

BACKGROUND

The *pbpkme* package is designed for solving classic compartmental pharmacokinetic (PK) or physiologically based pharmacokinetic (PBPK) models. These models are often characterized by large systems of linear ordinary differential equations (ODEs), but the dimensionality of PBPK models can be burdensome and inefficient. This function uses the eigenvalue/eigenvector solution to a system of linear ODEs.¹ Matrix manipulation is computationally fast, making it ideal for model fitting/parameter estimation, especially for large models. *pbpkme* allows the modeler to use a larger time step for comparable accuracy. It is common for larger systems to produce complex conjugate pairs in their solutions, which *pbpkme* handles automatically. The method is computationally fast; therefore, the solution over a sufficiently small time interval t can be calculated many times very quickly (which reduces propagation of error – a common flaw of numerical time stepping methods).

Some common numerical methods used to solve these systems include Euler's Method, Runge-Kutta Fourth Order method (RK45), and Runge-Kutta Fehlberg Adaptive Step method (RKF6).

Euler's Method	RK45	RKF6	pbpkme
Pros:	Pros:	Pros:	Pros:
-Simple	-Better accuracy and stability	-Handles stiff/non-stiff ODEs	-High accuracy, analytical solution at each time step
-Solves non-linear IVP	-Still needs small time step to capture dose	-Adaptive step more efficient	-No problem with stiffness
Cons:	Cons:	Cons:	Cons:
-Only accurate for small time step	-Cannot handle stiff equations	-Still extremely slow	-Computationally fast
-Slow		-Complicated	-Non-traditional formatting

