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Parameter Set Uniqueness and Confidence Limits in Model Identification of Insulin Transport Models for Simulation Data Diabetic Patient Models

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Abstract

Background—The use of patient models describing the dynamics of glucose, insulin, and possibly other metabolic species associated with glucose regulation allows diabetes researchers to gain insights regarding novel therapies via simulation. However, such models are only useful when model parameters are effectively estimated with patient data.

Methods—The use of least squares to effectively estimate model parameters from simulation data was investigated by observing factors that influence the accuracy of estimates for the model parameters from a data set generated using a model with known parameters. An intravenous insulin pharmacokinetic model was used to generate the insulin response of a patient with type 1 diabetes mellitus to a series of step changes in the insulin infusion rate from an external insulin pump. The effects of using user-defined gradient and Hessian calculations on both parameter estimations and the 95% confidence limits of the estimated parameter sets were investigated.

Results—Estimations performed by either solver without user-supplied quantities were highly dependent on the initial guess of the parameter set, with relative confidence limits greater than $\pm 100\%$. The use of user-defined quantities allowed the one-compartment model parameters to be effectively estimated. While the two-compartment model parameter estimation still depended on the initial parameter set specification, confidence limits were decreased, and all fits to simulation data were very good.

Conclusions—The use of user-defined gradients and Hessian matrices results in more accurate parameter estimations for insulin transport models. Improved estimation could result in more accurate simulations for use in glucose control system design.

Introduction

While there is no doubt that patients with type 1 diabetes mellitus are of critical importance for research and the development of successful novel therapeutic methods of effective glucose control, the use of models and simulation offers many benefits in diabetes research. First, the use of models and simulations allows for many different design configurations to be investigated in a small amount of time, resulting in higher-throughput screening of

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methods than experiments alone would allow. Second, by using simulations to eliminate unfeasible or potentially dangerous methods, research expenditures can be used more efficiently, and test subject well-being can be improved.

While the development of insulin transport model equations to be used for prediction, data interpretation, and simulation is important, models will not give meaningful predictions unless their parameters are accurately determined. For physiologically based modeling, this can often mean finding average parameter values in literature, such as the dog kinetic parameters used by Bolie¹ or the organ volumes and blood flow rates of dogs used by Tiran and Galle² and Tiran et al.³ or humans used by Sorensen.⁴ More often, however, patient parameters will have to be identified by fitting the model to patient data and selecting reasonable parameter values that give the closest fit to the data.

Parameters are normally chosen to minimize the sum of the squares of errors in the model fit relative to the data, as given by Eq. 1:

$$\Phi = \sum_i (y_i - \hat{y}(x_i))^2 \quad (1)$$

In Equation (1), y_i is the actual dependent variable value when the independent variable is at x_i . The term $\hat{y}(x_i)$ is the model prediction for the same independent variable value. As an optimization problem, an initial guess is required in order to search for the optimal set of parameters.

A linear system of differential equations with either no input or a simple input can be analytically solved and represented by algebraic functions. However, a noncontinuous input or nonlinearities in the equations result in the system no longer being analytically solved. When this is the case, the equations must be solved numerically. For such a data set, the global optimum parameter set cannot be determined using analytical means, and the initial guess of the parameter set, along with the confidence limits associated with the set, become important.

Often when optimal parameter sets are given, they are given without a discussion of the initial values used and without a discussion of the uncertainty of the parameters. Rawlings et al. (5) provided a review of parameter estimation of crystallization models and found that not only were confidence intervals not being reported, but those intervals, once determined were often so large that there was no real certainty associated with the reported parameter values. Another often overlooked area of model parameter estimation is the global identifiability of a system given the model structure and the experimental procedure. Often the use of experimental data for parameter estimation results in multiple parameter sets. Audoly et al. (6) developed an algorithm to help determine the global identifiability of the parameter set given a model type and the experimental setup.

