Biomedical
Image Quantification

PMOD Technologies Ltd
Sumatrastrasse 25
8006 Zürich Switzerland

T +41 44 350 46 00
F +41 44 350 46 01
info@pmod.com pmod.com

PET Image Quantification using PMOD

Principle of PET Imaging

PET imaging is based on the injection of minute amounts of radioactively labeled compounds (tracers) that are distributed throughout the body and taken up by tissue. There, the tracer takes part in physiologic processes according to its pharmacological properties, particularly in the process it is targeted at. As a consequence, the tracer concentration in the body tissues is dynamically changing.

PET is able to measure the tracer concentration in tissue within acquisition intervals ranging from seconds to minutes. In clinical scanning, only one single static PET image is acquired at a certain time after injection, when the tracer distribution provides the most useful uptake pattern. Such static images are functionally weighted and often very helpful for diagnostic purposes, yet they do not represent absolute measures of tissue function or composition.

Quantitative PET Imaging

Under specific conditions, the PET methodology is able to assess absolute measures of some tissue properties. The tracer needs to have particularly favorable properties, to which the data acquisition and post-processing techniques need to be tailored.

At the basis of PET quantification is the transient tracer distribution. It is measured by a dynamic PET sequence which is started at the time of injection, as illustrated below. The tracer uptake over time is analyzed using models, resulting in measures of tissue function and/or composition.

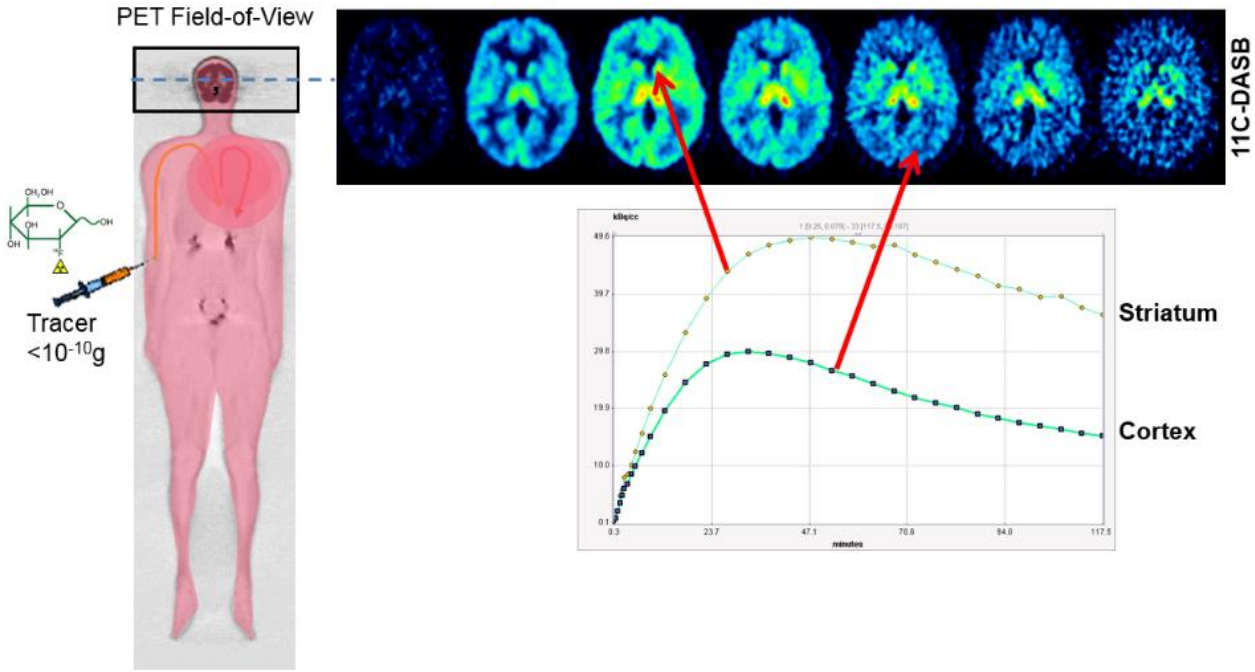

Fig. 1: Schematic of a dynamic PET acquisition. The scanner is started at the time of tracer injection. The tracer concentration in tissue varies locally and over time. The slice images illustrate the pattern change during 120 minutes, and the curves indicate the tracer concentration change in two tissue classes.

Compartment Modeling

The gold standard in PET quantification is compartment modeling. With this approach, the different forms of tracer in the target volume are sorted into so-called compartments, between which material is exchanged. Often, the following two tracer compartments in tissue are considered: tracer in tissue which is not specifically bound (C_1), and specifically bound tracer (C_2). Compartments are represented by boxes, and the mutual material exchange is depicted by directed arrows between them, as illustrated below.

