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
– 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), and organs
– 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 (64 measures)

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 statistics environment
– 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 research data:
– Operating system: Windows, Mac OS X, Linux
– RAM: ⩾ 32 GB
– Cores: ⩾ 4 (⩾ 8 for PNEURO tool)
– Graphics: dedicated mid- to high-range board
– USB connector

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)
– SyN methodology of ANTS (Advanced Normalization Tools)
Corresponding template information and parameter presets are available to bring human and animal brain images into standard anatomy spaces:
– Human (PET, T_1-MR, T_2-MR, probability maps) in the MNI space
– Mouse (FDG-PET, T_2-MR, CT)
– Rat (FDG-PET, T_2-MR) in the Paxinos space
– Pig (FDG-PET, HMPAO-SPECT, T_1-MR)
– Cynomolgus monkey (T_1-MR, FDOPA, DTBZ)
– Rhesus monkey (T_2-MR)
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
– MIP rendering of up to three fused images and production of rotation cines
– Visualization of up to four fused and synchronized images in parallel
– VOI definition directly in fused images
– Saving fused images as DICOM SC objects for later research

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)

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
– Macros to fit several models at once
– 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 (requires PXMOD option)
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.

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
– Quantification of blood flow from 4D Flow MR images

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

Data Preparation
Consistent data is essential for the success of the automatic processing stages. PNROD includes a convenient cropping facility for extracting the part relevant for the brain analysis from whole-body data.

Multi-Modality Image Registration
If an additional anatomical image of the same subject is available, PNROD tries to align the data. If the images originate from separate acquisitions, they are automatically matched. In difficult situations when automatic matching fails, the user can always resort to interactive matching.

Atlas Normalization
The spatial normalization of an image to the selected atlas is based on a template image, and results in an estimate of the transformation that brings the subject image into alignment with the template. Three transformation types are supported:
– Elastic image warping based on the SPM5 normalization methodology
– Affine transformation which supports scaling and shearing
– Rigid transformation (applicable if the subject anatomy is sufficiently similar to the atlas anatomy)
There is an automatic image matching procedure for all transformations. If it fails, the user can resort to interactively aligning the subject image to the atlas to solve the situation.

Atlases
PNROD includes 5 rat and 2 mouse brain atlases, each of them with their own set of normalization templates and brain region definitions.
Users can easily extend existing atlases by their own templates, modify the regions in the atlas to be better suited for their analysis, or create entirely new atlases using PMOD's VOI functionality.

Parametric Mapping (Option)
If the pixel-wise modeling tool PXMOD has been licensed, PNROD 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.

VOI Statistics
The main result of a workflow is the set of brain VOIs adjusted to the subject. If the alignment is not fully satisfactory, the VOIs can be further trimmed using a comprehensive set of interactive VOI tools. For instance, individual VOIs or groups of them can be scaled, shifted, and rotated, or individual contours can be adjusted.

The final VOIs can then be applied to the data or the parametric maps for statistics calculation. In the case of dynamic images, the regional time activity curves are also generated which can directly be submitted to the PKIN tool for kinetic modeling.

Partial Volume Correction (PVC)
PNROD includes two methods for correcting the spill-over of signal between the VOIs, which occurs in PET or SPECT images due to the limited spatial resolution. The methods are based on the GTM method developed by Rousset et al. (J Nucl Med. 1998;39(5):90411).

If PVC is enabled for the statistics, both the uncorrected and the corrected regional values are listed. It is highly recommended to critically assess the PVC-corrected results, as the process depends on various assumptions and tends to increase noise.

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[1–2]. However, the methodology is applicable for other human atlases and those for other species. Atlases are included for the pig, cynomolgus and rhesus monkeys.

Parametric Mapping (Option)

If the pixel-wise modeling tool PXMOD 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. [3] 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. [4] 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 ≥32 GB RAM and at least 8 cores is required. Batch procedures are available to run a job queue during off-peak hours.

References

[1] Hammers A, et al.: Implementation and application of a brain template for multiple volumes of interest. Hum Brain Mapp 2002, 15(3): 165–174.

[2] 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.

[3] 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.

[4] 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.

Image Data
The PCARDP tool has been optimized for the analysis of dynamic cardiac PET acquisitions started at the time of tracer injection. For modeling, it is important that the acquisition times are correctly encoded, and that the image units are calibrated in kBq/cc. More recently, the analysis of ECG-gated PET or SPECT series has been added. The gates of such series are handled similarly to the frames of a dynamic series. With static series, only a relative analysis can be performed. In that case, the results are given in % uptake relative to the maximum. Note that the PCARDP tool may be applied to data from humans, rats or mice.

