Some Deterministic Models in Mathematical Biology: *Physiologically Based Pharmacokinetic Models for Toxic Chemicals*

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Outline

- Introduction to compartment models
- Research examples
- Linear model
  - Analytics
  - Graphics
- Nonlinear model
- Exploration

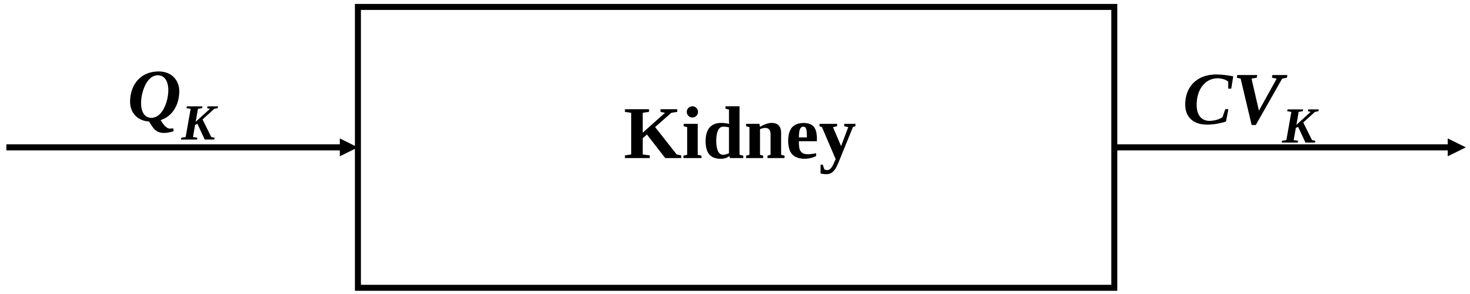
Physiologically Based Pharmacokinetic (PBPK) Models

A *physiologically based pharmacokinetic (PBPK) model* for the uptake and elimination of a chemical in rodents is developed to relate the amount of IV and orally administered chemical to the tissue doses of the chemical and its metabolite.

Characteristics of PBPK Models

- Compartments are to represent the amount or concentration of the chemical in a particular tissue.
- Model incorporates known tissue volumes and blood flow rates; this allows us to use the same model across multiple species.
- Similar tissues are grouped together.
- Compartments are assumed to be well-mixed.

Example of Compartment in PBPK Model



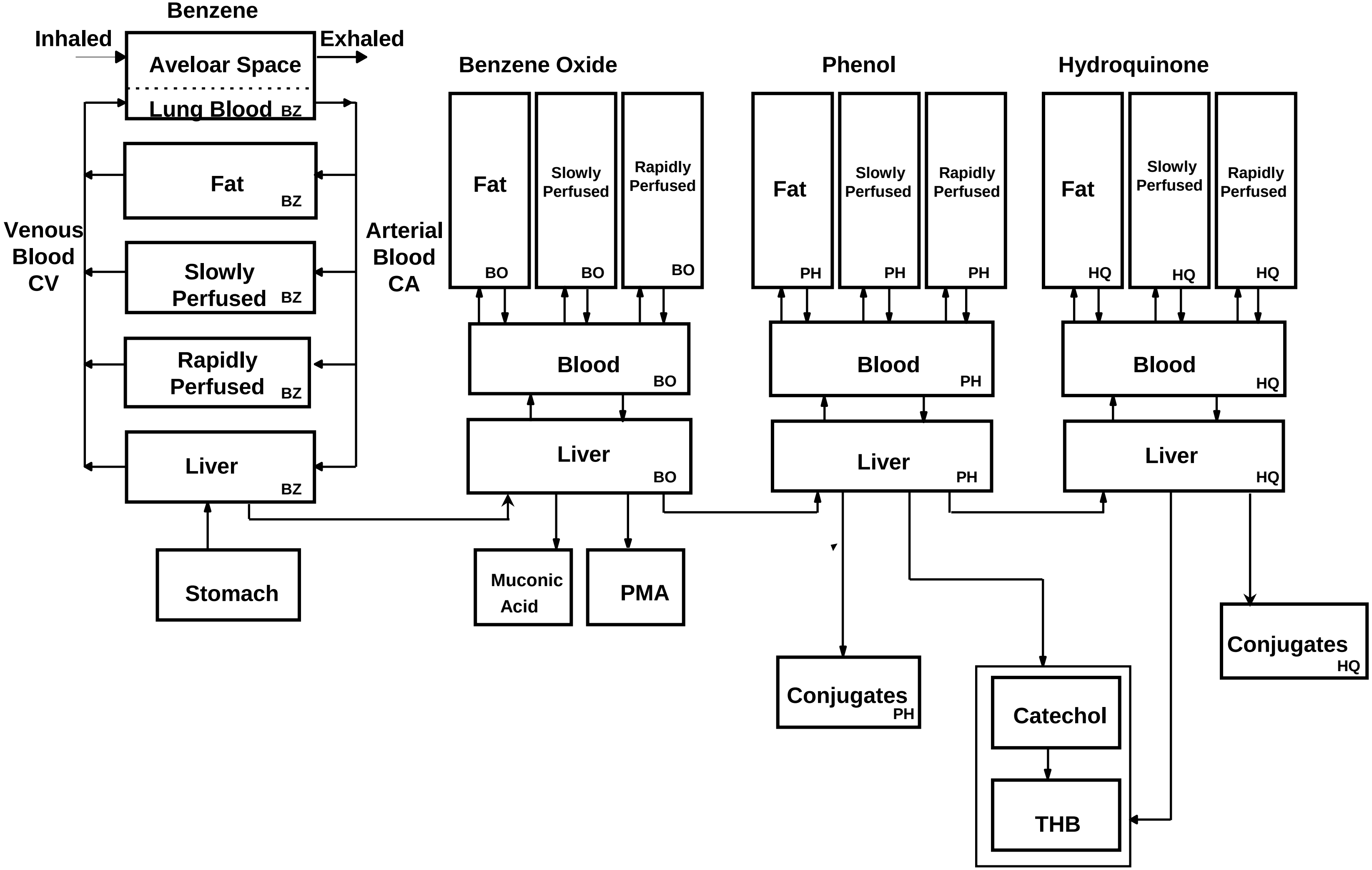
- Q_K is the blood flow into the kidney.
- CV_K is the concentration of drug in the venous blood leaving the kidney.

