

# PMOD Image Segmentation Tool (PSEG)

## USER MANUAL Version 4.2

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# 1 PMOD Image Segmentation Tool Introduction (PSEG)

The PSEG tool implements a framework for image segmentation workflows, both for static and dynamic data. Currently, it offers solutions for different scenarios, namely:

1. **PERCIST**: Semi-automatic lesion segmentation and assessment of static data according to the PERCIST (PET Response Criteria in Solid Tumors) [1,2] methodology. As an additional feature, texture analysis can be applied within the detected lesions.
2. **ORGAN SEPARATION**: Semi-automatic segmentation of dynamic rodent PET studies into functional organs within only a few minutes.
3. **CLUSTERING (K MEANS)**: Automatic segmentation of dynamic data into clusters of "kinetically similar" pixels using the k-means algorithm.
4. **CLUSTERING (Supervised)**: Automatic segmentation of dynamic data into clusters of "kinetically similar" pixels corresponding to a set of prescribed time-activity curves (TACs).
5. **MACHINE LEARNING**: Automatic segmentation of input image based on a Trained Network. It is mandatory to use input image with the same characteristics as the training images.

## 1.1 User Interface

### Starting the PSEG Tool

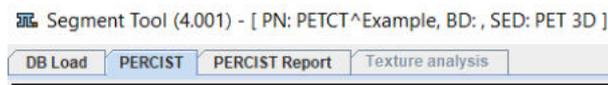
The PSEG tool is started with the **Segment** button



from the PMOD ToolBox or by directly dragging image files onto the above button.

### Organization of the PSEG User Interface

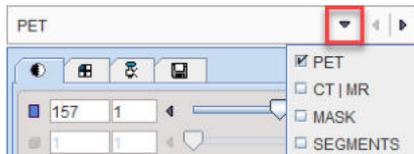
The user interface of PSEG consists of four pages which can be selected by tabs:



1. **DB Load** page: Loading of the images from a PMOD database. The images are transferred to the processing page according to their modality. This page is not shown if the database functionality is disabled.
2. Segmentation page named according to the selected workflow, in the example above **PERCIST**: Main segmentation page for creating VOIs by automatic and manual methods. The workflows are organized as a sequence of panels within this page.
3. Result page named according to the selected workflow, in the example above **PERCIST Report**: Whereas the segmentation results in a set of VOIs, the evaluation results withing these VOIs are shown on the result page.
4. **Texture analysis** page: PSEG supports the calculation of texture indexes within the result VOIs, which are shown on this page.

### Step-Wise Processing

Segmentation is consistently organized as a stepwise progression within the segmentation page. Each stage is represented by a panel, which can be selected in the upper right.



On each panel the user has to take some action such as data loading or parameter configuration, and then start the next processing step with the red action button located in the lower right, for example.

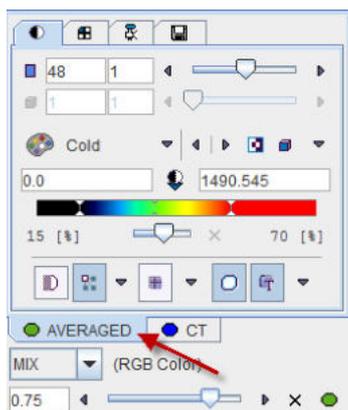


As soon as the result has been calculated, it is shown on the subsequent panel representing the new processing stage.

By selecting the processing panels with the down arrow, results of prior stages can be inspected without initiating any calculations. To repeat a calculation with modified parameters, please progress by activating the action button in the lower right again.

**Fusion Image Display**

The content of the image display area is controlled in the upper right. Often, more than one image contribute to the display. In these cases the tab corresponding to an image has to be first activated, before its color table or the color thresholds can be modified.



The fusion control section is located below the image control tabs. In the illustration above the colors of both images are mixed, whereby the weighting can be changed with the slider.

**Convenience Buttons**

Next to the action button in the lower right is an area with three buttons

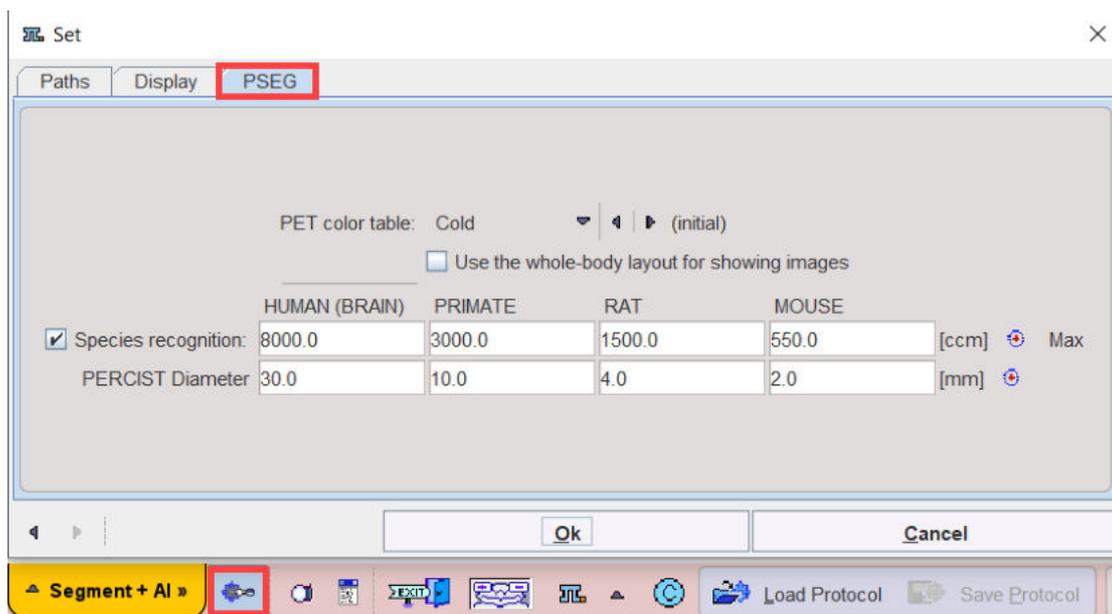


offering the following functions:

	Hide the parameters panel to free some space in the user interface. With the panel hidden, the icon changes to . When this button is activated, the panel is shown again.
	Reset the parameters on the page to their default values. If this button in the taskbar to the right is activated, the defaults are reset on all pages.
	Display help information for the current page.

**Configurations**

The PSEG tool can be configured according to user preferences in a dialog window as illustrated below.



The common configurations are available on the **Paths** and **Display** tabs, and in the upper part of the **PSEG** tab.

The **Use the whole-body layout for showing images** option allows configuring the whole-body layout in the view port for oncology users

If the **Species recognition** box is enabled, PSEG determines the imaged species based on the volume of the loaded data. The qualifying species volumes can be edited to tailor the behavior, if needed. The PERCIST methodology uses the uptake in a reference sphere for calculation of a contouring threshold. **PERCIST Diameter** allows configuring the sphere diameter for the different species.

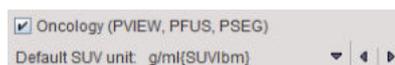
### Further Information

This guide is focused on the segmentation functionality. Please refer to the *PMOD Base Functionality Guide* for details about general functions such as data loading, image display and VOI definition.

## 1.2 Recommendations

### Use of SUV for PERCIST

For processing human FDG data with the PERCIST workflow it is recommended enabling the global **Oncology** settings (open **Users Configuration** facility, **SETTINGS/PRESETS** panel). It will establish use of SUV display units as the default, enable patient information overlay in the images, and always show the MIP with inverted grey color table in the orthogonal layout.



### Anatomical Reference Image

While segmentation is mostly based on the functional images, anatomical CT or MR images can provide additional information. They can be used for creating a mask which restricts the segmentation, for fusion with the functional image or the segments, and for adding segments manually.

Note that *multi-modal data needs to be matched before using them in PSEG*. In order to conserve the better resolution of the anatomical modalities, it is recommended to match the PET series to the MR or CT series, for instance using PMOD's fusion tool.

## Motion Correction of Dynamic Data

Movement during the dynamic acquisition should be avoided. While internal organ movement and bladder filling are difficult to handle, global relocation should be corrected before the segmentation process. PMOD's fusion tool includes a motion correction facility which has been successfully applied.

## Protocol File

A segmentation can be tedious and involve interactive work. All of this can be saved in a protocol file using the **Save Protocol** button in the lower status line. The state at the end of segmentation can then exactly be recovered by the **Load Protocol** functionality.



## 2 PSEG Workflow

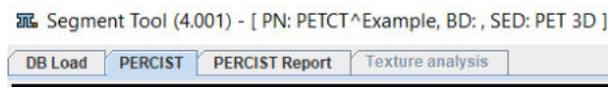
### 2.1 Overview

PSEG guides the user step by step through the segmentation of a study. All workflows follow the same sequence of steps:

1. First the PET image is loaded, which can be static or dynamic. If it is dynamic, the average of a selected frame range is created. The user can optionally define a cropping window on the loaded images and set image interpolation to a certain resolution. Before proceeding, the user has to specify from what data the segmentation mask is computed.
2. If a matched MR or CT image is available, it is loaded as the next step. The image is automatically cropped to the same bounding box and interpolated to the same resolution as PET.
3. A mask is created for restricting the segmentation procedure. Different methods are available for the different modalities. At this point the user has to configure the segmentation method which will be applied.
4. The segmentation-specific panel is opened. By user interaction, a list of VOIs is created which represent the segmentation result.
5. The PET uptake within the resulting VOIs is evaluated, and post-processing such as partial-volume correction or texture analysis applied. The results are shown on a separate page in the main PSEG interface.

#### Organization of Steps in the PSEG User Interface

The user interface has four pages.



Data can be loaded from the DB load page, if it is organized in a PMOD database. The images are then assigned to the different roles according to their modality.

The second page hosts all segmentation steps. Each of the steps 1-4 described above is represented by a panel within the second page, as illustrated below



The processing results are shown on the third and fourth main pages. In the following, the different workflows are described.

### 2.2 PERCIST

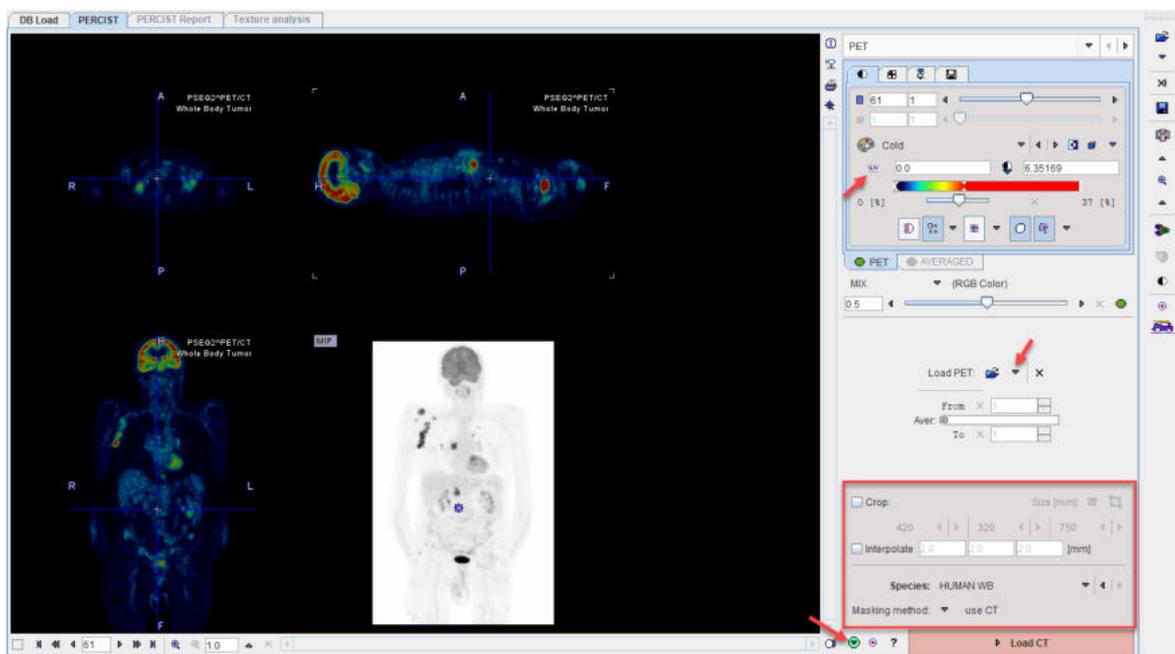
PERCIST (PET Response Criteria in Solid Tumors) [1,2] defines an objective methodology to assess the tumor burden and treatment response for FDG PET images. In summary, the following steps are performed:

1. A 3cm diameter reference sphere is (manually) placed in the right side of healthy liver, midway between the dome and inferior margin, excluding central ducts and vessels. If the liver is diseased, the reference should be placed into the blood pool of the descending aorta using the CT image. A cylinder (1cm diameter, 2cm long) is specified in [1], but in PSEG an ellipsoid is more practical.

- The *minimal level of tumor uptake* is calculated from the average and the standard deviation of the activity in the reference region. Liver:  $1.5 \times \text{Average} + 2 \times \text{Stdv}$ ; Blood:  $2 \times \text{Average} + 2 \times \text{Stdv}$ .
- An iso-contouring segmentation is performed at the calculated minimal level, resulting in a list of lesion VOIs. A restriction can be set to filter tiny VOIs representing noise and large VOIs representing organs like the brain, bladder or heart.
- The lesions are sorted according to their peak uptake (which corresponds to the maximum average of a 1mL sphere placed in the lesion).
- The lesion with highest peak uptake is considered the target lesion at baseline and also after treatment. Note that a non-target lesion at baseline can become the target lesion at follow-up due to poor treatment response.
- Although only a single target lesion is used for assessing treatment response in PERCIST, it is recommended saving additional exploratory data, particularly from the 5 hottest lesions.

### 2.2.1 PET Image Loading

Step-wise processing is started by selecting the second tab. It is labeled **Segment** when starting PSEG, and retains the labeling of the previous segmentation. The first sub-panel is called **PET**.



#### PET Image Loading

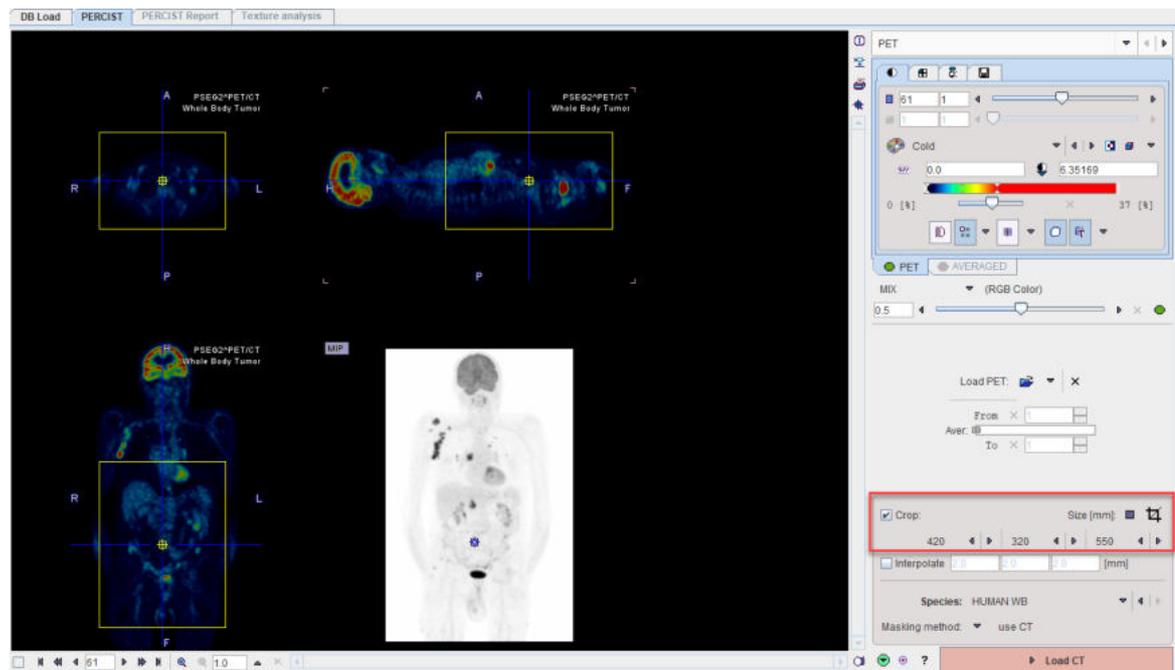
The **Load PET** button for loading the PET images is located in the right control area. It behaves as an option button which needs to be set to the appropriate data format with the indicated arrow. For loading images which are not saved in a PMOD database it is recommended to apply the **Autodetect** format which will figure out the appropriate image loader.

The image is displayed according to the configuration settings. In the example above the global **Oncology** setting is active, so that the PET image is shown in SUV units and the MIP image is shown in inverted grey.

If the loaded PET series is dynamic, PSEG generates a new series by averaging a range of frames and assigns it to the **AVERAGED** tab. The averaging range can be defined by the **From** and **To** number fields, or dragging the range indicators in the **Aver** bar. After any modification of the range, the average is recalculated and the display updated. The aim of the averaging is to generate an image which is useful as a reference for the segment interpretation, as well as for creating the body mask. The original and the averaged images are shown in a fusion rendering which can be adjusted in the fusion control area below the tabs for selecting the individual images.

## PET Image Cropping

If some cases, restriction to a sub-volume may be preferable to save RAM and optimize processing. To do so, please enable the **Crop** box and place the center of the yellow crop volume by clicking into the image. The edge size in [mm] of the box can be adjusted for each direction by selecting the size in the corresponding list, or by selecting the **Size** button and entering the three edge lengths. The  button initiates cropping, whereby the original data are replaced. If cropping is not activated manually, a request will be shown when proceeding to the next step. Note: The cropping operation is irreversible and only allowed once.



## Interpolation

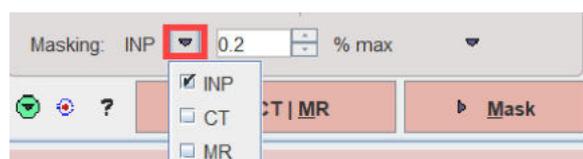
The analysis will be performed at the resolution of the PET image. If matched anatomical images are available, they may have better spatial resolution than the PET. In this case, or just to have a smoother appearance, an interpolation can be configured. To this end, activate the **Interpolate** box and specify the voxel dimensions in x,y and z in mm.

## Mask Definition

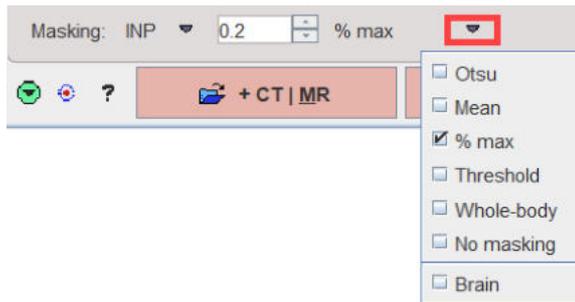
The segmentation procedure will operate on all pixels contained in a mask derived from the data. Please set the **Species** selection according to the studied subject. It establishes proper defaults for the morphological operations which are later applied to the data. The **Masking method** selection allows switching between three methods of mask derivation: **INP**, **CT** and **MR**.

## INP-Based Mask

When selecting **INP** masking



the segmentation mask is derived from the averaged PET series when the **INP** is a dynamic PET image. Several methods can be selected from the drop-down menu.



- **Otsu**: This method iteratively looks for the best threshold to separate an object from a background assuming two main gray-level regions.
- **Mean**: Includes all pixels above the image mean.
- **% max**: Includes all pixels above the specified percentage of the image maximum.
- **Threshold**: Includes all pixels above the specified absolute value. Note that the threshold needs to be specified in the display units of the PET image.
- **Whole-body**: This procedure calculates the image log-values and derives a threshold from the histogram.
- **No masking**: Do not apply a mask in the segmentation.
- **Brain**: This procedure is based on the Brain Extraction settings and is applicable to brain MR images.

Please select a definition appropriate for the **INP** data at hand. If there are no matched MR or CT images, proceed with the **Mask** action button, otherwise proceed to the additional image loading with the **+CT | MR** button.

### MR- or CT-Based Mask

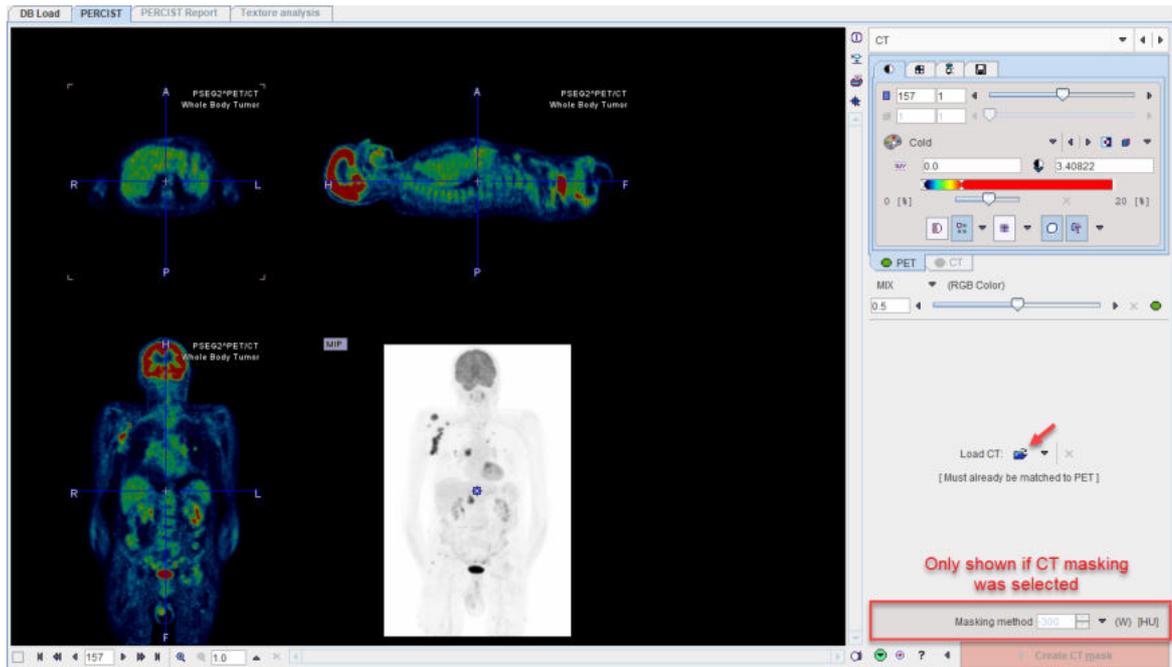
If matched CT or MR series are available, they cannot only be used as anatomical reference images in the fusion display, but also for mask creation. In order to apply MR- or CT-based masking please set the **Masking method** accordingly. The change is reflected in the parameter area as illustrated below.



The PET masking options are no longer available, and the action buttons are replaced by a single button for progressing to the corresponding image loading page.

## 2.2.2 CT or MR Reference Image Loading\_2

The layout of the second panel depends on the **Mask** setting on the **PET** panel. The situation illustrated below represents **CT**-based masking. Correspondingly, the page is titled **CT**, and in the lower right the **Masking methods** appear with a corresponding action button **Create CT mask**. The situation with MR-based masking is analogous.



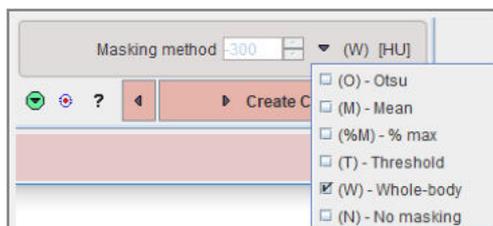
### Reference Image Loading

Please use the indicated button for loading the anatomical image series. It needs to already be matched to the PET series and to have the origins at the same location. In the case of non-matched data, matching should be performed beforehand using PMOD's image fusion tool.

The loaded image is immediately cropped to the same box as the PET and interpolated to the same resolution. The correspondence in the resulting images can be verified with the fusion slider.

### CT-based Mask

The selection of **Masking methods** illustrated below is only shown if **CT** has been chosen for masking on the **PET** panel.

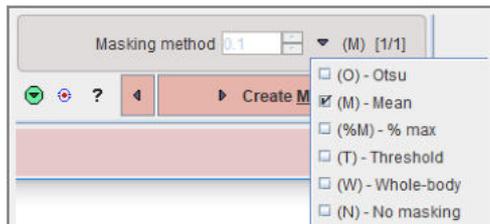


- **Otsu**: This method iteratively looks for the best threshold to separate an object from a background assuming two main gray-level regions.
- **Mean**: Includes all pixels above the image mean.
- **% max**: Includes all pixels above the specified percentage of the image maximum.
- **Threshold**: Includes all pixels above the specified absolute Hounsfield value.
- **Whole-body**: This method applies a threshold, followed by morphological operations for removal of the bed and filling of the airways.
- **No masking**: Do not apply a mask in the segmentation.

After selecting the method, please proceed with the **Create CT mask** button in the lower right.

### MR-based Mask

If **MR** has been chosen for masking on the **PET** panel the **Masking methods** are similar as described above.



The following methods are MR specific:

- **Whole-body:** This procedure calculates the image log-values and derives a threshold from the histogram.