In this article, we investigated the identification of kinetic parameters from a simple pharmacokinetic insulin model. Simulation test data were generated by using a multicompartment insulin pharmacokinetics model with known parameter values. Using the simulation data, the ability of a least squares optimization routine to estimate the model parameters was explored. Different initial guesses of the parameter set were used to estimate model parameters and confidence limits for a one- and two-compartment insulin model. Estimation was performed using both user-supplied gradients and Hessians and using the solver's built-in routines for these quantities. The different resulting parameter sets were

used to investigate the effectiveness of the different optimization routines for parameter set and confidence limit determination using simulation data.

Materials and Methods

Model Selection and Test Data Generation

To show the estimation methods for a specific set of simulation data, the pharmacokinetic insulin model of Hipszer et al.⁷ was used. The model equations are given by Eqs. 2-5 below:

$$\frac{dx_1}{dt} = -(A_{01} + A_{21} + A_{31})x_1(t) + A_{12}x_2(t) + A_{13}x_3(t) + U(t) \quad (2)$$

$$\frac{dx_2}{dt} = A_{21}x_1(t) - A_{12}x_2(t) \quad (3)$$

$$\frac{dx_3}{dt} = A_{31}x_1(t) - A_{13}x_3(t) \quad (4)$$

$$y = \frac{x_1}{V} \quad (5)$$

For the model, A_{ij} represents the fractional kinetic elimination rate of insulin from the j^{th} compartment to the i^{th} compartment. Compartment 0 represents degradation. The model, as defined, consists of three compartments. To decrease the number of compartments, the kinetic rates associated with compartments 2, 3, or both, are set to zero. The state variable x_i represents the mass of insulin in the i^{th} compartment. The variable V represents the insulin distribution volume in the central compartment. Finally, U represents the insulin infusion rate as a function of time. Model parameters were estimated by Hipszer et al. (7) by subjecting patients with type 1 diabetes mellitus to a series of insulin infusion rate step changes. The magnitude of the infusion rate was dependent upon frequent glucose measurements.

Given the dynamic model for insulin in one-, two-, or three-compartments within the body, a test set of data was generated. The initial condition of all states was set at zero mU. At time zero, an insulin pump was turned on, and a step in the insulin infusion rate from 0 to 20 mU/min was performed. At 150 minutes, a second step change occurs, with the insulin infusion rate increasing from 20 mU/min to 40 mU/min. The model parameters used for the test data generation were $A_{01} = 0.12 \text{ min}^{-1}$ and $V = 15 \text{ L}$. All parameters associated with the two- or three-compartment model were set to zero, resulting in a set of simulation data for a one-compartment model. The resulting profile of the test data is given in Figure 1. Given the simulation test data and a set of initial guesses for each parameter set, the optimization solver was used to minimize the objective function given by Eq. 1.

Confidence limit determination

The 95% confidence interval was determined for each parameter in order to determine (a) how narrow the range of potential values of the model parameters was and (b) whether or

not the actual parameter values associated with the simulation test data fell within the interval. The $(1 - \alpha)\%$ confidence interval was calculated using Eq. 6:

$$(\theta - \widehat{\theta})^T H \Big|_{\theta = \widehat{\theta}} (\theta - \widehat{\theta}) \leq 2s^2 n_p F(n_p, n_d - n_p, \alpha) \quad (6)$$

In Eq. 6, θ is the actual set of system parameters, $\widehat{\theta}$ is the estimated parameter set, and a corresponds to the $(1 - \alpha)\%$ confidence limit. F represents the F probability function.[8] H is the Hessian matrix, which is the matrix of second derivatives of the objective function with respect to the model parameters, as shown in Eq. 7:

$$H_{kj} = \frac{\partial^2 \Phi}{\partial \theta_k \partial \theta_j} = 2 \sum_i \left[\frac{\partial x_i}{\partial \theta_k} \frac{\partial x_i}{\partial \theta_j} - (\tilde{x}_i - x_i) \frac{\partial^2 x_i}{\partial \theta_k \partial \theta_j} \right] \quad (7)$$