Heart Segmentation and TAC Calculation
Segmentation according to the AHA definition and calculation of the TACs in the 17 segments uses the following procedure: A model of the left ventricle (LV) is obtained by contouring the myocardial centerlines within 22 interpolated slice images. The slices are assigned to basal (8), mid-cavity (7), apical (4) and apex parts (3). The basal and mid-cavity parts are divided into 6 sectors with 60 angles, whereas the apical part is divided into 4 sectors with 90 angles. For TAC calculation, a polar sampling strategy is used in the basal and mid parts, and conical sampling elsewhere. Two sampling variants are supported. The first uses the location of the radial maximum in a time-averaged image as the sampling position, the second the location where the radial ray intersects the heart mesh model.

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. PCARDP accounts for this situation with left and right ventricular spillover factors in the compartment models.

^{18}FDG: Glucose consumption for viability assessment
– Patlak plot
– 2-tissue compartment model

^{13}NH3: Perfusion
– 1-tissue compartment model, linear metabolite correction (de Grado 1996)
– 2-tissue compartment model, exponential metabolite correction (Hutchins 1993, van den Hoff 2001)
– 2-tissue compartment model, modified two-parameter model (Choi 1999)

^{82}Rb: Perfusion
– 1-tissue compartment model, correction for flow-dependent extraction fraction (Lortie 2007)
– 2-compartment model (Herrero 1992)

^{11}C-Acetate: Perfusion
– 1-tissue compartment model, correction for flow-dependent extraction fraction (van den Hoff 2001)

^{15}O-Water: Perfusion
– Pre-processing by factor analysis
– 1-tissue compartment model (Hermansen 1998)

Inspection of Modeling Results
As dynamic heart data may suffer from excessive motion and the data analysis sequence is inherently complex, a critical assessment of the results is highly recommended. In PCARDP, all intermediate results can be thoroughly inspected and manual corrections applied if necessary:
– Inspection of heart motion using cines and myocardial contour overlays
– Examination of sampling positions by interactive use of polar plots and triangulation of the corresponding location in the images
– Use of the interactive PKIN environment for model fitting of the myocardial TACs

Gated Analysis
Contouring of the myocardium is achieved by fitting an active contour model to the data. 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 1/3 filling rate and fraction.

Documentation of Results
The PCARDP results can be documented and exported in many ways for research purposes:
– 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

Function CMR Requirements

The FUNCTION workflow requires a cardiac cine MR series in short-axis orientation which portrays the heart shape throughout an entire heartbeat. For results representing the whole ventricle, a multi-slice series is required which covers the whole axial extent of the LV. Otherwise the volumetric results have to be interpreted accordingly.

Quantification of Function

The FUNCTION workflow is easy to perform. After loading the cardiac cine MR images, the heart can optionally be cropped from the volume. The main task then consists of defining the endocardial and epicardial boundaries of the left ventricle. Three different approaches are supported:

- Fully automatic, AI-based segmentation, available for human and mouse data (PAI licensing required).
- Semi-automatic segmentation by a rough manual LV definition and subsequent fitting of an active model to the boundaries.
- Manual method using the various VOI tools within PMOD.

The blood volume during contraction is then analyzed and the percent ejection fraction calculated from the volume difference at end systole and diastole. Additional reported results are the stroke volume and cardiac output.

Perfusion CMR Requirements

The full PERFUSION workflow requires the following MR scans:

- Dynamic gadolinium first-pass scan: A 3D sequence which is able to acquire contrast images covering the left ventricle within a breath hold. Utilizing ECG triggers, contrast images can be reconstructed which are practically devoid of motion.
- B_1 scan: Volumetric sequence for assessing the B_1 field inhomogeneity of the surface coils.
- T_1 scan: Single-slice sequence measuring global T_1 relaxation time in blood and myocardium for conversion of the MR signal to contrast agent concentration.

If these requirements are not fully met, only a partial analysis can be performed

Full Quantification of Perfusion

In the PERFUSION workflow, the user is guided in a step-by-step manner as follows:

- Loading of the perfusion series and cropping of the heart volume.
- Loading of the B_1 map and inhomogeneity correction of the perfusion series.
- Definition of the LV segments and blood volume.
- Calculation of the average signal time course in the LV segments and blood.
- Loading of the T_1 series and T_1 averaging in the LV segments and blood.
- Conversion of the resulting signal curves to contrast concentration.
- Model-based quantification of the segment perfusion in [ml/min/g] using blood concentration as the arterial input function.
- Calculation of the segmental perfusion reserves.

