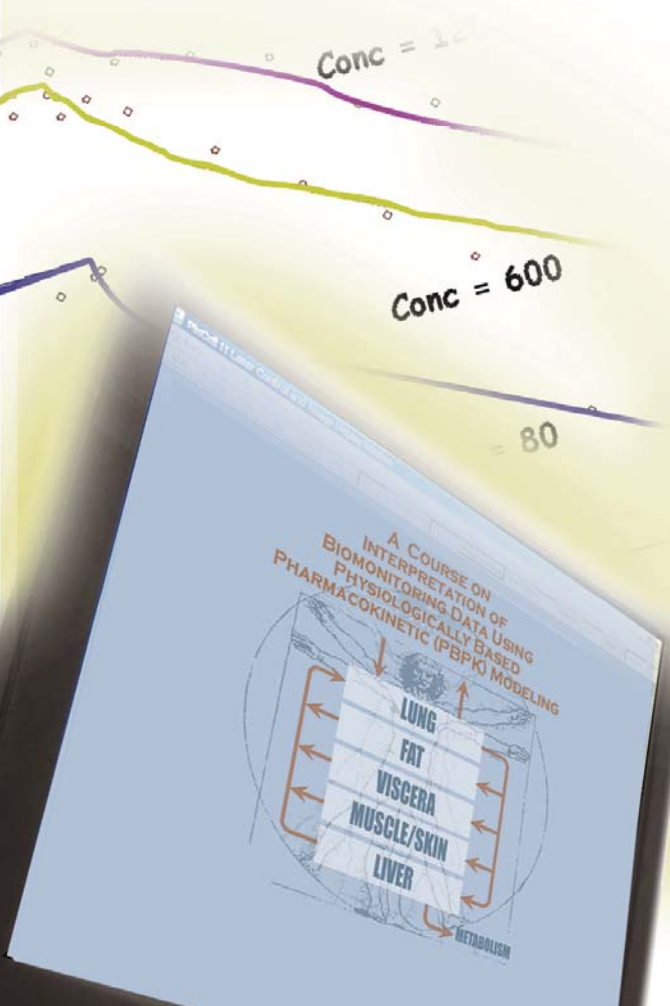


Demonstration of Berkeley Madonna

Center for Human Health Assessment
A Course on Physiologically Based Pharmacokinetic (PBPK)
Modeling and Risk Assessment

February 11 – February 15, 2008



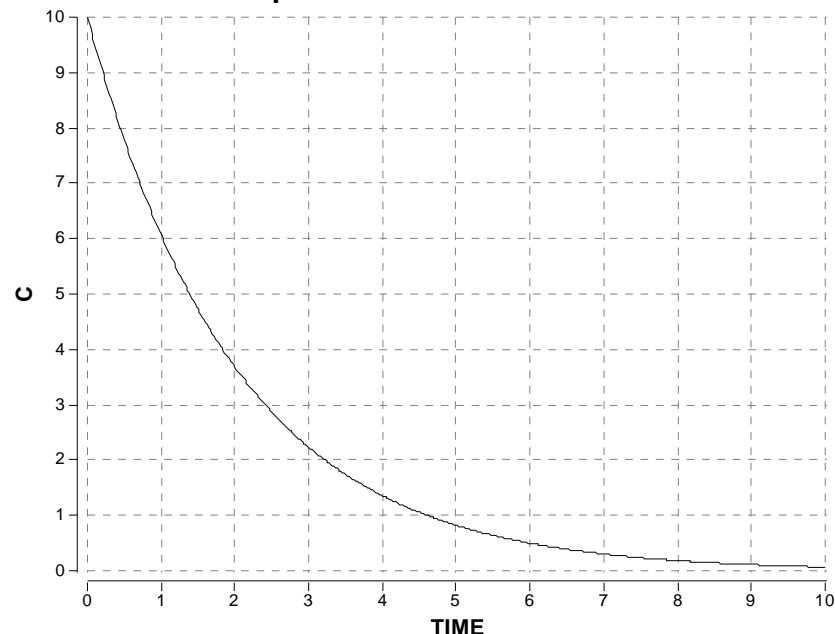
Three Modules

- Equation Editor
- Visual Model
- Chemical Reaction Module





Part 1. Build a Simple Model Using the Equation Editor

Build a Simple Model Using the Equation Editor

- Launch Berkeley Madonna
- Add the following equations to the equation window,
 $C_0 = 10$
 $k = 0.5$
 $C = C_0 * \exp(-k*time)$
 display C ;for plot window
 display C0,k ;for parameter window
- Choose Run from the Compute menu, or click the Run button.
 - Berkeley Madonna runs your model and plots the results for variable C

