Cardiac PET Workbook Version 3.8

Scope and Intended Use

This document aims at illustrating PCARDP operation for the quantification of dynamic cardiac PET data. It presents a step-by-step description of the analysis of a $^{13}$N-ammonia heart perfusion scan. Recommendations, tips and detailed explanations are included in each section of the workbook. Note that bold face is used for indicating strings corresponding to elements in the user interface of PCARDP.

Copyright and Disclaimer

The example data which are used for the exercises are available in the standard Pmod database. This database is available for download. The data are by courtesy of the Nuclear Medicine Department, University Hospital, Zürich, Switzerland. Note that the original data have been processed and optimized for training purposes.

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Introduction

The cardiac PET modelling tool, PCARDP, represents a flexible environment for the quantification of myocardial PET studies. The user is guided through the different processing stages in a streamlined workflow organized in different pages:

Different analysis scenarios are supported: the processing of the dynamic PET studies of the heart, the processing of static PET studies and the processing of gated studies. There is a main configuration switch in the lower status line for switching between the gated and non-gated mode.

The aim of this document is to guide the user through the quantification of cardiac perfusion PET studies using the $^{13}$N-Ammonia tracer. For the other two scenarios please refer to the PCARDP documentation.

PCARDP Processing Overview

Dynamic perfusion PET series are quantified using the following sequence of processing steps.

- Calculation of anatomical images representing blood volume (BLOOD) and myocardium (MYOCARDIUM) from the dynamic uptake series. Depending on the tracer, early and late images are averaged. These images are used for definition of the cardiac segments.
- Cropping of the images to remove background and geometrical reorientation such that the images appear in short-axis (SA) orientation.
- Definition of segments of the myocardium given by the American Society of Nuclear Cardiology (ASNC) or the American Heart Association (AHA).
- Calculation of blood time-activity curves (TAC) from the left ventricle (LV), the right ventricle (RV), as well as from the segments.
- Fitting of adequate kinetic models to the TACs to quantify the tissue perfusion.
- Calculation of parametric MBF maps (for NH3 data only).

Automatic procedures support several processing steps such as short-axis (SA) reorientation of the images and myocardial segmentation, but the user should check their performance and interactively correct the outcomes, if required. In the case of rest/stress perfusion studies, both PET series can be processed in parallel and the coronary flow reserve (CFR) calculated. The results are summarized in comprehensive reports, and can be exported numerically or in standard report formats.

PCARDP Data Processing

1. Configuration

The PCARDP tool can be applied for the quantification of a broad range of tracers. Depending on the tracer, the results represent myocardial blood flow (MBF) or a metabolic turnover such as the metabolic rate of glucose (MRGlu). The configuration of the data processing should be adjusted accordingly to make sure the right model is applied and the workflow is as smooth as possible.
The analysis will be demonstrated using the data set **PCARD1** which includes dynamic ammonia PET acquisitions at rest and pharmacological stress. The duration of each scan is 4 minutes.

Please start the PCARDP tool with the **Cardiac PET** button from the PMOD ToolBox.

Access the configuration with the configuration button in the status line at the bottom. An alternative is to adjust the configuration in the status line which also opens the configuration window. The following settings are recommended.

**1.1 Heart Model Type**

To begin select the **HUMAN Heart model type** such that the appropriate heart size is used in the automatic procedures. The **Long axis apex to base length** and the **Base radius** values are species sensitive. The default parameters can be changed in the case of a gross mismatch with the data.

**1.2 Tracer Configuration**

The tab selected in the window defines all the processing. Activate the **NH3** tab which corresponds to the data at hand and select the **Card. NH3 (de Grado)** model for the quantification. This 1-tissue compartment model with metabolite correction is suitable for the analysis of ammonia data dynamically acquired during 4 minutes after tracer injection. Note that in scans of longer duration data after 4 minutes is disregarded in the modeling.
Enter 0 and 40 into the **Blood Average Parameters** fields to average the first 40 seconds of uptake while blood is presumably in the ventricles, and apply a **Smoothing** of 6 mm. Enter 120 into the first field of **Myocardium Average Parameters** and select **End of Study** as **End time** for averaging the uptake from 2 minutes until the end of the study. Set also a **Smoothing** of 6 mm. In the **Blood * Factor[1/1]** field enter 0.05 to subtract 5% of the blood activity for making the cavities clearer. Note that myocardium averaging should be restricted to the frame range which is also used for modeling.

