User's Guide

PMOD Pixel-wise Modeling (PXMOD)

Version 3.6

PMOD Technologies

Printed on 15 October, 2014

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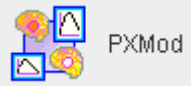
Pixel-wise Kinetic Modeling Tool (PXMOD)

The PMOD pixel-wise modeling tool (PXMOD) is aimed at the quantitative analysis of functional studies, mainly with Positron Emission Tomography (PET) or Single Photon Emission Tomography (SPECT). Such studies typically result in a sequence of images which monitor the uptake and distribution of an injected tracer over time. The image pixel values represent the average tracer activity concentration in tissue (TAC) throughout the acquisition.

The PXMOD tool provides a set of models which can be applied to each pixel-wise TAC. When a suitable model is chosen, the resulting model parameters quantify a physiologic process such as perfusion or glucose consumption, or a quantity such as the receptor binding potential. Functional maps are created by assembling images from the result parameter values in the individual pixels.

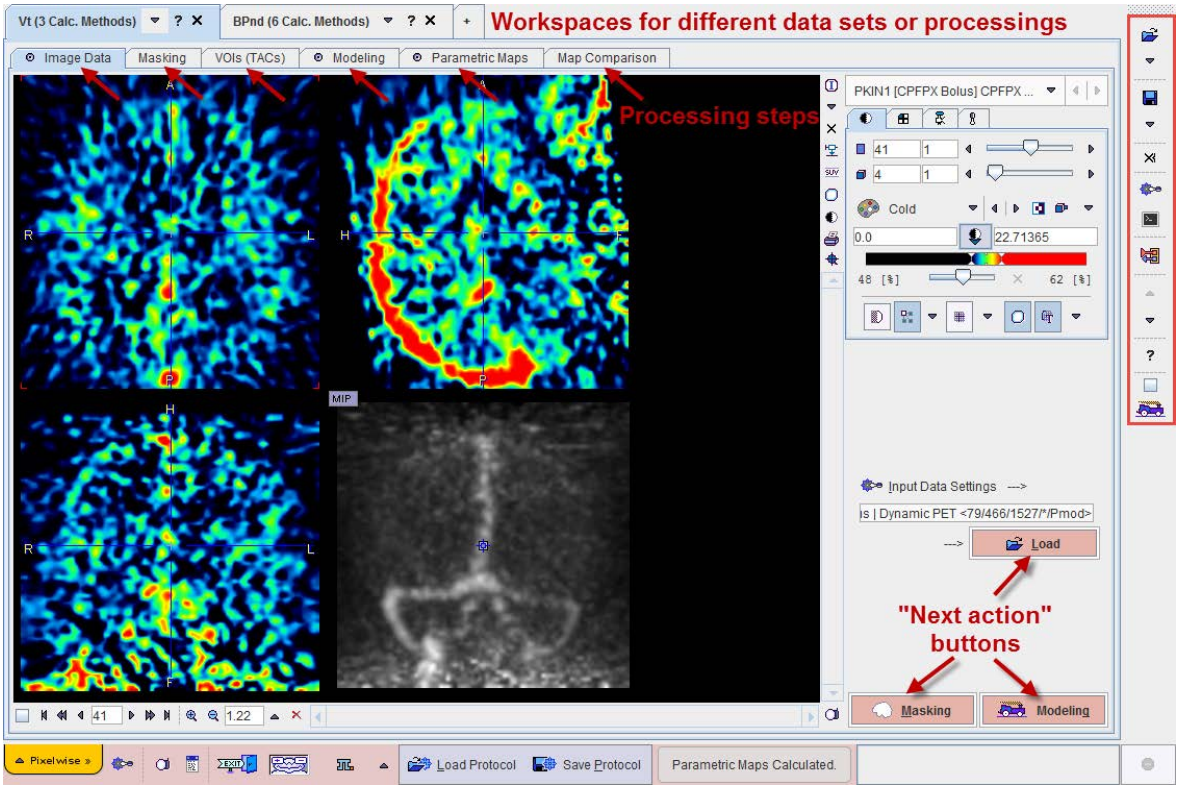
Starting the Pixel-wise Modeling Tool

The pixel-wise modeling tool is started with the **PXMod** button from the PMOD ToolBox



or by directly dragging an image file onto the above button.

The PXMOD user interface is organized as shown below after a data set has been processed using the **Vt (3 Calc. Methods)** model. Note the workspace tabs which allow to work on multiple data sets in parallel. To the right there is a taskbar available providing shortcuts to important functionality.



Step-by-Step Processing

PXMOD data processing is based on a step-by-step approach, whereby each step is performed on a separate pane. Once a processing step has been performed, the user moves to the next step using a red action button located in the lower right workspace corner. To go back to a previous step, one of the prior panes can be selected by its tab. If the tasks for all steps have been configured appropriately, the button in the taskbar can be used for a complete re-processing.

In contrast to earlier versions of PXMOD the use of transient data is not supported any longer. Rather, information pieces created during the processing session such as masks or volumes-of-interest (VOIs) need to be saved before they can be applied. Therefore, at the end of a processing session, it is always possible to save the whole processing configuration into a protocol file. The protocol allows to exactly recall all data processing elements for examination, or to repeat a processing with some changes.

Taskbar

The elements in the taskbar have the following functionality which is always directed to the currently selected workspace:

Load input image data. The arrow below the load button is used for switching among the available image formats.

Save all parametric maps. The arrow below the load button is used for switching among the image formats which can be used for saving.

Close all input and result images of the selected workspace.

Open the batch mode facility.

Send the blood data and all TACs used in preprocessing to the general kinetic modeling tool PKIN (Option).

Switch to the previous/next model configuration in the models list. The list order can be changed in the users configuration facility.

Show a short help information for the currently selected model.

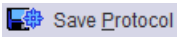
Open a dialog window with the configuration of all processing steps.

If this box is checked, the pixel-wise processing is restricted to the slice currently shown on the **Image Data** page.

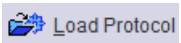
With this button, all intermediate data in the workspace are cleared, and then all processing steps including data loading performed using the current configuration.

Protocols

The complete processing configuration can be saved/retrieved with the corresponding buttons in the status line.



Save the processing session of the selected workspace as a PXMOD protocol file.

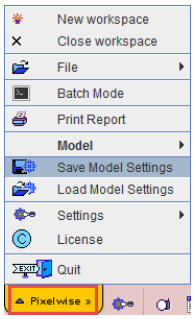


Load a PXMOD protocol file (aka configuration settings file) to restore a prior processing session.

The following sections describe how data is step-wise processed. The models themselves are explained in a separate ***section*** (on page 39).

Menu Entries

The PXMOD Menu **Pixel wise** contains the following functions.

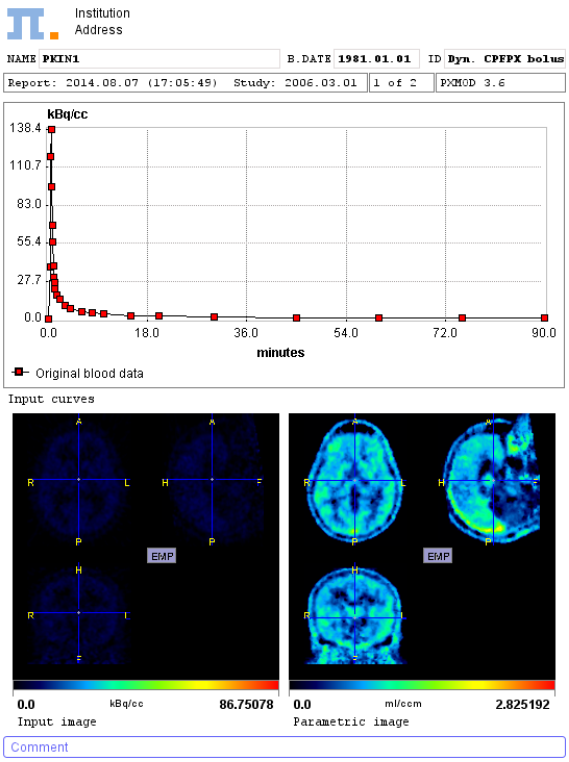


The **New workspace** entry allows adding a new page to the user interface for processing another data set without overwriting the existing data, or for processing the same data with some modifications. The latter is very easy because the configuration of the current workspace is inherited when creating a new workspace. If a workspace is not used any more, it can be removed by the **Close workspace** entry.

The **File** entry allows loading the different files required for a processing, and saving the results. By loading a data set, the data definition in the related configuration page is updated.

Batch Mode can be used for processing a series of prepared protocol files which may take significant computation time as described ***below*** (on page 38).

Print Report shows a report page as illustrated below which can be annotated, saved and printed.



Model provides the list of available models. Selecting a model will change the configuration of the currently selected workspace.

Save Model Settings and **Retrieve Model Settings** as well as the **Settings** items the are used to work with protocol files as described ***separately*** (on page 36).

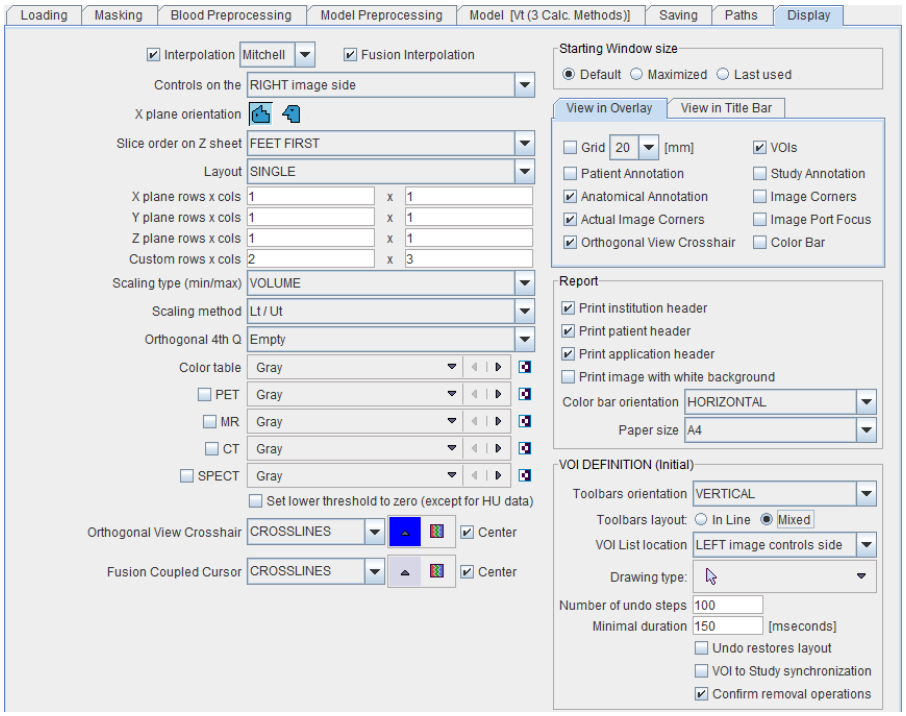
Finally, the **License ID** is used for displaying license information, and **Quit** to close PXMOD.

PXMOD Tool Configuration

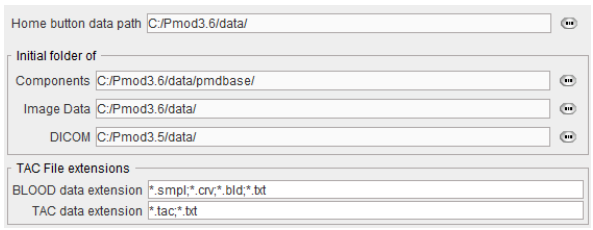
Layout and Appearance

The default appearance of the PXMOD tool can be changed using the menu **Pixel wise/Settings/Modify** entry or the configuration button in the status line.

The appearing dialog window has several tabs. The first tabs are identical with the configurations for data processing described ***below*** (on page 37). The additional **Display** panel is illustrated below and serves for the configuration of the user interface layout and behavior.



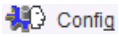
The **Paths** section may also be helpful. In particular, it is possible to modify the default suffixes of the different types of data which are used for filtering so that they match the convention used by the local site.



Availability and Ordering of the PXMOD Models

Each user of a PMOD installation may have a different sub-set of PXMOD models, and a customized order of the model list. This helps making the tool easier to use for dedicated purposes.

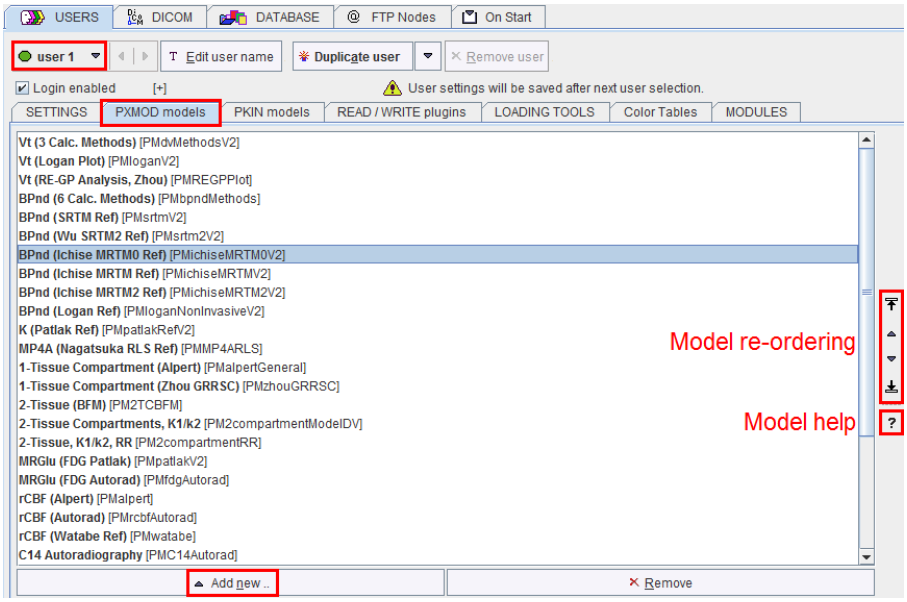
To configure the models list select the



button in the PMOD ToolBox.

In the appearing dialog window first select the appropriate user from the list (eg. **user 1**), and then activate the **PXMOD models** tab. The models which are currently available to the user in PXMOD are shown as a sorted list with the model name in bold and the java class name in brackets. Use the **?** button to show a quick information about the selected model.

To change the list position of a model select it and then move it using the arrow buttons to the right. **Remove** deletes the selected model from the list. To bring a removed model back to the list use the **Add new** button and select it in the appearing dialog window.



Example Data

Example data for practicing the use of the PXMOD tool are contained in the initial example database **Pmod** which can be selected as an option during the installation. Besides the actual data files there are various settings files (*.defpmod) which contain fully configured analysis sessions.

To run a prepared data example start PXMOD, select the entry **Load Model Settings** from the **Pixel wise** menu. In the appearing **Pmod** database dialog window a list of protocol files is shown. Select an entry, and **Retrieve**. Note how the all the PXMOD configuration elements are adjusted. Finally, use the button to perform all processing steps at once.

Note the section related to PXMOD in the **PMOD Workbook**. It provides step-by-step data processing examples based on the **Pmod** database so that they can easily be repeated by new users. This practical work is highly recommended and complementary to the detailed description of the PXMOD functionality in the following sections.

Chapter 1
PXMOD Data Processing

Processing Overview

The processing of a data set in PXMOD consists of the following steps which are performed interactively:

Model selection	The first step of a pixel-wise processing is to select an adequate model from the model list. As a consequence, the user-interface elements are configured according to the model requirements.
Image data loading	As a next step the image data is defined and then loaded. During loading, image transformations such as smoothing may be applied.
Image masking	Optionally, a mask can be created interactively to restrict pixel-wise processing to the area of interest. Masking mainly serves for removing background pixels which might result in disturbing outliers. The created mask needs to be saved and is automatically added to the protocol definition.
VOI definition	Often, dedicated time-activity curves (TACs) are required for the preprocessing and/or the pixel-wise processing. In this case there is an optional step for outlining appropriate tissue VOIs interactively. The resulting VOI definitions or the related TACs need to be saved and are automatically added to the protocol definition.
Blood preprocessing	As a next step the tracer activity in arterial plasma (the input curve) is selected and loaded. It may require some corrections, for example to compensate for a delayed arrival and a dispersed shape at the site of activity measurement. For some models the whole-blood activity can also be supplied for blood spillover correction. The result of blood preprocessing is shown on a separate pane. For all subsequent processing steps the corrected blood curve is used. Note: Blood data is not required for reference models and some other models. In this case the blood-related panels are not active.
Model preprocessing	Depending on the model some preliminary calculations may be required, for example lookup tables or the derivation of initial parameters for the pixel-wise fits. These calculations are typically based on the TACs obtained in the VOI definition step. Usually the preprocessing results should be inspected to see that the model works properly with the prepared configuration. Therefore the results are shown on a separate panel.

Pixel-wise processing	Once the preprocessing was successful, the user can specify which of the parametric maps are to be calculated, and whether they should be restricted to a certain (physiological) value range. For the rapid processing during a prototyping phase, e.g. for determining the adequate table lookup range range, the pixel-wise calculations can be limited to the current slice.
Results explorations	The results may be explored in many different ways such as: ⏩ Comparison of the different maps in the included fusion tool. ⏩ Pixel-wise arithmetics among the maps in the included fusion tool. ⏩ Comparison of the pixel-wise outcome with results when analyzing the TACs interactively in the kinetic modeling tool (PKIN, optional tool).
Saving of the parametric maps	Each fitted model parameter results in a separate functional map. These quantitative images can be saved in any of the different formats available.
Saving of the protocol	PXMOD only uses explicit information for the calculation. Therefore, at the end of a processing, a protocol file can be saved which will allow to exactly reproduce the processing.

Working Mode using Initial Configuration

A suitable initial configuration can be used as an alternative to the step-wise processing outlined above. In this case all required data elements are specified beforehand with the button from the taskbar, and then all processing steps executed with . This, however, is only possible if all the elements such as the VOIs are already existing. Therefore it is better applicable for repeateing a processing with slightly changed parameters based on a protocol, rather than to the processing of a new data set.

How To Continue

There following sections describe the sequence of steps required for processing a data set.

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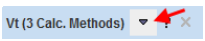
Model Selection

For processing a new data set it is recommended to start with an empty workspace. Either, one of the existing workspaces is cleared with the button, or a new workspace is created with the button of a workspace tab. In this case, all configurations of the currently active workspace will be copied.

As the first thing an adequate model should be selected from the menu **Pixelwise/Model** or from the option list in the workspace tab.



The reason is that the different user interface elements such as the TACs to be defined are adjusted to fit the requirements of the model.

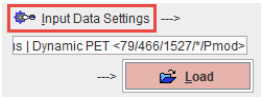
How To Continue

After the model selection, the actual data processing can start with image loading described below.

Image Data Loading

The image data can be directly loaded using the button from the taskbar. In this case the selected data set and how it was loaded (including any data transformations) is reflected in the data configuration.

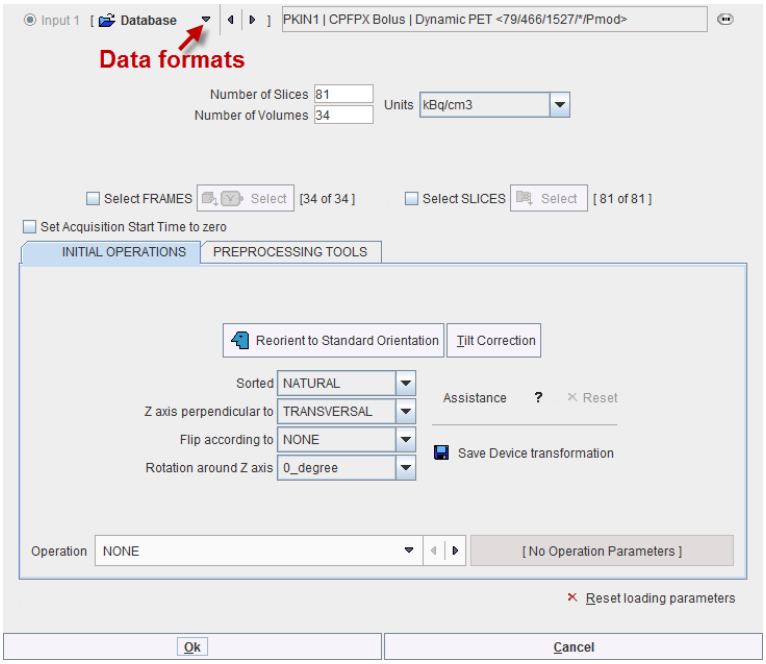
The alternative is defining and loading the images using the corresponding elements on the **Image Data** page.



This procedure is described below.

Input Data Settings

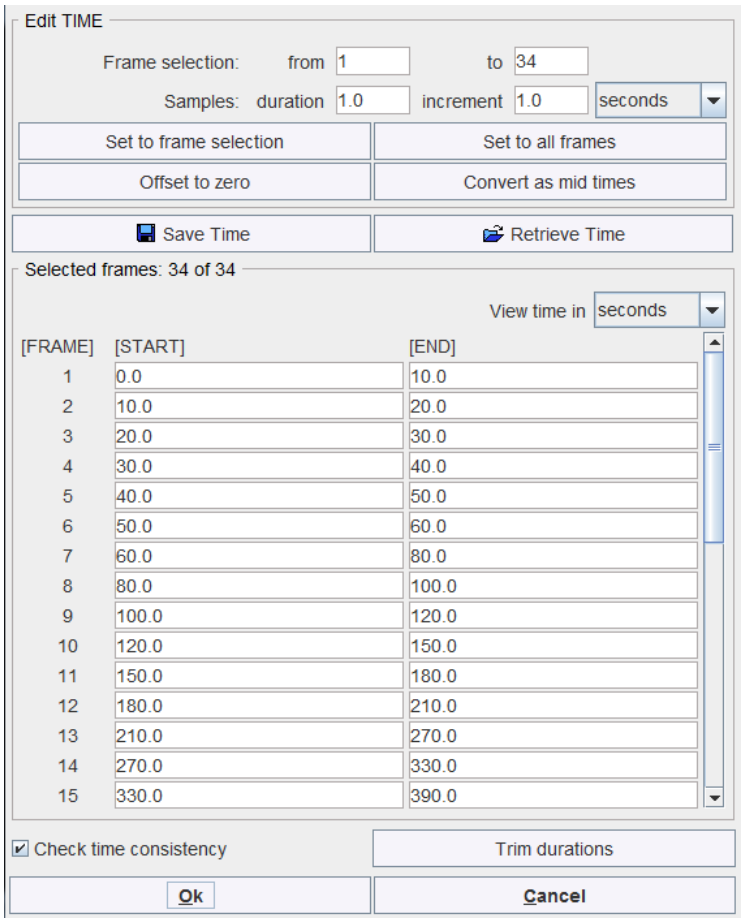
The first step consists of defining the image data set with the **Input Data Setting** button. It opens a window which allows switching between the different data formats and selecting one or multiple image series, depending on the model. The lower part of the window serves for the specification of data transformations during loading.



It represents the standard image loading dialog which changes according to the format of the image data. By checking **FRAMES** or the **SLICES** boxes, image loading can be restricted to a sub-range using the corresponding **Select** buttons. In the lower part of the dialog window, image processing options can be specified which will be applied during loading.

It is very important that the *acquisition timing* is correct when loading dynamic series. Wrong timing will in many cases produce erroneous results. For image formats which have this information defined in the file (such as DICOM), there is no way for editing the times. For image formats without timing information, the user needs to activate the **Edit Time** button. A dialog window is then shown in which the frame **START** and **END** times can be

modified. Correct timing can be retrieved from a file using the dedicated **Retrieve Time** button. In addition, the **Trim duration** button ensures the end times are not after the following start times.



The images are loaded when the **Input Data Settings** window is closed.

Notes:

1. The data loader retains the definition of the last successful loading operation. This is important when working with data formats which do not include time and unit information, or if image processing options were applied such as smoothing.

2. The fastest way to reset all operations is using the **Reset loading parameters** button.

3. Image data formats without timing information should be avoided in PXMOD. In such cases it is recommended to convert the data to a format with full timing support (DICOM, Interfile, Ecat) and proper frame times.

Data Loading

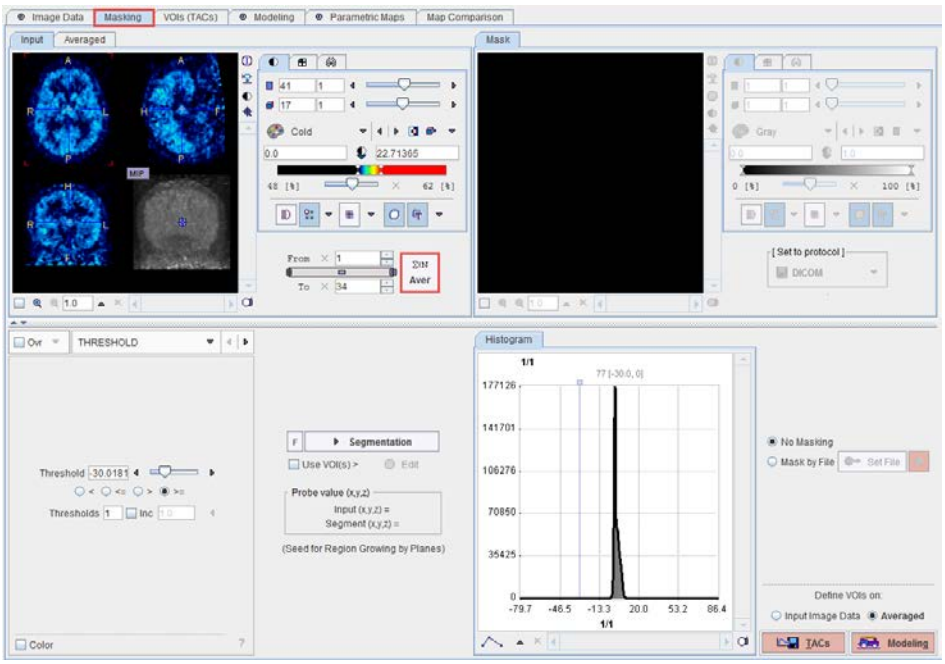
If a configuration was retrieved, the actual image loading can be performed with the red **Load** button.

How To Continue

There are two ways to continue. If you do not want to create a mask or outline VOIs then use the **Modeling** button to proceed to the **Modeling** page. Otherwise select the **Masking** button.

Image Masking

Initially the **Masking** page appears with the loaded images in the left display area.



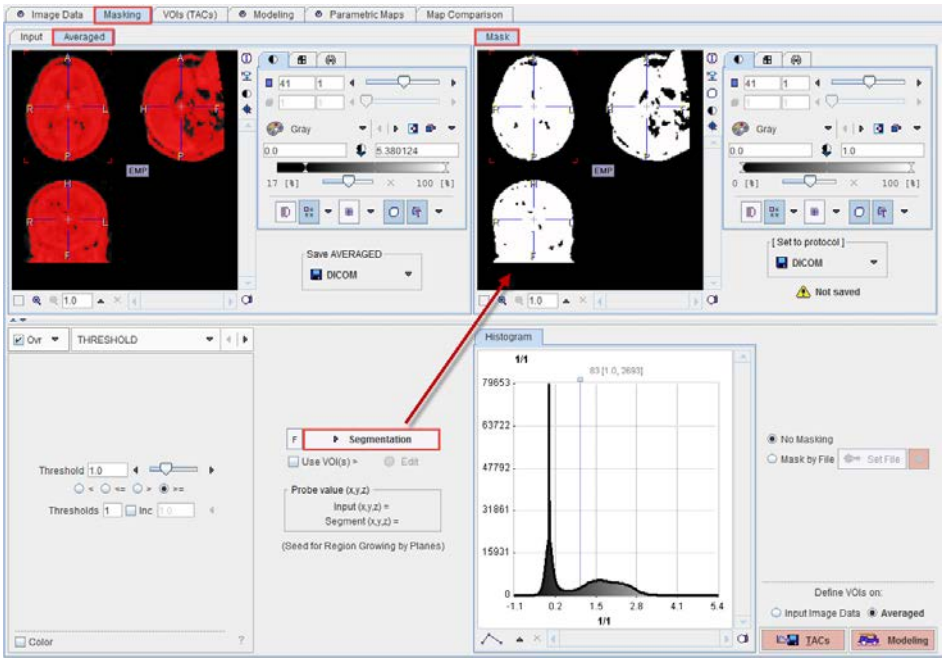
Averaging Frames

To obtain an appropriate data set for masking it is recommended to average the dynamic frames within an appropriate range. The range can be specified by the **From** and **To** numbers or using the slider handles. When the **Aver** button is activated, the average uptake in the specified frame range is calculated and the result image shown on the **Averaged** sub-pane.

Segmentation for Creating a Mask

The next step consists of generating segments which represent tissues of interest. The segments can then be combined into a single mask. Segmentation can be performed on the **Averaged** images, but also on the dynamic **Input** series, depending on which tab is selected. The **Histogram** of the pixel values is updated according to the selected images.

It is recommended to change the color table to **Gray**, and to enable the overlay **Ovr** box. Then, select one of the segmentation methods (described below) to specify an inclusion criterion. The pixels which satisfy the criterion are colored in red in the image overlay. Note that overlay updating might be slow when changing a segmentation parameter, depending on the segmentation method. **Segmentation** performs the actual segmentation and shows the result in the **Mask** tab to the right. While standard segmentations create binary images with 0 (background) and 1 (segment) pixel values, there are clustering approaches which generate multiple segments in a single calculation. These segments are distinguished by increasing integer pixel values. Each **Segmentation** activation overrides the previous contents in **Current**.



In certain circumstances, the segmentation methods alone may not be sufficient to separate an object form other structures. If this happens, the user can defined a VOI which prevents segmentation from leaving the area of main interest. To do so, the **Use VOI(s)** box has to be enabled and the **Edit** VOI button activated. The VOI tools interface appears and allows drawing a VOI. Outline the VOI. Quit the VOI tools with the **OK** button to confirm the VOI selection. Finally, activate the **Segmentation** button to perform the actual segmentation within the VOI. The result is shown in the **Mask** tab to the right.

Saving the Mask for Model Processing

In order to use a generated segment image as a mask in model processing it must be saved as a file and configured. Saving can be performed using the **Set to protocol** pane in any of the supported image formats. Note that automatically the mask configuration button switches from **No Masking** to **Mask by File**, and the saved file is configured. If the mask is not saved, a dialog window will appear when proceeding to the next processing step for mask saving.

If a mask file already exists, the interactions described above are not necessary and it can be simply configured with the **Set File** button after enabling **Mask by File**. The button next to **Set File** can be used to load the specified mask and show it in the **Combined** pane.

The **Set to protocol** save function can be applied on the **Current** or on the **Combined** panes. The corresponding image are saved as a mask.

Note that the saved mask is not binary in the case of multiple segments, so that the segments can be recovered. However, during the pixel-wise calculation only the non-zero mask pixels will be processed, while the other pixels are blanked.

How To Continue

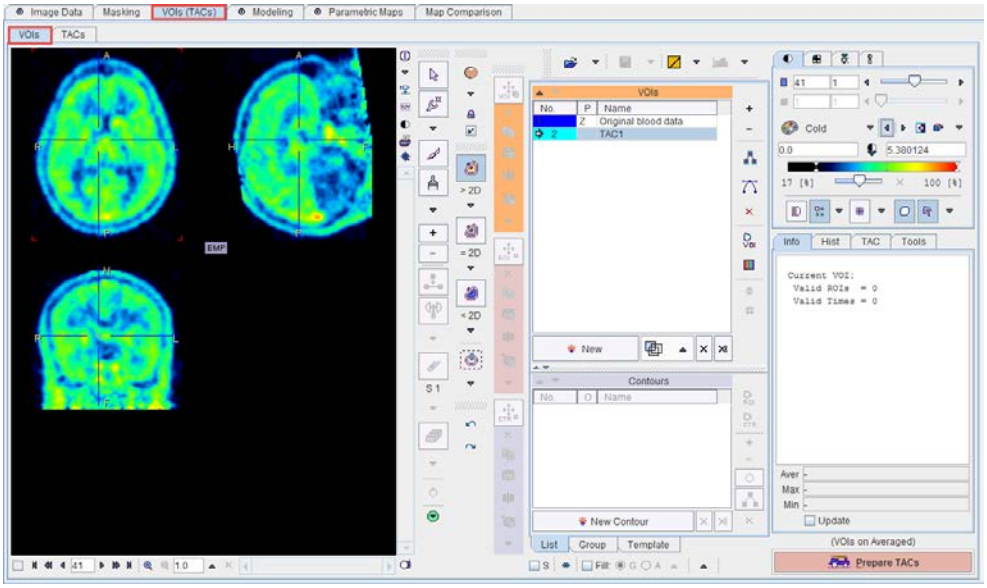
There are two ways to continue. If you do not want to interactively outline VOIs then use the **Modeling** button to proceed to the **Modeling** page. Otherwise first configure the image on which the VOIs should be outlined (**Input Image Data**, **Averaged**), and then select the **TACs** button.

VOI Definition

The **VOIs (TACs)** page supports two processing steps and therefore has two sub-pages **VOIs** and **TACs**. **VOIs** serves for the actual VOI outlining, while **TACs** allows saving either the VOIs or their corresponding TACs.

VOI Definition

Initially, **VOIs (TACs)** shows the **VOIs** page with the images selected in the **Masking** step, as well as a list of VOIs. These VOIs correspond to the activity curves required in the **Modeling** part. Therefore the list may show blood-related and tissue-related VOIs. In the example below one blood curve and one tissue TAC is required. The blood-related VOI could be used for specifying an image-derived input curve, but is most often disregarded. Rather, a processed blood curve will typically be imported in a later panel. For reference models, two tissue VOIs representing target and reference tissue are typically listed.



Interactive VOI Outlining

Initially all VOI definitions are empty. If no file containing suitable VOIs exists, contour VOIs can be outlined in a standard manner as described in the corresponding section of the **PMOD Base Functionality** guide. Briefly:

Navigate to a proper slice and adjust the color contrast.

Double-click at the VOI to be outlined in the **VOIs** list to select it.

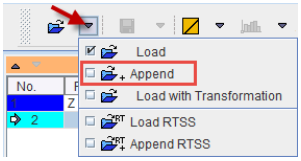
Select one of the VOI definition tools.

Outline a contour in the axial slice. Add a new contour in the same slice with the **New Contour** button, or scroll to the next slice and outline a new contour.

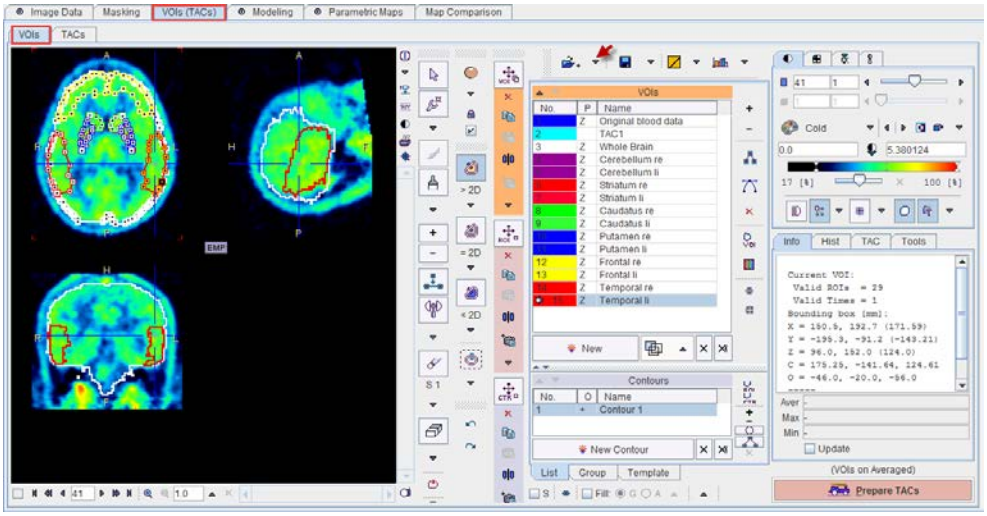
Repeat this procedure for all required VOIs.

Using Existing VOIs

If there exists already a file with suitable VOI definitions, they can be loaded with the **Append** button from the loading section.



As a result, the VOIs are added to the list and shown in the image as illustrated below.



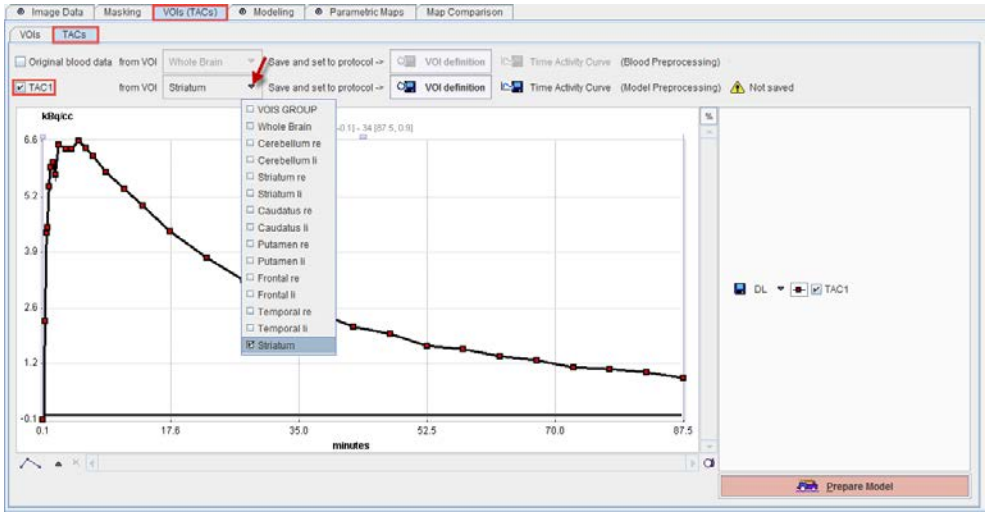
Now, all functions of outline VOIs are available. For instance, the two striatal regions **Striatum re** and **Striatum li** can be merged on the **Group** tab using the **Union** button to form a **Striatum** VOI which will then be used for TAC1.

How To Continue

As the aim of entering **VOIs (TACs)** was to outline VOIs, there is only one way to continue with the **Prepare TACs** button for saving the work.

VOIs or TACs Saving

The **TACs** page shows in the upper left part the list of modeling VOIs, and in the lower part their currently assigned TACs. Use the **from VOI** list to show the list of all defined (not empty) VOIs and change the assignment. In the example below only **TAC1** is relevant, and it is assigned the merged **Striatum** VOI.



