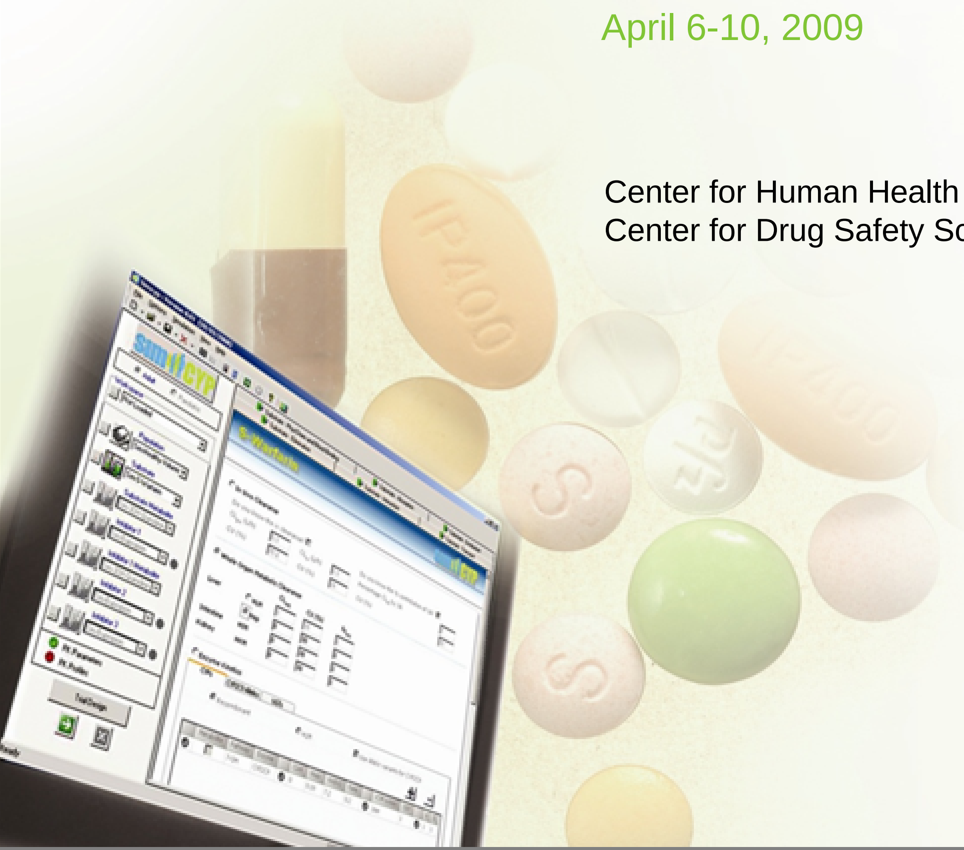
Day 1 Exercise
A two-compartment model for digoxin

