Title: pbpkme: A Flexible Fit Matrix-Based Framework for PK and PBPK Models in R

Authors: Hillary R. Husband and Eric A. Sherer

Institutions: College of Engineering and Science, Louisiana Tech University

Objectives: The pbpkme package is designed for solving classic compartmental 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. The objectives of this work are to:

- Construct a matrix-based framework for efficiently solving large systems of differential equations as often used to define PBPK models
- 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

Methods: This package uses the eigenvalue/eigenvector solution to a system of linear ODEs. Matrix manipulation is computationally fast, making it ideal for model fitting/parameter estimation, especially for large models. The equation for the analytical solution is

$$\mathbf{x}(t) = \boldsymbol{\phi}(t)\mathbf{x^0} + \boldsymbol{\phi}(t)\int_{t_0}^{t} \boldsymbol{\phi}^{-1}(s)\mathbf{g}(s)ds,$$

where $\mathbf{x}$ is a vector of amounts or concentrations, $\boldsymbol{\phi}(t)$ is the fundamental matrix derived from the eigenvalues/eigenvectors of the linear ODEs, $\mathbf{x^0}$ is the vector of initial conditions, and $\mathbf{g}(s)$ is the non-homogenous portion of the system, if one exists, representing an infusion profile. It is common for larger systems to produce complex conjugate pairs in their solutions, which pbpkme handles automatically. The method by itself solves for a solution to the model over the 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. 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).[2]

Results: The method was validated against an example with a known solution.[1] Results for varying time-steps illustrating the method's accuracy and speed are shown in Figure 1. To showcase pbpkme's computation speed compared to traditional approaches, a three-compartment PK model was computed in R using the fourth-order Runge-Kutta method (RK45) and the pbpkme function.[1] The pbpkme function was 43%-94% faster than RK45 at step-size 0.01 and 0.1, respectively. Finally, ODEs for a forty compartment PBPK model were converted into matrix form and its predictions were accurate compared to the original model's predictions, demonstrating the flexibility of this function.[4]

Conclusions: 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.

References

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

Figure 1: Exact Solution Versus pbpkme Method Numerical Approximations