Published in final edited form as:

Nucl Med Commun. 2015 February ; 36(2): 187–193. doi:10.1097/MNM.0000000000000231.

Image-derived input function with factor analysis and a priori information

Urban Simon i^{1,2} and Paolo Zanotti-Fregonara^{3,4}

¹Jožef Stefan Institute, Jamova 39, SI-1000 Ljubljana, Slovenia

²The Centre of Excellence for Biosensors, Instrumentation and Process Control - COBIK, Tovarniška 26, SI-5270 Ajdovš ina, Slovenia

³Univ. Bordeaux, CNRS, INCIA, UMR 5287, F-33400 Talence, France

⁴Molecular Imaging Branch, National Institute of Mental Health, National Institute of Health, Bethesda, Maryland, USA

Abstract

Background—Quantitative positron emission tomography (PET) studies often require the cumbersome and invasive procedure of arterial cannulation to measure the input function. This study sought to minimize the number of necessary blood samples by developing a factor-analysis based image-derived input function (IDIF) methodology for dynamic PET brain studies.

Methods—IDIF estimation was performed as follows: 1) carotid and background regions were segmented manually on early PET time frame; 2) blood-weighted and tissue-weighted time activity curves (TAC) were extracted with factor analysis; 3) factor analysis results were de-noised and scaled by using the voxels with the highest blood signal; 4) using population data and one blood sample at 40 minutes, the whole-blood TAC was estimated from post-processed factor analysis results; and 5) the parent concentration was finally estimated by correcting the whole blood curve with measured radiometabolite concentrations. The methodology was tested using data from 10 healthy subjects imaged with [¹¹C](R)-rolipram. The accuracy of IDIFs was assessed against full arterial sampling by comparing the area under the curve (AUC) of the input functions and by calculating the total distribution volume (V_T).

Results—The shape of the image-derived whole-blood TAC matched well the reference arterial curves, and the whole-blood AUCs was accurately estimated (mean error $1.0 \pm 4.3\%$). The relative Logan- V_T error was $-4.1 \pm 6.4\%$. Compartmental modeling and spectral analysis gave less accurate V_T results than Logan.

Conclusion—A factor-analysis based IDIF for [¹¹C](R)-rolipram brain PET studies that relies on single blood sample and population data can be used for accurate quantification of Logan- V_T values.

Correspondence: Urban Simon i, Jožef Stefan Institute, Jamova 39, SI-1000 Ljubljana, Slovenia, EU, Tel: +386 (0)1 5885 400, Fax: +386 (0)1 5885 454, urban.simoncic@gmail.com.

Conflict of Interest Notification

There is no conflict of interests.

Keywords

Image-derived input function; Factor analysis; [^{11}C](R)-rolipram; PET

Introduction

An important logistical limitation of quantitative positron emission tomography (PET) scans is the need to measure, during image acquisition, the concentration over time of the parent radiotracer in plasma, i.e. the input function. This is generally done by collecting serial arterial blood samples, then separating the fraction of parent compound from its radiometabolites. The whole procedure is labor-intensive, time-consuming and uncomfortable for the patient, and alternative techniques are needed to reduce – or possibly eliminate – the need for blood sampling. Towards this end, one of the most often studied techniques is image-derived input function (IDIF). This approach relies on using physiological time activity curves (TAC) obtained from a blood pool visible on dynamic images. After opportune partial volume effect and radiometabolite correction, these TACs might replace serial arterial sampling as an input for kinetic modeling. While large blood pools, such as the heart or the aortic segments, might give IDIFs of good quality [1], getting an usable signal from smaller vessels, such as the carotids for brain studies, is much more challenging, due to partial volume effects [2]. Several strategies to obtain an IDIF from carotid arteries have been proposed. These include using accurate anatomical information from the co-registered MRI [3], correcting partial-volume effect during the image reconstruction procedure [4], blind source separation algorithms to derive the input function through the source signal mixing process [5], correcting spill-in by linear least-squares analysis with some blood samples [6] and many others [2].

Factor analysis is a statistical technique that can extract the physiological TACs from dynamic image sequences [7–8], by separating the dynamic PET image into its blood and tissue signal components over time. Factor analysis assumes that the observed signals are linearly transformed into a lower number of unobserved signals, called factors. Factor analysis can be implemented as either an algebraic manipulation of the observed signals [8–9] or as a least-squares-based problem with additional constraints such as non-negativity of factors and factor images [10].

