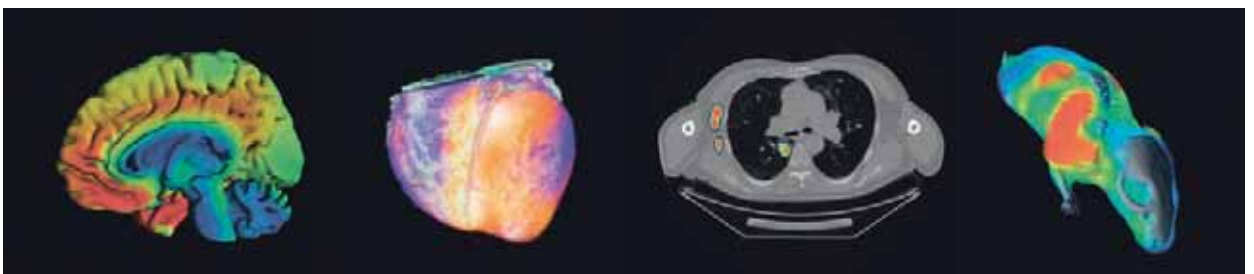


# $\pi$ .pmod

Neurology | Cardiology | Oncology | Preclinical



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# PBAS Image Processing and VOI Analysis

## Biomedical Image Data Infrastructure

The PBAS tool represents the backbone of PMOD's software environment and is mandatory for any PMOD license. It provides an infrastructure for receiving and sending images via DICOM, importing images from all relevant proprietary formats, and organizing them in a database together with any derived information. If desired, databases can easily be shared in a network to provide a central repository among collaborating PMOD users.

*PBAS supports the viewing and processing of images to an extent far beyond common reviewing software.*

## Image Viewing and Processing

PBAS supports the viewing and processing of images to an extent far beyond common reviewing software. In addition to standard image display options, PBAS offers many features for quantitative approaches, including the appropriate handling of calibration factors and value units, consideration of the acquisition timing as well as pertinent geometrical information. Additionally, a unique set of image processing solutions is included, ranging from gray/white matter segmentation of MR images to the partial-volume correction of PET SUV values.

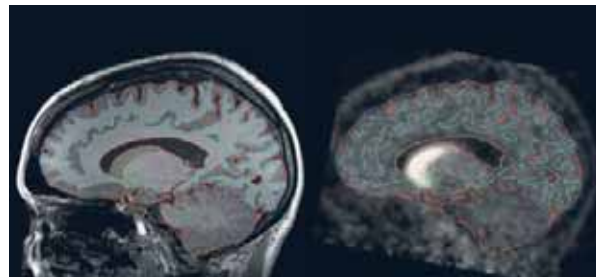
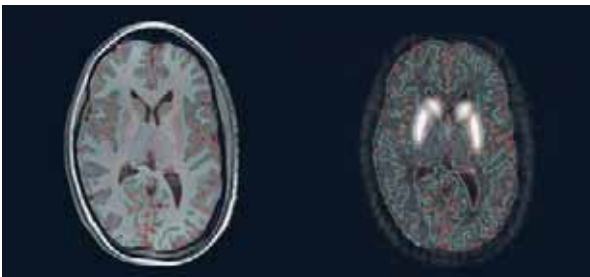
## Volumes of Interest

Many types of quantitative analyses are based on the averaged signal within tissue structures. PBAS includes arguably the largest and most flexible set of tools for volumes of interest (VOI) definition. The definition types include contour outlines, regular geometric objects, object maps, linear VOIs and VOIs with holes. The VOIs can be created using many versatile tools, and they can be involved in advanced operations such as the calculation of their common pixels, intersections with probability maps, or transformations to the geometry of a different image from the same patient.

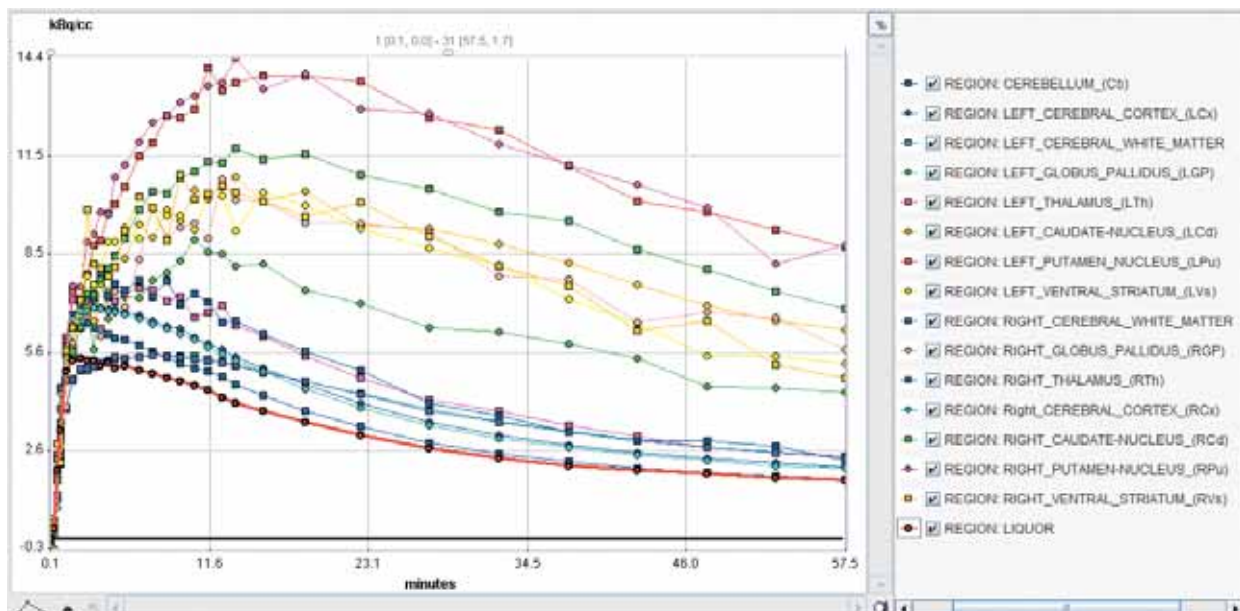
*PBAS includes arguably the largest and most flexible set of tools for defining volumes of interest.*

## Statistics

PBAS includes an interface to the well-known R statistics environment. The interface allows for the transfer of the aggregated results from a group of subjects to R, and it supports analysis using advanced scripts developed in collaboration with Prof. Karl Herholz.



Brain region contour VOIs derived from MRI and applied to a registered raclopride PET.



Regional statistics calculated from a dynamic raclopride PET and ready for transfer to kinetic modeling.

## Infrastructure

Organization of images and other information objects:

- DICOM server and client, see conformance statement
- Data management by embedded Java database
- Proprietary middleware for sharing data among PMOD installations

## Image Formats

Images can be read in more than 20 formats and saved in a subset thereof, including:

- DICOM (read/write)
- ECAT (read/write)
- Interfile (read/write)
- NIfTI (read/write)
- Analyze (read/write)
- MicroPET (read)
- Bruker Paravision (read)
- Philips par/rec files (read)

Units, calibration factors and acquisition timing in the image headers are meticulously interpreted.

## Image Viewing

Visualization of volumetric images, tailored for dynamic series:

- Tiling and orthogonal layouts
- Maximum/minimum intensity projections
- Cines across slices and time (dynamic)
- System and user-defined color tables
- SUV inspection; various types supported
- Pixel-wise time-activity curves
- Raw pixels, various interpolation methods

## Image Processing

Basic and advanced image processing procedures, including:

- Merging static into dynamic series
- Averaging in time or across slices
- Spatial filtering (Gaussian, median, Deriche)
- Morphological operations
- Interpolation to different pixel or field-of-view sizes
- Gray/white matter segmentation of brain MR images
- Skull-stripping of brain MR images
- Brain MR-based and VOI-based partial volume effect correction of PET SUV values
- Interface to ITK filtering and ImageJ

## Volumes of Interest (VOIs)

Unique VOI definition functionality, including:

- Import/export of DICOM RTSTRUCT VOI definitions
- Contouring in any plane direction (axial, coronal, sagittal)
- Interactive contour delineation using boundary clicking, pencil drawing, iso-contouring
- Contour interpolation across slices

- Regular VOIs in 2D (circle, rectangle, point) and 3D (ellipsoid, cuboid)
  - Region growing methods for hot and cold structures in 2D and 3D
  - Automatic brain VOI generation based on atlas templates
  - Interpretation of pixel-defined object maps
  - Predefined VOIs for the human, rat and mouse brain (stereotactic spaces)
  - Support for user-defined VOI atlases
- VOI-based operations:
- Statistics of VOI pixels; time-activity curves for dynamic series
  - Dumping of all pixel values in the VOIs into a text file
  - Shrinking or expansion of VOIs (morphological operations)
  - Common pixels of VOIs, intersection with probability map
  - Merging and subtraction of VOIs
  - Masking inside or outside of VOIs
  - Cropping image series to a VOI bounding box
  - VOI-based partial-volume effect correction (Rousset method)
  - Spatial transformation of VOIs between images
  - Texture analysis

## Pipeline Processing

The functionality of PBAS and that of other PMOD tools can be arranged into processing pipelines, which may be applied to the data of a whole study population. Example pipeline: motion correction of a dynamic PET series → registration to a brain MRI → automatic MR-based brain VOI outlining → regional TAC calculation → kinetic model fitting → result parameter aggregation.

## Statistics

Powerful statistics based on the R environment:

- Aggregation of regional results
- Transfer to R server
- Interactive data exploration
- Descriptive statistics and standard tests
- Sophisticated tests including handling of multiple comparisons (rm-ANOVA, Linear Mixed Effects Model)

## Computer System Requirements

For productive work with real data:

- Operating system: 64-bit, Windows, Mac OS X, Linux
- RAM:  $\geq 16$  GB
- Cores:  $\geq 4$  ( $\geq 8$  for PNEURO tool)
- Graphics: dedicated mid- to high-range board
- USB connector

# PKIN General Kinetic Modeling

## Quantitative PET and SPECT

Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) allow molecular target imaging down to picomolar concentrations. With suitable tracers and acquisition protocols, tissue properties may be quantified in absolute units. Therefore, PET and SPECT have been proven to be uniquely valuable for many in-vivo research domains. However, for real quantification, the data have to be processed with sophisticated modeling techniques.

## Modeling with PKIN

PMOD's PKIN tool is the ideal solution for the model-based analysis of PET and SPECT data. It offers a comprehensive toolbox which not only allows calculating quantitative information, but also features dedicated functionality to assess the meaningfulness of the results.

*A palette of more than 50 kinetic model configurations is available.*

Blood and tissue data can easily be imported into the user-friendly PKIN environment. A palette of more than 50 model configurations is available, including blood-based compartment models, reference tissue models, linearized models and many more. These models can be fitted to the data while making use of various options to ensure reliability and reproducibility. As an extension to conventional modeling, multiple data sets may be fitted at once to incorporate

physiological a-priori knowledge and thus improve the outcome.

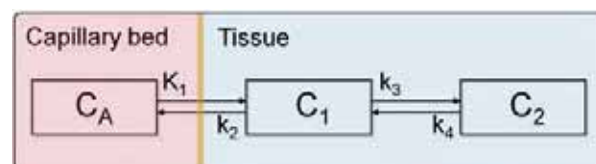
A further contribution to a meaningful result is the support and modeling of all blood-related input data such as plasma and metabolite fractions.

*In daily use by hundreds of PET and SPECT researchers for more than 15 years, PKIN is arguably the best-validated modeling tool available today.*

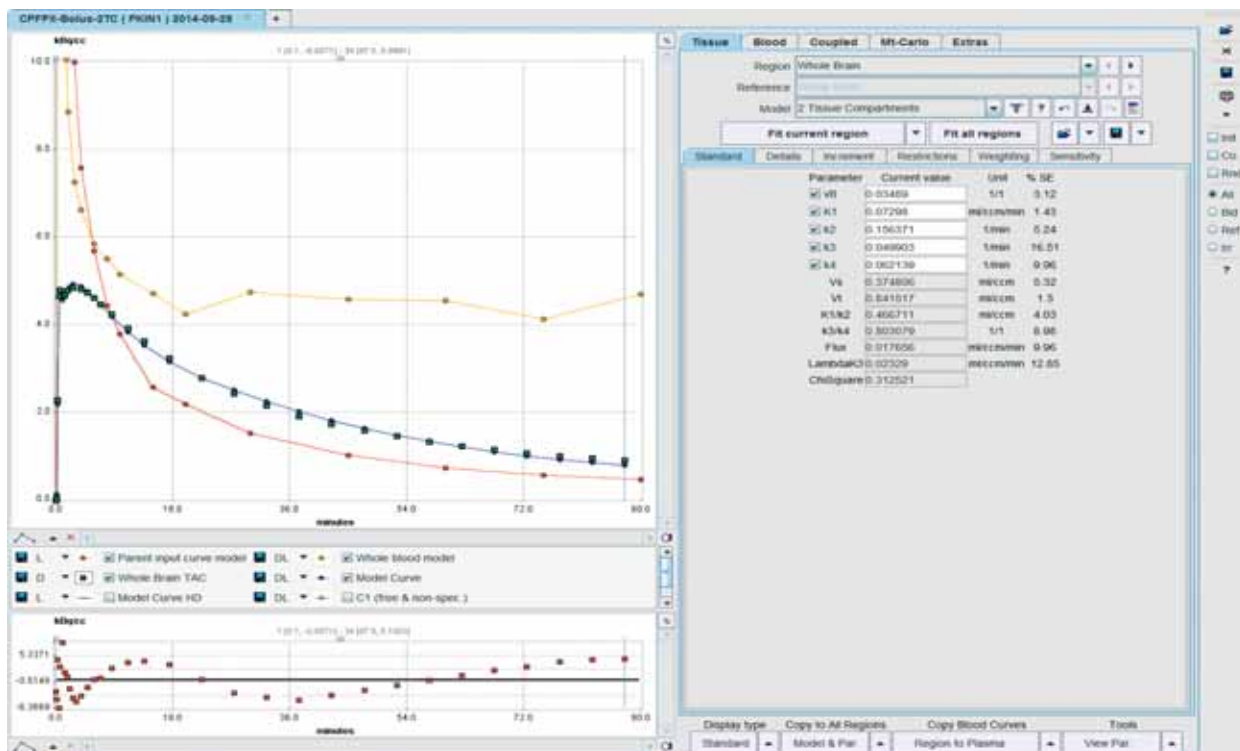
For efficient evaluation of the modeling results, the user is provided with convenient summaries and statistical decision criteria, which can easily be aggregated and transferred to the R environment for further statistical analysis.