The Hessian is a $n_p \times n_p$ matrix, in which n_p is the number of model parameters. To simplify this calculation the Gauss-Newton approximation was used, in which the second term of Eq. 7 was neglected. This approximation usually holds very well when the model fits the data very well or when the second derivatives are smaller than the first derivatives.(9) Expressed in matrix notation, the Gauss-Newton approximation of the Hessian is given by Eq. 8:

$$H = 2S^T S \quad (8)$$

In Eq. 8, S is the $n_d \times n_p$ sensitivity matrix, where n_d is the number of observations of the output variable y . Element (i,j) of the matrix is the sensitivity of state variable i with respect to model parameter j , as defined according to Eq. 9:

$$S_{ij} = \left(\frac{\partial x_i}{\partial \theta_j} \right)_{\theta_{k \neq j}} \quad (9)$$

The sensitivity of the output y with respect to each parameter was determined as a function of time for a particular set of model parameters by incorporating the differential equation given in Equation (10) into the solver:

$$\frac{dS}{dt} = f_x S + f_\theta \quad (10)$$

In Eq. 10, matrix f_x is the $m \times n$ matrix of the derivatives of the model system with respect to the individual states. The matrix f_θ is the $m \times n_p$ matrix of the first partial derivative of the model system with respect to the model parameters.(9) The final term from Eq. 6 is s^2 , the sample variance. It is determined by Eq. 11:

$$s^2 = \frac{\Phi(\hat{\theta})}{n_d - n_p} \quad (11)$$

Estimation with user-supplied gradients and Hessian

Because the Hessian matrix was calculated in the determination of confidence limits, it was easily supplied to the optimization routine. To supply the gradient to the routine, Eq. 12, which shows the relationship between the gradients and the sensitivity matrix, was used:

$$\nabla\Phi = -2S^T e \quad (12)$$

In Equation (12), Φ is the scalar value of the objective function. The vector e is a vector of length n_d , where each element is the difference between the measured output and the model prediction for each time. The estimations were again repeated for the different sets of initial parameter guesses for the different model frameworks. Estimations were also performed in which direct model correspondence was used to note any difficulties in estimating parameters for a higher order model when a low order model is used to generate test data. For this, a new set of test data was generated, using the literature parameter values of the two-compartment model for the simulated test data [10].

In order to observe how successful the estimation is with a real system, noise was added to the simulation test data. First, an alternating noise vector of magnitude 20% was added to the output signal. Second, a random noise vector was added to the test data in order to simulate a real unknown process. Estimation using the previously mentioned initial guess sets was performed a final time.

Finally, in order to determine the validity of the estimations, simulations were performed for a different set of conditions. Using six estimated parameter sets for the two-compartment model and the simulation test data of the one-compartment model, each model was subjected to a series of five step changes. At zero-time, the insulin infusion rate is increased to 15 mU/min. At 150 min, the rate is increased to 25 mU/min. At 300 min, the rate is increased to 35 mU/min. At 450 min, the rate is increased to 45 mU/min. Finally, at 600 min, the rate is increased to 55 mU/min. Each simulated response was plotted on the same graph in order to compare the responses of the different parameter sets to the same input set.

Computational methods

To solve the systems of ordinary differential equations, the MATLAB (The MathWorks, Natick, MA) solver ode45 was used. (11) The solver ode45 is a nonstiff solver implementing the 5th-order Runge-Kutta Dormand-Prince pair to solve the system for each specified time. To perform the optimization, the MATLAB function “fmincon” was used to perform the minimization of a constrained optimization problem. The function “fmincon” can be tailored to fit the desired optimization. For our problem, a line-search method was incorporated into the solver as the means to search for the minimum. The MATLAB source code used for parameter estimation can be acquired in Farmer. (12)

Results

Initial Parameter Estimation

Initially, the model parameters were estimated for the one- and two-compartment insulin pharmacokinetic models by an initial guess of the parameters that was within $\pm 200\%$ of the determined model parameters of similar models from literature [10], [13]. Table 1 shows the estimation results for the one-compartment model. The parameter estimation results for the two-compartment model are given in Table 2. Tables 1 and 2 show that the estimation of only two model parameters strongly depended on the initial starting values assigned to each parameter and that the task of estimating four model parameters was even more difficult. When the actual parameter set was chosen as the initial guess, the routine converged quickly on the actual parameters. The estimations for the higher-order model often resulted in solutions that violated constraints, and given that no constraint was defined for the volume V in the model, the extremely large values associated with the optimal V show that it also was violating physical constraints. The solver did not appear to do an effective job of finding the model parameters to be the actual values used for the simulation test data.

