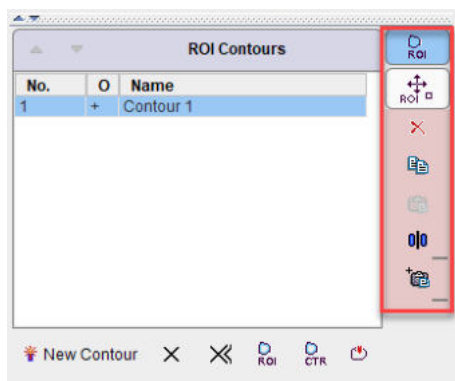
works in analogy to the CTR Toolbar⎡265⎤, except that all contours of the selected VOI in the current slice are changed at once.

⊕	**ROI Action**. If this button is selected, all contours in the slice can be moved or scaled as described below.
✕	**Clear**. Clears the contents of all contours of the selected VOI in the current plane. The user can immediately begin defining a contour.
▤	**Copy**. Copies the contours to the clipboard.
▥	**Paste**. Pastes the contours from the clipboard into the current ROI (which must be empty).
0❘0	**Mirror**. Opens a sub-menu for mirroring the contours in the current slice relative to the vertical or horizontal center line.

> **Propagate** option button. Propagation means copying all contours of the current slice and pasting it to a neighboring slice. Note that existing contours in the target slice are *overwritten*. The different propagation variants are described below.

ROI Action

As illustrated below, a bounding box enclosing all contours of the selected VOI in the current slice appears together with the move/rotation handle in the center. When dragging the edges of the bounding box, all contours are scaled.
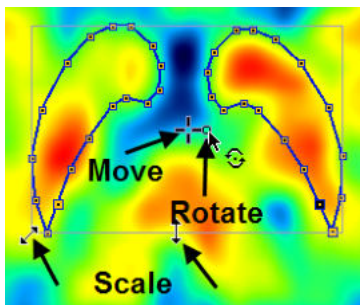
Alternatively the keyboard cursor arrows can be employed:

CURSOR UP, DOWN, LEFT, RIGHT	Move contours accordingly
CTRL + CURSOR UP, DOWN, LEFT, RIGHT	Scale the contours
SHIFT + CURSOR UP, DOWN, LEFT, RIGHT	Rotate the contours
ALT + one of the above	Perform the operation 5 times faster

Individual vertexes cannot be moved in ROI action mode. To edit individual vertexes first switch back to the **Edit Mode** by selecting the corresponding button in the toolbar.

ROI Propagation

The following propagation options are available:

ROI Propagate (slice) -	Pastes the ROI to the next slice in one direction (depending on the plane).
ROI Propagate (slice) +	Pastes the ROI to the next slice in the other direction.
ROI Propagate (frame) -	Pastes the ROI to the next frame (active for dynamic ROIs)
ROI Propagate (frame) +	Pastes the ROI to the next frame in the other direction (active for dynamic ROIs)
ROI ApplyToAll	Pastes to all slices of the series.
ROI SmartApply	Pastes to all neighboring slices which have no defined contours.
ROI Follow Max -	Pastes to the next slice in one direction and centers at the maximal value in the slice (eg to follow a vessel).

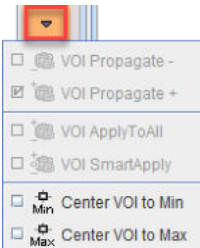| ROI Follow Max +	Pastes centered at the maximum in the other direction.

10.2.5.4 VOI Toolbar

The VOI toolbar
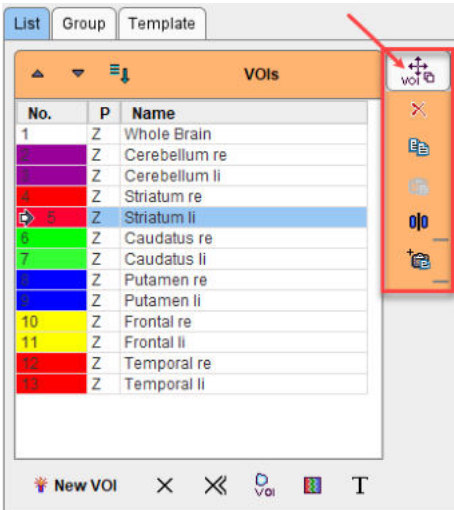
supports operations related to the entire VOI definition. Note that all the contours are affected, not just the ones in the visible slice images.

	VOI Action. If this button is selected, a VOI can be selected and then moved or scaled as described below.
	Clear. Clears all ROIs and contours of the selected VOI, leaving empty definitions.
	Copy. Copies the VOI to the buffer.
	Paste. Pastes the VOI from the buffer into the current VOI (which must be empty).
	Mirror. Opens a sub-menu for mirroring the selected VOI relative to the image center in the three directions. The **clone** variants first create a VOI copy, which is then mirrored.

The down arrow button allows to select a variety of further tools.

🔲	**Propagate** and **Apply** option buttons. Propagation for VOIs means copying a VOI from one time frame to another. This function is only available for dynamic series and VOIs which have the property set to dynamic. The different propagation variants are described below.
Min	**Center VOI to Min**. Positions the center of the VOI bounding box at the pixel within the current VOI which has the minimal value. Note that multiple activations of the button may result in different positions.
Max	**Center VOI to Max**. Positions the center of the VOI bounding box at the pixel within the current VOI which has the maximal value. This function can be applied during a PERCIST evaluation to center the spheres at the lesion maxima.

VOI Action

With the VOI Action mode all contours of a VOI can be modified at the same time. In most cases it will be advisable to use the orthogonal layout as illustrated below. After selecting the VOI by clicking at its contour or the entry in the **VOIs** list, several elements are shown in the overlay: the bounding box of the contours in the active slice, the bounding box of the VOI (maximum of the contour bounding boxes in all slices), and a handle for moving and rotating.
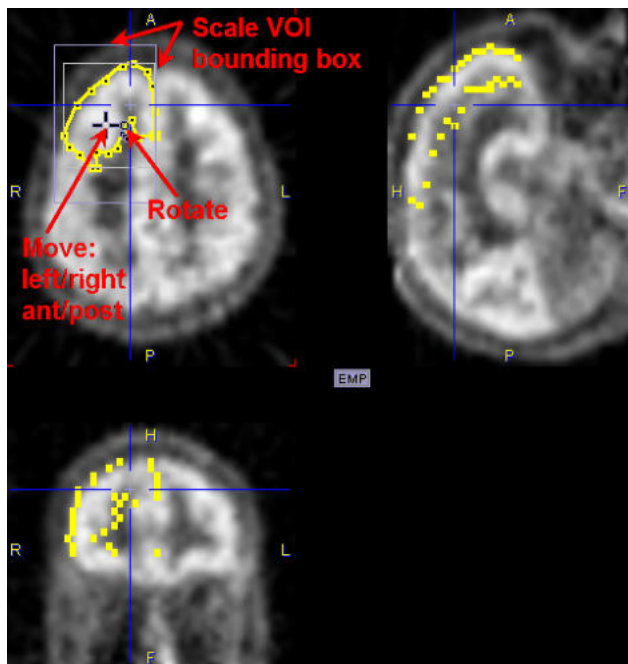
To move the VOI, drag the handle in the center with the left mouse button. Use the small rectangle for a rotation. To scale the VOI, drag the bounding box lines. After releasing the result will be updated in the other views. Note that not all operations are available in all directions:

- Scaling is only supported within the primary plane which was used for the contour definition. The reason for this behavior is the lack of contour interpolation across slices.
- Rotation is also only supported within the primary plane.
- Moving is supported in all directions. While it is arbitrary within the primary plane, shifts in the orthogonal direction (across the slices) are only possible in increments of the slice thickness.

Referring to the example above, the frontal VOI can only be scaled in the L/R and A/P directions, but not in the H/F direction. In the sagittal plane, there is no rotation handle, and the scaling is only active for the bounding box lines indicated in the illustration below (A/P).
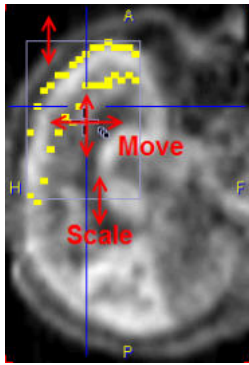
VOI Propagation

The **VOI Propagate** multi-function button serves for propagation over time and is therefore only active if

- the study is dynamic,

- and the properties of the VOI have been set to dynamic (⬚).

In this case, the VOI can consists of a differing definition at the different times. The button has the following options:

VOI Propagate -	Copies the current VOI, goes to the prior acquisition of the dynamic series, paste the VOI.
VOI Propagate +	Copies the current VOI, goes to the following acquisition of the dynamic series, and paste the VOI.
VOI ApplyToAll	Copies the current VOI and pastes it into all acquisitions.
VOI SmartApply	Copies the current VOI and pastes it into all subsequent acquisitions until an acquisition is encountered which already contains a VOI definition.

4D VOI Operations

When working with dynamic VOIs in dynamic series, an additional dimension needs to be considered, the time. Therefore, an area is available with similar tools as described above for the ROIs and VOIs. It is located on the **Tools** pane and allows a dynamic VOI to be cleared, copied, pasted, and mirrored in all frames at once. The load button allows inserting a static VOI in the currently selected frame.

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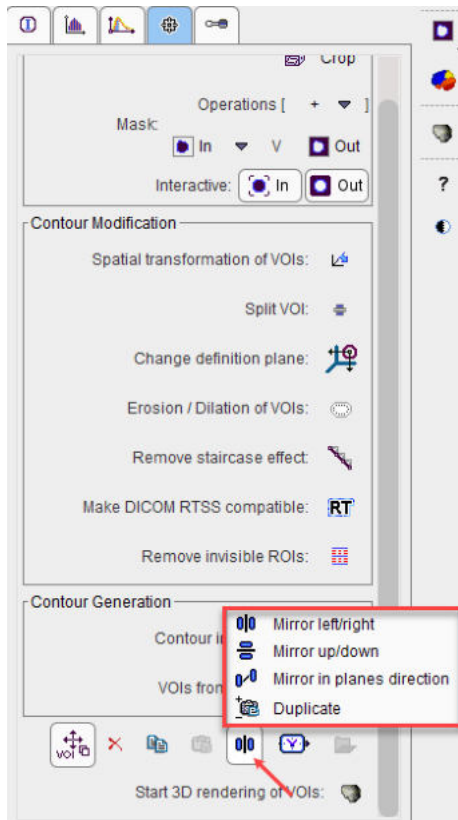
10.2.5.5 Spatial Transformation of VOIs

Spatial transformations can be applied to VOIs in order to transfer them from one image space to another. For instance, if VOIs were outlined on an MRI, and the MRI has been matched to a PET scan, the matching transformation can be applied to the MRI VOIs in order to adjust them to the PET image.

A transformation can be directly applied at VOI loading time as described in the <u>VOI Save/Load</u> [286] section, but it is also possible to just load the VOIs and apply the transformation using the **Spatial transformation of VOIs** facility in the VOI tools panel.
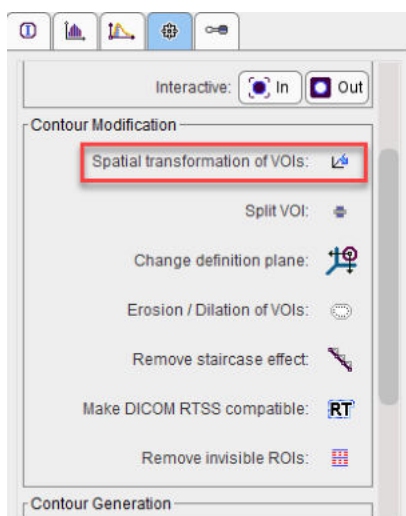
When activating the button, a dialog window appears for selecting the transformation.
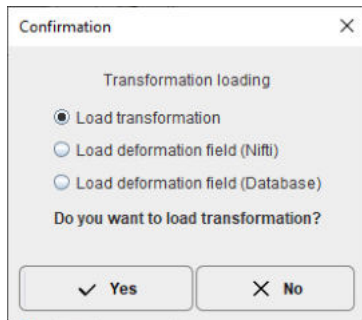
The user has to choose among the different types of transformations:

- **Load transformation** refers to .mat file transformations which result from rigid, affine or template matching procedures

- **Load deformation field** refers to probability matching which returns a transformation in form of an image, which can be read from the file system (**Nifti**), or from a PMOD **Database**.

Then, a corresponding transformation needs to be loaded.

10.2.5.6 Split VOI

The **Split VOI** function
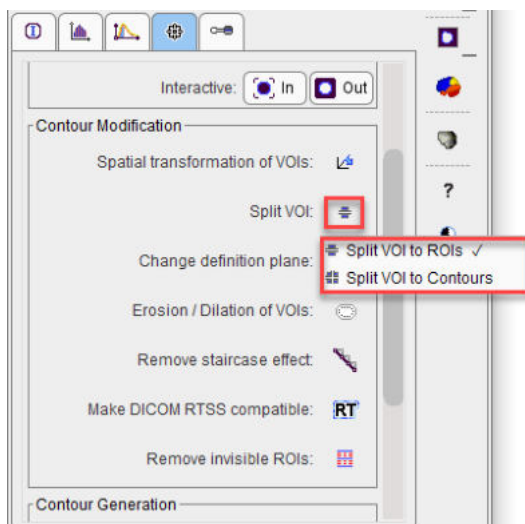
allows splitting a VOI in ROI or contours based on the selected option :

Split VOI to ROIs: generates a VOI from each ROI in the selected VOI;

Split VOI to COntours: generates a VOI from each contour in the selected VOI.

10.2.5.7 Change Definition Plane

The shape of contours can only be modified within the definition plane. The facility **Change definition plane** in the VOI tools
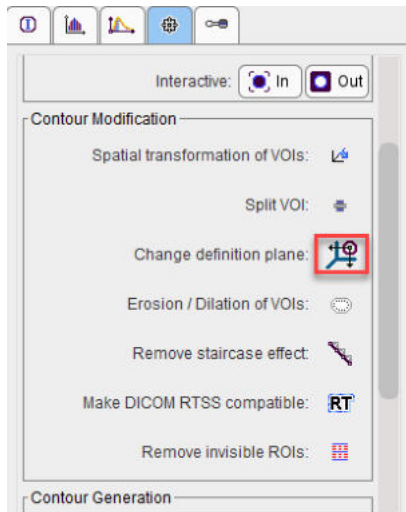
supports the conversion of the definition plane. A dialog window
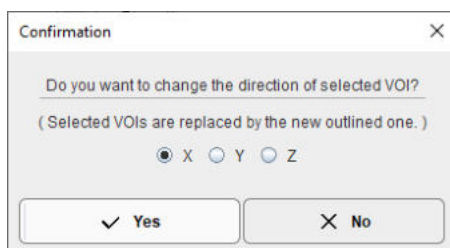
allows selecting the target plane direction. The original VOIs are replaced by VOIs enclosing the same volume, but with contours in the selected plane direction.

10.2.5.8 Erosion/Dilation

The **Erosion/Dilation of VOI** function
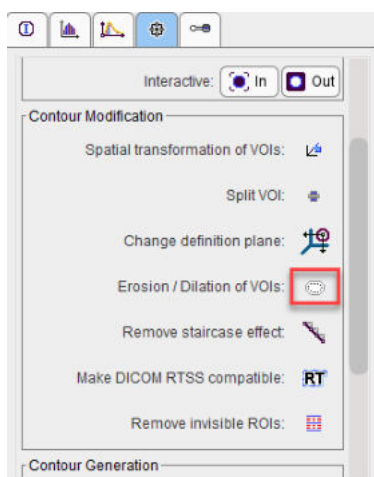
is useful for shrinking or inflating VOIs. It shows the interface described for the [morphological operations](#) [165]
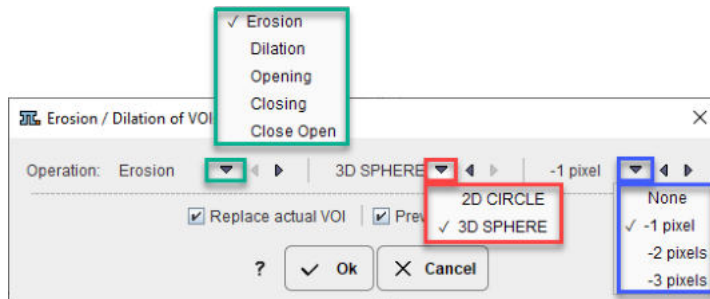
When applying an operation, the VOI is converted to a binary image, the operation applied, and then contouring applied to get a contour VOI. Therefore, object VOIs are converted into contour VOIs. The resulting VOI replaces the original VOI. Note that the operations can be applied to a whole group of VOIs at the same time.

10.2.5.9 Remove Staircase Effect

Contours using automatic outlining result in polygons following the pixel edges. The jagged appearance can be smoothed using the **Remove staircase effect**, located in the VOI tools panel.
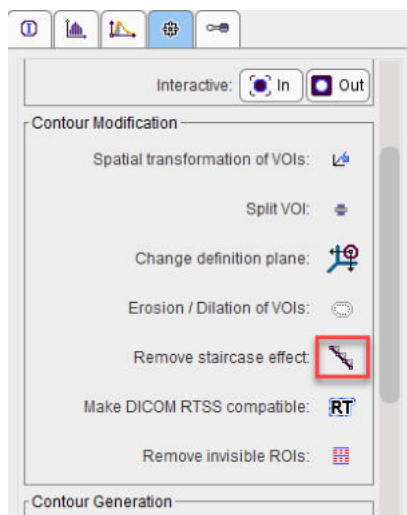
The example below illustrates the effect. The original contour is shown in green, the result of **Remove staircase effect** in blue.
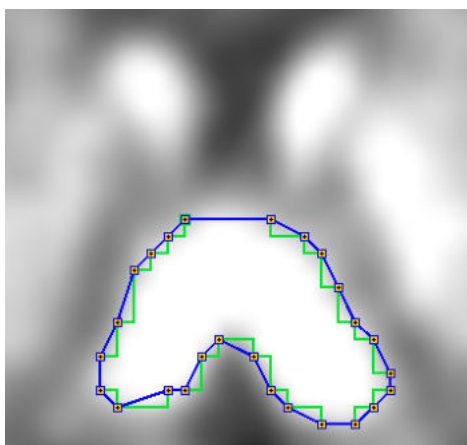
10.2.5.10 Make DICOM RTSS compatible

The PMOD VOI tools allow constructing VOIs which are more complex than supported by DICOM RT structure set (RTSS) definition. The **Make DICOM RTSS compatible** function located in the VOI tools panel converts the VOI representation into a form compatible with RTSS.
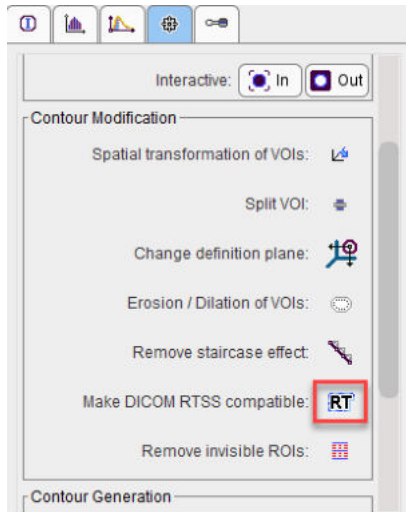
For instance, VOIs defined as analytic spheres are converted into a polygon representation. The RTSS compatible can then be used by other imaging workstations or radiotherapy (RT) planning systems. Note that the conversion is also supported as part of the <u>DICOM RTSS saving</u> ²⁸⁶ functionality.

10.2.5.11 Remove Invisible VOI

This function
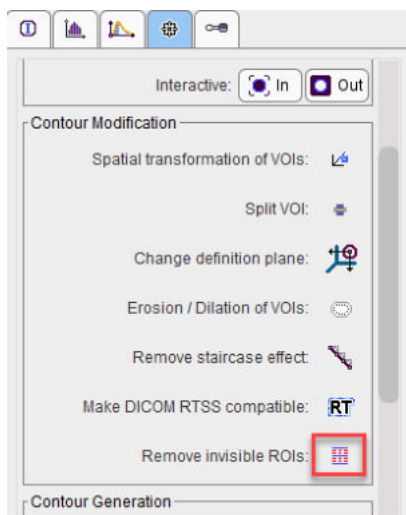
allows removing invisible VOIs from bigger resolution.

10.2.6   Mask-based VOI Tool: Raster VOIs

Starting with version 4.4, PMOD implements a new mask-based VOI functionality for rapid segmentation of the high-resolution data such as micro-CT. The result are labeled masked called raster VOIs.

In principle, the raster VOI is a mask and therefore observes the mask properties: overlaps are not allowed and dynamic format is not supported. The mask-based VOIs tool is taking advantage of the flexible **Segmentation interface** and allows editing in 3D.

The definition is started via the dedicated button in the VOI tools panel as illustrated below:
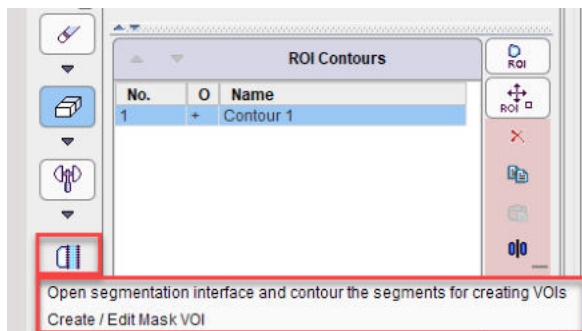
Two options are available: **Open Segmentation interface and contour the segments for creating VOIs** and **Create/Edit Mask VOI.** They are described in detail below.

10.2.6.1 Outline Segments to Mask VOIs

The mask-based VOIs tool is taking advantage of the flexible **Segmentation interface** and allows editing in 3D.

The **Open Segmentation interface and contour the segments for creating VOIs** starts the **Segmentation interface** implemented in PMOD. The appearing dialog window works as described in the **Segmentation** 175 section. The specific **Mask VOIs** radio button, when selected, allows returning the results as raster VOIs. The example below illustrates the segmentation result for the Otsu threshold method:
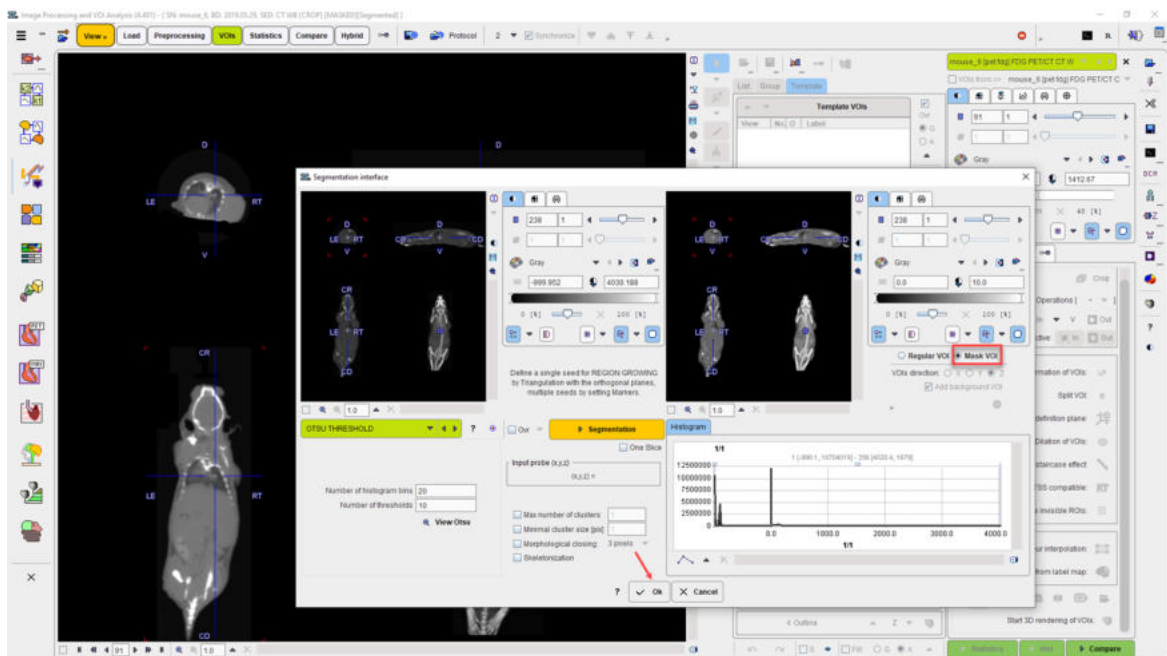

> **Note**: If a contour VOIs is already available on the VOIs **List** when the **Segmentation interface** is started, the segmentation algorithm can be restricted within the existing VOI by enabling the Restrict to VOI(s) check box.
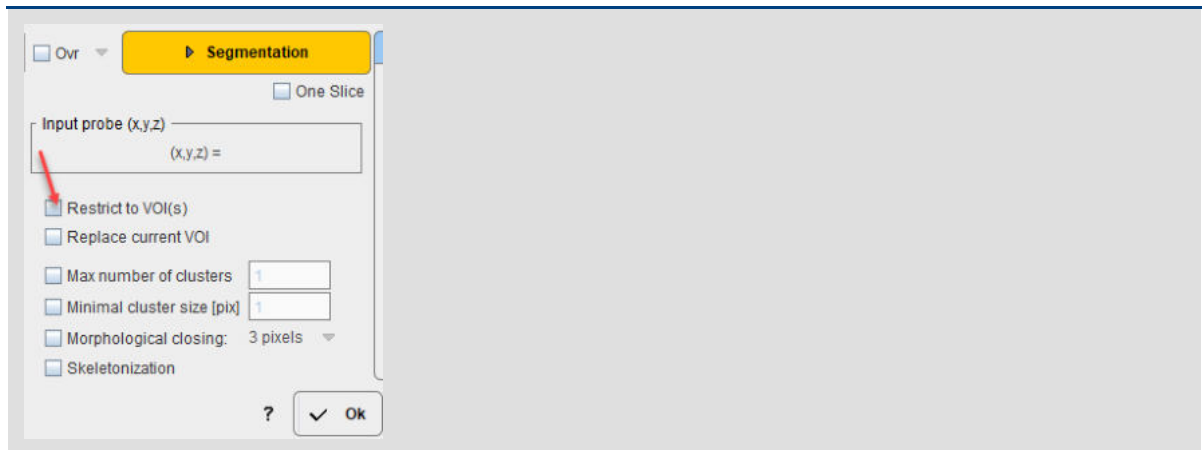
When closing the window with **Ok**, all the segments are converted to labeled masks and returned to the VOI environment as raster VOIs on the **Template/Mask** tab. Each label correspond to a segment.
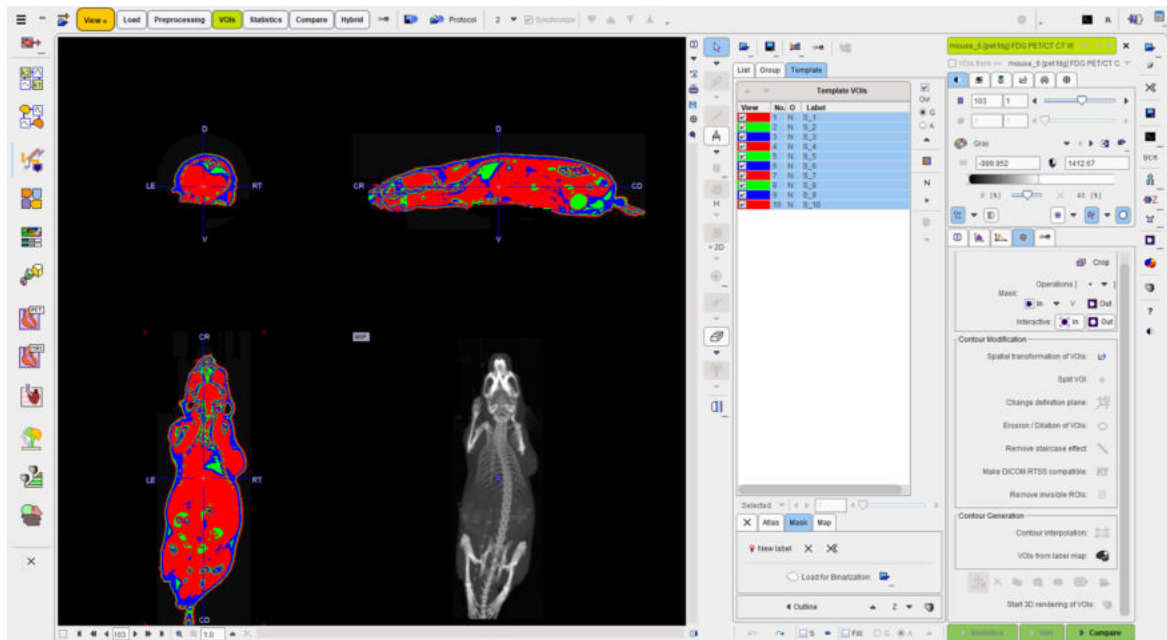

Currently, the raster VOIs are overlaid in the image as a grid (**G**) or as colored shaded areas (**A**). The enabled check boxes allow visualizing the raster VOIs overlaid on the image.
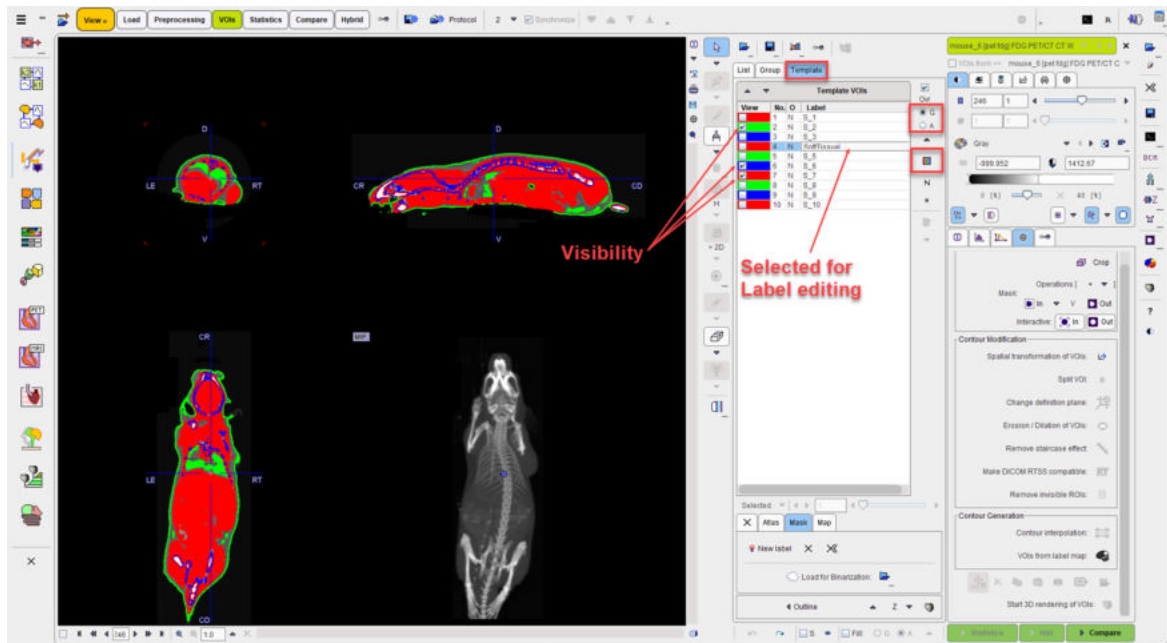
Click into a **Label** field to change the label name. The selected entry in the **Template VOIs** list appears highlighted. Confirm the change with the **Enter** key on your keyboard. Similar to the VOIs, the color of a raster may be changed by selecting first the entry in the list followed by activation of the color icon and selection of a new color. Close with OK the **Set color** interface to confirm the changes.

Raster VOIs may be converted to contour VOIs by outlining. First select the entries in the **Template VOIs** list for which contours should be generated. Use the SHIFT or CTRL key on the keyboard together with the left mouse button clicks for multiple selection. Make sure you click into the **No** field or into the **O** filed for selection. Activate the **Outline** button. Finally save the contours VOIs.

The illustration below shows the selection of two labels in the **Templates VOIs** that are converted into VOIs contours. Note that all the labels are visible in the display but only the ones that appear highlighted will be converted:
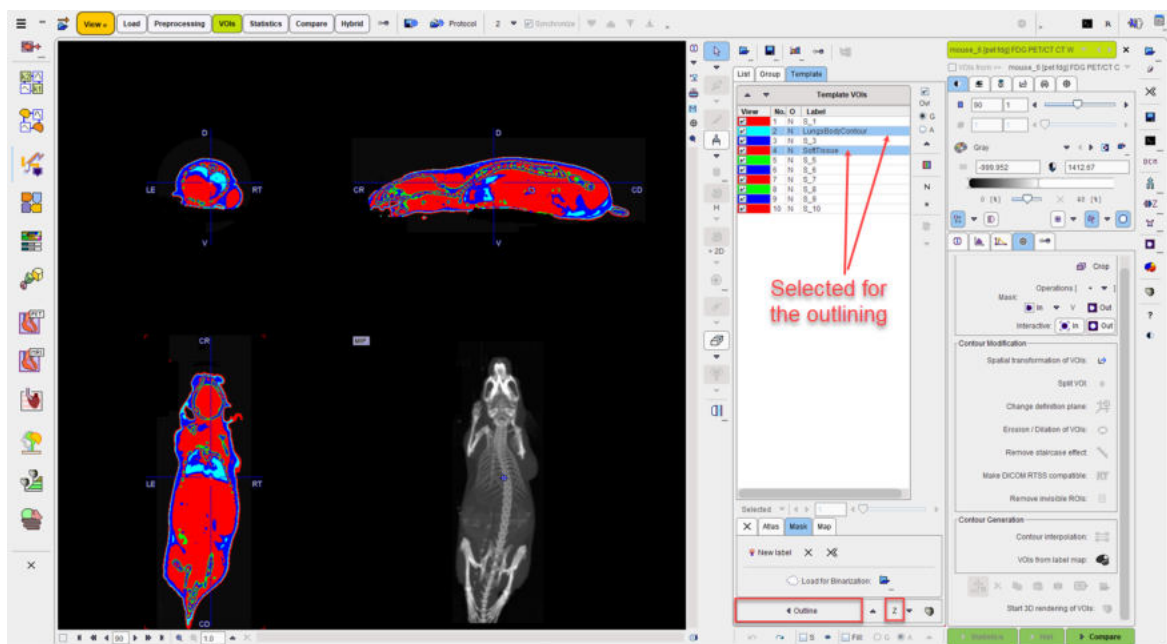
Activate the **Outline** button to start the conversion. The result is illustrated below:
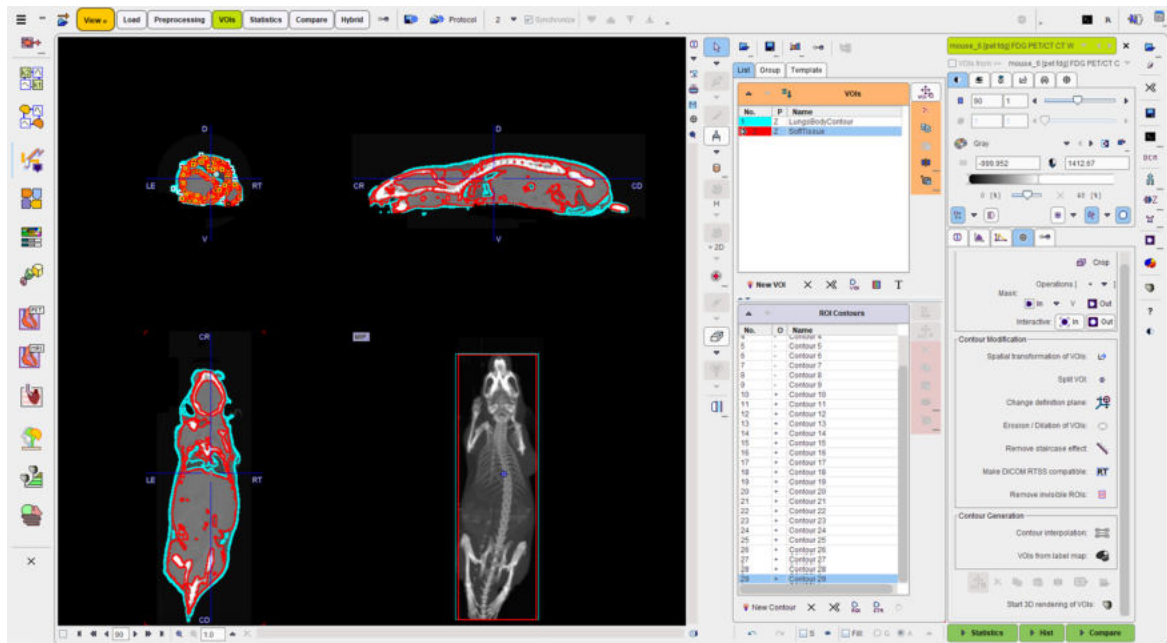
### 10.2.6.2 Create/Edit Mask VOI

Create/Edit Mask VOI

The **Create/Edit Mask VOI** switches the interface from the **VOIs List** to the **Template/Mask** tab and creates a new empty label. Consequently, a new data is created. This data has the same pixel size and matrix dimension like the image data that is currently displayed in the view port. Therefore, the first definition might be more time consuming compare to the subsequent one. Sometimes, a short delay might be noticed in the interface. The raster VOI is displayed as a matrix: voxel by voxel.

A limited number of 2D and 3D VOI tools is available for outlining and editing: the paint brush tool and the eraser respectively. Please note that the particular 2D and 3D options for these two VOIs tool are specific for Raster VOIs and can be accessed only when the **Template/Mask** tab is active.
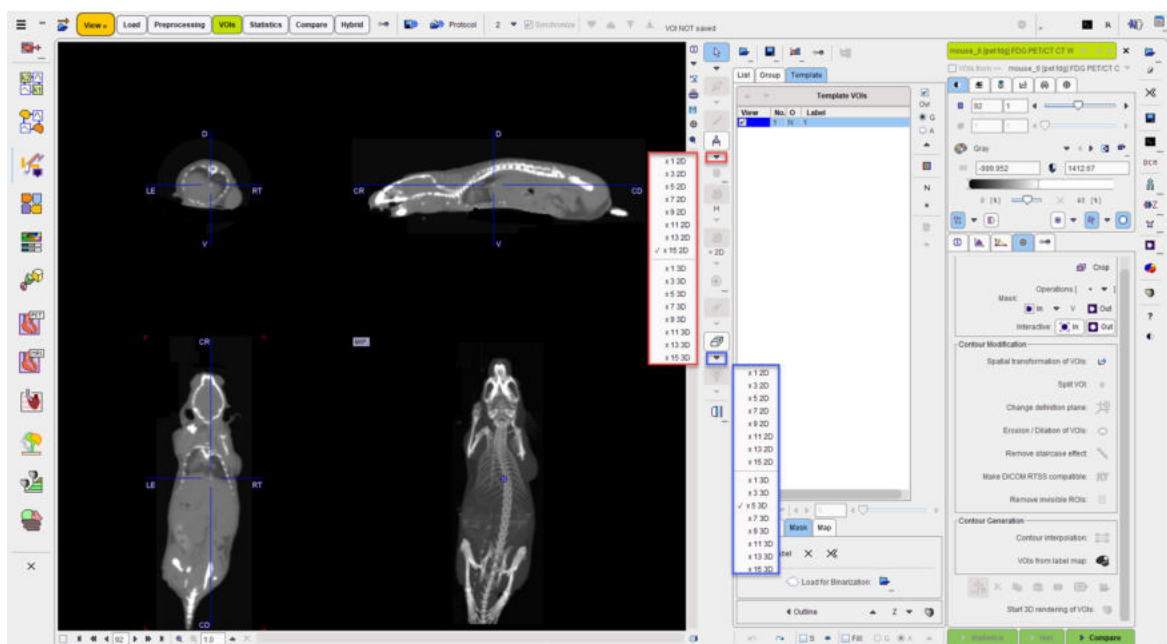
In order to visually observe how the raster VOI is created using the **3D Paint brush** tool please configure e.g a 2x3 display layout as illustrated below. The display layout can be configured according to the needs.
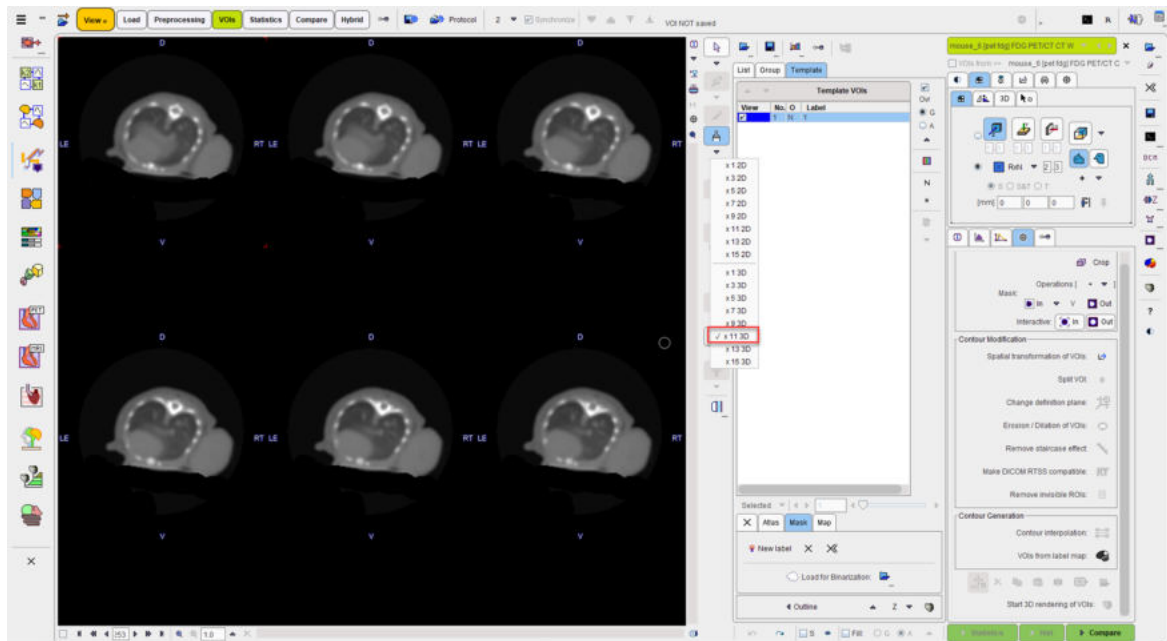
The raster VOIs is outlined only in the upper left corner, on the first slice. However, the outline progression is visible simultaneously on the subsequent slices:
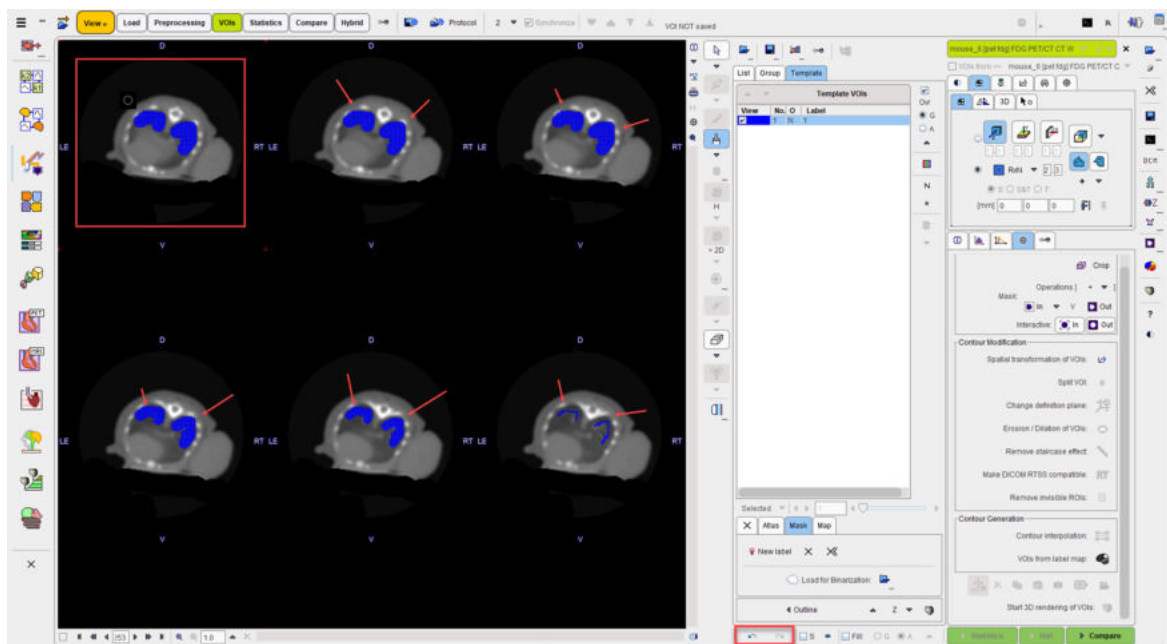
Note that **Undo/Redo** is active and can be used in the process of the outlining.

Similarly, use the **3D Eraser** tool to adjust the selected raster VOI in the list. Please note that the eraser tool can be applied on multiple selection on the **Template VOIs** list. Use the SHIFT or CTRL key on the keyboard together with the left mouse button clicks for multiple selection. Make sure you click into the **No** field or into the **O** filed for selection. Only the highlighted entries in the list will be modified by the eraser.

Activate the **New label** button to add a new empty raster VOI to the existing **Template VOIs** list. Proceed with the outlining as explained above.

10.2.6.3 Raster VOIs Statistics

Raster VOI Statistics

Statistics may be calculated for the selected raster VOIs. If contour VOIs are available on the VOIs list, the statistics will be calculated and displayed in the same interface.

The illustration below shows the selection of five out of ten labels in the **Templates VOIs** while there are two contour VOIs available on the VOIs **List:**
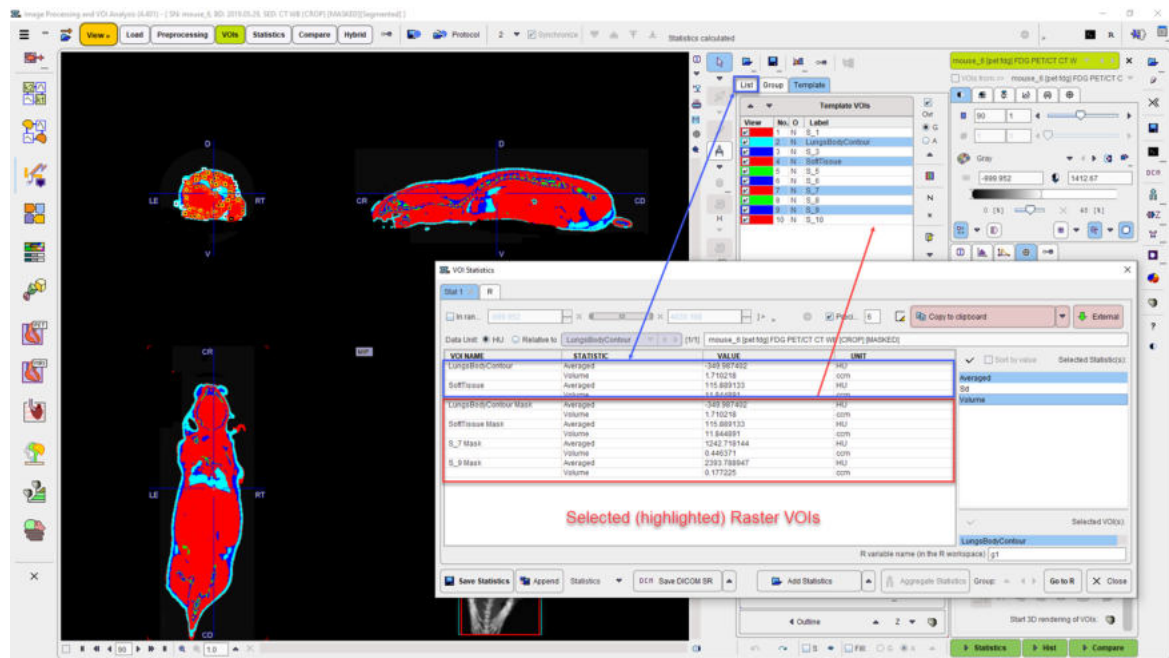

Use the **Save statics** button in this dialog window to save the selected statistics measures.

10.2.6.4 Save/Load of the Raster VOIs

Once a set of raster VOIs has been defined for an image study the definition can be saved using one of the dedicated **Save raster VOI** option:
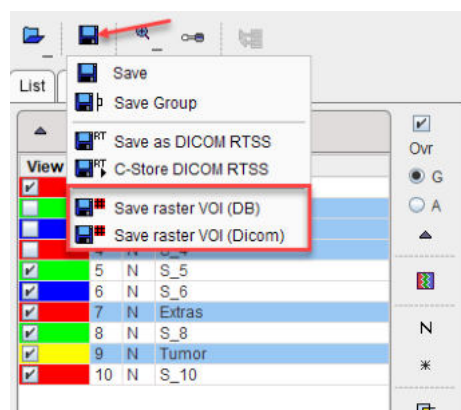
A dialog window will open with the default modality set to SEG [Segmentation]. Keep this setting to be able to save the definitions as a raster VOI file. The capture below illustrates the **Save raster VOI (DB)** dialog:
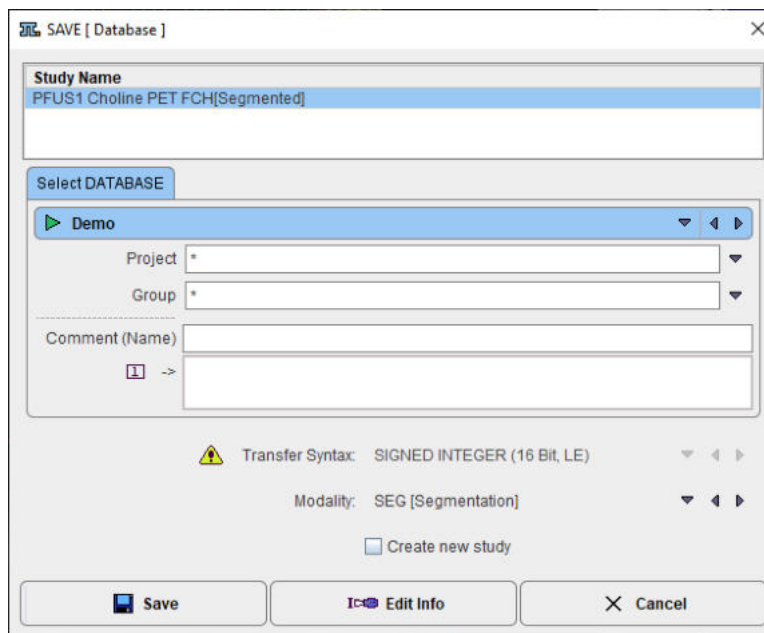
Close the dialog with the **Save** button to finalized the saving procedure. All the raster VOIs available in the Template VOIs list will be saved as a Dicom segmentation object in the database (**DB**) or on the file system (**Dicom**).

Note: All the changes done to the raster VOIs before saving (editing, label or color changing), will be stored in the saved Dicom segmentation object.

Conversely, raster VOIs definitions can be loaded using one of the **Load raster** options: **DB** or **DICOM**.
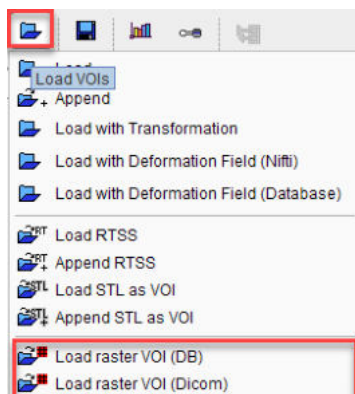
10.2.7   VOI Sorting

Once the VOIs have been defined, they can be ordered according to different criteria, such as size, MTV, SUVmean, SUVpeak, SUVmax. In this way, particularly for oncologic applications, the most relevant lesions are easily brought to the top of the list for further evaluation and documentation.
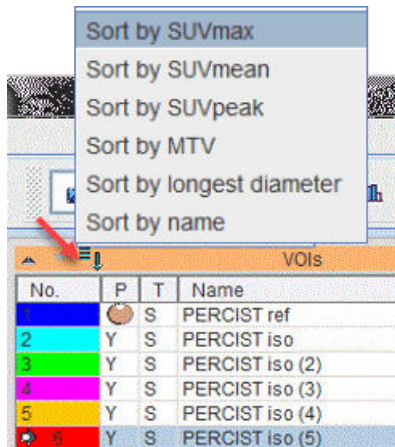
In contrast to RECIST, which employs the largest diameter in the measurement plane to quantify lesion size, PMOD supports the longest oblique diameter in three dimensional space.

10.2.8 VOI Grouping

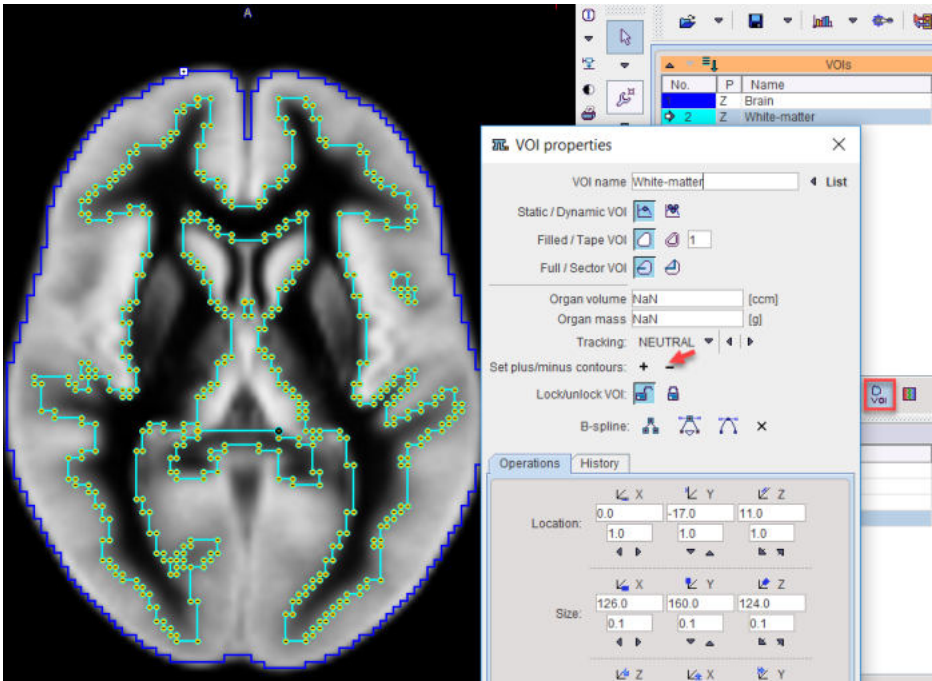The **Group** tab shows a list of all **List** VOIs with a selection box.
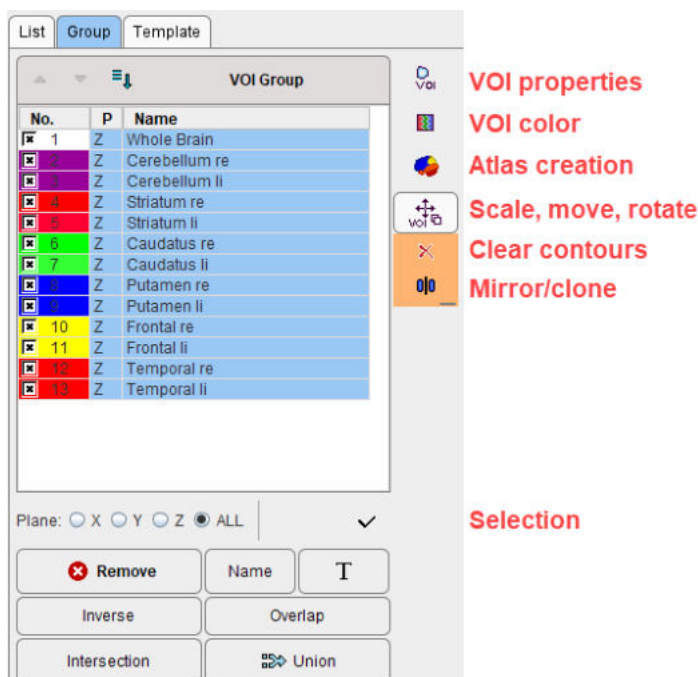
Initially, all VOIs are selected. The selection can be changed by dragging over the selection boxes and using `CTRL+Click` to selectively enable/disable VOIs. Additonally, `CTRL+A`, selects all entries, and the **Inverse** button reverts the selection. The **In plane** radio buttons restrict the selection to the VOIs defined in the plane selected.

Operations on Selection

In general, if the **Group** panel is selected, operations (e.g. erosion, scaling, translations etc) are applied to all selected VOIs, if possible. Some operation buttons are arranged to the right of the list and correspond to the VOI Toolbar, others are located below.

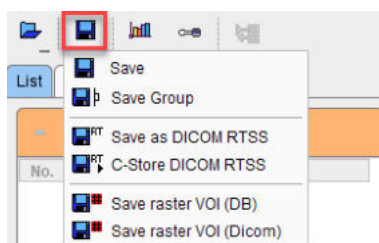|	
VOI	Changing properties to a common value.

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	Changing to a common.
	Create an atlas from the selected VOIs.
	Scale, move and rotate the selected VOIs interactively in all directions.
	Clear all contours of the selected VOIs, leaving empty VOIs.
Remove	Remove the selected VOIs entirely.
Name	Names the selected VOIs with the provided string, adding a running number.
T	Set a name from a predefined name list, as described for the VOI Toolbar 269.
Inverse	Shortcut to invert the list selection.
Overlap	Creates a new VOI consisting of all pixels which are included in at least two of the selected VOIs .
Intersection	Creates a new VOI consisting of all pixels which are common to all the selected VOIs.
Union	Combines the contours of all selected VOIs, whereby the **+/-** property 224 of the contours is maintained. A common application is to create a VOI with a hollow space. The example below illustrates the situation, that iso-contoring was used to create a brain VOI and a white-matter VOI. The latter is converted to "minus" contours with the **-** button in the VOI Level Properties 218. The **Union** of the two VOIs results in the difference VOI shown below.
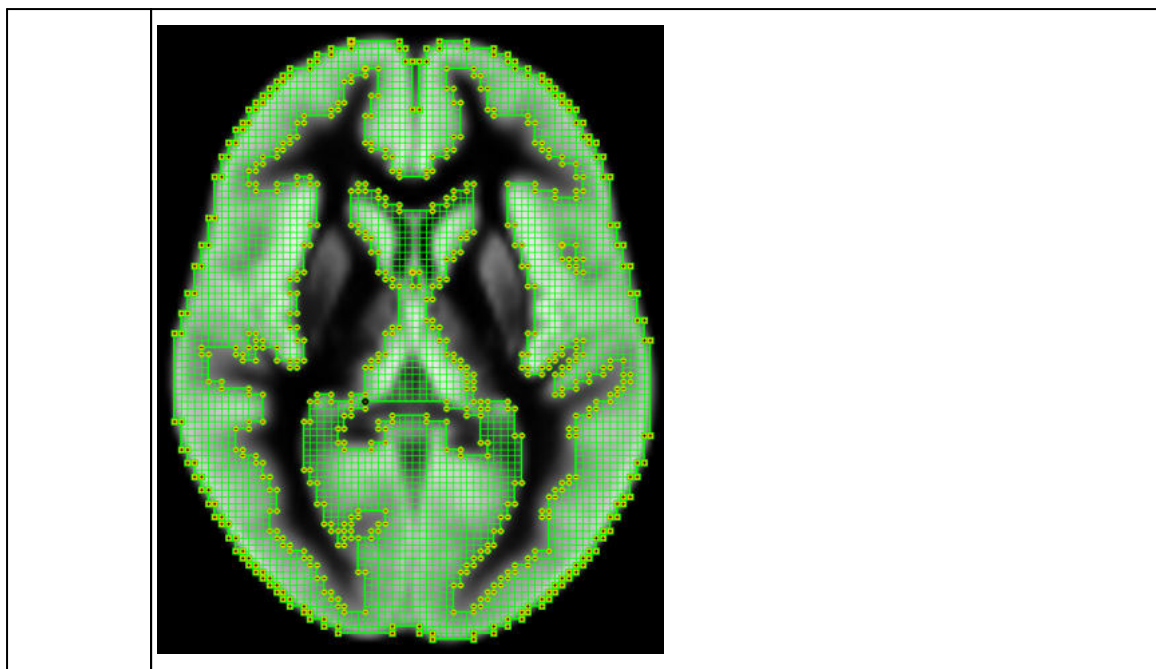
10.2.9   VOI Save/Load

Saving

Once a set of contour VOIs has been defined for an image study the VOI definition can be saved using one of the **Save** option buttons
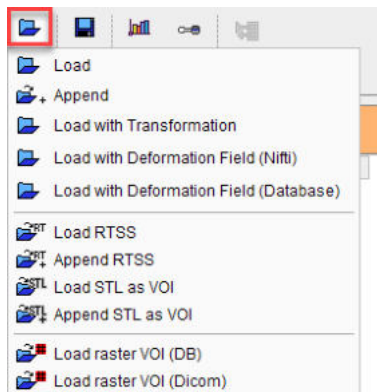

The buttons have the following function

Save	Saves all of the VOIs together with their names and color in a .voi file.
Save Group	Saves only those VOIs which are checked on the **Group** tab in a .voi file.
Save as DICOM RTSS	Saves all VOIs as DICOM structure set objects in a file. Such DICOM structure set objects can be used in image workstations and radiotherapy (RT) planning systems. As the PMOD VOI tools allow constructing VOIs which are more complex than supported by DICOM RT structure set (RTSS) definition, a dialog window asks whether a conversion should be applied

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C-Store DICOM RTSS	This function also creates DICOM structure set objects, but allows to directly send them to an image workstation or an RT planning system using the DICOM network protocol. A dialog box pops up for selecting the target system among the configured DICOM nodes.
Save raster VOI (DB)/ (Dicom)	Saves all raster VOIs from the **Template/Mask** tab as a Dicom segmentation object in the database (**DB**) or on the file system (**Dicom**).

Loading

Conversely, contour VOI definitions can be retrieved from files using the **Load** option buttons

The buttons have the following function

|	
Load	First removes all current VOI definitions and then loads the ones from the selected VOI files.
Append	Loads the VOIs from the selected file and appends them to the current VOI definitions.
Load with Transformation	First removes all current VOI definitions, loads the ones from the selected VOI files, and requests a spatial transformation which is applied to the VOIs. All transformations calculated in the PMOD Image Fusion tool are supported, rigid and elastic ones.
Load with Deformation field (Nifti) / (Database)	First removes all current VOI definitions, loads the one from the selected VOI files, and requests a deformation field. the deformation field refers to a probability matching which returns a transformation in form of an image, which can be read from the file system (**Nifti**), or from a PMOD **Database**.
Load RTSS	First removes all current VOI definitions and then loads the VOIs from a file containing DICOM RT structure set objects.
Append RTSS	Loads the VOIs from a file containing DICOM RT structure set objects and appends them to the current VOI definitions.
Load STL as VOI	Loads the STL file and it converts it to VOI contour. The result consist of single VOI file from each selected STL file. Please note there is no information in the STL file about the VOI coordinates. Use the VOI action to place the VOI on the image
Append STL as VOI	Loads the STL, it converts it to VOI contour and appends it to the current VOI definition.

| **Load raster VOI (DB)/ (Dicom)**	First removes all current raster VOI definition from the **Template/Mask** tab and then loads the raster VOIs (DICOM segmentation object) selected from the PMOD database (**DB**) or from the file system (**Dicom**)

10.2.10 3D VOI Visualization

If the P3D option is installed on the system the **Start 3D rendering of VOIs** button is available at the bottom of the VOI tools.
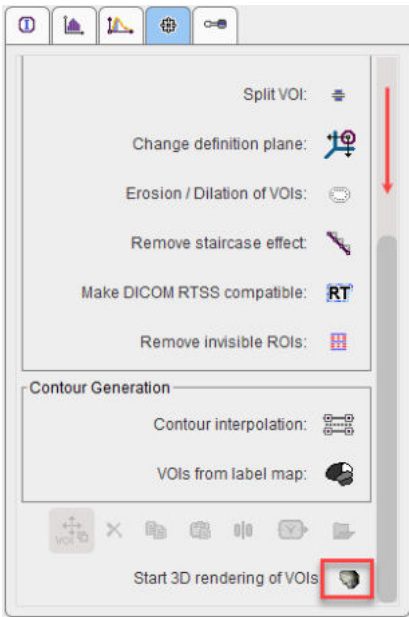
When it is activated, the contours can be rendered as ribbons with a width of the slice thickness, or as full surfaces. The example shown below is a rendering of the VOIs derived from outlining the AAL template.
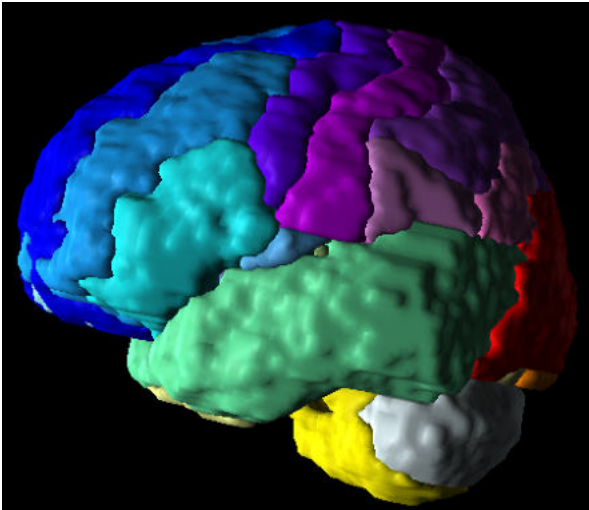
In the 3D tool, the VOIs are organized in a tree
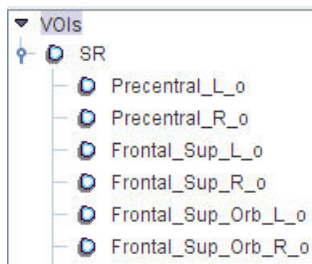
so that each structure can individually be shown, hidden and colored. This might be helpful for interactive demonstration purposes to visualize the spatial relationship of the structures.

When the 3D icon from the lateral task bar is activated, the VOIs together with the images are sent to the P3D interface. The simple 3D visualization does not require licensing the P3D module.

10.3 Using VOI Atlas Files

A VOI atlas is an image file which contains numeric label information for the different anatomic structures as the image information. This VOI information can be loaded into PMOD and used for statistics. The atlas VOI approach has the advantage that the structures can be arbitrarily complex, and that the results of external segmentation programs can easily be used within PMOD. The disadvantage is that the VOI definition cannot be modified. However, in PMOD it is simple to convert atlas VOIs into contour VOIs.

Brain atlas images are representative images of the (human, rat, etc.) brain imaged with a certain modality (PET, SPECT, T1 MR, T2 MR, etc.) showing a normal brain. Usually, the images of many normal subjects are brought into alignment and are then averaged. This results in somewhat blurry template images which show the characteristic pattern of the brain in the particular modality. The template images are used as a basis for the standard analysis of individual images. First, the images are spatially normalized (elastic warping) to the template, and then a set of standard VOIs is applied to the normalized images to obtain regional statistics. Typically, the VOIs in the atlas space are universally applicable, ulike contour VOIs which are program-specific.

The PMOD software includes several human, primate, pig, rat, and mouse atlases with corresponding normalization templates. For using the atlas VOIs a user should first spatially normalize the individual brain images using the corresponding normalization template.

10.3.1 Structure of VOI Atlases in PMOD

A VOI atlas in PMOD consists of the following components:

1. *Atlas image:* Image which encodes the atlas VOIs in a stereotactic space as numeric labels. Human atlases are defined in the MNI space (Montreal Neurological Institute).

2. *Label list:* Text file mapping the label values to the VOI names shown in the user interface.

3. *Manifest:* Text file for the defining the properties of the atlas.

4. *Normalization templates* for calculating the transformation between the subject anatomy and atlas anatomy.

The atlas information has to be organized in a sub-directory of *resources/templates/voitemplates* exactly as illustrated below for the **AAL-Merged** atlas.
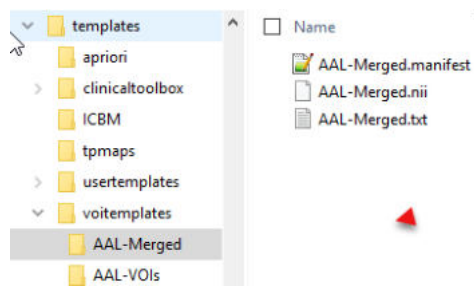
The atlas name (e.g. **AAL-Merged**) has to be used as the sub-directory name, the atlas image name (**AAL-Merged.nii**), the label list name (**AAL-Merged.txt**), and the manifest name (**AAL-Merged.manifest**). If the atlas is not a human atlas in the MNI space, it needs to include an additional *normalization* folder for the templates as described below.

By conforming to this structure it is possible for users to prepare their own VOI atlases. In PNEURO, all atlases can be used for the **Maximum Probability Atlas** approach, whereas the **Brain Parcellation** approach only supports human atlases in the MNI space.

Atlas Image

The atlas image must be prepared as a NifTI file and encode the atlas VOIs as numeric labels. Each pixel has a value of 0 if it is a background pixel, or otherwise an integer number. We recommend using the HFS anatomical orientation (head first, supine = radiological convention) for human data.

Label List File

The label list text file has the minimal form:
```
name1    outlined_name1    label_value1
name2    outlined_name2    label_value2
```
where each VOI is represented by a line.

The list can be extended with additional information for the VOI presentation as illustrated below for the **AAL-Merged.txt**. The first column starts with the name followed by a bracket construction which encodes a tree structure. For instance, **Precentral** belongs to the **Frontal_lobe** which is located in the left **Left** or right **Right_hemisphere** of the **Cerebral_cortex**. The second column indicates the name of a generated contour VOI. The third column contains the label value in the atlas file. Each pixel in **AAL-Merged.nii** with value 1 will belongs to the **Precentral_l** VOI, pixels with value **2** to **Precentral_r**, etc. The fourth column specifies the RGB color values for showing the VOI, and the last column the text to be shown as a tooltip.

Name	Outlined	Label	Color	Tooltip
Precentral[Frontal_lobe[Left_hemisphere[Cerebral_cortex]]]	Precentral_l	1	(100,0,255)	Precentral gyrus left (PRE)
Precentral[Frontal_lobe[Right_hemisphere[Cerebral_cortex]]]	Precentral_r	2	(100,0,255)	Precentral gyrus right (PRE)
Rolandic_Oper[Frontal_lobe[Left_hemisphere[Cerebral_cortex]]]	Rolandic_Oper_l	3	(93, 188, 255)	Rolandic operculum left (RO)
Rolandic_Oper[Frontal_lobe[Right_hemisphere[Cerebral_cortex]]]	Rolandic_Oper_r	4	(93, 188, 255)	Rolandic operculum right (RO)
Supp_Motor_Area[Frontal_lobe[Left_hemisphere[Cerebral_cortex]]]	Supp_Motor_Area_l	5	(0,114,255)	Supplementary motor area left (SMA)
Supp_Motor_Area[Frontal_lobe[Right_hemisphere[Cerebral_cortex]]]	Supp_Motor_Area_r	6	(0,114,255)	Supplementary motor area right (SMA)
Olfactory[Frontal_lobe[Left_hemisphere[Cerebral_cortex]]]	Olfactory_l	7	(100, 100, 255)	Olfactory cortex left (OC)
Olfactory[Frontal_lobe[Right_hemisphere[Cerebral_cortex]]]	Olfactory_r	8	(100, 100, 255)	Olfactory cortex right (OC)
Frontal_Sup[Frontal_lobe[Left_hemisphere[Cerebral_cortex]]]	Frontal_Sup_l	11	(0,0,255)	Superior frontal gyrus left (F1, F1O, F1M)
Frontal_Sup[Frontal_lobe[Right_hemisphere[Cerebral_cortex]]]	Frontal_Sup_r	12	(0,0,255)	Superior frontal gyrus right (F1, F1O, F1M)

Note: For all rows, all columns need to be filled. Spaces in the **Name** field are not allowed.

The corresponding atlas VOI structure is illustrated below.
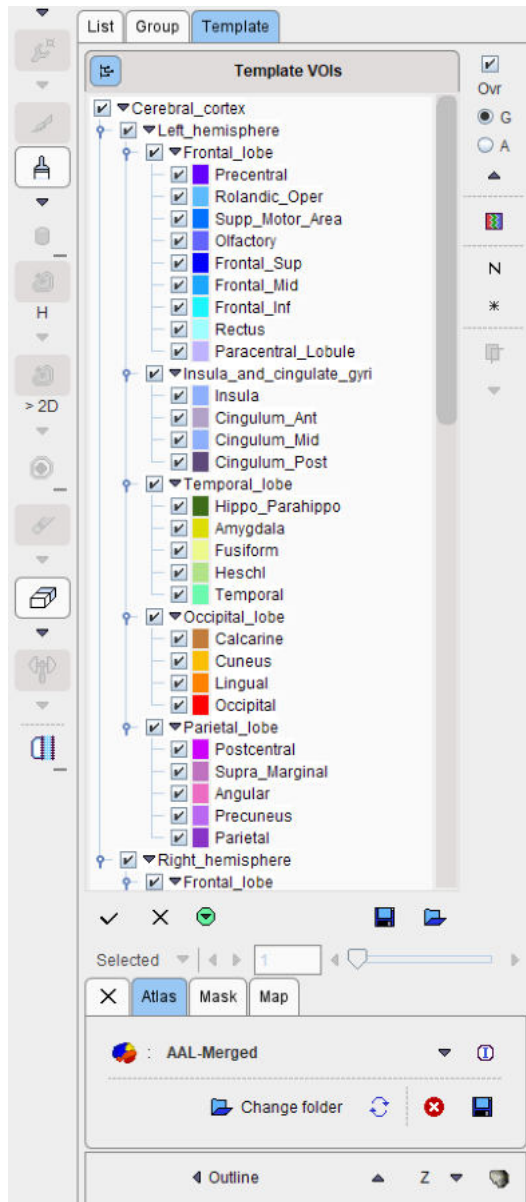
There are additional options to be added to the columns for use in PNEURO:

- **E**: Excluded from masking by the grey matter threshold.
- **O**: Indicates that the VOI is not brain matter.
- **H**: Indicates that the VOI should initially be hidden, i.e. not selected on the **Group** panel.
- **L**, **R**: Indicates that the VOI belongs to the left (L) or right (R) hemisphere. This information is used in sulci deformation.
- **C**: Indicates that the VOI belongs to the cerebellum. This information is also used in sulci deformation.

Example as shown in Excel:

S_nigra[Central_structures[L]]	S_nigra_l	74	(127,127,1	Substantia	E		
S_nigra[Central_structures[R]]	S_nigra_r	75	(127,127,1	Substantia	E		
Insula[Insula_and_cingulate_gyri[L]]	Insula_l	20	(143,175,2	Insula left	L		
Insula[Insula_and_cingulate_gyri[R]]	Insula_r	21	(143,175,2	Insula righ	R		
Cerebellum[Posterior_fossa[R]]	Cerebellum_r	17	(250,239,5	Cerebellun	C		
Cerebellum[Posterior_fossa[L]]	Cerebellum_l	18	(250,239,5	Cerebellun	C		
Brainstem[Posterior_fossa]	Brainstem	19	(151,72,6)	Brainstem	C	E	
FrontalHorn[Ventricles[R]]	FrontalHorn_r	45	(219,238,2	Lateral ver	E	O	H
FrontalHorn[Ventricles[L]]	FrontalHorn_l	46	(219,238,2	Lateral ver	E	O	H
TemporaHorn[Ventricles[R]]	TemporaHorn_r	47	(183,221,2	Lateral ver	E	O	H
TemporaHorn[Ventricles[L]]	TemporaHorn_l	48	(183,221,2	Lateral ver	E	O	H
ThirdVentricl[Ventricles]	ThirdVentricl	49	(146,205,2	Third ventr	E	O	H

Manifest File

The following entries are supported in the manifest text file describing the atlas:

`SPECIES = HUMAN`	The supported species include HUMAN, PRIMATE, PIG, RAT, MOUSE
`SPACE = MNI`	Only the MNI (Montreal Neurological Institute) space for humans is supported. If this line is present, a common set of template files with 2x2x2mm resolution is used.
`APPLICATION = NO_PNEURO`	If this line is present, the atlas is not listed in PNEURO.
`TYPE = PROBABILISTIC , RANGE 0 / 100`	The range specified for the data will be scaled to a probability value in the range [0,1]

Spatial Normalization Methods

Atlases can only be applied to images if they have the same resolution and show the anatomy with the same geometry. Therefore, images originating from real experiments first need a normalization step for the atlas to be applied. This is done by calculating a normalization transform between the subject image and a "template" image representing the standard anatomy imaged with a certain modality, and using it for warping the VOIs to the subject anatomy.

Name of method in PMOD	Methodology and template
Template-based normalization	Implementation of the spatial normalization in SPM5. It requires a template image in the atlas space which has a similar pattern as the image to normalize. The usual reference images are the PET, T1 and T2 SPM5 templates. The appropriate template has to be selected by the user.
3 Probability maps normalization	Implementation of the unified segmentation normalization in SPM8. It requires tissue probability maps of grey matter, white matter and CSF in the atlas space, which is organized in a dynamic file called **tpm.nii**. This normalization is mostly applicable to T_1-weighted MR images.
6 Probability maps normalization	Implementation of the unified segmentation normalization in SPM12. It uses three additional probability maps (bone, tissue and air), which are organized in a dynamic file **tpm_6.nii**. This normalization is mostly applicable to T_1-weighted MR images.

Template Files for Template-based Normalization

For atlases of the human brain anatomy which are defined in the 2x2x2mm MNI space and which have the entry `SPACE = MNI` defined in the manifest file, a common set of template files for the **Template-based normalization** is available in the *resources/templates* folder.
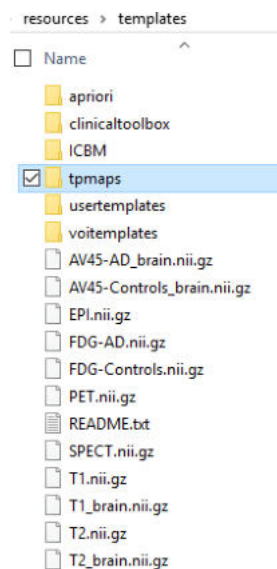

For atlases in other spaces than MNI corresponding normalization templates have to be included in a *normalization* sub-folder. As an example, for the **Mouse (Ma-Benveniste-Mirrione)** atlas illustrated below an FDG and a T2 MRI template are available.
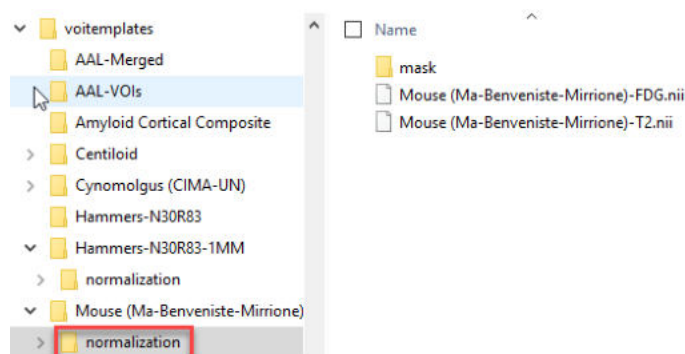
Normalization works best if the information is restricted to the relevant image part. Therefore, *normalization* should contain a *mask* sub-folder with a mask file **mask.nii** containing 1 for all relevant pixels and 0 for all others.

Resource Files for Probability Normalization Methods

Again, for a human atlas defined in the MNI space the tissue probability maps are already available in the *templates/tpmaps* directory.
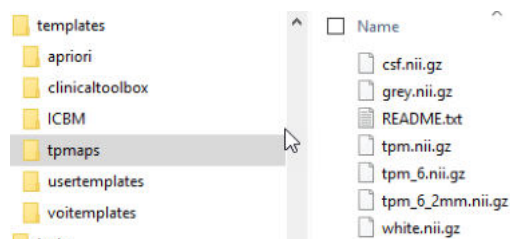
To use the methodology for other than MNI atlases, a *normalization/tpm* sub-directory has to be added to the atlas directory with the corresponding tissue probability maps. An example can be found in the **Pig (CH.Malbert)** atlas folder as illustrated below.
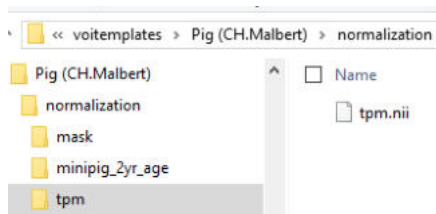
10.3.2 Tree Organization of Atlas VOIs

Atlas VOIs are structurally organized in a tree. The selection of a VOI subset is supported by a dedicated user interface illustrated below. It appears on the **Template** panel when selecting an atlas, and on the **Group** panel after the atlas VOIs have been converted to contour VOIs.
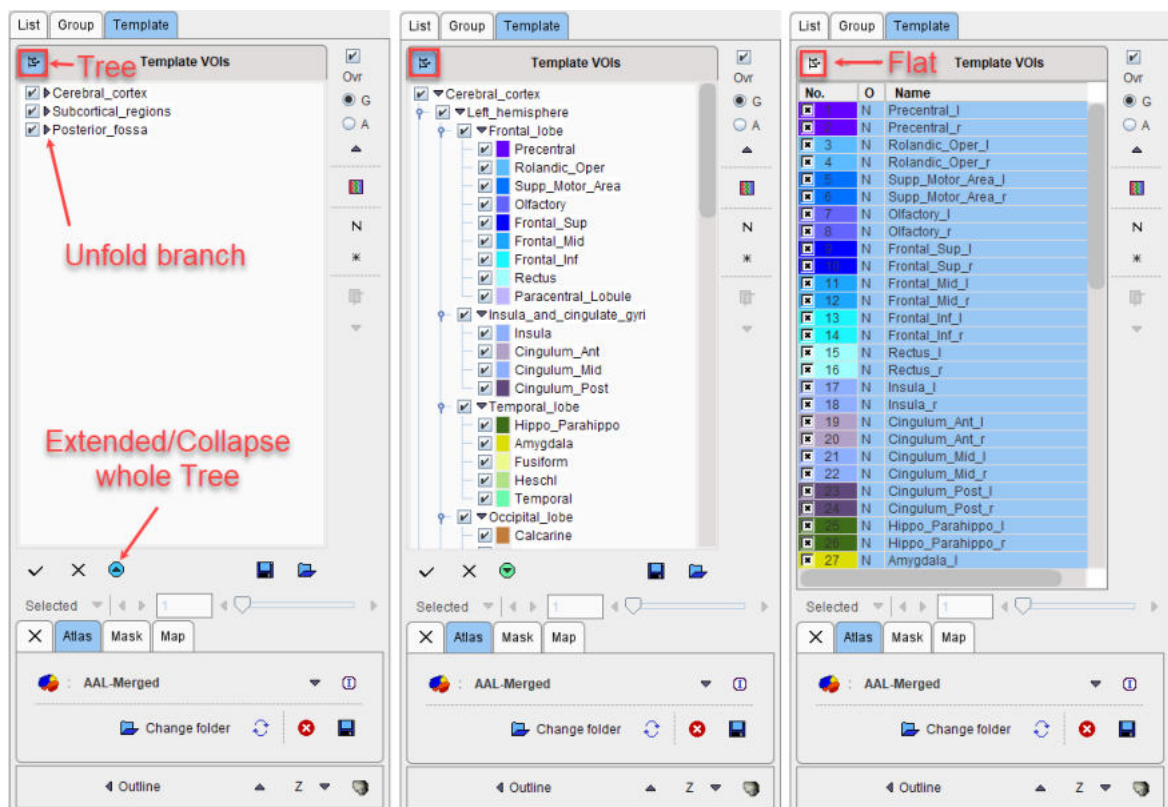
The branches on the top level in the example above are the **Cerebral_cortex**, **Subcortical_regions**, and the **Posterior_fossas** as illustrated in the left panel above. The full tree can be opened easily by the button indicated below the tree area. The tree view can be flattened to a simple list by the button at the top indicated in the right panel. The statistics will only be calculated for the selected VOIs.

Tree Manipulations

Branches in the tree can be opened/closed with the little arrows left to the branch names.
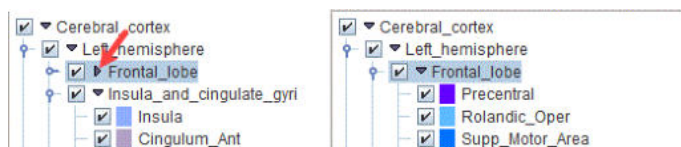
Tree Selections

The structures of interest are the ones with checked boxes to the left of their color code. Simply click into a box for changing the selection. In the example below the **Precentral** VOI has been de-selected.
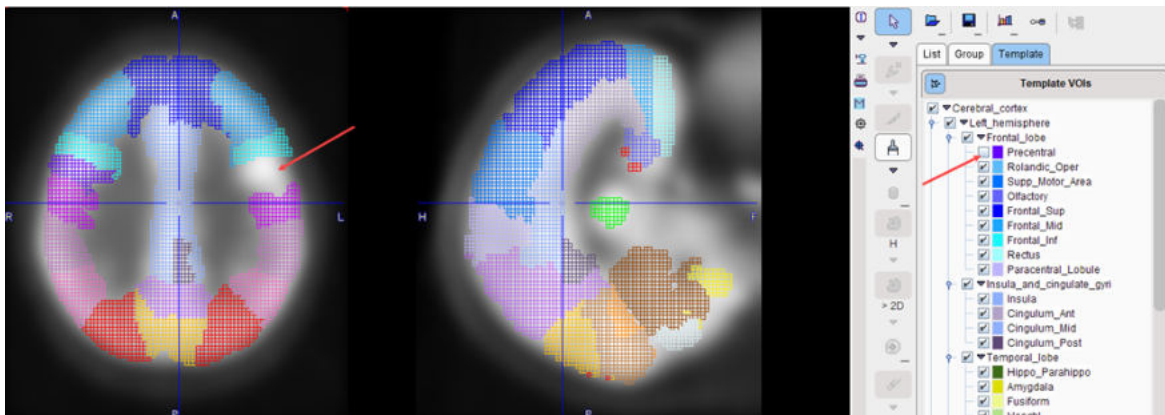
If the selection of a branch is removed, all VOIs belonging to it will be de-selected.
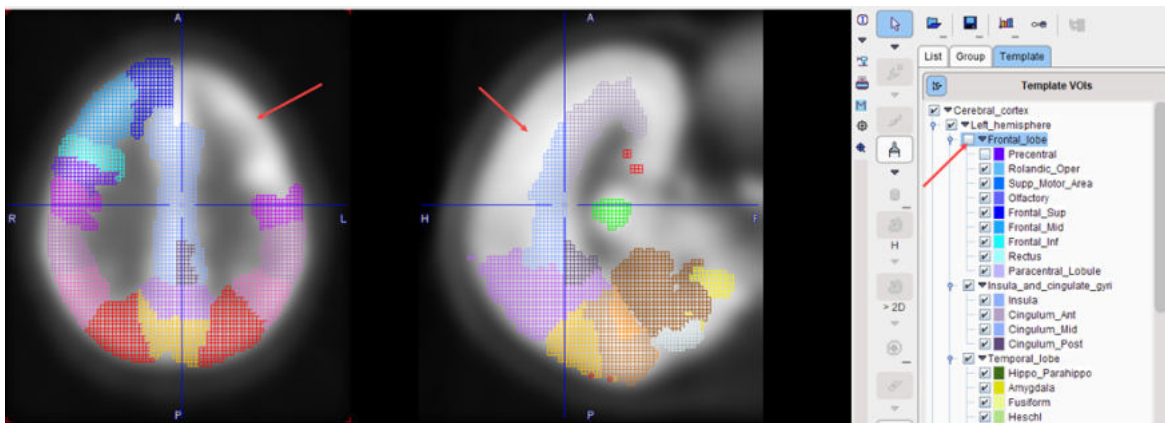
10.3.3 Atlas-based VOI Statistics

When an (presumably spatially normalized) image series has been loaded for which a suitable atlas exists, its use for VOI statistics is straightforward. First activate the VOI functionality, select the **Template** tab, and chose the atlas in the list on the **Atlas** pane.
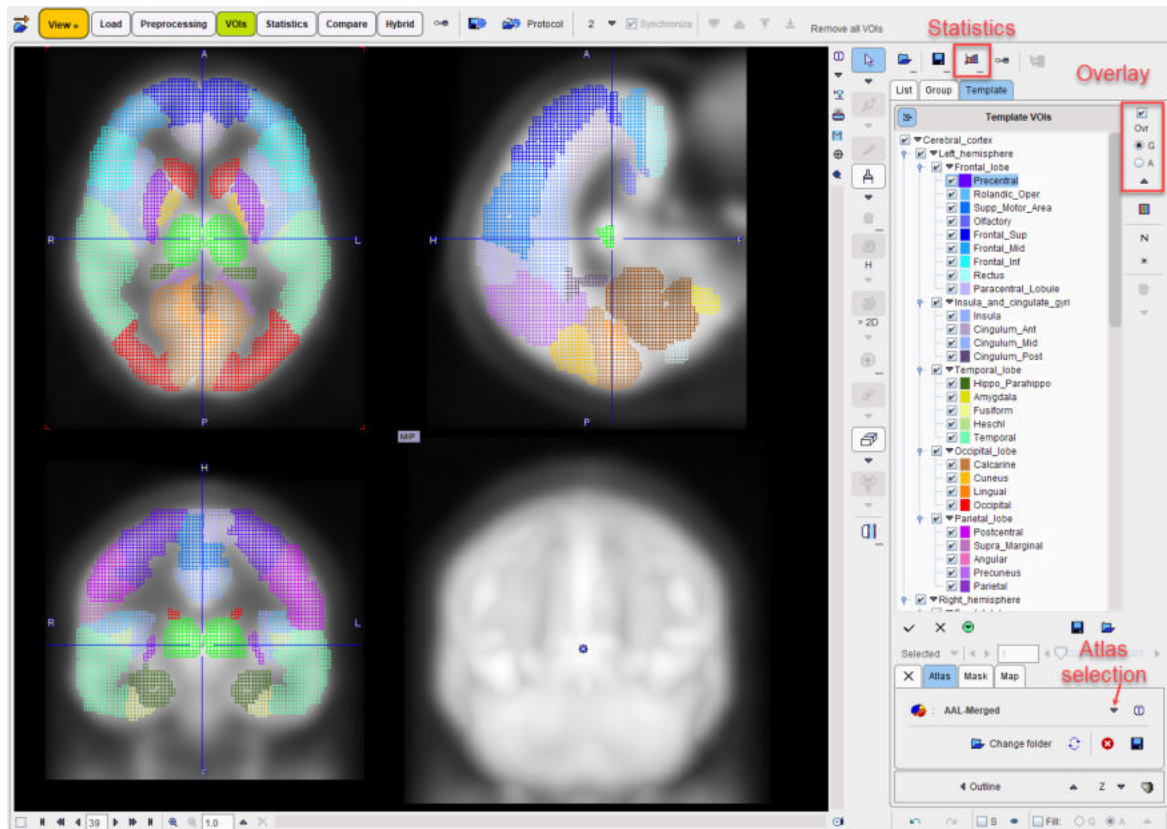
The atlas description is read and the list of VOI labels populated. Initially, all regions are selected, and an overlay on the images marks their locations. The overlay can either show an open or a filled pixel raster, depending on the setting of the radio box below the **Ovr** check. To hide all template VOIs at once please un-check the **Ovr**. To stop using the template VOIs select the **X** tab left to **Atlas**.