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

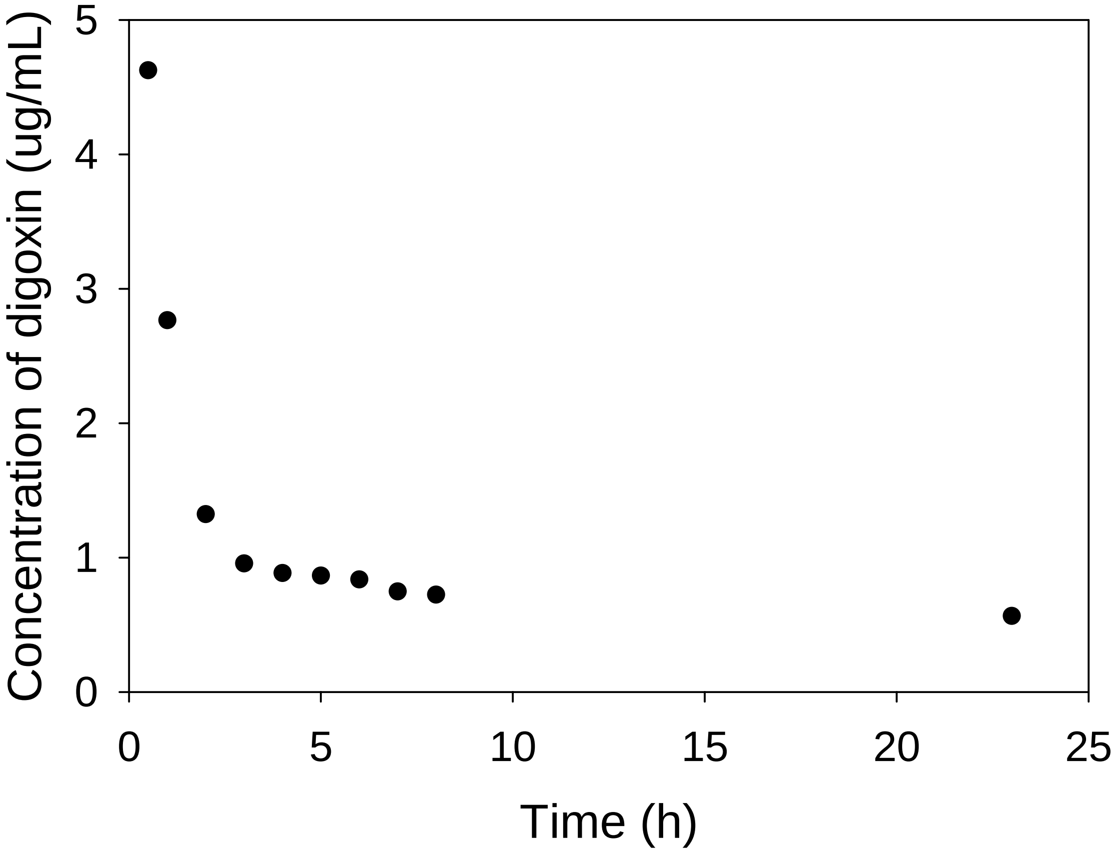
April 6-10, 2009



Center for Human Health Assessment
Center for Drug Safety Sciences

Concentrations of digoxin in blood following an intravenous dose

How can we describe the pharmacokinetics of digoxin based on these data?