Example of Compartment in PBPK Model

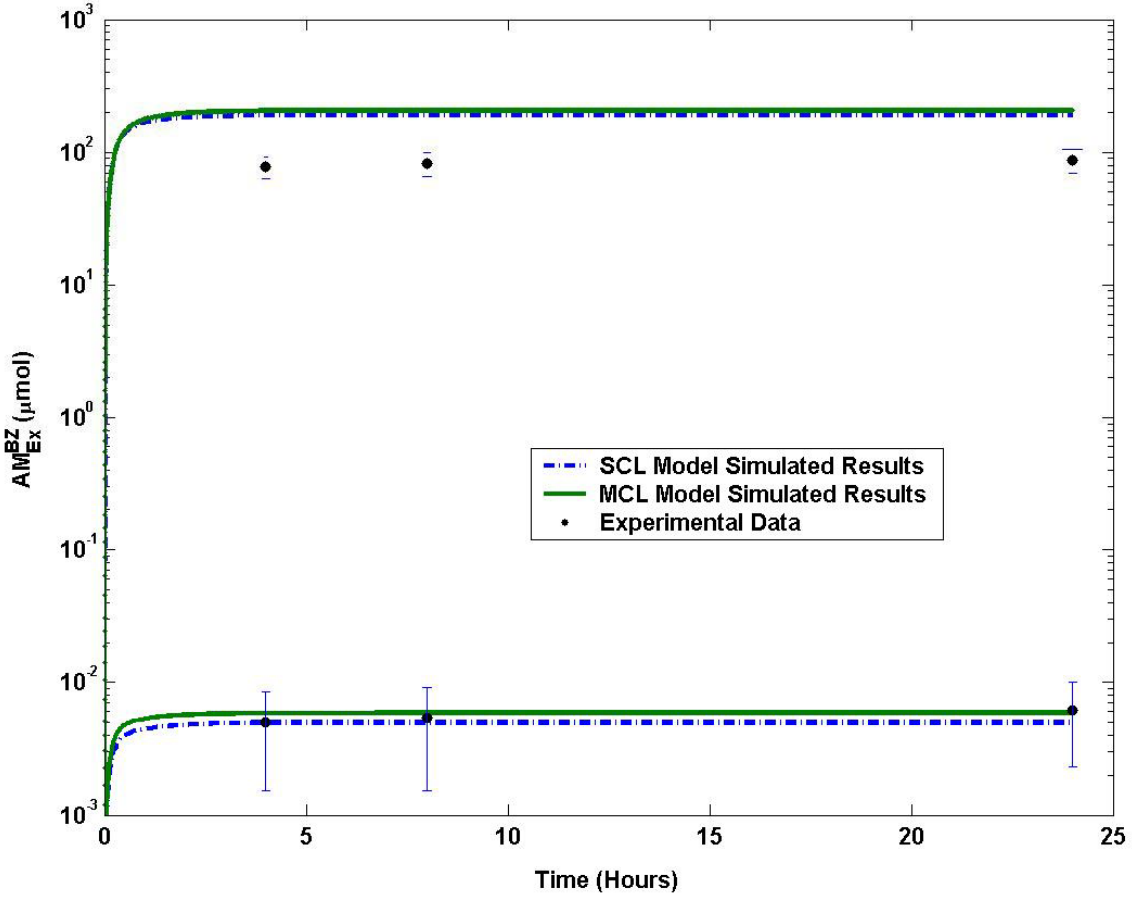
$$\frac{dC_K}{dt} = \frac{Q_K\left(C_K - CV_K\right)}{V_K}$$

