

User's Guide

PMOD Base Functionality (PBAS)

Version 3.8



PMOD Technologies

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PMOD Base Functionality Introduction

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

- » Loading medical images in different formats, including DICOM.
- » Viewing the images with different color tables and in different layouts.
- » Calculating new slice images in arbitrary new orientations.
- » Performing various image processing and manipulation operations.
- » Displaying fusion images of matched data sets (image registration is a separate option).
- » Performing volume-of-interest analyses and the calculation of time-activity curves from dynamic studies.
- » Saving images in different formats, including DICOM, and directly C-STORE them to a DICOM server.
- » Statistics of population outcomes via a console interface to R.

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

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

For getting started with PMOD we recommend the following approach:

- 1) Browse this document as it gives the foundation for all other PMOD tools.
- 2) Browse the **PMOD User's Guides** of the other PMOD tools you are interested in.
- 3) Perform some practical exercises based on the example data provided with the installation and the step-by-step descriptions in the **PMOD Workbook**.
- 4) Attend one of the proven bi-annual **PMOD Trainings** which are announced on **PMOD's website** <http://www.pmod.com>.

For in-depth understanding of PET Kinetic Modeling we strongly recommend the PMOD users to attend one of the excellent yearly *PET Pharmacokinetics Courses*. These courses include theory as well as practical work and are organized by the top experts in the domain. The 2017 course is likely scheduled March 30 - April 1, 2017, in Berlin, prior to the *BrainPET* <http://www.brain2017.net/> Meeting. Two other worthwhile courses are *PET Methodology* (King's College London) and *Basic Kinetic Modeling in Molecular Imaging* (Copenhagen). An additional source of valuable information is the *data analysis website* <http://www.turkupetcentre.net/petanalysis/index.htm> of the Turku PET Centre.

Chapter 1

PMOD Basics

In This Chapter

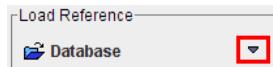
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Basic User Interface Elements

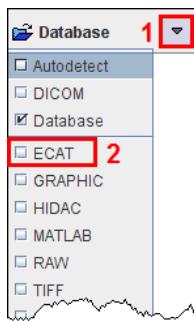
For efficient use of the PMOD programs it will be helpful being aware of the behavior of some user interface elements.

Option Buttons

Frequently used are option buttons. Their appearance is a button with an arrow next to it, for instance the loading button of image data



The arrow indicates that there is a selection. As soon as it is activated with the left mouse button, the different options appear as a list.



Select the appropriate option with the left mouse button, for example ECAT in the example above. The list closes, the button changes to the new option,



and the button operation is executed.

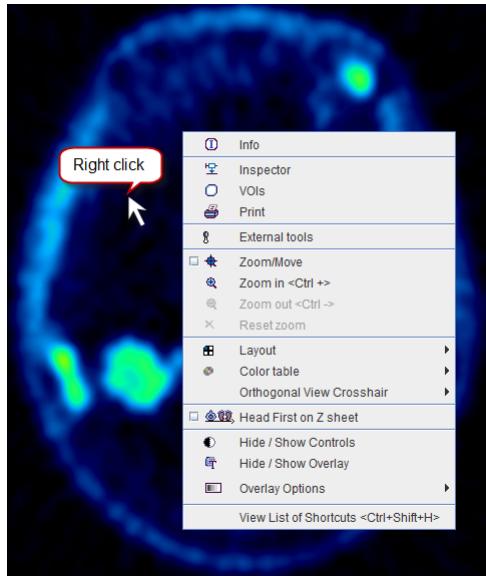
Option buttons allow organizing related functionality with minimal space requirements, but the hidden functionality might be overlooked. Therefore it is worthwhile to initially check the hidden list wherever you see a .

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



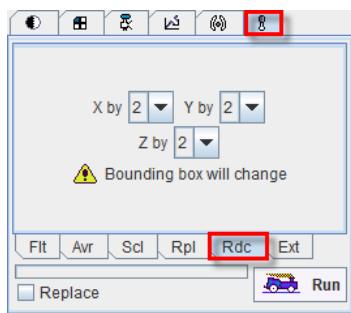
Context Menus

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



Tabbed Panes

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



Lists

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

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

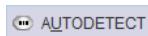
Toolips

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



Data Loading, Example Data, Relative Paths

As long as the database functionality is enabled, loading components such as VOIs will always first bring up the database loading interface. If your data resides outside the database, use the button



to start a file-based loader which can be pointed to a particular directory. In some situations the button is abbreviated to .

In case the user decided to install the example data with PMOD (recommended), there is a database **Pmod** available which contains examples for kinetic modeling (PKIN and PXMOD), cardiac modeling (PCARD) and image fusion (PFUS). This data is installed in a sub-directory data of the PMOD installation directory. The configuration of the database shows the paths



The leading part of the path ./ indicates a path which is relative to the installation directory, currently

Installation-path/Pmod3.8/data

where *Installation-path* might be something like C:, /opt, or /Applications, depending on the operating system.

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

Accelerator Keys and Mouse Dragging

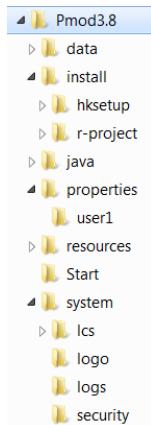
A substantial number of functions can be accessed using keyboard shortcuts. For instance, clicking into an image to activate it and then pressing the "Ctrl" and the "D" keyboard key (CTRL+D) will switch the layout to orthogonal planes.

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

These accelerator capabilities are describe in a separate *section* (on page 30).

Directory Tree

The installation of the PMOD software results in directory tree containing the Java classes, configuration information, installers for the USB key driver, and example data for kinetic modeling data and image analysis.



The content of the most important sub-directories is:

- data** Container for data. **DATABASES** contains the tables and data of JavaDB databases, for instance of the example **Pmod** database.
- doc** Directory containing the PMOD html documentation as well as the pdf application guides.
- install** Contains the driver installation files for the USB protection key. Each operating system has a dedicated sub-directory.
hksetup
- install r-project** Contains the installation files for the R software. Each operating system has a dedicated sub-directory.
- java** The **ext** sub-directory contains external Java libraries which support specific functions accessed from within PMOD. The **jre** sub-directory contains the Java Runtime Environment for running the PMOD applications.
- properties** Contains the configuration of PMOD and the different tools.
properties/user1, etc: Each PMOD user has a subdirectory containing his configuration of the different tools (*.props), the starting settings (*.ini), and the database queries (*.qry).
- system** system/lcs: license file pstarter.lcs.
system/logo: customer logo.
system/logs: log files of PMOD program and the servers.

Start The PMOD start scripts are located here. They are generated during the installation and take into account the installation directory and the operating system. Therefore, they can not simply be copied to another system or moved to a different directory.

- » **RunPmod:** starts the interactive PMOD environment.
- » **RunDbSvr:** starts the transaction server for publishing a database called **DbSvr**. Default port of the transaction server is 5100. Please edit the script for using a different port.
- » **RunDcmSvr:** starts the DICOM server for receiving DICOM images and saving them into the **DbSvr** database. Default port of the DICOM server is 5030.
- » **RunLcsSvr:** starts the transaction server for license serving only. This is only relevant if a network license file is contained in system/lcs.

Starting

Starting the Tools from the ToolBox

PMOD is started using the **RunPmod** script in the Pmod3.8/Start directory. Please refer to the system-specific installation guides if adjustments are needed. After starting, the PMOD ToolBox appears, initially with grayed tool buttons.



If multiple users have been configured, one of them needs to be selected and the **Log In** button activated. Otherwise, the login procedure proceeds automatically. Note the startup window which reminds you that PMOD is research software and shows license-related information.

After the login, the tool buttons are active and you can start working with PMOD. The ToolBox allows starting the different tools by activating the buttons. Alternatively, you can directly *drag* appropriate files (image files, or .km modeling files) onto the buttons.

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



Starts the **DICOM server** using the configuration of the current user. If it is already running, the configuration is shown. A blue background color indicates ongoing server activity, e.g. the receiving of images.



Starts the **Transaction Server** for publishing a local JDBC database. If the Transaction Server is already running, an information window is shown which describes the server status. A blue background color indicates ongoing server activity.



Access to the PSAMPLE Acquisition and Correction modules used with the Twilite Blood Sampling system

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

Starting PMOD Tools from the Command Line with Data

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

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

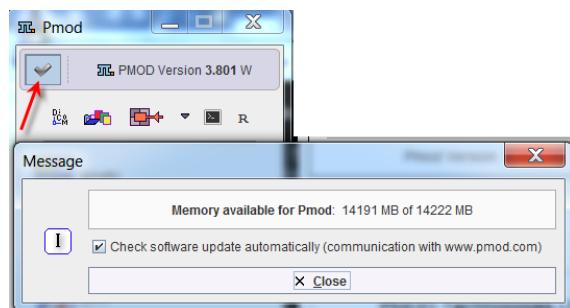
```
cd /Pmod3.8
./java/jre/bin/java -Xmx1200M -jar pmod.jar PFUS
C:/DICOM/20060815/38243299/00000210 C:/DICOM/20060815/38243299/00000888
```

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

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

PMOD Status

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



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

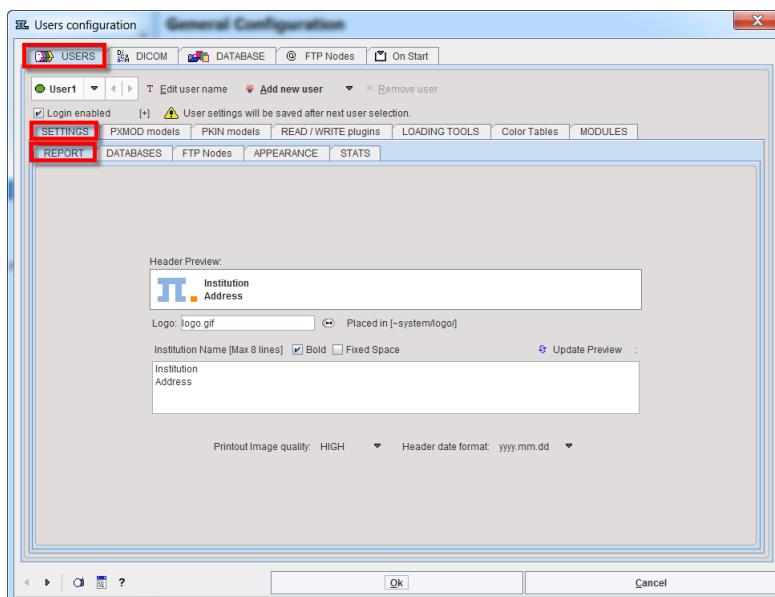
Note: New builds of the current PMOD version are uploaded at irregular intervals, mainly to fix bugs. We therefore recommend using the latest build of a version.

General Configuration

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



at the bottom of the PMOD ToolBox. It appears with four sections accessible by the main tabs.



The **DICOM** and **DATABASE** tabs are described in the *PMOD DICOM Functionality* (on page 35) and *PMOD Database Functionality* (on page 50) sections, respectively, and the **USERS** ad **On Start** tabs below.

USERS

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

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

User Creation

New user accounts are created with the option button:

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

The user name needs to be specified during user creation, but can be changed later using the **Edit user name** button. This name will be attached to data saved in a database and can be used in data filtering.

Note that no user passwords are required in the standard PMOD usage, since the accounts are rather aimed at separating the processing environments for different tasks than protecting data access. Only in the case of an ATL version which is aimed at controlled data processing are passwords enforced.

SETTINGS

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

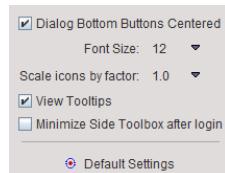
REPORT Configuration of the PMOD report pages. A **Logo** can be specified (a GIF file located in the system/logo sub-directory) as well as the institution address in the **Institution Name** section. The address can be set to **Bold** and to use **Fixed Space** by checking the corresponding boxes. Please use the **Update Preview** button to inspect the configured layout in the **Header Preview** section.

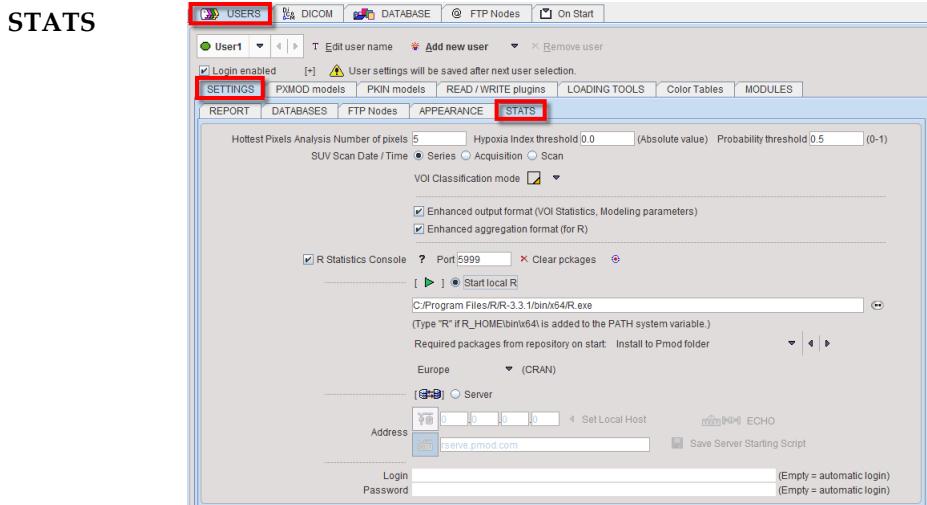
The **Printout Image quality** selection determines the resolution of the created jpeg pages and should normally be set to **HIGH** to achieve a satisfactory image and text quality. The **Header date format** allows choosing between year first/last variants.

DATABASE S Database usage profile. See PMOD *User-specific Database Configuration* (on page 61).

FTP nodes FTP nodes usage profile. See PMOD @ FTP Nodes.

APPEARAN CE Allows changing the location of the dialog buttons, the font size, whether tooltips should be shown, and whether the ToolBox should be collapsed automatically after login. The default settings can be retrieved activating the dedicated button.





One of the VOI statistics results is the average of the highest pixel values. The **Hottest Pixel Analysis Number of Pixels** specifies the default how many pixels are included in this analysis.

The **SUV** (on page 136) calculation requires information about the time the PET scan was started. This information may be encoded in different DICOM fields, depending on the manufacturer. The **SUV Scan Date/Time** allows establishing a convenient default for the user's environment.

The **PMOD R console** (on page 306) provides statistical analysis via the R package. In order to obtain the best results it is recommended to switch on the **Enhance output format (..)** and **Enhanced aggregation format (for R)**. Otherwise the information available in R will be limited.

The **R Statistics Console** is configured by default and should be *adjusted* (on page 307). If the user doesn't want to use this functionality, it should be disabled.

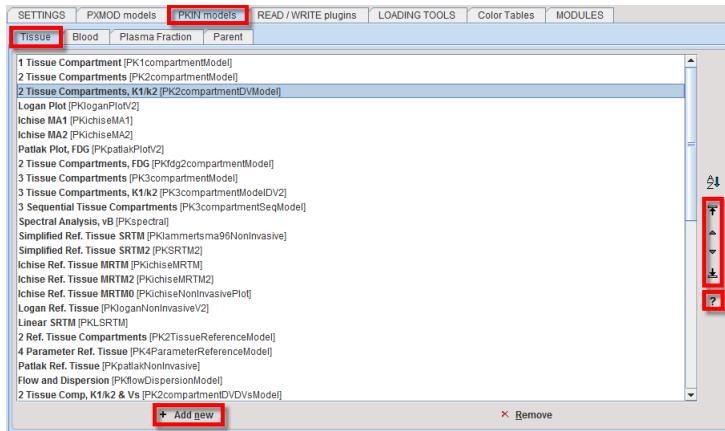
PXMOD, PKIN, READ/WRITE, LOADING, Color Tables Plug-ins

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

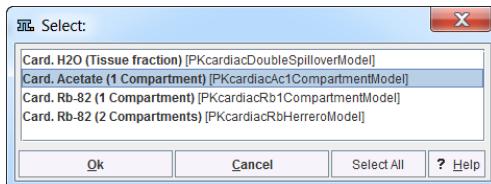
PKIN Models

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

To modify the order how the models appear in the PKIN application please select an entry and move it up/down using the arrows to the right. The ? button shows a quick model explanation.



To remove a model from the list just select its list entry and activate **Remove**. To add a model back to the list use the **Add new** button. The appearing dialog window allows selecting one or more plug-in(s) and adding them by the **Ok** button.



Contents of the different Plug-In Tabs

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

```

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

```

LOADING TOOLS

Configuration of image processing filters usable during loading.

Color Tables

Configuration of user-defined color tables. These files must be

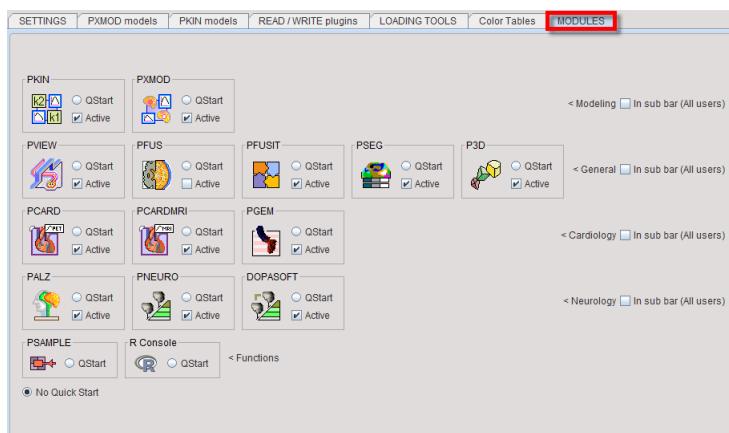
- ▶ located in the resources/colortables sub-directory (see the examples there),
- ▶ text files ending in .cltb, and
- ▶ contain 3 columns with the RGB values such as


```
# R G B
0 0 0
0 2 2
0 4 4
etc.
```

System color tables cannot be removed or arranged in a different order.

MODULES

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



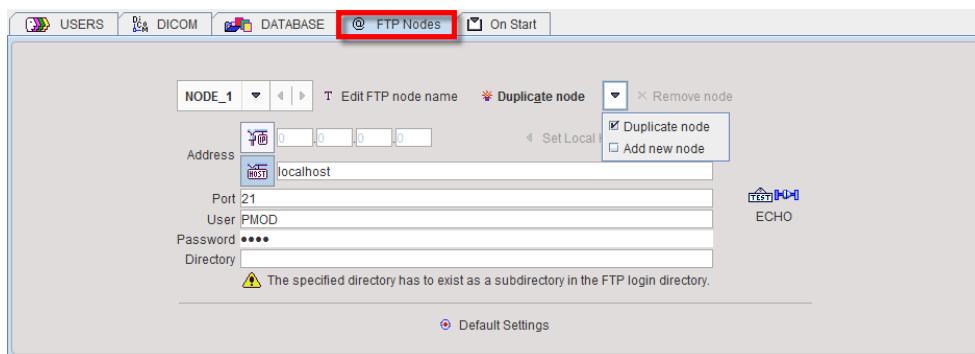
@ FTP Nodes

FTP nodes can be configured and used to remotely connect with external servers. These servers can be used only for sending data.

New nodes are created with the option button:

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

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



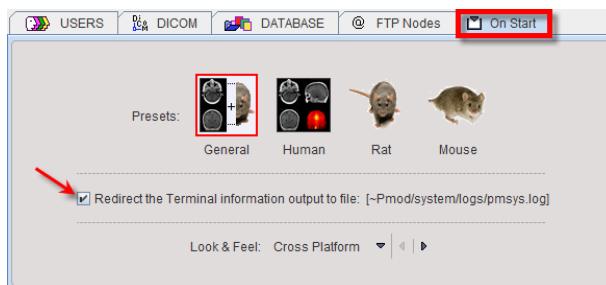
For each of them define the address by IP number or host name. The default port is 21 and supports only unsecured data export. Same port can be used for all nodes. As soon as the remote server has been started, it can be contacted and used for saving images.

The **User** and the **Password** need to be the same as the ones used for the login on the remote server. After configuration has been completed, the **C-ECHO** button can be used to test the connectivity.

In the **Directory** field should be specified a directory name that already exists as a subdirectory in the FTP login directory.

On Start

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



Presets

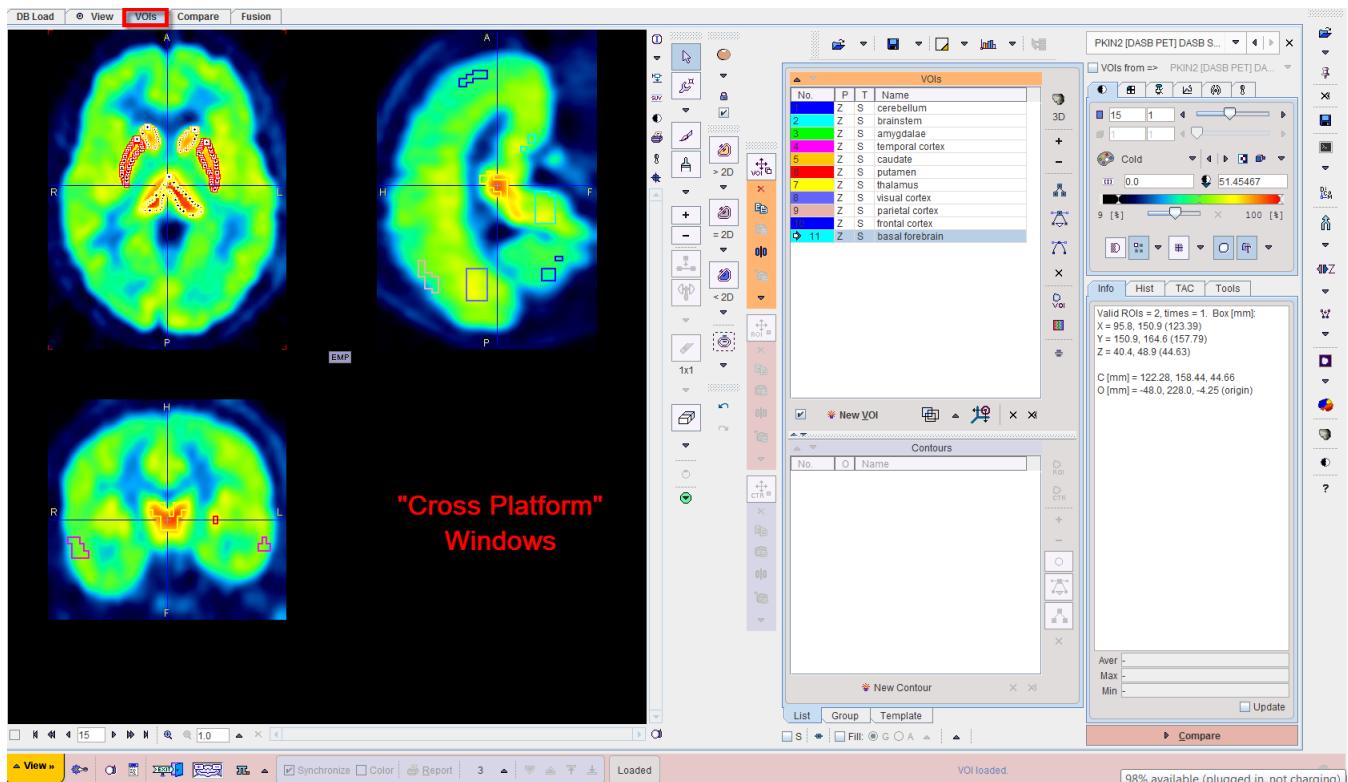
The type of the processed data may matter for some PMOD functions. For instance, animal data with small pixel sizes require also smaller default values for the sampling rates and filter sizes. If the user configures the **Human**, **Rat** or **Mouse** application domain PMOD is able to exploit appropriate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

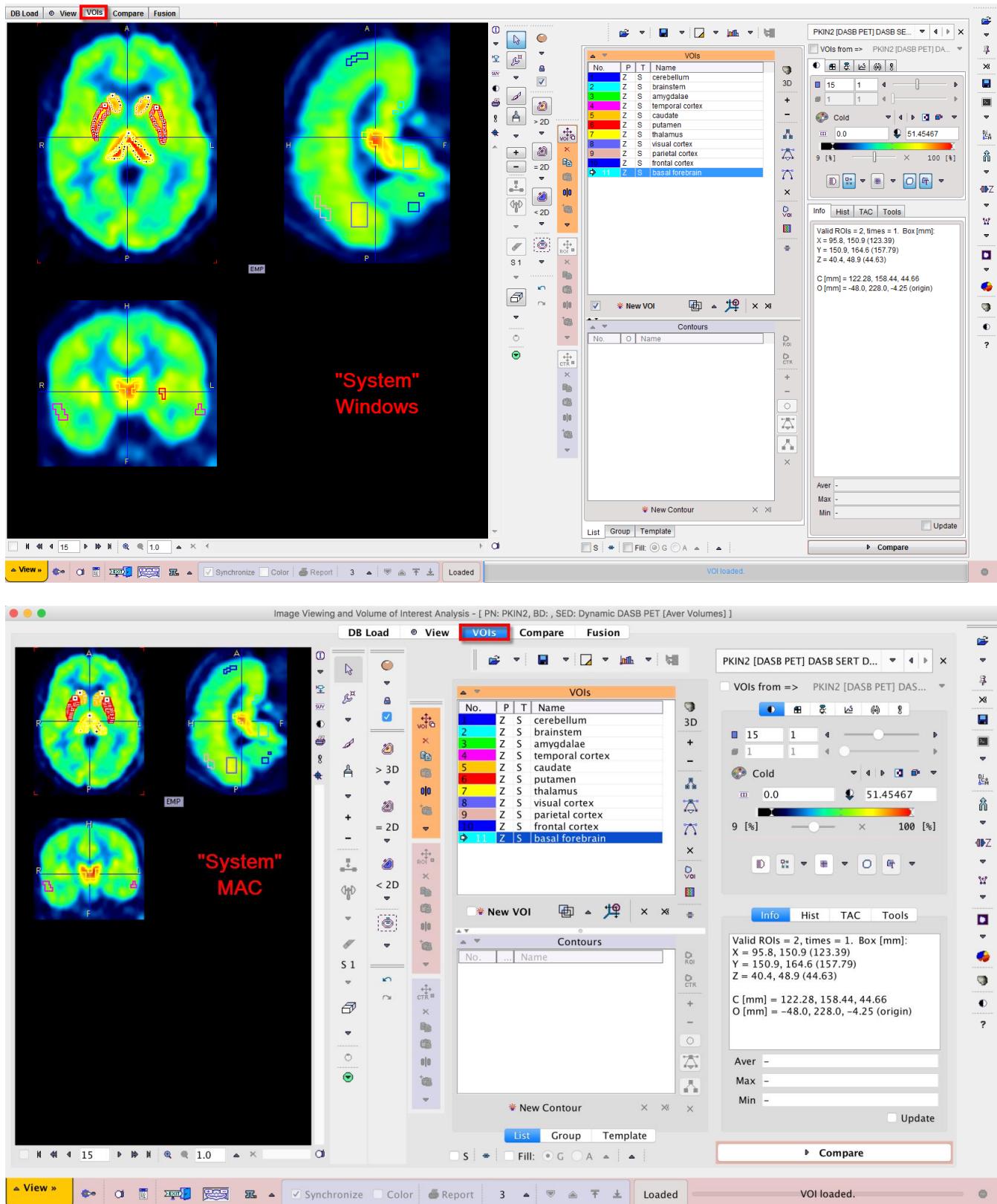
Log File

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

Look and Feel

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





The illustrations in the PMOD User's Guides use the **Cross Platform** look.

Dual Monitor

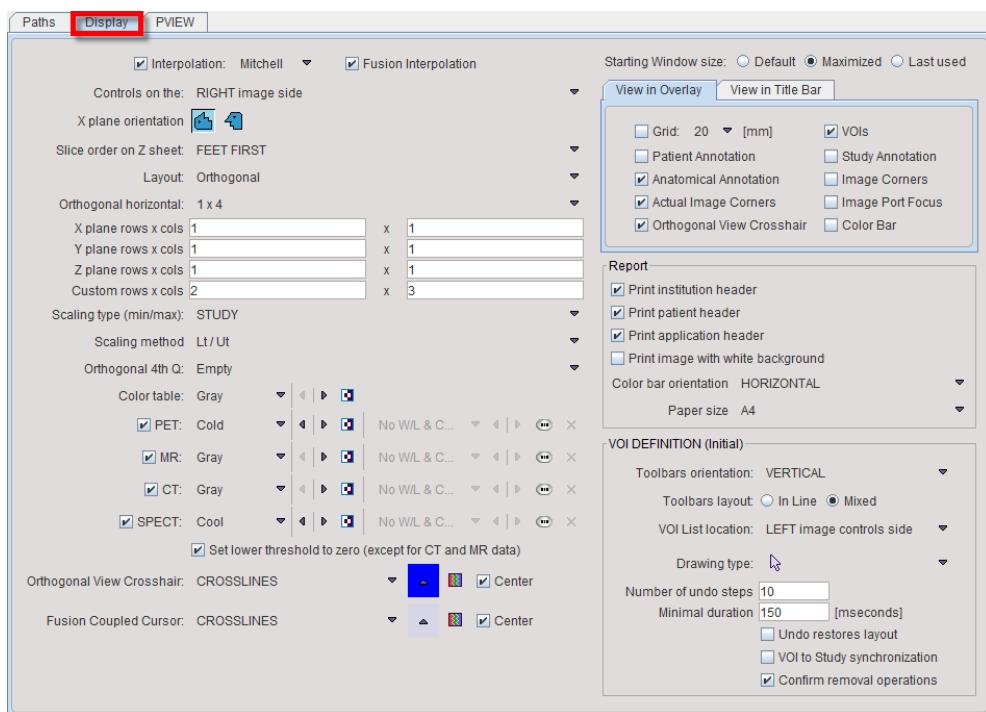
The support for two monitors in an extended screen mode by PMOD is limited. The user needs to arrange the windows himself appropriately. If the **Center dialog windows on the secondary screen** box is enabled, all dialog windows will be shown on the same secondary screen.

Tool Configurations

Each PMOD tool also has individual configuration settings which tailor it to the user's needs. These settings dialogs can be accessed by using the menu **View/Settings/Modify** entry or directly by the  button



in the lowest line of the tool. The example below shows the settings dialog window of the viewing tool.



The **Paths** tab contains the default input format definition, the default output format definition, and the data paths.

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

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

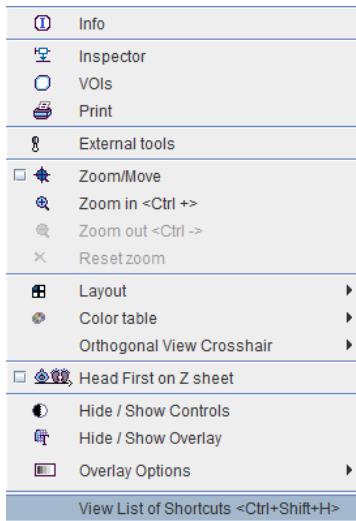
The last tab, in the example above **PVIEW**, is completely tool-specific.

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

Keyboard Shortcuts

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

While working in PMOD the list of keyboard shortcuts can be displayed via the image context menu, which is obtained by clicking with the right mouse button onto an image shown in PMOD.

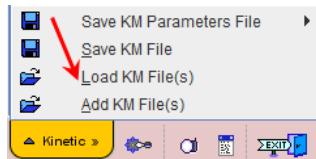


The last entry **View List of Shortcuts <Ctrl+Shift+H>** displays the window reproduced below. Note the arrow buttons to switch between pages.

Type	Shortcut	Effect / Test
LIST OF KEYBOARD SHORTCUTS: page 1 of 3 < > (Focus in the viewport required)		
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 + P>	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 m:m layout is not reasonable for a volume rendered display)		
Reporting:	<CTRL + D>	Print image report
	<CTRL + E>	Capture Display
	<CTRL + O>	Scientific Output
LIST OF KEYBOARD SHORTCUTS: page 3 of 3 < > (Global)		
Type	Shortcut	Effect / Test
Screen Capture:	<CTRL + SHIFT + P>	Capture Full Screen to the Console buffer
Save Data:	<SHIFT + S>	Save image data
Keyboard shortcut help:	<CTRL + SHIFT + H>	View this window. Test buttons disabled.
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>	Fusion Module
	<CTRL + SHIFT + D>	Fuse It Module
	<CTRL + SHIFT + S>	Segment Module
	<CTRL + SHIFT + D>	3D Module
	<CTRL + SHIFT + C>	Cardiac PET Module
	<CTRL + SHIFT + M>	Card CTMR 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 activated using the keyboard. In these cases, a letter in the item text is underlined. The action item can then be activated by combining the ALT key with the underlined letter. In dialog windows, ALT+C is typically used for the **Cancel** action.



For instance, when working in PKIN, the menu **Kinetic** can be brought up quickly by ALT+M. Once the menu is open, an underlined letter is sufficient to activate a menu item. So ALT+M and then an "L" will quickly perform the Load KM File(s) action.

Dialog Default Action

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

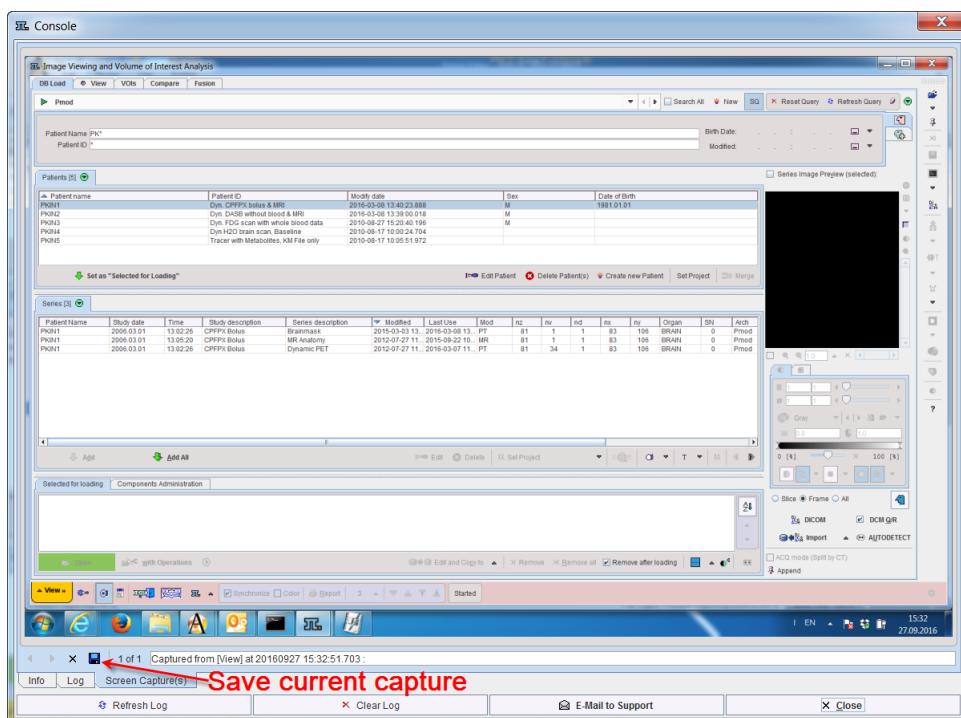
Problem Reporting

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

Every PMOD tool contains in the lower left bottom line the functions for creating the report.



The capture button creates a capture of the entire screen (not only the PMOD window) and adds it to a buffer of up to 20 captures. The console button opens the **Console** dialog window illustrated below.



The captures can be inspected on the **Screen Capture(s)** pane with the left/right arrow buttons, and the current one saved in JPEG. The **Log** pane contains the log messages, if the terminal output has been configured to be saved in a file on the **On Start tab** (on page 24) of the **Users Configuration**. Its contents can be updated by the **Refresh Log** button. Once in a while it is recommended to use **Clear Log**, to avoid excessive length of the log file. The **Info** contains some more general information.

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

The dialog box contains the following fields:

- Module: Kinetic PXMod Cardiac View Fusion 3D Alzheimer Brain DB
- Attach: Log Output Screen Capture(s)
- Problem description: A text area containing the placeholder "Enter your text here".
- Your email: cyril.burger@pmod.com
- Buttons at the bottom: Yes (highlighted in red) and No.

wherein the user can select the affected **Module**, and confirm whether the **Log Output** and the **Screen Capture(s)** should be included. The problem description should be typed into the text field, and the user's email address into the **Your email** field. Note that multiple addresses can be specified, separated by the colon character (:). use the **Yes** button to submit the report, or **No** to cancel.

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

Chapter 2

PMOD DICOM Functionality

DICOM

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

- » **Information Object Definitions (IOD):** For each modality it defines a set of data fields. Some of them are mandatory, others are optional. This approach allows saving demographical and acquisition information together with the actual images.
- » **Communication protocol:** DICOM has a client-server architecture. To send data from one host to the other the sender (client) must contact the potential receiver (server) whether it is ready to accept data. The server may reject the request because it has no space left, because the client is not allowed to send data, or because it does not understand the data to be sent. Otherwise it accepts the request and sends back a proposal how the data should be transmitted. The client then sends the data and gets an acknowledgment when the data have been correctly received.

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

- » The PMOD DICOM server allows clients such as a PET system to push images to PMOD. Additionally, it allows a user to query remote DICOM servers (such as imaging modalities or a Picture Archiving System) and fetch studies to process them locally.
- » The PMOD DICOM client allows sending image data using the C-STORE communication to any DICOM server which has been entered in the PMOD configuration.

Database for DICOM Data

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

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

DICOM Configuration

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



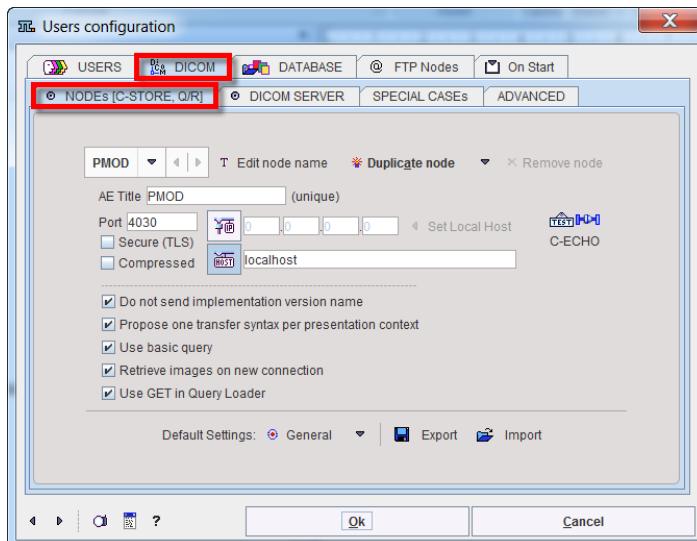
button from the PMOD ToolBox, and selecting the **DICOM** tab in the appearing dialog window.

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DICOM Query Loader (Auxiliary Server)	49

DICOM Client Configuration

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



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

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

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

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

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

DICOM Server Configuration

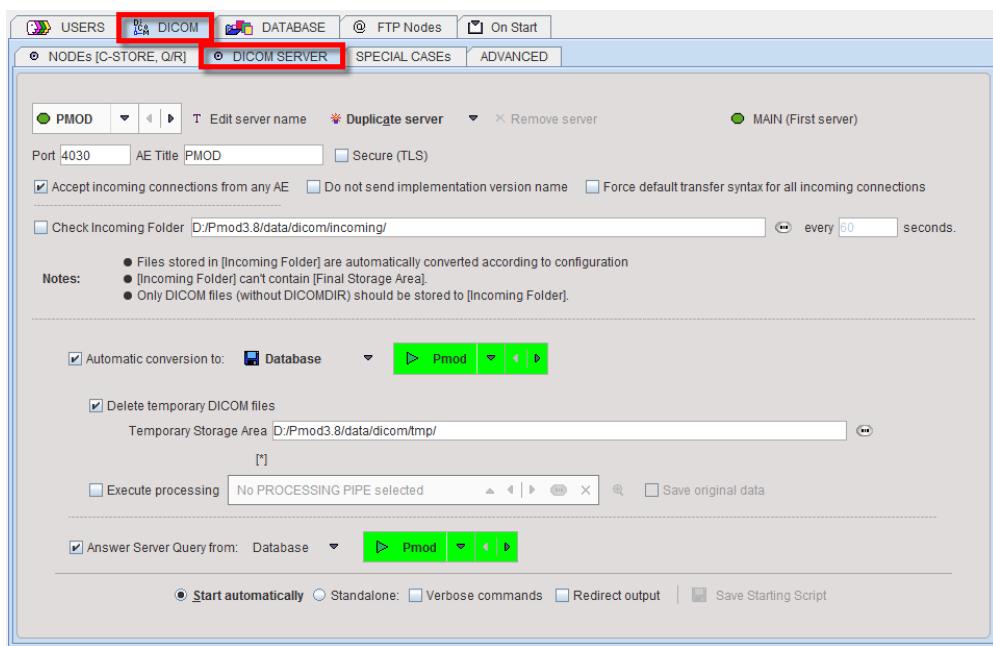
PMOD can run one or multiple DICOM server processes in the background which are able to receive data sent to it from modalities or a picture archiving system.

DICOM Server Properties

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

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

The **Port** and **AE Title** information of the PMOD DICOM server(s) is configured on the **DICOM / DICOM SERVER** pane.



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

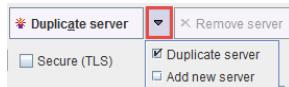
Besides the basic server information there are three checks relevant for the DICOM server operation:

- » **Accept incoming connections from any AE:** If this box is not checked, the DICOM server only accepts remote systems which are configured as remote DICOM clients. If it is checked, any association request will be accepted.
- » **Do not send implementation version name (server):** Allows switching off sending the implementation version component. This is required if a client does not handle this exchange properly and connection to the PMOD server fails.
- » **Force default transfer syntax for all incoming connections:** Transfer syntax negotiation may fail when a client proposes only one transfer syntax which is not the DICOM default and a PMOD server prefers another. In such cases the option forces the PMOD server to always negotiate the default Little Endian Implicit transfer syntax which all DICOM applications are required to support.

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

Multiple DICOM Server Creation

New Dicom servers are created with the option button



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

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

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

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

What happens with received DICOM Images

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

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

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

Saving the Images in a Database

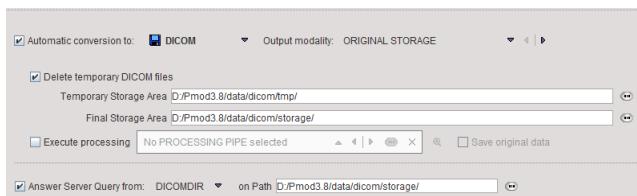
The following configuration is recommended for all users who run a local database.



In the example the DICOM server is receiving the images in the directory `C:/Pmod3.8/data/dicom/tmp`, saves them in the database **Pmod**, and then deletes the images in the temporary directory. When a remote DICOM client queries the PMOD DICOM server for studies, it will list all the studies in the **Pmod** database.

Saving the Images as DICOM Part 10 Offline-Files

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

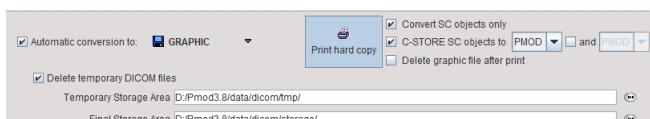


With this configuration, the images are stored in a directory hierarchy starting at `Pmod3.8/data/dicom/storage`. A DICOMDIR file will be maintained in the same root directory, and used to answer queries.

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

Filtering out Secondary Capture Images and Printing them

The configuration below illustrates another conversion ability.

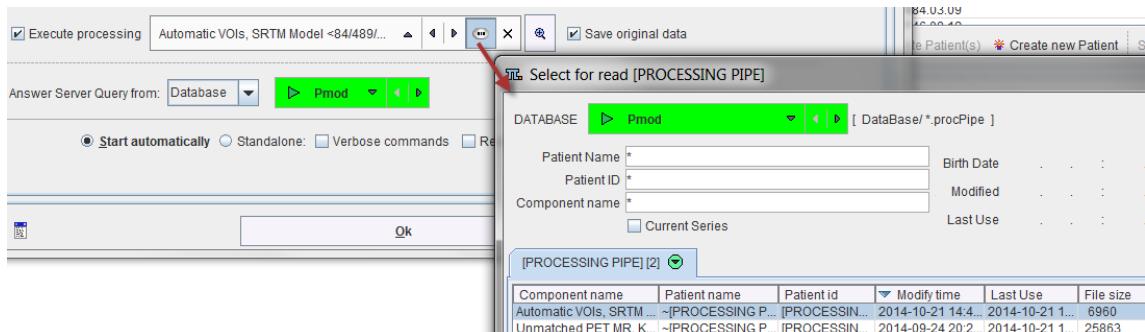


The images are converted to JPEG (**GRAPHIC**), a report page is prepared (**Print hard copy**) and sent to the system default printer, but only if the incoming object is of type Secondary Capture (**Convert SC objects only**). The original DICOM files are deleted, but the JPEG images are retained in the directory *Pmod3.8/data/graphic*. The additional checks allow routing the SC DICOM objects to a remote DICOM server such as a PACS, and deleting the JPEG files after printing.

Applying Processing to the Images

It is possible to set up DICOM servers which immediately apply an image processing pipeline to the received images. For instance dynamic brain PET images could first be motion corrected, then automatically a set of brain VOIs generated, the average TACs calculated and the SRTM model applied with the cerebellum TAC as the reference region. In this way, the regional set of kinetic parameters would immediately be available after the data have been received and processed.

The processing steps have to be prepared and saved in the **Pipeline Processing** (on page 420) interface. The pipeline is then set for **Execute Processing** as illustrated below.



Incoming Folder

Normally the DICOM server is receiving data over the network from DICOM clients. However, it is also possible to have the DICOM server scan a directory and treat found DICOM series in the same way as if they had arrived by the network.

This functionality can be configured by the **Check Incoming Folder** box. If it is checked, the directory to be scanned can be entered as well as a scanning interval **every ... seconds**. This import feature can be used to convert from DICOM to any other output format, or to add DICOM images to a PMOD database. Note that after processing the images by the DICOM server they are removed from the incoming folder.

DICOM Server Starting

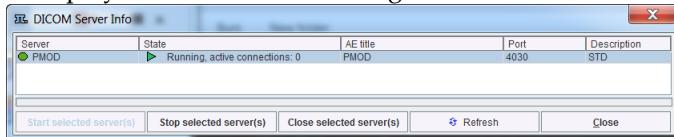
There are two ways of starting the DICOM server, as part of a PMOD processing session, or as a standalone process running independently. The latter has the advantage, that images can be received while PMOD is not in active use.

Interactive Starting

When the starting option is switched to **Start automatically**, the DICOM server is started with PMOD, and also stopped with it. Otherwise, with the **Stand alone** option, the DICOM server has to be started explicitly. With PMOD is running, this can be done with the DICOM button in the ToolBox.



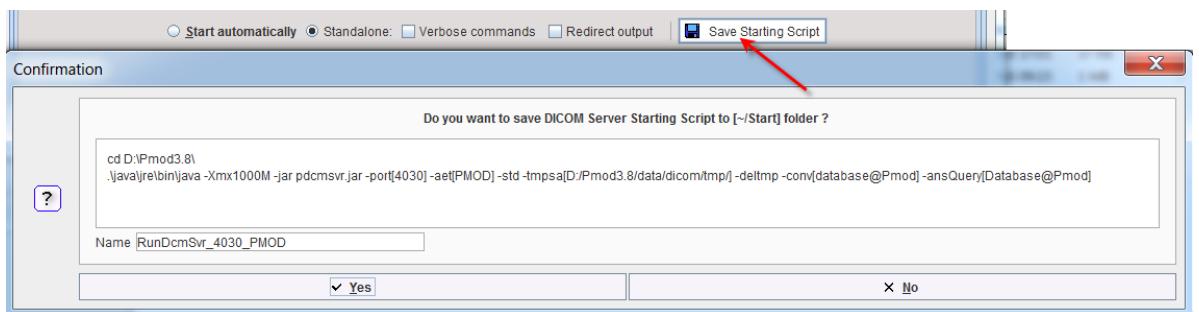
It displays the status of the configured DICOM servers in a dialog window, for example:



Each server can be individually started and stopped by selecting it in the list and using the corresponding buttons.

Script Starting

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



A DICOM server offers the following debug options:

- » **Verbose commands:** Serves for generating detailed communication information. While it slows the operation down, it may be helpful to troubleshoot connectivity problems. The corresponding script option is **-d**. In order to obtain even finer debugging information the **-f** can be appended additionally to the script. However, this inflates the log dramatically and requires careful usage.
- » **Redirect output:** Serves for redirecting the standalone server output to a file in *Pmod3.8/system/logs*. The corresponding script option is **-o**.

Implementation of DICOM Servers on a Dedicated Machine

Note that DICOM (and *transaction* (on page 57)) servers can be operated without a PMOD license. Only the process of their configuration requires a license. Therefore, particularly in a multi-user environment, the server processes should be moved to a dedicated machine with fast disks.

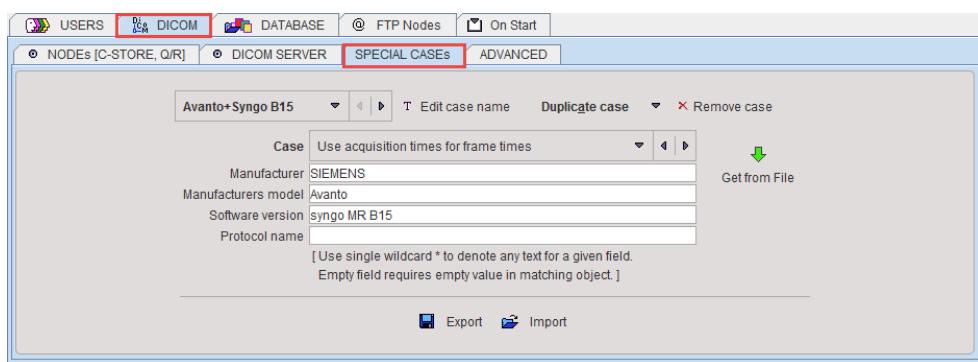
To establish such a configuration, please perform a standard PMOD installation on the server machine including the USB license protection key. Use the **Config** facility for the database and DICOM server configuration, and generate the server starting scripts. Thereafter, the USB key can be removed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

It is easy for Mac OSX and Linux to start programs like the transaction servers at system boot time and run them in the background. On Windows, this is not possible with normal programs. Rather, a command window is required which needs to stay open for the whole program duration, which is not convenient for shared server systems. A workaround is to purchase a third-party solution which wraps the DICOM servers into *service processes* (on page 483), such as the *AlwaysUp* <http://www.coretechnologies.com/products/AlwaysUp/> solution.

DICOM Special Cases

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

To create a new special case select **Add new case**, specify a name, and then select the appropriate behavior from the **Case** list. The requested information can be entered manually, but it is easier and safer to select **Get from file**, browse to the directory where the data resides, and select the appropriate series. PMOD reads the required information from the DICOM attributes and fills it into the **Manufacturer**, the **Manufacturer model** and **Software version** fields. Note that * can be used to indicate applicability for all possible strings, while an empty field requires that information is also empty in the corresponding DICOM field.



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

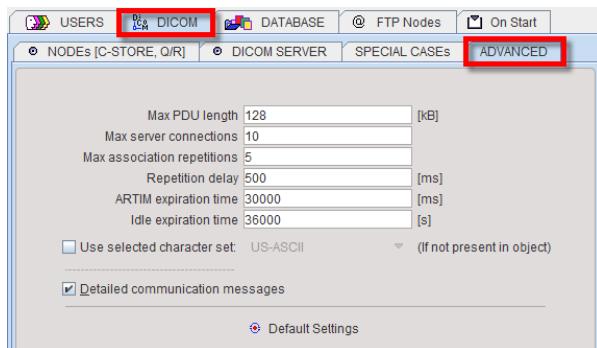
The **Case** selections are listed below with some example systems. However, the need and applicability of these special cases may depend on specific software versions of the originating system.

- » **Non identical images times for single volume:** Select this option if the slices of a single volume are interpreted as separate frames in a dynamic series (e.g. series with no positioning information like SC).
- » **Multivolume (sort by volume times):** To be used when the time sorting of a dynamic series is wrong (Siemens Sonata, Siemens Symbia).
- » **Multivolume (sort by slice position):** Another situation where the time sorting of dynamic volume data is wrong (Siemens Evolution EBCT scanner, GE Discovery LS, GE Discovery HR, GE Signa Excite).
- » **Multivolume MR (sort by trigger times):** A third situation with wrong time sorting (GE Signa Genesis).
- » **PET frame times in sec (instead of ms):** To be applied if the acquisition times presented in PMOD for PET objects are 1000 times too small.
- » **Volume SC:** For situations when a screen capture series representing a volume is displayed as a big number of separate series (GE Advantage Windows, GE Discovery HR, Siemens Somatom Emotion Duo).
- » **Wrong slice spacing (use slice thickness):** Try this case in case the slice thickness presented in PMOD differs from what you expected (some GE Xeleris versions).
- » **Wrong Image Index in PET objects:** Some PET/CT systems do not construct the Image Index (0054,1330) as specified in Dicom PS3.3 paragraph C.8.9.4.1.9. As a result PET images may be sorted wrongly (GE Discovery LS via Xeleris).
- » **Wrong frame reference time (use acquisition time):** Instead of the PET specific element 0054,1300 (Frame Reference Time) the general element 0008,0032 (Acquisition Time) is used to determine frame start and end times. If the acquisition time element is present and it is filled with the frame start time this usually solves the problem. (Philips, Protocol Guardian Bod; SUINSA animal PET system).
- » **Reference time at frame half (calc from duration):** The default behavior for PMOD is to calculate frame start and end times based on frame reference time and duration assuming that the reference time points to frame start. This special case uses the assumption that the reference time is at frame mid-time. (Philips)
- » **Times start not at zero (move to zero):** This case was introduced for Philips data that had a substantial offset in the 0054,1300 Frame Reference Time. It just offsets the times so the first frame starts at 0. It does the same as **Set acquisition start time to zero** in the loading parameters dialog.
- » **Wrong image class unique id:** This special case is to allow PMOD reading images that have wrong DICOM object class specified in the file.
- » **Use acquisition times for frame times:** This special case is instructs PMOD to use the acquisition time instead of the content time when determining the frame times for single slice objects.

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

DICOM Advanced Options

ADVANCED options allow changing some specific conditions and parameters of the dicom communication. The default settings are illustrated below. Changing these settings means tuning of PMOD to work with systems that are not 100% conformant with Dicom 3.0.



- » **Max PDU length** is a PDU (Protocol Data Unit) length that PMOD will propose to other communicating nodes as well as a maximal length PMOD will accept as a PDU. The minimal value for this field is 2. A zero value (that according to the DICOM standard means accept any size) is not allowed because problems may occur with some systems.
- » **Max server connections** is the maximal number of open connections handled by the PMOD server.
- » **Max association repetitions** instructs PMOD how many times it will attempt an association to an other node before reporting connection failure.
- » **Repetition delay** is the waiting time between association retries.
- » **ARTIM Expiration Time** is the time PMOD will wait for a reply from a remote DICOM system before it will close connection and report failure.
- » **Idle expiration time**: is the time after which the established DICOM connection will be closed if there is no activity (message exchange) on the connection.
- » **Use selected character set** ..: DICOM allows the specification of character sets in the file. If no character set is specified, PMOD uses the operating system default character set for the interpretation of non-ASCII characters. In case non-ASCII characters are not properly displayed, the user can explicitly define the proper character set. ISO 8859-1 will be appropriate for most western european languages. Please consult the ISO 8859-x standards to choose the right one for other languages.

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

DICOM Query/Retrieve

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

Configurations for DICOM Query/Retrieve (Q/R)

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

- 1) Locally in PMOD, the DICOM server must be configured and running because it receives the images sent from the remote system. The PMOD DICOM server configuration is explained *above* (on page 38).
- 2) Locally in PMOD, the remote DICOM systems from which images should be retrieved must be defined. Because they will send images to the PMOD DICOM server, they are configured as DICOM client nodes as described *above* (on page 37).
- 3) The PMOD DICOM server must be configured on the remote DICOM system by its administrator. Otherwise these systems will most likely reject the association request from PMOD, so that no images can be queried.

Retrieving Images per DICOM Query/Retrieve

The DICOM Q/R function can be called from

- » the **Menu** in the PVIEW tool, or
- » using the **Q/R** button on the **DB Load** page in any of the PMOD tools.

The dialog window shown below appears which allows the user to query and retrieve studies.

The screenshot shows the PMOD DICOM Query/Retrieve dialog window divided into four main sections:

- Step 1:** Top header and connection settings. The "Patient Root Query" tab is selected. The "Patient Name (L^F)" field contains "PFUS1". The "Get matching patients list" button is highlighted.
- Step 2:** Below the query results table, the "Get selected patient's studies list" button is highlighted.
- Step 3:** The bottom section displays a table of studies for patient PFUS1. The table has columns: Series no, Modality, Body part, Images, Study date, Study description, and Series description. The "Retrieve images" button is highlighted.
- Step 4:** Bottom left corner of the dialog.

Series no	Modality	Body part	Images	Study date	Study description	Series description
PT				2006.03.01	Choline PET	FCH
PT				2006.04.10	Tyrosine PET	FET
PT				2006.04.10	FDG PET	FDG
MR				2006.02.28	Magnetic Resonance Image	MRI

The following steps need to be performed:

- 1) **Query [Connect] to:** The selection lists all DICOM systems which have been configured as DICOM Clients. The connection is established as soon as the selection is activated..
- 2) **Retrieve to:** Typically, one would like to retrieve to the local DICOM server as shown in the example, but with **External node** it is also possible to select any of the configured DICOM clients (which must be a DICOM server) as the destination. Once the server is selected (configure, then activate), the connection can be tested with .
- 3) Select the query mode, **Patient Root Query** or **Study Root Query** by the tab. Note that some servers may not support both modes. If the query is not supported, **Get matching patients list** remains grey.
- 4) **Get matching patients list:** The purpose of this step is to get a list of studies, from which the ones of interest are retrieved. To avoid excessive numbers of matches some filter fields are available. In the example above, only patients with names starting with "P" are queried. When **Get matching patients list** is activated, the query is sent to the remote system, the response is received and the matching patients are listed.
- 5) **Get selected patients studies list:** Only studies from one patient can be retrieved at a time. Therefore a patient must be selected in the **Patients** list, and then the **Get selected patient's studies list** button activated. As a result, the remote system is asked for all studies of the selected patient, and the result is listed.
- 6) **Retrieve images:** To retrieve some of the studies select them in the **Studies** list (CTRL+Click), and then activate the **Retrieve images** button. A request is submitted to the remote system, which will send the requested images to the **Retrieve to DICOM** server. If the **Close after** box is checked, the dialog window will be closed while the receive process is going on in the background and will show a notification once the transfer completed. Otherwise, the dialog window remains open until the transfer completes.

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

DICOM Query Loader (Auxiliary Server)

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

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



To use the **Query Loader** functionality the data format **Query** must be added to the **READ/WRITE plugins** in the **Users** configuration dialog. Then **Query** will appear as an additional format for all image loading buttons.

Chapter 3

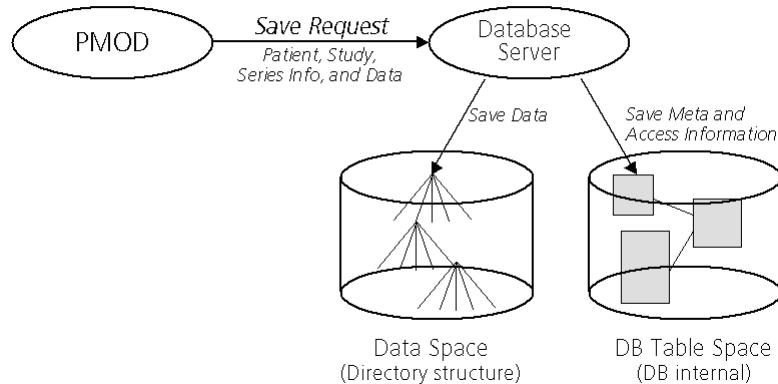
PMOD Database Functionality

DICOM Operations using a Database

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

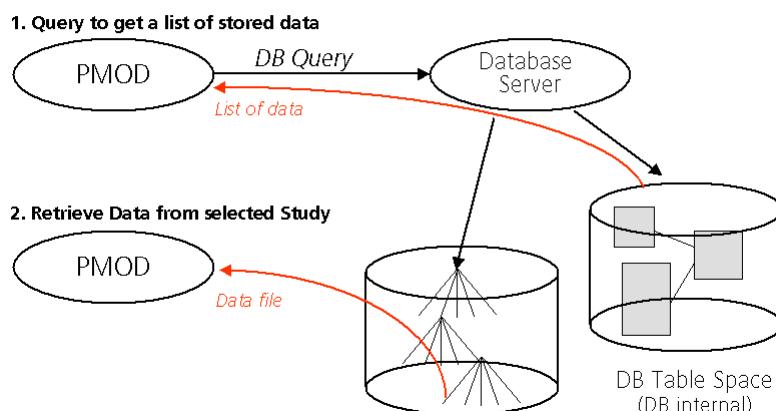
A **Save** operation sends a request to the database containing all relevant meta-information about the data (patient name, study, series, data type, etc) and the data itself. The database server then saves the data into a directory structure and adds the access information into its tables.

Use of Database for Saving from PMOD



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

Retrieving Data into PMOD from Database



Benefits of Using the Database

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

- » A unified user interface is shown when loading or saving all types of data.
- » The searching process supports many filters and is very fast.
- » Loading of the data itself, particularly the DICOM images, is fast.
- » The databases can be shared over the network between different PMOD installations.

Database Engines

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

- » **Derby** (default), an embedded database bundled with Java which requires no installation. The use of JavaDB is encouraged, and at some time point support of mySQL might be suspended.
- » **mySQL** (deprecated) is a database which runs on different platforms. Note that only mySQL server versions up to 5.0 are supported. Therefore, mySQL is only recommended for continuing legacy databases. In all other cases, JavaDB should be used.

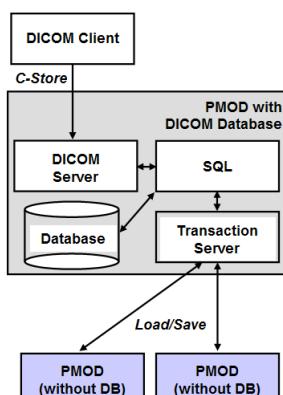
In this section it is assumed that the database engine is working properly.

Database Access Types

There are two different types of databases in PMOD:

- 1) **JDBC Databases:** These are SQL databases to which PMOD communicates using the Java Data Base Connection (JDBC) interface. Typically, the JDBC Databases reside on the local machine. The user can create new JDBC databases from the PMOD configuration utility. If he wants, he can make them available to PMOD installations on different computers by a PMOD protocol called **Transaction Server** (TS, see below).
- 2) **Transaction Server Databases:** These are SQL databases which are not directly accessed, but indirectly through a PMOD installation usually residing on a different computer. As the transaction server databases are managed by a different PMOD installation, they cannot be created or deleted, but only used for reading and writing.

The transaction server concept is most useful in an environment of multiple PMOD installations. On one of the PMOD installations, the PMOD JDBC databases are created. On the same system, the PMOD DICOM server is started, and saves the received images in one of the databases. All other PMOD installations access the databases just through the transaction server as illustrated below.



Note: After the installation of Pmod3.8, the **Pmod** database and the **DbSvr** transaction server for publishing this database are available. The **Pmod** database contains various example data if the example database was selected for installation. This database resides within the PMOD installation directory. Please create a new database for your productive work which resides on a disk which is regularly backed up.

In This Chapter

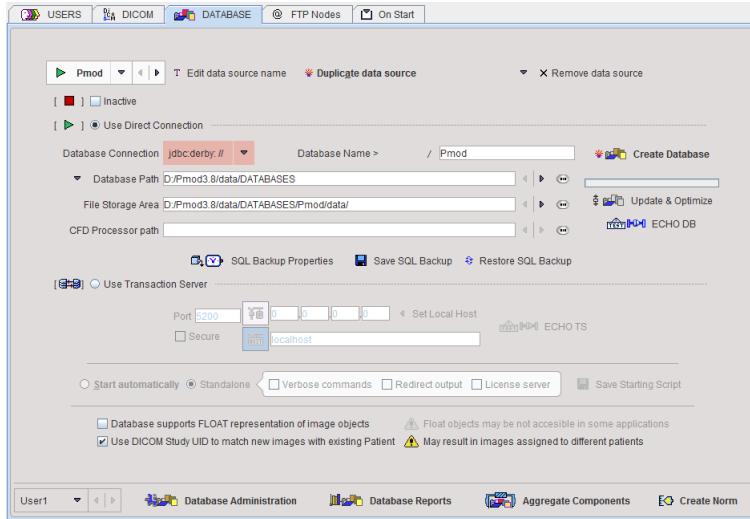
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Creation and Configuration of Databases

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



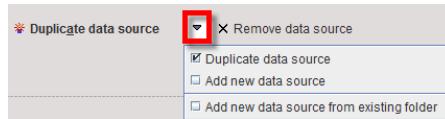
button from the PMOD ToolBox, and selecting the **DATABASE** tab in the appearing dialog window.



To create a new database please proceed as follows.

Derby JDBC Database Creation (default)

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



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

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

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

- 3) **Database Connection:** This entry defines the database access. The first part **jdbc:derby:** is the driver specification. The **Database Name** is the name by which the data source is known to the database engine. In principle the name can differ from the data source name, but this is not recommended.
- 4) **Database Path:** The directory where the database tables are stored (in a subdirectory named corresponding to the database name). It is highly recommended to *use an absolute path pointing to a central location outside the PMOD installation*. This will make it easier to perform version upgrades as well as backups. If relative path names are used starting with "./", the directory will be placed in *Pmod3.8/data*.
- 5) **File Storage Area Path:** This is the path of the root directory in which the data files will be stored. As for the **DATABASE Path** it is recommended using an absolute path, preferably in a common directory.
- 6) **Create Data Base:** Activating this button finally creates the JDBC database. Connectivity can be tested with the **ECHO DB** button.

Note: After the installation of Pmod3.8, the **Pmod** database illustrated above is already available and contains different types of example data, if the example database was selected for installation.

mySQL JDBC Database Creation (deprecated)

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

Database Connection	jdbc:mysql	//localhost	/Pmod
User : Password	root	:	
File Storage Area	/DATASETS/Pmod/data		

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

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

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

Configuring Transaction Server Databases

PMOD allows publishing a local data base to other PMOD installations by a server program called **Transaction Server** (on page 57). To address such a transaction server database, a data source must be defined as follows:

- 1) **Add new data source:** Again, a new data source must be created and adequately named.
- 2) **Use Transaction Server:** This radio button must be selected, and the transaction server address and port entered.



In this example, PMOD is installed on a host called *localhost* where a transaction server for a particular JDBC database has been started listening on port 5100. As the database is already existing, the initialization step is not necessary.

- 3) Note the two boxes **Secure** and **Compressed**. Please configure the communication with the properties that the transaction server is expecting (see below).
- 4) If the transaction server is running, connectivity can be tested with the **ECHO** button.

Numerical Accuracy of Images Stored in the Database

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

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

Multiple Access to Derby JDBC Database

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

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

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

Note: The default configuration of Pmod3.8 already includes a transaction server definition of the **Pmod** database which is called **DbSvr**. The transaction server will be automatically started with the first interactive PMOD session. Access to **Pmod** through the transaction server is configured as the **DbSvr** database.

Database Deactivation

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

Default Database

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

Database Upgrading

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

Note: Transaction server data sources must be upgraded on the site of installation.

Database Backup

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

Setting up a Transaction Server to Publish a Database

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

In PMOD multiple TSs can be started automatically. Therefore memory usage for multiple TS is optimized while providing a better management of the TSs.

Transaction Server Configuration

The transaction server requires several configuration items, which are available on the **DATABASE** panel. Perform the following steps to define the transaction server which is started automatically with PMOD.

- 1) Switch the radio button from **Use JDBC connection** to **Use Transaction Server**.



- 1) Configure the properties of the transaction server. The **Secure** box is for enabling secure communication. This mode should be used if the communication is not confined within the institution. Otherwise it will slow down the communication speed unnecessarily.
- 2) An important property is the IP **Port** for the communication. It must be a unique number not used by any other transaction server or other process. In the example above is **5200**.
- 3) Another important property is the IP **address**. It must contain the address of the host in which the servers are running, so typically the system on which the configuration is performed. For this system the **HOST** button is enabled and the host system is "localhost". In alternative, the IP **address** can be obtained by activating the **Set Local Host** button.
- 4) Check the box **Start automatically** such that the transaction server is started simultaneously with PMOD.

Starting a Transaction Server

The PMOD transaction server is a background process. It can be started in one of the following ways:

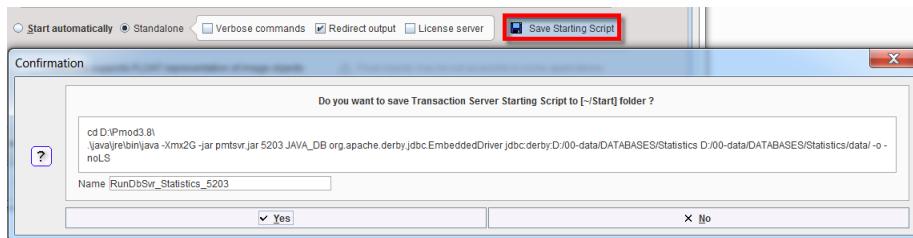
- 1) *Automatically:* If **Start automatically** has been configured in the **DATABASE** configuration page, the transaction server is started as soon as PMOD is started.
- 2) By running a *command script*: A script for starting a Transaction Server is specific for the operating system platform. A start script *RunDbSrv* with the default configuration is created at installation time in the *Start* directory. Transaction server scripts with a different configuration can easily be generated on the **DATABASE** configuration pane as described below. As an example, the *RunDbSrv* script for Windows looks as follows:

```
C:  
cd "C:\Pmod3.8  
.\\java\\jre\\bin\\java -Xmx2G -jar pmtsvr.jar 5100 JAVA_DBS
```

```
./DATABASES/DbSvr -noLS
pause
```

Transaction Server Scripts

The **Save Starting Script** button is a facility for generating scripts according to the configured transaction server properties. It becomes active when the **Start automatically** radio button is disabled and **Standalone** option is enabled. The script is dependent on the operating system. The example below is the result for a Windows system.



The **-noLS** text indicates that the TS is not used as license server.

The **License Server** box can be checked if the server is at the same time managing a network license. In this case the **-noLS** flag will disappear.

The **Verbose commands** box can be checked to enable verbose output. In this case a **-d** argument will appear. It is only recommended for debugging purposes, because it will slow communication down.

The **Redirect output** box can be enabled to redirect the output to a log file. In this case a **-o** argument will appear.

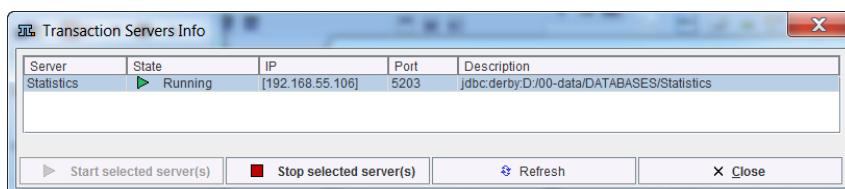
The **Yes** button saves the operating-system specific script illustrated in the commands area to the *Pmod3.8/Start* directory using the specified **Name**.

An additional command line flag which can be added to the script in an editor is **-optimize**. If it is present, the database table indexes will be optimized before the database gets accessible. As this may take notable time for large databases, it is recommended to perform it only when database performance drops. However, it can dramatically improve speed for aging, large databases

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

Transaction Server Status Information

All automatically started TSs are available for management from the PMOD ToolBox. The TS management and status information are available activating the button:

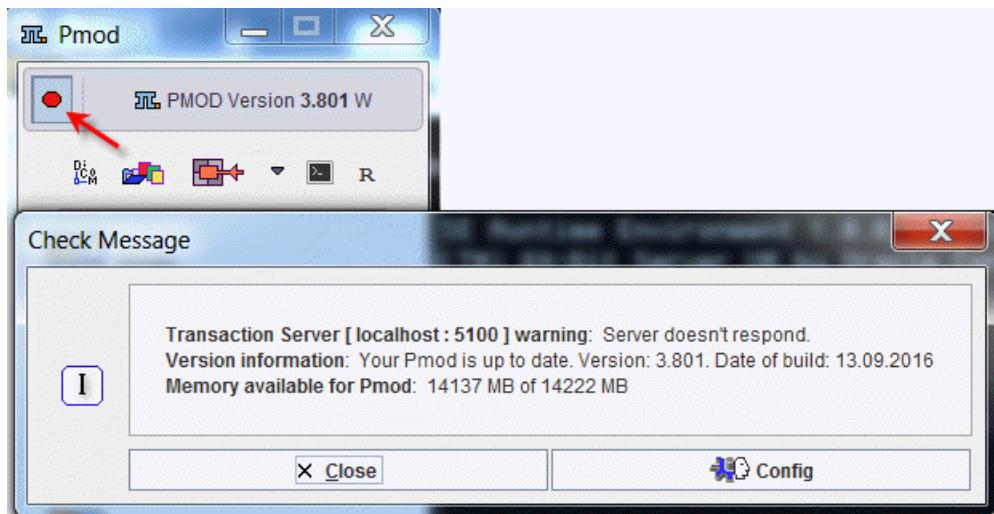


The current status is displayed in the **State** column. The status of a TS can be easily modified: initially the TS has to be selected in the **Server** list and then, depending on the status, the **Start selected server(s)** or **Stop selected server(s)** button need to be activated.

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

Pmod Status

In case of problems with the TS status the PMOD status button in the ToolBox shows a red bullet.



Dedicated Machine for Databases and Transaction Servers

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

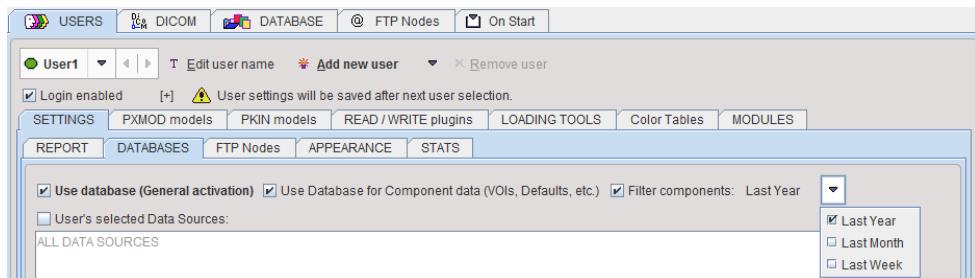
It is easy for Mac OSX and Linux to start programs like the transaction servers at system boot time and run them in the background. On Windows, this is not possible with normal programs. Rather, a command window is required which needs to stay open for the whole program duration, which is not convenient for shared server systems. A workaround is to purchase a third-party solution which *wraps the transaction servers* (on page 483) into service processes, such as the *AlwaysUp* <http://www.coretechnologies.com/products/AlwaysUp/> solution.

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

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

User-Specific Database Preferences

As the database behavior can be differently configured for each user, a user must first be selected, **User1** in the example below.



The configuration items are then available on the **DATABASE** sub-tab of the **SETTINGS** pane:

- » **Use Database (General activation):** This is the main switch. If the box is not checked, all databases are invisible for this particular user and all data loading/saving is file-based.
- » **Use Database for Component data (VOIs, Defaults, etc.):** Sometimes it is preferable to use the database only for the image data. In this case, the check can be removed from this box. Using the full database capability has the advantage that TACs and VOIs etc. are related to the image series they are derived from.
- » **Filter components:** For large databases, the listing of VOIs and other components can slow down. In order to speed the listing operation up and only showing recent data, a default date filter (**Last Year**, **Last Month**, **Last week**) can be enabled.
- » **User's selected Data Sources:** If there is a substantial number of different databases and a user requires only a few he can check this box, and then add the relevant ones with the **Add new** button. An additional advantage is that the user can sort the database list according to his preference.

Loading Data from Databases

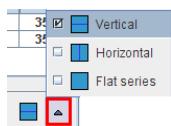
If the database is enabled the **Database** format is available in the list of input formats for image loading.

Image Data Loading

When loading images from the database the interface shown below allows searching for studies according to different criteria such as patient demographics, study date, modality, a project name or diagnosis. There is a basic filtering mode as illustrated below, and an advanced filtering mode illustrated later.

The screenshot shows the PMOD DB Load interface. At the top, there's a toolbar with buttons for DB Load, View, VOIs, Compare, and Fusion. A red box highlights the 'DB Load' button. Below the toolbar is a search bar with fields for Patient Name (PK*) and Patient ID (*). To the right of the search bar is a 'Database selection' dropdown with a red arrow pointing to it. Underneath the search bar is a section titled 'Basic filtering criteria' with a red box around it. It contains fields for Birth Date and Modified, and a 'Series Image Preview (selected)' checkbox with a red box around it, which is checked. To the right of this preview area is a small image viewer showing two brain slices. Below the filtering criteria is a table titled 'Patients [5]' with a red box around it, listing five patients (PKIN1 to PKIN4) with their names, IDs, and some study details. A red box also highlights the 'Set as "Selected for Loading"' button. Further down is a section titled 'Image series of the selected patient' with a red box around it, showing a table of image series for PKIN2. At the bottom is a 'Selected for loading [1]' section with a red box around it, showing the same PKIN2 entry. On the right side of the interface, there's a detailed image viewer with various controls like zoom, crop, and color settings, and a legend for slice/frame/all.

The layout can be organized vertically (as illustrated above), or horizontally with the **Series** tab stacked behind the **Patients** tab. This may be an advantage if patients tend to have many image series. The layout is switched by the option button



The **Flat series** is another arrangement which lists all image series in a single list. The **Flat series** DB layout mode allows searching in all active databases if the **Search All** checkbox is enabled.

Loading Overview

The uppermost section represents the filtering options. The use of filtering is recommended in large databases, because it substantially reduces the response time. Below the filters, the

list of **Patients** is shown which match the current selection criteria. When one of these patients is selected, his image series available in the database are updated in the **Series** list section.

One or several image series can be selected and brought into the **Selected for loading** area by the **Add** button or by a double-click at the series entry. On the right side there is a preview window to verify the image contents before actually loading the whole data set. If the **Series Image preview** box is checked, an image is displayed as soon as a series is selected.

Finally, by activating the **Open** button, all series in the **Selected for loading** area are loaded into the PMOD tool. **Append** pushpin button is important for the outcome of the loading operation: with the appending setting the images are added, while with the overwriting setting any already loaded images will be discarded.

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

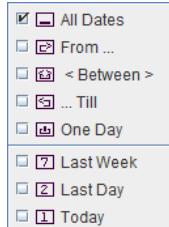
User Interface Elements for Filtering

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

Name Patient name, starting with the last name. The wildcard * can be used as a replacement for arbitrary sub-strings.

Patient ID The patient ID filter, also supporting wildcards.

Birth Date The filters for the birth date include an exact date, or a date range available from the selection list.



These specifications apply for all other filter dates.

Modified A date/time is maintained in the database recording when the data of the patients was modified the last time by adding an image series or by changing the patient information. For example, setting the field to **Last Week** only shows patients modified in the last seven days.

SQ Means *Save Query*. If this button is enabled, the same filter settings will be applied when the database window is opened again.

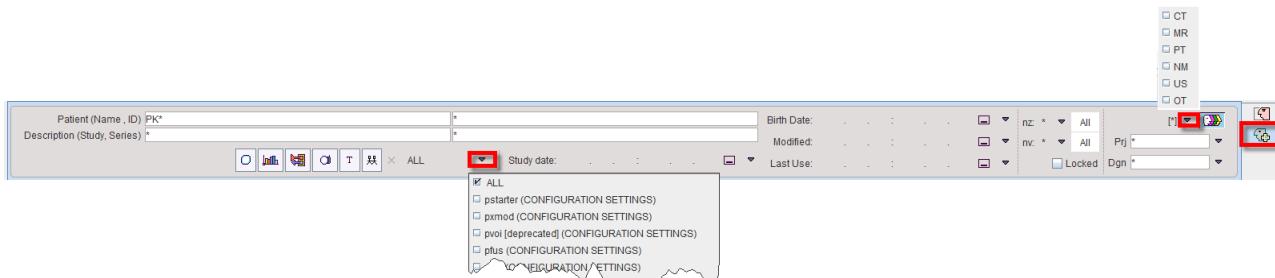
This button resets the filter settings by removing all specifications.

The refresh button to apply the query to the database potentially updated in the meantime, or after changing the filter and disabled automatic refreshing.

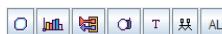


Toggle button to enable/disable automatic refreshing after changing a filter element

There is an extended filtering capability available on the second sub-tab which is illustrated below.



It contains several new elements:

Study Description	Filtering of text appearing in the study description. The * wildcard is supported.
Series Description	Filtering of text appearing in the series description. The * wildcard is supported.
ALL DATA TYPES	This selection lists all available data types in PMOD such as images, VOIs, etc. Setting this field to <i>VOI Templates</i> for example will only list patients who have a VOI definition attached to one of the image series.
	 These shortcut buttons allow filtering for frequently used data types such as VOIs, statistics, kinetic modeling files, comment texts, paired series. ALL resets all filter setting.
Last Use	A date/time is maintained in the database when data of the patients was accessed the last time. This information is listed for each database object. Selecting a date range allows browsing the database content based on a <i>least recently used</i> criterion.
nz	Filter to search for studies with a certain number of slices, including the criteria  For instance, planar only studies could be looked for by setting nz = 1.
nv	Filter to search for studies with a certain number of dynamic frames. For instance nv > 1 will only list dynamic series.
Locked	If the box is checked, only patients who have a <i>Locked</i> flag are listed.
Modality	A selection to restrict the search to a specific modality, e.g. to <i>PT</i> (PET) as in the example. Multiple modalities can be searched for at once.

Prj	Patients can be assigned to a Project . The selection allows choosing from the list of available project names.
Dgn	Similarly, patients can be given a Diagnosis . The selection allows choosing from the list of available diagnosis names.
 or 	Every time data is saved in the database, the PMOD name of the user who saved is recorded together with the data. This button allows restricting the search to the PMOD user currently logged in (button out), or to show data of all users (button in).

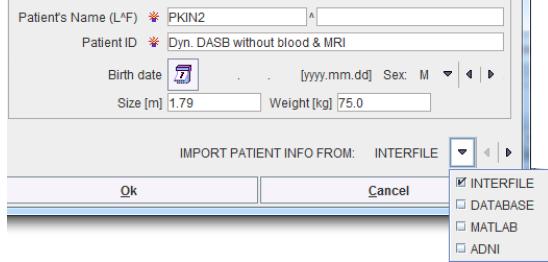
The green button  allows hiding the filter section. Upon activation the filter area collapses and the button appearance changes . This new button allows showing the hidden filtering settings.

Patient Operations

When a patient has been selected from the list, a row of buttons becomes active.

Set as "Selected for loading" Moves all series of the patient to the **Selected for loading** area.

Edit Patient Opens a dialog window for editing the patient demographic data.



The **IMPORT PATIENT INFO FROM** button allows importing this information from a file in the Interfile format, from an existing **DATABASE** patient, or from a **MATLAB** file. Note that the information in the DICOM object is not modified, just the database entries. However, when loading the images, the information in the database overrides the DICOM information, and when the data is saved or exported, it will contain the changed information in the file. Note that this replacement operation does not apply to weight and height, as these properties may change due to treatment and growth.

Set Project | Locked Allows defining three attributes for a patient:

<input checked="" type="checkbox"/> Project	FUSION	▼
<input checked="" type="checkbox"/> Diagnosis	▼	
<input checked="" type="checkbox"/> Lock:	<input checked="" type="radio"/> Enabled	<input type="radio"/> Disabled

A **Project** name can be entered, or if it already exists, selected from a list. Similarly, a **Diagnosis** can be specified, and the patient can be **Locked** to prevent erroneous deleting.

Delete Delete the patients selected in the list.

Patient(s)

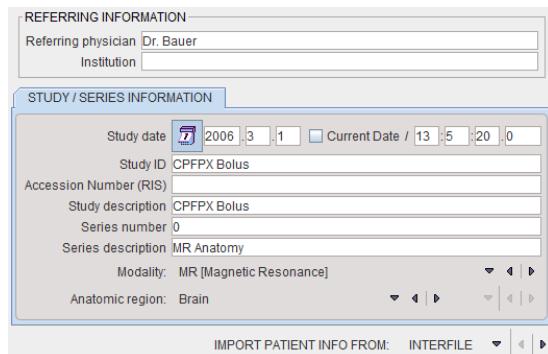
- Create new Patient** Create a new patient in the database, to whom information can be attached if there is no image series in the database.
- Merge** Sometimes several entries are created for a single patient because of a mismatch in the name/ID information. To merge such entries, select all of them in the **Patients** list (with **CTRL+Click**) and activate the **Merge** button. As a result all series end up under a single patient entry.

The / buttons allow hiding/showing the patient list controls.

Series Operations

When a series of the current patient is selected, the row of buttons below the list becomes active.

- Add** Moves the selected series of the patient to the **Selected for loading** area.
- Add All** Moves all series of the patient to the **Selected for loading** area.
- Edit Series** Opens a dialog window for editing the series information



- Set Project | Locked** Brings up the same dialog window as on the patient level to define project, diagnosis and locking on the series level.
- Pair Images** This option in the selection list serves for associating two (or more) series. This association is used in processing tools which require the information of two image series.
- Pair VOIs** This option in the selection list allows associating a VOI file to image series.
- Delete Serie(s)** Delete the series selected in the list.
- DICOM** Inspect the attributes of the selected series in a DICOM browser.
- Search JPEG or TIFF captures stored in the database. They can be opened in a viewer.

Comment editor. Allows creating a comment for the selected image series. Existing comments can be edited or read.

Search for a study which is associated to the selected series.

Buttons allowing to step from patient to patient

The / buttons allow hiding/showing the series list controls. The / buttons allow hiding/showing the series image preview.

Selected for Loading Area

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

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

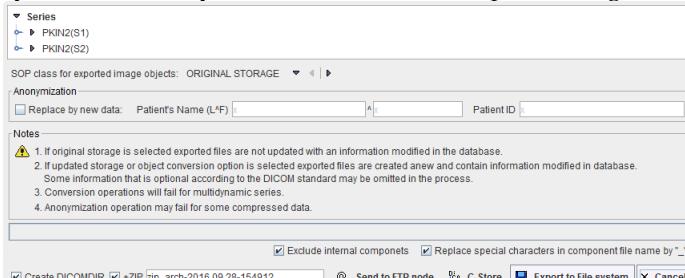
Open Starts loading the image series directly. The images are loaded without intervening dialog, and without any operations. Otherwise the dialog for specifying pre-processing options is shown. If the **Append** flag is on () , the selected series will be loaded as *additional* images to the tool, otherwise the tool will be cleared before loading.

with Operations Starts loading the image series. The dialog for specifying pre-processing options is shown. If the **Append** flag is on () , the selected series will be loaded as *additional* images to the tool, otherwise the tool will be cleared before loading.

This button serves for loading the selected data with a macro.

Replicate Copy the selected series including components to another database which can be selected in the appearing dialog window.

Export Export the series in the list from the database to a directory located on the file system or directly to an FTP node. The export dialog window



optionally allows anonymizing the images, generating a **DICOMDIR** file and compressing the whole data into a **ZIP** archive. The action can be aborted with the **Cancel** button.

C-Store This button allows sending the selected series directly to a DICOM server without first loading them into an image area. This has the advantage that *no*

modifications are done to the original DICOM objects. In contrast, when loading the images and sending them to a DICOM server, some changes are applied to the DICOM attributes.

Remove Removes the selected series from the selected for loading area, but does not delete from the database.

Remove All Clears the **Selected for loading** area.



This button allows setting defaults column order and width.



This button allows sorting the images **Selected for loading** by the selected column.



This buttons allow changing the images order in the list.

DICOM Query/Retrieve

Q/R This button underneath the image display area starts the dialog window for the **DICOM Query/Retrieve** (on page 47) functionality. If the box left to Q/R is checked the demographic patient information is copied to the Q/R dialog window.

Loading Images from the File System

AUTODETEC T This button allows loading image data from outside the database. Basically, it is an **Autodetect** loading, so the user can just browse to any directory and select any type of image file. PMOD will detect its file format and perform the image loading operation, if possible.

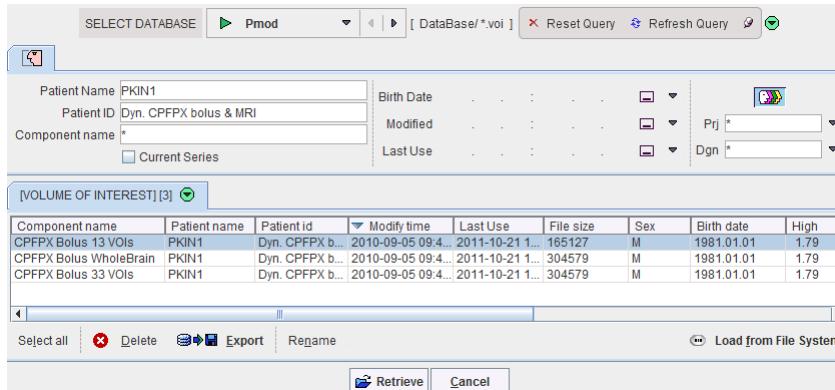
DICOM This button serves *loading DICOM part 10 images* (on page 93). The difference with the **Autodetect** loading is that the user has to select a directory, not a file.

Import This buttons allows direct importing of DICOM files to the current database.

Component Data Loading

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

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



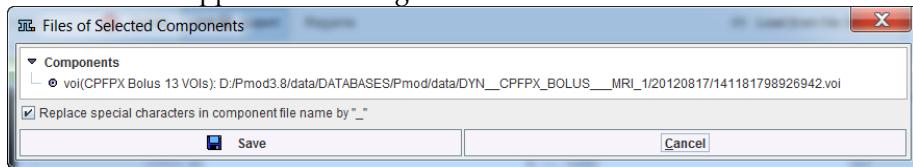
First, the database containing the data, here **Pmod**, must be selected. In the filter section similar options are available as described for image data loading. The **Patient Name** and **Patient ID** fields are normally filled in by the information of the image data which has already been loaded.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

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

Select all Selects all components of the list (also **CTRL+A**).

Delete Attention: Deletes the component data from the database and the disk!

Export Exports the selected component data out of the database into a disk file. Multiple selections are supported. A dialog



appears, and after the **Save** button has been activated the user is requested to specify the destination directory for the data export.

Rename For changing the **component name**.

Retrieve Starts loading the selected component.

Cancel Closes dialog without loading.

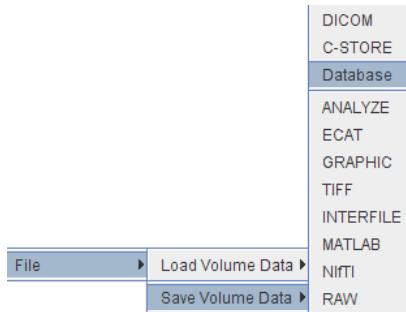
The **Load from File System** button changes to file-based loading directly from the disk.

Saving Data to Databases

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

Image Data Saving

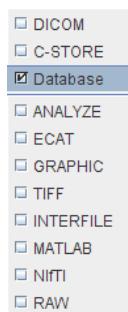
If the database has been configured the **Database** entry is available in the list of output image formats. Image saving can be either done from the **Menu** of a PMOD tool,



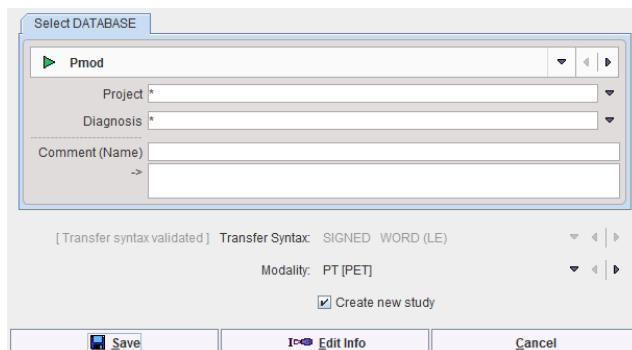
or using a **Save** button.



The **Save** button must be configured to the **Database** format beforehand using the arrow indicated in red.



Saving to the database brings up a dialog window



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

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

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

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

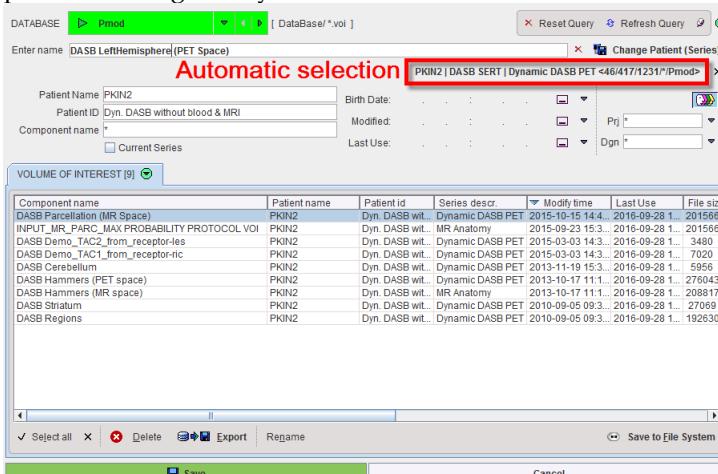
For databases with enabled float storage, images with internal float representation are saved as private enhanced PMOD objects.

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

Component Data Saving

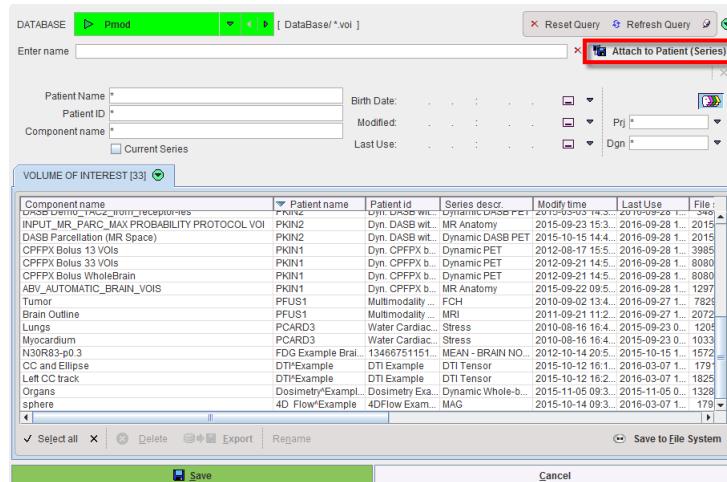
When saving component data to the database, the principle is that it is attached to the image series it was derived from. In practice, there are two situations to consider:

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



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

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



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

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

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

The screenshot shows the 'Components Administration' dialog. At the top, there's a table titled 'Series [14]' with columns for 'Patient Name', 'Study date', 'Time', 'Study description', 'Series description', 'Modified', 'Last Use', 'Mod', 'nz', 'nv', 'nd', and 'nx'. Several rows are highlighted with red boxes. In the middle, there's a table titled 'Selected for loading [1]' with columns for 'Series ID', 'Modified', 'Name', 'Type', 'Params', 'Size [B]', and 'File name'. One row is highlighted with a red box and labeled 'Attached Components'. At the bottom, there are buttons for 'Edit Name', 'Delete Component(s)', 'Select all', 'Export', and 'Edit Series', 'Delete Serie(s)', 'Set Project'.

Data Association

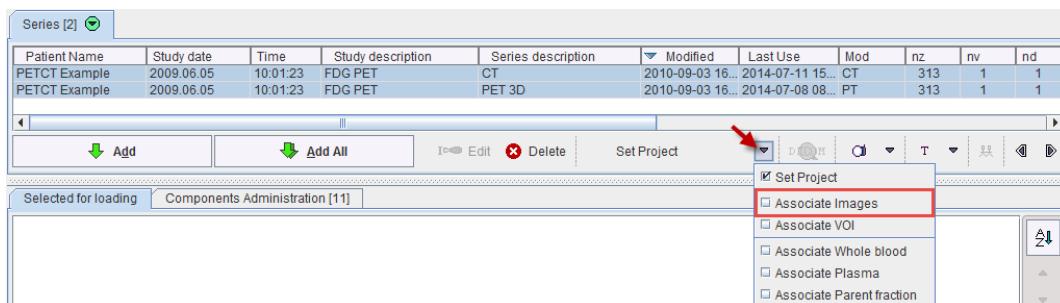
The database interface allows establishing relations between stored data objects which can be accounted for in some processing tools and in *pipeline processing* (on page 420).

For instance, the tool for *MR-based partial-volume correction* (on page 160) of brain PET data requires the grey matter, white matter and CSF tissue segments, which can be calculated with an external *tool* (on page 146). When this segment image is associated to the PET image, processing is simplified because when choosing PET the corresponding tissue segments are implicit.

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

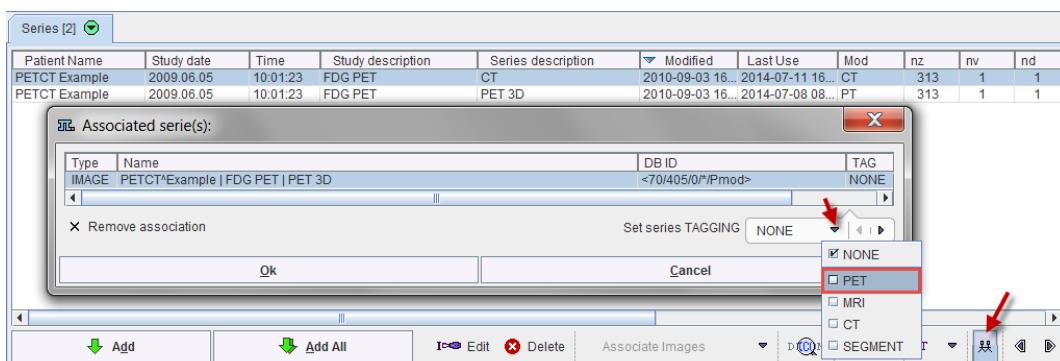
Image Association

In order to establish a relation between two images please select them in the **Series** list.



Then select the **Associate Images** entry from the **Set Project** list as illustrated above. The operation results in a confirmation window which can be closed.

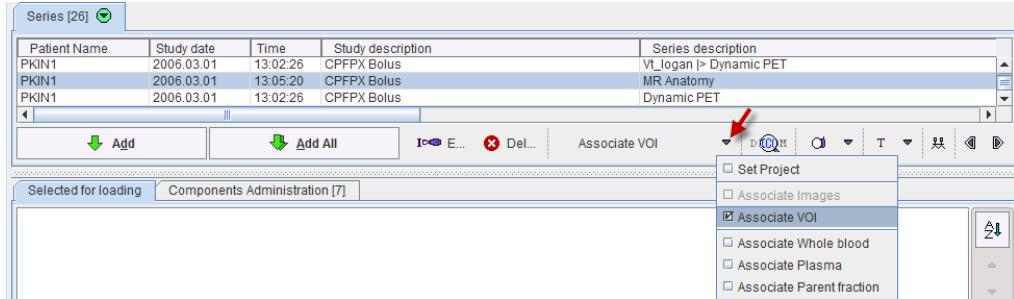
To view the images associated with a particular image please select the image in the **Series** list, and activate the button.



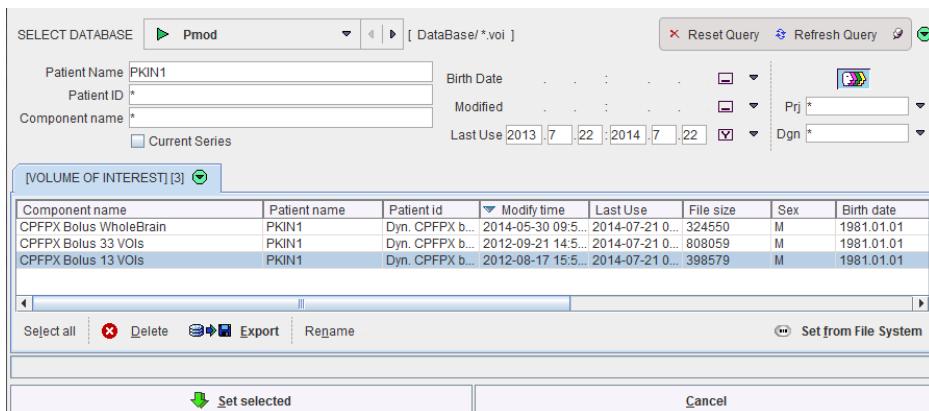
In the example below the **PET 3D** is associated to the selected **CT** series. In order to define its role in a potential processing pipeline an appropriate entry can be selected from the **Set series TAGGING** list.

VOI Association

VOI association can be used in order to establish the default VOIs for images. Select the **Dynamic PET** in the **Series** list, and open the association list as illustrated below.

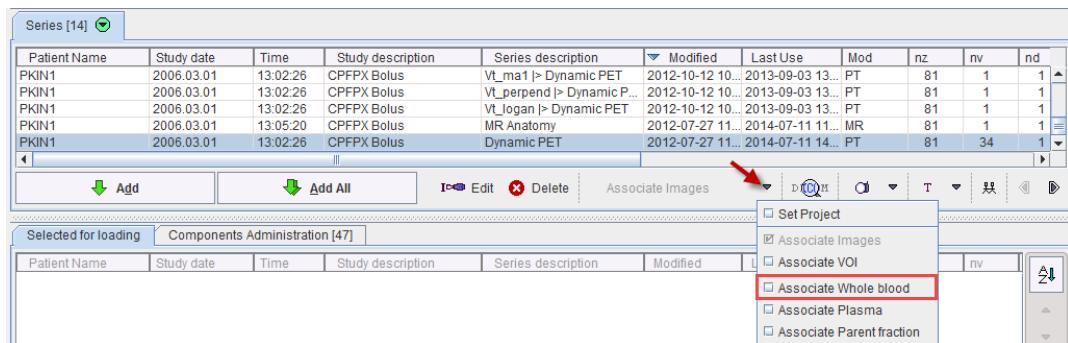


Choose **Associate VOI** to open a dialog window for selecting a VOI. Preferably it is already available in the database and can simply be selected in the **VOLUME OF INTEREST** list. Alternatively, **Set from File System** can be used to point directly to a disk file. Confirm the assignment with **Set selected**.



Curve Association

The association of curves to an image series works similarly. Select the **Dynamic PET** in the **Series** list, and open the association list as illustrated below.



Choose **Associate Whole blood** to define a whole-blood TAC for kinetic modeling purposes. A dialog window opens for selecting a curve. Preferably it is already available in the

database and can simply be selected in the CURVE list. Alternatively, **Set from File System** can be used to point directly to a disk file. Confirm the assignment with **Set selected**.

Component name	Patient name	Patient id	Modify time	Last Use	File size	Sex	Birth date	Size	Wei
Myo-Stress	PCARD1	NH3 Cardiac ...	2012-10-12 11:1...	2013-09-12 1...	491	F	1934.07.17	1.68	102
RV-Stress	PCARD1	NH3 Cardiac ...	2012-10-12 11:1...	2013-09-12 1...	497	F	1934.07.17	1.68	102
LV-Stress	PCARD1	NH3 Cardiac ...	2012-10-12 11:1...	2013-09-12 1...	492	F	1934.07.17	1.68	102
Authentic CPFPX in Pla...	PKIN1	Dyn. CPFPX b...	2012-07-27 12:1...	2014-07-11 1...	519	M	1981.01.01	1.79	75,
Total CPFPX in blood	PKIN1	Dyn. CPFPX b...	2012-07-27 12:0...	2014-07-11 1...	355	M	1981.01.01	1.79	75,
Total FDG in Blood	PKIN3	Dyn. FDG sca...	2010-09-05 09:4...	2014-07-10 1...	975	M		1.79	75,

Inspecting Associations

To find out which components are associated to and image series please select it in the **Series** list and activate the button indicated below.

Patient Name	Study date	Time	Study description	Series description	Modified	Last Use	Mod	nz	nv	nd
PKIN1	2006.03.01	13:02:26	CPFPX Bolus	Vt_ma1 > Dynamic PET	2012-10-12 10...	2013-09-03 13...	PT	81	1	1
PKIN1	2006.03.01	13:02:26	CPFPX Bolus	Vt_perpend > Dynamic P...	2012-10-12 10...	2013-09-03 13...	PT	81	1	1
PKIN1	2006.03.01	13:02:26	CPFPX Bolus	Vt_logan > Dynamic PET	2012-10-12 10...	2013-09-03 13...	PT	81	1	1
PKIN1	2006.03.01	13:05:20	CPFPX Bolus	MR Anatomy	2012-07-27 11...	2014-07-11 11...	MR	81	1	1
PKIN1	2006.03.01	13:02:26	CPFPX Bolus	Dynamic PET	2012-07-27 11...	2014-07-11 14...	PT	81	34	1

Note that if a processing refers to the associates of a series, it will use the first entry in the list if there are multiple entries with applicable definition.

Administrative Tools

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



Their function briefly:

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

Database Administration

The interface of the Data Base Administration tool is almost the same as explained in the section *image loading from the database* (on page 62).

Patient Name	Patient ID	Modify date	Sex	Date of Birth
PKIN1	Dyn_CPPPX bolus & MRI	2016-03-08 13:40:23.888	M	1981.01.01
PKIN2	Dyn_DASB without blood & MRI	2016-03-08 13:39:00.018	M	
PKIN3	Dyn_FDG scan with whole blood data	2010-08-27 15:20:40.196	M	
PKIN5	Tracer with Metabolites, KM file only	2010-08-17 10:05:51.972		
PKIN4	Dyn H2O brain scan, Baseline	2010-08-17 10:00:24.704		

Patient Name	Study date	Time	Study description	Series description	Modified	Last Use	Mod	nz	nv	nd	nx	ny	Organ	SN	Arch
PKIN1	2006.03.01	13:02:26	CPPPX Bolus	Brainmask	2015-03-08 13...	2016-03-08 13...	PT	81	1	1	83	106	BRAIN	0	Pmod
PKIN1	2006.03.01	13:05:20	CPPPX Bolus	MR Anatomy	2015-07-27 11...	2016-09-28 15...	MR	81	1	1	83	106	BRAIN	0	Pmod
PKIN1	2006.03.01	13:02:26	CPPPX Bolus	Dynamic PET	2015-07-27 11...	2016-09-28 15...	PT	81	34	1	83	106	BRAIN	0	Pmod

Selected for replication / export / DICOM C-Store	Components Administration (20)
466	2012-09-21 14:58:32.566 CPPPX Bolus 33 Vols voi 808059 DYN_CPPPX_BOLUS_MRI_1/20120921/107125...
466	2012-08-17 15:55:18.243 CPPPX Bolus 13 Vols voi 398579 DYN_CPPPX_BOLUS_MRI_1/20120817/141181...
466	2012-07-27 12:10:26.089 Authentic CPPPX in Plas. csv 519 DYN_CPPPX_BOLUS_MRI_1/20120727/005205...
466	2012-07-27 12:09:35.152 Total CPPPX in blood. crv 355 DYN_CPPPX_BOLUS_MRI_1/20120727/0057508...
466	2012-07-27 11:38:05.68 image_1 image 49886568 DYN_CPPPX_BOLUS_MRI/20060303/14/188445

The following elements are additional:

Check DB integrity When the button is activated the contents of the currently selected database is checked. If integrity constraints are violated, a dialog window is shown which allows fixing the problem.

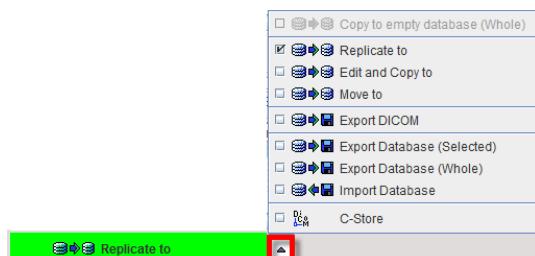
Selected for: This tab is used for the backup of data as described below.
replication / export /
DICOM C-Store

ALL DATA TYPES Selection to filter specific types of data, e.g. to list only VOI definitions, kinetic modeling files, etc. This element is not visible on the **Selected fo:**
replication/... tab.

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

Export and Backup of Database Contents

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



Replicate to Copy data from one database to another online database.

Move to Copy data to another online database and delete the original information.

Export DICOM Copy data to a directory.

Export Database (Selected) Export the selected data together with the describing database attributes into a composite backup file (.bkp).

Export Database (Whole) Export all data of the database into a composite backup file (.bkp).

Import Database Restore data from a composite backup into an arbitrary database.

C-Store Sends all selected images to a DICOM server.

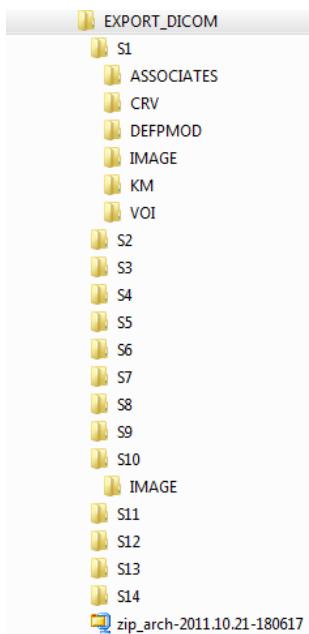
Export DICOM

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

- 1) Select the source database from which data should be exported. The **Components Administration** tab must be selected for switching databases.
- 2) Activate **Selected for: replication/..** tab.
- 3) "Select the patient(s) to be backed up, then activate the **Set as "Selected for Loading"** button. To incrementally add more data, select patients/series and then activate the **Add** or **Add all** buttons. Note that image and component data are backed up with this procedure.
- 4) Configure the operation selection to **Export DICOM**. A dialog window appears listing the series selected for export. A DICOMDIR can optionally be created which lists all image data, and the whole information can be packed into a zip archive.



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



Export/Import with DB Information

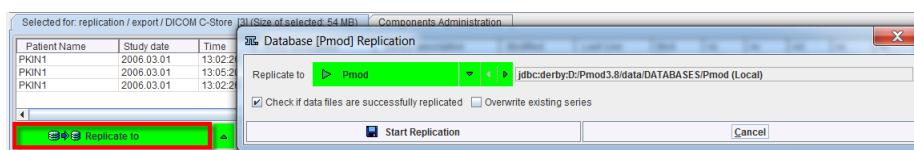
The purpose of this approach is to export data so that they can be re-imported to any other database, which need not be connected. The procedure is similar as described above. However, the result of **Export Database (Selected)** and **Export Database (Whole)** is a single file (.bkp) which contains both the data and the database information.

The information in the .bkp file is only accessible through **Import Database**. When a .bkp file is opened with **Import Database**, data can selectively be imported to any PMOD database.

CAUTION: The .bkp export is limited to a total size of 2GB due to system limitations and thus not intended as a backup facility. It can be used to exchange data within a PMOD version, while compatibility across different versions is limited.

Replication from one Database to Another

Data replication is a method to copy data between two PMOD databases without any interactive loading/saving operations. The preparation steps are the same as for export DICOM data. But instead of selecting the backup option button, the **Replicate to** button is selected and the appropriate target database configured among the available ones.



Activating **Replicate to** will then copy all selected data to the target database. For instance, data related to a single project could be copied to a newly created dedicated database, which will provide a faster response to queries than a big general database.

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

External Backup Procedure

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

- 1) Back up of the database tables.** To this end, automatic backups can be defined in the configuration section of the *data sources* (on page 53).

Another alternative is to directly backup the relevant SQL database directory, in Windows for example:

C:\Pmod3.8\data\DATABASES\dbname for JavaDB databases

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

Aggregate Components such as VOIs and Kinetic Parameters

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

The example below shows how VOI STATISTICS results can be exported. After selecting the component type **VOI STATISTICS** all corresponding results are listed.

Component name	Patient name	Patient Id	Series descr.	Modif. time	LastUse	File size	Sex	Birth date
Controls_Smoothed_VOI_STATISTICS H016	H010	static		2015-09-22 15:0...	2016-04-07 1...	10626	M	1972-03-21
Controls_Smoothed_VOI_STATISTICS H009	H009	static		2015-09-22 15:0...	2016-04-07 1...	10671	M	1958-02-06
Controls_Smoothed_VOI_STATISTICS H008	H008	static		2015-09-22 15:0...	2016-04-07 1...	10680	M	1959-06-14
Controls_Smoothed_VOI_STATISTICS H007	H007	static		2015-09-22 14:5...	2016-04-07 1...	10666	M	1973-05-26
Controls_Smoothed_VOI_STATISTICS H006	H006	static		2015-09-22 14:5...	2016-04-07 1...	10656	M	1956-10-03
Controls_Smoothed_VOI_STATISTICS H005	H005	static		2015-09-22 14:5...	2016-04-07 1...	10679	M	1955-04-08
Controls_Smoothed_VOI_STATISTICS H004	H004	static		2015-09-22 14:5...	2016-04-07 1...	10677	M	1968-05-27
Controls_Smoothed_VOI_STATISTICS H003	H003	static		2015-09-22 14:5...	2016-04-07 1...	10676	M	1959-01-03
Controls_Smoothed_VOI_STATISTICS H002	H002	static		2015-09-22 14:5...	2016-04-07 1...	10681	M	1971-07-08
Controls_Smoothed_VOI_STATISTICS H001	H001	static		2015-09-22 14:5...	2016-04-07 1...	10691	M	1959-03-27

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

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

Chapter 4

Data Loading and Saving

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

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

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

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

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

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

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

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Image Data Formats

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

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

Format Overview

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

Format	Read	Write	Units	Times	Write Precision	Patient Info	SUV Calculation Info
AFNI	yes	no	no	only identical duration for all frames	-	no	no
ANALYZE	yes	yes	no	only identical duration for all frames	16bit int (scaled), 32bit float	no	no
ANALYZE LPS	no	yes	Compatibility version to write images suitable for older PMOD versions				
ANALYZE SPM	yes	no	Compatibility version for reading SPM-generated images so that they are shown in HFS orientation (however, left and right are dependent on SPM settings)				
AVW	yes	no	no	no	-	no	no
BrainVISA	yes	no					

DICOM	yes	yes	yes	yes	16bit short (scaled), private objects with 32bit float precision	yes	yes, post-injection values only on private GE tags
ECAT 6	yes	no	yes	yes	-	yes	yes
ECAT 7	yes	yes	yes	yes	16bit int (scaled), 32bit float	yes	yes, during save no support for post-injection information
GE Advance	yes	no	yes	yes	-	yes	yes
Graphic	bmp, jpeg, tiff	jpeg	no	no	RGB	no	no
HIDAC	yes	no	no	yes	-	no	no
Interfile	yes	yes	yes	for dynamic study	16bit int (scaled), 32bit float	yes, some information on private tags including patient size, weight, study description, body part	yes, on save only standard elements are populated (no time values or postinjection values)
Matlab	yes	yes	yes	yes	32bit float	patient name, id and study id only	no
MicroPET	yes	no	yes	yes	-	yes	yes
Neurostat	yes	no			-		
NifTI	yes	yes	PMOD D Files	PMOD files, otherwise identical duration for all frames	16bit int (scaled), 32bit float	only comments supported as series description	no
MINC 1	yes	no	yes	(yes)	-	yes	yes

Philips ImageIO	yes	no	no	yes	-	yes	yes
Philips par/rec version 4	yes	no	no	yes	-	yes	no
Paravision							
Raw	yes	yes	no	no	8bit int (scaled), 16bit int (scaled), 32bit float	no	no
TIFF	yes	yes	no	no	RGB	no	no
Varian FDF	yes	no			-		

Format Descriptions

Autodetect (Read only)

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

DICOM (Read/Write)

Image data according to the **DICOM standard** <http://medical.nema.org/dicom/>. As input data, the following Information Objects have been tested: CT, Enhanced CT, MR, Enhanced MR, NM, PET, Enhanced PET, SC, SC multi-frame true color, US.

PMOD's DICOM Conformance Statement describes in detail the DICOM support implemented in PMOD. It can be downloaded from the *Support* <http://www.pmod.com/technologies/support/enter-support.php> page on the PMOD Website.

Database (Read/Write)

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

Query (Read only)

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

Interfile (Read/Write)

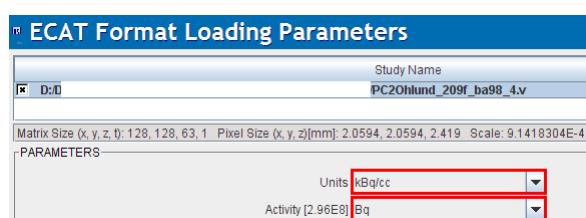
Interfile is a file format developed for data in Nuclear Medicine (Todd-Pokropek A, Cradduck TD, Deconinck F, A file format for the exchange of nuclear medicine image data: a specification of Interfile version 3.3, Nucl Med Commun. 1992 Sep;13(9):673-99).

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

Ecat 6/7 (Read/Write)

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

When loading Ecat data an additional choice appears to explicitly define the units of the patient dose values. This facility was introduced because Ecat files without well-defined units were encountered. Experience has shown that the *Bq* unit should be selected to arrive at the correct doses, but other examples were also encountered. The dose value is important for the SUV calculation and can be checked on the SUV-related panels.



When saving data in the Ecat format, after the specification of the file name, a dialog is presented to the user with a choice of transfer syntaxes. They define the byte ordering used for saving the data. In case you want to read the images using a program other than PMOD, you are recommended to select a *big-endian (BE) encoding*.

MicroPET (Read only)

Data format of the Siemens Inveon and MicroPET *preclinical systems*
http://www.medical.siemens.com/webapp/wcs/stores/servlet/CategoryDisplay~q_catalogId~e_-1~a_categoryId~e_1011531~a_catTree~e_100010,1007660,1011525,1011531~a_langId~e_-1~a_storeId~e_10001.htm. It is used both for PET and CT data.

NifTI (Read/Write)

Extended *variant* <http://nifti.nimh.nih.gov/nifti-1> of the analyze format by the Neuroimaging Informatics Technology Initiative. Both single file (.nii) and double file (.hdr + .img) images are accepted but only in uncompressed form.

PMOD reads the following NIfTI data types:

8-bit unsigned and signed byte (DT_UINT8 and DT_INT8), 16-bit unsigned and signed short (DT_UINT16 and DT_INT16), 32-bit unsigned and signed int (DT_UINT32 and DT_INT32),

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

NIfTI images produced by SPM require A/P mirroring (**TOP to BOTTOM** sorting) to get them into HFS position. Other NIfTI images should best be loaded with **Reorient to Standard Orientation enabled** (on page 98).

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

Analyze (Read/Write)

Data in the *Analyze 7.5 format* <http://www.mayo.edu/bir/PDF/ANALYZE75.pdf> consists of two files. The header file (*.hdr) contains information about dimensions, pixel representation (transfer syntax) and value scaling. The data file (*.img) contains the pixel data itself without any header offset. Value units and information about acquisition timing must be manually entered, or can be loaded from definition files.

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

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

AVW (Read only)

Newer version of the Analyze format.

Raw (Read/Write)

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

Graphic (Read/Write)

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

TIFF (Read/Write)

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

Matlab (Read/Write)

Image data can be read which has been prepared and saved in Matlab using the `save -v4` command (Note: only Matlab version 4 format is supported, thus the requirement of the `-v4` option). The following Matlab variable names/contents are expected:

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

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

Neurostat (Read only)

Neurostat <http://128.95.65.28/~Download/> uses the Interfile format (.hdr, .img) to save the 8 surface projections into an image file. Please note, that this is not a volumetric data set, and therefore should be viewed in a *planar layout* such as 2x4.

AFNI (Read only)

AFNI http://afni.nimh.nih.gov/afni/doc/edu/afni01_intro (acronym for Analysis of Functional NeuroImages) creates two-file data (.HEAD, .BRIK).

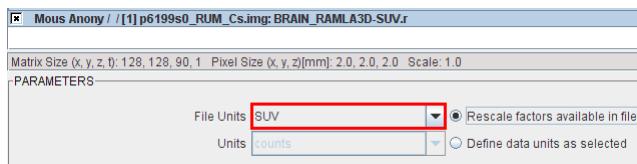
GE Advance (Read only)

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

Philips (Read only)

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

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



HIDAC (Read only)

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

BrainVISA (Read only)

Format used by the *Brainvisa software* <http://brainvisa.info/>.

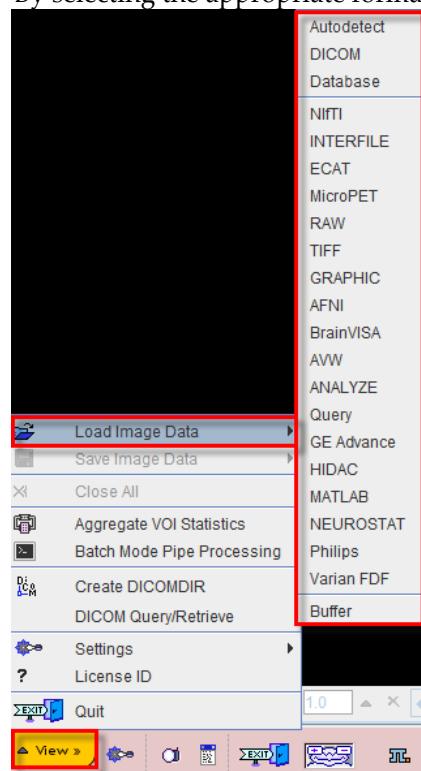
Varian FDF (Read only)

Flexible Image Format of Varian MR systems.

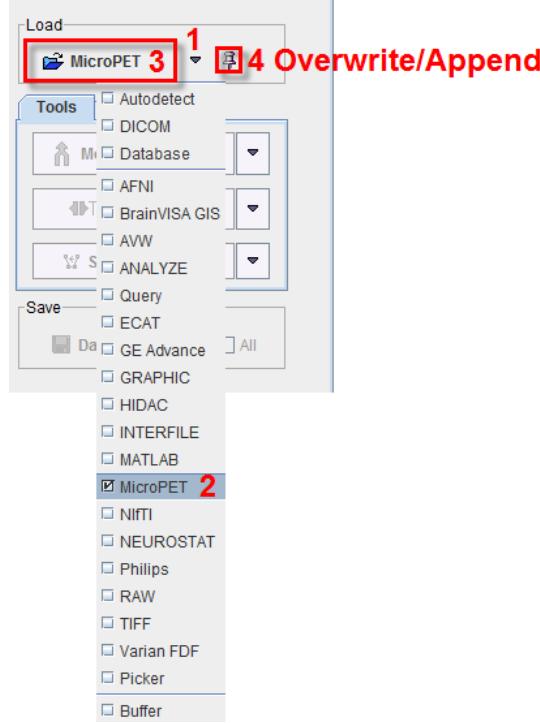
Image Data Loading

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

- 1) By **dragging** an image file from the desktop onto the title bar of the PMOD tool, or onto a tool button on the PMOD tool bar. PMOD will try to recognize the data type and read the images accordingly. If it is a data format without header information the information from the last successful loading operation will be applied.
- 2) By selecting the appropriate format from the menu **View/Load Image Data**, eg

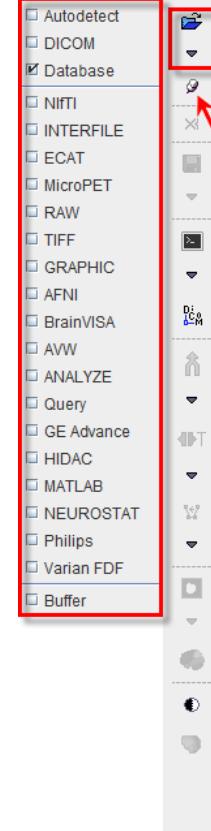


- 3) By configuring a multi-function Load button



to the correct type. The loading operation will be immediately started.

- 4) By selecting and configuring the appropriate format in the lateral toolbar using the Load



button

In many situations (indicated by the pin besides the format selector, 4) it is possible to load several files into a tool. In this case multiple file names can be selected in the file selection box, or multiple image series in the database loader. If images have already been loaded and

the pin is fixed , the newly selected studies will be *appended* to the present one(s). Otherwise the prior studies will be overwritten.

Data Units

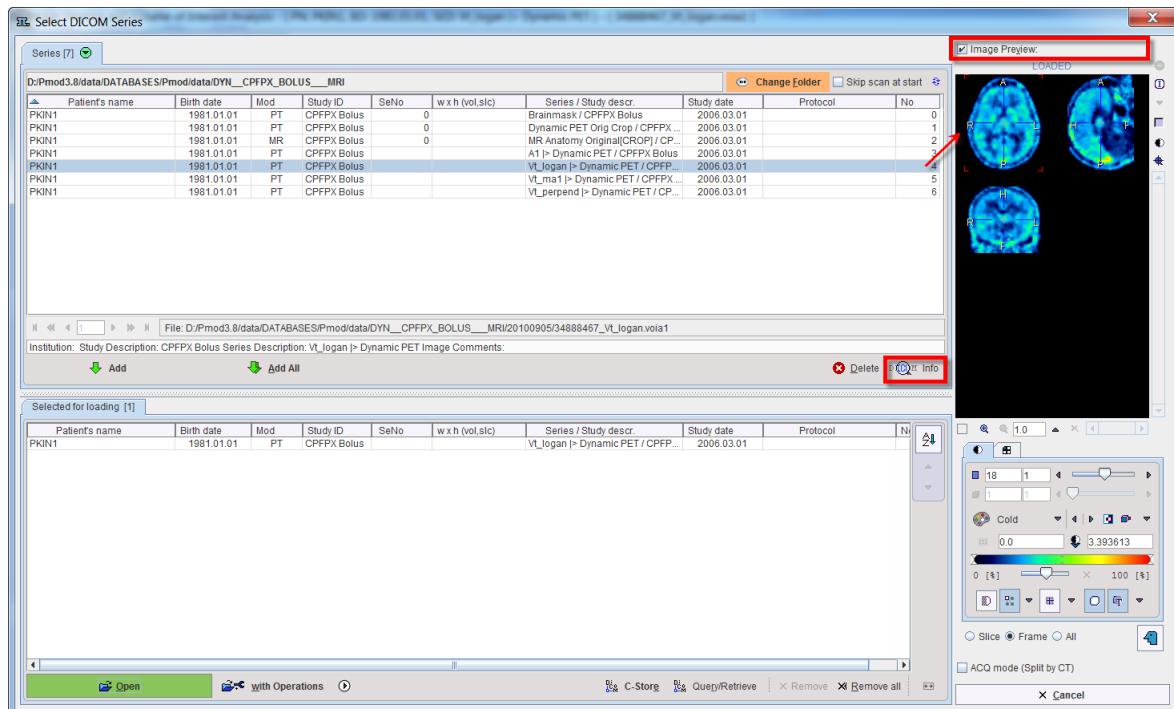
For any quantitative PET work you have to make sure that the right *input data* units are specified if the data is not read from DICOM, ECAT or the database. Activity concentration values are always converted to the internal representation of kBq/cc during a read operation. If the data is saved again,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

DICOM Part 10 Data Loading

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

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

The DICOM loader presents the selection of the available image series in a dialog window as illustrated below.



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

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

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

DICOM Query/Retrieve starts the dialog window for querying a remote DICOM node and pulling images from it as explained *above* (on page 47).

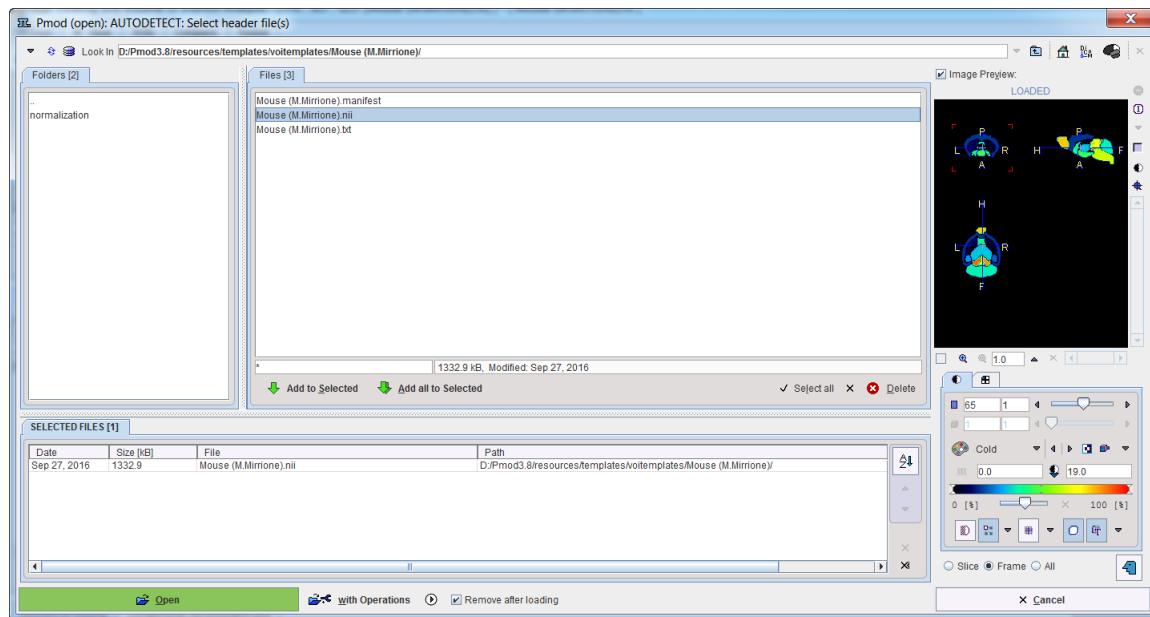
C-Store is a utility for sending selected data sets directly to a remote DICOM server without the need to open it for viewing, and then selecting the **C-Store** saving button. Direct sending has the advantage that the original DICOM images are transferred. Otherwise, if loaded images are sent, they contain information modified by PMOD.

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

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

File-based loading

For all non-DICOM type of image data the loading dialog looks like this example using the **Autodetect** format.



Use the navigation elements at the top to browse the directory hierarchy. The files to be viewed need to be brought to the **SELECTED FILES** area by double-clicking, or by using the **Add to SELECTED** or the **Add all to SELECTED** button. Note that in some contexts multiple file selection may not be possible. In that case, only one file can be brought to **SELECTED FILES**.

The images will be loaded in the order they appear on the list. This may be relevant in the fusion tool where the first image will serve as the reference, or if multiple static images are to be combined into a dynamic study. To modify the list order use the **Sort by selected column** button or **Up** and **Down** buttons, or **Remove from selected** a file and add it later back to the end of the list. Optionally, **Remove all from selected** using the button allows removing all images available in the **SELECTED FILES** area.

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

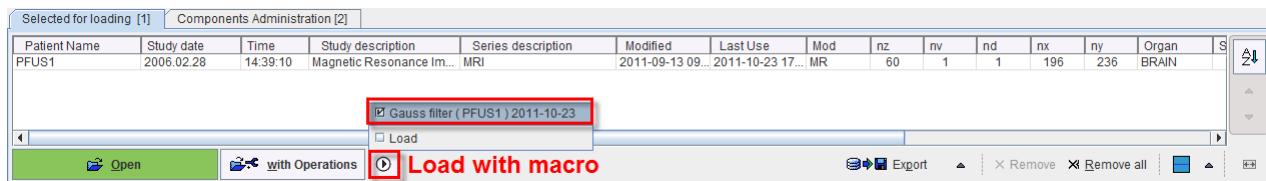
When **Open** is activated, the selected files are loaded directly. If **with Operations** button is activated, a dialog window is opened specifying loading transformations to be applied to the image as explained below.

Database Loading

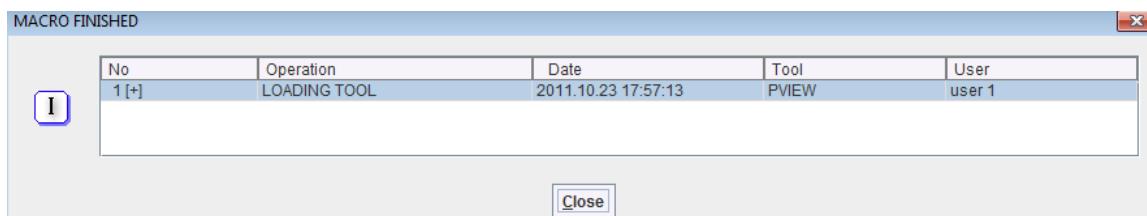
Database loading of images has already been described *above* (on page 62).

Loading Macros

Macros are applied as a data transformation during loading. To this end select one or several images for loading. Then, instead of using the **Open** button, use the  button next to it.



A list opens showing the currently available macros. To load a macro from a different source, use the **Load** entry. As soon as a macro is selected, the data is loaded, the processing steps applied, and finally a confirmation window **MACRO FINISHED** shown as illustrated below.



Macros can be prepared based on the *image history* (on page 120) of a representative data processing session.

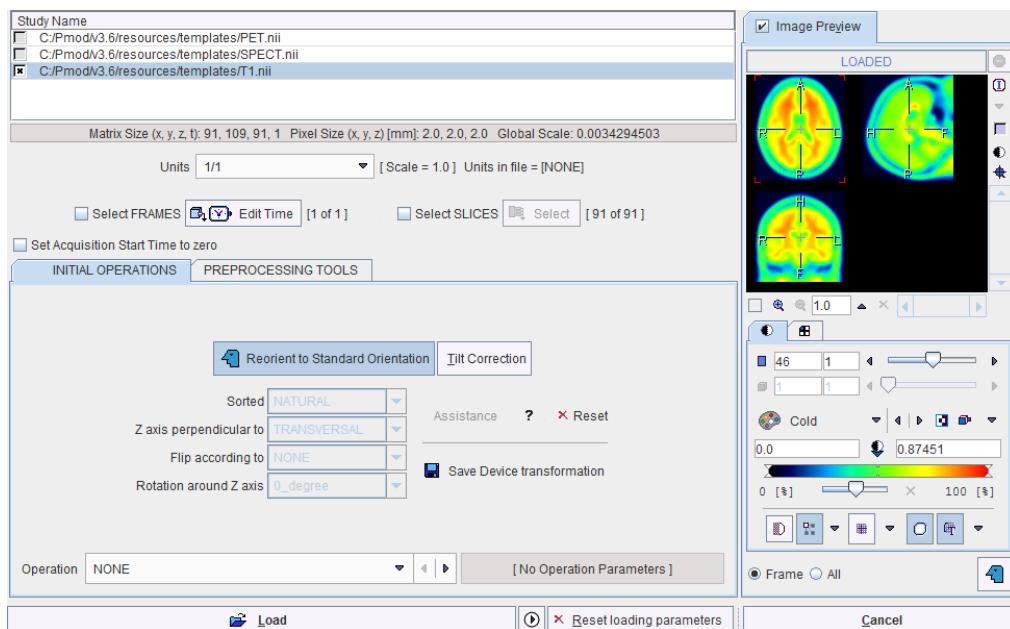
Buffer Loading

Note that to be able to load from the **Buffer**, the images need to be initially loaded in a PMOD tool and then saved to the **Buffer**. The procedure is described in the *Buffer Saving* (on page 110) section.

Image Data Transformations during Loading

There are two basic ways how images are loaded:

- 1) Direct loading: if the **Open**  button is selected on the image selection dialog; the images are immediately loaded without any data transformations.
- 2) If the **with Operations**  button is selected, an intermediate dialog window is shown which allows configuring the image data properties as well as optional pre-processing steps. Initially, the *settings of the last loading operation* are shown. The example below is an illustration of the loading dialog after three NiFTI files from the templates directory have been selected for loading.

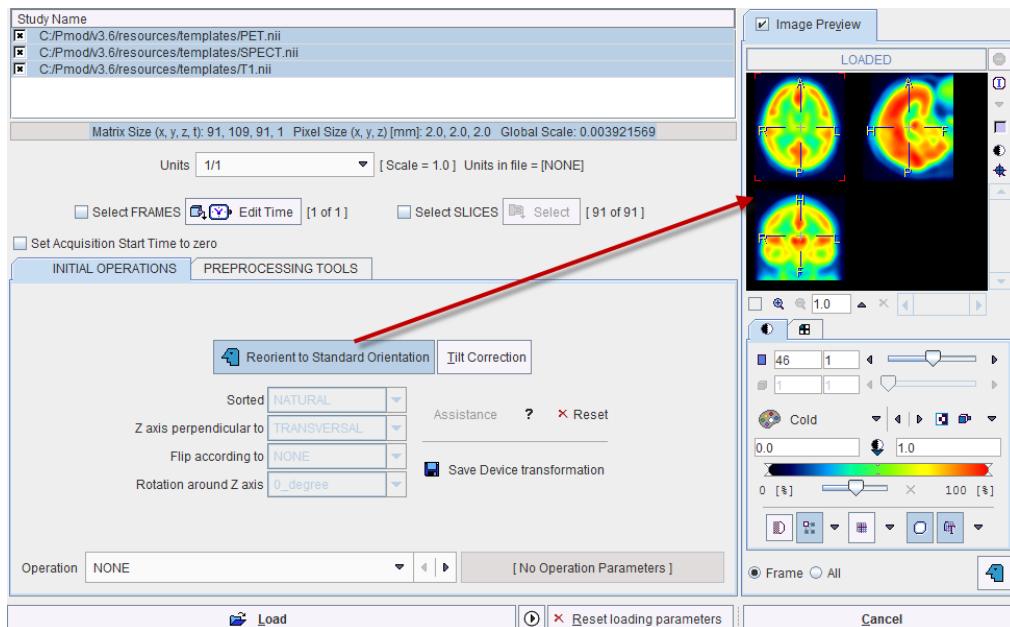


In the upper part the list of images selected for loading is shown. The rest of the dialog window allows defining the properties of the images and transformations which are to be applied to the selected image during loading.

