There might be slight variations in the graphical representations and plot options in the latest version 2.2.3. However, navigating through them should be intuitive, as the core principles remain consistent.

SAAM II Version 2.1
Advanced Tutorials

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Introduction

SAAM II is a very powerful software tool for model development and testing using multicompartmental models. Mathematically, these models translate into systems of ordinary linear or non-linear differential equations. A flexible, graphical user interface (GUI) makes the power of SAAM II easily available to researchers with diverse backgrounds.

The purpose of the "SAAM II" Tutorials is to amplify the information provided in the Help Menu and answer questions on how to use SAAM II. The philosophy behind the tutorials is to illustrate how different components of the SAAM II work using hands-on examples.

SAAM II Basic Tutorials illustrate SAAM II's most commonly used features, features that almost everyone will use at some time during the modeling exercises.

SAAM II Advanced Tutorials illustrate SAAM II's more sophisticated features that are needed to model more complex experimental protocols than is usually the case. These tutorials and a brief description of each are:

- **Creating Conditionals** deals with the need to model conditional statements such as "if-then-else". If a state variable such as a qi(t) is included in part of the conditional statement, then mathematically the problem can be unstable. More specifically, in some software packages that permit conditionals, incorrect answers can be returned because of this. In SAAM II, conditional statements are implemented using the "Heaviside Function". This function is continuous and differentiable, and can be tuned to appear almost as a step function.

- **Using Change Conditions** permit the modeling of an experimental perturbation such as changing dosing during an experiment, or collecting 24 hour urine samples. Mathematically, change conditions stops integration, interrogates what changes are needed, makes those changes, and resumes integration.

- **Using Delays** explains why the Delay Tool in SAAM II is created by a string of compartments. This tutorial explains how to use this tool. It also explains how to create an "absolute" delay using the Heaviside function.

- **Using Experimental Inputs (Advanced)** explains some of the advanced techniques that can be used to specify less common or more advanced types of input dosage and to conduct parametric deconvolution. These techniques have been designed for maximum flexibility.

- **Multiple Input-Multiple Output Experiments** explains how to deal with experimental protocols with one input-multiple outputs or multiple inputs-multiple outputs. This experimental protocol can be modeled in SAAM II in two ways; both permit the software to do the internal book keeping.

- **Using Forcing Functions** explains how to use the Forcing Function tool. Forcing functions are an engineering concept that allows the modeler to describe the effect of a driving section, or compartment, of a model without having to mathematically describe the compartment. The forcing function essentially enables all differential equations in your model to "see" the particular function. Forcing functions can be used as a convenient modeling tool in dealing with precursor-product models; they are also used as a model development tool.

- **Using Parameters (Advanced)** explains some of the more sophisticated ways of describing parameters, setting upper and lower limits, and using SAAM II's Bayesian capability to use prior information.

- **Saving and Restoring Solutions** is a feature of SAAM II that lets you save different model configurations and solutions so that you can compare solutions among different parameter or model configurations. This feature is used in model development and testing when you want to be able to compare different situations as you proceed.

- **Simulating Data** explains how to use your model to simulate experimental data for single-subject analysis. It illustrates how to simulate a single input-single output experiment and a single input-two output experiment.

The goal of these Advanced Tutorials is to help you explore and utilize the full functionality of SAAM II.

SAAM II Version 2.1
Advanced Tutorials

Creating Conditionals

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Creating Conditional Expressions

Prerequisites

The prerequisite for this tutorial is having worked through the **SAAM II** introductory tutorial, "Getting Started with **SAAM II Compartmental**."

What you will learn in this tutorial

The purpose of this tutorial is to show you how to create conditional statements in your **SAAM II Compartmental** model. You will learn

- How to create "if-then-else" ((Part 1)
- How to create zero-order inputs (Part 2)
- How to create an input pump (Part 3)

Files Required

Study Files: The study files for this tutorial are

if_then_else.stu
zero_order.stu
pump_1.stu
pump_2.stu

Data Files: The data files for this tutorial are

if_then_else.dat
zero_order.dat
pump_1.dat

Introduction

There may be times in your modeling work when you need to create what is called a conditional. This means you are interrogating some variable in your model, and changing another variable or parameter in the model depending upon the "question" being asked.

Conditional statements

Conditional statements provide a mechanism for switching an execution path or the value assigned to one of more variables or parameters. Thus the conditional statement is a means by which to specify a switching mechanism. The most common example is the "if-then-else" statement. An example of the "if-then-else" statement is:

k(2,1) = if (variable > 0) then 1 else 2

In this situation if the variable you are interrogating is greater than zero, then the parameter k(2,1) = 1; otherwise it equals 2.

SAAM II regards conditionals as *explicit* or *implicit*. An explicit conditional statement is one where the time at which the switching occurs is known (can be predicted in advance). An implicit conditional statement is one where this time at which the switch occurs is not known until the condition itself is evaluated. Examples are:

Explicit: k(2,1) = if (t ge 10) then 1 else 2
Implicit: k(2,1) = if (q1 < q2) then 1 else 2

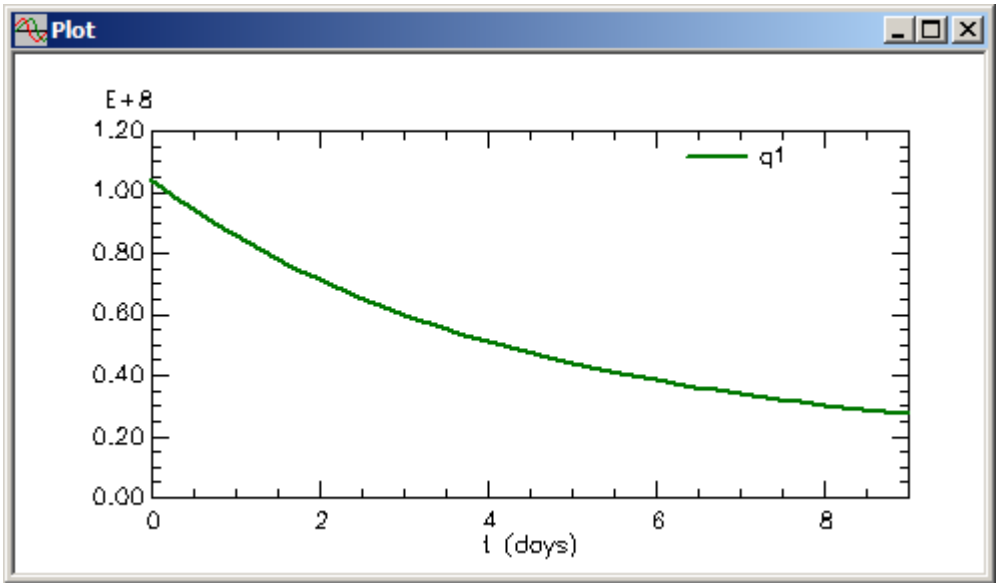
In these examples, "ge" is "greater than or equal to", and **q1** and **q2** are the contents of Compartments **1** and **2** at time "t".