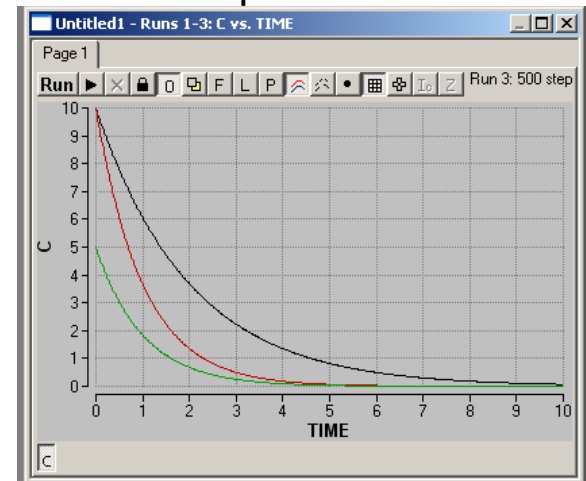


Parameter Window and Graph Window

- Open the parameter window (Parameter/Parameter Window)
- Select k and change it to 1. Run the model again.
- Click the  (Overlay Plots) button in the graph window.
 - Change k to 0.5 in the parameter window, and RUN
- Other buttons in the graph window
 -  Table: displays the numerical results in Tables, which can be saved and copied to the clipboard.
 -  Readout: displays coordinates of the selected point where the mouse is clicked.
 -  Grid: shows/hides the grid lines
- To change the scaling for axes, you can
 - Choose Axis Settings from the Graph menu and selecting the Scales tab.
 - Double-click on any of the plot's axes.




Define Sliders

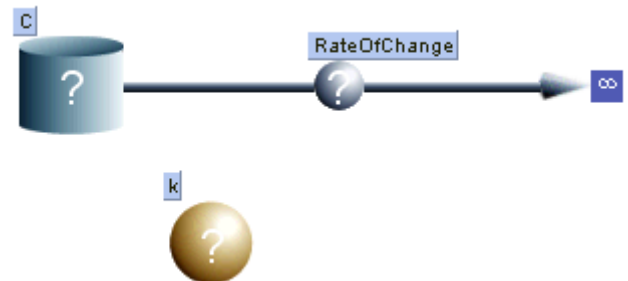
1. Parameter/Define Sliders
 2. Select a parameter and add it to the sliders list by clicking Add.
 - Add k and C_0
 3. To adjust single parameter, drag one of the sliders and release it
 - The parameter value is adjusted and your model is run automatically
 4. To adjust two parameters at the same time, hold down the control key while releasing the first slider
 - The parameter value is adjusted, but your model will not be run
 - Now you can adjust the second slider by following Step 3
- ** To remove old runs from the graph window while leaving Overlay Plots enabled, use the Discard Last Run and Discard All Runs commands in the Graph menu.