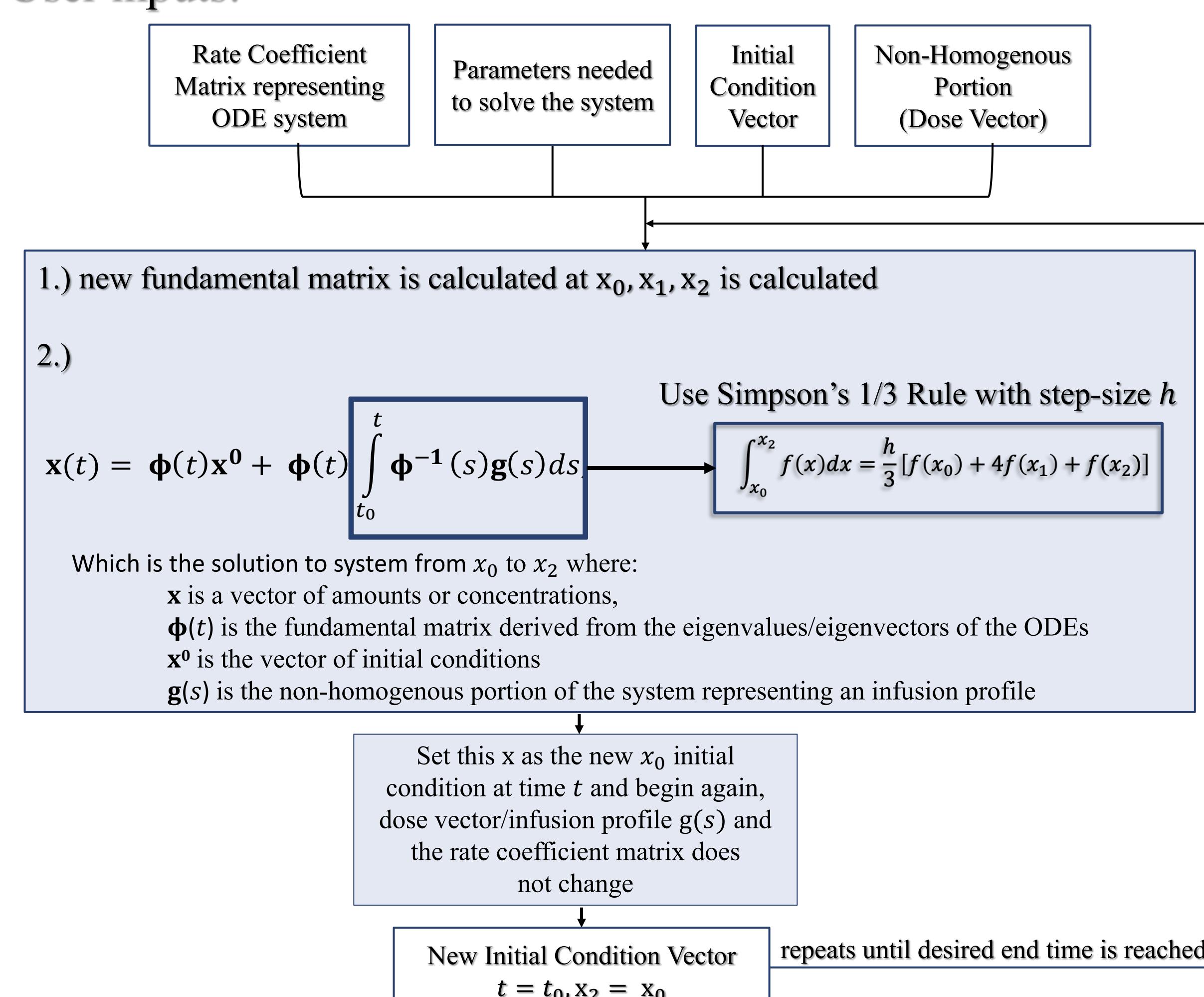
OBJECTIVES

The objectives of this work are to:

- I. Construct a matrix-based framework for efficiently solving large systems of differential equations as often used to define PBPK models
- II. Openly provide this framework in the form of an R package, *pbpkme*, which takes in rate coefficients, initial conditions, and dose information and returns drug concentrations in all compartments

PACKAGE FUNCTIONALITY

User inputs:



EXAMPLE 1 : SIMPLE SYSTEM W/ ANALYTICAL SOLUTION

A textbook example with a known solution was solved analytically at each extremely small time step and compared against the method's numerical solution. Results for varying time-steps illustrating the method's accuracy as well as computation times are shown in Figure 1.²

Consider the non-homogenous system of equations,

$$\frac{dx_1}{dt} = -2x_1 + x_2 + 2e^{-t}$$

$$\frac{dx_2}{dt} = x_1 - 2x_2 + 3t$$

which can be represented again as the following matrices.

$$x' = \begin{pmatrix} -2 & 1 \\ 1 & -2 \end{pmatrix} x + \begin{pmatrix} 2e^{-t} \\ 3t \end{pmatrix} = Ax + g(t)$$

We use Variation of Parameters to solve the system, with the fundamental matrix calculated from the homogenous case. The solution x of this system is given as $x = \phi(t)u(t)$, where $u(t)$ satisfies $\dot{u}(t)u(t) = g(t)$, or

$$\begin{pmatrix} e^{-t} & e^{-3t} \\ e^{-t} & -e^{-3t} \end{pmatrix} \begin{pmatrix} u'_1 \\ u'_2 \end{pmatrix} = \begin{pmatrix} 2e^{-t} \\ 3t \end{pmatrix}$$

By left-multiplying the fundamental matrix on both sides, the $u'(t)$ vector can be obtained. This approach is used in the consequent code, but for now, the following equations are obtained by row reduction.