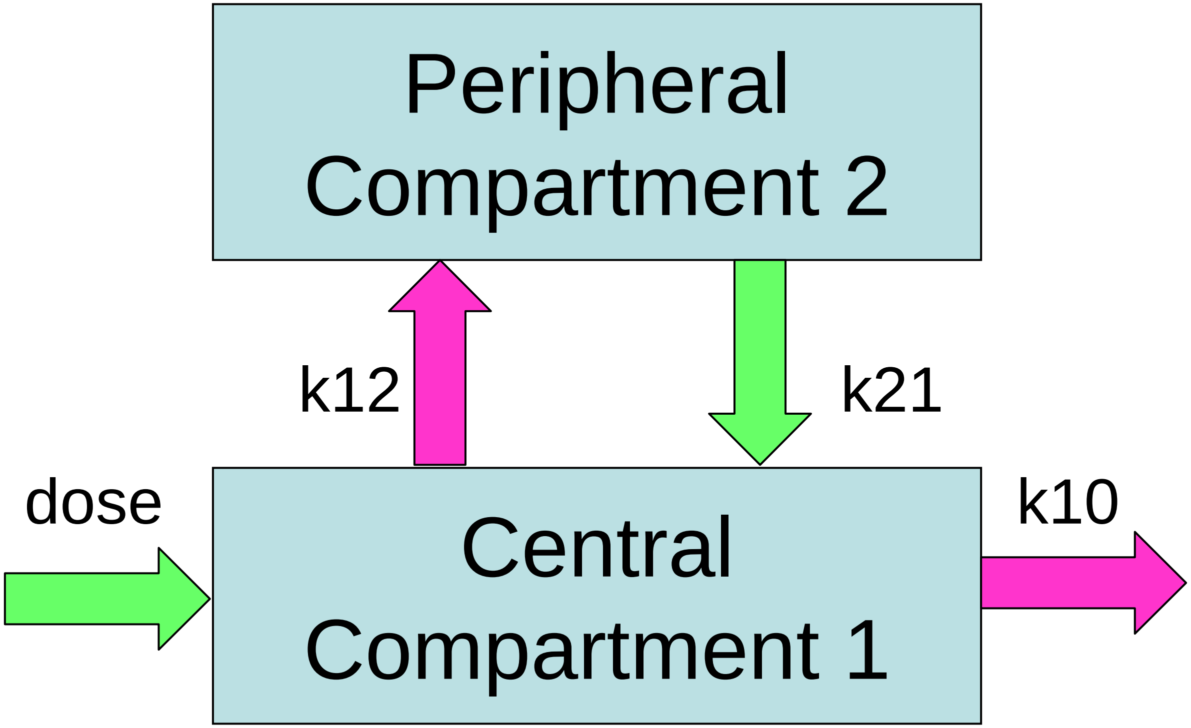


Data from Nyberg, L. *et al.* *Acta Pharmacol. Suec.,* 1974. 11:459-470.

Classical 2-compartment model of drug distribution in the body

- Two compartments
  - Central compartment: drug distributes uniformly and rapidly
  - Peripheral (deep) compartment: drug is not immediately available
- Bolus dose to central compartment
- 1st order elimination from central compartment
- 1st order transfer between central and peripheral compartments

Two-compartment model structure



Rate constants:

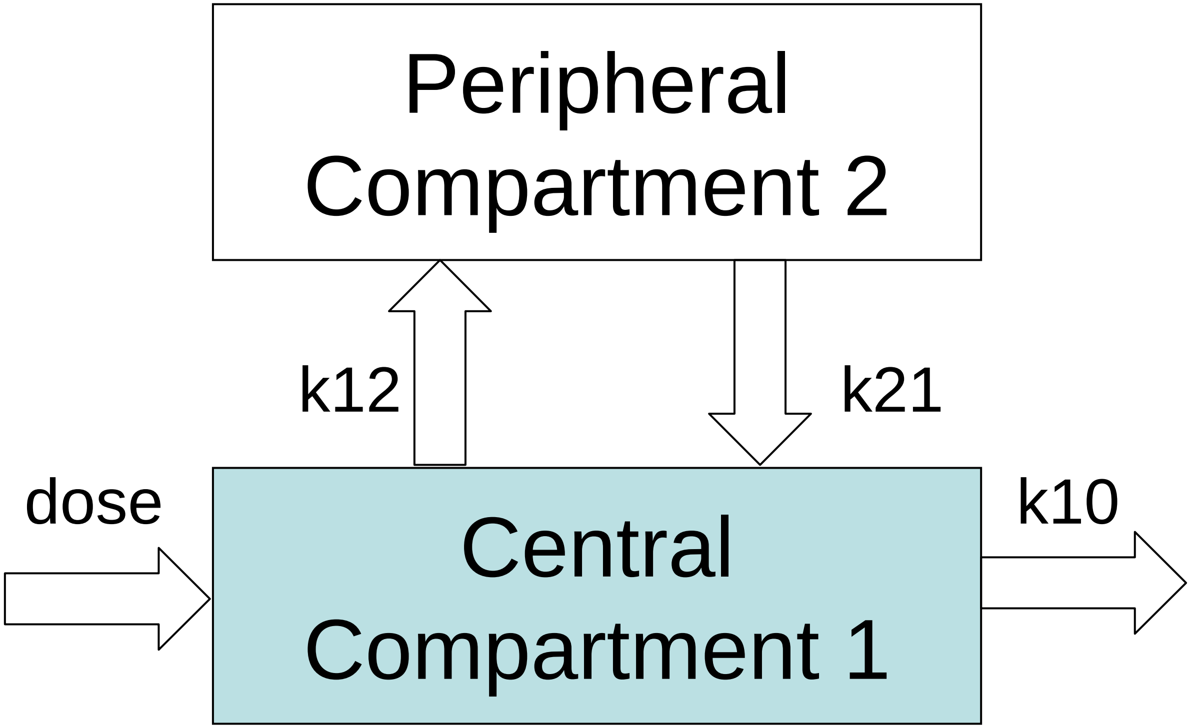
k_{12} => 1st transfer from Compartment 1 to Compartment 2

k_{21} => 1st order transfer from Compartment 2 to Compartment 1

k_{10} => 1st order elimination from Compartment 1

Two-compartment model exercise

Objective: Determine the concentration of digoxin in the blood (C1) by solving the numerical solution for the central compartment.