The purpose of averaging the early (BLOOD) and the late frames (MYOCARDIUM) is to obtain images with optimal anatomical information to be used for the short axis (SA) reorientation and myocardium detection. Their quality has a direct impact on the automatic procedures, and manual adjustments are also easier with clear images.

For the current processing outline please disable the **Calculate Pixelwise Parametrical MBF Map** checkbox. This feature is only available for the ammonia tracer.

When both STRESS and REST studies are analysed in parallel the results can be compared in terms of coronary flow reserve (CFR). In the **Modeling Results** panel set the **Compare Type** to **RESERVE(S/R)**. With this choice the perfusion reserve is calculated by dividing the segmental perfusion values at stress by the corresponding values at rest.

In the **Run Automatically** section it is recommended to remove the checks of all boxes because the fully automatic procedure usually only works for well-behaved data sets:

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**1.3 Contouring and Segmentation**

The myocardium definition and the sampling mode are configured in the **Myocardium TACs Generation & Segments Definition** panel:

PCARDP implements two main options for the myocardium detection procedure: the myocardium centerline and the EPI/ENDO methods. The **Centerline** detection is done by fitting a geometric model of the left ventricle to the Myocardium images and then adjusts it locally according to the tracer uptake pattern. The resulting outlines are shown as contour lines in the SA image. This procedure works reasonably with images showing most parts of the myocardium, but may result in a distorted shape in the case of severe defects. In that case, markers can be set into the myocardium to guide the model fitting process. The **Epi/Endo** method is based on the **Centerline** detection. A normal vector is calculated for each vertex of the myocardium centreline, and the epi and endo contours generated in a distance of half of the heart wall thickness.
The **Epi/Endo active model** method adds an additional step. The contours generated by **Epi/Endo** serve as starting condition for an iterative adjustment to the local intensity of the **MYOCARDIUM** image using the active models approach.

For quantification of the myocardial function the PET signal of different area of the heart (the segments) is averaged. **PCARDP** uses polar sampling for detecting myocardial activity by using radial and conical profiles as illustrated below:

![Profiles](image)

There are two different modes for determining the location of the myocardium along the sampling rays:

**Radial Maximum:** In this mode the maximum value of the **MYOCARDIUM** image along the profile determines the sampling location. The search is confined within a window around the centerline which represents the defined wall thickness, or by the epi/endo contours.

![Radial Maximum](image)

**Model Crossing:** In this mode, the intersection of the profile with the centerline defines the sampling location. With the epi/endo definition, the center between the contours is regarded as the centerline. **Radial Maximum** is recommended if there is reasonable uptake in tissue, while **Model Crossing** allows the user to tightly control the sampling, at the cost of having to exactly define the contours.

With the “**Averaged on ..**” variants more than a single sampling point is determined: the left/right and the inner/outer neighbors will also be included. The suitability of averaging is very dependent on the pixel size. It should only be applied with pixel sizes up to 2 mm to avoid including signal from outside the myocardium.

For the creation of the segmental TACs the subdivision of the heart area into tissue patches is relevant. Usually, the 17-segment AHA definition is applied as illustrated below. Correspondingly, every sampling point determined by the polar sampling is sorted into one of the 17 segments, and the signals of all sampling points in a segment are averaged to generate the segmental TACs.

The sampling in the apex is quite delicate because often no clear uptake is seen in the image. A likely reason for this effect is the reduced wall thickness of the tissue from 8-15mm down to 2mm, combined with the motion due to contraction and breathing.
Set **Segmentation type** to **Epi/Endo outline**. Set **Polar sampling** to **Radial Maximum** so that the maximal uptake value in the myocardium during polar sampling is used. Set **Wall thickness** to **20 mm** which restricts the search for the maximum within a 20 mm neighbourhood of the contour. Select the **AHA(17)** definition for calculating the results in the 17 standard cardiac segments. Close the configuration window with **OK**. The program is now prepared for processing the dynamic ammonia data of the PCARD1 example data.

