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**

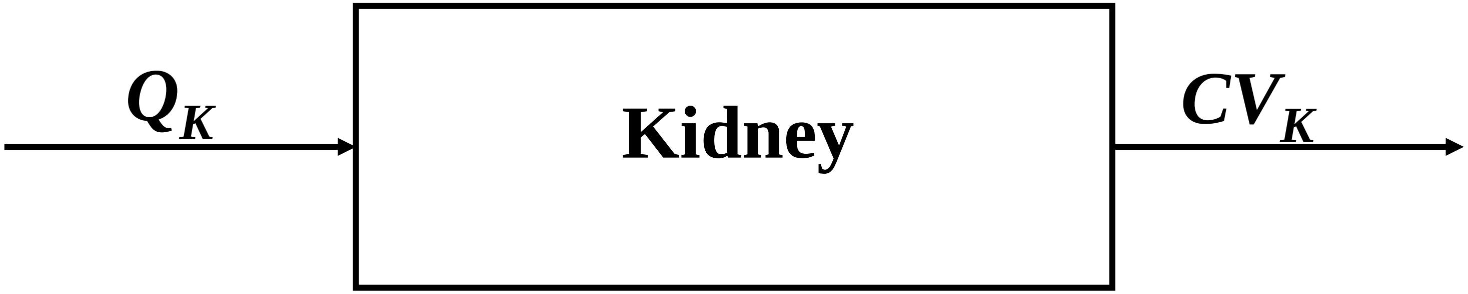
Physiologically Based Pharmacokinetic (PBPK) Models in Toxicology Research

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



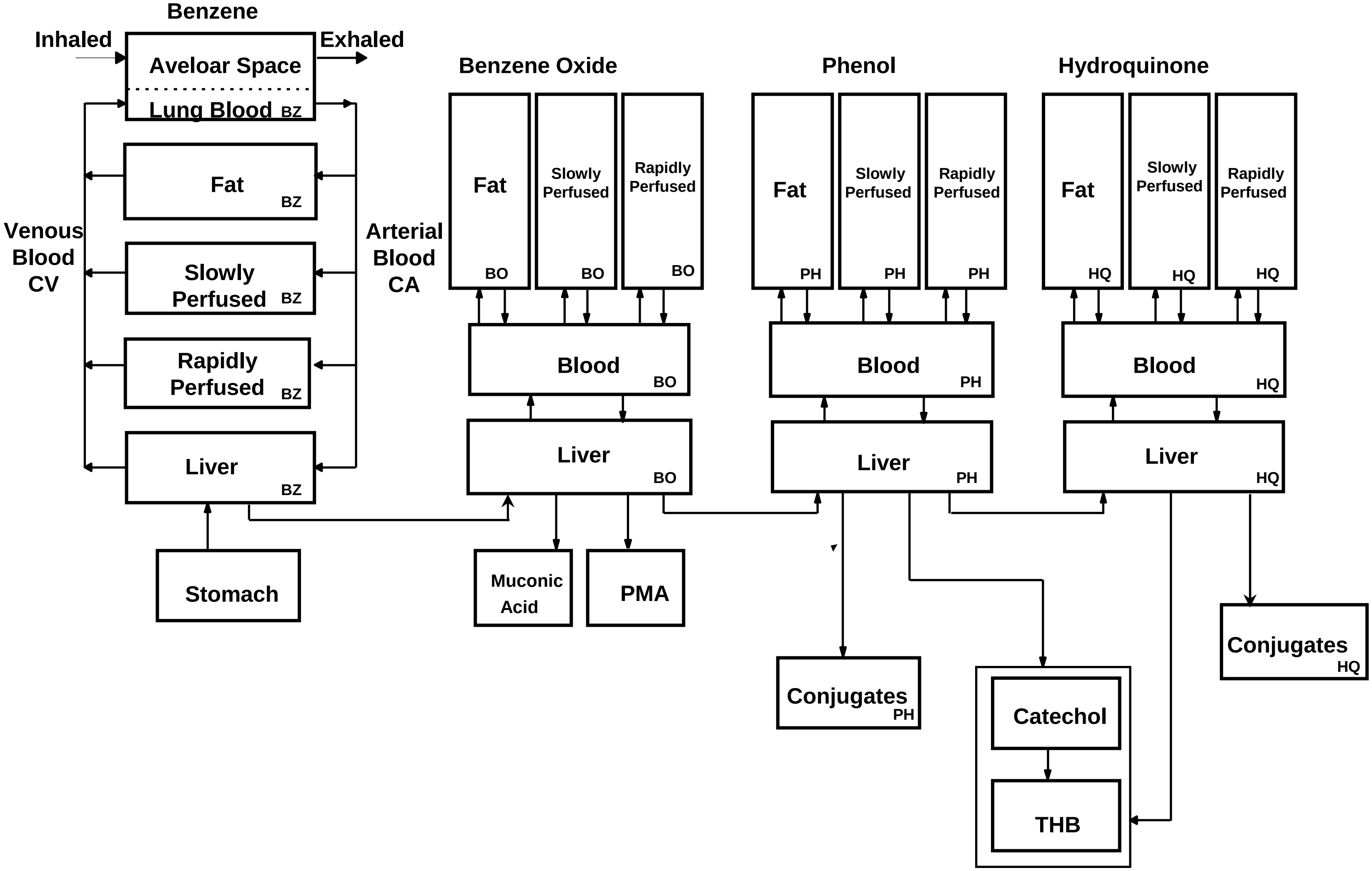
- Q_K **is the blood flow into the kidney.**
- CV_K **is the concentration of chemical in the venous blood leaving the kidney.**

