Day 2 Exercise 2
A PBPK model for methotrexate

A Course on Physiologically Based Pharmacokinetic (PBPK) Modeling in Drug Development and Evaluation

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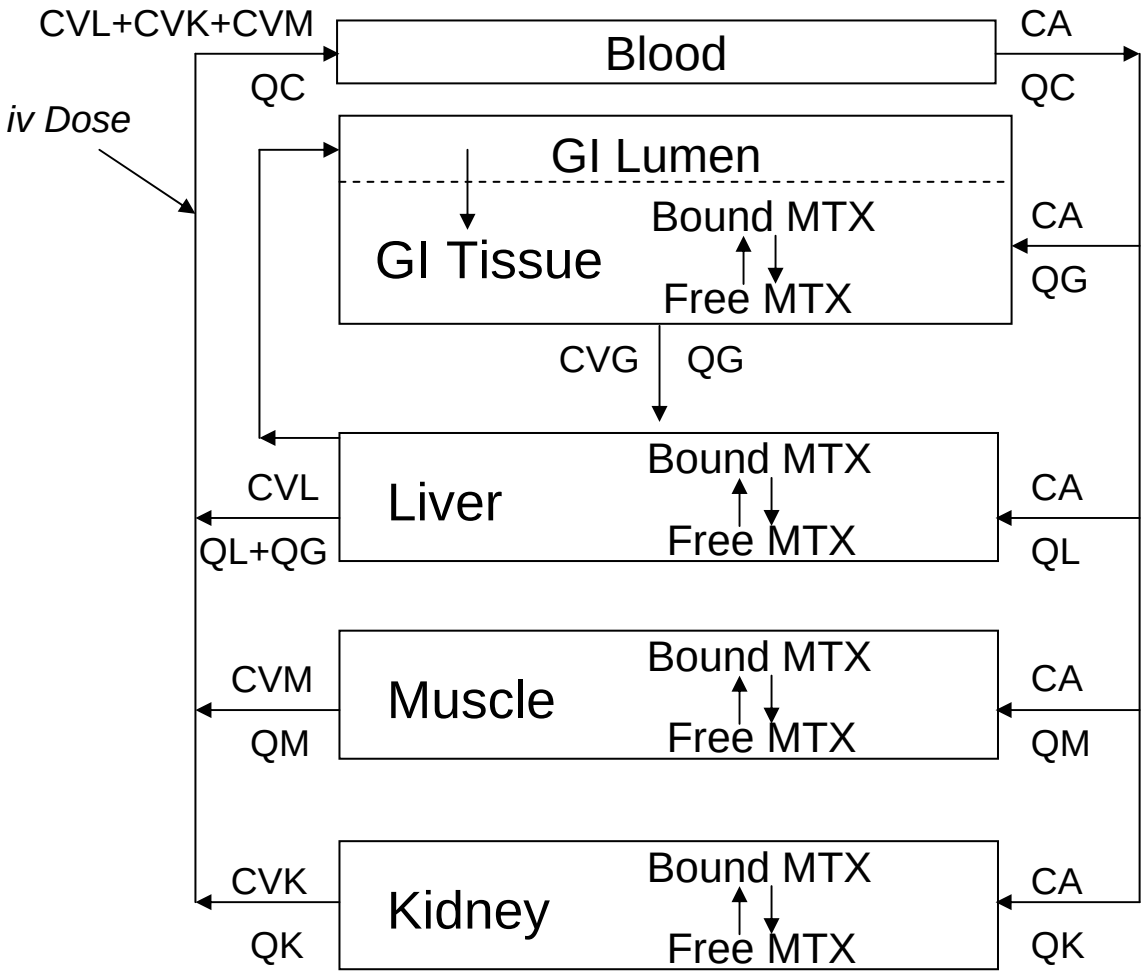
Center for Human Health Assessment
Center for Drug Safety Sciences

Background

- The methotrexate (MTX) model is one of the earliest examples of using PBPK models for pharmaceutical (anti-neoplastic) agents.
- Bishchoff et al. (1971) evaluated blood and tissue levels across doses and in several species (rat, mouse, dog, human).
- They found non-linear pharmacokinetic behavior in the tissues.
- In this exercise, you will use Bishchoff et al.'s model to examine the dose-dependent MTX kinetics.
- Even better, you will find out how specific biochemical processes govern the observed behavior!