- C_K **is the concentration of drug in the kidney at time** t**.**
- CV_K **is the concentration of drug in the venous blood leaving the kidney at time** t**.**
- Q_K **is the blood flow into the kidney.**
- V_K **is the volume of the kidney.**

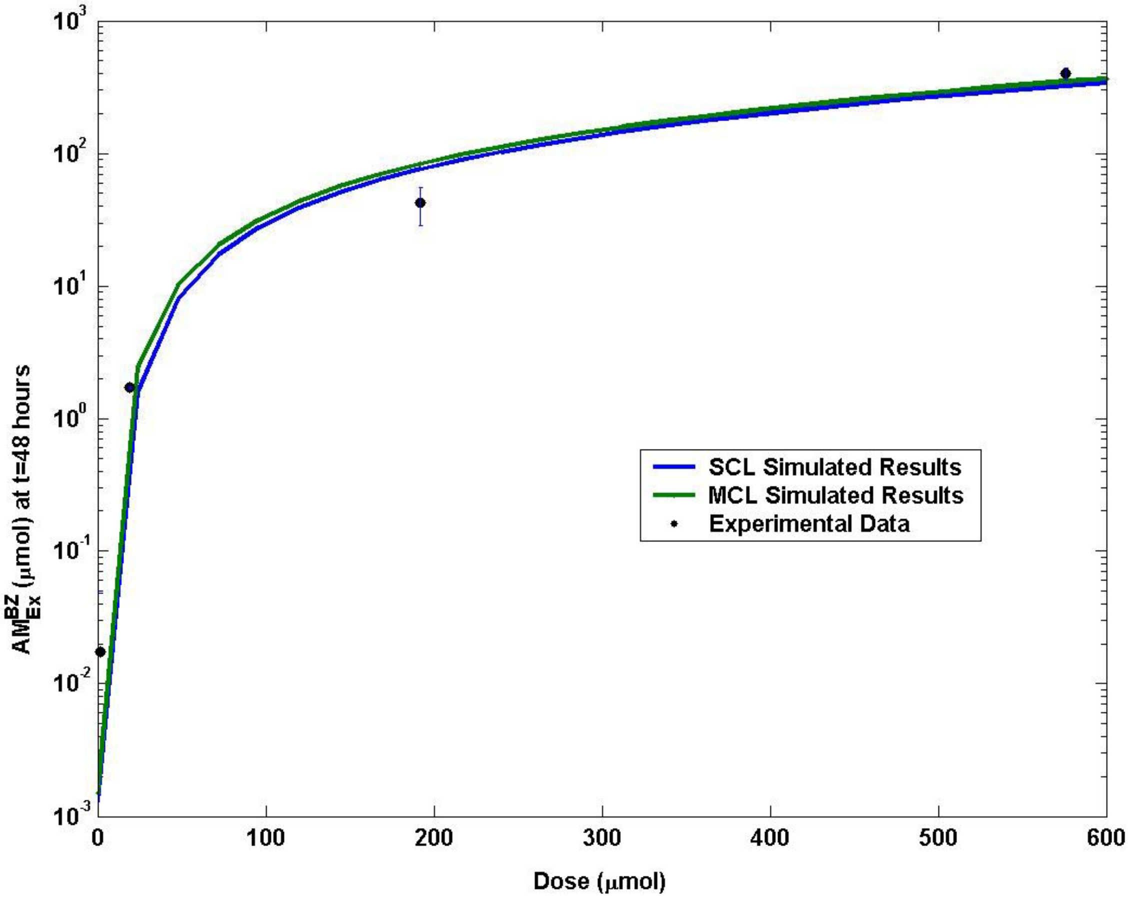
Benzene


Benzene
Inhaled
Exhaled
Aveloar Space
Lung Blood BZ
Fat BZ
Slowly Perfused BZ
Rapidly Perfused BZ
Liver BZ
Stomach
Venous Blood CV
Arterial Blood CA
Benzene Oxide
Fat BO
Slowly Perfused BO
Rapidly Perfused BO
Blood BO
Liver BO
Muconic Acid
PMA
Phenol
Fat PH
Slowly Perfused PH
Rapidly Perfused PH
Blood PH
Liver PH
Conjugates PH
Hydroquinone
Fat HQ
Slowly Perfused HQ
Rapidly Perfused HQ
Blood HQ
Liver HQ
Conjugates HQ
Catechol
THB

