User's Guide

# PMOD Kinetic Modeling (PKIN)

Version 3.3

PMOD Technologies

Printed on 28 October, 2011

# Contents

# PMOD Kinetic Modeling Tool (PKIN)

The PMOD kinetic modeling tool represents a flexible environment for the simulation and fitting of models over time. While initially aimed at the compartment models employed in Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT), models for other modalities such as magnetic resonance or optical imaging can also be easily incorporated due to the general approach and the plug-in structure for the models.

PKIN incorporates the following features:

- import of time-vectors from measurements of blood and tissue activity via text files or directly from the PMOD Volume-Of-Interest (VOI) tool,
- fitting of plasma fraction curves to derive tracer activity in plasma from whole blood activity,
- fitting of metabolite correction curves to derive free tracer activity from total plasma activity,
- representation of the plasma and whole-blood activity by a model for data smoothing and extension beyond the last measurement,
- selection of a comprehensive list of compartment models, reference models and graphical plots,
- weighted or non-weighted fitting of the selected model to the measurement whereby the parameter can be enabled or fixed, and can optionally be restricted within a physiological range,
- coupled fitting of measurements from different tissues to improve the accuracy for parameters assumed to be identical across tissues,
- calculation of goodness-of-fit criteria usable for model comparisons,
- Monte Carlo simulations to assess the identifiability of model parameters using a standard or user-defined distribution of the measurement errors,
- sensitivity analysis of compartment models to quantify the correlation between the model parameters,
- visualization of the relative contributions of the different compartments to the model curve,
- generation of synthetic studies representing compartmental kinetics for testing the performance of simplified pixel-wise models,
- batch mode operation to fit or Monte Carlo simulate a set of prepared studies,
- saving of the fitted parameters into text files for further statistical investigations.

Please note that the following description is intended as a reference and not as a tutorial. For practical examples how to work with the PKIN software please refer to the **PMOD Workbook**, which is also distributed as part of the PMOD documentation.

# Introduction to Modeling in PET

For the understanding of data processing in PKIN will be helpful to understand the basic modeling concepts in PET. The following sections present short introductions of compartment and reference models. Other model types are described in the ***PKIN Model Reference*** (on page 115) section.

For in-depth understanding of PET Kinetic Modeling we strongly recommend the PMOD users to attend one of the excellent yearly *PET Pharmacokinetics Course.* These courses include theory as well as practical work and are organized by the the top experts in the domain. Here the link to the 2011 ***website http://www.***.

## Compartment Models

A physiologic system is often described by decomposition into a number of interacting subsystems, called *compartments.* Compartments should not be understood as a physical volume, but rather as a mass of well-mixed, homogeneous material that behaves uniformly. Each compartment may exchange material with other compartments. Examples of frequently used compartments are

- Authentic (unchanged) tracer in the arterial plasma that can be extracted into the tissue. The concentration of authentic tracer as a function of time during the PET acquisition is called the "Arterial Input Function" (AIF), or simply the "Input Curve".
- Free tracer in tissue that can be bound or that may diffuse back into the blood.
- Tracer in tissue that has been specifically bound, for instance, at the target receptor site.
- Tracer in tissue that has been non-specifically bound to other than the targeted cell components.

Compartment models are visualized by diagrams wherein the rectangles symbolize compartments and the arrows represent material exchange, as illustrated for the different models below. Although the mechanisms of material transport between compartments may differ, models that can be reasonably analyzed with standard mathematical methods assume first-order processes. As a consequence, the change of tracer concentration in each compartment is a linear function of the concentrations in the other compartments. Because of the tiny amounts of tracer material applied in nuclear medicine it is usually assumed that the observed system is not disturbed by the tracer. It is furthermore assumed, that the physiologic conditions do not change during the study, so that the rate of the material exchange can be considered constant.

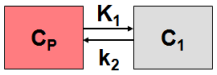
### Model Structure

In the following, the compartment models are illustrated using a tracer that is injected intravenously as a bolus and is not freely diffusible. Please refer to the consensus paper of ***Innis et al http://www.nature.com/jcbfm/journal/v27/n9/full/9600493a.html*** [56] for the

details of the nomenclature and the interpretation of the models in the context of brain receptor tracers.

When the tracer arrives in the heart chambers, it is well mixed with blood and distributed by the arterial circulation. It finally arrives at the capillary bed where exchange with the tissue can take place. Some fraction of the tracer is extracted into tissue and metabolized, the rest is transported back to the heart, from where a new circulation starts.

This simplified "physiologic" model can be translated into a 1-tissue compartment model (**1TCM**):




Because of mixing it is assumed that, the arterial tracer concentration is the same throughout the body, so that it can be measured in a peripheral artery. The tracer concentration in tissue $C_1(t)$ increases by the extraction of tracer from the arterial blood plasma. A usual condition for a quantitative analysis is, that only the unchanged tracer, called the *authentic tracer* or *parent*, can enter tissue, whereas labeled metabolites which may also circulate cannot. Because extraction is described by a first-order process, the transfer of material is proportional to the parent concentration $C_P(t)$. Parallel to the uptake, tracer in tissue is reduced by a backwards transfer (or washout), which is proportional to the concentration in tissue. Both processes compete, so that the change over time of the net tracer concentration in tissue ($dC_1(t)/dt$) can be expressed by the following differential equation

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - k_2 C_1(t)$$

The two transfer coefficients, $K_1$ and $k_2$, have a somewhat different meaning, indicated by using capital and small letters. $K_1$ includes a perfusion-dependent component and has units of milliliter per minute per milliliter tissue, whereas $k_2$ [$min^{-1}$] indicates the fraction of mass transferred per unit time. For example, if $k_2$ equals 0.1[$min^{-1}$], material leaves the tissue compartment at a rate of 10% per minute. The parent concentration $C_P(t)$ is not a compartment, but considered as a measured quantity and appears as the input curve driving the system.

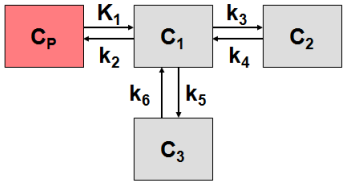
The differential equation of the 1-tissue compartment model can be analytically solved (integrated), yielding the following equation for the concentration of tracer in tissue:

$$C_1(t) = K_1 C_P(t) \otimes e^{-k_2 t} = K_1 \int_0^t C_P(t) e^{-k_2 (t-\tau)} d\tau$$

Hence the time course of the tissue concentration essentially results from a convolution $\otimes$ of the input curve with a decaying exponential. $K_1$ acts as a scaling factor of the concentration course, whereas the washout coefficient $k_2$ has an impact on its form.

More complex compartment models distinguish different forms of tracer in tissue, which is usually interpreted as follows. After entering a cell, the tracer is available for binding in a free form at a concentration $C_1(t)$. Free tracer can directly be bound to its target molecule, $C_2(t)$, but it also may bind to some cell components that are not known in detail, $C_3(t)$.

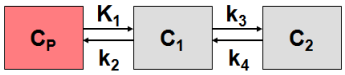
Considering these pathways, a 3-tissue compartment model (**3TCM**) with six transfer coefficients is established, whereby $C_2$ and $C_3$ communicate only by $C_1$.




The system of differential equations can be derived in analogy to the 1-tissue compartment model, but is much more complex. The equations describing this model are given by

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3 + k_5) C_1(t) + k_4 C_2(t) + k_6 C_3(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$
$$\frac{dC_3(t)}{dt} = k_5 C_1(t) - k_6 C_3(t)$$

This system contains six unknown parameters ($K_1$ to $k_6$) that are difficult to assess experimentally. For practical purposes, the system is therefore most often reduced to a 2-tissue compartment model (**2TCM**) by treating free and non-specifically bound tracer as a single compartment $C_1$ (non-displaceable compartment).




This simplification is justified if the exchange free ↔ nonspecific binding is significantly faster than the exchange free ↔ specific binding. Otherwise specific and nonspecific binding cannot be distinguished, and the resulting transfer coefficients cannot be attributed to specific binding alone. The simplified two-tissue compartment model is given by

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

By using a mathematical method called Laplace transformation, analytic solutions can be derived for linear multi-compartment models, but the mathematical formulas are complicated expressions already for two compartments. However, they demonstrate that generally $K_1$ represents a scaling factor like in the solution given for the one-tissue compartment.

## Model Simplification

While complex models are a more realistic description of the involved processes, they include many parameters. PET data from dynamic measurements has a limited statistical quality, and represents the summed contributions from all compartments. When trying to estimate a large number of model parameters from such data, the variance of the resulting parameters tends to be too high for reliable interpretation. Therefore, only relatively simple models with 2 to 4 (at most 6) parameters are feasible in practice.

When the 3-tissue compartment model is simplified to a 2-tissue compartment model, and further to a 1-tissue compartment model, the meaning of the transfer coefficients changes (except for $K_1$). The "lumped" parameters of the simplified models can be expressed by the parameters of the complex models as shown in the tables below. Note that $k_2$ and $k_3$ have a different meaning in the different models, as well as $C_1$.

| Parameters in 1TCM | Expressed by parameters of the 2TCM | Expressed by parameters of the 3TCM |
|---|---|---|
| $K_1$ | $K_1$ | $K_1$ |
| $k_2$ | $\frac{k_2}{1+k_3/k_4}$ | $\frac{k_2}{1+k_3/k_4+k_5/k_6}$ |

| Parameters in 2TCM | Expressed by parameters of the 3TCM |
|---|---|
| $K_1$ | $K_1$ |
| $k_2$ | $\frac{k_2}{1+k_5/k_6}$ |
| $k_3$ | $\frac{k_3}{1+k_5/k_6}$ |
| $k_4$ | $k_4$ |

The term $1/(1+k_5/k_6)$ represents the free fraction of tracer in the non-displaceable tissue compartment which is available for transfer back to blood or for specific binding, and is often called $f_2$.

A good summary on the configuration and interpretation of linear models for receptor tracers is given by ***Koeppe et al. http://www.*** [15]. Starting from the 3-tissue model it is nicely shown how the parameters of simplified models are related to the true rate constants. **PKIN** can take these relations into account when switching from a more complex model to a simpler one. This behavior can be switched on by the **Model Conversion** check on the **Extras** panel.

## Relation of K1 with Perfusion

As mentioned earlier, $K_1$ is related to tissue perfusion F. With a capillary model, the relation

$$K_1 = E\,F$$

can be derived. E represents the unidirectional first-pass extraction fraction (i.e., the fraction of tracer that penetrates the capillary wall and is extracted into the tissue during the first pass of tracer through the capillary). The reverse transport is not regarded in the calculation of E. Renkin [40] and C. Crone [41] calculated the extraction as

$$E = 1 - e^{-PS/F}$$

P denotes permeability, and S, the surface of the endothelium by which the capillary exchanges with the tissue. The relation demonstrates that the extraction depends on the properties of the endothelium with respect to the tracer (PS), as well as the perfusion F. The higher the perfusion, the smaller the extraction, because the average time spent close to the capillary wall decreases. However, total mass transport in general still increases with flow, as the reduced extraction is more than compensated by the higher abundance of tracer (F in the term *EF*). For tracers with very high permeability, the extraction is virtually independent of perfusion and E approaches 1 (such as for $^{15}$O-labeled water). In this case, $K_1$ equals perfusion.

## Volumes of Distribution for Receptor Tracers

For receptor tracers, it is important that the extraction from plasma to tissue is sufficient, such that the kinetics is not limited by the extraction step. Additionally, the relation of the transfer coefficients for specific and nonspecific binding determines whether these different types of binding can be distinguished.

Naturally, the main interest is in specific binding. Besides the individual rate constants $k_3$ and $k_4$, which are often difficult to estimate precisely, the distribution volume of specific binding $V_S$ is a measure which is often used to quantify specific binding. $V_S$ is defined by the ratio of specific binding concentration to total parent at equilibrium (which may not occur during the experiment). However, it can also be calculated from the rate constants of the 3-tissue compartment model as follows.

$V_s = K_1/k_2*k_3/k_4$ 3-Tissue Compartment Model

Under the assumption of a rapid equilibration between the free and non-specific compartment the same expression with the rate constants from the 2-tissue compartment model is often used as an approximation of $V_S$.

If the assumption of rapid equilibration is not justified one must resort to considering the entire tracer concentration in tissue as an indicator of specific binding. The measure used in these cases is called the "total distribution volume" $V_T$. In general it is defined as the ratio of the tracer concentration in tissue to total parent in plasma at equilibrium. A $V_T$ equal to 20 hence means that the tracer is being concentrated in tissue by 20:1. $V_T$ can be easily computed from the rate constants of the compartments model.

$V_T = K_1/k_2$ 1-Tissue Compartment Model

$V_T = K_1/k_2 (1+k_3/k_4)$ 2-Tissue Compartment Model

$K_1/k_2$ can be interpreted as the distribution volume of the first tissue compartment $C_1$. In receptor tracer experiments, this compartment is usually called the non-displaceable compartment, and $K_1/k_2$ the distribution volume $V_{ND}$ of non-displaceable uptake,

$V_{ND} = K_1/k_2$ 2-Tissue Compartment Model

This naming indicates that the concentration of free and non-specifically bound tracer in tissue is not reduced when a non-labeled ligand is brought into the tissue, competing with binding to the same receptor as the tracer. The rational for this assumption is that the

potential for non-specific binding to various cell components is practically unlimited as compared to the number of specific binding sites.

### Rate Constants and Binding Potential for Receptor Tracers

$k_2$ represents the fractional rate constant for the washout of free tracer from tissue to plasma. It it is a composite rate constant and is related to flow in the same way as $K_1$. Consequently it is often reasonable to assume that the ratio $K_1/k_2$ is insensitive to flow and regionally constant. This property can be exploited as a restriction in a model fit, hereby reducing the number of fitted parameters.

$k_3$ is regarded as the rate of association of the ligand with the specific binding sites. It is a function of the concentrations of the free radioligand, the available binding sites and intrinsic second order association rate constants. Consequently it is a pseudo first order rate constant incorporating the concentration of available binding sites.

$k_4$ is considered as the dissociation rate constant of the receptor-ligand complex; often it is assumed to be invariant, what is still a matter of debate.

The binding potential (BP) quantifies the equilibrium concentration of specific binding as a ratio to some other reference concentration. Particularly, the ratio at equilibrium of specifically bound radioligand to that of non-displaceable radioligand in tissue is referring to as $BP_{ND}$ (unitless) and equals the ratio $k_3/k_4$.

## Input Curve

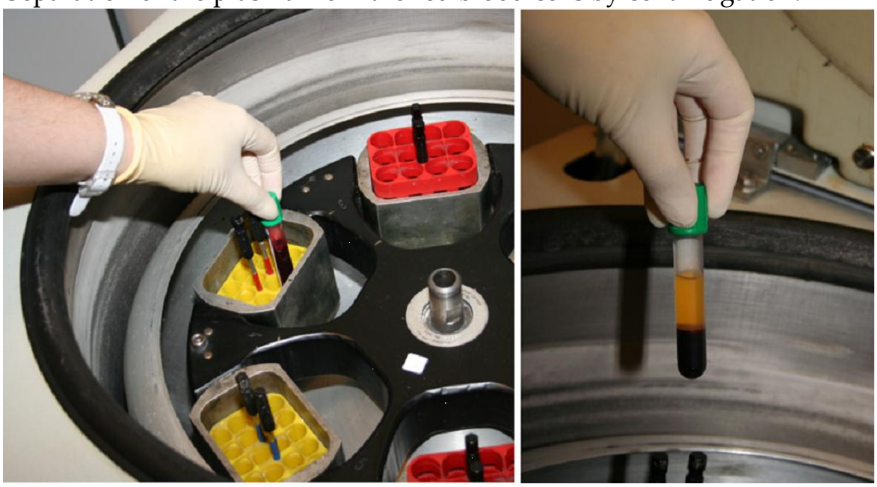
With rare exceptions only a fraction of the tracer in blood is exchangeable with tissue and thus needs to be determined from blood aliquots which are withdrawn from an artery during the whole study.

A whole blood sample comprises tracer in the red blood cells and different tracer categories in the plasma: free tracer, tracer bound to plasma proteins, tracer chemically changed by metabolite processes (metabolites). Depending on the tracer ligand, exchange processes are continuously going on between the different tracer pools in blood.

### Blood Sample Analysis

The following blood analysis steps are required in quantitative PET studies to determine the free tracer in plasma as the Arterial Input Function (AIF).

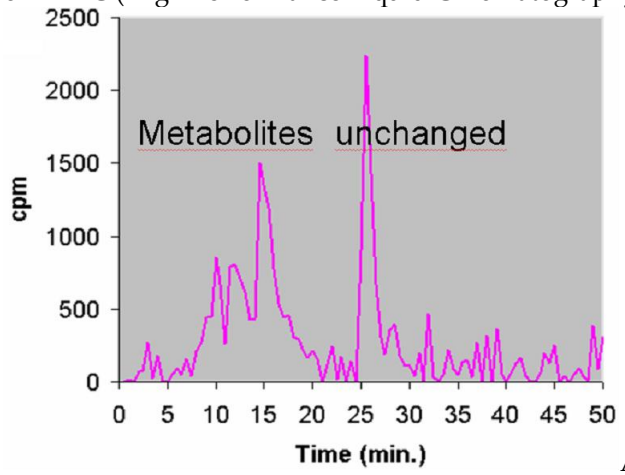
**1)** Separation of the plasma from the red blood cells by centrifugation.



Plasma represents about 60% of the total blood volume.

**2)** Further separation of tracer in plasma into tracer metabolites and unchanged tracer by filtration

or HPLC (High Performance Liquid Chromatography).




A

- Determination of the free fraction of unchanged tracer in plasma ($f_P$), i.e. the fraction of tracer not bound to plasma proteins. Often $f_P$ is difficult to measure and thus not explicitly used. Hereby, $f_P = 1$ is assumed, and the unchanged tracer concentration is regarded as the input function.

After the different tracer fractions in blood have been separated, it is necessary to calculate their activity concentrations. This is done by measuring them in a radioactivity counter and dividing the activity by the fractional volumes.

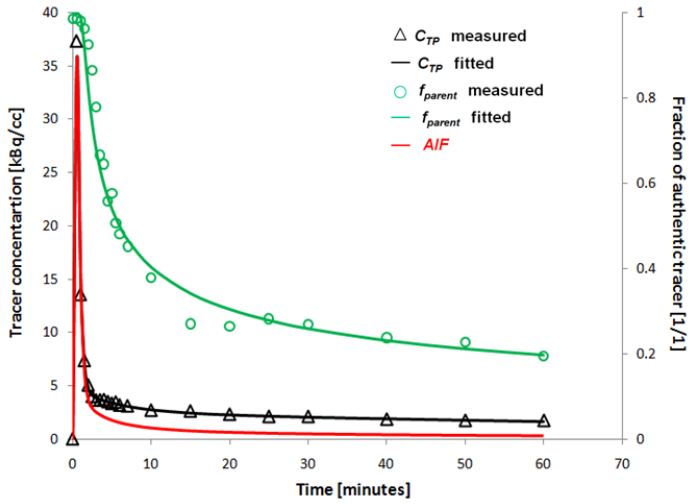
### Fitting of Blood Curves by Models

Due to the experimental procedures involved the blood activity measurements are typically noisy and contribute a considerable amount of uncertainty to the analysis. Therefore it is often reasonable to fit analytical functions to the blood-related measurements, which is also applied for the interpolation between the samples, as well as for the extrapolation at late times when blood samples might be lacking.

The example below illustrates the blood model approach.

- The black triangles represent the activity of tracer (free, bound to proteins, metabolites) in the arterial plasma during the study. A tri-exponential function which was fitted to these measurements and shown as the black line.
- The green circle represents the measurements of the fraction "Unchanged tracer in plasma" to "Total tracer in plasma". A model was fitted to these fraction values and shown as the green line.
- The arterial input function (AIF) is obtained by the multiplication of the two model functions and represented by the red curve, implicitly assuming $f_P = 1$.

Note the sharp concentration changes at the early times after injection. To capture these changes adequately, rapid blood sampling is required during the first minutes after tracer injection.




# Calculation of the Model Curve

The signal of a dynamic PET measurement represents the averaged activity in the image pixels at a number of acquisition times *t* starting at tracer injection. It is described by the **operational equation**

$$C_{Model}(t) = (1 - vB)\, C_{Tissue}\ (t) + vB\, C_{Blood}(t) \cong C_{PET}(t)$$

This equation means that the activity concentration $C_{PET}$ measured by PET in a certain tissue volume is composed of two contributions:

- tracer which has been extracted into tissue, where it has an instantaneous concentration of $C_{Tissue}(t)$.
- tracer which is circulating within the blood, with a concentration $C_{Blood}(t)$.

Hereby it is assumed, that the fractional volume vB is composed of small capillaries (2%-5%) filled with whole blood, and that the fraction (1-vB) represents tissue. The blood activity $C_{Blood}$ must be measured during the acquisition. In tissue, the tracer may be present in different spaces or forms (eg. *free*, *specifically bound*, *non-specifically bound*), which are described by the compartments of the model. All compartments contribute to the tissue signal, so that it is modeled by the expression

$$C_{Tissue}(t_k) = \sum_i \frac{1}{(t_k^{\,end} - t_k^{\,begin})} \int_{t_k begin}^{t_k end} C_i(t)dt$$

whereby

- $C_{Tissue}(t_k)$ represents the average concentration of tracer in tissue during the acquisition *k* which starts at $t_k^{begin}$ and and lasts until $t_k^{end}$
- $C_i(t)$ represents tracer concentration in compartment *i* at time *t*. These expected concentrations are calculated from the differential equations using the current model parameters and the plasma input curve(s).

The operational equations used for other than compartment models are specified in the PKIN Model Reference ***section*** (on page 83).

# Fitting and Residual Weighting

## Least Squares Optimization

The fitting methods available optimize the agreement between the measurements and the model curve. Effectively, they minimize the difference between them, whereby the difference is described by the Chi Squares criterion (cost function) below:

$$\chi^2 = \sum_i w_i \left[C_{PET}(t_i) - C_{Model}(t_i)\right]^2$$

This expression implies that the squared residuals (measured value minus estimated model value) are multiplied by weights. To satisfy the requirements of *least squares* fitting, the weights $w_i$ should be related to the variance $\sigma_i^2$ of the measurements by

$$w_i = \frac{1}{\sigma_i^{\,2}}$$

In this case, and provided that the distributions of the measurement error are normal, the estimate obtained is the *maximum likelihood* estimate. Under the same premise it is also possible to obtain standard errors of the model parameters as the square root of the diagonal elements in the covariance matrix.

### Weighting of PET Data

The variance of reconstructed PET data is dependent on many factors, including the duration of the acquisition, the time since the scan start which needs to be compensated by a decay correction, scatter and random correction, the sampling volume, the reconstruction method, etc. Therefore, PET variance models used in weighting of the residuals during fitting are always approximations.

In his presentation *Parameter Estimation: Least squares and why it gives you fits* (Handouts of Pharmakokinetic Course 2009) Richard E. Carson gives the following hints on using weights:

- Uniform weights (ordinary least squares fitting): Even if the data does not have uniform variance the estimates should be unbiased, but the parameter standard errors will be higher than they could be.
- Wrong weights: The greater the error in the weights, the larger the loss of precision in the parameter estimates (more important for $^{11}C$ than $^{18}F$).

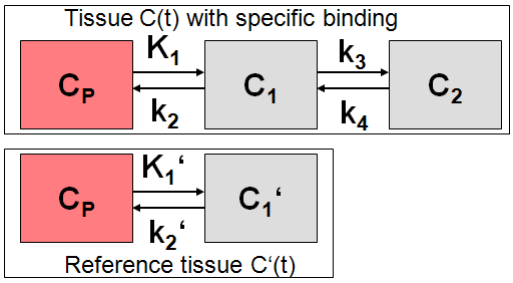
# Reference Tissue Models

The measurement and analysis of the blood samples for kinetic modeling is an invasive and demanding procedure. Therefore, methods have been developed to obviate the need for invasive blood sampling. The solutions found replace the arterial input curve by an indirect input curve, namely the time activity curve of some reference tissue. Therefore they are called *reference methods*. Reference methods are not able to provide a full kinetic analysis. However, assuming certain relations between the kinetics of the tissue of interest and the reference tissue, they can provide valuable measures of interest.

Most of these reference methods are dedicated to reversibly binding neuroreceptor tracers. A reference tissue must be found which is devoid of receptors, and then it is assumed that the distribution volume of the non-displaceable compartment (free tracer in tissue and non-specific binding) is the same among the tissues. Under these assumptions a measure of the receptor concentration called *binding potential* can be calculated from the two time-activity curves.

### Model Structure

The compartment models are usually based upon the following configuration:




In the model equations C'(t) represents the TAC from the reference region ($k_3$=0 in the 2-tissue compartment model), and C(t) the TAC from a receptor-rich region ($k_3$>0).

However, the various reference methods differ in their mathematical approaches, and they show substantial differences with regard to noise sensitivity and processing speed. They are described in the following sections.

## Determination of an average k2'

Some of the reference methods require an a priori average value of $k_2'$, while other methods such as the MRTM or the SRTM reference methods estimate $k_2'$ together with the other parameters.

Dr. Ichise recommendation how to calculate an "average" $k_2'$ value:

**1)** $k_2'$ is the tissue clearance rate from the reference region, e.g., cerebellum. This reference tissue is always a region (ROI), not a voxel for both ROI based PKIN or PXMOD parametric imaging. If you define a reference region, there should be only one correct $k_2'$ value for that particular subject (scan).

**2)** Logan in her original formulation of her reference tissue model suggested to determine $k_2'$ by using arterial data for a group of subjects and use this mean $k_2'$.

**3)** However, we showed that this $k_2'$ can be estimated for each individual without arterial data using MRTM or SRTM (three parameter estimation, one of the three parameters is $k_2'$).

**4)** I prefer to use $k_2'$ estimated this way for each subject for the subsequent MRTM2 or SRTM2. This would be more accurate than the mean $k_2'$ estimated for a group of subjects as above.

**5)** Now the accuracy of $k_2'$ estimation depends on the following (see [52]): A) noise in the PET data, B) the magnitude of $k_2'$ and C) the ratio of $k_2'/k_2$ or $k_2/k_2'$ determined by MRTM or SRTM.

**6)** The bias and variability of $k_2'$ estimation by MRTM is less as $k_2'$ is larger and $k_2'/k_2$ or $k_2/k_2'$ ratio is further away from unity. This ratio for fallypride using cerebellum and striatum should be greater than 3, I think. In that case, $k_2'$ estimation from cerebellum and striatum (use ROIs) should be minimum (see figs in the paper).

**7)** Even using the ROIs, $k_2'$ estimation is affected by noise and hence it is good to run MRTM a few times choosing ROIs with high $BP_{ND}$areas (say right striatum and left striatum) $k_2'/k_2$ ratio is further away from 1) and average the $k_2'$ values. This averaging is within the subject and totally different from population average.

**8)** Please use the $k_2'$ determined as above for estimation of $BP_{ND}$ for the cortical regions. The $k_2'$ estimated with cerebellum and cortical regions is not accurate because $k_2'/k_2$ is closer to unity.

**9)** One advantage of MRTM over SRTM. To use SRTM, both cerebellum and target must be 1 tissue (1T) kinetics (use of the SRTM for 2T will bias $BP_{ND}$). However, MRTM is good for tracers with 2T kinetics such as Fallypride. Only thing here is that you have to give a t* value.

Chapter 1

# PKIN Data Processing

## In This Chapter



# General Assumptions in PKIN

The following is generally assumed:

- All loaded data has been **decay corrected** to the same time point. This means that the PET scanner and the blood sampling times must have been synchronized.
- The **input curve** $C_P(t)$ represents the authentic ligand in arterial plasma which is available for exchange with tissue.
- The **total blood** curve $C_{Blood}(t)$ represents the activity of whole blood.
- A geometrical **spillover correction** can optionally be performed for the calculation of the operational equation in the form of
  $C_{Model} = vB*C_{Blood} +(1-vB)*C_{Tissue}$
  where $v_B$ represents the fractional volume of the blood space in the VOI, $C_{Blood}(t)$ the concentration of all forms of tracer in a sample of blood, and $C_{Tissue}(t)$ the summed concentrations in all tissue compartments.
- The results of non-cardiac flow models are returned per $cm^3$ tissue. To convert to flow per g tissue the values must be divided by the tissue density.

Exceptions to these rules are specified in the description of the individual models.

# Processing Overview

Data processing of studies with PET or SPECT tracers typically consists of the following parts:

| | |
|---|---|
| **1. Data Loading** | ▸▸ Create a new data set.<br>▸▸ Load the whole blood curve (total activity concentration of tracer in the blood samples). |

| | |
|---|---|
| | ⏩ Load the plasma *activity* curve. Depending on the preparation of the blood data the plasma activity curve can represent the unchanged tracer (parent) in plasma, or total tracer in the plasma of the blood samples including the metabolites. In the case of total tracer the metabolite correction has to be performed in PKIN.<br>⏩ An alternative to loading the plasma activity curve is loading the plasma *fraction* curve. In this case the total plasma activity is calculated by multiplying whole blood activity with the plasma fraction.<br>⏩ Load the parent fraction curve (fraction of unchanged tracer in plasma). This is only necessary if the loaded plasma curve represents total tracer activity in plasma including metabolites.<br>⏩ Load the average time-activity curves of one or multiple tissue regions. |
| **2. Input Curve Configuration** | ⏩ Define interpolation functions (called models) for the different types of blood data and fit them to the data.<br>⏩ The input curve is obtained as the multiplication of the plasma model with the parent fraction model. |
| **3. Kinetic Model Configuration** | ⏩ Select a region with a "typical" time-activity curve (TAC) from the **Region** list.<br>⏩ Select a simple model from the **Model** list.<br>⏩ Enable the parameters to be fitted by checking their boxes; unchecked parameters remain at the initial values entered.<br>⏩ Select a weighting scheme of the residuals; variable or constant (default) weighting is available. |
| **4. Kinetic Model Fitting** | ⏩ Fit the model parameters by activating the **Fit current region** button.<br>⏩ Consult the residuals to check whether the model is adequate; there should ideally be no bias in the residuals, just random noise.<br>⏩ If the model is fine, configure **Copy the model to all regions** to **Model & Par**, activate the button to establish then save initial model configuration for all TACs, then activate **Fit all regions**.<br>⏩ Check the fit result for all the TACs.<br>⏩ If the model is not yet fine, test more complex models. |
| **5. Kinetic Model Comparison** | ⏩ Switch between compartment models of different complexity and fit. The parameters are either maintained for each model type, or converted, according to the **Model conversion** setting in the **Menu**.<br>⏩ Check the residuals for judging model adequacy.<br>⏩ Check the different criteria on the **Details** tab (Schwartz Criterion **SC**, Akaike Information Criterion **AIC**, Model Selection Criterion **MSC**) to decide whether a more complex model is supported by the data.<br>⏩ Check for parameter identifiability. As an indicator of the parameter standard errors (**%SE**) are returned from the fit. They should remain limited for all relevant parameters. Additionally, Monte Carlo simulations can be performed to obtain statistics of the parameter |

| | |
|---|---|
| | estimates.<br>▸▸ If justified by physiology, try to improve the stability of parameter estimation by enforcing common parameters among regions in a coupled fitting procedure.<br>▸▸ Compare the outcome of compartment models with that of other models, such as reference models or graphical plots. |
| **6. Saving** | ▸▸ Save all model information together with the data in a composite text **.km** file which allows restoring a session.<br>▸▸ Save a summary of all regional parameters in an EXCEL-ready text file **.kinPar**. |
| **7. Batch Processing** | Lengthy calculations such as coupled fits with many regional TACs or Monte Carlo simulations can be run in a batch job. The results are saved both as .km files and in an EXCEL-ready text file. |

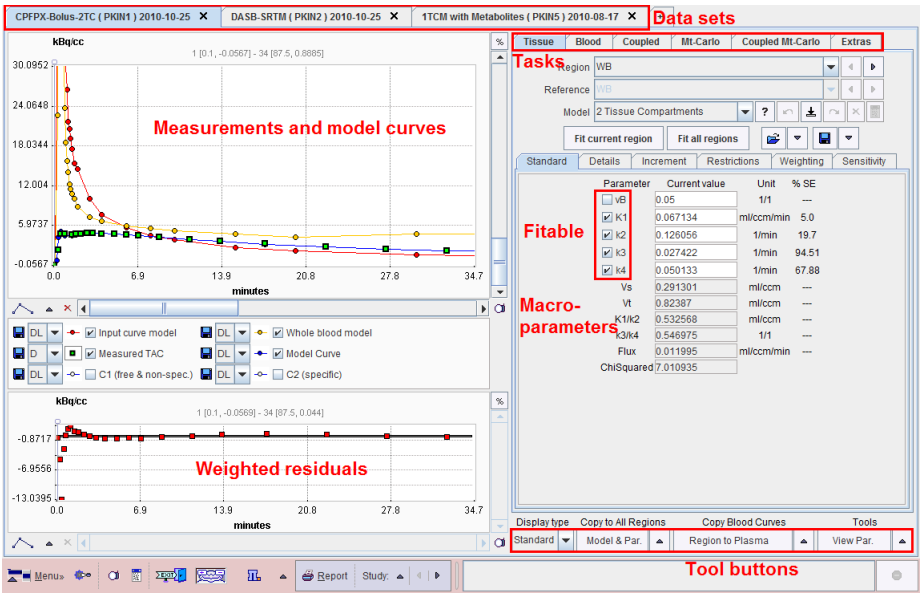
# Starting the Kinetic Modeling Tool

The kinetic modeling tool is started with the **Kinetic** button from the PMOD ToolBox

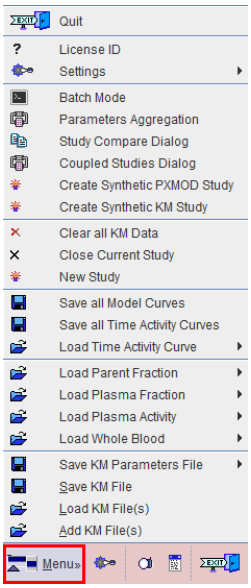

or by directly dragging kinetic modeling (.km) files onto the above button.

The user interface is organized as illustrated below. The left part of the display visualizes the data, the model and the fit. The green squares represent the tissue measurement values (tissue time-activity curve, TAC), the red circles the input curve, the yellow circles the blood spillover curve (whole blood time-activity curve), and the blue circles the calculated model curve with the current model configuration shown to the right. The lower curve display shows the residuals, i.e. the difference between the measurement and the model curve. Weighted and unweighted residuals can be shown.

The right part gives access to the different operations which are described in the following sections.




The **Menu** is located in the lower left corner and is used for data operations such as loading, saving or closing.




Loaded data sets can be added into new tabs, so multiple data sets can be available simultaneously and selected for processing using the named tabs.

# Data Loading/Saving

Most models require both blood and tissue data.

### Tissue Activity Data

The tissue TAC data can most easily be brought into PKIN by outlining VOIs in the PVIEW tool and sending the time-activity information in the different VOIs directly to PKIN. This approach has the advantage that the standard deviations within the VOIs are also transferred and can potentially be used for weighting. As an alternative, the information can be prepared in a text file and loaded.

### Blood Data

The blood information is typically the result of blood sampling, plasma separation and activity counting in a separate device. In these cases the measurement results must be arranged properly in a text file and loaded. If the separation of tracer metabolites in blood is not necessary or can be achieved by multiplication with a correction function, and blood activity can be derived directly from the images (eg. in cardiac studies), it is also possible to use the VOI approach.

### Data Organization

Several data sets can be processed in parallel. They are shown on separate pages in the PKIN tool, with selection through the upper tabs. The **New study** entry in the **Menu** can be used for creating a new empty data set, to which the blood and tissue measurements can be loaded. The same result can be obtained with the  tab. The **Load** entries *overwrite* the information in the currently selected data set. With **Add KM file** a complete study can be loaded into a newly created tab without overwriting existing data.

**Note:** All PKIN models assume that the loaded data have already been decay corrected.

## File-based Data Import

There are slightly different formats for the time-activity data of blood and tissue. With blood data it is assumed that instantaneous sampling was performed at well-defined time points. With tissue data it is assumed that the measurements represent the average tracer concentration during a certain observation period, the PET frame duration defined by start-time and end-time.

### Blood Data

PET tracers are usually applied by intra-venous injection and then brought to the tissue of interest by circulation. Often, a part of the tracer may be bound to red blood cells. Another part may be processed in organs and end up as labeled metabolites circulating in blood plasma. The remaining fraction of tracer (unchanged tracer, or parent) is available for exchange with tissue and represents the *input curve* for modeling.

In PKIN, the following four types of blood data are supported to model the contributions of the different forms of tracer in blood to the expected PET signal:

**1)** The concentration of all forms of tracer in **Whole Blood** samples: As the average signal from a VOI always contains a fraction of signal from blood vessels and capillaries, the

concentration in whole blood is needed for modeling the blood content in the expected PET signal.

**2)** The concentration of all forms of tracer in plasma (**Plasma Activity)** : Although the unchanged tracer in plasma is required as the input curve of the models, it is common practice to measure the tracer activity of the whole plasma sample.

**3)** The fraction of unchanged ligand in plasma (**Parent Fraction**): As a result of the metabolite analysis of plasma samples, the relative concentrations of the unchanged tracer and the metabolites are known. This information is represented by the ratio of unchanged tracer to total tracer. This fraction starts with a value of 1 at the time of injection (all tracer is unchanged), and gradually decreases as the metabolites build up. Since plasma analysis is often experimentally complex and therefore error-prone, it is advisable to fit a smooth curve to the measured parent fraction.

**4)** The **Plasma Fraction**: An alternative to using the measured plasma activity is the use of the ratio of plasma activity to whole blood activity, called the "Plasma Fraction". If the plasma fraction is known it can be multiplied with the whole blood activity to calculate the plasma activity. For tracers without metabolites this obviates the need for the actual blood analysis.