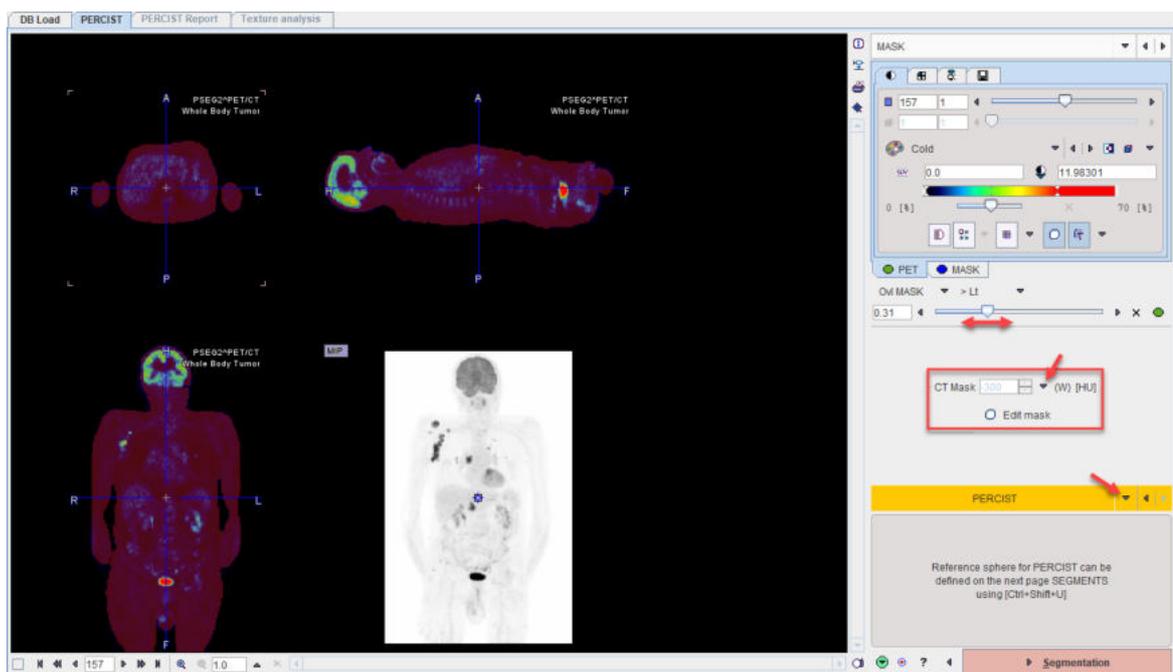
After selecting the method, please proceed with the **Create MR mask** button in the lower right.

### PET-based Mask

With PET-based masking the panel is labeled **CT | MR**. Please load the reference image with **Load Anatomical**, and proceed with **Create PET mask**.

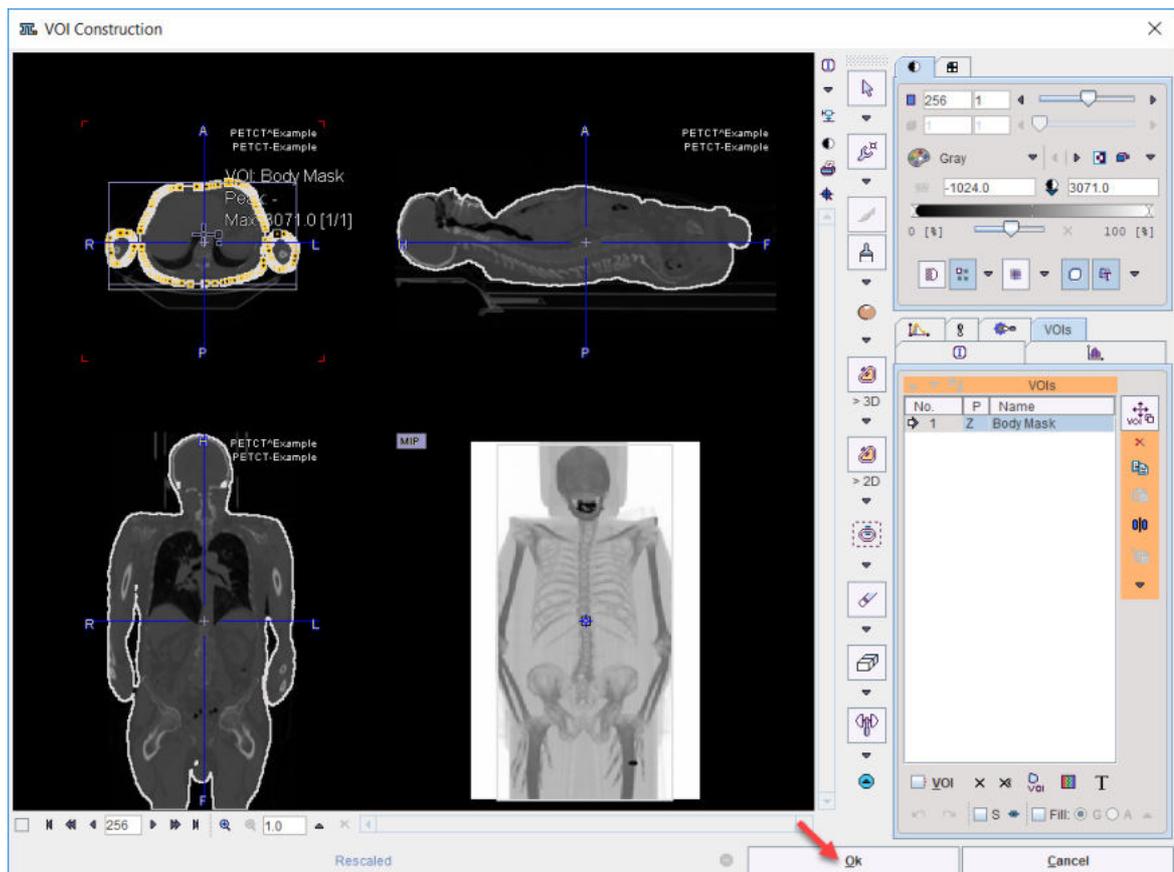
## 2.2.3 Mask Editing and Segmentation Configuration

When arriving at the **MASK** panel, the display shows a fusion of the average **PET** with the generated **MASK**.



### Mask Edition

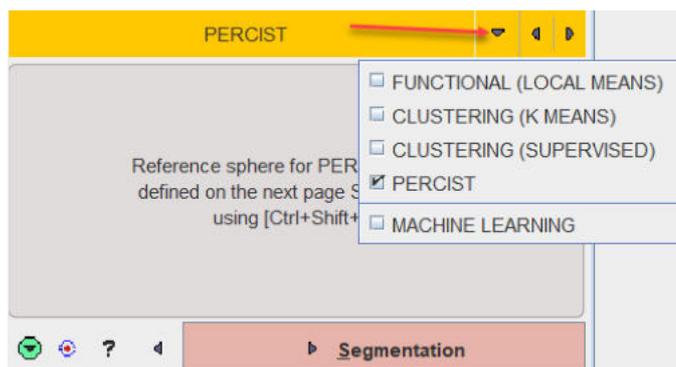
The options of the selected masking method are still available. If another option is selected, the corresponding mask is immediately calculated and shown. **Edit mask** converts the mask into an outline definition and opens it in a VOI dialog window for additional editing.



Here, the mask definition can be modified using all PMOD VOI tools. Please refer to the *PMOD Base Functionality User Guide* for VOI-related details. When closing the window with the **Ok** button, the mask is returned to PSEG.

### Segmentation Method Selection

At this point, the **PERCIST** segmentation method has to be selected in the lower right.

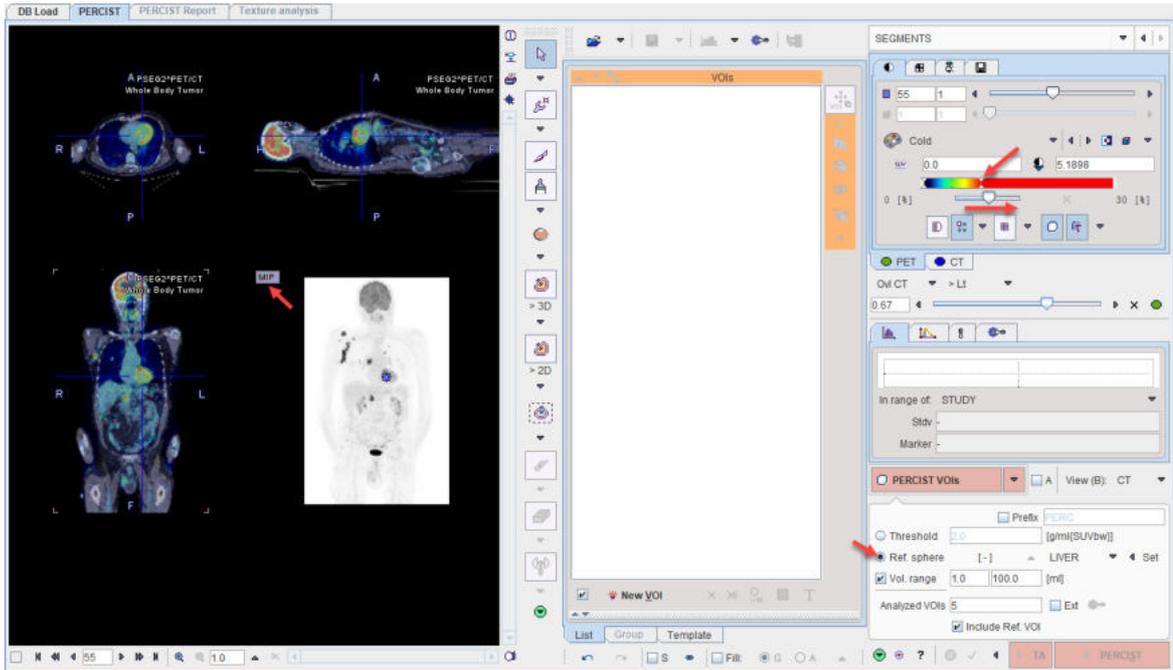


The panel below the selection is updated accordingly. For PERCIST as illustrated above it only informs about the procedure how to place the 3cm diameter reference sphere.

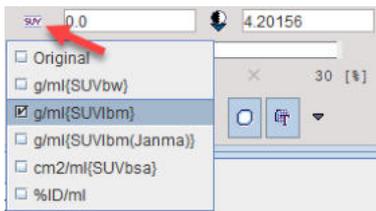
To finally start the PERCIST segmentation please activate the **Segmentation** action button.

## 2.2.4 PERCIST Segmentation

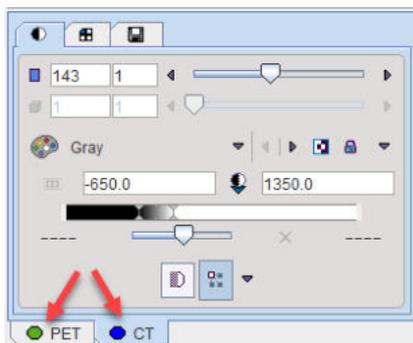
When arriving at the **SEGMENTS** panel, a fusion of the PET image with the CT is shown in an orthogonal layout.



For a dedicated PERCIST analysis the PET image should be displayed in **SUVIbm** units. If this is not the case, the display units should be switched accordingly. Note that SUVIbm requires weight and height to be defined in the data.



It is also recommended to adjust the settings of the color bars, the fusion slider, and the MIP to optimize the image display. The relevant user elements are indicated by the arrows above. Please refer to the *PMOD Base Functionality Guide* for details. In order to adjust the **CT** the corresponding tab has to be selected first.



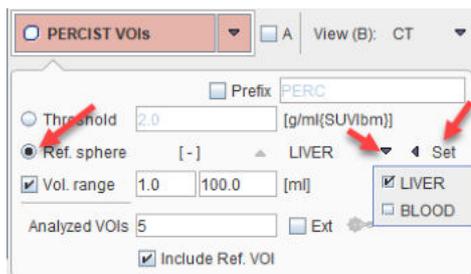
However note that before starting the segmentation procedure, it is important that the **PET** image tab is again selected.



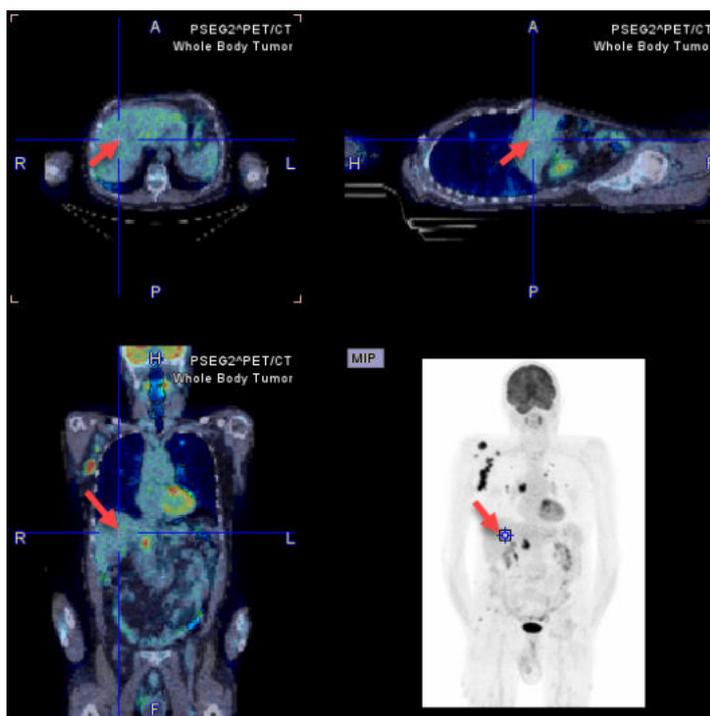
Otherwise the segmentation will fail, as it will operate on the CT image.

### Reference Sphere Placement

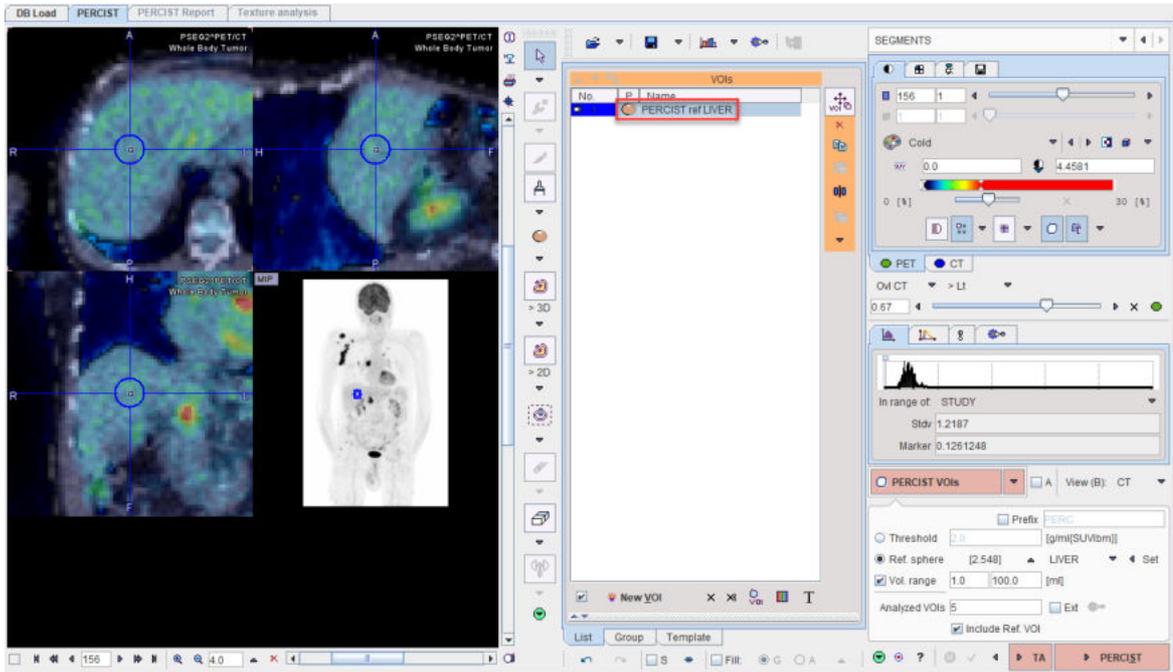
First, the **Ref. sphere** radio button needs to be selected. It has a related option button to choose whether the reference is placed within the **LIVER** or the **BLOOD** pool.



Next, in the image area, the position has to be triangulated where the reference sphere is to be placed. The easiest approach is to first click into the MIP image for rough localization, and then into the planar images for fine tuning.



When the triangulation point is properly localized, use the **Ctrl+Shift+U** keyboard shortcut or the **Set** button for generating the reference sphere. The result for the situation above is illustrated below, with the image zoomed by a factor of 4. Note the **PERCIST ref** VOI in the **VOIs** list, and the threshold of **2.548 SU/1bm** which was calculated as the *minimal level of tumor uptake*. With the **LIVER** setting it is obtained by 1.5 times the average plus twice the standard deviation within the sphere. In the **BLOOD** case it will be twice the average plus twice the standard deviation.



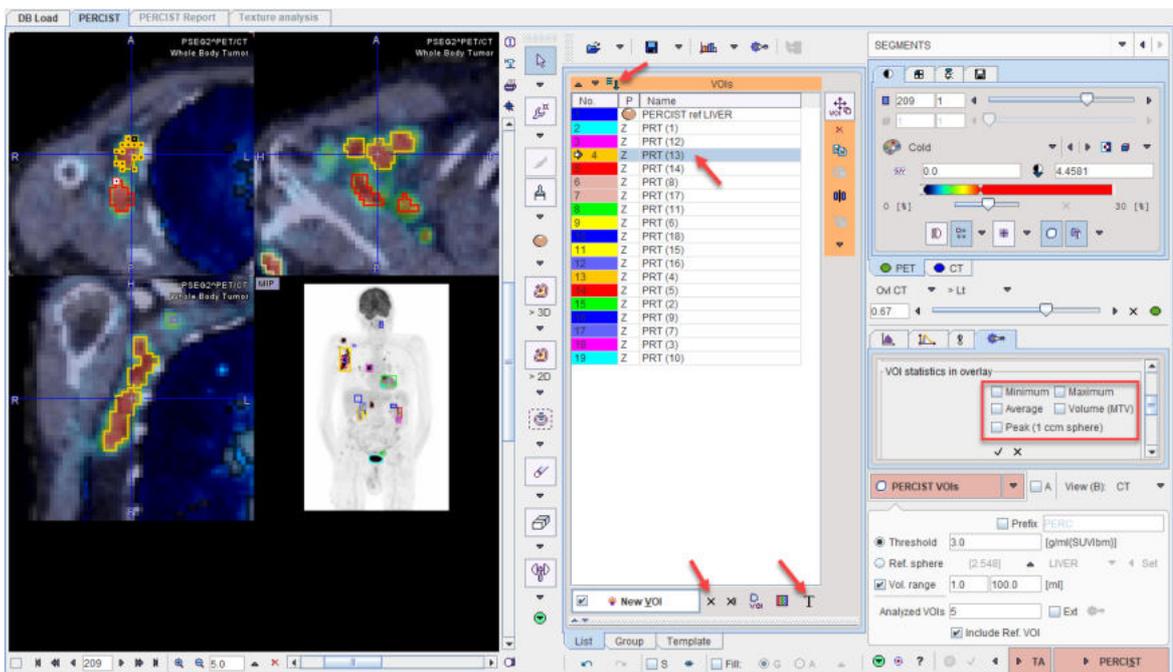
**Automatic VOI Generation**

For PERCIST the iso-contouring threshold is adaptively obtained from the reference VOI as described above. In other contexts it may be preferable to use a fixed **Threshold**, for instance **3.0 SUV<sub>lbm</sub>** as illustrated below.



Note the up-arrow which transfers the **Ref. sphere** determined value to the **Threshold** field.

The **PERCIST VOIs** button starts the iso-contouring of the PET image at the configured threshold. Note that it only considers voxels within the defined mask, and returns the segmented objects as a list of VOIs, sorted by decreasing  $SUV_{peak}$ .



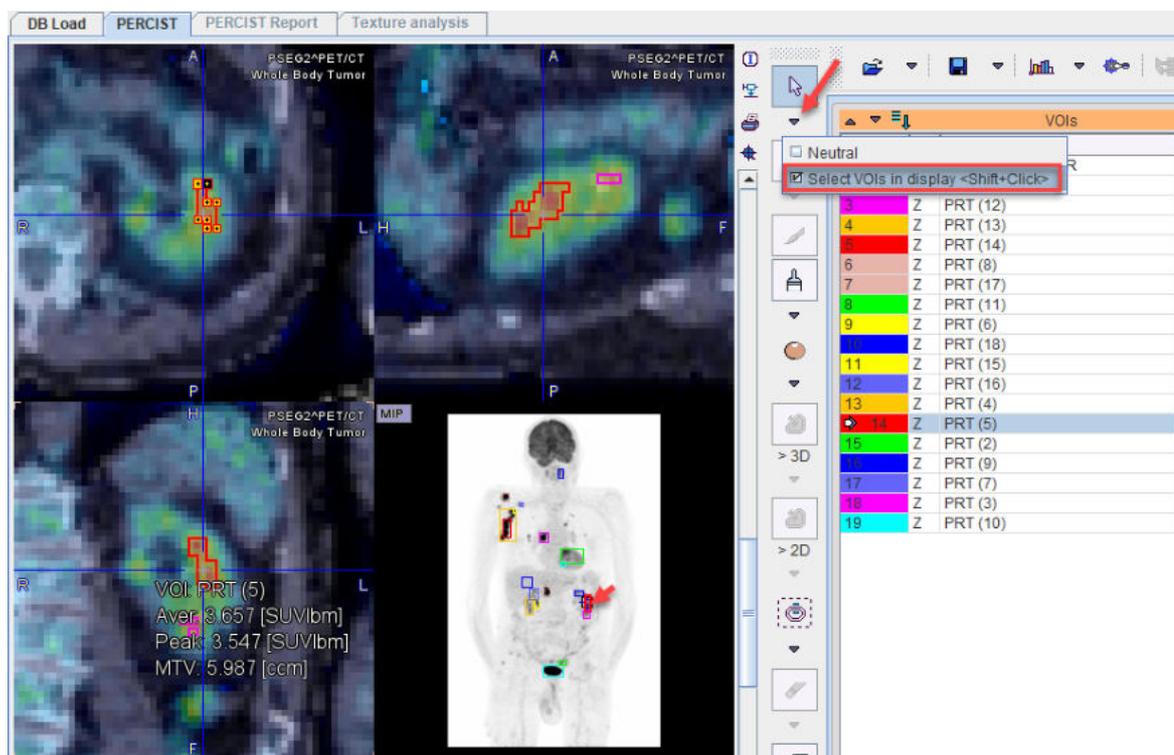
Some options modify the behavior of the VOI generation:

- **Prefix:** If the box is active, all VOIs are named with the string provided in the text field and an incremented number.
- **Appending:** If the **A** box is enabled, new VOIs are appended to the existing VOIs list. Otherwise, the existing VOIs are first removed.
- **Vol. range:** If this box is enabled, the two entered numbers define the minimum and maximum volumes of the detected VOIs. This feature is useful for omitting tiny spots or large accumulations such as the brain, heart or bladder.

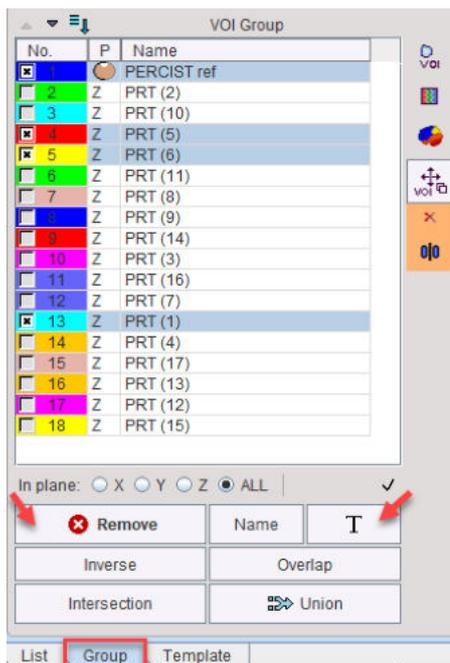
### VOI Selection and Removal

When clicking at a VOI in the list, the lesion is triangulated in the display. If some **VOI statistics in the overlay** elements are enabled, the results for the selected VOI are shown in the overlay.

As automatic contouring may result in VOIs which are not relevant, targeted VOI selection and removal is an important task. Direct localization within the image is a more more intuitive way of VOI selection than clicking into the VOIs list. This is possible after setting **Neutral** mode button to **Select VOIs in display** as illustrated below. Thereafter VOIs (e.g. the bladder) can be selected by clicking at them in the MIP or in the planes. Then, the selected VOI can be removed from the VOI list by the **X** button.

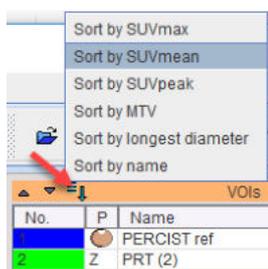


By holding down the **shift** key it is furthermore possible to select multiple VOIs. On the **Group** panel they appear as marked entries as illustrated below. There, the **Remove** button removes all marked entries. Note also the **T** button which allows renaming all of the selected VOIs in a structured way as described below.