$$u'_1 = e^{2t} - \frac{3}{2}te^{3t},$$

$$u'_2 = 1 + \frac{3}{2}te^t.$$

Hence,

$$u_1(t) = \frac{1}{2}e^{2t} - \frac{1}{2}te^{3t} + \frac{1}{6}e^{3t} + c_1,$$

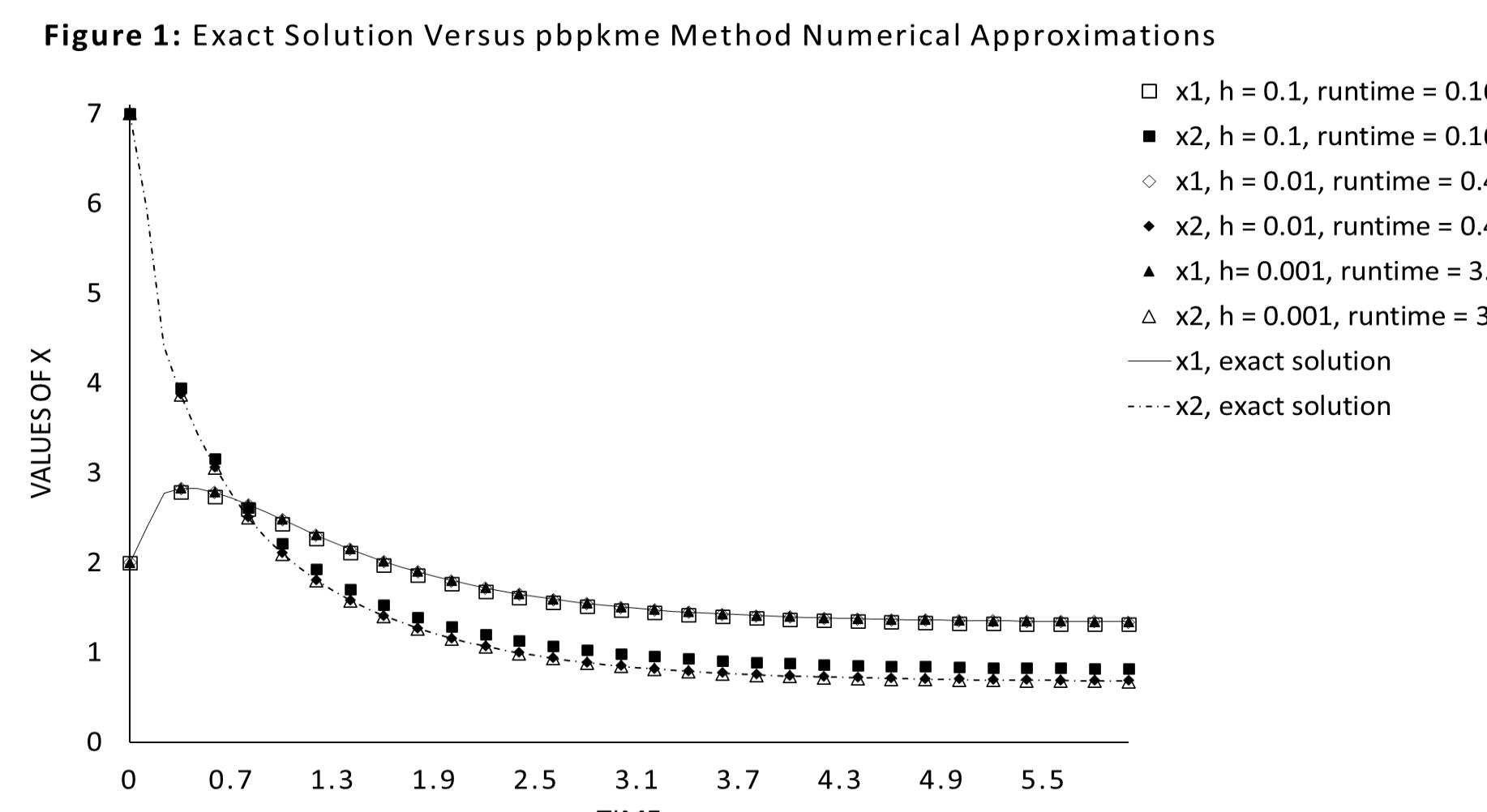
$$u_2(t) = t + \frac{3}{2}te^t - \frac{3}{2}e^t + c_2.$$