The aim of the present study was to develop and validate an IDIF method for [^{11}C](R)-rolipram brain PET studies based on factor analysis and relying on single blood sample and *a priori* information of radioligand's kinetic behavior, vessel geometry, and scanner characteristics.

Materials and methods

Radiotracer preparation

[^{11}C](R)-rolipram was synthesized as previously described [11] and according to Investigational New Drug Application #73,149, submitted to the US Food and Drug

Administration. A copy of the application is available at: <http://pdsp.med.unc.edu/snidd/nidpulldownPC.php>. The radiotracer was obtained in high radiochemical purity (> 99%).

Image acquisition

Data from 10 consecutive healthy subjects who participated in a previous study were used [12]. All subjects gave written informed consent. The protocol was approved by the Ethics Committee of the National Institutes of Health.

Dynamic PET images were acquired for 90 minutes after a bolus injection of [^{11}C](R)-rolipram (695 ± 152 MBq) with an Advance tomograph (GE Medical Systems, Waukesha, WI). The dynamic scan comprised 27 frames (six frames of 30 seconds each, then 3×60 s, 2×120 s, and 16×300 s). Images were reconstructed with filtered back-projection on a 128×128 matrix with a voxel size of $2.0 \times 2.0 \times 4.25$ mm. An eight-minute ^{68}Ge transmission scan was obtained before radiotracer injection for attenuation correction.

Input functions were obtained by drawing serial arterial samples from the radial artery: samples of 1 ml each were drawn from the radial artery at 15-second intervals until 150 seconds, followed by 3 ml samples at 3, 4, 6, 8, 10, 15, 20, 30, 40, and 50 minutes, and 4.5 ml at 60, 75, and 90 minutes. Decay-corrected whole-blood activity, the fraction of unchanged radiotracer in plasma, and the plasma/whole-blood ratio were calculated as described in previous studies [11, 13].

A 3D T1 weighted magnetic resonance imaging (MRI) scan was also obtained for each subject, using a 256×256 matrix. The machine used was either a 3-T Signa scanner (GE Medical Systems, Waukesha, WI; voxel size of $0.86 \times 0.86 \times 1.2$ mm) or an Achieva 3-T MRI scanner (Philips Health Care, Andover, MA; voxel size of $1 \times 0.94 \times 0.94$ mm).

Image analysis

The MR image from each subject was first coregistered to the average PET image using SPM5 (Wellcome Department of Imaging Neuroscience; University College London, UK). Then, the MR and PET images were normalized to a standard space (Montreal Neurological Institute space) using the transformation parameters from the MR images. Finally, a ROI template in the MNI space was used to derive the TACs of the regions used for kinetic modeling: thalamus (12.6 cm^3), caudate (5.6 cm^3), putamen (6.5 cm^3), cerebellum (51.2 cm^3), frontal (27.2 cm^3), parietal (26.6 cm^3), lateral temporal (25.0 cm^3), occipital (31.2 cm^3), anterior cingulate (7.5 cm^3), and medial temporal (14.3 cm^3) cortices.

Estimating the whole-blood TAC

Segmentation of carotid and background regions—Carotid and background regions of interest were manually drawn directly on the second PET frame (0.5 – 1 min) and then copied to all the frames (Figure 1). Carotid and background regions contained 110 ± 17 and 177 ± 31 voxels, respectively (i.e. the variation was slightly below 20%).

Factor analysis—The factor analysis assumes that the dynamic image with n time frames and m voxels can be decomposed into a p number of time signals or factors ($p < m$), and TAC

of each voxel can be represented with a linear combination of those p factors. In this particular case we assumed that two factors are sufficient – one for blood time signal and another for tissue time signal. Therefore, the image $\mathbf{I}$ of dimension $n \times m$ was formulated mathematically (Eq. 1) as the product of the factor matrix $\mathbf{F}$ of dimension $n \times 2$, which represents two factors, and the factor image matrix $\mathbf{A}$ of dimension $2 \times m$, which describes the spatial distribution of the factors. Obviously, the radioactivity concentration cannot be negative and the contribution of blood or tissue signal to the voxels' TAC cannot be negative. Therefore, the factor analysis results are physically viable only if the matrices $\mathbf{F}$ and $\mathbf{A}$ are non-negative.