Part 2. Build a Visual Model

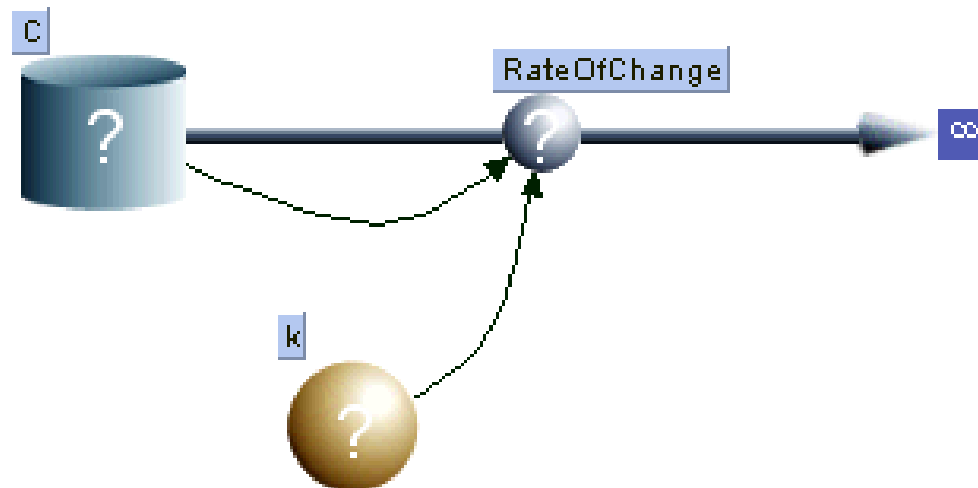
Build a Visual Model

- Open a new flowchart model (File/New Flowchart)
- Create a reservoir by dragging  from the toolbar to the flowchart
- Change the name of the reservoir to “C” by clicking the reservoir if it is not already selected and typing the new name.
- To create a flow to drain reservoir C
 - Click  (flow tool)
 - Move the mouse over the C reservoir
 - Press the mouse button and drag the mouse to the right
 - Release the mouse button.
 - Change the name of the flow to “RateOfChange” by typing the new name.
- To create a formula, drag  to the flowchart (approximately halfway between the reservoir and flow icons)
 - Change the name of the formula icon to “k”.



Build a Visual Model

- To create dependency relationships
 - Click  (arc tool)
 - Move the mouse over the C reservoir
 - Press the mouse button and drag the mouse to the right till it reaches RateOfChange icon
 - Release the mouse button.
 - Repeat these steps for an arc going from the formula icon (k) to the flow icon (RateOfChange).

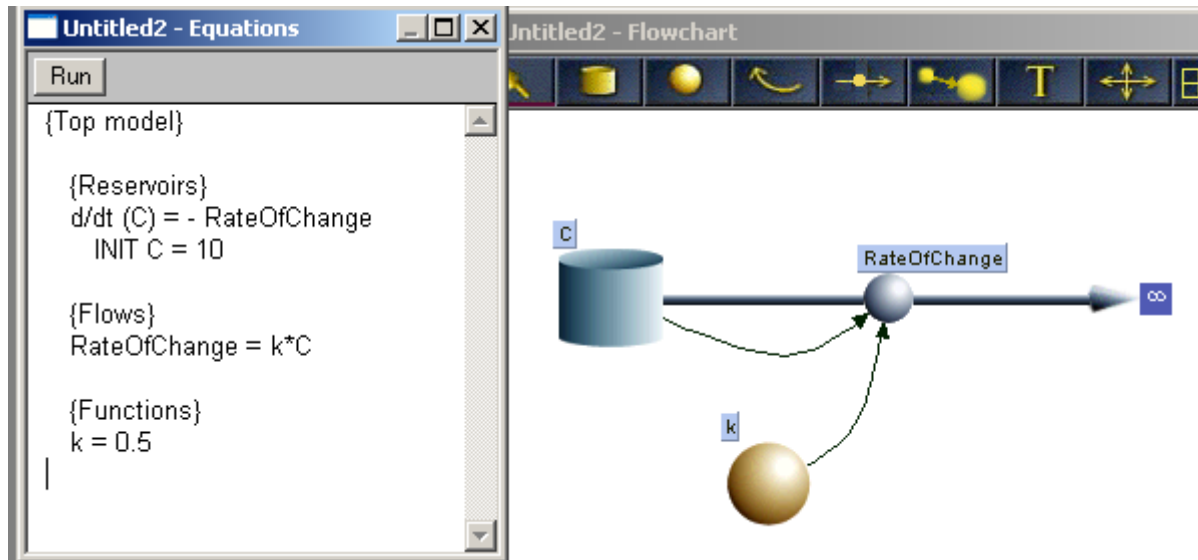


Build a Visual Model

- Double-click the “C” reservoir
 - Enter 10 for “init C” (initial value for the reservoir)
 - Click OK
- Double-click the “k” formula
 - Enter 0.5 for the formula’s right-hand side
 - Click OK
- Double-click the “RateOfChange” flow
 - Enter the following formula for the right-hand side: $k \cdot C$
 - Click OK
 - Note that “C” and “k” are required inputs, which means that these variables must be used in the right-hand side of the equation defining the icon’s value.
- Run your model by choosing Run from the Compute menu.