Then,

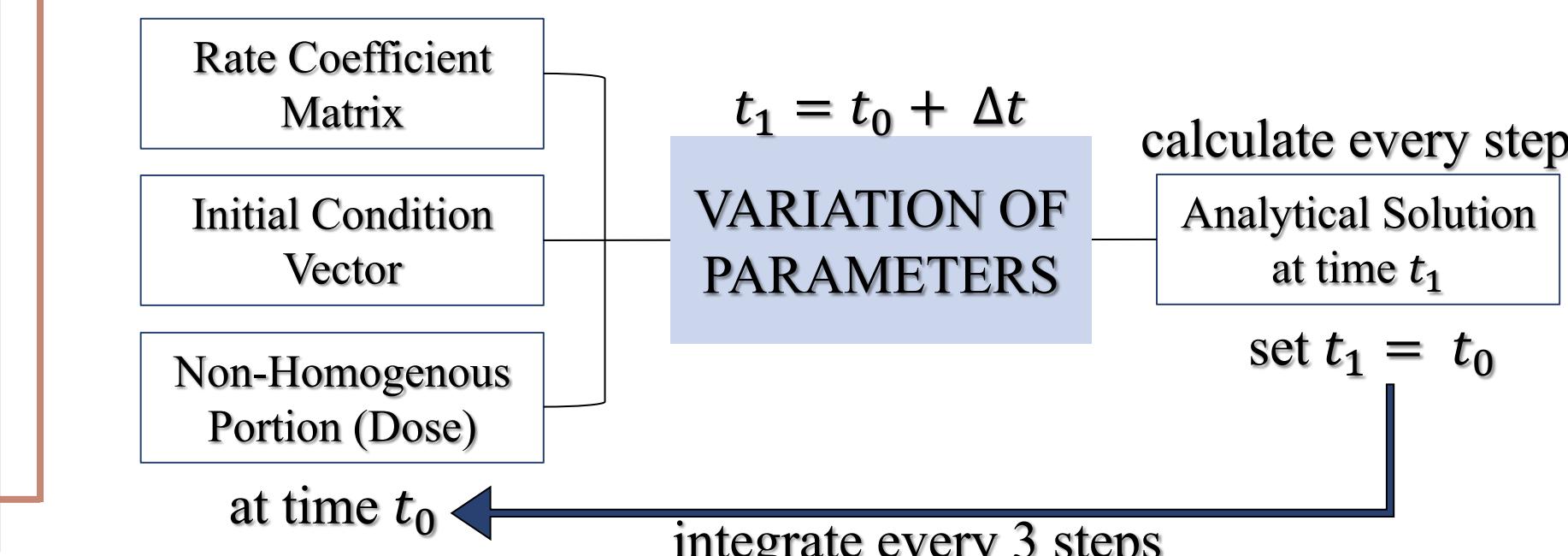
$$x = \phi(t)u(t)$$

$$= c_1 \begin{pmatrix} 1 \\ 1 \end{pmatrix} e^{-t} + c_2 \begin{pmatrix} 1 \\ -1 \end{pmatrix} e^{-3t} + \begin{pmatrix} 1 \\ 1 \end{pmatrix} te^{-t} + \frac{1}{2} \begin{pmatrix} 1 \\ -1 \end{pmatrix} e^{-t} + \begin{pmatrix} 1 \\ 2 \end{pmatrix} t - \frac{1}{3} \begin{pmatrix} 4 \\ 5 \end{pmatrix}.$$

When $x_0 = 0, t = 0$, constants c_1, c_2 are $\frac{2}{3}$ and $-\frac{3}{2}$, respectively.