Example of Compartment in PBPK Model

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

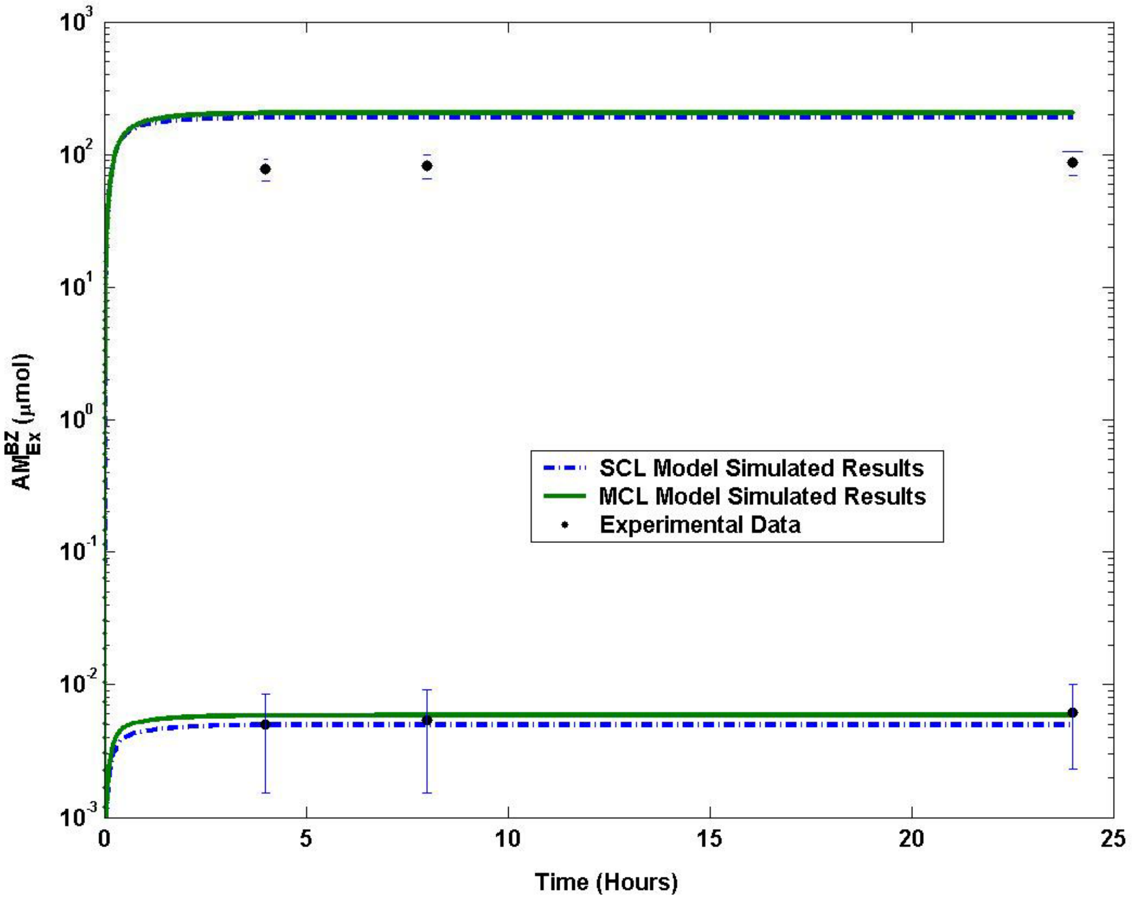
- C_K **is the concentration of chemical in the kidney at time** t**.**
- C_{Bl} **is the concentration of chemical in the blood at time** t**.**
- CV_K **is the concentration of chemical in the venous blood leaving the kidney at time** t**.**
- Q_K **is the blood flow into the kidney.**
- V_K **is the volume of the kidney.**