Write code for a 2-compartment model

- Step 1: Open Digoxin.mmd and examine the model (If you click "Run" now, what will happen?)

- Step 2: Write the rate equations for the two compartments

```
; Rate of amount change in compartment 1 (ug/h)
A1' = k21*A2 – k12*A1 – k10*A1

; Rate of amount change in compartment 2 (ug/h)
A2' = k12*A1 – k21*A2

; Concentration in compartment 1 (ug/L)
C1 = A1/V1
```

Model parameters

- Step 3: Define parameters to be displayed
  - The two display commands tell Berkeley Madonna which parameters to show in parameter window and which variables to show in graph window.
  - Hint 1: put the three parameters that will be estimated (i.e., rate constants) under one display command.
  - Hint 2: put the variable that you are predicting (i.e., concentration) under the other display command.

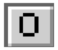
Data

- Step 4: Import the data set (#Digoxin_data.txt)
  - We will estimate k12, k21, and k10 by fitting the model-predicted C1 to the time-course data in file #Digoxin_data.txt.
  - Go to Model/Datasets.
  - You should see ‘#Digoxin_data.txt’ listed.
    - If not, Highlight ‘Digoxin_data.txt’ and click open.
    - Click OK to accept the default in the dialogue box.
  - Data should appear automatically in the graph window
    - If not, go to Graph/Choose Variables, and add the dataset.

Parameter Estimation

- Step 5: Plot C1 vs. data (#Digoxin_data.txt)
  – Click ‘Run’ in the Graph or Parameter or Model window.
- Step 6: Manual optimization of model parameters
  – Go to Parameters/Parameter Window if you don’t see your Parameter window.
  – In the Parameter window, adjust k12, k21, k10 to obtain the best fit of the model-predicted C1 to data in #Digoxin_data.
  – k12 = ________, k21 = ________, k10 = ________.

Define Sliders

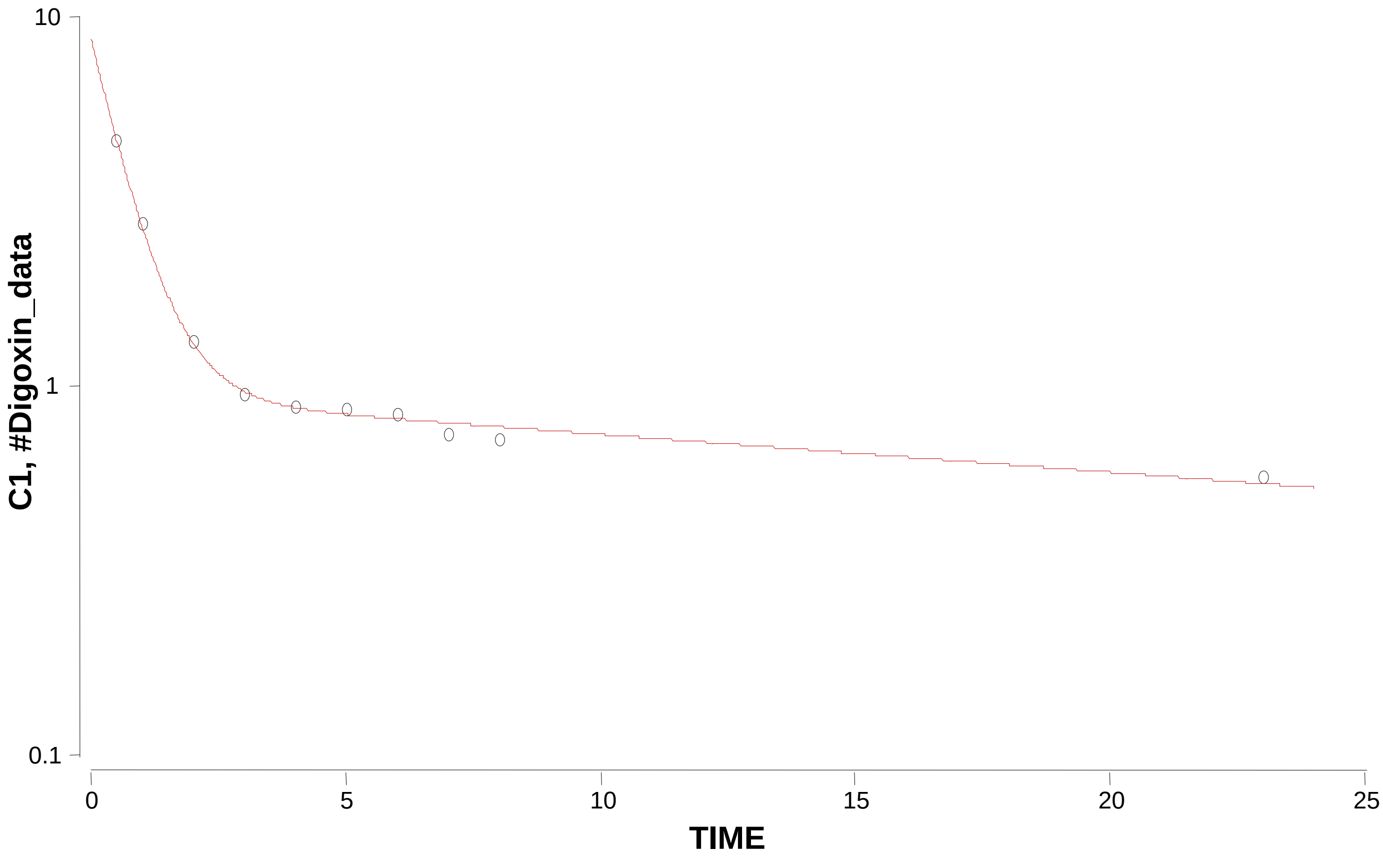
- Step 7: Use Sliders to estimate parameters
  - Go to Parameters/Define Sliders
  - Select k12, k21, and k10 and add them to the sliders list by clicking ‘Add’.
  - Drag any one of the sliders and release it to change the parameter value (the model will run automatically).
  - To adjust two or more parameters at the same time, hold down the ‘Ctrl’ key while moving the sliders. The model will not run when you release the ‘Ctrl’ key. Click ‘Run’ to see your prediction with the new set of parameter values.
  - If you want to see all runs in the graph window, click the 