Saving the VOI Information

As of now the assigned VOIs and the corresponding TACs are only transient. For use in modeling a "save" operation has to be performed for each of the relevant VOIs. There are two saving possibilities:

With this button the outline VOI definition can be saved in the database or as a file. The corresponding TAC will be calculated again each time it is required for the **Modeling**.

With this button the activity curve can be saved in the database or as a disk file. In this case, no recalculation will be required, so that processing might be faster. On the other hand, without the VOI definition, it will not be possible any more to recover the exact image pixels which produced the saved TAC.

As soon as either of the saving functions has completed, the saved file is entered correspondingly into the **Modeling** configuration. This approach has the advantage, that no transient information is used, so that the processing can be exactly repeated.

If the definition is not saved using the procedure described above, a dialog window will appear when proceeding and ask for saving of the VOIs. In this case, the user can provide a base name (e.g. "CPFPX"), and PXMOD will automatically save appropriately tagged VOI files (e.g "CPFPX_TAC1")

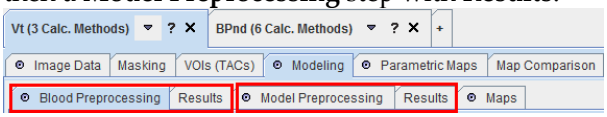
How To Continue

All preparations have been completed, so that **Prepare Model** can be activated for proceeding to **Modeling**.

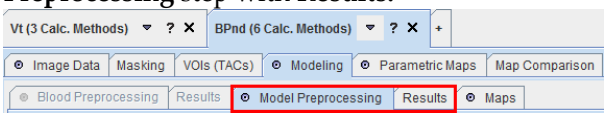
Model Processing

Model processing consists of several steps which depend on the selected model. Basically, two different model types can be distinguished.

1) Models using blood data consist of a **Blood Preprocessing** step with some **Results**, and then a **Model Preprocessing** step with **Results**.

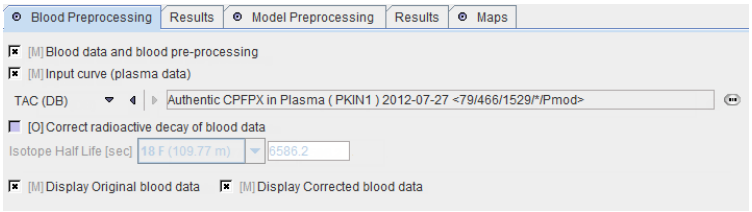


Reference models do not use blood data. Accordingly, they only require a **Model Preprocessing** step with **Results.**



Blood Preprocessing

In the case of a model with blood data the **Modeling** page starts with the **Blood Preprocessing** pane open. The window contents depends on the selected model and is documented for every model. A typical example is shown below.



The **Blood data** must always be specified. There are four blood definition methods which can be selected from the list: **FILE**, **THRESHOLD**, **VOI**, or **TAC(DB)**.

External Files

Initially, **FILE** will be selected to load the blood data from an externally prepared text file. In this case, a file must be specified which contains the blood data (usually the activity concentration of the unchanged tracer in arterial plasma) as well as a descriptive header line as follows:

sample-time[time_unit]	value[value_unit]
0.0	0.0
6.0	0.01
12.0	0.02999
...	...

Valid time units are **seconds, minutes** and **hours**, and value activity units are **kBq/cc**, **MBq/cc**, and **uCi/cc**. For **FILE** type data there appear also selections for specifying the units which are applied if no unit information is found in the file.

Adequate blood files can easily be prepared in text editors, or with MS Excel and saving as a tab delimited text file, such as

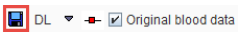
time[seconds]	value[kBq/cc]
0	0
6	0.01
12	0.02999997
18	37.9498862
24	118.469289

Note: The *header line is required* - otherwise the values in the first line will be skipped. If valid units are found in the file header they are used to convert the data into the internal representation [sec] and [kBq/cc]. If there are no valid units in the header line the import procedure uses the units configured in the configuration.

Blood Files in the Database

If the blood data is contained in a database, **TAC(DB)** is used to select the data. The organization of the data in the file is identical to that used for **FILE**. In the case of **TAC(DB)** it is assumed that the correct data units are contained in the file header.

Note that it is easy to store curve data appearing anywhere in PMOD to the database by using the button in the curve control area:



A database save dialog will open. It is recommended to attach the blood data to the PET studies. To this end select the **Attach to Patient (Serie) button**, and select the PET image series. Then define a name for the blood data in the **Enter name** field, and complete with **Save**.

Blood Activity from a VOI

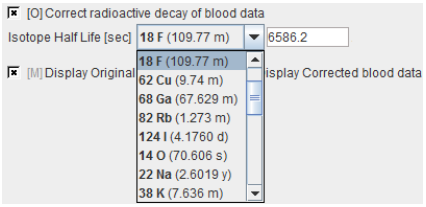
The **VOI** blood type is intended for image-derived input curves. If it is selected, a VOI must be defined. This VOI is applied to the dynamic study during loading and the calculated TAC is used as the blood time-activity curve. This option is probably most useful for cardiac studies.

Blood from a Threshold

If **THRESHOLD** is selected, a % threshold can be entered. All pixels above the threshold relative to the maximal value in the file will be considered as blood signal.

Decay Correction

If the **Correct radioactive decay of blood data** box is checked, the appropriate isotope should be selected from the isotopes list.



Important Note: For the decay correction it is assumed that the timing of the blood and image data have been synchronized. Because the image data are usually decay corrected to the start of the first acquisition, blood time zero must correspond to the scan start time, and decay correction is performed relative to time zero.

Results to be Shown

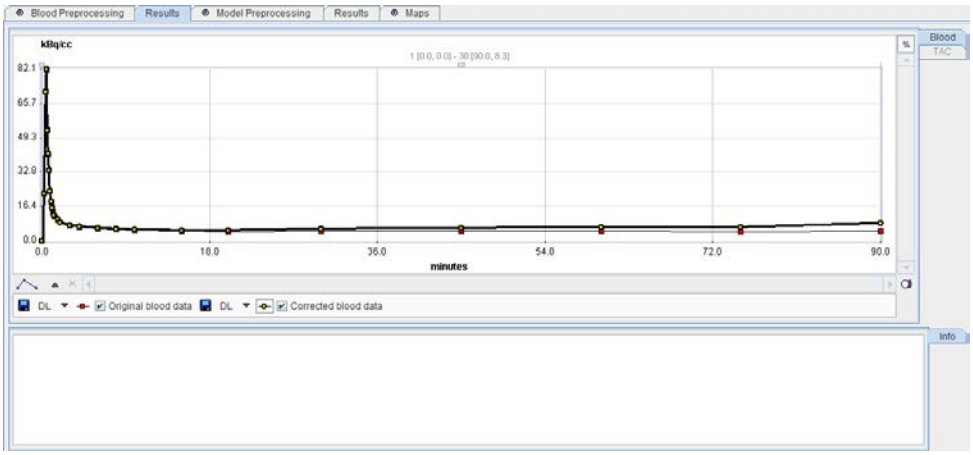
If the **Display Original blood data** and the **Display Corrected blood data** boxes are checked, the respective blood curves are shown on the **Result** page. Some of the checks are set by the model. They are mandatory, hence the **[M]** indication, whereas **[O]** boxes indicate options.

How To Continue

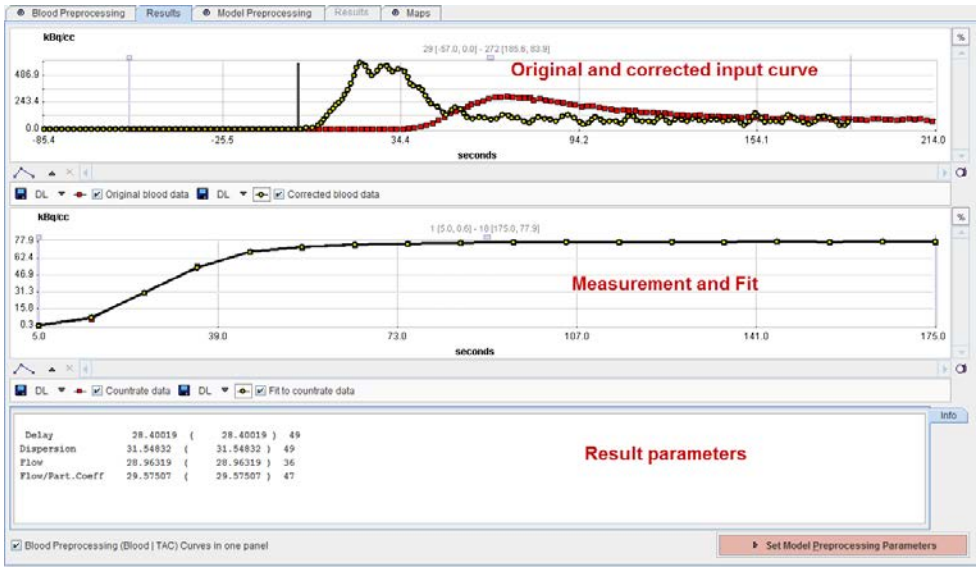
Once the configurations are completed the blood data can be loaded and preprocessed with the **Preprocess Blood** button.

Blood Preprocessing Results

The next tab shows the blood preprocessing **Results**. In most of the cases, the correction of the blood data will be performed outside of PXMOD, for instance in PKIN. Correspondingly, the **Original blood data** and the **Corrected blood data** are typically identical as in the example below.



The models for $H_2{}^{15}O$ are very sensitive to the delay and dispersion of the input curve and therefore include corresponding corrections. In this case the **Results** page shows much more information. Note that the blood curves and tissue TACs can be shown on two panels (Blood, TAC) as in the example above, or on a single panel as in the water example below.



How To Continue

There is nothing else to do on this page than to inspect the results. If the outcome is ok, proceed to the model preprocessing step with the **Set Model Preprocessing Parameters** button.

Model Preprocessing

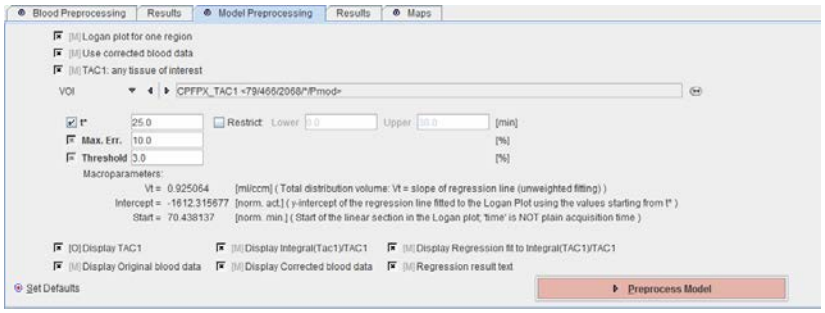
For many of the supported models some type of preprocessing or the specification of some information piece is required before the actual pixel-wise calculation can be started. Preprocessing operations may require certain input information, typically:

- Tissue time activity curves: They serve for the calculation of initial parameters such as t*, or for checking that the model is working properly with the current data.
- Model parameters: A typical case is the Logan plot (and derived methods) which requires the specification of the equilibration time t*. t* may be entered as a fixed value by removing the fit check ☐ and entering the number. Alternatively it can be fitted using the specified TAC and an error criterion (**Max. Err.**). In this case the fit box need to be checked ☑.
- Input parameters : Here user input is requested. The **Threshold** for background masking is such an input parameter.

In the **Model Preprocessing** panel, the preprocessing parameters of the current model are listed. Typically, there are input parameters which will also be used in the pixel-wise calculation, as well as parameters of interest calculated during preprocessing. These are shown in the **Macroparameters** section. The parameters of each model are described in a separate ***section*** (on page 39) of this document. Note the **Set Defaults** button which restores the configuration typically used with the model.

Logan Plot Example

In the case of the Logan plot shown below the equilibration time t* must be defined from which on the plot is considered linear and a regression line is fitted. To determine t* the user must provide a tissue time-activity curve (TAC1) to which the Logan plot will be applied and shown on the **Result** pane. A fit or visual inspection allows specifying t*.



The first mandatory box **Logan plot for one region** indicates that the Logan plot must be performed with representative time-activity data. It uses the corrected blood curve resulting from the blood preprocessing step (mandatory **Use corrected blood data** box). The information used as TAC1 must be specified. This can be done by referencing a previously defined VOI as in the example above (**VOI** selection), by referencing a TAC data file with the **FILE** selection, the **TAC (DB)** selection, or a **THRESHOLD** selection.

The check besides **t*** indicates that this parameter will be fitted during preprocessing using the error criterion specified in **Max. Err**. The **Threshold** is a common input parameter in preprocessing which serves for background masking. All pixels with energy below the specified percentage of the maximal energy will be masked to zero.

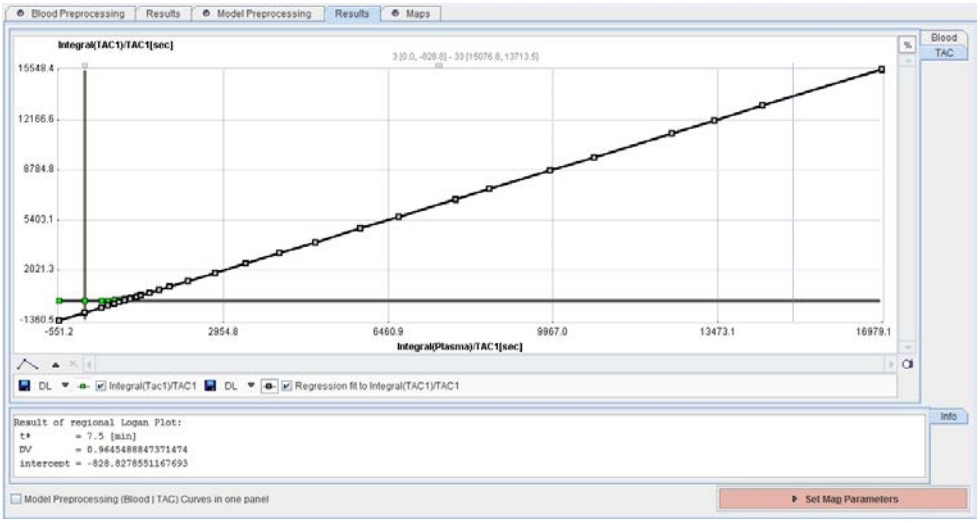
Below the parameters is a section related to the information seen on the **Results** panel of preprocessing. Again, some elements are **M**andatory, while others are **O**ptional. For example, to inspect the TAC used in the Logan plot the **Display TAC1** box can be checked. Note, however, that the axis scales differ between the TAC and the Logan plot in the **Results** curve plot.

How To Continue

If all required information for the selected model has been specified, start the model preprocessing step with the **Preprocess Model** button.

Model Preprocessing Results

The **Results** tab shows the outcome of the model preprocessing. Again, the information shown is highly model-dependent, and in some cases will be entirely empty. The example below shows the result of fitting t* for the Logan plot with an error criterion of 10%. The Logan plot with the regression line is shown in the **TAC** curve panel, whereas the numeric output can be found in the **Info** area. The **Blood** data can also be inspected using the corresponding tab.



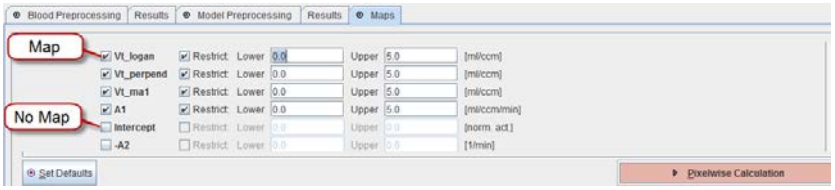
How To Continue

The purpose of this tab is to provide information for the user to decide whether the preprocessing was successfully. If this is the not the case, please select the **Model Preprocessing** tab and adjust the configuration. Otherwise proceed to the configuration of the desired parametric maps with the **Set Map Parameters** button.

Maps Configuration and Calculation

The **Maps** page lists all model parameters for which a map can be calculated. Only the maps with checked fit box will be created. Note that the omission of parameters will not always have an impact on speed, since the model calculation often results in all of the values.

The **Restrict** box allows forcing the parameters values within a physiologic value range limited by the **Lower** and **Upper** threshold values.



Note the **Set Defaults** button which restores the configuration typically used with the model.

How To Continue

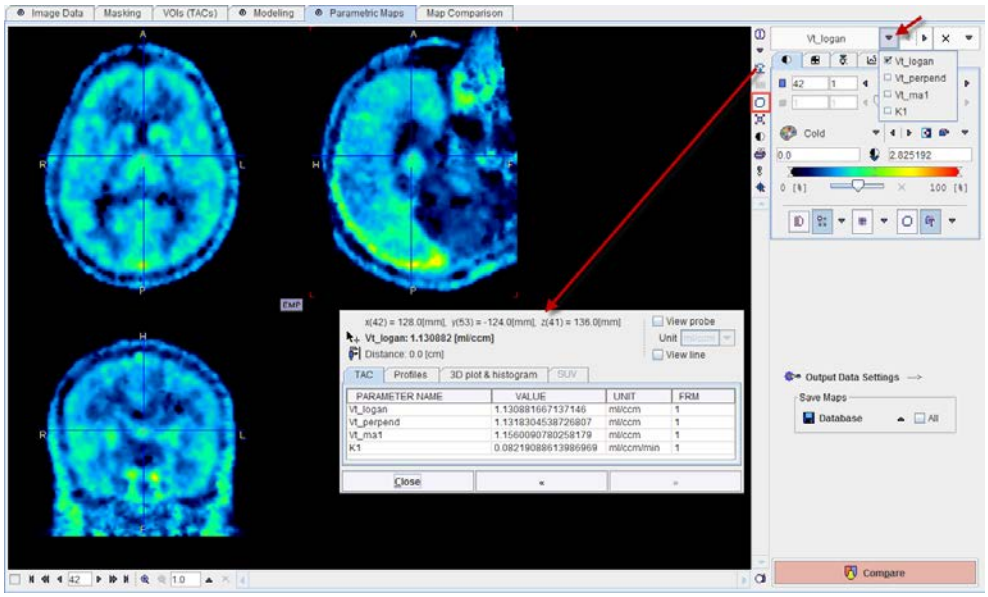
After configuration of the target maps and their restrictions the actual calculation can be started with the **Pixelwise Calculation** button. The calculation is limited to the slice currently shown on the **Image Data** page as long as the single slice box in the taskbar is checked as illustrated below.

Otherwise the parametric maps of the full data volume, optionally restricted by a mask, are calculated and shown on the **Parametric Maps** page.

Note: The calculation of time-consuming models has been parallelized. If the computer running PMOD has N>2 processors, pixel-wise processing will be distributed among N-1 processors and the overall calculation time is almost proportionally reduced.

Result Maps

As soon as pixel-wise calculation completes, the results are available on the **Parametric Maps** page. Initially, it shows the map of the first fitted model parameter. If multiple parameters have the fit check enabled, the corresponding maps are organized as separate studies and can be switched using the controls in the upper right.

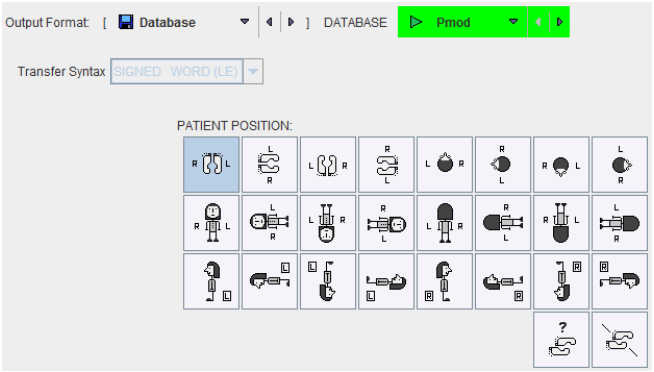


The following actions are supported on this page:

- Individual parameter values inspection: To see all the parameter values of a pixel start the data inspector with the button and extend it with the >> button. Click at different pixels to get the numbers updated.
- VOI statistics: To calculate statistics use the VOI button . The VOI tool is opened with all parametric maps loaded so that an outlined VOI can easily be applied to the different maps without the need of first saving the maps.
- Maps saving: Use the **Save Maps** button to save the currently shown map in any of the supported formats. If the **All** box is checked, all maps are saved in separate files. Note that the parameter name is added to the series description or the file name, so that the data meaning can be seen when loading the data.

Output Data Settings

This button is mainly used to specify the output data format for the batch mode. Note that when maps are interactively saved the existing configuration is overwritten by the format used.

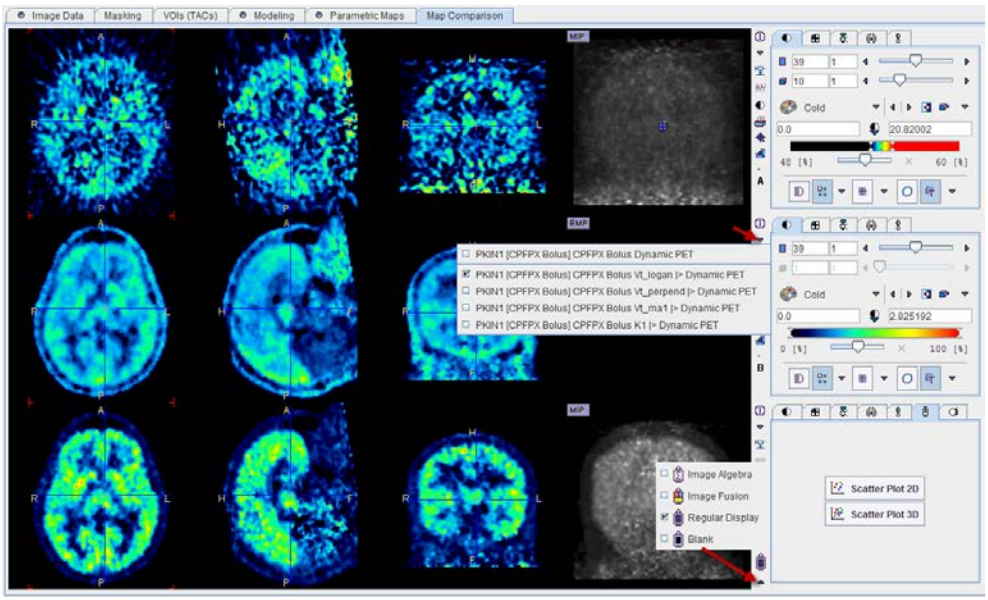


How To Continue

Proceed to explore the parametric maps with the fusion tools by activating the **Compare** button.

Map Comparison

The **Map Comparison** page is a subset of the PMOD Image Fusion tool (PFUS). Note that the dynamic input images as well as all maps are available and can be selected in the different rows by the indicated arrow button.



The page supports different layouts which can be switched using the button in the lower right image corner as illustrated above.

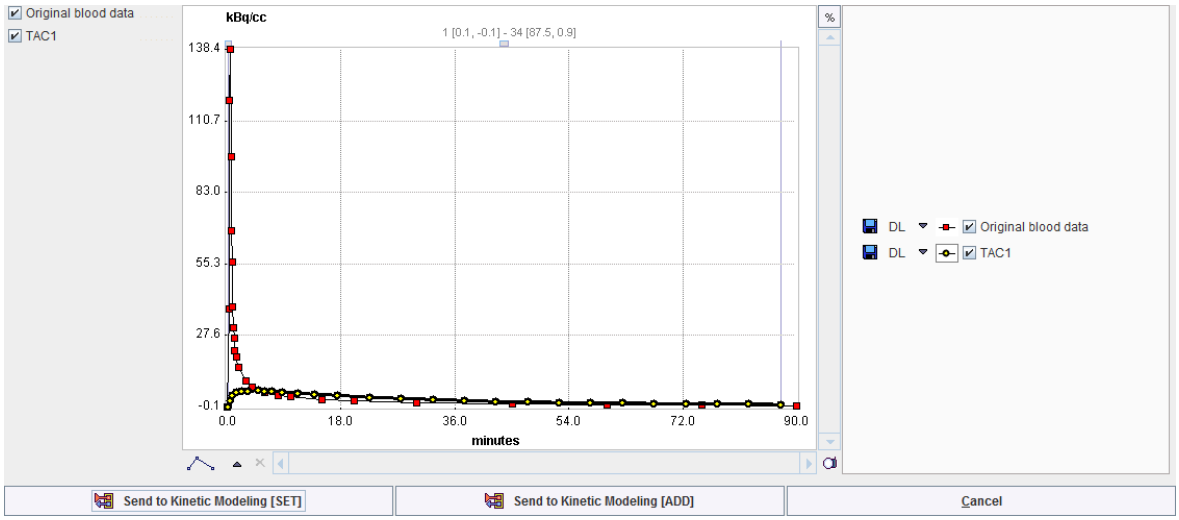
- **Image Algebra** supports pixel-wise arithmetic operations of two parametric maps. This can for instance be used to calculate the difference image of Vt assessed by distinct methods.
- **Image Fusion** shows the fused image of the first and second row in the third row. An example application of this feature would be the overlay of a parametric map on the input images.
- **Regular Display** allows inspecting three data sets in parallel. Additionally, 2D and 3D scatter plots of the pixels enclosed in VOIs can easily be generated.
- **Blank** is simply for blanking the third row.

To learn more about the functionality on this page please refer to the **PMOD Image Fusion** guide.

Interface to Kinetic Modeling (separate Option)

Sending VOI TACs to PKIN

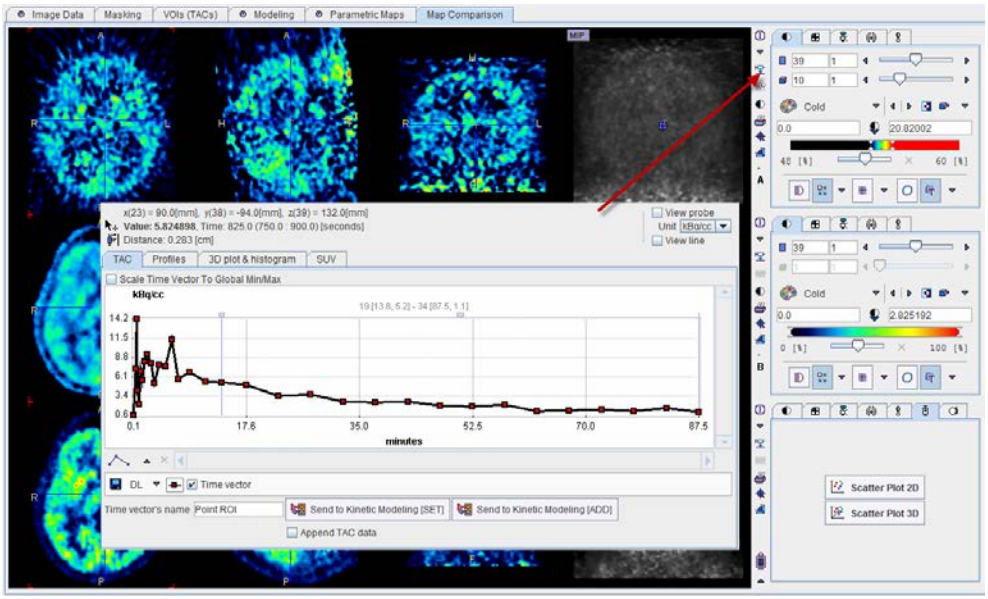
The PXMOD tool is not aimed at interactive modeling. However, if the PKIN tool has been licensed, the PXMOD blood and TAC data can be easily transferred to PKIN by the button in the taskbar. A dialog will be opened, showing the TAC data available.



Use a **Send to to Kinetic Modeling** button to copy the selected PXMOD information to PKIN. There are two variants available: the **[SET]** variant will overwrite the existing data in PKIN without asking for a confirmation, while the **[ADD]** variant will first create a new PKIN workspace. If PKIN is not yet running, it is started and loaded with the selected data. In PKIN, interactive modeling can be performed using all methods, and the information gained can be useful for improving the configuration of the PXMOD model.

Sending Pixel-wise TACs to PKIN

In addition to using the VOI TACs it is also possible to send pixel-wise TACs to PKIN. To this end configure in the first row of the **Map Comparison** page the dynamic input data, open and extend the data inspector window so that the pixel-wise TAC is shown when clicking at an image pixel.

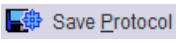


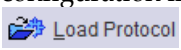
Use a **Send to to Kinetic Modeling** button as described above to copy the selected PXMOD information to PKIN. Note the **Append TAC data** box. If it is checked, the TACs are added to the current PKIN workspace, allowing to work with many pixel-wise TACs.

Using Protocol Files

The configuration of PXMOD can be saved in protocol files (with suffix .defpmod). By loading a protocol file the processing configuration can exactly be restored at any later time. This may help when the need arises to retrospectively check the exact processing details of a result data set, or it may serve as a template for similar analyses with other data sets. Therefore it is recommended to not only save the parametric maps, but also a protocol file when a processing session has been successfully completed. Note that only the configuration of the current workspace is saved in a protocol file.

There are two ways of saving and restoring the PXMOD configuration:

1) Model and data only: menu **Pixelwise/Save Model Settings** or 

from the status line saves the current model configuration including the data definitions. Menu **Pixelwise/Load Model Settings** or 

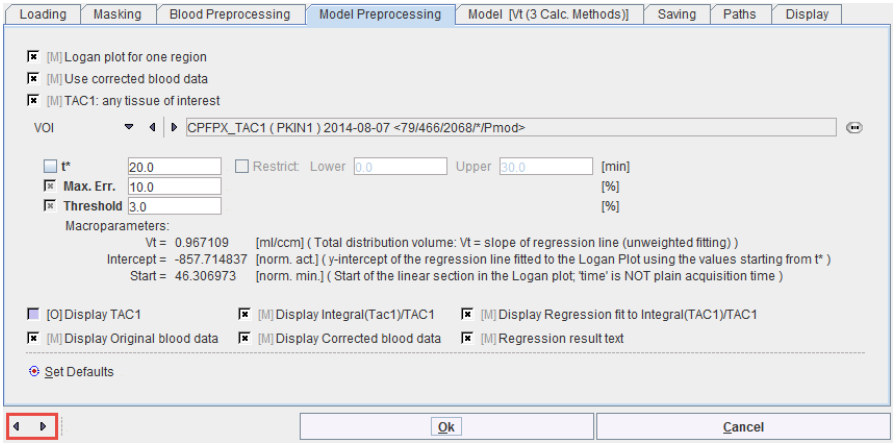
are used for restoring.

Model, data and PXMOD configurations: With menu **Pixelwise/Settings/Save** and menu **Pixel ise/Settings/Retrieve** the configurations of the PXMOD tool are considered in addition to the model configuration and the data.

Note: When closing PXMOD, the current configuration is written to the initial settings file of the PXMOD user. Upon restarting PXMOD, this configuration is restored so that the user can continue with his most recent environment.

Global Settings Modification

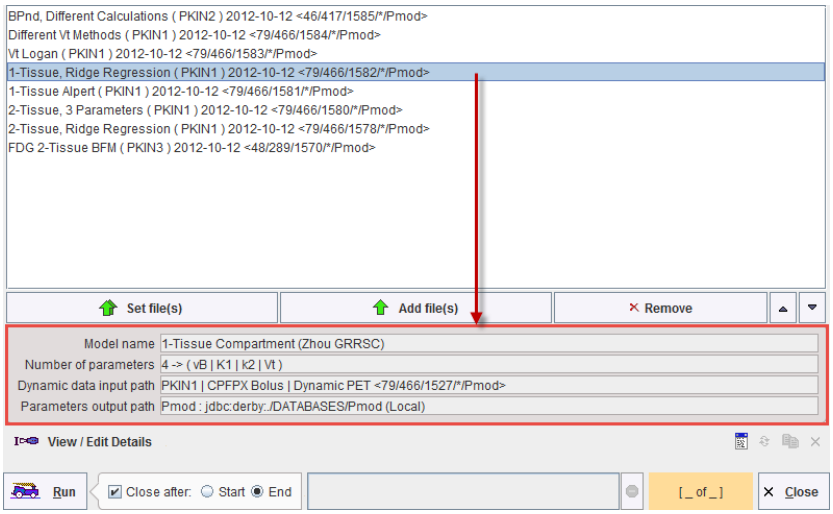
Pixelwise/Settings/Modify or the button open a dialog window which allows to inspect and modify the configuration settings very easily. As illustrated below it contains a tab for all processing steps steps, and each of the tabs contains the same configuration elements as the full processing pages.



For instance, after loading a protocol file, the configurations can be inspected very quickly by stepping through the pages with the arrow keys at the bottom.

Batch Processing

The **Batch Mode** menu entry starts a utility for running a set of pre-configured processing tasks which have been saved as .defpmod protocol files. Initially, a dialog window appears for selecting the protocols. After one or several of these have been selected and **Set** activated, the actual batch dialog window appears:



The list shows the tasks which are currently scheduled. The **Add file(s)** button allows to add more entries to the list. If protocol files are selected with the **Set file(s)** button, the list is first cleared before adding the new entries. Entries can also selectively be removed with the **Remove** button.

The model description area (red rectangle) summarizes the relevant information of the selected configuration entry. It shows the **Model name**, the **Number of parameters** in the model, the data which will be processed, and information how the resulting maps are saved. **View/Edit Details** serves for checking the selected configuration more closely and changing it if necessary. For instance, it is important to define a reasonable output path to find the results and to be able to relate them to a specific processing. So if the **Parameters output path** needs to be corrected, this can quickly be done using the **View/Edit Details** button and then selecting the **Ok** button.

When the **Run** button is activated, PXMOD performs one configured task after the other, writing out the results in the prescribed way. PXMOD will be blocked until the batch has been completed. If the **Close after** option is enabled, the user PXMOD window is closed after **Start**ing processing, otherwise at the **End** of processing. Otherwise, the batch interface will show the progress and the batch can be stopped after the next completed task with the button in the progress bar.

Chapter 2

PXMOD Model Reference

While the purpose and the usage of the PXMOD tool have been described above, this section presents background information about the available models and how they are implemented. For each model the relevant requirements and configurations are given in an own sub-section. The description per model specifies the:

- Reference(s) according to which the model has been implemented.
- Required input data such as the image data, blood data, and time-activity curves (TACs) for performing preprocessing steps, or serving as a reference TAC in reference models. Please remember that all the input data must be calibrated to calculate meaningful results, and that the right timing information and data units must be provided during data loading.
- Preprocessing of the blood data to optionally correct for radioactive decay, arrival delay and bolus dispersion.
- Model-related preprocessing steps required before the actual pixel-wise calculations can be started.
- Meaning of the model parameters.

To see how the PXMOD models should be set up it is recommended to load the prepared protocols from the example **Pmod** database, run the analysis, and inspect the different configuration parts.

Note: For a full understanding of the model applicability and the results interpretation please refer to the cited publications.

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Reference Models for Receptor and other Tracers 83
Brain Glucose Consumption 112
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List of Implemented Models

The following lists provides a quick overview of the implemented models. If one of the models does not appear in the **Model** list of the **Menu** it may have been hidden and can be added using the ***configuration*** (on page 8) facility.

Note that outdated models from previous versions have a "Legacy" in the name. These models are only supported for backward compatibility.

Models with Blood Data

Model Name	Data	Dynamic ?	Blood?
Vt (3 Calc Methods) (on page 45)	Tracers without irreversible uptake.	yes	yes
Vt (Logan Plot) (on page 49)	Tracers without irreversible uptake.	yes	yes
Vt (RE-GP Analysis, Zhou) (on page 52)	Tracers without irreversible uptake	yes	yes
1-Tissue (Alpert) (on page 55)	Tracers which allow time-weighted integral solution.	yes	yes
1-Tissue (Wu GRRSC) (on page 57)	Tracers with 1-tissue compartment kinetics	yes	yes
2-Tissue Compartments, K1/k2	Tracer with 2-tissue compartment kinetics; preferably with K_1/k_2 constant and k_4=0.	yes	yes
2-Tissue K1/k2, RR (on page 62)	Tracer with 2-tissue compartment kinetics. Fit with Ridge-Regression	yes	yes
2-Tissue (BFM) (on page 70)	Tracer with 2-tissue compartment kinetics, particularly suited for FDG. Basis function fit	yes	yes
MBF NH3 (BFM) (on page 70)	Dynamic NH_3 PET of the heart. Acquisition duration 4 minutes.	yes	no

Receptor Reference Models

Model Name	Data	Dynamic ?	Blood?
BPnd (6 Calc. Methods) (on	Reversible receptor tracers	yes	no

page 101)			
BPnd (Ichise MRTM0 Ref) (on page 93)	^{123}I IBF, ^{11}C Raclopride	yes	no
BPnd (Ichise MRTM Ref) (on page 96)	^{11}C DASB	yes	no
BPnd (Ichise MRTM2 Ref) (on page 99)	^{11}C DASB	yes	no
BPnd (Logan Ref (on page 91))	^{11}C Raclopride, ^{11}C dMP	yes	no
BPnd (Gunn SRTM Ref (on page 84))	^{11}C Raclopride, ^{11}C CH 23390, ^{11}C CTF	yes	no
BPnd (Wu SRTM2 Ref) (on page 88)	^{11}C Raclopride, ^{11}C Flumazenil, ^{18}F FCWAY	yes	no
K (Patlak Ref) (on page 104)	FDOPA or another irreversibly binding tracer with a suitable non-trapping reference	yes	no
MP4A (Nagatsuka RLS Ref) (on page 110)	^{11}C-MP4A, acetylcholine analog	yes	no

Brain Glucose Consumption

Model Name	Data	Dynamic?	Blood?
MRGlu (FDG Patlak) (on page 112)	^{18}FDG-PET	yes	yes
MRGlu (FDG Autorad) (on page 115)	^{18}FDG-PET	yes	yes
C14 Autoradiography (on page 117)	^{14}C labeled glucose, autoradiographic cuts	no	yes
C14 Autoradiography; Glucose variable	^{14}C labeled glucose, autoradiographic cuts	no	yes

Brain Perfusion and Blood Volume

Model Name	Data	Dynamic?	Blood?
rCBF (Alpert) (on page 123)	$H_2{}^{15}$O-PET	yes	yes
rCBF (Watabe Ref) (on page	$H_2{}^{15}$O-PET	yes	no

127)			
rCBF (Autorad) (on page 129)	$H_2{}^{15}O$-PET	no	yes
rBV (Autorad) (on page 131)	^{11}CO-PET	no	yes

Miscellaneous Models

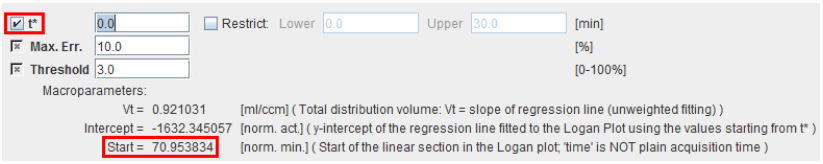
Model Name	Data	Dynamic ?	Blood?
Factor Analysis (2 TACs) (on page 133)	Any dynamic data set.	yes	no
Factor Analysis (H2O, Lung TAC) (on page 134)	Myocardial $H_2{}^{15}O$-PET.	yes	no
Correlation (on page 136)	Any dynamic Volume Data	yes	no
Regression (on page 137)	Any dynamic Volume Data	yes	no
Fourier Analysis (on page 138)	Any dynamic Volume Data	yes	no
Fractal Dimension (on page 139)	Any dynamic Volume Data	yes	no

Common Preprocessing Features

Fitting of t*

Several of the methods below involve fitting of a regression model which only becomes valid after a certain equilibration time t*. Typical examples are the Logan and the Patlak analyses. In these cases, t* can be manually specified, or fitted during model preprocessing. everal of the methods below involve fitting of a regression model which only becomes valid after a certain equilibration time t*. Typical examples are the Logan and the Patlak analyses. In these cases, t* can be manually specified, or fitted during model preprocessing.