Model schematic

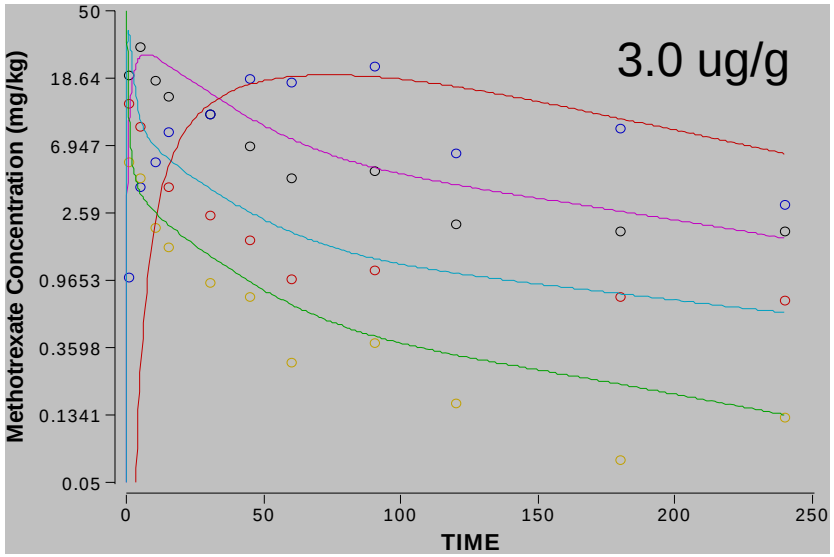


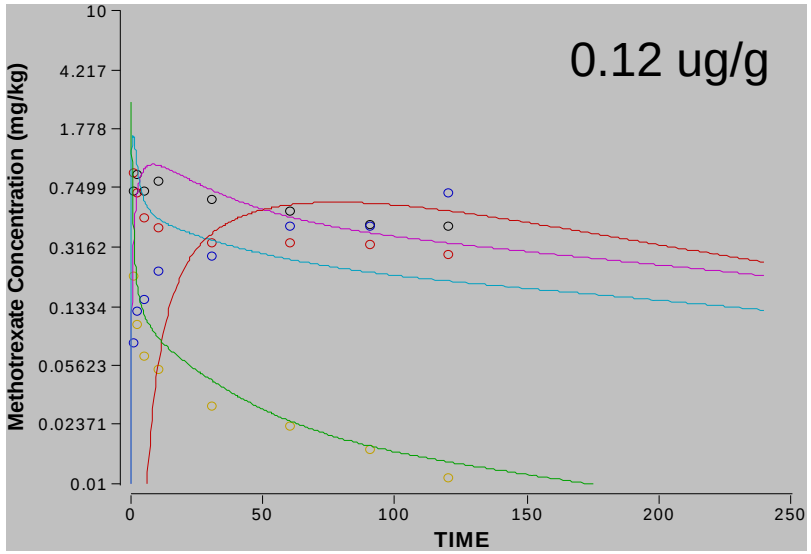
Note that the kidney, GI, liver, and muscle tissues having binding of the MTX.

Methotrexate model

- Step 1: Open the MTX model (MTX.mmd) and examine code.
- Step 2: Run the model for the 0.12 ug/g dose
  - In the Parameter window, set ‘ivdose’ to 0.12
  - Click ‘Run’
  - Lock  the Graph window for this run
- Step 3: Run the model for the 3 ug/g dose
  - Unlock the other Graph window
  - In the Parameter window, set ‘ivdose’ to 3
  - Click ‘Run’
  - Lock the second Graph window

Comparing model simulations with data





How do the tissue concentrations differ with dose?

How do you explain this dose-dependency?