## PKIN Validation and Usage

In daily use by hundreds of PET researchers for more than 15 years, PKIN is arguably the best-validated and most comprehensive modeling tool available today. Continuous feedback from our research users ensures that PKIN will also keep up with future advances in the field.



Schematic of a 2-tissue compartment model. Such a model is often applied for dynamic PET quantification.



PKIN user interface with the kinetic model configuration to the right, the tissue time-activity and the model curve in the upper left, and the residuals in the lower left.

## Tissue Activity Models (> 50)

The tissue models in PKIN predict the dynamic uptake of the radiotracer, given a blood or reference tissue input curve. A fitting procedure varies the model parameters until the prediction most closely fits the measurement. Model categories included:

- 1-, 2-, 3-tissue compartment models
- Models with receptor saturation
- Models with additional metabolite input curve
- Models for acquisitions with multiple injections
- Graphical plots such as Patlak, Logan, Ito, RE-GP plots
- Reference tissue models
- Cardiac dual-spillover models
- Spectral analysis
- Utilities such as cumulated (organ) activity calculation or bolus/infusion optimization

## Blood and Plasma Activity Models

Often, blood activity measurements are scarce and noisy. The blood models in PKIN support fitting smooth functions to such data for interpolation and noise reduction purposes. Supported functions:

- Tri-exponential function
- Modified gamma functions
- Compartment functions
- Deconvolution of dispersion for continuously sampled blood data

## Plasma Fraction

PKIN supports the use of plasma fractions for the calculation of plasma activity from whole-blood activity curves. This function is particularly important when using online blood-sampling systems. Supported functions:

- Linear interpolation of measurements
- 3-exponential function
- Sigmoid function
- Hill function
- Watabe function

## Parent Fraction

PKIN supports the use of parent fractions for the metabolite correction of plasma activity curves. Smooth parent fraction functions can be fitted to measured data, or used for population-based metabolite correction. Supported functions:

- Linear interpolation of measurements
- 1-, 2-, 3-exponential function
- Sigmoid function
- Hill function
- Watabe function
- Power-damped exponential function

## Fitting Options

PKIN implements various approaches for improving fitting reliability, including:

- Selective fixing/fitting of parameters
- Customizable sets of initial model parameters
- History of model fits
- Initialization of compartment model parameters by a linear least-squares fit
- Randomization of initial parameters to avoid local minima
- Grid-fitting within physiologic parameter boundaries
- Coupled fitting of common parameters across regions or subjects
- Data-derived or user-defined residual weighting
- Restriction of fit range and outlier masking
- Continuous shortening of data to investigate sensitivity of parameters to acquisition duration
- Batch mode allowing application of multiple models or Monte Carlo simulations to the data of a whole population.

## Options for Investigation of Results

PKIN not only provides fitting results, but also features several methods to assess their meaningfulness, such as:

- Standard error indication for resulting parameters derived from the covariance matrix
- Calculation of parameter correlation matrix and sensitivity functions
- Monte-Carlo simulations to address parameter variability
- Akaike and Schwarz criteria for comparison among models
- Parameter aggregation and transfer to R for statistical analysis

## Parametric Mapping

When transferring pixel-wise TACs to PKIN, their location in the image is recorded. Therefore, after fitting a certain model to these TACs, maps of all model parameters can readily be generated. An advantage of this approach is the leveraging of the fully interactive PKIN environment for parametric mapping of spatially limited structures such as tumors.

## Generation of Synthetic Data

Synthetic data generated from well-defined compartment models allow the user to investigate simplified analysis approaches. Two modes are supported by PKIN: generation of synthetic TACs to be analyzed by PKIN, and generation of dynamic images with varying parameter combinations to be analyzed in PXMOD or in an alternative parametric mapping program.

## General Kinetic and Pixelwise Modeling

PMOD's PKIN tool facilitates interactive testing of the full range of models for tissue-activity curves (TAC) from extended tissue volumes, and yields numerical tables for statistical processing. The PXMOD tool is complementary. It applies similar modeling techniques directly to the signals arising in the individual image pixels. Therefore, the results are again images, known as parametric maps, showing the value of a model parameter in each image pixel. Hereby, tissue functions or properties are visualized and can easily be compared against information from other sources, such as autoradiography. As the maps are quantitative, they can also be analyzed statistically, for example to compare population groups.

*PXMOD is the leading parametric mapping solution for quantitative PET and SPECT.*

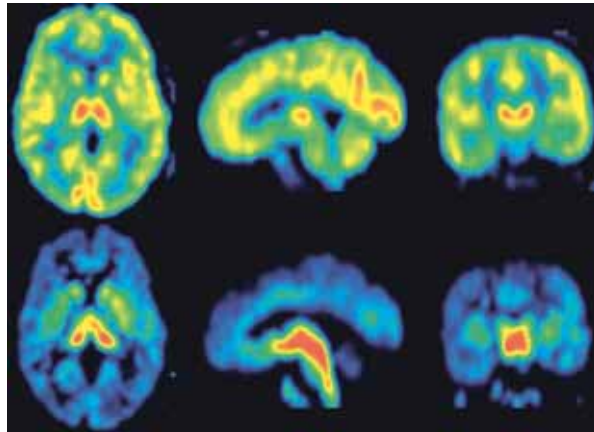
## Modeling with PXMOD

PMOD's PXMOD tool is the leading workflow-oriented solution for quantitative parametric mapping of PET and SPECT data. The user is guided through all tasks involved in a step-by-step fashion, namely data loading, mask generation, blood data import and correction, tissue VOI definition, parameter configuration and target map specification.

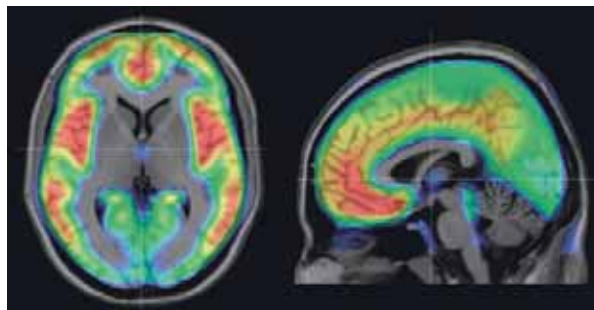
Once the parametric maps are calculated, PXMOD offers versatile tools for inspection of the results. There is a direct interface to the PKIN tool, which allows transfer of pixelwise TACs and analysis in the powerful, interactive PKIN environment. In this way, the PXMOD outcome can be verified and the cause of problematic results in certain pixels studied. An alternative is the comparative analysis of the maps in the embedded fusion component, for instance to study the outcome obtained with alternative modeling approaches.

*A seamless interface allows transfer of pixelwise TACs and analysis to the powerful, interactive PKIN tool.*

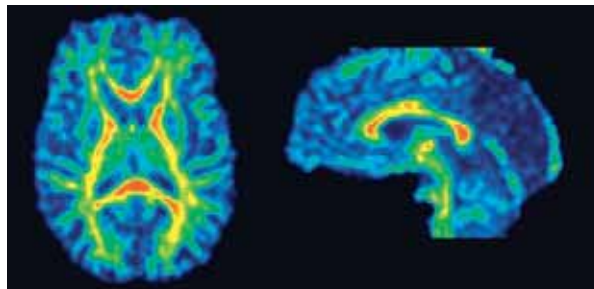
More than 30 models are available in PXMOD, both for situations with and without blood input. They range from simplified, robust, methods to full compartment models requiring iterative fitting. To make the latter more reliable, variants are available which implement priors and/or constraints. As some of the model calculations require considerable computing power, processing has been parallelized to take advantage of the multi-core computing systems now commonly available.



Parametric maps calculated using a reference model: Relative perfusion (top, SERT BP<sub>nd</sub> (bottom).



Population average of serotonin 5-HT1A BP<sub>nd</sub> maps fused with representative MRI. Courtesy of A. Hahn, M. Savli, R. Lanzenberger, Med. University Vienna. <http://www.meduniwien.ac.at/neuroimaging/>.



Parametric map of fractional anisotropy (FA) calculated from diffusion-weighted MR imaging.

## Input and Result Data

A dynamic image series is expected in any of the supported formats. Care has to be taken that the acquisition timing in the image header is accurate. If it is missing or wrong, the times can be corrected in PXMOD. The blood-based PET models require the preparation of the plasma tracer activity in a simple tab-delimited text file. Alternatively, if whole-blood activity is applicable for modeling, the input file can be replaced by a VOI-derived input curve. The resulting parametric maps can be saved in multiple formats, including direct transfer to a DICOM server. For reproduction and adjustment of the data processing at a later time, the complete configuration of a processing session can be saved in a protocol file.

## Parametric Mapping for Radiotracers

The radiotracer models (> 30) in PXMOD predict the dynamic PET or SPECT uptake, given a blood or reference tissue input curve. A fitting procedure determines the model parameters yielding the prediction closest to the measurement. Model categories include:

- Standard 1-, 2-tissue compartment models
- 1-tissue compartment model with time-weighted integral solution
- 1- and 2-tissue tissue compartment models with ridge regression
- 2-tissue compartment model fitted by a basis function approach
- Logan and Patlak plots
- Autoradiographic methods for MRGlu, CBF and CBV
- Spectral analysis for tracers with irreversible binding
- Simplified reference tissue model with fixed and fitted  $k_2'$
- Three multi-linear reference tissue methods
- Reference variants of Logan and Patlak plots
- Parametric mapping for dynamic whole-body FDG data with slice-wise timing, as acquired with a PET scanner that moves the imaging field-of-view dynamically during the acquisition

## Parametric Mapping of fMRI Data

The structure of PXMOD lends itself to other types of parametric mapping based on dynamic data, such as fMRI images:

- Calculation of fractional anisotropy (FA), various diffusivity maps and the diffusion tensors from DTI MR images
- Perfusion calculation from pCASL MRI
- Seed-based analysis of resting state fMRI

## Utilities

Additionally, some general analysis methods for data with a time dimension are available (correlation, regression, Fourier analysis, fractal analysis).

## Options for Investigation of Results

PXMOD not only provides parametric maps, but also features several methods for their investigation, such as:

- Inspector for parameter values in pixels
- Image fusion of input data and parametric maps
- Image algebra calculations among maps
- Transfer of pixelwise TACs to PKIN for interactive modeling



## Cardiac Functional Images

PET is routinely applied in the study of perfusion, metabolism, viability and function of the myocardium. It is considered the gold standard for quantitative assessment of cardiac perfusion. Over the past decade, cardiac MR has been developed to a degree that absolute quantification of perfusion is within reach.

*Modeling is performed on the basis of PKIN, leveraging the best-in-class quantification solution for the cardiac environment.*

## Quantification of Dynamic Cardiac PET and MR

PMOD offers two companion cardiac tools for PET and MR. They provide state-of-the-art methods for the model-based analysis of cardiac data, allowing researchers to directly compare the results of the two modalities. Both tools essentially use the same workflow, with some sub-steps pertinent to the two modalities. The images are processed in standard orientation showing the myocardium as short-axis cuts. This facilitates segmentation of the myocardial tissue into well-defined anatomical areas. All signals within each segment are averaged, resulting in representative tissue signals. An input curve representing the available tracer or contrast agent is derived from the signal in the left ventricular cavity. It is used for the analysis of the segmental signals with an appropriate kinetic model, resulting in the tissue property of interest.