Benzene

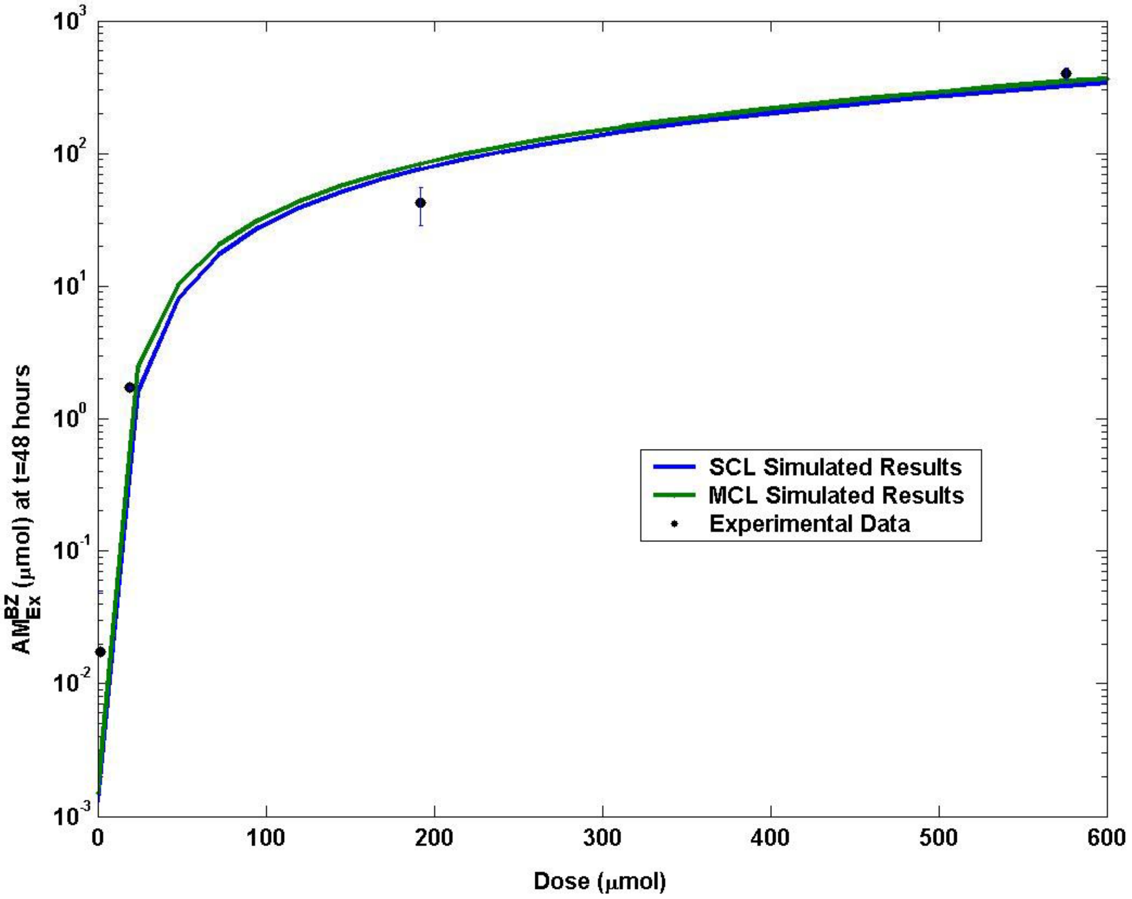


Benzene
Inhaled
Exhaled
Aveloar Space
Lung Blood BZ
Fat BZ
Slowly Perfused BZ
Rapidly Perfused BZ
Liver BZ
Stomach
Venous Blood CV
Arterial Blood CA
Benzene Oxide
Fat BO
Slowly Perfused BO
Rapidly Perfused BO
Blood BO
Liver BO
Muconic Acid
PMA
Phenol
Fat PH
Slowly Perfused PH
Rapidly Perfused PH
Blood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