### 2. Reorientation Page

The **Reorientation** page serves for loading the images, generating **BLOOD** and **MYOCARDIUM** images, transforming the images into standard SA orientation, outlining the myocardium and calculation of the segmental TACs.

On the **Reorientation** page, under the **Load STRESS** and **Load REST** sections, there are three buttons with check boxes to the left.

- **Sigma**: Button to start the cropping/averaging process for calculating the **BLOOD** (average of some early frames) and the **MYOCARDIUM** images.
- **Circle**: Button to start detection of the **Short Axis (SA)** orientation based on the **BLOOD** and the **MYOCARDIUM** images.
- **Rectangle**: Button to start detection of the myocardial centerline or the epi/endo boundaries. This is done by fitting a geometric model of the left ventricle (LV) shape to the **MYOCARDIUM** image and adjusting it locally to the uptake pattern. The results are shown as contour lines in the images.
A check means that the automatic processing is started as soon as the preceding step was finished. In the configuration above, the automatic reorientation will be run each time the averaging has been performed.

2.1. Data Loading
On the DB Load page, select patient PCARD1. In the Series list two entries are shown, NH3, Rest and NH3, Stress. Select the Add all button to get the series to the Selected for loading section. Note that the ordering is important: the upper entry in the list should always be the Stress series, and Rest the lower. By enabling sorting and clicking into the column header the list order can be changed.

Select Open for loading the data. The images are loaded on the Reorientation page.

2.2. Cropping and Revision of Frame Averaging for the Generation of the BLOOD and MYOCARDIUM Images
Depending on the field-of-view of the scanner and the reconstruction settings, the heart may only cover a small fraction of the image volume. In order to ease processing it is recommended using a cropping procedure for restricting the image volume to the heart. Ideally, however, cardiac PET images should already be reconstructed with limited field-of-view centered at the heart, and with pixel sizes in the order of 2 mm.

In order to generate optimal BLOOD and MYOCARDIUM images the series with better quality should be loaded. In this example the REST study is used, so select the corresponding button. A dialog window appears which allows specifying interactively a cropping window as well as the averaging ranges.
The upper part of the window shows the average of all frames. If the **Crop in box** check is enabled, a cropping volume is also indicated by a yellow sphere. The center of this sphere can be placed by clicking, holding and dragging the handle. Before proceeding the sphere should be placed such that the whole heart is included in the box and enough margin is allowed for the SA reorientation. To set all the pixels outside the cropping box to zero enable the **Mask** checkbox.

With each click into the image an average time-activity curve (TAC) is calculated and shown in the lower curve panel. The sampling is performed by averaging the signal around the triangulation mark with a configurable **TAC probe size**.

The two shaded area overlaid on the TAC represent the time ranges for frame averaging. First click into the blood pool of the LV. The TAC curve should show a clear initial peak. Adjust the left area by dragging with the mouse so that the peak is enclosed. Next click into the LV wall to generate a myocardium TAC. Adjust the right shaded area to cover the relevant portion of the late uptake. If modeling uses only 4 min of the data, the myocardium averaging should not extend past 4 min to avoid mismatch. Finally check that the crop box is placed properly.

The operation button to continue is located in the lower left. It changes the naming according to the enabled options. With all options enabled (recommended) the button is labeled **Crop/Timing/Averaging**. When it is activated, the images are cropped and an intermediate dialog window is shown if the **Direct** checkbox is disabled:

The settings displayed for the averaging operation correspond to the definition of the shaded ranges. Upon confirmation with **Yes**, the averaging is performed as prescribed. Because the “automatic” checks for the SA reorientation is on, this step performed after the averaging. At the end the reoriented images are shown. The BLOOD and MYOCARDIUM images can be inspected by switching the series selection as illustrated below.

![Confirmation dialog](image)

2.3. Short Axis (SA) Reorientation

The aim of the SA reorientation is to bring the anatomical images into the well-defined LV position illustrated below. It is important that the right ventricle (RV) RV is to the left in the axial SA images, the axes are horizontal and vertical, and the rectangle is centered in the left ventricle (LV). The successful result of the automatic orientation in the REST study is shown below:
If the automatic reorientation result is not satisfactory start manual reslicing with the \[ \text{\textcopyright} \] button to optimize the orientation. Adjust the rotation angles and bring the rectangle into the LV center using the reslicing handles. Drag the filled white square for rotations, and the open rectangle for translations.