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

Changing the Image Orientation

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



The following image re-orientations are supported

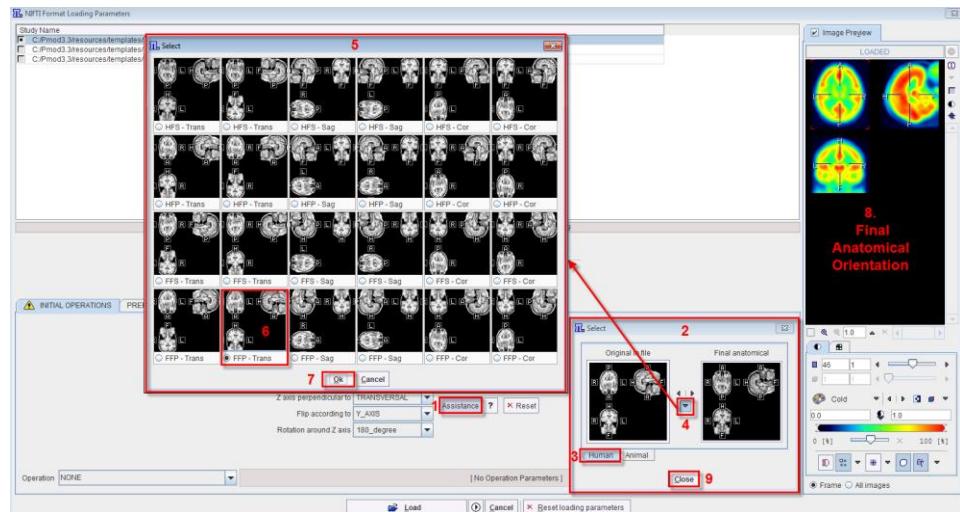
- » modification of the sorting order to interchange left-right, top-bottom in the image, and front-back (slice ordering);
- » rotation about the z axis;
- » orthogonal sections such as coronals or sagittals.

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

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

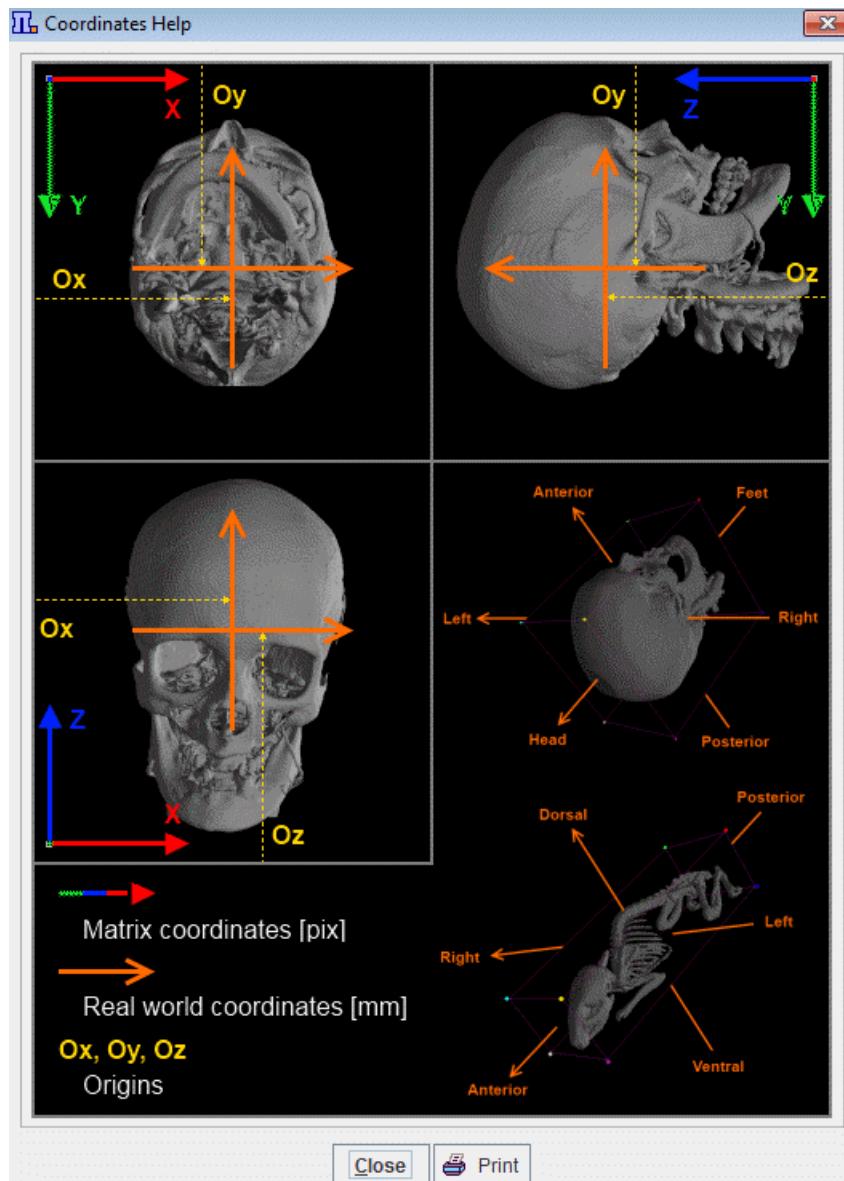
- 1) To start activate the **Assistance** button (1).
- 2) A selection window (2) appears allowing to choose the image type to be load: **Human** or **Animal** (3).
- 3) To select the original orientation in the image file the **Down ▾** arrow (4) need to be activated.
- 4) A dialog window pops up (5) allowing to select the original orientation in the image file (in the example FFP-Trans 6).
- 5) To set the selection for the original orientation in the file, the selection dialog window need to be closed with **OK** (7).

- 6) The result of re-orientation is immediately reflected in the **Image Preview** section if the corresponding checkbox is enabled (8).



- 7) Finally, **Close** the orientation selection window and load the image with the **Load** button.

More information and help about human and small animal matrix coordinates and real world coordinates are provided activating the question mark button next to the **Assistance** button.



The re-orientation settings may be easily cancelled activating the **Reset** button next to the **Assistance** button.

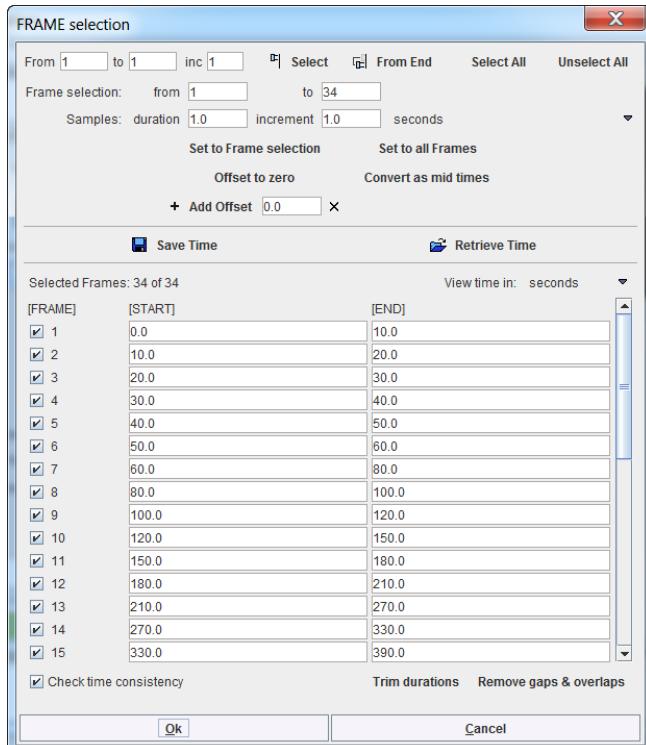
Reorient to Standard Orientation: This option will arrange the data such that the patient position is closest to the head first supine (HFS). The patient's head is directed into the display, looking up the display and left patient hand to the right side of the display. This adjustment is performed without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

Tilt Correction: If this option is selected, the corners of the slices are checked whether they are located on a line perpendicular to the slice plane. If this is not the case, as with CT data acquired with a tilted gantry, they will be resliced such that the new top left corner of the

image are aligned. The default reference frame is the frame closest to the origin. If **Reorient to Standard Orientation** is active tilt correction will always be checked and performed prior to data reorientation. As a result of this correction the orthogonal planes will not show displacement artifacts.

Defining the Acquisition Timing

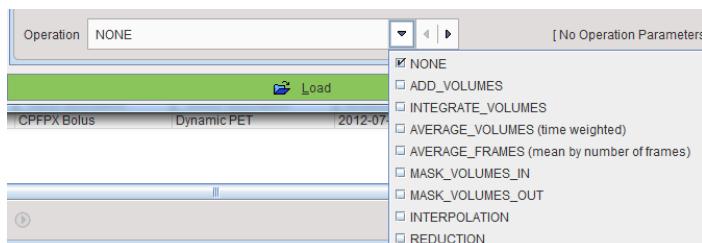
The specification of the acquisition times is important for using dynamic data in a quantification process. The times can be inspected and the definition overwritten using the **Edit Time** button, which shows the following dialog window.



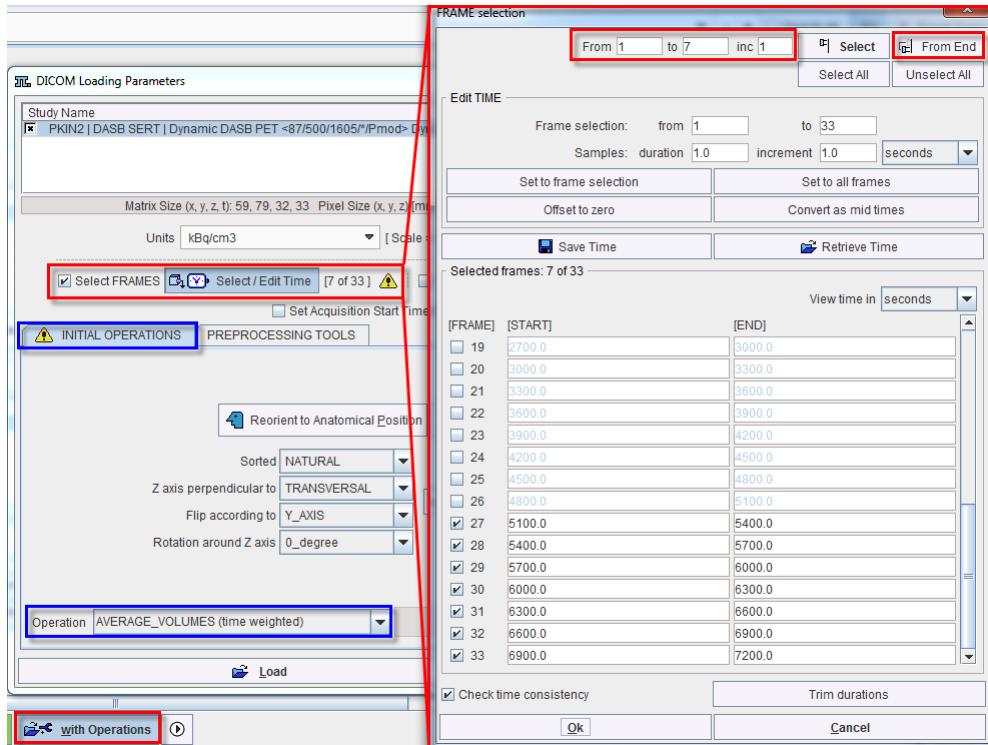
For DICOM, Ecat, MicroPET, Interfile and GE Advance data the times are read from the selected file and shown in the list. Note the **Save Time/Retrieve Time** buttons which allow saving/retrieving the timing of the dynamic frames to/from a file. If the **Select FRAMES** box is checked when opening the dialog window, it is additionally possible to arbitrarily select a subset of frames for loading. The **Trim durations** button ensures that the end times are not after the following start times.

Initial Operations

The **INITIAL OPERATIONS** tab offers several other **Operations**.

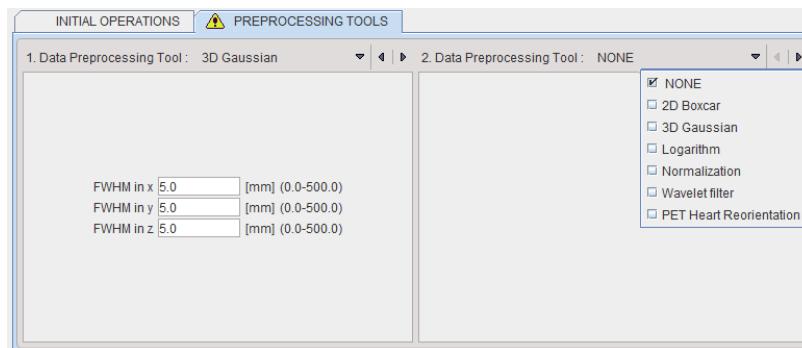


The example below illustrates how the last seven acquisitions of a dynamic study can be averaged by selecting the frames sub-range and setting the **Operation** selection from **NONE** to **AVERAGE_VOLUMES (time weighted)**.



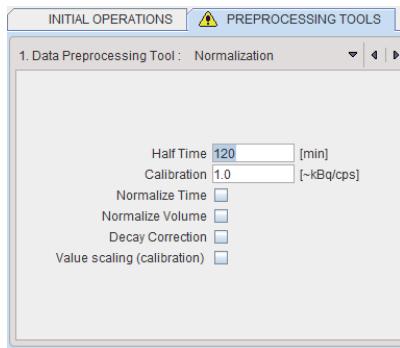
Enabling Pre-Processing Operations

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



Data Normalization

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

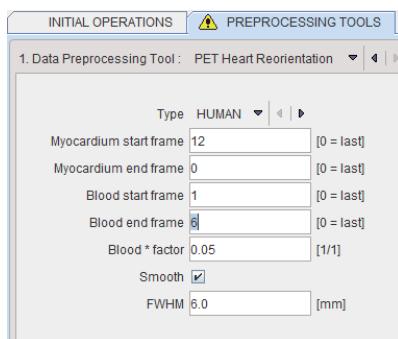


The following parameters are applied during the calibration process:

- » **Half Time** is used for a correction of the physical decay to the acquisition start, if the **Decay Correction** box is enabled.
- » **Calibration** is a factor for the conversion of the measured counts - which represent only a fraction of the emitted photons - into the true number of physical decays. It is applied if the **Value Scaling** flag is enabled.
Note: The calibration factor can be determined using a phantom filled with a known, representative activity concentration. Phantom images are acquired, corrected and reconstructed using the same protocol as the research study. Then, the image values are decay corrected, time and volume normalized, resulting in images with counts per ml per second. As the next step, a homogeneous VOI is outlined and the average pixel value calculated. Finally, the calibration factor is calculated by dividing the known true phantom activity concentration by the VOI average.
- » **Normalize Time** is a flag indicating whether the values in the file are already average counts per time (i.e. not total accumulated counts during the acquisition). If your image files contain counts and not count rates, check this box, and the image values are divided by the acquisition duration.
- » **Normalize Volume** is a flag indicating whether the values are already counts per unit volume. If not, check this box, and the values are divided by the image voxel size (known from the image header).
- » **Decay Correction:** Apply a decay correction to time zero. Note that under normal circumstances the start of the first frame will correspond to time zero, so decay correction is to the acquisition start. If this is not adequate, for instance in a PET image which is to be analyzed by an autoradiographic model, the frame start/end times should be edited (e.g. set to 40min and 50min for a 10-minute scan starting 40 minutes after injection), the image saved, and then loaded again for decay correcting to the injection time.

Heart Reorientation

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



The following parameters need to be defined:

- » **Type** is representing the heart model type and can be selected from the available selection list: **HUMAN**, **RAT** or **MOUSE** according to the image to be analyzed.
- » **Myocardium start frame** and **Myocardium end frame** are used to define the frames average range for creating the myocardium averaged image.
- » **Blood start frame** and **Blood end frame** are used to define the frames average range for creating the blood averaged image.
- » **Blood*factor**: as there may exist some activity in the cavities, a fraction of the blood volume image can be subtracted to improve the contrast. In the example above a fraction of 0.05 of the blood averaged image will be subtracted.
- » **Smooth** and **FWHM**: optionally, the blood and myocardium averaged image can be smoothed with a 3D Gaussian filter with full-width half maximum value defined in the FWHM text box.

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

Image Data Saving

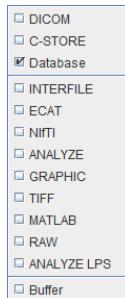
There are three types of image saving procedures:

- » **File formats:** The user selects a file format and the directory wherein the image files are saved.
- » **C-STORE:** The images are directly sent as DICOM objects to a DICOM server.
- » **Database:** The images are saved to one of the configured databases (local or remote). To do so, they are converted to DICOM.
- » **Buffer:** The images are saved to the buffer and can be loaded in any module with the **Buffer** option for loading.

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

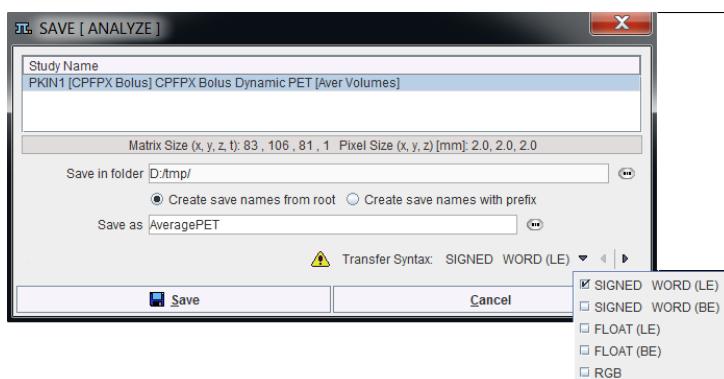


with the selections



File-based Saving

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



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

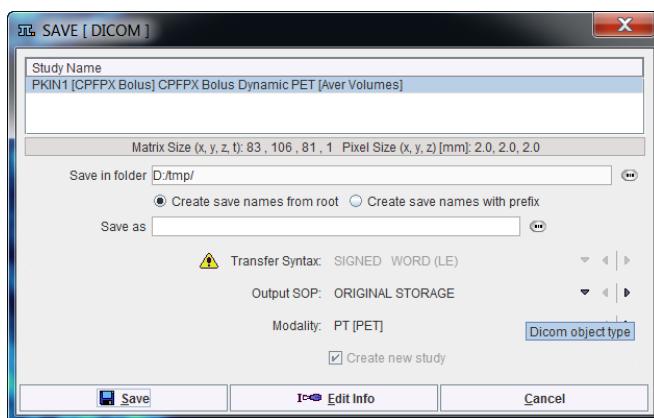
The accuracy of the data representation - and the disk space requirements - increases from top to bottom. If the dynamic range in the images is large, you are recommended to use a **FLOAT** format. For PMOD the number encoding does not matter. For other programs, however, there may be preferred formats.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

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

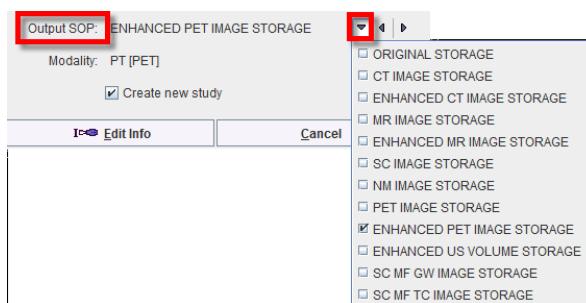
DICOM Part 10 Data, C-STORE

DICOM Part 10 Saving

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

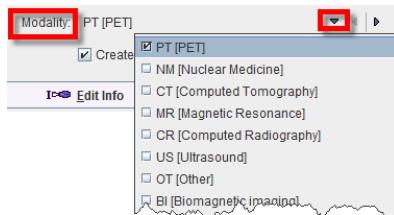


The **Output SOP** determines compatibility with other systems that may not support all types of objects. The list contains all DICOM IODs supported by PMOD. Initially, a suitable definition is proposed, but the user may change the list selection. For RGB image data and screen captures only Secondary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



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

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



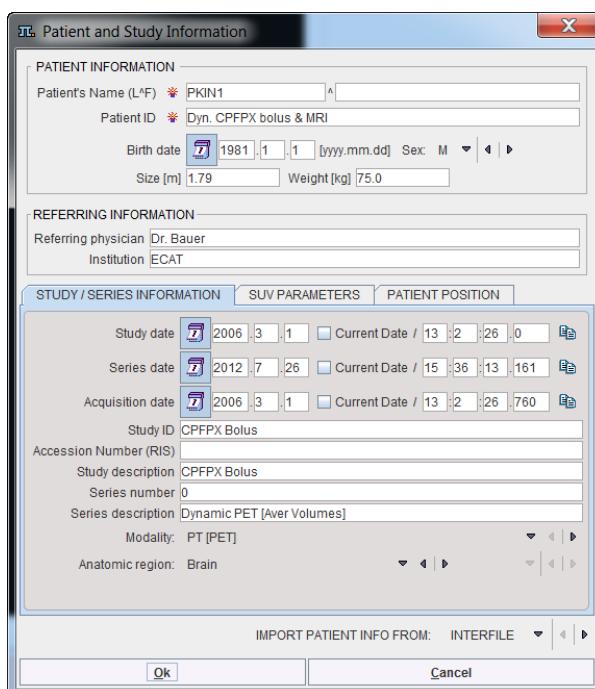
The **Create new study** box is only relevant for data originally loaded in DICOM:

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

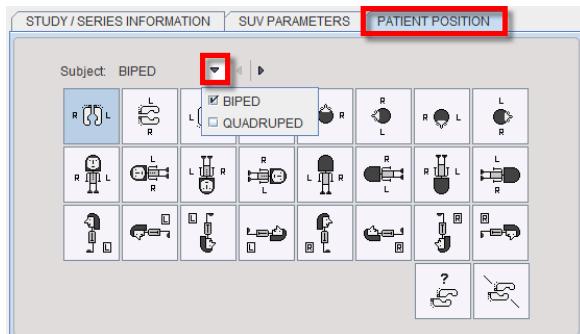
For non-DICOM data PMOD will always generate new study UIDs.

Editing DICOM Information

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



The elements on the SUV PARAMETERS pane are explained in the SUV section *below* (on page 136). The PATIENT POSITION panel allows the selection of Subject type: BIPED or QUADRUPED. For each type the panel displays an array of buttons which allow defining (or correcting) the subject orientation.

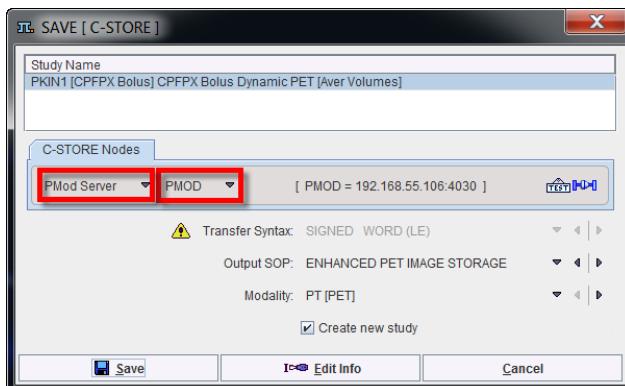


Note that after activating one of the buttons the anatomical annotations in the image overlay are adjusted. Please identify the button which generates an appropriate labeling. This information will then be saved with the data.

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

C-Store

When storing the data in **C-STORE**, a similar dialog window appears as for DICOM saving, but included is also a list of DICOM servers to which the data can be sent.



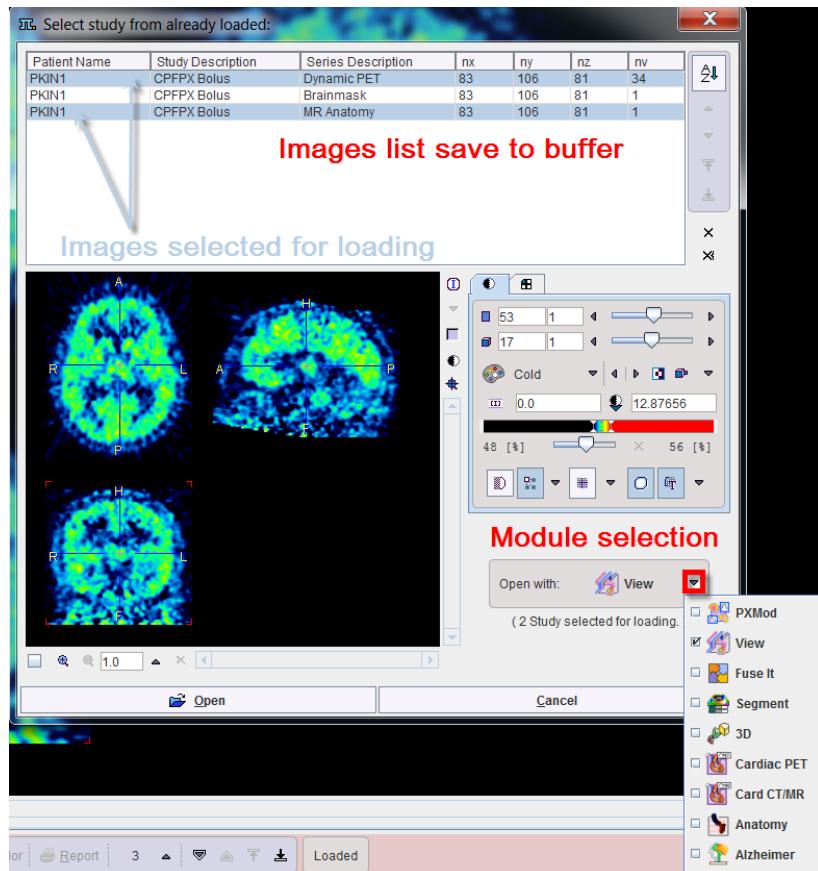
For details regarding DICOM support in PMOD please refer to the PMOD DICOM Conformance Statement.

Database Saving

The saving of images into a PMOD database is described *above* (on page 70).

Buffer Saving

Saving to the buffer does not involve selecting a destination directory or specifying a file name. All the images processed in, e.g., the **View** module can be saved to the **Buffer** and then loaded in a different module with **Load from Buffer** option. Additionally, a new module can be opened during the loading from buffer procedure as shown below:



When **Load from Buffer** is activated a dialog window as above appears. In the uppermost part the images saved to buffer are displayed. More than one image can be selected with **CTRL + click**. On the right side of the image preview display, an **Open with** button allows choosing the module where the selected images are going to be loaded. Finally, click **Open** to load the images.

Component Data Loading and Saving

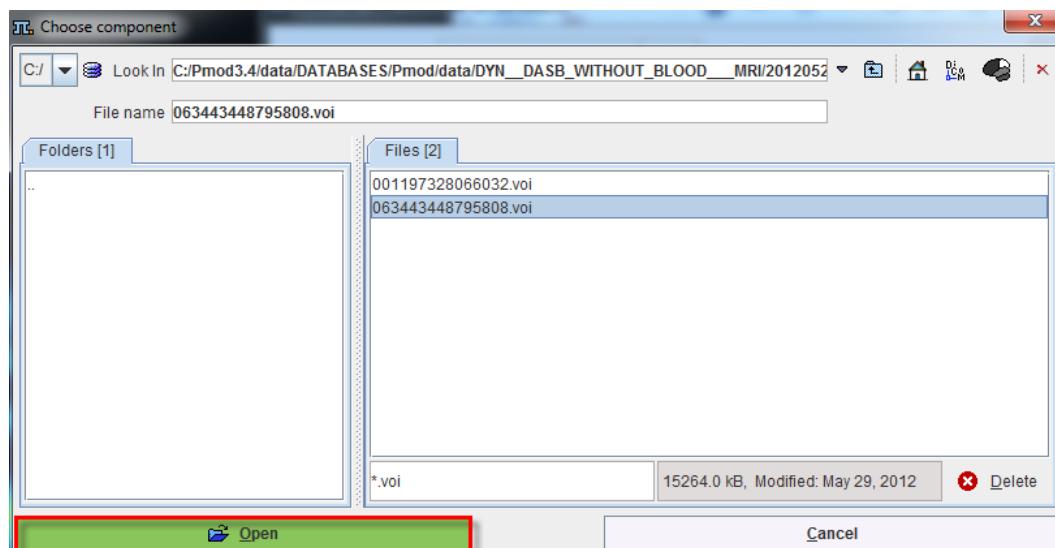
Component data such as pixel-wise modeling protocols (.defpmod), volume-of-interest definitions (.voi), kinetic modeling files (.km), matching transformations (.mat) etc. can be saved as disk files or database data using the component saving buttons  in the user interface.

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

Loading/Saving without Database Option

Loading

If there is no database installed or it is not enabled for component data, a dialog of the following type appears when loading component data.

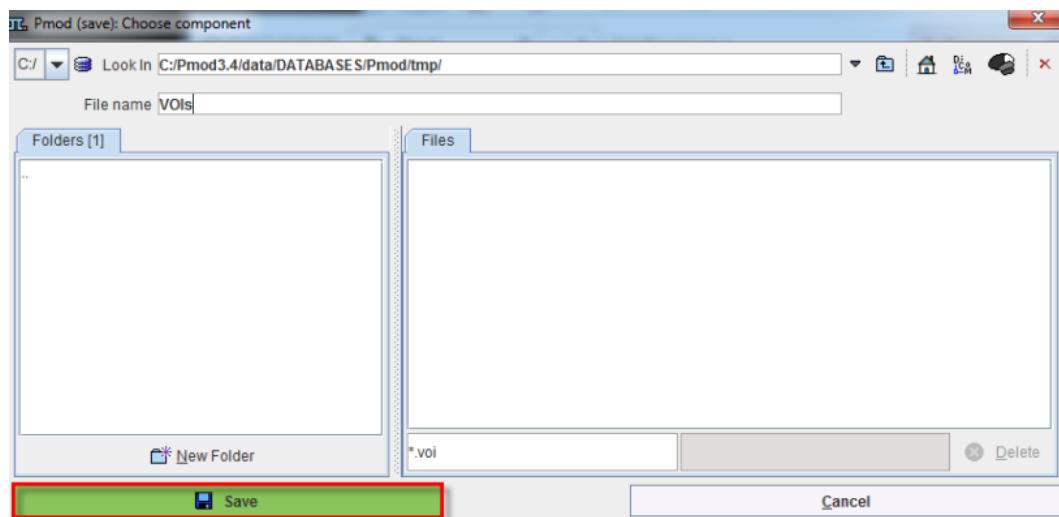


In the upper part the current search directory is indicated. Initially, it points to the directory of the last successful loading operation. To change the search directory, use the navigation buttons in the **Folders** section (.. indicates up one level).

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

Saving

When a component is saved, a dialog appears which is very similar to the loading dialog.



It has the same elements for changing the directory. The **File name** field allows specifying a name for the new data file, and the **Save** button will start saving.

Loading/Saving with Database Option

Database *loading* (on page 68) and *saving* (on page 71) of component data is described above.

Loading of Vector Data

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

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

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

Note: The *header line is required* - otherwise the values on the first line will be skipped. If valid units are found in the file header the values are converted to the internal

representation [sec] and [kBq/cc]. If there are no valid units in the header line, the import procedure assumes that the data units are equal to the ones in the configuration settings of the tool.

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

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

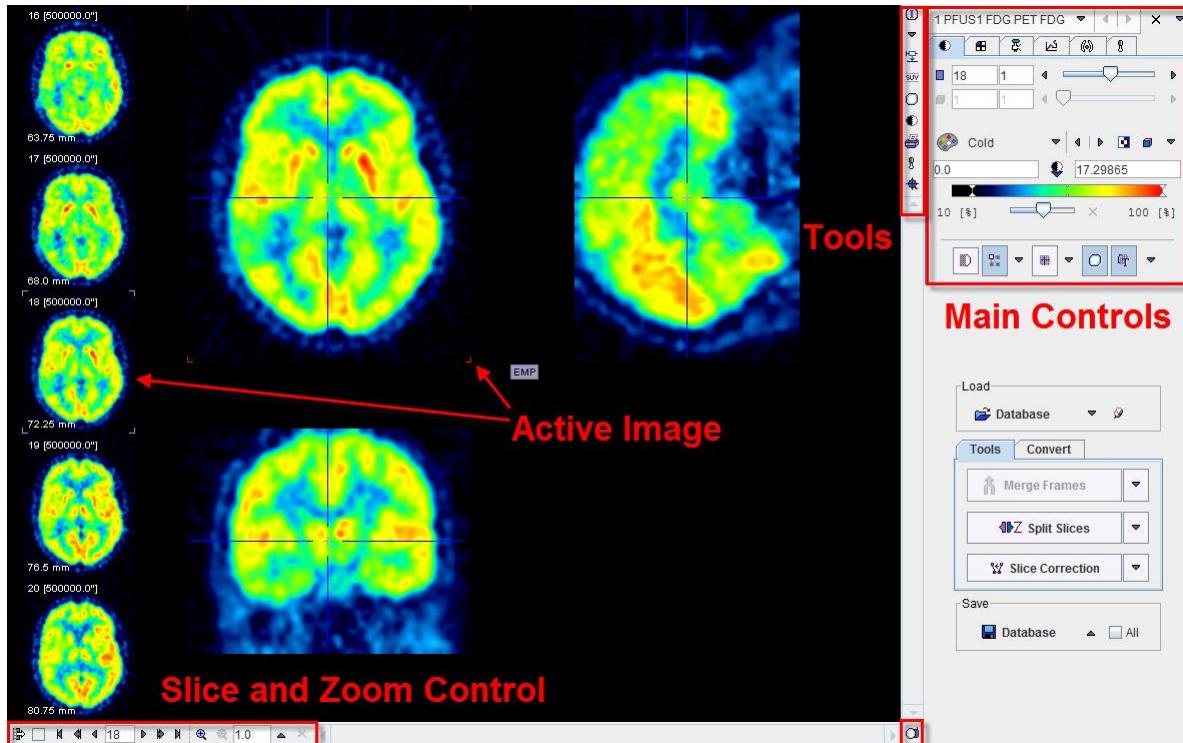
Again the header line is required, and the units are considered if they are recognized. Please note that the activity units are defined *after the header of the second time column*, not after the first value header.

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

Chapter 5

Image Display and Basic Processing

The same image display object is used in all PMOD tools. It consists of an image viewport, ie. the black area for the images, a set of image presentation and layout controls to the upper right of the viewport, and some tools grouped along the image.



The viewport shows one or several images of a series, depending on the image layout which can be modified by use of controls. Most PMOD tools allow for loading more than one image series. The image display may then be switched between the available series with the selection at the top of the controls, eg.



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

	Shows information related to the displayed image series and also allows changing timing and patient/study information.
	Selection between the stacked image series.
	Start the Data Inspector to examine the pixel values, time vectors of dynamic studies, the acquisition times, standard uptake values (SUV), and the origin.

	Start the SUV page of the data inspector directly.
	Start the Volume-of-Interest tool to outline VOIs and calculate statistics on the currently shown images.
	Start the Large View tool which allows looking at the same images but in a maximized viewport.
	Button to hide/show the image controls. Hiding the controls after the images are in a suitable presentation has the advantage of a larger viewing area.
	Generate a Report for printing or saving.
	Activate the mouse-operated zooming mode.
	Show the external tools list.

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

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

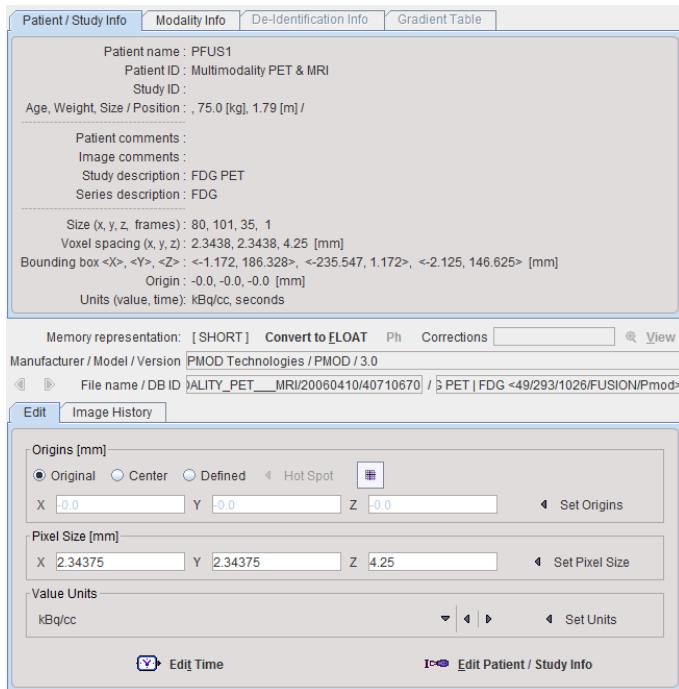
The image presentation can be modified in many ways by means of the control panels, which can be brought forward by clicking on the corresponding tab. Note that depending on the context some of the panels (e.g. oblique reslicing) and buttons may be missing.

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Viewing and Changing Study Information

In PMOD, each loaded image series has a set of attributes. Depending on the loaded image format they may be partly empty. Using the  button, the information can be shown in a dialog window as illustrated below, and edited.



Note that after changing information the data set needs to be saved to make the changes permanent.

Modality Info

If information regarding **Tracer activity** and **Dose** are stored in the original image file, these informations are available in the **Modality Info** tab.

Image Properties

Memory Representation

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

Edit the Image Origin

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

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

- » **Original:** With this setting the origin obtained with data loading is used. This is the standard setting.
- » **Center:** By selecting this button and activating **Sets Origins**, the center coordinate of the data volume is defined as the new coordinate origin.
- » **Defined:** When this button is set, the origin coordinate can be entered manually into the **X**, **Y** and **Z** fields, for instance the values from another study. As an alternative, the triangulation point can be set to the intended location of the origin, and then the button **Get from Hotspot** activated. This will transfer the triangulation coordinate to the origin to the pixel. **Sets Origins** has to be activated for making the coordinates actual.

Edit the Pixel Size

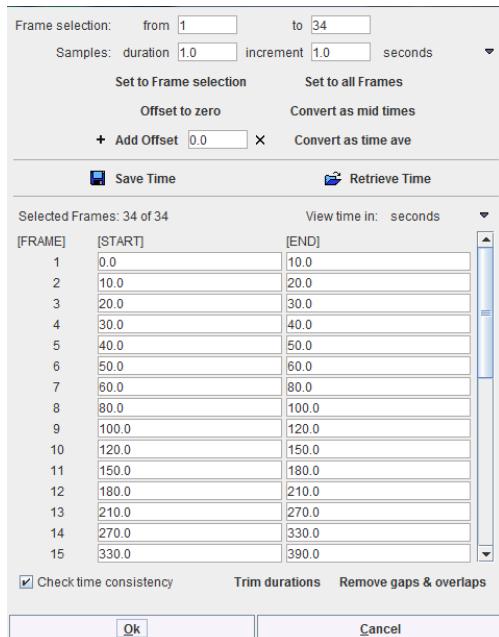
The **X**, **Y** and **Z** fields of **Pixel Size** shows the current pixel size. To change them edit the values and then activate **Set Pixel Size**.

Edit Value Units

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

Edit Acquisition Times

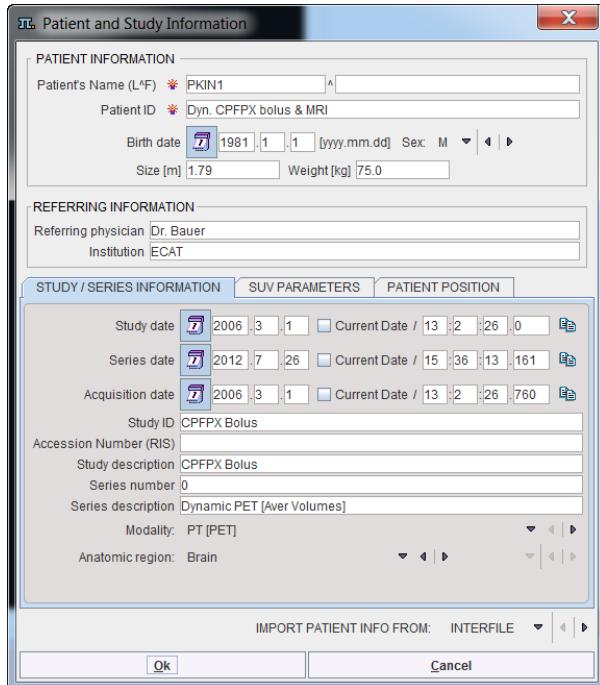
Correct acquisition times are very important for using dynamic data in a quantification process. The times can be inspected and overwritten using the **Edit Time** button, which shows the dialog window below.



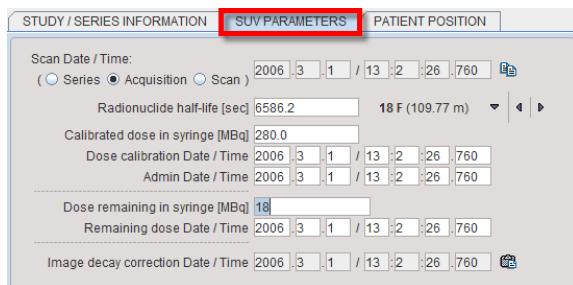
Note the **Save Time/Retrieve Time** buttons which allow saving/retrieving the timing of the dynamic frames to/from a file. If changes are required, the values can be overwritten and then saved with the **Ok** button.

Patient, Study and SUV-related Information

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



Note the **SUV PARAMETERS** tab which houses the information relevant for the SUV calculation. All these fields must be completed. For more information please refer to the section *Inspecting SUV Values* (on page 136).



If the anatomical annotations are not correct, for instance because wrong patient positioning information was entered at the acquisition console, the **PATIENT POSITION** tab can be used for correction purposes. There are two types of position annotation supported for **Subjects : BIPED** and **QUADRUPED**. The buttons represent the view when looking at the transaxial images. As soon as a button is activated, the annotations in the images are adjusted.

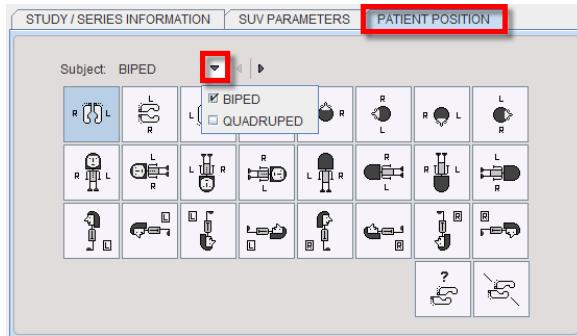


Image History and Macros

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

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

An example history is shown below.

Edit Image History				
No	Operation	Date	Tool	User
1	=> LOAD	2011.10.23 21:59:34	PVIEW	user 1
2	FILTER	2011.10.23 22:00:18	PVIEW	user 1
3	PROCESS	2011.10.23 22:00:30	PVIEW	user 1
4	SCALE	2011.10.23 22:01:05	PVIEW	user 1

Details Scale Values by: scale = 0.0050, offset = 0.0 All volumes, All slices

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

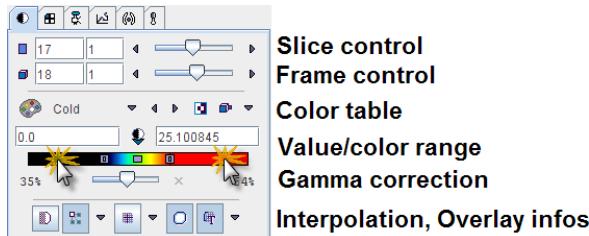
Macros

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

Macros can be applied as a data transformation during *loading* (on page 96) or in pipe processing.

Changing the Image Presentation

The first tab in the main controls contains most functions to modify the way how the images and the overlay information look like.



Control of Slice(s)

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

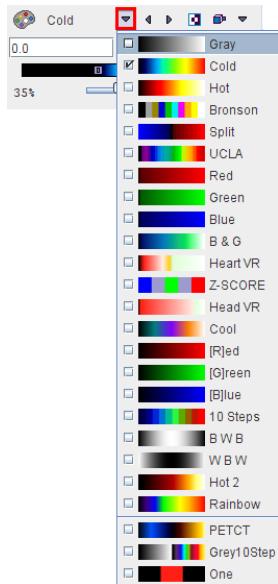
Instead of selecting slices using the controls, the user can also scroll slices by dragging the left mouse button over the image holding the **CTRL** key in the Up/Down direction (see the summary of shortcuts below), or with the mouse wheel.

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

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

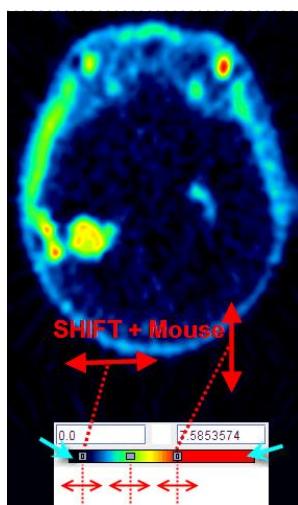
Color Tables

There is a selection of pre-defined gray and color tables which can be chosen with the list selection.



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

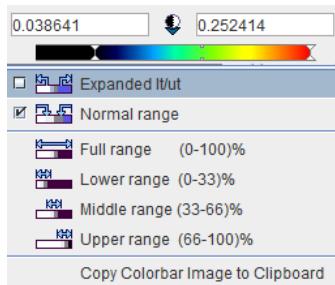
A minimal/maximal threshold value defines the range of displayed values. The thresholds can be entered numerically, or the handles in the color bar can be dragged with the mouse. Additionally, the user can modify them by dragging the left mouse button over the image holding the SHIFT key. Left/Right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



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

Zooming into Color Table

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



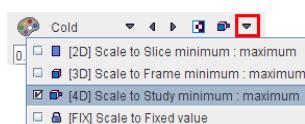
The first menu entry **Expand It/ut** then performs the desired task and makes the color bar change to



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

Color Table Modes

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



The different modes are:

<input checked="" type="checkbox"/>	Inversion of the color table order.
<input type="checkbox"/>	Slice mode: The same % threshold is applied to each individual slice. Hereby the dynamic color range is fully exploited per slice. However, <i>the same color will represent a different value in different slices</i> . Therefore, this mode is not recommended in most cases.
<input type="checkbox"/>	Frame mode: With this setting, the minimal/maximal value in an entire frame is determined, and the % threshold applied to them. As a consequence, the colors

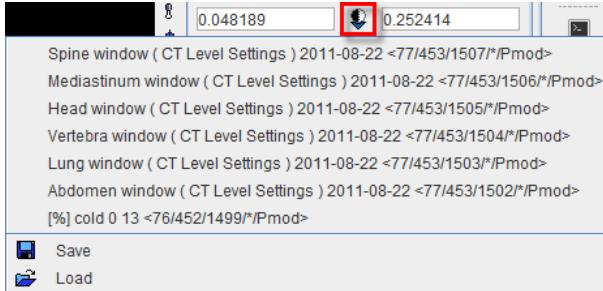
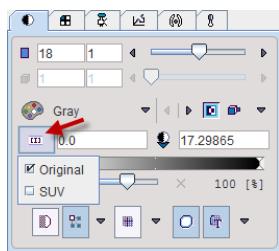
	represent fixed values when inspecting the slices of a frame. However, as the absolute minimal/maximal value will vary at different times of a dynamic acquisition, the <i>same color will most likely represent different values when comparing different frames</i> . This setting is recommended for static studies.
	Study mode: With this setting, the minimal/maximal value in the entire series is determined, and the % threshold applied to them. This setting is recommended for dynamic series and movies because the same color represents the same value at all times and in all slices.
	Fixed mode: This setting allows the user entering arbitrary minimal/maximal values which need not belong to the data range.
	This button allows saving or retrieving a color table configuration. During saving a dialog windows appears allowing to choose the thresholding save option: % Maximum-Minimum or Absolute values . Finally activate OK to save the level settings. Different level settings can be define and saved in the database as Absolute values for CT images and used for CT image presentations. These settings are available on the list when the button is selected. Alternatively, the predefined color properties can be retrieved from the file system selecting the Load button. 

Image Display in SUV Units

If all the relevant information is present for a data set the display units can be switched from original units to **SUV** (on page 136) with the button indicated below.

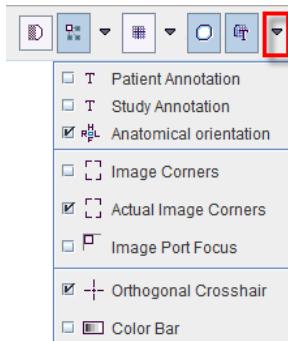


The image unit symbol changes and the color bar units are converted accordingly

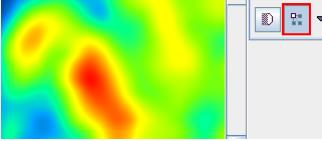
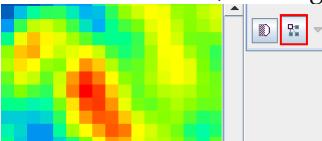


Information Overlays and Image Smoothing

The lowest row contains several control buttons.



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

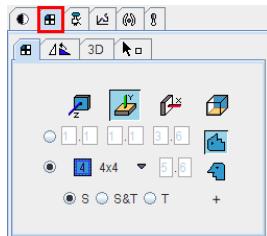
	Smoothing: Enables a temporary 9-point smoothing filter. The smoothing is only for display purposes and does not affect calculations.
	Interpolation: Enables image interpolation. Interpolation is needed because in most situations the resolution of the display viewport differs from the original image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

  : This option enables Display of the anatomical annotations in the images:
H - head, F - feet, A - anterior, P - posterior, R - right, L - left
For oblique orientations the letters are combined whereby the first letter indicates the direction closest to the current row/column direction.

Allows displaying the colorbar selected for the image.

Configuring the Layout

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



Slice Orientation

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

	z-Plane: Corresponding to the major slice orientation of the loaded data. Usually <i>axial</i> images. Keyboard shortcut: CTRL+Z.
	y-Plane: Usually the <i>coronal</i> images. Keyboard shortcut: CTRL+Y.
	x-Plane: Usually the <i>sagittal</i> images. Keyboard shortcut: CTRL+X. The x-plane image can be shown in two different ways depending on the modifier buttons.
	Orthogonal Planes: Layout showing three orthogonal slice images. The intersection point can be moved by clicking into the images.

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

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

Tiling Layouts

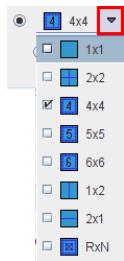
The second and third rows allow configuring the number of images shown concurrently.

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



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

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



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

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

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

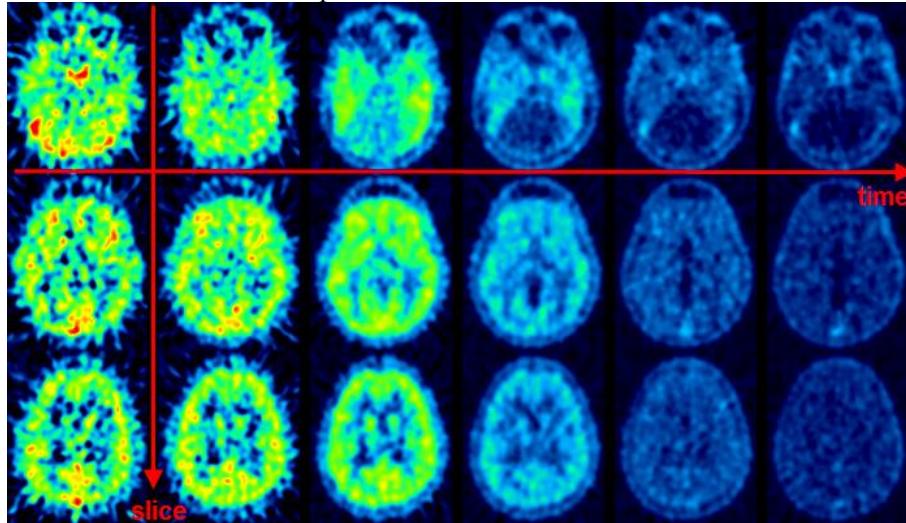
The radio button in the fourth row is only applicable for image tiling with dynamic studies.



If the radio button is in the position of

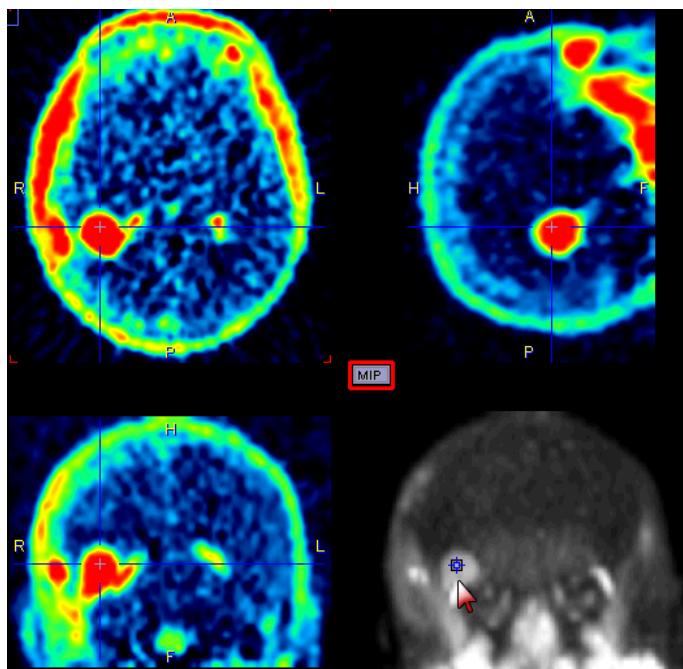
- » **S**: only slices acquired in a single time frame are shown in the image window.
- » **T**: only the images of a single slice are shown at different acquisition times.
- » **S&T**: the images are sorted by slice (vertically) and time (horizontally). Consequently each row corresponds to a slice at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

cover the brain and the acquisition duration.

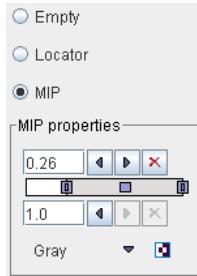


Orthogonal Layout

If the orthogonal layout is selected, three quadrants show the orthogonal slice images intersecting at the point indicated by the cross centered in the blue slice indication lines (triangulation point). As soon as the user clicks into an image, the images are updated by the slices intersecting at that new point.



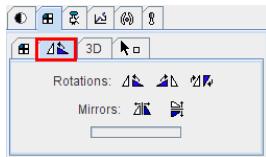
The fourth quadrant is available for different information. It can be configured by activating the button located in the upper left corner of that quadrant, indicated in red in the screen capture above. A dialog appears



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

Rotations and Mirroring

Image reorientation operations such as mirroring and rotations can be done using the buttons in the dedicated pane.



If the display is in the orthogonal viewing mode, first activate the appropriate plane by clicking onto the corresponding image (holding down the **CTRL** key avoids new reslicing), and then activate the appropriate button.

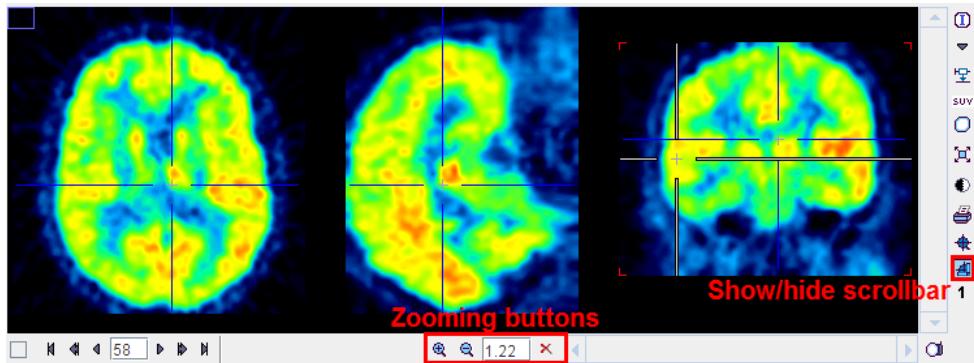
Note: For data with enough information about patient positioning PMOD will keep track of patient orientation and update the annotations accordingly.

Image Zooming

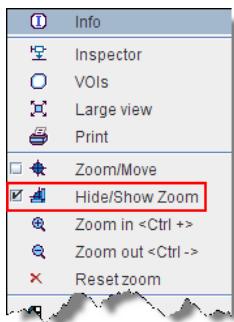
Sometimes it will be helpful to zoom the shown images, for instance during VOI outlining. Image zooming can be operated in different ways

Scrollbar Zooming

Often images ports have a scrollbar area around them. Then the zoom buttons can be used for zooming/shrinking, or a zooming factor can directly be entered. resets zooming. If the scrollbar is not visible, it can be shown by the indicated button to the image right.



If there is no such button, the image context menu (click right mouse button in image area) can be used instead.



The visible part of the image can be adjusted using the scrollbars around the image which appear as soon as the full image is not visible any more.

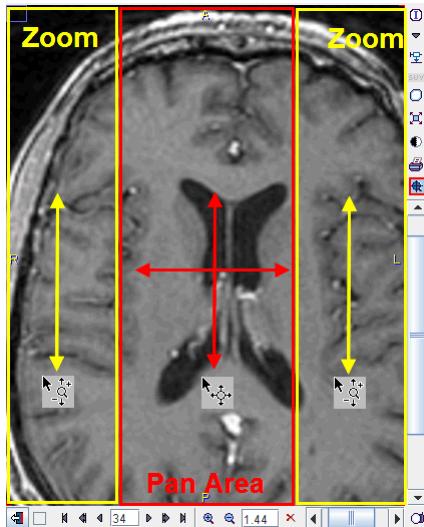
Mouse-driven Zooming

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

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

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

- 2) In the central area (panning area) it has a shape. To adjust the visible part of the image click the left mouse button into the center of the image and drag the image around



After appropriate zooming, the zoom mode should be quit by pressing once more, because some of other mouse-operated functions might not work.

Zooming with Mouse-Wheel

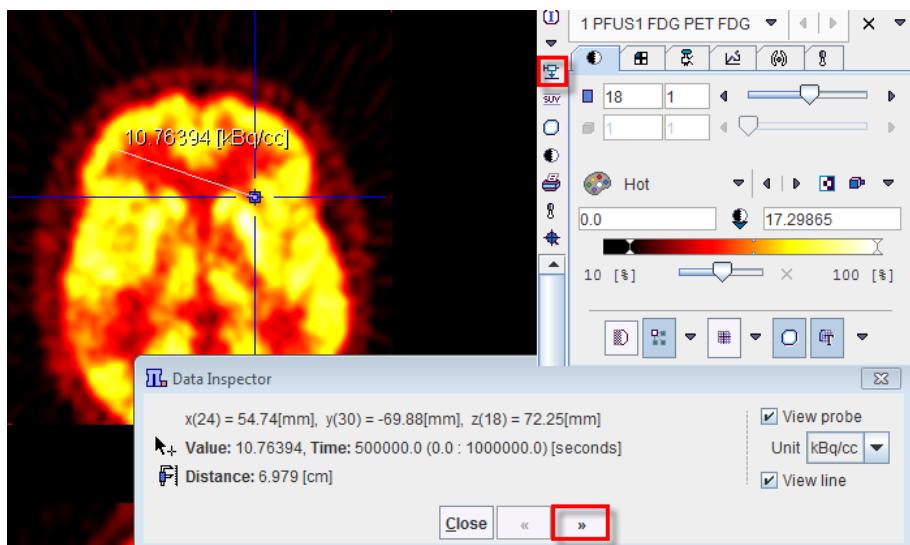
Similar to the zooming mode in other programs PMOD supports zooming with the mouse wheel while holding down the CTRL key. Note that in the orthogonal mode the triangulation point will be kept within the visible area.

Data Inspector

The data inspector tool is opened using the button

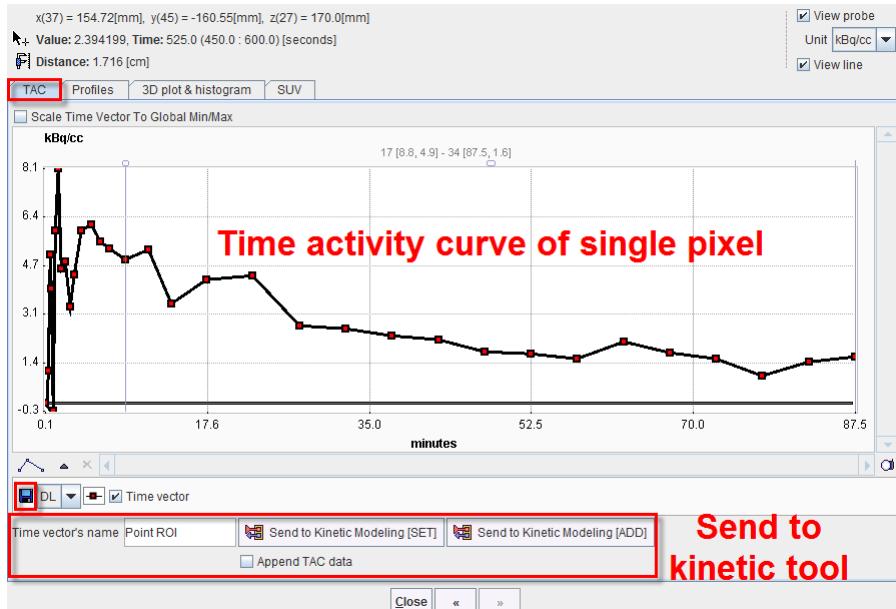


and initially shows the dialog window illustrated below.



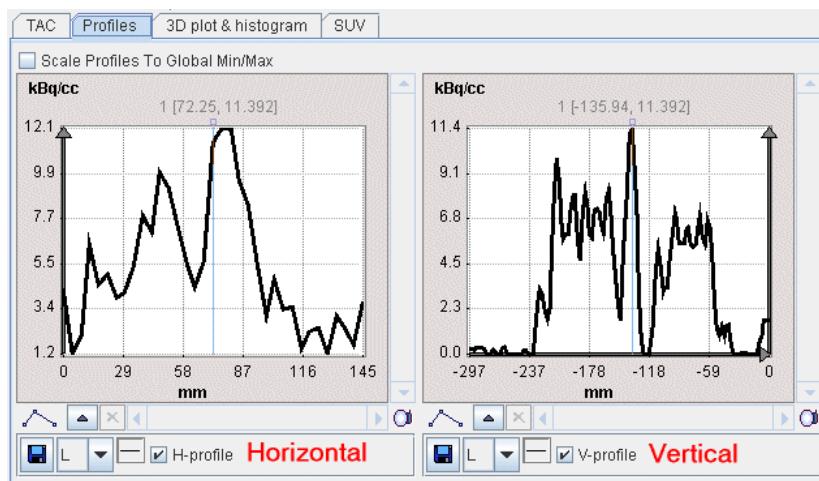
When the cursor is moved over the images, the information about the cursor location (in pixels, and mm from the coordinate system origin) and the pixel value at that location is continuously updated. A locator is shown in the image, marking the last position where the left mouse button was clicked into the image. The distance from the locator to the current cursor position is continuously updated. If the **View line** box is checked, a line indicates the measured distance. If the **View probe** box is checked, the pixel value is also shown close to the cursor and the units displayed. If the **SUV** option is selected in the **Unit** list while **View probe** box is enabled, the **SUV [g/ml]** is automatically calculated and displayed for each pixel. Note that in order to calculate the SUV, the patient weight and size as well as the injected dose are requested.

The >> button extends the dialog window to show more information



Using the **TAC** tab the time-activity curve of single pixels can be inspected (for dynamic studies only) and sent to the kinetic modeling tool. It gets updated as soon as the user clicks at a pixel.

The **Profiles** tab displays the horizontal and vertical profiles at the current location of the locator.



On the **3D plot & histogram** tab a 3D plot and the histogram of the slice values are shown, whereas the **SUV** tab allows to inspect the pixel values in SUV rather than kBq/cc, provided that all activity information is available. The **SUV** tab is explained in the next section.

SUV Value Inspection and Statistics

Standard Uptake Values (SUV)

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

For correcting the physical radioactive decay of all activities to the same time the program also requires information about radionuclide, the time of dose calibration, time of injection, the activity remaining in the syringe and when it was measured. Also required is the scan start time, because the PET measurements are usually decay-corrected to the scan start.

PMOD supports three variants of this calculation:

- 1) **SUV Body mass [g/ml]**: Directly uses the patient weight entered in the demographic patient information. This is the mostly used SUV.

$$\text{SUV Body mass} = (A/D) * W * 1000;$$
- 2) **SUV Lean Body Mass [g/ml]**: First calculates a mean body mass from the patient weight, the height and the gender, which is used in the actual SUV calculation.

$$\text{SUV Lean Body Mass} = (A/D) * LBM * 1000; \text{LBM(Female)} = 1.07 * W - 148 * (W/H)^2,$$

$$\text{LBM(Male)} = 1.10 * W - 120 * (W/H)^2;$$
- 3) **SUV Body Surface Area [cm²/ml]**: In this case the uptake is normalized to the body surface area, which is calculated from the weight, the height and the gender.

$$\text{SUV Body Surface Area} = (A/D) * BSA * 10000, \text{where BSA as in your equation } (W^{0.425} \times H^{0.725}) \times 0.007184.$$
- 4) Additionally, the **Injected dose per cc [%ID/ml]** is available for normalizing the uptake to the injected dose multiplied with 100.

The variables used are

- A Calibrated activity concentration in the image [Bq/cc]
- W Patient weight [kg]
- H Patient height [cm]
- D Injected dose [Bq]

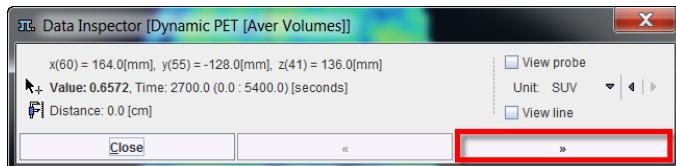
For correct SUV values it is important that all the entries are correctly filled in. PMOD tries to extract the information from the image header. However, dependent on the file format this information or part of it may be missing. Another factor is, whether the dose information has been entered by the technicians during the scan. If the information is incomplete, it has to be edited interactively in the dialog window before the SUV can be calculated.

SUV Value Inspection Window

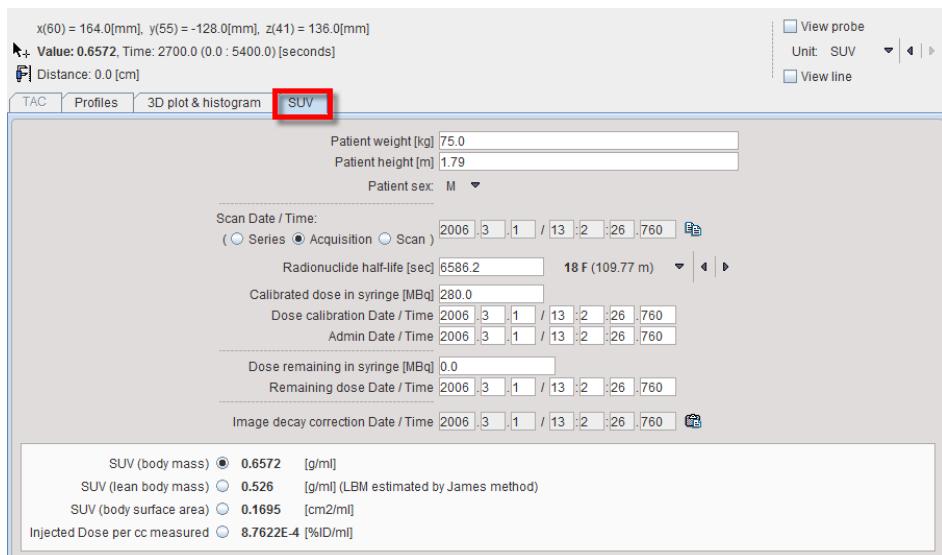
The SUV (Standard Uptake Value) button

SUV

below the data inspector button is a shortcut for opening the data inspector with the SUV tab selected



The window can be extended with the >> button for adjustments.



The upper part of the SUV panel shows the information which is involved in the calculation of the SUV. It requires that the image units are kBq/cc, and that all information fields in the dialog are correctly filled in. Per default, the scan start time is read from the acquisition time field of DICOM. However, as situations have been met where this information was wrong whereas the series time was correct, the **Scan Date/Time** radio button allows switching to the **Series** or the **Acquisition** time.

PMOD supports decay correction to the time frames during the merging procedure: in this situation the data are decay corrected to different times. Therefore, in the SUV inspector the **Image decay correction Date/Time** is also displayed. If this field is empty it is assumed to be the same as the scan start. According to DICOM the data can be also decay corrected to the administration time. Please note that in such case the SUV value will change when compared with previous version as an additional factor for the delay from the administration to the scan start will be calculated.

Note that using the **Copy to all-dose related dates and times** button the scan start time can be easily propagated to all the date and time fields.

The lower part serves for showing the different SUVs of the current pixel. The displayed SUV value changes whenever the cursor is moved over the image.

Image Display in SUV Units

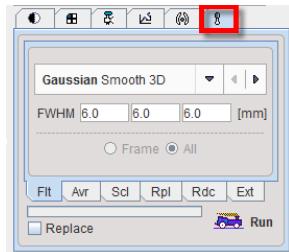
If all the relevant information is present for a data set the display units can be switched from original units to SUV as illustrated *above* (on page 122).

SUV Statistics

The calculation of statistics in SUV units is directly supported on the original image by the **VOI functionality** (on page 280), provided that all required information is available. Explicit SUV images can be calculated with the **SUV Image Calculation** external tool.

Handy Image Processing Tools

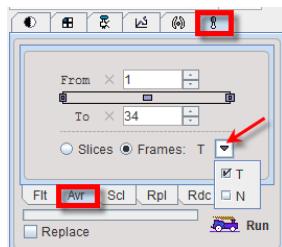
The processing tools pane offers a substantial range of image transformation methods.



There are 5 methods which can directly used via the sub tabs, and many other *external tools* (on page 140) via a list on the **Ext** tab. To process the current image select a sub-tab, configure the parameters of the method which appear in the pane, and then activate the **Run** button. If the **Replace** box is checked, the original data is overwritten, otherwise a new image series is created and added to the list.

The directly accessible functions are:

- » **Flt:** *Image filtering* (on page 145) in the spatial and temporal domain.
- » **Avr:** Averaging of a contiguous range of image frames or slices between the **From** and **To**.



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

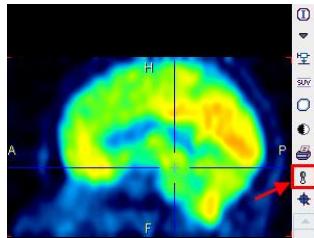
- » **Scl:** *Scaling* (on page 163) of the pixel values, for instance for calibration or to calculate relative uptake.
- » **Rpl:** *Replacing* (on page 162) of pixel values which satisfy a certain condition by a constant.
- » **Rdc:** Simple function for matrix size *reduction* (on page 160).

External Tools

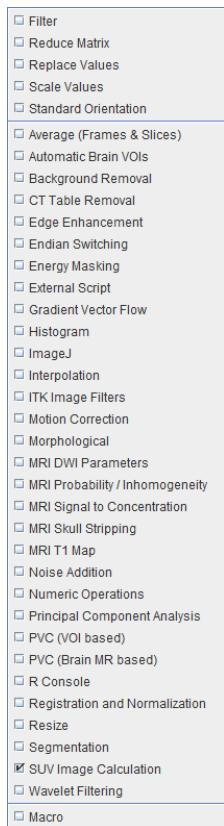
External tools are data processing plug-ins which take one or several images as input, and return a result image. The tools can be interactively called on individual images, or they can be used as stages in a *processing pipeline* (on page 420).

Tools Selection

External tools can be called interactively using the  button in the image sidebar.

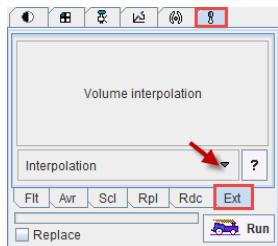


As a result, the list of available tools appears



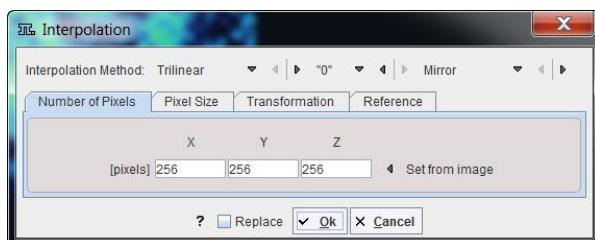
from which a tool can be selected.

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



Tool Operation

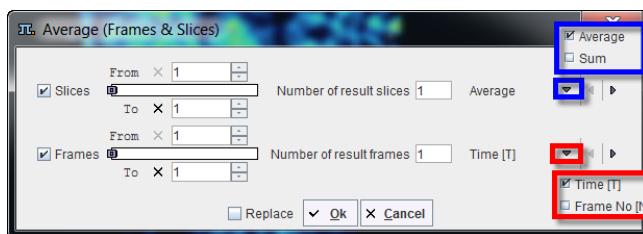
After selecting a tool from the list (and activating **Run** in the tool version), a specific dialog window is opened with a short explanation and the parameters needed for processing. Shown below is the **Filter** dialog window as an example.



The buttons at the bottom are common to all tools. If the **Replace** box is checked, the current images are overwritten by the results. Otherwise, a new image series is created for returning the results and added to the series list. **?** provides help information of the tool functionality. **Ok** start the actual data processing.

The functionality of the external tools is described below, except for the *Partial Volume Correction (PVC)* (on page 389) tools which are explained separately.

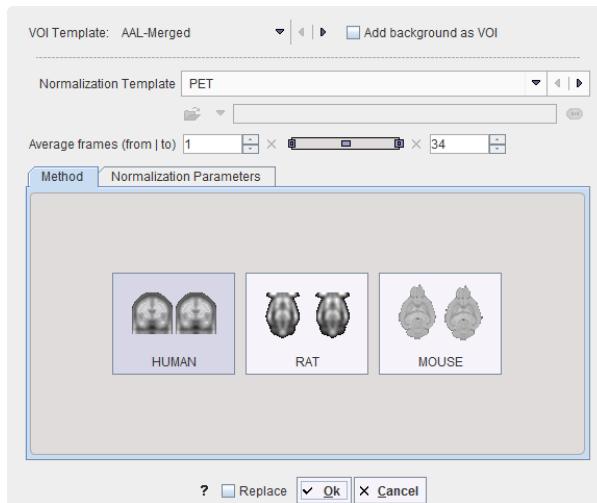
Average (Frames & Slices)



Allows simple averaging within a time range and/or within a slice range. The number of generated slices/frames can be entered numerically.

Automatic Brain VOIs (PFUS Option)

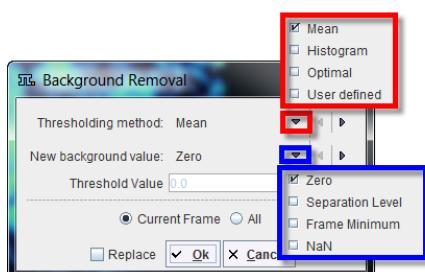
The tool allows generating contours VOIs in the input space according to the selected **VOI Template**. If the tool is called from pipe processing, the VOI statistics will also be evaluated and can be saved.



The **Method** is available for **HUMAN**, **RAT** and **MOUSE** studies. The **Input** study is normalized to the chosen **Normalization Template**. The algorithm applied is *Brain Normalization* and the inverse transformation is calculated. In case the input study is dynamic, an averaged input is created for the selected frame range **Average frames**. The selected template VOIs is transformed to the input space using the inverse transformation calculated during the normalization procedure. Finally the transformed VOIs are outlined.

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

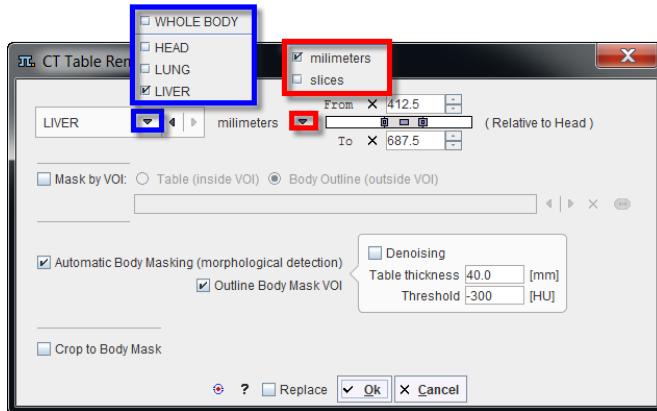
Background Removal



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

CT Table Removal

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



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

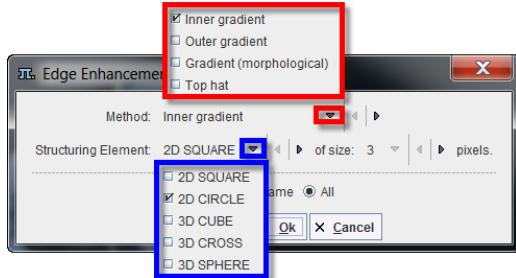
The **Mask by VOI** option allows masking the image with the specified VOI. There are two options available:

- » **Table (inside VOI)**: allows removing the table form the CT study by replacing the voxels inside the VOI with the minimum value.
- » **Body Outline (outside VOI)**: allows cropping the organ of interest if the **Crop to VOI** checkbox is enabled. It replaces the voxels outside the selected VOI by the minimum value.

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

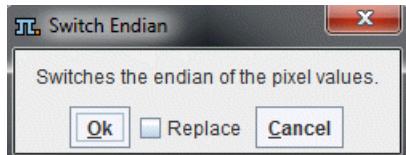
It is recommended to use the default settings and only experiment with other parameter values if the procedure fails. The default settings are available by activating the default settings button

Edge Enhancement



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

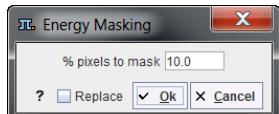
Endian Switching



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

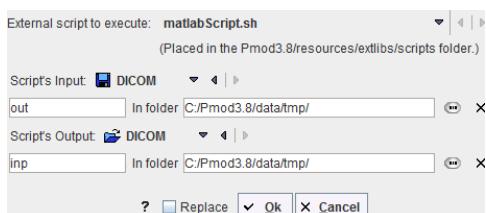
Energy Masking

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



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

External Script



This tool allows running an external program, which needs to be placed in *Pmod3.8/resources/extlibs/scripts*. It then shows up in the **External script to execute** list as a new entry. Input to the script is an image file with the name defined in the **Script's Input** field. The script may apply any processing to the image and needs to save the resulting

image under the name defined in the **Script's Output** field. Note also the image format definitions for the input and the output which must meet the file content.

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

Example: Execution of Matlab Script

A Matlab script example which requires Matlab's Image Processing Toolbox is available in *Pmod3.8/resources/extlibs/scripts*. It consists of two files:

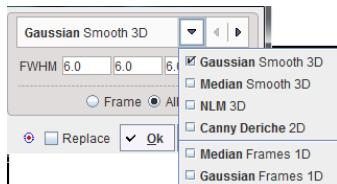
- » *matlabScript.sh* which starts Matlab and lets it execute the code in the mFile script. It essentially contains a system-specific matlab call:
`matlab -nosplash -r testScript`
- » *mfiles/testScript.m* which contains proper the actual image processing, eg


```
% Read data from disk. Info metadata is needed to preserve
% important image features, e.g. timing.
data = dicomread('C:/Pmod3.8/data/tmp/out');
info = dicominfo('C:/Pmod3.8/data/tmp/out');
% Processing.

...
...
% Write data to disk. This will be input to PMOD.
% To save data in DICOM multiframe mode, use
% 'Create Mode' option with 'copy' value.
dicomwrite(fData, 'C:/Pmod3.8/data/tmp/inp', info, 'CreateMode',
'copy')
quit
```

Filter

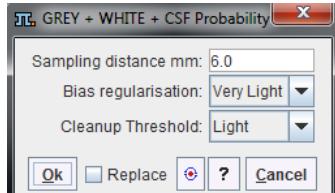
The **Filter** tool



offers the following image filters:

- » **Gaussian Smooth 3D** spatial filter with a full-width at half maximum (**FWHM**) in mm;
- » **Median Smooth 3D** spatial filter with a width in mm;
- » **NLM 3D** non-local means image denoising filter with **Low**, **Medium** and **Strong** settings;
- » **Canny Deriche 2D** edge enhancing spatial filter;
- » **Median Frames 1D** smoothing filter in the time domain.

GM & WM & CSF Probability (PFUS option)



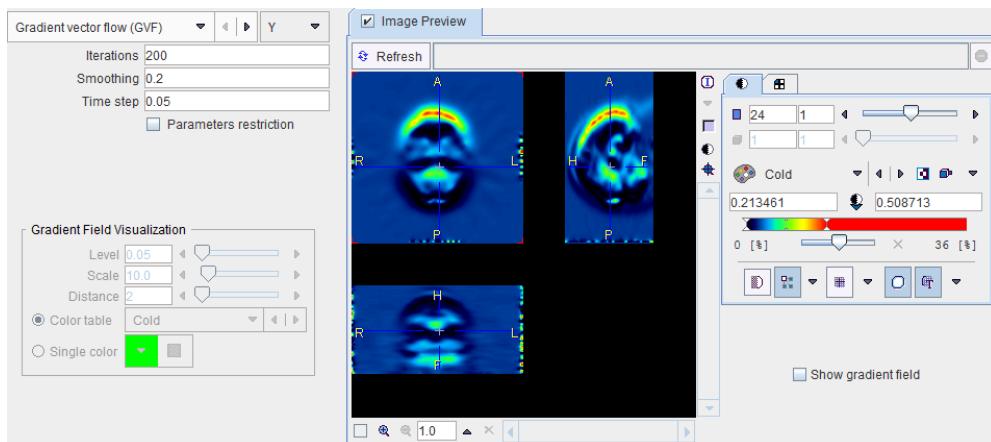
This tool calculates the grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) probability maps from a T₁-MRI of a human brain. The procedure has three parameters:

Sampling distance determines the density of pixels considered in the calculation. **Bias Regularisation** serves for compensating modulations of the image intensity across the field-of-view. Depending on the degree of the artifact, a corresponding setting can be selected from the list. **Cleanup** is a procedure for rectifying the segmentation along the boundaries. It is recommended to use the default settings and only experiment with other parameter values if the segmentation fails. The default settings are available by activating the default settings button .

The results are the three probability maps of GM, WM and CSF which are arranged in this order as the frames in a "dynamic" series.

Gradient Vector Flow

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



Different algorithms are supported:

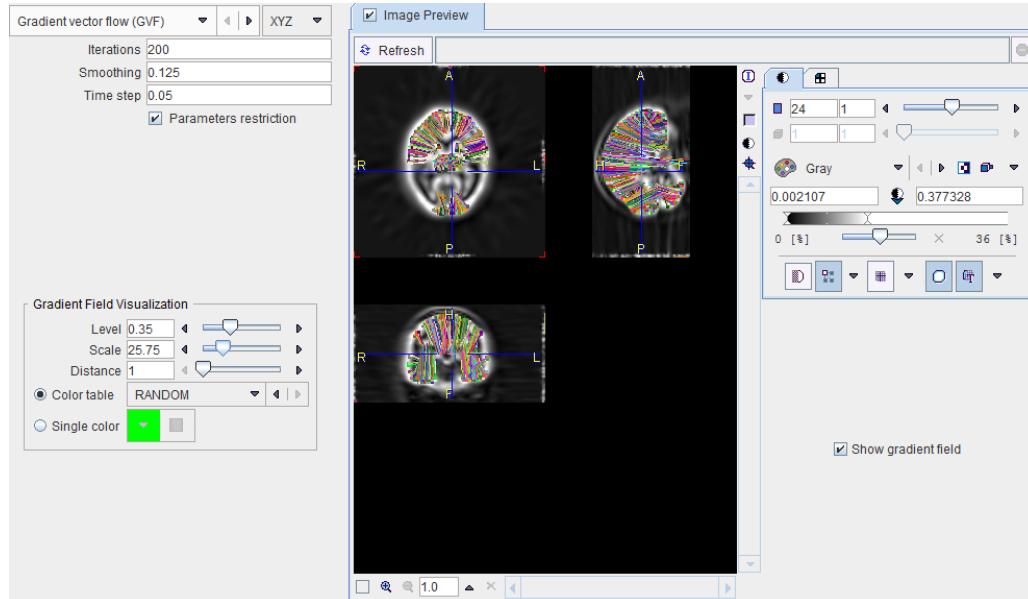
- » **GVF:** calculates the gradient using the gradient vector flow algorithm;
- » **General GVF:** calculates the gradient using a generalized gradient vector flow algorithm;
- » **Differential gradient:** calculates the gradient by subtracting values of neighbouring pixels;
- » **Sobel operator:** calculates the gradient by convolving filter mask with matrix consisting of image pixels.

During the estimation procedure the following parameters can be set:

- » **Gradient width:** distance (in pixels) between two points, the intensity difference which defines the gradient value;
- » **Iterations:** number of iterations performed during GVF and GGVF calculation;
- » Smoothing parameter (μ): regularization parameter governing the trade-off between the first and the second integral term. Smoothing parameters should be set according to the amount of noise present in the image: the higher the noise the bigger the value.
- » Time step (Δ): is representing the time length for each iteration.

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

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

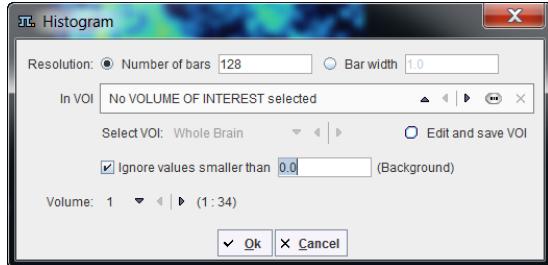


Reference

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

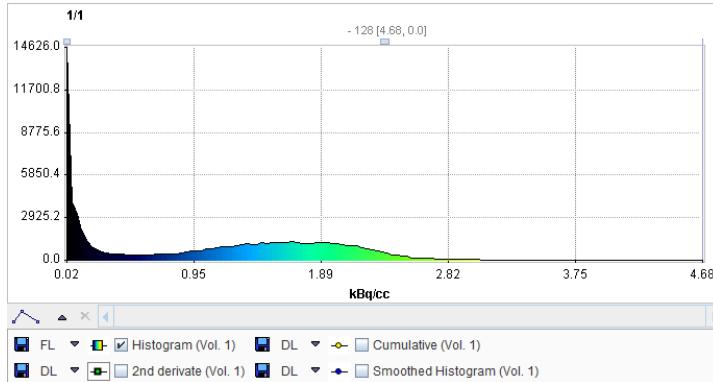
Histogram

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

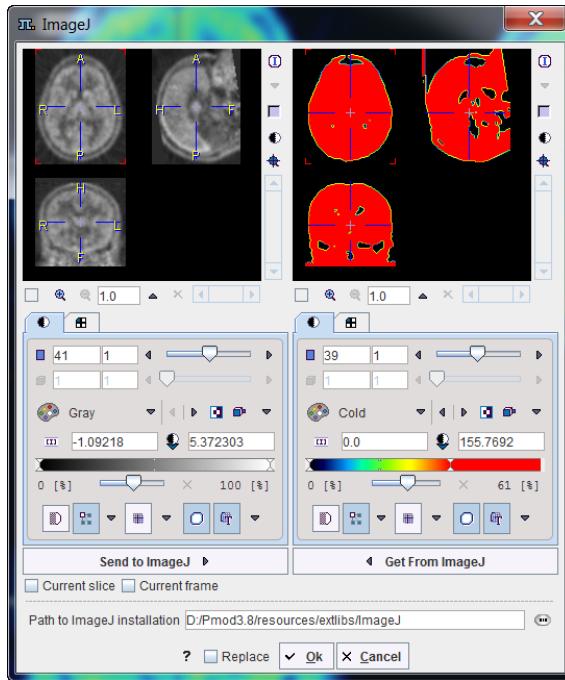


If **Number of bars** is enabled, the value range is divided into the specified number of equal intervals (e.g. 128). With **Bar width**, the interval size is directly specified. Values below a **Background level** can be excluded by checking **Ignore values smaller than** and specifying the **Background**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

The number of occurrences in each interval are counted and plotted as a curve. Additional curves (**2nd derivative**, **Cumulative**, **Smoothed Histogram**) can be enabled in the control area. Note that the numeric values of the histogram can be exported using the context menu (right mouse button in curve area, then **View Values**).



ImageJ

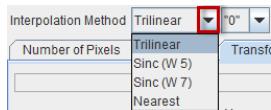


This tool allows transferring image data to *ImageJ* <http://rsbweb.nih.gov/ij/> with the **Send to ImageJ** button, process the images with dedicated procedures in ImageJ, and retrieving the results with the **Get from ImageJ** button back to PMOD. Included in the distribution is a basic ImageJ version. For using a different version with dedicated plug-ins please point to your own installation using **Path to ImageJ installation**.

Interpolation

The **Interpolation** tool serves for calculating a new image volume by an interpolating values from the current image volume.

There are four choices for the **Interpolation Method** which is applied when calculating the new image.



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

Matrix Size Specification

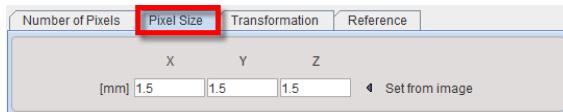
Using the **Number of Pixels** method



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

Pixel Size Specification

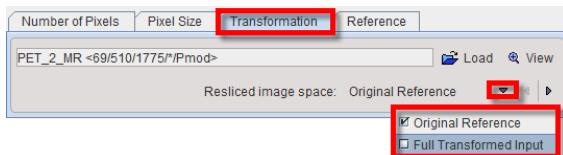
Using the **Pixel Size** method,



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

Spatial Transformation

Using the **Transformation** method

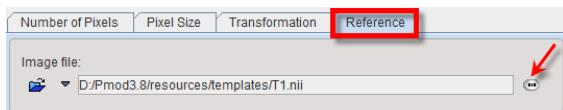


a spatial transformation matrix calculated by the fusion tool can be applied to the image. **Resliced image space** has three settings:

- » **Original Reference:** The transformation is applied with the resolution of the reference image used during matching, and the result is in the bounding box of the original reference image.
- » **Preserved Input Dimensions:** The transformation is applied with the current image resolution, and the result is in the bounding box of the original reference image.
- » **Preserved Input Space:** The transformation is applied within the bounding box of the input image. Large translations may move the image data completely outside the bounding box.

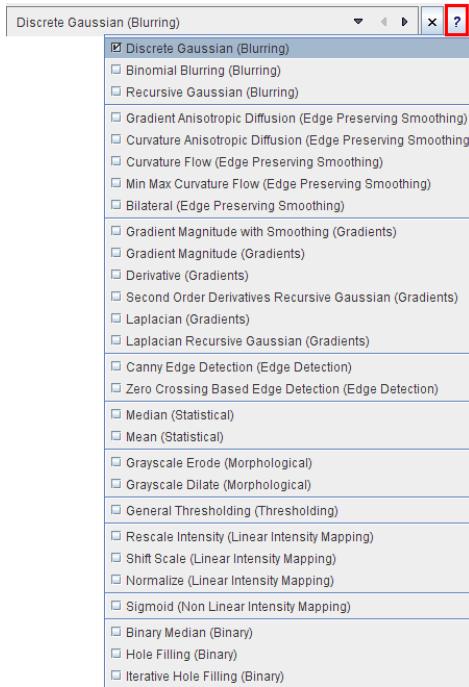
Interpolation to Reference

Using the **Reference** method



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

ITK Image Filters



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

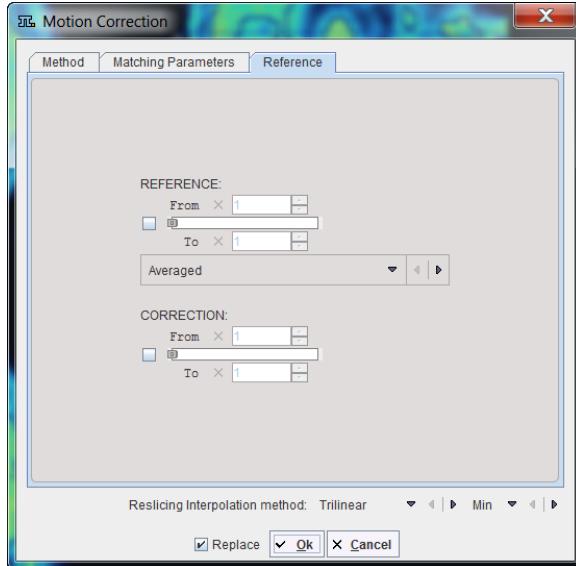
Note: PMOD Technologies can not be held liable for permanent support of the ITK interface, nor for the performance of the provided libraries.

Macro

This tool allows applying an image *macro* (on page 120) which is most useful in the context of *Pipe processing* (on page 420).

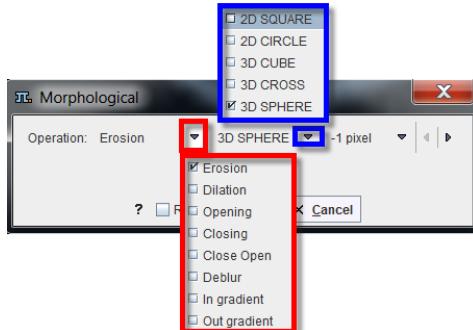
Motion Correction (PFUS option)

The motion correction in the external tools is mainly for the use in pipe processing. It is only available if the image fusion option is included in the PMOD license.



Please refer to the *PMOD Image Fusion Guide* for details about the matching options.

Morphological



Morphological operations http://en.wikipedia.org/wiki/Mathematical_morphology process images based on shapes. It applies a structuring element defined by a shape (2D SQUARE, 2D CIRCLE, 3D CUBE, 3D CROSS and 3D SPHERE) and a size in pixels.

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

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

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

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

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

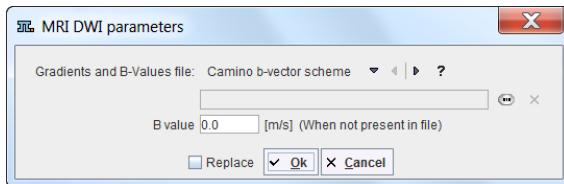
Deblur is a sharpening filter based on an erosion and a dilation.

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

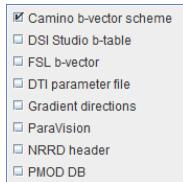
Out gradient uses a dilation to enhance edges in the image towards the inner.

MRI DWI

The purpose of the **MRI DWI Parameters** tool is to load gradient vector information for diffusion weighted MR images which are not contained in the image data. This information is required for the calculation of diffusion maps and diffusion tensors. When the series is saved as a DICOM object after using the tool, the gradient information is stored together with the images.



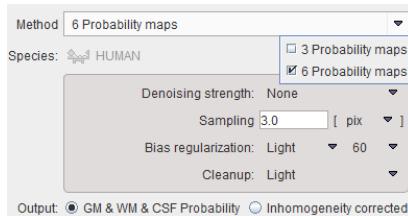
Several encoding types are supported and can be chosen from the **Gradients and B-Values file** selection:



- » **Camino b-vector scheme:** Text file containing four columns of data: x, y, and z coordinates of b-vectors and a b-value (last column) in s/m².
- » **DSI Studio b-table:** Text file containing four columns of data: b-value in s/mm², then x, y, and z coordinates of b-vectors.
- » **FSL b-vector:** Text file containing b-vector coordinates in three rows: x, y, and z values respectively. As PMOD does not support b-value files as a separate input you may add the b-values from b-value file as a fourth row in s/mm².
- » **DTI parameter file:** Text file (.dpf) from DTI Studio containing b-vector directions and b-values.
- » **Gradient directions file:** General option for text files with three to five columns. Three-column files are assumed to contain x, y, and z coordinates of b-vectors. Four-column files are assumed to have b-values in the last column. Five-column files are assumed to have gradient indexes in the first column. This option accepts gradient tables exported from the PMOD Info dialog window. B-values are in s/mm².
- » **ParaVision:** For loading b-vectors directions and b-values from a Bruker ParaVision Parameter List file.
- » **NRRD header:** For loading b-vectors directions and b-values from the DWMRI section of a NRRD format header file.
- » **PMOD DB:** For loading b-vector directions and b-values from the gradient table files stored to a PMOD database. The data in the file is arranged in five columns as in **Gradient directions** file. A comment line starts with #.

MRI Probability / Inhomogeneity

The **MRI Probability/Inhomogeneity** tool allows applying the unified segmentation methods of SPM8 or SPM12 to the loaded T1-MR image. Depending on the **Output** setting, the Grey Matter, White Matter, CSF probability maps are saved as frames in a dynamic series, or the MR image corrected for the spatial inhomogeneity.



Method

Two SPM-type segmentation variants are supported, the **3 Probability Maps** (SPM8) and the **6 Probability Maps** (SP12)

variant. Note that the normalization transform which is obtained as part of the segmentation can be applied for the spatial normalization of the patient brain anatomy in later stages.

Denoising strength

Denoising of the MR image may improve the segmentation of gray matter, white matter and CSF. If a **Denoising strength** other than **None** is selected, a non-local means denoising algorithm is applied which preserves structure boundaries unless the strength is too high.

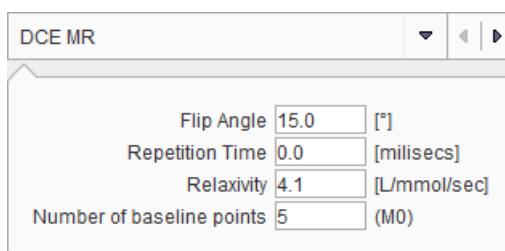
Sampling	Density of pixels considered in the calculation. It can be specified in pixel or mm units.
Bias regularization	Serves for compensating modulations of the image intensity across the field-of-view. Depending on the degree of the modulation, a corresponding setting can be selected from the list. The parameter to the right indicates the FWHM [mm] to be applied. The larger the FWHM, the smoother the variation is assumed.
Cleanup	Procedure for rectifying the segmentation along the boundaries.

It is recommended to use the default settings and only experiment with other parameter values if the segmentation fails. The default settings can be recovered by the  button.

MRI Signal to Concentration

The **MRI Signal to Concentration** tool was developed for converting the signal of dynamic MR sequences into concentration measurements of the contrast agent used. Three different acquisition sequences are supported

Dynamic Contrast-Enhanced MR (DCE)



The DCE method requires that in addition to the DCE data a matched T_1 map has been loaded. It is recognized by being a static series, whereas the DCE is dynamic. Note that there is the **MRI T1 Map** (on page 159) tool which supports the calculation of T_1 images from a sequence of gradient echo images acquired with variable flip angles q (FLASH sequence).

The equilibration magnetization M_0 is also required for the calculation. It is determined from the baseline average of the DCE signal before contrast arrival by

$$M_0 = S \frac{1 - \cos(\theta)E_{10}}{\sin(\theta)(1 - E_{10})}, \quad E_{10} = e^{(-TR/T_{10})}$$

where S is the steady state signal, and T_{10} the pre-contrast longitudinal relaxation time. Using M_0 and T_{10} the relaxation rate $R_1(t)$ during the DCE scan can be calculated by [1]

$$R_1(t) = -\frac{1}{TR} \ln \left(\frac{1 - (A(t) + B)}{1 - \cos(\theta)(A(t) + B)} \right), \quad A(t) = \frac{S(t) - S(0)}{M_0 \sin(\theta)}, \quad B = \frac{1 - E_{10}}{1 - \cos(\theta)E_{10}}$$

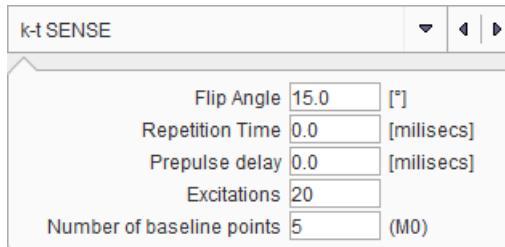
where $S(t)$ is the DCE signal, and $S(0)$ the baseline signal before the Gd contrast agent arrives in the tissue. Finally, using $R_1(t)$ and the relaxivity r_1 of the contrast agent used, the concentration of the contrast agent can finally be calculated by [1]

$$C(t) = \frac{1}{r_1} (R_1(t) - R_{10})$$

where r_1 is in [L/mmol/sec] units. Carbonaro et al. [2] provide the following relaxivity values for 1.5T:

Brand Name	Acronym	R1-relaxivity [L/mmol/sec]
Magnevist	Gd-DTPA	4.1
Dotarem	Gd-DOTA	3.6
ProHance	Gd-HP-DO3A	4.1
Omniscan	Gd-DTPA-BMA	4.3
Gadovist	Gd-BTO3A	5.2
OptiMARK	Gd-DTPA-BMEA	4.7
MultiHance	Gd-BOPTA	6.7

K-t SENSE Sequence



The k-t SENSE method [3] requires that in addition to the dynamic data a matched T_1 map has been loaded. The relaxivity R_1 is first calculated from the model function of the signal by an iterative fit.

For the signal intensity SI including readout trajectory, we have for each dynamic scan i :

$$SI(R_1) = M_0 \sin(\alpha) \left[\left[1 - \exp(-T_D R_1) \right] \cdot (\cos(\alpha) \exp(-T_R R_1))^{n-1} + \left[1 - \exp(-T_R R_1) \right] \cdot \frac{1 - (\cos(\alpha) \exp(-T_R R_1))^{n-1}}{1 - \cos(\alpha) \exp(-T_R R_1)} \right]$$

- where $SI(R_1)$ is the model for the signal intensity for each scan as a function of tissue relaxivity R_1 , i.e. the current TACs
 M_0 is the equilibrium magnetization (which must be guessed/evaluated from a scan)
 α is the flip angle used (DICOM field: (0018,1314): Flip Angle)
 T_D is the time from saturation prepulse to the centre of acquisition space (=k-space center)
(Private DICOM field: (2001,101b))
 T_R is the repetition time (DICOM field: (0018,0080): Repetition Time)
 n is the number of excitations (readout lines) processed before k-space center is reached, no DICOM field exists

The R_1 obtained is then used in the equation below, which is solved for the contrast concentration $C(t)$.

$$R_1(c(t)) = \frac{1}{T_1(c(t))} = \frac{1}{T_{1base}} + c(t) \cdot R$$

where T_{1base} is the T_1 value without contrast (which we measure with the T1 scan)
 $c(t)$ is the concentration of the contrast medium (here as fcn of time)
 $R = 4.5 \left(s \frac{mmol}{L} \right)^{-1}$ is the relaxivity of the pure contrast medium
 $R_1(c(t)) = \frac{1}{T_1(c(t))}$ is the relaxivity of the tissue with contrast medium applied,
which changes as contrast concentration changes with time.

Dynamic Susceptibility Contrast MR (DSC)

This tool calculates the contrast concentration for data acquired with the FLASH sequence [4].

DSC MR

Echo time (TE) [milisecs]
Number of baseline points (S0)
k (constant)

A linear relationship is assumed between the tissue contrast-agent concentration C and the change in T_2^* relaxation rate, ΔR_2^* . The concentration of the contrast agent is given by

$$C(t) = -\frac{1}{k TE} \ln \left(\frac{S(t)}{S_0} \right)$$

S_0 is the precontrast baseline signal, $S(t)$ the postcontrast signal, and TE the echo time, and k a proportionality constant.

References

1. D.L. Buckley, and G.J.M. Parker. Measuring contrast agent concentration in T1-weighted dynamic contrast-enhanced MRI. in: A. Jackson, D.L. Buckley, and G.J.M. Parker, (Eds.), Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Oncology, Springer, Berlin, pp. 69-79, 2005.
2. Carbonaro LA, Pediconi F, Verardi N, Trimboli RM, Calabrese M, Sardanelli F. Breast MRI using a high-relaxivity contrast agent: an overview. AJR Am J Roentgenol. 2011;196(4):942-55.
3. Wissmann L, Niemann M, Gotschy A, Manka R, Kozerke S: Quantitative three-dimensional myocardial perfusion cardiovascular magnetic resonance with accurate two-dimensional arterial input function assessment. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance 2015, 17:108.
4. Wirestam R, Andersson L, Ostergaard L, Bolling M, Aunola JP, Lindgren A, Geijer B, Holtas S, Stahlberg F: Assessment of regional cerebral blood flow by dynamic susceptibility contrast MRI using different deconvolution techniques. Magnetic resonance in medicine

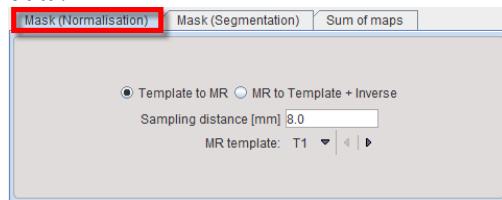
2000, 43(5):691-700. HTML [http://onlinelibrary.wiley.com/doi/10.1002/\(SICI\)1522-2594\(200005\)43:5%3C691::AID-MRM11%3E3.0.CO;2-B/full](http://onlinelibrary.wiley.com/doi/10.1002/(SICI)1522-2594(200005)43:5%3C691::AID-MRM11%3E3.0.CO;2-B/full)

MRI Skull Stripping (PFUS option)

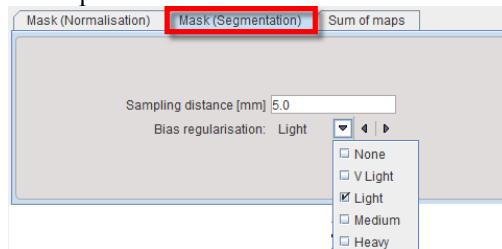
This tool serves for extracting the brain part from human anatomical MR images which need to be provided in HFS orientation.

There are three processing variants available:

- 1) Mask (Normalization):** This procedure is based on the **Brain Template Normalization** method implemented in the fusion tool. Depending on the setting **Template to MR** or **MR to Template + Inverse**, the normalization between the MR and the MR MNI template is calculated, and then applied to transform the standard MNI brain mask to the MRI space. Select the **T1** or the **T2 MR template**, depending on the type of input data.

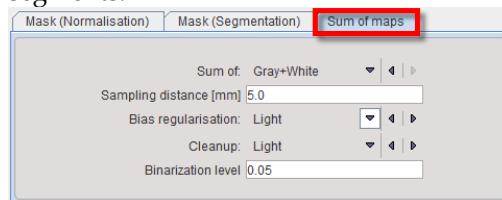


- 2) Mask (Segmentation):** The normalization between the MR and the MR MNI template is calculated based on the **3 Probability Maps** segmentation method (Unified Segmentation, SPM8). It is then applied to transform the standard MNI brain mask to the MRI space.



The **Bias regularisation** serves for compensating modulations of the image intensity across the field-of-view. Depending on the degree of the modulation, a corresponding setting can be selected from the list: None, Very Light, Light, Medium, Heavy, Very Heavy. The parameter to the right indicates the FWHM [mm] to be applied. The larger the FWHM, the smoother the variation that is assumed

- 3) Sum of maps:** The MR image is segmented using the **3 Probability Maps** method. The mask is created by applying a threshold at the **Binarization level** to the summed segments.

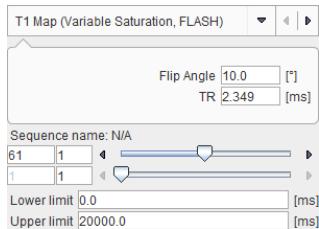


Finally, the mask is inverted and applied to the MR image for removing all non-brain pixels.

MRI T₁ Map

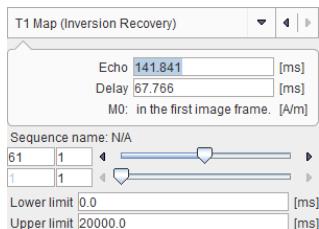
This tool supports the calculation of T₁ maps from dynamic MR series acquired with two different pulse sequences. The **Lower** and **Upper limits** serve for restricting the calculated values to a physiological range.

Variable Saturation Data (FLASH)



The equation for the signal intensity using a FLASH sequence can be rearranged such that T₁ may be calculated as the slope of a linear regression fit. See Buckley et al, equation (5.7).

Inversion Recovery Data

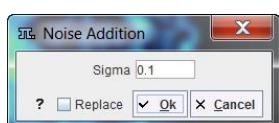


It is assumed that the first frame contains the equilibration magnetization M₀. T₁ is then estimated using a linear regression as described by McVeigh et al [2], using equation (2).

References

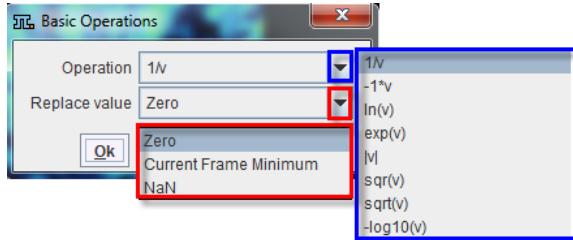
1. D.L. Buckley, and G.J.M. Parker, Measuring contrast agent concentration in T1-weighted dynamic contrast-enhanced MRI. in: A. Jackson, D.L. Buckley, and G.J.M. Parker, (Eds.), Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Oncology, Springer, Berlin, 2005, pp. 69-79.
2. McVeigh E, Yang A, Zerhouni E. Rapid measurement of T1 with spatially selective pre-inversion pulses. Medical Physics. 1990;17(1):131-134.

Noise Addition



Adds Gaussian noise with zero mean and a standard deviation **Sigma** to the image.

Numeric Operations



Applies the numeric function configured as **Operation** to every pixel value, and uses the defined **Replace value** if the operation is mathematically undefined.

Principal Component Analysis

No input is required for this function which is only applicable to *dynamic* series. The PCA performs a principal component analysis in the time domain. The generated series consists of the components sorted according to decreasing eigenvalues. The expectation is, that the PCA groups pixels with a similar uptake pattern over time in different components (representing "frames" in the generated series). The eigenvalues are written to the console.

PVC (VOI based)

General tool for partial-volume effect correction based on VOIs as explained in detail in a separate *section* (on page 389).

PVC (Brain MR based)

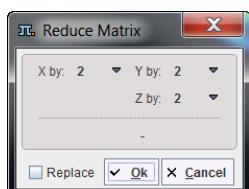
Tool for the partial-volume effect correction of a human brain PET based on the Muller-Gartner method as described in a separate *section* (on page 389).

R Console

Allows loading the image data displayed in the view port in the PMOD R interface for further statistic analysis.

Reduce Matrix

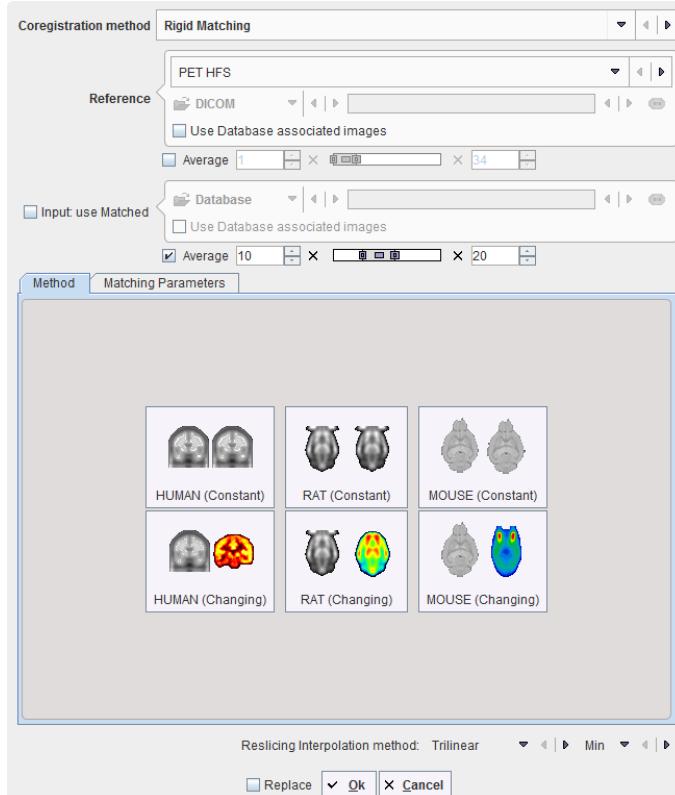
The **Reduce Matrix** tool serves for reducing the number of pixels in each direction.



It is intended for situations where the number of pixels is divisible without remainder by the selected reduction factor. If this is not the case, a warning is shown indicating that the bounding box is changed by the operation, and the **Interpolation** (on page 149) function should rather be applied.

Registration and Normalization (PFUS Option)

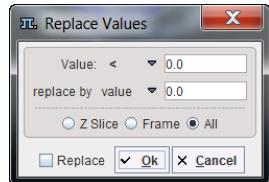
The matching in the external tools is mainly for the use in pipe processing. It is only available if the image fusion option is included in the PMOD license.



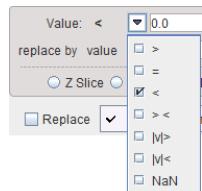
Please refer to the *PMOD Image Fusion Guide* for details about the matching options.

Replace Values

The Replace Values tool



serves for replacing pixel values which satisfy a certain condition by a constant. The available criteria

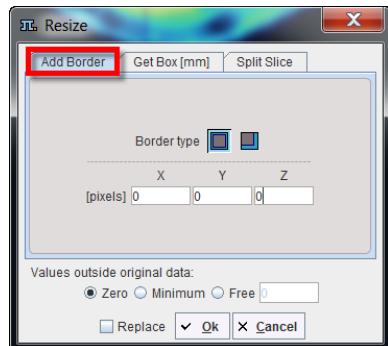


are

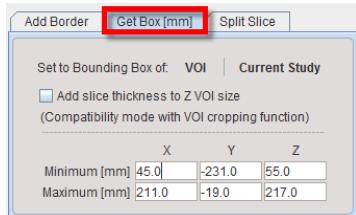
- » larger than ($>$) the specified value;
- » equal to ($=$) the specified value;
- » smaller than ($<$) the specified value;
- » within a value range ($><$) specified;
- » absolute value larger than ($|v|>$) the specified value;
- » absolute value smaller than ($|v|<$) the specified value;
- » is a NaN value (Not a Number).

Resize

The Resize tool has two tabs.



Add Border serves for padding pixels around the current series. There is a symmetrical and an unilateral variant. The number of padded pixels can be specified for each direction separately, and there are different options for the filling value.



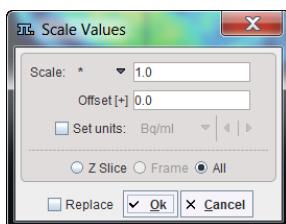
Get Box allows extracting a sub-volume of the current series (cropping). To this end, the new bounding box must be specified.

One way is to activate the **Current Study** button, which populates the **Minimum** and **Maximum** coordinates with that of the current study. Then the user can adjust the values appropriately to get a sub-volume.

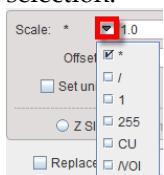
An alternative way is to base the extraction on the bounding box of a suitable VOI, which has been defined beforehand. Using the **VOI** button a VOI can be selected, its bounding box is read from the file and applied for sub-volume extraction. Note that the same functionality is also directly available in the VOI tool. Additionally, the slice thickness can be added to the Z VOI size enabling the **Add slice thickness to Z VOI size** box.

Scale Values

The **Scale Values** tool



can be used for transforming the pixel values by the following operations in the **Scale** selection.



- » *: multiply with a constant and add an **Offset** which defaults to 0;
- » /: divide by a constant and add an **Offset** which defaults to 0;
- » ->1: transform the value range to the interval [0,1];
- » ->255: transform the value range to the interval [0,255];
- » ->CU: transform the value range of CT Hounsfield numbers to the value range used in the template image of the clinical toolbox [1]. Values in [-1000..-100] are scaled to [0..900], values [-99..100] are scaled to [911...3100], values i>100 become [i+3000].
- » /VOI: divide by a VOI average and add an **Offset** which defaults to 0; the VOI has to be saved beforehand and needs to be selected.

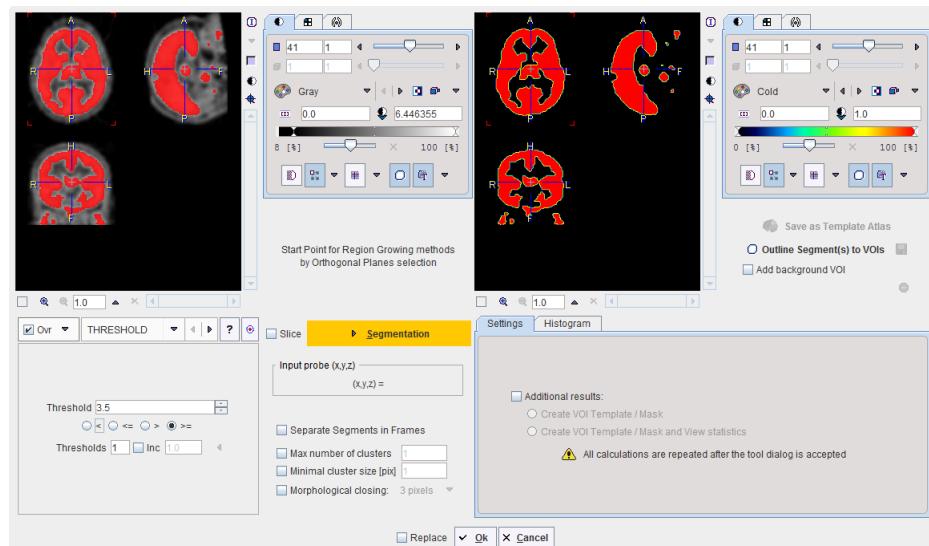
If **Set units** is enabled, units appropriate for the scaled image can be selected from the units list.

Reference

- Rorden C, Bonilha L, Fridriksson J, Bender B, Karnath HO: Age-specific CT and MRI templates for spatial normalization. Neuroimage 2012, 61(4):957-965. DOI <http://dx.doi.org/10.1016/j.neuroimage.2012.03.020>

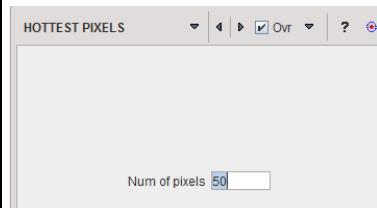
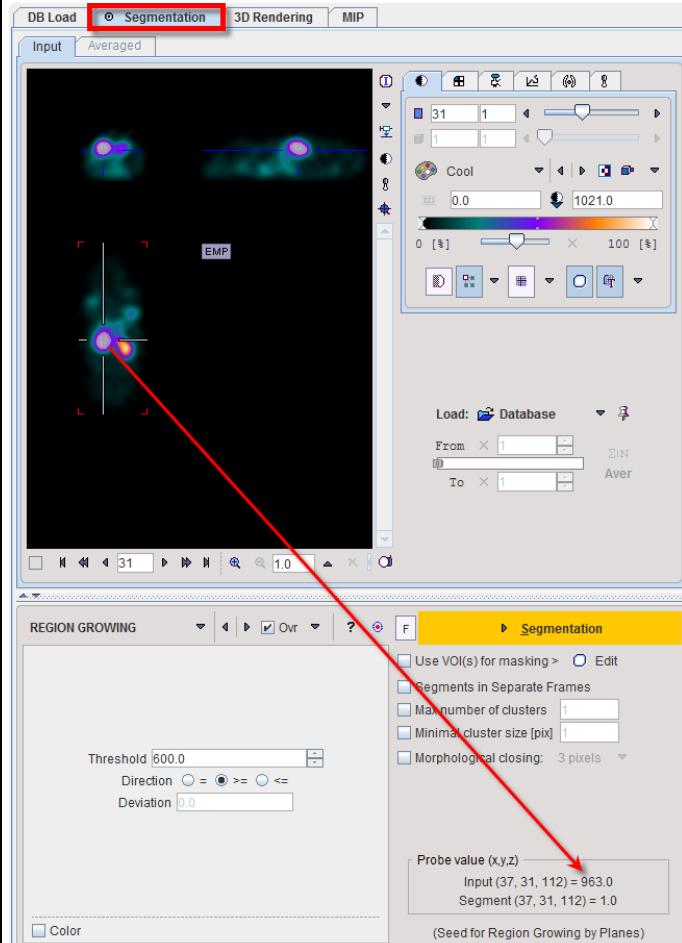
Segmentation

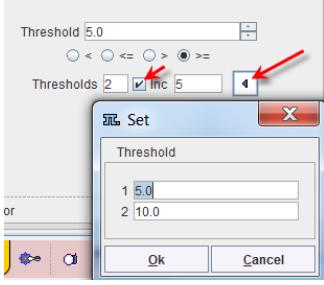
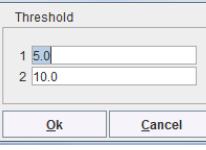
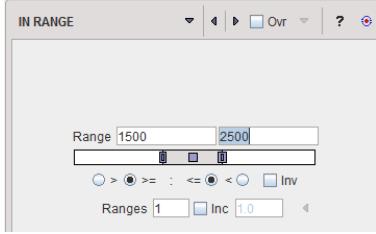
The **Segmentation** tool is a method for simple mask creation similar to the segmentation in the 3D tool. It opens the following dialog window.



The following segmentation methods are available.

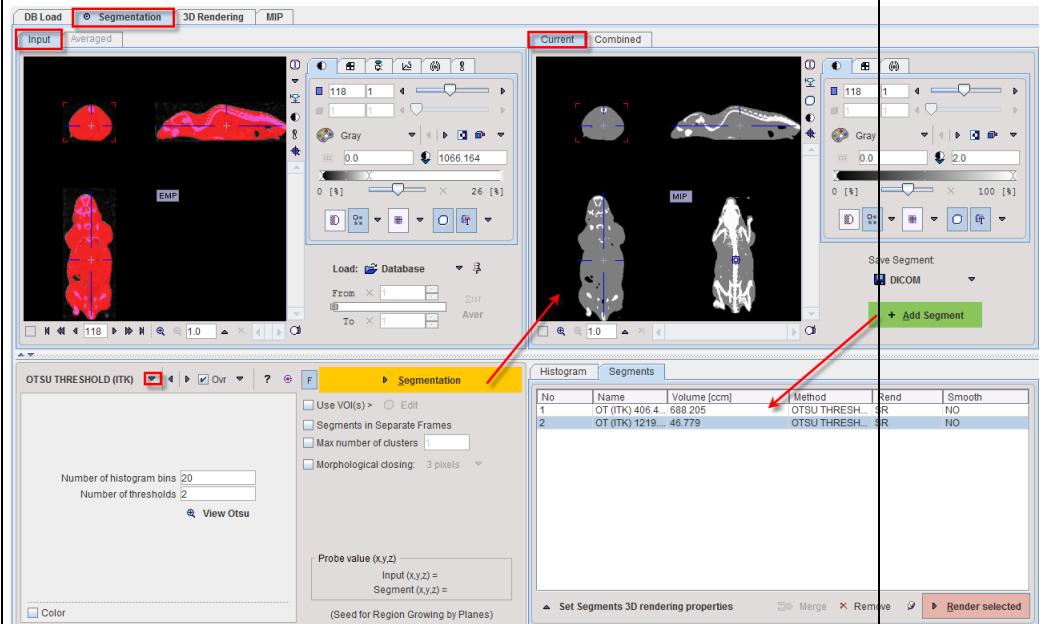
HOTTEST PIXELS	The HOTTEST PIXELS segmentation allows obtaining the (often disconnected) pixels with the highest values. The number of included pixels can be specified in the Num of pixels field.
-----------------------	--

	 <p>REGION GROWING is a method by which the user defines a starting point (seed) within the object of interest, and the algorithm tries to find all connected pixels which fulfill a certain criterion. It is required to triangulate the seed point with the orthogonal plane layout as illustrated below.</p>  <p>The inclusion criterion is formed by the Threshold value and the Direction specification:</p> <ul style="list-style-type: none"> » = include all connected pixels with a value Threshold \pm Deviation; » $>=$ include all connected pixels above the defined Threshold value; » $<=$ include all connected pixels below the defined Threshold value. <p>Note the Probe value which displays the image value at the position of the cursor, which is useful for finding appropriate Threshold setting.</p>
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THRESHOLD	<p>The THRESHOLD segmentation is conceptually simple. All pixels with value above or below the threshold are included in the segment, depending on the condition settings.</p>  <p>Sometimes it is helpful to segment at several threshold levels at once. This can easily be realized by setting the number in the Thresholds field accordingly, and entering the threshold values in the appearing Set dialog window.</p>   <p>Multiple threshold values can be incremented with a constant value enabling the Inc box and specifying the step in the dedicated text box.</p>
IN RANGE	<p>The IN RANGE segmentation is similar to the THRESHOLD method, except that two limits are defined. The boundary values are included or excluded, depending on the radio button settings. The complementary criterion is obtained by checking the Invert box.</p>  <p>Similar to the THRESHOLD segmentation, multiple Ranges can be defined and segmented at once.</p>
Otsu Threshold (ITK)	<p>The OTSU THRESHOLD method is based on the analysis of the pixel histogram and is described by <i>The ITK Software Guide</i> (http://www.itk.org/ItkSoftwareGuide.pdf) as follows: "Another criterion for classifying pixels is to minimize the error of misclassification. The goal is to find a threshold that classifies the image into two clusters such that we minimize the area under the histogram for one cluster that lies on the other cluster's side of the threshold. This</p>

is equivalent to minimizing the within class variance or equivalently maximizing the between class variance."

The **Number of histogram bins** defines the resolution of the histogram shape, whereas the **Number of thresholds** defines the number of distinct clusters. With the mouse CT, Otsu with the settings below finds appropriate thresholds for the skeleton object and the soft tissue, as illustrated below. Note that the threshold values can be inspected only after the actual segmentation by the **View Otsu** button.

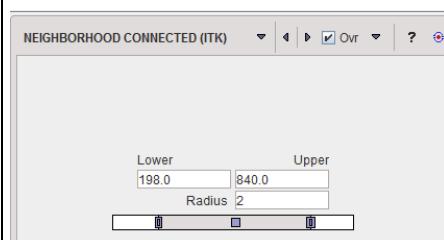


Neighborhood Connected (ITK)

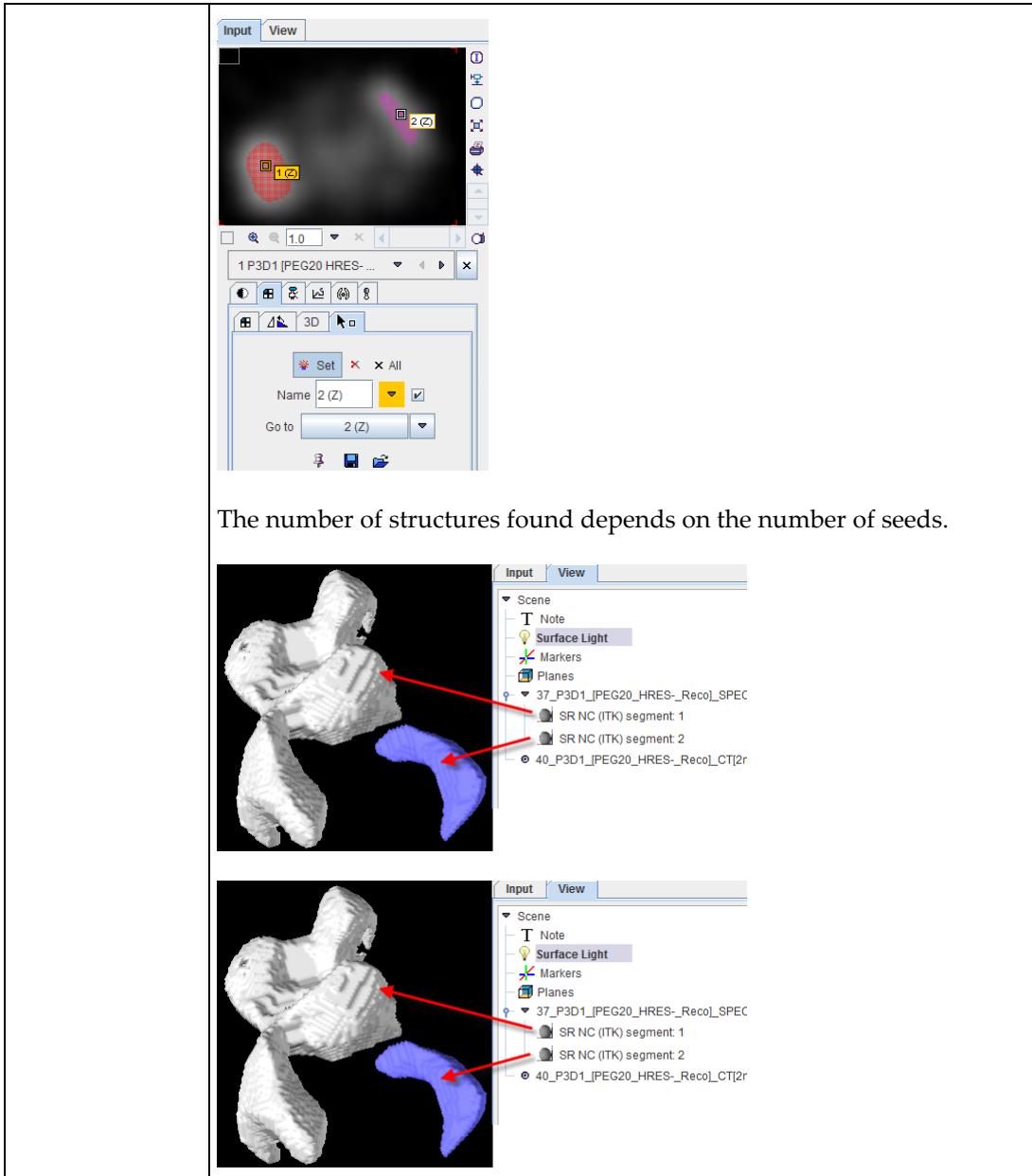
NEIGHBORHOOD CONNECTED is a region growing method which applies two grouping criteria:

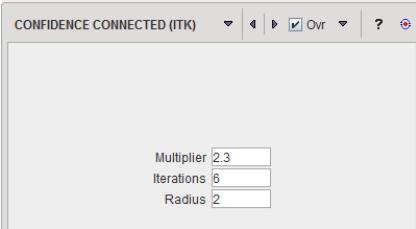
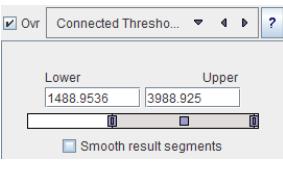
- 1) An included pixel must have a value in the range between the **Lower** and **Upper** threshold.
- 2) All pixels in its neighborhood within the specified pixel **Radius** must also be within the value range.

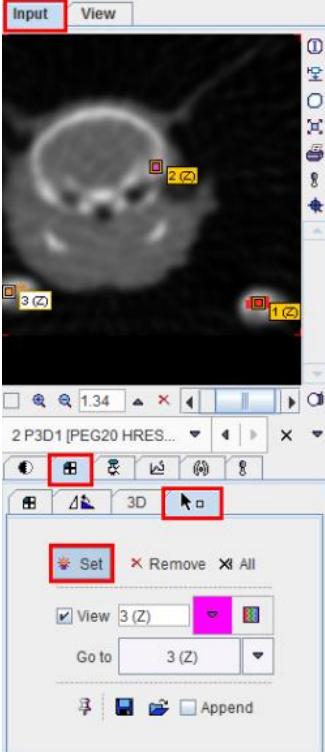
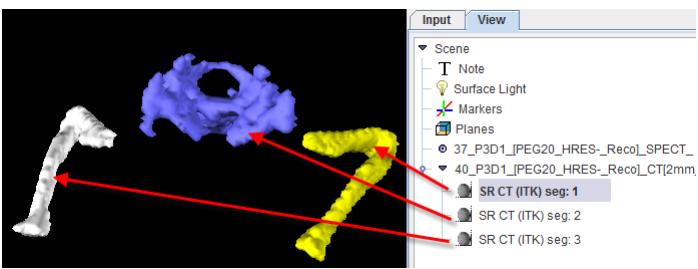
By the combination of these criteria small structures are less likely to be accepted in the region.



A single seed is provided by the triangulation point of the orthogonal planes. Multiple seed points can be specified by the use of markers.



	<p>From the <i>The ITK Software Guide</i> (http://www.itk.org/ItkSoftwareGuide.pdf): "The criterion used by the Confidence Connected method is based on simple statistics of the current region. First, the algorithm computes the mean and standard deviation of intensity values for all the pixels currently included in the region. A user-provided factor (Multiplier) is used to multiply the standard deviation and define a range around the mean. Neighbor pixels whose intensity values fall inside the range are accepted and included in the region. When no more neighbor pixels are found that satisfy the criterion, the algorithm is considered to have finished its first iteration. At that point, the mean and standard deviation of the intensity levels are recomputed using all the pixels currently included in the region. This mean and standard deviation defines a new intensity range that is used to visit current region neighbors and evaluate whether their intensity falls inside the range. This iterative process is repeated until no more pixels are added or the maximum number of iterations is reached.</p> <p>The number of Iterations is specified based on the homogeneity of the intensities of the anatomical structure to be segmented. Highly homogeneous regions may only require a couple of iterations. Regions with ramp effects, like MRI images with inhomogeneous fields, may require more iterations. In practice, it seems to be more important to carefully select the multiplier factor than the number of iterations. However, keep in mind that there is no reason to assume that this algorithm should converge to a stable region. It is possible that by letting the algorithm run for more iterations the region will end up engulfing the entire image."</p> <p>The initialization of the algorithm requires the user to provide a seed point. It is convenient to select this point to be placed in a typical region of the anatomical structure to be segmented. A small initial neighborhood Radius around the seed point will be used to compute the initial mean and standard deviation for the inclusion criterion.</p> 
Connected Threshold (ITK)	<p>Connected Threshold is a region growing method with the criterion that (similar to the IN RANGE method) the included pixels must have values between a Lower and Upper threshold.</p> 

	<p>As usual with region growing methods, the user has to specify a seed point by clicking into the image. The ITK region growing methods are particular in that multiple seed points can be specified at once by the use of markers as illustrated below.</p> 
	<p>Once the markers tab has been activated and the Set button enabled, a marker is created as a seed point for each clicking into the image. When the segmentation is started, the region growing with the specified value range is performed from each marker.</p> 
SCATTER in VOI	This particular method for localizing pixels from 2D scatter plots is described in a separate <i>section</i> (on page 171).

After specification of the segmentation method and its parameters, the segmentation can be started with the **Segmentation** button. The result is shown in the right image display port. Note that if the study is dynamic, an additional box **All Frames** appears. If it is checked, segmentation will be performed for all frames separately, otherwise with the frame which is currently shown.

The segmentation result can be used in different ways:

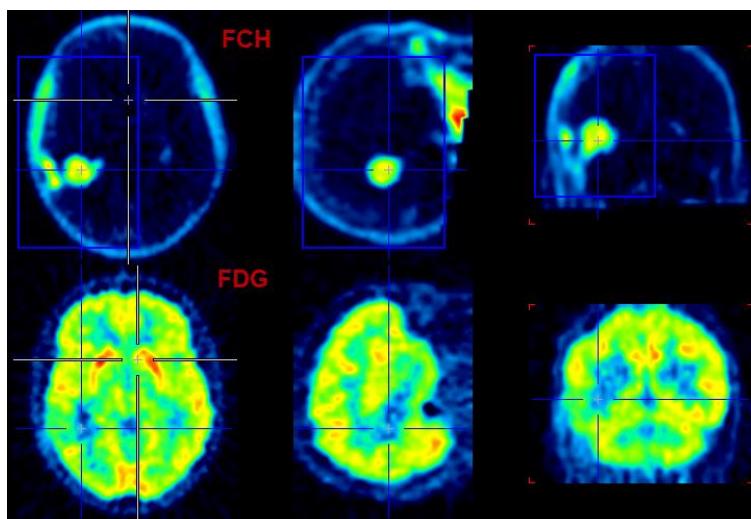
- » **Save as Template** Atlas directly saves the segmented series in an atlas format in the directory Pmod3.8/resources/templates/voitemplates. Subsequently, it can be used for statistics using the **Atlas** tab of the **Templates** pane in the VOI definition function.
- » The **Outline** button allows creating VOIs for each generated segment. Optionally, the background can be added as a VOI by enabling the **Add background VOI** box. The outlined VOIs can be saved as files and later used for statistics by the **Save** icon next to the **Outline** button.

With the **Ok** button the segmentation is performed again and the resulting segment returned as an image series which is binary for a simple segmentation and an object map in the case of a clustering method. The following **Additional results** can be returned.

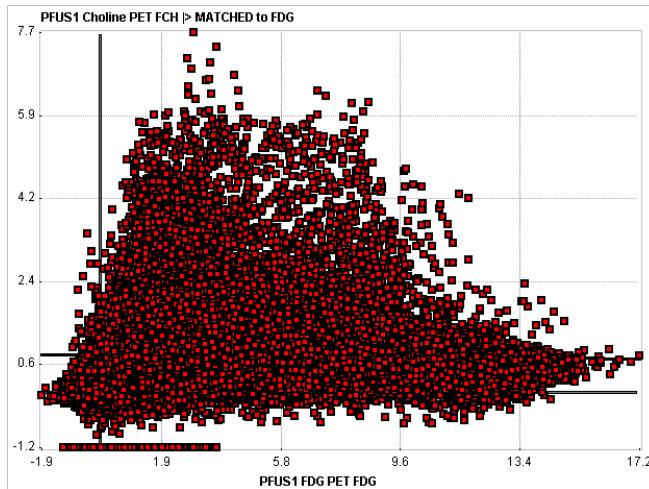
- 1) **Create VOI Template/Mask:** With this setting, the segments are also returned as a VOI template which can be activated by the **Mask** tab of the **VOI Template** function.
- 2) **Create VOI Template/Mask and View Statistics:** As 1), but the statistics on the current image are additionally calculated.

Mapping of Pixels from Scatter Plots

Scatter plots are a convenient method for exploring tissue function, if matched image series are available. With the brain PET example illustrated below,



we get the following scatter plot of the pixel values in the blue VOI box.

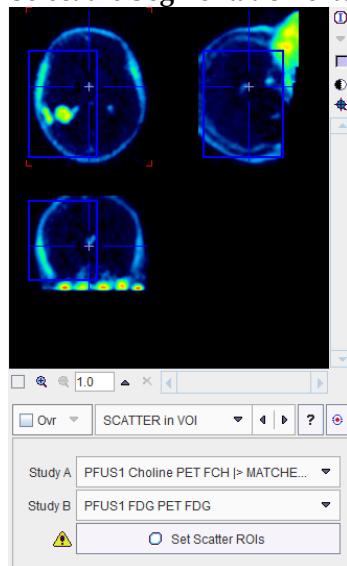


The FDG uptake of a pixel is plotted on the x-axis, and the corresponding PCH uptake on the y-axis. The **Segmentation** tool allows defining areas of interest in the scatter plot plane and mapping the enclosed pixels back to the image. The procedure converts the scatter plot to an image, in order to apply the standard PMOD VOI functionality for the area definition.