$$\mathbf{I} = \mathbf{F}\mathbf{A} + \varepsilon \quad 1.$$

$$\Phi_{FA}(\mathbf{A}, \mathbf{F}) = \|\mathbf{W} \circ (\mathbf{I} - \mathbf{F}\mathbf{A})\| \quad 2.$$

$$C_b(t) = \begin{cases} 0; & t < t_1 \\ Q \int_{t_1}^t \sum_{i=1}^3 A_i e^{-\delta_i(t-\tau)} d\tau; & t_1 < t < t_2 \\ Q \int_{t_1}^{t_2} \sum_{i=1}^3 A_i e^{-\delta_i(t-\tau)} d\tau; & t_2 < t \end{cases} \quad 3.$$

$$C_{wb}(t) = u \times C_{bf}(t) - v \times C_{tf}(t) \quad 4.$$

$$\Sigma = \begin{bmatrix} \text{Var}(u) & \text{Cov}(u, v) \\ \text{Cov}(u, v) & \text{Var}(v) \end{bmatrix} \quad 5.$$

$$u = \frac{C_{wb}(t_s) + v \times C_{tf}(t_s)}{C_{bf}(t_s)} \quad 6.$$

$$\Phi_{AP} = [u - u_{mean} \quad v - v_{mean}] \begin{bmatrix} \text{Var}(u) & \text{Cov}(u, v) \\ \text{Cov}(u, v) & \text{Var}(v) \end{bmatrix}^{-1} \begin{bmatrix} u - u_{mean} \\ v - v_{mean} \end{bmatrix} \quad 7.$$

Estimation of the factor images $\mathbf{A}$ and factors $\mathbf{F}$ was based on minimization of the least squares objective function Φ_{FA} .

$$\Phi_{FA}(\mathbf{A}, \mathbf{F}) = \|\mathbf{W} \circ (\mathbf{I} - \mathbf{F}\mathbf{A})\| \quad 2.$$

The least squares objective function Φ_{FA} is the second norm of the weighted difference between the matrix representation of the image $\mathbf{I}$ and the product of the factor matrix $\mathbf{F}$ and the factor image matrix $\mathbf{A}$. Symbol $\circ$ denotes the entrywise product, where each element in the resulting matrix is product of the elements on the same position of the input matrices. Elements in weighting matrix $\mathbf{W}$ of Eq. 2 were aimed to be inversely proportional to the

standard deviation of the corresponding element in the matrix representation of the image $\mathbf{I}$. In this study we assumed spatially uniform noise with the standard deviation being inversely proportional to the square root of PET frame duration. The factor matrix $\mathbf{F}$ and the factor image matrix $\mathbf{A}$ were restricted to non-negative values to ensure physically viable results. In addition, the mean values of both factors were constrained to unity in order to avoid two additional free parameters for scaling.

Minimization of objective function Φ_{FA} was done in Matlab (MathWorks, Natick, CA) using the routine *fmincon* that can find minimum of constrained nonlinear multivariable function [14]. The routine was set to use *interior-point* algorithm [15–17] and the analytical gradient was provided. The factors (two columns) in matrix $\mathbf{F}$ were initialized with the normalized mean of the carotid and background TACs. Factor images in matrix $\mathbf{A}$ were initialized by solving the system of equations in Eq. 1, using the initialized matrix $\mathbf{F}$. Non-negativity constraints and constrained mean values of both factors were specified in the routine optional arguments. If the blood-weighted factor appeared as the second factor in the resulting matrix $\mathbf{F}$, the columns of the matrix were exchanged, along with the rows in the matrix $\mathbf{A}$.

An intrinsic limitation of factor analysis is that the solution is not guaranteed to be unique [9]. In a preliminary version of this work we implemented an ambiguity correction procedure [18] which, in the present dataset, was found to have no impact on the shape of the input functions and was therefore removed from this work.