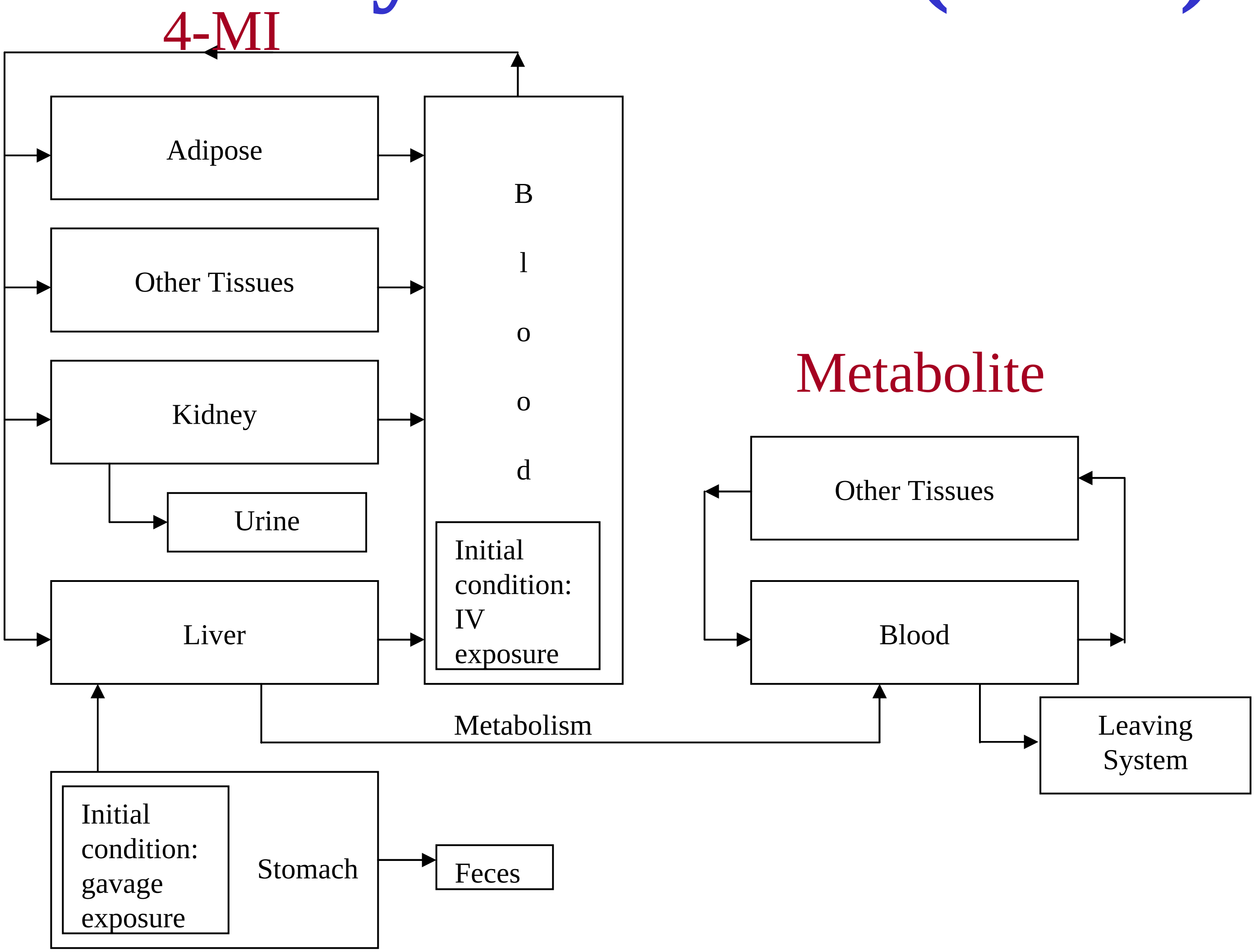
Benzene Plot



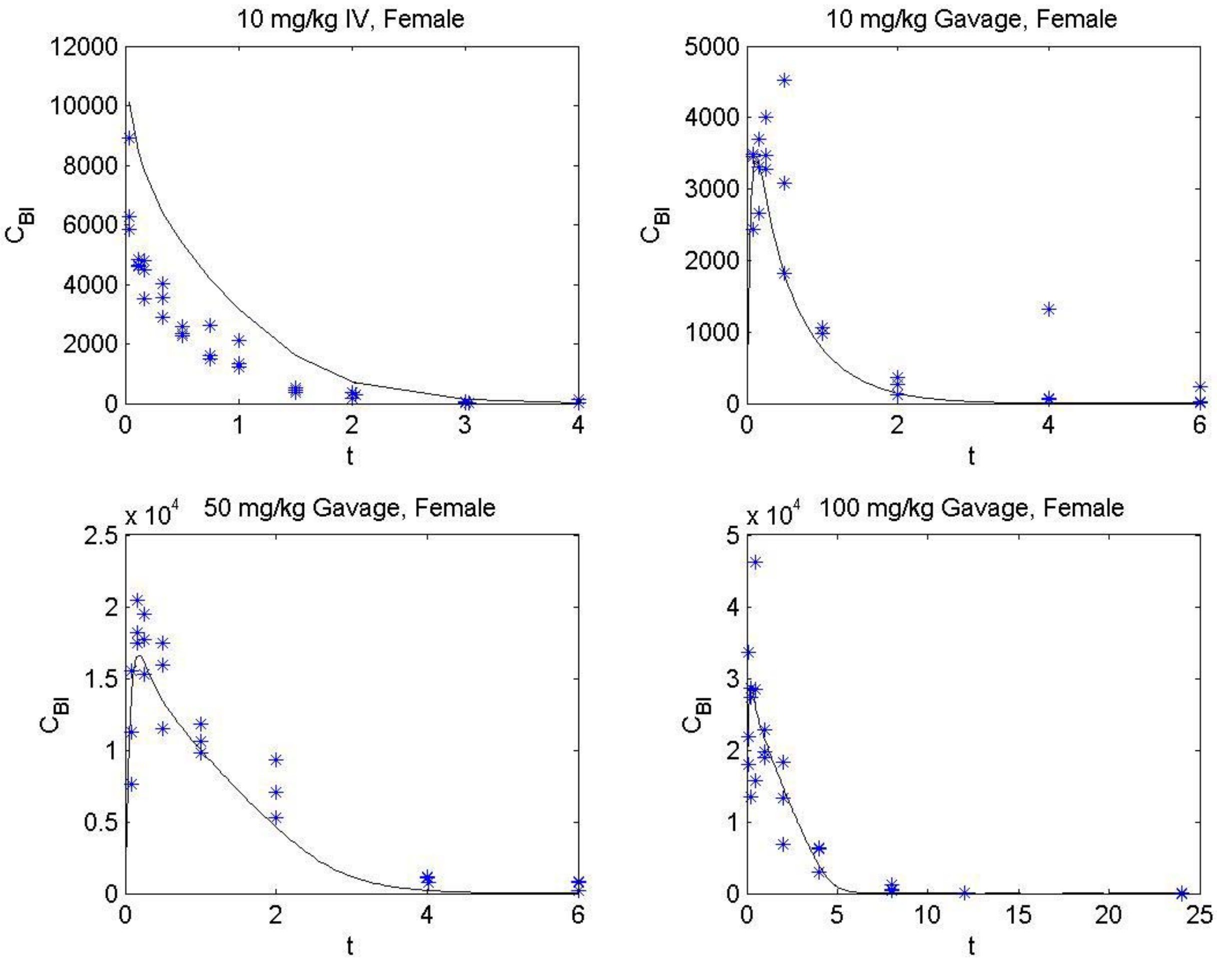
Benzene Plot



4-Methylimidazole (4-MI)



4-MI Female Rat Data (NTP TK)