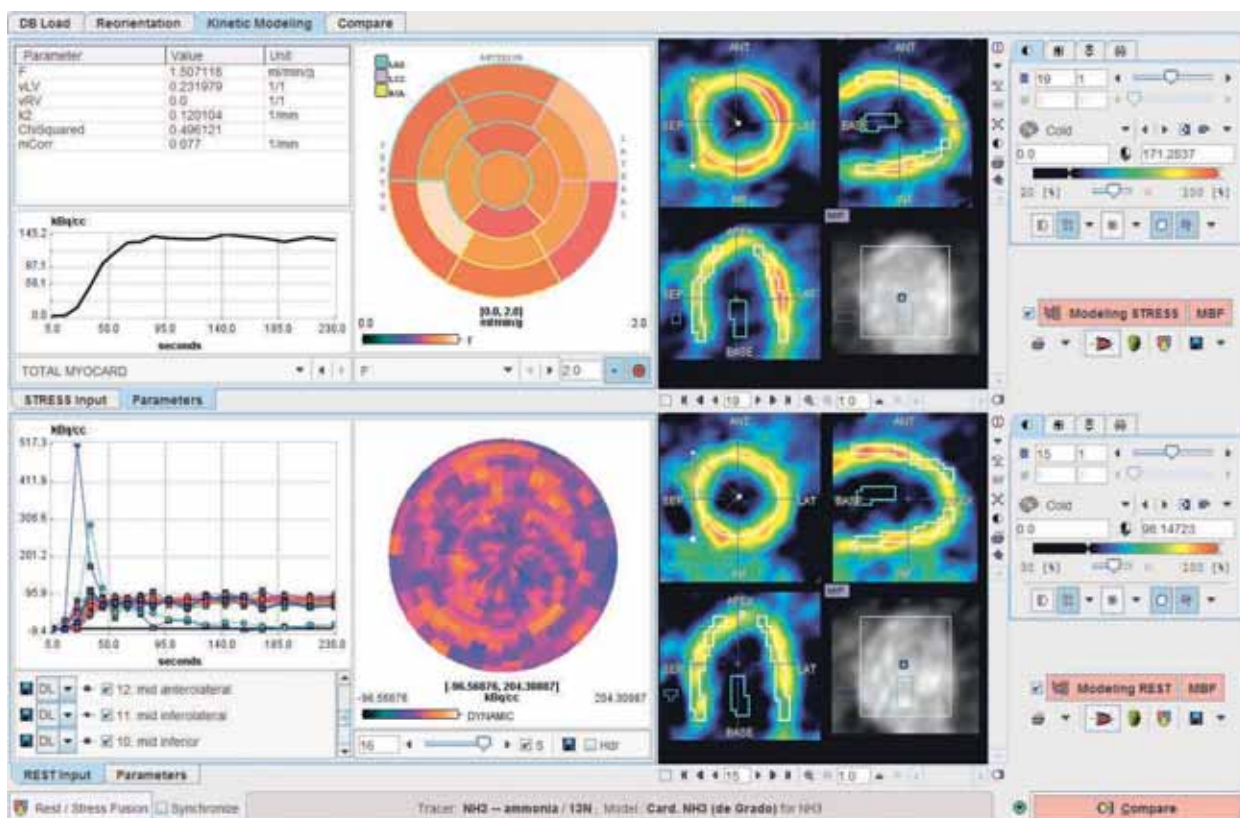
## Analysis of Gated Cardiac PET and MR Images

The analysis of ECG-gated PET and MR series is based on the contouring of the myocardium in each phase of contraction. The two tools derive cardiac function parameters such as ejection fraction and stroke volume from the beating endo- and epicardial contours and document them in comprehensive reports.

*Using PCARD, researchers may apply state-of-the-art perfusion quantification to their data and compare their results across modalities.*

## Cardiac Quantification with PCARDP

PMOD's PCARDP PET tool offers a comprehensive environment for the quantitative analysis of cardiac PET or SPECT images. The user is guided through the processing steps in a streamlined workflow. Automatic procedures are available for crucial steps such as short-axis reorientation of the images and myocardial segmentation, but the user can interactively correct all outcomes if required. Modeling is performed on the basis of PKIN, leveraging the best-in-class PET quantification solution for the cardiac environment. In the case of rest/stress studies, both series are processed in parallel. For perfusion studies, coronary flow reserve is readily calculated. The results are summarized in comprehensive reports, and can be saved numerically or in standard report formats.



PCARD PET user interface illustrating the input of the analysis in the lower part (rest) and the outcome in the upper part (stress).

## Image Data

The cardiac PET tool has been optimized for the analysis of dynamic PET acquisitions started at the time of tracer injection. The cardiac MR tool requires gadolinium first-pass MR images in short-axis orientation, preferably measured with accelerated sequences within a breath hold. For full quantification a B1 and a T1 scan are additionally required to correct field inhomogeneity and convert the MR signal to contrast agent concentration. Both tools also read and analyze ECG-gated images. The gates of such series are handled similarly to the frames of a dynamic series. Note that the cardiac tools may be applied to data from humans, rats or mice.

## Heart Segmentation and Signal Calculation

The myocardium is segmented according to the AHA definitions. Depending on the data, different segmentation strategies are supported, including automatic procedures as well as interactive outlining for difficult cases. In each segment, an average signal is calculated, representing its function.

## PET Tracers and Corresponding Models

Cardiac PET is particular in that the myocardial signal may include spillover components from blood in the left and right ventricular cavity. This is taken care of in the kinetic models applied.

<sup>18</sup>FDG: Glucose consumption for viability assessment (Patlak plot, 2-tissue compartment model)

<sup>13</sup>NH<sub>3</sub>: Perfusion (3 different compartment models)

<sup>82</sup>Rb: Perfusion (1- and 2-compartment models)

<sup>11</sup>C-Acetate: Perfusion (1-compartment model)

<sup>15</sup>O-Water: Perfusion (1-compartment model)

General: Tracer retention

## MR Perfusion Models

The following models are available for the quantification of first-pass cardiac MR (CMR) data.

- Fermi function
- Basis function method
- Model-independent approach

Analysis of conventional first-pass CMR images is reduced in comparison to the full quantification, in that no B1 and T1 correction is performed. However, assuming similar signal distortions in stress/rest studies, the ratio of the outcome can be considered as a measure of the coronary flow reserve.

## Interactive Modeling Environment

Both cardiac tools rely on the PKIN tool for the modeling. By default, the signals are processed in the background. However, they can also be explored in the interactive PKIN environment. This allows thorough investigation of the quantification results and gives access to all methods implemented in PKIN for improvement of fitting robustness.

## Qualitative MR Perfusion Analysis

Conventional perfusion scoring can also be performed in the cardiac MR tool. A separate panel allows interactive review of the rest and stress images, side by side, with the sectors in overlay, using cine mode. Three different grading schemes can be employed to assign defect scores to the sectors.

## Gated Analysis for PET and MR

The analysis of gated images requires contouring of the myocardium. This can be achieved by fitting of an active contour model to the data. If the result is not satisfactory, manual methods allow improvement of the contour definition. Analysis of the endo- and epicardial volume over the heart beat results in the classic function parameters ejection fraction (EF), end-systolic and end-diastolic volume, stroke volume, stroke index, myocardial mass (index), peak filling rate, time to peak filling rate, and  $\frac{1}{3}$  filling rate and fraction.

## Documentation of Results

The PCARD results can be documented and exported in many ways:

- Report pages with TACs, parameters, polar plots and a bar plot overview can be generated to quickly localize compromised segments. The report pages can be saved as graphic or DICOM objects
- The numerical results can be exported to standard statistical programs for further analysis
- The entire configuration can be recorded in a protocol file, so that processing can be exactly repeated at any later time

## Geometric Model Building

The PGEM tool leverages the power of the PMOD platform for various types of geometric analyses and simulations. A model builder enables the conversion of anatomic structures into three-dimensional geometric models. Such models may become educational tools, the input for external simulators, or they can be used to generate modality-specific phantom images such as a dynamic brain PET with individual kinetics in every brain structure.

*PGEM implements convenient workflows for the analysis and visualization of DWI and 4D flow MR data.*

## Fiber Tracking and Visualization

Diffusion weighted imaging (DWI) with MR is a proven tool in brain imaging. The diffusion analysis model in the PMOD tool processes DWI MR images and calculates diffusion tensors. PGEM implements fiber tracking based on such diffusion tensor information. Various calculation methodologies and boundary conditions are supported, building on the functionality of the proven CAMINO toolkit. The resulting fibers are visualized as 3D structures in PGEM, but they can also be exported for use in alternative packages.

## 4D Flow Analysis and Visualization

4D flow MR sequences acquire the velocity vector field of fluids in vessels at multiple times, e.g., across the phases of a heartbeat. PGEM enables connection of the velocity vectors from a given acquisition and visualization as 3D streamlines. When the streamlines are calculated for all acquisitions and animated as a movie, the change of the flow pattern over time becomes apparent.

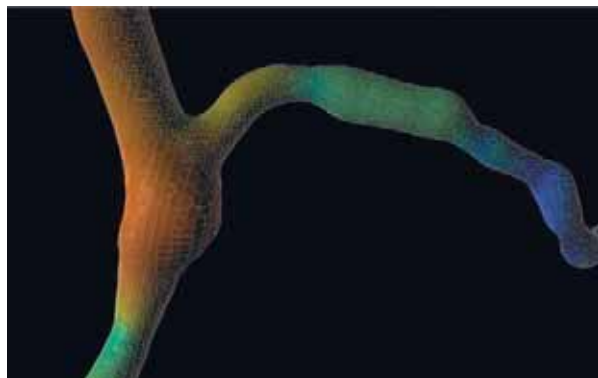
*PGEM supports all CFD preparation steps and offers a convenient interface to OpenFOAM®.*

## Computational Fluid Dynamics (CFD)

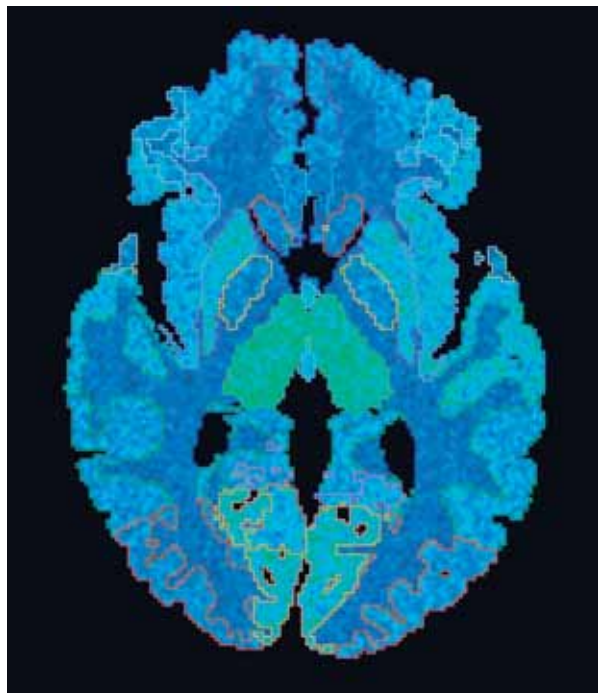
CFD is a research tool that has been used for analysis of the flow in vessels in a variety of medical conditions. CFD requires a model of the vessel geometry as an input and a computational engine to calculate the flow in the different parts of the lumen, as well as a visualization and assessment system of the results. PGEM supports all required parts for CFD research, delegating the actual flow simulation to the established open source CFD system OpenFOAM®.



White matter fiber tracks derived from a DWI MR image.



Mesh for CFD calculations in vessel together with the resulting pressure distribution in color.



Synthetic PET series with individual, slightly noisy kinetics in functional brain regions.

## Geometric Model Building

Geometric models are built from VOI definitions. The VOIs are converted into surfaces delineating the inner or outer of a structure part. Such parts can be connected to form hierarchical structures, for instance a model of a vessel tree for CFD simulations. By assigning physical properties to the individual parts, anatomical models can be designed which may be utilized for phantom image generation. One application is the synthetic generation of a dynamic PET image series from a brain atlas model, with different kinetics for each brain structure. Another application is the organization of the parts in an atlas-like manner, where high-level structures like organs are successively subdivided into smaller constituents. Each of the elements can be annotated using a range of media for educational purposes. An example model of the coronary arteries is included in the distribution for illustrative purposes.

## Fiber Tracking and Visualization

For the analysis of diffusion weighted MR (DWI) images, the gradient configuration during the acquisition needs to be known. PMOD reads this information from the DICOM header, if available. Otherwise, the gradient table can be loaded in 7 different formats, including FSL, Camino, DSI/DTI Studio and Paravision. All tractography calculations are based on the proven CAMINO toolkit code (<http://cmic.cs.ucl.ac.uk/camino/>). Four tracking algorithms are supported (FACT, EULER, RK4, probabilistic PICo), each with a number of parameters to tune the tracking process. VOIs are employed for definition of the seeding region, but also for imposition of restrictions on the resulting fibers, such as passing through or ending in a region.

The resulting fiber tracks are visualized as lines, colored by the direction cosines, by the local fractional anisotropy (FA), or by the seeding VOI color. Each track is an object in a 3D scene and can be manipulated individually. The scene may be enriched by adding FA or Mean Diffusivity (MD) image planes to the tracks. In order to calculate regional statistics from the FA and MD maps, tracks can be converted into VOIs and applied to the images. An alternative to evaluating the tracks in PGEM is export as vtk files. The whole tracking configuration can be saved in a protocol file for later reproduction of analysis.

## 4D Flow Analysis and Visualization

4D flow analysis requires two data sets, "Magnitude" and "Flow velocity", which are generated during MR image reconstruction. The magnitude image shows anatomical detail and has arbitrary scaling, whereas the flow velocity data is a 3D field of the flow vector in real-world units. Two formats for the vector field are supported, a format encoding all directions in one file,

and a format with separate files per direction. The maximal flow encoding vector of the acquisition needs to be known and manually entered.

Tracking uses the same algorithms as DTI fiber tracking described above, with the flow velocity vector taking the role of the principal tensor eigenvector. The results of the analysis are "streamlines", comparable to the DTI fiber tracks. Additionally, vorticity and helicity maps are calculated which provide information about further flow properties.

