

# Workbook for PMOD Version 3.9

## Scope and Intended Use

This workbook is a tutorial for novice users of PMOD. It contains a dedicated section for each of the major PMOD tools as well as for database management. The sections provide detailed descriptions of typical tasks accomplished with PMOD plus some additional background information. We recommend the users to start at the beginning of each section and work through the descriptions step-by-step. For more specific information, please refer to the product documentation which is part of any PMOD installation or which is available online at [http://www.pmod.com/web/?page\\_id=648](http://www.pmod.com/web/?page_id=648).

## Example Data and PMOD Installation

The example data for the exercises covered by this workbook are distributed as an optional part of any new PMOD installation and are contained in the default database called **Pmod**.

- Users who own a PMOD installation can use that installation to perform the training tasks. To perform tasks with PMOD tools not included in their purchased license, we recommend requesting a trial installation.
- Users working with a trial PMOD installation should download the example database and install it together with the program. Note that the results produced with trial licenses cannot be saved. However, save-enabled trial licenses are available on request.
- For loading the example data, the **Database** data format must be used. To try similar work with your own data, we recommend using the **Autodetect** format and pointing the image loader to the directory containing the data files.
- All example images in the database are in DICOM format, calibrated, decay corrected and with correct timing information. Vector data such as blood activities are text files conforming to the requirements of the PMOD tools. You can export them to the file system for inspection.

## Copyright and Disclaimer

The example data provided in the **Pmod** database are by courtesy of the following institutions.

- CFPX data: Institute of Medicine, Research Centre Jülich, 52425 Jülich, Germany; Dr. A. Bauer.
- DASB data: Molecular Imaging Branch, National Institute of Mental Health, Bethesda, USA; Dr. M. Ichise.
- All other data: Nuclear Medicine, University Hospital, Zürich, Switzerland; Dr. A. Buck.

Note that the original data have been processed and optimized for training purposes.

### IMPORTANT:

- The data from the **Pmod** database may only be used for PMOD training purposes. The owners of the original data reserve all rights regarding any type of public use of this data. Particularly, the data may not be used for any kind of publication purposes without getting written consent.
- The content of this workbook is proprietary and may not be reproduced without permission of PMOD Technologies. It corresponds to the functionality of PMOD at the time of writing and can be changed without notice.

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## **Section 1: PBAS Tool – Image Viewing & Processing**





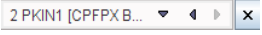
### **Topics:**

- Load/Save Data: Data Formats, Data Transformation during loading.
- Image Viewing: Color Tables, Window/Level, Layouts, Reports.
- Image Processing: Filtering, Time Averaging.
- VOI Definitions, Statistics.

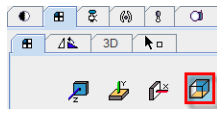
### **Exercises:**

#### **1. Data Loading/Saving**

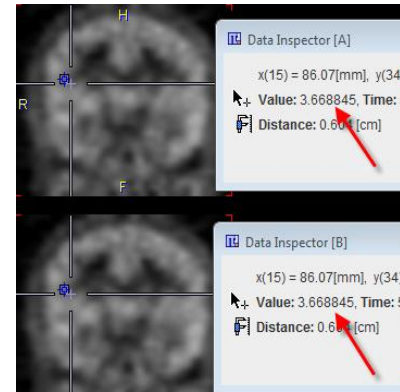
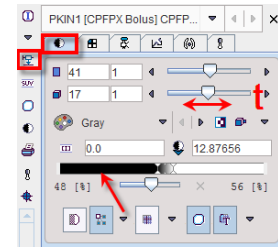
The images in the database are all in DICOM format and contain a complete description including timing. This makes data loading easy. In the following procedure you will load a data set, perform a transformation during loading, and save the same images in the Interfile format. Then the Interfile data are loaded again and compared with the original data.

- Open the **PBAS (View)** tool. Initially the **DB Load** page appears, showing the list of patients.
- Select patient **PKIN1**; several series are listed: the two original data sets (Dynamic PET, MR Anatomy) and some derived result series. Select the **Dynamic PET** in the **Series** list. Using **Add** (or by double-clicking) the **Dynamic PET** series can be brought to the **Selected for loading** area.
- Activate the **with Operations** button. An intermediate dialog window appears. It allows selecting a sub-range of slices or frames, and also performing some image processing operations during loading. A tool for correcting the image orientation after loading can be opened with the **Assistance** button.
- To apply a smoothing filter during loading select the tab **PREPROCESSING TOOLS**. In the list selection to the left select **3D Gaussian** and define the filter widths for the three directions.
- Load the data with the **Load** button. The smoothed images are shown on the **View** page.
- To save the smoothed data in the **Interfile** format change the **Save** button in the **Save** section to **INTERFILE**. The format is switched and a dialog box is shown. Browse to a local directory activating the selection button . Confirm with the **Select** button. Enable the **Create save name from root** radio button and in the **Save as** section specify the file name **CPFPX-Smoothed**. As there are different types of Interfile formats, a selection list is available in the **Transfer Syntax** section. It allows defining the number format, and whether two files or a combined file is written. Select a **FLOAT** format to avoid rounding errors, the two-file variant, and **Save**. Two files are written, **CPFPX-Smoothed.img** (data) and **CPFPX-Smoothed.hdr** (description, text file). Note that the Interfile data written by PMOD has all relevant information (timing, units) in the header file. This is not the case with some other formats (Analyze, Raw) which require manual specification during loading.
- Before loading the saved Interfile images again set the pushpin in the **Load** area or the sidebar from the “overwrite”  position to the “append”  position.
- Then switch the **Load** button on the **View** page to the **INTERFILE** format. This brings up a file selection dialog box with the suffix filter set to “\*.hdr;\*.hv”. It should already point to the right directory because PMOD remembers the path of the last successful load or write operation.
- Select the **with Operations** button. Again, the dialog box with the loading options appears. *Note that the last loading configuration is used per default!* In the example the 3D Gaussian filter is still configured. To alert the user a  icon is shown. The best way to get rid of all special settings is to activate the **Reset loading parameters** button. Check the **Select FRAMES** and **Select SLICES** boxes and use the **Select/Edit Time** button to verify the timing. Note the **Units** which are set to **kBq/cc**. This is because PMOD always displays activity values as kBq/cc, and the data were therefore saved with kBq/cc. Use **Load** to finally load the images. There are now two loaded image series in the **View** page, which can be switched using the  selection in the upper right. Depending on the format chosen, the min/max values may differ minimally due to rounding.
- Alternatively, to avoid the steps described above during the loading procedure, activate the **Open** button. The image is directly loaded and no preprocessing is applied.

- To compare the two images switch to the **Compare** page. This page is initially in the “fusion” mode. Hereby it synchronizes the two series in the upper rows and shows their fusion in the third row. Switch the layout to the orthogonal planes and browse through the slices using the mouse wheel or the sliders on the panel.



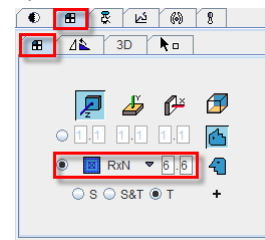
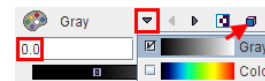
- To compare the values precisely, open the “data inspector” of both series by selecting to the upper right of the images. Initially the appearing dialog windows may be at the same location. Move one of them so that both are visible. When the cursor is moved over the images, the corresponding pixel values in both series are displayed and should be identical.
- To see the pixel-wise time-activity curves (TAC) select the button in the inspector dialog boxes. The boxes are now quite large and have to be arranged so that both curves can be seen simultaneously.



## 2. Image Viewing

Use the images loaded in PBAS and the **View** page to experiment with image viewing. Whenever images are shown in the PMOD modules, the image control elements are located to the right of the images. They are organized using tabs.

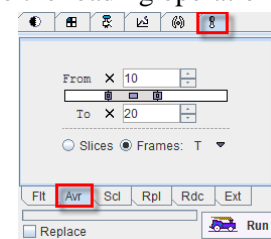
- Colors:** switch from **Gray** to **Cold**, then set the lower threshold to 0kBq/cc. This can be done by entering the number of **0** into the text box, or by double-clicking into left part of the color bar. Stepping through the different frames you may notice that the upper and lower thresholds change because they are defined in %. To establish a fix color↔value mapping for the whole study select the **Scale to study minimum: maximum**. This is particularly important for meaningful movies of dynamic tracer uptake.
- Layouts:** Prepare a 6x6 layout of a particular time frame with the „layout” tab as illustrated (**Ctrl+6**). Note that for dynamic series the layout can also mix the times and slices (**S&T**), or show a single slice at different times (**T**).
- Reslicing:** First switch the image display to the orthogonal planes using the “layout” tab or by clicking into the images and then typing **Ctrl+D**. Then enter **Ctrl+R**, or select the “reslicing” tab. Handles are then shown in the image centers which allow translating (open rectangle) or rotating (closed rectangle) the images. As an alternative, enter discrete numbers for the transformation parameters in the reslicing tab. Note how the anatomical annotations are updated accordingly if you are working with a proper DICOM series.
- Isocontours:** To see a histogram of the pixel values or get an isocontour overlay, select the tab and define a threshold by dragging the small rectangle above the histogram or entering a value. To see the isocontour after changing to a different tab, select before continuing.
- Report:** After a suitable layout has been defined, use the button to open the **Print Preview** window. Adjust the colors appropriately and use again to refresh. Try adding an annotation and a comment to the images and then save the report in one of the available capture formats.



## 3. Image Processing

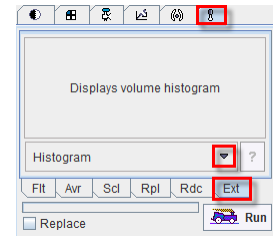
The “tools” tab offers a selection of handy processing tools. in addition to the loading operation.



- The main tools are immediately shown as sub-tabs. The working principle is that the user selects a data transformation, and then starts processing with the **Run** button. If the **Replace** box is not checked, a new data set is generated and added to the series list. Otherwise the original data are overwritten.
- As the images of dynamic studies are typically noisy, they are often averaged for creating images with sufficient anatomic information.




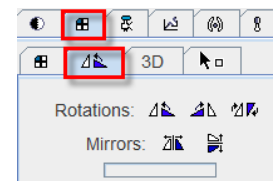
This can quickly be achieved with the average **Avr** sub-tab as illustrated to the right. Select the **Frames** mode, define **From/To** to 10/20 and then select **Run** to average the frames 10 to 20.

- Spatial filtering can be applied to dynamic series to reduce the noise at the cost of spatial resolution. The **Flt** sub-tab offers two such smoothing filters (**Gaussian**, **Median**), and also an edge enhancement filter (**Canny Deriche**).
- The **Ext** sub-tab is particular. It houses diverse processing routines which can be added by plug-in programming. The functions can be selected from a list with the indicated arrow. Probably the most interesting ones are the **Interpolation** to a different image matrix or resolution, the **Principal Component Analysis PCA**, **Resize** to add a border or extract a sub-volume, the **Segmentation** of structures, the calculation of a **SUV** image, **Partial Volume Correction (PVC)**, **MR Segmentation** and **Skull Stripping**.



After creating different processing results, use the study selection  3 [CPFPX-Sm... to switch among them. Unsuccessful results can be closed using the  button.









A set of helpful reorientation tools is available in the  section of the layout tab. They can be employed to bring the images into a specific orientation. Note that the anatomical annotations are consistently moved during the operations.

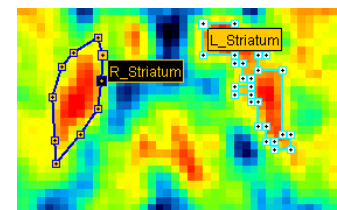




## 4. Volumes-Of-Interest (VOI)

### Outline VOIs





The **VOIs** page of the PBAS tool serves for defining and evaluating “Volumes-of-Interest” (VOIs). VOIs are built from planar polygons called “contours” (CTR), which can be defined in the axial, coronal or sagittal orientation. All contours belonging to a VOI in a certain plane are called a “Region-of-interest” (ROI). For each level (VOI, ROI, CTR) there is a dedicated toolbar highlighted in different color which houses the applicable tools. These toolbars can be detached by dragging, if needed.

- To start over close all open series using the  button in the sidebar, or by closing PBAS and starting it again.
- Load just the **Dynamic PET** of patient **PKIN1**. To get an image with enough anatomical information for VOI outlining open the tab  and average the frames 10 to 20.
- Switch to the **VOIs** page, and select the averaged series in the axial orientation. Browse to slice **40** and adjust the image for contrast (eg **Cold** color, **1.0** lower threshold, **7.0** upper threshold).
- Activate the  **New VOI** button below the **VOIs** list to get a new empty VOI, and label the new entry **R striatum**. Make sure that image **Interpolation** is switched **ON** . Select the **Add/Edit vertex** tool . Outline the first planar CTR of the VOI by clicking along the right striatum. Close the ROI by **double-clicking** or using the “finish” entry  in the context menu (right mouse button). Note the **Z** indication in the **VOIs** list which states that the definition was performed in the axial direction. Enable/disable the fill in checkbox ☒ **Fill** to check the pixels actually included in the VOI.
- Use the mouse wheel or the slices slider to scroll to the axial slices 39 and 38, and outline the right striatum there similarly. The **R striatum** VOI now consists of 3 ROIs, each containing 1 CTR.
- Now use  **New** button to create another empty VOI, label it **L striatum**. This time use the **HOT 2D isocontour ROI tool**  for outlining. Click at the edge of the left striatum in slice 40. An isocontour is immediately calculated and displayed. It has a step-wise appearance because it follows the pixel boundaries. Click at different seed points until you are satisfied with the calculated result. Repeat the isocontour ROI definition in slices 39 and 38 too. The result in slice 40 might look something like illustrated to the right.

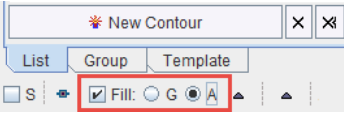
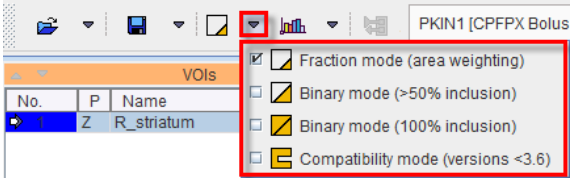


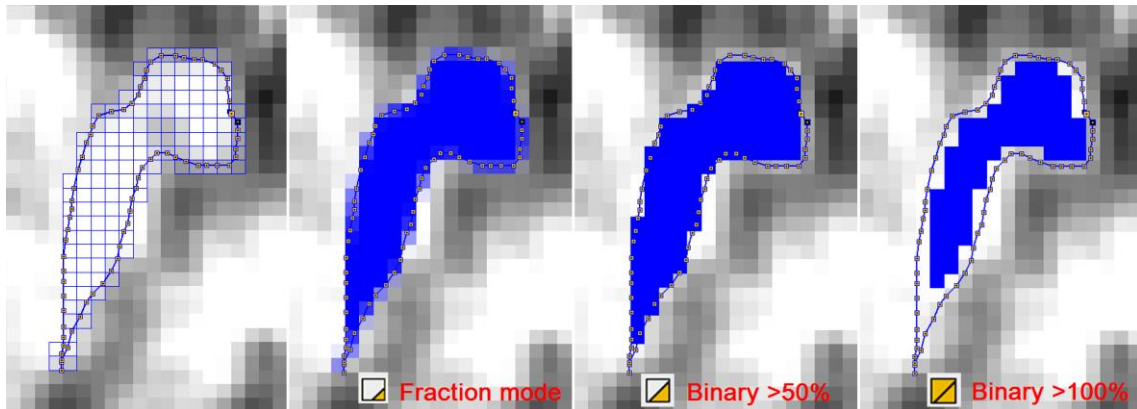
- For correcting the **R striatum** definition select that VOI by double-clicking the entry **1** in the **VOI** list. The display will jump to a slice showing a ROI of the selected VOI. Select the  tool and move individual vertices of the ROI polygon. When working with dense polygons it may be helpful using the  tool. Dragging the tool towards a contour will radially push away the vertices.



- Instead of modifying the existing contour it may be better to start over. Use the  button in the **ROI** toolbar to clear the ROI of the current slice (the  button in the **VOI** toolbar will clear the ROIs in all slices!). Then select the drawing tool  and draw along the right striatum holding down the left mouse button.
- After the VOIs have been defined, select the „neutral” mode by the  button. This will avoid creating ROIs when clicking into the images for reviewing the results.


### VOI Inclusion Criteria for Pixels

- Manually outlined VOIs are defined by polygons which don't exactly follow the edges of the image pixels, intersecting the pixel area. Select the **R striatum** in the VOIs list and set the layout to **Axial** view. Switch the image color table to **Gray** and adjust the image for contrast (set the upper Threshold to **5**). Make sure the image **Interpolation** is switched **OFF** such that the intersection between the contour lines and pixel area is visible. Zoom in **3** times and use the scroll bars to center the VOI in the viewport. Enable the **Fill** mode to see the effect of different classifications. The **G** option represents the classified pixels as a grid, the **A** option as filled area. 
- Select the **Fraction mode** entry in the classification list as shown to the right. All pixels with any part enclosed by the contour are classified as VOI pixels. Note (picture below) that when the **Fill A** option is activated, the color intensity of a pixel corresponds to the included fraction. 

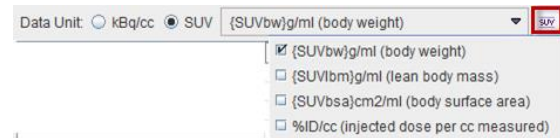


- In statistics, the fractional area included is used as a weighting factor in the average calculation.
- The statistics is unweighted and uses all classified pixels when any other entry is selected in the pixel classification list. In **>50% Binary mode**, all pixels are included for which the enclosed area is >50% of the full pixel area. In **100% Binary mode**, only fully enclosed pixels are included.
- The **Compatibility mode (versions<3.6)** has been used in PMOD versions before 3.6 and is available for compatibility reasons.