Segmentation Procedure

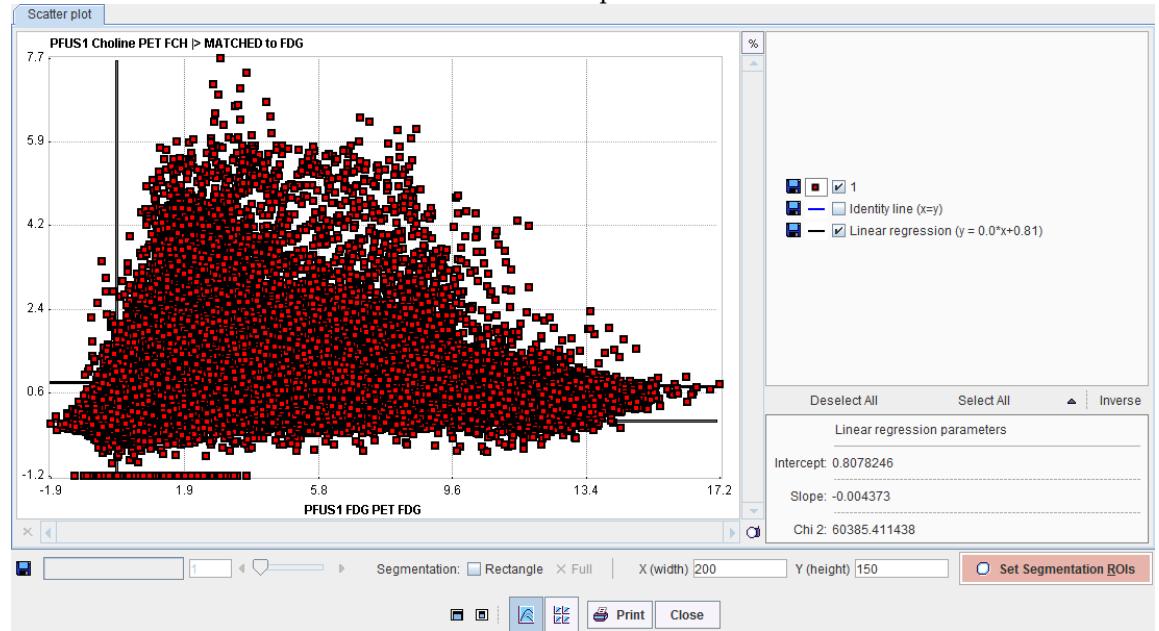
Please proceed as follows:

- 1) Load the two matched image series.
- 2) Define one or multiple VOIs on the first image series which enclose the tissue of interest, if needed the whole volume.
- 3) Select the **Segmentation** external tool, and chose the **SCATTER in VOI** method.

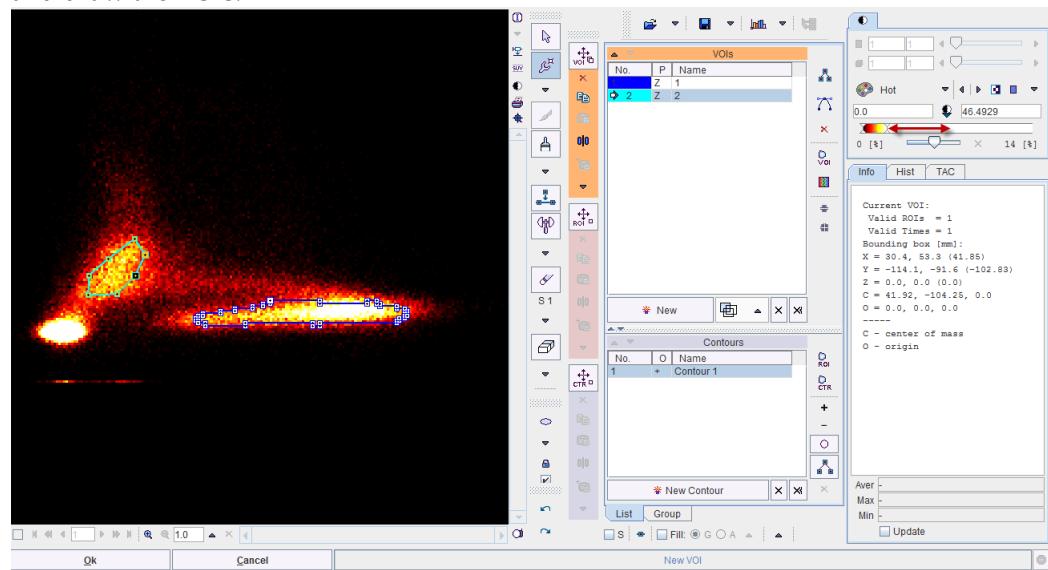


- 4) Using the list selection arrow, define the series with the defined VOI as **Study A**, and the other series as **Study B**.

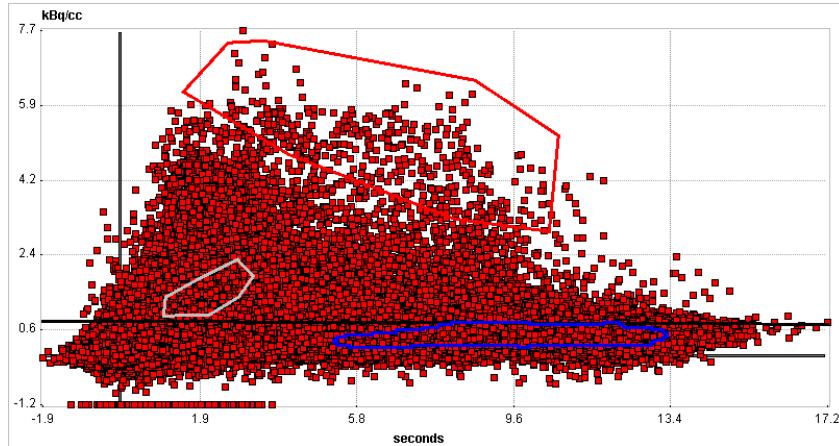
- 5) Activate Set Scatter ROIs to create the 2D scatter plot.



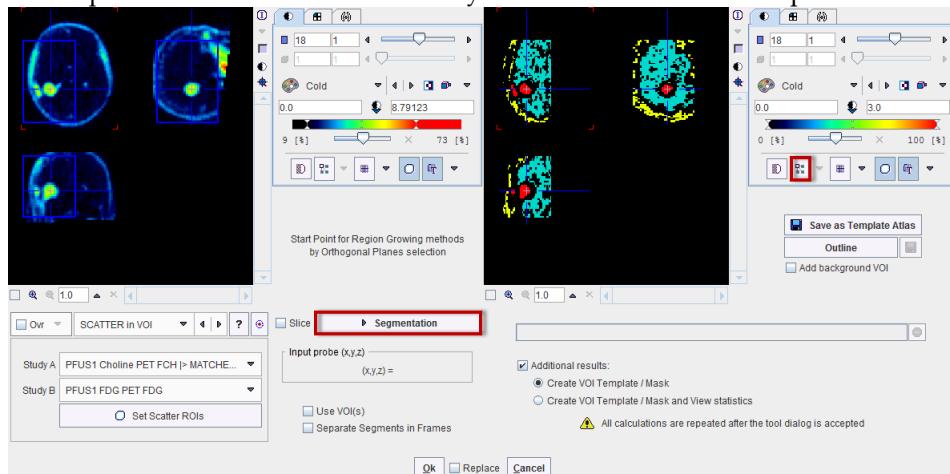
- 6) Convert the plot into an image by **Set Segmentation ROIs**. The **X(width)** and **Y(height)** define the number of image pixels in the two dimensions. The image value is given by the number of scatter points in the area of each image pixel.
- 7) A window appears showing the generated image together with the VOI definition interface. Adjust the color thresholds for localizing pixels with a specific uptake pattern and draw the ROIs.



- 8) Closing of the VOI interface with **OK** returns to the scatter plot which now also displays the ROIs.

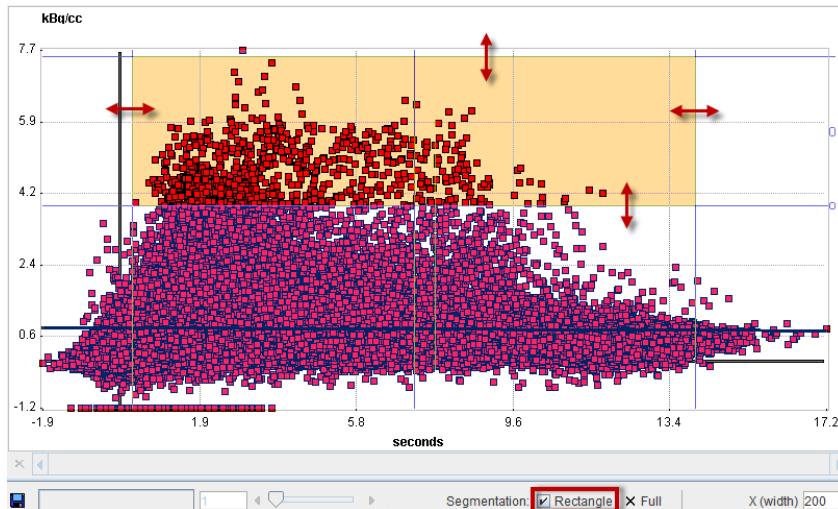


- 9) Complete the definition by the **Close** button to return to the **Segmentation** tool.
 10) Now the scatter pixels can be mapped with the **Segmentation** button. The interpolation should be disabled to better see the generated segments. The result indicates that the tumor pixels were well characterized by the red ROI in the scatter plot.



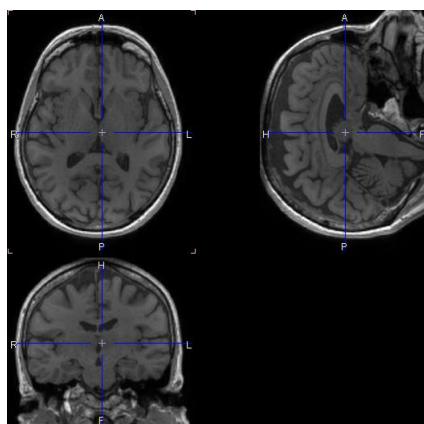
Rectangle ROI

A quick alternative to going through scatter plot rasterization and ROI outlining is to use a simple rectangular ROI. This functionality is enabled by the **Rectangle** box. A red-shaded area appears, which can be adjusted by dragging the edges. **Segmentation** will map the pixels in the defined rectangle.



Standard Orientation

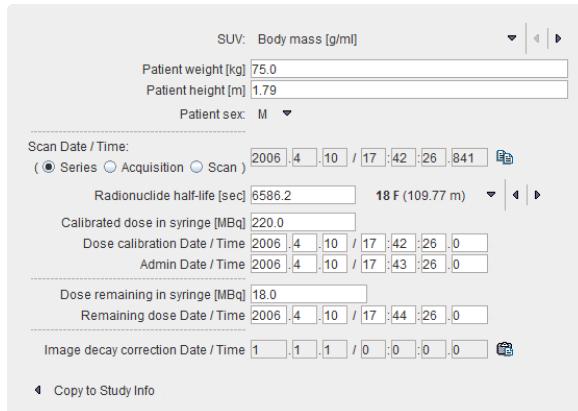
Reformats the loaded images such that they are displayed in the standard radiological head first supine (HFS) position illustrated below. This function requires that correct patient positioning information is available in the image data header.



An HFS orientation of the images is mostly relevant for the automatic generation of VOIs.

SUV Image Calculation

Explicit SUV images can be calculated with the **Calculate SUV Image** entry of the external tools. It shows a dialog window with information related to the administration of the tracer dose explained above.



The **SUV** selection determines the SUV type to be calculated. The **Ok** button starts the calculation. A new image series with changed units ([g/ml], [cm²/ml] or [%ID/ml]) is created if the **Replace** box is unchecked, otherwise the original series is overwritten.

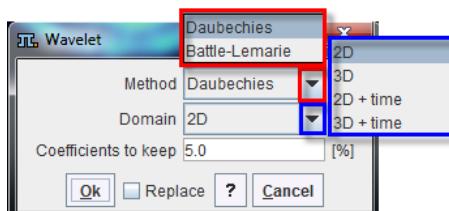
Note:

For regional statistics the explicit SUV image calculation is not necessary. The *statistics output* (on page 285) can be switched to SUV units, provided that all required information is available.

Using the **Copy to Study Info** button the corrected information can be saved for later use, and for saving it together with the data.

Wavelet Filtering

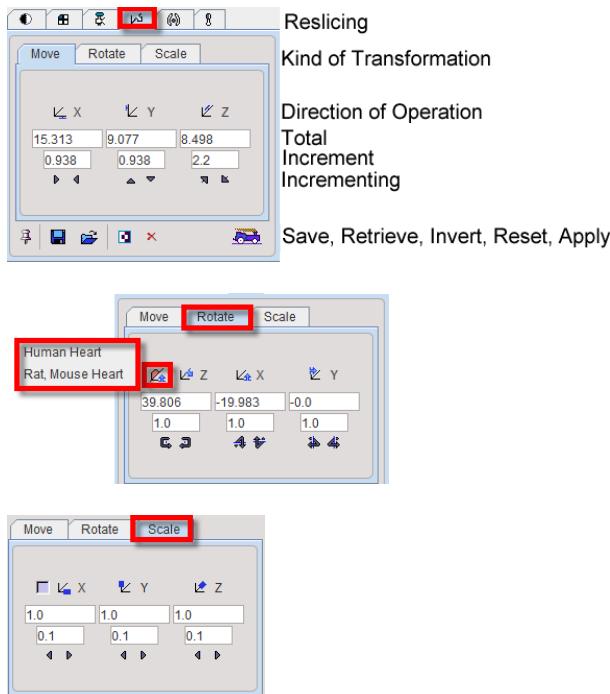
The **Wavelet** tool performs de-noising of the dynamic data.



Daubechies or **Battle-Lemarie** wavelets are supported. There are different modes of operation: each plane separately (**2D**), each frame separately (**3D**), each plane over time separately (**2D + time**), or the volume over time (**3D + time**). Image dimensions 2^n are required. The **coefficients to keep** determine the level of smoothing: the lower the % value entered, the smoother the image.

Reslicing of the Images at Oblique Orientations

To calculate slices at oblique orientations or rotate images the reslicing pane must be activated. Reslicing is defined by a transformation consisting of translations in all directions, rotations about all axes, and potentially scaling along the axes. Each of these transformation components has its own sub-pane.



Note that **Scale** values of 1 indicate that the pixel sizes read from the image header are correct. Any other number will scale the pixel size accordingly.

The transformation parameters can be specified in different ways, on the corresponding sub-panes **Move**, **Rotate**, **Scale**:

- ▶ by entering values for the shifts or rotations in the number fields, or
- ▶ by clicking on one of the arrows to increase/decrease the values by the shown increments.

In the **Rotate** tab a help re-orientation button is available for heart studies . This option button allows re-orienting the heart data such that is closest to the short axis orientation (SA). The heart type can be selected when the button is activated. Two options are available: **Human Heart** and **Rat Mouse Heart**.

After changing the transformation, new slice images are immediately calculated and shown. However, the entire data set is only generated when needed, for instance to save the images. The button serves for enforcing the reslicing process for the whole data volume.

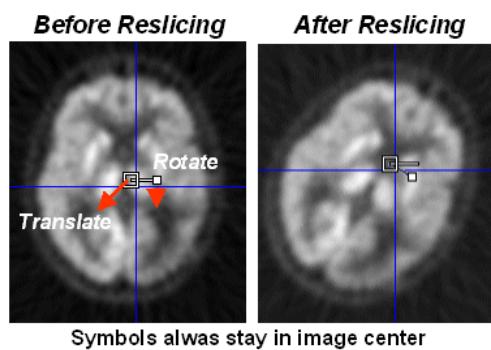
The button resets the transformation parameters. A transformation can be saved to disk using , and later retrieved with if needed.

Important Notes:

1. The facility buttons in the reslicing panel for **Save**, **Retrieve** and **Apply** transformation are not always available.
2. The manual transformations are not fully equivalent with the automatic rigid matching transforms of the fusion tool. Manual transformation can be used in PFUS activating the **Load Transformation** button in the **Auto** panel available on the **Initialize/Match** page. In PFUS, the **Inverse** transformation is possible to calculate for any type of transformation activating the dedicated button **Inverse**.

Mouse-driven Reslicing

As soon as the reslicing pane is activated, handles appear in the image overlay. They allow for interactive, mouse-driven reslicing.



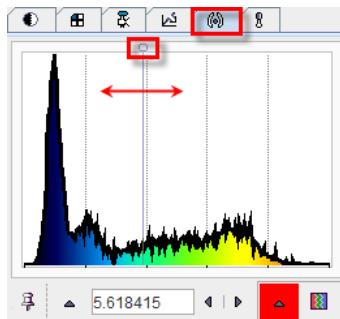
Translation: Move the mouse pointer to the open white rectangle. The cursor changes to . Click the left mouse button down, and then drag along the direction you want to move the image to.

Rotation: Move the mouse pointer to the filled small white rectangle. The cursor changes to . Click the left mouse button down, and then drag while the image gets rotated. To get finer control of rotation, the rectangle can first be dragged radially outward, so that the handle distance from center increases.

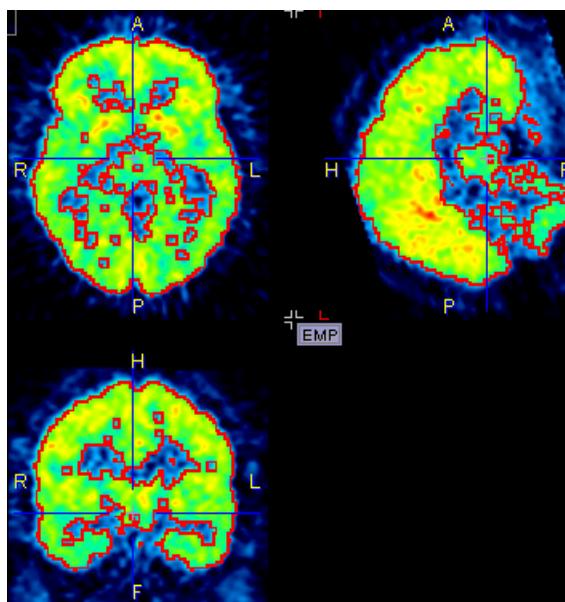
Per default, the reslicing handles are shown as long as the reslicing tab is selected. If another tab is selected, they disappear. To make them appear permanently in the images and enable mouse-driven reslicing at all times, the pin button can be fixed to . A quick alternative to show/hide the reslicing controls in the active image is the CTRL+R shortcut.

Adding Iso-Contour Lines to Images

The fourth tab



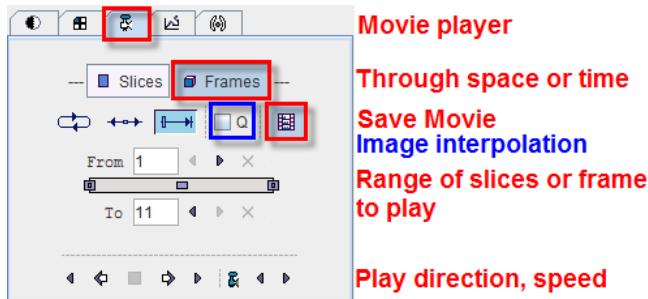
is used to overlay iso-contour lines onto the images. A histogram of the pixel values is shown, and the value at which the iso-contour lines are drawn can be adjusted by entering a numerical value, or by dragging the marker highlighted in the graphics above. The selection on the right allows choosing among several colors for the contour lines.



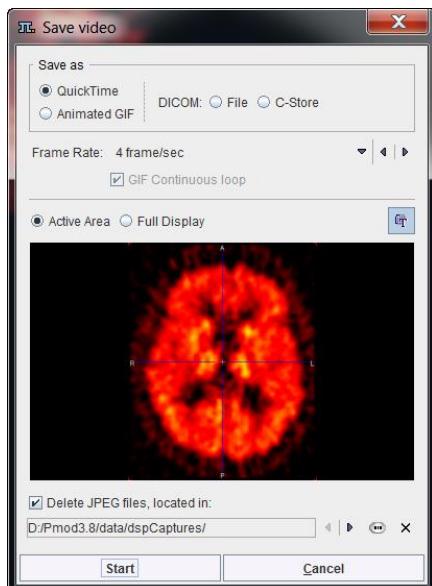
Per default, the iso-contour lines are shown as long as the iso-contour tab is selected. If another tab is selected, they disappear. To make them appear permanently in the images the pin button can be fixed to .

Showing and Saving Movies

The movie player allows showing movies of slice images through the volume or through time (dynamic studies only), as well as rotating MIPs if the 3D button was selected in the layout.



Please use the **Q** box to enable image interpolation when working with low-resolution images. If the save movie button is activated at the time the user hits the start button, a dialog window appears requesting information for movie generation.



The movie formats include Quicktime or DICOM, and the active image or the entire image viewport can be captured. The movies are generated from intermediate JPEG files, which can optionally be kept for other uses.

A movie of the active image can also be started/stopped with the **CTRL+M** shortcut without the need to open the movie tab.

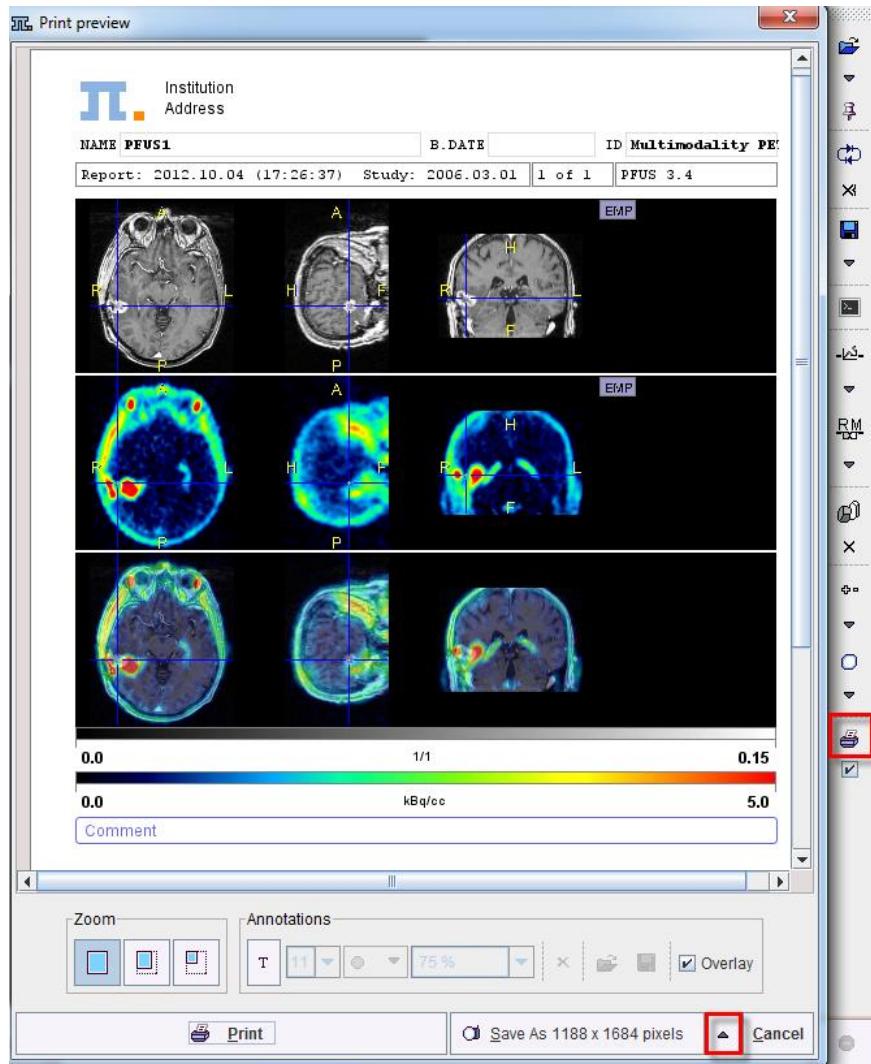
Reports

Reports of the current configuration in a single image display can always be generated using the report button  next to the image. In more complex configurations such as image fusion (PFUS) or image comparison (PVIEW) a dedicated report button is available which creates a composite report.

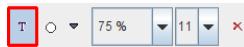
The report button opens a dialog window consisting of a header part, the image area, a comment field, and control buttons for adding annotations, saving and printing.

The logo and the institution address of the header can be configured using the  Config button in the PMOD ToolBox. The patient demographic information is extracted from the image header. It can only be changed by changing the image information itself with the **Edit Patient/Study Info** function.

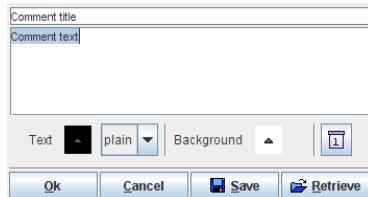
The central part contains the image(s) in the layout and color as on the image viewing port(s). As long as the presentation is not fully satisfactory, the user can change it in the application and then activating the  button again.



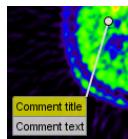
In addition to the provided content the user may add annotations. This can be achieved by enabling the  toggle button in the **Annotations** area



and then clicking into the report. A dialog window opens for entering a comment title and body.



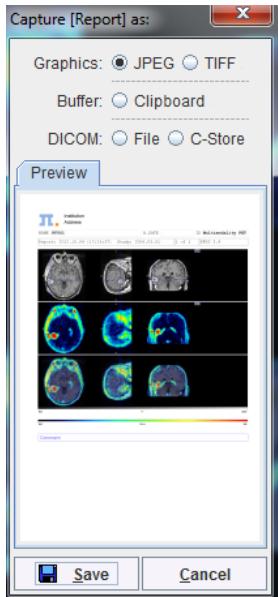
After closing with **Ok**, the comment text is shown together with a circular marker, connected by a line.



Both the text and the marker can be dragged around so as to properly label a point of interest without obstructing the view on relevant information. By changing the opacity and font size in the **Annotations** area, the comment appearance can be adjusted appropriately. To stop adding annotations, the  toggle button must be set to off by clicking it again.

When the report content is satisfactory, the page can be sent to a printer using the **Print** button. Alternatively it can be saved in different graphic formats using the **Save as** option button. Note that there are two resolutions available: **1188x1684** and **594x842**. With **1188x1684**, the generated graphic files have notable better quality (particularly the text), but are considerably larger in size.

Several saving formats are available in the appearing dialog:



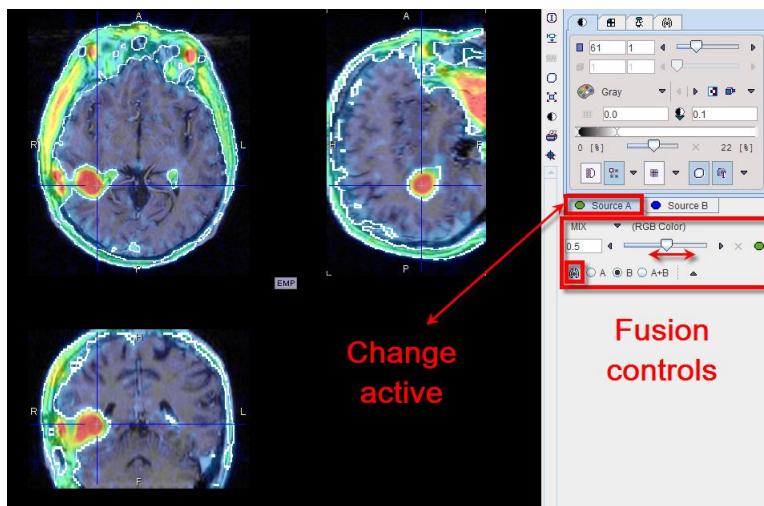
The report page can be saved as a graphic file (**JPEG** or **TIFF**) or copied to the **Clipboard** (for pasting it into a different application). Another alternative is to create a DICOM Secondary Capture object which can be saved to disk (**DICOM File**) or directly sent to a DICOM server (**DICOM C-Store**).

Presentation of Fused Images

There are multiple places in PMOD where two different image sets can be combined into a fused image. Depending on the context, there are two arrangements for performing the image fusion.

Fusion Images not Visible at the same Time as the Source Images

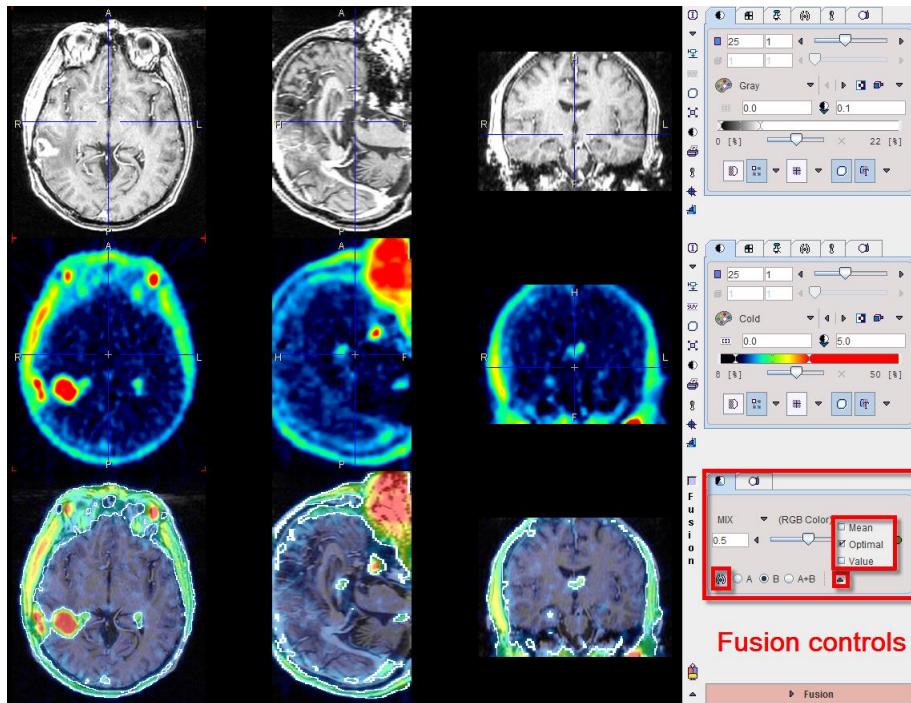
In this layout only the fusion of two source series is shown.



To adjust the presentation of either source image, select the appropriate tab **Source A** or **Source B**, and use the image controls. During such adjustments it will sometimes be helpful to only see the image you are working on, not the fusion. This can easily be achieved by moving the balance slider to one of the end positions left or right.

Separate Source and Fusion Images

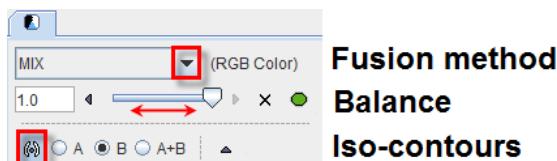
In this layout both the input images and the fusion images are visible at the same time, as in the example shown below.



In this example the first row shows a T₁-weighted MR image, and the second a matched ¹⁸F-Choline PET image with a highlighted tumor. To the right of the images the controls are available for changing the way how the images are displayed such as the color table, the thresholds, and the layouts. The third row shows the result of the fusion, depending both on the renderings of the source images, and on choice of the fusion controls located to the right.

Image Fusion Methods

The image fusion control



consists of three rows. The first row contains the selection(s) for choosing between the different fusion renderings, the second row allows enabling the balance to blend the contributions of the two images in the fusion, and the third row allows enabling the iso-contour overlays.

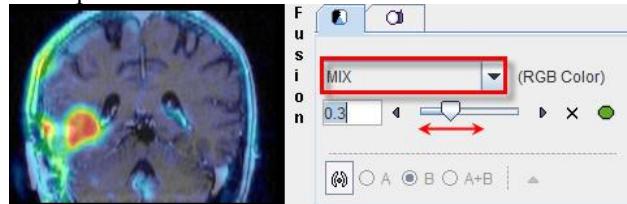
The fusion methods available are:

- | | |
|------------|---|
| MIX | Alpha Blending: weighted addition of the RGB values of both source images according to
$R_{\text{fusion}} = R_A * x + R_B * (1-x)$ |
|------------|---|

$$G_{\text{fusion}} = G_A * x + G_B * (1-x)$$

$$B_{\text{fusion}} = B_A * x + B_B * (1-x)$$

Example:



The slider allows defining the relative contributions of the source images. In the example shown image A contributes 30%, and image B 70%.

MERGE

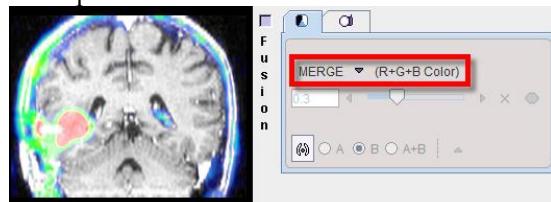
RGB merging uses the maximal RGB value of both source images according to

$$R_{\text{fusion}} = \text{Max}(R_A, R_B)$$

$$G_{\text{fusion}} = \text{Max}(G_A, G_B)$$

$$B_{\text{fusion}} = \text{Max}(B_A, B_B)$$

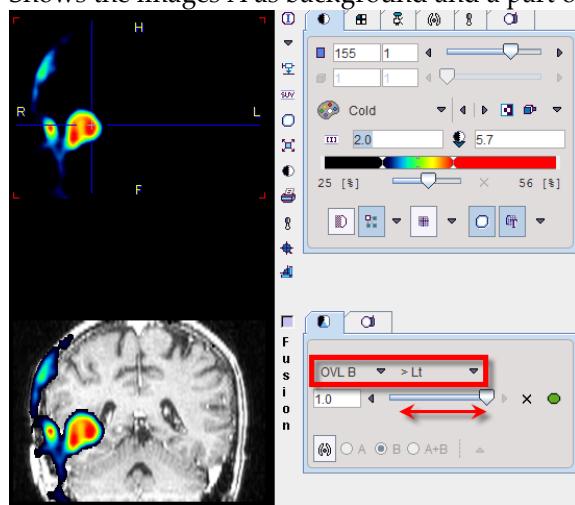
Example:



This fusion mode is most adequate for data arising from RGB sources, or when encoding the images with the [R]ed, [G]reen, [B]lue color tables.

OVL B

Shows the images A as background and a part of the images B as the overlay.



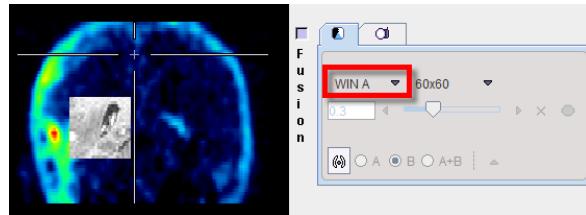
With the **>Lt** setting, all pixels in the PET image (B) below the lower threshold of the color table are replaced by the MR (A) values. Additionally, some transparency is added in the lesion by the balance slider. See below the description of the different threshold options.

OVL A

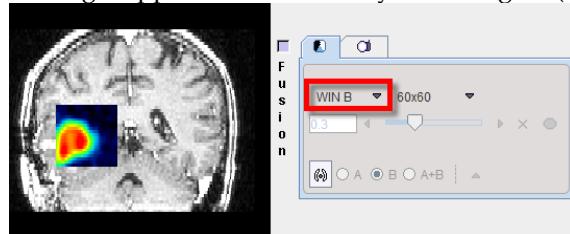
Is equivalent to **OVL B** except that the role of the images is reversed.

WIN A

Shows the images B (PET) as the background. When clicking into an image a rectangle appears which overlays the image A (MR).



WIN B Shows the images A (MR) as the background. When clicking into an image a rectangle appears which overlays the image B (PET).



When the **OVL A** or **OVL B** methods are selected, different threshold settings are available in the selection to the right:

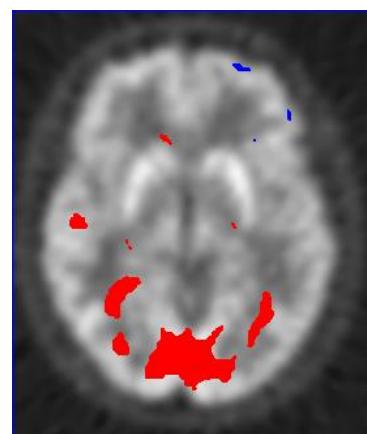
- > Lt Only the pixels (in A for **OVL A**, in B for **OVL B**) with values *above* the lower threshold are displayed. This is the most useful setting when a hot lesion is to be blended into an anatomical image (see example for **OVL B** above).
- < Ut Only the pixels (in A for **OVL A**, in B for **OVL B**) with values *below* the upper threshold are displayed.
- >Lt Ut< Only the pixels (in A for **OVL A**, in B for **OVL B**) with values *between* the lower and upper threshold are displayed.
- <Lt Ut> Only the pixels (in A for **OVL A**, in B for **OVL B**) with values *outside* the lower and upper threshold are displayed. Note that only the first and last color of the selected color table are applied in this setting. A suitable selection in this configuration is the **Split** color table.

An example of the <Lt Ut> method is shown below.

Image A represents normalized patient images, and image B the deviation from the normal pattern expressed as z-score values. The color table configuration of image B is



and the fusion settings

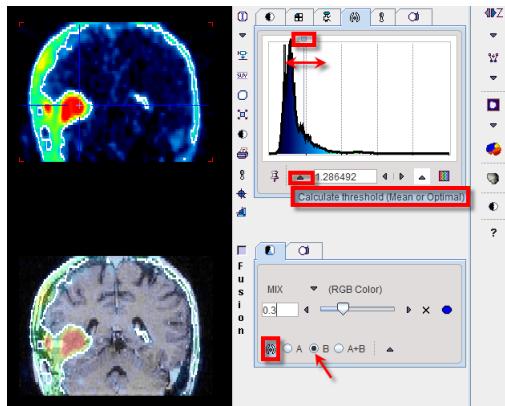


Only z-score values < -2 and > 2 are shown, without transparency. Because only the minimal and the maximal colors are used, the result has a binary character. Red are all

pixels with an activation of more than two standard deviations, and blue all the pixels with the uptake reduced by at least two standard deviations. This is probably the most useful configuration for exploring the deviations from the standard pattern.

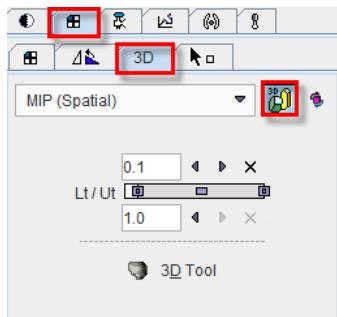
Iso-contours in Image Fusion

The contours radio box allows overlaying iso-contours derived from the source images A or B or both onto the fusion result. In the example below an iso-contour circumscribes the lesion clearly delineated in the FCH PET image. The iso-contour for the image B can be generated automatically selecting the **Optimal** option in the list in the **Contouring** tab. Setting the radio box **B** displays this contour in the fusion, which has been set to show mainly the MR image (A) by moving the balance slider to the left end. Another helpful application of the contours is in image matching.



3D Volume Rendering, Rotating MIP Images

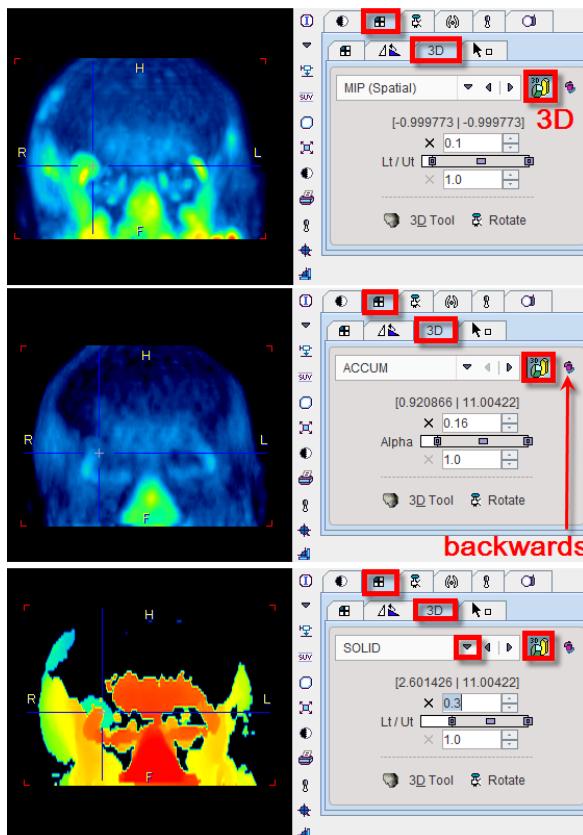
Instead of showing individual slice images, a volumetric data set can be volume rendered. Simple volume rendering can be enabled in the **3D** sub-pane



There are four methods to choose from the selection

- » MIP (Maximum Intensity Projection) being the most known one
- » MinIP (Minimal Intensity Projection)
- » ACCUM (Accumulation of color and opacity)
- » SOLID

As soon as the rendering button indicated in red is activated (or **CTRL+V** on the image) the image display switches from slice display to volumetric display, with the projection direction orthogonal to the image plane. Three renderings of an example PET using the same color table are shown below. Note that the value range considered in the renderings is somewhat different.



The button to the right of the 3D selection is a toggle to perform the 3D operation from backwards, which will result in a different image in the case of a depth-dependent weighting function.

Note that image scrolling is still enabled in 3D mode. When **CTRL+Drag** the left mouse button over the image, the 3D rendering disappears and the slice images are shown until the mouse button is released.

Rotating MIP

To create a rotating coronal MIP movie please proceed as follows:

- » In the **Layout** pane select the **Coronal** orientation (or **CTRL+Y** in the image).
- » In the **3D** pane enable MIP and 3D, then adjust the upper/lower thresholds.
- » In the **Movie** pane the number of slices has been replaced by the number of projections with a default value of 40 angles. Increase the number to get smoother rotations. Start playing.

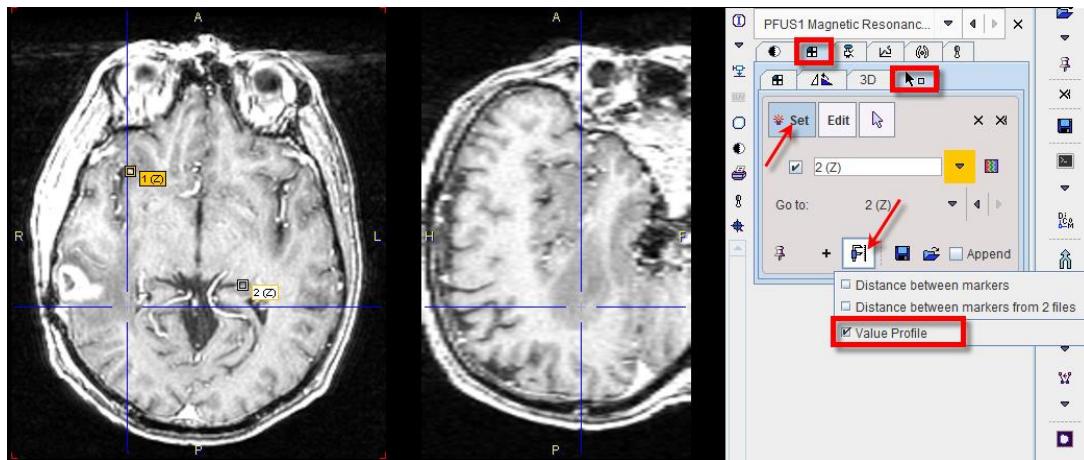
MIP images will be calculated from different viewpoints and displayed as a rotating cine. If you would like to save a movie, enable the saving button as explained in *Showing and Saving Movies* (on page 180).

Transfer to Full 3D Rendering

The  button in the 3D pane is only functional if the PMOD 3D option is installed. When this button is activated, the current data set is loaded into the full 3D rendering tool for advanced processing.

Markers

The **Markers** sub-pane serves for the definition of landmarks in the image.



The best way to define landmarks is to operate in the orthogonal layout. If the **Set** button is active the user may click into an image to define anatomical landmarks which are shown as squares in the image. Using the **+** button, a landmark can be defined by entering its coordinates in a dialog window. To avoid marker generation, hold **CTRL+SHIFT** when clicking, or disable **Set** beforehand. The slices can be scrolled by the mouse wheel or by **CTRL+DRAG**. The spatial arrangement of landmarks can be saved for later use with **H**.

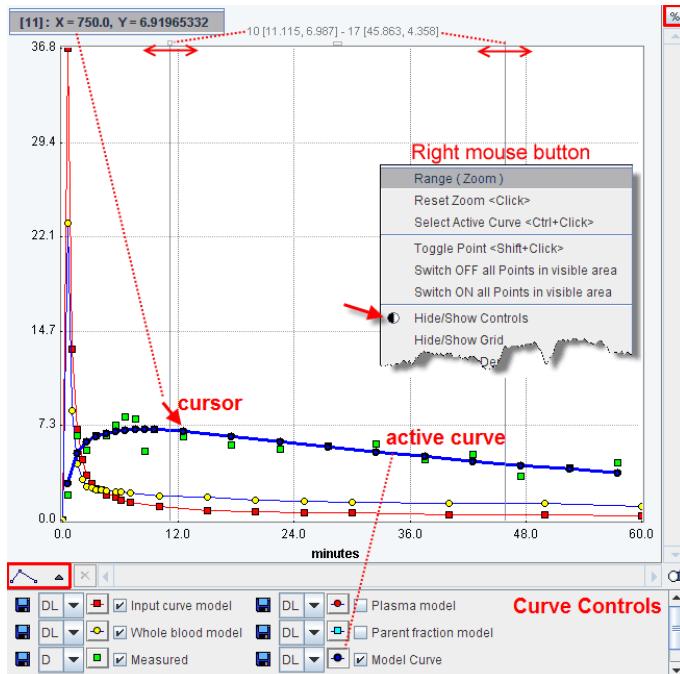
The defined landmarks are numbered and organized in a list. The planes can be centered on a defined landmark by the **Go to** list selection. There are three types of landmark-based measurements:

- » **Distance between markers** calculates the distances between any two landmarks and shows them in a table.
- » **Distance between markers from two files** allows loading a second landmark set and calculating the distances between corresponding landmarks.
- » **Value Profile** generates a plot of the values between the landmarks, connecting them sequentially with lines.



Curve Display

A common curve display object is used in all PMOD tools. It consists of a curve area and a controls area underneath.



In some contexts the control area may initially be hidden. The context menu can be used to show it

Curve Area

The curve area shows the curves which are enabled for display. There is always an *active curve*, which is shown in bold. A curve can be made active by holding down the CTRL key and clicking at one of its points, or by pushing its button in the controls area as illustrated with the **Model Curve** above.

The definition of the active curve is relevant for the tools which interrogate the curve values:

- » There are two small handles at the top of the curve area: a little rectangle to the left, and a line to the right. These are handles which can be moved left/right using the mouse, and the gray vertical lines move with them. The values at the top center of the curve area represent the interpolated (x/y) values of the active curve at the location of the handles. To get the measurements of a different curve just CTRL+Click at that curve to get the values updated.
- » Only in some curve displays: When the cursor is brought close to a point of the active curve, its x/y value pair is shown at the upper left of the curve area.

To *zoom* into an area of the curve just click the left mouse button to the corner of the area of interest and drag a rectangle. After releasing the mouse button the display is zoomed into the defined rectangle. An alternative is to define the axes **Range** in the context menu. A single mouse click into the curve area is sufficient to reset the zoom.

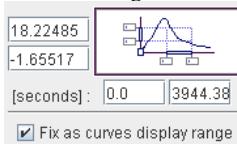
Context Menu

By clicking the right mouse button into the curve area a context menu with some additional options can be opened.



The functions are:

Range (Zoom) Set the range of the x- and y-axis by entering a numeric value.



If the box is checked, the range is maintained during all manipulations. Otherwise, a single click resets the range to the default.

Reset Zoom

To reset the curve range to the default full range. It is grayed if the display is not zoomed or the range is fixed.

Mouse operation: single Click into curve area.

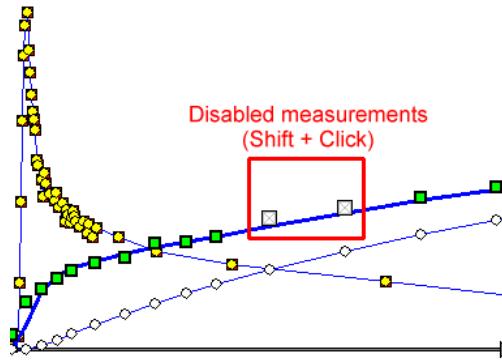
Select Active Curve

Selects the curve nearest to the point clicked with the right mouse button to open the context menu.

Mouse operation: CTRL+Click at a curve.

Toggle point

Disable a measurement of the active curve. This is reflected by setting the symbol to gray.



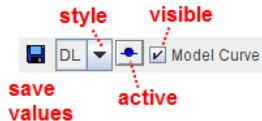
In the context of model fitting measurements marked in gray are regarded as outliers and not considered when evaluating the cost function.

Mouse operation: select the relevant curve to active, then SHIFT+Click at measurement.

Switch ON/OFF all points in visible area	In combination with zooming this option allows to quickly disable/enable contiguous points of the active curve.
Hide/Show Controls	Allows hiding the controls if the curve display area is small, and to show them again.
Hide/Show Grid	Controls the display of the grid lines.
Hide/Show Density	Reflects the density (coded distance) of points in the graph as a colored map. More points close together produce a "higher" color.
Hide/Show Markers	Controls whether the measurement markers are shown.
View in Separate Window	With this option, the curve display can be opened in a separate, large window to closely examine the plot.
Properties	With this entry a configuration dialog is opened for setting the annotation Font size , and for enabling curve Antialiasing (smooth curve appearance).
Save All Curves	Allows saving the numeric data of all curves in a single or separate text files.
View values (visible curves)	Opens a dialog window which shows the numeric values of all visible curves in a dialog window. The window contents can be copied to the Clipboard and pasted to a different application.
Save All Curves ON/OFF	To quickly change the visibility of all curves. When switching all off, the active curve is still shown.

Curve Control Area

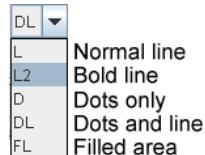
The control area lists the curves which are available for display. There are several elements to modify the curve appearance:



Show/Hide To show/hide a curve check/uncheck the *visible* box.

Active curve To set a curve to active click at the *active* button, or directly CTRL+Click on the curve itself. The line/symbols get bold.

Style The list selection can be used to change the style of a curve:



Further useful interface elements:

Connection Changes the shape of the lines defined by the measurements:



Note that calculations are not based on the display representation of a curve.

Saves the numeric data of a curve as a text file with two columns. These files obtain a .crv suffix and can easily be opened in Excel or a text editor.

When working with a database the curve can be attached to a particular image using the **Attach to Patient (Serie)** in the appearing dialog.



If this button is enabled, each curve is normalized to its own maximum and shown as percent values. This mode is helpful for comparing shapes when the dynamic range of the curves is very different.



Creates a capture of the curve area. The captured image can be saved as a JPEG, TIFF or DICOM file. It can also be copied to the **Clipboard** to paste it into some office application.

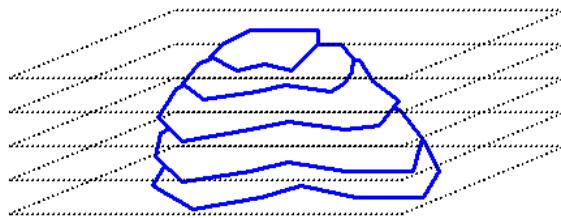
Chapter 6

Volume-of-Interest (VOI) Analysis

The purpose of a VOI analysis is to calculate the distribution of pixel values within delineated tissue structures. There are several VOI definitions available in PMOD.

Contour VOIs

In PMOD a contour VOI is defined as a stack of planar, closed polygons which are named ROIs (region-of-interest). The contours are manually or semi-automatically outlined on the loaded images, and the pixels contained within the contour boundaries are considered for the VOI statistics.



There are a few principles to bear in mind when working with contour VOIs.

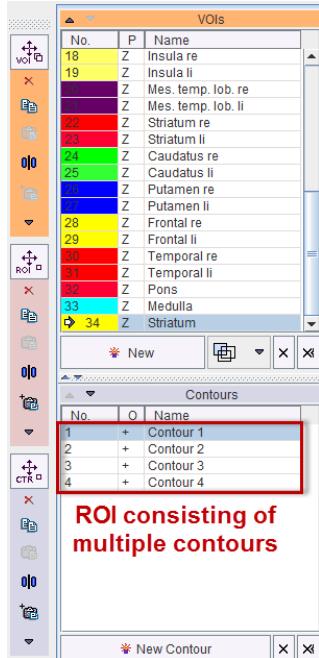
- » The coordinates of the contour vertices are defined as the (x/y/z) triples. The x and y offsets are in [mm] from the image origin, whereas z represents the slice number. This makes the definition independent of the planar image resolution and the zoom factor. However, note that modification of the origin coordinate results in a shift of all VOIs defined for the image study.
- » A contour VOI can be defined in each of the orthogonal directions. Naturally however, a single VOI can only consist of contours in the same direction.
- » Contour VOIs consist of one ROI per slice.
- » An ROI can have multiple independent contours per slice. For each contour the user can define, whether the included pixels should be included into the statistics or excluded from it. By defining contours with exclusion, VOIs with hollow parts can be created.
- » Single pixels are a special case of contours. They can be easily added to the VOI, or removed from the contour VOI.
- » For dynamic data the VOI can be extended to the temporal dimension as well. This means that the VOI may have a varying shape or location at different acquisitions over time, allowing to track moving organs over time. As long as the VOI has only been defined at one time point, it is applied equally at all times (static VOI). When defining the VOI differently at different times, care must be taken that a VOI is defined at *all* times.
- » Many studies can be loaded and processed in parallel. Hereby it is possible to have individual VOIs for the different studies, but the VOIs can also be shared among spatially matched images.

This hierarchy of three levels

- 1) VOI, consisting of ROIs in different slices

- 2) ROI, consisting of contours within a slice
- 3) Contour, a closed polygon

is reflected in the VOI user interface. Each level has a corresponding tool bar for object manipulations. For instance, when selecting the VOI button and shifting, the contours in all slices will be shift. When selecting the ROI button and shifting, only the contours in the current slice will be shifted.



Template VOIs

A template VOI is an image file which contains numeric label information for the different anatomic structures as the image information. This VOI information can be loaded into PMOD and used for statistics. The template VOI approach has the advantage that the structures can be arbitrarily complex, and that the results of external segmentation programs can easily be used within PMOD. The disadvantage is that the VOI definition cannot be modified. However, in PMOD it is simple to convert template VOIs into contour VOIs.

Often, template VOIs are used in combination with atlas images. Brain atlas images are representative images of the (human, rat, etc.) brain imaged with a certain modality (PET, SPECT, T1 MR, T2 MR, etc.) showing a normal brain. Usually, the images of many normal subjects are brought into alignment and are then averaged. This results in somewhat blurry template images which show the characteristic pattern of the brain in the particular modality. The template images are used as a basis for the standard analysis of individual images. First, the images are spatially normalized (elastic warping) to the template, and then a set of standard VOIs is applied to the normalized images to obtain regional statistics. Typically, the VOIs in the template space are template VOIs which are universally applicable, not contour VOIs which are program-specific.

The PMOD software includes a human brain template VOI (AAL), two rat brain template VOI (Sprague-Dawley by W. Schiffer and Wistar by Tohoku), a mouse brain template VOI (M. Mirrione) and a primate brain template VOI (Cynomologus Monkey) with corresponding normalization templates in the image fusion tool. For using the template

VOIs a user should first spatially normalize the individual brain images using the corresponding normalization template.

Map VOIs

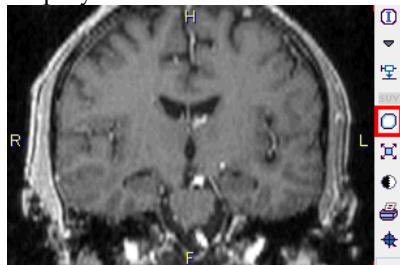
A map is a file, which contains label numbers in all pixels which identify different objects in the image. PMOD can load and analyze such a file and create a VOI template out of it. A special case are the object maps (*.obj) resulting from segmentations in AnalyzeAVW. These can directly be loaded as Map VOIs.

Mask VOIs

A mask is a binary file, which contains 1 in all pixels belonging to the tissue of interest, and 0 in all other pixels. It is most likely the result of some threshold or segmentation operation of the images to be analyzed. A mask-based VOI analysis provides two pixel distributions, from the tissue of interest and from the background. Any image can be loaded and used as a mask VOI. If it is not a binary image, the user can specify the threshold below which the pixels are converted to 0, while the other pixels are converted to 1.

Starting VOI Analysis

PMOD supports the access to VOI analysis in almost all situations when an image is displayed. The VOI button in the tools list next to the image



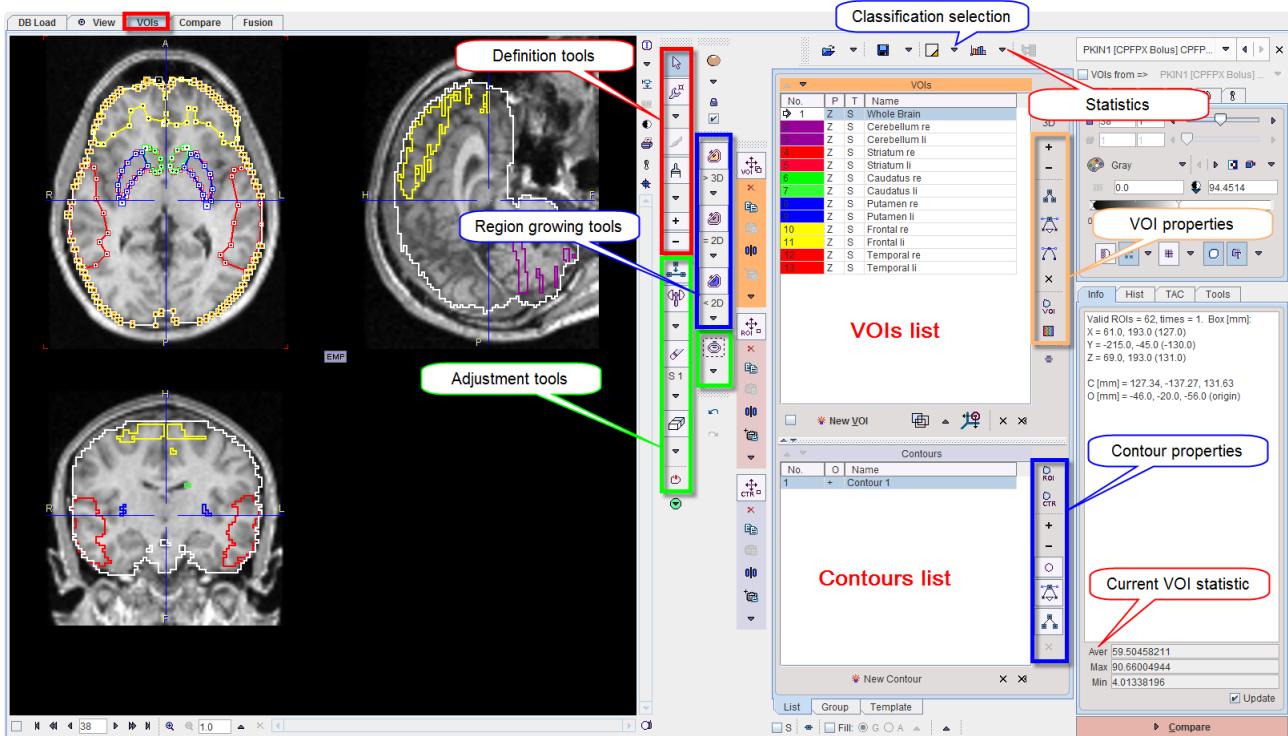
immediately starts the VOI tool with the current images. In the PVIEW tool, there is a separate tab **VOIs** for entering the VOI definition mode.

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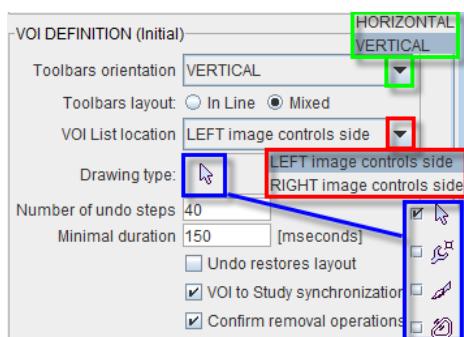
VOI Interface

When starting VOI definition a set of user interface items appears.



Layout Options

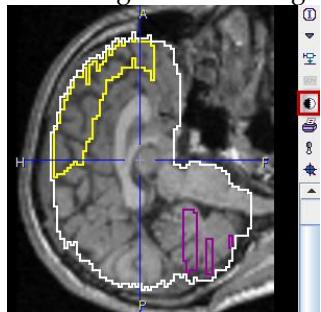
Note that a substantial part of the functionality is grouped on toolbars which can be detached and dragged to a suitable location by their handle . The VOI toolbars can be organized vertically as illustrated above or horizontally, according to the **Toolbars Orientation** in the **Display/Report** pane of the *tool configuration* (on page 29).



Tool Hiding Options

If during image inspection the image space is too much reduced by the VOI tools, there are two ways to reduce the tool area:

Activating this button right to the image



will hide all the tools. Activating it again recovers the original layout.



This toggle button hides the list of VOIs and contours, while giving still access to the VOI definition and editing tools. Another activation brings the list back.

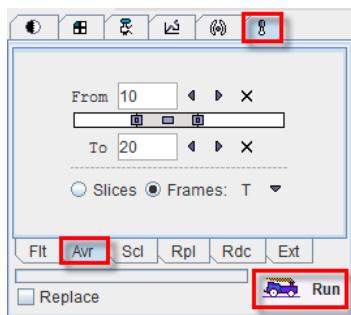
Using Contour VOIs

Preparations

Before starting contour definitions it is recommended to first take the time to locate the slice of interest, zoom and pan, so that the structures to be delineated are clearly seen. Also, it should be decided which of the orientations is best suited for the outlining.

VOIs for Dynamic Studies

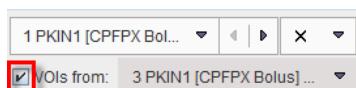
Often the anatomical information in dynamic studies is not sufficient to delineate VOIs. In some cases, averaging of a part of the acquisitions provides a clearer picture. A quick way for time-averaging is to select the tools tab and average some frames without replacing the study.



Another method is to define the VOIs in matched anatomical images of the same patient. Such a set of VOIs can then be applied to the dynamic study to derive time-activity curves.

Using Multiple Files Simultaneously

When multiple images have been loaded (or additional ones have been created by averaging frames as shown above), each of them has its own set of VOIs. The image series and the VOIs can be switched using the selection at the top

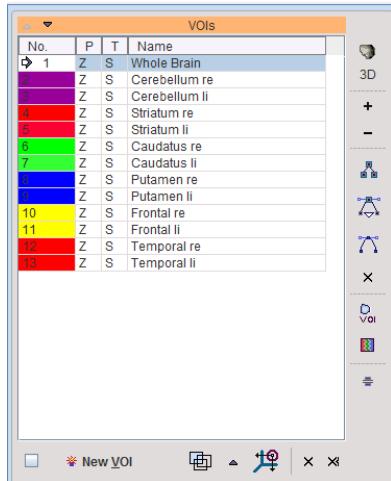


Please note the synchronization box **VOIs from**. If it is checked, the studies and the VOIs can be selected independent from each other. If it is not checked, each study uses its own VOIs, and the VOI selection is not active.

CAUTION: If VOIs are to be defined in one study and used in another, the two studies must be matched beforehand, meaning that both of them have the image origin at exactly the same anatomical location. This type of matching can be performed with the PMOD Image Fusion tool.

VOI Level Properties

The VOIs section on the **List** tab contains the list of defined contour VOIs, and VOIs which are in the progress of outlining.



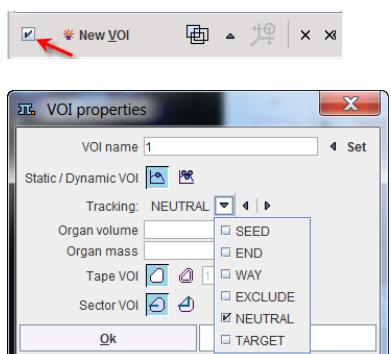
The **New VOI** button creates an empty VOI in the list, with the plane direction **P** according to the currently selected plane in the image area.

The buttons serve for deleting the selected VOI, or all VOIs, respectively. The arrow buttons on top of the list allow changing the VOI ordering by moving the selected VOI. represents the mode, how VOI overlapping is handled. The + and - buttons to the right set all contours of the selected VOI to + and - respectively as described *below* (on page 209). Similary, the and set the contour mode to straight line or B-spline connection. The button transforms the vertex VOI in B splines reducing the number of vertices.

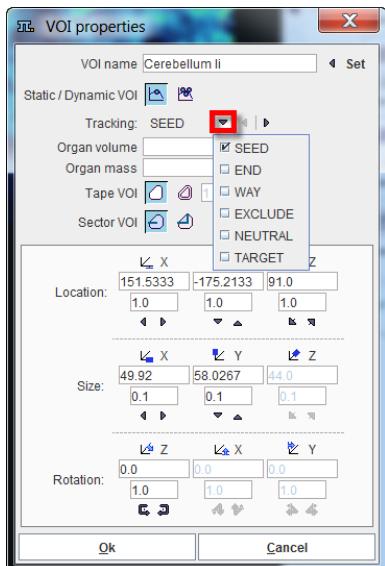
The button serves for changing the VOI direction. The new VOI is generated in the new direction (X, Y or Z) based on the mask of the original VOI.

VOI Properties

VOI properties can be set while creating a **New VOI** if the **Open properties** check box is enabled:



or can be changed using the  button. It shows the VOI properties dialog window illustrated below.



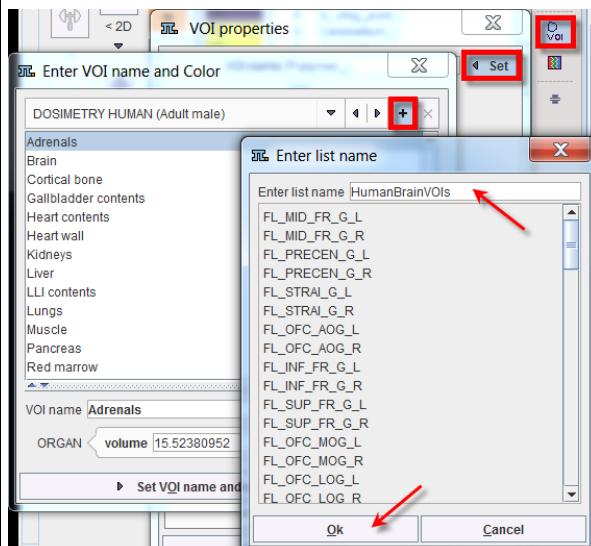
In addition to the plane orientation the window allows changing the properties, and immediately updates the display for providing a visual feedback. The property elements have the following meaning:

VOI name 	Allows assigning a name to the VOI in the list. The name can be typed in or it can be Set using a predefine list of VOI names. When the Set button is activated a dialog window opens for defining the name and the color: Four lists with pre-defined organ names are available: DICOM , SMALL ANIMAL , DOSIMETRY HUMAN(Adult male) and DOSIMETRY HUMAN(Adult female) . Select the appropriate one in the list selection in the upper left and proceed as follows: 1) Select an organ name from the selected list. Note: In the SMALL ANIMAL list, organs with trailing >> such as
---------------------	---

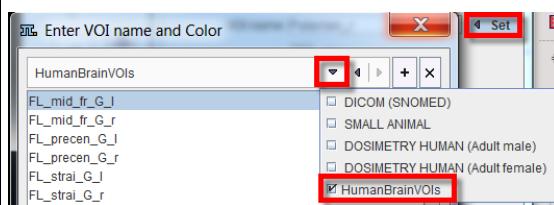
- Tumor>>** offer a substructure list. Other organs like the **Kidneys** offer a **Laterality** choice. Select as appropriate.
- 2) The **VOI name** shown in the text entry field is composed from the selections, but can be edited or completely redefined.
CAUTION: An existing VOI with exactly the same name will be overwritten. In this case please add a suffix to differentiate (e.g. CerebellumLeft in the example above)
 - 3) The **ORGAN volume** and **mass** are relevant for dosimetry studies. There are predefined values for **HUMAN** selection lists. These values can be edited if necessary for any selection.
 - 4) Change the VOI color.
 - 5) The **Set VOI name and color** button sets the **VOI name** in the **VOI properties** window. The **Cancel** button discards the definition.

Custom Organ List

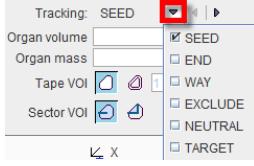
In the end the **VOIs** list contains all structures of interest. It can easily be converted into a custom list of names for the assignment as illustrated below. Select a VOI in the list and access its properties. Activate the **Set** button and subsequently the **+** button. Specify a **list name** in the appearing dialog window and confirm the dialog window with **ok**.



From now on, this list can be used alternatively to the pre-defined lists.

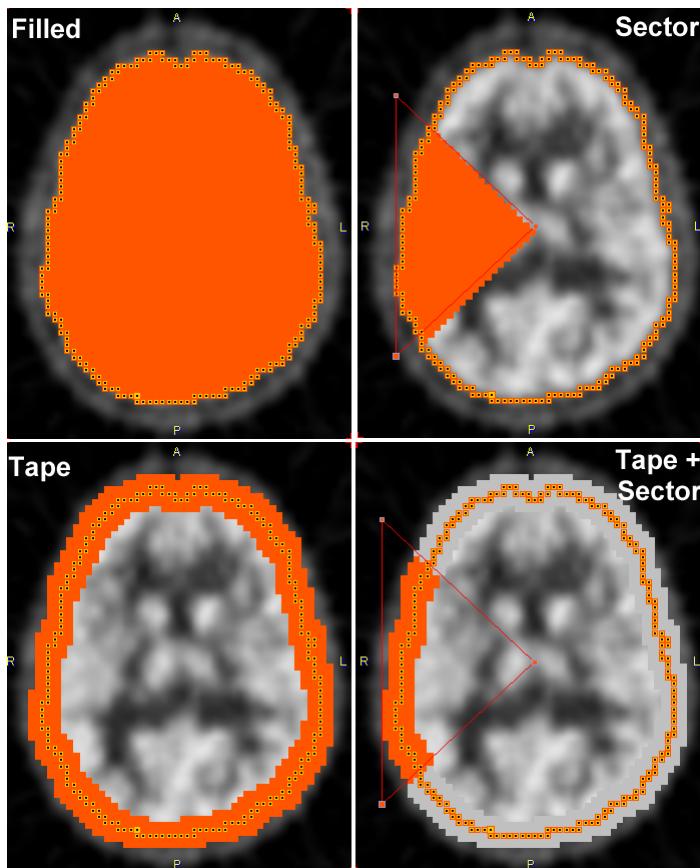


Tracking	Allows defining the VOI type encoded in the VOIs list in the T column.
-----------------	--

	 <p>This definition is relevant for the tractography which is performed in the PGEM module. The tractography is based on VOIs which can play different roles:</p> <ul style="list-style-type: none"> ► SEED VOIs: Tractography is started from the pixels in seed VOIs, following the local vector directions. ► END VOIs: Only tracks ending in this VOI will be used. To avoid excessive pruning of tracks, an END VOI should have sufficient volume. ► WAY VOIs: Only tracks passing through the WAY VOI will be used. ► EXCLUDE VOIs: Tracks passing through an EXCLUDE VOI will be removed. ► NEUTRAL VOIs: Such VOIs have no impact on tractography. Setting VOIs to NEUTRAL allows assessing the effect of END, WAY and EXCLUDE VOIs without the need of removing them.
	<p>Static VOI : This property is only relevant for dynamic series. If a VOI is static, the same VOI definition is applied and shown at all times.</p> <p>Dynamic VOI : This property is only relevant for dynamic series. For dynamic VOIs, a different VOI definition can be used at different times. Note that a dynamic VOI is only shown when viewing the images of the time frame it was defined on. As long as only one VOI is defined, statistics calculation will apply this VOI at all times as with a static VOI. However, as soon as VOIs have been defined at more than one time, it is required that VOIs are defined at <i>all</i> times. Here the VOI propagate functionality may be helpful.</p>
	<p>Filled VOI : All pixels inside the contours belong to the VOI.</p> <p>Tape VOI : The contour is interpreted as the center line of a VOI which includes pixels inside a band along the contour. The number of pixels inside and outside can be specified. This type of VOI was introduced for myocardium VOIs.</p>
	<p>Full VOI : Uses pixels from all directions.</p> <p>Sector VOI : Only the pixels in a defined angular sector will be considered. The sector angle can be defined in the VOI Action Mode using the handles at the angle corners. This type of VOI was introduced for myocardium VOIs.</p>
Location	X, Y and Z position of the VOI relative to the origin in [mm]. The location can be changed by entering new coordinates or using the incrementing arrow buttons.

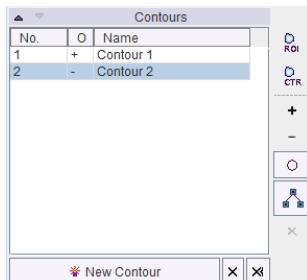
Size	Size of the VOI bounding box in mm. The sizes can be changed and result in a proportional scaling in the corresponding direction. The sizes can be edited or incremented by the arrow buttons. Note that for contour VOIs consisting of planar ROIs the scaling is only supported within the ROI planes, not orthogonal to it. Object VOIs can be scaled in all directions.
Rotation	The VOI can be rotated in space. Note that for contour VOIs consisting of planar ROIs rotation is only supported around the axis orthogonal to the ROI plane. Object VOIs can be rotated around all directions. The angles can be numerically specified in degrees, or incremented using the arrow buttons.
	Color Palette. Allows changing the contour color. All contours belonging to a VOI have the same color.

The illustration below illustrates the effect of the different properties on the pixels used for VOI statistics.



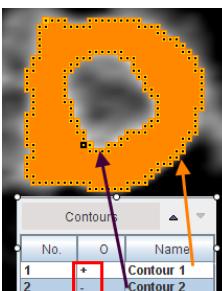
ROI and Contour Level Properties

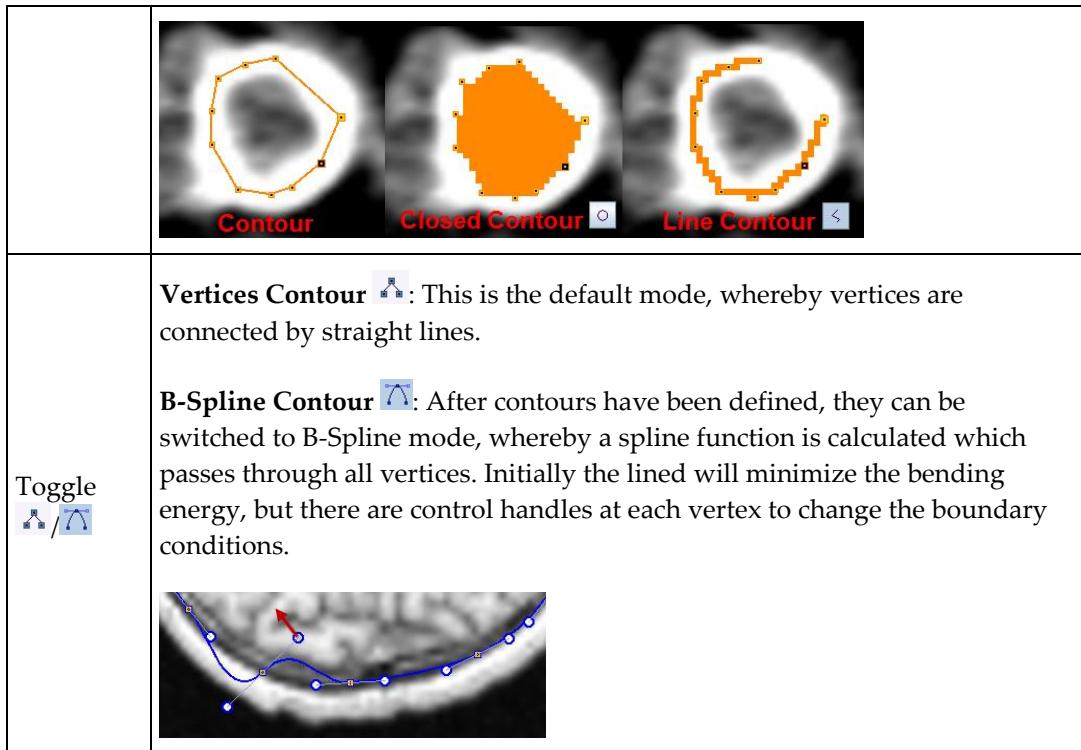
The **Contours** section contains the list of the contours defined in the current slice of the image series for the VOI selected in the **VOIs** list. All contours belonging to a VOI in a single plane form together the planar ROI. When



The arrow buttons on top of the list allow changing the location of the selected contour in the list.

Each contour has properties, which can be changed with the buttons on the right of the list.

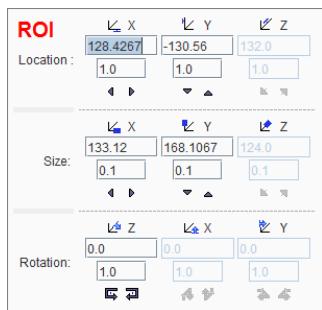
+ <small>+ / -</small>	<p>Plus Contour: This button sets all contours selected in the list to + in the operation column O. The meaning of a + contour is that the pixels enclosed by the contour are included in the statistics. This operation mode is equivalent to the OR set operation.</p>
- <small>+ / -</small>	<p>Minus Contour: This button sets all contours selected in the list to -. The meaning of a - contour is that all enclosed pixels are excluded from the statistics. This operation mode is equivalent to the AND NOT set operation.</p> <p>Cardiac example illustrating how a negative inner contour can be used to create a hollow VOI.</p>  <p>The image shows a grayscale cardiac scan with a hollow VOI highlighted in orange. A small inset shows the 'Contours' dialog with two contours: 'Contour 1' is a positive contour (+) and 'Contour 2' is a negative contour (-). Arrows point from the image to the corresponding rows in the dialog.</p> <p>CAUTION: The first contour in the list needs to be a + contour.</p>
○ / ↴ <small>○ / ↴</small>	<p>Closed Contour ○: The last vertex is connected to the first vertex, defining the VOI as the inner of the polygon.</p> <p>Line Contour ↴: Only the pixels along the trajectory from the first to the last contour vertex are included into the VOI.</p>



Similar to the VOI level, the size and angle can be changed on the contour level by two approaches.

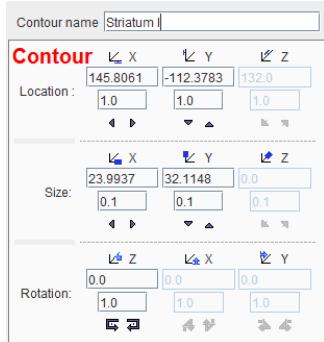
ROI Properties

All contours belonging to a VOI in a single plane form together the planar ROI. The properties of all ROI contours can be changed at once by the button, which shows the dialog window below. It allows changing the **Location**, **Size** and **Rotation** angles of the ROIs. The translation and scaling operations are restricted within the contour plane, and the rotation around the orthogonal.



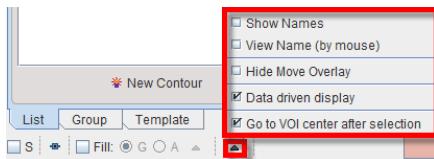
Contour Properties

The properties of individual contours can be changed by the  button, which works similar as the  button. It additionally offers changing the **Contour name**.



Contour Display Properties

In the lower right, there are some properties defining how the VOIs are displayed in the image overlay.

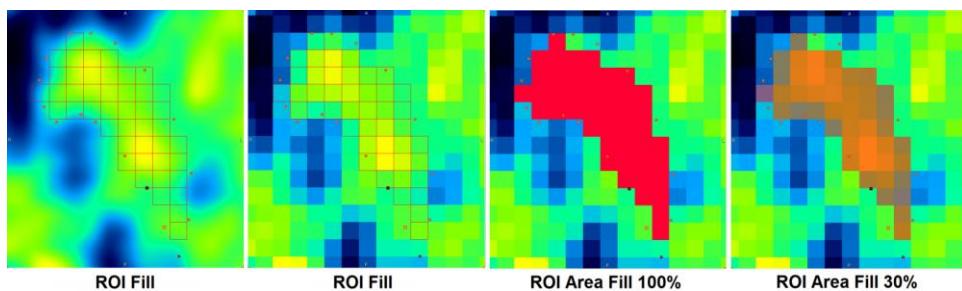


The following properties can be configured in the option menu:

Show Names	Shows the VOI names next to the contours in the image overlay. Note: The location of the names can not be changed.
View Name (by mouse)	Shows the names of the VOIs below the cursor in a separate section at the top of the image. Overlapping regions are shown as a list of names.
Hide Move Overlay	Hides the handle for moving the VOI to avoid obstructing the view with small VOIs. The VOI shifting/rotation operations have to be performed with the keyboard arrow cursors.
Data driven display	Determines the behavior of the image layout when switching between different series. If the box is checked, each image has its own properties such as layout, zoom, color etc. Otherwise, the images are shown with the same layout properties.

Usually contours are outlined on images displayed with interpolation, often combined with image zooming. In such a representation the images look smooth, even if the original pixels are big as with modalities suffering from low spatial resolution relative to the structure being outlined. To make sure that the right pixels are included in the VOI it is recommended - especially for small structures - to examine the VOI pixels as follows:

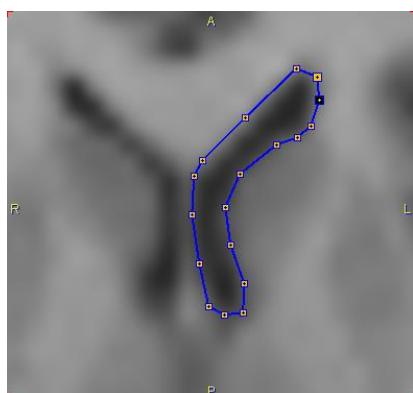
- 1) Check the **S** box. The display shows only the contours of the currently selected VOI to avoid confusion in the presence of multiple VOIs.
- 2) Check the icon. The VOIs vertexes are hidden.
- 3) Check the **Fill** box. The display now shows a grid with the VOI pixels (**G**). The grid can also be filled by setting the radio button to **A** (opaque filling). The degree of opacity can be change using the UP arrow right to the **A** button, whereby 100% indicates full opacity.
- 4) Disable image smoothing by disabling the button in the image control section.
- 5) Modify the VOI contours with the **Fill** box checked, for instance by moving a vertex. The grid is updated as soon as the changes are completed.



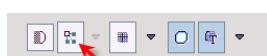
Note: PMOD only considers the entire pixels for the statistics calculation which are visualized with the **Fill** functionality.

Inclusion Criteria for Pixels

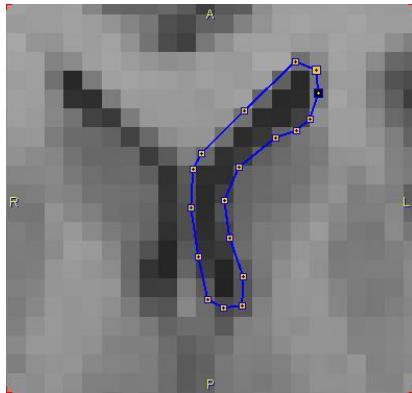
Because the contours are defined by polygons, the contour lines may not exactly follow the edges of the image pixels, but cut across the pixel area. PMOD supports different ways of handling this situation. Consider a contour which was manually drawn in the interpolated image.



Switching interpolation off

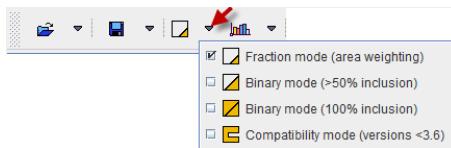


shows how the contour lines intersect the pixel area.



Classification Selection

The list selection illustrated below allows choosing between the different classification modes.

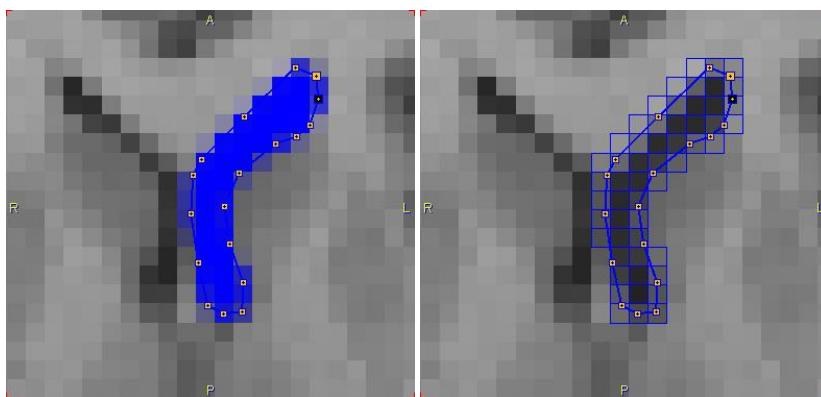


The **Fill** mode can be used for visualizing the classification effect.

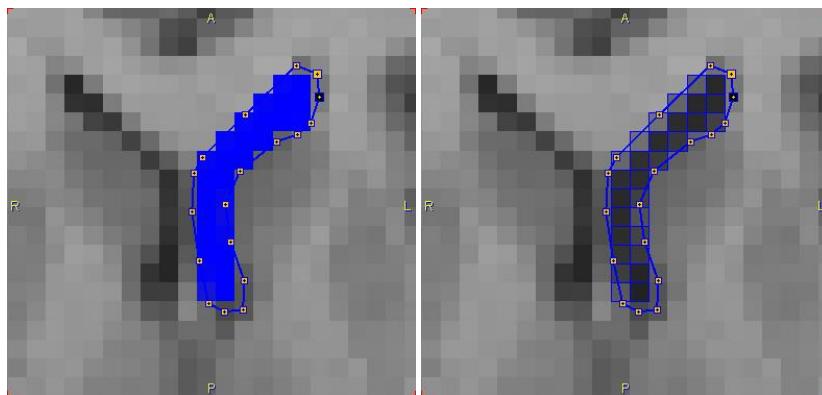


The **G** option represents the classified pixels as a grid, the **A** option as an area.

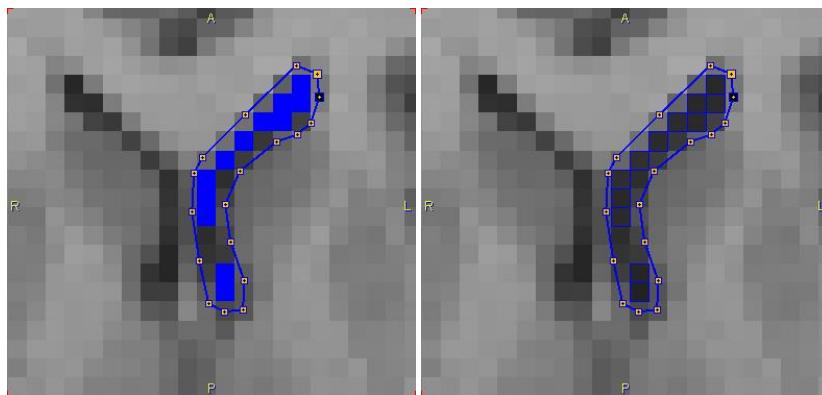
Fraction Mode (Area Weighting)



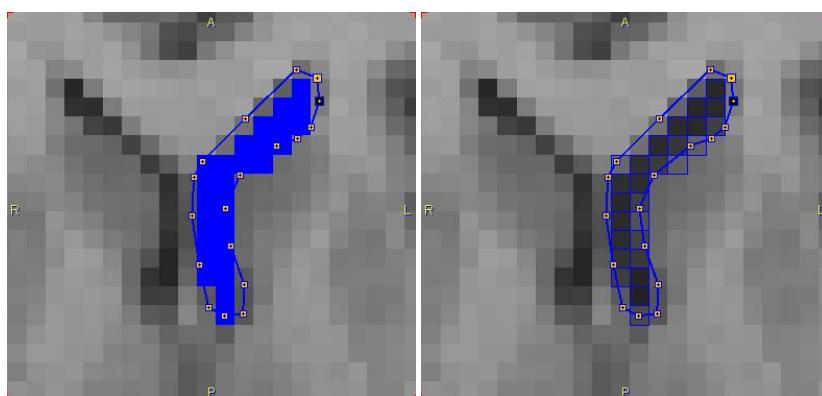
In **Fraction mode**, all pixels with any part enclosed by the contour are classified as VOI pixels. In statistics, the fractional area included is used as a weighting factor in the average *calculation* (on page 280). Note that when the **Fill A** option is activated, the color intensity of a pixel corresponds to the included fraction.

Binary Mode (>50% inclusion)

In **>50% Binary mode**, all pixels are included for which the enclosed area is >50% relative to the full pixel area. The statistics is unweighted using all classified pixels.

Binary Mode (100% inclusion)

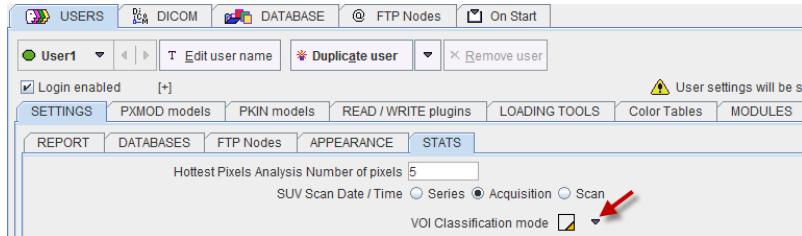
In **100% Binary mode**, only fully enclosed pixels are included. The statistics is unweighted using all classified pixels.

Compatibility Mode (Versions <3.6)

This classification has been used in PMOD versions before 3.6 and is available for compatibility.

Default Classification

The default VOI Classification mode to be used can be *configured* (on page 19) for each user as illustrated below.



Overlapping Control

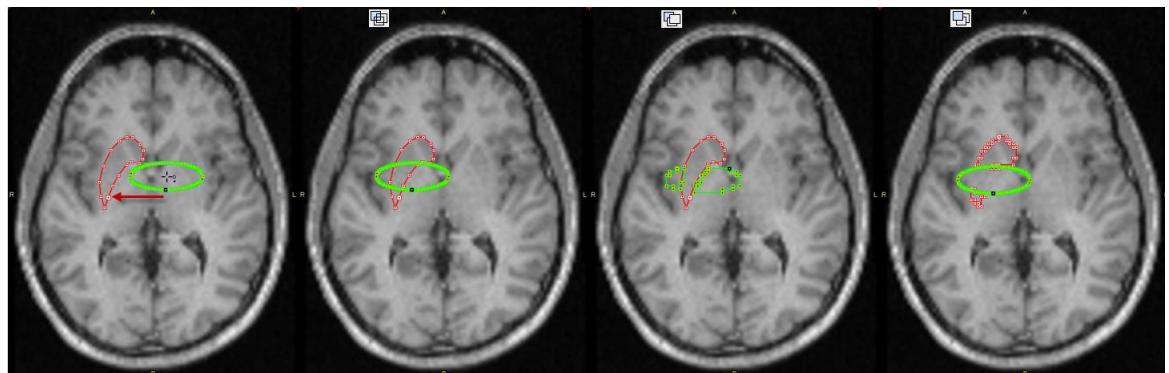
When defining several VOIs, the user may want to control whether they can overlap, or not. To this end, the editing can be set to one of three different modes as illustrated below.



Their effect is as follows.

	No control of VOI overlapping , contours can intersect arbitrarily.
	Trim new/modified VOIs along existing VOIs. The existing VOIs have priority. The new VOI is modified by removing any intersection area with the existing VOIs.
	Trim existing VOI along new/modified VOIs. The new VOI has priority. The existing VOIs are modified by removing any intersection area with the new VOI.

The example below illustrates the effect when shifting the green ellipse left in the different control modes.



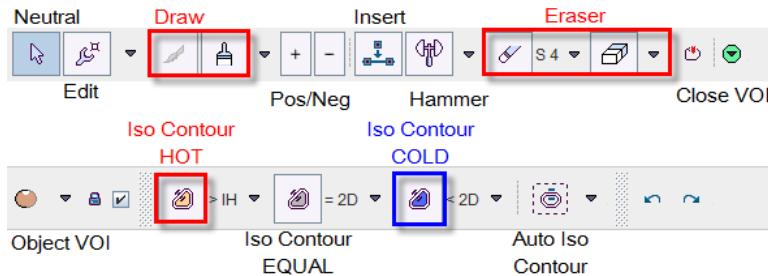
Contour Definition Tools

VOI Contour Generation Modes

There are several methods for generating contours:

- 1) **Edit Mode:** Manually outlining a contour polygon by clicking with the left mouse button at vertex points. This will create a contour with relatively sparse vertices. It is easy to adjust, but tends to be coarse.
- 2) **Draw Mode:** Drawing a trajectory with closely spaced vertices by holding down the left mouse button and dragging along an anatomical structure. This will create a contour which is well-defined but relatively difficult to adjust because of the many vertices which have to be moved.
- 3) **Iso-contour ROI Mode:** There is a "pseudo-snake" function which follows pixels with similar values to enclose the largest object in the slice. It can look for cold or hot spots. This is an easy way to outline objects with a clear contrast to background in a single slice (2D), but can be extended in an easy way to consistently outline the same object in multiple slices (3D).
- 4) **Iso-contour ROI Interactive Mode:** Interactive 3D VOI outlining is based on region growing as long as the mouse button is held. It can look for cold, hot or equal spots. Depending on the selected option, the algorithm is looking for the pixels above (for HOT), below (for COLD) or which equal (for Maps) the threshold, allowing or not the inner sparing.
- 5) **Single Pixel Mode:** The user can click at individual image pixels to add or remove them from a contour VOI. This way of defining VOIs is most flexible, and recommended when tight control is required, for example when working with small animal data.
- 6) **Auto-Iso-contour Mode:** This mode is similar to the **Iso-contour ROI Mode**, but is generating iso-contours at a well-defined threshold in a whole volume. The function can look for cold or hot objects, and can also generate multiple contours per slice to outline disconnected structures. Optionally, allows inner sparing, similar to the **Iso-contour ROI Interactive Mode**. In addition, the **Auto-Iso-contour Mode** algorithm can be restricted to an object VOI, within which the outlining is performed.
- 7) **Regular VOIs:** There is a list of regular objects (cube, sphere, etc) which can be generated centered at a defined point in the image. Some of the objects generate a stack of contours in a number of contiguous slices. After the creation they behave like normal contour VOIs. Other object VOIs remain analytically defined and can easily be scaled and moved in all directions. These VOIs are very helpful for cropping the image to a part of interest (for instance the brain in rat images), and also as restrictions to be applied in region-growing VOIs.

There is a toolbar in the VOI interface which collects the different VOI editing modes. Note that the arrangement can be horizontal as illustrated below, or vertical, depending on the tool configuration. The toolbar can also be detached for placing it at a convenient location on the screen.



Contour Outlining Process

After creation with **New**, a VOI is ready for the definition of a single contour per slice. Once a contour has been created in a slice, contour drawing is no more active. For adding another contour definition in the same slice, the user has to activate the **New Contour** button first.

During contour outlining or editing, it is important that the right VOI/contour is selected. A VOI can be selected by clicking at the entry in the **VOIs** list. If contours have already been outlined, the display will position on a slice with a contour of the selected VOI.

Alternatively, a VOI can be selected by directly clicking at a contour vertex in the image.

It is recommended to complete the definitions of one VOI before the next is created. To this end, the user should work through the slices containing the object: In each slice outline the required contour(s) and then step to the next slice using the mouse wheel. Alternatively, if the contours are similar in neighboring slices, the contour(s) can be propagated to the next slice and then adjusted.

Undo/Redo/Neutral

VOI definition is a tedious task, and many situations may occur where the user would like to undo a change. To this end an **Undo** function for most manipulations of contour VOIs is available on a separate taskbar.



The arrow to the left undoes operations (goes back through history), while the button to the right redo operations (goes forward through history).

Note: The Undo function is not applicable to changes to the image information itself.

Neutral Mode

Browsing the image in the orthogonal layout involves clicking into the image. When VOI definition modes such as iso-contouring are active, clicks may introduce unwanted changes to the VOI definitions. This can be avoided by selecting the **Neutral Mode** with the .

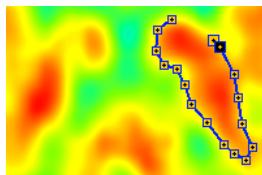
Note that while working in a VOI editing mode, the VOI functionality can momentarily be disabled by holding down **CTRL+SHIFT** during clicking.

Vertex Edit Mode

In the **Edit Mode** the cursor changes to



By clicking the left mouse button into a slice without a contour of the selected VOI, the contour definition is immediately started and the first vertex appears. Additional clicks add more vertices to the ROI in the current plane.



There are two possibilities to close the contour,

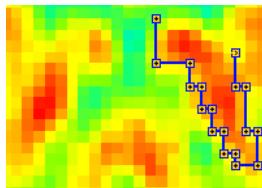
- 1) by double-clicking
- 2) by selecting the finish button  on the toolbar or the context menu.

Closing connects the last defined vertex with the first vertex. This operation can be undone by the unfinish button . Once a contour is closed, no vertices can be added any more, but the existing one can be moved by clicking at them and dragging them around.

Another option in **Edit Mode** is the cursor **Edit snap to grid**:



The snapping of the VOI polygon edges to the pixel grid during the drawing procedure clearly indicates the included pixels.



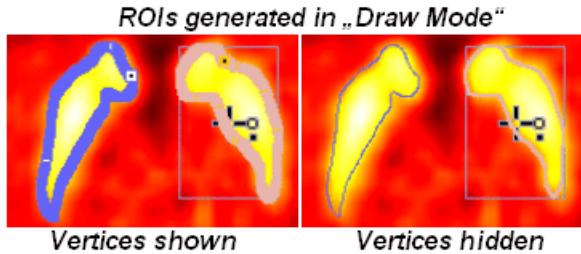
It is recommended to switch off the image **Interpolation** button  when using this ROI definition mode.

Contour Drawing Mode

In the **Draw Mode** the cursor changes to



A contour can be generated by holding the left mouse button and dragging the cursor along the desired trajectory.



As soon as the mouse button is released, the contour is closed. This contouring mode generates many closely spaced vertices. To view the contour more clearly, the vertices can be hidden by checking the **Hide Vertices** box.

Paint ROI by Circle (2D)

In the **Paint ROI by circle (2D)** the cursor changes to



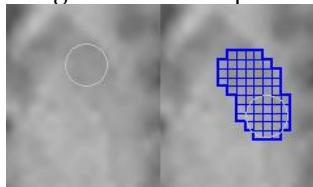
The 2D paint brush of the PMOD VOI tool is a circle and can have different sizes which may be selected from the option list close to the brush button.



A contour can be generated by holding the left mouse button and dragging the brush along the desired area.

To create a contour VOI:

- 1) Activate the 2D paint brush button
- 2) Drag the brush shape over the area which should be within the VOI.

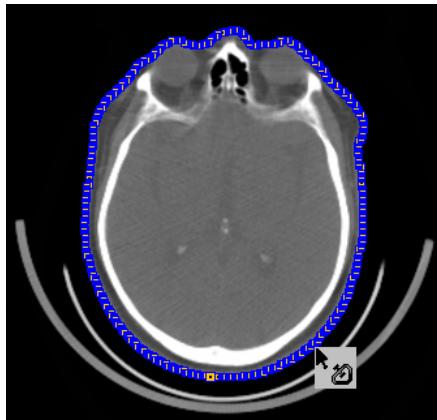


Iso-contour Mode (Pseudo-Snake)

In the **Iso-contour Mode** the cursor changes to

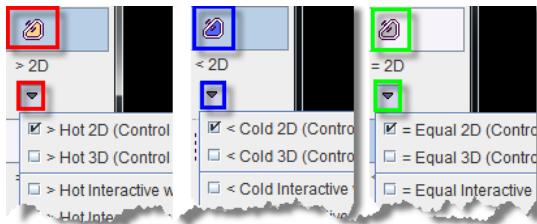
HOT  or COLD  or EQUAL 

As soon as the left mouse button is clicked into an image, the pseudo-snake algorithm tries finding the largest closed iso-contour at the clicked image value and represents it as a closed polygon.



Note: Each time the button is clicked, the contour is replaced by a new iso-contour. This behavior is in contrast to the other drawing modes which require to first clear a contour, or opening it. To add a new iso-contour make sure you press the control button and the left mouse button simultaneously (CTRL+click)

The user can select the appropriate mode from the option list next to the iso-contour button as illustrated below. The automatic mode of iso-contouring can be 2D or 3D and dependent whether the user is aiming at a hot, cold or equal contour.



Iso-contour Interactive Mode

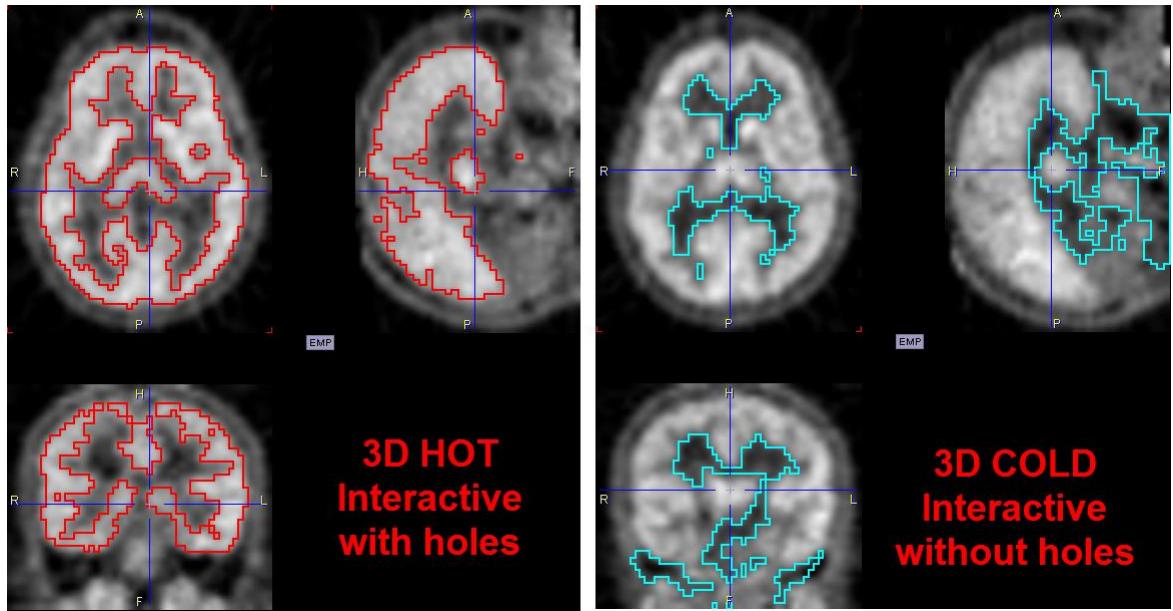
Similar to the **Iso-contour Mode (Pseudo-Snake)** the cursor changes to

HOT  or COLD  or EQUAL 

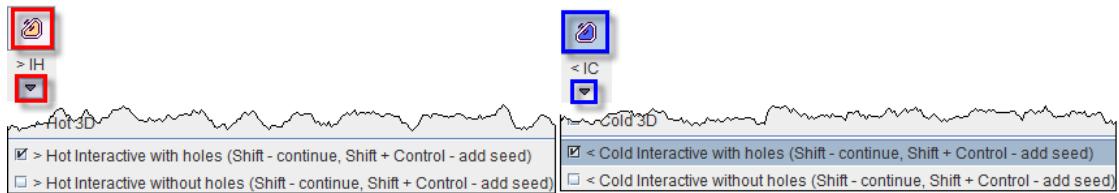
Interactive 3D VOI outlining is based on region growing as long as the mouse button is held. It can look for cold, hot or equal spots. Depending on the selected option, the algorithm is looking for the pixels above (for HOT), below (for COLD) or which equal (for EQUAL) the threshold, allowing or not the inner sparsings.

Initially, the area to include within the VOI need to be located. Then the mouse button need to be clicked at the edge and held until the outlined VOI completely encompasses the area of interest. After completion of outlining, the VOI can still be extended. There are two options: the first (SHIFT+click+hold) allows continuing the region growing from the original seed,

while the second (CTRL+click+hold) allows adding a new seed and continuing region growing from the new point.



The user can select the appropriate mode from the option list next to the iso-contour button as illustrated below. The automatic mode of iso-contouring is 3D and dependent whether the user is aiming at a hot, cold or equal contour.

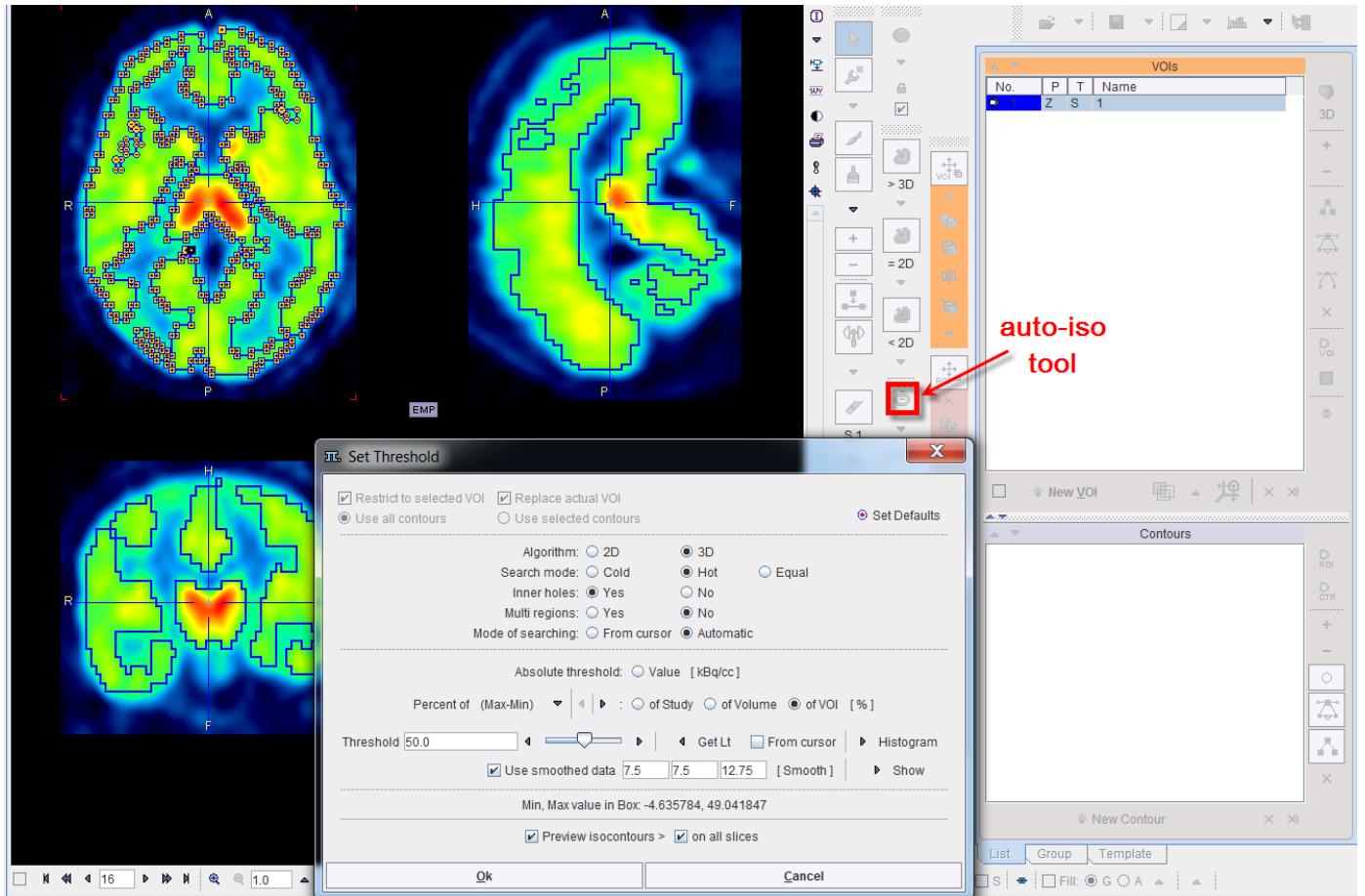


Auto Iso-contour VOIs

The auto iso-contour tool ("auto-iso") serves for the contouring of structures based on an intensity threshold by region growing. This process can be restricted within an existing VOI, otherwise it will work on the whole image volume.

Contouring without Restriction

The whole image volume will be processed, if the auto-iso tool  is started without selecting a non-empty VOI in the **VOIs** list. This situation is given before VOI definitions have started yet, or by creating an empty **New VOI**. The situation below illustrates the initial situation when starting auto-iso on an FDG Brain image: One single **Hot** contour is shown at a threshold level of **50%**, without allowing **Inner holes**. The procedure operates in **2D** and defines the contours in the **Z** plane, because this plane was active at the time the tool was started.



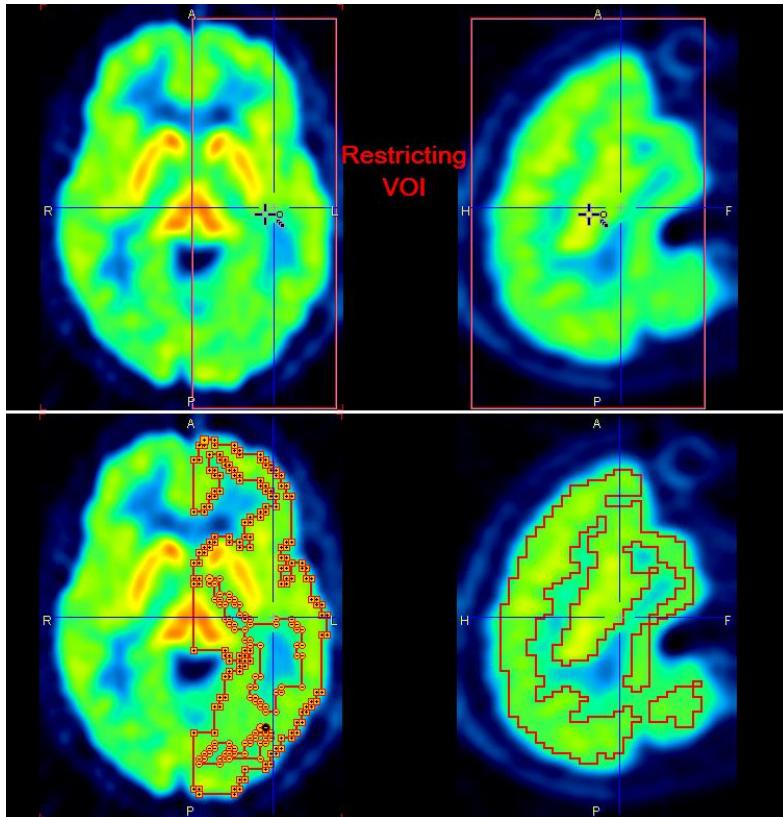
There are various parameters which change the behavior of the algorithm:

- » **Threshold** options: The user can choose between various types of threshold definitions using the radio boxes. With **Absolute threshold** the iso-contouring value should be entered in image units into the **Threshold** number field. With **Percent of Study**, **Percent of Volume**, **Percent of VOI**, the value entered in the **Threshold** field is interpreted as a percentage of the dynamic range (**Max-Min**) of the whole study, the current frame of the study, or the enclosing VOI, respectively. Instead of the **Max-Min**, the percent threshold can be related to the **Max** only. There are two alternatives to entering the values manually: **Get Lt** copies the value of the lower threshold in the color table. With the **From cursor** check box enabled, the value is updated with the pixel value whenever one clicks into the image.
- » **Algorithm:** 2D processes each slice individually, whereas 3D performs the searching in all 3 dimensions.
- » **Search mode:** **Hot** (**Cold**, **Equal**) is including pixels above (below, equal to) the threshold value, respectively.
- » **Inner holes:** In the case of **Yes**, pixels not meeting the criterion which are fully enclosed by pixels meeting the criterion are removed from the resulting VOI. Otherwise, the VOI will be completely filled.
- » **Multi contours:** With **Yes**, the generation of multiple VOIs is allowed. Otherwise, only the largest VOI will be returned.
- » **Mode of searching:** Automatic is starting region-growing with the aim to detect structures of maximal volume, whereas **From cursor** allows starting the search from a manually defined location. In the latter case the **From cursor** checkbox next to **Get Lt** should also be enabled.

The updated contours are shown in the image, whenever a parameter is changed. For a complete visualization, **Preview on all slices** should be enabled. To accept the VOI definition, close the dialog window with the **Ok** button.

Contouring with Restriction

The process described above can be restricted to the volume of an existing VOI. To do so, select the restriction VOI in the VOIs list, and start the auto-iso tool. The example below illustrates contouring in a box VOI placed on the left brain hemisphere.



Depending on the setting of **Replace actual contour**, the bounding VOI will be overwritten, or a new VOI will be created with the contouring result.

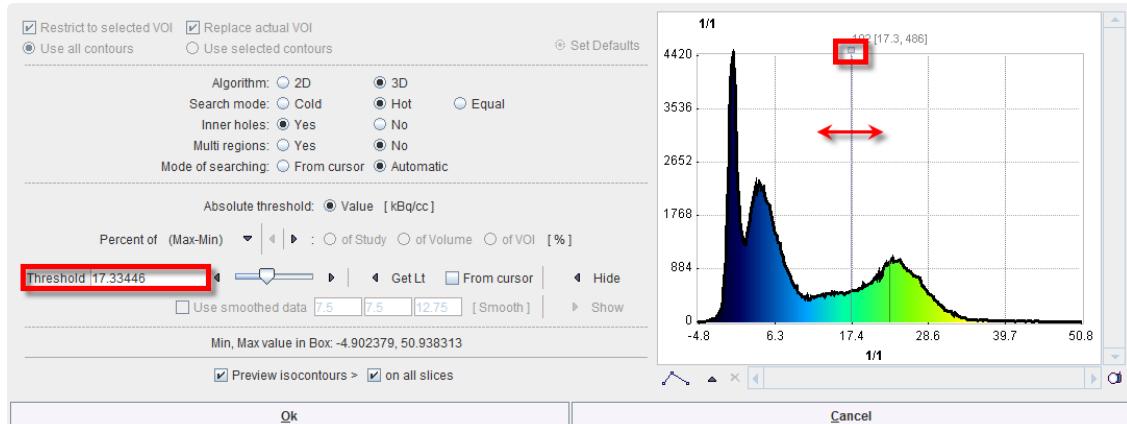
Contouring with Smoothing

In order to get smoother contours than the original data supports, the procedure can work on a smoothed copy of the data. This functionality is activated with the **Use smoothed data** box. Each time the **Smooth** button is activated, the data copy is filtered with a Gaussian function using the three numbers as the FWHM in mm along x, y and z. By adjusting the filter sizes and repeated filtering, a gradually smoother copy and correspondingly smoother contours in the original image can be generated. The **Show>>** button can be activated to see the smoothed copy as illustrated below.



Contouring with Histogram

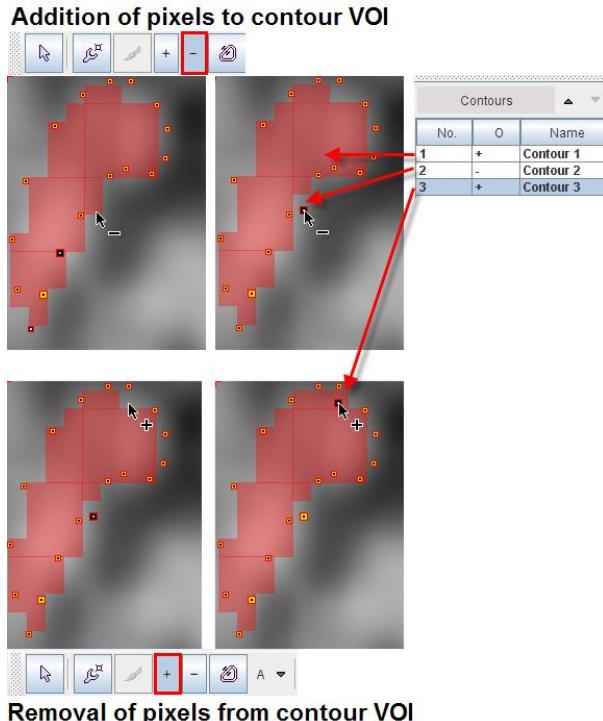
A histogram can be used to set the **Threshold** value for the iso-contouring. This functionality is activated with the **Histogram** button. A histogram of the pixel values is shown, and the value at which the iso-contours are drawn can be adjusted by dragging the marker highlighted in the graphics below. The **Threshold** value is updated each time the marker position is changed and the updated contours are shown in the image.



Adding/Removing individual Pixels

Whenever working with contour VOIs, the user can add or remove individual pixels as illustrated below. The initial **contour 1** is filled in transparent mode. First pixel removal is activated by selecting the **-** button in the toolbar. The cursor shape changes accordingly, and by clicking at a shaded pixel the negative **Contour 2** is created and the pixel removed (upper row). Whenever the user clicks into the image, the corresponding pixel will be removed from the VOI and a corresponding **-** contour is added to the list.

Pixel adding works in the same way. It is activated by selecting the + button in the toolbar, and the cursor shape changes accordingly. Whenever the user clicks into the image, the corresponding pixel will be added to the VOI and a corresponding + contour is added to the list (lower row).



Note that it is possible to create VOIs which consist of individual pixels only. The + button is active as soon as a **New VOI** has been created.

Contour Interpolation

Contour Interpolator is a fast way of outlining a VOI which contains two ROI outlined on different slices.

The procedure is simple:

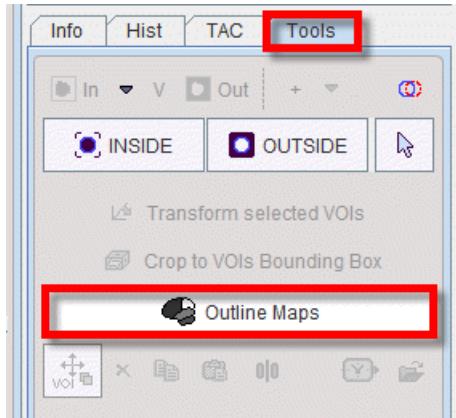
- 1) To start, create a new VOI and outline two ROIs on different slices.
- 2) Select the **Contour Interpolator**. The algorithm finds contours which will be morphed from the first ROI to the second one.

Note: This tool makes interpolation between two contours and doesn't use data information. At least two ROI contours need to be available before selecting the algorithm.

Outline Object Label Maps

A map is a file which contains integer pixel values called object labels. The labels typically identify different objects in the image volume. Such maps are often the product of segmentation procedures.

Map files in different image format can be loaded into PMOD. In the **VOI** page of the **View** tool map files can be converted in contour VOIs. The functionality is located in the **Tools** tab:



When **Outline Maps** option is selected a dialog window appears which allows specifying the bin size for the label histogram.

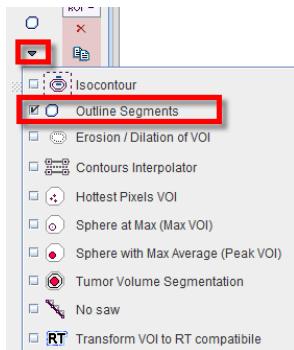


A **Step value** of 1 should normally work fine. The file is scanned and for each label found a contour VOI is created. Now the names can be edited and the VOIs saved.

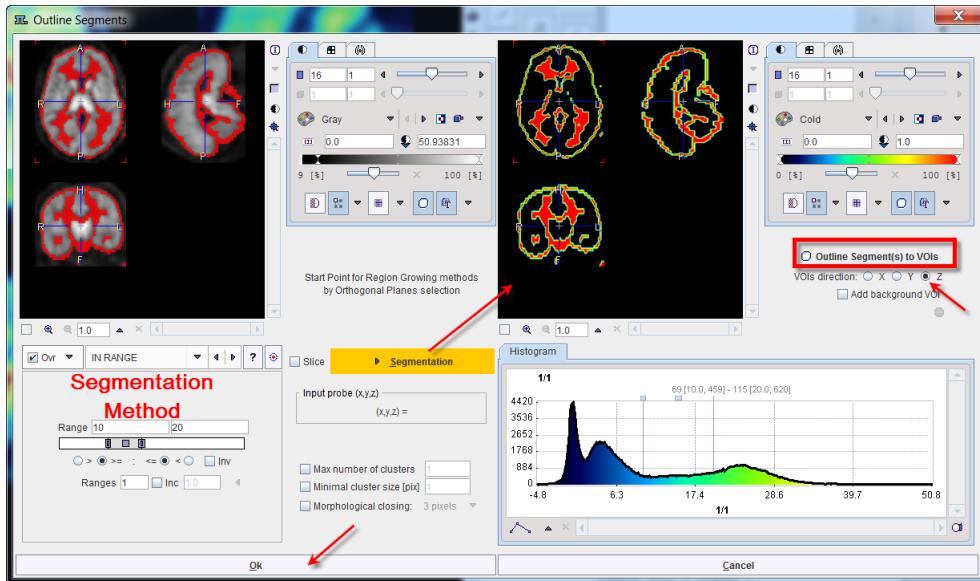
An alternative is direct loading of label maps via that Template functionality as described *below* (on page 279).

Outline Segments

The functionality is located in the auto **Iso-contour** selection list.



It allows outlining VOIs based on a mask segment. The interface is similar to the segmentation in the 3D tool. It opens the following dialog window.



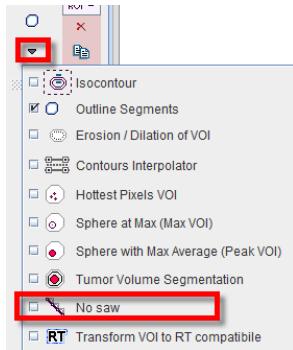
After specification of the segmentation method and its parameters, the segmentation can be started with the **Segmentation** button. The result is shown in the right image display port. Note that an additional box **Slice** is available. If it is checked, segmentation will be performed for the currently displayed slice.

The **VOIs direction**, **X**, **Y** and **Z**, allows setting the plane direction for the VOI outlining.

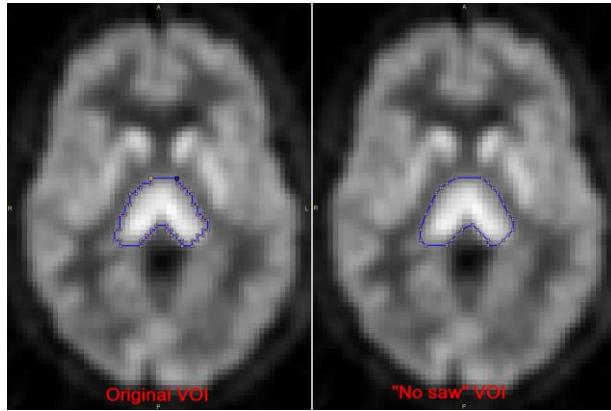
The **Outline Segment(s) to VOIs** button allows creating VOIs for the generated segment. Optionally, the background can be added as a VOI by enabling the **Add background VOI** box. With the **OK** button the outline results are return as VOIs on the image.

No Saw

The functionality is located in the auto **Iso-contour** selection list.

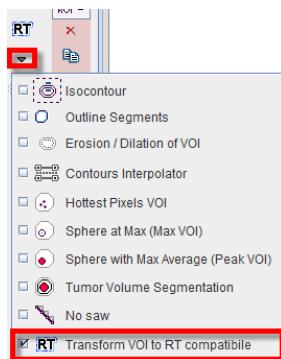


The tool allows removing some vertices from the VOIs. The result is a smoothed looking VOI.



Transform VOI to RT compatible

The functionality is located in the auto Isocontour selection list.

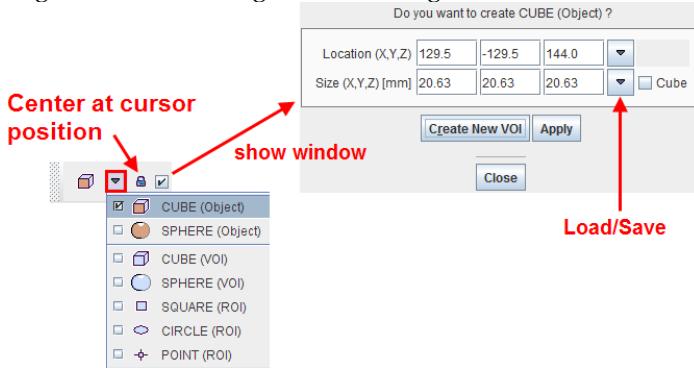


It allows transforming the selected VOI in the VOIs list in RT compatible structure.

Regular VOIs

The PMOD VOI functionality supports the easy generation of regular geometric objects. They are helpful for creating bounding boxes and for statistics based on regular objects like spheres of a certain size rather than free-form contours.

Regular VOIs can be generated using the multi-function button illustrated below.

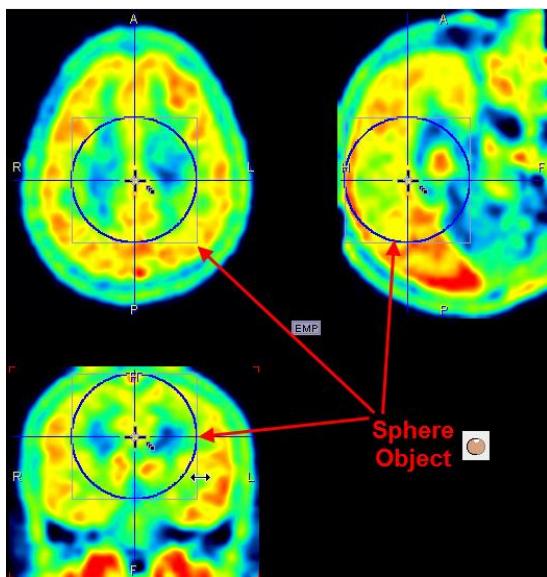


The list contains two sections. The **CUBE (Object)** and the **SPHERE (Object)** are based on an analytical definition of the shape and the center coordinate. The other VOIs are generated from an analytical description, but the result is a set of standard outline contours.

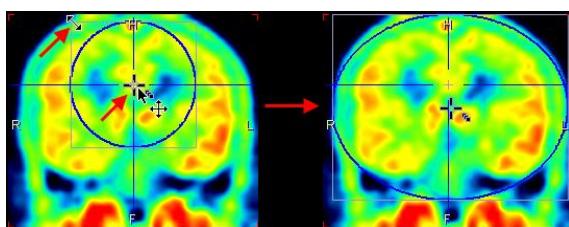
The regular objects are defined by the center location as well as some shape-dependent parameters. These definitions can be modified in a dialog window which is shown if the box indicated in the illustration above is checked. If it is not checked, the standard shape parameters will be applied. There are two modes for the center **Location** defined by the toggle. In the position the location is defined by the last click into the image. In the position the location is not changed by mouse clicks. Activating **Yes** finally creates the object.

Object VOIs

The shapes can be scaled, so that ellipsoids of arbitrary sizes can be created from a **SPHERE (Object)**, and cuboids from a **CUBE (Object)**. The dialog window contains **Location** and **Size** fields for the exact object specification. If the box for proportional is checked (**Cube** in the illustration above), only one size field is shown. The **Create New VOI** button generates a new VOI in the list with the specified sizes, while the **Apply** button overwrites the currently selected VOI. The illustration below shows an example result with a sphere object.

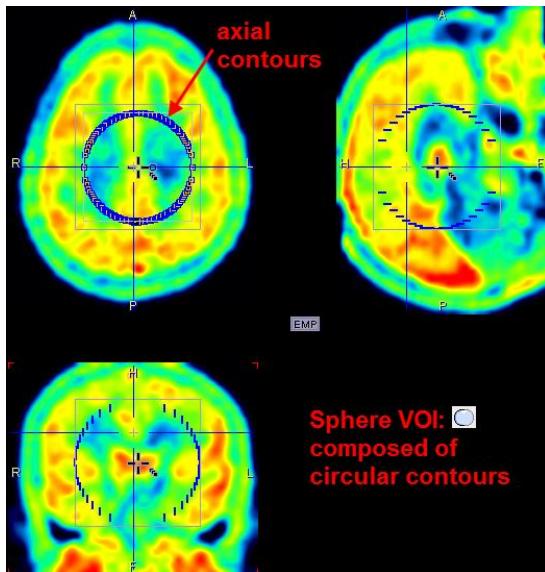


To change the location and size of the object please ensure that the **VOI Action** button is active  so that the handles for object manipulation are shown. The center of the object can then be dragged by the central handle with the left mouse button, and the shape can be scaled by dragging the sides or the corner of the bounding box in any direction. Note that holding the **SHIFT** key during dragging will maintain the aspect ratio in two dimensions. The result is an object with the shape of an ellipsoid.



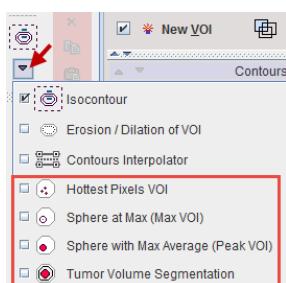
Non-Object VOIs

The non-object regular VOIs are formed out of planar polygons. The example **SPHERE (VOI)** illustrated below has been created with the axial plane active. Therefore circular contours were generated in the axial planes which together form a sphere. Such VOIs can be edited in the same way as normal contour VOIs. For instance they can be scaled within the definition (axial in the example) plane, but not in the other dimension.



Special-purpose Sub-VOIs

Existing VOIs can be used as boundary restrictions when generating certain types of VOIs. Iso-contouring within a VOI is an example described *above* (on page 221). Three other approaches are available via the selection illustrated below.

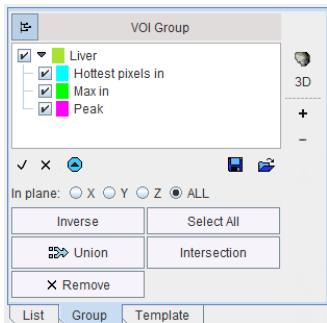


In order to apply them, the enclosing VOI first has to be selected.

For instance, if a **Liver** VOI is used for applying the three approaches are applied in turn, the following list of VOIs is obtained.

VOIs		
No.	P	Name
1	X	Liver
2	Z	Hottest pixels in [Liver]
3		Max in [Liver]
4		Peak [Liver]

When switching to the **Group** tab the enclosed VOIs are arranged as sub-entries of the enclosing **Liver** VOI.



Hottest Pixels

The **Hottest Pixels** function is useful for localizing the pixels with highest values in the selected VOI. The actual number can be specified in the interface window.

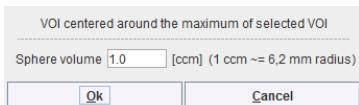


Result is a new VOI called **Hottest pixels in [enclosing-name]** with a separate contour for each of the pixels as illustrated below.

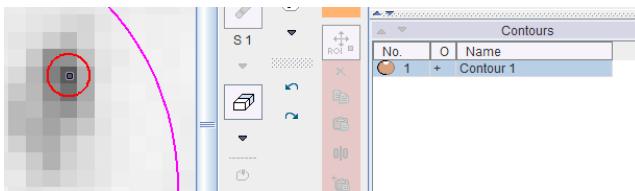


Sphere at Max

The **Sphere at Max** function creates a sphere object VOI of well-defined volume and centers it at the maximal pixel of the selected VOI. The actual volume can be specified in the interface window.

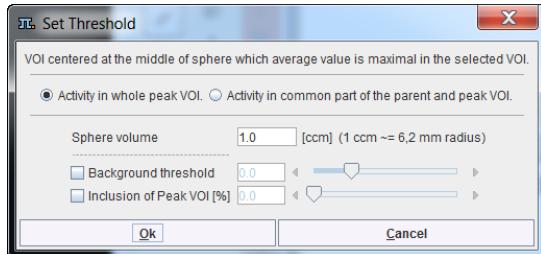


The resulting sphere is called **Max in [enclosing-name]**.

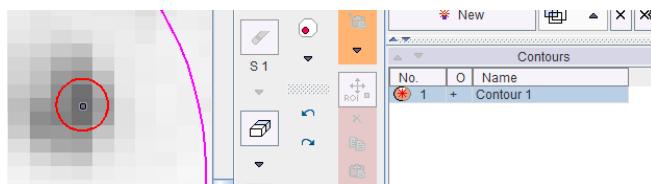


Sphere with Max Average (Peak VOI)

The **Sphere with Max Average (Peak VOI)** function creates a sphere object VOI of well-defined volume and centers in such a manner in the selected VOI that the average is maximal. The actual volume can be specified in the interface window. Note that for the statistics only pixels are considered which are included in the original VOI.



The resulting sphere object is called **Peak[enclosing-name]**.



PET Tumor Volume Segmentation

There are various approaches for outlining a lesion in a PET. The **PET Tumor volume segmentation** method implements an automatic model-based approach [1, 2] for determining an iso-contouring threshold which is independent of the signal-to-background ratio and provides accurate volume measurements down to the resolution of the PET scanner.

Principle

The method performs an iterative adjustment of the iso-contouring level, taking into account the scanner resolution and the background activity. In this process, the lesion geometry is approximated by a sphere and the appropriate threshold level determined by a lookup procedure which refers to a homogeneous sphere imaged at scanner resolution. During the iteration, each threshold setting results in a new tumor volume obtained by iso-contouring, which allows calculating the next threshold approximation. The process is repeated until the tumor volume becomes stable.

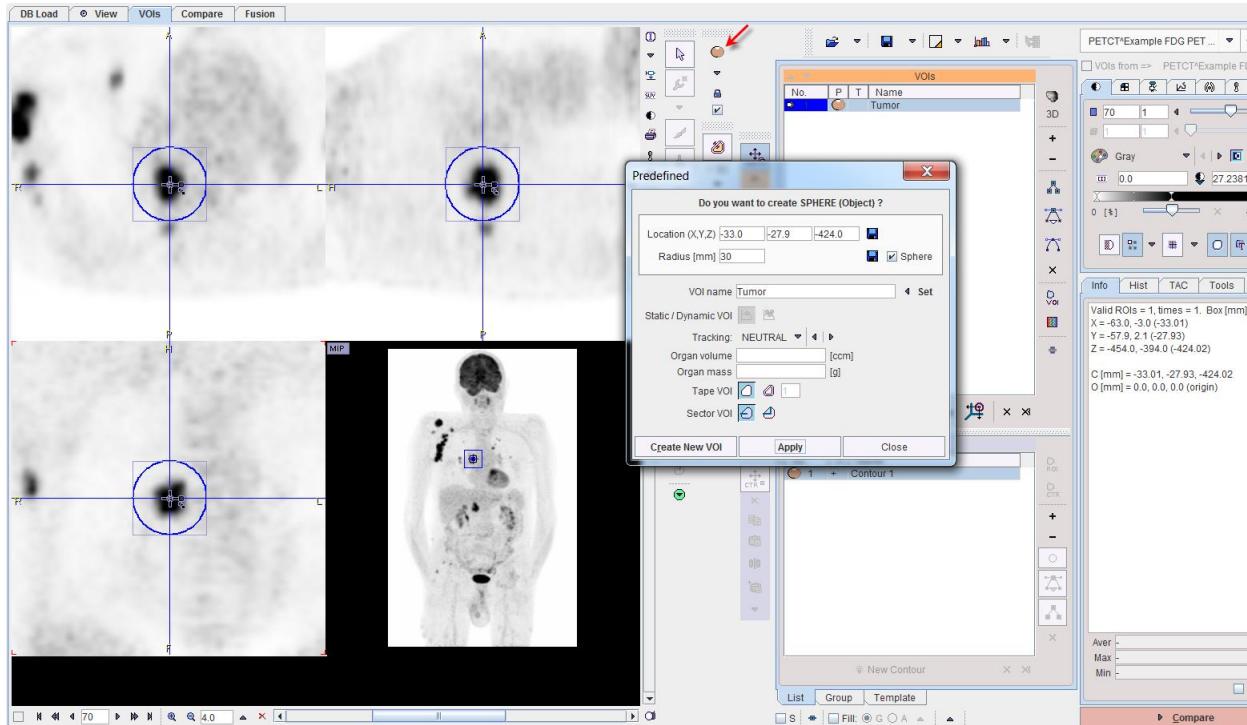
Required for applying this segmentation method is:

- 1) An initial approximation of the tumor VOI.
- 2) The background activity which is subtracted.
- 3) The PET scanner resolution.

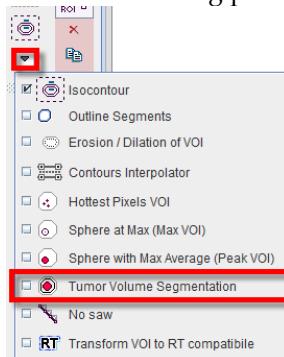
Use without Background VOI

If the tumor is isolated from the surroundings, the background can easily be obtained from the initial VOI definition. Please proceed as follows:

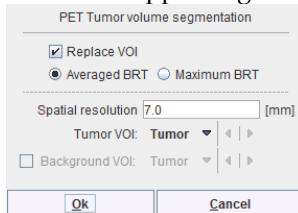
- 1) Define a VOI enclosing the tumor, with sufficient distance to the rising edge. A sphere is used in the illustration below.



- 2) Start the outlining procedure



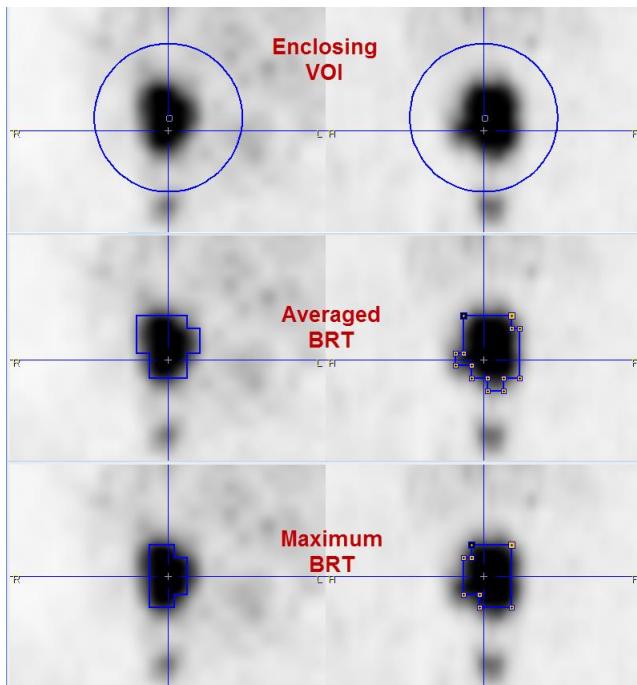
and in the appearing dialog window enter the **Spatial resolution** of image.



If the **Averaged BRT** (Boundary-Reproducing Threshold), the average activity in the iteratively segmented VOI is used [1], with **Maximum BRT** the maximal activity [2].