Perfusion Quantification Models

PMOD's PKIN modeling tool is leveraged for the quantification of the segmental concentration curves, offering the following quantification methods:

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

Reduced Quantification of Perfusion

If no B_1 and T_1 data are available, simplified processing can still be applied. Assuming similar signal distortions in stress/rest studies, the ratio of their outcome can be considered as a measure of the coronary flow reserve.

Qualitative Perfusion Analysis

Non-quantitative perfusion analysis can also be performed in PCARDM. A separate panel supports interactive reviewing of the rest and stress images side by side with the sectors in the overlay. Three different grading schemes can be employed for assigning defect scores to the sectors.

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 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
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
– STL (ASCII, binary) output of surface-rendered objects
– Image captures of the scene

Software Infrastructure
PAI uses the PMOD viewing tool for preparation of the training data and using the trained neural network for predictions. For the actual AI processes the best-in-class tools Python and TensorFlow are leveraged through the PMOD R console. Consequently, a PMOD installation has to be extended with the corresponding libraries.

As AI is developing rapidly, PMOD defines the toolkit versions which are compatible with a PAI version.

Hardware Infrastructure
PAI users have to be aware that the training of neural networks with a sufficient amount of data is a computational challenge and therefore not possible on personal computers. It requires at least a multicore workstation with large RAM and NVIDIA CUDA GPU, or alternatively a cloud computing solution.

PAI has proven to work efficiently on the Amazon AWS in various instance configurations. However, once a network has been trained, it can easily be deployed and used for prediction on any standard computer with sufficient RAM.

Data Preparation
A significant and crucial part of developing an AI solution is the collection and preparation of the training data. For image data, preparation includes bringing them into the same matrix dimensions and normalizing the value range. Furthermore, for the supervised learning approach implemented in PAI, each image must be paired with its corresponding teaching content.

Data preparation is supported by a dedicated training set editor in the viewing tool. It allows specifying the image preprocessing functions such as interpolation to a common resolution and cropping of the target area, and supports pairing the images with their teaching content.

As reliable AI solutions require hundreds of training data sets, auxiliary tools have been developed in PMOD to reduce the amount of manual preparation work.

When applying a prediction to an input image, it has to be similar to the training data. Furthermore, the same preprocessing steps need to be applied, which however occurs transparently for the user.

Neural Networks
Note that PAI is not an AI solution for a specialized purpose. Rather, it is intended as a framework which allows users to develop novel AI solutions based on their own data and a chosen neural network architecture.

The specification of neural networks for PAI is based on the Keras API for TensorFlow. It requires programming of the network structure in Python and embedding the code appropriately within the PAI framework. Added networks are detected and will be immediately accessible for new developments.

The PMOD distribution includes several trained networks with different architectures. They are working examples, but should be considered as illustrative case studies because they only have been trained with limited data sets. The applications encompass segmentations of deep nuclei in human MR brain images, of myocardium in cardiac cine MRI, of trabecular bone in CT images, as well as the positive/negative classification of human amyloid PET images.

Training
Once the training data has been prepared, a selected neural network can be trained in runs of a certain batch size. The number of epochs to perform is a parameter of the process and may depend on the behavior of the loss function as the training proceeds. A manifest file records the details of the training progress such that the training can be performed in batches and additional training data can be integrated as it becomes available.

Prediction
In the viewing tool a trained network can be applied for data consistent with the training data. The required pre- processing steps will automatically be performed before the network applies its prediction, resulting in a content type for which it has been trained for. In the case of the example brain segmentation network, it will generate a contour representing the tumor. Prediction is very fast, and because a trained network can be deployed to any computer equipped with PAI, a working solution can easily be made widely available.

Requirements

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

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

Analysis Procedure

The PALZ tool performs the following analysis steps:

– The subject 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 subject's age is calculated and the difference to the subject 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: PET Score = $\log_2$(AD t-sum/11089+1).
– A cluster analysis of the t-map is performed, grouping $\geqslant$ 216 contiguous pixels with $p < 0.05$.

Results

The PALZ tool provides the following research 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

The PALZ research 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.

References

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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 images[1,2]:
- 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[3] 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, optionally with partial volume correction
- Transfer of TACs to kinetic modeling tool

K-Means Segmentation

General k-means clustering for subdividing dynamic data into clusters of "kinetically similar" pixels[4]. 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[5]. Requires preparation of representative class TACs. Implements the variant described for use with [11C]PIB[6]:
- 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

Morphological Segmentation
- Use of standard morphological operators for creating segments (threshold, range, region growing, Otsu, hottest pixels, hottest connected pixels

AI-based Segmentation (Option)
- See PAI product description

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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://camino.cs.ucl.ac.uk/). 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). 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.

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.