The streamlines are visualized in the same way as fiber tracks, with velocity as a color option instead of FA, and in the 3D scene they can be combined with plane images of the flow magnitude. An additional feature is a summary report that lists the average flow, vorticity and helicity in user-defined regions.

## Computational Fluid Dynamics (CFD)

A CFD simulation requires the geometric model of a vessel wall as a starting point. In a first step, the wall surface is converted from VOIs into a mesh representation. If an external STL file is available, the surface mesh can alternatively be loaded. In a next step, the enclosed volume is decomposed into small elements, the cells for the simulation. Parameters for this "volume meshing" process allow trimming of the cell size locally – particularly along the surfaces – in order to minimize the discretization error. The resulting volume mesh may be exported for external use in Fluent® (ANSYS) format. Next, inlet and outlet planes need to be defined, along with initial conditions of pressure and velocity vector. Kinematic pressure can be set as a fixed value that will be maintained throughout the simulation, or by a zero gradient property which will enforce that there is no pressure change at the boundary. Velocity can be configured similarly, with an additional option to keep the surface normal of the flow fixed. Pressure and velocity conditions along the wall surface need to be specified in the same way.

The actual CFD simulation is performed in a client-server setup. All configuration information is compiled into a simulation task, which is sent to a server middleware developed by PMOD for the open source CFD system OpenFOAM® ([www.openfoam.org](http://www.openfoam.org)). The server converts the information into an OpenFOAM case and runs the simulation. PGEM can list the status of the running simulation cases, and retrieve the resulting pressure maps and velocity fields of completed cases for analysis and visualization in 3D.

## Image Registration

It is routine that multiple functional and anatomical images are acquired in the process of a thorough disease investigation. If this is not achieved in a single hybrid scanning session, the images will show the organs in different orientations due to variable patient positioning. The visual or numerical comparison of such heterogeneous images can be approximate at best. A much better approach is to bring all images into a common frame of reference and then start the actual assessment with matched images.

*PFUS features a rich set of automatic methods for the registration of multi-modal images.*

## Stereotactic Normalization of Brain Images

Research has demonstrated that brain anatomy is comparable between the subjects of a species, and approaches were developed to derive representative brain images. Such template images establish a standard stereotactic space, into which the individual patient images must be mapped by a spatial normalization procedure. This kind of normalization requires not only proportional scaling of the dimensions, but also an elastic component for anatomical fine-adjustment.

## Image Registration and Fusion with PFUS

PMOD's PFUS tool provides a comprehensive environment for all kinds of tasks related to image regis-

tration and brain image normalization. It supports convenient workflows so that a user can extract optimal results from multi-modal images even in the most challenging situations met in human or preclinical research.

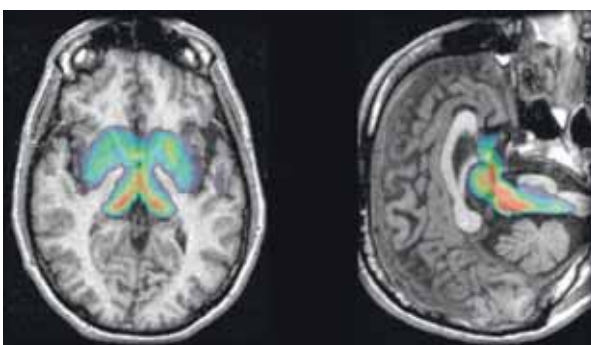
PFUS features a rich set of automatic methods for the registration of multi-modal images, and facilitates interactive precision adjustment of the alignment. Brain images of humans, primates, rats and mice can readily be normalized using templates for different imaging modalities and species. A unique functionality of PFUS is the mathematical combination of spatial transformations, and the calculation of inverse transformations. This allows, for instance, calculation of the spatial normalization with an MR image and using it to indirectly normalize a functional PET image.

*Brain images of humans, rats and mice can readily be normalized using templates for different imaging modalities.*

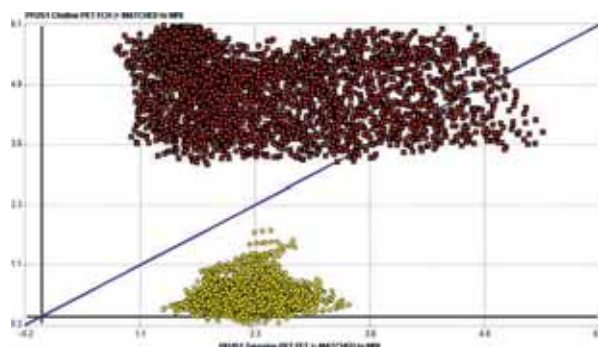
Once the images are registered, PFUS offers powerful tools for their joint analysis. The methods range from various types of fusion renderings, region outlining in the fused images, automatic delineation of standard brain regions, arithmetic operations between images, to the easy generation of scatter plots.



PET-derived dopamine D2/D3 map matched to CT (20 g mouse images).



PET-derived serotonin transporter map automatically matched to individual's MRI.



Scatter plot of corresponding Choline and Tyrosine pixel values in tumor (red) and contralateral (yellow).

## Rigid Image Registration

Techniques for rigidly aligning multimodal images:

- Automatic rigid matching using 6 metrics and various fine-tuning parameters
- Interactive manual rigid matching
- Landmark matching
- Motion correction of dynamic series

## Deformable Image Registration

Three deformable registration approaches are available:

- Template based normalization (SPM5 compatible)
- Normalization based on 3 tissue probability maps (unified segmentation approach, SPM8 compatible)
- Normalization based on 6 tissue probability maps (SPM12 compatible)

Corresponding template information and parameter presets are available to bring human and animal brain images into standard anatomy spaces:

- Human (PET, T<sub>1</sub>-MR, T<sub>2</sub>-MR, probability maps) in the MNI space
- Rat (FDG-PET, T<sub>2</sub>-MR) in the Paxinos space
- Pig (FDG-PET, HMPAO-SPECT, T<sub>1</sub>-MR)
- Cynomolgus monkey (T<sub>1</sub>-MR, FDOPA, DTBZ)

Standard VOI sets of brain areas are available in the above spaces. Users can easily add and apply their own VOI atlases.

## Use of Transformations

Image registrations and normalizations are represented by mathematical transformations or deformation fields. The following operations are supported:

- Visualization of the deformation field
- Calculation of the inverse transformation
- Combination of transformations
- Application of a transformation to map VOIs from one image space to another

## Image Interpolation

Control over the image interpolation process after registration is important for the subsequent visual or quantitative analyses. Supported interpolations:

- Nearest neighbor (for atlas applications)
- Trilinear
- Sinc (kernel with 5 or 7 voxels)
- Cubic spline

## Image Fusion

Once the images are registered to a common space, they can be evaluated on a pixel-by-pixel basis.

Available fusion options:

- Alpha blending
- Exchange of iso-contours
- Overlay of image parts above threshold
- Moving spyglass

- Combination of three images in a fused rendering
- MIP rendering of up to three fused images and production of rotation cines
- Visualization of up to six fused and synchronized images in parallel
- VOI definition directly in fused images
- Saving fused images as DICOM SC objects

## Pixelwise Operations

- Handheld calculator-like algebra operations between images
- 2D and 3D scatter plots of the corresponding image values (including restriction to user-defined VOIs)

## 3D Rendering in Medical Imaging

The amazing improvements in medical imaging devices have led to situations where physicians are confronted with many thousands of slice images covering single organs or the entire body. In such huge data sets, the relevant information may be difficult to localize. Therefore, flexible and targeted data reduction techniques are highly important. One approach is the rendering of selected image parts in pseudo-realistic 3D scenes, which has become the reviewing standard in domains such as angio-CT exams. The added value for the physician is the ability to interactively compose and manipulate the scene and thus come to a true understanding of the clinical case.

*P3D allows the construction of 3D scenes from any number of matched input series.*

## Multi-Modality Rendering

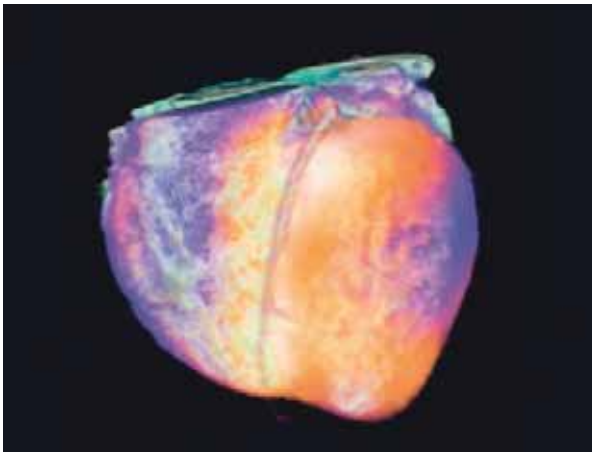
Often, patients are scanned using several modalities in order to assess complementary aspects of disease. A unique way of integrating such information is to generate 3D scenes from multi-modal data sets.

For instance, the left ventricle anatomy, assessed with angio-CT, can be augmented by color shading representing myocardial tissue perfusion.

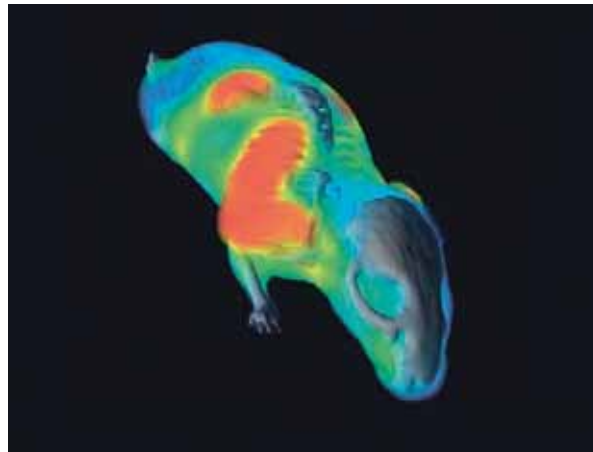
*Volume and surface rendering can be textured with static or even dynamic information.*

## Image Rendering with P3D

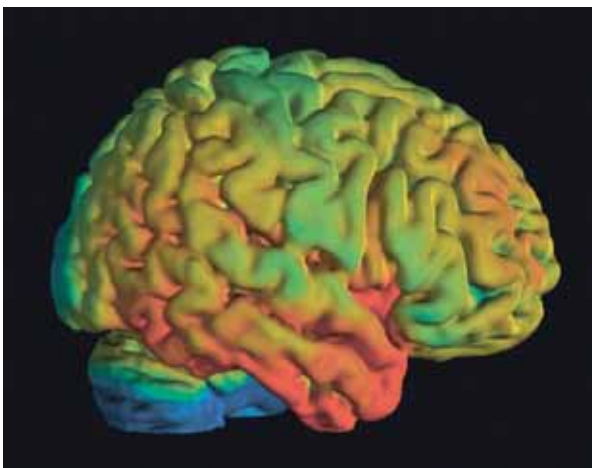
PMOD's P3D rendering tool offers a unique environment for visualization of information from anatomical and functional studies. It allows the construction of 3D scenes from any number of matched input series. Volume and surface rendering can readily be mixed in order to apply the most adequate technique for any data type. As a particular feature, both rendering types can be textured with static or even dynamic information. Additional elements such as image planes or VOIs enrich the scene, while a cutting facility allows exposure of inner parts of the scene. All of these features are easily available in a highly interactive fashion and make P3D the ideal tool for powerful presentation of research results.



Human heart: Angio-CT derived anatomy combined with SPECT perfusion texture.

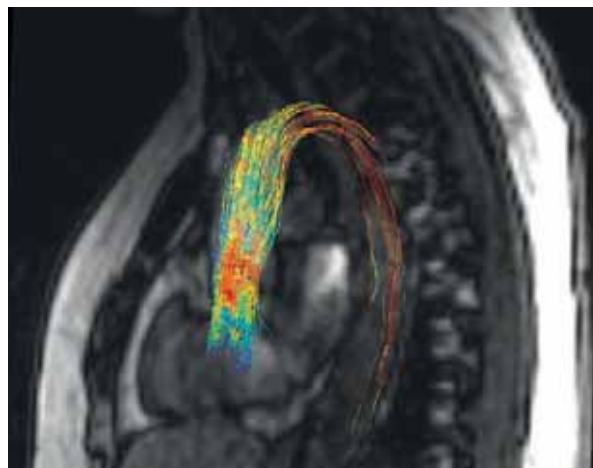


20 g mouse: Surface rendering of CT-derived skeleton combined with volume rendering of a matched SPECT image.



Human brain: Population  $BP_{nd}$  average of serotonin 5-HT1A receptor textured on brain surface.

Courtesy of A. Hahn, M. Savli, R. Lanzenberger,  
<http://www.meduniwien.ac.at/neuroimaging/>.



Streamlines visualizing blood flow velocity in the aorta, derived from a 4D flow MR acquisition.

## Input Data

Objects from several image series can be rendered in a single scene if they have been registered to a common reference before loading. Volumes of interest (VOI) outlined in the images may also be loaded and rendered as surface objects. Furthermore, it is possible to import objects saved in the VRML (Virtual Reality Modeling Language), STL (STereo Lithography), VTK tracks, and openFOAM polymesh formats.