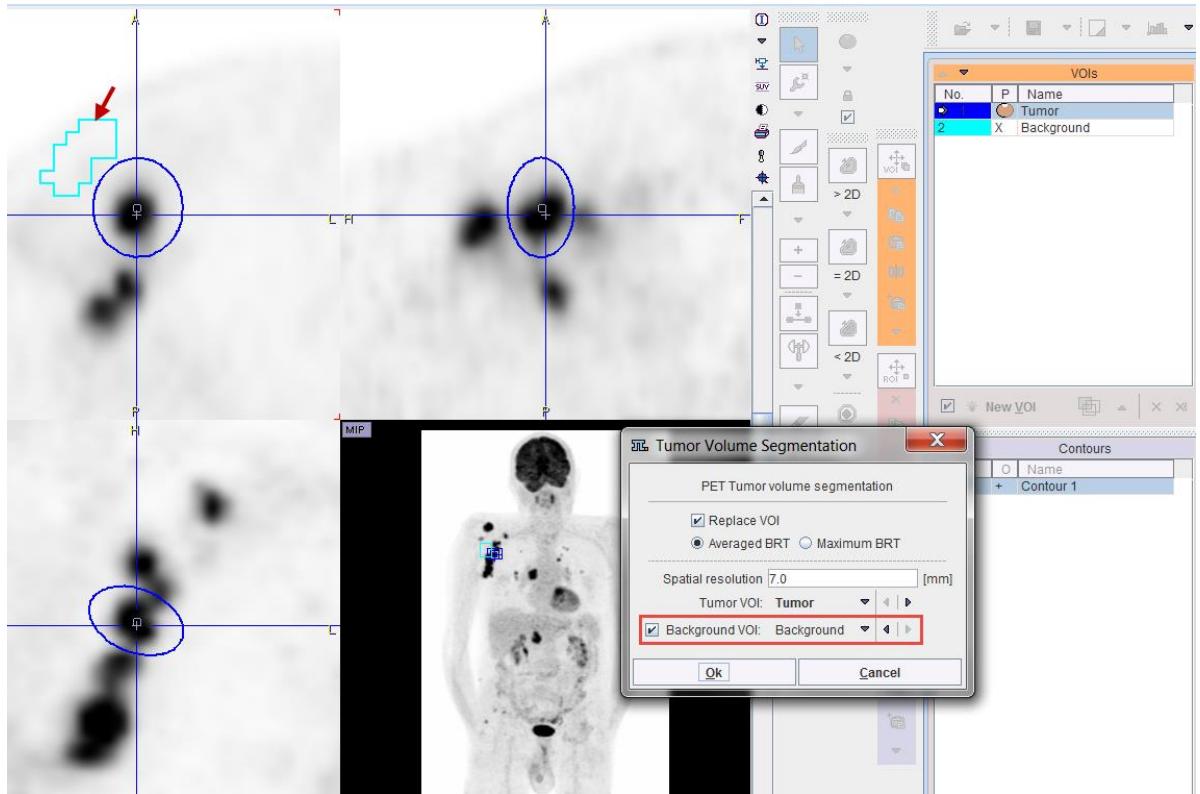
According to Jentzen [1], the Averaged BRT is preferable for larger objects, and it is less sensitive to noise and non-uniform uptake.

- 3) Check **Replace VOI**, if the initial VOI is not used any further.
- 4) **Ok** starts the iteration. The program first calculates the background activity by dilating the enclosing VOI by 3 pixels and averaging the pixels along the extended contour. Then the optimal iso-contouring threshold is calculated as outlined above. The results obtained with the different criteria are illustrated below.



Use with Background VOI

If higher uptake than background is close to the tumor, the initial VOI should be close to the tumor boundaries, and an explicit background VOI should additionally be outlined as in the example below. Note that the **Background VOI** box needs to be checked, and the proper VOI selected from the list next to it.



References

- [1] Jentzen W.: An improved iterative thresholding method to delineate PET volumes using the delineation-averaged signal instead of the enclosed maximum signal. Journal of nuclear medicine technology 2015, 43(1):28-35. DOI <http://dx.doi.org/10.2967/jnmt.114.152678>
- [2] van Dalen JA, Hoffmann AL, Dicken V, Vogel WV, Wiering B, Ruers TJ, Karssemeijer N, Oyen WJ: A novel iterative method for lesion delineation and volumetric quantification with FDG PET. Nuclear medicine communications 2007, 28(6):485-493. DOI <http://dx.doi.org/10.1097/MNM.0b013e328155d154>

VOI Adjustment Tools

Contour VOIs are formed from a stack of planar ROIs, which themselves consist of a set of contours per slice. On each of these three levels a set of similar operations are supported.

- » **Scaling:** The shape can be adjusted by dragging the edges of the object bounding box.
- » **Clearing:** The contents of the object is cleared, but the object continues to exist and can be used again for a new definition.
- » **Copy/Paste:** An object can be copied to the clipboard, and then pasted into an empty object on the same hierarchy level.
- » **Mirroring:** An object can be mirrored with respect to the central axes of the image volume.
- » **Propagation:** The aim of propagating an object is to easily get a copy of an existing object in a neighboring slice or frame. Propagation can work in both directions.

These operations are organized as function buttons on toolbars corresponding to the three levels. They can be configured to appear with a horizontal or vertical layout. The following sections illustrate the vertical layout.

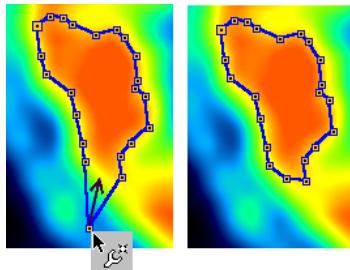
Contour Operations

Editing Contour Shapes

The following tools are available for adjusting the shape of completed contours.

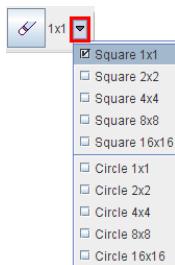
Moving Individual Vertices

When the **Edit Mode** is active, the user can click at individual contour vertices and then drag them to more appropriate positions. Clicking at contours from different VOIs will automatically select the corresponding VOI in the **VOIs** list.



Deleting Vertices

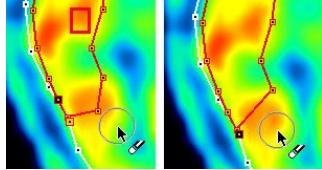
The eraser of the PMOD VOI tool can have different shapes and sizes which may be selected from the option list close to the eraser button.



To delete pixels from a contour VOI:

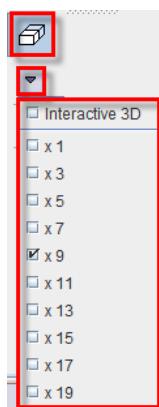
- 1) Select the affected contour by selection in the **VOIs** and **Contours** list.

- 2) Activate the eraser button .
- 3) Drag the eraser shape against the contour vertices which should be removed.



Erase 2D and erase 3D IH

The 2D eraser of the PMOD VOI tool is a circle which size can be selected from the option list:



To delete parts from a contour VOI:

- 1) Select the affected VOI by selection in the **VOIs** list.
- 2) Activate the 2D eraser button .
- 3) Click the eraser shape on the ROI area which should be removed.

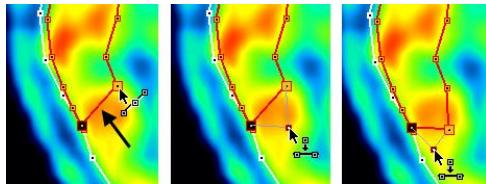


The **Interactive 3D** removal is based on a sphere region growing algorithm. Initially, the area to be excluded from the VOI need to be located. Then the mouse button need to be clicked and held until the 'growing' sphere completely deletes the area of interest. After completion, the removal can still be extended simply by click+hold. The 3D removal based on region growing continues from the new point.

Inserting Vertices

It is also possible to insert vertices at any location into contours. As soon as the insertion tool is activated , the cursor shape changes accordingly. The contour to be edited can be selected by clicking at a vertex point, or by selection in the **VOIs** and **Contours** list. The segment into which a new vertex is inserted is determined by the vertex at which the user clicks, and is indicated by the emphasized vertices at both ends. When moving the cursor,

the prospective two new segments are indicated by two faint lines. When the user clicks, the vertex is placed and the two new segments added. This procedure will continue for one of the created segments. To modify a different part of the contour please click at one of the vertices there. Note that the vertex locations cannot be changed in the insertion mode.



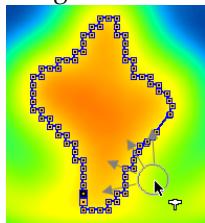
Shape Deformations

For the shape adjustment of densely populated contours a dedicated hammer tool is available. Similar to the eraser tool it can be configured for different sizes.



To change the contour shape with the hammer tool:

- 1) Select the affected contour by selection in the VOIs and Contours list.
- 2) Activate the hammer tool
- 3) Drag the circular shape towards the contour vertices which are pushed radially away.



CTR Toolbar

The contour toolbar



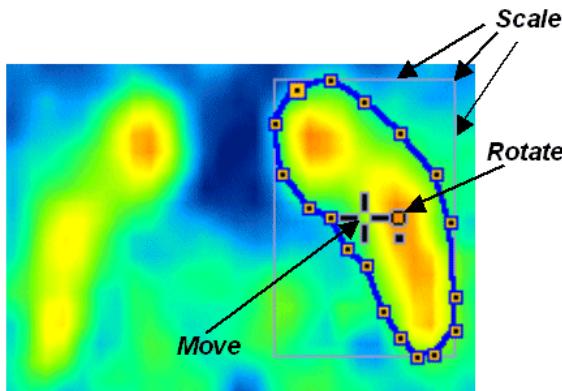
facilitates the operations related to contours. Note that only the selected contour is affected, whereas all others remain untouched.

	CTR Action. If this button is selected, a contour can be selected and then moved or scaled as described below.
--	---

	Clear. Clears the selected contour of the selected VOI in the current plane. The contour remains in the list, but has no defined polygon associated.
	Copy. Copies the selected contour to the clipboard.
	Paste. Pastes the contour from the clipboard into the current contour (which must be empty).
	Mirror Vertical. Opens a sub-menu for mirroring the active contours in the current slice relative to the vertical or horizontal center line.

CTR Action

In the **CTR Action** mode an entire contour can be translated, rotated or scaled within the plane. If a VOI has multiple contours, select the target contour in the **Contours** list. As illustrated below, the operations can be performed using mouse dragging. The handle in the center of the contour allows translations and rotations. When dragging the edges of the bounding box, the contour is scaled.



Alternatively the keyboard cursor arrows can be employed:

CURSOR UP, DOWN, LEFT, RIGHT	Move contour accordingly
CTRL + CURSOR UP, DOWN, LEFT, RIGHT	Scale the contour
SHIFT + CURSOR UP, DOWN, LEFT, RIGHT	Rotate the contour
ALT + one of the above	Perform the operation 5 times faster

Individual vertices cannot be moved in CTR action mode. To edit individual vertices first switch back to the **Edit Mode** by selecting the corresponding button in the toolbar.

CTR Propagation

The following propagation options are available:

Contour Propagate -	Pastes to the next slice in one direction (depending on the plane sorting order).
Contour Propagate +	Pastes to the next slice in the other direction.
Contour ApplyToAll	Pastes to all slices of the series.
Contour SmartApply	Pastes to all neighbouring slices which have no defined contours.
Contour Follow Max -	Pastes to the next slice in one direction and centers the contour at the maximal value in the slice (eg to follow a vessel).
Contour Follow Max +	Pastes centered at the maximum in the other direction.

Contour propagation may have advantages in the following situations:

- » if it is easier to adjust the propagated contour than to outline it from scratch, and
- » to create a bounding VOI which roughly encloses a structure, and then using the iso-contour auto-VOI tool.

ROI Toolbar

The **ROI toolbar**



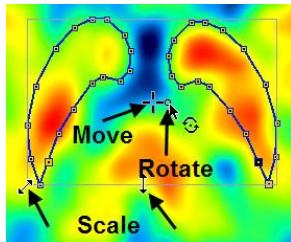
works in analogy to the **CTR toolbar**, except that all contours of the selected VOI in the current slice are changed at once.

	ROI Action. If this button is selected, all contours in the slice can be moved or scaled as described below.
	Clear. Removes the contours of the selected VOI in the current plane. The user can immediately begin defining a contour.
	Copy. Copies the contours to the clipboard.
	Paste. Pastes the contours from the clipboard into the current ROI (which must be empty).
	Mirror. Opens a sub-menu for mirroring the contours in the current slice relative to the vertical or horizontal center line.

	<input type="checkbox"/> Mirror left/right <input type="checkbox"/> Mirror up/down <input checked="" type="checkbox"/>
	Propagate option button. Propagation means copying all contours of the current slice and pasting it to a neighboring slice. Note that existing contours in the target slice are <i>overwritten</i> . The different propagation variants are described below.

ROI Action

As illustrated below, a bounding box enclosing all contours of the selected VOI in the current slice appears together with the move/rotation handle in the center. When dragging the edges of the bounding box, all contours are scaled.



Alternatively the keyboard cursor arrows can be employed:

CURSOR UP, DOWN, LEFT, RIGHT	Move contours accordingly
CTRL + CURSOR UP, DOWN, LEFT, RIGHT	Scale the contours
SHIFT + CURSOR UP, DOWN, LEFT, RIGHT	Rotate the contours
ALT + one of the above	Perform the operation 5 times faster

Individual vertices cannot be moved in ROI action mode. To edit individual vertices first switch back to the **Edit Mode** by selecting the corresponding button in the toolbar.

ROI Propagation

The following propagation options are available:

ROI Propagate -	Pastes to the next slice in one direction (depending on the plane).
ROI Propagate +	Pastes to the next slice in the other direction.
ROI ApplyToAll	Pastes to all slices of the series.
ROI SmartApply	Pastes to all neighboring slices which have no defined contours.
ROI Follow	Pastes to the next slice in one direction and centers at the maximal

Max -	value in the slice (eg to follow a vessel).
ROI Follow Max +	Pastes centered at the maximum in the other direction.

VOI Toolbar

The VOI toolbar



supports operations related to the entire VOI definition. Note that all the contours are affected, not just the ones in the visible slice images.

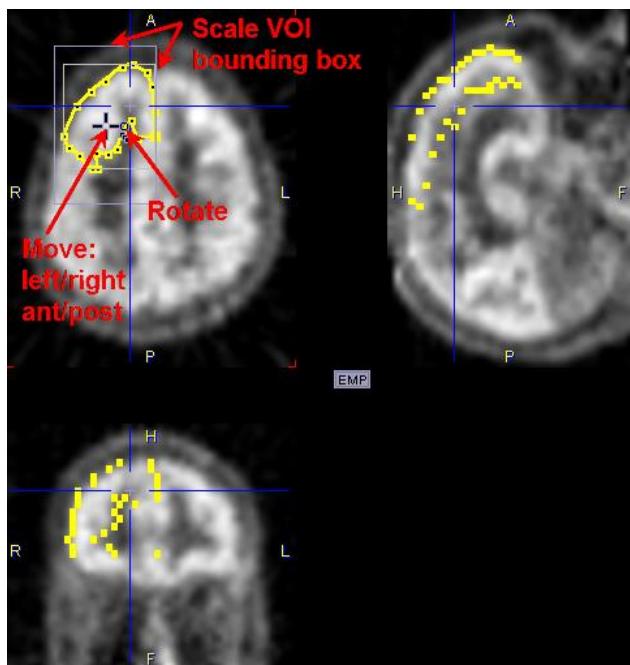
	VOI Action. If this button is selected, a VOI can be selected and then moved or scaled as described below.
	Clear. Clears all ROIs and contours of the selected VOI, leaving an empty definition.
	Copy. Copies the VOI to the buffer.
	Paste. Pastes the VOI from the buffer into the current VOI (which must be empty).
	Mirror. Opens a sub-menu for mirroring the selected VOI relative to the image center in the three directions. The clone variants first create a VOI copy, which is then mirrored.
	Center VOI to Min. Positions the center of the VOI bounding box at the pixel within the current VOI which has the minimal value. Note that multiple activations of the button may result in different positions.
	Center VOI to Max. Positions the center of the VOI bounding box at the pixel within the current VOI which has the maximal value. This function can be applied during a PERCIST evaluation to center the spheres at the lesion maxima.
	Propagate option button. Propagation for VOIs means copying a VOI from one time frame to another. This function is only available for dynamic series and VOIs which have the property set to dynamic. The different propagation variants are described below.

Usage of VOI Mirroring

This function can be used for creating a mirrored copy of a VOI as follows: Copy the VOI into the buffer, create a new VOI, and paste the VOI from the buffer. The two VOIs are now congruent, and one of them can be mirrored with a mirror button and moved to the destination place.

VOI Action

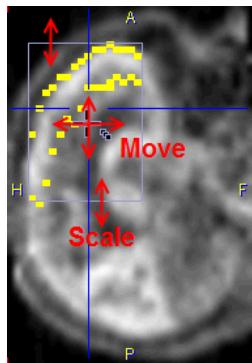
With the VOI Action mode all contours of a VOI can be modified at the same time. In most cases it will be advisable to use the orthogonal layout as illustrated below. After selecting the VOI by clicking at its contour or the entry in the VOIs list, several elements are shown in the overlay: the bounding box of the contours in the active slice, the bounding box of the VOI (maximum of the contour bounding boxes in all slices), and a handle for moving and rotating.



To move the VOI, drag the handle in the center with the left mouse button. Use the small rectangle for a rotation. To scale the VOI, drag the bounding box lines. After releasing the result will be updated in the other views. Note that not all operations are available in all directions:

- » Scaling is only supported within the primary plane which was used for the contour definition. The reason for this behavior is the lack of contour interpolation across slices.
- » Rotation is also only supported within the primary plane.
- » Moving is supported in all directions. While it is arbitrary within the primary plane, shifts in the orthogonal direction (across the slices) are only possible in increments of the slice thickness.

Referring to the example above, the frontal VOI can only be scaled in the L/R and A/P directions, but not in the H/F direction. In the sagittal plane, there is no rotation handle, and the scaling is only active for the bounding box lines indicated in the illustration below (A/P).



VOI Propagation

The **VOI Propagate** multi-function button serves for propagation over time and is therefore only active if

- » the study is dynamic,
- » and the properties of the VOI have been set to dynamic (blue).

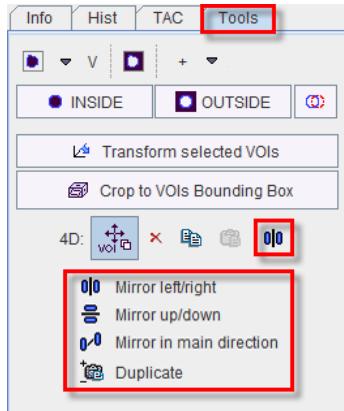
In this case, the VOI can consist of a differing definition at the different times. The button has the following options:



VOI Propagate -	Copies the current VOI, goes to the prior acquisition of the dynamic series, paste the VOI.
VOI Propagate +	Copies the current VOI, goes to the following acquisition of the dynamic series, and paste the VOI.
VOI ApplyToAll	Copies the current VOI and pastes it into all acquisitions.
VOI SmartApply	Copies the current VOI and pastes it into all subsequent acquisitions until an acquisition is encountered which already contains a VOI definition.

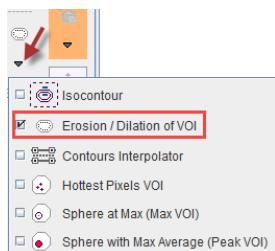
4D VOI Operations

When working with dynamic VOIs in dynamic series, an additional dimension needs to be considered, the time. Therefore, an area is available with similar tools as described above for the ROIs and VOIs. It is located on the **Tools** pane and allows a dynamic VOI to be cleared, copied, pasted, and mirrored in all frames at once.

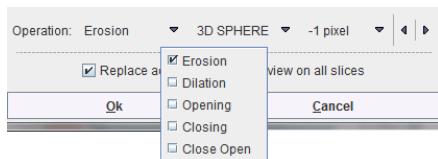


Erosion/Dilation

The **Erosion/Dilation of VOI** function



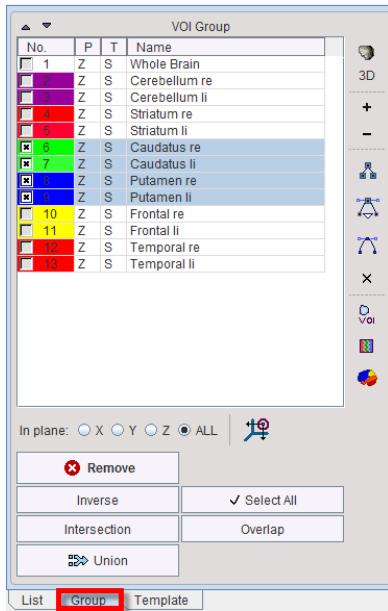
is useful for shrinking or inflating VOIs. It shows the interface described for the *morphological operations* (on page 152)



When applying an operation, the VOI is converted to a binary image, the operation applied, and then contouring applied to get a contour VOI. Therefore, object VOIs are converted into contour VOIs. The resulting VOI replaces the original VOI. Note that the operations can be applied to a whole group of VOIs at the same time.

VOI Grouping

The **Group** tab shows a list of all **List** VOIs with a selection box.



Initially, all VOIs are selected. The selection can be changed by dragging over the selection boxes and using **CTRL+Click** to selectively enable/disable VOIs. Additionally, **CTRL+A** or **Select All** selects all entries, and the **Inverse** button reverts the selection.

The buttons to the right act on the current selection. For instance, the **+** button sets the contours of all selected VOIs to positive.

VOI Union

The **Union** button serves for creating a new VOI from the selected ones. The resulting VOI includes the contours of all source VOIs, whereby the **+/- property** (on page 209) of these contours is maintained. This function is useful for creating a VOI from sub-structures, but also to subtract a smaller VOI from a larger one.

VOI Intersection

The **Intersection** button outlines the intersection volume of two VOIs and adds it as a new VOI to the List. Two VOIs have to be selected in the **VOI** list in the **Group** tab.

Operations on a Group of VOIs

While the **Group** tab is active rather than the **List** tab, the operations on the **VOI** toolbar will be applied to the entire group. For example, using **VOI Action**, all grouped VOIs can be moved, rotated, scaled at once. Furthermore, they can be cleared, mirrored, and masking applied.

The group operations can be refined using the radio buttons below the VOIs list. With **X pln** (**Y pln**, **Z pln**), only the selected VOIs with **X** (**Y**, **Z**) orientation will be included in the operation. With **ALL**, the operation will be applied to all selected VOIs.

Note: These group operations are only active as long as the **Group** tab is selected.

The grouped VOIs can also be saved together in a new VOI file, excluding the non-selected VOIs. To this end, use **Save Group** from the VOI saving menu.



Furthermore, when calculating statistics, there is always a **Group** entry. It represents the statistics of the pixels in all the selected VOIs on the **Group** tab, even if the **Group** tab has never been actively selected.

Tree Organization of Atlas VOIs

The brain VOIs are structurally organized in a tree on the **Group** tab of the VOI editing page. The selection of a VOI subset is supported by a dedicated user interface illustrated below.

No.	P	Name
1	Z	FL_mid_fr_G_l
2	Z	FL_mid_fr_G_r
3	Z	FL_preccen_G_l
4	Z	FL_preccen_G_r
5	Z	FL_striat_G_l
6	Z	FL_striat_G_r
7	Z	FL_OFC_AOG_l
8	Z	FL_OFC_AOG_r
9	Z	FL_inf_fr_G_l
10	Z	FL_inf_fr_G_r
11	Z	FL_sup_fr_G_l
12	Z	FL_sup_fr_G_r
13	Z	FL_OFC_MOG_l
14	Z	FL_OFC_MOG_r
15	Z	FL_OFC_LOG_l
16	Z	FL_OFC_LOG_r
17	Z	FL_OFC_POG_l
18	Z	FL_OFC_POG_r
19	Z	Subgen_antCing_l
20	Z	Subgen_antCing_r
21	Z	Subcal_area_l
22	Z	Subcal_area_r
23	Z	Presubgen_antCing_l
24	Z	Presubgen_antCing_r
25	Z	Hippocampus_l
26	Z	Hippocampus_r
27	Z	Amygdala_r
28	Z	Amygdala_l
29	Z	Ant_TL_med_r
30	Z	Ant_TL_med_l
31	Z	Ant_TL_inf_lat_r
32	Z	Ant_TL_inf_lat_l
33	Z	G_parah_amb_r
34	Z	G_parah_amb_l
35	Z	G_sup_temp_post_r
36	Z	G_sup_temp_post_l
37	Z	G_tem_midin_r

The branches on the top level are the left (**L**) and right (**R**) structures, **Central structures**, **Posterior fossa**, and the **Ventricles** as illustrated in the left panel above. The full tree can be opened easily by the button indicated in the middle panel. The tree view can be flattened to a simple list by the button at the top indicated in the right panel. The statistics will only be calculated for the selected VOIs.

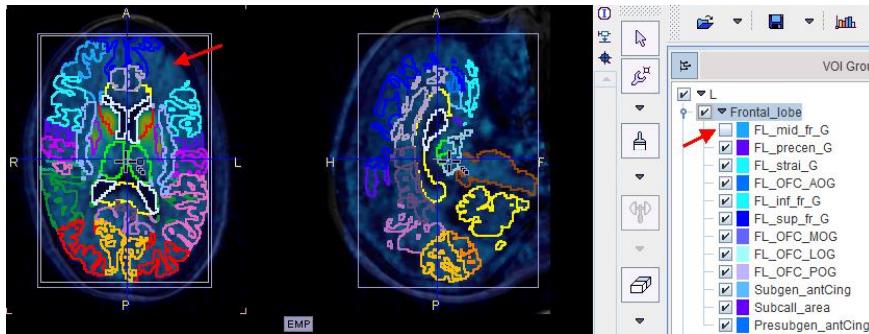
Tree Manipulations

Branches in the tree can be opened/closed with the little arrows left to the branch names.

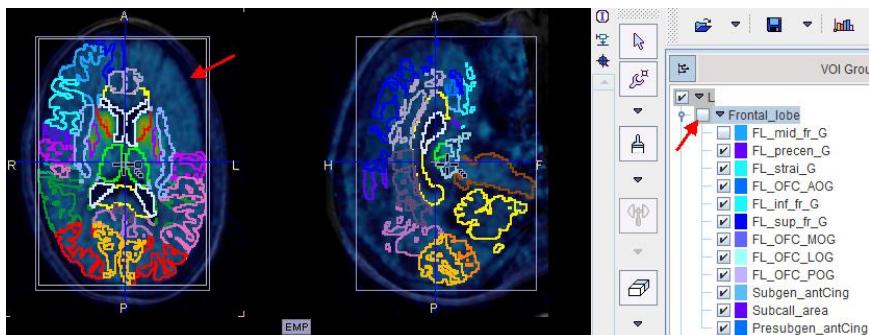


Tree Selections

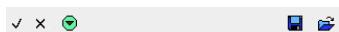
The structures of interest are the ones with checked boxes to the left of their color code. Simply click into a box for changing the selection. In the example below the **FL_mid_fr_G** VOI has been de-selected.



If the selection of a branch is removed, all VOIs belonging to it will be de-selected.



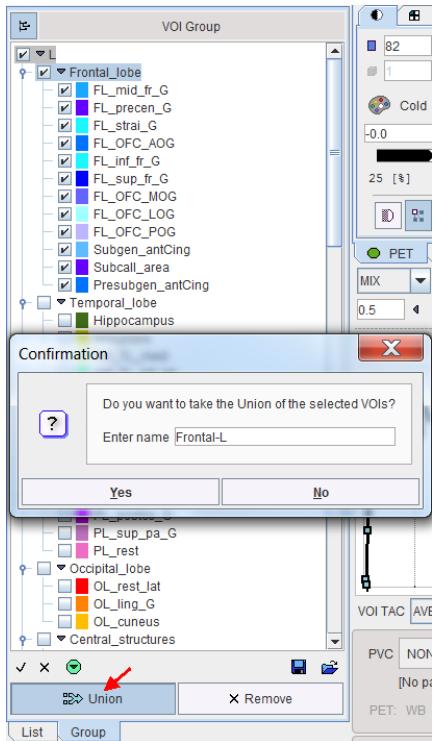
The task of selecting parts in the tree is supported by shortcuts in the area at the tree bottom:



- Remove the selection check of all VOIs.
- Set the selection check of all VOIs
- Save the current selection set to a file.
- Load a selection set from a file.

VOI Union

The currently selected VOIs can be combined into a larger structure by the **Union** button. In the example below the selection was first reset by **X**, and then all left frontal lobe VOIs selected by checking the **Frontal_lobe** entry.



Note that in PNEURO the original VOIs are removed during the **Union** process. This is necessary for the proper functioning of the partial volume correction. However, the VOIs can easily be recovered by stepping to the prior page and activating the **Outline** button again.

VOI Save/Load

Saving

Once a set of contour VOIs has been defined for an image study the VOI definition can be saved using one of the **Save** option buttons



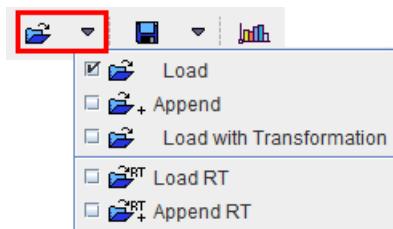
The buttons have the following function

Save	Saves all of the VOIs together with their names and color in a .voi file.
Save Group	Saves only those VOIs which are checked on the Group tab in a .voi file.

Save RT	Saves all VOIs as DICOM structure set objects in a file. Such DICOM structure set objects can be used in radiotherapy (RT) planning systems.
Export RT	This function also creates DICOM structure set objects, but allows to directly send them to an RT planning system using the DICOM network protocol. A dialog box pops up for selecting the target system among the configured DICOM nodes.

Loading

Conversely, contour VOI definitions can be retrieved from files using the **Load** option buttons



The buttons have the following function

Load	First removes all current VOI definitions and then loads the ones from the selected VOI files.
Append	Loads the VOIs from the selected file and appends them to the current VOI definitions.
Load with transformation	First removes all current VOI definitions, loads the ones from the selected VOI files, and requests a spatial transformation which is applied to the VOIs. All transformations calculated in the PMOD Image Fusion tool are supported, rigid and elastic ones.
Load RT	First removes all current VOI definitions and then loads the VOIs from a file containing DICOM RT structure set objects.
Append RT	Loads the VOIs from a file containing DICOM RT structure set objects and appends them to the current VOI definitions.

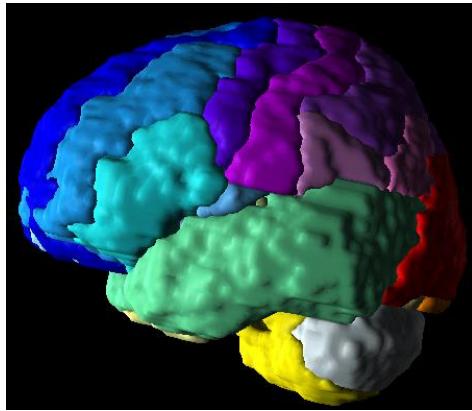
3D VOI Visualization

If the P3D option is installed on the system the button

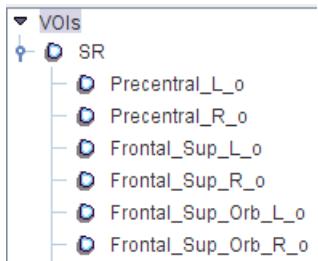


is shown in the upper right corner of the VOI user interface. When it is activated, the contours can be rendered as ribbons with a width of the slice thickness, or as full surfaces.

The example shown below is a rendering of the VOIs derived from outlining the AAL template.



In the 3D tool, the VOIs are organized in a tree



so that each structure can individually be shown, hidden and colored. This might be helpful for interactive demonstration purposes to visualize the spatial relationship of the structures.

Using VOI Atlas Files

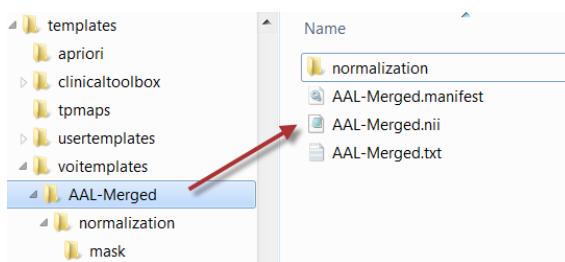
VOI atlases are image files which represent a standard anatomy. Human atlases are defined in the *MNI space* <http://www.nitrc.org/nipspace.html> (Montreal Neurological Institute). The values in the image pixels are label numbers, and each label number corresponds to a certain anatomical region. The correspondence between label value and name is contained in a text file.

Structure of VOI Atlases in PMOD

A VOI atlas in PMOD consists of the following components:

- 1) *Atlas image*: Image which encodes the atlas VOIs as numeric labels.
- 2) *Label list*: Text file mapping the label values to VOI names.
- 3) *Manifest*: Text file for the defining of the species type (HUMAN, PRIMATE, RAT, MOUSE) by a simple line entry, e.g.
SPECIES = HUMAN
If the VOI atlas is not applicable in PNEURO then the line
APPLICATION = NO_PNEURO
should be added. For probabilistic atlases the line
TYPE = PROBABILISTIC, RANGE 0 / 100
The range specified for the data will be scaled to a probability value in the range [0,1].
- 4) *Normalization* files for calculating the transformation between the subject anatomy and atlas anatomy.

This information has to be organized in a subdirectory of *resources/templates/voitemplates* in a particular way as illustrated below.



The atlas name (e.g. **AAL-Merged**) has to be used as the name of the sub-directory, the atlas image (**AAL-Merged.nii**), the label list (**AAL-Merged.txt**), and the manifest (**AAL-Merged.manifest**).

By conforming to this structure it is possible for users to prepare their own VOI atlases. Note however, that in PNEURO they are only applicable for **Maximum Probability Atlas** approach, not for the **Brain Parcellation** approach.

Atlas Image

The atlas image must be prepared as a NifTI file and encode the atlas VOIs as numeric labels. Each pixel has a value of 0 if it is a background pixel, or otherwise an integer number. We recommend using the HFS anatomical orientation (head first, supine = radiological convention) for human data.

Label List

The label list text file has the minimal form:

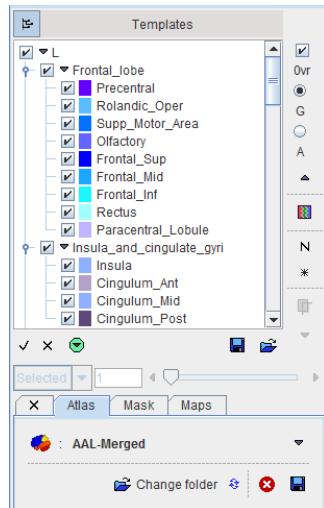
```
name1    outlined_name1  label_value1
name2    outlined_name2  label_value2
```

where each VOI is represented by a line.

The list can be extended with additional information for the VOI presentation as illustrated below for the **AAL-Merged.txt**. The first column starts with the name followed by a bracket construction which encodes a tree structure. For instance, **Precentral** belongs to the **Frontal_Lobe** which is located in the left **L** or right **R** hemisphere. The second column indicates the name of a generated contour VOI. The third column contains the label value in the atlas file. Each pixel in **AAL-Merged.nii** with value 1 will belong to the **Precentral_1** VOI, pixels with value 2 to **Precentral_1**, etc. The third column specifies the RGB color values for showing the VOI, and the last column the text to be shown as a tooltip.

Name	Outlined	Label	Color	Tooltip
Precentral[Frontal_lobe[L]]	Precentral_I	1	(100,0,255)	Precentral gyrus left (PRE)
Precentral[Frontal_lobe[R]]	Precentral_r	2	(100,0,255)	Precentral gyrus right (PRE)
Rolandic_Oper[Frontal_lobe[L]]	Rolandic_Oper_I	3	(93,188,255)	Rolandic operculum left (RO)
Rolandic_Oper[Frontal_lobe[R]]	Rolandic_Oper_r	4	(93,188,255)	Rolandic operculum right (RO)
Supp_Motor_Area[Frontal_lobe[L]]	Supp_Motor_Are_I	5	(0,114,255)	Supplementary motor area left (SMA)
Supp_Motor_Area[Frontal_lobe[R]]	Supp_Motor_Are_r	6	(0,114,255)	Supplementary motor area right (SMA)
Olfactory[Frontal_lobe[L]]	Olfactory_I	7	(100,100,255)	Olfactory cortex left (OC)
Olfactory[Frontal_lobe[R]]	Olfactory_r	8	(100,100,255)	Olfactory cortex right (OC)
Frontal_Sup[Frontal_lobe[L]]	Frontal_Sup_I	11	(0,0,255)	Superior frontal gyrus left (F1, F1O, F1M)
Frontal_Sup[Frontal_lobe[R]]	Frontal_Sup_r	12	(0,0,255)	Superior frontal gyrus right (F1, F1O, F1M)

The corresponding atlas VOI structure is illustrated below.



There are additional options to be added in the columns for use in PNEURO:

- » **E:** Excluded from masking by the grey matter threshold.
- » **O:** Indicates that the VOI is not brain matter.
- » **H:** Indicates that the VOI should initially be hidden, i.e. not selected on the **Group** panel.
- » **L, R:** Indicates that the VOI belongs to the left (L) or right (R) hemisphere. This information is used in sulci deformation.
- » **C:** Indicates that the VOI belongs to the cerebellum. This information is also used in sulci deformation.

Example as shown in Excel:

S_nigra[Central_structures[L]]	S_nigra_I	74 (127,127,1	Substantia E		
S_nigra[Central_structures[R]]	S_nigra_r	75 (127,127,1	Substantia E		
Insula[Insula_and_cingulate_gyri[L]]	Insula_I	20 (143,175,2	Insula left L		
Insula[Insula_and_cingulate_gyri[R]]	Insula_r	21 (143,175,2	Insula right R		
Cerebellum[Posterior_fossa[R]]	Cerebellum_r	17 (250,239,5	Cerebellum C		
Cerebellum[Posterior_fossa[L]]	Cerebellum_l	18 (250,239,5	Cerebellum C		
Brainstem[Posterior_fossa]	Brainstem	19 (151,72,6)	Brainstem C	E	
FrontalHorn[Ventricles[R]]	FrontalHorn_r	45 (219,238,2	Lateral ver E	O	H
FrontalHorn[Ventricles[L]]	FrontalHorn_l	46 (219,238,2	Lateral ver E	O	H
TemporaHorn[Ventricles[R]]	TemporaHorn_r	47 (183,221,2	Lateral ver E	O	H
TemporaHorn[Ventricles[L]]	TemporaHorn_l	48 (183,221,2	Lateral ver E	O	H
ThirdVentricl[Ventricles]	ThirdVentricl	49 (146,205,2	Third ventr E	O	H

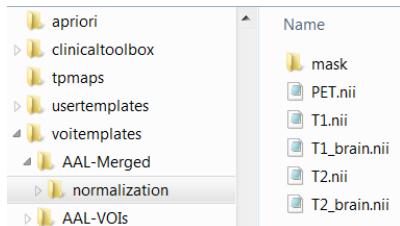
Spatial Normalization

Atlases can only be applied to images if they have the same resolution and show the anatomy with the same geometry. Therefore, images originating from real experiments first need a normalization step for the atlas to be applied. This is done by calculating a normalization transform between the subject image and a "template" image representing the standard anatomy imaged with a certain modality, and using it for warping the VOIs to the subject anatomy.

Name of method in PMOD	Methodology and template
Template-based normalization	Implementation of the spatial normalization in SPM5. It requires a template image in the atlas space which has a similar pattern as the image to normalize. The usual reference images are the PET, T1 and T2 SPM5 templates.
3 Probability maps normalization	Implementation of the unified segmentation normalization in SPM8. It requires tissue probability maps of grey matter, white matter and CSF in the atlas space, which is organized in a dynamic file called tpm.nii . This normalization is mostly applicable to T ₁ -weighted MR images.
6 Probability maps normalization	Implementation of the unified segmentation normalization in SPM12. It uses three additional probability maps (bone, tissue and air), which are organized in a dynamic file tpm_6.nii .

Template Normalization Files

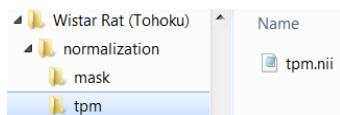
Appropriate template images for the **Template-based normalization (SPM5)** need to be copied to a **normalization** sub-folder. In the example below **normalization** contains T1 and T2 MR templates with and without skull, as well as a PET template. All of these templates show the anatomy in the MNI space in which the AAL VOIs were defined.



The normalization works best if the information is restricted to the relevant image part. Therefore, **normalization** should contain a **mask** sub-folder with a mask file **mask.nii** containing 1 for all relevant pixels and 0 for all others.

Probability Normalization Files

The normalization files for the two probability maps approaches need to be prepared in a **normalization/tmp** subdirectory as illustrated below.



Note: For atlases with **HUMAN** in the manifest preparation of the **tpm** subdirectory is not required, as the universal files for the human brain are available in the **tpmaps** directory.

Tree Organization of Atlas VOIs

The brain VOIs are structurally organized in a tree on the **Group** tab of the VOI editing page. The selection of a VOI subset is supported by a dedicated user interface illustrated below.

The figure displays three panels of the VOI Group interface:

- Left Panel (Tree view):** Shows a hierarchical tree structure. The root branches are L and R. Under L, there are Central_structures, Posterior_fossa, and Ventricles. Under Central_structures, there are Frontal_llobe, Temporal_llobe, Parietal_llobe, and Occipital_llobe. Each of these further branches into specific regions like Hippocampus, Amygdala, etc. A red arrow points to the 'Open tree leaves' button at the bottom of the tree panel.
- Middle Panel (Full tree view):** Shows the same hierarchical structure as the tree view, but all branches are expanded. A red arrow points to the 'Full tree' button at the bottom of the middle panel.
- Right Panel (Flat view):** Shows a flat list of 37 items, each with a number, a checkmark, and a Z-value. The items are color-coded by region. A red arrow points to the 'Flat view' button at the top of the right panel.

The branches on the top level are the left (**L**) and right (**R**) structures, **Central structures**, **Posterior fossa**, and the **Ventricles** as illustrated in the left panel above. The full tree can be opened easily by the button indicated in the middle panel. The tree view can be flattened to a simple list by the button at the top indicated in the right panel. The statistics will only be calculated for the selected VOIs.

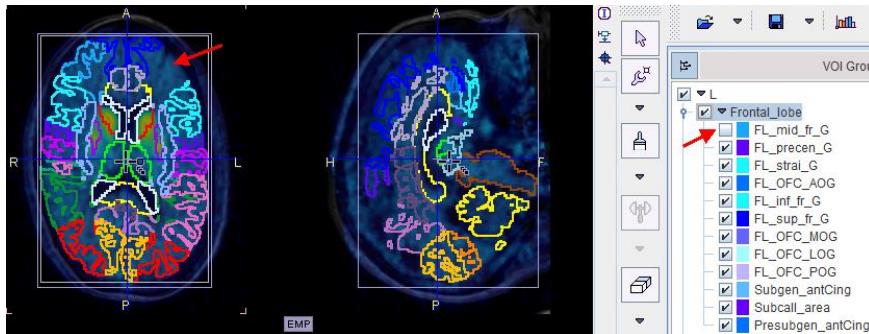
Tree Manipulations

Branches in the tree can be opened/closed with the little arrows left to the branch names.

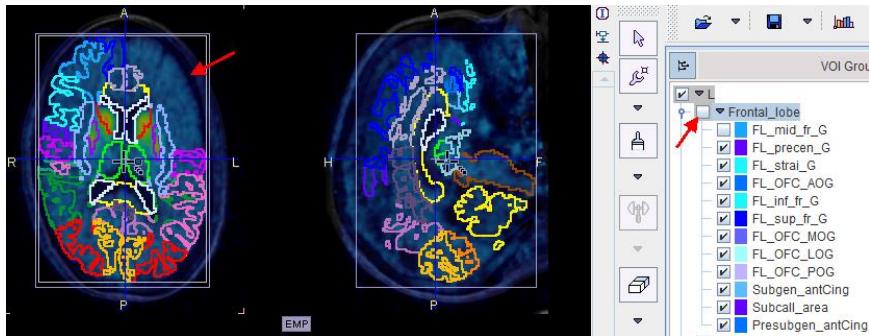


Tree Selections

The structures of interest are the ones with checked boxes to the left of their color code. Simply click into a box for changing the selection. In the example below the **FL_mid_fr_G** VOI has been de-selected.



If the selection of a branch is removed, all VOIs belonging to it will be de-selected.

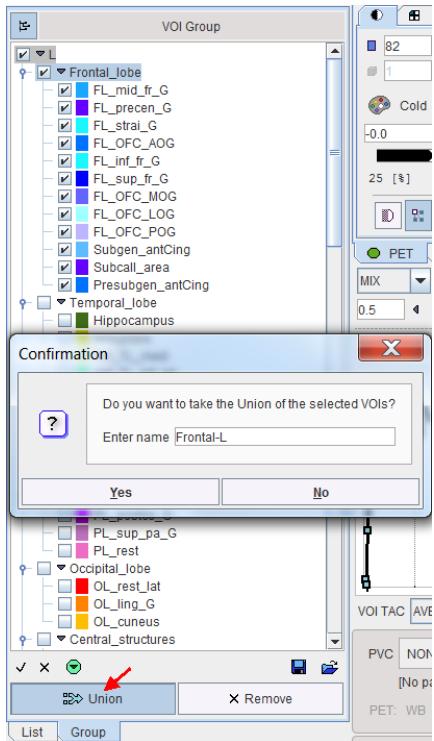


The task of selecting parts in the tree is supported by shortcuts in the area at the tree bottom:

- Remove the selection check of all VOIs.
- Set the selection check of all VOIs
- Save the current selection set to a file.
- Load a selection set from a file.

VOI Union

The currently selected VOIs can be combined into a larger structure by the **Union** button. In the example below the selection was first reset by **X**, and then all left frontal lobe VOIs selected by checking the **Frontal_lobe** entry.



Note that in PNEURO the original VOIs are removed during the **Union** process. This is necessary for the proper functioning of the partial volume correction. However, the VOIs can easily be recovered by stepping to the prior page and activating the **Outline** button again.

Probabilistic VOI Atlas

Atlas Structure

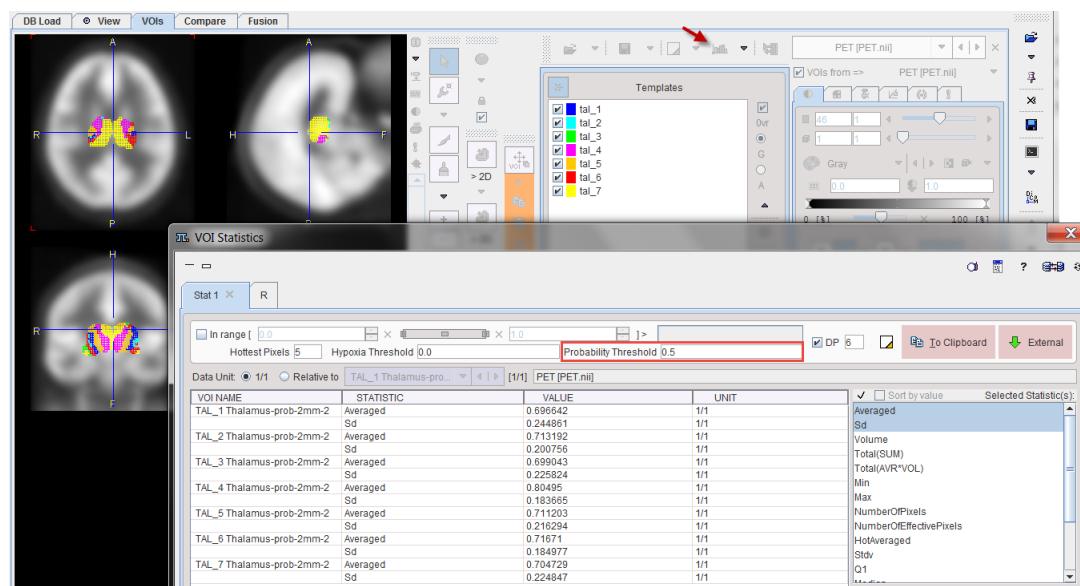
Regular VOI atlases in PMOD are based on a label image which specifies for each pixel to which VOI it belongs. The situation is different for a probabilistic atlas. There, each pixel has a probability value assigned for belonging to a specific VOI. Therefore, probabilistic atlases require a real-valued image for every VOI in the atlas. In PMOD, the probability images are arranged as frames in a dynamic series. In the label list file the third column therefore corresponds to the frame encoding a VOI's probability, rather than its label number in a static image.

Name	Outlined	Frame	Color	Tooltip
Precentral[Frontal_lobe[L]]	Precentral_l	1	(100,0,255)	Precentral gyrus left (PRE)
Precentral[Frontal_lobe[R]]	Precentral_r	2	(100,0,255)	Precentral gyrus right (PRE)
Rolandic_Oper[Frontal_lobe[L]]	Rolandic_Oper_l	3	(93,188,255)	Rolandic operculum left (RO)
Rolandic_Oper[Frontal_lobe[R]]	Rolandic_Oper_r	4	(93,188,255)	Rolandic operculum right (RO)
Supp_Motor_Area[Frontal_lobe[L]]	Supp_Motor_Area_l	5	(0,114,255)	Supplementary motor area left (SMA)
Supp_Motor_Area[Frontal_lobe[R]]	Supp_Motor_Area_r	6	(0,114,255)	Supplementary motor area right (SMA)
Olfactory[Frontal_lobe[L]]	Olfactory_l	7	(100,100,255)	Olfactory cortex left (OC)
Olfactory[Frontal_lobe[R]]	Olfactory_r	8	(100,100,255)	Olfactory cortex right (OC)
Frontal_Sup[Frontal_lobe[L]]	Frontal_Sup_l	11	(0,0,255)	Superior frontal gyrus left (F1, F1O, F1M)
Frontal_Sup[Frontal_lobe[R]]	Frontal_Sup_r	12	(0,0,255)	Superior frontal gyrus right (F1, F1O, F1M)

Note: Probabilistic atlases can only be applied to already normalized images. The normalization functionality is not supported.

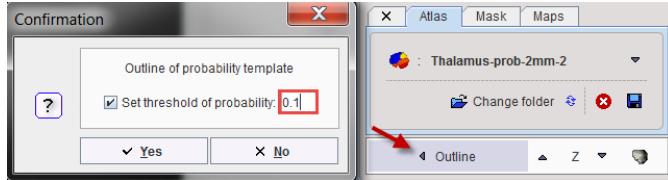
Statistics

When applying a probabilistic atlas for statistics, calculation takes the probabilities into account as described for the different **measures** (on page 280). For some of them a threshold criterion is required, which can be entered in the **Probability Threshold** field. The example below illustrates the functionality using a probabilistic atlas with seven Thalamus sub-regions.



Outline Definition

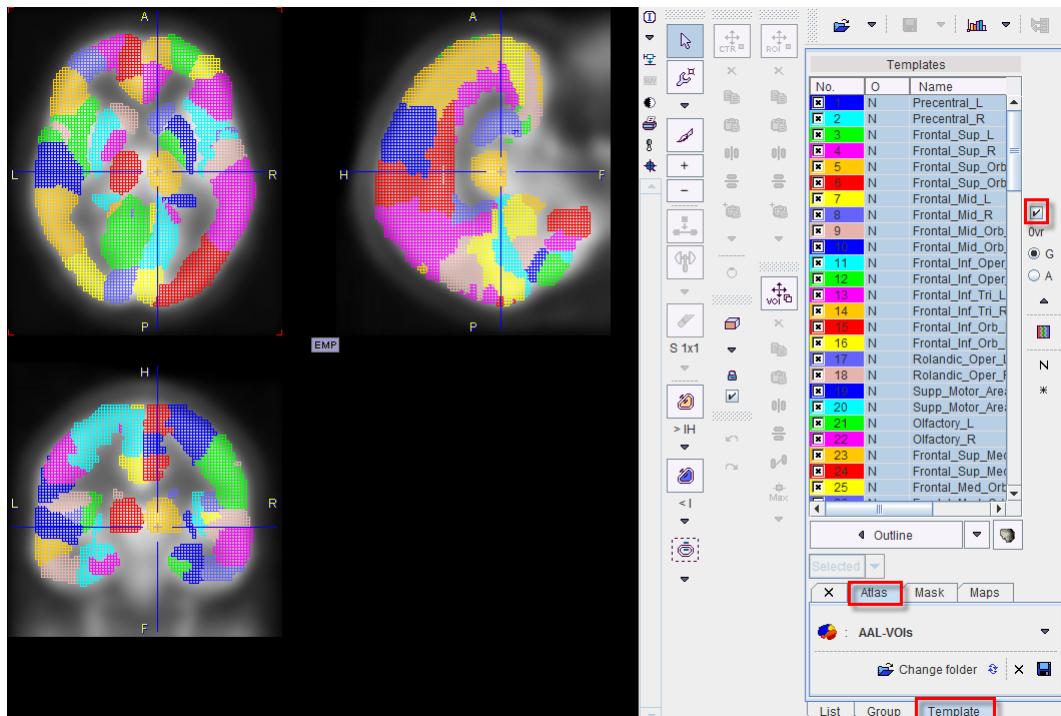
The conversion of probabilistic VOIs into contour VOIs requires specification of a discretization threshold in the **Set threshold of probability** field of the outlining window.



Note that with multiple selected VOIs the outlining procedure constructs non-intersecting VOIs by assigning a pixel to the VOI with the highest p-value.

Atlas-based VOI Statistics

When an image series has been loaded for which a suitable atlas exists, its use for VOI statistics is straightforward. First activate the VOI functionality, select the **Template** tab, and chose the template in the list on the **Atlas** pane.



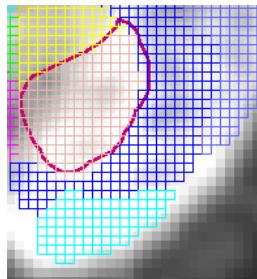
The atlas description is read and the list of VOI labels populated. Initially, all regions are selected, and an overlay on the images marks their locations. The overlay can either show an open or a filled pixel raster, depending on the setting of the radio box above the **Ovr** check. To hide all template VOIs at once please un-check the **Ovr** box on the **Template** tab. To stop using the template VOIs select the **X** tab next to **Atlas**.

VOI Selection

Only the selected atlas regions are shown as VOIs and used for statistics calculations. The usual operations can be applied to select or de-select entries in the VOI list.

- » **CTRL+A:** Select all entries.
- » **CTRL+Click:** Check or un-check an entry without changing the others.
- » **SHIFT+Click:** Select the range until the clicked entry.

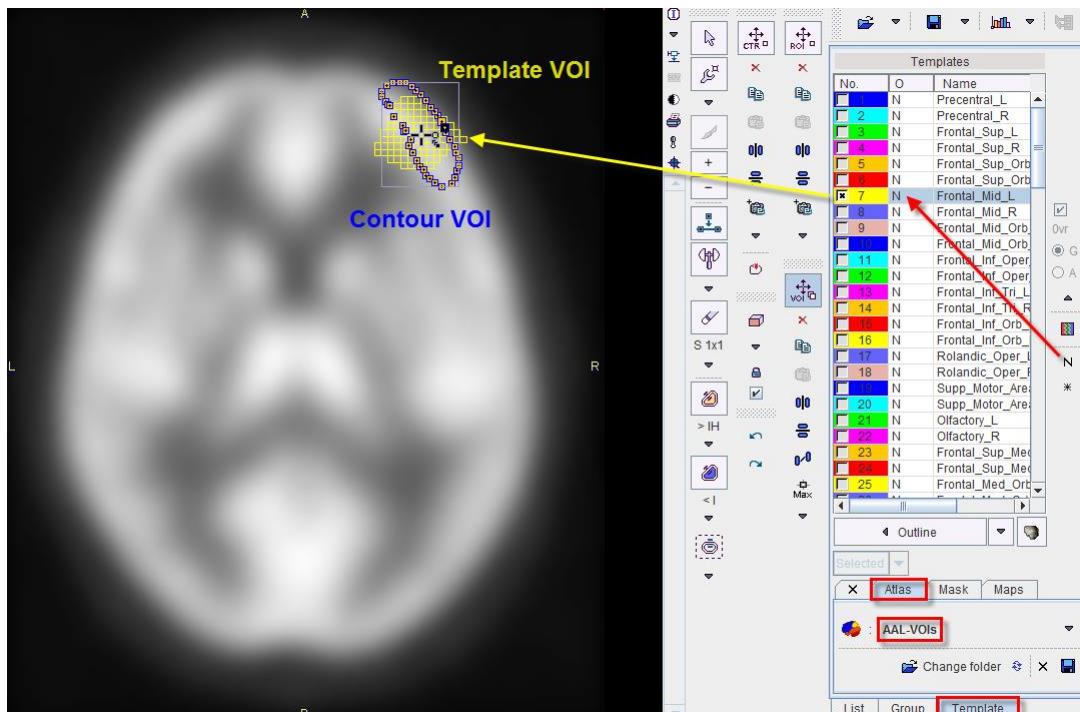
VOI templates can co-exist with the standard VOI contours.



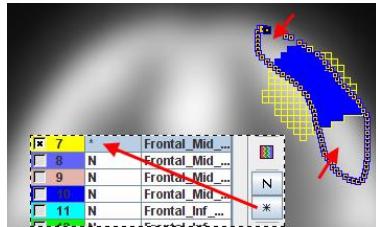
To modify the contour VOIs , select the **List** tab and use all of the functionality described for the contour VOIs sections above. **Statistics** calculates the statistics of the contour VOIs and the active template VOIs.

Using Atlas VOIs as Masks

In addition to using template VOIs for statistics, they can also be applied for masking contour VOIs. Illustrated below are a contour VOI from the **List** tab and a selected VOI from the **Template** tab which overlap. The indication in the **O** operation column is **N** for normal operation.

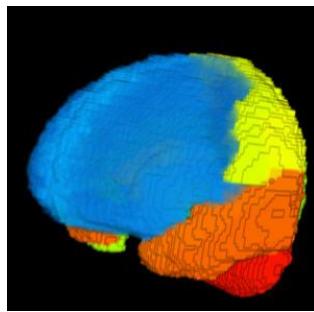


If the operation mode is changed to * for **Mask** operation by the indicated button, the atlas VOI acts as a mask for the contour VOI as shown below.



Atlas Visualization

If the 3D option has been purchased, the atlas can be rendered using the **View all in 3D**  button located below the VOIs list.

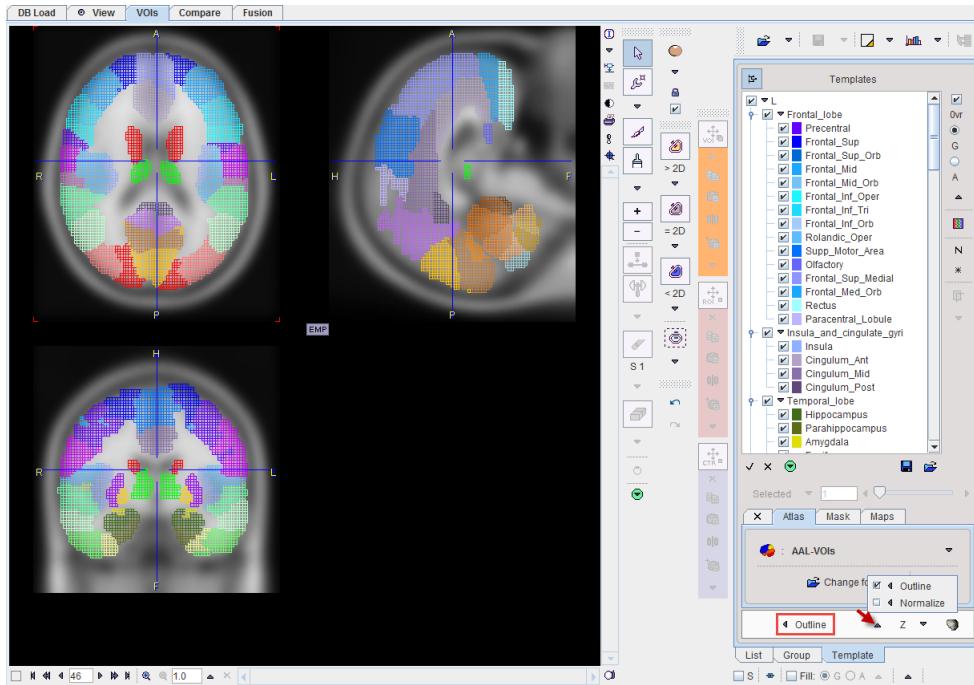


Converting Atlas VOIs to Contour VOIs using Outline

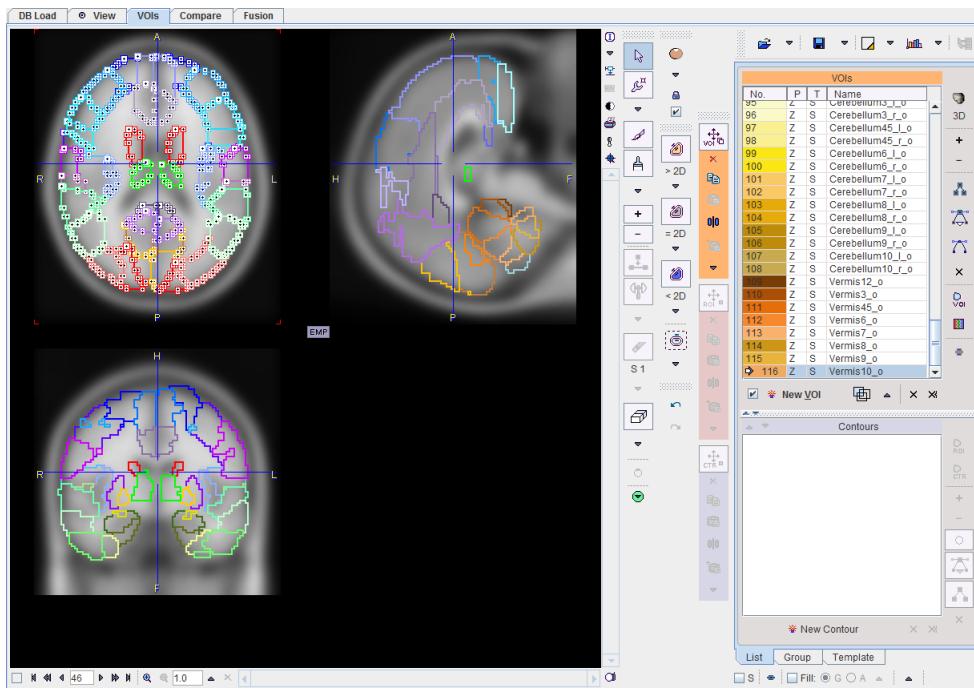
Unlike contour VOIs, atlas VOIs cannot be adjusted. Therefore, a mechanism has been implemented in the PMOD VOI tool to convert atlas VOIs into contour VOIs. The procedure is very simple:

- 1) Select the atlas VOIs for which contours should be generated (Template/Atlas/AAL-VOIs).
- 2) Activate the **Outline** button.
- 3) Save the contour VOIs.

The illustration below shows the example of an image in the MNI space with the AAL atlas selected. The AAL VOIs are organized as a tree structure.



Using **Outline** results in the following contour outlines shown on the **List** tab.



Converting Atlas VOIs to Contour VOIs using Normalize

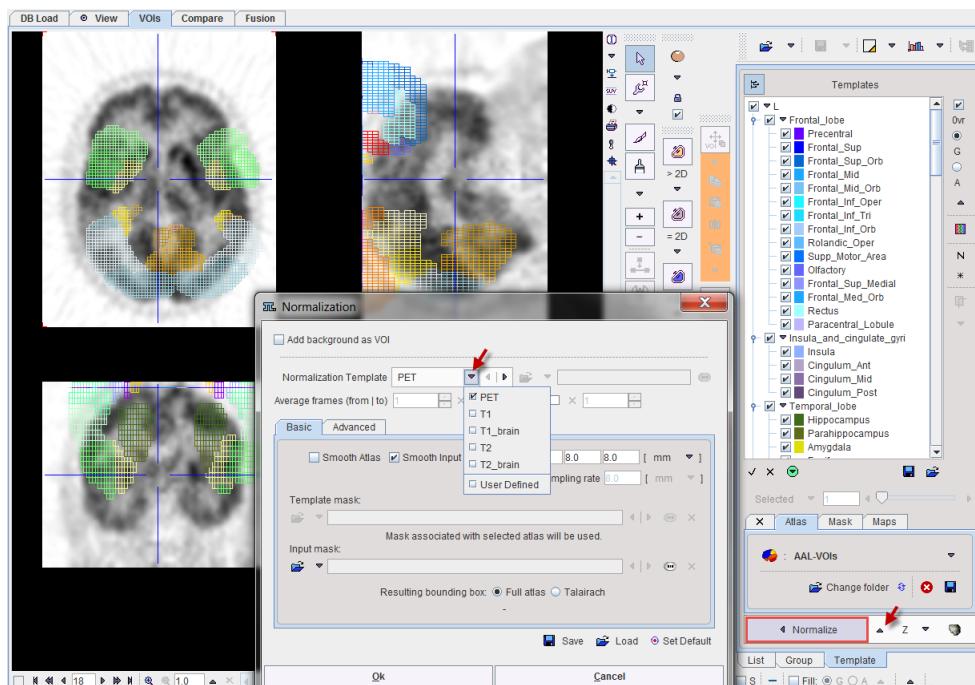
A mechanism has been implemented in the PMOD VOI tool which allows transforming atlas VOIs into the original subject anatomy. Note, however, that the normalization procedure may fail if there is no template image available with a similar pattern than the target image, and that the resulting VOIs may need adjustment.

NOTE: This approach will succeed ONLY if a well define strategy for data normalization is available in the Fusion.

The procedure is as follows:

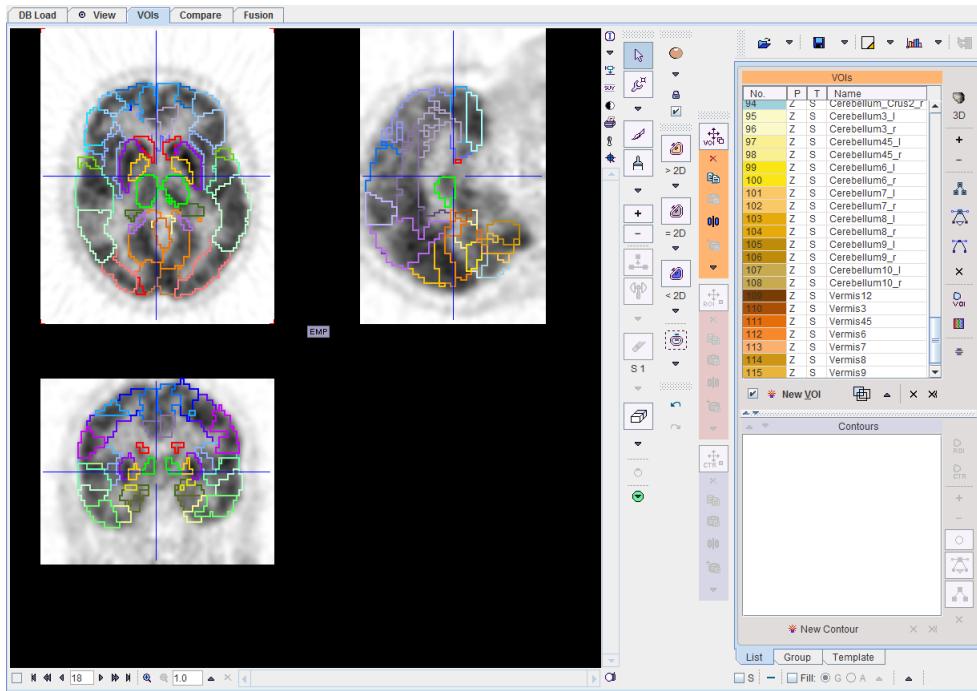
- 1) Select the atlas VOIs for which contours should be generated (e.g. Template/Atlas/AAL-VOIs).
- 2) Activate the **Normalize** button.
- 3) A dialog window appears allowing to configure the normalization.
- 4) In the uppermost part of the window the **Normalization Template** can be set according to the image. In case dynamic data are analyzed, an **Average** frame range can be defined to be used for the normalization.
- 5) The algorithm performs the data normalization using the **Basic** and **Advance** settings available in the **Normalization Parameters** tab. More information about the settings is available in the **Deformable Registration** section of the PFUSIT documentation. It calculates the inverse transformation which is then applied to the VOI atlas. Optionally, the image background can be added to VOIs if **Add background as VOI** checkbox is enabled.
- 6) Finally, the transformed VOI atlas is outlined.

The AAL atlas with grid filled overlay looks as follows:



Note the misalignment of the atlas and the image before transformation.

The result of **Normalize** algorithm is shown below:



VOI Atlases included in PMOD

Several atlases are included in the PMOD distribution. Beyond their direct use, they may serve as examples for user-defined atlases or form the basis for user-specific adjustments like the merging of VOIs.

Human atlases are defined in the *MNI space*

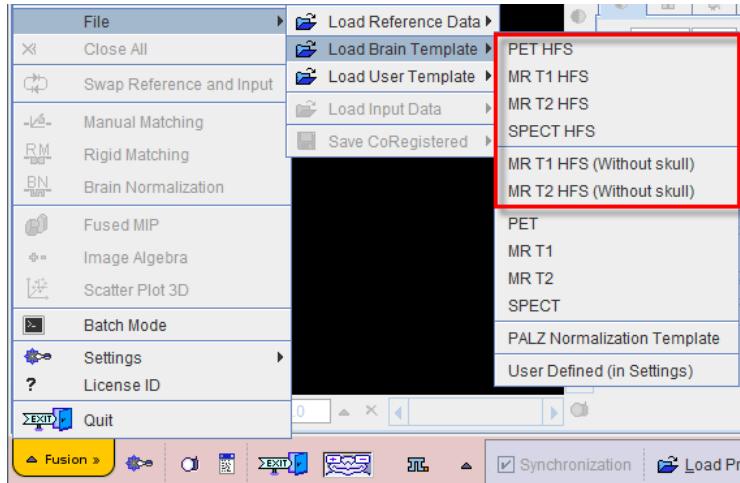
<http://www.nil.wustl.edu/labs/kevin/man/answers/mnispace.html> (Montreal Neurological Institute).

Single-Subject AAL Human Brain Atlas

For the analysis of human brain data the **AAL-VOIs** VOI atlas is available. It is the result of an automatic anatomical labeling [1] of the spatially normalized, single subject, high resolution T₁ MRI data set provided by the Montreal Neurological Institute (MNI)[2]. The atlas is provided in HFS orientation (radiological convention) in the *MNI atlas space* <http://www.nil.wustl.edu/labs/kevin/man/answers/mnispace.html>. All images which have been spatially normalized to one of the HFS templates in the fusion tool can be analyzed with the AAL atlas.

Spatial Normalization

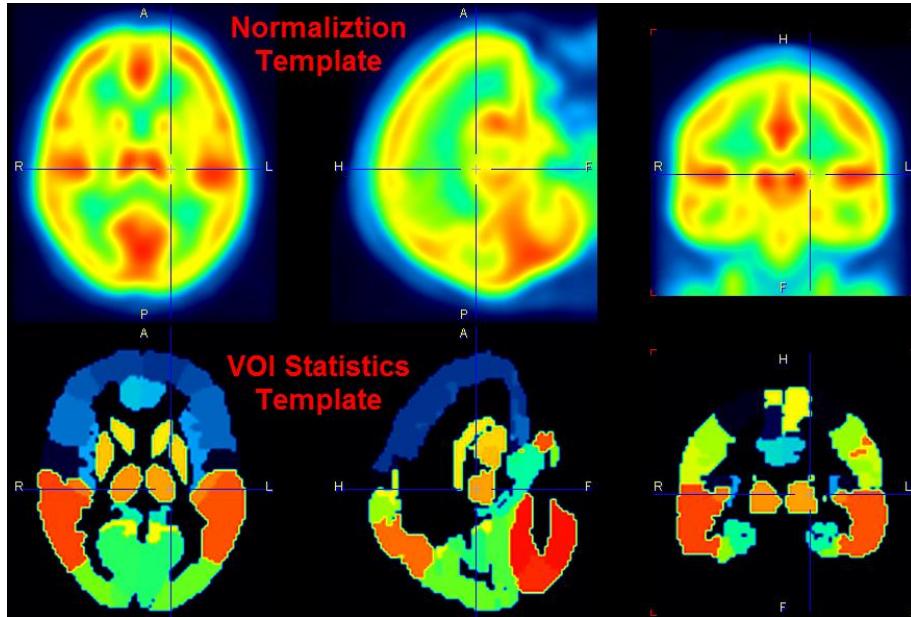
Several normalization templates are available in the fusion tool as menu entries **Fusion/File/Load Brain Template** as illustrated below.



The user should select the reference which is most similar to his experimental data. The images of these templates can be found in the *resources/templates* directory.

AAL VOI Atlas

For the statistical analysis, the **AAL-VOIs** VOI atlas can be selected in the list of included VOI atlases. The corresponding files can be found in the *resources/templates/voitemplates/AAL-VOIs* directory.



There is also the VOI template **AAL-Merged** available wherein some of the small AAL regions have been combined.

Note: There is a slight asymmetry in the AAL template VOIs which corresponds to the natural asymmetry of normal brains and which is also part of the MNI template. The resolution of the AAL atlas is 2mm in all directions. Stereotactic data with other resolution must be interpolated to 2mm and brought into HFS orientation in order to apply the AAL template within PMOD.

[1] Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in spm using a macroscopic anatomical parcellation of the MNI MRI single subject brain. Neuroimage 2002; 15: 273-289. **DOI** <http://dx.doi.org/10.1006/nimg.2001.0978>

[2] Collins DL, Zijdenbos AP, Kollokian V, Sled JG, Kabani NJ, Holmes CJ, Evans AC. Design and construction of a realistic digital brain phantom. IEEE Trans Med Imaging. 1998 Jun;17(3):463-8.

Sprague-Dawley Rat Brain Atlas (Schiffer)

For the analysis of rat brain data the **Px Rat (W.Schiffer)** [1] VOI atlas is available. We would like to thank Wynne Schiffer for providing the data and helping with the integrations. The atlas incorporates adult male Sprague-Dawley rats (250-300g, age 52-62 days). This template implements the Paxinos coordinates.

Spatial Normalization

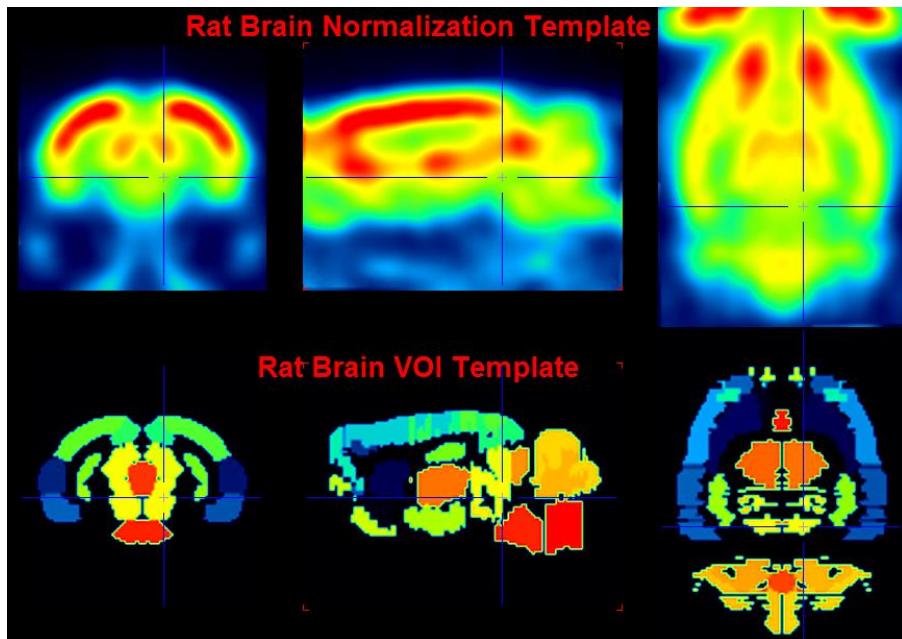
Three normalization templates are available in the fusion tool:

- » **Px Rat (W.Schiffer)-FDG:** This is an FDG PET template as illustrated below.
- » **Px Rat (W.Schiffer)-masked:** This is a masked version of the FDG PET which has been masked outside the brain. It may be helpful if the additional activity of the Harderian glands is not present in the rat images to be normalized.
- » **Px Rat (W.Schiffer)-T2:** This is a T₂-weighted MRI PET template which is in the same space as the PET templates.

The images of these templates can be found in the *resources/templates/usertemplates* directory.

VOI Atlas

The VOI atlas **Px Rat (W.Schiffer)** can be selected in the list of included VOI atlases. The corresponding files can be found in the *resources/templates/voitemplates/Px Rat (W.Schiffer)* directory.



Reference

- [1] Schiffer WK, Mirrione MM, Biegon A, Alexoff DL, Patel V, Dewey SL. Serial microPET measures of the metabolic reaction to a microdialysis probe implant. *J Neurosci Methods*. 2006;155(2):272-84. DOI <http://dx.doi.org/10.1016/j.jneumeth.2006.01.027>

Wistar Rat Brain Atlas (Tohoku)

Overview

The **Wistar Rat (Tohoku)** atlas was developed by Valdes-Hernandez et al [1] using 7T T₂-MRIs from 30 Wistar rats. The template image was constructed as a "minimal-deformation" template, and the coordinates are thus not in Paxinos space. In the same space, gray matter, white matter and CSF probability maps were calculated, so that the 3-probability maps normalization can be applied in addition to the template-based normalization. 48 bi-lateral cortical structures were digitized from the Paxinos atlas and registered them to the template image. This atlas can be used for VOI statistics and for the anatomical interpretation of fMRI results.

The atlas is distributed with PMOD by courtesy of Prof. Akira Sumiyoshi, Tohoku University, Japan (*atlas website* <http://www.idac.tohoku.ac.jp/bir/en/db/rb/101028.html>).

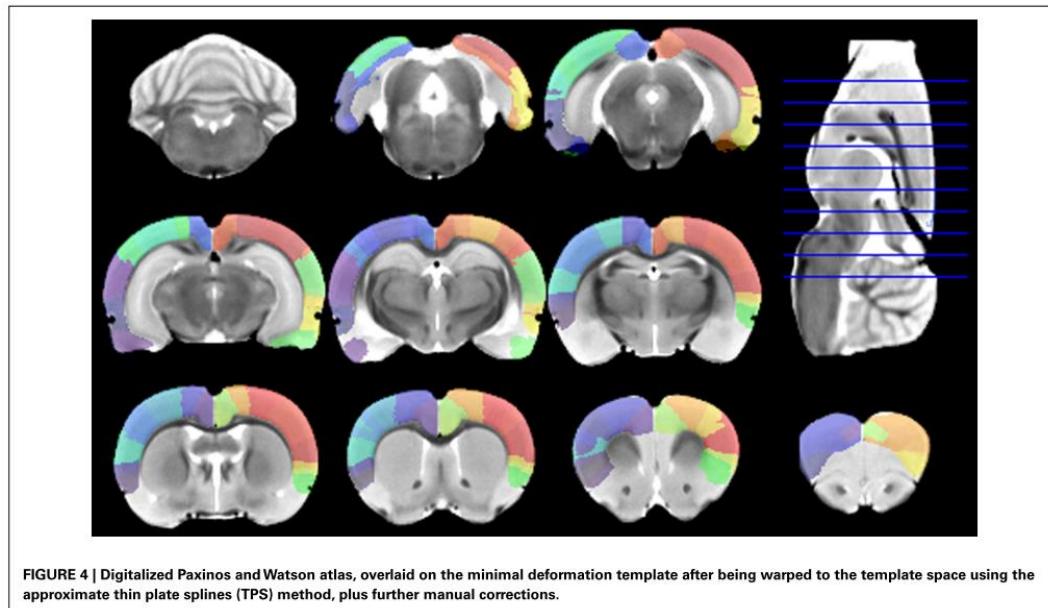


FIGURE 4 | Digitalized Paxinos and Watson atlas, overlaid on the minimal deformation template after being warped to the template space using the approximate thin plate splines (TPS) method, plus further manual corrections.

Spatial Normalization

Two normalization approaches are supported:

- » Template-based normalization using the **Wistar Rat (Tohoku)-MR** skull-stripped T₂-MR template illustrated above.
- » 3-tissue probability maps normalization using Gray matter, White matter and CSF combined in a single **tpm.nii** file.

The images of these templates can be found in the *resources/templates/voitemplates/Wistar Rat (Tohoku)* directory.

Reference

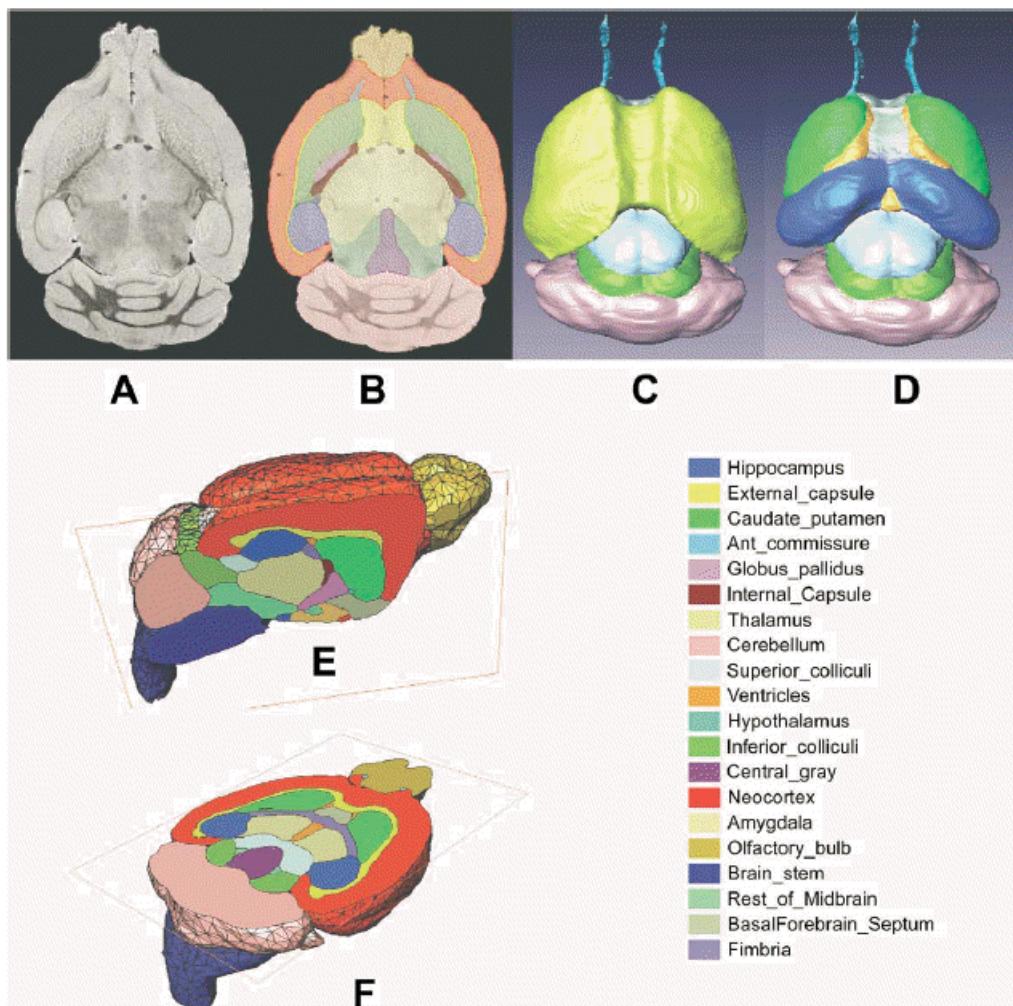
- [1] Valdes-Hernandez PA, Sumiyoshi A, Nonaka H, Haga R, Aubert-Vasquez E, Ogawa T, Iturria-Medina Y, Riera JJ, Kawashima R: An *in vivo* MRI Template Set for Morphometry, Tissue Segmentation, and fMRI Localization in Rats. *Frontiers in neuroinformatics* 2011, 5:26. DOI <http://dx.doi.org/10.3389/fninf.2011.00026>

Mouse Brain Atlas (Mirrione)

For the analysis of mouse brain data the **Mouse_M.Mirrione** VOI atlas [1,2] is available. It represents the minimum deformation atlas of 10 C57BL/6J mice (male, 12-14 weeks, 25-30g). We would like to thank Martine Mirrione for providing the data and helping with the integrations.

Y. Ma et al. / Neuroscience 135 (2005) 1203–1215

1207



Spatial Normalization

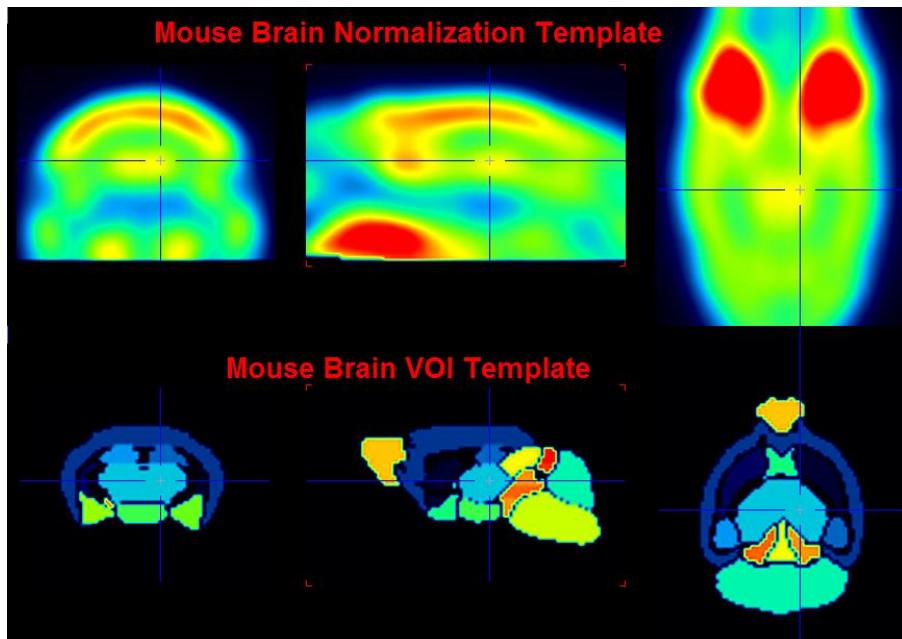
Two normalization templates are available in the fusion tool:

- » **Mouse_M.Mirrione-FDG:** This is an FDG baseline PET template as illustrated below.
- » **Mouse_M.Mirrione-T2:** This is a T₂-weighted MRI PET template which is in the same space as the PET templates.

The images of these templates can be found in the *resources/templates/usertemplates* directory.

VOI Atlas

The VOI atlas **Mouse_M.Mirrione** can be selected in the list of included template VOIs. The corresponding files can be found in the *resources/templates/voitemplates/Mouse_M.Mirrione* directory.



References

- [1] Ma Y, Hof PR, Grant SC, Blackband SJ, Bennett R, Slates L, McGuigan MD, Benveniste H. A three-dimensional digital atlas database of the adult C57BL/6J mouse brain by magnetic resonance microscopy. *Neuroscience*. 2005;135(4):1203-15. DOI <http://dx.doi.org/10.1016/j.neuroscience.2005.07.014>
- [2] Mirrione MM, Schiffer WK, Fowler JS, Alexoff DL, Dewey SL, Tsirka SE. A novel approach for imaging brain-behavior relationships in mice reveals unexpected metabolic patterns during seizures in the absence of tissue plasminogen activator. *Neuroimage*. 2007;38(1):34-42. DOI <http://dx.doi.org/10.1016/j.neuroimage.2007.06.032>

Cynomolgus Monkey Atlas

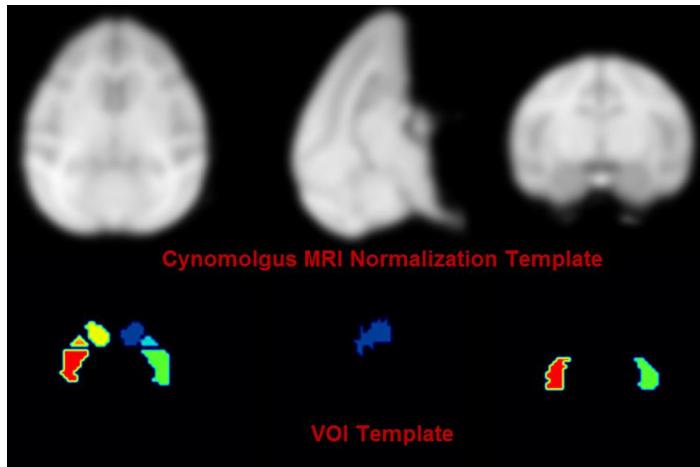
For the analysis of cynomolgus monkey (*Macaca Fascialis*) brain data the **Cynomolgus_CIMA-UN** VOI atlas [1] is available. We would like to thank Elena Prieto and Maria Collantes from the Centro de Investigacion Medica Aplicada (CIMA), Universidad de Navarra, for providing the data and helping with the integrations.

Spatial Normalization

A T_1 -weighted MRI normalization template created from 15 healthy animals is available as **Cynomolgus_CIMA-UN-MRI**. Two PET templates in the same space are also provided: **Cynomolgus_CIMA-UN-Dopa** and **Cynomolgus_CIMA-UN-DTBZ**.

VOI Atlas

The VOIs were hand drawn in the striatum (VOI size 400 mm³) and occipital lobe (VOI size 310 mm³) on axial MRI slices based on anatomical borders.



Reference

- [1] Collantes M, Prieto E, Penuelas I, Blesa J, Juri C, Martí-Climent JM, Quincoces G, Arbizu J, Riverol M, Zubietta JL, Rodriguez-Oroz MC, Luquin MR, Richter JA, Obeso JA. New MRI, 18F-DOPA and 11C-(+)-alpha-dihydrotetrabenazine templates for Macaca fascicularis neuroimaging: advantages to improve PET quantification. Neuroimage. 2009;47(2):533-9.
DOI <http://dx.doi.org/10.1016/j.neuroimage.2009.04.078>

Preparation of VOI Atlas Files for PMOD

Atlas Definition

VOI atlases can be easily prepared for use in PMOD. Three sets of data are required, the

- 1) *Atlas images:* They must be prepared as NifTI files and encode the atlas VOIs as numeric labels. Each pixel has a value of 0 if it is a background pixel, or is otherwise an integer number. We recommend using the HFS orientation (head first, supine = radiological convention) for human data.
- 2) *Label list:* A text file ending in .txt containing at least three columns. Each VOI is represented by a line of the form:

```
name1    label_name1    label_value1
name2    label_name2    label_value2
...

```

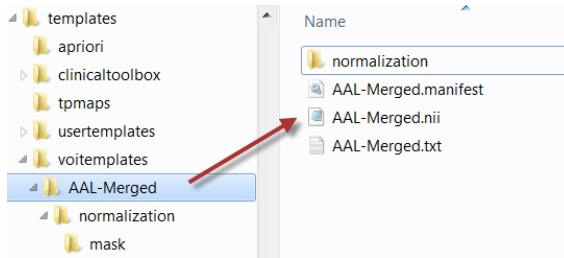
There must not be blank characters within the abbreviations or the names.
- 3) A manifest text file for the encoding of the species, for instance containing

```
SPECIES = HUMAN
```

The four species supported are HUMAN, PRIMATE, RAT, MOUSE.

Note that the name of the atlas sub-directory in *resources/templates/voitemplates* must also be used for the template images, the label list, and the manifest. This name then shows up in the list of available atlases in the VOI analysis tool.

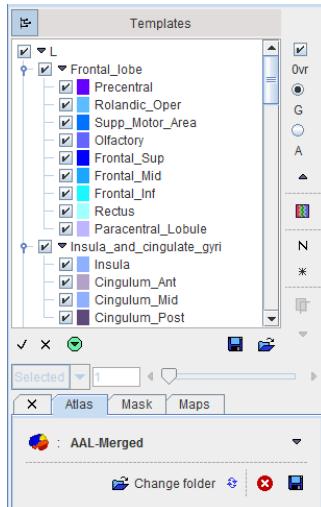
Included in the distribution are several templates. The naming and the arrangement of the files are illustrated below using the **AAL-Merged** atlas as an example.



The **AAL-Merged.txt** contains the following 5 columns. The first column starts with the name followed by a bracket construction which encodes a tree structure. For instance, **Precentral** belongs to the **Frontal_Lobe** which is located in the **L** or right **R** hemisphere. The second column indicates the name of a generated contour VOI. The third column contains the label value in the atlas file. Each pixel in **AAL-Merged.nii** with value 1 will belong to the **Precentral_1** VOI, pixels with value 2 to **Precentral_1**, etc.

Name	Outlined	Label	Color	Tooltip
Precentral[Frontal_lobe[L]]	Precentral_I	1	(100,0,255)	Precentral gyrus left (PRE)
Precentral[Frontal_lobe[R]]	Precentral_r	2	(100,0,255)	Precentral gyrus right (PRE)
Rolandic_Oper[Frontal_lobe[L]]	Rolandic_Oper_I	3	(93,188,255)	Rolandic operculum left (RO)
Rolandic_Oper[Frontal_lobe[R]]	Rolandic_Oper_r	4	(93,188,255)	Rolandic operculum right (RO)
Supp_Motor_Area[Frontal_lobe[L]]	Supp_Motor_Are_I	5	(0,114,255)	Supplementary motor area left (SMA)
Supp_Motor_Area[Frontal_lobe[R]]	Supp_Motor_Are_r	6	(0,114,255)	Supplementary motor area right (SMA)
Olfactory[Frontal_lobe[L]]	Olfactory_I	7	(100,100,255)	Olfactory cortex left (OC)
Olfactory[Frontal_lobe[R]]	Olfactory_r	8	(100,100,255)	Olfactory cortex right (OC)
Frontal_Sup[Frontal_lobe[L]]	Frontal_Sup_I	11	(0,0,255)	Superior frontal gyrus left (F1, F1O, F1M)
Frontal_Sup[Frontal_lobe[R]]	Frontal_Sup_r	12	(0,0,255)	Superior frontal gyrus right (F1, F1O, F1M)

The corresponding VOI atlas structure is illustrated below.

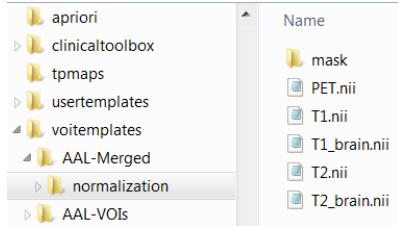


Normalization Files

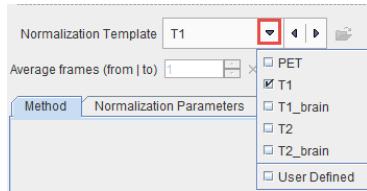
Atlases can only be applied to images if they have the same resolution and show the anatomy with the same geometry. Therefore, images originating from real experiments first need a normalization step for the atlas to be applied. This is done by calculating a normalization transform between the subject image and a "template" image representing the

standard anatomy imaged with a certain modality, and using it for warping the VOIs to the subject anatomy.

Appropriate template images need to be copied to a **normalization** sub-folder. In the example below **normalization** contains T1 and T2 MR templates with and without skull, as well as a PET template. All of these templates show the anatomy in the MNI space in which the AAL VOIs were defined.



Correspondingly the **Normalization Template** list has the following entries.

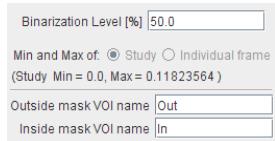


The normalization works best if the information is restricted to the relevant image part. Therefore, **normalization** should contain a **mask** sub-folder with a mask file **mask.nii** containing 1 for all relevant pixels and 0 for all others.

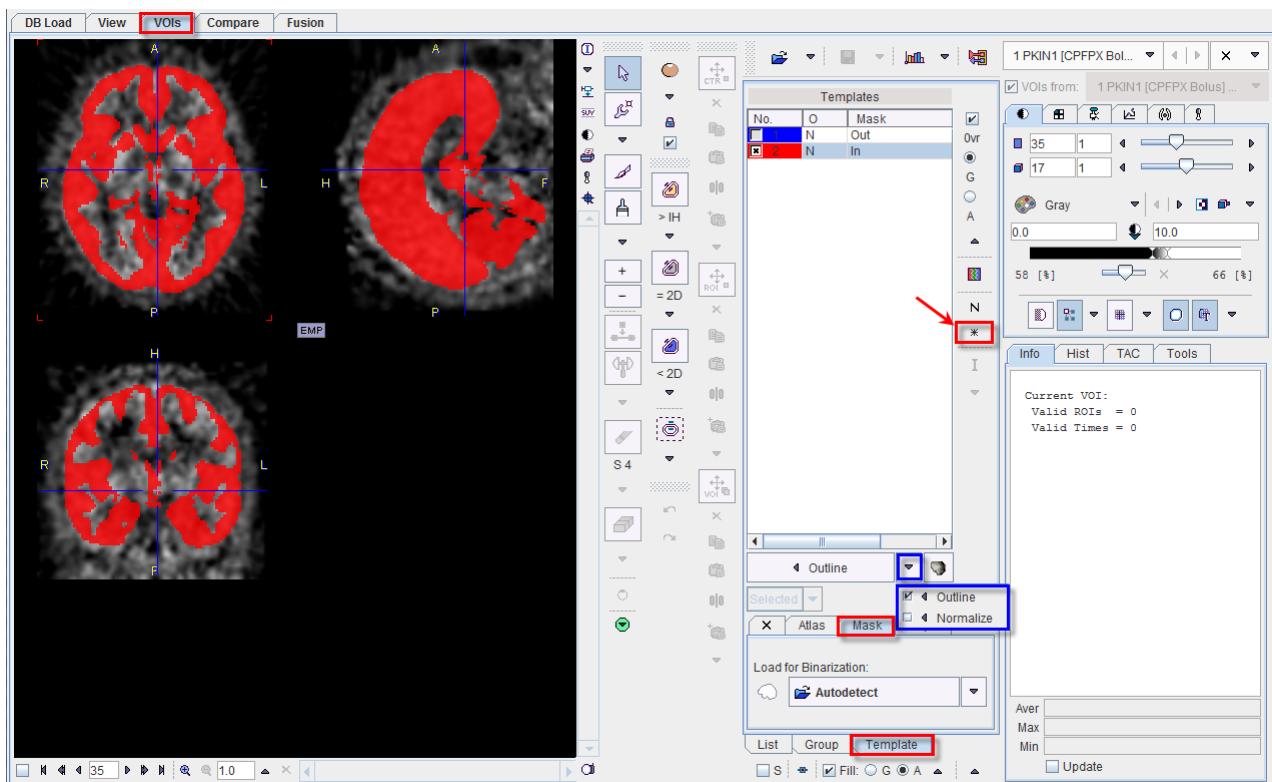
Using Mask Files

Standard templates can only be created and applied if it is possible to reliably map the organ of interest to a standard anatomy. Otherwise, masks created by some sort of thresholding or segmentation are often useful in individual analyses. Such binary masks can also be used for statistics calculations in PMOD.

To load a mask for VOI analysis first select the **Template** tab, and then **Mask**. A loading button becomes active and allows to loading a binary file. If the data in the file is not binary a dialog window appears



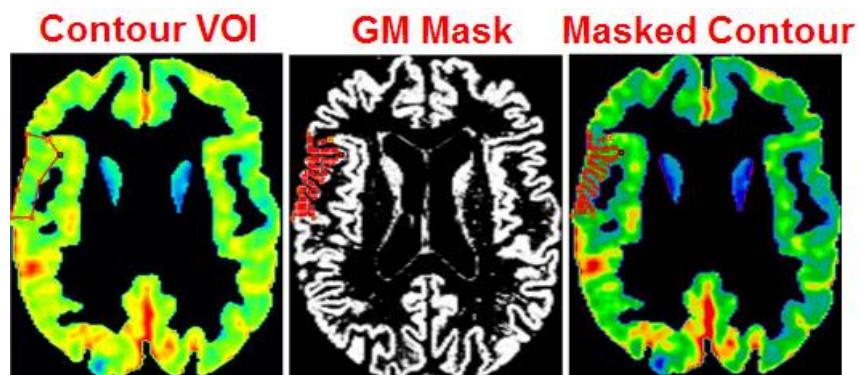
for defining the **Binarization Level [%]** and the names for the mask and the background.



A mask template only contains two VOIs, the **Mask** pixels **In**, and all background pixels **Out**. Most of the times only the **In** region will provide reasonable values, but the **Out** region can also be evaluated on demand.

The same operations are supported as for the *template VOIs* (on page 254): statistics can be calculated in the mask VOIs, contour VOIs can be defined in parallel and masked, and mask VOIs can be converted to contour VOIs by the **Outline** or **Normalize** option button. A notable application of masking is the restriction of contour VOIs to the gray matter pixels which can easily be achieved if a gray matter segment is available from a matched MRI data

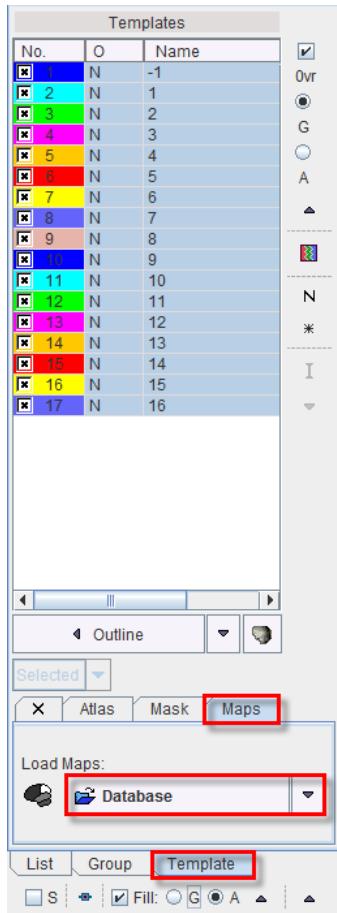
set. An example of restricting a contour VOI shown on a PET to gray matter is illustrated below.



Using Label Maps Files

A map is a file which contains integer pixel values called object labels. The labels typically identify different objects in the image volume. Such maps are often the product of segmentation procedures.

PMOD is able to load and analyze map files and create a template VOI out of it. The functionality is located on the **Template** panel, in the **Maps** sub-panel as illustrated below.



To load a map file choose the file format in the **Load Maps** area and select the map file. A dialog window appears which allows specifying the bin size for the label histogram.



A **Step value** of 1 should normally work fine. The file is scanned and for each label found a list entry is created in the **Templates** list. Now the names can be edited, the VOIs outlined and further used as for the prepared *template VOIs* (on page 254).

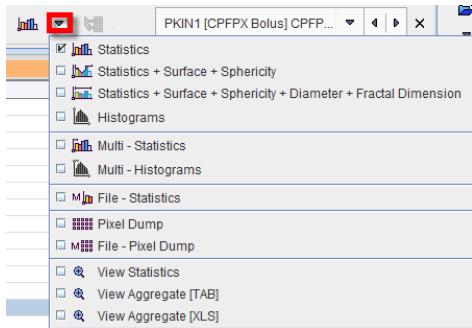
AnalyzeAVW Object Maps

Using the **Autodetect** format, PMOD can directly load AnalyzeAVW object maps (*.obj). It will not only create the VOIs, but also restore the VOI names and the VOI colors.

Applying VOI Definitions

Statistics

There is a multitude of ways how VOIs can be applied to images for calculating statistical measures which are available via the **Statistics** function button on the VOI panel.



Modes of Statistics Calculation

The following statistics modes are supported:

- » **Statistics:** Apply the VOIs to the current image and show the resulting statistics on a panel.
- » **Multi-Statistics:** Apply the VOIs to all loaded images and show the resulting statistics on one panel per image. The outcome can then easily be merged into an aggregate.
- » **File-Statistics:** Apply the VOIs to a set of image files and save the resulting statistics in a file. This procedure requires explicit image loading and is most useful when the images are in a normal (e.g. MNI) space, so that a standard set of VOIs can be applied.
- » **Pixel Dump:** Extract the values in all classified VOI pixels of the selected image and save the values together with the pixel coordinates in a file. This procedure gives the user the full raw data and allows him implementing his own statistical analysis.
- » **Histograms:** Extract the values in all classified VOI pixels and calculate a histogram per VOI showing the value distribution.

VOIs used for Statistics

The following VOIs are considered in the interactive statistics calculation:

- » All contour VOIs on the **List** tab.
- » The VOI named **Group** which consists of all the contour VOIs selected on the **Group** tab.
- » If on the **Template** tabs **Atlas** or **Mask** is active, the corresponding VOIs are also considered. Please enable the **Ovr** box to see these VOIs in the overlay.
- » If a masking operation is configured on the **Atlas** or **Mask** sub-tab, it is applied to the contour VOIs during the statistics. Please enable the **Fill ROI** box to verify the actual coverage of the masked contour VOIs.

Statistics Measures

Except for the **Pixel Dump** different levels of statistics can be collected:

- » **Statistics:** Standard descriptive statistics measures.
- » **Statistics + Surface + Sphericity:** Standard descriptive statistics measures, a VOI surface estimate and an index of how sphere-shaped the VOI is.
- » **Statistics + Surface + Sphericity + Diameter + Fractal dimension:** As above, plus the maximum VOI diameter and the fractal dimension.

The selected statistic type is calculated for each VOI.

Statistics Measures

The following basic descriptive statistics are calculated using the values of all pixel classified for a VOI. With binary *classifications* (on page 212) each included pixel contributes equally. Pixels with NaN value are excluded from statistics. Correspondingly, they don't contribute to **Volume** or **NumberOfPixels**.

With the **Fraction mode** classification, however the contribution of a pixel is proportional to the fractional area f_i included in the contour ($f_i=1$ fully included, $f_i=0.5$ 50% included). This weighting applies for the **Average**, the **Standard Deviation**, the **Volume**, the **Total** and the **AUC**. For the other measures, which don't support fractional contributions, only the pixels with $f_i>0.5$ are used.

The statistics calculation using a *probabilistic atlas* (on page 261) is similar to the fraction mode. The contribution of a pixel is proportional to its probability p_i for belonging to the VOI ($p_i=1$ certainly included, $p_i=0.5$ included with 50% probability). For measures, which don't support fractional contributions, only the pixels with probability above a user-defined threshold ($p_i>p_t$) are used.

Notes:

1. Due to calculation of the fractional area, statistics using the **Fraction mode** is substantially more time-consuming.
 2. The fraction mode is not effective for automatically generated VOIs (iso-contouring, atlases), because the contours follow the pixel boundaries.
-

Averaged	Average of the pixel values. Fraction mode: $\text{Sum}(f_i \cdot v_i) / \text{Sum}(f_i)$. v_i value of pixel i. Probabilistic atlas: $\text{Sum}(f_i \cdot p_i) / \text{Sum}(p_i)$. p_i probability of pixel i for belonging to VOI_i .
Sd	<p>Population standard deviation of the pixel values.</p> $\sigma = \sqrt{\frac{\sum(X - \mu)^2}{n}}$ <p>Fraction mode: a weighted standard deviation is <i>calculated</i> http://en.wikipedia.org/wiki/Weighted_arithmetic_mean#Weighted_sample_variance accounting for the pixel area included in the contour.</p> <p>Probabilistic atlas: a weighted standard deviation is <i>calculated</i> http://en.wikipedia.org/wiki/Weighted_arithmetic_mean#Weighted_sample_variance accounting for the probability of pixel i for belonging to VOI_i.</p>

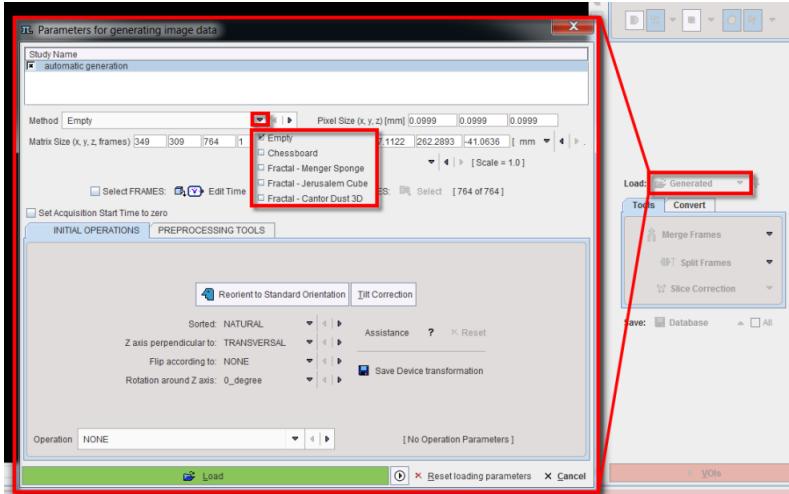
Stdv	Sample standard deviation of the pixel values. $s = \sqrt{\frac{\sum(X - \bar{X})^2}{n - 1}}$ <p>Fraction mode, Probabilistic atlas: analogous to Sd.</p>
Volume	Volume of the VOI pixels. It is based on the pixel size in x and y and the slice thickness in z. Fraction mode: $\text{Sum}(f_i) * \text{pixel-volume}$. Probabilistic atlas: $\text{NumberOfPixels} * \text{pixel-volume}$.
Total(SUM)	Sum of the pixel values. The interpretation depends on the image contents. In the case of activity units the result will be total activity in the VOI. Fraction mode: $\text{Sum}(f_i * v_i)$, Probabilistic atlas: $\text{Sum}(p_i * v_i)$.
Total(AVR*VOL)	Average of the pixel values multiplied by the VOI volume. The interpretation depends on the image contents. In the case of activity <i>concentration</i> units, the result represents total activity in the VOI. Fraction mode: $\text{Sum}(f_i * v_i) * \text{pixel-volume}$, Probabilistic atlas: Average*Volume . In the case of SUV units, the result is called <i>Total Lesion Glycolysis (TLG)</i> . The TLG is usually calculated in combination with a lower range.
Min	Minimum pixel value. Fraction mode: Considers pixels with $f_i > 0.5$. Probabilistic atlas: Considers pixels with $p_i > p_t$.
Max	Maximum pixel value. Fraction mode: Considers pixels with $f_i > 0.5$. Probabilistic atlas: Considers pixels with $f_i > p_t$.
NumberOfPixels	Number of pixels included in the VOI. Fraction mode: Considers pixels with $f_i > 0.5$, Probabilistic atlas: Considers pixels with $p_i > p_t$.
NumberOfEffect ivePixels	Fraction mode: $\text{Sum}(f_i)$. Probabilistic atlas: $\text{Sum}(p_i)$. Otherwise equal to NumberOfPixels .
HotAveraged	The highest pixel values averaged. The default Number of Hottest Pixels values to be averaged can be set in the <i>User configuration</i> (on page 20), and can be changed in the upper part of the statistics window. Fraction mode: Considers pixels with $f_i > 0.5$. Probabilistic atlas: Considers pixels with $p_i > p_t$.
Q1	First quartile of the VOI pixel values. Fraction mode: Considers pixels with $f_i > 0.5$. Probabilistic atlas: Considers pixels with $p_i > p_t$.
Median	Median value of the VOI pixel values. Fraction mode: Considers pixels with $f_i > 0.5$. Probabilistic atlas: Considers pixels with $p_i > p_t$.

Q3	Third quartile of the VOI pixel values. Fraction mode: Considers pixels with $f_i > 0.5$. Probabilistic atlas: Considers pixels with $p_i > p_t$.
AreaUnderCurve	Static data: Averaged times frame duration. Fraction mode: $\text{Sum}(f_i * v_i * t) / \text{Sum}(f_i)$ ($t = \text{acquisition duration}$). Probabilistic atlas: $\text{Sum}(p_i * v_i * t) / \text{Sum}(p_i)$. Dynamic data: Integral of the Averaged curve.
HypoxiaIndex	Fraction of pixels in the VOI which have a value above the threshold in the Hypoxia Threshold field. Fraction mode: Considers pixels with $f_i > 0.5$. Probabilistic atlas: Considers pixels with $p_i > p_t$.
HypoxicVolume	Represents the number of voxels inside a VOIs with value greater than the hypoxia threshold multiplied by the volume of the pixel size. Fraction and the Binary mode - consider only the voxels with $f_i > 0.5$.
NumberOfNaNs	Represents the number of voxel with NaN value inside the VOI
VolumeWithoutNaNs	Volume of the VOI pixels which value is different from NaN. It is based on the pixel size in x and y and the slice thickness in z. Fraction mode: $\text{Sum}(f_i) * \text{pixel-volume}$.

Additional Measures

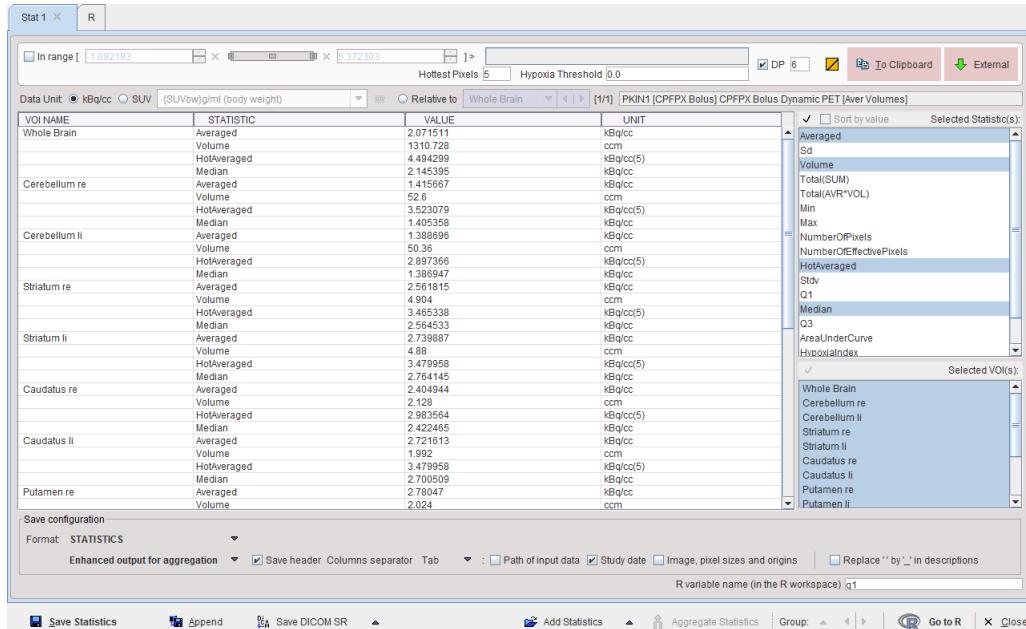
The following additional VOI measures can be obtained with the corresponding statistics button:

SurfaceArea	Estimate of the VOI surface which is obtained by triangulating the contours and accumulating the triangle areas. Fraction mode: Considers pixels with $f_i > 0.5$.
Sphericity	Index of how spherical a VOI is. The values range between 0 and 1 (perfect sphere). <i>Wikipedia</i> http://en.wikipedia.org/wiki/Sphericity . Fraction mode: Considers pixels with $f_i > 0.5$.
DiameterMax	Maximal distance between any two pixels in the VOI. The calculation can take substantial time and is restricted to VOIs enclosing less than 100'000 pixels. Fraction mode: Considers pixels with $f_i > 0.5$.

<h3>Fractal Dimension (FD)</h3>	<p>Measures the complexity of a 3-dimensional structure, approximated by a sphere, by calculating its box-counting dimension.</p> <p>Is an index for characterizing fractal patterns or sets by quantifying their complexity as a ratio of the change in detail to the change in scale. <i>Wikipedia</i> https://en.wikipedia.org/wiki/Fractal_dimension. It does not provide an absolute quantification and it is a real value between 0 and 3. Small values of FD in 3D VOIs indicate a complex structure. Fraction mode: considers pixel with $f_i > 0$.</p> <p>For 2-dimensional ROIs (ROIs on one slice) the FD value is between 0 and 2.</p> <p>A convenient tool, the fractal generator, is available in Pmod. It is accessible with the Load button configured on Generated:</p>  <p>The tool allows creating data with well known fractals like Menger Sponge, Jerusalem Cube, Cantor Dust 3D. The FD value calculated with PMOD for a known fractal structure is very similar to the theoretical value. <i>Wikipedia</i> https://en.wikipedia.org/wiki/List_of_fractals_by_Hausdorff_dimension. The difference is due to the limited sample size.</p>
FD_LConfidence Interval	Low confidence interval of the FD. Fraction mode: considers pixel with $f_i > 0$.
FD_HConfidence Interval	High confidence interval of the FD. Fraction mode: considers pixel with $f_i > 0$.

Statistics Viewer

The dialog window for the statistics output is illustrated below. The R page only appears when **R statistics** (on page 306) is enabled.



The calculated information is comprehensive and can be tailored by several user interface elements.

Selected Statistics

The list to the right shows all available statistics figures. It serves for selecting the statistics of interest. Only the selected elements are being shown in the table and will be exported. The default selection includes the **Averaged** and the **Sd**.

Selected VOIs

The second list in the lower right shows all available VOIs which were evaluated as well as a **Group** element. Only the selected elements are shown in the table and will be exported.

Range Restriction

Note the **In range** box which allows restricting the statistics to the subset of pixels with values in a specific range. For example, by setting the lower threshold to 40% of the maximum it is possible to calculate the average value and the volume of all pixels above 40%.

SUV Statistics

If the statistics are calculated for activity concentration images, the uptake results can be converted to different types of **SUV** (on page 136) images under the condition that the related activity information is available in the image header. If not, but the information is available, it can be entered after activating the SUV button



SUVR Statistics

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 other statistical measures.



Saving Options

There are several options to choose from when saving the statistics. The **Format** selection has three choices.



STATISTICS is a tabular text file format aimed at statistics programs. **PKIN TAC(s)** is aimed at loading the saved information as tissue curves into the kinetic PKIN tool. **PXMod TAC** will only export the time-activity curve of the **Group** VOI in a two-column format. This data is intended for use in the pixelwise modeling tool PXMOD.

The second option choice



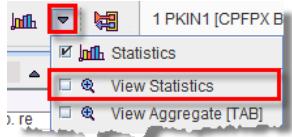
is only available for the **STATISTICS** output. The **Enhanced output for aggregation** is the recommended format, whereas the **Include additional** options allows adding some additional pieces of information like data path or pixel size.

Please use **Save** for saving the data in a new tab-delimited text file with extension **.voistat**, and **Append** for appending it to an existing statistics file. Furthermore, the statistic results can be saved as a DICOM Structured Report with the **Save Dicom SR** option or directly sent to a DICOM server with the **Export Dicom SR**.

Load Statistics Files

Statistics files saved in the **STATISTIC/Enhanced output for aggregation** format can be loaded back into the statistics viewer. There are several ways to do so:

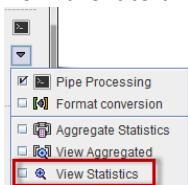
from the VOI interface using the **View Statistics** option in the **Statistic** selection list;



- 1) from the open statistics viewer using the **Add Statistics** option



- 2) from the lateral taskbar of the PVIEW tool



Multiple Statistics

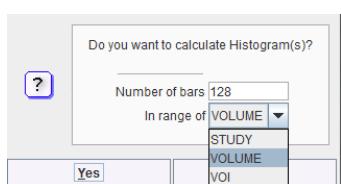
If the statistics is calculated for multiple files, the results are shown in the statistics viewer on separate pages. Similarly, when loading a statistics from a file, a new page is added to the statistics viewer. In this case, the **Aggregate Statistics** button becomes active and allows creating an aggregate from all open statistics pages.

Transfer to R

The statistics viewer includes an interface to the R statistics environment, if this feature is configured. The **Go to R** button will transfer the statistics of all open data to the **R console** (on page 310) creating one R variable per tab with the name taken from the **R variable name** field.

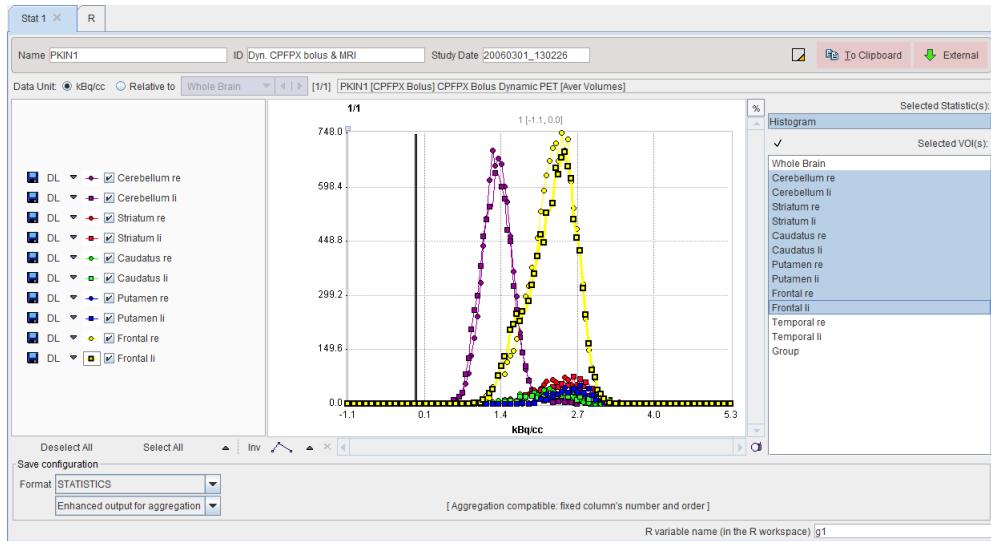
Histogram

The **Histogram** mode analyzes the distribution of pixel values in the VOI by sorting them into a number of value ranges (bins) with equal width. The bin width is obtained by dividing the overall value range by the **Number of bars**. There are three options for defining the overall value range:



STUDY uses the min/max values of the entire data set, **VOLUME** the min/max of the current frame, and **VOI** the min/max of all pixels enclosed by a VOI. The appearing dialog

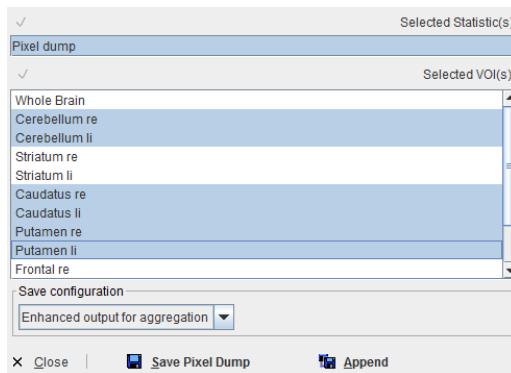
window represents the VOI histograms as curves with the mid-value of the bin on the x-axis, and the number of pixels with values in the bin range on the y-axis.



The histograms can be saved and exported in various ways, as statistics or curves.

Pixel Dump

The **Pixel Dump** serves for saving the raw values of all classified VOI pixels into a file. It shows a dialog window for defining the VOI selection.



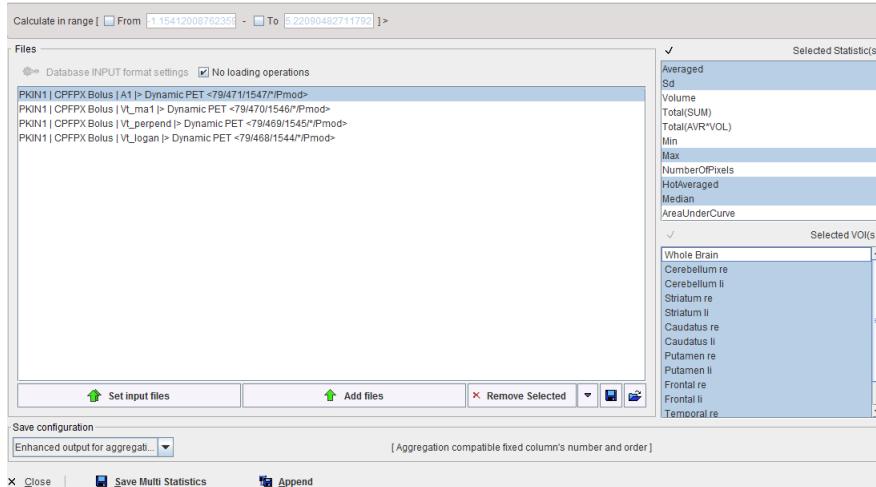
The results can be saved to a new file or appended to an existing one. The output has a tabular format, with the main part being the pixel coordinates and the value.

X [pixel]	Y [pixel]	Z [pixel]	Value [kBq/cc]
28	50	36	2.51422
28	51	36	2.506756
28	52	36	2.645055
28	53	36	2.725984
29	45	36	2.522795
29	46	36	2.58447
29	47	36	2.823405

It can easily be imported into statistics programs for a detailed analysis of the value distribution.

File-Based Statistics

The **File Statistics** allow applying the same statistics to a set of files in a batch mode operation. A dialog window appears for selecting the VOIs of interest and the files to be processed. Note that only files in a same format as the open image with the VOIs can be used.



No loading operations If the box is checked the image are loaded without any data transformation. Otherwise a pre-processing can be specified using the **INPUT format settings** button.

Set Input files For selecting the images to be analyzed.

Add files For adding additional files to the list.

Remove selected For removing the selected files from the list.

Remove all Clears the file list.

For saving the file list as a configuration.

For loading a list configuration.

After activating **Save**, PMOD will prompt for an output file name, and the calculations will be started.

Time-Activity Curve Generation with Transfer to PKIN

An important usage of the VOI analysis is the generation of time-activity curves (TAC) for subsequent kinetic modeling. This can easily be achieved in PVIEW by the following steps

VOI Definition

The image data is loaded as a dynamic series with the *correct acquisition times* and the *correct input units*. This is important, because otherwise the acquisition start/end times in kinetic

modeling will be wrong, and the TACs may be different in magnitude with respect to the blood data. Such problems result in erroneous model parameters.

In dynamic image series there is generally not enough anatomical information to delineate VOIs. Often, averaging of a subset of the acquisition frames resolves the problem. The VOIs are then delineated in the summed images, transferred to the dynamic images, and optionally saved to a file.

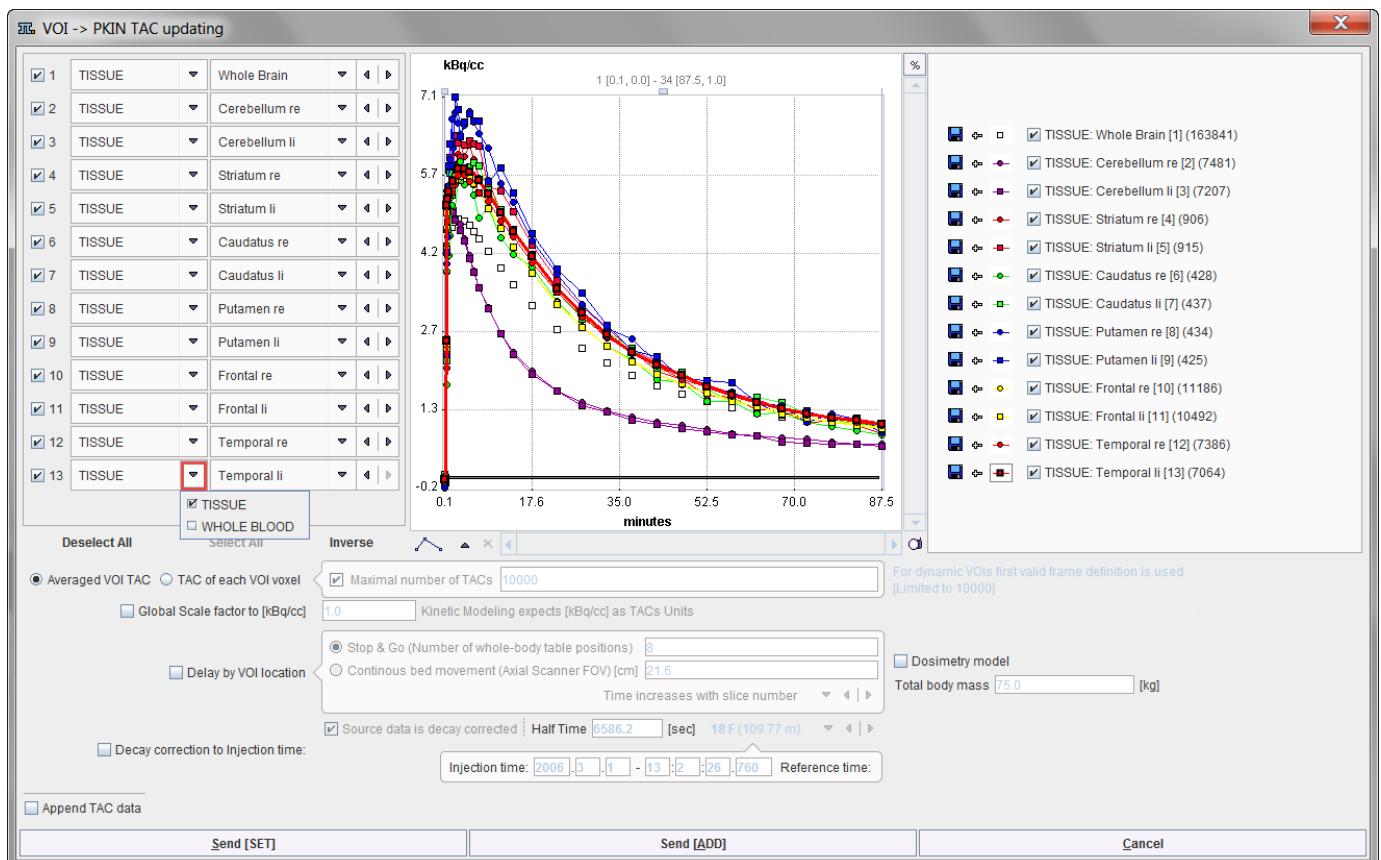
TAC generation

Switch the tool to the dynamic study, and activate the button



A dialog window appears which is organized in three panels:

- 1) The left area allows defining the proper type (TISSUE, WHOLE BLOOD) of the calculated TACs and selecting the regions to be sent to the **Kinetic modeling** tool.
- 2) The central area shows the TACs.
- 3) The right area controls the displayed TACs. Additionally, the +- buttons allow for simple arithmetic operations with the curve values before transfer to PKIN.



Average TACs

The standard and default procedure is to use the signal average in the VOIs, corresponding to the radio button **Averaged VOI TAC**. With this setting, not only the average is calculated

and transferred, but also the standard deviation which may be used for weighted fits in PKIN.

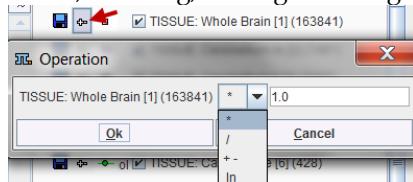
Voxel-wise TACs

When the transfer mode is set to **TAC of each VOI voxel**, the individual voxel-wise TACs are transferred. There is a maximum number of TACs which will be considered for the transfer, per default set to **10'000**. The number of voxels in the selected VOIs is shown in brackets in the control section. Naturally, the standard deviation is zero in this case.

TAC Value Operations

The calculated TAC values can be modified in two ways.

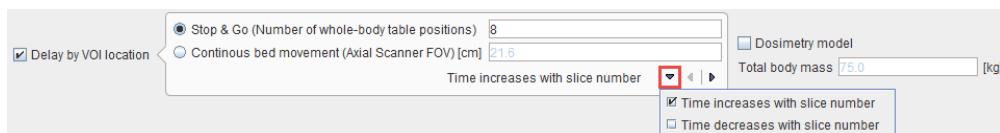
- 1) Every individual curve has a **+-** button which allows multiplying the values with a factor, dividing, adding or taking the logarithm.



- 2) All generated curves can be scaled with a factor defined by the **Global scale factor to kBq/cc** option.

TAC Time Shifting

If image data acquisition requires multiple table positions (e.g. dynamic whole-body PET), the timing between VOIs may differ. The timing relative to the injection is crucial for modeling and also for dosimetry. Therefore, the **Delay by VOI location** option is supported



with two alternatives:

- **Stop & Go** corresponds to the standard acquisition mode with the table halting in adjacent, overlapping field of views. As there is usually not enough information in the image headers to know for each slice the exact timing, the timing of the different table positions is obtained by dividing the acquisition duration by their number.
- **Continuous bed movement** assumes that the patient is scanned while the table is continuously moving. Here the axial scanner field of view is required for approximating the time when a VOI is scanned.

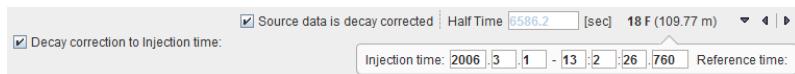
Note that the timing derived from these settings can only be approximate and may need correction. The resulting timing of the TAC curves is updated in the curve window whenever one of the settings is changed. Depending on the scanning, the time shifts may be applied in the wrong direction. For instance, the bladder curve may start before the brain curve although the data was acquired in head-in position. To rectify such a case there is a switch **Time increases with slice number/Time decreases with slice number**.

Dosimetry Model

If the flag **Dosimetry model** is enabled, the **OLINDA Residence Times** model will be set after the TAC data have been transferred to the PKIN tool together with the **Total body mass** of the patient. This information is extracted from the demographic information in the image, and can be edited if it is not present.

Decay Correction

If the **Decay correction to Injection time** flag allows correcting the TACs to a n injection time which may be before the first acquisition. If the **Source data is decay corrected**, only a scaling factor is applied. Otherwise, a time-dependent correction is used.



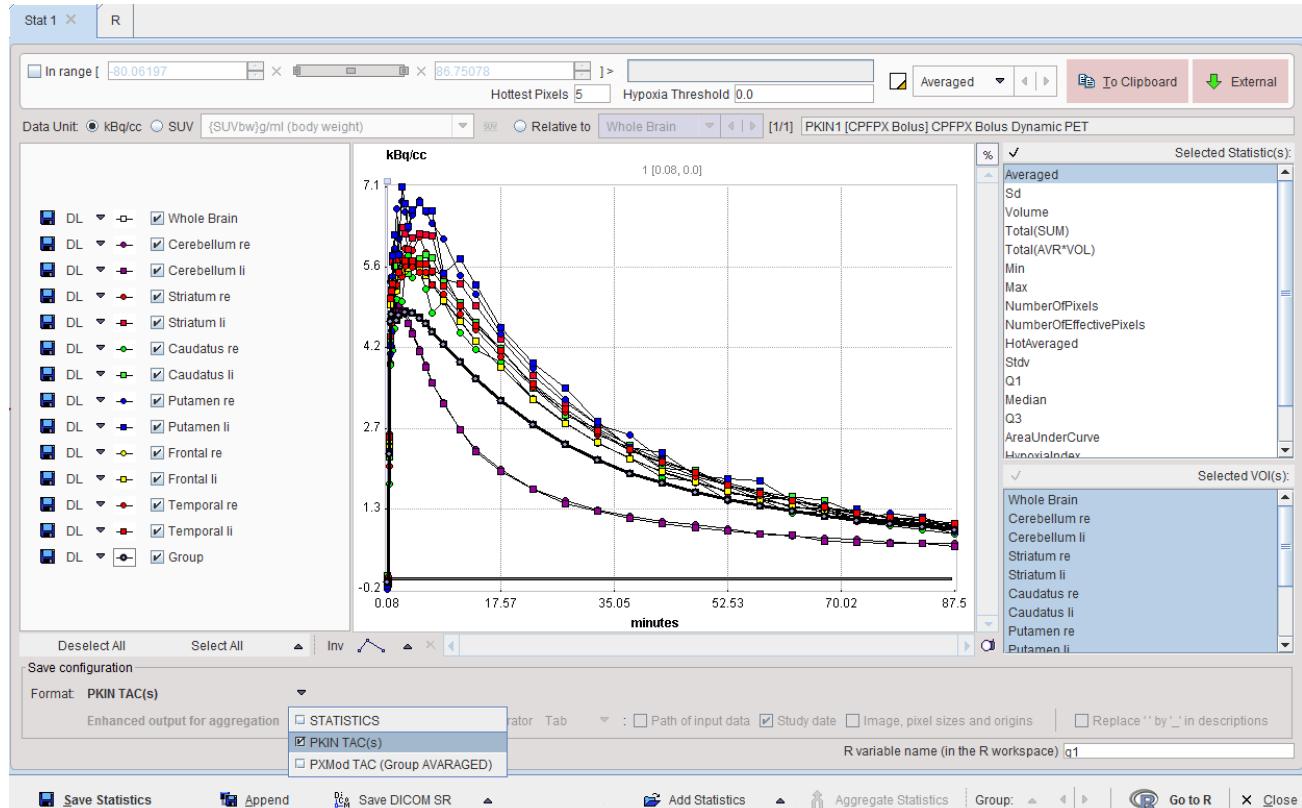
Data Transfer

The **Send** buttons initiate the transfer of the activity curve data to the PKIN tool. Selecting **Send[SET]** transfers the TACs to the currently selected tab in an open PKIN tool. With the **Append TAC Data** box checked, the curves are appended as new regions to the existing data, otherwise the current data is over-written. **Send[ADD]** first creates a new tab in PKIN, to which the data is added. If PKIN is not running, the tool is first started and the data added.

Both the average value and the standard deviation within the VOIs are transferred, as well as patient and study related information. The standard deviation may be used for weighted fits in PKIN.

Time-Activity Curve Generation with Statistics

If the PKIN option is not available, the TACs of a dynamic series can also be obtained with the regular statistics button , resulting in the dialog window illustrated below.

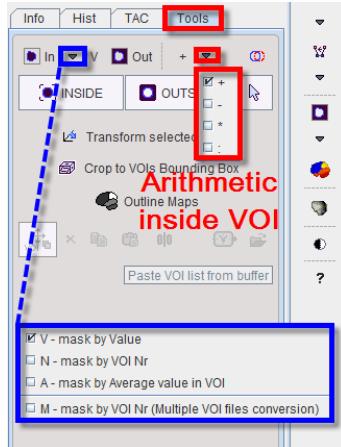


In **Selected Statistic(s)** enable the **Averaged** entry, choose the **PKIN TAC(s)** format and then use **Save Statistics** to create a simple text file with VOI average values at the different acquisitions in the columns as illustrated below. This file can directly be loaded in PKIN.

start[seconds]	end[kBq/cc]	Group	Whole Bra	Cerebellum re	Cerebellum li	Striatum re	Striatum li	Caudatus re	Caudatus li	Putamen re	Putamen li	Frontal re	Frontal li	Temporal re	Temporal li
0	10	-0.05713	-0.05709	-0.06256	-0.06269	-0.10772	-0.03457	-0.04228	0.066949	-0.18658	-0.12335	-0.04016	-0.04073	-0.071	
10	20	0.015029	0.014963	-0.05756	-0.0629	-0.073	-0.05132	-0.13887	-0.06886	-0.01763	-0.07502	0.044762	0.03986	0.0469	
20	30	2.269081	2.268364	2.433337	2.223745	2.041686	2.306371	1.707154	2.196768	2.352334	2.473349	2.396696	2.498618	2.6163	
30	40	4.65126	4.648449	5.370504	5.071967	3.899469	4.365991	3.856465	4.28211	4.058806	4.224457	4.685052	4.953163	5.1015	
40	50	4.784605	4.783243	5.207803	5.413832	4.195986	4.630343	3.896166	4.27838	4.47612	4.986944	4.939526	5.2229	5.0996	
50	60	4.719459	4.719956	5.263382	5.294201	4.78192	5.719754	4.119841	5.43466	5.468351	5.835935	5.257427	5.173898	5.2438	
60	80	4.731911	4.733198	5.265077	4.988845	5.200914	5.937181	4.517336	5.653295	5.964794	6.205755	5.262044	5.28565	5.2713	

Masking Inside and Outside of VOIs

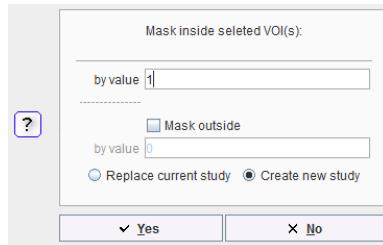
The VOI Tools tab offers some **Masking & Algebra** functions. They will be applied to the selected VOIs when the **List** or **Group** tab is active, and also to the selected VOIs when using a **Template** or a **Mask**.