To enable fitting, the **t*** box must be checked in the **Model Preprocess** panel, and a suitable error criterion **Max. Err.** entered as illustrated below.



Then the following optimization is performed during preprocessing:

1) **t*** is set to the beginning of the first frame.

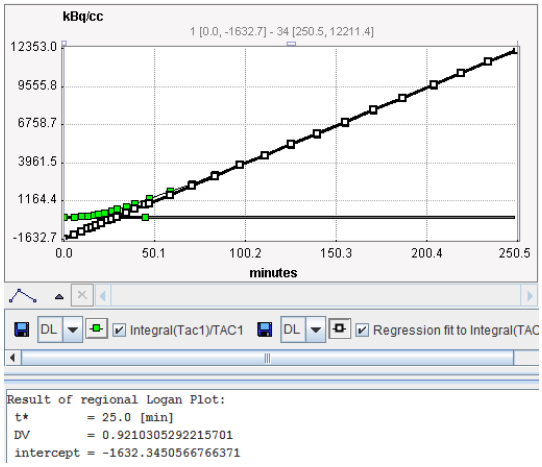
The regression model is calculated using the data from **t*** to the last frame.

The maximal relative difference (measured-predicted)/predicted between the regression value and the data value is calculated.

If the maximal difference exceeds **Max. Err**, then **t*** is set to the subsequent frame and the loop continues with 2.

Otherwise, the current value of **t*** is returned and the final regression is calculated.

The result will be shown on the model preprocessing **Result** panel as illustrated below for the Logan plot. In this example, a t* of 25 minutes was found. This means that the frame starting at 25 minutes and all following frames are employed for the analysis, both in the preprocessing as well as in the pixel-wise processing. Note that t* is always entered in real acquisition time, while the "time" used in regression is sometimes the result of a transformation. In these cases the corresponding **Start** time in the analysis plot is provided in the macroparameters section.



Background Masking by Energy Threshold

The **Model Preprocessing** panel of most models contains a **Threshold** input parameter which is used for background masking. The threshold is entered as a percentage of the maximal signal energy, which is calculated as the sum of all squared samples in a time-activity curve. All pixels which have a signal energy below the threshold will be masked to zero in all generated maps.

Models with Blood Data

Vt (3 Calc. Methods)

The **Vt (3 Calc Methods)** model is a convenience model for calculating the total distribution volume of reversible receptor tracers with three different methods:

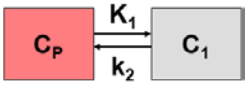
1) the **Logan Plot** method [1] with standard linear regression (yielding **Vt_logan**),

the **Logan Plot** with a linear regression based on the perpendicular distances [2] (**Vt_perpend**),

Ichise's MA1 bilinear method [3] (**Vt_ma1**)

Logan Plot

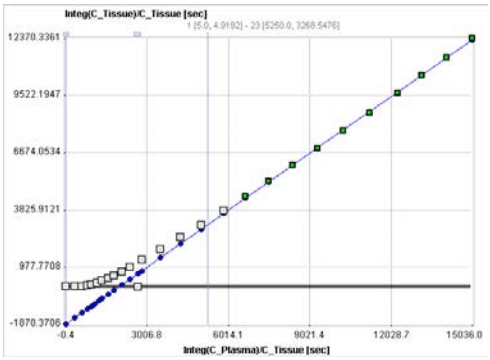
The **Logan plot** has been developed by Logan et al. [1] for ligands that bind reversibly to receptors and enzymes and is used for estimating the total distribution volume V_T. Its results can be interpreted with respect to the 1- and 2-tissue compartment models.



The Logan plot belongs to a group of *Graphical Analysis* techniques, whereby the measured tissue TAC $C_T(T)$ undergoes a mathematical transformation and is plotted against some sort of "normalized time". The Logan plot is given by the expression

$$\frac{\int_0^t C_T(\tau)d\tau}{C_T(t)} = K\frac{\int_0^t C_P(\tau)d\tau}{C_T(t)} + b$$

with the input curve $C_p(t)$. This means that the tissue activity integrated from the time of injection is divided by the instantaneous tissue activity, and plotted at a "normalized time" (integral of the input curve from the injection time divided by the instantaneous tissue activity). For systems with reversible compartments this plot will result in a straight line after an equilibration time t*.



In the derivation of the Logan plot the PET signal is described as a sum of tissue activity plus a fractional plasma signal

$$C_{Model}(t) = C_T t) + v_P C_P(t)$$

unlike the operational equation of the compartment model. Under these premises the slope represents the total distribution volume V_T plus the plasma space v_P in the VOI, which is usually neglected. Therefore

$$K \cong V_T = K_1 / k_2 \qquad 1-\text{tissue compartment model}$$
$$K \cong V_T = K_1 / k_2 (1 + k_3 / k_4) \qquad 2-\text{tissue compartment model}$$

It has been found that the Logan plot is susceptible to noise in the data. Noise causes the true V_T to be underestimated, to a degree which not only depends on the noise level, but also on the local kinetics. The underestimation problem is particularly relevant in parametric mapping, where the pixelwise TACs suffer from a high noise level.

The reason for the underestimation effect is the fact that noise is not only present in the y-values (dependent variable) as the linear regression assumes, but also in the x-values (independent variable). To arrive at more accurate results it was therefore proposed to measure the residuals perpendicular to the regression line, rather than vertical to the x-axis [2].

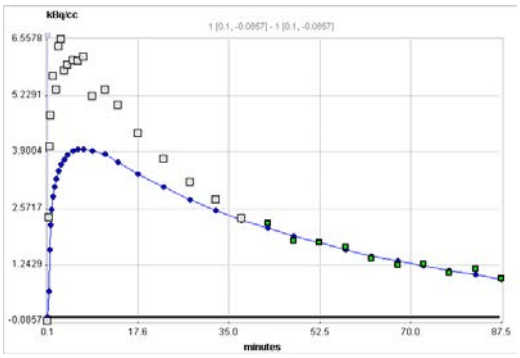
Ichise's MA1 Method

Ichise's **MA1** analysis method [3] is a further development of the Logan plot aimed at minimizing the bias induced by noise in the measurements.

The following bilinear relationship was derived

$$C_{Model}(t) = -\frac{V_T}{b}\int_0^t C_P(\tau)d\tau + \frac{1}{b}\int_0^t C_T(\tau)d\tau$$

where $C_T(t)$ represents the tissue time-activity curve, $C_P(t)$ the plasma activity, V_T the total distribution volume, and b the intercept of the Logan plot which becomes constant after an equilibration time t*.



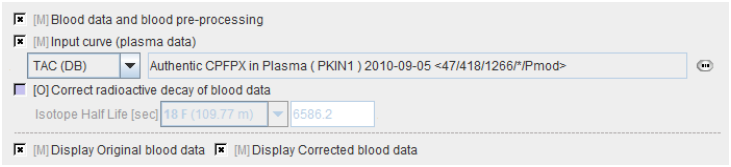
Based on simulation and experimental data the authors show that MA1 demonstrates the largest bias reduction among several methods. Therefore they conclude, that MA1 is the method of choice for calculating the total distribution volume, if t* can accurately be defined.

Acquisition and Data Requirements

Image Data	A dynamic PET data set.
Blood Data	Blood activity sampled at a peripheral artery from the time of injection until the end of the acquisition.
Tissue TAC	A regional time-activity curve from a representative brain region. It is presented as a Logan plot and can be used to define the linear segment where regression analysis should be done.

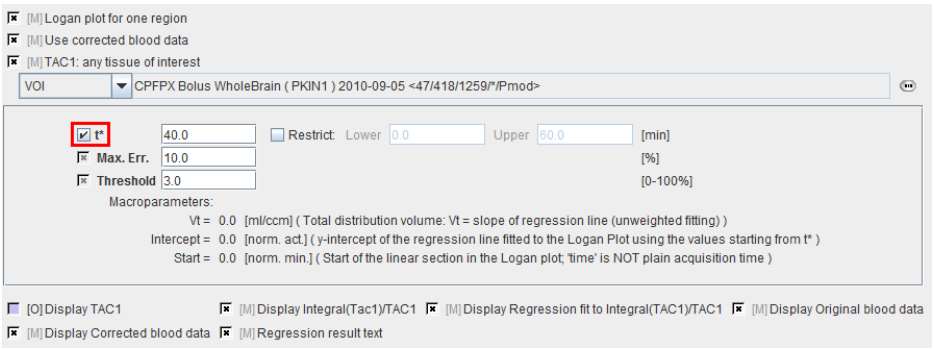
Blood Preprocessing

Decay correction is the only blood correction option.



Model Preprocessing

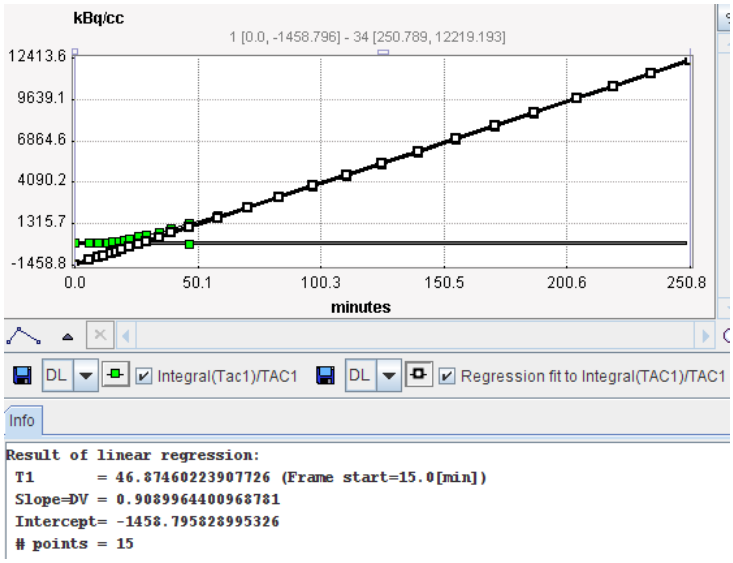
The Logan graphical plot is performed with the TAC from a tissue VOI (**TAC1**) and presented to the user. In this plot, the TAC should become linear after an equilibration time. The slope of the linear segment equals the total distribution volume. The user must decide on the beginning of the linear segment and specify this time (which is NOT in acquisition time) in the model configuration. An alternative is to apply an automatic criterion for determining this start time.



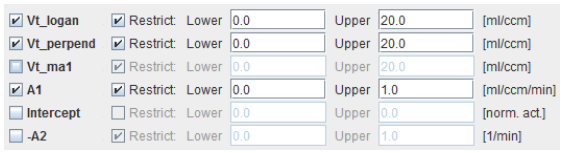
t*	The linear regression estimation should be restricted to a range after an equilibration time. **t*** marks the beginning of the range used in the multi-linear regression analysis. It can be fitted based on the **Max. Err.** criterion. Note that the t* is in acquisition time.
Max Err.	Maximum relative error ((measured-predicted)/predicted) allowed between the linear regression and the Logan-transformed measurements in the segment starting from **t***.

Threshold	Discrimination threshold for background masking.
Vt	Distribution volume = slope of the linear regression to the Logan plot.
Intersect	Intercept of the linear regression line.
Start	Start time of the first frame in the linear section .

The Logan plot is shown in the preprocessing **Result**. The user should consult this plot in order to check whether the **Start** time is adequate.



Map Parameters



The regressions in pixel-wise processing (all 3 methods) only use the data segment determined by **Start Lin** in the **Model Pre-Processing** area.

Vt_logan	Total distribution volume calculated with standard Logan plot.
Vt_perpend	Total distribution volume calculated with the Logan plot using perpendicular distances.
Vt_ma1	Total distribution calculated using Ichise's MA1 method. This method has less bias, but more variance and the maps often are contaminated by outliers.
A1	First regression coefficient of the MA1 method. Provides a sort of "perfusion" image which may be helpful for the anatomical correlation or matching.

Intercept	y-Intercept of standard regression line.
-A2	Second regression coefficient of the MA1 method.

References

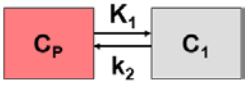
1. Logan J, Fowler JS, Volkow ND, Wolf AP, Dewey SL, Schlyer DJ, MacGregor RR, Hitzemann R, Bendriem B, Gatley SJ et al: Graphical analysis of reversible radioligand binding from time-activity measurements applied to [N-11C-methyl]-(-)-cocaine PET studies in human subjects. J Cereb Blood Flow Metab 1990, 10(5):740-747. ***DOI http://dx.doi.org/10.1038/jcbfm.1990.127***

2. Varga J, Szabo Z: Modified regression model for the Logan plot. J Cereb Blood Flow Metab 2002, 22(2):240-244. ***DOI http://dx.doi.org/10.1097/00004647-200202000-00012***

3. Ichise M, Toyama H, Innis RB, Carson RE: Strategies to improve neuroreceptor parameter estimation by linear regression analysis. J Cereb Blood Flow Metab 2002, 22(10):1271-1281. ***DOI http://dx.doi.org/10.1097/00004647-200210000-00015***

Vt (Logan Plot)

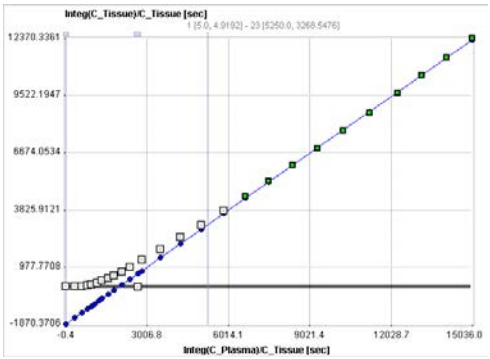
The **Logan plot** has been developed by Logan et al. [1] for ligands that bind reversibly to receptors and enzymes and is used for estimating the total distribution volume V_T. Its results can be interpreted with respect to the 1- and 2-tissue compartment models.



The Logan plot belongs to a group of *Graphical Analysis* techniques, whereby the measured tissue TAC $C_T(T)$ undergoes a mathematical transformation and is plotted against some sort of "normalized time". The Logan plot is given by the expression

$$\frac{\int_0^t C_T(\tau)d\tau}{C_T(t)} = K\frac{\int_0^t C_P(\tau)d\tau}{C_T(t)} + b$$

with the input curve $C_P(t)$. This means that the tissue activity integrated from the time of injection is divided by the instantaneous tissue activity, and plotted at a "normalized time" (integral of the input curve from the injection time divided by the instantaneous tissue activity). For systems with reversible compartments this plot will result in a straight line after an equilibration time t*.



In the derivation of the Logan plot the PET signal is described as a sum of tissue activity plus a fractional plasma signal

$$C_{Model}(t) = C_T t) + v_P C_P(t)$$

unlike the operational equation of the compartment model. Under these premises the slope represents the total distribution volume V_T plus the plasma space v_P in the VOI, which is usually neglected. Therefore

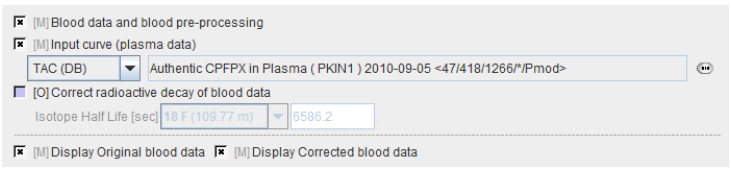
$$K \cong V_T = K_1 / k_2 \qquad 1-\text{tissue compartment model}$$
$$K \cong V_T = K_1 / k_2 (1 + k_3 / k_4) \qquad 2-\text{tissue compartment model}$$

Acquisition and Data Requirements

Image Data	A dynamic PET data set.
Blood Data	Blood activity sampled at a peripheral artery from the time of injection until the end of the acquisition.
Tissue TAC	A regional time-activity curve from a representative brain region. It is presented as a Logan plot and can be used to define the linear segment where regression analysis should be done.

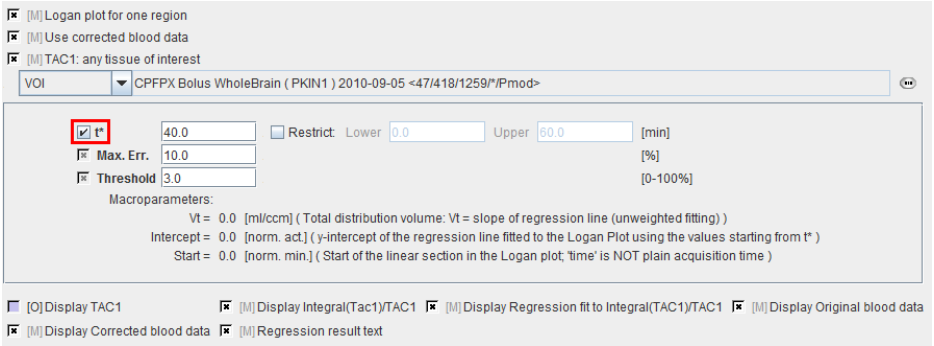
Blood Preprocessing

Decay correction is the only blood correction option.



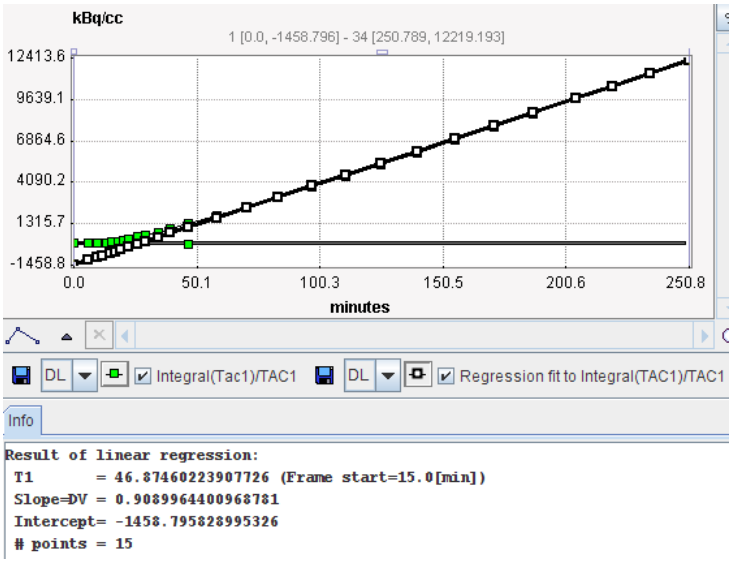
Model Preprocessing

The Logan graphical plot is performed with the TAC from a tissue VOI (**TAC1**) and presented to the user. In this plot, the TAC should become linear after an equilibration time. The slope of the linear segment equals the total distribution volume. The user must decide on the beginning of the linear segment and specify this time in the model configuration. An alternative is to apply an automatic criterion for determining this start time.

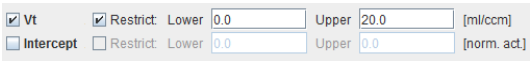


t*	The linear regression estimation should be restricted to a range after an equilibration time. **t*** marks the beginning of the range used in the multi-linear regression analysis. It can be fitted based on the **Max. Err.** criterion. Note that the t* is in acquisition time.
Max. Err.	Maximum relative error ((measured-predicted)/predicted) allowed between the linear regression and the Logan-transformed measurements in the segment starting from **t***.
Threshold	Discrimination threshold for background masking.
Vt	Distribution volume = slope of the linear regression to the Logan plot.
Intersect	Intercept of the linear regression line.
Start	Time corresponding to **t*** in the Logan plot.

The Logan plot is shown in the preprocessing **Result**. The user should consult this plot in order to check whether the **Start** time is adequate.



Map Parameters



Vt	Distribution volume = slope of the linear regression to Logan plot from t*.
Intersect	Intercept of the linear regression.

Reference

1. Logan J, Fowler JS, Volkow ND, Wolf AP, Dewey SL, Schlyer DJ, MacGregor RR, Hitzemann R, Bendriem B, Gatley SJ et al: Graphical analysis of reversible radioligand binding from time-activity measurements applied to [N-11C-methyl]-(-)-cocaine PET studies in human subjects. J Cereb Blood Flow Metab 1990, 10(5):740-747. ***DOI http://dx.doi.org/10.1038/jcbfm.1990.127***

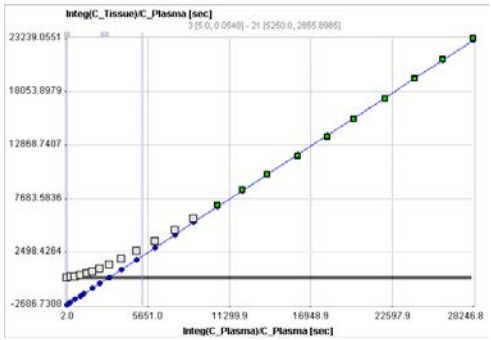
Vt (RE-GP Analysis, Zhou)

In 2009 Zhou et al. introduced a new graphical method, the Relative-Equilibrium (**RE**) plot [1]. It can be applied with a plasma input curve for the calculation of the distribution volume, and with a reference tissue curve for the calculation of the binding potential. It was shown with Raclopride data and with simulations, that unlike the Logan plot the RE plot is not suffering from bias due to high noise levels. As a consequence, the results obtained with VOI-averaged TACs is consistent to the results obtained in pixel-wise applications.

However, it was found that violation of the relative equilibrium condition did introduce bias. To compensate this bias Zhou et al [2] combined the RE plot with the Gjedde-Patlak plot in a bi-graphical manner called the **RE-GP Analysis.**

The operational equation of the RE Plot is given by:

$$\frac{\int_0^t C_T(\tau)d\tau}{C_P(t)} = V_{T\,RE}\,\frac{\int_0^t C_p(\tau)d\tau}{C_p(t)} + \alpha$$



For the RE plot to be applicable there must exist a time t* after which two conditions are fulfilled:

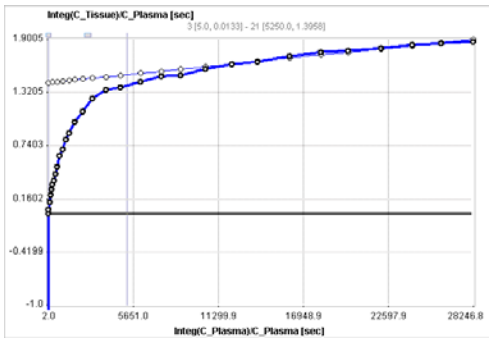
1) The plasma input curve must be mono-exponential. This condition can be verified by fitting a single exponential to the late part of the plasma curve on the **Blood** tab of PKIN.

The ratio of C_T/C_p is constant. This condition can be verified by switching the **KM** model to the **Tissue/Plasma Ratio** model.

Under these conditions the tracer in all tissue compartments reaches equilibrium relative to plasma. Note that the conditions must be verified explicitly, because the linear appearance of the RE plot is not a sufficient criterion.

Violation of the relative equilibrium condition above introduces bias. To compensate this bias the RE plot was combined with the Patlak plot

$$\frac{C_T(t)}{C_p(t)} = K\,\frac{\int_0^t C_p(\tau)d\tau}{C_p(t)} + \beta$$



using the same t* for fitting two respective regression lines. A consistent and unbiased distribution volume is then obtained by combining the slopes and intercepts of the two plots:

$$V_T = V_{T\,RE} - \frac{\alpha K}{\beta}$$

Overview of the RE-GP Processing in PXMOD

The preprocessing section of the **Vt (RE-GP Analysis, Zhou)** model serves for the specification of t* and the smoothing parameters. The user may specify an error criterion and fit t* for a representative tissue TAC, or directly enter t*. The t* resulting from preprocessing is applied for the pixel-wise fits.

For each pixel, the slope and intercept of the regression line to the Patlak plot are calculated. The resulting parametric maps are then smoothed. Finally, the regression line to the RE plot in each pixel is calculated in each pixel. Vt obtained from the RE plot is corrected using the smoothed outcome of the Patlak analysis according to

$$V_T = V_{TRE} - \frac{\alpha K_s}{\beta_s}$$

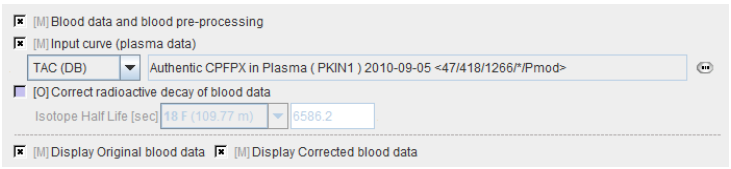
where K_s and β_s are obtained from spatially smoothed maps of K and β.

Acquisition and Data Requirements

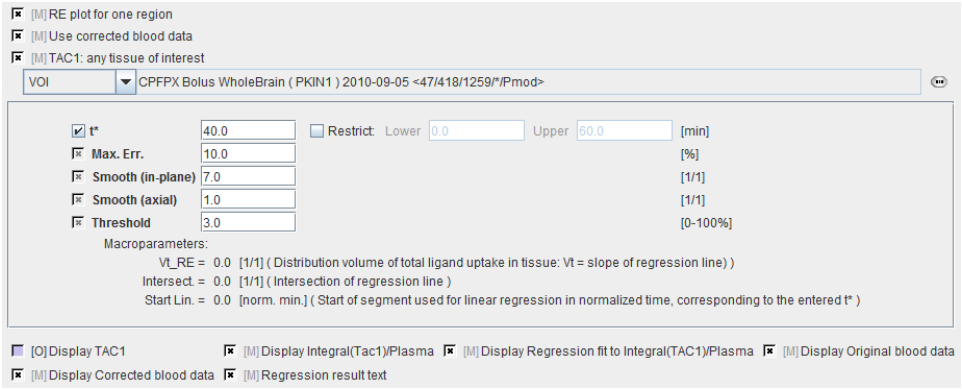
Image Data	A dynamic PET data from a receptor tracer with reversible binding.
Blood Data	The plasma activity from the time of injection until the end of the PET acquisition.

Blood Preprocessing

Decay correction is the only blood correction option.



Model Preprocessing

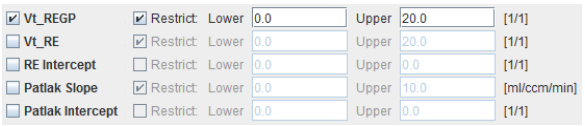


t*	Start time of the data segment used in the analysis. If **t*** is checked for fitting, the **Max. Err.** criterion will be applied to the RE plot of the specified tissue TAC.

Max. Err.	Maximum relative error ((measured-predicted)/predicted) allowed between the linear regression and the RE-transformed measurements in the segment starting from t*.
Smooth (axial)	Spatial smoothing window along z in number of pixels. A number of 1 means planar smoothing.
Resampling	Sampling increment applied during the basis function calculation.
Threshold	Discrimination threshold for background masking.

Map Parameters

The example below shows a typical configuration for an irreversible mode ($k_4 = 0$ fixed)



Vt-REGP	Distribution volume of total ligand uptake in tissue. Insensitive to non-equilibration bias.
Vt_RE	Slope of the regression line to the RE plot and also a distribution volume estimate. If the equilibrium condition is not satisfied, this Vt estimate is biased. Default is therefore not to use **Vt_RE**, but it can enabled for inspection.
RE Intercept	y-Intercept of the regression line to the RE plot.
Patlak Slope	Slope of the regression line to the Patlak plot.
Patlak Intercept	y-Intercept of the regression line to Patlak plot

References

1. Zhou Y, Ye W, Brasic JR, Crabb AH, Hilton J, Wong DF: A consistent and efficient graphical analysis method to improve the quantification of reversible tracer binding in radioligand receptor dynamic PET studies. Neuroimage 2009, 44(3):661-670. ***DOI http://dx.doi.org/10.1016/j.neuroimage.2008.09.021***

2. Zhou Y, Ye W, Brasic JR, Wong DF: Multi-graphical analysis of dynamic PET. Neuroimage 2010, 49(4):2947-2957. ***DOI http://dx.doi.org/10.1016/j.neuroimage.2009.11.028***

1-Tissue Compartment Model (Alpert)

This model is intended to calculate the parameters of a 1-tissue compartment model. It is just a slightly modified version of the classical implementation of ***Alpert's time-weighted integral approach for brain perfusion*** (on page 123).

There are two changes:

1) The parameters are expressed as K_1, k_2, and Vt (rather than f, f/p, p).

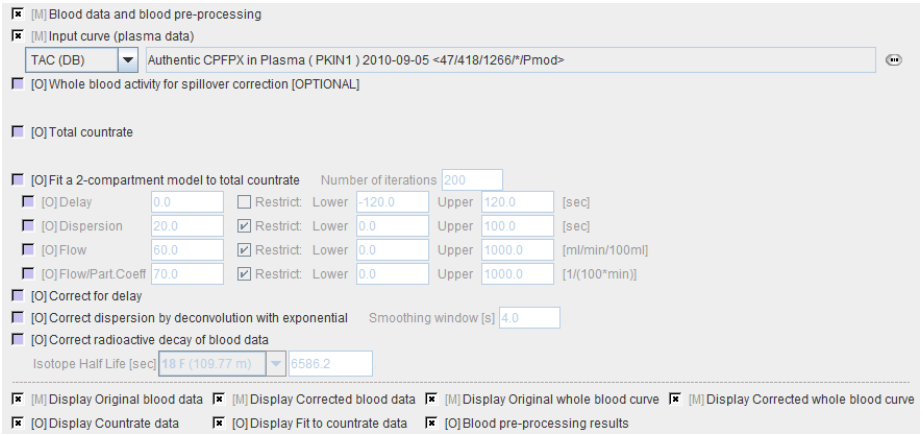
Whole blood activity can be subtracted for spillover correction.

Acquisition and Data Requirements

Image Data	A dynamic PET data set.
Blood Data	The plasma activity from the time of injection until the end of the acquisition. Optionally: whole blood activity to be subtracted from the pixel-wise TACs, loaded as **Whole Blood Data** in Blood Pre-processing.
Blood-related TAC	Optional. The delay and dispersion fit can be applied for brain perfusion data with [15O]-H_2O scans.

Blood Preprocessing

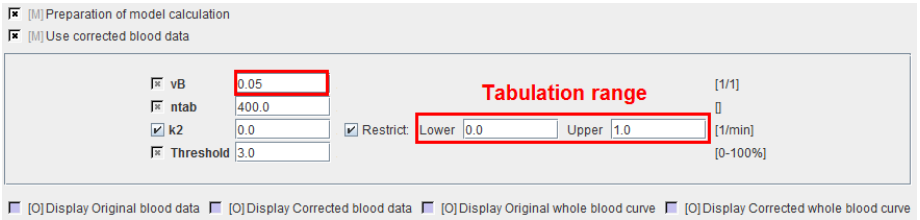
The same blood Preprocessing steps are available as for the brain perfusion model, but except for the data definition field all options are initially disabled as shown below.



If no whole-blood TAC is defined, the plasma curve will be used for spillover correction.

Model Preprocessing

During model Preprocessing a lookup table is calculated within a range of k_2 values. The specifications include an optional TAC which is interpreted as whole-blood activity to be subtracted from the pixel-wise TACs.



vB	Blood volume fraction defining the pixel-wise blood spillover correction. The corrected TACs before estimation of k_2 are calculated by $TAC_{corr} = (TAC - vB*C_{BloodTot})/(1-vB)$
ntab	Number of pre-calculated values in the lookup table. Should be an even number.
k_2	Efflux rate constant. The lower and upper limit of tabulation must be entered in the k_2 restriction fields.
Threshold	Discrimination threshold for background masking.

Map Parameters

K1	K_1 rate constant of 1-tissue compartment model.
k2	k_2 rate constant of 1-tissue compartment model.
Vt	Distribution volume.

1-Tissue Compartment Model (Zhou GRRSC)

The **1-Tissue (Zhou GRRSC)** model implements fitting a 1-tissue compartment model in each image pixel. It is based on a multi-linear formulation of the operational equation, which can be fitted by a fast and reliable weighted linear regression (WLR) method. To improve the signal-to-noise ratio in the calculated parametric maps Zhou et al. [1] have extended the method by ridge regression (RR). In short, the parametric map calculation performs the following steps:

1) A WLR fit is performed for the TAC in each image pixel.

The resulting parametric maps of vB, K_1 and k_2 are then spatially smoothed.

A *ridge factor* is calculated for each pixel using the smoothed parametric maps and the estimated noise variance (difference between signal and fit). It is proportional to the noise.

The cost function is extended by a penalty term which is driven by the ridge factor. The noisier a pixel, the higher the penalty.

Ridge regression estimates the optimal parameter set vB, K_1, k_2 a for the penalized cost function. The noisier a pixel, the more will the solution tend towards the smoothed parametric map of the WLR step.

Implementation details of the **1-Tissue (Zhou GRRSC)** model:

- The weighted linear regression and the ridge factor calculation are performed during the PXMOD Preprocessing step, whereas the ridge regression runs during the pixel-wise processing.
- The Generalized Ridge regression with Spatial Constraint variant of ridge regression described by Zhou et al [1] is implemented which supports spatially varying ridge factors.
- Multi-linear fitting employs the singular value decomposition (SVD) method, using the frame durations as weighting factors.
- The operational equation (16) in [1] has been re-written to accomodate the geometrical variant of the operational equation:

$$C_{Model}(t) = (1 - vB)\, C_{Tissue}(t) + vB\, C_{Blood}(t) \cong C_{PET}(t)$$

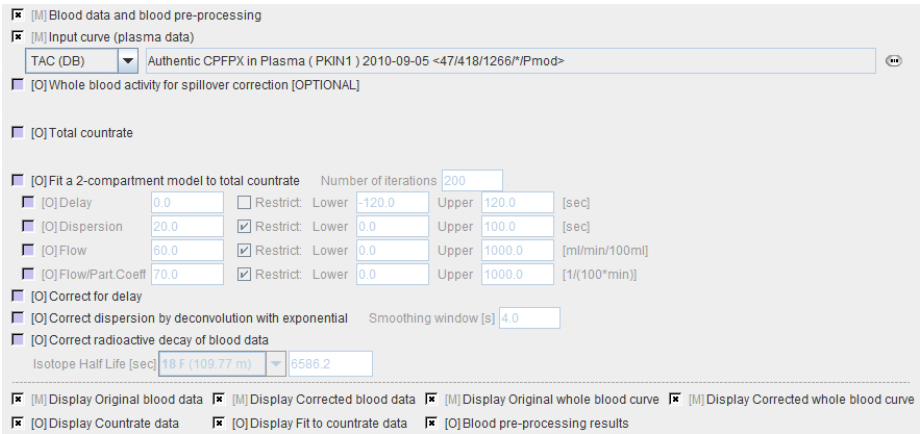
- The blood volume fraction vB can be fixed at a certain value, or fitted in each individual pixel.
- The smoothness of the result maps is determined by the width of the smoothing filter.

Acquisition and Data Requirements

Image Data	A dynamic PET data set.
Blood Data	The plasma activity from the time of injection until the end of the acquisition. Optionally: whole blood activity to be subtracted from the pixel-wise TACs, loaded as **Whole Blood Data** in Blood Preprocessing.
Blood-related TAC	Optional. The delay and dispersion fit can be applied for brain perfusion data with [15O]-H_2O scans.

Blood Preprocessing

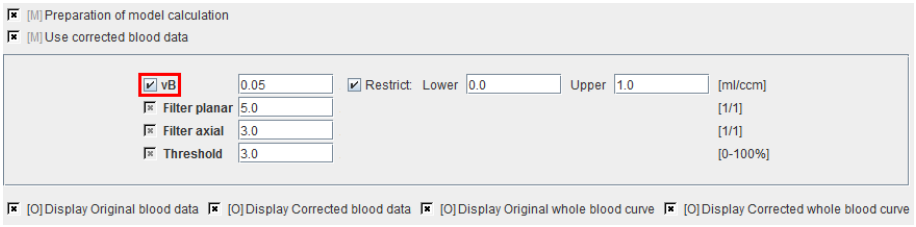
The same blood Preprocessing steps are available as for the brain perfusion model, but except for the data definition field all options are initially disabled as shown below.



If no whole-blood TAC is defined, the plasma curve will be used for spillover correction.

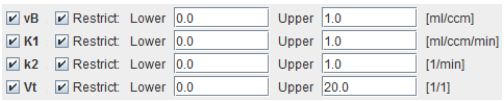
Model Preprocessing

During model Preprocessing a lookup table is calculated within a range of k_2 values. The specifications include an optional TAC which is interpreted as whole-blood activity to be subtracted from the pixel-wise TACs.



vB	Blood volume fraction defining the pixel-wise blood spillover correction.
Filter planar	Number of pixels in the smoothing filter in x and y.
Filter axial	Number of pixels in the smoothing filter in z.
Threshold	Discrimination threshold for background masking.

Map Parameters



vB	Blood volume fraction defining the pixel-wise blood spillover correction. To fit, please activate in the Preprocessing tab.
K1	K_1 rate constant of 1-tissue compartment model.
k2	k_2 rate constant of 1-tissue compartment model.
Vt	Distribution volume.

Reference

[1] Zhou Y, Huang S, Bergsneider M. Linear Ridge Regression with Spatial Constraint for Generation of Parametric Images in Dynamic Positron Emission Tomography Studies. IEEE Tans Nucl Sci. 2001;48(1):125-130.

Two-Tissue Compartment Model with Iterative Fitting

The **2-Tissue Compartment, K1/k2** model implements fitting a two-tissue compartment model in each image pixel. However, because of the high noise level in pixel-wise TACs the fitting of a full 2-tissue compartment model is often not successful. One way to alleviate this problem is to reduce the number of fitted parameters, for instance by fixing the values of k_4

and/or K_1/k_2 at a value which can be reasonably assumed as constant across all tissues. As an example, with PMP, Koeppe et al. [1] fixed k_4 at a value of zero and the distribution volume of the non-displacable compartment K_1/k_2 at a value determined beforehand with a regional TAC analysis.