## Segmentation Procedures

The surface of objects is obtained using a segmentation process. The following segmentations are supported and can also be used to restrict the scope of rendering:

- Volumes-of-interest outlining
- Threshold-based segmentations
- Seeded region-growing techniques
- K-means clustering of dynamic series
- ITK-library based segmentations: Otsu Threshold, Connected Threshold, Neighborhood Connected and Confidence Connected (Insight Toolkit, [www.itk.org](http://www.itk.org))

Objects segmented from dynamic images can have a different shape over time.

## Object Properties and Rendering

Scenes in P3D may contain the following objects, each supporting dedicated properties:

- Surface objects (shaded/wire-frame/points, transparency, color, texture)
- Volume-rendered objects (opacity functions, color transfer functions, texture)
- Vector path calculated from a vessel skeleton
- Oblique plane bound to a path (always orthogonal to path; with texturing)
- Orthogonal slice images (opaque/transparent/threshold)
- Markers for pin-pointing locations of interest in the scene (cross, sphere)
- Volumes of interest (stripes, closed surface)
- Fiber tracks from diffusion tensor analysis
- Streamlines from 4D flow studies
- Visualization of vector fields such as matching deformation
- Fused MIP rendering of up to three series
- Dynamic objects can be played over time

## Interactive Scene Manipulations

The 3D scene can be interactively explored using the mouse and dedicated user interface elements:

- Incrementally add objects to the scene
- Show/hide/remove/cut individual objects
- Cut objects by oblique plane within a definable radius
- Change the object properties
- Add light source
- Change viewpoint, zoom
- Let the scene rotate around any axis
- Run the texture derived from a dynamic scan through time

## Results

P3D results can be saved in several formats, including:

- Protocol files encoding entire scene configurations enabling reproduction at any time later
- Images of the segmentation results
- Rotation movies
- VRML or STL (ASCII, binary) output of surface-rendered objects
- Image captures of the scene



## Analysis of Brain PET and MR Images

Precise knowledge of the functional brain areas in the individual patient is crucial for the accurate quantitative analysis of brain PET images and their meaningful interpretation. Often however, functional regions are manually outlined in a casual manner, with subjective results as the outcome. This fundamental flaw can be overcome with PMOD's PNEURO tool, which offers both objective region outlining as well as pattern analysis methods via straightforward step-by-step procedures. These methods are provided as three individual tool sets.

*PNEURO offers automated processing for brain PET/MR, including parametric mapping.*

## Automatic Brain Regions by T1-MRI Parcellation

It is desirable that every brain PET study be complemented with a T1-weighted brain MRI that precisely represents the patient's anatomy. PMOD's PNEURO tool includes a sophisticated component to take advantage of this complementary information. Applying knowledge-base technology, it accurately segments the cortex and the basal ganglia from human T1-MRIs. These segments are then projected onto the PET images, and the regional signals are calculated, after which quantitative analysis can be performed.

## Automatic Brain Regions by Atlas Normalization

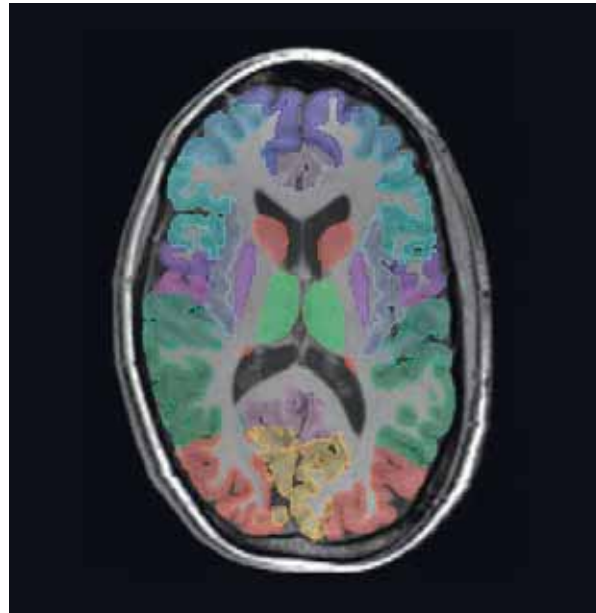
An alternative way of obtaining brain volumes of interest (VOIs) automatically is by leveraging the localization of brain areas as encoded in an atlas. The corresponding PNEURO component allows the user to adjust the atlas to the individual patient anatomy using a spatial normalization procedure, preferably obtained from the T1-MR image, or directly from the PET image. This solution has the advantage that it is also applicable for PET-only studies. The tool provides the probabilistic Hammers atlas but can also leverage alternative atlases, even from non-human species.

*PNEURO offers easy-to-use methods for objective region outlining and for pattern analysis.*

## Normal Brain PET Databases

Often a static image of the PET tracer concentration is acquired after an appropriate equilibration time. In this situation, the analysis is based on the fact that, with consistent study protocols, the normal brain uptake exhibits a characteristic pattern. The database component in PMOD's PNEURO tool enables pooling of tracer uptake across a set of normal volunteers,

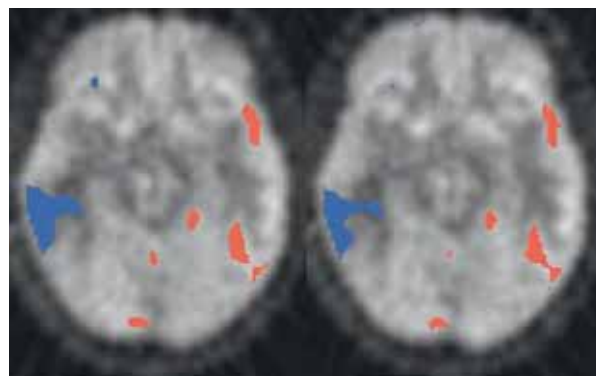
thus establishing the normal pattern and its variability. Once such a normal database has been created, the anomalies of the tracer uptake in an individual patient's brain PET scan can be easily localized without any prior assumptions or operator variability.



Brain parcellation result overlaid on T<sub>1</sub>-MRI.



3D rendering of the VOIs from a brain parcellation combined with the volume rendered T<sub>1</sub>-M.



Pixels deviating by more than two standard deviations from normal database values highlighted in red (> normal) and blue (< normal).

## Automatic Brain Regions by T1-MRI Parcellation

This module implements a methodology licensed from CEA, Orsay, France. It uses a knowledge base of 26 normal human brains which were carefully segmented by a neurologist. The procedure can be optimized with several options:

- MR denoising strength
- Gray/white matter separation weight
- Number of used subjects from the knowledge base used
- PET averaging range for matching with the MRI
- Space for the regional statistics: MR or PET
- PET scanner resolution for partial-volume correction

Results:

- Segments or outline VOIs in the MR space
- Structures with separate left/right parts: gray matter, caudate, putamen, thalamus, globus pallidus
- Structures without laterality: cerebellum, liquor
- Statistics on MR-matched or original PET images
- Cortical area subdivision of gray matter
- Optional partial-volume correction of statistics

## Automatic Brain Regions by Atlas Normalization

This module includes the following functionality:

- Adjustment of the VOI atlas to subject images by spatial normalization
- Normalization based on PET or MR images
- Intersection of VOIs with a gray and white matter probability mask
- Transfer of VOIs between spaces
- VOI statistics on template-matched, MR-matched or original PET images
- Optional partial-volume correction of statistics

The module bundles the Hammers Maximum Probability VOI Atlas (N30R83), which is licensed from Imperial College, London<sup>1-3</sup>. However, the methodology is applicable for other human atlases and those for other species. Atlases are included for the rat, mouse, pig, cynomolgus monkey.

## Parametric Mapping

If the pixel-wise modeling tool PXM0D has been licensed, PNEURO supports PET and MR parametric mapping as part of the workflow. At the end of the workflow, the parametric maps can readily be evaluated within the outlined VOIs.

## Normal Brain PET Databases

This module supports the creation of normal PET databases from a consistent set of normal volunteer images. The following options are available:

- Normalization template: Standard MNI or user-defined templates
- Value scaling: relative to average, maximum, average of % highest values, average in percentile range; within a mask or VOI

- z-score calculation: using the individual standard deviation in each pixel or a regional average (variance pooling)
- Result mask for background removal
- Smoothing filters

The comparison of a PET image against a database results in a z-score map of the deviation from the normal pattern. It can be explored visually and analyzed numerically:

- Fusion of z-score map with PET or template image
- Saving of z-score maps for pooled SPM analysis
- VOI statistics

## PNEURO for Amyloid PET

In a recent study, Brendel et al. [4] studied the effects of reference region selection and partial-volume correction on the analysis of amyloid PET. They fully automatically processed the data of 962 subjects using PNEURO. Their conclusion was that detection of longitudinal amyloid increases is optimized when using partial-volume correction and white matter as reference tissue. Another study by Tuszynski et al. [5] compares software tools, including PNEURO, for the automatic contouring of brain structures. It clearly documents the value and reliability of PNEURO in the analysis of amyloid PET images, making it a useful alternative to tedious standard manual outlining.

## Performance

Brain parcellation involves heavy number crunching and therefore requires an appropriate computer system. A 64-bit operating system with  $\geq 16$  GB RAM and at least 8 cores is required. Batch procedures are available to run a job queue during off-peak hours.

## References

- <sup>1</sup> Hammers A, et al.: Implementation and application of a brain template for multiple volumes of interest. *Hum Brain Mapp* 2002, 15(3): 165–174.
- <sup>2</sup> Hammers A, et al.: Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. *Hum Brain Mapp* 2003, 19(4): 224–247.
- <sup>3</sup> Gousias IS, et al: Automatic segmentation of brain MRIs of 2-year-olds into 83 regions of interest. *Neuroimage* 2008, 40(2): 672–684.
- <sup>4</sup> Brendel M, et al.: Improved longitudinal (18F)-AV45 amyloid PET by white matter reference and VOI-based partial volume effect correction. *NeuroImage* 2015, 108(0): 450–459.
- <sup>5</sup> Tuszynski T, et al: Evaluation of software tools for automated identification of neuroanatomical structures in quantitative beta-amyloid PET imaging to diagnose Alzheimer's disease. *Eur J Nucl Med Mol Imaging* 2016.

## FDG PET in Alzheimer's Disease

FDG brain PET images address the local glucose metabolism, which can be considered as a proxy for neuronal activity at rest<sup>1</sup>. Therefore, impaired neuronal activity is reflected by a reduced FDG uptake in the affected brain areas. In patients suffering from Alzheimer's Disease (AD), the reduction is evident as a characteristic pattern and becomes detectable as a significant deviation from normal controls 1 to 2 years before onset of dementia.

*PALZ implements a licensed and validated analysis of FDG brain PET scans particularly targeting Alzheimer's Disease.*

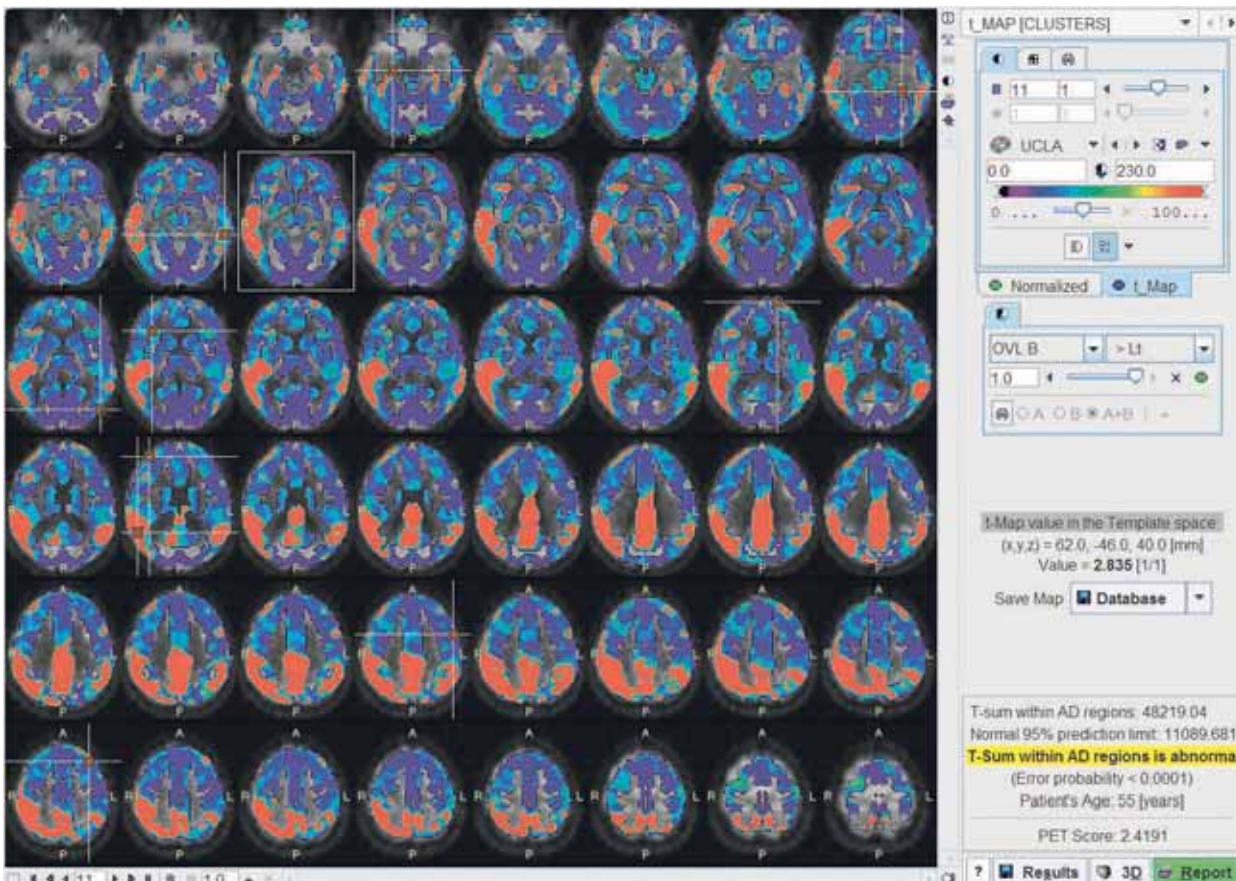
## Discrimination from Normal Controls

In a large multi-center trial, it was found that it is possible to discriminate AD patients from normal controls based on the FDG uptake pattern in the brain<sup>2</sup>. The methodology developed calculates a criterion that states, together with a statistical probability, whether the finding is abnormal. The method has been successfully validated several times<sup>2,3,4</sup> with several data sets, and resulted in high sensitivity/specificity outcomes which are somewhat dependent on the sample selection: ADNI (83% / 78%), NEST-DD (78% / 94%)<sup>3</sup>. In addition, it has recently been shown that the outcome can be transformed into a biomarker for tracking the progression of MCI to AD in clinical trials<sup>2</sup>.