### Whole Blood and Plasma Activity

The whole blood and plasma activity concentrations must be prepared in text files, and can be loaded using **Load Whole Blood** and **Load Plasma Activity** from **Menu**. Such text files with the blood data can be prepared for example in MS Excel and then saved as tab-delimited or csv separated text files. There are two variants of the format:

**1)** Separate files for whole blood and plasma activity. In this case separate files are prepared with a header line, the sample time in the first column and the sample value in the second column.

| sample-time[seconds] | plasma[kBq/cc] |
|---|---|
| 0 | 0 |
| 6 | 0.01 |
| 12 | 0.02999997 |
| 18 | 37.94988615 |
| 24 | 118.4692892 |
| 30 | 138.4187542 |
| 36 | 96.68874303 |
| 42 | 68.22877186 |
| 48 | 55.90871407 |
| 54 | 38.498845 |

and

| sample-time[seconds] | whole-blood[kBq/cc] |
|---|---|
| 0 | 0 |
| 6 | 0 |
| 12 | 0.02 |
| 18 | 22.64 |
| 24 | 71.19 |
| 30 | 81.84 |
| 36 | 52.8 |
| 42 | 41.62 |
| 48 | 33.72 |
| 54 | 23.76 |

**2)** A composite file containing whole blood and plasma activity. Note that in this case the keywords **sample-time**, **plasma** and **whole-blood** are required to define the meaning of

the columns.

| sample-time[seconds] | plasma[kBq/cc] | whole-blood[kBq/cc] |
|---|---|---|
| 0 | 0 | 0 |
| 6 | 0.01 | 0 |
| 12 | 0.02999997 | 0.02 |
| 18 | 37.94988615 | 22.64 |
| 24 | 118.4692892 | 71.19 |
| 30 | 138.4187542 | 81.84 |
| 36 | 96.68874303 | 52.8 |
| 42 | 68.22877186 | 41.62 |
| 48 | 55.90871407 | 33.72 |
| 54 | 38.498845 | 23.76 |

## Plasma and Parent Fractions

The plasma and parent fractions need to be prepared in a similar file

| time[minutes] | parent-fraction[1/1] |
|---|---|
| 0 | 0.27184857 |
| 0.5 | 0.986298884 |
| 1 | 0.980287666 |
| 1.5 | 0.96249071 |
| 2 | 0.92520486 |
| 2.5 | 0.865100226 |
| 3 | 0.779710538 |
| 3.5 | 0.666156902 |
| 4 | 0.645169911 |
| 4.5 | 0.558181271 |
| 5 | 0.577178078 |
| 5.5 | 0.50647541 |
| 6 | 0.480742985 |

and loaded using **Load Plasma Fraction** or **Load Parent Fraction** from **Menu.**

**Notes:**

1. If no whole blood data is loaded into PKIN, the plasma concentration is used for blood correction.
2. If the activity of unchanged tracer in plasma is loaded instead of the total plasma activity, no correction with the parent fraction is required. No further action is required in this case, because per default it is assumed that the parent fraction equals the constant of 1.
3. There are models which require two input curves, and in principle models with up to 10 input curves can be handled in PKIN. For these models the sub-menu contains appropriately labeled entries.

### Tissue Time-Activity Data

Tissue time-activity curves are similarly organized in tab-delimited text files. The frame start and end times are arranged in the first two columns. Next come columns with the measurements from different tissues. Note that the TAC value units are specified after the heading of the *second* column.

| start[seconds] | end[kBq/cc] | amy re | amy li | mtl re |
|---|---|---|---|---|
| 0 | 60 | 2.29234465 | 1.98046206 | 2.74814255 |
| 60 | 120 | 5.01681393 | 6.57439037 | 6.81311774 |
| 120 | 180 | 6.18648905 | 5.47218649 | 6.87476477 |
| 180 | 240 | 6.57449309 | 6.58147725 | 7.33382369 |
| 240 | 300 | 5.95458466 | 6.59546425 | 7.65397945 |
| 300 | 360 | 7.06336248 | 7.3919664 | 7.21261065 |
| 360 | 420 | 7.07207865 | 8.066492 | 6.83445489 |
| 420 | 480 | 6.44191169 | 7.89309654 | 7.34035093 |
| 480 | 540 | 5.73063921 | 5.38436545 | 7.231256 |
| 540 | 600 | 6.35527845 | 7.03980869 | 7.31066749 |
| 600 | 900 | 6.04079722 | 6.51268169 | 6.96765792 |

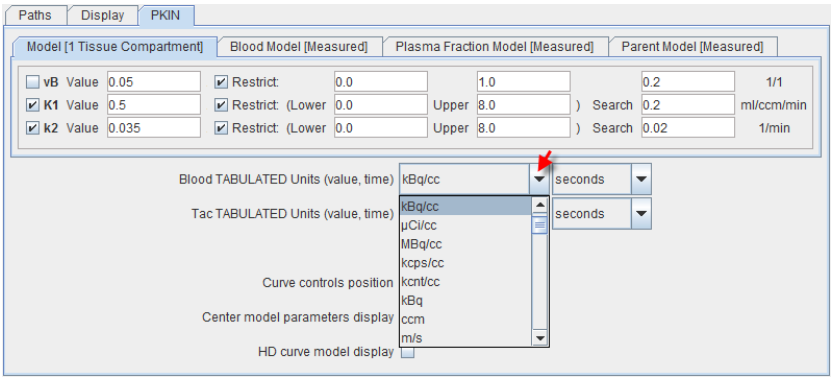
Tissue time-activity curves are loaded using **Load Time Activity Curve** from **Menu**.

### Data Units

Typically the data will arise in the following units:

- [seconds], [minutes] or [hours] for the time specification, and
- [kBq/cc], [uCi/cc] or [1/1] for the value specification.

The unit string in square brackets should immediately follow the column header. If units are not defined in the column headers or not recognized, it is assumed that the units specified in the configuration apply. They can be defined in the configuration dialog as illustrated below.




**Note:** During loading, the input unit specification will be used to convert the activity values into the internal representation of kBq/cc. All loaded data will be displayed with these values after conversion.

## Data Import from VOIs

An important usage of the VOI analysis is the generation of time-activity curves (TAC) for subsequent kinetic modeling. This can easily be achieved in PVIEW by the following steps

## 1. Definition of the VOIs

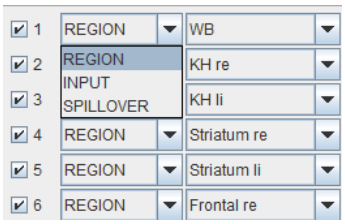
The image data is loaded as a dynamic series with the *correct acquisition times* and the *correct input units*. This is important, because otherwise the acquisition start/end times in kinetic modeling will be wrong, and the TACs may be different in magnitude with respect to the blood data. Such problems result in erroneous model parameters.

In dynamic image series there is generally not enough anatomical information to delineate VOIs. Often, averaging of a subset of the acquisition frames resolves the problem. The VOIs are then delineated in the summed images, transferred to the dynamic images, and optionally saved to a file.

## 2. TAC generation

Switch the tool to the dynamic study, and activate the button

A dialog window appears which allows defining the proper type of the calculated TACs (REGION = tissue TAC, INPUT = plasma curve, SPILLOVER= total blood curve)



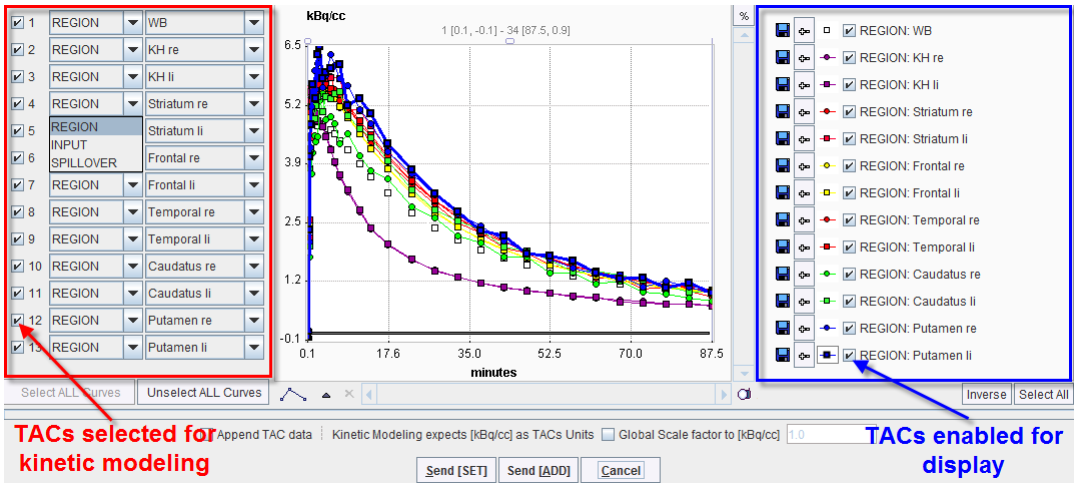

The window is organized in three panels:

**1)** The left panel (red) allows defining the proper type of the calculated TACs. All the TACs selected in this panel are going to be send to the **Kinetic modeling** tool.

**2)** The central panel is a plot which displays the calculated TACs.

**3)** The right panel (blue) allows the selection of the the TACs to be displayed in the graphic area.

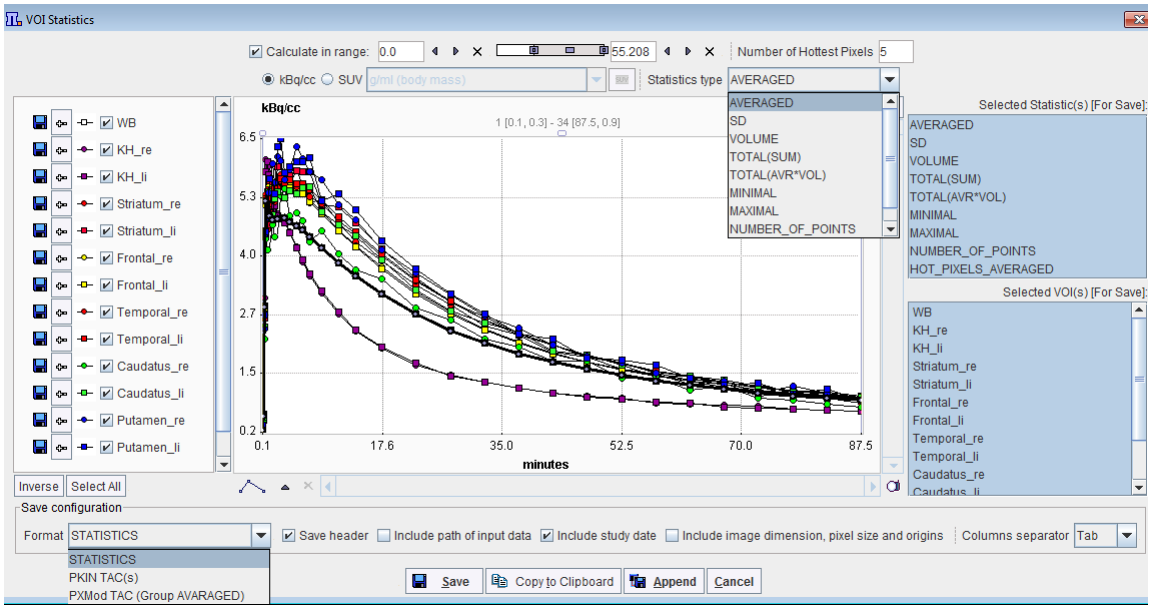
NOTE: The selection in the right panel (blue) does not affect the selection on the left panel (red) while the selection on left panel is immediatly reflected in both display area and right panel.




The **Send** buttons initiate the transfer of the activity curve data to the PKIN tool. Selecting the **Send[SET]** button transfers the TAC data to the currently selected tab in the PKIN tool. If the **Append TAC Data** box is checked, the curves are appended as new curves to the data existing on the PKIN tab, otherwise the data is over-written. **Send[ADD]** first creates a new tab in PKIN, to which the data is added. If PKIN is not running, the tool is first started and the data added.

The **+-** button in the curve controls allow for simple operations such as curve scaling before sending the data to PKIN. Both the average value and the standard deviation within the VOIs are transferred, as well as patient and study information. The standard deviation may be used for weighted fits in PKIN.

If the PKIN option is not available, the TACs of a dynamic series can also by obtained with the statistics button as illustrated below.



The **Calculate in range** box allows restricting the TACs statistics to the subset of pixels with values in a specific range.

Note the radio box in the upper section which allows switching between **kBq/cc** and the **SUV**, if all required information is available. The **Statistic type** selection list allows choosing the type of statistics to be displayed in the graphic area.

The statistics numbers selected in the **Selected Statistic(s) [For Save]** area of the VOIs selected in **Selected VOI(s) [For Save]** can be saved into a text file with **Save,** appended to an existing one using **Append**, or copied or the **Clipboard**.

There are different statistic formats available for saving procedure:

- **STATISTICS** saves all selected information.
- **PKIN TAC(s)** saves the acquisition times and regional averages in a text file which can directly be loaded with the **Load Time Activity Curve** entry of the PKIN **Menu**.
- **PXMod TAC (Group AVERAGED)** saves the average of all grouped VOIs in a two-column text file suitable for usage with PXMOD.

## Data Saving

Data can be saved in various formats using the following **Menu** entries:

| | |
|---|---|
| **Save KM File** | Saves all data and the configuration in a comprehensive text file with suffix **.km**. Loading a .km file restores the state of the previous processing with the exception of the display settings. |
| **Save KM Parameters File** | Generates and saves a summary of the model parameters in all regions. Result is a tab-delimited text file with extension **.kinPar**, which is readable with any text editor and with numerical programs such as Excel. There is a **Save** and an **Append** sub-menu, the latter for combining results of several studies in a single file. |
| **Save all Time Activity Curves** | Saves just the time-activity data in a multi-column text file. This option may be helpful to export TAC data for visualization in a different tool.<br><br>Another useful application of **Save/Load Time Activity Curve** is to append a TAC from a different tissue: first save the current TACs, add the TAC of a additional TAC as a new column in Excel, then load the **.tac** file again. |
| **Save all Model Curves** | Exports the tissue model curves of all regions into a text file. Note that these curves are not interpolated between the frame mid-times. To obtain smoother curves please use the **Create Synthetic KM Study** menu item. |

**Note:** Units of the saved data are always [kBq/cc] and [seconds].

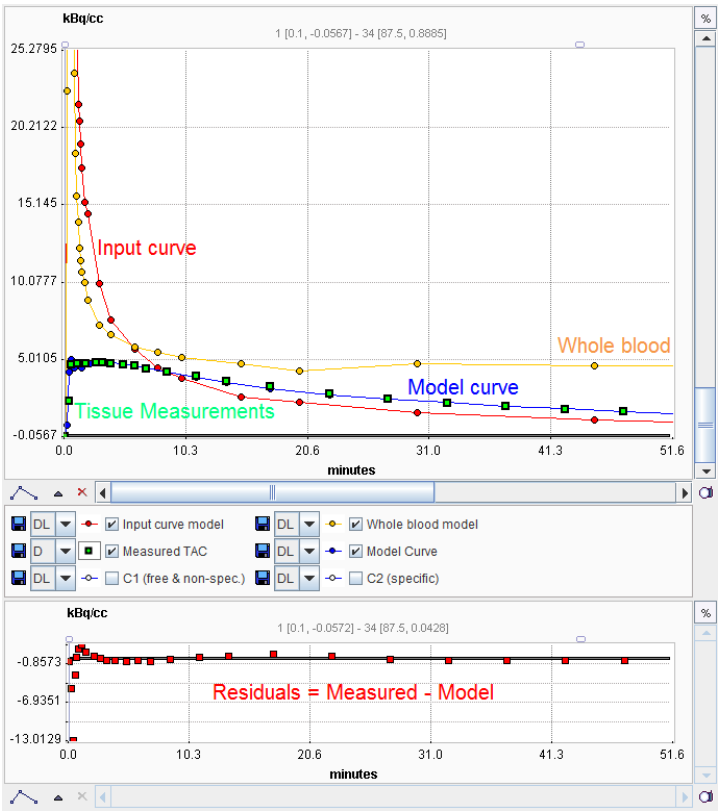
# Curve Layout

The curve display supports the visualization of the different loaded measurement as well as the calculated model curves. The available curves depends on the selected tab.

## Curves with selected Tissue Tab

After data loading the time-activity informations of the current region are shown in the curve display in a default layout. The large area contains

- the **Measured TAC** values representing the tissue TAC;
- the **Input curve model** which is used as the input curve for the model calculations; it is calculated from the available plasma data;
- the **Whole blood model** used for blood spillover corrections;
- and the **Model Curve** which results from evaluating the current model configuration with the input curve.
- Initially, only the Measured TAC and the Model Curve are enabled for display by the check box in the control area. Depending on the context some additional curves available for display which are hidden per default (box initially not checked). In the example below the compartment concentrations $C_1$ and $C_2$ of the 2-Tissue compartment model can be shown.

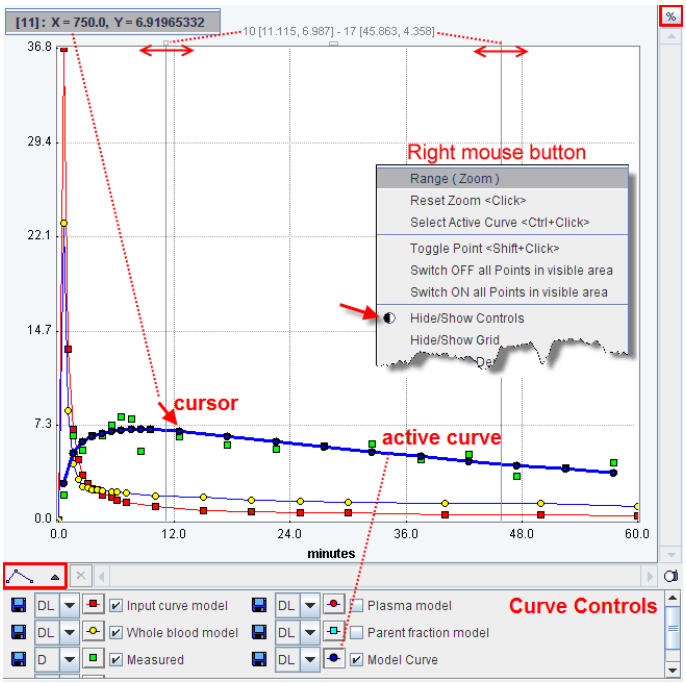



The small residuals curve display at the bottom visualizes the agreement between the measurements and the model curve. The aim is to find a model which has no significant trend in the residuals left.

The general manipulations available in the PMOD curve display are explained in the next section.

# General Curve Display Functionality

A common curve display object is used in all PMOD tools. It consists of a curve area and a controls area underneath.




In some contexts the control area may initially be hidden. The context menu can be used to show it

## Curve Area

The curve area shows the curves which are enabled for display. There is always an *active curve*, which is shown in bold. A curve can be made active by holding down the `CTRL` key and clicking at one of its points, or by pushing its button in the controls area as illustrated with the **Model Curve** above.

The definition of the active curve is relevant for the tools which interrogate the curve values:

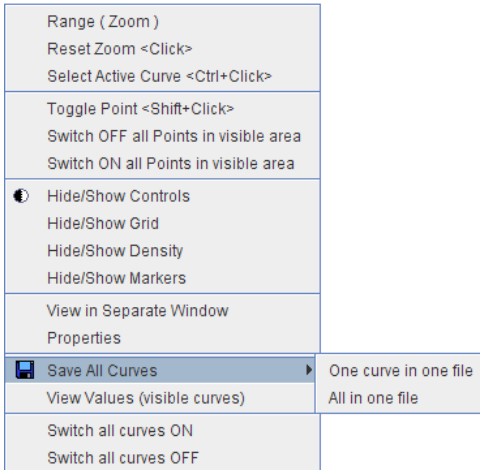
- There are two small handles at the top of the curve area: a little rectangle to the left, and a line to the right. These are handles which can be moved left/right using the mouse, and the gray vertical lines move with them. The values at the top center of the curve area represent the interpolated (x/y) values of the active curve at the location of the handles. To get the measurements of a different curve just `CTRL+Click` at that curve to get the values updated.
- Only in some curve displays: When the cursor is brought close to a point of the active curve, its x/y value pair is shown at the upper left of the curve area.

To *zoom* into an area of the curve just click the left mouse button to the corner of the area of interest and drag a rectangle. After releasing the mouse button the display is zoomed into

the defined rectangle. An alternative is to define the axes **Range** in the context menu. A single mouse click into the curve area is sufficient to reset the zoom.

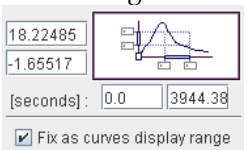
### Context Menu

By clicking the right mouse button into the curve area a context menu with some additional options can be opened.




The functions are:

**Range (Zoom)** Set the range of the x- and y-axis by entering a numeric value.




If the box is checked, the range is maintained during all manipulations. Otherwise, a single click resets the range to the default.

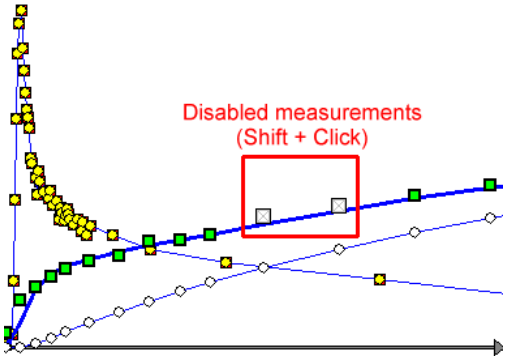
**Reset Zoom** To reset the curve range to the default full range. It is grayed if the display is not zoomed or the range is fixed.

Mouse operation: single `Click` into curve area.

**Select Active Curve** Selects the curve nearest to the point clicked with the right mouse button to open the context menu.

Mouse operation: `CTRL+Click` at a curve.

**Toggle point** Disable a measurement of the active curve. This is reflected by setting the symbol to gray.




In the context of model fitting measurements marked in gray are regarded as outliers and not considered when evaluating the cost function.

Mouse operation: select the relevant curve to active, then `SHIFT+Click` at measurement.

**Switch ON/OFF all points in visible area** — In combination with zooming this option allows to quickly disable/enable contiguous points of the active curve.

**Hide/Show Controls** — Allows hiding the controls if the curve display area is small, and to show them again.

**Hide/Show Grid** — Controls the display of the grid lines.

**Hide/Show Density** — Reflects the density (coded distance) of points in the graph as a colored map. More points close together produce a "higher" color.

**Hide/Show Markers** — Controls whether the measurement markers are shown.

**View in Separate Window** — With this option, the curve display can be opened in a separate, large window to closely examine the plot.

**Properties** — With this entry a configuration dialog is opened for setting the annotation **Font size**, and for enabling curve **Antialiasing** (smooth curve appearance).

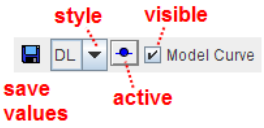
**Save All Curves** — Allows saving the numeric data of all curves in a single or separate text files.

**View values (visible curves)** — Opens a dialog window which shows the numeric values of all visible curves in a dialog window. The window contents can be copied to the **Clipboard** and pasted to a different application.

**Save All Curves ON/OFF** — To quickly change the visibility of all curves. When switching all off, the active curve is still shown.

## Curve Control Area

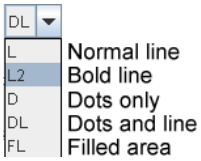
The control area lists the curves which are available for display. There are several elements to modify the curve appearance:




**Show/Hide** To show/hide a curve check/uncheck the *visible* box.

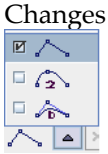
**Active curve** To set a curve to active click at the *active* button, or directly `CTRL+Click` on the curve itself. The line/symbols get bold.

**Style** The list selection can be used to change the style of a curve:




## Further useful interface elements:

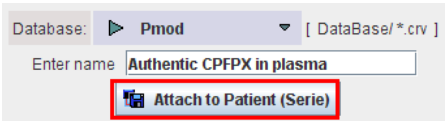
**Connections** Changes the shape of the lines defined by the measurements:




Note that calculations are not based on the display representation of a curve.

Saves the numeric data of a curve as a text file with two columns. These files obtain a **.crv** suffix and can easily be opened in Excel or a text editor.

When working with a database the curve can be attached to a particular image using the **Attach to Patient (Serie)** in the appearing dialog.





If this button is enabled, each curve is normalized to its own maximum and shown as percent values. This mode is helpful for comparing shapes when the dynamic range of the curves is very different.

Creates a capture of the curve area. The captured image can be saved as a **JPEG**, **TIFF** or **DICOM** file. It can also be copied to the **Clipboard** to paste it into some office application.

# Blood Model Configuration

The tracer activity in blood is normally only sampled at a few time points during the acquisition. However, when calculating the operational equations (eg. by numerically integrating a system of differential equations), the blood activities must be available at any arbitrary time point during the acquisition period. This means that the blood curves must be interpolated according to some underlying model, hence called a "blood model". The models available for the different blood curves are described in the next sections.

## Input Curve (AIF)

PKIN supports four types of blood data which together allow computing the input curve. All of them are functions of the acquisition time which are represented as curves in the display window.

**1)** The tracer activity concentration in whole blood. This information is used for the spillover term in the compartment models as well as in combination with the plasma fraction.

**2)** The total activity concentration of tracer in plasma.

**3)** The plasma fraction, the ratio of tracer in plasma to tracer in whole blood. The plasma fraction is multiplied with the whole blood concentration to calculate the total concentration of tracer in plasma.

**4)** The parent fraction (ratio of unchanged tracer to total tracer in plasma). The parent fraction is multiplied with the total plasma concentration to calculate the input curve.

For the evaluation of the kinetic models, the input curve needs to be available at any arbitrary time. It is calculated by multiplying the interpolated plasma concentration with the interpolated parent fraction at any particular time.

Note that the plasma options 2. and 3. above are excluding each other. If plasma activity has been loaded, the plasma fraction option can not be used. On the other hand, if the plasma fraction has been loaded, the plasma activity option can not be used.

The different possibilities to calculate the input curve work as follows:

- As soon as a whole blood curve is loaded and no other information is available, the plasma mode is set to "fractional" and a **Fix** model is applied with a factor of 1. This means in practice that the plasma activity is set equal to the whole blood activity.
- As soon as a plasma activity curve is loaded any plasma fraction data is discarded, and the plasma mode set to "activity". The activity interpolation mode defaults to **Measured**. The parent fraction is not changed.
- As soon as a plasma fraction curve is loaded any plasma activity data is discarded, and the plasma mode set to "fractional". The fraction interpolation mode defaults to **Measured**. The parent fraction is not changed.
- A parent fraction equal to 1 is applied as long as no parent fraction curve is loaded, or no analytical parent fraction model selected.

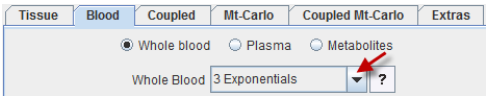
The different blood-related informations are readily available for inspection in the curve area of the **Tissue** tab as illustrated below.

# Whole Blood and Plasma Activity

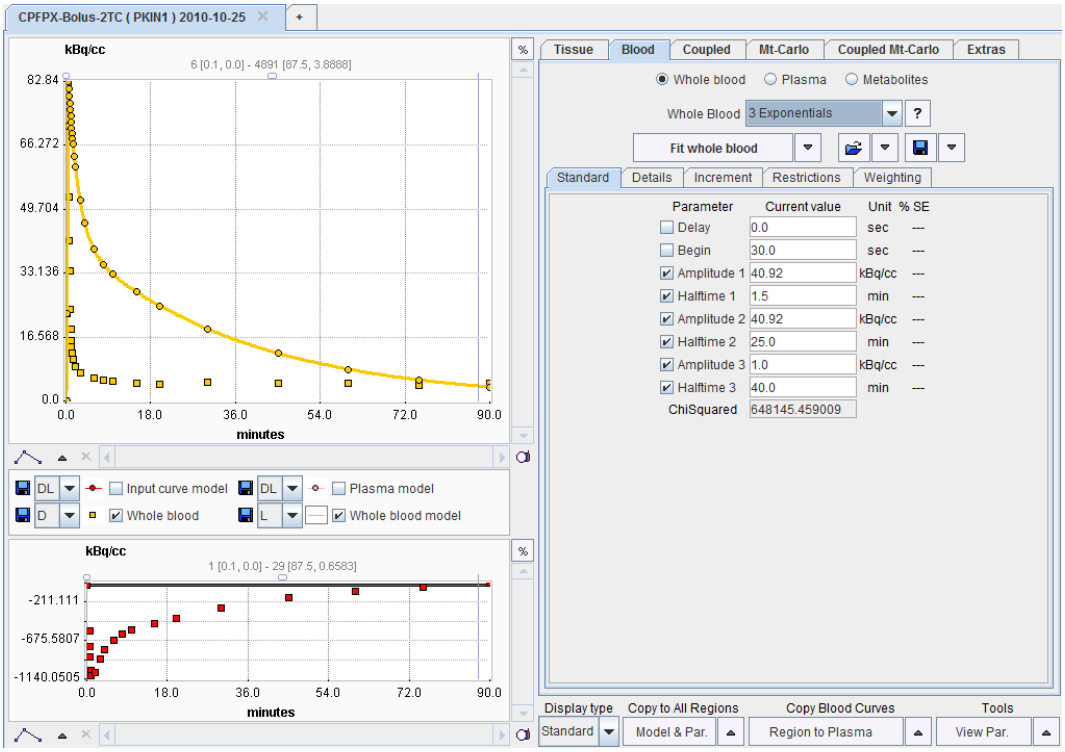
The interpolation of the activity curves of whole blood and plasma are performed in the same way.

## Whole Blood Model Configuration

It is assumed that the time-course of the tracer activity in whole blood has been loaded with **Menu/Load Whole Blood.** To configure the interpolation model of whole blood please select the **Blood** tab, and set the **Whole blood** radio button. A list of models is available which can be shown with the arrow button indicated below.



Default is **Measured**, which just represents linear interpolation between sample times. To replace linear interpolation by a smoother function select an appropriate definition from the list. As soon as a model is selected, the parameters are updated in the **Standard** pane, and a corresponding model curve is shown in the curve window as **Whole blood model**.

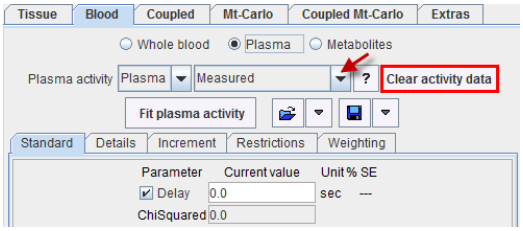



In the example above the model has not yet been fitted so that the distinction between the measurement and the model (sum of exponentials) is clearly visible. The parameters of the blood model can be configured for fitting purposes by enabling the check boxes. Activating the **Fit Whole Blood** button starts a fitting process which adjusts the model parameters such that the interpolation curve comes into optimal agreement with the measurements. Fitting works exactly in the same way as explained for the tissue model ***below*** (on page 49).

## Plasma Activity Model Configuration

It is assumed that the time-course of the tracer activity in the arterial plasma has been loaded with **Menu/Load Plasma Activity**. The configuration of the interpolation model works in exactly the same way as for whole blood.

Please select the **Blood** tab, and set the **Plasma** radio button. Note the label **Plasma activity** which indicates that the current working mode uses measured activities, not a derivation from whole blood activity. The **Clear activity data** button is available to change this mode. If it is activated, the loaded plasma activity data is discarded and the mode of plasma switched to plasma fraction. In that case the assumption is that an analytical plasma fraction function will be applied to the whole blood activity curve to derive the plasma activity.




The same list of models is available as for the plasma activity as for whole blood.

## Available Whole Blood and Plasma Activity Models

PKIN provides the following choice of interpolation functions for blood or plasma activity.

**Measured:**

This is the default model, whereby the input curve is linearly interpolated between measured values. Outside the measured values the interpolation rules are as follows: The input curve is

- set to zero for all times t<=0,
- linearly interpolated from t=0 until the first sample,
- remains at the value of the last measurement for times past the last sample. For short blood curves it is therefore recommended to interpolate the tail by using the sum-of-exponentials model.

**3 Exponentials:**

In this model the *tail* of the input curve from a starting point to be specified is replaced by a sum of up to three exponentials. The input curve before the start time is linearly interpolated as for the measured model.

$$C_{Plasma}(t) = \begin{cases} lin.\ interpolated\ between\ samples & t < Begin \\ \sum_{i=1}^{3} A_i\, e^{-u \ln 2 / T_i} & t \geq Begin, u = t - Begin \end{cases}$$

**Compartment Model, 3 Eigenvalues:**

This model has been developed for the FDG tracer [14]. It is the result from modeling the distribution and delivery of FDG in the circulatory system by a compartment model, and is given by

$$C_{Plasma}(t) = \begin{cases} 0 & t < Begin \\ \left[A_1 u - A_2 - A_3\right] e^{-u \ln 2 / T_1} + A_2\, e^{-u \ln 2 / T_2} + A_3\, e^{-u \ln 2 / T3} & t \geq Begin, u = t - Begin \end{cases}$$

**Compartment Model, 2 Eigenvalues:**

This is a reduced version of the above model given by

$$C_{Plasma}(t) = \begin{cases} 0 & t < Begin \\ [A_1 u - A_2]\, e^{-u \ln 2 / T_1} + A_2\, e^{-u \ln 2 / T_2} & t \geq Begin, u = t - Begin \end{cases}$$

**Metabolite correction (deprecated):**

This model has been developed for correcting the buildup of the $CO_2$ metabolite in $^{11}C$ acetate studies [22]. The model assumes that the concentration of authentic ligand in plasma can be calculated from total blood activity by the following simple equation

$$C_{plasma}(t) = C_{arterial}(t)\left(1 - met\left[1 - e^{-\frac{\ln 2}{T}t}\right]\right)$$

where *met* denotes the metabolite level which is finally reached, and $T$ represents the half-time of the exponential metabolite build-up. This model can be applied for other tracers with a similar behavior of metabolite buildup.

---

**Note:** the **Metabolite correction** model can *not* be fitted against the blood data. One way to use this metabolite correction is to determine the two parameters externally and enter them as constants in the model. An alternative is to estimate the metabolite parameters together with the kinetic parameters during a fit of the kinetic model (with the **Fit blood parameters** check enabled).

---

**Bolus/Infusion optimization:**

This model has been developed for the optimization of the activity ratio between an initial bolus and a subsequent infusion [23]. The aim is, that the activity level in plasma and in the tissue gets constant as soon as possible.

**Multiinjection, HOT or COLD:**

These models are used in combination with the model for multi-injection studies with $^{11}C$-Flumazenil as described by Delforge et al. [26]. With the HOT model, there is an analytical correction for the buildup of metabolites included. The COLD model is entirely derived from the hot input curve based on the relative doses and includes similar metabolite correction.

## The Blood Delay Parameter

All standard blood models have a **Delay** parameter to correct for a timing error between tissue and blood data. Positive delays represent delayed blood information and hence shift the blood curves to earlier times (to the left). This parameter is only relevant for fitting of the *kinetic* model. Therefore, when fitting the *shape* of the blood curve with **Fit plasma** or **Fit whole blood**, it is automatically *disabled.*

However, when fitting **Tissue** compartment models, it is possible to fit the blood delay as an additional parameter to the parameters of the kinetic model.

### *Blood delay fitting*

**1)** On the **Blood** tab, select **Plasma**, and then check the fitting box of the **Delay** parameter.

**2)** Disable the fit boxes of all parameters except Delay in all blood models

**3)** On the **Tissue** tab, check the **Fit blood param** box.

**4)** Then activate **Fit current region** the **Tissue** tab.

To find out the fitted blood delay, select the **Blood** tab after fitting. The fit value is shown, and the input curve model appears shifted accordingly.

**CAUTION:** When **Fit blood param** is enabled, *all* checked parameters of the input curve model are fitted. So if other parameters than **Delay** are also enabled, the *shape* of the input curve will also change!

### Default Values of Model Parameters

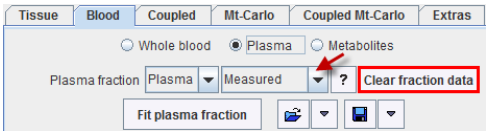
Each model has default values. Initially, they are factory settings, but they can be re-defined by the user if he wants to establish a default configurations which is more adequate from him. Note that the configurations are valid per PMOD login, so different logins could be prepared for processing types of data requiring different initial parameter values.

Saves the current configuration of the model as the new default. Included are the values, the fit flags, and the restrictions of all parameters.

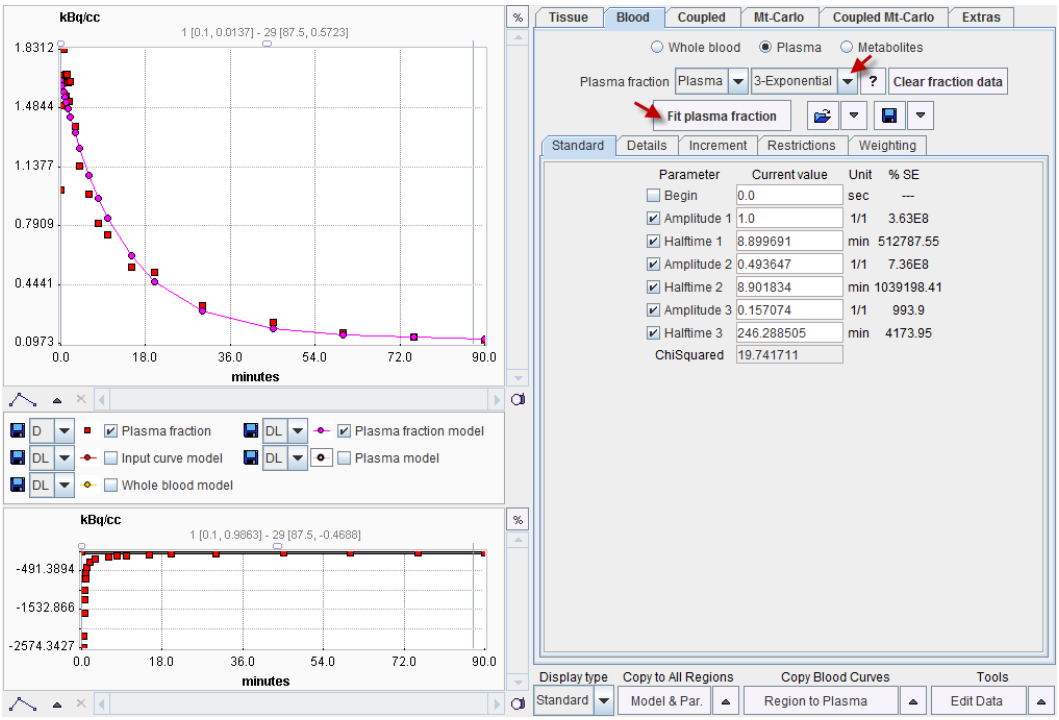
Retrieves the default configuration of the model.