Linear Model Example

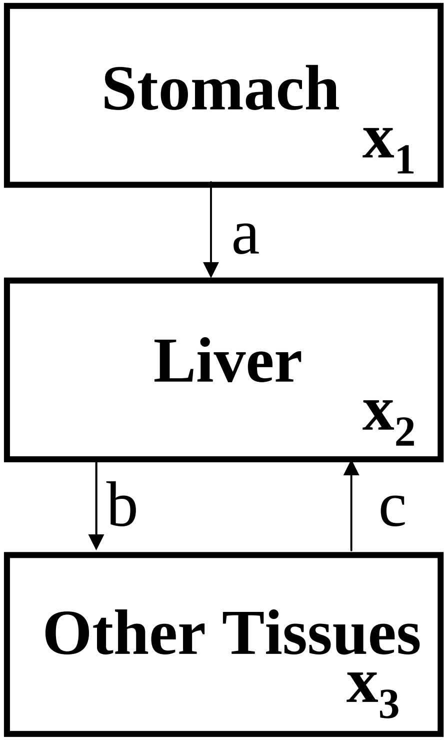
A drug or chemical enters the body via the stomach. Where does it go?

Assume we can think about the body as three compartments:

- Stomach (where drug enters)
- Liver (where drug is metabolized)
- All other tissues

Assume that once the drug leaves the stomach, it can not return to the stomach.

Schematic of Linear Model



- x_1, x_2 , and x_3 represent amounts of the drug.
- a, b, and c represent flow rates.

Linear Model Equations

Let's look at the change of amounts in each compartment, assuming the mass balance principle is applied.

$$\frac{dx_1}{dt} = -ax_1$$

$$\frac{dx_2}{dt} = ax_1 - bx_2 + cx_3$$

$$\frac{dx_3}{dt} = bx_2 - cx_3$$

Linear Model (continued)

Let's now write the system in matrix form.

$$\frac{d}{dt}\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} = \begin{bmatrix} -a & 0 & 0 \\ a & -b & c \\ 0 & b & -c \end{bmatrix}\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}$$

Linear Model (continued)

- **Find the eigenvectors and eigenvalues.**
- **Write general solution of the differential equation.**
- **Use initial conditions of the system to determine particular solution.**

Linear Model (continued)

For our example, let *a*=3, *b*=4, and *c*=11. Then, our general solution would be given by:

$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} = k_1 \begin{bmatrix} 0 \\ 11 \\ 4 \end{bmatrix} + k_2 \begin{bmatrix} -3 \\ 2 \\ 1 \end{bmatrix} e^{-3t} + k_3 \begin{bmatrix} 0 \\ -1 \\ 1 \end{bmatrix} e^{-15t}$$