Confidence limit determination

Using the different sets of initial parameter guesses for each model, the 95% confidence limits were determined. They are shown in Tables 1 and 2 for the one- and two-compartment models, respectively. Estimation using the one-compartment model and simulation test data from the one-compartment model had fairly low confidence limits, typically lower than 10% of the estimated parameter value. However, in many instances, the actual parameter value was not within the 95% confidence limits of the estimated parameter value. Such an observation casts doubt on the ability to use least squares to estimate parameters of dynamic systems. The limits were much larger for the higher-order model. Parameters for the two-compartment model were observed to have 95% confidence limits greater than $\pm 200\%$, meaning that there was no real way to know what the parameter value was with any certainty. Ideally, the estimation should produce confidence limits that are fairly narrow but that still contain the actual parameter value within the interval. Using only the system of equations and the optimization routine did not result in an estimate of parameters that could be considered accurate with any real level of certainty.

Parameter estimation with user-supplied gradients and Hessian

Table 3 shows the estimated parameter values and confidence limits for the one-compartment insulin model when the user-supplied gradients and Hessian matrix were included in the optimization routine. Two observations can be made. First, the estimated model parameters were much closer to the actual model parameters when sensitivity calculations were included in the routine. Second, the calculated 95% confidence limits were very small, with the largest confidence interval being within $\pm 2\%$ of the estimated parameter value. For the one compartment model, parameter estimation that employed the parameter sensitivity dynamics demonstrated superiority over solvers that did not.

To further test the effectiveness of the estimation of the one-compartment model parameters, different types of noise were added to the simulation data. The first type of noise assumed that each point was 20% larger or 20% smaller in value than the actual test data point. The second type was random noise added to the output variable given by the simulation test data. The estimation results for the one-compartment model are given by Table 4. The parameters were estimated fairly closely to the actual parameter values in spite of the appearance of noise, although the parameter set is clearly dependent on the initial estimate. The model fits for the noisy simulation data are shown in Figures 2 and 3. The parameter estimation routine

employing the parameter sensitivities was able to accurately determine the parameter values with moderate confidence intervals.

Table 5 shows the parameter estimation results for the one-compartment simulation test data with the two-compartment model. There appeared to be minimal improvement to the parameter estimation of the higher-order model. The optimal parameters were still highly dependent upon the initial guess of the parameter set. While there was an improvement in the size of the confidence intervals, the actual parameter values routinely fell out of this 95% confidence range, demonstrating the inability of the routine to be able to effectively estimate model parameters with any sort of certainty.

Although estimation of higher-order model parameters appeared to not be improved by the use of user-supplied quantities, Figure 4 shows that the actual model fits were fairly good. Figure 4 shows the fit of the two-compartment parameters that resulted in the highest Φ value to the test data generated. The model fit the simulation data very well, implying that multiple parameter sets were able to fit the simulation data reasonably well.

One reason that the two-compartment model may fit the one-compartment model well with multiple parameter sets is because of the general differences in the responses between the two models to the same input. To investigate this hypothesis, a set of simulation data from the two-compartment model was generated, and the two-compartment model was used to estimate the parameters. The results of the estimation are given in Table 6. The estimated parameter set was highly dependent on the choice of initial guess for the parameter set. Figure 5 demonstrates that the estimated parameter set with the worst Φ value was still able to fit the simulation data particularly well.

Given the ability of the estimated parameters, whether the actual parameters or not, to fit the simulation data reasonably well, the ability of the estimated parameter sets to make accurate predictions was investigated by subjecting the model patients to a series of five step changes, including changes outside the range of the test data. Figure 6 shows the results. While the parameter sets differed considerably in some cases, the predictions were basically exactly the same for all the different model parameter sets. This gives a stronger argument for the presence of multiple optimal parameter sets when a numerical solver is used for the model versus analytical solutions.