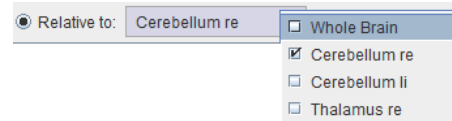
### VOI Statistics

- Make sure the **Fraction mode** is set for pixel classification. Now calculate the pixel statistics of the two VOIs using the “statistics” button . The mean and standard deviation of the two VOIs are shown by default in a dialog window. Other statistics values like max, min, volume, can be shown by selecting them in the **Selected Statistic(s)** list. The **Group** entry is the result of the statistics using the pixels contained in the VOIs selected on the **Group** tab. By default, all VOIs are included in the group, but the feature can be used for grouping a suitable sub-set of VOIs using the keyboard **CTRL+click**.

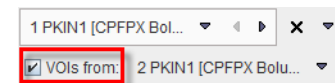
- If the statistics are calculated for activity concentration images, the uptake results can be converted to different types of SUV image. To achieve this enable the SUV radio button in the statistic interface. Please note that information related to the patient, tracer activity and acquisition timing is required. If this information is not included in the image header, it can be entered manually after activating the SUV button.



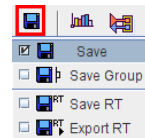
- The so-called SUVR statistics is the uptake divided by a reference uptake. It can easily be obtained by switching to the **Relative to** radio button and selecting the reference region from the VOI list. Note that the ratio is also calculated for all statistical measures, not just the average.



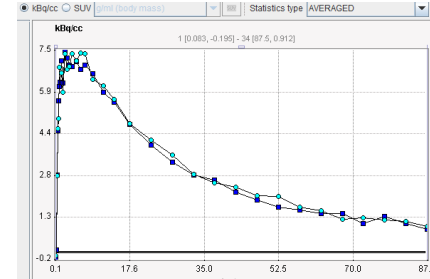
- The statistics operation was applied to the averaged series and thus resulted in individual numbers of the statistical measures. In order to calculate the time-activity curves within the two VOIs they must be projected to the dynamic series, which is still available but currently not shown. When switching to it with the series selection, the VOIs may disappear because each series can have its own set of VOIs, and so far the dynamic series has no defined VOIs. To disable this synchronization check the box **VOIs from..** while the average series is shown. Now the dynamic images can be selected with the series selection button.



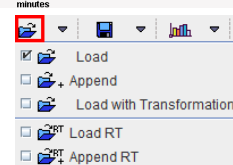
- Activate the statistics button again. This time the VOIs are evaluated at each time frame and the results are shown as time-activity curves in a dialog box. Note that not only the average can be shown as a TAC, but also the Standard Deviation (SD), the minimum, maximum, etc.
- The TACs can be saved in different formats depending on the future use.



- Once the outlining of VOIs has been completed, the definition can be saved to a ".voi" file using the VOI saving option button. The option button supports saving of all VOIs (**Save**) or only the grouped VOIs (**Save Group**). Note that the VOI definition is relative to the coordinate origin of the current image series, and therefore also applicable if the resolution of the series is changed, for instance by reducing the number of pixels or by interpolation to a different pixel size. However, if the origin changes its position in the data volume the VOIs will be shifted accordingly.

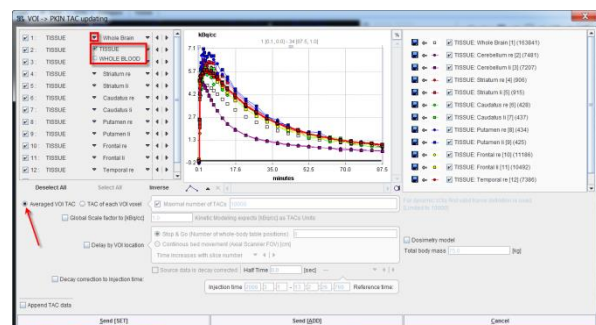


- The VOI definitions can be retrieved by the VOI loading option button. **Load** will first clear the current VOI definitions, while **Append** adds the loaded VOIs to the current list. An example VOI set for the current image series is available in the database. Select the **Load** button. In the appearing DB load dialog box chose the **CPFPX Bolus 13 VOIs** component, then **Retrieve**.




- When preparing TACs for kinetic modeling, it is recommended using the

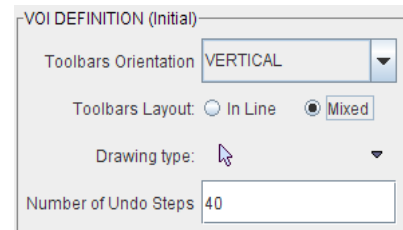
general kinetic modeling button **KM** (the button is grayed for static data) instead of the statistics button. In that case, the average TACs are prepared and shown in a dialog box. There the user can define what the role of the individual TACs in the subsequent kinetic modeling will be: **TISSUE** (default) or whole blood used for spillover correction (**WHOLE BLOOD**). There are two **SEND** buttons for transferring the average TACs to the PKIN tool, either overwriting [**SET**] its current contents, or adding a new tab to it [**ADD**].



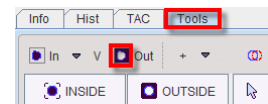
- Try sending the 13 TACs of the example VOI set. If PKIN is already running the data is loaded, otherwise PKIN will be started and then the data loaded. A warning message will be shown which indicates that kinetic modeling is not yet possible because blood data is missing. Then close PKIN again.

## Further VOI applications and Hints:


- **Undo/Redo Operations:** Defining VOIs is a time-consuming and iterative procedure. Sometimes unexpected or unwanted effects occur, which destroy all or part of the efforts done so far. To resort from such a situation, the VOI tool maintains a list of historic states of VOI definition. Using the arrow buttons, you can go back in history to undo changes, and then go forward again to redo. The number of undo/redo steps saved can be defined in the settings area of the PBAS tool. Select the “application settings” button  and then the **Display** tab. In the **VOI DEFINITION** area set the **Number of Undo Steps** to a number of your choice.

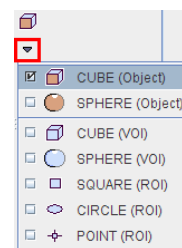



- **VOI Masking:** Select the dynamic series, with the example VOIs list active. Select the **Whole Brain** VOI. Then activate the **VOI Tools** tab which has a masking section. Select the **Mask voxels outside selected VOI** icon. In the dialog window set **Mask by value** to 0, then **Yes**. All pixels outside the selected **Whole Brain** VOI are set to the value of 0 at all times. This masked data set could be saved, and used in a pixel-wise data analysis.

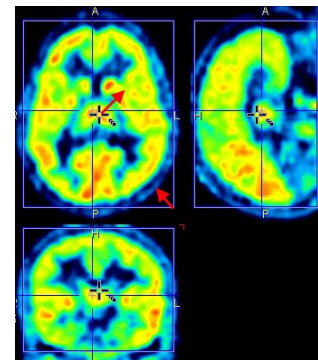






- **VOI Cropping:** The pixels in the masked data set outside the VOI are no longer relevant for the analysis. They can be removed by a cropping operation with the bounding box of the masking VOI. Select the **Whole Brain** again and activate **Crop to VOI Bounding Box** on the **VOI Tools** tab. Note that the VOIs still fit the structures in the cropped data set because the definitions are relative to the origin which remains at the same anatomical location.

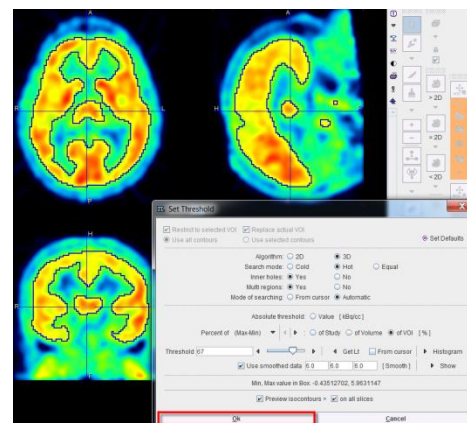
- **Object VOIs:** Standard VOIs are built from planar polygons. This definition is highly flexible because each contour can be individually adjusted. On the other hand, sometimes it is more adequate to change the gross shape of VOIs for roughly encompassing structures. For this purpose, two VOI objects are available with analytically defined boundaries, the **SPHERE** and the **CUBE** object VOIs. Remove the existing VOIs using the “delete all” button  below the VOIs list, then create a new VOI called **Box**. Switch to the averaged series, configure an orthogonal layout, and triangulate the center of the brain. Then select the **CUBE (Object)**



from the list of regular objects as illustrated to the right. In the appearing dialog window set the **Size** of the cube to **100mm**, then **Apply**. A box is created and shown in the images, centered at the location you clicked before. This box can be shifted and scaled in all dimensions. To enclose the brain with the box first activate the  button to enter the mode for moving/scaling the entire VOI. With the left mouse, shift the box by dragging the handle in the center of the box. Move the cursor to any corner of the box and drag, until the brain is entirely enclosed in the box. Similarly, the **SPHERE** object VOI could be applied, which would result in an ellipsoid after scaling.



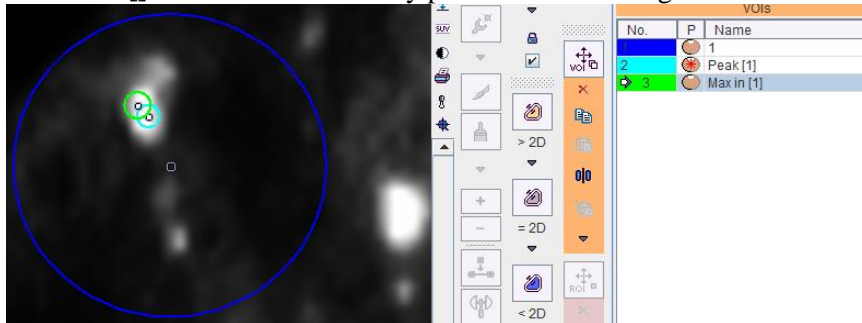
- **Isocontour Auto-VOI:** The “Isocontour Auto-VOI”  tool serves for detecting outlines based on a value threshold. It is particularly useful to find organ or lesion boundaries. The Isocontour Auto-VOI can be confined to a bounding VOI which is replaced by the result. So the first step for getting a brain outline is to create a copy of the **Box** object VOI: Select the **Box** VOI, activate  in the **VOI toolbar** to copy to the clipboard, create a new VOI and call it **Iso**, then paste using . Select the **Iso** VOI, and then activate the  tool. In the appearing dialog window activate the **3D** algorithm, enable the **Hot** search mode and the **Inner holes** radio button. Finally adjust the **Threshold** slider and observe the created isocontour. Check the **Preview isocontours** and **on all slices** boxes, and inspect the contours in different slices using the mouse wheel. Optionally, enable the **Multi**





**regions** radio button for including disconnected parts of the brain. Click **Ok** to accept the result. The initial result may not yet be satisfactory because of the image noise level. In this case enable **Use smoothed data** with an appropriate filter. Consequently, the contour outlines will be smoother.

- **Peak VOI:** A standard lesion evaluation procedure consists of placing a small sphere in the lesion such that the average uptake of the sphere is maximized. The procedure to do this in PMOD is to first create a VOI enclosing the lesion, and then calling the **Sphere with Max Average (Peak VOI)** function as illustrated to the right. The volume of the sphere can be defined in a dialog window as well as two options which are mainly relevant for small lesions: the background threshold to be ignored during calculation and the volume fraction of the sphere which must be contained in the VOI. Result is a new sphere VOI **Peak[]** which is automatically positioned according to the criteria.

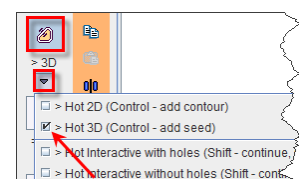
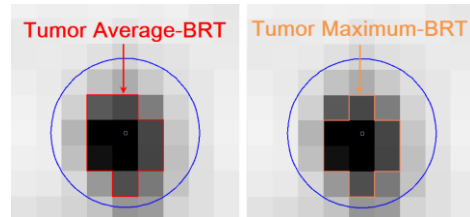
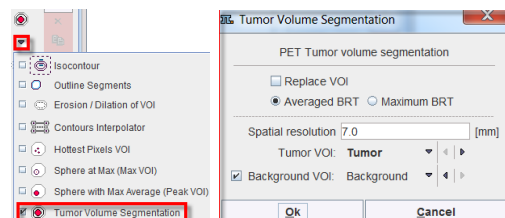
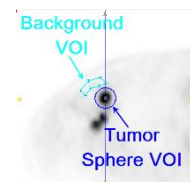
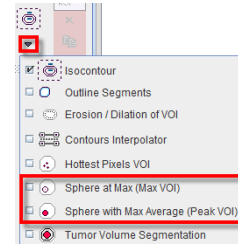


- **Max VOI:** Alternatively to positioning the sphere such that the average uptake is maximized, it can be positioned at the pixel with maximal uptake. This operation is performed by **Sphere at Max**, resulting in a sphere VOI called **Max in []**.
- **PET Tumor Volume Segmentation:** Is an automatic model based approach which requires the initial approximation of the tumor VOI with a sphere, the background activity which is subtracted and the PET scanner resolution. If higher uptake than background is close to the tumor, the initial VOI should be close to the tumor boundaries, and an explicit background VOI should additionally be outlined.

To start the outlining procedure select the **Tumor Volume Segmentation** tool. In the appearing dialog window enter the **Spatial resolution** of the image. The **Background VOI** box needs to be checked, and the proper VOI selected from the list next to it. To use the average activity in the iteratively segmented VOI please enable the **Averaged BRT** (Boundary-Reproducing Threshold). Deselect **Replace VOI**, if you intent to keep the initial VOI. To start the iteration activate the **Ok** button.

In case the tumor is well isolated from the surroundings, the background can easily be obtained from the initial VOI definition. In such situation please define a sphere VOI enclosing the tumor, with sufficient distance to the rising edge. When iteration is started the program first calculates the background activity by enlarging the enclosing VOI and averaging the pixels along the extended contour. Then the optimal iso-contouring threshold is calculated as outlined above.

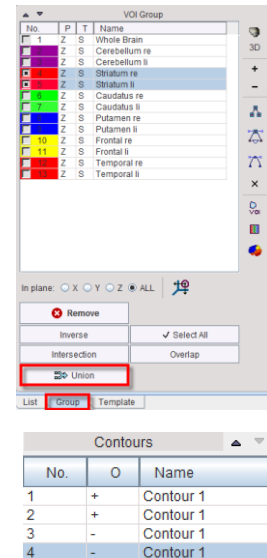
- **3D HOT/COLD:** The 3D VOI outlining is based on region growing. Create a **New VOI**. Select **3D Hot** to look for pixels with values above a threshold. Locate the structure in the image you would like to include within the VOI. Click the left mouse button at the edge of the area of interest. A pseudo-snake algorithm finds the largest closed iso-contour at the clicked image value and represents it as a closed




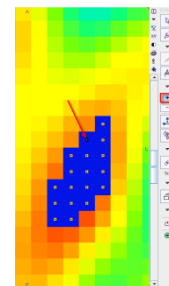


polygon. Please note that each time the button is clicked, the contour is replaced by a new iso-contour. This can be avoided by holding down the **CTRL** key while clicking. In this case a new iso-contour part is added to the existing structure.

- Merging of VOIs, Partial Exclusion of Pixels:** Sometimes it is useful to combine VOIs to form a new VOI. This can be achieved with the **Union** functionality. Select the **Group** tab, and in the VOIs list mark **Striatum re** and **Striatum li**. Then activate **Union** which creates a new VOI called **United**, which can be renamed. Do NOT **Remove the union source VOIs**. Note that the union operation can not only be used to include pixels, but also for more advanced set operations: For example, select the two **Striatum** VOIs and activate the “+” button. Select the two **Caudatus** regions, and then activate the “-“ button to change all its contours on the List panel to “-“. Now select all 4 VOIs and perform the union. (*Note:* it is important to have in the Contour tab as first contours the “+” ones and then the “-“ ones.) The result is a VOI which contains 4 contours per slice, two included and two excluded ones as illustrated to the right. The resulting pixels which will count for the VOI evaluation can be visualized by enabling the **Fill ROI** box. After the union operation make sure to set the **Caudatus** contours back to “+” by selecting the VOIs on the **List** panel and activating the “+” button right to the VOIs list.



- VOIs composed of Single Pixels:** When working with small structures it may be preferable to manually define individual pixels to be included in the VOI, rather than adjusting contours until these pixels are properly circumscribed. To work precisely switch off the image interpolation,  and zoom the average image by a factor of 4. Remove all VOIs, then create a **New VOI**. Then activate the “+” button in the editing tools and click into the image for adding pixels to the VOI. Make sure that the **Fill ROI** box is checked so that the included pixels are visualized (blue pixels in the image to the right).
- Removing pixels from VOIs:** The single pixel contour functionality can also be used to remove arbitrary pixels from VOIs (except for object VOIs). Outline a contour ROI, then enable **Fill ROI** to see which pixels are included. Select the “-“ button, and then successively click into the area of the ROI. Each time a contour is created with a “-“ sign (exclusion) in the **O** column, and the selected pixel is excluded from the VOI.



## Section 2: PKIN Tool – Kinetic Modeling



### Topics:

- Importing data: TACs from PBAS, blood data from DB files.
- Compartment modeling and graphical plots with tissue time-activity data.
- Reference models for receptor tracers without blood information.
- Assessment of parameter identifiability with Monte Carlo Simulations.

### Exercises:

#### 1. Data Import (PBAS, PKIN)

The TACs needed for modeling are calculated using the PBAS tool, and the blood data is added by loading prepared data files in PKIN. (Note: The kinetic modeling data have already been added to the database. Instead of the preparation detailed below they can be loaded into new tabs using menu **Kinetic/Add KM File(s)** and then selecting **CPFPX-Bolus-2TC** and **DASB MRTM**, respectively.)