## Plasma Fraction

It is assumed that the time-course of the plasma fraction has been loaded with **Menu/Load Plasma Fraction**. To configure the interpolation model please select the **Blood** tab, and set the **Plasma** radio button.



Note the label **Plasma fraction** which indicates that the current working mode uses a function to derive plasma activity from whole blood activity. There is a list of models which can be fitted to the plasma fraction data. As soon as a model is selected, the parameters are updated in the **Standard** pane, and a corresponding model curve is shown in the curve window as **Plasma fraction model**.




The **Clear fraction data** button is available to remove the loaded plasma fraction data. In that case the assumption is that an entirely analytical plasma fraction function will be applied to the whole blood activity curve in order to derive the plasma activity.

## Plasma Fraction Models

The following plasma fraction models are available. For information about model fitting options please refer to ***fitting of kinetic models*** (on page 41).

**Fix** — The concentration of free tracer is proportional to the concentration of the loaded whole blood curve. The proportionality constant **Fraction** has to be specified by the user.

There is nothing to fit with the **Fix** model.

**Measured** — Only available if a plasma fraction curve has been loaded. Linear interpolation is used for the calculation of intermediate fraction values.

There is nothing to fit with the **Measured** model.

**3-Exponential** — Sum of three decaying exponentials, starting after a time **Begin**. For the interpolation of values before **Begin** linear interpolation of the

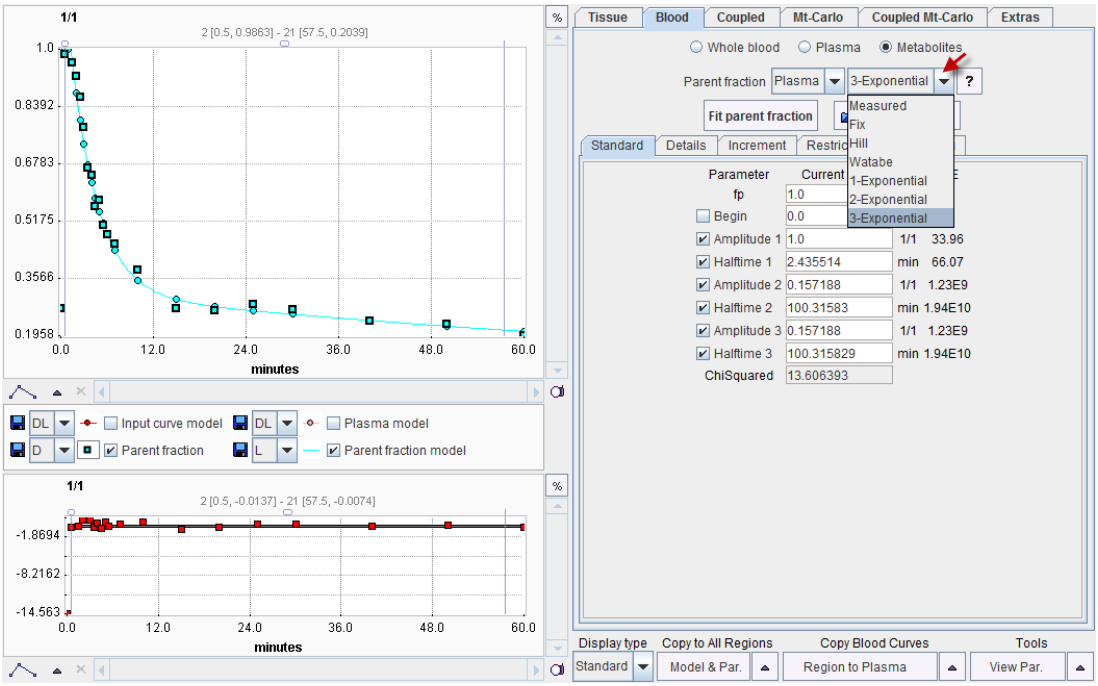
measured values will be used.

# Parent Fraction

The transformation of the plasma activity curve into the input curve is governed by the configuration on the **Metabolites** tab. Two cases are to be distinguished.

## Measured Parent Fraction Data is available

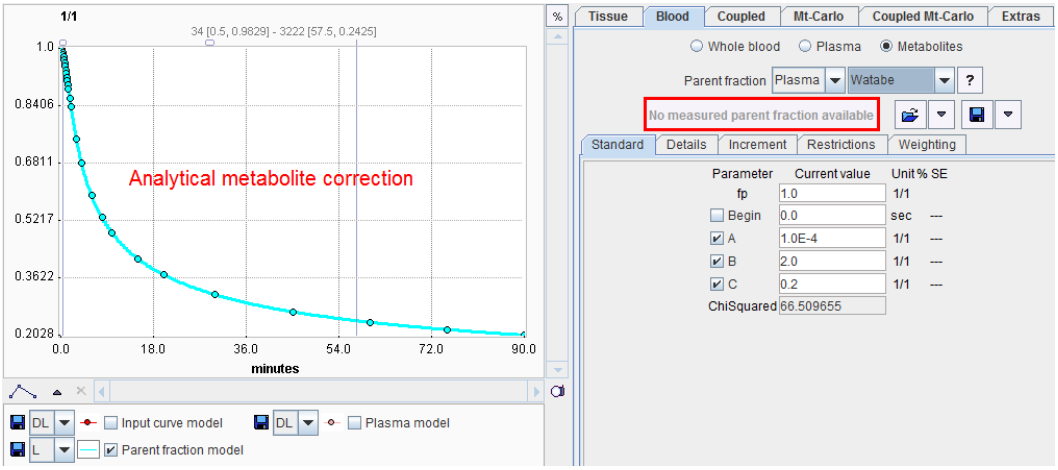
If a parent fraction curve has been loaded, it is shown in the curve area. Initially, the parent fraction model is set to **Measured** so that linear interpolation between the samples is used to calculated intermediate parent fractions. The model selection choice allows to select smoother models, and fit them to the measurements using the **Fit parent fraction** button as illustrated below.




## No Parent Fraction Data available

If no data parent fraction data have been loaded, the parent fraction model is set to **Fix** with a free parent fraction $f_p$=1. This is adequate for all tracers which do not require metabolite correction, and for cases when the metabolite correction has already been applied to the plasma data prior to loading them with **Load Plasma Curve**.

In the case of a tracer which shows a characteristic buildup of the metabolites it may be possible to derive an average parent fraction curve and fit a model to it. To apply a metabolite correction the user can then simply select the appropriate model function and enter the demographic parameter values, as illustrated below. To apply a demographic correction, it must be ensured that time zero of plasma data always represents the time of tracer injection. Naturally, no fit will be possible in this situation.




## Parent Fraction Models

The following parent fraction models are available. All of them include the constant $f_P$ which must be determined externally and which is set to 1 per default. For information about the fitting options please refer to ***fitting of kinetic models*** (on page 41).

**Fix** (Default)

The concentration of free tracer is proportional to the concentration of the loaded plasma curve.

$$f_{parent}(t) = f_p$$

There is nothing to fit with the **Fix** model.

**Measured**

The ratio unchanged/total tracer in plasma has been experimentally determined and loaded. Linear interpolation is used for the calculation of intermediate fraction values.

$$f_{parent}(t) = f_p \cdot Interpol\left(\frac{P_i}{P_i + M_i}\right)$$

There is nothing to fit with the **Measured** model.

**Hill**

The parent fraction is described by a Hill function

$$f_{parent}(t) = f_p \cdot \begin{cases} 1 & t \le t_0 \\ 1 - \left( \frac{A(t - t_o)^B}{(t - t_0)^B + C} \right) & t > t_o \end{cases}$$

with a delay $t_0$, and 0<A<=1, B>0, C>0. The delay allows for an initial phase during the infusion without tracer metabolites. This function was used with 11C-WAY-100635 data [53].

**Watabe** The functional form introduced by Watabe for 11C-MDL-100907 data [54]:

$$f_{parent}(t) = f_p \cdot \begin{Bmatrix} 1 & t \le t_0 \\ \frac{1}{\left[1+\{A(t-t_o)\}^B\right]^C} & t > t_0 \end{Bmatrix}$$

with a delay $t_0$.

**1-Exponential** The functional form described by Wu et al for 11C-WAY-100635 data [55]:

$$f_{parent}(t) = f_p \cdot \begin{Bmatrix} 1 & t \le t_0 \\ A\,e^{-B(t-t_0)} + (1-A) & t > t_0 \end{Bmatrix}$$

with a delay $t_0$. $f_{parent}(t)$ is forced to $f_p$ at time $t_0$.

**2-Exponential** The functional form described by Wu et al for 11C-WAY-100635 data [55]:

$$f_{parent}(t) = f_p \cdot \begin{Bmatrix} 1 & t \le t_0 \\ A\,e^{-B(t-t_0)} + (1-A)e^{-Ct} & t > t_0 \end{Bmatrix}$$

with a delay $t_0$. $f_{parent}(t)$ is forced to $f_p$ at time $t_0$.

**3-Exponential** Sum of three decaying exponentials

$$f_{parent}(t) = f_p \cdot \begin{Bmatrix} 1 & t \le t_0 \\ A_1 e^{-B_1 t} + A_2 e^{-B_2 t} + A_3 e^{-B_3 t} & t > t_0, B_i = \ln 2 / T_{1/} \end{Bmatrix}$$

with a delay $t_0$. There is no restriction that $f_{parent}(t)$ equals $f_p$ at time $t_0$.

**Note:** The metabolite correction is applied to the plasma curve using the original plasma sampling times. The assumption is that the parent fraction and the plasma curve have a common time scale. Only after the metabolite correction has been applied is the input curve shifted by the blood sampling time delay.

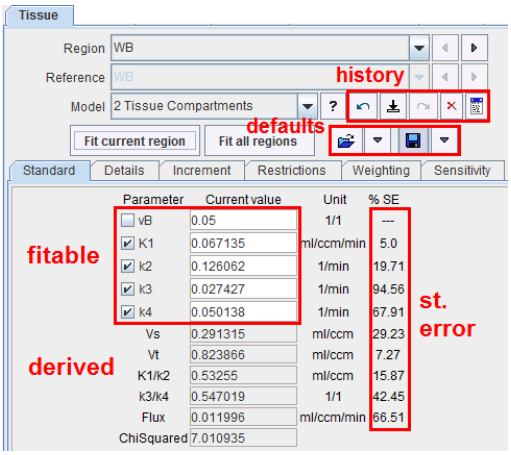
# Fitting of Kinetic Models

As soon as a kinetic model has been selected a model curve is calculated and shown in the curve display. The model curve represents the values PET would measure if the model correctly described the observed physical processes. Fitting assumes that the model configuration is adequate and tries to find the set of model parameters for which the model curve is in optimal agreement with the measurement.

The following sections explain how a model is configured, fitted to data, and assessed for goodness-of-fit.

# Kinetic Model Configuration

The main functionality for the definition and fitting of kinetic models is available on the **Tissue** pane. The upper part contains data and model selections, while the lower part gives access to the model details and fitting results.




The main elements for the model configuration on the **Tissue** pane are:

**Region** When several regional TACs have been defined and imported, the current regional TAC can be set using this list selection. The left and right arrows allow stepping forwards and backwards through the TACs.

After region switching, the display is updated with the configured model and the curves of the selected region.

**Reference** Selection of the regional TAC serving as reference in models which have the input curve replaced by a tissue TAC.

**Model** The PKIN tool includes a comprehensive list of standard kinetic models and some auxiliary calculations. This list allows selecting among all currently configured models. As soon as the model is changed, the pane in the lower section is updated to show the parameters of this model.

Note that the models in the list can be rearranged, added or deleted using the **PKIN Models** tab after selecting **Config** from the PMOD ToolBox.

**?** Button for showing a quick information about the current model.

### Model Parameters

The **Standard** sub-tab shows the configuration of the currently selected model. It encompasses different types of parameters:

- Input parameters which are needed to specify information used for model calculations.
- Fitable parameters which require a starting value and show the results of model fitting. A parameter is only optimized if its fit box is checked, otherwise it remains fixed.
- Derived parameters are calculated from model parameters in the upper part to instantly provide composite information such as the distribution volume or the flux.

The fitable and derived parameters have four columns of information:

- The **Parameter** name. In order to see a brief explanation of the parameter place the mouse pointer over the name a. The explanation text is then displayed in the status line at the bottom.
- The **Current value**, which can be edited, and which is updated as the result of a fit.
- The **Unit** of the parameter value.
- The standard error **%SE** of the parameter expressed as a percentage of the parameter value itself. It is only available, if a fit has been performed using the **Marquardt-Levenberg** method.

### Default Values of Model Parameters

Each model has default values. Initially, they are factory settings, but they can be re-defined by the user if he wants to establish a default configuration which is more adequate from him. There are four buttons for saving and retrieving the parameter values.

Saves the current parameter configuration of the model as the new default for the model type. Included are the values, the fit flags, and the restrictions of all parameters.

Saves the current parameter configuration in a file to be specified. In this way defaults per tracer can be set up.

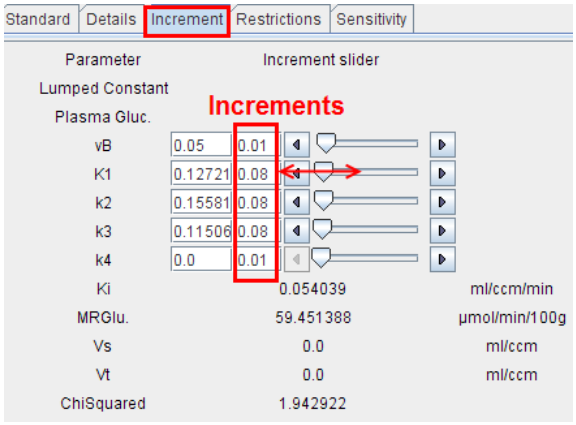
Retrieves the default configuration of the model.

Retrieves a configuration of the model which was saved in a file.

Note that the configurations are valid per PMOD login, so different logins could be prepared for processing types of data requiring different initial parameter values.

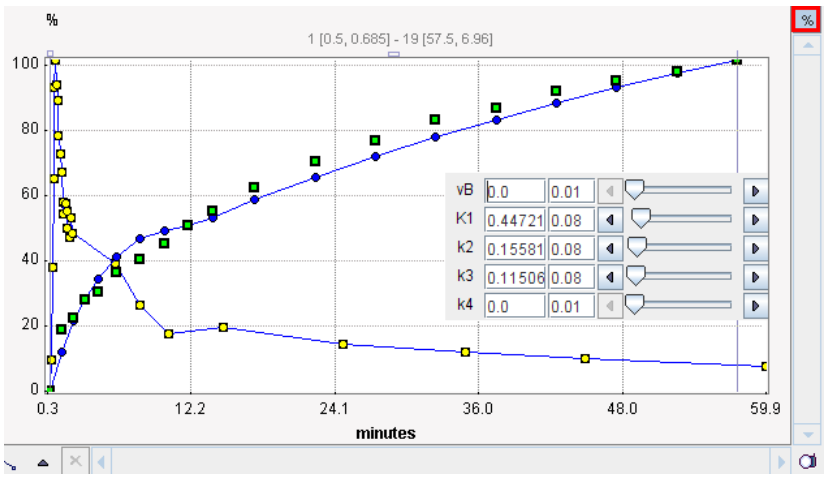
## Visualization of Parameter Dependency

The **Increment** sub-tab is mainly used for visualization purposes. For each fitable parameter the current value is shown next to an increment value and an increment slider. When the arrow buttons are selected, the parameter value is incremented or decremented accordingly. The slider allows to increment/decrement a parameter smoothly. The minimal and maximal values for the slider as well as the initial increment are obtained from the values on the **Restrictions** tab.




After every parameter change the curve display is updated, so that the user can observe its effect on the global uptake (model curve) and on the uptake in the different compartments ($C_1(t)$, $C_2(t)$).

For instance, as shown below, it can be nicely demonstrated that a change in $K_1$ simply scales the model curve, but does not change the curve shape: Set the curve display to relative scaling by selecting the % in the upper right and then change $K_1$. Nothing changes in the % display, provided that the blood volume fraction is set to 0. Any modification of the other parameters changes the curve shapes notably.

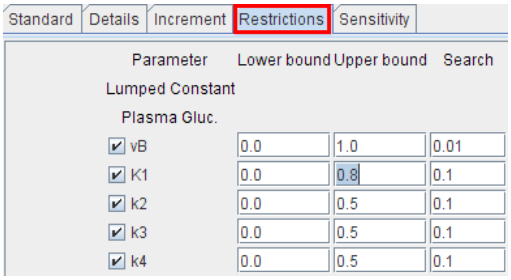



## Restriction of Parameter Range

The **Restrictions** sub-tab is relevant for fitting. For each fitable parameter there is a box for enabling the restriction which is defined by the **Lower bound** and the **Upper bound** value. The purpose of parameter restrictions is to ensure that the resulting parameters remain

within a reasonable physiologic range. Without restrictions, there is a higher chance to end up with a meaningless solution. Note that these bounds are also used for the sliders on the **Increment** pane.

The **Search** value is used as an initial step-size for iterative fitting. It is recommended to set this value to about the same size as the parameter value itself, as it is automatically decreased if needed. This approach is not successful if the value is very small from the beginning.

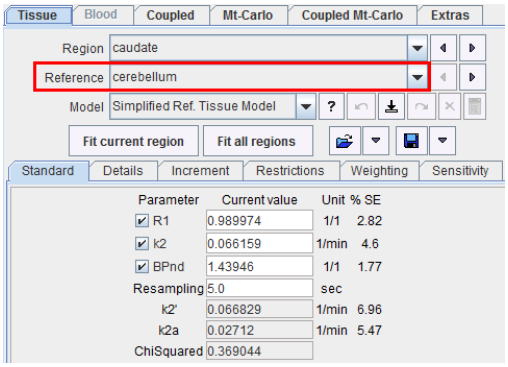



### Conversion of Model Parameters with Model Switching

There are certain ***relations*** (on page 5) between the parameters of compartment models of different complexity. Accordingly, PKIN can be configured to convert the rate constants when switching between compartment models. This mode is mainly useful when developing from a simple model towards a more complex one. Conversion is enabled with the **Model conversion** check in the **Extras** pane.

### Reference Models

When a reference **Model** is selected which uses the activity in a reference region as an implicit input curve, the blood-related items become disabled and the **Reference** region selection becomes active.



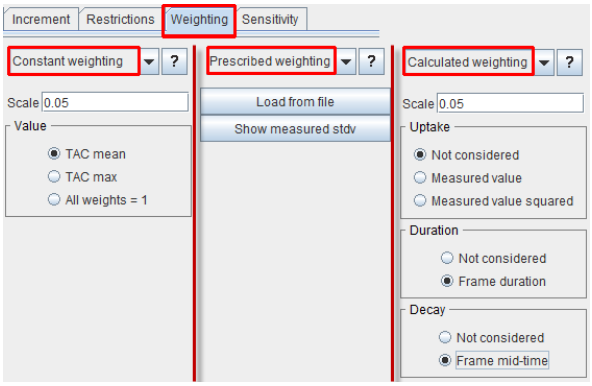

Please select an adequate regional TAC as the model reference and then **Fit current region**.

## Residual Weighting

### Residual Weighting in PKIN

In PKIN, several different weight definitions are supported. They can be specified on the **Weighting** pane using the list selection with the three entries **Constant weighting**,

**Prescribed weighting** and **Calculated weighting**. The contents of the different selections are illustrated in parallel below.

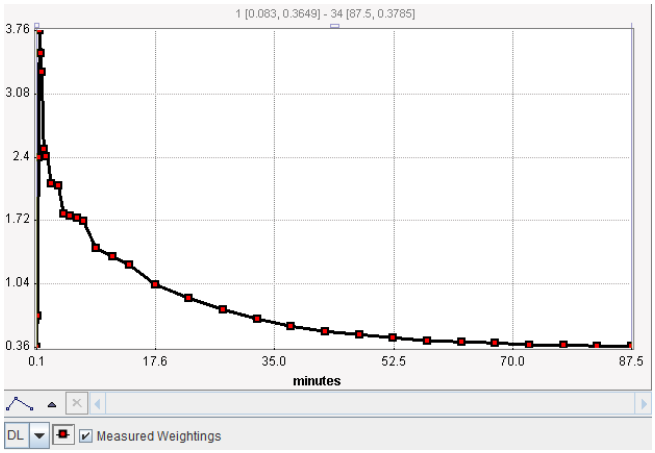



**Constant weighting**

With constant weighting the same weight is applied to all residuals. Its size can be adjusted by the **Scale** factor and the radio button setting. In the case of **TAC mean** $\sigma_i$ is obtained as the average of all values in the TAC multiplied by the **Scale** factor. Similarly, with **TAC max** $\sigma_i$ is obtained as the maximal TAC value multiplied by the **Scale** value. With **All weights = 1** the weights are all set equal to 1 independent of the **Scale** ($\sigma_i = \sigma_i^2 = w_i = 1$).

**Prescribed weighting**

The default behavior of this method is to use the standard deviation of the pixel values in the VOI for calculating the TAC for weighting. This information is automatically available if the TACs have been sent from the PMOD viewing tool to PKIN, and can be visualized using the button **Show measured stdv** as illustrated below.




This definition can be overwritten by user-defined weights which are to be loaded with the **Load stdv from file** button. Please see below how the file has to be formatted.

**Calculated weighting**

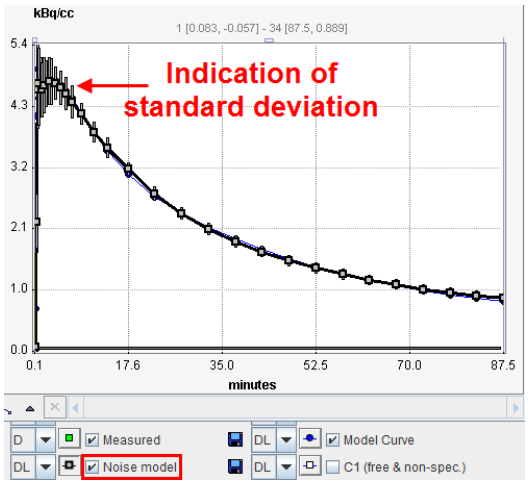
With this selection the variance is calculated for each TAC value from an equation which may take into account the measured uptake, the correction of the radioactive decay, and the duration of the acquisition. The full equation is as follows:

$$\sigma_i^2 = \alpha \frac{C_{PET}(t_i)}{\Delta t_i \, e^{-\lambda t_i}}, \qquad \lambda = \frac{\ln 2}{T_{1/2}}$$

It includes a **Scale** factor α, the decay-corrected **Uptake** $C_{PET}(t_i)$ at frame mid-time $t_i$, the frame **Duration** $\Delta t_i$, and the **Decay** constant λ which is obtained from the half-life $T_{1/2}$ of the isotope.
The settings of the radio buttons have the following effect on the equation above for calculating $\sigma_i^2$:

- **Uptake**:
  **Not considered**: $C_{PET}(t_i)$ is replaced by 1.
  **Measured value**: $C_{PET}(t_i)$ is used, corresponding to *Poisson weighting*. The effect is that more emphasis is given on low-uptake values than on high-uptake values. This may be helpful for example if the fit seems to not account enough for the tail of a decreasing function such as the input curve.
  **Measured value squared**: $C_{PET}(t_i)$ is replaced by $C_{PET}^2(t_i)$, corresponding to *Relative weighting*. With this option the influence of the uptake is further increased. It should be used with care because by squaring small uptake values (<<1) very small variances are generated which transform into heavy weighting. As a consequence, a few small uptake values may have too much impact on the fit.
- **Duration**:
  **Not considered**: $\Delta t_i$ is replaced by 1.
  **Measured value**: The individual frame durations $\Delta t_i$ are used, so that longer acquisitions are considered more reliable.
- **Decay**:
  **Not considered**: $e^{-\lambda t_i}$ is replaced by 1.
  **Frame mid-time**: $e^{-\lambda t_i}$ is used, so that earlier acquisitions are considered more reliable.

Each time the configuration is changed, the standard deviation $\sigma_i$ is calculated and plotted as an error bar around the measurements. This feedback gives the user a visual feedback as a help in judging the adequacy of the specified weighting.



## Loading Externally Defined Weights

Some users might want to implement their own residual weighting schemes. To this end they should calculate the standard deviations $\sigma_i$ for the different acquisition frames from which the weights will be calculated according to

$$w_i = \frac{1}{\sigma_i^2}$$

The $\sigma_i$ should be prepared in a tab-delimited text file of the following form:

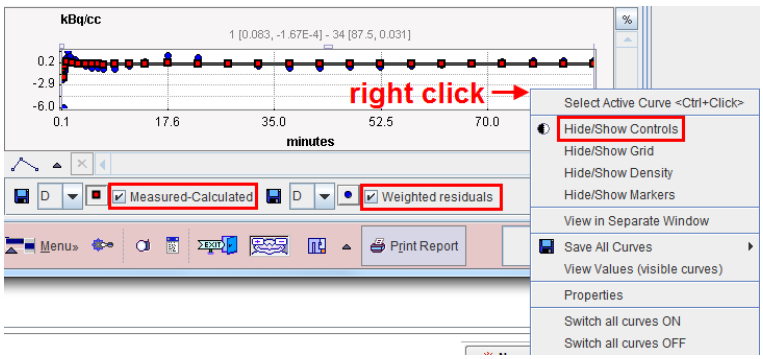
| t[seconds] | standard-dev[kBq/cc] |
|---|---|
| 10 | 0.10300076 |
| 30 | 0.01717448 |
| 50 | 0.01195735 |
| 70 | 0.01010257 |
| etc | ... |

The header line is required. The first column represents the frame mid-times (although the values are not interpreted), and the second column the standard deviations in appropriate units. The number of entries must be equal the number of acquisitions, and the columns separated by spaces or tabs. For example, such a file can be prepared in MS Excel and then saved as a text file with tab delineation.

This definition can be loaded by the **Load stdv from file** button available with **Prescribed weighting**.

## Display of the Residuals

The curve area with the residuals contains the information of the raw unweighted as well as the weighted residuals. The context menu as illustrated below (right mouse click into the curve area) can be employed for showing/hiding the curve controls and using them for changing the displayed information.



### Use of the Weights in Monte Carlo Simulations

Monte Carlo simulations require the generation of noise which is defined by a distribution type as well as its deviation characteristics. Assuming that the weights specification corresponds to the standard deviation of the measurement noise, the regional weighting specification is used in the Monte Carlo noise generation together with the distribution type. Note that the **Scale** factor has no impact on fitting, but that it is highly relevant in Monte Carlo simulations.

## Kinetic Model Fitting

The main elements on the **Tissue** pane for model fitting are:

**Fit current region** Starts the process which fits the model curve to the measurements of the selected regional TAC. For compartment models the fit is an iterative optimization, while for other models only a single calculation may be sufficient.

In case randomized fitting with a number n of trials is enabled, the button text is changed to **Randomized fit current region[n]**.

**Fit all regions** Performs fitting for all TACs of the study using the current regional model definitions.

In case randomized fitting with a number n of trials is enabled, the button text is changed to **Randomized fit all regions**.

### Fitting and Initial Parameter Values

Except for linear and multi-linear regression, minimization of the Chi square expression requires an iterative approach. The procedure starts with a set of initial parameter values, generates the corresponding model curve, calculates the Chi square criterion, and adjusts the model parameters such that Chi square is expected to be reduced. The cycle

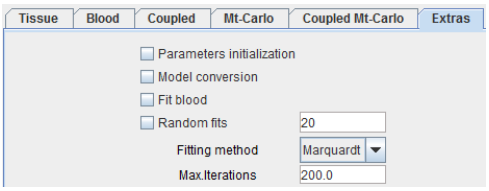
- chi square calculation
- parameter adjustment

is then repeated until a further reduction of Chi square is not any more possible. The final set of parameters upon termination is regarded as the best-fit result. It is not analytically exact and may depend on the initial parameters, on the optimization procedure, and on the termination criterion of the iterations. Fitting is started using the **Fit current region** button.

It is recommended to provide a set of reasonable parameter values at the start of the optimization procedure. If the initial parameters are too far from the optimal solution, there is a higher danger of getting stuck in a local minimum. When fitting complex models, it may be worthwhile to first start with a simpler model and derive initial values from those results.

### Automatic Parameter Initialization and Randomized Fitting

The **Extras** pane contains some settings related to fitting.




**Parameters initialization**

This configuration is only related to the compartment models and determines which initial values are used for the iterative fitting:

- Disabled: the user-defined parameters are used.
- Enabled: an automatic procedure determines initial parameters which should be reasonably close to the solution. This is done by the ***linear least squares method*** (on page 86). Note that the initial values are not shown to the user. However, to see the values, please switch to the linear least squares method and fit.

**Model conversion**

This configuration is only related to the compartment models and determines the behavior if the user switches the model between different compartment models:

- Disabled: the first time a model is selected, its default values are used, and thereafter most recent set of parameter values of that particular model. This behavior works on a per-region bases.
- Enabled: Each time, the user switches between the models, the parameters are converted. If switching is between models with the same number of compartments, the conversion is exact. If the number of compartments is decreased, the lumped parameters of the reduced model are ***calculated*** (on page 5). If the number of compartments is increased, the same values are used for corresponding parameters, and the additional parameters set to the default values.
  Note that when switching the model from 1-tissue to 2-tissue and then back, you will end up with differing $K_1$ and $k_2$ values due to this conversion process.

**Random Fits**

This configuration is only related to models which require iterative fitting:

- Disabled: Only a single fit is performed and the result parameters returned.
- Enabled: Multiple fits are performed, and the result parameters of the fit with minimal chi squared returned. The fits are started with randomized sets of initial parameters using a uniform distribution with ±100% range.
  Note: If **Parameters initialization** is enabled, randomization uses the automatically determined parameters for the random number generation.

**Note:** The purpose of randomized fitting is to avoid local minima, but there is a chance that the returned solution may contain unphysiologic parameter combinations.

**Fit blood** If this box it is checked on, *all* parameters of the **Input** curves which have the fit box checked are also included into the set of fitted parameters. This feature has two uses:

- Fitting the relative time delay between the tissue and the blood data simultaneously with the kinetic rate constants.
- (Rarely) Fitting a shape parameter such as the half-time of a metabolite build-up together with the rate constants.

**Fitting method** Selection of the numerical optimization method applied for iterative fitting:

- **Marquardt**: Marquardt-Levenberg algorithm [59]. Usually works faster and has the additional advantage that it accumulates information about the covariance matrix. Therefore, an estimate of the standard error can be calculated for the fitted parameters. They are shown as **%COV** (coefficient of variation), ie. as a percentage of the parameter value.
- **Powell**: Conjugate direction set method [59].

The iterative optimizations terminate, when no substantial improvement can be found any more, or when the **Max iterations** restriction is hit.

---

**Note:** Several models (linear and multi-linear regression) are not fitted iteratively because they have closed form solutions. In these cases the **Fitting type** settings are not relevant.

---

**Max. iterations** Maximal number of iterations which are allowed in the **Marquardt** and **Powell** fitting.

## Potential Fitting Problems

In the case of a failed fit it is worthwhile to check the console output. For example, the output text reproduced below clearly indicates that the 4th fit parameter caused a problem.

```
Singular Matrix-2
covar[1][1] = 2.1652603147908747E-6
covar[1][2] = -5.120936302955895E-4
covar[1][3] = 2.862241687078937E-7
covar[1][4] = 0.0
covar[2][1] = -5.120936302955895E-4
covar[2][2] = 0.3918087002588389
covar[2][3] = -2.0406232308544742E-4
covar[2][4] = 0.0
covar[3][1] = 2.862241687078937E-7
covar[3][2] = -2.0406232308544742E-4
covar[3][3] = 1.4044964781403112E-7
covar[3][4] = 0.0
covar[4][1] = 0.0
covar[4][2] = 0.0
covar[4][3] = 0.0
covar[4][4] = 0.0
```

Such problems might be caused by initial values very close to parameter restrictions.

# Model History

The system maintains a history of model configurations for each region. Each time the **Fit** button is activated, the result is added to the history. The user can also manually add configurations. The user can display a list of the configuration history, edit the list, and select one of the historic configurations. This functionality is accessible by the elements close to the model configuration


Adds the current model configuration to the history list.

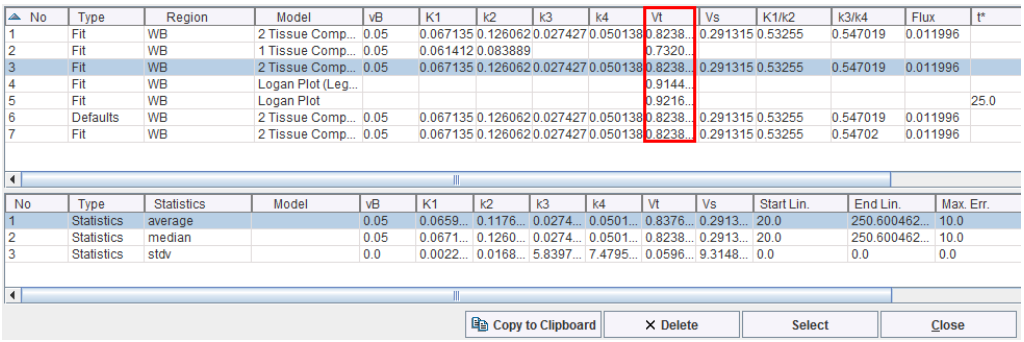
Switches to the prior model configuration.

Switches to the following model configuration.

Clears all history entries.

Shows the history.

The history is shown in a dialog window which contains in the upper part the model configurations, and in the lower part statistics.



| No | Type | Region | Model | vB | K1 | k2 | k3 | k4 | Vt | Vs | K1/k2 | k3/k4 | Flux | t* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Fit | WB | 2 Tissue Comp... | 0.05 | 0.067135 | 0.126062 | 0.027427 | 0.050138 | 0.8238... | 0.291315 | 0.53255 | 0.547019 | 0.011996 | |
| 2 | Fit | WB | 1 Tissue Comp... | 0.05 | 0.061412 | 0.083889 | | | 0.7320... | | | | | |
| 3 | Fit | WB | 2 Tissue Comp... | 0.05 | 0.067135 | 0.126062 | 0.027427 | 0.050138 | 0.8238... | 0.291315 | 0.53255 | 0.547019 | 0.011996 | |
| 4 | Fit | WB | Logan Plot (Leg... | | | | | | 0.9144... | | | | | |
| 5 | Fit | WB | Logan Plot | | | | | | 0.9216... | | | | | 25.0 |
| 6 | Defaults | WB | 2 Tissue Comp... | 0.05 | 0.067135 | 0.126062 | 0.027427 | 0.050138 | 0.8238... | 0.291315 | 0.53255 | 0.547019 | 0.011996 | |
| 7 | Fit | WB | 2 Tissue Comp... | 0.05 | 0.067135 | 0.126062 | 0.027427 | 0.050138 | 0.8238... | 0.291315 | 0.53255 | 0.54702 | 0.011996 | |

| No | Type | Statistics | Model | vB | K1 | k2 | k3 | k4 | Vt | Vs | Start Lin. | End Lin. | Max. Err. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Statistics | average | | 0.05 | 0.0659... | 0.1176... | 0.0274... | 0.0501... | 0.8376... | 0.2913... | 20.0 | 250.600462... | 10.0 |
| 2 | Statistics | median | | 0.05 | 0.0671... | 0.1260... | 0.0274... | 0.0501... | 0.8238... | 0.2913... | 20.0 | 250.600462... | 10.0 |
| 3 | Statistics | stdv | | 0.0 | 0.0022... | 0.0168... | 5.8397... | 7.4795... | 0.0596... | 9.3148... | 0.0 | 0.0 | 0.0 |



**Fit** indicates that the configuration was automatically added as a fit result. **Defaults** indicates that the user added the configuration manually by using a defaults button. The list can be sorted by clicking on the column headers. Activated list entries can be removed with the **Delete** button. **Select** or double-clicking into the list restores the selected configuration and closes the dialog window. **Copy to Clipboard** copies the numbers, so that they can be pasted into another application. **Close** just closes the window.

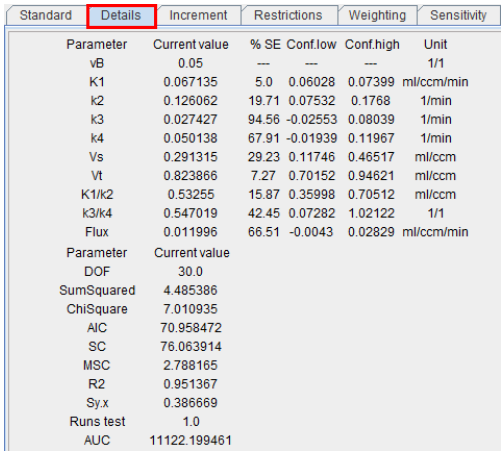
Note that the parameters of the different models are sorted into appropriate columns. For instance, Vt resulting from the different compartment models appear in the same column so that they can easily be compared. The user can change the sorting order by clicking on an arbitrary column header.

**CAUTION:** This history mechanism does not account for changes in the loaded data or changes in the configuration of the blood-related models. However, it includes the definition of the residual weighting and the valid points.

# Assessing Fit Results

The physiologic behavior of PET tracers is usually quite complex. A comprehensive model accurately describing its kinetics therefore requires many compartments and exchange parameters. However, as the PET signal is limited in quality and only represents the sum of all tracer radioactivity, the model must be simplified to a degree that only a few parameters remain. When estimating a model with many parameters, the variance of the parameter estimates tends to be very high, so that a reliable interpretation of the results becomes impossible. A simplified model with fewer parameters will provide more precise results, but these parameters may be biased. Therefore, the optimal trade-off between bias and uncertainty has to be sought by testing models of decreasing complexity.