The buttons have the following function:

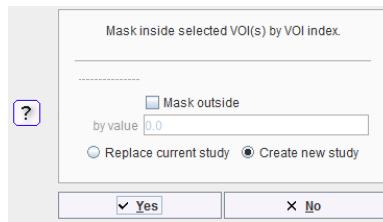
Mask voxels inside. This button replaces the values of all pixels within a VOI by a constant value. There are four variants:

- 1) If the configuration is set to **V**, the selected VOI will be filled with the value entered in the **by value** number field as shown below:



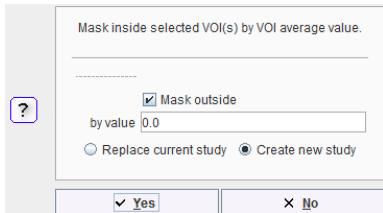
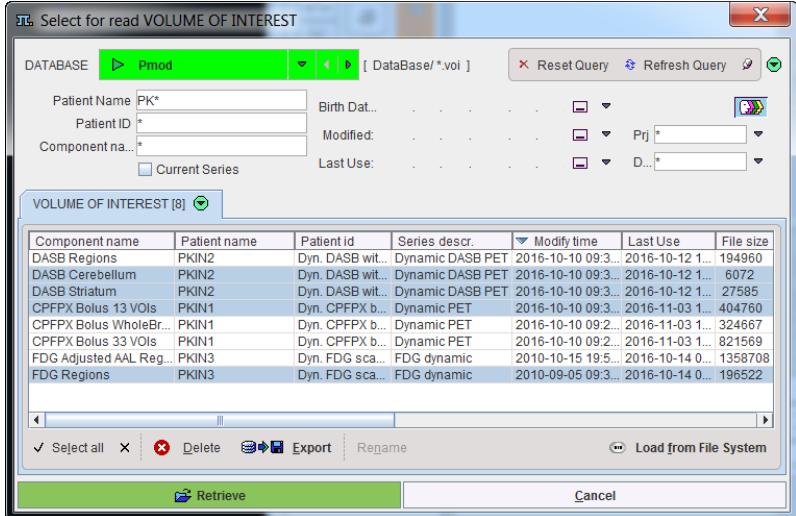
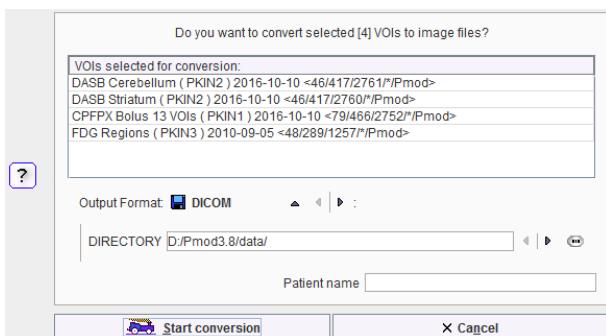
Optionally, the values of all pixels outside the VOI can be replaced by a specified constant value if the **Mask outside** box is enabled and a number is entered in the **by value** number field.

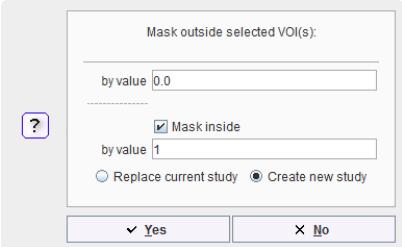
- 2) If the configuration is set to **N**, then the selected VOI(s) will be filled with sequential number VOI numbers starting from 1.



Optionally, the values of all pixels outside the VOI can be replaced by a specified constant value if the **Mask outside** box is enabled and a number is entered in the **by value** number field.

- 3) If the configuration is set to **A** then the selected VOI(s) will be filled with the

	<p>average value in VOI.</p>  <p>Optionally, the values of all pixels outside the VOI can be replaced by a specified constant value if the Mask outside box is enabled and a number is entered in the by value number field.</p>
4)	<p>The M selection allows converting multiple *.voi files in images.</p> <p>With the selection set to M, a dialog window opens allowing to select multiple *.voi files with <i>CTRL+click</i>.</p> 
Out	<p>Once the Retrieve button is activated a dialog window opens allowing settings for the image Output Format and the Directory location for the image saving.</p>  <p>The conversion is started with the Start conversion button.</p> <p>Mask voxels outside. All pixels outside the selected VOIs will be set to the value defined in the by value number field.</p>

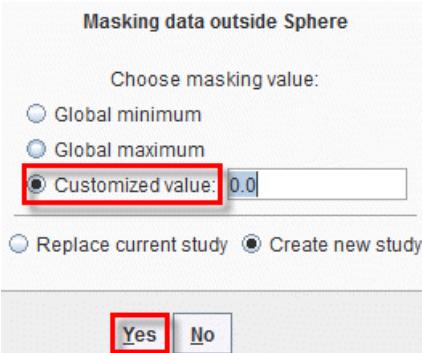
	 <p>Optionally, the values of all pixels inside the VOI can be replaced by a specified constant value if the Mask inside box is enabled and a number is entered in the by value number field.</p>
+	<p>Algebra. The operation can be configured to addition, subtraction, multiplication or division. All pixels inside the selected VOIs will undergo the same operation. With * and a number of 2, for example, the VOI pixel values will be doubled.</p>

Interactive Masking

The interactive masking algorithm is based on the interactive outlining of a sphere. It allows the fast removal of disturbing parts in the image.

The algorithm consists in the following steps:

- 1) Select either inside or outside **Removal**.
- 2) Locate the center of the anatomic structure to be masked.
- 3) Click and hold the left mouse button until the image area of interest is located within the interactive sphere.
- 4) Upon the completion of the previous steps a dialog window appears. It allows specifying the masking value, creating a new study or replacing the current one.



Masking data outside Sphere

Choose masking value:

Global minimum
 Global maximum
 Customized value:

Replace current study Create new study

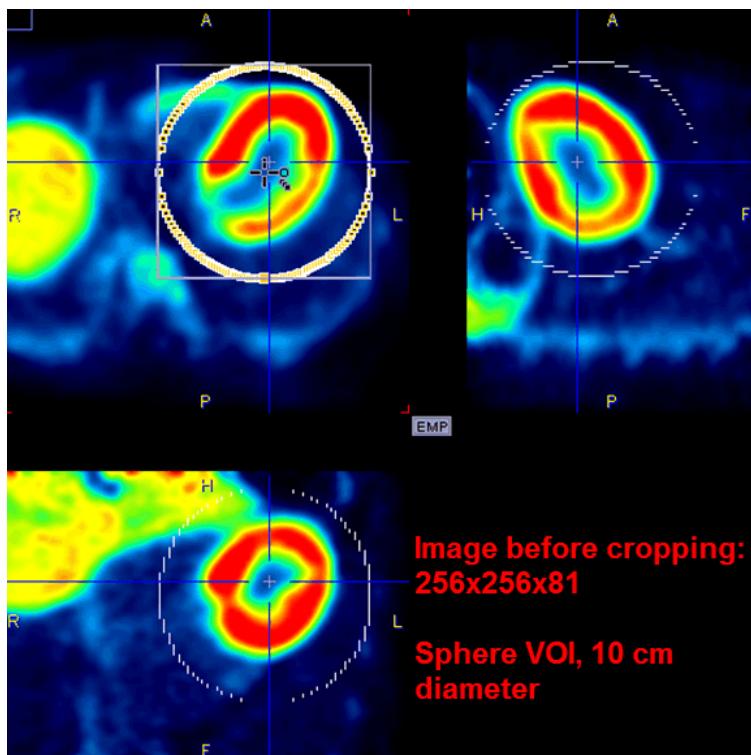
Yes **No**

- 5) Finally, activate **Yes** to perform the interactive removal.

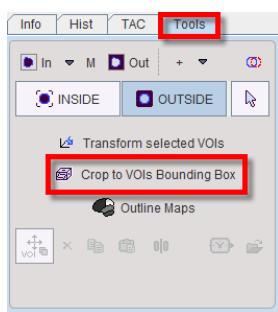
Note: The dialog window confirmation (Step 4) can be disabled. To do so, activate the **VIEW** configuration button and select the **Display** tab. In **VOI DEFINITION** area turn **OFF** the **Confirm removal operation** checkbox.

VOI-based Image Cropping

Contour VOIs can be used for cropping image series to a sub-volume of interest. The image below shows the images reconstructed from a cardiac study with a large field-of-view and a 256x256 matrix size. The orthogonal planes are displayed with a zoom factor of 3. A sphere VOI of 10 cm diameter has been positioned around the left ventricle with the purpose of defining the volume of interest.



The data was then cropped using the **Crop to VOI Bounding Box** button on the Tools tab.



The resulting series is shown below with a zoom factor of 1. It still contains the full information regarding the left ventricle, but requires a factor of about 40 less space.

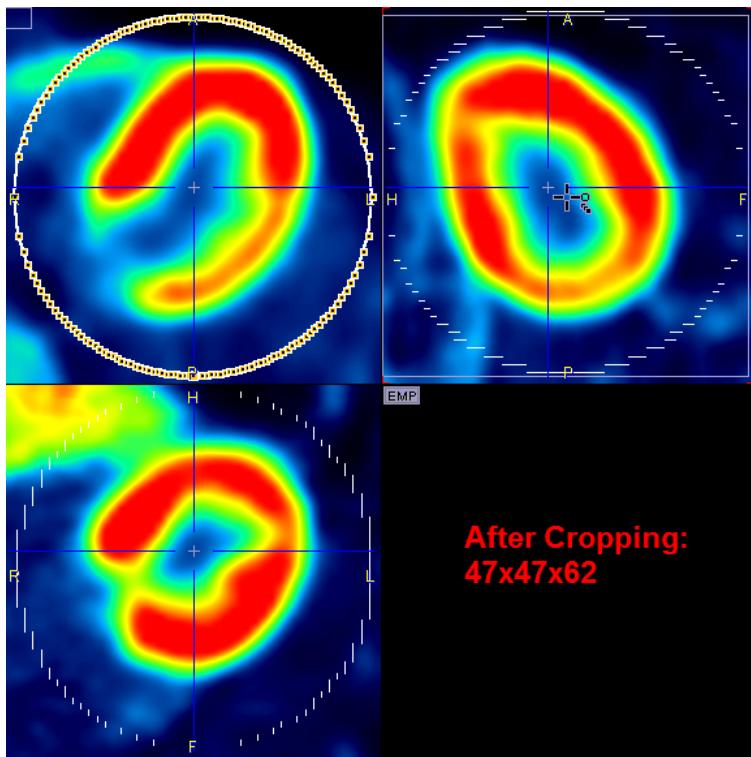
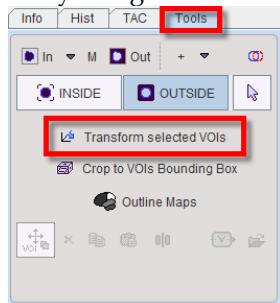


Image cropping is particularly useful as a pre-processing step to image registration. When matching a dynamic series to high-resolved MRI or CT images as a reference, it is highly recommended to crop the reference to the organ of interest before the registration. Hereby, the RAM requirements are reduced by factors without losing information, and processing speed is improved accordingly.

Spatial VOI Transformation

If the user has a set of VOIs defined on a different image and a spatial transformation which maps the other image to the current, this transformation can be applied to the VOIs in two ways:

- 1) By applying the transformation during the *loading operation* (on page 251),
- 2) or by using the **Transform selected VOIs** button in the **VOI Tools** panel.

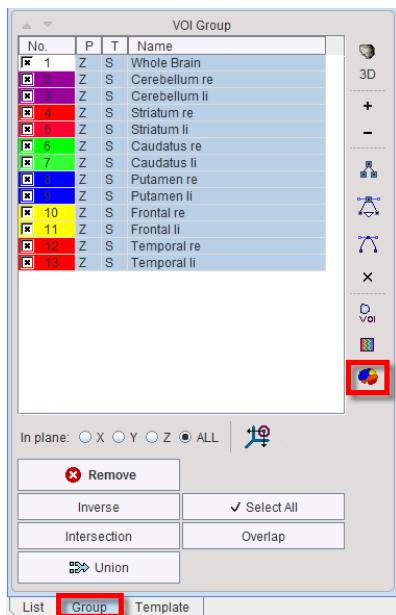


Note that the **Transform selected VOIs** button also works on template VOIs.

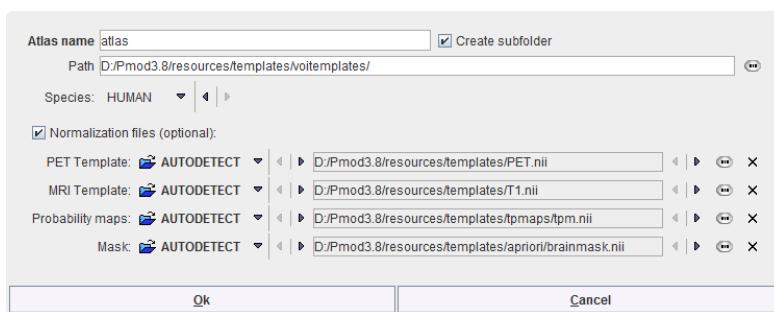
Creation of Atlas VOIs

An image series for which a set of contour VOIs has been defined can easily be converted into a VOI atlas as follows:

- 1) Load the image series in the PVIEW tool.
- 2) Outline a set of contour VOIs in the VOIs page.
- 3) On the **Group** tab, select the VOIs to be included in the template.
Important: do NOT include VOIs (such as a whole-brain VOI) which cover other VOIs.
- 4) Activate the **Create Template Atlas** icon available on the right side of the **VOI Group**. The same icon is available in the lateral taskbar.



A dialog window appears which requests an **Atlas name** for template.



Using this name a subdirectory is created in the **Path** directory which defaults to *resources/templates/voitemplates*, but which can be changed. The **Species** selection allows tagging the VOI atlas so that it will be shown in the corresponding context.

An image series is generated which encodes each VOI pixel as an appropriate numeric label and saved in NifTI format. Additionally, a text file is created for the mapping of the numeric labels to VOI names. After activating the refresh button  in the **Atlas** panel of **Template**, the new template appears and can be used for statistics.

Important: Because each pixel can only have one numeric label, the VOIs used for the Atlas generation may not be overlapping.

Optionally, files for the spatial normalization can be defined for the template. To this end enable the **Normalization files (optional)** box and select a **Template** file and a **Mask** file, which will be used for the deformable registration. To also use the Probability Maps Normalization a **Probability maps** file should be selected which encodes the Grey matter, white matter and CSF probability maps as a dynamic data set. In this case, a **normalization** folder is created with the normalization image in NifTI format (norm_template.nii). It also contains a **mask** sub-folder for the mask image (mask.nii), and a **tpm** folder for the tissue probability map (tpm.nii).

Statistics Aggregation

The numeric output of VOI statistics as well as the numerical output of other tools can be compiled into a single aggregate file for further statistic analysis. Aggregation is supported for

- » VOI statistics (.voistat files);
- » kinetic tissue parameters from the PKIN tool (.kinPar files);
- » the cardiac perfusion results of PCARD tool(.pcardRes files);
- » the discrimination results of the PALZ tool (.palzRes files).

Each of the tools has an appropriate button  **Aggregate Statistics** for starting the aggregation tool, and the aggregation interface works similarly.

Recommended Data Organization

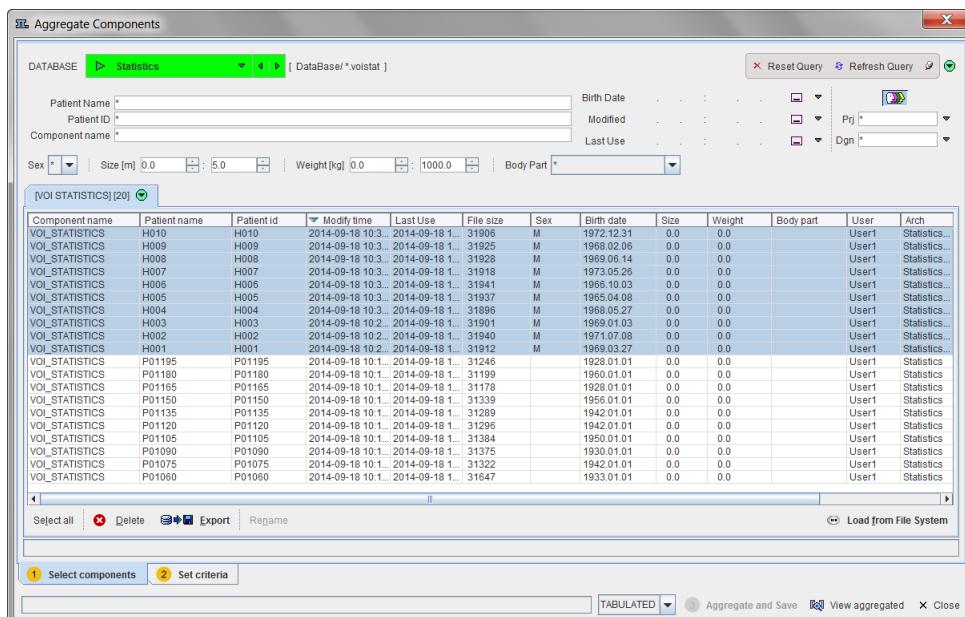
Typically, the results of a population (control group, patient group) in a certain condition (test, retest) should be compiled into a single aggregate, and comparisons or tests performed between the aggregates.

It is recommended using the labeling facility of PMOD databases which allows defining a **Project** and **Diagnosis** label on the level of the image series. This information can be used for results filtering as described below.

In the example used below a VOI analysis has been performed with consistent VOI names using a brain VOI atlas and the results were saved with appropriate component names.

Data Selection

After aggregation has been started, a dialog window appears with the first page **1 Select components** open.



The screenshot shows the 'Aggregate Components' dialog window. At the top, there's a dropdown menu set to 'DATABASE' and a search bar containing 'DataBase/*.voistat'. Below the search bar are several filter fields: 'Patient Name', 'Patient ID', 'Component name', 'Sex', 'Size [m]', 'Weight [kg]', 'Last Use', 'Birth Date', 'Modified', 'Last Use', 'Prj', 'Dgn', and 'Body Part'. A large table titled '[VOI STATISTICS] (20)' displays 20 rows of data. Each row contains columns for Component name, Patient name, Patient Id, Modify time, Last Use, File size, Sex, Birth date, Size, Weight, Body part, User, and Arch. The data includes various patient IDs (H010, H009, H008, etc.) and dates (2014-09-18). At the bottom of the dialog, there are buttons for 'Select all', 'Delete', 'Export', 'Rename', 'Load from File System', and tabs for 'TABULATED' (selected), 'Aggregate and Save', 'View aggregated', and 'Close'.

Component name	Patient name	Patient Id	Modify time	Last Use	File size	Sex	Birth date	Size	Weight	Body part	User	Arch
VOI_STATISTICS	H010	P0110	2014-09-18 10:3...	2014-09-18 1...	31906	M	1972.12.31	0.0	0.0		User1	Statistics...
VOI_STATISTICS	H009	P0109	2014-09-18 10:3...	2014-09-18 1...	31925	M	1968.02.06	0.0	0.0		User1	Statistics...
VOI_STATISTICS	H008	P0108	2014-09-18 10:3...	2014-09-18 1...	31928	M	1969.06.14	0.0	0.0		User1	Statistics...
VOI_STATISTICS	H007	P0107	2014-09-18 10:3...	2014-09-18 1...	31918	M	1973.05.26	0.0	0.0		User1	Statistics...
VOI_STATISTICS	H006	P0106	2014-09-18 10:3...	2014-09-18 1...	31941	M	1966.10.03	0.0	0.0		User1	Statistics...
VOI_STATISTICS	H005	P0105	2014-09-18 10:3...	2014-09-18 1...	31937	M	1965.04.08	0.0	0.0		User1	Statistics...
VOI_STATISTICS	H004	P0104	2014-09-18 10:3...	2014-09-18 1...	31896	M	1968.05.27	0.0	0.0		User1	Statistics...
VOI_STATISTICS	H003	P0103	2014-09-18 10:3...	2014-09-18 1...	31901	M	1969.01.03	0.0	0.0		User1	Statistics...
VOI_STATISTICS	H002	P0102	2014-09-18 10:3...	2014-09-18 1...	31940	M	1971.07.08	0.0	0.0		User1	Statistics...
VOI_STATISTICS	H001	P0101	2014-09-18 10:3...	2014-09-18 1...	31912	M	1969.01.07	0.0	0.0		User1	Statistics...
VOI_STATISTICS	P01195	P01195	2014-09-18 10:1...	2014-09-18 1...	31246		1928.01.01	0.0	0.0		User1	Statistics...
VOI_STATISTICS	P01180	P01180	2014-09-18 10:1...	2014-09-18 1...	31109		1960.01.01	0.0	0.0		User1	Statistics...
VOI_STATISTICS	P01165	P01165	2014-09-18 10:1...	2014-09-18 1...	31178		1928.01.01	0.0	0.0		User1	Statistics...
VOI_STATISTICS	P01150	P01150	2014-09-18 10:1...	2014-09-18 1...	31339		1956.01.01	0.0	0.0		User1	Statistics...
VOI_STATISTICS	P01135	P01135	2014-09-18 10:1...	2014-09-18 1...	31289		1942.01.01	0.0	0.0		User1	Statistics...
VOI_STATISTICS	P01120	P01120	2014-09-18 10:1...	2014-09-18 1...	31296		1942.01.01	0.0	0.0		User1	Statistics...
VOI_STATISTICS	P01105	P01105	2014-09-18 10:1...	2014-09-18 1...	31384		1950.01.01	0.0	0.0		User1	Statistics...
VOI_STATISTICS	P01090	P01090	2014-09-18 10:1...	2014-09-18 1...	31375		1930.01.01	0.0	0.0		User1	Statistics...
VOI_STATISTICS	P01075	P01075	2014-09-18 10:1...	2014-09-18 1...	31322		1942.01.01	0.0	0.0		User1	Statistics...
VOI_STATISTICS	P01060	P01060	2014-09-18 10:1...	2014-09-18 1...	31647		1933.01.01	0.0	0.0		User1	Statistics...

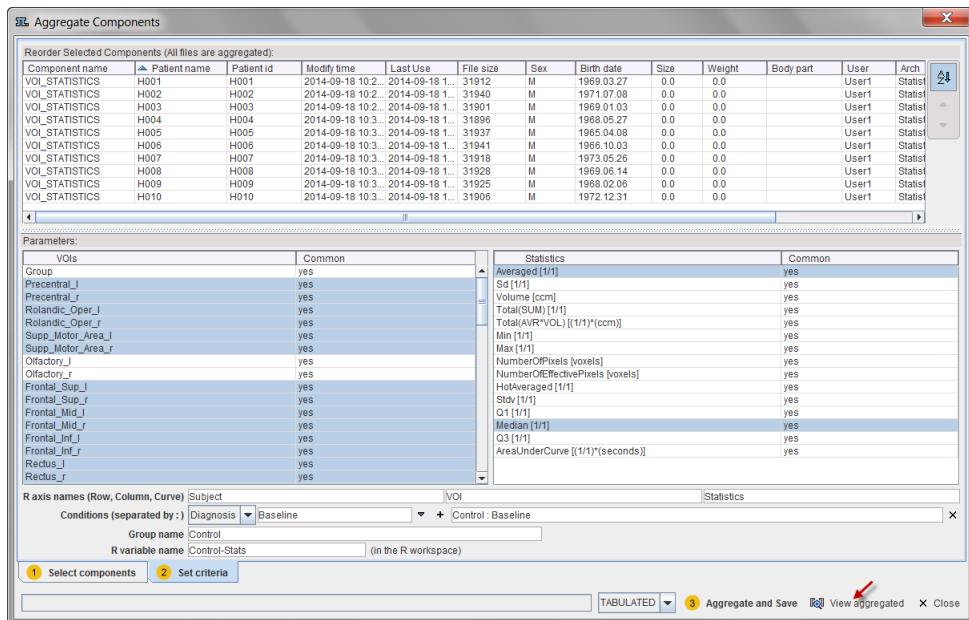
It lists all VOI statistics (.voistat files) which are available in the selected DATABASE.

The task on this page is to select the statistics components which should be concentrated into a single aggregate. This is done by selecting the appropriate entries in the list so that they appear highlighted, in the example above the ones of the healthy controls (see *above* (on page 10)). Note the filter elements in the upper part which allow reducing the number of listed components. For instance the string H* could be entered in the **Patient Name** field to list only the results for the controls.

If no database has been used for saving the .voistat files, the **Load from File System** function has to be used instead.

Information Selection

Select the **2 Set Criteria** pane to move on to defining the information parts to be included in the aggregate.



The upper list consists of the data sets selected in the prior step. This list is mainly for information. The elements can be sorted or reordered, but no entries can be removed or added.

Selection of the Aggregate Information

The lower **Parameters** area shows the list of **VOIs** used for the statistics to the left, and the calculated **Statistics** to the right. Note the **Common** column. A **Yes** entry indicates that the VOI/Statistics is available in all data sets. Correspondingly a **No** entry indicates that the information is missing in at least one of the data sets. If the information is still used despite of the **No** indication, a **NaN** value will be entered in the aggregated to signal the absence of useful information. **NaN** values are disregarded in the statistics script provided in the R console.

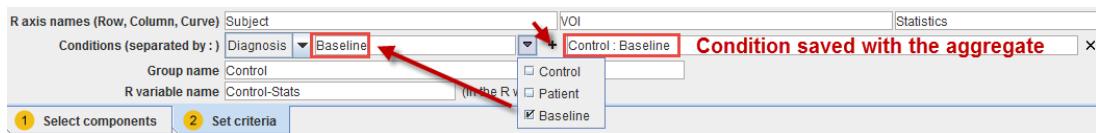
In the left list select the **VOIs** to be included in the aggregate, and in the right list the **Statistics**.

Encoding Group and Condition Information

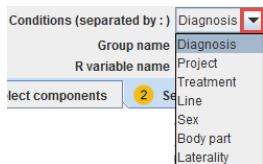
The lower part of the window serves for providing information which will be useful when using the aggregates for statistics.

The aggregation will generate a three-dimensional data set, which will be represented in the R console as a table indexed by **Row** and **Column**, and each table element is a vector and therefore called **Curve**. The three **R axis names** fields allow defining the names of the three dimensions, which for VOI statistics default to **Subject**, **VOI** and **Statistics**.

The **Conditions** line serves for generating a code describing the current aggregate. The rational is, that the subjects of a group may be studied in different conditions, or that different types of analysis are performed.



The way to generate the condition string is to enter a string in the left field, and then activate the + button. As a result the string is appended to the current condition with a preceding ":". Since the condition string has to be consistent among aggregates, there are two lists for generation pre-defined strings. The first list serves for choosing the condition group.

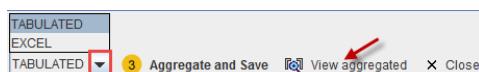


Consequently the elements of the second list are populated and can be selected.

Additional informations to be specified are the **Group name**, as well as the **R variable name** which will be useful when transferring the aggregate to the R console.

Aggregate Generation and Saving

Finally the aggregate is created by the **Aggregate and Save** button, which enforces a saving operation.



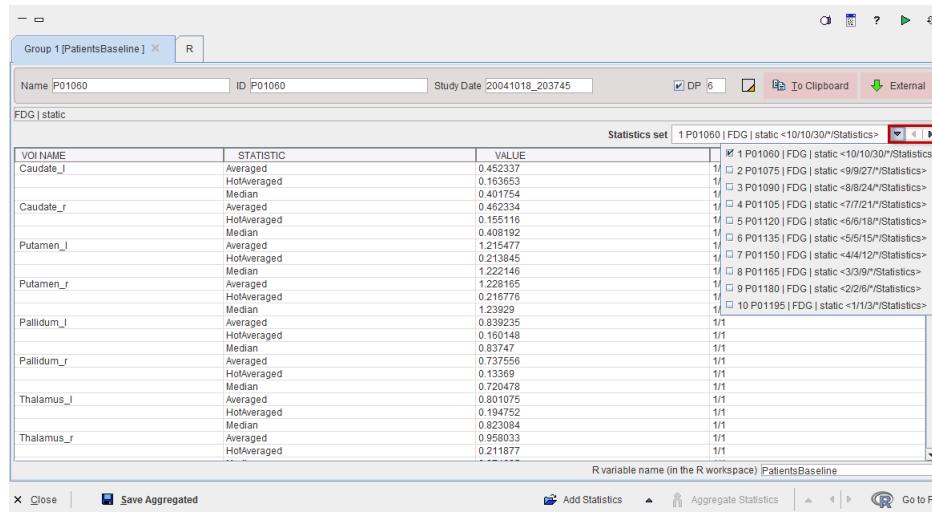
There are two formats available, **TABULATED** and **EXCEL**. For internal use in PMOD the **TABULATED** format is recommended.

Aggregate Export and R Transfer

The aggregate can directly be transferred to the R statistics console via the **Go to R** button. As a result, a variable with the name specified by the **R variable name** will be created. **To Clipboard** copies the contents of the aggregate, so that it can be pasted into alternate programs such as Excel.

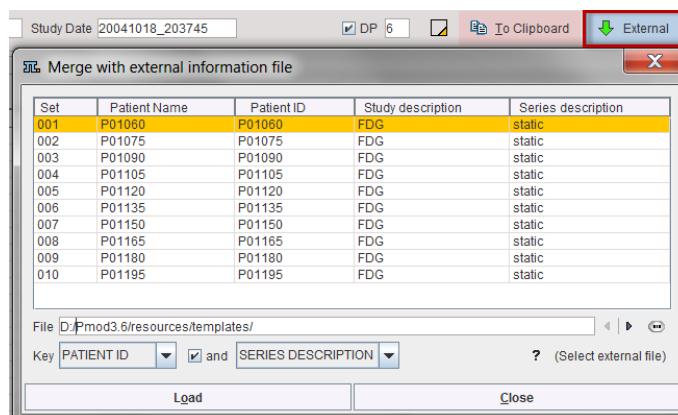
Aggregate Inspection and Combination with External Data

View aggregated opens the dialog window illustrated below for inspecting the contents of an aggregate. The information of a single statistics file is shown in the list area, and the arrows of the **Statistics set** allow stepping through the different data sets.



Combination with External Data

For the statistical analysis, additional data might be relevant, for instance the blood pressure at scan time, or a mini mental test score. Such data can be included with the aggregate using the **External** button. It shows a dialog window listing the four identifiers **Patient Name**, **Patient ID**, **Study description** and **Series description** of the included data.



A tab-delimited text File with the external data has to be prepared and selected. It has the following structure, which is also summarized by the ? button:

# PMOD_EXTERNAL_DATA			
# FORMAT[UNI]			
# EXTERNAL			
// PatientName	D[mmHg]	MMS[1/1]	Code[string]
P01060	70	20	NORM
P01075	71	18	HYP0
P01090	72	22	HYP0
P01105	73	19	HYP0
P01120	74	21	NORM
P01135	75	17	HYP0
P01150	76	15	HYP0
P01165	77	18	NORM
P01180	78	23	HYP0
P01195	79	12	NORM

PATIENT ID or PATIENT NAME can be used as the **Key** for relating the information in the aggregate and in the file, and if this is not unique, it can be combined with **STUDY DESCRIPTION** or **SERIES DESCRIPTION**. Use **Load** to perform to extend the aggregate, and **Save Aggregated** to save the result.

Note that the added external information is not visible in the **Group** window. However, after transferring the information to R using **Go to R**, the external values are encoded in the **EXT** column as illustrated below.

ROW	INF	FLT	EXT	Caudate_l_C1	Caudate_r_C2	Putamen_l_C3	Putamen_r_C3
P01060_R1	P01060	Baseline	20	0.4523366234503612	0.4623344296472664	1.2154766889744923	1.2281650591
P01075_R2	P01075	Baseline	18	0.5875037279035086	0.719591641381907	1.2512258149737856	1.2248811751
P01090_R3	P01090	Baseline	22	0.2430224279176291	0.2848102513852428	1.0798934888188207	1.1472380602
P01105_R4	P01105	Baseline	19	0.7395012551302497	0.5006850808981337	1.089376376638307	1.0604979702
P01120_R5	P01120	Baseline	21	0.8220601126099986	0.9100197249789856	1.173050670626432	1.1864748741
P01135_R6	P01135	Baseline	17	0.578035331074512	0.6646997421049375	1.131527128708134	1.2338782101
P01150_R7	P01150	Baseline	15	0.91264752020552	0.8140952113928638	1.1025238148303644	1.0438225091
P01165_R8	P01165	Baseline	18	0.5755065138510149	0.5799827398065646	1.130212852586413	1.1457797261
P01180_R9	P01180	Baseline	23	0.783696978579083	0.7839810852557377	1.1403903939134856	1.1206056541
P01195_R10	P01195	Baseline	12	0.485098051876947	0.4424495952545533	1.2033660966580788	1.2054394831

No	Key	Value
1	D	70
2	MMS	20
3	Code	NORM

Chapter 7

R Statistics in PMOD

R is an open-source statistical environment and programming language for data analysis and graphical display (*R-project* <http://www.r-project.org/>). Recently it has gained increased attention in the analysis of biomedical data, see for example the overview article of Tabelow et al: *Image analysis and statistical inference in neuroimaging with R*. Neuroimage 2011, 55(4):1686-1693. DOI <http://dx.doi.org/10.1016/j.neuroimage.2011.01.013..>

The PMOD R console provides an interface to the R package and leverages the entire R functionality including the statistical analysis of PMOD results from populations. The methods can be applied to the outcome of VOI statistics, regional kinetic modeling, cardiac perfusion quantification and the PALZ analysis.

Standard analysis types are directly supported via the graphical user interface. They can be as simple as a performing scatter plots, but range to more complicated techniques such as ANOVA, test-retest analysis or Bland-Altman comparison.

Beyond using the graphical interface for invoking R functionality, users can also develop their own analysis scripts in a command window interface. In this situation, the PMOD R console serves as a prototyping interface which allows entering R code, executing it, inspecting the result, and improving the code.

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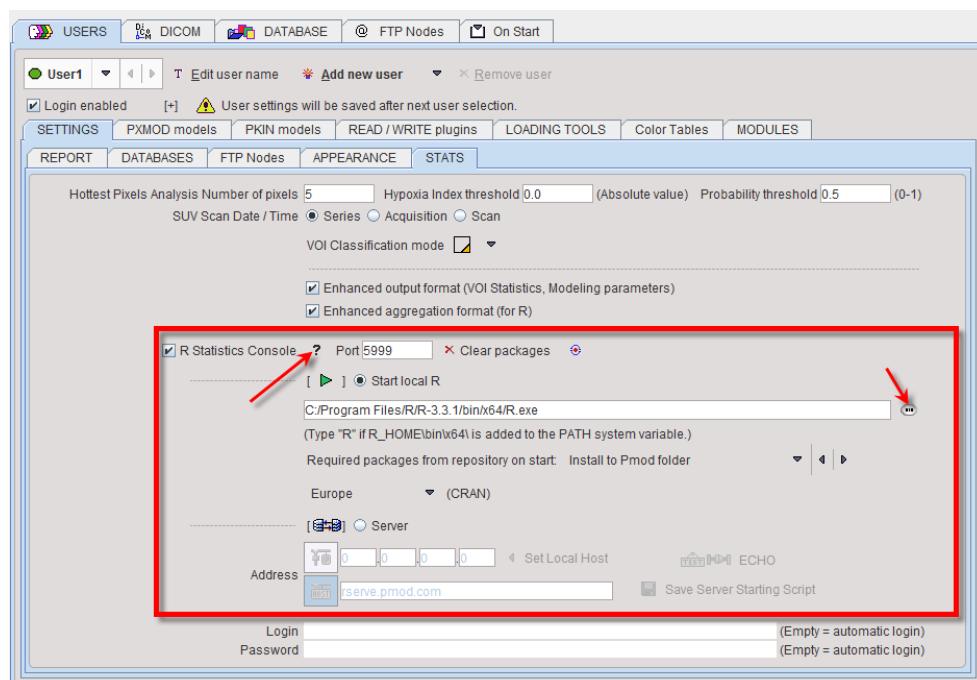
R Installation and Configuration

R Server

R can be set up as a processing server which is listening on a certain IP port. The server can receive data from a client and save it to an internal workspace. It can also receive processing commands, apply them to the data, and return the results to the client on the same channel. PMOD uses this R server mechanism for implementing R-based statistics and therefore relies on a responding R server.

PMOD Configuration for Using R Statistics

The R server to be used for statistics is configured in the **Users configuration** window, **SETTINGS/STAT** tab as illustrated below.



Per default, PMOD comes with enabled R statistics using an R server hosted on a PMOD machine (rserve.pmod.com:5999). However, this R server should only be used for tests, and not for productive data processing. We recommend users to set up their own R server, which is easy to do and free of charge. There are two alternative setups:

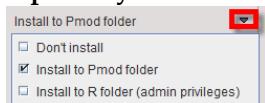
- 1) In a multi-user environment it is possible to set up a single R server interacting with several PMOD clients. However, due to limitations of the R server on Windows, the R server should be installed on a Mac or Linux system in this case.
- 2) However, it is recommended installing an R server on every machine running PMOD.

Information about the installation of R on Window systems is given below. Please refer to the explanations available via the ? button to install an R server on Mac and Linux systems.

Local R Server on Windows

To set up a local R server on a windows machine please proceed as follows.

- 1) Download and perform a local installation of the R package as described on the *R download* <http://cran.r-project.org/mirrors.html> website.
- 2) Configure the R section as illustrated above. Enable **Start local R** and provide the path to the R executable using the indicated button.
- 3) Define the location of the additional R packages which are required beyond the downloaded core installation. Recommended is to set **Required packages from repository**



to **Install to Pmod folder**. Effectively, the packages will end up in the directory *Pmod3.8/resources/extlibs/r/packages*. The alternative option **Install to R folder** has the drawback that a user with administrator privileges needs to perform the installation.

- 4) Set the **CRAN** package repository according to your country. This repository will be used for the package loading. It is only needed the first time the R server is started, or when new packages are added.
- 5) Confirm the settings with **OK** and close PMOD.

Starting the R Console

The PMOD R console can be started in different ways:

- 1) From the PMOD ToolBox



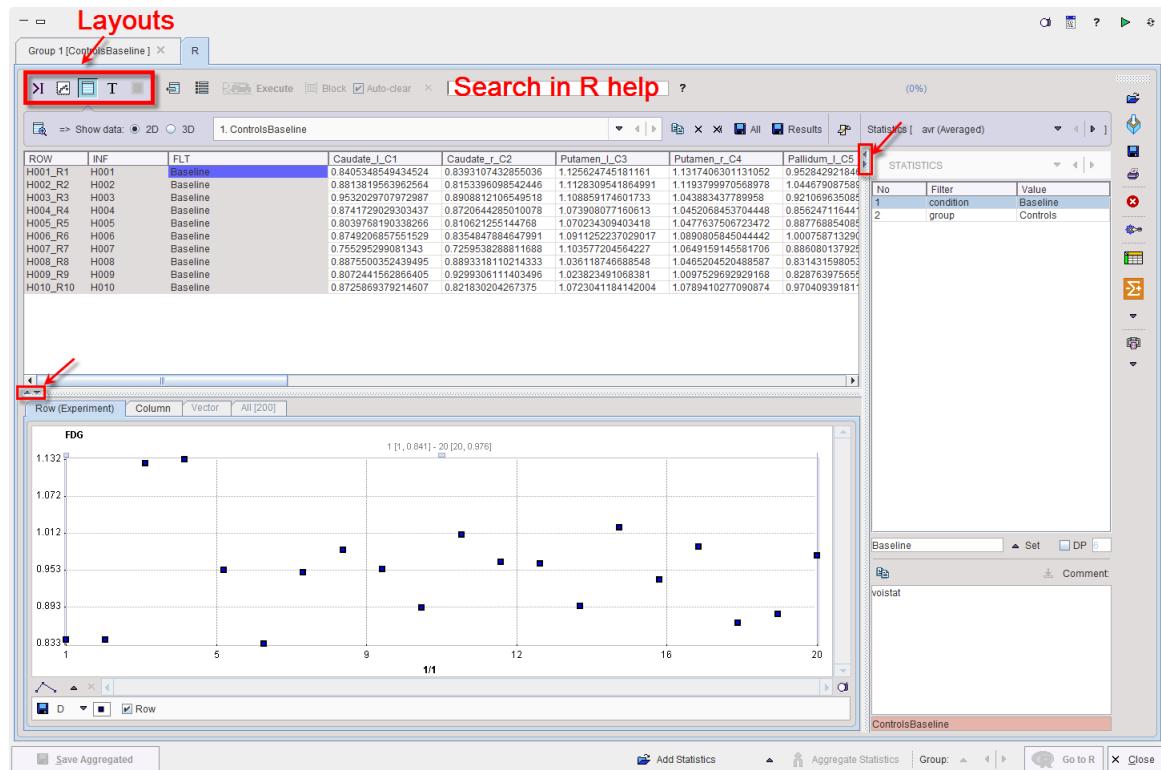
- 2) using the keyboard keys SHIFT+CTRL+R,
- 3) by transferring data using the **Go to R** button from the PMOD statistics or aggregate viewers illustrated below.

VOI NAME	STATISTIC	VALUE	UNIT
Caudate_I	Averaged	0.481313	1/1
	HotAveraged	0.202139	1/1
	Median	0.412257	1/1
Caudate_r	Averaged	0.49733	1/1
	HotAveraged	0.2073	1/1
	Median	0.42725	1/1
Putamen_I	Averaged	1.171809	1/1
	HotAveraged	0.265297	1/1
	Median	1.199189	1/1
Putamen_r	Averaged	1.186596	1/1
	HotAveraged	0.281061	1/1
	Median	1.198017	1/1
Pallidum_I	Averaged	0.879904	1/1
	HotAveraged	0.210671	1/1
	Median	0.95147	1/1
Pallidum_r	Averaged	0.792307	1/1
	HotAveraged	0.188129	1/1
	Median	0.793185	1/1
Thalamus_I	Averaged	0.783577	1/1
	HotAveraged	0.210391	1/1
	Median	0.821259	1/1
Thalamus_r	Averaged	0.92793	1/1
	HotAveraged	0.257962	1/1
	Median	0.955283	1/1
Frontal_lobe_I	Averaged	0.94544	1/1
	HotAveraged	0.252476	1/1
	Median	0.998424	1/1
Frontal_lobe_r	Averaged	0.955716	1/1

The console opens as a dialog window. If **Go to R** has been invoked, the workspace will contain data which is already shown in the user interface. When starting with an empty console, data needs to be loaded using the loading button from the lateral taskbar.

R Console Organization

The user interface of the R console has some framework operations, a main part and a taskbar to the right.



Framework

There are some convenience buttons at the top of the window:



Buttons to minimize/maximize the R console window.



Captures the entire screen (not only the PMOD window) and adds it to a console buffer.



Opens the **Console** dialog window for checking the log output and *reporting problems* (on page 33) to support@pmod.com.



Open help window.



Button for opening the R server configuration window.



Button for reconnecting to the R server, if a connection problem occurred.



Dividers between different parts of the layout allow extending/shrinking the respective areas.

Main Window Layouts

The main statistics part has 5 different layouts depending on selection in the upper left:

- **Command layout:** Allows invoking existing analysis scripts as well as editing and executing native R commands on the loaded data.
-  **Plotting layout:** Allows producing different plots of the data, and inspecting the plots produced by analysis scripts.
-  **Table layout:** Allows inspecting the data variables of the R workspace. Initially, the loaded data appear as variables g1, g2, etc. Scripts add variables to the workspace. Data can be copied to the clipboard for external usage.
- T **Text layout:** Allows extracting the contents of numerical variables into a text field.
-  **Image layout:** Allows visualizing images. Is only active after image data have been transferred.

Next to the layout buttons is an area containing several buttons



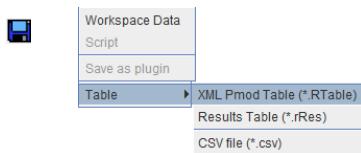
which are related to programming in R and effective in different contexts:

-  Generates R code for extracting parts of the workspace variables.
-  Lists the variables in the workspace and inserts the selected variable into the command line.
-  Execute the whole code in the command window.
-  Executes the selected code in the command window.
-  Clears the contents of the command window after execution.

Lateral Taskbar

The elements in the taskbar have the following functionality:

-  ► Loading of information as described *below* (on page 315).
-  Input files can be dragged to this box for opening them



Saving of

- ▶ the contents of the command window in two ways: as a new **Script**, which can be loaded, or as a **plugin**, which can directly be selected from a list;
- ▶ all data variables as an R workspace (**Workspace Data**, .RData file) which can be loaded back into the PMOD R console, but also directly to R or other graphical front-ends of R (e.g. R Studio).

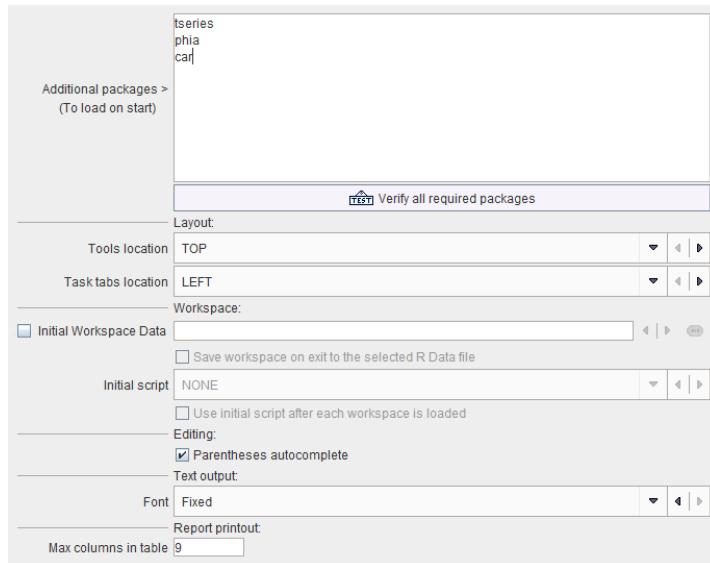


Printing a report which may include plots, tables and/or images, depending on the analysis performed.



Clears all the variables in the R workspace.

-  Opens the configuration settings window:



If user scripts require additional R packages, they can be typed into the **Additional packages ...** window and checked with the **Verify ...** button.

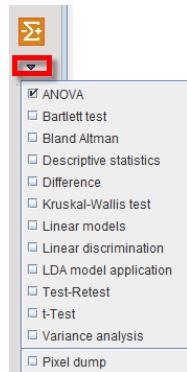


Tools location is layout option. The tools section may be arranged at the **Top** (as in this documentation), or at the **Bottom**.

Initial Workspace Data directs the R console to load an R workspace file whenever it is started. This file might include R functions developed by the user.

-  Opens the **Console** dialog window for checking the log output and *reporting problems* (on page 33) to support@pmod.com.

-  Shortcut for opening the scripts selection. System scripts are listed first, followed by scripts which were saved as plugins.

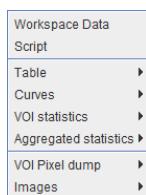


-  Opens the *aggregation window* (on page 301) for compiling individual statistics into an aggregate table.

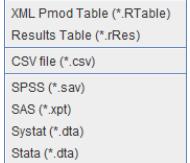
Data Loading

Loading of Data into the R Console

The  button in the lateral taskbar with the sub-menu



allows loading the different types of data which are accepted by the R console.

- » A saved R workspace containing the (**Workspace Data**, .RData file).
- » R processing scripts (**Script**, .r file).
- » Tables saved from R (**Table**, .RTable file) or several statistics programs.
 - 
- » PMOD VOI statistics data (**Statistics**, .voistat file). The **Enhanced output format** and **Enhanced aggregation format** should be enabled in the *configuration* (on page 20). Note that the statistics may include a time dimension if the image file was dynamic.
- » *Aggregated PMOD results* (on page 301) (**Aggregated**, .dbTab file) from multiple result files. Typically, the results of a population (controls, patients) or a condition (test, retest) should be compiled into a single aggregate.
- » *Dumps* (on page 288) of the pixel values within VOIs: **VOI Pixel dump** (.pixDump file);
- » **Images** in any of the supported formats. At this time, however, no dedicated statistics on images are yet provided through the PMOD R console.

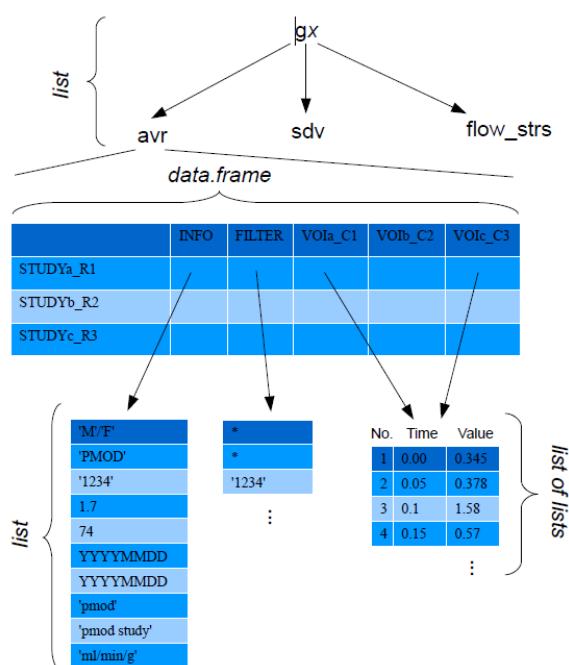
Transfer of Statistics to R

The **Go to R** button in the *statistics viewer* (on page 285) or *aggregate viewer* (on page 303) transfers the data of all open statistics to the R server, generating one R variable per tab in the R workspace. Per default, the variables are labeled sequentially in the order of the tabs as **g1**, **g2**, .. etc, but explicit names can also be specified.

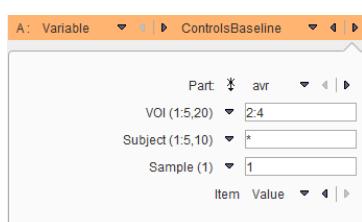
R Variable Structure

The variables created by the transfer of statistics and aggregates to R or by loading them have the following structure:

- » The names have the form **g1**, **g2**, etc if there was not explicit variable name defined.
- » The highest level consists of a list corresponding to the different statistic types such as average and standard deviation for VOI statistics, Vt for aggregated modeling results, etc.
- » The next level is a data frame with a header line and data rows. The data rows correspond to the rows in an aggregate and are thus dependent on the aggregated data. Typically, the rows correspond to the different subjects in a population.
- » Each cell in the data frame table is in itself a list. The list structure depends on the aggregated table and on the column. An INFO list contains demographic data, while a VOI list contains 3 lists for the elements "number", "time" and "value".



Most PMOD scripts require the specification of which part of a variable should be processed. Therefore, they show dialog windows such as the one illustrated below.



After choosing a **Variable**, the elements in the lower part are updated according to the variable contents. **Parameter** represents the statistics to be analyzed. The **VOI** selection corresponds to the columns, the **Experiment** to the rows, and the **Sample** to the location in

the **value** or **time** list. **Item** finally allows switching from **Value** to **Time**, if the acquisition timing rather than the sample value is needed.

The selections in text fields represent standard R expressions, for example:

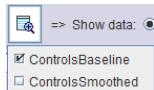
- » Use all available elements, eg all VOIs: "*"
- » Use a range, e.g. elements 2 to 4: "2:4"
- » Use one specific element, e.g. the first: "1". It can be combined with a range in the form of e.g. "1, 3:5".

As a convenience, the shortcut button  propagates the "*" definition to all components.

Table Layout

Variable Selection

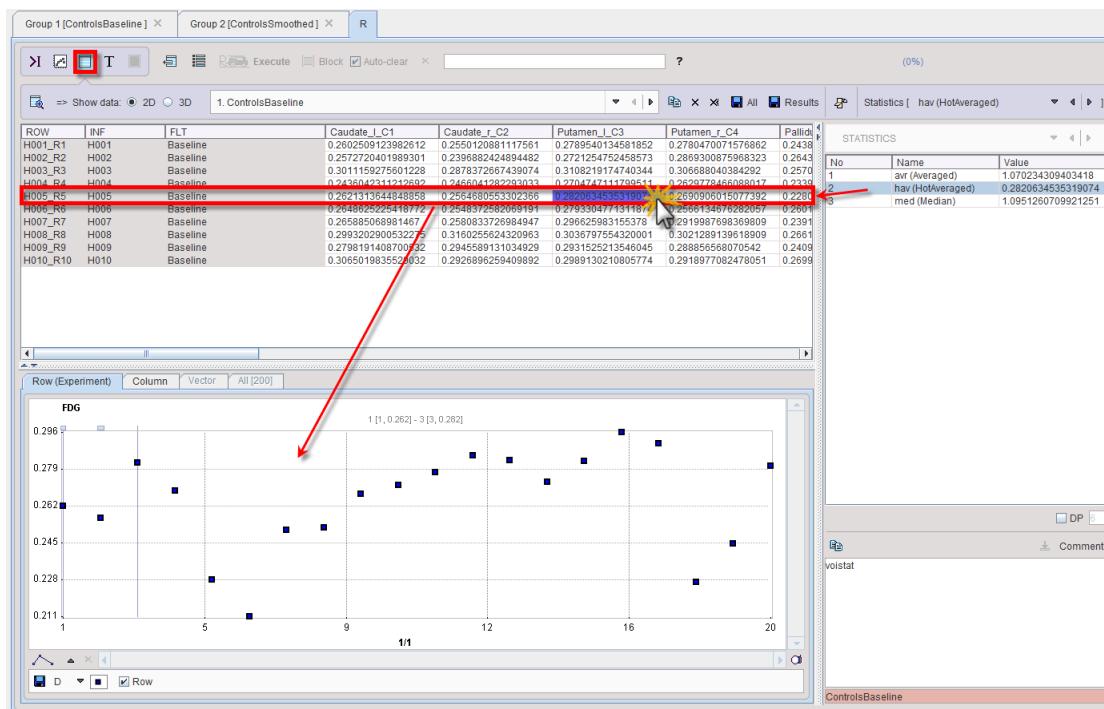
The  button activates the **Table layout** for inspecting the data in the R workspace. The R variables can be selected from the **Preview** list indicated below.



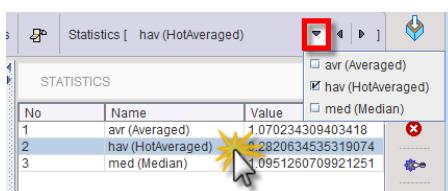
The list will show the original variables as well as variables created by the scripts and R commands.

Table View Layout

After selecting a variable, its content can be inspected. The default **2D** view illustrated below shows the table of the data frame.



The lower plot area shows scatter plots of a data **Row** or **Column**. One variable may have different data frames for different aggregated outcome statistics such as **avr**, **hav**, and **med**. The **Statistics** selection can be used to change between statistics, as well as direct double-clicking into the **Statistics** list.



In order to keep track of the variable meaning, comments can be added in the lower right. Please select the variable of interest, enter the comment, and then activate the copy button illustrated below. When saving the R workspace, this comment will be included, so that it will be available when resuming work.

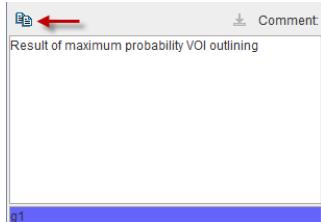


Table Buffer

Note that each visualization of a table is stored in a buffer list so that it can be quickly recalled. While a variable exists only once, there might be multiple entries in the buffer which may represent the visualization of different variable parts.

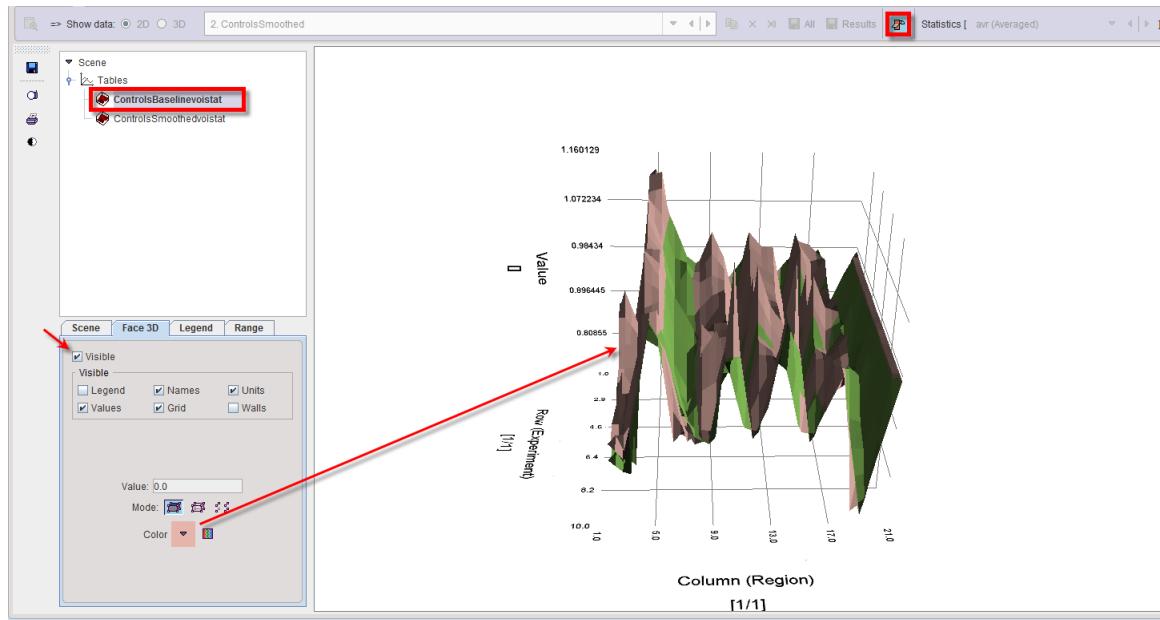
5. Differences													All	Results
Caudate_r_C2	Putamen_l_C3	Putamen_r_C4	P										1. ControlsBaseline	gallium_r_l
0.01729075929218915	0.021956567400160942	0.020345007367773338	-0.1										2. ControlsSmoothed	0.04067099
0.021353409836307957	0.009761416780156074	0.015071000592201456	-0.1										3. 1st matrix	0.2299762
0.031234117385573024	0.01852834052910235	0.0032150889082147582	-0.1										4. 2nd matrix	0.01277417
0.036165275548598164	0.014698497856190595	0.016882118148523917	-0.1										5. Differences	0.03367884
0.018947597331691712	0.01652037057339717	0.015719454065730165	-0.1											0.02820369

The buffer list can be edited with the buttons to its right:

- Remove current table from the list.
- Save all tables into a file.
- Copy the current table to the clipboard.
- Clear the buffer list.

Surface Plot Visualization (Option)

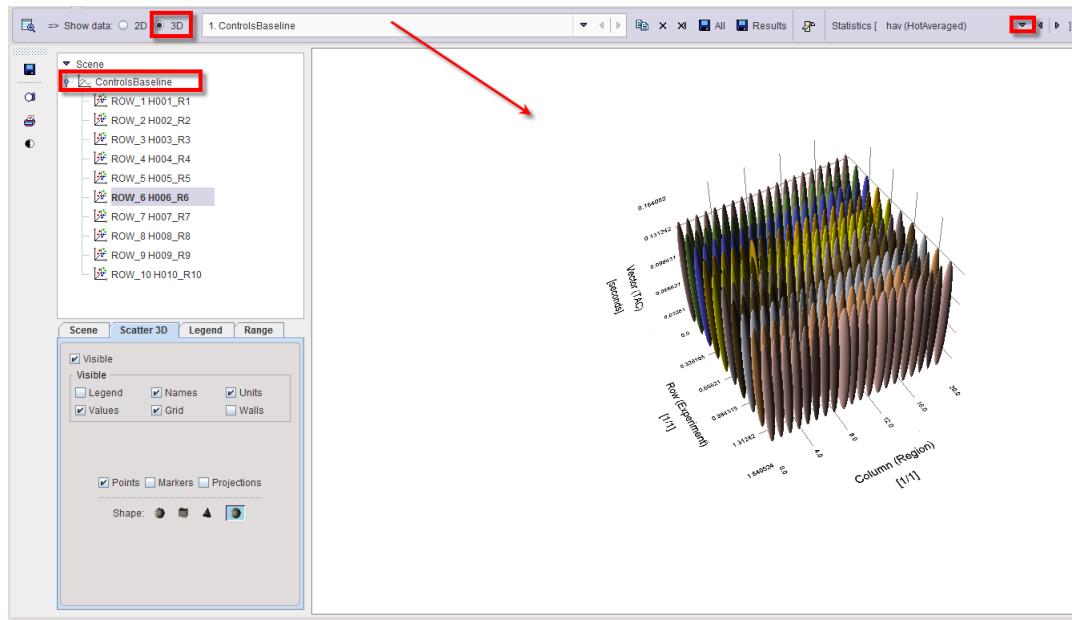
The tables from the buffer can also be visualized as 3D surfaces as illustrated below.



It is essential, that before enabling this display the buffer is prepared so that only meaningful tables remain. Please remove the other tables with the **x** button. For information about the 3D rendering please refer to the *PMOD 3D Rendering User's Guide*.

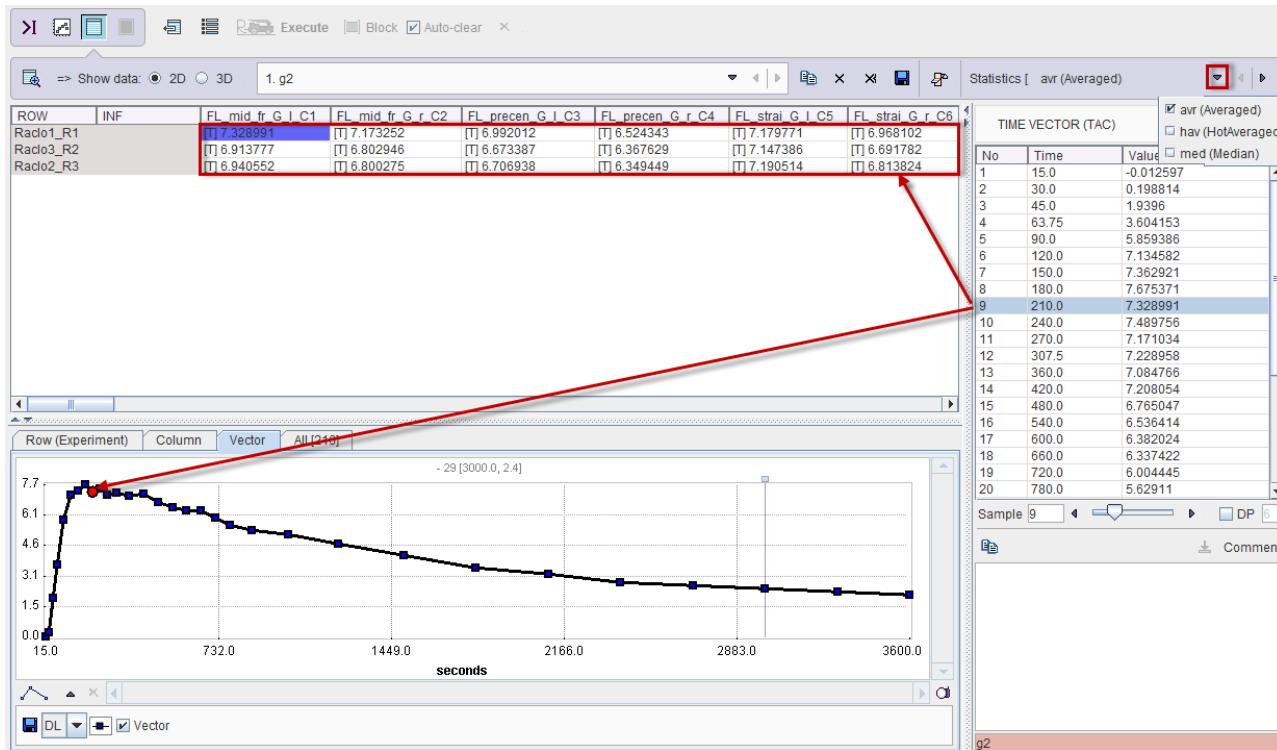
3D Visualization (Option)

When the **3D** radio button is enabled, the selected buffer table is displayed as shown below.



Dynamic Data

If the loaded statistic has a time dimension, the table represents the values at a certain time which can be selected in the **TIME VECTOR** list or by moving the **Sample** slider.

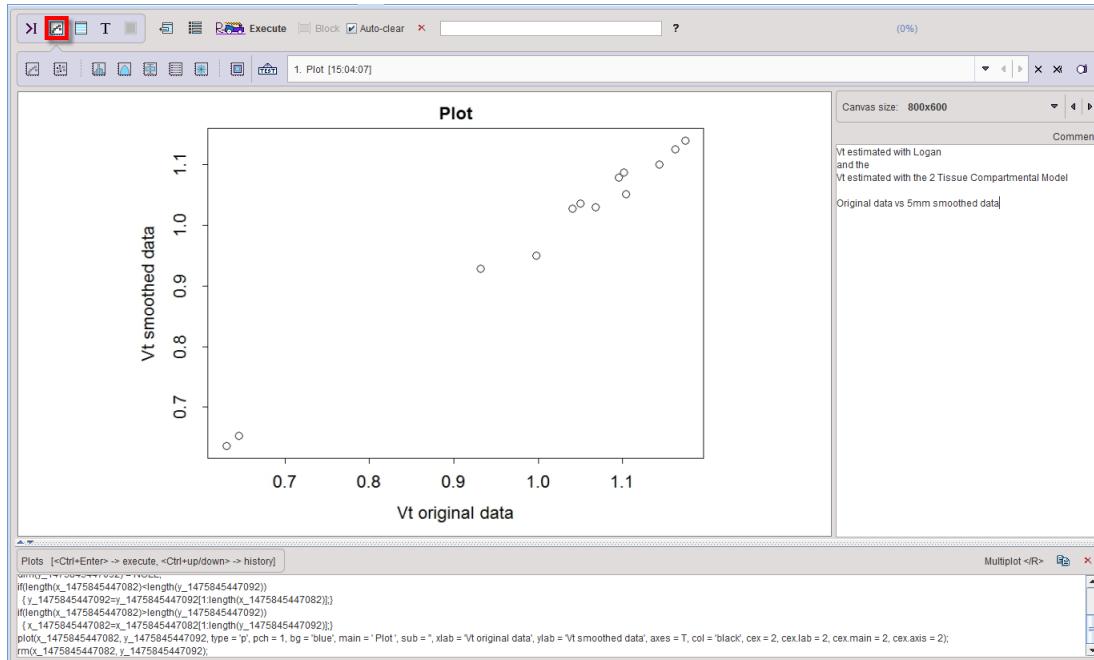


The TAC corresponding to the selected cell (subject/VOI) and the selected **Statistics** is plotted in the **Vector** tab, and all TACs in the **All** tab.

Plotting Layout

The contents of variables in the R workspace can be plotted in various ways. Note, however, that the structure of the aggregates used for comparative plotting (eg. scatter plots) needs to be identical, meaning that the number of rows and columns as well as the sorting order must be the same. *No attempt is made to pair corresponding data.*

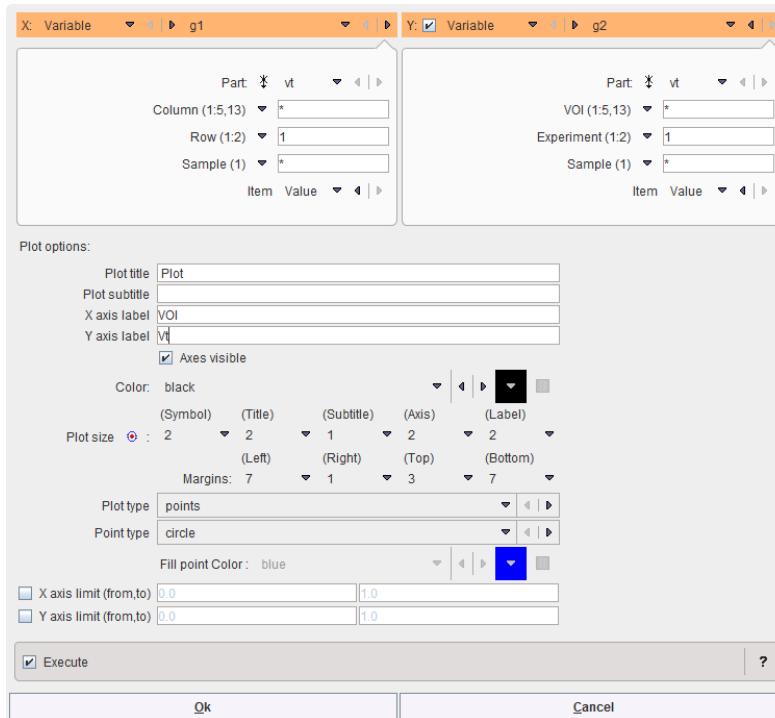
The button switches the R console to the **Plotting Layout** as illustrated below.



The different available types of plots are represented by the icons in the upper left. When one of the plot icons is activated, it shows a dialog window for the specification of the input data and the plotting parameters.

Plotting User Interface

The interface for the different plots shares common features. The example below shows the **Plot** interface.



The upper part represents the specification of the data to be plotted, as described *above* (on page 316). Depending on the situation, one or more data sets labeled **A**, **B**, **C** can be plotted. Some plots may generate variables which are of general interest. They are labeled with **Variable prefix** so that they can easily be identified in the workspace.

Most **Plot options** are straightforward, except for the **Plot size**. It relates to the default size of the R plotting function, which is variable. The plot sizes may need adjustment, when the canvas size is changed.

Plotting Code

From the specification in the dialog window R code is generated. If the **Execute** flag is enabled, the code is immediately executed and the graphics is shown in the main window. Otherwise the code is added to the history of the **Plots** command window and may be edited before execution, for instance to change a plotting option.

All executed code is added to the history of the **Plots** command window. On demand prior code can be recovered using the keyboard keys **Ctrl+Up-arrow** and **Ctrl+Down-arrow** similar to the **command window** (on page 380).

Plot Buffer

The plots created by any plotting actions (including scripts) end up in a plot buffer, so that they can be inspected at any time during a processing session by simply switching the list.

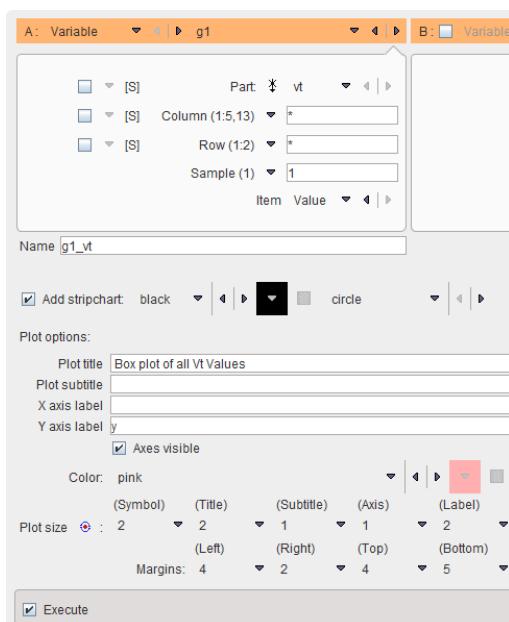


The buffer list can be edited with the buttons to its right:

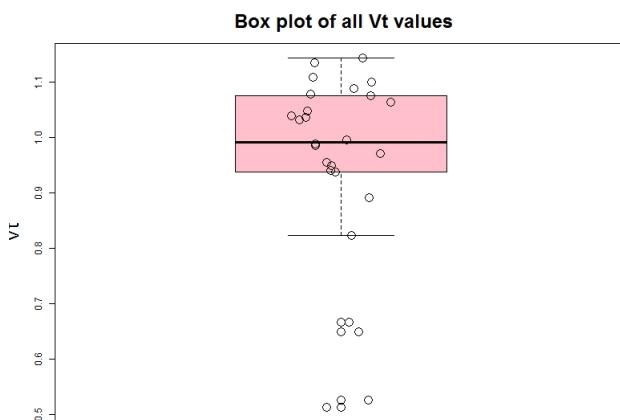
- Remove current table from the list.
- Clear the buffer list.
- Save the graphics to a file.

Box Plots

Box plots are widely used in descriptive statistics. They are particularly useful for comparing populations. The  button opens the box plot interface.



It produces from the data vector a plot with the following structure.



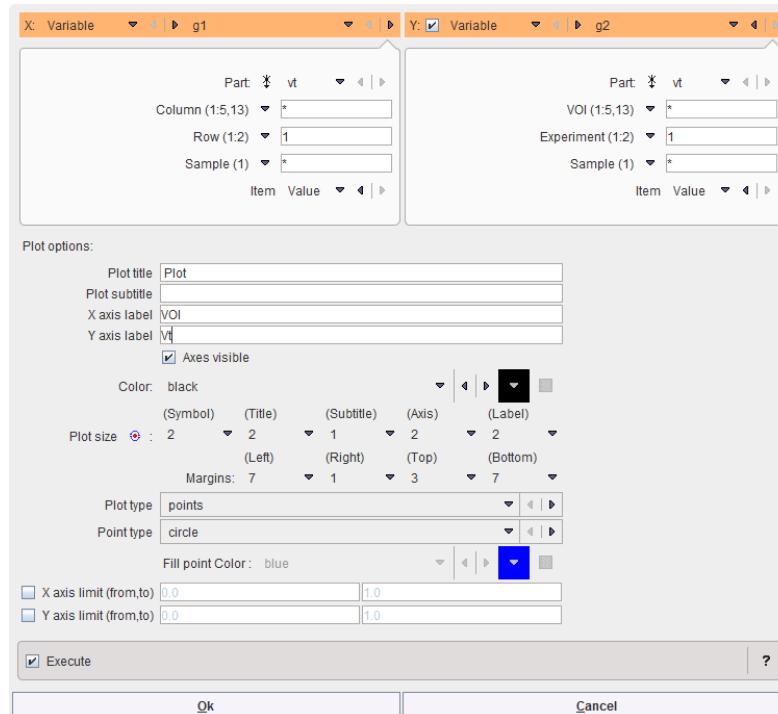
The lines of the box represent the first and third quartiles (Q1, Q3). The bold line in the box represents the median. The whiskers are calculated from the data according to Tukey's

method from the interquartile distance (Q3-Q1) and the data. Data points outside the whisker range are outliers.

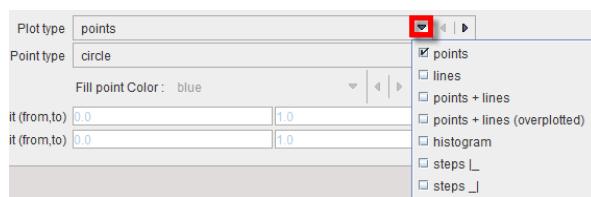
Note that the box plot is applied in the **Descriptive Statistics** script.

Data Plots

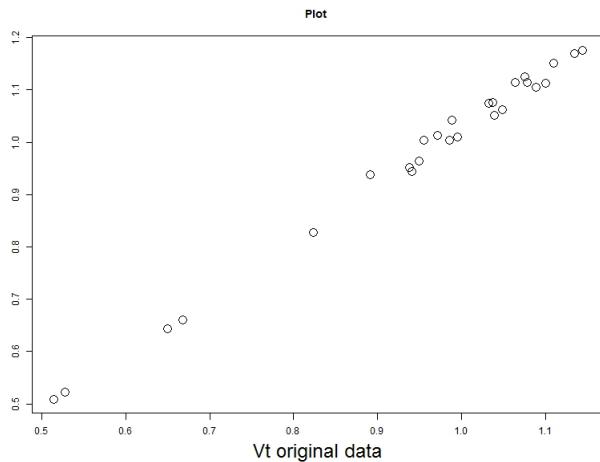
There is a general plotting procedure which can be called with the  icon. The user interface allows tailoring it to the plotting task.



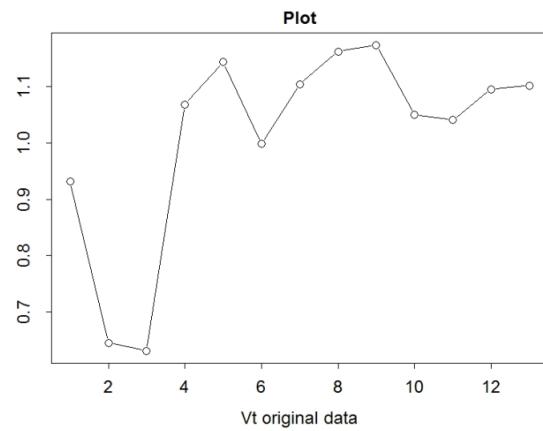
This function is more suited for plotting a single data vector, but x-y plots of two data vectors with equal length are also possible. The **Plot types** list offers the following choices for the plot presentation:



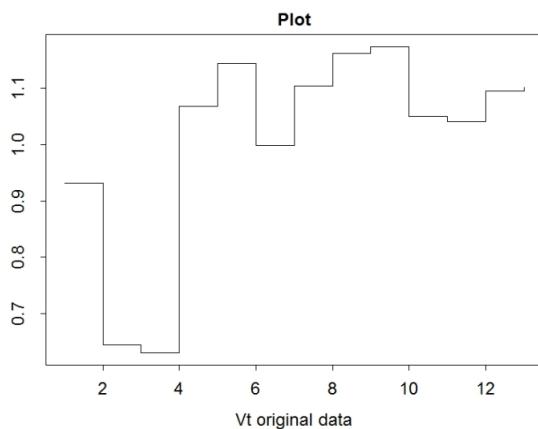
Some example plots: **points** plot with two variables **A** and **B**. Note that regression fits are not supported in this function.



Points + lines plot with a single data vector

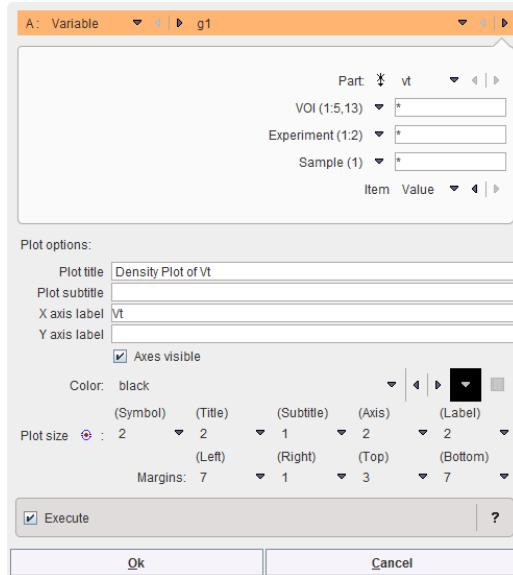


Steps plot with a single data vector

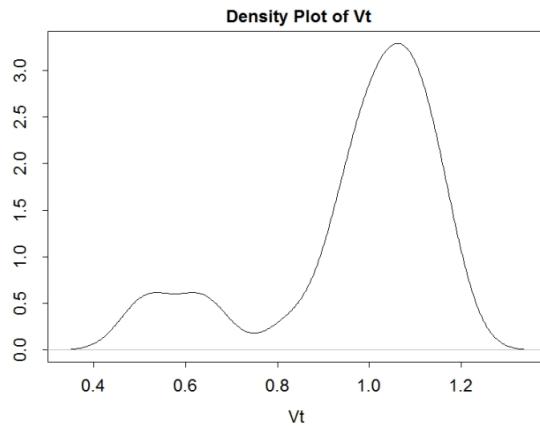


Density Plots

The fourth button  provides access to density plotting. This is an extension of the histogram approach and has the advantage that it doesn't depend on a bin size. The setting

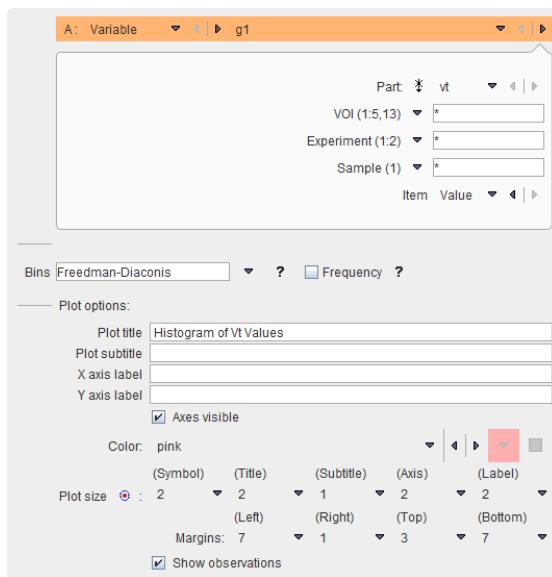


uses the Vt from all VOIs and Experiments (= analysis methods in the example data) and results in the plot below.

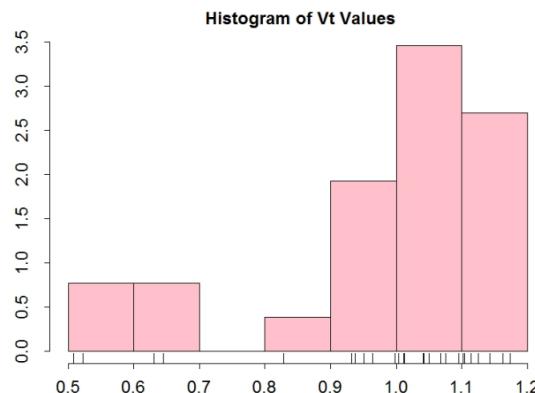


Histogram Plots

The third button  serves for plotting a histogram of a data vector.



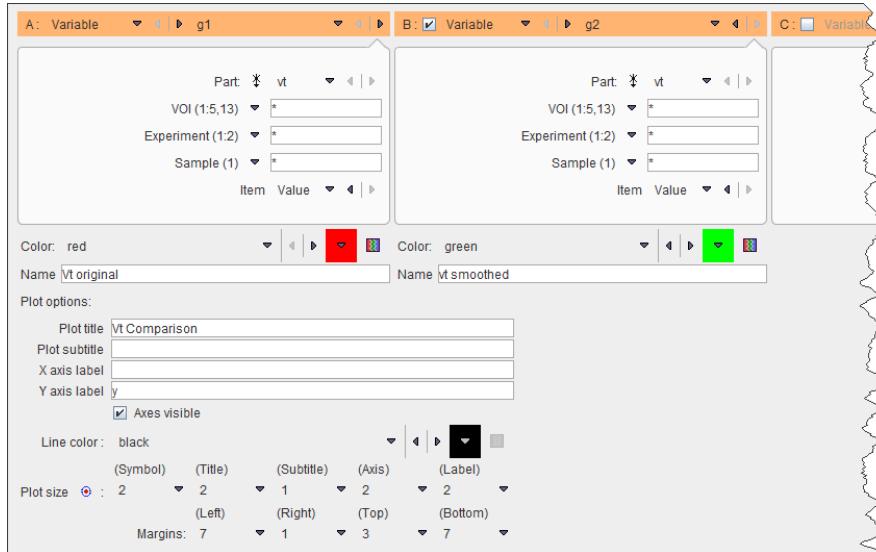
The number of **Bins** can be entered numerically or automatically calculated by 3 methods (**Sturges**, **Freedman-Diaconis**, **Scott**). The example results in the histogram below.



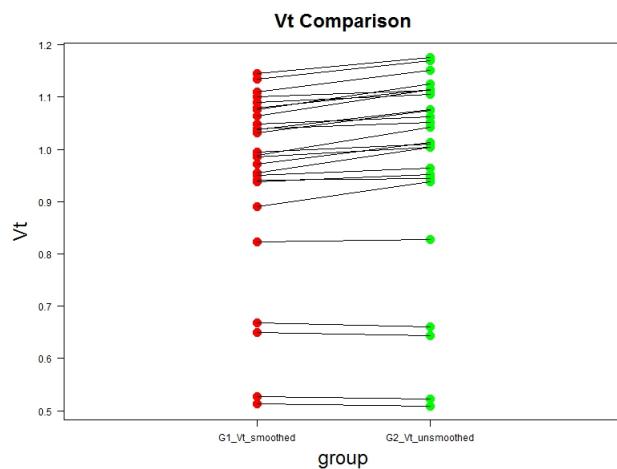
Note the indication of the values and the value ranges because **Show observations** and **Axes visible** are enabled.

Ladder Plots

Ladder plots visualize the relation of a test variable in two or more conditions, for instance pre-and post-treatment. It is called with the  button.

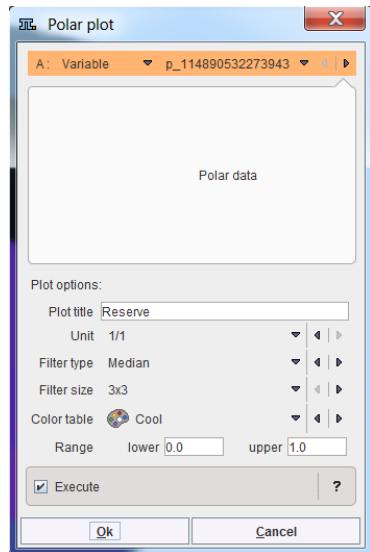


Up to 4 conditions can be connected. However, note that the implementation requires identical ordering of the subjects in the data vectors. The example below illustrates a comparison between two conditions.

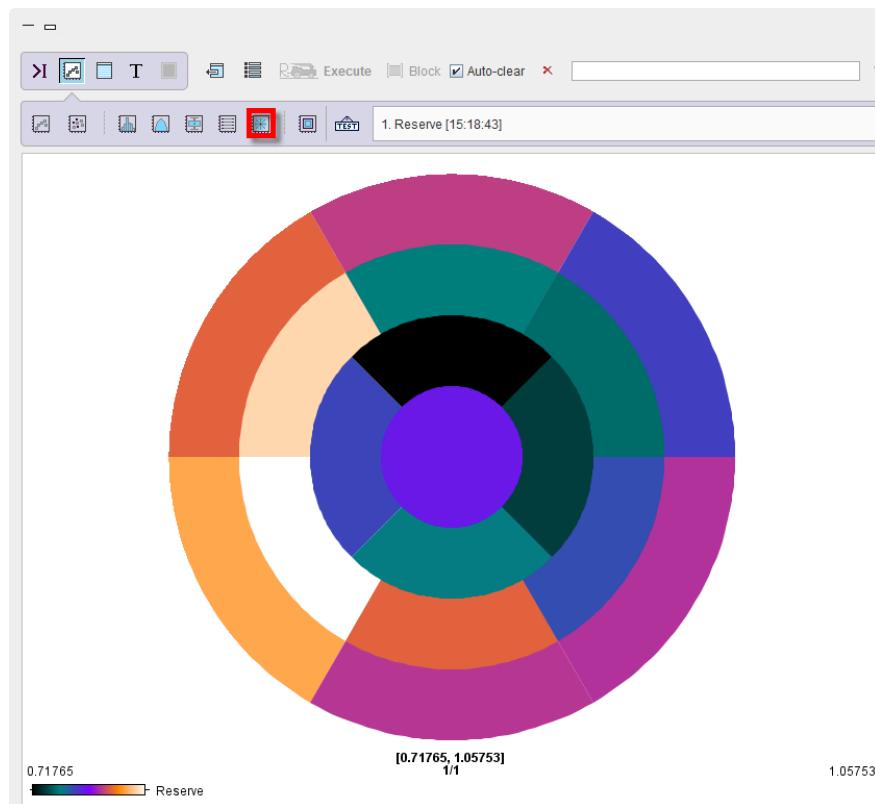


Polar Plots

The polar plotting function is called with the  button and opens the following dialog window:

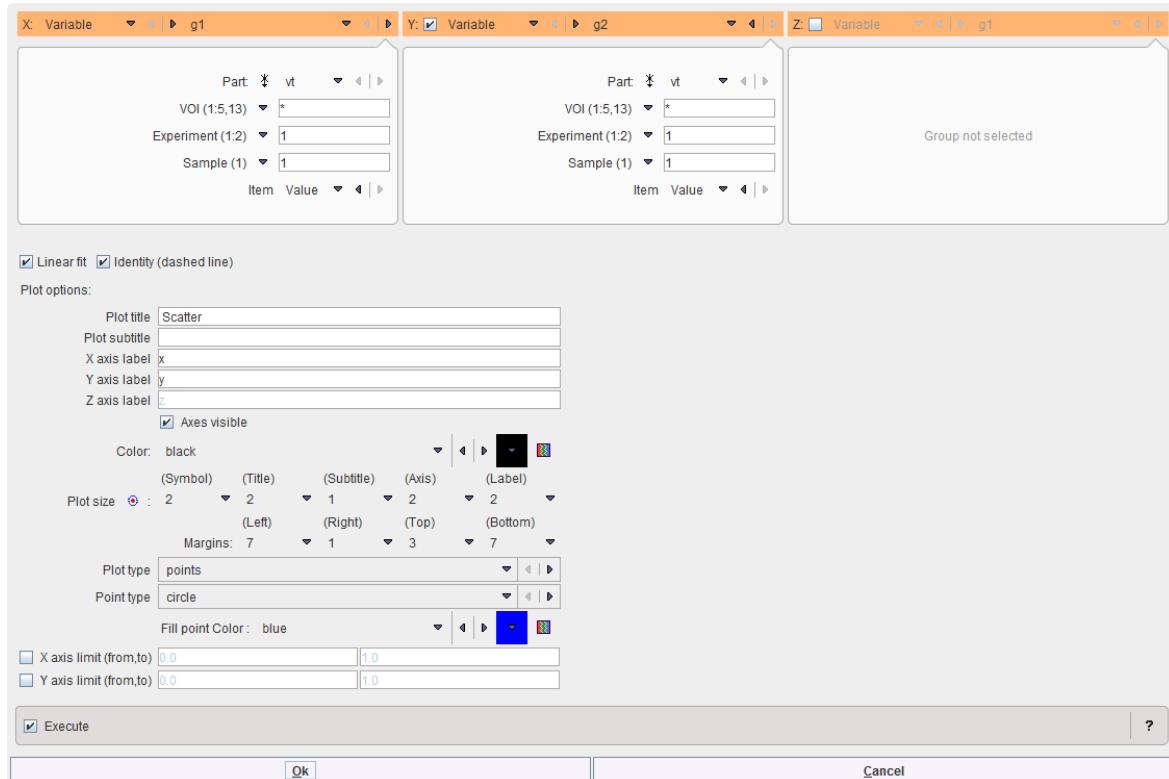


The user interface allows tailoring it to the plotting task and **Plot options** for the selected **Variable** are available. The result is shown below



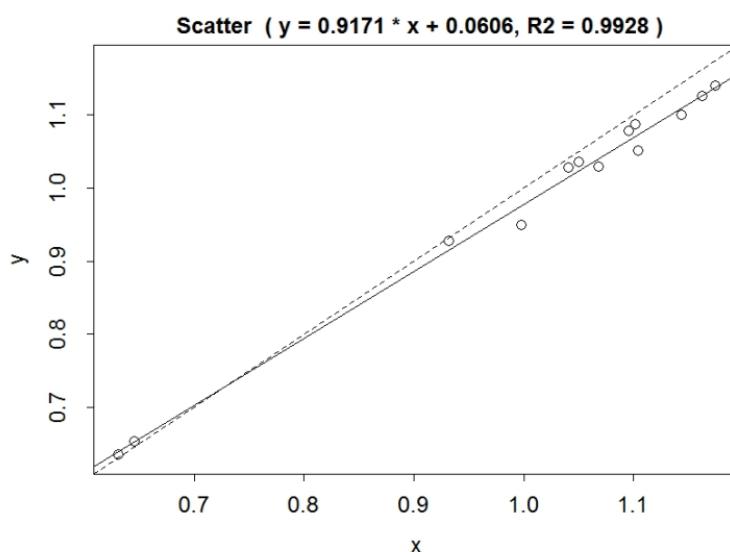
Scatter Plots

The scatter plotting function is called with the  button and opens the following dialog window.



Typically, the values of variable A will be plotted against variable B. If a third variable C is enabled (option), the plot is shown as a 3D scene in the PMOD 3D rendering tool.

The example below shows a scatter plot with a fitted regression line.



Analysis Scripts for Aggregates

PMOD has developed several scripts to support users with the statistical analysis of results arising in the comparison of populations or analysis methods. To use them efficiently, the outcome measures should be organized in groups by *aggregation* (on page 301).

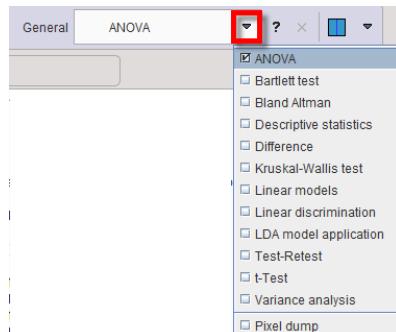
For example, if healthy controls are studied twice to determine the repeatability of an acquisition/data processing methodology, the results of the first study should be aggregated in a test group g1, and the results of the second study in a retest group g2. These groups can then be loaded into the R-console of PMOD, and analyzed with the **Test-Retest** script.

Another typical example is the comparison of analysis methods. The same set of population data will be processed twice with different methods, for instance to calculate the regional binding potential BP_{nd} . All BP_{nd} estimates resulting from method 1 are aggregated into a group g1, and all BP_{nd} estimates resulting from method 2 in group g2. The method comparison is then done by applying the script **Bland Altman Plot** to g1 and g2.

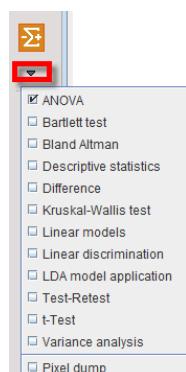
The scripts generate and execute native R code which can be inspected in the command console and serve as a basis for users to develop their own, modified scripts.

Invoking Scripts

After loading the data to be analyzed, scripts can be called either from the **Scripts** list of the command layout



or via the lateral taskbar by the indicated arrow button



The following sections describe each of the scripts. Most practical details are included in the **Descriptive Statistics** section, so please make sure to read this section first.

ANOVA for 3 or 4 Groups

The one-way ANOVA http://en.wikipedia.org/wiki/One-way_analysis_of_variance test compares the means between groups and determines whether any of those means is significantly different from the others. It can only detect that least two groups are different, but not which ones. Therefore, a pair-wise *post-hoc* comparison needs to be applied in the case significance. The ANOVA script applies the Tukey's HSD (Honest Significant Difference) *post-hoc* test.

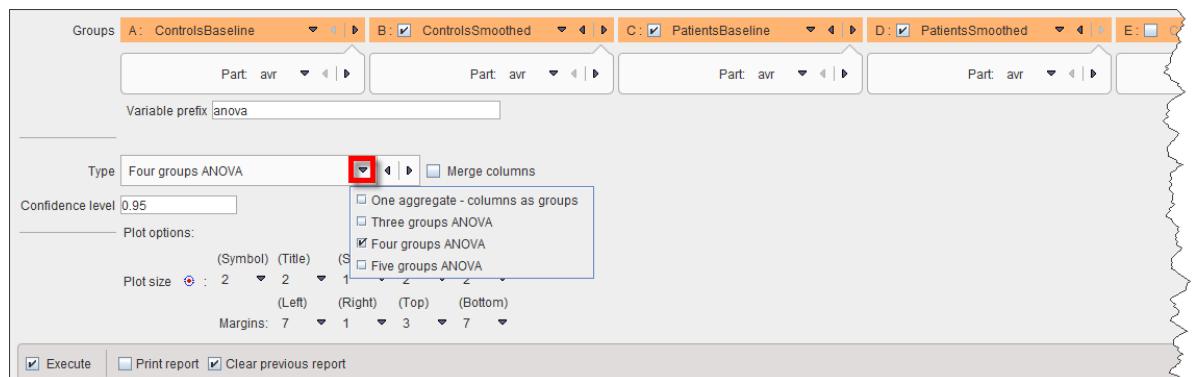
Assumptions

One-way ANOVA is based on the following assumptions:

- » the response variable (the dependent variable) is normally distributed;
- » the samples are independent;
- » the group variances are equal.

ANOVA Configuration

The ANOVA configuration window is illustrated below.



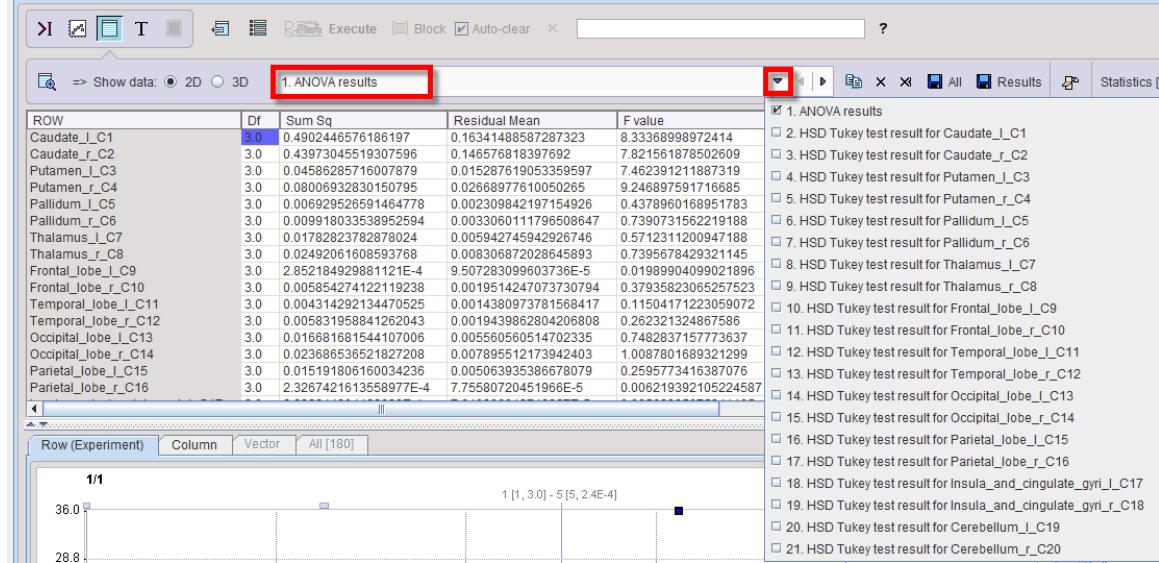
There are two **Types** of data organizations for the ANOVA script:

- 1) **One aggregate - columns as groups:** In this case the groups to be compared are arranged as columns in a single aggregate.
- 2) **Three groups ANOVA, Four groups ANOVA:** In these cases the groups to be compared are represented by separate aggregates. If **Merge columns** is enabled, the data of all columns will be pooled, otherwise the ANOVA analysis is performed between the respective columns of the aggregates which may represent different VOIs.

The **Confidence level** setting (default 95%) is related to Tukey's HSD test.

ANOVA Results

The script produces result two tables per VOI: one related to ANOVA (**anova_result**), and one related to Tukey HSD (**anova_tukey**).



A **p-value <0.05** in the ANOVA result table as in the example below indicates that there is a significant difference among the group means.

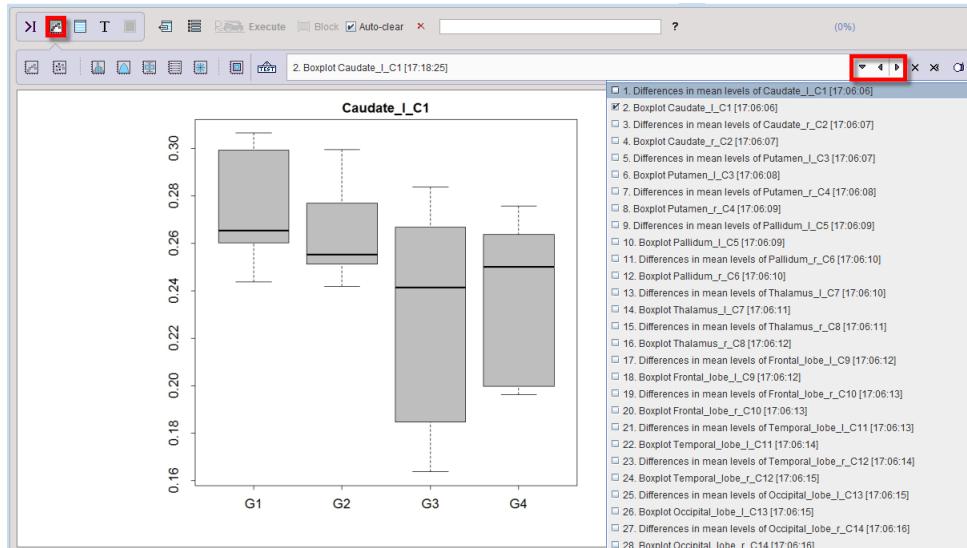
ROW	DF	Sum Sq	Residual Mean	F value	p value	Residual Df
Caudate_l_C1	3.0	0.01410560605464747	0.004701869684882492	4.983305546524553	0.005406579160438516	36.0
Caudate_r_C2	3.0	0.019400460248521073	0.00646820082840358	6.849285039201635	9.076730395220419E-4	36.0
Putamen_l_C3	3.0	0.004687531852089703	0.0015625106173632341	3.82034437769067	0.017869673091360408	36.0
Putamen_r_C4	3.0	0.0015376047306945198	5.125349102315066E-4	1.2007464658409468	0.3233702226141421	36.0
Pallidum_l_C5	3.0	0.008416899416275922	0.0028056331387586405	5.408945704627632	0.003548018217515405	36.0
Pallidum_r_C6	3.0	0.007719802175606428	0.0025732673918688093	5.011916164739707	0.005254218928524431	36.0
Thalamus_l_C7	3.0	0.0032245509864294994	0.0010748503288098331	1.6881292206263416	0.1868242110693498	36.0
Thalamus_r_C8	3.0	3.224590170847356E-4	1.0748633902832452E-4	0.343864910181384574	0.79374602023340618	36.0
Frontal_lobe_l_C9	3.0	0.009604458722075555	0.0032014862406918518	3.5806806889288173	0.023048609069433776	36.0
Frontal_lobe_r_C10	3.0	0.005167668174213824	0.0017225560580712747	5.360310907823661	0.0037213414314131916	36.0
Temporal_l* ^a r_C11	3.0	0.00889595827203	0.002963186081342401	4.19325208905931	0.1061314879430713	36.0

The corresponding Tukey HSD table

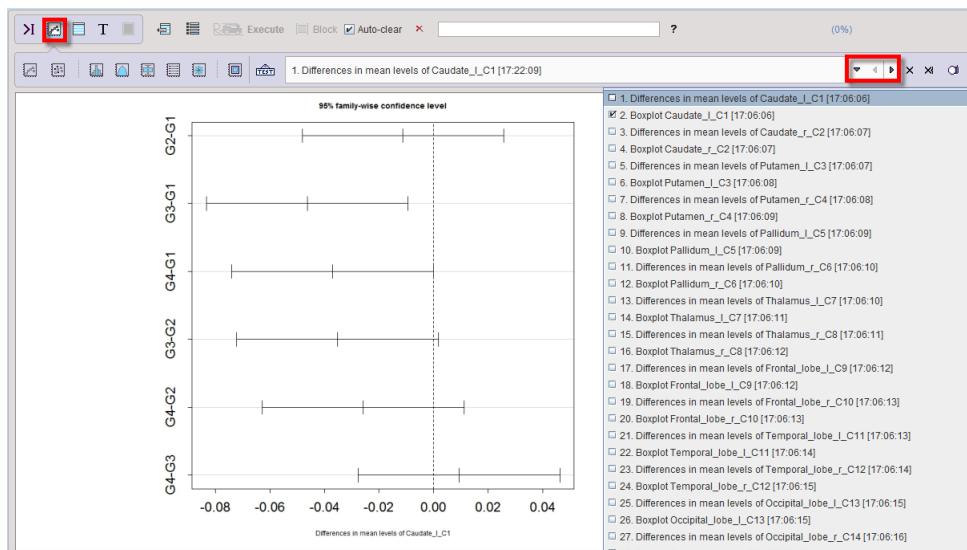
ROW	mean_diff	conf_low	conf_high	p-value	significance
G2 ControlsSmoothed_hav-G1 ControlsBaseline_hav	-0.011213827240208474	-0.048210653805054036	0.02578299932463709	0.8463573954414958	
G3 PatientsBaseline_hav-G1 ControlsBaseline_hav	-0.04638616210051297	-0.08338298866535854	-0.0093893553567405	0.009178199863940972	***
G4 PatientsSmoothed_hav-G1 ControlsBaseline_hav	-0.03705325909402321	-0.07405008565886878	-5.643252917764824E-5	0.0495311190656657	
G3 PatientsBaseline_hav-G2 ControlsSmoothed_hav	-0.03517234880304494	-0.07216916142515006	0.0018244917045410688	0.06741349884569432	*
G4 PatientsSmoothed_hav-G2 ControlsSmoothed_hav	-0.025839431853814737	-0.0628382584186603	0.01157394711030826	0.2540279449889604	
G4 PatientsSmoothed_hav-G3 PatientsBaseline_hav	0.009332903006489757	-0.027663923558355806	0.04632972957133532	0.9042347241422231	

allows identifying G3 being different from G1 and G2, since the p-value is <0.05 for **G3-G1** and **G3-G2**, whereas it is not significant for **G2-G1**.

The results are illustrated by two plots per VOI: a *box plot* (on page 324) summarizing the regional statistics,



and a plot of the **Confidence intervals** of the group differences from the Tukey's HSD test. If the zero difference is not included in the confidence interval, the group difference is significant.

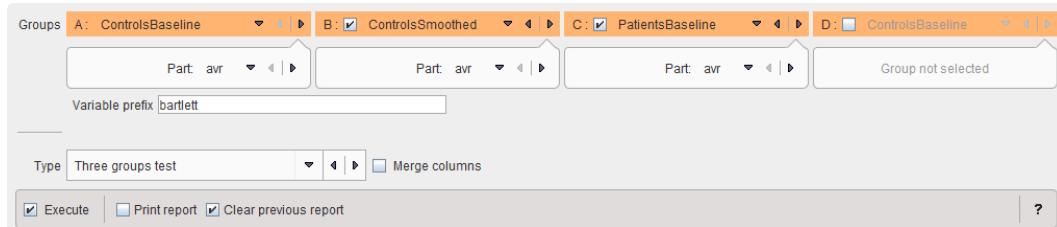


Bartlett Test

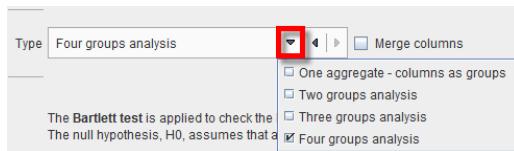
The **Bartlett test** http://en.wikipedia.org/wiki/Bartlett's_test is used to test whether the variances of groups to be compared is equal (homoscedasticity, or homogeneity of variances). Some statistical test such as *ANOVA* (on page 333) assume equal variances. The Bartlett test can be used to verify that assumption.

ANOVA Configuration

The Bartlett Test configuration window is illustrated below.



Up to four groups can be compared, according to the **Type** selection



If **Merge columns** is enabled, the data of all columns will be pooled, otherwise the test is performed between the respective columns of the aggregates.

With the **One aggregate - columns as groups** setting it is assumed that the groups to be compared are arranged as columns in a single aggregate.

Bartlett Results

The script produces a result table (**bartlett_result**) listing the **p-value** for each aggregate column and indicating its significance.

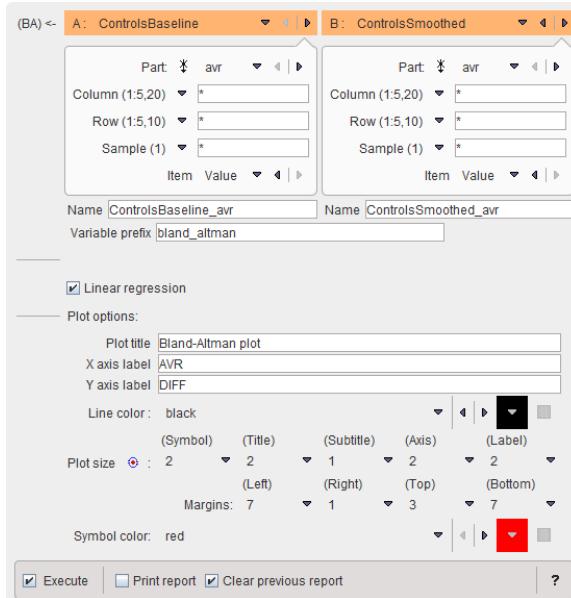
ROW	chi-squared	df	p-value	significance
Caudate_l_C1	21.543223145051826	2.0	2.0986911582439567E-5	***
Caudate_r_C2	21.069389647452073	2.0	2.6597460312034135E-5	***
Putamen_l_C3	4.159271648082747	2.0	0.12497571706375729	
Putamen_r_C4	4.765302822319387	2.0	0.09230551290337977	*
Pallidum_l_C5	0.2136026021347471	2.0	0.8987042268211065	
Pallidum_r_C6	0.31645526703179333	2.0	0.8536554392608608	
Thalamus_l_C7	8.488653748835473	2.0	0.01434538676566669	**
Thalamus_r_C8	12.508485785733843	2.0	0.0019222807969696877	***
Frontal_lobe_l_C9	0.3697189654353505	2.0	0.8312210765729267	
Frontal_lobe_r_C10	26.24008639618145	2.0	2.0046457460250256E-6	***
Temporal_lobe_l_C11	13.58515886814922	2.0	0.0011220707306488084	***
Temporal_lobe_r_C12	38.01502682744144	2.0	5.560858057399242E-9	***
Occipital_lobe_l_C13	3.6784444290680245	2.0	0.1589410004346848	
Occipital_lobe_r_C14	37.63280056182575	2.0	6.7319547591259065E-9	***
Parietal_lobe_l_C15	19.729706850290814	2.0	5.196950648475217E-5	***
Parietal_lobe_r_C16	35.2393798770715	2.0	2.2277270266428418E-8	***
Insula_and_cingulate_gyril_l_C17	18.16594387435063	2.0	1.1358354219969377E-4	***
Insula_and_cingulate_gyril_r_C18	2.6785066426683	2.0	0.26204125616625185	
Cerebellum_l_C19	5.178270226551125	2.0	0.07508495198873942	*
Cerebellum_r_C20	16.74367055603604	2.0	2.3129068127468311E-4	***

Bland Altman Plot

The Bland-Altman plot is aimed at comparing two measurement methods [1]. It simply plots the difference between the measurements against their average. The mean difference is the estimated bias, and from the standard deviation of the differences the 95% *limits of agreement* can be calculated (mean±1.96std).

Bland Altman Plot Configuration

The **Bland Altman Plot** script shows the following dialog window.



Two variables have to be defined, which will be sorted so that the correspondence between samples is ensured. The **Linear regression** convenience option allows getting a scatter plot with a regression line at the same time as the Bland Altman plot.

Bland Altman Plot Results

There are three numeric result tables: the data for the plot (**AVR** on x-axis, **DIFF** on y-axis) in the **BA** table,

T Execute Block <input checked="" type="checkbox"/> Auto-clear					
=> Show data: <input checked="" type="radio"/> 2D <input type="radio"/> 3D 1. bland_altman_BA					
<hr/>					
ROW	AVR	DIFF			
1	0.8296661665443734	0.021737376798157904			
2	0.865866155735673	0.031030681645378255			
3	0.9336023090393769	0.03920132351584349			
4	0.8551258276962364	0.03809415046821463			
5	0.7935018255101541	0.020949987047344854			
6	0.8618187879113204	0.026203795687665177			
7	0.7488828290219817	0.012824940118722594			

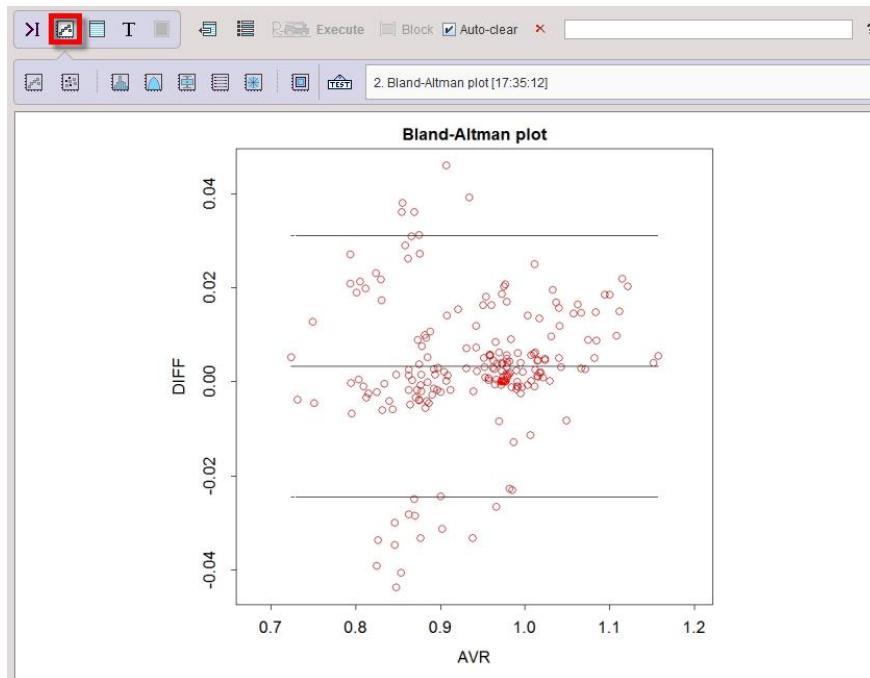
the analysis results in the **diff_result** table,

=> Show data: <input checked="" type="radio"/> 2D <input type="radio"/> 3D 1. Difference				
<hr/>				
ROW	mean	sd	lower limit	upper limit
1	0.0033036346103496477	0.014210751311158606	-0.02454943795952122	0.031156707180220518

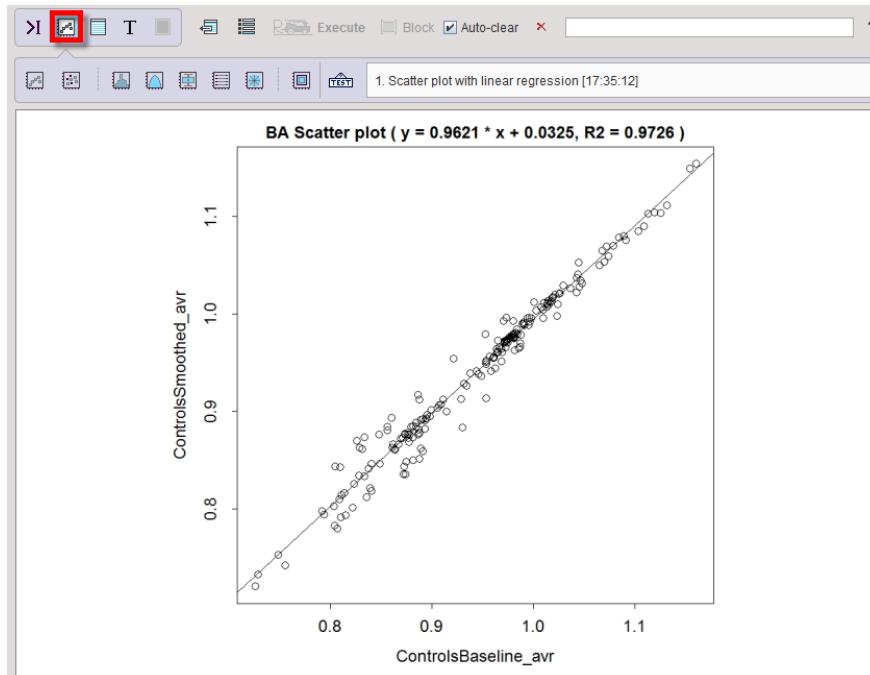
and the equation of the linear regression in the **regression** table.

=> Show data: <input checked="" type="radio"/> 2D <input type="radio"/> 3D 2. Regression			
<hr/>			
ROW	Slope	Intercept	R squared
1	0.9621	0.0325	0.9726

The corresponding plots can be inspected in the plot layout:



and



Reference:

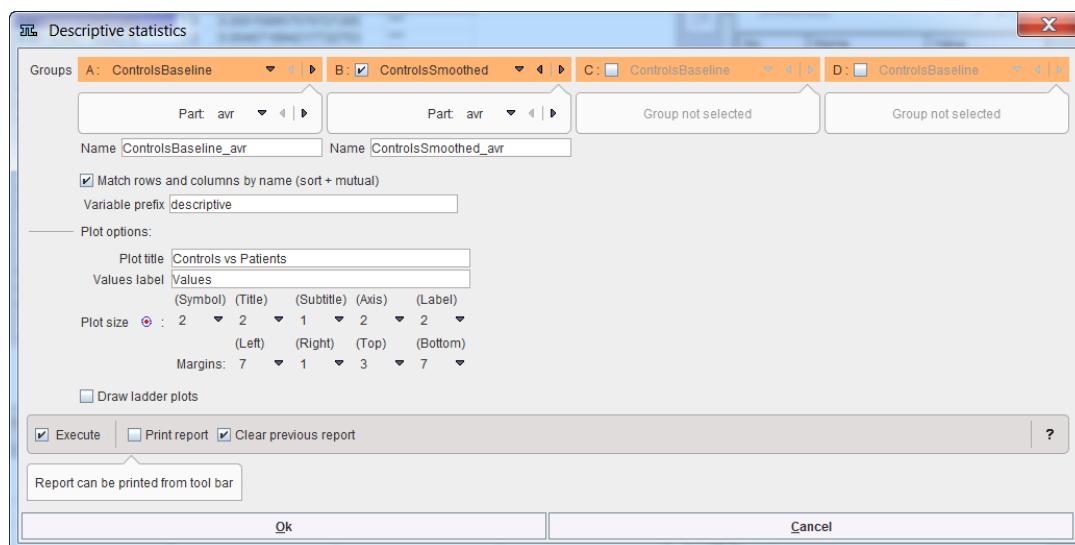
1. Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986, 1(8476):307-310.

Descriptive Statistics

The **Descriptive statistics** script serves for summarizing the statistical properties of outcomes assembled in one or several PMOD aggregates.

Descriptive Statistics Configuration

The **Descriptive Statistics** script shows the following dialog window.



Note that up to 4 data sets can be compared. In the example case 2 **Groups** are selected and the variables **ControlsBaseline** and **PatientsBaseline**. Only one statistic can be compared at a time, to be selected from the **Part** list. If the parameter names don't match, the program will complain, but still perform the calculation.

The results consist of tables as well as graphic plots. To group the table results a **Variable prefix** can be specified. **Plot title** and **Values label** should be edited such that the plots are meaningfully annotated. The **Draw ladder** plot option allows visualizing each data point across the three data sets. This is only reasonable, if all groups include the same subjects. In this case, the **Match rows and columns by name** box should be checked.

Descriptive Statistics Results

After running the script the workspace is populated with new variables, and plots have been generated and added to the plot history. The R console is in the table layout and shows a statistic summary table of the last group. For each VOI it lists the minimum, first quartile (Q1), median, mean, standard deviation, third Quartile (Q3) and maximum across the subjects. The

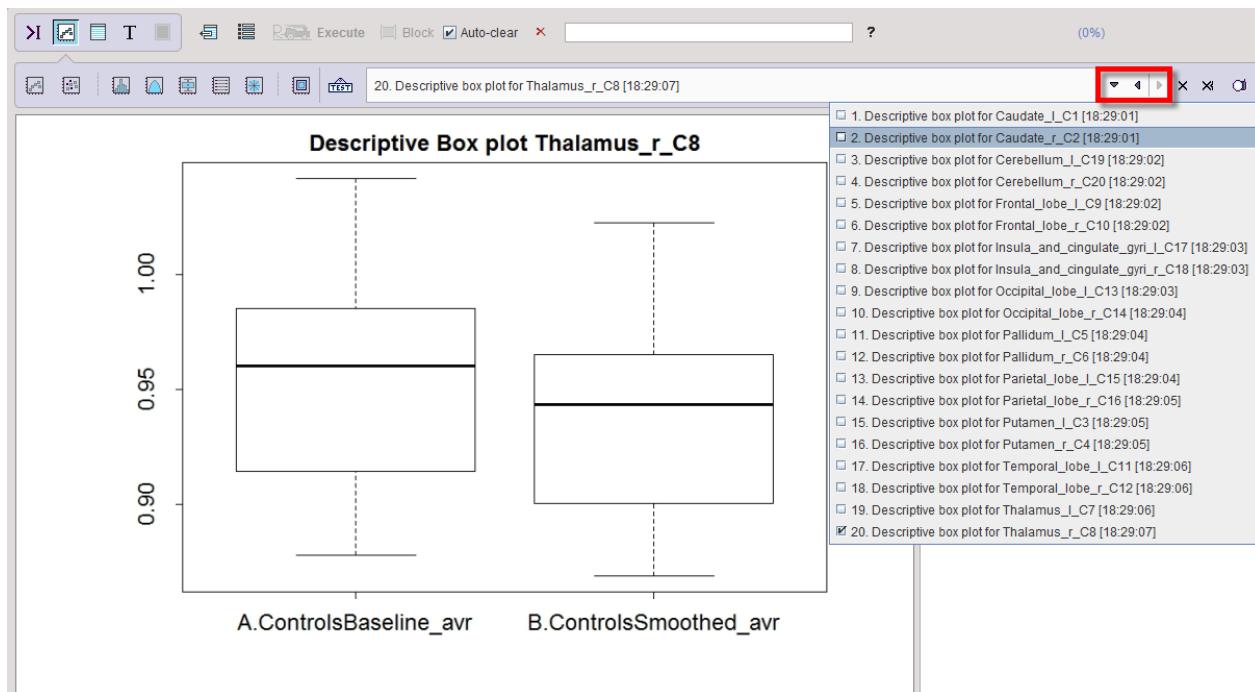
ROW	min	Q1	median	mean	sdev	Q3
Caudate_l_C1	0.74247	0.78303	0.83984	0.82686	0.04817	0.8503
Caudate_r_C2	0.72066	0.79399	0.81716	0.8184	0.04641	0.8596
Cerebellum_l_C19	0.753	0.81444	0.85567	0.84538	0.04761	0.88553
Cerebellum_r_C20	0.9714	0.97277	0.97448	0.97451	0.00222	0.97669
Frontal_lobe_l_C9	0.92892	0.9487	0.95786	0.97492	0.06356	0.96609
Frontal_lobe_r_C10	0.83375	0.863	0.88763	0.88105	0.02215	0.89337
Insula_and_cingulate_gyri_l_C17	0.98023	0.99146	0.99663	0.99734	0.0105	1.00713
Insula_and_cingulate_gyri_r_C18	0.733	0.80999	0.84396	0.83602	0.05018	0.86671
Occipital_lobe_l_C13	0.94155	0.95568	0.96597	0.98623	0.06179	0.97984
Occipital_lobe_r_C14	0.84695	0.87315	0.87788	0.88166	0.01915	0.89665
Pallidum_l_C5	0.86142	0.88126	0.93585	0.94275	0.06603	0.99311
Pallidum_r_C6	0.84317	0.8699	0.8805	0.90488	0.05956	0.97344
Parietal_lobe_l_C15	0.87291	0.97369	1.00545	0.99373	0.05234	1.02136
Parietal_lobe_r_C16	0.93965	0.9565	0.97358	0.97474	0.0255	0.9886
Putamen_l_C3	1.01029	1.05371	1.07289	1.06776	0.03109	1.09033
Putamen_r_C4	0.99567	1.03204	1.04549	1.05477	0.03633	1.0803
Temporal_lobe_l_C11	0.87659	0.98104	1.00743	0.9996	0.05201	1.01724
Temporal_lobe_r_C12	0.96465	0.97111	0.97639	0.98344	0.01784	0.99233
Thalamus_l_C7	0.80274	0.87651	0.93167	0.91665	0.05628	0.96548
Thalamus_r_C8	0.8688	0.90037	0.94335	0.93966	0.0501	0.96511
1.02261						

Using the buffer selection, the table can easily be switched to the other groups, as well as the **VOI Means** table which just shows the VOI means and standard deviations for all groups.

ROW	A.ControlsBaseline_avr_mean	A.ControlsBaseline_avr_sdv	B.ControlsSmoothed_avr_mean	B.ControlsSmoothed_avr_sdv
Caudate_l_C1	0.85609	0.05528	0.82686	0.04817
Caudate_r_C2	0.84307	0.05664	0.8184	0.04641
Cerebellum_l_C19	0.84104	0.04793	0.84538	0.04761
Cerebellum_r_C20	0.97464	0.00221	0.97451	0.00222
Frontal_lobe_l_C9	0.97969	0.06343	0.97492	0.06356
Frontal_lobe_r_C10	0.88159	0.02235	0.88105	0.02215
Insula_and_cingulate_gyri_l_C17	0.99833	0.01235	0.99734	0.0105
Insula_and_cingulate_gyri_r_C18	0.83333	0.05021	0.83602	0.05018
Occipital_lobe_l_C13	0.99127	0.06212	0.98623	0.06179
Occipital_lobe_r_C14	0.88226	0.01923	0.88166	0.01915
Pallidum_l_C5	0.91801	0.07308	0.94275	0.06603
Pallidum_r_C6	0.87574	0.06955	0.90488	0.05956
Parietal_lobe_l_C15	0.99493	0.05385	0.99373	0.05234
Parietal_lobe_r_C16	0.97619	0.02636	0.97474	0.0255
Putamen_l_C3	1.08184	0.03318	1.06776	0.03109
Putamen_r_C4	1.06772	0.03748	1.05477	0.03633
Temporal_lobe_l_C11	1.00144	0.05284	0.9996	0.05201
Temporal_lobe_r_C12	0.98625	0.01878	0.98344	0.01784
Thalamus_l_C7	0.92777	0.06083	0.91665	0.05628
Thalamus_r_C8	0.95626	0.0546	0.93966	0.0501

Note the copy and save buttons in the buffer controls for exporting the table data.

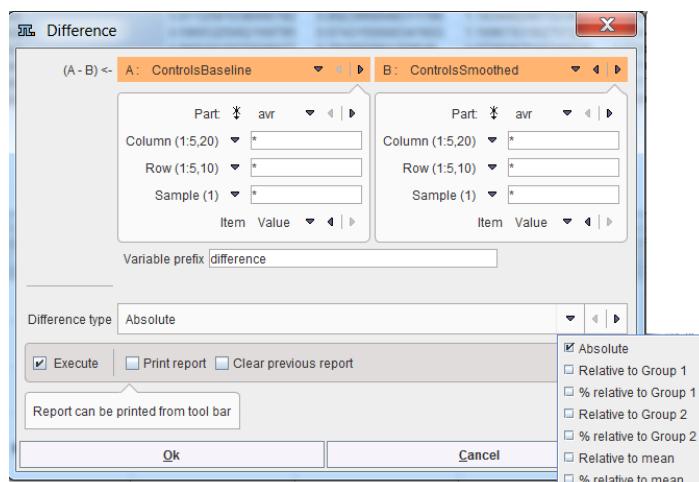
The same information as in the tables is visualized by one *box plot* (on page 324) per VOI, providing a convenient side by side comparison of the groups. Please activate the plot layout and use the buffer arrows to browse through the different VOIs.



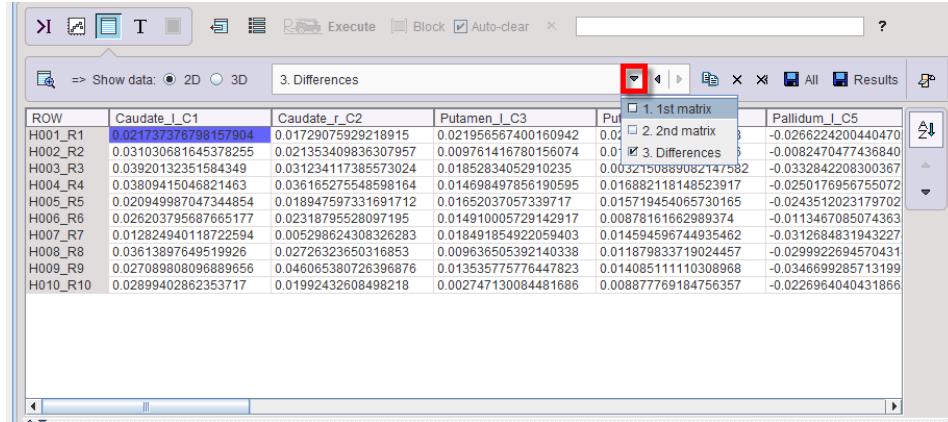
If the **Ladder** plot option was enabled, box plots are alternated with *ladder plots* (on page 329).

Difference

The **Difference** script is a simple facility for calculating the difference between two groups. Besides the **Absolute** difference there are various relative differences available, which can be configured with the **Difference type** option list.



The results of the script are three tables, available through the buffer



ROW	Caudate_I_C1	Caudate_r_C2	Putamen_I_C3	Pu...	1. 1st matrix	Pallidum_I_C5
H001_R1	0.021737376798157904	0.01729075929218915	0.021956567400160942	0.0...	<input type="checkbox"/> 1. 1st matrix	-0.0266224200440470
H002_R2	0.031030681645378255	0.021353409836307957	0.009761416780156074	0.0...	<input type="checkbox"/> 2. 2nd matrix	-0.0082470477436840
H003_R3	0.03920132351584349	0.03123411738573024	0.01852834052910235	0.0032150889082147582	<input checked="" type="checkbox"/> 3. Differences	-0.0332842208300367
H004_R4	0.03809415046821463	0.036165275548598164	0.014698497856190595	0.016882118149523917	<input type="checkbox"/> 4. 3rd matrix	-0.0250176956755072
H005_R5	0.02094987047344854	0.018947597331691712	0.016562037057339717	0.015719454065730165	<input type="checkbox"/> 5. 4th matrix	-0.0243512023179702
H006_R6	0.026203795687665177	0.02318795528097195	0.014910005729142917	0.00878161662989374	<input type="checkbox"/> 6. 5th matrix	-0.0113467085074363
H007_R7	0.012824940118722594	0.005298624308326283	0.018491854922059403	0.014594596744935462	<input type="checkbox"/> 7. 6th matrix	-0.0312684831943227
H008_R8	0.03613897649519926	0.02726323650316853	0.009636505392140338	0.011879833719024457	<input type="checkbox"/> 8. 7th matrix	-0.0299922694570431
H009_R9	0.02708980809688955	0.046065380726396876	0.013535757776447823	0.014085111110308968	<input type="checkbox"/> 9. 8th matrix	-0.0346599285713199
H010_R10	0.02899402862353717	0.01992432608498218	0.002747130084481686	0.008877769184756357	<input type="checkbox"/> 10. 9th matrix	-0.0226964040431866

diff_g1_g2 represents the calculated difference, whereas **diff_mat1** and **diff_mat2** contain the extracted input data for the calculation.

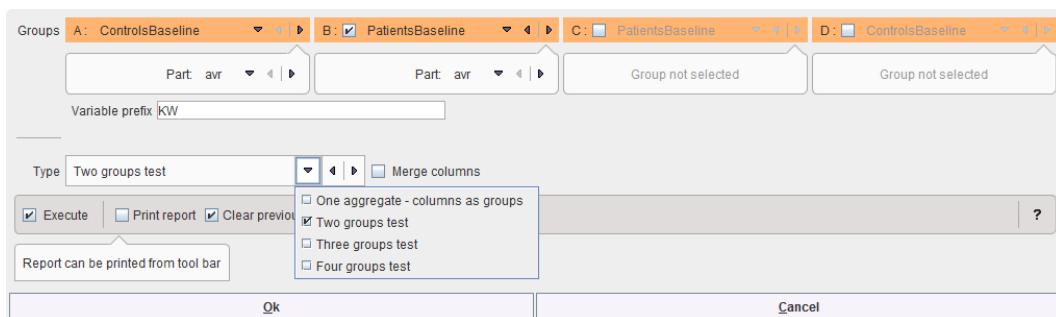
Kruskal-Wallis Test

The *Kruskal-Wallis one-way analysis of variance by ranks*

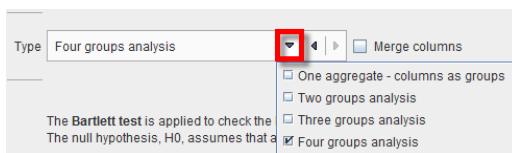
http://en.wikipedia.org/wiki/Kruskal%20%80%93Wallis_one-way_analysis_of_variance is a non-parametric equivalent of the one-way ANOVA (on page 333). It assumes independent samples and has the null hypothesis, that the distribution is identical. If the calculated p-value is <0.05, it is concluded that the distributions are nonidentical at the 0.05 significance level (*R example* <http://www.r-tutor.com/elementary-statistics/non-parametric-methods/kruskal-wallis-test>).

Kruskal-Wallis Configuration

The Kruskal-Wallis configuration window is illustrated below.



Up to four groups can be compared, according to the **Type** selection



If **Merge columns** is enabled, the data of all columns will be pooled, otherwise the test is performed between the respective columns of the aggregates.

With the **One aggregate - columns as groups** setting it is assumed that the groups to be compared are arranged as columns in a single aggregate.

Kruskal-Wallis Results

The script produces a result table (**kruskal_wallis_result**) listing the **p-value** for each aggregate column and indicating its significance.

ROW	chi-squared	df	p-value	significance
Caudate_l_C1	7.822857142857146	1.0	0.005158957570721305	***
Caudate_r_C2	8.251428571428576	1.0	0.004071994217732753	***
Putamen_l_C3	7.405714285714282	1.0	0.006501702373081834	***
Putamen_r_C4	7.0	1.0	0.008150971593502698	***
Pallidum_l_C5	0.02285714285714846	1.0	0.8798291600118152	
Pallidum_r_C6	0.05142857142857336	1.0	0.8205958397554377	
Thalamus_l_C7	0.09142857142856542	1.0	0.7623688184698475	
Thalamus_r_C8	0.09142857142856542	1.0	0.7623688184698475	
Frontal_lobe_l_C9	0.05142857142857338	1.0	0.8205958397554377	
Frontal_lobe_r_C10	0.09142857142856542	1.0	0.7623688184698475	
Temporal_lobe_l_C11	0.02285714285714846	1.0	0.8798291600118152	
Temporal_lobe_r_C12	0.005714285714283562	1.0	0.9397429895770847	
Occipital_lobe_l_C13	1.651428571428582	1.0	0.1987646063732338	
Occipital_lobe_r_C14	1.8514285714285705	1.0	0.17361733442494376	
Parietal_lobe_l_C15	1.1199999999999903	1.0	0.28991845394257193	
Parietal_lobe_r_C16	0.0	1.0		
Insula_and_cingulate_gyri_l_C17	0.005714285714283562	1.0	0.9397429895770847	
Insula_and_cingulate_gyri_r_C18	9.605714285714285	1.0	0.0019397281129030432	***
Cerebellum_l_C19	7.0	1.0	0.008150971593502698	***
Cerebellum_r_C20	4.805714285714274	1.0	0.02836505605210208	**

Linear Models: Statistical Analysis of Regional Imaging Data

Advanced statistical techniques based on linear statistical model are implemented in the PMOD R interface. These solutions have been developed by Prof Karl Herholz, University of Manchester, UK, who is a renowned expert and consultant in the field of neuroimaging, with particular interest in dementia and brain tumors. His statistical expertise was sharpened as the coordinator of multiple international multicenter studies, and by the development of automated image analysis procedures, such as the one employed in PMOD's PALZ module.

Images provide a wealth of information. They are essential for demonstration and analysis of normal and pathological anatomy and function in medicine and biomedical sciences. Computerized tomography (CT) and related techniques, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), have made huge progress in the recent decades. They are frequently being used to provide diagnostic images interpreted visually by trained observers (e.g., radiologists).

Recently, it is increasingly being recognized that some images can also be regarded as data sets representing a quantitative parameter measured simultaneously in a large number of anatomical regions. Particularly, as each region in an image (with image pixels or voxels as the smallest regions that could potentially be studied) provides a separate dependent variable, their number may be very large and will often exceed the number of individuals under study. This situation creates a particular statistical challenge, which will be addressed in the current section.

These challenges can best be addressed by procedures which:

- » take into account that regional data originating from the same individual are not independent from each other, and describe their dependency by a covariance matrix;
- » provide tests for comparing the experimental effects between regions;
- » provide proper correction for multiple comparisons.

The procedures are based on linear statistics models. Two approaches fulfilling these requirements will be described:

- 1) Repeated measures and multivariate analysis of variance (rm-ANOVA, MANOVA)
- 2) Linear mixed effect models (LME).

The table below summarizes the benefits and limits of the two linear statistics models:

MANOVA	LME
Analytical minimization of residual variance within groups for general linear model	Iterative minimization of residual variance for general linear model
Analytical separation of variance components for within-subject and between-subject factors	Fitting the mean effects for all specified experimental factors, and the variance of a random factor associated with individuals
Automatic inclusion of interactions between within and between-subject factors	All interactions need to be specified in the model for inclusion
May fail if too many highly correlated regions are included in model	Can accommodate a large number of regions
Requires a balanced design (groups of equal size) for correct separation of variance components	Works for balanced and unbalanced designs
Does not allow missing values	In presence of missing values effect sizes can still be fitted, but statistical tests to determine their significance may fail

Data Structure - Master Table

The data structure to be used in the linear models statistical analysis can best be visualized by a master table where columns represent regions and rows represent individuals. To build up the master table, aggregated files are required. It is essential that consistent group and condition names are correctly encoded for each aggregated file. Detail information about the aggregation procedure is available *above* (on page 302).