In the explicit example, the time at which the switch occurs is known to equal 10. In the implicit case, there is no way to predict in advance when **q1** will be less than **q2**; values for **q1** and **q2** must be obtained at every integration step, and the test for "q1 < q2." performed.

Continuity and differentiability

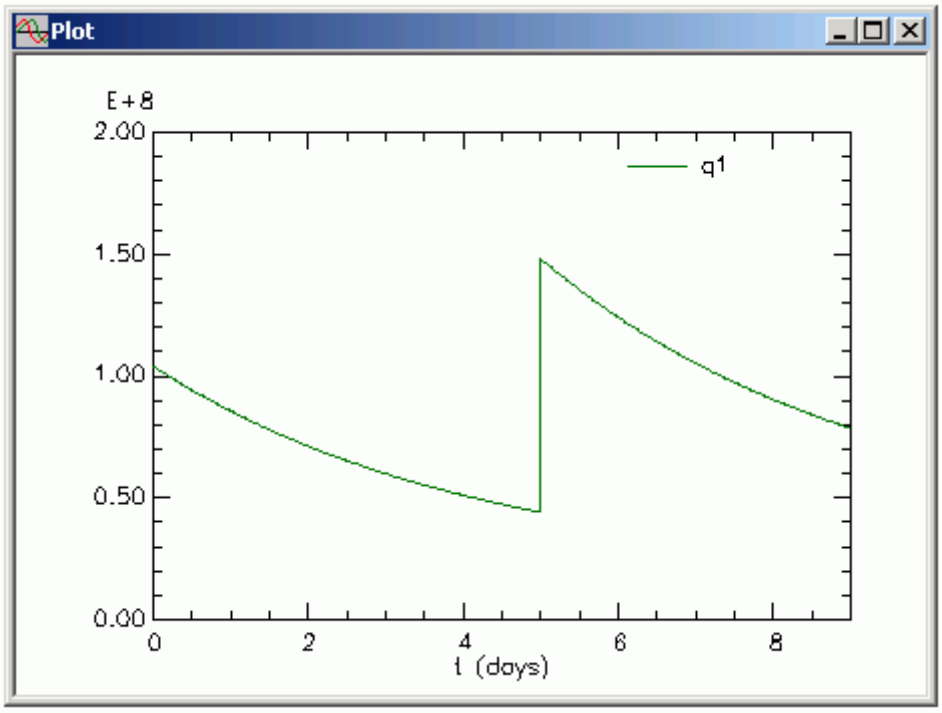
It is essential to understand the difference between continuity and differentiability because both are involved in how SAAM II "Solves" and "Fits". During either a "Solve" or a "Fit", SAAM II must perform numerical integration of the differential equations of your model. In order for the integrator to perform correctly, the functions (the qi) must be both continuous and differentiable.

What do we mean by continuous and differentiable? Consider the following plot of **q1** from **study_0**:

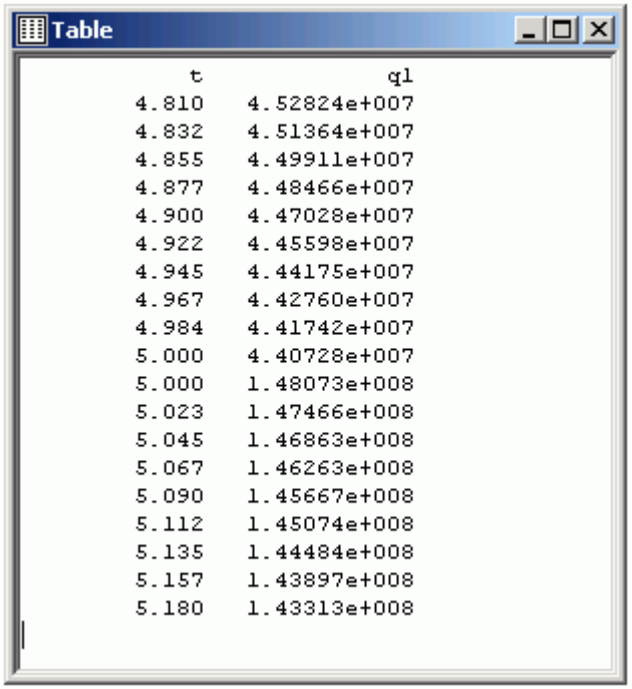


This curve is "smooth". That is, pick any point on the curve. Then start from a point on the curve to the left of this point. Move to the point along the curve. Then start from a point on the curve to the right of this point. Move to the point along the curve. You will reach the same final point no matter which side you start from and where. You can try this using the point at time equal to 5 days.

Now consider the following curve:



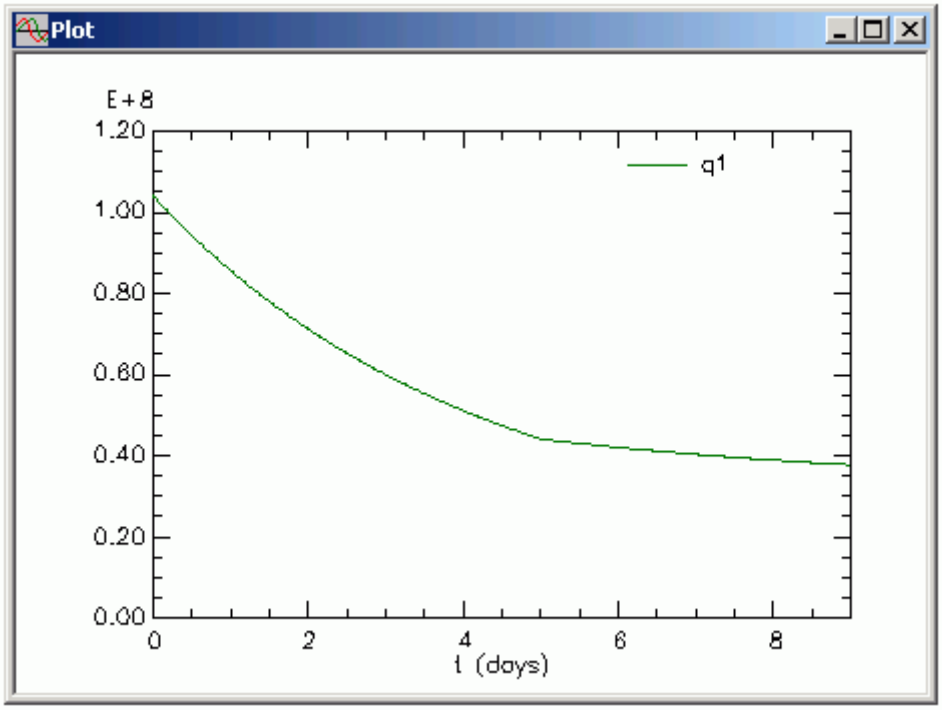
If you pick time equal to 5 days, and move to five days from the left (e.g. starting from 4) you will arrive at a different point than if you move to five days from the right (e.g. starting at 6). We say q1 is not continuous (or discontinuous, or has a discontinuity) when t = 5. You can see this even more clearly by looking at the table of values around t = 5:



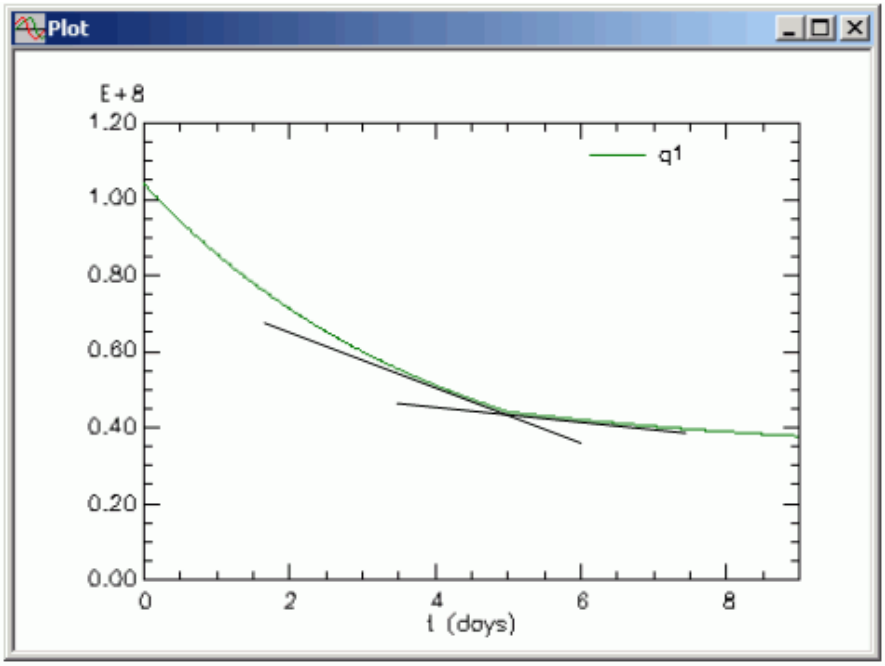
Moving in from a point less than time equal to 5 days you will end up at about 4.41e+07; moving from a point to the right hand side of time equal to 5 days you will end up at 1.48E+08, two very different values. This also is why there are two values reported by SAAM II at time equal to 5 days since this simulation was set up using **Change Conditions**.

What about differentiable? Differentiable is similar to continuity but deals with tangent lines. In the solution of **q1** in study_0, pick an arbitrary point on the curve. Then move away from that point, and draw a tangent line to the curve. Then move the tangent line to the point you picked. You can see that no matter whether you start from the left or right side of your chosen point, you will end up with the same tangent line.

Now consider the following curve:



There is a break at day 5. The function is continuous, but, as shown in the figure below, you will end up with two different tangent lines at t = 5 depending on whether you start to the right or left of t = 5:



In this case, when the tangent lines do not coincide, we say the function is non-differentiable at that point. In this case, **q1** is not differentiable when t = 5.

Explicit and implicit conditionals.

An explicit conditional is allowed because the time at which it occurs is known. Integration can stop at the prescribed time, be reset, and continue. An implicit conditional can create either a discontinuity or non-differentiable function, or both. For this reason, implicit conditionals are not allowed in the **SAAMI II Compartmental** application.

Explicit conditionals are allowed in the **SAAM II Compartmental** application. They are implemented using the **Change Condition** tool in the **SAAM II Compartmental Toolbox**. When using Change Conditions, it is assumed that the time at which the change takes place is known exactly. For more information on the **Change Condition** tool, see the Using SAAM II tutorial "Working with Change Conditions."

There is no equivalent to **Change Condition** in the **SAAM II Numerical** application. However, the explicit form of the "if-then-else" statement is allowed. An example is the following:

$$y(t) = \text{if } (t < 300) \text{ then yrise}(t) \text{ else ywash}(t)$$

This is an example of fitting a sum of exponentials to a constant infusion study where a washout phase was included starting at t = 300. Two functions, yrise(t) and ywash(t), are required. One describes the rise during the infusion and the other the washout. It is known that the infusion stops at "300." The function that is fitted to the data, y(t), then equals yrise(t) for t less than 300, and equals ywash(t) when t is greater than or equal to 300.

Implicit conditionals and the Heaviside function

How can one deal with implicit conditionals in SAAM II? The "work-around" is to use the Heaviside function. The conditional statement specified by the Heaviside function approximates the desired switch by assuming a value of zero or 1 at a given point. While virtually instantaneous, the function is continuous and differentiable! Thus switches can be created using this function, and one does not need to worry during the "Solve" or "Fit" about the continuity and differentiability assumptions.

The Heaviside function is

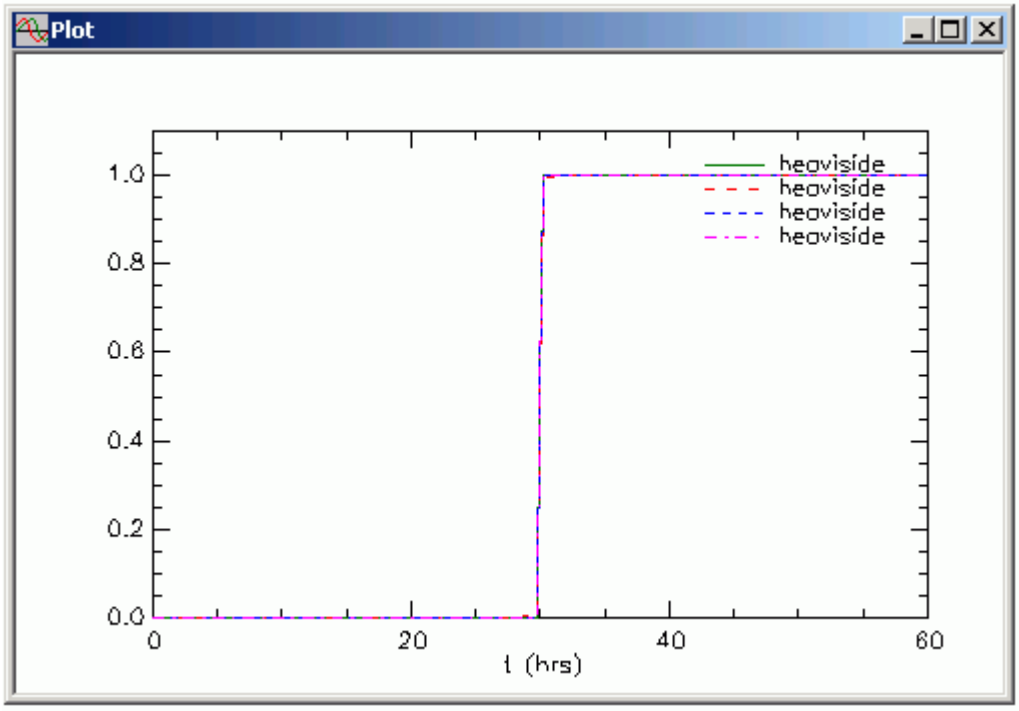
$$\text{heaviside}=0.5*(1.0+\text{atan}(\text{lambda}*(x - \text{xlag}))*2/3.141592653)$$