### VOI Sorting

Sorting of the lesion VOIs according to various criteria is possible via the option button above the VOIs list. The sorting order is relevant for the PERCIST report, as it includes the uppermost entries in the list.



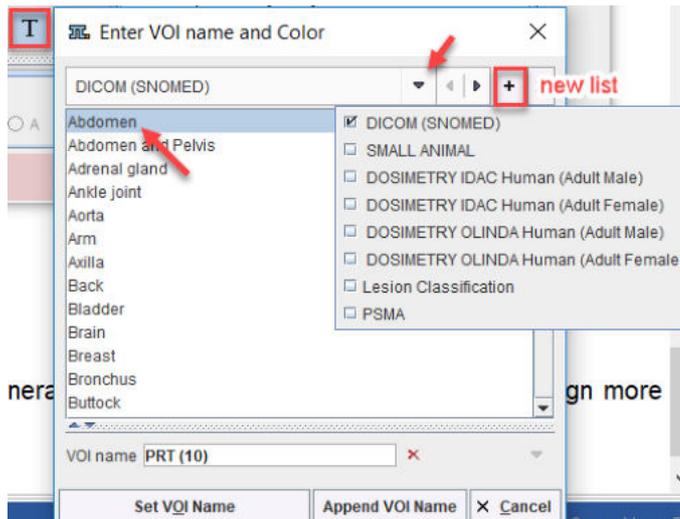
### VOI Labeling

The automatically generated VOIs are simply numbered. In order to generate a useful report it is recommended to assign more informative names. VOI names can interactively edited in the list.

Alternatively, predefined names can be used either by right-clicking into the VOI list,



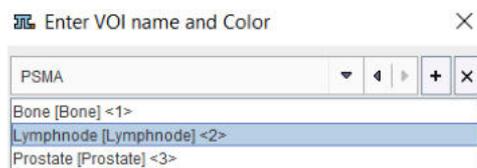
or by selecting a VOI in the list and activating the **T** button below the list. A dialog window is opened as illustrated below.



Several lists containing predefined names are available and can be selected at the top. By clicking at a name in the list, the **VOI name** field is updated. **Set VOI name** (or double-click) replaces the name of the selected VOI, whereas **Append VOI Name** adds the string to the present VOI name.

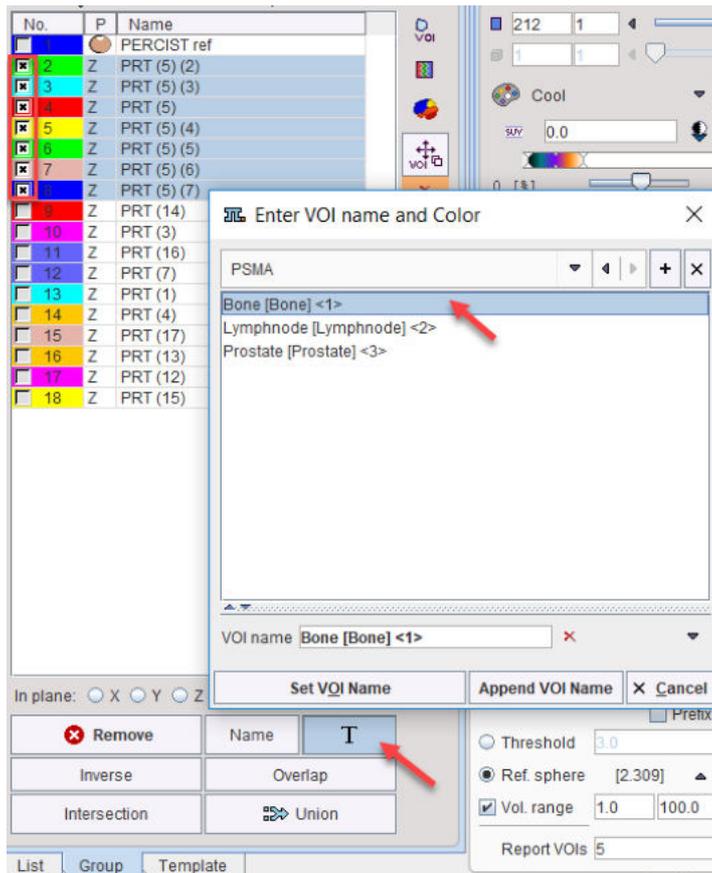
It is easy to prepare user-defined lists such as PSMA in the example above. To do so, process an arbitrary data set and name the VOIs meaningfully. Then activate the **+** button of the window indicated above. A new dialog appears which shows the VOI names to become the list entries, and requests a list name. After saving, the list will be present as a new entry in the list selection.

There is a specific convention for creating names which produce a tree structure on the **Group** panel. As an example, the PSMA list entries may look as follows.

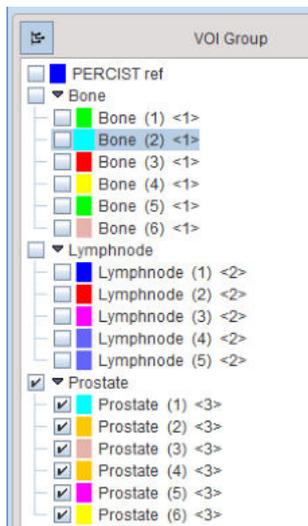


They follow the naming structure "Label1[label2]<number>" which allows generating VOI groups and label maps.

The **T** naming feature is also available on the **Group** panel to label multiple VOIs at once. For instance, a selection of VOIs is assigned the **Bone[Bone]<1>** name in the example below.



The other VOIs are similarly assigned to the **Lymphnode** and **Prostate** entries. These operations create the following tree structure of VOIs with the first label as the root name, and the second label as the branch names numbered from (1).



The numeric label between the <> brackets at the end of the VOI name will be used at the time a label map is created from the VOIs (not yet available).

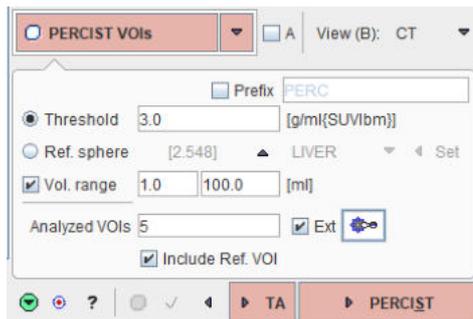
There is a particular VOI naming feature intended for labeling VOIs which need further evaluation. When hitting the **Ctrl+Shift+B** keyboard shortcut, the tag **{UNCLEAR}** is added to the name of the currently selected VOI as illustrated below. The shortcut works as a toggle: if it is hit again, the tag is removed. VOIs tagged with **{UNCLEAR}** in the list have a particular behavior in sorting operations. Independent of the order they always stay at the top with the idea that the user has to clarify the nature of the lesion.

No.	P	Name
1	Z	{UNCLEAR} PRT (2)
2	Z	PERCIST ref
3	Z	PRT (1)

## 2.2.5 PERCIST Report

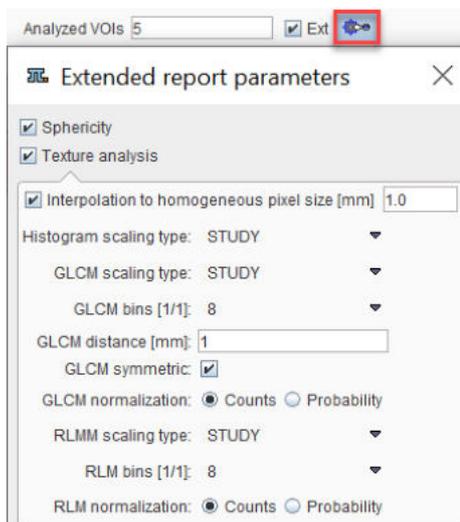
### PERCIST Report Generation

Once the lesion VOIs are properly named and sorted, a report can be generated with the **PERCIST** button in the lower right.



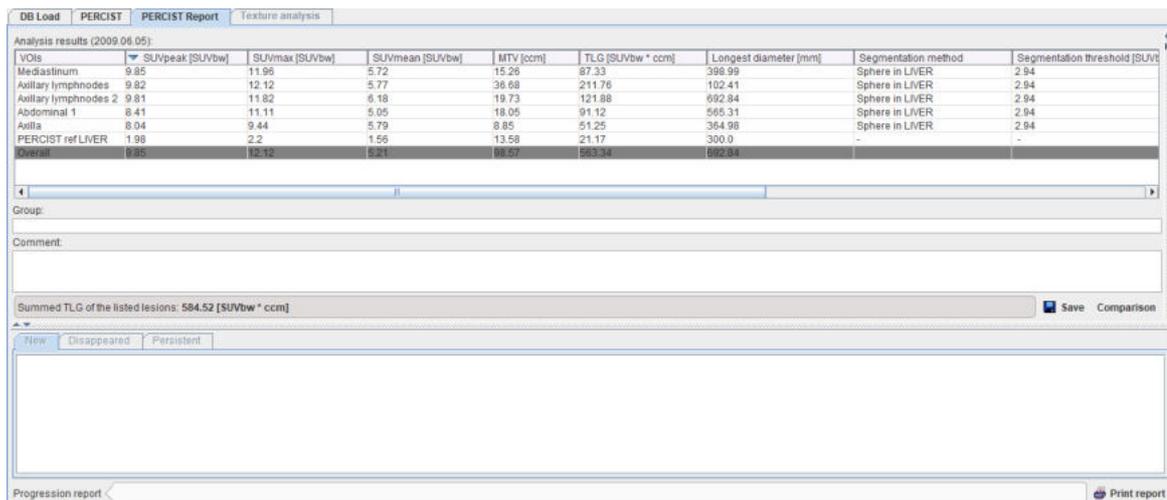
The number in the **Report VOIs** field determines how many of the VOIs from the list top down are evaluated. Entering a value of **0** has the effect that *all* VOIs are included. If **Include Ref. VOI** is checked, the reference sphere statistics are included in the report, which may give relevant information about the background in longitudinal scans.

If the **Ext** field is checked, selected shape and [Texture Analysis](#)<sup>[24]</sup> results can also be included in the report. This content is configured as illustrated below.



### PERCIST Report Content

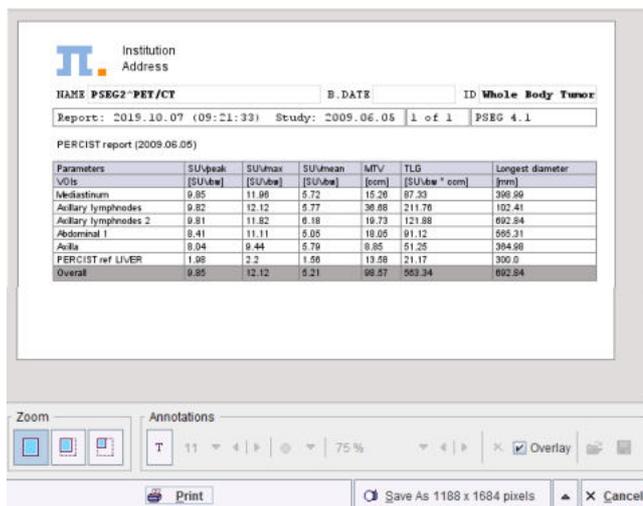
The results are shown on the dedicated **PERCIST Report** page.



The **Analysis results** sections lists the specified number of lesions with the relevant measures in the columns. Note that the list is sortable by clicking into the column headers. In addition to **SUVpeak**, **SUVmax**, **SUVmean**, **MTV**, **TLG**, and **Longest diameter** there are columns with information about the segmentation method and the VOI location.

Segmentation method	Segmentation threshold [SUVlbm]	Lesion label...	Label value	Location X [mm]	Location Y [mm]	Location Z [mm]
Sphere in LIVER	2.48		0	-5.08	-20.31	-836.03
Sphere in LIVER	2.48		0	-33.01	-27.93	-425.66
Sphere in LIVER	2.48		0	-142.19	27.93	-386.42
Sphere in LIVER	2.48		0	-144.73	-10.16	-396.23
Sphere in LIVER	2.48		0	-22.85	58.4	-590.79
-	-		0	-114.26	2.54	-567.9

The **Group** and **Comment** text fields are intended for documentation purposes. If the image has been loaded from a PMOD database which already contained a group definition and comments for the image, this information is automatically copied into the corresponding fields. The **Save** button stores the information shown to a text file for longitudinal comparison. **Print report** opens a dialog window showing the list contents in the standard PMOD report printing environment.



### Result Comparison

The **PERCIST Report** page can show two results in parallel. For a longitudinal comparison please activate the **Comparison** button. Consequently, the window is split into two areas with the current results to the left.

To the right use the **Load** button for retrieving the result of the prior analysis. Two strategies can be applied to order and link the lesions. Per default the **Pair by VOI Name** tries to place entries with the same name in the same table row. In the example below the empty row in the table to the right indicates a lesion which has disappeared. The TLG column of the table to the left (current

examination) shows an indication of the TLG change in fields colored according to the change (red = increase, green = decrease).

The screenshot displays two side-by-side comparison tables for VOI metrics. The left table, titled 'Analysis results (2009.06.05)', and the right table, titled 'Baseline results (2009.06.05)', both list metrics such as SUVpeak, SUVmax, SUVmean, MTV, and TLG for various VOIs. The TLG values are highlighted in red (increase) or green (decrease). Below the tables are sections for 'New', 'Disappeared', and 'Persistent' lesions, and a 'Print report' button.

In the lower sections there are three additional tabs for listing **New**, **Disappeared** and **Persistent** lesions separately. The latter provides a comparison of the uptake measures between the two examinations. In this situation **Print Report** will produce three report pages, one for each of the analysis results, and a comparison page.

VOIs	Progression	SUV/peak [SUVbw]	Δ SUV/peak (%)	SUVmax [SUVbw]	Δ SUVmax (%)	SUV/mean [SUVbw]	Δ SUV/mean (%)	MTV [ccm]
Abdominal 1	Green	4.83	-42.54%	7.73	-30.39%	4.14	-18.0%	3.88
Axillary lymphnodes	Red	9.82	0.0%	12.12	0.0%	5.54	-4.11%	64.09
Axillary lymphnodes 2	Red	8.41	-14.3%	11.11	-6.02%	4.64	-24.83%	21.92
Mediastinum	Red	9.85	0.0%	11.96	0.0%	5.44	-4.97%	16.86
PERCIST ref LIVER	Green	1.75	-11.39%	2.02	-8.14%	1.43	-8.16%	13.58
Overall		8.85		12.12		4.97		906.75

**Pair by location** employs the VOI centers for aligning the entries in the upper comparison table, but does not have an effect on the comparison tables.

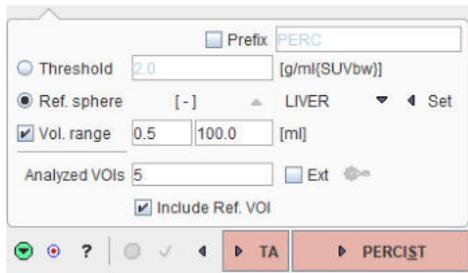
**Note:** Consistent naming of the lesions is crucial for the longitudinal comparison.

### 2.2.6 Texture Analysis

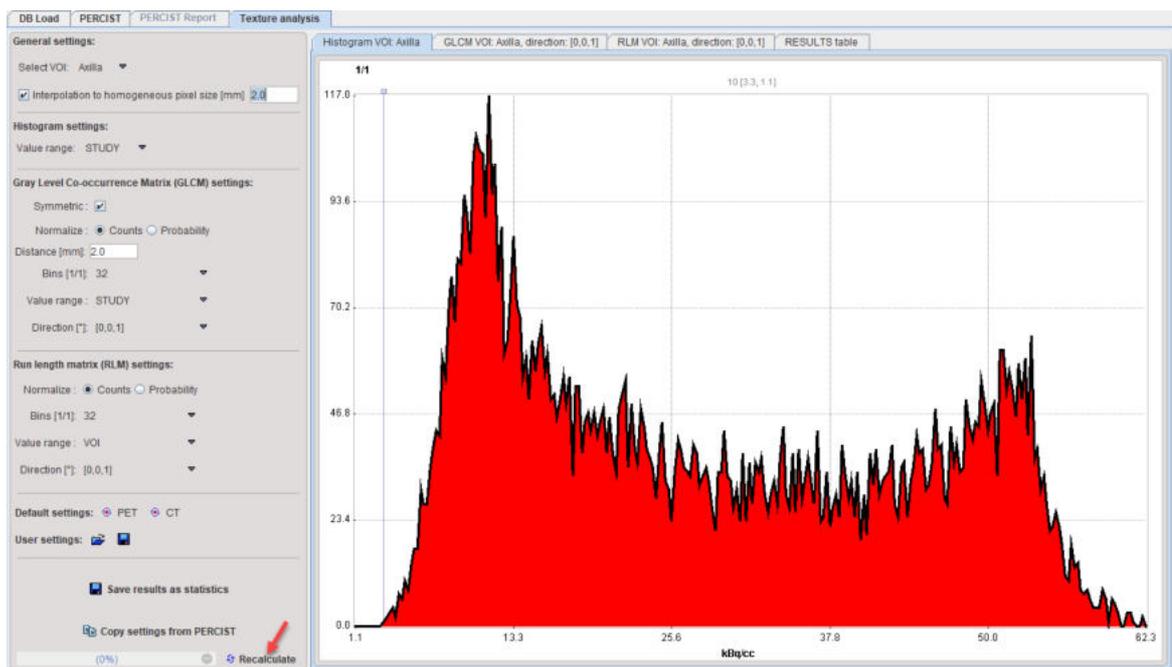
Texture analysis quantifies the variability of the pixel intensities within a structure such as a tumor. There is a plethora of metrics, which is discussed for instance by Hatt et al. [1] or Sollini et al. [2]. The hope is that (some of) these metrics permit in vivo lesion characterization and provide predictive information about the tumor malignancy.

Rather than calculating hundreds of indexes, the texture analysis implemented in PMOD provides a collection of 64 indexes which have been found to be most valuable in the context of PET imaging. 23 are based on the pixel histogram within a VOI, 25 based on the gray level co-occurrence matrix (GLCM) and 16 based on the gray level run length matrix (RLM). The calculations have been implemented and tested according to the report of the Image Biomarker Standardisation Initiative ([IBSI Documentation](#)).

Once the VOIs have been outlined, a texture analysis can be started with the **TA** action button.



PSEG performs the texture analysis within the VOIs and shows the result in the **Texture Analysis** page. The controls to the left allow configuring the analysis parameters, and the four panels to the right show information related to the texture calculation.



**Select VOI** allows choosing a representative VOI for which the information in the panels is updated. **Interpolation to homogeneous pixel size** is recommended for data which doesn't have isotropic resolution, and uses trilinear interpolation.

### Histogram Analysis Configuration

The **Histogram** panel shows the histogram of the values within the selected VOI. The **Value range** selection defines whether the 256 bins cover the range of the **STUDY**, the current **VOLUME**, or just the **VOI** itself. This will be the input into the histogram-based analysis.

### Gray Level Co-occurrence Matrix (GLCM) Analysis Configuration

The GLCM calculation is configured on the **Gray Level Co-occurrence Matrix settings**: The pixel values are quantized into a small number (N) of discrete values. Similar to the histogram, this process is defined by the specified number of **Bins** (eg. **32**) which cover the range of the **STUDY**, the current **VOLUME**, or just the **VOI** itself, according to the **Value range** selection.

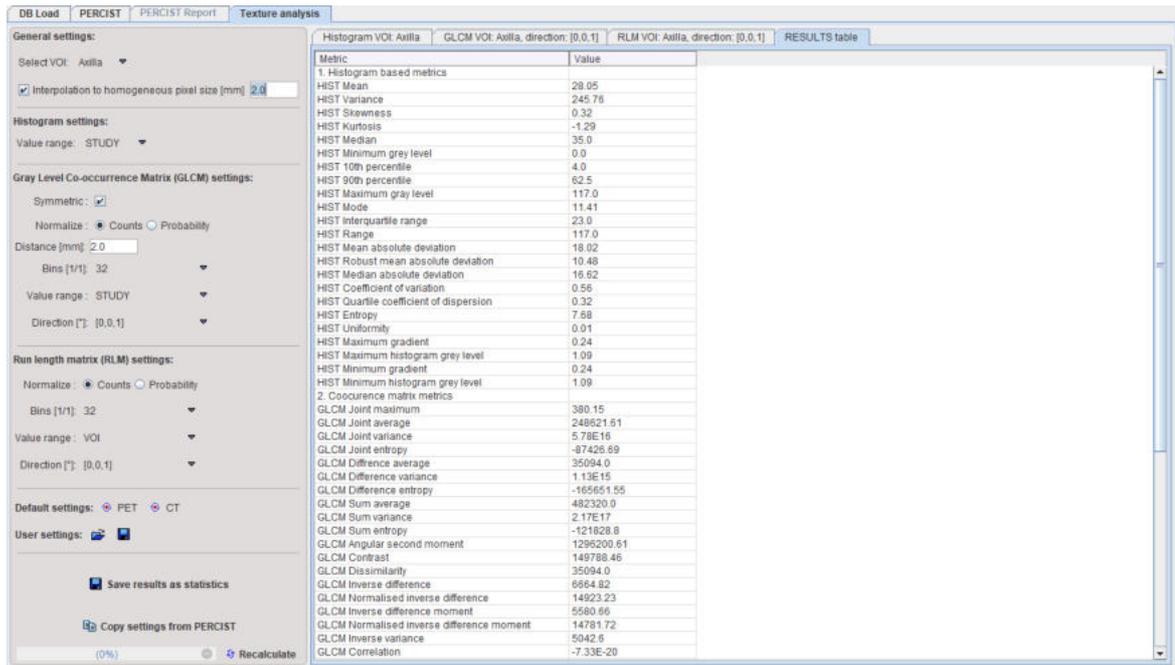
The occurrence of the quantized values in neighbouring pixels is analyzed, and co-occurrences recorded in a NxN matrix (GLCM): A value  $i$  next to a value  $k$  will increment the number in the co-occurrence matrix at coordinate  $(i, k)$  by 1. If **Symmetric** is enabled, coordinate  $(k, i)$  is incremented as well, producing a symmetric GLCM. A pixel has several neighbors in different **Directions** at a certain **Distance**. The co-occurrence can be analyzed in any direction individually. In fact the matrix resulting from the direction specified with the **Direction** selection is visualized in the GLCM tab. Note, however, that the average matrix of all directions is used for the calculation of the GLCM-based indexes.

### Gray Level Run Length Matrix (RLM) Analysis Configuration

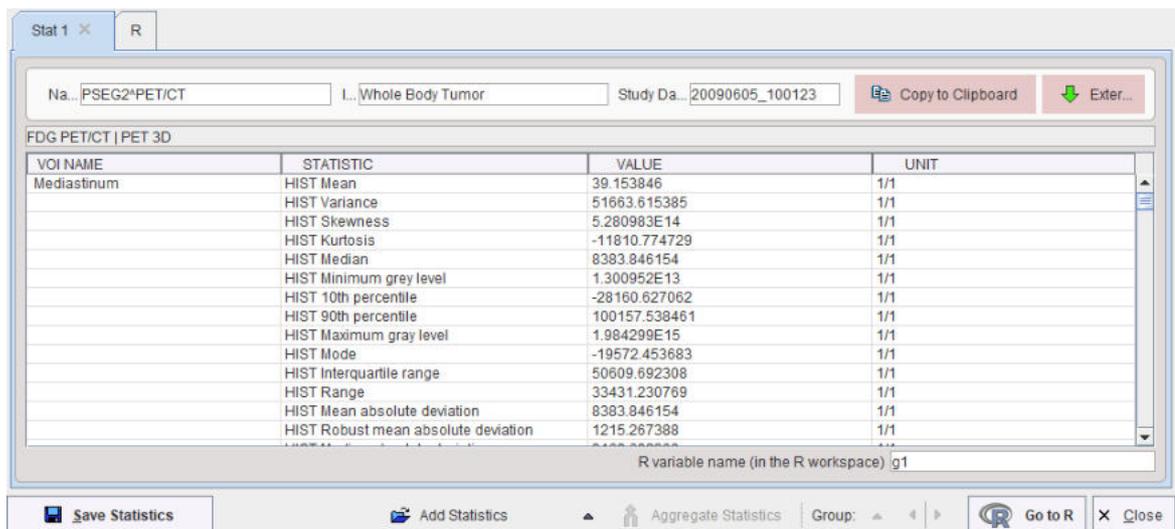
The RLM consists of the following steps to be configured on the **Run Length Matrix (RLM) settings**: As for the GLCM, the pixel values are quantized into a small number (N) of discrete values. A run length is defined as the length of a consecutive sequence of pixels with the same gray level along direction a certain direction.

### Texture Calculation

**Recalculate** initiates calculation of the Histogram and the GLCM/RLM matrices for the VOI with the configured parameters and shows them for preview in the first three panels, and the texture metrics in the **RESULTS table**.



While only one VOI at the time can be evaluated in the user interface, **Save results as statistics** allows saving the results of all VOIs via the usual PMOD statistics interface illustrated below.