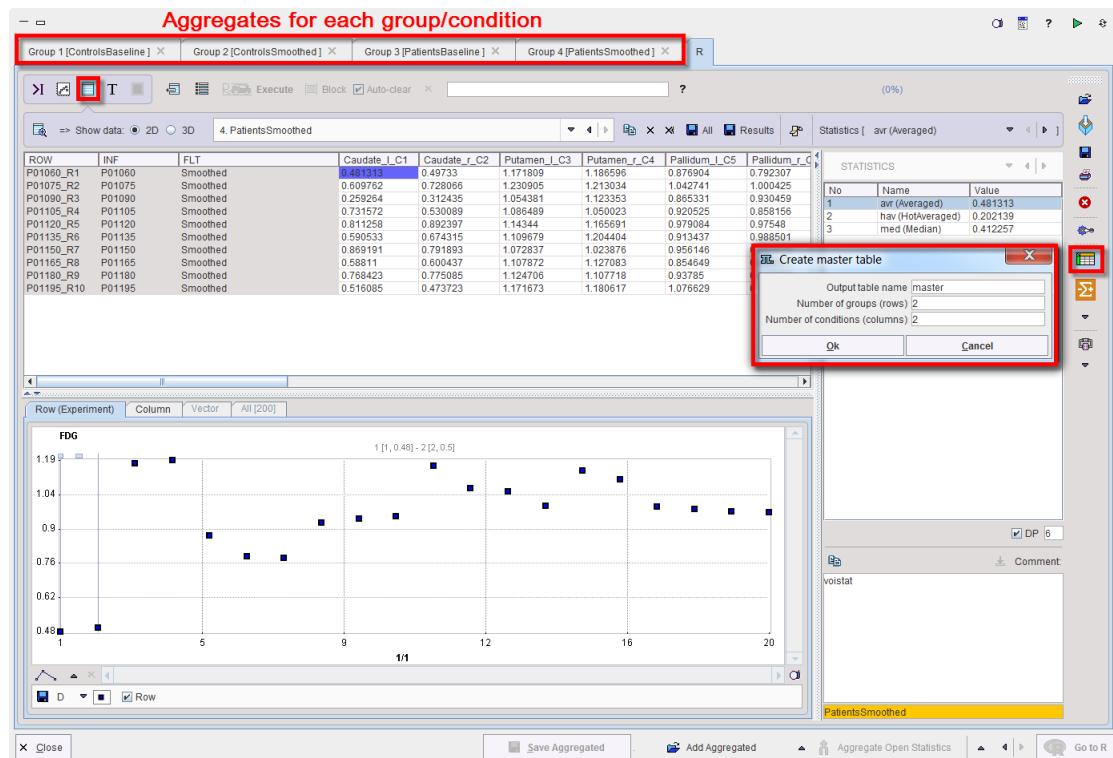
Statistically, individuals (rows) are independent from each other while regions (columns) are not, which is an important distinction for the analysis structure. Each classification axis can have further subdivisions. E.g., individuals could be split into experimental groups, while the same regions might be present in the left and the right brain hemisphere. We would then

have the experimental group classification as a “between-subject” variable, and regions and hemispheres as nested “within-subject” variables.

In-vivo imaging studies will often repeat scans in the same individuals. One could then analyze the difference between baseline and follow-up as the dependent variable of interest. Alternatively, measurement instance (baseline and repeat, optionally also further repeat measurements) could be represented as a within-subject variable (analyzing the same set of regions at all measurement times). Note, that repeat measurements would not represent another group of individuals, thus they are to be added as columns, not as rows.

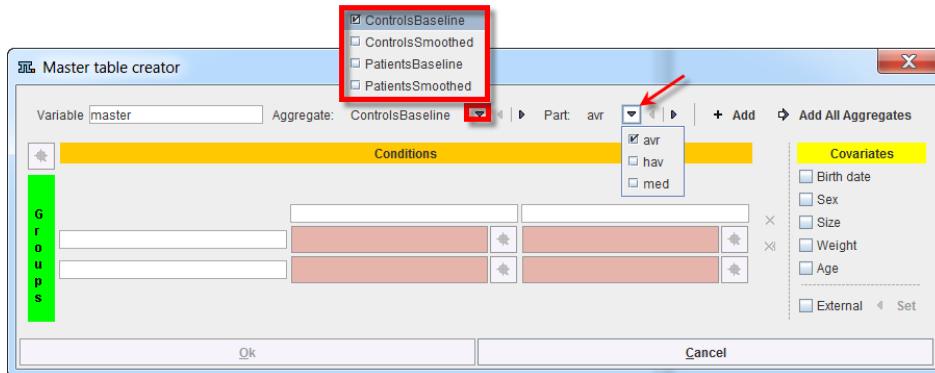
The example below illustrates how to build the master table. To this purpose, four aggregates were created and transferred to the R console. Two groups, Control and Patient were analyzed in two conditions: *Baseline* and *Smoothed*. Please note that an aggregate was prepared beforehand for each group and condition.

Use the master table  icon from the lateral taskbar to start the interface for preparing the data for population statistics.



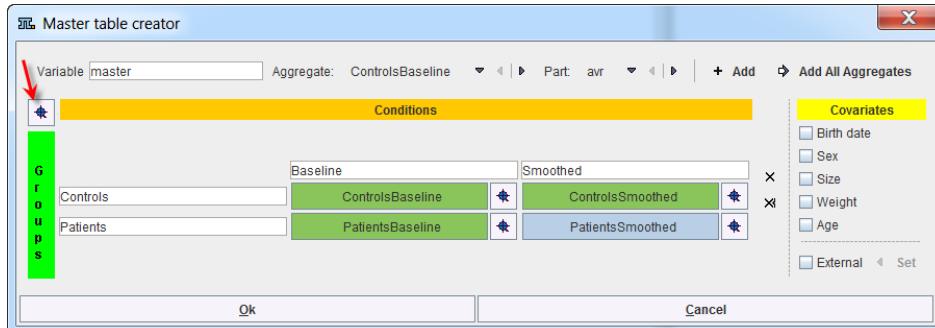
A dialog window opens allowing the definition of the number of rows and columns for the master table. The rows and columns correspond to the groups and conditions, respectively. The name of the master table can be edited in the **Output table name** field. To continue activate the **OK** button.

The Master table creator interface appears:

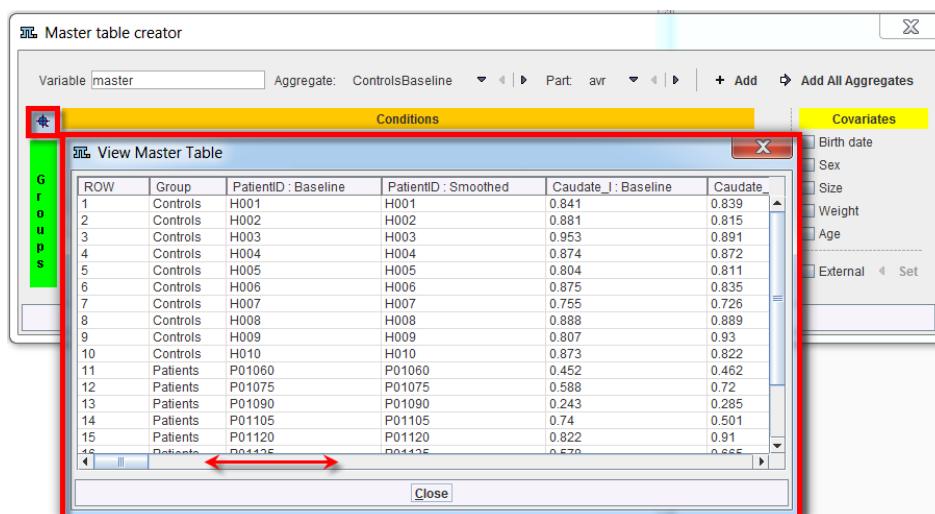


To fill in the master table select the **Aggregate** file to start with and the statistics **Part** to be analyzed. To transfer the **avr** part of all aggregates to the master table activate **Add all Aggregates**. The procedure uses the group and condition names encoded during aggregation for the arrangement of the aggregates in the table. This step will not work properly if the encoding was not consistent.

The result of the example is shown below:



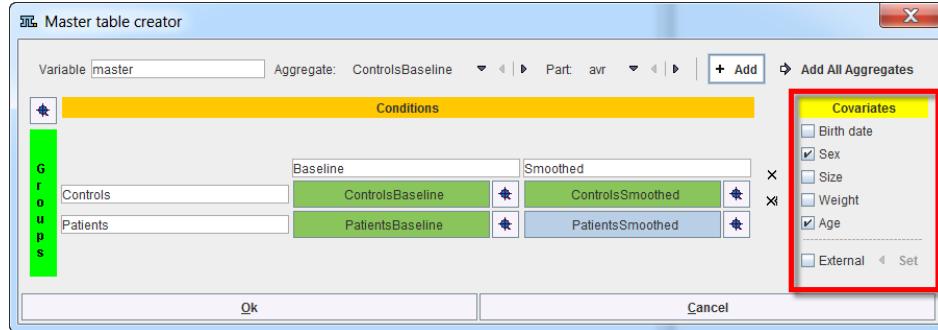
The master table has a structure consisting in blocks, each block corresponding to a group and condition. To preview the content of the master table activate the **View value** icons as indicated below:



Use the bar sliders to navigate through the master table content preview. Similarly, the content of each element of the master table can be visualized.

Individuals may also be characterized by additional variables. These can be demographic variables, such as sex and age, or experimental variables, such as functional performance scores. Researchers will often be interested in the effect of these variables on regional values.

The covariates can be easily included in the master table by enabling the corresponding checkboxes in the **Covariates** section:



Please note that the covariates have to be available in the aggregates for each condition and group. Alternatively, they can be loaded as External files during the loading procedure of the aggregate. To transfer the external information to the master table the **External** checkbox has to be enabled and the **Set** button activated. Statistically they are treated as covariates, and they are added as extra columns to the master table. Logically, these additional columns represent independent variables, while the columns of regional values are dependent variables.

Finally, to instantiate the master table, activate the **Ok** button. A new **Variable MasterTable** is added to the workspace. It can be visualized in the Table layout as shown below:

Rows represent individuals, the independent variables: "between-subjects"

Columns represent ROI, the dependent variables: "within-subjects"

rm-ANOVA/MANOVA

Overview

Multivariate analysis of variance (MANOVA) and repeated measures analysis of variance (rm-ANOVA) are closely related generalizations of analysis of variance (ANOVA) to deal with multiple regions of interest [4]. They represent general linear models with regional values as multiple dependent parameters, which are being considered jointly within the same model.

MANOVA and rm-ANOVA minimize the residual variance that cannot be explained by the factors included in the model. They also provide an analytical separation of the various components of total variance while also considering the covariance among within-subject variables, which requires a complete and balanced data structure comprising groups of equal size. Results are presented as ANOVA tables and appropriate F-tests to determine the significance of main effects for within-subject and between-subject factors (including covariates), as well as for their interactions (see example below). MANOVA is assuming that the within-subject dependent variable vector has multivariate normal distribution within groups. Rm-ANOVA assumes homogeneous variance across all variables and groups and also of the variance of differences between groups (sphericity). It is typically more sensitive to detect within-subject differences than MANOVA, and p-values can be adjusted in case of sphericity violation by procedures according to Greenhouse-Geisser or Huynh-Feldt. Similar to univariate ANOVA, post-hoc comparisons are available for main effects with proper corrections for multiple comparisons to examine individual differences between those groups or regions that demonstrated a significant main effect or interaction.

The available correction for multiple comparison used in (M)ANOVA are:

- 1) Holm correction, described by Holm et al [2], is a modified version of Bonferroni correction: relaxing requirements step-wise subsequently after reaching significance for the strongest signal according to the number of remaining tests. Still, it does not take into account possible correlations among regional values. The Holm correction controls the family wise errors (FWER) without assuming independence. The benefit is that tests are made more powerful (smaller adjusted p values) while maintaining control of FWER. It is more conservative. The FWER is the probability of getting at least one wrong significance (=one false positive test) <5%
- 2) Alternatively, the false discovery rate (FDR) can be controlled by procedures described by Benjamini and Hochberg [3]. The FDR correction controls the "false discovery rate" (FDR) and not the FWER.

rm_ANOVA/MANOVA PMOD-R Implementation

As an example, we are considering data described by Volkow et al. [5]. In their study the effect of alcohol on brain uptake of ¹¹C-acetate was examined in two groups, heavy drinkers (HD) and occasional social drinkers (OSD). PET measurements of SUV in 7 brain regions (ROIs) was performed twice in each individual, under the condition (COND) of exposure to placebo or alcohol.

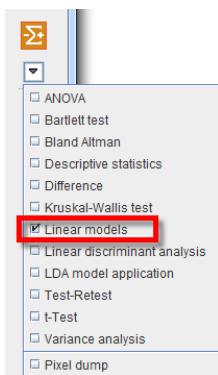
Simulated data were generated based on the summary data shown in figure 4B of the paper with 15 subjects in each group. Two sources of Gaussian variance were assumed, one component (S.D. = 0.1) having the same effect on all regions of each individual, and residual variance as another component affecting all regional values independently (with same S.D.).

In the paper, a strong effect of condition (higher uptake of ^{11}C -acetate during exposure to alcohol) was described in all regions, and there was a tendency for HD to have higher brain uptake of ^{11}C -acetate than OSD when exposed to alcohol.

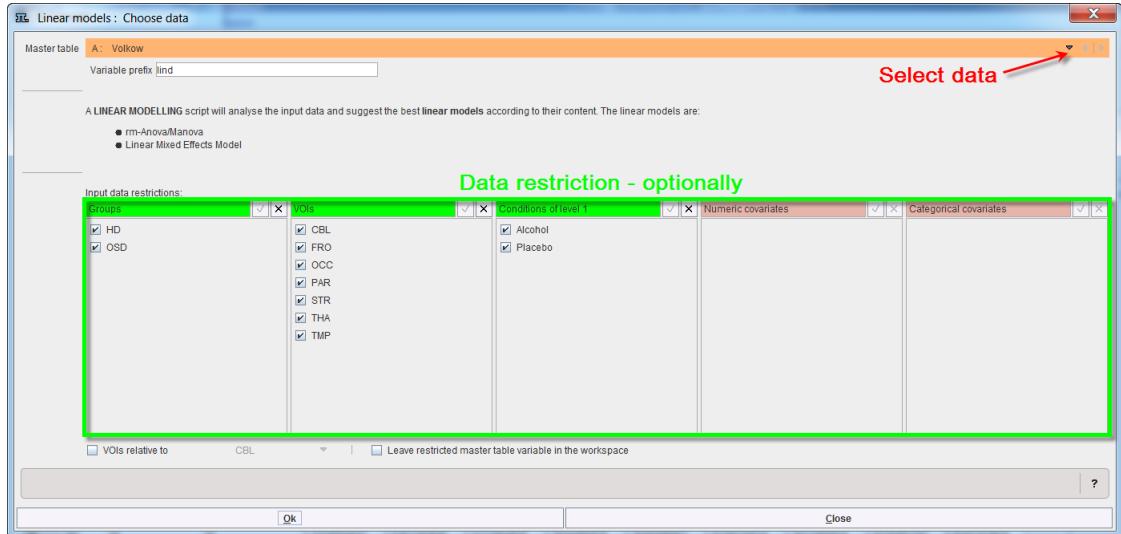
To start the analysis load the example **Volkow_rmAnova.RData** workspace which is available in the **Pmod** example database. Use the **Load/Workspace Data** option from the lateral task bar. It already contains the master table which forms the basis for the analysis. To visualize the master table select the Table layout icon as shown below:

ROW	Group	PatientID:Alcohol	PatientID:Placebo	FRO:Placebo	FRO:Alcohol	PAR:Placebo	PAR:Alcohol	TMP:Placebo	TMP:Alcohol	OCC:Placebo	OCC:Alcohol	STR:Placebo	
1	OSD	1	1	1.160372288	1.3271223439	1.1522746024	1.2700023714	1.2340621755	1.2737390845	1.2197564601	1.1032422173	0.8704132572	
2	OSD	2	2	1.1548566265	1.3832648373	1.2013078397	1.4092458133	1.2681546757	1.5345793494	1.2606789858	1.3818153725	0.9851433937	
3	OSD	3	3	0.9336172526	1.2990691094	1.0527306587	1.2495241254	1.2187778752	1.2541852891	1.0179514799	1.2716183288	0.9544471291	
4	OSD	4	4	1.0373120217	1.3537378458	1.20141140182	1.1425623016	0.8435228607	1.2047022774	1.1491962674	1.1044143483	0.8891683933	
5	OSD	5	5	0.8680305063	1.1024175746	1.0084497838	1.3750159183	1.0316813294	1.2359876967	1.1518877027	1.4511234609	0.8207087662	
6	OSD	6	6	1.3513864776	1.4405875439	1.1713269368	1.3070337372	1.2511876236	1.3083537803	1.0412639472	1.3015674326	0.8227410597	
7	OSD	7	7	1.0500000000	1.1771771771	1.1771771771	1.2500000000	1.2500000000	1.2500000000	1.0412639472	1.3015674326	0.8227410597	
8	OSD	8	8	1.1424036983	1.3701088688	1.2024674001	1.1870288183	0.8916989719	1.2540346449	1.1616384386	1.1722360532	0.8890748931	
9	OSD	9	9	0.7026919649	0.8974701033	0.8043981397	1.0568954741	1.0247063409	1.1677052399	0.9184305024	1.0156744268	0.5875307701	
10	OSD	10	10	1.0179719098	0.9764448585	0.9706238316	1.1553023686	1.14540433707	1.0707789007	1.1930234655	1.1834880478	0.8284014476	
11	OSD	11	11	0.7081337774	0.9810508716	0.8397323022	0.9832780471	1.057907259	1.0052294455	1.2770745692	0.9210950466	0.5014530828	
12	OSD	12	12	1.0781787242	1.2082312369	1.0870525436	1.1274417083	0.9290774248	1.1070989328	1.2343751183	0.679330005		
13	OSD	13	13	0.9331484207	1.2744567677	1.0562285602	1.1042530415	0.9775274215	0.8808636652	0.901281208	1.1581823311	0.7651755965	
14	OSD	14	14	1.1426797965	1.3899242336	1.0290428558	1.1702311098	0.9919246571	1.2392278509	0.9378770454	1.2014668701	0.9763614817	
15	OSD	15	15	0.9261042573	1.1643922417	1.0415313013	1.1215272791	0.944889239	1.2776921262	1.0453373309	1.449561707	0.9501972434	
16	HD	16	16	1.3072635494	1.4033360489	1.3288686064	1.5675947644	1.2927904667	1.5470127438	1.2453373309	1.3931462464	0.8641645716	
17	HD	17	17	1.1166724536	1.2589805781	1.1987347168	1.3848165563	1.0840125154	1.4459996656	1.048249056	1.3391462464	0.8641645716	
18	HD	18	18	0.8510393776	1.2333591041	0.930951268	1.450511722	1.209846847	1.1856752742	1.187707255	1.2418336748	0.80010055229	
19	HD	19	19	1.1424041602	1.1867899652	1.1484644048	1.187707255	1.1258186393	1.1740127208	1.0785879751	1.1808689781	0.8181670426	
20	HD	20	20	0.8992402625	1.0808446545	0.8992402625	1.09871574	1.088641417	1.1205641449	0.9908993006	1.2140808993	0.80912552	
21	HD	21	21	1.0260183303	1.0588976284	1.030849845	0.99789511276	0.935260267	1.0205547365	0.895243566	1.1070516355	0.8677125701	
22	HD	22	22	0.9897233004	1.1146105249	0.9532852721	1.1887393061	1.0255598078	1.3338677996	0.8749765588	1.2505247665	0.8278563047	
23	HD	23	23	1.1003046082	1.1369491652	1.0989843231	1.2129705016	0.9631528017	1.3223948777	1.0884552249	1.3126063189	0.8778753539	
24	HD	24	24	1.111272722	1.3131849489	1.0867460943	1.1777682912	0.974318491	1.24298575	1.0816912032	1.370867142	0.7848520674	
25	HD	25	25	1.3533842576	1.5852840404	1.427425058	1.4089187795	1.414116955	1.5993398528	1.4702509174	1.5478563443	1.0124734143	
26	HD	26	26	1.1364368629	1.2222660491	0.8758276331	1.116228995	0.7051702255	1.3247842548	1.0680054532	1.2606577075	0.8012038712	
27	HD	27	27	1.0997669785	1.3686007007	1.2596727798	1.367720894	1.1639876352	1.3929143338	1.1175267909	1.403350234	0.9556477492	
28	HD	28	28	1.1400818493	1.1636715598	1.2981421637	1.0571749505	1.4380936172	1.073725456	1.1659979855	1.2758608656	1.1991865175	0.9330851859
29	HD	29	29	1.1636715598	1.2981421637	1.0571749505	1.4380936172	1.073725456	1.1659979855	1.2758608656	1.1991865175	0.9330851859	
30	HD	30	30	1.3324564647	1.5361782845	1.2717864825	1.3504485976	1.3645588957	1.4728210534	1.3071460934	1.4276497787	0.9242153824	

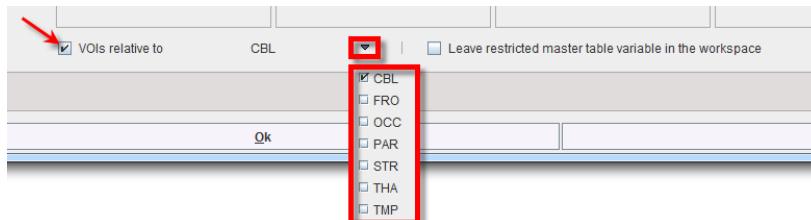
Select the **Linear models** entry in the scripts list as illustrated below:



The linear model interface opens. To select the **Master table** for the analysis use the selection arrow on the top. Correspondingly, summary of the master table content is shown in the lower part. Optionally the data to be analyzed can be restricted to a subset of the original master table by unchecking some of the boxes.



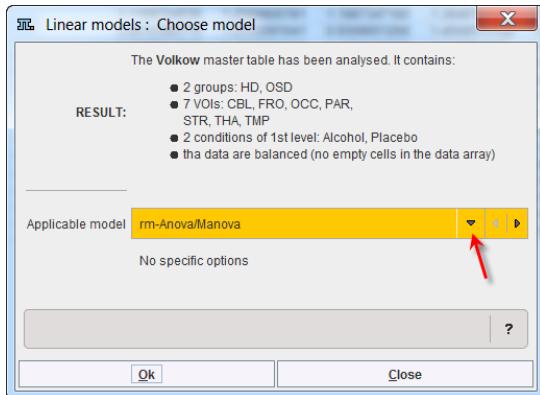
In addition, relative values can be easily obtained and used in the analysis enabling the **VOIs relative to** check box and selecting the reference region from the VOIs list:



The checkbox **Create restricted master table variable in the workspace** allows saving the new content of the restricted master table in the workspace.

Confirm the setting with the **Ok** button.

The program analyses the content of the "restricted" master table and provides a summary of the analysis and the suggestion for the linear model to be applied. In case the data are balanced the rm_Anova/Manova analysis is suggested by default, but the LME analysis is still available for selection.

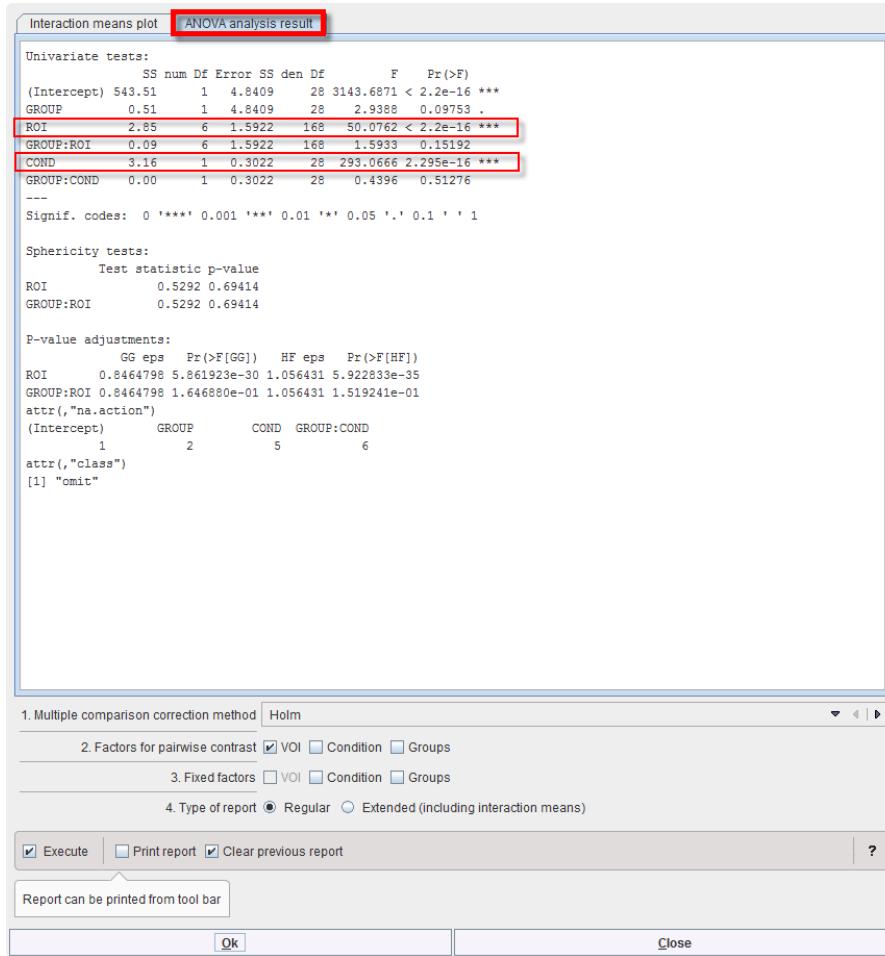


To continue the analysis activate the **Ok** button.

The statistical analysis is performed in the background and consists in two main step:

- 1) The (M)ANOVA procedure provides a preliminary result summarized in a table. This summary may reveal whether there is a significant main effect of covariates on the results, a possible interaction between ROIs and one of the covariates, or a main effect of one of the conditions.
- 2) The post-hoc comparisons are available for main effects with proper corrections for multiple comparisons. The user may define contrast to test significance for different interactions.

In the rm-Anova/MANOVA test the data columns are used as the matrix of dependent variables by the R module “lm” (R package “stats”), using a simple analysis model (columns ~ GROUP) [6]. Repeated measures ANOVA and MANOVA are then performed by the “Anova” module (package “car”) using a separate model (~ ROI + COND) for the within-subject variables [7]. Interactions between the within and between-subject variables are included by default. The result is:

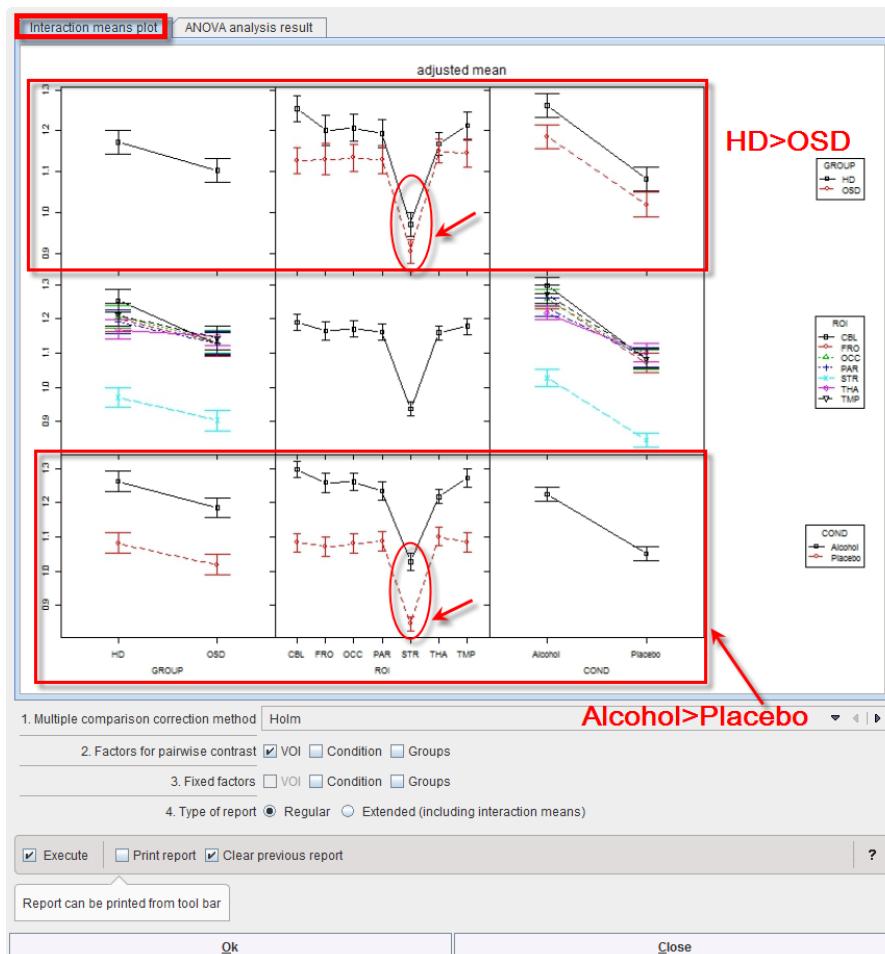


The intercept just indicates the trivial result that values are globally different from 0. Highly significant differences indicated by *** exist among ROIs (as to be expected), and between conditions (COND), which is an important experimental result. There is a trend only for a difference between groups ($p=0.09$). Interactions are generally non-significant. Thus, the effect of alcohol exposure on ^{11}C -acetate uptake does not differ between groups (which is somewhat different from the results reported by the authors of the paper using actual rather than simulated data), and regional differences are similar in both groups.

Testing for sphericity does not reveal significant deviation, and accordingly the corrected P-values for ROI and the GROUP:ROI interaction do not result in a change of significance.

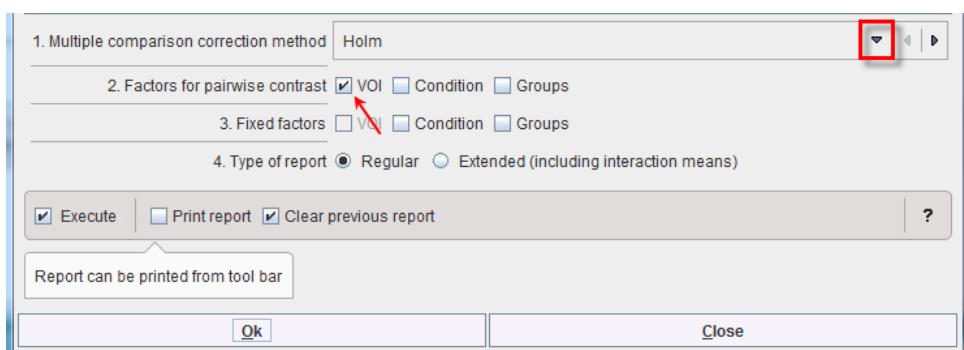
Mean values within groups and subgroups as provided by module “interactionMeans” (R package “phia” <http://cran.r-project.org/web/packages/phia/vignettes/phia.pdf>) are illustrated as a plot in the capture below. The graphic has as many rows and column as factors. The off-diagonal panels show the first-order interaction means for each pair of

factors. The lack of parallelism between lines reveals how one factor changes the other one. The diagonal panels represent the marginal means of each factor.



The preliminary analysis demonstrates a tendency towards higher values in group HD than OSD (top left), which is actually the case for all ROIs and conditions top row. Striatum (STR) shows much lower values than all other regions (middle panel), with minor interactions with group and condition (middle row). Values under alcohol exposure are generally higher than under placebo (bottom row).

Differences between ROIs seem obvious. A pairwise analysis of their significance is provided by the module “testInteractions” from the same R package with the “Holm” method to correct for multiple comparisons and “ROI” factor for pairwise testing, while averaging over the other factors.



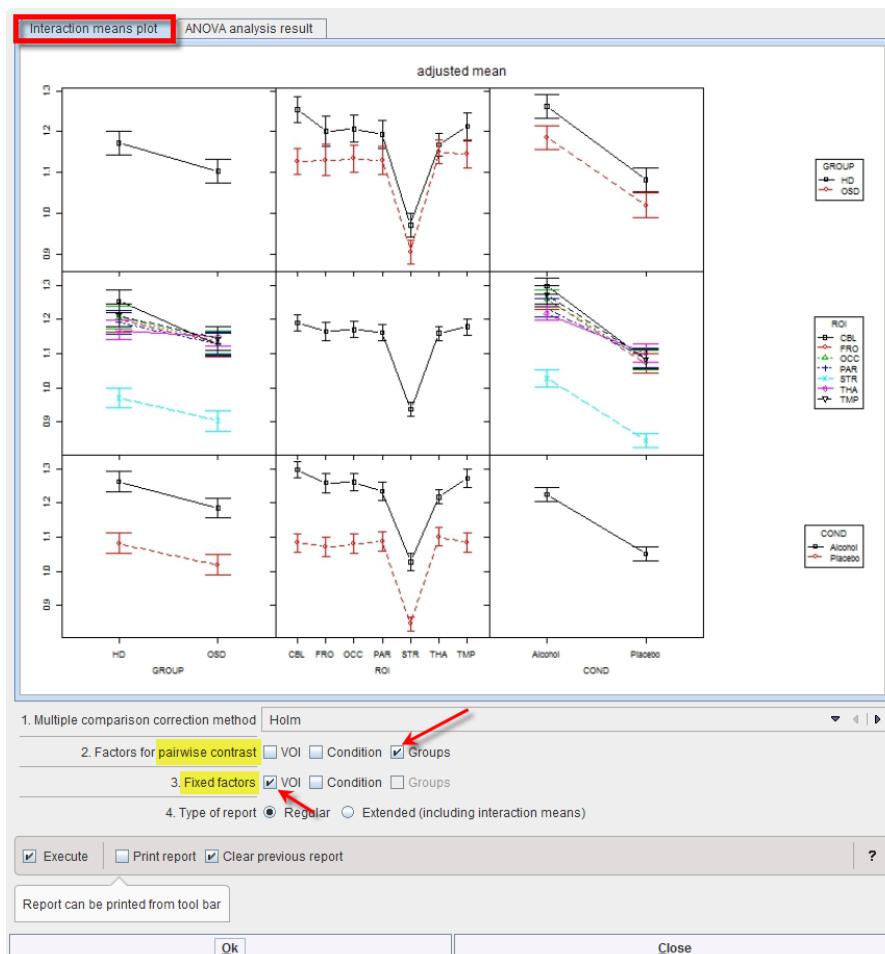
Confirm the settings for the model parameter with the **Ok** button. The results are displayed in the Text layout and reveal that contrasts of all regions with striatum (**STR**) are highly significant, but none of the other regional differences reach significance.

Multivariate Test: Pillai test statistic							
P-value adjustment method: holm							
	Value	DF	test stat	approx F	num Df	den Df	Pr(>F)
CBL-FRO	0.024994	1	0.05888	1.752	1	28	1.0000
CBL-OCC	0.020116	1	0.04494	1.318	1	28	1.0000
CBL-PAR	0.029101	1	0.16555	5.555	1	28	0.3848
CBL-STR	0.253130	1	0.90644	271.273	1	28	1.232e-14 ***
CBL-THA	0.031042	1	0.10105	3.147	1	28	1.0000
CBL-TMP	0.012037	1	0.01397	0.397	1	28	1.0000
FRO-OCC	-0.004878	1	0.00206	0.058	1	28	1.0000
FRO-PAR	0.004107	1	0.00180	0.051	1	28	1.0000
FRO-STR	0.228136	1	0.82222	129.500	1	28	8.247e-11 ***
FRO-THA	0.006048	1	0.00271	0.076	1	28	1.0000
FRO-TMP	-0.012957	1	0.01233	0.349	1	28	1.0000
OCC-PAR	0.008986	1	0.01222	0.346	1	28	1.0000
OCC-STR	0.233014	1	0.86190	174.745	1	28	2.499e-12 ***
OCC-THA	0.010927	1	0.01409	0.400	1	28	1.0000
OCC-TMP	-0.008079	1	0.00715	0.202	1	28	1.0000
PAR-STR	0.224028	1	0.90841	277.724	1	28	9.588e-15 ***
PAR-THA	0.001941	1	0.00044	0.012	1	28	1.0000
PAR-TMP	-0.017064	1	0.03676	1.069	1	28	1.0000
STR-THA	-0.222087	1	0.88099	207.282	1	28	3.442e-13 ***
STR-TMP	-0.241093	1	0.87823	201.947	1	28	4.502e-13 ***
THA-TMP	-0.019005	1	0.03527	1.024	1	28	1.0000

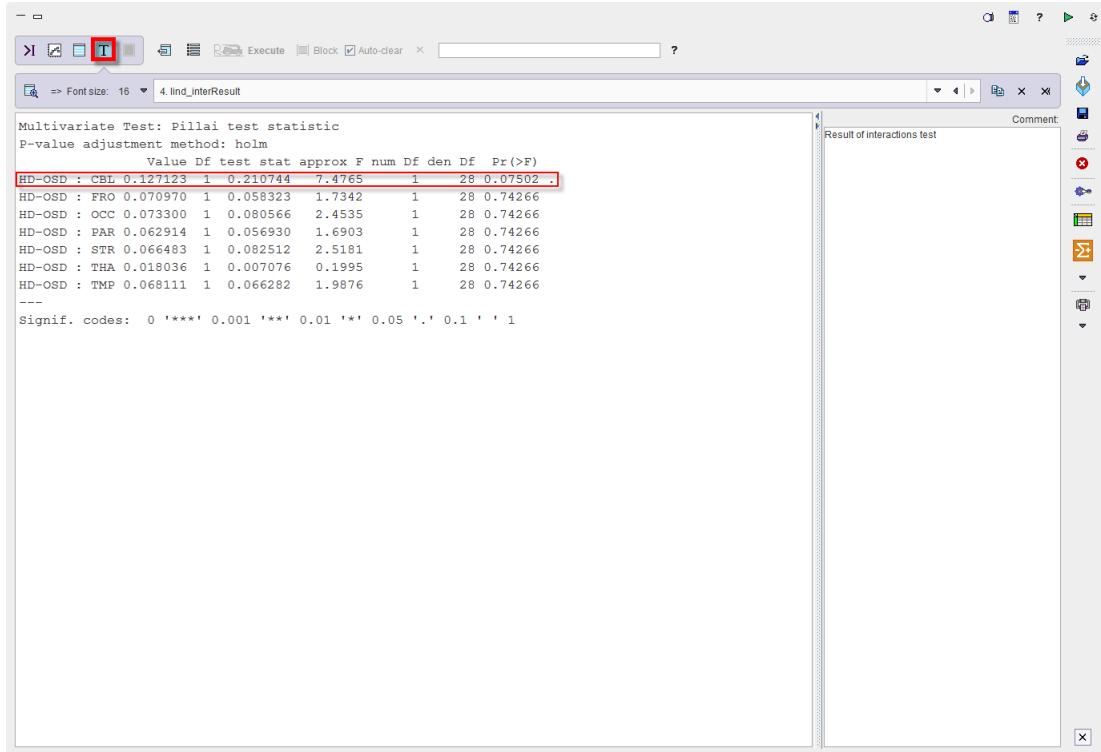
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1							

The results can be saved as a report activating the dedicated button in the lateral taskbar.

Although none of the interactions was significant, one might be interested in which region showed the strongest trend towards a difference between subject groups. To achieve this, start the **Linear models** script again. In the **Set module parameters** step module “testInteractions” use VOIs as **Fixed factor**, and **pairwise contrast of Groups** as illustrated below:



The program provides the following result:



```

Multivariate Test: Pillai test statistic
P-value adjustment method: holm
Value Df test stat approx F num Df den Df Pr(>F)
HD-OSD : CBL 0.127123 1 0.210744 7.4765 1 28 0.07502 .
HD-OSD : FRO 0.070970 1 0.058323 1.7342 1 28 0.74266
HD-OSD : OCC 0.073300 1 0.080566 2.4535 1 28 0.74266
HD-OSD : PAR 0.062914 1 0.056930 1.6903 1 28 0.74266
HD-OSD : STR 0.066483 1 0.082512 2.5181 1 28 0.74266
HD-OSD : THA 0.018036 1 0.007076 0.1995 1 28 0.74266
HD-OSD : TMP 0.068111 1 0.066282 1.9876 1 28 0.74266
---
Signif. codes: 0 '****' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Thus, there is a trend for cerebellum ($p=0.075$) while all other regions are far from significance.

Overall this example demonstrates that differences between within-subject variables can be detected with high sensitivity, while differences between subject groups are more difficult to detect. In the present example, the magnitude of mean differences between groups was about half of the difference between conditions, but there was only a trend for groups, while the effect on condition was very highly significant ($p<10^{-14}$). Basically this reflects the much higher power of repeat studies within subjects than comparisons between different groups of subjects, similar to the higher power of a paired t-test compared to a t-test for independent groups.

Linear Mixed Effect Models (LME)

Overview

Linear mixed effect (LME) models [8] are very similar to the (M)ANOVA models described *above* (on page 348), while there are some differences in scope and performance. Instead of classifying model factors as “within-subject” or “between-subject”, they include a random variable to account for the variance component that is common to all regional values of the same individual. The spread of this interindividual variance is fitted iteratively together with a global mean (across all dependent variables), the mean effects of all model factors (regions, groups, etc) and specified interactions to minimize the residual error. Significance of each factor is determined by comparing the complete model with the next simpler model not including that factor. Because a random variable (with a normal distribution) accounts for most of the interindividual variance in this model, this also will absorb most of those covariate effects that affect all regions to the same degree. LME models may therefore be

less suited than rm-ANOVA or MANOVA to analyze common effects of covariates, but they do not require balanced designs. In principle, they also tolerate a moderate amount of missing data, but in the current implementation statistical tests are not possible with missing data. Flexible and comprehensive post-hoc tests for main effects and interactions are available.

The available correction for multiple comparison used in LME are:

- 1) Holm correction, described by Holm et al [2] is a modified version of Bonferroni correction: relaxing requirements step-wise subsequently after reaching significance for the strongest signal according to the number of remaining tests. Still, it does not take into account possible correlations among regional values. The Holm correction controls the family wise errors (FWER) without assuming independence. The benefit is that tests are made more powerful (smaller adjusted p values) while maintaining control of FWER. It is more conservative. The FWER is the probability of getting at least one wrong significance (=one false positive test) <5%
- 2) Alternatively, the false discovery rate (FDR) can be controlled by procedures described by Benjamini and Hochberg [3]. The FDR correction controls the "false discovery rate" (FDR) and not the FWER.

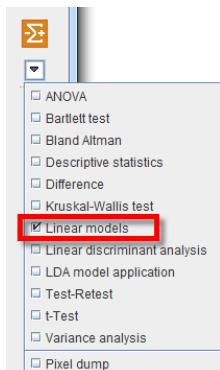
LME PMOD-R Implementation

The example is from a study by Varnas et al. [9], who actually used a LME model for the analysis of their data. A new PET ligand for 5HT1B receptors was tested once at baseline, twice under medication with zolmitriptan, and once more after 1 week free of medication. Complete data were acquired in 5 normal volunteers. Binding potentials (BP) were analyzed in two large regions of interest (VOIs), occipital cortex (OCC) and the rest of cerebral cortex (CC). A master table of BP was constructed containing the two VOIs at 4 time points (BL, T1, T2, T3) in 5 individuals.

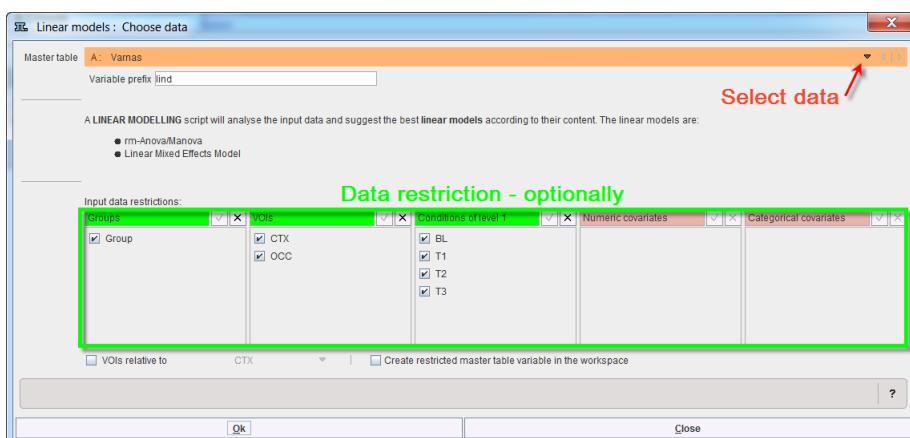
To start the analysis load the example Varnas_LME.RData workspace which is available in the **Pmod** example database. Use the **Load/Workspace Data** option from the lateral task bar. It already contains the master table which forms the basis for the analysis. To visualize the master table select the Table layout icon as shown below:

ROW	Group	PatientID:BL	PatientID:T1	PatientID:T2	PatientID:T3	CTX:BL	OCC:BL	CTX:T1	OCC:T1	CTX:T2	OCC:T2	CTX:T3	OCC:T3
1	Group 1	1	1	1	1.26	1.69	1.29	1.7	1.23	1.61	1.39	1.84	
2	Group 2	2	2	2	0.98	1.37	1.03	1.37	0.88	1.28	1.03	1.42	
3	Group 3	3	3	3	1.03	1.63	1.07	1.51	1.2	1.76	1.35	1.88	
4	Group 4	4	4	4	1.35	1.86	1.19	1.61	1.26	1.72	1.46	1.92	
5	Group 5	5	5	5	1.25	1.85	1.11	1.77	1.15	1.84	1.28	1.66	

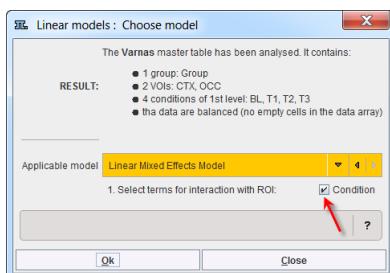
To start the analysis please select the **Linear models** entry in the scripts list:



The content of the master table is summarized.



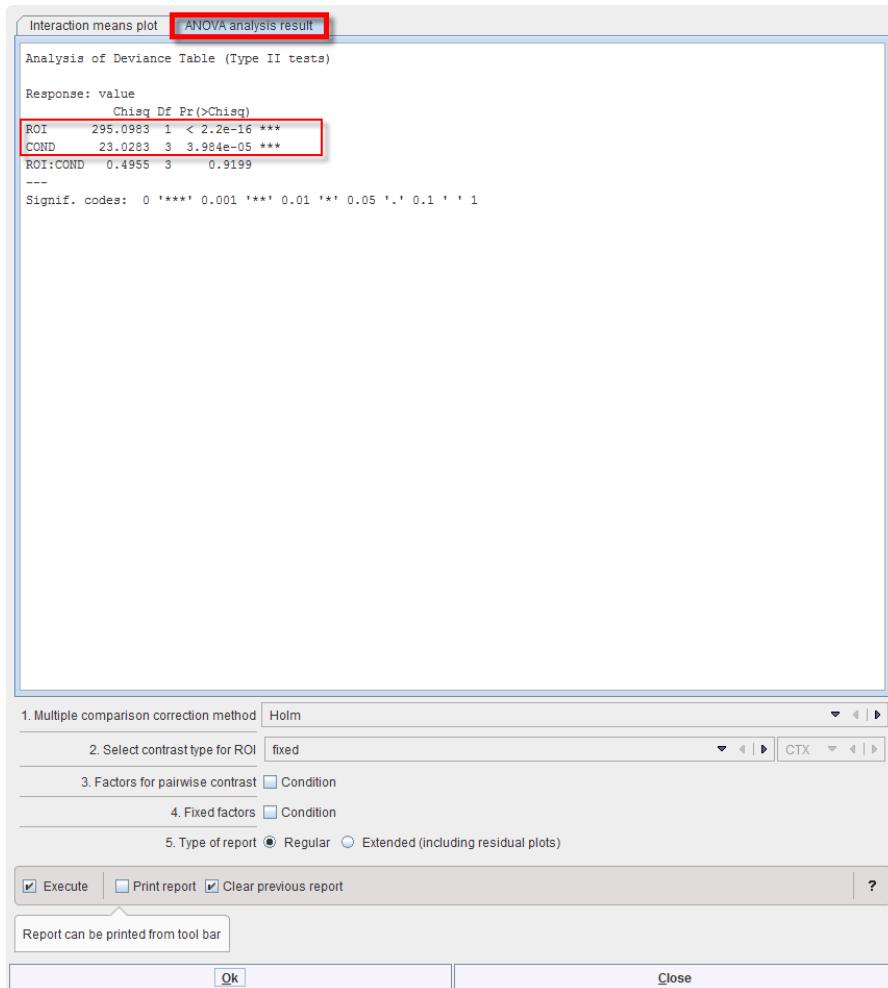
Confirm the setting with the **Ok** button. The program analyses the content of the "restricted" master table and provides a summary of the analysis and the suggestion for the linear model to be applied. When a single group is studied in different conditions only the linear mixed effects (LME) model can be used for the analysis. Therefore, the selection is blocked and set to **Linear Mixed Effects Model**:



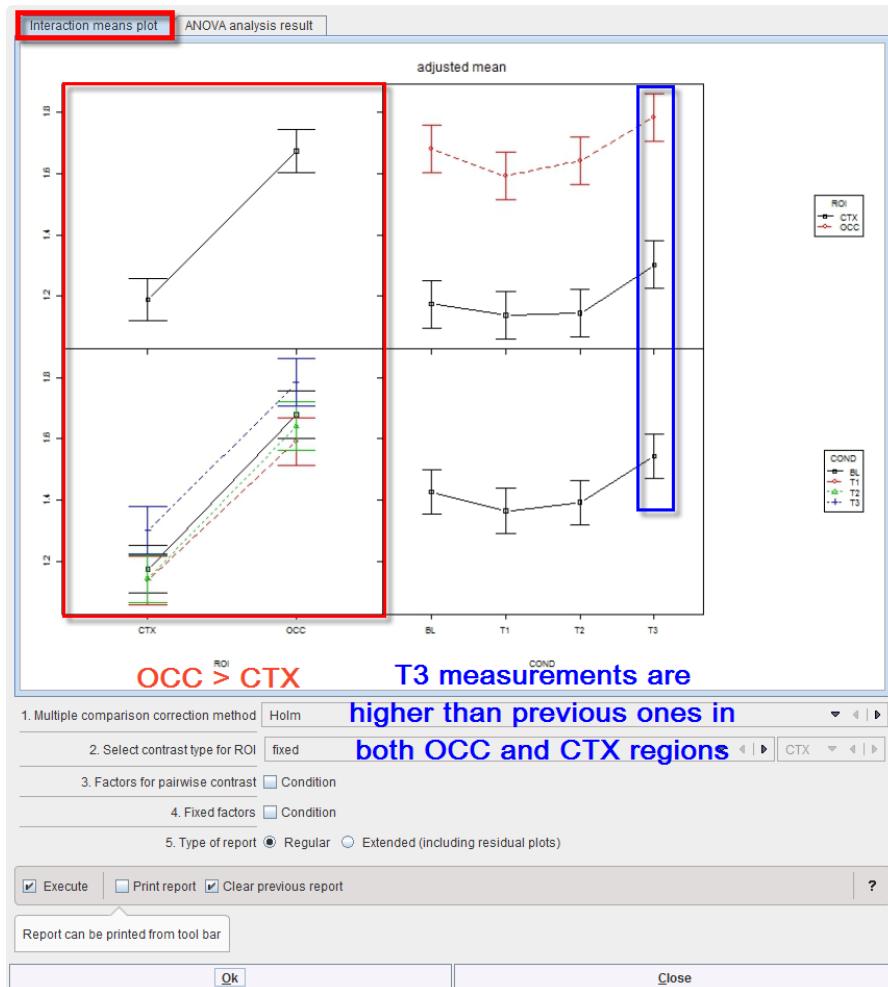
Please note that additional settings are available for the LME: the interactions. The number of available interactions depends on the number of factors and covariates in the master table. To consider an interaction enable the corresponding checkbox. In the example above the interaction ROI:Condition is enabled. Start the analysis with **Ok**.

The MANOVA preliminary results indicate that, as an expected trivial result, BP differs between the two regions. More interestingly, it is also significantly differs between

conditions. There is no ROI:COND interaction – thus, both regions respond in a similar way to the conditions:

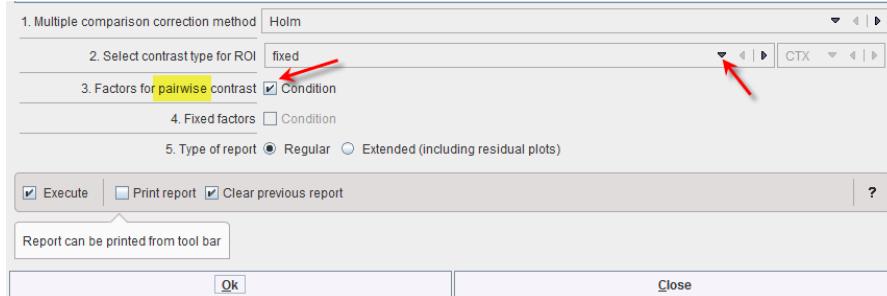


As for MANOVA, “interactionMeans” (R package “phia”) provides an informative graph of the mean effects and their interactions. It demonstrates higher values for region OCC than CTX (top left), which is actually the case under all 4 conditions (bottom left). The last measurement (T3) tends to be higher than the previous ones (bottom right), and that is evident in both regions (top right):



The off-diagonal panels show the first-order interaction means for each pair of factors. The lack of parallelism between lines reveals how one factor changes the other one. The diagonal panels represent the marginal means of each factor.

From this graph and the **Deviance Table** above, the difference between the two regions is clear, but we still are interested in the significance of the pairwise differences between the conditions. We therefore select the appropriate contrasts: “fixed” for ROI and “pairwise” for COND, also using the default correction “Holm” for multiple comparisons:



The result, provided by routine “testInteractions”, is shown in the Text layout:

```

Chisq Test:
p-value adjustment method: holm
      Value Df   Chisq Pr(>Chisq)
BL-T1 : CTX  0.036  1  0.4065  1.000000
BL-T2 : CTX  0.030  1  0.2823  1.000000
BL-T3 : CTX -0.128  1  5.1386  0.187198
T1-T2 : CTX -0.006  1  0.0113  1.000000
T1-T3 : CTX -0.164  1  8.4355  0.040476 *
T2-T3 : CTX -0.158  1  7.8296  0.051399 .
BL-T1 : OCC  0.088  1  2.4288  0.714752
BL-T2 : OCC  0.038  1  0.4529  1.000000
BL-T3 : OCC -0.104  1  3.3923  0.458520
T1-T2 : OCC -0.050  1  0.7841  1.000000
T1-T3 : OCC -0.192  1  11.5618  0.008078 **
T2-T3 : OCC -0.142  1  6.3241  0.107196
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

In both regions, a significant difference is present between T3 and T1, with the BP being higher 1 week after stopping the medication (T3) than after its start (T1). A similar tendency is seen for T3 versus T2, while the other differences are far from significance. In that study, this was a somewhat unexpected result suggesting receptor upregulation after medication, requiring further research.

To save the results activate the report button  in the lateral taskbar.

Discrimination Analysis

Overview

Linear discriminant analysis (LDA) aims at identifying combinations of parameters (typically ROIs in the context of our presentation) that provide the best discrimination between two groups of subjects, e.g. patients and controls. It is in many respects similar to the multivariate analysis of regional differences between groups, as discussed above, but has the aim of providing a discriminant function instead of determining the significance of regional differences. That discriminant function can then be applied to future cases to determine with which group they fit best, e.g. to determine whether a data set belongs to the control or to the patient group. Various methods have been developed for LDA [10], with logistic regression probably being the most widely used and generally applicable method. The linear discriminant function is determined by maximizing the likelihood of the data fit. In R, logistic regression is implemented within the generalized linear models procedure "glm".

As with all data fitting, there is a danger of overfitting by including too many variables as predictors. A useful criteria to control for that is the Akaike Information Criterium (AIC), which penalizes the quality of fit by the number of predictors used with reference to information theory. It can be used to eliminate variables from the model that are only providing minor improvements to the fit while probably mostly fitting data noise. A stepwise elimination of predictor variables is implemented in R by the procedure "stepAIC".

Quality of discrimination can be checked by using the Receiver Operating Characteristic (ROC), which provides a graphical illustration of sensitivity and specificity as the threshold used for discrimination is varied. As a numeric parameter the area under discrimination curve (AUC) is being used, which is independent from the logistic regression model used above. AUC values range between 0.5 (no discrimination) and 1.0 (perfect discrimination). ROC is implemented in R by procedure "roc".

The discriminant analysis using logistic regression is providing discriminant functions that can be used for classification of individual test cases, with potential diagnostic applications.

LDA PMOD-R Implementation

The example data were downloaded from the ADNI website (<http://adni.loni.usc.edu>) in January 2016.

ADNI acknowledgement

Data used in preparation of this section were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at:

http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

The PET scans represented the brain activity 30-60 minutes after 18F-FDG injection and were downloaded as pre-processed data (standardized image and voxel size). Briefly, this data is

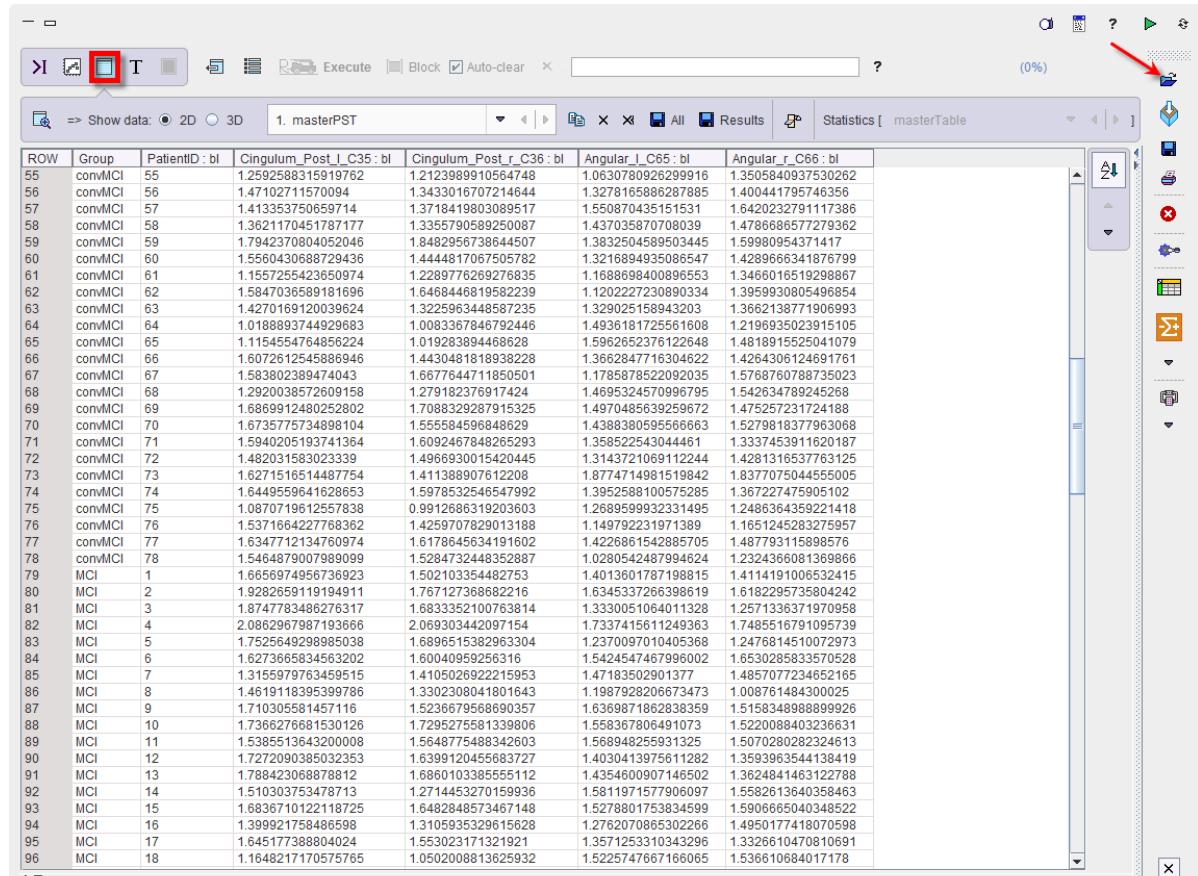
already scaled to a common global averaged value, reoriented into a standard 160 x 160 x 96 voxel imaged grid (voxel size, 1.5 x 1.5 x 1.5 mm) along the anterior commissure-posterior commissure (AC-PC) plane and formatted as DICOM or ECAT files.

The downloaded PET images were then processed using the PNEURO module in the PMOD software package (version 3.8; PMOD technologies). Particularly, the AAL-Atlas VOI was adjusted to the individual data with an SPM 5 equivalent normalization procedure and average regional statistics were calculated in each VOI.

The baseline FDG data in two patient groups with mild cognitive impairment (MCI) are used for the present analysis: one group of 129 subjects with stable MCI (age 74.93 ± 7.45 years), the other of 78 subjects (age 75.37 ± 6.56 years) progressing to dementia within 2 years of clinical follow-up. We are focusing on two brain areas known to be predictors of progression, the posterior cingulate (PCC) and the angular cortex (AngC). The respective variables are Cingulum_Post_l_C35 and Cingulum_Post_r_C36 (left and right PCC) and Angular_1_C65 and Angular_r_C66 (left and right AngC). Values were normalized to pons as reference region.

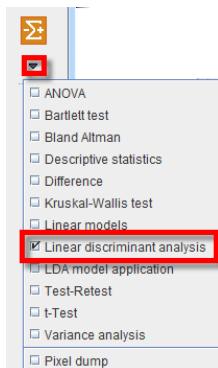
Identification of the LDA Function

To start the analysis load the example **Example_LDA.RData** workspace which is available in the **Pmod** example database. Use the **Load/Workspace Data** option from the lateral task bar. It already contains the master table which forms the basis for the analysis. To visualize the master table select the Table layout icon as shown below:

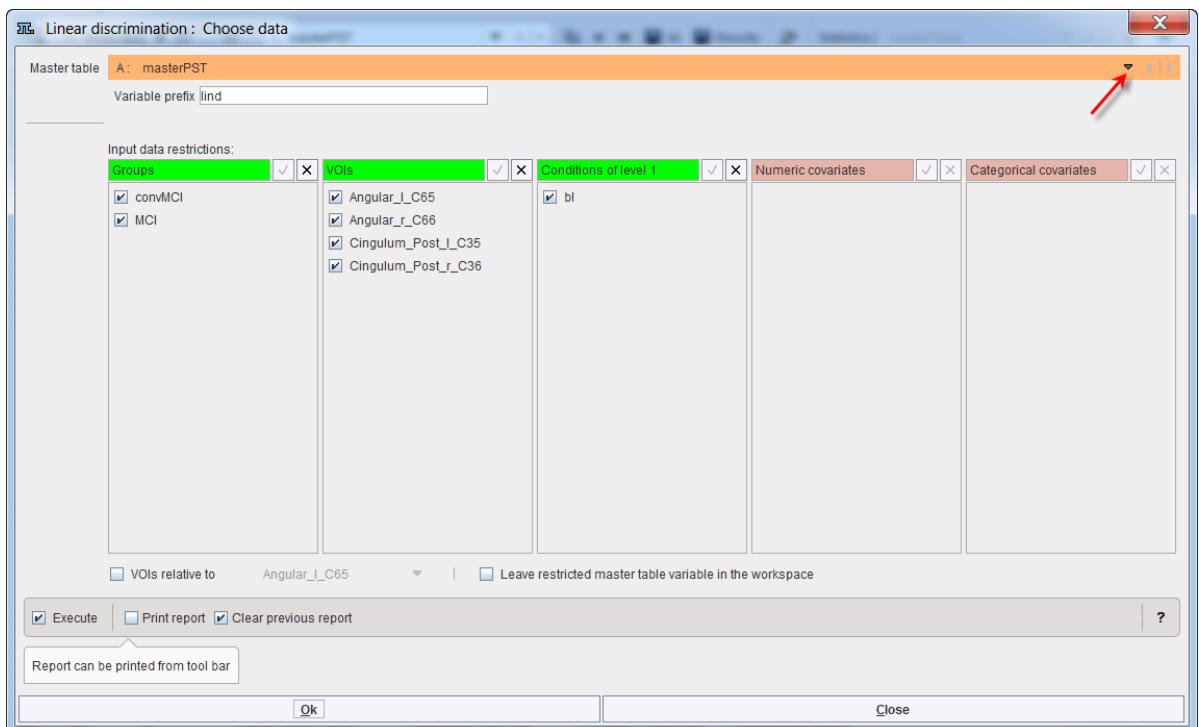


ROW	Group	PatientID : bl	Cingulum_Post_l_C35 : bl	Cingulum_Post_r_C36 : bl	Angular_l_C65 : bl	Angular_r_C66 : bl
55	comMCI	55	1.2592588315919762	1.2123989910564748	1.0630780926299916	1.3505840937530262
56	comMCI	56	1.47102711570094	1.3433016707214644	1.3278165886287885	1.400441795746356
57	comMCI	57	1.413353750659714	1.3718419803089517	1.5050870435151531	1.6420232791117386
58	comMCI	58	1.3621170451787177	1.3355790589250087	1.437035870708039	1.4786686577279362
59	comMCI	59	1.7942370804052046	1.8482956738644507	1.3832504589503445	1.5980954371417
60	comMCI	60	1.55604303688729436	1.4444817067505782	1.3216894935086547	1.4289666341876799
61	comMCI	61	1.1557255423650974	1.2289776269276835	1.1688698400896553	1.3466016519298867
62	comMCI	62	1.5847036589181696	1.6468446819582239	1.1202227230890334	1.395930805496854
63	comMCI	63	1.4270169120039624	1.3225983448587235	1.32902158943203	1.3662138771906993
64	comMCI	64	1.018893744929683	1.0083367846792446	1.4936181725561608	1.2196935023915105
65	comMCI	65	1.1154554764856224	1.019283894468628	1.5962652376122648	1.4818915525041079
66	comMCI	66	1.6072612545886946	1.44304818938228	1.3662847716304622	1.4264306124691761
67	comMCI	67	1.583802389474043	1.667764471850501	1.1785878522092035	1.5768760788735023
68	comMCI	68	1.2902038572609158	1.279182376917424	1.4695324570996795	1.542634789245268
69	comMCI	69	1.6869912480252802	1.708832987915325	1.4970485639259872	1.475257231724188
70	comMCI	70	1.673577534898104	1.555884596846829	1.438838059556663	1.5279818377963068
71	comMCI	71	1.5940205193741364	1.6092467848265293	1.35852543044461	1.337453911620187
72	comMCI	72	1.482031583023339	1.4966930015420445	1.3143721069112244	1.4281316537763125
73	comMCI	73	1.6271516514487754	1.411388970612208	1.8774714981519842	1.837707504455005
74	comMCI	74	1.6449559641628653	1.5978532546547992	1.3952588100575285	1.367227475905102
75	comMCI	75	1.0870719612557838	0.9912686319203603	1.268959932331495	1.2486364359221418
76	comMCI	76	1.5371664227768362	1.4259707829013188	1.149792231971389	1.165124528275957
77	comMCI	77	1.6347712134760974	1.6178645364191602	1.4226861542885705	1.487793115898576
78	comMCI	78	1.5464879007989099	1.5284732448352887	1.0280542487994624	1.2324366081369866
79	MCI	1	1.6656974956736923	1.502103354482753	1.4013601787198815	1.4114919006532415
80	MCI	2	1.9282659119194911	1.767127368682216	1.6345337266396819	1.6182295735804242
81	MCI	3	1.8747783486276317	1.683335210763814	1.33005010640111328	1.2571336371970958
82	MCI	4	2.0862967987193666	2.069303442097154	1.7337415611249363	1.748516791095739
83	MCI	5	1.75256492998980538	1.6896515382963304	1.237097010405368	1.2476814510072973
84	MCI	6	1.6273665834563202	1.600409592563116	1.5424547467996002	1.6530285833570528
85	MCI	7	1.3155979736459515	1.410502692215953	1.47183502901377	1.4857077234652165
86	MCI	8	1.461911839539788	1.3302308041801643	1.1987928206673473	1.008761484300025
87	MCI	9	1.710305581457116	1.5236679568690357	1.6359871862838359	1.515834898889926
88	MCI	10	1.7366276681530126	1.7295275581339806	1.558367806491073	1.5220088403236631
89	MCI	11	1.5385513643200008	1.5648775488342603	1.568948255931328	1.5070280282324613
90	MCI	12	1.727209038502353	1.6399120455683727	1.4030413975611282	1.3593963544138419
91	MCI	13	1.78423068878812	1.686010385555112	1.4354600907146502	1.3624841463122788
92	MCI	14	1.510303753478713	1.2714453270159396	1.581791577906097	1.5582613640358463
93	MCI	15	1.683671022118725	1.6482848573467148	1.5278801753834599	1.5906665040348522
94	MCI	16	1.399921758486598	1.3105935329615628	1.2762070865302266	1.4950177418070598
95	MCI	17	1.645177388804024	1.553023171321921	1.3571253310343296	1.3326610470810691
96	MCI	18	1.16482171075765	1.0502008813625932	1.5225747667166065	1.536610684017178

To start the analysis please select the **Linear discriminant analysis** entry in the scripts list:



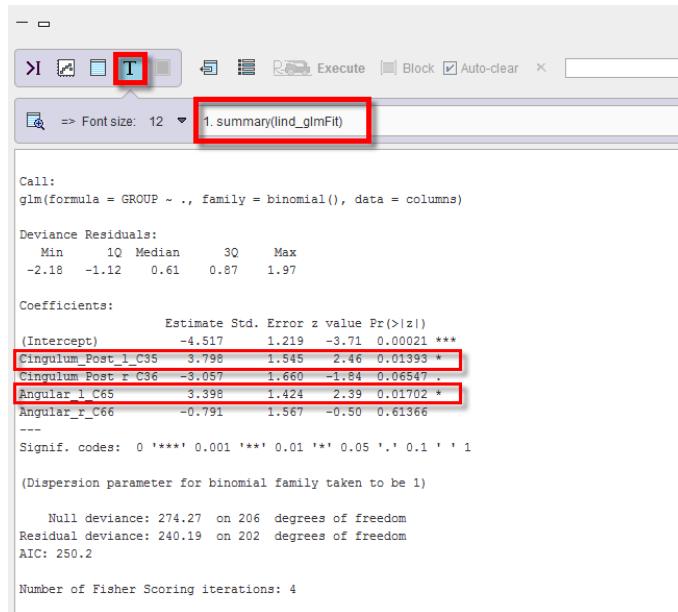
The linear discrimination interface opens. To select the **Master table** for the analysis use the selection arrow on the top. Correspondingly, summary of the master table content is shown in the **Input data restriction** section. Make sure all **Groups** and **VOIs** are selected.



The analysis is started with the **Ok** button.

Logistic regression produces the following output accessible via the **Text** layout:

- 1) The **summary(lind_glmFit)**: this indicates that both, left PCC and left angular gyrus contribute significantly to discrimination (p value of 0.01393 and 0.01702 respectively). Interestingly, the right PCC is included marginally ($p = 0.065$) but with a negative slope estimate, indicating that it is the left/right difference that provides better discrimination than either side alone. The contribution of the right angular gyrus is considered nonsignificant.



```

Call:
glm(formula = GROUP ~ ., family = binomial(), data = columns)

Deviance Residuals:
    Min      1Q  Median      3Q     Max 
-2.18   -1.12    0.61    0.87   1.97 

Coefficients:
            Estimate Std. Error z value Pr(>|z|)    
(Intercept) -4.517     1.219   -3.71  0.00021 *** 
Cingulum_Post_l_C35 3.798     1.545   2.46  0.01393 ** 
Cingulum_Post_r_C36 -3.057     1.660  -1.84  0.06547 .  
Angular_l_C65       3.398     1.424   2.39  0.01702 *  
Angular_r_C66      -0.791     1.567  -0.50  0.61366    
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

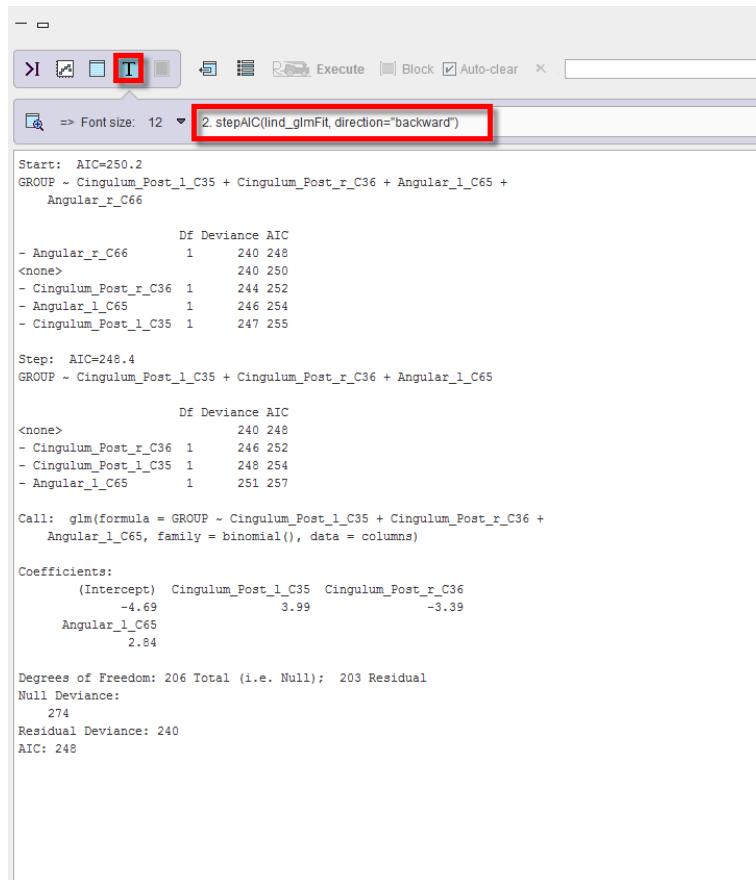
(Dispersion parameter for binomial family taken to be 1)

Null deviance: 274.27 on 206 degrees of freedom
Residual deviance: 240.19 on 202 degrees of freedom
AIC: 250.2

Number of Fisher Scoring iterations: 4

```

- 2) The `stepAIC(fit, direction="backward")` is displaying the stepwise procedure to eliminate unneeded predictors progresses. The result indicates that, only removing right angular gyrus improves AIC (smaller values are better), while removing any of the other predictors worsens the fit more (increasing deviance) than the reduction of predictors is worth.



```

Start:  AIC=250.2
GROUP ~ Cingulum_Post_l_C35 + Cingulum_Post_r_C36 + Angular_l_C65 +
      Angular_r_C66

          Df Deviance AIC
- Angular_r_C66  1    240 248
<none>           240 250
- Cingulum_Post_r_C36 1    244 252
- Angular_l_C65  1    246 254
- Cingulum_Post_l_C35 1    247 255

Step:  AIC=248.4
GROUP ~ Cingulum_Post_l_C35 + Cingulum_Post_r_C36 + Angular_l_C65

          Df Deviance AIC
<none>           240 248
- Cingulum_Post_r_C36 1    246 252
- Cingulum_Post_l_C35 1    248 254
- Angular_l_C65      1    251 257

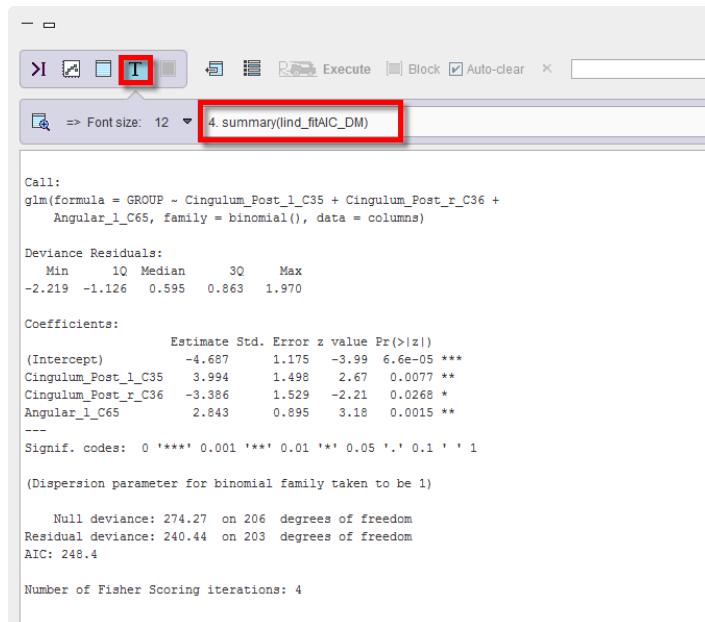
Call:  glm(formula = GROUP ~ Cingulum_Post_l_C35 + Cingulum_Post_r_C36 +
      Angular_l_C65, family = binomial(), data = columns)

Coefficients:
            (Intercept)  Cingulum_Post_l_C35  Cingulum_Post_r_C36 
                -4.69                  3.99                 -3.39 
            Angular_l_C65        2.84                  

Degrees of Freedom: 206 Total (i.e. Null);  203 Residual
Null Deviance: 274
Residual Deviance: 240
AIC: 248

```

- 3) The final fit **summary(lind_fitAIC_DM)** is, with all three remaining regions providing a significant contribution:



The screenshot shows the R Statistics in PMOD interface. The top menu bar includes 'Execute', 'Block', and 'Auto-clear' options. A red box highlights the input field containing the command '4. summary(lind_fitAIC_DM)'. The output window displays the results of a GLM model fit. The 'Call:' section shows the formula: `glm(formula = GROUP ~ Cingulum_Post_l_C35 + Cingulum_Post_r_C36 + Angular_l_C65, family = binomial(), data = columns)`. The 'Deviance Residuals' table provides summary statistics for the fit. The 'Coefficients' table lists the estimated coefficients, standard errors, z-values, and p-values for each term, including the intercept and three regional terms. The output concludes with information about the dispersion parameter, null deviance, residual deviance, and AIC.

```

Call:
glm(formula = GROUP ~ Cingulum_Post_l_C35 + Cingulum_Post_r_C36 +
    Angular_l_C65, family = binomial(), data = columns)

Deviance Residuals:
    Min      1Q  Median      3Q     Max 
-2.219 -1.126  0.595  0.863  1.970 

Coefficients:
            Estimate Std. Error z value Pr(>|z|)    
(Intercept) -4.687     1.175   -3.99  6.6e-05 *** 
Cingulum_Post_l_C35 3.994     1.498    2.67  0.0077 **  
Cingulum_Post_r_C36 -3.386     1.529   -2.21  0.0268 *   
Angular_l_C65       2.843     0.895    3.18  0.0015 **  
---
Signif. codes:  0 '****' 0.001 '***' 0.01 '**' 0.05 '*' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 274.27 on 206 degrees of freedom
Residual deviance: 240.44 on 203 degrees of freedom
AIC: 248.4

Number of Fisher Scoring iterations: 4

```

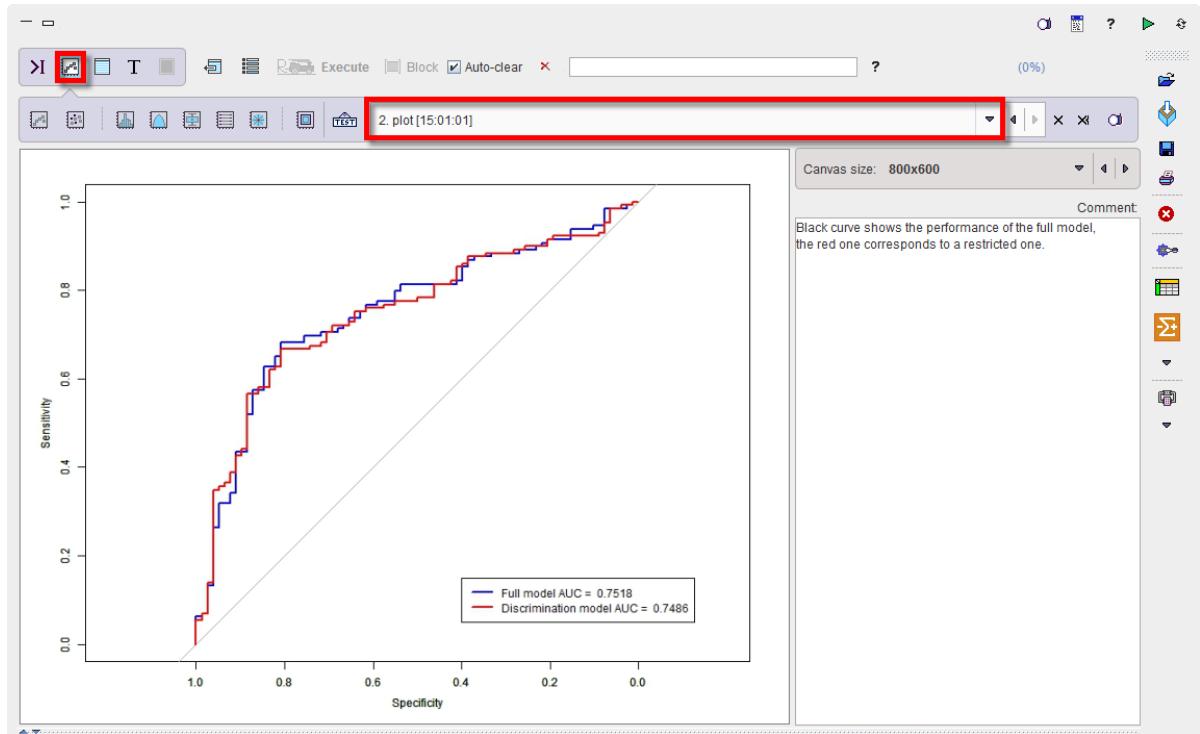
- 4) The **lind_fitAIC_DMCoef** is representing the linear coefficients of the discrimination model and is also accessible in the **Table** layout. This result will be used in the prediction step



The screenshot shows the R Statistics in PMOD interface. The top menu bar includes 'Execute', 'Block', and 'Auto-clear' options. A red box highlights the input field containing the command '1. lind_fitAIC_DMCoef'. The output window displays a table titled '1. lind_fitAIC_DMCoef' with four columns: (Intercept), Cingulum_Post_l_C35, Cingulum_Post_r_C36, and Angular_l_C65. The first row shows the values: -4.68650100709704, 3.9941482939647495, -3.3858508025720755, and 2.84341877099374 respectively.

ROW	(Intercept)	Cingulum_Post_l_C35	Cingulum_Post_r_C36	Angular_l_C65
1	-4.68650100709704	3.9941482939647495	-3.3858508025720755	2.84341877099374

The quality of the discrimination can be checked via the **Plot** layout:



The blue line is representing the ROC curve of the full model based on four predictors with an area under the curve (AUC) of 0.7518. The *roc.formula* in the code is producing the following output:

Call:

```
roc.formula(formula = GROUP ~ fit$fitted.values, data = columns)
```

Data: fit\$fitted.values in 78 controls (GROUP convMCI) < 129 cases (GROUP MCI).

Area under the curve: 0.7518

The red line is representing the the ROC curve of the final fit based on three predictors instead of four. As to be expected it has a minimally smaller AUC of 0.7486. The *roc.formula* in the code is producing the following output:

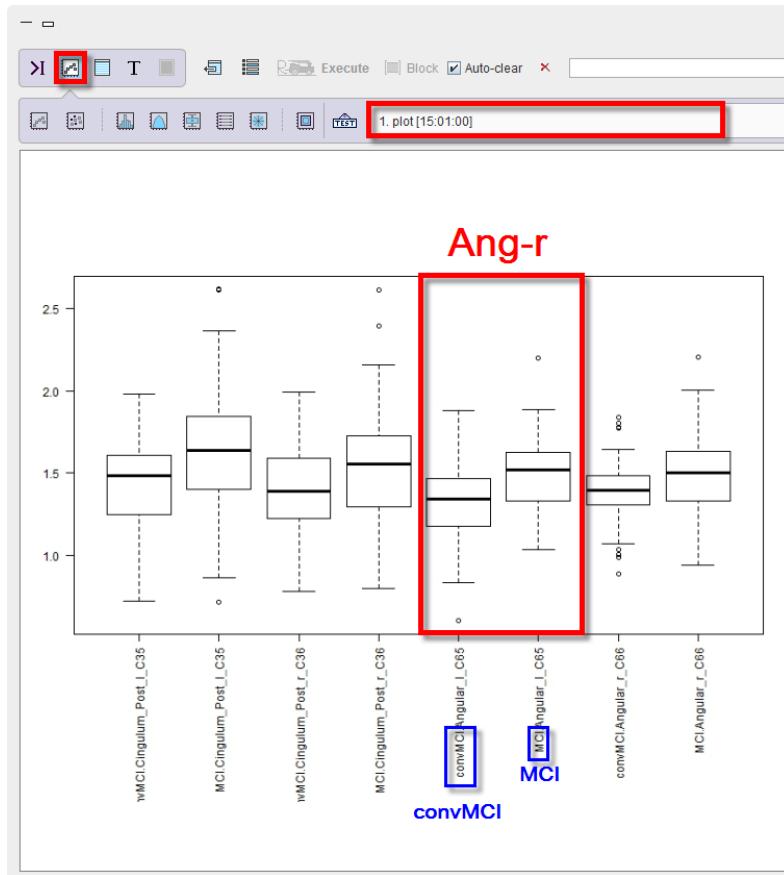
Call:

```
roc.formula(formula = GROUP ~ fitAIC$fitted.values, data = columns)
```

Data: fitAIC\$fitted.values in 78 controls (GROUP convMCI) < 129 cases (GROUP MCI).

Area under the curve: 0.7486

The script produces a *box plot* (on page 324) of the master table data selected for the LDA analysis.



The box plot is providing a side by side comparison of the groups and VOIs.

The purpose of the linear discriminant analysis (LDA) in the example above was to find the linear combinations of the original variables (here indicating the FDG concentrations in the ROIs) that gives the best possible separation between the MCI which progress to dementia and those who remain stable. The discriminant function is representing the linear combination of the variables:

$$t = -4.687 + 3.994 * \text{leftPCC} - 3.386 * \text{rightPCC} + 2.843 * \text{leftAngC}$$

It is recommended to save the LDA results as a workspace using the save icon in the lateral taskbar.

Prediction

The logistic regression is providing the linear fit to the log odds using the linear discriminant function, i.e. the linear combination of the predictors and the corresponding set of the regression coefficients that are specific to the model but the same for all test cases. To convert it into the probability value the following logistic function is used [11]:

$$\sigma(t) = \frac{1}{1+e^{-t}}$$

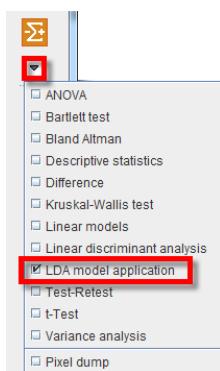
The $\sigma(t)$ is the probability p of the test data set to belong to the stable MCI group. As only two groups are being analyzed, the probability to belong to the other group is then $1-p$. The cut-off value for p is 0.5.

As an example, the linear discriminant function is applied to two individual test cases available in the **Pmod** database as a workspace: **TestCases_LDA.RData**. The AAL VOIs statistics information of the two subjects is available in the workspace as two variables: **g1** and **g2**. Use the **Load/Workspace** entry from the lateral taskbar to load the **TestCases_LDA.RData** in the Pmod-R interface.

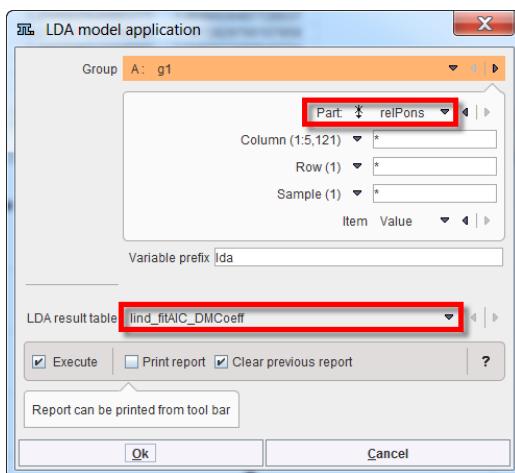
Note: The discriminat model can be applied to VOIs statistics or to aggregated files.

The prediction script requires the linear discriminant function to be available. Load in appending mode the **Function_LDA.RData** workspace available in the **Pmod** example database. This workspace contains the LDA function.

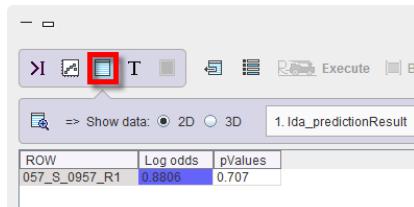
To start the analysis please select the **LDA model application** entry in the scripts list:



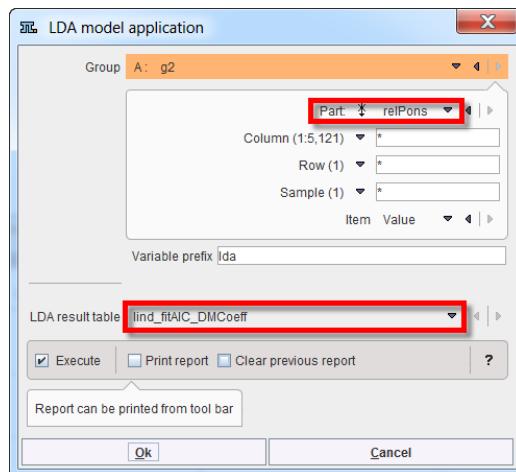
The prediction is run first for the **g1** variable in the workspace. Therefore the **g1** variable is selected in the dialog window as **Group**. The **relPons** statistics is representing the VOIs statistics relative to Pons and is set as **Part**. The **lind_fitAIC_DMCoef** is set as the **LDA result table**.



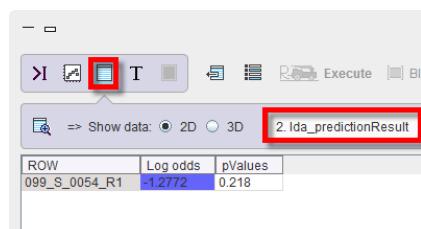
The results are accessible in the **Table** layout:



The prediction is run for the **g2** variable using the same settings in the interface:



and the results are shown below:



The first column in the prediction tables are representing the subject ID while the second and the third columns are listing the log odds and the probability value respectively.

Particularly, the test case with log odds results in the positive range and a prediction value of $p > 0.5$ most likely is representing a stable MCI subject. The test case with negative log odds results and a $p < 0.5$ is indicating a MCI subject most likely belonging to the MCI group which will progress to dementia.

References

- 1) Friston KJ. Commentary and opinion: II. Statistical parametric mapping: ontology and current issues. *J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab*. 1995 May;15(3):361–70.
- 2) Ludbrook J. Multiple Comparison Procedures Updated. *Clin Exp Pharmacol Physiol*. 1998 Dec 1;25(12):1032–7.

- 3) Hochberg Y, Benjamini Y. More powerful procedures for multiple significance testing. *Stat Med*. 1990 Jul;9(7):811–8.
- 4) Fox J. An R Companion to Applied Regression. Auflage: Revised. Thousand Oaks, Calif: Sage Pubn Inc; 2010. 472 p.
- 5) Volkow ND, Kim SW, Wang G-J, Alexoff D, Logan J, Muench L, et al. Acute alcohol intoxication decreases glucose metabolism but increases acetate uptake in the human brain. *NeuroImage*. 2013 Jan 1;64:277–83.
- 6) Wilkinson GN, Rogers CE. Symbolic Description of Factorial Models for Analysis of Variance. *Appl Stat*. 1973;22(3):392.
- 7) O'Brien RG, Kaiser MK. MANOVA method for analyzing repeated measures designs: an extensive primer. *Psychol Bull*. 1985 Mar;97(2):316–33.
- 8) Pinheiro JC, Bates DM. Mixed-Effects Models in S and S-PLUS. Springer Science & Business Media; 2000. 560 p.
- 9) Varnäs K, Jučaitė A, McCarthy DJ, Stenkrona P, Nord M, Halldin C, et al. A PET study with [11C]AZ10419369 to determine brain 5-HT1B receptor occupancy of zolmitriptan in healthy male volunteers. *Cephalgia Int J Headache*. 2013 Jul;33(10):853–60.

Test-Retest

Once a quantitative methodology has been established, the variability of the outcome parameters needs to be assessed in order to find out, what effect sizes can be detected.

Test-Retest Variability and ICC

A test-retest study should be performed with about 10 subjects to evaluate the variability of the relevant outcome parameters. Each subject is studied twice, whereby the physiological and experimental conditions should be as similar as possible. Due to biologic variability, both acquisitions are preferably done on the same day.

The data quantification method in question is applied for all regions of interest and the results from all subjects pooled. The test-retest variability (VAR, also called within subject variability) is then calculated for each region as follows:

$$VAR = \frac{1}{N} \sum_{i=1}^N \frac{|test_i - retest_i|}{(test_i + retest_i)/2} \cdot 100\%$$

where N represents the number of subjects and $test_i$ and $retest_i$ the result values of the quantification method. Hence, the test-retest variability represents the average percent difference of the regional results across the subjects. As an example, the variability of the macro-parameters (V_t , BP_{ND}) in PET is typically in the range of about 5–10%. Brain perfusion is known to be subject to significant physiological variability, and therefore has 20% test-retest variability.

The same data can be used to calculate the variability across the study population. This between-subject variability for a specific region is defined as the coefficient of variation BS(%COV) of the outcome across the population, hence

$$COV = \frac{SD}{Mean} \cdot 100\%$$

where SD represents the standard deviation of the results across subjects.

Another important measure which can be calculated from test-retest data is the intraclass correlation coefficient (ICC). It estimates the reliability of the measurement per region by comparing the within-subject (WS) variability to the between-subject (BS) variability. For the test-retest situation it can be calculated as follows:

$$ICC = \frac{BSMSS - WSMSS}{BSMSS + WSMSS}$$

whereby the MSS represents mean sum of squares and is calculated for the WS and the BS situation by

$$\begin{aligned} WSMSS &= \frac{\sum_{i=1}^N \sum_{k=1}^2 (m_{ik} - \bar{m}_i)^2}{N} \\ BSMSS &= \frac{\sum_{i=1}^N 2(\bar{m}_i - \bar{m})^2}{N-1} \end{aligned}$$

m_{ik} represents a result of subject i (k=1 test, k=2 retest), \bar{m}_i the test-retest mean of subject i, and \bar{m} the overall mean across all studies and subjects.

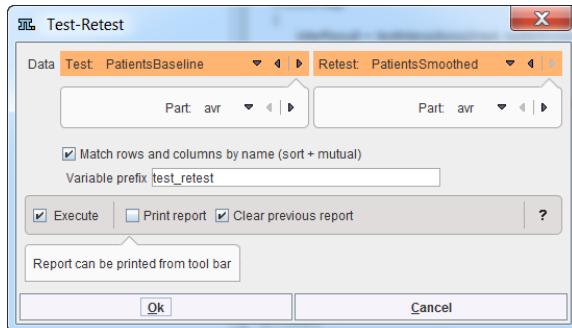
Expected ICC values range between 0 (no reliability) and 1 (maximum reliability, achieved in the case of identity between test and retest). However, in certain circumstances even negative ICC values may occur in actual data sets (indicating no reliability): particularly, in case more differences are observed within than between subjects.

ICC values reflect the relation between measurement reproducibility and the spread of target values. They are commonly considered excellent above 0.75 and acceptable when ranging between 0.5 and 0.75.

See [1] for an application in PET modeling.

Test-Retest Configuration

The Test-Retest script performs the calculations described above between two variables in the workspace for all VOIs. The only choices in the user interface are the **Data** variables, and the statistics within the variables (**Part**)



Test-Retest Results

This script only provides a result table **Test_Retest_Result**

ROW	Mean	BS	BS(%COV)	WS	WS(%COV)	VAR(%)	VAR SD(%)	ICC
Caudate_l_C1	0.52	0.073	0.237	2.67E-4	8.685E-4	3.673	2.112	0.993
Caudate_r_C2	0.622	0.069	0.232	2.648E-4	8.842E-4	4.101	2.943	0.992
Cerebellum_l_C19	0.945	0.016	0.171	8.56E-6	8.954E-5	0.295	0.392	0.999
Cerebellum_r_C20	0.969	1.039E-4	0.014	7.802E-9	1.049E-6	0.008	0.01	1.0
Frontal_lobe_l_C9	0.978	0.011	0.145	2.735E-5	3.601E-4	0.624	0.385	0.995
Frontal_lobe_r_C10	0.905	0.02	0.179	2.14E-5	1.959E-4	0.496	0.439	0.998
Insula_and_cingulate_gyri_l_C17	1.002	0.003	0.077	5.439E-6	1.425E-4	0.29	0.176	0.996
Insula_and_cingulate_gyri_r_C18	0.95	0.013	0.152	7.324E-6	8.682E-5	0.337	0.274	0.999
Occipital_lobe_l_C13	1.029	0.022	0.216	4.67E-5	4.578E-4	0.821	0.393	0.996
Occipital_lobe_r_C14	0.931	0.031	0.23	2.459E-5	1.851E-4	0.604	0.43	0.998
Pallidum_l_C5	0.928	0.011	0.14	4.121E-4	0.005	3.026	0.983	0.93
Pallidum_r_C6	0.895	0.009	0.123	6.214E-4	0.008	3.753	1.672	0.876
Parietal_lobe_l_C15	1.033	0.072	0.393	2.91E-5	1.581E-4	0.592	0.424	0.999
Parietal_lobe_r_C16	0.972	0.049	0.303	3.42E-5	2.134E-4	0.669	0.44	0.999
Putamen_l_C3	1.139	0.006	0.126	3.482E-4	0.007	2.124	0.916	0.891
Putamen_r_C4	1.149	0.009	0.152	2.689E-4	0.005	1.851	0.747	0.941
Temporal_lobe_l_C11	1.021	0.044	0.305	1.339E-5	9.167E-5	0.391	0.279	0.999
Temporal_lobe_r_C12	0.961	0.029	0.231	2.101E-5	1.678E-4	0.515	0.37	0.999
Thalamus_l_C7	0.883	0.035	0.233	1.759E-4	0.001	2.0	0.484	0.99
Thalamus_r_C8	0.901	0.039	0.253	2.231E-4	0.001	2.038	0.879	0.989

with the following results per VOI:

- Mean** The mean value of the test and retest data.
- BS** The between subject variability.
- BS (%COV)** The between subject coefficient of variation.
- WS** The within subject variability.
- WS (%COV)** The within subject coefficient of variation.
- VAR (%)** Test-retest variability.
- VAR SD (%)** Test-retest variability standard deviation.

ICC The intraclass correlation coefficient.

- Parsey RV, Slifstein M, Hwang DR, Abi-Dargham A, Simpson N, Mawlawi O, Guo NN, Van Heertum R, Mann JJ, Laruelle M: Validation and reproducibility of measurement of 5-HT1A receptor parameters with [carbonyl-11C]WAY-100635 in humans: comparison of arterial and reference tissue input functions. *J Cereb Blood Flow Metab* 2000, 20(7):1111-1133. DOI <http://dx.doi.org/10.1097/00004647-200007000-00011>
- Weir JP: Quantifying Test-Retest reliability using the intraclass correlation coefficient and the SEM. *J. Strength Cond. Res.* 2005, 19(1): 231-240

t-Test

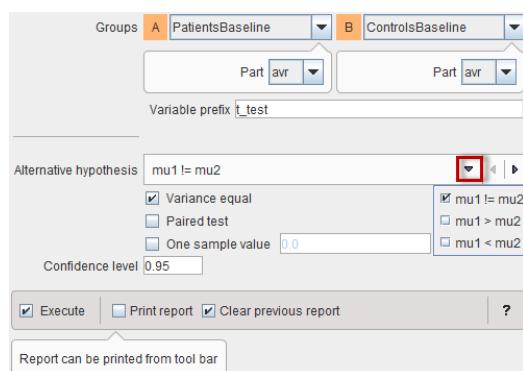
The t-test is a family of statistical hypothesis tests which can be used to determine if two sets of data are significantly different from each other. An instructive summary of the background and the application of the t-test can be found on *Wikipedia* https://en.wikipedia.org/wiki/Student's_t-test [1].

Depending on the application case (null hypothesis, data) a different test formula needs to be applied to the data. They all result in a t-value, which can be converted into a p-value using a table of values from Student's t-distribution.

The p-value is the probability of obtaining at least the observed t-value, assuming that the null hypothesis is true. Therefore, if the calculated p-value is below the threshold chosen for statistical significance (usually the 0.10, the 0.05, or 0.01 level) and therefore highly unlikely, the null hypothesis is rejected in favor of the alternative hypothesis.

t-Test Configuration

The **t-Test** script has the configuration window below.



Please first define, whether a **One sample** location test against a specified population mean should be performed. In this case only one **Group** can be selected, and the hypothesis value entered. The **Alternative hypotheses** change to the choices below (unequal, larger or smaller than value).



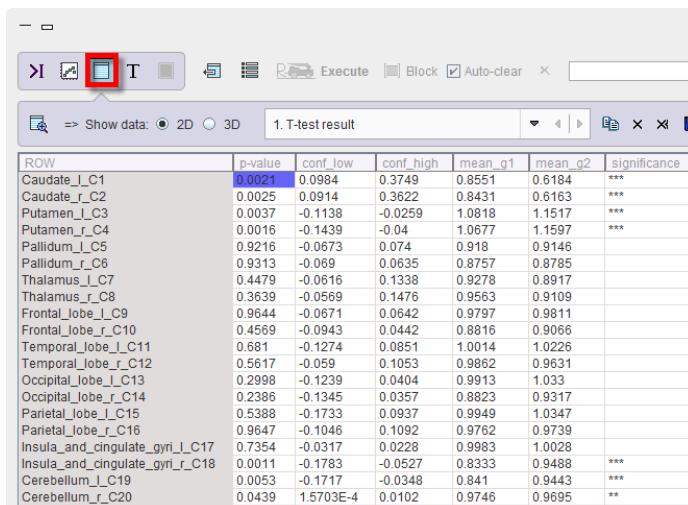
Otherwise, a two-sample t-test will be performed. The two **Groups** to be compared need to be selected, and the appropriate **Alternate hypothesis** configured:

- » **mu1!=mu2**: null hypothesis of equal group means (two-sided test)
- » **mu1>mu2**: null hypothesis of group2 mean is equal or larger than group 1 mean (one-sided test)
- » **mu1<mu2**: null hypothesis of group1 mean is equal or larger than group 2 mean (one-sided test)

If the variance in the two samples is equal, the **Variance equal** box should be checked for using the pooled variance rather than an approximation. The **Paired test** should only be enabled if this condition is met by the two samples. In this case, the script will try to pair the group samples.

t-Test Results

The script only returns numeric results in the form of the **ttest_t_results** table. The example below illustrates the outcome with an unpaired two-sided test.



ROW	p-value	conf_low	conf_high	mean_g1	mean_g2	significance
Caudate_l_C1	0.0021	0.0984	0.3749	0.8551	0.6184	***
Caudate_r_C2	0.0025	0.0914	0.3622	0.8431	0.6163	***
Putamen_l_C3	0.0037	-0.1138	-0.0259	1.0818	1.1517	***
Putamen_r_C4	0.0016	-0.1439	-0.04	1.0677	1.1597	***
Pallidum_l_C5	0.9216	-0.0673	0.074	0.918	0.9146	
Pallidum_r_C6	0.9313	-0.069	0.0635	0.8757	0.8785	
Thalamus_l_C7	0.4479	-0.0616	0.1338	0.9278	0.8917	
Thalamus_r_C8	0.3639	-0.0569	0.1476	0.9563	0.9109	
Frontal_lobe_l_C9	0.9644	-0.0671	0.0642	0.9797	0.9811	
Frontal_lobe_r_C10	0.4569	-0.0943	0.0442	0.8816	0.9066	
Temporal_lobe_l_C11	0.681	-0.1274	0.0851	1.0014	1.0226	
Temporal_lobe_r_C12	0.5617	-0.059	0.1053	0.9862	0.9631	
Occipital_lobe_l_C13	0.2998	-0.1239	0.0404	0.9913	1.033	
Occipital_lobe_r_C14	0.2386	-0.1345	0.0357	0.8823	0.9317	
Parietal_lobe_l_C15	0.5388	-0.1733	0.0937	0.9949	1.0347	
Parietal_lobe_r_C16	0.9647	-0.1046	0.1092	0.9762	0.9739	
Insula_and_cingulate_gyril_C17	0.7354	-0.0317	0.0228	0.9983	1.0028	
Insula_and_cingulate_gyrir_C18	0.0011	-0.1783	-0.0527	0.8333	0.9488	***
Cerebellum_l_C19	0.0053	-0.1717	-0.0348	0.841	0.9443	***
Cerebellum_r_C20	0.0439	1.5703E-4	0.0102	0.9746	0.9695	**

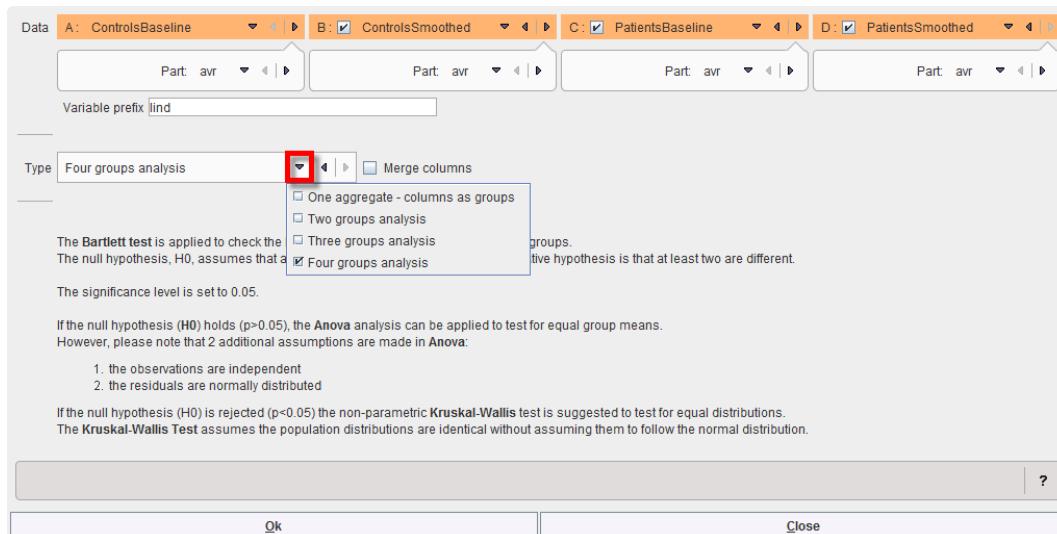
For each region the **p-value**, the lower and upper confidence intervals (**conf_low**, **conf_high**) as well as the two group means (**mean_g1**, **mean_g2**) are listed. In the example above, the first four regional means are significantly different, since their p-values are below 5%.

Variance Analysis

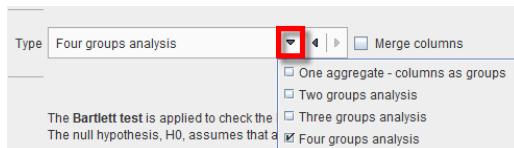
Variance Analysis is a convenience script for comparing three or four groups. It first applies the **Bartlett test** (on page 335) to establish, whether the group variances are equal. If yes, it proposes **one-way ANOVA** (on page 333) for testing for significant differences between the group means. Otherwise, the non-parametric **Kruskal-Wallis test** (on page 342) is proposed for testing whether the distributions are identical.

Variance Analysis Configuration

The Variance Analysis configuration window is illustrated below.



Up to four groups can be compared, according to the **Type** selection

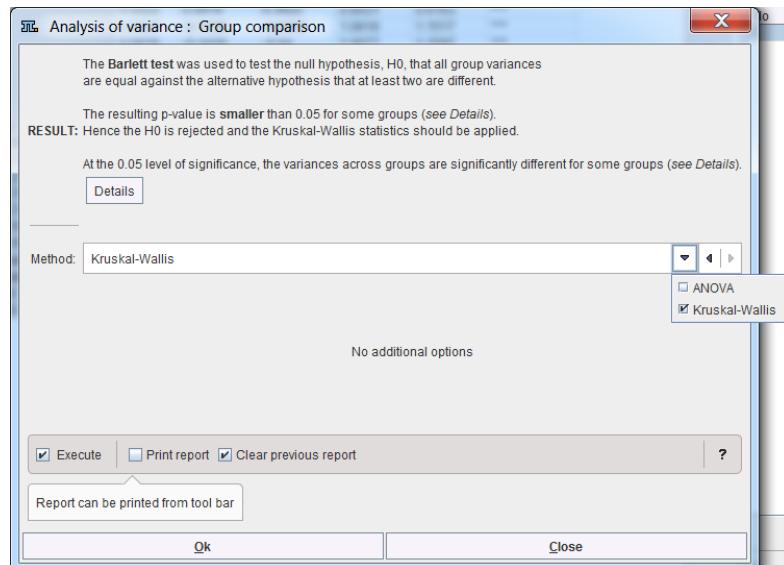


If **Merge columns** is enabled, the data of all columns will be pooled, otherwise the test is performed between the respective columns of the aggregates.

With the **One aggregate - columns as groups** setting it is assumed that the groups to be compared are arranged as columns in a single aggregate.

Variance Analysis Results

As a first step, the **Bartlett Test** is applied for comparing the variances, and the result shown.



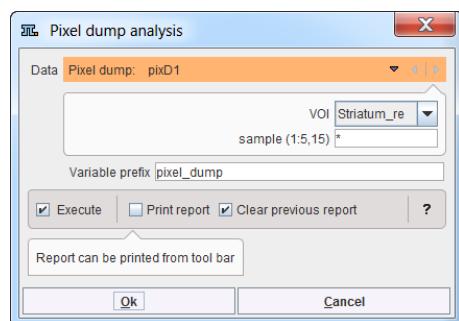
Depending on the outcome, ANOVA or Kruskal-Wallis are proposed as the follow-up test, but both are available. When applying either test as the second step, the results correspond to that of the individual test.

Pixel Dump

The **Pixel Dump** (on page 288) script serves for visualizing the distribution of pixel values in VOIs by means of histograms.

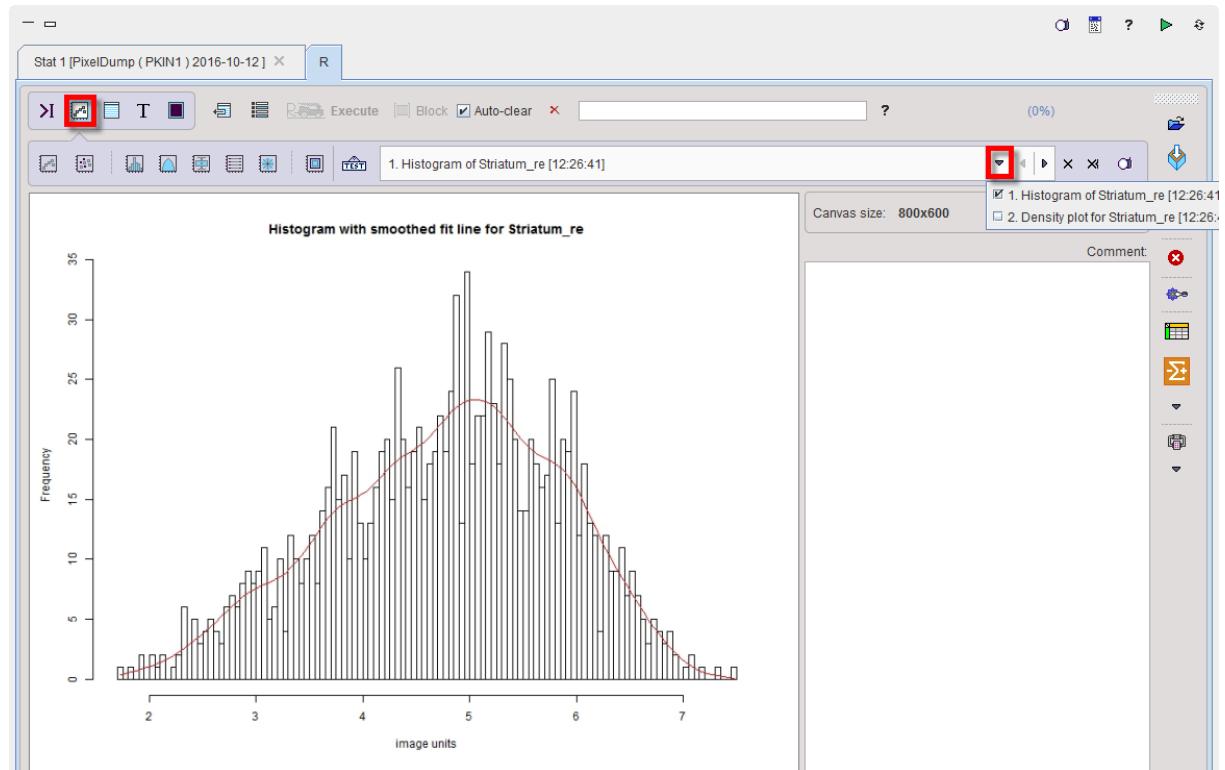
Pixel Dump Configuration

The loaded pixel dump is selected with the **Data** choice. The contents analyzed in order to list the included VOIs.



Pixel Dump Results

After selecting a VOI and running the analysis, two plots are generated: a **Histogram** as illustrated below,



and a **Kernel Density Plot** which is often a much more effective way to view the distribution of a variable.

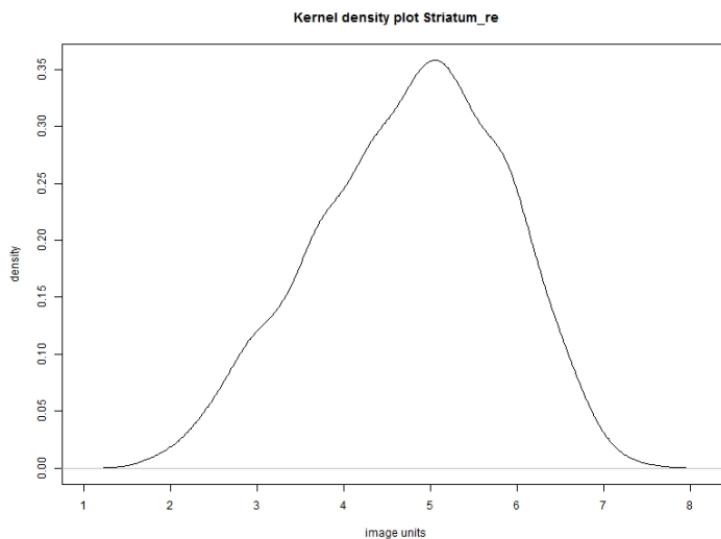
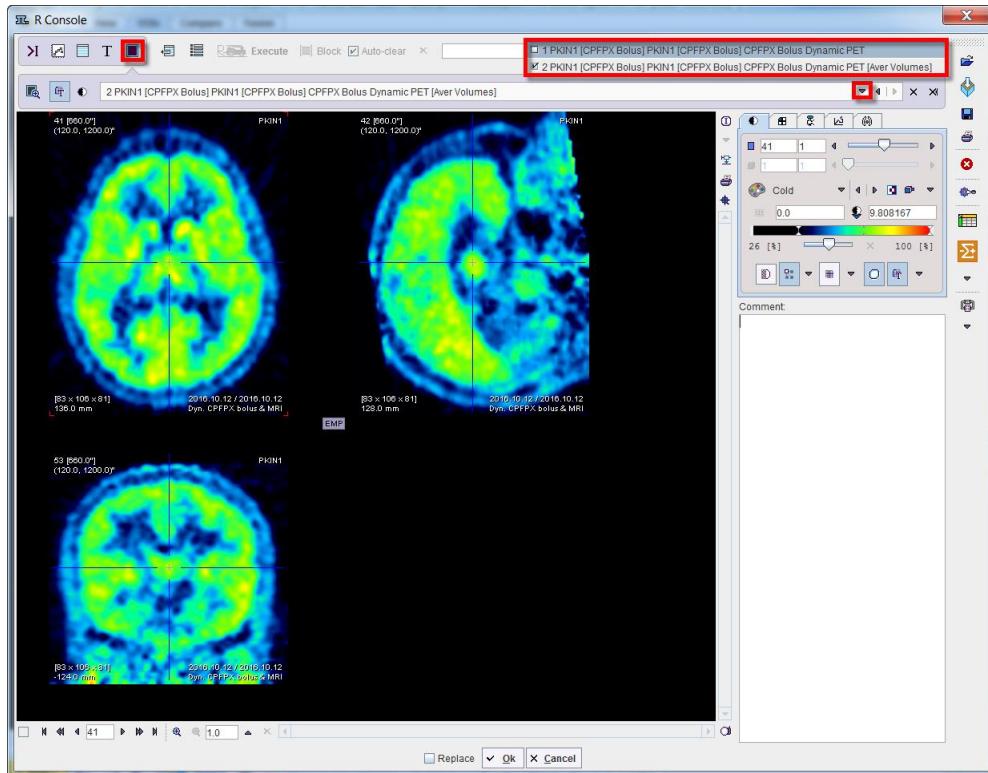


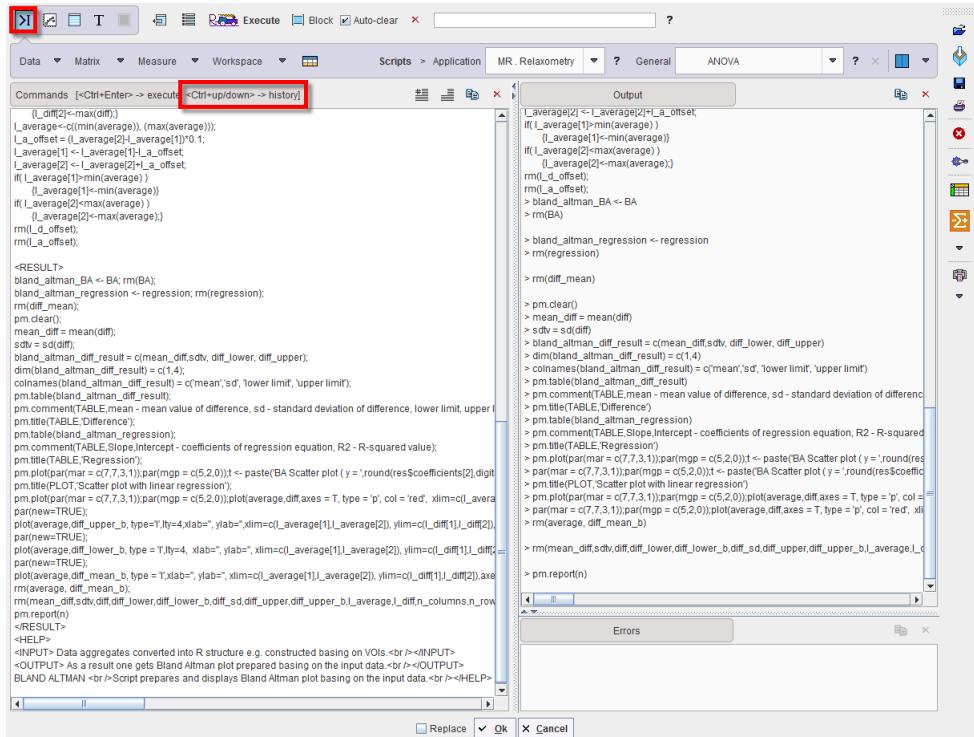
Image Layout

The image window serves for the visualization of the image data transferred to the R interface using the **R console external tool** (on page 140).



Command Layout

The command window provides a graphic user interface for developing and executing R commands and scripts. The illustration below shows the organization using the horizontal layout.



Commands Area

The **Commands** area serves the following purposes:

- 1) Interactive R command execution: R commands can be manually typed into the area and executed with the Execute button. If multiple code lines were entered, execution can be restricted to a highlighted part by the Block button.
- 2) Code generated by Scripts: Whenever a script is called, its R code is copied to the **Commands** area and then executed.
- 3) Execution history: Whenever the **Commands** contents is executed, it is copied to a history buffer. If the **Auto-clear** box is checked, the **Command** area is cleared after command execution. However, using the keyboard keys **Ctrl+up-arrow** and **Ctrl+down-arrow**, prior execution code can be retrieved from the history for inspection/modification. For users interested in R it may be of interest to recall and review the code of in-built scripts.

Output Area

Connecting to the server localhost ... Connected.

Loading default settings ... Loaded.

R version 3.3.1 (2016-06-21) Windows

```

Loading input data 1/2 ... Loaded.

Loading input data 2/2 ... Loaded.

> summary(g1);
      Length Class      Mode
vt 16     data.frame list

> ls();
[1] "g1"          "g2"          "pm.getc"       "pm.gete"
"pm.getf"
[6] "pm.geti"      "pm.getm"       "pm.getp"       "pm.getr"
"pm.gets1c"
[11] "pm.getv"      "pm.getx"       "pm.mutualc"   "pm.mutualr"
"pm.mutualrc"
[16] "pm.setc"      "pm.setm"       "pm.setp"       "pm.setr"
"pm.sets1c"
[21] "pm.size"      "pm.sortc"     "pm.sortr"     "pm.sortrc"
"pm.trim"
[26] "zz"

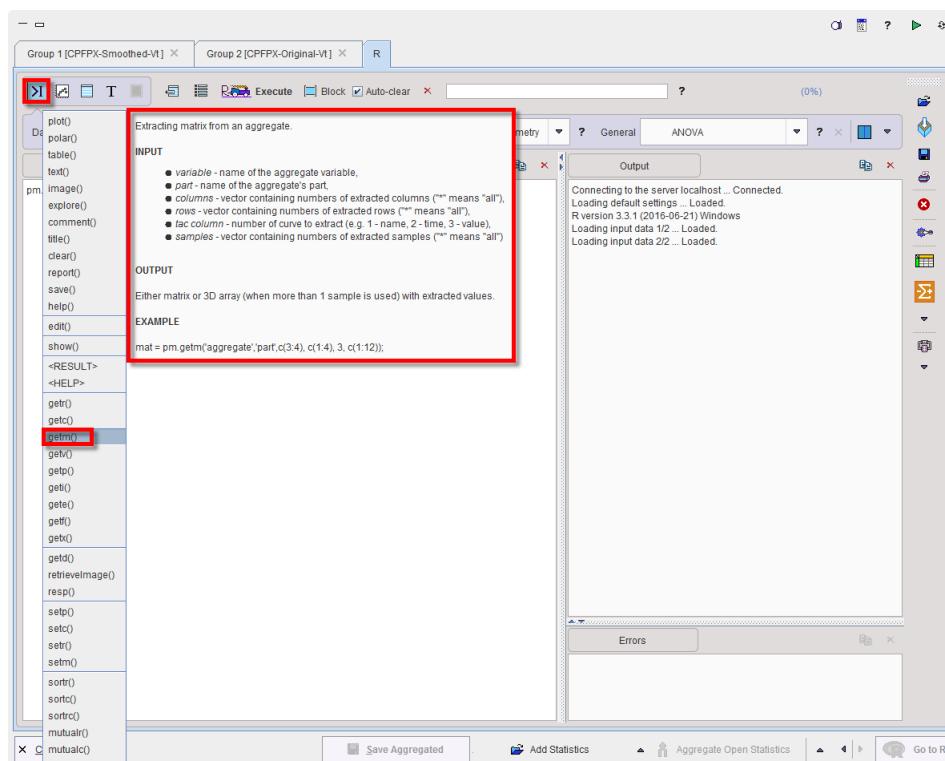
```

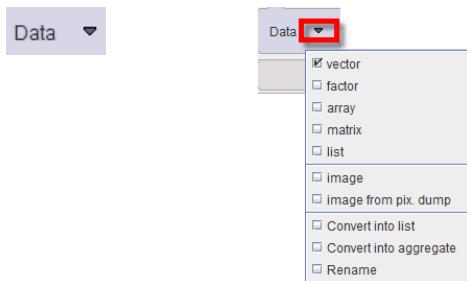
Errors Area

Please check the contents of the **Errors** area, if the behavior of the R console is unexpected.

PMOD R Commands and Code Generator

PMOD has implemented a set of commands dedicated to the PMOD **Command** console. This commands list is accessible typing the **pm.** in the **Command** console. Their description is available upon selection from the pop-up menu as shown below:



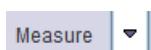
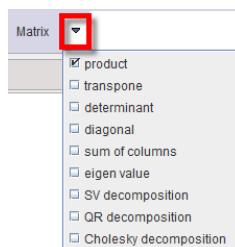


Allows:

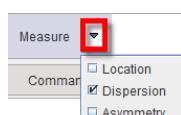
- ▶ creating new data structures such as vector, array , matrix or list
- ▶ creating images based on specified parameters or from pixel-dump files
- ▶ converting a vector into list specifying a vector function
- ▶ converting a data frame into an aggregated file
- ▶ renaming a variable in teh workspace



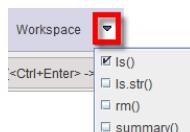
Basic operations on matrices.



Allows applying predefined statistic operations to the variables available in the workspace.

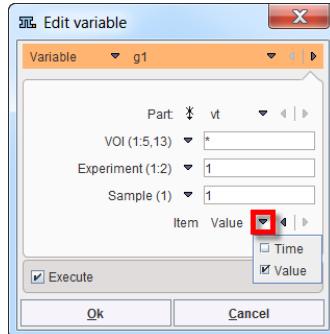


Allows performing various quick operation like listing (ls()), removing(rm()) and accessing the summary (summary()) of the variables available in the workspace. The results are displayed in the **Output** console.

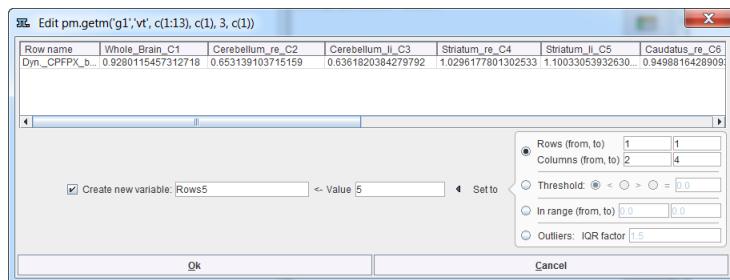




Allows editing a variable available in the workspace. Upon activation the list of variables available in the workspace is displayed. The data type is detected automatically. Two options are available: either **Choose variable** or **Define expression**.



The user can decide which **Part** of the selected variable has to be edited: **Time** or **Value**. The confirmation of the settings opens a dialog window which allows performing the editing.



There are four ways to replace with the specified **Value** the content of the displayed table:

- ▶ specifying the **Rows** and **Columns** in the dedicated text fields
- ▶ using a **Threshold** definition based on one of the three criteria: >, <, =. All the pixels above, below or equal to the specified value will be replaced by the **Value**.
- ▶ **In range** is similar to the **Threshold** except that two limits are defined in the *from* and *to* text fields
- ▶ the **Outliers** will be considered all the observations that fall below $Q1 - factor^*(IQR)$ or above $Q3 + factor^*(IQR)$. The **IQR** is representing the interquartile range and is calculated as $IQR = Q3 - Q1$. The **Q1** and **Q3** are representing the first and third quartile respectively. In a boxplot, the highest and lowest occurring value within this limit are drawn as bar of the whiskers, and the outliers as individual points.

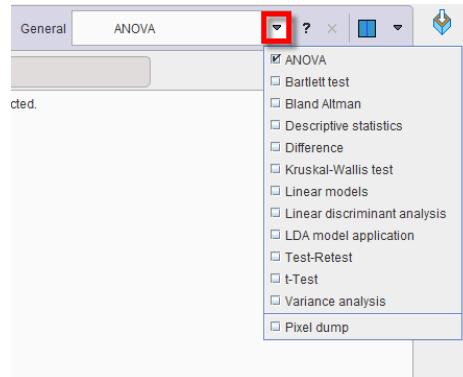
Once the method is selected and all the parameters specified the **Set to** button allows setting the new **Value** in the table. Activate the **Create new variable** checkbox and specify a name in order to avoid overwriting the original variable. Close the dialog window with the **OK** button.

ANOVA

Allows selecting and running general predefined R scripts. Detailed information of the scripts is available in the dedicated section in this documentation.

The predefined scripts are available for selection with the small arrow closed to the button. To add a R script to the predefined list, please copy the *.r file in the Pmod installation folder *in*

C:\Pmod3.8\resources\extlibs\r



If any help section was included in the script this can be visualized activating the ? icon close to the scripts selection list.



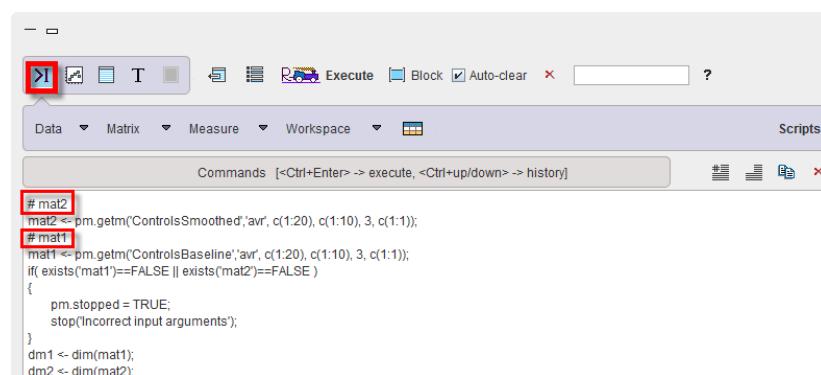
Allows deleting a script from the scripts predefined list.



Allows switching between the two layout options: horizontal and vertical.



Allows commenting the command lines. First, the lines have to be selected and the icon activated.



Allows uncommenting the selected command lines in the command console. First, the lines have to be selected and the icon activated.



In the **Commands** console: allows copying commands console to the clipboard.

In the **Output** console: allows copying output content to clipboard.

In the **Errors** console: allows copying the errors messages to the clipboard.



In the **Commands** console: allows deleting the content of the command console.

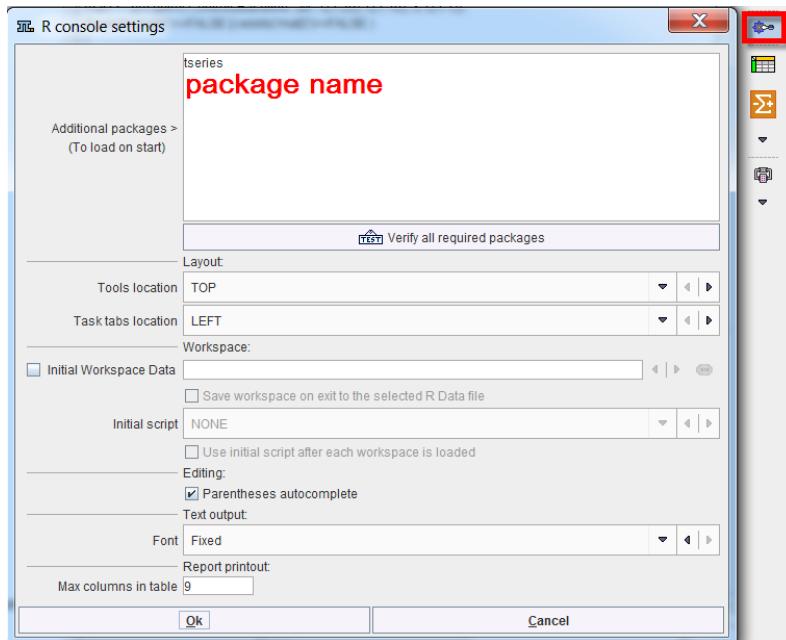
In the **Output** console: allows clearing the output content .

In the **Errors** console: allows deleting the errors messages.

User Programming and Scripts

Package Use

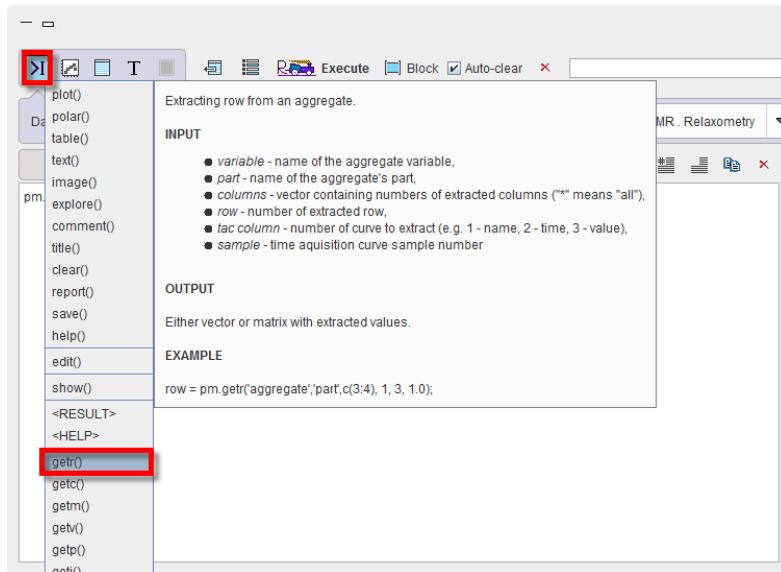
There is a huge number of public packages available covering a large spectrum of functionality. Users may want to use functions contained in such packages for their own developments. To do so, the package name needs to be added to the **Additional packages** list



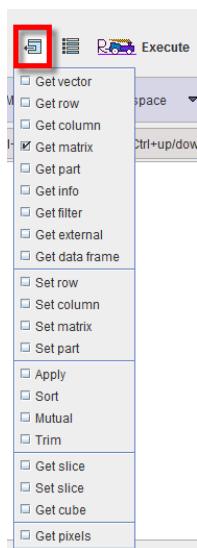
After closing with **Ok** and restarting PMOD, the package should be loaded and become available.

Accessing PMOD R Variables

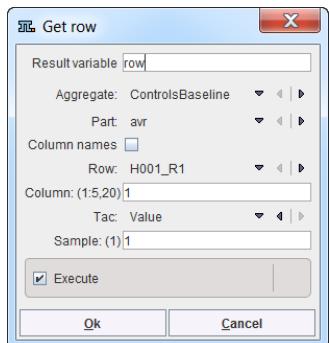
The structure of PMOD R variables is described *above* (on page 316). A user may want to program scripts which address and process such variables. A list of functions can be obtained by simply typing "pm." into the command window. Moving the cursor over the list entries pops up a window with a syntax description and an example.



Another approach which is particularly helpful when beginning with scripts is using the extraction button



After selecting an entry, a dialog window is shown, in the case of **Get experiment**

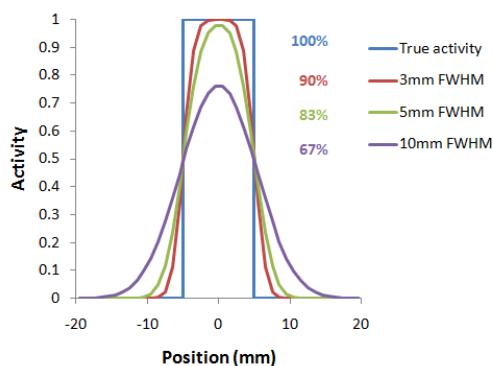


When confirming the window, corresponding R code is generated
`experiment = pm.getr("g1", "vt", c(1:13), 1, 3, 1.0);`
which can be seen if the **Execute** box is not enabled.

Chapter 8

Partial-Volume Correction (PVC)

PET and SPECT images are inherently affected by the *partial-volume effect*. This term means that the measured tracer activity concentrations are not accurate due to the relatively low image resolution and the limited tissue sampling. Basically, the low resolution causes a blurring of the image, so that high activities (from a hot lesion) are spread to the surrounding as illustrated below. This effect is called *spill-out*. The same effect also causes a *spill-in* of background activity into the volume of interest.



As a consequence, hot lesions tend to appear less aggressive (reduced maximum) but bigger (spreading) than they are in reality.

Spill-in and spill-out depend on the geometry of the objects, the activity distribution of the tracer, and on the resolution of the scanner which may vary across the imaging field-of-view. Therefore, practical correction approaches have to assume certain conditions and can only be approximate. For a nice overview of the topic please refer to the publication of Soret et al. [1].

Solutions Implemented in PMOD

PMOD provides two PVC solutions:

- 1) **PVC VOI-based:** This correction is based on the assumption, that the imaging volume can be separated into tissue volumes (VOIs) with homogeneous uptake. If the resolution of the PET scanner is known, the mutual signal contaminations across the VOIs can be calculated and corrected for. This method is known as the GTM (Geometric Transfer Matrix) method and was introduced by Rousset et al. [2,3].
The implementation in PMOD allows the user applying the GTM correction with any set of manually outlined VOIs. Additionally, for the analysis of human brain uptake, the user may take advantage of standard VOIs which are automatically adjusted to the patient's anatomy.
- 2) **PVC Brain MR based :** This correction is based on the assumption that white matter uptake is homogeneous. All brain pixels are classified as white matter (WM) or grey matter (GM) and sorted into respective segments. Based on these segments and the assumed PET resolution the spill-out from WM to GM can be estimated and subtracted. Similarly, the spill-out from GM to the surroundings can be estimated and compensated

for. The result is a grey matter image with corrected activity values in all pixels. This method was introduced by Muller-Gartner et al. [4].

Given a brain PET and an anatomical MRI of a patient, the implementation in PMOD allows the user performing the segmentation and apply the Muller-Gartner PVC in a fully automated way.

The two PVC methods are implemented as *external tools* (on page 164), although they have a much broader scope and require more user interaction than typical external tools. Therefore, their implementations are described in the respective sub-sections below.

Step-wise and Background Calculation Modes

The different PVC methods typically involve several processing steps, some of them using input parameters. There are two ways how a user can apply the PVC calculation:

- 1) **Background calculation:** The user enters all required information and adjusts the different parameters, and then starts the processing. The tool window closes, the computations run in a separate thread in the background, and finally returns the corrected images for statistical analysis.
- 2) **Step-wise processing:** The user performs the processing steps one by one interactively with a  button, and inspects the intermediate results in the tool. If required, he can change a parameter and initiates the calculation again. After the last step, the final results are returned and the tool closed.

The step-wise processing mode has the advantage that all intermediate data remains available, and processing can be repeated from any intermediate step. When data is returned, it is already quality checked, whereas in the background mode the user can not always be sure that all processing steps were successful without inspecting some of the supplementary images returned by the tool.

The **All Steps** button performs all processing steps sequentially, but does not close the dialog window so that after a first run the different steps can be interactively explored.

Note that the parameters can always be reset to the recommended default values by the  button to establish a well defined situation after some experiments.