Discussion

Given a published insulin pharmacokinetic model, test data were generated, and the ability of an optimization routine to effectively estimate the actual parameter set used for simulation data generation was evaluated for differential equations without analytical solutions. The optimal parameter set of a dynamic model consisting of an insulin input was highly dependent on the initial guess of the parameter values. The estimated parameter sets were not known with any degree of certainty, as 95% confidence limit calculations showed. Estimation was improved for a one-compartment model by including user-supplied gradients and the Hessian in the estimation routine. This improved routine has demonstrated the ability to determine the parameter set in different types of noise as well. For higher-order models, the parameter estimate was still highly dependent on the initial guess of the parameter set, but models generated using the estimated parameters were able both to fit the simulation data and to make predictions nearly equal to those of the actual parameter set, demonstrating the possibility of multiple parameter sets that accurately match the simulation data.

For patient models with a large number of parameters, model identification is best performed by using as many data sets as possible to identify as few parameters at a time as

possible. Clearly blood values of each species would not be sufficient to accurately estimate hundreds of parameters, as it was not sufficient to estimate even four parameters in a two-compartment model. However, given literature values of parameters, the possibility of the existence of multiple optimal parameter sets should give the user confidence that the value is likely reasonable enough to make effective predictions. The fact that this particular system and simulated input sequence does not result in global identifiability could likely have been predicted using tools that assess the global identifiability of systems. As such, the specific experiments used to generate data should be developed in such a way as to ensure global identifiability of model parameters without subjecting patients to severe hyper- or hypoglycemia.

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FIG. 1.

Graph of test data for insulin as a function of time in response to two step changes in the infusion rate of insulin from a pump. At zero-time, the patient of known one-compartment model parameters is subjected to step change in insulin infusion from 0 to 20 mU/min. At 150 min, the patient is again subjected to an insulin infusion step change from 20 to 40 mU/min.

FIG. 2.

Model fit for test data generated with the one-compartment model and 20% bias for each measurement. Model parameters are $A_{01} = 0.132 \text{ min}^{-1}$ and $V = 13.66 \text{ L}$. The model fits within the data, and the actual parameter set is within the confidence interval given by the estimation.

FIG. 3. Model fit for random noise added to test data. Model fit is for $A_{01} = 0.1369 \text{ min}^{-1}$ and $V = 13.3 \text{ L}$. The model fits within the data, and the actual parameter set is within the confidence interval given by the estimation.

FIG. 4.

Model fitting of the two-compartment model to one-compartment test data. $A_{01} = 0.34 \text{ min}^{-1}$, $A_{12} = 0.338 \text{ min}^{-1}$, $A_{21} = 0.6 \text{ min}^{-1}$, and $V = 5.29 \text{ L}$. The model fit appears to be nearly on top of the plot.

FIG. 5.

Two-compartment model fit for test data generated by the two-compartment model. Data parameters are $A_{01} = 0.2 \text{ min}^{-1}$, $A_{12} = 0.05 \text{ min}^{-1}$, $A_{21} = 0.06 \text{ min}^{-1}$, and $V = 6 \text{ L}$. Model parameters are $A_{01} = 0.2922 \text{ min}^{-1}$, $A_{12} = 0.085 \text{ min}^{-1}$, $A_{21} = 0.16 \text{ min}^{-1}$, and $V = 4.12 \text{ L}$. The model fit appears to be directly on top of the data plot.

FIG. 6.

Generation of data for different parameter sets of the two-compartment model. Model parameters are based on estimation of two-compartment parameters using one-compartment test data. All parameter sets fit on the same trajectory, with very little difference among the predicted profiles. Each legend entry represents the optimal parameter set from that particular initial guess parameter set.