In this expression, "atan" is the arctangent function. The expression "x – xlag" creates the switch. "x" can be any function of "t", and xlag is the value at which the Heaviside function changes between 0 and 1. Normally "x" will be "t", time. but the expression is general, and there may be time when "x" may equal one of the "qi(t)" in your model. For values of "x" less than "xlag", the value of the Heaviside function equals "zero." For values of "x" greater than "xlag", the value is "one." Thus the values of the Heaviside function are, for all practical purposes, either zero or 1. That is, the change from 0 to 1 is extremely rapid yet the function remains continuous and differentiable. The parameter, *lambda*, controls the sharpness of the function, i.e. how fast the values change between zero and 1. This can be seen in the following

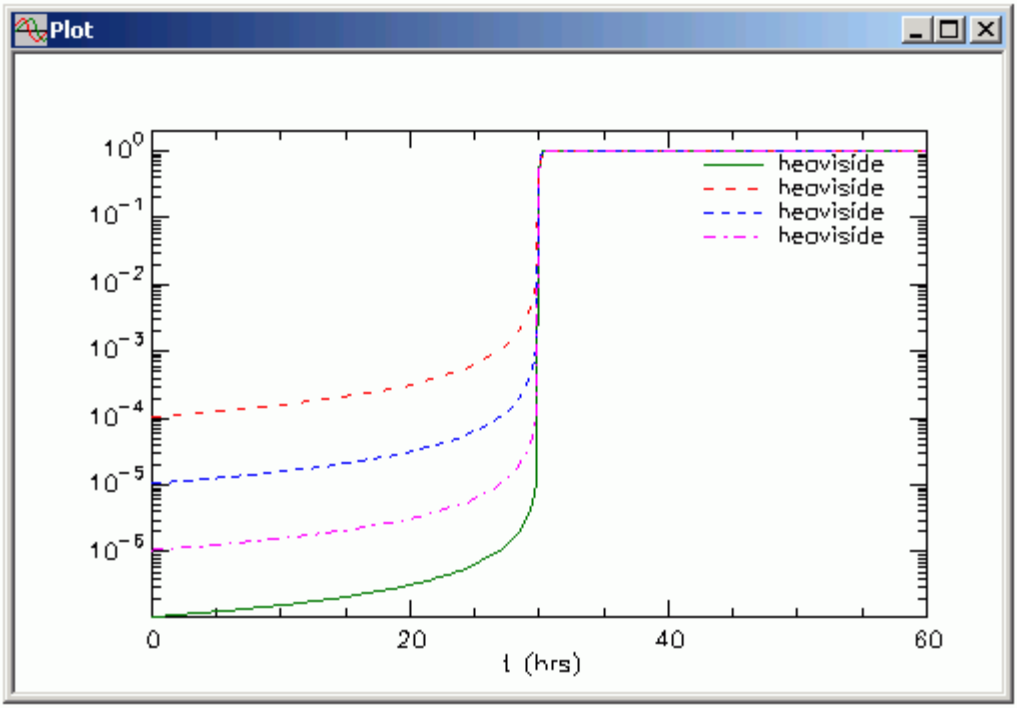
figure where the Heaviside function is calculated for *lambda* equal to 100, 1.000, 10.000 and 100,000 respectively where the Heaviside function is written

heaviside=0.5*(1.0+atan(lambda*(t - tlag))*2/3.141592653)

where "t" is the independent variable "time" and tlag is set equal to 30. (In this example, then, "x" is specifically defined as "t", time.) Thus when t = 30, the Heaviside function changes from zero to 1.



In the linear plot shown above, you can see how abrupt the change is; it almost looks discontinuous and nondifferentiable. To see what is really happening, and the role that *lambda* plays, one must look at the plot in semilog mode:



In this figure, you can see the function is continuous and differentiable despite the "sharp" change from zero to "1." As *lambda* increases, the value of the Heaviside function between zero and 30 becomes smaller, i.e. closer to zero, and the "sharpness" of the change from zero to 1 is increased. "Zero", as you can see, is not true zero, but is arbitrarily small relative to the other values you are calculating so, for all practical purposes, it can be regarded as zero.

When you use the Heaviside function to create a conditional, you must set a value for *lambda*. Typical values for *lambda* are usually between 1,000 and 1.0e+08 depending upon the situation. But you need to "tune" *lambda* for your particular situation. What happens is the following. When you Fit your model to your data, the results may depend on the value of *lambda*. What you want to do, and this will be illustrated below, is change (usually increase) the value for *lambda* so that the final values for the adjustable parameters and their error estimates do not change. This will be a function of the sharpness of the Heaviside function mentioned above. It also depends upon the magnitude of "x – xlag".

Example

Suppose you have a loss, *k(0,1)* from your model which you believe, up to a certain unknown time, exhibits Michaelis-Menten behavior and thereafter is an unknown constant. If "tlag" is the unknown time at which the change occurs, you can write the Heaviside function as

heaviside=0.5*(1.0+atan(lambda*(t - tlag))*2/3.141592653)

in the **Equations** window of the **SAAM II Compartmental** application. *tlag* will be a parameter which will appear in the **Parameters** dialog box; it can be either fixed or adjustable. You can then write in the **Equations** window:

Loss1 = Vm/(Kd+q1)

The expression you would write for *k(0,1)* is

k(0,1) = (1-heaviside)*Loss1 + heaviside*Loss2

Up to time *tlag*, "t – tlag" is negative hence "1-heaviside" equals 1, and *k(0,1)* will equal Loss1, the Michaelis-Menten loss. For values of t greater than *tlag*, the Heaviside function will equal 1, and *k(0,1)* will be equal to *Loss2*. *Loss2* will be recognized by SAAM II as a parameter which will appear in the **Parameters** dialog box; it can be either fixed or adjustable.

This is a specific example of the more general case when

heaviside=0.5*(1.0+atan(lambda*(x - xlag))*2/3.141592653)

i.e. you do not need "t – tlag". One can then write

y = heaviside*expression1 + (1 – heaviside)*expression2

For values of "x – xlag" that are positive, y will equal expression 1; when "x – xlag is negative, y will equal expression2. expression1 and expression 2 can be a single value, parameter, a function such as "q1/vol", or the Michaelis-Menten expression used above.