### References

1. Hatt M, Tixier F, Pierce L, Kinahan PE, Le Rest CC, Visvikis D: Characterization of PET/CT images using texture analysis: the past, the present... any future? Eur J Nucl Med Mol Imaging 2017, 44(1):151-165. [DOI](#)

2. Sollini M, Cozzi L, Antunovic L, Chiti A, Kirienko M: PET Radiomics in NSCLC: state of the art and a proposal for harmonization of methodology. Scientific reports 2017, 7(1):358. [DOI](#)

## 2.3 ORGAN SEGMENTATION

### Background

Preclinical imaging systems allow following the uptake and metabolism of labeled compounds in whole mice and major parts of rats. To exploit this wealth of information with regard to pharmacokinetics, it is necessary to localize all relevant tissue structures and assess their tracer concentration in time, which is then analyzed with kinetic models.

Manual segmentation is a tedious process and prone to considerable subjective variability. It is challenging for studies involving many animals, has a direct impact on the accuracy of the study endpoint and consequently on the required sample size.

### Solution Overview

The **ORGAN SEPARATION** approach in the PSEG tool supports the semi-automatic segmentation of dynamic rodent PET studies within only a few minutes. It applies a patented clustering approach for grouping neighboring image pixels with similar kinetic behaviors. This process creates a hierarchy of compact tissue segments covering the whole body. Segments on low hierarchy levels are small and highly homogeneous regarding kinetics, whereas they grow towards higher levels and become kinetically more variable. The user can interactively browse through the hierarchy levels and assign an organ label when an appropriate representation has been found. If tissue structures cannot directly be represented by a segment or a union of segments, the user can interactively outline them in an anatomical reference image.

Once all relevant tissue structures have been segmented, PSEG readily calculates their average PET uptake curves (also time-activity curves, TAC) and optionally corrects them for the partial-volume effect.

### Segmentation Methodology

PSEG implements the local means analysis (LMA) method licensed from CEA, Orsay, France. This method aims at segmenting "functional organs" characterized by a particular pharmacokinetics. A functional organ only corresponds to an entire anatomical organ if the organ is functionally homogeneous. Otherwise, the functionality of different organ parts are separated and can be treated individually. The patented LMA method has been shown to be robust regarding the low signal-to-noise ratio, the limited spatial resolution and potential organ movement of dynamic rodent PET studies [3,4,5].

The LMA segmentation includes the following processing steps:

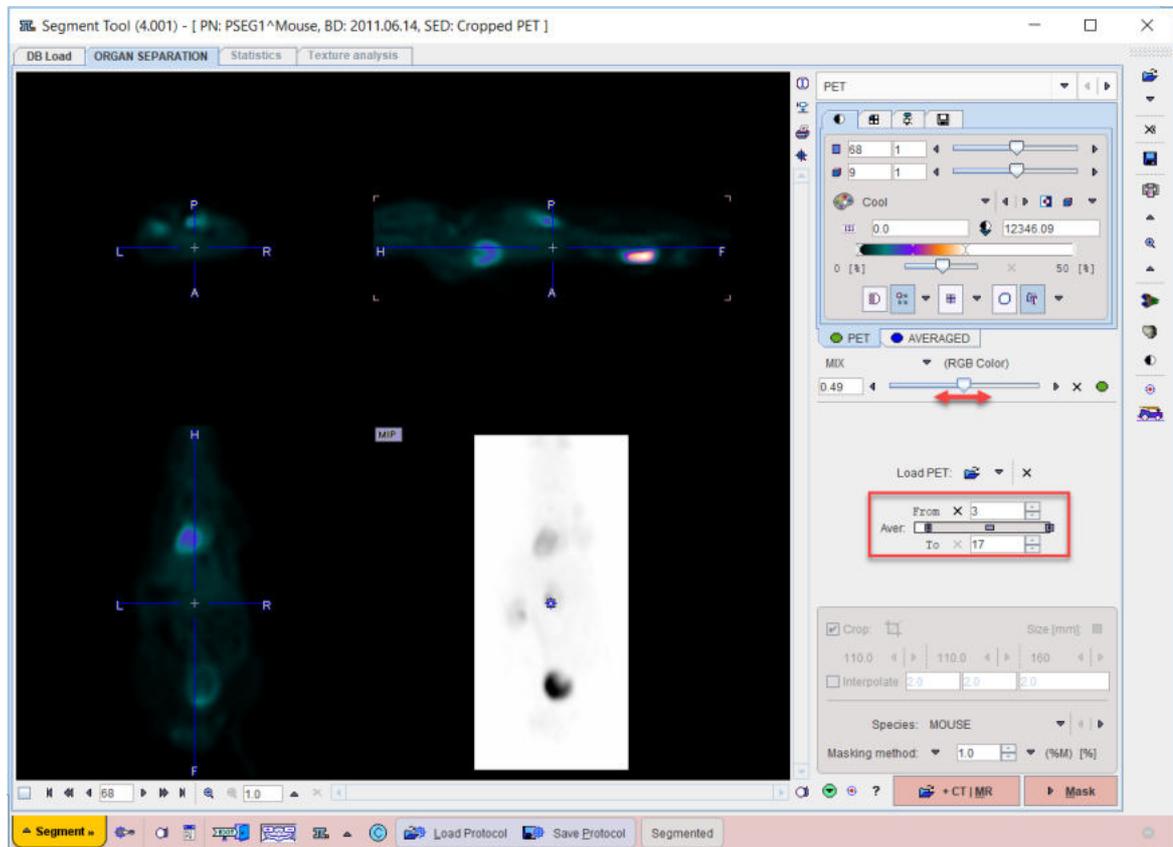
- Exclusion of the noisy background from segmentation.
- Automated localization of pixels in the organ centers.
- Computation of the local pharmacokinetics and global noise parameters.
- Parcellation of the body volume in the image into a predefined number of regions.
- Hierarchical fusion of the regions to form increasingly larger, connected regions. On each level of the hierarchy, the whole body is covered by disjoint regions.

Tissue structures which cannot be isolated by the LMA segmentation because they do not kinetically differ from the neighborhood need to be outlined using the general VOI features of PMOD.

The following sections describe the stepwise workflow for performing an ORGAN SEPARATION segmentation. For details of the common parts data loading and masking, the user is referred to the corresponding sections of the PERCIST segmentation.

### 2.3.1 PET Image Loading and Time Averaging

Step-wise processing is started by selecting the second tab, initially labeled **Segment**, and thereafter **ORGAN SEPARATION**.



On the first panel labeled **PET**, the PET image is loaded, optionally cropped and interpolated, and the mask configured as described [above](#) <sup>9</sup>.

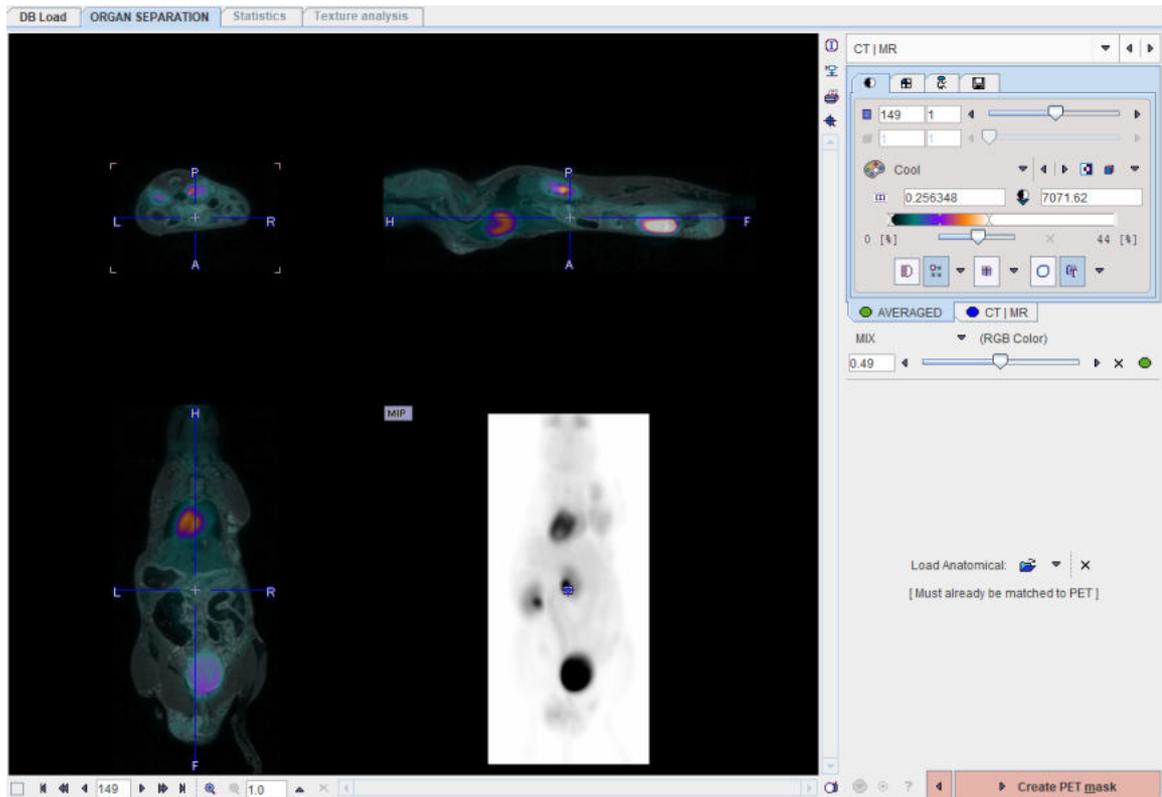
As the ORGAN SEGMENTATION method requires dynamic data, an additional static series is generated by averaging a range of frames. The aim is to generate an image which is useful as anatomical reference for the segment interpretation, as well as for creating the body mask.

The averaging range can be defined by the **From** and **To** number fields, or dragging the range indicators in the **Aver** bar. The averaged image is assigned to the **AVGERAGED** image tab. The original and the averaged images are shown in a fusion rendering which can be adjusted in the fusion control area below the image selection tabs. After any modification of the frame range, the average image is recalculated and the display updated.

Depending on the availability of CT or MR images and the mask configuration, an appropriate action button should be activated in the lower right.

### 2.3.2 MR or CT Reference Image Loading

The layout of the second panel depends on the settings on the **PET** panel (see [above](#) <sup>9</sup>). The situation illustrated below represents the situation of **PET-based** masking. The panel is titled **CT | MR**, and in the lower right there is only one action button **Create PET mask**. Other configurations are described [here](#) <sup>11</sup>.

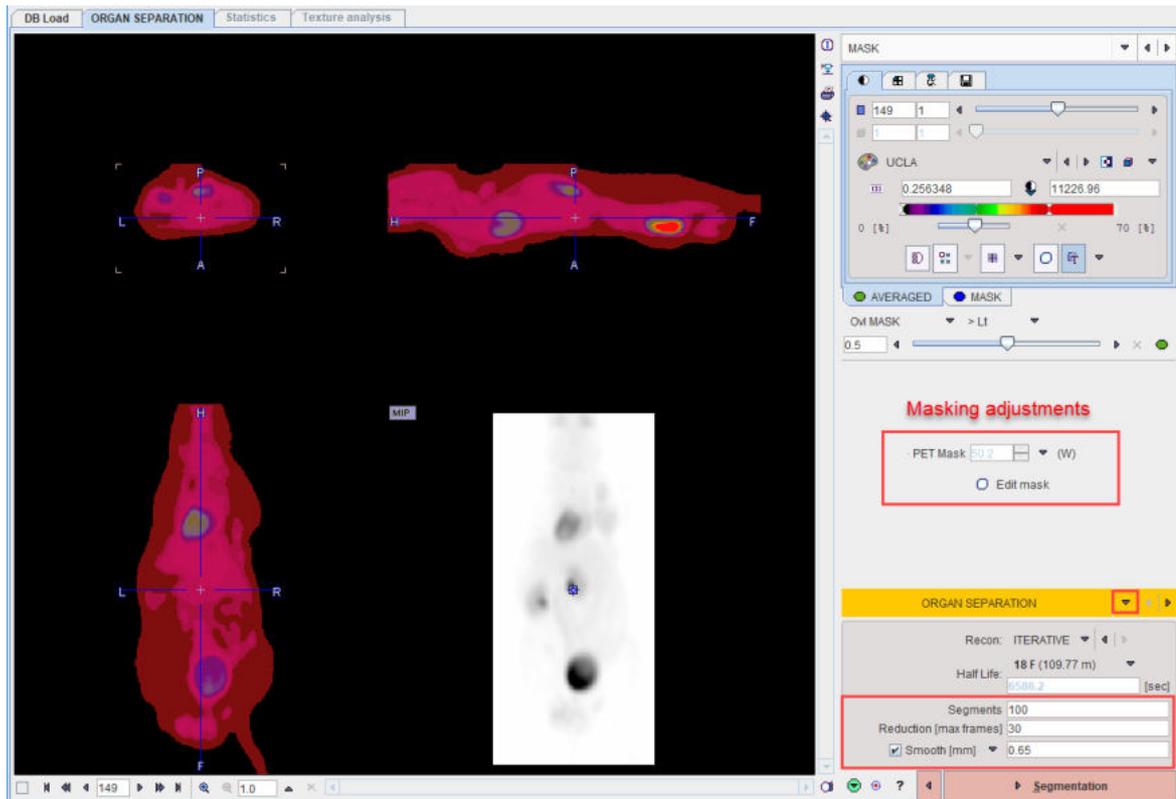


On this panel, the MR or CT image have to be loaded and the mask configured, if MR or CT based masking was selected on the **PET** panel.

Processing is continued by activating the action button in the lower right, **Create PET mask** in the example shown. The result is displayed on the next panel **MASK**.

### 2.3.3 Body Mask Creation and Segmentation Configuration

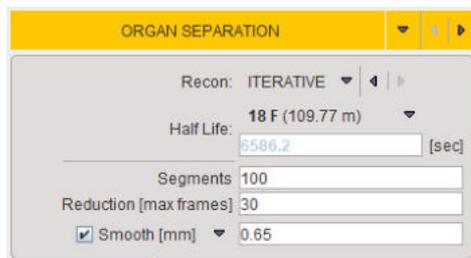
When arriving at the **MASK** panel, the display shows a fusion of the **AVERAGED** PET with the generated **MASK**.



As described [above](#) <sup>13</sup>, the mask can be edited if necessary.

### Segmentation Configuration

Next, the segmentation method in the lower section needs to be switched to **ORGAN SEPARATION**. Consequently, its configuration parameters are shown.



As the method has been developed for the functional segmentation of dynamic rodent images, it incorporates related prior knowledge. Particularly, it accounts for specific noise characteristics in the PET image. Therefore, the image **Reconstruction** method (**FBP** or **ITERATIVE**) and the isotope **Half Life** need to be specified properly.

Additionally, three parameters need to be set for the segmentation:

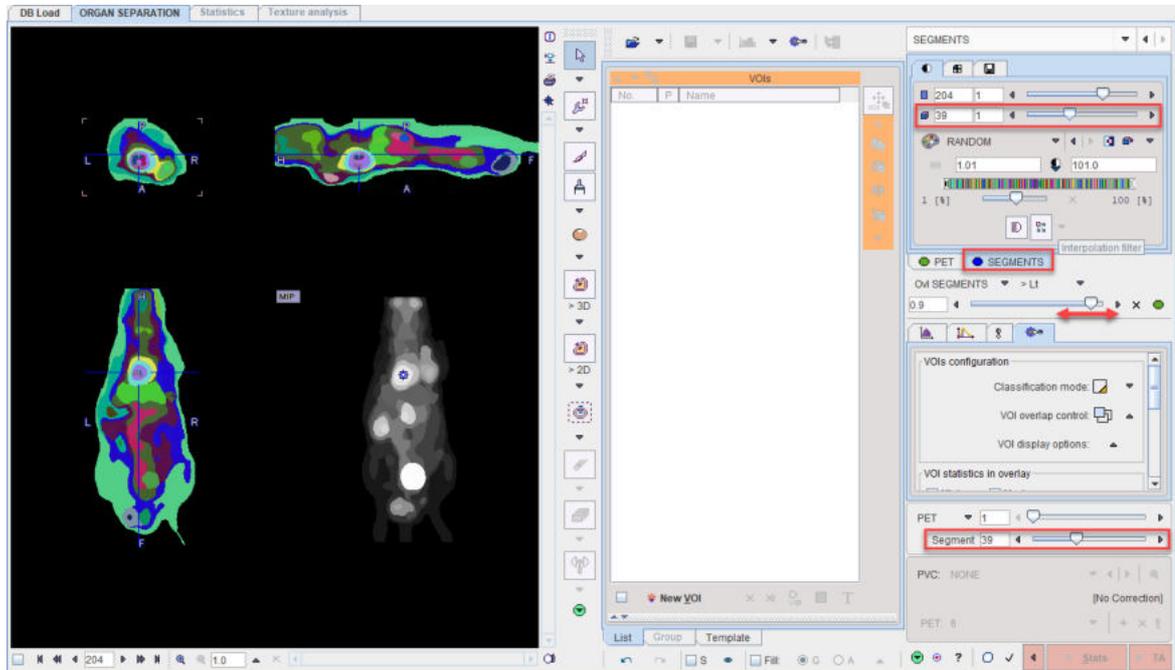
- **Segments:** Specifies the maximal number of segments. As the method applies a hierarchical approach, decompositions with any smaller number of segments down to 1 will also be available.
- **Reduction:** If the **Reduction** number is smaller than the number of frames in the dynamic PET, the frames are averaged accordingly.
- **Smooth:** Optional spatial smoothing of the data. The Gaussian kernel size can be entered in mm, or by selecting a specific PET system with the down-arrow. Note that smoothing reduces the level of detail which can be obtained by the segmentation.

Once an appropriate body mask is ready and the segmentation parameters have been defined, please start calculations with the **Segmentation** button. The required processing time depends on

several factors including the matrix size, and may take several minutes. The segmentation result is shown on the next **SEGMENTS** panel.

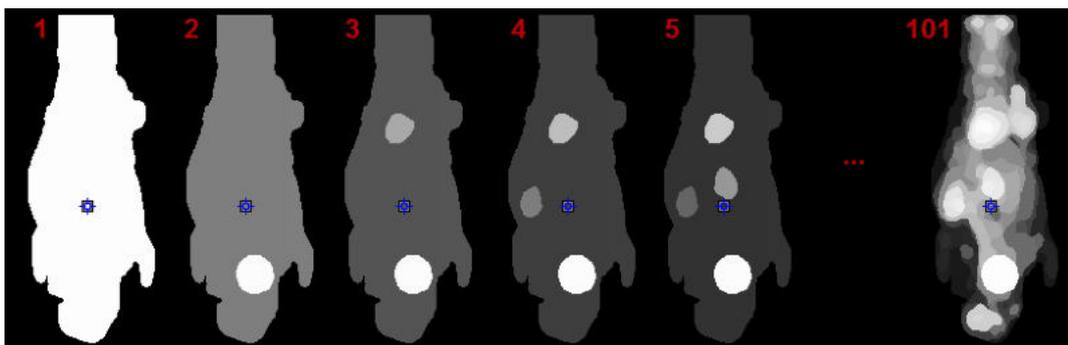
### 2.3.4 ORGAN SEPARATION Segmentation

The initial layout of the **SEGMENTS** panel shown below. The display shows a fusion of the segmentation result (**SEGMENTS**) with the dynamic **PET** image as the reference.



#### SEGMENTS Image

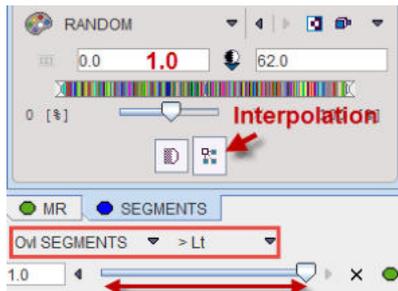
The ORGAN SEPARATION results in a hierarchy of segments which is organized as a "dynamic" series with increasing number of segments. The first "frame" has only a single segment which corresponds to the whole body mask. The second segment decomposes the area of the body mask into a background and a single segment, the third shows two segments, and so on, as illustrated below.



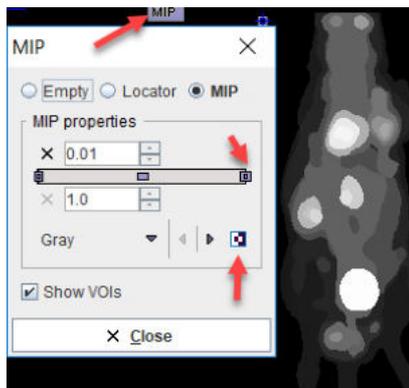
The number of segments can be adjusted by entering the number into indicated fields or dragging the slider. In contrast, the k-means CLUSTER ANALYSIS doesn't provide a hierarchical segmentation, just a single decomposition.

**Note:** On each hierarchical level, the segments decompose the body mask into disjoint, compact volumes.

Per default the **RANDOM** color table is applied for showing the segments decomposition with the aim of separating neighboring segments. Interpolation is switched off to avoid distracting color effects at segment boundaries.

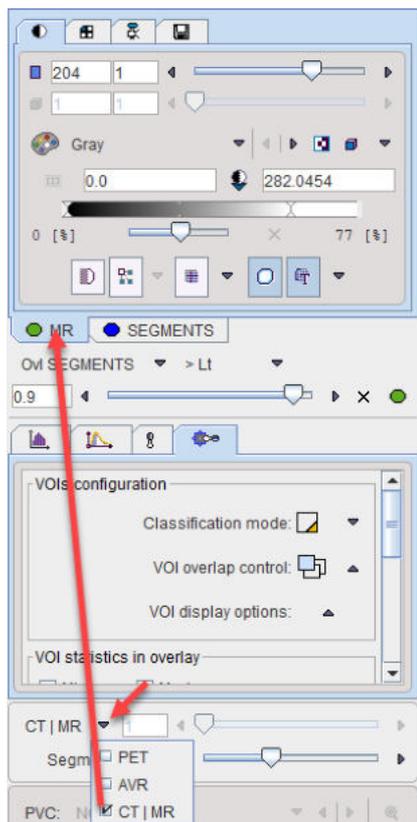


The **MIP** representation of the **SEGMENTS** image is a valuable tool for detecting segments of interest. To have it available please make sure the **SEGMENTS** tab is selected. Furthermore, the full range should be enabled for the MIP.



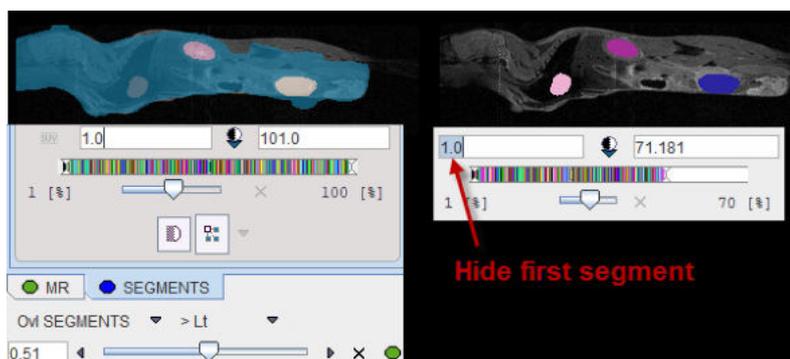
### Reference Image

The reference image which is used as a backdrop for the segments can be selected as illustrated below. The dynamic **PET** as well as the averaged PET (**AVR**), are always available, and the anatomical images optionally. Note that after switching between the PET and anatomical images, the color table most likely requires adjustments.



### Image Fusion

Per default the fusion mode is set to **OVL SEGMENTS > Lt**, meaning that only the segments above the lower threshold are shown in the image. It may be helpful to set the threshold to 1.0 in order to hide the first "background segment". Please use the blending slider to inspect the reference image below the segments.