- Start **PBAS (VIEW)**, select **PKIN1** and load all frames of the **Dynamic PET** series.
- Select the **VOIs** tab. Since there is already a set of VOIs in the database, the VOI drawing step can be skipped. Select the button for VOI loading. In the appearing **DB load** dialog chose the **CPFPX Bolus 13 VOIs** component, then **Retrieve**. In the confirmation window select **Keep current pixel classification**. A set of 13 VOIs is shown in the overlay.
- Use the kinetic modeling button  to prepare the TACs, and then **Send[SET]** them to the PKIN tool. **PKIN** is automatically started and the TACs loaded. A message dialog window appears because no blood data is available yet. It can be closed.
- Work continues in **PKIN**. To load the blood data open the menu **Kinetic**, item **Load Plasma Activity**, and then the sub-item **Parent**. A dialog box appears showing all blood data in the database. Select **Authentic CPFPX in plasma** of Patient **PKIN1** (plasma activity corrected for metabolites) and **Retrieve**. Confirm the message regarding the missing spillover curve. The loaded plasma data is a simple text file and has the form shown to the right. Such files can be read from disk activating the **Load from File system** button in the above loading dialog.
- Similarly load the activity of CPFPX in whole blood using menu **Kinetic/Load Whole Blood Activity** and retrieve **Total CPFPX in blood** of patient **PKIN1**.
- Now the CPFPX data set is complete and you can save it to the DB or to your local hard disk using menu **Kinetic/Save KM File**. In the **Write as** dialog select **Save to File System** to save outside the **DB** in one of your local directories.
- Go back to the **PBAS** tool for preparing the second data set similarly. On **DB Load** select patient **PKIN2** and load series **Dynamic DASB PET**. On the **VOIs** tab **Load** the **DASB Regions** component. In the confirmation window select **Keep current pixel classification**. 11 VOIs are shown. Use the  button to prepare the TACs, and then **Send[ADD]** (*not SET to avoid overwriting*) to the PKIN tool. Note that the data is added as a new page of the **PKIN** tool, which is still open. Since no blood data is available for this study, the data set is already complete.
- Try to save the data set – it fails with an error message. The reason is that the **1 Tissue Compartment** model was selected per default, and this model requires blood data. So switch the **PKIN Model** of the **thalamus** region to **Ichise Ref Tissue MRTM** and set the **Reference** region to **cerebellum**. Then use the button **Model & Par** of the **Copy to All Regions** list selection to propagate the model definition to all regions. Now the data set can be saved without problems.


time[seconds]	value[kBq/cc]
40.2	7.61
60	7.75
120	7.46
180	6.32
240	5.02
300	3.55
360	6.54
420	2.78
480	2.26

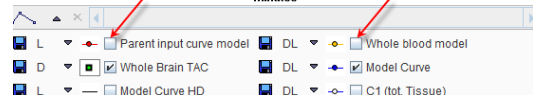
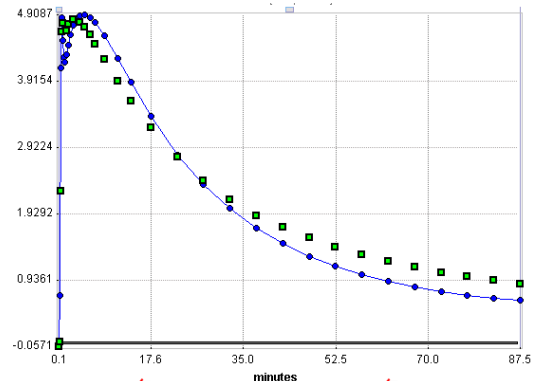
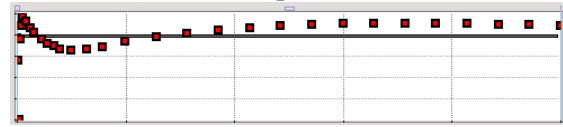
#### 2. Basic Kinetic Modeling with Blood Data (PKIN)

Compartment models of different complexity as well as the Logan graphical plot can be applied to the CPFPX TAC data of PKIN1.

- In **PKIN**, select the tab with the CPFPX data. If the data was prepared as described above all regional TACs will have the **1 Tissue Compartment** model (1TCM) selected, and the default

starting parameters. Therefore the blue model curve does not match the green measurement points in the curve area.

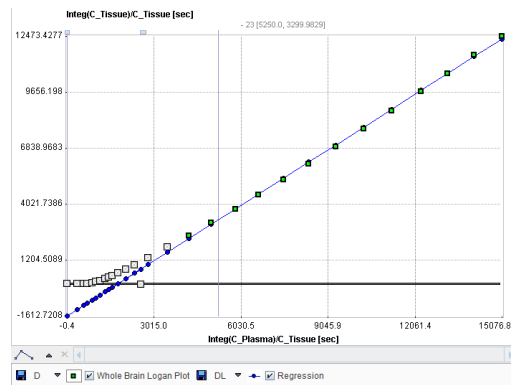
- Select the **Whole Brain Region** and activate **Fit current region**. The optimizer finds the set of model parameters so that the agreement between model and measurement is optimal in a least squares sense. However: note the bias of the residuals which clearly indicates that the 1TCM model is not successful in explaining the CPFPX uptake in Whole Brain (illustration above).
- In the main curve area the agreement cannot be visualized reasonably because the display is scaled relative to the huge initial peak of the blood curves. To focus on the TAC remove the display checks of **Parent input curve model** and **Whole blood model**. The result is illustrated to the right. As alternatives, (1) zoom into a display area using the left mouse button, or (2) select **Range (Zoom)** from the context menu of the plot.
- From the mismatch it is clear that model complexity must be increased. Therefore switch the **Model to 2 Tissue Compartments (2TCM)**. Note that the  $K_1$  and  $k_2$  values are not copied from the 1TCM but set to the model defaults because **Model Conversion** on the **Extras** tab is not enabled. Use **Fit current region** to adjust the  $K_1$  to  $k_4$  parameters of the model. The result shows that the systematic bias in the residuals is almost removed for late data points with a small mismatch remaining at early samples.
- To apply this 2TCM model configuration to all other 12 regional TACs use the button **Model & Par** of the **Copy to All Regions** list selection. It propagates the model definition with the current parameter values to all regions. Then apply **Fit all regions** to adjust the regional parameters.
- The results can be screened by stepping through the regions using the “arrow” button indicated to the right. The agreement between the measurements and the model curve should be ok in all regions.
- To get a quick overview of the resulting parameter values a parameter summary can be obtained as follows: in the **Tools** list to the lower right select the entry **View Par**. A dialog box shows all direct model parameters as well as the macro parameters. The smallest and the highest values of each parameter are highlighted in green and red, respectively. Note how  $K_1$  is similar in all regions. This summary can be saved using **Copy to Clipboard** and pasting the values into a program such as Excel.
- An alternative for saving the parameters is the menu selection **Kinetic/Save KM Parameters File**. Once a model configuration seems meaningful, it is advised to save the full information including data and models using **Kinetic/Save KM File**.
- An important and stable parameter which has been shown to be related to receptor density with CPFPX is the total distribution volume ( $V_t$ ). This value is a model macro parameter and is also shown in the summary above.
- Because the tracer is reversible ( $k_4 > 0$ ), the Logan plot can be applied for estimating  $V_t$ . Switch the **Model** of the **Whole Brain** region to **Logan Plot**. The data is transformed and a linear regression fitted, because theory predicts that after an equilibration time the plot should become linear. To see an explanation of the transformation please use the  button. From the equation it becomes clear why the time scale shown is not any more real acquisition time.



Region	vB	K <sub>1</sub>	k <sub>2</sub>	k <sub>3</sub>	k <sub>4</sub>	V <sub>s</sub>	V <sub>t</sub>
Whole Brain	0.05	0.067...	0.125...	0.026...	0.050...	0.288...	0.828...
Cerebellum re	0.05	0.081...	0.227...	0.018...	0.039...	0.167...	0.525...
Cerebellum li	0.05	0.079...	0.221...	0.017...	0.041...	0.150...	0.507...
Striatum re	0.05	0.076...	0.085...	0.003...	0.028...	0.117...	1.007...
Striatum li	0.05	0.082270	0.092...	0.007...	0.036...	0.191...	1.081...
Caudatus re	0.05	0.067...	0.080...	0.002...	0.019...	0.11269	0.946...
Caudatus li	0.05	0.075...	0.087...	0.006...	0.027...	0.197...	1.055...
Putamen re	0.05	0.086...	0.089...	0.003...	0.023...	0.145...	1.117...
Putamen li	0.05	0.088...	0.093...	0.007...	0.040...	0.169...	1.119...
Frontal re	0.05	0.076...	0.106...	0.015...	0.045...	0.241...	0.960...
Frontal li	0.05	0.078...	0.113...	0.020...	0.054...	0.261...	0.949...
Temporal re	0.05	0.077...	0.113...	0.031...	0.068...	0.313...	0.997...
Temporal li	0.05	0.078...	0.106...	0.023...	0.060...	0.283...	1.022...

Model	vB	K <sub>1</sub>	k <sub>2</sub>	k <sub>3</sub>	k <sub>4</sub>	V <sub>s</sub>	V <sub>t</sub>
average	0.05	0.078...	0.118...	0.014...	0.041...	0.203...	0.932...
median	0.05	0.078...	0.106...	0.015...	0.040...	0.191...	0.997...
stdv	0.0	0.005...	0.046...	0.009...	0.014...	0.065...	0.192...

- The Logan plot requires an appropriate definition of the time, from when on the transformed samples show a linear behavior. The user can decide intuitively the value (eg. 25) and enter it into the **t\*** parameter field. As soon as the value is entered, it is adjusted to match the closest acquisition, the regression is re-calculated and the points before the start are set to gray color (not considered in fit). As an alternative, a criterion **Max Err.** (eg. 10%) can be specified, and **Fit current region** invoked to find the time point from which on all curve points deviate less



than the specified percentage from the line. The smaller the criterion, the later the start time found.

- To get  $V_t$  by the Logan method in all regions with a fixed  $t^*$  identified above by removing the check of its fit box, use **Copy Model & Par** to propagate to all regions as before, and **Fit all regions**. Again, display a summary and compare the  $V_t$  values with the ones calculated with the 2TCM. The Logan  $V_t$  values tend to be higher. This is due to the fact that a 5% blood volume was subtracted in the 2TCM, whereas it is included in the Logan method.
- An essential question to answer for a novel tracer is, which model complexity is needed to describe the kinetic behavior of the tracer. PKIN provides statistical parameters that can be used: the **Schwartz** Criterion (SC), the **Akaike** Information Criterion and the Model Selection Criterion (SC, AIC: smaller=better model; MSC: bigger=better model). These and other statistical criteria are available on the **Details** tab, and they are also saved with the fit results. Verify with the CFPFX data whether the criteria confirm that a 1-tissue compartment model is not sufficient.

Region	Vt
Whole Brain	0.925...
Cerebellum re	0.640...
Cerebellum li	0.621...
Striatum re	1.069...
Striatum li	1.141...
Caudatus re	0.995...
Caudatus li	1.104...
Putamen re	1.155...
Putamen li	1.175...
Frontal re	1.040...
Frontal li	1.034...

### 3. Kinetic Modeling with Reference Models

The DASB TAC data of PKIN2 must be analyzed with reference methods, because no blood data is available. Cerebellum is a suitable reference tissue for the DASB tracer.

- In **PKIN**, select the tab with the DASB data. Use the **caudate** region to start with.
- There is a series of different reference models available which all calculate a measure of the binding potential relative to non-displaceable uptake  $BP_{nd}$  ( $= k_3/k_4$ ). To see a short model description use [?](#) to the right of the selected model.
- Note that some of the models require the *prior information of  $k_2'$* , the clearance rate of the reference tissue (**MRTM2**, **Simplified Reference Tissue Model 2**). These models are aimed at pixel-wise applications where  $k_2'$  is common because the same reference is used for all pixels. Such a  $k_2'$  can be calculated using the **MRTM** or the **Simplified Reference Tissue Model** models.
- Select the **Ichise Ref Tissue MRTM** model, and **cerebellum** in the **Reference** list.
- Note the parameter **t\*** which describes the equilibration time. Only measurements after this time are considered in the fit. **t\*** can be fitted according to a **Max Err** criterion. Set **Max Err** to 10% and **Fit current region**. The start time found is 2.5 min. Note the  $BP_{nd}$  result in the derived parameters area which has a value of 1.40. To quickly assess the impact of the start time on  $BP_{nd}$  select the **Increment** tab. Use the slider or the increment button to steadily increase **t\*** and observe  $BP_{nd}$  which is continually updated. It remains quite stable until about 60 minutes.
- Fit current region** again to switch back to the **Standard** tab and set **t\*** again to 2.5 min. Remove the fit check of **t\***, copy **Model & Par** to all regions, and **Fit all regions**. All fits are done with the same starting time and the results can be summarized with **View Par** (left column in illustration above).


Region	caudate
Reference	cerebellum
Model	Ichise Ref. Tissue MRTM

Parameter	Increment slider	min
t*	60	5.0
Max. Err.	10.0	%
BPnd	1.472042	1/1

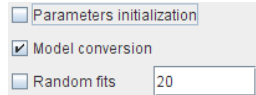


Region	BPnd	BPnd
amygdalae	1.125706	1.12135
basal forebrain	0.94975	0.950233
brainstem	0.97803	0.978392
caudate	1.400217	1.401239
cerebellum	9.376866E-7	
frontal cortex	0.201099	0.199912
parietal cortex	0.130778	0.131012
putamen	1.625375	1.622412
temporal cortex	0.288998	0.288669
thalamus	2.039675	2.036471
visual cortex	0.391423	0.391518


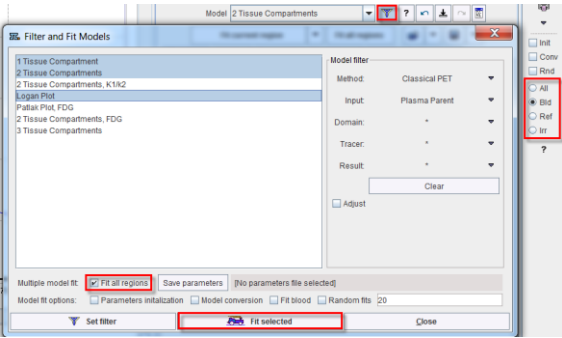


- As an alternative, switch to the **Simplified Reference Tissue Model, Fit current region** (to get reasonable fit starting values for the other regions), copy **Model & Par** to all regions, and **Fit all regions**. The fit fails in cerebellum, which is the reference and thus not relevant. The fit failure is available activating the changed View Console icon  in the status bar. Display the results summary with **View Par** (right column in illustration). The results of both methods are very comparable.
- On the **Extras** panel, enable the **Model Conversion** flag. Note the value of  $k_2'$  in the derived parameters section, then switch the model of **caudate** to the **MRTM2** (or **SRTM2**) method. After model switching,  $k_2'$  has the value which was determined with **SRTM** (or **MRTM**).
- There are different ways for obtaining an average  $k_2'$  which can be applied for pixel-wise fitting: One approach is to apply **SRTM** or **MRTM** to several regional TACs with high  $BP_{ND}$  and average the obtained  $k_2'$  values. The averaging should be within the subject and not across a population.

#### 4. Fitting Options in Kinetic Modeling

Iterative model fitting is crucially dependent on a set of reasonable initial parameter values. If they are too far from the optimal solution, there is a higher danger of getting stuck in a local minimum.

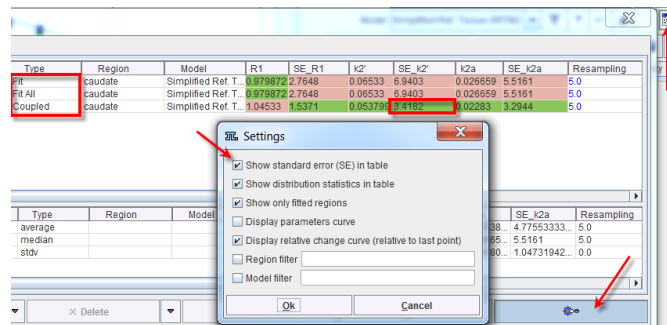
- One strategy for arriving at suitable initial compartment model parameters is to start with a simple model, and use its result for the more complex model. This can be achieved by enabling **Model Conversion** on the **Extras** pane. Once suitable parameters for the complex model have been found, the function should be disabled again. 
- Another strategy for compartment models is to derive initial parameters by applying a linear least solution. These solutions are known to be susceptible for biased parameter estimates, but most likely they are sufficiently close to serve as initial parameter values. This behavior can be enabled with the **Parameters initialization** flag. Note that with the flag enabled manually entered parameters will not be relevant any more for the fitting outcome.
- A strategy for avoiding local minima is to explore the parameter space from random sets of initial parameters, and to consider the solution with minimal Chi square as the result parameter set. This strategy can be enabled with the **Random fits** flag which applies to all iterative fitting, not just the compartment models. The number of trials per fit can be specified in the number field.
- A **history** functionality is available which records the fitted models for each region. The users can also manually add configurations of interest. Using the  arrows they can go through the history, and they can inspect it as a list. Configure the **2TC** model, then **Fit**, the **1TC** model then **Fit**, **Logan** then **Fit**. Open the history list with . Note that the parameter values are sorted into common columns, so that eg.  $V_t$  can be easily compared across models. 

