

# Demonstration of Berkeley Madonna

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



# Three Modules

- Equation Editor
- Visual Model
- Chemical Reaction Module

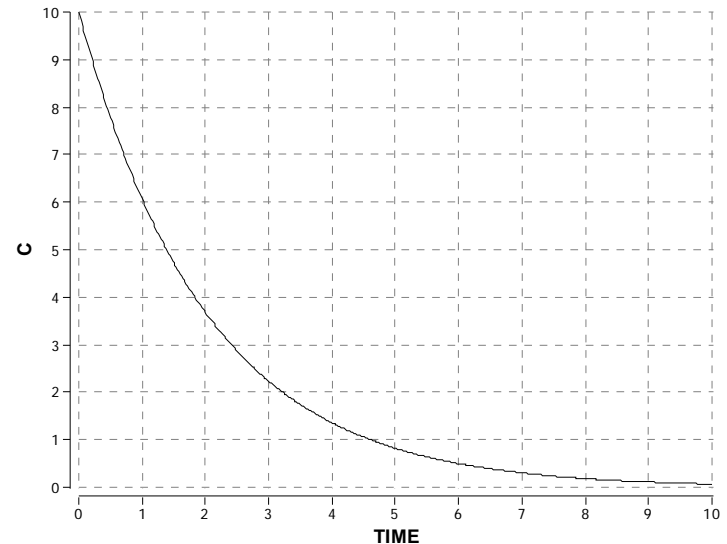
# Module 1. Equation Editor

# Build a simple model using the Equation Editor





- Step 1: Launch Berkeley Madonna
- Step 2: Add the following equations to the equation window:

```
C0 = 10
k = 0.5
C = C0 * exp(-k*time)
display C                ;for plot window
display C0,k            ;for parameter window
```

- Step 3: Click 'Run'
  - Berkeley Madonna runs your model and plots the results for variable C.






# Parameter window & Graph window


- Step 4: Go to Parameters/Parameter Window.
- Step 5: Select k and change it to 1. Run the model again.
- Step 6: Click the  (Overlay) 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.

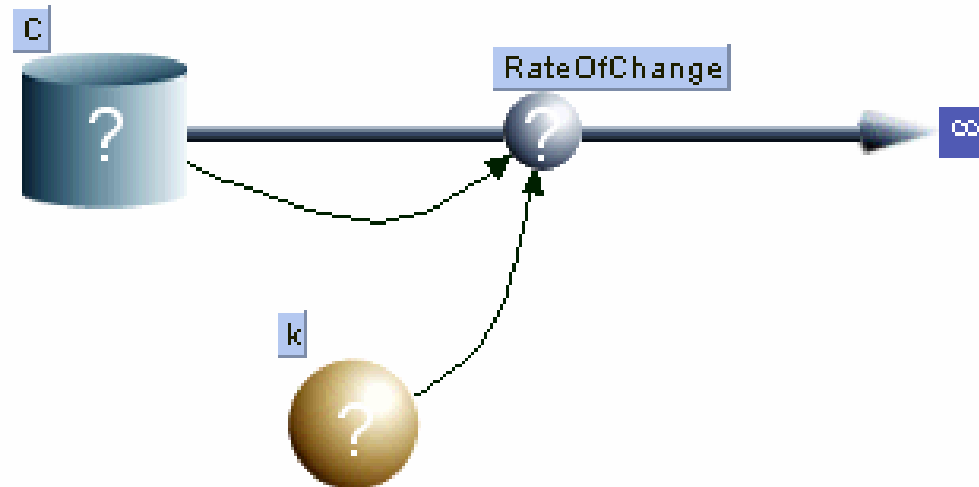
# Module 2. Visual Model

# Build a Visual Model

- Step 1: Go to File/New Flowchart
- Step 2: Create a reservoir by dragging  from the toolbar to the flowchart.
- Step 3: Change the name of the reservoir to “C” by clicking the reservoir if it is not already selected and typing the new name.
- Step 4: 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.
- Step 5: Create a formula by dragging  to the flowchart (approximately halfway between the reservoir and flow icons)
  - Change the name of the formula icon to “k”.