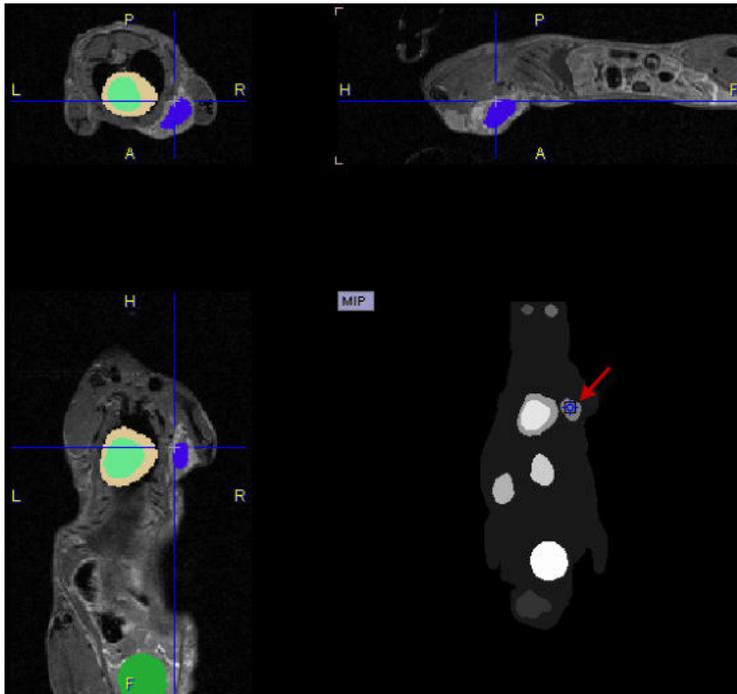


### Navigational Elements

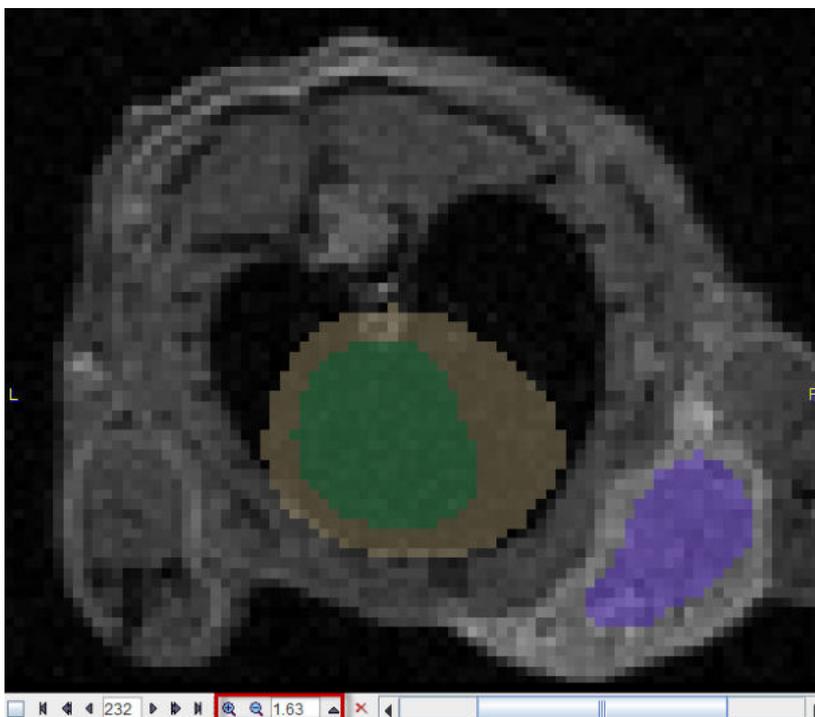
The number of segments is best changed in the lower right slider area. The recommended procedure is to set the **Segment** number to **1**, and then gradually increase it by the increment arrow.



The easiest way to localize segments in the image is via the MIP image: Clicking at a segment will update the orthogonal image planes with intersection at the segment. To center the intersection point on the segment please click on the slice images, or use the mouse wheel for scrolling slices.



Close examination might require switching the image layout from the orthogonal layout to a single plane layout and some zooming, and then adjusting the blending. There are zooming elements available below the image, but the image can also be zoomed by the mouse wheel when holding down the **Ctrl** key.

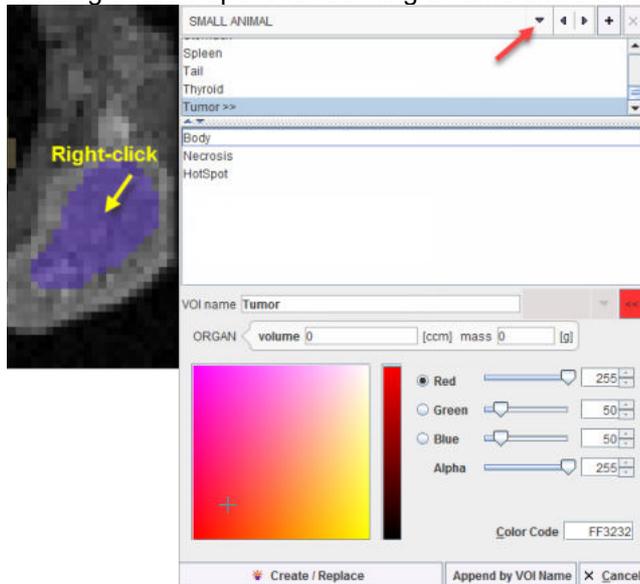


### Segment Assignment to VOIs

The basic idea of the whole processing is that the segmentation produces (on some decomposition level) segment definitions which represent meaningful tissue structures in the body. Please use the following procedure for creating a named VOI corresponding to a tissue structure of interest (called "organ" or "lesion" in the following):

1. Select an appropriate reference image wherein the organs can be seen.

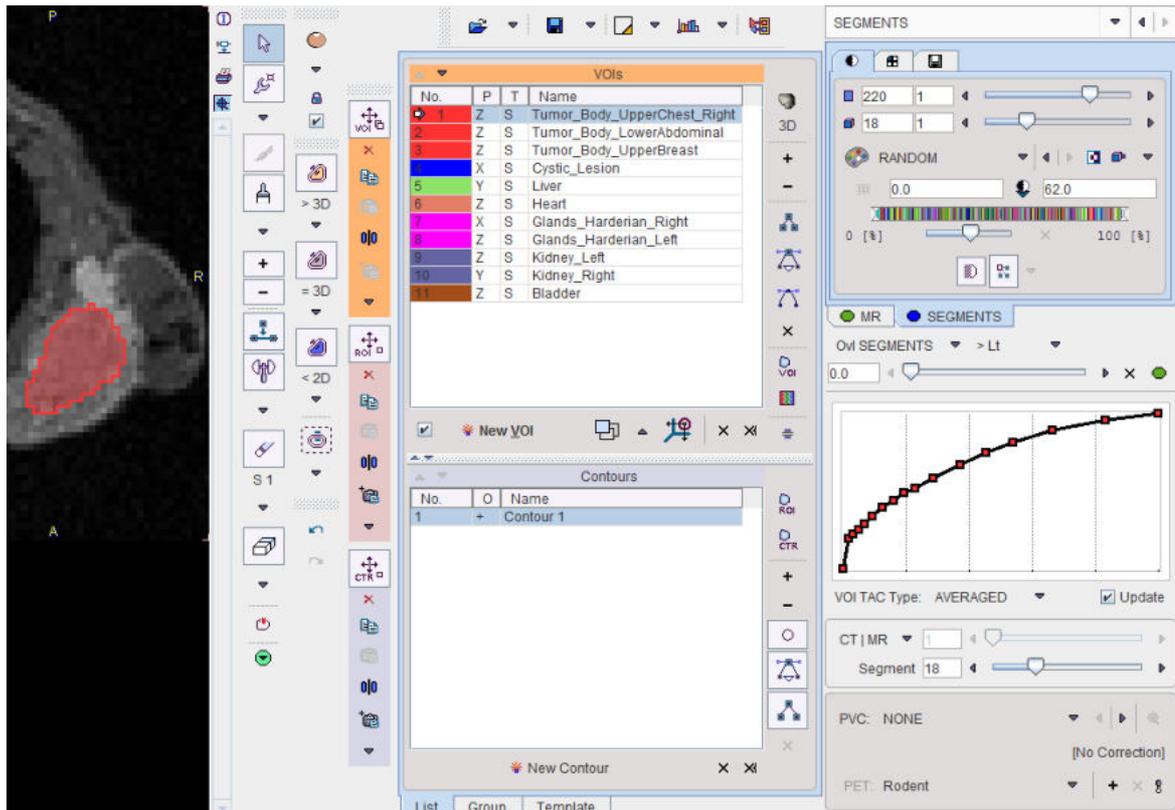
2. Adjust the transparency with the fusion slider so that the organ is visible below the segment image.
3. Operate the **Segment** slider until one of the segments in the image corresponds to the organ.
4. Make sure the **SEGMENTS** tab is selected. Otherwise the assignment will not work as expected.
5. Right click into at the segment in any of the slice images shown (NOT the MIP image).
6. A dialog window opens for defining a name and a color.



Several lists with pre-defined organ names are available such as **DICOM**, **SMALL ANIMAL** and some **DOSIMETRY** lists. Select either in upper selection. Custom name lists can also be prepared as described below.

7. Select an organ name from the list. Organs with trailing **>>** such as **Tumor>>** offer a substructure list. Other organs like the **Kidneys** offer a **Laterality** choice. Select as appropriate.
8. The **VOI name** shown in the text entry field is composed from the selections, but can be edited or completely redefined.
9. Change the VOI color.
10. Confirm the dialog window with one of the buttons. **Create/Replace** adds the VOI to the list, and overwrites any VOI with the same name. **Append by VOI name** causes the current VOI to be merged with an existing VOI of the same name. **Cancel** discards the definition.

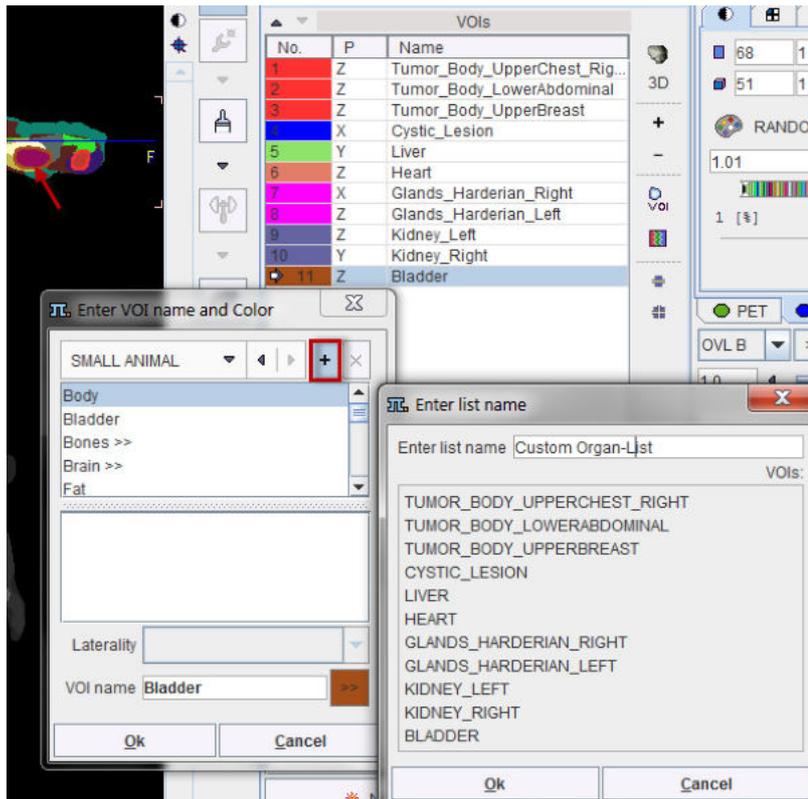
The VOI name appears in the VOIs list, the contours are shown in the image, and the time-activity curve is calculated.



Please repeat the sequence above for all organs and lesions of interest.

### Custom VOI Name List

A **VOIs** list with manually edited names can easily be converted into a custom name list: Right click into any segment to open the assignment window. Activate the **+** button, specify a **list name** in the appearing dialog window and confirm the dialog window with ok.

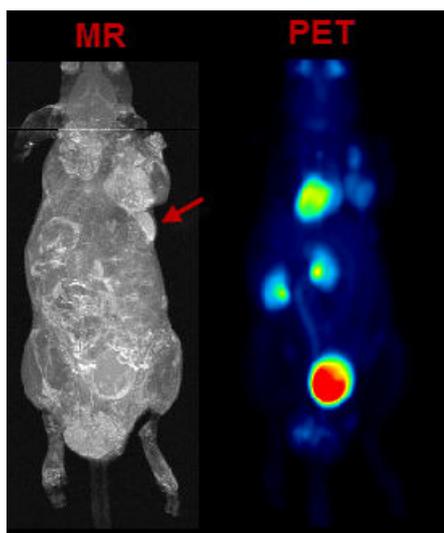


From then on, this list can be used alternatively to the pre-defined lists.

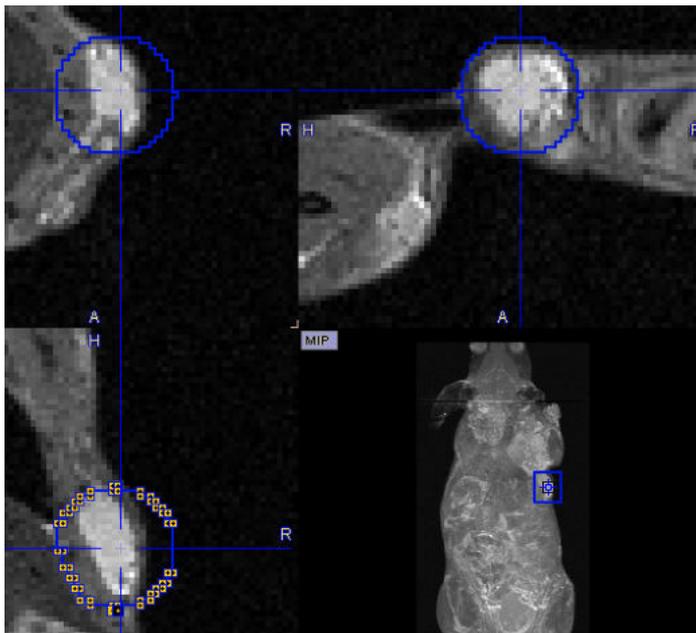
### VOI Adjustments and Addition

The VOIs created by segment assignment are regular PMOD contour VOIs which can be adjusted in many ways. For instance, if the segmentation produced two complementary parts of a structure, their VOIs can easily be merged into a single VOI.

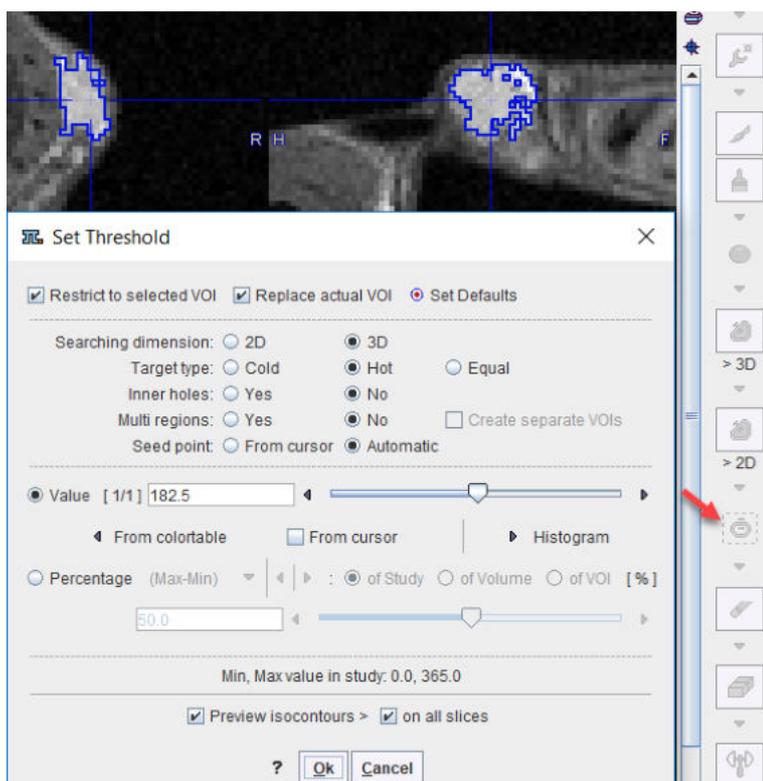
VOIs can also be added in a completely manual manner. In the example data set, for example, there is a bright part in the MR image which does not take up FDG.



In the present situation, a VOI can be obtained from the MRI image as illustrated below. First, the MR image tab is selected to direct the contouring operation to the **MR** image content, not the **SEGMENTS**. Then, a sphere object is placed for enclosing the lesion.



Next, the iso-contouring is started. The parameters are set to **3D** with **Multi regions** off to create a single compact VOI. The iso-contour is shown in the image, and the contouring level may be adjusted by the **Value** setting.

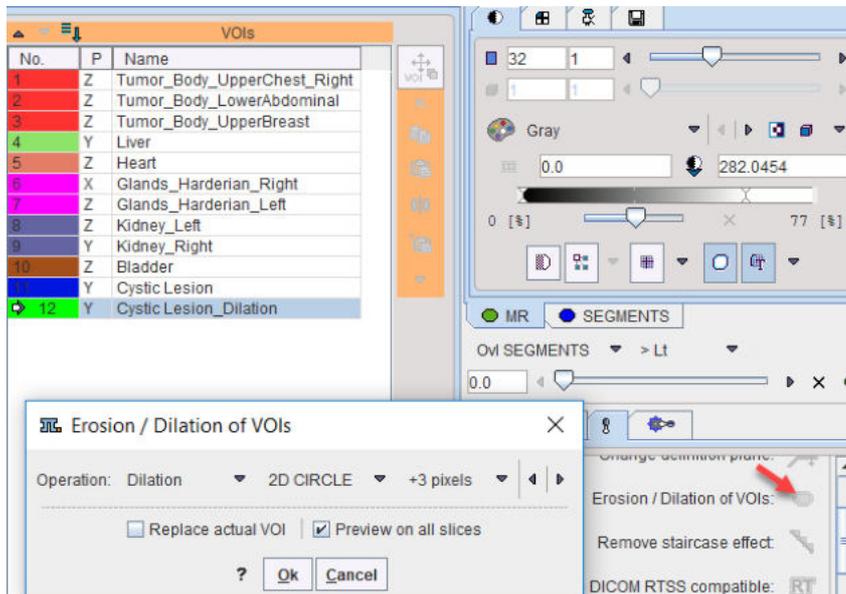


After closing the dialog window with **Ok**, the contouring result is shown, and the VOI can be labeled.

### Morphological Operations

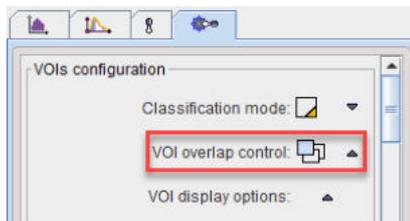
Morphological operations support convenient functions for modifying the created VOIs, such as shrinking, growing, removing holes and single pixels. Please select the VOI to be modified in the list, then activate the **Erosion/Dilation** function from the VOI tools area. A dialog window appears offering a list of **Methods** with corresponding **Structuring Elements** and their **size**. The changes

to the VOI are immediately reflected when configuring the operation. Note that the result may replace the existing VOI, or be added as a new VOI.



### Non-overlapping of VOIs

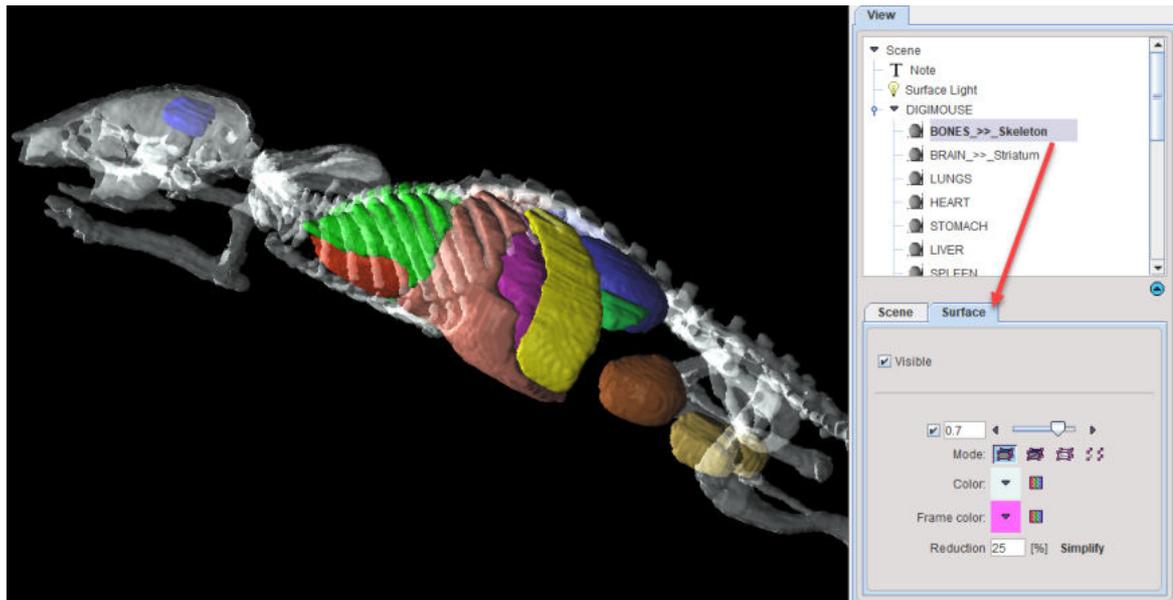
In order to avoid the creation of overlapping of VOIs (which causes problems with partial-volume correction), the VOI **Edit mode** is pre-configured accordingly.



If VOIs are created by the merging of existing VOIs, please make sure that the original VOIs are removed.

### Digimouse Visualization

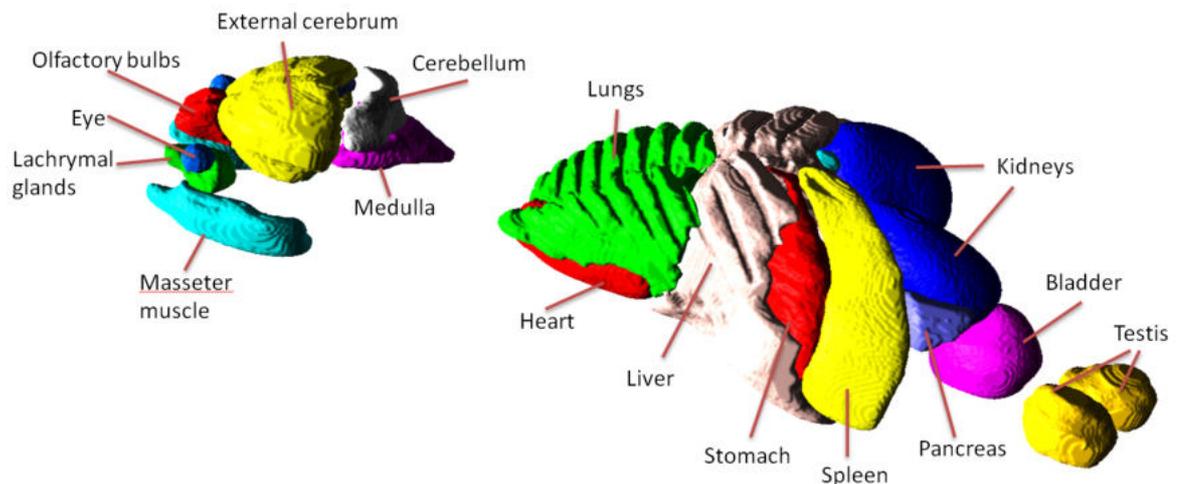
During the assignment of segments to organs it may be helpful to relate the information in the image display with an anatomical whole-body mouse atlas. The PSEG tool includes a 3D rendering of the [Digimouse Atlas](#) [1,2] which is only available if the PMOD license contains the P3D rendering option. In this case the corresponding  button in the lateral taskbar is active and launches the tool as illustrated below.



Note the organ list in the **View** panel to the right which allows selecting individual objects and changing their representation. In the example above, the **BONES** object is selected, with the corresponding **Surface** panel giving access to its properties. For instance, by removing the **Visible** check the bones could be hidden from the rendering. Note that multiple objects can be selected and a property such as transparency changed for all of them at once. Please refer to the *PMOD 3D Rendering Tool Guide* for more information about the renderings options.

**Note:** The 3D Digimouse window can remain open while assigning the segments. After hiding irrelevant structures it is recommended to reduce the window size and hide the control area with the  button in the lateral taskbar.

The structures available in the Digimouse phantom are illustrated below.