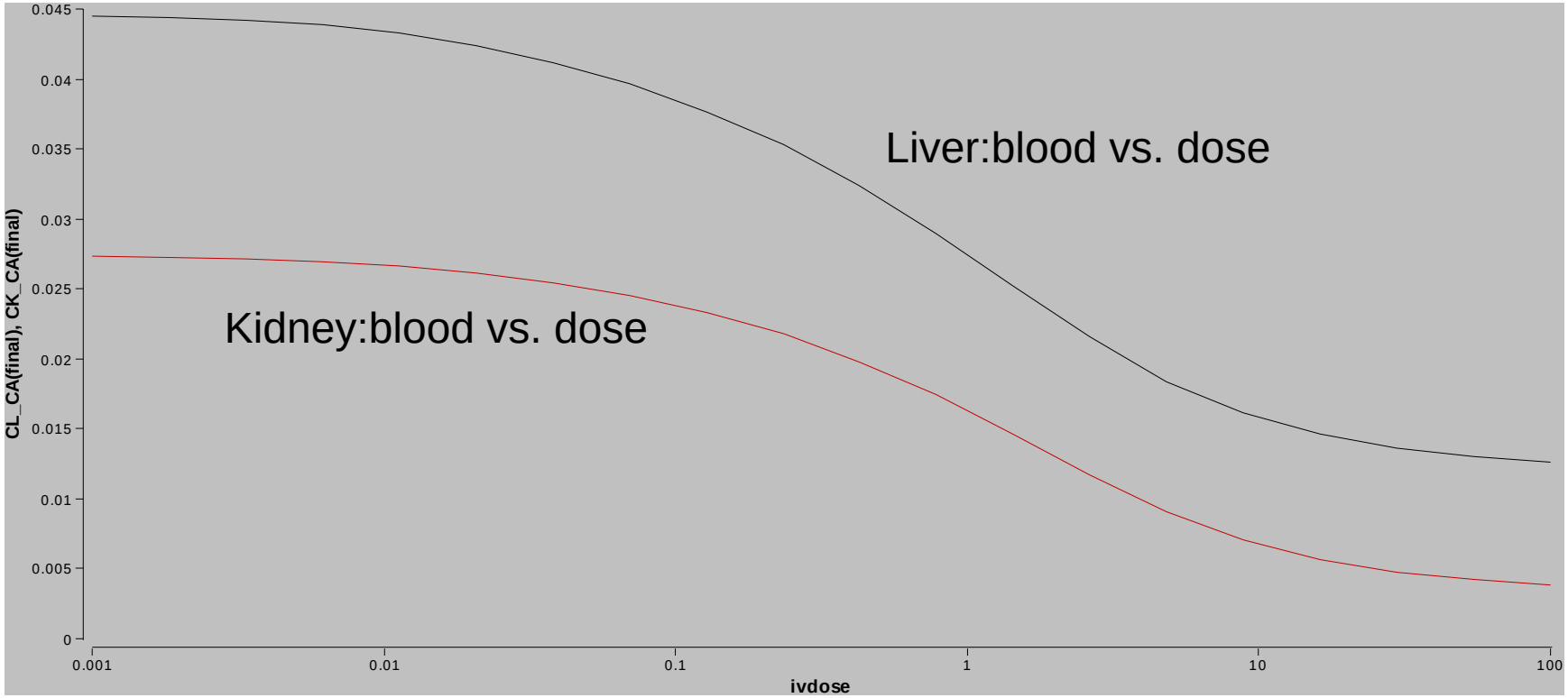
Batch runs

- Now let us use “Batch Runs” to see how tissue concentrations differ at other doses.
- Step 4: Go to Graph/New Window
  - Go to Graph/Choose Variable
  - Select a tissue concentration (e.g., CL) & add it to the Y axis by clicking Add. Click ‘OK’.
- Step 5: Go to Parameters/Batch Runs
  - Select “ivdose” for Parameter box
  - Set # of Runs = 11, Initial value = 0.001, Final value = 100, and Select ‘Geometric’.
  - Click OK.
  - Do you see how tissue concentrations differ with dose?

Parameter plots

- Now let us use a “Parameter Plot” to look at the predicted dose-response behavior more ‘directly’.
  - The Parameter Plot allows you to plot two model variables against each other.
  - Plot tissue:blood ratio vs. MTX dose.
- Step 6:Go to Parameters/Parameter Plots
  - Select ‘ivdose’ from the parameter list.
  - Set # of Runs = 20, Initial value = 0.001, Final value = 100, and Select ‘Geometric’.
  - Select ‘CL_CA’ and ‘CK_CA’ from the variable list, and make sure to click ‘Final’ for both.
  - Click ‘Run’.