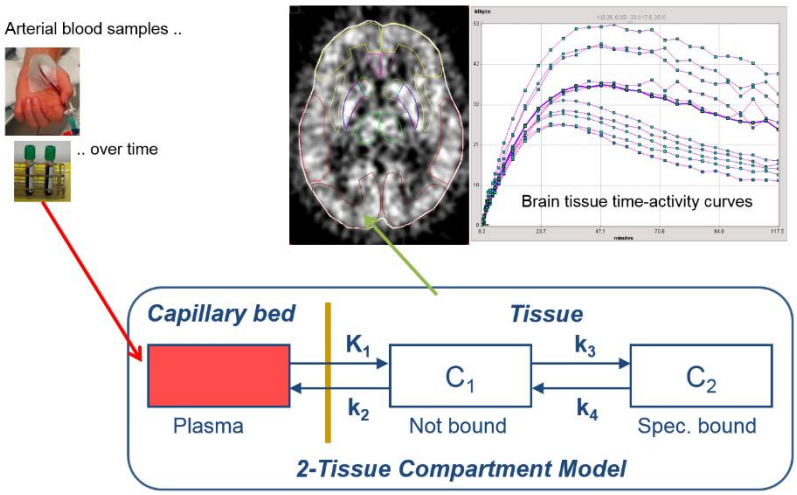

Fig. 2: 2-Tissue Compartment Model. The tracer concentration in arterial plasma is measured by blood sampling and blood analytics. Two tracer forms in tissue are considered and described as compartments: the non-specific (non-displaceable tracer) and the specific compartments. Material exchanges are described by directed arrows, and they are quantified by transfer coefficients k_i [min^{-1}]. A value of 0.1 [min^{-1}] means that 10% of the material is transferred per minute to the target compartment. The PET signal from a tissue corresponds to the summed compartment concentrations.

Input Curve for Compartment Modeling

The tracer is delivered in the arterial plasma to the capillaries and then taken up into tissue. The plasma concentration is highly time-dependent. Initially, a peak is notable after the tracer is injected, but then the concentration will decrease in a subject-dependent way by tissue uptake, metabolism and excretion. Because the arterial plasma cannot be resolved in the PET image, arterial blood samples have to be collected from the subject throughout the acquisition, and the concentration of tracer in arterial plasma must be determined by blood analytics. The result is the experimental *Input Curve*, representing the available tracer and thus driving the compartment model.

Data Analysis using Compartment Models

The advantage of compartment models is that they can predict the tracer concentration in tissue and therefore the expected PET measurement. The prerequisites for such a prediction are the measured input curve and some assumptions regarding the exchange between the different compartments. Usually, each directional tracer exchange is characterized by a transfer coefficient k_i which is constant during the study. The analysis of a dynamic PET uptake curve consists of finding a set of coefficients k_i such that the prediction optimally matches the measurement. This task can be solved by a computer program which iteratively changes the k_i values until the best match is found (non-linear least squares method). In principle, a complex model with several compartments is desirable to resolve the different sub-processes. In practice however, only one to two tissue compartments are being supported, because with more than 4 unknowns, the resulting k_i estimates are not reliable enough.