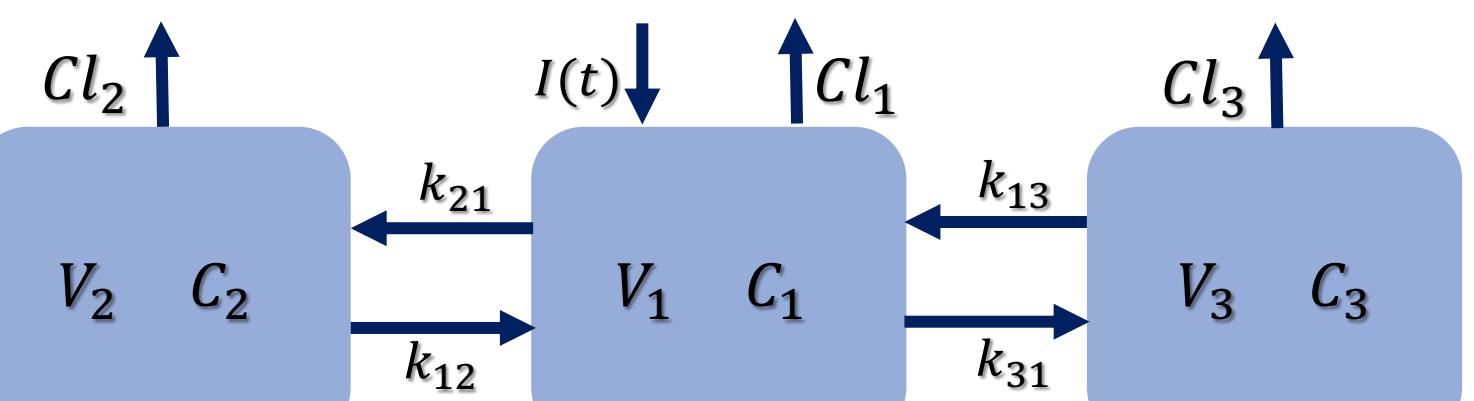


Once the integration constants are determined – This process provides a solution to the system at a specified time; its limitation being it only produces a solution for the last time point. However, we are able to use that solution as the initial condition for the next iteration of the function. As shown in Figure 1, the accuracy for larger step sizes is comparable to smaller ones.



EXAMPLE 2 : THREE-COMPARTMENT PK MODEL

A three-compartment human PK model of Remifentanil from Cascone et al. was computed in R using the fourth-order Runge-Kutta method (RK45) and the *pbpkme* function.³



Central compartment:
 $V_1 \cdot \frac{dc_1}{dt} = -Cl_1 \cdot C_1 + k_{21} \cdot C_2 + k_{31} \cdot C_3 - [k_{12} + k_{13} + k_{10}] \cdot C_1 - V_1 \cdot I(t)$

Highly perfused compartment:
 $V_2 \cdot \frac{dc_2}{dt} = k_{12} \cdot C_1 - k_{21} \cdot C_2 - Cl_2 \cdot C_2$

Scarcely perfused compartment:
 $V_3 \cdot \frac{dc_3}{dt} = k_{13} \cdot C_1 - k_{31} \cdot C_3 - Cl_3 \cdot C_3$

External clearance:
 $Cl_2 = k_{12} \cdot C_1 - k_{21} \cdot C_2 - Cl_2 \cdot C_2$

Rate coefficient matrix:

$$\begin{pmatrix} -\left(\frac{Cl_1}{V_1}\right) + k_{12} + k_{13} + k_{10} + I(t) & k_{21} \cdot V_2/V_1 & k_{31} \cdot V_3/V_1 \\ k_{12} \cdot V_1/V_2 & -\left(\frac{Cl_2}{V_2}\right) + k_{21} & 0 \\ k_{13} \cdot V_1/V_3 & 0 & -\left(\frac{Cl_3}{V_3}\right) + k_{31} \end{pmatrix}$$