After every model fit detailed information about the parameter estimates and the goodness-of-fit is available on the **Details** tab.




| Parameter | Current value | % SE | Conf.low | Conf.high | Unit |
|---|---|---|---|---|---|
| vB | 0.05 | --- | --- | --- | 1/1 |
| K1 | 0.067135 | 5.0 | 0.06028 | 0.07399 | ml/ccm/min |
| k2 | 0.126062 | 19.71 | 0.07532 | 0.1768 | 1/min |
| k3 | 0.027427 | 94.56 | -0.02553 | 0.08039 | 1/min |
| k4 | 0.050138 | 67.91 | -0.01939 | 0.11967 | 1/min |
| Vs | 0.291315 | 29.23 | 0.11746 | 0.46517 | ml/ccm |
| Vt | 0.823866 | 7.27 | 0.70152 | 0.94621 | ml/ccm |
| K1/k2 | 0.53255 | 15.87 | 0.35998 | 0.70512 | ml/ccm |
| k3/k4 | 0.547019 | 42.45 | 0.07282 | 1.02122 | 1/1 |
| Flux | 0.011996 | 66.51 | -0.0043 | 0.02829 | ml/ccm/min |

| Parameter | Current value |
|---|---|
| DOF | 30.0 |
| SumSquared | 4.485386 |
| ChiSquare | 7.010935 |
| AIC | 70.958472 |
| SC | 76.063914 |
| MSC | 2.788165 |
| R2 | 0.951367 |
| Sy.x | 0.386669 |
| Runs test | 1.0 |
| AUC | 11122.199461 |

## Parameter Confidence Intervals

Nonlinear regression using the Marquart-Levenberg optimization reports a standard error for each fitted parameter value. If the inherent fitting assumptions are true, a 95% confidence interval can be approximated by the result parameter plus/minus two standard errors. This confidence interval is displayed for each fitted parameter (**Conf.low**, **Conf.high**).

There will be a 95% chance that the confidence interval contains the true parameter value. A sufficiently narrow confidence interval indicates that the parameter could be determined with a reasonable certainty, whereas a wide interval makes it necessary to revise the configuration of the used model, or look for a more appropriate model.

## Goodness-of-Fit

The following measures are defined which allow a direct or indirect assessment of the goodness-of-fit:

**DOF** **Degrees of freedom** defined as the number of valid measurements minus the number of fitted parameters.

**SumSquared** Sum of squared (unweighted) residuals.

**ChiSquare** **Reduced Chi square**. Sum of squared, weighted residuals, divided by the degrees of freedom.

The reduced chi-square provides a useful measure of goodness-of-fit. If the model describes the measured data, the reduced chi-square will mostly represent the variance of the data and will be close to 1.0 (when weighting is appropriate).

**AIC** **Akaike Information Criterion**. The AIC methodology attempts to find the model that best explains the data with a minimum of free parameters. The AIC is calculated with the second order correction for small sample size (<40).

The preferred model is the one with the lowest AIC value.

**SC** **Schwartz Criterion**, also called Bayesian Information Criterion (BIC).

The preferred model is the one with the lowest SC value.

**MSC** Another criterion used in the *Scientist* Software (MicroMath, Saint Louis, Missouri USA) is the **Model Selection Criterion.**

The preferred model is the one with the highest MSC value.

**R2** There is also a measure of the goodness-of-fit, the **coefficient of determination R2**, a number between 0 and 1. A value of 0 means that the fit is not better than a horizontal line through the mean of all measurements, whereas a value of 1 means that all measurements lie exactly on the curve. High R2 values indicate that the model curve is close to the measurement.

**Sy.x** Another information about the residuals is provided by the **root mean square value Sy,x**. It is defined as the standard deviation of the residuals and can be used to generate synthetic measurements in Monte Carlo simulations, provided all measurements have the same variability.

**Runs test** The runs test is a statistical test to decide whether the model curve deviates systematically from the data. It is based on the number of runs resulting from the fit. A run is a set of consecutive measurements which are above (positive residuals) or below (negative residuals) the measurement. Given the assumption that the residuals are randomly distributed, the probability p of the occurrence of a number of runs can be calculated. If p is small (eg. p<0.05) the measurements systematically deviate from the model curve. Such a finding signals that most likely an inadequate model was fitted and further investigations of the result are not sensible. The test is only applicable for a sufficient number of positive and negative runs (>8).

**1** means that the systematic deviation between model and measurement (p<0.05). **0** means there is no significant deviation.

**AUC** Area under the model curve.

## Criteria for Comparing Models

The following criteria can be used for comparing different models which use the same weighting and are fitted to the same data. The notation is:

n: Number of independent measurements considered in the fit
p: Number of fitted parameters
$w_i$: Weight applied to residual of acquisition i

### Akaike Information Criterion (AIC)

The Akaike Information Criterion [29] is defined by the formula

$$AIC = n \ln\left( \sum_i w_i \left[ y(t_i) - \hat{y}(t_i) \right]^2 / n \right) + 2p$$

If applicable, PKIN uses an adjusted procedure with a second order correction for small sample size (<40) [58]

$$AIC = n \ln\left( \sum_i w_i \left[ y(t_i) - \hat{y}(t_i) \right]^2 / n \right) + 2p + \frac{2p(p+1)}{n-p-1}$$

The more appropriate model is the one with the *smaller* AIC value.

### Schwartz Criterion (SC)

The Schwartz Criterion is defined by the formula

$$SC = n \ln\left( \sum_i w_i \left[ y(t_i) - \hat{y}(t_i) \right]^2 / n \right) + p \ln(n)$$

The more appropriate model is the one with the *smaller* SC value.

### Model Selection Criterion

Another criterion used in the *Scientist* Software (MicroMath, Saint Louis, Missouri USA) is the **Model Selection Criterion**

$$MSC = \ln\left( \frac{\sum_i w_i \left[ y(t_i) - \bar{y}(t_i) \right]^2}{\sum_i w_i \left[ y(t_i) - \hat{y}(t_i) \right]^2} \right) - 2p/n$$

This criterion has the advantage that it is independent of the magnitude of the $y_i$. Opposed to the AIC and the SC the more appropriate model is that with the *larger* MSC.

### F-Test

Two nested models can be compared by an F-test of their sum of squared residuals [38]. The idea is to compare the total sum of squares into a component removed by the simpler model and into a component additionally removed by the more complex model. For each component, the mean square (sum of squares per degree of freedom) is calculated. The residual mean square is an estimate of the variance of the original data. The ratio of the two mean squares is the F-statistic used to test for significance of the variance reduction by the additional parameters, as follows:

$$F = \frac{(Q_1 - Q_2)/(p_2 - p_1)}{Q_2/(n - p_2)}$$

where

$Q_1$ represent the sum of squares or the simple model with $p_1$ parameters,
$Q_2$ the sum of squares or the more complex model with $p_2$ parameters,
$p_1 < p_2$

The F-statistics has $(p_2-p_1, n-p_2)$ degrees of freedom. If the calculated F is larger than the tabulated value at a specified p value, the reduction of the residual variation by the addition of the $(p_2 - p_1)$ extra parameters of the more complex model is statistically significant. Usually, significance p=0.05.

Note: in MS Excel the $F_P(p_2-p_1, n-p_2)$ can be calculated by the function FINV(p;$p_2-p_1$;$n-p_2$).

## Analysis of Sensitivity and Identifiability

The following two approaches can be employed to investigate whether a selected model is too complex for the data. The implementation in PKIN is based on the handout *Kinetic model evaluation with sensitivity functions and correlation matrices* by Dr. M.M. Graham, University of Washington at the Technical Exhibition of the Society of Nuclear Medicine Annual Meeting 1995 (JNM vol 36, no 5, P1208). As to our knowledge, there is no follow-up paper about this subject.

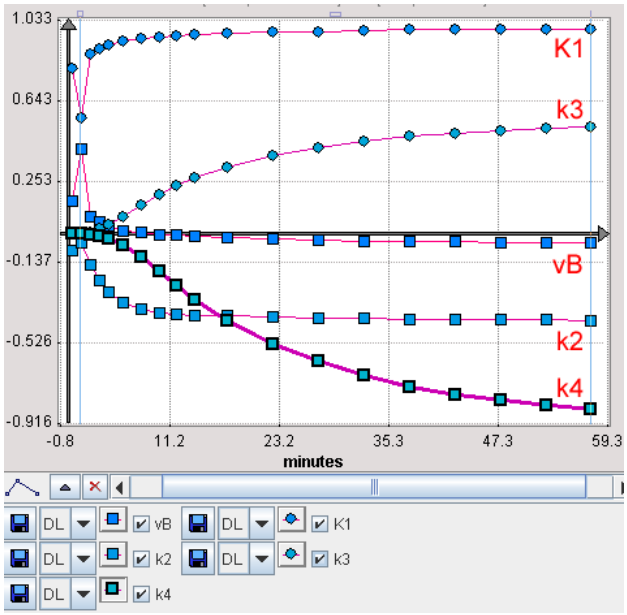
### Sensitivity

If a parameter value is changed there should be some visual change in the model output. Some parameters will cause more change than other. The model is more sensitive to a parameter that causes more change in the output.

The sensitivity functions $Sens(k_i)$ for the different parameters $k_i$ are obtained by calculating the model function twice: with the initial parameter set, and after changing the parameter $k_i$ by 1%. Then, the expression

$Sens(k_i,t)= 100*[Model(k_i*(1.01), t)-Model(k_i, t)]/Model(k_i, t)$

is calculated over time. When the 1% change of $k_i$ has changed the output by 1% at a certain time the sensitivity function is equal to 1. In PKIN, the sensitivity functions are calculated for all model parameters, whenever the **Sensitivity** pane is selected. The example below shows the sensitivity functions of a FDG data set.




Examination of the sensitivity curves shows at what time a parameter has significant sensitivity and how sensitive a parameter is compared to another. If the sensitivity curves of two parameters have the same shape it is unlikely that one can tell which parameter has changed (ie. they are not identifiable).

In the FDG example above the model is quite insensitive to vB. Furthermore, the $K_1$ and $k_2$ curves have a quite similar (but opposite) shape throughout the acquisition duration, indicating that there is a substantial correlation between these parameters.

## Identifiability

The model output must change in a unique way when changing a model parameter. If the change in the model output is the same when changing either of two parameters they can not be independently identified. In this situation the model must be simplified further, or one of the parameters can be fixed at a physiologic value. The latter approach is better since simplification usually means essentially setting one of the parameters equal to zero or infinity.

A more quantitative way to look at parameter identifiability is to generate a correlation matrix. It shows how the various parameters tend to correlate with each other. A low value, close to 0, means they do not correlate and that they are identifiable from one another. A high value, close to 1, means they are highly correlated and not independently identifiable.

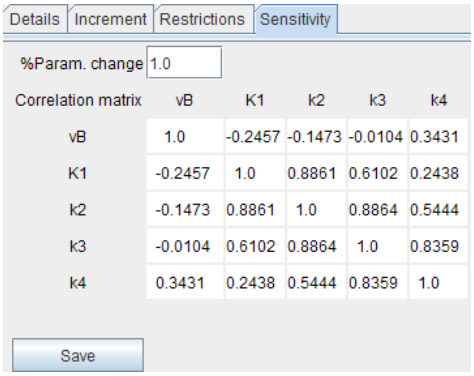
The correlation matrix is calculated by:

**1)** generating the sensitivity matrix SM given from the sensitivity functions by SM(i,j)=Integral(Sens(ki,t)*Sens(kj,t));

**2)** inverting the sensitivity matrix SM(i,j), resulting in the covariance matrix;

**3)** normalizing the covariance matrix by dividing each element by the square root of the product of the corresponding diagonal elements; result is the correlation matrix .

The correlation matrix is shown in the **Sensitivity** pane. Using the **Save** button the correlation matrix and the sensitivity functions can be save into a text file.




**Note:** Sensitivity functions are currently only supported for compartment models.

### Comparison by Data Cloning

PKIN allows to examine different models and compare their numerical output using the ***History*** (on page 52) mechanism. Sometimes it is also helpful to compare the model curves resulting from different model configurations in question. This can be achieved using the **Study Compare Dialog** in the **Menu**.

A new dialog window is opened with a clone of the current data set. It supports all features of PKIN except for the functions related to data management. So the user can arrange the original PKIN window and the dialog window next to each other and process/visualize the same data in parallel.

# Coupled Fitting for Improving Parameter Estimates

In some situations the introduction of prior knowledge can help to improve the stability of model fitting. In receptor experiments it may be adequate to assume that the distribution volume ($K_1/k_2$) of the non-displaceable compartment and/or the dissociation rate from specific binding sites ($k_4$) are equal in certain tissues of the brain. Hence, a simultaneous fit of selected regional TACs of a scan can be performed which finds separate $K_1$ and $k_3$ values per TAC, but which delivers a $K_1/k_2$ and $k_4$ which is common for all TACs. As an example, Sanabria-Bohorquez et al [63] have used a coupled $k_4$ for solving the problem of unstable fits. In PKIN this type of fitting is called **Coupled Fitting**.

The concept can be extended to the fitting of data from different scans of the same subject, for instance test/retest scans which are replicate measurements under the same conditions and where the parameters should be very similar if the regions are consistently outlined. Plisson et al. [64] have applied simultaneous fitting with the data of pigs which were studied in a baseline condition and with different degrees of receptor blocking by cold compound. By applying the simultaneous fitting, they were able to get stable estimates, which was not possible with independent fitting. In PKIN this type of fitting is called Coupled Studies Fitting and distinguishes two variants of coupling. GLOBAL coupling of a parameter results

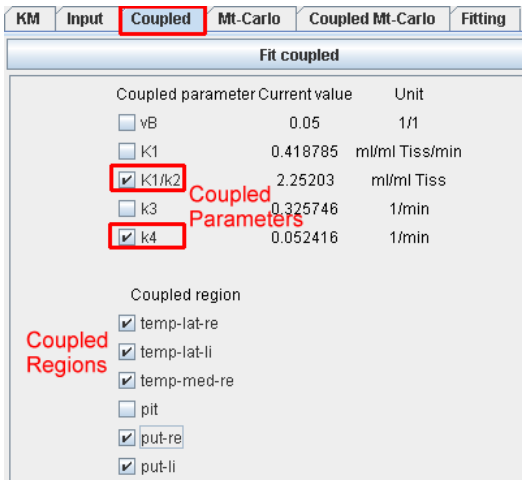
in single value which is common for all fitted TACs. **REGIONAL** coupling of a parameter results in common value per region. For instance, if $k_3$ is defined as a parameter with **REGIONAL** coupling and the coupled regions from two scans are *caudate*, *putamen* and *frontal*, a different $k_3$ estimate will result for each of these three regions, but each of them is common across the TACs of the two scans.

The requirements for coupled fitting in PKIN are:

- The same kinetic compartment model applies to the TACs of several tissue regions. (non-compartment models may not be coupled).
- There exists one or more parameter in the model configuration which can be assumed to have a common value in the model for different TACs.

## Common Parameters across Regional TACs of a Single Study

For a simultaneous fit of TACs from a single study the user specifies the coupling on the **Coupled** pane:




In the upper section the kinetic model parameters are listed. Check those parameters which are to be coupled among regions. The lower section lists all selectable regional TACs (having the same model). Check all regions which are to be included in coupled fitting.

**Fit coupled** starts the fitting process as follows:

- A global target curve is created by stacking the TACs of the checked regions (valid points only).
- The corresponding weights are calculated according to the weighting configuration for each TAC.
- A table of fitted parameters is formed by entering the common parameters once and adding all the other fit enabled parameters in the coupled regions. The initial values of common parameters are taken from the first checked region, for the other parameters from the individual regional models. If **Fit blood parameters** is enabled on the **Fitting** pane, the fit-enabled parameters of the blood curves are also taken into account.
- The optimizer calculates the model curve in all checked regions, creates the global result curve corresponding to the target curve, weighs all the residuals and forms the global sum of squares as the figure of merit. The parameters are adjusted until the cost function

has been minimized, and the resulting parameters are copied back to the individual models.

**Note:** Coupled fitting may take significant processing time. Thus the **Batch mode** facility may be a helpful option to run such jobs at less busy times.

# Common Parameters across Regional TACs from Different Studies

## Preparations

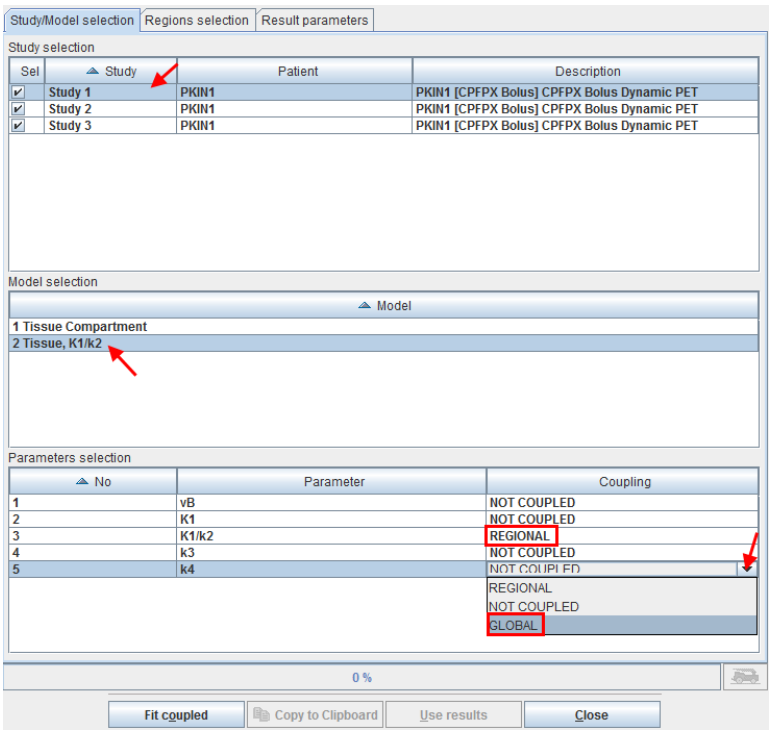
For a simultaneous fit of TACs from multiple studies the user first has to

- load all of the data sets so that they are available on different tabs;
- ensure that all of the TACs to be coupled have the same compartment model configuration and the same residual weighting;
- ensure that all models parameters have reasonable initial values by either fitting the models, or propagating a model configuration.

The coupling is performed on a separate dialog window which can be opened from the **Menu** with **Coupled Studies Dialog** entry.

## Study and Model Selection

The dialog window opens on the first tab **Study/Model selection** containing three sections.




The **Study selection** lists all open data sets. As soon as one of them is selected in the list, the **Model selection** list is updated, showing the different models which are used for the TACs of the study. In the example shown above one of the regions (which is not used four

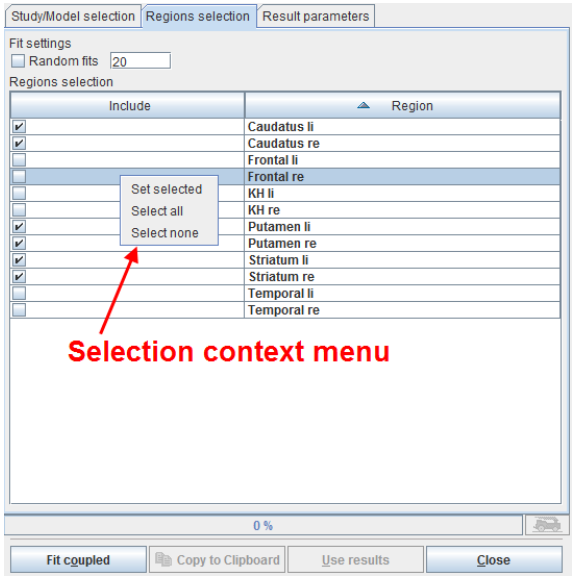
coupling) uses a **1 Tissue Compartment** model, whereas the regions intended for coupling use the **2 Tissue K1/k2** model.

After selecting the appropriate model, the **Parameters selection** list is updated showing all parameters of the model together with a **Coupling** selection. A parameter can have one out of three configurations:

- **NOT COUPLED**: The parameter will be individually fitted in the different regional models or kept fix depending on the state of the individual fit box.
- **REGIONAL**: The parameter will be coupled among all regions with the same name. For instance, the parameter will have a common value for all *caudate* regions, a different common one for all *putamen* regions, etc. Note that with this configuration the state of the individual parameter fit boxes is not relevant, the parameter will be modified in all coupled regions.
- **GLOBAL**: The parameter will be coupled among all coupled regions with the same name. For instance, the parameter will have the same common value among all *caudate*, *putamen*, etc regions. Note that with this configuration the states of the individual parameter fit boxes is not relevant, the parameter will be modified in all coupled regions.

## Regions Selection and Fitting

The next step is defining the TACs included in the coupled fit on the **Regions selection** pane as illustrated below.




The list contains all regions which are defined in the coupled studies with *exactly the same names*. Initially all regions are selected for inclusion. Regions can selectively be unselected by checking their box. When working with large number of regions (e.g. from atlas definitions) the context menu may be helpful which can be opened by right clicking into the list. It contains **Select all** and **Select none** for quickly selecting or de-selecting all regions, respectively.

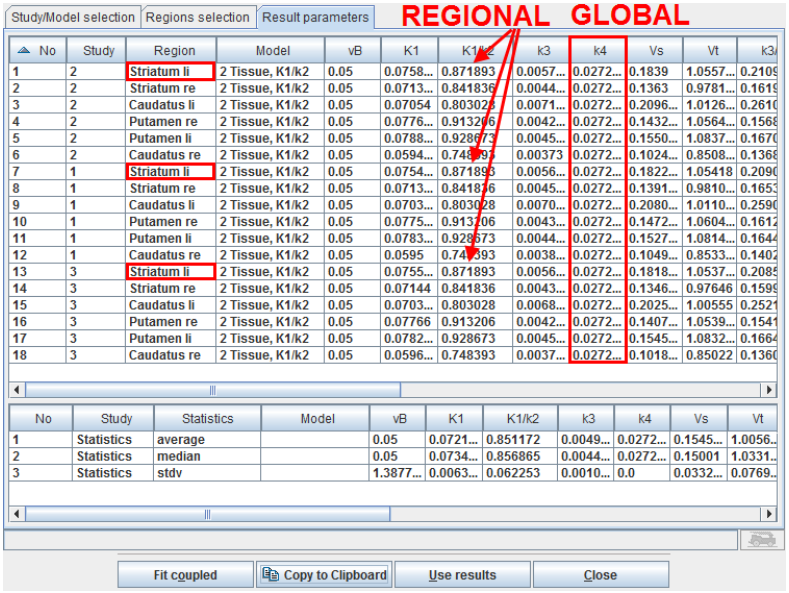
Coupled fitting is started using the **Fit coupled** button and proceeds as follows:

- A global target curve is created by stacking the TACs of all coupled regions from the selected studies (valid points only).
- The corresponding weights are calculated according to the weighting configuration for each TAC.
- A table of fitted parameters is formed by entering the **GLOBAL** parameters once, the **REGIONAL** parameters once per region, and adding all the other fit enabled parameters in the coupled regions. The initial values of common parameters are taken from the first study, for the other parameters from the individual regional models. Note that **Fit blood parameters** has no impact on fitting, all the parameters of the blood curves remain fixed.

The optimizer calculates all model curves, creates the global result curve corresponding to the target curve, weighs all the residuals and forms the global sum of squares as the figure of merit. The parameters are adjusted until the cost function has been minimized. If the box **Random Fits** is checked, the fitting will be repeated as many times as specified with randomly changed starting parameters and the result with minimal global chi square returned.

## Result Parameters

After the coupled fit has completed the resulting parameters in the coupled regions are listed on the **Result parameters** pane which is immediately shown.




| No | Study | Region | Model | vB | K1 | K1/k2 | k3 | k4 | Vs | Vt | k3 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | Striatum li | 2 Tissue, K1/k2 | 0.05 | 0.0758... | 0.871893 | 0.0057... | 0.0272... | 0.1839 | 1.0557... | 0.210 |
| 2 | 2 | Striatum re | 2 Tissue, K1/k2 | 0.05 | 0.0713... | 0.841836 | 0.0044... | 0.0272... | 0.1363 | 0.9781... | 0.161 |
| 3 | 2 | Caudatus li | 2 Tissue, K1/k2 | 0.05 | 0.07054 | 0.803028 | 0.0071... | 0.0272... | 0.2096... | 1.0126... | 0.261 |
| 4 | 2 | Putamen re | 2 Tissue, K1/k2 | 0.05 | 0.0776... | 0.913206 | 0.0042... | 0.0272... | 0.1432... | 1.0564... | 0.156 |
| 5 | 2 | Putamen li | 2 Tissue, K1/k2 | 0.05 | 0.0788... | 0.928673 | 0.0045... | 0.0272... | 0.1550... | 1.0837... | 0.167 |
| 6 | 2 | Caudatus re | 2 Tissue, K1/k2 | 0.05 | 0.0594... | 0.748393 | 0.00373 | 0.0272... | 0.1024... | 0.8508... | 0.136 |
| 7 | 1 | Striatum li | 2 Tissue, K1/k2 | 0.05 | 0.0754... | 0.871893 | 0.0056... | 0.0272... | 0.1822... | 1.05418 | 0.209 |
| 8 | 1 | Striatum re | 2 Tissue, K1/k2 | 0.05 | 0.0713... | 0.841836 | 0.0045... | 0.0272... | 0.1391... | 0.9810... | 0.165 |
| 9 | 1 | Caudatus li | 2 Tissue, K1/k2 | 0.05 | 0.0703... | 0.803028 | 0.0070... | 0.0272... | 0.2080... | 1.0110... | 0.259 |
| 10 | 1 | Putamen re | 2 Tissue, K1/k2 | 0.05 | 0.0775... | 0.913206 | 0.0043... | 0.0272... | 0.1472... | 1.0604... | 0.161 |
| 11 | 1 | Putamen li | 2 Tissue, K1/k2 | 0.05 | 0.0783... | 0.928673 | 0.0044... | 0.0272... | 0.1527... | 1.0814... | 0.164 |
| 12 | 1 | Caudatus re | 2 Tissue, K1/k2 | 0.05 | 0.0595 | 0.748393 | 0.0038... | 0.0272... | 0.1049... | 0.8533... | 0.140 |
| 13 | 3 | Striatum li | 2 Tissue, K1/k2 | 0.05 | 0.0755... | 0.871893 | 0.0056... | 0.0272... | 0.1818... | 1.0537... | 0.208 |
| 14 | 3 | Striatum re | 2 Tissue, K1/k2 | 0.05 | 0.07144 | 0.841836 | 0.0043... | 0.0272... | 0.1346... | 0.97646 | 0.159 |
| 15 | 3 | Caudatus li | 2 Tissue, K1/k2 | 0.05 | 0.0703... | 0.803028 | 0.0068... | 0.0272... | 0.2025... | 1.00555 | 0.252 |
| 16 | 3 | Putamen re | 2 Tissue, K1/k2 | 0.05 | 0.07766 | 0.913206 | 0.0042... | 0.0272... | 0.1407... | 1.0539... | 0.154 |
| 17 | 3 | Putamen li | 2 Tissue, K1/k2 | 0.05 | 0.0782... | 0.928673 | 0.0045... | 0.0272... | 0.1545... | 1.0832... | 0.166 |
| 18 | 3 | Caudatus re | 2 Tissue, K1/k2 | 0.05 | 0.0596... | 0.748393 | 0.0037... | 0.0272... | 0.1018... | 0.85022 | 0.136 |

| No | Study | Statistics | Model | vB | K1 | K1/k2 | k3 | k4 | Vs | Vt |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Statistics | average | | 0.05 | 0.0721... | 0.851172 | 0.0049... | 0.0272... | 0.1545... | 1.0056.. |
| 2 | Statistics | median | | 0.05 | 0.0734... | 0.856865 | 0.0044... | 0.0272... | 0.15001 | 1.0331.. |
| 3 | Statistics | stdv | | 1.3877... | 0.0063... | 0.062253 | 0.0010... | 0.0 | 0.0332... | 0.0769.. |

Note in the example above that the **REGIONAL** parameter $K_1/k_2$ has the same value in all regions with the same name, whereas the **GLOBAL** parameter $k_4$ has the same value in all regions.

The results can be prepared for use in another program such as MS Excel with the **Copy to Clipboard** button. The **Use results** button transfers the result parameters together with their standard errors to the individual models and closes the dialog window, whereas the results are discarded by the **Close** button.

# Special Processing Modes

## Monte Carlo Simulations

The purpose of performing Monte Carlo simulations in kinetic modeling is to get information about the standard error of the parameter values found in a fit. There are two different kinds of sources which contribute to the uncertainty of the parameters:

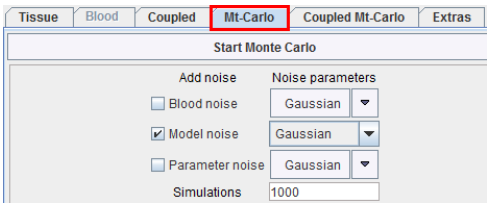
**1)** All the input data are measured and hence prone to measurement errors.

**2)** The model may contain more parameters than supported by the data, so that the effect of one parameter may be counter-balanced by another parameter.

The paradigm used for performing Monte Carlo simulations is described by Flannery et al. [11]. The basic idea is to simulate a series of measurements and statistically analyze the results when modeling these synthetic "measurements".

In PKIN Monte Carlo simulations can be performed for compartment models applied to a single tissue (**Mt-Carlo**) and models coupled across several tissues (**Coupled Mt-Carlo**) by selecting the respective panes.

### Single Tissue



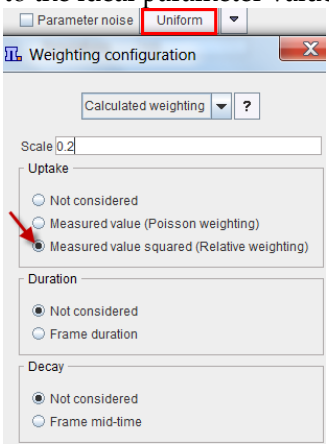

Three types of "noise" can be defined. For each "noise" the distribution type as well as the variance has to be configured. After selecting the distribution a dialog window appears for defining the variance as described in the ***Residual weighting*** (on page 45) for model fitting.

**1)** **Blood noise** to be added to the blood data for simulating noisy input curves. This option is only supported for blood models of type **Measured**.

**2)** **Model noise** to be added to the tissue model curve for simulating TAC noise. Note that here only the noise distribution needs to be selected. The noise variance is adopted from the **Weigthing** tab on the **Tissue** pane.

**3)** **Parameter noise** to be added to the starting parameters for disturbing the starting conditions from the ideal solution. The setting below is recommended to add 20% noise

to the ideal parameter values.



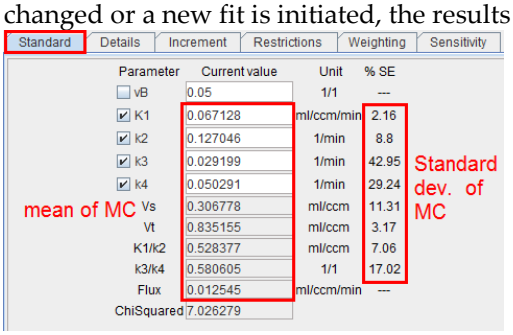

Three distributions are available for noise generation, **Gaussian**, **Poisson** and **Uniform**. They are applied for each individual measurement with the prescribed variance. There are definitions with constant standard deviations for all time points, and others with variable standard deviations.

When the **Start Monte Carlo** button is selected the following processing starts:

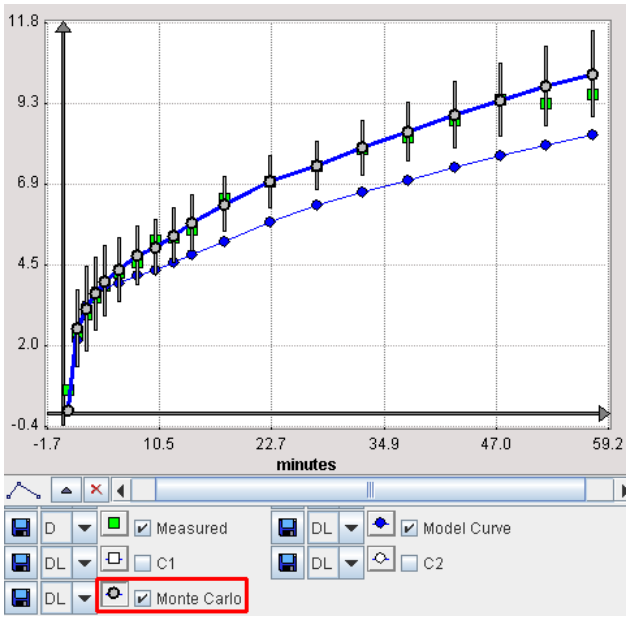
**1)** An initial fit is performed. From then on it is assumed that the result parameters represent the "true" parameters, and the model curve represents the "true" measurement curve.

**2)** The number of **Simulations** times a noisy data set is prepared according to the definitions and then fitted. Noise is added to the "true" curve (and optionally the input curve). The "true" parameters, optionally disturbed by some noise, are used as starting values, and the fit to the noisy data performed. The resulting parameter values are recorded.

**3)** After all runs have completed, the distribution of the result parameters is analyzed resulting in a mean and a standard deviation value for each fitted parameter. These values are shown on the **Tissue** page, and the model curve with the mean parameters is shown. Often, it does not follow the measurement as well as with the fitted parameters. The Monte Carlo results should now be saved, because as soon as a parameter is changed or a new fit is initiated, the results get overwritten.



It is possible to visualize a summary of the fit results during the Monte Carlo runs by switching back from the **Tissue** to the **Mt-Carlo** pane. In the curve display, a new curve **Monte Carlo** appears with vertical bars. The end points of these bars mark the minimal and the maximal value that any of the resulting model curves reached at a particular time point.




### Several Tissues Coupled

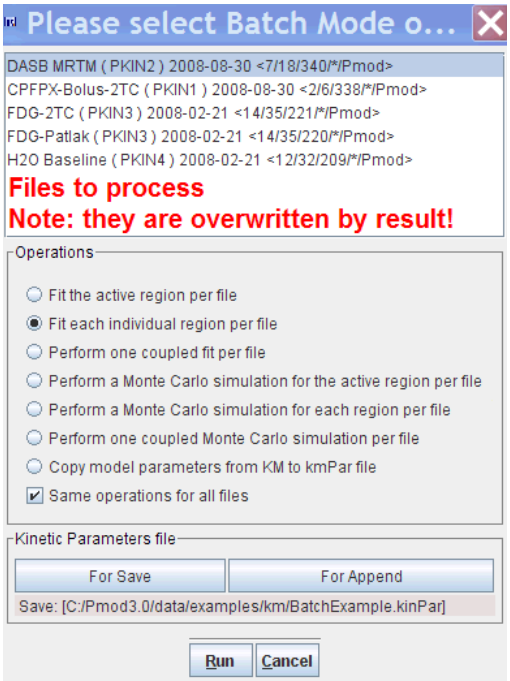
The same principle as for the single tissue Monte Carlo simulation applies to the Coupled Monte Carlo simulation (**Coupled Mt- Carlo** tab). In the upper section, the coupled parameters and the regions to couple are defined. In the lower section, blood and parameter noise can be specified. When starting, an initial coupled fit is performed to find the "true" parameters and the "true" model curves. Then, noisy curves are generated and coupled fits performed. At the end, the mean and standard errors are available as the regional parameters.

## Batch Mode

The **Batch Mode** serves for running a sequence of fits or Monte Carlo simulations with pre-configured files. In principle it consists of the following steps:

- The user first selects a list of **.km** files configured with the right model definitions,
- defines the type of processing,
- specifies a result file into which the result parameters will be saved,
- and starts the batch run.

To set up batch processing select the **Batch Mode** entry from the **Menu**. A multiple-file selection dialog is opened which allows to add **.km** files from a database or from different directories. For file-based selection, browse to the directories, select the files to be processed, and bring them to the **Selected** area using **Add to SELECTED**. After selecting **Open** the following batch configuration dialog appears.




It shows the list of selected .km files at the top. If the box **Same operations for all files** is not checked, a file can be selected in the list and an action defined individually. If it is checked, the same operation is performed for all files. The operations are:

| | |
|---|---|
| **Fit active region per file** | Only the TAC of the active region (ie. the current region when saving the .km file) is fitted with the model as defined in the .km file. |
| **Fit each individual region per file** | All regional TACs are fitted with the models as defined in the .km file. |
| **Perform one coupled fit** | Performs coupled fitting with the model and coupling as defined in the .km file. |
| **Perform a Monte Carlo simulation for the active region** | Using the noise and model definitions in the file a Monte Carlo simulation of the current TAC is performed. |
| **Perform a Monte Carlo simulation for each region** | As above, but applied to all regional TACs. Can be used to evaluate the sensitivity at different parameter combinations. |

| | |
|---|---|
| **Perform a coupled Monte Carlo simulation** | Monte Carlo simulation using coupled fitting as defined in the file. |
| **Copy model parameters from KM to kinPar file** | Just a convenience to summarize the parameters of a series of files into one tabular text file. Note that a result file must first be defined for the option to become available. |

The **For Save** and the **For Append** buttons can be used to specify a file for saving the result parameters of the batch run.

After the **Run** button has been activated each file is loaded, the processing performed, the resulting parameters written into the result text file, and **the input .km file is overwritten by the result.**

The recommended approach for batch processing therefore is:

- Prepare all **.km** files to be processed with appropriate configurations (# iterations, coupling, Monte Carlo parameters, etc) in an *input* directory,
- copy all of them to a new *output* directory,
- select the files in the *output* directory for batch processing
- and **Run**.

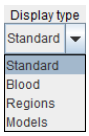
With this strategy the original files are maintained for a different usage.

# Convenience Tools

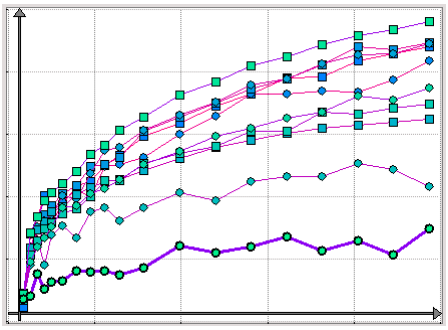
In the lower right part of PKIN there is an ensemble of user interface elements supporting some auxiliary tasks.