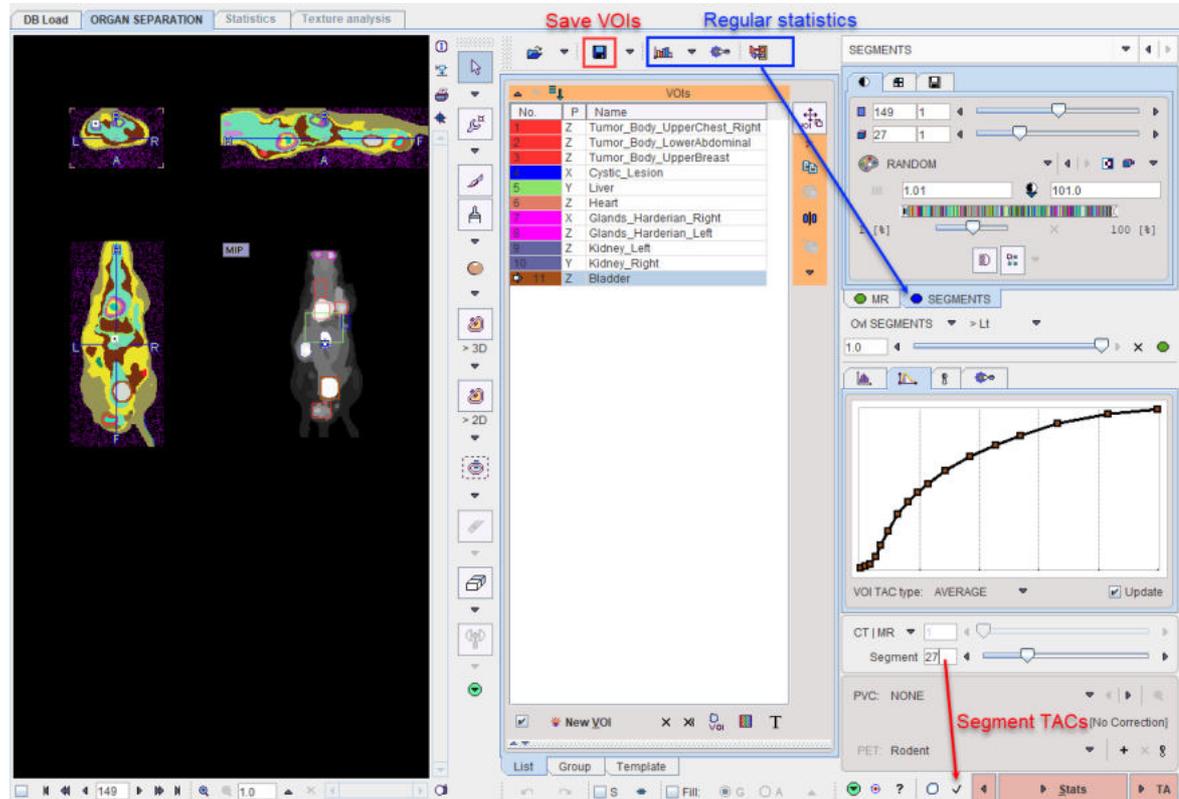


## References

1. B. Dogdas, D. Stout, A. Chatziioannou, R. M. Leahy, Digimouse: A 3D Whole Body Mouse Atlas from CT and Cryosection Data, *Phys. Med. Bio*, 52: 577-587, 2007. <http://dx.doi.org/10.1088/0031-9155/52/3/003>
2. D. Stout, P. Chow, R. Silverman, R. M. Leahy, X. Lewis, S. Gambhir, A. Chatziioannou, Creating a whole body digital mouse atlas with PET, CT and cryosection images, *Molecular Imaging and Biology*.2002; 4(4): S27

### 2.3.5 Time-Activity Curve Calculation and Statistics

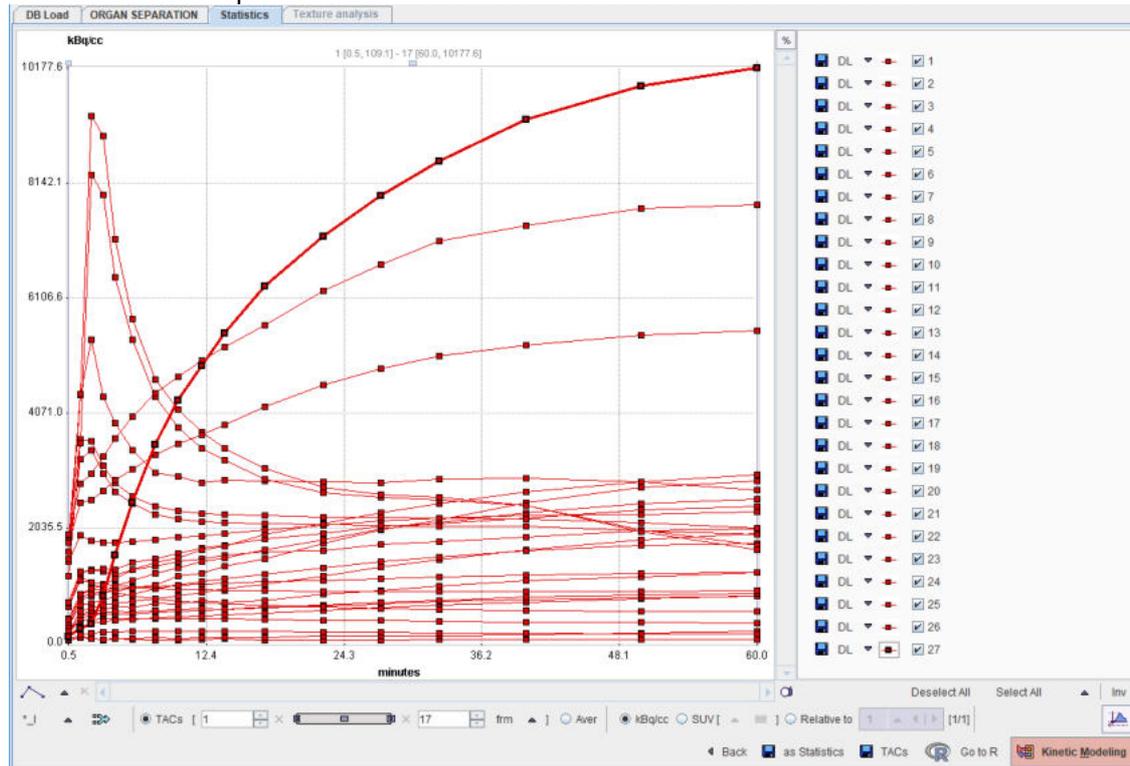
At the end of segment assignment and VOI editing the **VOIs** list contains all defined structures of interest. It is recommended saving them separately using the **Save VOIs** button illustrated below.



There are different variants for calculating statistics.

1. The regular statistics buttons above the **VOIs** list will operate on the selected image. In the example above, statistics would be calculated from the **SEGMENTS** image and be useless. However, the user might select the first image tab and the averaged PET as the reference image. In this case, statistics will result in the average PET uptake.
2. The  button in the lower right calculates the TACs of all segments decomposing the body mask at the level defined by the **Segment** number. The example result with 27 **Segments** is

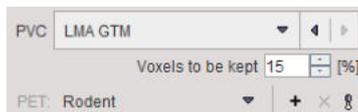
illustrated below. It provides a convenient overview of the kinetics in the data.



3. Normally the **Calculate TACs** action button will be used for producing the end result: The average PET uptake curves in all defined VOIs are calculated and presented on the **Statistics** page.

### Partial-Volume Correction (PVC)

Optionally, the **PVC** can be enabled for applying .



The **LMA GTM** method uses information from the segmentation process. Assuming that the inner-most part of the segments is least affected by the partial-volume effect, it uses only a fraction of the segment data for the segment average calculation. The percentage can be set by the **Voxels to be kept** parameter. The algorithm uses the Geometric Transfer Matrix (GTM) approach for spillover compensation at a fine segmentation level which is not shown to the user. The corrected signal for all user-assigned segments is then constructed from the corrected signals contained in the segments. The PVC procedure requires that the defined VOIs are non-overlapping. If there is overlap, the results will not be correct.

The resolution of the imaging system is crucial for the GTM method. There is a list-selection for pre-defined scanners in the lower part of the PVC area, and new scanners can easily be added. Default is the generic **Rodent** scanner with isotropic resolution of 1.5mm FWHM.

With PVC enabled, PSEG will provide both the corrected and uncorrected uptake curves on the **Statistics** page.

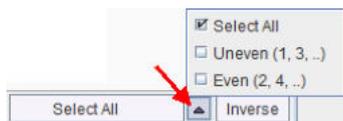
## 2.3.6 Statistics Results

The **Statistics** page is dedicated to the visualization and further use of the time-activity curves. The example below illustrates the result of calculating TACs with PVC enabled.

The **Back** arrow in the lower right is a convenience button for switching back to the **Segment** page of PSEG which generated the statistics.

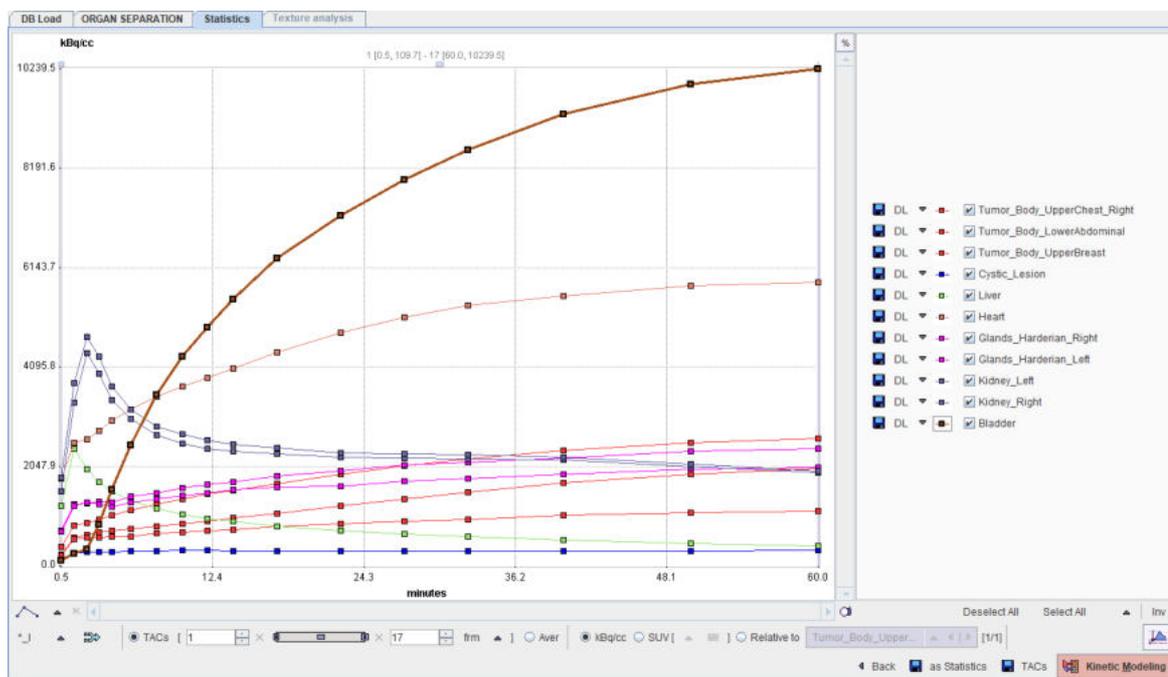
### Selection of Curve Subsets

Sometimes, only a subset of the TACs may be relevant for further processing and should be selected in the list to the right. For instance, if the optional partial-volume correction is enabled for the statistics calculation there will be pairs of curves for all VOIs: one curve representing the original data, and one curve ending with **\_C** representing the partial volume corrected data. There are some convenience buttons supporting this selection: **Deselect All** switches all curves off. **Select All** switches all curves on. **Inverse** inverts the current selection. Note the arrow button which allows to quickly select dedicated subsets.



### Transfer of TACs to the PKIN Tool

The **Kinetic Modeling** button allows directly transferring the TACs to the PKIN tool for modeling. It opens the following dialog window.



TACs can be transferred to PKIN using the **Kinetic Modeling** button. It opens a dialog window which is described in detail in the *PMOD Base Functionality User Guide*. Briefly, the TACs for transfer can be selected by checking the box in the left column. The right side lists the currently selected TACs. **Send [SET]** transfers the selection to the active workspace in PKIN. If the **Append TAC data** is enabled, the TACs will be added as additional tissue regions, otherwise the existing tissue data is overwritten. **Send [ADD]** first creates a new workspace in PKIN before actually transferring the selection.

### Saving the Statistics

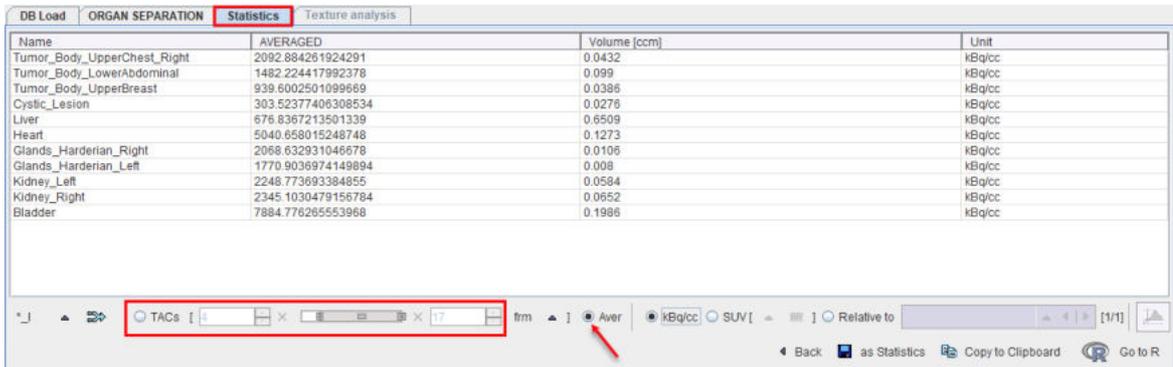
The Save **TACs** button allows saving all curves in a simple tab-delimited text file as illustrated below. Such a file can easily be imported into other programs for processing and visualization.

start[seconds]	end[kBq/cc]	Tumor_Bo	Tumor_Bo	Tumor_Bo	Cystic_Les	Liver	Heart	Glands_Ha	Glands_Ha	Kidney_Le	Kidney_Rig	Bladder	Tumor_Bo	Tumor_Bo	Tu
0	60	380.114	221.5528	207.4992	102.6775	1238.673	1803.045	725.8459	707.2146	1535.606	1806.721	109.6588	387.7057	267.4343	1
60	120	820.8457	576.1053	539.8545	243.1883	2402.688	2528.803	1260.343	1227.332	3365.928	3770.818	249.8382	854.3848	692.7699	2
120	180	880.5907	640.0921	579.2888	279.2121	1988.089	2597.902	1276.144	1295.933	4378.474	4721.757	330.0487	950.0287	774.1116	3
180	240	944.6486	682.1565	580.5773	278.2239	1731.391	2780.089	1321.961	1267.1	3953.037	4303.564	838.6104	1043.522	796.8466	4
240	300	1031.131	713.262	602.1958	289.8592	1532.681	2987.612	1296.596	1209.838	3421.908	3700.216	1570.082	1123.159	846.2061	5
300	420	1134.957	758.1786	605.9648	301.8691	1341.723	3215.362	1418.684	1293.919	3030.759	3218.521	2486.536	1287.885	889.2018	6
420	540	1261.409	803.9566	661.589	292.8661	1172.9	3480.49	1495.719	1368.695	2683.507	2866.252	3519.747	1424.484	921.5853	7
540	660	1365.036	858.1505	682.6136	321.1853	1061.131	3695.217	1592.272	1445.226	2518.211	2702.75	4307.815	1527.267	1041.758	8
660	780	1470.753	917.2937	720.9745	308.083	972.9532	3876.665	1678.036	1495.743	2408.823	2578.388	4908.41	1681.522	1080.932	9
780	900	1542.412	979.6508	741.7846	306.457	906.2761	4061.367	1726.597	1559.568	2363.485	2506.825	5493.842	1749.019	1196.057	10
900	1200	1691.433	1075.638	801.5291	303.2694	813.1308	4392.316	1845.886	1620.312	2297.27	2422.741	6327.608	1944.444	1319.51	11
1200	1500	1874.588	1224.403	858.6415	303.1281	719.8015	4799.821	1946.554	1641.805	2235.158	2329.366	7218.813	2136.715	1523.124	12
1500	1800	2060.648	1379.77	919.2335	290.6183	650.2844	5121.743	2070.251	1750.531	2209.377	2302.028	7945.154	2323.963	1746.191	13
1800	2100	2192.781	1519.666	956.6143	301.2032	592.5841	5361.922	2122.306	1792.865	2193.197	2279.914	8575.592	2464.544	1919.583	14
2100	2700	2368.967	1704.15	1032.841	301.993	523.9605	5567.85	2216.431	1879.409	2174.376	2241.131	9307.16	2657.097	2160.183	15
2700	3300	2526.163	1880.994	1091.014	307.5017	456.5826	5764.392	2355.619	1990.5	2038.278	2100.789	9921.196	2838.526	2383.876	16
3300	3900	2618.536	2001.92	1132.796	310.3426	410.5404	5839.346	2416.858	2026.613	1923.791	1955.769	10239.54	2953.921	2509.716	17

**Save as Statistics** allows storing the information in a format suitable for statistical analysis.

### Average in Frame Range

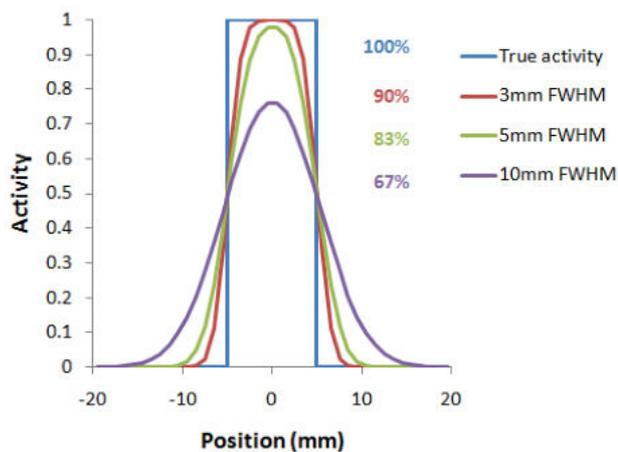
For dynamic data there is an easy way to calculate the average regional uptake in the regions in a certain frame range: with the **TACs** radio button selected define the frame range to be averaged. As soon as the **Aver** radio button is switched on, the averaged uptake statistics is calculated and listed, replacing the curves display.



## 2.3.7 Partial-Volume Effect

### Partial-Volume Effect

PET images are inherently affected by the partial-volume effect. This means that the measured tracer activity concentration is not accurate due to the relatively low image resolution and the limited tissue sampling. The low spatial resolution of the PET system 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.

Partial-volume effects are complex: 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.

#### VOI Based Partial-Volume Correction (GTM Method)

The Geometric Transfer Matrix (GTM) method according to Rousset et al. [6] restricts partial volume correction to the signal of the true objects which are constituted by VOIs. The relation of measured PET values (affected by the partial-volume effect) to the true PET values is given by the matrix equation below

$$\vec{C}_{measured} = [GTM] \times \vec{C}_{true}$$

with the following notations:

$C_{true}$	Vector of the true average activity concentration in the different VOIs of interest. The vector length $n$ equals the number of object VOIs.
$C_{measured}$	Actually measured average activity concentration in the different VOIs. Each VOI is assumed to have a homogeneous concentration.
GTM	Geometric Transfer Matrix which describes the spill-over among all the VOIs. The matrix is square with $n \times n$ weighting elements $w_{ij}$ which express the fraction of true activity spilled over from VOI <sub><math>i</math></sub> into VOI <sub><math>j</math></sub> .  In practice, $w_{ij}$ is calculated as follows: A binary map is created with 1 in all pixels of VOI <sub><math>i</math></sub> and 0 elsewhere. The map is convolved with the imaging Point-Spread Function (PSF), and in the resulting spillover map the weighted average of all VOI <sub><math>j</math></sub> 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. It has been shown [4] that this algorithm is robust to noise propagation during the correction process.

#### LMA Variant of GTM Method

The LMA (Local Means Analysis) GTM method [3] uses the homogeneous regions localized by the segmentation and calculates the average uptake in the inner of the structures. The percentage of pixels per segment considered for averaging is a parameter of the method. With 100% pixels included, the LMA GTM method equals the standard GTM method.

## 2.4 CLUSTER ANALYSIS (K MEANS)

In addition to the ORGAN SEPARATION method which incorporates prior knowledge, PSEG offers k-means clustering as a general method for subdividing a volume into clusters of "kinetically similar" pixels [7]. The time-weighted Euclidean distance is used as the measure of dissimilarity (or distance) between TACs. In PSEG, the procedure performs the following steps for the pixels within a mask, given a prescribed number N of clusters

1. N non-background pixels serving as initial cluster centroids are randomly assigned.
2. Each pixel is assigned to that centroid with minimal distance between the TACs, thus forming N initial clusters.
3. For each cluster a new centroid TAC is calculated as the average TAC of all pixels in the cluster.
4. An iterative process with a maximal number of iterations is started which repeats the following two steps:
  - a. Each pixel TAC is compared with all centroid TACs and assigned to the cluster with minimal distance.
  - b. All centroid TACs are recalculated to reflect the updated cluster population.

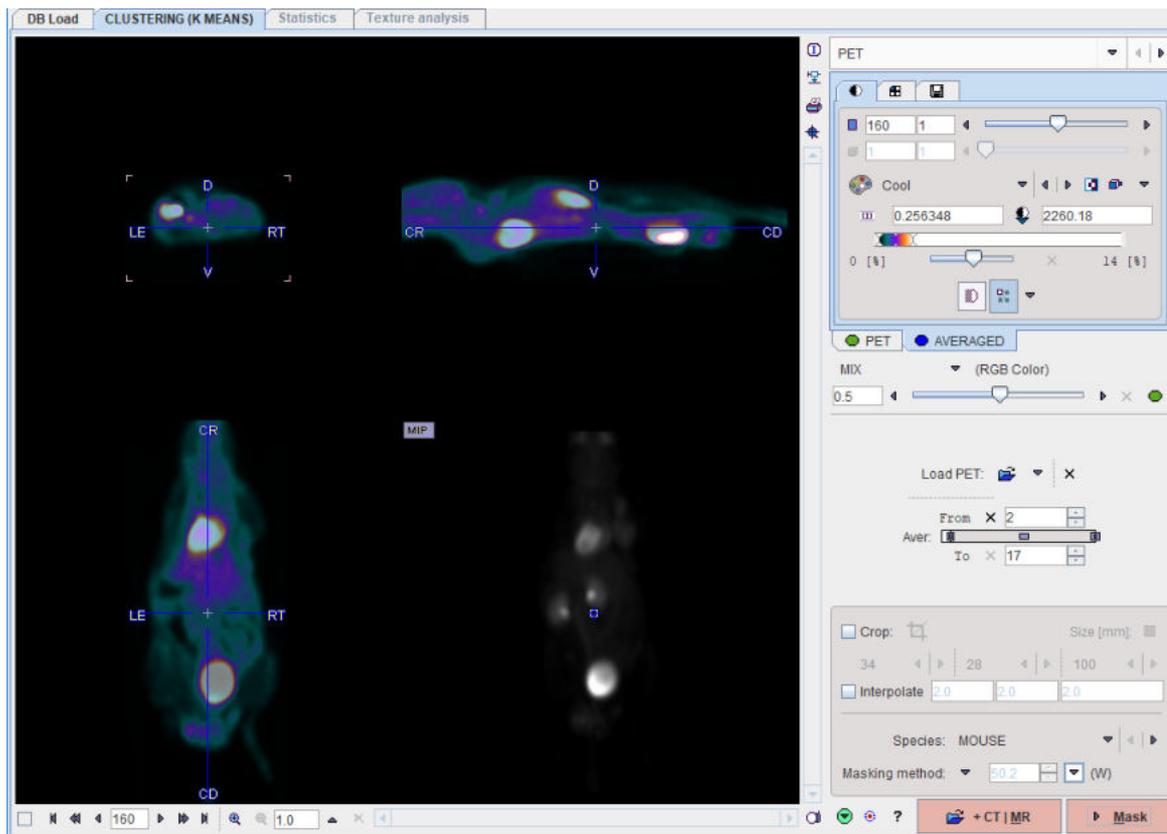
The iterations are repeated until no pixels are re-assigned to a different cluster, or the maximal number of iterations is exhausted.

Note that because no geometric information is used for the clustering, spatially disconnected pixels will most likely be included in the resulting clusters.

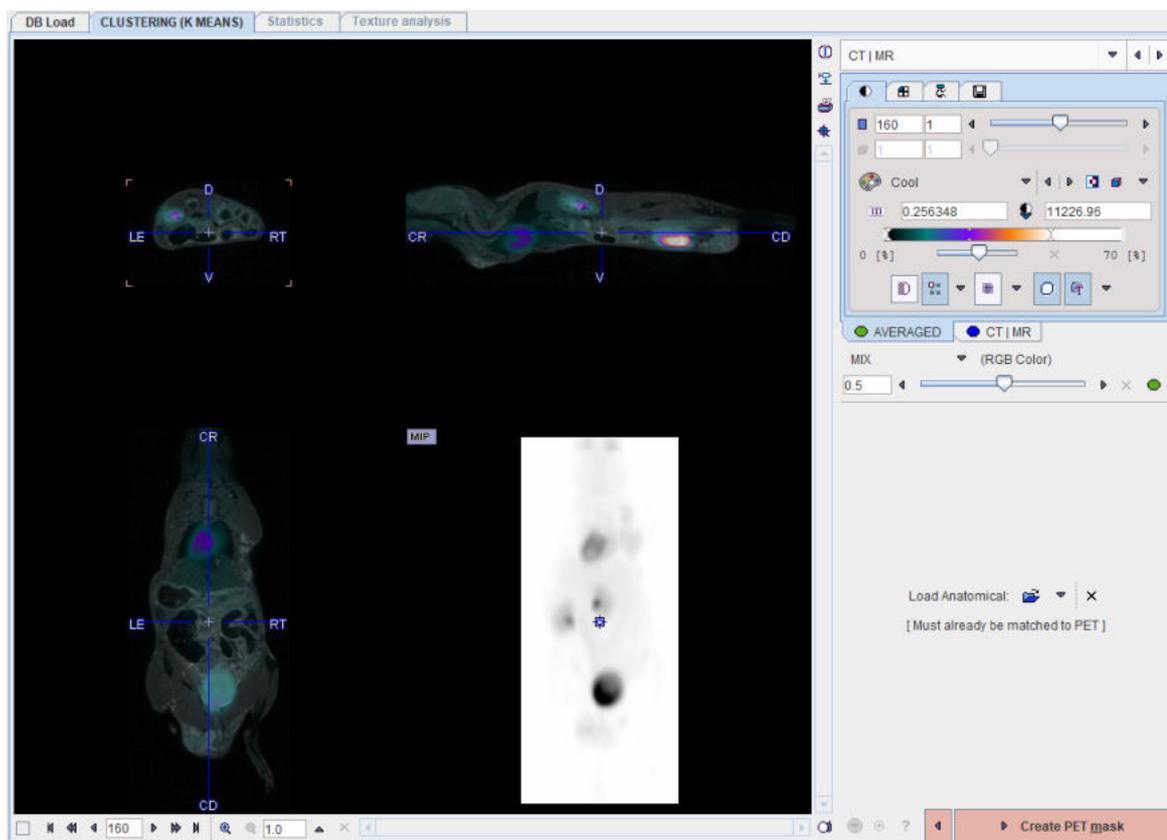
### 2.4.1 Image Loading

The [PET Image Loading](#)<sup>[9]</sup> and the [Reference Image Loading](#)<sup>[11]</sup> have been described above.