Initial Conditions

Using the initial conditions of

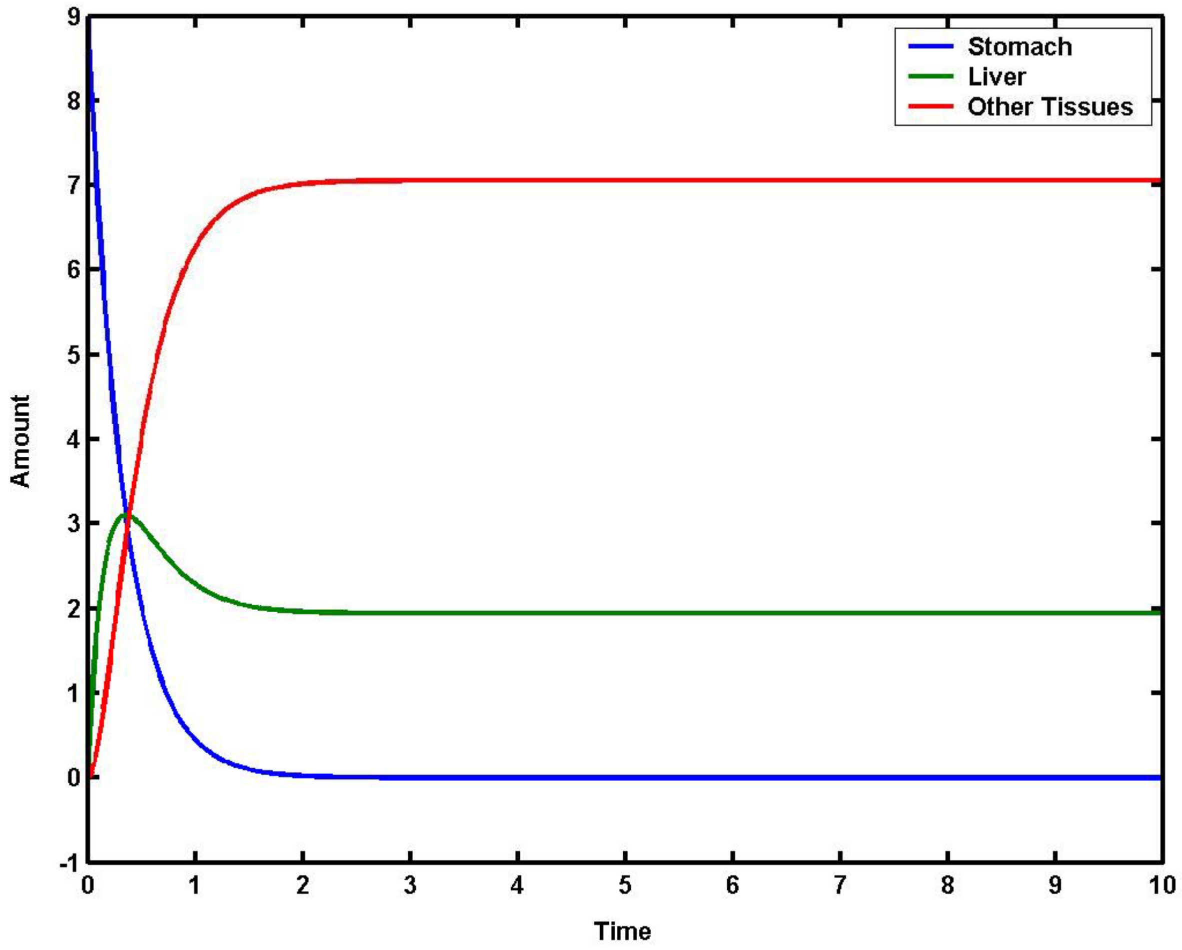
$$x_1(0) = 9$$

$$x_2(0) = 0$$

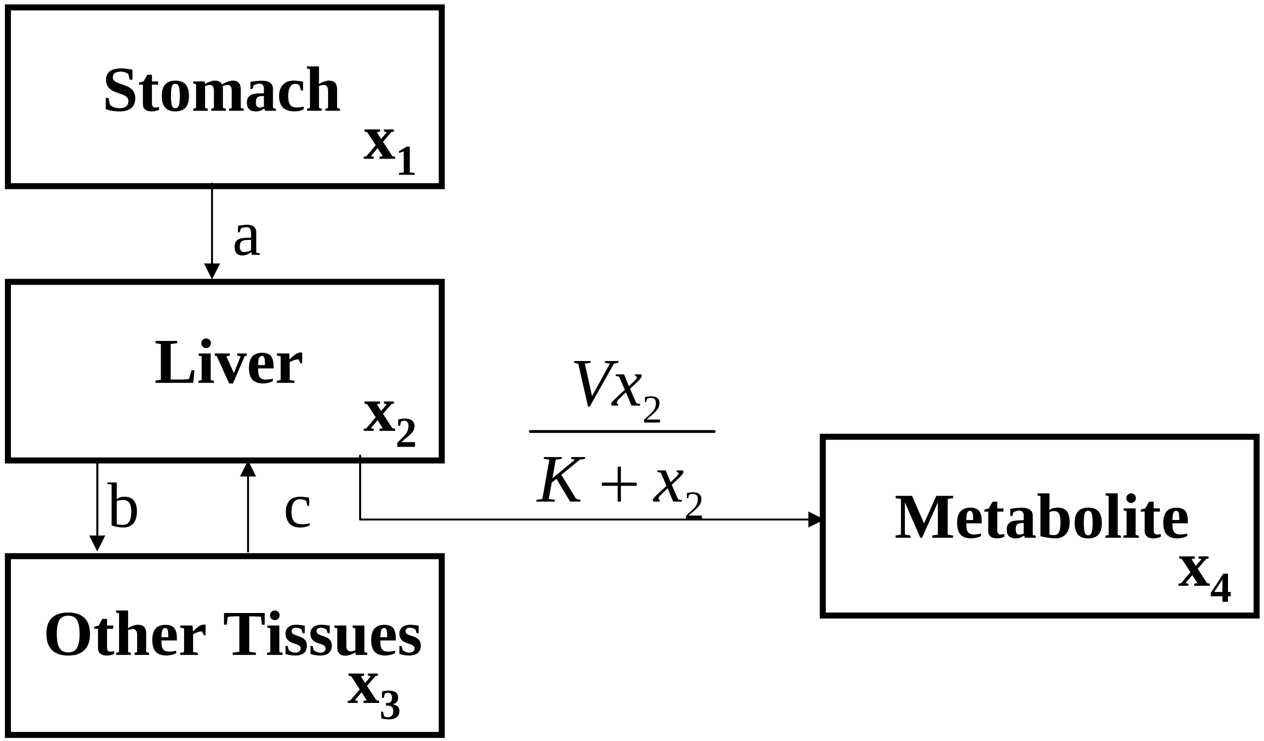
$$x_3(0) = 0,$$

we are representing the fact that the drug began in the stomach and there were no background levels of the drug in the system.