Build a Visual Model

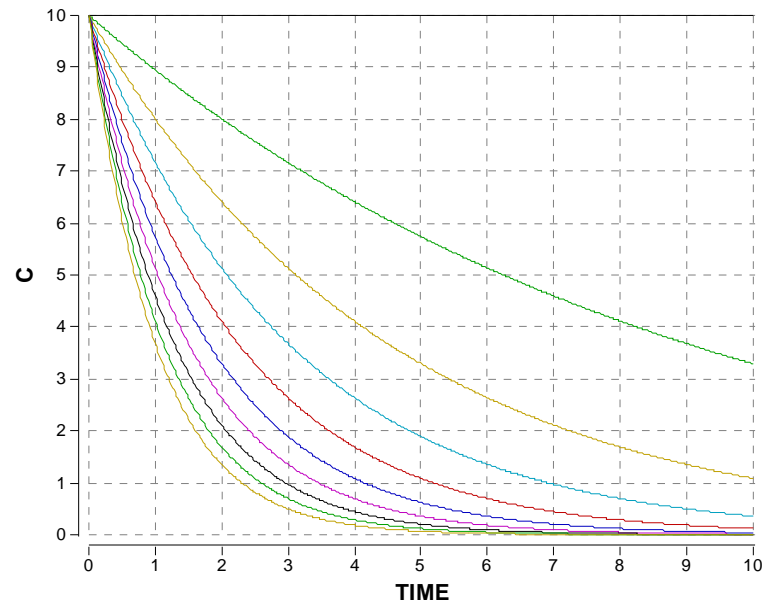
- Examine the equations generated by Berkeley Madonna (Model/Equations)



- If you select any icon in the flowchart with the mouse, Berkeley Madonna will highlight the equation(s) associated with the icon in the equation window.
- Equations can only be edited in the icon dialog (double-clicking the icons or choosing Icon Info... from the Flowchart menu).

Batch Runs

- Open Batch Run window (Parameters/Batch Runs)
 - Select “k” for Parameter box
 - Enter 11 for # of runs
 - Enter 0 and 1 for initial and final values, respectively, of k
 - Check “Arithmetic” box for Series Type
 - Check Keep Run Separate in Mode box
 - Click OK
- ** To hide unwanted results, click on the variable buttons in the graph window



Part 3. Use Chemical Reaction Module

Use Chemical Reaction Module

- Open a new model (File/New)
- Open Chemical Reactions window (Model/Modules/Chemical Reactions...)
- To create the reaction: $A \rightarrow B$
 - Enter “A” for Reactants, and “B” for Products
 - Enter 10 for Kf, and 0 for Kr
 - Click Add
 - Select “init A = 0” (Initial Concentrations box), and change the value to 20
- Add the reaction: $B \rightarrow C$
 - Kf = 5, Kr = 0
- Add the reaction: $C \rightarrow D$
 - Kf = 2, Kr = 0
- Click OK
- Run the model

```
Untitled1 - Equations
Run
1: A <-> B
   RXN1 = K1f*A - K1r*B
   K1f = 10
   K1r = 0
   INIT A = 20
   INIT B = 0
   d/dt(A) = -RXN1
   d/dt(B) = +RXN1-RXN2

2: B <-> C
   RXN2 = K2f*B - K2r*C
   K2f = 5
   K2r = 0
   INIT C = 0
   d/dt(C) = +RXN2-RXN3

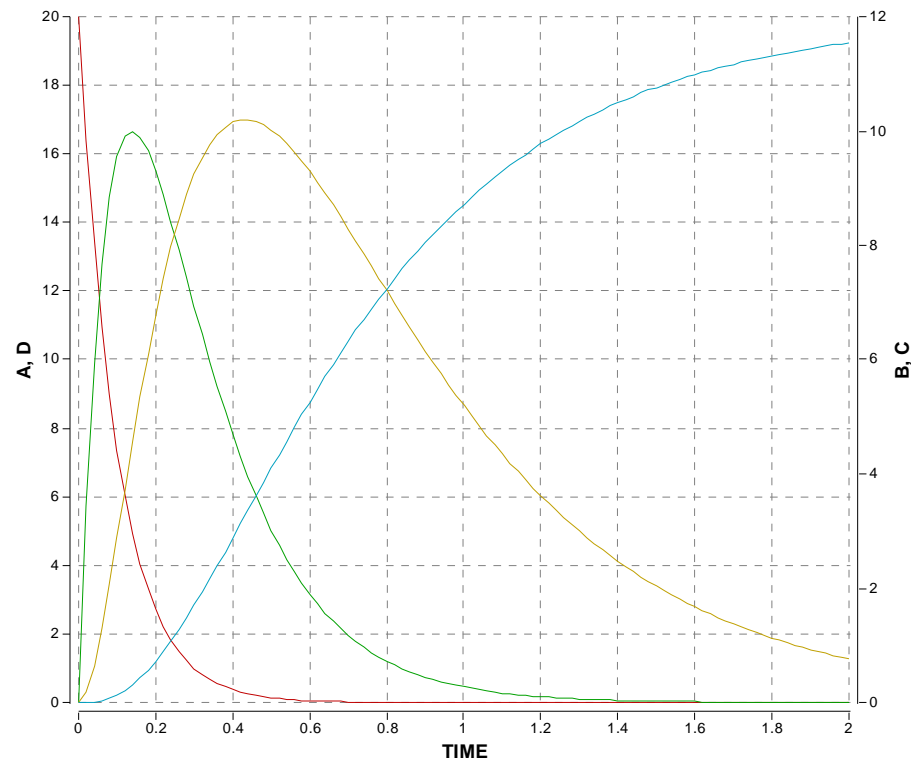
3: C <-> D
   RXN3 = K3f*C - K3r*D
   K3f = 2
   K3r = 0
   INIT D = 0
   d/dt(D) = +RXN3

METHOD RK4

STARTTIME = 0
STOPTIME = 10
DT = 0.02
```