## Changing Display Types

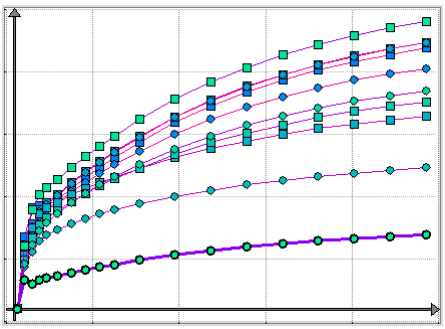
The **Display type** selection allows choosing which information is shown in the main curve area.



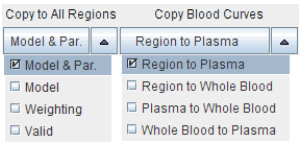

**Standard** shows all curves related to the current region. **Blood** shows only the blood measurements. **Regions** shows all regional TACs,



and **Models** all fitted model curves



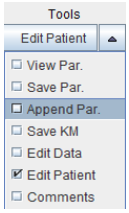
# Copy Operations




**Copy to all Regions** This multi-function button can be used to propagate a model from the current region to all regions in the study.
**Model & Par.** copies the model with the parameters (which can then be used as starting values for **Fit all regions**).
**Model** copies the model structure, with the current parameters.
**Weighting** copies the current definition how the residuals are weighted.
**Valid** copies the definition of the currently valid points to all regional TACs.

**Copy Blood Curves** This multi-function button allows transferring activity curves between the tissue and the blood.
**Region to Plasma** copies the current TAC to the input curve.
**Region to Whole Blood** copies the current TAC to the whole blood curve.
**Plasma to Whole Blood** copies the input curve to the whole blood curve.
**Whole Blood to Plasma** copies the whole blood curve to the input curve.

# Auxiliary Tools




The **Tools** multi-function button is particularly helpful, if the PKIN tool is opened as an intermediate dialog and hence has no menu available. In this case, **Save KM**, **Save Par**, **Append Par** just allow to save the data as a .km file, as a parameter summary text file, and to append to a latter file.

**View Par** opens a dialog box and shows a quick summary of all regional model parameters.

| Region | vB | K1 | K1/k2 | k3 | k4 | DV | DVtot | k3/k4 |
|---|---|---|---|---|---|---|---|---|
| temp-med-li | 0.05 | 0.9863... | 0.290259 | 1.0056... | 0.0126... | 23.0990... | 23.389292 | 79.580636 |
| temp-med-re | 0.05 | 0.5799... | 0.540739 | 0.8762... | 0.0292... | 16.1950... | 16.735745 | 29.949771 |
| thal-re | 0.05 | 1.0174... | 0.644251 | 0.9772... | 0.0226... | 27.7964... | 28.440699 | 43.145348 |
| par-li | 0.05 | 0.3570... | 0.670814 | 0.77528 | 0.0426... | 12.2008... | 12.871701 | 18.188176 |
| thal-li | 0.05 | 0.6378 | 0.762385 | 1.3881... | 0.0390... | 27.1281... | 27.890519 | 35.583258 |
| caud-li | 0.05 | 0.8298... | 0.848832 | 0.7026... | 0.0256... | 23.2505... | 24.099408 | 27.391274 |
| front-lat-li | 0.05 | 0.5039... | 1.155919 | 0.6253... | 0.05029 | 14.3736... | 15.529568 | 12.434827 |
| front-med-re | 0.05 | 0.5727... | 1.203624 | 0.6377... | 0.0527... | 14.5465... | 15.750216 | 12.085657 |
| put-re | 0.05 | 0.5862... | 1.50568 | 0.6709... | 0.0370... | 27.2841... | 28.789807 | 18.120805 |
| put-li | 0.05 | 0.5614... | 1.534177 | 0.6394... | 0.0361... | 27.1606... | 28.694798 | 17.703702 |
| par-re | 0.05 | 0.4298... | 1.641537 | 0.4168... | 0.0484... | 14.1228... | 15.764425 | 8.603453 |
| front-med-li | 0.05 | 0.5047... | 1.908844 | 0.5068... | 0.0702... | 13.7693... | 15.678224 | 7.213464 |
| cer-li | 0.05 | 0.5251... | 1.966003 | 0.4807... | 0.0802... | 11.7789... | 13.744926 | 5.991299 |
| cer-re | 0.05 | 0.5240... | 1.973798 | 0.3827... | 0.0562... | 13.4274... | 15.401288 | 6.802869 |
| temp-lat-re | 0.05 | 0.4187... | 2.25203 | 0.3257... | 0.0524... | 13.9954... | 16.247434 | 6.214573 |
| temp-lat-li | 0.05 | 0.4478... | 2.33575 | 0.2849... | 0.0478... | 13.9084... | 16.244231 | 5.95461 |
| pit | 0.05 | 0.3535... | 2.339431 | 0.1154... | 0.0233... | 11.5835... | 13.923019 | 4.951455 |
| caud-re | 0.05 | 0.6627... | 2.750456 | 0.2296... | 0.0203... | 31.0287... | 33.779252 | 11.281328 |
| front-lat-re | 0.05 | 0.4339... | 2.913144 | 0.2868... | 0.0617... | 13.5437... | 16.45693 | 4.649198 |
| pons | 0.05 | 0.3388... | 3.884893 | 0.1211... | 0.0233... | 20.1306... | 24.015535 | 5.181775 |
| occ-rad-li | 0.05 | 0.4232... | 4.6675 | 0.1550... | 0.0415... | 17.4211... | 22.088604 | 3.732427 |
| occ-med-re | 0.05 | 0.5072... | 5.070544 | 0.1634... | 0.0623... | 13.2920... | 18.36256 | 2.621418 |
| occ-rad-re | 0.05 | 0.3917... | 5.11826 | 0.2015... | 0.0714... | 14.4310... | 19.549334 | 2.819528 |
| occ-med-li | 0.05 | 0.4517... | 6.759734 | 0.1000... | 0.0622... | 10.8642... | 17.623968 | 1.607199 |

| Statistic | vB | K1 | K1/k2 | k3 | k4 | DV | DVtot | k3/k4 |
|---|---|---|---|---|---|---|---|---|
| average | 0.05 | 0.5435... | 2.280775 | 0.5029... | 0.04458 | 17.763... | 20.044645 | 15.492002 |
| median | 0.05 | 0.5072... | 1.966003 | 0.4807... | 0.0478... | 14.431... | 17.623968 | 8.603453 |
| stdv | 1.3877... | 0.1760... | 1.654951 | 0.3293... | 0.01786 | 6.1589... | 5.800757 | 17.242344 |

Save Par. Copy to Clipboard Close

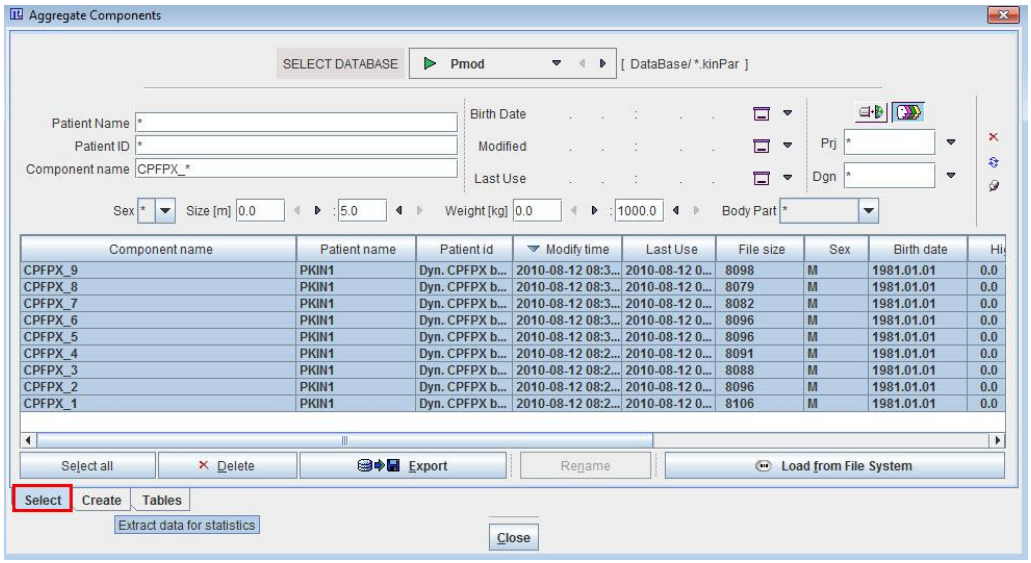
**Edit Data** allows editing/processing the data values and generating new TACs, for instance by averaging TACs or adding noise, see ***below*** (on page 73).

**Edit Patient** allows changing the demographic patient data as well as the radionuclide, see ***below*** (on page 75).

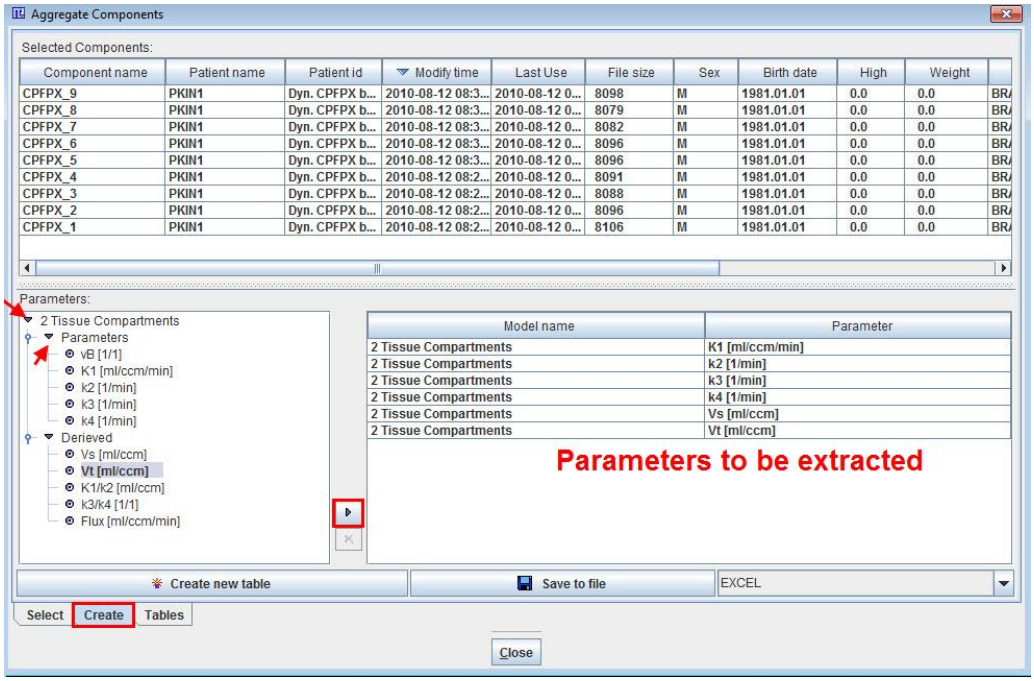
**Comments** opens a dialog window for entering arbitrary comments, see ***below*** (on page 75).

# Parameters Aggregation

The PKIN **Menu** contains an entry **Parameters Aggregation**. Its purpose is to concentrate the parameter values which have been saved in **KM Parameters Files** for statistical analysis. It opens a dialog window with three tabs as illustrated below.




The **Select** pane allows defining the files from which the parameters are extracted. The may be available in a database as in the example, or alternatively using the **Load from File System** button to define the directory were the files reside. All appropriate data sets are listed. Select all entries to be used, and then switch to the **Create** pane.




The **Selected Components** list again shows which data sets have been selected. The **Parameter** section has a tree structure and initially shows the different models which have been used in any of the data sets. The parameters of these models can be shown by double-

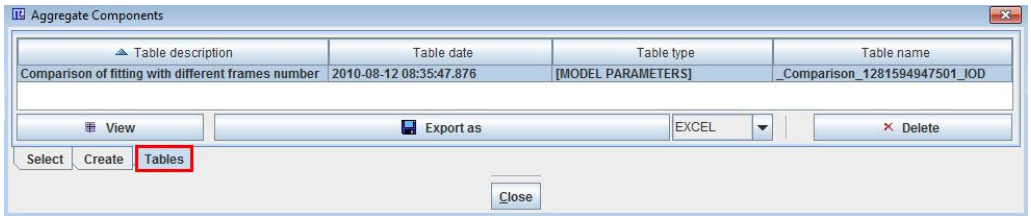
clicking the arrow buttons as indicated above. Any of these parameters can be selected and copied to the right for defining which parameters shall be extracted from the data. The copy operation operates on all levels of the tree. With the top node selected, all parameters are copied at once.

Data extraction is started can be started in two ways:

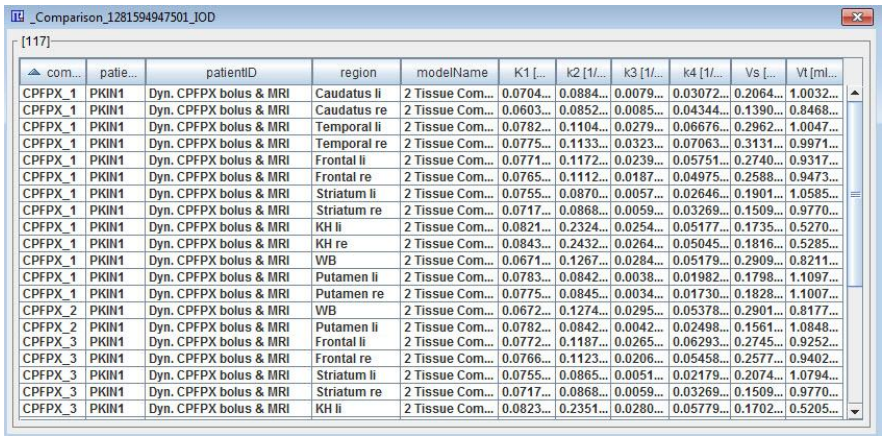
1) **Save to file**: This function extracts the parameters and saves them in a file which has to be specified by the user. There are the file formats **EXCEL**, **TABULATED**, **XML** available which has to be selected beforehand. Default output is **EXCEL**.

2) **Create new table**: This function extracts the parameters and saves them in a database table which has to be named by the user.

The created database tables can be seen on the **Tables** tab.




Tables can be deleted with the **Delete** button, exported into files with the **Export as** button, and inspected with the **View** button as illustrated below.



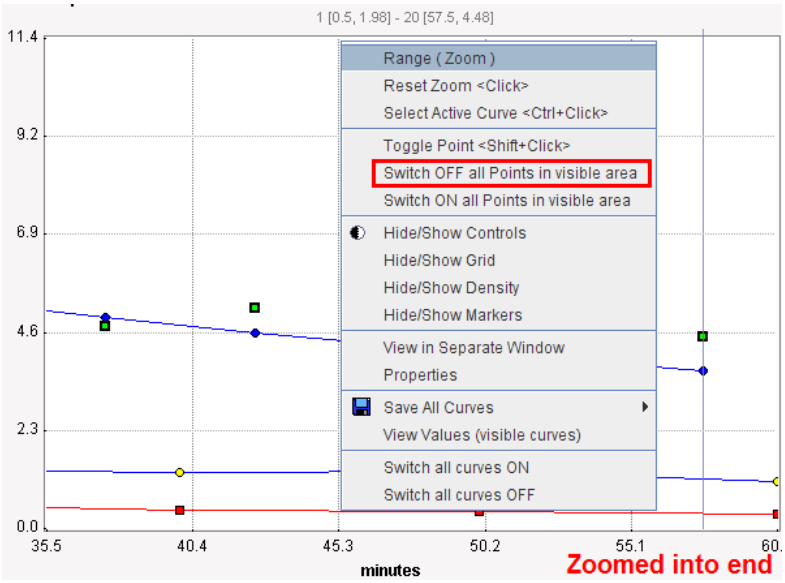

# Editing Facilities

## Disable Measurements for Removing Outliers or Shortening the Fitted Data Segment

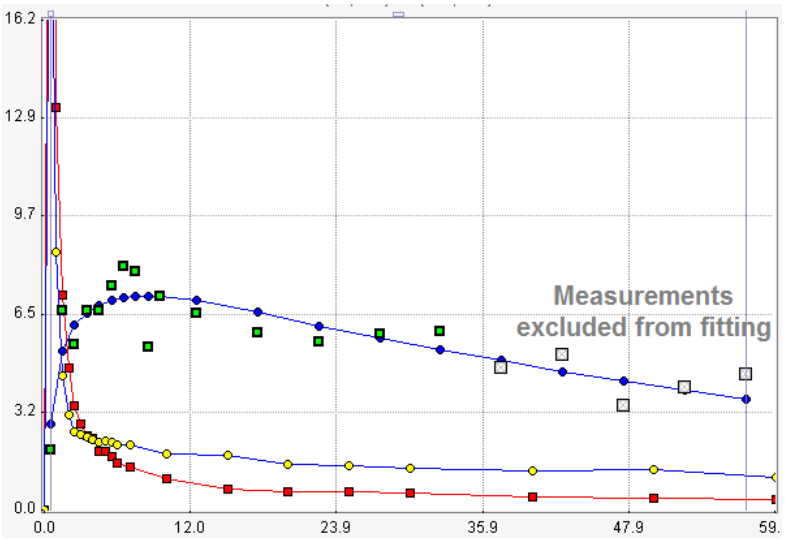
Occasionally there might be the need to disregard sample points when evaluating the matching criterion, for example to exclude an outlier, or to study the stability of model estimates with successive shortening of the acquisition duration.

In PKIN this can be easily achieved by (temporarily) disabling samples. First select the **Measured** curve by selecting it in the controls area or by **CTRL+Click** at a point. The green measurement points must appear highlighted in the display. Then individual points can be

disabled by **SHIFT+Click** on them. For entire ranges it is advised to zoom into the region (drag left mouse button), then activate the context menu (right mouse button) and **Switch OFF all Points in visible area**. This operation is illustrated below




resulting in a "shortened" acquisition for fitting purposes:




Disabled measurements appear in grey. They can again be enabled by a second **SHIFT+Click,** or by **Switch ON all Points in visible area** in the context menu.

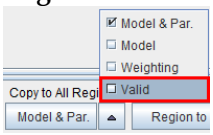
## Testing the Impact of Study Duration on Parameter Estimates

A frequent task is to find out the minimal study duration which allows the reliable estimation of a parameter. Such an analysis can be performed in PKIN as follows:

**1)** Ensure that the appropriate model has been configured for all regional TACs and **Fit all Regions**. Save the result parameters to a file using **Menu/Save KM Parameters File/Save**.

2) Disable the last valid measurement for a regional TAC.

3) Propagate this definition of valid points to all regional TACs using **Copy to All Regions/Valid** as illustrated below:



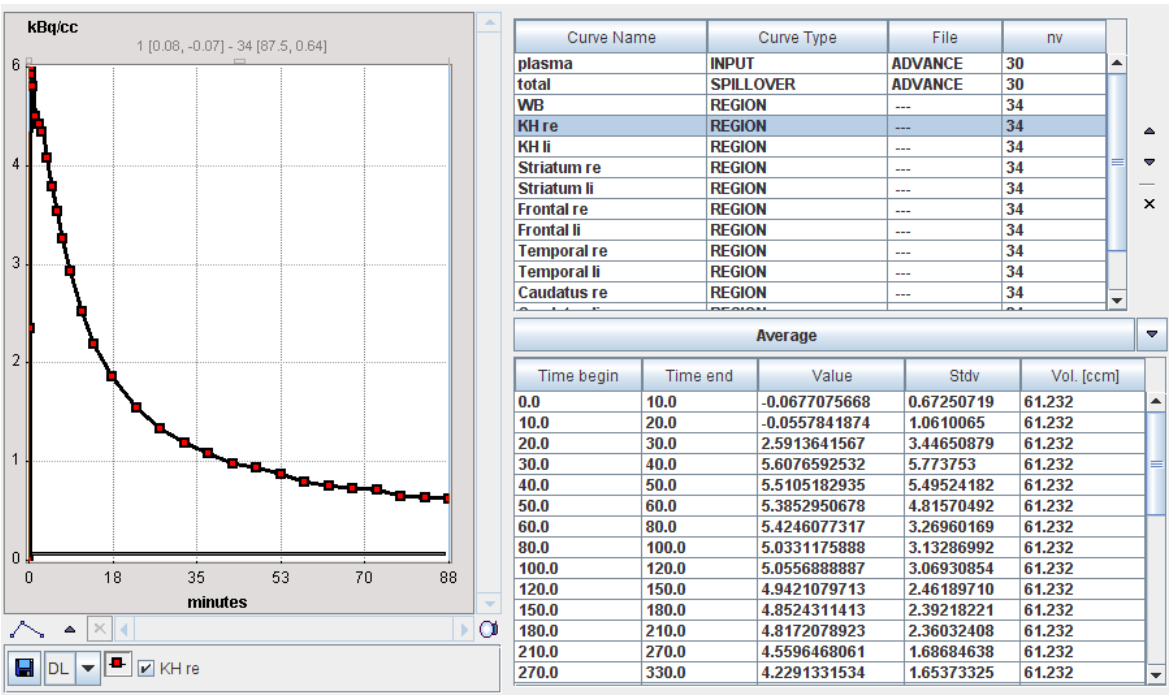

4) Fit again the model in all regions using the **Fit all Regions** button.

5) Add the parameter results from the shortened acquisition to the previous results using **Menu/Save KM Parameters File/Append**.

Repeat steps 2-5 continually shortening the acquisition until the parameter estimates degenerate. Then all data is available in a single file which can be opened in a program such as MS Excel for a statistical analysis.

# Edit Data and Create New Curves

The **Edit Data** button in the **Tools** list brings up a dialog which allows to examine and manipulate the TAC data of the current data set.

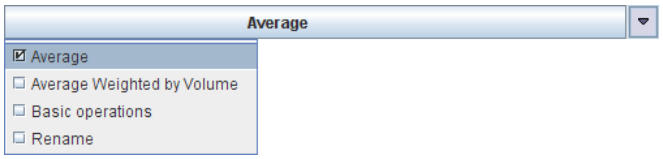



The upper section lists the different curves. The blood-related curves are at the top, then come the regional TACs. The arrows to the right can be used to change the TAC ordering, and a TAC can be removed by the x button.

The lower section lists the data of the selected curve. Shown for each sample are the acquisition start and end times, the measurement value (usually the VOI average), its standard deviation (the VOI stdv, if available), and the VOI volume. Note that the volume may vary if the VOI definition changes throughout the time course.

The values of the tissue TACs can be interactively edited by clicking into a cell and changing the number. Note: due to a system problem, **Windows** users experience a strange behavior: they have to click across different *columns* to get into the edit mode.

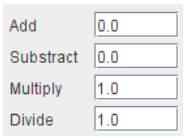
The configuration button between the lists houses the following operations:




**Average** When several curves are selected, this button allows calculating the average TAC.

**Average Weighted by Volume** This TAC curve averaging takes into account the VOI volumes, so big VOIs will have more weight during averaging.

**Basic operations** Applies simple arithmetic operations

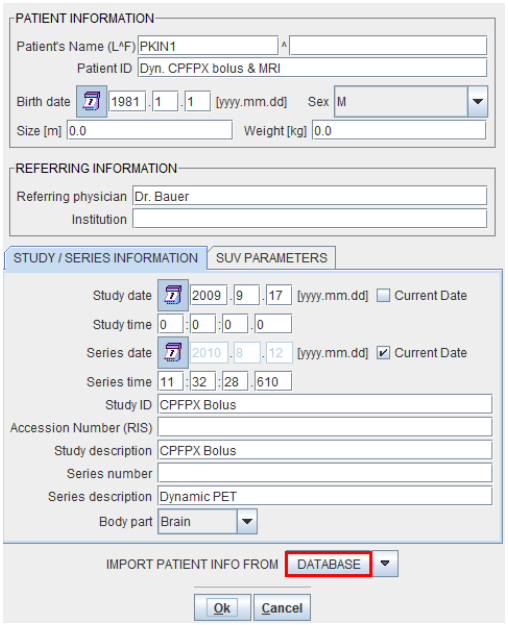



to the currently selected curve.

**Rename** For renaming of the currently selected curve.

# Edit Patient and Change Isotope

The **Edit Patient** button in the **Tools** list brings up a dialog window which allows you to examine and change the demographic data of the current data set.

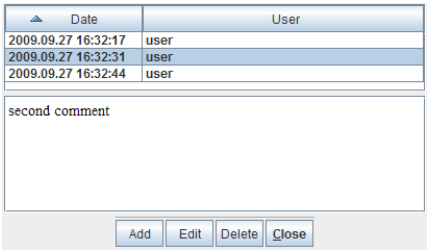



In case the TAC data was transferred from PVIEW to PKIN, this information is automatically filled in from the image data (if available in the data format). However, the contents can also be edited and saved if required. If the patient is already in the database, the **IMPORT PATIENT INFO FROM** facility can be used. With the **DATABASE** button a selection window opens which allows choosing an image series from the database. The required information will be retrieved and filled into the text fields.

Note the **SUV PARAMETERS** tab which gives access to the isotope definition.

# Comment a Data Set

The **Comments** button in the **Tools** list brings up a dialog which allows incrementally adding descriptive text to the data set being processed. It opens a dialog window with two areas: a list of comment entries with date and name of the creator in the upper part, and the actual text of the selected comment entry in the lower part.




To create a new comment entry select **Add**, type the comment into the lower text window, and complete editing by **Set**. This operation creates a new list entry which can be selected to show its contents, changed with the **Edit** button, or removed with **Delete**.

Note that you have to use **Save KM File** to include updated comments permanently into the data set.

# Synthetic Data Generation

The compartment models in PKIN can be employed for creating data sets representing a perfect measurements with a certain acquisition protocol of the tissue and blood activities.

## Synthetic Modeling Study for PKIN

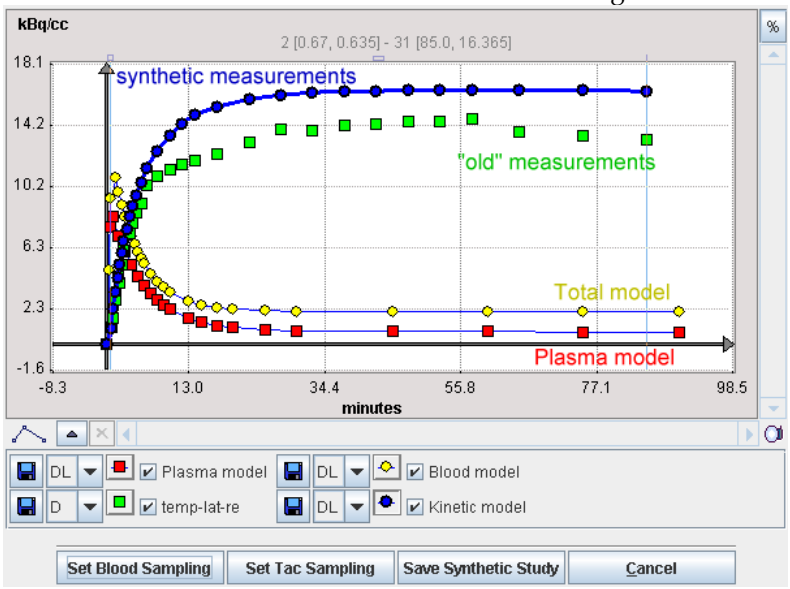
PKIN always shows the model curve given the loaded input curve(s) and the configured regional kinetic model with the timing of the current study. The user may modify any of the defining parameters and observe the effect on the model curve, which represents the expected PET measurement. With the **Create Synthetic KM Study** facility well-defined and smooth TACs and blood curves can be generated which represent an ideal acquisition.

### *Synthetic Modeling Study Generation*

**1)** Define a suitable kinetic model (compartment model, parameter values) in all regions.

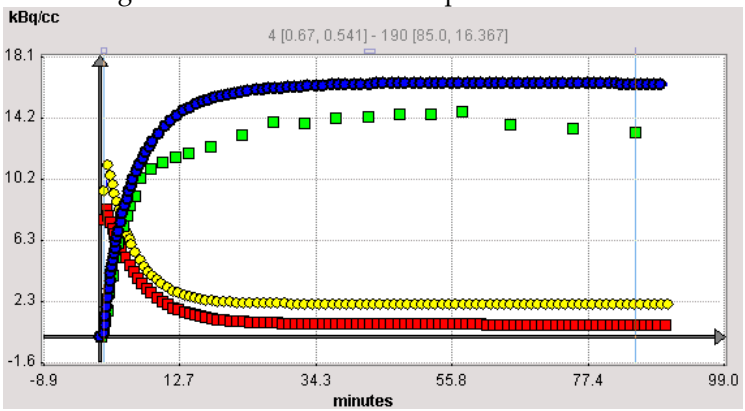
**2)** Define a suitable input curve model, for instance a smooth curve fitted to the actual input curve.

**3)** Select the entry **Synthetic KM Study** in the **File** menu. A dialog appears showing the blood models and the model curve of the current region.




**4)** Initially all curves have the original sampling times. To modify sampling, use the buttons **Set Blood Sampling** and **Set Tac Sampling**. For instance, very fine sampling

allows to generate smooth curves for publication or simulation purposes.




**5)** When **Save Synthetic Study** is activated, all regional TACs are recalculated with the current sampling, the old measurements are replaced by the values of the model curve, the original blood values are replaced by the values calculated with the current blood models, and the data is saved in a file specified by the user. Then, the original data are shown again.

**6)** Finally, to see and work with the synthetic study, load the created file. The synthetic model curves are now the measured TACs, and the resampled blood curves have the **Measured** model associated. So any underlying model of the blood curve (which has been used for synthetic model calculation) gets lost. This may cause small deviations between the calculated model curve and the saved synthetic TAC, depending on the density of blood sampling.

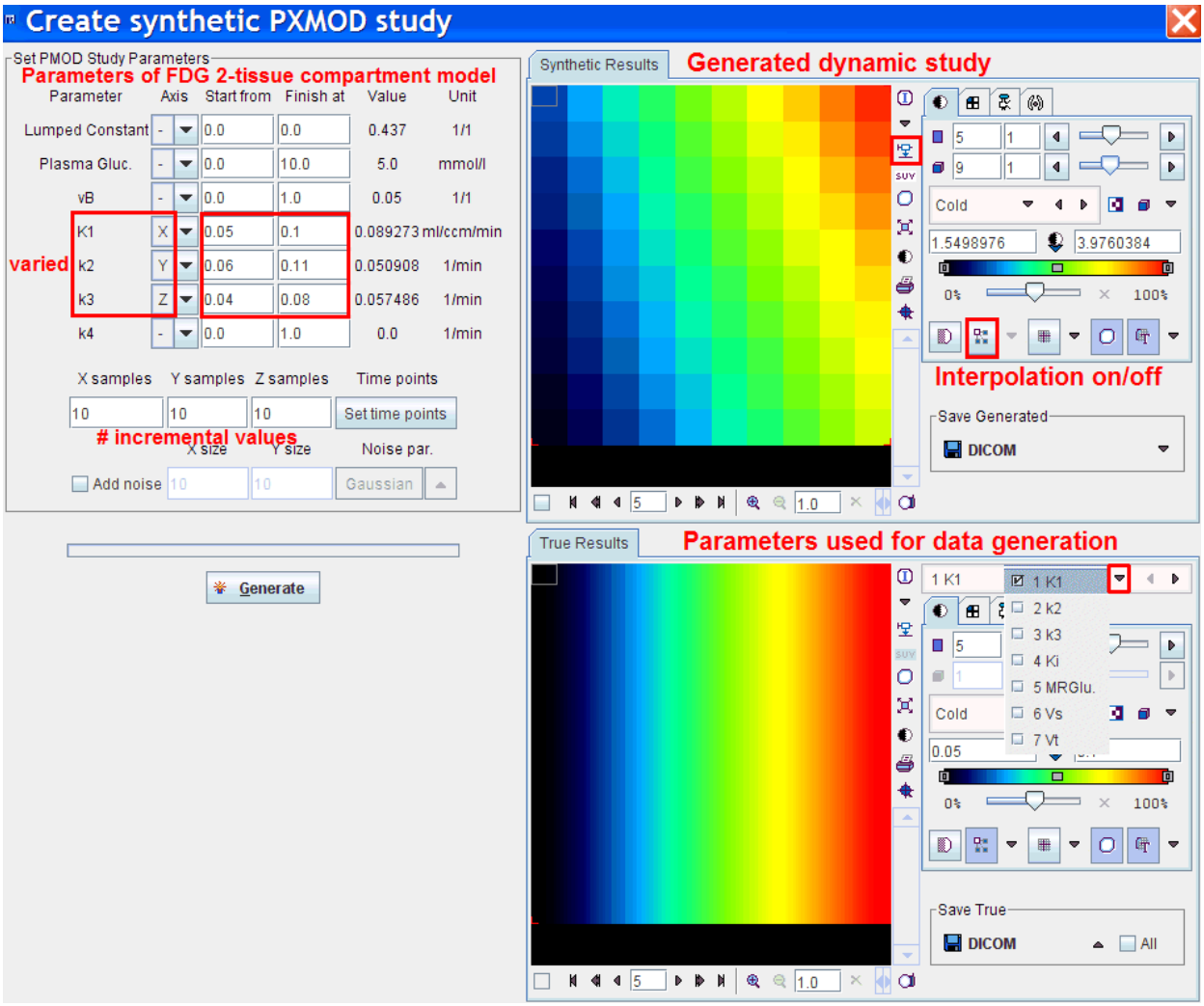
## Synthetic Imaging Study for PXMOD Tests

**Create Synthetic PXMOD Study** is an extension of the **Create Synthetic KM Study** approach. The idea is that synthetic model curves can be generated for many different "tissues", ie. combinations of model parameters, at once. These curves are compiled into images, so that a synthetic study is generated which has a different combination of model parameters in each pixel.

For instance, FDG TACs can be simulated by loading a FDG .km file, selecting the FDG 2-tissue compartment model and using the parameter ranges

| Parameter | From | To |
|---|---|---|
| $K_1$ | 0.05 | 0.1 |
| $k_2$ | 0.06 | 0.11 |
| $k_3$ | 0.04 | 0.08 |
| $k_4$ | fixed to 0.0 | |

To enter these parameter ranges select **Create Synthetic PMOD Study** from the **File**. The following dialog appears showing the parameters of the current model.




To define the synthetic study the following configurations must be set:

- Which parameters are varied along the X, Y, and Z axis,
- the value ranges of the varied parameters,
- the number of parameter increments to cover the ranges,
- the acquisition times; initially the times of the loaded .km study are used, but they can be changed using the **Set time points**.

With **Generate** the model curves of all parameter combinations are generated and the data arranged as a 4-dimensional study. This synthetic study, which is suitable for pixel-wise modeling, is shown in the upper image display. In the example above the interpolation has been disabled to show the 10x10 layout of parameter combinations in plane. Use the **Save Generated** button to save the study in any supported output format.

The lower image display contains the true parameter images. These generation parameters can be saved using the **Save True** button. They will be helpful for the analysis of the outcome from a pixel-wise analysis of the synthetic study.

Chapter 2

# PKIN Configuration

There are two places where the functionality and layout of PKIN can be configured. The available models are managed on the general configuration panel, the layout with the local configuration button of the PKIN tool.

## In This Chapter



# Global Configuration with Config Button

Use the

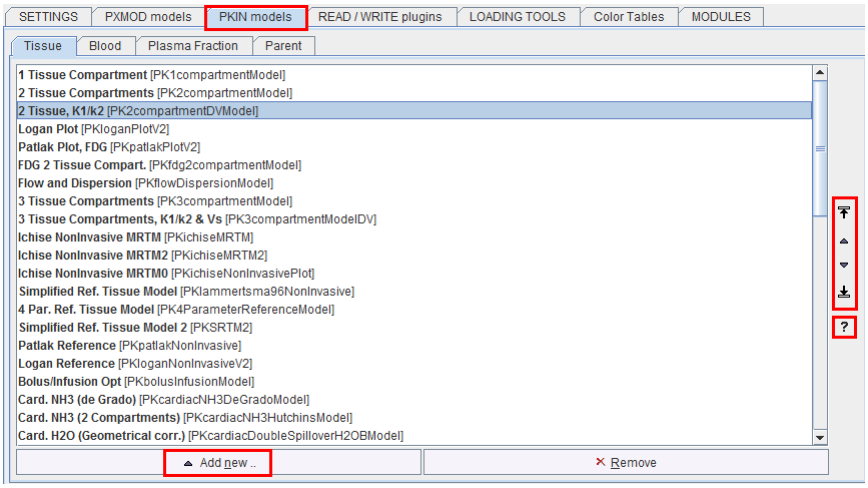
on the PMOD ToolBox to show the general configuration dialog.

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

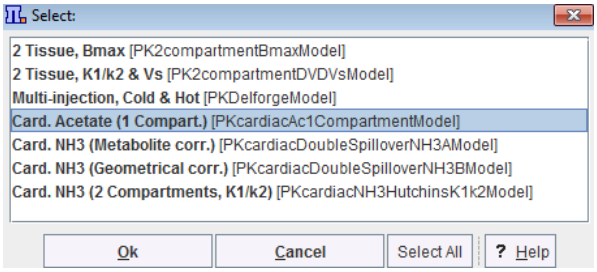
### PKIN Models

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

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



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




## Contents of the different Plug-In Tabs

**PXMOD models** Configuration of the models which appear in the pixel-wise modeling (PXMOD) tool.

**PKIN models** Configuration of the models which appear in the modeling tool for time-activity curves (PKIN). **Tissue** contains the actual kinetic models for the tissue TACs, **Blood** the models for interpolation of the blood activity, **Plasma fraction** the models for plasma fraction activity and **Parent** the models for metabolite correction.

**READ/WRITE plug-ins** Configuration of the image data file formats. Note that only a subset ot the formats can be written.


**LOADING TOOLS** Configuration of image processing filters usable during loading.

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

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

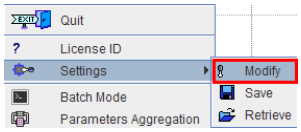
```
# R G B
0 0 0
0 2 2
0 4 4
```

etc.