(Overlay) button in the Graph window.
  - To remove old runs from the Graph window, go to Graph/Discard Last Run or Graph/Discard all Runs.
  - k12 = ________, k21 = ________, k10 = ________.

An easy way to estimate parameters

- Step 8: Automated optimization of model parameters
  - Go to Parameters/Curve Fit and add k12, k21, and k10 to the list.
  - Set reasonable bounds for each parameter (Hint: no negative value for rate constants).
  - Select C1 to be the Fit Variable.
  - Select Dataset, and click OK.
  - Go to the Parameter window to see the estimated values for k12, k21, and k10.
    - How does the fit compare to yours?
    - Are these values similar to your estimates in Steps 6 and 7?
    - Why do we have to go through Steps 6 and 7?

Digoxin concentrations in blood



What have you learned about the kinetics of the central compartment?

Typical elements in a Berkeley Madonna model

- Parameter assignments — Dose = 509
- Variable calculations — C1 = A1/V1
- State variable definitions — A2’ = k12*A1-k21*A2
  init A2 = 0.0
- Exposure control — ci = cix * (mod(time,24.)<=length)
- Simulation control — Method RK4
  STARTTIME = 0
  STOPTIME = 24
  DT = 0.02
- Output Control — display c1 ;for graph window
  display k12 ;for parameter window

Integration methods in Berkeley Madonna

- Fixed-stepsize methods
  - Euler's method
  - Runge-Kutta 2
  - Runge-Kutta 4
  - Model steps in increments of DT
- Variable-stepsize methods
  - Auto-stepsize
  - Rosenbrock (stiff)
  - Step size is specified with DTMIN, DTMAX, and TOLERANCE parameters.

Fixed-stepsize method – RK4

- In our exercise, DT is set to 0.02.
- Click the 'Overlay' button on the graph window.
- Change DT to 1 in the Parameter window and click 'Run'. What happened?
- Change DT to 2 in the Parameter window and click 'Run'. What happened?