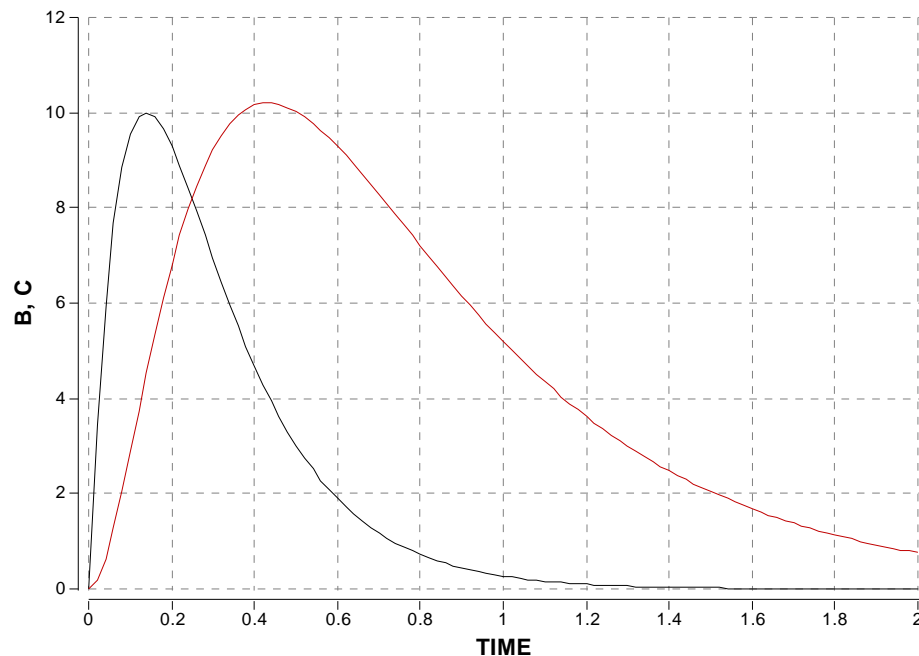
Show/Hide Results in Graph Window

- Toggle the variable buttons at the bottom of the graph window to show/hide the results
 - Show results of A, B, C, and D
 - To move one variable from one Y axis to the other, hold the shift key and click on that variable button.
- Change Stoptime to 2 in the parameter window, and Run