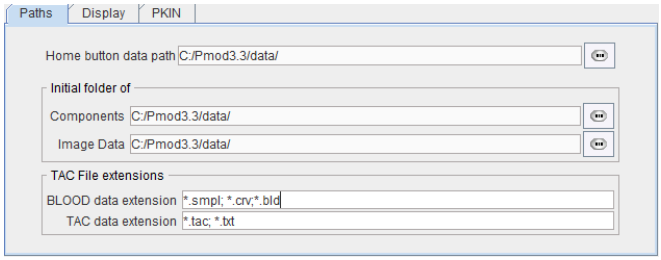
System color tables cannot be removed or arranged in a different order.

# Local PKIN Configuration

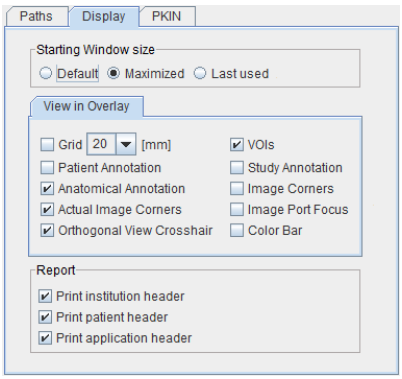
The configuration of PKIN can be adjusted by **Menu/Settings/Modify**




or using the configuration button from the status line. It opens the following dialog with the current definitions, which can be modified. The **Paths** tab allows setting the initial data paths of file-based loading as well as the file extension filters.

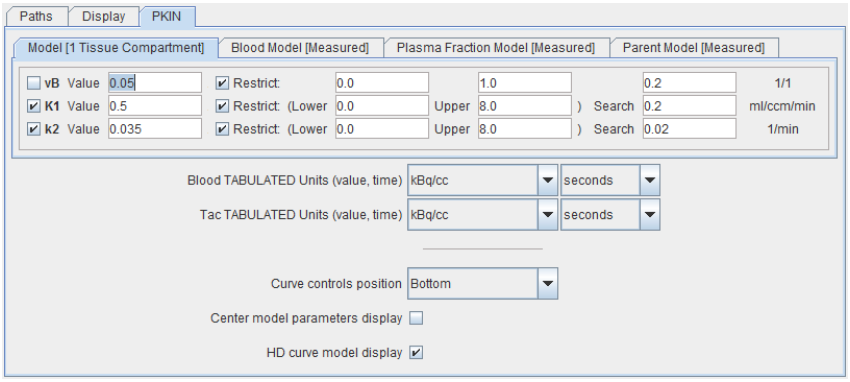



The **Display** pane gives access to the settings of the initial PKIN appearance and the appearance of the report page.




The **PKIN** pane shows the current models of tissue, whole blood plsma and the parent fraction with their respective default parameters. Changing the parameters here and saving will establish new default parameters.

The next section allows specifying the time and value units of data loaded from text files. If the header lines in the data file do not contain valid units, these units are applied to the imported data.




The lower section serves for modifying the layout:

- **Curve controls position** allows displaying the curve controls to the **Right**, **Left** or at the **Bottom**. Their purpose is to optimize the layout depending on the display aspect ratio. **Left** and **Right** are recommended for wide screens, otherwise **Bottom**.
- **Center model parameters display**: if this box is enabled the parameters area is centered vertically within the available space.
- **HD curve model display**: If this box is checked the model curves are calculated for display purposes at many intermediate points, not just at the measurement times. The result is a smooth appearance of the model curves. However, when exporting the model curves, these interpolated points may be disturbing. Note that for the fitting only the original acquisition times are used.

Chapter 3

# PKIN Model Reference

PKIN implements different types of models with somewhat different properties.

**1)** Compartment Models require an input curve for the calculation of the expected concentrations in the different compartments. Most of them also support a blood spillover correction term.

**2)** Reference models do not use explicit blood information. Rather, a reference TAC is specified which must satisfy specific criteria. The reference TAC is used to calculate the response in the tissue of interest.

**3)** Non-compartment models perform different types of analyses which are not based on a compartment structure of the model. Most of them use the input curve.

**Note:** It is assumed that all data used has been **decay corrected** to the same time point.

## In This Chapter



# Compartmental Models

## List of PKIN Compartment Models

PKIN features a comprehensive set of compartment models as listed below. The number of tissue compartments ranges from 1 to 3. There are different variants of the same model structure, so that prior information can be entered easily, and that coupling of physiologic parameters across region is possible.

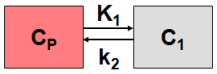
For instance, the 2-tissue compartment model has the standard parameters $K_1$, $k_2$, $k_3$, $k_4$ . An equivalent description is by the parameters $K_1$, $K_1/k_2$, $k_3$, $k_4$ . The advantage is, that the $K_1/k_2$, represents the distribution volume of the non-displacement compartment in tissue (free and non-specifically bound tracer), which can often be assumed to be the same across different tissues. Therefore, $K_1/k_2$ can be included as a common parameter in a coupled fit, hereby reducing the number of fitted parameters and thus potentially improving the identifiability of all.

| Model Name | Description |
|---|---|
| ***1-Tissue Compartment*** (on page 85) | Most basic compartment model with the blood compartment and one tissue compartment. |
| ***2-Tissue Compartments*** (on page 85) | Compartment model with the blood |

| | |
|---|---|
| | compartment and two sequential tissue compartments. Often used for receptor studies. |
| ***FDG-2 Tissue Compartments*** (on page 85) | The 2-Tissue compartment model including the plasma glucose and the lumped constant to calculate the metabolic rate of glucose. |
| ***2-Tissue Compartments, K1/k2*** (on page 85) | The same model as the 2-Tissue compartment model, except that $K_1/k_2$ is used as a model parameter instead of $k_2$. This facilitates coupled fitting. |
| ***2-Tissue Compartments, K1/k2 &Vs*** (on page 85) | The same model as the 2-Tissue compartment model, except that $K_1/k_2$ and the specific distribution volume are used as model parameters instead of $k_2$ and $k_4$. This facilitates coupled fitting and the easy generation of synthetic model curves. |
| ***Linear Least Squares*** (on page 86) | 2-Tissue Compartment model solved by the Linear Least Squares method. |
| ***2-Tissue Compartments, Bmax*** (on page 86) | Non-linear 2-Tissue compartment model for receptor tracer studies taking care of the saturation of receptor sites. |
| ***3-Tissue Compartments*** (on page 88) | Most detailed compartment model which separates free tracer in tissue from non-specific binding. |
| ***Flow & Dispersion*** (on page 92) | Specific for dynamic $H_2{}^{15}O$- PET Data with implicit deconvolution of the input curve dispersion |
| ***Model with Metabolites, 3 Compartments*** (on page 88) | Extends the 2 tissue compartment model by an additional input of labeled metabolites from the plasma. |
| ***Model with Metabolites, 3 Compartments and Constraints*** (on page 88) | Same model as above, with constraints usable for fixing or coupled fitting. |
| ***Model with Metabolites, 4 Compartments*** (on page 90) | 2-compartment model for authentic ligand and metabolites, linked by a transfer constant between the tissue compartments |
| ***Delforge Triple- injection Protocol for Flumazenil*** (on page 90) | During a single imaging study three injections are applied: hot ligand first, then cold ligand for displacement, then a mixture of cold & hot ligand. The individual receptor parameters can be estimated. |

# 1-Tissue Compartment Model

All tracer in tissue is included in one compartment $C_1$.



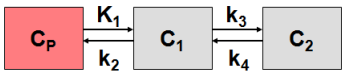

The system of differential equations is:

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - k_2 C_1(t)$$

with instantaneous tissue concentration $C_1(t)$, uptake rate constant $K_1$ and clearance rate constant $k_2$.

# 2-Tissue Compartment Models

Tracer in tissue is attributed to two different compartments in the following linear configuration. Tracer is taken up ($K_1$) from arterial plasma into compartment $C_1$. A fraction of it diffuses back to plasma ($k_2$), another fraction moves further to compartment $C_2$ ($k_3$). Unless tracer is trapped in the $C_2$ compartment ($k_4$=0), transfer back to the intermediate compartment is also going on.




The typical interpretation is that $C_1$ represents free and non-specifically bound tracer in tissue (non-displaceable compartment), and $C_2$ represents specifically bound tracer.

System of differential equations:

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

In the auxiliary 2-tissue compartment models a direct model parameter (rate constant) is replaced by a combination of the basic parameters:

| | |
|---|---|
| **2-Tissue Compartment Model, K1/k2** | The parameter $K_1/k_2$ (DV, distribution volume of free tracer and non-specific binding) is used as a fit parameter instead of $k_2$, and $k_2$ is derived from the estimated $K_1$ and $K_1/k_2$. |
| **2-Tissue Compartment Model, K1/k2 & DVs** | The parameters $K_1/k_2$ and $K_1/k_2*k_3/k_4$ (DVs, distribution volume of specific binding) are used as fit parameters instead of $k_2$ and $k_4$; $k_2$ and $k_4$ are derived from the fit results. |

This approach allows using the non-specific distribution volume $K_1/k_2$ and DVs as common parameters in a coupled fit, as well as for the generation of synthetic curves with fixed DV and DVs.

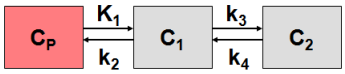
### FDG 2 Tissue Compartment Model

The FDG model is a standard 2-tissue compartment model with two additional input parameters, the lumped constant (LC) and the plasma glucose concentration (PG). In combination with the estimated $K_1$, $k_2$, and $k_3$ parameters they allow to calculate the metabolic rate of glucose. When switching back and forth with the Patlak model, LC and PG are maintained, if the checkbox **Model conversion** in the **Configuration** menu is enabled.

**Note:** In the FDG model $k_4$ is initially set to 0 assuming metabolic trapping, but can also be fitted.

## 2-Tissue Compartment Model including Receptor Saturation

This is a standard receptor-ligand model with two tissue compartments defined by




$C_1$ represents free and non- specifically bound tracer in tissue, and $C_2$ tracer bound to the receptors. The model accounts for the saturation of receptor sites due to a low specific activity $S_{act}$ of the injected tracer. In this situation, $k_3$ is given by $k_{on}(B_{max}-C_2/S_{act})$, and hence is time-dependent. $B_{max}$ is the total receptor concentration, $k_{on}$ the bi-molecular association rate, and $k_4$ the dissociation rate constant $k_{off}$.

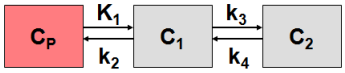
System of differential equations [10]:

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - k_2 C_1(t) - k_{on} C_1(t)\left(B_{\max} - \frac{C_2(t)}{S_{act}}\right) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_{on} C_1(t)\left(B_{\max} - \frac{C_2(t)}{S_{act}}\right) - k_4 C_2(t)$$

## 2-Tissue Compartment by Linear Least Squares Method

As described above the 2-tissue compartment model can be described by the linear arrangement of compartments




and the system of differential equations:

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

Given the input curve $C_{plasma}(t)$ and a set of model parameters $K_1$, .. , $k_4$, the tissue concentrations $C_1(t)$ and $C_2(t)$ can be calculated by integration of the equation system. However, alternative solutions of the system are possible. With linearized solutions, the equations are integrated twice on both sides, substitutions performed and finally rearranged. This can be done in different ways. The **Linear Least Squares** method implemented in PKIN uses the derivation of Cai et al. [57], equation (6):

$$C_{PET}(t) = P_1 C_{Blood}(t) + P_2 \int_0^t C_P(\tau)d\tau + P_3 \int_0^t \int_0^\tau C_P(s)dsd\tau + P_4 \int_0^t C_{PET}(\tau)d\tau + P_5 \int_0^t \int_0^\tau C_{PET}(s)dsd\tau$$

Note that the tissue curve $C_{PET}(t)$ which is the target function appears on both sides of the equation. It also includes whole-blood activity $C_{Blood}(t)$ for spillover correction as well as the input curve $C_P(t)$. This multi-linear expression can be solved in a least squares sense in one step without iterations. The present implementation uses a singular value decomposition method. As a result the 5 parameters $P_1$, .. , $P_5$ are obtained from which the target parameters can be calculated as follows: [57], equation (9)

$$vB = P_1 \qquad k_3 = -(k_2 + k_4 + P_4)$$

$$K_1 = \frac{P_1P_4 + P_2}{1 - P_1} \qquad k_4 = \frac{-P_5}{k_2}$$

$$k_2 = -\frac{P_1P_5 + P_3}{P_1P_4 + P_2} - P_4$$

## Recommended Use of the Linear Least Squares Method

aThe advantage of the linearized approach is the fast calculation, a well-defined solution, and no danger to get stuck in a local minimum such as the iterative methods. However, it is well known that it is susceptible to bias, and that small TAC perturbations can cause large changes of the parameter estimates. Therefore it is recommended that the **Linear Least Squares** method is only used for getting a quick solution which is further refined by the iterative methods. In fact, if **Parameters Initialization** is configured in **Extras**, the initial starting parameters of the compartment models are obtained by the **Linear Least Squares** method.

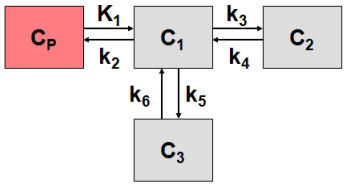
## Implementation Notes

The **Linear Least Squares** method can be used for different model configurations:

- Irreversible model: if $k_4$ is disabled from fitting, the program automatically sets $k_4 = 0$. and uses a linearized equation which is modified accordingly.
- 1-tissue compartment model: if $k_3$ is disabled from fitting, the program automatically sets $k_3 = k_4 = 0$ and uses a modified equation.
- In all configurations the vB parameter can optionally be disabled from fitting and fixed at a specific user-defined value.

# 3-Tissue Compartment Model

This 3-tissue compartment model separates free tracer $C_1(t)$ from non-specifically bound tracer $C_3(t)$. Again, $C_2$ represents specifically bound tracer. $K_1$ and $k_2$ describe the exchange between arterial plasma and tissue, $k_3$ and $k_4$ between free and specifically bound tracer in tissue, and $k_5$ and $k_6$ between free and non-specifically bound tracer.

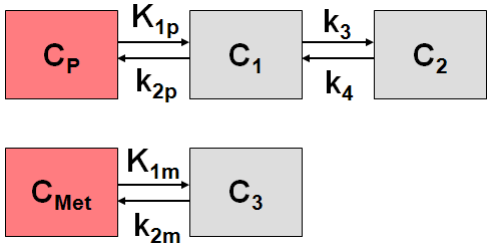



System of differential equations:

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3 + k_5) C_1(t) + k_4 C_2(t) + k_6 C_3(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$
$$\frac{dC_3(t)}{dt} = k_5 C_1(t) - k_6 C_3(t)$$

# Model with Metabolites, 3 Compartments

The **3 Comp, Metabolites** model has been used for modeling $^{123}$I epidepride as described by Fujita et al. [39]. It is a receptor model with two input curves, the usual input curve of free ligand in plasma, but also a second input curve of lipophilic metabolites which may cross the blood-brain-barrier and undergo non-specific binding in brain tissue.




$C_1$ includes free and non-specific binding of authentic ligand (non-displaceable), $C_2$ represents the specific binding of interest, and $C_3$ represents free and non-specific binding of metabolized ligand.

The differential equations are as follows:

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$
$$\frac{dC_3(t)}{dt} = K_{1m} C_{Met}(t) - k_{2m} C_3(t)$$

## Implementation Notes

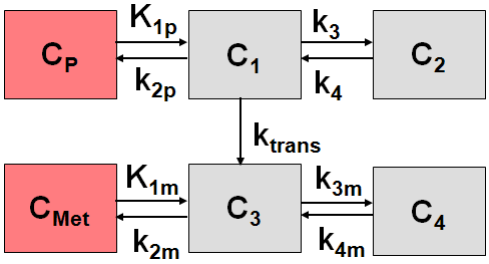
The **Load input curve** entry in the **File** menu has two sub-menus **Plasma** and **Metabolites** for loading the two input curves. There are two implementations of the model, one with the direct rate constants, and another with three ratios of rate constants. The ratios represent the distribution volumes of non-displaceable binding and the metabolites in tissue, as well as the delivery ratio (see parameter tooltips in PKIN). The purpose of these ratios is to introduce constraints for coupled fitting as described in [39].

## Abstract [39]

Quantitative SPECT measures of dopamine D(2) like receptors with [(123)I]epidepride is complicated by its high affinity and lipophilic metabolites. The purpose of this study was to use both parent (P) and lipophilic metabolites (M) as input functions in a kinetic paradigm and in comparison to the results of equilibrium studies. Kinetic studies on eleven healthy human subjects, ages 32+/- 10 were performed following i.v. injection of approximately 370 MBq of [(123)I]epidepride. Images were acquired for 13.5+/-1.0 hours. Equilibrium studies were done on seven of eleven subjects with a bolus injection of approximately 140 MBq, bolus/infusion ratio of 10 hours, and infusion for 30-32 hours. High (striatum) and low (temporal cortex) density regions were studied. Two (P and M) and one (P) input function models were applied in the kinetic studies. In receptor-rich regions, the distribution volumes in nondisplaceable compartments were fixed to those in cerebellum. In addition, in the two input function model, K(1)(P)/K(1)(M) was fixed to the values in the cerebellum. The one input function model provided V'(3) values (=f(1)*B'(max)/K(D)) which were consistent with those obtained in equilibrium studies in both receptor-rich regions, while the two input function model provided consistent values only in striatum. Poor identifiability of the rate constants of metabolites seemed to be the source of errors in the two input function model. These results suggest that correct V'(3) values can be obtained with the one input function model both in high- and low-density regions.

# Model with Metabolites, 4 Compartments, K1/k2, Vs

The **4 Comp, Metabolites, Vs & Vnd** model is a general compartment model for ligands which have recirculation metabolites entering tissue and contribution to the retained tissue activity. Two input curves are required: $C_P(t)$ the authentic ligand in plasma, and $C_m(t)$ the metabolites exchanging with tissue. Both the authentic ligand as well as the metabolites are described by a 2-tissue compartment model, and a transfer $k_{trans}$ constant links the exchangeable compartments.




$$\frac{dC_1(t)}{dt} = K_{1p}C_P(t) - (k_{2p} + k_{3p} + k_{trans})C_1(t) + k_{4p}C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_{3p}C_1(t) - k_{4p}C_2(t)$$

$$\frac{dC_3(t)}{dt} = K_{1m}C_{Met}(t) - (k_{2m} + k_{3m})C_3(t) + k_{trans}C_1(t) + k_{4m}C_4(t)$$

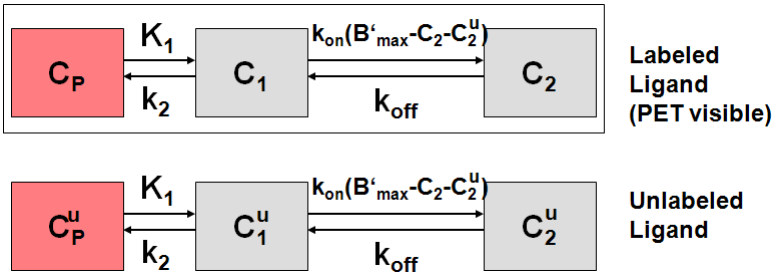
$$\frac{dC_4(t)}{dt} = k_{3m}C_3(t) - k_{4m}C_4(t)$$

### Implementation Notes

The **Load input curve** entry in the **File** menu has two sub-menus **Plasma** and **Metabolites** for loading the two input curves. The model has more parameters than can be fitted at once. Therefore it has been implemented with $K_1/k_2$ , $K_{1m}/k_{2m}$ and Vs as fit parameters to allow fixing the distribution volume of the exchangeable compartment model, or to use them as common parameters in a coupled fit.

# Flumazenil Triple-injection Model

The model developed by Delforge et. al [26] for $^{11}$C-Flumazenil consists of two parallel compartment models



They are linked by common model parameters and the system of differential equations

$$\begin{aligned}
\frac{dC_1(t)}{dt} &= k_1 C_P(t) - k_2 C_1(t) - \frac{k_{on}}{V_R} C_1(t)\left[B'_{\max} - C_2(t) - C^u{}_2(t)\right] + k_{off} C_2(t) \\
\frac{dC_2(t)}{dt} &= \frac{k_{on}}{V_R} C_1(t)\left[B'_{\max} - C_2(t) - C^u{}_2(t)\right] - k_{off} C_2(t) \\
\frac{dC^u{}_1(t)}{dt} &= k_1 C^u{}_P(t) - k_2 C^u{}_1(t) - \frac{k_{on}}{V_R} C^u{}_1(t)\left[B'_{\max} - C_2(t) - C^u{}_2(t)\right] + k_{off} C_2{}^u(t) \\
\frac{dC^u{}_2(t)}{dt} &= \frac{k_{on}}{V_R} C^u{}_1(t)\left[B'_{\max} - C_2(t) - C^u{}_2(t)\right] - k_{off} C^u{}_2(t)
\end{aligned}$$

It is important to understand that only the labeled ligand can be measured, both in PET and in blood sampling. This has consequences:

- The input curve of unlabeled ligand must be derived from the input curves of labeled ligand.
- Only the compartments in the upper model can be used for forming the operational equation

The task to derive the input curve is further complicated by the fact of metabolite buildup in plasma which must be corrected for. The input curves must be calculated from the plasma samples $C_{plasma}(t)$ as follows. Let $T_1$, $T_2$ and $T_3$ be the time of the three injections.

Input curve $C_P(t)$ of hot (labeled) tracer is given by the following expression

$$C_{plasma-corrected}(t) = \begin{cases} C_{plasma}\left(A_1 e^{B_1(t-T_1)} + A_2 e^{B_2(t-T_1)}\right) & T_1 < t < T_3 \quad \text{decay since 1st injection} \\ C_{plasma}\left(A_1 e^{B_1(t-T_3)} + A_2 e^{B_2(t-T_3)}\right) & t > T_3 \quad \text{decay since 3rd injection} \end{cases}$$

which has been implemented as the input curve model **Multiinjection, HOT**.

Input curve $C^u{}_P(t)$ of cold (unlabeled) tracer is given by the expression

$$C^u{}_p(t) = \begin{cases} Dose_2 / Dose_1 \; C_p(t - T_2) & T_2 < t < T_3 \\ Dose_3{}^{Cold} / Dose_3{}^{Hot} \; C_p(t - T_3) + C^u{}_p(T_3)\left(A_1 e^{B_1(t-T_3)} + A_2 e^{B_2(t-T_3)}\right) & t > T_3 \end{cases}$$

which has been implemented as the input curve model **Multiinjection, COLD**.

## Acknowledgement

The model implementation was supported in helpful discussions by Dr. Philippe Millet, University Hospital Geneva, Switzerland [31].

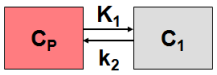
## Abstract [26]

"A kinetic method using a multiinjection protocol, positron emission tomography (PET), and [11C]flumazenil as a specific ligand was used to study in vivo the flumazenil-benzodiazepine receptor interactions in the human brain. The model structure is composed of three compartments (plasma, free, and bound ligand) and five parameters (including the benzodiazepine receptor concentration). The arterial plasma concentration, after correction

for metabolites, was used as the input function. The experimental protocol, which consisted of three injections of labeled and/or unlabeled ligand, allowed the evaluation of the five model parameters in various brain regions from a single experiment. In particular, the concentration of receptor sites available for binding ($B'_{max}$) and the equilibrium dissociation constant (KDVR, VR being the volume of reaction) were estimated in five brain regions, including the pons, in which these parameters are identified for the first time ($B'_{max}$ = 4.7 +/- 1.7 pmol/ml and KDVR = 4.4 +/- 1.3 pmol/ml). Due to the large range of measured receptor concentrations, a linear correlation between $B'_{max}$ and KDVR was pointed out ($r = 0.88$, $p < 0.0005$) and was interpreted as a linear relationship between B'max and VR, the parameter KD being assumed constant. This result and its concordance with the published data are discussed. Simulation of the usual two-experiment Scatchard analysis, using the pons as a reference region, showed that the bias on the receptor concentration estimates introduced by this method is significant (from 20 to 40%) but can be corrected using an estimate of the receptor concentration in the pons. Furthermore, we propose a new experimental protocol, based on a Scatchard analysis of the PET data obtained with a partial-saturation experiment. This single-injection protocol is entirely noninvasive, and thus the estimation of the benzodiazepine receptor concentration and of the flumazenil affinity is now possible in human patients using a single 1-h experiment without blood sampling."

# Water PET Model with Flow and Dispersion

This model implements the 1-tissue compartment model for $^{1}H_{2}{}^{15}O$ water PET studies.




Additionally it is assumed that the true input curve has been convolved with a kernel

$$d(t) = \frac{1}{\tau} e^{-t/\tau}$$

whereby the parameter τ is called "Dispersion". This expression is incorporated into the 1-tissue compartment model and solved using the Laplace transform to yield the equation below, as described by E. Meyer [16].

The original operational equation

$$\overline{C_{PET}}(t) = \tau\, K_1\, C_P(t) + (1 - \tau k_2) K_1\, e^{-k_2 t} \int_0^t C_P(\tau) e^{k_2 \tau} d\tau$$

has been modified to

$$C_{PET}(t) = (1 - vB)\, \overline{C_{PET}}(t) + vB\, C_{Blood}(t)$$

to allow for a spillover term. The interpretation for a freely diffusible model is: $K_1$ represents flow and $k_2$ is flow divided by the partition coefficient p.

Unlike the standard compartment models in PKIN the model curve of the operational equation is not calculated by integrating a set of differential equations, but rather using the analytical solution given above. This convolution integral is approximated by summing up

rectangles of 0.1sec in length, assuming that the acquisition time of dynamic water studies is short.

**Note:** The **delay** parameter is not part of the TAC model, but as usual must be enabled for fitting in the input curve model.

### Abstract [16]

"The difference in tracer arrival times between the radial artery and the brain following i.v. injection of 15O-labeled water plus the difference in dispersion of the tracer bolus between these two sites have to be accounted for in order to quantify cerebral blood flow by the autoradiographic approach and positron emission tomography (PET). We describe a method that simultaneously corrects for these two effects by means of a four-parameter fit to the dynamically acquired data. Unlike with other methods, where the two corrections are performed sequentially, no additional measurement of the dispersion time constant is required. We have validated and tested the method by means of simulations and application to data from six human studies. The mean dispersion time constant of 4.0 +/- 1.2 sec, estimated by the new method for the six studies, is in fair agreement with estimates of 3 to 5 sec derived from cardiac PET."

# Compartment Models for Cardiac PET

| Model Name | Description |
|---|---|
| ***Card. NH3 (de Grado)*** (on page 94) | 1-Tissue compartment model with two spillover terms. Has been developed for cardiac $NH_3$-PET studies with bolus administration. The left ventricle input curve is linearly corrected for metabolites. |
| ***Card. NH3 (2 Compartments)*** (on page 96) | 2-Tissue compartment model with metabolic trapping. Has been developed for cardiac $NH_3$-PET studies with bolus administration. Also implements metabolite correction. |
| ***Card. Rb-82 (1 Compartment)*** (on page 98) | 1-compartment model for the quantification of myocardial perfusion with Rubidium-82 PET data. |
| ***Card. Rb-82 (2 Compartment)*** (on page 99) | Two-compartment model for the quantification of myocardial perfusion with Rubidium-82 PET data. |
| ***Card. H2O (Tissue fraction)*** (on page 101) | 1-Tissue compartment model with two spillover terms. Has been developed for cardiac $H_2{}^{15}O$- PET studies with bolus administration. |
| ***Card. H2O (Geometrical corr.)*** (on page 102) | As above, but with geometrical spillover correction. |
| ***Card. Acetate (1 Compartment)*** (on page 103) | 1-compartment model for the quantification of myocardial perfusion with $^{11}C$ Acetate PET data. |

### Assumptions of the Cardiac Models

- The cardiac models usually apply a geometrical spillover with two correction terms: correction for signal from the left and right ventricle.
- For calculating the myocardial perfusion per g tissue using a density of 1.04 g/ml for myocardial tissue is applied.
- Usually the PET signal from the left ventricle or the atrium is used as a measure of the tracer activity in blood. Depending on the tracer, corrections are applied to this blood curve for calculation the concentration of parent tracer with is required as the input curve of the models.

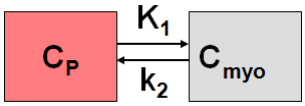
Exceptions to these rules are specified in the description of the individual models.

## Cardiac Flow from Ammonia PET

Two models are available for the quantification of myocardial blood flow from $^{13}NH_3$ ammonia bolus PET data, the 1-tissue compartment model and the 2-tissue compartment model with metabolic trapping. The 1-tissue model is preferably used with the first 2-4 minutes of a dynamic measurement, while the 2-tissue model is also adequate for longer durations. This may compensate to some extent the increased vulnerability to identifiability problems due to the higher number of fit parameters in the 2-tissue model.

### Card. NH3 (de Grado)

This 1-tissue compartment model has been developed by DeGrado et al. [30] for cardiac PET studies using $^{13}NH_3$ ammonia bolus injection.




It includes a linear metabolite correction and describes the exchange of the $NH_3$ between blood and the myocardium by the following differential equation

$$\frac{dC_{myo}(t)}{dt} = K_1(1 - mCorr * t)C_{lv}(t) - k_2 C_{myo}(t)$$

The factor *mCorr* represents the metabolite correction factor. A value of 0.077 [1/min] has been found for *mCorr* in humans [30].

Additionally, the model incorporates a cardiac dual spillover correction by the operational equation

$$C_{PET}(t) = (1 - V_{lv} - V_{rv})\, C_{myo}(t) + V_{lv} C_{lv}(t) + V_{rv} C_{rv}(t)$$

where

$V_{lv}$ = spill-over fraction of the blood activity in the left ventricle $C_{lv}(t)$,
$V_{rv}$ = spill-over fraction of the blood activity in the right ventricle $C_{rv}(t)$ .

DeGrado et al. recommend to only use the first 4 minutes of data after injection of the tracer to reduce the effects of metabolite buildup and washout.

### Implementation Notes:

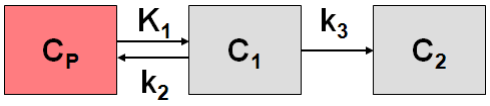
- The right ventricle curve is only used for spillover correction of septal TACs. It must be loaded as the **Total blood** curve.
- The left ventricle curve serves two purposes: (1) multiplied by the metabolite correction (1-mCorr*t) it serves as the input curve, (2) it is used for spillover correction of all myocardial TACs. It must be loaded as the **Input curve**.
- The spill-over fraction from the right ventricle $V_{rv}$ is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only. The reason for this automatism is usage of the model in the **PCARD** tool.
- To set $V_{rv} = 0$ in all regional models proceed as follows: in one region, set $V_{rv} = 0$ and disable the fit checkbox; fit the region; configure the button below **Copy to all regions** to **Model and Par.** and activate it.
- To set *mCorr* to a different value in all regions (eg. for animal studies) proceed as described for $V_{rv}$ above.

### Abstract [30]

"BACKGROUND: Although several modeling strategies have been developed and validated for quantification of myocardial blood flow (MBF) from $^{13}$N- labeled ammonia positron emission tomographic data, a comparison of noise characteristics of the various techniques in serial studies is lacking. METHODS AND RESULTS: Dynamic $^{13}$N-labeled ammonia positron emission tomographic imaging was performed at baseline and after pharmacologic stress in (1) single studies of four dogs with concomitant measurement of microsphere blood flow and (2) initial and follow-up studies of eight normal volunteers. Data were obtained from short-axis images for the blood pool and myocardial regions corresponding to the three arterial vascular territories. Indexes of MBF were obtained by four distinct techniques: (1) University of California, Los Angeles, two-compartment model, (2) Michigan two-compartment model, and (3) a one- compartment model with variable blood volume term. Coronary flow reserve (CFR) was measured as the ratio of stress/rest MBF. The estimated standard deviation of the measurement error for the relative change between studies of rest and stress MBF and CFR was determined for each technique. Estimates of MBF from all techniques showed good correlation with microsphere blood flow (r = 0.95 to 0.96) in canine myocardium. In human studies, similar mean estimates of MBF were found with all techniques. Techniques 1 and 3 showed the smallest interstudy variability in MBF and CFR. The estimated standard deviations for these techniques were approximately 20%, 30%, and 27% for rest MBF, stress MBF, and CFR, respectively. CONCLUSION: Noninvasive quantification of MBF and CFR from dynamic $^{13}$N-labeled ammonia positron emission tomography is most reproducible with technique 1 or 3. The ability to account for differences in myocardial partial volume gives preference to technique 3. However, substantial interstudy variability in regional MBF remains, suggesting the importance of procedural factors or real temporal fluctuations in MBF."

## Card. NH3 (2 Compartments)

The **Card NH3 (2-Tissue)** model developed by Hutchins et al. [45] is an implementation of the irreversible 2-tissue-compartment model for cardiac PET studies using $^{13}NH_3$ ammonia bolus injection. The compartment model has the following structure




where $C_1$ is free tracer in tissue, and $C_2$ is metabolically trapped tracer in the form of $^{13}N$ glutamine. Because ammonia is considered in this model as freely diffusible across the capillary wall, the unidirectional uptake parameter $K_1$ equals the myocardial perfusion.

The system of differential equations is

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t)$$

To allow the fitting of data over an extended period, the model includes the exponential metabolite correction described by van den Hoff et al. [46]

$$C_P(t) = \begin{cases} C_{lv}(t) & t \le t_0 \\ e^{-\ln 2 (t - t_0)/T_{1/2}} C_{lv}(t) & t > t_0 \end{cases}$$

with delay $t_0$=0.48 min and half-time $T_{1/2}$=6.69 min. $C_{lv}(t)$ is the total tracer concentration measured in the left ventricle, including metabolites.

Additionally, the model incorporates a cardiac dual spillover correction by the operational equation

$$C_{PET}(t) = (1 - V_{lv} - V_{rv})(C_1(t) + C_2(t)) + V_{lv} C_{lv}(t) + V_{rv} C_{rv}(t)$$

where

$V_{lv}$ = spill-over fraction of the blood activity in the left ventricle $C_{lv}(t)$,
$V_{rv}$ = spill-over fraction of the blood activity in the right ventricle $C_{rv}(t)$ .

### Card NH3 (2-Tissue, $K_1/k_2$)

Due to the increased number of fit parameters it has been found, that the **Card NH3 (2-Tissue)** may suffer from identifiability problems. Therefore, the variant **Card NH3 (2-Tissue, K1/k2)** has been developed using the parameter $K_1/k_2$ (DV, distribution volume of free tracer is used as a fit parameter instead of $k_2$, and $k_2$ is derived from the estimated $K_1$ and $K_1/k_2$. In this configuration physiological restrictions can be imposed on $K_1/k_2$ , or $K_1/k_2$ can be used as a common parameter in a ***coupled fit*** (on page 32).

### Implementation Notes:

- The right ventricle curve is only used for spillover correction of septal TACs. It must be loaded as the **Total blood** curve.
- The left ventricle curve serves two purposes: (1) corrected for metabolites it serves as the input curve, (2) it is used for spillover correction of all myocardial TACs. It must be loaded as the **Input curve**.
- The delay and half-time of the metabolite correction are input parameters of the kinetic model.
- The spill-over fraction from the right ventricle $V_{rv}$ is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only. The reason for this automatism is usage of the model in the **PCARD** tool.
- To set $V_{rv} = 0$ in all regional models proceed as follows: in one region, set $V_{rv} = 0$ and disable the fit checkbox; fit the region; configure the button below **Copy to all regions** to **Model and Par.** and activate it.

Abstract [45]

"Evaluation of regional myocardial blood flow by conventional scintigraphic techniques is limited to the qualitative assessment of regional tracer distribution. Dynamic imaging with positron emission tomography allows the quantitative delineation of myocardial tracer kinetics and, hence, the measurement of physiologic processes such as myocardial blood flow. To test this hypothesis, positron emission tomographic imaging in combination with N-13 ammonia was performed at rest and after pharmacologically induced vasodilation in seven healthy volunteers. Myocardial and blood time-activity curves derived from regions of interest over the heart and ventricular chamber were fitted using a three compartment model for N-13 ammonia, yielding rate constants for tracer uptake and retention. Myocardial blood flow (K1) averaged 88 +/- 17 ml/min per 100 g at rest and increased to 417 +/- 112 ml/min per 100 g after dipyridamole infusion (0.56 mg/kg) and handgrip exercise. The coronary reserve averaged 4.8 +/- 1.3 and was not significantly different in the septal, anterior and lateral walls of the left ventricle. Blood flow values showed only a minor dependence on the correction for blood metabolites of N-13 ammonia. These data demonstrate that quantification of regional myocardial blood flow is feasible by dynamic positron emission tomographic imaging. The observed coronary flow reserve after dipyridamole is in close agreement with the results obtained by invasive techniques, indicating accurate flow estimates over a wide range. Thus, positron emission tomography may provide accurate and noninvasive definition of the functional significance of coronary artery disease and may allow the improved selection of patients for revascularization."

## Cardiac Flow from Rubidium-82 PET

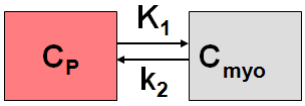
Two kinetic models are available for the quantification of myocardial perfusion from $^{82}$Rb bolus PET data.

**1)** A 1-tissue compartment model with geometrical spillover correction and correction for flow-dependent extraction.

**2)** A 2-tissue compartment model with recovery and spillover correction.

## Card. Rb-82 (1 Compartment)

The model has the standard 1-compartment form




with the differential equation

$$\frac{dC_{myo}(t)}{dt} = K_1 C_{lv}(t) - k_2 C_{myo}(t)$$

The equation assumes that the activity in the left ventricle $C_{lv}(t)$ is used as the input curve.

Rb is known to have a flow-dependent extraction fraction, so that $K_1$ , which is the product of flow F times extraction fraction E, is described by the expression

$$K_1 = F\,E = F\,(1 - Ae^{-B/F})$$

The values of the correction factors reported by Lortie et al. [44] are

A = 0.77
B = 0.63 [ml/min/g]

The model implements a geometric double spillover correction for activity from the left and right ventricle in the form

$$C_{PET}(t) = (1 - V_{lv} - V_{rv})\,C_{myo}(t) + V_{lv} C_{lv}(t) + V_{rv} C_{rv}(t)$$

where

$V_{lv}$ = spill-over fraction of the blood activity in the left ventricle $C_{lv}(t)$,
$V_{rv}$ = spill-over fraction of the blood activity in the right ventricle $C_{rv}(t)$ .