Model	vB	K1	k2	k3	k4	Vt
1 Tissue Comp...	0.05	0.0623...	0.0846...			0.7363...
2 Tissue Comp...	0.05	0.0679...	0.1259...	0.0267...	0.0501...	0.8282...
Logan Plot						0.9250...
- The radio buttons available in the lateral taskbar support filtering of the model list based on the input type, blood (**Bld**) or reference region (**Ref**). The **Irr** radio button allows listing the models developed for irreversible tracer. For instance, the list is reduced to blood-based models by selecting the **Bld** radio button. The filtering  button next to the model selection allows additional filter refinement for a particular task. For example set the **Method** to **Classical PET** to have only the classic models listed. When **Fit selected** is activated with **Fit all regions** enabled, the highlighted subset of models is fitted for all TACs and the dialog window is closed. Note that thereafter only the blood-based models appear in the **Model** list. To reset the list enable the **All** radio button in the lateral taskbar. 
- Instead of fitting each regional TAC independently, multiple TACs can be fitted at the same time. The main application of this feature is to introduce a priori knowledge and maximize the information content per parameter. As an example, the reference tissue properties such as the washout rate  $k_2'$  should be the same when using it for fitting different target regions. The solution

is to perform a combined model fitting of the different regions which uses the same  $k_2'$  for all models. This option is called **Coupled** fitting in PKIN.

- Open the DASB data set. The first step is to select a model which supports coupled fitting and has  $k_2'$  as a fitting parameter rather than as a derived parameter. Such a model is SRTM2. For the **caudate** region, select the **SRTM2** model with **cerebellum** as the **Reference** region. Use **Fit Current Region** to get an initial model estimate, and propagate it with **Copy Mode & Par**. Activate **Fit all regions** to establish reasonable starting parameters.
- Select the **Coupled** tab and enable the box of  $k_2'$  in the model area to define it as a common parameter in the fit. In the lower part check the boxes of the receptor-rich tissues **brainstem**, **caudate**, **putamen**, and **thalamus**.
- Activate **Fit coupled** to start the common fit of the 4 regional TACs. It will result in individual **R1** and **k2a** values, and a common  $k_2'$ .
- The result is best inspected with the **View Par** summary, sorting the rows by the value of  $k_2'$ . It proves that indeed the coupled fitting resulted in a common  $k_2'$  for **brainstem**, **caudate**, **putamen**, and **thalamus**.
- Coupling improved the reliability  $k_2'$  estimate. This can be verified by opening the fitting history and enabling **Show standard error in table** as illustrated to the right. SE\_ $k_2'$  of the Coupled fitting is reduced compared to that of the individual fit.

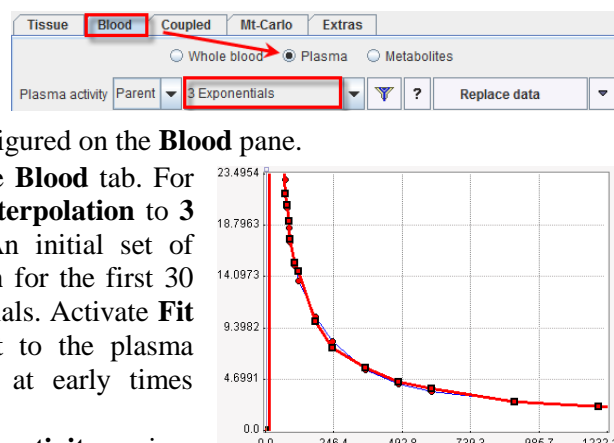
No	Region	Model	R1	k2'	k2a
1	cerebellum	Simplified Ref. T...	1.0	0.1	0.1
3	amygdalae	Simplified Ref. T...	0.724	0.064398	0.021992
7	thalamus	Simplified Ref. T...	1.180	0.053799	0.021643
6	putamen	Simplified Ref. T...	1.059	0.053799	0.021761
5	caudate	Simplified Ref. T...	1.045	0.053799	0.02283
2	brainstem	Simplified Ref. T...	0.833	0.053799	0.02266
8	visual cortex	Simplified Ref. T...	1.029	0.049139	0.03637
11	basal forebrain	Simplified Ref. T...	0.930	0.047607	0.022719
4	temporal cortex	Simplified Ref. T...	0.944	0.046149	0.033807
10	frontal cortex	Simplified Ref. T...	0.979	0.035103	0.028645
9	parietal cortex	Simplified Ref. T...	0.916	0.031845	0.02581



## 5. Modeling of Blood Data in Kinetic Modeling


The calculation of the model functions requires the interpolation of the blood activity curves. If no action is performed after loading the blood activity data, simple linear interpolation is applied. Other interpolation behaviors can be configured on the **Blood** pane.

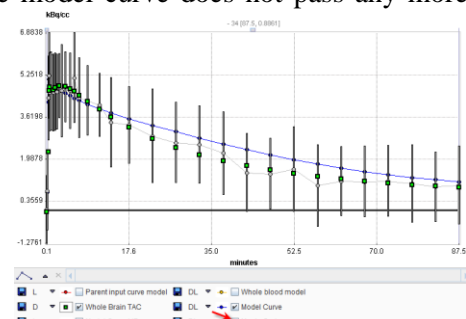
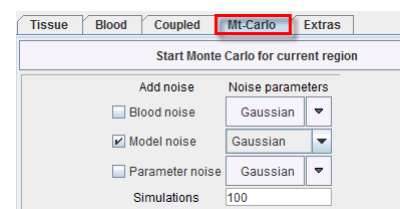
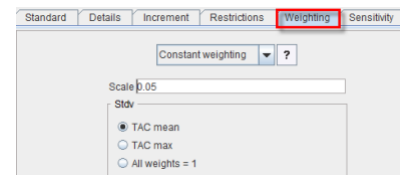
- Select the tab with the CPFEX data, then the **Blood** tab. For the **Plasma** data set the model from **Lin. Interpolation** to **3 Exponentials**. Keep the default settings. An initial set of parameters is shown with linear interpolation for the first 30 seconds and then interpolation by 3 exponentials. Activate **Fit plasma activity** to fit the exponential part to the plasma measurements. There is some discrepancy at early times because of the very steep peak.
- Set the **Begin** time to **200** sec and **Fit plasma activity** again – there is now a good agreement between the Plasma measurement and the **Plasma model** curve at all times.
- If the plasma activity data has not yet been corrected for metabolites, this can be done using the **Metabolites** correction in PKIN. To see an example load **1TCM with Metabolites** from the database and enable the **Metabolites** radio button on the **Blood** tab.



## 6. Assessing Parameter Identifiability

Any fitting procedure will result in parameter values. However, the reliability of these estimates must always be questioned. It is possible that parameters are correlated, so that a change of one parameter can be compensated by the change of a second parameter (correlated parameter). In that case it is not possible to get independent estimates.

- In **PKIN**, select the tab with the CPFPX data. Make sure that the 2TCM model has been selected and fitted in all regions. Note that if the Marquardt fitting method was used, the **%SE** is shown for each fitted parameter. %SE is the estimate of the standard error (expressed in percent of the parameter value). It is calculated as the square root of the diagonal elements in the covariance matrix. The macro parameters also show a %SE indication which is derived from the standard error of the fitted parameters which are involved in the macro parameter calculation.
- Use the arrow  to step through the regions and look at the %SE values. It is obvious that  $K_1$  is the most robust parameter, followed by  $k_2$ .  $k_3$  and  $k_4$  generally show high %SE with the maximum in the **Caudatus re** region.
- Subsequently, we perform a **Monte Carlo (MC)** simulation to get a more “experimental” measure of the distribution of the parameter values. The principle of the MC procedure is the following: (1) it assumes the current model represents the truth; (2) then adds realistic noise to the model; (3) fits the model to the noisy curve. MC performs (2) and (3) many times (eg. 1000) and calculates the mean and standard deviation of the (e.g. 1000) parameter results.
- The noise distribution is essential for the simulation. The **Weighting** tab allows defining how the standard deviation in each time point is calculated. The default shown is to use 5% of the TAC average as the standard deviation of a Gaussian distribution at all times (Constant weighting). There are other settings which add more or less noise depending on the signal value (Calculated weighting).
- Switch to the **Mt-Carlo** tab and set the **Model noise** to **Gaussian**. Set the number of **Simulations** to a value of 100 (1000 takes quite long), then activate **Start Monte Carlo for current region**. The 100 noisy curves are calculated and fitted in the background, while PKIN is locked. After completion, the **Tissue** tab is shown. Now, the parameter values represent the average of the 100 results, and the %SE their standard deviation. The %SE found are substantially smaller than the %SE from the covariance matrix, but the relation between the %SE values of  $K_1$ ,  $k_2$ ,  $k_3$  and  $k_4$  is similar as before.
- Repeat the Monte Carlo simulation with more noise. Set the noise scale factor of the Gaussian distribution to 20% in the **Weighting** tab. Then start the Monte Carlo simulation. The %SE of all parameters has clearly been increased. Most probably, the model curve does not pass any more through the measurement points. The reason is that the average parameter results are used for the model calculation, and they can be significantly distorted due to outliers, particularly of  $k_3$  and  $k_4$ .
- To visualize the noisy data used in the Monte Carlo simulation switch back to the **Mt-Carlo** tab. In the curve display, a new curve **Monte Carlo** appears with vertical bars. The end points of these bars mark the minimal and the maximal value that any of the noisy curves reached at a particular time point.
- Save the parameter values to record the Monte Carlo results.



## Section 3: PXMOD Tool – Pixel-Wise Modeling

### Topics:

- Step-wise data processing.
- Examples with blood-based and reference models.
- Results exploration.

### PXMOD Exercises:

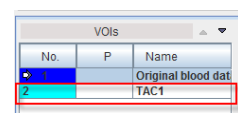
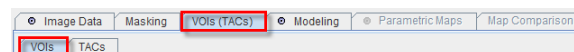
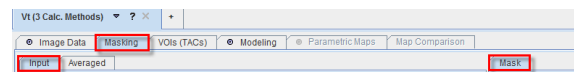
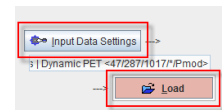
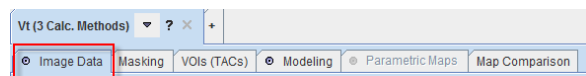
#### 1. Step-by-Step Parametric Map Calculation (PXMOD)

The PXMOD tool implements a step-wise processing strategy: (1) The model is selected so that the program can load the requirements. (2) The image data are defined and loaded. (3) Optionally, a mask can be created to eliminate the background from modeling. (4) Depending on the model, tissue TACs need to be defined. (5) The blood curves are specified, loaded and corrected for some distortions, if necessary. (6) Some model preprocessing is performed for gathering information needed in the pixel-wise calculations. Typically, the regional TACs from (4) are involved. (7) The selected model is applied to the pixel-wise TACs for calculating the parametric maps.

In the program interface, each step is represented by a dedicated panel. During a processing session, the user works from left to right through the panels. Each panel has a red button in the lower right corner to proceed to the next panel. Note that all information created during a processing session, such as masks or VOIs, need to be saved. This has the effect that at the end of a processing session a complete configuration can be saved which allows exactly repeating the analysis.

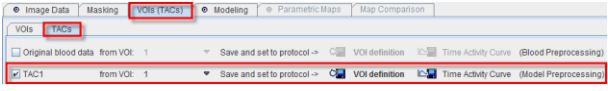


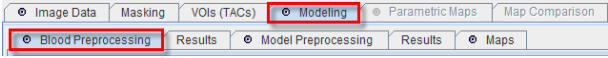




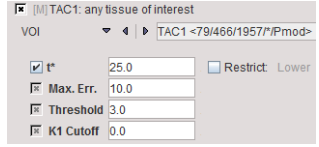
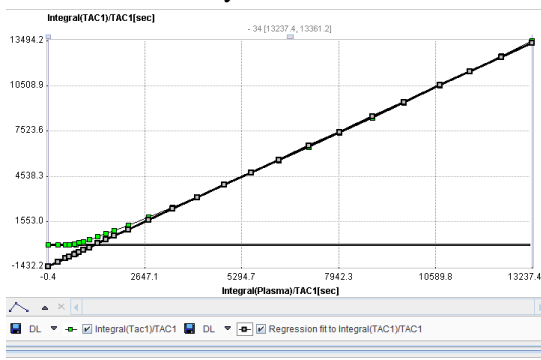
In the following, the step-by-step data analysis procedure will be described.

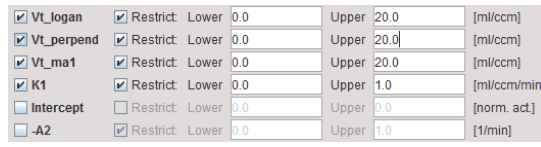
- Start **PXMOD** to calculate the total distribution volume  $V_t$  of the example CPF PX bolus study. First, select the **Vt (3 Calc. Methods)** model from menu **Pixel wise/Model** or directly in the model list of the workspace tab. By this model selection the configuration requirements are adjusted accordingly.
- Define the image data using the **Input Data Settings** button in the **Image Data** tab of the workspace. In the new dialog window make sure the **Input 1** format is **Database**, then use the **Load** button to display the database series selection box. Select the series **Dynamic PET** of patient **PKIN1** and quit the dialog window with **Set series**. Make sure no processing is applied to the data at loading time by activating the **Reset loading parameters** button. Select **OK**. Finally, use the red button to **Load** the image.
- As an optional step generate a mask to restrict modeling only to the brain area and ignore the background. Activate the red **Masking** button in the lower right of the **Image Data** panel to proceed. The program automatically switches to the **Masking** tab. Average 20 frames by entering **10** and **30** into the **From** and **To** fields, and activating **Aver**. With the **Averaged** tab selected, choose the **THRESHOLD** procedure in the **Segmentation** list and set the threshold to **1.0**. Set the color scale for the **Averaged** image to **Gray**. Check the **Ovr** box, so that all pixels fulfilling the criterion are highlighted in red. Activate **Segmentation** to actually create the binary segment image which is shown in the **Mask** panel. Configure the **Set to protocol** button to the **Database** format and activate it. In the appearing dialog window use **Edit info** to change the **Series Description** to **Mask thr 1.0**. Close with **OK** then **Save**. The saved mask is automatically used for the **Mask by File** configuration.
- Proceed with the red **TACs** button to specify TACs for the model pre-processing. The program automatically switches to the **VOIs (TACs)** – **VOIs** tab. In the VOIs list two empty VOI definitions are shown which originate from the model: **Original blood data** and **TAC1**. Select the **TAC1** VOI, navigate to slice 40, select the **✎** button and click into the axial slice in order to generate













an iso-contour VOI (e.g. temporal cortex).

- Proceed with the red **Prepare TACs** button to the **TACs** tab. Since no image-derived input curve is needed, make sure that the **Original blood data** box is not checked. In contrast, enable the **TAC1** box to show the curves from the **TAC1** VOI definition in the curve area. At this point the TAC information must be saved for later use in model preprocessing. There are two possibilities: **Save and set to protocol** saves the **VOI definition** itself (recommended), whereas **Time Activity Curve** saves the TAC resulting from the VOI definition. Activate the **VOI definition** button and save the VOI with **Enter name** set to **TAC1**.  

- Select the red **Prepare Model** button to proceed. The program switches to the **Modeling** page, starting with the **Blood Preprocessing** panel. Set the format selection of **Blood data** to **TAC(DB)** to read the prepared blood data from the database. Activate the  button to open the DB selection and reset the filter fields with . The blood curves from all the patients and studies are now listed. Select **Authentic CFPX in plasma of PKIN1** which will serve as the input curve, then **Set selected**. The blood data is already decay corrected, so do not use the available correction.  

- The blood pre-processing step is started with the red **Preprocess Blood** button. The blood data is loaded and displayed in the **Results** panel right to **Blood Preprocessing**. For this particular model, no other action is performed during blood preprocessing.
- Proceed to model preprocessing with the red **Set Model Preprocessing Parameters** button. The program switches to the **Model Preprocessing** tab, where the user has to tailor the model calculation. Note that the **TAC1** VOI prepared above is already configured. The section below the **TAC1** specification contains the parameters configuration:  parameters are for input purposes only,  parameters are fitted, and  are parameters which could be fitted but are fixed at the entered value. For the selected model  $t^*$  of the Logan plot (start time of the linear section) has to be defined. The Logan plot is therefore applied to the specified tissue TAC. In the example above  next to  $t^*$  has the effect that  $t^*$  is fitted using the error criterion of **10% Max Err. Threshold** values  $>0$  are useful for background masking in cases where no mask was created and set to the protocol; **3-5%** usually work well. **K1 Cutoff** is representing an alternative method for masking based on K1 estimate. Note that the parameters can be set to recommended default values by the **Set Defaults** button  

- Start preprocessing with the red **Preprocess Model** button. In the **Results** tab to the right the Logan graphical plot is displayed for visual inspection, and the numerical outcome is available in the **Info** area. The visual inspection should confirm that the regression line is an adequate fit to the late part of the curve.  
  

Result of regional Logan Plot:  
 $t^* = 25.0$  [min]  
 $DV = 1.1175114719868309$   
 $intercept = -1431.7612719633237$
- Proceed with the **Set Map Parameters** button. Use the checks to specify the parameters for which maps should be generated. In the example below the  $V_t$  maps are calculated using two methods: the standard Logan plot (**Vt\_logan**), the Logan plot with linear regression based on orthogonal distances (**Vt\_perpend**), while the Ichise's MA1 method (**Vt\_ma1**) is not active. The **K1** map also belongs to the MA1 method and essentially represents a perfusion map usable for anatomical correlations. Because the analyses with the noisy TACs sometimes result in outliers dominating the image dynamics, the result ranges of the  $V_t$  parameters are **Restricted** between a lower value of **0** and an upper value of **20**.  