*Data processing is fully automatic and results in an objective measure of Alzheimer's Disease probability.*

## Analysis of FDG PET Images with PALZ

PMOD's PALZ tool is a licensed and streamlined implementation of the validated AD discrimination analysis. It is applicable to FDG brain PET scans of patients with clinical symptoms of AD. Data processing is fully automatic and results in an objective discrimination criterion, substantiated by an error probability of abnormality. The numerical outcome is complemented by a visual summary highlighting the significantly abnormal brain areas. These unique features make it easy to get an overview of disease extent and gain confidence for clinical decisions. Naturally, all results can be documented in DICOM and exported numerically for dedicated statistical analyses.



PALZ user interface illustrating the abnormal outcome of an AD patient.

## Requirements

In order to interpret the outcome of a PALZ analysis with regard to a potential diagnosis of AD, the following requirements must be met:

- The FDG brain PET images are corrected for attenuation and scatter
- The patient has clinical symptoms of AD
- The patient is at least 49 years old

## Analysis Procedure

The PALZ tool performs the following analysis steps:

- The patient images are stereotactically normalized and smoothed with a 12-mm Gaussian filter.
- The image values are normalized with reference to an area that is known to have AD-preserved activity.
- The normal image at the patient's age is calculated and the difference to the patient image calculated as a t-map.
- All abnormal t-values within a predefined AD-mask are summed, yielding the AD t-sum. The t-sum is a criterion of scan abnormality with a 95% prediction limit of 11089.
- The AD t-sum is tested for significance of abnormality.
- The PET Score is calculated from the AD t-sum by:  
$$\text{PET Score} = \log_2(\text{AD t-sum}/11089+1).$$
- A cluster analysis of the t-map is performed, grouping  $\geq 216$  contiguous pixels with  $p < 0.05$ .

## Results

The PALZ tool provides the following results from a discrimination analysis:

- The AD t-sum criterion of scan abnormality together with its statistical error probability.
- The PET Score, an imaging biomarker for monitoring the progression of Mild Cognitive Impairment to Alzheimer's Disease.
- The t-map, representing the deviation from the age-corrected normal uptake.
- A cluster map showing groups of pixels with significantly reduced uptake.
- A summary report which includes the statistical outcome.

## Limitations and Disclaimer

- The PALZ tool is not a general FDG brain PET analysis tool and thus not suited to searches for non AD-related defects. Any other disease that affects the associated brain areas may also lead to a significantly abnormal result.
- The PALZ tool has no clearance for clinical use.

## References

- <sup>1</sup>Herholz K., Westwood S., Haense K., Dunn G. Evaluation of a Calibrated 18F-FDG PET Score as a Biomarker for Progression in Alzheimer Disease and Mild Cognitive Impairment. *J Nucl Med* 2011; 52:1218–1226.
- <sup>2</sup>K. Herholz, E. Salmon, D. Perani, et al., Discrimination between Alzheimer Dementia and Controls by Automated Analysis of Multicenter FDG PET. *Neuroimage* 2002; 17(1): 302–316.
- <sup>3</sup>Haense C, Herholz K, Jagust WJ, Heiss WD. Performance of FDG PET for detection of Alzheimer's disease in two independent multicentre samples (NEST-DD and ADNI). *Dement Geriatr Cogn Disord*. 2009; 28(3): 259–66.
- <sup>4</sup>Caroli A, Prestia A, Chen K, Ayutyanont N, Landau SM, Madison CM, Haense C, Herholz K, Nobili F, Reiman EM, Jagust WJ, Frisoni GB. Summary Metrics to Assess Alzheimer Disease-Related Hypometabolic Pattern with 18F-FDG PET: Head-to-Head Comparison. *J Nucl Med*. 2012; 53(4): 592–600.

## Image Segmentation

Image segmentation plays an important role in objective image assessment. Segmented anatomic structures are the basis for a multitude of quantitative approaches analyzing shape, texture and dynamic uptake of tracer. PSEG supports tailored segmentation workflows for static and dynamic imaging scenarios.

## PERCIST-type Segmentation

PERCIST<sup>1,2</sup> defines an objective methodology to assess the tumor burden and treatment response from static FDG PET images. Lesions are segmented based on the uptake in a reference organ, and their relevant properties (SUVpeak, MTV, TLG, etc.) listed in a report. In PSEG, the same workflow is also applicable when segmenting on an absolute threshold in SUVlbm or other calibrated units.

*PERCIST-type lesion segmentation in PSEG is comprehensive and flexible.*

## Functional Organ Segmentation

Dynamic rodent PET studies are often used early in tracer or drug development. PSEG includes a patented clustering approach for grouping image pixels with similar kinetics in a local neighborhood<sup>3</sup>. Semi-automatic segmentation of such studies can be achieved within only a few minutes.

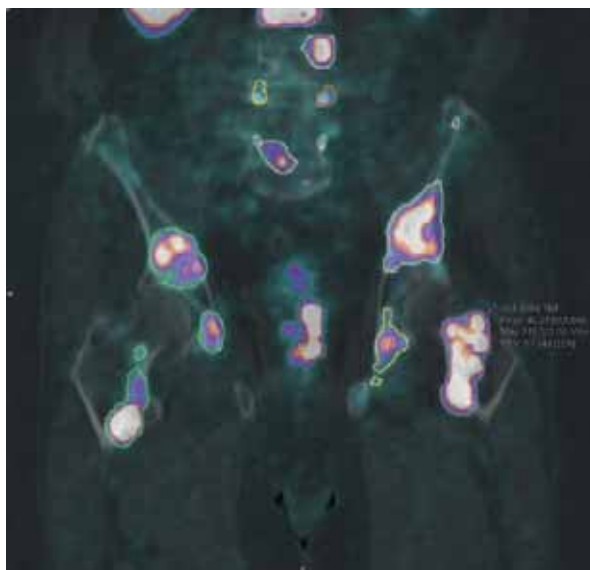
## K-Means Segmentation

The K-means method is a general clustering approach. The implementation in PSEG is aimed at subdividing a dynamic image into clusters of “kinetically similar” pixels<sup>4</sup>. It uses the time-weighted Euclidean distance as the measure of dissimilarity (or distance) between TACs.

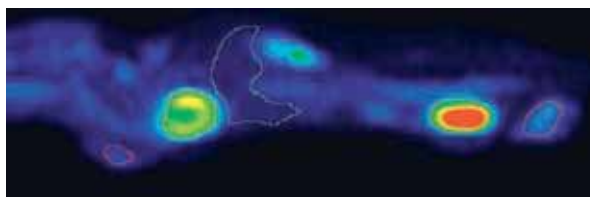
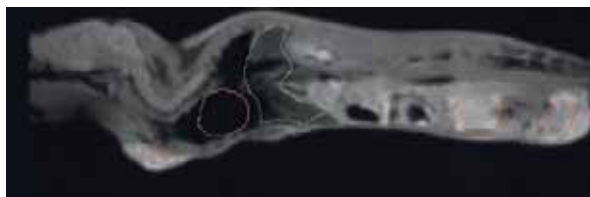
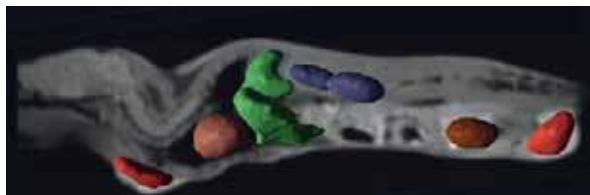
*PSEG supports the semi-automatic segmentation of dynamic rodent PET studies within just a few minutes.*

## Supervised Segmentation

Whereas K-means is completely data-driven, supervised clustering is driven by a set of time-activity curves specified by the user<sup>5</sup>. They represent the kinetic behavior of the tissues of interest, which are to be segmented from the data. This approach has been developed for data-driven reference region determination.



Segmentation of human PSMA PET on SUVbw = 3.5 threshold



Organs and lesions derived by segmentation of dynamic FDG PET, shown in overlay on sagittal mouse MR sections.

## Workflow

All methods use a consistent workflow:

- Load the functional data to be segmented
- Option: Load matched anatomical data
- Crop to relevant volume
- Interpolate to suitable resolution
- Generate a segmentation mask
- Apply segmentation method within mask
- Analyze the functional data within the segments
- Save protocol file for exact reproduction

## PERCIST Segmentation

Implements the PERCIST methodology for the oncologic assessment of static human FDG PET<sup>1,2</sup>:

- Interactive placement of 3cm diameter sphere in liver or blood
- Automatic iso-contouring on “minimal level of tumor uptake”
- Lesion sorting by SUVpeak
- Report of hottest lesions with exploratory measures incl. SUVmax, MTV, TLG, max. diameter

Special features:

- Texture analysis within lesions
- Segmentation on absolute SUV thresholds
- Comparison baseline – follow-up
- Label map generation of lesions as input to machine learning
- Applicable for animal data (reference sphere scales automatically)

## Functional Organ Segmentation

Local means analysis method licensed from CEA, Orsay, France<sup>3</sup> for dynamic PET data. Segments “functional organs” characterized by independent pharmacokinetics.

- Localization of pixels in the organ centers
- Computation of local pharmacokinetics and global noise
- Parcellation of mask volume into a configurable number of regions
- Hierarchical fusion of regions forming increasingly larger regions
- Interactive assignment of organs to segments on suitable hierarchy levels
- Organ time-activity curve (TAC) calculation
- Transfer of TACs to kinetic modeling tool

## Special feature

- Partial volume correction

## K-Means Segmentation

General k-means clustering for subdividing dynamic data into clusters of “kinetically similar” pixels<sup>4</sup>. The time-weighted Euclidean distance is used as the measure of distance between TACs. Performs the following steps for a specified number N of clusters:

- Randomly selects N pixels as initial cluster centroids
- Assigns each pixel to the centroid with minimal distance between the TACs
- Calculates new centroid TAC as average TAC of all cluster pixels
- Repeats cycle: 1) Assign each pixel to centroid with minimal distance, 2) Recalculate centroid TAC, until no pixel is assigned to a different cluster, or iteration exceeds a prescribed maximum.

As no geometric information is used in the process, the resulting clusters likely include spatially disconnected pixels.

## Supervised Segmentation

Method for subdividing dynamic data into clusters following distinct kinetic behavior. Developed for derivation of reference brain region in [11C]PK11195 studies<sup>5</sup>. Requires preparation of representative class TACs. Implements the variant described for use with [11C]PIB<sup>6</sup>:

- Fits pixel TAC by linear combination of all kinetic class curves with non-negative coefficients (NNLS)
  - Assigns pixel to class with highest coefficient
- Special feature:

- Mechanism (weight ratio) to assign only pixels with clear preference for one class curve

## References

- <sup>1</sup> Wahl RL et al.: From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med 2009, 50 Suppl 1: 122S–150S.
- <sup>2</sup> O JH, Lodge MA, Wahl RL: Practical PERCIST: A Simplified Guide to PET Response Criteria in Solid Tumors 1.0. Radiology 2016, 280(2): 576–584.
- <sup>3</sup> Maroy R et al. Segmentation of rodent whole-body dynamic PET images: an unsupervised method based on voxel dynamics. IEEE Trans Med Imag. 2008; 27(3): 342–54.
- <sup>4</sup> Velamuru PK et al. Robust Clustering of Positron Emission Tomography Data. Paper presented 2005; St. Louis.
- <sup>5</sup> Turkheimer FE et al: Reference and target region modeling of 11C-PK11195 brain studies. J Nucl Med 2007, 48(1): 158–167.
- <sup>6</sup> Ikoma Y et al: Reference region automatic extraction in dynamic 11C-PIB. J Cereb Blood Flow Metab 2013, 33(11): 1725–1731.

## Role of PMOD Software in Clinical Trials

The evaluation of new drugs is ever more frequently based on molecular imaging techniques, leveraging the unique insights they offer. For instance, changes in receptor occupancy or the amyloid burden in the brain can be assessed with PET in a fully quantitative manner. PMOD has been the quantitation workhorse for hundreds of researchers in exactly this domain for more than a decade. The Audit Trail License (ATL) of PMOD provides dedicated quantitation support for clinical trials with their regulatory and logistic demands.