# Build a Visual Model

- Step 6: 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).

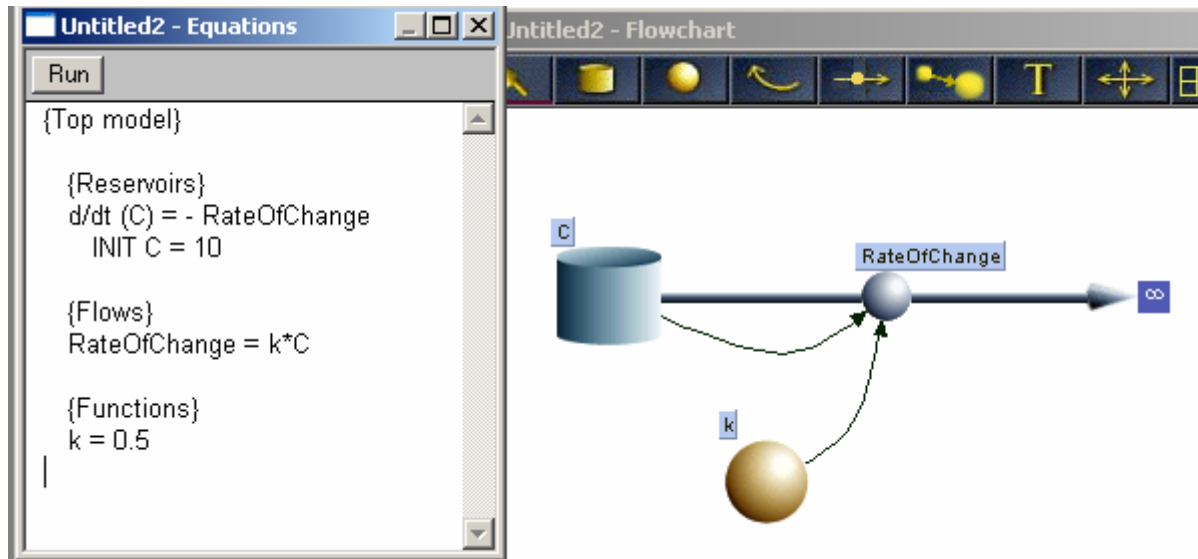


# Build a Visual Model

- Step 7: Double-click the “C” reservoir
  - Enter 10 for “init C” (initial value for the reservoir)
  - Click OK
- Step 8: Double-click the “k” formula
  - Enter 0.5 for the formula’s right-hand side
  - Click OK
- Step 9: 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.
- Step 10: 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).

# Module 3. Chemical Reaction Module

# Use Chemical Reaction Module

- Step 1: Open a new model (File/New)
- Step 2: Open Chemical Reactions window (Model/Modules/Chemical Reactions)
- Step 3: 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
- Step 4: Add the reaction:  $B \rightarrow C$ 
  - Kf = 5, Kr = 0
- Step 5: Add the reaction:  $C \rightarrow D$ 
  - Kf = 2, Kr = 0
  - Click OK
- Step 6: 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