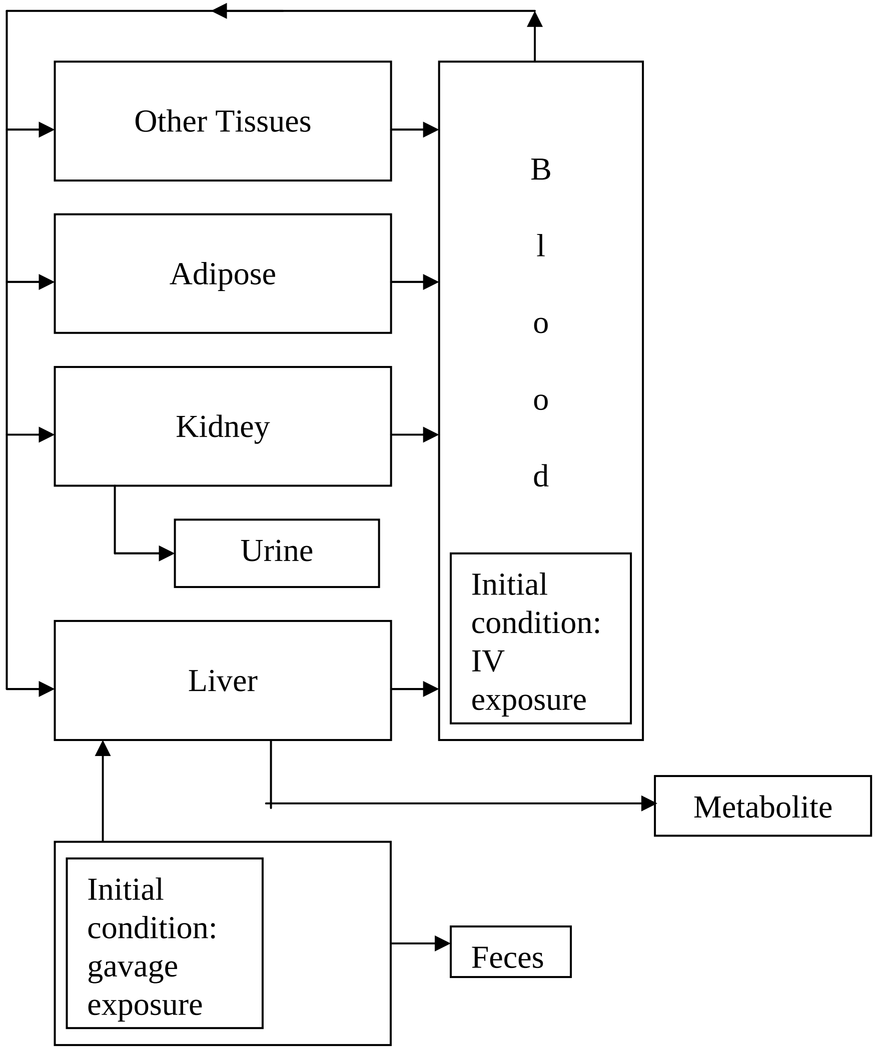
Benzene Plot



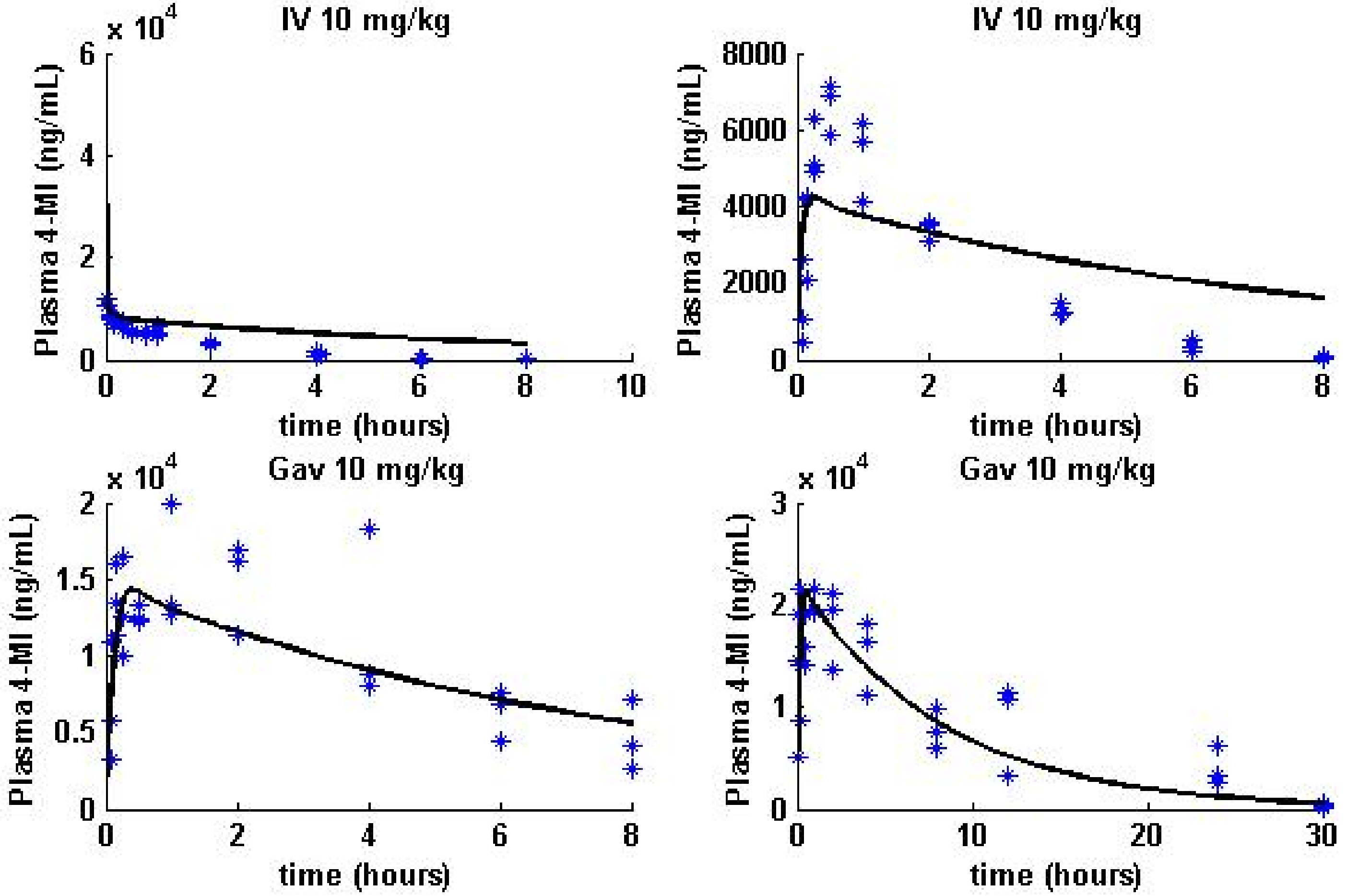
Benzene Plot



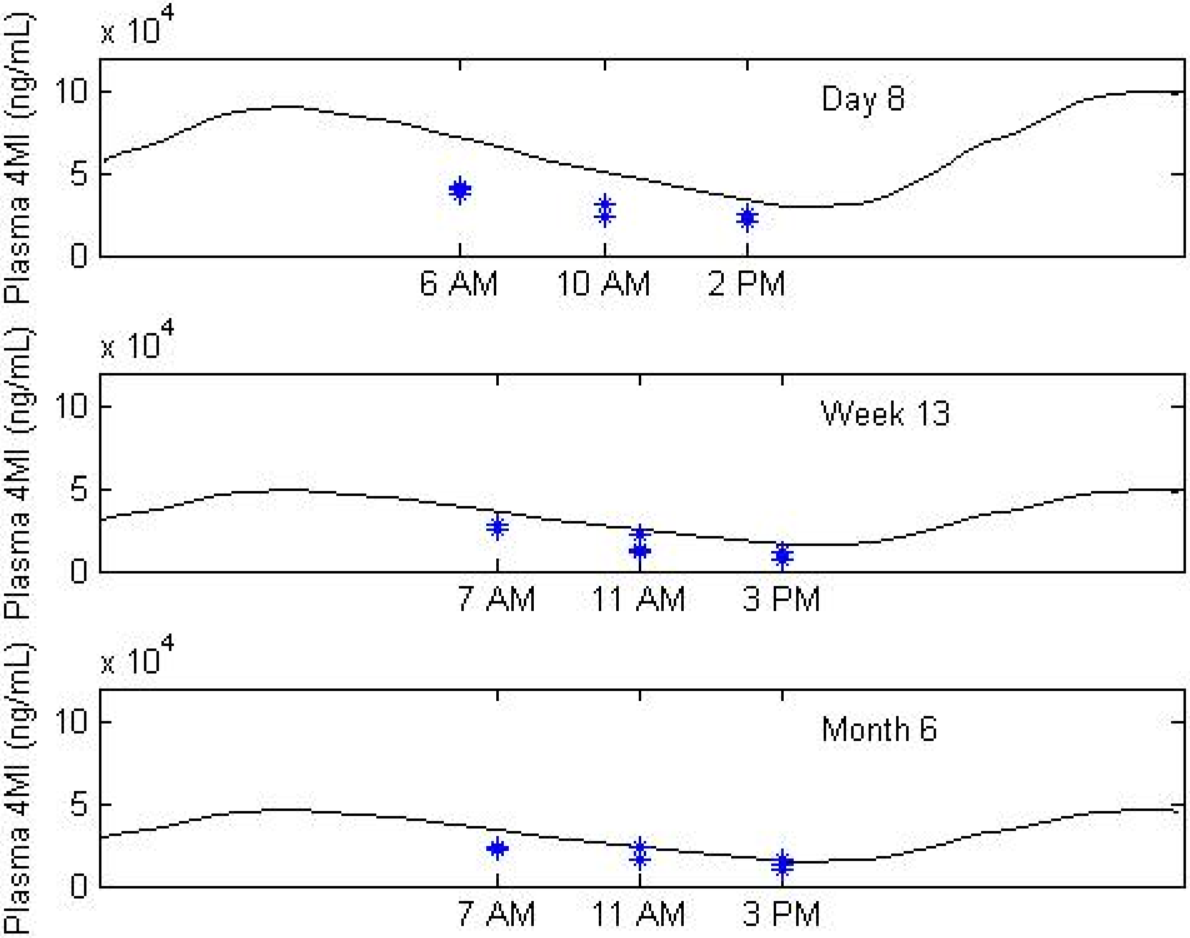
4-Methylimidazole (4-MI)



4-MI Female Rat Data (NTP TK)



4-MI Female Rat Data (Chronic)



Linear Model Example

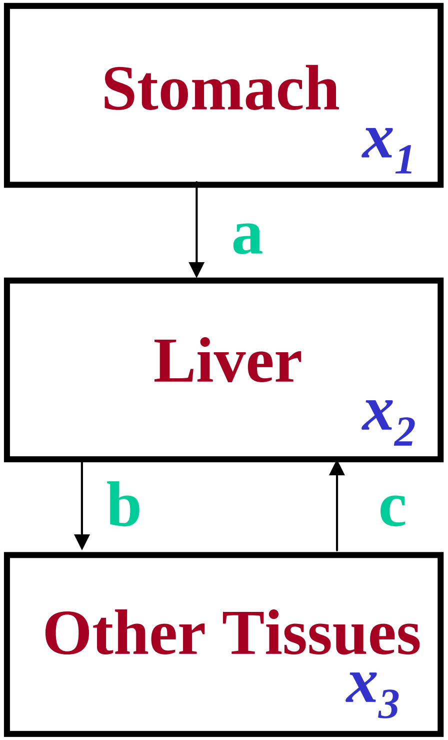
A drug or chemical enters the body via the stomach. Where does it go?