Table 1

Initial Parameter Estimation for One-Compartment Model

Initial A_{01} (mm^{-1})	Initial V (L)	Φ (mU^2/L^2)	Optimal A_{01} (min^{-1})	Confidence limit A_{01} (%)	Optimal V (L)	Confidence limit V (%)
0.12	15	0	0.12	0	15	0
0.1333	10.1	38.5	0.165	2	10.98	2
0.06	15	284	0.0597	11	29.5	10
0.12	22.5	560	0.0505	2	35.6	2

The actual parameter set is $A_{01} = 0.12 \text{ min}^{-1}$ and $V = 15 \text{ L}$. Given the initial guesses for A_{01} and V , the optimal values of the parameters are given the result in the minimum value for Φ , the sum of squared residuals. The confidence limits of each parameter are expressed as a percentage of the optimal value, in which the upper and lower limits are expressed as optimal value $\pm$ (confidence limit [in %]) (optimal parameter value).

Table 2

Initial Parameters Estimation for Two-Compartment Model.

Initial A_{01} (min ⁻¹)	Initial V (L)	Initial A_{12} (min ⁻¹)	Initial A_{21} (min ⁻¹)	Optimal A_{01} (min ⁻¹)	Confidence limit A_{01} (%)	Optimal V (L)	Confidence limit V (%)	Optimal A_{12} (min ⁻¹)	Confidence limit A_{12} (%)	Optimal A_{21} (min ⁻¹)	Confidence limit A_{21} (%)	Φ (mU ² /L ²)
0.12	15	0	0	0.12	0	15	0	0	0	0	0	0
0.2	6	0.2	0.2	0.229	92	6.7	92	0.0463	166	0.462	308	1,060
0.1	6	0.2	0.2	0.6	1.6×10^9	1.1772	1.6×10^9	0	2.2×10^9	0.4694	4×10^9	2.00×10^4
0.2	6	0.1	0.2	0.318	244	5.67	244	0.273	134	0.433	442	21.1
0.2	6	0.2	0.1	0.106	70	16.1697	70	0.4079	134	0.35	213	303
0.2	3	0.2	0.2	0	66	2.121×10^5	66	0.6	80	4.17×10^{-4}	202	8.76×10^4

The actual parameter set is $A_{01} = 0.12$ min⁻¹, $A_{21} = 0$ min⁻¹, and $V = 15$ L. The optimal parameters values are those that result in the minimization of Φ , the sum of squared residuals. The confidence limits of each parameter are expressed as a percentage of the optimal value, in which the upper and lower limits are expressed as optimal value $\pm$ (confidence limit [in %]) (optimal parameter value).

Table 3
Parameters Estimation for One-Compartment Model, User-Defined Gradients, and Hessian Matrix

Initial A_{01} (min^{-1})	Initial V (L)	Φ (mU^2/L^2)	Optimal A_{01} (min^{-1})	Confidence limit A_{01} (%)	Optimal V (L)	Confidence limit V (%)
0.12	15	0	0.12	0	15	0
0.1333	10.1	11.1	0.113	2	15.8	2
0.06	15	9.37	0.1212	2	14.8184	2
0.12	22.5	11.8	0.125	2	14.4	2

The actual parameter set is $A_{01} = 0.12 \text{ min}^{-1}$ and $V = 15 \text{ L}$. Given the initial guesses for A_{01} and V , the optimal values of the parameters are those that result in the minimum value for Φ , the sum of squared residuals. The confidence limits of each parameter are expressed as a percentage of the optimal value, in which the upper and lower limits are expressed as optimal value $\pm$ (confidence limit [in %]) (optimal parameter value)

Table 4

Noisy Data Parameter Estimation for One-Compartment Model, User-Defined Gradients, and Hessian Matrix.