Processing is done in the following way:

During Preprocessing a TAC is read from a file or averaged in a specified VOI. The TAC is then iteratively fitted to a 2-tissue compartment model which is described by the parameters K_1, K_1/k_2, k_3, k_4. Each of the parameters can be estimated or, alternatively, fixed at a value which is known *a priori*. With PMP, for example, k_4 was fixed at a value of zero. K_1/k_2 represents the distribution volume of non-specific binding. It is used as a fit parameter instead of k_2 because often K_1/k_2 can be assumed to be identical in tissues with and without specific binding.

During model-processing, the same 2-tissue compartment model is fitted to the TAC in each individual image pixel. The parameters resulting from the Preprocessing fit are used per default as the starting values of the pixel-wise iterative fits. These values, however, can be modified in the model parameters dialog, as well as the fitting flags. The default behaviour is suitable for a tracer such as PMP: K_1, and k_3 are fit-enabled, while K_1/k_2, is fixed.

Note that iterative fitting in all image pixels is a computationally intensive process. For efficiently working with this model it is recommended:

- Use a computer system with multiple processing cores.
- To apply a mask to the image data and set all background areas to zero beforehand.
- To first test the model configuration by processing only the current slice (enable the **1S** flag, see screen capture below).
- During model processing lower the priority of the `java` process, so that interactive working is still possible on the computer if needed.
- Or to set up a batch and run the fitting over night.

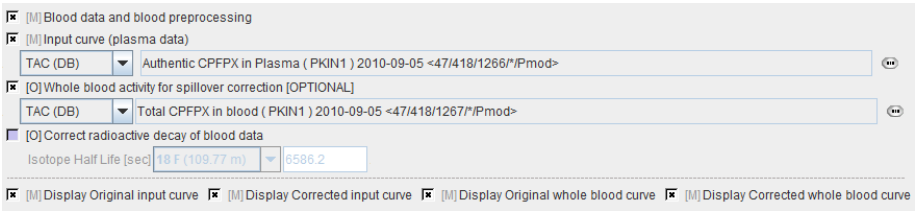
Note: By fixing k_3 and k_4 at a value of 0 the **2-Tissue Compartment, DV** model can be used to fit a 1-tissue compartment model.

Acquisition and Data Requirements

Image Data	A dynamic PET data set with 2-tissue kinetics.
Blood Data	The plasma activity from the time of injection until the end of the acquisition. Optionally whole-blood activity can be used for spillover correction.
TAC1	A time-activity curve (or VOI) of representative tissue used to determine the starting parameters and the K_1/k_2 ratio.

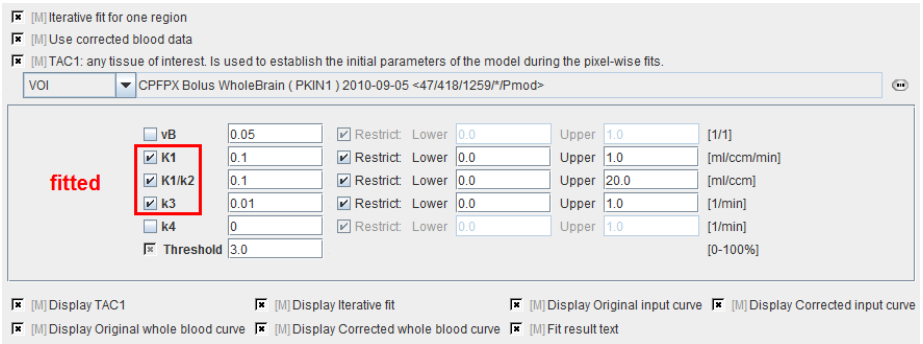
Blood Preprocessing

It is assumed that no Preprocessing other than an optional decay correction must be applied to the plasma activity. This blood data serves as the input curve of the 2-tissue compartment model.



Model Preprocessing

The Preprocessing dialog specifies a tissue time-activity curve (**TAC1**, FILE or VOI), optionally the total blood activity for spillover correction, and in the **Preprocessing parameters** a 2-tissue compartment model configuration. The model is fitted to the TAC during Preprocessing and the values updated accordingly.

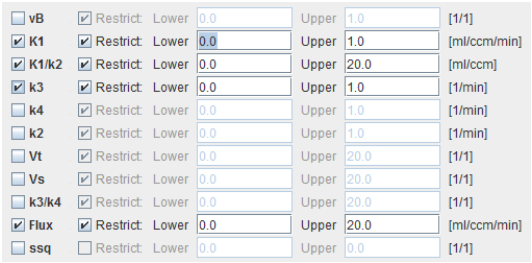


vB	Blood volume fraction defining the pixel-wise blood spillover correction. To fit, please activate in the Preprocessing tab.
K1,k2,k3, k4	Rate constants of the 2-tissue compartment model.
Threshold	Discrimination threshold for background masking.

Note that the user must initially provide reasonable starting values for the fit-enabled parameters. They are most easily obtained in the PKIN tool. The parameters will be adjusted after model preprocessing and serving as the initial values of pixel-wise fitting.

Map Parameters

The model dialog contains the parameters of the 2-tissue compartment model. Maps can only be generated for parameters which have been enabled for fitting in the **Model Preprocessing** panel, because the others remain fix for all pixels.



vB	Blood volume fraction defining the pixel-wise blood spillover correction. To fit, please activate in the Preprocessing tab.
K1,k2,k3, k4	Rate constants of the 2-tissue compartment model.
K1/k2	Distribution volume of the non-displaceable compartment. This is a fitting parameter, while k_2 is calculated from K_1 and K_1/k_2.
Vt	Distribution volume.
Vs	Distribution volume of the second compartment. It is only defined for a reversible configuration where **k4** has been checked for fitting.
k3/k4	Binding potential of receptor tracers.
Flux	Flux to the second compartment: Flux = $(K_1k_3)/(k_2+k_3)$
ssq	Sum-of-squares of the resulting fit. This map can be used to isolate regions with poor fits.

Reference

1. Koeppe RA, Frey KA, Snyder SE, Meyer P, Kilbourn MR, Kuhl DE: Kinetic modeling of N-[11C]methylpiperidin-4-yl propionate: alternatives for analysis of an irreversible positron emission tomography trace for measurement of acetylcholinesterase activity in human brain. J Cereb Blood Flow Metab 1999, 19(10):1150-1163. ***DOI http://dx.doi.org/10.1097/00004647-199910000-00012***

Two-Tissue Compartment Model with Ridge-Regression Fitting

Overview of Ridge-Regression Fitting

Because of the high noise level in pixel-wise TACs the fitting of a full 2-tissue compartment model is often not successful. One way to alleviate this problem is to reduce the number of

fitted parameters, for instance by fixing the values of k_4 and/or K_1/k_2 at a value which can be reasonably assumed as constant across all tissues. As an example, with PMP, Koeppe et al. [1] fixed k_4 at a value of zero and the distribution volume of the non-displacable compartment K_1/k_2 at a value determined beforehand with a regional TAC analysis.

Another approach (which can be combined with parameter fixing) is to try improving the fitting stability by the introduction of constraints. The **2-Tissue Compartment, K1/k2, RR** model implements such an approach called *ridge-regression fitting*. Basically, ridge-regression fitting works as follows:

1) It determines for each image pixel initial values of the model parameters which are relatively close to the final result.

It determines a penalty called *ridge factor* for changing the individual parameters from their respective starting values. Less stable parameters are subject to a stronger penalty. The ridge factors could also vary spatially, but they are asssumed as constant in this implementation.

Using the initial parameters it performs a model fit in each pixel. The adjustment of the model parameters is not only dependent on the difference between the model curve and the pixel-TAC, but also on the difference between the initial and the actual model parameters and their penalties.

CAUTION: While the ridge-regression constraints make fitting more stable, there is a danger that the fit results are biased. For instance, if the penalties are very high, the parameters will not be varied at all, and the fit will return the initial parameters. Therefore, the user should experiment with the ridge factors and compare the results of pixel-wise fitting with the results when fitting regional TACs before accepting the pixel-wise fitting results.

K-Means Clustering

The initial values of the model parameters are automatically determined by the following approach:

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. These remaining pixels are classified into N clusters using a k-means algorithm [2]. The time-weighted Euclidean distance distance can be used as the measurement of dissimilarity (or distance) between TACs.

N non-background pixels serving as initial cluster centroids are randomly assigned.

Each pixel is assigned to that centroid with minimal distance between the TACs, thus forming N initial clusters.

For each cluster a new centroid TAC is calculated as the average TAC of all pixels in the cluster.

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.

The final centroid TACs are fitted by a standard two-tissue compartment model without penalties, yielding N sets of fit parameters (K_1, K_1/k_2, k_3, k_4) together with estimates of their standard errors derived from the fitting covariance matrix of the Marquardt-Levenberg algorithm.

Non-Linear Ridge Regression

For the ridge-regression fitting of the pixel-wise TACs with a two-tissue compartment model, the standard cost function WRSS (weighted residuals sum of squares) is extended by a term which penalizes the local parameter variation [3,4]. This TSS (total sum of squares) criterion is given by the expression [5]

$$TSS(\theta) = WRSS(\theta) + \sum_{i=1}^{p} h_i(\theta_i - \beta_i)^2$$

where θ denotes the parameter set to be optimized, β_i the initial parameter estimates, and h_i the ridge factors for the p fitted parameters. This TSS criterion is integrated into the Marquardt-Levenberg optimization, including the calculation of the Hessian and gradient matrices.

For performing the pixel-wise ridge-regression fits, for each parameter a β_i image is needed which provides a reasonable approximation of the final parameter value. Assuming successful clustering and stable fits of the centroid TACs, β_i images are obtained by creating cluster images using the parameter values resulting from the centroid fits, and applying a spatial filter to accommodate smooth transitions. A simple average filter is used which replaces a pixel value by the average within a certain spatial neighbourhood.

The ridge factors h_i should be chosen such that changes of unstable parameters are penalized to a stronger extent. Assuming that a large standard error (ste) indicates a parameter which suffers from a high variability, it is included in the ridge factors [3]. To allow more variation for parameters with a large value range across the clusters, the ridge factors are calculated by

$$h_i = \left(\frac{median(ste_i)}{median(\beta_i)range(\beta_i)} \right)^2$$

Median(β_i) represents the median of the parameter θ_i across the N cluster fits, and range(β_i) the absolute difference between the maximal and the minimal fit value. The ridge factors are smoothed in the same way as the initial parameters. Additionally, the user interface supports a scaling factor for each h_i value to allow for manual adjustments of the individual parameter penalties. Finally, the TSS cost funcion is iteratively optimized using the extended Marquardt-Levenberg method.

Overview of the Processing in PXMOD

During Preprocessing, a cluster analysis is performed for suppressing the background and grouping the remaining pixels into clusters of similar uptake over time. Then, a 2-tissue compartment model is fitted without constraints to the average TAC of the clusters. To obtain initial parameter values per pixel, the parameter values resulting from the cluster

TAC fits are assembled into parametric maps, which are smoothed. *The user should check the clustering and the initial parameter maps to verify that the number of clusters is adequate and the grouping successful.* The system also derives estimates of the ridge factors from the fit results, which can be separately scaled by the user.

Since processing of the whole data set will take substantial time, the user should then pixel-wise fit (now with ridge regression) a single image slice for confirming that the settings of the ridge factors are suitable. He can do so by comparing the parametric maps of the inital parameters with the result parameters. If there is no change, the ridge factor is too strong; if there are changes but the noise is too high, the ridge factor is too weak. The user should adjust the ridge factors of the individual parameters accordingly, and then try again.

Note that the iterative fitting of all image pixel TACs is a computationally intensive process and may well take hours. For efficiently working with this model it is recommended:

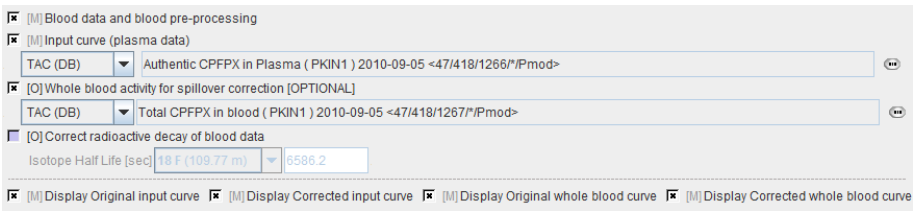
- To make sure background is properly masked to avoid unnecessary, time-consuming fits.
- To first test the model configuration by processing only the current slice (enable the **1S** flag).
- Possibly set up a batch and run the fitting with different ridge factor settings over night.

Acquisition and Data Requirements

Image Data	A dynamic PET data set with 2-tissue kinetics.
Blood Data	The plasma activity from the time of injection until the end of the acquisition. Optionally, whole-blood activity can be used for spillover correction.
TAC1	A time-activity curve (or VOI) of representative tissue used to determine the initial model parameters which are used for the cluster TAC fitting.

Blood Preprocessing

It is assumed that no reprocessing other than an optional decay correction must be applied to the blood activities. This plasma activity serves as the input curve of the 2-tissue compartment model, and the whole blood activity for spillover correction.

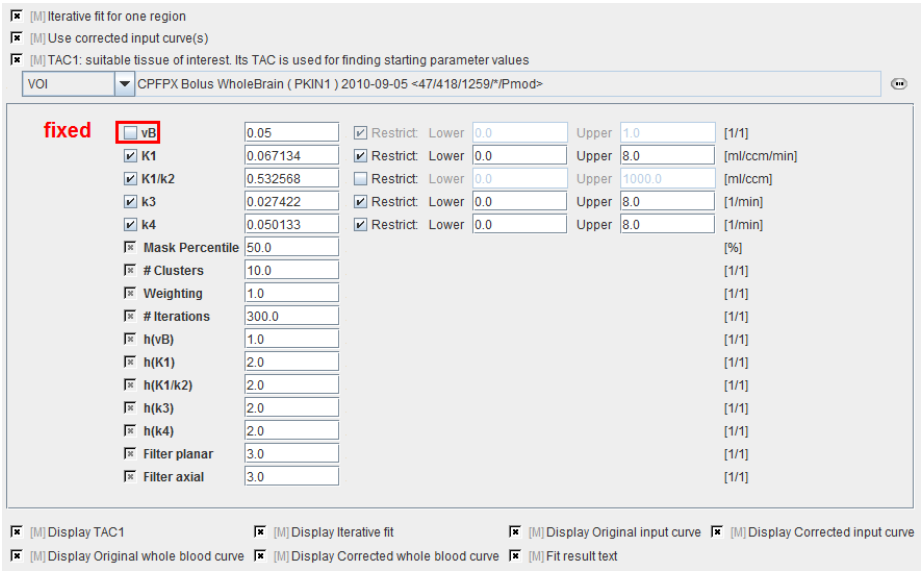


Model Preprocessing

The model preprocessing panel specifies a tissue time-activity curve (**TAC1**, FILE or VOI), and the **parameters** a 2-tissue compartment model configuration. Only the parameters which have the fit flag enabled are varied, while the other ones are kept fixed. The user should enter reasonable initial parameter values. They are most easily obtained in the PKIN tool. To transfer the current data quickly to the PKIN tool, just select the ***kinetic modeling button*** (on

page 34). Additionally, the dialog window contains parameters related to the clustering and ridge regression fitting.

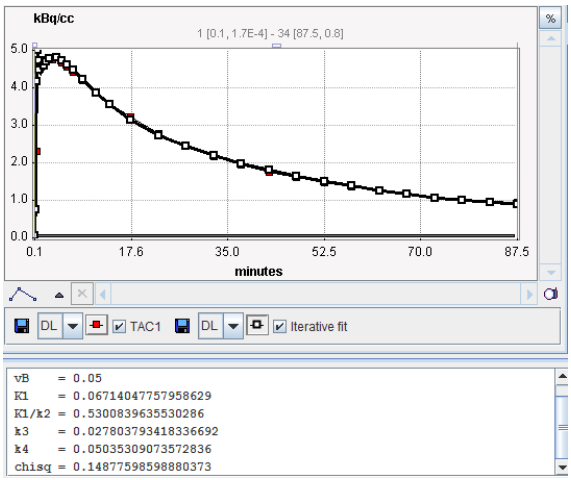
During Preprocessing the TAC1 is iteratively fitted, and the model parameter values updated accordingly. Then the cluster analysis is performed, the centroid TACs fitted, and the fitting results used for setting up the maps of initial fitting parameters.



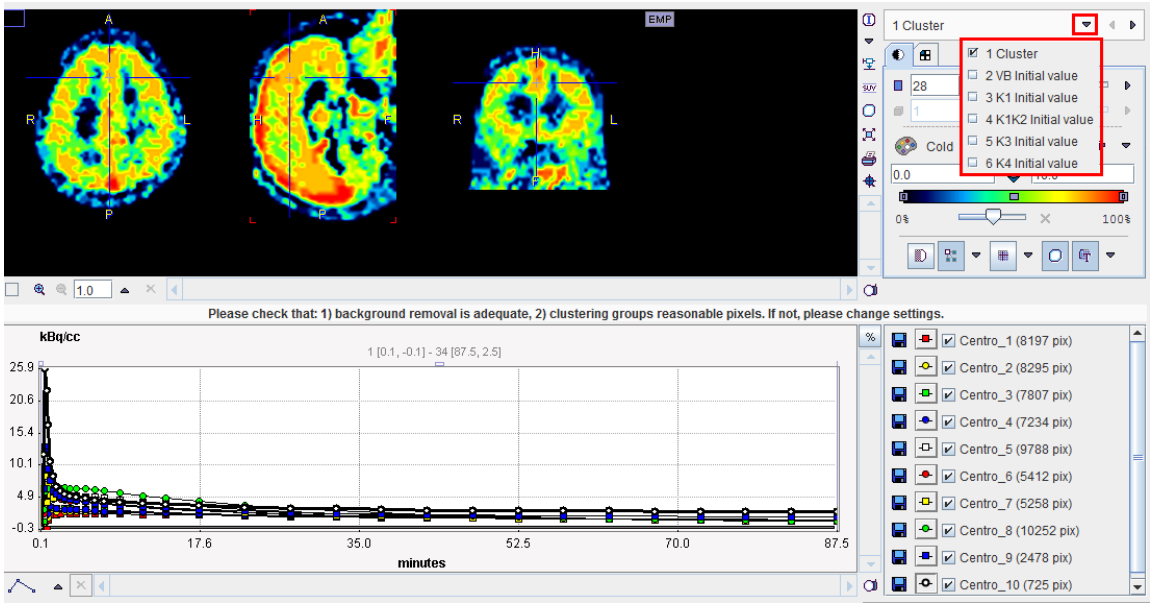
vB	Blood volume fraction. Is usually fixed at a value of 0.05 representing that 5% of the signal is from the blood space.
K1, K1/k2, k3, k4	Fit parameters of the two-tissue compartment model using the non-specific distribution volume K_1/k_2 as a fitting parameter instead of k_2. They are updated by the results of fitting the model to **TAC1**.
Mask Percentile	To mask out backgound pixels, a map of the TAC signal energy is calculated. The signal energy is the sum of all squared values of a TAC. A histogram analysis is performed, and all pixels which have a signal energy below a specified percentile are considered as background pixels. Specification of a 20% percentile means the 80% pixels with the highest energy are used.
# Clusters	Number of clusters into which the non-background pixels are grouped.
Weighting [1|2]	During the clustering, the distance between the TACs is calculated as the sum of the squared weighted differences. The valid choices are: 1 = equal weighting of all squared differences (default) 2 = the differences are weighted by the frame durations
# Iterations	Maximal number of refinements during the cluster analysis. Is required to avoid loops.

h(vB)	User-defined scaling factor for the ridge factor of the vB model parameter. The behavior is exponential, so entering values of 0, 1, 2, etc result in scaling factors of 1, 10, 100 (10^h). Higher ridge factors punish parameter variation.
h(K1), h(K1/k2), h(k3), h(k4)	User-defined scaling factors for the other ridge factors as described above.
Filter planar	In-plane width of the averaging filter for spatially smoothing the initial parameters. Specification of a planar filter size of 5 and an axial filter size of 3 results in a (5x5x3) averaging filter.
Filter axial	Axial width of the averaging filter, see above.

The results of model preprocessing are available on the dedicated **Results** and the dedicated **Clustering Results** panels. The **Results** panel shows the fit to the TAC1 curve together with the parameter values.



The **Clustering Results** panels allows inspecting the parametric images of clustering and the initial parameters for the pixel-wise fit. The curve area in the lower part shows the cluster centroid TACs, ie the average TAC of all pixels in the cluster.



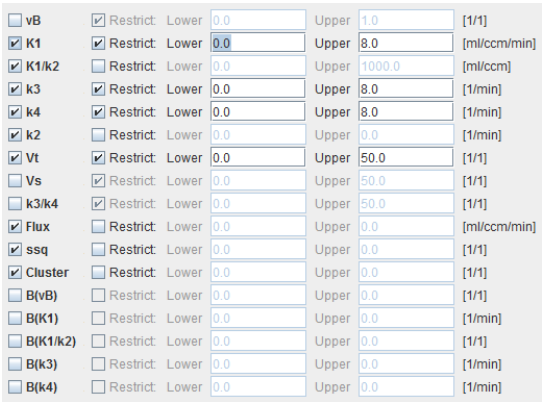
Map Parameters

The model dialog contains a substantial number of parameters for which maps can be calculated. They are arranged in 3 groups:

1) The actual fit parameters vB, K_1, K_1/k_2, k_3, k_4 of the 2-tissue compartment model. Note that the same parameters should be enabled for fitting as during the Preprocessing. The values shown are copied from the result of fitting the TAC1 curve, but they are NOT used as inital values for pixel-wise fitting.

Parameters which are derived from the fitted model parameters such as the distribution volumes and the flux.

The inital values of the model parameters calculated during Preprocessing which are used for pixel-wise fitting. They are helpful for assessing to what extent the parameters were adjusted during ridge-regression fitting.



vB, K1, K1/k2, k3, k4	The parameters of the 2-tissue compartment model. The fit flag determines, which parameters are actually fitted, and which are fixed. Note that the same parameters should be fitted as in Preprocessing.

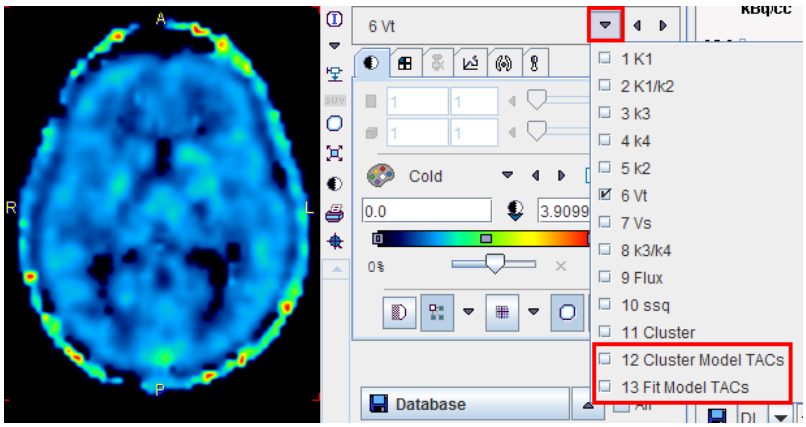
k2	The k_2 rate constant $k_2 = K_1/(K_1/k_2)$
Vt	Total volume of distribution: $Vt = K_1/k_2(1+k_3/k_4)$
Vs	Distribution volume of specific binding: $Vs = K_1/k_2 * k_3/k_4$
k3/k4	Binding potential: $BP_{ND} = k_3/k_4$
Flux	Flux to the second compartment: $Flux = (K_1k_3)/(k_2+k_3)$
ssq	Chi squared of the fit. The corresponding map shows where the fitting was not able to achieve a good match, for instance in pixels of the blood pool.
Cluster	Index of the cluster to which the pixel belongs. 0 represents a background pixel. Cluster images could be helpful for VOI analysis.
B(vB), B(K1), B(K1/k2), B(k3), B(k4)	Initial values of the model parameters for fitting the 2-tissue compartment model in the individual pixels.

Additional Results: Synthetic dynamic series

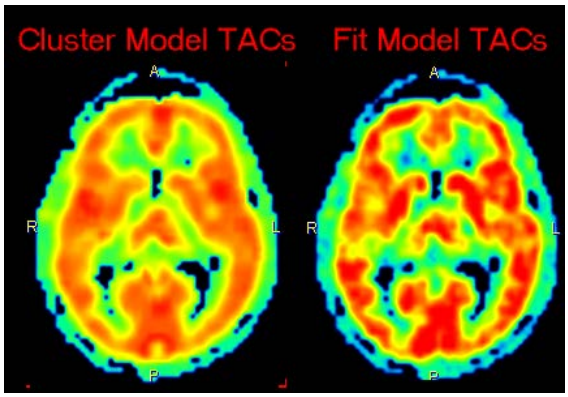
In addition to the parametric maps the model also calculates two dynamic image series:

1) **Cluster Model TACs**: Synthetic image series assembled from the model TAC in each pixel which is calculated using the 2-tissue compartment model and the initial parameters.

Fit Model TACs: Synthetic image series assembled from the model TAC in each pixel which is calculated using the 2-tissue compartment model and the fitted parameters.



These image series can serve as phantom images for research, because the uptake in each pixel represents ideal 2-tissue kinetics, and the model parameters are exactly known. So other quantification methods can be applied to analyze these synthetic data and the results compared with the true parameters, which are available as parametric maps.



References

1. Koeppe RA, Frey KA, Snyder SE, Meyer P, Kilbourn MR, Kuhl DE: Kinetic modeling of N-[11C]methylpiperidin-4-yl propionate: alternatives for analysis of an irreversible positron emission tomography trace for measurement of acetylcholinesterase activity in human brain. J Cereb Blood Flow Metab 1999, 19(10):1150-1163. ***DOI http://dx.doi.org/10.1097/00004647-199910000-00012***

2. Velamuru PK, Renaut RA, Guo H, Chen K. Robust Clustering of Positron Emission Tomography Data. Paper presented at: Joint Conference of the Classication Society of North America and Interface Foundation of North America, 2005; St. Louis.

3. Byrtek M, O'Sullivan F, Muzi M, Spence M. Use of ridge regression for improved estimation of kinetic constants from PET data. IEEE Trans Nuclear Science. 2005;52(1):63-68.

4. Zhou Y, Huang SC, Bergsneider M, Wong DF: Improved parametric image generation using spatial-temporal analysis of dynamic PET studies. Neuroimage 2002, 15(3):697-707.

5. O'Sullivan F, Saha A: Use of ridge regression for improved estimation of kinetic constants from PET data. IEEE Trans Med Imaging 1999, 18(2):115-125.

Two-Tissue Compartment Model with Basis Functions

The **2-Tissue (BFM)** model implements fitting a two-tissue compartment model in each image pixel. It is based on an analytic solution of the system of differential equations which results in the calculation of two eigenvalues α_1 and α_2.

$$\alpha_{1,2} = \frac{(k_2 + k_3 + k_4) \mp \sqrt{(k_2 + k_3 k_4)^2 - 4k_2 k_4}}{2}$$

The expected tissue activity is obtained by the convolution of the input function with a sum of two decaying exponentials plus a contribution from whole blood.

$$C_{Model}(t) = \left(\theta_1 e^{-\alpha_1 t} + \theta_2 e^{-\alpha_2 t}\right) \otimes C_P(t) + v_B C_B$$

This operational equation which can be fitted to the data has 5 parameters: θ_1, θ_2, α_1, α_2, v_B . It is linear in the parameters θ_1, θ_2, v_B, and nonlinear in α_1, α_2 . The θ_1 and θ_2 parameters are also a combination of the rate constants.

The basis function method by Hong and Fryer [1] performs the data fitting in the following way:

1) For a certain tracer the physiological range of k_2, k_3, k_4 can be determined. These values can be translated into a range of α_1 and α_2 values which can be expected in the data. With FDG, for instance, $\alpha_1 \in [0.0005,0.015]\text{min}^{-1}$ and $\alpha_2 \in [0.06,0.6]\text{min}^{-1}$.

The functions e^{-a1} and e^{-a2} are called the basis functions. They are pre-calculated for tabulated α_1 and α_2 values which span the prescribed ranges.

In fitting the data, each combination of α_1 and α_2 is examined: the input curve is convolved with the pre-calculated exponentials, and then the operational equation is fitted with respect to the remaining parameters θ_1, θ_2, v_B. Since all of them enter linearly, the solution is unique and can be quickly calculated. For each of the calculations the chi-square criterion is recorded.

Since the fitting has to be performed for each combination of α_1 and α_2, N^2 results are obtained if N is the number of table entries. Finally the combination θ_1, θ_2, v_B, α_1, α_2 with minimal chi square is considered as the solution.

In the case of irreversible binding k_4 is assumed to be zero. Hereby the number of fitted parameters is reduced and the operational equation simplifies to

$$C_{Model}(t) = \left(\theta_1 + \theta_2 e^{-\alpha_2 t}\right) \otimes C_P(t) + v_B C_B$$

It is notable that in this case only one basis function appears in the equation. Therefore, the number of linear fits is reduce from N^2 to N, making pixel-wise fitting very fast.

Overview of the BFM Processing in PXMOD

In PXMOD, both the reversible and the irreversible configuration are supported. Furthermore, it is possible to allow fitting of the blood volume fraction, or to fix it at a specific value. The linear fitting is done without weighting using the singular value decomposition method.

The configurations (k_4 fitted or 0, v_B fitted or fixed) are specified as parameters of preprocessing. During preprocessing, the 2xN basis functions are pre-calculated and stored for pixel-wise processing. Then, the BFM analysis is applied to the TAC and the result shown for inspection. Finally, pixel-wise processing calculates maps of all parameters.

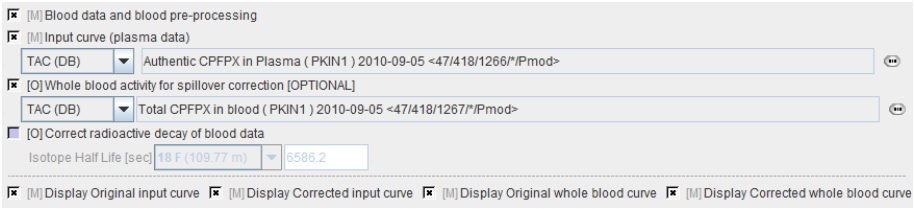
In setting up the processing for a new tracer it is recommended to enable the calculation of the α_1 and α_2 maps and inspect them regarding the prescribed range. If the prescribed maximum or minimum value is very frequently encountered this indicates that the range should be expanded.

Acquisition and Data Requirements

Image Data	A dynamic PET data set.
Blood Data	The plasma activity from the time of injection until the end of the PET acquisition. Optionally: whole blood activity to be subtracted from the pixel-wise TACs, loaded as **Whole Blood Activity** in Blood Preprocessing.

Blood Preprocessing

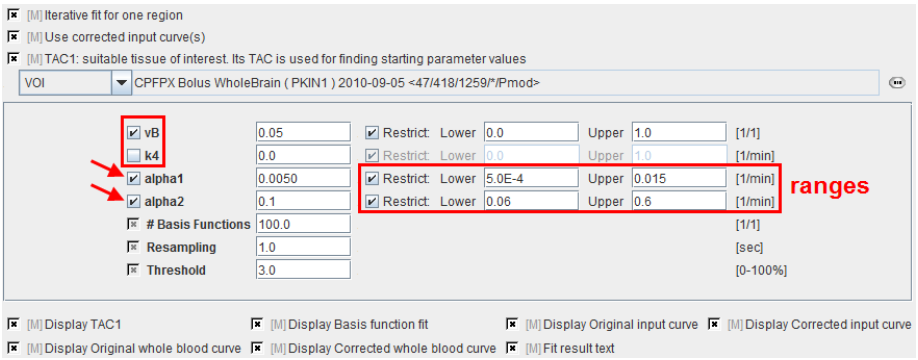
Data to be provided are the input curve, and optionally a whole-blood TAC for spillover correction. No whole-blood curve is defined, the input curve will also be used for spillover correction.



Model Preprocessing

During model preprocessing the basis functions are calculated for the prescribed range of α_1 and α_2 values. The default ranges ar $\alpha_1 \in [0.0005,0.015]\text{min}^{-1}$ and $\alpha_2 \in [0.06,0.6]\text{min}^{-1}$ are suitable for FDG. To change the ranges please first enable the **alpha1** or **alpha2** parameter and then adjust the **Lower** and **Upper** values.

Also important is the fit flag of **vB** and **k4**. If **vB** is checked, the blood fraction will be fitted in model preprocessing and also in the map calculation. Otherwise, the specified value will be used for spillover correction. If **k4** is checked, the full 2-tissue compartment model with four parameters will be fitted in model preprocessing and map calculation. Otherwise, the specified value will be disregarded and k_4 set to zero in all fits.

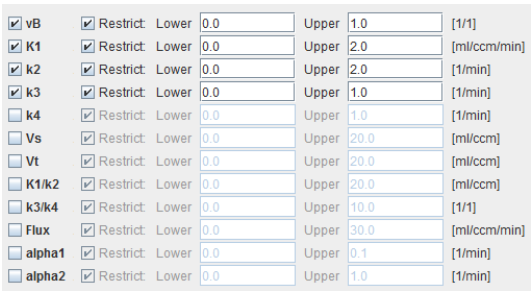


vB	Blood volume fraction. Can be fitted or fixed.
k4	Rate constant k_4 in the 2-tissue compartment model. Can be fitted, otherwise

	it is set to 0.
alpha1 **alpha2**	First and second eigenvalue. The **Lower/Upper** values are used for defining the basis function ranges.
#Basis Functions	Number of intermediate α_i values generated between **Lower** and **Upper**. The increments are logarithmically spaced.
Resampling	Sampling increment applied during the basis function calculation.
Threshold	Discrimination threshold for background masking. All pixels with energy below **Threshold**[%] of the maximal energy will be masked to zero.

Map Parameters

The example below shows a typical configuration for an irreversible mode ($k_4 = 0$ fixed)



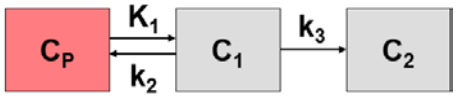
vB	Blood volume fraction defining the pixel-wise blood spillover correction. To fit, please activate in the Preprocessing tab.
K1,k2,k3	Rate constants of the 2-tissue compartment model.
k4	Rate constant of the 2-tissue compartment model. A map can only be obtained if **k4** has been checked for fitting in the preprocessing configuration. Otherwise the map will be zero.
Vs	Distribution volume of the second compartment. It is only defined for a reversible configuration where **k4** has been checked for fitting.
Vt	Distribution volume.
K1/k2	Distribution volume of the non-displaceable compartment.
k3/k4	Binding potential of receptor tracers.
Flux	Influx of the tracer, also called K_i.
alpha1 **alpha2**	Shows the α_1 and α_2 values of the found solution. These values can be used to check whether the defined range was adequate.

Reference

1. Hong YT, Fryer TD: Kinetic modelling using basis functions derived from two-tissue compartmental models with a plasma input function: general principle and application to [18F]fluorodeoxyglucose positron emission tomography. Neuroimage 2010, 51(1):164-172.

Multiple Linear Analysis for Irreversible Radiotracers (MLAIR)

The MLAIR method has been developed by Kim et al. [1] for tracers undergoing irreversible trapping. It is an alternative to the ***Patlak plot*** (on page 112) analysis which is dependent on the specification of an equilibration time t* which may vary among tissues, and may suffer from bias when applied to noisy data. It has applied for the analysis of FDG, which can be modeled as a 2-tissue compartment model with k_4=0, and 11C-labeled MeNTI [1].



Operational Model Curve

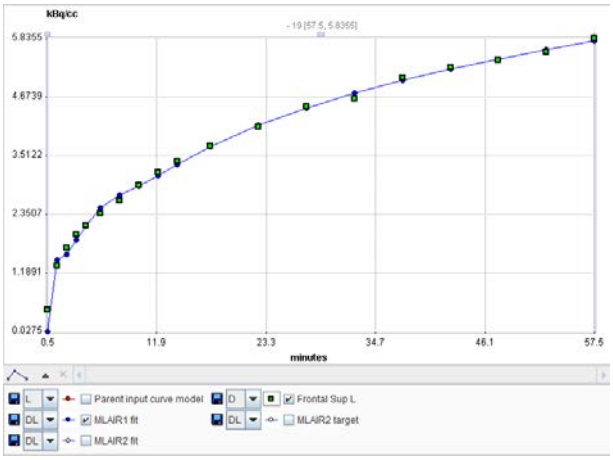
The authors develop two approaches, both of which are included in the **Irreversible Ki (MLAIR)** model. The 2-tissue compartment model structure with k_4=0 is assumed. A blood volume fraction v_B is taken into account, but applied to the metabolite-corrected input curve $C_p(t)$ rather than the whole-blood activity.

The operational equation of method **MLAIR1** for the the measured tissue TAC $C_T(t)$ is given by

$$C_{Model}(t) = P_1 C_P(t) + P_2 \int_0^t C_P(\tau)d\tau + P_3 \int_0^t C_T(\tau)d\tau + P_4 \int_0^t \int_0^\tau C_P(s)ds d\tau$$

The linear coefficients are related to the model parameters as follows, allowing to calculate the influx K_i from P_3 and P_4.