Computational considerations

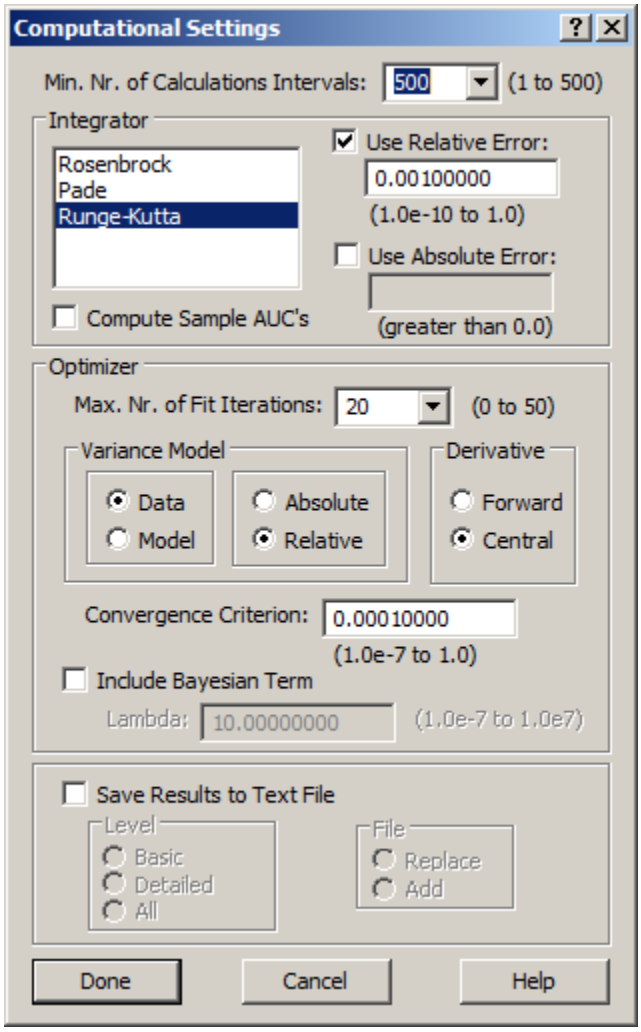
As you might expect, the Heaviside function, because of its sharpness, has the potential to create some problems when you Solve or Fit your model to your data. In general if there is only one conditional statement, the default **Computational Settings** will be sufficient although it is recommended you set the **Minimum Number of Calculation Intervals** equal to their maximum (500). You will see this is the case in the first two parts of this tutorial.

There may be other times when the switch specified by the conditional statement is active several times during the simulation of your experiment. An example is provided in Part 3 where an input pump is simulated to maintain plasma concentration at a certain level. In this case, the Heaviside function changes rapidly.

In this situation, the following Computational Settings are recommended:

- Set the **Minimum Number of Calculation Intervals** equal to 500.
- Change the **Integrator** to the "Runge-Kutta".
- Set **Derivative** calculation to "Central".

The **Computational Settings** dialog box will appear as follows:



Even with these setting, there are other adjustments you may need to make; most are suggested by SAAM II. As an example, you may need to change the value of the **Relative Error**. If you get such a warning message, first try decreasing this from 0.001 to 0.01.

The most important point is that when the switch specified by the conditional statement is rapidly turning on and off, you must be very careful that the software is operating correctly. This is why you should "tune" *lambda* until the solutions do not change.

Conclusion

Finally, besides being used to specify implicit conditionals, the Heaviside function is used to create "absolute" delays. You can learn about "absolute" delays in the Using SAAM II tutorial "Working with Delays."

Part 1. Creating a model with the conditional "if-then-else."

The example given below is a modification of the experiment in **study_0**. In the experiment described below, it is hypothesized that, for plasma concentration above a certain value, the loss from Compartment **1** exhibits Michaelis-Menten nonlinear behavior, and for concentration below this value, the loss is a constant rate. Information about the Michaelis-Menten constants, Vmax and Km, is available from the literature, so these parameters are entered using the SAAM II Bayesian option (for more information on this option, see the Using SAAM II tutorial "Working with Parameters.")

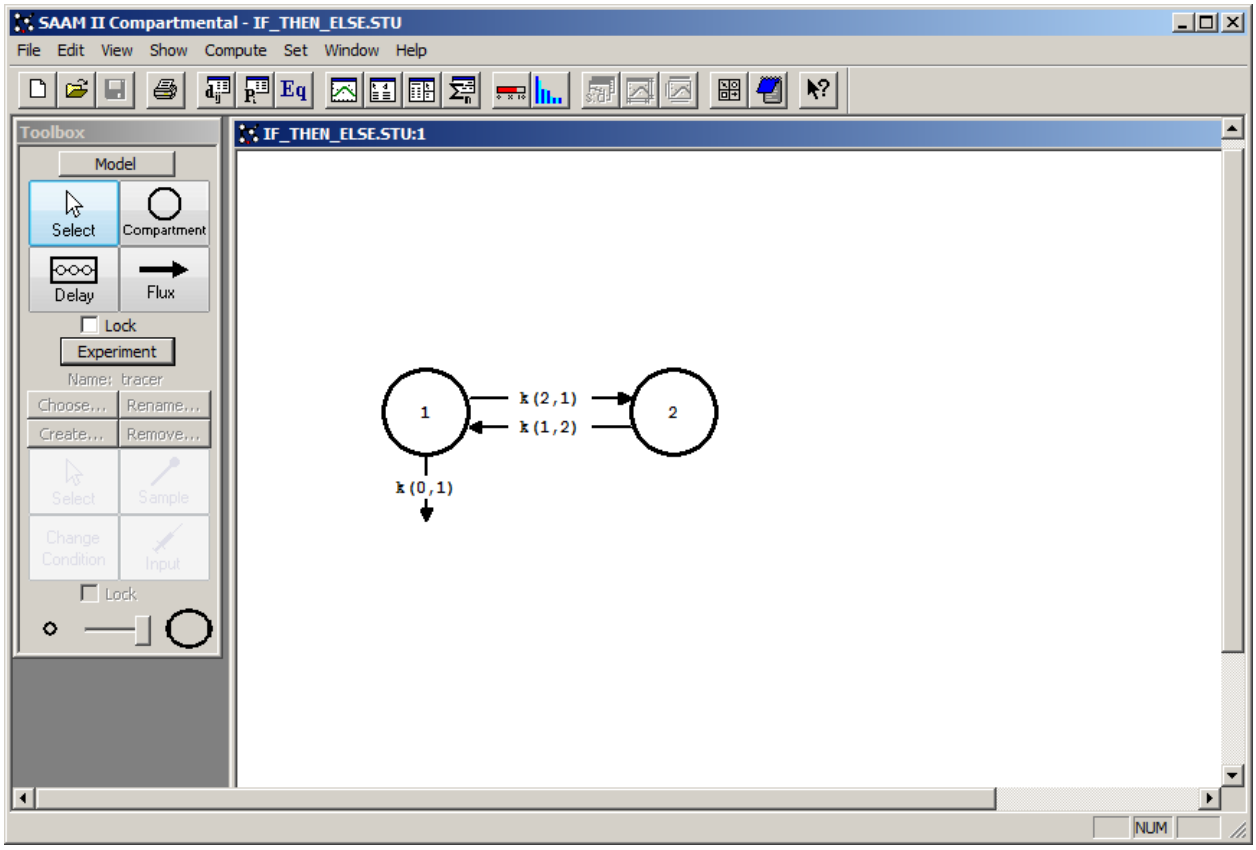
You will use the study file **if_then_else**. This file has been created with the conditional expressed and the parameter values entered. The data file is included separately in case you would like to reconstruct the study file yourself. Each particular entry will be explained in detail.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