VOI Selection

Only the selected atlas regions are shown as VOIs and used for statistics calculations. The usual operations can be applied to select or de-select entries in the VOI list.

- `CTRL+A`: Select all entries.

- `CTRL+Click`: Check or un-check an entry without changing the others.

- `SHIFT+Click`: Select the range until the clicked entry.

VOI templates can co-exist with the standard VOI contours.
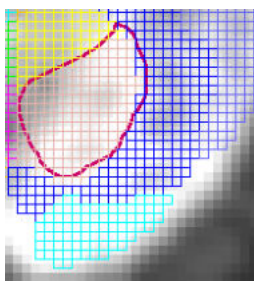
To modify the contour VOIs, select the **List** tab and use all of the functionality described for the contour VOIs sections above. Statistics [323] calculates the statistics of all contour VOIs and the selected atlas VOIs.

Using Atlas VOIs as Masks

In addition to using template VOIs for statistics, they can also be applied for masking contour VOIs. Illustrated below are a contour VOI from the **List** tab and a selected VOI from the **Template** tab which overlap.
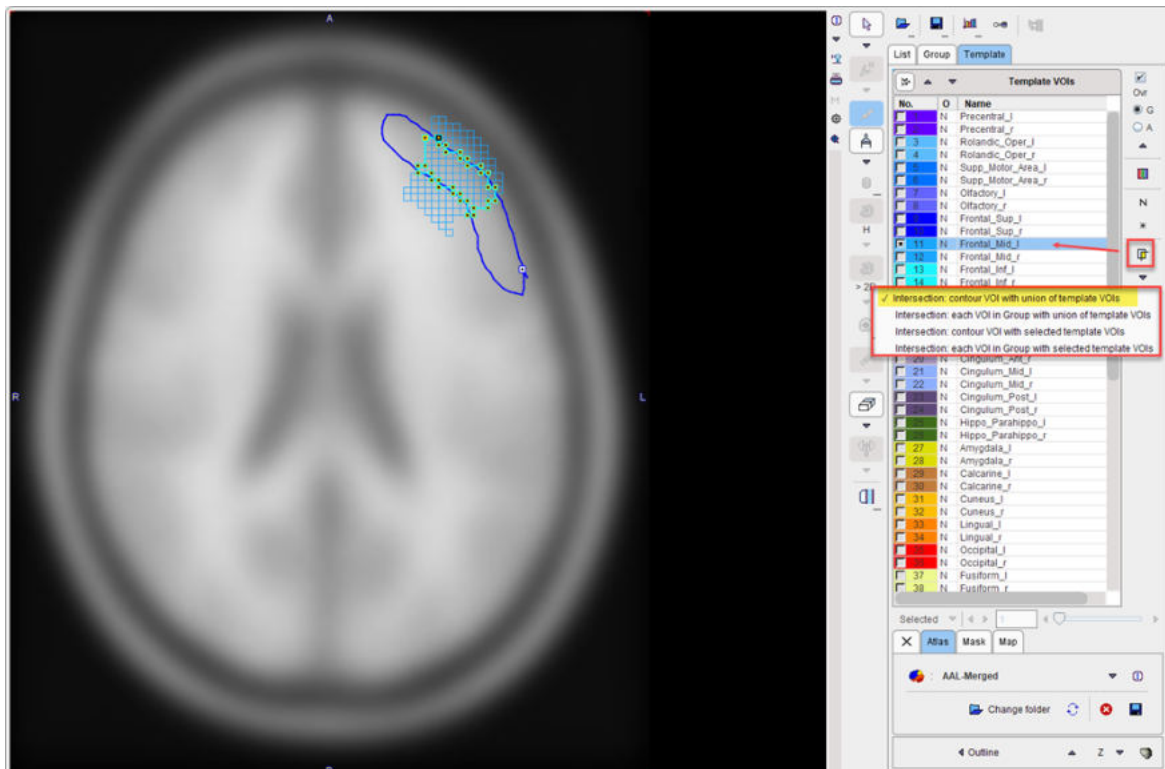
If the operation mode is changed to * for **Mask** operation by the indicated button, the atlas VOI acts as a mask for the contour VOI and a corresponding contour VOI is created.

10.3.4   Converting Atlas VOIs to Contour VOIs using Outline

Unlike contour VOIs, atlas VOIs cannot be adjusted. Therefore, a mechanism has been implemented in the PMOD VOI tool to convert atlas VOIs into contour VOIs. The procedure is very simple:

1. Load an image with the geometry of the atlas space.

2. Select the atlas VOIs for which contours should be generated (Template/Atlas/AAL-VOIs).

3. Activate the **Outline** button.

4. Save the contour VOIs.

The illustration below shows the example of an image in the MNI space with the AAL atlas selected. The AAL VOIs are organized as a tree structure.
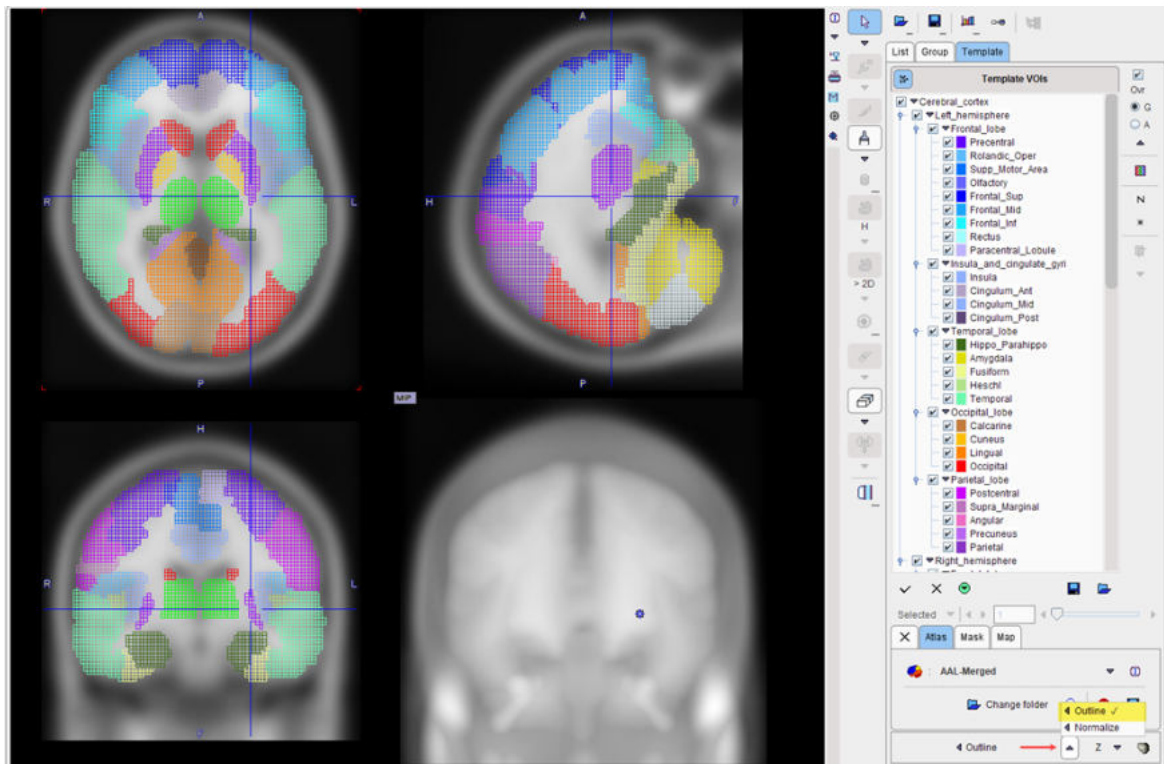
Using **Outline** results in contour outlines which still maintain the tree structure, as can be seen on the **Group** tab.
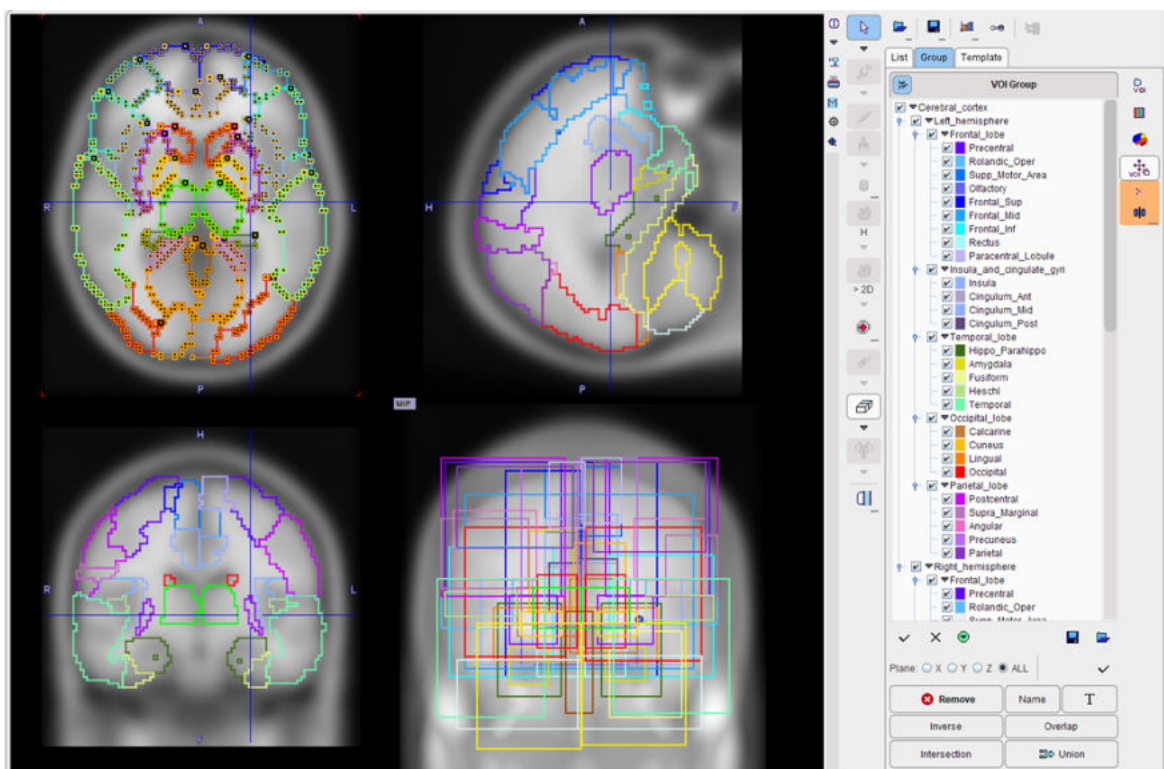
Ththere the task of selecting parts in the tree is supported by shortcuts in the area at the tree bottom:
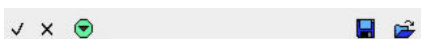
✓	Set the selection check of all VOIs

✕	Remove the selection check of all VOIs.
💾	Save the current selection set to a file.
📂	Load a selection set from a file.

10.3.5 Converting Atlas VOIs to Contour VOIs using Normalize

A mechanism has been implemented in the PMOD VOI tool which allows transforming atlas VOIs into the original subject anatomy. Note, however, that the normalization procedure may fail if there is no template image available with a similar pattern than the target image, and that the resulting VOIs may need adjustment. As the normalization methods originate from the PMOD image fusion tool, please refer to its documentation for the normalization details.

The procedure is as follows:

1. Load the original image of the subject (which is not in the atlas space).

2. Select the atlas on the **Template/Atlas** panel (e.g. AAL-Merged).

3. Activate the **Normalize** button.

4. A dialog window appears to configure the normalization procedure which establishes a transformation between the subject and the atlas anatomy.

5. In the uppermost part of the window the **Normalization Template** can be set according to the image. In case dynamic data are analyzed, an **Average** frame range can be defined to be used for the normalization.

6. The algorithm performs the data normalization using the **Basic** and **Advanced** settings available in the **Normalization Parameters** tab. More information about the settings is available in the **Deformable Registration** section of the PFUSIT documentation. It calculates the inverse transformation which is then applied to the VOI atlas. Optionally, the image background can be added to VOIs if **Add background as VOI** checkbox is enabled.

7. Finally, the transformed VOI atlas is outlined.

The AAL atlas with grid filled overlay looks as follows:
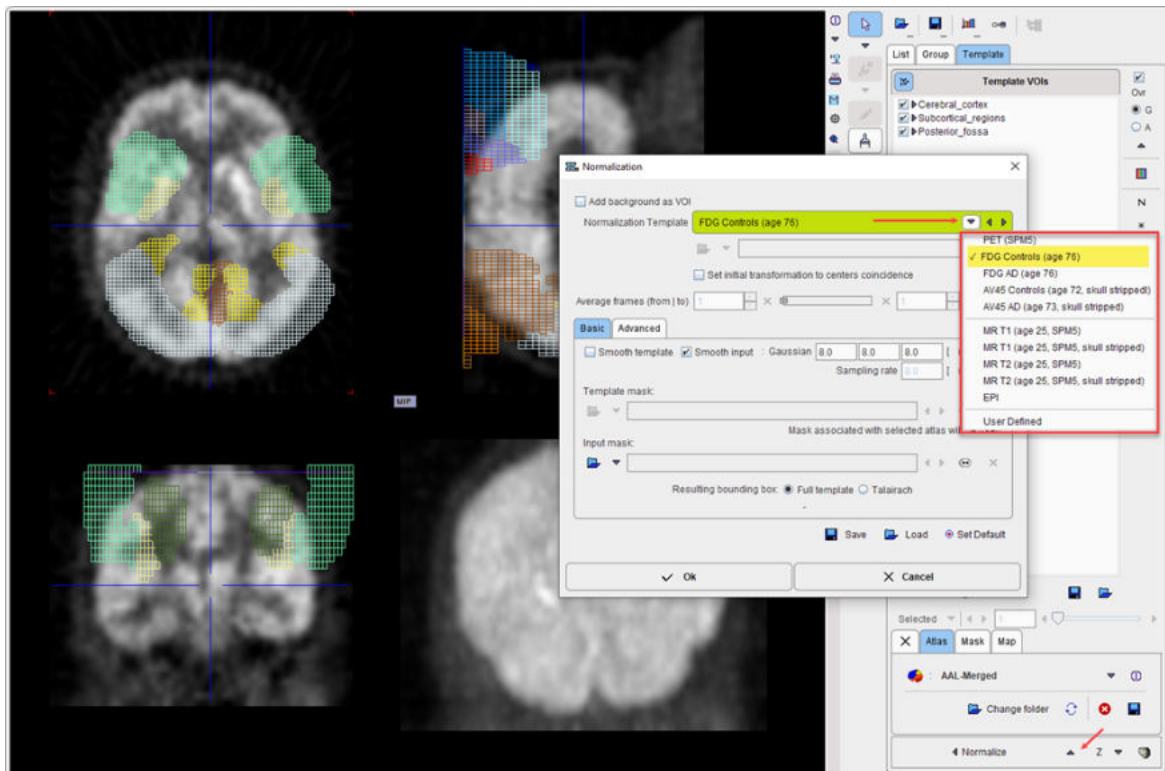
Note the misalignment of the atlas and the image before transformation. As a result, contour VOIs appear on the **List** panel as illustrated below.
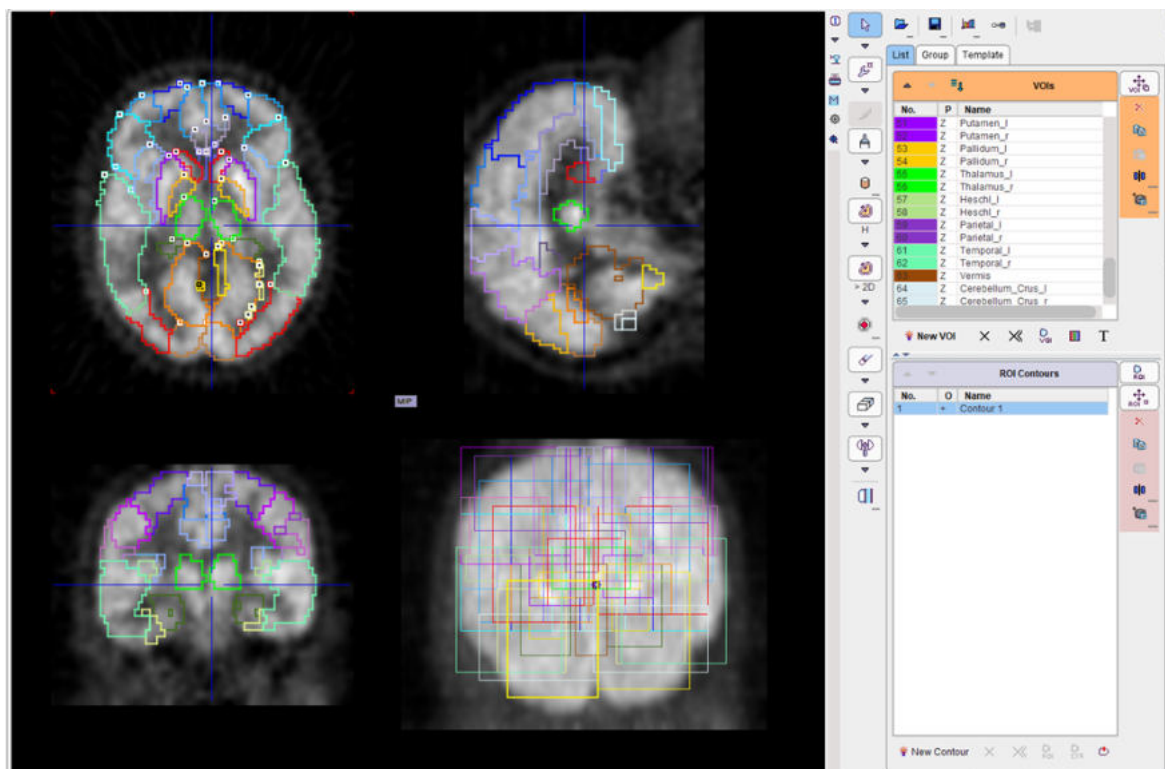
On the **Group** panel the atlas tree structure is maintained, whereas on the **Template** panel the atlas has been switched off
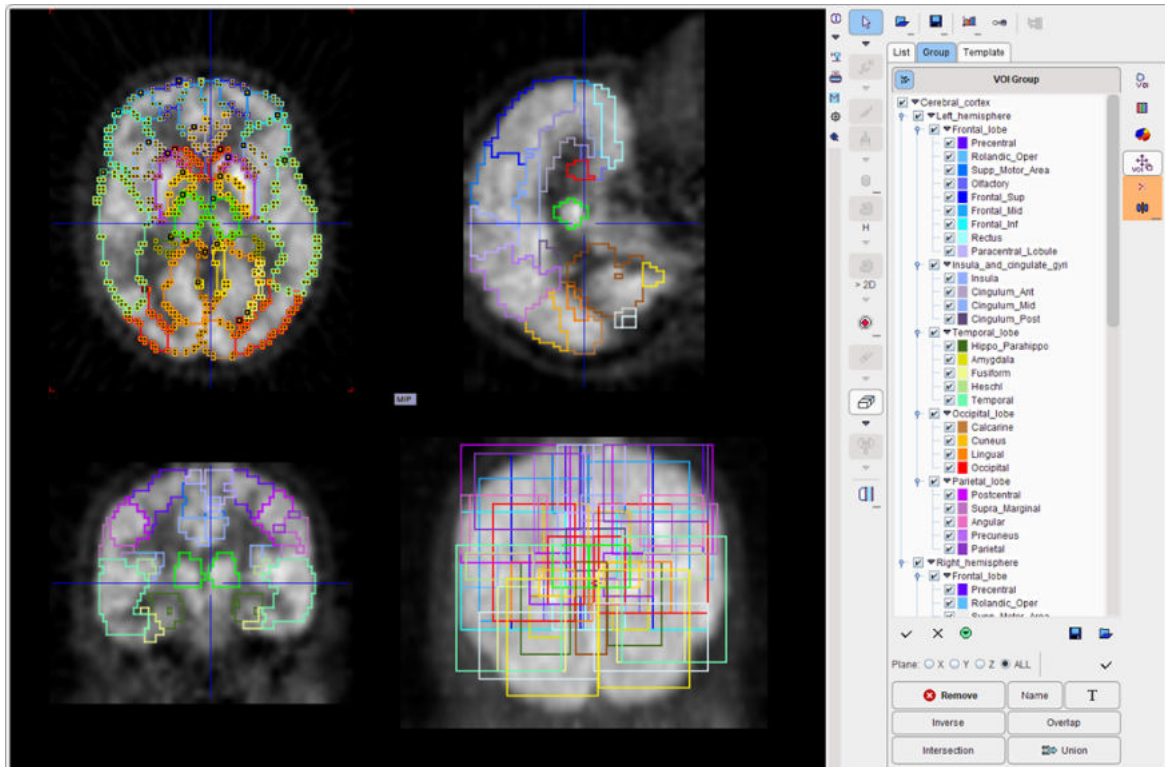
10.3.6   Probabilistic VOI Atlas

Atlas Structure

Regular VOI atlases in PMOD are based on a label image which specifies for each pixel to which VOI it belongs. The situation is different for a probabilistic atlas. There, each pixel has a probability value assigned for belonging to a specific VOI. Therefore, probabilistic atlases require a real-valued image for every VOI in the atlas. In PMOD, the probability images are arranged as frames in a dynamic series. In the label list file the third column therefore corresponds to the frame encoding a VOI's probability, rather than its label number in a static image.

Name	Outlined	Frame	Color	Tooltip
Precentral[Frontal_lobe[L]]	Precentral_l	1	(100,0,255)	Precentral gyrus left (PRE)
Precentral[Frontal_lobe[R]]	Precentral_r	2	(100,0,255)	Precentral gyrus right (PRE)
Rolandic_Oper[Frontal_lobe[L]]	Rolandic_Oper_l	3	(93,188,255)	Rolandic operculum left (RO)
Rolandic_Oper[Frontal_lobe[R]]	Rolandic_Oper_r	4	(93,188,255)	Rolandic operculum right (RO)
Supp_Motor_Area[Frontal_lobe[L]]	Supp_Motor_Are	5	(0,114,255)	Supplementary motor area left (SMA)
Supp_Motor_Area[Frontal_lobe[R]]	Supp_Motor_Are	6	(0,114,255)	Supplementary motor area right (SMA)
Olfactory[Frontal_lobe[L]]	Olfactory_l	7	(100,100,255)	Olfactory cortex left (OC)
Olfactory[Frontal_lobe[R]]	Olfactory_r	8	(100,100,255)	Olfactory cortex right (OC)
Frontal_Sup[Frontal_lobe[L]]	Frontal_Sup_l	11	(0,0,255)	Superior frontal gyrus left (F1, F1O, F1M)
Frontal_Sup[Frontal_lobe[R]]	Frontal_Sup_r	12	(0,0,255)	Superior frontal gyrus right (F1, F1O, F1M)

Note: Probabilistic atlases can only be applied to already normalized images. The normalization functionality is not supported.

Statistics

When applying a probabilistic atlas for statistics, calculation takes the probabilities into account as describe for the different **measures**[324]. For some of them a threshold criterion is required, which can be entered in the **Probability Threshold** field. The example below illustrates the functionality using a probabilistic atlas with seven Thalamus sub-regions.
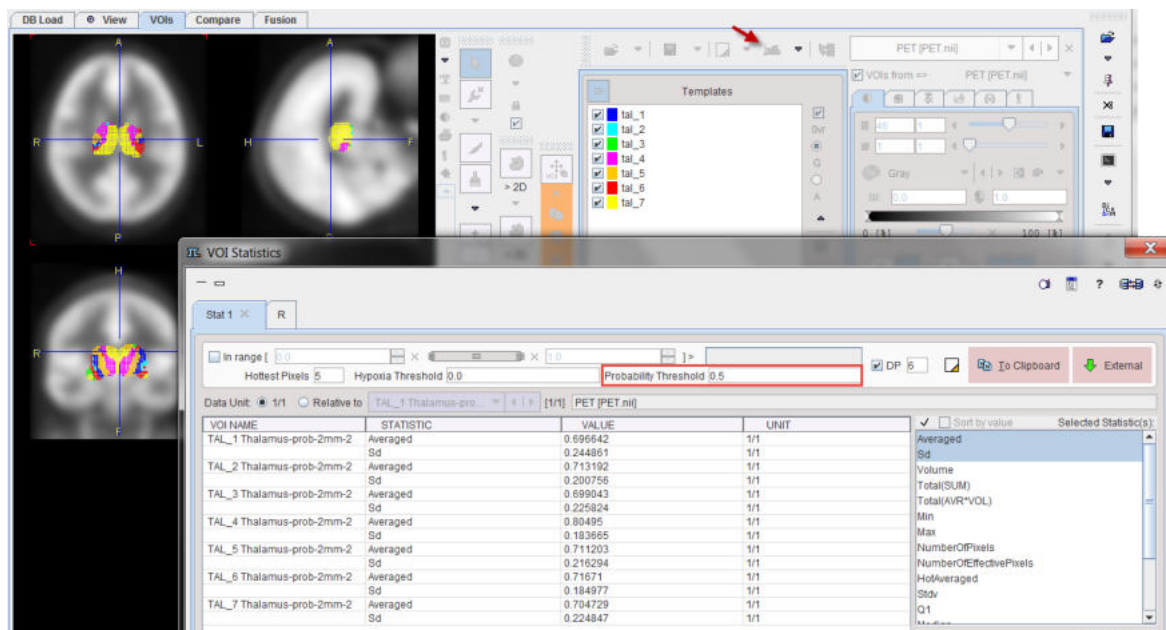
Outline Definition

The conversion of probabilistic VOIs into contour VOIs requires specification of a discretization threshold in the **Set threshold of probability** field of the outlining window.
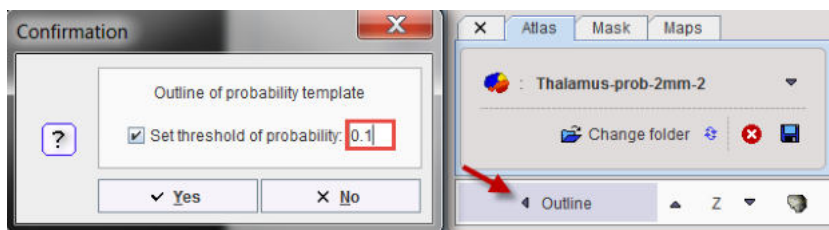
Note that with multiple selected VOIs the outlining procedure constructs non-intersecting VOIs by assigning a pixel to the VOI with the highest p-value.

10.3.7   VOI Atlases included in PMOD

Several atlases are included in the PMOD distribution. Beyond their direct use, they may serve as examples for user-defined atlases or form the basis for user-specific adjustments like the merging of VOIs. Human atlases are defined in the MNI space (Montreal Neurological Institute).

10.3.7.1   Single-Subject AAL Human Brain Atlas

For the analysis of human brain data the **AAL-VOIs** VOI atlas is available. It is the result of an automatic anatomical labeling [1] of the spatially normalized, single subject, high resolution T_1 MRI data set provided by the Montreal Neurological Institute (MNI)[2]. The atlas is provided in HFS orientation (radiological convention) in the MNI atlas space. All images which have been spatially normalized to one of the HFS templates in the fusion tool can be analyzed with the AAL atlas.

Spatial Normalization

The user should select the reference which is most similar to his experimental data. The images of these templates can be found in the *resources/templates* directory.

AAL VOI Atlas

For the statistical analysis, the **AAL-VOIs** VOI atlas can be selected in the list of included VOI atlases. The corresponding files can be found in the *resources/templates/voitemplates/AAL-VOIs* directory.
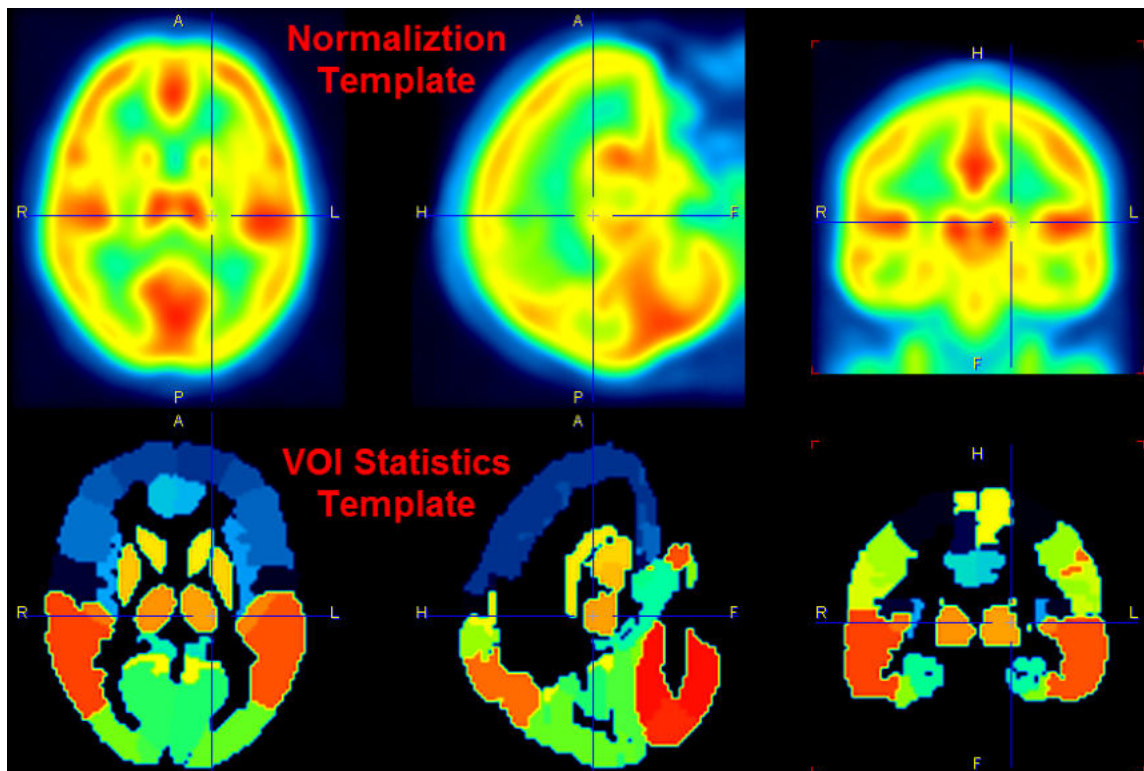
There is also the VOI template **AAL-Merged** available wherein some of the small AAL regions have been combined.

> **Note:** There is a slight asymmetry in the AAL template VOIs which corresponds to the natural asymmetry of normal brains and which is also part of the MNI template. The resolution of the AAL atlas is 2mm in all directions. Stereotactic data with other resolution must be interpolated to 2mm and brought into HFS orientation in order to apply the AAL template within PMOD.

References:

1. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in spm using a macroscopic anatomical parcellation of the MNI MRI single subject brain. Neuroimage 2002; 15: 273-289. DOI

2. Collins DL, Zijdenbos AP, Kollokian V, Sled JG, Kabani NJ, Holmes CJ, Evans AC. Design and construction of a realistic digital brain phantom. IEEE Trans Med Imaging. 1998 Jun;17(3):463-8.

10.3.7.2 Amyloid Cortical Composite Atlas

In the last years the analysis of the amyloid deposition in the brain using composite cortical VOI became common. There have been slight variations regarding which brain regions are included in amyloid cortical composites. The most common amyloid cortical composite includes frontal, temporal, and parietal cortices, including cingulate regions as well as precuneus [1-8]. These amyloid cortical composite regions have been published and validated using various amyloid PET radioligands such as and not limited to [11C]PIB, [18F]Florbetapir (Amyvid, Eli Lilly), [18F] flutemetamol (Vizamyl, GE Healthcare) and [18F]florbetaben (NeuraCeq, Piramal Pharma).

Various reference regions have been used to calculate standardized uptake value ratio (SUVr) such as whole cerebellum, cerebellar grey matter, pons, brainstem and white matter. In addition, an amyloid cortical composite combined with a composite reference region (e.g., whole cerebellum,

brainstem/pons and white matter) has been shown to improve the longitudinal measures of amyloid [3, 9].

Thus, we provide our users the most common pre-defined amyloid cortical composite template including various reference regions used for calculating SUVr.

VOI Atlas

The VOI atlas **Amyloid Cortical Composite** can be selected in the list of included VOI atlases. The corresponding files can be found in the *resources/templates/voitemplates/Amyloid Cortical Composite* directory.

The capture below illustrates the VOIs structures overlaid on the gray matter probability map in MNI space.

There are 5 brain structures included in the Amyloid Cortical Composite atlas. In comparison to the the original Hammers N30R83 atlas the *Cortical Composite* and the *Cerebellum* listed structures were created pooling the specified regions. The even label numbers denote left structures, the uneven numbers right structures in the Hammers N30R83 atlas. The *Midbrain*, *Medulla Oblongata* and the *Pons* were manually segmented from the original Hammers N30R83 Brainstem structure. The segmentation was performed in such manner to avoid contour overlapping in the new structures.

1. Cortical Composite [1-9]	
28; 29	Middle frontal gyrus
52; 53	Straight gyrus
58; 59	Superior frontal gyrus
68; 69	Medial orbital gyrus
70; 71	Lateral orbital gyrus
72; 73	Posterior orbital gyrus
76; 77	Subgenual anterior cingulate gyrus
78; 79	Subcallosal area
11; 12	Superior temporal gyrus posterior part
13; 14	Middle and inferior temporal gyrus
82; 83	Superior temporal gyrus, anterior part
62; 63	Superior parietal gyrus
32; 33	Inferiolateral remainder of parietal lobe
24; 25	Cingulate gyrus (gyrus cinguli), anterior part
26; 27	Cingulate gyurs (gyrus cinguli), posterior part
2. Cerebellum	
17; 18	Cerebellum

3. Midbrain *	
19	Structure of the Brainstem

4. Medulla Oblongata *	
19	Structure of the Brainstem

5. Pons *	
19	Structure of the Brainstem

References

1. Hutton, C., et al., Quantification of [18F]florbetapir PET: comparison of two analysis methods. Eur J Nucl Med Mol Imaging, 2015. 42(5): p. 725-32.

2. Johnson, K.A., et al., Florbetapir [18F]AV-45) PET to assess amyloid burden in Alzheimer's disease dementia, mild cognitive impairment, and normal aging. Alzheimers Dement, 2013. 9(5 Suppl): p. S72-83.

3. Landau, S.M., et al., Amyloid-beta imaging with Pittsburgh compound B and florbetapir: comparing radiotracers and quantification methods. J Nucl Med, 2013. 54(1): p. 70-7.

4. Liu, E., et al., Amyloid-beta [11C]PiB-PET imaging results from 2 randomized bapineuzumab phase 3 AD trials. Neurology, 2015. 85(8): p. 692-700.

5. Nayate, A.P., et al., Use of Standardized Uptake Value Ratios Decreases Interreader Variability of [18F]Florbetapir PET Brain Scan Interpretation. AJNR Am J Neuroradiol, 2015. 36(7): p. 1237-44.

6. Ostrowitzki, S., et al., Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. Arch Neurol, 2012. 69(2): p. 198-207.

7. Sevigny, J., et al., Amyloid PET Screening for Enrichment of Early-Stage Alzheimer Disease Clinical Trials: Experience in a Phase 1b Clinical Trial. Alzheimer Dis Assoc Disord, 2016. 30(1): p. 1-7.

8. Wolk, D.A., et al., Amyloid imaging in Alzheimer's disease: comparison of florbetapir and Pittsburgh compound-B positron emission tomography. J Neurol Neurosurg Psychiatry, 2012. 83(9): p. 923-6.

9. Landau, S.M.a.J., W., Florbetapir processing methods. ADNI PET core, 2015.

10.3.7.3 Centiloid Atlas

"Centiloid" was introduced as a "standard" method for the quantification of the amyloid load by Klunk et al. [1]. It uses a lumped SUVr value obtained with PiB PET as the standard, and describes a scaling method to transform the outcome using other amyloid PET tracers into a comparable measure.

The lumped SUVr is defined by a cortical target region **CTX** and a reference region in the MNI space. **CTX** is a data-driven cortex VOI which includes the typical brain regions with high amyloid load in Alzheimer's Disease including the frontal, temporal and parietal cortices, precuneus, the anterior striatum and insular cortex. While different reference regions were tested, use of whole cerebellum **WC** is the final recommendation.

The **Centiloid** atlas in PMOD only includes the **CTX** and **WC** VOIs, as illustrated below on top of the ICBM152T1 template. Note that the locations are correct, although they don't follow the anatomical boundaries. This behavior is due to the PET data-driven process for their derivation, and has been confirmed by the authors.
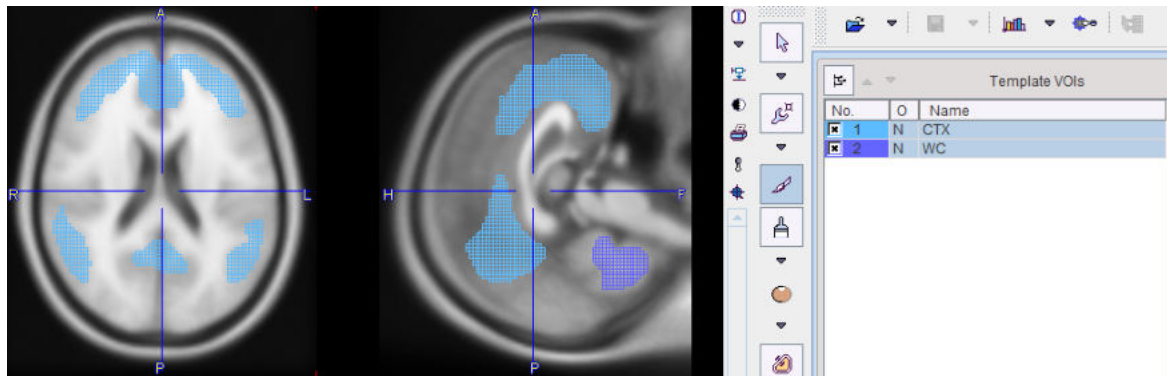
Reference

1. Klunk WE, Koeppe RA, Price JC, Benzinger TL, Devous MD Sr, Jagust WJ, Johnson KA, Mathis CA, Minhas D, Pontecorvo MJ, Rowe CC, Skovronsky DM, Mintun MA. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. Alzheimers Dement. 2015; 11(1):1-15.e1-4. DOI:

10.3.7.4 Cynomolgus Monkey Atlas

For the analysis of cynomolgus monkey (Macaca Fascialis) brain data the **Cynomolgus_CIMA-UN** VOI atlas [1] is available. We would like to thank Elena Prieto and Maria Collantes from the Centro de Investigacion Medica Aplicada (CIMA), Universidad de Navarra, for providing the data and helping with the integrations.

Spatial Normalization

A T_1-weighted MRI normalization template created from 15 healthy animals is available as **Cynomolgus_CIMA-UN-MRI**. Two PET templates in the same space are also provided: **Cynomolgus_CIMA-UN-Dopa** and **Cynomolgus_CIMA-UN-DTBZ**.

VOI Atlas

The VOIs were hand drawn in the striatum (VOI size 400 mm^3) and occipital lobe (VOI size 310 mm^3) on axial MRI slices based on anatomical borders.
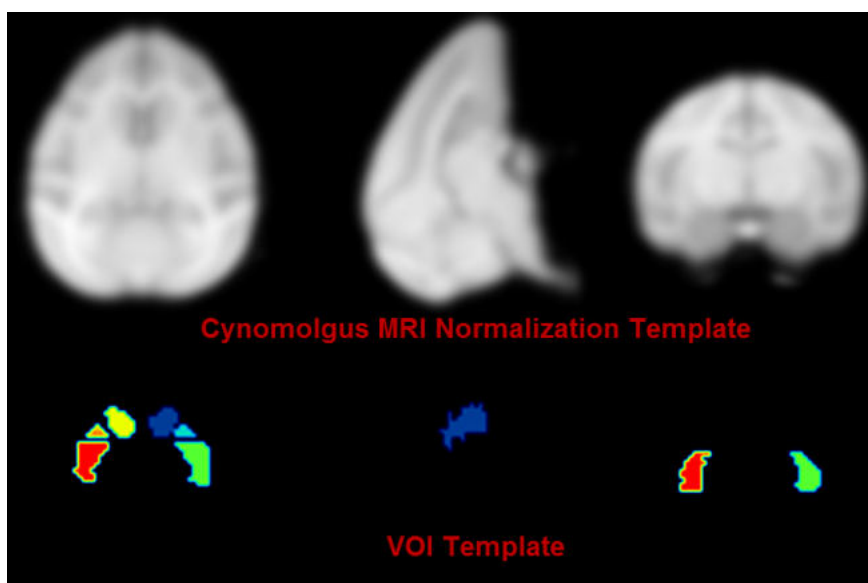
Reference

1. Collantes M, Prieto E, Penuelas I, Blesa J, Juri C, Marti-Climent JM, Quincoces G, Arbizu J, Riverol M, Zubieta JL, Rodriguez-Oroz MC, Luquin MR, Richter JA, Obeso JA. New MRI, 18F-DOPA and 11C-(+)-alpha-dihydrotetrabenazine templates for Macaca fascicularis neuroimaging: advantages to improve PET quantification. Neuroimage. 2009;47(2):533-9. DOI

10.3.7.5 Rhesus Macaque (INIA19)

The INIA19 atlas has been developed for the rhesus macaque by Rohlfing et al. [1] and made available to the scientific community (http://nitrc.org/projects/inia19/). It includes 1014 VOI definitions, an MR template for template-based normalization and three tissue probability maps for normalization using the unified segmentation approach.
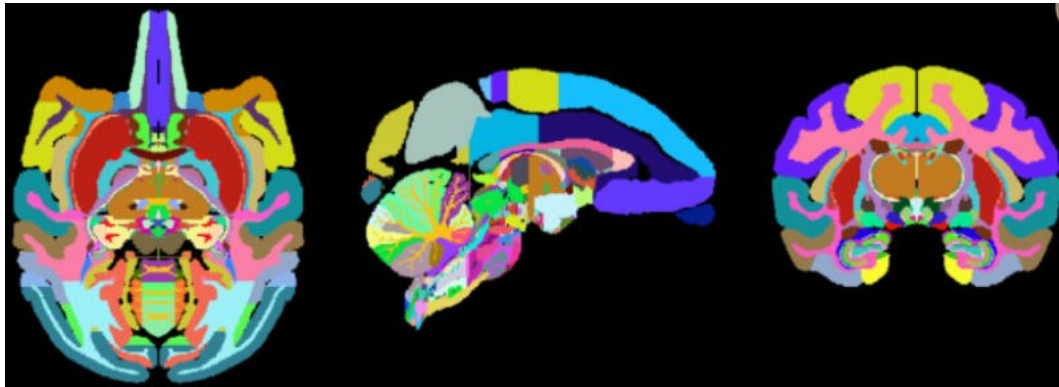
The atlas was created from high-resolution, T1-weighted MR images of 19 rhesus macaque (Macaca mulatta) animals. Combined with the comprehensive cortical and sub-cortical label map, the INIA19 is equally suitable for studies requiring both spatial normalization and atlas label propagation.

Reference

1. Rohlfing T, Kroenke CD, Sullivan EV, Dubach MF, Bowden DM, Grant KA, Pfefferbaum A: The INIA19 Template and NeuroMaps Atlas for Primate Brain Image Parcellation and Spatial Normalization. Frontiers in neuroinformatics 2012, 6:27. DOI

10.3.7.6 Domestic Pig / Minipig Brain Atlas (CH.Malbert)

Overview

The **Pig (CH.Malbert)** atlas is based on brain scans of 5 6-month-old female domestic pigs (Sus scrofa domesticus). An ex vivo T2-weighted MRI was used by Saikali et al. [1] to construct the atlas, and a T1 MRI is provided for image coregistration. Subsequently, the same group constructed a 99mTc-HMPAO SPECT template [2] and FDG PET template [3] in the same image space. Matched tissue probability maps were subsequently provided to PMOD. Additionally, an FDG PET template for Yucatan miniature pigs was developed in the same image space as the domestic pig atlas [4]. The atlas was initially constructed at high resolution (100 x 150 x 100 um) in one hemisphere, and then mirrored to create the full brain atlas. The VOI atlas contains 173 cortical and subcortical regions (reduced from 178 in the original high resolution atlas). The atlas is distributed with PMOD by courtesy of Dr. Charles-Henri Malbert, director of research at the Unité Ani-Scan, Département de Nutrition Humaine, INRA, France.

Spatial Normalization

Four normalization templates are available in the Fuse It tool. They can be selected on the Reference page using the Template button when Pig is selected as Species:

- **Pig (CH.Malbert)-PET-domestic**: This is an FDG PET template derived from static scans in 4 month old domestic pigs, shown below.

- **Pig (CH.Malbert)-PET-minipig**: This is an FDG PET template derived from dynamic scans in 2 year old minipigs, shown below. Correspondence to the domestic pig template and MRI is high.

- **Pig (CH.Malbert)-SPECT:** This is a 99mTc-HMPAO SPECT template derived from scans in 4 month old domestic pigs.

- **Pig (CH.Malbert)-T1**: This is a T1-weighted MRI PET template in the same image space as the PET templates. The VOI atlas was derived from this image.

The image files corresponding to these templates can be found in the *resources/templates/voitemplates/Pig (CH.Malbert)* folder. Additionally, mask files corresponding to each template, and tissue probability maps are available.
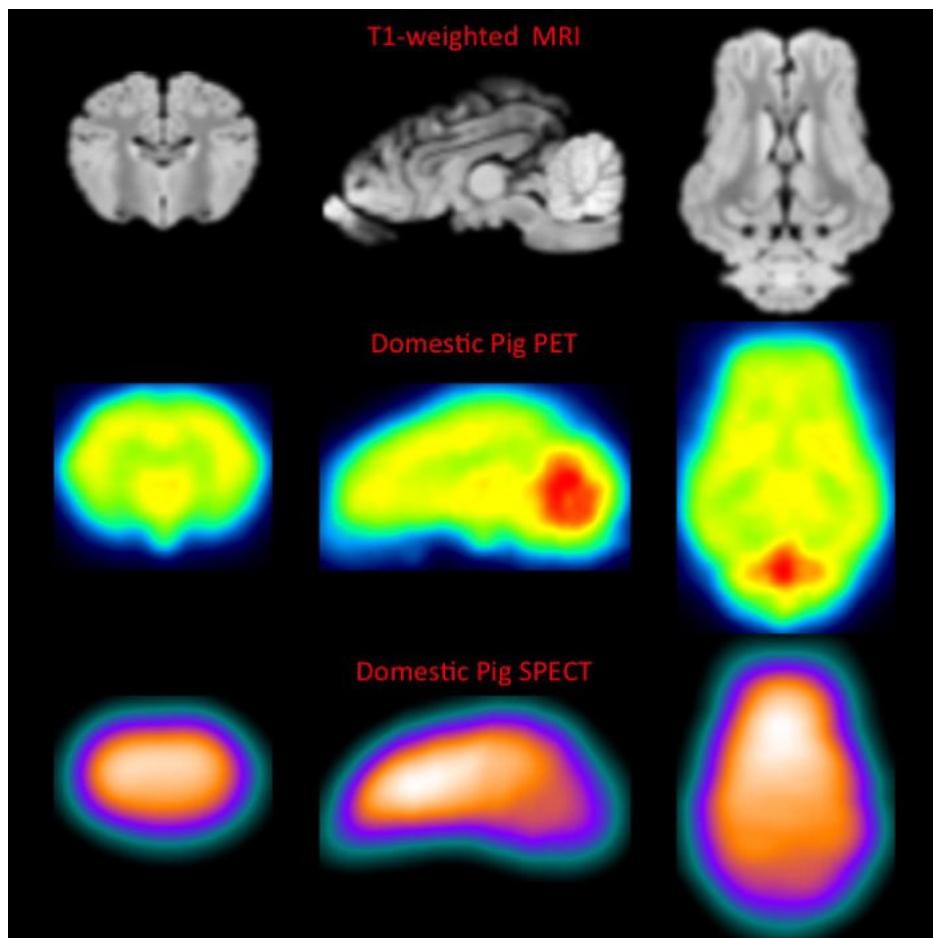
Selection and generation of appropriate masks is critical to successful spatial normalization with these templates. The mask corresponding to the template selected should be identified in the **Normalization Settings** dialog. The PBAS functionality (e.g. via the **View** tool) can be used to generate a mask for the input image. Accurate exclusion of activity outside the brain, and the olfactory bulbs, is necessary. This user-defined mask should also be identified in the **Normalization Settings** dialog.
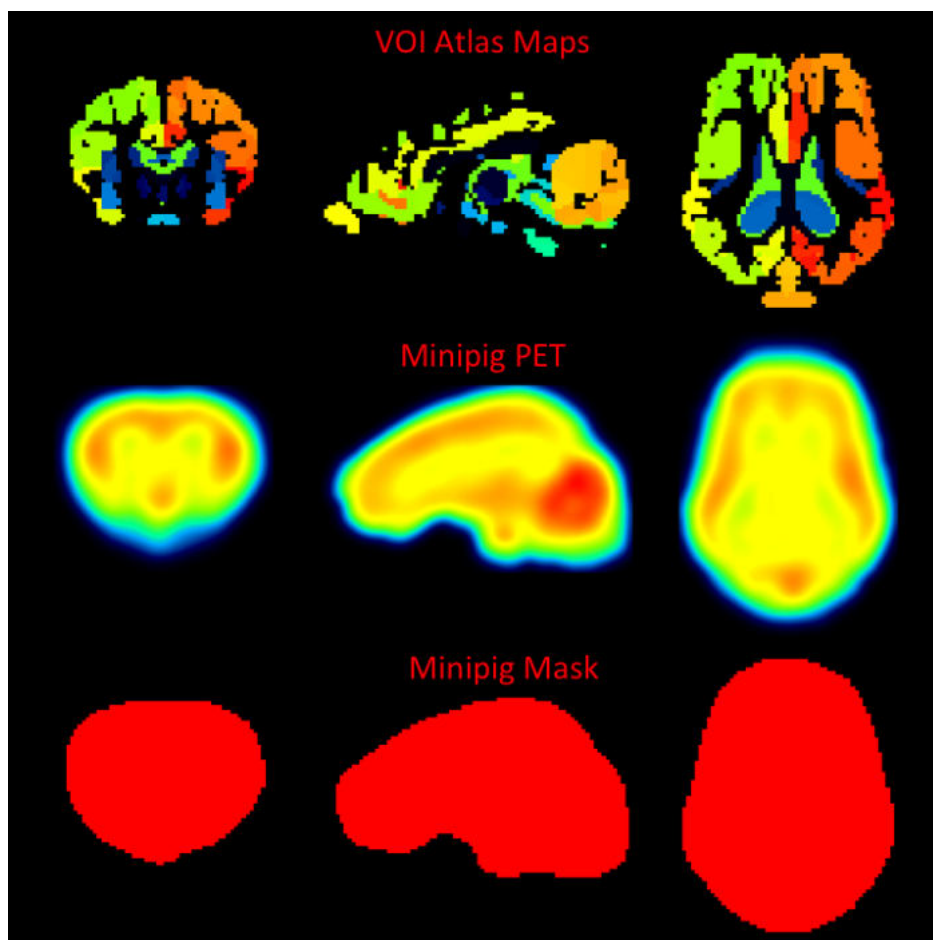
VOI Atlas

The VOI atlas Pig (CH.Malbert) can be selected in the list of included VOI atlases. The corresponding map files in Nifti format can be found in the *resources/templates/voitemplates/Pig (CH.Malbert)* directory. The brain VOIs are structurally organized in a tree on the **Group** tab of the VOI editing page. The selection of a VOI subset is supported by a dedicated **user interface** 294.
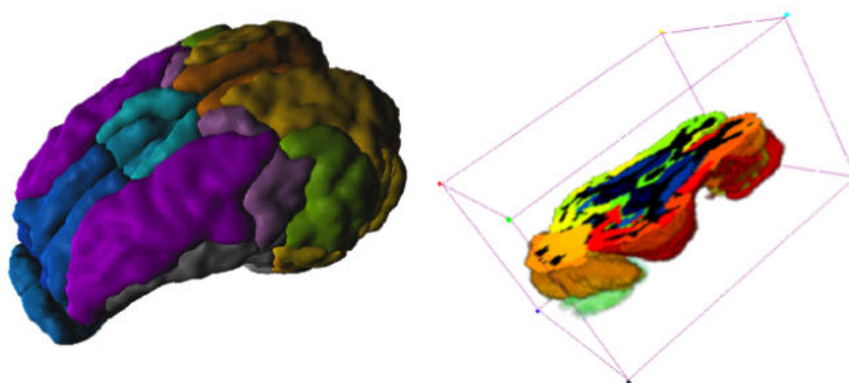
References

1. Saikali S, Meurice P, Sauleau P, Eliat PA, Bellaud P, Randuineau G, Vérin M, Malbert CH. A three-dimensional digital segmented and deformable brain atlas of the domestic pig. J Neurosci Methods. 2010; 192(1):102-9. **DOI**.

2. Boubaker J, Val-Laillet D, Guérin S, Malbert CH. Brain processing of duodenal and portal glucose sensing. J Neuroendocrinol. 2012 Aug;24(8):1096-105. **DOI**.

3. Gaultier A, Meunier-Salaün MC, Malbert CH, Val-Laillet D. Flavour exposures after conditioned aversion or preference trigger different brain processes in anaesthetised pigs. Eur J Neurosci. 2011 Nov;34(9):1500-11. **DOI**.

4. Ochoa M, Malbert CH, Meurice P, Val-Laillet D. Effects of Chronic Consumption of Sugar-Enriched Diets on Brain Metabolism and Insulin Sensitivity in Adult Yucatan Minipigs. PLoS One. 2016 Sep 1;11(9):e0161228. **DOI**.

10.3.7.7 Sprague-Dawley Rat Brain Atlas (A.Schwarz) & PET/SPECT Templates (Groningen)

Overview

The **Px Rat (A.Schwarz)** atlas is based on 97 anatomical MR images of adult male Sprague-Dawley rats (250-300g). For the original atlas [1] a volumetric reconstruction of the Paxinos and Watson rat brain atlas was created and adapted to the averaged anatomy. This version of the atlas was used as part of a proposed standardized methodology for the creation of small animal brain PET templates [2]. For application in PMOD the atlas and templates were interpolated to 0.1 mm resolution and VOIs merged to avoid small regions, which would result in poor statistics. The VOI atlas contains 60 cortical and subcortical regions. The atlas is distributed with PMOD by courtesy of Dr. Adam Schwarz, Department of Psychological and Brain Sciences, Indiana University, and the PET/SPECT templates courtesy of University Medical Center Groningen, The Netherlands (with thanks to Dr. D. Vallez Garcia, UMC Groningen, Nuclear Medicine & Imaging).

Spatial Normalization

The T_2-weighted MR template, five PET templates and a single SPECT template are available in the Fuse It tool when **Rat** is selected as **Species**.

- **Px Rat (A.Schwarz)-MR**, **Px Rat (Groningen)-MR**: This is the T_2-weighted MR anatomical reference for the A.Schwarz VOI atlas.

- **Px Rat (Groningen) 11C-MeDAS-PET**: This is a PET template for the tracer [11C]MeDAS, coregistered to the MR anatomical reference above.

- **Px Rat (Groningen) 11C-PBR28-PET**: This is a PET template for the tracer [11C]PBR28, coregistered to the MR anatomical reference above.

- **Px Rat (Groningen) 11C-PK11195-PET**: This is a PET template for the tracer [11C]PK11195, coregistered to the MR anatomical reference above.

- **Px Rat (Groningen) 11C-Raclopride-PET**: This is a PET template for the tracer [11C] Raclopride, coregistered to the MR anatomical reference above.

- **Px Rat (Groningen) 18F-FDG-PET**: This is a PET template for the tracer [18F]FDG, coregistered to the MR anatomical reference above.

- **Px Rat (Groningen) 99mTc-HMPAO-SPECT**: This is a SPECT template for the tracer [99mTc] HMPAO, coregistered to the MR anatomical reference above.

The image files corresponding to these templates can be found in the *resources/templates/voitemplates/Px Rat (A.Schwarz)* and *resources/templates/voitemplates/Px Rat (Groningen)* folders, specifically in the **normalization** sub-folder. Mask files for use during normalization and coregistration are also available.
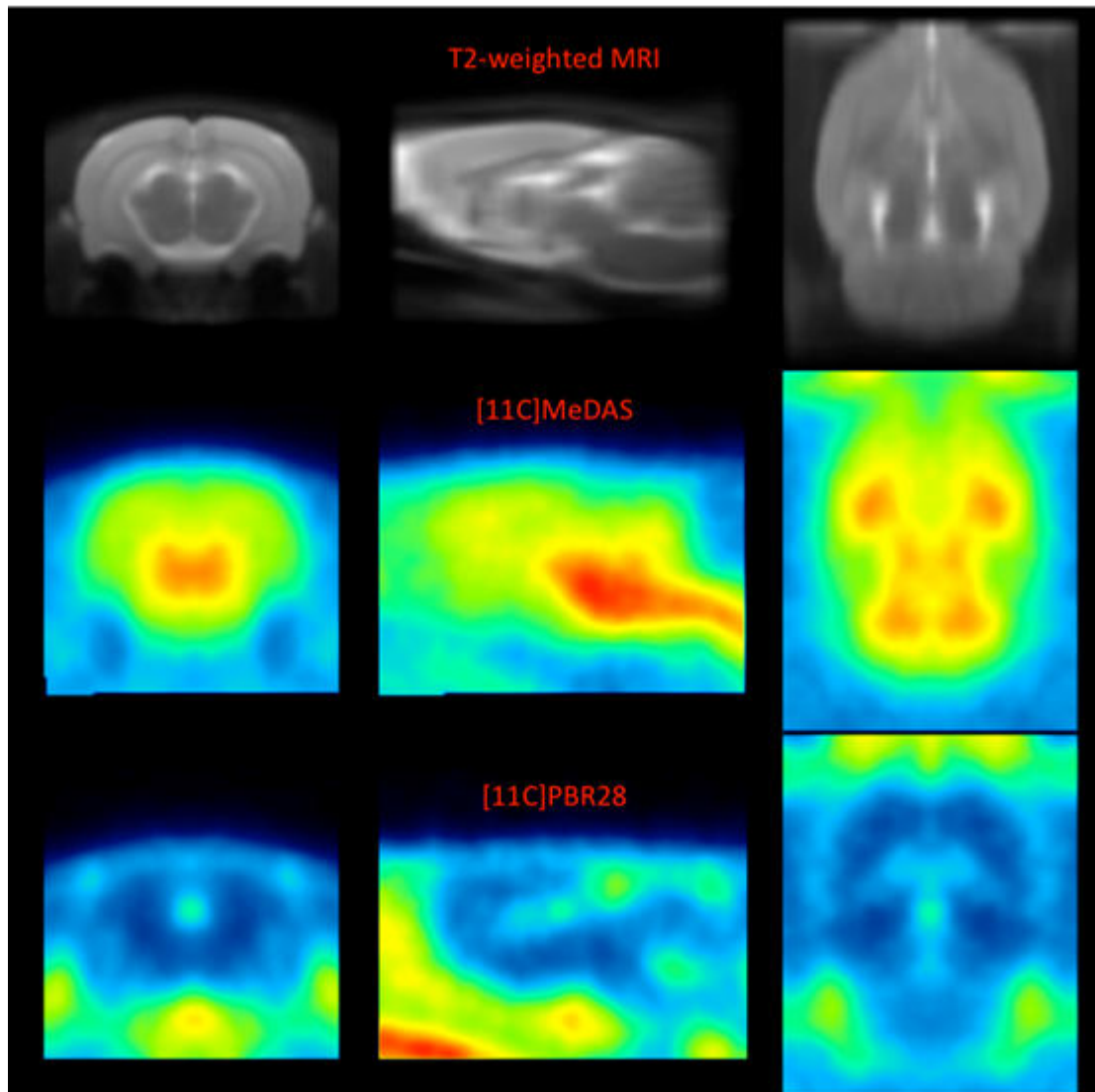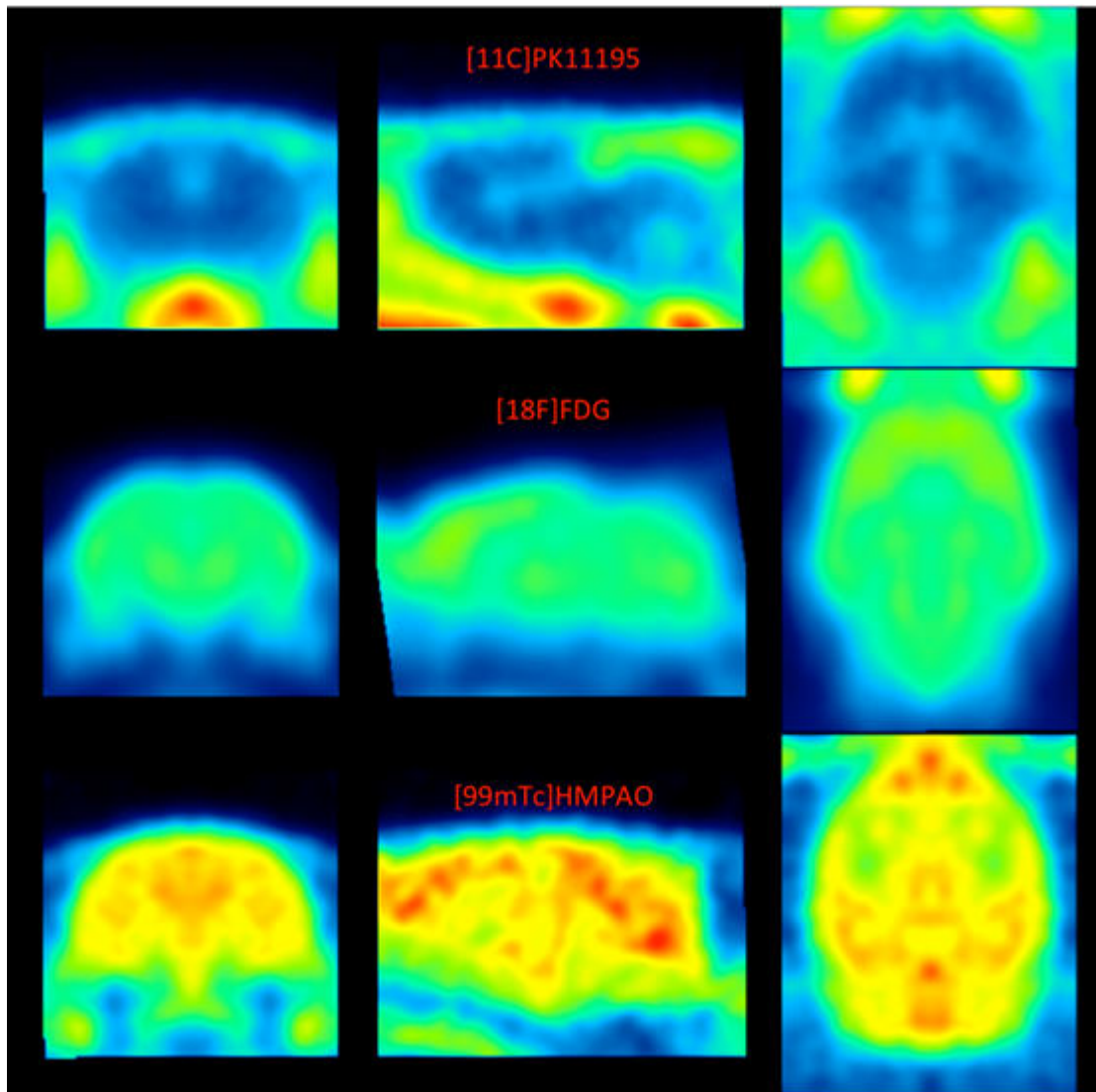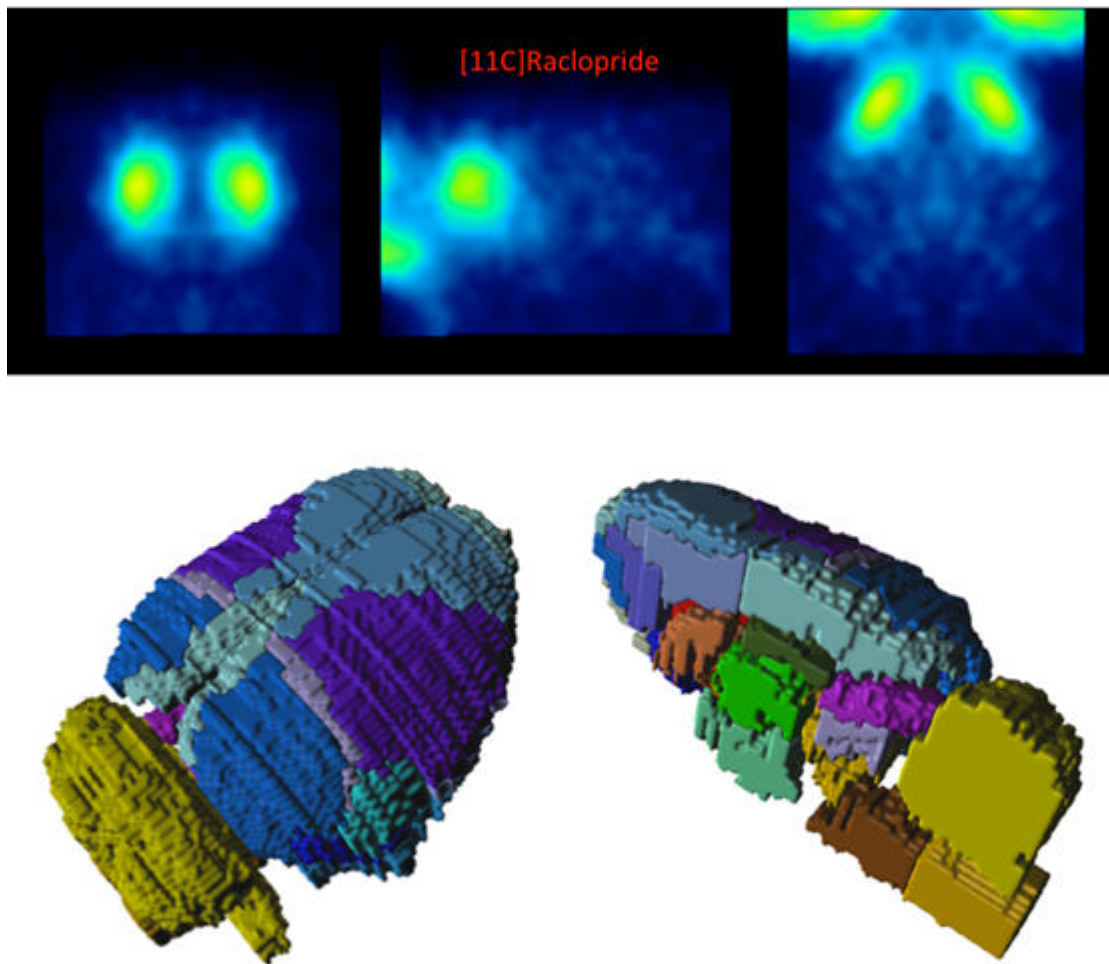
VOI Atlas

The VOI atlas **Px Rat (A.Schwarz)** (and identical atlas through **Px Rat (Groningen)**) can be selected in the list of included VOI atlases. The corresponding map files in Nifti format can be found in the *resources/templates/voitemplates/Px Rat (A.Schwarz)* directory.

The brain VOIs are structurally organized in a tree on the Group tab of the VOI editing page. The selection of a VOI subset is supported by a dedicated **user interface** 294.

Reference

1. Schwarz AJ, Danckaert A, Reese T, Gozzi A, Paxinos G, Watson C, Merlo-Pich EV, Bifone A. A stereotaxic MRI template set for the rat brain with tissue class distribution maps and co-registered anatomical atlas: application to pharmacological MRI. Neuroimage. 2006 Aug 15;32(2):538-50. **DOI**.

2. Vallez Garcia D, Casteels C, Schwarz AJ, Dierckx RA, Koole M, Doorduin J. A standardized method for the construction of tracer specific PET and SPECT rat brain templates: validation and implementation of a toolbox. PLoS One. 2015;10(3):e0122363. **DOI**.

10.3.7.8 Sprague-Dawley Rat Brain Atlas (Schiffer)

For the analysis of rat brain data the **Px Rat (W.Schiffer)** [1] VOI atlas is available. We would like to thank Wynne Schiffer for providing the data and helping with the integrations. The atlas incorporates

π.pmod

adult male Sprague-Dawley rats (250-300g, age 52-62 days). This template implements the Paxinos coordinates.

Spatial Normalization

Three normalization templates are available in the fusion tool:

- **Px Rat (W.Schiffer)-FDG**: This is an FDG PET template as illustrated below.

- **Px Rat (W.Schiffer)-masked**: This is a masked version of the FDG PET which has been masked outside the brain. It may be helpful if the additional activity of the Harderian glands is not present in the rat images to be normalized.

- **Px Rat (W.Schiffer)-T2**: This is a T_2-weighted MRI PET template which is in the same space as the PET templates.

The images of these templates can be found in the *resources/templates/usertemplates* directory.

VOI Atlas

The VOI atlas **Px Rat (W.Schiffer)** can be selected in the list of included VOI atlases. The corresponding files can be found in the *resources/templates/voitemplates/Px Rat (W.Schiffer)* directory.
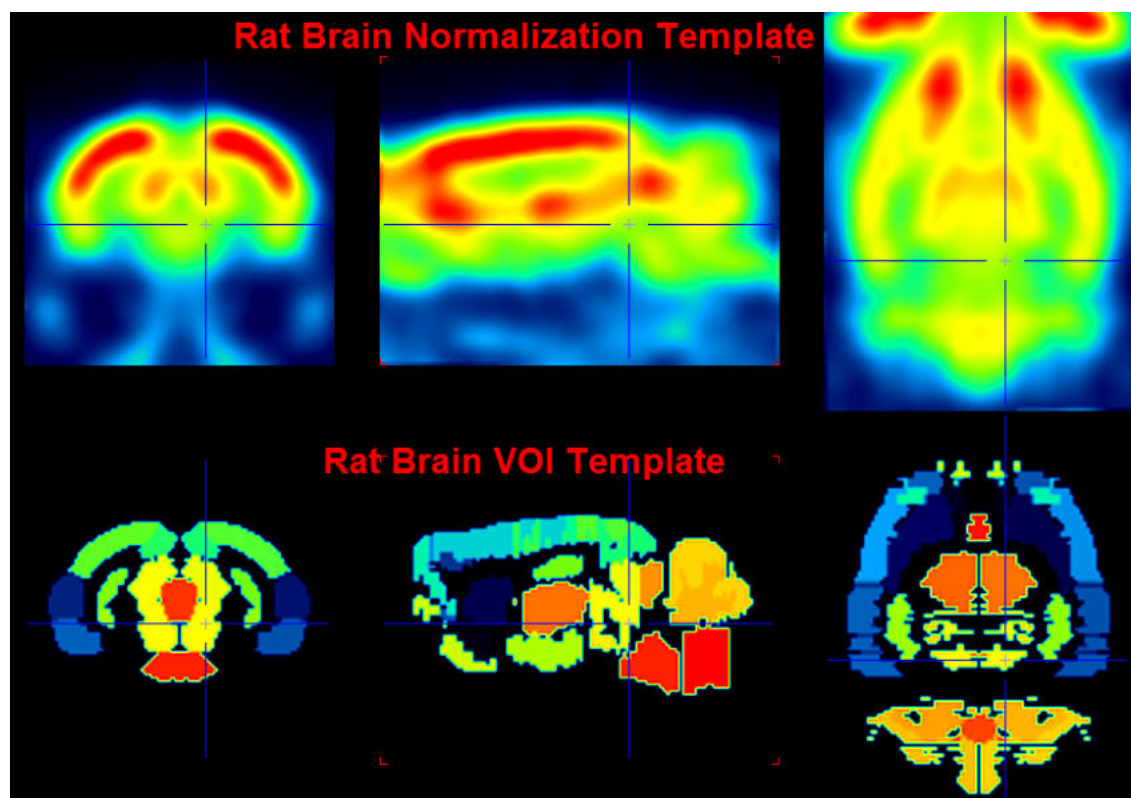
Reference

1. Schiffer WK, Mirrione MM, Biegon A, Alexoff DL, Patel V, Dewey SL. Serial microPET measures of the metabolic reaction to a microdialysis probe implant. J Neurosci Methods. 2006;155(2):272-84. DOI

10.3.7.9 Wistar Rat Brain Atlas (Tohoku)

Overview

The **Wistar Rat (Tohoku)** atlas was developed by Valdes-Hernandez et al [1] using 7T T_2-MRIs from 30 Wistar rats. The template image was constructed as a "minimal-deformation" template, and the coordinates are thus not in Paxinos space. In the same space, gray matter, white matter and CSF probability maps were calculated, so that the 3-probability maps normalization can be applied in addition to the template-based normalization. 48 bi-lateral cortical structures were digitized from the Paxinos atlas and registered them to the template image. This atlas can be used for VOI statistics and for the anatomical interpretation of fMRI results.

The atlas is distributed with PMOD by courtesy of Prof. Akira Sumiyoshi, Tohoku University, Japan (**atlas website**).

FIGURE 4 | Digitalized Paxinos and Watson atlas, overlaid on the minimal deformation template after being warped to the template space using the approximate thin plate splines (TPS) method, plus further manual corrections.
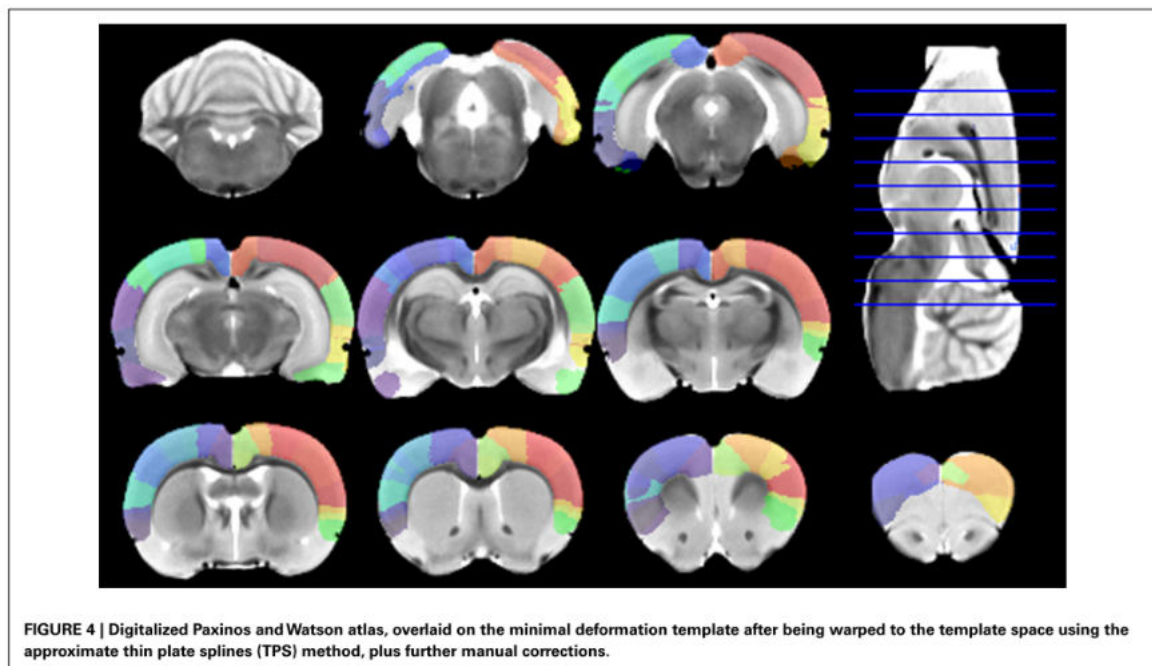
Spatial Normalization

Two normalization approaches are supported:

- Template-based normalization using the **Wistar Rat (Tohoku)-MR** skull-stripped T_2-MR template illustrated above.
- 3-tissue probability maps normalization using Gray matter, White matter and CSF combined in a single **tpm.nii** file.

The images of these templates can be found in the *resources/templates/voitemplates/Wistar Rat (Tohoku)* directory.

Reference

1. Valdes-Hernandez PA, Sumiyoshi A, Nonaka H, Haga R, Aubert-Vasquez E, Ogawa T, Iturria-Medina Y, Riera JJ, Kawashima R: An in vivo MRI Template Set for Morphometry, Tissue Segmentation, and fMRI Localization in Rats. Frontiers in neuroinformatics 2011, 5:26. **DOI**

10.3.7.10 Mouse Brain Atlas (Ma-Benveniste-Mirrione)

For the analysis of mouse brain data the **Mouse (Ma-Benveniste-Mirrione)** VOI atlas [1,2] is available. It represents the minimum deformation atlas of 10 C57BL/6J mice (male, 12-14 weeks, 25-

30g). We would like to thank Helene Benveniste and Martine Mirrione for providing the data and helping with the integrations.
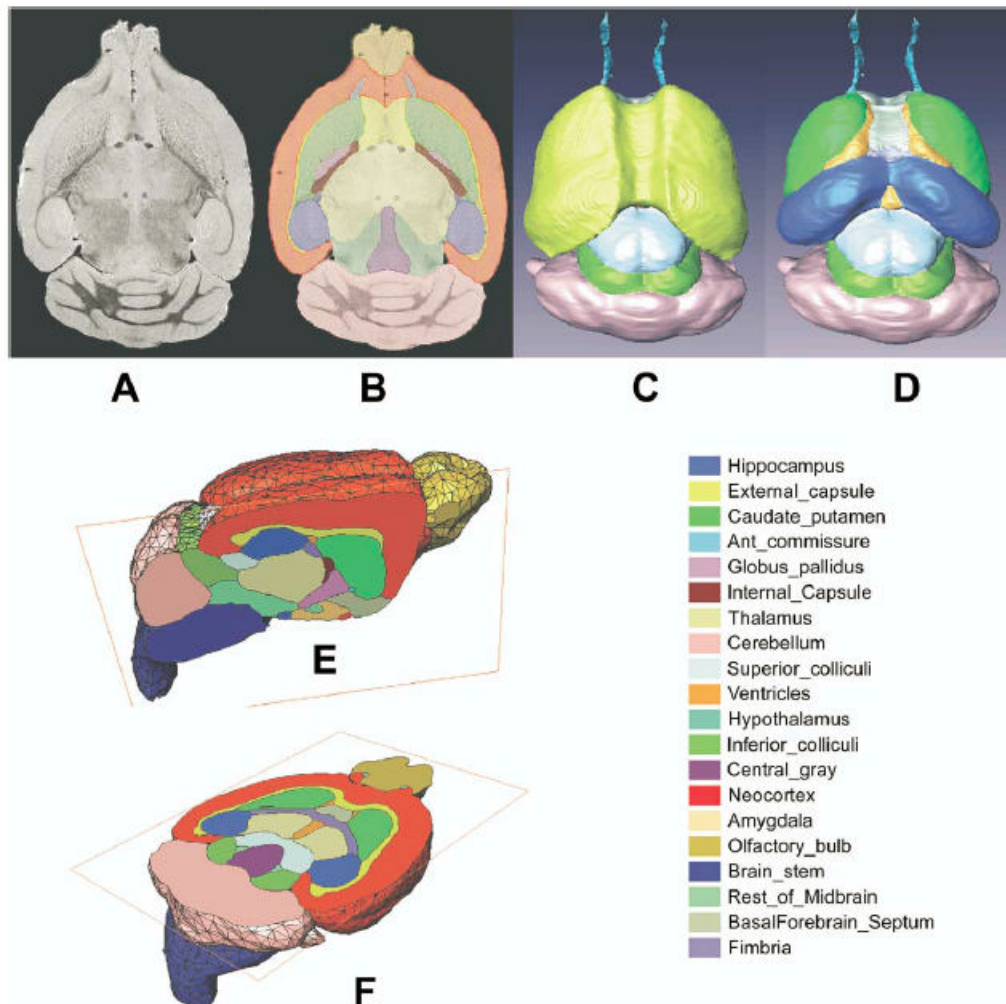
Spatial Normalization

Two normalization templates are available in the fusion tool:

- **Mouse (Ma-Benveniste-Mirrione)-FDG**: This is an FDG baseline PET template as illustrated below.

- **Mouse (Ma-Benveniste-Mirrione)-T2**: This is a T_2-weighted MRI PET template which is in the same space as the PET templates.

The images of these templates can be found in the *resources/templates/usertemplates* directory.

VOI Atlas

The VOI atlas **Mouse (Ma-Benveniste-Mirrione)** can be selected in the list of included template VOIs. The corresponding files can be found in the *resources/templates/voitemplates/Mouse (Ma-Benveniste-Mirrione)* directory.
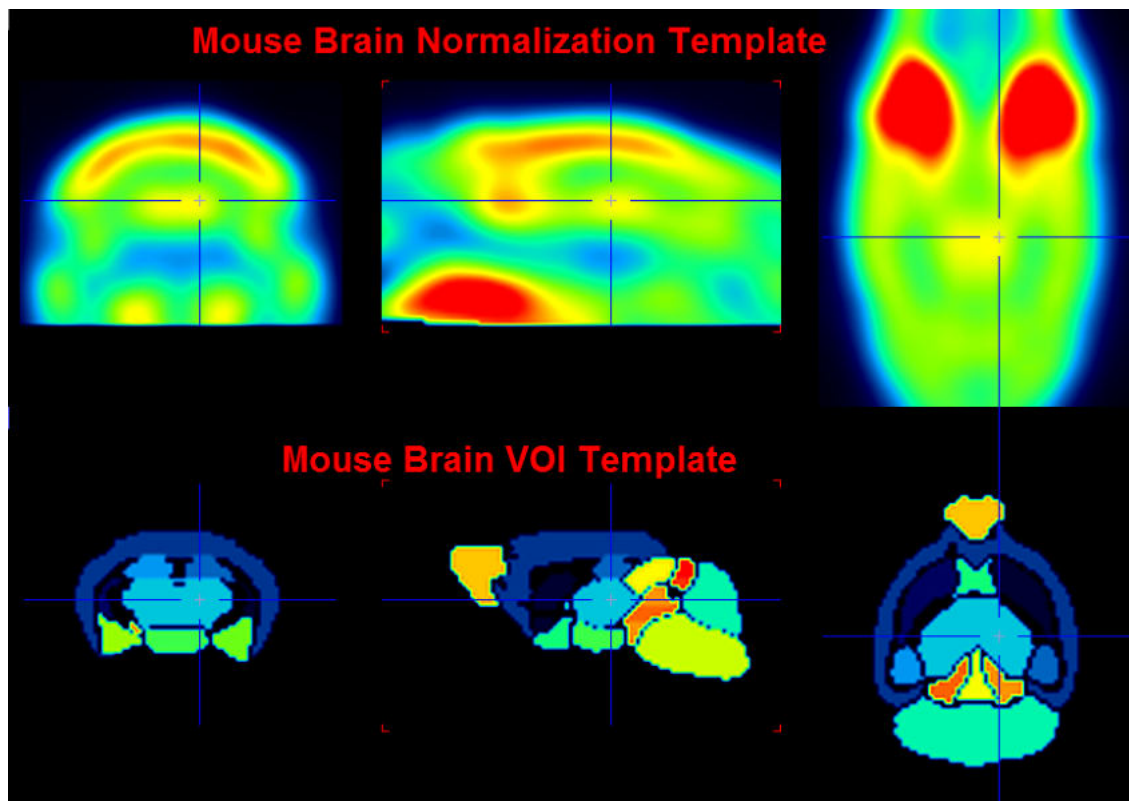
References

1. Ma Y, Hof PR, Grant SC, Blackband SJ, Bennett R, Slatest L, McGuigan MD, Benveniste H. A three-dimensional digital atlas database of the adult C57BL/6J mouse brain by magnetic resonance microscopy. Neuroscience. 2005;135(4):1203-15. DOI

2. Mirrione MM, Schiffer WK, Fowler JS, Alexoff DL, Dewey SL, Tsirka SE. A novel approach for imaging brain-behavior relationships in mice reveals unexpected metabolic patterns during seizures in the absence of tissue plasminogen activator. Neuroimage. 2007;38(1):34-42. DOI

10.3.7.11 Preparation of VOI Atlas Files for PMOD

Atlas Definition

VOI atlases can be easily prepared for use in PMOD. Three sets of data are required, the

1. *Atlas images:* They must be prepared as NifTI files and encode the atlas VOIs as numeric labels. Each pixel has a value of 0 if it is a background pixel, or is otherwise an integer number. We recommend using the HFS orientation (head first, supine = radiological convention) for human data.

2. *Label list:* A text file ending in .txt containing at least three columns. Each VOI is represented by a line of the form:
```
name1    label_name1   label_value1
name2    label_name2   label_value2
...
```
There must not be blank characters within the abbreviations or the names.

3. A manifest text file for the encoding of the species, for instance containing
SPECIES = HUMAN
The species supported are HUMAN, PRIMATE, PIG, RAT, MOUSE.

Note that the name of the atlas sub-directory in *resources/templates/voitemplates* must also be used for the template images, the label list, and the manifest. This name then shows up in the list of available atlases in the VOI analysis tool.

Included in the distribution are several templates. The naming and the arrangement of the files are illustrated below using the **AAL-Merged** atlas as an example.
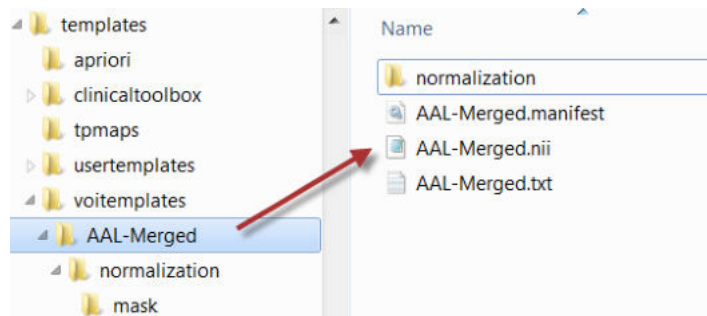
The **AAL-Merged.txt** contains the following 5 columns. The first column starts with the name followed by a bracket construction which encodes a tree structure. For instance, **Precentral** belongs to the **Frontal_Lobe** which is located in the **L** or right **R** hemisphere. The second column indicates the name of a generated contour VOI. The third column contains the label value in the atlas file. Each pixel in **AAL-Merged.nii** with value 1 will belong the **Precentral_l** VOI, pixels with value **2** to **Precentral_l**, etc.