Create a New Graph Window

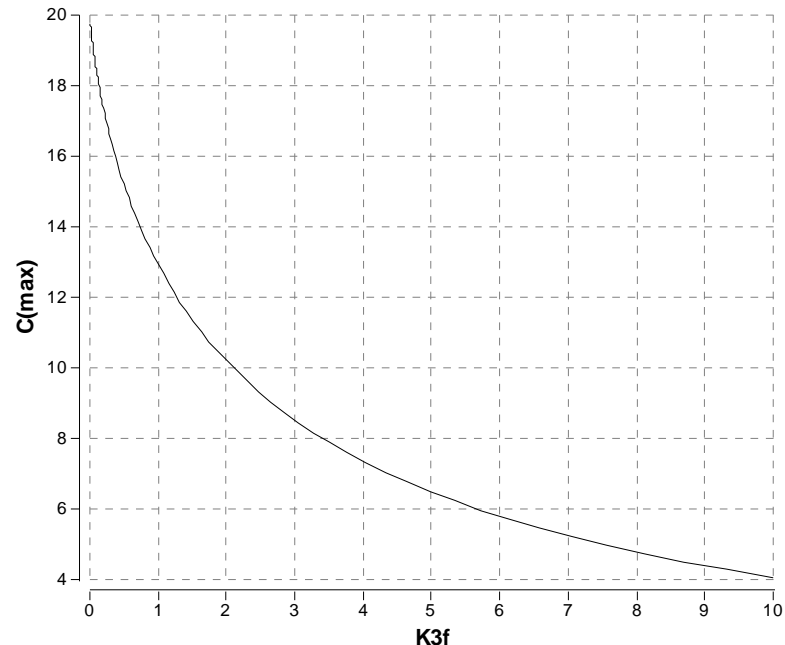
1. Graph/New Window
2. Graph/Choose Variables (while the new graph window is selected)
3. Select a variable and add it to the Y axis list by clicking Add
 - Select B and C
4. Click OK
5. Run



** Berkeley Madonna plots TIME on the X axis by default. You can change this to another variable using the X axis control in the Choose Variables dialog.

Parameter Plot

- We will use Parameter Plot to calculate the peak concentration of C as a function of k_{3f}
- Open Parameter Plot window (Parameters/Parameter Plot...)
 - Select “ k_{3f} ” for Parameter box
 - Enter 100 for # of runs
 - Enter 0.01 and 10 for initial and final values, respectively, of k_{3f}
 - Check “Geometric” box for Series Type
 - Add “C” to Y-axis box, and check “maximum” box
 - RUN



Typical Elements in a Berkeley Madonna Model

- Parameter assignments: $BW = 0.3$
- Variable calculations: $CVL = CL / PL$
- State variable definitions: $AUCL' = CL$
init $AUCL = 0$
- Exposure control: $ci = cix * (\text{mod}(\text{time}, 24.) \leq \text{length})$
- Simulation control:

```
method stiff           ;Rosenbrock stiff system solver
starttime = 0
stoptime = 24
dtmin = 0.0001        ;minimum (and initial) step size
dtmax=1               ;maximum step size
tolerance=0.0001     ;error tolerance for stiff solver
```
- Output Control:

```
display cv, cx, ca, cf, ci, am           ;for plot window
display conc, length, bw, qp, qc, pb    ;for parameter window
```

Identifying State Variables in a Berkeley Madonna Model

The most important elements in the model definition are the "state variables" which are to be integrated. They can be identified by using a prime (') in the equation defining their derivative, and their initial values must be provided in an "init" statement.

For example, in the code below, AI is defined to be a state variable which is calculated by integrating the equation defining the variable AI', using an initial value of AI0.

(A semicolon indicates that the rest of the line is a comment)

```
; Concentration in inhaled air (mg/L)  
AI' = (RATS*QP*(CA/PB-CI)) - (KL*AI) ; Derivative equation  
init AI = AI0 ; Initial value of AI  
CI = (AI/VCH) ; Concentration in air
```

Taking Advantage of Berkeley Madonna's Automatic Sorting:

Typical "Ramseyan" Code for the Liver

$$AL' = (QL \bullet (CA - CVL)) + RAO - RAM$$

$$init AL = 0.0$$

$$RAM = ((VMAX \bullet CVL) / (KM + CVL)) + (KF \bullet CVL \bullet VL)$$

$$RAO = KA \bullet MR$$

$$CL = AL / VL$$

$$CVL = CL / PL$$

$$AUCL' = CL$$

$$init AUCL = 0.0$$