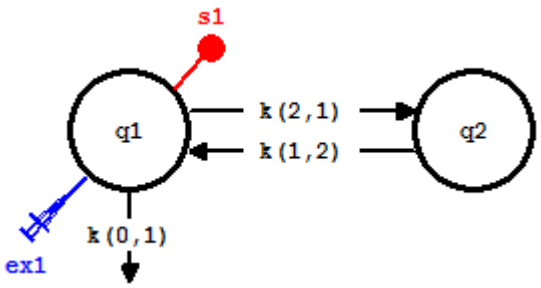
2. Open the **SAAM II Compartmental** study file **, if_then_else**.

   a. The file **, if_then_else** should appear in the file list; if it does not, find the folder where you put this file.

   b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as follows:



3. View the model and the experiment on the model, and change the model. In the **SAAM II Toolbox**, click **Experiment**. The experiment on the model will appear as follows:

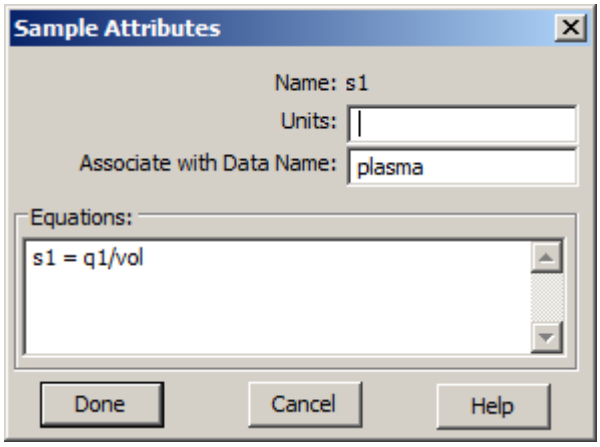


The model of the experiment appears the same as the model of the experiment in study_0 structurally. The way in which the input and equations are specified in order to deal with the "if-then-else" makes the model different .

4. View the different components of the experiment on the model.

   a. View the **Sample Attributes** dialog box associated with **s1**.

      (1) Double-click **s1**. The **Sample Attributes** dialog box will open as follows:

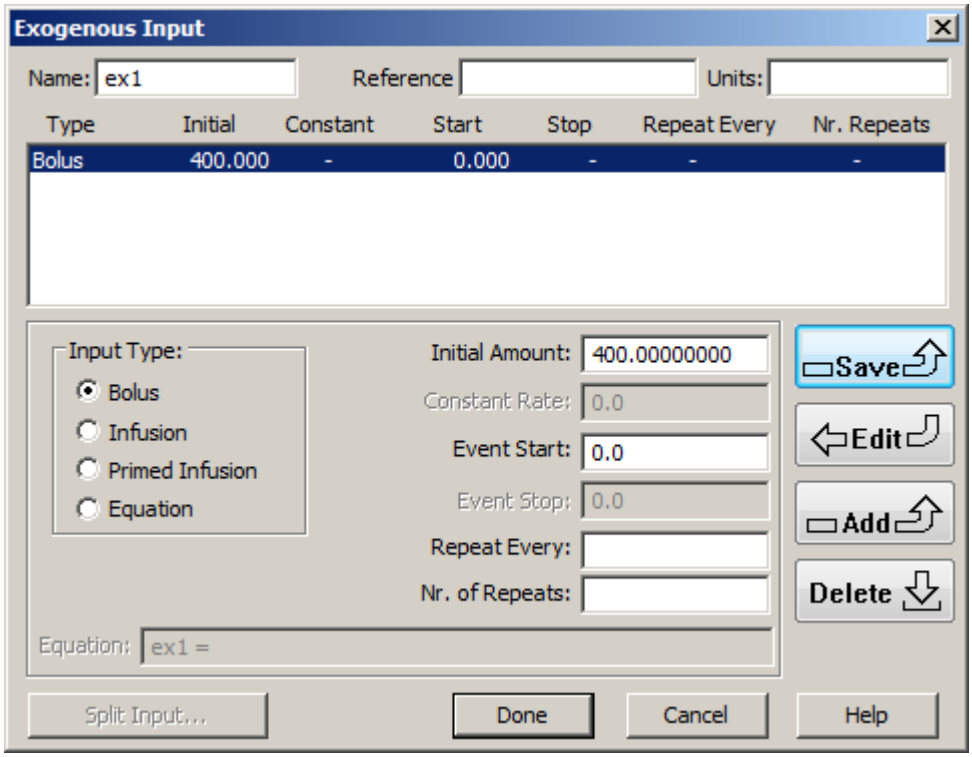


The information in the **Sample Attributes** dialog box is standard in that the sample is associated with the **Data Name** "plasma", and the sample equation "s1=q1/vol" will introduce the new parameter *vol*. You can open the **Data** window if you wish to view the "plasma" data.

(2) Click **Done**.

b. View the **Exogenous Input** dialog box associated with **ex1**.

(1) Double-click **ex1**. The **Exogenous Input** dialog box will open as follows:



The information in the **Exogenous Input** dialog box is standard in that the input is a single bolus of 400 units.

(2) Click **Done**.

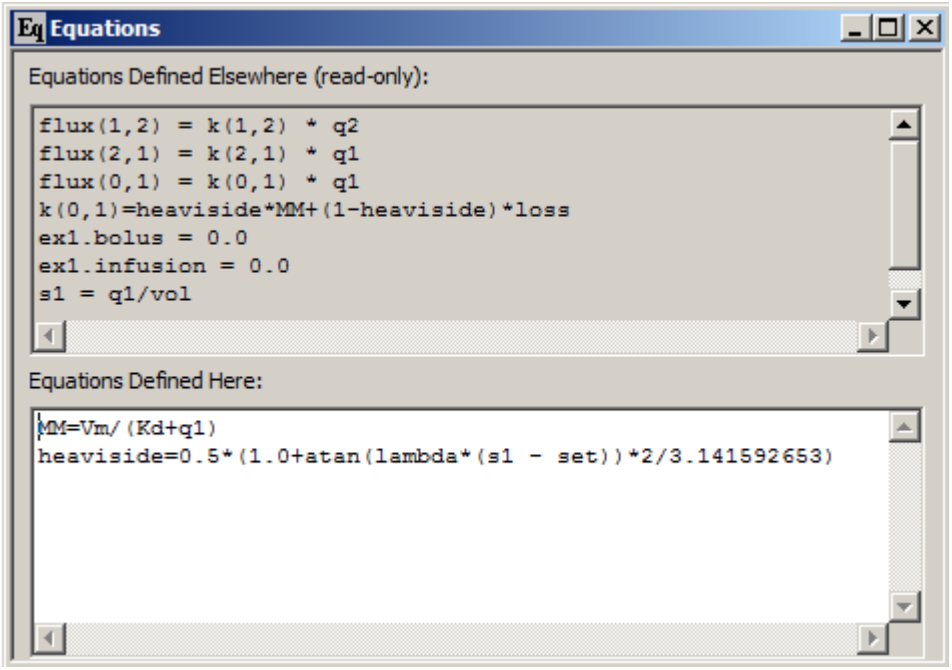
5. Creating the conditional.