Name	Outlined	Label	Color	Tooltip
Precentral[Frontal_lobe[L]]	Precentral_l	1	(100,0,255)	Precentral gyrus left (PRE)
Precentral[Frontal_lobe[R]]	Precentral_r	2	(100,0,255)	Precentral gyrus right (PRE)
Rolandic_Oper[Frontal_lobe[L]]	Rolandic_Oper_l	3	(93,188,255)	Rolandic operculum left (RO)
Rolandic_Oper[Frontal_lobe[R]]	Rolandic_Oper_r	4	(93,188,255)	Rolandic operculum right (RO)
Supp_Motor_Area[Frontal_lobe[L]]	Supp_Motor_Are.	5	(0,114,255)	Supplementary motor area left (SMA)
Supp_Motor_Area[Frontal_lobe[R]]	Supp_Motor_Are.	6	(0,114,255)	Supplementary motor area right (SMA)
Olfactory[Frontal_lobe[L]]	Olfactory_l	7	(100,100,255)	Olfactory cortex left (OC)
Olfactory[Frontal_lobe[R]]	Olfactory_r	8	(100,100,255)	Olfactory cortex right (OC)
Frontal_Sup[Frontal_lobe[L]]	Frontal_Sup_l	11	(0,0,255)	Superior frontal gyrus left (F1, F1O, F1M)
Frontal_Sup[Frontal_lobe[R]]	Frontal_Sup_r	12	(0,0,255)	Superior frontal gyrus right (F1, F1O, F1M)

The corresponding VOI atlas structure is illustrated below.
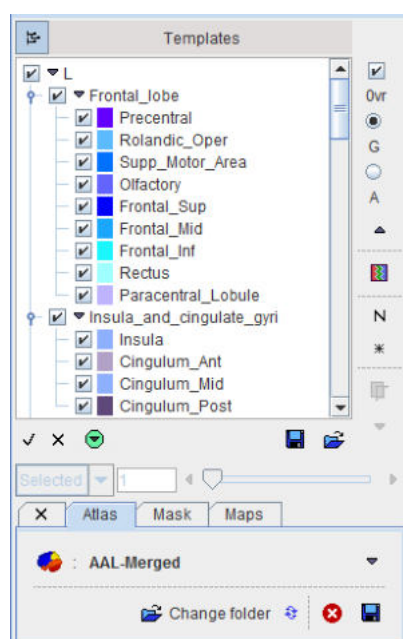
Normalization Files

Atlases can only be applied to images if they have the same resolution and show the anatomy with the same geometry. Therefore, images originating from real experiments first need a normalization step for the atlas to be applied. This is done by calculating a normalization transform between the subject image and a "template" image representing the standard anatomy imaged with a certain modality, and using it for warping the VOIs to the subject anatomy.

Appropriate template images need to be copied to a **normalization** sub-folder. In the example below **normalization** contains a T1 MR template with skull, as well as a PET template. Note that user defined templates names have to start with the atlas specific name, e.g. **BRAIN_AAL_Merged**, followed by the corresponding template modality **-PET** or **-MRI.** All of these templates show the anatomy in the space in which the BRAIN_AAL_Merged VOIs were defined.
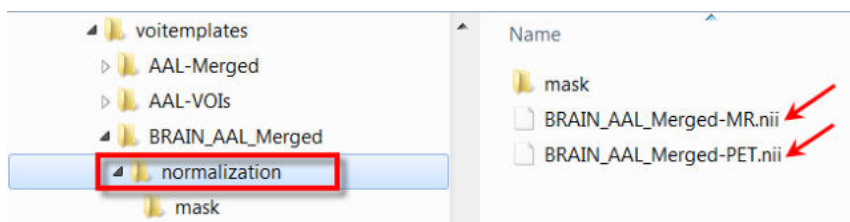
Correspondingly the **Normalization Template** list has the following entries.
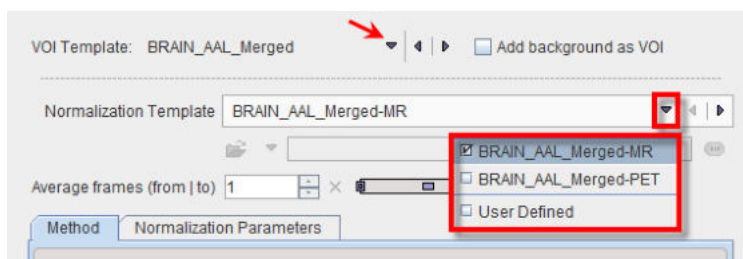
The normalization works best if the information is restricted to the relevant image part. Therefore, **normalization** should contain a **mask** sub-folder with a mask file **mask.nii** containing 1 for all relevant pixels and 0 for all others.

Note: For atlases with **SPECIES = HUMAN** and **SPACE = MNI** in the manifest file the preparation of the **normalization** subdirectory is not required, as the universal files for the human brain are available in the **template** and the **tpmaps** directories.

10.4 Using Label Map Files

A label map is a file, which contains label numbers in all pixels which identify different objects in the image. Such maps are often the product of segmentation procedures. PMOD can load and analyze these files and create a VOI template out of it.

The functionality is located on the **Template** panel, in the **Map** sub-panel as illustrated below.
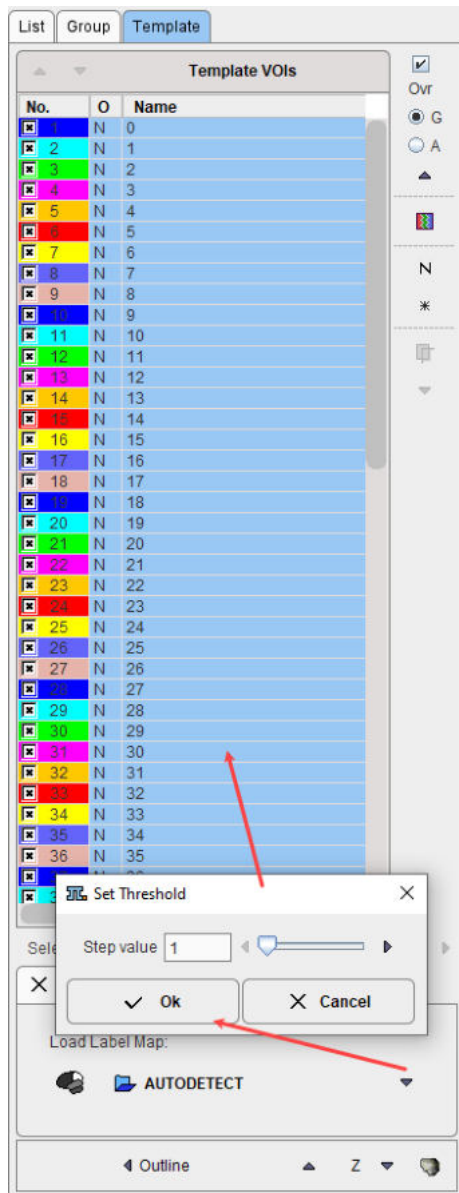
To load a map file choose the file format in the **Load Label Map** area and select the map file. A dialog window appears which allows specifying the bin size for the label histogram. A **Step value** of 1 should normally work fine. The file is scanned and for each label found a list entry is created in the **Template VOIs** list. Now the names can be edited, the VOIs outlined and further used as for the prepared template VOIs 289.

AnalyzeAVW Object Maps

Using the **AUTODETECT** format, PMOD can directly load AnalyzeAVW object maps (*.obj). It will not only create the VOIs, but also restore the VOI names and the VOI colors.

10.5   Using Mask Files

A mask is a binary file, which contains 1 in all pixels belonging to the object of interest, and 0 in all other pixels. It is most likely the result of some threshold or segmentation operation of the images to be analyzed. Any image can be loaded and used as a mask VOI. If it is not a binary image, the user can specify the threshold below which the pixels are converted to 0, while the other pixels are converted to 1.

To load a mask for VOI analysis first select the **Template** tab, and then **Mask**. A loading button becomes active and allows loading a binary file. If the data in the file is not binary a dialog window appears for defining the **Binarization Level [%]** and the names for the mask and the background.
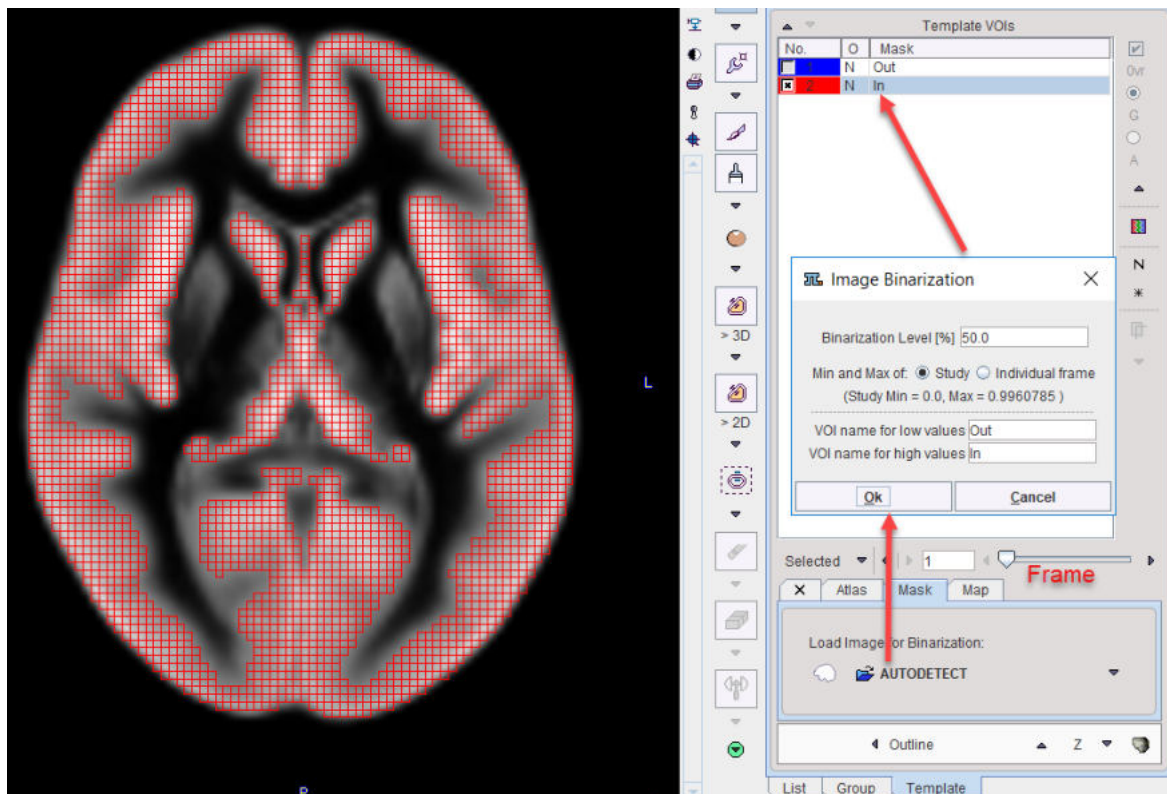
A mask template only contains two VOIs, the **Mask** pixels **In**, and all background pixels **Out**. Most of the times only the **In** region will provide reasonable values, but the **Out** region can also be evaluated on demand.

The same operations are supported as for the atlas VOIs[289]: statistics can be calculated in the mask VOIs, contour VOIs can be defined in parallel and masked, and mask VOIs can be converted to contour VOIs by the **Outline** or **Normalize** option button. A notable application of masking is the restriction of contour VOIs to the gray matter pixels which can easily be achieved if a gray matter segment is available from a matched MRI data set. An example of restricting a contour VOI shown on a PET to gray matter is illustrated below.
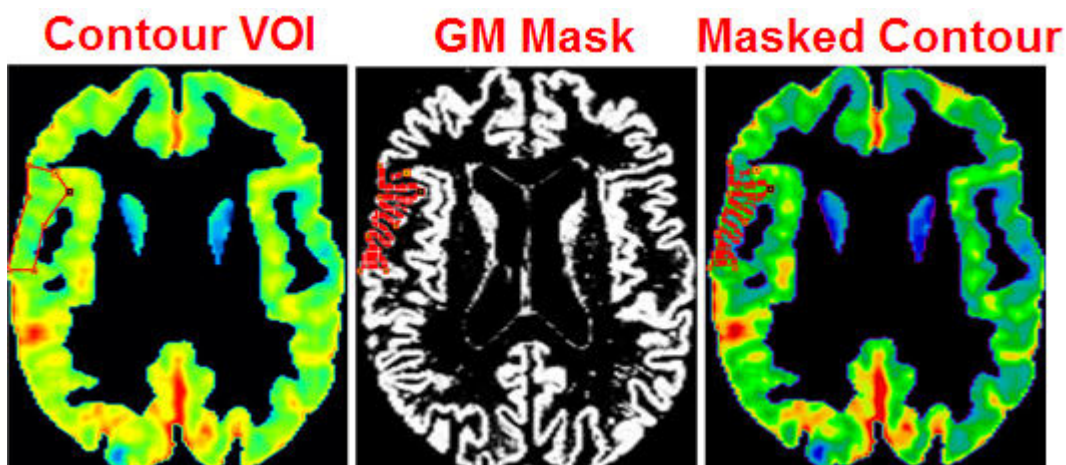
10.6 Applying VOI Definitions

Once VOIs have been defined, they can be applied to the underlying data in various ways, to

- analyze the distribution of the pixel values enclosed in the VOIs;

- assess the geometry of the VOIs themselves like volume, surface area, sphericity;

- use the VOI geometry for modifying the data such as masking or cropping;

- create an atlas from the contour VOIs.

The calculations are started from two different locations, using the buttons above the **VOIs** list,
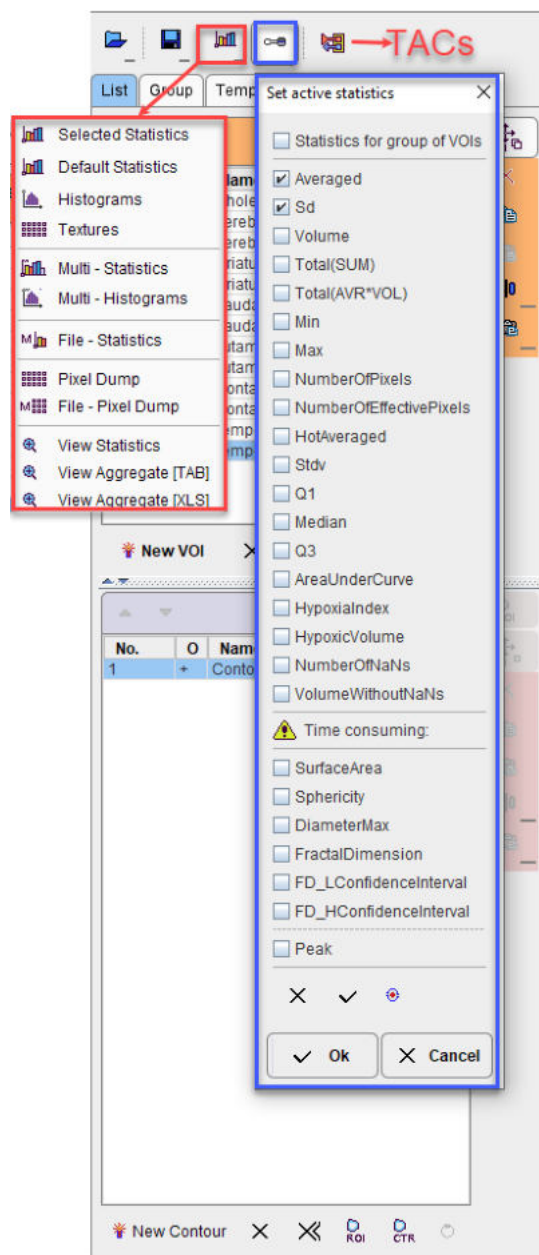
and using the tools in the panel in the lower right.
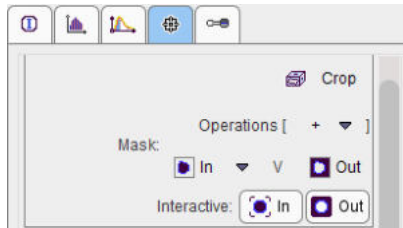
10.6.1 Statistics of VOI Pixel Values

The statistics menu offers various types of calculations
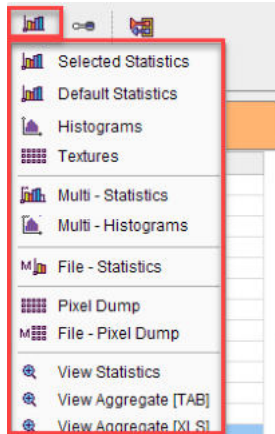
- **Selected Statistics:** Applies the VOIs to the current image and shows the results of the configured statistics on the Statistics Viewer 327 panel.

- **Default Statistics**: Applies the VOIs to the current image and shows the default statistics (which don't require too much calculation time).

- **Histograms**: Calculates and shows a pixel value histogram per VOI illustrating the value distribution.

- **Textures**: Quantifies the variability of the pixel intensities within a structure such as a tumor. With this selection 25 texture features 332 within the VOIs will be estimated.

- **Multi-Statistics**: Calculates the **Default Statistics** for all loaded images and shows the results on one panel per image. The outcome can then easily be merged into an aggregate.

- **Multi-Histograms**: Calculates the VOI histograms for all loaded images and shows them on one panel per image.

- **File-Statistics**: Performs the **Default Statistics** for a list of files image and saves the resulting statistics in a file. This procedure requires explicit image loading and is most useful when the images are in a normal (e.g. MNI) space, so that a standard set of VOIs can be applied.

- **Pixel Dump**: Extracts the VOI pixel values in the selected image and saves them together with the pixel coordinates in a file. This procedure gives the user the full raw data and allows him implementing his own statistical analysis.

- **File-Pixel Dump**: Performs the **Pixel Dump** for a list of files.

VOIs used for Statistics

The following VOIs are considered in the statistics calculations described above:

- All contour VOIs on the **List** tab.

- The VOI named **Group** which consists of the union of all contour VOIs selected on the **Group** tab.

- If on the **Template** tabs **Atlas** or **Mask** is active, the corresponding VOIs are also considered. Please enable the **Ovr** box to see these VOIs in the overlay.

- If a masking operation is configured on the **Atlas** or **Mask** sub-tab, it is applied to the contour VOIs during the statistics. Please enable the **Fill ROI** box to verify the actual coverage of the masked contour VOIs.

10.6.1.1 Statistics Measures

Statistics Calculation

The descriptive statistics are calculated using the values of all pixels classified for a VOI. With **Binary** classifications[228] each included pixel contributes equally. Pixels with NaN value are excluded from statistics. Correspondingly, they don't contribute to **Volume** or **NumberOfPixels**.

With **Fraction mode** classification, however the contribution of a pixel is proportional to the fractional area f_i included in the contour (f_i=1 fully included, f_i=0.5 50% included). This weighting applies for the **Average**, the **Standard Deviation**, the **Volume**, the **Total** and the **AUC**. For the other measures, which don't support fractional contributions, only the pixels with f_i>0.5 are used.

The statistics calculation using a probabilistic atlas[301] is similar to the fraction mode. The contribution of a pixel is proportional to its probability p_i for belonging to the VOI (p_i=1 certainly included, p_i=0.5 included with 50% probability). For measures, which don't support fractional contributions, only the pixels with probability above a user-defined threshold (p_i>p_t) are used.

Notes:
1. Due to calculation of the fractional area, statistics using the **Fraction mode** is substantially more time-consuming.
2. The fraction mode is not effective for automatically generated VOIs (iso-contouring, atlases), because the contours follow the pixel boundaries.

Statistics Measures

The statistics measures of interests can be configured with the configuration button 🔧 as illustrated below:
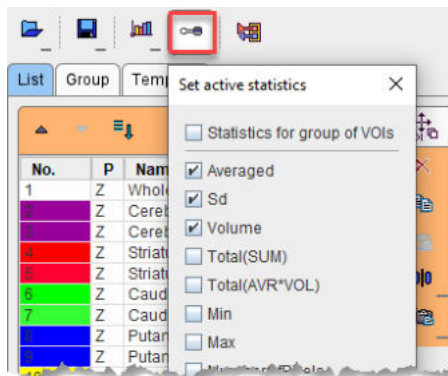
The selection is serialized. Please note that at least one statistic measure is required to be configured. Following measures can be configured:

Averaged	Average of the pixel values. **Fraction mode**: Sum(f_i*v_i)/Sum(f_i). v_i value of pixel i. **Probabilistic atlas**: Sum(f_i*p_i)/Sum(p_i). p_i probability of pixel i for belonging to VOI$_i$.
Sd	Population standard deviation of the pixel values. $$\sigma = \sqrt{\frac{\sum (X - \mu)^2}{n}}$$

	Fraction mode: a weighted standard deviation is [calculated](#) accounting for the pixel area included in the contour. **Probabilistic atlas**: a weighted standard deviation is [calculated](#) accounting for the probability of pixel i for belonging to VOI_i.
Volume or **MTV**	Volume of the VOI pixels. It is based on the pixel size in x and y and the slice thickness in z. **Fraction mode**: $Sum(f_i)$*pixel-volume. **Probabilistic atlas**: **NumberOfPixels***pixel-volume. In the context of oncology, the volume is called **MTV** (Metabolic Tumor Volume).
Total(SUM)	Sum of the pixel values. The interpretation depends on the image contents. In the case of activity units the result will be total activity in the VOI. **Fraction mode**: $Sum(f_i^*v_i)$, **Probabilistic atlas**: $Sum(p_i^*v_i)$.
Total(AVR*VOL) or **TLG**	Average of the pixel values multiplied by the VOI volume. The interpretation depends on the image contents. In the case of activity *concentration* units, the result represents total activity in the VOI. **Fraction mode**: $Sum(f_i^*v_i)$*pixel-volume, **Probabilistic atlas**: **Average***Volume. In the case of SUV units, the result is called *Total Lesion Glycolysis* (**TLG**). The TLG is usually calculated in combination with a lower range.
Min	Minimum pixel value. **Fraction mode**: Considers pixels with $f_i>0.5$. **Probabilistic atlas**: Considers pixels with $p_i>p_t$.
Max	Maximum pixel value. **Fraction mode**: Considers pixels with $f_i>0.5$. **Probabilistic atlas**: Considers pixels with $f_i>p_t$.
NumberOfPixels	Number of pixels included in the VOI. **Fraction mode**: Considers pixels with $f_i>0.5$, **Probabilistic atlas**: Considers pixels with $p_i>p_t$.
NumberOfEffectivePixels	**Fraction mode**: $Sum(f_i)$. **Probabilistic atlas**: $Sum(p_i)$. Otherwise equal to **NumberOfPixels**.
HotAveraged	The highest pixel values averaged. The default **Number of Hottest Pixels** values to be averaged can be set in the [User configuration](#) [33], and can be changed in the upper part of the statistics window. **Fraction mode**: Considers pixels with $f_i>0.5$. **Probabilistic atlas**: Considers pixels with $p_i>p_t$.
Stdv	Sample standard deviation of the pixel values. $$s = \sqrt{\frac{\sum(X-\bar{X})^2}{n-1}}$$ **Fraction mode, Probabilistic atlas**: analogous to **Sd**.
Q1	First quartile of the VOI pixel values. **Fraction mode**: Considers pixels with $f_i>0.5$. **Probabilistic atlas**: Considers pixels with $p_i>p_t$.

Median	Median value of the VOI pixel values. **Fraction mode**: Considers pixels with $f_i>0.5$. **Probabilistic atlas**: Considers pixels with $p_i>p_t$.
Q3	Third quartile of the VOI pixel values. **Fraction mode**: Considers pixels with $f_i>0.5$. **Probabilistic atlas**: Considers pixels with $p_i>p_t$.
AreaUnderCurve	Static data: **Averaged** times frame duration. **Fraction mode**: Sum(f_i*v_i*t)/Sum(f_i) (t = acquisition duration). **Probabilistic atlas**: Sum(p_i*v_i*t)/Sum(p_i). Dynamic data: Integral of the **Averaged** curve.
HypoxiaIndex	Fraction of pixels in the VOI which have a value above the threshold in the **Hypoxia Threshold** field. **Fraction mode**: Considers pixels with $f_i>0.5$. **Probabilistic atlas**: Considers pixels with $p_i>p_t$.
HypoxicVolume	Represents the number of voxels inside a VOIs with value greater than the hypoxia threshold multiplied by the volume of the pixel size. **Fraction** and the **Binary mode** - consider only the voxels with $f_i > 0.5$.
NumberOfNaNs	Represents the number of voxel with NaN value inside the VOI
VolumeWithoutNaNs	Volume of the VOI pixels which value is different from NaN. It is based on the pixel size in x and y and the slice thickness in z. **Fraction mode**: Sum(f_i)*pixel-volume.

Additional Measures with Time-consuming Calculations

SurfaceArea	Estimate of the VOI surface which is obtained by triangulating the contours and accumulating the triangle areas. **Fraction mode**: Considers pixels with $f_i>0.5$.
Sphericity	Index of how spherical a VOI is. The values range between 0 and 1 (perfect sphere). Wikipedia. **Fraction mode**: Considers pixels with $f_i>0.5$.
DiameterMax	Maximal distance between any two pixels in the VOI. The calculation can take substantial time and is restricted to VOIs enclosing less than 100'000 pixels. **Fraction mode**: Considers pixels with $f_i>0.5$.
Fractal Dimension (FD)	Measures the complexity of a 3-dimensional structure, approximated by a sphere, by calculating its box-counting dimension. Is an index for characterizing fractal patterns or sets by quantifying their complexity as a ratio of the change in detail to the change in scale. Wikipedia. It does not provide an absolute quantification and it is a real value between 0 and 3. Small values of FD in 3D VOIs indicate a complex structure. **Fraction mode**: considers pixel with $f_i>0$. For 2-dimensional ROIs (ROIs on one slice) the FD value is between 0 and 2.
FD_LConfidence Interval	Low confidence interval of the FD. **Fraction mode**: considers pixel with $f_i>0$.

FD_HConfidence Interval	High confidence interval of the FD. **Fraction mode**: considers pixel with $f_i > 0$.
Peak	Average of a sphere with predefine volume (default: 1ml) which is placed in the VOI such that the average is maximized.

A convenient tool, the fractal generator, is available in Pmod. It is accessible with the **Load** button configured on **Generated**:
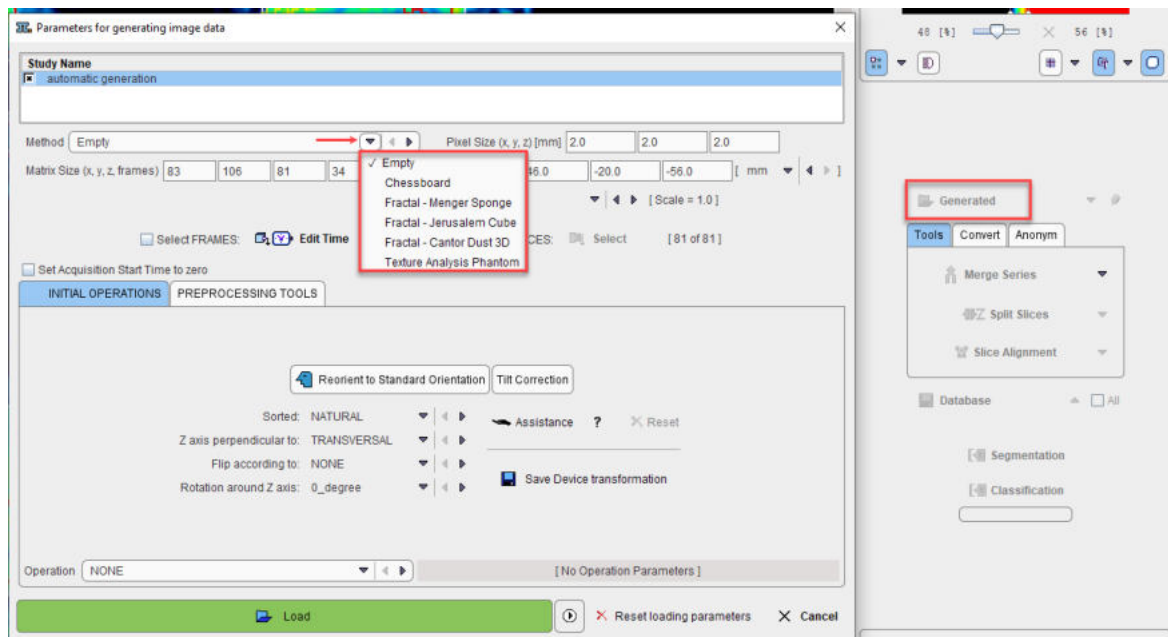
The tool allows creating data with well known fractals like **Menger Sponge**, **Jerusalem Cube**, **Cantor Dust 3D**. The FD value calculated with PMOD for a known fractal structure is very similar to the theoretical value. Wikipedia. The difference is due to the limited sample size.

10.6.1.2 Statistics Viewer

The dialog window for the **Statistics** output is illustrated below. The R page only appears when R statistics 350 is enabled.
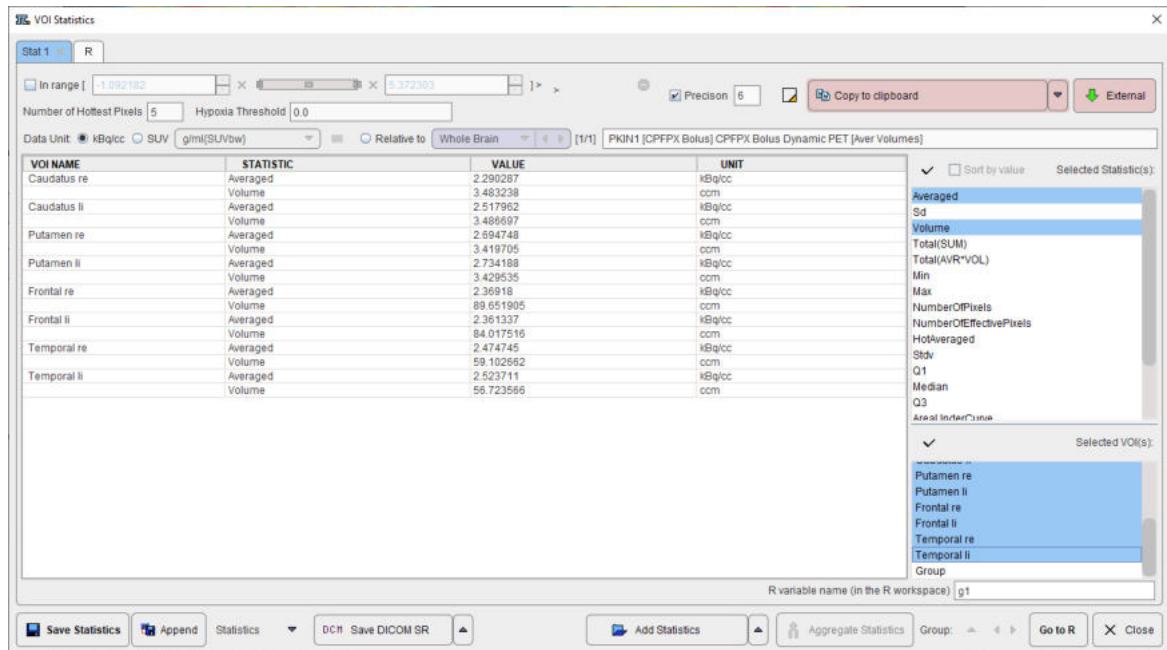
The calculated information is comprehensive and can be tailored by several user interface elements.

The list in the **Selected Statistics** area to the right shows all available statistics. Only the selected elements are shown in the table and will be exported. The default selection includes the **Averaged** and the **Sd**.

The **Selected VOI(s)** list in the lower right shows all VOIs and the Group VOI (if enabled) which were evaluated. Only the selected elements are shown in the table and will be exported.

The **In range** box allows restricting the statistics to the subset of pixels with values in a specific range. For example, by setting the lower threshold to 40% of the maximum it is possible to calculate the average value and the volume of all pixels above 40%.
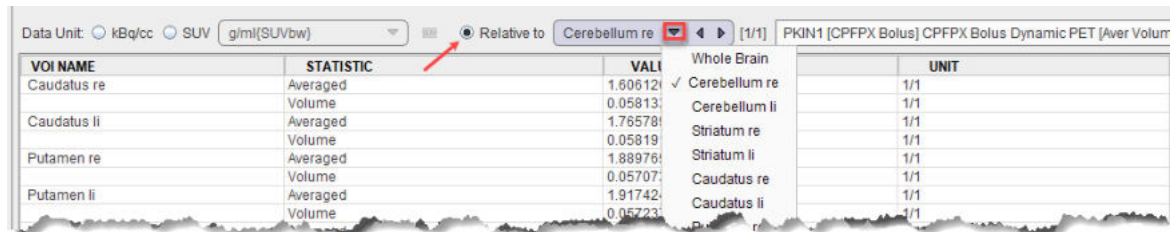
SUV Statistics

If the statistics are calculated from activity concentration images, the uptake results can be converted to different types of SUV 147 values if the related activity information is contained in the image header. If this is not the case, the information can be entered after activating the **SUV** button.
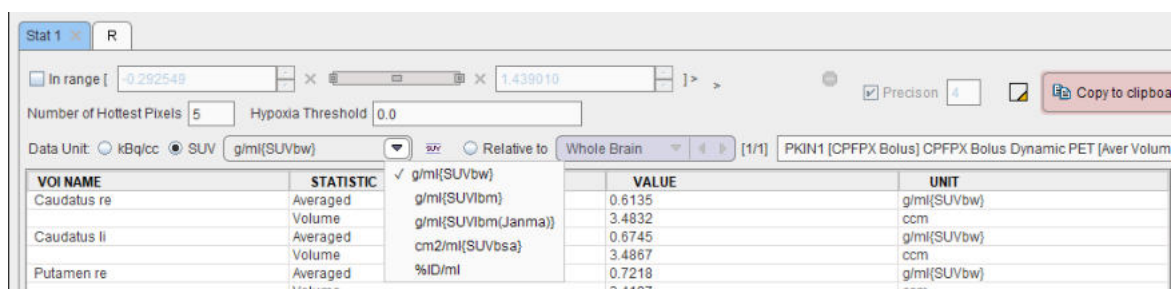
SUV Ratio Statistics

The SUV ratio SUVR is defined as the regional uptake value divided by reference tissue uptake. It is a frequently used semi-quantitative measure which removes many biases. SUVR calculation can be enabled with the **Relative to** radio button and selecting the reference region from the VOI list. Note that the ratio is not only calculated for the average, but also for all other measures.

Saving Options

There are several options to choose from when saving the statistics. The **Format** selection has three choices.
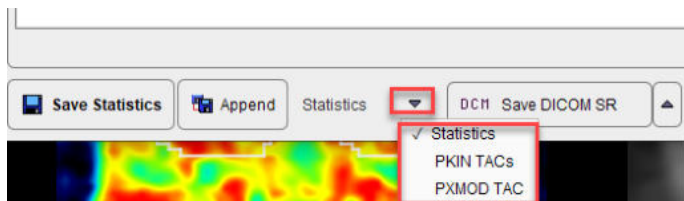
Statistics is a tabular text file format aimed at statistics programs. Starting with version 4.2 the **Enhanced statistics** format is exclusively used.

PKIN TAC(s) is aimed at loading the saved information as tissue curves into the kinetic PKIN tool.

PXMod TAC will only export the time-activity curve of the **Group** VOI in a two-column format. This data is intended for use in the pixelwise modeling tool PXMOD.

Please use **Save Statistics** for saving the data in a new tab-delimited text file with extension **.voistat**, and **Append** for appending it to an existing statistics file. Furthermore, the statistic results can be saved as a DICOM Structured Report with the **Save DICOM SR** option or directly sent to a DICOM server with the **Export DICOM SR**.

Load Statistics Files into Viewer

Statistics files saved in the **Statistics** format can be loaded back into the statistics viewer. There are several ways to do so:

1. from the VOI interface using the **View Statistics** option in the **Statistic** selection list;
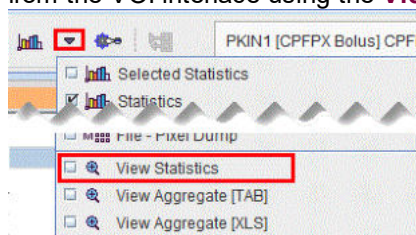
2. from the open statistics viewer using the **Add Statistics** option
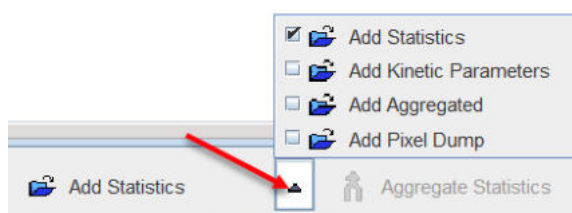
3. from the lateral taskbar of the PVIEW tool
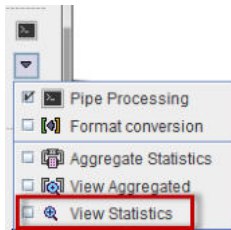
Multiple Statistics

If the statistics is calculated for multiple files, the results are shown in the statistics viewer on separate pages. Similarly, when loading a statistics from a file, a new page is added to the statistics viewer. In this case, the **Aggregate Statistics** button becomes active and allows creating an aggregate from all open statistics pages.

Transfer to R

The statistics viewer includes an interface to the R statistics environment, if this feature is configured. The **Go to R** button will transfer the statistics of all open data to the R console ₃₆₀ creating one R variable per tab.

10.6.1.3 Histogram

The **Histogram** mode analyzes the distribution of pixel values in the VOI by sorting them into a number of value ranges (bins) with equal width. The bin width is obtained by dividing the overall value range by the **Number of bars**. There are three options for defining the overall value range:
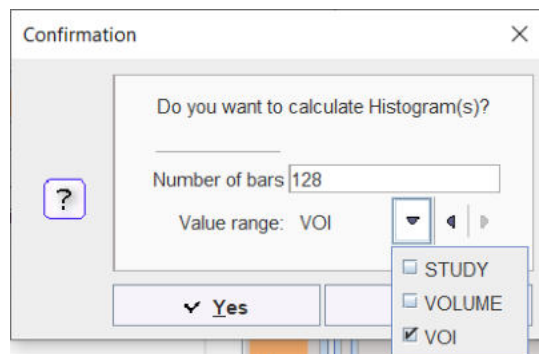
STUDY uses the min/max values of the entire data set, **VOLUME** the min/max of the current frame, and **VOI** the min/max of all pixels enclosed by a VOI. The appearing statistics viewer window represents the VOI histograms as curves with the mid-value of the bin on the x-axis, and the number of pixels with values in the bin range on the y-axis.

π.pmod
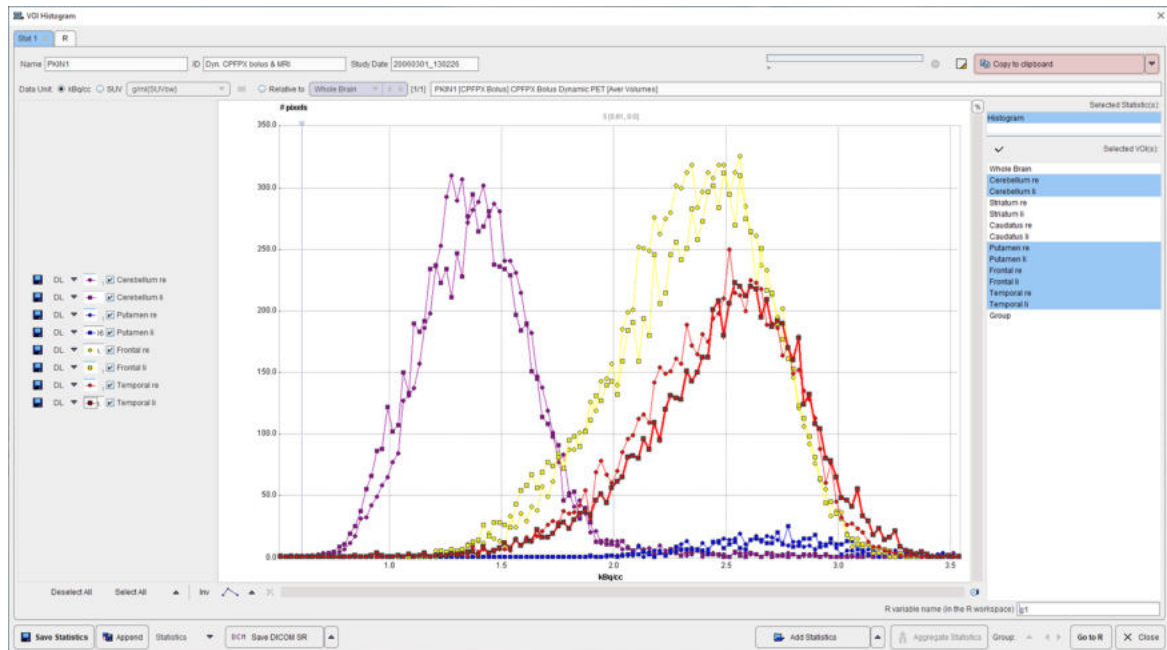
The histograms can be saved and exported in various ways, as statistics or curves.

10.6.1.4 Pixel Dump

The **Pixel Dump** serves for saving the raw values of all classified VOI pixels into a file. It shows a dialog window for defining the VOI selection.
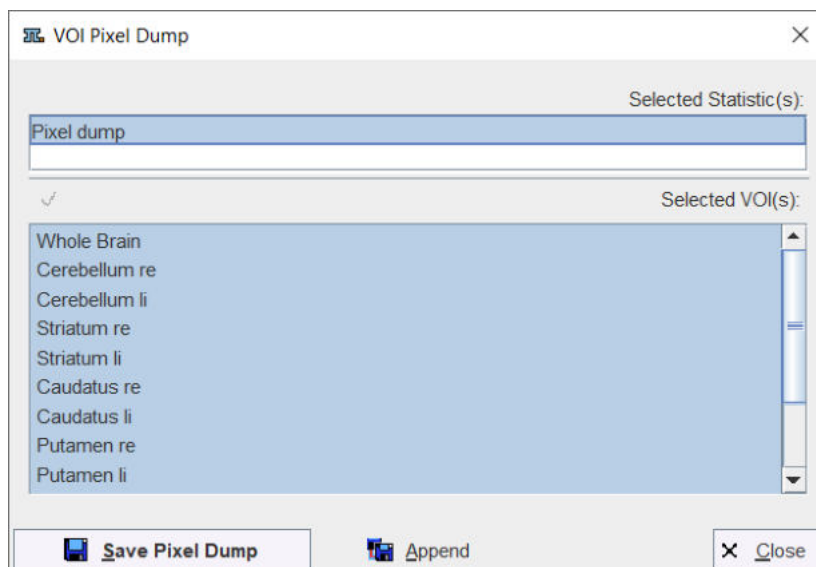
The results can be saved to a new file or appended to an existing one. The output has a tabular format, with the main part being the pixel coordinates and the value.

X [pixel]	Y [pixel]	Z [pixel]	Value [kBq/cc]
28	50	36	2.51422
28	51	36	2.506756
28	52	36	2.645055
28	53	36	2.725984
29	45	36	2.522795
29	46	36	2.58447
29	47	36	2.823405

It can easily be imported into statistics programs for a detailed analysis of the value distribution.

10.6.1.5 File-Based Statistics

The **File Statistics** allow applying the same statistics to a set of files in a batch mode operation. A dialog window appears for selecting the VOIs of interest and the files to be processed. Note that only files in a same format as the open image with the VOIs can be used.
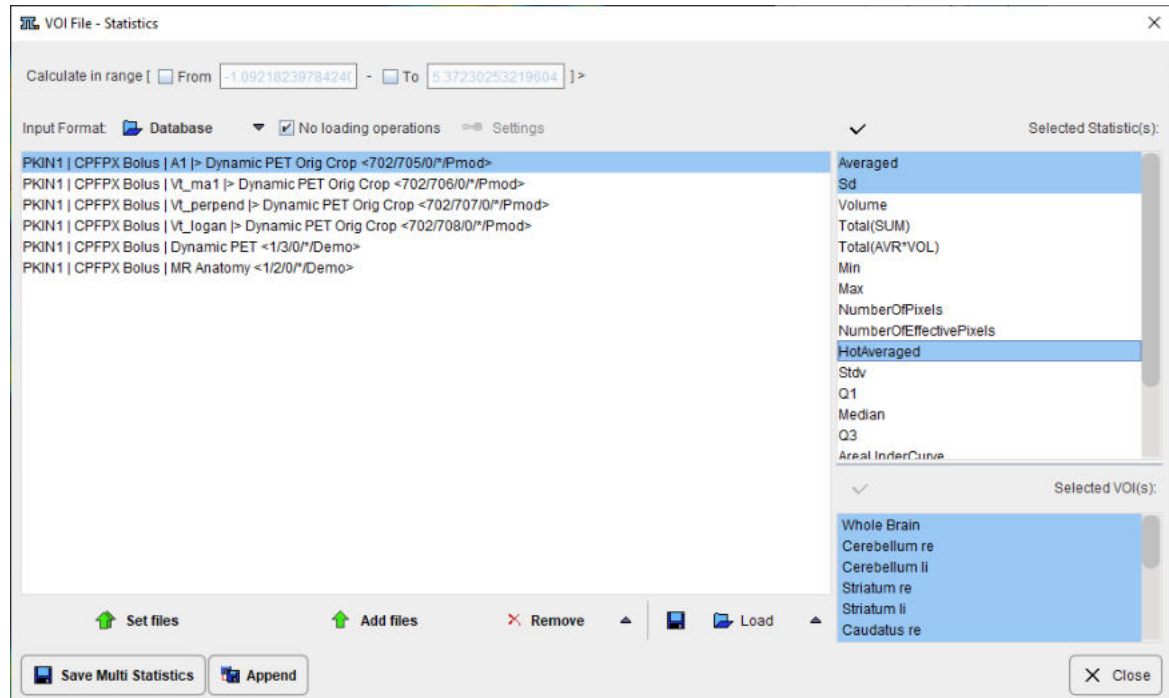
Calculate in range	Restrict the pixels to be included within a value range.
No loading operations	If the box is checked the image are loaded without any data transformation. Otherwise a pre-processing can be specified using the **INPUT format settings** button.
Set files	For selecting the images to be analyzed.
Add files	For adding additional files to the list.
Remove	For removing the selected files from the list.
🖫 Save 📂 Load	For saving/loading a file list configuration.

After activating **Save Multi Statistics**, PMOD will prompt for an output file name, and the calculations will be started.

10.6.1.6 Texture Analysis

Texture analysis quantifies the variability of the pixel intensities within a structure such as a tumor. There is a plethora of metrics, which is discussed for instance by Hatt et al. [1] or Sollini et al. [2]. The hope is that (some of) these metrics permit in vivo lesion characterization and provide predictive information about the tumor malignancy.

Rather than calculating hundreds of indexes, the texture analysis implemented in PMOD provides a collection of 64 indexes which have been found to be most valuable in the context of PET imaging. 23 are based on the pixel histogram within a VOI, 25 based on the gray level co-occurrence matrix (GLCM) and 16 based on the gray level run length matrix (RLM). The calculations have been

implemented and tested according to the report of the Image Biomarker Standardisation Initiative (IBSI Documentation).

Once the VOIs have been outlined, texture analysis is started from the statistics menu. A dialog window is opened which allows configuring the analysis parameters in the left part and shows information related to the texture calculation in the two panels to the right.
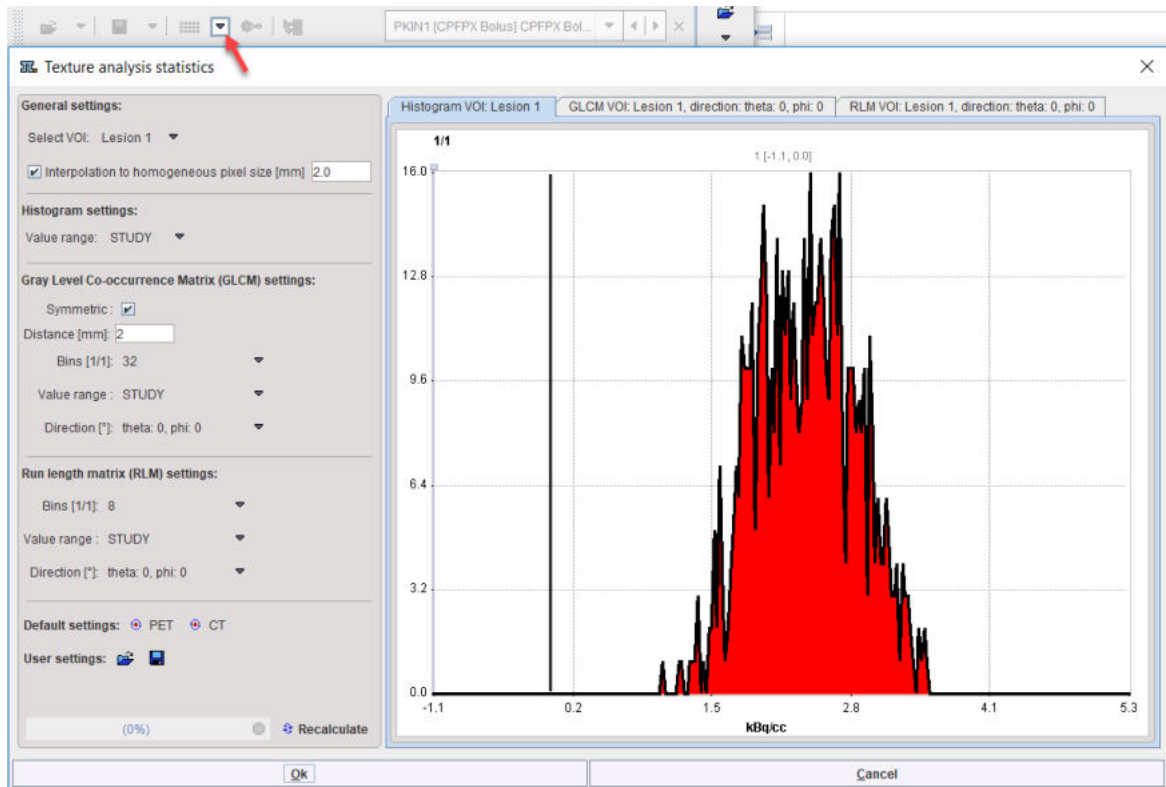
Select VOI allows choosing a representative VOI for which the information in the panels is updated. **Interpolation to homogeneous pixel size** is recommended for data which doesn't have isotropic resolution, and uses trilinear interpolation.

Histogram Analysis Configuration

The **Histogram** panel shows the histogram of the values within the selected VOI. The **Value range** selection defines whether the 256 bins cover the range of the **STUDY**, the current **VOLUME**, or just the **VOI** itself. This will be the input into the histogram-based analysis.

Gray Level Co-occurrence Matrix (GLCM) Analysis Configuration

The GLCM calculation is configured on the **Gray Level Co-occurrence Matrix settings**: The pixel values are quantized into a small number (N) of discrete values. Similar to the histogram, this process is defined by the specified number of **Bins** (eg. **32)** which cover the range of the **STUDY**, the current **VOLUME**, or just the **VOI** itself, according to the **Value range** selection.

The occurrence of the quantified values in neighbouring pixels is analyzed, and co-occurrences recorded in a NxN matrix (GLCM): A value i next to a value k will increment the number in the co-occurrence matrix at coordinate (i,k) by 1. If **Symmetric** is enabled, coordinate (k,i) is incremented as well, producing a symmetric GLCM. A pixel has several neighbors in different **Direction**s at a certain **Distance**. The co-occurrence can be analyzed in any direction individually. In fact the matrix resulting from the direction specified with the **Direction** selection is visualized in the GLCM tab. Note, however, that the average matrix of all directions is used for the calculation of the GLCM-based indexes.

Gray Level Run Length Matrix (RLM) Analysis Configuration
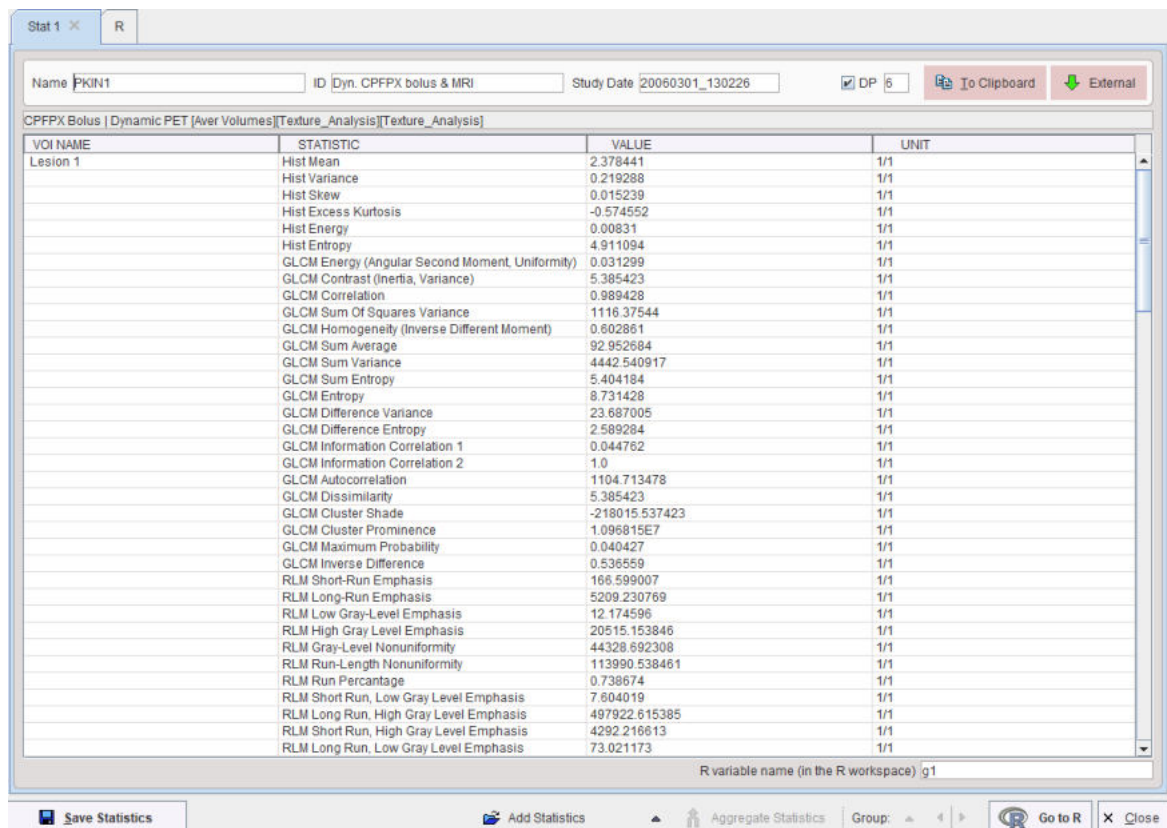
The RLM consists of the following steps to be configured on the **Run Length Matrix (RLM) settings**: As for the GLCM, the pixel values are quantized into a small number (N) of discrete values. A run length is defined as the length of a consecutive sequence of pixels with the same gray level along direction a certain direction.

Texture Calculation

Recalculate initiates calculation of the Histogram and the GLCM/RLM matrices for the VOI with the configured parameters and shows them for preview in the three panels.
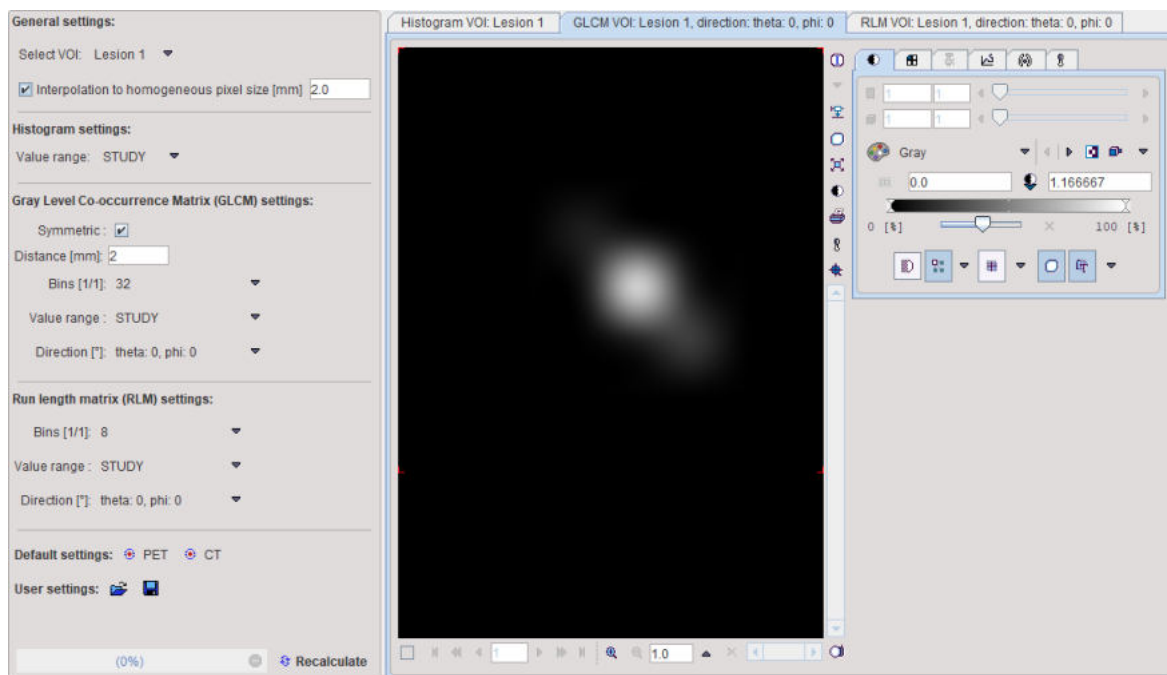
The metrics are calculated according to the formulas specified in the supplemental material of [1], please see there for explanations. They are obtained for all defined VOIs by activating the **Ok** button, and are shown in a Statistics Viewer 327 window, whereas the configuration window is closed.

References

1. Hatt M, Tixier F, Pierce L, Kinahan PE, Le Rest CC, Visvikis D: Characterization of PET/CT images using texture analysis: the past, the present... any future? Eur J Nucl Med Mol Imaging 2017, 44(1):151-165. DOI

2. Sollini M, Cozzi L, Antunovic L, Chiti A, Kirienko M: PET Radiomics in NSCLC: state of the art and a proposal for harmonization of methodology. Scientific reports 2017, 7(1):358. DOI

10.6.2 Data Modification

VOI definitions can be used to modify the data inside or outside of the VOI. The related tools are grouped in the **Data Modification** section of the VOI tools panel.
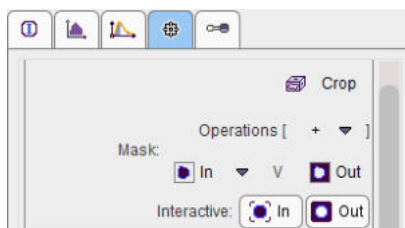
They are descibed in the following sections.

10.6.2.1 VOI-based Image Cropping

The bounding box of contour or object VOIs can be used for cropping image series to a sub-volume of interest. The example below illustrates the following situation:

1. A sphere VOI was placed on the brain part of a whole-body PET.

2. After activating the **VOI action** button the sphere was scaled to and ellipsoid enclosing the brain with some margin.

3. The **Crop** button was activated.
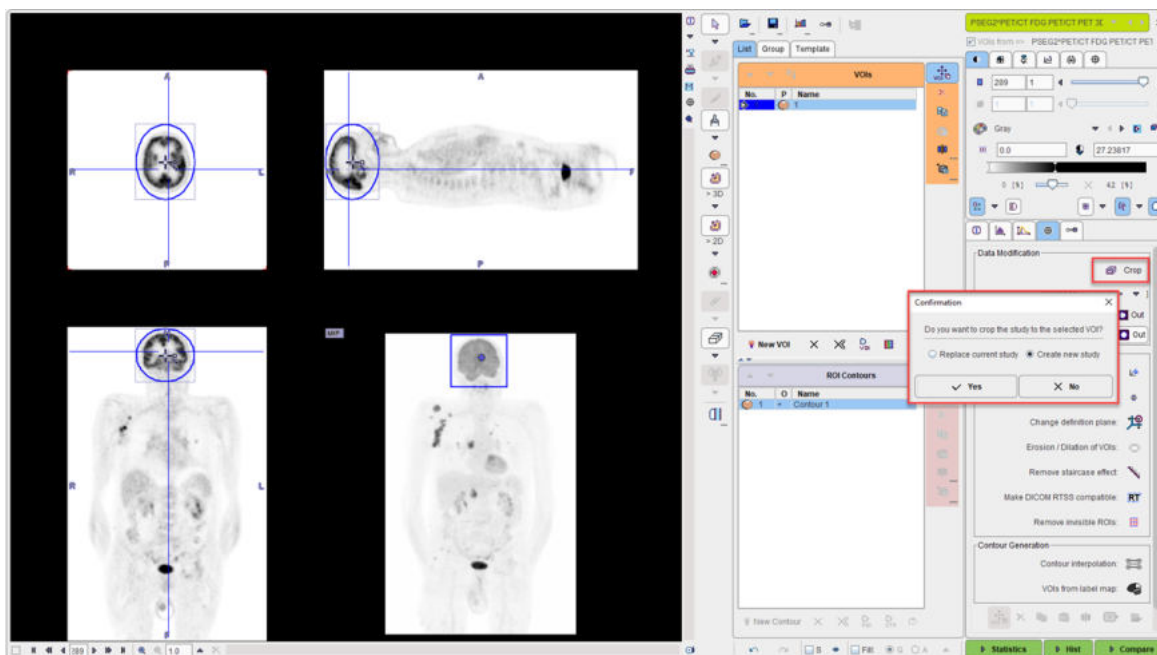
When accepting the **Confirmation** dialog the resulting image series just includes the data volume defined by the bounding box of the ellipsoid.
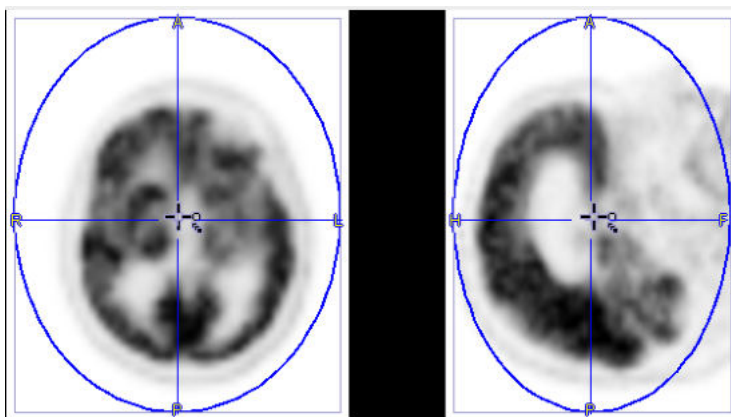
Note that if the **Group** panel is selected, the cropping volume is defined by the bounding box enclosing all selected VOIs.
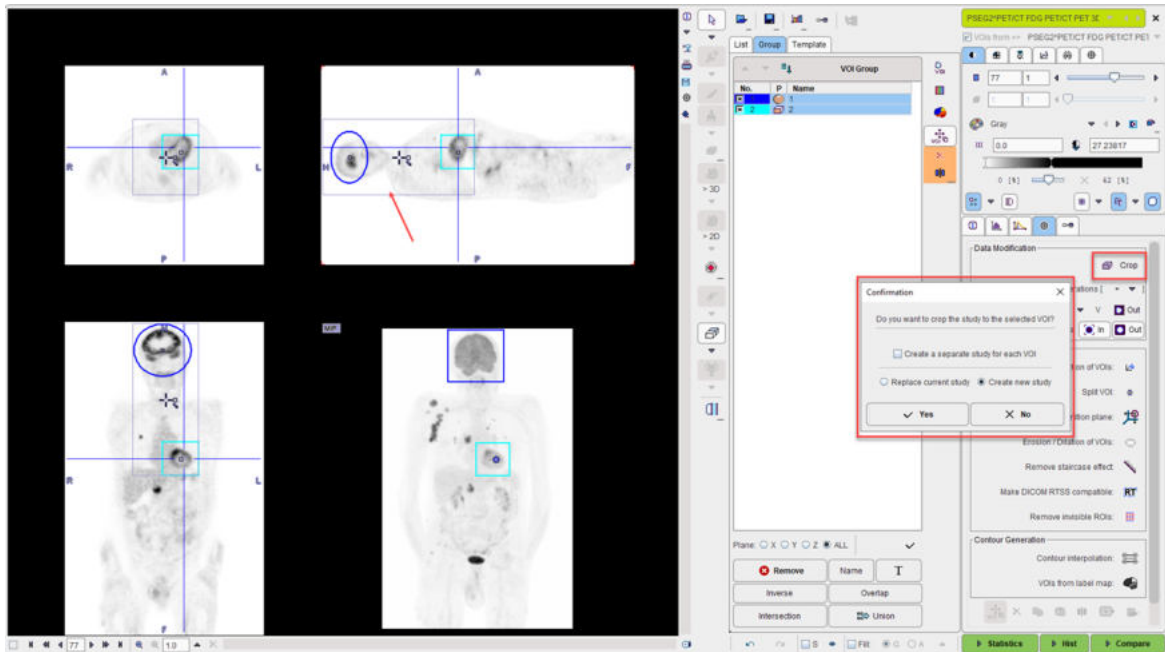
The cropping of images allows reducing the RAM requirements, and may focus data processing on the relevant parts of the image.

10.6.2.2 Data Masking Inside and Outside of VOIs

The **Mask In** and **Out** functionality allows replacing the pixel values by constants. For masking **In** there are four different variants
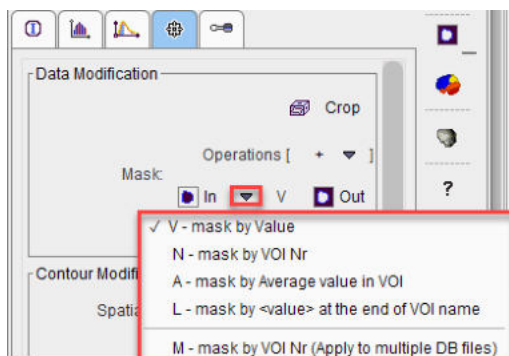
for specifying the replacement value

- **V - Mask by Value**: provides a field to specify the replacement value;

- **N - Mask by VOI nr**: uses the index of the VOI in the **VOIs** list;

- **A - Mask by Average value in VOI**: uses the VOI average;

- **L - Mask by <value> at the end of VOI name**: assumes a VOI encoding of the form "VOI-name<val>" and uses val for masking;

- **M - Mask by VOI nr (Apply to multiple DB files)**: allows selecting multiple VOI files; for each of the VOI files an image is saved using the **Mask by VOI nr** procedure.

The dialog window which appears is dependent on the method selected, but looks similar as the one illustrated below. As additional option it allows setting non-VOI pixels to a certain value, and to overwrite the data or create an additional data set.
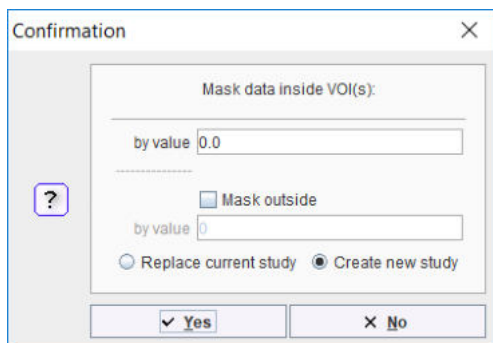
For masking **Out**side there are no variants. The dialog window allows specifying the background value, and optionally a value for masking inside.
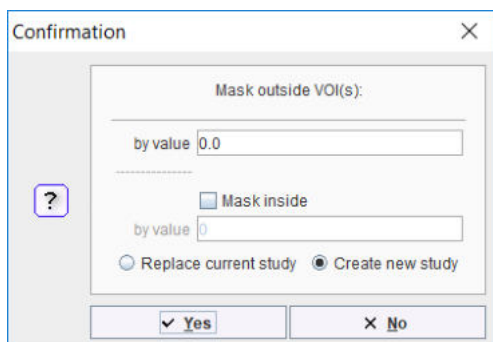
10.6.2.3 Algebra within VOIs

The algebra functionality allows applying an arithmetic operation to the pixel values within the VOIs. The four basic operations are available and can be selected from the list as illustrated below.
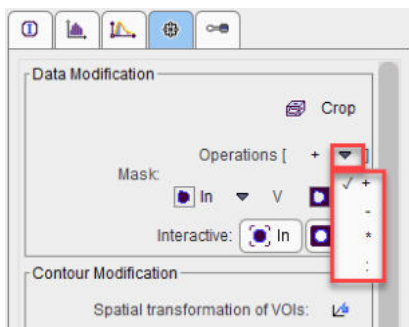
A **Confirmation** dialog appears for defining the operator argument, and optionally a background masking value.
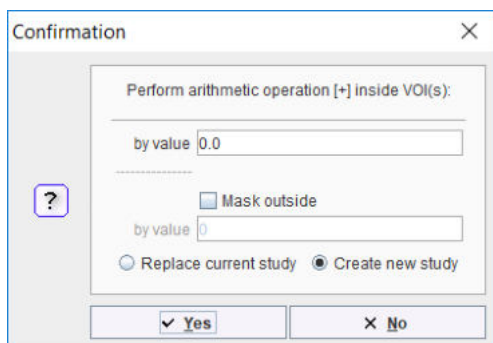
10.6.2.4 Interactive Data Masking

The **Interactive** masking methods do not work with existing VOIs. Rather, the user clicks at central point of the object to be masked and holds down the mouse button. While holding down, a growing sphere is shown, centered at the clicked point. A **Confirmation** dialog appears as when releasing the mouse button as illustrated below for the case of **Interactive Inside** masking. It allows defining the masking value, and whether the masking should be applied to a cloned series. The **Outside** masking works in strict analogy.
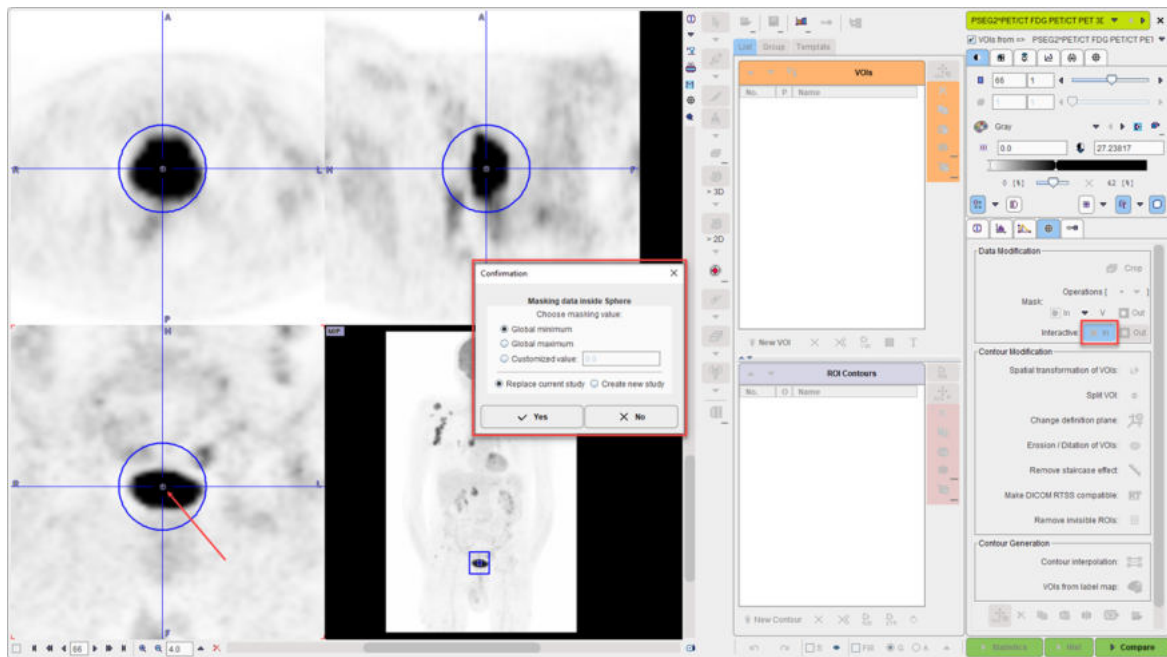
The resulting data is void in the masking area.
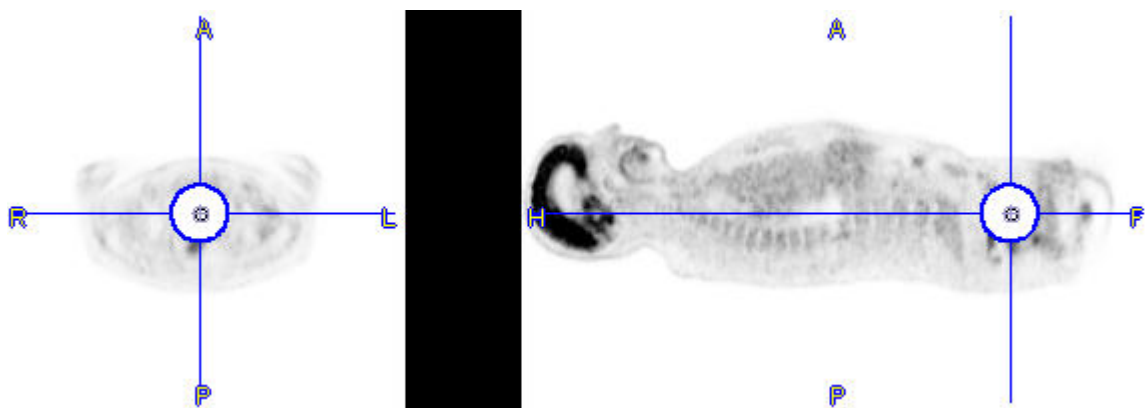
The masking operation with successive dialog window repeats with each click into the image. To stop this behavior, please select the **Neutral** button indicated in the example above.

Note: The dialog window can be omitted to facilitate quick interactive data adjustments. To do so, disable the **Confirm removal operation** box in the configuration of the **View** tool, on the **Display** tab in **VOI DEFINITION** area.

10.6.3 Time-Activity Curves

An important usage of the VOI analysis is the generation of time-activity curves (TAC) from dynamic PET series for subsequent kinetic modeling. Naturally, the first step is to outline an appropriate set of VOIs, for instance by:

- loading the dynamic series, averaging a frame range so that the result shows enough anatomical information, and outline the VOIs on the average;

- trying to normalize an atlas to the average image and use the resulting atlas VOIs; or

- matching the PET series to an anatomical MR series which is used for the VOI outlining

Once the VOIs are defined in the space of the dynamic PET image, the TAC can be calculated as the VOI average for each frame.

Note: The dynamic image data needs to be loaded with the *correct acquisition times* and the *correct input units*. This is important, because otherwise the acquisition start/end times in kinetic modeling will be wrong, and the TACs may be different in magnitude with respect to the blood data. Such problems result in erroneous model parameters.

10.6.3.1 Time-Activity Curve Generation with Transfer to PKIN

If a dynamic series has been loaded and VOIs are defined, the 🔲 becomes active, it the PKIN option is included in the PMOD license. At allows calculating the TACs and transferring them directly to the PKIN tool.

A dialog window appears which is organized in four areas:

1. The left area allows defining the proper type (TISSUE, WHOLE BLOOD) of the calculated TACs and selecting the regions to be transferred.

2. The central area shows the selected TACs.

3. The right area controls the displayed TACs. Additionally, the **+-** buttons allow for simple arithmetic operations with the curve values before transfer to PKIN.

4. The lower area offers several options to modify the calculated TACs.
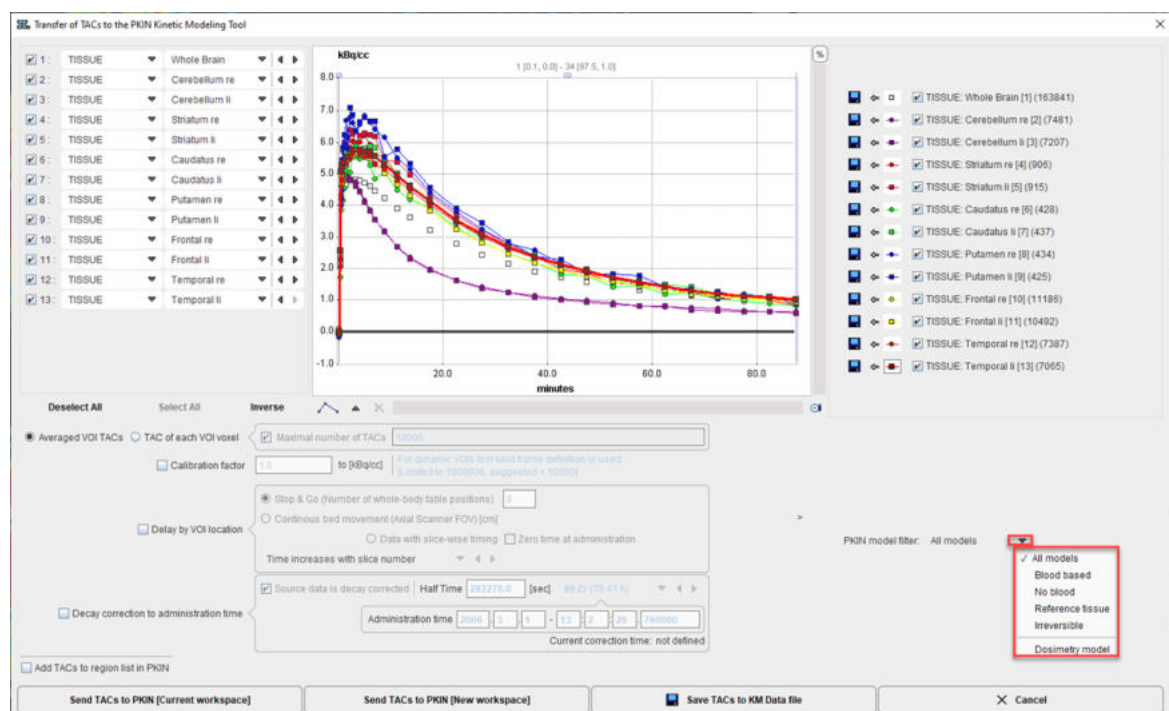
The following options are supported

Averaged VOI TAC

The standard and default procedure is to transfer the signal average in the VOIs, corresponding to the radio button **Averaged VOI TAC**. In addition to the average the standard deviation is also calculated and transferred as it is potentially useful for weighted fitting in PKIN.

TACs of each voxel

Instead of transferring the average signal per VOI, the individual TACs of the voxels enclosed in the VOIs can be transferred. This behavior is set by the **TAC of each VOI voxel** button. For performance reason there is a maximum number of TACs which will be considered for the transfer, per default set to **10'000**. The number of voxels in the selected VOIs is shown in brackets in the control section. Naturally, the standard deviation is zero in this case.

TAC Value Operations

The calculated TAC values can be modified in two ways.

1. Every individual curve has a **+-** button which allows multiplying the values with a factor, dividing, adding or taking the logarithm.
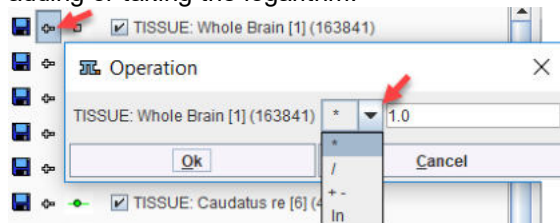
2. All generated curves can be scaled with a factor defined by the **Global scale factor to kBq/cc** option.

TAC Time Shifting

If image data acquisition requires multiple table positions (e.g. dynamic whole-body PET), the timing between VOIs may differ. The timing relative to the injection is crucial for modeling and also for dosimetry. Therefore, the **Delay by VOI location** option is supported
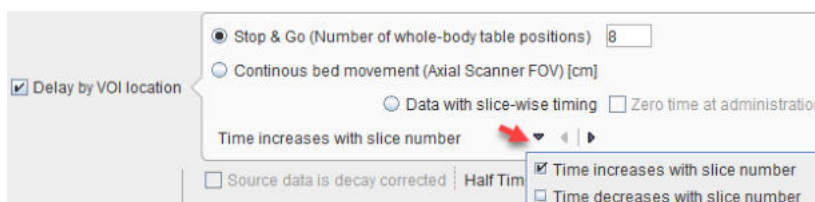
with three alternatives:

- **Stop & Go** corresponds to the standard acquisition mode with the table halting in adjacent, overlapping field of views. As there is usually not enough information in the image headers to know for each slice the exact timing, the timing of the different table positions is obtained by dividing the acquisition duration by their number.

- **Continuous bed movement** assumes that the subject is scanned while the table is continuously moving. Here the axial scanner field of view is required for approximating the time when a VOI is scanned.

- **Data with slice-wise timing** was introduced to handle data acquired on scanners with continuously moving tables. In this case each slice has an individual time. If the series was acquired after tracer administration (which is recorded in the image), the **Zero time at administration** box can be enabled to add the time offset to the reference times of the slices.

Note that the timing derived from these settings can only be approximate and may need correction. The resulting timing of the TAC curves is updated in the curve window whenever one of the settings is changed. Depending on the scanning, the time shifts may be applied in the wrong direction. For instance, the bladder curve may start before the brain curve although the data was acquired in head-in position. To rectify such a case there is a switch **Time increases with slice number**/**Time decreases with slice number**. For **Averaged VOI TAC** transfer, the timing of the VOI center will be used.

Model Selection

The **Model Selection** option allows filtering the list of the PKIN models according to the intended modeling. For the **Dosimetry model** the **Cumulated Activity (OLINDA, IDAC)** model will be set after the TAC data have been transferred to the PKIN tool together with the **Total body mass** of the subject. This information is extracted from the demographic information in the image, and can be edited if it is not present.

Decay Correction

If the **Decay correction to Injection time** flag allows correcting the TACs to a n injection time which may be before the first acquisition. If the **Source data is decay corrected**, only a scaling factor is applied. Otherwise, a time-dependent correction is used.

Data Transfer

The **Send** buttons initiates the transfer of the activity curve data to the PKIN tool. Selecting **Send TACs to PKIN [Current workspace]** transfers the TACs to the currently selected tab in an open PKIN tool. With the **Append TAC Data** box checked, the curves are appended as new regions to the existing data, otherwise the current data is over-written. **SendTACs to PKIN [New workspace]** first creates a new tab in PKIN, to which the data is added. If PKIN is not running, the tool is first started and the data added. Save **TACs to kmData** file allows creating a text file which is ready to be used in PKIN batch processing or to process at any later time point in PKIN by loading it through the menu **Kinetic/Load KM file**.

In addition to the TACs, subject and study related information is also transferred.

10.6.3.2 Time-Activity Curve Generation with Statistics

If the PKIN option is not available, the TACs of a dynamic series can also by obtained with the **Default Statistics** button , resulting in the dialog window illustrated below.
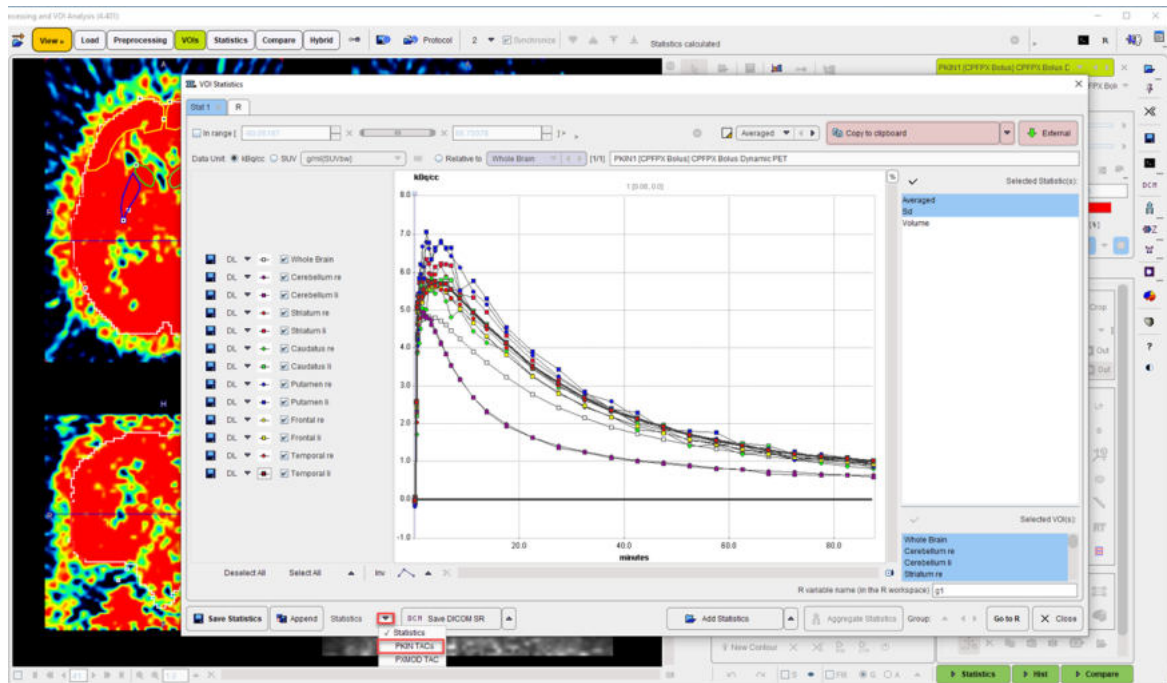
In **Selected Statistic(s)** enable the **Averaged** entry, choose the **PKIN TAC(s) Format** and then use **Save Statistics** to create a simple text file with VOI average values at the different acquisitions in the columns as illustrated below. This file can directly be loaded in PKIN.

start[seconds]	end[kBq/cc]	Group	Whole Bra	Cerebellur	Cerebellun	Striatum r	Striatum li	Caudatus	Caudatus l	Putamen r	Putamen li	Frontal re	Frontal li	Temporal	Temporal li
0	10	-0.05713	-0.05709	-0.06256	-0.06269	-0.10772	-0.03457	-0.04228	0.066949	-0.18658	-0.12335	-0.04016	-0.04073	-0.07194	-0.04171
10	20	0.015029	0.014963	-0.05756	-0.0629	-0.073	-0.05132	-0.13887	-0.06886	-0.01763	-0.07502	0.044762	0.03986	0.046922	0.028082
20	30	2.269081	2.268364	2.433337	2.223745	2.041686	2.306371	1.707154	2.196768	2.352334	2.473349	2.396696	2.498618	2.616396	2.557255
30	40	4.65126	4.648449	5.370504	5.071967	3.899469	4.365991	3.856465	4.28211	4.058806	4.224457	4.685052	4.953163	5.101523	5.064997
40	50	4.784605	4.783243	5.207803	5.413832	4.195986	4.630343	3.896166	4.27838	4.47612	4.986944	4.939526	5.2229	5.099642	5.193522
50	60	4.719459	4.719956	5.263382	5.294201	4.78192	5.719754	4.119841	5.43466	5.468351	5.835935	5.257427	5.173898	5.243883	5.336207
60	80	4.731911	4.733198	5.265077	4.988845	5.200914	5.937181	4.517336	5.653295	5.964794	6.205755	5.262044	5.28565	5.271394	5.296321

10.6.4 Creation of a VOI Atlas

An image series for which a set of contour VOIs has been defined can easily be converted into a VOI atlas as follows:

1. Load the image series in the PVIEW tool.

2. Load the contour VOIs in the **VOIs** page.

3. On the **Group** tab, select the VOIs to be included in the atlas.

4. Activate the **Create Template Atlas** icon on the right side of the **VOI Group**.
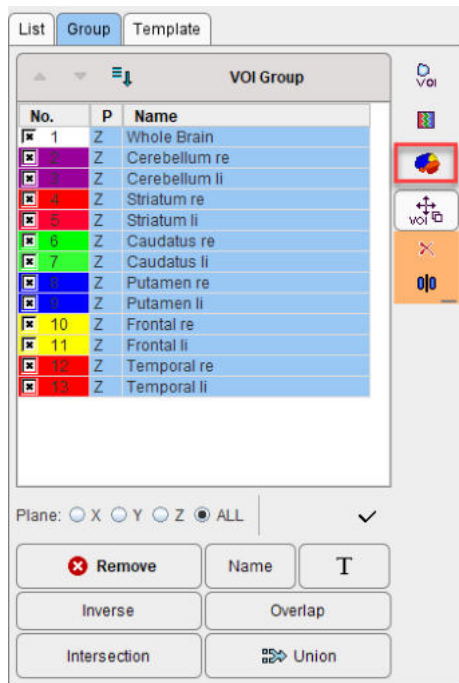
A dialog window appears which requests an **Atlas name** for template.
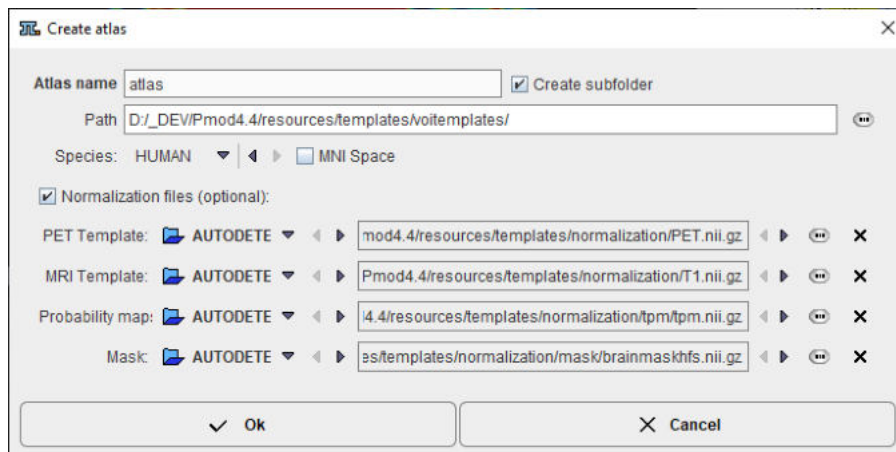
Using this name a subdirectory is created in the **Path** directory which defaults to *resources/templates/voitemplates*, but which can be changed. The **Species** selection allows tagging the VOI atlas so that it will be shown in the corresponding context.