If the orientation is completely off, use the \[ \text{\textcopyright} \] button to initialize the reorientation. This operation corresponds to bringing a heart with “average” rotation angles relative to the patient axis into SA orientation. Then finalize the reorientation interactively as described above.

Often, the orientation of the Rest and Stress scans is very similar. Therefore, e.g. the Rest SA orientation is a good starting point for the Stress series. It can be easily transferred by the small arrow above the checkbox of the “automatic reorientation” button \[ \text{\textcopyright} \]. Note that this is only possible after the cropping/averaging has already been done on the other study.

### 2.4. Contouring of the Myocardium

The automatic contouring process requires sufficient anatomical information in the myocardium and blood images and a proper SA orientation. The program tries to find a VOI in the right cavity (RV VOI), in the left cavity (LV VOI), and according to the configuration the Epi/Endo contours of the myocardium (Myo). It is started with the \[ \text{\textcopyright} \] button and takes a while. First, a heart model is fitted to the image, which is then adjusted locally. The green buttons indicate that VOIs have been successfully found for all the structures.
In the process of verifying the outlining switch the images also to BLOOD. In this way locations can be detected where the contours reach into the blood volume. An example of this problem is shown below for the REST study where the EPI contour goes into the RV:

To modify the behavior of the automatic outlining the user may add landmarks indicating the location of the myocardium. The button \( \text{Set} \) starts the marker placement procedure. As soon as the \textbf{Set} button on the appearing markers panel is enabled, each click into the images places a marker which is considered being located in myocardium. Markers should be placed in different locations of the LV, both across planes and angles. Misplaced markers can be dragged with the mouse or deleted with the \textbf{Remove} button. The easiest way to triangulate the images at different locations without placing markers is to hold down the \text{Ctrl+Shift} keys while clicking. Another way of changing the anatomical location is to place the cursor over an image (SA, VLA, or HLA) and scroll slices using the mouse wheel.

After placing enough markers retry the outlining with the \( \text{Set} \) button. It should result in contours closer to the markers.

Note, however, that potentially the BLOOD and the MYOCARDIUM images may not be exactly aligned, since they are offset in time and the heart or patient may have moved. The alignment of the two images can be inspected with the \( \text{Set} \) button. It opens a fusion tool with the MYOCARDIUM loaded in the first row, BLOOD in the second row, and their fusion in the third row. In the REST study illustrated below the alignment seems quite good:
The definition of the apex is often relatively difficult. In some cases the contours are quite reasonable, but in the HLA and VLA views they seem shifted slightly towards the base. A solution which can be tried in such a situation is to shift the images, rather than the contours. To do so, enable reslicing with the \( \text{Reslice} \) button and drag the images until the contours fit. Take care to avoid rotations by only dragging the open rectangle or using the increment buttons in the Move panel.

At the end of these operations there should be sufficient confidence that the contours describe the LV myocardium EPI/ENDO appropriately.

**Manual Contour Editing**

If it is not possible to find a solution with an appropriate EPI/ENDO definition in all SA slices, the contours can be interactively edited. To this end select the button which opens the VOI tool with the Myocardium VOI selected.

Note that initially the SA slice images are shown, and the “VOI action” \( \text{Scale} \) mode is active. This means that you can grab any edge of the enclosing bounding box and drag to scale the whole VOI. To change only the contour of the current slice, select the “ROI action” \( \text{ROI scaling} \). VOI scaling followed by ROI scaling is often sufficient to rectify the contour, particularly if the Radial Maximum sampling is used. Alternatives for changing the contour shape are using the \( \text{Move} \) tool and shifting individual vertices by mouse dragging, or using the “hammering” \( \text{Hammer} \) tool and dragging against the contour. It is not recommended to delete the contour and draw it from scratch, but this would also work. If something goes wrong, remember that there is an Undo history available via the \( \text{Undo} \) button to go back to earlier states of VOI definition.
It is in principle possible to start the VOI definition from scratch without using the result of the automatic outlining. However, this approach has drawbacks in the further processing. Therefore it is highly recommended to try using the automatic approach first and getting at least an approximate solution which can be manually adjusted.