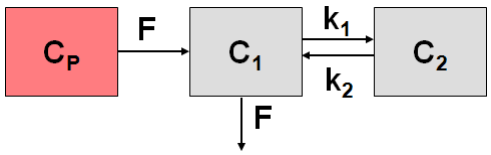
### Implementation Notes:

- The right ventricle curve is only used for spillover correction of septal TACs. It must be loaded as the **Total blood** curve.
- The left ventricle curve serves two purposes: (1) as the input curve, (2) it is used for spillover correction of all myocardial TACs. It must be loaded as the **Input curve**.
- In practice, the expression for $K_1$ is inserted into the differential equation, so that F becomes a fit parameter, and $K_1$ is a derived parameter.
- To allow the user to change the form of the extraction function the scale factor A and the exponent B an be entered as input parameters.
- The spill-over fraction from the right ventricle $V_{rv}$ is automatically fixed to zero if the string "Sep" is *not* contained in the name of the regional TAC. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only. The reason for this automatism is usage of the model in the **PCARD** tool.
- To set $V_{rv} = 0$ in all regional models proceed as follows: in one region, set $V_{rv} = 0$ and disable the fit checkbox; fit the region; configure the button below **Copy to all regions** to **Model and Par.** and activate it.

This model is also usable in the cardiac modeling tool **PCARD**.

## Card. Rb-82 (2 Compartments)

The model has been implemented according to the method described and evaluated by Herrero et al [35]. Their $^{82}$Rb model is based on the following compartment structure to describe the kinetics of rubidium in the myocardium:




where $C_1(t)$ represents the fast exchangeable compartment (vascular and interstitial spaces), and $C_2(t)$ the slow exchangeable compartment (intracellular space), myocardium flow F, and rate constants $k_1$ and $k_2$.

The differential equations for the activity concentrations in the different compartments are given by

$$\frac{dC_1(t)}{dt} = F(C_a(t) - C_1(t)/V_d) - k_1 C_1(t) + k_2 C_2(t)$$
$$\frac{dC_2(t)}{dt} = k_1 C_1(t) - k_2 C_2(t)$$

with the arterial blood activity $C_p$ and a fractional volume of distribution $V_d$ in the first compartment .

The operational equation which is fitted to the measured data is

$$C_{PET} = F_{MM}\,(C_1(t) + C_2(t)) + F_{BM} C_a(t)$$

where $F_{MM}$ denotes the tissue recovery coefficient and the blood to myocardium spillover fraction $F_{BM}$.

The model encompasses 6 fitable parameters. However, in practice it is impossible to estimate so many parameters from a time-activity curve with reasonable identifiability. Therefore, at least the distribution volume $V_d$ and the recovery coefficient $F_{MM}$ are usually fixed (proposed values from [35]: 0.75 and 0.65 respectively). The recovery coefficient depends on the image resolution and should be determined experimentally.

This model is also usable in the cardiac modeling tool **PCARD**.

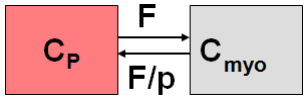
## Abstract [35]

"Positron emission tomography offers the ability to noninvasively assess regional myocardial perfusion in absolute terms (i.e., milliliters per gram per minute). Accurate estimates have been difficult to achieve with generator-produced 82Rb because of the complex behavior of this tracer in the myocardium. The aim of the present study was to determine whether regional myocardial blood flow could be assessed quantitatively with 82Rb and positron emission tomography by using a two-compartment kinetic model. Regional perfusion in milliliters per gram per minute was estimated from dynamic tomographic scans after intravenous administration of 82Rb in 18 studies in 13 intact dogs studied without intervention, after 2 and 24 hours of induced ischemia, during reperfusion after transient occlusion, or at rest and after pharmacological hyperemia after induced coronary artery stenosis. Regional flow was estimated along with the forward and backward rates of transport (k1 and k2 [minutes-1]) after the relative volume of distribution of the first compartment was fixed to 0.53 ml/ml and the tomographic parameters, the recovery and spillover fractions, were fixed to averaged values obtained in previous studies. In 36 comparisons, estimates of regional flow with 82Rb correlated well with flow measured with concomitantly administered radiolabeled microspheres (r = 0.91, p less than 0.05) over the flow range from 0.14 to 4.25 ml/g/min. A putative index of viability, k2, increased significantly in regions with severe ischemia. The results suggest that quantification of regional myocardial perfusion is possible in centers using 82Rb for estimates of myocardial perfusion when a physiologically appropriate, two-compartment model is used. Positron emission tomography offers the ability to noninvasively assess regional myocardial perfusion in absolute terms (i.e., milliliters per gram per minute). Accurate estimates have been difficult to achieve with generator-produced 82Rb because of the complex behavior of this tracer in the myocardium. The aim of the present study was to determine whether regional myocardial blood flow could be assessed quantitatively with 82Rb and positron emission tomography by using a two-compartment kinetic model. Regional perfusion in milliliters per gram per minute was estimated from dynamic tomographic scans after intravenous administration of 82Rb in 18 studies in 13 intact dogs studied without intervention, after 2 and 24 hours of induced ischemia, during reperfusion after transient occlusion, or at rest and after pharmacological hyperemia after induced coronary artery stenosis. Regional flow was estimated along with the forward and backward rates of transport (k1 and k2 [minutes-1]) after the relative volume of distribution of the first compartment was fixed to 0.53 ml/ml and the tomographic parameters, the recovery and spillover fractions, were fixed to averaged values obtained in previous studies. In 36 comparisons, estimates of regional flow with 82Rb correlated well with flow measured with concomitantly administered radiolabeled microspheres (r = 0.91, p less than 0.05) over the flow range from 0.14 to 4.25 ml/g/min. A putative index of viability, k2, increased significantly in regions with severe ischemia. The results suggest that quantification of

regional myocardial perfusion is possible in centers using 82Rb for estimates of myocardial perfusion when a physiologically appropriate, two-compartment model is used."

# Cardiac Flow from Water PET

Two models are available for the quantification of myocardial perfusion PET studies using $H_2{}^{15}O$ water bolus injection. They only differ in the way how they handle spill-over correction. The model configuration is a 1-tissue compartment model below.




The distribution of the freely diffusible inert tracer $H_2{}^{15}O$ in myocardium can be described by a 1-tissue compartment model

$$\frac{dC_{myo}(t)}{dt} = FC_p(t) - \frac{F}{p}C_{myo}(t)$$

with the myocardial blood flow F and the myocardium to blood partition coefficient of water p.

## Card. H2O (Tissue fraction)

This model has been developed by Hermannsen et al. [27] for cardiac PET studies using $H_2{}^{15}O$ water bolus injection. It incorporates two spill-over terms from blood in the left and the right ventricles which are relatively displaced in time. So the operational equation which is fitted to the measured data is

$$C_{PET}(t) = TF\ C_{myo}(t) + V_{lv}C_{lv}(t) + V_{rv}C_{rv}(t)$$

where TF = tissue fraction, $V_{lv}$ = spill-over fraction from the left ventricle, $V_{rv}$ = spill-over fraction from the right ventricle. In practice, the left ventricular time-activity curve is also used as the input curve $C_P(t)$.

### Implementation Notes

As opposed to standard PKIN models a tissue fraction is used rather than a strict geometrical correction for compliance with the original model. The right ventricle curve is only used for spillover correction of septal TACs. It must be loaded as the **Total blood** curve. The left ventricle curve serves both as the input curve as well as for spillover correction of all myocardial TACs. It must be loaded as the **Input curve**.

The right ventricle spill-over fraction $V_{rv}$ is automatically fixed to zero if the string "Sep" is *not* contained in the name of the region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with single spill-over from the left ventricle. The reason of this behavior is the usage of this model in the PCARD tool.

### Abstract [27]

"Positron emission tomography (PET) in conjunction with $C^{15}O_2$ or $H_2^{15}O$ can be used to measure myocardial blood flow (MBF) and tissue fraction (TF), i.e. the fraction of the tissue mass in the volume of the region of interest. However, with $C^{15}O_2$ inhalation, the tissue fraction in the septum is overestimated. Bolus injection of $H_2^{15}O$ together with arterial cannulation gives very precise results but is invasive. The purpose of this study was to develop a method which circumvents these problems. A four- parameter model with parameters for MBF, TF and spill- over fractions from both left and right ventricular cavities was developed. This method was compared with a three- parameter model (no right ventricular cavity spill-over) in both septal and non-septal regions of interest for three different administration protocols: bolus injection of $H_2^{15}O$, infusion of $H_2^{15}O$ and inhalation of $C^{15}O_2$ . It was found that MBF can be measured with intravenous administration of $H_2^{15}O$ without the requirement for arterial cannulation. The four-parameter protocol with bolus injection was stable in clinical studies. The four-parameter model proved essential for the septum, where it gave highly significantly better fits than did the three-parameter model ($P<0.00003$ in each of 15 subjects). Administration of $H_2^{15}O$ together with this four-parameter model also circumvented the problem of overestimation of TF in the septum seen with $C^{15}O_2$ inhalation. In addition, the radiation dose of $H_2^{15}O$ protocols is lower than that of $C^{15}O_2$ inhalation. Using a left atrial input curve instead of a left ventricular cavity input curve gave the same mean MBF and TF."

## Card. H2O (Geometrical corr.)

This model is the same as the one above developed by Hermannsen et al. [27], except that it uses a geometrical spillover correction. The operational equation which is fitted to the measured data is

$$C_{PET}(t) = (1 - V_{lv} - V_{rv})\, C_{myo}(t) + V_{lv} C_{lv}(t) + V_{rv} C_{rv}(t)$$

where $V_{lv}$ = spill-over fraction from the left ventricle, $V_{rv}$ = spill-over fraction from the right ventricle. In practice, the left ventricular time-activity curve is also used as the input curve $C_P(t)$.

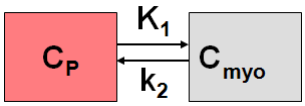
### Implementation Notes

The right ventricle curve is only used for spillover correction of septal TACs. It must be loaded as the **Total blood** curve. The left ventricle curve serves both as the input curve as well as for spillover correction of all myocardial TACs. It must be loaded as the **Input curve**.

The right ventricle spill-over fraction $V_{rv}$ is automatically fixed to zero if the string "Sep" is *not* contained in the name of the region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with single spill-over from the left ventricle. The reason of this behavior is the usage of this model in the PCARD tool.

# Cardiac Flow from Acetate PET

Van den Hoff et al. [46] have investigated and validated $^{11}$C-acetate as a flow tracer. This methodology is implemented as the **Card Acetate (1 Compartment)** model. It employs a single tissue compartment model




with tracer exchange between arterial plasma $C_a$ and myocardial tissue $C_{myo}$ and a differential equation

$$\frac{dC_{myo}(t)}{dt} = K_1\, C_P(t) - k_2\, C_{myo}(t) = EF\, C_P(t) - k_2\, C_{myo}(t)$$

A metabolite correction is necessary to derive the plasma activity from whole blood measured in the left cavity.

$$C_P = 0.91e^{-\ln 2(t/T_{1/2})}C_{lv}(t)$$

with $T_{1/2}$=5.3 min. $K_1$ is the product of flow F and extraction E which is flow dependent for acetate. The relation found [46] is described by the following relation

$$E(F) = 1 - 0.64e^{-1.2/F}$$

Additionally, the model incorporates a cardiac dual spillover correction by the operational equation

$$C_{PET}(t) \quad = \quad (1 - V_{lv} - V_{rv})\, C_{myo}(t) + V_{lv} C_{lv}(t) + V_{rv} C_{rv}(t)$$

where

$V_{lv}$ = spill-over fraction of the blood activity in the left ventricle $C_{lv}(t)$,
$V_{rv}$ = spill-over fraction of the blood activity in the right ventricle $C_{rv}(t)$ .

### Implementation Notes:

- The right ventricle curve is only used for spillover correction of septal TACs. It must be loaded as the **Total blood** curve.
- The left ventricle curve serves two purposes: (1) corrected by the metabolite buildup it serves as the input curve, (2) it is used for spillover correction of all myocardial TACs. It must be loaded as the **Input curve**.
- The spill-over fraction from the right ventricle $V_{rv}$ is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only. The reason for this automatism is usage of the model in the **PCARD** tool.
- To set $V_{rv}$ = 0 in all regional models proceed as follows: in one region, set $V_{rv}$ =0 and disable the fit checkbox; fit the region; configure the button below **Copy to all regions** to **Model and Par.** and activate it.

# Reference Models

PKIN features the following list of reference models:

| Model Name | Description |
|---|---|
| ***4 Parameter Reference Tissue Model*** (on page 104) | 4 Parameter Reference Tissue Model by Lammertsma et al. |
| ***SRTM*** (on page 106) | Simplified reference Tissue Model by Lammertsma and Hume |
| ***SRTM2*** (on page 107) | Modification of Simplified Reference Tissue Model modified by Wu and Carson to reduce BP bias induced by noise |
| ***MRTM0*** (on page 108) | Multilinear Reference Tissue Model by Ichise et al. |
| ***MRTM*** (on page 110) | Multilinear Reference Tissue Model by Ichise et al modified to reduce bias induced by noise |
| ***MRTM2*** (on page 111) | Multilinear Reference Tissue Model by Ichise et al modified to reduce bias and variability induced by noise |
| ***Logan Non- Invasive*** (on page 112) | Reference tissue method which is based on an average $k_2$ |
| 2 Tissue Reference Model | Watabe's reference tissue model with a 2-tissue compartment model in the reference region |
| ***MP4A RLS (Nagatsuka)*** (on page 114) | Multi-linear Reference Tissue Model for [11C]-MP4A (RLS) |

## 4 Parameter Reference Tissue Model

The 4 parameter reference tissue method of Lammertsma et al. [28] requires two time-activity curves: one from a receptor-rich region and one from a reference region devoid of receptors. It then assumes that the distribution volume of the non-displaceable compartment is the same for the tissue of interest and the reference tissue: $K_1/k_2=K_1'/k_2'$

Defining $R_1=K_1/K_1'$ as the ratio of tracer delivery, and the binding potential BP as $k_3/k_4$, the following operational equation can be derived for the measured TAC in the receptor-rich region:

$$C_{PET}(t) = R_1\left\{C'(t) + aC'(t)\otimes e^{-ct} + bC'(t)\otimes e^{-dt}\right\}$$
$$a = (k_3 + k_4 - c)(c - r)/p$$
$$b = (d - k_3 - k_4)(d - r)/p$$
$$c = (s + p)/2$$
$$d = (s - p)/2$$
$$p = \sqrt{s^2 - q}$$
$$q = 4k_2k_4$$
$$r = k_2/R_1$$
$$s = k_2 + k_3 + k_4$$

This equation includes four unknowns: $R_1$, $k_2$, $k_3$, and BP (after substitution of $BP=k_3/k_4$) , which can be fitted using nonlinear fitting techniques.

## Implementation Notes

After switching to the **4 Par Ref Tissue Model** in PKIN a suitable reference region must be selected. For convolution with the exponentials, the reference tissue TAC is resampled on a regular grid, which can be specified by the **resampling interval** parameter in PKIN.

## Abstract [28]

"Five different methods for the estimation of the binding potential, a measure of Bmax/Kd, of [11C]raclopride in human striatum were compared using data from a dose ranging study of the neuroleptic CP- 88,059-01. Binding potential was estimated indirectly, from distribution volumes in striatum and cerebellum, using both single- and two-tissue compartment models with a metabolite-corrected plasma curve as input function. The two-tissue compartment model was also used for a direct estimate of the binding potential. In addition, a direct estimate was obtained from the reference tissue compartment model using the cerebellum as indirect input function. Finally, an estimate of binding potential was calculated from the ratio of striatum over cerebellum counts at late times after injection. The estimates of striatum binding potential from all methods, except the direct determination using a two-tissue compartment model with metabolite-corrected plasma input function, correlated with each other. Use of an average metabolite correction resulted in only a small reduction in accuracy in this series of normal subjects. The reference tissue model provided estimates of the binding potential with the same sensitivity for detecting changes as those methods that required a metabolite-corrected plasma input function. This indicates that for routine analysis of clinical [11C]raclopride studies, no arterial cannulation is required. The range of normal values was significantly less variable with the reference tissue method than when simple striatum-to-cerebellum ratios were used."

# Simplified Reference Tissue Model (SRTM)

The simplified reference tissue model (SRTM) of Lammertsma et al. [21] is a further development of the 4 parameter reference tissue model. Introducing a new constraint, it reduces the number of fit parameters from four to three.

SRTM is based on the following assumptions:

**1)** The distribution volume is the same for the tissue of interest and the reference tissue: $K_1/k_2=K_1'/k_2'$.

**2)** The kinetics in the receptor-rich tissue of interest is such, that it is difficult to distinguish between the specific and the free/non-specific compartment; ie. the TAC can be fitted by a 1-tissue compartment model. This assumption may not be valid for all tracers. (Even in the test data, the approximation is not accurate at early time points.)

Defining $R_1=K_1/K_1'$ as the ratio of tracer delivery, and the binding potential BP as $k_3/k_4$, the following operational equation can be derived for the measured TAC in the receptor-rich region:

$$C(t) = R_1\, C'(t) + R_1\left[k'_2 - k_{2a}\right] C'(t) \otimes e^{-k_{2a}t}$$

The three unknowns $R_1$, $k_2$, BP, in this equation can be fitted using nonlinear regression techniques.

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**Note:** In cases where the 1-tissue compartment model assumption does not apply, BP estimates from SRTM have found to be biased [43].

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## Implementation Notes

After switching to the **Simplified Ref Tissue Model** in PKIN a suitable reference region must be selected. For convolution with the exponentials, the reference tissue TAC is resampled on a regular grid, which can be specified by the **resampling interval** parameter in PKIN.

Note that $\mathbf{k_2'}$, the transfer of tracer from the reference tissue back to the plasma, is also calculated as a derived parameter. This value can be used in the SRTM2 and the MRTM2 reference methods.

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**Note:** The reference methods MRTM2 and SRTM2 require $k_2'$ as an input parameter. The $k_2'$ resulting from the SRTM method above is a suitable estimate. Therefore, when switching in PKIN from the SRTM model to the SRTM2 or MRTM2, $k_2'$ is automatically copied from SRTM, as long as **Model conversion** in the **Configuration** menu is enabled.

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## Abstract [21]

"The reference tissue model allows for quantification of receptor kinetics without measuring the arterial input function, thus avoiding arterial cannulation and time-consuming metabolite measurements. The model contains four parameters, of which the binding potential (BP) is the parameter of interest. Although BP is robust, convergence rates are slow

and the other parameters can have large standard errors. To overcome this problem, a simplified reference tissue containing only three parameters was developed. This new three-parameter model was compared with the previous four-parameter model using a variety of PET studies: [11C]SCH 23390 (D1 receptor) and [11C]raclopride (D2 receptor) in humans, and [11C]SCH 23390, [11C]raclopride and [11C]RTI-121 (dopamine transporter) in rats. The BP values obtained from both models were essentially the same for all cases. In addition, the three-parameter model was insensitive to starting values, produced stable results for the other parameters (small standard errors), and converged rapidly. In conclusion, for the ligands tested the three-parameter model is a better choice, combining increased convergence rate with increased stability."

## Simplified Reference Tissue Model 2 (SRTM2)

Wu and Carson [32] aimed at making the Simplified Reference Tissue Model (SRTM) more robust for pixel-wise applications and called it Simplified Reference Tissue Model 2 (SRTM2). They noted that with SRTM $k_2'$ is calculated with each pixel TAC, although the same reference TAC is used for all pixels. Therefore they implemented a two-step approach:

**1)** Calculate $k_2'$ using SRTM in all pixels except for pixels without specific binding.

**2)** Fix $k_2'$ : Average $k_2'$ in all brain pixels outside the reference region. Use this fixed value for the pixel-wise SRTM calculations, reducing the number of fitted parameters from 3 to 2.

The operational equation of the SRTM was re-written to allow for fixing of $k_2'$

$$C(t) = R_1 C'(t) + R_1\left[k'_2 - k_{2a}\right]C'(t) \otimes e^{-k_{2a}t}$$

The three parameters R1, k2a and k'2 are estimated in step 1. In step 2 $k_2'$ is fixed, and only R1 and k2a are estimated. k2a is the apparent k2 (k2a = k2 /(1+BP)).

The binding potential can then be calculated as

$$BP = R_1 \frac{k'_2}{k_{2a}} - 1.0$$

SRTM2 is based on the same assumptions as SRTM:

**1)** The distribution volume is the same for the tissue of interest and the reference tissue: $K_1/k_2=K_1'/k_2'$.

**2)** The kinetics in the receptor-rich tissue of interest is such, that it is difficult to distinguish between the specific and the free/non-specific compartment; ie. the TAC can be fitted by a 1-tissue compartment model. This assumption may not be valid for all tracers. (Even in the test data, the approximation is not accurate at early time points.)

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**Note:** As with the SRTM method, BP estimates from SRTM2 tend to be biased if the 1-tissue compartment model assumption does not apply. The magnitude of the bias is even larger for the SRTM2 estimates, most likely because the fixed $k_2'$ can not compensate any more a part of the model inadequacy [32].

### Implementation Notes

After switching to the **Simplified Ref Tissue Model 2** in PKIN a suitable reference region must be selected. For convolution with the exponentials, the reference tissue TAC is resampled on a regular grid, which can be specified by the **resampling interval** parameter in PKIN.

Note that $\mathbf{k}_2'$, the transfer of tracer from the reference tissue back to the plasma, can also be fitted. After removing the fit check of $\mathbf{k}_2'$, it remains fix at the entered value. This allows to study the bias when fixing $\mathbf{k}_2'$.

### Abstract [32]

"The Simplified Reference Tissue Model (SRTM) produces functional images of receptor binding parameters using an input function derived from a reference region and assuming a model with one tissue compartment. Three parameters are estimated: binding potential (BP), relative delivery ($R_1$), and the reference region clearance constant $k_2'$. Since $k'_2$ should not vary across brain pixels, the authors developed a two-step method ($SRTM_2$) using a global value of $k_2'$. Whole-brain simulations were performed using human input functions and rate constants for [18F]FCWAY, [11C]flumazenil, and [11C]raclopride, and parameter SD and bias were determined for SRTM and $SRTM_2$. The global mean of $k_2'$ was slightly biased (2% to 6%), but the median was unbiased (<1%) and was used as the global value. Binding potential noise reductions with SRTM2 were 4% to 14%, 20% to 53%, and 10% to 30% for [18F]FCWAY, [11C]flumazenil, and [11C]raclopride, respectively, with larger reductions for shorter scans. R1 noise reduction was larger than that of BP. Simulations were also performed to assess bias when the reference and/or tissue regions followed a two-tissue compartment model. Owing to the constrained $k_2'$, $SRTM_2$ showed somewhat larger biases due to violations of the one- compartment model assumption. These studies demonstrate that $SRTM_2$ should be a useful method to improve the quality of neuroreceptor functional images."

## Ichise's Non- Invasive Plot (MRTM0)

The $MRTM_0$ reference model approach of Ichise et al. [20] is based on the Logan plot and applies for receptor studies. The assumption is, that there is a reference TAC C'(t) from a region without receptors ($k_3$=0 in the 2-Tissue compartment model), and a TAC C(t) from a receptor-rich region ($k_3$>0). If the Logan plot is applied for both TACs, then the input curve can be eliminated and the following multi-linear expression be found.

$$\frac{\int_0^T C(t)dt}{C(T)} = \frac{V}{V'}\frac{\int_0^T C'(t)dt}{C(T)} + \frac{V}{V'k'_2}\frac{C'(T)}{C(T)} + b$$

V and V' are the total distribution volumes of C(t) and C'(t), $k'_2$ is the clearance rate constant from the reference region to plasma, and b is the intercept term, which becomes constant for T > t*.

The multi-linear relationship above can be solved using multi-linear regression, yielding three regression coefficients. From the first coefficient the binding potential can be calculated by

$$BP = \frac{V}{V'} - 1.0$$

assuming that the non-displaceable distribution volumes in the tissue and reference regions are identical.

For radioligands with 1-tissue kinetics such as [11C]DASB the multi-linear equation is correct from T = 0, i.e., t* = 0, and b is equal to ($-1/k_2$ ), where $k_2$ is the clearance rate constant from the tissue to plasma. Furthermore, $R_1 = K_1/K'_1$, the relative radioligand delivery, can be calculated from the ratio of the second and third regression coefficients.

## Implementation Notes

After switching to the **Ichise NonInvasive MRTM0** in PKIN a suitable reference region must be selected. It allows to fit a multilinear regression within a range defined by the parameters **Start Lin.** and **End Lin**. The results are the three regression coefficients, and the derived binding potential BP.

There is also an error criterion **Max Err.** to fit **Start Lin**. For instance, if **Max Err.** is set to 10% and the fit box of **Start Lin**. is checked, the model searches the earliest sample so that the deviation between the regression and all measurements is less than 10%. Samples earlier than the **Start Lin**. time are disregarded for regression and thus painted in gray.

## Abstract [20]

"Iodine-123-iodobenzofuran (IBF) is a potent dopamine D2 receptor ligand suited for quantitative receptor studies. The purpose of this study was to evaluate three noninvasive methods of estimating the receptor parameter $k_3/k_4$ in humans with IBF-SPECT. METHODS: Scans were acquired every 5 min for 180 min using a triple-headed SPECT system following a bolus injection of IBF (296 +/- 37 MBq) in 14 normal volunteers. $k_3/k_4$ was estimated by the peak equilibrium ratio (RPE) method and two proposed methods: a variation of the graphic method that derives the ratio of ligand distribution volumes (RV) and area ratio (RA) method, in which the ratio is calculated from the areas under the specific binding and nondisplaceable activity curves. RESULTS: The mean RPE, RV and RA were 2.74 +/- 0.40, 3.06 +/- 0.42 and 2.26 +/- 0.28, respectively. Both RPE and RA underestimated RV. The relationship between RPE or RA and RV was linear (p < or = 10(-5), RA showed higher correlation (r = 0.94) with RV than did RPE (r = 0.90). Simulations based on a tracer kinetic model showed that RV, unlike RPE or RA, is affected by neither regional cerebral blood flow (rCBF) nor peripheral clearance rate (CR) of IBF. All three measures showed a significant decline with increasing age (r = 0.54-0.58, p < 0.05). CONCLUSION: RV is preferred because it provides a theoretically valid estimate of $k_3/k_4$ , independently of rCBF or CR. Alternatively, RA might be preferred to RPE because the former is simpler than the latter to implement yet the former provides a measure that equally well correlates with $k_3/k_4$ ."

**Note:** please see also Ichise et al. [33] for explanations and the notation.

# Ichise's Multilinear Reference Tissue Model (MRTM)

To reduce noise-related bias effects arising in the $MRTM_0$ method Ichise et al. [33] applied a strategy known to be effective in reducing the noise-induced bias for the models requiring blood data. To this end the equation of the $MRTM_0$ was rearranged to remove the noisy tissue radioactivity term C(t) from the independent variables. This approach resulted in a new method called MRTM with operational equation

$$C(T) = -\frac{V}{V'b}\int_0^T C'(t)dt + \frac{1}{b}\int_0^T C(t)dt - \frac{V}{V'k'_2 b}C'(T)$$

C(t) is the TAC from a receptor-rich region ($k_3>0$), and C'(t) the TAC from a region without receptors ($k_3=0$ in the 2-Tissue compartment model).

The multi-linear relationship above can be solved using multi-linear regression, yielding three regression coefficients. The binding potential can then be calculated from the first two regression coefficients $\gamma_1$ and $\gamma_2$ by

$$BP = -(\gamma_1/\gamma_2 + 1) = -(-\frac{V\,b}{V'b} + 1) = \frac{V}{V'} - 1.0$$

Furthermore, division of the first by the third regression coefficient yields an estimate of $\mathbf{k_2'}$ .

### Implementation Notes

After switching to the **Ichise NonInvasive MRTM** in PKIN a suitable reference region must be selected. It allows to fit a multilinear regression within a range starting at the parameters **Start Lin**. The results are the three regression coefficients, and the derived binding potential BP.

There is also an error criterion **Max Err.** to fit **Start Lin**. For instance, if **Max Err.** is set to 10% and the fit box of **Start Lin**. is checked, the model searches the earliest sample so that the deviation between the regression and all measurements is less than 10%. Samples earlier than the **Start Lin**. time are disregarded for regression and thus painted in gray.

---

**Note:** The reference methods MRTM2 and SRTM2 require $k'_2$ as an input parameter. The $k_2'$ resulting from the MRTM method above is a suitable estimate. Therefore, when switching in PKIN from the MRTM model to MRTM2 or SRTM2, $k_2'$ is automatically copied from MRTM, as long as **Model conversion** in the **Configuration** menu is enabled. ***See also*** (on page 113).

---

### Abstract [33]

"We developed and applied two new linearized reference tissue models for parametric images of binding potential (BP) and relative delivery (R1) for [11C]DASB PET imaging of 5-HT transporters in human brain. The original multilinear reference tissue model (MRTM0) was modified (MRTM) and used to estimate a clearance rate ($k'_2$) from the cerebellum (reference). Then, the number of parameters was reduced from three (MRTM) to two ($MRTM_2$) by fixing $k_2'$ . The resulting BP and $R_1$ estimates were compared with the corresponding nonlinear reference tissue models, SRTM and $SRTM_2$, and one-tissue kinetic

analysis (1TKA), for simulated and actual [11C]DASB data. MRTM gave $k'_2$ estimates with little bias (<1%) and small variability (<6%). MRTM2 was effectively identical to SRTM2 and 1TKA, reducing BP bias markedly over MRTMO from 12-70% to 1-4% at the expense of somewhat increased variability. MRTM2 substantially reduced BP variability by a factor of 2-3 over MRTM or SRTM. $MRTM_2$, $SRTM_2$ and 1TKA had $R_1$ bias < 0.3% and variability at least a factor of 2 lower than MRTM or SRTM. $MRTM_2$ allowed rapid generation of parametric images with the noise reductions consistent with the simulations. Rapid parametric imaging by $MRTM_2$ should be a useful method for human [11C]DASB PET studies.

# Ichise's Multilinear Reference Tissue Model 2 (MRTM2)

MRTM can be turned into a more robust method called MRTM2 for pixel-wise applications with the same two-step approach applied in SRTM2:

**1)** Calculate the clearance rate $k_2'$ of the reference TAC by MRTM or SRTM with VOI data which has a limited level of noise. To reduce the variability of the $k_2'$ estimate, the result from different high-BP VOIs can be averaged.

**2)** Fix $k_2'$: Use the estimated $k_2'$ value for the pixel-wise MRTM calculations, reducing the number of fitted parameters from 3 to 2.

If $k'_2$ is fixed, the equation of MRTM reduces to

$$C(T) = -\frac{V}{V'b}\left(\int_0^T C'(t)dt + \frac{1}{k'_2}C'(T)\right) + \frac{1}{b}\int_0^T C(t)dt$$

with only two regression coefficients V/(V'b) and 1/b for T > t*. BP is then calculated from the ratio of the two regression coefficients as

$$BP = -(\gamma_1/\gamma_2 + 1) = -(-\frac{V\,b}{V'b} + 1) = \frac{V}{V'} - 1.0$$

## Implementation Notes

After switching to the **Ichise NonInvasive MRTM2** in PKIN a suitable reference region must be selected. $k_2'$ is an input parameter which must be manually edited, or estimated by using first the MRTM or SRTM model. MRTM2 allows to fit a multilinear regression within a range starting at the parameters **Start Lin**. The results are two regression coefficients, and the derived binding potential BP.

There is also an error criterion **Max Err.** to fit **Start Lin**. For instance, if **Max Err.** is set to 10% and the fit box of **Start Lin**. is checked, the model searches the earliest sample so that the deviation between the regression and all measurements is less than 10%. Samples earlier than the **Start Lin**. time are disregarded for regression and thus painted in gray.

---

**Note:** The $k_2'$ resulting from the SRTM or MRTM method is a suitable estimate. Therefore, when switching in PKIN from the SRTM or MRTM model to MRTM2, $k_2'$ is automatically copied , as long as **Model conversion** in the **Configuration** menu is enabled. ***See also*** (on page 113).

---

### Abstract [33]

"We developed and applied two new linearized reference tissue models for parametric images of binding potential (BP) and relative delivery ($R_1$) for [11C]DASB PET imaging of 5-HT transporters in human brain. The original multilinear reference tissue model (MRTMO) was modified (MRTM) and used to estimate a clearance rate ($k_2'$) from the cerebellum (reference). Then, the number of parameters was reduced from three (MRTM) to two ($MRTM_2$) by fixing $k_2'$. The resulting BP and $R_1$ estimates were compared with the corresponding nonlinear reference tissue models, SRTM and $SRTM_2$, and one-tissue kinetic analysis (1TKA), for simulated and actual [11C]DASB data. MRTM gave $k_2'$ estimates with little bias (<1%) and small variability (<6%). MRTM2 was effectively identical to SRTM2 and 1TKA, reducing BP bias markedly over MRTMO from 12-70% to 1-4% at the expense of somewhat increased variability. MRTM2 substantially reduced BP variability by a factor of 2-3 over MRTM or SRTM. $MRTM_2$, $SRTM_2$ and 1TKA had $R_1$ bias < 0.3% and variability at least a factor of 2 lower than MRTM or SRTM. $MRTM_2$ allowed rapid generation of parametric images with the noise reductions consistent with the simulations. Rapid parametric imaging by $MRTM_2$ should be a useful method for human [11C]DASB PET studies."

# Logan's Reference Tissue Model based on Average k2'

The distribution volume ratio (DVR) can directly be calculated from the graphical method by using data from a reference region C'(t) with an average tissue-to-plasma clearance $k_2'$. Result is the linear regression equation

$$\frac{\int_0^T C(t)dt}{C(T)} = DVR\left[\frac{\int_0^T C'(t)dt + C'(T)/k'_2}{C(T)}\right] + \text{int}'$$

which contains DVR as the regression slope and an intercept int' which becomes constant after an equilibration time t*. The method does not require a 1-tissue compartment model structure of the data.

### Implementation Notes

After switching to the **Logan NonInvasive** model in PKIN a suitable reference region must be selected. $k_2'$ is an input parameter which must be manually edited, or estimated by using first the MRTM or SRTM model. **Logan NonInvasive** allows to fit a linear regression within a range starting at the parameters **Start Lin**. The results are the regression slope (= DVR = $k_3/k_4+1$) and intercept. Derived from the slope is binding potential $BP=k_3/k_4$.

There is also an error criterion **Max Err.** to fit **Start Lin**. For instance, if **Max Err.** is set to 10% and the fit box of **Start Lin**. is checked, the model searches the earliest sample so that the deviation between the regression and all measurements is less than 10%. Samples earlier than the **Start Lin** time are disregarded for regression and thus painted in gray.

---

**Note:** The $k_2'$ resulting from the SRTM or MRTM method might be a reasonable estimate for the average clearance rate $k_2'$. Therefore, when switching in PKIN from the SRTM or MRTM

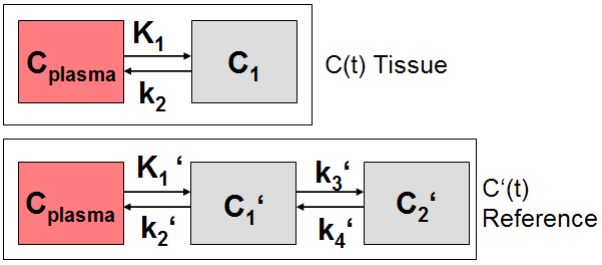
model to Logan NonInvasive, $k_2'$ of those methods is automatically copied to $k_2'$, as long as **Model conversion** in the **Configuration** menu is enabled. ***See also*** (on page 113).

### Abstract [36]

"The distribution volume ratio (DVR), which is a linear function of receptor availability, is widely used as a model parameter in imaging studies. The DVR corresponds to the ratio of the DV of a receptor-containing region to a nonreceptor region and generally requires the measurement of an arterial input function. Here we propose a graphical method for determining the DVR that does not require blood sampling. This method uses data from a nonreceptor region with an average tissue-to-plasma efflux constant $k_2$ to approximate the plasma integral. Data from positron emission tomography studies with [11C]raclopride (n = 20) and [11C]d-threo-methylphenidate ([11C]dMP) (n = 8) in which plasma data were taken and used to compare results from two graphical methods, one that uses plasma data and one that does not. $k_2$ was 0.163 and 0.051 min-1 for [11C]raclopride and [11C]dMP, respectively. Results from both methods were very similar, and the average percentage difference between the methods was -0.11% for [11C]raclopride and 0.46% for [11C]dMP for DVR of basal ganglia (BG) to cerebellum (CB). Good agreement between the two methods was also achieved for DVR images created by both methods. This technique provides an alternative method of analysis not requiring blood sampling that gives equivalent results for the two ligands studied. It requires initial studies with blood sampling to determine the average kinetic constant and to test applicability. In some cases, it may be possible to neglect the $k_2$ term if the BG/CB ratio becomes reasonably constant for a sufficiently long period of time over the course of the experiment."

## Watabe's Reference Tissue Model with 2 Compartments

An extension of the simplified reference model has been developed by Watabe et al. [49] for ligands which do not follow the usual assumptions of the reference tissue models. Instead of a 1-tissue compartment model, the reference tissue is described by a 2-tissue model as illustrated below.



Assuming that the non-specific distribution volume of both tissues is the same, the following operational equation for fitting the tissue TAC can be derived (see Millet et al [50], appendix C):

$$C(t) = R_1 \left[ C'(t) + aC'(t) \otimes e^{-(k_3' + k_4')t} + bC'(t) \otimes e^{-k_2 t} \right]$$

$$a = \frac{k_3' k_2'}{k_3' + k_4' - k_2}$$

$$a = \frac{k_2^{\ 2} - k_2(k_2' + k_3' + k_4') + k_2' k_4'}{k_3' + k_4' - k_2 \ +}$$

$$BP_{ND} = \frac{K_1 k_2'}{K_1' k_2 (1 + k_3' / k_4')} - 1$$

When the parameters $k_2'$, $k_3'$, and $k_4'$ are fixed to constants determined with receptor-rich tissue, only $R_1$ and $k_2$ need to be fitted for estimating the binding potential BP.