As stated above, it is hypothesized that for plasma concentrations above a certain, known level, the loss *k(0,1)* exhibits Michaelis-Menten kinetics while below that level, the loss rate is a constant. The plasma concentration ranges from approximately 0.2mg/ml to 0.04mg/ml. The concentration at which the loss changes from Michaelis-Menten to a constant is known to be 0.1mg/ml, but the exact time at which this occurs is unknown.

The following describes how to specify *k(0,1)* equal to a Michaelis-Menten expression for values of **s1** greater than 0.1 and equal to a constant for values of **s1** less than 0.1.

a. View the equations setting up the Michaelis-Menten loss and the conditional expression to create the switch.

(1) In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar,** click **Equations** Eq. The **Equations** dialog box will open as shown below:



There are two equations in the **Equations Defined Here** pane.

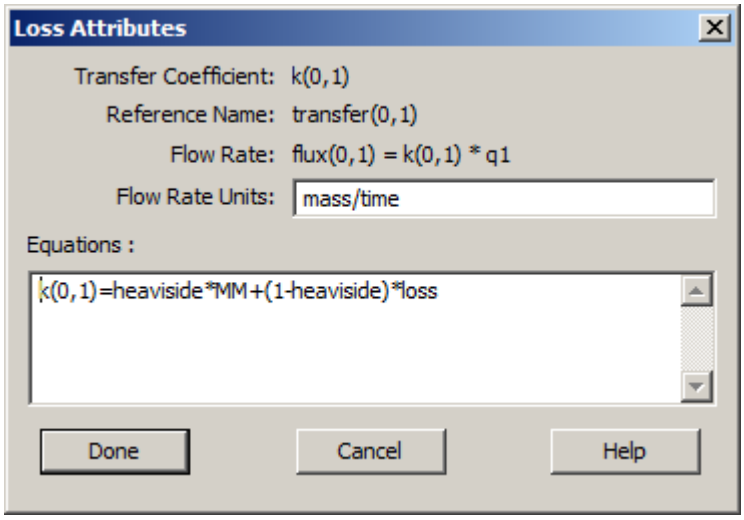
The equation "MM" defines the Michaelis-Menten term which will be used to defined *k(0,1)*. This will introduce two new parameters in the model, *Vm* and *Kd*.

The second equation is the Heaviside equation. In this equation, the concentration s1 is being compared to the parameter *set*. **s1** is the model calculated value for the concentration, and *set* will be entered as a fixed parameter, in this case equal to 0.1. When **s1** is greater than or equal to *set*, the value of heaviside will equal 1, otherwise it will equal zero.

(2) Close the **Equations** dialog box.

b. View the definition of *k(0,1)*.

(1) Double-click *k(0,1)*. The **Loss Attributes** dialog box will appear as follows:



The equation specifying *k(0,1)* now is the key to understand how the conditional expression is working. The expression is:

k(0,1)=heaviside*MM+(1-heaviside)*loss

When the Heaviside function equals 1, i.e. when **s1** is greater than or equal to *set*, *k(0,1)* will equal "MM". Otherwise it will equal "loss"; "loss" will be recognized by SAAM II as a parameter appearing in the **Parameters** window. Thus this expression is equivalent to

k(0,1) = if (s1 ge set) then MM else loss.

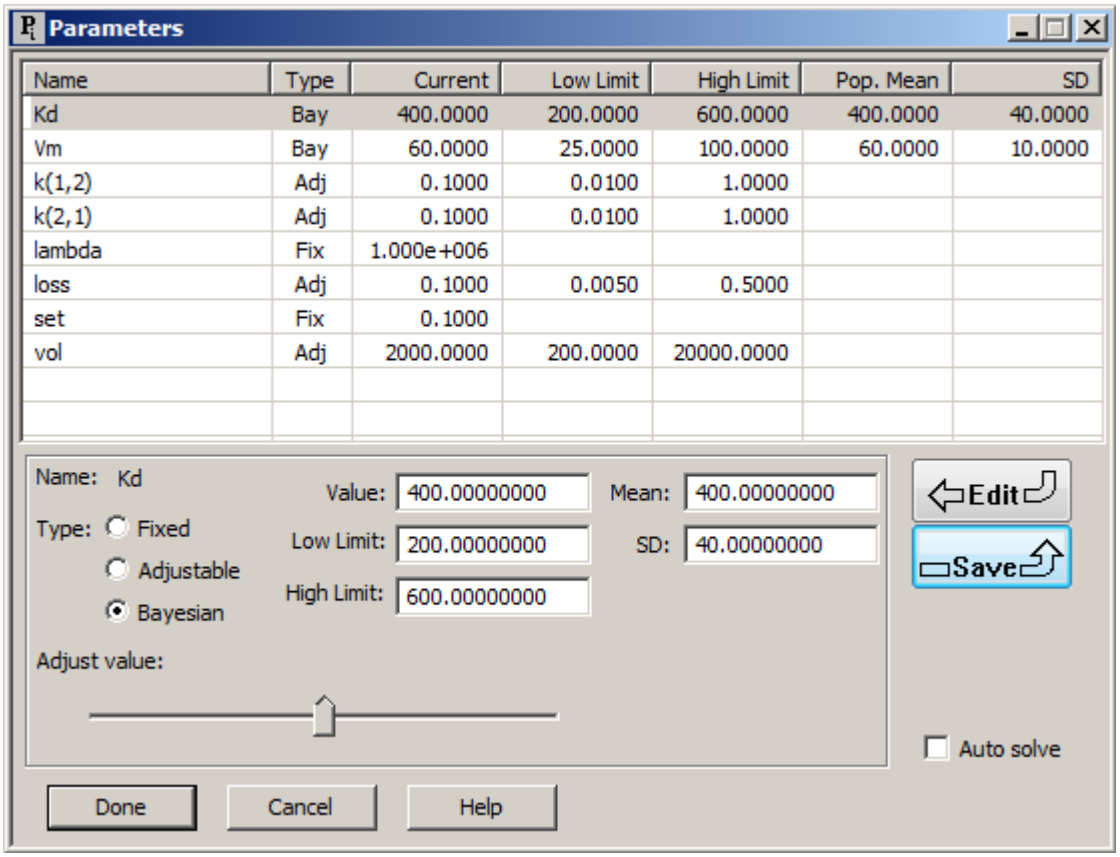
If-then-else and the Heaviside function. The Heaviside function can be used to create if-then-else statement by recognizing that the "then" part of the statement occurs when the value of the Heaviside function is 1, and the "else" part of the statement occurs when the value of the Heaviside function is zero.