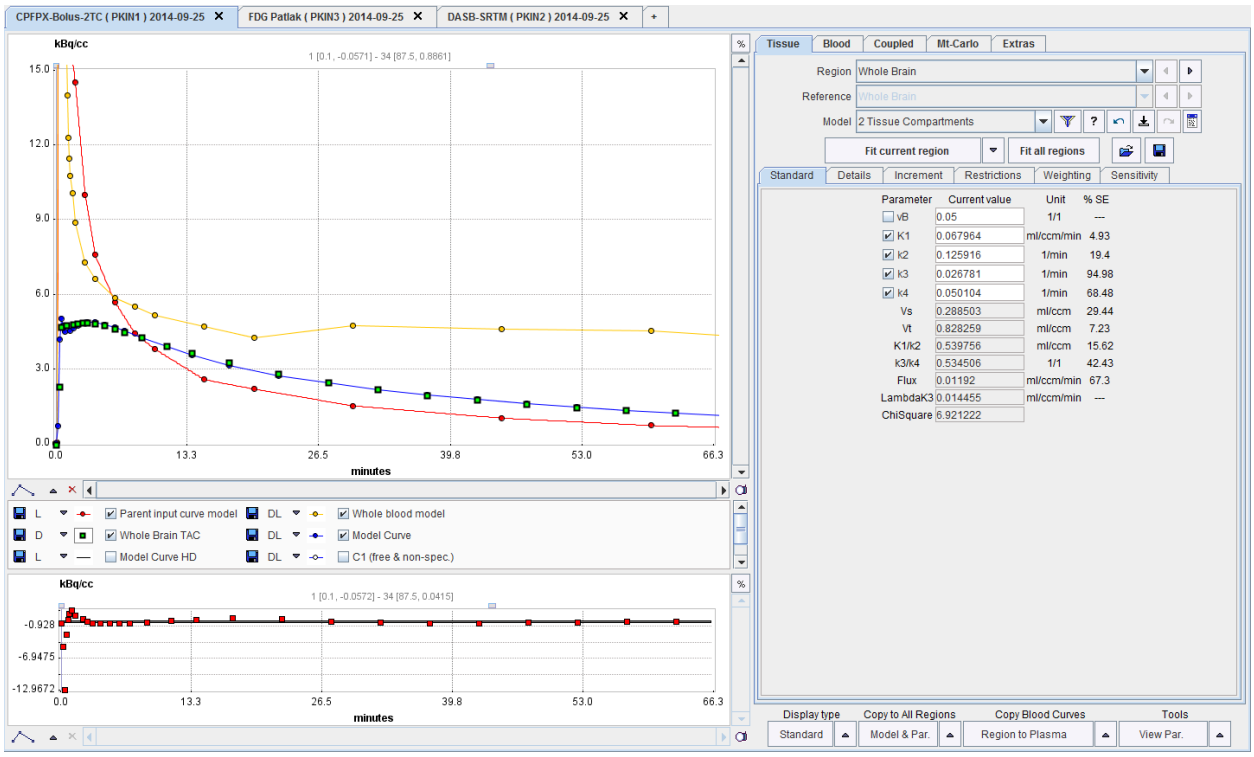

Fig. 3: Compartment analysis of regional PET time-activity data. The green squares represent the PET measurements, the blue curve depicts the predicted uptake, and the input curve is shown in red. A 2-tissue compartment model was used for the analysis, resulting in the k_i values shown to the right.

Outcome of Quantitative PET

The compartmental analysis results in optimal model parameters, which must be interpreted in terms of tissue properties. Rarely, absolutely pure measures such as receptor concentration can be obtained. Mostly, lumped measures have to be employed, such as the *Binding Potential* which is highly correlated with the receptor density, or the *Total Distribution Volume* which correlates well with specific tracer binding if that is dominant. While the technical part of the data analysis is easy to perform with suitable programs such as PMOD, the assessment and interpretation of the outcome demands an experienced modeler. He or she has to compare the model parameters with existing knowledge about the tracer target, for example in-vitro receptor assays or the known physiologic distribution of a receptor.

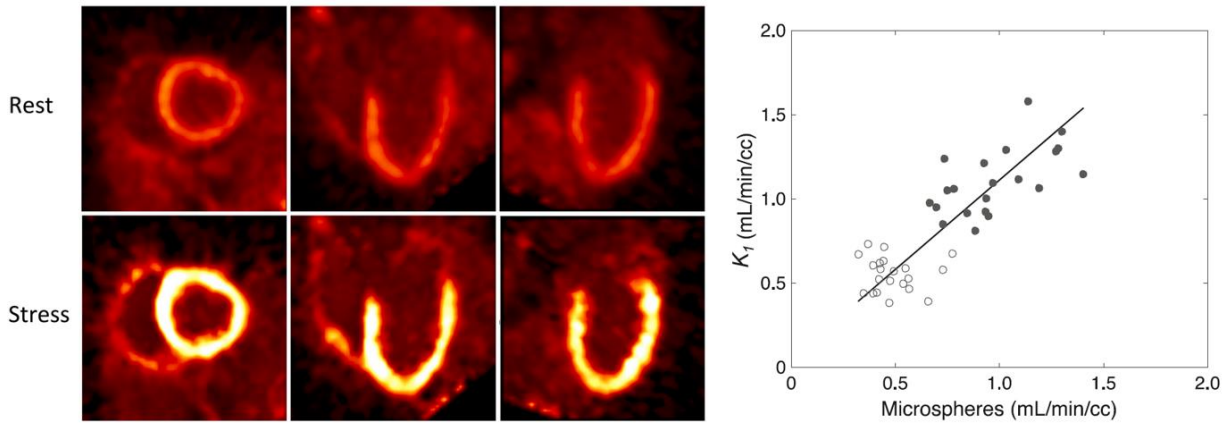

Fig. 4: K_1 as a measure of cardiac perfusion. Correlation of K_1 resulting from compartment modeling of dynamic cardiac PET data with the outcome of corresponding microsphere flow measurements. (Guehl et al. *Single-scan rest/stress imaging: validation in a porcine model with 18F-Flurpiridaz.* EJNM 2017.)