An image series is generated which encodes each VOI pixel as an appropriate numeric label and saved in NifTI format. Additionally, a text file is created for the mapping of the numeric labels to VOI names. The procedure also creates a manifest text file which will contain information about the selected **Species**: "SPECIES = HUMAN". After activating the refresh button 🔄 in the **Atlas** panel of **Template**, the new template appears and can be used for statistics.

For human VOI atlases created in standard MNI space it is recommended to enabled the **MNI Space** box. It creates an entry "SPACE = MNI" in the manifest file which contains information about the species, so that the standard set of normalization templates will be used as normalization files. In such scenario there is no need of definition for the **Normalization files** (optional).

> **Important**: Because each pixel can only have one numeric label, the VOIs used for the atlas generation may not be overlapping.

Optionally, files for the spatial normalization can be defined for the template which are not in standard MNI space. To this end enable the **Normalization files (optional)** box and select as

many template files as available: The **PET Template, MRI Template**, and the **Mask** will be used for the deformable registration. To also use the Probability Maps Normalization a **Probability maps** file should be selected which encodes the Grey matter, White matter and CSF probability maps as a dynamic data set. In this case, a **normalization** folder is created with the normalization images in NifTI format. It also contains a **mask** sub-folder for the mask image (mask.nii), and a **tpm** folder for the tissue probability map (tpm.nii).

10.7   Statistics Aggregation

The numeric output of VOI statistics as well as the numerical output of other tools can be compiled into a single aggregate file for further statistic analysis. Aggregation is supported for

- VOI statistics (.voistat files);

- kinetic tissue parameters from the PKIN tool (.kinPar files);

- the cardiac perfusion results of PCARD tool(.pcardRes files);

- the discrimination results of the PALZ tool (.palzRes files).

Each of the tools has an appropriate button Aggregate Statistics for starting the aggregation tool, and the aggregation interface works similarly.

Recommended Data Organization

Typically, the results of a population (control group, subject group) in a certain condition (test, retest) should be compiled into a single aggregate, and comparisons or tests performed between the aggregates.

It is recommended using the labeling facility of PMOD databases which allows defining a **Project (Prj)** and **Group (Grp)** label on the level of the image series. This information can be used for results filtering as described below.

In the example used below a VOI analysis has been performed with consistent VOI names using a brain VOI atlas and the results were saved with appropriate component names.

10.7.1   Data Selection

After aggregation has been started, a dialog window appears with the first page **1 Select components** open.
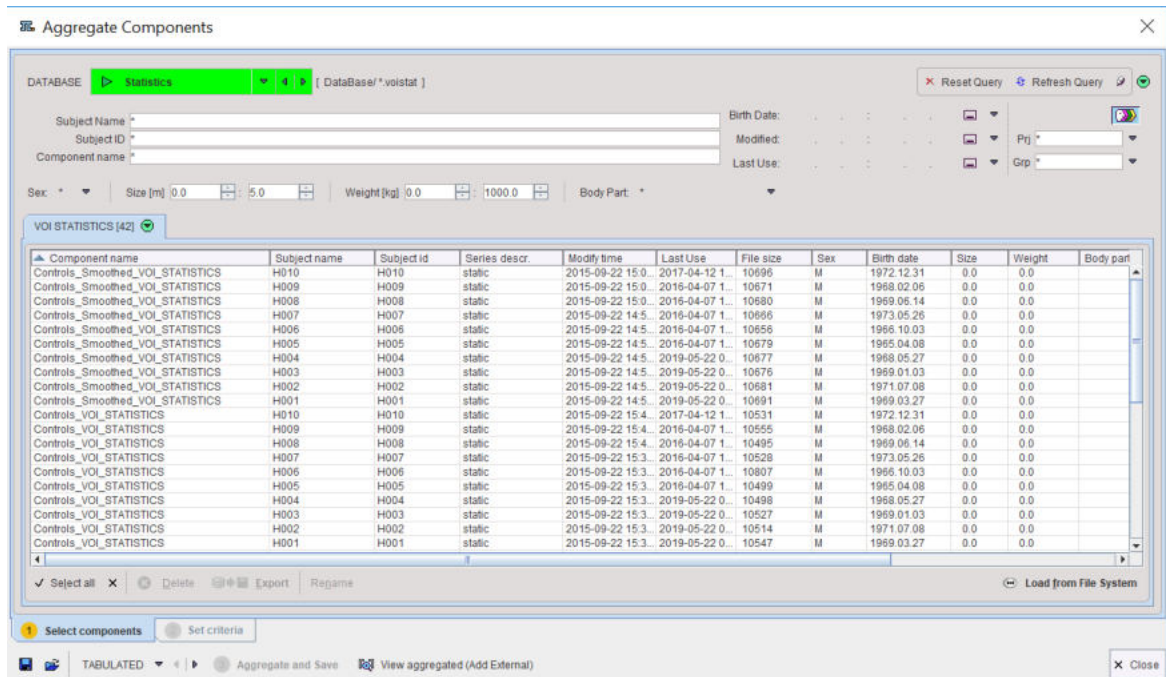
It lists all VOI statistics (**.voistat** files) which are available in the selected **DATABASE**.

The task on this page is to select the statistics components which should be concentrated into a single aggregate. This is done by selecting the appropriate entries in the list so that they appear highlighted, in the example above the ones of the healthy controls (see above[21]). Note the filter elements in the upper part which allow reducing the number of listed components. For instance the string **H*** could be entered in the **Subject Name** field to list only the results for the controls.

If no database has been used for saving the .voistat files, the **Load from File System** function has to be used instead.

10.7.2   Information Selection

Select the **2 Set Criteria** pane to move on to defining the information parts to be included in the aggregate.
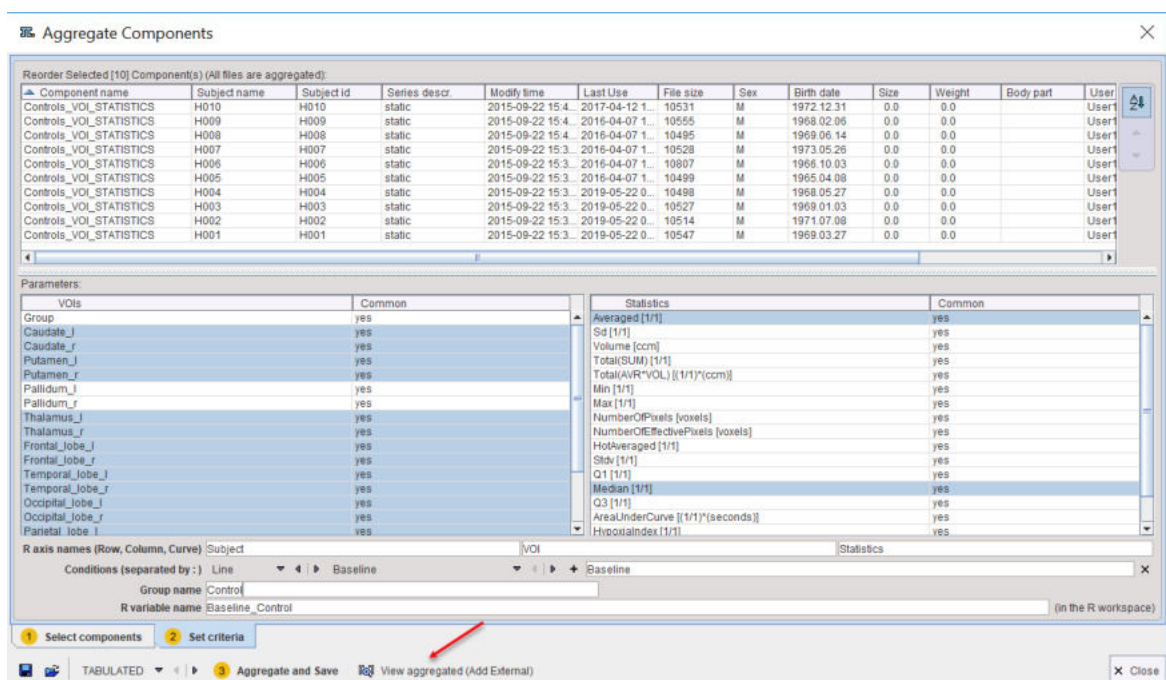
The upper list consists of the data sets selected in the prior step. This list is mainly for information. The elements can be sorted or reordered, but no entries can be removed or added.

Selection of the Aggregate Information

The lower **Parameters** area shows the list of **VOIs** used for the statistics to the left, and the calculated **Statistics** to the right. Note the **Common** column. A **Yes** entry indicates that the VOI/Statistics is available in all data sets. Correspondingly a **No** entry indicates that the information is missing in at least one of the data sets. If the information is still used despite of the **No** indication, a **NaN** value will be entered in the aggregated to signal the absence of useful information. NaN values are disregarded in the statistics script provided in the R console.

In the left list select the **VOIs** to be included in the aggregate, and in the right list the **Statistics**.

Encoding Group and Condition Information

The lower part of the window serves for providing information which will be useful when using the aggregates for statistics.

The aggregation will generate a three-dimensional data set, which will be represented in the R console as a table indexed by **Row** and **Column**, and each table element is a vector and therefore called **Curve**. The three **R axis names** fields allow defining the names of the three dimensions, which for VOI statistics default to **Subject**, **VOI** and **Statistics**.

The **Conditions** and the **Group name** lines serve for generating a code describing the current aggregate. The rational is, that the subjects of a group may be studied in different conditions, or that different types of analysis are performed.
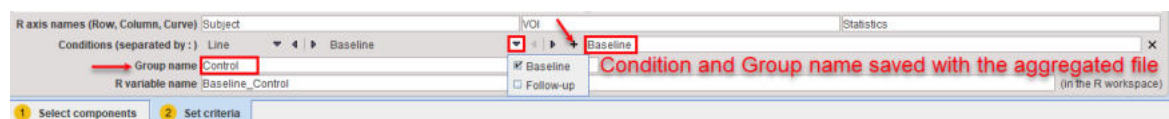
The way to generate the condition string is to enter a string in the left field, and then activate the **+** button. As soon as the condition is defined it is assigned automatically to the the **R variable name** field.

Additional conditions can be defined: e.g the laterality (**Left**). As a result the string is appended to the current condition with a preceding " **:** ".
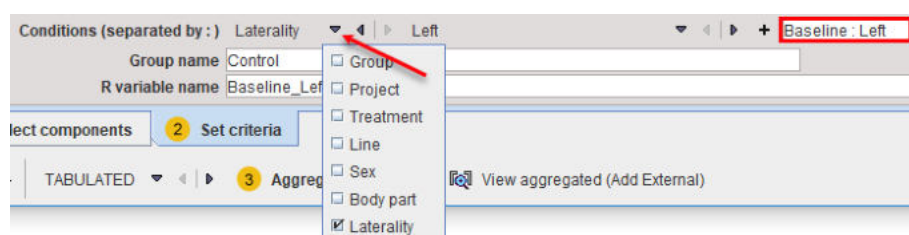
Since the condition string has to be consistent among aggregates, there are lists for generation pre-defined strings. The first list serves for choosing the condition group.
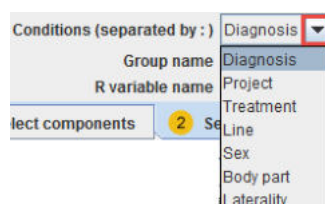
Consequently the elements of the second list are populated and can be selected.

The **Group name** definition, when specified and confirmed with the **Enter** key button from the keyboard is appended to the **R variable name** field.

The condition and the group definitions are saved together with the aggregated file.

The **R variable name** can be edited and the name will be use when transferring the aggregate to the R console.

10.7.3 Aggregate Generation and Saving

Finally the aggregate is created by the **Aggregate and Save** button, which enforces a saving operation.

There are two formats available, **TABULATED** and **EXCEL**. For internal use in PMOD the **TABULATED** format is recommended.

10.7.4 Aggregate Export and R Transfer

The aggregate can directly be transferred to the R statistics console via the **Go to R** button. As a result, a variable with the name specified by the **R variable name** will be created. **To Clipboard** copies the contents of the aggregate, so that it can be pasted into alternate programs such as Excel.

Note: The NaN information is not removed when the statistics are transfer to the R console.

10.7.5 Aggregate Inspection and Combination with External Data

View aggregated opens the dialog window illustrated below for inspecting the contents of an aggregate. The information of a single statistics file is shown in the list area, and the arrows of the **Statistics set** allow stepping through the different data sets.
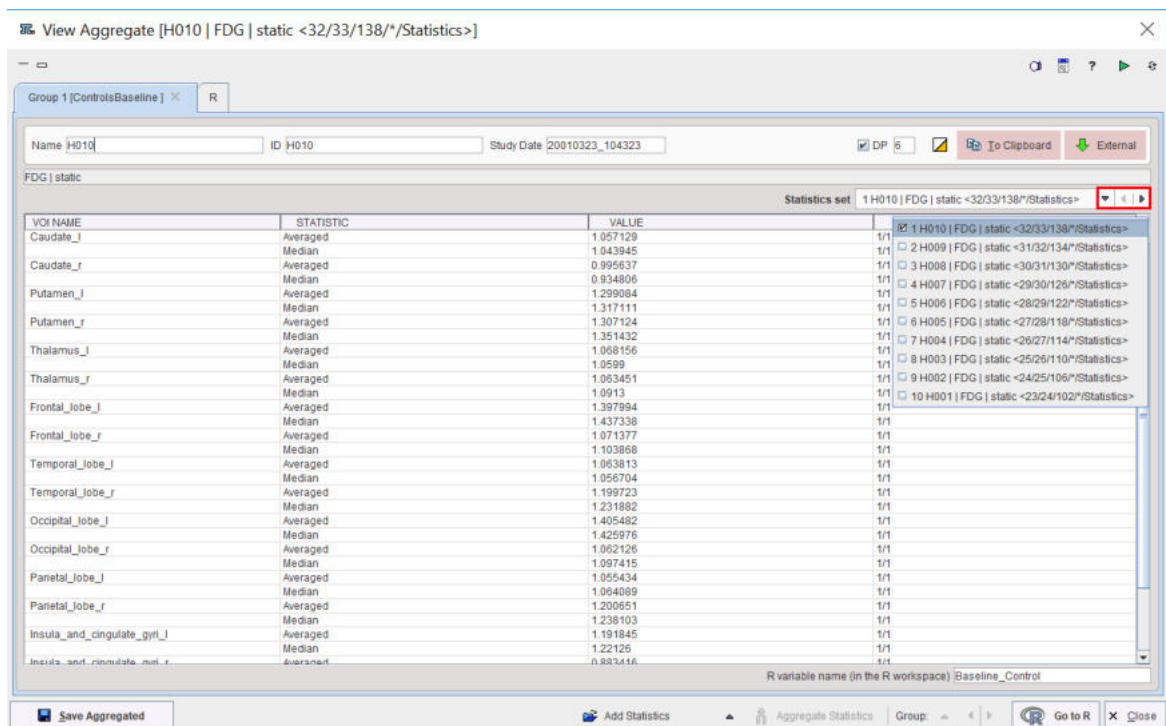
Combination with External Data

For the statistical analysis, additional data might be relevant, for instance the blood pressure at scan time, or a mini mental test score. Such data can be included with the aggregate using the **External**

button. It shows a dialog window listing the four identifiers **Subject Name**, **Subject ID**, **Study description** and **Series description** of the included data.
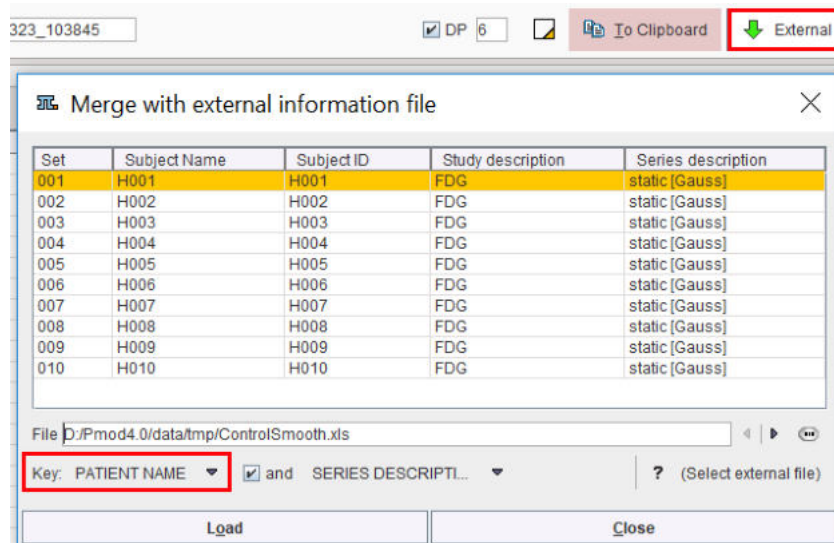
A tab-delimited text **File** with the external data has to be prepared and selected. It has the following structure, which is also summarized by the **?** button:

# PMOD_EXTERNAL_DATA			
# FORMAT[UNI]			
# EXTERNAL			
// PatientName	D[mmHg]	MMS[1/1]	Code[string]
P01060	70	20	NORM
P01075	71	18	HYPO
P01090	72	22	HYPO
P01105	73	19	HYPO
P01120	74	21	NORM
P01135	75	17	HYPO
P01150	76	15	HYPO
P01165	77	18	NORM
P01180	78	23	HYPO
P01195	79	12	NORM

PatientID or **PatientName** can be used as the **Key** for relating the information in the aggregate and in the file, and if this is not unique, it can be combined with **STUDY DESCRIPTION** or **SERIES DESCRIPTION**. Use **Load** to perform to extend the aggregate, and **Save Aggregated** to save the result.

Note that the added external information is not visible in the **Group** window. However, after transferring the information to R using **Go to R,** the external values are encoded in the **EXT** column as illustrated below.
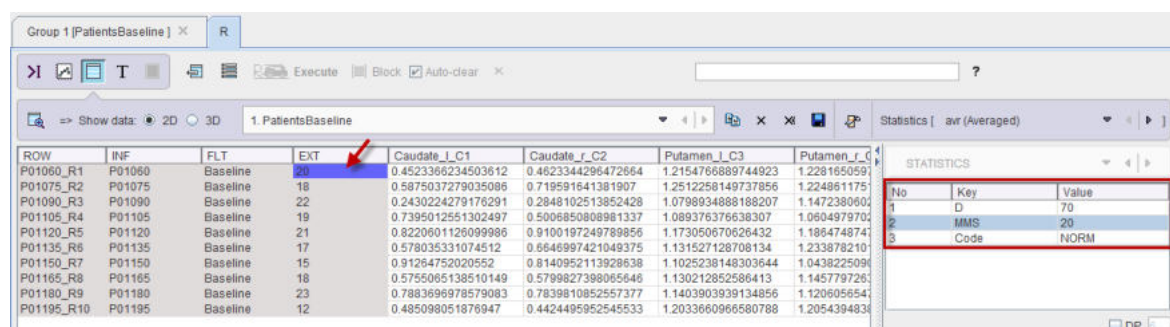
> **Note**: Please note that when numeric **PatientName** or **PatientID** are defined, they have to be converted in "char" format in Excel. This can be easily done forcing the content of the Excell cell to a text representation using the character apostrophe **'** at the beginning of each name/ID definition (eg. **'10**). Otherwise the external data will not be read by Pmod.

11   R Statistics in PMOD

R is an open-source statistical environment and programming language for data analysis and graphical display (R-project). Recently it has gained increased attention in the analysis of biomedical data, see for example the overview article of Tabelow et al: *Image analysis and statistical inference in neuroimaging with R*. Neuroimage 2011, 55(4):1686-1693. DOI.

The PMOD **R** console provides an interface to the R package and leverages the entire R functionality including the statistical analysis of PMOD results from populations. The methods can be applied to the outcome of VOI statistics, regional kinetic modeling, cardiac perfusion quantification and the PALZ analysis.

Standard analysis types are directly supported via the graphical user interface. They can be as simple as a performing scatter plots, but range to more complicated techniques such as ANOVA, test-retest analysis or Bland-Altman comparison.

Beyond using the graphical interface for invoking R functionality, users can also develop their own analysis scripts in a command window interface. In this situation, the PMOD **R** console serves as a prototyping interface which allows entering R code, executing it, inspecting the result, and improving the code.

Additionally, the PMOD R console is used for the training and prediction in the artificial intelligence (PAI) module. Please refer to the PMOD *Artificial Intelligence Framework (PAI)* user guide for additional information on the topic.

11.1   R Installation and Configuration

Please download and install **R version 4.2.1** for Windows, MAC and Linux from https://cran.r-project.org/

There is no need to manually install additional R packages for Windows and MAC OS. PMOD will automatically download and install the necessary packages when the PMOD R Console is started for the first time. The Linux package installation is described in detailed in the dedicated section 357.

11.1.1 Windows

Following R installation, start PMOD and open the **Configuration** facility from docking interface:
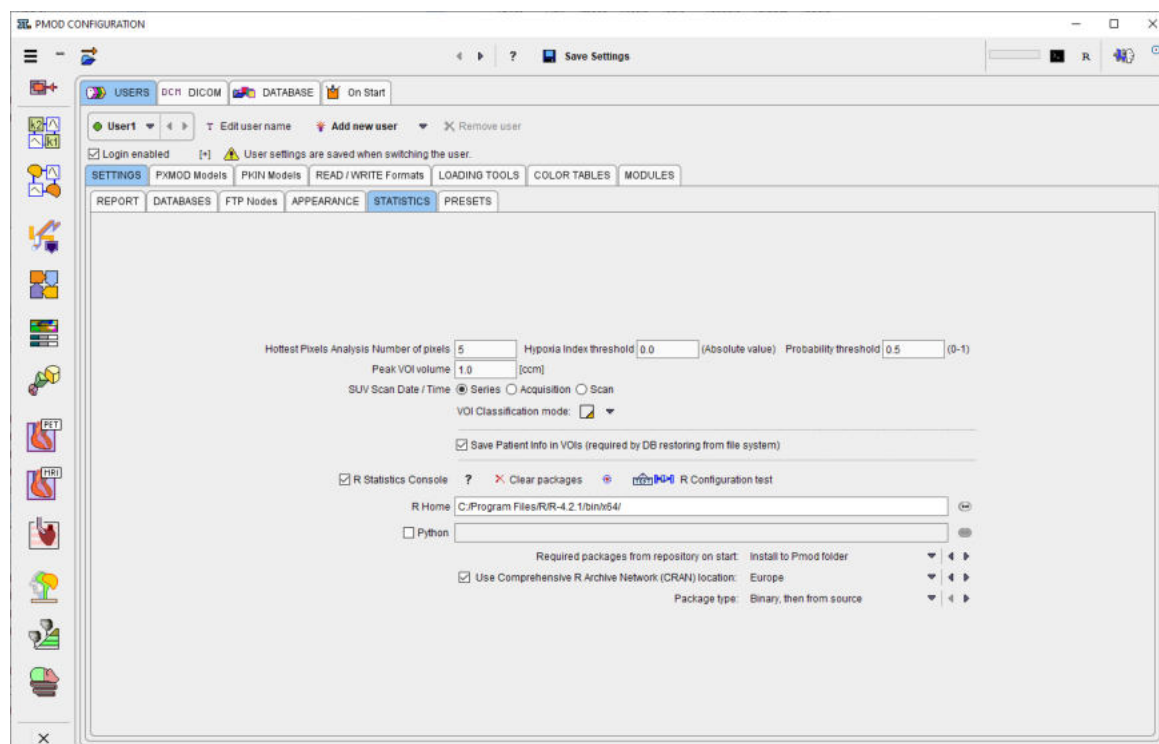
On the **Users/Settings STATISTICS** tab ensure that the checkbox **R Statistics Console** is checked and verify that the path to the local R installation is correct. Select **Install to Pmod folder** to avoid permission problems when installing the R packages.

Restart PMOD and wait for the **R** icon on the top line to become active.

Then click on the **R** icon to open the **PMOD Console**. The required packages are downloaded and installed, followed by an execution test and printing of the R version information:
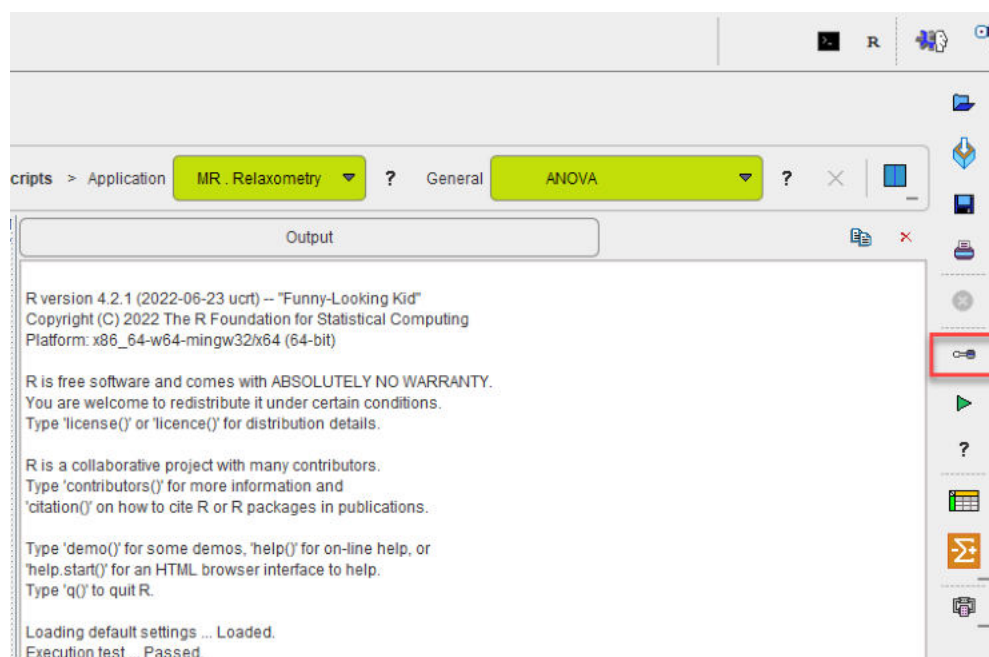
The settings button indicated above opens the dialog window below.
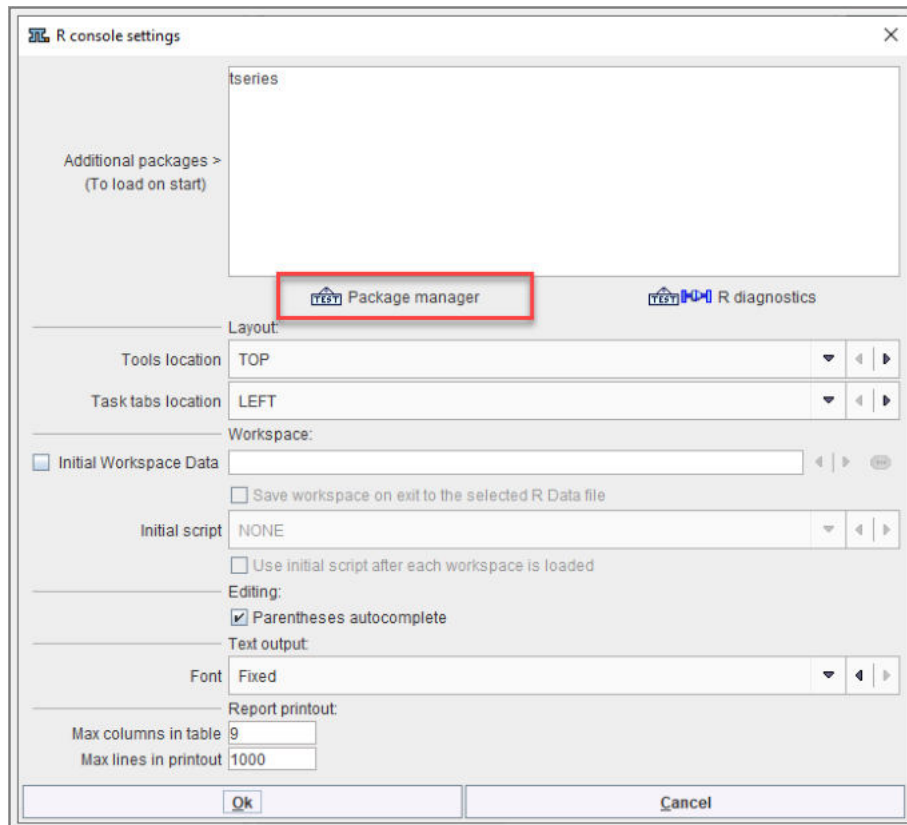
Note that in case of problems connecting to Python when using PAI (if licensed), the path to **Python** can be configured in the **Configuration** facility from the main ToolBox:

Next open the **Package Manager**. All packages should have status **OK**.

Package	Type	Status	Installed version	CRAN version
Rcpp	CRAN	OK	1.0.9	1.0.9
doBy	CRAN	OK	4.6.14	4.6.14
psych	CRAN	OK	2.2.9	2.2.9
e1071	CRAN	OK	1.7.12	1.7-12
UsingR	CRAN	OK	2.0.7	2.0-7
lawstat	CRAN	OK	3.5	3.5
tseries	CRAN	OK	0.10.52	0.10-52
np	CRAN	OK	0.60.16	0.60-16
openair	CRAN	OK	2.12	2.12
foreign	CRAN	OK	0.8.82	0.8-83
Hmisc	CRAN	OK	4.7.1	4.7-2
car	CRAN	OK	3.1.1	3.1-1
phia	CRAN	OK	0.2.1	0.2-1
compare	CRAN	OK	0.2.6	0.2-6
reshape	CRAN	OK	0.8.9	0.8.9
sfsmisc	CRAN	OK	1.1.13	1.1-14
Cairo	CRAN	OK	1.6.0	1.6-0
pROC	CRAN	OK	1.18.0	1.18.0
survival	CRAN	OK	3.3.1	3.4-0
glmnet	CRAN	OK	4.1.4	4.1-6
stringr	CRAN	OK	1.4.1	1.5.0
mcr	CRAN	OK	1.3.1	1.3.1
reticulate	CRAN	OK	1.26	1.26
jsonlite	CRAN	OK	1.8.3	1.8.3
lubridate	CRAN	OK	1.9.0	1.9.0
sfsmisc	CRAN	OK	1.1.13	1.1-14
RNifti	CRAN	OK	1.4.3	1.4.3
memuse	CRAN	OK	4.2.2	4.2-2
pm.base	Local	OK	4.401.1	-
pm.ai	Local	OK	4.401.1	-

Note: If package installation fails, please check your firewall settings or contact your IT service.

11.1.2 MAC OS

Following R installation, start PMOD and open the **Configuration** facility from the main ToolBox.

On the **STATISTICS** tab ensure that the checkbox R Statistics Console is checked. Select **Install to Pmod folder** to avoid permission problems when installing the R packages. We recommend selecting **Use Comprehensive R Archive Network (CRAN) location**. In rare cases the connection to CRAN may be unsuccessful. In this case, unselect **Use Comprehensive R Archive Network (CRAN) location**, then select the CRAN location from the native R dialog that appears when R Console is started. This situation has been encountered on MacOS Catalina.
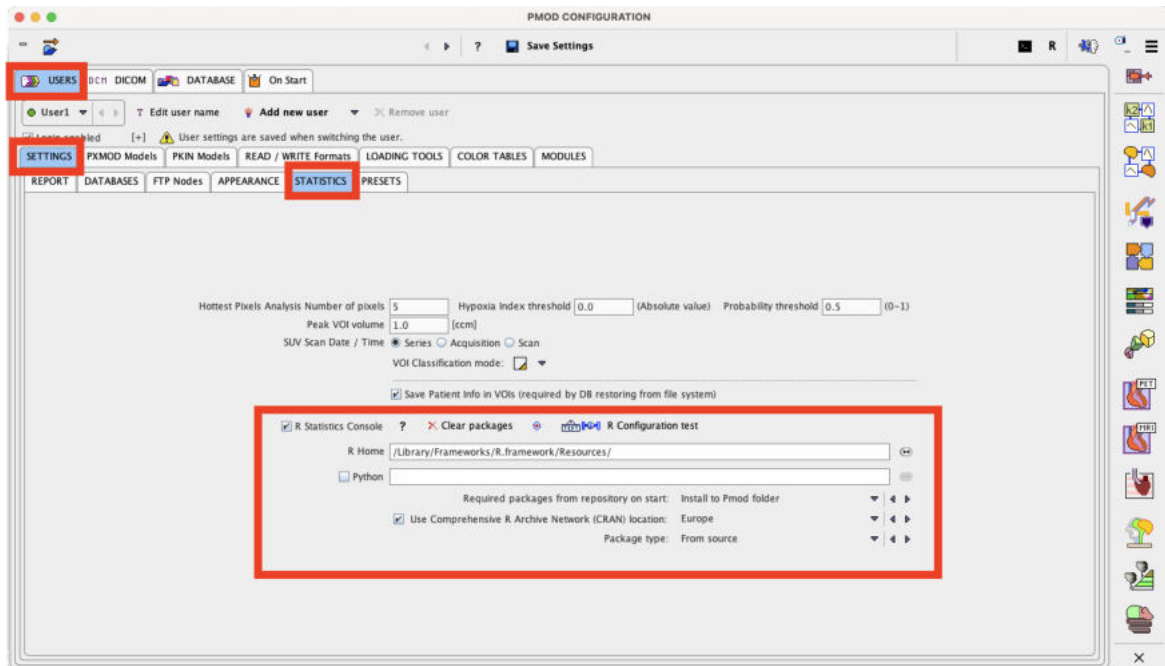
Restart PMOD and wait for the **R** icon on the top menu to become active.
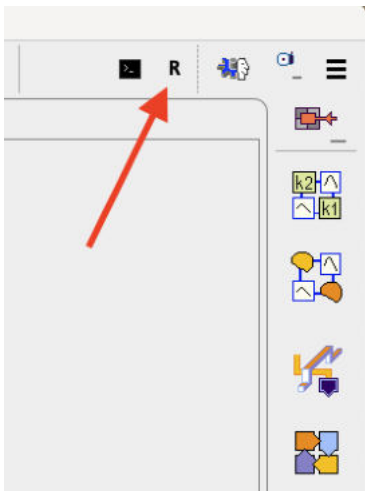
Then click on the **R** icon to open the **PMOD Console**. The required packages are downloaded and installed, followed by an execution test and printing of the R version information:
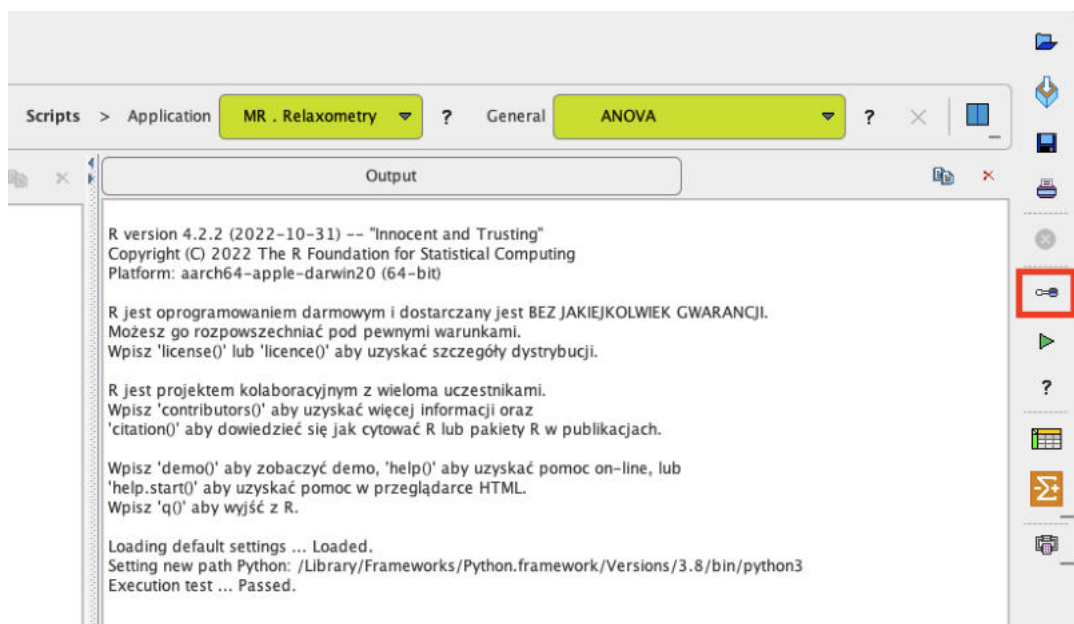
The **Settings** button indicated above opens the dialog window below.
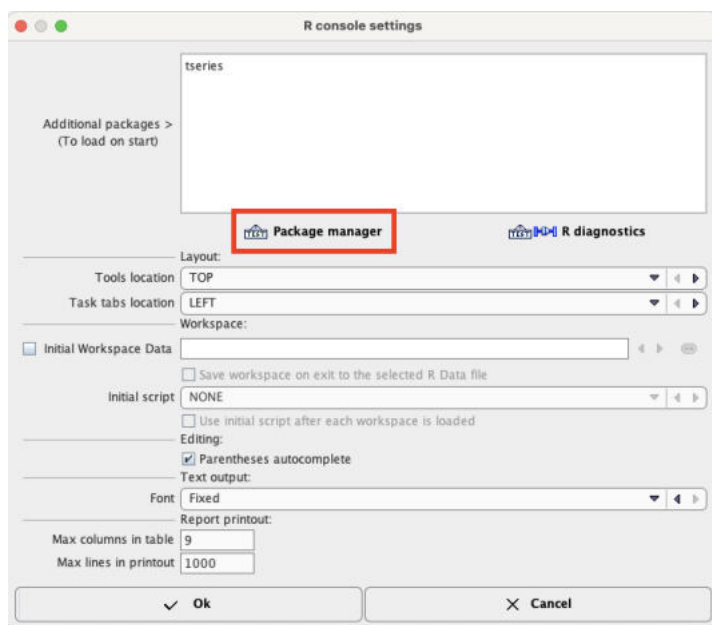
Note that in case of problems connecting to Python when using PAI (if licensed), the path to **Python** can be configured in the main **PMOD Configuration** window:

Open the **Package Manager**. All packages should have status **OK**.

Package	Type	Status	Installed version	CRAN version
Rcpp	CRAN	OK	1.0.9	1.0.9
doBy	CRAN	OK	4.6.13	4.6.14
psych	CRAN	OK	2.2.5	2.2.9
e1071	CRAN	OK	1.7.11	1.7-12
UsingR	CRAN	OK	2.0.7	2.0-7
lawstat	CRAN	OK	3.4	3.5
tseries	CRAN	OK	0.10.51	0.10-52
np	CRAN	OK	0.60.13	0.60-16
openair	CRAN	OK	2.10.0	2.12
foreign	CRAN	OK	0.8.83	0.8-83
Hmisc	CRAN	OK	4.7.1	4.7-2
car	CRAN	OK	3.1.0	3.1-1
phia	CRAN	OK	0.2.1	0.2-1
compare	CRAN	OK	0.2.6	0.2-6
reshape	CRAN	OK	0.8.9	0.8.9
sfsmisc	CRAN	OK	1.1.13	1.1-14
Cairo	CRAN	OK	1.6.0	1.6-0
pROC	CRAN	OK	1.18.0	1.18.0
survival	CRAN	OK	3.4.0	3.4-0
glmnet	CRAN	OK	4.1.4	4.1-6
stringr	CRAN	OK	1.4.0	1.4.1
mcr	CRAN	OK	1.2.2	1.3.1
reticulate	CRAN	OK	1.26	1.26
jsonlite	CRAN	OK	1.8.0	1.8.3
lubridate	CRAN	OK	1.8.0	1.9.0
sfsmisc	CRAN	OK	1.1.13	1.1-14
RNifti	CRAN	OK	1.4.1	1.4.3
memuse	CRAN	OK	4.2.1	4.2-2
pm.base	Local	OK	4.401.1	–
pm.ai	Local	OK	4.401.5	–

> **Note**: If package installation fails, please check your firewall settings or contact your IT service.

11.1.3 Linux

Please perform the following installation steps (Ubuntu 18.04):

Install R:

```
sudo apt-key adv --keyserver keyserver.ubuntu.com --recv-keys
E298A3A825C0D65DFD57CBB651716619E084DAB9

sudo add-apt-repository 'deb https://cloud.r-
project.org/bin/linux/ubuntu bionic-cran40/' sudo apt update

sudo apt install r-recommended
```

Install the required libraries:

```
sudo apt install libcurl4-openssl-dev

sudo apt install libcairo2-dev

sudo apt install xorg-dev

sudo apt install libssl-dev

sudo add-apt-repository ppa:c2d4u.team/c2d4u4.0+

sudo apt-get update

sudo apt-get install r-cran-lme4

sudo apt-get install r-cran-snow

sudo apt-get install r-cran-vgam
```

Start R at the command line as administrator ("sudo R") and install the required packages:

```
install.packages("doBy")

install.packages("psych")

install.packages("e1071")

install.packages("UsingR")

install.packages("lawstat")

install.packages("tseries")

install.packages("np")

install.packages("openair")

install.packages("foreign")

install.packages("Hmisc")
```

```
install.packages("car")

install.packages("phia")

install.packages("compare")

install.packages("reshape")

install.packages("sfsmisc")

install.packages("Cairo")

install.packages("pROC")

install.packages("survival")

install.packages("glmnet")

install.packages("mcr")

install.packages("stringr")

install.packages("reticulate")

install.packages("jsonlite")

install.packages("session")

install.packages("keras")
```

Main Configuration in PMOD User Interface

Following R and package installation, launch PMOD and check that R Statistics Console is activated in the Main Configuration, on the **USERS, STATISTICS** tab:
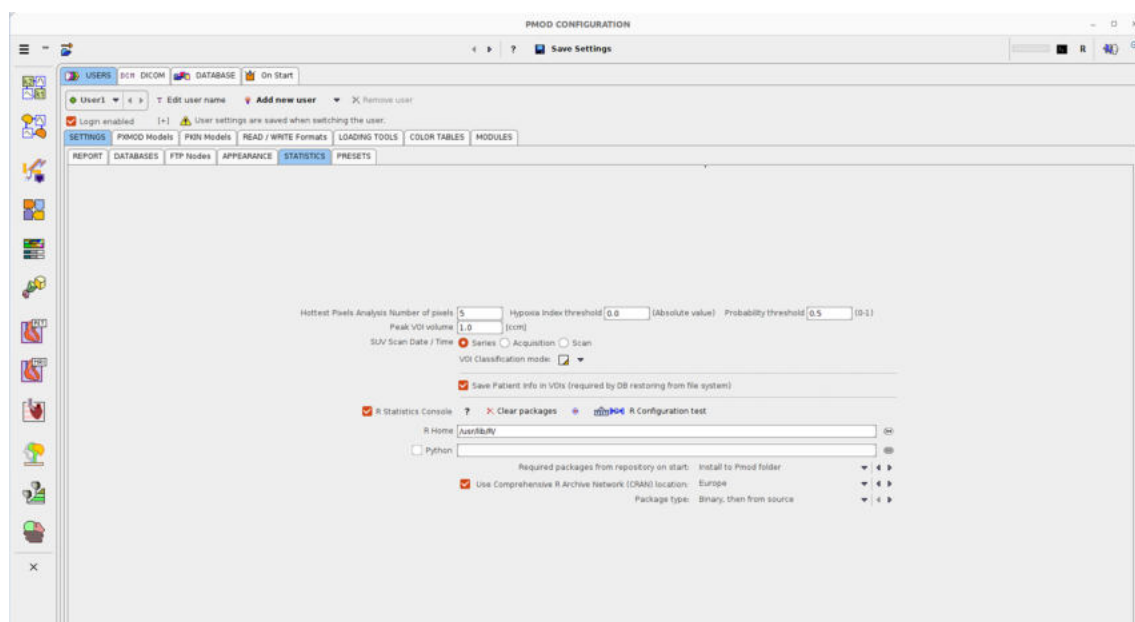
After the installation the **Package Manager content** should look like illustrated below:
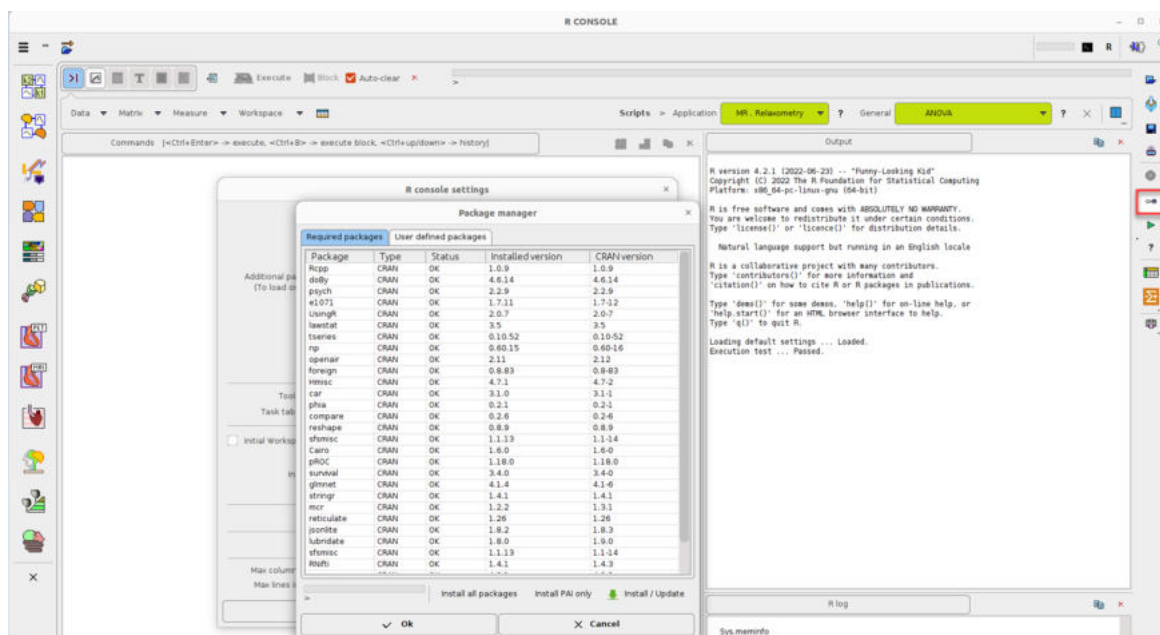
11.2 Starting the R Console

The PMOD R console can be started in different ways:

1. From the top line of the docking interface
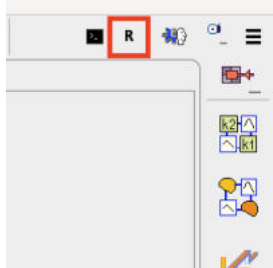
2. using the keyboard keys SHIFT+CTRL+R,

3. by transferring data using the **Go to R** button from the PMOD statistics or aggregate viewers illustrated below.
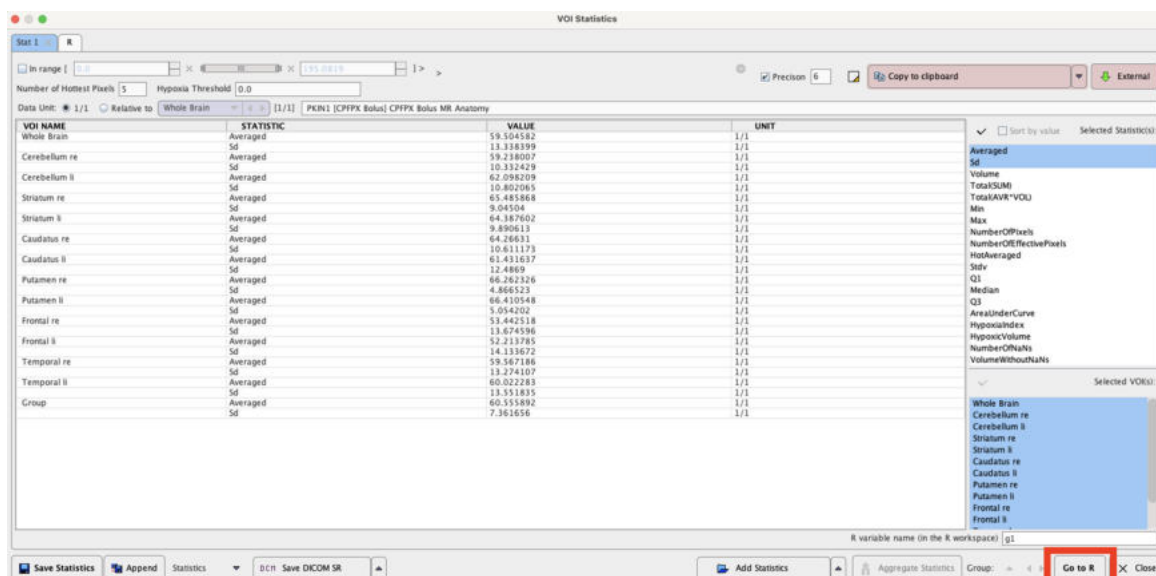
The console opens as a dialog window. If **Go to R** has been invoked, the workspace will contain data which is already shown in the user interface. When starting with an empty console, data needs to be loaded using the loading button from the lateral taskbar.

11.3   R Console Organization

The user interface of the R console has some framework operations, a main part and a taskbar to the right.
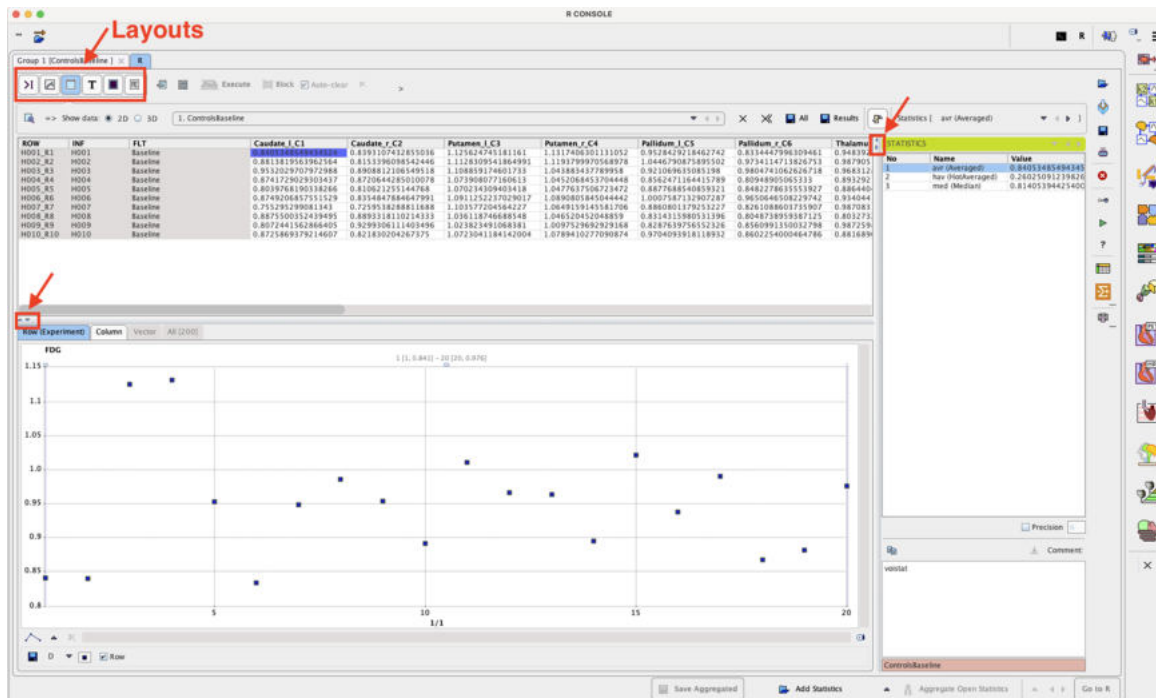
Framework

There are some convenience buttons at the top of the window:

— ☐	Buttons to minimize/maximize the docking window.
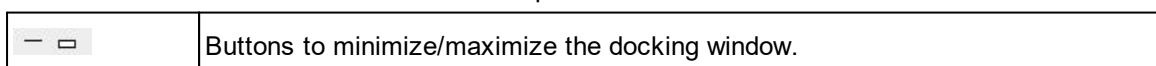
	Captures the entire screen (not only the PMOD window) and adds it to a console buffer.
	Opens the **Console** dialog window for checking the log output and reporting problems 27 to support@pmod.com.
?	Open help window.
▷	Button for opening the R server configuration window.
↻	Button for reconnecting to the R server, if a connection problem occurred.
	Dividers between different parts of the layout allow extending/shrinking the respective areas.

Main Window Layouts

The main statistics part has 5 different layouts depending on selection in the upper left:

>I	**Command layout**: Allows invoking existing analysis scripts as well as editing and executing native R commands on the loaded data.
	Plotting layout: Allows producing different plots of the data, and inspecting the plots produced by analysis scripts.
	Table layout: Allows inspecting the data variables of the R workspace. Initially, the loaded data appear as variables g1, g2, etc. Scripts add variables to the workspace. Data can be copied to the clipboard for external usage.
T	**Text layout**: Allows extracting the contents of numerical variables into a text field.
■	**Image layout**: Allows visualizing images. Is only active after image data have been transferred.
🄰🄸	**PAI Monitor:** Allows visualizing the PAI training progress.

Next to the layout buttons is an area containing several buttons
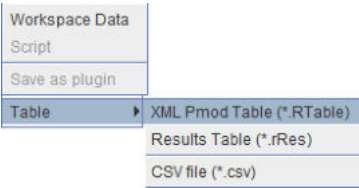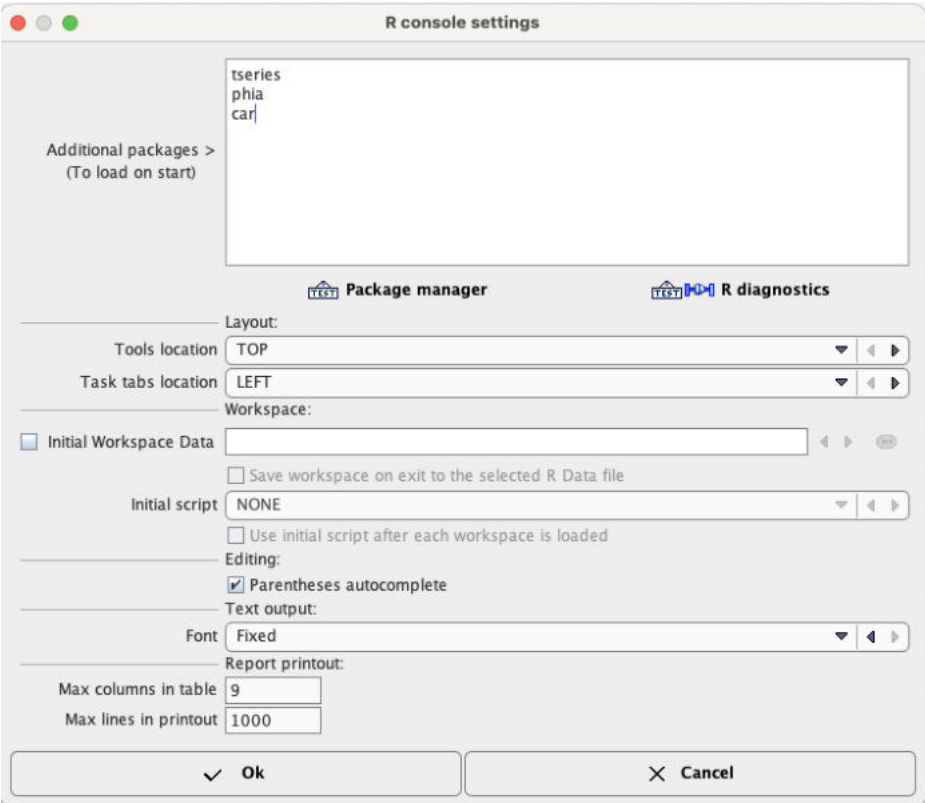
which are related to programming in R and effective in different contexts:

	Generates R code for extracting parts of the workspace variables.
	Lists the variables in the workspace and inserts the selected variable into the command line.
Execute	Executes the whole code in the command window.
Block	Executes the selected code in the command window.
☑ Auto-clear	Clears the contents of the command window after execution.

Lateral Taskbar

The elements in the taskbar have the following functionality:

📂	▪ Loading of information as described below 365.
⬇	Input files can be dragged to this box for opening them

💾	Workspace Data
	Script
	Save as plugin
	Table ▸ XML Pmod Table (*.RTable)
	                   Results Table (*.rRes)
	                   CSV file (*.csv)
	
	Saving of
	
	▪ the contents of the command window in two ways: as a new **Script** , which can be loaded, or as a **plugin**, which can directly be selected from a list;
	
	▪ all data variables as an R workspace (**Workspace Data**, .RData file) which can be loaded back into the PMOD R console, but also directly to R or other graphical front-ends of R (e.g. R Studio).
	
	▪ matrices can be saved as Table CSV files.

🖨	Printing a report which may include plots, tables and/or images, depending on the analysis performed.
⊗	Clears all the variables in the R workspace.

🔧	Opens the configuration settings window:
	
	R console settings
	
	Additional packages >
	(To load on start)
	
	tseries
	phia
	car
	
	📋 **Package manager** 📋 **R diagnostics**
	
	Layout:
	Tools location TOP
	Task tabs location LEFT
	Workspace:
	☐ Initial Workspace Data
	     ☐ Save workspace on exit to the selected R Data file
	Initial script NONE
	     ☐ Use initial script after each workspace is loaded
	Editing:
	☑ Parentheses autocomplete
	Text output:
	Font Fixed
	Report printout:
	Max columns in table 9
	Max lines in printout 1000
	
	✓ Ok ✕ Cancel

Tools location is layout option. The tools section may be arranged at the **Top** (as in this documentation), or at the **Bottom**.

Initial Workspace Data directs the R console to load an R workspace file whenever it is started. This file might include R functions developed by the user.

If user scripts require additional R packages, they can be typed into the **Additional packages ...** window and checked with the **Verify ...** button.

Package	Type	Status	Installed version	CRAN version
Rcpp	CRAN	OK	1.0.9	1.0.9
doBy	CRAN	OK	4.6.13	4.6.14
psych	CRAN	OK	2.2.5	2.2.9
e1071	CRAN	OK	1.7.11	1.7-12
UsingR	CRAN	OK	2.0.7	2.0-7
lawstat	CRAN	OK	3.4	3.5
tseries	CRAN	OK	0.10.51	0.10-52
np	CRAN	OK	0.60.13	0.60-16
openair	CRAN	OK	2.10.0	2.12
foreign	CRAN	OK	0.8.83	0.8-83
Hmisc	CRAN	OK	4.7.1	4.7-2
car	CRAN	OK	3.1.0	3.1-1
phia	CRAN	OK	0.2.1	0.2-1
compare	CRAN	OK	0.2.6	0.2-6
reshape	CRAN	OK	0.8.9	0.8.9
sfsmisc	CRAN	OK	1.1.13	1.1-14
Cairo	CRAN	OK	1.6.0	1.6-0
pROC	CRAN	OK	1.18.0	1.18.0
survival	CRAN	OK	3.4.0	3.4-0
glmnet	CRAN	OK	4.1.4	4.1-6
stringr	CRAN	OK	1.4.0	1.4.1
mcr	CRAN	OK	1.2.2	1.3.1
reticulate	CRAN	OK	1.26	1.26
jsonlite	CRAN	OK	1.8.0	1.8.3
lubridate	CRAN	OK	1.8.0	1.9.0
sfsmisc	CRAN	OK	1.1.13	1.1-14
RNifti	CRAN	OK	1.4.1	1.4.3
memuse	CRAN	OK	4.2.1	4.2-2
pm.base	Local	OK	4.401.1	–
pm.ai	Local	OK	4.401.1	–

> Install all packages   Install PAI only   Install / Update

✓ Ok   ✗ Cancel

If user scripts require additional R packages, they can be typed into the **New packages ...** field in the **User defined packages** panel and activate the **+Add** button.

	Opens the **Console** dialog window for checking the log output and reporting problems 27 to support@pmod.com.
	Shortcut for opening the scripts selection. System scripts are listed first, followed by scripts which were saved as plugins.
	Opens the aggregation window 345 for compiling individual statistics into an aggregate table.

11.4   Data Loading

Loading of Data into the R Console

The 📂 button in the lateral taskbar with the sub-menu

Workspace Data
Script

Table   »
Curves   »
VOI statistics   »
Aggregated statistics

VOI Pixel dump   »
Images   »

allows loading the different types of data which are accepted by the R console.

- A saved R workspace containing the (**Workspace Data**, .RData file).

- R processing scripts (**Script**, .r file).

- Tables saved from R (**Table,** .RTable file) or several statistics programs.

  XML Pmod Table (*.RTable)
  Results Table (*.rRes)

  CSV file (*.csv)

  SPSS (*.sav)
  SAS (*.xpt)
  Systat (*.dta)
  Stata (*.dta)
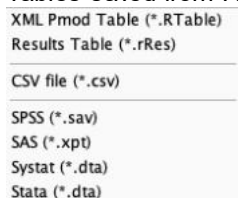
- PMOD VOI statistics data (**Statistics**, .voistat file). The **Enhanced output format** and **Enhanced aggregation format** should be enabled in the **configuration** 33. Note that the statistics may included a time dimension if the image file was dynamic.

- **Aggregated PMOD results** 345 (**Aggregated**, .dbTab file) from multiple result files. Typically, the results of a population (controls, patients) or a condition (test, retest) should be compiled into a single aggregate.

- **Dumps** 331 of the pixel values within VOIs: **VOI Pixle dump** (.pixDump file);

- **Images** in any of the supported formats. At this time, however, no dedicated statistics on images are yet provided through the PMOD R console.

Transfer of Statistics to R

The **Go to R** button in the **statistics viewer** 327 or **aggregate viewer** 348 transfers the data of all open statistics to the R server, generating one R variable per tab in the R workspace. Per default, the variables are labeled sequentially in the order of the tabs as **g1**, **g2**, .. etc, but explicit names can also be specified.

Note: The NaN entries in the **statistics viewer** 327 or **aggregate viewer** 348 are transfered when the statistics are sent to the R console.

11.5   R Variable Structure

The variables created by the transfer of statistics and aggregates to R or by loading them have the following structure:

- The names have the form **g1**, **g2**, etc if there was not explicit variable name defined.

- The highest level consists of a list corresponding to the different statistic types such as average and standard deviation for VOI statistics, Vt for aggregated modeling results, etc.

- The next level is a data frame with a header line and data rows. The data rows correspond to the rows in an aggregate and are thus dependent on the aggregated data. Typically, the rows correspond to the different subjects in a population.

- Each cell in the data frame table is in itself a list. The list structure depends on the aggregated table and on the column. An INFO list contains demographic data, while a VOI list contains 3 lists for the elements "number", "time" and "value".
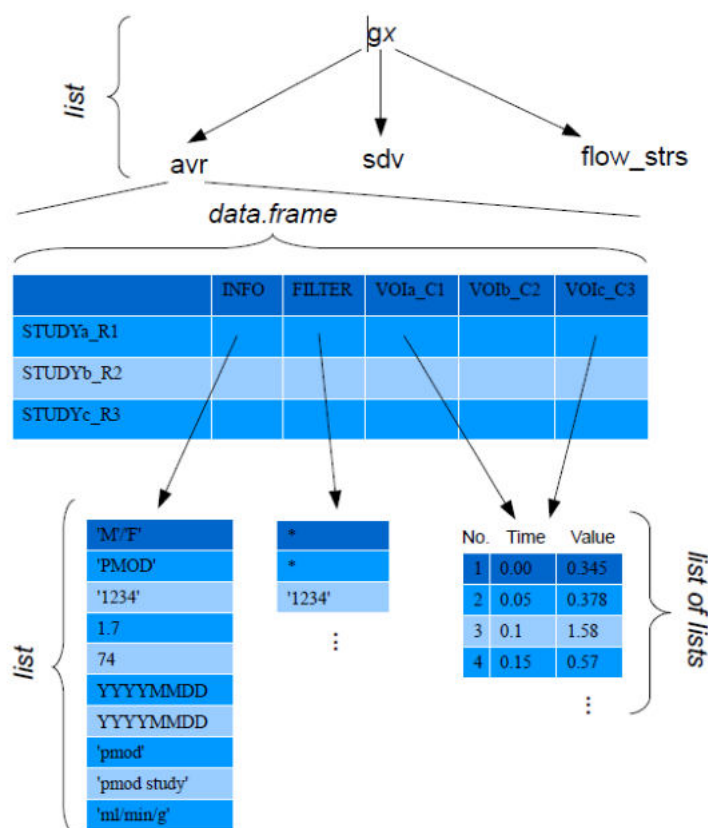
Most PMOD scripts require the specification of which part of a variable should be processed. Therefore, they show dialog windows such as the one illustrated below.
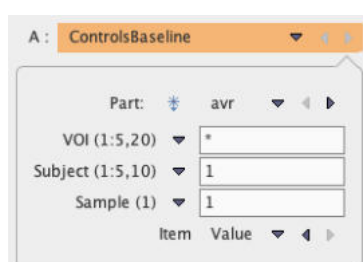
After choosing a **Variable**, the elements in the lower part are updated according to the variable contents. **Part** represents the statistics to be analyzed. The **VOI** selection corresponds to the columns, the **Subject** to the rows, and the **Sample** to the location in the **value** or **time** list. **Item** finally allows switching from **Value** to **Time**, if the acquisition timing rather than the sample value is needed.

The selections in text fields represent standard R expressions, for example:

- Use all available elements, eg all VOIs: "*****"

- Use a range, e.g. elements 2 to 4: "**2:4**"

- Use one specific element, e.g. the first: "**1**". It can be combined with a range in the form of e.g. "**1, 3:5**".

As a convenience, the shortcut button ⁑ propagates the "*" definition to all components.

11.6   Table Layout

Variable Selection

The [icon] button activates the **Table layout** for inspecting the data in the R workspace. The R variables can be selected from the **Preview** list indicated below.
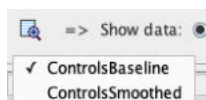
The list will show the original variables as well as variables created by the scripts and R commands.

Table View Layout

After selecting a variable, its content can be inspected. The default **2D** view illustrated below shows the table of the data frame.
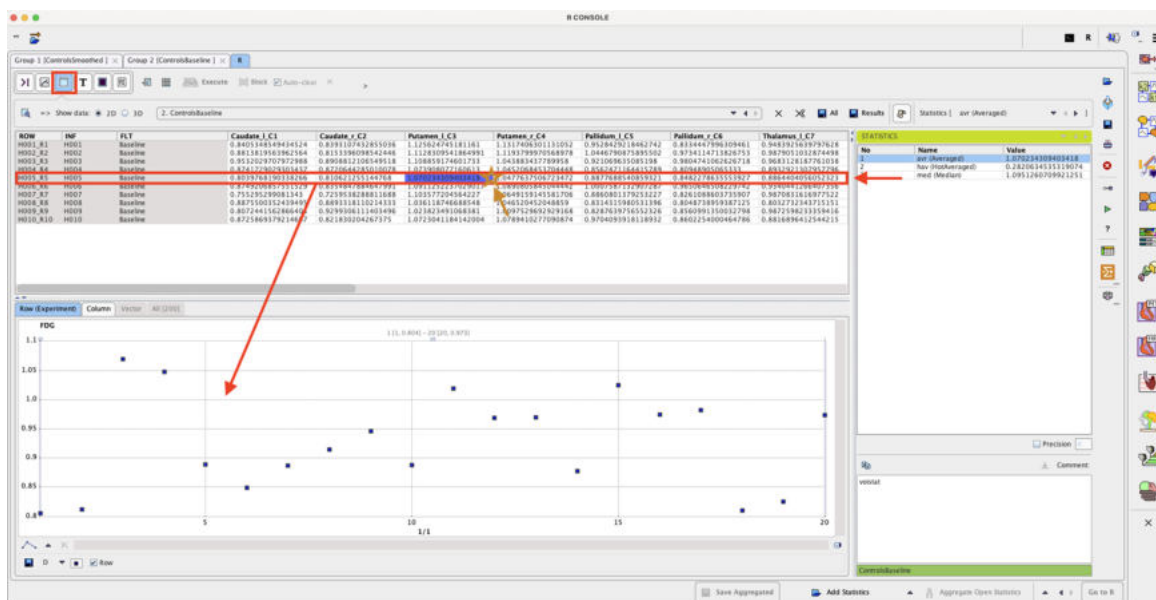
The lower plot area shows scatter plots of a data **Row** or **Column**. One variable may have different data frames for different aggregated outcome statistics such as **avr**, **hav**, and **med**. The **Statistics** selection can be used to change between statistics, as well as direct double-clicking into the **Statistics** list.
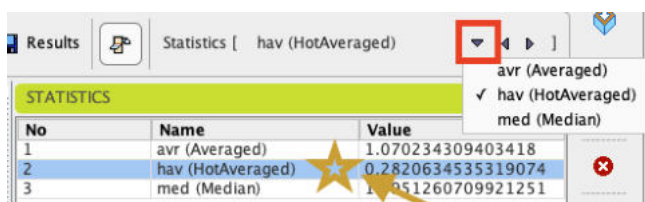
In order to keep track of the variable meaning, comments can be added in the lower right. Please select the variable of interest, enter the comment, and then activate the copy button illustrated below. When saving the R workspace, this comment will be included, so that it will be available when resuming work.
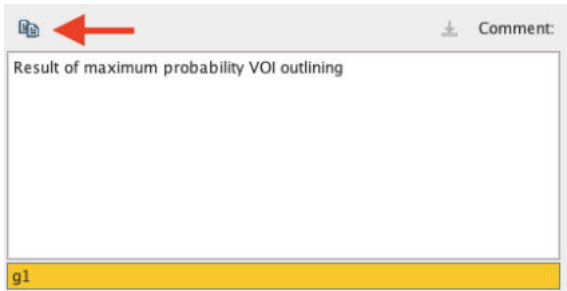
Table Buffer

Note that each visualization of a table is stored in a buffer list so that it can be quickly recalled. While a variable exists only once, there might be multiple entries in the buffer which may represent the visualization of different variable parts.

The buffer list can be edited with the buttons to its right:

✕	Remove current table from the list.
💾	Save all tables into a file.
📋	Copy the current table to the clipboard.
✕✕	Clear the buffer list.

Surface Plot Visualization (Option)

The tables from the buffer can also be visualized as 3D surfaces as illustrated below.
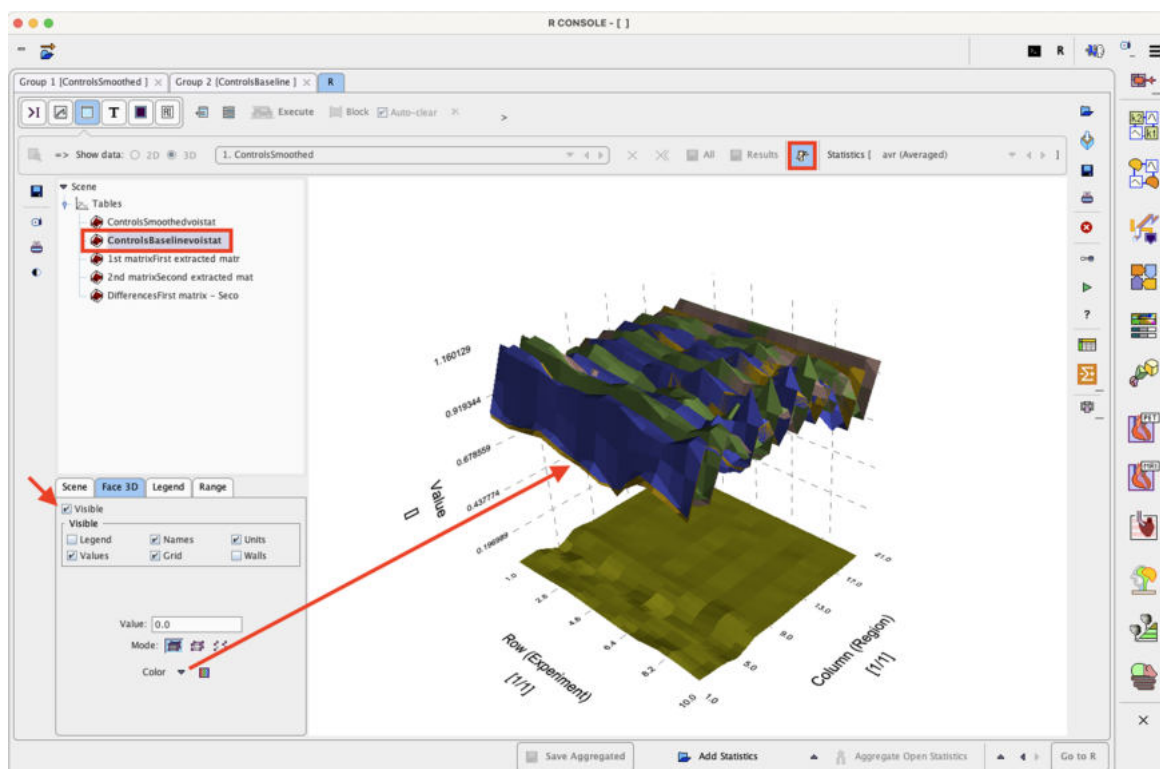
It is essential, that before enabling this display the buffer is prepared so that only meaningful tables remain. Please remove the other tables with the **x** button. For information about the 3D rendering please refer to the *PMOD 3D Rendering User's Guide*.

3D Visualization (Option)

When the **3D** radio button is enabled, the selected buffer table is displayed as shown below.
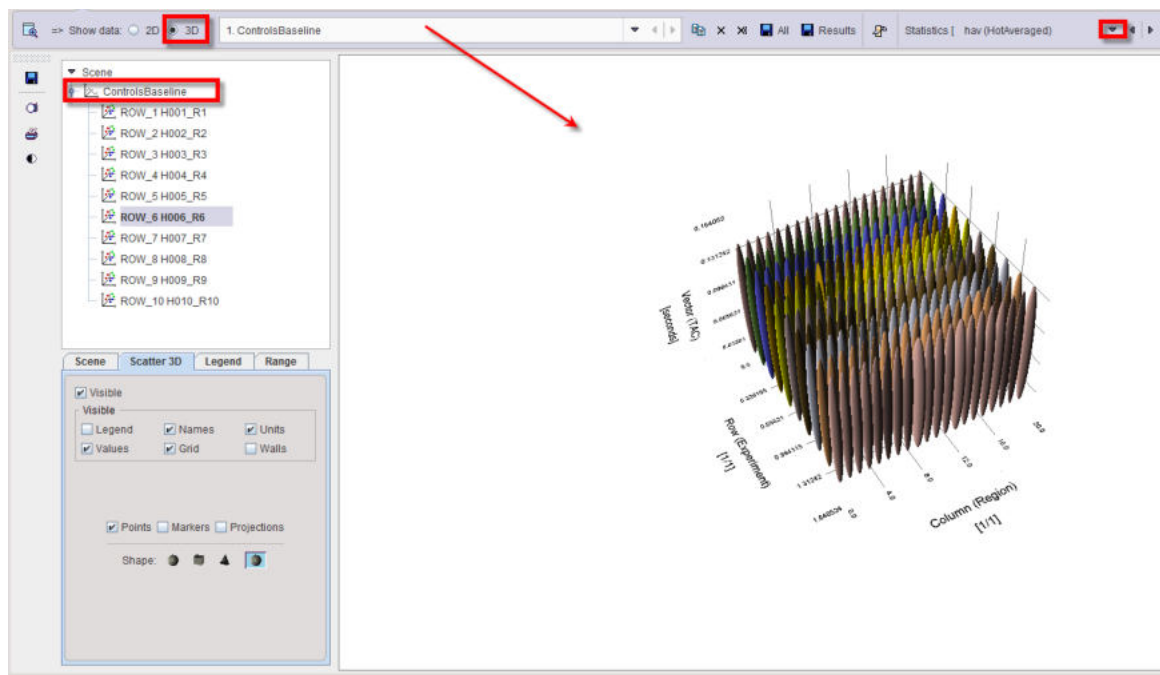
Dynamic Data

If the loaded statistic has a time dimension, the table represents the values at a certain time which can be selected in the **TIME VECTOR** list or by moving the **Sample** slider.
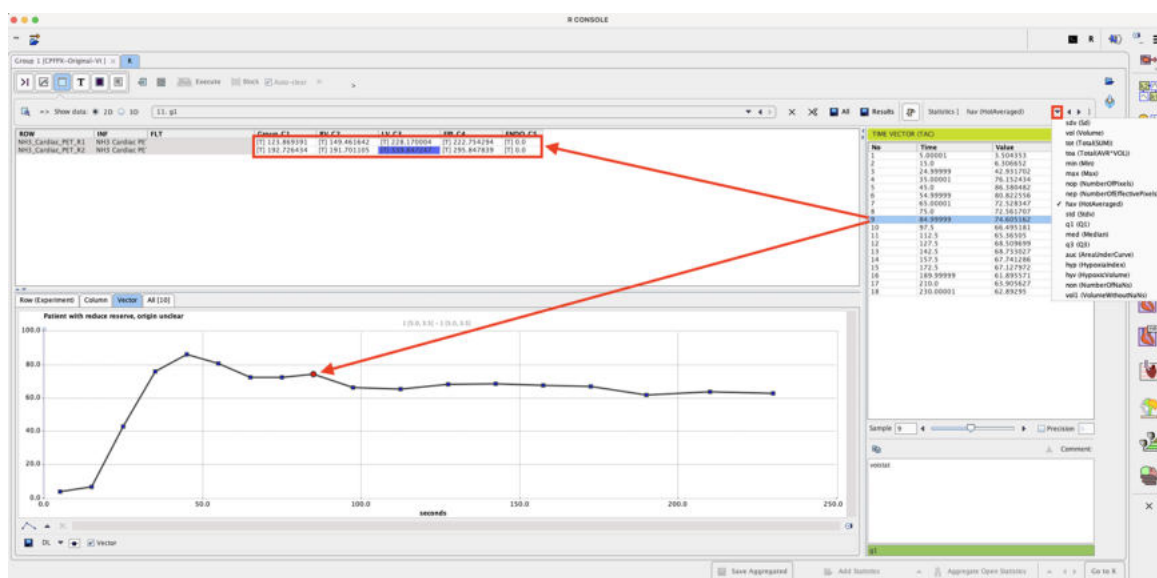
The TAC corresponding to the selected cell (subject/VOI) and the selected **Statistics** is plotted in the **Vector** tab, and all TACs in the **All** tab.

11.7 Plotting Layout

The contents of variables in the R workspace can be plotted in various ways. Note, however, that the structure of the aggregates used for comparative plotting (eg. scatter plots) needs to be identical, meaning that the number of rows and columns as well as the sorting order must be the same. *No attempt is made to pair corresponding data.*

The ▦ button switches the R console to the **Plotting Layout** as illustrated below.
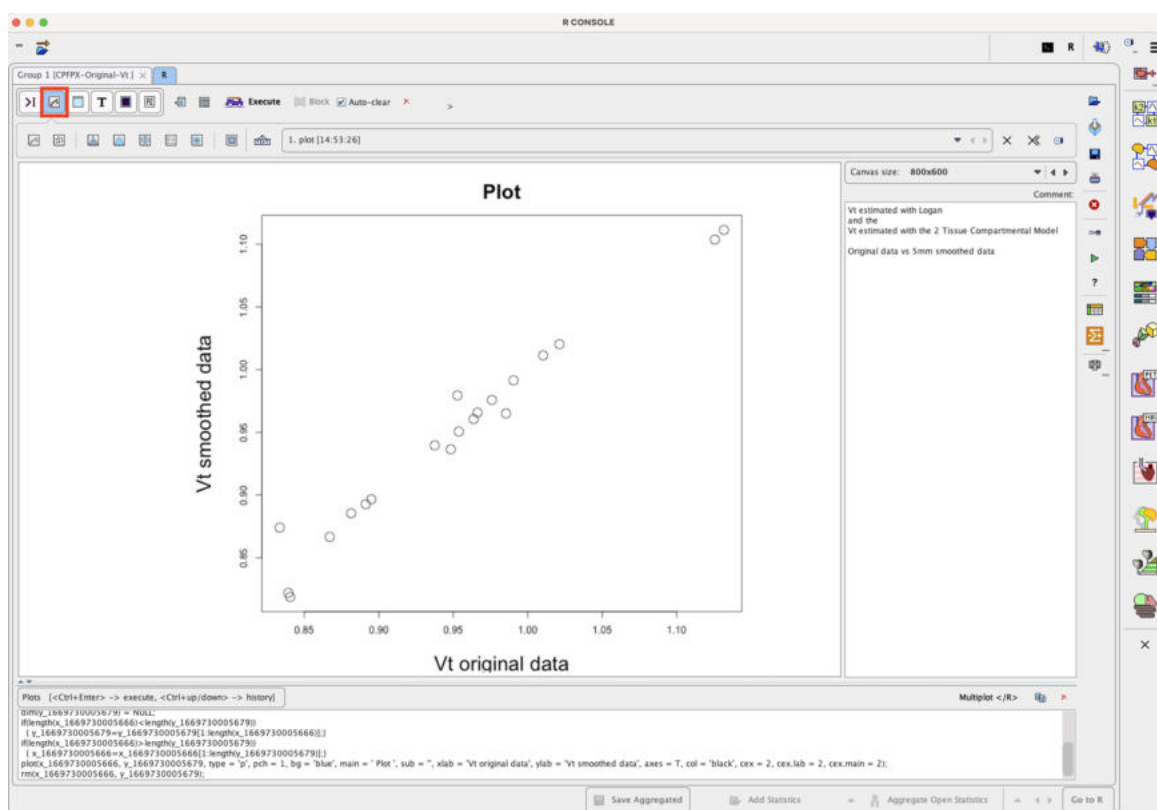
The different available types of plots are represented by the icons in the upper left. When one of the plot icons is activated, it shows a dialog window for the specification of the input data and the plotting parameters.

Plotting User Interface

The interface for the different plots shares common features. The example below shows the **Plot** interface.

The upper part represents the specification of the data to be plotted, as described above 365. Depending on the situation, one or more data sets labeled **A**, **B**, **C** can be plotted. Some plots may generate variables which are of general interest. They are labeled with **Variable prefix** so that they can easily be identified in the workspace.

Most **Plot options** are straightforward, except for the **Plot size**. It relates to the default size of the R plotting function, which is variable. The plot sizes may need adjustment, when the canvas size is changed.

Plotting Code

From the specification in the dialog window R code is generated. If the **Execute** flag is enabled, the code is immediately executed and the graphics is shown in the main window. Otherwise the code is added to the history of the **Plots** command window and may be edited before execution, for instance to change a plotting option.

All executed code is added to the history of the **Plots** command window. On demand prior code can be recovered using the keyboard keys `Ctrl+Up-arrow` and `Ctrl+Down-arrow` similar to the command window 427.

Plot Buffer

The plots created by any plotting actions (including scripts) end up in a plot buffer, so that they can be inspected at any time during a processing session by simply switching the list.
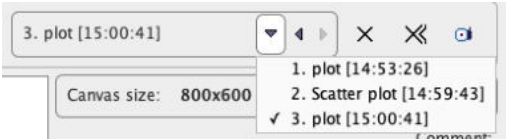
×	Remove current table from the list.
✕	Clear the buffer list.
⊡	Save the graphics to a file.

The buffer list can be edited with the buttons to its right:

11.7.1 Box Plots

Box plots are widely used in descriptive statistics. They are particularly useful for comparing populations. The button opens the box plot interface.
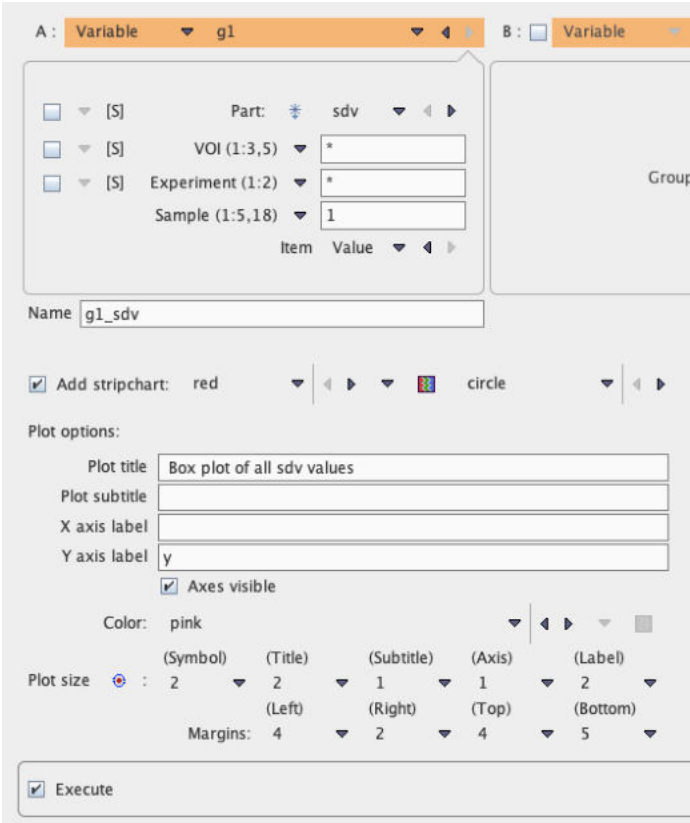
It produces from the data vector a plot with the following structure.

Box plot of all Vt values
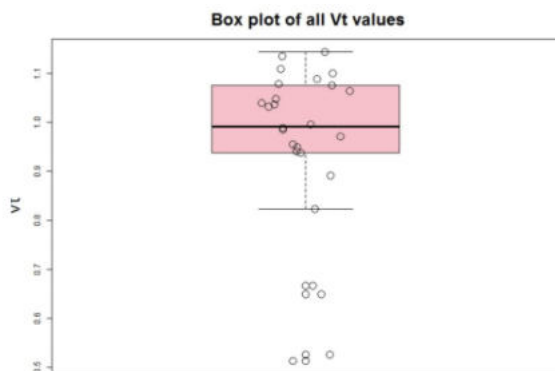
The lines of the box represent the first and third quartiles (Q1, Q3). The bold line in the box represents the median. The whiskers are calculated from the data according to Tukey's method from the interquartile distance (Q3-Q1) and the data. Data points outside the whisker range are outliers.

Note that the box plot is applied in the **Descriptive Statistics** script.

11.7.2   Data Plots

There is a general plotting procedure which can be called with the ⬜ icon. The user interface allows tailoring it to the plotting task.