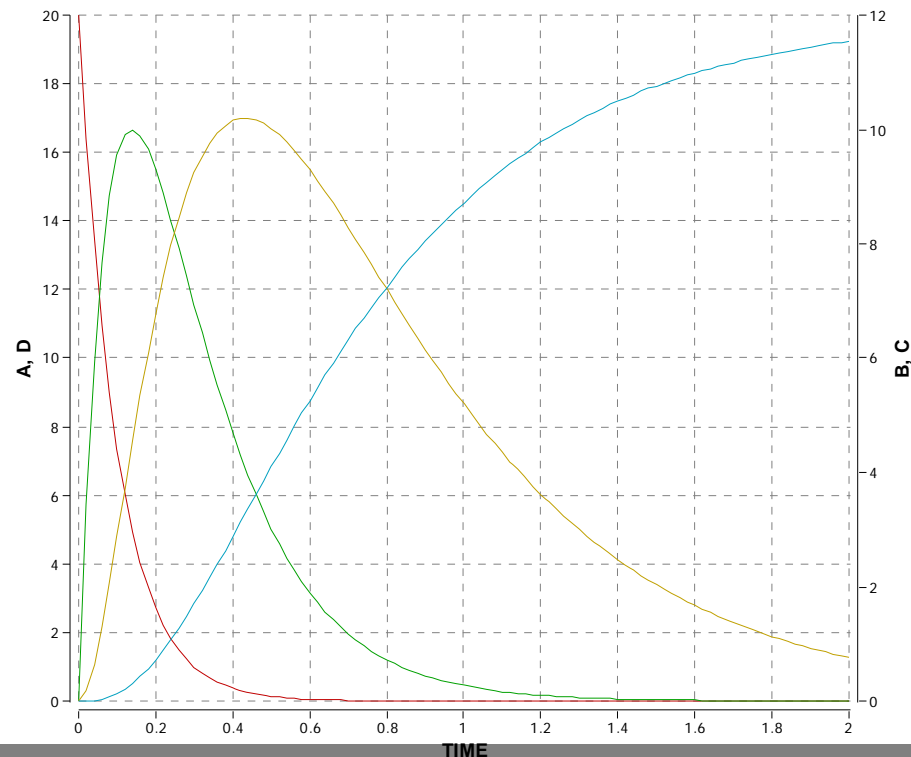
3: C <--> D
RXN3 = K3f*C - K3r*D
K3f = 2
K3r = 0
INIT D = 0
d/dt(D) = +RXN3

METHOD RK4

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

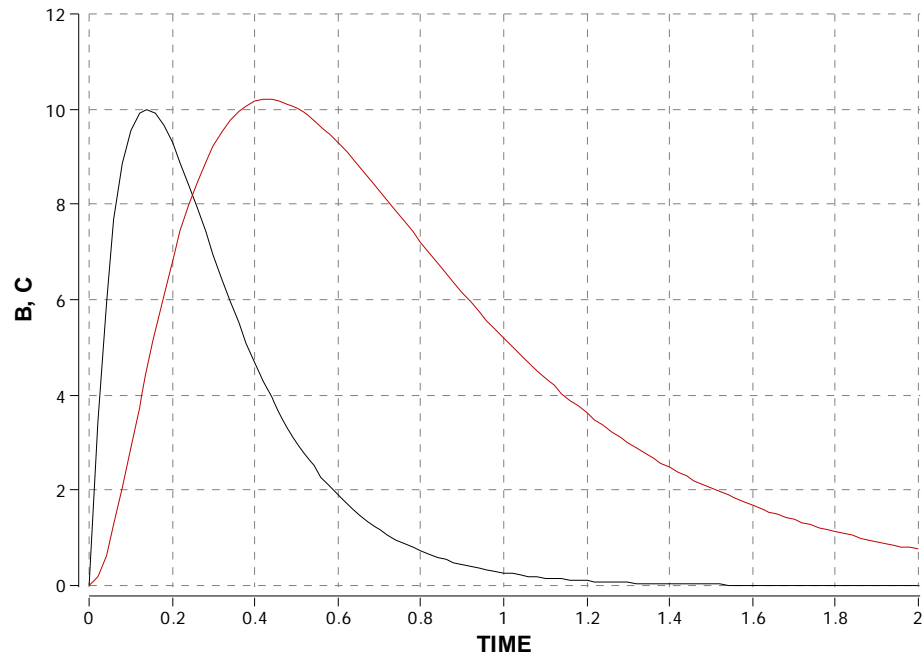
# Show/Hide Results in Graph Window

- Step 7: 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.
- Step 8: Change STOPTIME to 2 in the Parameter window, and Run



# Create a New Graph Window

- Step 9: Graph/New Window
- Step 10: Graph/Choose Variables (while the new graph window is selected)
- Step 11: Select a variable and add it to the Y axis list
  - Select B and C and click OK
- Step 12: Run the model.



\*\* 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.

# 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

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

$$init AL = 0.0$$

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

$$RAO = KA \bullet MR$$

$$CL = AL / VL$$

$$CVL = CL / PL$$

$$AUCL' = CL$$

$$init AUCL = 0.0$$