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 in the compartments.
- a, b, and c represent linear flow rate constants.

Linear Model Equations

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

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

$$\frac{dx_2}{dt} =$$

$$\frac{dx_3}{dt} =$$

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.**

Finding Eigenvalues of A

Set the determinant of $A-\lambda I$ equal to zero and solve for λ.

$$\begin{vmatrix} -a-\lambda & 0 & 0 \\ a & -b-\lambda & c \\ 0 & b & -c-\lambda \end{vmatrix}$$

$$= (-a-\lambda)\left[(-b-\lambda)(-c-\lambda)-bc\right]$$

$$= (-a-\lambda)\left[bc+b\lambda+c\lambda+\lambda^2-bc\right]$$

$$= (-a-\lambda)\left[(b+c)\lambda+\lambda^2\right]$$

$$= \lambda(-a-\lambda)(\lambda+b+c)$$

$$\lambda = 0, -a, -(b+c)$$

Finding Eigenvectors

Consider $\lambda = 0.$

$$A - 0I = \begin{bmatrix} -a & 0 & 0 \\ a & -b & c \\ 0 & b & -c \end{bmatrix}$$

Finding Eigenvectors

$\lambda = 0$

$$\begin{bmatrix} 0 \\ c \\ b \end{bmatrix}$$

Finding Eigenvectors

Consider $\lambda = -a.$

$$A - aI = \begin{bmatrix} -a-(-a) & 0 & 0 \\ a & -b-(-a) & c \\ 0 & b & -c-(-a) \end{bmatrix}$$

$$= \begin{bmatrix} 0 & 0 & 0 \\ a & -b+a & c \\ 0 & b & -c+a \end{bmatrix}$$

Finding Eigenvectors

$$\lambda = -a$$

$$\begin{bmatrix} ab + ac - a^2 \\ a^2 - ac \\ -ab \end{bmatrix}$$

Finding Eigenvectors

Consider $\lambda = -(b+c)$.

$$A+(b+c)I = \begin{bmatrix} -a+(b+c) & 0 & 0 \\ a & -b+(b+c) & c \\ 0 & b & -c+(b+c) \end{bmatrix}$$

$$= \begin{bmatrix} -a+(b+c) & 0 & 0 \\ a & c & c \\ 0 & b & b \end{bmatrix}$$

Finding Eigenvectors

$\lambda = -(b+c)$

$$\begin{bmatrix} 0 \\ 1 \\ -1 \end{bmatrix}$$

Linear Model (continued)

Then, our general solution would be given by:

$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} = k_1 \begin{bmatrix} 0 \\ c \\ b \end{bmatrix} + k_2 \begin{bmatrix} ab + ac - a^2 \\ a^2 - ac \\ -ab \end{bmatrix} e^{-at}$$

$$+ k_3 \begin{bmatrix} 0 \\ 1 \\ -1 \end{bmatrix} e^{-(b+c)t}$$

Parameter Values and Initial Conditions

For our example, let *a*=3, *b*=4, and *c*=1, and use 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.

Linear Model (continued)