This function is more suited for plotting a single data vector, but x-y plots of two data vectors with equal length are also possible. The **Plot types** list offers the following choices for the plot presentation:
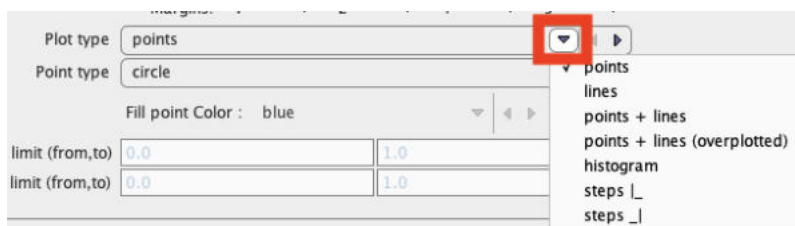
Some example plots: **points** plot with two variables **A** and **B**. Note that regression fits are not supported in this function.
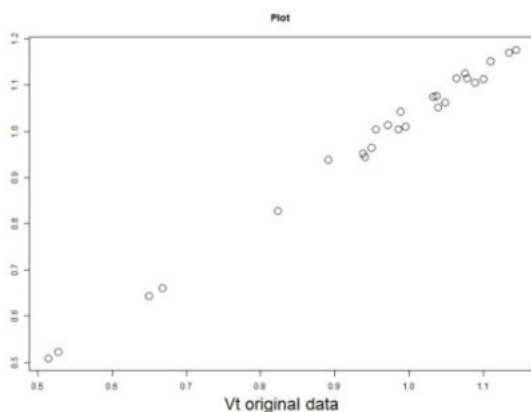
Points + lines plot with a single data vector
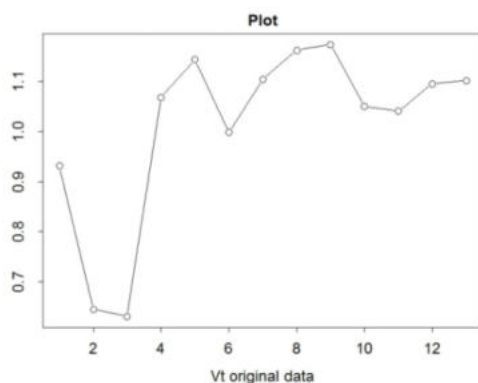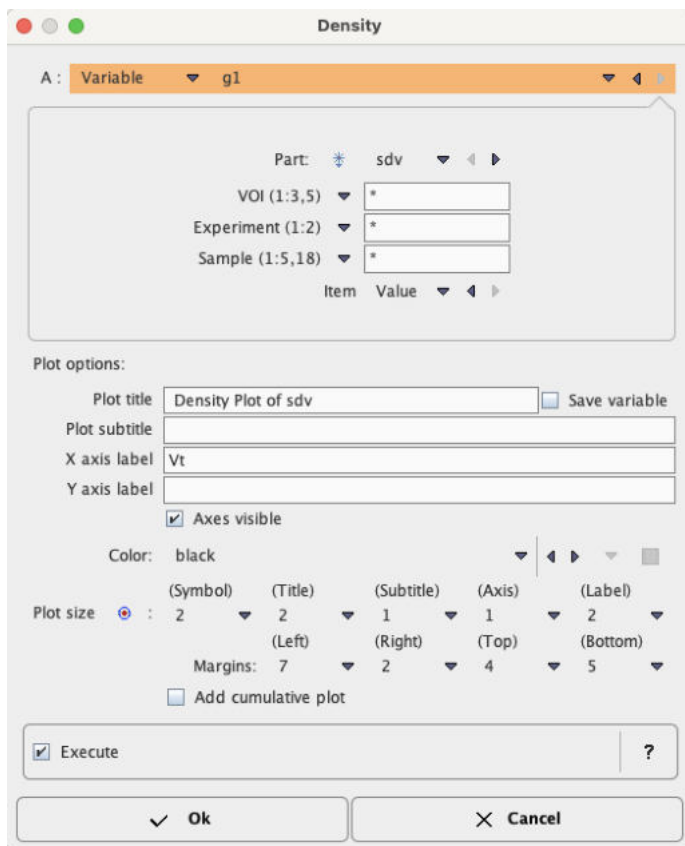
Steps plot with a single data vector
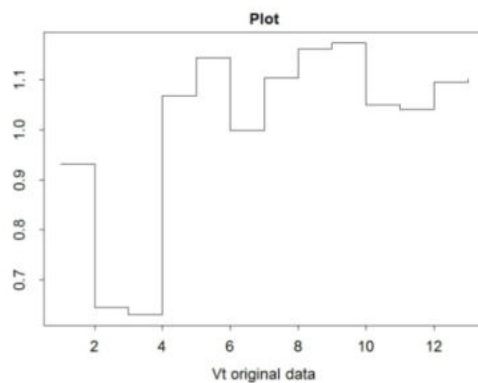
11.7.3 Density Plots

The fourth button [icon] provides access to density plotting. This is an extension of the histogram approach and has the advantage that it doesn't depend on a bin size. The setting
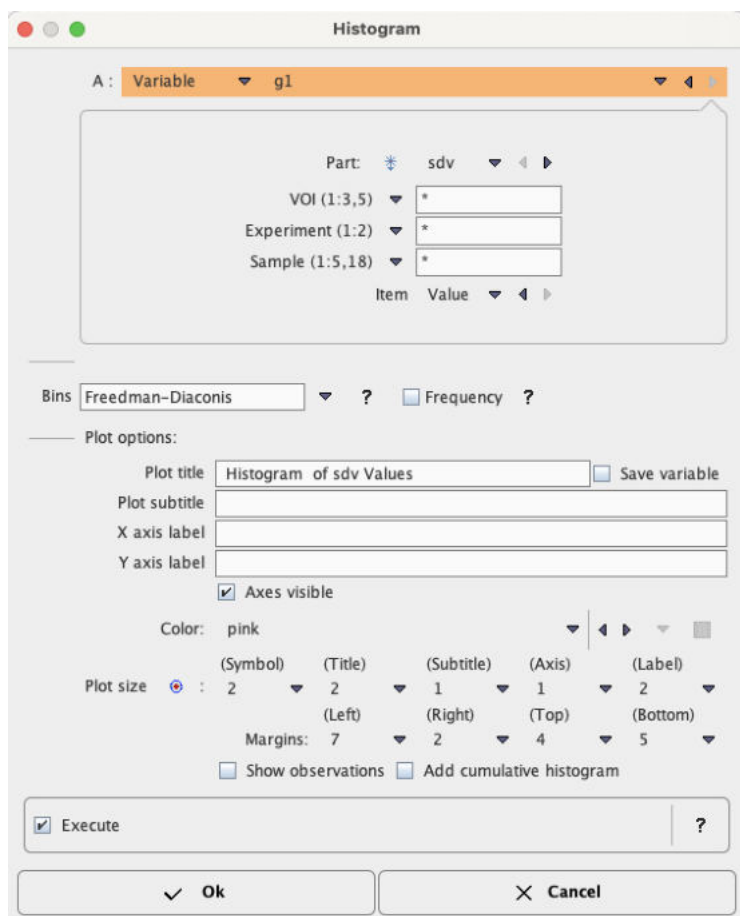
uses the Vt from all VOIs and Experiments (= analysis methods in the example data) and results in the plot below.
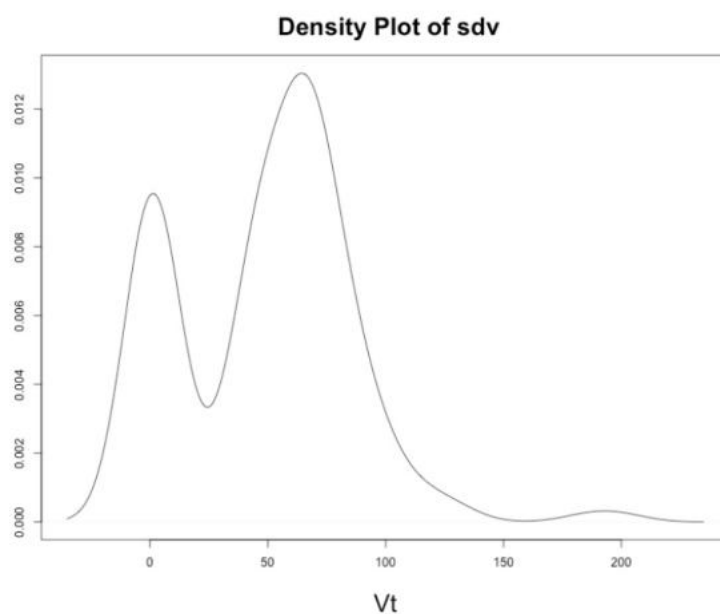
11.7.4   Histogram Plots

The third button serves for plotting a histogram of a data vector.
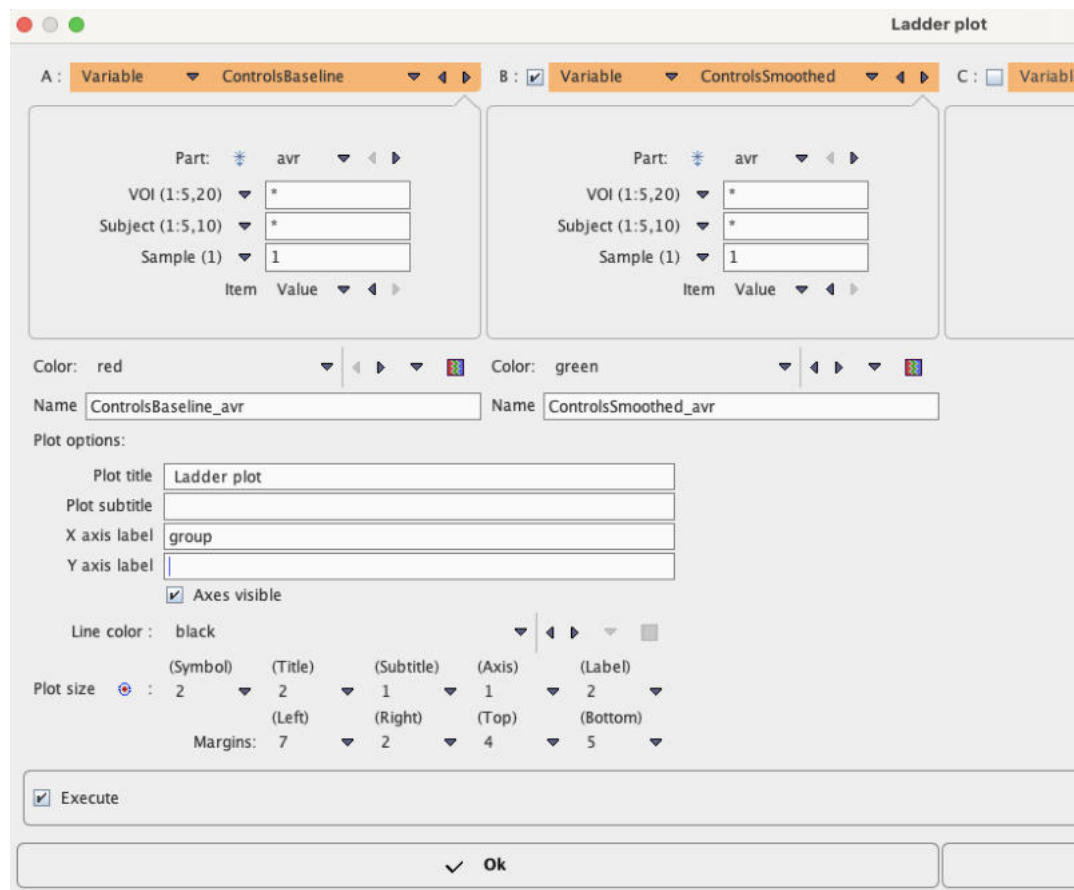
The number of **Bins** can be entered numerically or automatically calculated by 3 methods (**Sturges**, **Freedman-Diaconis**, **Scott**). The example results in the histogram below.

Note the indication of the values and the value ranges because **Show observations** and **Axes visible** are enabled.

11.7.5 Ladder Plots

Ladder plots visualize the relation of a test variable in two or more conditions, for instance pre-and post-treatment. It is called with the ▤ button.

Up to 4 conditions can be connected. However, note that the implementation requires identical ordering of the subjects in the data vectors. The example below illustrates a comparison between two conditions.
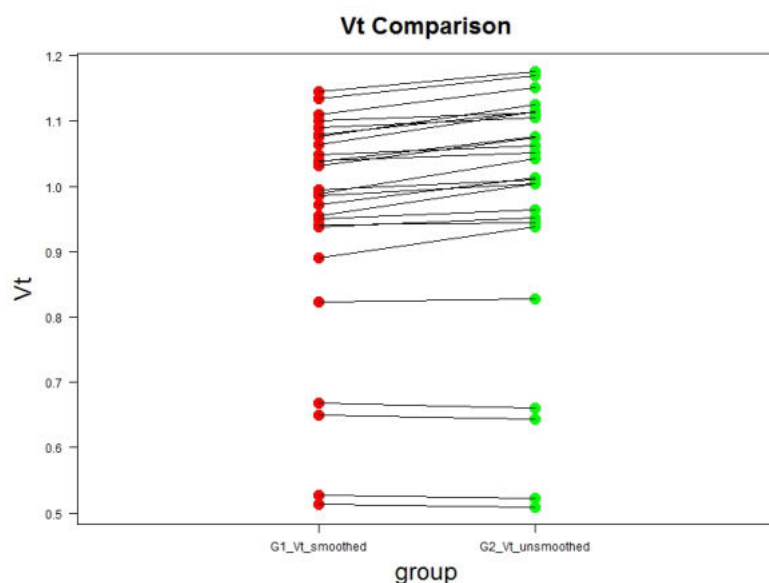
11.7.6   Polar Plots

The polar plotting function is called with the ⊞ button and opens the following dialog window:

A : Variable ▼	p_42994738441129 ▼

Polar data

Plot options:

Plot title	Stress
Unit:	kBq/cc ▼ ◀ ▶
Filter type:	No filter ▼ ◀ ▶
Filter size:	3x3 ▼ ◀ ▶
Color table:	🎨 Cool ▼ ◀ ▶
Range:	lower 0.0 upper 1.0

☐ Execute ☐ New line   ?

✓ Ok   ✕ Cancel
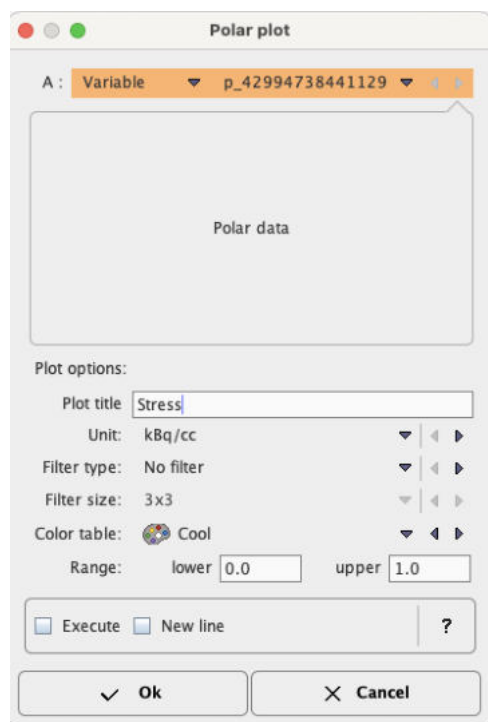
The user interface allows tailoring it to the plotting task and **Plot options** for the selected **Variable** are available. The result is shown below
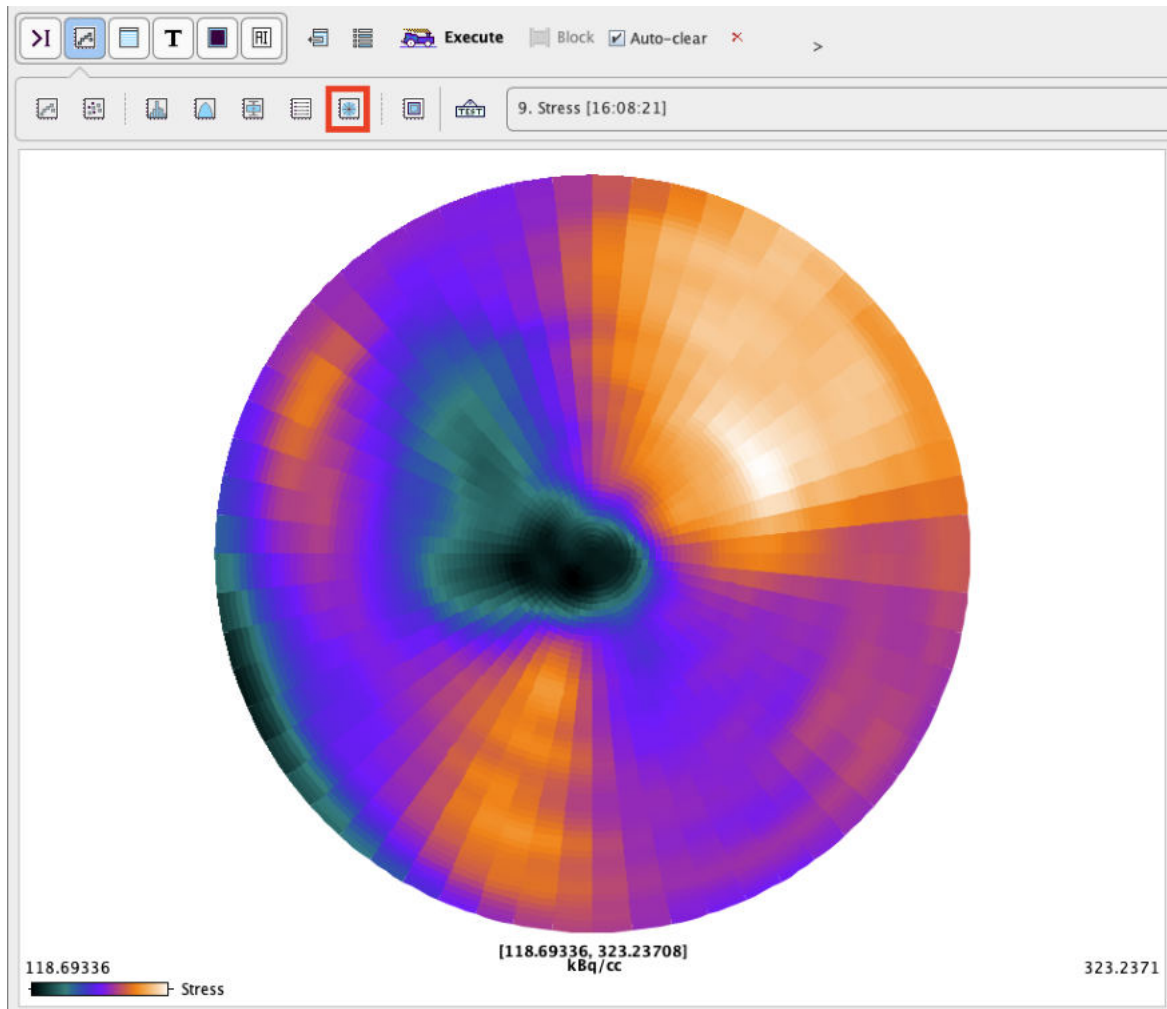
11.7.7 Scatter Plots

The scatter plotting function is called with the ⊞ button and opens the following dialog window.

Typically, the values of variable **A** will be plotted against variable **B**. If a third variable **C** is enabled (option), the plot is shown as a 3D scene in the PMOD 3D rendering tool.

The example below shows a scatter plot with a fitted regression line.

Scatter (y = 0.9621 * x + 0.0325, R2 = 0.9726)
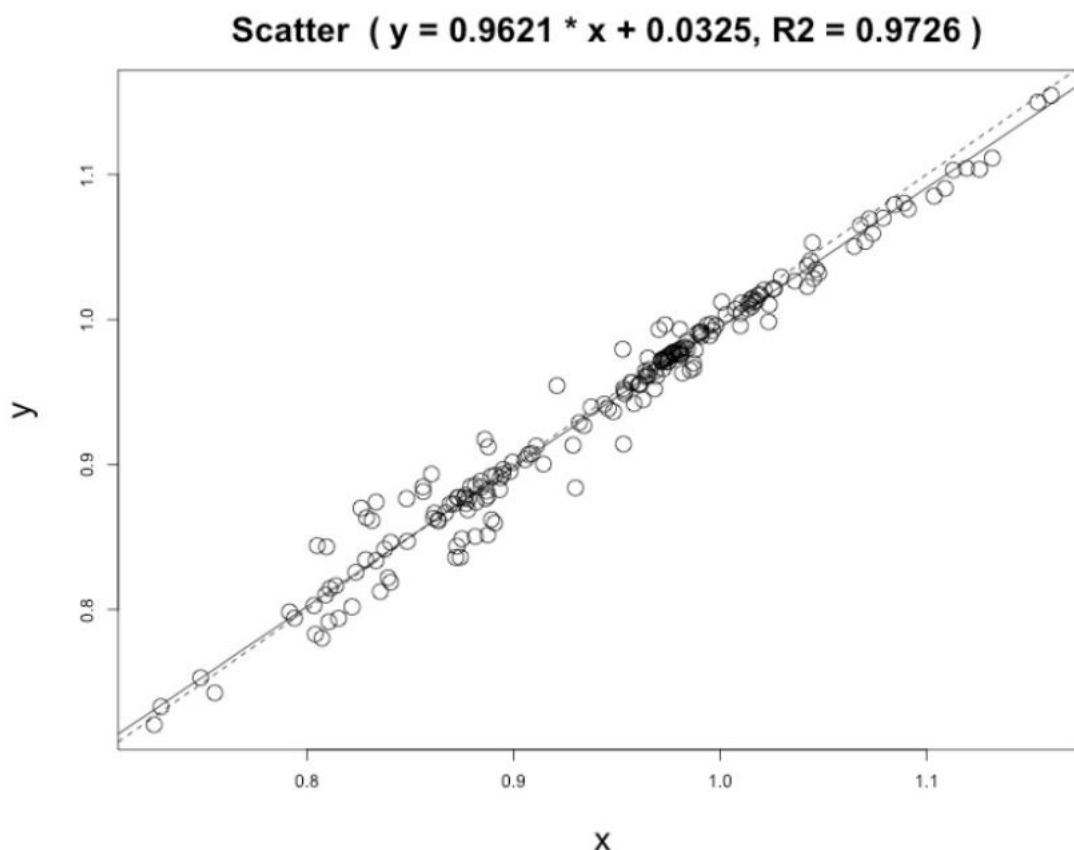
11.8 Analysis Scripts for Aggregates

PMOD has developed several scripts to support users with the statistical analysis of results arising in the comparison of populations or analysis methods. To use them efficiently, the outcome measures should be organized in groups by aggregation 345.

For example, if healthy controls are studied twice to determine the repeatability of an acquisition/data processing methodology, the results of the first study should be aggregated in a test group g1, and the results of the second study in a retest group g2. These groups can then be loaded into the R-console of PMOD, and analyzed with the **Test-Retest** script.

Another typical example is the comparison of analysis methods. The same set of population data will be processed twice with different methods, for instance to calculate the regional binding potential BP_{nd}. All BP_{nd} estimates resulting from method 1 are aggregated into a group g1, and all BP_{nd} estimates resulting from method 2 in group g2. The method comparison is then done by applying the script **Bland Altman Plot** to g1 and g2.

The scripts generate and execute native R code which can be inspected in the command console and serve as a basis for users to develop their own, modified scripts.

Invoking Scripts

After loading the data to be analyzed, scripts can be called either from the **Scripts** list of the command layout
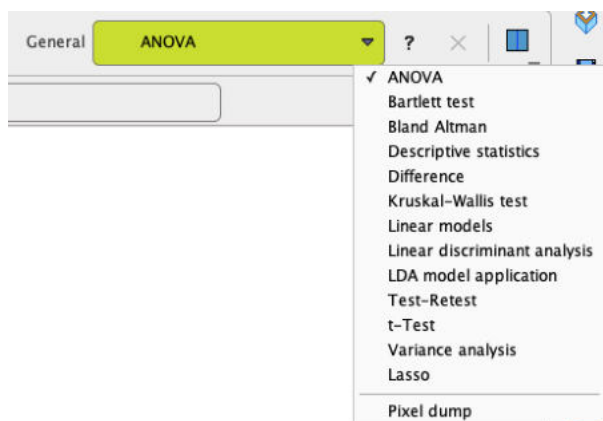
or via the lateral taskbar by the indicated arrow button
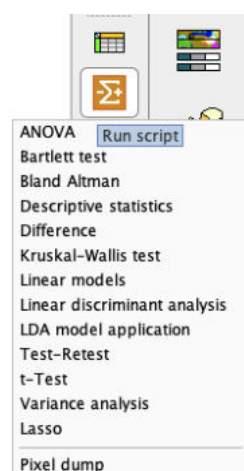
The following sections describe each of the scripts. Most practical details are included in the **Descriptive Statistics** section, so please make sure to read this section first.

11.8.1 ANOVA for 3 or 4 Groups

The one-way ANOVA test compares the means between groups and determines whether any of those means is significantly different from the others. It can only detect that least two groups are different, but not which ones. Therefore, a pair-wise *post-hoc* comparison needs to be applied in the case significance. The **ANOVA** script applies the Tukey's HSD (Honest Significant Difference) *post-hoc* test.

Assumptions

One-way ANOVA is based on the following assumptions:

- the response variable (the dependent variable) is normally distributed;
- the samples are independent;
- the group variances are equal.

ANOVA Configuration

The ANOVA configuration window is illustrated below.
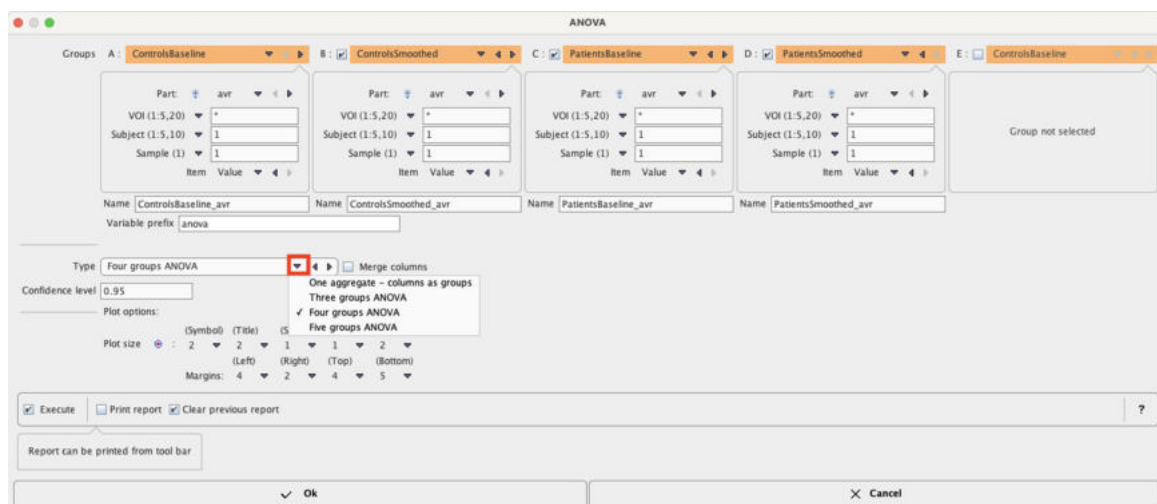
There are two **Type**s of data organizations for the ANOVA script:

1. **One aggregate - columns as groups**: In this case the groups to be compared are arranged as columns in a single aggregate.

2. **Three groups ANOVA, Four groups, Five Groups ANOVA**: In these cases the groups to be compared are represented by separate aggregates. If **Merge columns** is enabled, the data of all columns will be pooled, otherwise the ANOVA analysis is performed between the respective columns of the aggregates which may represent different VOIs.

The **Confidence level** setting (default 95%) is related to Tukey's HSD test.

ANOVA Results
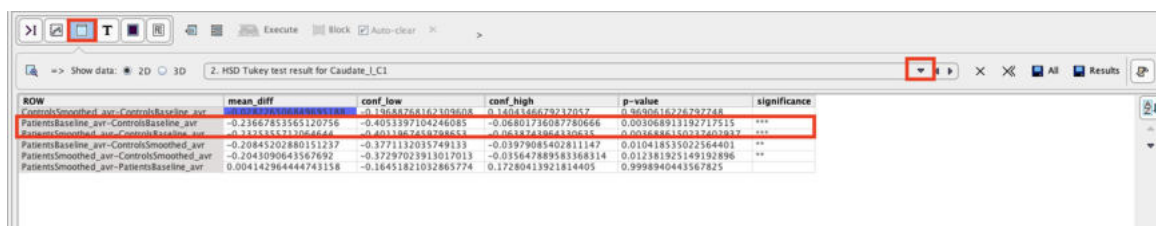
The script produces result two tables per VOI: one related to ANOVA (**anova_result**), and one related to Tukey HSD (**anova_tukey**).

A **p-value** <0.05 in the ANOVA result table as in the example below indicates that there is a significant difference among the group means.

The corresponding Tukey HSD table

allows identifying G3 being different from G1 and G2, since the **p**-value is <0.05 for **G3-G1** and **G3-G2**, whereas it is not significant for **G2-G1.**

The results are illustrated by two plots per VOI: a box plot 372 summarizing the regional statistics,
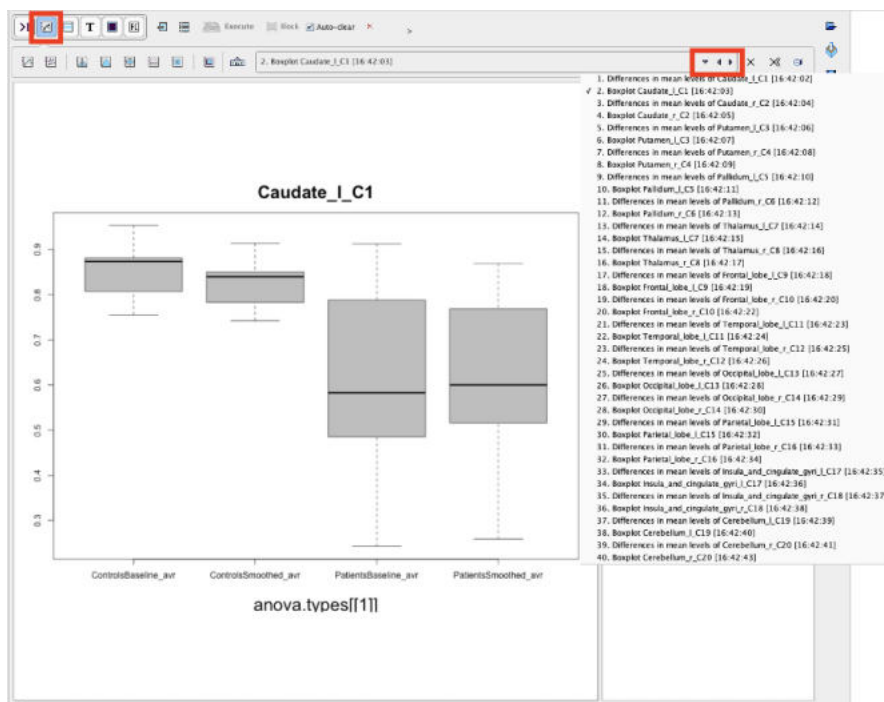
and a plot of the **Confidence intervals** of the group differences from the Tukey's HSD test. If the zero difference is not included in the confidence interval, the group difference is significant.
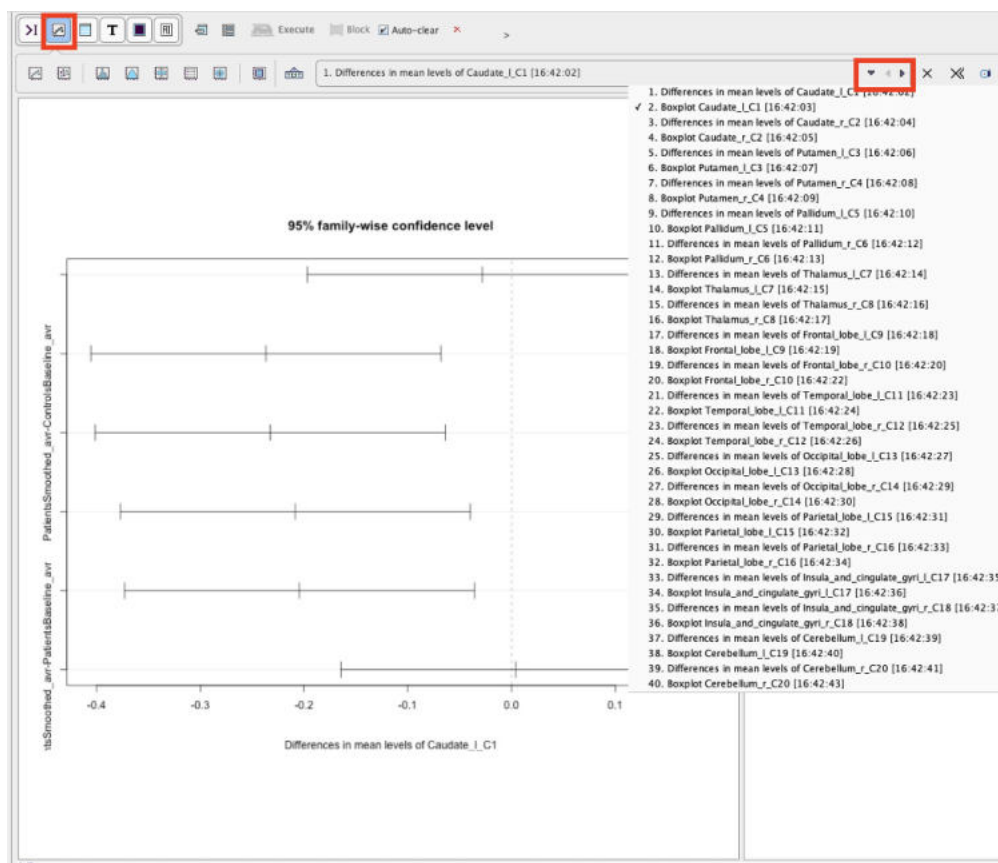
11.8.2   Bartlett Test

The **Bartlett** test is used to test whether the variances of groups to be compared are equal (homoscedasticity, or homogeneity of variances). Some statistical test such as assume equal variances. The Bartlett test can be used to verify that assumption.

ANOVA Configuration

The **Bartlett Test** configuration window is illustrated below.

Up to four groups can be compared, according to the **Type** selection
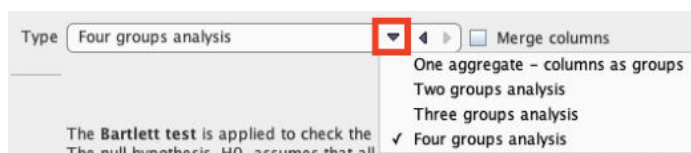
If **Merge columns** is enabled, the data of all columns will be pooled, otherwise the test is performed between the respective columns of the aggregates.

With the **One aggregate - columns as groups** setting it is assumed that the groups to be compared are arranged as columns in a single aggregate.

Bartlett Results

The script produces a result table (**bartlett_result**) listing the **p-value** for each aggregate column and indicating its significance.

11.8.3 Bland Altman Plot

The Bland-Altman plot is aimed at comparing two measurement methods [1]. It simply plots the difference between the measurements against their average. The mean difference is the estimated bias, and from the standard deviation of the differences the *95% limits of agreement* can be calculated (mean±1.96std).

Bland Altman Plot Configuration
The **Bland Altman Plot** script shows the following dialog window.

Two variables have to be defined, which will be sorted so that the correspondence between samples is ensured. The **Linear regression** convenience option allows getting a scatter plot with a regression line at the same time as the Bland Altman plot.

Bland Altman Plot Results

There are three numeric result tables: the data for the plot (**AVR** on x-axis, **DIFF** on y-axis) in the **BA** table,

the analysis results in the **diff_result** table,

and the equation of the linear regression in the **regression** table.

The corresponding plots can be inspected in the plot layout:
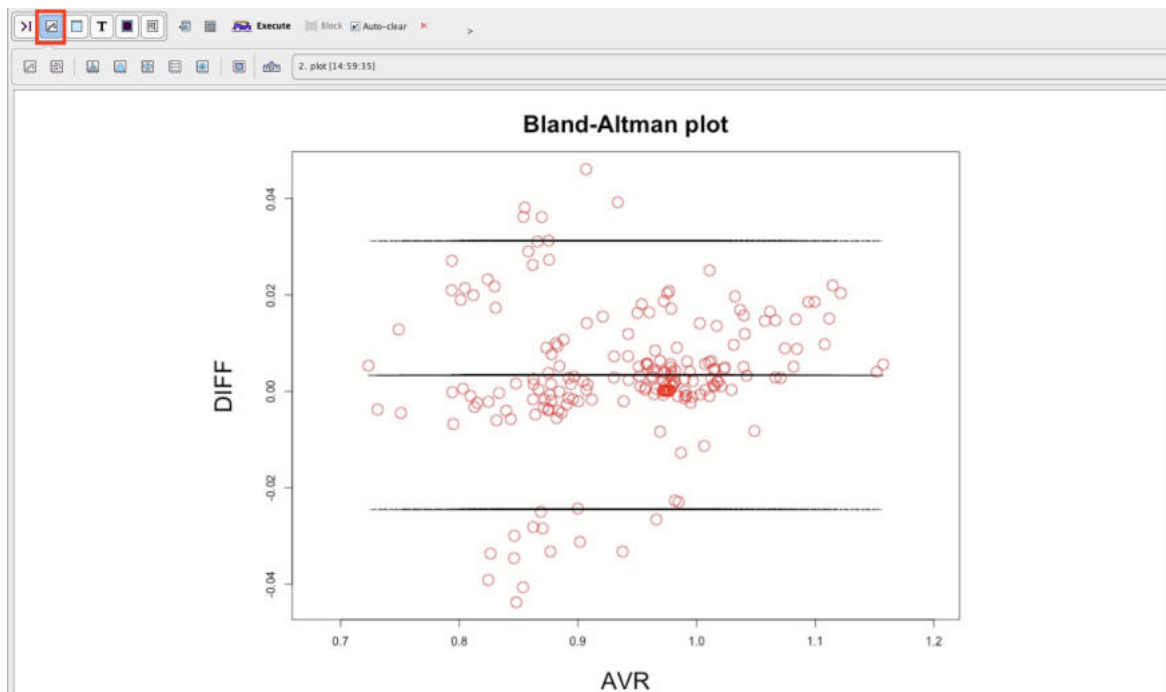
and
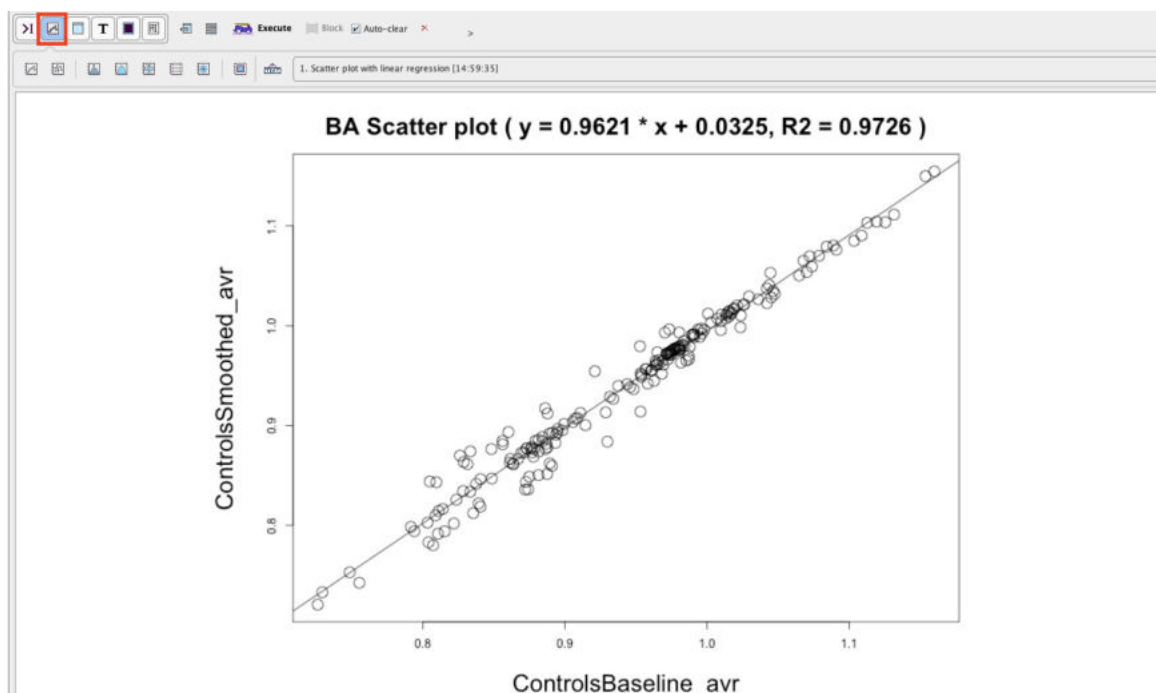
Reference:

1. Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986, 1(8476):307-310.

11.8.4 Descriptive Statistics

The **Descriptive statistics** script serves for summarizing the statistical properties of outcomes assembled in one or several PMOD aggregates.

Descriptive Statistics Configuration

The **Descriptive Statistics** script shows the following dialog window.
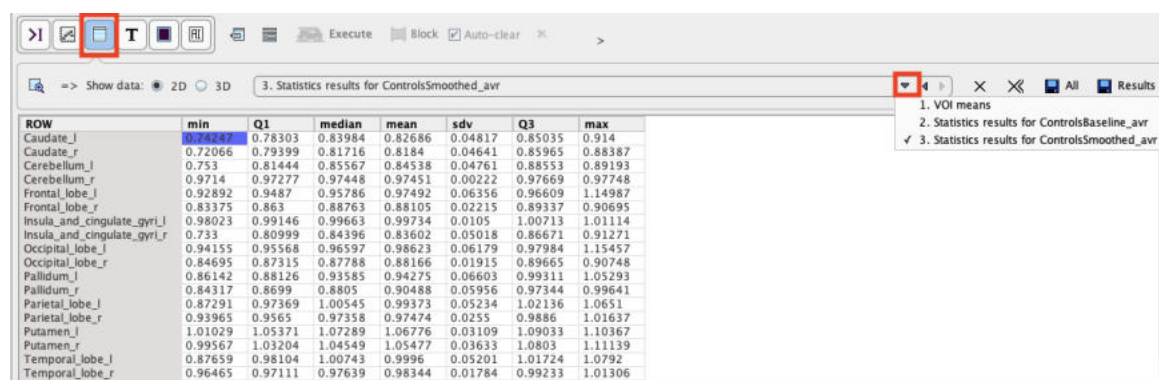
Note that up to 4 data sets can be compared. In the example case 2 **Groups** are selected and the variables **ControlsBaseline** and **PatientsBaseline**. Only one statistic can be compared at a time,

to be selected from the **Part** list. If the parameter names don't match, the program will complain, but still perform the calculation.

The results consist of tables as well as graphic plots. To group the table results a **Variable prefix** can be specified. **Plot title** and **Values label** should be edited such that the plots are meaningfully annotated. The **Draw ladder** plot option allows visualizing each data point across the three data sets. This is only reasonable, if all groups include the same subjects. In this case, the **Match rows and columns by name** box should be checked.
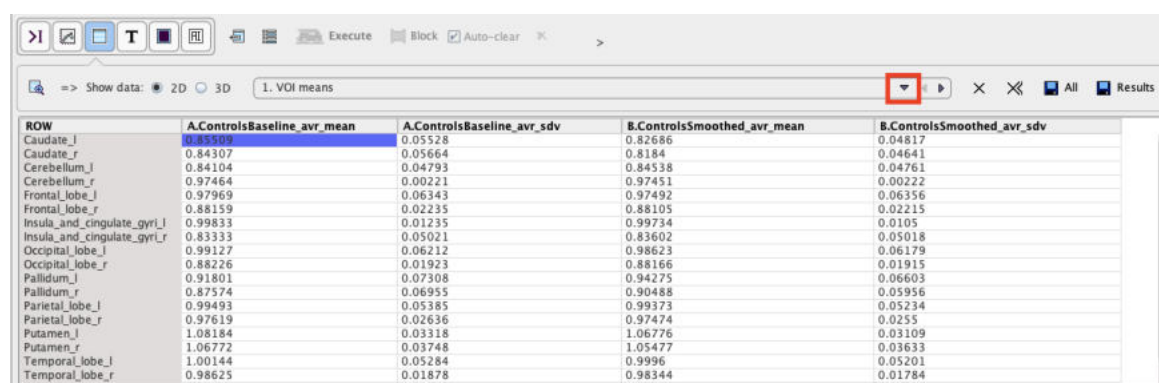
Descriptive Statistics Results

After running the script the workspace is populated with new variables, and plots have been generated and added to the plot history. The R console is in the table layout and shows a statistic summary table of the last group. For each VOI it lists the minimum, first quartile (Q1), median, mean, standard deviation, third Quartile (Q3) and maximum across the subjects. The

Using the buffer selection, the table can easily switched to the other groups, as well as the **VOI Means** table which just shows the VOI means and standard deviations for all groups.

Note the copy and save buttons in the buffer controls for exporting the table data.

The same information as in the tables is visualized by one box plot 372 per VOI, providing a convenient side by side comparison of the groups. Please activate the plot layout and use the buffer arrows to browse through the different VOIs.

π.pmod
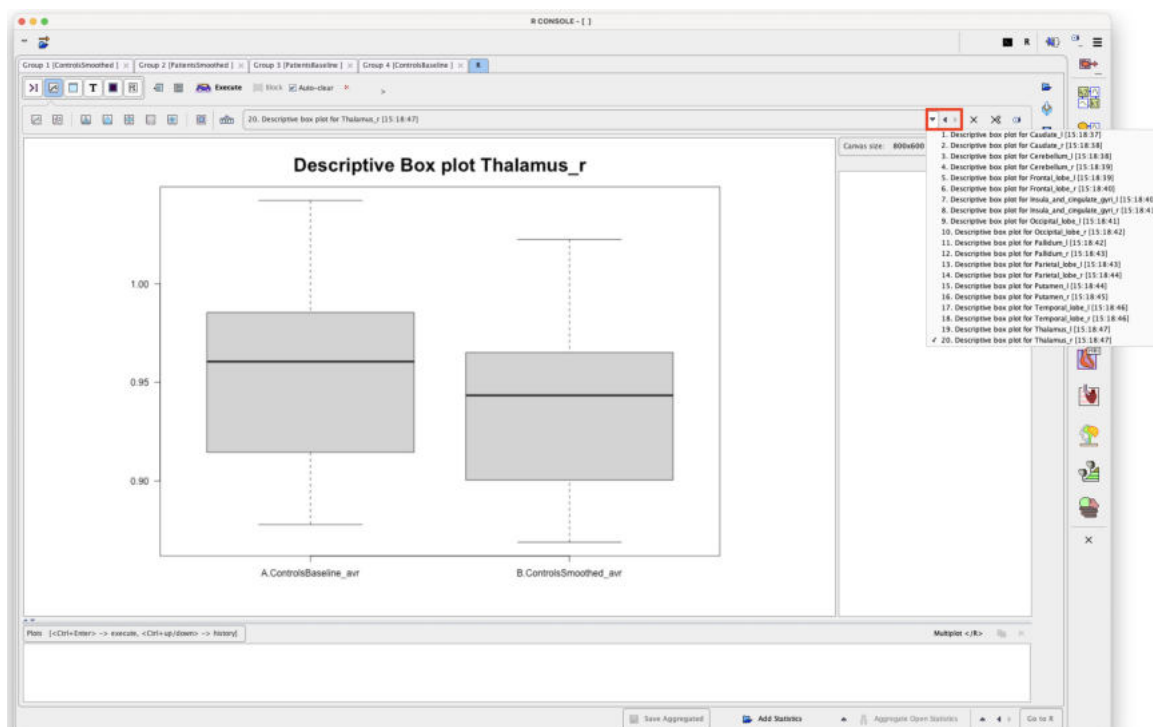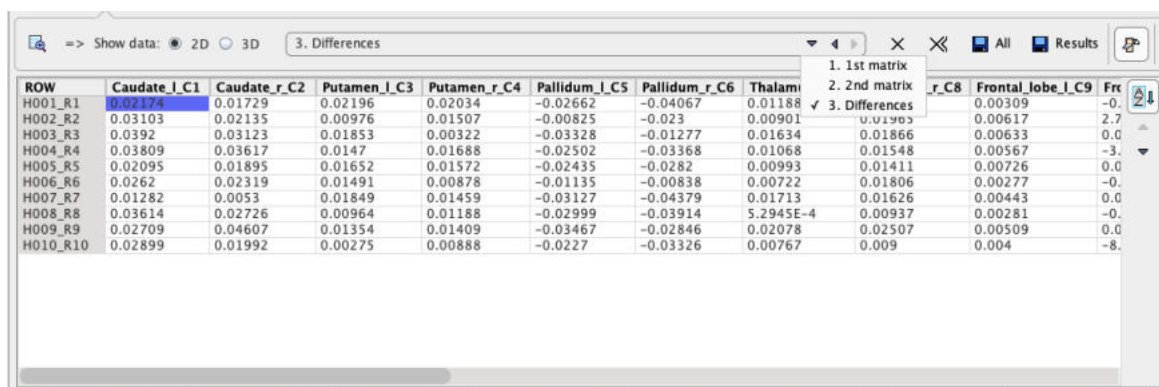
If the **Ladder** plot option was enabled, box plots are alternated with ladder plots [377].

11.8.5   Difference

The **Difference** script is a simple facility for calculating the difference between two groups. Besides the **Absolute** difference there are various relative differences available, which can be configured with the **Difference type** option list.

The results of the script are three tables, available through the buffer

ROW	Caudate_l_C1	Caudate_r_C2	Putamen_l_C3	Putamen_r_C4	Pallidum_l_C5	Pallidum_r_C6	Thalam...	...r_C8	Frontal_lobe_l_C9	Fro...
H001_R1	0.02174	0.01729	0.02196	0.02034	−0.02662	−0.04067	0.01188		0.00309	−0.
H002_R2	0.03103	0.02135	0.00976	0.01507	−0.00825	−0.023	0.00901	0.01965	0.00617	2.7
H003_R3	0.0392	0.03123	0.01853	0.00322	−0.03328	−0.01277	0.01634	0.01866	0.00633	0.0
H004_R4	0.03809	0.03617	0.0147	0.01688	−0.02502	−0.03368	0.01068	0.01548	0.00567	−3.
H005_R5	0.02095	0.01895	0.01652	0.01572	−0.02435	−0.0282	0.00993	0.01411	0.00726	0.0
H006_R6	0.0262	0.02319	0.01491	0.00878	−0.01135	−0.00838	0.00722	0.01806	0.00277	−0.
H007_R7	0.01282	0.0053	0.01849	0.01459	−0.03127	−0.04379	0.01713	0.01626	0.00443	0.0
H008_R8	0.03614	0.02726	0.00964	0.01188	−0.02999	−0.03914	5.2945E-4	0.00937	0.00281	−0.
H009_R9	0.02709	0.04607	0.01354	0.01409	−0.03467	−0.02846	0.02078	0.02507	0.00509	0.0
H010_R10	0.02899	0.01992	0.00275	0.00888	−0.0227	−0.03326	0.00767	0.009	0.004	−8.
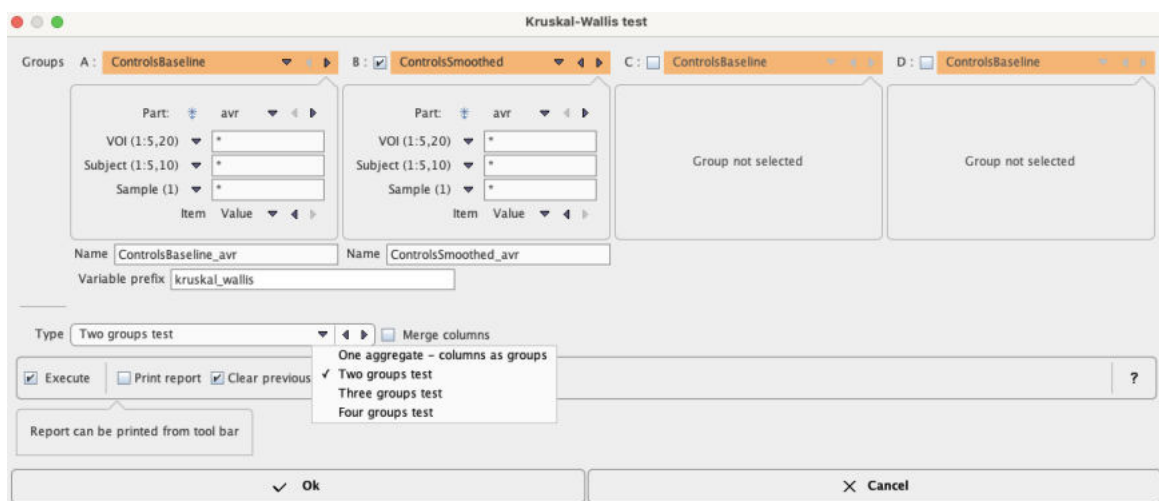
diff_g1_g2 represents the calculated difference, whereas **diff_mat1** and **diff_mat2** contain the extracted input data for the calculation.

11.8.6 Kruskal-Wallis Test
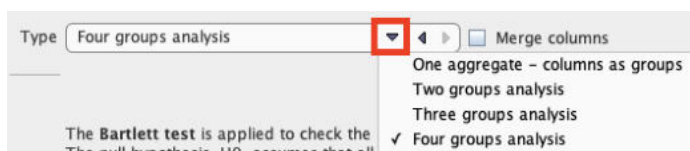
The Kruskal–Wallis one-way analysis of variance by ranks is a non-parametric equivalent of the one-way ANOVA [382]. It assumes independent samples and has the null hypothesis, that the distribution is identical. If the calculated p-value is <0.05, it is concluded that the distributions are nonidentical at the 0.05 significance level (R example).

Kruskal-Wallis Configuration

The Kruskal-Wallis configuration window is illustrated below.

Up to four groups can be compared, according to the **Type** selection
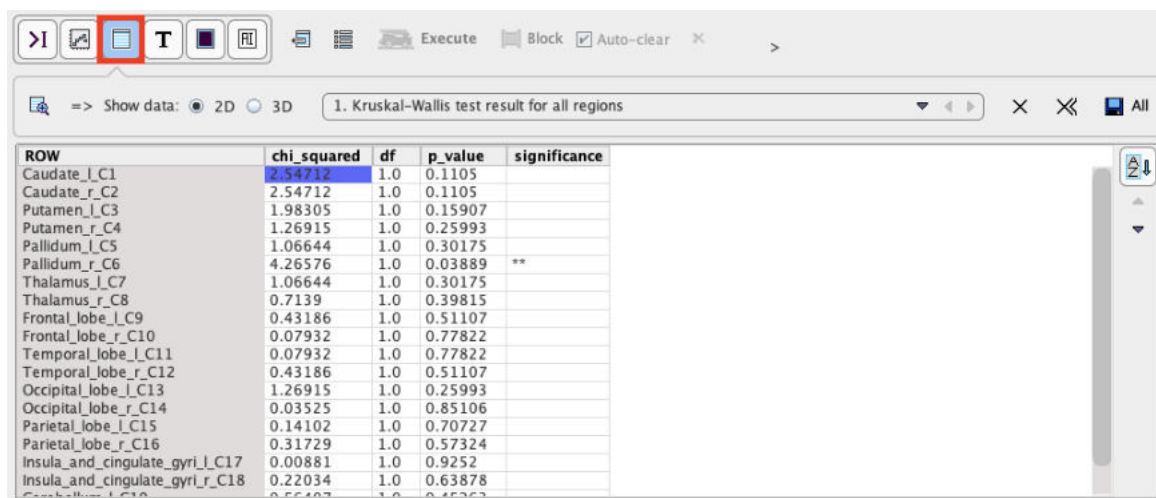
If **Merge columns** is enabled, the data of all columns will be pooled, otherwise the test is performed between the respective columns of the aggregates.

With the **One aggregate - columns as groups** setting it is assumed that the groups to be compared are arranged as columns in a single aggregate.

Kruskal-Wallis Results

The script produces a result table (**kruskal_wallis_result**) listing the **p-value** for each aggregate column and indicating its significance.

11.8.7 Linear Models: Statistical Analysis of Regional Imaging Data

Advanced statistical techniques based on linear statistical model are implemented in the PMOD R interface. These solutions have been developed by Prof Karl Herholz, University of Manchester, UK, who is a renowned expert and consultant in the field of neuroimaging, with particular interest in dementia and brain tumors. His statistical expertise was sharpened as the coordinator of multiple international multicenter studies, and by the development of automated image analysis procedures, such as the one employed in PMOD's PALZ module.

Images provide a wealth of information. They are essential for demonstration and analysis of normal and pathological anatomy and function in medicine and biomedical sciences. Computerized tomography (CT) and related techniques, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), have made huge progress in the recent decades. They are frequently being used to provide diagnostic images interpreted visually by trained observers (e.g., radiologists).

Recently, it is increasingly being recognized that some images can also be regarded as data sets representing a quantitative parameter measured simultaneously in a large number of anatomical regions. Particularly, as each region in an image (with image pixels or voxels as the smallest regions that could potentially be studied) provides a separate dependent variable, their number may be very large and will often exceed the number of individuals under study. This situation creates a particular statistical challenge, which will be addressed in the current section.

These challenges can best be addressed by procedures which:

- take into account that regional data originating from the same individual are not independent from each other, and describe their dependency by a covariance matrix;
- provide tests for comparing the experimental effects between regions;
- provide proper correction for multiple comparisons.

The procedures are based on linear statistics models. Two approaches fulfilling these requirements will be described:

1. Repeated measures and multivariate analysis of variance (rm-ANOVA, MANOVA)

2. Linear mixed effect models (LME).

The table below summarizes the benefits and limits of the two linear statistics models:

MANOVA	LME

Analytical minimization of residual variance within groups for general linear model	Iterative minimization of residual variance for general linear model
Analytical separation of variance components for within-subject and between-subject factors	Fitting the mean effects for all specified experimental factors, and the variance of a random factor associated with individuals
Automatic inclusion of interactions between within and between-subject factors	All interactions need to be specified in the model for inclusion
May fail if too many highly correlated regions are included in model	Can accommodate a large number of regions
Requires a balanced design (groups of equal size) for correct separation of variance components	Works for balanced and unbalanced designs
Does not allow missing values	In presence of missing values effect sizes can still be fitted, but statistical tests to determine their significance may fail

11.8.7.1 Data Structure - Master Table

The data structure to be used in the linear models statistical analysis can best be visualized by a master table where columns represent regions and rows represent individuals. To build up the master table, aggregated files are required. It is essential that consistent group and condition names are correctly encoded for each aggregated file. Detail information about the aggregation procedure is available above 346.

Statistically, individuals (rows) are independent from each other while regions (columns) are not, which is an important distinction for the analysis structure. Each classification axis can have further subdivisions. E.g., individuals could be split into experimental groups, while the same regions might be present in the left and the right brain hemisphere. We would then have the experimental group classification as a "between-subject" variable, and regions and hemispheres as nested "within-subject" variables.

In-vivo imaging studies will often repeat scans in the same individuals. One could then analyze the difference between baseline and follow-up as the dependent variable of interest. Alternatively, measurement instance (baseline and repeat, optionally also further repeat measurements) could be represented as a within-subject variable (analyzing the same set of regions at all measurement times). Note, that repeat measurements would not represent another group of individuals, thus they are to be added as columns, not as rows.

The example below illustrates how to build the master table. To this purpose, four aggregates were created and transferred to the **R** console. Two groups, Control and Patient were analyzed in two conditions: *Baseline* and *Smoothed*. Please note that an aggregate was prepared beforehand for each group and condition.

Use the master table ⊞ icon from the lateral taskbar to start the interface for preparing the data for population statistics.
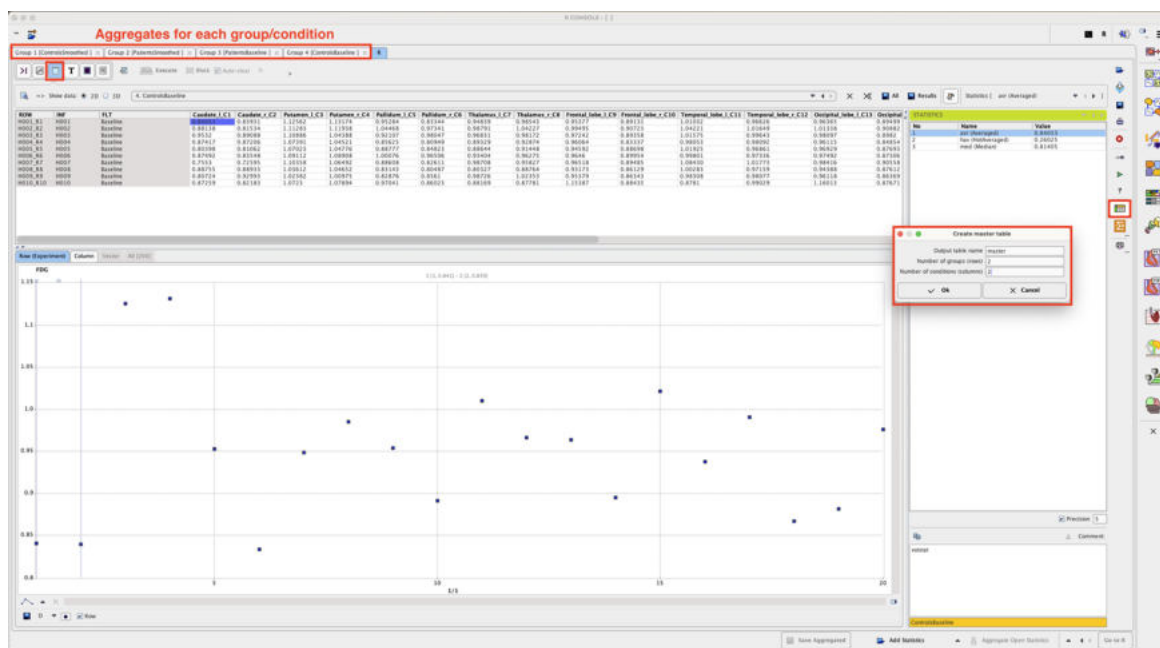
A dialog window opens allowing the definition of the number of rows and columns for the master table. The rows and columns correspond to the groups and conditions, respectively. The name of the master table can be edited in the **Output table name** field. To continue activate the **OK** button.

The **Master table creator** interface appears:
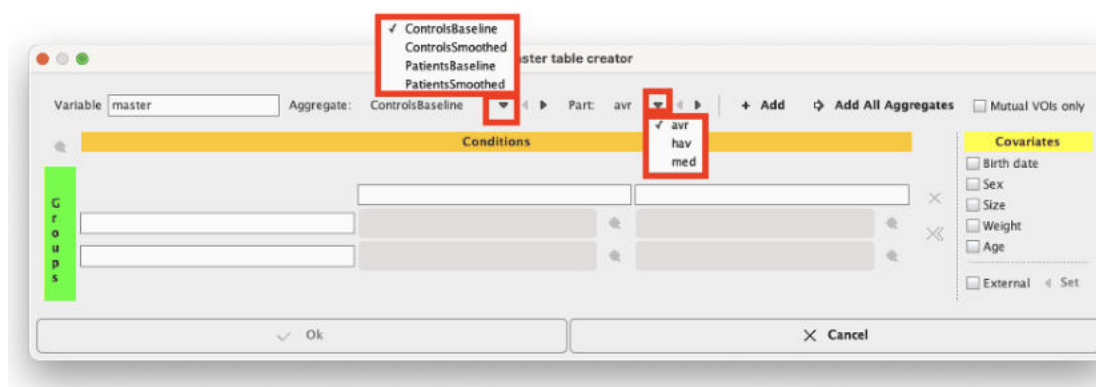
To fill in the master table select the **Aggregate** file to start with and the statistics **Part** to be analyzed. To transfer the **avr** part of all aggregates to the master table activate **Add all Aggregates**. The procedure uses the group and condition names encoded during aggregation for the arrangement of the aggregates in the table. This step will not work properly if the encoding was not consistent.

The **Mutual VOIs only** box enabled allows creating the master table based on VOIs information common in all the **Aggregate** files. This functionality is useful when the user is not certain about the information stored in the aggregated files.

The result of the example is shown below:
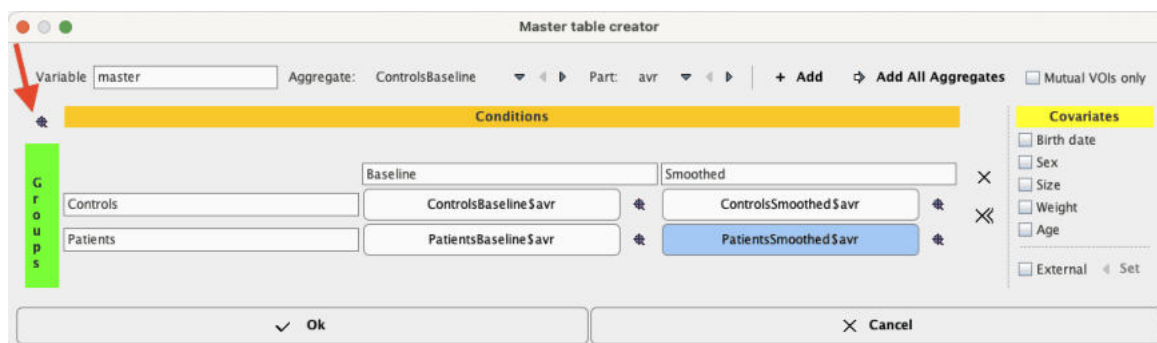
The master table has a structure consisting in blocks, each block corresponding to a group and condition. To preview the content of the master table activate the **View value** icons ✦ as indicated below:
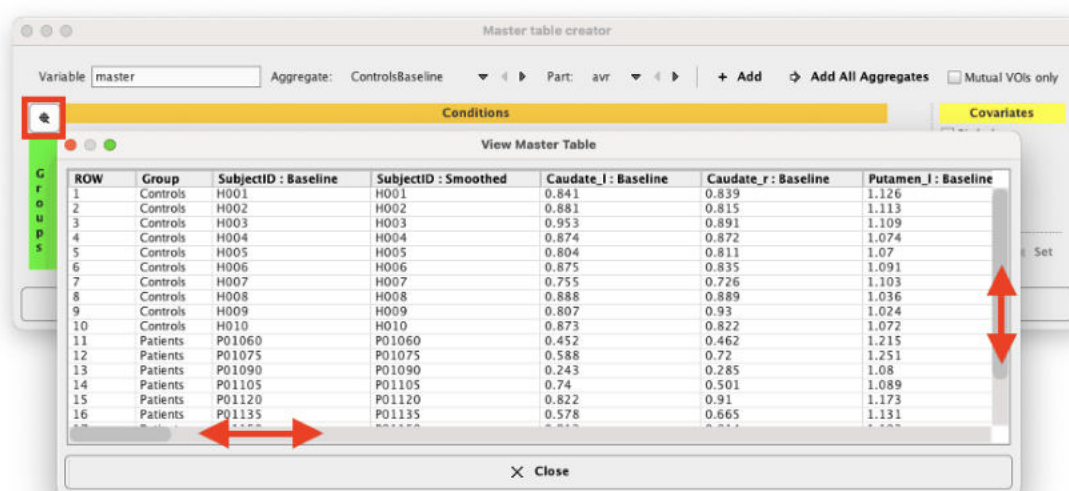
Use the bar sliders to navigate through the master table content preview. Similarly, the content of each element of the master table can be visualized.

Individuals may also be characterized by additional variables. These can be demographic variables, such as sex and age, or experimental variables, such as functional performance scores. Researchers will often be interested in the effect of these variables on regional values.

The covariates can be easily included in the master table by enabling the corresponding checkboxes in the **Covariates** section:
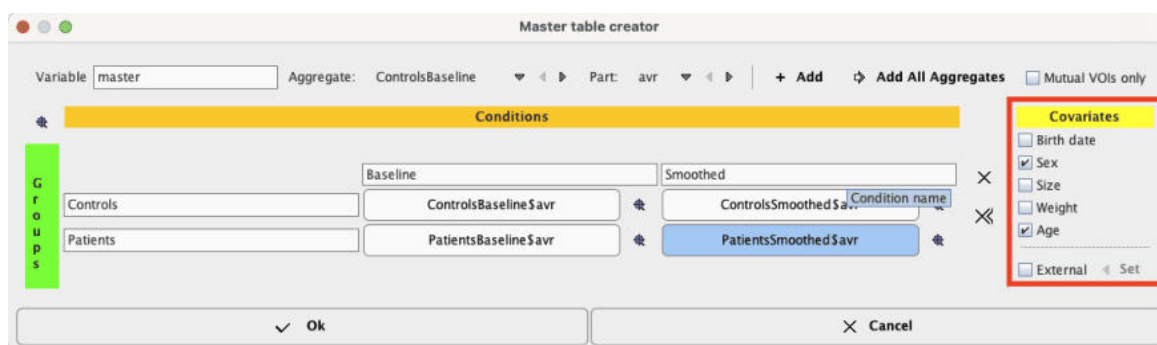
Please note that the covariates have to be available in the aggregates for each condition and group. Alternatively, they can be loaded as External files during the loading procedure of the aggregate. To transfer the external information to the master table the **External** checkbox has to be enabled and the **Set** button activated. Statistically they are treated as covariates, and they are added as extra

columns to the master table. Logically, these additional columns represent independent variables, while the columns of regional values are dependent variables.

Finally, to instantiate the master table, activate the **Ok** button. A new **Variable** MasterTable is added to the workspace. It can be visualized in the Table layout as shown below:

11.8.7.2 rm-ANOVA/MANOVA

11.8.7.2.1 Overview

Multivariate analysis of variance (MANOVA) and repeated measures analysis of variance (rm-ANOVA) are closely related generalizations of analysis of variance (ANOVA) to deal with multiple regions of interest [4]. They represent general linear models with regional values as multiple dependent parameters, which are being considered jointly within the same model.

MANOVA and rm-ANOVA minimize the residual variance that cannot be explained by the factors included in the model. They also provide an analytical separation of the various components of total variance while also considering the covariance among within-subject variables, which requires a complete and balanced data structure comprising groups of equal size. Results are presented as ANOVA tables and appropriate F-tests to determine the significance of main effects for within-subject and between-subject factors (including covariates), as well as for their interactions (see example below). MANOVA is assuming that the within-subject dependent variable vector has multivariate normal distribution within groups. Rm-ANOVA assumes homogeneous variance across all variables and groups and also of the variance of differences between groups (sphericity). It is typically more sensitive to detect within-subject differences than MANOVA, and p-values can be adjusted in case of sphericity violation by procedures according to Greenhouse-Geisser or Huynh-Feldt. Similar to univariate ANOVA, post-hoc comparisons are available for main effects with proper corrections for multiple comparisons to examine individual differences between those groups or regions that demonstrated a significant main effect or interaction.

The available correction for multiple comparison used in (M)ANOVA are:

1. Holm correction, described by Holm et al [2], is a modified version of Bonferroni correction: relaxing requirements step-wise subsequently after reaching significance for the strongest signal according to the number of remaining tests. Still, it does not take into account possible correlations among regional values. The Holm correction controls the family wise errors (FWER) without assuming independence. The benefit is that tests are made more powerful (smaller adjusted p values) while maintaining control of FWER. It is more conservative. The FWER is the probability of getting at least one wrong significance (=one false positive test) <5%

2. Alternatively, the false discovery rate (FDR) can be controlled by procedures described by Benjamini and Hochberg [3]. The FDR correction controls the "false discovery rate" (FDR) and not the FWER.

11.8.7.2.2 rm_ANOVA/MANOVA PMOD-R Implementation

As an example, we are considering data described by Volkow et al. [5]. In their study the effect of alcohol on brain uptake of 11C-acetate was examined in two groups, heavy drinkers (HD) and occasional social drinkers (OSD). PET measurements of SUV in 7 brain regions (ROIs) was performed twice in each individual, under the condition (COND) of exposure to placebo or alcohol.

Simulated data were generated based on the summary data shown in figure 4B of the paper with 15 subjects in each group. Two sources of Gaussian variance were assumed, one component (S.D. = 0.1) having the same effect on all regions of each individual, and residual variance as another component affecting all regional values independently (with same S.D.). In the paper, a strong effect of condition (higher uptake of 11C-acetate during exposure to alcohol) was described in all regions, and there was a tendency for HD to have higher brain uptake of 11C-acetate than OSD when exposed to alcohol.

To start the analysis load the example **Volkow_rmAnova.RData** workspace which is available in the **Pmod** example database. Use the **Load/Workspace Data** option from the lateral task bar. It already contains the master table which forms the basis for the analysis. To visualize the master table select the Table layout icon as shown below:
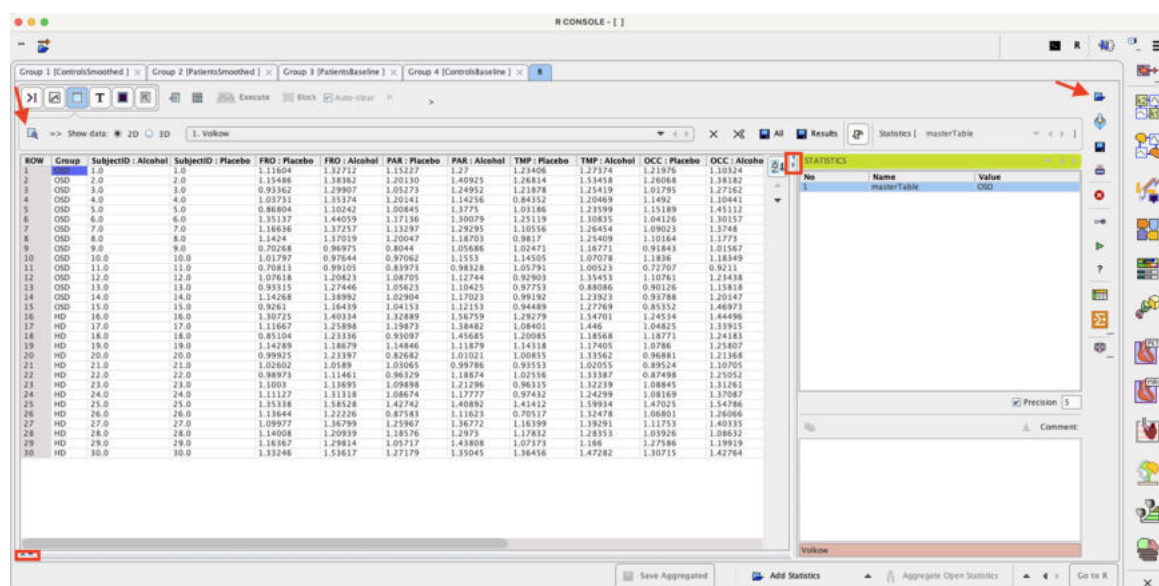
Select the **Linear models** entry in the scripts list as illustrated below:
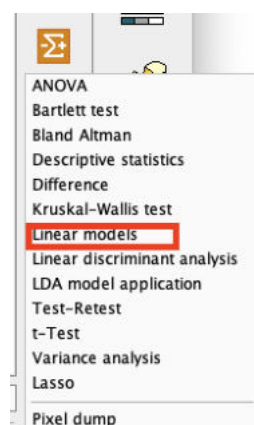
The linear model interface opens. To select the **Master table** for the analysis use the selection arrow on the top. Correspondingly, summary of the master table content is shown in the lower part. Optionally the data to be analyzed can be restricted to a subset of the original master table by unchecking some of the boxes.
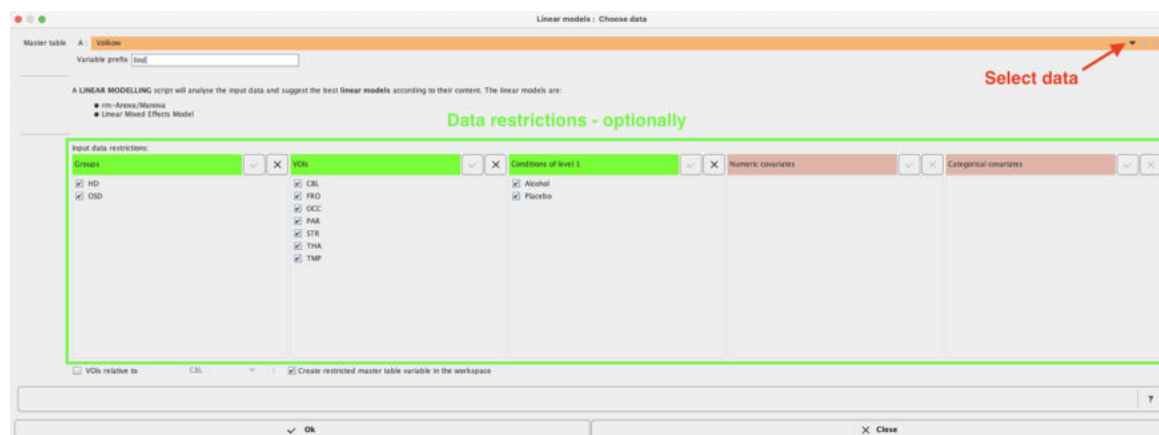
In addition, relative values can be easily obtained and used in the analysis enabling the **VOIs relative to** check box and selecting the reference region from the VOIs list:
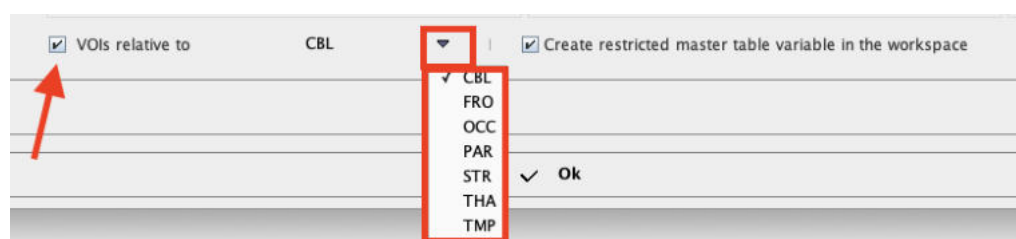
The checkbox **Create restricted master table variable in the workspace** allows saving the new content of the restricted master table in the workspace.

Confirm the setting with the **Ok** button.

The program analyses the content of the "restricted" master table and provides a summary of the analysis and the suggestion for the linear model to be applied. In case the data are balanced the rm_Anova/Manova analysis is suggested by default, but the LME analysis is still available for selection.
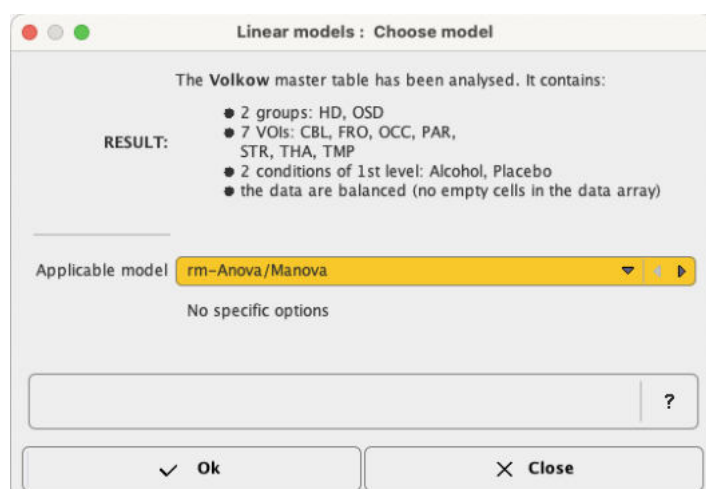
To continue the analysis activate the **Ok** button.

The statistical analysis is performed in the background and consists in two main step:

1. The (M)ANOVA procedure provides a preliminary result summarized in a table. This summary may reveal whether there is a significant main effect of covariates on the results, a possible interaction between ROIs and one of the covariates, or a main effect of one of the conditions.

2. The post-hoc comparisons are available for main effects with proper corrections for multiple comparisons. The user may define contrast to test significance for different interactions.

In the rm-Anova/MANOVA test the data columns are used as the matrix of dependent variables by the R module "lm" (R package "stats"), using a simple analysis model (columns ~ GROUP) [6]. Repeated measures ANOVA and MANOVA are then performed by the "Anova" module (package "car") using a separate model (~ ROI + COND) for the within-subject variables [7]. Interactions between the within and between-subject variables are included by default. The result is:

The intercept just indicates the trivial result that values are globally different from 0. Highly significant differences indicated by *** exist among ROIs (as to be expected), and between conditions (COND), which is an important experimental result. There is a trend only for a difference between groups (p=0.09). Interactions are generally non-significant. Thus, the effect of alcohol exposure on 11C-acetate uptake does not differ between groups (which is somewhat different from the results reported by the authors of the paper using actual rather than simulated data), and regional differences are similar in both groups.

Testing for sphericity does not reveal significant deviation, and accordingly the corrected P-values for ROI and the GROUP:ROI interaction do not result in a change of significance.

Mean values within groups and subgroups as provided by module "interactionMeans" (R package "phia") are illustrated as a plot in the capture below. The graphic has as many rows and column as factors. The off-diagonal panels show the first-order interaction means for each pair of factors. The lack of parallelism between lines reveals how one factor changes the other one. The diagonal panels represent the marginal means of each factor.
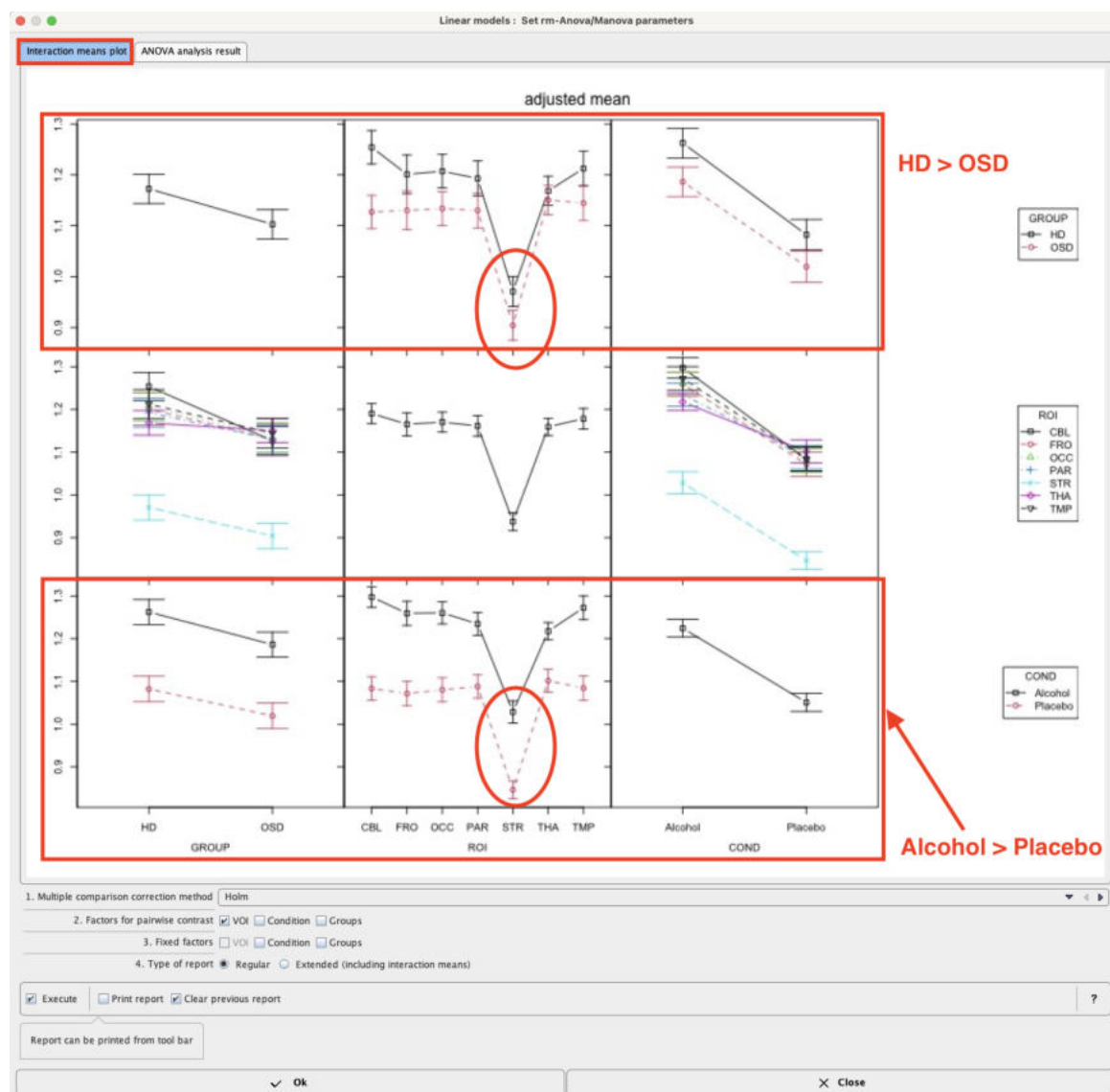
The preliminary analysis demonstrates a tendency towards higher values in group HD than OSD (top left), which is actually the case for all ROIs and conditions top row. Striatum (STR) shows much lower values than all other regions (middle panel), with minor interactions with group and condition (middle row). Values under alcohol exposure are generally higher than under placebo (bottom row).

Differences between ROIs seem obvious. A pairwise analysis of their significance is provided by the module "testInteractions" from the same R package with the "Holm" method to correct for multiple comparisons and "ROI" factor for pairwise testing, while averaging over the other factors.

Confirm the settings for the model parameter with the **Ok** button. The results are displayed in the Text layout and reveal that contrasts of all regions with striatum (**STR**) are highly significant, but none of the other regional differences reach significance.

The results can be saved as a report activating the dedicated button in the lateral taskbar.

Although none of the interactions was significant, one might be interested in which region showed the strongest trend towards a difference between subject groups. To achieve this, start the **Linear models** script again. In the **Set module parameters** step module "testInteractions" use VOIs as **Fixed factor**, and **pairwise contrast** of **Groups** as illustrated below:
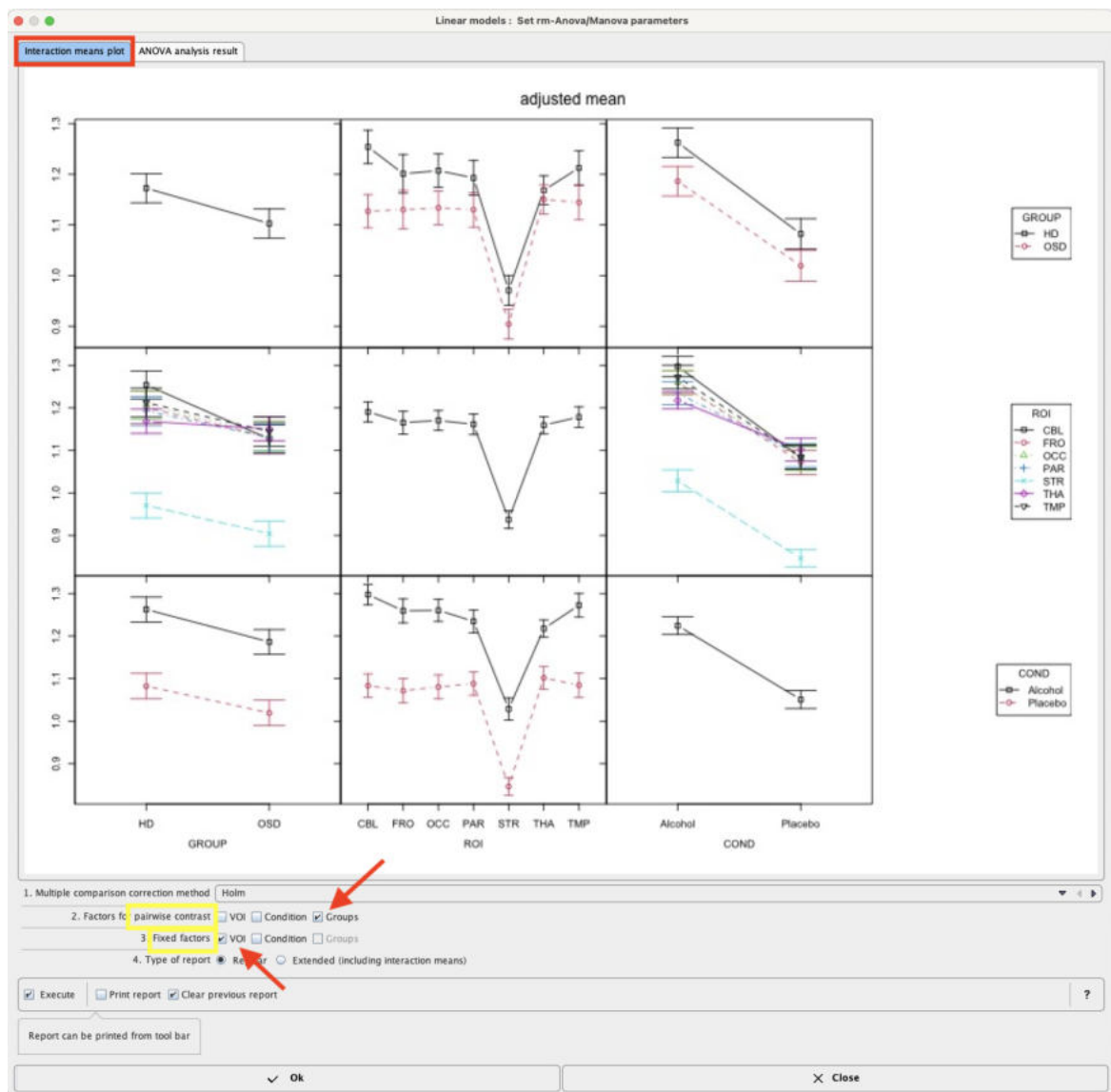
The program provides the following result:

Thus, there is a trend for cerebellum (p=0.075) while all other regions are far from significance.