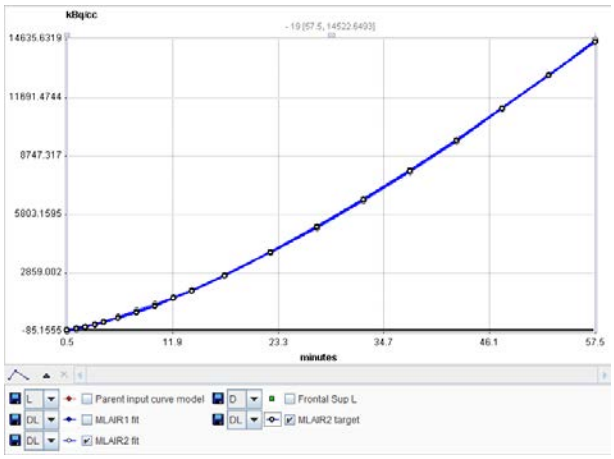
$$\begin{aligned} P_1 &= v_B & P_3 &= -(k_2 + k_3) \\ P_2 &= K_1 + k_2 v_B + k_3 v_B & P_4 &= K_1 k_3 \\ K_i &= -P_4 / P_3 \end{aligned}$$



In order to avoid the P_4/P_3 division of MLAIR1 which might intorduce artefacts for noisy data, a second second multilinear operational equation MLAIR2 was developed which estimates K_i as a direct regression parameter. **MLAIR2** has the following operational equation for the integrated tissue activity curve:

$$C_{Model}(t) = \int_0^t C_T(\tau)d\tau = P_1 C_P(t) + P_2 \int_0^t C_P(\tau)d\tau + P_3 C_T(t) + P_4 \int_0^t \int_0^\tau C_P(s)ds d\tau$$

$$P_1 = v_B/(k_2+k_3) \qquad P_3 = -1/(k_2+k_3)$$
$$P_2 = K_1/(k_2+k_3)+v_B \qquad P_4 = K_i$$



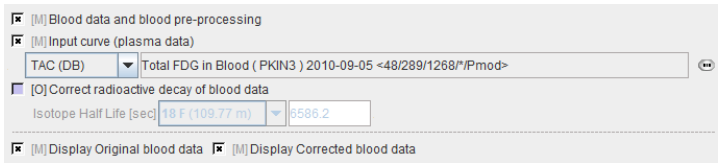
MLAIR2 is more robust and preferred for pixel-wise noisy TACs, whereas **MLAIR1** is less biased and preferred for VOI based TACs. SVD-based multi-linear regression is applied for model fitting.

Acquisition and Data Requirements

Image Data	A dynamic PET data set of a tracer with irreversible uptake.
Blood Data	Blood activity sampled at a peripheral artery from the time of injection until the end of the acquisition, and corrected for metabolites
Tissue TAC	A regional time-activity curve from a representative brain region. It is presented as a Logan plot and can be used to define the linear segment where regression analysis should be done.

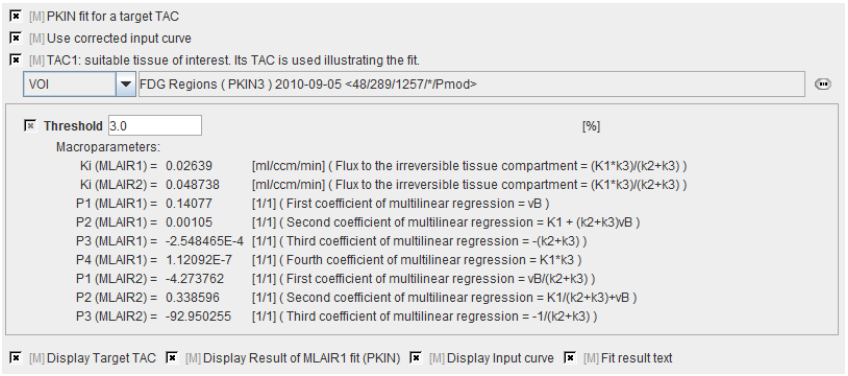
Blood Preprocessing

Decay correction is the only blood correction option.



Model Preprocessing

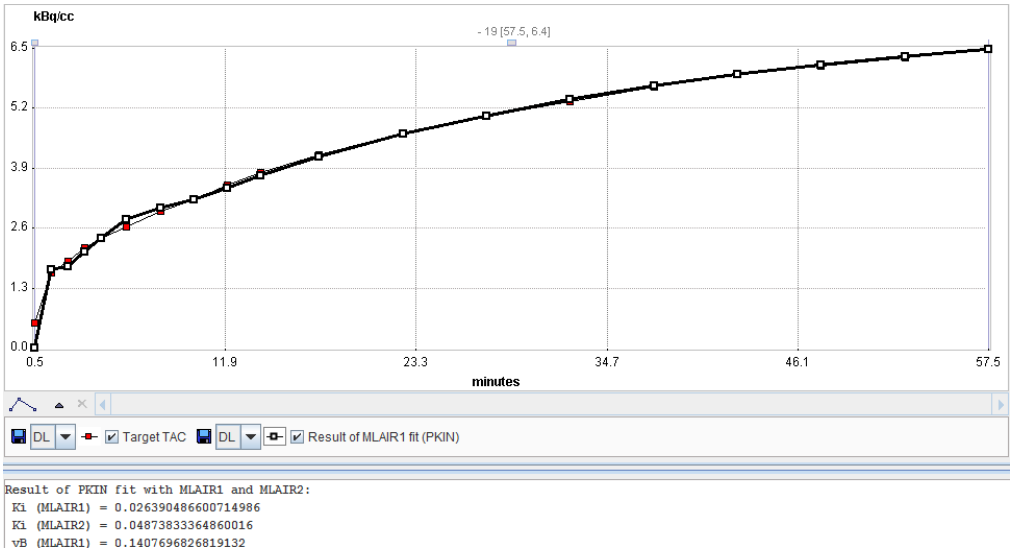
The preprocessing perfoms an MLAIR analysis of the **TAC1** specified. It uses the MLAIR model implementation in PKIN.



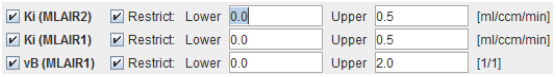
There are no parameters to configure except for the background thresholding.

Threshold	Discrimination threshold for background masking.

The **MLAIR1** fit is shown in the preprocessing **Result**. In order to see the result of **MLAIR2** please transfer the data to PKIN and apply the model there.



Map Parameters



Ki (MLAIR2)	Influx rate estimated with the more robust variant **MLAIR2**, which may suffer from more bias.
Ki (MLAIR1)	Influx rate estimated with the less robust variant **MLAIR1**.

vB	Estimate the blood volume fraction by **MLAIR1**.

Reference:

1. Kim SJ, Lee JS, Kim YK, Frost J, Wand G, McCaul ME, Lee DS: Multiple linear analysis methods for the quantification of irreversibly binding radiotracers. J Cereb Blood Flow Metab 2008, 28(12):1965-1977. ***DOI http://dx.doi.org/10.1038/jcbfm.2008.84***

Myocardial Blood Flow for Ammonia PET Scans

The **MBF NH3 (BFM)** model implements the pixelwise fitting of a cardiac model for dynamic ammonia PET scans. The model was derived from the parametric mapping method developed by Harms et al [1] for water scans.

The operational equation for cardiac PET includes two geometric spillover fractions (V_{lv}, V_{rv}) from left ventricular and right ventricular blood (C_{lv}, C_{rv}):

$$C_{Model}(t) = (1 - V_{LV} - V_{RV})C_{myo}(t) + V_{LV}C_{LV}(t) + V_{RV}C_{RV}(t)$$

The tracer concentration in myocardium $C_{myo}(t)$ is modeled by a one-tissue compartment model and can be obtained by the convolution of the metabolite-corrected input curve with a decaying exponential, multiplied by K_1:

$$C_{myo}(t) = K_1(1 - mCorr \cdot t)C_{LV}(t) \otimes e^{-k_2 t}$$

For the ammonia tracer K_1 corresponds to mycocardial blood flow (MBF), and k_2 to the tissue washout. The linear metabolite correction with slope -mCorr which is applied in this equation was derived by de Grado et al [2] and is only valid for scan durations up to 4 minutes.

The solution of the operational equation uses basis functions of the form

$$B_i(t) = (1 - mCorr \cdot t)C_{LV}(t) \otimes e^{-k_2 t}$$

With the basis functions, the operational equation can be reformulated as a multi-linear equation

$$C_{Model}(t) = \theta_1 B_i(t) + V_{LV}C_{LV}(t) + V_{RV}C_{RV}(t)$$

with

$$\theta_1 = K_1(1 - V_{LV} - V_{RV})$$

The data analysis methodology then consists of the following two steps:

1) As a preprocessing step the basis functions are calculated for a set of k_2 values which span the physiologic relevant range.

In each pixel the TAC is fitted by solving the operational equation for all basis functions and selecting the solution which best fits the measurement. From the resulting parameters θ_1, V_{lv}, and V_{rv} the MBF (=K_1) can readily be calculated.

If the blood contribution in a pixel is too high ($V_{lv}+V_{rv}>0.75$), the MBF result is discarded.

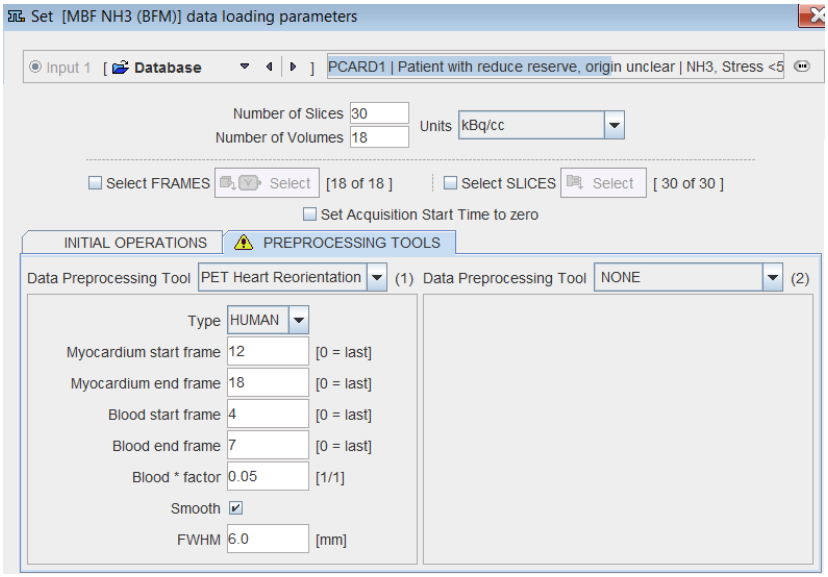
Note: The same model is also applied for the MBF parametric mapping ina the cardiac PET tool PCARDP

Data Requirements

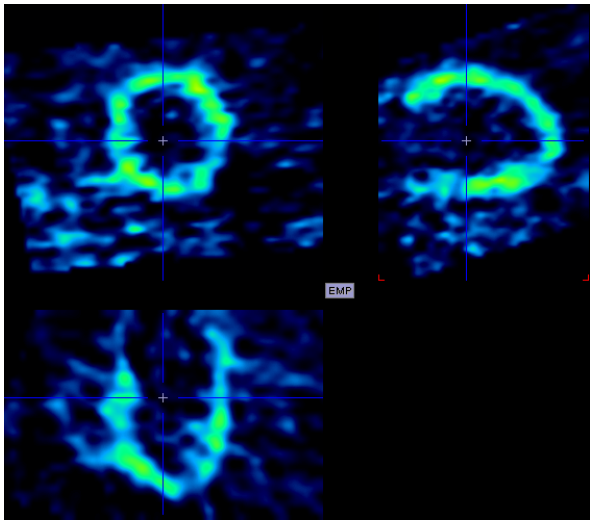
Image Data	A cardiac PET data set using the ammonia tracer and acquired for 4 minutes. If the acquisition was longer, only the first 4 minutes should be loaded.
Blood Data	The TAC of blood in the left ventricle and right ventricles is required. Both TACs are applied for a geometrical spillover correction. The LV TAC is also metabolite-corrected and used as the input curve for the 1-tissue compartment model of ammonia.

Data Loading

It is recommended to reorient the images into short-axis (SA) orientation for the processing. This operation can be performed outside of PXMOD. An alternative is to try the **PET Heart Reorientation** during data loading by the configuration illustrated below. Essentially, the early and the late phases are averaged and an automatic procedure tries finding the SA orientation. For details please refer to the guide of the cardiac PET tool PCARDP which explains the background in more detail.

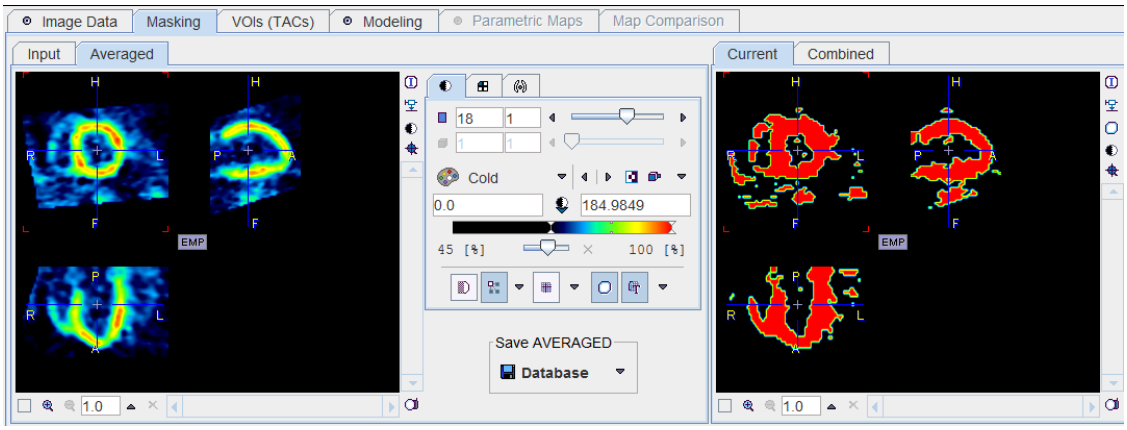


The example below illustrates a successful reorientation result. If it fails, it is recommended to try optimizing the frame ranges used for averaging.



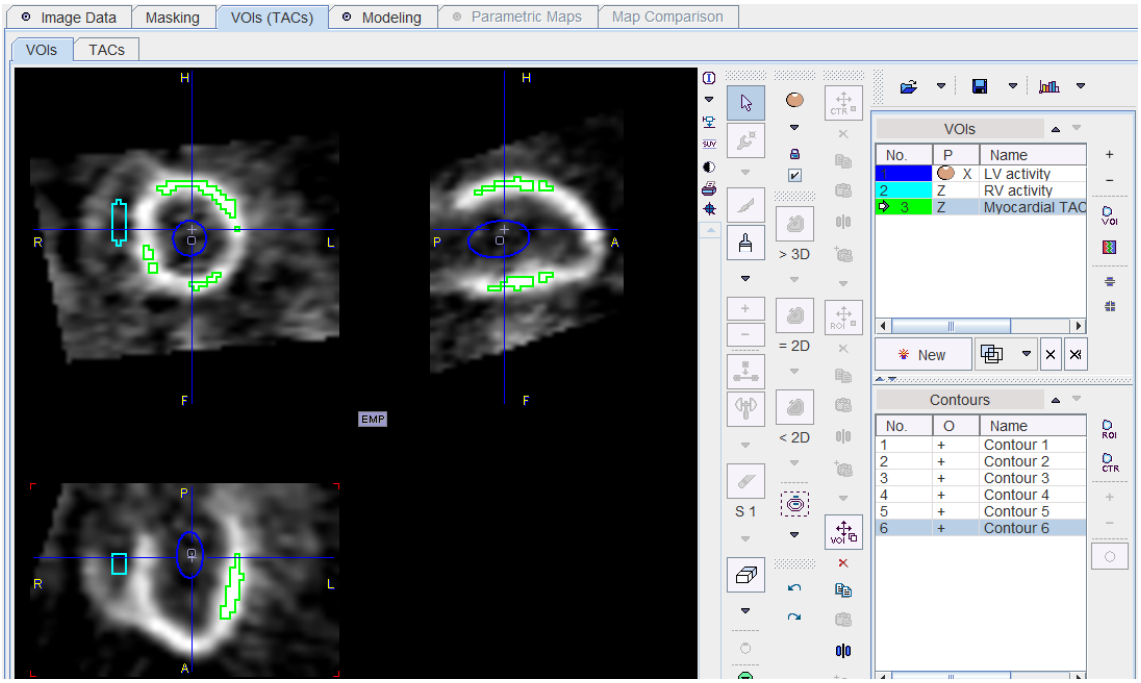
Masking

It is recommended generating a mask which restricts parametric mapping to the myocardium. This can easily be achieved by a threshold segmentation of the averaged late frames.



TACs

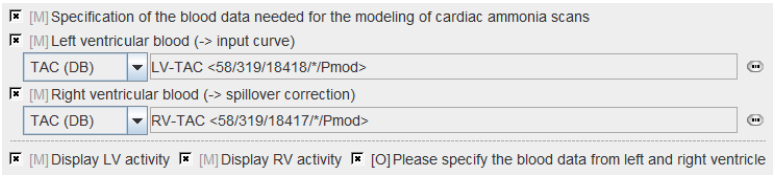
In SA orientation the definition of VOIs should be relatively easy. In the example below a regular sphere was placed in the **LV**, scaled and slightly rotated. The RV VOI was created using the paintbrush, and the Myocardial VOI using the **>3D** region growing.



In order to be independent of the image orientation it is recommended to save the actual curves rather than the VOI definition by the Time Activity Curve button ton the **TACs** panel.

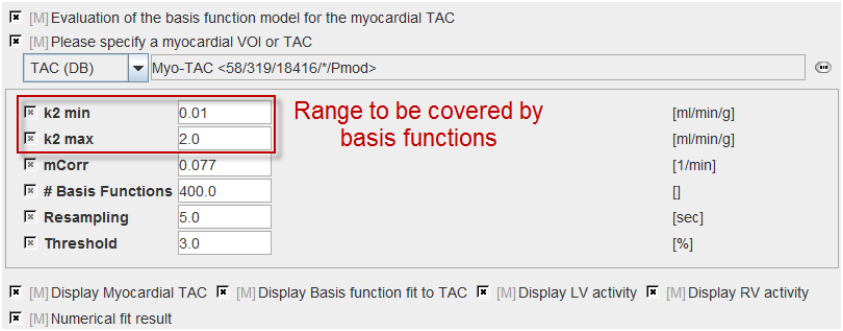
Blood Preprocessing

By the saving of the TACs from the **TACs** panel the references to the curves are directly stored to the **Blood Preprocessing** panel.



Model Preprocessing

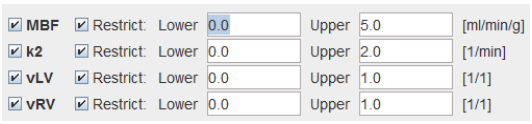
During model preprocessing the basis functions are calculated for the prescribed range of k_2. The default range is $\alpha_1 \in [0.01,2]min^{-1}$. Using these basis functions, the myocardial TAC is then fitted.



k2 min **k2 max**	Define the k_2 range covered by the basis functions.
mCorr	Slope of the linear metabolite correction which is applicable for 4 minutes.
#Basis Functions	Number of intermediate k_2 values generated between **k2 min** and **k2 max**. The increments are logarithmically spaced.
Resampling	Sampling increment applied during the basis function calculation.
Threshold	Discrimination threshold for background masking. All pixels with energy below **Threshold**[%] of the maximal energy will be masked to zero.

Map Parameters

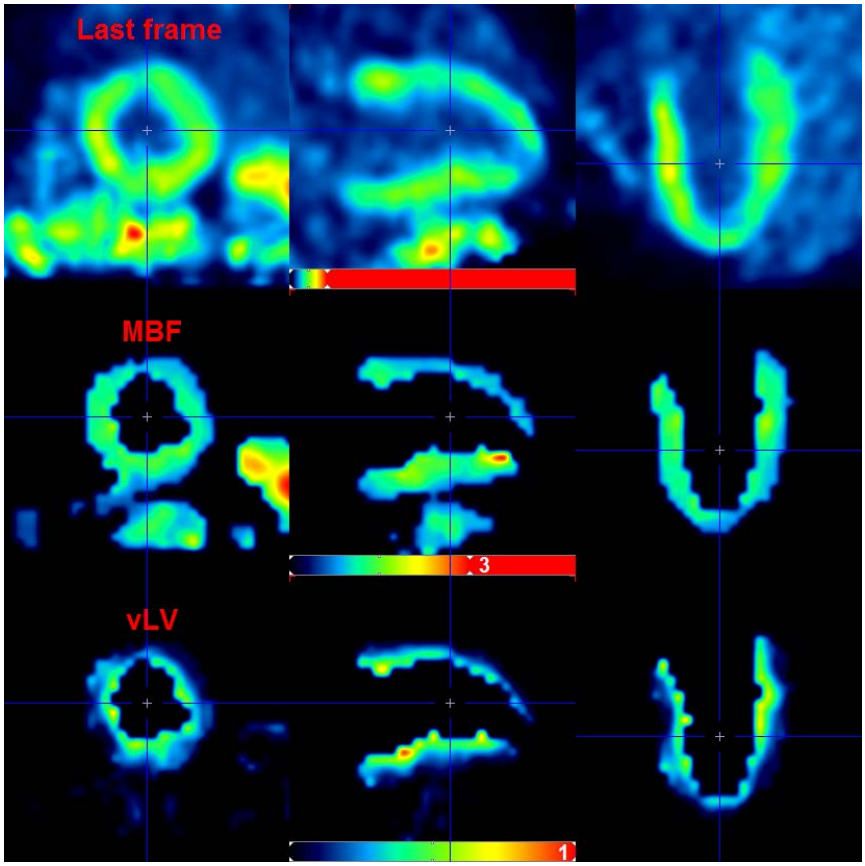
The example below shows the default configuration.



MBF	Myocardial blood flow, equal to K_1 in the 1-tissue compartment model.
k2	The k_2 value which basis function provided the best fit of the data.
vLV	Fraction of blood spillover from the left ventricle.
vRV	Fraction of blood spillover from the right ventricle.

Example

The example below shows the parametric map of the rest scan with a normal volunteer.



References

1. Harms HJ, Knaapen P, de Haan S, Halbmeijer R, Lammertsma AA, Lubberink M: Automatic generation of absolute myocardial blood flow images using [15O]H2O and a clinical PET/CT scanner. Eur J Nucl Med Mol Imaging 2011, 38(5):930-939.

2. DeGrado TR, Hanson MW, Turkington TG, Delong DM, Brezinski DA, Vallee JP, Hedlund LW, Zhang J, Cobb F, Sullivan MJ et al: Estimation of myocardial blood flow for longitudinal studies with 13N-labeled ammonia and positron emission tomography. J Nucl Cardiol 1996, 3(6 Pt 1):494-507.

Reference Models for Receptor and other Tracers

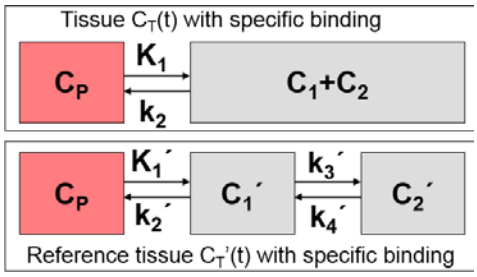
Principle of Reference Models

The measurement and analysis of the blood samples for kinetic modeling is an invasive and demanding procedure. Therefore, methods have been developed to obviate the need for invasive blood sampling. The solutions found replace the arterial input curve by an indirect input curve, namely the time activity curve of some reference tissue. Therefore they are called *reference methods*. Reference methods are not able to provide a full kinetic analysis. However, assuming certain relations between the kinetics of the tissue of interest and the reference tissue, they can provide valuable measures of interest.

Model Structure

Most of the reference methods are dedicated to reversibly binding neuroreceptor tracers. A reference tissue must be found which is devoid of receptors, and then it is assumed that the distribution volume of the non-displaceable compartment (free tracer in tissue and non-specific binding) is the same among the tissues. Under these assumptions a measure of the receptor concentration called *binding potential* (BP) can be calculated from the two time-activity curves.

The reference methods differ in their mathematical approaches, and they show substantial differences with regard to noise sensitivity and processing speed. They are described in the following sections. The compartment models are based upon the following configuration:



In the model equations C'(t) represents the TAC from the reference region (k_3=0 in the 2-tissue compartment model), and C(t) the TAC from a receptor-rich region (k_3>0).

PXMOD Implementations

The measurements required for the receptor reference methods are a dynamic PET or SPECT acquisition without the need for external blood sampling. The operator must delineate a reference region devoid of receptors (e.g. frontal cortex for D2 receptors). For the model preprocessing step he also must delineate a receptor-rich region (e.g. basal ganglia for D2 receptors). The model then applies the reference model to the TACs from both regions and presents the results to the user for inspection. If the result is not satisfactory, the user may change some of the parameters and try the fit again. At the end of preprocessing some parameters such as the regression start time t* or k_2' have been determined which will be used for the pixel-wise fits. The pixel-wise calculations result in BP maps. To avoid meaningless values which mix up the display it is recommended to restrict the accepted BP values to a reasonable range.

Models with Fixed k2'

Some of the reference methods require an a priori average value of k_2', while other methods such as the MRTM or the SRTM reference methods estimate k_2' together with the other parameters in each individual pixel. There are two ways of obtaining a value of k_2'

1) Calculation of k2' with several regional TACs in the PKIN kinetic tool (recommended): In this case regional TACs are derived from the dynamic PET study and loaded into PKIN. One of the TACs should represent appropriate reference tissue (without receptors), while the others should be derived from tissue with high specific binding. The latter TACs are then fitted with one of the reference models which yield k_2' (MRTM, SRTM), and the resulting k_2' values are averaged. An alternative is the use of SRTM2 and coupled fitting, with k_2' being estimated as a common parameter. More detail on these approaches is available in the PKIN Users Guide. After k_2' has been calculated it has to be entered in the model preprocessing pane and the fit flag be removed.

Calculation of k_2' with a single regional TAC in PXMOD during preprocessing: This approach has the advantage of simplicity, but it is not possible to get an average value from different tissues. A work-around would be to define a representative VOI which encompasses several tissue types, but it is not exactly equivalent to the first method._

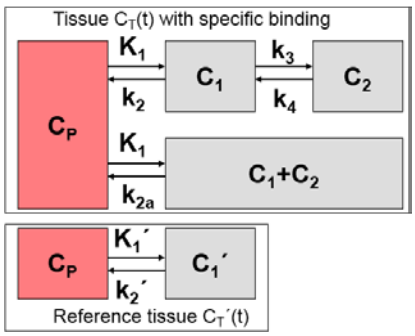
BPnd (SRTM Ref): Simplified Reference Tissue Model

The Simplified Reference Tissue Model (SRTM) of Lammertsma and Hume [1] is used for the analysis of studies with reversibly binding neuroreceptor tracers. A reference tissue devoid of receptors is required which can be modeled by a single-tissue compartment model.

The assumptions of the model are:

1) The distribution volume is the same for the tissue of interest and the reference tissue: $K_1/k_2=K_1'/k_2'$.

The kinetics in the receptor-rich tissue of interest is such that it is difficult to distinguish between the specific and the non-displaceable compartment; ie. the tissue TAC can be fitted by a 1-tissue compartment model with an uptake rate constant $k_{2a} = k_2/(1+BP_{ND})$. Note that this assumption may not be valid for all tracers, and in this case SRTM calculates biased BP_{ND} estimates.



Defining the ratio of tracer delivery R_1 as K_1/K_1' and the binding potential BP_{ND} as k_3/k_4, the following operational equation can be derived for the measured tissue TAC in a receptor-rich region:

$$C_{Model}(t) = R_1 C_T'(t) + \left[k_2 - R_1 k_2/(1+BP_{ND})\right] C_T'(t) \otimes e^{-k_2 t/(1+BP_{ND})}$$

For convolution with the exponentials, the reference tissue TAC C'(t) is resampled on a regular grid, which can be specified by the **Resampling** parameter.

Gunn et al [2] transformed the SRTM model into a solution which is better suited for pixel-wise application. It is based on a set of basis functions which are generated by convolving the reference TAC with decaying exponentials. The exponents employed should cover a range which is reasonable for the tracer considered. To calculate the binding potential of a TAC a least squares fit is performed with each of the basis functions. That fit with minimal deviation between the TAC and the model curve is regarded as the solution, and the binding potential is calculated from the set of fit parameters.

The PXMOD implementation in the **BPnd (SRTM Ref)** model differs from that described in [2] by the following points

1) It is assumed that the dynamic PET images are decay corrected. Accordingly, there are no appropriate weights for the least squares fit, and unweighted fitting is employed.

The additional factorization Rm=Q^Tgiven in [34] which is intended at improving speed has not been implemented. Rather, the linear least squares problem given by Eq. 4, is solved explicitly for each basis function at each voxel by means of a singular value decomposition (SVD). Hence, nx*ny*nz*nBasis SVD operations are performed, which may take substantial time.

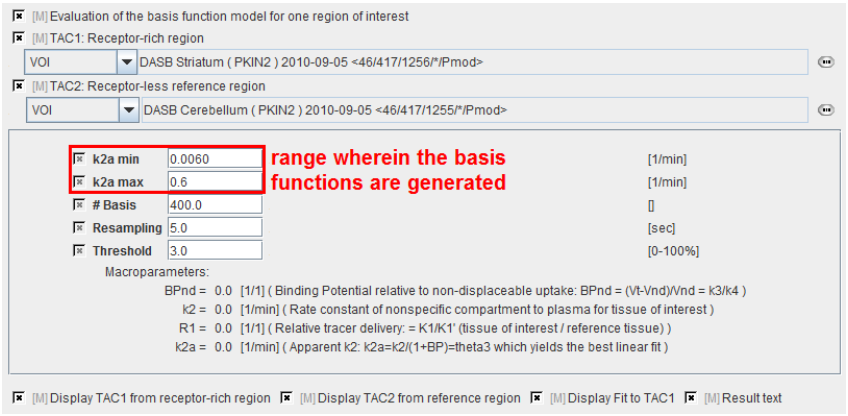
The term k_{2a} instead of theta3 is used. $k_{2a}=k_2/(1+BPnd)$ represents the apparent k_2.

Acquisition and Data Requirements

Image Data	A dynamic PET data set with an neuroreceptor tracer which behaves kinetically similar to a 1-tissue compartment model.
TAC 1	TAC from a receptor-rich region (such as basal ganglia for D2 receptors).
TAC 2	TAC from a receptor-devoid region (such as cerebellum or frontal cortex for D2 receptors).

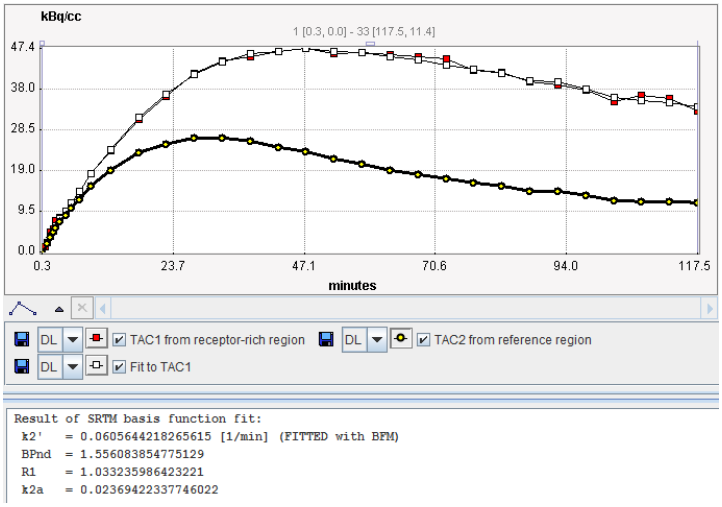
Model Preprocessing

Two regional TACs (**TAC1** and **TAC2**) are needed for **Model Preprocessing**.

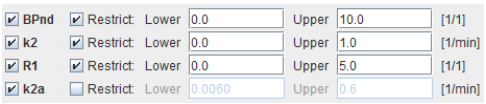


k2a min	Minimal value of k_{2a} (slowest decay of exponential).
k2a max	Maximal value of k_{2a} (fastest decay of exponential).
# Basis	Number of basis functions between **k2a min** and **k2a max**. Note that increments are taken at logarithmic steps. This number is directly proportional to processing time.
Resampling	Specifies the interval of curve resampling which is required for performing the operation of exponential convolution. **Resampling** should be equal or smaller than the shortest frame duration.
Threshold	Discrimination threshold for background masking.
BPnd	Estimated binding potential (= k_3/k_4 according to the underlying model).
R1	Ratio of tracer delivery in each pixel relative to the reference tissue ($R1=K_1/K_1'$).
k2	Estimated rate constant k_2.
k2a	k_{2a} value which provides the best least squares fit in each voxel.

The result of the fit during **Model Preprocessing** is shown in the **Result** panel for inspection.



Map Parameters



BPnd	Estimated binding potential (BPnd= k_3/k_4 according to the underlying model).
k2	Estimated efflux rate constant k_2 .
R1	Ratio of tracer delivery in each pixel relative to the reference tissue ($R_1=K_1/K_1'$). Therefore the map often has a similar appearance to a perfusion image.
k2a	k_{2a} value which provides the best least squares fit.

Notes:
1. The **k2a** parametric map should be checked in the initial setup of a processing protocol. The estimated **k2a** values should not be truncated by too narrow **k2a min** and **k2a max** values.
2. The calculation is slow relative to other reference models and might take several minutes to complete.

References

1. Lammertsma AA, Hume SP: Simplified reference tissue model for PET receptor studies. Neuroimage 1996, 4(3 Pt 1):153-158. ***DOI http://dx.doi.org/10.1006/nimg.1996.0066***

2. Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ: Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. Neuroimage 1997, 6(4):279-287. ***DOI http://dx.doi.org/10.1006/nimg.1997.0303***

BPnd (Wu SRTM2 Ref): Simplified Reference Tissue Model with fixed k2'

Wu and Carson [1] aimed at making the ***SRTM basis function*** (on page 84) approach even more robust and called it Simplified Reference Tissue Model 2 (**SRTM2**). They noted that with SRTM k_2' is calculated with each pixel TAC, although the same reference TAC is used for all pixels. Therefore they implemented a two-step approach:

1) Calculate k_2' using SRTM in all pixels.

Fix k_2' : Average k_2' in all brain pixels outside the reference region. Use this fixed value for the pixel-wise SRTM calculations, reducing the number of fitted parameters from 3 to 2.

The operational equation of the SRTM was re-written to allow for fixing of k_2'. This is relevant for parametric mapping because the model in each pixel TAC uses the same reference TAC and therefore should employ the same k_2'. Defining the ratio of tracer delivery R_1 as K_1/K_1' and the binding potential BP_{ND} as k_3/k_4, the following operational equation can be derived for the measured TAC in a receptor-rich region:

$$C_{Model}(t) = R_1 C_T'(t) + R_1\left[k'_2 - k_{2a}\right] C_T'(t) \otimes e^{-k_{2a}t}$$

The three unknowns R_1, k_2 and k_{2a} in this equation can be fitted using nonlinear regression techniques. The binding potential can then be calculated as

$$BP_{ND} = R_1 \frac{k'_2}{k_{2a}} - 1.0$$

The PXMOD implementation **BPnd (Wu SRTM2 Ref)** differs from that described in [1] in the following points

1) An unweighted fitting is employed.

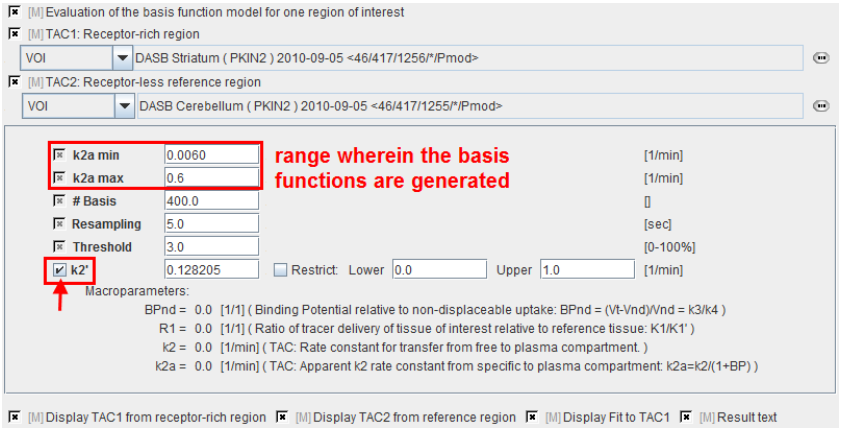
Instead of performing a pixel-wise SRTM calculation and averaging k_2' in non-reference pixels, k_2' is calculated by applying SRTM to an averaged TAC from a VOI covering non-reference pixels.

Acquisition and Data Requirements

Image Data	A dynamic PET data set with an neuroreceptor tracer which behaves kinetically similar to a 1-tissue compartment model.
TAC 1	TAC from a receptor-rich region (such as basal ganglia for D2 receptors).
TAC 2	TAC from a receptor-devoid region (such as cerebellum or frontal cortex for D2 receptors).

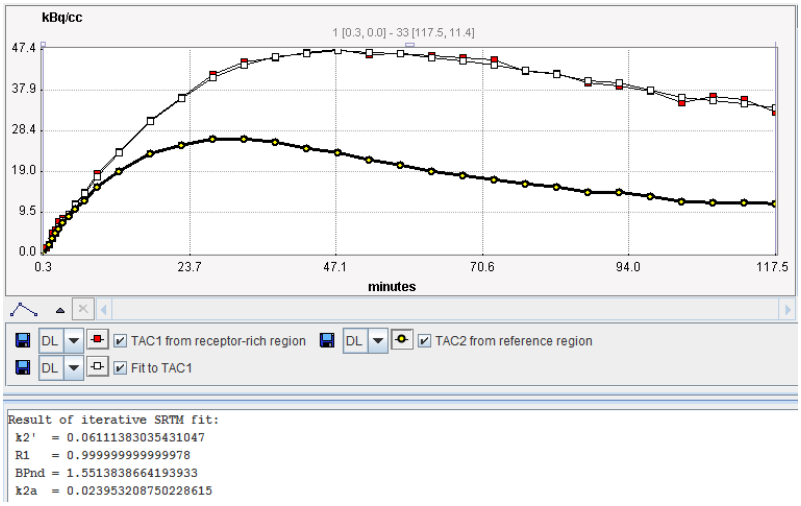
Model Preprocessing

Two regional TACs (**TAC1** and **TAC2**) are needed for **Model Preprocessing**.



k2a min	Minimal value of k_{2a} (slowest decay of exponential).
k2a max	Maximal value of k_{2a} (fastest decay of exponential).
# Basis	Number of basis functions between **k2a min** and **k2a max**. Note that increments are taken at logarithmic steps. This number is directly proportional to processing time.
Resampling	Specifies the interval of curve resampling which is required for performing the operation of exponential convolution. **Resampling** should be equal or smaller than the shortest frame duration.
Threshold	Discrimination threshold for background masking.
k2'	k_2 of the reference tissue. It can be fixed at a specified value, or fitted. If it is checked, **k2'** is fitted using the SRTM method implemented in PKIN. This value will be used in pixel-wise SRTM2.
BPnd	Estimated binding potential (= k_3/k_4 according to the underlying model).
R1	Ratio of tracer delivery in each pixel relative to the reference tissue ($R1=K_1/K_1'$).
k2	Estimated rate constant k_2.
k2a	k_{2a} value which provides the best least squares fit in each voxel.

The result of the fit during **Model Preprocessing** is shown in the **Result** panel for inspection.