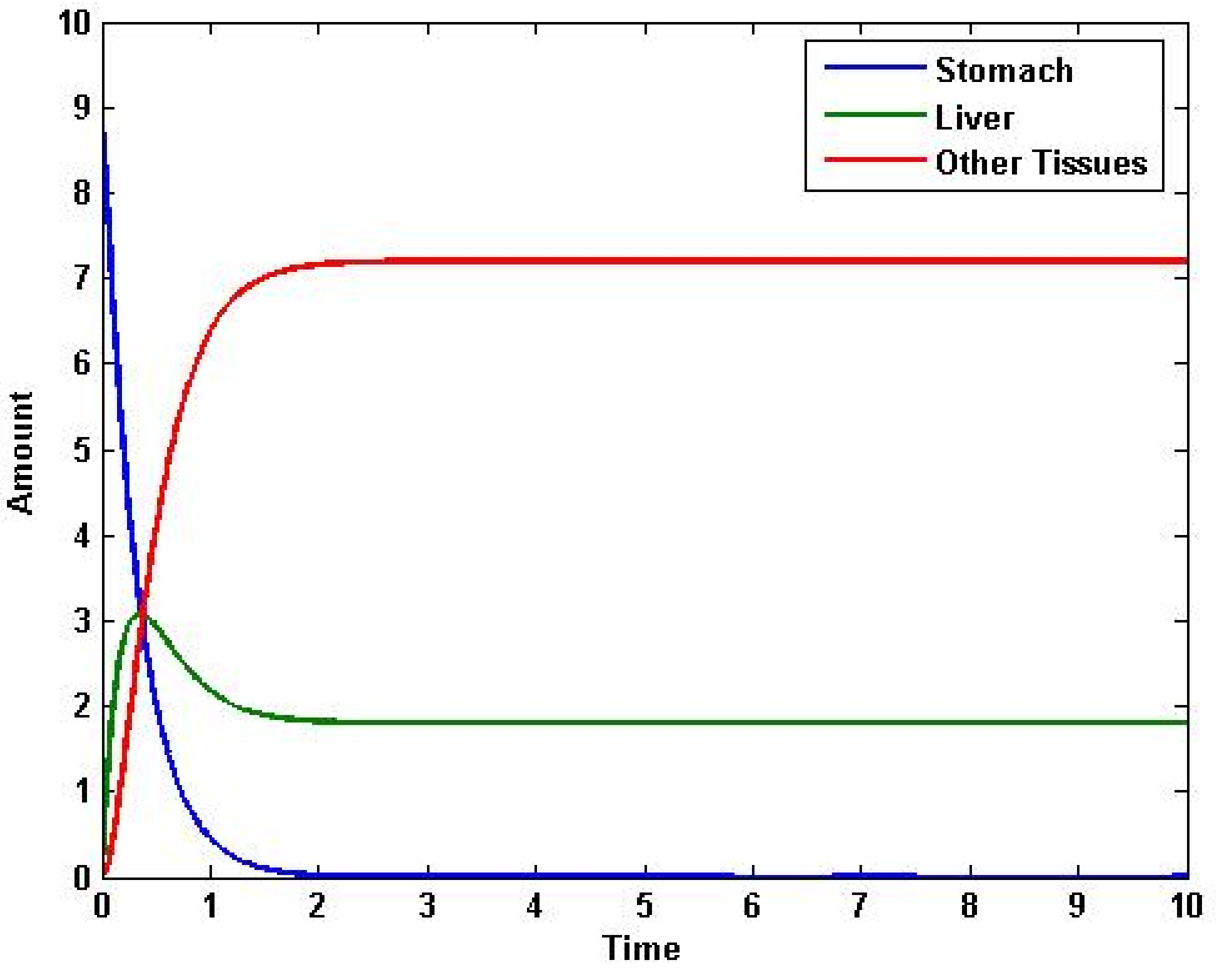
Then, our particular solution would be given by:

$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} = k_1 \begin{bmatrix} 0 \\ 1 \\ 4 \end{bmatrix} + k_2 \begin{bmatrix} 6 \\ 6 \\ -12 \end{bmatrix} e^{-3t} + k_3 \begin{bmatrix} 0 \\ 1 \\ -1 \end{bmatrix} e^{-5t}$$