- At this time the last configuration step has been completed and pixel-wise calculation can be started with the **Pixelwise Calculation** button. The resulting maps are shown on the **Parametric Maps** page.
- When the ☐ box in the lateral toolbar is checked, only the parametric maps of the currently shown slice in the **Image Data** tab are calculated. This feature is intended for the prototyping phase of models which take substantial calculation time. 
- The maps can be saved using the  button from the lateral toolbar or using the **Save Maps** button. In the example to the right the format has been configured to **DICOM**. If the **All**  box is checked, the maps of all parameters will be saved, otherwise only the current one. To be able to distinguish between the maps, PMOD adds the parameter name to the series description (or the file name for non-DICOM data formats).
- It is generally recommended to not only save the result images, but also the full processing configuration. This is done with the  button in the **Status bar** (or from menu **Pixel wise / Save Model Settings**). By loading such a setting later on, all the processing details can be reviewed, edited if necessary, and the processing repeated. Save the configuration of your processing to the database or a directory on your local disk, load it again with , and try running it with the  button.
- Once all the information pieces are available, there is an alternative to the step-wise processing: With the  button a dialog window can be opened which contains the panels of all processing steps, so that the definitions can be changed very quickly. This feature is particularly useful in combination with loading a configuration file and adjusting it for further usage.
- Note that the  button always performs a full processing of all steps, including data loading.

## 2. Examples with Different Models

This section illustrates the use of various models with different data sets.

### 1-Tissue Compartment Models:

The CPFPX data of PKIN1 can be fitted with a 1-tissue compartment model. Corresponding settings for testing the different models are available in the database for retrieval.

- Select from the **Model list 1-Tissue Compartment (Alpert)**. Define the **Dynamic PET** of PKIN1 as **Loading** data. Go to the **Blood Preprocessing** tab, and in addition to the input curve define also the whole blood activity concentration for spillover correction as illustrated to the right.
- In **Model Preprocessing**, the blood volume fraction is 5% (0.05) per default, and the lookup table configurations should normally work. Enable the generation of **K<sub>1</sub>**, **k<sub>2</sub>** and **V<sub>t</sub>** parametric maps in the **Maps** panel, then run the analysis with the  button. Inspect the parametric maps of the 1-tissue compartment model.
- To compare with an alternative model create a new page with menu **Pixel wise/New Workspace** or using the workspace tab with the + button. All configurations are copied from the current workspace to the new one. Switch the model to **1-Tissue Compartment (Zhou GRRSC)**. This is a model with inherent spatial constraints, so that the result will look smoothed. The **Loading** data and the **Blood Preprocessing** configurations are already correct, because they are inherited from the prior model. In the **Model Preprocessing** panel, set the **Filter planar** to 3 pixels because the data set has large pixels, and leave the other parameters as-is. Then activate  and inspect the resulting parametric maps. Compare the values of the two methods by setting the upper thresholds to common values and switching back and forth between the two workspaces.

Different Vt Methods	PKIN1
Logan Plot	PKIN1
1-Tissue Ridge Regression	PKIN1
1-Tissue Alpert	PKIN1
2-Tissue, Ridge Regression	PKIN1
2-Tissue, 3 Parameters variable	PKIN1
2-Tissue, 4 Parameters variable	PKIN1

Set [1-Tissue Compartment (Alpert)]

Loading Masking Blood Preprocessing Model Preprocessing Model [1-Tis

☒ [M] Blood data and blood pre-processing

☒ [M] Input curve (plasma data)

TAC (DB) Authentic CPFPX in plasma ( PKIN1 ) 2010-08-16 <47/2

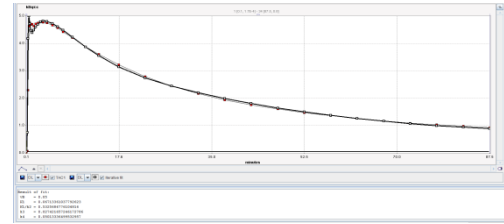
☒ [Q] Whole blood activity for spillover correction [OPTIONAL]

TAC (DB) Total CPFPX in blood ( PKIN1 ) 2010-08-16 <47/287/103

### 2-Tissue Compartment Models:

- Create a **New Workspace**. Select from the **Model list 2-Tissue Compartments, K<sub>1</sub>/k<sub>2</sub>**. This is a model with K<sub>1</sub>/k<sub>2</sub> as a fit parameter instead of k<sub>2</sub>. The K<sub>1</sub>/k<sub>2</sub> approach is helpful because often it is reasonable to fix K<sub>1</sub>/k<sub>2</sub> (non-displaceable compartment) at a common value for all pixels. Hereby the number of fitted parameters is reduced, making the fit more stable (and faster).

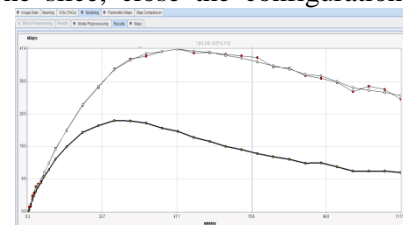
- The **Loading** and the **Blood Preprocessing** configurations are already correct from the 1-Tissue compartment model. In Model **Preprocessing** a tissue TAC is required. Proceed by specifying the **VOI** format and selecting **CPFPX Bolus Whole Brain** from the database. In **Maps** leave the configuration as is. Then make sure that you first only fit the current slice by checking the box ☒ from the lateral toolbar.
- Run the processing, which may take several minutes. After fitting, inspect the model preprocessing fitting result of the 2TC model to the whole brain TAC by checking the curves and the parameter values in the **Modeling Results** panel. Inspect the parametric maps. Compare the  $V_t$  map with the corresponding maps of the 1TC methods by switching between the different workspaces.
- Now investigate the effect of fixing  $K_1/k_2$ . To this end create a **New Workspace**. There, remove the fit flag of  **$K_1/k_2$**  both in **Model Preprocessing** and **Maps** panels. Then, run the processing again and with the same slice as before, but now with only 3 parameters. Fitting is faster, and the result contains less outliers.
- There is another model for fitting a 2-tissue compartment model: **2-Tissue  $K_1/k_2$ , RR**. It implements a ridge-regression approach, i.e. it imposes spatial constraints on the smoothness of the parameters. After creating a new workspace, load the model setting **2-Tissue, Ridge Regression**, and run the processing. Please check the PXMOD User's Guide to understand the different processing steps and the outcome of this rather complex model.



### Reference Tissue Models:

The DASB data of PKIN2 can be fitted with multiple reference models. Corresponding settings for testing the models are available in the database for retrieval.

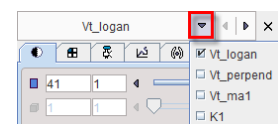
- Create a **New Workspace**. Select from the **Model** list the simplified reference tissue model **BPnd (STRM Ref)**. Activate the configuration button . The **Blood Preprocessing** is not available anymore because no blood data is required. In the **Loading** tab select the **Dynamic DASB PET** of patient **PKIN2**.
- In the **Model Preprocessing** tab define the two TACs needed as illustrated to the right. The **DASB Striatum VOI** represents receptor-rich tissue which is used to test whether the fitting works properly. The **DASB Cerebellum VOI** represents the signal from reference tissue without specific binding. The parameters in the lower part are needed for the basis function method which locates the solution in a certain range of the apparent  $k_2$  ( **$k_{2a}$** ). The default setting should work for the DASB data. In **Model** check all parameters. This will not have an impact on speed and allows inspecting also secondary information.
- Enable the lateral box ☒ from the toolbar to process only one slice, close the configuration window and then run the processing with .
- The **Modeling Results** tab should indicate a good curve fit as illustrated to the right, and the parametric maps show reasonable results. It is important to check that the  **$k_{2a}$**  values are not truncated by the prescribed range in the relevant parts of the image. This is not the case; the maximal value is only obtained for peripheral pixels.
- Please use the prepared settings in the example database for experimenting with the other reference tissue models (particularly with the **BPnd (Different Methods)** that allows the estimation of the BPnd with SRTM, SRTM2, MRTM0, MRTM, MRTM2, and Logon).







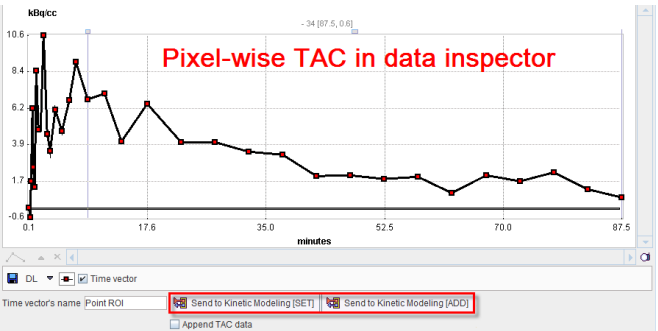
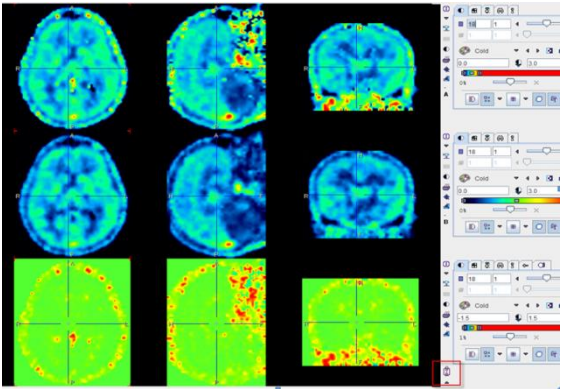
### 3. Results Exploration (PXMOD, PKIN)

There are several facilities to investigate the PXMOD results.




- To get a data set with multiple parametric maps retrieve the **Different  $V_t$  Methods** protocol using the **Load protocol** button and perform the analysis. The parametric maps are available in the **Parametric Maps** panel in a stacked mode so that only one map is visible. They may be switched using the arrows as illustrated above.



- To probe all calculated parameters of a pixel open the “data inspector” of the maps via the  button in the upper right image corner. Use the  button to extend the information shown. When clicking into a map, the parameter values of the selected pixel are updated in the inspector panel. The example to the right illustrates the known fact that the standard Logan plot tends to underestimate  $V_t$  in the presence of noise.
 

PARAMETER NAME	VALUE
Vt_logan	1.26583719
Vt_perpend	1.26866042
Vt_ma1	1.31234502
K1	0.06615235
- Select the **Map Comparison** tab to see the image fusion panel. In the first line select the dynamic input image, in the second the Vt\_Logan parametric image. Now open the data inspector  for both images, and extend with  for the dynamic image. In the extended area the **pixel-wise TAC** of the current pixel is seen. Navigate through the parametric map and localize points of interest. As soon as you click at them, the TAC and the parameter values are updated in the two inspectors.
- The pixel-wise models are usually simplified and cannot be interactively examined. Therefore, to allow a full analysis, the pixel-wise TACs can be sent to the **PKIN** tool with the **Send to Kinetic Modeling** buttons. If blood data has been loaded by the model, it is also transferred. **SET** replaces the data of the current PKIN tab, while **ADD** creates a new PKIN tab to put the data into. With **SET** and the **Append TAC data** box checked, the TAC is added as a new **Region** to the current PKIN tab. This allows including data from multiple pixels into one PKIN data set.
 
- As an example, click at a point in the parametric map with both inspectors open. Transfer the TAC of the particular pixel with **Send to Kinetic Modeling** to PKIN. In PKIN, switch the model to **1 Tissue Compartment** model, and **Fit current region**. Now compare the value of  $V_t$  shown with the different  $V_t$  values in the inspector. It is probably similar but not the same. Now remember that  $V_t$  calculated with the Logan plot includes also the blood space. To have the same situation with the 1TCM, set the blood volume **vB** from 0.05 to 0.0 and fit again. You can try the same with the **2 Tissue Compartment** model, but the signal is probably too noisy for 4 fitted parameters. You can also try with the **Logan plot**. Close the inspectors and continue in PXMOD.
- The parametric maps themselves are best compared using the **Map Comparison** panel. Arrange Vt\_MA1 in the first row and Vt\_Logan in the second row. Set the same lower and upper thresholds to allow for a visual comparison (e.g. 3). Switch to the algebra mode and perform a subtraction of the two maps. The result is shown in the third line as illustrated to the right. From this result it is clear that the MA1 method tends to higher  $V_t$  values, and that this effect is depending on the tissue.
 

#### Further PXMOD Examples with Prepared Model Settings:

- The **Pmod** database contains the PXMOD configuration settings of several different types of analyses. To try them out we propose the following procedure: (1) Create a new empty workspace. (2) Use  to retrieve a configuration setting. To see all protocols in the DB, activate the  button in the **Read from DB** box. (3) . In this way you will get results on different tabbed pages.
- PKIN3**, setting **FDG Patlak**: Calculates MRGlu maps from dynamic FDG data using the Patlak plot.

**PKIN4**, setting **H2O Perfusion (Alpert)**: Calculates the rCBF perfusion maps from a dynamic  $H_2^{15}O$  PET scan with arterial sampling using the Alpert time-weighted integral method.



## Section 4: Fuse It Tool – Image Registration & Fusion

### Topics:

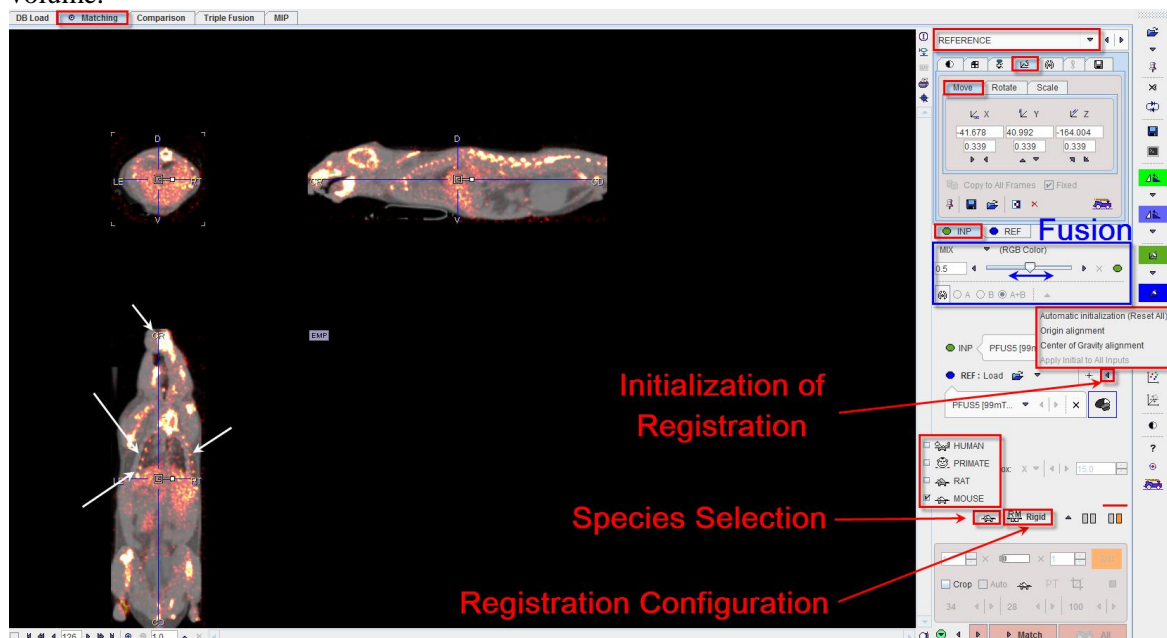
- Interactive and automatic registration of whole body mouse images.
- Maximum Intensity Projection of matched images.
- Automatic registration of multi-modal brain images.
- Stereotactic normalization of brain PET data and subsequent application of standard VOIs.
- Results saving and documentation.

### Fuse It Exercises:

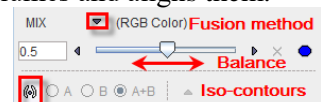
#### 1. Manual Registration of Whole Body Mouse Images

In this section whole-body SPECT images of a mouse are manually matched to CT images. The data sets were acquired with the same bed, so applying a rigid transform is sufficient.






- First the SPECT images have to be loaded. Start **Fuse It** and select the **Matching** page, **INPUT** sub-page. Make sure the **Load** button is set to the **Database** format. Using **INP Load**, load the **SPECT FB** series of patient **PFUS5**. The system detects that the images originate from a mouse and applies corresponding presets. Adjust the color settings to make the image appear brighter. Proceed by activating the **Rigid Matching** action button **RM**. **Fuse It** switches to the next page **REFERENCE**.
- Load the **CT FB masked** series with the **REF Load** button. Consequently, the SPECT images are interpolated to the resolution of the **Reference**. The program tries to align the two studies based on DICOM landmarks (**Origins**) in the data. If they are not available, the centers of the two data volumes are aligned. The initialization results in a translation matrix, which can be inspected on the reslicing tab of the **INP** series. Note that there is a slight initial mismatch in the fused SPECT and CT images (white arrows below), due to differences in coordinate system and reconstructed volume.

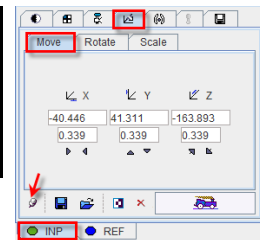
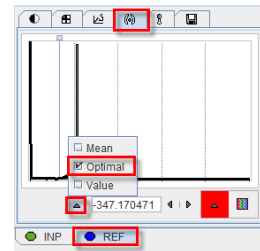
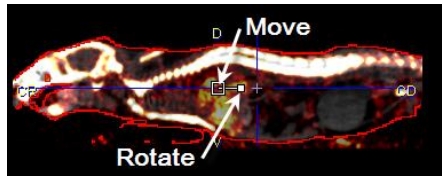


- A reasonable initial alignment should be achieved before continuing, because it will make the manual and the automatic matching easier. If this is not the case, try the following options:
- **+** aligns the geometric centers of the data volumes independent of resolution and field-of-view.
- **Origin alignment** enforces the alignment of the coordinate origins in the two data sets.
- **Center of Gravity** calculates the “mass” centers of the two data volumes and aligns them.
- The fusion image can be adjusted using the fusion control area (indicated above by the blue box). The control area consists of three rows. The first row contains the selection for the different fusion methods, the second row the slider to change the balance between the contributions of the two










fused images, and the third row controls for iso-contour overlays. The appearance of the individual images is adjusted by selecting the corresponding tab and using the image presentation controls, e.g. adjustment of the color thresholds. Set the fusion method to **MIX** and shift the blending slider completely to the left, such that only the SPECT **INP** image is shown. It is obvious that it is affected by granular noise.