Removing the noise in blood-weighted factors—In order to minimize noise in the estimated TACs, blood-weighted factors were fitted with a three-exponential model. Although this step is not strictly necessary, it allows obtaining less noisy whole blood TACs. The model assumes that the injection of the radiotracer is of finite duration from t_1 to t_2 . In this time-window, there is a constant flow (Q) of the radiotracer into the blood. After the peak, radiotracer concentration decreases following a three-exponential decay. The blood TAC can thus be calculated as the convolution between the square injection function and the three-exponential decay of radiotracer concentration in the blood.

$$C_b(t) = \begin{cases} 0; & t < t_1 \\ Q \int_{t_1}^t \sum_{i=1}^3 A_i e^{-\delta_i(t-\tau)} d\tau; & t_1 < t < t_2 \\ Q \int_{t_1}^{t_2} \sum_{i=1}^3 A_i e^{-\delta_i(t-\tau)} d\tau; & t_2 < t \end{cases} \quad 3.$$

This model has eight free parameters that are set when fitting the model to the blood-weighted factor. First two parameters are time points t_1 and t_2 . In addition, there are three pairs of parameters A_i and δ_i that determine exponential weight and decay constant. The value of Q is set to unity, because this parameter can be accounted for by adjusting the factors A_i in the three-exponential model. Having Q as an additional free parameter would cause the ambiguity of parameters.

Scaling factor analysis solutions—After de-noising by three-exponential model, the factors were scaled using the approach proposed by Sitek and colleagues [10, 19]. This step is necessary in order to account for the variability of TACs amplitudes, determined by the different partial volume effects among clinical subjects. Four voxels with the highest blood factor image values were selected within the carotid region. Factor analysis solutions were scaled so that the average factor image value among those four hottest voxels was equal to 1.

Generation of a priori input function data—The blood signal is reduced due to partial volume effects and contaminated by surrounding tissue activity. So, the actual concentration in blood $C_{wb}(t)$ is:

$$C_{wb}(t) = u \times C_{bf}(t) - v \times C_{tf}(t) \quad 4.$$

where the $C_{bf}(t)$ and $C_{tf}(t)$ are the blood-weighted and tissue-weighted factors, respectively. If multiple measured values from blood-sampling are available, the coefficients u and v can be determined by linear least squares method, following the principle described by Chen and colleagues [6]. In the present study, the different u_i and v_i values from the various subjects were obtained by fitting the model in Eq. 4 to blood sampling data. Appropriate u_i and v_i values were averaged to obtain the average coefficients u_{mean} and v_{mean} and the corresponding covariance matrix:

$$\Sigma = \begin{bmatrix} \text{Var}(u) & \text{Cov}(u, v) \\ \text{Cov}(u, v) & \text{Var}(v) \end{bmatrix} \quad 5.$$

The average coefficients u_{mean} and v_{mean} , their correlation and the corresponding covariance matrix, calculated on the data from all 10 subjects, are in Table 1. To validate the methodology, *a priori* input function data were generated from 9 subjects and tested on the remaining 1 – a leave-one-out approach.

To assess whether 9 subjects were sufficient to produce a stable estimate of the population parameters, we generated parameters using 3, 5 or 7 subjects, covering all possible combinations. The within-subject variations of the resulting AUC were $12.0 \pm 3.8\%$, $4.5 \pm 1.4\%$ and $2.0 \pm 0.8\%$ when using 3, 5 and 7 subjects, respectively. This suggests that 9 subjects can provide an accurate estimate of the *a priori* input function data.

Generating whole-blood TACs—The relationship between coefficient u and v was determined using a single blood sample acquired at $t=t_s$.

$$u = \frac{C_{wb}(t_s) + v \times C_{tf}(t_s)}{C_{bf}(t_s)} \quad 6.$$

As the coefficient v is unknown, it was determined by minimizing the objective function Φ_{AP} that describes the deviation of coefficients u and v from the average coefficients u_{mean} and v_{mean} , weighted with the corresponding inverse of the covariance matrix:

$$\Phi_{AP} = [u - u_{mean}v - v_{mean}] \begin{bmatrix} Var(u) & Cov(u, v) \\ Cov(u, v) & Var(v) \end{bmatrix}^{-1} \begin{bmatrix} u - u_{mean} \\ v - v_{mean} \end{bmatrix} \quad 7.$$

The time point t_s was chosen at 40 minutes because it gave the highest Pearson's correlation coefficient between the concentrations in plasma and the input function area under the curve in a previous study with [^{11}C](R)-rolipram [20]. The final input functions were obtained by correcting for radiometabolites the whole blood TACs using four measured time-points, as previously described [21–22].