In difficult cases it may also help to define the VOIs in the better of the Rest/Stress series, and then copy the contour to the other series using the small arrow left to the "contouring" button. This should provide a reasonable starting condition if the SA reorientation was done with a similar transformation.

After completing the VOI definitions for REST and STRESS select the Modeling button in the lower right to start the TAC generation process. The full DYNAMIC study is resliced into the short axis orientation and interpolated, so that the range from the apex to the base is covered by 22 slices. At the same time, the data set is truncated to a box enclosing only the heart. These operations are also applied to the BLOOD and the MYOCARDIUM data sets. Next, the blood time activity curves are calculated in the LV and RV VOIs. Finally, the time-activity curves in the different myocardial sectors are calculated according to the segmentation model defined in the configuration, and the program switches to the next page Kinetic Modeling.

3. Kinetic Modeling Page

The Kinetic Modeling page serves for kinetic modeling as well as inspection, evaluation and saving of the results.

Usually the fitting of the TACs with a kinetic model is not critical. Therefore, background fitting can be enabled by checking the Auto boxes on the Kinetic Modeling page.

With this setting, PCARDP starts model fitting in the background immediately after completion of the TAC calculations. The model TACs and the parameters are returned and then shown on the Kinetic Modeling page for inspection.
3.1. Interactive Kinetic Modeling

If there is a need to look into the kinetic modelling process the Auto checkbox should be disabled. Consequently the STRESS and the REST buttons have to be individually activated to start the fitting.

Select the REST button. A dialog window appears.

Enable the box Show Kinetic Modeling Tool. With this setting the PKIN tool will be shown with the current cardiac TACs loaded, and modeling can be performed interactively. Otherwise, fitting will be done in the background and the result parameters returned assuming the fitting was ok. The Model selection allows switching among the models appropriate for the loaded data. Below the Model the initial model parameters are shown. They can be edited, for instance to set the perfusion value from the default 1 ml/min/g to 2 ml/min/g for the stress study.

Select the Yes button for starting interactive kinetic modeling. The PKIN dialog window opens, with the model Card. NH3 (de Grado) selected. With the Region list selection, switch to the TOTAL MYOCARD region which represents the average of all sampling points. If it is not available at the end of the list (because it was not configured) use another region, preferably not the apex which is often very noisy.
Activate **Fit current region** to fit the model to the measurement. The blue model curve should follow the green measurements reasonably well in the upper curve area. Inspect also the %SE column to the right of the parameters which shows their standard error. Use **Fit all regions** for fitting all TACs, and the arrow buttons for browsing through the regions. The agreement between the measurement and the model curve should be satisfactory in all regions. Otherwise, try to improve fitting by interactively changing the initial parameters, or masking outlier measurements. Use **Ok** to return to the PCARDP program and return the fit parameters. **Cancel** will discard the fitting result.

### 3.2. Inspection of the Modeling Results

Kinetic modeling returns the final quantification results. Processing is complete, and the reports can be shown and printed. However, it is recommended to inspect the results to ensure that all processing steps were successful.

It is important to remember that the result of perfusion quantification by kinetic modeling is crucially dependent on the input curve, i.e. the LV TAC. If the input curve is scaled, all resulting flow values will be scaled in inverse proportion. As a consequence, scaling the Rest or Stress input curve evenly scales the CFR in all segments.

Therefore, inspection of the LV curves is important. This can be easily done by selecting the **STRESS Input** and **REST Input** tabs on the **Modeling** page. The input curve should be in a reasonable relation to the uptake in the myocardium. Furthermore, it is important that the scan was started early enough so that the entire shape of the input curve was sampled. Additionally, the frame duration must be short enough so that the initial uptake dynamics can be resolved.

In the example below it is obvious that the LV curve (light blue) in Stress is much smaller relative to the segmental TACs compared to Rest. Consequently, Stress flow must be significantly higher than rest flow, resulting in a substantial overall CFR value.