Common Requirements for Partial-volume Correction in PMOD

The PVC methods implemented in PMOD assume a homogeneous, Gaussian-shaped point-spread function (PSF) of the scanner which is specified by its full-width at half maximum (FWHM) in all directions. The user needs to determine reasonable FWHM values for his reconstructed images and specify them to the algorithm. If possible, a PET reconstruction method with homogeneous resolution should be used, so that the assumption of a stationary PSF is justified. Furthermore, the brain PET images should be reconstructed with a small pixel size not larger than 2.5 mm.

Important Note: The PVC tools expect that the image data is loaded in the HFS orientation. It is a precondition for segmentation and matching procedures.

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PVC based on Manual and Brain Template VOIs

Methodology Description

VOI based Partial-Volume Correction (GTM Method)

The GTM method according to Rousset [2] restricts the partial volume correction to the signal of the true objects which are constituted by VOIs. The relation of measured PET values (affected by the partial-volume effect) to the true PET values is given by the matrix equation below

$$\vec{C}_{\text{measured}} = [\text{GTM}] \times \vec{C}_{\text{true}}$$

with the following notations:

C_{true}	Vector of the true average activity concentration in the different VOIs of interest. The vector length n equals the number of object VOIs.
C_{measured}	Actually measured average activity concentration in the different VOIs.
GTM	Geometric Transfer Matrix which describes the spill-over among all the VOIs. The matrix is square with nxn weighting elements $w_{i,j}$ which express the fraction of true activity spilled over from VOI _i into VOI _j .

In practice, $w_{i,j}$ is calculated as follows: A binary map is created with 1 in all pixels of VOI_i and 0 elsewhere. The map is convolved with the imaging Point-Spread Function (PSF), and in the resulting spillover map the average of all VOI_j pixels calculated.

The GTM equation above represents a system of linear equations. Once the weights have been calculated, the system can be solved for the true values C_{true} by matrix inversion. Rousset [2] has shown that this algorithm is robust to noise propagation during the correction process.

Region-based Voxel-wise (RBV)

The RBV correction introduced by Thomas et al [6] extends the GTM method and performs a voxel-wise correction of the entire image.

In a first step the standard GTM correction is performed, resulting in a synthetic image C_{GTM} , which consists of the VOIs filled with the corrected average values.

In a second step a corrected image is calculated, which is not any more homogeneous within the VOIs, and which shows an image of the entire brain, not just the GM pixels. The calculation uses the formula

$$C_{\text{PVC-RBV}} = C_{\text{Measured}} \left[\frac{C_{\text{GTM}}}{C_{\text{GTM}} \otimes \text{PSF}} \right]$$

whereby the measured PET image C_{Measured} is multiplied by a correction term calculated from the GTM corrected image and the point-spread function.

The method applied for the PVC calculation is available for selection on the bottom of the PVC interface:



Implemented VOI-based PVC Variants

The PVC (**VOI based**) method provides three variants which are based on the same GTM methodology. The difference is, how the VOIs are obtained.

- 1) **Manual VOIs:** The user outlines all VOIs manually.
- 2) **Template VOIs based on standard masks:** VOI templates defined in the MNI space are used and adjusted to the PET image. This method can only be applied for human brain images.
- 3) **Template VOIs based on individual masks:** The same VOI templates as above are used. The difference is, that the user has to provide an anatomical MRI image which is employed for a better individual adjustment for the VOIs.
- 4) **Template VOIs based on Plain VOIs:** the same VOI templates as above are used. No Anatomical MRI image is needed.

Methods 2,3 and 4 can only be applied for human brain images, whereas method 1 is generic. Note that the user may also derive himself contour VOIs from standard VOI templates, adjust them to the subject anatomy, and apply method 1. This allows him to take advantage of the rat and mouse templates for which an automated work-flow is not yet available.

The details of the methods are explained in the corresponding sections below.

Common Requirements

The VOI-based PVC methods can be applied to PET or SPECT images, both static and dynamic. A set of VOIs is required which define objects of common functional properties.

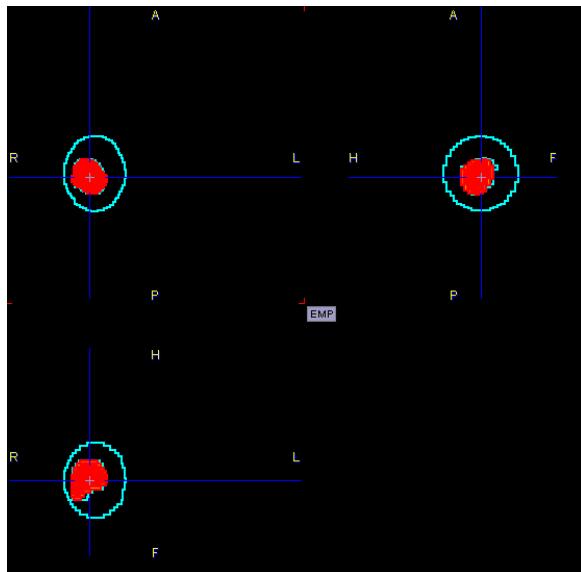
Important Note: The VOIs used for PVC may not be overlapping each other! If they do, a warning message will be shown. All activities in the neighborhood of the target should be taken into consideration and included into appropriate VOIs.

Results of VOI-based PVC

When closing the dialog window, the results of VOI-based partial-volume correction are returned in the form of an additional image series, indicated in the description by a **VOI based PVE corrected** string. Note that if the **Replace** box is checked the original images are replaced by the partial-volume corrected images.

VOI Based Uniform (GTM)

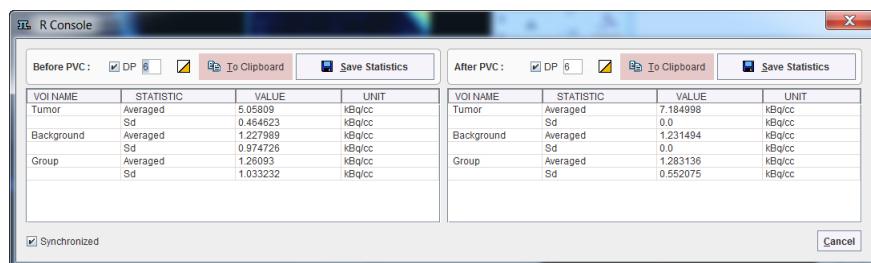
In these images, all pixels belonging to a VOI are set to the value obtained as the partial-volume corrected average value of that VOI. Pixels not included in a VOI are set to NaN. The example below illustrates a case with only two manually outlined VOIs, a tumor VOI and an enclosing background VOI.



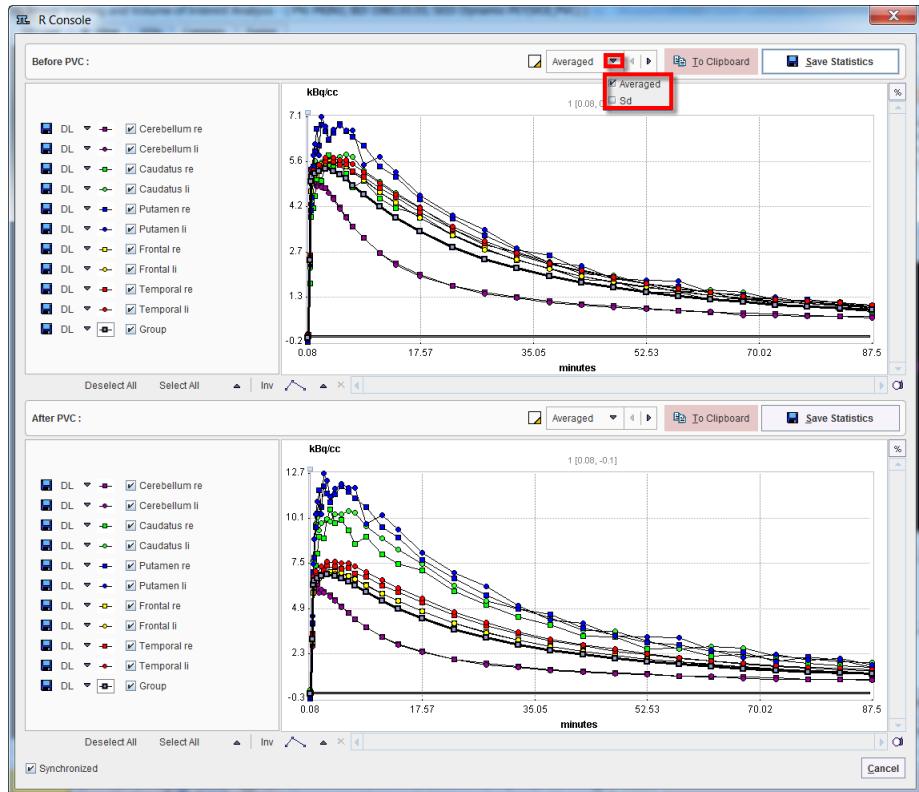
To obtain the partial-volume corrected VOI averages please open the result images in the VOI tool, load the VOIs employed for the PVC, and calculate the statistics.

Statistics in Step-wise Mode

The step-wise mode has the advantage, that the statistics can directly be calculated with the **View Statistics** button. For static series, simple VOI statistics will be generated which are shown in a side-by-side manner as illustrated below.



In the case of dynamic series the results are TACs as illustrated below.



The statistic results can be saved as statistics *.voistat file with the **Save Statistics** button. In alternative, the **Before PVC** or **After PVC** content of the page can be copied **To Clipboard** and paste in Excel.

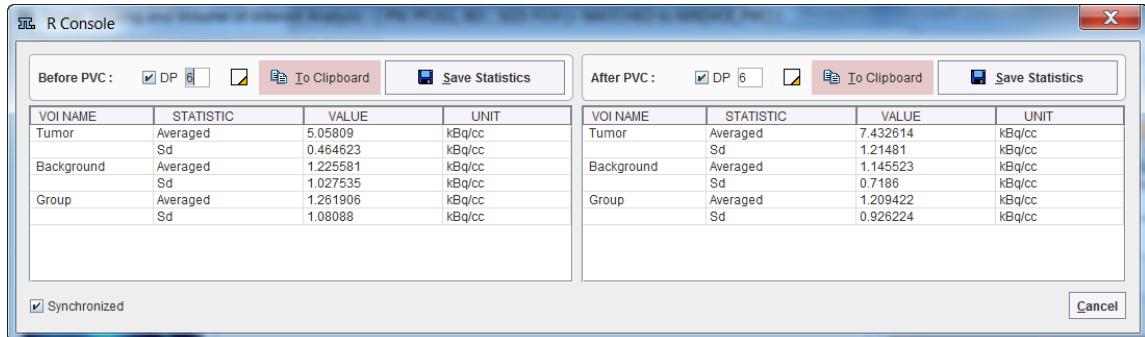
Region-Based Voxelwise (RBV)

The corrected image is not anymore homogeneous within the VOI: each pixel in the VOI is set to the value obtain as the partial volume corrected value of that pixel. Pixels not included in a VOI are set to NaN.

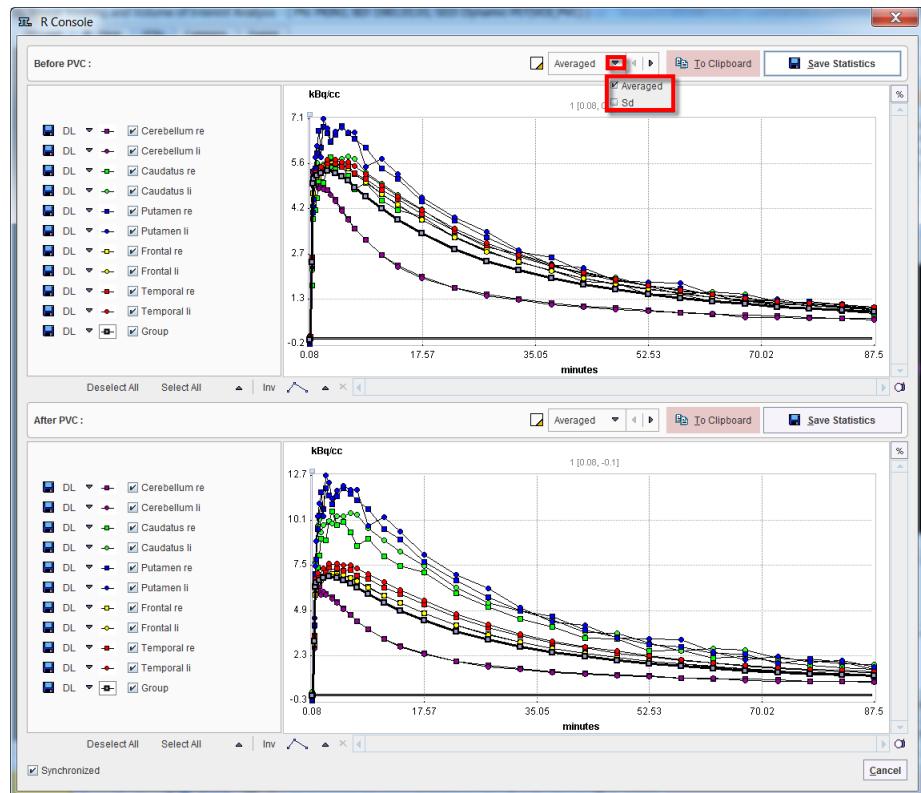
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In the case of dynamic series the results are TACs as illustrated below.



The statistic results can be saved as statistics *.voistat file with the **Save Statistics** button. In alternative, the **Before PVC** or **After PVC** content of the page can be copied **To Clipboard** and paste in Excel.

PVC using Manual VOIs

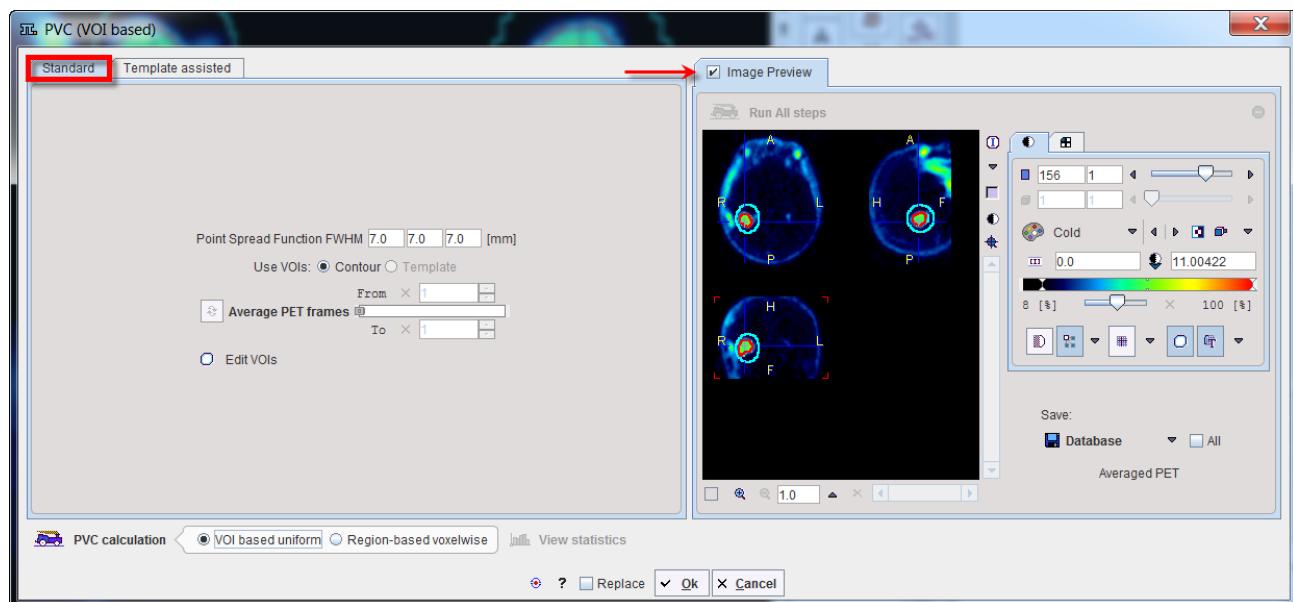
Overview

The most general case of VOI based PVC is, that the user himself generates a set of suitable VOIs to which he applies the GTM correction as described below.

Starting the PVC

As a first step, load the PET images into the PVIEW tool. Define or load a set of VOIs. Then activate the button to the right of the image and select the **PVC (VOI based)** method from the list of external tools. A dialog window is shown which allows performing the processing in a step-by-step mode or as a background process.

Select the **Standard** tab for performing a correction based on your manually defined VOIs.



Step-by-Step PVC Processing Mode

The step-wise mode is activated by checking the box next to the **Enable preview** label. It activates buttons for the individual processing steps, as well as the **Edit VOIs** and once the PVC was calculated also the **View statistics** buttons.

Point Spread Function FWHM:

The PSF is assumed to be a three-dimensional Gaussian function. The FWHM values in the three directions have to be specified according to the resolution of the reconstructed image. Default is 7 mm isotropic FWHM.

Use VOIs:

Both contour VOIs and template VOIs can exist in parallel. If two definitions exist, the user has to decide whether to use the **Contour** or the **Template** VOIs.

Average PET frames:

If the study is dynamic, this option gets active in the step-wise mode. The purpose is to provide an averaged PET image for the purpose of VOI outlining. This averaging step is optional, and PVC will always be performed on the original images. The **Averaged PET** will also be shown in the **Image Preview** window

Edit VOIs:

This button opens a VOI tool dialog window showing the averaged PET images. If VOIs were defined beforehand, they can be edited, and VOIs can be loaded from a file. To return modified VOIs, close the window with the **Ok** button, otherwise **Cancel**.

PVC Calculation:

This button performs the actual PVC calculation. The result is returned in the form of an image series and shown in the **Image Preview** window.

View Statistics:

This button calculates the VOI statistics in the original and the PVC corrected images. Depending on the input images the results are simple statistics, or tissue time-activity curves.

Returning the Results:

To return the results close the window with the **Ok** button.

Background PVC Processing Mode

If no interactive processing is desired, the user interaction is minimal.

- 1) If desired, edit the FWHM parameters, or reset them by the  button.
- 2) Start the PVC calculation with the **Ok** button.

The window will be closed and processing will run in the background. The processing time depends on the number of VOIs and the FWHM. Once the result was calculated and returned to PVIEW, a confirmation message will be shown.

PVC using Template VOIs based on Standard Masks**Overview**

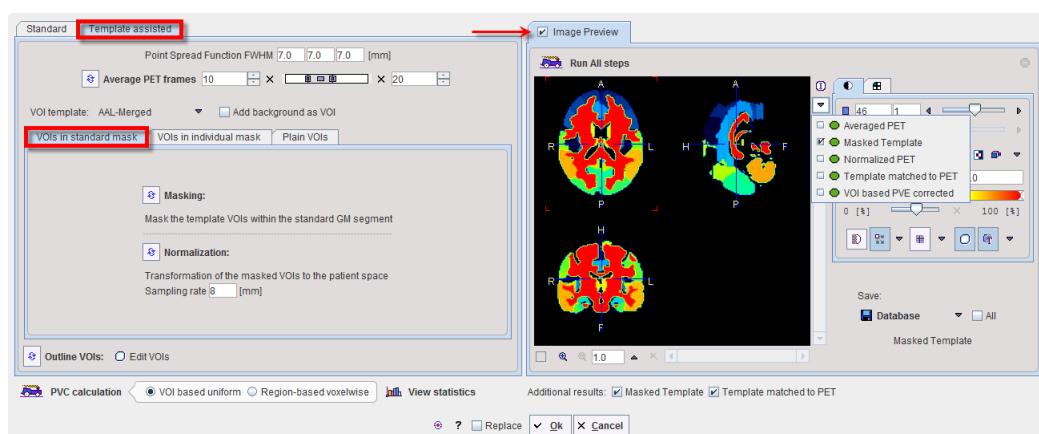
PMOD provides templates of human brain VOIs in the standard MNI space, as well as masks of the grey and white matter pixels. The PVC method described below employs this prior information for constructing a set of individual brain VOIs matching a PET scan as follows:

- 1) The template VOIs are intersected with the GM mask to obtain standard GM VOIs.
- 2) The WM mask is converted into a WM VOI.

- 3) The PET image is normalized to the MNI PET template using the **Brain Norm. II** method.
- 4) The standard GM and WM VOIs are transformed to the space of the PET image using the inverse normalization transform.
- 5) A contouring procedure is applied to get contour definitions of all VOIs, which the user can view together with the PET image and edit.
- 6) The GTM PVC method is applied to the original PET series using this set of template-based VOIs.

Starting the PVC

As a first step, load the PET images into the PVIEW tool. Then activate the button to the right of the image and select the **PVC (VOI based)** method from the list of external tools. A dialog window is shown which allows performing partial-volume correction in a step-by-step mode or as a background process.



Step-by-Step PVC Processing Mode

The step-wise mode is activated by checking the box next to the **Image Preview** label. Note the buttons which are used to start the individual processing steps. Initially, several of them are inactive because the prior steps are missing.

The result images of the different steps are collected in the **Image Preview** area. In the image selection list, available results appear with a green mark, while yet unavailable ones are marked in red. The example above shows the **Masked Template** calculated by step 2. The selected image series can be exported for later use by the **Save** button.

The advantage of step-wise processing is that steps can be repeated with different parameters until the outcome is satisfactory.

Point Spread Function FWHM:

The PSF is assumed to be a three-dimensional Gaussian function. The FWHM values in the three directions have to be specified according to the resolution of the reconstructed image. Default is 7 mm isotropic FWHM.

Average PET frames:

Dynamic images can be processed and will result in a corrected dynamic series. However, for the **Normalization** step, a static PET image showing anatomical information is required. Therefore, the user should define a suitable range for averaging time frames, and then activate . In the case of a static scan this step is not required and the button therefore not active. The **Averaged PET** is shown in the **Image Preview** window.

Masking:

The masking requires no parameters. It shows the **Masked Template** in the **Image Preview** window.

Normalization:

The normalization of the averaged PET image to the MNI PET template has one parameter, **Sampling rate**. After calculating the normalization, the normalization inverse is applied to transform the masked template to the PET space. The results **Normalized PET** and **Template matched to PET** are shown in the **Image Preview** window.

Outline VOIs:

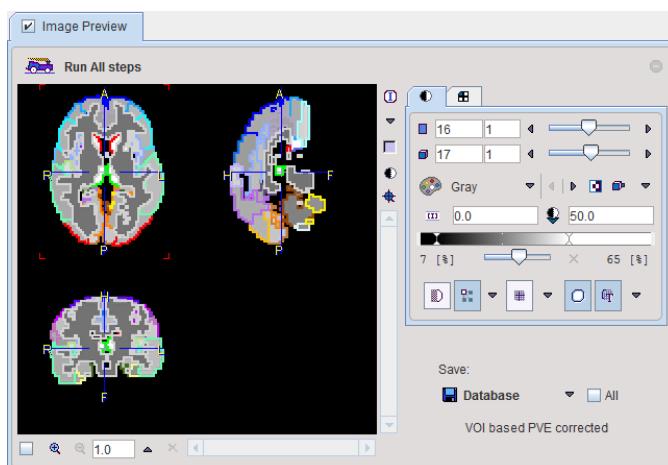
This step calculates contour VOIs from **Template matched to PET** and shows them together with the **Averaged PET** in the **Image Preview** window. This is the VOI set which will be used in the PVC.

Edit VOIs:

This button opens a VOI dialog window showing the VOIs on top of the **Averaged PET**. Note the extended **White Matter** VOI which has been derived from the WM mask. The VOIs can be inspected and edited, or saved for later use. To return modified VOIs, close the window with the **Ok** button, otherwise **Cancel**.

PVC Calculation:

This step performs the actual PVC calculation. Because of the large number of VOIs contained in the standard templates the processing takes a while. The result is returned in the form of an image series and shown in the **Image Preview** window. If the input series was dynamic, the result is also dynamic as in the example below.



View Statistics:

This button calculates the VOI statistics in the original and the PVC corrected images. Depending on the input images the results are simple statistics, or tissue time-activity curves.

Returning the Results:

Make sure that the **Additional results** of interest are checked. Then close the window with the **Ok** button to return the results.

Background PVC Processing Mode

If no interactive processing is desired, the user interaction is minimal.

- 1) If desired, edit the FWHM parameters, or reset them by the  button.
- 2) If the PET series is dynamic, define an appropriate frame range for averaging.
- 3) Make sure that the **Additional results** of interest are checked.
- 4) Start the PVC calculation with the **Ok** button.

The dialog window will be closed and processing will run in the background. Once the result were calculated and returned, a confirmation message will be shown.

PVC using Template VOIs based on Individual Masks

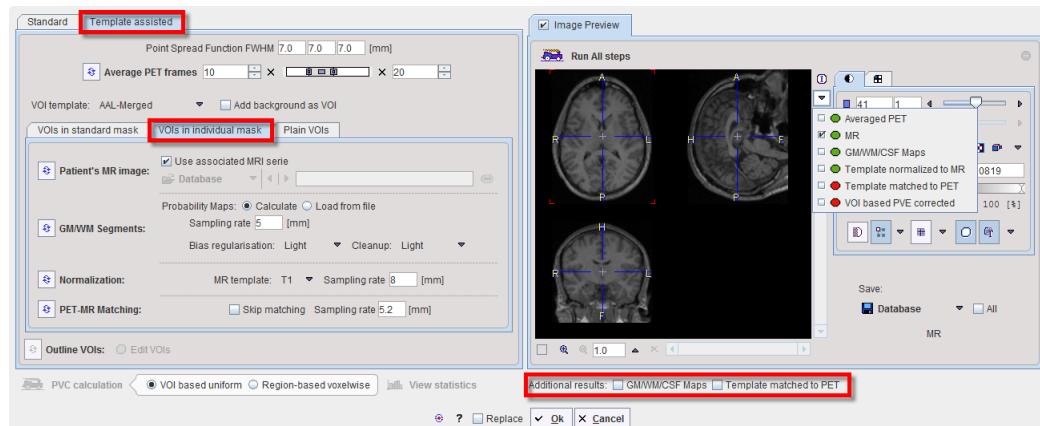
Overview

PMOD provides templates of human brain VOIs in the standard MNI space. The PVC method described below combines this information with the grey and white matter masks derived from an individual patient MR image as follows:

- 1) The anatomical MRI of the patient is segmented and the GM and WM masks calculated.
- 2) The MR image is normalized to the MNI MR template using the **Brain Normalization** method.
- 3) The VOI template is transformed to the MR space using the inverse of the normalization transform.
- 4) The transformed VOI template is intersected with the GM mask to obtain the GM VOIs in the MR space.
- 5) The WM mask is converted into a WM VOI.
- 6) The PET images are rigidly matched to the MR images.
- 7) The GM and WM VOIs are transformed to the PET space using the inverse rigid transform.
- 8) A contouring procedure is applied to get contour definitions of all VOIs, which the user can view and edit.
- 9) The GTM PVC method is applied to the original PET series using this set of template-based VOIs.

Starting the PVC

As a first step, load the PET images into the PVIEW tool. Then activate the button to the right of the image and select the **PVC (VOI based)** method from the list of external tools. A dialog window is shown which allows performing partial-volume correction in a step-by-step mode or as a background process.



Step-by-Step PVC Processing Mode

The step-wise mode is activated by checking the box next to the **Image Preview** label. Note the buttons which are used to start the individual processing steps. Initially, several of them are inactive because the prior steps are missing.

The result images of the different steps are collected in the **Image Preview** area. In the image selection list, available results appear with a green mark, while yet unavailable ones are marked in red. The example above shows the **MR** loaded by step **Patient's MR image**. The images selected in the **Image Preview** can be exported for later use by the **Save** button.

The advantage of step-wise processing is that steps can be repeated with different parameters until the outcome is satisfactory.

Point Spread Function FWHM:

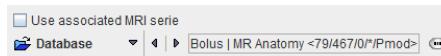
The PSF is assumed to be a three-dimensional Gaussian function. The FWHM values in the three directions have to be specified according to the resolution of the reconstructed image. Default is 7 mm isotropic FWHM.

Average PET frames:

Dynamic images can be processed and will result in a corrected dynamic series. However, for the **PET-MR Matching** step, a static PET image showing anatomical information is required. Therefore, the user should define a suitable range for averaging time frames and then activate . In the case of a static scan this step is not required and the button therefore not active. The **Averaged PET** is shown in the **Image Preview** window.

Patient's MR image:

The user must specify an anatomical MR image of the same patient which will be segmented. He can choose the format, select the image and then activate for loading the MRI.

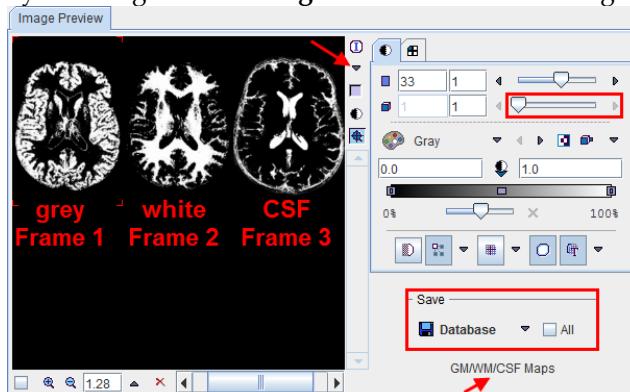


The **Use first series associated in Database by "Pair" function** box allows taking advantage of the feature that two series can be associated as a pair in PMOD databases.

GM/WM Segmentation:

This step needs to provide the different tissue segments. If **Probability Maps** is configured as **Calculate**, the button calls a segmentation procedure which may take several minutes to complete. The procedure has three parameters: **Sampling rate** determines the density of pixels considered in the calculation. **Bias Regularisation** serves for compensating modulations of the image intensity across the field-of-view. Depending on the degree of the artifact, a corresponding setting can be selected from the list. **Cleanup** is a procedure for rectifying the segmentation along the boundaries. It is recommended to use the default settings and only experiment with other parameter values if the segmentation fails.

The results are three segments, WM, GM and CSF. They are arranged as frames in a "dynamic" series. In the illustration below, the three frames are arranged in three columns. Because the calculation takes long, it may be helpful to save the segment images for later use by selecting them in **Image Preview** and then using the **Save** button.



If segment images are already available, **Probability Maps** can be configured as **Load from file**, and the corresponding segment file selected. Note that the segment images must be matched to the MR image and different segments should appear as dynamic frames in the indicated order. In this case the button just loads the segments.

Normalization:

The normalization of the MR image to the MNI template has two parameters, the **MR template** which should be set to T_1 or T_2 as appropriate, and the **Sampling rate**. After calculating the normalization its inverse is applied for transforming the VOI template to the MR space. It is then intersected with the individual GM mask, and the WM mask is used to create the WM VOI. The resulting VOI template is shown in the **Image Preview** window as **Template normalized to MR**.

PET-MR Matching:

Upon activating the  button, the PET image is rigidly matched to the selected MR image. The inverse transformation is applied for transforming the VOI template from the MR to the PET space. The result **Template matched to PET** is shown in the **Image Preview** window.

If the PET and MR images are already matched, the **Skip Matching** box can be checked to skip this processing step. However, please note that in this case the MRI and the PET images must have identical pixel size and image matrix. If the automatic matching in the PVC tool is not feasible, matching can be performed manually in the fusion tool and the results saved for use in the PVC tool.

Outline VOIs:

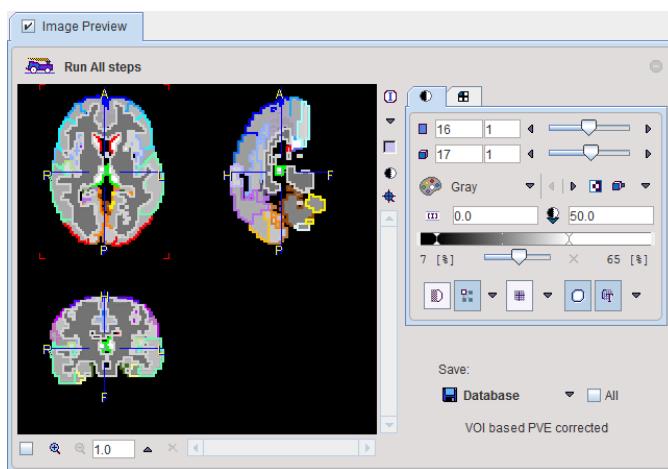
This step calculates contour VOIs from **Template matched to PET** and shows them together with the **Averaged PET** in the **Image Preview** window. This is the VOI set which will be used for PVC.

Edit VOIs:

This button opens a VOI dialog window showing the VOIs on top of the **Averaged PET**. Note the extended **White Matter** VOI which has been derived from the WM mask. The VOIs can be inspected and edited, or saved for later use. To return modified VOIs, close the window with the **Ok** button, otherwise **Cancel**.

PVC Calculation:

This step performs the actual PVC calculation. Because of the large number of VOIs in the standard templates the processing takes a while. The result is returned in the form of an image series and shown in the **Image Preview** window. If the input series was dynamic, the result is also dynamic as in the example shown below.



View Statistics:

This button calculates the VOI statistics in the original and the PVC corrected images. Depending on the input images the results are simple statistics, or tissue time-activity curves.

Returning the Results:

Make sure that the **Additional results** of interest are checked. Then close the window with the **Ok** button to return the results.

Background PVC Processing Mode

If no interactive processing is desired, the user interaction is minimal.

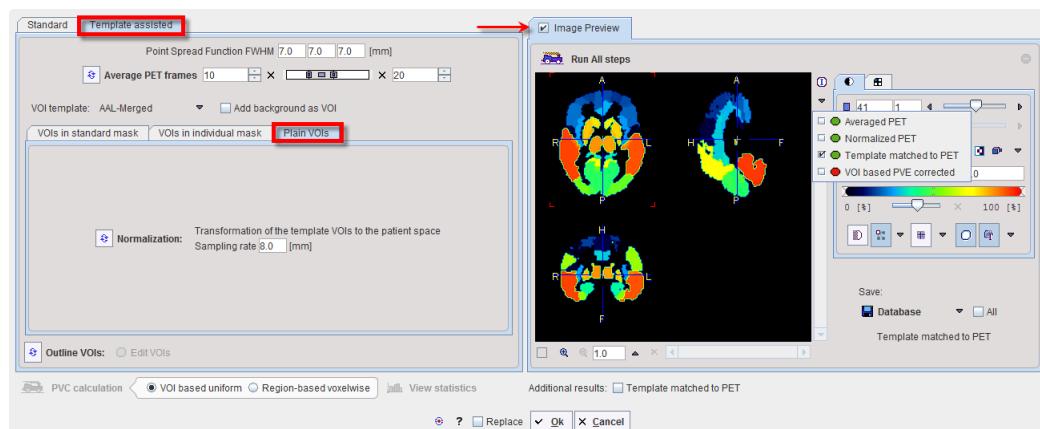
- 1) If desired, edit any of the parameters, or reset them by the  button.
- 2) If the PET series is dynamic, define an appropriate frame range for averaging.
- 3) Select the anatomical MRI of the same patient.
- 4) Make sure that the **Additional results** of interest are checked.
- 5) Start the PVC calculation with the **Ok** button.

The dialog window will be closed and processing will run in the background. Once the result were calculated and returned to PVIEW, a confirmation message will be shown.

PVC using Template VOIs based on Plain VOIs

Starting the PVC

As a first step, load the PET images into the PVIEW tool. Then activate the  button to the right of the image and select the **PVC (VOI based)** method from the list of external tools. A dialog window is shown which allows performing partial-volume correction in a step-by-step mode or as a background process.



Step-by-Step PVC Processing Mode

The step-wise mode is activated by checking the box next to the **Image Preview** label. Note the  buttons which are used to start the individual processing steps. Initially, several of them are inactive because the prior steps are missing.

The result images of the different steps are collected in the **Image Preview** area. In the image selection list, available results appear with a green mark, while yet unavailable ones are marked in red. The example above shows the **Template matched to PET**. The images selected in the **Image Preview** can be exported for later use by the **Save** button.

The advantage of step-wise processing is that steps can be repeated with different parameters until the outcome is satisfactory.

Point Spread Function FWHM:

The PSF is assumed to be a three-dimensional Gaussian function. The FWHM values in the three directions have to be specified according to the resolution of the reconstructed image. Default is 7 mm isotropic FWHM.

Average PET frames:

Dynamic images can be processed and will result in a corrected dynamic series. However, for the **Normalization** step, a static PET image showing anatomical information is required. Therefore, the user should define a suitable range for averaging time frames, and then activate . In the case of a static scan this step is not required and the button therefore not active. The **Averaged PET** is shown in the **Image Preview** window.

Normalization:

The normalization of the averaged PET image to the MNI PET template has one parameter, **Sampling rate**. After calculating the normalization, the normalization inverse is applied to transform the masked template to the PET space. The results **Normalized PET** and **Template matched to PET** are shown in the **Image Preview** window.

Outline VOIs:

This step calculates contour VOIs from **Template matched to PET** and shows them together with the **Averaged PET** in the **Image Preview** window. This is the VOI set which will be used in the PVC.

Edit VOIs:

This button opens a VOI dialog window showing the VOIs on top of the **Averaged PET**. The VOIs can be inspected and edited, or saved for later use. To return modified VOIs, close the window with the **Ok** button, otherwise **Cancel**.

PVC Calculation:

This step performs the actual PVC calculation. Because of the large number of VOIs contained in the standard templates the processing takes a while. The result is returned in the form of an image series and shown in the **Image Preview** window. If the input series was dynamic, the result is also dynamic as in the example below.

View Statistics:

This button calculates the VOI statistics in the original and the PVC corrected images. Depending on the input images the results are simple statistics, or tissue time-activity curves.

Returning the Results:

Make sure that the **Additional results** of interest are checked. Then close the window with the **Ok** button to return the results.

Background PVC Processing Mode

If no interactive processing is desired, the user interaction is minimal.

- 1) If desired, edit the FWHM parameters, or reset them by the  button.
- 2) If the PET series is dynamic, define an appropriate frame range for averaging.
- 3) Make sure that the **Additional results** of interest are checked.
- 4) Start the PVC calculation with the **Ok** button.

The dialog window will be closed and processing will run in the background. Once the result were calculated and returned, a confirmation message will be shown.

Note: This PVC procedure does not use a grey matter mask intersection with the VOI template. Otherwise it corresponds to the Template VOIs based method on Standard Masks.

Recommendations

Findings by Rousset et al. [2]

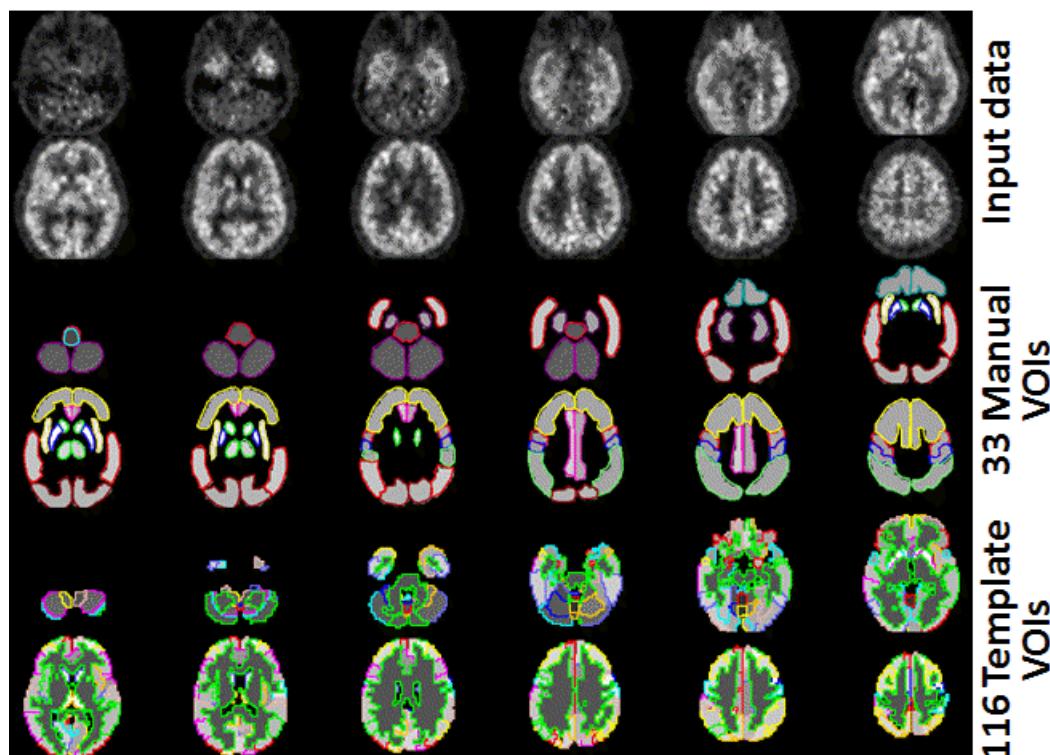
According to Rousset et al. [2], the accuracy of the GTM method depends primarily on the proper identification of the tissues which have different functional properties. If this is the case, the GTM algorithm is capable of accurately correcting the regional concentration within small structures such as the human basal ganglia. Furthermore, the propagation of statistical noise during partial-volume correction was found to be easily predictable and suitable for the application in dynamic PET.

Findings with the PMOD Implementation

The application of the GTM method to simulated PET images with realistic, spatially variant PSF resulted in the following observations (unpublished work Olivier Barret, PhD, Institute for Neurodegenerative Disorders, New Haven, CT, USA):

- » GM VOIs are always corrected into the right direction, up- and downwards.
- » A FWHM of 7mm is a reasonable default setting for the Gaussian PSF.
- » If a patient MRI is available, the individual segments result in a better partial-volume correction than the standard GM, WM and CSF segments.

Shown below is an example of a patient data set corrected with 33 manually outlined VOIs, and with 116 VOIs derived from the AAL template combined with individual segments. Note the homogeneous values within the VOIs which are equal the partial-volume corrected average value of each VOI.



PVC of Brain Images based on MRI Segmentation

Methodology Description

The PVC (Brain MR based) method implemented in PMOD consists of the following steps:

1. Segmentation of the Anatomical MRI

To perform the segmentation, a normalization transform of the patient MRI anatomy to the MNI anatomy (or *space*) is calculated. In the MNI space, there are probability maps available for grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF).



These priors are inversely transformed to the MRI space and employed in the image segmentation. The results are three probability images in the MRI space, called the GM, WM and CSF segments. They form the basis for the PVC.

2. Matching of the PET and MR Images

In order to perform the PVC, the information of the MRI and the PET must be aligned. Because the GM segments are relatively fine, they cannot be resampled to a typical PET resolution without severe information loss. Therefore, the PET image is rigidly matched to the MRI, and the PVC performed in the MRI space on the up-sampled PET images.

3. Partial-volume Effect Correction

First, the uptake in WM is obtained either by analyzing the PET uptake in pixels with very high WM probability, or by using a value provided by the user. Then, the following correction formula of Muller-Gartner is applied:

$$C_{PVC-GM} = \frac{C_{measured} - C_{WM} \times (WM \otimes PSF)}{GM \otimes PSF}$$

Corrects WM spill-in
Corrects GM spill-out

with the following notations:

C_{PVC-GM} Corrected activity concentration. This is the result of the PVC correction in each GM pixel.

$C_{measured}$ Actually measured activity concentration in a GM pixel which may be distorted due to spill-out and spill-in.

C_{WM} Activity concentration in WM which is assumed to be homogeneous and just blurred by the PSF.

WM, GM	WM (GM) segment image which represents the WM (GM) probability of each pixel in the image as a value between 0 and 1. These images are assumed to represent the true anatomy with ideal resolution.
PSF	Point-spread function of the imaging system which is assumed to be constant across the image and represented by a three-dimensional Gaussian function.
WM \otimes PSF	Mathematical convolution of the WM segment image with the PSF. The result represents the image of the ideal WM segment when detected with a real imaging system characterized by the PSF function.



The expected WM image is obtained by scaling WM \otimes PSF by the WM concentration C_{wm} . It is subtracted from the measured image to compensate for spill-in from WM to GM.

GM \otimes PSF	Mathematical convolution of the GM segment image with the PSF.
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A division of the WM-corrected image by GM \otimes PSF represents a deconvolution operation and corrects for the spill-out effect from GM. The operation of division may introduce over-corrections at the GM boundary. Therefore, the result image is masked at a certain threshold of the convolved GM image

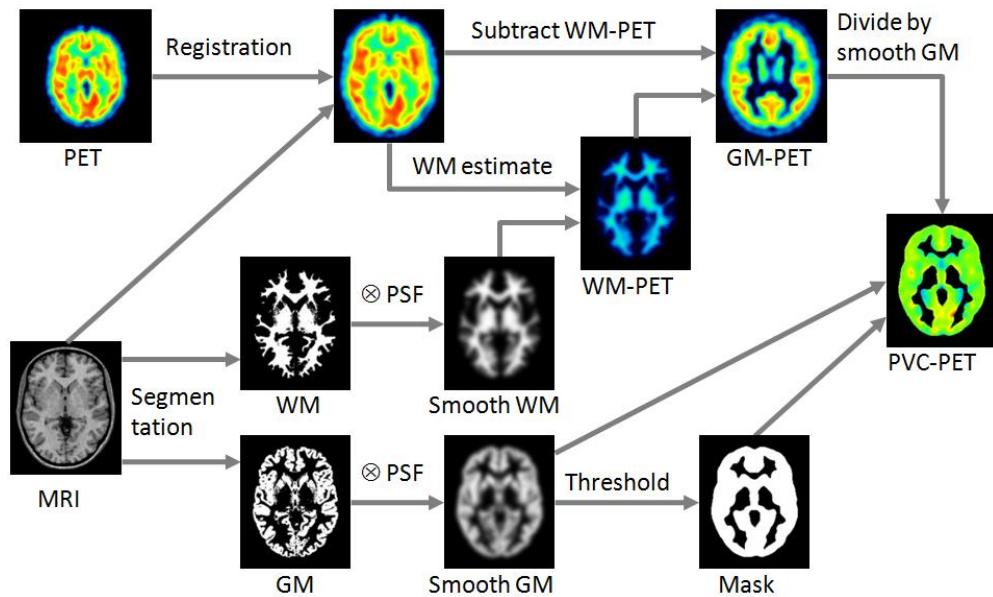
Spill-out Correction Only

If, however, the segmentation of white and grey matter fails, the correction can be reduced to a spill-out only correction. In this case a *Brain* segment is formed from all pixels which are not CSF. This segment is convolved with the PSF, and the PET image divided by the result as described by the equation below.

$$C_{PVC-Brain} = \frac{C_{measured}}{\text{Brain} \otimes \text{PSF}}$$

Schematic of the Correction Workflow

The following illustration provides a graphical overview of the different processing steps as well as the resulting intermediate images.



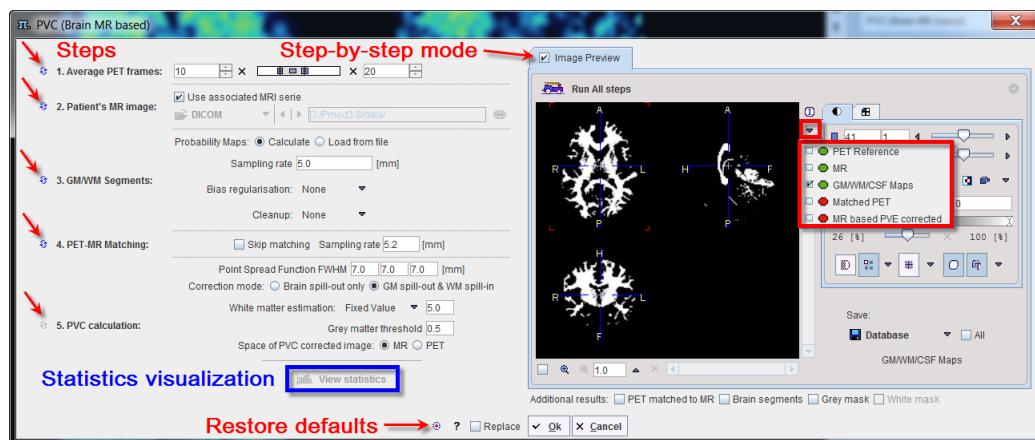
Requirements

The MRI-based PVC is only applicable to PET or SPECT images of the human brain. It can be applied to static or dynamic series. A well resolved anatomical T₁- or T₂-weighted brain MR image of the same patient is required, but there is no need for matching the two image series beforehand.

Performing MRI-based PVC

Starting the PVC

As a first step, load the brain PET images into the PVIEW tool. Loading of the MR series is not required at this stage. Then activate the button to the right of the image and select the **PVC (Brain MR based)** method on the list of external tools. A dialog window is shown which allows performing the processing in a step-by-step mode or as a background process.



Note the following:

- 1) Minimally, the user has to provide an anatomical MRI image.

- 2) It is recommended to inspect and analyze the outcome of the PVC procedure, for instance the outcome of the segmentation and the PET-MR matching. To this end, **Additional results** can be returned. The user should make sure that with in the background mode the corresponding boxes **PET matched to MR**, **Brain Segments** and **Grey mask** are enabled before closing the window with the **Ok** button.
- 3) If the **Replace** box is checked the original images are replaced by the partial-volume corrected images.

Step-by-Step PVC Processing Mode

The step-wise mode is activated by checking the box next to the **Enable preview** label. Note the  buttons along the left border which are used to activate the individual processing steps. Initially, most of them are inactive because the prior steps are missing. In the example above, steps 1 - 3 have been performed. Therefore, step 4 can also be started, but step 5 not yet as it requires that the images have already been matched.

Note that the result images of the different steps are collected in the **Image Preview** area. In the image selection list, available results appear with a green mark, while yet unavailable ones are marked in red. The example above shows the WM map calculated by step 3. The images selected in the **Image Preview** can be exported for later use by the **Save** button.

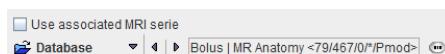
The advantage of step-wise processing is that the steps can be repeated with different parameters until the outcome is satisfactory.

1. Average PET frames:

Dynamic PET images can be processed and will result in a corrected dynamic series. However, for the matching in step 4, a static PET image showing anatomical information is required. Therefore, the user should define a suitable range for averaging time frames and then activate . In the case of a static scan, as in the example above, this step is not required and therefore not active.

2. Patient's MR image:

The user must specify an anatomical MR image which will be segmented. He can choose the format, select the image and then activate  for loading the MRI.



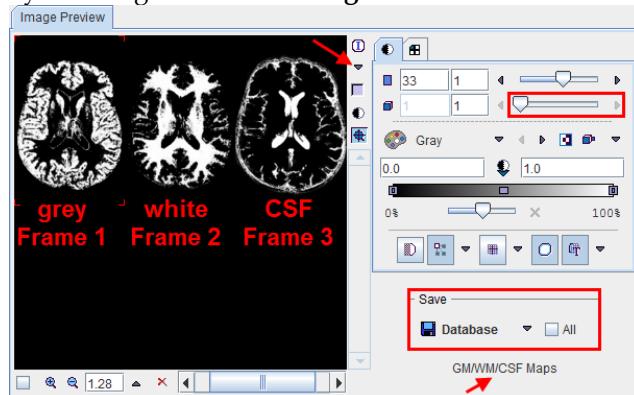
The **Use first series associated in Database by "Pair" function** box allows taking advantage of the feature that two series can be associated as a pair in PMOD databases.

3. GM/WM Segmentation:

This step needs to provide the different tissue segments. If **Probability Maps** is configured as **Calculate**, the  button calls a segmentation procedure which may take several minutes to complete. The procedure has three parameters: **Sampling rate** determines the density of pixels considered in the calculation. **Bias Regularisation** serves for compensating modulations of the image intensity across the field-of-view. Depending on the degree of the artifact, a corresponding setting can be selected from the list. **Cleanup** is a procedure for

rectifying the segmentation along the boundaries. It is recommended to use the default settings and only experiment with other parameter values if the segmentation fails.

The results are three segments, WM, GM and CSF. They are arranged as frames in a "dynamic" series. In the illustration below, the three frames are arranged in three columns. Because the calculation takes long it may be helpful to save the segment images for later use by selecting them in the **Image Preview** and then using the **Save** button.



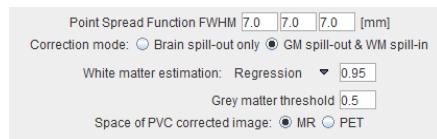
If segment images are already available, **Probability Maps** can be configured as **Load from file**, and the corresponding segment file selected. Note that the segment images must be matched to the MR image and different segments should appear as dynamic frames in the indicated order. In this case the button just loads the segments.

4. PET-MR Matching:

Upon activating the button, the PET image is rigidly matched to the selected MR image. If the matching fails, the **Sampling rate** can be reduced and matching tried again. In case the images are known to be already matched, the **Skip Matching** box can be checked in order to skip the matching step. However, please note that in this case the MRI and the PET images must have identical pixel size and image matrix. If automatic matching in the PVC tool is not feasible, matching can be performed manually in the fusion tool and the results saved for use in the PVC tool.

5. PVC Calculation:

The last step is the actual partial-volume correction procedure which has several parameters.



The **Point Spread Function FWHM** represents the assumed point-spread function. Default is 7 mm isotropic FWHM.

The **Correction mode** is normally set do **GM spill-out and WM spill-in**. If, however, the segmentation of white and grey matter does not give an accurate result, the correction can be reduced to **Brain spill-out only**.

The **White matter estimation** provides three choices: Default is the **Regression** approach. It collects the PET uptake of all pixels with a WM probability higher than the specified value

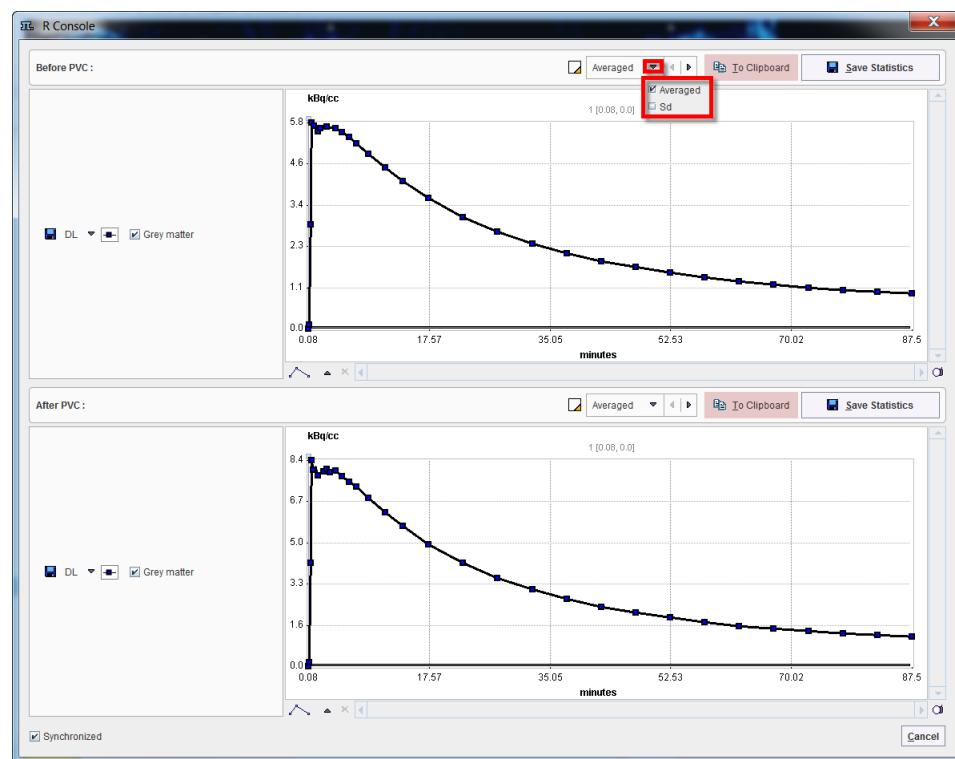
(e.g. 0.95), and performs a linear regression to estimate the WM value at the probability of 1. [5] With **Average**, the average is calculated instead of using the regression. Finally, the user can specify a known WM uptake value with the **Fixed value** setting.

The PVC is only appropriate for GM pixels. All other pixels in the corrected image may therefore not be evaluated and are masked. To this end, a **Grey matter threshold** can be specified. It is applied to the convolved GM segment for getting a smooth appearance. Note that if the threshold is small, outlier values might appear along the mask boundaries as over-correction artifacts.

The PVC correction is always performed in the space of the MR image using the matched, interpolated PET image. If **Space of PVC corrected image** is set to **MR**, this corrected PET series is returned as-is. With the **PET** setting, however, the corrected series is transformed to the PET space using the inverse of the PET to MR transform.

6. View Statistics:

This button calculates the VOI statistics in the original and the PVC corrected images. Depending on the input images the results are simple statistics, or tissue time-activity curves for the gray matter.



The statistic results can be saved as a Dicom structured report with the **Save Dicom SR** option or exported as a structured report with the **Export Dicom SR**. In alternative, the content of the statistic page can be **Copy to Clipboard** and paste in Excel.

The **Go to R** button allows sending directly the statistic results to the PMOD R interface for further analysis.

Returning the Results:

Before closing the window make sure that the appropriate **Additional results** boxes are checked, then select the **Ok** button.

Background PVC Processing Mode

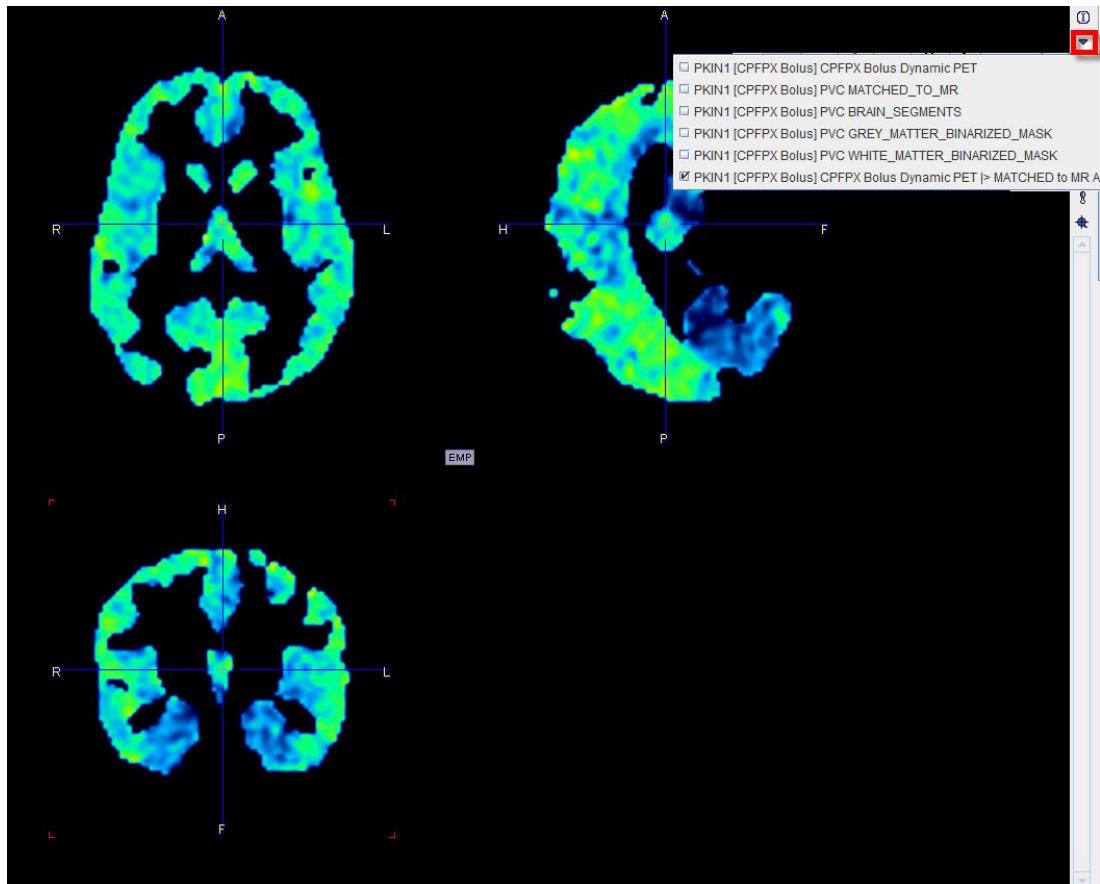
If no interactive processing is required, the PVC procedure is very easy. Only the following actions are required:

- 1) If the PET data is dynamic, the averaging range has to be defined.
- 2) The anatomical MRI has to be selected.
- 3) If desired, some of the parameters can be edited in the different processing steps, or they can be reset by the  button.
- 4) The appropriate **Additional results** boxes should be checked.
- 5) The PVC can be started with the **Ok** button.

The window will be closed and processing will run in the background for several minutes. Once the results were calculated and returned to PVIEW, a confirmation message will be shown.

Result Images

The results are returned as additional image series, as illustrated below. The original data is the first on the list, then come three auxiliary image series, and the last series marked by **PVE CORRECTED** is final outcome of PVC. Note the masking which may cause the disappearance of GM pixels if the cortex is thin and the PET resolution low.



Validation and Recommendations

Validation

The performance of the **PVC (Brain MR based)** method has been studied by Olivier Barret, PhD, Institute for Neurodegenerative Disorders, New Haven, CT, USA, and the results presented at the Symposium on Functional Neuroreceptor Mapping of the Living Brain 2010 in Glasgow. The abstract is reproduced below.

Performance Evaluation of PMOD integrated Partial Volume Correction Method for Brain PET data

Partial volume effects in emission tomography (PET) come from the limited resolution of the cameras and are due to two factors: the underlying heterogeneity of the tissues (grey and white matter in brain tissue) and the cross contamination of adjacent regions by the point spread function (PSF) of the tomographs. The result of these effects is an erroneous estimation of the true local tissue radioactivity concentration and in studies where quantitative estimates are required, it is often essential to perform partial volume corrections (PVC), in particular to take into account pathological or structural changes for instance as

these can have a significant impact. Several correction methods, often requiring an additional structural imaging, have been proposed to attempt recovery of the true signal, and among these, one of the correction the most commonly used is an MR-based solution.

We report here of a fully integrated implementation of such an MR-based correction in the PMOD software, where the MR is automatically segmented into grey matter and white matter maps and subsequently registered with the PET image. Activity concentration in white matter is automatically determined by linear regression and the functional image is corrected by the maps smoothed by the PSF of the system, approximated by a 3-dimensional Gaussian distribution with a full-width half-maximum (FWHM) adjustable by the user. At the end of the process, the user is presented with a grey matter partial volume corrected functional image. The correction has been validated using simulated subjects from a Monte Carlo database built using the PET-SORTEO simulator which implements a realistic model of the ECAT EXACT HR+ tomograph. Ten subjects simulated with a FDG functional model were used to estimate the recovery coefficient as a function of the set FWHM and to evaluate the robustness of the correction with regard to the white matter activity concentration estimate.

Results for the simulated subjects show a very good recovery of the cortical regions with corrected values within 3% of the simulated activity concentration for an optimal FWHM around 6-7mm, in agreement with an effective resolution of the space-variant published resolution of the simulated scanner. The recovery coefficient also showed good stability against the user defined FWHM, with variation of 4-5% for a FWHM set between 5mm and 9mm. The method was shown to be robust against the white matter activity concentration estimates, with variation of only 2-3% of the final grey matter corrected values for large errors of 10% in the WM estimates.

An MR-based PVC method fully automated and integrated with all the steps necessary to perform the correction has been implemented in the PMOD software and validated against a simulated data set. The pertinence of the correction is being evaluated for different tracers (FDOPA from the PET-SORTEO database) and also for patient data from the ADNI database, in particular for the beta amyloid PIB tracer where this correction might prove to be critical because of the high white matter uptake.

Recommendations

The **PVC (Brain MR based)** method is a fully automatic procedure which has been tested in detail. However, the user should be aware that in practical situations there are several sources of potential errors which may affect the PVC outcome, particularly

- » distortions of the grey and white matter segments, and
- » inaccurate matching of the PET to the MRI.

Therefore the user is advised to inspect the additional PVC results. He should fuse the segment images with the anatomical MRI, and the matched PET image with the MRI to ensure that the anatomical information, which is used for the PVC, is correct and aligned.

Furthermore, VOI statistics should be calculated both with the original as well as with the PVC corrected images in order to detect consistencies in the data.

PVC References

- 1) Soret M, Bacharach SL, Buvat I. Partial-volume effect in PET tumor imaging. *J Nucl Med.* 2007;48(6):932-45
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Chapter 9

Pipeline Processing

Basic Concept

The PMOD batch pipeline supports fully automatic image processing. A pipeline is configured as a series of processing steps, each receiving the results of the prior step, performing an additional analysis, and forwarding the results to the next step, with the last step producing the end results. A pipeline definition can be applied to a whole set of input images for obtaining objective results in a group analysis. To inspect intermediate results, a quality control (QC) breakpoint can be enabled. Furthermore, these auxiliary results may be saved for closer interactive inspection.

Use of Pipelines with DICOM Server

DICOM servers are able to *execute a specific processing pipeline* (on page 39) when they receive images. This feature allows setting up special purpose DICOM server which perform well-defined and potentially time-consuming processing steps in the background.

Assumptions and Recommendations

PMOD includes a powerful *database* (on page 50) for the storage and organization of all kinds of relevant data. It is highly recommended that the data for pipeline processing is organized in such a database, because some processing tools will take advantage from specific relationships among data elements which can only be provided by a database. Furthermore, the output produced by the pipeline can directly be inserted at the appropriate database level, which is more difficult when working with directory structures.

A study may comprise data of several groups (e.g. controls, patients) and conditions (baseline, follow-up). In this case a separate pipeline for each group/condition pair should be prepared as explained *below* (on page 448). All pipelines can then be submitted for processing at once, and the results will be conveniently aggregated for population statistics.

Pipeline Elements

A processing pipeline can easily be set up via the interactive user interface explained below. It allows choosing and configuring an arbitrary number of processing steps from a list including

- » the *external tools* (on page 140) which are available in every PMOD license;
- » automatic brain VOIs, image registration, normalization and motion correction which are tied to the fusion option (PFUS);
- » kinetic modeling of regional TACs which belongs to the modeling option (PKIN), and some
- » pipeline controlling elements.

The pipeline definitions can be saved for later retrieval and processing.

Use Cases of Pipeline Processing

This documentation includes pipeline processing examples representing practical scenarios. Please make sure to read the *first* (on page 435) example as it provides a detailed step-by-step explanation, which is not repeated in the other examples. Furthermore, the demo database of the PMOD distribution includes working examples which can be retrieved with **Load Processing** and directly executed.

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Starting Pipeline Definition

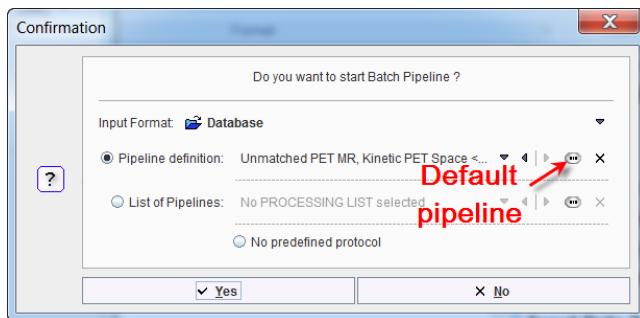
Starting

Batch pipeline processing can be started from different places:

- » the **Batch Pipeline** item in the menu of the viewing tool;
- » the  button in the lateral taskbar of the viewing tool;
- » the  button in the main PMOD Toolbox.

Input Data Format

Pipeline processing is restricted to images of a single file format. Therefore, a dialog window appears first for defining the **Input Format**. Additionally, a default pipeline can be configured with **Pipeline definition**, so that the processing sequence is already defined when the pipeline interface opens.

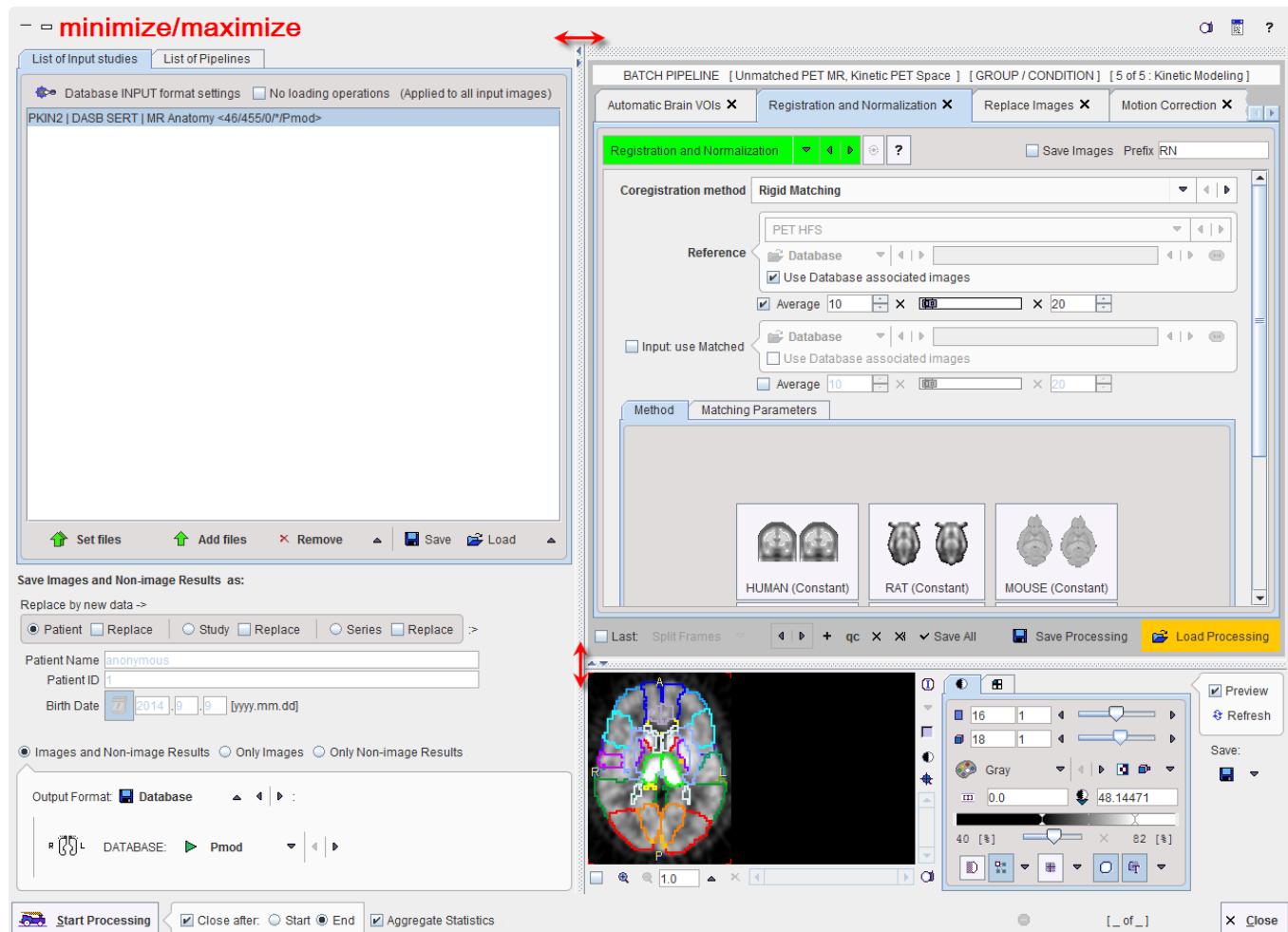


Please select the appropriate format from the list and continue with **Yes**.

In the following description the **Database** format will be used, which is strongly recommended.

Pipeline Definition User Interface

The interface of the batch pipeline tool is illustrated below.



The window has four areas, which are described below. Note the divider buttons and which can be used for enlarging/reducing the relative areas. The modal window can't be closed, but it can be reduced in size by the button in the upper left. The upper right provides buttons for taking a screen capture, showing the console window, and opening the help information.

Data to be Processed

Input data specification is in the upper left. While the data format has already been specified, *operations during the image loading* (on page 97) can be configured with the **INPUT format settings** button. For instance, smoothing filters can be applied, or data interpolated to a certain (e.g. isotropic) pixel size. Another candidate operation is **Reorient to Standard Orientation**, which brings the images at loading time into the radiological standard HFS orientation. Note that all images will undergo these operations, also secondary images specified in the pipeline tools. The box **No loading operations** can be used for ruling out any data transformations.

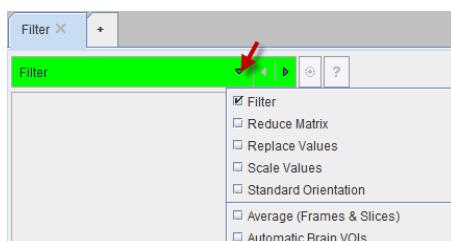
The images to be processed are defined by the **Set input files** or **Add files** buttons, which open a dialog window for selecting image files.



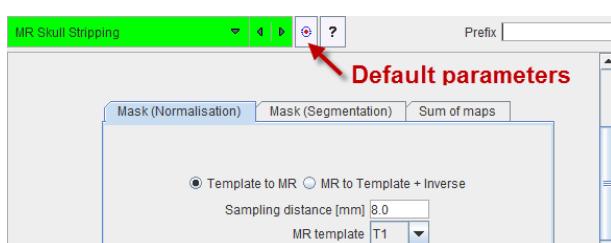
The data selections build up the data list for processing. While **Remove** deletes a selected entry from the list, **Remove all** clears the whole list. An input data list can be saved for later use with the button right to **Remove**.

Processing Definition

The processing pipeline is configured in the upper right area. Each processing stage is added as a tab, with processing working from the left towards the right. Tabs can be appended using the **+** tab, and removed by the **x** in its tab. The tool to be applied is selected from the list selection on the tab indicated below. Note that some entries in the list are labeled by **(pipeline only)** to indicate they are not available in other contexts.

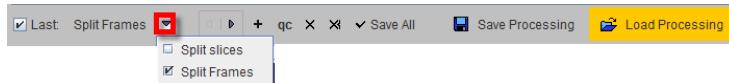


A selected tool shows its parameters on the lower part of the tab for configuration.



Right to the tool selection there is a button for setting the parameters to the tool default values, and a ? for showing help information about the tool. The **Prefix** string can be used to tag the images and non-image results produced by the tool.

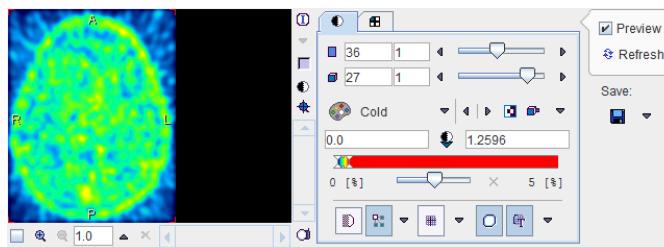
Below the parameter are there are some convenience buttons.



The **Last operation** box is relevant, if the resulting images should be split into individual frames, or even slices. The left/right arrows are a shortcut to select the previous/next tab for fast browsing. The + button adds a new tab *before* the selected tab, and x removes the selected tab. **Save Processing** and **Load Processing** allow saving/retrieving a pipeline definition, optionally with the list of images to process. qc adds a *quality control* (on page 429) breakpoint *after* the selected tab.

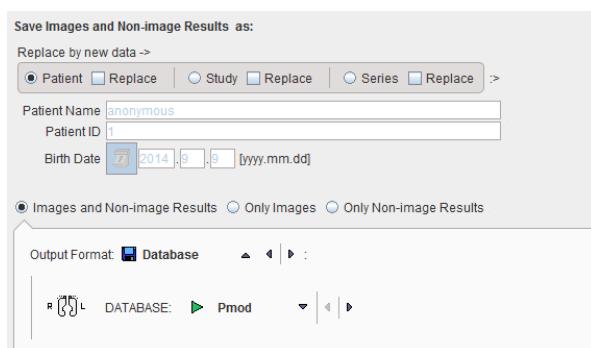
Processing Preview

In order to verify the pipeline setup, the **Preview** box in the lower right can be enabled. As a consequence, the current pipeline definition is applied to the data set selected in the **List of Input Studies** and the result image shown. According to the results, some tool parameters may be edited and the result updated using the **Refresh** button. The result images can optionally be stored with the **Save** button.



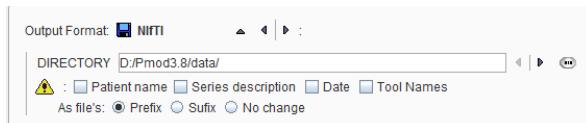
Output Configuration

A pipeline produces images, but can also result in some derived information such as VOIs, regional statistics or kinetic modeling files. The radio button in the **Save Images and Non-image Results** area serves for defining the information of interest: **Images and Non-image Results**, **Only Images**, and **Only Non-image results**.



The format of the saved images is defined by the **Output Format** selection. Depending on the format, some parameters need to be configured, such as the output **DATABASE** in the example above.

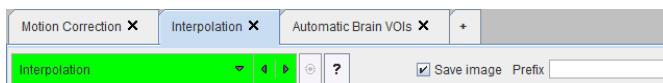
With file-based formats such as NIfTI



the file system path where all files will be stored needs to be defined with **SET DIRECTORY**. The check boxes **Patient name**, **Series description** and **Date** instruct the program to include these elements into the generated filenames to avoid overwriting due to non-unique file naming.

Output of Intermediate Tools

It is assumed, that the main output is produced by the last (right-most) tool in the pipeline. Therefore, its result images are always saved. The intermediate tools have a **Save images** box which may be enabled for saving their images too, either during pipeline setup for testing, or during production processing for later validation procedures. The **Prefix** string serves for meaningfully tagging the saved data. Saving of the non-image results is also tied to the **Save images** box, but only occurs with the general saving options **Images and Non-image Results** and **Only Non-image results**.



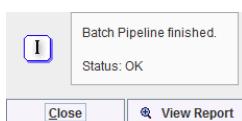
Processing the Data

It is recommended saving the pipeline definition first, and then activate **Start Processing**.



The **Aggregate Statistics** option is only relevant for non-image results such as regional uptakes or regional kinetic parameters. If the option is enabled, the results of all data sets are concentrated into a single aggregation table, which can immediately be used for statistical analysis. In case both regional uptakes and kinetic parameters are produced, aggregation of the kinetic parameters takes priority.

Preferably, **Close after Start** is enabled. In this way the dialog window is closed and the processing runs in the background. At the end of processing a dialog window is shown which indicates that processing was ok, or otherwise provides a problem report.



View Report provides information about the input and output of the pipeline, as well as the processing steps, as illustrated below.



The screenshot shows a software window titled "View Report" with the following content:

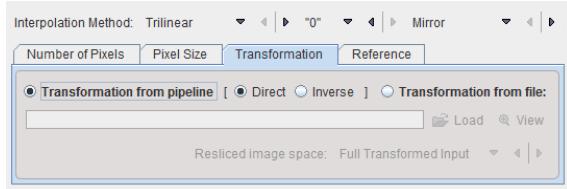
```
> Batch Pipeline [ Unmatched PET MR, Kinetic PET Space ]:  
1. Automatic Brain VOIs  
2. Registration and Normalization  
3. Replace Images (pipeline only)  
4. Motion Correction  
5. Kinetic Modeling (pipeline only)  
INPUT: PKIN2 | DASB SERT | MR Anatomy <46/455/1490/*|Pmod>  
OUTPUT:  
Image data [PKIN2 | KM_KINETIC_MODELING_DASB SERT | Dynamic DASB PET] > MATCHED to Dynamic DASB PET [Aver Volumes] <46/577/0/*|Pmod>  
VOIs [ABV_AUTOMATIC BRAIN VOIs <46/577/1977/*|Pmod>]  
VOIs [KM_KINETIC_MODELING <46/577/1978/*|Pmod>]  
KM [KM_KINETIC_MODELING <46/577/1979/*|Pmod>]  
Kinetic Parameters [KM_KINETIC_MODELING <46/577/1980/*|Pmod>]  
Normalization transformation direct [RN_REGISTRATION_AND_NORMALIZATION_DIRECT <46/577/1981/*|Pmod>]  
Normalization transformation inverse [RN_REGISTRATION_AND_NORMALIZATION_INVERSE <46/577/1982/*|Pmod>]  
Output Path [C:/Pmod/v3.6/data/DATABASES/Pmod/data/]  
Group Name [GROUP]  
Condition Name [CONDITION]  
Status: OK
```

At the bottom of the window are four buttons: Close, Save, Load, and Copy to Clipboard.

Use of External Tools for Pipeline Processing

Most of the tools applicable in pipeline processing can also be used interactively on loaded images. Hence, they are described in the *External Tools* (on page 140) section.

For some of the external tools additional pipeline-related options appear such as **Transformation from pipeline** for the **Interpolation** tool:



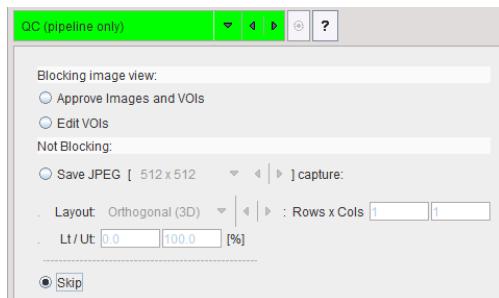
This allows applying a registration or normalization transform calculated at an earlier pipeline stage to the current image.

Pipeline-only Tools

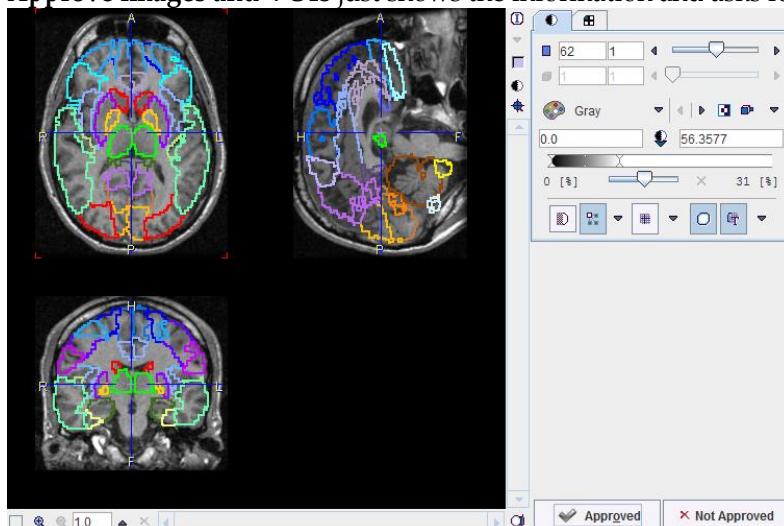
In addition to the regular external tools there are some specific pipeline tools available. They are either needed for controlling pipeline operation (*Quality Control* (on page 429), *Replace Images* (on page 430)), or interface to functions which don't directly operate on images (*Kinetic Modeling* (on page 432)).

Quality Control (QC)

In order to stop pipeline processing and inspect the results a **QC** breakpoint can be inserted with the **qc** button. The **QC** tool has four options.



- » **Approve images and VOIs** just shows the information and asks for acceptance.



With **Approved** processing will continue the current pipeline, while **Not Approved** causes processing to terminate and start over with the next data set.

- » **Edit VOIs** shows the current VOIs and images of the pipeline in a VOI dialog window for interactive VOI adjustments. When closing with **OK**, the current VOIs are overwritten by the potentially modified ones, whereas **Cancel** just closes the window. In both cases the pipeline is continued.
- » **Save JPEG** creates a JPEG image with the prescribed layout and saves it for later inspection.
- » **Skip** allows switching off the QC step for the remaining data sets.

Replace Images

The main purpose of **Replace Images** is to switch processing to a new data set, while the results generated so far (transformation, VOIs) are still available.



The main replacement mechanism is via *image association* (on page 73).

As an *example* (on page 435), consider that a PET and an MR are associated, and processing is started with loading the MR for generating VOIs. **Replace Images** swaps the role: The PET images are loaded, and from then on the (original) MR images are considered as the associated images.

If the images are not matched, a transformation calculated previously in the pipeline (or its inverse) can be applied to the images swapped in.

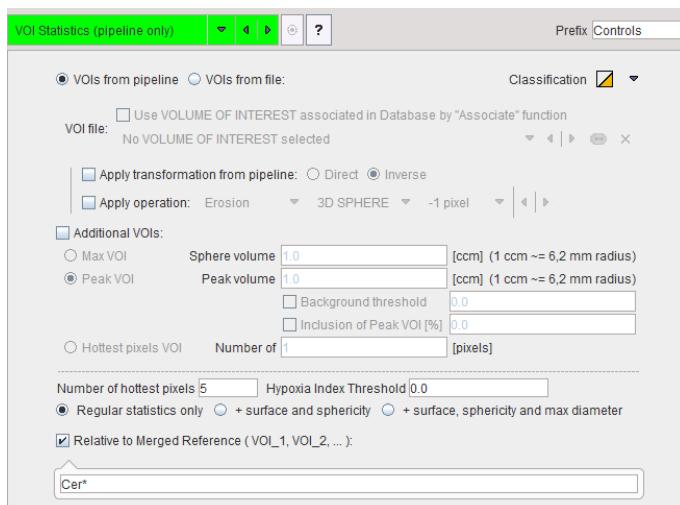
Macro

Macros (on page 120) are a prescription of several data processing steps like data editing or filtering. They may be useful for shortening a pipeline, but don't support the inspection of the intermediate results. To apply a macro it has to be selected using the indicated button.



VOI Statistics

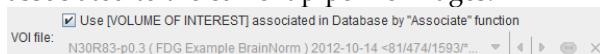
The **VOI Statistics** tool allows applying a set of VOIs to the current images in the pipeline.



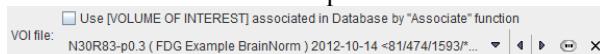
Definition of VOI Set

The VOIs can be provided in three ways:

- » **VOIs from pipeline:** The last VOIs produced in the pipeline are applied.
- » **VOIs from file:** One option is to use VOIs which have been produced previously and associated to the current pipeline images.



- » **VOIs from file:** Another option is to use a fixed VOI set.



This is particularly useful for data which have been transformed to a template space, such as the MNI space.

The selected VOIs can optionally be transformed before application to the images:

- » **Apply transformation from pipeline:** The idea here is that the VOIs have been derived using an image different from the current images, and that the pipeline has recorded the appropriate transformation for bringing the VOIs into the space of the current image. Such an application is described in the *example* (on page 435) below. The **Direct** or the **Inverse** transformation can be applied, as appropriate.
- » **Apply operation:** The operations offered for VOI modification are the **Erosion** or **Dilation** by a number of pixels. Erosion allows shrinking VOIs from the outside. This may be useful for reducing the partial-volume effect. Dilation grows the VOIs by adding additional layers.

The **Additional VOIs** option triggers calculation of additional VOIs which are derived from the VOI set:

- » **Max VOI:** For each VOI the maximal pixel will be located and sphere VOI with the defined **Sphere volume** created.
- » **Peak VOI:** For each VOI a sphere VOI with the defined **Peak volume** will be created in such a way that the included uptake is maximal.
- » **Hottest pixels VOI:** For each VOI a VOI will be created consisting of the **Number of** individual pixels with highest uptake.

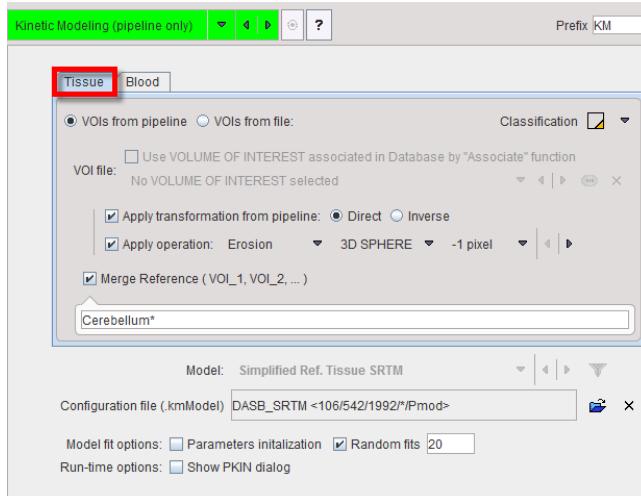
Definition of Statistics Type

The statistics calculation will result in the same *measures* (on page 280) as with interactive VOI evaluation. The **Classification** switch defines the inclusion criterion of boundary pixels, and the **+ surface and sphericity** and **+ surface, sphericity and diameter** options allow obtaining extended statistics.

The **Relative to Merged Reference** option allows calculation of the uptake relative to a reference tissue, often called SUVR. The VOI names to serve as the reference can be specified by a comma-separated list of exact VOI names like **Cerebellum_l**, **Cerebellum_r**, or using the "*" wildcard character such as in **Cerebellum*** to enclose all VOI names starting with "Cerebellum". With this example specification, the average uptake in any region will be divided by the average uptake in all cerebellum VOIs.

Kinetic Modeling (PKIN Option)

The **Kinetic Modeling** tool in the pipeline has the following interface. Please refer to *PMOD Kinetic Modeling Users Guide* for details regarding the modeling configuration.



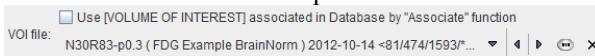
Volumes of Interest for Tissue TACs

The kinetic tool generates the average tissue TACs from VOIs which are applied to the current pipeline data. They are specified on the **Tissue** tab and can be provided in three ways:

- » **VOIs from pipeline:** The last VOIs produced in the pipeline are applied.
- » **VOIs from file:** One option is to use VOIs which have been produced previously and associated to the current pipeline images.



- » **VOIs from file:** Another option is to use a fixed VOI set.



This is particularly useful for data which have been transformed to a template space, such as the MNI space.

The selected VOIs can optionally be transformed before application to the images:

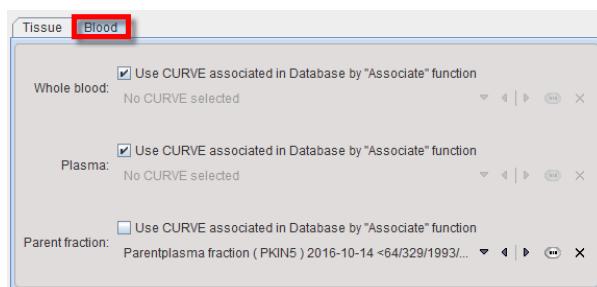
- » **Apply transformation from pipeline:** The idea here is that the VOIs have been derived using an image different from the current images, and that the pipeline has recorded the appropriate transformation for bringing the VOIs into the space of the current image. Such an application is described in the *example* (on page 435) below. The **Direct** or the **Inverse** transformation can be applied, as appropriate.
- » **Apply Operation:** The operations offered for VOI modification are the **Erosion** or **Dilation** by a number of pixels. Erosion allows shrinking VOIs from the outside. This may be useful for reducing the partial-volume effect. Dilation grows the VOIs by adding additional layers.

As a convenience for applying reference tissue models a sub-set of VOIs can be merged with the **Merge Reference VOI** option. The specification is by a comma-separated list of exact

VOI names like **Cerebellum_l**, **Cerebellum_r**, or using the "*" wildcard character such as **Cerebellum*** to enclose all VOI names starting with "Cerebellum".

Blood Activity Information

If blood-based kinetic models are applied in pipeline processing, blood information must be available for each data set processed. Unless the information is common among data sets, the blood information must have been *associated* (on page 74) to the PET data beforehand. The **Blood** tab needs to be selected for the specification as illustrated below. In this example the **Whole blood** activity and the **Plasma** activity are referenced by association, whereas a constant **Parent Fraction** is applied which assumes that the metabolite buildup is common among the population processed.



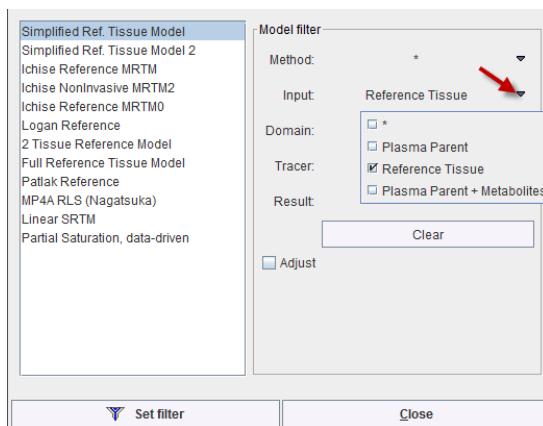
Note that at this time the plasma fraction variant for specification of the plasma activity is not supported in pipeline processing.

Model Selection

The tissue model to be applied in fitting can be selected from the **Model** list.



Because of the large model number the list is initially filtered to only show reference tissue models. Please use the filter button indicated above for showing the filter setting window. There, filtering can be switched off with the **Clear** button, or set to different criteria. **Set filter** closes the dialog window and updates the **Model** list.



Fitting Options

Each tissue model has its default regarding initial parameters and fitting flags. These defaults can be changed in the kinetic tool (PKIN). Alternatively, an explicit model configuration file can be prepared beforehand in PKIN and selected as the **Configuration file**.



The **Model fit options** allow applying some of the fitting options available in interactive modeling. Briefly:

- » **Parameters initialization:** This option is only effective for compartment models. If enabled, the initial parameters are calculated using a linear least squares method.
- » **Random fits:** If the option is enabled, the regional fits are repeated the specified number of times with randomly varied initial parameters. In the end, the fit with minimal Chi square will be returned as the result.

Detailed Pipeline Example: Kinetic Modeling with SRTM, Brain VOIs in PET Space

Available Data

The pipeline discussed in detail below assumes the following available scenario: A patient had two separate scanning sessions, resulting in a dynamic brain PET and a non-matched T₁-weighted MRI.

Intended Analysis

The MRI, which has superior resolution and anatomical information, is used for the automatic outlining of brain regions. These VOIs are then projected to the PET, and the average PET uptake in each region is calculated. The resulting TACs are analyzed with the SRTM kinetic model using the average cerebellum uptake as the reference TAC.

Processing Pipeline Outline

It is assumed that the user has imported the data into a PMOD database and *associated* (on page 73) the PET and the MR series. The described analysis can then be implemented by the following pipeline sequence.

- 1) Because the anatomical information in the MR image is better than in the PET, the MR is first loaded into the pipeline. So the MR is the **Input study**.
- 2) The **Automatic Brain VOIs** tool is then applied. It generates the VOIs in the MR image space. These VOIs will continue existing in the following pipeline stages.
- 3) The rigid transformation between the MR and the PET is determined using the **Registration & Normalization** tool. Because the uptake calculation should use the non-interpolated PET values the PET image serves as the reference image, so that the rigid transform goes from the MR to the PET space. This rigid transform will continue existing in the following pipeline stages.
- 4) The PET images are brought into the pipeline using the **Replace Images** tool which swaps the current (MR) image with its associate (PET). From now on, the associated image is the MR.
- 5) If necessary, patient motion in the dynamic brain PET can be corrected with the **Motion Correction** tool. Note however that after this step the PET values will be interpolated.
- 6) Transform the VOIs from the MR to the PET space using the result from 3. (still in the pipeline), calculate the average regional TACs, generate the reference TAC by merging all cerebellum TACs, and perform the SRTM kinetic modeling. All this is done by the **Kinetic Modeling** tool.

In practice, the pipeline has the following appearance. Note that this pipeline setup is only possible if the Kinetic Modeling tool (PKIN) and the Image Fusion tool (PFUS) have been licensed from PMOD.



The following sections describe each tool configuration in detail. The steps can be reproduced with the **PKIN2** data set in the **Pmod** example database. Furthermore, the corresponding pipeline definition is already available and can be retrieved with **Load Processing**.

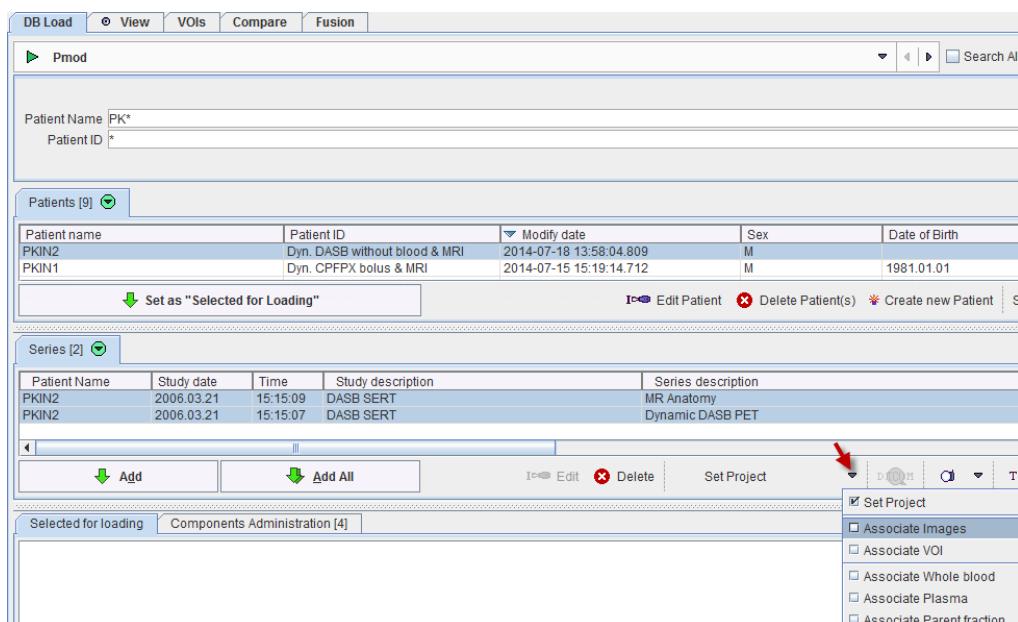
Required PMOD Modules

Note that this pipeline requires that the following modules are available in the PMOD license:

- » Image fusion (PFUS): for using the **Automatic Brain VOIs, Registration & Normalization, Motion Correction** tools.
- » Neuro tool (PNEURO): for using the Hammers atlas. However, the AAL atlas can be used alternatively if PNEURO is not available.
- » Kinetic modeling (PKIN): for applying the SRTM model to the tissue TACs.

Association of MR and PET Series

The first step is to prepare the input data. Start the viewing tool to perform the image association in the database viewer as illustrated below.



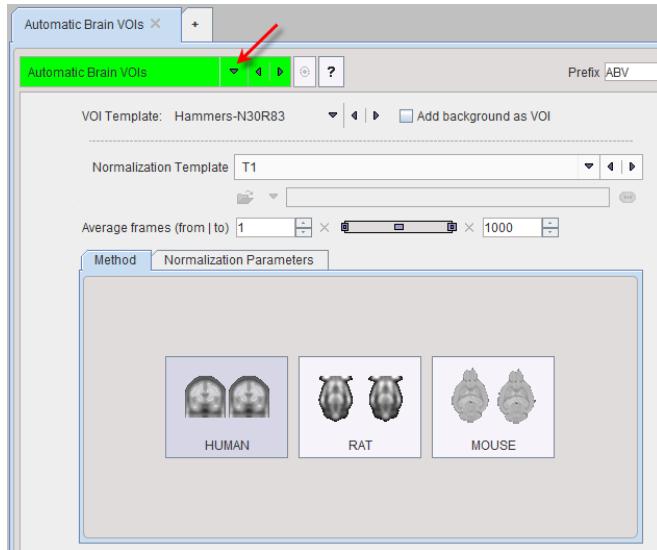
Select patient **PKIN2** in the **Patients** list. Use SHIFT+Click to select the two image series **MR Anatomy** and **Dynamic DASB PET** which will be used in the pipeline processing. From the **Set Project** list activate the **Associate Images** entry to establish the mutual relation between the image series.

This operation would be repeated for all patients to be processed. It is a one-time action which can be taken advantage of in multiple analysis procedures.

Automatic Brain VOIs

This step produces brain VOIs which match the anatomy in the MR image.

After data preparation proceed to the processing definition. *Start* (on page 422) pipeline processing and configure the image format to **Database**. In the **BATCH PIPELINE DEFINITION** area use the tool selection button indicated below to select the **Automatic Brain VOIs** tool.

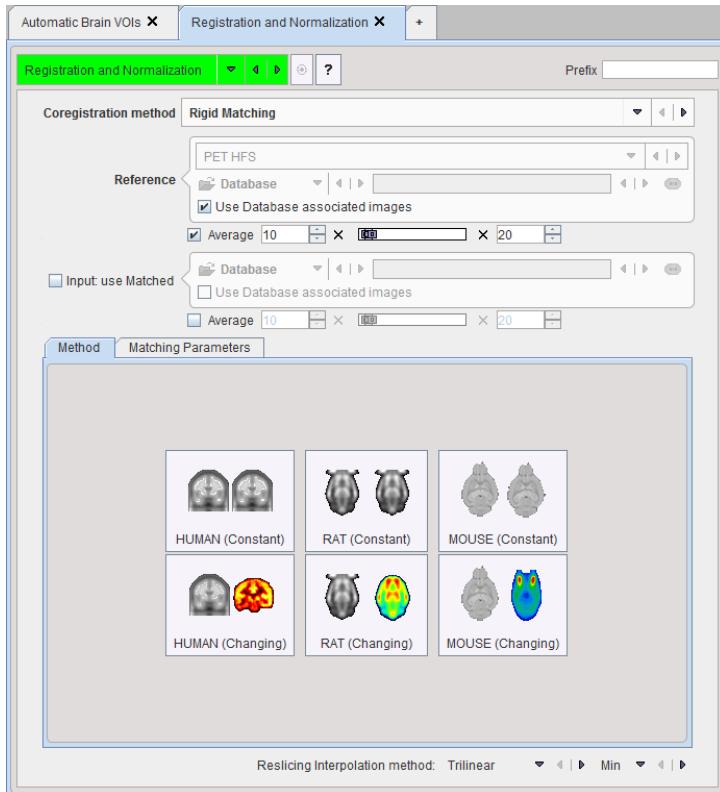


Set the **VOI template** to **Hammers-N30R83**. If it's not available in the list, select **AAL-Merged** instead. Because the VOIs are derived from the brain MRI series, select **T1** in the **Normalization Template** list. Activate the **HUMAN** button to set the normalization procedure to proper defaults.

Registration and Normalization

This step calculates the rigid transformation from the MR image to the PET image, so that the VOIs delineated in the MR can be projected into the PET.

Use the **+ tab** to add a second processing tab and select **Registration and Normalization** from the tool list.



Set the **Coregistration method** to **Rigid Matching**. In the **Reference** section, activate the **Use Database associated images**. In this way, the PET image (which is associated to the current input, the MR) becomes the reference. Consequently the calculated transformation will go from the MR (input) to the PET (reference) space.

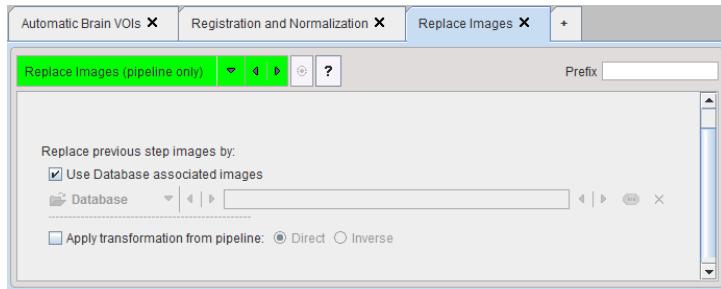
Because the PET is dynamic, the average uptake from frame **10** to **20** is used for matching. This is enabled by the **Average** flag, and entering the start and end frames into the corresponding number fields.

Activate the **HUMAN (Changing)** button to set appropriate matching parameters for cross-modality matching.

Replace Images

This step brings the dynamic PET images into the pipeline.

Use the **+ tab** to add an third processing tab and select **Replace Images** from the tool list.

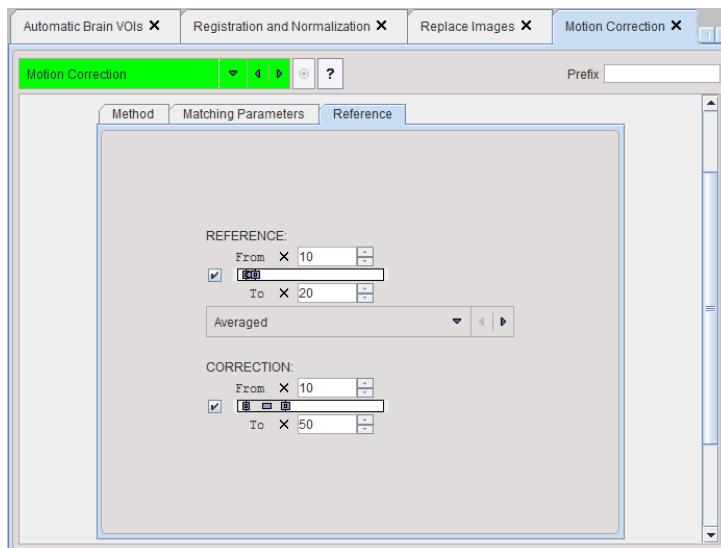


Check the **Use Database associated** images box. The effect is the loading of the images associated to MR, the PET which is the main target of the analysis.

Motion Correction

This step performs a motion correction of the dynamic PET series.

Use the **+ tab** to add an third processing tab and select **Motion Correction** from the tool list.



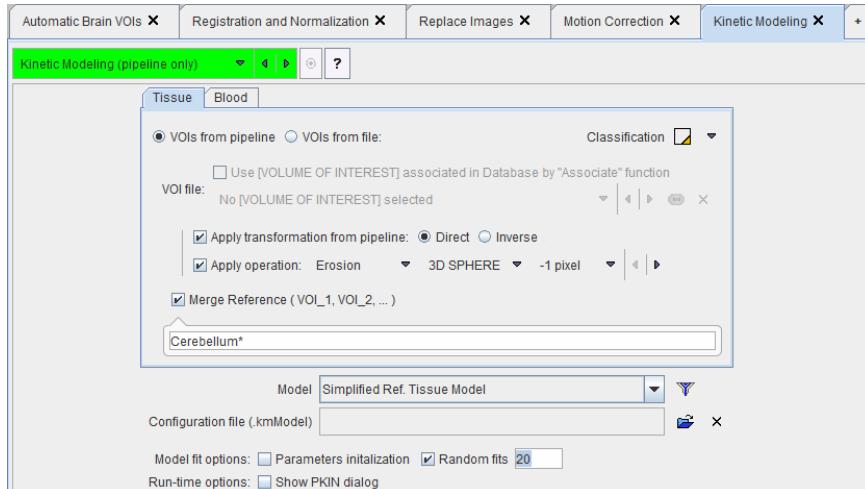
Make sure that the **Averaged** reference is selected. With this approach, a reference image is created by averaging the frames between **From** and **To** in the **REFERENCE** section. In this example a range from **10** to **20** is applied, omitting the noisy short frames at the beginning. Note that the same range had been averaged to create a reference for the registration between PET and MR. In this way, the transformation will correctly map from MR to the motion corrected PET.

The **CORRECTION** section specifies the frames which will be matched to the frame average which serves as the reference. Assuming that there was negligible motion in the initial frames, a range from **10** to **50** is specified. Note that as a convenience the end number can be higher than the number of frames in the actual series.

Kinetic Modeling

This step calculates the average TACs of all brain regions and performs the kinetic modeling.

Use the **+ tab** to add a third processing tab and select **Kinetic Modeling** from the tool list.



VOI Definition

Set the radio button **VOIs from pipeline** to use the brain VOIs which have been produced in the first step of the pipeline. However, because they are in the MR space, they first have to be projected into the PET space. This is configured by checking **Apply transformation from pipeline** with the **Direct** option. This setting is correct, because the PET was the reference in the registration of pipeline step 2.

In order to reduce the VOI size slightly the **Apply Operation option** is enabled and a 3-dimensional **Erosion** with 1 pixel. Set the **Classification** to the indicated mode which weighs the contribution of each pixel relative to its VOI inclusion fraction.

As a convenience for applying reference tissue models a sub-set of VOIs can be merged with the **Merge as Reference VOI** option. The specification is by a comma-separated list of exact VOI names like **Cerebellum_l**, **Cerebellum_r**, or using the "*" wildcard character such as **Cerebellum*** to enclose all VOI names starting with "Cerebellum".

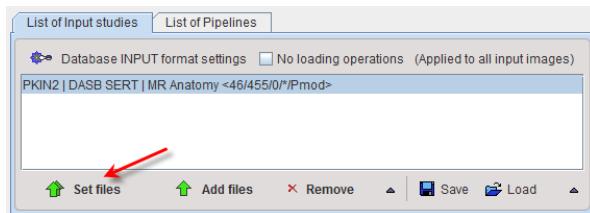
Model Definition

The Model list is initially set to show the reference tissue models. Select the **Simplified Ref. Tissue Model**, and enable the **Random fit** option to try each fit with 20 different initial parameters. The fitting will use the standard defaults for the model and the weighting. If specific initial parameters or a particular weighting scheme are required, the configuration should be prepared in the PKIN tool and referred to by the **Configuration file** selection.

Pipeline Input Data

The data to be processed is assembled on the **List of Input studies**. Note that for the example pipe setup the MR series have to be selected, and that the PET series must have been associated to those MRs beforehand. In the example below the **MR Anatomy** series of

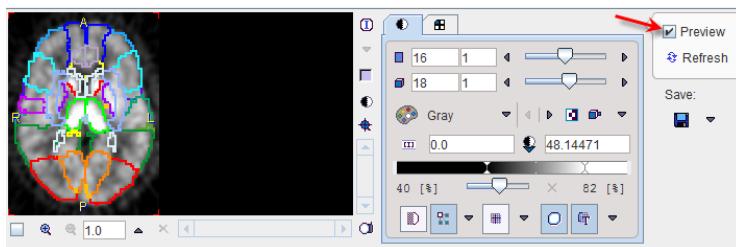
patient PKIN2 was selected using the **Set input files** button. Note that for incrementally appending to an existing list the **Add files** button should be used.



Testing the Pipeline

Initial Testing

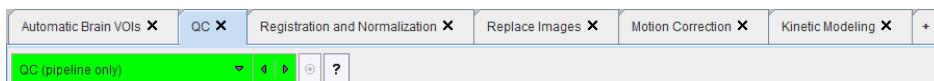
As an initial test of the pipeline enable the **Preview** box. The whole pipeline will be run with the data selected in the list of input studies and the resulting images shown together with the VOIs in the lower right, if no error occurs.



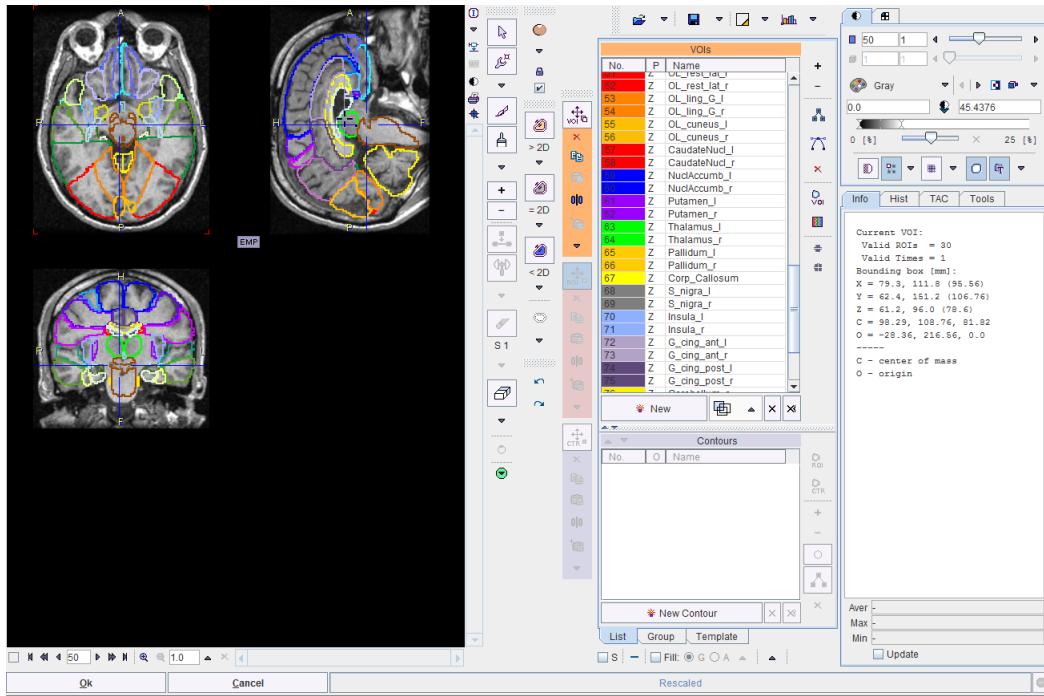
Note that the VOIs are shown on top of the motion corrected PET, after transformation from the MR space.

Setting Quality Control Breakpoints

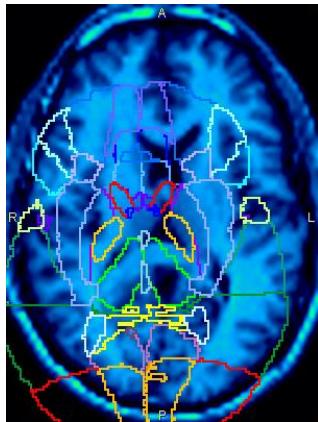
In order to evaluate the quality of VOI outlining a QC breakpoint can be added after the **Automatic Brain VOIs** tab and enable the **Edit VOIs** option.



Activate the **Refresh** button to restart the calculation. This time the pipeline is interrupted and the VOIs shown on top of the MR images. Note that there are more options to inspect the VOIs, such as VOI filling, showing only VOI subsets, etc.



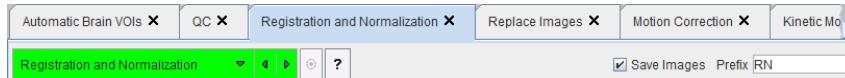
Note that depending on where the QC breakpoint is placed, the VOIs might not match the images. In the example pipeline discussed the VOIs will not match any more after the **Replace Images** step as they are still in the MR space.



Only the **Kinetic Modeling** step will bring them from the MR to the PET space, and from there on they will match again.

Saving Intermediate Images

Some operations cannot be fully verified in the pipeline environment. In this example, for instance, the PET-MR matching evaluation is not possible because the QC can only show one image, namely the current one. By enabling **Save Images** of the **Registration and Normalization** step the pipeline is instructed to save the MR images which were matched to the PET with a **Prefix RN**.



As the **Preview** facility doesn't save images, the data have to be fully processed with **Start Processing**. The intermediate images will appear in the **Series** list of the patient.

Patient Name	Study date	Time	Study description	Series description
PKIN2	2006.03.21	15:15:07	KM_KINETIC_MODELING_DASB SERT	Dynamic DASB PET > MATCHED to Dynamic DASB PET [Aver Volumes]
PKIN2	2006.03.21	15:15:07	MC_MOTION_CORRECTION_DASB SERT	Dynamic DASB PET > MATCHED to Dynamic DASB PET [Aver Volumes]
PKIN2	2006.03.21	15:15:09	RN_REGISTRATION_AND_NORMALIZATION_DASB SERT	MR Anatomy > MATCHED to Dynamic DASB PET
PKIN2	2006.03.21	15:15:09	DASB SERT	MR Anatomy
PKIN2	2006.03.21	15:15:07	DASB SERT	Dynamic DASB PET

For the evaluation of the matching the average of frames 10-20 of the Dynamic DASB PET should be fused together with the highlighted registration result RN_REGISTRATION_AND_NORMALIZATION.

Running the Pipeline

Finally the pipeline with the configured input data can be executed with the Start

Pipeline Example: Brain Uptake Statistics, MR Space

Available Data

The pipeline outlined below assumes the following available scenario: A patient had two separate scanning sessions, resulting in a dynamic brain PET and an non-matched T¹-weighted MRI.

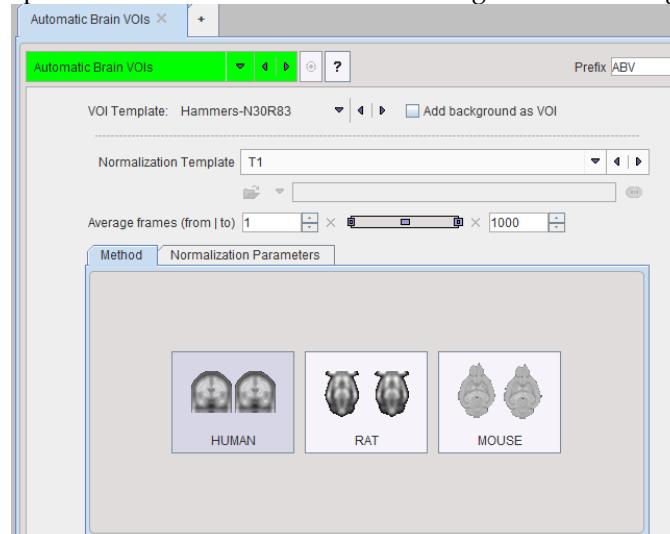
Intended Analysis

To provide a complementary example to the one *above* (on page 435) in this case the statistics is performed in the MR space, and instead of performing kinetic modeling, the PET uptake is averaged during a certain frame range.

Processing Pipeline Outline

It is assumed that the user has imported the data into a PMOD database and *associated* (on page 73) the PET and the MR series. The described analysis can then be implemented by the following pipeline sequence.

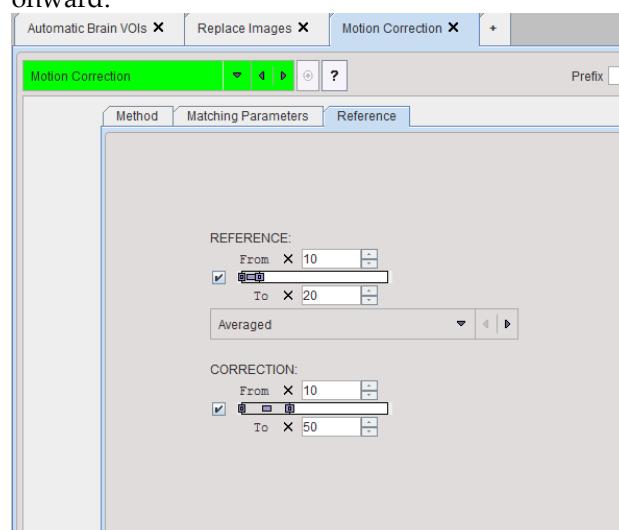
- 1) Because the anatomical information in the MR image is better than in the PET, the MR is first loaded into the pipeline. So the MR is the **Input study**.
- 2) The **Automatic Brain VOIs** tool is then applied. It generates the VOIs in the MR image space. These VOIs will continue existing in the following pipeline stages.



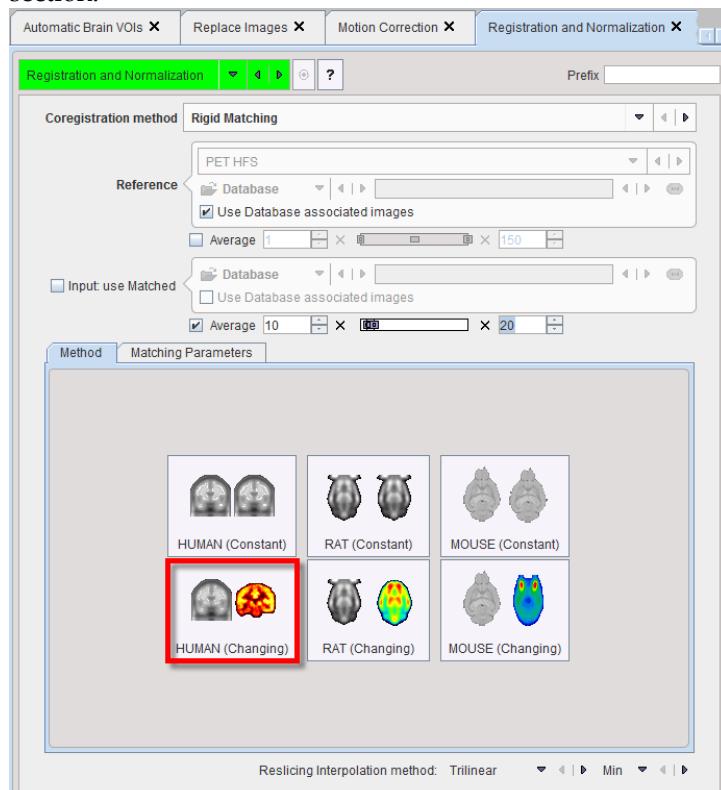
- 3) The PET images are brought into the pipeline using the **Replace Images** tool which swaps the current (MR) image with its associate (PET). From now on, the associated image is the MR.



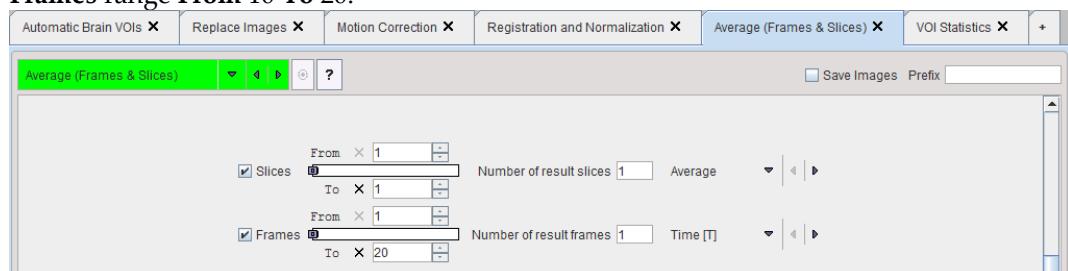
- 4) If necessary, patient motion in the dynamic brain PET can be corrected with the **Motion Correction** tool. Make sure that the **Averaged** reference is selected. With this approach, a reference image is created by averaging the frames between **From** and **To** in the **REFERENCE** section. In this example a range from **10** to **20** is applied, omitting the noisy short frames at the beginning. The **CORRECTION** is then applied from frame **10** onward.



- 5) The rigid transformation between the MR and the PET is determined using the **Registration & Normalization** tool. In this example the MR should serve as the reference. As PET is currently in the pipeline, this can be configured by the **Use Database associated images for the Reference**. For the rigid matching the average PET image between frames **10** and **20** will be used which is configured below the input section.

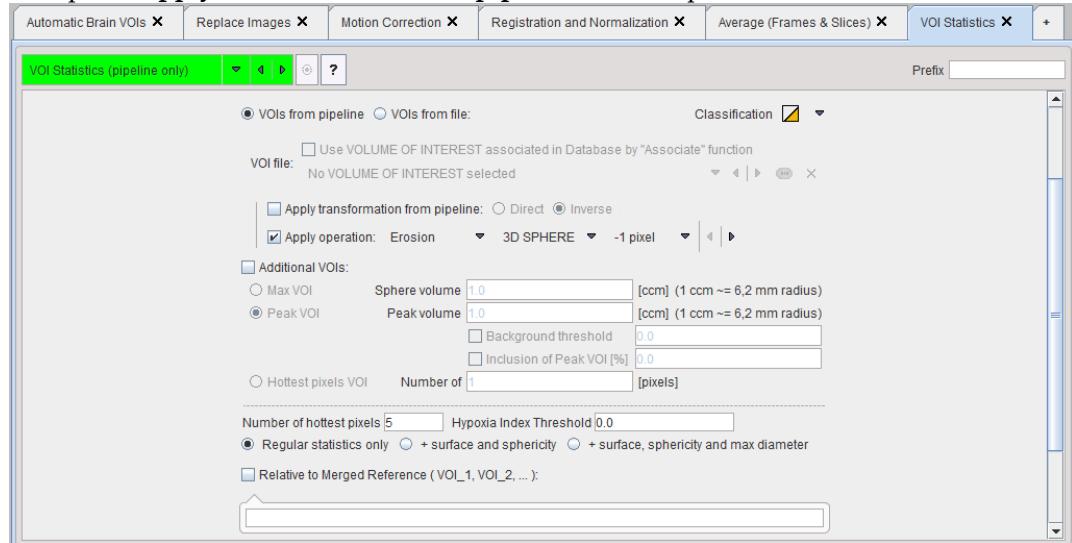


- 6) The PET uptake is then averaged with the **Average (Frames & Slices)** tool within the **Frames range From 10 To 20**.



- 7) The final step is calculation of the regional statistics. Note that the PET image has already been transformed to the MR space in the registration step, so that in this pipeline

the option **Apply transformation from pipeline** is not required.



Required PMOD License

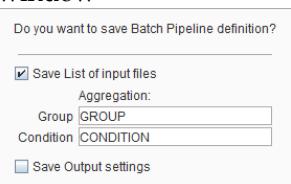
Note that this pipeline requires that the following modules are available in the PMOD license:

- » Image fusion (PFUS): for using the **Automatic Brain VOIs, Registration & Normalization, Motion Correction** tools.
- » Neuro tool (PNEURO): for using the Hammers atlas. However, the AAL atlas can be used alternatively if PNEURO is not available.

List of Pipelines

Setup of a Pipeline per Group/Condition

- 1) Configure the processing steps of the pipeline. After testing its performance with some example data, remove all files from the list and save it as the processing template with **Save Processing**.
- 2) Configure a meaningful set of input files (e.g. control group, baseline scans) in the **List of Input Studies**. Use **Save processing** for saving this processing batch. In the dialog window

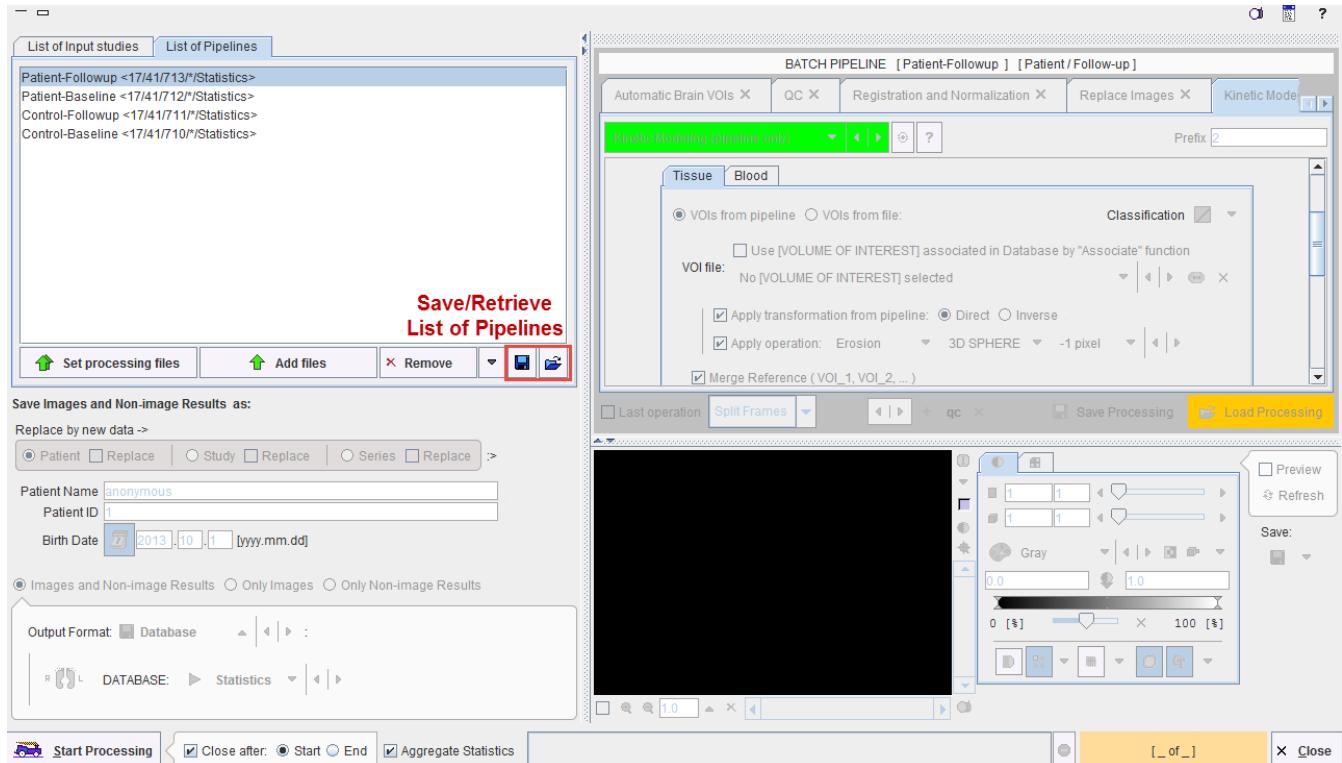


enable **Save List of Input files** so that the currently selected files are stored together with the processing definition. In order to prepare aggregating the VOI statistic or kinetic parameters of this batch into an overall table specify the **Group** and the **Condition** identifiers in the corresponding fields (e.g. "Control" and "Baseline"). Choose a corresponding name for the file and save.

- 3) Remove all input files, then configure the next set of input files (e.g. control group, follow-up scan). Save the processing list as in 2. with appropriate aggregation information (e.g. "Control" and "Follow-Up").
- 4) Repeat 3. for all subject groups and conditions (e.g. "Patient", "Baseline"; "Patient", "Follow-Up"). Make sure to use consistent identifier names.

List of Pipelines

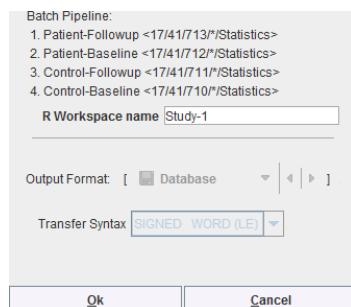
For setting up an overall batch processing load all the prepared pipelines into the **List of Pipelines** tab using the **Set processing files** and **Add files** buttons.



The **Aggregate Statistics** option enables the creation of an aggregate per pipeline, which summarizes the group results and is named according to the **Group** and **Condition** identifiers. Note the functionality for saving the whole definition and retrieving it at a later time.

Execution of Pipelines List

After setting the pipelines up or retrieving them, the batch can be launched with **Start Processing**. A dialog window appears which summarizes the tasks to be performed



and allows defining an **R Workspace name**. This is a convenience and only relevant if the R functionality is enabled. In that case, all group aggregates are imported into the R environment and saved as a workspace, which can directly be employed for the population analysis.

The example below illustrates the situation at the end of processing the configuration above: Four aggregates were created, transferred to the R console which automatically started, and the interface for the population statistics is opened.

The screenshot shows the R Console interface with four tabs open: Group 1 [1_Patient_Follow-up], Group 2 [2_Patient_Baseline], Group 3 [3_Control_Follow-up], and Group 4 [4_Control_Baseline]. The Group 4 tab is active. Below the tabs, there are buttons for Show data (2D or 3D), Execute, Block, Auto-clear, and a search bar. To the right, a Statistics panel displays various R objects like r1 (R1) and their values. A Master table creator dialog is overlaid on the console, showing conditions for Baseline and Follow-up groups (Control and Patient) and covariates (Sex, Size, Weight, Birth date, Age). The dialog has OK and Cancel buttons.

The individual pipeline aggregates are also available and appear as the following entries in the database.

[AGGREGATE (TAB)] [19]				
Component name	Patient name	Patient id	Modify time	Last Use
4_Control_Baseline	[AGGREGATE (T...]	[AGGREGATE ...	2014-08-05 15:0...	2014-08-05 1...
3_Control_Follow-up	[AGGREGATE (T...]	[AGGREGATE ...	2014-08-05 14:4...	2014-08-05 1...
2_Patient_Baseline	[AGGREGATE (T...]	[AGGREGATE ...	2014-08-05 14:2...	2014-08-05 1...
1_Patient_Follow-up	[AGGREGATE (T...]	[AGGREGATE ...	2014-08-05 13:0...	2014-08-05 1...

Chapter 10

PMOD Image Viewing and VOI Tool (PVIEW)

PVIEW is a versatile image and Volume-of-Interest (VOI) analysis tool which belongs to the base installation of PMOD. It supports many operations for image reviewing and scientific data analysis including:

- » Loading medical images in different formats, including DICOM.
- » Viewing the images with different color tables and in different layouts.
- » Calculating new slice images in arbitrary new orientations.
- » Performing many image processing and manipulation operations.
- » Displaying fusion images of matched data sets (image registration is a separate option).
- » Performing volume-of-interest analyses and the calculation of time-activity curves from dynamic studies.
- » Saving images in different formats, including DICOM, and directly C-STORE them to a DICOM server.

The PVIEW tool is started from the PMOD ToolBox with the



Like many other PMOD tools it organizes the functionality on different pages which can be selected by the upper tabs.

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Volume-of-Interest Analysis - Page 3	462
Image Comparison - Page 4	463
Image Fusion - Page 5 (Optional)	465
Creation of a DICOMDIR File	466

Database Loading - Page 1 (Option)

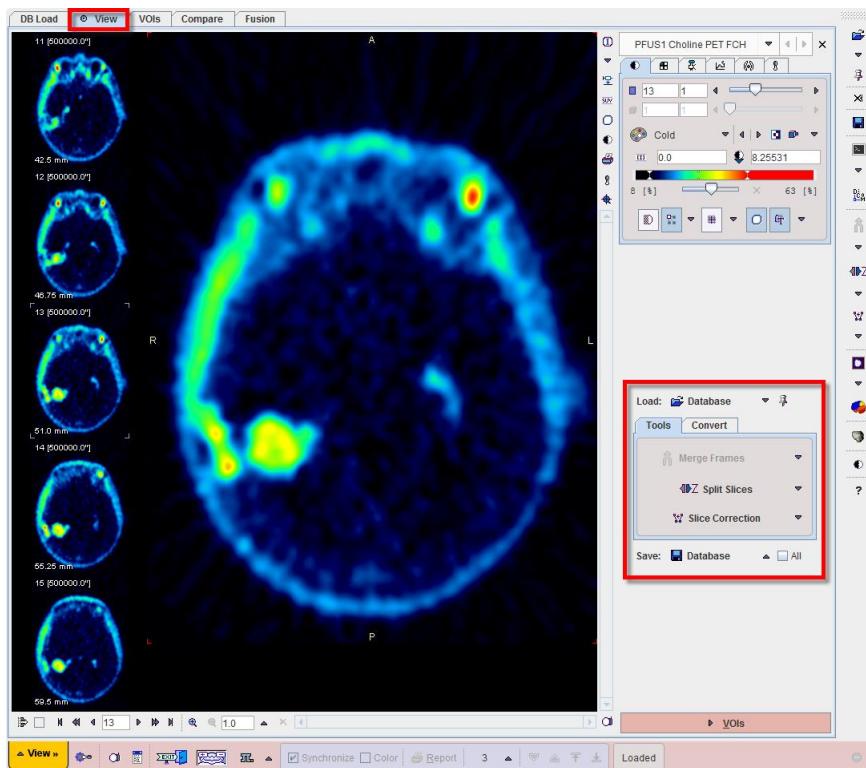
The first page **DB Load** shows the database interface. It is only available if the database functionality is enabled and a local or remote database has been configured to access images in DICOM format. Note that it is highly recommended to use the database for accessing DICOM images, because the image access is much slower otherwise. The database load page offers an efficient interface for loading images stored in one of the configured databases. A detailed description can be found in the *Image Data Load section* (on page 91).

The screenshot displays the PMOD PVIEW DB Load interface. At the top, there's a toolbar with buttons for DB Load, View, VOIs, Compare, and Fusion. The main window is titled "Database selection" with a red arrow pointing to it. Below this is a "Basic filtering criteria" section with fields for Patient Name (PK*) and Patient ID (*). To the right are filters for Birth Date and Modified. A "Patients [5]" list table shows five entries (PKIN1 to PKIN4) with details like Patient ID, Modify date, Sex, and Date of Birth. To the right of the patients is a "Series Image Preview (selected)" section with three brain MRI slices. A red box highlights this area. Below the patients is a "Series [2]" list table for PKIN2, showing study details like Study date, Time, Study description, Series description, and various metadata columns. A red arrow points from the "Selected for loading" button in this table to the "Selected for loading [1]" list at the bottom. The bottom section, also with a red arrow pointing to it, is titled "Series in the loading list" and contains a table with one entry (PKIN2) and buttons for Open, with Operations, Edit and Copy to, Remove, Remove all, Remove after loading, and Append.

Image Viewing - Page 2

The purpose of the **View** page is

- ▶ loading images in all kinds of image formats,
- ▶ viewing the loaded images and performing processing operations, and
- ▶ saving (modified) images in one of the supported output formats.

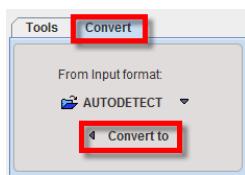


Several images can be loaded, but only one at the time can be viewed on this page. The **View** page essentially implements the basic PMOD capabilities which are described in the *Image Loading* (on page 62) and the *Image Display* (on page 114) sections. Additionally, there are some extra functions available which are accessible by the tabs in the lower right.

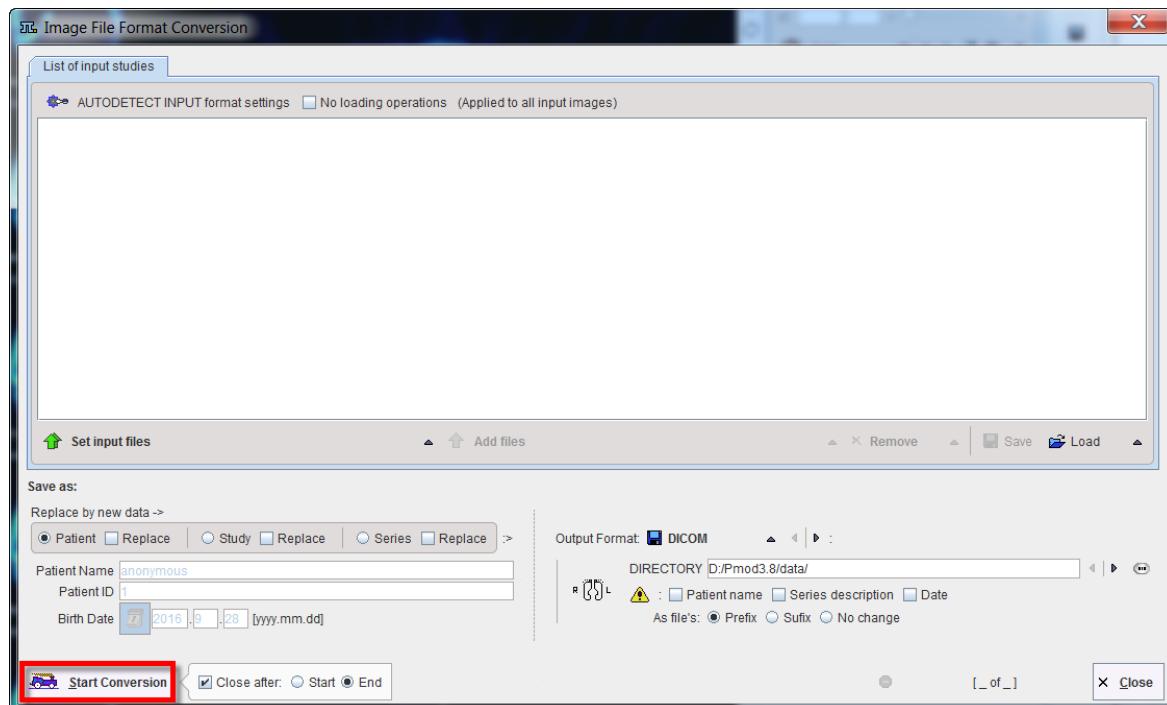
The **Load/Save** sections contains the **Load** and the **Save** buttons, configurable to different image formats. Note the **All** box which can be checked to save all loaded images at once.