Figures of merit

The accuracy of whole-blood TAC obtained with factor analysis and one blood sample was assessed 1) visually, 2) by calculating the relative error in AUCs for the whole-blood TACs at 5 min and 90 min post-injection, and 3) by comparing the IDIF-derived total distribution volume (V_T) to the reference values obtained with full arterial input. V_T was calculated in three different ways: with the Logan plot, with a two-tissue compartment model (2TCM) and with spectral analysis (SA). To our knowledge, this is the first time that SA is evaluated in association with IDIF. For 2TCM, blood volume was set at 5% and the curves were fitted for blood delay. For SA, the β_j grid was defined by 100 components and a logarithmic distribution ranging from 0.01 to 1 (1/min). Kinetic analysis was performed with PMOD 3.1 (PMOD Technologies, Zurich, Switzerland) and the SAKE spectral analysis software [23].

Results

Visual analysis

The shape of the image-derived whole-blood TACs was consistently similar to the blood-sampling arterial whole-blood TAC. The peak was in most cases slightly underestimated, whereas the TACs at later times matched better to the reference arterial curves. shows the best and the worst example of image-derived whole-blood TACs obtained by factor analysis.

Area under the curve

Consistently with visual analysis, the IDIFs were less accurate in the estimation of the early part of the input function (AUC error over the first 5 minutes was $-2.7 \pm 8.7\%$), although the total AUC was more accurately estimated (mean error: $1.0 \pm 4.3\%$).

To assess the robustness of the final TAC AUC with regards to operator's variability in drawing the ROIs, the manually-defined carotid and background regions were expanded or eroded by 20%. The resulting within-subject AUC variations were very small ($0.67 \pm 0.39\%$; highest variation: 1.6% in one subject).

Kinetic analysis

Logan- V_T calculated with IDIF showed little bias and a moderate variability compared to three reference arterial Logan- V_T values (mean error: $-4.1 \pm 6.4\%$; maximum error in one subject was 11%). When IDIF was used to calculate V_T using 2TCM, the bias compared to

2TCM- V_T obtained with the full arterial input was similar, but the variability substantially higher (mean error: $-4.5 \pm 9.6\%$, maximum error: 21%). Moreover, similarly to what we previously found [24–25] individual rate constants showed important and unpredictable errors (Table 2). Finally, although SA- V_T values were unbiased with regards to SA quantification with full input, they also displayed the highest variability (mean error: $0.4 \pm 15.0\%$; maximum error: 28%).

Discussion

The present study found that a factor analysis-derived IDIF and a single blood sample allows the estimation of an accurate input function, to be used for kinetic modeling with the Logan plot.

Typically, in brain PET studies, TACs from blood vessels cannot be directly used as a substitute for the arterial input function, because of the low spatial resolution of the machine. Due to this poor resolution, the blood signal in the vessel is not only underestimated, but it is also contaminated by the activity coming from the surrounding tissue, and each voxel would contain a mixture of the two signals in variable proportions. One possibility to recover the blood signal would be by using some blood measurements and a least squares analysis, as initially proposed by Chen and colleagues for [^{18}F]-FDG [6] and subsequently by our laboratory for [^{11}C](R)-rolipram [20–21, 25–26]. While only two samples are theoretically necessary to solve this system of equations, in practice more samples are necessary because of uncertainties in the sample measurements and the similarity between blood and tissue signals.

By using factor analysis we were able to obtain very reproducible blood-weighted and tissue-weighted TACs, which allowed us to generate the whole-blood TAC using a single blood sample and population data. Factor analysis does not aim to fully decompose the dynamic PET image into separate blood and tissue signals, but into a fixed combination, so that the amount of contamination of the blood-weighted factor from the tissue signal was constant, and therefore predictable. Notably, the amount of contamination of the blood-weighted factor with tissue signal depends on scanner resolution, vessel size, and degree of uptake of the radiotracer into the tissue. Therefore, the population-based approach to obtain whole-blood TAC from blood-weighted and tissue-weighted factors might be applicable only when using the scanner, the image reconstruction parameters, and the radiotracer from which the population parameters were derived.

In some cases, the technique might be simplified. For example, if the vessel was large enough or if the scanner resolution was higher, the partial volume correction factor could be set at one. Alternatively, if radiotracer tissue uptake was very low, the spill-over effect could be ignored. In these cases, the whole-blood TAC could be obtained directly from factor analysis results using only a single blood sample or only the population data. When a large blood pool is in the field-of-view, it might be already possible to estimate a fully non-invasive whole-blood TAC with the present technique. For brain PET studies, it would be possible after an improvement of current scanners resolution.