Table 1: Comparison of run times for the Remifentanil model

Step Size	RK45	pbpkme
0.1	1.76 sec	0.08 sec
0.01	1.85 sec	0.61 sec

Conc vs Time Curve of Remifentanil 30 microgram/kg bolus

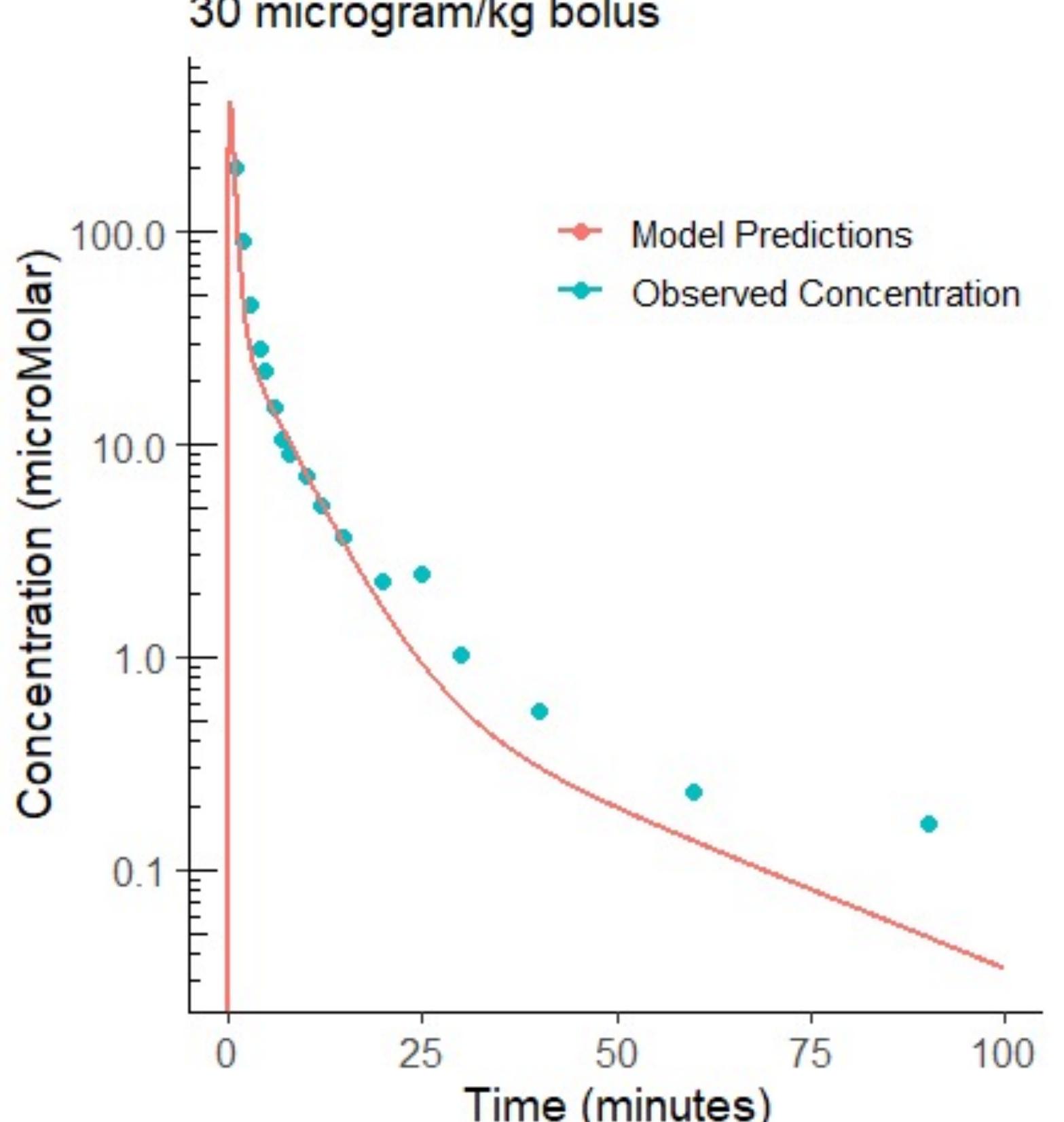


Figure 2: Plot of observed versus model predicted values for the human Remifentanil model, illustrating that the *pbpkme* method works at least as well as traditional numerical methods on classic compartmental pharmacokinetic models

EXAMPLE 3 : EXPANSION TO PBPK

Ordinary differential equations for a forty compartment PBPK pig model of doxorubicin from Dubbelboer et al. (Figure 3) was converted into matrix format and run with *pbpkme*.⁴

