

Description of Codes for Chapter 3: Pharmacokinetic Modeling

Section 3.1.2: Comparison of distributed and lumped transport models

The script to generate the comparison between the distributed blood-tissue exchange model and the two-compartment model of this section is 'BTEX_vs_compartmental.m'. This script generates Figure 3.3a. (The lower panel, Figure 3.3b, can be generated with a parameter modification.) The code 'BTEX.m' solves the blood-tissue exchange model of Equations (3.2), with an exponential arterial input concentration $c_A(t) = 1 - e^{-kt}$ mM. The code 'dXdT1.m' computes the right-hand side of the ordinary differential equations of Equation (3.5). The driver script first computes and plots the distributed model solution, then computes and plots the ODE model solution.

Section 3.1.3: Quasi-steady model reduction

The script to generate the comparison between the two-compartment model and the reduced quasi-steady reduced model on this section is 'qs_reduction.m'. This script generates the plots in Figure 3.4. As above, the code 'dXdT1.m' is used to compute the right-hand side of Equation (3.5), this time with the input function $c_A(t) = e^{-kt}$ mM. The code 'dXdT2.m' computes the right-hand side of the reduced model of Equation (3.8).

Section 3.4.1 and 3.4.2: Permeability-limited PBPK transport

Figures 3.8 and 3.9 are generated from two different versions of the permeability-limited rat matrine PBPK model. The scripts for these simulations are found in 'MakePlots1.m', which calls the initialization script 'InitializeData', which assigns values to model volumes and data.

'MakePlots1.m' calls the full permeability-limited PBPK model of Sections 3.4.1 and 3.4.2. Other than the fact that they employ different parameter values, these simulations are identical. The different parameter sets are attained by setting the argument pflag, which is sent to the ODE function 'dCdT.m', as described in the comments. The ODE function 'dCdT.m' computes the right-hand side of the differential equations for the permeability-limited model. Note that these scripts generate simulations for the mean parameter values in Tables 3.2 and 3.3. Thus, these scripts do not return the ensemble fits illustrated in Chapter 3.

Section 3.4.3: Flow-limited PBPK transport

The simulations in Figures 3.11 and 3.12 are generated from two different versions of the flow-limited rat matrine PBPK model. The scripts for these simulations are found in 'MakePlots2.m', which calls the initialization script 'InitializeData', which assigns values to model volumes and data. The ODE function 'dCdT_fl.m' computes the right-hand side of the differential equations for the flow-limited model.

As for the above, the only difference between these two sets of simulations is in the parameter values. As above, these scripts generate simulations for the mean parameter values, not the ensemble fits illustrated in Chapter 3.

Section 3.4.4: Model validation and discrimination

The simulations for Section 3.4.4 make use of the ODE file 'dCdT_fl.m' for the flow-limited rat matrine model. The script 'Oral_and_IV_dose.m' simulations the model for oral and IV doses, using parameter classes 1 and 2, to generate the plots in Figure 3.13.

Additional Material

A series of recent publications explore the PBPK modeling structures developed in this chapter. One of those papers (reference 3, below) introduces a formulation of the flow-limited model that is as accurate

and somewhat more convenient than the asymptotic approximation developed in Chapter 3 of *Biosimulation*. For further reading, please see:

1. Thompson MD, Beard DA. Development of appropriate equations for physiologically based pharmacokinetic modeling of permeability-limited and flow-limited transport. *J Pharmacokinet Pharmacodyn*. 2011 Aug;38(4):405-21.
2. Thompson MD, Beard DA. Physiologically based pharmacokinetic tissue compartment model selection in drug development and risk assessment. *J Pharm Sci*. 2012 Jan;101(1):424-35. doi: 10.1002/jps.22768.
3. Thompson MD, Beard DA. Use of partition coefficients in flow-limited physiologically-based pharmacokinetic modeling. *J Pharmacokinet Pharmacodyn* 2012.