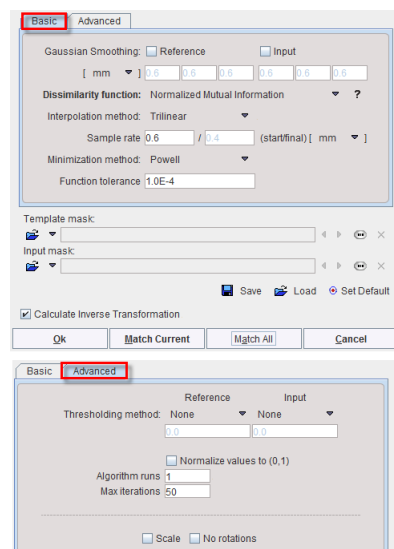
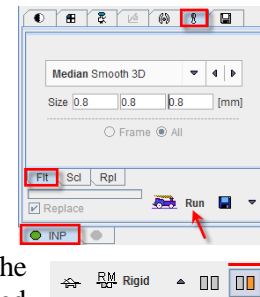
- As an aid for the manual registration enable the “isocontours” for highlighting the body contour. It is best defined on the CT images. As illustrated to the right, select an **Optimal** contour level for the **REF** image and set the contour color to red. To see only the CT contours in the fusion display set the radio button to **B** in the fusion control area.
- To start interactive matching select  in the toolbar to the right. Reslicing handles are then shown in the image center and allow translating (empty white box) or rotating (solid white box) the SPECT images. The handles are hidden when switching to a different tab. To see them permanently, set the  on the tab to the “fixed” mode . As an alternative for interactive dragging, enter discrete numbers for the transformation parameters in the corresponding number fields on the reslicing tab. Note that the reslicing controls always remain in the image center.
- Try to manually align the SPECT images to the CT. Click at points located centrally, and then move and rotate the SPECT series until the SPECT image follows the CT whole body outline in all directions. At this time the transformation parameters can be saved with the  button on the reslicing tab.
- To save the registered SPECT images use the  button in the toolbar to the right.



## 2. Automatic Registration of Whole Body Mouse Images




In the following the SPECT images are automatically registered to the CT reference and the result compared with the result of manual coregistration.

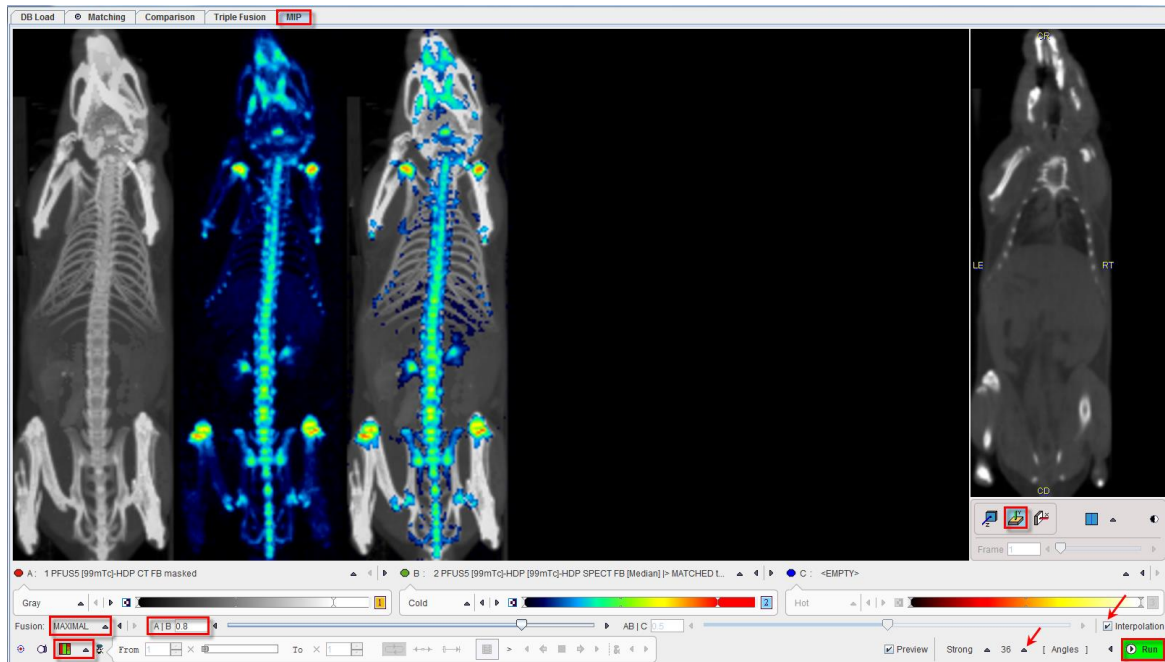
- On the **Matching INPUT** sub-page switch **INP Load** to the “append” mode by enabling the pushpin . Then load the **SPECT** series a second time. It is added as a second entry in the **INP** list. Apply a 0.8 mm median filter to reduce the granular noise present in the SPECT image as illustrated to the right. The original image is replaced by the smoothed one.
- Proceed to the next step activating the **Rigid Matching** action button . The program switches to the **REFERENCE** sub-page. Make sure the smoothed SPECT image is selected as the input data on the **INP** list. Check that the correct species is selected (**MOUSE**) and the registration method is set to **Rigid Matching** as illustrated. The red bar above the buttons indicates which parameter preset is active. To edit the parameters used in the automatic matching activate the cross-modality preset button . A dialog window opens and shows the active configuration in the **Basic** and **Advanced** tabs of the dialog window. Note that the default parameters are species dependent. The default parameters can be recalled anytime with the  button. To start the registration procedure select the **Match** action button.
- Calculations take a while. Then the result is shown in the **MATCHED** sub-page. The image and transformations can be saved with the **Save**  button in the toolbar to the right. To save only the transformation use the  **Transformation** button in the expanded control area at the bottom.
- Switch to the **Comparison** page and select the **Whole body layout** icon .



- Finally compare the results from your initial manual registration with the automatic registration result. To this end, configure as **A** the **SPECT FB** image series, and as **B** the **SPECT FB[Median]>MATCHED to CT FB masked**.
- Try to illustrate the difference by setting the isocontour level to 0.02 for both studies, and switch the contours radio box to **A**. Use the fusion slider to evaluate the alignment in different parts of the body, particularly the spine.



### 3. Maximum Intensity Projection: MIP

- On the **Comparison** page, activate the **MIP** action button. The program transfers the images and switches to the **MIP** main page. Per default, the reference image is arranged as series **A**, and the matched input images sequentially as series **B** and **C**. Make sure the color scale of the CT image in **A** is set to **Gray**. Configure **SPECT FB[Median]>MATCHED to CT FB masked** as the second image **B** and set its color scale to **Cold**. Adjust the color scale settings to emphasize the spine and the joints. Select the **<Empty>** entry for image **C** to avoid using a third image in the fusion. Enable projection of the coronal  plane. Set the **Fusion** blending type to **MAXIMAL** and enter a value of **0.8** for the **A|B** ratio. Select **Strong** for distance weighting and **36** projection **Angles**. To show all individual MIPs in combination with the fusion MIP configure the  **ABC+F** selection. Enable the **Interpolation** and the **Preview** checkboxes. Finally, start the calculation of the configured projections with the  **Run** button. Calculations take a while, then a rotation cine is started.

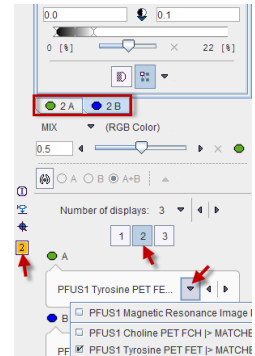


### 4. Automatic Registration of Multi-modal Brain Images without Interaction

In the following example, images acquired with three different PET tracers are registered to an anatomical MRI. For this brain tumor case, an unattended rigid matching workflow can successfully be applied. Note that for such a workflow the images have to reside in the database.








- Open the configuration of **Fuse It** with the  button in the lower left. In the **PFUSIT** tab, **default matching** should be set to **Rigid**, and **Species recognition** enabled. Consequently, default species-dependent parameters will be applied for the rigid matching procedure. If the same automatic matching method is applied in routine work, it is not necessary to select a particular method. In this case, **Selected** will be preferable as it will apply the last used method. Finally, select **Compare 3 rows** for the **Comparison layout**, confirm the settings with **OK** and restart **Fuse It**.
- On the **DB Load** page, select the **PFUS1** patient in the **Pmod** database and activate **Set as "Selected for loading"** to bring all four image series to the **Selected for loading** area. Start the default matching with the  button in the lateral taskbar. As PMOD's default is to use an anatomical series as the reference and apply rigid cross-modality matching, no further interaction is needed.

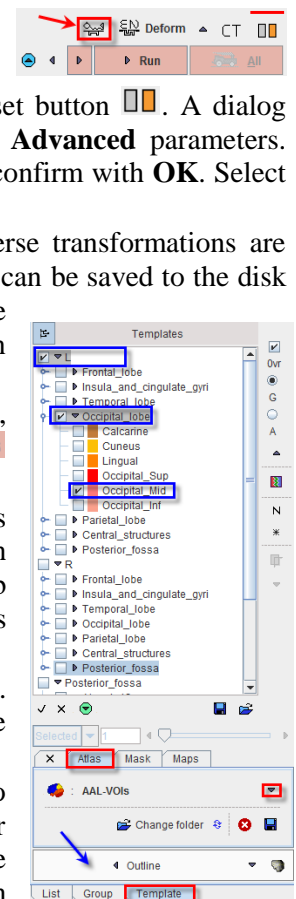
- The result is shown on the **Comparison** page in a 3 rows layout. Each row shows a fusion image generated from an **A** and a **B** series, whereby **B** plays the role of the reference per default. Therefore, the MR is initially set as **B** series for all rows. Note however, that color adjustments are only applied within a row, not across rows, even if the same image is shown.
- To adjust a row it has to be activated first either by clicking the number to the right of the image, or by selecting the row number in the button row below **Number of displays** as illustrated to the right. The number next to the selected row is highlighted in yellow (e.g. **2**), and the image control tabs are labeled accordingly (e.g. **2A** and **2B**). Any series can be selected for the **A** and **B** tabs using the corresponding selections.
- Set the matched **FDG**, Tyrosine (**FET**) and Choline (**FCH**) series as **1A**, **2A** and respectively **3A** images. Make sure to keep the MR series as **B** image and set its upper threshold value to 0.1 for all rows. Clearly, all registrations were successful, and all tracer uptakes have an exact anatomical correspondence.



## 5. Spatial Normalization of Brain Images, AAL VOIs

**Fuse It** includes MRI and PET brain templates for the stereotactic normalization. In this section the normalization of FDG brain images is illustrated.


- Start **Fuse It** from scratch to avoid mixing with already loaded data.
- On the **Matching INPUT** sub-page load the **FDG** series. The system detects that the data originate from a **HUMAN** and applies corresponding presets. Proceed to the next step activating the action button  for deformable matching. The program automatically switches to the **REFERENCE** sub-page.
- The deformable registration approach is mainly suited for the stereotactic normalization of brain images to modality-specific template images. To select the template activate the  button below the **REF Load** section and select **PET** from the list of normalization templates. The template with coordinates in MNI space (the same as in SPM8) is loaded into the **REF** area with radiological orientation (**Head First Supine**).
- Check that the proper species is selected (**HUMAN**) and the registration method is set to **Deform**. The horizontal red bar indicates the active preset. To edit the matching parameters activate the cross-modality preset button . A dialog window opens and shows the current configuration for the **Basic** and **Advanced** parameters. Activate  to ensure that the default parameters are applied and confirm with **OK**. Select the **Run** action button to start the matching procedure.
- The result is shown in the **MATCHED** sub-page. The direct and inverse transformations are accessible in the expanded control area at the bottom. The transformation can be saved to the disk for later use with the  **Transformation** button. For instance, it could be applied to another study of the same patient which has already been registered to the FDG series (eg. the FET or the FCH series).
- As the normalized patient images are now in the standard MNI space, standard VOIs can be applied for the statistical analysis. Use the  **VOIs** action button to enter the VOI analysis dialog window.
- The **AAL** data set is a label image file which assigns the individual pixels in the MNI space to a set of pre-defined standard VOIs. This definition can be loaded as follows: To the right, in the VOIs list, select the **Template** tab instead of **List** and then the **Atlas** sub-tab. Switch it to **AAL-VOIs** as illustrated to the right.
- Now, the VOIs are overlayed in the images as grids of different colors. Use the statistics button  to calculate the average VOI values of the standard VOIs.
- You may note that the VOIs do not seem to suit perfectly to the data. To create an adjusted VOI of a structure of interest select only that particular element in the tree of AAL VOIs, eg the **Occipital\_Mid** structure of the **Occipital\_lobe** in the left hemisphere **L**. Now only **Occipital\_Mid** is an overlay in the image. Activate the **Outline** button. A contour VOI **Occipital\_Mid\_1\_o** is created

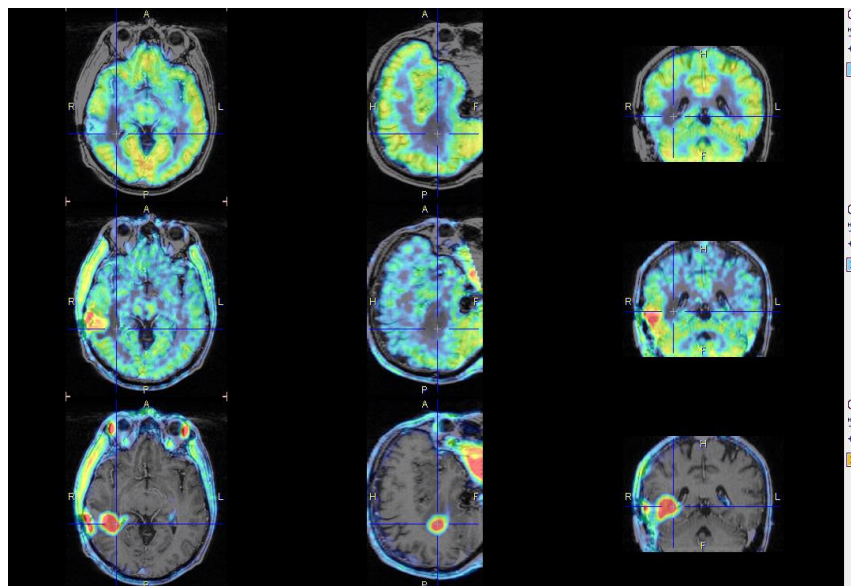




which encloses all pixels of the standard VOI, and the layout is switched back to **List**. Perform **Statistics** and compare the results of the AAL label VOI and the outline VOI: they should be identical. The advantage of the created outline VOI is that it can be adjusted to the individual brain by scaling, deformations, addition or removal of voxels, and then saved.

## 6. Results Saving and Documentation

- As described above, the results can be saved by storing the transformation and/or the registered images to disk. An alternative to explicit saving is to save the definition of the current layout with the **Save Protocol** button in the status line. Save your current fusion layout, quit **Fuse It**, start it again and retrieve the layout using **Load Protocol** to restore the layout at the time of saving the protocol. Note, however, that protocols don't restore calculated images.
- The "report" button  in the status line allows printing or saving a report. First configure the fusion layout suitably. For example, the result of the automatic registration of the PFUS1 series without interaction is shown below as a 3 row layout on the **Comparison** page.



### Further Data Examples for Practicing

- PFUS2:**  $^{99m}\text{Tc}$ -tetrofosmin SPECT and  $^{13}\text{N}$ - $\text{NH}_3$  PET heart images (SPECT Heart & NH3 Heart).
- PFUS3:** Dynamic FDG Brain PET scan (FDG Brain) for testing **motion correction**.
- PFUS4:** MRI and SPM contrast maps for trying the MIP.

## Section 5: P3D Tool – 3D Rendering

### Topics:

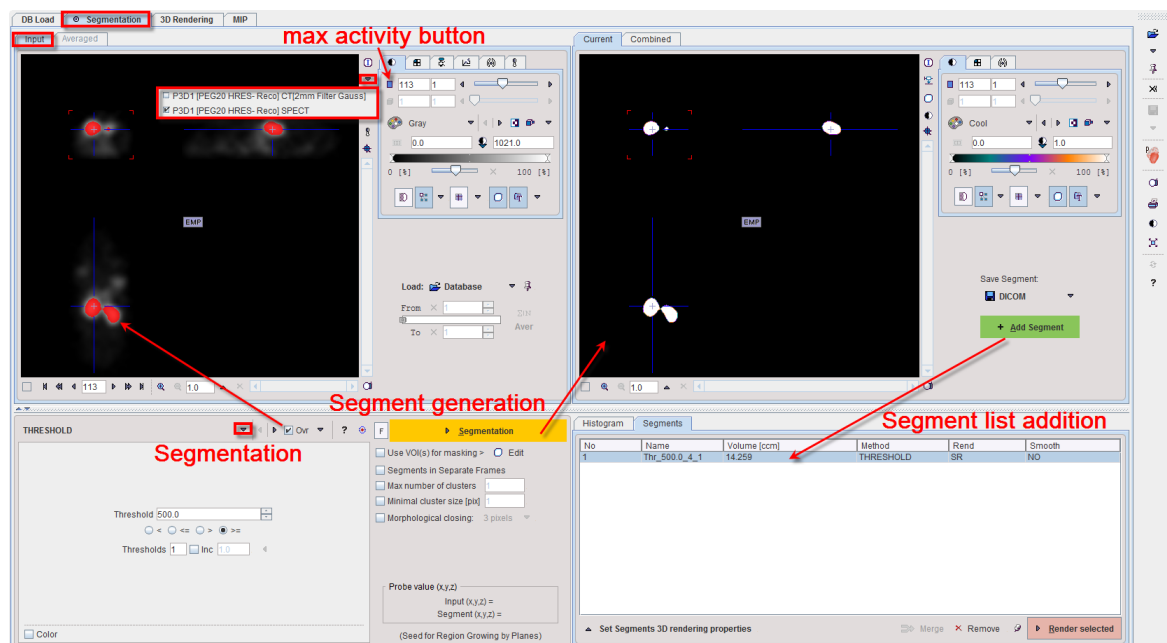
- Segmentation by thresholding and region growing.
- Rendering properties.
- Object rendering.
- Exploration of the virtual scene.