Map Parameters

BPnd	Estimated binding potential (BPnd= k_3/k_4 according to the underlying model).
k2	Estimated efflux rate constant k_2 .
R1	Ratio of tracer delivery in each pixel relative to the reference tissue ($R_1=K_1/K_1'$). Therefore the map often has a similar appearance to a perfusion image.
k2a	k_{2a} value which provides the best least squares fit.

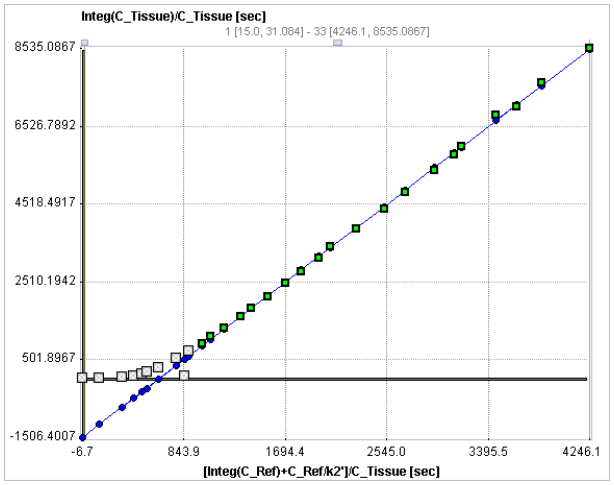
Note: The **k2a** parametric map should be checked in the initial setup of a processing protocol. The estimated **k2a** values should not be truncated by too narrow **k2a min** and **k2a max** values.

Reference

1. Wu Y, Carson RE: Noise reduction in the simplified reference tissue model for neuroreceptor functional imaging. J Cereb Blood Flow Metab 2002, 22(12):1440-1452. ***DOI http://dx.doi.org/10.1097/00004647-200212000-00004***

BPnd (Logan Ref): Logan Reference Plot with fixed k2'

Logan et al. [1] developed a reference tissue method for reversible receptor ligands which does not depend on a specific model structure of the reference tissue. Assuming the presence of reference region TAC $C_T'(t)$ with an average tissue-to-plasma clearance k_2', the target tissue TAC $C_T(t)$ is transformed and plotted as a function of the transformed reference TAC, as illustrated below.



The operational equation resembles a linear equation with the distribution volume ratio (DVR = BP_{ND}+1) as the slope plus an error term which decreases over time. Therefore the late part starting from a time t* of the plotted samples can be fitted by a regression line and the slope used for calculating BP_{ND}. The time t* can be determined as the time after which no further significant increases in slope are observed.

The graphical plot of the **Logan Reference Tissue** method is described by the following equation with the form resembling a linear equation.

$$\frac{\int_0^t C_T(\tau)d\tau}{C_T(t)} = DVR\left[\frac{\int_0^t C_T'(\tau)d\tau + C_T'(t)/k'_2}{C_T(t)}\right] + b = (BP_{ND}+1)\left[\frac{\int_0^t C_T'(\tau)d\tau + C_T'(t)/k'_2}{C_T(t)}\right] + b$$

k_2' in the original publication was the population average k_2 determined for the reference tissue using blood sampling, but using the subject's own k_2' may be preferable.

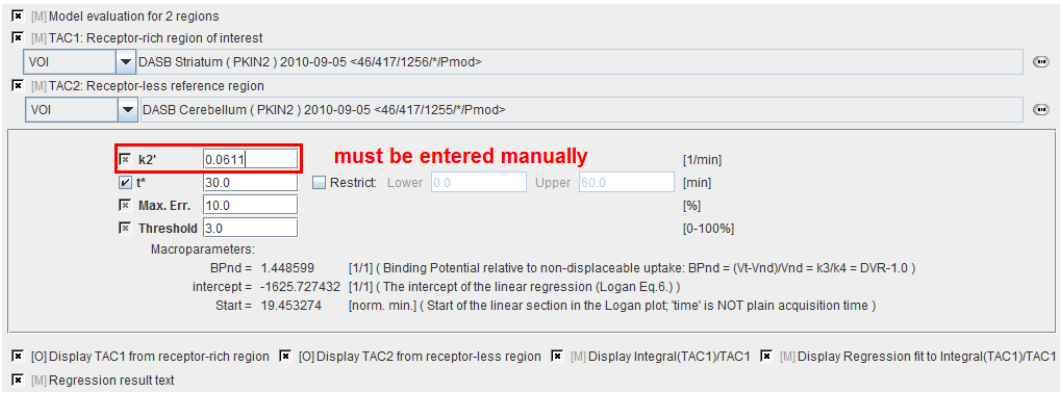
Acquisition and Data Requirements

Image Data	A dynamic data set acquired long enough that the equilibrium relation is approximately fulfilled.
TAC 1	TAC from a receptor-rich region (such as basal ganglia for D2 receptors).
TAC 2	TAC from a receptor-devoid region (such as cerebellum or frontal cortex for D2 receptors).

k2'	A average value of the efflux rate constant from regions without receptors, which has been previously determined.

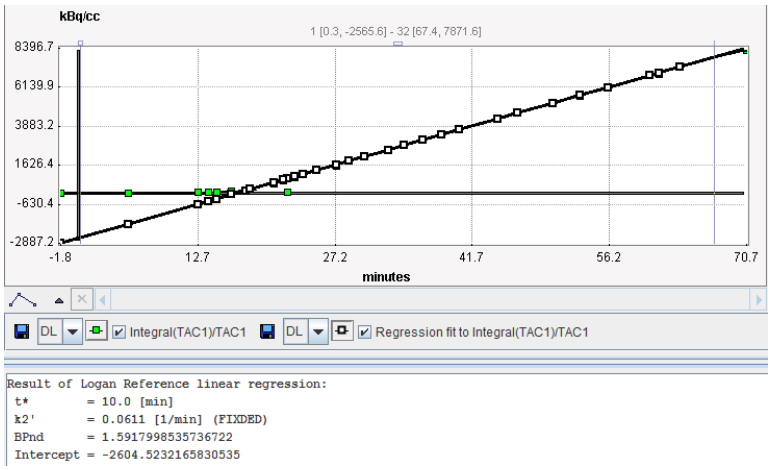
Model Preprocessing

Two regional TACs (**TAC1** and **TAC2**) are needed for **Model Preprocessing**.



k2'	The average value of the efflux constant k2. It must have been determined separately and is only an input parameter to be manually entered. Note that the value of k2' also has an impact on fitting t*.
t*	The linear regression estimation should be restricted to a range after an equilibration time. t* marks the beginning of the range used in the linear regression analysis. It can be fitted based on the Max. Err. criterion. Note: Time is in acquisition time, not in the normalized time of the graphical plot.
Max. Err.	Maximum relative error allowed between the linear regression and the Logan-transformed measurements in the segment starting from t*.
Threshold	Discrimination threshold for background masking.
BPnd	Binding potential, calculated by as: BPnd = k3/k4 = DVR-1.0
intercept	The intercept of the linear regression (Logan Eq.6.)
Start	Time in the plot which corresponds to **t***.

The result of the fit during **Model Preprocessing** is shown in the **Result** panel for inspection.



Map Parameters

BPnd	Binding potential, calculated by as: BPnd = k3/k4 = DVR-1.0 where DVR is the slope of the fitted regression line.
intercept	Intercept of the linear regression (Logan Eq.6.)

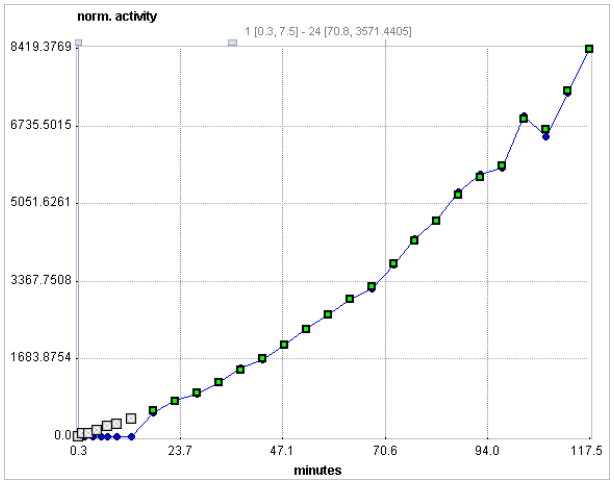
Reference

1. Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL: Distribution volume ratios without blood sampling from graphical analysis of PET data. J Cereb Blood Flow Metab 1996, 16(5):834-840. ***DOI http://dx.doi.org/10.1097/00004647-199609000-00008***

BPnd (Ichise MRTM0 Ref): Ichise Multi-linear Reference Tissue Model

Starting from the operational equation of the blood-based ***Logan plot,*** (on page 49) Ichise et al. derived three multi-linear reference tissue model variants MRTM0, MRTM and MRTM2 [1,2]. They all assume an initial equilibration time t* from which on the derived multi-linear relation holds. However, if kinetics in the target tissue can be described by a 1-tissue compartment model (an assumption required for the SRTM), all data can be used for the fitting (t*=0). Otherwise an adequate t* value has to be determined.

Assuming the presence of receptor-devoid reference region TAC $C_T'(t)$, the target tissue TAC $C_T(t)$ is transformed and plotted as a function of the transformed reference TAC, as illustrated below. For the calculation of BP_{ND} it is assumed that the non-displaceable distribution volumes in the tissue and reference regions are identical.



The **MRTM0** model curve is described by

$$\frac{\int_0^t C_T(\tau)d\tau}{C_T(t)} = \frac{V_T}{V_T'}\frac{\int_0^t C_T'(\tau)d\tau}{C_T(t)} + \frac{V_T}{V_T'k'_2}\frac{C_T'(t)}{C_T(t)} + b$$

where V_T and V_T' are the total distribution volumes of $C_T(t)$ and $C_T'(t)$, k'_2 is the clearance rate constant from the reference region to plasma, and b is the intercept term, which becomes constant for T > t*. The multi-linear relationship above can be fitted using multi-linear regression, yielding three regression coefficients. From the first coefficient the binding potential can be calculated by

$$BP_{ND} = \frac{V_T}{V_T'} - 1.0 = DVR - 1$$

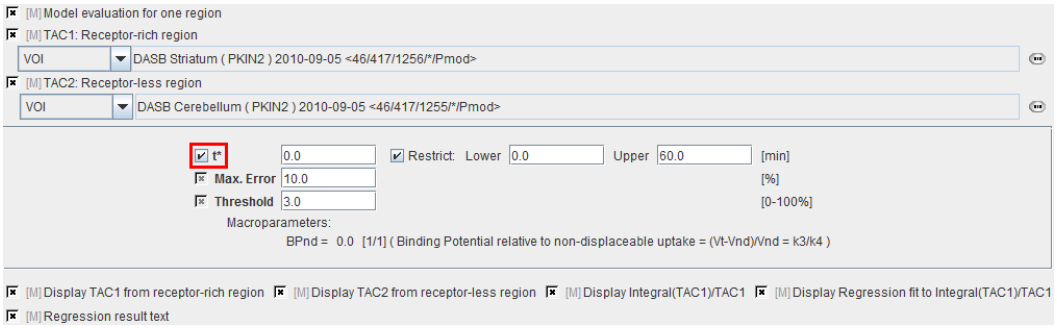
For radioligands with 1-tissue kinetics such as ^{11}C DASB the multi-linear equation is correct from T = 0, i.e., t* = 0, and b is equal to $(-1/k_2)$, where k_2 is the clearance rate constant from the tissue to plasma. Furthermore, $R_1 = K_1/K'_1$, the relative radioligand delivery, can be calculated from the ratio of the second and third regression coefficients.

Acquisition and Data Requirements

Image Data	A dynamic data set acquired long enough that the equilibrium relation is approximately fulfilled.
TAC 1	TAC from a receptor-rich region (such as basal ganglia for D2 receptors).
TAC 2	TAC from a receptor-devoid region (such as cerebellum or frontal cortex for D2 receptors).

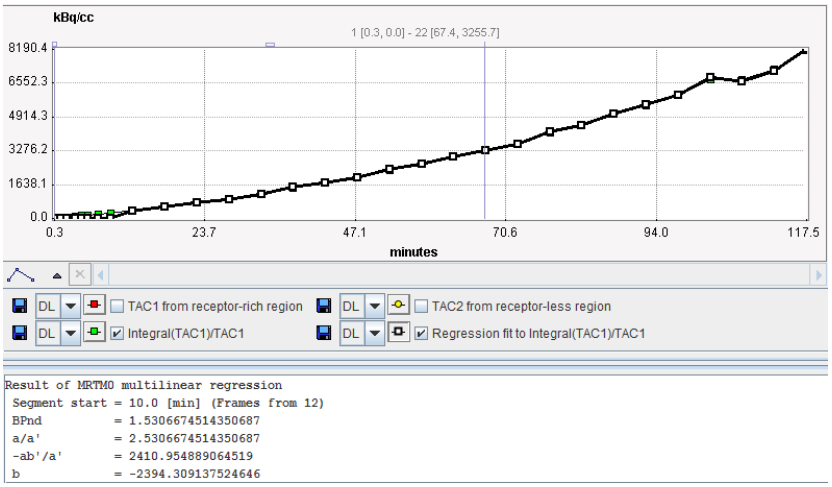
Model Preprocessing

Two regional TACs (**TAC1** and **TAC2**) are needed for **Model Preprocessing**.

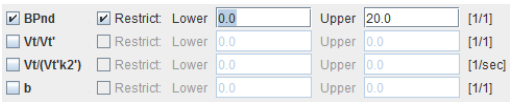


t*	The least squares estimation should be restricted to a range after an equilibration time. **t*** marks the beginning of the range used in the multi-linear regression analysis. It can be fitted based on the **Max. Err.** criterion.
Max. Err.	The maximal relative error allowed if **t*** is fitted.
Threshold	Discrimination threshold for background masking.
BPnd	Binding potential, calculated by: **BPnd** = k_3/k_4 = a/a'-1.0

The result of the multi-linear fit during **Model Preprocessing** is shown in the **Result** panel for inspection. Note that the initial points which are not taken into account (before the **t*** time) are set to 0.



Map Parameters



BPnd	Binding potential, calculated by: BPnd = k_3/k_4 = Vt/Vt'-1.0.

Vt/Vt'	First multi-linear regression coefficient of the operational equation.
Vt/(Vt'k2')	Second multi-linear regression coefficient of the operational equation.
b	Intercept in the operational equation.

References

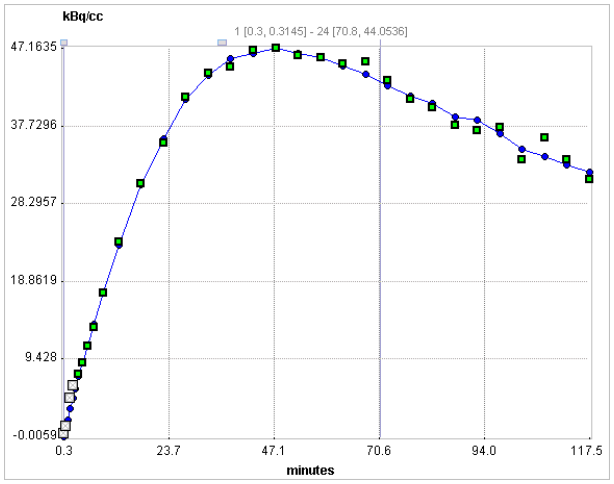
1. MRTM0: Ichise M, Ballinger JR, Golan H, Vines D, Luong A, Tsai S, Kung HF: Noninvasive quantification of dopamine D2 receptors with iodine-123-IBF SPECT. J Nucl Med 1996, 37(3):513-520.

2. Comparison of the MRTM and SRTM models: Ichise M, Liow JS, Lu JQ, Takano A, Model K, Toyama H, Suhara T, Suzuki K, Innis RB, Carson RE: Linearized reference tissue parametric imaging methods: application to [11C]DASB positron emission tomography studies of the serotonin transporter in human brain. J Cereb Blood Flow Metab 2003, 23(9):1096-1112. ***DOI http://dx.doi.org/10.1097/01.WCB.0000085441.37552.CA***

BPnd (Ichise MRTM Ref) Ichise Multi-linear Reference Tissue Model

Starting from the operational equation of the blood-based Logan plot, Ichise et al. derived three multi-linear reference tissue model variants MRTM0, MRTM and MRTM2 [1]. They all assume an initial equilibration time t* from which on the derived multi-linear relation holds. However, if kinetics in the target tissue can be described by a 1-tissue compartment model (an assumption required for the SRTM), all data can be used for the fitting (t*=0). Otherwise an adequate t* value has to be determined.

Assuming the presence of receptor-devoid reference region TAC $C_T'(t)$, the target tissue TAC $C_T(t)$ is plotted as a function of the transformed tissue TACs as illustrated below. For the calculation of BP_{ND} it is assumed that the non-displaceable distribution volumes in the tissue and reference regions are identical.



To reduce noise-related bias effects arising in the MRTM0 method Ichise et al. applied a strategy known to be effective in reducing the noise-induced bias for the models requiring blood data. To this end the equation of the ***MRTM0*** (on page 93) method was rearranged to

remove the noisy tissue radioactivity term $C_T(t)$ from the independent variables. This approach resulted in a new method called **MRTM** with following operational equation for $C_T(t)$:

$$C_{Model}(t) = -\frac{V_T}{V_T'b}\int_0^t C_T'(\tau)d\tau + \frac{1}{b}\int_0^t C_T(\tau)d\tau - \frac{V_T}{V_T'k_2'b}C_T'(t)$$

The multi-linear relationship above can be fitted using multi-linear regression, yielding three regression coefficients. The binding potential can then be calculated by dividing the first two regression coefficients

$$BP_{ND} = = \frac{V_T}{V_T'} - 1.0 = DVR - 1$$

Furthermore, division of the first by the third regression coefficient yields an estimate of k_2' .

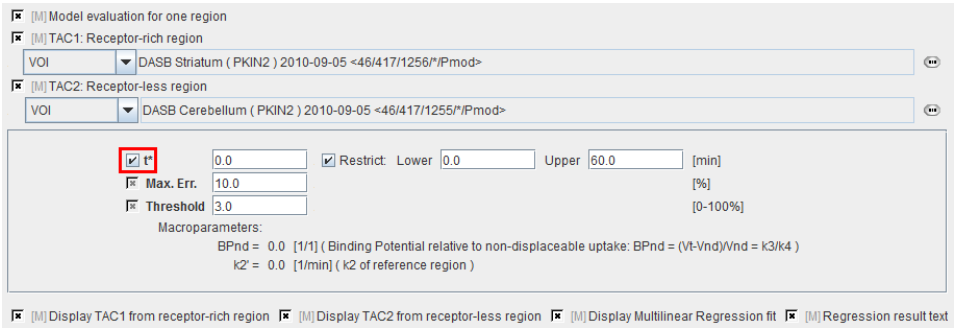
For receptor ligands with 1-tissue kinetics such as [11C]DASB the multi-linear equation is correct from t*=0, and the clearance rate constant from the tissue to plasma k_2 is equal to the negative value of the second regression coefficient, -(1/b). Furthermore, $R_1 = K_1/K'_1$, the relative radioligand delivery, equals the third regression coefficient.

Acquisition and Data Requirements

Image Data	A dynamic data set acquired long enough that the equilibrium relation is approximately fulfilled.
TAC 1	TAC from a receptor-rich region (such as basal ganglia for D2 receptors).
TAC 2	TAC from a receptor-devoid region (such as cerebellum or frontal cortex for D2 receptors).

Model Preprocessing

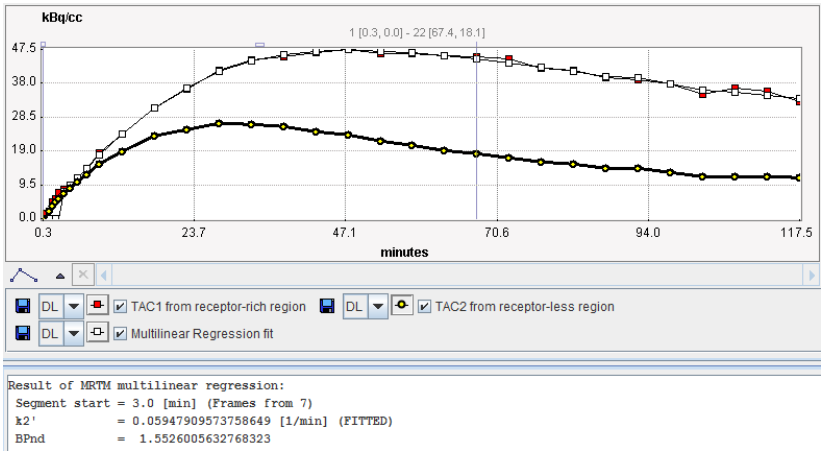
Two regional TACs (**TAC1** and **TAC2**) are needed for **Model Preprocessing**.



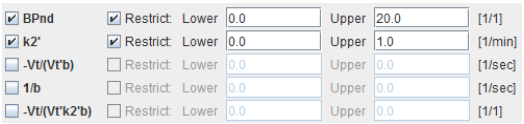
t*	The least squares estimation should be restricted to a range after an equilibration time. **t*** marks the beginning of the range used in the multi-linear regression analysis. It can be fitted based on the **Max. Err.** criterion.
Max. Err.	The maximal relative error allowed if **t*** is fitted.

BPnd	Binding potential of the receptor-rich region TAC (**BPnd** = k_3/k_4).
Threshold	Discrimination threshold for background masking.

The result of the multi-linear fit during **Model Preprocessing** is shown in the **Result** panel for inspection. The initial points which are not taken into account (before the **t*** time) are set to 0.



Map Parameters



BPnd	Binding potential **BPnd** = k_3/k_4.
k2'	Clearance rate of the reference tissue.
-Vt/(Vt'b)	First multi-linear regression coefficient of the operational equation (Ichise Eq.2.)
1/b	Second multi-linear regression coefficient of the operational equation (Ichise Eq.2.)
-Vt/(Vt'k2'b)	Third multi-linear regression coefficient of the operational equation (Ichise Eq.2.)

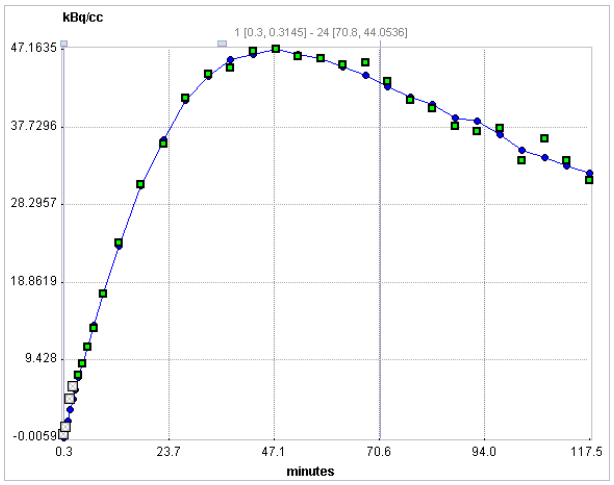
Reference

1. Ichise M, Liow JS, Lu JQ, Takano A, Model K, Toyama H, Suhara T, Suzuki K, Innis RB, Carson RE: Linearized reference tissue parametric imaging methods: application to [11C]DASB positron emission tomography studies of the serotonin transporter in human brain. J Cereb Blood Flow Metab 2003, 23(9):1096-1112. ***DOI http://dx.doi.org/10.1097/01.WCB.0000085441.37552.CA***

BPnd (Ichise MRTM2 Ref): Ichise MRTM with fixed k2'

Starting from the operational equation of the blood-based Logan plot, Ichise et al. derived three multi-linear reference tissue model variants MRTM0, MRTM and MRTM2 [1]. They all assume an initial equilibration time t* from which on the derived multi-linear relation holds. However, if kinetics in the target tissue can be described by a 1-tissue compartment model (an assumption required for the SRTM), all data can be used for the fitting (t*=0). Otherwise an adequate t* value has to be determined.

Assuming the presence of receptor-devoid reference region TAC $C_T'(t)$, the target tissue TAC $C_T(t)$ is plotted as a function of the transformed tissue TACs as illustrated below. For the calculation of BP_{ND} it is assumed that the non-displaceable distribution volumes in the tissue and reference regions are identical.



When applied to noisy data such as single-pixel TACs in parametric mapping, the MRTM method still suffers from a high variability. Assuming a known value of the reference tissue clearance rate k_2' the ***MRTM*** (on page 96) operational equation can be reformulated as the MRTM2 operational equation:

$$C_{Model}(t) = -\frac{V_T}{V_T'b}\left(\int_0^t C_T'(\tau)d\tau + \frac{1}{k'_2}C_T'(t)\right) + \frac{1}{b}\int_0^t C_T(\tau)d\tau$$

with only two regression coefficients $V_T/(V_T'b)$ and $1/b$ for $T > t^*$. The multi-linear relationship above can be fitted using multi-linear regression, yielding three regression coefficients. The binding potential is then calculated from the ratio of the two regression coefficients as

$$BP_{ND} = = \frac{V_T}{V_T'} - 1.0 = DVR - 1$$

For receptor ligands with 1-tissue kinetics such as [11C]DASB the multi-linear equation is correct from t*=0, and the clearance rate constant from the tissue to plasma k_2 is equal to the negative value of the second regression coefficient, -(1/b). Furthermore, $R_1 = K_1/K'_1$, the relative radioligand delivery, equals the first regression coefficient divided by k_2'.

For pixel-wise applications the same two-step approach applied in the ***SRTM2*** (on page 88) model is applied:

1) Calculate in the model preprocessing step the clearance rate k_2' of the reference TAC by the MRTM method with VOI data which has a limited level of noise.

Fix k_2': Use the estimated k_2' value for the pixel-wise MRTM calculations, reducing the number of fitted parameters from 3 to 2.

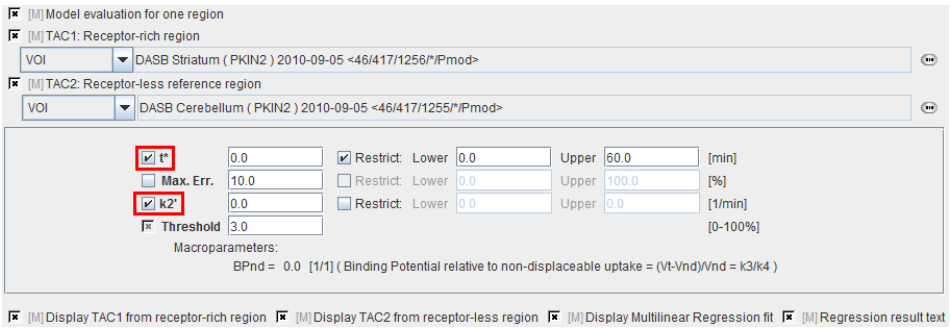
Alternatively, k_2' can be determined for externally (for instance in PKIN), manually entered and fixed.

Acquisition and Data Requirements

Image Data	A dynamic data set acquired long enough that the equilibrium relation is approximately fulfilled.
TAC 1	TAC from a receptor-rich region (such as basal ganglia for D2 receptors).
TAC 2	TAC from a receptor-devoid region (such as cerebellum or frontal cortex for D2 receptors).

Model Preprocessing

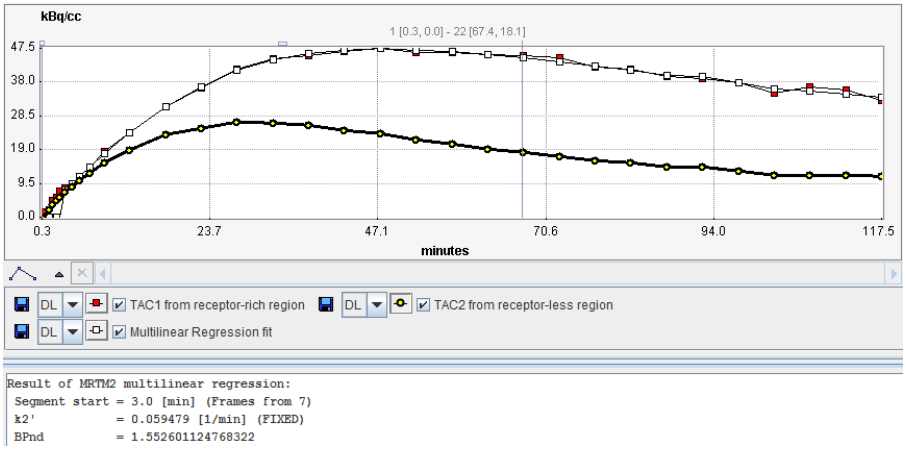
Two regional TACs (**TAC1** and **TAC2**) are needed for **Model Preprocessing**.



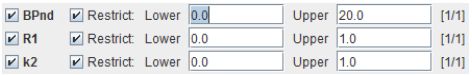
t*	The least squares estimation should be restricted to a range after an equilibration time. **t*** marks the beginning of the range used in the multi-linear regression analysis. It can be fitted based on the **Max. Err.** criterion.
Max. Err.	The maximal relative error allowed if **t*** is fitted.
k2'	Clearance rate of the receptor-less reference tissue. If the fit box is checked, k_2' is estimated in **Model Preprocessing** using MRTM, otherwise MRTM2 is applied with the fixed k_2' which is entered by the user. The value of k_2' resulting from **Model Preprocessing** will be used for the pixel-wise MRTM2 analysis. Note the recommendation of Dr. Ichise to determine k_2' as the average of k_2' determined with MRTM in several regions with high BP. As a convenience, however, k_2' may be fitted with a single TAC in **Model Preprocessing**.

Threshold	Discrimination threshold for background masking.
BPnd	Binding potential of the receptor-rich region TAC (**BPnd** = k_3/k_4).

The result of the multi-linear fit during **Model Preprocessing** is shown in the **Result** panel for inspection. The initial points which are not taken into account (before the **t*** time) are set to 0.



Map Parameters



BPnd	Binding potential **BPnd** = k_3/k_4.
R1	**R1** = K_1/K_1' relative ligand delivery (for 1-tissue kinetics). The calculated image often looks similar to a perfusion image and can sometimes used for matching purposes. It is recommended to restrict the range of fitted values.
k2	Clearance rate in the pixel (for 1-tissue kinetics).

Reference

1. Ichise M, Liow JS, Lu JQ, Takano A, Model K, Toyama H, Suhara T, Suzuki K, Innis RB, Carson RE: Linearized reference tissue parametric imaging methods: application to [11C]DASB positron emission tomography studies of the serotonin transporter in human brain. J Cereb Blood Flow Metab 2003, 23(9):1096-1112. ***DOI http://dx.doi.org/10.1097/01.WCB.0000085441.37552.CA***

BPnd (6 Calc. Methods): Calculation of BPnd with all 6 Reference Methods

As a facility for the user the **BPnd (6 Calc. Methods)** "model" has been implemented which calculates BPnd using six reference methods in a single processing. For a description of the idividual models please refer to the following links: ***SRTM*** (on page 84), ***SRTM2*** (on page 88), ***Logan*** (on page 91), ***MRTM0*** (on page 93), ***MRTM*** (on page 96) and ***MRTM2*** (on page 99).

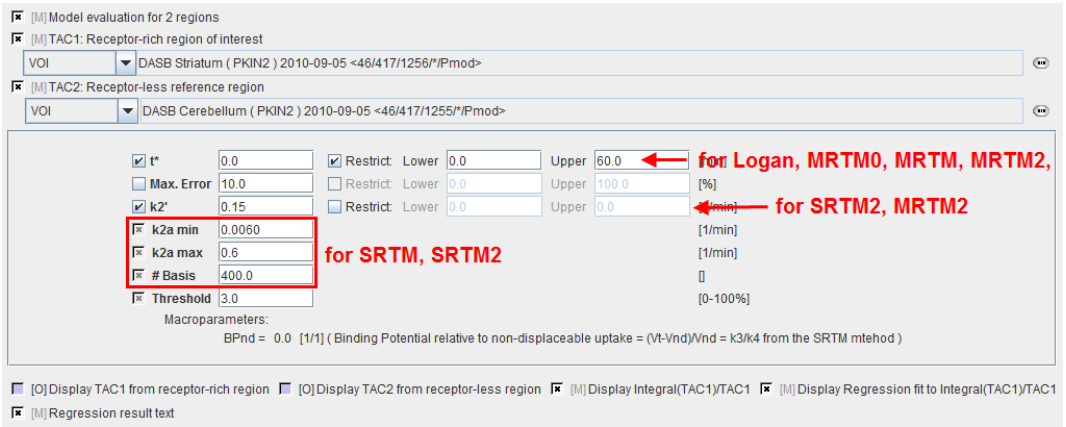
This model allows fitting a reference tissue k_2' which is used in the SRTM2 and MRTM2 methods using the SRTM method. If this option is not used, an appropriate k_2' has to be manually entered. The model also allows fitting a t* using the Logan reference plot based on the k_2' determined beforehand.

Acquisition and Data Requirements

Image Data	A dynamic PET data set with an appropriate neuroreceptor tracer.
TAC 1	TAC from a receptor-rich region (such as basal ganglia for D2 receptors).
TAC 2	TAC from a receptor-devoid region (such as cerebellum or frontal cortex for D2 receptors).

Model Preprocessing

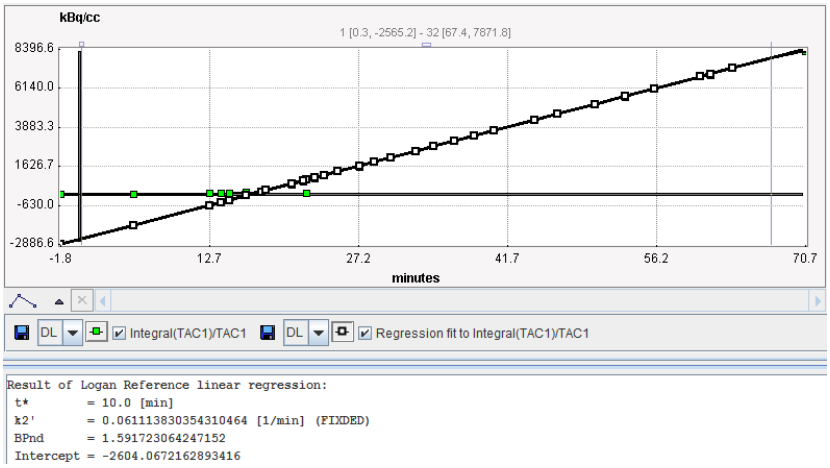
Two regional TACs (**TAC1** and **TAC2**) are needed for **Model Preprocessing**.



t*	Start time of the data segment used for the estimation of BPnd. If the box of **t*** is checked it is fitted using the **Logan Reference** method and the specified **Max. Err.** criterion. Otherwise, the specified **t*** value is applied. Note that all methods requiring a **t*** will use the same value from this preprocessing step.
Max. Err.	Maximal allowed relative error between measurement and prediction in the data segment starting from **t***.
k2'	k_2 of the reference tissue. It can be fixed at a specified value, or fitted using SRTM. This value will be used by SRTM2 and MRTM2 in the pixel-wise calculation.
k2a min	Minimal value of $k_{2a} = k_2/(1+BP)$ (slowest decay of exponential). Is used for creating the SRTM and SRTM2 basis functions.
k2a max	Maximal value of $k_{2a} = k_2/(1+BP)$ (fastest decay of exponential). Is used for creating the SRTM and SRTM2 basis functions.
# Basis	Number of basis functions between **k2a min** and **k2a max**. Note that

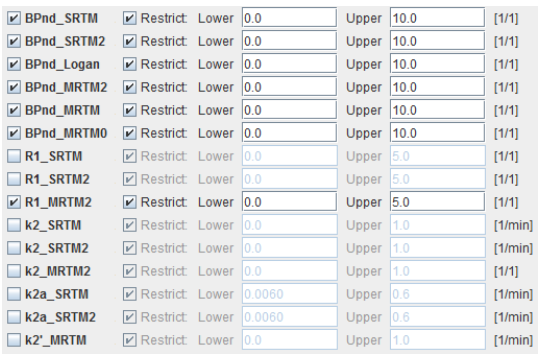
	increments are taken at logarithmic steps. This number has a big impact on processing time.
BPnd	Binding potential (= k_3/k_4 according to the underlying model) estimated by STRM.

The result of the fit during preprocessing is shown in the preprocessing **Results** panel.



Note that the **Model Preprocessing** of all models is shown in the **Info** are and can be inspected by scrolling the window.

Map Parameters



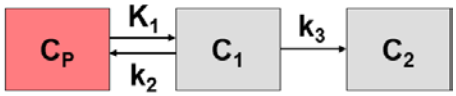
BPnd_X	Binding potential estimated with the methods X = SRTM, SRTM2, Logan, MRTM2, MRTM, MRTM0
R1_X	Ratio of tracer delivery in each pixel relative to the reference tissue (RI=K_1/K_1'). This map is often similar to a perfusion image and can therefore be helpful as an anatomical reference.
k2_X	Estimated efflux rate constant k_2.
k2a_X	Map of the k_{2a} value which provides the best fit.

k2'_MRTM	k_2 of the reference tissue which is fitted by MRTM in each pixel. It will show variation, although it should be constant as always the same reference tissue is used.

Note: The **k2a** parametric map should be checked in the initial setup of a processing protocol. The estimated **k2a** values should not be truncated by too narrow **k2a min** and **k2a max** values.

K (Patlak Ref): Patlak Reference Plot for FDOPA

The Patlak plot has been developed by Patlak and Blasberg [1] for tracers undergoing irreversible trapping. Most often it is applied for the analysis of FDG, which can be modeled as a 2-tissue compartment model with k_4=0.



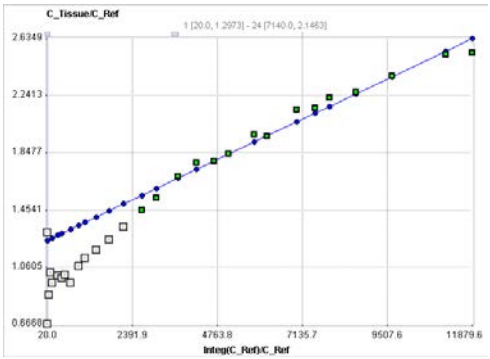
However, this model structure is not necessary for the application of the method. It is sufficient to have any compartment in the system which binds irreversibly.

When the plasma activity is not available, the Patlak plot can be employed as a reference method provided that there exists some tissue wherein tracer is not irreversibly trapped. The procedure simply replaces the input curve by the reference tissue TAC.

The Patlak plot belongs to a group of *Graphical Analysis* techniques, whereby the measured tissue TAC $C_T(T)$ undergoes a mathematical transformation and is plotted against some sort of "normalized time". The Patlak plot using reference tissue is given by the expression

$$\frac{C_T(t)}{C_T'(t)} = K \frac{\int_0^t C_T'(\tau)d\tau}{C_T'(t)} + V$$

with the reference tissue TAC $C_T'(t)$. This means that the measured PET activity is divided by the reference tissue activity, and plotted at a "normalized time" (integral of the reference TAC from the injection time divided by the instantaneous reference activity). For systems with irreversible compartments this plot will result in a straight line after an equilibration time t*.