Solver	Initial A_{01} (min^{-1})	Initial V (L)	Φ (mU^2/L^2)	Optimal A_{01} (min^{-1})	Confidence limit A_{01} (%)	Optimal V (L)	Confidence limit V (%)
20%	0.12	15	2,709	0.1199	35.2	15.00	34.3
Random	0.12	15	2,601	0.1210	35.1	15.06	34.2
20%	0.1333	10.1	2,712	0.132	36.7	13.66	35.8
Random	0.1333	10.1	2,293	0.1369	34.6	13.30	33.8
20%	0.06	15	2,554	0.1128	34.1	15.89	33.2
Random	0.06	15	2,320	0.1132	31.6	15.84	30.7
20%	0.12	22.5	2,715	0.1206	35.1	14.80	34.2
Random	0.12	22.5	2,970	0.1213	37.3	14.89	36.3

The actual parameter set is $A_{01} = 0.12 \text{ min}^{-1}$, $A_{12} = A_{21} = 0 \text{ min}^{-1}$, and $V = 15 \text{ L}$. The optimal parameter values are those that result in the minimization of Φ , the sum of squared residuals. The confidence limits of each parameter are expressed as a percentage of the optimal value, in which the upper and lower limits are expressed as optimal value $\pm$ (confidence limit [in %]) (optimal parameter value).

Table 5

Parameter Estimation For Two-Compartment Model, User-Defined Gradients, and Hessian Matrix

Initial A_{01} (min ⁻¹)	Initial V (L)	Initial A_{12} (min ⁻¹)	Initial A_{21} (min ⁻¹)	Optimal A_{01} (min ⁻¹)	Confidence limit A_{01} (%)	Optimal V (L)	Confidence limit V (%)	Optimal A_{12} (min ⁻¹)	Confidence limit A_{12} (%)	Optimal A_{21} (min ⁻¹)	Confidence limit A_{21} (%)	Φ (mU ² /L ²)
0.12	15	0	0	0.12	0	15	0	0	0	0	0	0
0.2	6	0.2	0.2	0.231	47	7.78	47	0.558	71	0.439	169	9.88
0.1	6	0.2	0.2	0.2407	48	7.47	48	0.5548	62	0.4778	163	9.92
0.2	6	0.1	0.2	0.263	50	6.84	50	0.543	59	0.558	150	10.1
0.2	6	0.2	0.1	0.281	48	6.40	48	0.5052	51	0.5867	134	10.48
0.2	3	0.2	0.2	0.3744	41	4.80	41	0.32	33	0.6	88	17

The actual parameter set is $A_{01} = 0.12 \text{ min}^{-1}$ and $V = 15 \text{ L}$. Given the initial guesses for A_{01} and V , the optimal values of the parameters are those that result in the minimum value for Φ , the sum of squared residuals. The confidence limits of each parameter are expressed as a percentage of the optimal value, in which the upper and lower limits are expressed as optimal value $\pm$ (confidence limit [in %]) (optimal parameter value).

Table 6

Two-Compartment Model Parameter Estimation Using Two-Compartment Model Test Data

Initial A_{01} (min ⁻¹)	Initial V (L)	Initial A_{12} (min ⁻¹)	Initial A_{21} (min ⁻¹)	Confidence limit A_{01} (%)	Optimal V (L)	Confidence limit V (%)	Optimal A_{12} (min ⁻¹)	Confidence limit A_{12} (%)	Optimal A_{21} (min ⁻¹)	Confidence limit A_{21} (%)	Φ (mU ² /L ²)
0.2	6	0.05	0.06	0	6.00	0	0.05	0	0.06	0	0
0.3	6	0.05	0.06	3	5.03	3	0.0655	7	0.0967	9	3.03
0.1	6	0.05	0.06	7	6.26	7	0.047	2	0.054	2	0.241
0.2	9	0.05	0.06	3	7.57	3	0.0299	17	0.0288	13	9.44
0.2	3	0.05	0.06	9	4.09	9	0.086	12	0.162	19	15
0.2	6	0.08	0.06	<1	5.99	<1	0.0504	<1	0.0606	<1	0.002

The actual parameter set is $A_{01} = 0.2 \text{ min}^{-1}$, $A_{12} = 0.06 \text{ min}^{-1}$ and $V = 6 \text{ L}$. Given the initial guesses for A_{01} and V , the optimal values of the parameters are those that result in the minimum value for Φ , the sum of squared residuals. The confidence limits of each parameter are expressed as a percentage of the optimal value, in which the upper and lower limits are expressed as optimal value $\pm$ (confidence limit [in %]) (optimal parameter value).