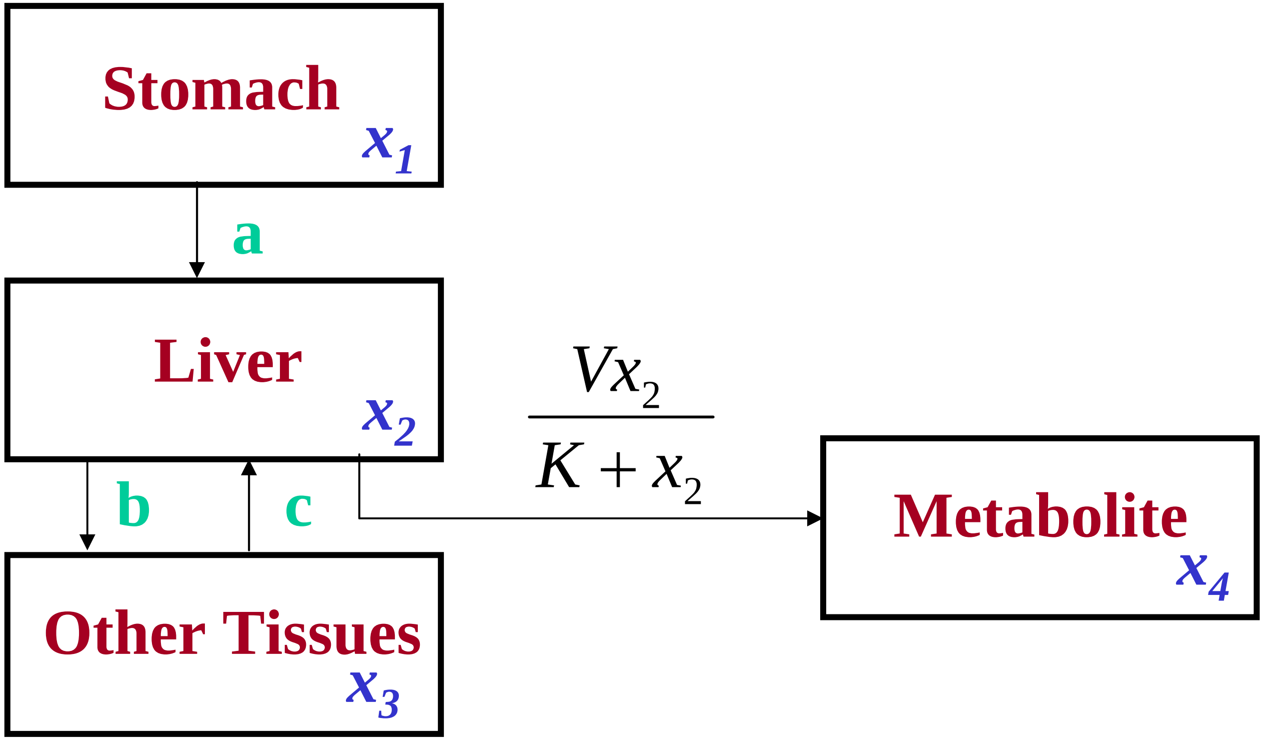
with

$$k_1 = \frac{4}{5}, \quad k_2 = \frac{2}{3}, \quad k_3 = -\frac{24}{5}$$

Graphical Results Link1 Link2



Schematic of Nonlinear Model



x_1, x_2 , x_3, and x_4 represent amounts of the drug (or its metabolite).

Nonlinear Model Equations

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

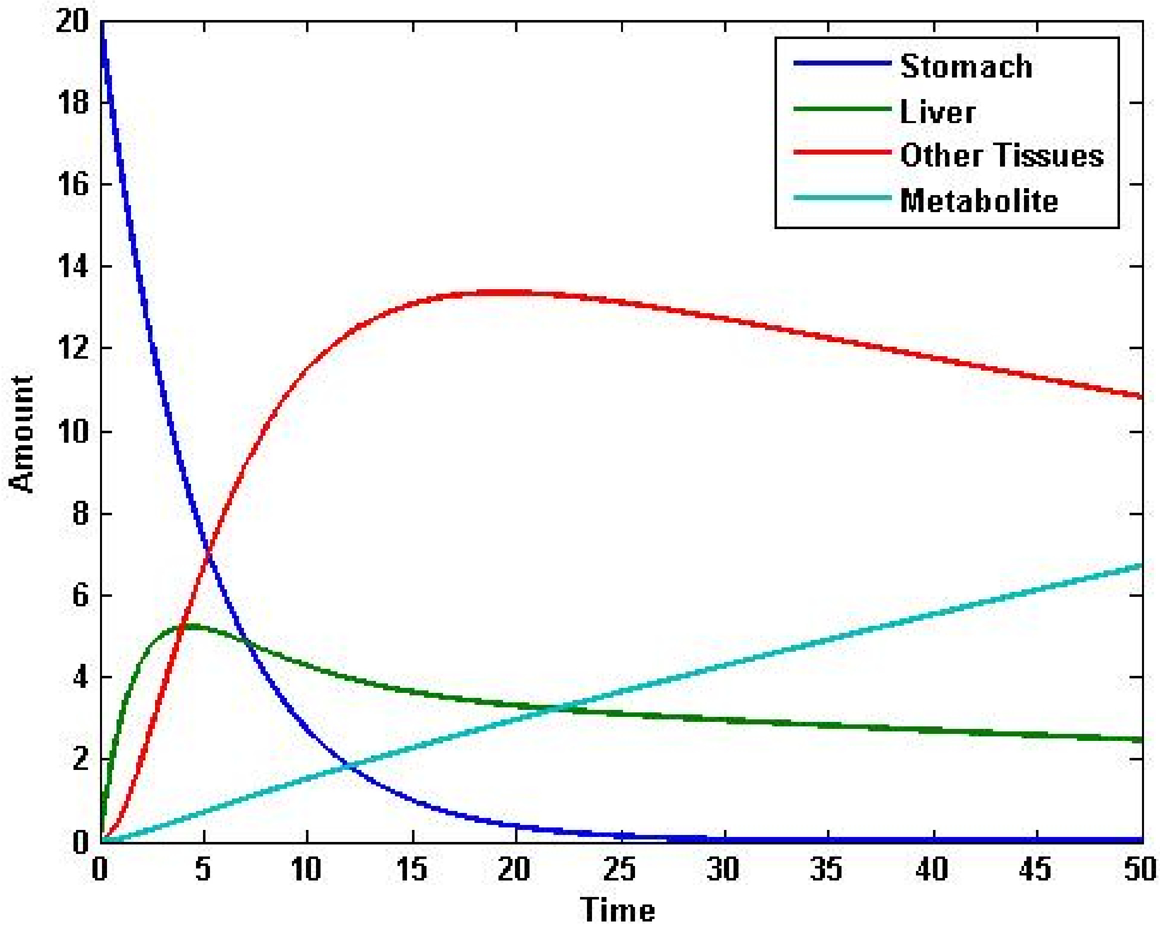
$$\frac{dx_2}{dt} = ax_1 - bx_2 + cx_3 - \frac{V\,x_2}{K + x_2}$$

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

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

Nonlinear Model Link 1 Link2

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



Exploration

- **What would happen if one of the parameter values were doubled? halved?**
- **What would happen if the initial conditions were changed to represent some background level present in the liver or other tissues?**

We will now use Phaser to explore these questions.