Under several assumptions, including a common K_1/k_2, the slope of the linear regression represents the following relation

$$slope = K = \frac{k_2 k_3}{(k_2 + k_3)(1 - K_{eq})}$$

with the equilibrium constant K_{eq}.

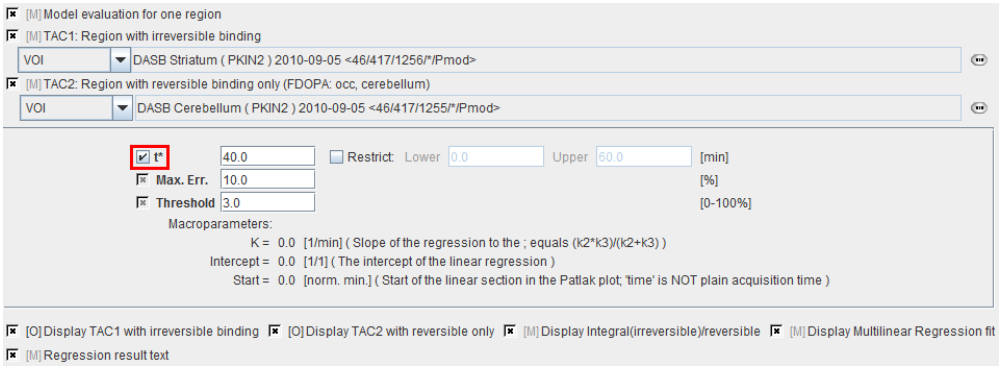
The reference Patlak plot has been applied for the FDOPA PET tracer for calculating an index of the influx K_i. Both the cerebellum and the occipital lobe have been used as the reference [2].

Acquisition and Data Requirements

Image Data	A dynamic PET data set with an appropriate tracer.
TAC 1	TAC from a region with irreversible binding (such as caudate for FDOPA).
TAC 2	TAC from a region without irreversible binding (such as occipital or cerebellum for FDOPA).

Model Preprocessing

Two regional TACs (**TAC1** and **TAC2**) are needed for **Model Preprocessing**.



t*	The linear regression estimation should be restricted to a range after an equilibration time. **t*** marks the beginning of the range used in the multi-linear regression analysis. It can be fitted based on the **Max. Err.** criterion. Note that the t* is in acquisition time.
Max. Err.	Maximum relative error allowed between the linear regression and the Patlak-transformed measurements in the segment starting from **t***.
Threshold	Discrimination threshold for background masking.
K	Slope of the linear regression. $K=(k_2*k_3)/(k_2+k_3)$.

Intercept	Intercept of the linear regression.
Start	Time in the plot which corresponds to **t*** .

Map Parameters

K	Slope of the linear regression. $K=(k_2*k_3)/(k_2+k_3)$.
Intercept	Intercept of the linear regression.

References:

[1] Patlak CS, Blasberg RG: Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. J Cereb Blood Flow Metab 1985, 5(4):584-590. ***DOI http://dx.doi.org/10.1038/jcbfm.1985.87***

[2] Sossi V, Holden JE, de la Fuente-Fernandez R, Ruth TJ, Stoessl AJ: Effect of dopamine loss and the metabolite 3-O-methyl-[18F]fluoro-dopa on the relation between the 18F-fluorodopa tissue input uptake rate constant Kocc and the [18F]fluorodopa plasma input uptake rate constant Ki. J Cereb Blood Flow Metab 2003, 23(3):301-309. DOI

Displacement (LSRTM)

This model was developed by Alpert et al. [1] to extend the concept of activation studies for including measurements targeting neurotransmitters and specific receptor populations. It uses the fact that cognitive activation increases neuronal firing rate, hereby increasing the endogenous neurotransmitter level and altering the kinetics of specifically bound radioligands. The methodology uses a single PET injection. The scan starts with an acquisition of the subject at rest (baseline), followed by an acquisition with the subject performing a task (activation). The data (after motion correction of the lengthy scan) is analyzed modeling the change of the endogenous neurotransmitter level as an effect which occurs immediately after the task onset, and diminishes exponentially over time. The method has been applied to [11C]raclopride [1] and more recently to [18F]fallypride data [2,3].

Note: The model has been called LSSRM [1,2] and LSRRM [3], but was renamed to LSRTM to correspond to the commonly used notation of the Simplified Reference Tissue Model SRTM.

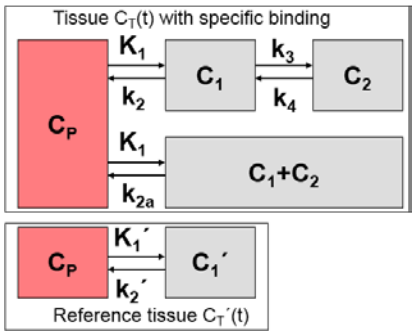
Model Configuration and Assumptions

The model uses the same assumptions as the **Simplified Reference Tissue Model** (SRTM):

1) A reference tissue devoid of receptors exists which can be modeled by a single-tissue compartment model.

The distribution volume is the same for the tissue of interest and the reference tissue: $K_1/k_2=K_1'/k_2'$.

The kinetics in the receptor-rich tissue of interest is such that it is difficult to distinguish between the specific and the non-displaceable compartment; ie. the tissue TAC can be fitted by a 1-tissue compartment model with an apparent uptake rate constant $k_{2a} = k_2/(1+BP_{ND})$.



Additionally, it is assumed that at the onset of the activation, k_{2a} is increased by the amplitude γ of ligand displacement, and that the effect dies away with a decay constant τ. This behavior is described by a time-dependent k_{2a} as follows:

$$k_{2a}(t) = k_{2a} + \gamma\, h(t)$$
$$h(t) = \begin{cases} 0 & t < Begin \\ e^{-\tau u} & t \geq Begin,\ u = t - Begin \end{cases}$$

Operational Model Curve

Defining the ratio of tracer delivery R_1 as K_1/K_1', the following operational equation can be derived for the measured tissue TAC in a receptor-rich region:

$$C_{Model}(t) = R_1\, C_T'(t) + k_2 \int_0^t C_T'(s)ds - k_{2a} \int_0^t C_T(s)ds - \gamma \int_0^t h(s) C_T(s)ds$$

For the parametric mapping it is assumed that τ is constant, so that the equation can be solved using multi-linear regression. From the resulting parameters the binding potential BP_{ND} can be calculated as

$$BP_{ND} = \frac{k_2}{k_{2a}} - 1.0$$

The main outcome of the model, however, is the amplitude γ of ligand displacement, for which a t-score value and its p-value for a one-tailed t-test are also provided.

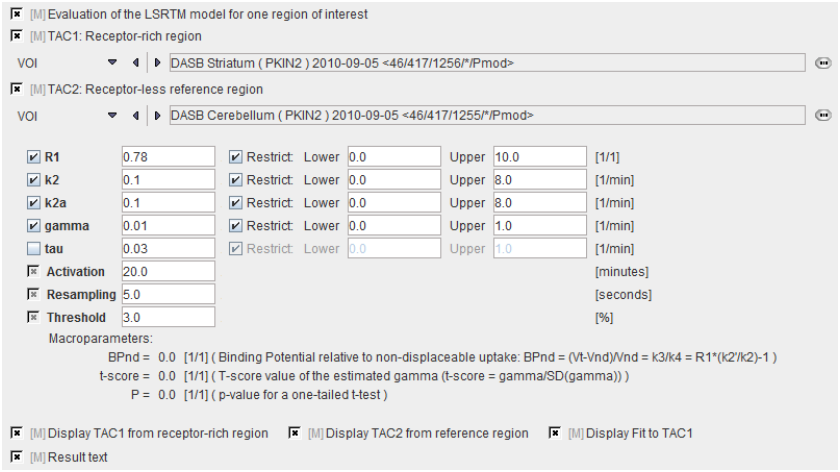
Acquisition and Data Requirements

Image Data	A dynamic PET data set with a baseline part and an activation part. Due to the extended length, motion correction should have been applied.
TAC 1	TAC from a receptor-rich region (such as basal ganglia for D2 receptors).

TAC 2	TAC from a receptor-devoid region (such as cerebellum or frontal cortex for D2 receptors).

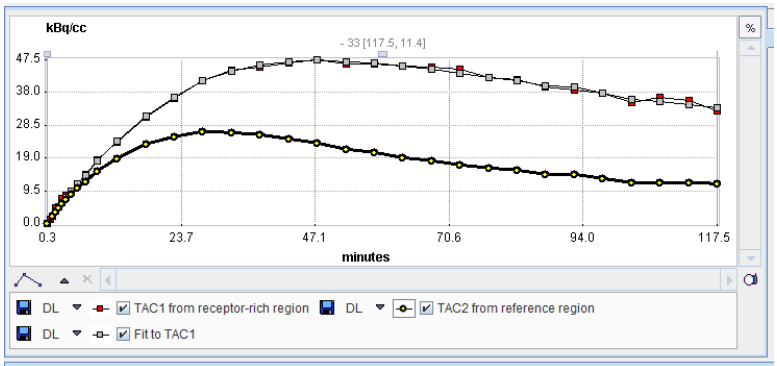
Model Preprocessing

Two regional TACs (**TAC1** and **TAC2**) are needed for **Model Preprocessing**. The iterative LSRTM procedure implemented in PKIN is applied to fit the enabled parameters.



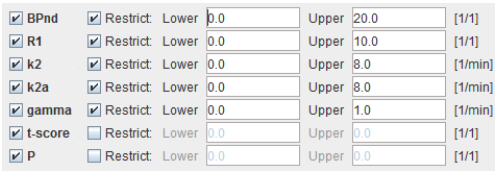
R1	Relative delivery: R1 = K_1/K_1'.
k2	Tissue to plasma efflux constant in target tissue.
k2a	Apparent k2 of the target tissue (k2a=k2/(1+BPnd))
gamma	Amplitude of ligand displacement.
tau	Decay constant controlling how the activation effect dies away. The value can be fitted in pre-processing, but is usually fixed. Default: 0.03min^{-1}. This value will be applied in the pixel-wise fitting.
Activation	Time relative to the scan start when the activation task was started.
Resampling	Interval of the curve resampling which is required for performing the operation of exponential convolution. Should be equal or smaller than the shortest frame duration.
threshold	Discrimination threshold for background masking.

The result of the fit during **Model Preprocessing** is shown in the **Result** panel for inspection.




```
Result of LSRTM fit using PKIN:
R1      = 1.027563919088754
k2      = 0.06115533991402911
k2a     = 0.023986903272585222
gamma   = 6.072375222186014E-100
tau     = 0.030000000000000002
BPnd    = 1.5495304341316922
t-score= 2.3062696867917014E-97
```

Map Parameters



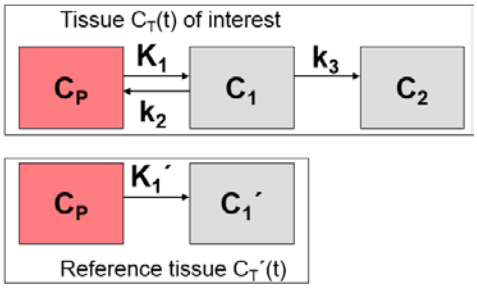
BPnd	Estimated binding potential (BPnd= k_3/k_4 according to the underlying model).
R1	Ratio of tracer delivery in each pixel relative to the reference tissue ($R_1=K_1/K_1'$). Therefore the map often has a similar appearance to a perfusion image.
k2	Estimated efflux rate constant k_2 .
k2a	Apparent k2 of the target tissue (k2a=k2/(1+BPnd))
gamma	Amplitude of ligand displacement.
t-score	t-score value of gamma.
P	t-score value converted to a p-value for a one-tailed t-test.

References

[1] Alpert NM, Badgaiyan RD, Livni E, Fischman AJ. A novel method for noninvasive detection of neuromodulatory changes in specific neurotransmitter systems. Neuroimage. 2003;19(3):1049-60. ***DOI http://dx.doi.org/10.1016/S1053-8119(03)00186-1***
[2] Christian BT, Lehrer DS, Shi B, Narayanan TK, Strohmeyer PS, Buchsbaum MS, Mantil JC. Measuring dopamine neuromodulation in the thalamus: using [F-18]fallypride PET to study dopamine release during a spatial attention task. Neuroimage. 2006;31(1):139-52. DOI
[3] Ceccarini J, Vrieze E, Koole M, Muylle T, Bormans G, Claes S, Van Laere K. Optimized in vivo detection of dopamine release using 18F-fallypride PET. J Nucl Med. 2012;53(10):1565-72. DOI

MP4A (Nagatsuka RLS Ref): Multi-linear Reference Tissue Model for [11C]-MP4A (RLS)

The **MP4A (Nagatsuka RLS Ref)** model has been developed for the non-invasive quantification method (RLS) of the acetylcholinesterase (AChE) activity in the human brain from measurements with the ^{11}C-MP4A acetylcholine analog [1]. In contrast to reference methods for receptor tracers which use a reference devoid of specific binding, the present method uses a reference with very high AChE activity which immediately traps the tracer so there is no washout. $C_T(t)$ is the TAC from a cortical target region, and $C_T'(t)$ the TAC from the reference region (striatum or cerebellum). k_3 represents the rate of tracer hydrolysis by AChE.



By applying the method of Blomqvist, the following multi-linear equation is derived

$$C_{Model}(t) = p_1 C_T'(t) + p_2 \int_0^t C_T'(\tau)d\tau + p_3 \int_0^t C_T(\tau)d\tau$$

It can be fitted to $C_T(t)$ using multi-linear regression, yielding three regression coefficients from which three parameters of interest can be calculated:

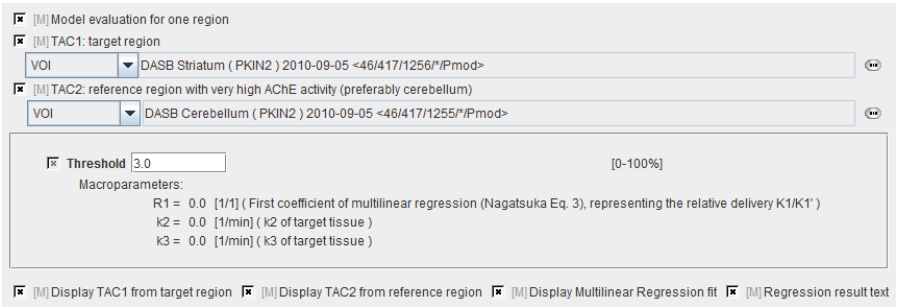
$$R_1 = K_1 / K_1' = p_1$$
$$k_2 = -(p_3 + p_2 / p_1)$$
$$k_3 = p_2 / p_1$$

Acquisition and Data Requirements

Image Data	A dynamic PET data set with [11C]-MP4A.
TAC 1	TAC from a cortical target region.
TAC 2	A suitable reference region must be selected as TAC 2. The findings in different publications indicate that cerebellum yields more stable results than striatum, most likely due to the higher impact of motion on the signal from the small striatum than the large cerebellum.

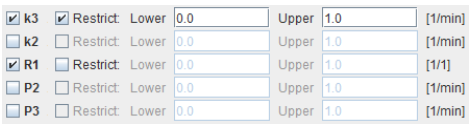
Model Preprocessing

Two regional TACs (**TAC1** and **TAC2**) are needed for **Model Preprocessing**.



Threshold	Discrimination threshold for background masking.
R1	The delivery in the target region relative to the reference.
k2	The rate of washout from brain to blood.
k3	The main parameter, the rate of tracer hydrolysis by AChE.

Map Parameters



k3	The main parameter, the rate of tracer hydrolysis by AChE.
k2	The rate of washout from brain to blood.
R1	First coefficient of multilinear regression (Nagatsuka Eq. 3), representing the relative delivery K_1/K_1'.
P2	Second coefficient of multilinear regression (Nagatsuka Eq. 3), representing $Rl*k_3$
P3	Third coefficient of multilinear regression (Nagatsuka Eq. 3), representing $-(k_2+k_3)$

Reference

1. Nagatsuka Si S, Fukushi K, Shinotoh H, Namba H, Iyo M, Tanaka N, Aotsuka A, Ota T, Tanada S, Irie T: Kinetic analysis of [(11)C]MP4A using a high-radioactivity brain region that represents an integrated input function for measurement of cerebral acetylcholinesterase activity without arterial blood sampling. J Cereb Blood Flow Metab 2001, 21(11):1354-1366. ***DOI http://dx.doi.org/10.1097/00004647-200111000-00011***

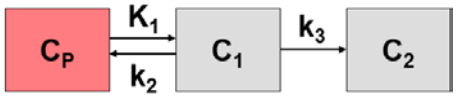
Brain Glucose Consumption

The brain glucose metabolism can be investigated with radioactively labeled glucose. There are two models available for the quantification of ^{18}F-Deoxy-Glucose (FDG) data. One requires a dynamic acquisition, the other only a single static scan, but both require that the FDG activity in blood is sampled from the time of injection until the end of the acquisition.

Two other models can be applied for data from quantitative autoradiography experiments with ^{14}C labeled glucose. One model assumes a constant plasma glucose level, while the other can account for changes.

MRGlu (FDG Patlak): Graphical Plot of Dynamic Data

The **MRGlu (FDG Patlak)** model is intended for the quantitative assessment of the regional metabolic rate of glucose (MRGlu) with FDG. The required measurements are a dynamic PET scan after the injection of a FDG bolus and external blood sampling. The analysis is done using the Patlak graphical plot method [1] which has been developed for systems with irreversible trapping, ie. k_4=0 in a 2-tissue compartment model.

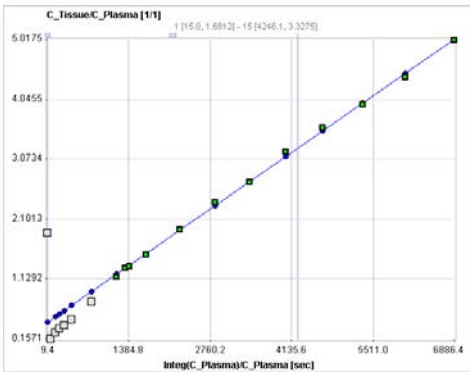


However, this model structure is not necessary for the application of the method. It is sufficient to have any compartment in the system which binds irreversibly.

The Patlak plot belongs to a group of *Graphical Analysis* techniques, whereby the measured tissue TAC $C_T(T)$ undergoes a mathematical transformation and is plotted against some sort of "normalized time". The Patlak plot is given by the expression

$$\frac{C_T(t)}{C_P(t)} = K \frac{\int_0^t C_P(\tau)d\tau}{C_P(t)} + V$$

with the input curve $C_p(t)$. This means that the measured PET activity is divided by plasma activity, and plotted at a "normalized time" (integral of the input curve from the injection time divided by the instantaneous plasma activity). For systems with irreversible compartments this plot will result in a straight line after an equilibration time t*.



The slope K and the intercept V must be interpreted according to the underlying compartment model. For the FDG tracer, the slope K equals $K_1k_3/(k_2+k_3)$ and represents the metabolic flux, while the intercept V equals V_0+vB with the distribution volume V_0 of the reversible compartment C_1 and the fractional blood volume vB.

For the analysis of FDG data, the **Lumped Constant** (LC) and the **Plasma glucose** level (PG) of the patient need to be entered. The metabolic rate of glucose **MRGlu** is then obtained from the regression slope K by

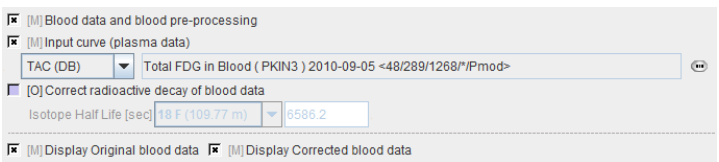
$$MRGlu = slope \frac{PG}{LC}$$

Acquisition and Data Requirements

Image Data	A dynamic PET data set representing the measurements of brain activity from the time of injecting of a ^{18}F-Deoxy-Glucose (FDG) bolus.
Blood Data	Plasma activity of blood sampled at a peripheral artery from the time of injection until the end of the acquisition.
Tissue TAC	A regional time-activity curve from a brain region. It is presented as a Patlak plot and can be used to define the linear segment where the regression analysis should be done.

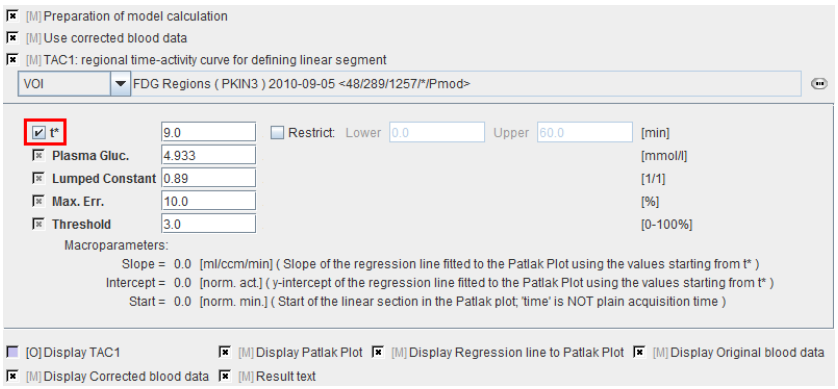
Blood Preprocessing

Decay correction is the only blood correction option. Note that an uncorrected relative time shift of blood data by 30 sec does not markedly change the calculated glucose consumption.



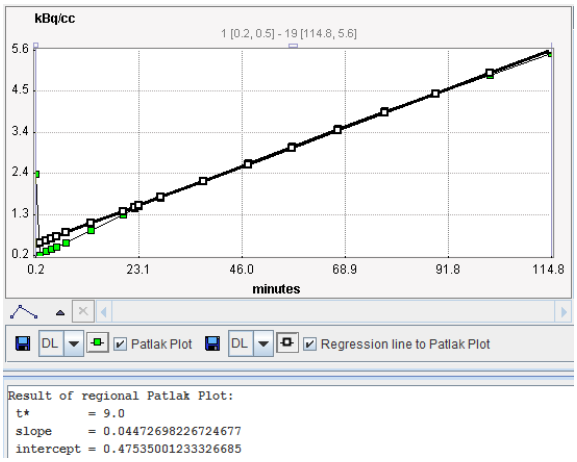
Model Preprocessing

The Patlak graphical plot is performed with the TAC from the specified tissue VOI and presented to the user. Essentially, it is a plot of the TAC with "normalized time" along the x-axis and "normalized" tissue activity on the y-axis. In this plot, the TAC becomes linear after an equilibration time due to irreversible trapping (k_4=0). The slope of the linear segment equals the influx constant K_i and can be used to calculate metabolic rate of glucose. The user must decide on the begin of the linear segment in the "normalized" time units and specify the corresponding acquisition start time **t*** in the model configuration. An alternative is to apply the automatic criterion **Max. Err.** for fitting **t***.

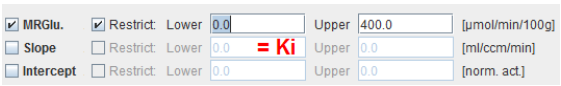


t*	The linear regression estimation should be restricted to a range after an equilibration time. **t*** marks the beginning of the range used in the multi-linear regression analysis. It can be fitted based on the **Max. Err.** criterion. Note that the t* is in acquisition time.
Plasma glucose	Plasma glucose in [mmol/l] measured with a blood sample of the patient.
Lumped constant	The **Lumped constant** is used to compensate for the difference in uptake between normal glucose and Fluoro-Deoxyglucose (FDG). Proposed as the default is the value determined by Graham et al (J Nucl Med 2002; 43:1157–1166) using ^{11}C Glucose and FDG in 2002. Their results: Normal brain: 0.89+/-0.08; cerebellum: 0.78+/-0.11.
Max. Err.	Maximum relative error ((measured-predicted)/predicted) allowed between the linear regression and the Patlak-transformed measurements in the segment starting from **t***.
Threshold	Discrimination threshold for background masking.
Slope	Slope of the linear regression, ie. K_i.
Intercept	Intercept of the linear regression.
Start	Time corresponding to **t*** in the Patlak plot.

The Patlak plot is shown in the preprocessing **Result**. The user should consult this plot in order to check whether the **t*** time is adequate.



Map Parameters



MRGlu	Metabolic Rate of Glucose in [µmol/min/100ml], the actual result of the model. It is calculated as: MRGlu = (1/Lumped_Constant)*Slope*Plasma_Glucose
Slope	Slope of the linear regression. It equals the influx $K_i=(K_1*k_3)/(k_2+k_3)$ of the 2-tissue compartment model and is directly proportional to MRGlu.
Intercept	Intercept of the linear regression.

Reference:

1. Patlak CS, Blasberg RG, Fenstermacher JD: Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metab 1983, 3(1):1-7. ***DOI http://dx.doi.org/10.1038/jcbfm.1983.1***

MRGlu (FDG Autorad): Quantification with one Static Scan

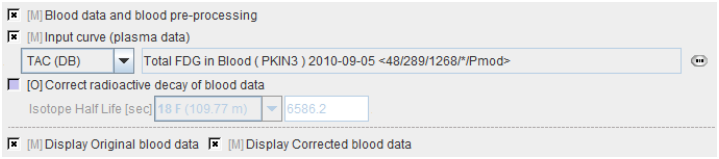
The **MRGlu (FDG Autorad)** model is intended for the quantitative assessment of the regional metabolic rate of glucose (MRGlu). The required measurements are a static PET scan between 40 and 55 min after the injection of a FDG bolus, and external blood sampling from the time of injection until the end of the PET acquisition, as well as the analysis of one blood sample for the plasma glucose concentration. The analysis is based on an autoradiographic solution of the 2-tissue compartment model. It provides an operational equation (eq. (8) in [1]) as to how calculate the metabolic rate of glucose from the blood curve, the PET value, the plasma glucose, and 5 fixed (but modifiable) parameters: the lumped constant, K_1, k_2, k_3, and k_4.

Acquisition and Data Requirements

Image Data	A static PET data set representing the measurement of the average brain activity between 40 to 55 min after injection of a FDG bolus. Note: if a dynamic study is loaded, the activity of all loaded frames is averaged at the time of pixel-wise model calculation.
Blood Data	Plasma activity of blood sampled at a peripheral artery from the time of injection until the end of the acquisition.

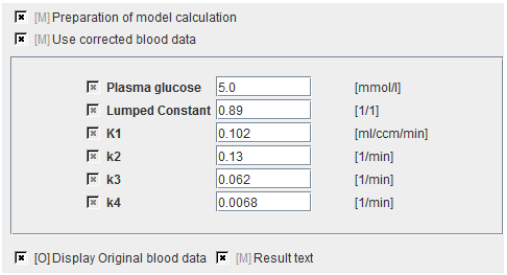
Blood Preprocessing

Decay correction is the only blood correction option. Note that an uncorrected relative time shift of blood data by 30 sec does not markedly change the calculated glucose consumption.



Model Preprocessing

The rate constants applied in the autoradiographic calculation of MRGlu must be entered in the **Model Preprocessing** dialog.



Plasma glucose	Plasma glucose in [mmol/l] measured with a blood sample of the patient.
Lumped constant	The **Lumped constant** is used to compensate for the difference in uptake between normal glucose and Fluoro-Deoxyglucose (FDG). Proposed as the default is the value determined by Graham et al (J Nucl Med 2002; 43:1157–1166) using ^{11}C Glucose and FDG in 2002. Their results: Normal brain: 0.89+/-0.08; cerebellum: 0.78+/-0.11.
K1	Unidirectional transfer of FDG into tissue. Grey matter: 0.102. White Matter: 0.054.
k2	Clearance of FDG from the tissue. Grey matter: 0.130. White Matter: 0.109.
k3	Phosphorylation rate in tissue. Grey matter: 0.062. White Matter: 0.045.

k4	Dephosphorylation of glucose-phosphate in tissue. Grey matter: 0.0068. White Matter: 0.0058.

Map Parameters

MRGlu	Metabolic Rate of Glucose in [µmol/min/100ml] calculated according to eq. (8) in [13].

Reference

1. Huang SC, Phelps ME, Hoffman EJ, Sideris K, Selin CJ, Kuhl DE: Noninvasive determination of local cerebral metabolic rate of glucose in man. The American journal of physiology 1980, 238(1):E69-82.

C14 Autoradiography

This is the model which supports the quantitative data analysis for the classical autoradiography with ^{14}C-deoxyglucose (DG) [1]. In fact it is this model from which the PET ***FDG autoradiography*** (on page 115) model is derived from, and both have the same underlying assumptions and equations.

In summary, an autoradiographic experiment is performed as follows:

1) The ^{14}C-labeled deoxyglucose is injected.

Blood is sampled and counted until the end of the experiment.

The glucose concentration in plasma is measured for one sample.

After 50 minutes the deoxyglucose has been trapped and the animal is sacrificed.

The brain is isolated, then frozen, and sectioned into very thin slices.

The slices are put onto a flat support and mounted into a radioactivity counter together with reference sheets of known activity concentration.

The radioactivity is counted during several days.

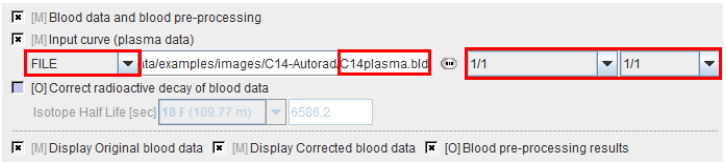
The result is a set of images either on a conventional film or as a digital file in one of the popular graphic formats. These images can be turned into radioactivity units by a translation table which needs to be obtained from the reference sheets.

Acquisition and Data Requirements

Image Data	A data set representing the autoradiographical slices in arbitrary units. Select 1/1 as the loading units as the values are transformed into nCi/g during the model calculations. An appropriate translation table must be derived from the image representation of the reference sheets and supplied as the TAC1 curve in the model preprocessing panel. Note that the *duration of the acquisition must be specified as the time from injection until sacrificing the animal*.

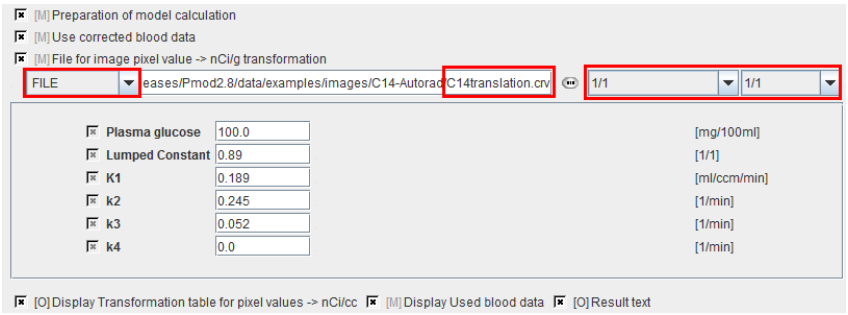
Blood Data	Plasma activity of blood sampled at a peripheral artery from the time of injection until sacrificing the animal. Important: Select 1/1 as the units and ensure that the values in the data file are already in nCi/g.

Blood Preprocessing



Model Preprocessing

The parameters applied in the autoradiographic calculation of MRGlu must be entered in the model pre-processing dialog



Plasma glucose	Plasma glucose measured with a blood sample of the animal.
Lumped constant	It is used to account for the difference in uptake between normal glucose and DG.
K1	Unidirectional transfer of DG into tissue.
k2	Clearance of DG from the tissue.
k3	Phosphorylation rate in tissue.
k4	Dephosphorylation of glucose-phosphate in tissue.

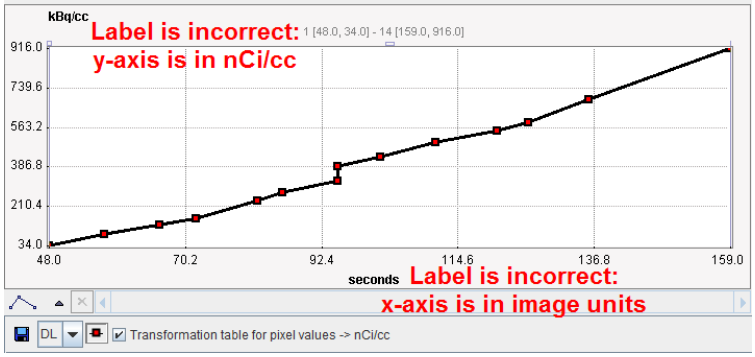
As mentioned before it is assumed that the input images are in arbitrary units and must be converted to radioactivity. This is done by the application of a translation table which must be specified as shown in the **Model pre-processing** dialog above (**C14translation.crv**). The contents of this text file should look like :

Graphic[1/1] Activity[1/1]
46 0
48 34
57 84
66 126

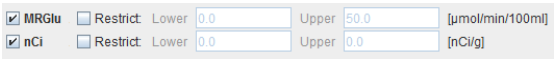
72 157
82 233
86 270
95 323
95 391
102 433
111 497
121 549
126 585
136 688
159 916

So in the above example the image pixel values have an original range up to 159, and the resulting activity values range up to 916nCi/g as determined by the reference sheets. Note that linear interpolation is applied between the specified time points.

The translation curve is shown in the preprocessing **Result** area as



Map Parameters



MRGlu	Metabolic Rate of Glucose in [µmol/min/100ml], the actual result of the model. It is calculated according to eq. (8) in [13].
nCi/g	This is just a utility parameter showing the activity in the pixels after application of the conversion table.

Reference

1. Huang SC, Phelps ME, Hoffman EJ, Sideris K, Selin CJ, Kuhl DE: Noninvasive determination of local cerebral metabolic rate of glucose in man. The American journal of physiology 1980, 238(1):E69-82.

C14 Autoradiography; Glucose variable

This is the same model as the **C14 Autoradiography** (on page 117), except that a correction for the changing of plasma glucose during the experiment is included [1].

The autoradiographic experiment is performed as follows:

1) The ^{14}C-labeled deoxyglucose is injected.

Blood is sampled and counted until the end of the experiment.

The glucose concentration in plasma is measured *for several samples*.

After 50 minutes the deoxyglucose has been trapped and the animal is sacrificed.

The brain is isolated, then frozen, and sectioned into very thin slices.

The slices are put onto a flat support and mounted into a radioactivity counter together with reference sheets of known activity concentration.

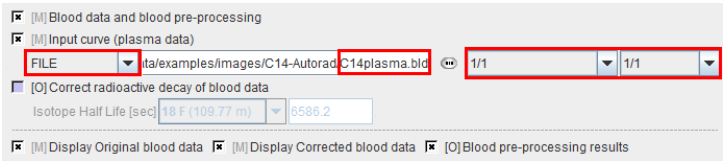
The radioactivity is counted during several days.

The result is a set of images either on a conventional film or as a digital file in one of the popular graphic formats. These images can be turned into radioactivity units by a translation table which needs to be obtained from the reference sheets.

Acquisition and Data Requirements

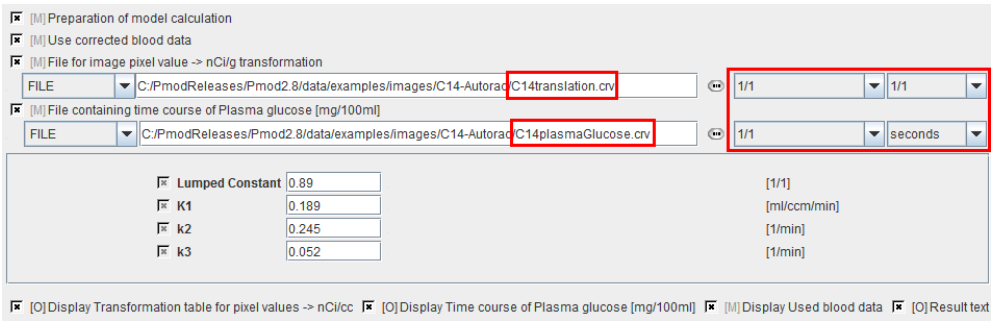
Image Data	A data set representing the autoradiographical slices in arbitrary units. Select 1/1 as the loading units as the values are transformed into nCi/g during the model calculations. An appropriate translation table must be derived from the image representation of the reference sheets and supplied as the TAC1 curve in the model preprocessing panel. Note that the *duration of the acquisition must be specified as the time from injection until sacrificing the animal*.
Blood Data	Plasma activity of blood sampled at a peripheral artery from the time of injection until sacrificing the animal. Important: Select 1/1 as the units and ensure that the values in the data file are already in nCi/g.

Blood Preprocessing



Model Preprocessing

The parameters applied in the autoradiographic calculation of MRGlu must be entered in the model pre-processing dialog



Lumped constant	It is used to account for the difference in uptake between normal glucose and DG.
K1	Unidirectional transfer of DG into tissue.
k2	Clearance of DG from the tissue.
k3	Phosphorylation rate in tissue.

As mentioned before it is assumed that the input images are in arbitrary units and must be converted to radioactivity. This is done by the application of a translation table which must be specified as **File for image pixel value -> nCi transformation** on the **Model Preprocessing** panel (**C14translation.crv**). The contents of this text file should look like :

Graphic[1/1] Activity[1/1]
46 0
48 34
57 84
66 126
72 157
82 233
86 270
95 323
95 391
102 433
111 497
121 549
126 585
136 688
159 916

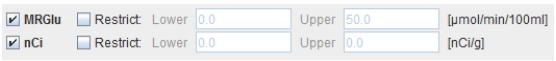
So in the above example the image pixel values have an original range up to 159, and the resulting activity values range up to 916 nCi/g.

Additionally a **File containing the course of Plasma glucose over time** in mg/100ml must be specified (**C14plasmaGlucose.crv**). This text file should look like :

time[seconds] glucose[1/1]
0 115.2
2700 97.2

Note that linear interpolation is applied between the tabulated values in the lookup files.

Map Parameters



MRGlu	Metabolic Rate of Glucose in [µmol/min/100ml], the actual result of the model. It is calculated according to eq. (7) in [23].
nCi/g	This is just a utility parameter showing the activity in the pixels after application of the conversion table.

Reference

1. Savaki HE, Davidsen L, Smith C, Sokoloff L: Measurement of free glucose turnover in brain. J Neurochem 1980, 35(2):495-502.

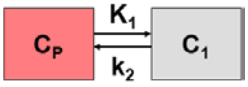
Brain Perfusion and Blood Volume

There are three models available for calculating pixel-wise estimates of regional cerebral blood (rCBF) from $H_2{}^{15}O$ bolus PET measurements. Note that the result is given in units of ml/min/100ml.