In the example illustrated below a dynamic mouse FDG PET was loaded, and PET is used as **Masking method**. The **Species** is set to **MOUSE** for adequate presets.



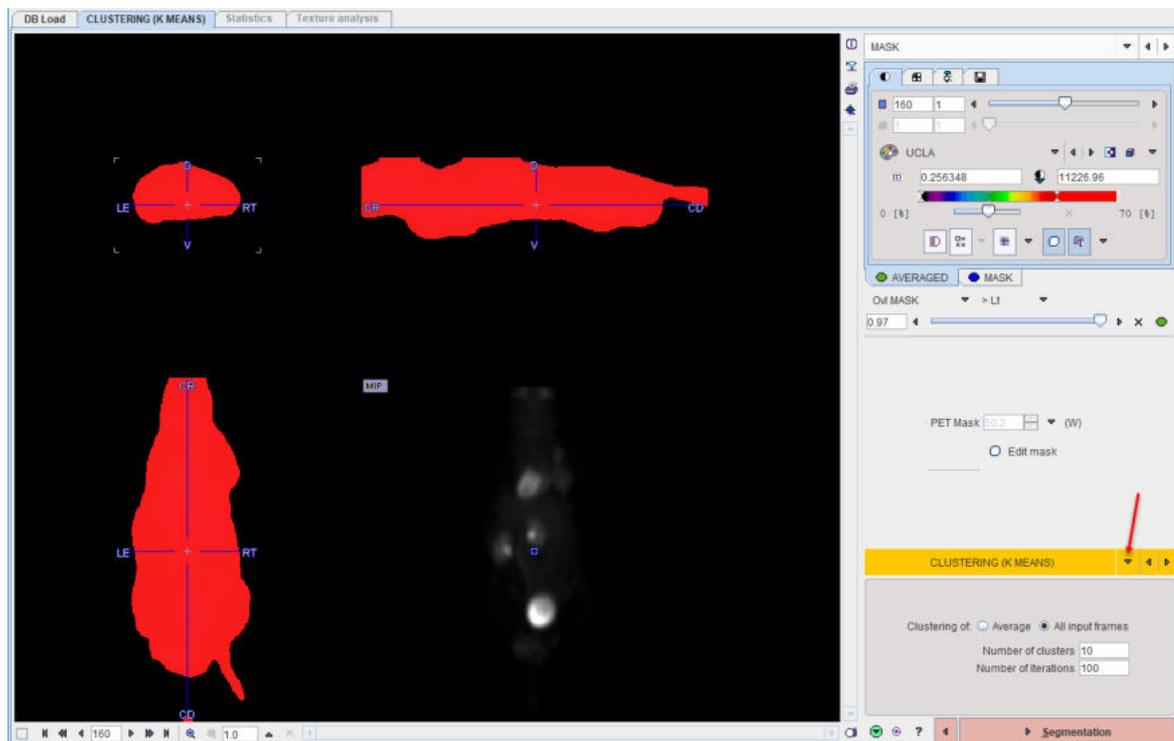
Loading was continued using the **+CT | MR** button, and the MR loaded.



The segmentation mask was calculated with **Create PET mask**, arriving at the **MASK** panel for the segmentation configuration

## 2.4.2 Mask Editing and Segmentation Configuration

The mask shown up on the **MASK** panel may be edited as described in a previous [section](#) <sup>13</sup>.



### Segmentation Method Selection

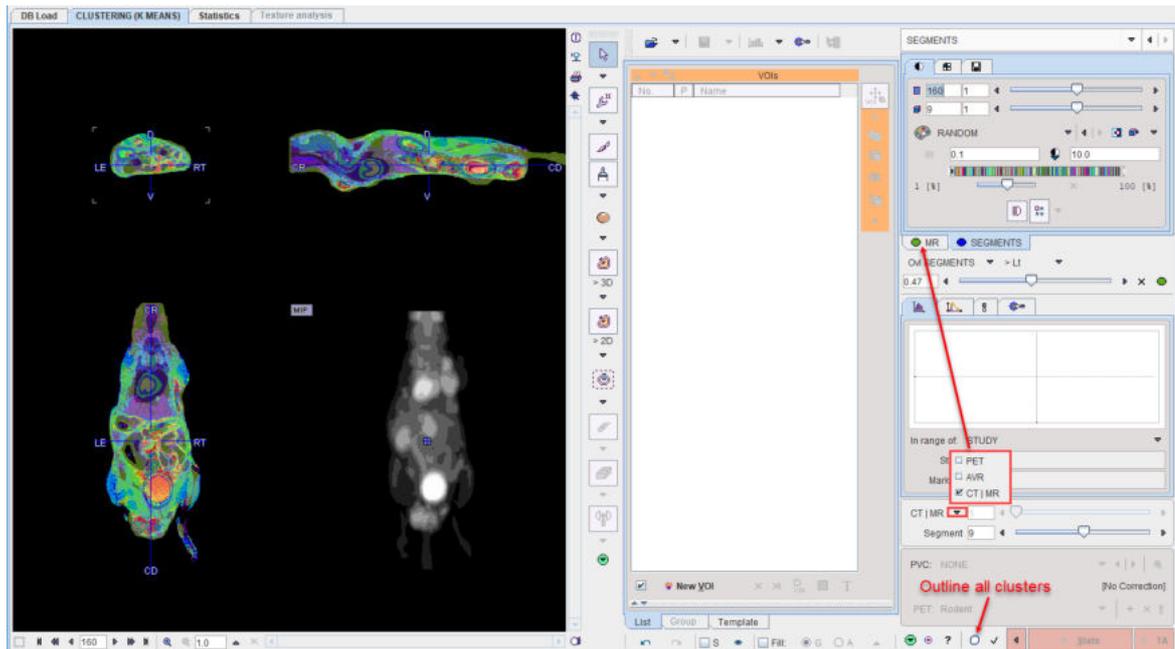
At this point, the **CLUSTERING (K MEANS)** segmentation method has to be selected in the lower right. The panel below the selection then shows the parameters to be configured, namely the **Number of clusters** as well as the **Number of iterations** during which the clusters are adjusted.

Note that all pixels within the mask are assigned to one of the clusters, and the process doesn't include any kind of neighborhood relation. The classification is solely based on the signal time course in each pixel.

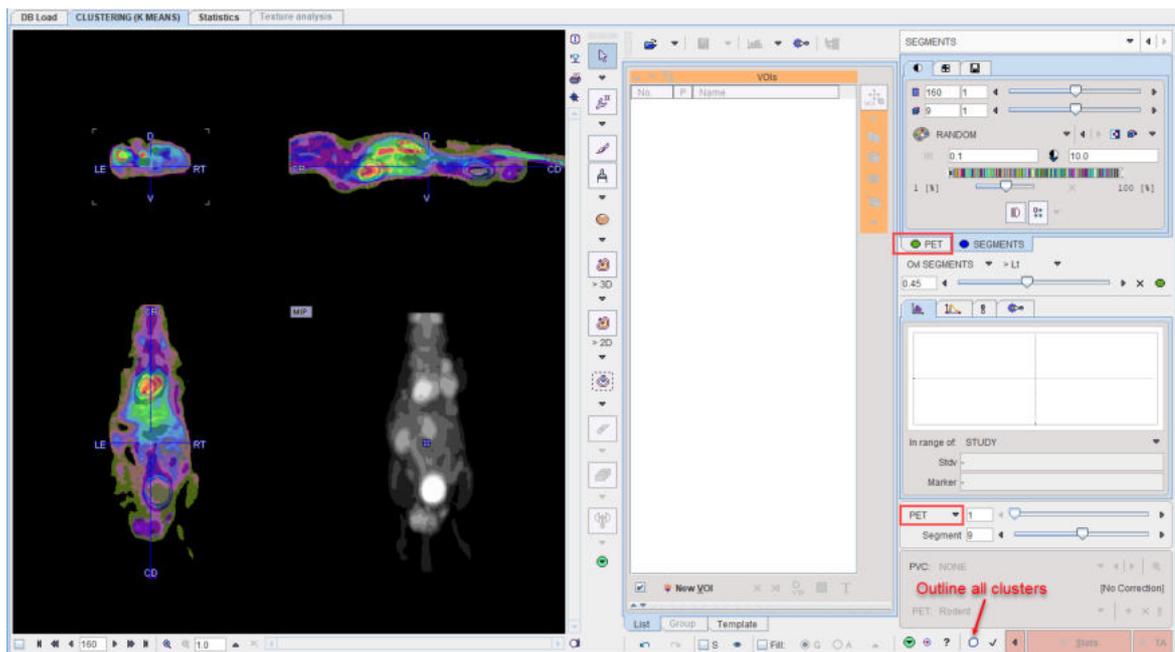
To start the k-means segmentation please activate the **Segmentation** action button. The required processing time depends on several factors, particularly the number of iterations, and may take several minutes. The segmentation result is finally shown on the **SEGMENTS** panel.

## 2.4.3 K-MEANS Segmentation

The display on the **SEGMENTS** panel shows a fusion of the segmentation result **SEGMENTS** with either the **PET** or the anatomical image as the reference.

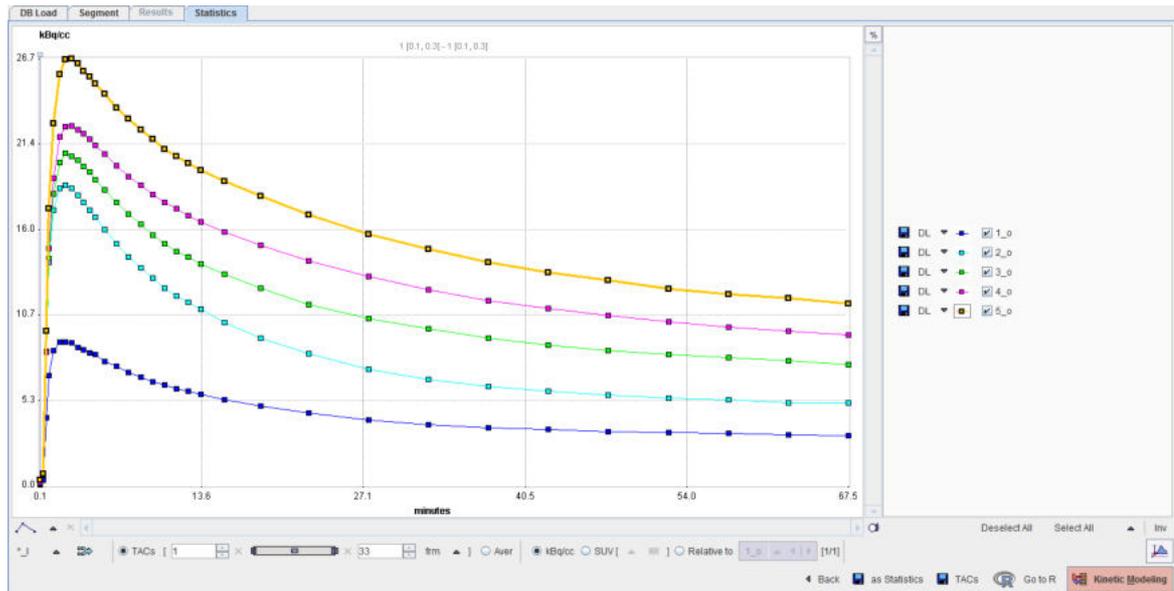


The display below shows a fusion of the segmentation result (**SEGMENTS**) with the **PET** image as the reference:



The procedures for convert [converting cluster into VOIs](#) <sup>37</sup> are the same as for the **ORGAN SEGMENTATION**, except that the clustering only provides a single decomposition of the volume. Correspondingly, there is a static label images in the **SEGMENTS** tab rather than a dynamic series showing the volume in a hierarchical structure of decompositions, and the **Segment** slider is inactive. All clusters can be outlined at once using the **Outline Maps** button, as indicated above.

Finally, **Statistics** will calculate the average TACs of the clusters and show them on the **Statistics** page.



## 2.5 CLUSTER ANALYSIS (SUPERVISED)

k-means clustering of dynamic data is working completely data-driven without any prior knowledge apart from the number of clusters. The **SUPERVISED** clustering approach is complementary. Here the user specifies a set of TACs which are characteristic for the kinetics of different tissues. The algorithm then decomposes the data into clusters with kinetics similar to the prescribed TACs.

This method was introduced by Turkheimer et al. [8] for determination of gray matter tissue without specific binding as a reference in [11C]PK11195 brain studies. It requires preparation of time-activity curves which are representative for different tissues in the brain. For [11C]PK11195 the authors found that the method worked best after normalizing the data frame-wise by subtracting from each pixel value the frame average and dividing by the frame standard deviation. Note that this pre-processing is not part of the **CLUSTER ANALYSIS (SUPERVISED)** method. Rather, the images have to be normalized beforehand using the z-score external tool. As a result of this normalization, the image characteristics change remarkably.

The implementation in PSEG is close to the supervised clustering variant presented by Ikoma et al. [9] for use with [11C]PIB. Particularly, the weight ratio (eq. 3 in [9]) is used to assign each pixel to one of the classes, or to background. The illustration below shows the classification TACs used for normalized [11C]PIB data [9].

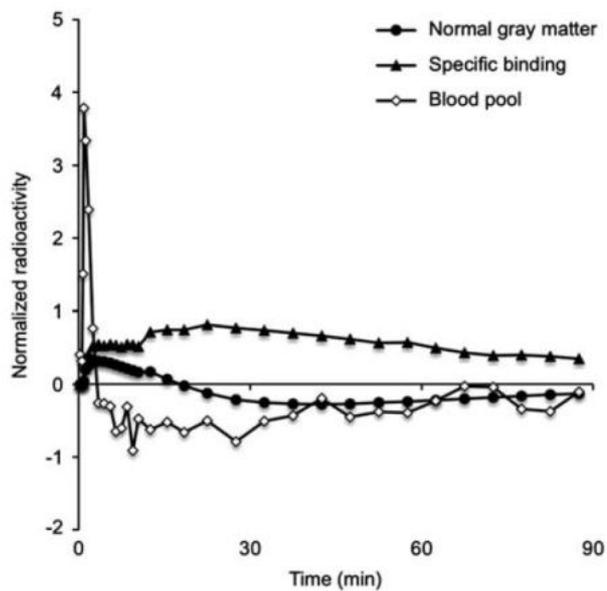
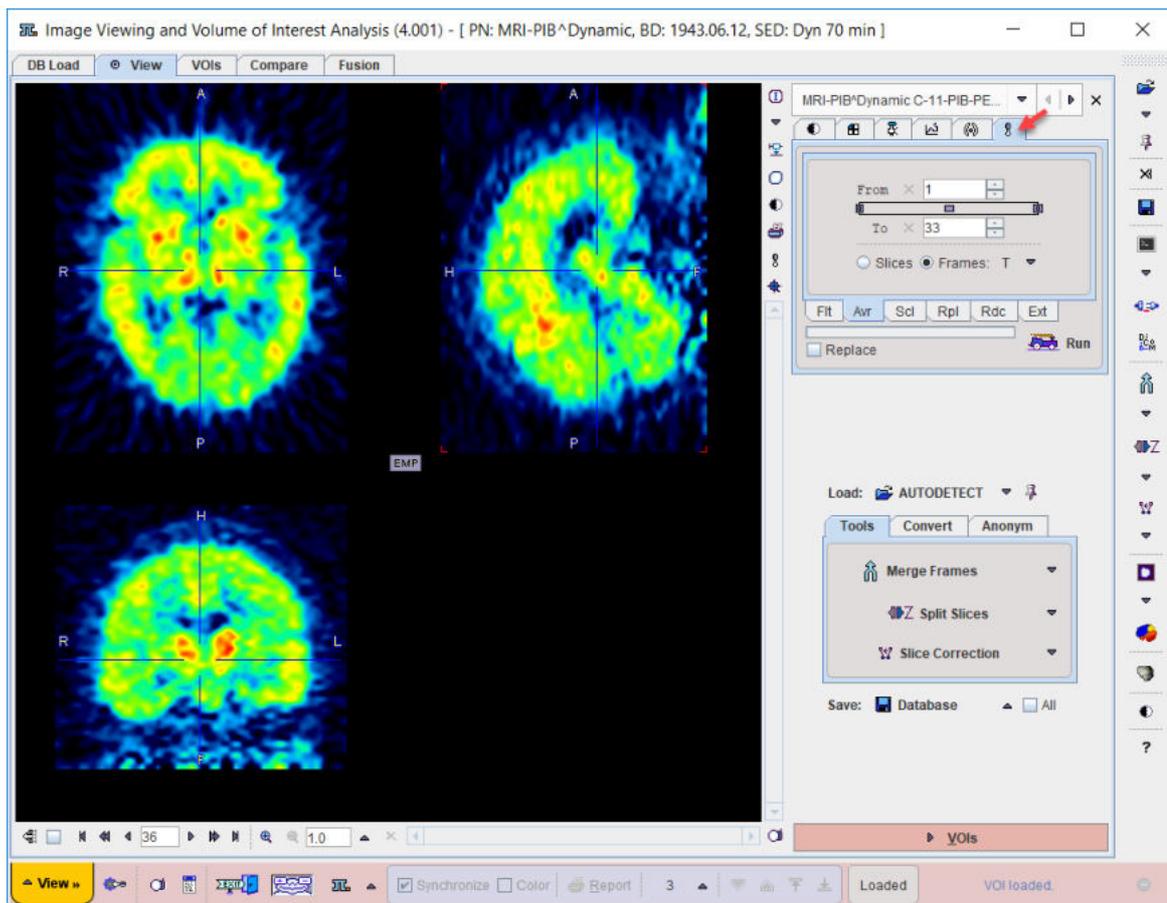


Figure 1. Normalized time-activity curve of the predefined three classes; normal gray matter, specific-binding gray matter, and blood pool.

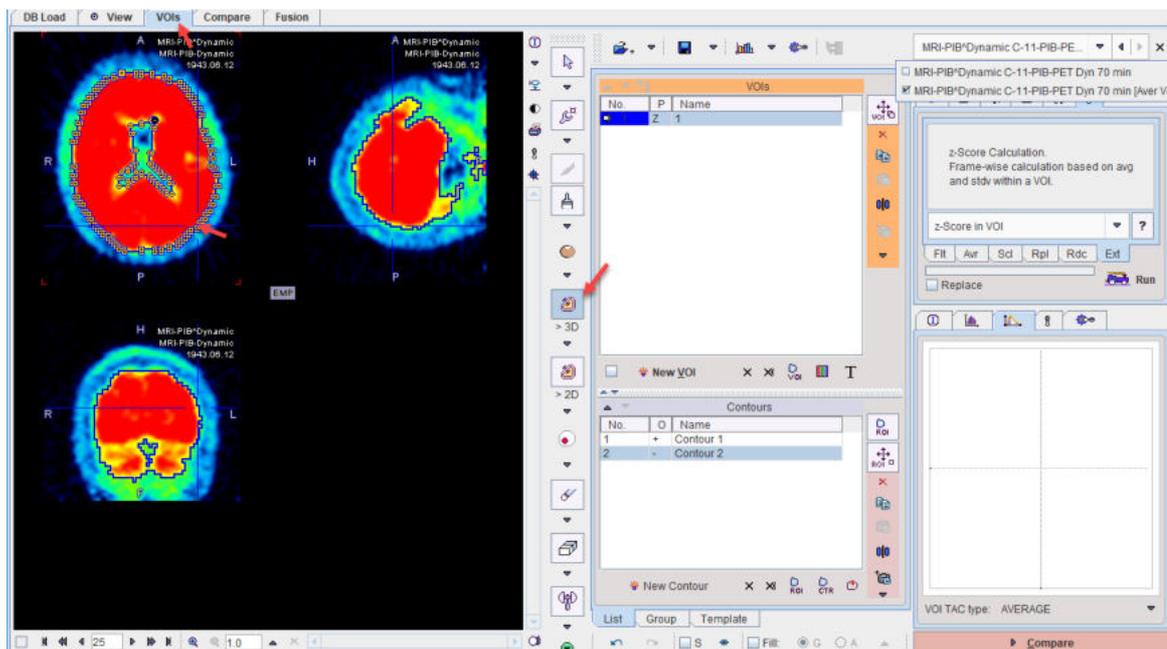
### 2.5.1 Image Value Normalization

Image normalization applied for  $[^{11}\text{C}]\text{PK11195}$  [8] and  $[^{11}\text{C}]\text{PIB}$  [9] consists of a z-score calculation, which can be performed in the PMOD viewing tool (PVIEW).

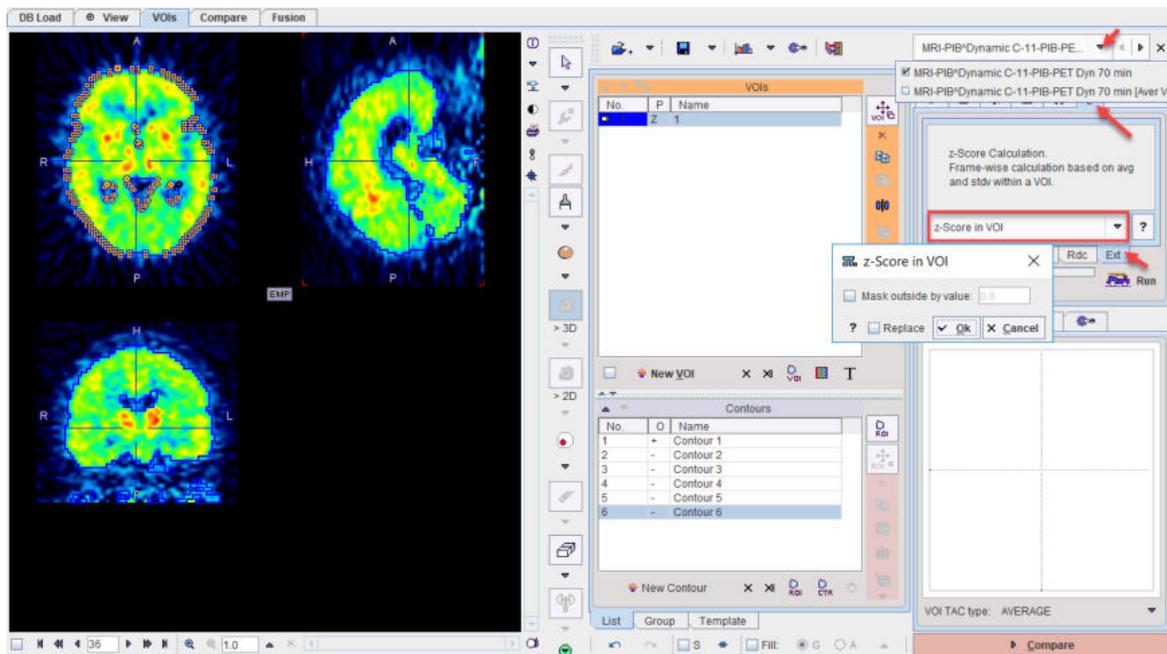
In PVIEW, first load the dynamic PET data. Next, average the image frames to get a better anatomical image.