### Exercises:

#### 1. Segmentation

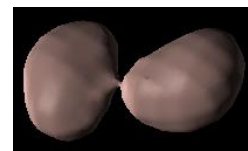
Surface rendering (SR) is based on the segmentation (edge definition) of an object. The surface of the object is then constructed using the marching cubes algorithm and rendered in various styles.



- Start **P3D**. On the **DB Load** page load the **SPECT** and **CT** series of patient **P3D1**. The loading order is not important. The program automatically switches to the **Segmentation** page. The input images are shown in the upper left panel.

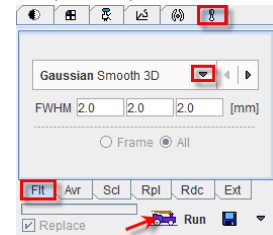


In the **Input** panel switch the actual series to **SPECT** using the series selection. Select as active plane the coronal view. To find the slice with **maximal activity** use the button next to the current slice number **113**. You should arrive at slice **113**.

- The segmentation method is configured in the lower left by a selection list. Define a threshold-based segmentation by setting the method selection to **THRESHOLD**. To see an indication of the pixels which will be included in the segment check the **Ovr** (Overlay) box as illustrated above. The color of the overlay is dependent on the color scale. Change the threshold value to see how the segmentation changes. Finally, set the threshold value to **500**.
- Initiate the actual segmentation with the **Segmentation** button. The result is shown as a binary image in the **Current** tab to the right. Activate the **Add Segment** button to enter the **Current** segment into the **Segments** list. The **No** entry in the **Segments** list indicates the number by which a segment is identified in the **Combined** image, **Name** provides some descriptive information, **Volume** its physical volume, and **Method** identifies the applied segmentation method. Each segment in the list has its own property. By default, all segments are set to be rendered as Surface Rendering objects.
- Start object generation by activating the **Render selected** button. The rendering is performed and the program switches to the **3D Rendering** page. Two connected spheroids appear in the scene. Try manipulating the scene by dragging the mouse buttons in the scene area.

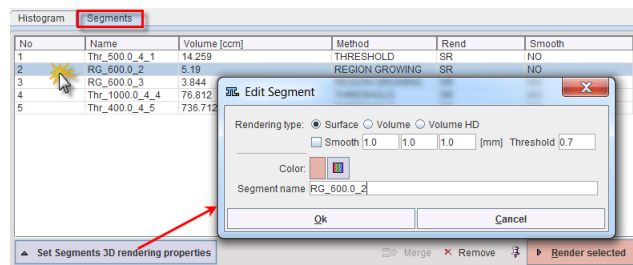


- To get two independent objects for the kidneys switch back to the **Segmentation** page. Set the segmentation method to **REGION GROWING**, and the threshold value to **600**, with the  $\geq$  criterion selected. Go to slice **103**, click into the center of the hot area to the right, then activate the **Segmentation** button. The result is displayed as a binary image in the **Current** tab to the right, overwriting any existing content. Append the **Current** segment to the **Segments** list with the **Add segment** button.
- To get the second kidney segment, in the **Input** panel, click into the center of the left hot area. Activate the **Segmentation** button and **Add segment** to the **Segments** list.
- The next step is to construct a skeletal object from the CT image. In the **Input** panel select the **CT** image. Note that the segment definition switches to the default **THRESHOLD** setting. This happens because each input data set maintains its own segmentation definition. Since the images are quite dark, adjust the colors. As you may notice, the images are relatively noisy. Therefore, before starting the segmentation, we will create a smoothed CT data set.
- To determine an appropriate smoothing kernel use the “Study Information” button  to find out the pixel dimension (1x1x1mm). Select the “tools” tab , then the **Flt** sub-tab, and enter 2mm as the FWHM of the **Gaussian Smooth 3D**. Activate **Run**. A new smoothed CT series is calculated, replacing the original in the series list.
- For the **Input** image lower the upper image threshold and go to slice **136** where the ribs are visible. In the **THRESHOLD** segmentation area try finding a threshold so that primarily the ribs will be included in the segment, for example **1000**. Activate the **Segmentation** button and **Add segment** to the **Segments** list.
- Go back to the **Input** panel for creating a new object of the entire body based on the smoothed **CT[Gauss]** series. Lower the threshold value of the **THRESHOLD** segmentation to **400**. As indicated by the segment overlay, the background pixels will be removed, and practically all body pixels will be included in the segment. Activate the **Segmentation** button and **Add segment** to the **Segments** list.





## 2. Rendering Properties

- Each entry in the **Segments** list has its own rendering properties which can easily be changed. To do so, select the first kidney **RG\_600** entry in the list and activate the **Set Segments 3D rendering properties** button as indicated in the capture to the right. A dialog window opens allowing editing. Set the **Rendering type** to **Surface** and its **Color** to red. Confirm settings with the **OK** button. Do the same with the second kidney object **RG\_600** with a yellow **Color**.
- In the **Segments** list double click the **Thr\_1000** entry representing the skeleton. In the **Edit Segment** dialog enable the **Surface** radio button and choose a light gray as **Color**.
- Finally, edit the rendering properties for the **Thr\_400** object representing the whole body of the mouse. Set the **Rendering type** to **Volume** and the **Color** table to **HeartVR**.



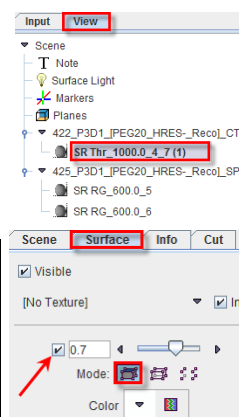
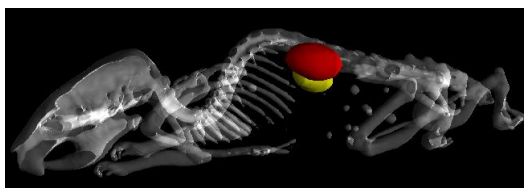
## 3. Object Rendering

### Surface Rendering (SR)

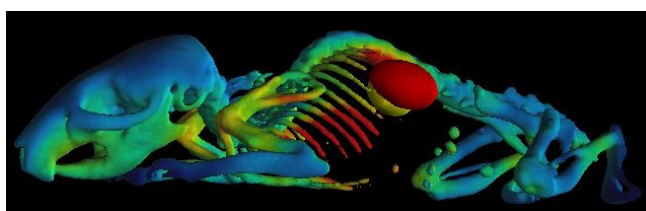
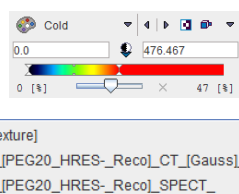
- Rendering of the segments in the list is selective. In the **Segments** list select the two **RG\_600** entries representing the kidneys. To begin rendering activate the **Render selected** button. As long as the "Append" pushpin  is not active, the 3D scene is cleared before each rendering. The program automatically switches to the **3D Rendering** page. The scene now shows two disconnected objects (red and yellow) representing the two mouse kidneys.
- The next step is to append the skeletal object from the CT image. Switch back to the **Segmentation** page tab and select the **Thr\_1000** entry in the **Segments** list. Before rendering, set the pushpin to the “append”  mode to avoid removing the already existing objects. Activate the

**Render selected** button. The scene now shows 3 surface rendered objects, the left and right kidneys and the skeleton.

- Use the **Zoom** slider on the **Scene** tab to enlarge the scene, and try rotating the scene by dragging the left mouse button in the scene area.
- Go to the **View** tab to change the appearance of the objects. In the object tree select the object **SR Thr\_1000** representing the skeleton.
- To see the inner structures of the skull make the skeleton transparent. Check the box for “blended” transparency as illustrated to the right. The transparency slider allows adjusting the degree of transparency. Note the difference when unchecking the box. Transparency is then set to “screen door” mode with an initial transparency of 0.7. Move the slider and observe the change in transparency which is created by punching holes into the surfaces. Finally set the transparency value back to 0 for getting an **opaque** surface.

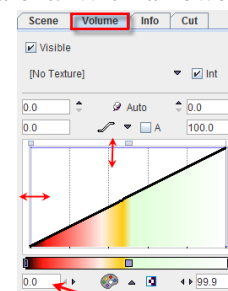
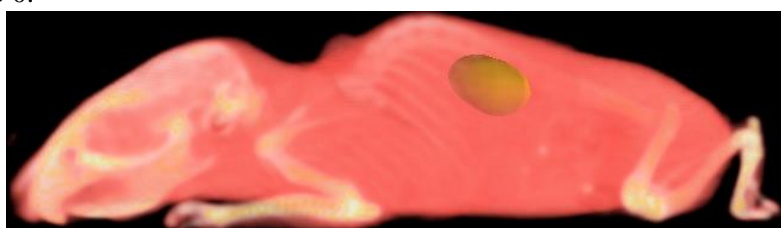


- Next we will add a texture color representing the SPECT uptake value to the skeleton surface. Select the **Input** tab and apply a color table different from **Gray** such as **Cold** to the SPECT series. Switch back to **View**, and highlight the skeleton object **SR Thr\_1000** in the tree. In the **Surface** properties area use the arrow to switch the texture from **[No Texture]** to the **SPECT** study as illustrated to the right.
- Initially, the colors applied to the skeleton are probably very dark because of the low uptake in the bone areas. The colors are adjusted as follows: switch back to the **Input** tab and decrease the upper threshold. This change is immediately reflected in the texture color of the skeleton.




### Volume Rendering (VR)

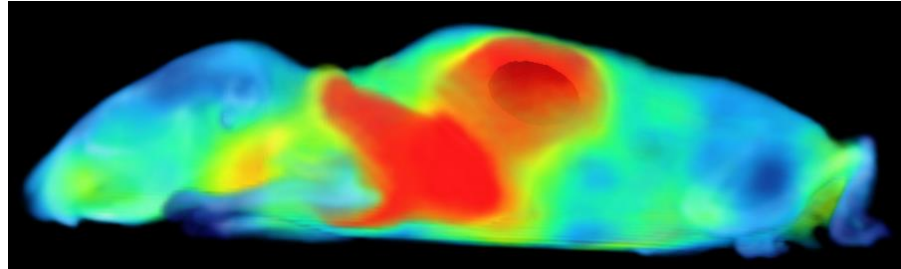
- Next we will add the VR object of the whole body mouse CT scan to the existing scene of SR objects. As a consequence the blended transparency will not be available any more, only screen-door transparency (punched holes).
- Switch back to the **Segmentation** page and select the **Thr\_400** entry in the **Segments** list.
- Make sure the “append” pushpin button is still fixed and activate **Render selected** button. Immediately, the rendering is performed and a VR object with defined properties is added to the scene.
- On the **View** tab, in the tree, select the skeleton object **SR Thr\_1000**, and remove the **Visible** check in the **Surface** panel.
- The scene should now show the mouse with a white skeleton and semi-transparent red body mass. Make sure the **A** (absolute values) box is not checked, meaning that the opacity profile and the colors are defined in percent of the value range. The lower part of the value range can be removed by changing the lower threshold of the profile range. Enter a value of **5%** into the lower left number field and refresh. The body is still visible, but seems more transparent. With a lower threshold value of **10%**, only the skeleton remains. Finally set the lower threshold to 0.






- A nice effect can be obtained by adding the SPECT color to the VR object: Select the **VR Thr\_400** object in the tree. In the **Volume** tab switch from **[No Texture]** to the **SPECT** series.
- Note the  button which has appeared in the taskbar. This indicates that a scene “refresh” is required. As such a refresh can be quite time-consuming for VR objects, the users have to initiate refreshing after they have completed all desired property changes. Perform a refresh. The scene

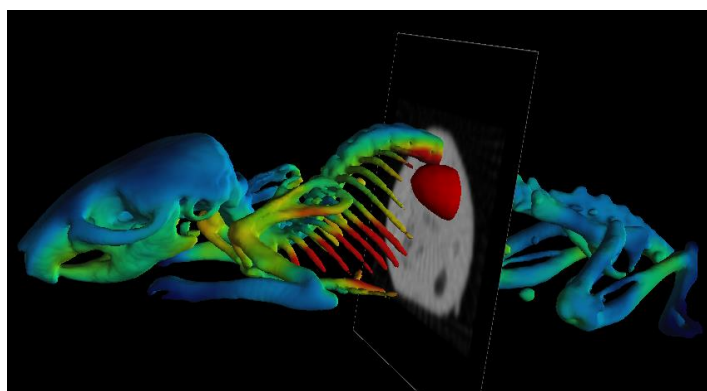
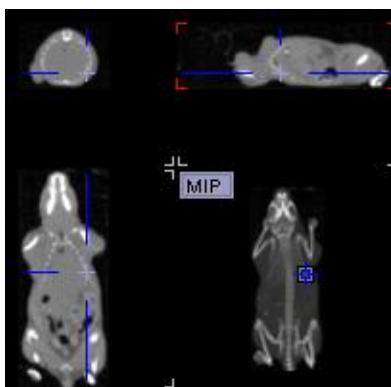
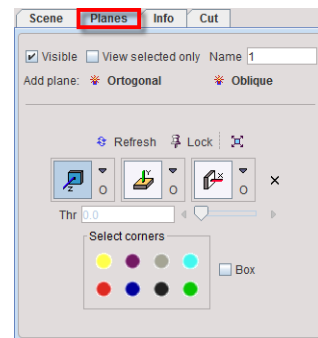
now shows a semi-transparent mouse in which the SPECT tracer distribution is nicely seen. Note also the SR objects of the kidneys in the inner of the mouse.



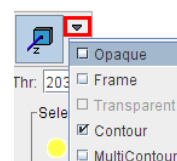
#### 4. Virtual Scene Exploration

Besides changing the object properties, the scene can be enhanced by adding image planes, and by removing obstructing parts. Furthermore, cines of rotating objects can be created and saved as Quicktime or DICOM movies.

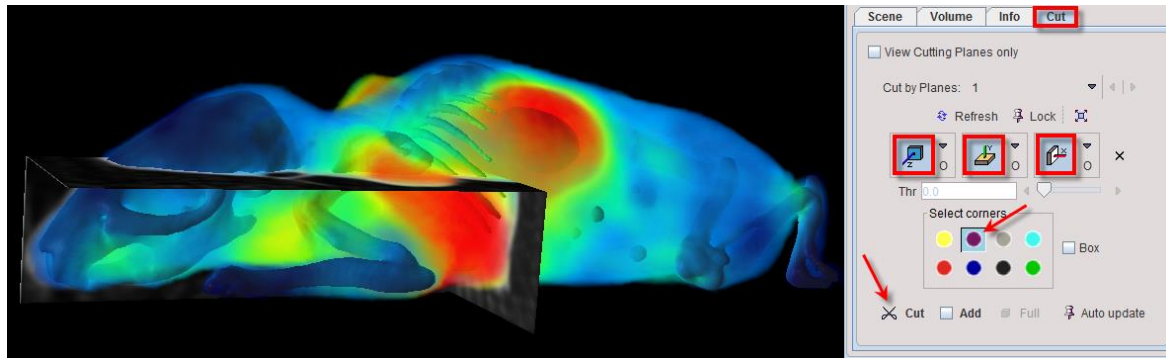
- Hide the VR object from the scene by removing the **Visible** check of **VR Thr\_400**. Instead, show the skeleton SR object by enabling the **Visible** check of **SR Thr\_1000**.
- Select the **Planes** object in the **Scene** tree, then **Add plane** activating the **Orthogonal** button. Use the **Z**, **Y**, **X** buttons to switch on/off the axial plane images. The **Input** tab allows defining whether the plane images originate from the **CT** or **SPECT** series. In the case illustrated below the **Input CT** images are shown, namely the smoothed CT images. To change the slice position, in the **Input** tab, scroll through the slices, or even start a movie running through the axial slices. Changes applied to the presentation of the **Input** images are also immediately reflected in the scene.
- Try also the “navigator” tool for quickly triangulating the planes. It is particularly useful if orthogonal planes are shown in the scene. The navigator is started using the  button in the taskbar. It also has a list selection to define which series is shown.




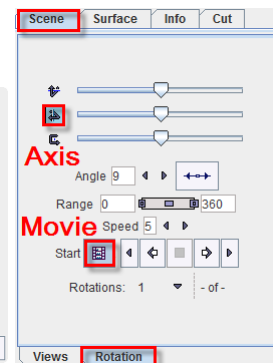
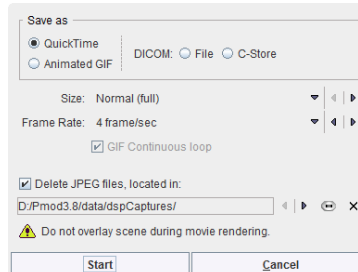
- The planes can be rendered in different styles, which can be selected from the list to the right of the plane buttons. **Opaque** planes are shown in the example above. **Transparent** would not obstruct the view, but is not applicable if a VR object has been rendered. **Contour** allows suppressing image information below a threshold defined with the **Thr** slider. Only the biggest connected area will be shown. In contrast, **MultiContour** shows all area above the threshold.



- The planes can also be used for defining octants to cut information from objects. Select the **VR Thr\_400** VR object in the tree and show it again with the **Visible** check. Then select the **Cut** tab and enable the **Box** check. With the navigator position the planes appropriately, define one or more cutting octants by selecting the corresponding color circles in the **Select corners** area. Finally activate the **Cut** button. The scene is updated accordingly. To cut the same quadrant(s) from other objects **Lock** the planes position, select another object from the tree, and cut in the same way as described above. Alternatively, multiple objects can be selected at the same time in the tree and cut in a single operation.