Overall this example demonstrates that differences between within-subject variables can be detected with high sensitivity, while differences between subject groups are more difficult to detect. In the present example, the magnitude of mean differences between groups was about half of the difference between conditions, but there was only a trend for groups, while the effect on condition was very highly significant ($p<10^{-14}$). Basically this reflects the much higher power of repeat studies within subjects than comparisons between different groups of subjects, similar to the higher power of a paired t-test compared to a t-test for independent groups.

11.8.7.3 Linear Mixed Effect Models (LME)

11.8.7.3.1 Overview

Linear mixed effect (LME) models [8] are very similar to the (M)ANOVA models described above[397], while there are some differences in scope and performance Instead of classifying model factors as "within-subject" or "between-subject", they include a random variable to account for the variance component that is common to all regional values of the same individual. The spread of this interindividual variance is fitted iteratively together with a global mean (across all dependent variables), the mean effects of all model factors (regions, groups, etc) and specified interactions to minimize the residual error. Significance of each factor is determined by comparing the complete model with the next simpler model not including that factor. Because a random variable (with a normal distribution) accounts for most of the interindividual variance in this model, this also will absorb most of those covariate effects that affect all regions to the same degree. LME models may therefore be less suited than rm-ANOVA or MANOVA to analyze common effects of covariates, but they do not require balanced designs. In principle, they also tolerate a moderate amount of missing data. Flexible and comprehensive post-hoc tests for main effects and interactions are available.

The available correction for multiple comparison used in LME are:

1. Holm correction, described by Holm et al [2] is a modified version of Bonferroni correction: relaxing requirements step-wise subsequently after reaching significance for the strongest signal according to the number of remaining tests. Still, it does not take into account possible correlations among regional values. The Holm correction controls the family wise errors (FWER) without assuming independence. The benefit is that tests are made more powerful (smaller adjusted p values) while maintaining control of FWER. It is more conservative. The FWER is the probability of getting at least one wrong significance (=one false positive test) <5%

2. Alternatively, the false discovery rate (FDR) can be controlled by procedures described by Benjamini and Hochberg [3]. The FDR correction controls the "false discovery rate" (FDR) and not the FWER.

11.8.7.3.2 LME PMOD-R Implementation

The example is from a study by Varnas et al. [9], who actually used a LME model for the analysis of their data. A new PET ligand for 5HT1B receptors was tested once at baseline, twice under medication with zolmitriptan, and once more after 1 week free of medication. Complete data were acquired in 5 normal volunteers. Binding potentials (BP) were analyzed in two large regions of interest (VOIs), occipital cortex (OCC) and the rest of cerebral cortex (CC). A master table of BP was constructed containing the two VOIs at 4 time points (BL, T1, T2, T3) in 5 individuals.

To start the analysis load the example Varnas_LME.RData workspace which is available in the **Pmod** example database. Use the **Load/Workspace Data** option from the lateral task bar. It already contains the master table which forms the basis for the analysis. To visualize the master table select the Table layout icon as shown below:
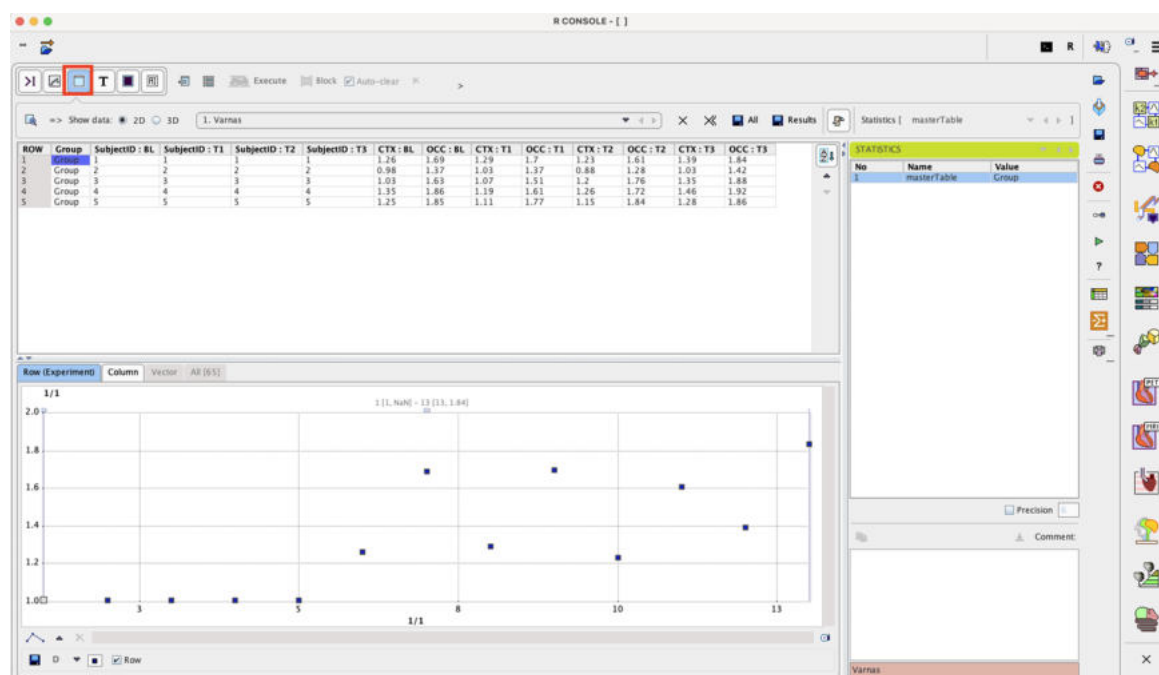
To start the analysis please select the **Linear models** entry in the scripts list:
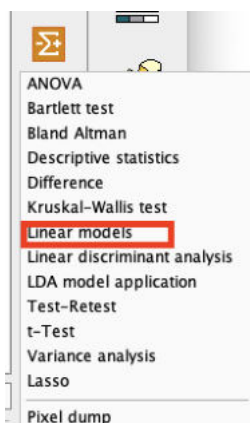
The content of the master table is summarized.
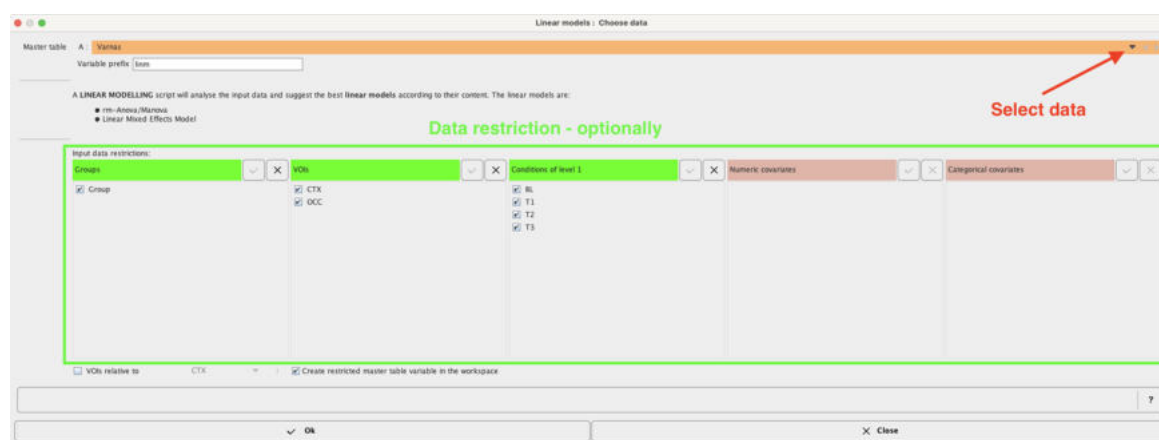
Confirm the setting with the **Ok** button. The program analyses the content of the "restricted" master table and provides a summary of the analysis and the suggestion for the linear model to be applied. When a single group is studied in different conditions only the linear mixed effects (LME) model can be used for the analysis. Therefore, the selection is blocked and set to **Linear Mixed Effects Model**:
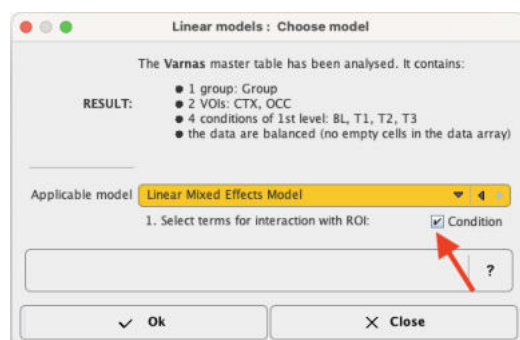
Please note that additional settings are available for the LME: the interactions. The number of available interactions depends on the number of factors and covariates in the master table. To consider an interaction enable the corresponding checkbox. In the example above the interaction ROI:Condition is enabled. Start the analysis with **Ok**.

The MANOVA preliminary results indicate that, as an expected trivial result, BP differs between the two regions. More interestingly, it is also significantly differs between conditions. There is no ROI:COND interaction – thus, both regions respond in a similar way to the conditions:
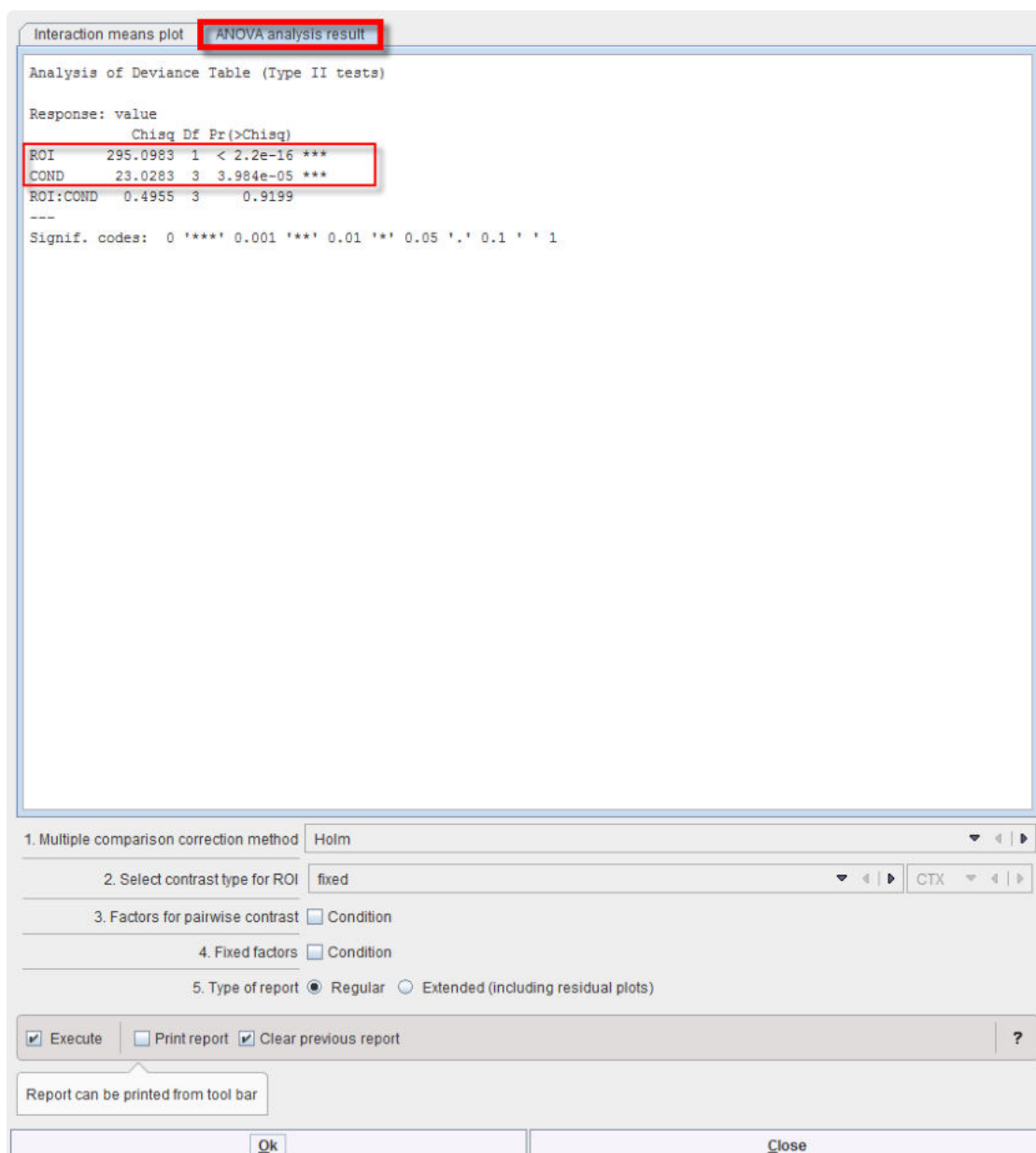
As for MANOVA, "interactionMeans" (R package "phia") provides an informative graph of the mean effects and their interactions. It demonstrates higher values for region OCC than CTX (top left), which is actually the case under all 4 conditions (bottom left). The last measurement (T3) tends to be higher than the previous ones (bottom right), and that is evident in both regions (top right):
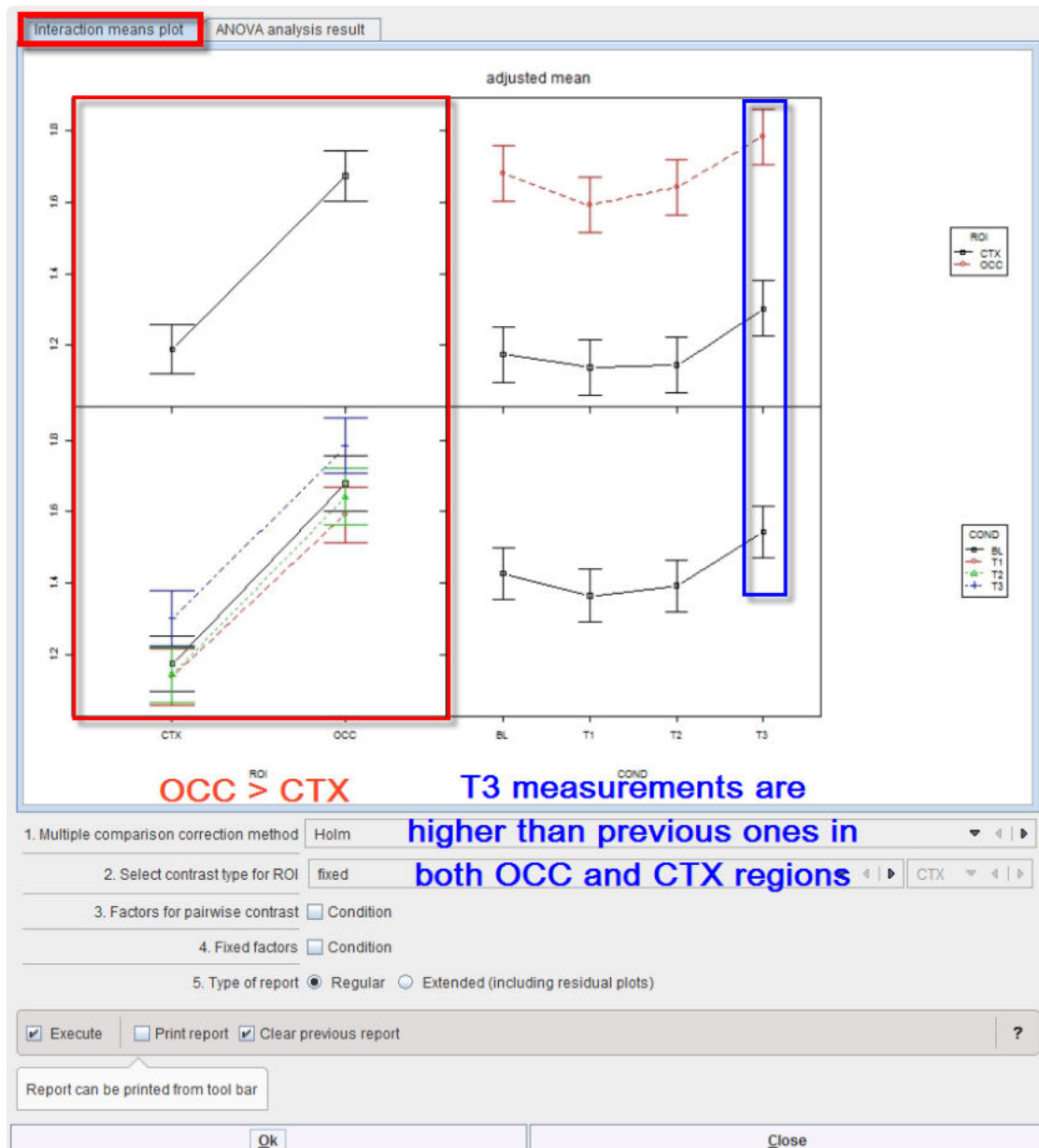
The off-diagonal panels show the first-order interaction means for each pair of factors. The lack of parallelism between lines reveals how one factor changes the other one. The diagonal panels represent the marginal means of each factor.

From this graph and the **Deviance Table** above, the difference between the two regions is clear, but we still are interested in the significance of the pairwise differences between the conditions. We therefore select the appropriate contrasts: "fixed" for ROI and "pairwise" for COND, also using the default correction "Holm" for multiple comparisons:

The result, provided by routine "testInteractions", is shown in the Text layout:

In both regions, a significant difference is present between T3 and T1, with the BP being higher 1 week after stopping the medication (T3) than after its start (T1). A similar tendency is seen for T3 versus T2, while the other differences are far from significance. In that study, this was a somewhat unexpected result suggesting receptor upregulation after medication, requiring further research.

To save the results activate the report button   in the lateral taskbar.

11.8.7.4 Discrimination Analysis

11.8.7.4.1 Overview

Linear discriminant analysis (LDA) aims at identifying combinations of parameters (typically ROIs in the context of our presentation) that provide the best discrimination between two groups of subjects, e.g. patients and controls. It is in many respects similar to the multivariate analysis of regional

differences between groups, as discussed above, but has the aim of providing a discriminant function instead of determining the significance of regional differences. That discriminant function can then be applied to future cases to determine with which group they fit best, e.g. to determine whether a data set belongs to the control or to the patient group. Various methods have been developed for LDA [10], with logistic regression probably being the most widely used and generally applicable method. The linear discriminant function is determined by maximizing the likelihood of the data fit. In R, logistic regression is implemented within the generalized linear models procedure "glm".

As with all data fitting, there is a danger of overfitting by including too many variables as predictors. A useful criteria to control for that is the Akaike Information Criterium (AIC), which penalizes the quality of fit by the number of predictors used with reference to information theory. It can be used to eliminate variables from the model that are only providing minor improvements to the fit while probably mostly fitting data noise. A stepwise elimination of predictor variables is implemented in R by the procedure "stepAIC".

Quality of discrimination can be checked by using the Receiver Operating Characteristic (ROC), which provides a graphical illustration of sensitivity and specificity as the threshold used for discrimination is varied. As a numeric parameter the area under discrimination curve (AUC) is being used, which is independent from the logistic regression model used above. AUC values range between 0.5 (no discrimination) and 1.0 (perfect discrimination). ROC is implemented in R by procedure "roc".

The discriminant analysis using logistic regression is providing discriminant functions that can be used for classification of individual test cases, with potential diagnostic applications.

11.8.7.4.2 LDA PMOD-R Implementation

The example data were downloaded from the ADNI website (http://adni.loni.usc.edu) in January 2016.

ADNI acknowledgement

Data used in preparation of this section were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at:

http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

The PET scans represented the brain activity 30-60 minutes after 18F-FDG injection and were downloaded as pre-processed data (standardized image and voxel size). Briefly, this data is already scaled to a common global averaged value, reoriented into a standard 160 x 160 x96 voxel imaged grid (voxel size, 1.5 x 1.5 x 1.5 mm) along the anterior commissure-posterior commissure (AC-PC) plane and formatted as DICOM or ECAT files.

The downloaded PET images were then processed using the PNEURO module in the PMOD software package (version 3.9; PMOD technologies). Particularly, the AAL-Atlas VOI was adjusted to the individual data with an SPM 5 equivalent normalization procedure and average regional statistics were calculated in each VOI.

The baseline FDG data in two patient groups with mild cognitive impairment (MCI) are used for the present analysis: one group of 129 subjects with stable MCI (age 74.93 ± 7.45 years), the other of 78 subjects (age 75.37 ± 6.56 years) progressing to dementia within 2 years of clinical follow-up. We are focusing on two brain areas known to be predictors of progression, the posterior cingulate (PCC) and the angular cortex (AngC). The respective variables are Cingulum_Post_l_C35 and Cingulum_Post_r_C36 (left and right PCC) and Angular_l_C65 and Angular_r_C66 (left and right AngC). Values were normalized to pons as reference region.

11.8.7.4.2.1 Identification of the LDA Function

To start the analysis load the example **Example_LDA.RData** workspace which is available in the **Pmod** example database. Use the **Load/Workspace Data** option from the lateral task bar. It already contains the master table which forms the basis for the analysis. To visualize the master table select the Table layout icon as shown below:

To start the analysis please select the **Linear discriminant analysis** entry in the scripts list:
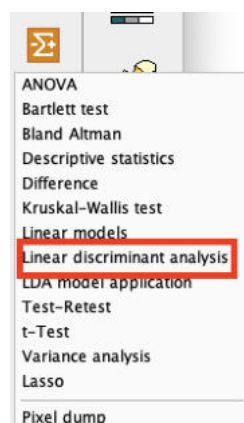
The linear discrimination interface opens. To select the **Master table** for the analysis use the selection arrow on the top. Correspondingly, summary of the master table content is shown in the **Input data restriction** section. Make sure all **Groups** and **VOIs** are selected.
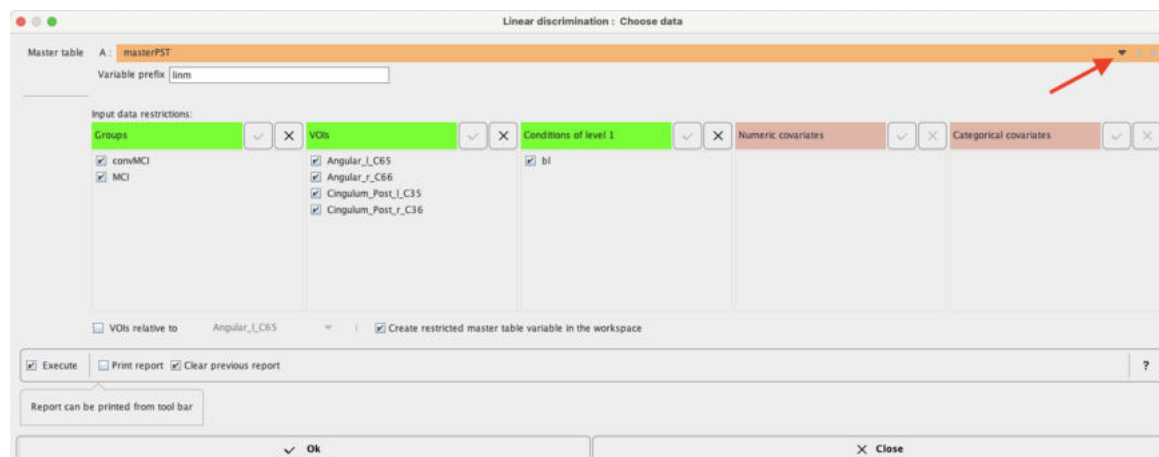
The analysis is started with the **Ok** button.

Logistic regression produces the following output accessible via the **Text** layout:

1. The **summary(lind_glmFit)**: this indicates that both, left PCC and left angular gyrus contribute significantly to discrimination (p value of 0.01393 and 0.01702 respectively). Interestingly, the right PCC is included marginally (p = 0.065) but with a negative slope estimate, indicating that it is the left/right difference that provides better discrimination than either side alone. The contribution of the right angular gyrus is considered nonsignificant.
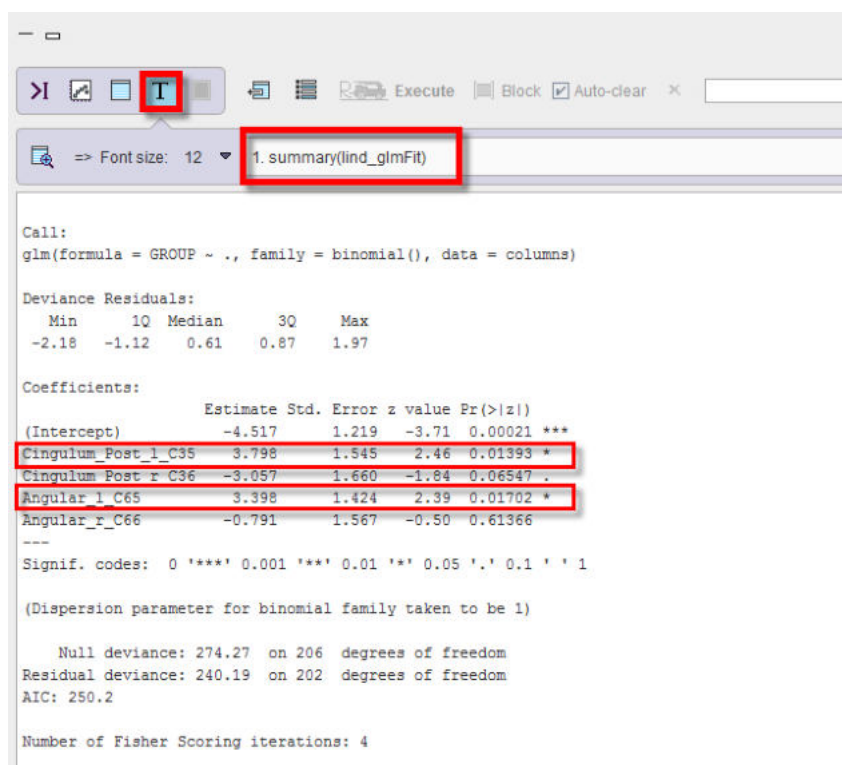
2. The **stepAIC(fit, direction="backward")** is displaying the stepwise procedure to eliminate unneeded predictors progresses. The result indicates that, only removing right angular gyrus improves AIC (smaller values are better), while removing any of the other predictors worsens the fit more (increasing deviance) than the reduction of predictors is worth.

3. The final fit **summary(lind_fitAIC_DM)** is, with all three remaining regions providing a significant contribution:

4. The **lind_fitAIC_DMCoeff** is representing the linear coefficients of the discrimination model and is also accessible in the **Table** layout. This result will be used in the prediction step

The quality of the discrimination can be checked via the **Plot** layout:
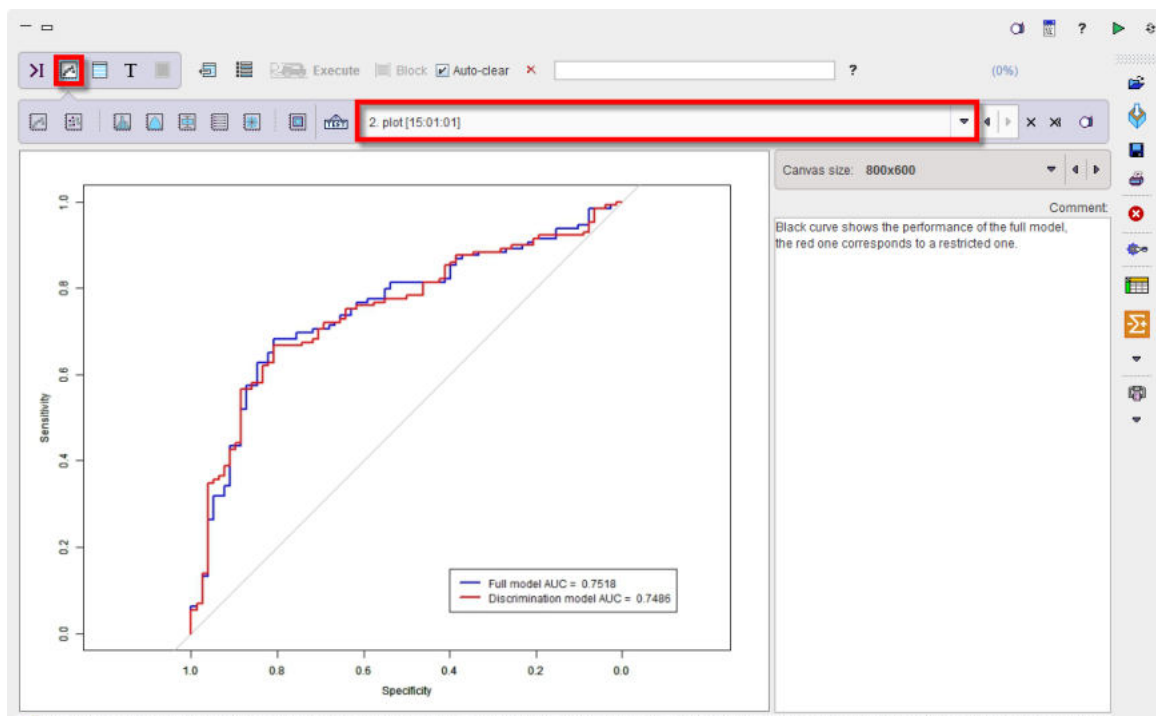
The blue line is respresenting the ROC curve of the full model based on four predictors with an area under the curve (AUC) of 0.7518. The *roc.formula* in the code is producing the following output:

Call:

roc.formula(formula = GROUP ~ fit$fitted.values, data = columns)

Data: fit$fitted.values in 78 controls (GROUP convMCI) < 129 cases (GROUP MCI).

Area under the curve: 0.7518

The red line is representing the the ROC curve of the final fit based on three predictors instead of four. As to be expected it has a minimally smaller AUC of 0.7486. The *roc.formula* in the code is producing the following output:

Call:

roc.formula(formula = GROUP ~ fitAIC$fitted.values, data = columns)

Data: fitAIC$fitted.values in 78 controls (GROUP convMCI) < 129 cases (GROUP MCI).

Area under the curve: 0.7486

The script produces a box plot 372 of the master table data selected for the LDA analysis.
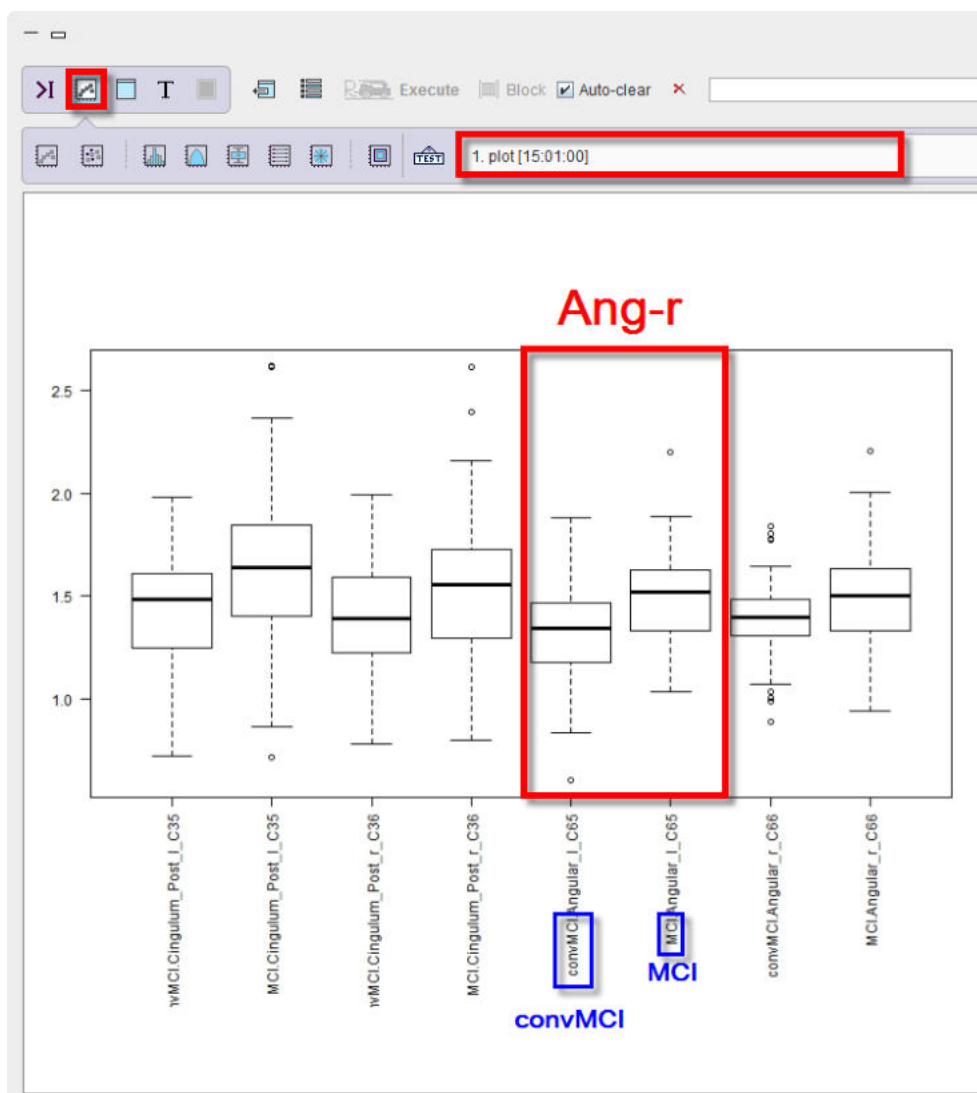
The box plot is providing a side by side comparison of the groups and VOIs.

The purpose of the linear discriminant analysis (LDA) in the example above was to find the linear combinations of the original variables (here indicating the FDG concentrations in the ROIs) that gives the best possible separation between the MCI which progress to dementia and those who remain stable. The discriminant function is representing the linear combination of the variables:

t = -4.687+3.994*leftPCC-3.386*rightPCC+2.843*leftAngC

It is recommended to save the LDA results as a workspace using the save icon in the lateral taskbar.

11.8.7.4.2.2 Prediction

The logistic regression is providing the linear fit to the log odds using the linear discriminant function, i.e. the linear combination of the predictors and the corresponding set of the regression coefficients that are specific to the model but the same for all test cases. To convert it into the probability value the following logistic function is used [11]:

$$\sigma(t) = \frac{1}{1+e^{-t}}:$$

The $\sigma(t)$ is the probability p of the test data set to belong to the stable MCI group. As only two groups are being analyzed, the probability to belong to the other group is then 1-p. The cut-off value for p is 0.5.

As an example, the linear discriminant function is applied to two individual test cases available in the **Pmod** database as a workspace: **TestCases_LDA.RData**. The AAL VOIs statistics information of the two subjects is available in the workspace as two variables: **g1** and **g2**. Use the **Load/Workspace** entry from the lateral taskbar to load the **TestCases_LDA.RData** in the Pmod-R interface.

> **Note**: The discriminat model can be applied to VOIs statistics or to aggregated files.

The prediction script requires the linear discriminant function to be available. Load in appending mode the **Function_LDA.RData** workspace available in the **Pmod** example database. This workspace contains the LDA function.
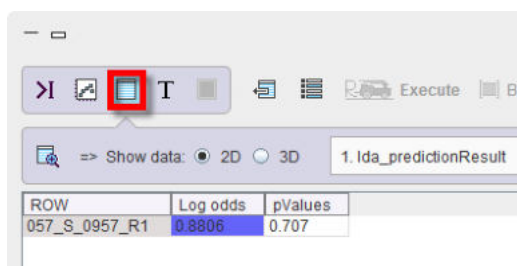
To start the analysis please select the **LDA model application** entry in the scripts list:
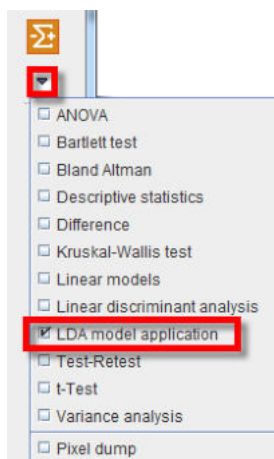
The prediction is run first for the **g1** variable in the workspace. Therefore the **g1** variable is selected in the dialog window as **Group.** The **relPons** statistics is representing the VOIs statistics relative to Pons and is set as **Part.** The **lind_fitAIC_DMCoeff** is set as the **LDA result table**.
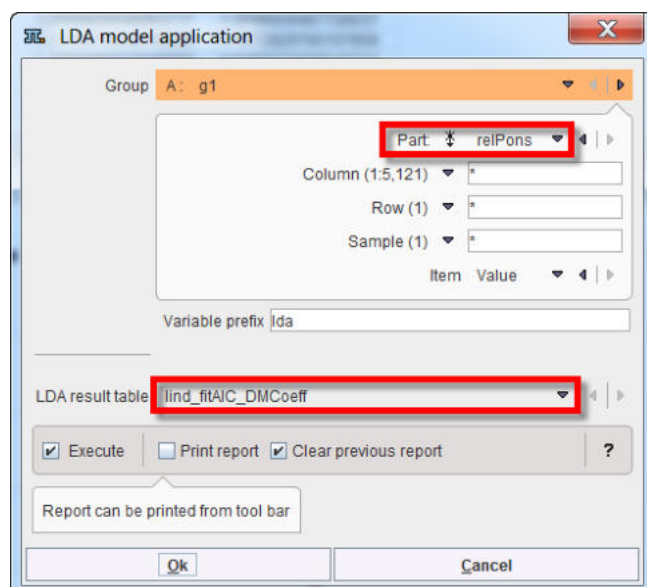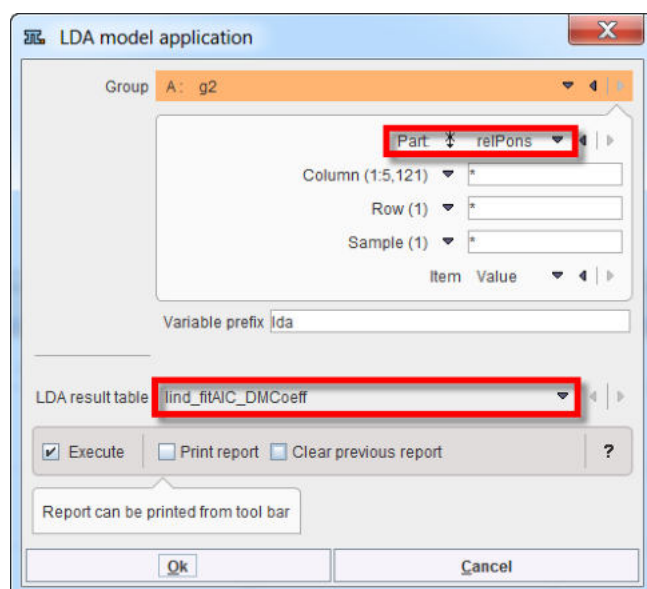
The results are accessible in the **Table** layout:

The prediction is run for the **g2** variable using the same settings in the interface:
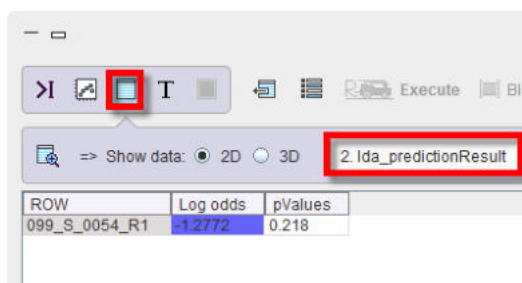
and the results are shown below:

The first column in the prediction tables are representing the subject ID while the second and the third columns are listing the log odds and the probability value respectively.

Particularly, the test case with log odds results in the positive range and a prediction value of $p > 0.5$ most likely is representing a stable MCI subject. The test case with negative log odds results and a $p < 0.5$ is indicating a MCI subject most likely belonging to the MCI group which will progress to dementia.

11.8.7.5 References

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11.8.8 Test-Retest

Once a quantitative methodology has been established, the variability of the outcome parameters needs to be assessed in order to find out, what effect sizes can be detected.

Test-Retest Variability and ICC

A test-retest study should be performed with about 10 subjects to evaluate the variability of the relevant outcome parameters. Each subject is studied twice, whereby the physiological and experimental conditions should be as similar as possible. Due to biologic variability, both acquisitions are preferably done on the same day.

The data quantification method in question is applied for all regions of interest and the results from all subjects pooled. The test-retest variability (VAR, also called within subject variability) is then calculated for each region as follows:

$$VAR = \frac{1}{N} \sum_{i=1}^{N} \frac{\left| test_i - retest_i \right|}{(test_i + retest_i)/2} \cdot 100\%$$

where N represents the number of subjects and $test_i$ and $retest_i$ the result values of the quantification method. Hence, the test-retest variability represents the average percent difference of the regional results across the subjects. As an example, the variability of the macro-parameters (Vt, BP_{ND}) in PET is typically in the range of about 5–10%. Brain perfusion is known to be subject to significant physiological variability, and therefore has 20% test-retest variability.

The same data can be used to calculate the variability across the study population. This between-subject variability for a specific region is defined as the coefficient of variation BS(%COV) of the outcome across the population, hence

$$COV = \frac{SD}{Mean} \cdot 100\%$$

where SD represents the standard deviation of the results across subjects.

Another important measure which can be calculated from test-retest data is the intraclass correlation coefficient (ICC). It estimates the reliability of the measurement per region by comparing the within-

subject (WS) variability to the between-subject (BS) variability. For the test-retest situation it can be calculated as follows:

$$ICC = \frac{BSMSS - WSMSS}{BSMSS + WSMSS}$$

whereby the MSS represents mean sum of squares and is calculated for the WS and the BS situation by

$$WSMSS = \frac{\sum_{i=1}^{N}\sum_{k=1}^{2}(m_{ik} - \overline{m_i})^2}{N}$$

$$BSMSS = \frac{\sum_{i=1}^{N} 2(\overline{m_i} - \overline{m})^2}{N-1}$$

m_{ik} represents a result of subject i (k=1 test, k=2 retest), $\overline{m_i}$ the test-retest mean of subject i, and $\overline{m}$ the overall mean across all studies and subjects.
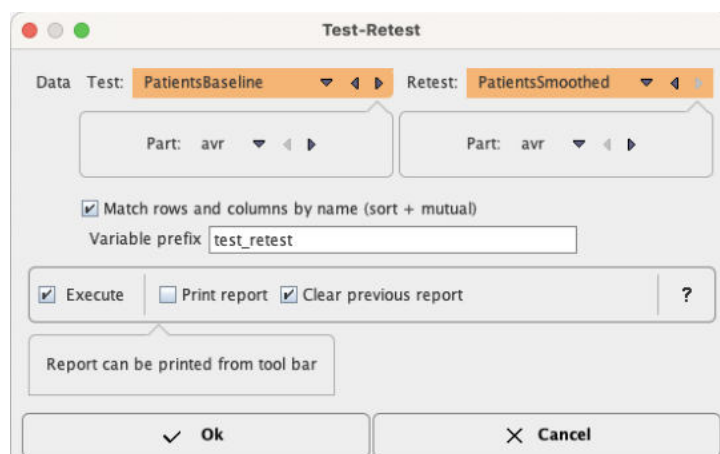
Expected ICC values range between 0 (no reliability) and 1 (maximum reliability, achieved in the case of identity between test and retest). However, in certain circumstances even negative ICC values may occur in actual data sets (indicating no reliability): particularly, in case more differences are observed within than between subjects.

ICC values reflect the relation between measurement reproducibility and the spread of target values. They are commonly considered excellent above 0.75 and acceptable when ranging between 0.5 and 0.75.

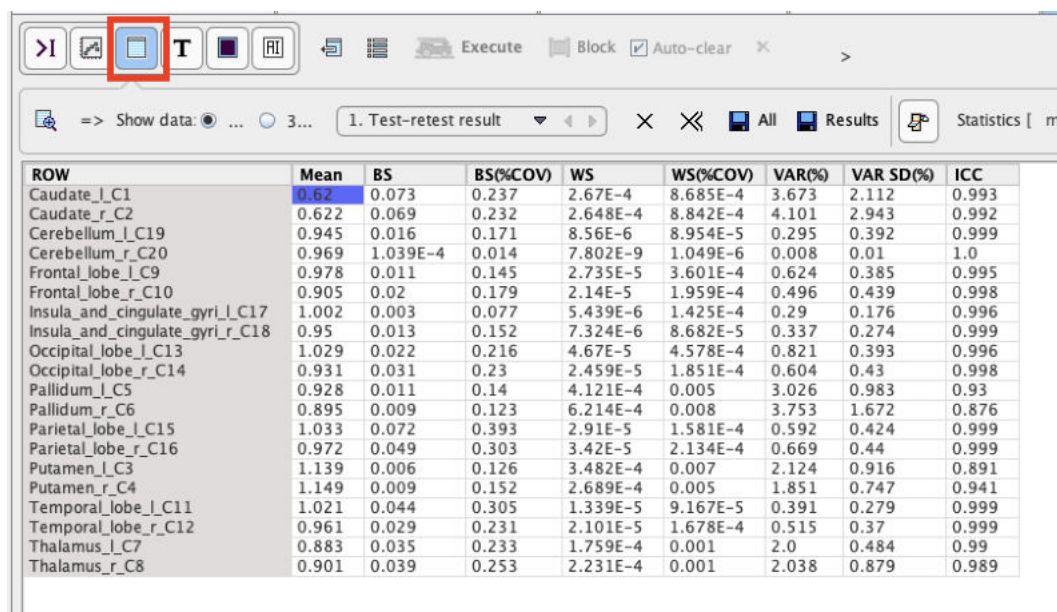See [1] for an application in PET modeling.

Test-Retest Configuration

The Test-Retest script performs the calculations described above between two variables in the workspace for all VOIs. The only choices in the user interface are the **Data** variables, and the statistics within the variables (**Part**)

Test-Retest Results

This script only provides a result table **Test_Retest_Result**

with the following results per VOI:

Mean	The mean value of the test and retest data.
BS	The between subject variability.
BS (%COV)	The between subject coefficient of variation.
WS	The within subject variability.
WS (%COV)	The within subject coefficient of variation.
VAR (%)	Test-retest variability.
VAR SD (%)	Test-retest variability standard deviation.
ICC	The intraclass correlation coefficient.

References

1. Parsey RV, Slifstein M, Hwang DR, Abi-Dargham A, Simpson N, Mawlawi O, Guo NN, Van Heertum R, Mann JJ, Laruelle M: Validation and reproducibility of measurement of 5-HT1A receptor parameters with [carbonyl-11C]WAY-100635 in humans: comparison of arterial and reference tissue input functions. J Cereb Blood Flow Metab 2000, 20(7):1111-1133. DOI

2. Weir JP: Quantifying Test-Retest reliability using the intraclass correlation coefficient and the SEM. J. Strenght Cond. Res. 2005, 19(1): 231-240

11.8.9 t-Test

The t-test is a family of statistical hypothesis tests which can be used to determine if two sets of data are significantly different from each other. An instructive summary of the background and the application of the t-test can be found on Wikipedia [1].

Depending on the application case (null hypothesis, data) a different test formula needs to be applied to the data. They all result in a t-value, which can be converted into a p-value using a table of values from Student's t-distribution.

The p-value is the probability of the obtaining at least the observed t-value, assuming that the null hypothesis is true. Therefore, if the calculated p-value is below the threshold chosen for statistical

significance (usually the 0.10, the 0.05, or 0.01 level) and therefore highly unlikely, the null hypothesis is rejected in favor of the alternative hypothesis.

t-Test Configuration

The **t-Test** script has the configuration window below.
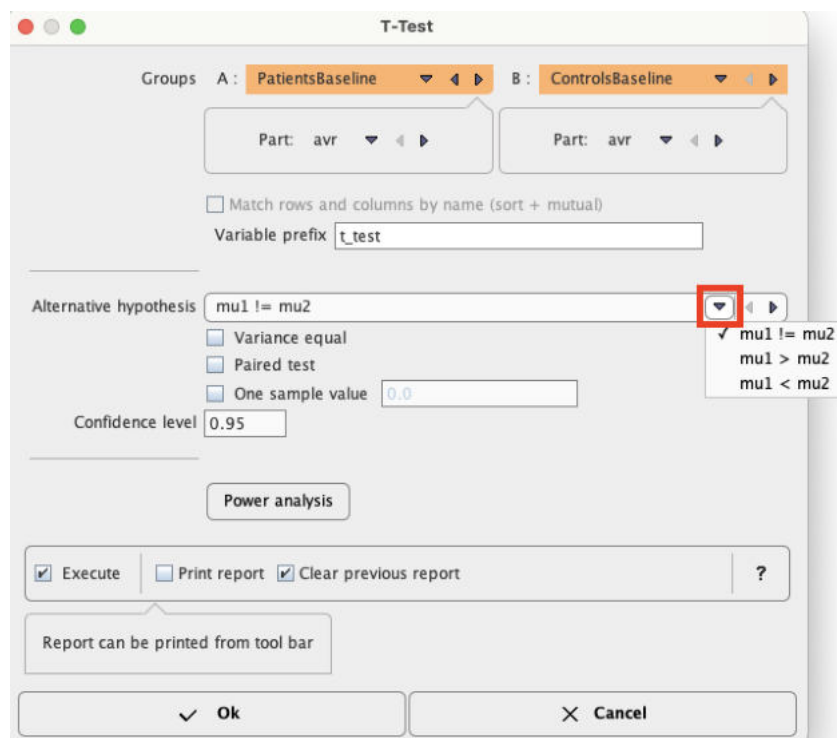
Please first define, whether a **One sample** location test against a specified population mean should be performed. In this case only one **Group** can be selected, and the hypothesis value entered. The **Alternative hypotheses** change to the choices below (unequal, larger or smaller than value).
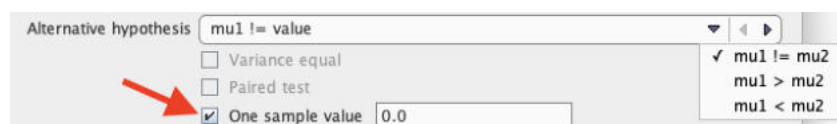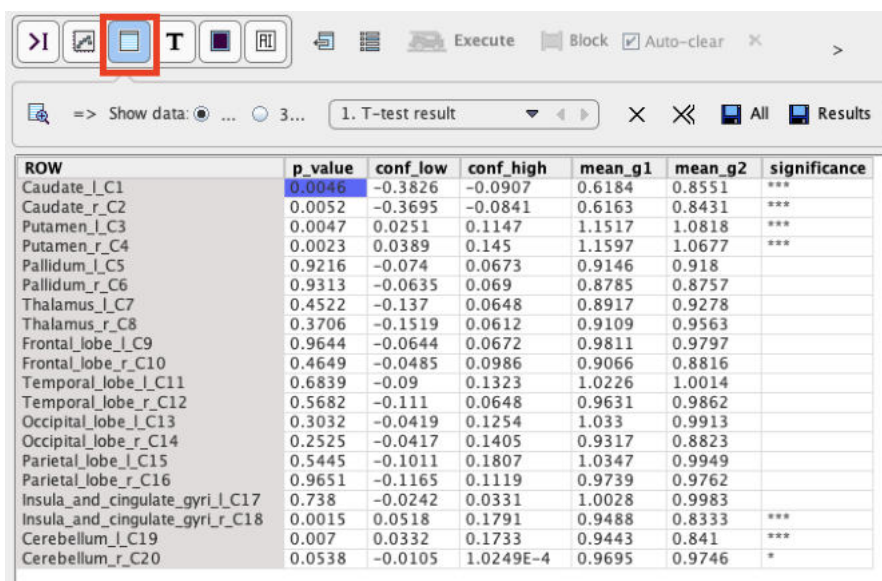
Otherwise, a two-sample t-test will be performed. The two **Groups** to be compared need to be selected, and the appropriate **Alternate hypothesis** configured:

- **mu1!=mu2**: null hypothesis of equal group means (two-sided test)

- **mu1>mu2**: null hypothesis of group2 mean is equal or larger than group 1 mean (one-sided test)

- **mu1<mu2**: null hypothesis of group1 mean is equal or larger than group 2 mean (one-sided test)

If the variance in the two samples is equal, the **Variance equal** box should be checked for using the pooled variance rather than an approximation. The **Paired test** should only be enabled if this condition is met by the two samples. In this case, the script will try to pair the group samples.

t-Test Results

The script only returns numeric results in the form of the **ttest_t_results** table. The example below illustrates the outcome with an unpaired two-sided test.

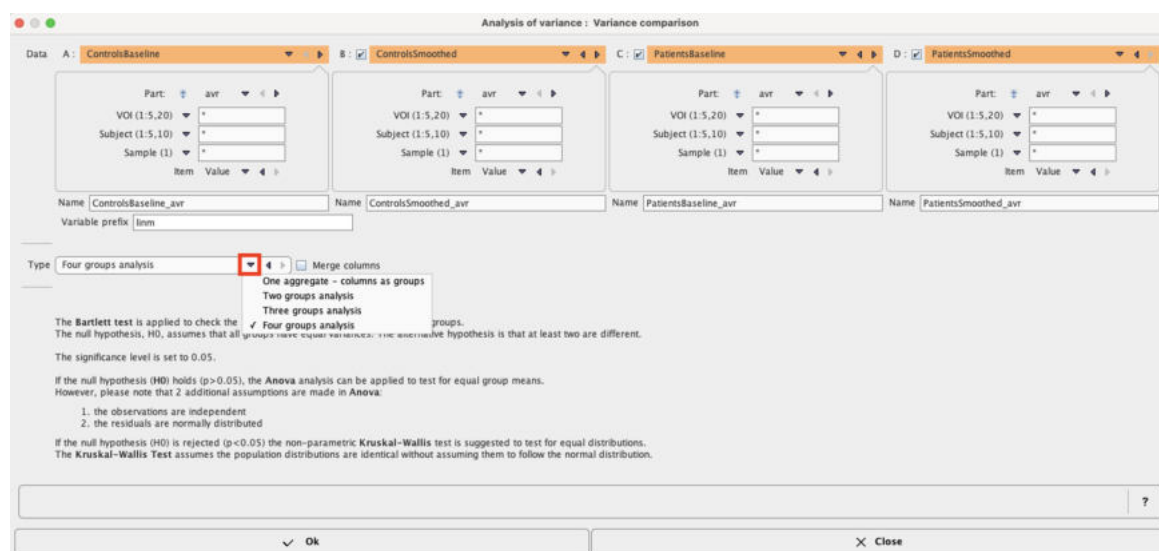| ROW	p_value	conf_low	conf_high	mean_g1	mean_g2	significance
Caudate_l_C1	0.0046	-0.3826	-0.0907	0.6184	0.8551	***
Caudate_r_C2	0.0052	-0.3695	-0.0841	0.6163	0.8431	***
Putamen_l_C3	0.0047	0.0251	0.1147	1.1517	1.0818	***
Putamen_r_C4	0.0023	0.0389	0.145	1.1597	1.0677	***
Pallidum_l_C5	0.9216	-0.074	0.0673	0.9146	0.918	
Pallidum_r_C6	0.9313	-0.0635	0.069	0.8785	0.8757	
Thalamus_l_C7	0.4522	-0.137	0.0648	0.8917	0.9278	
Thalamus_r_C8	0.3706	-0.1519	0.0612	0.9109	0.9563	
Frontal_lobe_l_C9	0.9644	-0.0644	0.0672	0.9811	0.9797	
Frontal_lobe_r_C10	0.4649	-0.0485	0.0986	0.9066	0.8816	
Temporal_lobe_l_C11	0.6839	-0.09	0.1323	1.0226	1.0014	
Temporal_lobe_r_C12	0.5682	-0.111	0.0648	0.9631	0.9862	
Occipital_lobe_l_C13	0.3032	-0.0419	0.1254	1.033	0.9913	
Occipital_lobe_r_C14	0.2525	-0.0417	0.1405	0.9317	0.8823	
Parietal_lobe_l_C15	0.5445	-0.1011	0.1807	1.0347	0.9949	
Parietal_lobe_r_C16	0.9651	-0.1165	0.1119	0.9739	0.9762	
Insula_and_cingulate_gyri_l_C17	0.738	-0.0242	0.0331	1.0028	0.9983	
Insula_and_cingulate_gyri_r_C18	0.0015	0.0518	0.1791	0.9488	0.8333	***
Cerebellum_l_C19	0.007	0.0332	0.1733	0.9443	0.841	***
Cerebellum_r_C20	0.0538	-0.0105	1.0249E-4	0.9695	0.9746	*

For each region the **p-value**, the lower and upper confidence intervals (**conf_low**, **conf_high**) as well as the two group means (**mean_g1**, **mean_g2**) are listed. In the example above, the first four regional means are significantly different, since their p-values are below 5%.

11.8.10 Variance Analysis

Variance Analysis is a convenience script for comparing three or four groups. It first applies the **Bartlett** test to establish, whether the group variances are equal. If yes, it proposes one-way ANOVA [382] for testing for significant differences between the group means. Otherwise, the non-parametric Kruskal-Wallis test [392] is proposed for testing whether the distributions are identical.

Variance Analysis Configuration

The **Variance Analysis** configuration window is illustrated below.

Up to four groups can be compared, according to the **Type** selection

If **Merge columns** is enabled, the data of all columns will be pooled, otherwise the test is performed between the respective columns of the aggregates.

With the **One aggregate - columns as groups** setting it is assumed that the groups to be compared are arranged as columns in a single aggregate.

Variance Analysis Results

As a first step, the **Bartlett Test** is applied for comparing the variances, and the result shown.
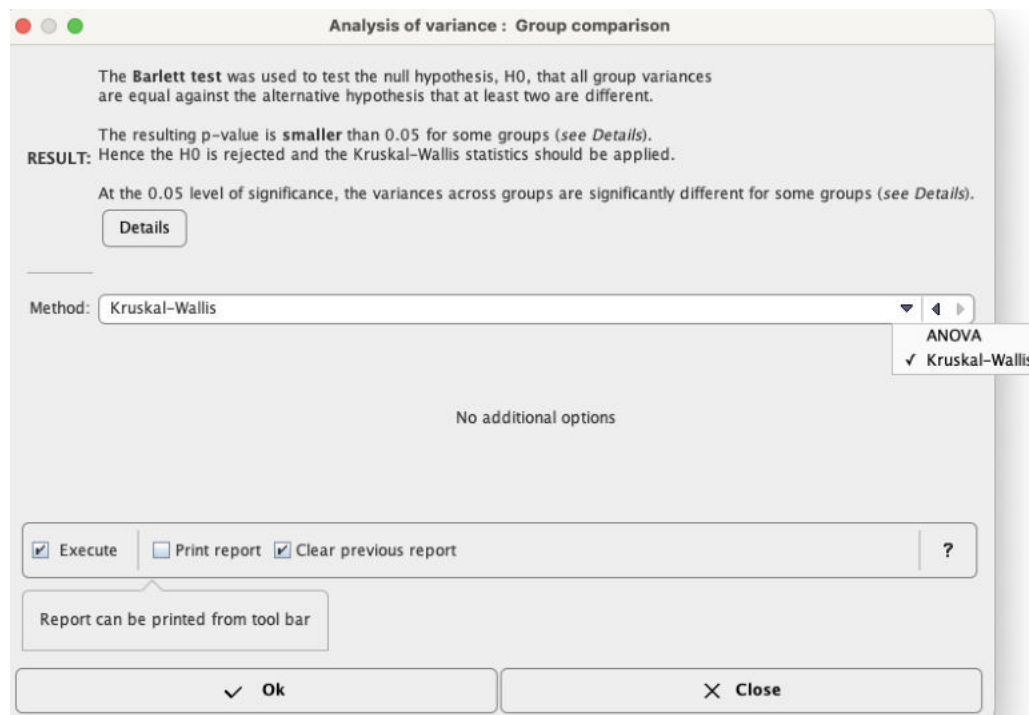
Depending on the outcome, ANOVA or Kruskal-Wallis are proposed as the follow-up test, but both are available. When applying either test as the second step, the results correspond to that of the individual test.

11.8.11 Pixel Dump

The **Pixel Dump** script serves for visualizing the distribution of pixel values in VOIs by means of histograms.

Pixel Dump Configuration

The loaded pixel dump is selected with the **Data** choice. The contents analyzed in order to list the included **VOI**s.
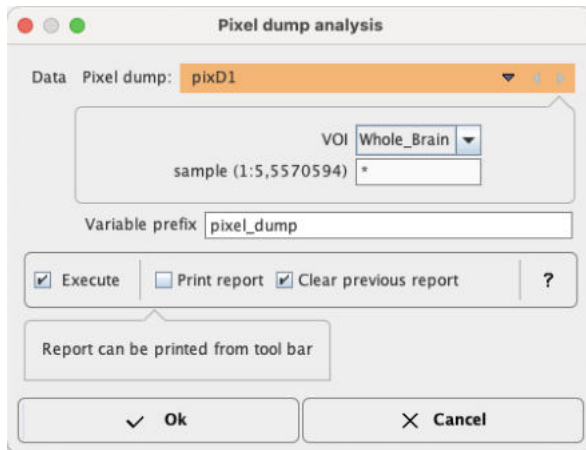
Pixel Dump Results

After selecting a VOI and running the analysis, two plots are generated: a **Histogram** as illustrated below,
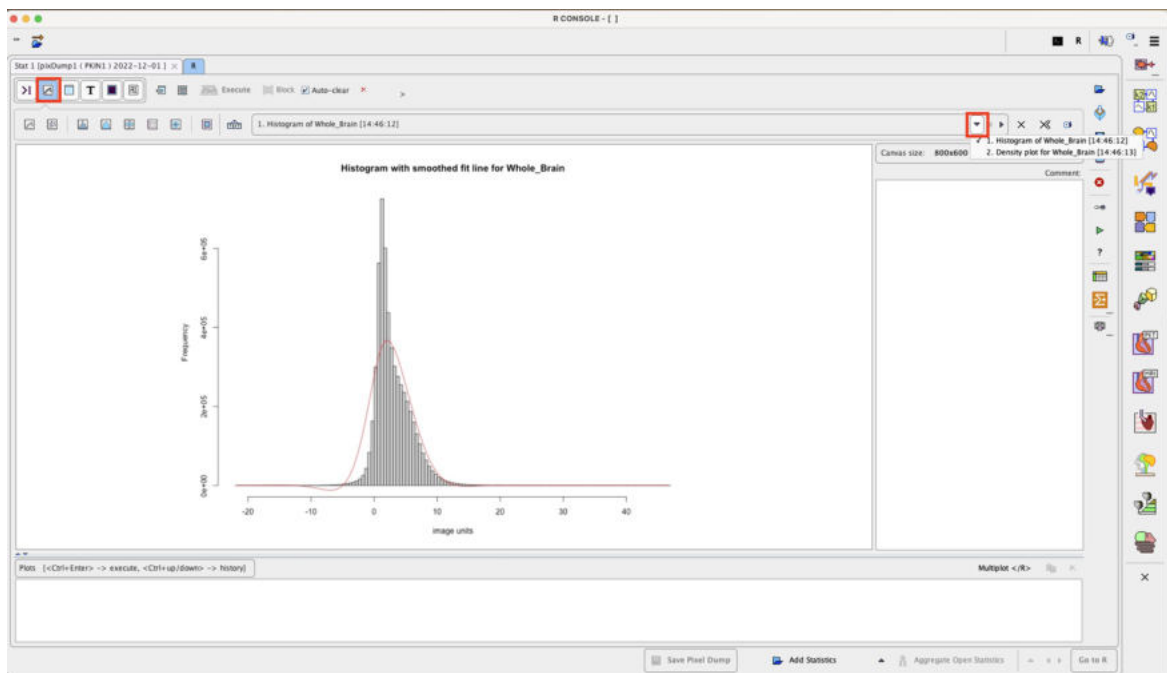
and a **Kernel Density Plot** which is often a much more effective way to view the distribution of a variable.

π.pmod

Kernel density plot Whole_Brain
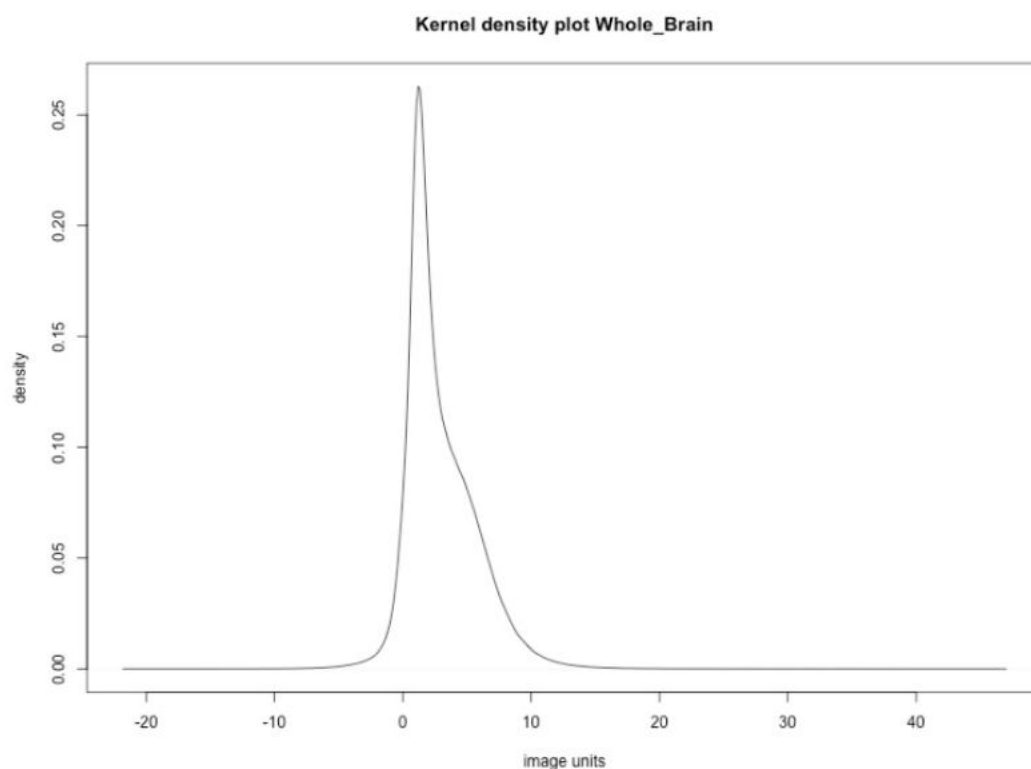
11.9   Image Layout

The image window serves for the visualization of the image data transferred to the R interface using the **R console** external tool [151].
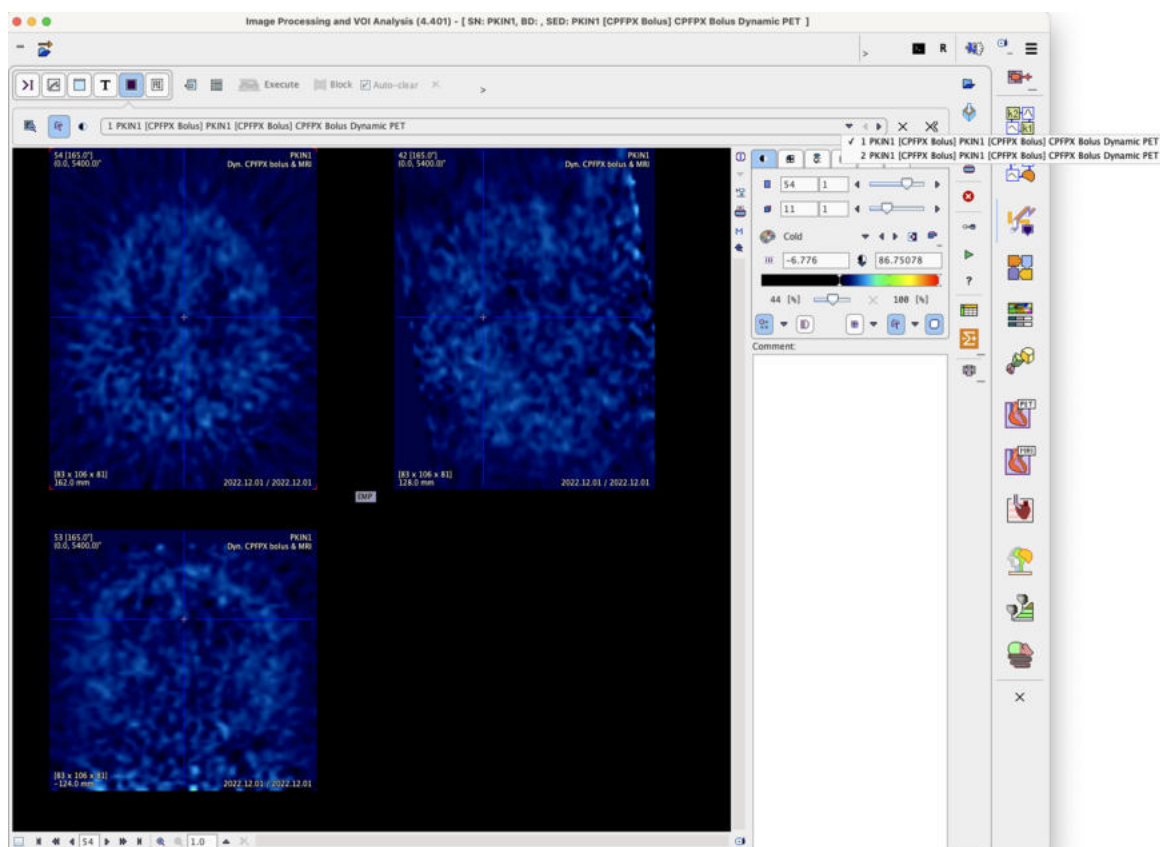
11.10 Command Layout

The command window provides a graphic user interface for developing and executing R commands and scripts. The illustration below shows the organization using the horizontal layout.
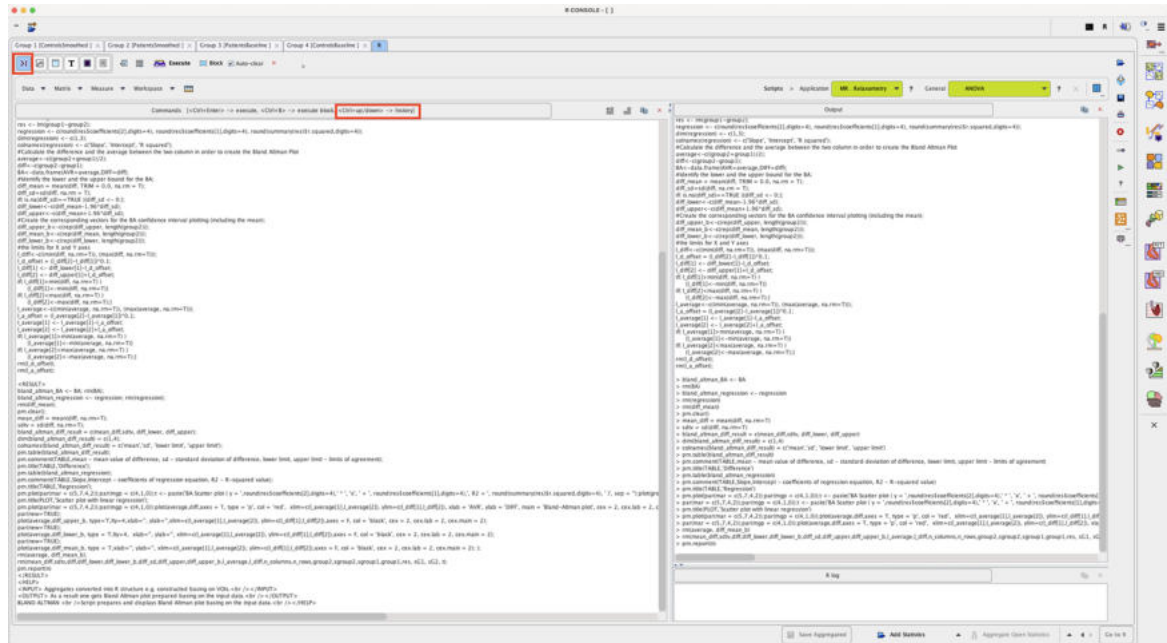
Commands Area

The **Commands** area serves the following purposes:

1. Interactive R command execution: R commands can be manually typed into the area and executed with the ![Execute] Execute button. If multiple code lines were entered, execution can be restricted to a highlighted part by the ![Block] Block button.

2. Code generated by Scripts: Whenever a script is called, its R code is copied to the **Commands** area and then executed.

3. Execution history: Whenever the **Commands** contents is executed, it is copied to a history buffer. If the **Auto-clear** box is checked, the **Command** area is cleared after command execution. However, using the keyboard keys `Ctrl+up-arrow` and `Ctrl+down-arrow`, prior execution code can be retrieved from the history for inspection/modification. For users interested in R it may be of interest to recall and review the code of in-built scripts.

Output Area

```
Connecting to the server localhost ... Connected.

Loading default settings ... Loaded.

R version 3.4.2 (2017-09-28) Windows

Loading input data 1/2 ... Loaded.

Loading input data 2/2 ... Loaded.

> summary(g1);
   Length Class      Mode
vt 16     data.frame list

> ls();
[1] "g1"            "g2"            "pm.getc"        "pm.gete"
```

```
"pm.getf"
[6]  "pm.geti"        "pm.getm"        "pm.getp"        "pm.getr"
"pm.getslc"
[11]  "pm.getv"        "pm.getx"        "pm.mutualc"     "pm.mutualr"
"pm.mutualrc"
[16]  "pm.setc"    "pm.setm"     "pm.setp"     "pm.setr"     "pm.setslc"

[21]  "pm.size"    "pm.sortc"    "pm.sortr"    "pm.sortrc"    "pm.trim"

[26]  "zz"
```
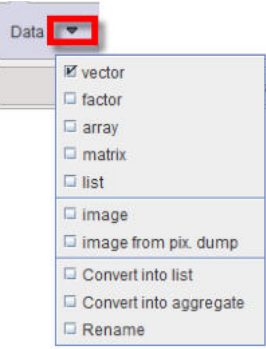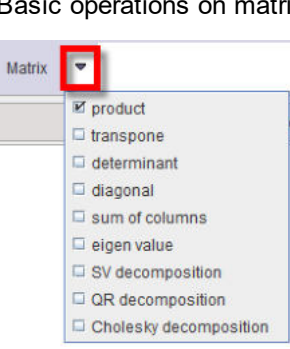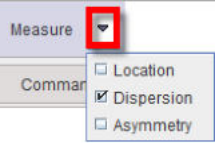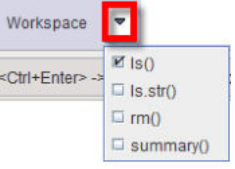
Errors Area

Please check the contents of the **Errors** area, if the behavior of the R console is unexpected.

PMOD R Commands and Code Generator

PMOD has implemented a set of commands dedicated to the PMOD **Command** console. This commands list is accessible typing the **pm.** in the **Command** console. Their description is available upon selection from the pop-up menu as shown below:

Data ▽	 Allows: • creating new data structures such as vector, array , matrix or list • creating images based on specified parameters or from pixel-dump files • converting a vector into list specifying a vector function • converting a data frame into an aggregated file • renaming a variable in teh workspace
Matrix ▽	Basic operations on matrices.
Measure ▽	Allows applying predefined statistic operations to the variables available in the workspace.
Workspace ▽	Allows performing various quick operation like listing (ls()), removing(rm()) and accessing the summary (summary()) of the variables available in the workspace. The results are displayed in the **Output** console.
▦	Allows editing a variable available in the workspace. Upon activation the list of variables available in the workspace is displayed. The data type is detected automatically. Two options are available: either **Choose variable** or **Define expression**.

π.pmod

The user can decide which **Part** of the selected variable has to be edited: **Time** or **Value**. The confirmation of the settings opens a dialog window which allows performing the editing.
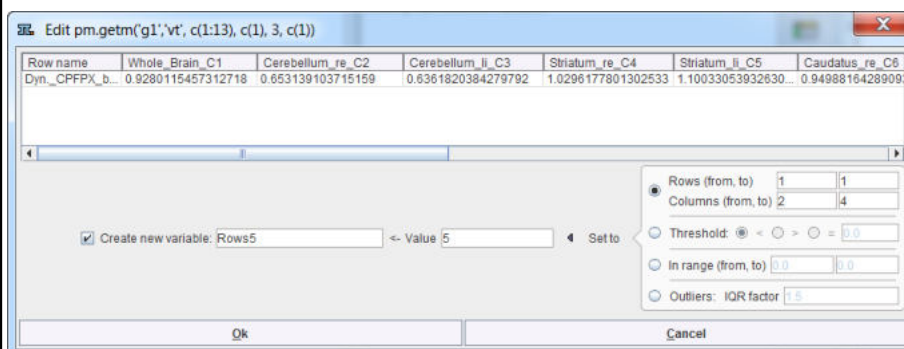
There are four ways to replace with the specified **Value** the content of the displayed table:
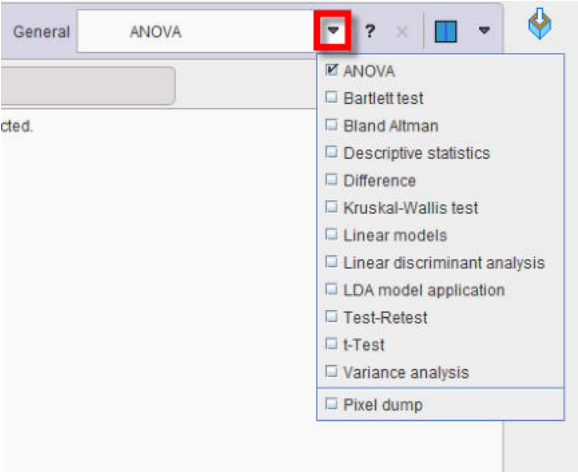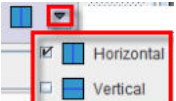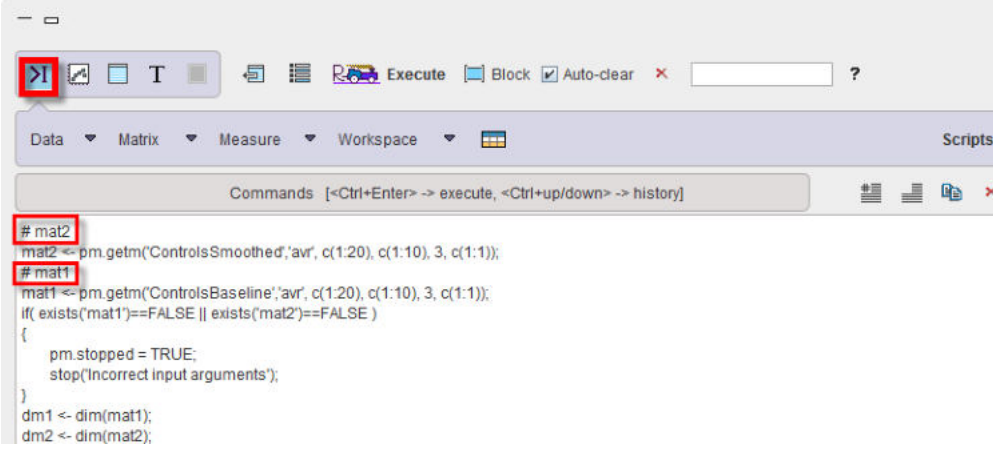
- specifying the **Rows** and **Columns** in the dedicated text fields

- using a **Threshold** definition based on one of the three criteria: **>**, **<**, **=.** All the pixels above, below or equal to the specified value will be replaced by the **Value**.

- **In range** is similar to the **Threshold** except that two limits are defined in the *from* and *to* text fields

- the **Outliers** will be considered all the observations that fall below Q1 - **factor***(**IQR**) or above Q3 + **factor***(**IQR**). The **IQR** is representing the interquartile range and is calculated as IQR=Q3-Q1. The Q1 and Q3 are respresenting the first and third quartile respectively. In a boxplot, the highest and lowest occurring value within this limit are drawn as bar of the whiskers, and the outliers as individual points.

Once the method is selected and all the parameters specified the **Set to** button allows setting the new **Value** in the table. Activate the **Create new variable** checkbox and specify a name in order to avoid overwritting the original variable. Close the dialog window with the **OK** button.

| ANOVA ▼ | Allows selecting and running general predefined R scripts. Detailed information of the scripts is available in the dedicated section in this documentation.

The predefined scripts are available for selection with the small arrow closed to the button. To add a R script to the predefined list, please copy the ***.r** file in the Pmod installation folder *in C:\Pmod4.4\resources\extlibs\r* |

	  If any help section was included in the script this can be visualized activating the **?** icon close to the scripts selection list.
⊗	Allows deleting a script from the scripts predefined list.
▯▮ ▾	Allows switching between the two layout options: horizontal and vertical.
▤	Allows commenting the command lines. First, the lines have to be selected and the icon activated.
▤	Allows uncommenting the selected command lines in the command console. First, the lines have to be selected and the icon activated.
📋	In the **Commands** console: allows copying commands console to the clipboard. In the **Output** console: allows copying output content to clipboard. In the **Errors** console: allows copying the errors messages to the clipboard.
✕	In the **Commands** console: allows deleting the content of the command console. In the **Output** console: allows clearing the output content . In the **Errors** console: allows deleting the errors messages.

11.11 User Programming and Scripts

11.11.1 Package Manager

The **Package Manager** displays all the **Required packages** that are available after configuration and installation of the PMOD R. All packages should have status **OK** as illustrated in the capture below:
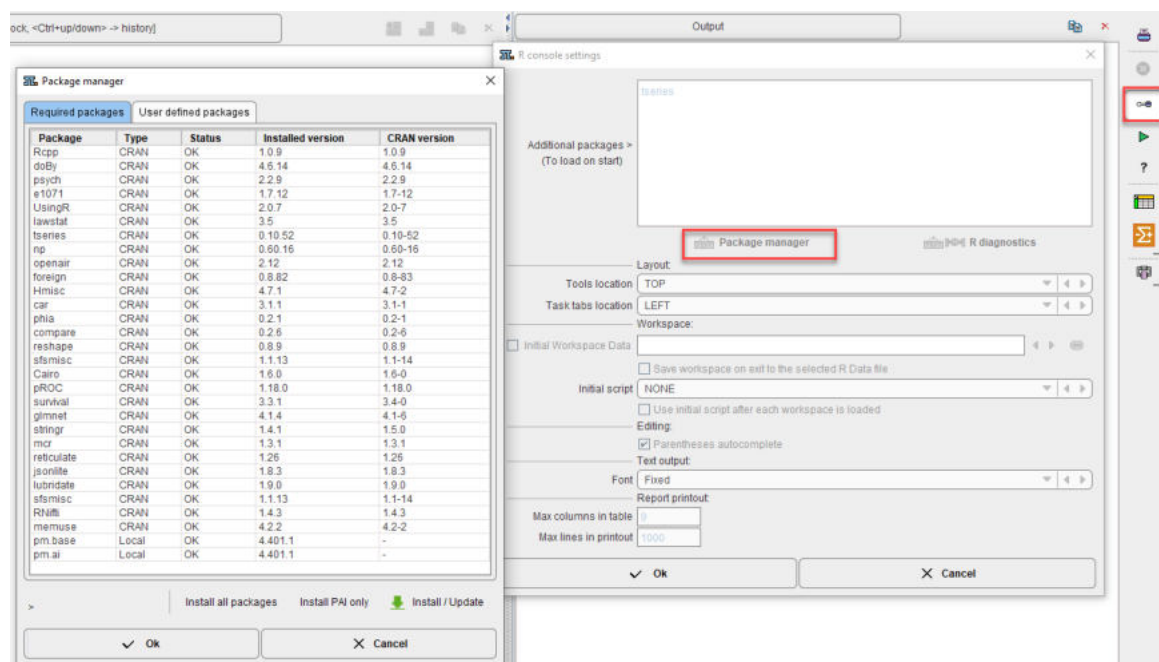
There is a huge number of public packages available covering a large spectrum of functionality. Users may want to use functions contained in such packages for their own developments. To do so, the package needs to be added to the **User define packages** list. First, type the package name in the **New package** field and activate the **+Add** button. A **Confirmation** window appears with information about the package version available, as shown below.
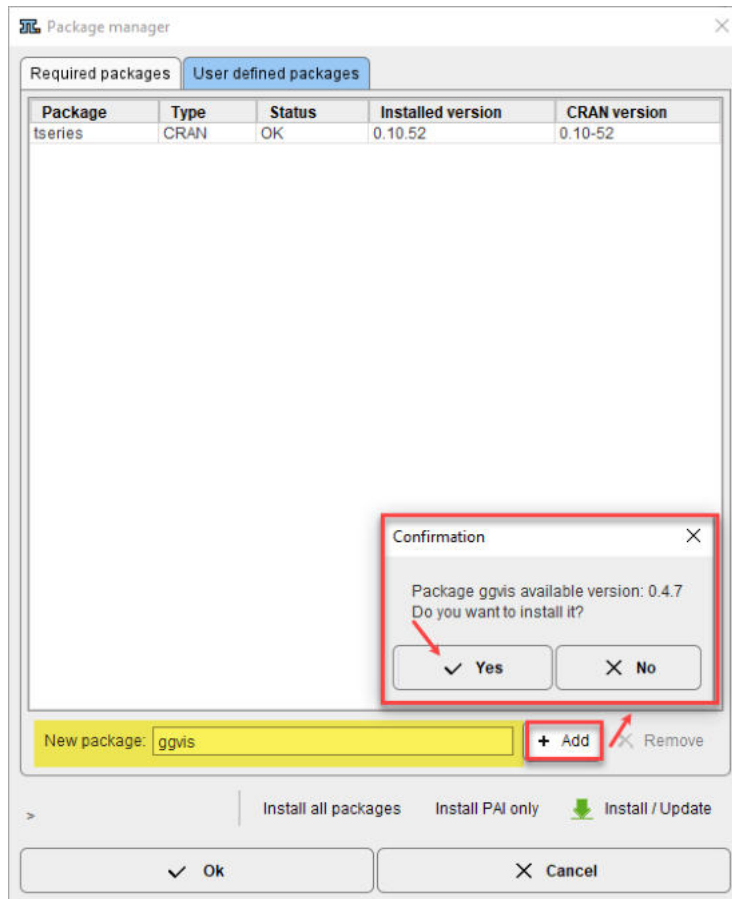
Closing with **Yes** to proceed with the installation. Once completed, the package should be loaded and become available on the **User defined packages** list:
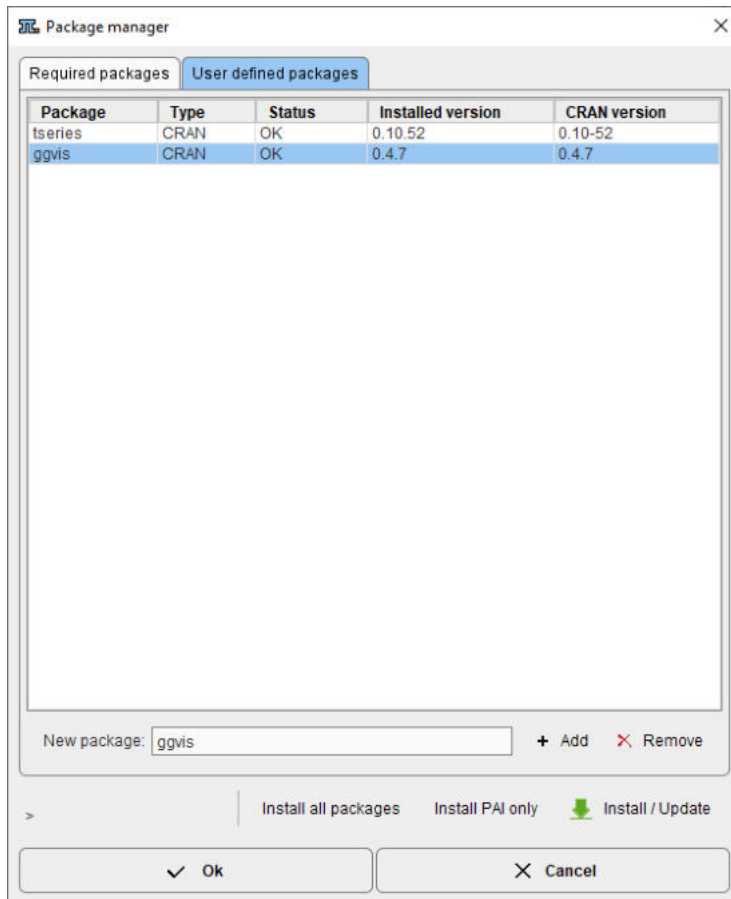
With more than one package on the list the **X Remove** button becomes active.