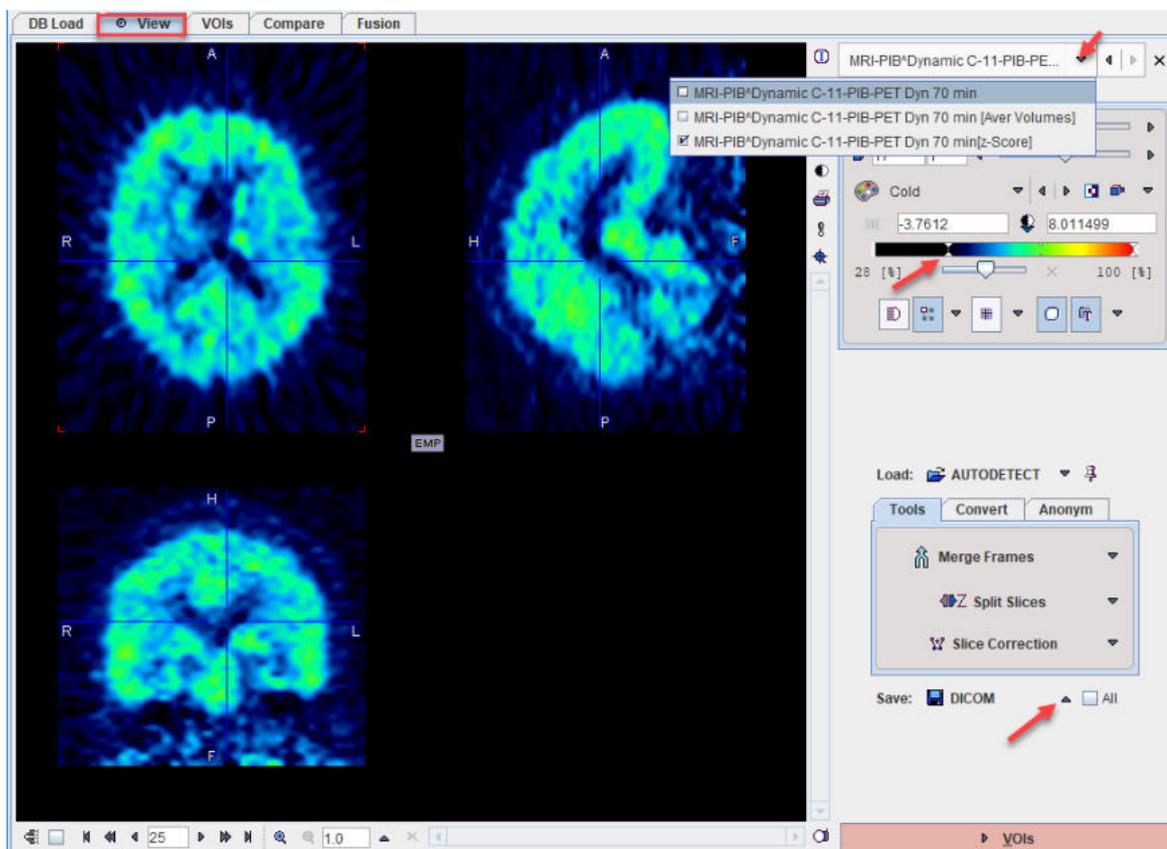
Use the averaged image for defining a bounding VOI for the mean and standard deviation calculation. In the example below the **VOI** page was selected, the **3D** iso-contouring tool activated, and by clicking at the brain edge a VOI obtained which encloses the brain. Alternatively, other approaches can be developed which define the VOI more objectively. Ikoma et al. [9] used a VOI enclosing grey and white matter.



After VOI creation, switch back to the original data, select the tools tab, the **Ext** sub-tab, and start z-score calculation with the **Run** button.



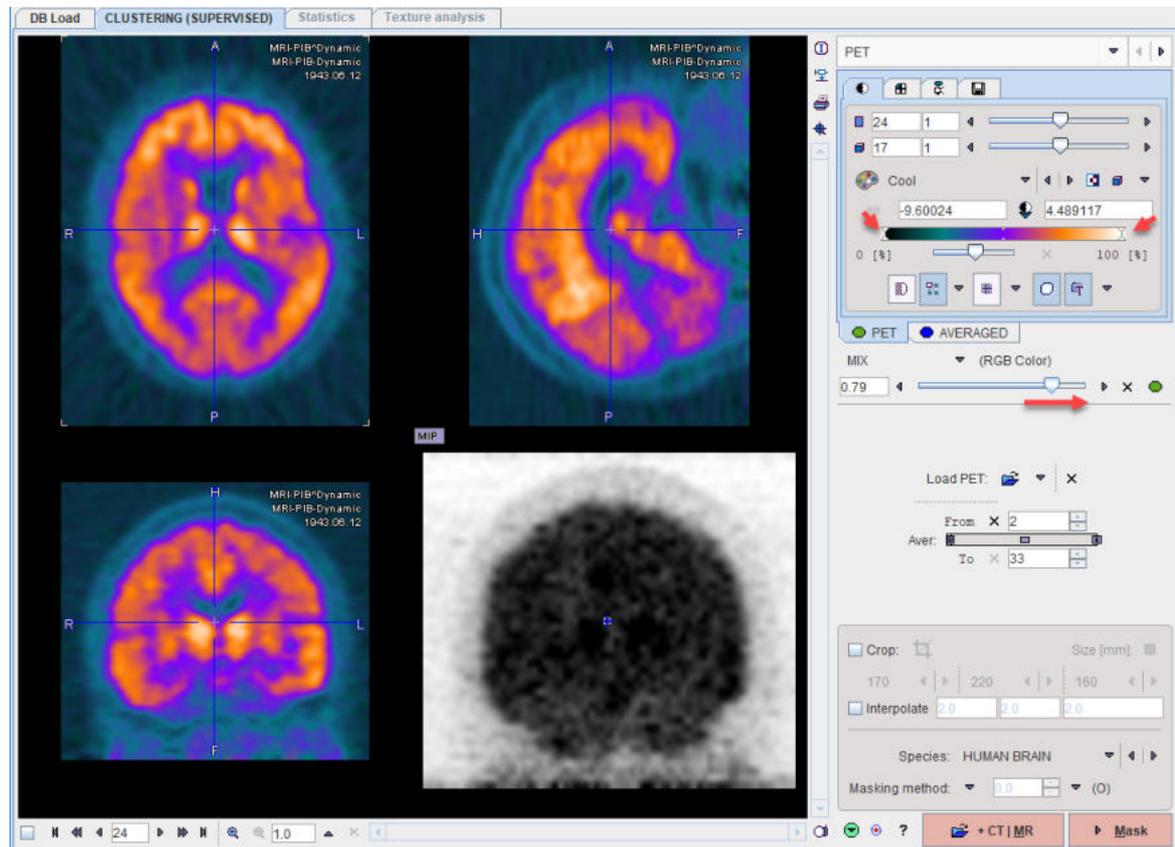
The resulting normalized dynamic images are added as the third series. It can be saved on the **View** page as illustrated below. Note that the color table thresholds may not be adequate any more due to the change of the value range, and may need adjustments.



## 2.5.2 Image loading

The [PET Image Loading](#)<sup>[9]</sup> (in this case of the normalized data) and the [Reference Image Loading](#)<sup>[11]</sup> have been described above.

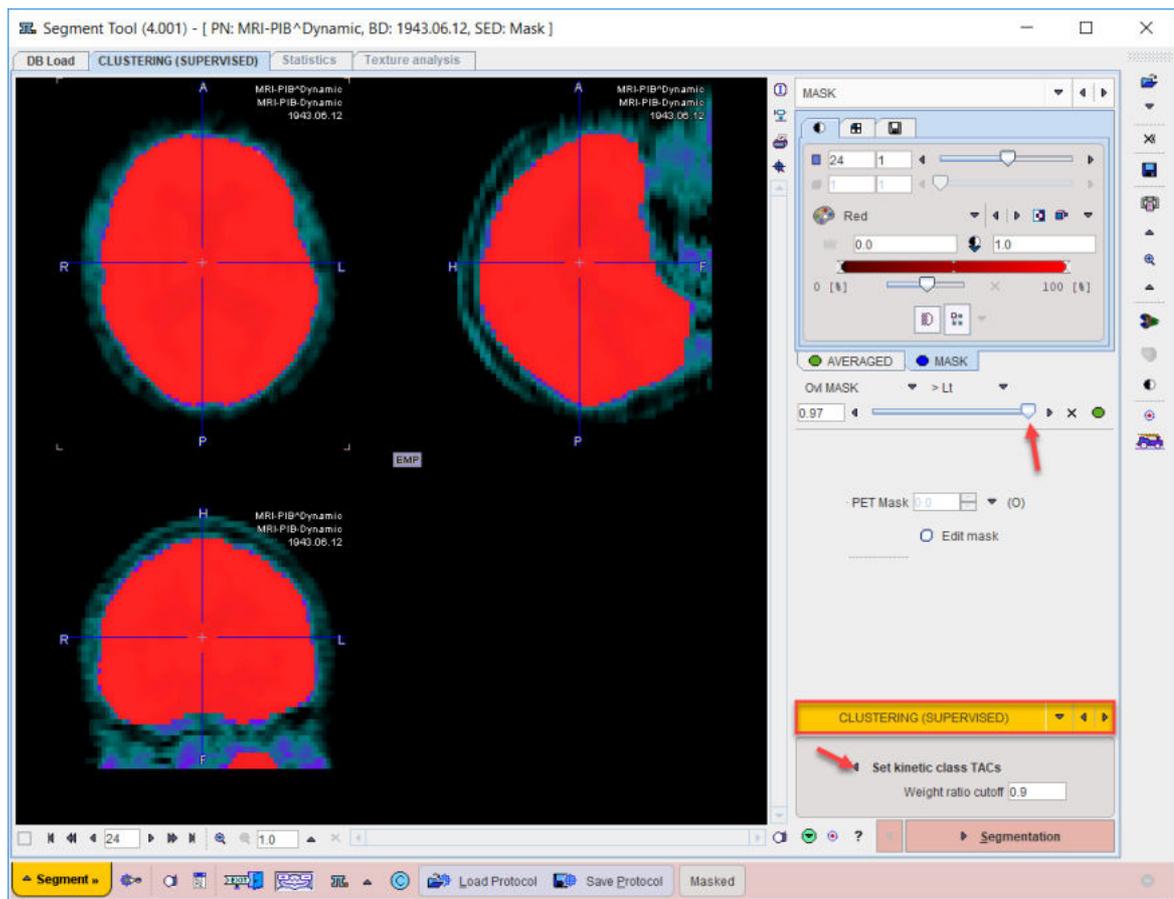
In the example illustrated below a normalized dynamic PIB PET was loaded, and **PET** is used as **Masking method**. The **Species** is set to **HUMAN BRAIN** for adequate presets.



In absence of matched anatomical images, proceed with the **Mask** button to start the mask creation and arrive at the **MASK** panel.

## 2.5.3 Mask Editing and Segmentation Configuration

The mask shown on the **MASK** panel may be edited using **Edit mask** as described in a previous [section](#)<sup>[13]</sup>.

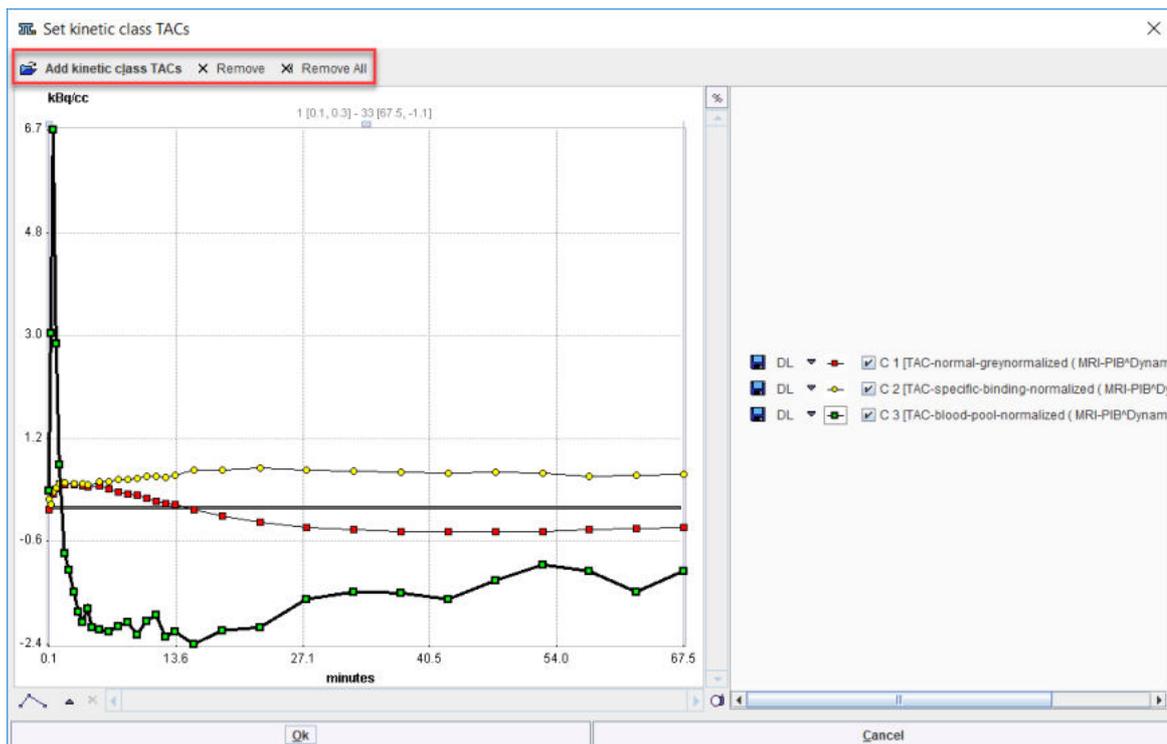


### Segmentation Method Selection

At this point, the **CLUSTERING (SUPERVISED)** segmentation method has to be selected in the lower right. The panel below the selection then shows the parameters to be configured, namely the **kinetic class TACs** as well as a **Weight ratio cutoff**.

Use the **Set kinetic class TACs** button for opening a dialog window. There, use **Add kinetic class TACs** to select curves either from the database or from the file system. The curves are loaded and shown as illustrated below. Curves can incrementally be added. To discard a curve select it to the right and **Remove**, or **Remove all**.

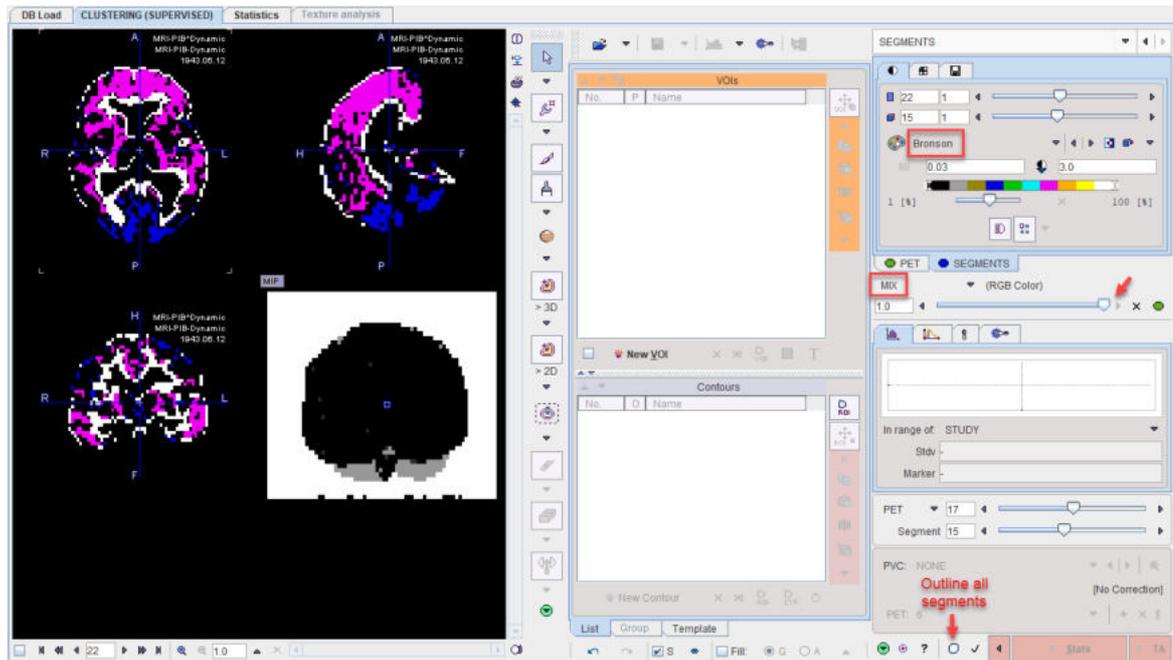
In the illustration below C1 corresponds to normal grey matter, C2 to specific binding, and C3 to the blood pool similar to Fig. 1 in [9]. Note the normalized curve shapes which are very different from normal uptake TACs.



**Segmentation** starts the classification procedure. For each pixel in the mask it finds the optimal linear combination of all kinetic class curves so that all coefficients are non-negative (NNLS, non-negative least squares). It then assigns the pixel to the class with the highest coefficient (or weight), if its ratio to the sum of all coefficients is greater than **Weight ratio cutoff**. Otherwise, the pixel is classified as background with a label value of zero. The segmentation result is shown on the **SEGMENTS** page.

## 2.5.4 SUPERVISED Segmentation

The resulting segment image is shown on the **SEGMENTS** page. It may be required to adjust the display as illustrated below for getting a clear picture of the segmentation result. Here, the color table was changed to **Bronson**, and the fusion mode to **MIX** with the slider to the right. A dedicated button in the lower right contours all segments and lists the corresponding VOIs in the list.



The VOIs can then be saved and the appropriate one used for instance as reference region in in parametric mapping.

## 2.6 MACHINE LEARNING

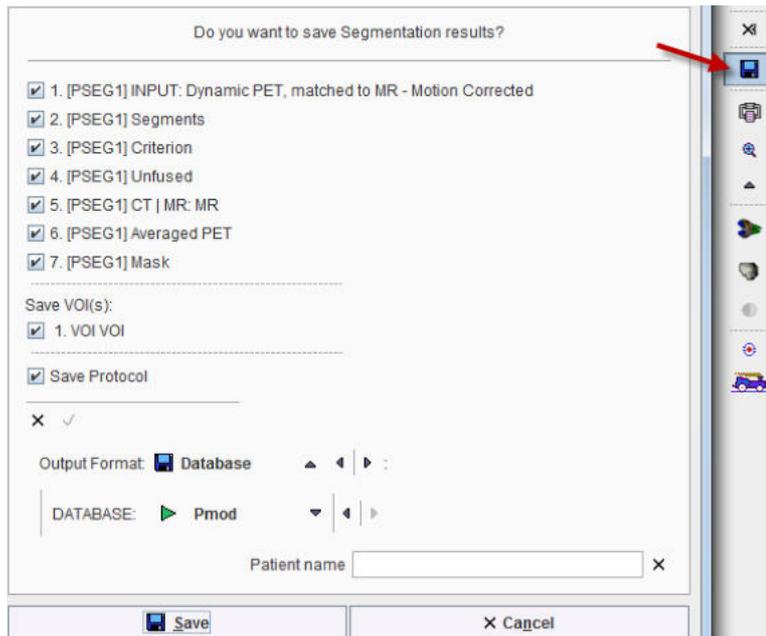
The PMOD **MACHINE LEARNING** workflow supports the learning as well as the prediction part. The users can prepare sets of images with their corresponding segmentation. The learning sets can be submitted to TensorFlow for training a neural network of suitable structure. The resulting network can finally be applied to segment input images with characteristics similar to the ones in the learning set.

Please refer to the [PAI Documentation](#) for details about the creation of a learning set, the training of a network, the prediction-based image segmentation, as well for all information related to the infrastructure requirements.

## 2.7 Results Saving

### Saving of Data

The easiest way to save information is via the *Save all* button in the lateral taskbar as illustrated below.



All images arising during processing are available for saving, as well as the final VOIs and a protocol. Please select the information of interest and save them to a database or a directory.

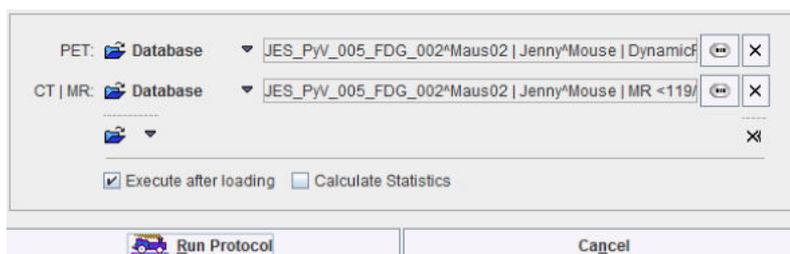
### Protocol Saving

The final processing configuration can separately be saved using the **Save Protocol** button.



Such a protocol includes definition of the input data, the parameters of the different processing stages as well as the resulting VOIs generated. It is recommended saving a protocol after every completed data processing, so that at any later time the configuration can be retrieved, verified and modified to try variations of the processing parameters.

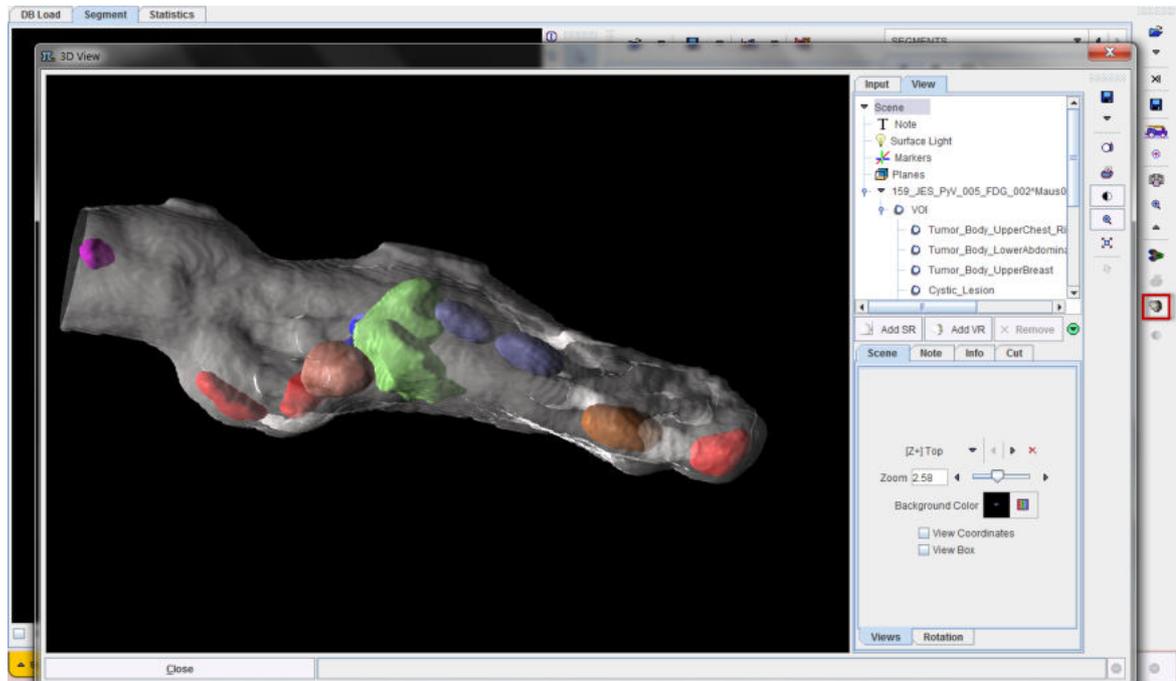
**Load Protocol** allows retrieving a protocol. It shows the following dialog window.



The data sources may be redefined. If **Execute after loading** is disabled, only the data will be loaded and the configurations recovered. Otherwise, the full segmentation will be performed and the result shown together with all VOIs of the saved session.

### 3 3D Visualization (Option)

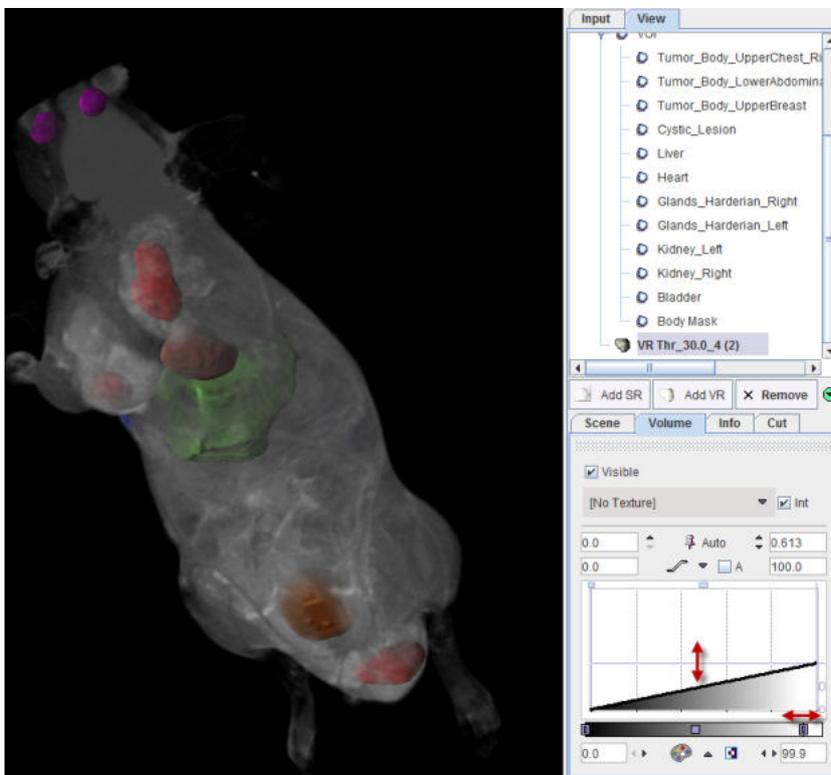
If the 3D option is part of the PMOD license, the VOIs created in the PSEG tool can be conveniently visualized as a 3D scene. When activating the  button in the lateral taskbar, a **3D View** window is opened, the data loaded, and the VOIs rendered as surfaces together with the segmentation mask. The illustrations below use the result of the **ORGAN SEPARATION** workflow, but the functionality is similar for **PERCIST**.



The image data is also available for the scene. Illustrated below is adding a volume-rendering (VR) of the MRI. The **Input** tab is selected, a **Threshold** level set such that all body pixels are included (**Ovr** check), the "Append" pushpin set for adding to the existing VOI renderings, and **Volume HD** activated.



The result after switching off the body mask and increasing the transparency of the VR object is illustrated below. Interactive exploration of such a scene will greatly add to the understanding of the lesion localization.



Please refer to the *PMOD 3D Rendering Tool User's Guide* for more information about how to explore and enrich the 3D scene.

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## 5 *PMOD Copyright Notice*

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