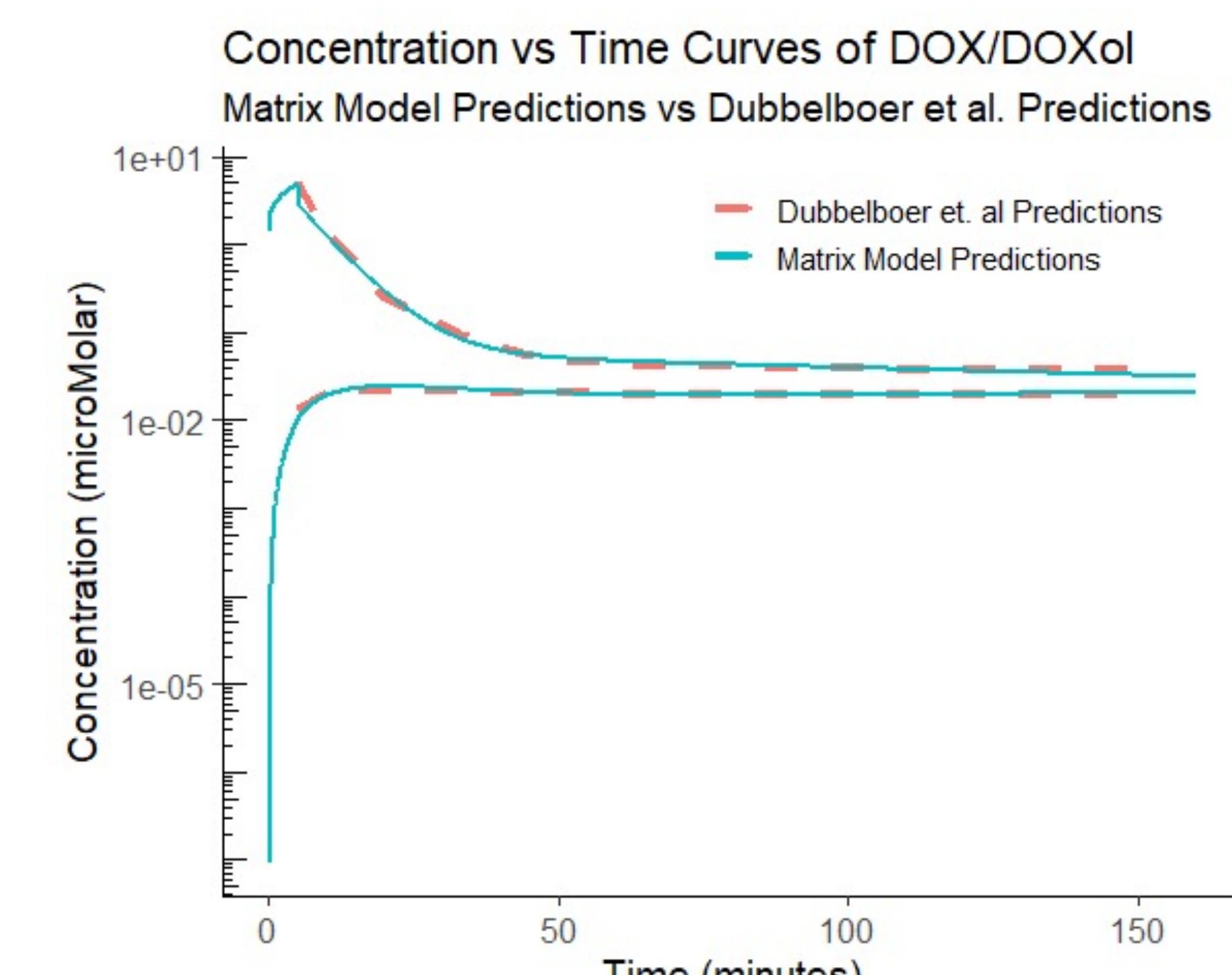
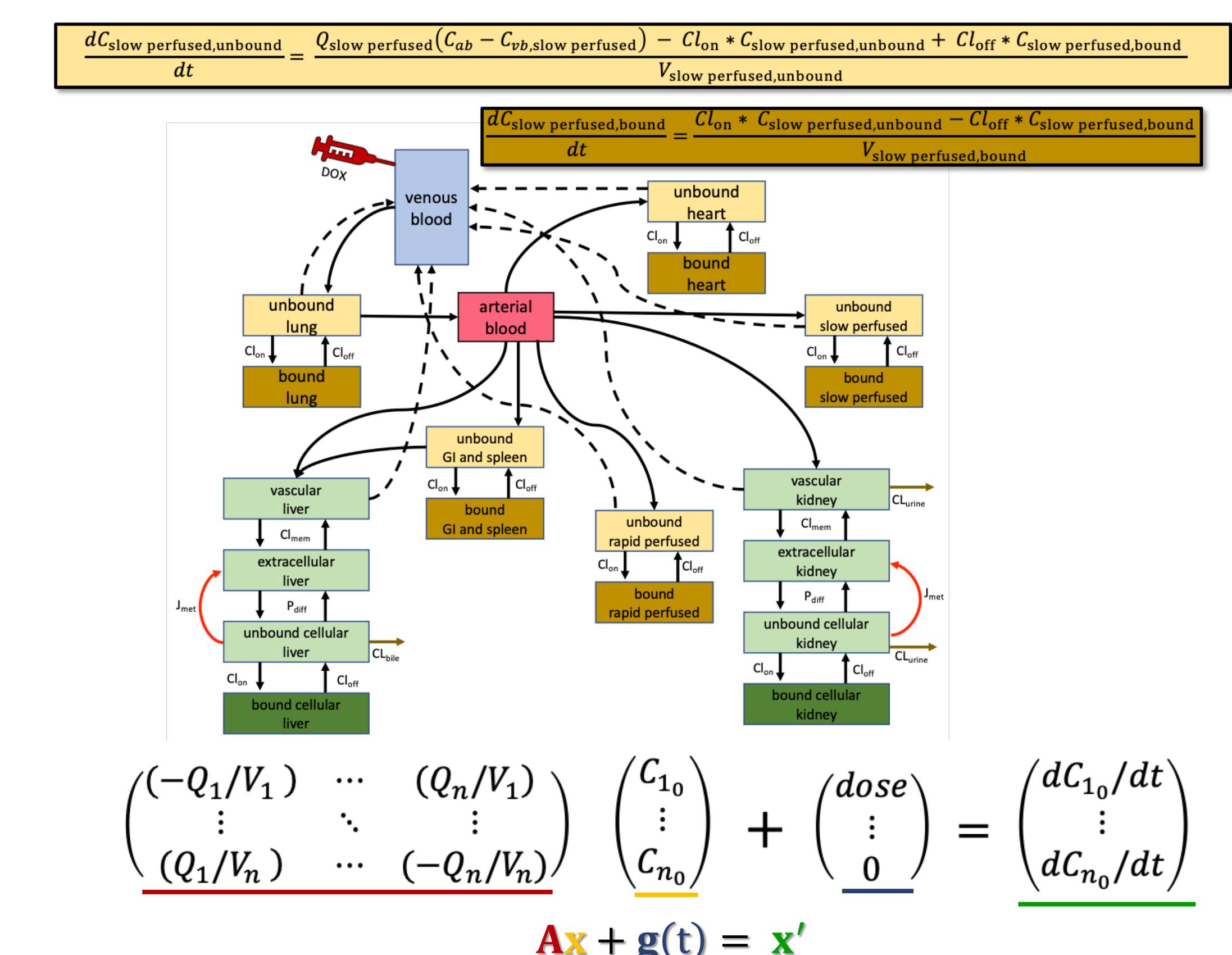


Figure 3: *pbpkme* model predictions were accurate compared to the original model's predictions

pbpkme is not susceptible to issues with stiffness since the analytical solution for each small time interval is calculated and then numerically integrated using Simpson's 1/3 Rule. *pbpkme* allows the modeler to use a larger time step for the same accuracy. Thus, any linear or approximately linear system can be described using the method in *pbpkme* in a more efficient way than traditional adaptive-step methods.

CONCLUSION

Using a matrix-based approach to model systems of first-order ODEs is a computationally efficient and accurate technique. The *pbpkme* package simplifies the use of this mathematical method for general use in the pharmacometrics community.

ACKNOWLEDGEMENTS

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REFERENCE

- [1] Hegarty, G, and SB Duffull. 2012. School of Pharmacy, University of Otago.
- [2] Boyce, WE and RC Prima. 1996. New York. John Wiley & Sons.
- [3] Cascone et al. 2013. *Transl. Med. UniSa*. 7:18-22
- [4] Dubbelboer, et al. 2017. *Mol. Pharmaceutics*, 14(3):686-698.