### Implementation Notes

After switching to the **2 Tissue Reference Model** in PKIN a suitable reference region must be selected. For convolution with the exponentials, the reference tissue TAC is resampled on a regular grid, which can be specified by the **sampl. interval** parameter in PKIN.

## Multi-linear Reference Tissue Model for [11C]-MP4A (RLS)

The **MP4A RLS (Nagatsuka)** model has been developed for the non-invasive quantification method (RLS) of the acetylcholinesterase (AChE) activity in the human brain from measurements with the $^{11}$C-MP4A acetylcholine analog. In contrast to reference methods for receptor tracers which use a reference devoid of specific binding, the present method uses a reference with very high AChE activity.

By applying the method of Blomqvist, the following multi-linear equation is derived

$$C(T) = p_1 C'(T) + p_2 \int_0^T C'(t)dt + p_3 \int_0^T C(t)dt$$

C(t) is the TAC from a cortical target region, and C'(t) the TAC from the reference region (striatum or cerebellum). It can be solved using multi-linear regression, yielding three regression coefficients from which three parameters of interest can be calculated:

**$R_1$** = $K_1/K'_1$ = $p_1$, the delivery in the target region relative to the reference;
**$k_2$** = $-p_3 - p_2/p_1$, the rate of back-diffusion from brain to blood;

**$k_3$** = $p_2/p_1$, the rate of tracer hydrolysis by AChE.

### Implementation Notes

After switching to the **MP4A RLS (Nagatsuka)** in PKIN a suitable reference region must be selected. The findings in different publications indicate that cerebellum yields more stable

results than striatum, most likely due to the higher impact of motion on the signal from the small striatum than the large cerebellum.

While the regression coefficients represent the fitting parameters, the rate constants are shown in the derived parameter section.

### Abstract [48]:

N -[(11)C]methylpiperidin-4-yl acetate ([(11)C]MP4A) is an acetylcholine analog. It has been used successfully for the quantitative measurement of acetylcholinesterase (AChE) activity in the human brain with positron emission tomography (PET). [(11)C]MP4A is specifically hydrolyzed by AChE in the brain to a hydrophilic metabolite, which is irreversibly trapped locally in the brain. The authors propose a new method of kinetic analysis of brain AChE activity by PET without arterial blood sampling, that is, reference tissue-based linear least squares (RLS) analysis. In this method, cerebellum or striatum is used as a reference tissue. These regions, because of their high AChE activity, act as a biologic integrator of plasma input function during PET scanning, when regional metabolic rates of [(11)C]MP4A through AChE (k(3); an AChE index) are calculated by using Blomqvist's linear least squares analysis. Computer simulation studies showed that RLS analysis yielded k(3) with almost the same accuracy as the standard nonlinear least squares (NLS) analysis in brain regions with low (such as neocortex and hippocampus) and moderately high (thalamus) k(3) values. The authors then applied these methods to [(11) C]MP4A PET data in 12 healthy subjects and 26 patients with Alzheimer disease (AD) using the cerebellum as the reference region. There was a highly significant linear correlation in regional k(3) estimates between RLS and NLS analyses (456 cerebral regions, [RLS k(3) ] = 0.98 x [NLS k(3) ], r = 0.92, P < 0.001). Significant reductions were observed in k(3) estimates of frontal, temporal, parietal, occipital, and sensorimotor cerebral neocortices (P < 0.001, single-tailed t-test), and hippocampus (P = 0.012) in patients with AD as compared with controls when using RLS analysis. Mean reductions (19.6%) in these 6 regions by RLS were almost the same as those by NLS analysis (20.5%). The sensitivity of RLS analysis for detecting cortical regions with abnormally low k 3 in the 26 patients with AD (138 of 312 regions, 44%) was somewhat less than NLS analysis (52%), but was greater than shape analysis (33%), another method of [(11)C]MP4A kinetic analysis without blood sampling. The authors conclude that RLS analysis is practical and useful for routine analysis of clinical [(11)C]MP4A studies.

# Non-Compartmental Models

PKIN includes some additional models, which are neither explicit compartment nor reference models. They include the important linear regression methods **Logan Plot** and **Patlak Plot**, recent alternative methods for estimating the total distribution volume, as well as simple methods to quickly calculate ratios between tissue TACs and/or the plasma concentration.

| Model Name | Description |
|---|---|
| ***Logan Plot*** (on page 118) | Graphical analysis of reversible system to calculate the total distribution volume. |
| ***Ichise MA1*** (on page 123) | Reformulation of the Logan plot as a multilinear analysis to reduce noise-induced bias. Result is the total distribution volume. |

| | |
|---|---|
| ***Ichise MA2*** (on page 124) | Multilinear analysis derived from the two-compartment model. Results are the total as well as the specific distribution volume. |
| ***Patlak Plot*** (on page 116) | Graphical analysis of irreversible system. Applied to FDG studies it allows to estimate glucose turnover. |
| Bolus/Infusion Optimization | Based on a bolus study, the bolus/infusion ratio for an equilibrium study can be estimated |
| Tissue/Plasma Ratio | Calculate the ratio of tissue binding to plasma concentration in order to get an estimate of the total DV |
| ***Ratio Methods*** (on page 127) | Calculate the ratio of specific binding to non-specific binding. |
| ***Retention Fraction*** (on page 128) | Calculate the fraction of pased tracer which is accumulated in tissue |
| ***Fractal Dimension*** (on page 129) | Calculation of the box-counting dimension of curves |

# Patlak Plot

The Patlak plot has been developed for systems with irreversible trapping [17,18]. Most often it is applied for the analysis of FDG, which can be modeled as a 2-tissue compartment model with $k_4$=0. The Patlak plot belongs to a group of *graphical analysis* techniques, whereby the measured TAC undergoes a transformation and is plotted against some sort of "normalized time".

The Patlak plot is given by the expression

$$\frac{C_{Tissue}(t)}{C_P(t)} = K \frac{\int_0^t C_P(\tau)d\tau}{C_P(t)} + V$$

This means that the measured PET activity is divided by plasma activity, and plotted at a "normalized time" (integral of input curve from injection divided by instantaneous plasma activity). For systems with irreversible compartments this plot will result in a straight line after sufficient equilibration time. The slope and the intercept must be interpreted according to the underlying compartment model. For the FDG model mentioned, the slope equals $K_1k_3/(k_2+k_3)$ and represents the influx, while the intercept V equals $V_0$+vB with the distribution volume $V_0$ of the reversible compartment $C_1$ and the fractional blood volume vB.

### Application of Patlak Plot as a Reference Method

When the plasma activity is not available, the Patlak plot can be employed as a reference method provided that there exists some tissue wherein tracer is not irreversibly trapped [42]. The procedure simply replaces $C_{plasma}(t)$ in the above equation by the TAC of the reference

tissue. Under several assumptions, including a common $K_1/k_2$, the slope of the linear regression represents the following relation

$$slope = K = \frac{k_2 k_3}{(k_2 + k_3)(1 - K_{eq})}$$

with the equilibrium constant $K_{eq}$.

For instance, the Patlak plot has been applied in this way to calculate an index of the influx $K_i$ of FDOPA using a cerebellum or occipital lobe TAC as the reference.

## Implementation Notes

The **Patlak Plot** model calculates and displays the transformed measurements as described by the formula above. It allows fitting a regression line within a range defined by the parameters **t***. The results are the regression slope and the intercept. There is also an error criterion **Max Err.** to fit **t*** . For instance, if **Max Err.** is set to 10% and the fit box of **t*** is checked, the model searches the earliest sample so that the deviation between the regression and all measurements is less than 10%. Samples earlier than the **t*** time are disregarded for regression and thus painted in gray. Note that **t*** must be specified in real acquisition time, although the x-axis units are in "normalized time". The corresponding normalized time which can be looked up in the plot is shown as a non-fitable result parameter **Start**.

For FDG data, the Lumped constant (LC) and the plasma glucose level (PG) of the patient should be entered. The metabolic rate of glucose MRGlu is then obtained from the regression slope by MRGlu = slope * PG / LC.

## Abstract [17]:

"A theoretical model of blood-brain exchange is developed and a procedure is derived that can be used for graphing multiple-time tissue uptake data and determining whether a unidirectional transfer process was dominant during part or all of the experimental period. If the graph indicates unidirectionality of uptake, then an influx constant ($K_i$) can be calculated. The model is general, assumes linear transfer kinetics, and consists of a blood-plasma compartment, a reversible tissue region with an arbitrary number of compartments, and one or more irreversible tissue regions. The solution of the equations for this model shows that a graph of the ratio of the total tissue solute concentration at the times of sampling to the plasma concentration at the respective times ($C_p$) versus the ratio of the arterial plasma concentration-time integral to $C_p$ should be drawn. If the data are consistent with this model, then this graph will yield a curve that eventually becomes linear, with a slope of $K_i$ and an ordinate intercept less than or equal to the vascular plus steady-state space of the reversible tissue region."

# Logan Plot

The Logan plot [19] is a *graphical analysis* technique developed for reversible receptor systems which allows estimating the total distribution volume Vt. The measured TAC $C_{Tissue}(t)$ is plotted as follows using the measured and integrated plasma activity:

$$\frac{\int_0^t C_{Tissue}(\tau)d\tau}{C_{Tissue}(t)} = K\frac{\int_0^t C_p(\tau)d\tau}{C_{Tissue}(t)} + V$$

For suitable systems and after sufficient equilibration time this plot will approach a straight line. The slope and the intercept of the line must be interpreted according to the underlying compartment model. The slope represents the total distribution volume $V_t$ of the tracer (including the blood space), for the 1-tissue compartment model

$K = K_1 / k_2 + vB = Vt$

and for the 2-tissue compartment model

$K = K_1 / k_2 (1+ k_3/k_4 + vB) = Vt$

### Implementation Notes

The **Logan Plot** model calculates and displays the measurements transformed as described by the formula above. It allows to fit a regression line within a range defined by the start time of the linear section **t***. The results are the distribution volume (slope) and the intercept. There is also an error criterion **Max Err** to fit **t***. For instance, if **Max Err** is set to 10% and the fit box of **t*** is checked, the model searches the earliest sample so that the deviation between the regression and all measurements is less than 10%. Samples earlier than the **t*** time are disregarded for regression and thus painted in gray. Note that **t*** must be specified in real acquisition time, although the x-axis units are in "normalized time". The corresponding normalized time which can be looked up in the plot is shown as a non-fitable result parameter **Start**.

The regression line is calculated using the traditional and the perpendicular distances, resulting in the **Vt** and **Vt_perpend**, respectively. It has been found that **Vt** has a tendency to underestimate the distribution volume at increasing noise levels. **Vt_perpend** shows less bias due to noise, but suffers from a somewhat increased variability.

### Standard Logan Plot, Abstract [19]

"A graphical method of analysis applicable to ligands that bind reversibly to receptors or enzymes requiring the simultaneous measurement of plasma and tissue radioactivities for multiple times after the injection of a radiolabeled tracer is presented. It is shown that there is a time t after which a plot of integral of ROI(t')dt'/ROI(t) versus integral of Cp(t')dt'/ROI(t) (where ROI and Cp are functions of time describing the variation of tissue radioactivity and plasma radioactivity, respectively) is linear with a slope that corresponds to the steady-state space of the ligand plus the plasma volume,.Vp. For a two- compartment model, the slope is given by lambda + Vp, where lambda is the partition coefficient and the intercept is -1/[kappa 2(1 + Vp/lambda)]. For a three-compartment model, the slope is lambda(1 +

Bmax/Kd) + Vp and the intercept is -[1 + Bmax/Kd)/k2 + [koff(1 + Kd/Bmax)]-1) [1 + Vp/lambda(1 + Bmax/Kd)]-1 (where Bmax represents the concentration of ligand binding sites and Kd the equilibrium dissociation constant of the ligand-binding site complex, koff (k4) the ligand-binding site dissociation constant, and k2 is the transfer constant from tissue to plasma). This graphical method provides the ratio Bmax/Kd from the slope for comparison with in vitro measures of the same parameter. It also provides an easy, rapid method for comparison of the reproducibility of repeated measures in a single subject, for longitudinal or drug intervention protocols, or for comparing experimental results between subjects. Although the linearity of this plot holds when ROI/Cp is constant, it can be shown that, for many systems, linearity is effectively reached some time before this. This analysis has been applied to data from [N-methyl-11C]-(-)-cocaine ([11C]cocaine) studies in normal human volunteers and the results are compared to the standard nonlinear least- squares analysis. The calculated value of Bmax/Kd for the high-affinity binding site for cocaine is 0.62 +/- 0.20, in agreement with literature values."

### Logan Plot with Perpendicular Distances in Regression, Abstract [51]

"Logan's graphical model is a robust estimation of the total distribution volume (DVt) of reversibly bound radiopharmaceuticals, but the resulting DVt values decrease with increasing noise. The authors hypothesized that the noise dependence can be reduced by a linear regression model that minimizes the sum of squared perpendicular rather than vertical (y) distances between the data points and fitted straight line. To test the new method, 15 levels of simulated noise (repeated 2,000 times) were added to synthetic tissue activity curves, calculated from two different sets of kinetic parameters. Contrary to the traditional method, there was no ( P > 0.05) or dramatically decreased noise dependence with the perpendicular model. Real dynamic 11C (+) McN5652 serotonin transporter binding data were processed either by applying Logan analysis to average counts of large areas or by averaging the Logan slopes of individual-voxel data. There were no significant differences between the parameters when the perpendicular regression method was used with both approaches. The presented experiments show that the DVt calculated from the Logan plot is much less noise dependent if the linear regression model accounts for errors in both the x and y variables, allowing fast creation of unbiased parametric images from dynamic positron-emission tomography studies."

## RE-GP Analysis

In 2009 Zhou et al. introduced a new graphical method [60]. It can be applied with a plasma input curve for the calculation of the distribution volume, and with a reference tissue curve for the calculation of the binding potential. The equation of the graphical plot called "RE plot" (for Relative Equilibrium) is given by

$$\frac{\int_0^t C_{Tissue}(\tau)d\tau}{C_p(t)} = Vt_{RE}\frac{\int_0^t C_P(\tau)d\tau}{C_p(t)} + \alpha$$

For the RE plot to be applicable there must exist a time t* after which two conditions are fulfilled:

1) The plasma input curve must be mono-exponential. This condition can be verified by fitting a single exponential to the late part of the plasma curve on the **Blood** tab of PKIN.

2) The ratio of $C_{Tissue}/C_p$ is constant. This condition can be verified by switching the **KM** model to the **Tissue/Plasma Ratio** model.

Under these conditions the tracer in all tissue compartments reaches equilibrium relative to plasma. Note that the conditions must be verified explicitly, because the linear appearance of the RE plot is not a sufficient criterion.

It was shown with Raclopride data and with simulations, that unlike the Logan plot the RE plot is not suffering from bias due to high noise levels. As a consequence, the results obtained with VOI-averaged TACs is consistent to the results obtained in pixel-wise applications. However, it was found that violation of the relative equilibrium condition did introduce bias. To compensate this bias Zhou et al [61] combined the RE plot with the Patlak plot in the following bi-graphical manner which is called the **RE-GP Analysis**:

The same data is analyzed with the RE plot above and the Patlak plot,

$$\frac{C_{Tissue}(t)}{C_P(t)} = K \frac{\int_0^t C_P(\tau)d\tau}{C_P(t)} + \beta$$

using the same t* for fitting two respective regression lines. A consistent and unbiased distribution volume is then obtained by combining the slopes and intercepts of the two plots:

$$V_t = Vt_{RE} - \frac{\alpha K}{\beta}$$

For the pixel-wise application of the RE-GP Analysis the results of the Patlak plot are smoothed, so that the calculation turns into

$$V_t = Vt_{RE} - \frac{\alpha K_s}{\beta_s}$$

where $K_s$ and $\beta_s$ are obtained from spatially smoothed maps of K and β.

### Implementation Notes

The **RE-GP Analysis** model calculates and displays the measurements transformed as described by the RE plot formula above. It allows fitting a regression line using the data points after a time **t***. Note that **t*** must be specified in real acquisition time, although the x-axis units are in "normalized time". The corresponding normalized time which can be looked up in the plot is shown as a non-fitable result parameter **Start**.

If **t*** is changed to define a new data segment, the program finds the closest acquisition start time, fits the two regression lines to the RE plot and the Patlak plot, and updates the calculated parameters. The main outcome is the distribution volumes calculated with the

RE-GP analysis (**Vt-REGP**). For a comparison, Vt calculated with the RE plot alone (**Vt-RE**) is also shown.

Per default, only the curves of the RE plot and its regression line are shown in the curve area. However, the Patlak plot and its regression line can also be visualized by enabling their boxes in the curve control area. Note that the values of the Patlak plot may have a very different dynamic range than the RE plot. Therefore it is recommended switching off the RE curves when switching on the Patlak ones.

### RE-GP Plot Publication, Abstract [61]

"In quantitative dynamic PET studies, graphical analysis methods including the Gjedde–Patlak plot, the Logan plot, and the relative equilibrium-based graphical plot (RE plot) (Zhou Y., Ye W., Brašić J.R., Crabb A.H., Hilton J., Wong D.F. 2009. A consistent and efficient graphical analysis method to improve the quantification of reversible tracer binding in radioligand receptor dynamic PET studies. Neuroimage 44(3):661–670) are based on the theory of a compartmental model with assumptions on tissue tracer kinetics. If those assumptions are violated, then the resulting estimates may be biased. In this study, a multi-graphical analysis method was developed to characterize the non-relative equilibrium effects on the estimates of total distribution volume (Vt) from the RE plot. A novel bi-graphical analysis method using the RE plot with the Gjedde–Patlak plot (RE-GP plots) was proposed to estimate Vt for the quantification of reversible tracer kinetics that may not be at relative equilibrium states during PET study period. The RE-GP plots and the Logan plot were evaluated by 19 [11C]WIN35,428 and 10 [11C]MDL100,907 normal human dynamic PET studies with brain tissue tracer kinetics measured at both region of interest (ROI) and pixel levels. A 2-tissue compartment model (2TCM) was used to fit ROI time activity curves (TACs). By applying multi-graphical plots to the 2TCM fitted ROI TACs which were considered as the noise-free tracer kinetics, the estimates of Vt from the RE-GP plots, the Logan plot, and the 2TCM fitting were equal to each other. For the measured ROI TACs, there was no significant difference between the estimates of the Vt from the RE-GP plots and those from 2TCM fitting ($p=0.77$), but the estimates of the DVT from the Logan plot were significantly ($p < 0.001$) lower, 2.3% on average, than those from 2TCM fitting. There was a highly linear correlation between the ROI DVT from the parametric images (Y) and those from the ROI kinetics (X) by using the RE-GP plots ($Y=1.01X+0.23$, $R^2=0.99$). For the Logan plot, the ROI estimates from the parametric images were 13% to 83% lower than those from ROI kinetics. The computational time for generating parametric images was reduced by 69% on average by the RE-GP plots in contrast to the Logan plot. In conclusion, the bigraphical analysis method using the RE-GP plots was a reliable, robust and computationally efficient kinetic modeling approach to improve the quantification of dynamic PET."

## Ito Plot

In 2010 Ito et al. introduced a new graphical method for the analysis of receptor ligand binding [62]. It is applied with a plasma input curve for the calculation of the total distribution volume $V_t$, the distribution volume of the nondisplaceable compartment $V_{ND}$, and therefore also allows calculation of the binding potential $BP_{ND}$. Furthermore, the shape of the plot gives an indication whether there is specific binding or not not.

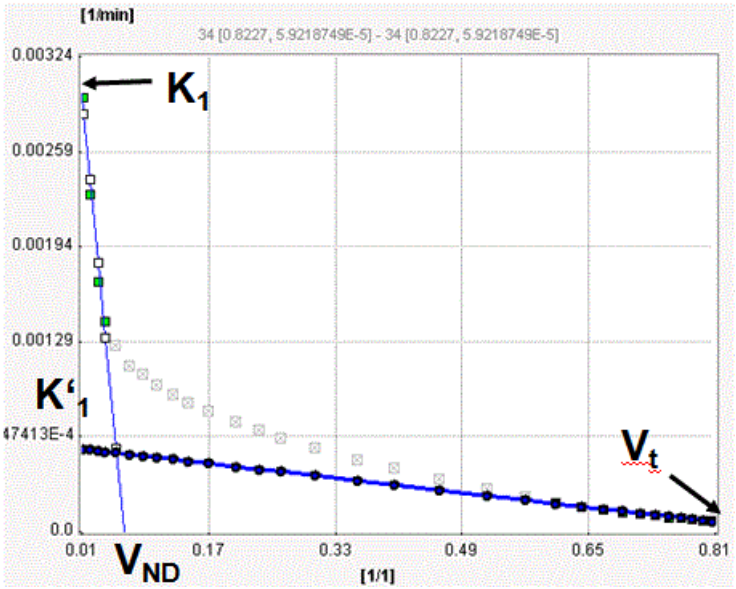
The equation of the graphical plot called is given by the equation

$$\frac{C_{Tissue}}{\int_0^t C_P(\tau)d\tau} = a - b\frac{\int_0^t C_{Tissue}(\tau)d\tau}{\int_0^t C_P(\tau)d\tau}$$

The following cases can be distinguished:

**1)** The plot is a straight line, indicating the absence of specific binding. In this case the line equation parameters have the following interpretation in terms of a 2-tissue compartment model:
a = $K_1$ (y-intercept), b = $k_2$ (slope), and the x-intercept equals $V_{ND}$.

**2)** The plot has a curved shape, indicating the presence of specific binding. In this case two regression lines are fitted to the plot: a line to the early part within a short time segment $T_1$ to $T_2$, and a line to the end part after an equilibration time t*. The parameters of the resulting lines can be interpreted as follows:
Early line: $a_1 = K_1$, $b_1 = k_2$, x-intercept = $V_{ND}$ of a 2-tissue compartment model.
Late line: $a_2 = K'_1$, $b_2 = k'_2$, x-intercept = $V_t$ of a 1-tissue compartment model.




The binding potential can finally be calculated by $BP_{ND} = (V_t - V_{ND})/V_{ND}$

## Implementation Notes

The **Ito Plot** model calculates and displays the measurements transformed as described by the Ito plot formula above. It allows fitting two regression lines as follows:

**1)** The first regression line is fitted within the data segment specified by the times **T1** and **T2** (in acquisition time).

**2)** The second regression line is fitted to the late data segment starting at equilibration time **t***.

If any of the times is changed to define a new data segment, the program finds the closest acquisition start time, fits the two regression lines, and updates the calculated parameters.

Per default, only the Ito Plot and the late regression line is shown in the curve area. However, the early regression line can also be visualized as illustrated above by enabling its box in the curve control area.

### Ito Plot Publication, Abstract [62]

"In positron emission tomography (PET) studies with radioligands for neuroreceptors, tracer kinetics have been described by the standard two-tissue compartment model that includes the compartments of nondisplaceable binding and specific binding to receptors. In the present study, we have developed a new graphic plot analysis to determine the total distribution volume (V(T)) and nondisplaceable distribution volume (V(ND)) independently, and therefore the binding potential (BP(ND)). In this plot, Y(t) is the ratio of brain tissue activity to time-integrated arterial input function, and X(t) is the ratio of time-integrated brain tissue activity to time-integrated arterial input function. The x-intercept of linear regression of the plots for early phase represents V(ND), and the x-intercept of linear regression of the plots for delayed phase after the equilibrium time represents V(T). BP(ND) can be calculated by BP(ND)=V(T)/V(ND)-1. Dynamic PET scanning with measurement of arterial input function was performed on six healthy men after intravenous rapid bolus injection of [(11)C]FLB457. The plot yielded a curve in regions with specific binding while it yielded a straight line through all plot data in regions with no specific binding. V(ND), V(T), and BP(ND) values calculated by the present method were in good agreement with those by conventional non-linear least-squares fitting procedure. This method can be used to distinguish graphically whether the radioligand binding includes specific binding or not."

## Ichise Multilinear Analyis MA1

Ichise's MA1 analysis method is a technique for calculating the total distribution volume of reversible receptor systems. It is a further development of the Logan Plot aimed at minimizing the bias induced by noise in the measurements. The following bilinear relationship was derived [34]:

$$C(t) = -\frac{V}{b}\int_0^t C_P(\tau)d\tau + \frac{1}{b}\int_0^t C(\tau)d\tau$$

where C(t) represents the tissue time-activity curve, $C_a(t)$ the plasma activity, V the total distribution volume, and b the intercept of the Logan plot which becomes constant after an equilibration time t*. In PKIN, the bilinear regression is performed using a singular value decomposition. The result are the two coefficients V/b and b, from which V can easily be derived.

Based on simulation and experimental data the authors show that MA1 demonstrates the largest bias reduction among several methods. Therefore they conclude, that MA1 is the method of choice for calculating the total distribution volume, if t* can accurately be defined.

### Implementation Notes

The MA1 method requires the specification of the the equilibration time as the **t*** parameter. Similar to the Patlak and Logan methods, **t*** can be fitted. As it equals the equilibration time of the Logan plot, it is also possible to perform a Logan plot first and use its equilibration time.

### Abstract [34]

"In an attempt to improve neuroreceptor distribution volume (V) estimates, the authors evaluated three alternative linear methods to Logan graphical analysis (GA): GA using total least squares (TLS), and two multilinear analyses, MA1 and MA2, based on mathematical rearrangement of GA equation and two-tissue compartments, respectively, using simulated and actual PET data of two receptor tracers, [(18)F]FCWAY and [(11)C]MDL 100,907. For simulations, all three methods decreased the noise-induced GA bias (up to 30%) at the expense of increased variability. The bias reduction was most pronounced for MA1, moderate to large for MA2, and modest to moderate for TLS. In addition, GA, TLS, and MA1, methods that used only a portion of the data (T > t*, chosen by an automatic process), showed a small underestimation for [(11)C]MDL 100,907 with its slow kinetics, due to selection of t* before the true point of linearity. These noniterative methods are computationally simple, allowing efficient pixelwise parameter estimation. For tracers with kinetics that permit t* to be accurately identified within the study duration, MA1 appears to be the best. For tracers with slow kinetics and low to moderate noise, however, MA2 may provide the lowest bias while maintaining computational ease for pixelwise parameter estimation."

## Ichise Multilinear Analyis MA2

Similar to MA1, Ichise's MA2 analysis method is another alternative technique developed to calculate the total distribution volume of reversible receptor systems with minimal bias. Based on the 2-tissue compartment model equations the following multilinear relationship was derived [34]:

$$C(T) = \gamma_1 \int_0^T \int_0^s C_P(t)\,dtds + \gamma_2 \int_0^T \int_0^s C(t)\,dtds + \gamma_3 \int_0^T C(t)\,dt + \gamma_4 \int_0^T C_P(t)\,dt$$

where C(t) represents the tissue time-activity curve, and $C_P(t)$ the plasma activity. A multilinear regression can be performed to calculate the four regression coefficients from the transformed data. The total distribution volume V is then calculated as the ratio $-\gamma_1/\gamma_2$ of the first two regression coefficients, and the distribution volume of specific binding by the expression

$$V_S = \frac{-\gamma(\gamma_1 + \gamma_3\gamma_4) + \gamma_2\gamma_4^2}{\gamma_2(\gamma_1 + \gamma_3\gamma_4)}$$

The MA2 method has two advantages:

1) It is independent of an equilibration time, so that the data from the first acquisition can be included into the regression.

2) An estimate of the specific distribution volume is also obtained. The authors state, that although the method has been derived with the 2-tissue model, it still shows a good performance with the data representing only 1-tissue characteristics [34].

The authors conclude that for tracers with slow kinetics and low to moderate noise, MA2 may provide the lowest bias while maintaining computational ease.

### Implementation Notes

In PKIN, the multilinear regression is performed using a singular value decomposition. Although no equilibration time is required for MA2, there is a **Start** parameter to disregard early samples from the regression as for the graphical plots and MA1.

### Abstract [34]

"In an attempt to improve neuroreceptor distribution volume (V) estimates, the authors evaluated three alternative linear methods to Logan graphical analysis (GA): GA using total least squares (TLS), and two multilinear analyses, MA1 and MA2, based on mathematical rearrangement of GA equation and two- tissue compartments, respectively, using simulated and actual PET data of two receptor tracers, [(18)F]FCWAY and [(11)C]MDL 100,907. For simulations, all three methods decreased the noise-induced GA bias (up to 30%) at the expense of increased variability. The bias reduction was most pronounced for MA1, moderate to large for MA2, and modest to moderate for TLS. In addition, GA, TLS, and MA1, methods that used only a portion of the data (T > t*, chosen by an automatic process), showed a small underestimation for [(11)C]MDL 100,907 with its slow kinetics, due to selection of t* before the true point of linearity. These noniterative methods are computationally simple, allowing efficient pixelwise parameter estimation. For tracers with kinetics that permit t* to be accurately identified within the study duration, MA1 appears to be the best. For tracers with slow kinetics and low to moderate noise, however, MA2 may provide the lowest bias while maintaining computational ease for pixelwise parameter estimation."

## Bolus/Infusion Optimization

When a compartment system has equilibrated, the total distribution volume can be calculated easily as the ratio of tracer concentration in tissue to the metabolite-corrected plasma concentration with a single static scan. It has been found that the time required to reach equilibrium can be shortened by an optimized tracer delivery. A setup which does not require a sophisticated tracer delivery system is to apply an initial bolus and continue with a constant infusion.

Carson et al. [23] have developed a method to optimize the ratio between the activity given as the initial bolus and the activity level of the subsequent infusion for quickly reaching an equilibrium (Appendix B in [23]). It is assumed that tissue TACs as well as the input curve have been measured beforehand in a bolus experiment. Ideally then, the measured activities represent the impulse response of the system. Under this assumption it is possible to calculate the tissue response for any given input curve by just convolving the TACs with the input curve. For a bolus and infusion (B/I) experiment the input function can be described as

an initial impulse followed by a step function, and the convolution can be analytically solved as

$$C_{\text{expected}}(t) = \frac{K_{bol} C_{bolus}(t) + \int_0^t C_{bolus}(\tau) d\tau}{K_{bol} + T}$$

$K_{bol}$ [min] defines the contribution of the bolus in minutes of infusion, and T is the total duration of the infusion (end of last frame).

## Implementation Notes

It is assumed that the data of a bolus study has been loaded. When the **Bolus/Infusion Opt** model is selected, the expected tissue activity according to the formula above is calculated using the default parameters, and shown as the model curve.

$K_{bol}$ can be estimated. The user has to enter a reasonable equilibration time as the input parameter **Start Equilibr.** When **Fit current region** is activated, the optimal $K_{bol}$ is calculated. The criterion for an equilibrium is that the calculated activities from **Start Equilibr** on are as constant as possible. Also, please note the following:

**1)** The same formulation holds for both TACs and input curves. However, $K_{bol}$ can only be fitted with the TAC curve, not the input curve. For the blood curve, the **Bolus/Infusion Opt** model is only usable for visualizing the plasma response with an entered $K_{bol}$ value which was obtained in TAC fitting.

**2)** If the **Bolus/Infusion Opt** model is applied to a TAC and the **Fit blood param** is enabled, the **Bolus/Infusion Opt** model is applied to the plasma curve as well during a fit using the plasma model curve. Therefore the plasma model should be an interpolation model, NOT THE B/I model! $K_{bol}$ is a common parameter in the fit, and the criterion is that both the expected TAC and the expected input curve are constant.

**3)** The **Bolus/Infusion Opt** model can be used for coupled fitting to find the optimal dose for several tissues. In a coupled fit, only the TACs are used, and the input curve is currently neglected (as opposed to 2).

**4)** The residual weighting of all curves involved in the fit should be set to constant weighting.

**5)** With the **Bolus/Infusion Opt** model it is not possible to switch off individual points after the specified equilibration start time.

## Abstract [23]

"Positron emission tomography studies with the opiate antagonist [18F]cyclofoxy ([18F]CF) were performed in baboons. Bolus injection studies demonstrated initial uptake dependent on blood flow. The late uptake showed highest binding in caudate nuclei, amygdala, thalamus, and brainstem and the least accumulation in cerebellum. By 60 min postinjection, regional brain radioactivity cleared at the same rate as metabolite- corrected plasma, i.e., transient equilibrium was achieved. Compartmental modeling methods were applied to time- activity curves from brain and metabolite-corrected plasma. Individual rate constants were estimated with poor precision. The model estimate of the total volume of distribution (VT), representing the ratio of tissue radioactivity to metabolite-corrected plasma at

equilibrium, was reliably determined. The apparent volume of distribution (Va), the concentration ratio of tissue to metabolite-corrected plasma during transient equilibrium, was compared with the fitted VT values to determine if single-scan methods could provide accurate receptor measurements. Va significantly overestimated VT and produced artificially high image contrast. These differences were predicted by compartment model theory and were caused by a plasma clearance rate that was close to the slowest tissue clearance rate. To develop a simple method to measure VT, an infusion protocol consisting of bolus plus continuous infusion (B/I) of CF was designed and applied in a separate set of studies. The Va values from the B/I studies agreed with the VT values from both B/I and bolus studies. This infusion approach can produce accurate receptor measurements and has the potential to shorten scan time and simplify the acquisition and processing of scan and blood data."

## Tissue/Plasma Ratio

This auxiliary model simply divides the tissue TAC at each sampling time by the interpolated plasma activity at that time and displays it as a curve called **Tissue/Plasma Ratio**.

Under equilibrium conditions this ratio is equal to the total distribution volume of tracer in tissue. Therefore, the plot of the **Tissue/Plasma Ratio** against time is a quick means to check whether the system has equilibrated (plot becomes constant) or not.

## Tissue Ratio Methods

This auxiliary model is aimed at receptor tracers for which a reference tissue without specific binding is available. It allows getting a quick estimate of the binding potential BP using two different methods as described by Ito et al. [24].

At the time, when specific binding $C_2$ peaks, its derivative equals zero (transient equilibrium) and $BP=k_3/k_4=C_2/C_1$ (non-specific/specific binding). In principle, however, neither $C_1$ nor $C_2$ of a tissue TAC are known. It is assumed that specific binding is equal among tissues, so the $TAC_{ns}$ from a tissue without specific binding (reference) is regarded as $C_1$, and $C_2$ is calculated by TAC- $TAC_{ns}$.

Two different ratios are calculated by the **Tissue Ratio Methods** model:

$$BP_{ND} = \frac{k_3}{k_4} = \frac{C_2(t_{trans.equ.})}{C_1(t_{trans.equ.})}$$

This ratio is calculated for all times, but it is only valid at the time of transient equilibrium. There is no automatic routine for detecting this peak at the moment. However, the user can easily find this time by looking at the **Tac - Reference** curve (enable check box).

The second ratio calculated is called the **interval method** in [24].

$$BP_{ND} = \frac{k_3}{k_4} = \frac{\int_{tb}^{te} C_2(t)dt}{\int_{tb}^{te} C_1(t)dt}$$

Here, the two curves are integrated in a time interval which must include the time of transient equilibrium ($t_b$=9min. $t_e$=45 min for raclopride, where the time of transient equilibrium is in the range 20 to 24 min [24]).

### Implementation Notes

**1)** After switching to **Tissue Ratio Methods** a suitable reference tissue without specific binding must be selected.

**2)** The integration start time of the interval method must be specified by the user as the input parameter **Integral start time**.

**3)** The BP estimates are calculated for all times (for the integral method only after the **Integral start time**) and presented as curves. These curves can easily be exported as values using the ***save button*** (on page 28).

### Abstract [24]

"Several approaches have been applied for quantification of D2 dopamine receptors in positron emission tomography studies using [11C]raclopride. Initial approaches were based on analyses of data obtained after rapid bolus injection of [11C]raclopride. A continuous infusion paradigm has more recently been applied. The current study compares these approaches in healthy men. Two positron emission tomography measurements were performed in each of six healthy men, the first with rapid bolus injection and the second with continuous infusion of [11C]raclopride. In rapid bolus injection, the binding potential was calculated by the following methods. One approach is the kinetic analysis using the standard three- compartment model. Another is to define a transient equilibrium at the moment when the specific binding reaches its maximum. In continuous infusion, binding potential was calculated by using time-activity data at equilibrium condition. All methods gave almost identical binding potential, representing cross-validation of these methods. The continuous infusion method can provide "true" equilibrium condition. The kinetic analysis is a sophisticated approach but requires determination of an arterial input function. The transient equilibrium method thus is suitable for routine clinical research, since it does not require determination of an arterial input function."

## Retention Fraction

The **retention fraction** is the fraction of the total tracer delivered to an organ that is extracted into and retained by the tissue. It is the residual after clearances of the vascular component and the portion of the tracer that rapidly back diffuses from tissue to blood. Usually this fraction of tracer is sequestered in more slowly turning over metabolic or membrane binding processes. Glossary [47]

Given a time-activity curve and an approximate value of tissue perfusion F, this auxiliary model allows calculating the retention fraction R by

$$R(t) = \frac{C_{Tissue}(t)}{F\int_0^t C_P(\tau)d\tau}$$

dividing the tissue TAC at each sampling time by F times the plasma activity integrated from the beginning to frame mid-time.

## Fractal Dimension

The **Fractal Dimension** model measures the complexity of a 2-dimensional structure by calculating its box-counting dimension [25]. The idea is to subdivide the area into a number of square boxes and simply count the number of boxes containing some part of the structure. The mesh size is defined as s, so 1/s gives the number of segments in each of the 2 dimensions. Specifying 1/s=5 therefore means a subdivision into 5*5=25 boxes. This counting process is repeated with increasing the number of intervals to a specified maximum number given as a model parameter. Next, the data are plotted in a double-logarithmic way, namely log(N(s)) on the y axis and log(1/s) on the x-axis. The box-counting dimension is then obtained as the slope of a linear regression through the plotted points.

We would like to thank Prof. Ludwig G. Strauss (l.strauss@dkfz-heidelberg.de) for the model implementation and for making it publicly available.

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