Another model serves for the quantitative assessment of the regional blood volume (rBV) from PET measurements after a bolus inhalation of ^{11}CO.

rCBF (Alpert): Time-weighted Integral Method

The **rCBF(Alpert)** model is used for calculating parametric perfusion maps from dynamic $H_2{}^{15}O$ brain PET images. A 1-tissue compartment model is applied



with operational equation

$$C_T(t) = K_1 \int_0^t C_P(\tau) e^{-k_2(t-\tau)} d\tau = F \int_0^t C_P(\tau) e^{-F/p(t-\tau)} d\tau$$

where K_1 represents perfusion F, and k_2 equals perfusion divided by the particion coefficient of water p. Alpert et al. [1] introduce weighting functions $w_1(t)$ and $w_2(t)$ which are multiplied with both sides of the equation above. Resolving the equation multiplied by $w_1(t)$ yields

$$F = \frac{\int_0^T w_1(t) C_T(t)}{\int_0^T w_1(t) \int_0^t C_P(\tau) e^{-k_2(t-\tau)} d\tau dt}$$

Dividing both multiplied equations results in an expression which only contains k_2.

$$\frac{\int_0^T w_1(t) C_T(t)}{\int_0^T w_2(t) C_T(t)} = \frac{\int_0^T w_1(t) \int_0^t C_P(\tau) e^{-k_2(t-\tau)} d\tau dt}{\int_0^T w_2(t) \int_0^t C_P(\tau) e^{-k_2(t-\tau)} d\tau dt}$$

Based on the latter two equations the following methodology for calculating perfusion was developed [1]:

1) The weighting functions are defined as $w_1(t)=1$ and $w_2(t)=t$.

Since the input curve $C_P(t)$ and the physiologic range of k_2 are known (the particion coefficient is more or less constant at a value of about 0.9), the right side of the third equation can be evaluated and tabulated for a pre-defined k_2-range. This table was called the *R-Table* and contains the evaluated ratios r_i for all k_{2i}.

For a tissue curve $C_T(t)$ to analyze, the left side of the third equation is evaluated, resulting a value r. It is then looked up in the R-Table which value of k_2 results in the r_i value closest to r.

Using the obtained k_2, the second equation can be evaluated, resulting in the perfusion value F.

Acquisition and Data Requirements

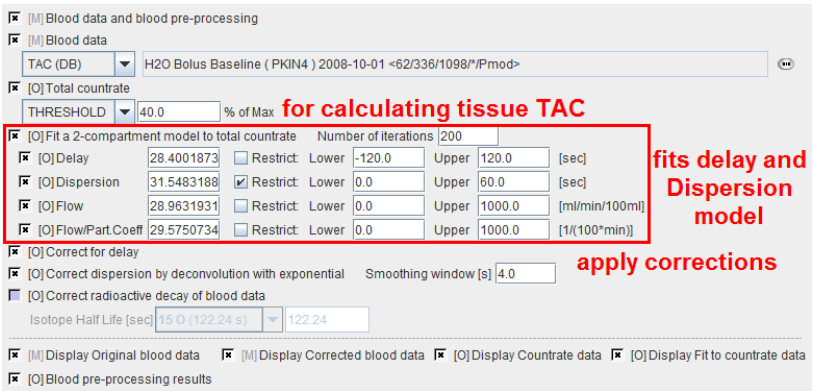
Image Data	A dynamic PET data set representing the measurements of brain activity after the injection of a $H_2{}^{15}O$ bolus.
Blood Data	Blood activity sampled at a peripheral artery from the time of injection until about 30 seconds post acquisition. The sampling past the end of the PET acquisition is required because of the delayed arrival of blood in an external radioactivity counter.
TAC for Blood Preprocessing	A tissue TAC is required to fit a compartment model during blood preprocessing. Candidate TACs would be the imported system count rate, or the average activity calculated in a brain VOI as shown in the example below.

Blood Preprocessing

The instantaneous blood activity during the acquisition is needed as the input curve of the perfusion model. However, because blood activity is monitored with an external device, the measured activity is distorted relative to the activity arriving in the brain by two effects: a relative time delay, and a broadening of the activity shape (bolus dispersion). For accurate rCBF measurements the delay and dispersion of the blood measurements must therefore be corrected for.

The blood preprocessing step of the **rCBF (Alpert)** model applies the methodology developed by Meyer et al. [2] for the delay and dispersion correction. It fits a 1-tissue compartment model including a delay and a dispersion parameter to a tissue time-activity curve provided. The blood curve is then explicitly shifted by the found delay, and deconvolved with the exponential dispersion.

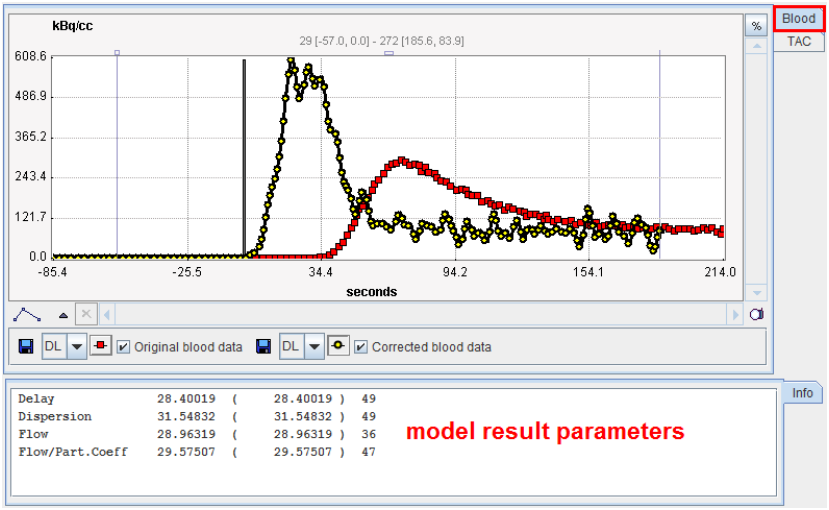
A typical definition provided with the example $H_2{}^{15}O$ data set is shown below.



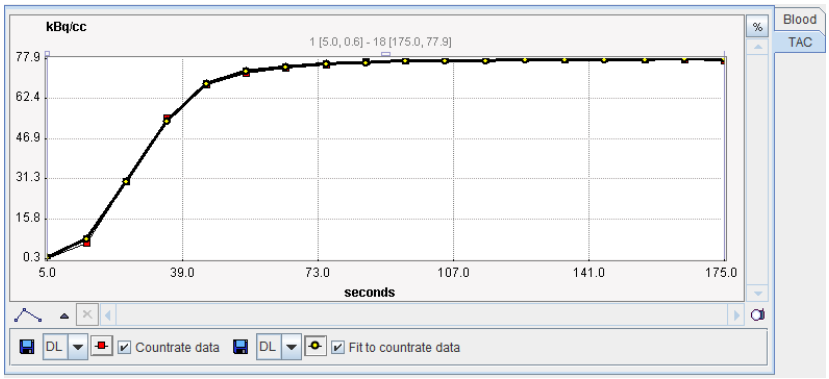
The measured blood activity is read from the file **H2O Bolus Baseline** in the database. The brain TAC which is used for fitting the 1-tissue compartment model is derived from a **40% THRESHOLD**. Alternatively, a user-defined VOI could be used.

After the blood preprocessing has been performed, the result is shown in the **Result** panel. The parameters resulting from the fit are shown in the **Info** area. There are two sub-panels, one showing the corrected blood and the other showing the fit to the TAC.

The **Blood** curve area shows the original blood measurements and the input curve after correction for the **Delay** (28.4 sec) and **Dispersion** (31.5 sec). The **Corrected blood data** is used for the further calculations.



The **TAC** panel should also be inspected to verify that the fit was successful.

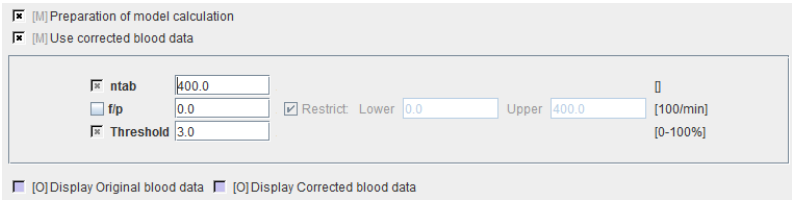


Some published results regarding the dispersion parameter:

- Net internal dispersion due to the longer distance left ventricle-radialis than left ventricle-brain: 4sec [8], 4-6sec [5].
- External dispersion in the sampling tubes: 0.5sec (10mm catheter, 0.5mm inner diameter, no three-way taps, 10ml/min) [5]; 10-12sec, 5-6sec, 1-2sec for 5,10, 20 ml/min (40mm catheter, 1.0mm inner diameter, three-way taps) [8].

Model Preprocessing

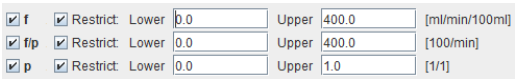
Model preprocessing for Alpert's time-weighted integral method consists of calculating lookup tables of the model response within a range of f/p values (f = Flow, p = partition coefficient; f/p = k_2 of the 1-tissue compartment model). The f/p range and the number of tabulated values must be specified in the preprocessing dialog as illustrated below. Normally there is no need for changing any of the input parameters.



ntab	Number of pre-calculated values in the lookup table. Should be an even number.
f /p	Flow/partition coefficient ("k" in Alpert's paper). The **Lower** and **Upper** bound should be specified reasonably, otherwise there will not be a meaningful result. This range is used for setting up Alpert's "r-table".
Threshold	Discrimination threshold for background masking.

Map Parameters

The main result of the processing is the rCBF value f. Therefore it should be enabled in the **Model** dialog. f/p and p can also be mapped if needed.



f	Regional brain perfusion in [ml/min/100ml]. It is calculated for each pixel by a table look-up procedure (Alpert's eq. 5). Reasonable values are about 30 (white matter) and 60 (gray matter) ml/min/100ml [11].
f/p	The f/p value found in the table lookup procedure and used to calculate f.
p	Partition coefficient or distribution volume of water in brain. It is calculated by dividing the two previously calculated parameters. Reasonable values are around 0.9.

Reference

1. Alpert NM, Eriksson L, Chang JY, Bergstrom M, Litton JE, Correia JA, Bohm C, Ackerman RH, Taveras JM: Strategy for the measurement of regional cerebral blood flow using short-

lived tracers and emission tomography. J Cereb Blood Flow Metab 1984, 4(1):28-34. ***DOI http://dx.doi.org/10.1038/jcbfm.1984.4***

2. Meyer E: Simultaneous correction for tracer arrival delay and dispersion in CBF measurements by the H215O autoradiographic method and dynamic PET. J Nucl Med 1989, 30(6):1069-1078.

rCBF (Watabe Ref): Method without Blood Sampling

The **rCBF (Watabe)** model was intended for the quantitative assessment of the regional cerebral blood flow. The only required measurement is a dynamic PET acquisition after the injection of a $H_2{}^{15}O$ bolus, obviating the need for blood sampling. What is required instead are the time-activity curves of two cerebral regions - a *low-flow* and a *high-flow* region. By comparing the TACs of these regions their flows (f_1, f_2) and distribution volumes (DV_1, DV_2) can be estimated. Then, the TAC from each pixel can be compared to that of the low-flow region. Its flow and distribution volume are hereby estimated, whereby the previously obtained parameter values of the low-flow region (f_1, DV_1) and a fixed DV are contained in the calculation prescription.

CAUTION: With practical data it has turned out that the fitting is too dependent on the initial parameter values and does not provide sufficiently stable results.

Acquisition and Data Requirements

Image Data	A dynamic PET data set representing the measurements of brain activity after injection of a $H_2{}^{15}O$ bolus.

Model Preprocessing

A methodology has been implemented to automatically extract low-flow and high-flow TACs as follows:

1) The signals are integrated over the acquisition duration in all pixels.

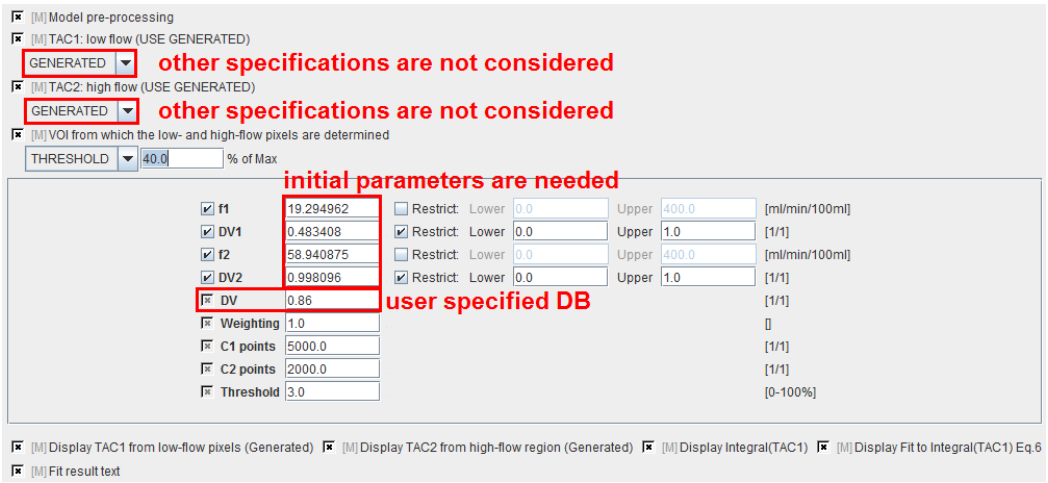
A lower threshold (40% in the example below) is applied to restrict the volume-of-interest to brain.

A histogram within the threshold volume is calculated.

The C1 (ex. 5000) pixels at the lower end of the histogram are assumed to represent low-flow pixels; their average curve TAC1 is calculated. Only this GENERATED approach is supported, no manual TAC specification.

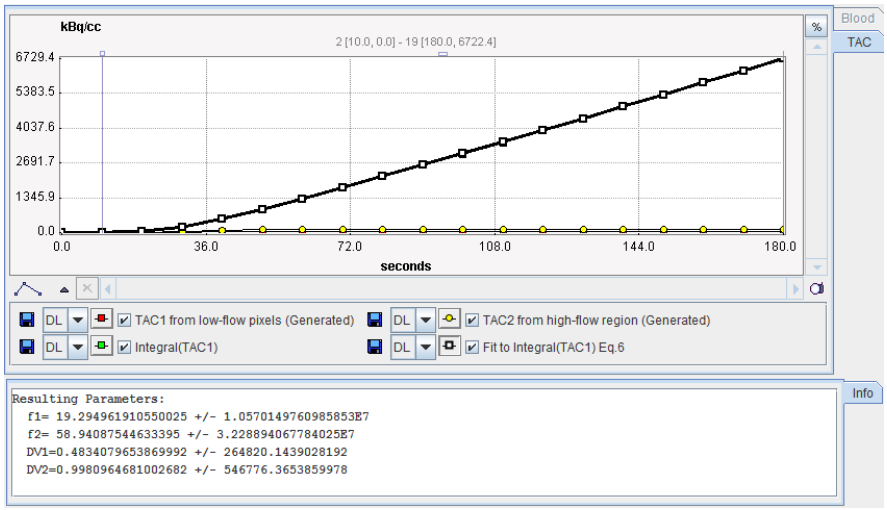
The C2 (ex. 2000) pixels at the upper end of the histogram are assumed to represent high-flow pixels; their average curve TAC2 is calculated. Only this GENERATED approach is supported, no manual TAC specification.

Then an iterative fit of Watabe's eq. (7) is performed to calculate the flows (f_1,f_2) and distribution volumes (DV_1,DV_2) of the two TACs. The resulting f_1 and DV_1 together with an assumed distribution volume DV (which must be specified by the user) are then used for the pixel-wise flow calculations by Watabe's eq. (8).



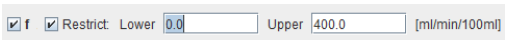
f1	Flow in low-flow region estimated during preprocessing and subsequently used in pixel-wise calculations.
DV1	Distribution volume in low-flow region estimated during preprocessing and subsequently used in pixel-wise calculations.
f2	Flow in high-flow region estimated during preprocessing but NOT further used.
DV2	Distribution volume in high-flow region estimated during preprocessing but NOT further used.
DV	Fixed distribution volume which is assumed for each pixel-wise TAC.
Weighting	Different schemes for residual weighting in the iterative preprocessing fit.
C1 points	Number of points used for the generation of TAC1.
C2 points	Number of points used for the generation of TAC2.
Threshold	Discrimination threshold for background masking.

After preprocessing, the Watabe plot is shown on the **Results** panel for inspection. Note that the the integral curves can be deactivated using the check boxes to see the generated TACs.



Important Note: Experience has shown that the results of this reference method highly depend on the iterative fit with 4 parameters. As illustrated in this example, the identifiability of the parameters is often poor, and the results may heavily depend on the starting values. In an attempt to make the method more stable, one can fix **VD2** to a reasonable value such as 0.9. To this end, just deactivate the box next to **VD2** .

Map Parameters



f	Regional perfusion in [ml/min/100ml]. It is calculated for each pixel by a closed-form calculation (Watabe's eq. 8). Reasonable values are about 30 (white matter) and 60 (gray matter) ml/min/100ml [11].

Reference

1. Watabe H, Itoh M, Cunningham V, Lammertsma AA, Bloomfield P, Mejia M, Fujiwara T, Jones AK, Jones T, Nakamura T: Noninvasive quantification of rCBF using positron emission tomography. J Cereb Blood Flow Metab 1996, 16(2):311-319.

rCBF (Autorad): Quantification with one Static Scan

The **rCBF (Autorad)** model is intended for the quantitative assessment of the regional cerebral blood flow. The required measurements are a static PET after the injection of a $H_2{}^{15}O$ bolus and external blood sampling from the start of injection. An autoradiographic solution of the 1-tissue compartment model for the exchange of an inert tracer is applied [1]. The solution is based on the convolution of the blood activity with an exponential which contains the flow and the partition coefficient in the exponent. The convolved function is integrated over the acquisition time and compared with the integrated PET value. Given a specified value for the partition coefficient, the perfusion can be estimated by a table lookup approach.

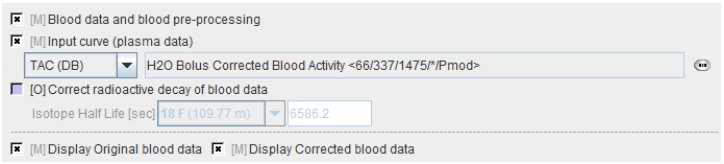
Acquisition and Data Requirements

Image Data	A static PET data set representing the average brain activity after injection of a $H_2{}^{15}O$ bolus. If a dynamic data set is loaded, the average pixel activity over the acquisition period will automatically be calculated during pixel-wise processing. The acquisition duration should only cover the uptake phase.
Blood Data	Blood activity sampled at a peripheral artery from the time of injection until the end of the PET acquisition.

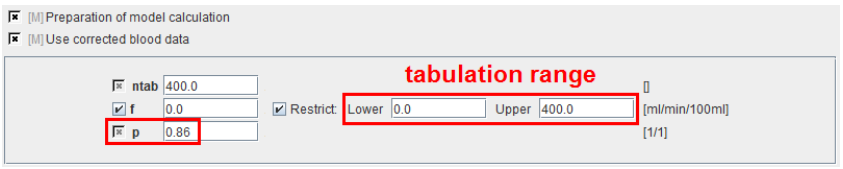
Blood Preprocessing

Because autoradiographic data is usually static, the 1-tissue compartment fit for estimating the delay and dispersion can not be applied. Therefore the only available blood preprocessing option is decay correction.

Note: The loaded blood data should have been corrected for delay and dispersion beforehand. This processing can be done on the **Blood** panel of in **PKIN**.

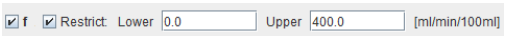


Model Preprocessing



ntab	Number of pre-calculated values in the lookup table. Should be an even number.
f	Perfusion in [ml/min/100ml]. Please specify the range within which the tabulation is performed.
p	Partition coefficient or distribution volume of water in brain. This input parameter must be specified by the user.

Map Parameters



f	Regional perfusion in [ml/min/100ml]. It is calculated for each pixel by a table look-up procedure. Reasonable values are about 30 (white matter) and 60 (gray matter) ml/min/100ml [11]

	Note: The results are accurate only for voxels with the partition coefficient equal to that entered in the **p**-field.

Reference

1. Herscovitch P, Markham J, Raichle ME: Brain blood flow measured with intravenous H2(15)O. I. Theory and error analysis. J Nucl Med 1983, 24(9):782-789.

rBV (Autorad): Quantification with one Static Scan

The **rBV (Autorad)** model is intended for the quantitative assessment of the regional blood volume (rBV). The required measurements are a static $C^{15}O$ PET scan and external blood sampling. After a bolus inhalation of $C^{15}O$ inhalation an equilibration period should be allowed for 5 min. Then, blood data are sampled while a static PET acquisition is performed. The rBV can finally be calculated by dividing the PET activity by the integrated blood activity.

Acquisition and Data Requirements

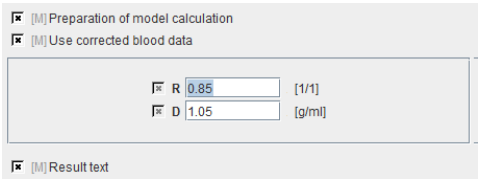
Image Data	A static PET data set representing the equilibrium brain activity during $C^{15}O$ inhalation. If more than one frame has been loaded, the average PET activity is calculated during the pixel-wise calculations.
Blood Data	Blood activity sampled at a peripheral artery after equilibration from beginning until the end of the PET acquisition.

Blood Preprocessing

The only available blood preprocessing option is decay correction.

Model Preprocessing

Just reads numerical data needed for pixel-wise processing in two input fields.



R	Haematokrit Ratio Small/Large Vessels. Mean ratio: 0.85.
D	Density of brain tissue: 1.05 [g/ml].

Map Parameters

rBV	Regional blood volume in [ml/100g]. It is calculated as: rBV = PET*100/(R*D*integrated_blood)

Reference

1. Mintun MA, Raichle ME, Martin WR, Herscovitch P: Brain oxygen utilization measured with O-15 radiotracers and positron emission tomography. J Nucl Med 1984, 25(2):177-187.

Note: The main focus of the cited reference is the calculation of regional brain oxygen extraction ($CMRO_2$). That model requires the pixel-wise knowledge of the rBV and the rCBF. These functional maps could be determined with models supported in this software. The calculation of the $CMRO_2$, however, is currently not available.

Miscellaneous Models

Factor Analysis (2 TACs)

This model performs a factor analysis (FA) on dynamic data. Two TACs must be specified:

1) One TAC which reflects the temporal evolution of activity in the tissue of interest (variate TAC; e.g. myocardium in cardiac studies).

One TAC which reflects the temporal evolution of activity opposite to the tissue of interest (covariate TAC; e.g. ventricle in cardiac studies).

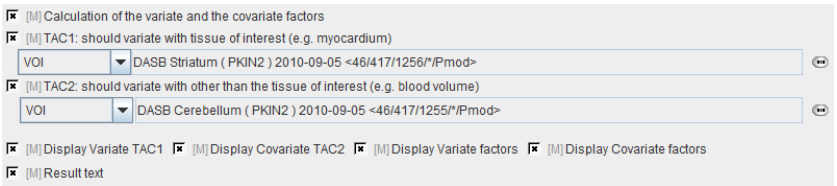
With these time activity curves a factor analysis is performed, resulting in two sets of factors (one factor per time). These factors are applied during pixel-wise processing to calculate the variate and covariate factor images.

Acquisition and Data Requirements

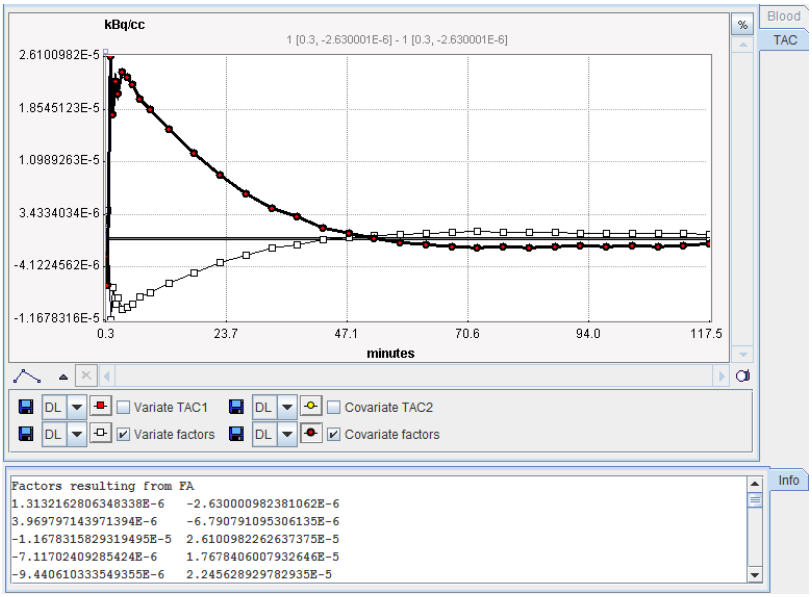
Image Data	Any dynamic volume data.
TAC 1	Time-activity curve of the tissue of interest.
TAC 2	Time-activity curve of the tissue to be differentiated from the tissue of interest.

Model Preprocessing

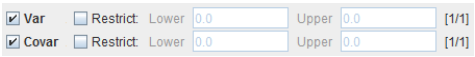
During preprocessing the variate and covariate factors are calculated using the two specified TACs.



The factors are displayed in the **Results** panel together with the TACs to be examined or exported.



Map Parameters



Var	The variate image is calculated by summing the products var_i*TAC_i over all time points. Here var_i represents the variate weights, and TAC_i the value at the i-th frame of the pixel.
Covar	Covariate calculated by summing the products $covar_i$*TAC_i over all time points. $covar_i$ represents the covariate weights, and TAC_i the value at the i-th frame of the pixel.

Factor Analysis (H2O, Lung TAC)

The **Factor Analysis (H2O, Lung TAC)** model performs a factor analysis (FA) on dynamic cardiac $H_2{}^{15}O$ PET data to obtain anatomical images of the heart. Please refer to the guide of the cardiac modeling tool PCARD for details.

Principle

One TAC must be specified which is assumed to represent $H_2{}^{15}O$ activity in the lung. The model then proceeds as follows:

During model preprocessing three TACs are mathematically derived from the Lung TAC

1) Blood activity in the right ventricle (negative time shift of lung TAC)

Blood activity in the left ventricle (positive time shift of lung TAC)

Activity in myocardium: it is calculated using a 1-tissue compartment model and pre-defined values for myocardial perfusion, partition coefficient, and the shifted lung TAC as the input curve.

During pixel-wise processing myocardium and blood pool images are calculated by a factor analyis:

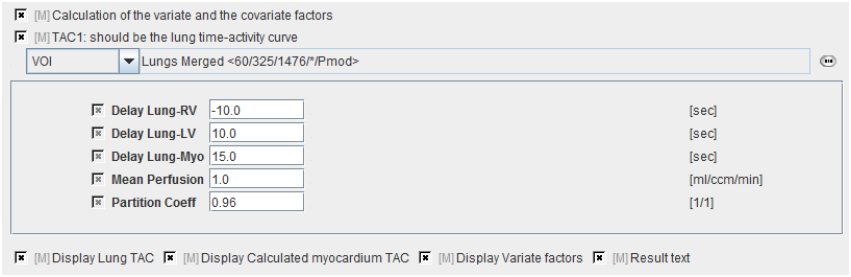
- Myocardium: variate is $TAC_{myocardium}$; covariates are TAC_{LV}, TAC_{RV}
- Blood Pool: variate is TAC_{lung}; covariates are $TAC_{myocardium}$

Acquisition and Data Requirements

Image Data	Dynamic cardiac $H_2{}^{15}O$ PET study (decay corrected).
TAC 1	Time-activity curve representing blood activity in the lungs.

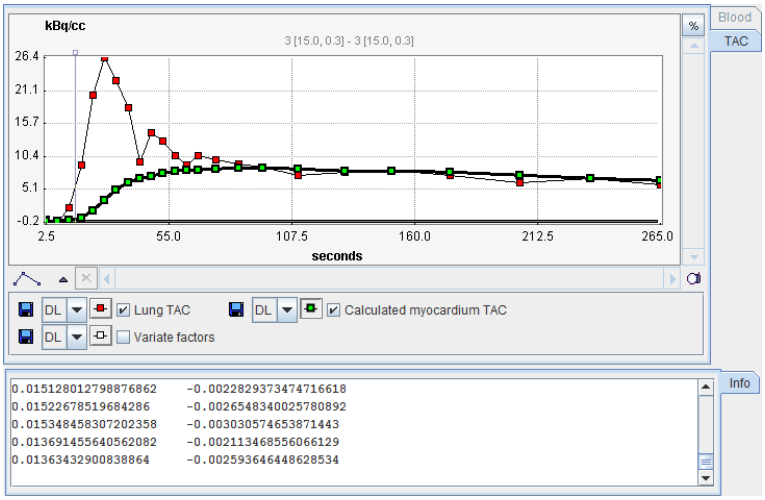
Model Preprocessing

The lung TAC must be specified as a VOI or a file. It is then used together with the input parameters to calculate the expected TACs in the left ventricle (LV), the right ventricle (RV), and the myocardium.



Delay Lung-RV	Left shift of the lung TAC to the time when the bolus arrived in the RV.
Delay Lung-LV	Right shift of the lung TAC to the time when the bolus arrived in the LV.
Delay Lung-Myo	Right shift of the lung TAC to the time when the bolus arrived in the myocardium.
Mean Perfusion	Expected mean perfusion of the myocardium.
Partition Coefficient	Partition coefficient of water in myocardium

The results of preprocessing is shown in the **Results** panel.



Map Parameters

Myo	The myocardium factor images which should represent an anatomical image of myocardium.
BV	Blood volume factor images which should show the blood volume.

Correlation

The **Correlation** model allows correlating the time vectors in each pixel with an arbitrary reference signal, for instance an activation vector.

Acquisition and Data Requirements

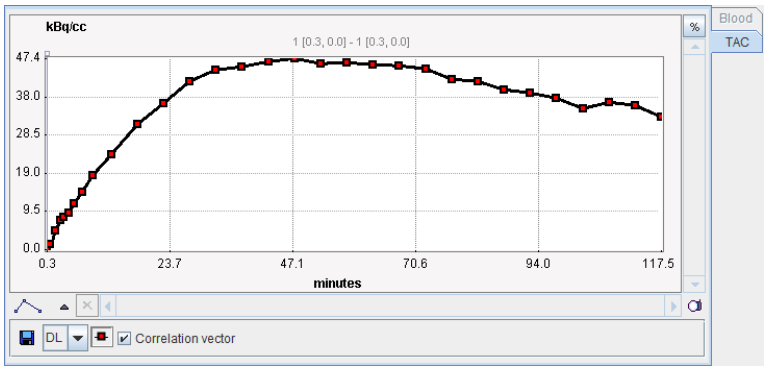
Image Data	Any dynamic volume data.

Model Preprocessing

The reference signal will be used for the pixel-wise correlation must be defined as a file or as a VOI.

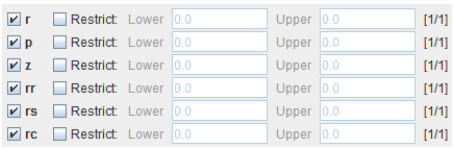
Index	The index of the element in the cross correlation vector to return as rc.

It is shown in the **Results** panel of model preprocessing.



Map Parameters

Images of the following parameters can be generated



r	Pearson correlation coefficient.
p	Significance level, at which the null hypothesis of zero Pearson correlation is disproved.
z	Fisher's z for Pearson correlation.
rr	Spearman's rank correlation.
rs	Two-sided significance that rank correlation deviates from zero.
rc	The value of the signal cross correlation vector a the index defined below.

Regression

The **Regression** auxiliary model performs a pixel-wise linear regression & correlation analysis.

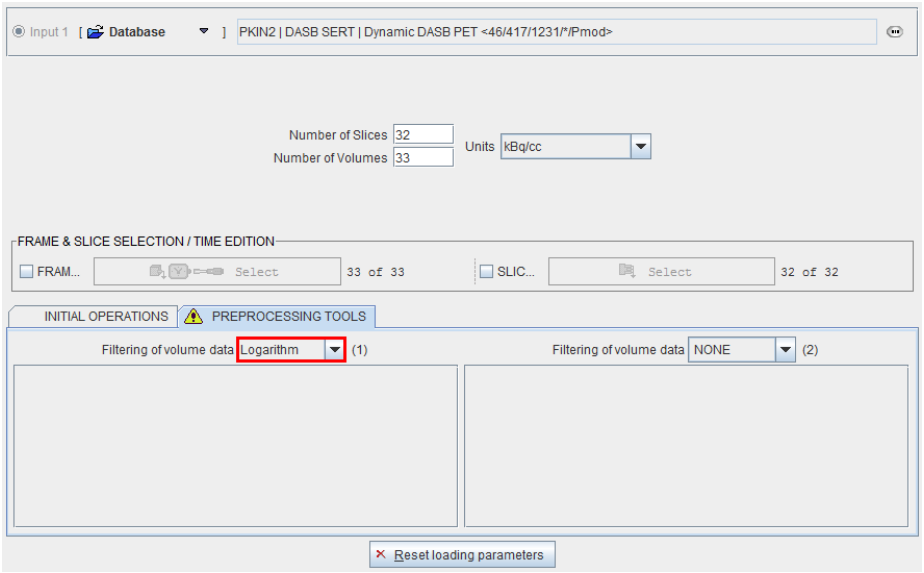
Acquisition and Data Requirements

Image Data	Any dynamic volume data.

Volume Data

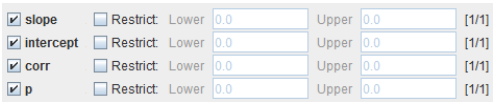
The pixel-wise linear regression uses the acquisition mid-times as the x-values. Therefore, the times must be set to appropriate values.

Note that the **Regression** model can be used to indirectly fit exponentials: To this end the exponentials are transformed into linear functions by selecting the **Logarithm** in the **PREPROCESSING TOOLS** section as illustrated below. When the linear regression is fitted to the transformed data, the slopes represent the exponents.



Map Parameters

Images of the following parameters can be generated



slope	Slope of the regression line.
intercept	y-intercept of regression line.
corr	Pearson correlation coefficient for linear correlation (+/-1=complete correlation, 0=no correlation).
p	Significance level at which the null hypothesis of zero correlation is disproved (small value = significant correlation)

Fourier Analysis

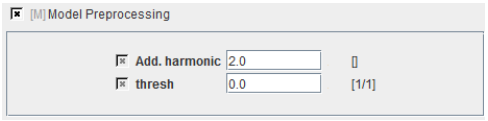
The **Fourier Analysis** model performs a Discrete Fourier Transform (DFT) in each pixel and returns the amplitude and phase of two harmonics as parametric images.

Acquisition and Data Requirements

Image Data	Any dynamic volume data. Note that the acquisition time information is

	relevant for the results.

Model Preprocessing



Add. Harmonic	Index defining which harmonic to return in **amp+** and **pha+**.
thresh	If the amplitude of the first harmonic is below the specified value of **thresh**, all parameters values are set to 0.

Map Parameters

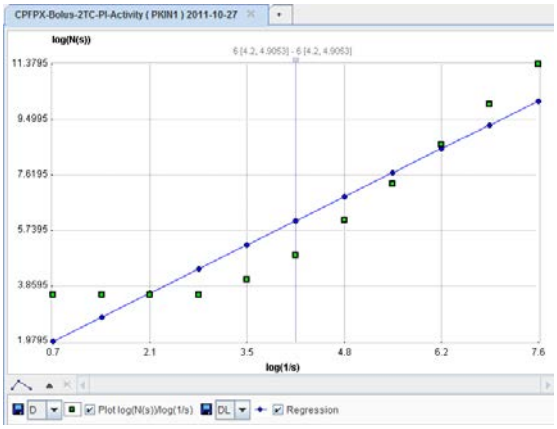
amp1	Amplitude of first harmonic in the Fourier analysis.
pha1	Phase in [deg] of first harmonic in the Fourier analysis.
amp+	Amplitude of an additional harmonic in the Fourier analysis.
pha+	Phase in [deg] of the additional harmonic in the Fourier analysis.

Fractal Dimension

The **Fractal Dimension** model measures the complexity of a 2-dimensional structure by calculating its box-counting dimension [1]. This concept has been applied in oncologic studies for assessing the heterogeneity of tissue kinetics [2].

The idea is to subdivide the area under the tissue TAC into a number of square boxes and simply count the number of boxes containing some part of the structure. The mesh size is defined as s, so 1/s gives the number of segments in each of the 2 dimensions. For instance, specifying 1/s=5 therefore means a subdivision into 5*5=25 boxes.

The counting process is performed with increasing number of intervals up to the specified 1/s. Next, the data are plotted in a double-logarithmic way, namely log(N(s)) on the y axis and log(1/s) on the x-axis.



The box-counting dimension is finally obtained as the slope of a linear regression through the plotted points.

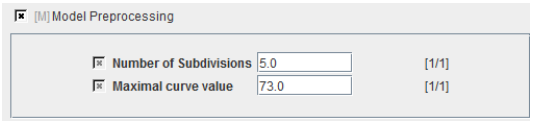
Implementation

After switching to the **Fractal dimension** model, two input parameters are available for specifying the box-counting process: **1/s**, and **Maximal value** the highest TAC value which might occur in the data.

Acquisition and Data Requirements

Image Data	Any dynamic volume data. Note that the time information is relevant for the results.

Model Preprocessing



Number of subdivisions	Maximal number of interval subdivisions in boxplot; 1/s=5 means $1/(2^5)$ intervals
Maximal curve value	The global maximal value. It is corrected upwards if the actual curve maximum exceeds this value. Note that the total area is relevant for the box subdivisions. To cover the same area for all TACs a common maximum value is required.

Map Parameters

Db	Box-counting dimension calculated with boxplot method.

References

1. Peitgen H-O, Jürgens H, Saupe D: Chaos and fractals : new frontiers of science. New York: Springer-Verlag; 1992.

2. Strauss LG, Dimitrakopoulou-Strauss A, Koczan D, Bernd L, Haberkorn U, Ewerbeck V, Thiesen HJ: 18F-FDG kinetics and gene expression in giant cell tumors. J Nucl Med 2004, 45(9):1528-1535.

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PMOD Technologies Ltd
Sumatrastrasse 25
8006 Zürich
Switzerland
+41 (44) 350 46 00
support@pmod.com
http://www.pmod.com

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