*ATL provides all components required for compliance of image processing workflows.*

## Mechanisms for Supporting 21 CFR Part 11

Clinical trials must comply with the regulatory requirements of FDA's 21 CFR part 11 guideline, which establishes rules for trustworthy electronic records and signatures. Image processing software needs to offer appropriate mechanisms to duly meet these requirements in the context of standard operating pro-

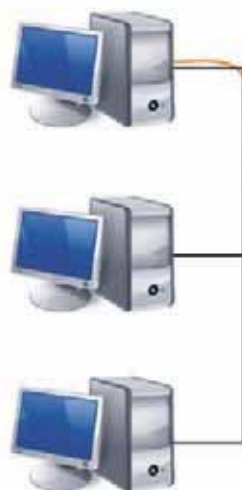
cedures. PMOD has integrated into its ATL version all constituents necessary for compliant image processing workflows into its ATL. The main ATL features beyond the standard PMOD functionality include: tight access control, strong data protection, detailed change tracking, sophisticated logging of all activities, and flexible report generation.

*Several CROs have integrated ATL into their 21 CFR part 11 compliant environment and use it in daily routine on their trial images.*

## Usage of ATL by CROs

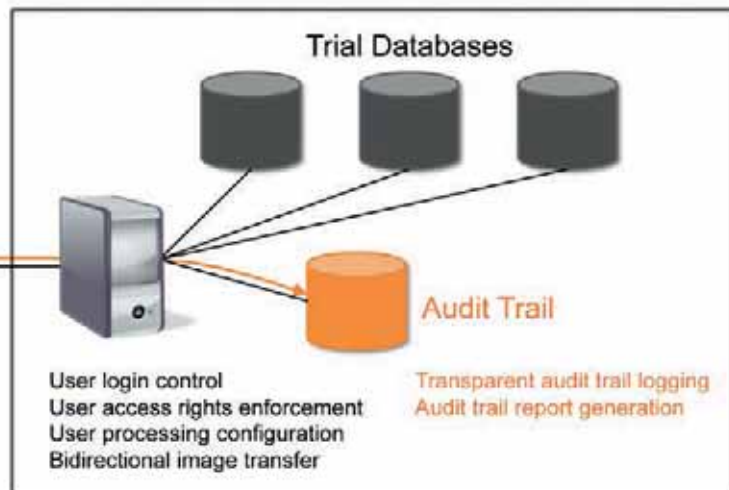
PMOD's ATL was initially developed in close collaboration with a major Clinical Research Organization (CRO) specialized in molecular imaging. Meanwhile, several other CROs have integrated it into their 21 CFR part 11 compliant environment and successfully passed FDA audits. The ATL has been proven to run productively in enterprise setups with more than 30 data analysts, simultaneously working with the data from over 75 trial databases.

## Clients for data analysis



Encryption  
(if needed)

## Server in secured room



Schematic of the client-server organization used in PMOD's ATL.

Operation time	User	Module	Level	Operation	Patient name	Patient ID	Complex DBID	Details
2016-01-12 14:40:59.369	Manager	PVIEW	IMAGE	LOAD	137_S_0686	137_S_0686	<178/839/3356/...	LOADED
2016-01-12 14:40:57.689	Manager	PVIEW	COMPONENT	LOAD	137_S_0686	137_S_0686	<178/839/3356/...	[DEVTRANSFORM] DEVICE_TRANSFORMATION = Loaded
2016-01-12 14:40:47.361	Manager	PVIEW	IMAGE	SAVE	137_S_0972	137_S_0972	<173/1263/0/1/2...	SAVED as Database 137_S_0972   HC_SUV_Irk_mc...   ADNI Static Brain (6x5
2016-01-12 14:40:47.151	Manager	PVIEW	COMPONENT	SAVE	137_S_0972	137_S_0972	<173/1263/486...	[IMAGEHISTORY] IMAGE_HISTORY = Saved to Database folder: 137_S_0972/2
2016-01-12 14:40:45.541	Manager	PVIEW	COMPONENT	SAVE	137_S_0972	137_S_0972	<173/814/4861/...	[IMAGEHISTORY] IMAGE_HISTORY = Saved to Database folder: 137_S_0972/2
2016-01-12 14:40:42.411	Manager	PVIEW	SERIES	UPDATE	137_S_0972	137_S_0972	<173/1263/0/1/2...	Total image objects in series = 1, image objects already in DB = 0, objects upd
2016-01-12 14:40:41.371	Manager	PVIEW	SERIES	CREATE	137_S_0972	137_S_0972	<173/1263/0/1/2...	
2016-01-12 14:40:36.864	Manager	PVIEW	IMAGE	SAVE	137_S_0972	137_S_0972	<173/1262/0/1/2...	SAVED as Database 137_S_0972   ADNI Static Brain (6x5)  > MATCHED to AC
2016-01-12 14:40:36.654	Manager	PVIEW	COMPONENT	SAVE	137_S_0972	137_S_0972	<173/1262/485...	[IMAGEHISTORY] IMAGE_HISTORY = Saved to Database folder: 137_S_0972/2
2016-01-12 14:40:35.334	Manager	PVIEW	COMPONENT	SAVE	137_S_0972	137_S_0972	<173/814/4858/...	[IMAGEHISTORY] IMAGE_HISTORY = Saved to Database folder: 137_S_0972/2
2016-01-12 14:40:31.944	Manager	PVIEW	SERIES	UPDATE	137_S_0972	137_S_0972	<173/1262/0/1/2...	Total image objects in series = 1, image objects already in DB = 0, objects upd
2016-01-12 14:40:30.924	Manager	PVIEW	SERIES	CREATE	137_S_0972	137_S_0972	<173/1262/0/1/2...	
2016-01-12 14:40:23.071	Manager	PVIEW	IMAGE	SAVE	137_S_0972	137_S_0972	<173/1261/0/1/2...	SAVED as Database 137_S_0972   ADNI Static Brain (6x5)  > MATCHED to AC
2016-01-12 14:40:22.861	Manager	PVIEW	COMPONENT	SAVE	137_S_0972	137_S_0972	<173/1261/485...	[IMAGEHISTORY] IMAGE_HISTORY = Saved to Database folder: 137_S_0972/2
2016-01-12 14:40:21.211	Manager	PVIEW	COMPONENT	SAVE	137_S_0972	137_S_0972	<173/814/4855/...	[IMAGEHISTORY] IMAGE_HISTORY = Saved to Database folder: 137_S_0972/2
2016-01-12 14:40:17.441	Manager	PVIEW	SERIES	UPDATE	137_S_0972	137_S_0972	<173/1261/0/1/2...	Total image objects in series = 1, image objects already in DB = 0, objects upd

Example of the log entries in the audit trail database.

## System Organization

PMOD's ATL provides all components necessary for 21 CFR part 11 compliant image analysis. However, it must be complemented by an appropriate organizational setup in order to effectively implement compliance. Most importantly, management of the user rights and the image databases should be handled with the greatest care.

The ATL requires a client-server setup of the computer environment. The server hosts data and user management and should be located in a secured room preventing unauthorized access. Image analysis is performed on remote clients. At client sign-on, user permissions are verified by interaction with the server. Upon successful login, the working environment assigned to the particular user is retrieved from the server. That user will then have access to just the relevant databases, and perform the actual analysis tasks following standard operating procedures. Audit trail information is sent to the server and archived during all processing steps, without disruption to the user. The audit trail information can be condensed into reports for regulatory and documentation purposes at any time.

## Security Mechanisms

- Central data storage in protected server databases.
- Central administration of data and user privileges.
- Secure user authentication, optionally integrated into the operating system login.
- Access list control (read/write, delete) for databases at the user level.
- Remote data processing employing secure client-server communication.

## Traceability of Results

- A history record is created when the original image is imported.
- This history is retrieved whenever images are loaded, and any processing applied to the images is appended to the record.
- When processed images are saved, the updated history is saved at the same time, establishing a life-long data processing record.
- In case regional image statistics are saved, the corresponding volumes of interest are also automatically saved.
- Similarly, spatial transformations are automatically saved with transformed images.

## Tracking of Processing Progress

An optional tracking mechanism allows the progress of the data analysis to be monitored.

- The series to be tracked are added to the tracking list.
- Each series from the list is quality controlled and assigned to an analyst.
- All intermediate results are added to a processing tree.
- The final result is marked as an endpoint of processing.
- Each step in the processing tree can be inspected for quality control purposes.

## Audit Trail Logging

- Secure and user transparent audit log databases.
- User as well as administrator activity logging.
- Comprehensive logging of any processing in the PBAS and PFUS tools.
- Logging of read/write operations in all PMOD tools.

## Advanced Report Generation

- Versatile filtering of the audit log database according to many criteria for creation and printing of reports.
- Interactive inspection of the details of events recorded in the audit trail.



PMOD supports all kinds of biomedical modalities and their formats. The image viewing, image processing and volume-of-interest definition functionality goes much beyond the scope of other imaging software and provides unmatched flexibility. This strong basic functionality is complemented by dedicated quantification tools.

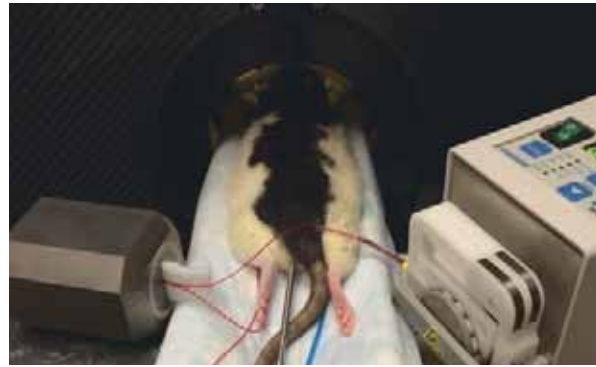


PMOD, the Swiss knife for quantification of biomedical images.

## Characterization of New Radioligands

Newly developed radioligands have to undergo rigorous testing. PMOD tools support all characterization steps after the in-vitro assays:

- PMOD allows all images to be brought into a common analysis environment. By applying suitable registration methods, data from different sources can be fused for joint evaluation.
- Biodistribution is readily assessed and documented in PBAS or PSEG. The comprehensive set of contouring and segmentation methods leverages fast and reproducible regional uptake measurements.
- The kinetic modeling tools PKIN and PXM0D provide all state-of-art methods needed to evaluate ligand binding characteristics and develop a robust quantification methodology.
- PKIN's simulation capabilities can be leveraged in the development of an optimal data acquisition protocol and to assess the sensitivity of the results.
- Variability assessed in test-retest studies is crucial in estimating the detectable effect size. The R console in PBAS offers boxed scripts for the statistical analysis of such kinetic group results.

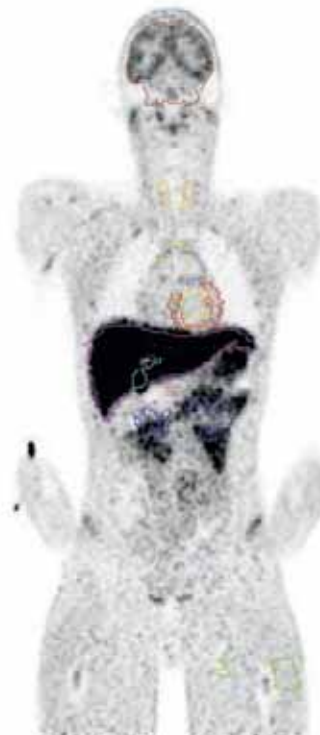


PET scan of rat with simultaneous online blood sampling

## Radiation Dosimetry

Internal radiation dose estimation is an essential requirement for novel radiotracers. It is based on the cumulated radioactive decays in the critical organs. PMOD offers a tailored workflow for the necessary pre-processing steps using the base tool PBAS and the kinetic modeling tool PKIN.

A sequence of static images can readily be combined into a dynamic series with common decay correction. After organ outlining, their activity time course is calculated and transferred to the modeling tool. There, decay correction is undone and the activity curve integral calculated. The resulting cumulated organ activities are finally exported into files directly compatible with OLINDA or IDAC for calculation of the effective radiation dose.

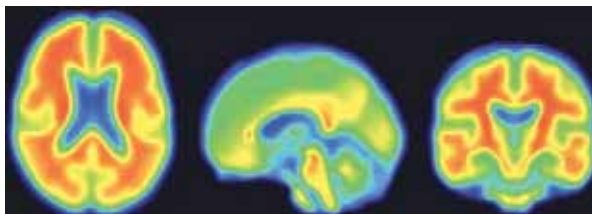


Outlines of organs and representative tissue for dose calculation

## Large-scale Brain Data Processing

While studies within individual research centers typically include a limited number of subjects, there is a trend towards multi-center studies with large sample sizes and pooled repositories. Automated procedures are required for the efficient, yet objective, analysis of such data.

The PNEURO tool is ideally suited to the batch processing of PET and MR brain data. The AV45 PET data, for more than 600 subjects, in the ADNI database ([www.adni-info.org](http://www.adni-info.org)) was used to study the spatial distribution of A $\beta$  deposition at different stages of disease. Using AV45 normalization templates, the SUVR was calculated in PNEURO, with and without partial volume correction. The statistics were transferred to the PMOD R console and analyzed with the linear mixed effects method.