- In addition to the interactive manipulation of the scene, cines are attractive for getting an overview of the situation, or for creating movies. To start a cine, select the **Rotation** sub-tab on the **Scene** pane, and with the angle sliders find suitable initial angles. Define the rotation axis and start the cine with the **Axis** or **Movie** button. Note that you can change the rotation smoothness (**Angle**) and the rotation **Speed** during animation. It is also possible to intervene interactively during the animation directly with the mouse button in the scene. Rotation will always continue.
- To save a rotating cine as a movie to disk, enable the “movie” button  before starting the cine. In this case a dialog window pops up for defining the movie quality, a saving directory for the temporary files, and the final output format. After starting, a configured number of rotations are performed and all calculated images saved to disk in JPEG format. Finally the images are combined into the prescribed movie file.



## Section 6: Database Management


### Topics:

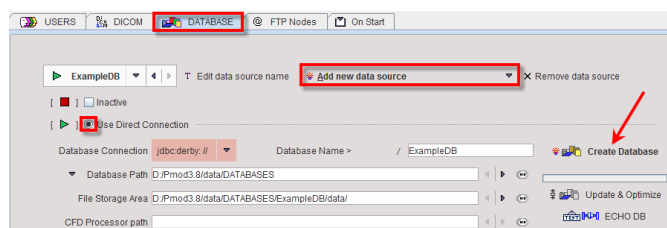
- Creation of a new database.
- Exchange of data between databases.
- Export of Data from a database.

### Exercises:


#### 1. Database Creation and Data Migration

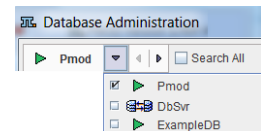
The PMOD software includes the ability to organize all types of data in one or several databases. After installation, a single database called **Pmod** is available which contains the training data sets. In the following a new database is created and some data sets “migrated” between the two databases.

- Select the  **Config** button from the PMOD “ToolBox”. In the appearing **Users configuration** window select the **DATABASE** tab. Activate the button **Add new data source** and enter the **ExampleDB** as its name. Make sure the **Use JDBC connection** button is selected to use the embedded Java database. Defaults are used to fill the entries defining the path for the database files (**Database Path**) and the actual data files (**File Storage Area Path**). Activate **Create Database** to create the database tables. A confirmation message appears stating that the database creation was successful.



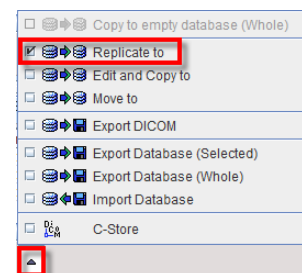
- The **ExampleDB** is now shown as the visible entry in the data sources list. This means that **ExampleDB** will serve as the default database. To avoid this behavior as long as it is an empty database set the list entry back to **Pmod**.
- PMOD requires a restart to use the new **ExampleDB**. Quit the **Users Configuration** with **Ok**. In **Save Configuration** dialog window enable **Quit Pmod to restart** checkbox and confirm the setting with **Save and Quit** button. Start again PMOD.

- Using  **Config** as above and select the **DATABASE** tab. For data migration start the **Database Administration** functionality with the button in the lower left. The appearing window is similar to the window used for image data loading. To migrate data from **Pmod** to **ExampleDB** make sure the **Pmod** database is selected as illustrated to the right.



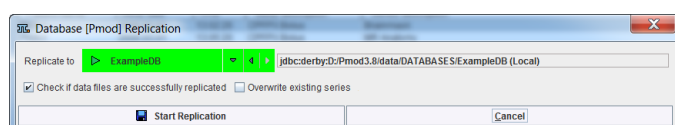
- To migrate patient PKIN1 (ie copy all of its data) to the new database select **PKIN1** in the **Patients** list and activate **Set as “Selected for Loading”**. If this button cannot be selected because it is gray, first activate the tab **Selected for: replication / export ...** to make it active. The “Add All” operation brings all image series together with all attached data such as VOIs, kinetic modeling files, blood files, into the transport area.
- Below the list of selected files there is a configuration button to specify the operation to be done. Select **Replicate to** as illustrated to the right.

- A **Database Replication** window appears. Set the **Replicate to** database to the new **ExampleDB** database and begin data duplication by the **Replicate to** button. At the end of the operation a confirmation appears that the replication was successful, so both DBs contain identical data.



- Instead of a replication it is also possible to move the data from one database to the other with the **Move to** operation. In this case, the original data will be removed after replication has succeeded.

- Close the **Database Administration** and the **Users Configuration** window.



## 2. Data Export from a Database

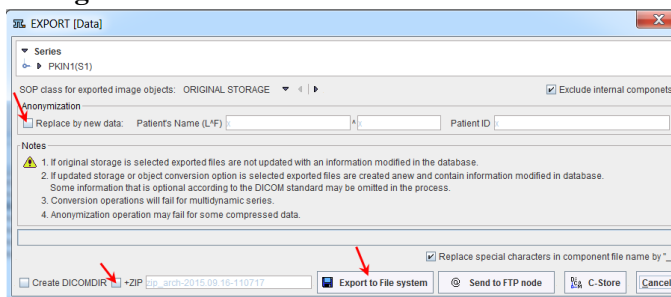
Sometimes there is a need to export data from a database to process it in a different program. Data export can be done from within the **Database Administration** window, but there is also an export facility in all the windows where data can be loaded from or saved to a database. The example below illustrates how blood files and image files belonging to patient PKIN1 are exported.

- Start the **PBAS** tool with the **View** button of the ToolBox. On the **DB Load** page switch the database selection to the new **ExampleDB** database which only lists the replicated patient **PKIN1** with its 6 image series.

- In the **Series** list select the **Dynamic PET** series. This series has several different types of data attached as components which can be seen in a list if you select the **Components Administration** tab instead of the default **Selected for loading**. To

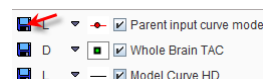
Series ID	Modified	Name	Type
8	2012-09-21 14:59:29.748	CFFPX Bolus WholeBrain	voi
8	2012-09-21 14:58:32.666	CFFPX Bolus 33 VOIs	voi
8	2012-08-17 15:55:18.243	CFFPX Bolus 13 VOIs	voi
8	2012-07-27 12:10:26.089	Authentic CFFPX in Plasma	crv
8	2012-07-27 12:09:35.152	Total CFFPX in blood	crv
8	2012-07-27 11:38:05.688	image_1	image

selectively export the plasma activity select the **Authentic CFFPX in plasma** component in the list as illustrated to the right and then the **Export** button. An **EXPORT** dialog box appears. For image data is possible to anonymize the data by enabling the **Replace by new data** and specifying different name and ID strings. Remove the **+ZIP** flag to avoid the creation of a zip archive, and then activate the **Export to File system** button. With the appearing dialog box navigate to the destination directory (**Set Storage Area new directory** in this example) and then activate **Select**. The data is exported into a directory structure within **Export** as illustrated above right. At the top of the export structure is the patient name **PKIN1(S1)**. Since the blood data is a curve, it can be found in its **CRV** subdirectory. Open the file in a text editor or MS Excel to see how the data is organized.

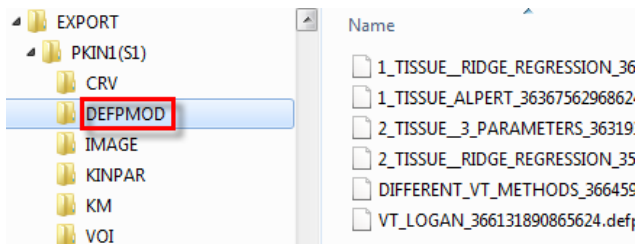


- Note that curves can be saved into the database from the curve control area. In PKIN for instance, you can save the input curve to the database by the **Save** button left to the **Parent input curve model**.

- Let's continue with the export of the dynamic PET images. Select the **image\_1** component in the **Components Administration** tab and repeat the export procedure described above with the same export directory. The image file ends up in a new subdirectory **IMAGE**. You can now read it from any program which is able to import DICOM data.



- There is an alternative to exporting individual components. All data attached to the **Dynamic PET** series can be exported in a single operation from the **Selected for loading** tab. Select **Dynamic PET** and start the **Export** function from the **Selected for loading** tab to the same export directory. This operation creates some additional subdirectories, one for each component type. The different protocols for PXMOD can be found in **DEFPMOD** as illustrated to the right, the PKIN kinetic modeling files in **KM**, and the VOI definitions in **VOI**.



- Note that images received by the DICOM server are saved in original form into the database. The database export function returns these original objects. This is in contrast to the approach of loading the images from that database and then saving to an export directory. In that case new objects are created and a part of the original information (e.g. the private fields of the manufacturers) may be lost. Therefore, the database export is strongly recommended for image data.



## **Appendix 1: Short Description of Data Sets**

- **PKIN1:** Dynamic  $^{18}\text{F}$ -CPFPX PET data (90 minutes) using bolus injection, with blood data, and matched MR images. CPFPX is a ligand for assessing the  $A_1$  adenosine receptor in the human brain. There is no tissue without specific binding sites, so reference tissue methods are *not* possible. A two-tissue compartment model is needed for describing the CPFPX kinetics.
- **PKIN2:** Dynamic  $^{11}\text{C}$ -DASB PET data and MRI images of the same patient (not matched). Blood data is not available. DASB is a ligand for assessing the serotonin transporter (SERT) in the human brain. The cerebellum can be used as a reference region because there are only few SERT binding sites. The DASB kinetics can be described by a single-tissue compartment model so that the simplified reference tissue model can be applied.
- **PKIN3:** Dynamic FDG brain PET data using bolus injection with whole blood data. The data set can be used for testing the pixel-wise Patlak plot.
- **PKIN4:** Dynamic  $\text{H}_2^{15}\text{O}$  brain PET data at rest, with externally sampled blood data. This example illustrates the usage of delay and dispersion correction which is relevant for online-sampled blood data where the bolus is delayed and dispersed in the blood-drawing catheters.
- **PKIN5:** This patient just contains a single kinetic modeling file for testing the metabolite correction function in the PKIN tool.
- **PFUS1:** Static FDG, FET and FCH Brain PET images as well as a MR image. The images are not matched. They can be used for testing the rigid matching method with different dissimilarity measures, as well as the pixel-wise scatter plots.
- **PFUS2:** Static  $^{99\text{m}}\text{Tc}$ -tetrofosmin SPECT and  $^{13}\text{N}$ - $\text{NH}_3$  PET heart images. This is an example for the application of matching with heart data.
- **PFUS3:** Dynamic FDG Brain PET data with markers for testing the motion correction in the FuseIt tool. This is a data set where motion has been synthetically generated.
- **PFUS4:** MRI and SPM contrast maps for trying the MIP in the FuseIt tool.
- **PFUS5:** CT and SPECT images for testing the rigid matching whole body mouse and the MIP in the FuseIt tool.
- **P3D1:** Matched CT and SPECT images of a hybrid mouse scan for testing the 3D rendering tool. Several rendering protocols are available for demonstration purposes.
- **P3D2:** Matched human CT and SPECT images of the heart. The CT data has been edited to remove the bone parts of the thorax which would be disturbing in the volume rendering.
- **PALZ1:** Highly abnormal FDG scan of an Alzheimer's patient for testing the PALZ tool.
- **PCARD1:** Dynamic images from ammonia heart scans at rest and at pharmacological stress of a patient with reduced perfusion reserve due to unclear origin. This data can be used to test the cardiac kinetic modeling tool PCARD.
- **PCARD2:** Dynamic images from rubidium heart scans at rest and at pharmacological stress of a healthy volunteer. This data can be used to test the cardiac kinetic modeling tool PCARD.
- **PCARD3:** Dynamic images from water heart scans under pharmacological stress of a healthy volunteer. The matched CT scan is provided to be used in lung VOI definition. This data can be used to test the cardiac kinetic modeling tool PCARD.
- **Example Brainnorm:** The images (normalization template, mean, standard deviation, mask) of this pseudo-patient constitute an example FDG normal database. This database can be used as an example in the PMOD BrainDB tool. For instance, the FDG images of patient PFUS1 can be compared against this norm.
- **Dosimetry Example:** Dynamic whole body PET merged and decay corrected from an  $^{18}\text{F}$  labeled tracer. This data can be used to test the residence time calculation as implemented in PKIN.
- **DTI Example:** DWI MR data can be used in PXMOM for the calculation of various diffusion-related parametric maps. The results are not only various types of diffusion maps, but also diffusion tensors which can subsequently be used for tractography in PGEM.
- **4D Flow Example:** Dynamic flow and magnitude images generated by 4D Flow MRI acquisition. This data can be used in PGEM to calculate streamlines at every acquisition time. The change of the flow pattern over time can be visualized as a movie.

## Appendix 2: Using Keyboard Shortcuts in PMOD

### Image-Related Shortcuts

Many of the viewing functions can be activated and are much faster to use by keyboard shortcuts. To direct the keyboard shortcuts to the right images it is essential that they are active. Clicking into an image activates it. To avoid reslicing in the orthogonal viewing mode, please hold down the **Ctrl** key when clicking. In configurations with several viewports it is the image port focus which indicates to which of them the shortcut action is directed to.

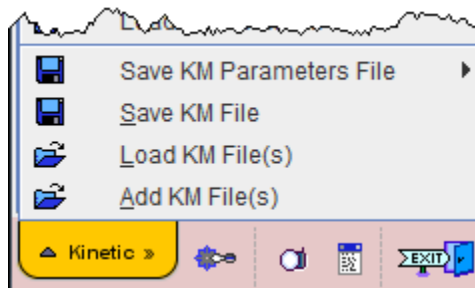
LIST of KEYBOARD SHORTCUTS: page 1 of 3			( Focus in the viewport required )	×
Type	Shortcut	Effect / Test		
Data Loading:	<SHIFT + L>	Load image data		
	<SHIFT + Q>	Close the currently displayed study		
	<Alt + Mouse_Wheel>, <Ctrl + N>	Display next study		
	<Alt + Mouse_Wheel>, <Ctrl + P>	Display previous study		
Layouts:	<CTRL + X,Y,Z>	Switch to x,y,z-planes (f.e.: <Ctrl+X> = x-plane (sagittal))		
	<CTRL + D>	Switch to orthogonal views		
	<CTRL + />	Switch to next orthogonal plane		
	<CTRL + 1 .. 9>	N x M image display (f.e.: <Ctrl+2> = 2 x 2)		
	<CTRL + Click>	Switch 1 x 1 and N x M image display		
Reslicing:	<Ctrl+ R>	Enable / disable the oblique image reslicing handles		
Slice selection:	<Page Up,Down>	Replace the display by the previous / next page of slices (f.e.: <Up> previous page of slices)		
	<Arrows>	Increment / decrement the currently shown slices by one (f.e.: <Right> next slice)		
	<Home,End>	Go to first / last slice (f.e.: <Home> first slice)		
	<SHIFT + Page Up,Down>	Show the same slices at previous / next page of acquisition times (f.e.: <SHIFT + Up> previous page of frames)		
	<SHIFT + Arrows>	Show the same slices at incremented / decremented acquisition times (f.e.: <SHIFT + Right> next frame)		
	<SHIFT + Home,End>	For a dynamic study, go to first / last acquisition (f.e.: <SHIFT + Home> first frame)		
	<Mouse_Wheel>, <CTRL + Drag>	Scroll through the slices in a movie mode fashion		
	<CTRL + M>	Start / Stop movie		

LIST of KEYBOARD SHORTCUTS: page 2 of 3			( Focus in the viewport required )	×
Type	Shortcut	Effect / Test		
Zoom:	<CTRL + Mouse_Wheel,+,->	Zoom in / out (f.e.: <CTRL + "+"> Zoom in)		
Color Table Manipulation:	<SHIFT + Drag>	Modify color table thresholds: horizontal: left = decrease, right = increase lower threshold vertical: down = decrease, up = increase upper threshold		
	<CTRL + T>	Invert color map		
	<F1>	Switch to next color map		
	<CTRL + F1>	Switch to previous color map		
	<CTRL + S>	Apply the color table thresholds for each slice individually (slice)		
	<CTRL + G>	Apply common color table thresholds over all slices of individual time (frame)		
	<CTRL + A>	Apply common color table thresholds over all slices of all times (study)		
	<CTRL + F>	Allows for entering absolute values for the upper and lower color table thresholds (fixed)		
Contour Overlay:	<CTRL + C>	Enable / Disable showing the contour with currently defined threshold in the overlay		
Volume Rendering:	<CTRL + V>	Enable / Disable the volume rendering display		
		(Note that the layout is switched accordingly, as a n*m layout is not reasonable for a volume rendered display)		
Reporting:	<CTRL + I>	Print image report		
	<CTRL + E>	Capture Display		
	<CTRL + O>	Scientific Output		

LIST of KEYBOARD SHORTCUTS: page 3 of 3			( Global )	X
Type	Shortcut	Effect / Test		
Screen Capture:	<CTRL + SHIFT + P>	Capture Full Screen to the Console buffer		
Save Data:	<SHIFT + S>	Save image data		
Keyboard shortcuts help:	<CTRL + SHIFT + H>	<a href="#">View this window. Test buttons disabled.</a>		
R console	<CTRL + SHIFT + R>	Open R console if not disabled by user settings		
Application:	<CTRL + SHIFT + K>	Kinetic Module		
	<CTRL + SHIFT + X>	PXMod Module		
	<CTRL + SHIFT + V>	View Module		
	<CTRL + SHIFT + I>	Fuse It Module		
	<CTRL + SHIFT + S>	Segment Module		
	<CTRL + SHIFT + D>	3D Module		
	<CTRL + SHIFT + C>	Cardiac PET Module		
	<CTRL + SHIFT + M>	Card CT/MR Module		
	<CTRL + SHIFT + L>	Anatomy Module		
	<CTRL + SHIFT + A>	Alzheimer Module		
	<CTRL + SHIFT + N>	Neuro Module		

## Button- and Menu-Related Shortcuts

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



## Dialog Window Default Action

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