To update an available package, select an entry in the list and activate the **Install Update**. Finally close the **Package manager** with **OK**. The next time the local R configuration is open the **Additional packages list (to load on start)** is update according to the content of the **Users define packages** tab:
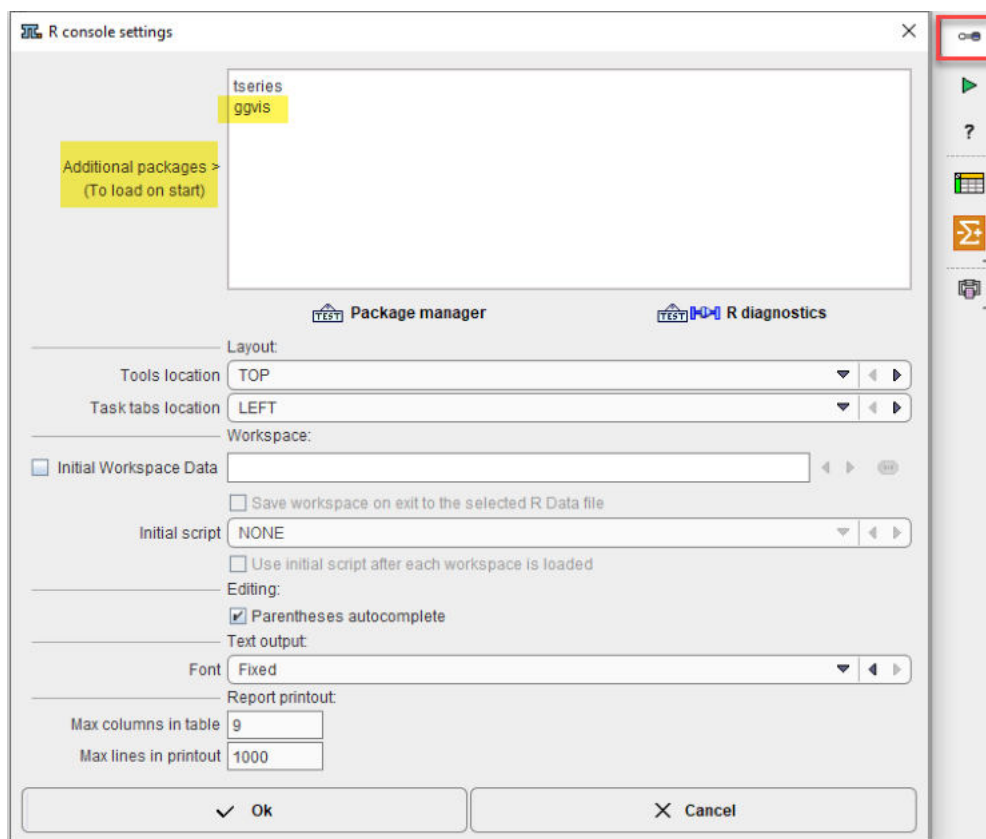
11.11.2 Accessing PMOD R Variables

The structure of PMOD R variables is described above [365]. A user may want to program scripts which address and process such variables. A list of functions can be obtained by simply typing `"pm."` into the command window. Moving the cursor over the list entries pops up a window with a syntax description and an example.
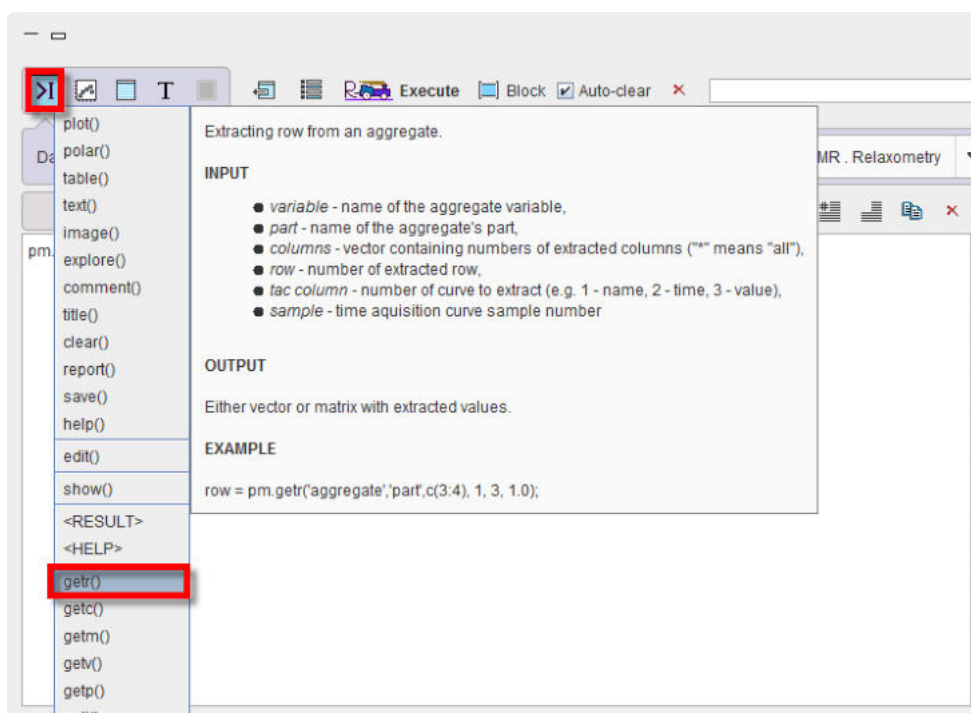
Another approach which is particularly helpful when beginning with scripts is using the extraction button
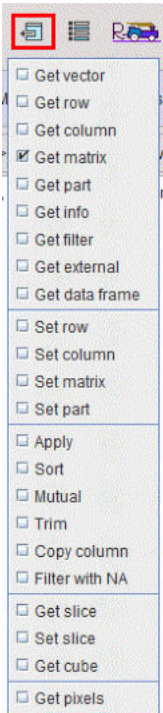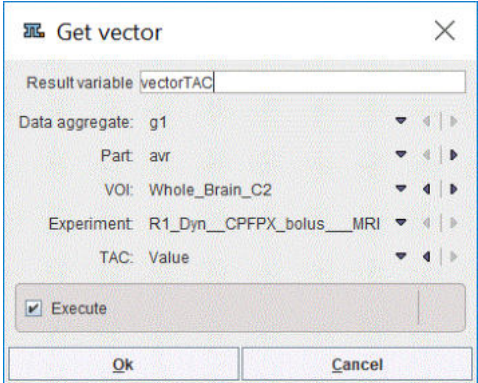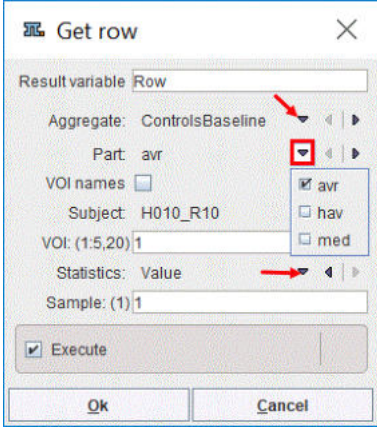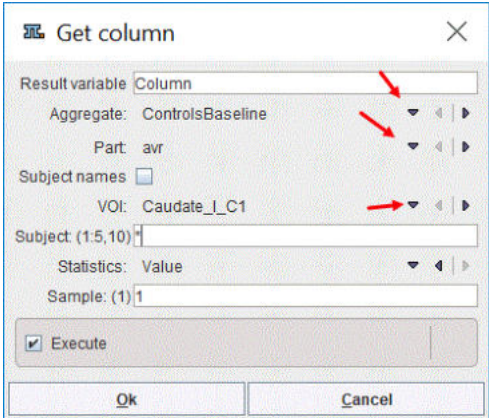
After selecting an entry, a dialog window is shown, in the case of **Get row**
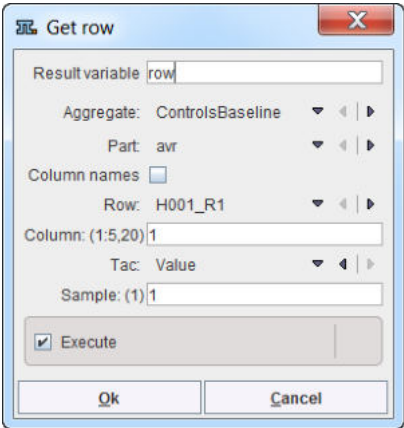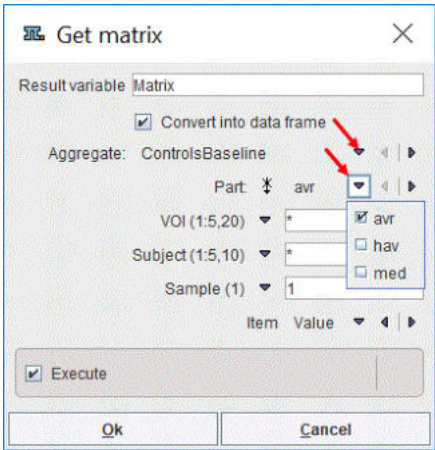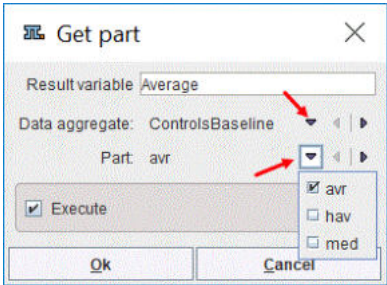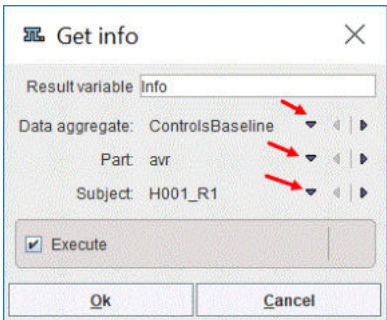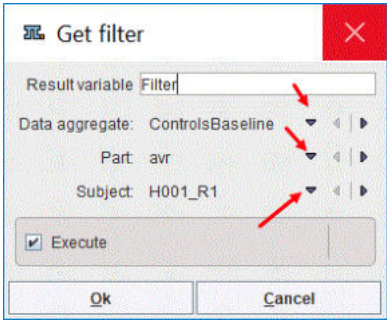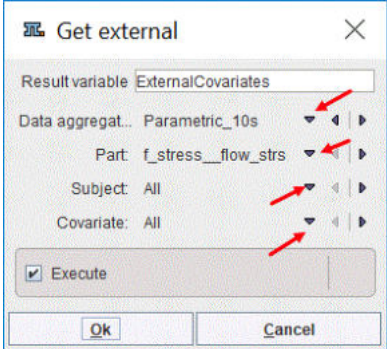
When confirming the window, corresponding R code is generated

```
experiment = pm.getr("g1", "vt",c(1:13), 1, 3, 1.0);
```

which can be seen if the **Execute** box is not enabled.
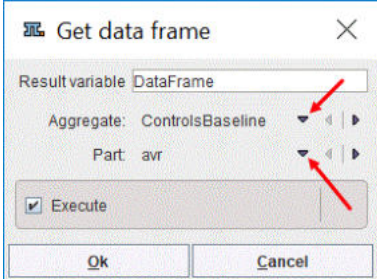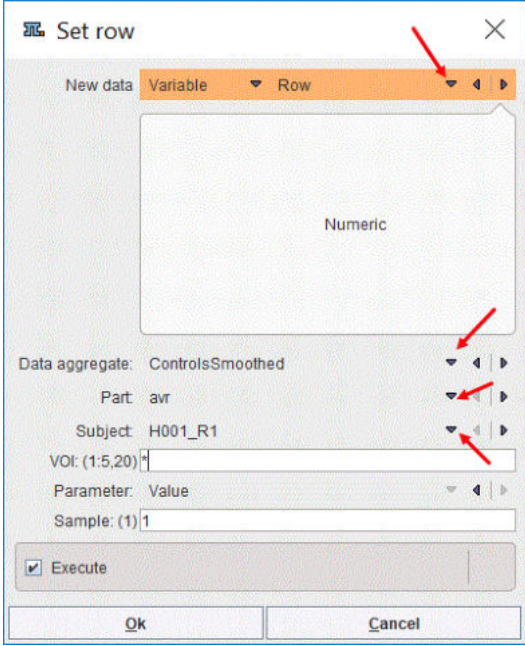
Get vector	Allows extracting a TAC vector from a data structure:
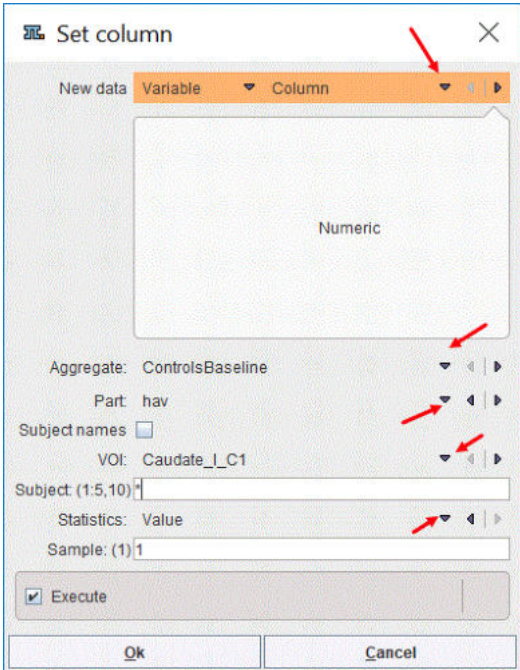
	The name of the new variable is define in the **Result variable** field.
Get row	Allows extracting a row (**Subject**) from the selected statistic **Part** of the selected **Aggregate** variable: The name of the new variable is define in the **Result variable** field. The **OK** button will execute the instruction that will appear in the **Ouput** window , for example: ``` Row = pm.getr("ControlsBaseline", "avr",c(1), 10, 3, 1.0); ``` It indicates that a new **Result variable**_Row_ was created in the workspace. With the **VOI names** box enabled the new variable will consist of the **VOI** specified column headers. The **VOI** setting may consist of: ▪ a single number, e.g. **1**, indicating which **VOI** (column) of the selected **Statistics** (**Name**, **Time** or **Value**) in the **Aggregate Part** will be stored as **Result variable**; ▪ an interval range, e.g. **1:5**, indicating which range of **VOI** (columns) of the selected **Statistics** (**Name**, **Time** or **Value**) in the **Aggregate Part** will be stored as **Result variable**; ▪ a combination of the above two separated by "**,**"; ▪ the symbol ***** indincating that all the **VOI** (columns) of the selected **Statistics** (**Name**, **Time** or **Value**) in the **Aggregate Part** will be stored as **Result variable**;
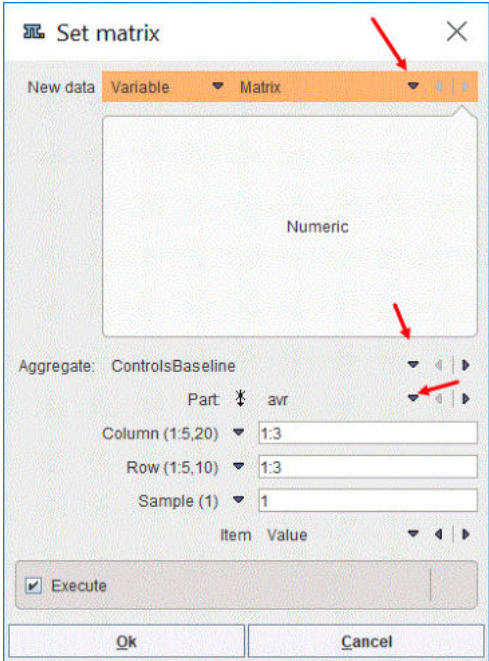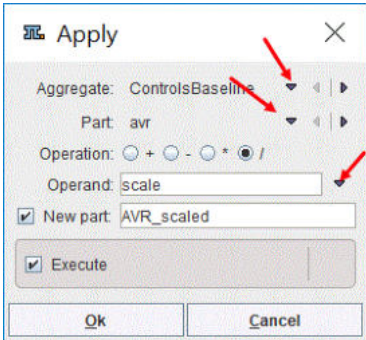
Get column	Allows extracting a column (**Subject**) from the selected statistic **Part** of the selected **Aggregate** variable: The name of the new variable is define in the **Result variable** field. The **OK** button will execute the instruction that will appear in the **Ouput** window , for example: `Column = pm.getc("ControlsBaseline", "avr", 1,c(1:10), 3, 1.0);` It indicates a new **Result variable** *Column* was created in the workspace. With the **Subject names** box enabled the new variable will consist of the specified **Subject** row names. The **Subject** setting may consist of: - a single number, e.g. **1**, indicating which **Subject** (row) of the selected **Statistics** (**Name**, **Time** or **Value**) in the **Aggregate Part** will be stored as **Result variable**; - an interval range, e.g. **1:5,** indicating which range of **Subject** (rows) of the selected **Statistics** (**Name**, **Time** or **Value**) in the **Aggregate Part** will be stored as **Result variable**; - a combination of the above two separated by "**,**"; - the symbol ***** , indincating that all the **Subjects** (rows) of the selected **Statistics** (**Name**, **Time** or **Value**) in the **Aggregate Part** will be stored as **Result variable**;
Get matrix	Allows extracting a matrix from the selected statistic **Part** of the selected **Aggregate** variable:
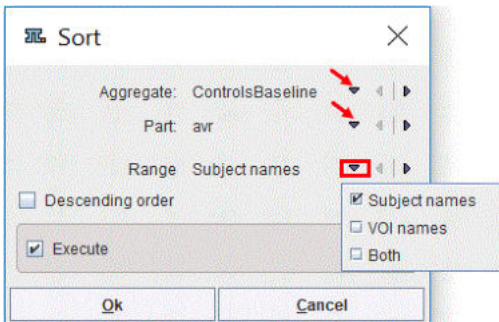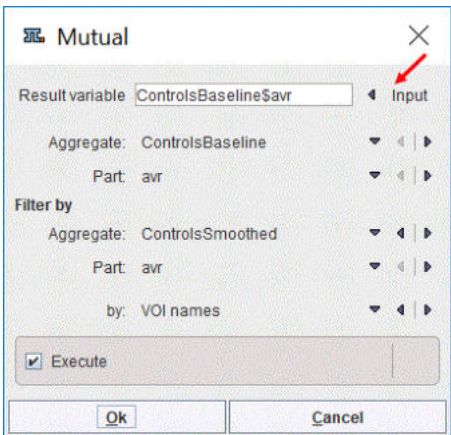
The name of the new variable is define in the **Result variable** field.

The **OK** button will execute the instruction that will appear in the **Ouput** window, for example:

```
Matrix   =   pm.getm('ControlsBaseline','avr',   c(1:20),
c(1:10), 3, c(1));
```

With the **Convert into data frame** box enabled the new variable will be converted into a data frame and an additional script line will appear:

```
Matrix= as.data.frame(Matrix, stringsAsFactors = FALSE);
```

The **Subject** and the **VOI** settings may consist of:

- a single number, e.g. **1**, indicating which **VOI** (column) and **Subject** (row) of the selected **Statistics** (**Name**, **Time** or **Value**) in the **Aggregate Part** will be stored as **Result variable**;

- an interval range, e.g. **1:5,** indicating which range of **VOI** (columns) and **Subject** (row) of the selected **Statistics** (**Name**, **Time** or **Value**) in the **Aggregate Part** will be stored as **Result variable**;

- a combination of the above two separated by "**,**";

- the symbol *****, indincating that all the **VOI** (columns) and **Subjects** (rows) of the selected **Statistics** (**Name**, **Time** or **Value**) in the **Aggregate Part** will be stored as **Result variable**;

Get part	Allows extracting the selected statistics **Part** from the **Data aggregate** available in the workspace: The name of the new variable is define in the **Result variable** field. The **OK** button will execute the instruction that will appear in the **Ouput** window, for example: `Average = pm.getp("ControlsBaseline", "avr");`
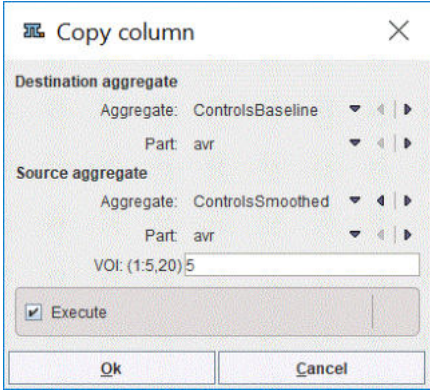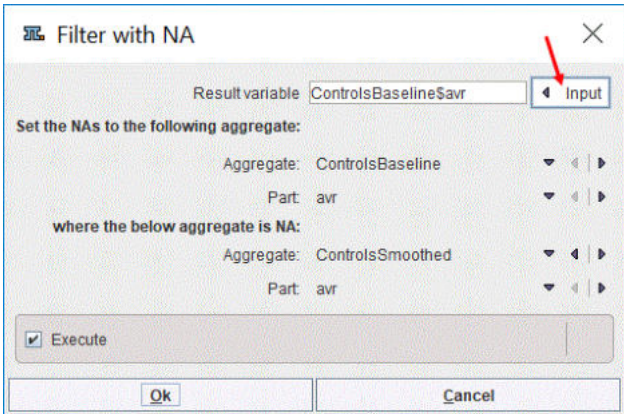
Get info	Allows extracting image information of the selected **Subject** from the selected **Data aggregate**:
	The name of the new variable is define in the **Result variable** field.
	The **OK** button will execute the instruction that will appear in the **Ouput** window, for example:
	`Info = pm.geti("ControlsBaseline", "avr",1);`
Get filter	Allows extracting filter information for the selected **Subject.** The filters generally are defined during the aggregation process of the selected **Data aggregate**:
	The name of the new variable is define in the **Result variable** field.
	The **OK** button will execute the instruction that will appear in the **Ouput** window, for example:
	`Filter = pm.gete("ControlsBaseline", "avr",1);`
Get external	Allows extracting external covariates, when available:
	This information can be extracted for a single subject or for **All** the subjects available in the selected **Data aggregate** variable.
	The name of the new variable is define in the **Result variable** field.

	The **OK** button will execute the instruction that will appear in the **Ouput** window, for example: `ExternalCovariates = pm.getAllX("Parametric_10s", "f_stress__flow_strs");`
Get data frame	Allows extracting a **Part** of the selected **Aggregate** as a data frame: The name of the new variable is define in the **Result variable** field. The **OK** button will execute the instruction that will appear in the **Ouput** window, for example: `DataFrame = pm.getf("ControlsBaseline", "avr");`
Set row	Allows setting new value(s) for the selected **VOI** and **Subject** in the selected **Part** of the active **Data aggregate**: The **New data** may be a **Variable** available in the workspace or an **Expression**. The **OK** button will execute the instruction that will appear in the **Ouput** window, for example: `ControlsSmoothed = pm.setr("ControlsSmoothed", "avr", "Row",c(1:20), 1, 3, 1.0);` The **VOI** setting may consist of:

<table>
<tr>
<td></td>
<td>

- a single number, e.g. **1**, indicating which **VOI** (column) of the selected **Parameter** (**Name**, **Time** or **Value**) in the **AggregatePart** will be replaced by the **New data**.

- an interval range, e.g. **1:5,** indicating which range of **VOI** (columns) of the selected **Parameter** (**Name**, **Time** or **Value**) in the **AggregatePart** will be replaced by the **New data**.

- a combination of the above two separated by "**,**";

- the symbol ***** indincating that the full content of the selected **Parameter** (**Name**, **Time** or **Value**) in the **AggregatePart** will be replaced by the **New Data.**

</td>
</tr>
<tr>
<td>

Set column

</td>
<td>

It is similar to **Set Row** function and allows setting new values for the selected **VOI** and **Subject**:

The **New data** may be a **Variable** available in the workspace or an **Expression**.

The **OK** button will execute the instruction that will appear in the **Ouput** window, for example:

```
ControlsBaseline = pm.setc("ControlsBaseline", "hav",
"Column", 1,c(1:10), 3, 1.0);
```

The **Subject** setting may consist of:

- a single number, eg **1**, indicating which **Subject** (row) of the selected **Statistics** (**Name**, **Time** or **Value**) in the **AggregatePart** will be replaced by the **New data**.

- an interval range, eg **1:5,** indicating which range of **Subject** (rows) of the selected **Statistics** (**Name**, **Time** or **Value**) in the **Aggregate Part** will be raplaced by the **New data**;

- a combination of the above two separated by "**,**";

- the symbol *****, indincating that the full content of the selected **Statistics** (**Name**, **Time** or **Value**) in the **AggregatePart** will be replaced by the **New Data.**

</td>
</tr>
</table>

Set matrix	Allows setting new value(s) for the defined **Column** and **Row** in the selected **Part** of the active **Aggregate**:
	The **New data** may be a **Variable** available in the workspace or an **Expression**.
	The **OK** button will execute the instruction that will appear in the **Ouput** window, for example:
	`ControlsBaseline  <-  pm.setm('ControlsBasline','avr', Matrix, c(1:3), c(1:3), 3, c(1));`
	The **Column** and **Row** settings may consist of:
	▪ a single number, eg **1**, indicating which **Column** and **Row** of the selected **Item** (**Name**, **Time** or **Value**) in the **AggregatePart** will be replaced by the **New data**.
	▪ an interval range, eg **1:5,** indicating which range of **Column** and **Row** of the selected **Item** (**Name**, **Time** or **Value**) in the **AggregatePart** will be replaced by the **New Data**.
	▪ a combination of the above two separated by "**,**";
	▪ the symbol *****, indincating that the full content of the selected **Item** (**Name**, **Time** or **Value**) in the **AggregatePart** will be replaced by the **New Data**.
Apply	Allows applying a mathematical **Operation** to the selected **AgregatePart**:

	The **Operation** is defined by the selection of one of the *Plus*, *Minus*, *Multiplied by*, *Divided by* radio buttons. The **Operand** should be a scalar variable already available in the workspace. With the **New part** box enabled, a statistic part with the specified name, e.g. *AVR_scaled*, will be appended to the selected **Aggregate** file. Otherwise the curretly selected **Part** will be overwritten. The **OK** button will execute the instruction that will appear in the **Ouput** window, for example: `ControlsBaseline = pm.aggApply('ControlsBaseline', 'avr', scale, operation = '/', newPart = 'AVR_scaled');`
Sort	Allows sorting the **Aggregate Part** based on the selected **Range** criteria: With the **Descending order** box enabled the sorting is performed accordingly. The **OK** button will execute the instruction that will appear in the **Ouput** window, for example: `ControlsBaseline$avr = pm.sortc('ControlsBaseline', 'avr', desc=TRUE);`
Mutual	Allows filtering the content of the first **Aggregate Part** based on the selected **by** criteria set for the **Filtered by** aggregate: The **Input** button allows assigning the result to the input aggregate part. Otherwise, a new variable will be created in the workspace with the name specified in the **Result variable** field. The **OK** button will execute the instruction that will appear in the **Ouput** window, for example:

| | ```
ControlsBaseline$avr   =   pm.mutualc('ControlsBaseline',
'avr', 'ControlsSmoothed', 'avr');
``` |
| **Copy column** | Allows copying a column from the **Source aggregate** into the **Destination aggregate:**<br><br>**Copy column**<br>Destination aggregate<br>  Aggregate: ControlsBaseline<br>  Part: avr<br>Source aggregate<br>  Aggregate: ControlsSmoothed<br>  Part: avr<br>  VOI: (1:5,20) 5<br>☑ Execute<br>Ok     Cancel<br><br>The **OK** button will execute the instruction that will appear in the **Ouput** window, for example:<br><br>```
ControlsBaseline   =   pm.copyColumns('ControlsSmoothed',
'avr', 'ControlsBaseline', 'avr',c(5));
```<br><br>The specified **VOI**(s)will be appended at the end of the selected **Part** in the **Destination aggregate** file. |
| **Filter with NaN** | Allows identifying the location of the NaN elements in the source **Aggregate Part** (**where the below aggregtae is NA**) and setting to NaN the corresponding elements in the destination aggregate (**Set to NAs to the following aggregate**)<br><br>**Filter with NA**<br>Result variable ControlsBaseline$avr   ◀ Input<br>Set the NAs to the following aggregate:<br>  Aggregate: ControlsBaseline<br>  Part: avr<br>  where the below aggregate is NA:<br>  Aggregate: ControlsSmoothed<br>  Part: avr<br>☑ Execute<br>Ok     Cancel<br><br>The **Input** button allows assigning the result to the destination aggregate part. Please note that in this situation the original content will be overwritten. Otherwise, a new variable will be created in the workspace with the name specified in the **Result variable** field.<br><br>The **OK** button will execute the instruction that will appear in the **Ouput** window, for example:<br><br>```
ControlsBaseline$avr                            =
pm.filterWithNA('ControlsBaseline',           'avr',
'ControlsSmoothed', 'avr');
``` |

12   Partial-Volume Correction (PVC)

PET and SPECT images are inherently affected by the *partial-volume effect*. This term means that the measured tracer activity concentrations are not accurate due to the relatively low image resolution and the limited tissue sampling. Basically, the low resolution causes a blurring of the image, so that high activities (from a hot lesion) are spread to the surrounding as illustrated below. This effect is called *spill-out*. The same effect also causes a *spill-in* of background activity into the volume of interest.

As a consequence, hot lesions tend to appear less aggressive (reduced maximum) but bigger (spreading) than they are in reality.

Spill-in and spill-out depend on the geometry of the objects, the activity distribution of the tracer, and on the resolution of the scanner which may vary across the imaging field-of-view. Therefore, practical correction approaches have to assume certain conditions and can only be approximate. For a nice overview of the topic please refer to the publication of Soret et al. [1].

Solutions Implemented in PMOD

PMOD provides two PVC solutions:

1. **PVC VOI-based:** This correction is based on the assumption, that the imaging volume can be separated into tissue volumes (VOIs) with homogeneous uptake. If the resolution of the PET scanner is known, the mutual signal contaminations across the VOIs can be calculated and corrected for. This method is known as the GTM (Geometric Transfer Matrix) method and was introduced by Rousset et al. [2,3].
    The implementation in PMOD allows the user applying the GTM correction with any set of manually outlined VOIs. Additionally, for the analysis of human brain uptake, the user may take advantage of standard VOIs which are automatically adjusted to the subject's anatomy.

2. **PVC Brain MR based:** This correction is based on the assumption that white matter uptake is homogeneous. All brain pixels are classified as white matter (WM) or grey matter (GM) and sorted into respective segments. Based on these segments and the assumed PET resolution the spill-out from WM to GM can be estimated and subtracted. Similarly, the spill-out from GM to the surroundings can be estimated and compensated for. The result is a grey matter image with corrected activity values in all pixels. This method was introduced by Muller-Gartner et al. [4].
    Given a brain PET and an anatomical MRI of a subject, the implementation in PMOD allows the user performing the segmentation and apply the Muller-Gartner PVC in a fully automated way.

The two PVC methods are implemented as external tools 175, although they have a much broader scope and require more user interaction than typical external tools. Therefore, their implementations are described in the respective sub-sections below.

Step-wise and Background Calculation Modes

The different PVC methods typically involve several processing steps, some of them using input parameters. There are two ways how a user can apply the PVC calculation:

1. **Background calculation:** The user enters all required information and adjusts the different parameters, and then starts the processing. The tool window closes, the computations run in a separate thread in the background, and finally returns the corrected images for statistical analysis.

2. **Step-wise processing:** The user performs the processing steps one by one interactively with a ⟳ button, and inspects the intermediate results in the tool. If required, he can change a parameter and initiates the calculation again. After the last step, the final results are returned and the tool closed.

The step-wise processing mode has the advantage that all intermediate data remains available, and processing can be repeated from any intermediate step. When data is returned, it is already quality checked, whereas in the background mode the user can not always be sure that all processing steps were successful without inspecting some of the supplementary images returned by the tool.

The **All Steps** button performs all processing steps sequentially, but does not close the dialog window so that after a first run the different steps can be interactively explored.

Note that the parameters can always be reset to the recommended default values by the ⊙ button to establish a well defined situation after some experiments.

Common Requirements for Partial-volume Correction in PMOD

The PVC methods implemented in PMOD assume a homogeneous, Gaussian-shaped point-spread function (PSF) of the scanner which is specified by its full-width at half maximum (FWHM) in all directions. The user needs to determine reasonable FWHM values for his reconstructed images and specify them to the algorithm. If possible, a PET reconstruction method with homogeneous resolution should be used, so that the assumption of a stationary PSF is justified. Furthermore, the brain PET images should be reconstructed with a small pixel size not larger than 2.5 mm.

> **Important Note**: The PVC tools expect that the image data is loaded in the HFS orientation. It is a precondition for segmentation and matching procedures.

12.1   PVC based on Manual and Brain Template VOIs

This correction is based on the assumption, that the imaging volume can be separated into tissue volumes (VOIs) with homogeneous uptake. If the resolution of the PET scanner is known, the mutual signal contaminations across the VOIs can be calculated and corrected for. This method is known as the GTM (Geometric Transfer Matrix) method and was introduced by Rousset et al. [2,3].
The implementation in PMOD allows the user applying the GTM correction with any set of manually outlined VOIs. Additionally, for the analysis of human brain uptake, the user may take advantage of standard VOIs which are automatically adjusted to the subject's anatomy.

12.1.1   Methodology Description

VOI based Partial-Volume Correction (GTM Method)

The GTM method according to Rousset [2] restricts the partial volume correction to the signal of the true objects which are constituted by VOIs. The relation of measured PET values (affected by the partial-volume effect) to the true PET values is given by the matrix equation below

$$\vec{C}_{measured} = [GTM] \times \vec{C}_{true}$$

with the following notations:

C_{true}	Vector of the true average activity concentration in the different VOIs of interest. The vector length n equals the number of object VOIs.
$C_{measured}$	Actually measured average activity concentration in the different VOIs.
GTM	Geometric Transfer Matrix which describes the spill-over among all the VOIs. The matrix is square with nxn weighting elements $w_{i,j}$ which express the fraction of true activity spilled over from VOI_i into VOI_j. In practice, $w_{i,j}$ is calculated as follows: A binary map is created with 1 in all pixels of VOI_i and 0 elsewhere. The map is convolved with the imaging Point-Spread Function (PSF), and in the resulting spillover map the average of all VOI_j pixels calculated.

The GTM equation above represents a system of linear equations. Once the weights have been calculated, the system can be solved for the true values C_{true} by matrix inversion. Rousset [2] has shown that this algorithm is robust to noise propagation during the correction process.

Region-based Voxel-wise (RBV)

The RBV correction introduced by Thomas et al [6] extends the GTM method and performs a voxel-wise correction of the entire image.

In a first step the **standard GTM** correction is performed, resulting in a synthetic image C_{GTM}, which consist of the VOIs filled with the corrected average values.

In a second step a corrected image is calculated, which is not any more homogeneous within the VOIs, and which shows an image of the entire brain, not just the GM pixels. The calculation uses the formula

$$C_{PVC-RBV} = C_{Measured}\left[\frac{C_{GTM}}{C_{GTM} \otimes PSF}\right]$$

whereby the measured PET image $C_{Measured}$ is multiplied by a correction term calculated from the GTM corrected image and the point-spread function.

The method applied for the PVC calculation is available for selection on the bottom of the PVC interface:

12.1.2 Implemented VOI-based PVC Variants

The **PVC (VOI based)** method provides three variants which are based on the same GTM methodology. The difference is, how the VOIs are obtained.

1. **Manual VOIs:** The user outlines all VOIs manually.

2. **Template VOIs based on standard masks:** VOI templates defined in the MNI space are used and adjusted to the PET image. This method can only be applied for human brain images.

3. **Template VOIs based on individual masks:** The same VOI templates as above are used. The difference is, that the user has to provide an anatomical MRI image which is employed for a better individual adjustment for the VOIs.

4. **Template VOIs based on Plain VOIs**: the same VOI templates as above are used. No Anatomical MRI image is needed.

Methods 2,3 and 4 can only be applied for human brain images, whereas method 1 is generic. Note that the user may also derive himself contour VOIs from standard VOI templates, adjust them to the subject anatomy, and apply method 1. This allows him to take advantage of the rat and mouse templates for which an automated work-flow is not yet available.

The details of the methods are explained in the corresponding sections below.

12.1.3 Common Requirements

The VOI-based PVC methods can be applied to PET or SPECT images, both static and dynamic. A set of VOIs is required which define objects of common functional properties.

Important Note: The VOIs used for PVC may not be overlapping each other! If they do, a warning message will be shown. All activities in the neighborhood of the target should be taken into consideration and included into appropriate VOIs.

12.1.4 Results of VOI-based PVC

When closing the dialog window, the results of VOI-based partial-volume correction are returned in the form of an additional image series, indicated in the description by a **VOI based PVE corrected** string. Note that if the **Replace** box is checked the original images are replaced by the partial-volume corrected images.

12.1.4.1 VOI Based Uniform (GTM)

In these images, all pixels belonging to a VOI are set to the value obtained as the partial-volume corrected average value of that VOI. Pixels not included in a VOI are set to NaN. The example below illustrates a case with only two manually outlined VOIs, a tumor VOI and an enclosing background VOI.

To obtain the partial-volume corrected VOI averages please open the result images in the VOI tool, load the VOIs employed for the PVC, and calculate the statistics.

Statistics in Step-wise Mode

The step-wise mode has the advantage, that the statistics can directly be calculated with the **View Statistics** button. For static series, simple VOI statistics will be generated which are shown in a side-by-side manner as illustrated below.

In the case of dynamic series the results are TACs as illustrated below.

The statistic results can be saved as statistics *.voistat* file with the **Save Statistics** button. In alternative, the **Before PVC** or **After PVC** content of the page can be **Copy to Clipboard** and paste in Excel.

12.1.4.2 Region-Based Voxelwise (RBV)

The corrected image is not anymore homogeneous within the VOI: each pixel in the VOI is set to the value obtain as the partial volume corrected value of that pixel. Pixels not included in a VOI are set to NaN.

To obtain the partial-volume corrected VOI averages please open the result images in the VOI tool, load the VOIs employed for the PVC, and calculate the statistics.

Statistics in Step-wise Mode

The step-wise mode has the advantage, that the statistics can directly be calculated with the **View Statistics** button. For static series, simple VOI statistics will be generated which are shown in a side-by-side manner as illustrated below.

In the case of dynamic series the results are TACs as illustrated below.

The statistic results can be saved as statistics *.voistat* file with the **Save Statistics** button. In alternative, the **Before PVC** or **After PVC** content of the page can be copied **To Clipboard** and paste in Excel.

12.1.5 PVC using Manual VOIs

Overview

The most general case of VOI based PVC is, that the user himself generates a set of suitable VOIs to which he applies the GTM correction as described below.

Starting the PVC

As a first step, load the PET images into the PVIEW tool. Define or load a set of VOIs. Then activate the 🔧 button to the right of the image and select the **PVC (VOI based)** method from the list of external tools. A dialog window is shown which allows performing the processing in a step-by-step mode or as a background process.

Select the **Standard** tab for performing a correction based on your manually defined VOIs.

Step-by-Step PVC Processing Mode

The step-wise mode is activated by checking the box next to the **Enable preview** label. It activates ↻ buttons for the individual processing steps, as well as the **Edit VOIs** and once the PVC was calculated also the **View statistics** buttons.

Point Spread Function FWHM:

The PSF is assumed to be a three-dimensional Gaussian function. The FWHM values in the three directions have to be specified according to the resolution of the reconstructed image. Default is 7 mm isotropic FWHM.

Use VOIs:

Both contour VOIs and template VOIs can exist in parallel. If two definitions exist, the user has to decide whether to use the **Contour** or the **Template** VOIs.

Average PET frames:

If the study is dynamic, this option gets active in the step-wise mode. The purpose is to provide an averaged PET image for the purpose of VOI outlining. This averaging step is optional, and PVC will always be performed on the original images. The **Averaged PET** will also be shown in the **Image Preview** window

Edit VOIs:

This button opens a VOI tool dialog window showing the averaged PET images. If VOIs were defined beforehand, they can be edited, and VOIs can be loaded from a file. To return modified VOIs, close the window with the **Ok** button, otherwise **Cancel**.

PVC Calculation:

This button performs the actual PVC calculation. The result is returned in the form of an image series and shown in the **Image Preview** window.

View Statistics:

This button calculates the VOI statistics in the original and the PVC corrected images. Depending on the input images the results are simple statistics, or tissue time-activity curves.

Returning the Results:

To return the results close the window with the **Ok** button.

Background PVC Processing Mode

If no interactive processing is desired, the user interaction is minimal.

1. If desired, edit the FWHM parameters, or reset them by the ⊙ button.

2. Start the PVC calculation with the **Ok** button.

The window will be closed and processing will run in the background. The processing time depends on the number of VOIs and the FWHM. Once the result was calculated and returned to PVIEW, a confirmation message will be shown.

12.1.6 PVC using Template VOIs based on Standard Masks

Overview

PMOD provides templates of human brain VOIs in the standard MNI space, as well as masks of the grey and white matter pixels. The PVC method described below employs this prior information for constructing a set of individual brain VOIs matching a PET scan as follows:

1. The template VOIs are intersected with the GM mask to obtain standard GM VOIs.

2. The WM mask is converted into a WM VOI.

3. The PET image is normalized to the MNI PET template using the **Brain Norm. II** method.

4. The standard GM and WM VOIs are transformed to the space of the PET image using the inverse normalization transform.

5. A contouring procedure is applied to get contour definitions of all VOIs, which the user can view together with the PET image and edit.

6. The GTM PVC method is applied to the original PET series using this set of template-based VOIs.

Starting the PVC

As a first step, load the PET images into the PVIEW tool. Then activate the ⏽ button to the right of the image and select the **PVC (VOI based)** method from the list of external tools. A dialog window is shown which allows performing partial-volume correction in a step-by-step mode or as a background process.

Step-by-Step PVC Processing Mode

The step-wise mode is activated by checking the box next to the **Image Preview** label. Note the ⟳ buttons which are used to start the individual processing steps. Initially, several of them are inactive because the prior steps are missing.

The result images of the different steps are collected in the **Image Preview** area. In the image selection list, available results appear with a green mark, while yet unavailable ones are marked in red. The example above shows the **Masked Template** calculated by step 2. The selected image series can be exported for later use in the **Save** panel configuring the image format for saving.

The advantage of step-wise processing is that steps can be repeated with different parameters until the outcome is satisfactory.

Point Spread Function FWHM:

The PSF is assumed to be a three-dimensional Gaussian function. The FWHM values in the three directions have to be specified according to the resolution of the reconstructed image. Default is 7 mm isotropic FWHM.

Average PET frames:

Dynamic images can be processed and will result in a corrected dynamic series. However, for the **Normalization** step, a static PET image showing anatomical information is required. Therefore, the user should define a suitable range for averaging time frames, and then activate ⟳. In the case of a static scan this step is not required and the button therefore not active. The **Averaged PET** is shown in the **Image Preview** window.

Masking:

The masking requires no parameters. It shows the **Masked Template** in the **Image Preview** window.

Normalization:

The normalization of the averaged PET image to the MNI PET template has one parameter, **Sampling rate**. After calculating the normalization, the normalization inverse is applied to transform the masked template to the PET space. The results **Normalized PET** and **Template matched to PET** are shown in the **Image Preview** window.

Outline VOIs:

This step calculates contour VOIs from **Template matched to PET** and shows them together with the **Averaged PET** in the **Image Preview** window. This is the VOI set which will be used in the PVC.

Edit VOIs:

This button opens a VOI dialog window showing the VOIs on top of the **Averaged PET**. Note the extended **White Matter** VOI which has been derived from the WM mask. The VOIs can be inspected and edited, or saved for later use. To return modified VOIs, close the window with the **Ok** button, otherwise **Cancel**.

PVC Calculation:

This step performs the actual PVC calculation. Because of the large number of VOIs contained in the standard templates the processing takes a while. The result is returned in the form of an image series and shown in the **Image Preview** window. If the input series was dynamic, the result is also dynamic as in the example below.

View Statistics:

This button calculates the VOI statistics in the original and the PVC corrected images. Depending on the input images the results are simple statistics, or tissue time-activity curves.

Returning the Results:

Make sure that the **Additional results** of interest are checked. Then close the window with the **Ok** button to return the results.

Background PVC Processing Mode

If no interactive processing is desired, the user interaction is minimal.

1. If desired, edit the FWHM parameters, or reset them by the ⊙ button.

2. If the PET series is dynamic, define an appropriate frame range for averaging.

3. Make sure that the **Additional results** of interest are checked.

4. Start the PVC calculation with the **Ok** button.

The dialog window will be closed and processing will run in the background. Once the result were calculated and returned, a confirmation message will be shown.

12.1.7 PVC using Template VOIs based on Individual Masks

Overview

PMOD provides templates of human brain VOIs in the standard MNI space. The PVC method described below combines this information with the grey and white matter masks derived from an individual subject MR image as follows:

1. The anatomical MRI of the subject is segmented and the GM and WM masks calculated.

2. The MR image is normalized to the MNI MR template using the **Brain Normalization** method.

3. The VOI template is transformed to the MR space using the inverse of the normalization transform.

4. The transformed VOI template is intersected with the GM mask to obtain the GM VOIs in the MR space.

5. The WM mask is converted into a WM VOI.

6. The PET images are rigidly matched to the MR images.

7. The GM and WM VOIs are transformed to the PET space using the inverse rigid transform.

8. A contouring procedure is applied to get contour definitions of all VOIs, which the user can view and edit.

9. The GTM PVC method is applied to the original PET series using this set of template-based VOIs.

Starting the PVC

As a first step, load the PET images into the PVIEW tool. Then activate the ▯ button to the right of the image and select the **PVC (VOI based)** method from the list of external tools. A dialog window is shown which allows performing partial-volume correction in a step-by-step mode or as a background process.

Step-by-Step PVC Processing Mode

The step-wise mode is activated by checking the box next to the **Image Preview** label. Note the ⟳ buttons which are used to start the individual processing steps. Initially, several of them are inactive because the prior steps are missing.

The result images of the different steps are collected in the **Image Preview** area. In the image selection list, available results appear with a green mark, while yet unavailable ones are marked in red. The example above shows the **MR** loaded by step **Subject's MR image**. The images selected in the **Image Preview** can be exported for later use by the **Save** button.

The advantage of step-wise processing is that steps can be repeated with different parameters until the outcome is satisfactory.

Point Spread Function FWHM:

The PSF is assumed to be a three-dimensional Gaussian function. The FWHM values in the three directions have to be specified according to the resolution of the reconstructed image. Default is 7 mm isotropic FWHM.

Average PET frames:

Dynamic images can be processed and will result in a corrected dynamic series. However, for the **PET-MR Matching** step, a static PET image showing anatomical information is required. Therefore, the user should define a suitable range for averaging time frames and then activate ⟳. In the case of a static scan this step is not required and the button therefore not active. The **Averaged PET** is shown in the **Image Preview** window.

Subject's MR image:

The user must specify an anatomical MR image of the same subject which will be segmented. He can choose the format, select the image and then activate ⟳ for loading the MRI.

The **Use associated MRI series** box allows taking advantage of the feature that two series can be associated as a pair in PMOD databases.

GM/WM Segmentation:

This step needs to provide the different tissue segments. If **Probability Maps** is configured as **Calculate**, the ⟳ button calls a segmentation procedure which may take several minutes to complete. The procedure has three parameters: **Sampling rate** determines the density of pixels considered in the calculation. **Bias Regularisation** serves for compensating modulations of the image intensity across the field-of-view. Depending on the degree of the artifact, a corresponding setting can be selected from the list. **Cleanup** is a procedure for rectifying the segmentation along the boundaries. It is recommended to use the default settings and only experiment with other parameter values if the segmentation fails.

The results are three segments, WM, GM and CSF. They are arranged as frames in a "dynamic" series. In the illustration below, the three frames are arranged in three columns. Because the calculation takes long, it may be helpful to save the segment images for later use by selecting them

in **Image Preview** and then using the **Save** button.

If segment images are already available, **Probability Maps** can be configured as **Load from file**, and the corresponding segment file selected. Note that the segment images must be matched to the MR image and different segments should appear as dynamic frames in the indicated order. In this case the ⟳ button just loads the segments.

Normalization:

The normalization of the MR image to the MNI template has two parameters, the **MR template** which should be set to T_1 or T_2 as appropriate, and the **Sampling rate**. After calculating the normalization its inverse is applied for transforming the VOI template to the MR space. It is then intersected with the individual GM mask, and the WM mask is used to create the WM VOI. The resulting VOI template is shown in the **Image Preview** window as **Template normalized to MR**.

PET-MR Matching:

Upon activating the ⟳ button, the PET image is rigidly matched to the selected MR image. The inverse transformation is applied for transforming the VOI template from the MR to the PET space. The result **Template matched to PET** is shown in the **Image Preview** window.

If the PET and MR images are already matched, the **Skip Matching** box can be checked to skip this processing step. However, please note that in this case the MRI and the PET images must have identical pixel size and image matrix. If the automatic matching in the PVC tool is not feasible, matching can be performed manually in the fusion tool and the results saved for use in the PVC tool.

Outline VOIs:

This step calculates contour VOIs from **Template matched to PET** and shows them together with the **Averaged PET** in the **Image Preview** window. This is the VOI set which will be used for PVC.

Edit VOIs:

This button opens a VOI dialog window showing the VOIs on top of the **Averaged PET**. Note the extended **White Matter** VOI which has been derived from the WM mask. The VOIs can be inspected and edited, or saved for later use. To return modified VOIs, close the window with the **Ok** button, otherwise **Cancel**.

PVC Calculation:

This step performs the actual PVC calculation. Because of the large number of VOIs in the standard templates the processing takes a while. The result is returned in the form of an image series and shown in the **Image Preview** window. If the input series was dynamic, the result is also dynamic as in the example shown below.

View Statistics:

This button calculates the VOI statistics in the original and the PVC corrected images. Depending on the input images the results are simple statistics, or tissue time-activity curves.

Returning the Results:

Make sure that the **Additional results** of interest are checked. Then close the window with the **Ok** button to return the results.

Background PVC Processing Mode

If no interactive processing is desired, the user interaction is minimal.

1. If desired, edit any of the parameters, or reset them by the ⊙ button.

2. If the PET series is dynamic, define an appropriate frame range for averaging.

3. Select the anatomical MRI of the same subject.

4. Make sure that the **Additional results** of interest are checked.

5. Start the PVC calculation with the **Ok** button.

The dialog window will be closed and processing will run in the background. Once the result were calculated and returned to PVIEW, a confirmation message will be shown.

12.1.8 PVC using Template VOIs based on Plain VOIs

Starting the PVC

As a first step, load the PET images into the PVIEW tool. Then activate the 🕯 button to the right of the image and select the **PVC (VOI based)** method from the list of external tools. A dialog window is shown which allows performing partial-volume correction in a step-by-step mode or as a background process.

Step-by-Step PVC Processing Mode

The step-wise mode is activated by checking the box next to the **Image Preview** label. Note the ⟳ buttons which are used to start the individual processing steps. Initially, several of them are inactive because the prior steps are missing.

The result images of the different steps are collected in the **Image Preview** area. In the image selection list, available results appear with a green mark, while yet unavailable ones are marked in red. The example above shows the **Template matched to PET**. The images selected in the **Image Preview** can be exported for later use by the **Save** button.

The advantage of step-wise processing is that steps can be repeated with different parameters until the outcome is satisfactory.

Point Spread Function FWHM:

The PSF is assumed to be a three-dimensional Gaussian function. The FWHM values in the three directions have to be specified according to the resolution of the reconstructed image. Default is 7 mm isotropic FWHM.

Average PET frames:

Dynamic images can be processed and will result in a corrected dynamic series. However, for the **Normalization** step, a static PET image showing anatomical information is required. Therefore, the user should define a suitable range for averaging time frames, and then activate ⟳. In the case of a static scan this step is not required and the button therefore not active. The **Averaged PET** is shown in the **Image Preview** window.

Normalization:

The normalization of the averaged PET image to the MNI PET template has one parameter, **Sampling rate**. After calculating the normalization, the normalization inverse is applied to transform the masked template to the PET space. The results **Normalized PET** and **Template matched to PET** are shown in the the **Image Preview** window.

Outline VOIs:

This step calculates contour VOIs from **Template matched to PET** and shows them together with the **Averaged PET** in the **Image Preview** window. This is the VOI set which will be used in the PVC.

Edit VOIs:

This button opens a VOI dialog window showing the VOIs on top of the **Averaged PET**. The VOIs can be inspected and edited, or saved for later use. To return modified VOIs, close the window with the **Ok** button, otherwise **Cancel**.

PVC Calculation:

This step performs the actual PVC calculation. Because of the large number of VOIs contained in the standard templates the processing takes a while. The result is returned in the form of an image series and shown in the **Image Preview** window. If the input series was dynamic, the result is also dynamic as in the example below.

View Statistics:

This button calculates the VOI statistics in the original and the PVC corrected images. Depending on the input images the results are simple statistics, or tissue time-activity curves.

Returning the Results:

Make sure that the **Additional results** of interest are checked. Then close the window with the **Ok** button to return the results.

Background PVC Processing Mode

If no interactive processing is desired, the user interaction is minimal.

1. If desired, edit the FWHM parameters, or reset them by the ⊙ button.

2. If the PET series is dynamic, define an appropriate frame range for averaging.

3. Make sure that the **Additional results** of interest are checked.

4. Start the PVC calculation with the **Ok** button.

The dialog window will be closed and processing will run in the background. Once the result were calculated and returned, a confirmation message will be shown.

Note: This PVC procedure does not use a grey matter mask intersection with the VOI template. Otherwise it corresponds to the Template VOIs based method on Standard Masks.

12.1.9 Recommendations

Findings by Rousset et al. [2]

According to Rousset et al. [2], the accuracy of the GTM method depends primarily on the proper identification of the tissues which have different functional properties. If this is the case, the GTM algorithm is capable of accurately correcting the regional concentration within small structures such as the human basal ganglia. Furthermore, the propagation of statistical noise during partial-volume correction was found to be easily predictable and suitable for the application in dynamic PET.

Findings with the PMOD Implementation

The application of the GTM method to simulated PET images with realistic, spatially variant PSF resulted in the following observations (unpublished work Olivier Barret, PhD, Institute for Neurodegenerative Disorders, New Haven, CT, USA):

- GM VOIs are always corrected into the right direction, up- and downwards.

- A FWHM of 7mm is a reasonable default setting for the Gaussian PSF.

- If a subject MRI is available, the individual segments result in a better partial-volume correction than the standard GM, WM and CSF segments.

Shown below is an example of a subject data set corrected with 33 manually outlined VOIs, and with 116 VOIs derived from the AAL template combined with individual segments. Note the homogeneous values within the VOIs which are equal the partial-volume corrected average value of each VOI.

12.2 PVC of Brain Images based on MRI Segmentation

This correction is based on the assumption that white matter uptake is homogeneous. All brain pixels are classified as white matter (WM) or grey matter (GM) and sorted into respective segments. Based on these segments and the assumed PET resolution the spill-out from WM to GM can be estimated and subtracted. Similarly, the spill-out from GM to the surroundings can be estimated and compensated for. The result is a grey matter image with corrected activity values in all pixels. This method was introduced by Muller-Gartner et al. [4].

Given a brain PET and an anatomical MRI of a subject, the implementation in PMOD allows the user performing the segmentation and apply the Muller-Gartner PVC in a fully automated way.

12.2.1 Methodology Description

The **PVC (Brain MR based)** method implemented in PMOD consists of the following steps:

1. Segmentation of the Anatomical MRI

To perform the segmentation, a normalization transform of the subject MRI anatomy to the MNI anatomy (or *space*) is calculated. In the MNI space, there are probability maps available for grey matter (GM), white matted (WM) and cerebrospinal fluid (CSF).

These priors are inversely transformed to the MRI space and employed in the image segmentation. The results are three probability images in the MRI space, called the GM, WM and CSF segments. They form the basis for the PVC.

2. Matching of the PET and MR Images

In order to perform the PVC, the information of the MRI and the PET must be aligned. Because the GM segments are relatively fine, they cannot be resampled to a typical PET resolution without severe information loss. Therefore, the PET image is rigidly matched to the MRI, and the PVC performed in the MRI space on the up-sampled PET images.

3. Partial-volume Effect Correction

First, the uptake in WM is obtained either by analyzing the PET uptake in pixels with very high WM probability, or by using a value provided by the user. Then, the following correction formula of Muller-Gartner is applied:

$$C_{PVC-GM} = \frac{C_{measured} - \overbrace{C_{WM} \times (WM \otimes PSF)}^{\text{Corrects WM spill-in}}}{\underbrace{GM \otimes PSF}_{\text{Corrects GM spill-out}}}$$

with the following notations:

C_{PVC-GM}	Corrected activity concentration. This is the result of the PVC correction in each GM pixel.
$C_{measured}$	Actually measured activity concentration in a GM pixel which may be distorted due to spill-out and spill-in.
C_{WM}	Activity concentration in WM which is assumed to be homogeneous and just blurred by the PSF.
WM, GM	WM (GM) segment image which represents the WM (GM) probability of each pixel in the image as a value between 0 and 1. These images are assumed to represent the true anatomy with ideal resolution.
PSF	Point-spread function of the imaging system which is assumed to be constant across the image and represented by a three-dimensional Gaussian function.
WM⊗PSF	Mathematical convolution of the WM segment image with the PSF. The result represents the image of the ideal WM segment when detected with a real imaging system characterized by the PSF function. The expected WM image is obtained by scaling WM⊗PSF by the WM concentration C_{WM}. It is subtracted from the measured image to compensate for spill-in from WM to GM.

GM⊗PSF	Mathematical convolution of the GM segment image with the PSF. A division of the WM-corrected image by GM⊗PSF represents a deconvolution operation and corrects for the spill-out effect from GM. The operation of division may introduce over-corrections at the GM boundary. Therefore, the result image is masked at a certain threshold of the convolved GM image

Spill-out Correction Only

If, however, the segmentation of white and grey matter fails, the correction can be reduced to a spill-out only correction. In this case a *Brain* segment is formed from all pixels which are not CSF. This segment is convolved with the PSF, and the PET image divided by the result as described by the equation below.

$$C_{PVC-Brain} = \frac{C_{measured}}{Brain \otimes PSF}$$

Schematic of the Correction Workflow

The following illustration provides a graphical overview of the different processing steps as well as the resulting intermediate images.

12.2.2 Requirements

The MRI-based PVC is only applicable to PET or SPECT images of the human brain. It can be applied to static or dynamic series. A well resolved anatomical T_1-weighted brain MR image of the

same subject is required, but there is no need for matching the two image series beforehand.

12.2.3 Performing MRI-based PVC

Starting the PVC

As a first step, load the brain PET images into the PVIEW tool. Loading of the MR series is not required at this stage. Then activate the 🔧 button to the right of the image and select the **PVC (Brain MR based)** method on the list of external tools. A dialog window is shown which allows performing the processing in a step-by-step mode or as a background process.

Note the following:

1. Minimally, the user has to provide an anatomical MRI image.

2. It is recommended to inspect and analyze the outcome of the PVC procedure, for instance the outcome of the segmentation and the PET-MR matching. To this end, **Additional results** can be returned. The user should make sure that with the background mode the corresponding boxes **PET matched to MR**, **Brain Segments** and **Grey mask** are enabled before closing the window with the **Ok** button.

3. If the **Replace** box is checked the original images are replaced by the partial-volume corrected images.

Step-by-Step PVC Processing Mode

The step-wise mode is activated by checking the box next to the **Enable preview** label. Note the 🔄 buttons along the left border which are used to activate the individual processing steps. Initially, most of them are inactive because the prior steps are missing. In the example above, steps 1 - 3 have been performed. Therefore, step 4 can also be started, but step 5 not yet as it requires that the images have already been matched.

Note that the result images of the different steps are collected in the **Image Preview** area. In the image selection list, available results appear with a green mark, while yet unavailable ones are marked in red. The example above shows the WM map calculated by step 3. The images selected in the **Image Preview** can be exported for later use by the **Save** button.

The advantage of step-wise processing is that the steps can be repeated with different parameters until the outcome is satisfactory.

1. Average PET frames:

Dynamic PET images can be processed and will result in a corrected dynamic series. However, for the matching in step 4, a static PET image showing anatomical information is required. Therefore,

the user should define a suitable range for averaging time frames and then activate ↻. In the case of a static scan, as in the example above, this step is not required and therefore not active.

2. Subject's MR image:

The user must specify an anatomical MR image which will be segmented. He can choose the format, select the image and then activate ↻ for loading the MRI.

The **Use associated MRI series** box allows taking advantage of the feature that two series can be associated as a pair in PMOD databases.

3. GM/WM Segmentation:

This step needs to provide the different tissue segments. If **Probability Maps** is configured as **Calculate**, the ↻ button calls a segmentation procedure which may take several minutes to complete. The procedure has three parameters: **Sampling rate** determines the density of pixels considered in the calculation. **Bias Regularisation** serves for compensating modulations of the image intensity across the field-of-view. Depending on the degree of the artifact, a corresponding setting can be selected from the list. **Cleanup** is a procedure for rectifying the segmentation along the boundaries. It is recommended to use the default settings and only experiment with other parameter values if the segmentation fails.

The results are three segments, WM, GM and CSF. They are arranged as frames in a "dynamic" series. In the illustration below, the three frames are arranged in three columns. Because the calculation takes long it may be helpful to save the segment images for later use by selecting them in the **Image Preview** and then using the **Save** button.

If segment images are already available, **Probability Maps** can be configured as **Load from file**, and the corresponding segment file selected. Note that the segment images must be matched to the MR image and different segments should appear as dynamic frames in the indicated order. In this case the ↻ button just loads the segments.

4. PET-MR Matching:

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Upon activating the ↻ button, the PET image is rigidly matched to the selected MR image. If the matching fails, the **Sampling rate** can be reduced and matching tried again. In case the images are known to be already matched, the **Skip Matching** box can be checked in order to skip the matching step. However, please note that in this case the MRI and the PET images must have identical pixel size and image matrix. If automatic matching in the PVC tool is not feasible, matching can be performed manually in the fusion tool and the results saved for use in the PVC tool.

5. PVC Calculation:

The last step is the actual partial-volume correction procedure which has several parameters.

The **Point Spread Function FWHM** represents the assumed point-spread function. Default is 7 mm isotropic FWHM.

The **Correction mode** is normally set do **GM spill-out and WM spill-in** to obtain an image with corrected gray matter pixels. **WM spill-out and GM spill-in** is useful in situations where the main uptake is in WM and the corrected WM pixels are the target of the analysis. If, the segmentation of white and grey matter does not give an accurate result, the correction can be reduced to **Brain spill-out**, resulting in all brain pixels corrected for mutual spillover and for spill-out of the brain.

The **White matter estimation** provides three choices: Default is the **Regression** approach. It collects the PET uptake of all pixels with a WM probability higher than the specified value (e.g. **0.95**), and performs a linear regression to estimate the WM value at the probability of 1. [5] With **Average**, the average is calculated instead of using the regression. Finally, the user can specify a known WM uptake value with the **Fixed value** setting.

The PVC is only appropriate for GM pixels. All other pixels in the corrected image may therefore not be evaluated and are masked. To this end, a **Grey matter threshold** can be specified. It is applied to the convolved GM segment for getting a smooth appearance. Note that if the threshold is small, outlier values might appear along the mask boundaries as over-correction artifacts.

The PVC correction is always performed in the space of the MR image using the matched, interpolated PET image. If **Space of PVC corrected image** is set to **MR**, this corrected PET series is returned as-is. With the **PET** setting, however, the corrected series is transformed to the PET space using the inverse of the PET to MR transform.

6. View Statistics:

This button calculates the VOI statistics in the original and the PVC corrected images. Depending on the input images the results are simple statistics, or tissue time-activity curves for the gray matter.

The statistic results can be saved as a .voistat file with the **Save Statistics** button. In alternative, the Before PVC and After PVC content of the page can be copied **to Clipboard** and paste in Excel.

Returning the Results:

Before closing the window make sure that the appropriate **Additional results** boxes are checked, then select the **Ok** button.

Background PVC Processing Mode

If no interactive processing is required, the PVC procedure is very easy. Only the following actions are required:

1. If the PET data is dynamic, the averaging range has to be defined.

2. The anatomical MRI has to be selected.

3. If desired, some of the parameters can be edited in the different processing steps, or they can be reset by the [⊙] button.

4. The appropriate **Additional results** boxes should be checked.

5. The PVC can be started with the **Ok** button.

The window will be closed and processing will run in the background for several minutes. Once the results were calculated and returned to PVIEW, a confirmation message will be shown.

Result Images

The results are returned as additional image series, as illustrated below. The original data is the first on the list, then come three auxiliary image series, and the last series marked by **PVE CORRECTED** is final outcome of PVC. Note the masking which may cause the disappearance of GM pixels if the cortex is thin and the PET resolution low.

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12.2.4 Validation and Recommendations

Validation

The performance of the **PVC (Brain MR based)** method has been studied by Olivier Barret, PhD, Institute for Neurodegenerative Disorders, New Haven, CT, USA, and the results presented at the Symposium on Functional Neuroreceptor Mapping of the Living Brain 2010 in Glasgow. The abstract is reproduced below.

Performance Evaluation of PMOD integrated Partial Volume Correction Method for Brain PET data

Partial volume effects in emission tomography (PET) come from the limited resolution of the cameras and are due to two factors: the underlying heterogeneity of the tissues (grey and white matter in brain tissue) and the cross contamination of adjacent regions by the point spread function (PSF) of the tomographs. The result of these effects is an erroneous estimation of the true local tissue radioactivity concentration and in studies where quantitative estimates are required, it is often essential to perform partial volume corrections (PVC), in particular to take into account pathological or structural changes for instance as these can have a significant impact. Several correction methods, often requiring an additional structural imaging, have been proposed to attempt recovery of the true signal, and among these, one of the correction the most commonly used is an MR-based solution.

We report here of a fully integrated implementation of such an MR-based correction in the PMOD software, where the MR is automatically segmented into grey matter and white matter maps and subsequently registered with the PET image. Activity concentration in white matter is automatically determined by linear regression and the functional image is corrected by the maps smoothed by the PSF of the system, approximated by a 3-dimensional Gaussian distribution with a full-width half-maximum (FWHM) adjustable by the user. At the end of the process, the user is presented with a

grey matter partial volume corrected functional image. The correction has been validated using simulated subjects from a Monte Carlo database built using the PET-SORTEO simulator which implements a realistic model of the ECAT EXACT HR+ tomograph. Ten subjects simulated with a FDG functional model were used to estimate the recovery coefficient as a function of the set FWHM and to evaluate the robustness of the correction with regard to the white matter activity concentration estimate.

Results for the simulated subjects show a very good recovery of the cortical regions with corrected values within 3% of the simulated activity concentration for an optimal FWHM around 6-7mm, in agreement with an effective resolution of the space-variant published resolution of the simulated scanner. The recovery coefficient also showed good stability against the user defined FWHM, with variation of 4-5% for a FWHM set between 5mm and 9mm. The method was shown to be robust against the white matter activity concentration estimates, with variation of only 2-3% of the final grey matter corrected values for large errors of 10% in the WM estimates.

An MR-based PVC method fully automated and integrated with all the steps necessary to perform the correction has been implemented in the PMOD software and validated against a simulated data set. The pertinence of the correction is being evaluated for different tracers (FDOPA from the PET-SORTEO database) and also for subject data from the ADNI database, in particular for the beta amyloid PIB tracer where this correction might prove to be critical because of the high white matter uptake.

Recommendations

The **PVC (Brain MR based)** method is a fully automatic procedure which has been tested in detail. However, the user should be aware that in practical situations there are several sources of potential errors which may affect the PVC outcome, particularly

- distortions of the grey and white matter segments, and
- inaccurate matching of the PET to the MRI.

Therefore the user is advised to inspect the additional PVC results. He should fuse the segment images with the anatomical MRI, and the matched PET image with the MRI to ensure that the anatomical information, which is used for the PVC, is correct and aligned.

Furthermore, VOI statistics should be calculated both with the original as well as with the PVC corrected images in order to detect consistencies in the data.

12.3 PVC References

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13 Pipeline Processing

Basic Concept

The PMOD batch pipeline supports fully automatic image processing. A pipeline is configured as a series of processing steps, each receiving the results of the prior step, performing an additional analysis, and forwarding the results to the next step, with the last step producing the end results. A pipeline definition can be applied to a whole set of input images for obtaining objective results in a group analysis. To inspect intermediate results, a quality control (QC) breakpoint can be enabled. Furthermore, these auxiliary results may be saved for closer interactive inspection.

Use of Pipelines with DICOM Server

Toolbox based DICOM servers are able to **execute a specific processing pipeline** 43 when they receive images. This feature allows setting up special purpose toolbox DICOM server which perform simple and well-defined processing steps in the background.

Note: Pipelines cannot be used by DICOM servers started from a command script.

Assumptions and Recommendations

PMOD includes a powerful **database** 54 for the storage and organization of all kinds of relevant data. It is highly recommended that the data for pipeline processing is organized in such a database, because some processing tools will take advantage from specific relationships among data elements which can only be provided by a database. Furthermore, the output produced by the pipeline can directly be inserted at the appropriate database level, which is more difficult when working with directory structures.

A study may comprise data of several groups (e.g. controls, subjects) and conditions (baseline, follow-up). In this case a separate pipeline for each group/condition pair should be prepared as explained **below** 495. All pipelines can then be submitted for processing at once, and the results will be conveniently aggregated for group statistics.

Pipeline Elements

A processing pipeline can easily be set up via the interactive user interface explained below. It allows choosing and configuring an arbitrary number of processing steps from a list including

- the **external tools** 151 which are available in every PMOD license;
- automatic brain VOIs, image registration, normalization and motion correction which are tied to the fusion option (PFUS);
- kinetic modeling of regional TACs which belongs to the modeling option (PKIN), and some
- pipeline controlling elements.

The pipeline definitions can be saved for later retrieval and processing.

Use Cases of Pipeline Processing

This documentation includes pipeline processing examples representing practical scenarios. Please make sure to read the **first** 482 example as it provides a detailed step-by-step explanation, which is not repeated in the other examples. Furthermore, the **Demo** database of the PMOD distribution includes working examples which can be retrieved with **Load Processing** and directly executed.

13.1   Starting Pipeline Definition

Starting

Batch pipeline processing can be started from different places:

- the ▶️ button in upper right side of the docked interface;
- the **Batch Pipeline** item in the menu of the View tool;
- the ▶️ button in the lateral taskbar of the View tool

Input Data Format

Pipeline processing is restricted to images of a single file format. Therefore, a dialog window appears first for defining the **Input Format**. Additionally, a default pipeline can be configured with **Pipeline definition**, so that the processing sequence is already defined when the pipeline interface opens.

Please select the appropriate format from the list, select an existing **Pipeline definition**, an entire **List of pipelines**, or start with **No predefined protocol**, and continue with **Yes**.

In the following description the **Database** format will be used, which is strongly recommended.

13.2 Pipeline Definition User Interface

The interface of the batch pipeline tool is illustrated below.

The window has four areas, which are described below. Note the divider buttons which can be used for enlarging/reducing the relative areas.

Data to be Processed

Input data specification is in the upper left panel. While the data format has already been specified, operations during the image loading [108] can be configured with the **Settings** button. For instance, smoothing filters can be applied, or data interpolated to a certain (e.g. isotropic) pixel size. Another candidate operation is **Reorient to Standard Orientation**, which brings the images at loading time into the radiological standard HFS orientation. Note that all images will undergo these operations, also secondary images specified in the pipeline tools. The box **No loading operations** can be used for ruling out any data transformations.

The images to be processed are defined by the **Set input files** or **Add files** buttons, which open a dialog window for selecting image files.

The data selections build up the data list for processing. While **Remove** deletes a selected entry from the list, **Remove all** clears the whole list. An input data list can be saved for later use with the button right to **Remove**.

Processing Definition

The processing pipeline is configured in the upper right area. Each processing stage is added as a tab, with processing working from the left towards the right. Tabs can be appended using the **+** tab, and removed by the **x** in its tab. The tool to be applied is selected from the list selection on the tab indicated below. Note that some entries in the list are labeled by **(pipeline only)** to indicate they are not available in other contexts.

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A selected tool shows its parameters on the lower part of the tab for configuration.

Right to the tool selection there is a button for setting the parameters to the tool default values, and a **?** for showing help information about the tool. The **Prefix** string can be used to tag the images and non-image results produced by the tool.

Below the parameter there are some convenience buttons.

The **Last operation** box is relevant, if the resulting images should be split into individual frames, or even slices or a multi-bed images is processed. The left/right arrows are a shortcut to select the previous/next tab for fast browsing. The **QC** adds a quality control 477 breakpoint *after* the selected tab. The **+** button adds a new tab *before* the selected tab, and **x** removes the selected tab. **Save** processing and **Load Processing** allow saving/retrieving a pipeline definition, optionally with the list of images to process.

Processing Preview

In order to verify the pipeline setup, the **Preview** box in the lower right can be enabled. As a consequence, the current pipeline definition is applied to the data set selected in the **List of Input Studies** and the result image shown. According to the results, some tool parameters may be edited and the result updated using the **Refresh** button. The result images can optionally be stored with the **Save** button.

Output Configuration

A pipeline produces images, but can also result in some derived information such as VOIs, regional statistics or kinetic modeling files. The radio button in the **Save Images and Non-image Results** area serves for defining the information of interest: **Images and Non-image Results**, **Only Images**, and **Only Non-image results**.

With images configured for saving there are three option radio buttons:

- **No operation**: stores the original information available for the subject.

- **Replace selected**: information on the **Subject**, **Study** and **Series** level can be replaced. Select the corresponding level, edit the information in the lower part, then enable the **Replace** box.

- **Replace by algorithm (Anonymization)**: with this option the image data can be anonymized. This function is equivalent to the Batch Anonymization [515].

The format of the saved images is defined by the **Output Format** selection. Depending on the format, some parameters need to be configured, such as the output **DATABASE** in the example above.

With file-based formats such as **NIfTI**

the file system path where all files will be stored needs to be defined in the **DIRECTORY** field. The check boxes **Subject name**, **Series description** and **Date** instruct the program to include these elements into the generated filenames to avoid overwriting due to non-unique file naming.

Output of Intermediate Tools

It is assumed, that the main output is produced by the last (right-most) tool in the pipeline. Therefore, its result images are always saved. The intermediate tools have a **Save images** box which may be enabled for saving their images too, either during pipeline setup for testing, or during production processing for later validation procedures. The **Prefix** string serves for meaningfully tagging the saved data. Saving of the non-image results is also tied to the **Save images** box, but only occurs with the general saving options **Images and Non-image Results** and **Only Non-image results**.

Processing the Data

It is recommended saving the pipeline definition first, and then activate **Start Processing**.

A dialog window appears summarizing the tasks to be performed:

The **OK** button starts the pipeline processing. The **Cancel** button returns to the **Batch Pipeline** interface.

The **Aggregate Statistics** option is only relevant for non-image results such as regional uptakes or regional kinetic parameters. If the option is enabled, the results of all data sets are concentrated into a single aggregation table, which can immediately be used for statistical analysis. In case both regional uptakes and kinetic parameters are produced, aggregation of the kinetic parameters takes priority.

Preferably, **Close after Start** is enabled. In this way the dialog window is closed and the processing runs in the background. At the end of processing a dialog window is shown which indicates that processing was ok, or otherwise provides a problem report.

View Report provides information about the input and output of the pipeline, as well as the processing steps, as illustrated below.

13.3   Use of External Tools for Pipeline Processing

Most of the tools applicable in pipeline processing can also be used interactively on loaded images. Hence, they are described in the External Tools 151 section.

For some of the external tools additional pipeline-related options appear such as **Transformation from pipeline** for the **Interpolation** tool:

This allows applying a registration or normalization transform calculated at an earlier pipeline stage to the current image.

13.4   Pipeline-only Tools

In addition to the regular external tools there are some specific pipeline tools available. They are either needed for controlling pipeline operation (Quality Control 477, Replace Images 478), or interface to functions which don't directly operate on images (Kinetic Modeling 480).

13.4.1   Quality Control (QC)

In order to stop pipeline processing and inspect the results a **QC** breakpoint can be inserted with the **qc** button. The **QC** tool has four options.

▪ **Approve images and VOIs** just shows the information and asks for acceptance.

With **Approved** processing will continue the current pipeline, while **Not Approved** causes processing to terminate and start over with the next data set.

▪ **Edit VOIs** shows the current VOIs and images of the pipeline in a VOI dialog window for interactive VOI adjustments. When closing with **OK**, the current VOIs are overwritten by the potentially modified ones, whereas **Cancel** just closes the window. In both cases the pipeline is continued.

▪ **Save JPEG** creates a JPEG image with the prescribed layout and saves it for later inspection.

▪ **Skip** allows switching off the QC step for the remaining data sets.

13.4.2 Replace Images

The main purpose of **Replace Images** is to switch processing to a new data set, while the results generated so far (transformation, VOIs) are still available.

The main replacement mechanism is via image association 80 .

As an example 482 , consider that a PET and an MR are associated, and processing is started with loading the MR for generating VOIs. **Replace Images** swaps the role: The PET images are loaded, and from then on the (original) MR images are considered as the associated images.

If the images are not matched, a transformation calculated previously in the pipeline (or its inverse) can be applied to the images swapped in.

13.4.3 Macro

Macros 132 are a prescription of several data processing steps like data editing or filtering. They may be useful for shortening a pipeline, but don't support the inspection of the intermediate results. To apply a macro it has to be selected using the indicated button.

13.4.4 VOI Statistics

The **VOI Statistics** tool allows applying a set of VOIs to the current images in the pipeline.

Definition of VOI Set

The VOIs can be provided in three ways:

- **VOIs from pipeline**: The last VOIs produced in the pipeline are applied.

- **VOIs from file**: One option is to use VOIs which have been produced previously and associated to the current pipeline images.

- **VOIs from file**: Another option is to use a fixed VOI set.

This is particularly useful for data which have been transformed to a template space, such as the MNI space.

The selected VOIs can optionally be transformed before application to the images:

- **Apply transformation from pipeline**: The idea here is that the VOIs have been derived using an image different from the current images, and that the pipeline has recorded the appropriate transformation for bringing the VOIs into the space of the current image. Such an application is described in the <u>example</u> 482 below. The **Direct** or the **Inverse** transformation can be applied, as appropriate.

- **Apply operation**: The operations offered for VOI modification are the **Erosion** or **Dilation** by a number of pixels. Erosion allows shrinking VOIs from the outside. This may be useful for reducing the partial-volume effect. Dilation grows the VOIs by adding additional layers.

The **Additional VOIs** option triggers calculation of additional VOIs which are derived from the VOI set:

- **Max VOI**: For each VOI the maximal pixel will be located and sphere VOI with the defined **Sphere volume** created.

- **Peak VOI**: For each VOI a sphere VOI with the defined **Peak volume** will be created in such a way that the included uptake is maximal.

- **Hottest pixels VOI**: For each VOI a VOI will be created consisting of the **Number of** individual pixels with highest uptake.

Definition of Statistics Type

The statistics calculation will result in the same measures 324 as with interactive VOI evaluation. The **Classification** switch defines the inclusion criterion of boundary pixels, and the **+ surface and sphericity** and **+ surface, sphericity and diameter** options allow obtaining extended statistics.

The **Relative to Merged Reference** option allows calculation of the uptake relative to a reference tissue, often called SUVR. The VOI names to serve as the reference can be specified by a comma-separated list of exact VOI names like **Cerebellum_l, Cerebellum_r**, or using the "*" wildcard character such as in **Cerebellum*** to enclose all VOI names starting with "Cerebellum". With this example specification, the average uptake in any region will be divided by the average uptake in all cerebellum VOIs.

13.4.5 Kinetic Modeling (PKIN Option)

The **Kinetic Modeling** tool in the pipeline has the following interface. Please refer to *PMOD Kinetic Modeling Users Guide* for details regarding the modeling configuration.

Volumes of Interest for Tissue TACs

The kinetic tool generates the average tissue TACs from VOIs which are applied to the current pipeline data. They are specified on the **Tissue** tab and can be provided in three ways:

- **VOIs from pipeline**: The last VOIs produced in the pipeline are applied.

- **VOIs from file**: One option is to use VOIs which have been produced previously and associated to the current pipeline images.

- VOIs from file: Another option is to use a fixed VOI set.

This is particularly useful for data which have been transformed to a template space, such as the MNI space.

The selected VOIs can optionally be transformed before application to the images:

- **Apply transformation from pipeline**: The idea here is that the VOIs have been derived using an image different from the current images, and that the pipeline has recorded the appropriate transformation for bringing the VOIs into the space of the current image. Such an application is described in the example 482 below. The **Direct** or the **Inverse** transformation can be applied, as appropriate.

- **Apply Operation**: The operations offered for VOI modification are the **Erosion** or **Dilation** by a number of pixels. Erosion allows shrinking VOIs from the outside. This may be useful for reducing the partial-volume effect. Dilation grows the VOIs by adding additional layers.

As a convenience for applying reference tissue models a sub-set of VOIs can be merged with the **Merge Reference VOI** option. The specification is by a comma-separated list of exact VOI names like **Cerebellum_l, Cerebellum_r**, or using the "*" wildcard character such as **Cerebellum*** to enclose all VOI names starting with "Cerebellum".

Blood Activity Information

If blood-based kinetic models are applied in pipeline processing, blood information must be available for each data set processed. Unless the information is common among data sets, the blood information must have been associated 82 to the PET data beforehand. The **Blood** tab needs to be selected for the specification as illustrated below. In this example the **Whole blood** activity and the **Plasma** activity are referenced by association, whereas a constant **Parent Fraction** is applied which assumes that the metabolite buildup is common among the population processed.

Note that at this time the plasma fraction variant for specification of the plasma activity is not supported in pipeline processing.

Model Selection

The tissue model to be applied in fitting can be selected from the **Model** list.

Because of the large number of models in the list is initially filtered to only show reference tissue models. Please use the filter button indicated above for showing the filter setting window. There, filtering can be switched off with the **Reset** button, or set to different criteria. Use **Filter only** to close the dialog window and update the **Model** list.

Fitting Options

Each tissue model has its default regarding initial parameters and fitting flags. These defaults can be changed in the kinetic tool (PKIN). Alternatively, an explicit model configuration file can be prepared beforehand in PKIN and selected as the **Configuration file**.

The **Model fit options** allow applying some of the fitting options available in interactive modeling. Briefly:

- **Parameters initialization**: This option is only effective for compartment models. If enabled, the initial parameters are calculated using a linear least squares method.

- **Random fits**: If the option is enabled, the regional fits are repeated the specified number of times with randomly varied initial parameters. In the end, the fit with minimal Chi square will be returned as the result.

The **Run-time options** allow the batch to shown the fitting results in a **PKIN dialog** window, and saving a QC capture image of the fit result for the first regional TAC.

13.5 Detailed Pipeline Example: Kinetic Modeling with SRTM, Brain VOIs in PET Space

Available Data

The pipeline discussed in detail below assumes the following available scenario: A subject had two separate scanning sessions, resulting in a dynamic brain PET and a non-matched T_1-weighted MRI.

Intended Analysis

The MRI, which has superior resolution and anatomical information, is used for the automatic outlining of brain regions. These VOIs are then projected to the PET, and the average PET uptake in each region is calculated. The resulting TACs are analyzed with the SRTM kinetic model using the average cerebellum uptake as the reference TAC.

Processing Pipeline Outline

It is assumed that the user has imported the data into a PMOD database and **associated**[80] the PET and the MR series. The analysis can then be implemented by the following pipeline sequence.

1. Because the anatomical information in the MR image is better than in the PET, the MR is first loaded into the pipeline. So the MR is the **Input study**.

2. The **Automatic Brain VOIs** tool is then applied. It generates the VOIs in the MR image space. These VOIs will continue existing in the following pipeline stages.

3. The rigid transformation between the MR and the PET is determined using the **Registration & Normalization** tool. Because the uptake calculation should use the non-interpolated PET values, the PET image serves as the reference image, so that the rigid transform goes from the MR to the PET space. This rigid transform will continue existing in the following pipeline stages.

4. The PET images are brought into the pipeline using the **Replace Images** tool which swaps the current (MR) image with its associate (PET). From now on, the associated image is the MR.

5. If necessary, subject motion in the dynamic brain PET can be corrected with the **Motion Correction** tool. Note however that after this step the PET values will be interpolated.

6. Transform the VOIs from the MR to the PET space using the result from 3. (still in the pipeline), calculate the average regional TACs, generate the reference TAC by merging all cerebellum TACs, and perform the SRTM kinetic modeling. All this is done by the **Kinetic Modeling** tool.

In practice, the pipeline has the following appearance. Note that this pipeline setup is only possible if the Kinetic Modeling tool (PKIN) and the Image Fusion tool (PFUS) have been licensed from PMOD.

Automatic Brain VOIs ✕	Registration and Normalization ✕	Replace Images ✕	Motion Correction ✕	Kinetic Modeling ✕	+

The following sections describe each tool configuration in detail. The steps can be reproduced with the **PKIN2** data set in the **Pmod** example database. Furthermore, the corresponding pipeline definition is already available and can be retrieved with **Load Processing**.

Required PMOD Modules

Note that this pipeline requires that the following modules are available in the PMOD license:

- Image fusion (PFUS): for using the **Automatic Brain VOIs**, **Registration & Normalization, Motion Correction** tools.

- Neuro tool (PNEURO): for using the Hammers atlas. However, the AAL atlas can be used alternatively if PNEURO is not available.

- Kinetic modeling (PKIN): for applying the SRTM model to the tissue TACs.

13.5.1 Association of MR and PET Series

The first step is to prepare the input data. Start the viewing tool to perform the image association in the database viewer as illustrated below.

Select subject **PKIN2** in the **Subjects** list. Use SHIFT+Click to select the two image series **MR Anatomy** and **Dynamic DASB PET** which will be used in the pipeline processing. From the **Assign Project | Group** list activate the **Associate Images** entry to establish the mutual relation between the image series.

This operation would be repeated for all subjects to be processed. It is a one-time action which can be taken advantage of in multiple analysis procedures.

13.5.2 Automatic Brain VOIs

This step produces brain VOIs which match the anatomy in the MR image.

After data preparation proceed to the processing definition. Start|472| pipeline processing and configure the image format to **Database**. In the **BATCH PIPELINE DEFINITION** area use the tool selection button indicated below to select the **Automatic Brain VOIs** tool.

Set the **VOI template** to **Hammers-N30R83**. If it s not available in the list, select AAL-Merged instead. Because the VOIs are derived from the brain MRI series, select T1 in the **Normalization Template** list. Activate the HUMAN button to set the normalization procedure to proper defaults.

13.5.3 Registration and Normalization

This step calculates the rigid transformation from the MR image to the PET image, so that the VOIs delineated in the MR can be projected into the PET.

Use the **+ tab** to add a second processing tab and select **Registration and Normalization** from the tool list.

Set the **Coregistration method** to **Rigid Matching**. In the **Reference** section, activate the **Use Database associated images**. In this way, the PET image (which is associated to the current input, the MR) becomes the reference. Consequently the calculated transformation will go from the MR (input) to the PET (reference) space.

Because the PET is dynamic, the average uptake from frame **10** to **20** is used for matching. This is enabled by the **Average** flag, and entering the start and end frames into the corresponding number fields.

Activate the **HUMAN (Different)** button to set appropriate matching parameters for cross-modality matching.

13.5.4   Replace Images

This step brings the dynamic PET images into the pipeline.

Use the **+ tab** to add an third processing tab and select **Replace Images** from the tool list.

Check the **Use Database associated** images box. The effect is the loading of the images associated to MR, the PET which is the main target of the analysis.

13.5.5 Motion Correction

This step performs a motion correction of the dynamic PET series.

Use the **+ tab** to add an third processing tab and select **Motion Correction** from the tool list.

Make sure that the **To frame average** is selected for the **REFERENCE**. With this approach, a reference image is created by averaging the frames between **From** and **To**. In this example a range from **10** to **20** is applied, omitting the noisy short frames at the beginning. Note that the same range had been averaged to create a reference for the registration between PET and MR. In this way, the transformation will correctly map from MR to the motion corrected PET.

The **CORRECTION** section specifies the frames which will be matched to the frame average which serves as the reference. Assuming that there was negligible motion in the initial frames, a range from **10** to **50** is specified. Note that as a convenience the end number can be higher than the number of frames in the actual series.

13.5.6 Kinetic Modeling

This step calculates the average TACs of all brain regions and performs the kinetic modeling.

Use the **+ tab** to add a fourth processing tab and select **Kinetic Modeling** from the tool list.

VOI Definition

Set the radio button **VOIs from pipeline** to use the brain VOIs which have been produced in the first step of the pipeline. However, because they are in the MR space, they first have to be projected into the PET space. This is configured by checking **Apply transformation from pipeline** with the **Direct** option. This setting is correct, because the PET was the reference in the registration of pipeline step 2.

In order to reduce the VOI size slightly the **Apply Operation option** is enabled and a 3-dimensional **Erosion** with 1 pixel. Set the **Classification** to the indicated mode which weighs the contribution of each pixel relative to its VOI inclusion fraction.

As a convenience for applying reference tissue models, a sub-set of VOIs can be merged with the **Merge Reference** option. The specification is by a comma-separated list of exact VOI names like **Cerebellum_l, Cerebellum_r**, or using the "*" wildcard character such as **Cerebellum*** to enclose all VOI names starting with "Cerebellum".

Model Definition

The **Model** list is initially set to show the reference tissue models. Select the **Simplified Ref. Tissue SRTM** model, and enable the **Random fits** option to try each fit with **20** different initial parameters. The fitting will use the standard defaults for the model and the weighting. If specific initial parameters or a particular weighting scheme are required, the configuration should be prepared in the PKIN tool and referred to by the **Configuration file (.kmModel)** selection.

13.5.7 Pipeline Input Data

The data to be processed is assembled on the **List of Input studies**. Note that for the example setup the MR series have to be selected, and that the PET series must have been associated to this MR series beforehand. In the example below the **MR Anatomy** series of patient **PKIN2** was selected using the **Set files** button. Note that for incrementally appending to an existing list the **Add files** button should be used.

13.5.8 Testing the Pipeline

Initial Testing

As an initial test of the pipeline enable the **Preview** box. The whole pipeline will be run with the data selected in the list of input studies and the resulting images shown together with the VOIs in the lower right, if no error occurs.

Note that the VOIs are shown on top of the motion corrected PET, after transformation from the MR space.

Setting Quality Control Breakpoints

In order to evaluate the quality of VOI outlining a QC breakpoint can be added after the **Automatic Brain VOIs** tab and enable the **Edit VOIs** option.

Activate the **Refresh** button to restart the calculation. This time the pipeline is interrupted and the VOIs shown on top of the MR images. Note that there are more options to inspect the VOIs, such as VOI filling, showing only VOI subsets, etc.

Note that depending on where the QC breakpoint is placed, the VOIs might not match the images. In the example pipeline discussed the VOIs will not match any more after the **Replace Images** step as they are still in the MR space.

Only the **Kinetic Modeling** step will bring them from the MR to the PET space, and from there on they will match again.

Saving Intermediate Images

Some operations cannot be fully verified in the pipeline environment. In this example, for instance, the PET-MR matching evaluation is not possible because the QC can only show one image, namely the current one. By enabling **Save Images** of the **Registration and Normalization** step the pipeline is instructed to save the MR images which were matched to the PET with a **PrefixRN**.

As the **Preview** facility doesn't save images, the data have to be fully processed with **Start Processing**. The intermediate images will appear in the **Series** list of the patient.

For the evaluation of the matching the average of frames 10-20 of the Dynamic DASB PET should be fused together with the highlighted registration result RN_DASB_SERT.

13.5.9 Running the Pipeline

Finally the pipeline with the configured input data can be executed with the **Start Processing** button

13.6 Pipeline Example: Brain Uptake Statistics, MR Space

Available Data

The pipeline outlined below assumes the following available scenario: A subject had two separate scanning sessions, resulting in a dynamic brain PET and an non-matched T[1]-weighted MRI.

Intended Analysis

To provide a complementary example to the one **above** 482 in this case the statistics is performed in the MR space, and instead of performing kinetic modeling, the PET uptake is averaged during a certain frame range.

Processing Pipeline Outline

It is assumed that the user has imported the data into a PMOD database and **associated** 80 the PET and the MR series. The described analysis can then be implemented by the following pipeline sequence.

1. Because the anatomical information in the MR image is better than in the PET, the MR is first loaded into the pipeline. So the MR is the **Input study**.

2. The **Automatic Brain VOIs** tool is then applied. It generates the VOIs in the MR image space. These VOIs will continue existing in the following pipeline stages.

3. The PET images are brought into the pipeline using the **Replace Images** tool which swaps the current (MR) image with its associate (PET). From now on, the associated image is the MR.

4. If necessary, subject motion in the dynamic brain PET can be corrected with the **Motion Correction** tool. Make sure that the **Averaged** reference is selected. With this approach, a reference image is created by averaging the frames between **From** and **To** in the **REFERENCE** section. In this example a range from **10** to **20** is applied, omitting the noisy short frames at the

beginning. The **CORRECTION** is then applied from frame 10 onward.

5. The rigid transformation between the MR and the PET is determined using the **Registration & Normalization** tool. In this example the MR should serve as the reference. As PET is currently in the pipeline, this can be configured by the **Use Database associated images** for the **Reference**. For the rigid matching the average PET image between frames **10** and **20** will be

used which is configured below the input section.

6. The PET uptake is then averaged with the **Average (Frames & Slices)** tool within the **Frames** range **From** 10 **To** 20.

7. The final step is calculation of the regional statistics. Note that the PET image has already been transformed to the MR space in the registration step, so that in this pipeline the option **Apply**

transformation from pipeline is not required.

Required PMOD License

Note that this pipeline requires that the following modules are available in the PMOD license:

- Image fusion (PFUS): for using the **Automatic Brain VOIs**, **Registration & Normalization, Motion Correction** tools.

- Neuro tool (PNEURO): for using the Hammers atlas. However, the AAL atlas can be used alternatively if PNEURO is not available.

13.7   List of Pipelines

Setup of a Pipeline per Group/Condition

1. Configure the processing steps of the pipeline. After testing its performance with some example data, remove all files from the list and save it as the processing template with **Save Processing**.

2. Configure a meaningful set of input files (e.g. control group, baseline scans) in the **List of Input Studies**. Use **Save processing** for saving this processing batch. In the dialog window

enable **Save List of Input files** so that the currently selected files are stored together with the processing definition. In order to prepare aggregating the VOI statistic or kinetic parameters of this batch into an overall table specify the **Group** and the **Condition** identifiers in the

corresponding fields (e.g. "Control" and "Baseline"). Choose a corresponding name for the file and save.

3. Remove all input files, then configure the next set of input files (e.g. control group, follow-up scan). Save the processing list as in 2. with appropriate aggregation information (e.g. "Control" and "Follow-Up".

4. Repeat 3. for all subject groups and conditions (e.g. "Patient", "Baseline"; "Patient", "Follow-Up"). Make sure to use consistent identifier names.

List of Pipelines

For setting up an overall batch processing load all the prepared pipelines into the **List of Pipelines** tab using the **Set processing files** and **Add files** buttons.

The **Aggregate Statistics** option enables the creation of an aggregate per pipeline, which summarizes the group results and is named according to the **Group** and **Condition** identifiers. Note the functionality for saving the whole definition and retrieving it at a later time.

Execution of Pipelines List

After setting the pipelines up or retrieving them, the batch can be launched with **Start Processing**. A dialog window appears which summarizes the tasks to be performed

and allows defining an **R Workspace name**. This is a convenience and only relevant if the R functionality is enabled. In that case, all group aggregates are imported into the R environment and saved as a workspace, which can directly be employed for the population analysis.

The example below illustrates the situation at the end of processing the configuration above: Four aggregates were created, transferred to the **R** console which automatically started, and the interface for the population statistics is opened.

The individual pipeline aggregates are also available and appear as the following entries in the database.

13.8 Call PMOD Pipeline Processing from Command Script

As a convenience PMOD pipeline processing can be called from an external script. This allows for instance to schedule processing at times the computer is not interactively used.

In order for this type of pipeline processing to work the following conditions must be met:

- A license including the all required modules must be available.
- An appropriate folder structure for the input and output files has been set up.
- A pipeline definition specifying the processing steps and the input files is available.
- A command script executing the PMOD pipeline processing has been been prepared

These elements are described in the following sections.

> **Note:** Execution can be started at any time, but only instance can run at a time. Starting multiple instances can lead into unpredictable results.

13.8.1 Folder Structure

The appropriate folder structure should consist of a root folder containing three additional folders: one for the input files, one for the output files and one for the processing definitions.

The recommended folder structure is illustrated below:

The **pipe** folder in the *Pmod4.4/data* directory represents the root folder. It consists of three sub-folders:

- **def**: pipeline processing definition;
- **in**: input files for processing;
- **out**: processing results when not using the database.

13.8.2 Pipeline Definition

In order to prepare appropriate pipeline definitions please perform as follows:

1. Define the pipeline steps in the <u>Pipeline Definition User Interface</u>⟨473⟩.

2. Include one or two example files in the **List of input studies.**

3. Define the output: the results to be saved and the output destination. When the output destination is the file system the path to the **out** folder is required. With the database setting the selected database will be used as output destination for saving.

4. Test the pipeline to make sure the processing and the output settings are working properly.

5. Save the processing definition in the **def** folder location on the file system. Note that the **Save List of input files** and **Save Output settings** boxes have to be enabled.

An example of a pipeline with output saving configured for the file system is illustrated below:

The output configuration set to the **Demo** database should look similar to:

13.8.3 Script Definition

The external script basically performs the following steps:

1. It prepares a .procPipe pipeline definition file which specifies the files to be processed.

2. It calls PMOD in pipeline processing mode, providing the .procPipe file as an argument. PMOD acquires a license which has to include all required tools, performs pipeline processing, saves the results, releases the license and exits.

3. The script performs a cleanup removing unneeded files.

The script definition can be based on the **RunPmod** script located in the *Pmod4.4/Start* folder from the installation directory. Create a copy of the **RunPmod** script, name it *RunExamplePipeline* and edit it as follows:

1. After the **pmod.jar** add the switch **PIPELINE** or **PIPELINE_NOGUI**. With **PIPELINE** the script starts the processing with the full user interface. With **PIPELINE_NOGUI** no interface is visible and output goes to the console.

2. Append the full path and name of the pipeline located in the **def** folder. Note that the pipe processing definition files have suffix *.procPipe*. For all operating systems **/** must be used as folder separator (NOT Windows backslash "\") .

The *RunExamplePipeline* script file may look like illustrated below:

```
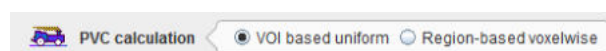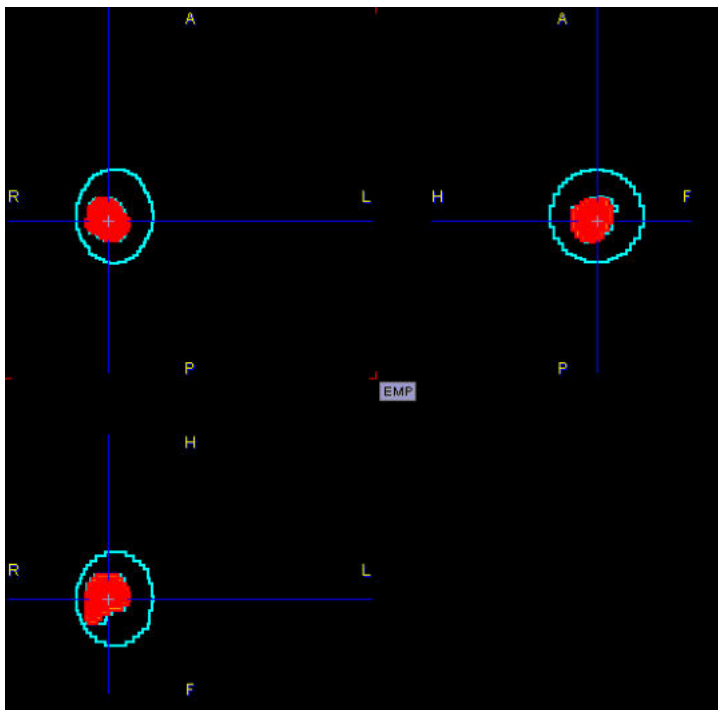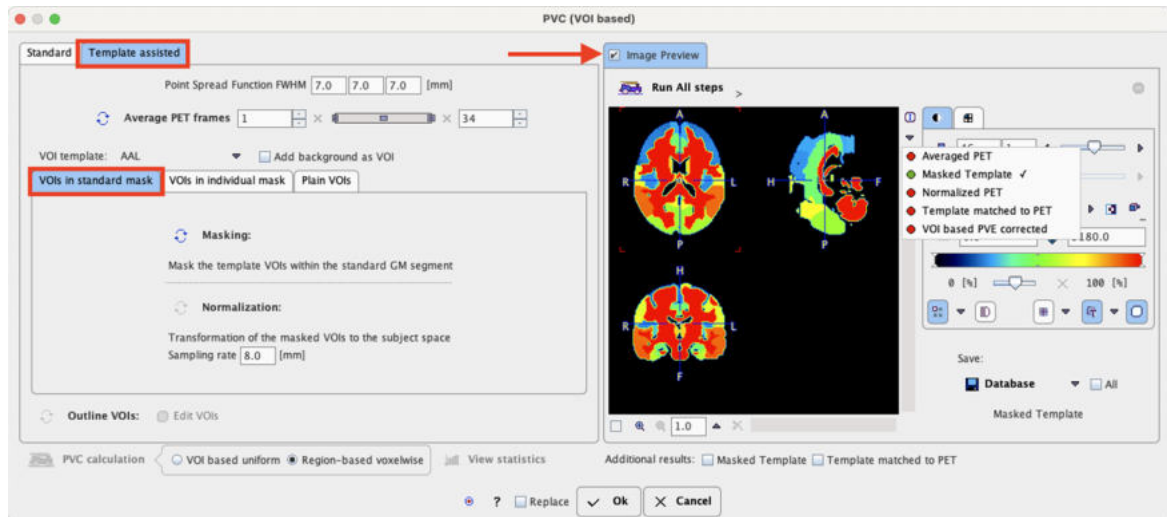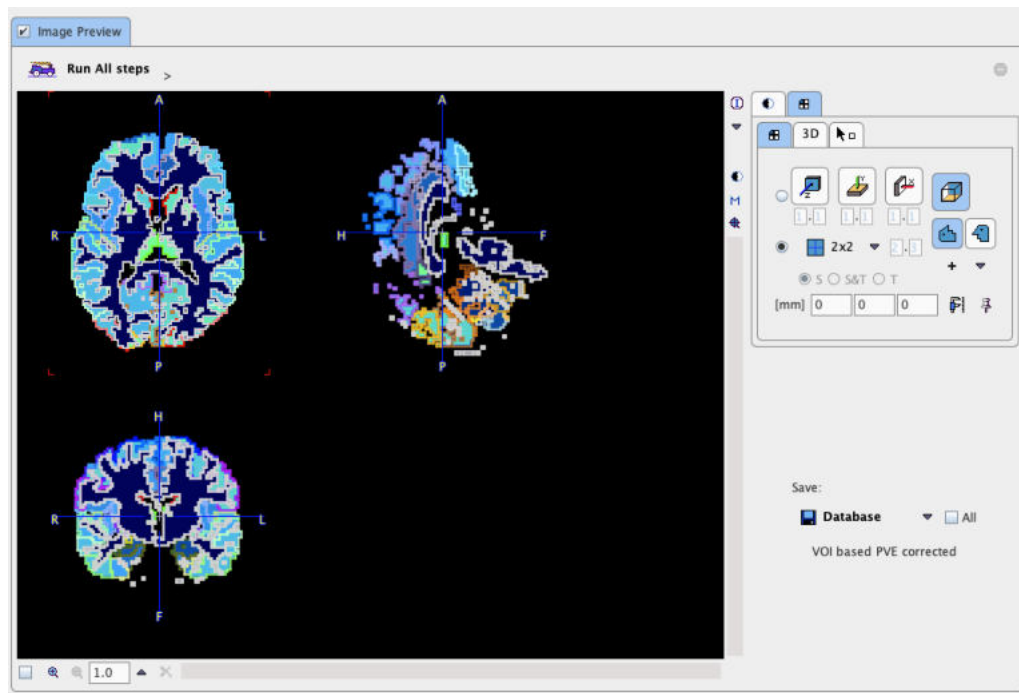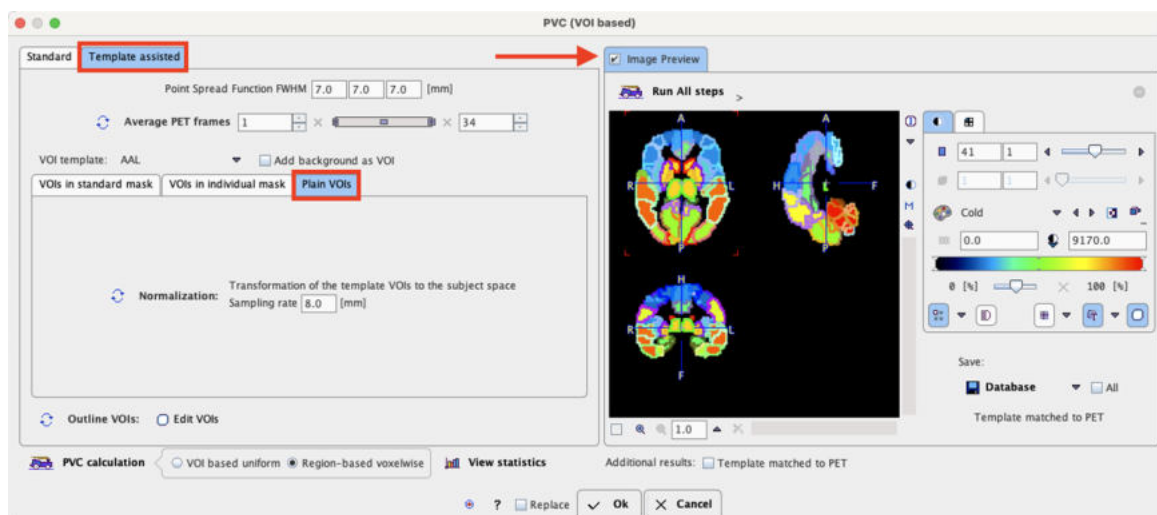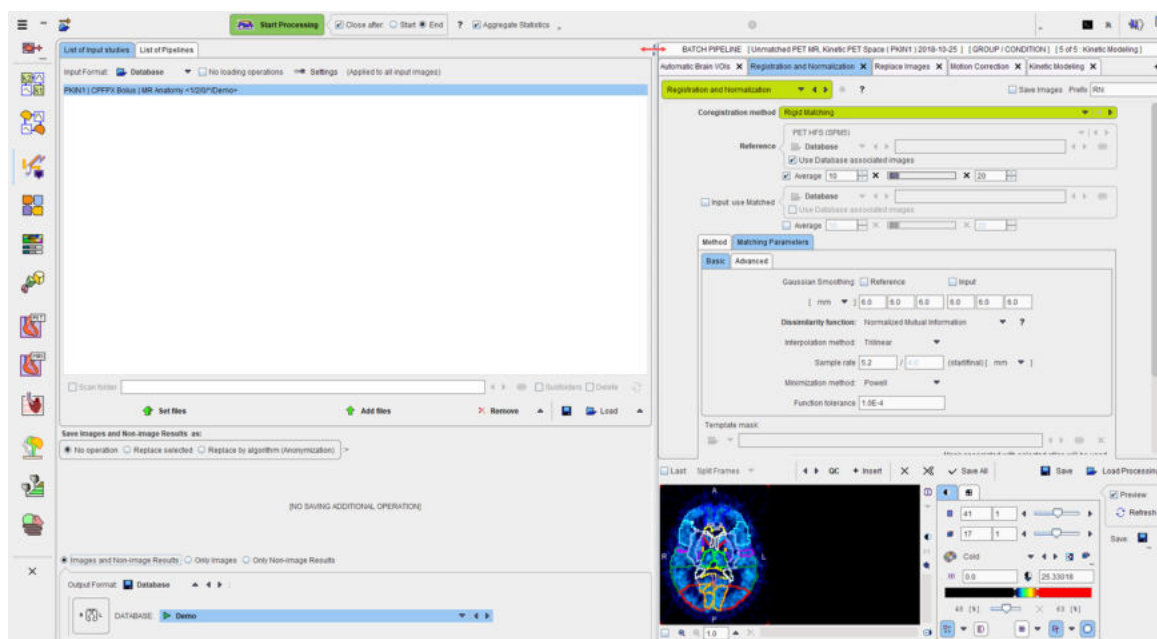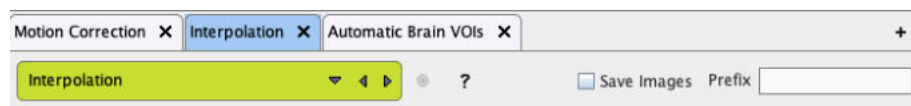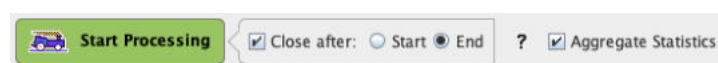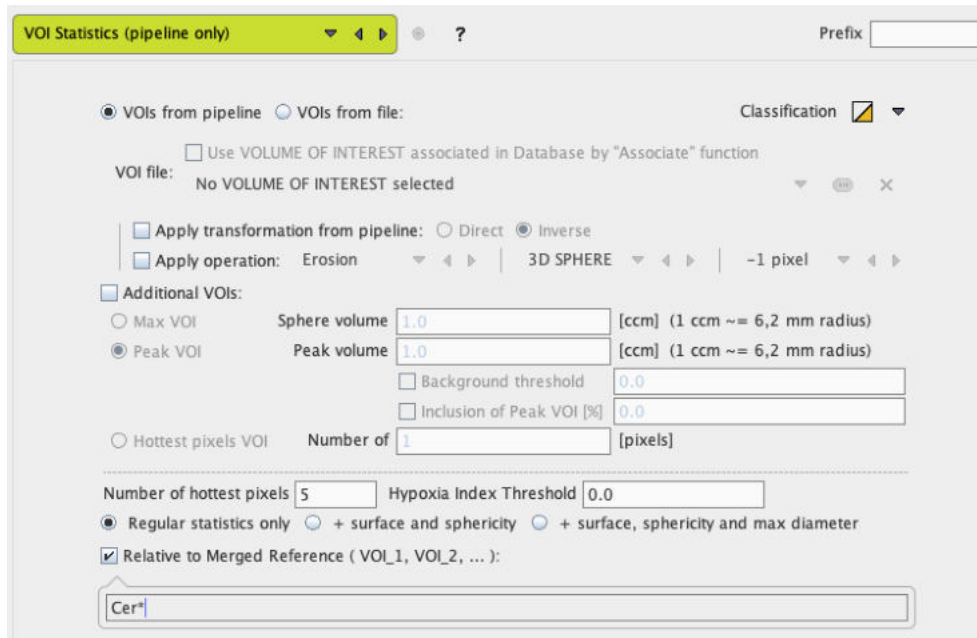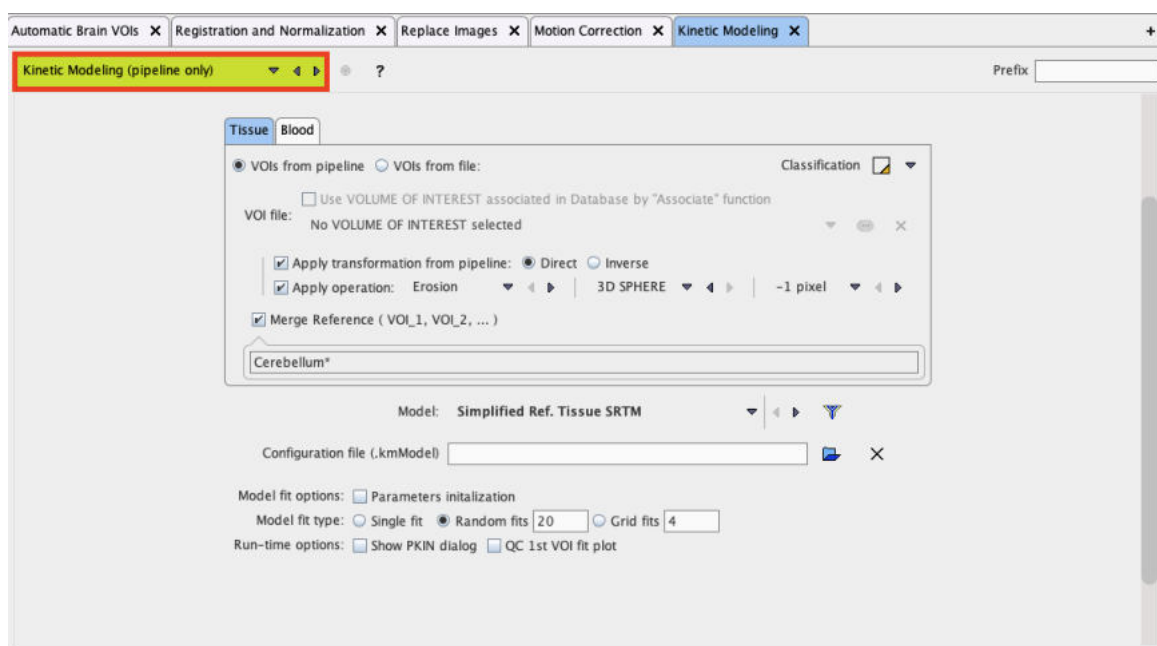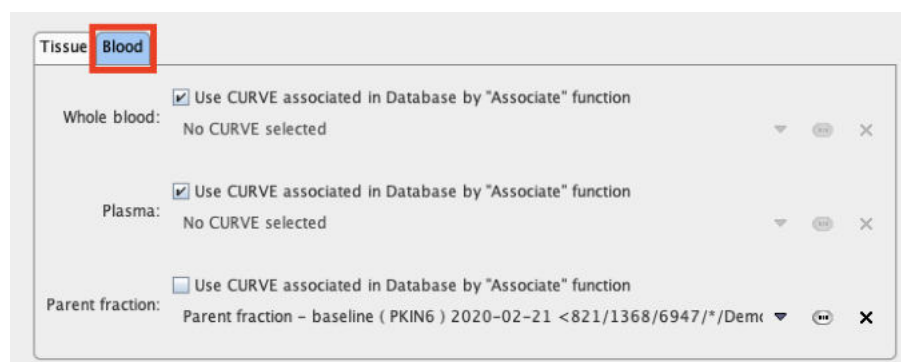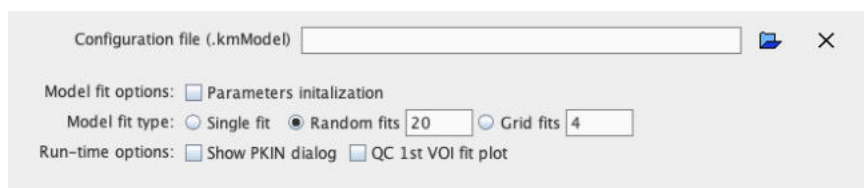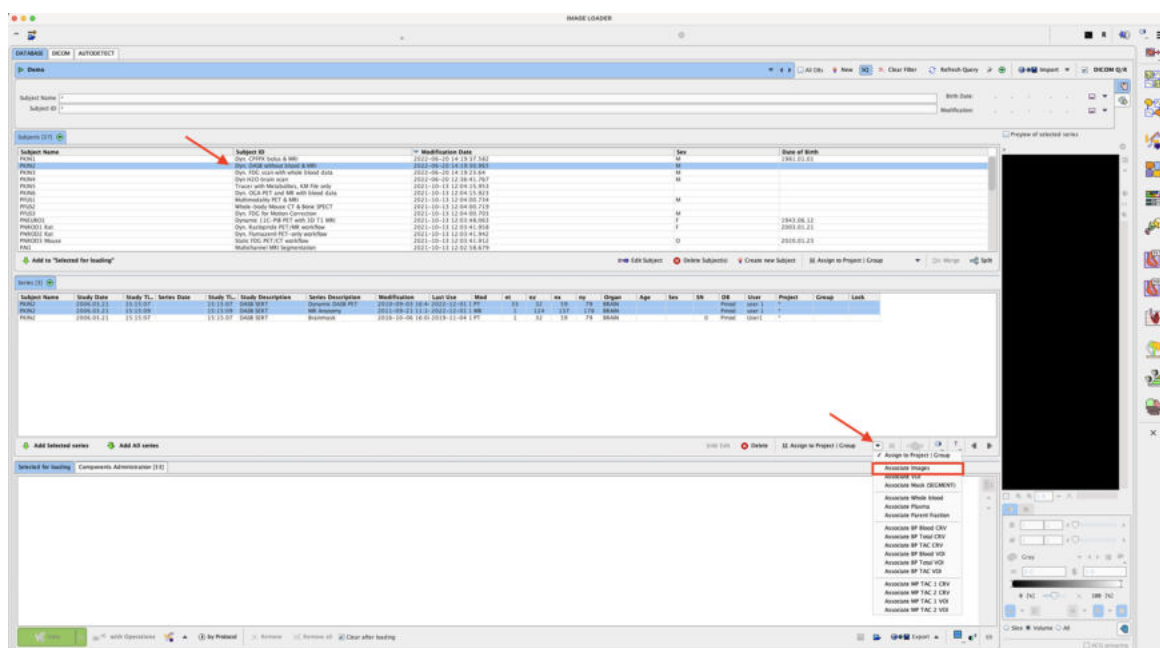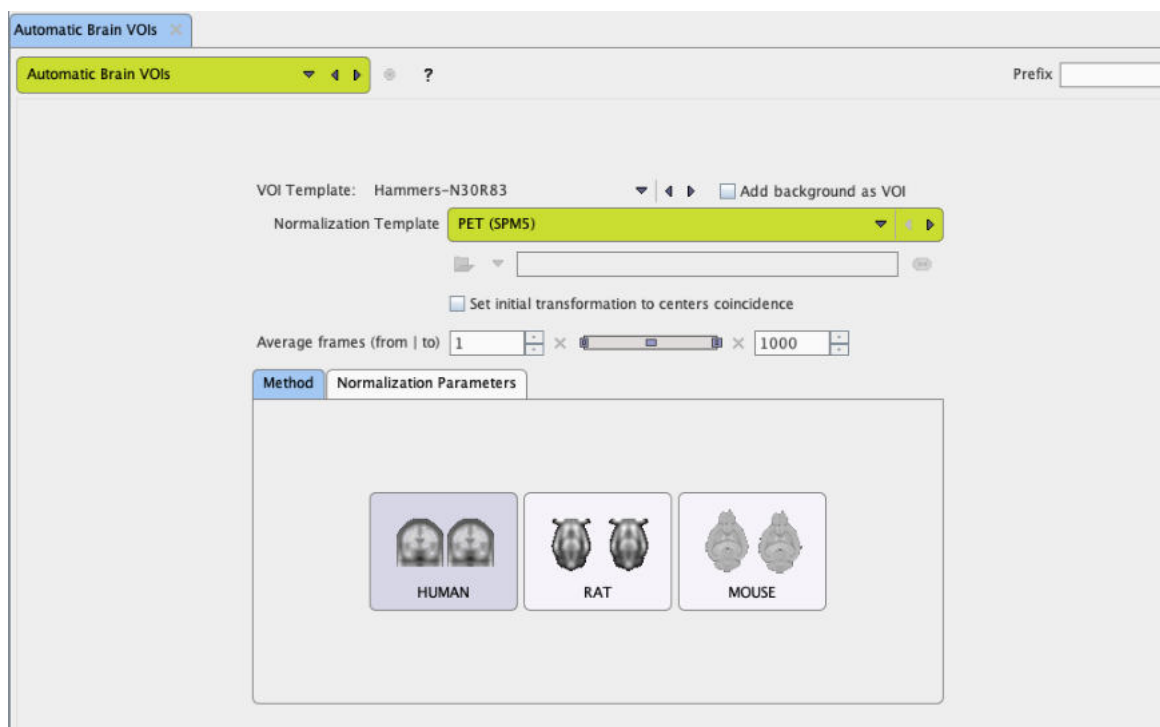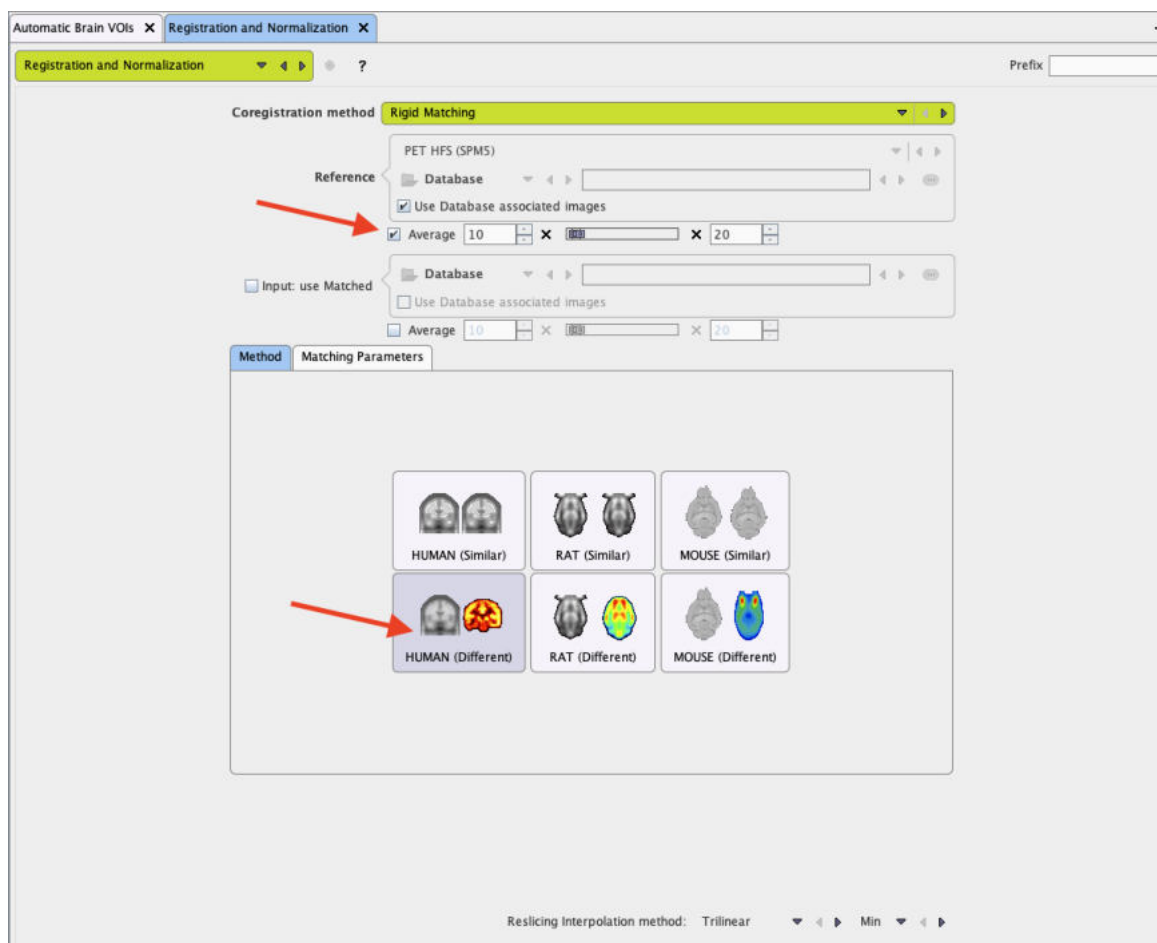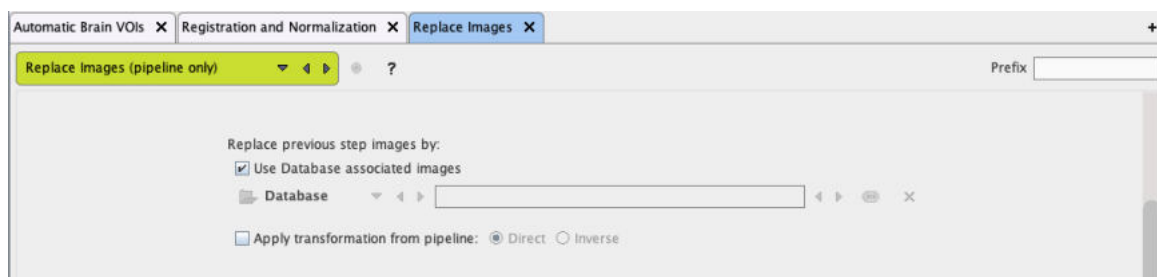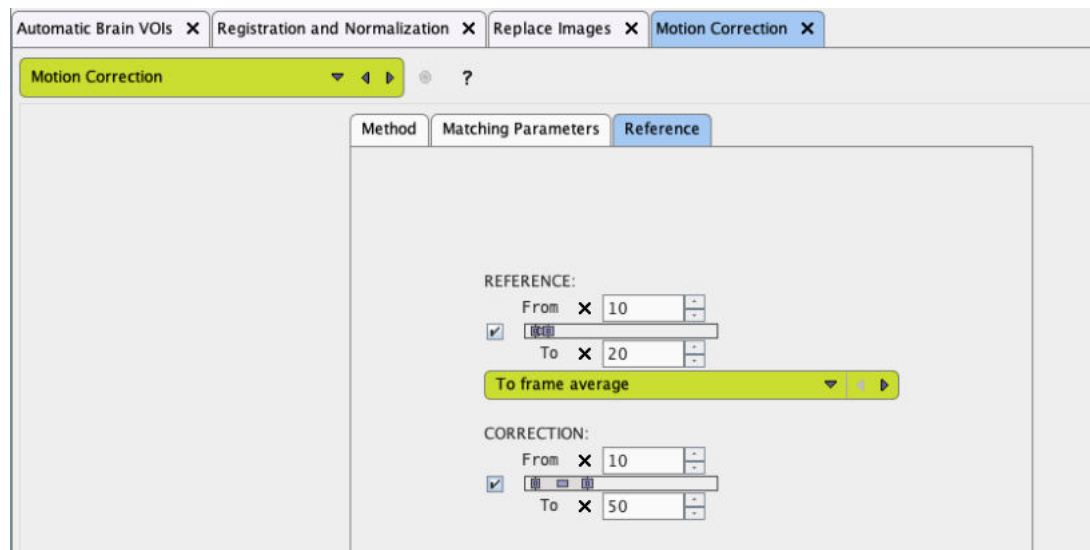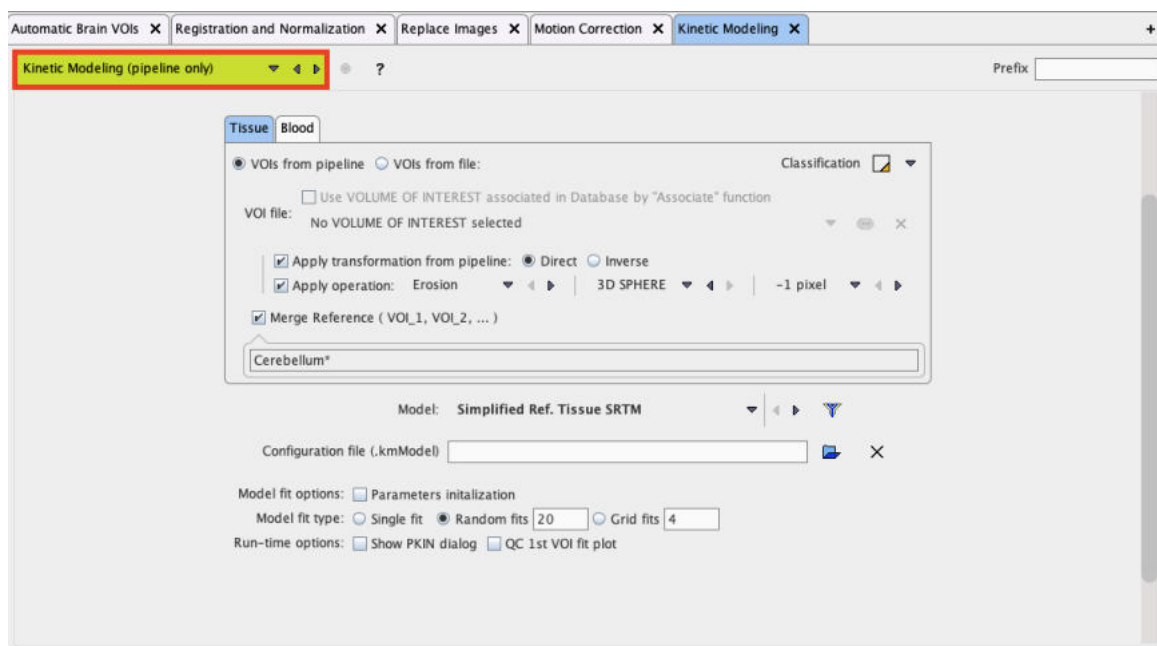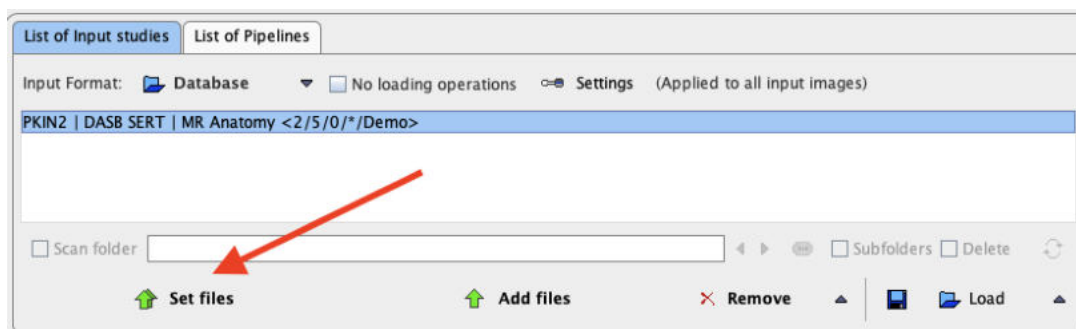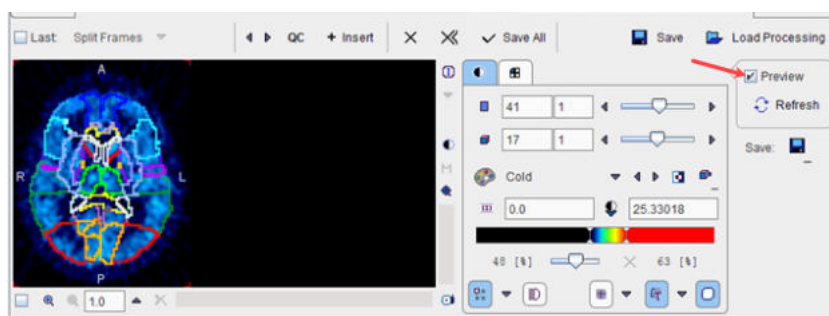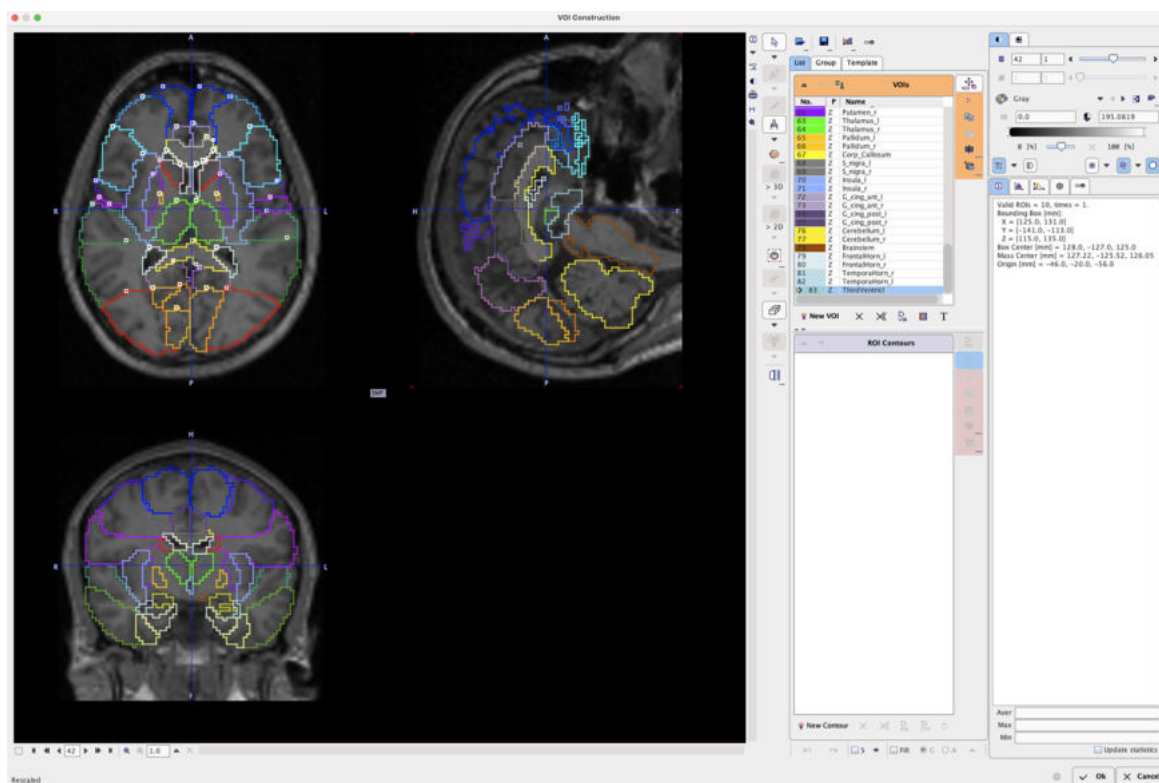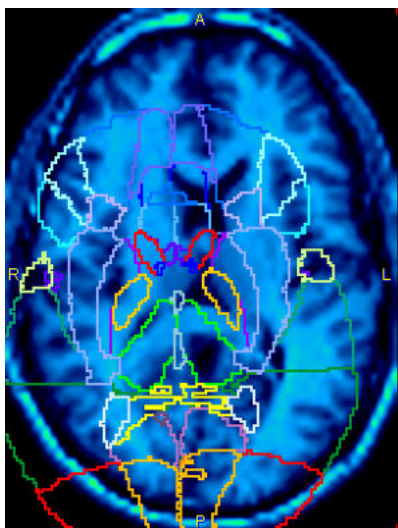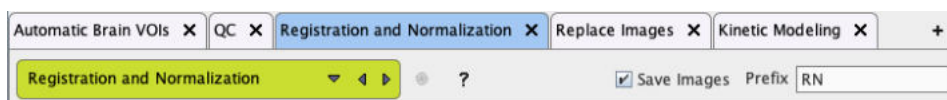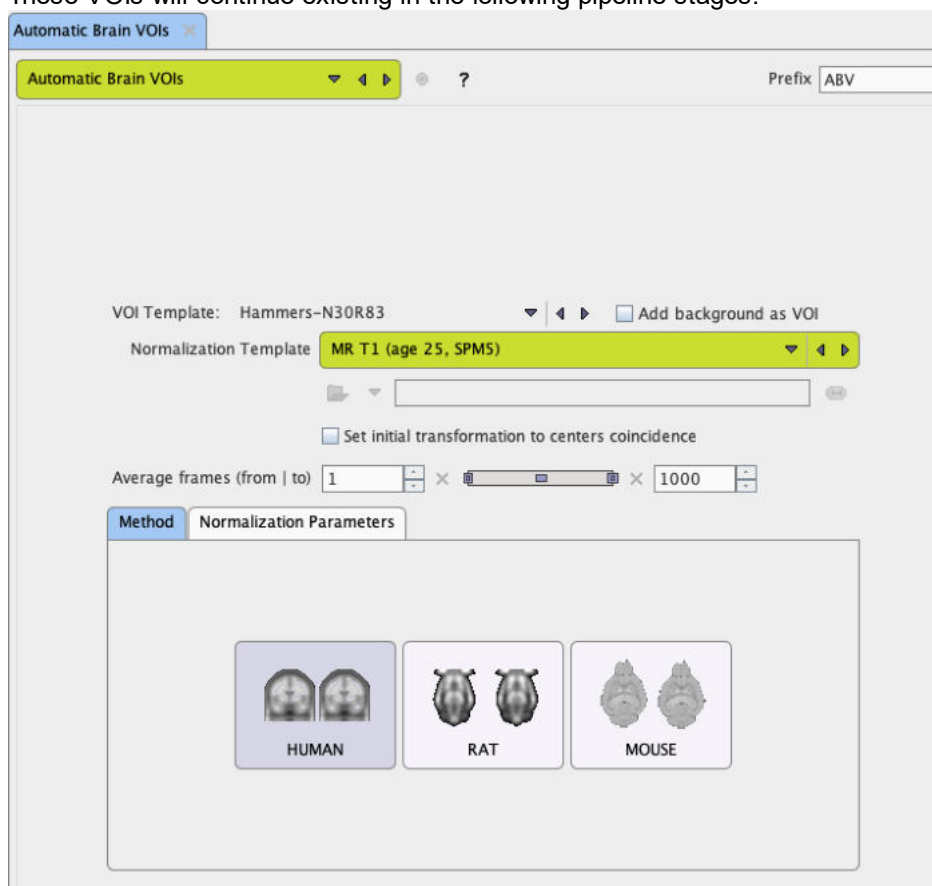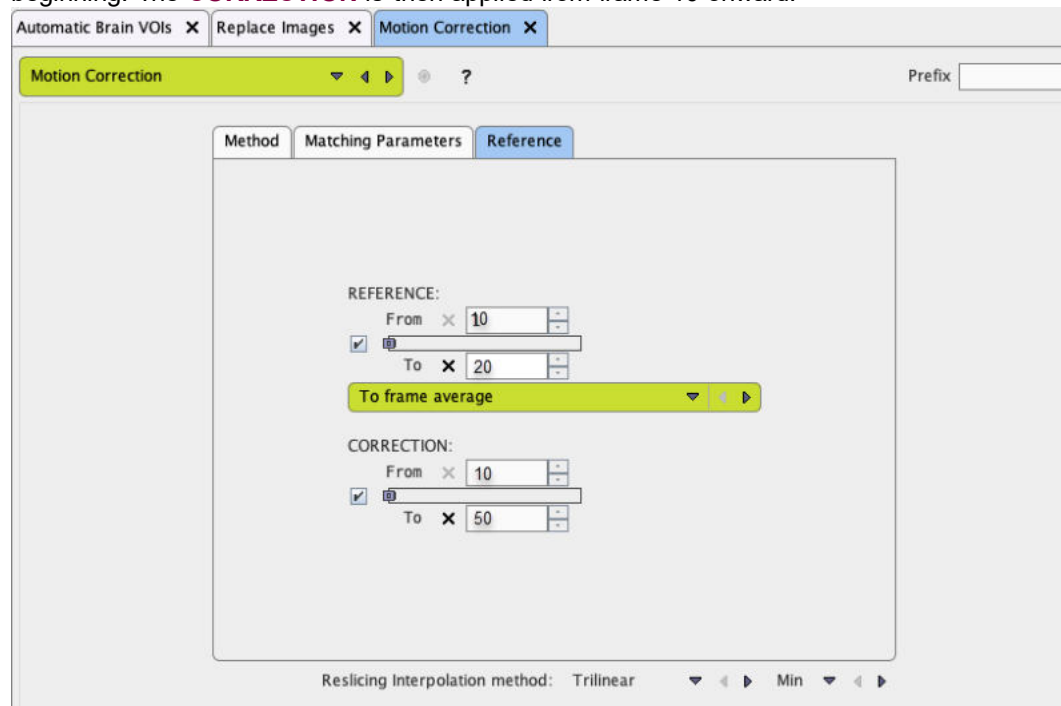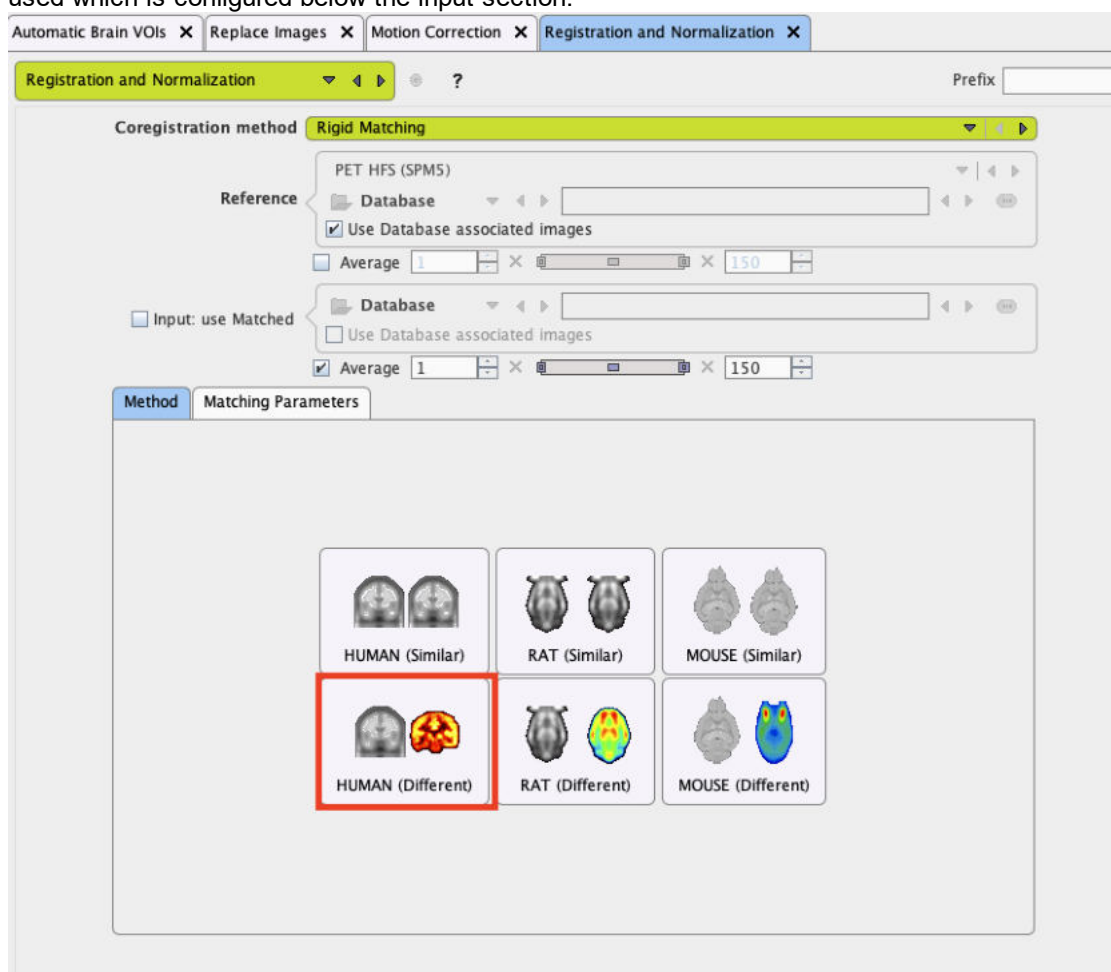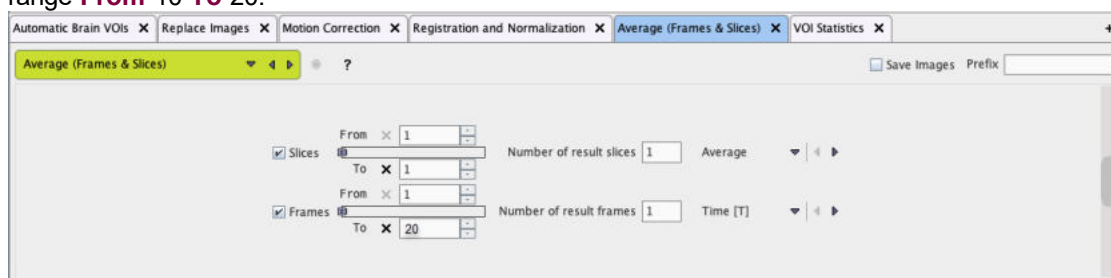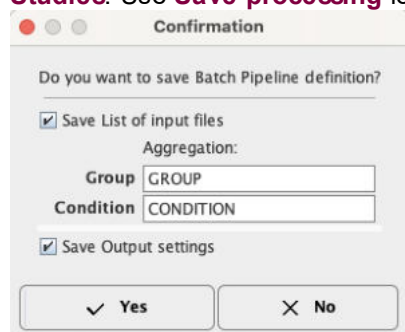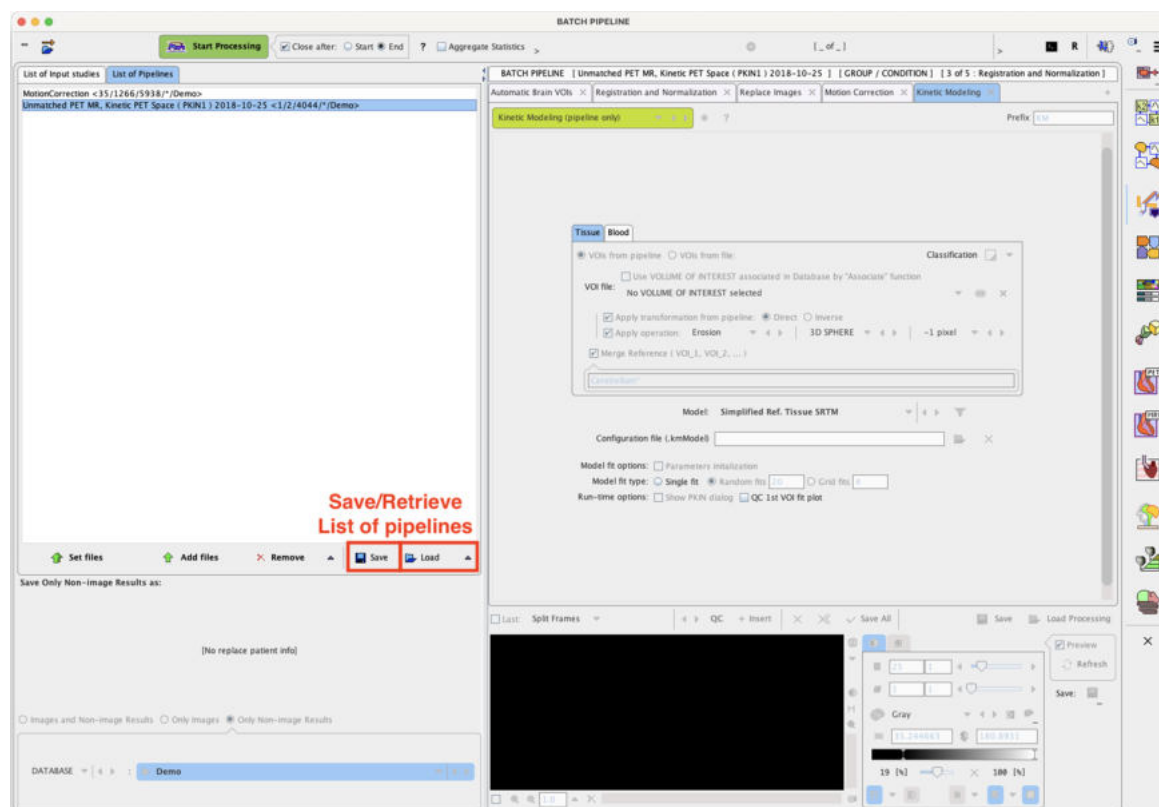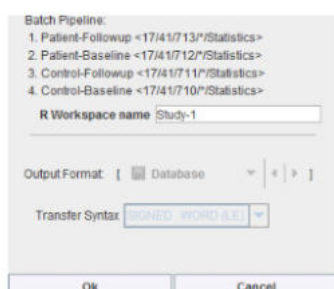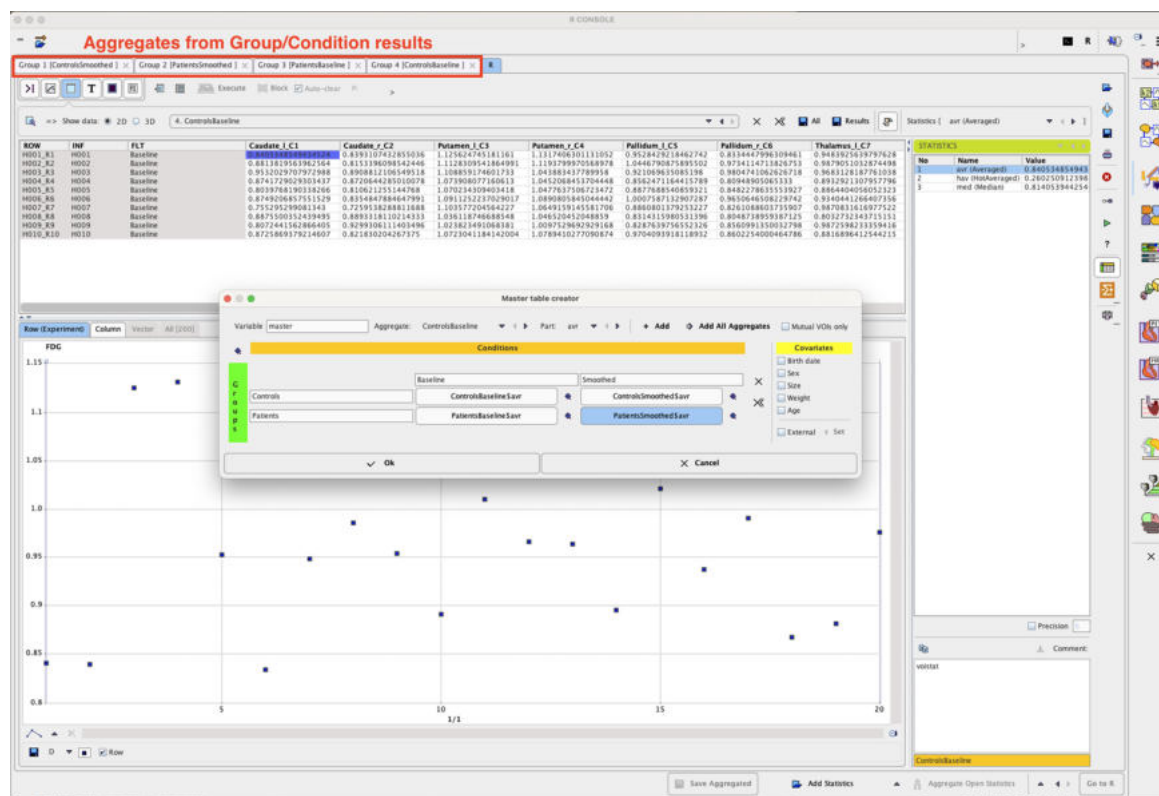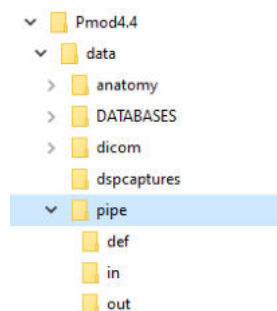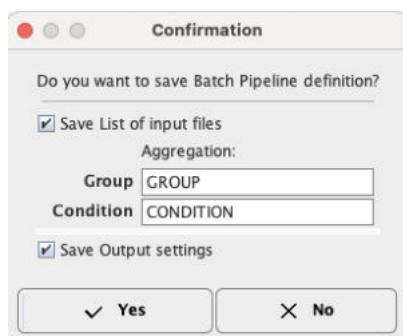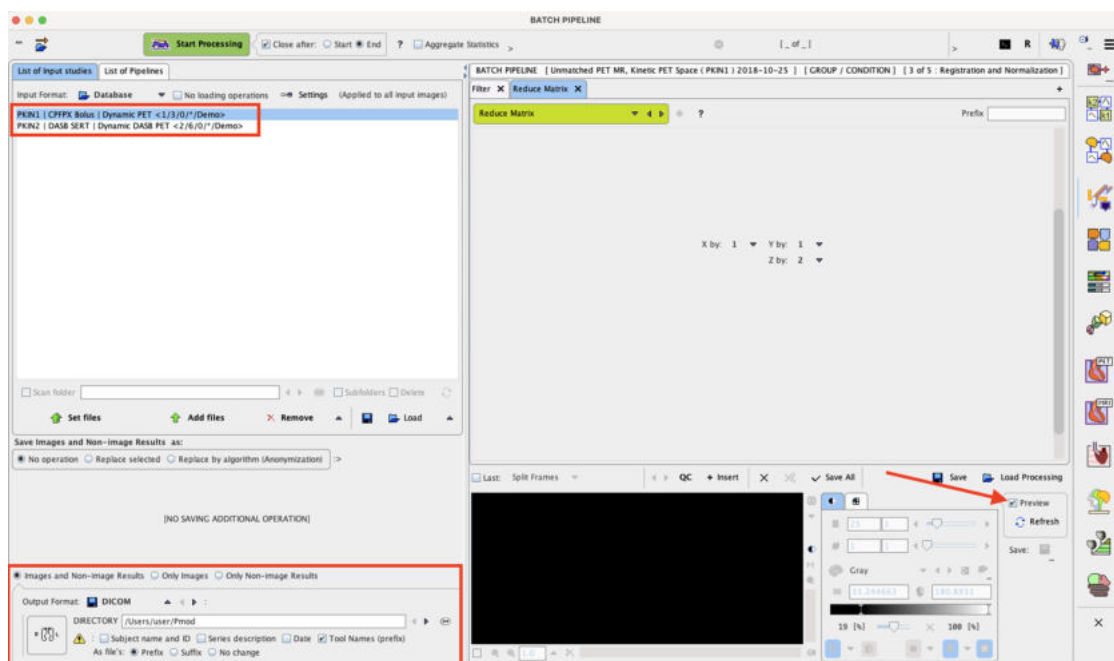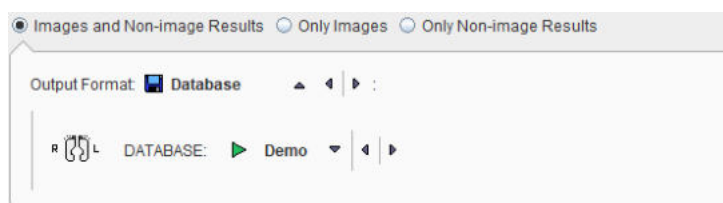D:
cd "D:\Pmod4.4"
rem external preprocessing: include input files in example.procPipe
.\java\jre\bin\java -Xmx8G -jar pmod.jar PIPELINE
```

```
D:/Pmod4.4/data/pipe/def/example.procPipe
rem external cleanup: remove input files
```

The external preprocessing is referring to a program created by the user that populates input file entries in the pipeline definition (.procPipe) file.

The external cleanup is referring to a program created by the user that removes processed input files from the **in** folder.

The following tags have to be updated in the .procPipe file:

1. **PIPE_FILE_NAME_<num>** Entries defining the input images. A slash **/** has to be used as folder separator.

2. **NUMBER_OF_PIPE_FILES** Number of input data files.

An example is illustrated below:

```
PIPE_FILE_NAME_1=D\:/Pmod4.4/data/pipe/in/06371770//\:0
PIPE_FILE_NAME_2=D\:/Pmod4.4/data/pipe/in/41891912//\:0
PIPE_FILE_NAME_3=D\:/Pmod4.4/data/pipe/in/41884445//\:0
NUMBER_OF_PIPE_FILES=3
```

> **Note**: A pipeline template (template.procPipe) can easily be created from an interactively defined pipeline which performs the intended processing. Open the file, remove the **PIPE_FILENAME_<num>** and the **NUMBER_OF_PIPE_FILES** lines. The external routine can then simply append the **PIPE_FILENAME_<num>** and **NUMBER_OF_PIPE_FILES** lines according to the data for creating the actual .procPipe file for the batch.

Execution Return Codes

There are a few return codes which can be defined to diagnose the execution:

1. EX_OK = 0 // Indicates successful termination of the processing.

2. EX_UNAVAILABLE = 69 // Indicates the service is unavailable: no license is available for the processing.

3. EX_CONFIG = 78 // Indicates a configuration error: the memory allocated to run Pmod is too low.

If no license is available, the behavior depends on the processing mode:

- PIPELINE: the standard license dialog is shown and PMOD waits for user interaction;

- PIPELINE_NOGUI: PMOD exits returning code 69.

14   PMOD Image Viewing and VOI Tool (PVIEW)

PVIEW is a versatile image and Volume-of-Interest (VOI) analysis tool which belongs to the base installation of PMOD. It supports many operations for image reviewing and scientific data analysis including:

- Loading medical images in different formats, including DICOM.

- Viewing the images with different color tables and in different layouts.

- Calculating new slice images in arbitrary new orientations.

- Performing many image processing and manipulation operations.

- Displaying fusion images of matched data sets (image registration is a separate option).

- Performing volume-of-interest analyses and the calculation of time-activity curves from dynamic studies.

- Saving images in different formats, including DICOM, and directly C-STORE them to a DICOM server.

▪

The PVIEW tool is started from the PMOD application bar with the dedicated icon

Like many other PMOD tools it organizes the functionality on different pages which can be selected by the upper tabs.

14.1 Top Menu Line

The **View** menu line is located at the top of the docking interface. It consist of the yellow menu button, **View**, followed by the main module pages, functional buttons, an area for progress information and other buttons common for all PMOD modules. The currently active page, e.g. **VOIs** in the example below, is highlighted in green color.

Only the local menu, the configuration, and protocol functionality are documented in this section, the other elements are standard in PMOD and documented in the _PMOD Docked Interface_ 13 .

Menu Content

The yellow menu button allows: accessing options for the data loading and saving, the aggregation interface, the Pipeline batch processing interface, creating DICOMDIR, starting the DICOM Query/Retrieve, the acceptance test, the local configuration and the View **Quit** button.

In addition, the Learning Sets for AI projects are prepared via the **Edit Learning Set(Training)** option in the main **View** menu. Simulated data to be used for the AI trainings can be prepared via the **Generate Data** option in the same menu. Please refer to the dedicated _PMOD Artificial_

Intelligence Framework (PAI) user guide for detailed information about the learning sets preparation, prediction, classification and case studies.

Configuration

See Tool configuration ⌐96¬ section.

Protocols

PMOD supports protocols in the **View** module. It is used for the acceptance test and for repeat data loading. By loading a protocol file the processing can exactly be restored at any later time. The protocol also supports VOIs saving when available.

14.2   Load - Page 1 (Option)

The first page **Load** shows the database interface as part of the unified data loader. It is only available if the database functionality is enabled and a local or remote database has been configured to access images in DICOM format. Note that it is highly recommended to use the database for easy data management. The database load page offers an efficient interface for loading images stored in one of the configured databases. A detailed description can be found in the Image Data Load section ⌐103¬.

14.3   Preprocessing - Page 2

The purpose of the **Preprocessing** page is

- loading images in all kinds of image formats,
- viewing the loaded images and performing processing operations, and

▪ saving (modified) images in one of the supported output formats.

Several images can be loaded, but only one at the time can be viewed on this page. The **View** page essentially implements the basic PMOD capabilities which are described in the Image Loading 62 and the Image Display 124 sections. Additionally, there are some extra functions available which are accessible by the tabs in the lower right.

Images can be loaded 103 using the **Load** button or the corresponding icon in the taskbar to the right, whereby the image format is selected using the down arrow. Similarly, images are saved 117 using the **Save** button or using the icon in the taskbar. The advantage of the latter is that a dialog window is shown to choose the image series and the VOIs list to be saved.

Enabling the **Select all** icon ✔ has the effect, that all current series and VOIs (if available) are saved when using the **Save** button. Enable the **Change Subject name** box to save the image series under a different name.

AI Segmentation and Classification shortcut buttons

With the **PAI** module licensed shortcuts to **AI Segmentation** and **Classification** become available on the **View** page, below the **Load/Save** section. The **Machine Learning** is available as an option in the **Segmentation** interface:

The Learning Sets for AI projects are prepared via the **Edit Learning Set(Training)** option in the main **View** menu:

PMOD's PAI framework aims to make training and deploying ML-based segmentation more accessible to non-expert users. PMOD's well-tested tools for image processing and traditional segmentation provide an excellent base to prepare the training data needed for supervised machine learning.

In addition to AI-based segmentation, PAI also supports **Classification** tasks. An example of classification in imaging is the assignment of a label "amyloid positive" or "amyloid negative" to

amyloid PET images for tracers such as ^{11}C-PiB. PMOD's database functionality provides the base to organise data into classes for training of a neural network. The trained neural network then returns the probability of the image to belong to a given class.

Please refer to the dedicated *PMOD Artificial Intelligence Framework (PAI)* user guide for detailed information about the learning sets preparation, prediction, classification and case studies.

Image Cropping and Interpolation

If the image field-of-view is larger than the structure of interest, the data set should be reduced in order to save RAM and optimize processing. This can be achieved by enabling the **Crop** box and defining the size of the box which appears as yellow rectangles in the image overlay. Species selection triggers pre-defined sizes for the cropping box.

Place the yellow crop box by clicking at the center of the anatomical structure of interest. The structure of interest should be fully enclosed. If this is not the case, the edge size in **[mm]** can be adjusted for each direction by selecting the size in the corresponding list. An alternative is entering the edge sizes using the button indicated below:

The button initiates cropping, whereby the original data are replaced. If cropping is not activated manually, a request will be shown when proceeding to the next step. Note: The cropping operation is irreversible and only allowed once.

With **All input series** box enabled the cropping is applied to all images available in the list.

To have a smoother appearance, an interpolation can be configured. To this end, activate the **Interpolate** box and specify the voxel dimensions in x,y and z in mm.

14.3.1   Tools

In addition to standard image viewing the PVIEW tool allows performing the following distinct operations available on the **Tools** tab:

Most functions only get active when more than one image series have been loaded into PVIEW.

Functionality:

Merge Series	*Merging a number of static image series into one dynamic study.* This function is explained in a separate section 508 .
Merge Slices	*Merging of a number of static image series in axial direction.* Activating **Merge Slices** opens a dialog window for choosing among the loaded series and changing their order. The studies selected for merging are then combined in the axial direction to form a static series with extended coverage. There are two options available for merging: **Merge one single frame study** and **Merge frame by frame**. This function is only reasonable for image series covering adjacent axial fields-of-view such as in whole-body scanning. Note that at least two studies have to be selected for merging
Rearrange Z&T	The result is a one multiframe study with a new number of slices and frames.

Average series	*Calculating the average value of each pixel across the loaded image series.* Result is the average image series, while the individual image series are removed from PVIEW.
Standard Deviation	*Calculating the standard deviation of the values in each pixel across the loaded image series.* Result is the standard deviation image series, while the individual image series are removed from PVIEW.
Average with reslicing	*Allows reslicing to a common space and averaging.* Result is an averaged image series, while the individual image series are removed from PVIEW
Split Frames	*Splitting a dynamic image series into a set of static series.* Activating the button causes PVIEW to split the current dynamic series into a set of static series (one per time frame) which can be separately displayed. If the **To disk** box is checked, the **Output Format** selection becomes active. In this configuration, a saving dialog appears when the **Split Volumes** button is activated, and the new static series are saved to disk.
Split Slices	*Splitting a 3D static image into a set of 2D static series.* If the **To disk** box is checked, a dialog window appears allowing to select the **Output Format**.
Split Beds	*Supports multiple mouse bed splitting.* Result consists of independent bed series from parts of the selected series. When activated a dialog windows open allowing to select the number of beds in the image: To save the result on the database or on the file system enable the **Directly to disk** box. IN the new dialog window configure the **Save as** and the **Output Format** and start the procedure with the split button.

The results are saved to the configured location. In the capture below is shown the result of a 4 beds split with the output format configured for the the database:

Slice Alignment	*Calculates a rigid 2D transformation between marker pairs defined on slices.*
	The first slice with valid markers serves as the reference. This function could be useful when merging slices which have been acquired separately (eg. by autoradiography of small animals) into a volume.
	Note that at least three markers on two slices need to be defined.
Frame Alignment	*Motion correction for a dynamic series with external markers (translations only).*
	Calculates the transformation between frames and corrects them based on the assumption that the maximal value contained in a VOI should remain stable.
	Note that at least one VOI must be defined (in case of multiple VOIs the first one on the list is going to be used during the correction). It is important that VOIs are in dynamic mode.

14.3.1.1 Merge Series Tool

The **Merge Series** tool allows combining image series with the same geometry into a joint dynamic series.

Activating **Merge Series** opens a dialog window as illustrated below. The list in the upper left shows the loaded image series in loading order. The list in the upper right shows the image series which will be combined into a dynamic series. Initially, all series appear in sorted by **Acq Date/time**. The

options related to applying decay correction during merging and generating the timing of the new dynamic series is located in the lower part.

Merging List Preparation

Series can be copied from left to right by double clicking in the left list, or selecting a list element and activating the arrow between the list. The double arrow copies all loaded series to the right.

The order of the **Selected for Merge to one multi-frame study** list can be modified by selecting a list element and shifting its position by the arrows to the right.

If the columns contain information which is suitable for sorting, the sorting button **AZ** can be enabled and sorting started by clicking into the column header. In the example above, the acquisition time was used for sorting the static series into the proper acquisition order.

Decay Correction Setup

When joining PET or SPECT data into a dynamic series, a consistent decay correction has to be ensured. Usually, such data is corrected to the acquisition start. Therefore, when joining static series into a dynamic series, later series have to be decay corrected to the start of the first acquisition by scaling them with a corresponding factor. The proper setting for this situation is to enable **Decay Correction**, confirm that **Source data is decay corrected**, and check that the isotope **Half Time** is correct. The zero time of the common decay correction of all series is

indicated in the **Scan Start Time** field. Note that this information is indicative only and cannot be changed. It corresponds to the start time of the first series in the **Selected for Merge to one multi-frame study** list.

Note: The decay correction should not be enabled when the isotope information is not present in the images: e.g. for nifti data the check box correction have to be switched off.

Dynamic Series Timing

The timing of the created dynamic series needs to be constructed for use in decay correciton. It can be specified using the **Create time vector based on** selection

Frames duration: allows merging the data with no reliable start time information and no gaps between frames acquisition. The time vector is created based on the frames duration.

Frames start time:allows copying information from the time vectors of the series that are merged.

Frames series time: uses the series time of the first image as the base for the time vector and uses the offset to series time of other images to obtain the start times for the other frames.

Frames acquisition time: uses the acquisition time of the first image as the base for the time vector and uses the offset to aquisition time of other images to obtain the start times for the other frames.

Please use the 🔍 buttom to inspect the time vector with the current selection. In the example below which was generated using **frames acquisition time,** there are gaps of about 40 seconds between the acquisitions. They occurred because the scanner had to be restarted for the subsequent whole-body acquisitions. Using **frames duration**, this information would have been missed.

Select the **Preview Merge (MIP)** subtab and activate the **Preview Merged** button to see the preview of the merged series:

Processing is started with the **Merge** button. Before the new series is created and optionally decay corrected, the timing is displayed in a dialog window for confirmation and editing.

14.3.1.2 Merge Slices & Stitching

The **Merge Slices & Stitching** tool allows combining in the axial direction the selected studies to form a static series with extended coverage.

Activating **Merge Slices & Stitching** opens a dialog window as illustrated below:

The list in the upper left shows the loaded image series in loading order. The list in the upper right shows the image series which will be combined into a static series with the current sorting order. Initially, all series appear in the original order.

Merging List Preparation

Series can be copied from left to right by double clicking in the left list, or selecting a list element and activating the arrow between the lists. The double arrow copies all loaded series to the right.

The order of the **Merge** list can be modified by selecting a list element and shifting its position by the arrows to the right.

If the columns contain information which is suitable for sorting, the sorting button **AZ** can be enabled and sorting started by clicking into the column header.

This function is only reasonable for image series covering adjacent axial fields-of-view such as in whole-body scanning.

Note that at least two studies have to be selected for merging.

Stitch by Origins

The procedure assumes the images have the same spatial frame of reference and merges them based on slices position. The first image in the merging list is set as reference.

The interface is organized in 3 main areas:

1. Fusion controls and source settings on the right hand side

2. Fusion display of the source images in the central viewport

3. Settings for the stitching procedure and the preview of the results on the right hand side.

CoRegister and Stitch

The procedure can be applied for two images. It consists in a matching step followed by the merging step. Two types of matching are supported: the manual matching and the rigid matching procedure. Fore detail information about the matching procedures please refer to the **Fusion** guide.

14.3.2 Batch Format Conversion

The **Convert** tab is used for batch format conversion of image series.

Begin by setting the **Input format selection** to the appropriate image format, then activate **File selection**. A dialog appears, which allows selecting the files to be converted, and to define processing and output properties as well as the **Output format**. The contents of the dialog window differs slightly depending on the selected format.

Input Files

The first step is to select the files to be converted using the **Set Files** button. In the appearing dialog window (format dependent) select all target files and close with **Set series**. As a result, the selected files are shown as entries in the **List of input studies**. **Add files** allows incrementally adding to the list, whereas **Remove** removes the selected list entries. **Save** and **Load** allow saving/loading the list of selected input files.

It is possible to apply certain operations while loading the images, for instance to bring all images to a standard orientation. When unchecking the **No loading operations** box a button named **.... format settings** becomes available and serves for configuring such operations.

Information Replacement

In the **Save as** area there are three radio buttons **No operation**, **Replace selected**, and **Replace by algorithm**.

With **Replace selected**, information on the **subject**, **Study** and **Series** level can be replaced. Select the corresponding level, edit the information in the lower part, then enable the **Replace** box.

With **Replace by algorithm**, image data can be anonymized. This function is equivalent to the Batch Anonymization .

Output Specification

The target file format can be selected with the **Output Format** choice. Each format requires different detail configurations. For the **Database** format used above the target database needs to be selected, whereas for the **DICOM** format below the output directory needs to be defined and options for filename creation are available.

After activating **Start Conversion**, PVIEW reads, converts and saves the selected series in the prescribed manner.

14.3.3 Batch Anonymization

The **Anonym** tab is a dedicated version of the batch format conversion which enforces de-identification of the input images. See the description above for an explanation of the working procedure.

ANONYMIZE brings up the configuration dialog window below.

De-identification of the images is performed according to <u>DICOM PS3.15 Annex E</u>. It implements the E.2 "Basic Application Level Confidentiality Profile" intended for use in Clinical Trials. It is extremely conservative and removes all information related to identity and demographics of the subject, his family, personnel and the organization. The following options allow keeping a part of this information.

Id / Name	This option is useful if subject name and id were already replaced and should be kept.
Keep dates	Check enabled corresponds to "Retain Longitudinal Temporal Information with Full Dates" in section E.3.6 in the Annex. In this case the dates are not modified. Check disabled corresponds to "Retain Longitudinal Temporal Information with Modified Dates". In this case the dates and times will be changed in such a way that calculations such as SUV still work and the temporal relation between longitudinal acquisitions should still be maintained.
Keep subject characteristics	Check enabled corresponds to "Retain subject Characteristics" in section E.3.7 in the Annex and concerns information about sex, size, age, status. Without this option, SUV calculation will not be possible.
Keep save private fields	Private elements considered as safe in DICOM PS3.15 Annex E or indicated as safe in the object will be kept.
Deface	Removes facial features from the image.
Create name mapping file	With this option the export procedure generates a text file *deident.map* which lists the original names/IDs with their replacement values. Note that a hashing procedure generates the same values if the names and IDs are consistent among studies.

Original name	Replaced by	Original ID	Replaced by
PKIN1	1404078708	Dyn. CPFPX bolus & MRI	1861520522
PKIN1	1404078708	Dyn. CPFPX bolus & MRI	1861520522
PKIN1	1404078708	Dyn. CPFPX bolus & MRI	1861520522
PKIN2	1114056224	Dyn. DASB without blood & MRI	984611690
PKIN2	1114056224	Dyn. DASB without blood & MRI	984611690
PKIN2	1114056224	Dyn. DASB without blood & MRI	984611690
PKIN3	1837605584	Dyn. FDG scan with whole blood data	410510312
PKIN3	1837605584	Dyn. FDG scan with whole blood data	410510312
PKIN4	1973782262	Dyn H2O brain scan, Baseline	591072104

14.4   Volume-of-Interest Analysis - Page 3

The purpose of the **VOIs** page is to support Volume-of-Interest analyses on the currently loaded image series. This functionality is described in detail in a previous chapter 213.

14.5   Statistics - Page 4

It is the dedicated page where the last calculated statistics results are permanently available. The statistics are obtained activating the **Statistics** or **Hist** action button on the **VOIs** page.

The page displays the:

- Selected statistics results for the selected image and VOIs when the **Statistics** red action button is activated on the **VOIs** page . It shows time activity curves for dynamic images (details available in the Time-Activity Curve Generation with Statistics 342)

or regional values for 3D images (details available in the Statistics Viewer 327):

- Histograms for the selected image and VOIs when the **Hist** red action button is activated on the **VOIs** page (details available in the Histogram 330).

The **Compare** red action button allows proceeding to the **Compare** page for comparing images.

The **Hybrid** red action button allows proceeding to the **Hybrid** page for an images fusion acquired on a hybrid system. Note that it fuses the images available on the first two rows in the **Compare** page.

14.6 Compare - Page 5

After images have been loaded, the user can switch to the parallel image viewing page by selecting the **Compare** tab. PVIEW now shows three horizontal image display layouts. There are two display modes available, regular image display, and image fusion.

Regular Image Display Mode

The example below illustrates the regular image display mode, whereby each of the studies may have an independent layout. Note the **Synchronize** (for *Synchronize compare display 1,2,3*) and **Color** boxes highlighted in red. If they are checked, PVIEW switches all three rows to the same layout and synchronizes the images shown. This will only be successful for studies which have the origin at the same location and which cover the same image volume (the pixel size, however, might differ as in the case of a PET/CT study with the same reconstructed field-of-view).

Image Fusion Display Mode

In the fusion display mode the studies in the upper two rows are synchronized, while the third row shows the fusion image. As for synchronized image comparison, the studies must have the origin at the same location and cover the same image volume.

A PET/CT example is shown below.

In the fusion mode all fusion renderings [201] are available to prepare a meaningful fusion image.

The manual rigid matching procedure is available with the fusion modality set. To adjust the alignment of the two images by rotation and translation the reslicing pane need to be activated in the second row. Reslicing is defined by a transformation consisting of translations in all directions, rotations about all axes, and potentially scaling along the axes. Each of these transformation components has its own sub-pane: **Move**, **Rotate** and **Scale** respectively. See further details here [192].

Additionally, by activating the **Hybrid** tab it is possible to bring up a larger display of the active fusion image.

Fused Image Saving

The fused images can also be saved using the Capture button on the Capture panel. A dialog window appears for defining the format of the RGB images.

The **DICOM** output is of particular interest because with the **All slices** option it can create a full volume of fused images which can be saved for archival in a PACS system and inspected with any reviewing workstation. With the File the DICOM SC images are saved to disk, whereas the C-Store option supports direct network transfer to a DICOM server.

Switching the Display Mode

The display modes can be switched using the button close to the right lower corner, which changes according to the situation.

	Selects the image fusion mode.
	Selects the regular image display mode with independent series.
	Sets the third row to blank.

14.7   Image Hybrid - Page 6

The fusion images in the third row of the **Compare** page are relatively small. To investigate them closer please select the **Hybrid** tab which shows a page with just the fusion image and the image controls.

To adjust the color of the studies, either of the tabs **Source A** or **Source B** must first be selected. To show different studies on this page, please go back to the **Compare** page and display them in the upper two rows, then switch again to **Fusion**. All fusion capabilities are available, and the fused representation can be saved in JPEG or in DICOM format.

> **Note:** In contrast to the image fusion tool it is not possible to outline VOIs directly in the fusion images. Selecting the VOI button just switches the display back to the **VOIs** page.

14.8   Creation of a DICOMDIR File

The DICOMDIR file format has been defined to organize the access to off-line DICOM part 10 files. For instance, DICOM-compliant data CDs contain a DICOMDIR at the root level which contains a description and access information for all the studies on the CD. In PMOD, the DICOMDIR similarly describes the DICOM files residing under a root directory, eg. *Pmod4.4/data/dicom*. This file can be maintained by PMOD's DICOM server which updates the information after receiving and storing new images (see also the PMOD DICOM Functionality 39).

The PVIEW tool has a handy function to create a DICOMDIR file which registers all DICOM files contained in a directory tree (see also the section DICOM Part 10 Data Loading 105). This function is called by the **Create Dicomdir** entry in the menu **View** and opens the following dialog.

The **Change Folder** opens a file browser to select the root directory of the tree containing the DICOM files to be registered. When **Gather statistics** is activated, all files in the directory tree are analyzed, and the information in the **STATISTICS** section updated. However, to really create the DICOMDIR file, the **Create** button must be activated. Using **Load from DICOMDIR**, the DICOM Part 10 Data Loading 105 window can directly be opened for selecting images.

15 PMOD Disclaimer

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