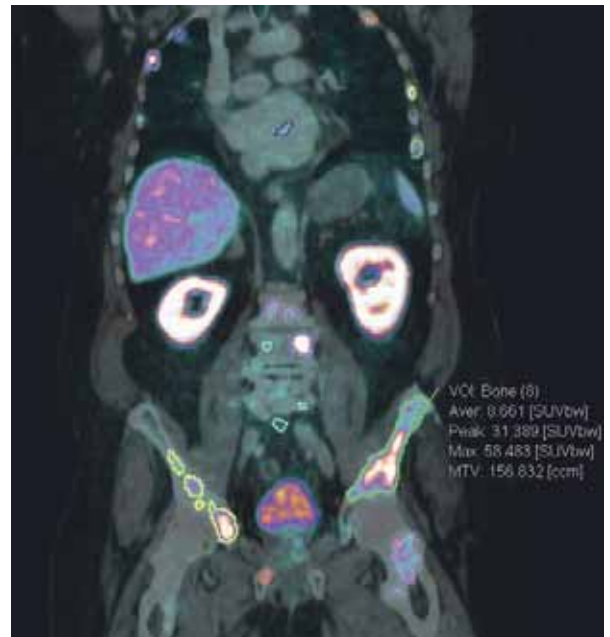
AV45 normalization template for AD patient images, now also available from ADNI.

## Lesions in Oncology PET

Oncology is the most prevalent application domain of PET scanning. Oncologic lesions typically show up in PET images as bright areas of high uptake. Over the years, many approaches have been described to quantify severity and spatial extent of such lesions. PMOD provides flexible implementations of such methodologies to objectively assess tumor burden and therapy response. Whereas the PSEG module features a complete oncologic workflow, the general VOI environment of PMOD already includes a rich set of tools for segmenting and assessing lesions.

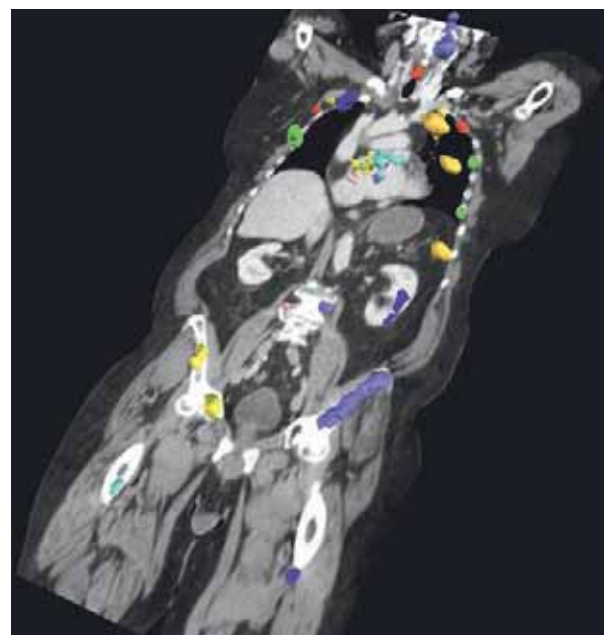
Iso-contouring in a restricted neighborhood is a widely applicable segmentation method. Hereby, specification of the contouring threshold is the critical element. PMOD supports absolute thresholds specified in SUV units, adaptive thresholds in percentage of SUVmax or SUVpeak in the neighborhood, and relative thresholds determined from reference or background tissue.

Using quick MIP navigation and hot-key driven segmentation, lesion assessment becomes a fast and objective process. An exhaustive set of measures is calculated from the uptake within the segments, including SUVmean, SUVpeak, SUVmax, MTV, sphericity and longest diameter. These measures can be displayed next to the lesions for convenient documentation, as well as leveraged for sorting the lesion order.



Lesions obtained by iso-contouring of PSMA PET scan at an absolute SUVbw threshold.

Texture analysis quantifies the variability of pixel intensities within a segmented lesion. A large number of texture metrics have been described for in vivo lesion characterization, which might provide predictive information. PMOD offers a collection of the 25 indexes which have been found to be most valuable in the context of PET imaging. They can readily be calculated in addition to the more standard VOI statistics, giving PMOD users an easy handle to radiomics research. In addition to numeric assessment, the lesions can be visually explored in many ways. As an example, the PSMA bone lesions are rendered as 3D surfaces and shown together with a coronal plane of the CT scan in the illustration below.



Rendering of segmented lesions in the PMOD 3D tool.

Beyond its proven biomedical imaging analysis software, PMOD offers tailored support for pre-clinical studies in animals and clinical imaging studies. In this space, PMOD's own in-house expertise is complemented by a scientific advisory board which includes several international medical imaging experts.

### Input into Study Design for Medical Imaging Studies

Practical factors crucial to a successful implementation include equipment setup, calibration and validation, scanning protocol optimization, appropriate image reconstruction as well as imaging data management. Sub-optimal preparation will have an impact on the quality of the data and limit the insight which can be achieved with imaging data. Our experts are able to offer support during any phase of study development, according to the direct needs of the study team.

### Post-Processing of Medical Imaging Data

The analysis of medical imaging data is demanding, time-consuming and needs to be standardized. Medical imaging data analysis methods have to be evaluated, trading detail against robustness and taking the physiological background into account. The optimum method should be defined on statistical grounds and on the method's sensitivity for detecting changes. Our experts can help with method selection, proper use of the PMOD software, quality control of the data, and data analysis.

### Generation and Delivery of Study Results

Individual processing results need to be pooled for overall statistical analysis. This is a delicate task, which has to properly account for the study design and the structure of the data. The PMOD software supports the aggregation of study results as well as sophisticated statistics via the open-source R software. This infrastructure has been streamlined for the analysis of standard types of medical imaging studies. Our experts can provide support for data analysis, interpretation, and report writing.

### Custom Software Development

The PMOD software development team has a long and successful track record of delivering fit-for-need software applications. Thanks to the modular structure of the PMOD software, new functions or entire applications can be designed and refined in short development cycles. The scale of projects we can support ranges from adding individual quantification measures and dedicated model structures to the PMOD infrastructure, to providing full-blown tools tailored for proprietary use.

### Contracting Options

The degree of support offered on contract by PMOD is highly adjustable: it may range from individual coaching on a dedicated topic to deploying customized software solutions. As each imaging center's requirements are unique, we encourage interested study teams to contact us for personalized discussion of their needs.



The PMOD software is a modular suite of tools, which interact to enable smooth and efficient data analysis workflows. It targets researchers in neurology, cardiology and oncology working with human or animal image data. As every researcher has unique data processing needs, the selection of the tools included into an individual PMOD license must ensure that all essential tasks can be accomplished.

The table below is intended to guide tool selection. It lists typical application domains together with the re-

quired tools, additionally indicating tools which could increase functionality and flexibility. If the functionality required spreads across multiple table rows, the corresponding tools should be added. Please ask for advice by contacting [info@pmod.com](mailto:info@pmod.com) in case you need further assistance with selection.

Note that the PMOD website features an online quoting facility which calculates the license cost of any tool configuration.

Data Processing Task	PBAS	PKIN	PXMOD	PCARD	PGEM	PFUS	P3D	PNEURO	PALZ	PSEG
Image reviewing and VOIs (PET, SPECT, MR, CT)	required	nice to have	nice to have	nice to have	nice to have	required	required	required	required	nice to have
Multimodal images and oncology (PET, SPECT, MR, CT)	required	nice to have	nice to have	nice to have	nice to have	required	required	required	required	nice to have
Advanced modeling and quantification (PET, SPECT, MR)	required	required	required	nice to have	required	required	required	required	required	required
Regional quantification of brain data (MR, PET, SPECT, CT)	required	required	required	nice to have	required	required	required	required	required	nice to have
Quantification of heart images (PET, SPECT, MR, CT)	required	required	nice to have	required	required	required	required	nice to have	nice to have	nice to have
Biodistribution and dosimetry studies (PET, SPECT)	required	required	nice to have	nice to have	nice to have	required	required	nice to have	nice to have	required
Diffusion mapping and tractography of DWI/DTI MR data	required	nice to have	required	nice to have	required	required	required	required	nice to have	nice to have
Streamline calculation from 4D flow MR data	required	nice to have	nice to have	nice to have	required	required	required	nice to have	nice to have	nice to have
Computational fluid dynamics (CFD) simulations	required	nice to have	nice to have	nice to have	required	nice to have	required	nice to have	nice to have	nice to have
FDG PET images of patients with suspected AD	required	nice to have	nice to have	nice to have	nice to have	nice to have	required	nice to have	required	nice to have

required                      nice to have

PMOD is a software environment dedicated to the quantification of images in biomedical research. It consists of a number of unique and flexible software tools that have become the preferred solution in the quantification domain. Key success factors include:

## Functionality

PMOD covers all data processing steps for true image quantification. Thus, PMOD users are freed from struggling with disparate tools and tricky data transfers. While focused primarily on PET, many of the quantification methods are generic and can be applied to other imaging modalities such as SPECT, MR and CT.

## Ease of Use

PMOD provides an intuitive user interface. Many tasks are supported by straightforward workflows and protocols, facilitating the use of sophisticated techniques.

## Reference

PMOD is clearly regarded as the reference tool for PET tracer characterization. No other software can refer to a similar number of kinetic modeling publications. More than 2000 peer-reviewed publications document the value of PMOD in biomedical research.

## Innovation

PMOD keeps up with the state-of-the-art. Thanks to numerous collaborations with leading research centers and a dynamic development team, new methodologies and solutions come to the end user at unprecedented speed. Whenever needed, corrective maintenance builds are made available. Occasionally, dedicated functionality for individual users is implemented as contracted work.

## Customer Base

PMOD boasts an expanding customer base comprising more than 600 sites with over 2000 active users worldwide. Many of them found it justifiable to abandon their in-house software programs and instead focus all their efforts on science without being distracted by software maintenance.

## Independence of Modality, Species and Platform

PMOD is applicable to human and preclinical images from a wide range of modalities, and is computer- as well as scanner-independent. Therefore investments in PMOD are not compromised by evolving infrastructure.

## Clinical Trial Usage

PMOD was built for scientific and educational purposes. However, the Audit Trail License (ATL) type has been added to support the mechanisms for 21 CFR Part 11 compliant data processing. The ATL leverages PMOD functionality for the analysis of clinical trial data while keeping an audit trail.

## Licensing

PMOD offers a modular and flexible licensing scheme. Licenses are standalone or network-based, and can be used without restrictions in time. Complete licensing information including pricing is available on the PMOD website.

## Training

PMOD users can get started with easy-to-grasp entry-level tutorials, and are backed up by comprehensive documentation. For deeper insights or discussions, they also have the opportunity to attend the proven PMOD training courses. Dedicated application training is offered as a service.

## Support & Maintenance

Technical support is provided via e-mail, within short response cycles, and by Skype or phone if needed. Face-to-face interaction and in-depth discussions are possible at the major conferences in the field at which PMOD regularly exhibits. PMOD's Maintenance Agreements provide the annual version upgrades and support at privileged terms. Extended support is offered at cost via PMOD's Support Packages.

## About PMOD Technologies

PMOD Technologies aims to equip researchers with best-in-class software tools for biomedical imaging in humans and animals. Founded in 2003 as a spin-off from the Zurich PET center, PMOD has a strong background in image quantification. The PMOD suite of software tools is a comprehensive platform for quantitative biomedical imaging across modalities. It arguably represents the leading solution for PET kinetic modeling, and supports all required pre- and post-processing steps such as image matching, brain image normalization, automated volume-of-interest definition, and statistics.

*“PMOD is a very useful and versatile tool for image and data analysis of PET data, providing a variety of solutions for optimal quantification of neuroreceptor PET studies.”*

Prof. Christer Halldin, Karolinska Institutet PET Centre, Stockholm, Sweden

*“PMOD is a simple and easy to use, but very powerful and fantastic tool for preclinical and clinical PET imaging studies with quantification analysis.”*

Prof. Hirotaka Onoe, Riken, Japan

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The PMOD suite of software tools is a comprehensive platform for quantitative biomedical imaging. It arguably represents the leading solution for PET kinetic modeling, and supports all required image pre-processing steps such as image matching, brain image normalization, and automated volume-of-in-

terest definition. Furthermore, it encompasses solutions for the pattern analysis of brain images and for attractive 3D image visualization.

PMOD boasts an expanding customer base comprising more than 600 sites with over 2000 active users worldwide. At the end of 2017, use of PMOD has been reported in more than 2000 publications. Vibrant collaborations with a number of flagship institutions ensure that the methodology and scope of the PMOD software remain leading-edge and come to the end user at unprecedented speed.

*“PMOD provides state-of-the-art solutions in processing and analysis of medical image data. Its built-in audit trail is a must-have to comply with regulatory requirements in clinical trials.*

*We really appreciate the responsiveness of PMOD’s support team.”*

Dr. Marcus Bronzel, ABX-CRO Advanced Pharmaceutical Services, Dresden, Germany

*“At our institution, PMOD is used for neuroimaging, oncology and preclinical applications, and it allows for reliable standardized processing across different research groups and image formats. The comprehensive functionality and superb applications support make it a uniquely first-rate product.”*

Prof. Julie C. Price, University of Pittsburgh, U.S.A.

*“PMOD has been a great investment for us with our current expanding clinical and preclinical research as it has allowed us to roll out quantitative image processing to a wide range of researchers.”*

Dr. Graeme O’Keefe, Austin Health Centre for PET, Melbourne, Australia