An input curve will be scaled towards lower values if its LV VOI is not placed completely within the blood volume. The LV VOI is automatically placed as a function of the LV model: it consists of circle ROIs which are centered within the basal part of the LV model. If this is not adequate for some reason, the input curve will be wrong. In this case the LV VOI should be manually edited as described in the previous section.
Also available on the **STRESS Input** and **REST Input** tabs is the result of radial sampling in the form of the raw data polar plots. Use the time slider to inspect the uptake pattern at different acquisition times.

Click at different locations into the polar plot. The images to the right are triangulated at the corresponding sampling point. Note that the image content can be switched with the indicated red rectangle for assessing different types of information.

This mechanism works similarly with the results polar plot on the **Parameters** tab:

By clicking at the segment in the polar plot, the corresponding TAC and its quantification result is brought to the left panel, while the images in the display to the right are triangulated by the blue lines.

### 3.3. Sampling points

The locations determined by the sampling algorithm can be visualized activating the 3D rendering button (only available if the P3D tool has been licensed). In this example case the sampling points are represented by spheres and shown together with the EPI/ENDO contour models which are rendered as a surface objects (see below). Planes with the uptake information can also be shown.

To demonstrate the difference between the sampling methods activate the “configuration” button and set **Polar sampling** from **Radial Maximum** to **Model Crossing**, then close the configuration window with **Ok**. Consequently, the **Kinetic Modeling** page is cleared. On the **Reorientation** page activate the **Modeling** button and visualize at the sampling points in 3D again. They are now exactly centered between the EPI and ENDO contours. Therefore it is recommended to select **Model Crossing** in cases where the sampling should be manually controlled, for example with perfusion defects in the neighborhood of liver uptake.
3.4. Reports and Results Saving

After inspection has confirmed validity of the analysis, different types of reports can easily be generated separately for the STRESS and REST studies. Additionally, data can be saved for processing in external tools, or for exact repeating of the performed processing. All required information is available on the Kinetic Modeling page.

On the Kinetic Modeling page select the STRESS Report entry of the list. It opens a report window with three pages: the first page shows all fit parameter values, the second page displays the segmental TACs while the third page presents 30 slices of the selected image in SA orientation.

The report can be annotated, a Comment added, and the final version printed with the Print (All pages) button. Use the Save Results entry of the list for saving the parameter values numerically to a text file which can easily be loaded in a program such as MS Excel.

Use the Compare button on the Kinetic Modeling page for combining the Stress and Rest results and for calculating the reserve outcome. The program switches to the Compare page.

4. Compare Page

The Compare page serves for inspection and saving of the combined results. By default, the STRESS results are displayed on the upper row while the REST results are on the lower row.

The polar plots are shown together with the values that they represent. Select the RESERVE in the list selection to switch to the reserve information.
Note that the Reserve was calculated as the Stress/Rest ratio according to the configuration setting.

Select the **Save Results** button to save the numeric data to a text file for external processing purposes.

Select the **Compare Report** button to create the main report which summarizes the Stress and Rest results. It shows a comprehensive report window with two pages which can be annotated, printed and saved as usual. The main page is illustrated below.
Because the processing of a data set in PCARDP is quite involved and later inspection may be required, it is highly recommended to save not only the quantifications results, but also all auxiliary information such as the SA transformation and the VOI definitions. This can most easily be achieved by saving the processing state as a “protocol” with the **Save Protocol** button.

Select the **Save Protocol** button and save your work using the name of your choice, for example **RadialMaxEE**. Activate the **Load Protocol** button, and in the appearing window select **RadialMaxEE** protocol, then **Retrieve**.

![Protocol dialog window](image)

The dialog window illustrated above appears. With the default settings the analysis will be exactly reproduced. To test the analysis with a different model, change the model configuration with the **...** button and remove the check of the **Model and model Settings** box. Activate **Run Protocol** to start processing from scratch.

### Concluding Remarks

The quantification of dynamic cardiac PET data is a complex task with several potential pitfalls. Accurate results can only be obtained, if the heart did not move “too much” during the acquisition. This should always be inspected using the dynamic images in SA orientation. Only under this premise should the methodology in PCARDP be applied.

Although PCARDP embodies automatic approaches, the outcome always has to be carefully inspected and corrections applied if necessary. This will require understanding of the principles and mastering the tools of PCARDP, but with growing experience the processing will deliver reliable results as documented in several publications.