Applications of Quantitative PET

The unique sensitivity of PET, which is able to detect picomolar concentrations, together with its high specificity due to the targeted tracers make quantitative PET a widely used and highly successful technique in basic research. Quantitative PET is applied for the characterization of new tracers, the investigation of metabolic and disease processes, as well as the function of receptor systems.

A valuable application in human research is the investigation of drugs to measure their therapeutic action and to find the appropriate dosing. Consequently, pharmaceutical companies increasingly apply quantitative PET early in drug development to avoid costly failures.

Due to practical constraints, quantitative PET is rarely used in human diagnostics, although it may improve sensitivity and specificity.

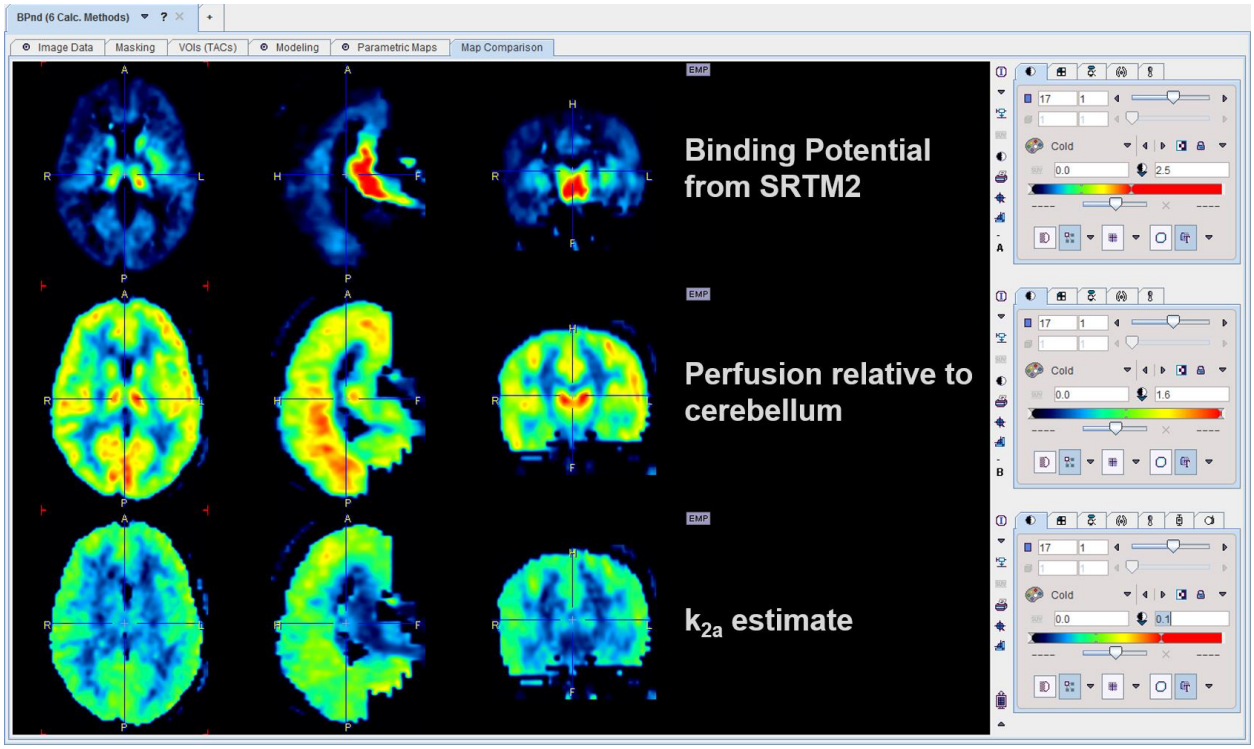

Fig. 5: Quantitative parametric mapping of dynamic PET images using a reference tissue model. The binding potential corresponds to receptor density. Relative perfusion is an additional analysis outcome.

PMOD Software for Quantitative PET

PMOD consists of a comprehensive set of user-friendly and powerful tools, each corresponding to a major task involved in image quantification. Due to their smooth interaction, the tools form a flexible workbench for all kinds of research data from humans and other species.

The PMOD user community comprises more than 600 sites with an estimated 2000 active users worldwide. Most of them are dedicated to PET or SPECT research. Many users also take advantage of the software's unique image analysis capabilities for solving difficult questions in other types of scientific work. The application of PMOD for research is documented in over 2000 peer-reviewed publications.

PMOD is compatible with the image data from all major human and preclinical system vendors. Images can be read and written in DICOM as well as in multiple native formats. Therefore, PMOD is immediately productive in virtually all environments without additional efforts or investments.