Although this technique minimizes the number of blood samples, it is not entirely blood-free. Therefore, an arterial line is still necessary. If the radioligand concentrations are the same in the artery and the vein, then a venous sample can effectively replace arterial blood. Unfortunately, [^{11}C](R)-rolipram does not have a suitable artero-venous equilibrium [20], but some tracers do [6, 27]. Thus, we believe the methodology outlined in this work might have a practical interest for the quantification of tracers showing artero-venous equilibrium.

Using one blood sample allows reducing the workload to estimate each input function. This, however, comes with a cost, namely that the whole input function heavily depends on the accuracy of the radioactivity measurement of that single blood sample. Using the average of two or three samples, instead of one, would likely ensure an optimal estimation of the input function even if one of the samples happens to be wrongly measured. Similarly, in a previous study of 51 subjects scanned with [^{11}C](R)-rolipram, three had inaccurate measurements in a single late blood sample. These errors were sufficient to cause a significant V_T estimation error when using a population-based input function, but the impact of these wrong measurements was minimized by using the average of three blood samples [20].

Our technique has two limitations, which are however commonly shared by all IDIF techniques:

1. Only the whole-blood TAC can be estimated from PET images. To obtain the parent plasma concentration (i.e. the actual input function), radiometabolite correction must be performed. In the present study, radiometabolite correction was performed using some blood samples. For some tracers, the use of a standardized metabolite curve might provide usable results [28–30]. This approach however should be validated for each radioligand.
2. The use of IDIF techniques essentially restricts the choice of kinetic modeling approaches to graphical analyses, such as the Logan or Patlak plots. In fact, in the present study, compartmental modeling and spectral analysis provided less accurate results than Logan. Although the average V_T values showed little or no bias, the variability was substantially higher. These results echo those we previously obtained using different tracers and different machines [24–25]. The relative robustness of the Logan plot is explained by the fact that this modeling technique relies on the total AUC of the input function, and is therefore less sensitive to the unavoidable errors in the estimation of the peak that are usually associated to the use of IDIFs.

Conclusions

An image-derived input function for [^{11}C](R)-rolipram brain PET studies can be obtained with factor analysis, *a priori* information of radioligand's kinetic behavior and PET scanner characteristics and a single blood sample.

Acknowledgements

The authors thank Drs. Robert B. Innis, Masahiro Fujita, Sami S. Zoghbi, Victor W. Pike and the staff of the Molecular Imaging Branch of the NIMH for kindly providing the [^{11}C](R)-rolipram images. Ioline Henter (NIMH) provided excellent editorial assistance.

Funding Source: This work was supported by the Slovenian Research Agency (ARRS); the Centre of Excellence for Biosensors, Instrumentation, and Process Control; the European Union; the European Regional Development Fund; the Ministry of Higher Education, Science and Technology of the Republic of Slovenia; and the Intramural Research Program of the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH).

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Figure 1.
Manually delineated carotid and background regions of interest.

Figure 2.

Two examples of image-derived whole-blood TACs obtained by factor analysis (solid line) compared to the reference arterial samples (dots). Inner plots magnify the first 10 minutes. The (A) plot is for the subject in whom factor analysis provided the most accurate estimation, while the (B) plot shows the worst case (AUC error of 7.7%). Please note that the peak estimation was better in the (B) curve. This underscores the fact that the peak contributes little to the estimation of the whole AUC for tracers like [^{11}C](*R*)-rolipram, whose wash-out from the vascular compartment is very slow.

Table 1

Population data for coefficients u and v from the Eq. 4 in terms of mean, correlation between u and v , and covariance matrix. These figures are for all 10 subjects. When a leave-one-out procedure was used to validate the input function extraction, new figures, derived each time from 9 subjects, were used.

Coefficient	Mean	Correlation	Covariance matrix	
			u	v
u	2.40	0.36	0.037	0.017
v	0.66		0.017	0.061

Table 2

Relative errors of kinetic parameters from compartmental modeling, Logan plot and spectral analysis.

Parameter	2TCM				Logan		SA
	K_I	k_2	k_3	k_4	V_T	V_T	V_T
Mean error (SD) [%]	24.1 (34.8)	41.5 (71.7)	37.9 (9.4)	20.7 (69.1)	-4.5 (9.6)	-4.1 (6.4)	0.4 (15.0)