Batch Format Conversion

The **Convert** tab is used for batch format conversion.



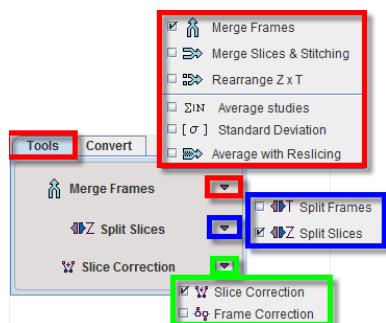
Begin by setting the **Input Format** then activate the **Convert to** button. A dialog appears, which allows selecting the files to be converted, and to define processing and output properties as well as the **Output format**.



The contents of the dialog window may differ depending on the selected formats. The first step is to select the files to be converted using the **Set input files** button. Activating the **INPUT format settings** button brings up the loading dialog, where data pre-processing operations (eg. rotations, filtering) can be specified. Another dialog is shown when selecting the **Output Format** settings button. In the DICOM example shown above the output modality and the patient position can be specified. Finally, an output path must be defined in the **DIRECTORY** section. After activating **Start Conversion**, PVIEW reads, converts and saves the selected series in the prescribed manner.

Tools

In addition to standard image viewing the PVIEW tool allows performing the following distinct operations available on the **Tools** tab:



Most functions only get active when more than one image series have been loaded into PVIEW.

Functionality:

Merge Frames

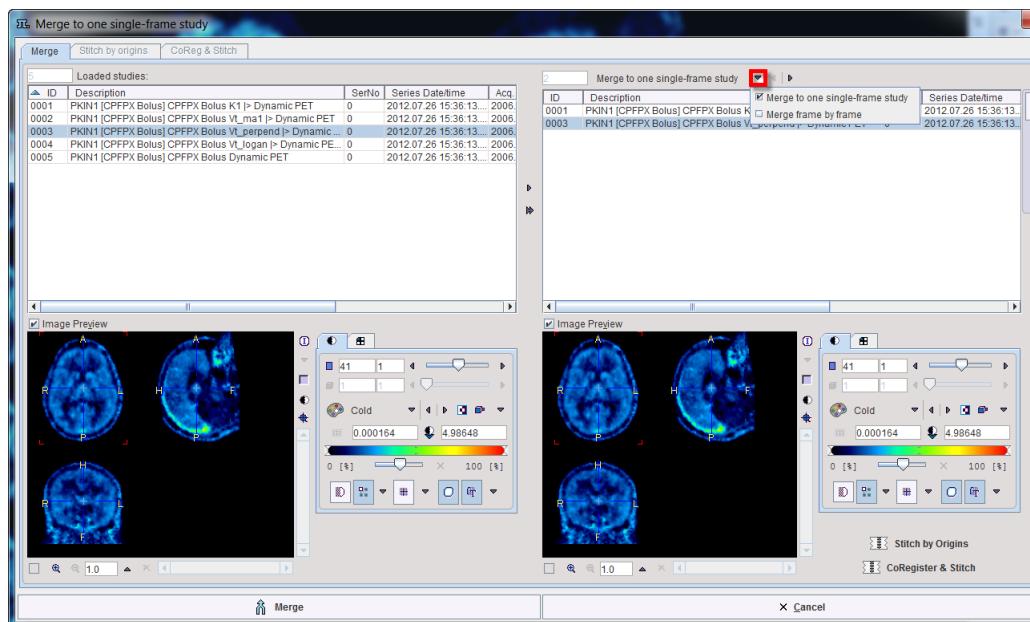
Merging a number of static image series into one dynamic study.

This function is explained in a separate *section* (on page 456).

Merge Slices

Merging of a number of static image series in axial direction.

Activating **Merge Slices** opens a dialog window for choosing among the loaded series and changing their order. The studies selected for merging are then combined in the axial direction to form a static series with extended coverage.



There are two options available for merging: **Merge one single frame study** and **Merge frame by frame**.

This function is only reasonable for image series covering adjacent axial fields-of-view such as in whole-body scanning.

Note that at least two studies have to be selected for merging

Rearrange Z&T

The result is a one multiframe study with a new number of slices and frames.

Average studies

Calculating the average value of each pixel across the loaded image series.

Result is the average image series, while the individual image series are removed from PVIEW.

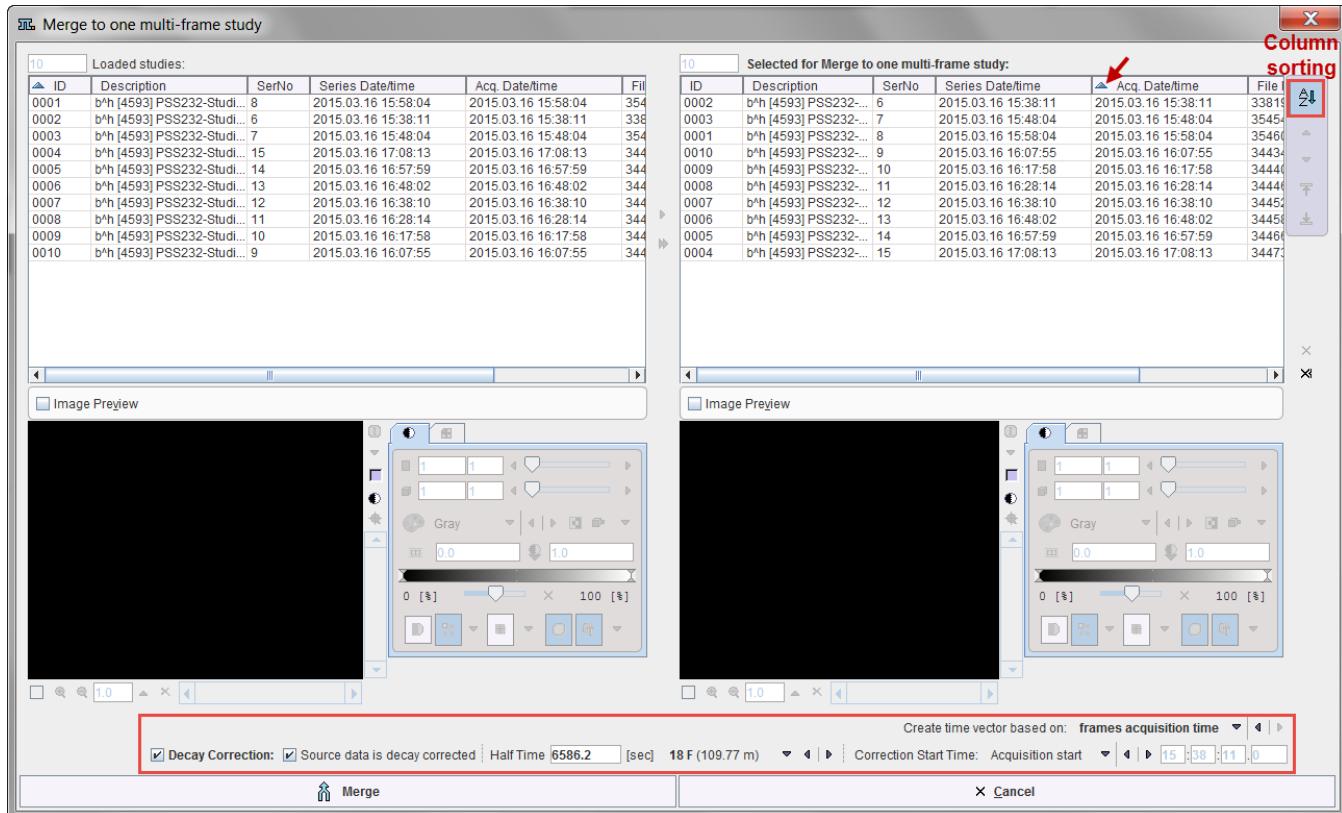
Standard Deviation	<i>Calculating the standard deviation of the values in each pixel across the loaded image series.</i>
	Result is the standard deviation image series, while the individual image series are removed from PVIEW.
Split Frames	<i>Splitting a dynamic image series into a set of static series.</i>
	Activating the button causes PVIEW to split the current dynamic series into a set of static series (one per time frame) which can be separately displayed.
	If the To disk box is checked, the Output Format selection becomes active. In this configuration, a saving dialog appears when the Split Volumes button is activated, and the new static series are saved to disk.
Split Slices	<i>Splitting a 3D static image into a set of 2D static series.</i>
	If the To disk box is checked, a dialog window appears allowing to select the Output Format .
Slice corr.	<i>Calculates a rigid 2D transformation between marker pairs defined on slices.</i>
	The first slice with valid markers serves as the reference. This function could be useful when merging slices which have been acquired separately (eg. by autoradiography of small animals) into a volume.
	Note that at least three markers on two slices need to be defined.
Frame corr.	<i>Motion correction for a dynamic series with external markers (translations only).</i>
	Calculates the transformation between frames and corrects them based on the assumption that the maximal value contained in a VOI should remain stable.
	Note that at least one VOI must be defined (in case of multiple VOIs the first one on the list is going to be used during the correction). It is important that VOIs are in dynamic mode.

Merge Frames Tool

The **Merge Frames** tool allows combining image series with the same geometry into a joint dynamic series.

Activating **Merge Frames** opens a dialog window as illustrated below. The list in the upper left shows the loaded image series in loading order. The list in the upper right shows the

image series which will be combined into a dynamic series with current the sorting order. Initially, all series appear in the original order. The options related to applying decay correction during merging and generating the timing of the new dynamic series is located in the lower part.



Merging List Preparation

Series can be copied from left to right by double clicking in the left list, or selecting a list element and activating the arrow between the list. The double arrow copies all loaded series to the right.

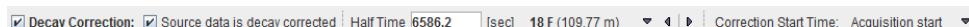
The order of the **Selected for Merge** list can be modified by selecting a list element and shifting its position by the arrows to the right.



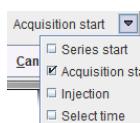
If the columns contain information which is suitable for sorting, the sorting button AZ can be enabled and sorting started by clicking into the column header. In the example above, the acquisition time was used for sorting the static series into the proper acquisition order.

Decay Correction Setup

When joining PET or SPECT data into a dynamic series, a consistent decay correction has to be ensured. Usually, such data is corrected to the acquisition start. Therefore, when joining static series into a dynamic series, later series have to be decay corrected to the start of the first acquisition by scaling them with a corresponding factor. The proper setting for this situation is to enable **Decay Correction**, confirm that **Source data is decay corrected**, check that the isotope **Half Time** is correct, and set the **Correction Start Time** to **Acquisition start** as illustrated below.



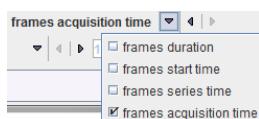
The other options for defining the time point of decay correction are



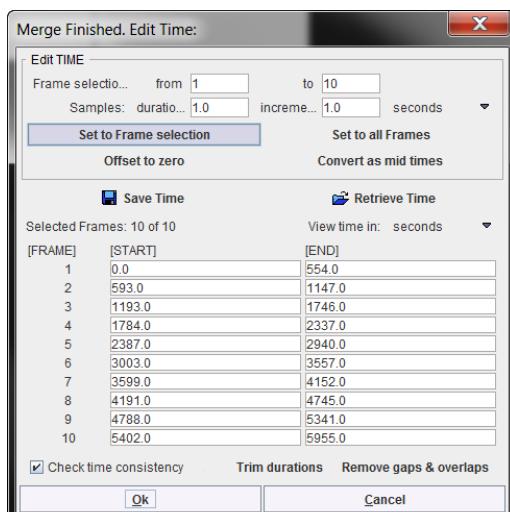
It depends on the data encoding, which times are actually available and proper.

Dynamic Series Timing

The timing of the created dynamic series needs to be constructed. It can be specified using the **Create time vector based on** selection



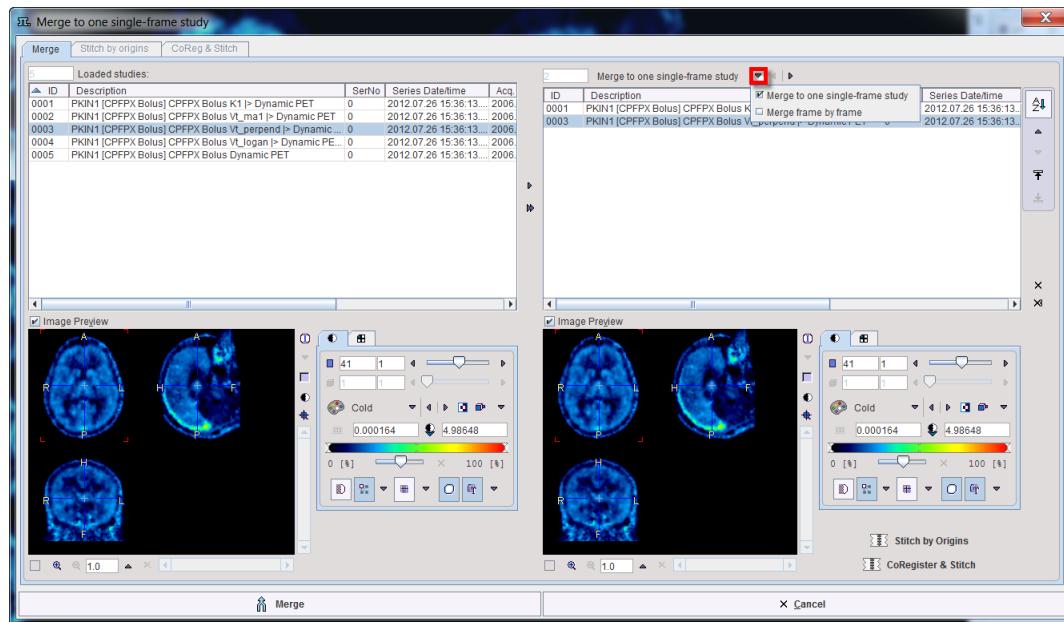
Processing is started with the **Merge** button. Before the new series is created and optionally decay corrected, the timing is displayed in a dialog window for confirmation and editing. In the example below which was generated using **frames acquisition times**, there are gaps of about 40 seconds between the acquisitions. They occurred because the scanner had to be restarted for the subsequent whole-body acquisitions. Using **frames duration**, this information would have been missed.



Merge Slices & Stitching

The **Merge Slices & Stitching** tool allows combining in the axial direction the selected studies to form a static series with extended coverage.

Activating **Merge Slices & Stitching** opens a dialog window as illustrated below:



The list in the upper left shows the loaded image series in loading order. The list in the upper right shows the image series which will be combined into a static series with the current sorting order. Initially, all series appear in the original order.

Merging List Preparation

Series can be copied from left to right by double clicking in the left list, or selecting a list element and activating the arrow between the lists. The double arrow copies all loaded series to the right.

The order of the **Merge** list can be modified by selecting a list element and shifting its position by the arrows to the right.



If the columns contain information which is suitable for sorting, the sorting button **AZ** can be enabled and sorting started by clicking into the column header.

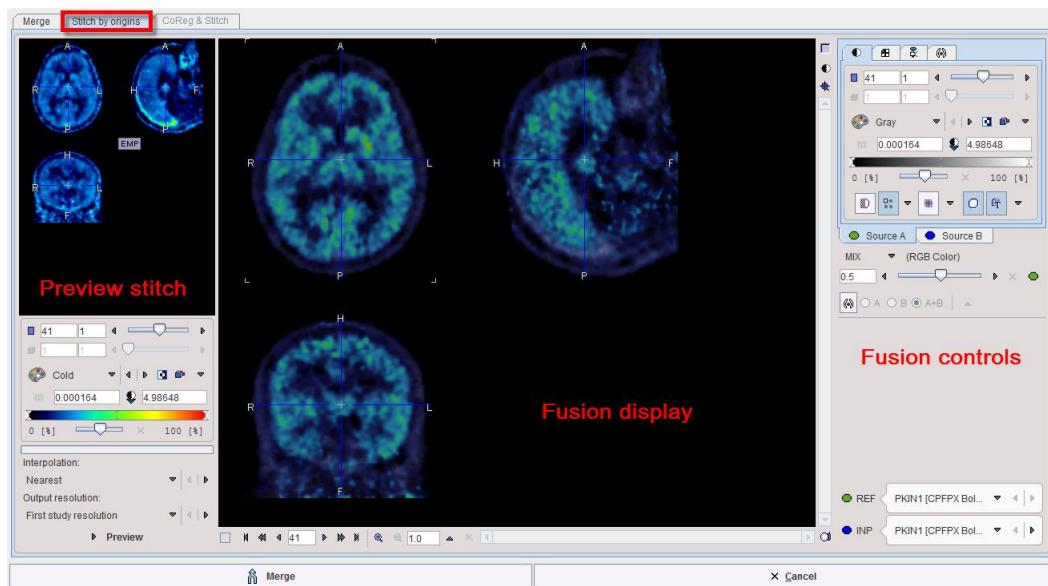
There are two options available for simple merging: **Merge one single frame study** and **Merge frame by frame**.

This function is only reasonable for image series covering adjacent axial fields-of-view such as in whole-body scanning.

Note that at least two studies have to be selected for merging.

Stitch by Origins

The procedure assumes the images have the same spatial frame of reference and merges them based on slices position. The first image in the merging list is set as reference.

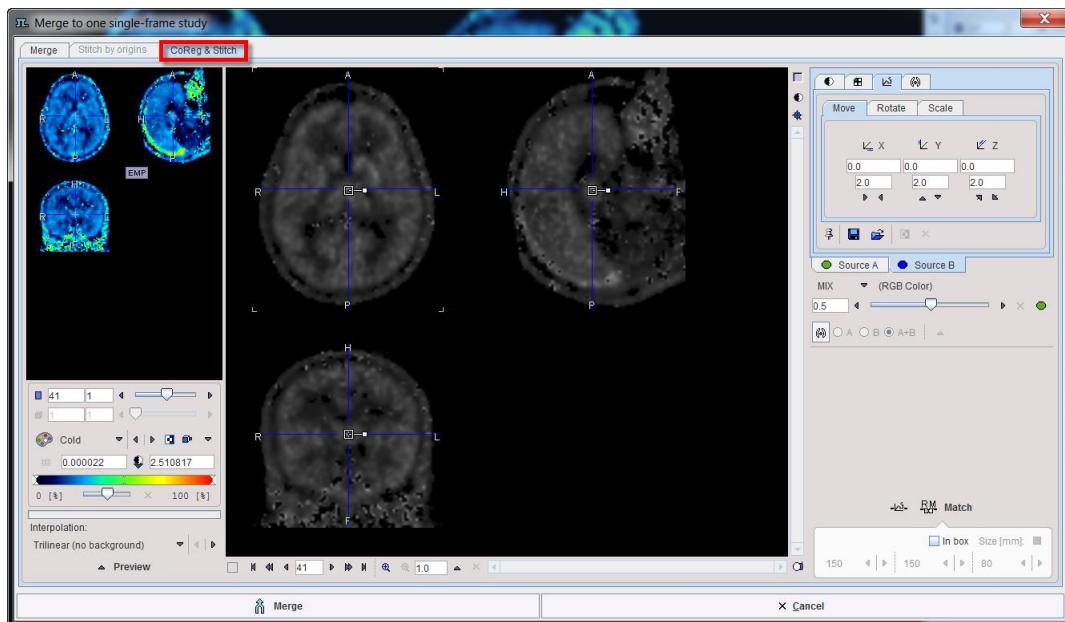


The interface is organized in 3 main areas:

- 1) Fusion controls and source settings on the right hand side
- 2) Fusion display of the source images in the central viewport
- 3) Settings for the stitching procedure and the preview of the results on the right hand side.

CoRegister and Stitch

The procedure can be applied for two images. It consists in a matching step followed by the merging step. Two types of matching are supported: the manual matching and the rigid matching procedure. For detail information about the matching procedures please refer to the **Fusion** guide.



Volume-of-Interest Analysis - Page 3

The purpose of the **VOIs** page is to support Volume-of-Interest analyses on the currently loaded image series. This functionality is described in detail in a *previous chapter* (on page 198).

Image Comparison - Page 4

After images have been loaded, the user can switch to the parallel image viewing page by selecting the **Compare** tab. PVIEW now shows three horizontal image display layouts. There are two display modes available, regular image display, and image fusion.

Regular Image Display Mode

The example below illustrates the regular image display mode, whereby each of the studies may have an independent layout. Note the **Synchronize** (for *Synchronize compare display 1,2,3*) and **Color** boxes highlighted in red. If they are checked, PVIEW switches all three rows to the same layout and synchronizes the images shown. This will only be successful for studies which have the origin at the same location and which cover the same image volume (the pixel size, however, might differ as in the case of a PET/CT study with the same reconstructed field-of-view).

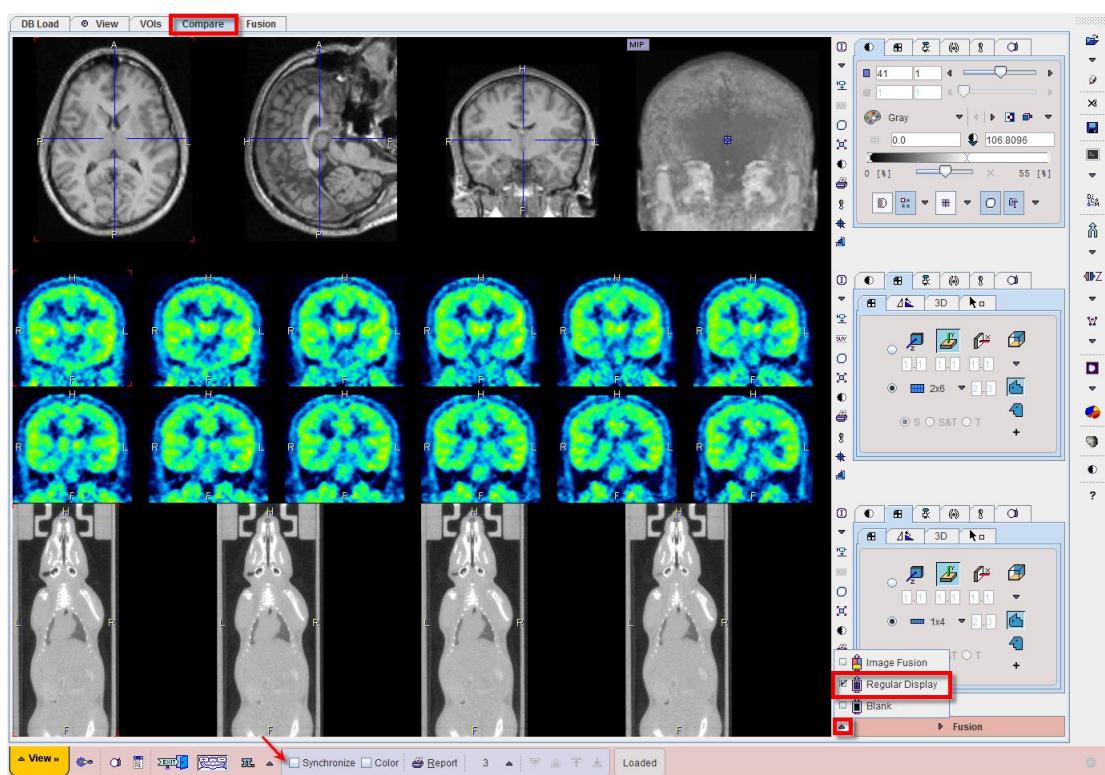
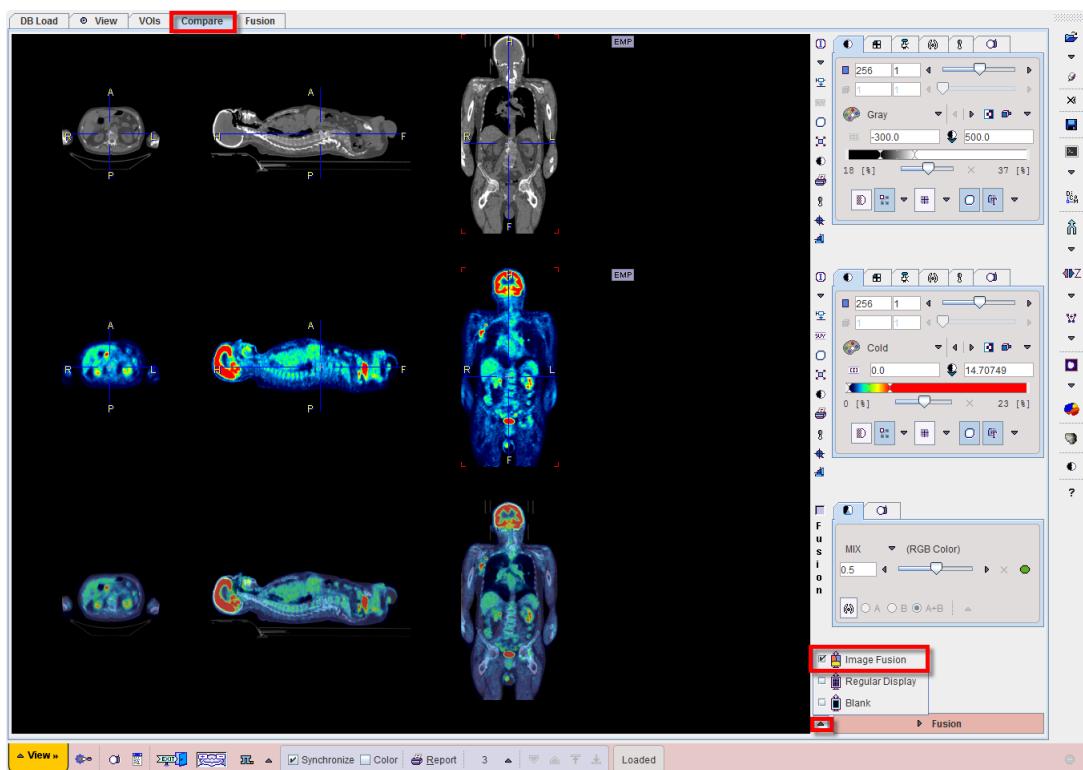


Image Fusion Display Mode

In the fusion display mode the studies in the upper two rows are synchronized, while the third row shows the fusion image. As for synchronized image comparison, the studies must have the origin at the same location and cover the same image volume. A PET/CT example is shown below.



In the fusion mode all *fusion renderings* (on page 184) are available to prepare a meaningful fusion image. Additionally, by activating the **Fusion** tab it is possible to bring up a larger display of the active fusion image.

Switching the Display Mode

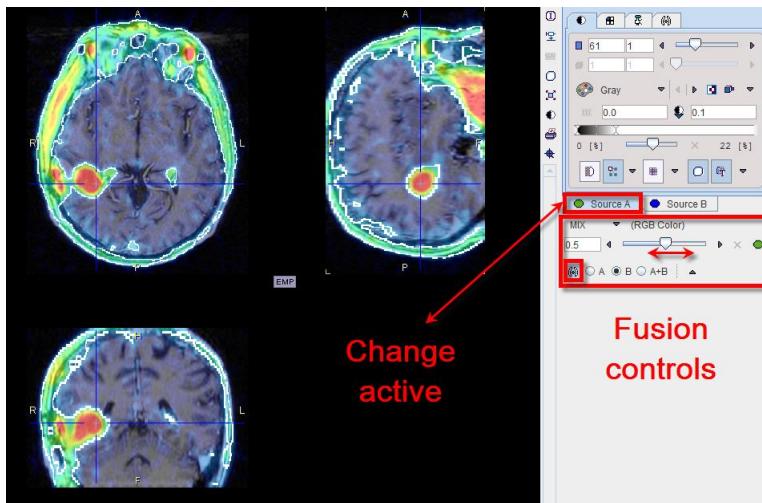
The display modes can be switched using the button close to the right lower corner, which changes according to the situation.

- Selects the image fusion mode.
- Selects the regular image display mode with independent series.
- Sets the third row to blank.

Image Fusion - Page 5 (Optional)

The fusion images in the third row of the **Compare** page are relatively small. To investigate them closer please select the **Fusion** tab which shows a page with just the fusion image and the image controls.

Note: the **Fusion** page is only available if the image fusion tool (PFUS) has been purchased.



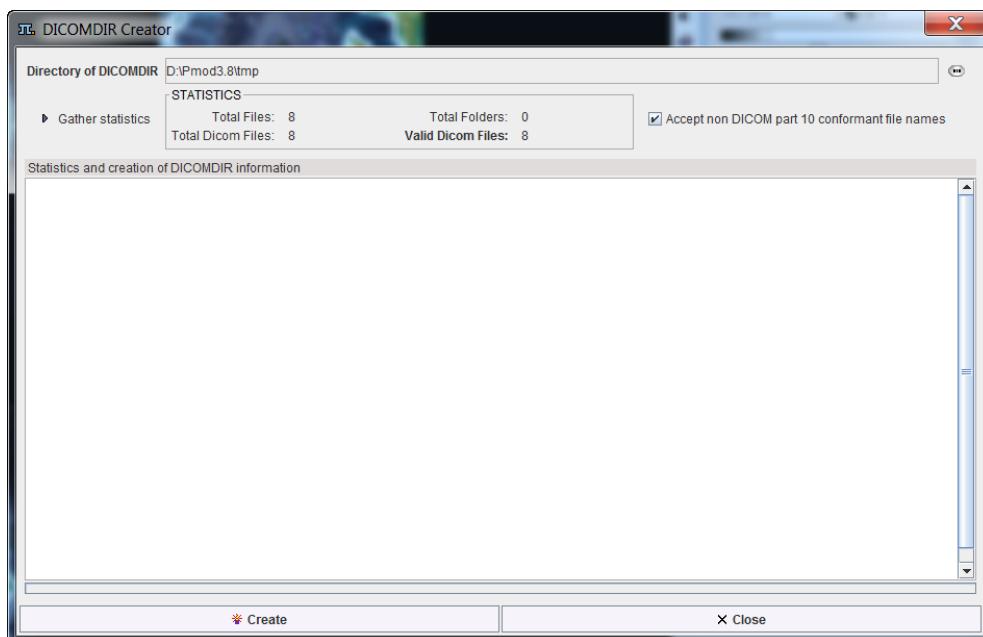
To adjust the color of the studies, either of the tabs **Source A** or **Source B** must first be selected. To show different studies on this page, please go back to the **Compare** page and display them in the upper two rows, then switch again to **Fusion**. All fusion capabilities are available, and the fused representation can be saved in JPEG or in DICOM format.

Note: In contrast to the image fusion tool it is not possible to outline VOIs directly in the fusion images. Selecting the VOI button just switches the display back to the **VOIs** page.

Creation of a DICOMDIR File

The DICOMDIR file format has been defined to organize the access to off-line DICOM part 10 files. For instance, DICOM-compliant data CDs contain a DICOMDIR at the root level which contains a description and access information for all the studies on the CD. In PMOD, the DICOMDIR similarly describes the DICOM files residing under a root directory, eg. *Pmod3.8/data/dicom*. This file can be maintained by PMOD's DICOM server which updates the information after receiving and storing new images (see also the *PMOD DICOM Functionality* (on page 35)).

The PVIEW tool has a handy function to create a DICOMDIR file which registers all DICOM files contained in a directory tree (see also the section *DICOM Part 10 Data Loading* (on page 93)). This function is called by the **Create Dicomdir** entry in the menu **View** and opens the following dialog.



The **Change Folder** opens a file browser to select the root directory of the tree containing the DICOM files to be registered. When **Gather statistics** is activated, all files in the directory tree are analyzed, and the information in the **STATISTICS** section updated. However, to really create the DICOMDIR file, the **Create** button must be activated.

Chapter 11

PMOD Installation and Maintenance

Please read the following information carefully and perform the installation of PMOD and the required supplementary components as described in the sections for the different operating systems.

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Server Administration Interface.....	517

Supported Platforms

Operating Systems

Currently, the full functionality of the PMOD modules is offered on three 64-Bit platforms:

- » Windows Operating Systems starting from Windows 7
- » Linux
- » MacOSX

Java Compatibility

PMOD is based on the Java Runtime Environment (JRE) which evolves over time. In order to avoid compatibility problems PMOD is deployed with a tailored JRE.

Performance

The performance of PMOD is crucially dependent on the the following system characteristics:

- » CPU clock: Java performance increases approximately linearly with the CPU clock; a better internal organization of a CPU usually does not compensate a higher clock rate.
- » Processing Cores: The PKIN, PXMOD and PNEURO tools supports parallel calculations, if a system has more than two cores or CPUs and will be significantly faster. For using the parcellation methodology in PNEURO eight cores or more are recommended.
- » Operating system: Only 64-Bit operating systems are supported because otherwise the RAM available to PMOD is not sufficient for real image processing.
- » RAM: The equipment of the system with at least 16GB RAM is required to avoid swapping and running out of memory for the productive analysis of experimental data.

Windows Installation

The installation for all types of PMOD systems starts with the software extraction from the installation DVD. No other installation is required for PMOD network clients. For PMOD standalone systems and PMOD license server systems, the USB protection key drivers must then be installed and the dedicated license file copied to the *system/lcs* folder.

Note that the USB key driver installation requires administrator privileges.

Installation Overview

PMOD supports two licensing schemes: stand-alone and network licenses.

Licensing, Stand-alone License

The PMOD software stand-alone licensing mechanism consists of two components:

- 1) a **USB protection key** (WIBU-Box/RU, WIBU-SYSTEMS AG, <http://www.wibu.com>), and
- 2) a license file **pstarter.lcs** (in sub-directory *system/lcs* of the PMOD installation).

During PMOD startup the license information encoded in the USB key is read and compared to that in the license file. Only if the two informations match, startup proceeds. Next is a check whether the PMOD version purchased allows running the currently installed version. If all checks are successful, the PMOD ToolBox appears showing the purchased modules, and processing can start. Note that the USB key must remain connected while running PMOD.

Licensing, Network License

The PMOD network licensing scheme consists of a PMOD license server which manages a pool of purchased licenses, and an arbitrary number of PMOD clients which can check out unused licenses from the server. As soon as the PMOD program on a client is closed, the license is returned to the managed server pool. If the PMOD client crashes for some reason, the license is re-collected to the pool after about 15 minutes. On the other hand, if the license server is stopped, the clients show a warning message to the user and allow to continue work for a few minutes. Then, the clients will be stopped, unless the server has been started again.

On the license server PMOD is installed in the same way as for a stand-alone license with the USB key, but the license file turns it into a license server.

On the clients PMOD is also installed in the standard way, *except* that

- » installation of the drivers for the USB protection key is not required;
- » no license file is required.

Note the following:

- » The license server PMOD installation is only intended for server purposes and not for data processing.
- » The license server must be running and the USB key must be connected at all times.
- » The license server and the clients must run the same PMOD version.
- » It is not required that the license server and the clients have the same operating system.

Java Runtime Environment (JRE)

The entire PMOD software has been programmed in Java and therefore requires an appropriate Java Runtime Environment (JRE) to be executed. During PMOD installation, an appropriately configured JRE is extracted into the *java* sub-directory of the PMOD installation. This dedicated JRE will then be used for running PMOD. By this controlled

environment, PMOD will remain unaffected from changes due to automatic upgrade procedures.

Installation Steps

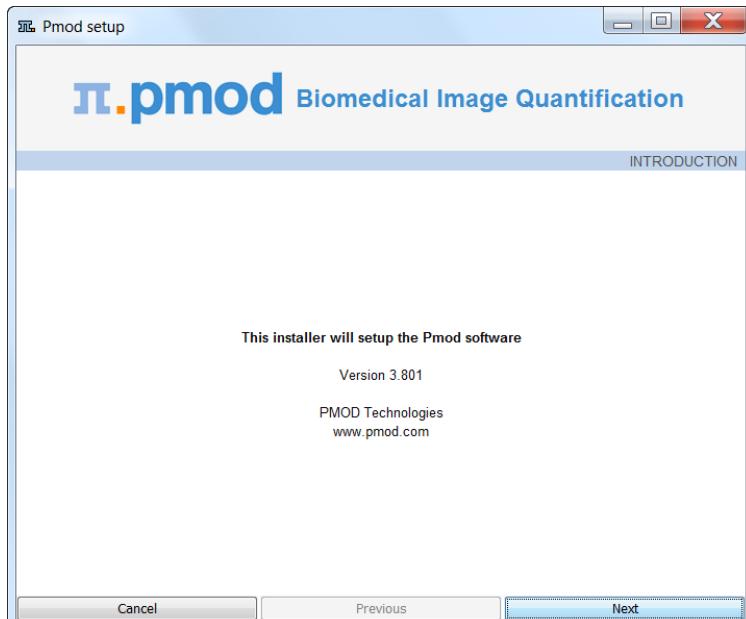
The installation of the PMOD software consists of the following steps which should be performed in the proposed sequence. They are explained in detail in the following installation sections.

- 1) Extraction of the PMOD program files, the JRE, and optionally the example data to the *Pmod3.8* directory in a user-defined directory.
This installation step is required for: **Stand-alone Installation, License Server, Network Clients.**
- 2) Installation of the USB protection key drivers for reading the information from the WIBU-Box/RU plugged into the USB port. *Please do not connect the PMOD USB protection key before this installation has been completed.*
This installation step is required for: **Stand-alone Installation, License Server.**
- 3) Installation of the PMOD license file *pstarter.lcs*. The license file can be downloaded from the **Support** area of the PMOD *website* <http://www.pmod.com> after the personalized login (please refer to the delivery note of your PMOD package for login information).
This installation step is required for: **Stand-alone Installation, License Server.**

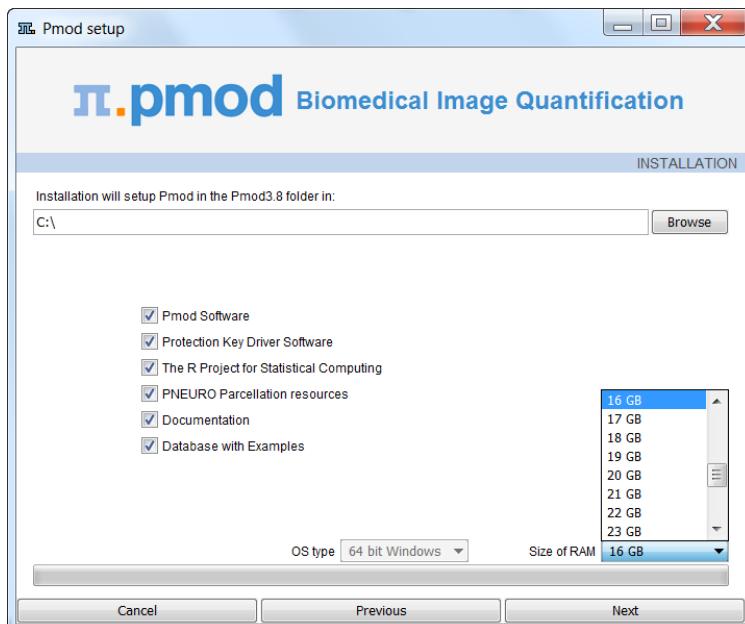
PMOD Software Extraction

The following software extraction procedure must be performed for standalone PMOD installations, for PMOD servers, and also for all PMOD network clients.

Please begin by inserting the PMOD installation DVD. Then start the installer by starting the **RunSetup.bat** in the *Setup/Windows* directory on the DVD by double-clicking. The following installation screen appears



Please use **Next** to proceed and accept the license agreement in the appearing dialog window. After activating **Next** the window for configuring the installation appears.



Please perform the following configurations:

Installation Path

Use the **Browse** button to select the parent directory for the installation. There, the installer will create a new directory **Pmod3.8** for the program files and the data. Please make sure that 3.3GB of free space is available for the full package, and 1.5GB without PNEURO.

Packages

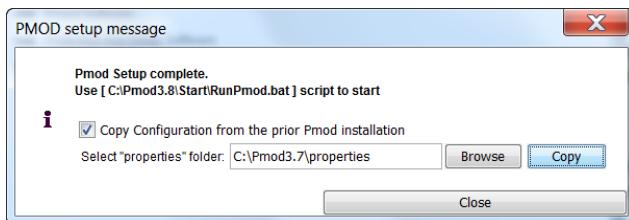
It is highly recommended to install the four packages, the **Pmod Software**, the **Protection Key Driver Software**, the **Documentation**, and the **Database with Examples**. The **Database with Examples** requires about 380MB and will show up as database called **Pmod**. This database will allow getting acquainted with the programs because it contains examples for the different types of data analysis. Note, however, that it is recommended establishing a new database externally to PMOD for productive data processing. The **PNEURO parcellation resources**, should only be enabled, if the PNEURO tool has been licensed, as the required space is 1.8GB.

Properties of Operating System and RAM

The operating system of your target computer needs to be 64-Bit. **Size of RAM** can be set to any size. However, if the specified size exceeds the physical RAM, the system will start swapping after RAM space is exhausted and will become very slow. Therefore it is recommended setting **Size of RAM < physical RAM**.

Installation of the PMOD Environment

The installation is started by the **Install** button. The Pmod3.8 directory is created wherein all PMOD-related files are extracted. At the end of the installation a dialog window is shown. It indicates the command script for starting Pmod3.8, and allows importing the configurations from a prior version. To this end, select the **properties** folder of your prior PMOD installation with the **Browse** button as illustrated below, and activate **Copy Configurations**. This import will also copy the license file, so that Pmod3.8 should immediately run with the familiar environment if your license is valid with the Pmod3.8 version.



PMOD Stand-alone License Installation

Install USB Key Drivers

All the files required for the driver installation have been extracted during the installation of the PMOD software and stored in the PMOD directory tree. The following two steps must be performed to install the USB protection key hardware drivers.

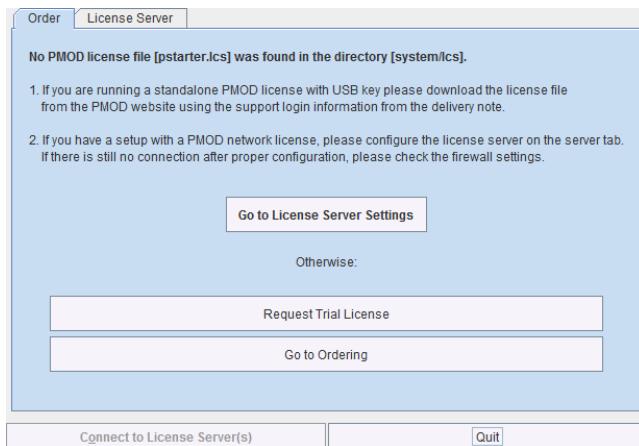
- 1) **Driver installation:** The purpose of this step is to install programs for reading the information from the WIBU-Box/RU plugged into the USB port. The driver installer is located in the directory *Pmod3.8/install/hksetup/Windows*. Please start the program **WkRuntime.exe** and perform a standard installation procedure.
- 2) Now the USB key can be connected to any of the free ports.

Note: If you experience problems during driver installation, you are recommended to download the most recent drivers for the WIBU-KEY (Runtime Kit) from http://wibu.com/download_user.php (http://wibu.com/download_user.php) and try the installation again.

Copy License File

The delivery note that you have received with the PMOD DVD contains account information for logging into the support area of www.pmod.com (<http://www.pmod.com/technologies/support/enter-support.php>). There you will find a license report, and a button for downloading the license file (pstarter.lcs) for your purchased configuration. Please download pstarter.lcs and copy it to the directory *Pmod3.8/system/lcs*.

If the license file is missing when PMOD is started, the following dialog window is shown.



The button **Request Trial License** opens a web browser and points to the location, where the user can fill out a form for requesting a trial license file. The button **Go to ordering** opens a web browser and points to the PMOD ordering form.

The **Go to License Server** panel is only applicable for network licenses. In this case please refer to the next *section* (on page 475).

Important Note: Please do not change pstarter.lcs in any way - a modified license file will not be accepted. Do not open pstarter.lcs in any program, do not rename it, and if you transfer it per FTP, use binary transfer.

Starting PMOD

PMOD can now be started with the command script **RunPmod.bat** in *Pmod3.8/Start*.
Example:

```
C:  
cd "C:\Pmod3.8"  
.\\java\\jre\\bin\\java -Xmx16000M -jar pmod.jar  
pause
```

Notes:

The starting script has been tailored to the installation directory. Therefore, if the Pmod3.8 directory is moved to a different location, the path needs to be adjusted.

The **-Xmx16000M** option specifies the maximum heap memory (16000 MB) that PMOD can allocate. To process large data sets this number should be increased. Caution: The P3D tool may crash, when the reserved space approaches the physical RAM size.

Create a PMOD Starter Shortcut on your Windows desktop:

- 1) Start a Windows explorer and drag the file *Pmod3.8/Start/RunPmod.bat* to the Desktop while pressing CTRL+SHIFT simultaneously.
- 2) Then rename the shortcut to *PMOD*.

- 3) Change its icon by pressing the right mouse button on the shortcut, select **Properties**, and then in **Change Icon** point to *Pmod3.8/resources/icons/Pmod.ico*.

PMOD Network License Installation

PMOD License Server Installation

PMOD Software Installation

The computer for the PMOD license server doesn't require a high performance (e.g. 2GB RAM, 20GB free space on HDD, 64-bit OS), but needs to have access to the WIBU key USB dongle and run continually. Therefore, a robust vintage machine is sufficient as a PMOD license server. Preferably, it is dedicated to serving the PMOD license, because the license server is a standard process rather than a Windows service.

When using a Virtual Machine for PMOD license serving, the USB device from the host server needs to be mapped to the selected Virtual Machine. If there are no USB ports in a host server or the mapping is not possible, a Network USB Device Server can be used. USB hubs from Digi Network, *Silex* <http://www.silexamerica.com/products/connectivity-solutions/device-networking/usb-parallel-connectivity/>, and Belkin have been tested by Wibu-Systems. In such a setup, the WIBU key can be served over the network and mapped to the Virtual Machine. The standard WIBU drivers can be installed and used at the Virtual Machine.

To install the PMOD license server first perform the steps described in the *Stand-alone PMOD Installation* (on page 493) including copying of the license file and plugging the USB key in.

Starting the License Server

The PMOD license server can then be started by executing the *Pmod3.8/Start/RunLcsSvr.bat* script containing the following lines

```
C:  
cd "C:\Pmod3.8"  
.\\java\\jre\\bin\\java -Xmx2G -jar pmtsvr.jar 5000 -ls  
pause
```

The meaning of the command arguments is:

-Xmx2G: Size allocated to the license server
5000: IP port over which the license server communicates
-ls: license server only, no data sharing
-d: This option can be added for more verbose output

Note: The script has been tailored to the installation directory. Therefore, if the Pmod3.8 directory is moved to a different location, the path needs to be adjusted. The USB key needs to remain connected at all times during license server operation.

Log Output

The command window will show startup information and log the checking out/in events as illustrated below.

```
C:\Pmod3.8\Start>C:
C:\Pmod3.8\Start>cd "C:\Pmod3.7"
C:\Pmod3.8>.\java\jre\bin\java -Xmx2G -jar pmtsvr.jar 5000 -ls
Java version: 1.8.0_25
***
Started on license [9]
***
License Server [Version 3.801 A (c) 1996 - 2014 by PMOD
Technologies]
Verbose: false, Secure: false, Compressed: false
***
Port: 5000
Started on: PMOD-CB2/192.168.55.103
License Server: [ ON ] STANDALONE (Use <Ctrl+C> to stop), Number of
Server Licenses: 3
Memory Assigned: 1820 MB
--> License Server started [Fri Jul 25 16:43:40 CEST 2014] : on port
5000
1) 127.0.0.1-192.168.55.103
Number of free licenses: 2

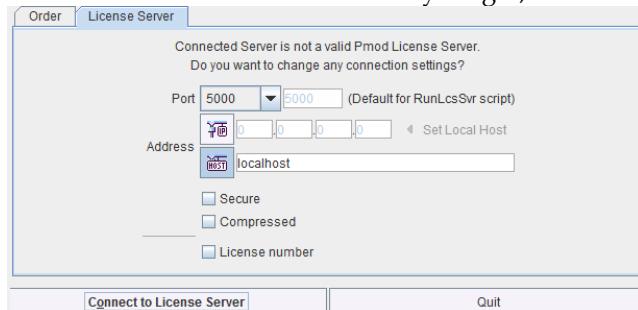
1) 127.0.0.1-192.168.55.103
2) 192.168.55.104-192.168.55.104
Number of free licenses: 1

==> REMOVE: 192.168.55.104-192.168.55.104, 1406299586017
1) 127.0.0.1-192.168.55.103
Number of free licenses: 2

==> REMOVE: 192.168.55.104-192.168.55.104, 1406299586017
1) 127.0.0.1-192.168.55.103
2) 192.168.55.104-192.168.55.104
Number of free licenses: 1

1) 127.0.0.1-192.168.55.103
2) 192.168.55.104-192.168.55.104
3) 127.0.0.1-192.168.55.103
Number of free licenses: 0
```

At this time clients can't connect any longer, but will see the window illustrated below.



Another client needs to stop

```
==> REMOVE: 192.168.55.104-192.168.55.104, 1406299700154
```

```
1) 127.0.0.1-192.168.55.103
2) 127.0.0.1-192.168.55.103
Number of free licenses: 1
```

before connection is possible again and **Connect to License Server** will work.

Multiple Licenses Management

Multiple licenses can be served by a single PMOD installation. In order to use this feature please rename the different license files (*pstarter.lcs*) by appending the license numbers in square brackets (*pstarter[1324].lcs*, *pstarter[427].lcs*, ...) and copy them into the *Pmod3.7/system/lcs* folder. There are two scenarios, a single license server managing multiple licenses simultaneously, or a separate license server for each license.

If the license server script *RunLcsSrv.bat* is started without modification, it will manage all licenses found in the directory. A specific license can then be defined in the *RunPmod.bat* script of the client by the command line option "-

```
lsn[<PORT_NO>.<OPTIONAL_LICENSE_NO>@<IP_ADDRESS>], e.g.:
.\java\jre\bin\java -Xmx16G -jar pmod.jar -
lsn[5000.1324@192.168.55.103] - to acquire license 1324
.\java\jre\bin\java -Xmx16G -jar pmod.jar -
lsn[5000.427@192.168.55.103] - to acquire license 427
```

In order to operate a dedicated server for each license please create a separate server script for each license with the "-lic[<pattern>]" option included, e.g.

```
java -Xmx2G -jar pmtsvr.jar 5000 -ls -lic[1324]
java -Xmx2G -jar pmtsvr.jar 5001 -ls -lic[427]
```

A specific license can then be defined in the *RunPmod.bat* script of the client by the command line option "-lsn[<PORT_NO>@<IP_ADDRESS>]" e.g.

```
.\java\jre\bin\java -Xmx16G -jar pmod.jar -lsn[5000@192.168.55.103] -
to acquire license 1324
.\java\jre\bin\java -Xmx16G -jar pmod.jar -lsn[5001@192.168.55.103] -
to acquire license 427
```

The advantage of separate servers is that the processes can be independently started, stopped and monitored.

Emergency Restart

In the case of connection or license management problems the following procedure is recommended for restoring clean license handling:

- 1) Stop the license server.
- 2) Delete the contents of the *Pmod3.8/system/lcs/lct/* directory.
- 3) Start the license server again.

If this procedure is completed within 5 minutes, no shutdown of running PMOD clients is required.

Client Processing on License Server Machine

Although it is not recommended, client processing can be done on the same machine. To do so, a second PMOD installation has to be prepared as follows:

- 1) Copy Pmod3.8 to Pmod3.8LS. Pmod3.8 will be used for client processing, Pmod3.8LS for license serving.
- 2) Ensure that the license file (pstarter.lcs) is copied to Pmod3.8LS/system/lcs.
- 3) Remove the license file from Pmod3.8/system/lcs.
- 4) Modify Pmod3.8LS/Start/RunLcsSvr.bat to use the new path (Pmod3.8LS). Remove the other .bat files from this Start directory.
- 5) Remove RunLcsSvr.bat from Pmod3.8/Start.
- 6) Use Windows Switch User to login as different user (dedicated to run the License Server) e.g.: admin.pmod.
- 7) Start Pmod3.7LS/Start/RunLcsSvr.bat as admin.pmod user.
- 8) Switch back to the standard user and run Pmod3.8/Start/RunPmod.bat. Provide the computer name or the local IP to access the license server.

Please note that you need to provide proper RW privileges:

- » admin.pmod - RW access to Pmod3.8LS
- » other Pmod users - RW access to Pmod3.8
- » all other non-Pmod users - no access to Pmod3.8 nor Pmod3.8LS

In this way the License Server will be running for all users, as long as the computer is not shut down.

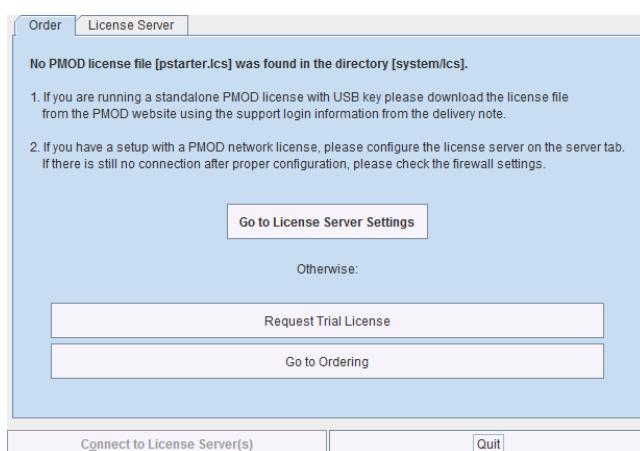
PMOD Network Clients Installation and Configuration

PMOD Software Installation

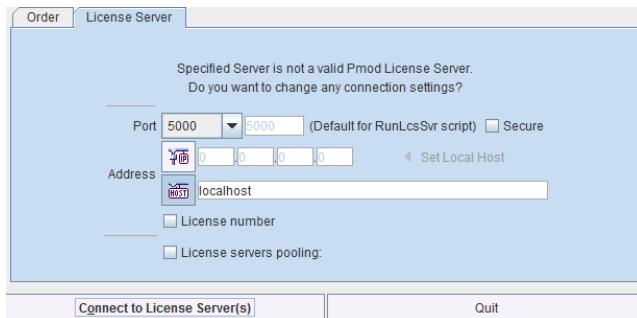
For a PMOD client only the software extraction of the *Stand-Alone PMOD installation* (on page 473) is required. *The license file should not be copied.*

Configuration of the License Server

The PMOD client can then be started by the command script **RunPmod.bat** in the *Pmod3.8/Start* directory. Because no license file is found, the following dialog window is shown.

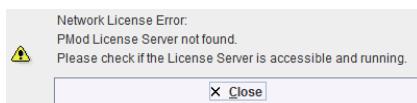


Please select **Go to License Server Settings** to open the **License server** panel illustrated below.



There configure the same **Port** that was configured for the license server (or transaction server), and specify the server **Address** either by entering its IP address, or by entering its host name. If the process employed for license serving uses encryption, please check the appropriate box. If the license server manages several licenses at the same time, enable the **License number** box and enter the number of the license to which you want to connect.

Then activate **Connect to License Server(s)**. If the connection succeeds, the dialog window disappears and PMOD starts up. Otherwise the dialog window



is shown. In this case, please check the configuration of the license server and try again.

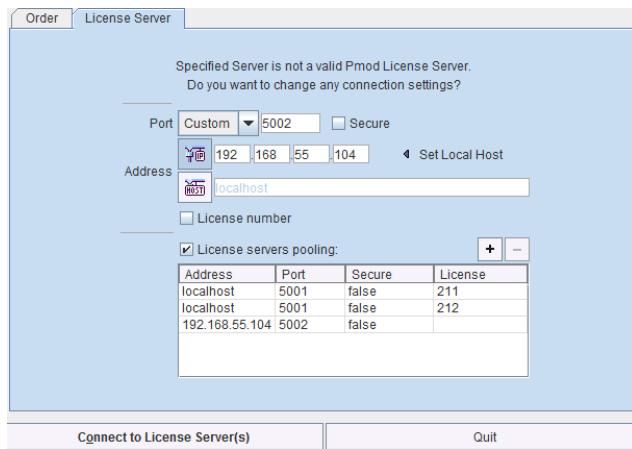
Note: The definition is saved in a file `system/lcs/lcserver.ini`. To provoke display of the License Server dialog window, this file may be deleted.

Multiple License Servers

If a customer has multiple license servers, the proper license server can also directly be specified in **RunPmod.bat** as a client command line option "-

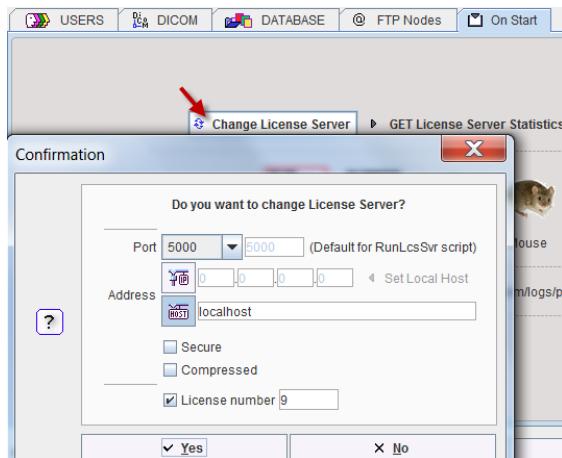
```
lsn [<PORT_NO>.<OPTIONAL_LICENSE_NO>@<IP_ADDRESS>], e.g.  
.\\java\\jre\\bin\\java -Xmx16G -jar pmod.jar -  
lsn[5000.1324@192.168.55.103]
```

Alternatively multiple license servers can be added in the **License servers pooling** configuration by entering their definition in the upper area and then using the + button. Each time the client is started it will connect to the first license server in the list which responds.



License Server Change and Statistics

The license server setting is available on the **On Start** panel of the *Config* (on page 19) tool. The **Change License Server** button opens a dialog window for changing the license server address. If a license server handles multiple network licenses, the **License number** field can be used to address a specific license.



The **GET License Server Statistics** button allows finding out whether there are free licenses left.

LIST OF USED LICENSES:			Number of free licenses: 2
No.	IP	Last use	
1	192.168.55.104	Thu Oct 20 12:18:12 CEST 2016	

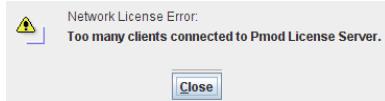
Starting and Stopping a PMOD Client

After the license server has been properly configured, PMOD can be started in exactly the same way as with a stand-alone installation. However, for stopping PMOD the main **Quit** button of the ToolBox should always be used. This will initiate a proper shutdown procedure which returns the license to the license server. Otherwise, when simply killing the

client, it will take about 15 minutes until the license server diagnoses loss of connection and reclaims the lost license.

Connection Problems

If at client startup no more licenses are available from the license server because all are in use, the **License Server** connection dialog window is shown again to give the user a chance for connecting to a different license server. In case the connection is repeated with the same server following message is shown.



If a connection problem with the license server occurs while working, the **License Server** connection dialog window is shown. If it is not possible to re-establish the connection (for instance by restarting the license server) the following warning is displayed



and after five more minutes the PMOD client is finally stopped.

Combination of License and Database Server

Please note that the license server process is based on the transaction server mechanism used for publishing a database. Therefore, if the user is already running a transaction server process on the server system (RunDbSvr.bat, see *Setting up a Transaction Server* (on page 57)), it is *not* necessary to start a dedicated process (RunLcsSrv.bat) just for the license management. The clients can use the same port for requesting a license as for requesting data from the transaction server.

In this context the transaction server option

`-noLS`: database server only

is relevant. This option should be used when running multiple transaction servers. In this case, only one of the transaction servers should start without `-noLS`, namely the one used for license serving.

Version Upgrade in a Complex PMOD Environment

Upgrading a standalone installation of PMOD is straightforward. When using absolute paths for the databases the new PMOD version should be immediately functional after copying the properties folder as the last installation step.

In a more complex environment with clients and servers the following rules should be observed:

- 1) Absolute paths outside the PMOD installation directory should be used for the databases. If this is not the case they should be moved and the paths adjusted in the configuration.
- 2) The databases should be backed up before the migration.
- 3) Server and clients should preferably run the same PMOD version. (To some extent, newer server versions can support older client versions, but not reverse.)
- 4) The PMOD version on the server should be updated first, followed by the clients.

Server Update

Please perform the following tasks sequentially:

- 1) Stop all PMOD servers in the order DICOM servers (DS), transaction servers (TS), license servers (LS).
- 2) Install the new PMOD version and import the properties from the old installation.
- 3) In **Config/DATABASE** switch each database to **Use Direct Connection**, verify it with **Echo DB**, and run **Update & Optimize**. Then switch back to **Use Transaction Server** and generate new starting scripts for the transaction and license servers.
- 4) In **Config/DICOM/DICOM SERVER** generate new scripts for the DICOM Servers.
- 5) Save the configuration and exit PMOD.
- 6) Start the DICOM, transaction and license servers using the new scripts.
- 7) Start PMOD and verify with the **Config** utility, that the TS and DS are working properly. To this end use **Echo TS** and **C-Echo**.
- 8) In case of a network license: Exit PMOD and restart the license server (otherwise a license is blocked).

Client Update

- 1) Install the new PMOD version and import the properties from the old installation. For ATL installations the old properties are not required, as the configuration is centrally stored.
- 2) Start PMOD, provide the license server details when using a network license, and verify the connections with the transaction and DICOM servers.

Troubleshooting

Error reporting

Internal errors typically leave messages of the form

```
java.lang.NullPointerException
at
pmclass.applications.pmgateway.PMgatewayDefaults.getConversionSettings(PMgatewayDefaults.java:143)
at
pmclass.applications.pmgateway.PMgatewayFrame.convert(PMgatewayFrame.java:854)
at
pmclass.applications.pmgateway.PMgatewayFrame.run(PMgatewayFrame.jav
```

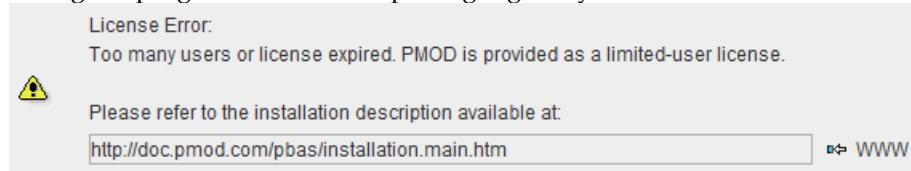
```
a:911)
at java.lang.Thread.run(Thread.java:484)
in the command window or the log file.
```

To allow PMOD Technologies tracking the problem please report the error using the in-built reporting mechanism as described in the problem reporting section. If this is not possible due to a firewall problem please log into the support section on the www.pmod.com website and fill the error message together with a description into the problem report form.

License Errors

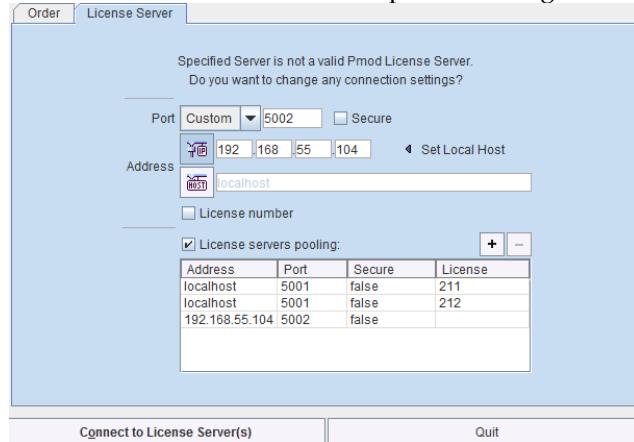
Some of the most likely license errors are:

- » The following error message might appear when restarting PMOD after a crash or after killing the program rather than quitting regularly



In order to be able to restart without waiting time please remove the folder *Pmod3.8/system/lcs/lct* which contains outdated information.

- » If the license file has not been copied to the right directory, you will see a message dialog



Please make sure you copy *pstarter.lcs* to *Pmod3.8/system/lcs*.

- » If the license file has been modified somehow, you will see a message *License Error. Invalid license file (2)*
Please try extracting *pstarter.lcs* again from your e-mail without any modifications.
- » If the USB key cannot be interrogated, because it is not connected or because the driver installation is not up to date, you will see an error message *Hardware license key not accessible*, with additional details. Please make sure that the USB key is connected and the installation was done as described. The driver installation may have to be repeated after an operating system upgrade.

PMOD Server Processes as Windows Services

The PMOD software offers various server processes such as

- » DICOM servers for receiving image data over the network;
- » transaction servers for organizing the access to central databases;
- » license servers for managing the processing clients for a network license.

These processes should be running reliably and at all times. The following sections describe, how they can be implemented as Windows Services, improving their manageability and minimizing the administrative overhead. The advantages of such a setup include:

- » no need for open console or terminal sessions;
- » automatic process restart after system restart or a process termination;
- » service events are stored to the Windows log;
- » information about service starting/rebooting can be mailed to the administrator;
- » PMOD Server output can be redirected to a file;
- » user friendly management tool for checking the server state;
- » remote administration via web browser.

Two solutions are described. One is based on the affordable 3rd party software AlwaysUp from Core Technologies Consulting, LLC. Alternatively, there is a free service manager software available at <https://nssm.cc/> <https://nssm.cc/> which also works.

This services documentation uses PMOD version 3.6, but everything is similar for other versions.

Environment and Prerequisites

Test environment includes following components:

- 1) PMOD software
- 2) NSSM (<https://nssm.cc/> <https://nssm.cc/>)
- 3) Microsoft Windows Server

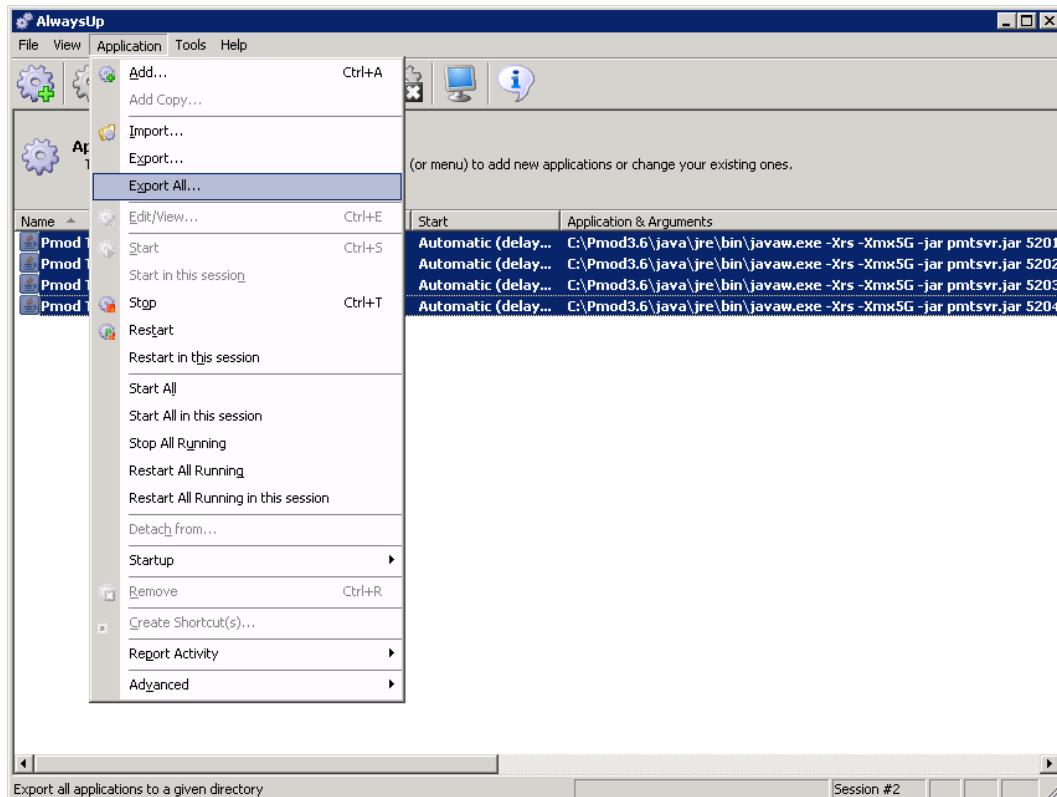
There should be a dedicated Windows account to start services:

- » Account name: pmod.services
- » Account type: Local Administrator

Services Administration

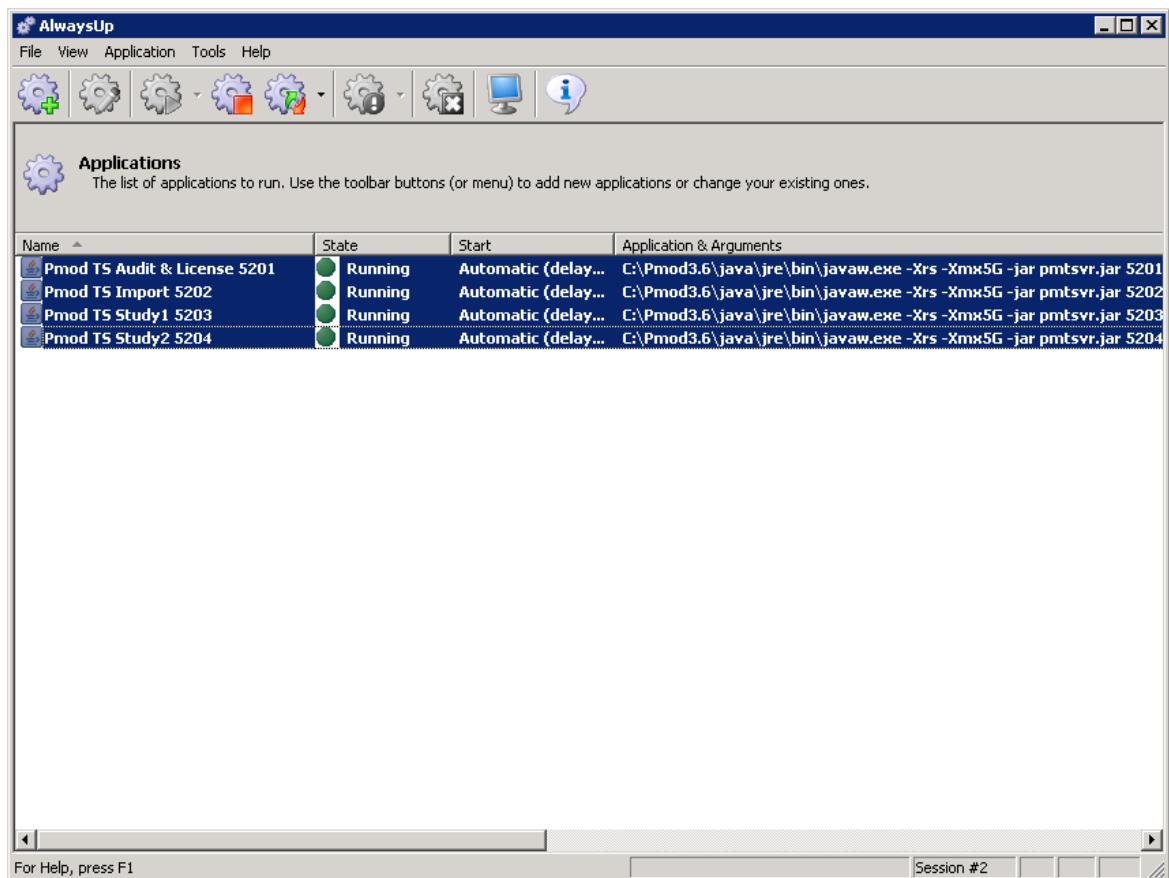
Configuration Backup/Restore

AlwaysUp supports exporting/importing of the services configuration (without stored passwords). It is highly recommended saving a working configuration as a backup. This can also be useful during reconfiguration or migration to a new server.



Server Starting/Stopping

In the **AlwaysUp** interface, the servers can be selected and started/stopped/restarted with one mouse click.

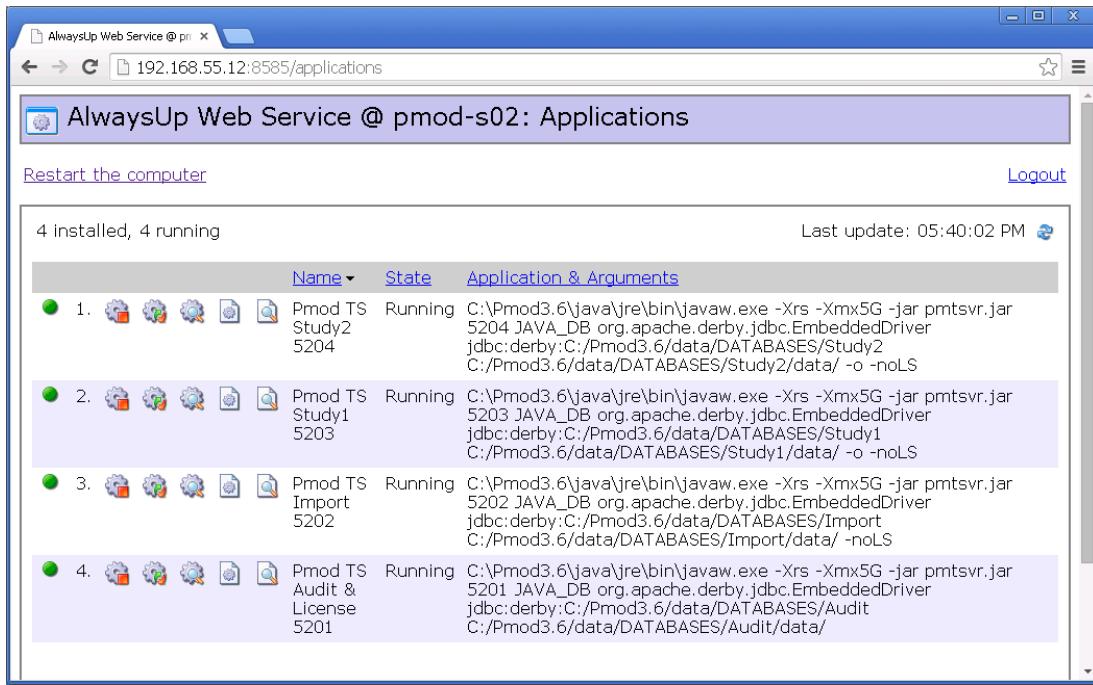


Access to Console Output

If the console output has been redirected to a file, it can easily be inspected using standard text viewers.

Management using AlwaysUp Web Service

Web management is useful for remote administration of the services. It shows the following interface.



It offers:

- » service start/stop/restart,
- » service configuration overview, service report (daily usage, memory usage, events),

Summary

	Tuesday 10/21/14	Monday 10/20/14	Sunday 10/19/14	Saturday 10/18/14	Friday 10/17/14	Thursday 10/16/14	Wednesday 10/15/14
Number of times run	1	0	0	0	1	1	1
Number of restarts	0	0	0	0	0	0	0
Memory: Average / Peak	78.0 / 80.0 MB	78.0 / 80.0 MB	78.0 / 80.0 MB	78.0 / 80.0 MB	77.2 / 80.0 MB	72.8 / 80.0 MB	72.0 / 80.0 MB
CPU: Average / Peak	0 / 1 %	0 / 0 %	0 / 0 %	0 / 1 %	0 / 12 %	0 / 9 %	0 / 10 %
Time running	17.0 hours	24.0 hours	24.0 hours	24.0 hours	23.9 hours	23.8 hours	23.9 hours
Availability	71 %	100 %	100 %	100 %	100 %	99 %	100 %

- » quick output view,
- » Windows Server restart (this option can be disabled).

Mac OS X Installation

The installation for all types of PMOD systems starts with the software extraction from the installation DVD. No other installation is required for PMOD network clients. For PMOD standalone systems and PMOD license server systems, the USB protection key drivers must then be installed and the dedicated license file copied to the *system/lcs* folder.

Some parts of the PMOD installation may require administrator privileges. If your account does not have these rights, please ask your IT support to perform the following installation steps.

Installation Overview

PMOD supports two licensing schemes: stand-alone and network licenses.

Licensing, Stand-alone License

The PMOD software stand-alone licensing mechanism consists of two components:

- 1) a **USB protection key** (WIBU-Box/RU, WIBU-SYSTEMS AG, <http://www.wibu.com>), and
- 2) a license file **pstarter.lcs** (in sub-directory *system/lcs* of the PMOD installation).

During PMOD startup the license information encoded in the USB key is read and compared to that in the license file. Only if the two informations match, startup proceeds. Next is a check whether the PMOD version purchased allows running the currently installed version. If all checks are successful, the PMOD ToolBox appears showing the purchased modules, and processing can start. Note that the USB key must remain connected while running PMOD.

Licensing, Network License

The PMOD network licensing scheme consists of a PMOD license server which manages a pool of purchased licenses, and an arbitrary number of PMOD clients which can check out unused licenses from the server. As soon as the PMOD program on a client is closed, the license is returned to the managed server pool. If the PMOD client crashes for some reason, the license is re-collected to the pool after about 15 minutes. On the other hand, if the license server is stopped, the clients show a warning message to the user and allow to continue work for a few minutes. Then, the clients will be stopped, unless the server has been started again.

On the license server PMOD is installed in the same way as for a stand-alone license with the USB key, but the license file turns it into a license server.

On the clients PMOD is also installed in the standard way, *except* that

- » installation of the drivers for the USB protection key is not required;
- » no license file is required.

Note the following:

- » The license server PMOD installation is only intended for server purposes and not for data processing.
- » The license server must be running and the USB key must be connected at all times.
- » The license server and the clients must run the same PMOD version.
- » It is not required that the license server and the clients have the same operating system.

Java Runtime Environment (JRE)

The entire PMOD software has been programmed in Java and therefore requires an appropriate Java Runtime Environment (JRE) to be executed. During PMOD installation, an appropriately configured JRE is extracted into the *java* sub-directory of the PMOD installation. This dedicated JRE will then be used for running PMOD. By this controlled

environment, PMOD will remain unaffected from changes due to automatic upgrade procedures.

Installation Steps

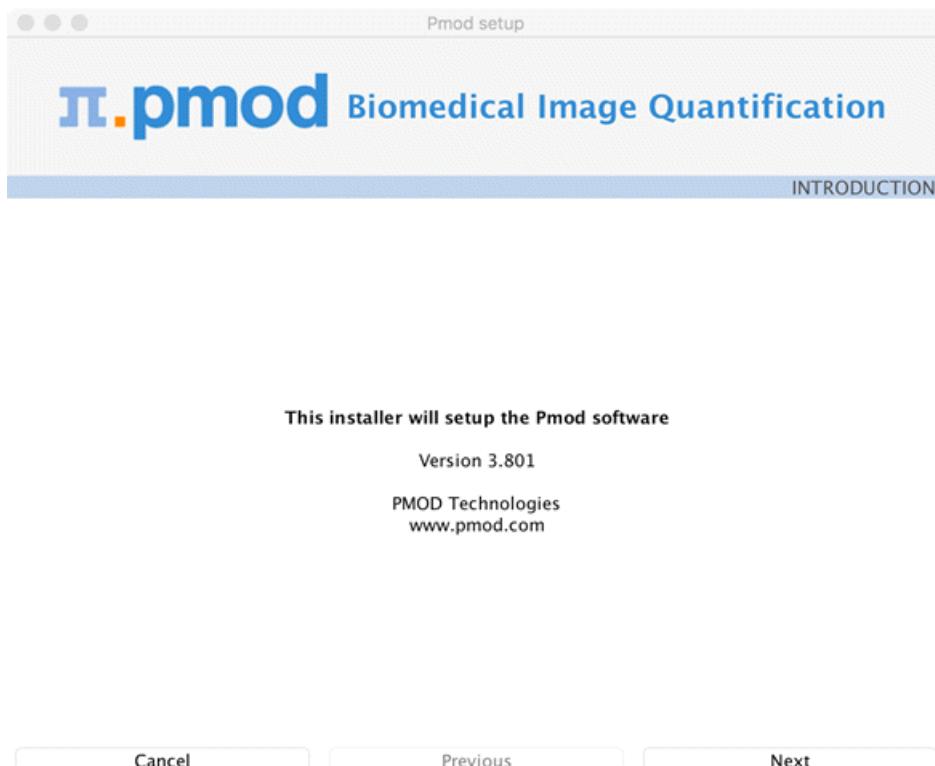
The installation of the PMOD software consists of the following steps which should be performed in the proposed sequence. They are explained in detail in the following installation sections.

- 1) Extraction of the PMOD program files, the JRE, and optionally the example data to the *Pmod3.8* directory in a user-defined directory.
This installation step is required for: **Stand-alone Installation, License Server, Network Clients.**
- 2) Installation of the USB protection key drivers for reading the information from the WIBU-Box/RU plugged into the USB port. *Please do not connect the PMOD USB protection key before this installation has been completed.*
This installation step is required for: **Stand-alone Installation, License Server.**
- 3) Installation of the PMOD license file *pstarter.lcs*. The license file can be downloaded from the **Support** area of the PMOD *website* <http://www.pmod.com> after the personalized login (please refer to the delivery note of your PMOD package for login information).
This installation step is required for: **Stand-alone Installation, License Server.**

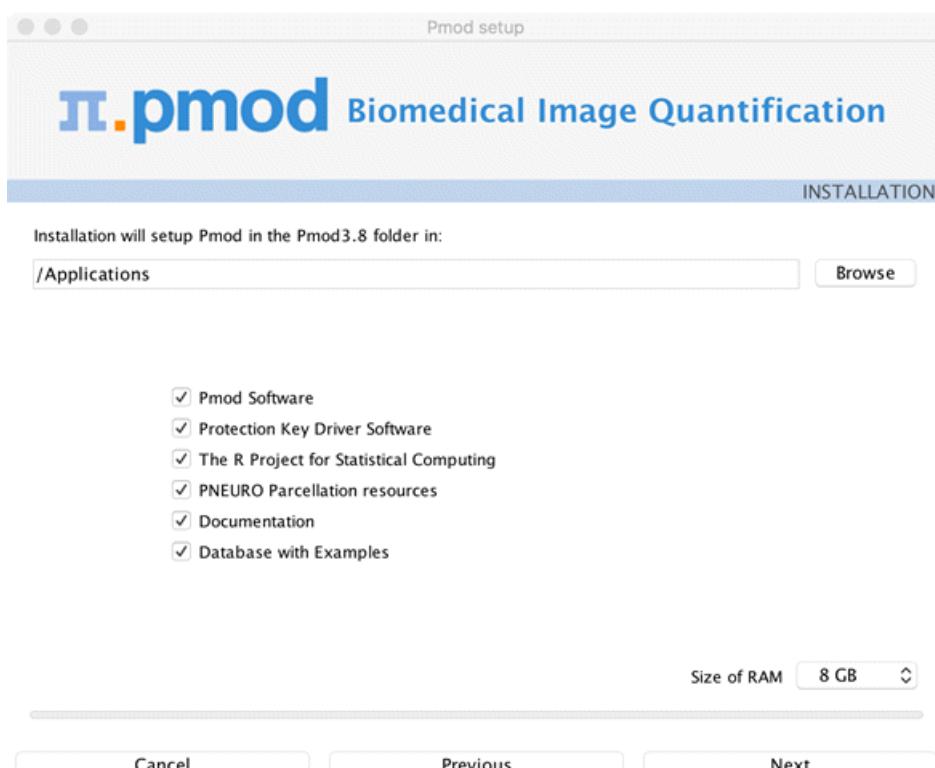
PMOD Software Extraction

The following software extraction procedure must be performed for standalone PMOD installations, for PMOD servers, and also for all PMOD network clients.

Please begin by inserting the PMOD installation DVD. Then start the installer by starting the **RunSetup.command** in the *Setup/MacOSX* directory on the DVD by double-clicking. The following installation screen appears



Please use **Next** to proceed and accept the license agreement in the appearing dialog window. After activating **Next** the window for configuring the installation appears.



Please perform the following configurations:

Installation Path

Use the **Browse** button to select the parent directory for the installation. There, the installer will create a new directory **Pmod3.8** for the program files and the data. Please make sure that 3.3GB of free space is available for the full package, and 1.5GB without PNEURO.

Packages

It is highly recommended to install the four packages, the **Pmod Software**, the **Protection Key Driver Software**, the **Documentation**, and the **Database with Examples**. The **Database with Examples** requires about 380MB and will show up as database called **Pmod**. This database will allow getting acquainted with the programs because it contains examples for the different types of data analysis. Note, however, that it is recommended establishing a new database externally to PMOD for productive data processing. The **PNEURO parcellation resources**, should only be enabled, if the PNEURO tool has been licensed, as the required space is 1.8GB.

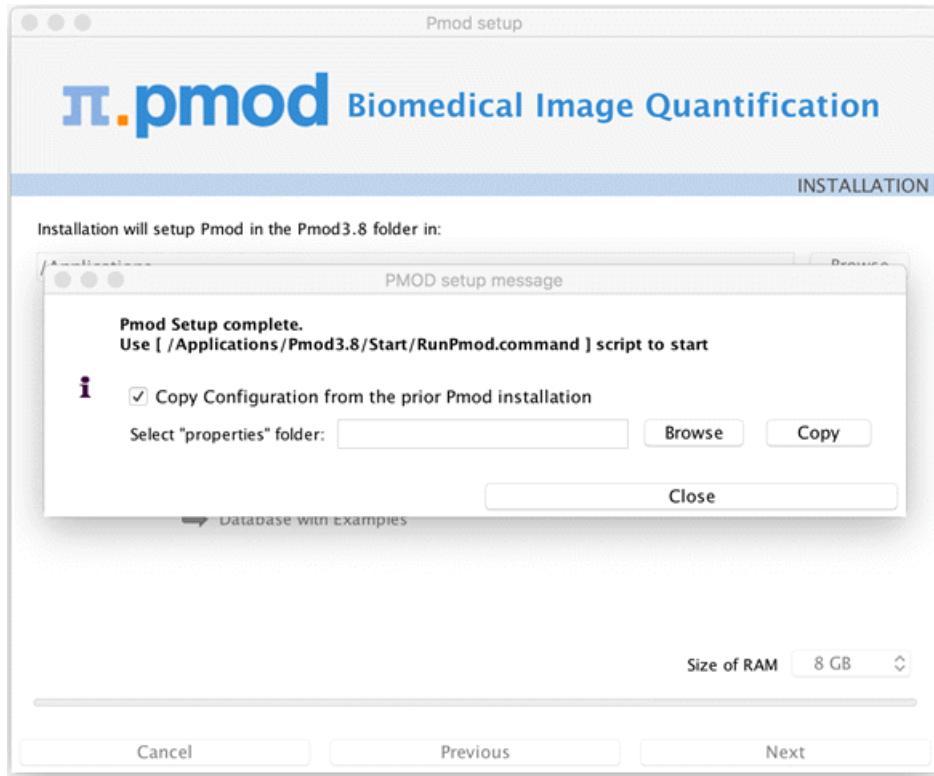
Properties of Operating System and RAM

The operating system of your target computer needs to be 64-Bit. **Size of RAM** can be set to any size. However, if the specified size exceeds the physical RAM, the system will start swapping after RAM space is exhausted and will become very slow. Therefore it is recommended setting **Size of RAM < physical RAM**.

Installation of the PMOD Environment

The installation is started by the **Install** button. The Pmod3.8 directory is created wherein all PMOD-related files are extracted. If the installing user has no write permission in the parent directory, a dialog window appears which reports an installation problem. In this case please change the writing permissions of the installation as root user, or try the installation again using a different installation directory.

At the end of the installation a dialog window is shown. It indicates the command script for starting Pmod3.8, and allows importing the configurations from a prior version. To this end, select the **properties** folder of your prior PMOD installation with the **Browse** button as illustrated below, and activate **Copy Configurations**. This import will also copy the license file, so that Pmod3.8 should immediately run with the familiar environment if your license is valid with the Pmod3.8 version.



PMOD Stand-alone License Installation

Install USB Key Drivers

All the files required for the driver installation have been extracted during the installation of the PMOD software and stored in the PMOD directory tree. Browse to the directory */Applications/Pmod3.8/install/hksetup/MacOSX*

First double-click **WkRuntimeUser_6.32.500.dmg**, then **WkInstall.pkg**, and perform a standard installation



Note: If you experience problems during driver installation, you are recommended downloading the most recent drivers for the WIBU-KEY (Runtime Kit) from http://wibu.com/download_user.php (http://wibu.com/download_user.php) and try the installation again. Also, in some cases, a reboot may be required after driver installation.

License File

The delivery note you have received with the PMOD CD contains account information for logging into the support area of www.pmod.com (<http://www.pmod.com/technologies/support/enter-support.php>). There you will find a license report, and a button for downloading the license file for your purchased configuration. Please download pstarter.lcs and copy it to the directory /Applications/Pmod3.8/system/lcs.

Important Note: Please do not change pstarter.lcs in any way - a modified license file will not be accepted. Do not open pstarter.lcs in any program, do not rename it, and if you transfer it per FTP, use binary transfer.

Start PMOD

PMOD can now be started by double-clicking the **RunPmod.command** script in /Applications/Pmod3.8/Start/. Depending on the selected configuration it contains the following commands:

```
cd '/Applications/Pmod3.8'  
./java/jre/bin/java -Xmx16000M -jar pmod.jar
```

Alternatively, the script can be dragged once from the finder to the Mac OS X taskbar to create a shortcut. From then on, PMOD can be started using this shortcut.

Notes:

The script has been tailored to the installation directory. Therefore, if the Pmod3.8 directory is moved to a different location, the path needs to be adjusted.

The **-Xmx16000M** option specifies the maximum heap memory (8000 MB) that PMOD can allocate. To process large data sets this number should be increased. Caution: The P3D tool may crash, when the reserved space approaches the physical RAM size.

Change Permission Settings of Directories for writing

To allow other users than root the full usage of PMOD it is important to open some key PMOD directories for writing:

```
chmod -R ugo+w /Applications/Pmod3.8/properties  
chmod -R ugo+w /Applications/Pmod3.8/data
```

There may be other directories you have to open for writing later on, if several users are working with the same PMOD installation.

PMOD Network License Installation

PMOD License Server Installation

PMOD Software Installation

The computer for the PMOD license server doesn't require a high performance (e.g. 2GB RAM, 20GB free space on HDD, 64-bit OS), but needs to have access to the WIBU key USB dongle and run continually. Therefore, a robust vintage machine is sufficient as a PMOD license server. Preferably, it is dedicated to serving the PMOD license, because the license server is a standard process rather than a Windows service.

When using a Virtual Machine for PMOD license serving, the USB device from the host server needs to be mapped to the selected Virtual Machine. If there are no USB ports in a host server or the mapping is not possible, a Network USB Device Server can be used. USB hubs from Digi Network, *Silex* <http://www.silexamerica.com/products/connectivity-solutions/device-networking/usb-parallel-connectivity/>, and Belkin have been tested by Wibu-Systems. In such a setup, the WIBU key can be served over the network and mapped to the Virtual Machine. The standard WIBU drivers can be installed and used at the Virtual Machine.

To install the PMOD license server first perform the steps described in the *Stand-alone PMOD Installation* (on page 493) including copying of the license file and plugging the USB key in.

Starting the License Server

The PMOD license server can then be started by executing the **RunLcsSvr.command** script in */Applications/Pmod3.7/Start* containing the following lines (64-Bit version)

```
cd '/Applications/Pmod3.8'
./java/jre/bin/java -Xmx2G -jar pmtsvr.jar 5000 -ls
```

The meaning of the command arguments is:

- Xmx2G: Size allocated to the license server
- 5000: IP port over which the license server communicates
- ls: license server only, no data sharing
- d: This option can be added for more verbose output

Note: The script has been tailored to the installation directory. Therefore, if the Pmod3.8 directory is moved to a different location, the path needs to be adjusted.

Log Output

The command window will show startup information and log the checking out/in events as illustrated below. In this example, two clients are started, and then the one of them is stopped again.

```
MD03845:/Applications/Pmod3.8/Start/RunLcsSvr.command
 ***
 Started on license [9]
```

```
***  

License Server [Version 3.801 A (c) 1996 - 2016 by PMOD  

Technologies]  

Verbose: false, Secure: false, Compressed: false  

***  

Port: 5000  

Started on: PMOD-CB2/192.168.55.103  

License Server: [ ON ] STANDALONE (Use <Ctrl+C> to stop), Number of  

Server Licenses: 3  

Memory Assigned: 1820 MB  

--> License Server started [Fri Jul 25 16:43:40 CEST 2014] : on port  

5000  

1) 127.0.0.1-192.168.55.103  

Number of free licenses: 2  

1) 127.0.0.1-192.168.55.103  

2) 192.168.55.104-192.168.55.104  

Number of free licenses: 1  

==> REMOVE: 192.168.55.104-192.168.55.104, 1406299586017  

1) 127.0.0.1-192.168.55.103  

Number of free licenses: 2  

==> REMOVE: 192.168.55.104-192.168.55.104, 1406299586017  

1) 127.0.0.1-192.168.55.103  

2) 192.168.55.104-192.168.55.104  

Number of free licenses: 1  

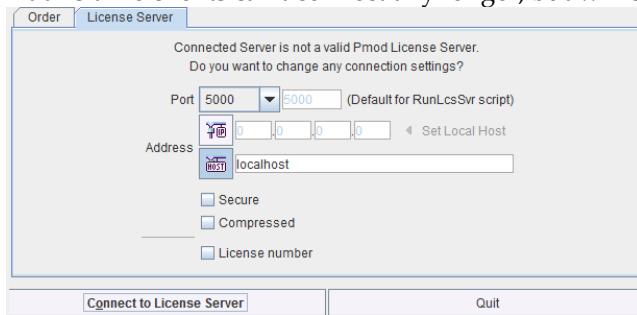
1) 127.0.0.1-192.168.55.103  

2) 192.168.55.104-192.168.55.104  

3) 127.0.0.1-192.168.55.103  

Number of free licenses: 0
```

At this time clients can't connect any longer, but will see the window illustrated below.



Another client needs to stop

```
==> REMOVE: 192.168.55.104-192.168.55.104, 1406299700154  

1) 127.0.0.1-192.168.55.103  

2) 127.0.0.1-192.168.55.103  

Number of free licenses: 1
```

before connection is possible again and **Connect to License Server** will work.

Multiple Licenses Management

Multiple licenses can be served by a single PMOD installation. In order to use this feature please rename the different license files (*pstarter.lcs*) by appending the license numbers in square brackets (*pstarter[1324].lcs*, *pstarter[427].lcs*, ...) and copy them into the

Pmod3.7/system/lcs folder. There are two scenarios, a single license server managing multiple licenses simultaneously, or a separate license server for each license.

If the license server script *RunLcsSvr.bat* is started without modification, it will manage all licenses found in the directory. A specific license can then be defined in the *RunPmod.bat* script of the client by the command line option "-

```
lsn[<PORT_NO>.<OPTIONAL_LICENSE_NO>@<IP_ADDRESS>], e.g.:  
.\\java\\jre\\bin\\java -Xmx16G -jar pmod.jar -  
lsn[5000.1324@192.168.55.103] - to acquire license 1324  
.\\java\\jre\\bin\\java -Xmx16G -jar pmod.jar -  
lsn[5000.427@192.168.55.103] - to acquire license 427
```

In order to operate a dedicated server for each license please create a separate server script for each license with the "-lic[<pattern>]" option included, e.g.

```
java -Xmx2G -jar pmtsvr.jar 5000 -ls -lic[1324]  
java -Xmx2G -jar pmtsvr.jar 5001 -ls -lic[427]
```

A specific license can then be defined in the *RunPmod.bat* script of the client by the command line option "-lsn[<PORT_NO>@<IP_ADDRESS>]" e.g.

```
.\\java\\jre\\bin\\java -Xmx16G -jar pmod.jar -lsn[5000@192.168.55.103] -  
to acquire license 1324  
.\\java\\jre\\bin\\java -Xmx16G -jar pmod.jar -lsn[5001@192.168.55.103] -  
to acquire license 427
```

The advantage of separate servers is that the processes can be independently started, stopped and monitored.

Emergency Restart

In the case of connection or license management problems the following procedure is recommended for restoring clean license handling:

- 1) Stop the license server.
- 2) Delete the contents of the *Pmod3.8/system/lcs/lct/* directory.
- 3) Start the license server again.

If this procedure is completed within 5 minutes, no shutdown of running PMOD clients is required.

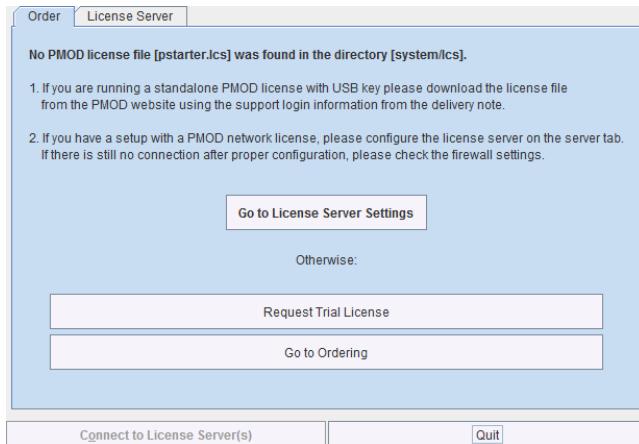
PMOD Network Clients Installation and Configuration

PMOD Software Installation

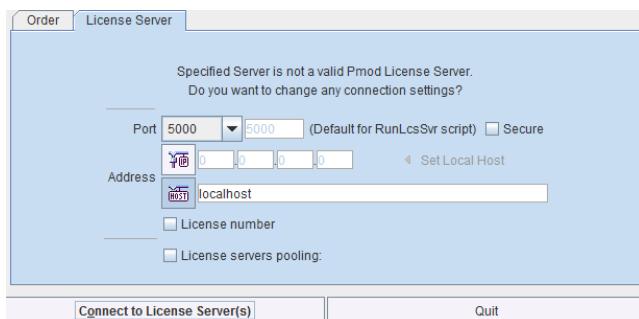
For a PMOD client only the software extraction of the *Stand-Alone PMOD installation* (on page 473) is required. *The license file should not be copied.*

Configuration of the License Server

The PMOD client can then be started by the command script **RunPmod.command** in the *Pmod3.8/Start* directory. As no license file is found, the following dialog window is shown.

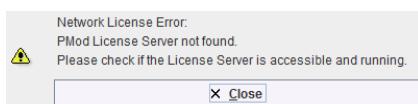


Please select the **Go to License Server Settings** button to open the License server panel illustrated below.



Please configure the same **Port** that you have configured for the license server (or transaction server), and specify the server **Address** either by entering its IP address, or by entering its host name. If the process employed for license serving uses compression or encryption, please check the appropriate boxes. If the license server manages several licenses at the same time, enable the **License number** box and enter the number of the license to which you want to connect. Then activate **Yes**.

If the connection succeeds, the dialog window disappears and PMOD starts up. Otherwise the dialog

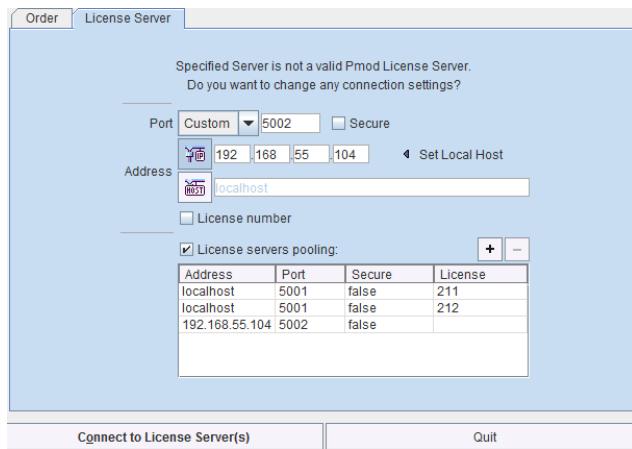


is shown. In this case, please check the configuration of the license server and try again.

If a customer has multiple license servers, the proper license server can also be specified in **RunPmod.command** as a client command line option by:

`-lsn [<PORT_NO>.]<OPTIONAL_LICENSE_NO>@<IP_ADDRESS>]`

Alternatively multiple license servers can be added in the **License servers pooling** configuration by entering their definition in the upper area and then using the + button. Each time the client is started it will connect to the first license server in the list which responds.

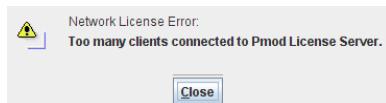


Starting and Stopping a PMOD Client

After the license server has been properly configured, PMOD can be started in exactly the same way as with a stand-alone installation. However, for stopping PMOD the main **Quit** button of the ToolBox should always be used. This will initiate a proper shutdown procedure which returns the license to the license server. Otherwise, when simply killing the client, it will take about 15 minutes until the license server diagnoses loss of connection and reclaims the lost license.

Connection Problems

If at client startup no more licenses are available from the license server because all are in use, the **License Server** connection dialog window is shown again to give the user a chance for connecting to a different license server. In case the connection is repeated with the same server following message is shown.



If a connection problem with the license server occurs while working, the **License Server** connection dialog window is shown. If it is not possible to re-establish the connection (for instance by restarting the license server) the following warning is displayed



and after five more minutes the PMOD client is finally stopped.

Combination of License and Database Server

Please note that the license server process is based on the transaction server mechanism used for publishing a database. Therefore, if the user is already running a transaction server process on the server system (RunDbSvr.command, see *Setting up a Transaction Server* (on page 57)), it is *not* necessary to start a dedicated process (RunLcsSvr.command) just for the license management. The clients can use the same port for requesting a license as for requesting data from the transaction server.

In this context the transaction server option

`-noLS`: database server only

is relevant. This option should be used when running multiple transaction servers. In this case, only one of the transaction servers should start without `-noLS`, namely the one used for license serving.

Version Upgrade in a Complex PMOD Environment

Upgrading a standalone installation of PMOD is straightforward. When using absolute paths for the databases the new PMOD version should be immediately functional after copying the properties folder as the last installation step.

In a more complex environment with clients and servers the following rules should be observed:

- 1) Absolute paths outside the PMOD installation directory should be used for the databases. If this is not the case they should be moved and the paths adjusted in the configuration.
- 2) The databases should be backed up before the migration.
- 3) Server and clients should preferably run the same PMOD version. (To some extent, newer server versions can support older client versions, but not reverse.)
- 4) The PMOD version on the server should be updated first, followed by the clients.

Server Update

Please perform the following tasks sequentially:

- 1) Stop all PMOD servers in the order DICOM servers (DS), transaction servers (TS), license servers (LS).
- 2) Install the new PMOD version and import the properties from the old installation.
- 3) In **Config/DATABASE** switch each database to **Use Direct Connection**, verify it with **Echo DB**, and run **Update & Optimize**. Then switch back to **Use Transaction Server** and generate new starting scripts for the transaction and license servers.
- 4) In **Config/DICOM/DICOM SERVER** generate new scripts for the DICOM Servers.
- 5) Save the configuration and exit PMOD.
- 6) Start the DICOM, transaction and license servers using the new scripts.
- 7) Start PMOD and verify with the **Config** utility, that the TS and DS are working properly. To this end use **Echo TS** and **C-Echo**.

- 8) In case of a network license: Exit PMOD and restart the license server (otherwise a license is blocked).

Client Update

- 1) Install the new PMOD version and import the properties from the old installation. For ATL installations the old properties are not required, as the configuration is centrally stored.
- 2) Start PMOD, provide the license server details when using a network license, and verify the connections with the transaction and DICOM servers.

Troubleshooting

Error reporting

Internal errors typically leave messages of the form

```
java.lang.NullPointerException
at
pmclass.applications.pmgateway.PMgatewayDefaults.getConversionSettings(PMgatewayDefaults.java:143)
at
pmclass.applications.pmgateway.PMgatewayFrame.convert(PMgatewayFrame.java:854)
at
pmclass.applications.pmgateway.PMgatewayFrame.run(PMgatewayFrame.java:911)
at java.lang.Thread.run(Thread.java:484)
```

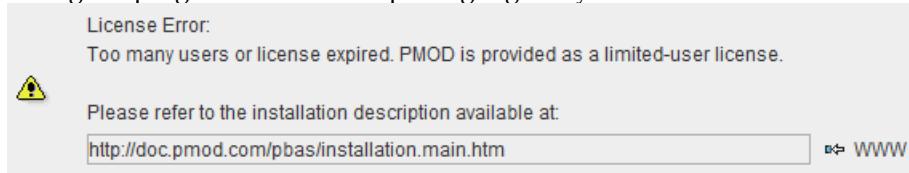
in the command window or the log file.

To allow PMOD Technologies tracking the problem please report the error using the in-built reporting mechanism as described in the problem reporting section. If this is not possible due to a firewall problem please log into the support section on the www.pmod.com website and fill the error message together with a description into the problem report form.

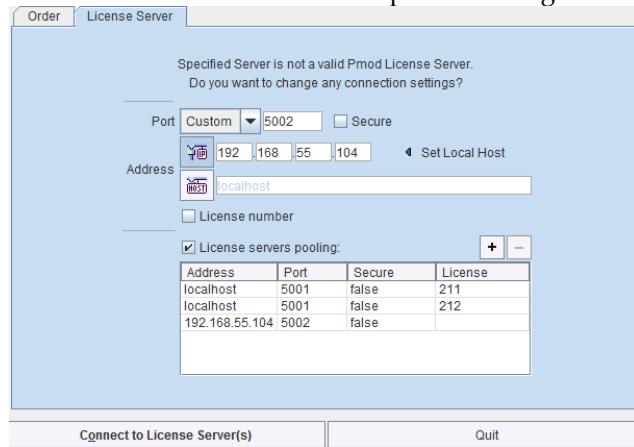
License Errors

Some of the most likely license errors are:

- » The following error message might appear when restarting PMOD after a crash or after killing the program rather than quitting regularly



- » If the license file has not been copied to the right directory, you will see a message



Please copy *pstarter.lcs* to */Applications/Pmod3.8/system/lcs*

- » If the license file has been modified somehow, you will see a message *License Error. Invalid license file (2)*
Please try to extract *pstarter.lcs* again from your e-mail without any modifications.
- » If the USB key cannot be read because it is not connected or because the driver installation is not up to date, you will see an error message *Hardware license key not accessible* with additional details.
Please make sure that the USB key is connected and the installation was done as described. The installation may have to be repeated after an operating system upgrade.

3D Rendering Problems

The 3D rendering solution of PMOD may fail on some older MacOSX systems. Please try solving the problem as follows:

- 1) Java is already installed on Machine:
 - » copy content of "Pmod3.8/Pmod/java/ext/j3d" to "/Library/Java/Extensions"
 - » check whether 3D works in PMOD
 - » if not, install Java 1.8 using the latest installer form the Oracle *download page* <http://www.oracle.com/technetwork/java/javase/downloads/jdk8-downloads-2133151.html> and copy content of "Pmod3.8/java/ext/j3d" to "/Library/Java/Extensions"
 - » check whether 3D works in PMOD
 - » if not, there is no simple solution at this time.
- 1) Java is not yet installed on Machine
 - » install Java 1.8 using the latest installer form the Oracle *download page* <http://www.oracle.com/technetwork/java/javase/downloads/jdk8-downloads-2133151.html> and copy content of "Pmod3.8/java/ext/j3d" to "/Library/Java/Extensions"
 - » check whether 3D works in PMOD
 - » if not, there is no simple solution at this time, please contact support@pmod.com.

R Plotting Problems

If plots are not shown or very slowly, an update of X11 is required. Please install XQuartz from <http://xquartz.macosforge.org/>.

Linux Installation

The installation for all types of PMOD systems starts with the software extraction from the installation DVD. No other installation is required for PMOD network clients. For PMOD standalone systems and PMOD license server systems, the USB protection key drivers must then be installed and the dedicated license file copied to the *system/lcs* folder.

Some parts of the PMOD installation may require root privileges. If your account does not have these rights, please ask your IT support to perform the following installation steps.

Installation Overview

PMOD supports two licensing schemes: stand-alone and network licenses.

Licensing, Stand-alone License

The PMOD software stand-alone licensing mechanism consists of two components:

- 1) a **USB protection key** (WIBU-Box/RU, WIBU-SYSTEMS AG, <http://www.wibu.com>), and
- 2) a license file **pstarter.lcs** (in sub-directory *system/lcs* of the PMOD installation).

During PMOD startup the license information encoded in the USB key is read and compared to that in the license file. Only if the two informations match, startup proceeds. Next is a check whether the PMOD version purchased allows running the currently installed version. If all checks are successful, the PMOD ToolBox appears showing the purchased modules, and processing can start. Note that the USB key must remain connected while running PMOD.

Licensing, Network License

The PMOD network licensing scheme consists of a PMOD license server which manages a pool of purchased licenses, and an arbitrary number of PMOD clients which can check out unused licenses from the server. As soon as the PMOD program on a client is closed, the license is returned to the managed server pool. If the PMOD client crashes for some reason, the license is re-collected to the pool after about 15 minutes. On the other hand, if the license server is stopped, the clients show a warning message to the user and allow to continue work for a few minutes. Then, the clients will be stopped, unless the server has been started again.

On the license server PMOD is installed in the same way as for a stand-alone license with the USB key, but the license file turns it into a license server.

On the clients PMOD is also installed in the standard way, *except* that

- » installation of the drivers for the USB protection key is not required;
- » no license file is required.

Note the following:

- » The license server PMOD installation is only intended for server purposes and not for data processing.
- » The license server must be running and the USB key must be connected at all times.
- » The license server and the clients must run the same PMOD version.
- » It is not required that the license server and the clients have the same operating system.

Java Runtime Environment (JRE)

The entire PMOD software has been programmed in Java and therefore requires an appropriate Java Runtime Environment (JRE) to be executed. During PMOD installation, an appropriately configured JRE is extracted into the *java* sub-directory of the PMOD installation. This dedicated JRE will then be used for running PMOD. By this controlled

environment, PMOD will remain unaffected from changes due to automatic upgrade procedures.

Installation Steps

The installation of the PMOD software consists of the following steps which should be performed in the proposed sequence. They are explained in detail in the following installation sections.

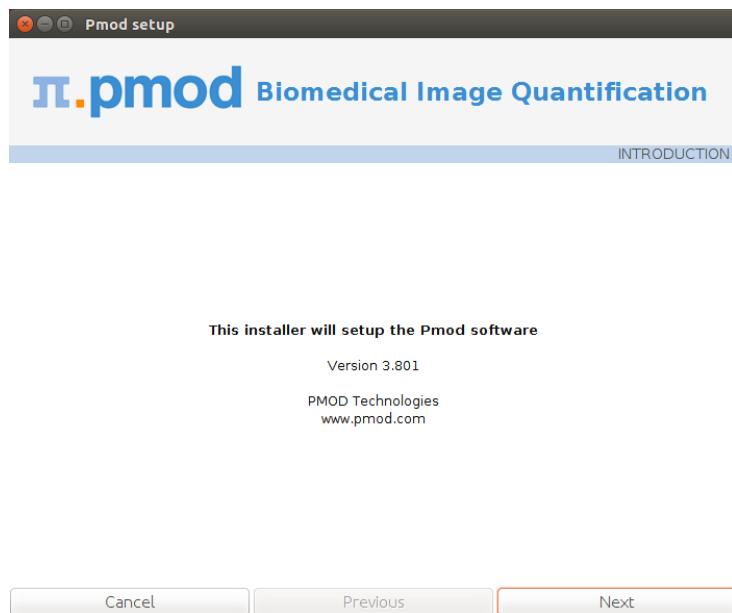
- 1) Extraction of the PMOD program files, the JRE, and optionally the example data to the *Pmod3.8* directory in a user-defined directory.
This installation step is required for: **Stand-alone Installation, License Server, Network Clients.**
- 2) Installation of the USB protection key drivers for reading the information from the WIBU-Box/RU plugged into the USB port. *Please do not connect the PMOD USB protection key before this installation has been completed.*
This installation step is required for: **Stand-alone Installation, License Server.**
- 3) Installation of the PMOD license file *pstarter.lcs*. The license file can be downloaded from the **Support** area of the PMOD *website* <http://www.pmod.com> after the personalized login (please refer to the delivery note of your PMOD package for login information).
This installation step is required for: **Stand-alone Installation, License Server.**

PMOD Software Extraction

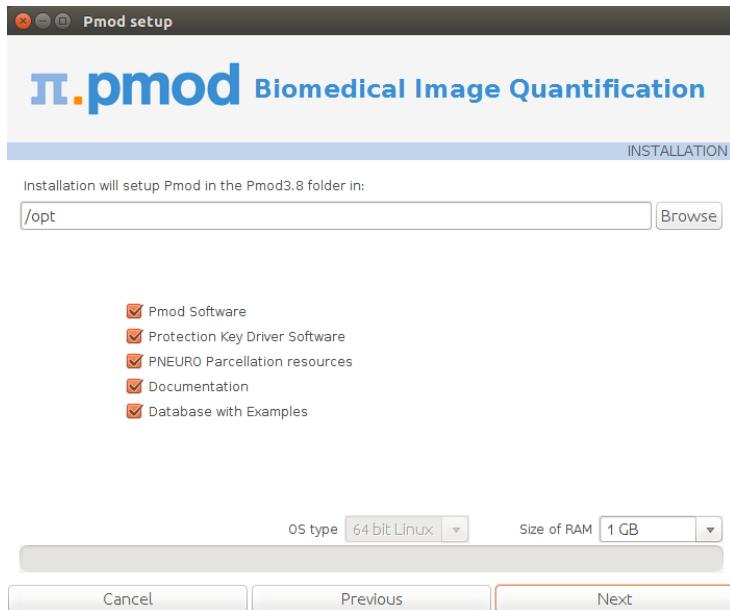
The following software extraction procedure must be performed for standalone PMOD installations, for PMOD servers, and also for all PMOD network clients.

Please begin by inserting the PMOD installation DVD. Then start the installer by executing **RunSetup** in the *Setup/Linux* directory on the DVD by double-clicking, depending on your operating system.

The following installation screen appears



Please use **Next** to proceed and accept the license agreement in the appearing dialog window. After activating **Next** the window for configuring the installation appears.



Please perform the following configurations:

Installation Path

Use the **Browse** button to select the parent directory for the installation for which the installing user has writing permissions. There, the installer will create a new directory **Pmod3.8** for the program files and the data. Please make sure that 450MB of free space is available.

Packages

It is highly recommended to install the four packages, the **Pmod Software**, the **Protection Key Driver Software**, the **Documentation**, and the **Database with Examples**. The **Database with Examples** requires about 380MB and will show up as database called **Pmod**. This database will allow getting acquainted with the programs because it contains examples for the different types of data analysis. Note, however, that it is recommended establishing an new database externally to PMOD for productive data processing. The **PNEURO parcellation resources**, should only be enabled, if the PNEURO tool has been licensed, as the required space is 1.8GB.

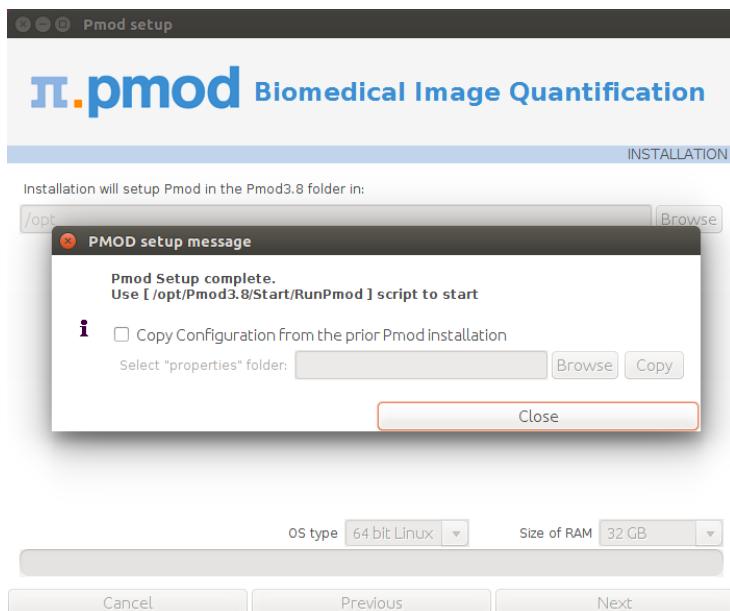
Properties of Operating System and RAM

The operating system of your target computer needs to be 64-Bit. **Size of RAM** can be set to any size. However, if the specified size exceeds the physical RAM, the system will start swapping after RAM space is exhausted and will become very slow. Therefore it is recommended setting **Size of RAM < physical RAM**.

Installation of the PMOD Environment

The installation is started by the **Install** button. The Pmod3.8 directory is created wherein all PMOD-related files are extracted. If the installing user has no write permission in the parent directory, a dialog window appears which reports an installation problem. In this case please change the writing permissions of the installation as root user, or try the installation again using a different installation directory.

At the end of the installation a dialog window is shown. It indicates the command script for starting Pmod3.8, and allows importing the configurations from a prior version. To this end, select the **properties** folder of your prior installation with the **Browse** button as illustrated below, and activate **Copy Configurations**. This import will also copy the license file, so that Pmod3.8 should immediately run with the familiar environment if your license is valid with the Pmod3.8 version.



PMOD Stand-alone License Installation

Install USB Key Drivers

All the files required for the driver installation have been extracted during the installation of the PMOD software and stored in the PMOD *hksetup* sub-directory. For Linux, it includes four installation files, the 64-Bit installers for RedHat/Fedora as well as Ubuntu/Debian systems. The driver installation should be performed as *root* user.

On Ubuntu/Debian Linux systems double-click **wkrt-lin_6.32.1504.500_amd64.deb** and then install the package.

Similarly, on RedHat/Fedora Linux systems use **WkRt-Lin-6.32.1504.500.x86_64.rpm**. If the installation per double-clicking does not work open a terminal and enter the command

```
cd /opt/Pmod3.8/install/hksetup/Linux
rpm -i WkRt-Lin-6.32.1504-500.x86_64.rpm
```

If messages occur in the console window indicating a conflict with an older version of the driver please uninstall that prior version (eg. WkRt-Lin-5.10.501-1.i386) by entering the command:

```
rpm -e WkRt-Lin-5.10.501-1.i386
```

After these cleaning procedures try the installation again.

Note: If you experience problems during driver installation, you are recommended downloading the most recent drivers for the WIBU-KEY (Runtime Kit) from http://wibu.com/download_user.php (http://wibu.com/download_user.php) and try the installation again. Also, in some cases, a reboot may be required after driver installation.

License File

The delivery note you have received with the PMOD CD contains account information for logging into the support area of www.pmod.com (<http://www.pmod.com/technologies/support/enter-support.php>). There you will find a license report, and a button for downloading the license file for your purchased configuration. Please download pstarter.lcs and copy it to the directory *Pmod3.8/system/lcs*.

Important Note: Please do not change pstarter.lcs in any way - a modified license file will not be accepted. Do not open pstarter.lcs in any program, do not rename it, and if you transfer it per FTP, use binary transfer.

Start PMOD

PMOD can now be started with command script **RunPmod** in *Pmod3.8/Start*. Example:

```
#!/bin/sh
cd /opt/Pmod3.8
./java/jre/bin/java -Xmx16000M -jar pmod.jar
```

Notes:

The script has been tailored to the installation directory. Therefore, if the Pmod3.8 directory is moved to a different location, the path needs to be adjusted.

The **-Xmx16000M** option specifies the maximum heap memory (16000 MB) that PMOD can allocate. To process large data sets this number should be increased. Caution: The P3D tool may crash, when the reserved space approaches the physical RAM size.

Change Permission Settings of Directories for writing

To allow other users than root the full usage of PMOD it is important to open some PMOD directories for writing:

```
chmod -R ugo+w /opt/Pmod3.8/properties
chmod -R ugo+w /opt/Pmod3.8/data/
```

There may be other directories you have to open for writing later on, if several users are working with the same PMOD installation.

PMOD Network License Installation

PMOD License Server Installation

PMOD Software Installation

The computer for the PMOD license server doesn't require a high performance (e.g. 2GB RAM, 20GB free space on HDD, 64-bit OS), but needs to have access to the WIBU key USB dongle and run continually. Therefore, a robust vintage machine is sufficient as a PMOD license server. Preferably, it is dedicated to serving the PMOD license, because the license server is a standard process rather than a Windows service.

When using a Virtual Machine for PMOD license serving, the USB device from the host server needs to be mapped to the selected Virtual Machine. If there are no USB ports in a host server or the mapping is not possible, a Network USB Device Server can be used. USB hubs from Digi Network, *Silex* <http://www.silexamerica.com/products/connectivity-solutions/device-networking/usb-parallel-connectivity/>, and Belkin have been tested by Wibu-Systems. In such a setup, the WIBU key can be served over the network and mapped to the Virtual Machine. The standard WIBU drivers can be installed and used at the Virtual Machine.

To install the PMOD license server first perform the steps described in the *Stand-alone PMOD Installation* (on page 493) including copying of the license file and plugging the USB key in.

Starting the License Server

The PMOD license server can then be started by executing the **RunLcsSvr** script in *Pmod3.7/Start* containing the following lines

```
#!/bin/sh
cd /opt/Pmod3.8
./java/jre/bin/java -Xmx2G -jar pmtsvr.jar 5000 -ls -d
```

The meaning of the command arguments is:

- Xmx2G: Size allocated to the license server
- 5000: IP port over which the license server communicates
- ls: license server only, no data sharing
- d: verbose output

Note: The script has been tailored to the installation directory. Therefore, if the Pmod3.7 directory is moved to a different location, the path needs to be adjusted.

Log Output

The command window will show startup information and log the checking out/in events as illustrated below.

```
Java version: 1.8.0_25
 ***
 Started on license [9]
```

```
***  

License Server [Version 3.801 A (c) 1996 - 2016 by PMOD  

Technologies]  

Verbose: false, Secure: false, Compressed: false  

***  

Port: 5000  

Started on: PMOD-CB2/192.168.55.103  

License Server: [ ON ] STANDALONE (Use <Ctrl+C> to stop), Number of  

Server Licenses: 3  

Memory Assigned: 1820 MB  

--> License Server started [Fri Jul 25 16:43:40 CEST 2014] : on port  

5000  

1) 127.0.0.1-192.168.55.103  

Number of free licenses: 2  

1) 127.0.0.1-192.168.55.103  

2) 192.168.55.104-192.168.55.104  

Number of free licenses: 1  

==> REMOVE: 192.168.55.104-192.168.55.104, 1406299586017  

1) 127.0.0.1-192.168.55.103  

Number of free licenses: 2  

==> REMOVE: 192.168.55.104-192.168.55.104, 1406299586017  

1) 127.0.0.1-192.168.55.103  

2) 192.168.55.104-192.168.55.104  

Number of free licenses: 1  

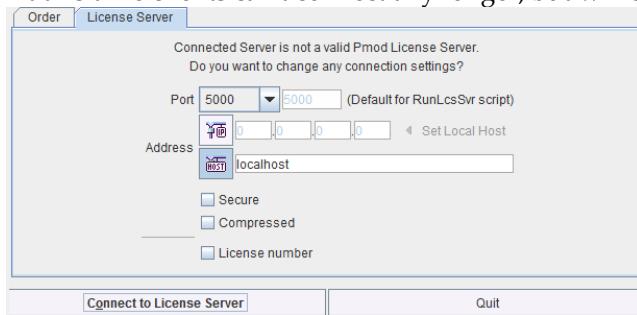
1) 127.0.0.1-192.168.55.103  

2) 192.168.55.104-192.168.55.104  

3) 127.0.0.1-192.168.55.103  

Number of free licenses: 0
```

At this time clients can't connect any longer, but will see the window illustrated below.



Another client needs to stop

```
==> REMOVE: 192.168.55.104-192.168.55.104, 1406299700154  

1) 127.0.0.1-192.168.55.103  

2) 127.0.0.1-192.168.55.103  

Number of free licenses: 1
```

before connection is possible again and **Connect to License Server** will work.

Multiple Licenses Management

Multiple licenses can be served by a single PMOD installation. In order to use this feature please rename the different license files (*pstarter.lcs*) by appending the license numbers in square brackets (*pstarter[1324].lcs*, *pstarter[427].lcs*, ...) and copy them into the

Pmod3.7/system/lcs folder. There are two scenarios, a single license server managing multiple licenses simultaneously, or a separate license server for each license.

If the license server script *RunLcsSrv.bat* is started without modification, it will manage all licenses found in the directory. A specific license can then be defined in the *RunPmod.bat* script of the client by the command line option "-

```
lsn[<PORT_NO>.<OPTIONAL_LICENSE_NO>@<IP_ADDRESS>], e.g.:  
.\\java\\jre\\bin\\java -Xmx16G -jar pmod.jar -  
lsn[5000.1324@192.168.55.103] - to acquire license 1324  
.\\java\\jre\\bin\\java -Xmx16G -jar pmod.jar -  
lsn[5000.427@192.168.55.103] - to acquire license 427
```

In order to operate a dedicated server for each license please create a separate server script for each license with the "-lic[<pattern>]" option included, e.g.

```
java -Xmx2G -jar pmtsvr.jar 5000 -ls -lic[1324]  
java -Xmx2G -jar pmtsvr.jar 5001 -ls -lic[427]
```

A specific license can then be defined in the *RunPmod.bat* script of the client by the command line option "-lsn[<PORT_NO>@<IP_ADDRESS>]" e.g.

```
.\\java\\jre\\bin\\java -Xmx16G -jar pmod.jar -lsn[5000@192.168.55.103] -  
to acquire license 1324  
.\\java\\jre\\bin\\java -Xmx16G -jar pmod.jar -lsn[5001@192.168.55.103] -  
to acquire license 427
```

The advantage of separate servers is that the processes can be independently started, stopped and monitored.

Emergency Restart

In the case of connection or license management problems the following procedure is recommended for restoring clean license handling:

- 1) Stop the license server.
- 2) Delete the contents of the *Pmod3.8/system/lcs/lct/* directory.
- 3) Start the license server again.

If this procedure is completed within 5 minutes, no shutdown of running PMOD clients is required.

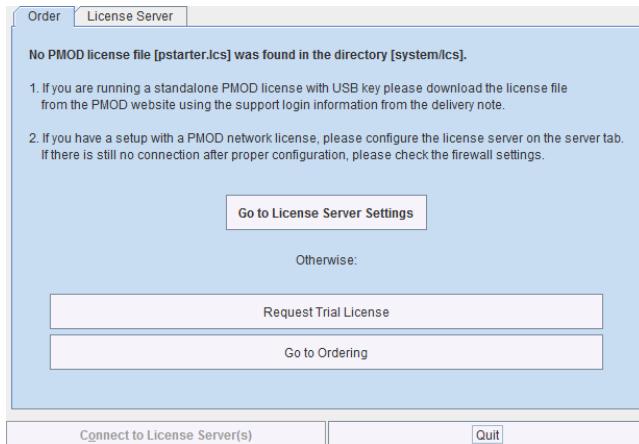
PMOD Network Clients Installation and Configuration

PMOD Software Installation

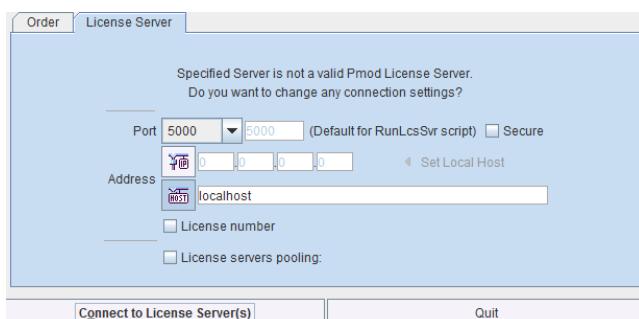
For a PMOD client only the software extraction of the *Stand-Alone PMOD installation* (on page 473) is required. *The license file should not be copied.*

Configuration of the License Server

The PMOD client can be started by the command script **RunPmod** in the *Pmod3.8/Start* directory. As no license file is found, the following dialog window is shown.



Please select the **Go to License Server Settings** button to open the License server panel illustrated below.



Please configure the same **Port** that you have configured for the license server (or transaction server), and specify the server **Address** either by entering its IP address, or by entering its host name. If the process employed for license serving uses compression or encryption, please check the appropriate boxes. If the license server manages several licenses at the same time, enable the **License number** box and enter the number of the license to which you want to connect. Then activate **Yes**.

If the connection succeeds, the dialog window disappears and PMOD starts up. Otherwise the dialog

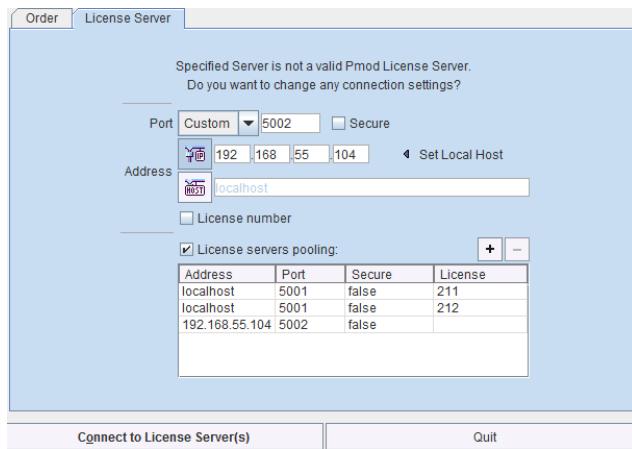


is shown. In this case, please check the configuration of the license server and try again.

If a customer has multiple license servers, the proper license server can also be specified in **RunPmod** as a client command line option by:

```
-lsn [<PORT_NO>.]<OPTIONAL_LICENSE_NO>@<IP_ADDRESS>]
```

Alternatively multiple license servers can be added in the **License servers pooling** configuration by entering their definition in the upper area and then using the + button. Each time the client is started it will connect to the first license server in the list which responds.

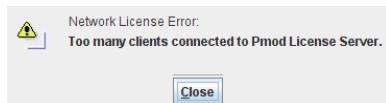


Starting and Stopping a PMOD Client

After the license server has been properly configured, PMOD can be started in exactly the same way as with a stand-alone installation. However, for stopping PMOD the main **Quit** button of the ToolBox should always be used. This will initiate a proper shutdown procedure which returns the license to the license server. Otherwise, when simply killing the client, it will take about 15 minutes until the license server diagnoses loss of connection and reclaims the lost license.

Connection Problems

If at client startup no more licenses are available from the license server because all are in use, the **License Server** connection dialog window is shown again to give the user a chance for connecting to a different license server. In case the connection is repeated with the same server following message is shown.



If a connection problem with the license server occurs while working, the **License Server** connection dialog window is shown. If it is not possible to re-establish the connection (for instance by restarting the license server) the following warning is displayed.



and after five more minutes the PMOD client is finally stopped.

Combination of License and Database Server

Please note that the license server process is based on the transaction server mechanism used for publishing a database. Therefore, if the user is already running a transaction server process on the server system (RunDbSvr, see *Setting up a Transaction Server* (on page 57)), it is *not* necessary to start a dedicated process (RunLcsSvr) just for the license management. The clients can use the same port for requesting a license as for requesting data from the transaction server.

In this context the transaction server option

`-noLS`: database server only

is relevant. This option should be used when running multiple transaction servers. In this case, only one of the transaction servers should start without `-noLS`, namely the one used for license serving.

Version Upgrade in a Complex PMOD Environment

Upgrading a standalone installation of PMOD is straightforward. When using absolute paths for the databases the new PMOD version should be immediately functional after copying the properties folder as the last installation step.

In a more complex environment with clients and servers the following rules should be observed:

- 1) Absolute paths outside the PMOD installation directory should be used for the databases. If this is not the case they should be moved and the paths adjusted in the configuration.
- 2) The databases should be backed up before the migration.
- 3) Server and clients should preferably run the same PMOD version. (To some extent, newer server versions can support older client versions, but not reverse.)
- 4) The PMOD version on the server should be updated first, followed by the clients.

Server Update

Please perform the following tasks sequentially:

- 1) Stop all PMOD servers in the order DICOM servers (DS), transaction servers (TS), license servers (LS).
- 2) Install the new PMOD version and import the properties from the old installation.
- 3) In **Config/DATABASE** switch each database to **Use Direct Connection**, verify it with **Echo DB**, and run **Update & Optimize**. Then switch back to **Use Transaction Server** and generate new starting scripts for the transaction and license servers.
- 4) In **Config/DICOM/DICOM SERVER** generate new scripts for the DICOM Servers.
- 5) Save the configuration and exit PMOD.
- 6) Start the DICOM, transaction and license servers using the new scripts.
- 7) Start PMOD and verify with the **Config** utility, that the TS and DS are working properly. To this end use **Echo TS** and **C-Echo**.

- 8) In case of a network license: Exit PMOD and restart the license server (otherwise a license is blocked).

Client Update

- 1) Install the new PMOD version and import the properties from the old installation. For ATL installations the old properties are not required, as the configuration is centrally stored.
- 2) Start PMOD, provide the license server details when using a network license, and verify the connections with the transaction and DICOM servers.

Troubleshooting

Error reporting

Internal errors typically leave messages of the form

```
java.lang.NullPointerException
at
pmclass.applications.pmgateway.PMgatewayDefaults.getConversionSettings(PMgatewayDefaults.java:143)
at
pmclass.applications.pmgateway.PMgatewayFrame.convert(PMgatewayFrame.java:854)
at
pmclass.applications.pmgateway.PMgatewayFrame.run(PMgatewayFrame.java:911)
at java.lang.Thread.run(Thread.java:484)
```

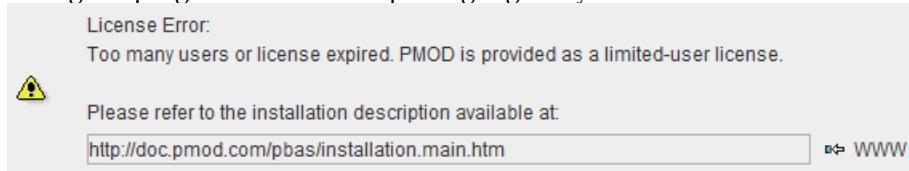
in the command window or the log file.

To allow PMOD Technologies tracking the problem please report the error using the in-built reporting mechanism as described in the problem reporting section. If this is not possible due to a firewall problem please log into the support section on the www.pmod.com website and fill the error message together with a description into the problem report form.

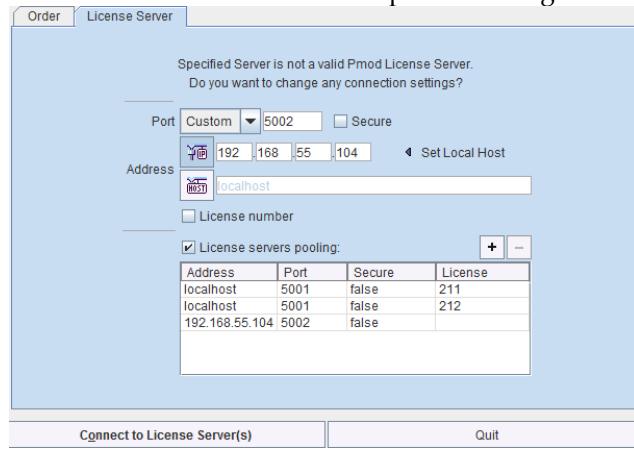
License Errors

Some of the most likely license errors are:

- » The following error message might appear when restarting PMOD after a crash or after killing the program rather than quitting regularly



- » If the license file has not been copied to the right directory, you will see a message



Please copy *pstarter.lcs* to *Pmod3.8/system/lcs*

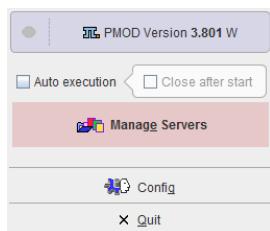
- » If the license file has been modified somehow, you will see a message *License Error. Invalid license file (2)*
Please try to extract *pstarter.lcs* again from your e-mail without any modifications.
- » If the USB key cannot be read because it is not connected or because the driver installation is not up to date, you will see an error message *Hardware license key not accessible* with additional details.
Please make sure that the USB key is connected and the installation was done as described. The installation may have to be repeated after an operating system upgrade.
- » In order to be able to run PMOD with the USB key, the JNI must be found during startup. To this end the environment variable LD_LIBRARY_PATH must contain the path */usr/lib*. The most appropriate location to define it would be in a global definition file, eg */etc/csh.cshrc*. If not already defined so, add
`setenv LD_LIBRARY_PATH /usr/lib`

Server Administration Interface

Installations with multiple Transaction (TS) and DICOM (DS) servers may use an administration tool for server monitoring and controlling the servers. It is started by appending **-admin** to the command in RunPmod. A script for running this administration console would contain

```
D:  
cd "D:\PmodReleases\Pmod3.8"  
.\\java\\jre\\bin\\java -Xmx16000M -jar pmod.jar -admin  
pause
```

It starts the following small toolbox.

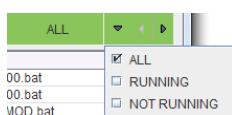


Config starts the standard configuration tool for adjustment.

Manage Servers opens a dialog window for monitoring the status of all configured servers, and starting or stopping them. It scans the directory specified in the **Scripts folder** and lists the servers found in the scripts with status information. If the **Auto execution** check is enabled, an attempt will be made to start all server scripts.

Server	Port	-TLS (Cfg/Scri..)	Type	State	Executed	Address	Script
Pmod	5200	No / No	DATABASE	Stopped	YES	localhost	RunDbSrv_Pmod_5200.bat
DbSvr	5100	No / No	DATABASE	Stopped	YES	localhost	RunDbSrv_DbSvr_5100.bat
PMOD	4030	No / No	DICOM	Running	YES	localhost	RunDcmSrv_4030_PMOD.bat
	5030	No / No	DICOM	Stopped	YES	localhost	RunDcmSrv.bat
	5000	No / No	LICENSE	Stopped	YES	localhost	RunLcsSrv.bat

Three server **Types** are possible, **DATABASE** (TS), **DICOM** (DS) and **LICENSE**. Each server listens on a **Port** at a server **Address**. If a server process is not running, its **State** is **Stopped**, otherwise **Running**. Using the **View** setting the list may be filtered according to the **State** of the entries.



If a script has been called at least once, its **Executed** attribute is set to **YES**, and the process output can be inspected with **View Output**. **Running** processes can be stopped by selecting

them in the list, and activating **Stop selected server(s)**. Reversely, **Stopped** servers can be started by selecting them in the list, and activating **Start selected server(s)**.

For a selected LICENSE server the **License Server Statistics** can be shown with the corresponding button, and in the case of an ATL version licenses can be recovered.

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