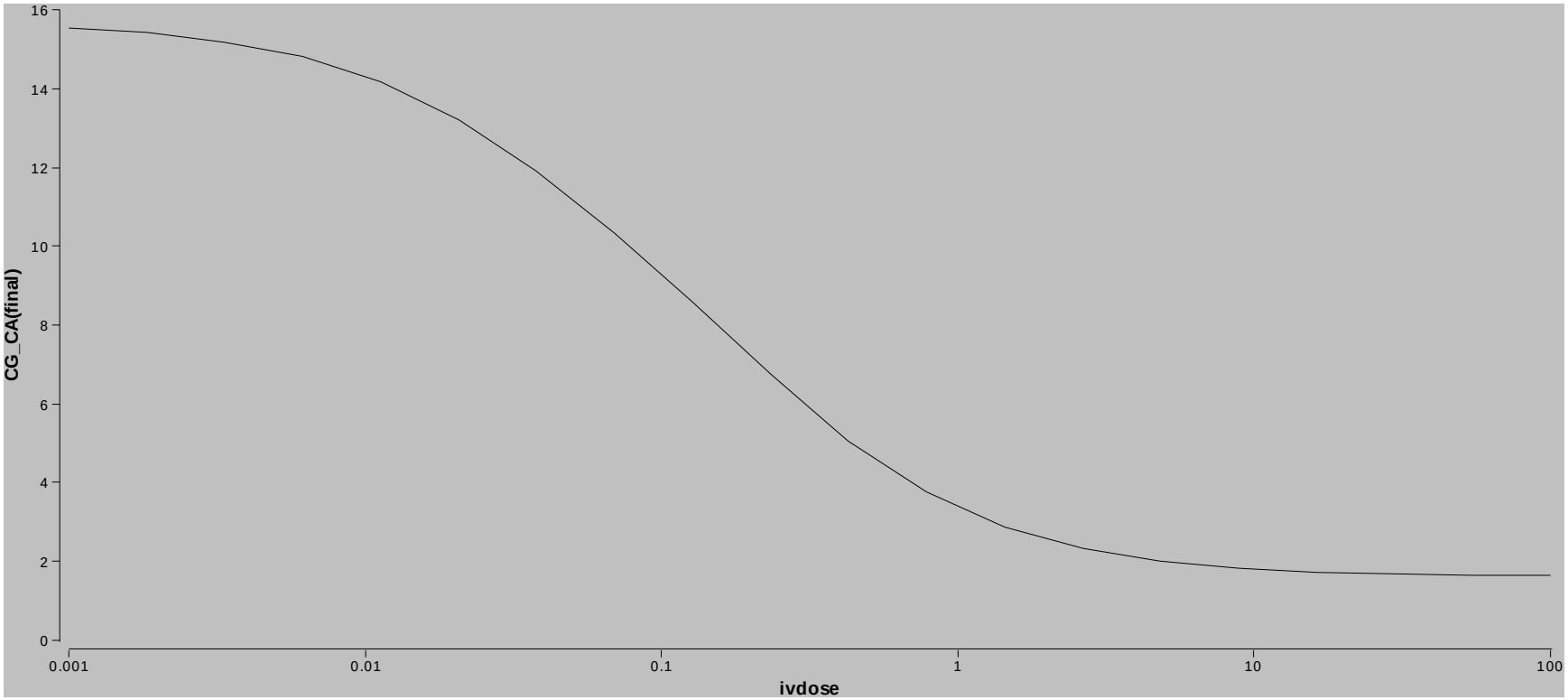
Parameter plots for kidney:blood and liver:blood



Note: To display the x-axis in log-scale, double click the x-axis and click ‘log’.

Next, try plotting Gut:blood (CG_CA) vs. MTX dose.

Parameter plot for gut:blood



Examining model behavior

- Try changing STOPTIME and run the parameter plot again (Click ‘Run’ on your parameter plot).
- Why might the tissue:blood ratios differ with different STOPTIME?

- With this exercise, you can see how Bishchoff et al. (1971) were able to describe non-linear *in vivo* kinetics using a few simple equations to account for drug transport and storage process.