Graphical Results



Schematic of Nonlinear Model



x_1, x_2 , x_3, and x_4 represent amounts of the drug.

Nonlinear Model Equations

$$\frac{dx_1}{dt} = -ax_1$$

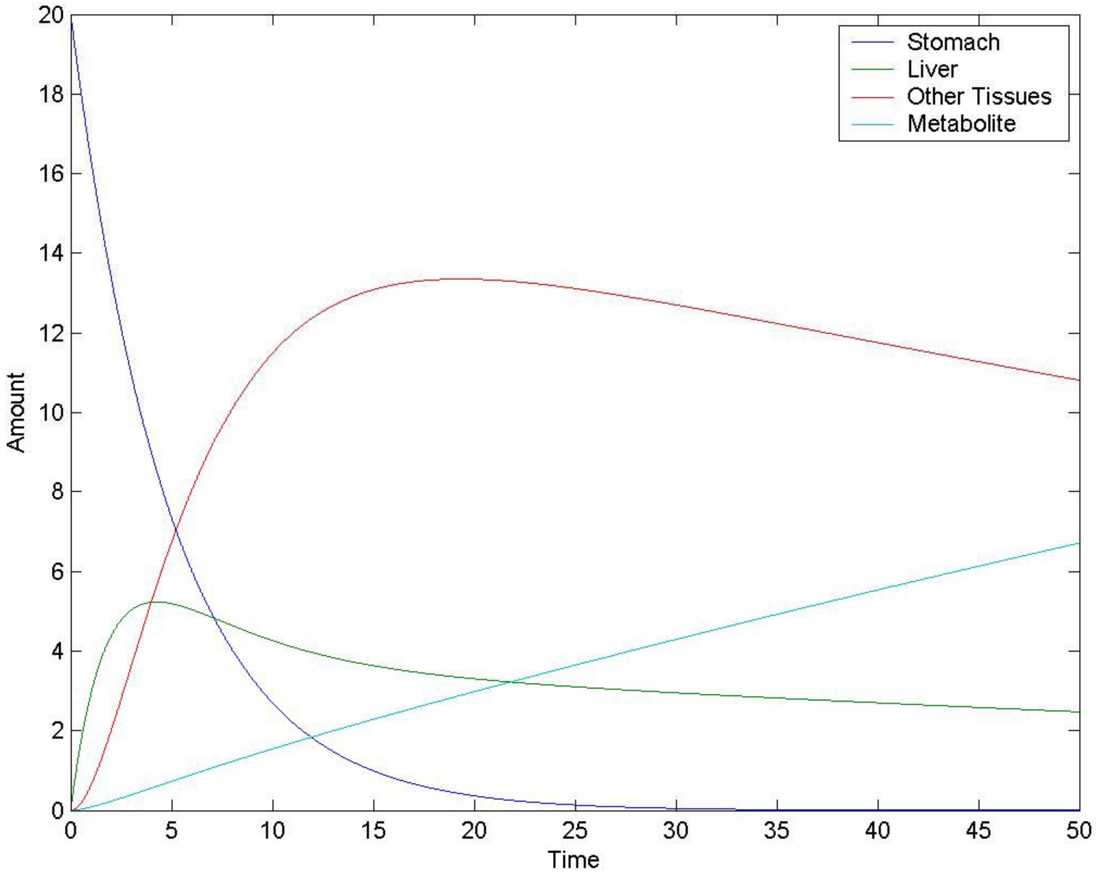
$$\frac{dx_2}{dt} = ax_1 - bx_2 + cx_3 - \frac{V\,x_2}{K + x_2}$$

$$\frac{dx_3}{dt} = bx_2 - cx_3$$

$$\frac{dx_4}{dt} = \frac{V\,x_2}{K + x_2}$$

Nonlinear Model

***a*=0.2, *b*=0.4, *c*=0.1, *V*=0.3, *K*=4**



Exploration

- **What would happen if the parameters were changed?**
- **What would happen if the initial conditions were changed?**

We will now use Phaser to explore these questions. Phaser files are on the website:

www.meredith.edu/math/faculty/cole/maaworkshop/pbpkmodels.htm