(2) Click Done.

At this point, the model is fully specified. It remains to examine the **Parameters** window. Then you can proceed to Solve and Fit the model to the data.

6. View the **Parameters** window.

   a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters**  . The **Parameters** dialog box will open as shown below:



The first two parameters, *Kd* and *Vm*, are the Michaelis-Menten parameters. Since prior information is available about these parameters, they are entered as Bayesian (for more information on SAAM II Bayesian parameters, see the Using SAAM II tutorial "Working with Parameters." The next two parameters, *k(2,1)* and *k(1,2)*, are the exchange rate constants. The parameter *lambda* is fixed; it is part of the Heaviside function. The "tuning" of *lambda* will be explained below. The initial value of 1.0e+06 is usually a reliable starting point; it can be changed during the tuning process. The parameter *loss* is the constant rate of loss once **s1** falls below *set*, the concentration at which *k(0,1)* changes from Michaelis-Menten to a constant. *vol* is just the volume of Compartment **1**.

b. Click **Done**.

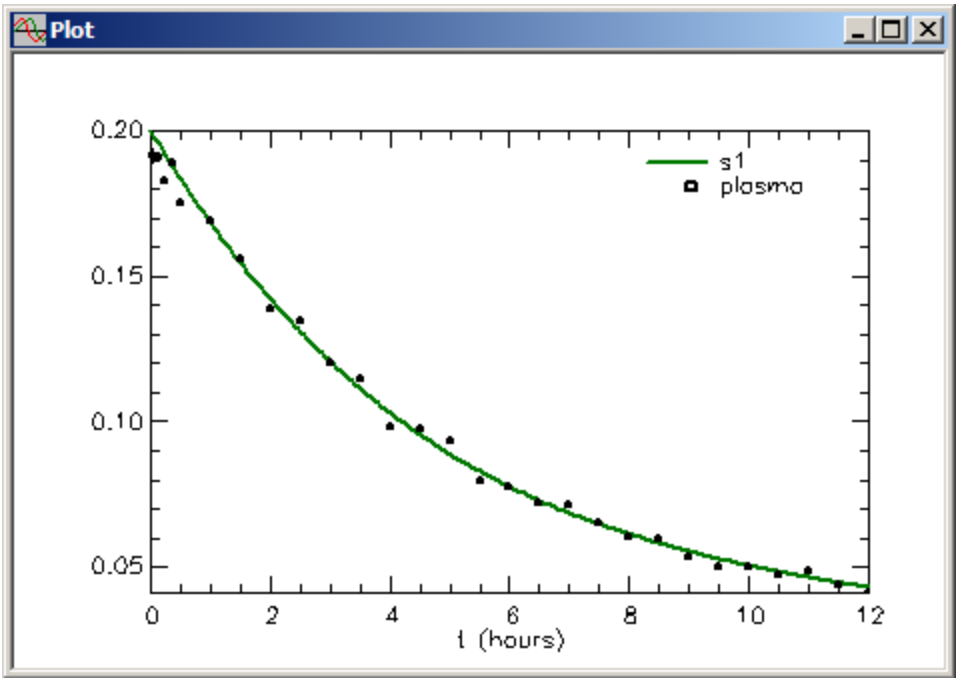
7. Solve the model and save the solution.

   a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve**  .

   b. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot**  . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is not selected.

   c. Click **s1:plasma** to move this to the **Current Selection** pane.

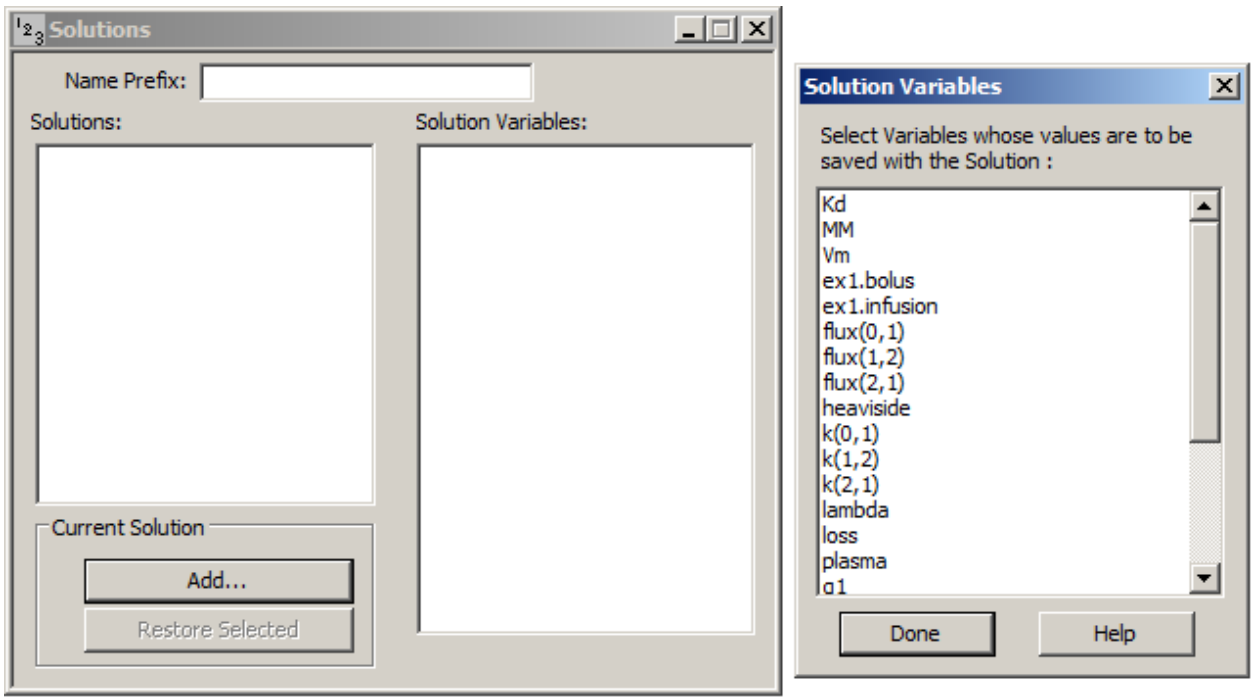
   d. Click **Done**. If the plot is not in semilog, in the **View** menu, click **Semilog**. The plot will appear as follows:



   e. Close the **Plot** window.

   f. In the **Compute** menu, click **Solutions**. The **Solutions** dialog box will open.

   g. Click **Add**. The **Solution Variables** dialog box will open. Scroll through the variables and click **s1**. The two dialog boxes will appear as follows:



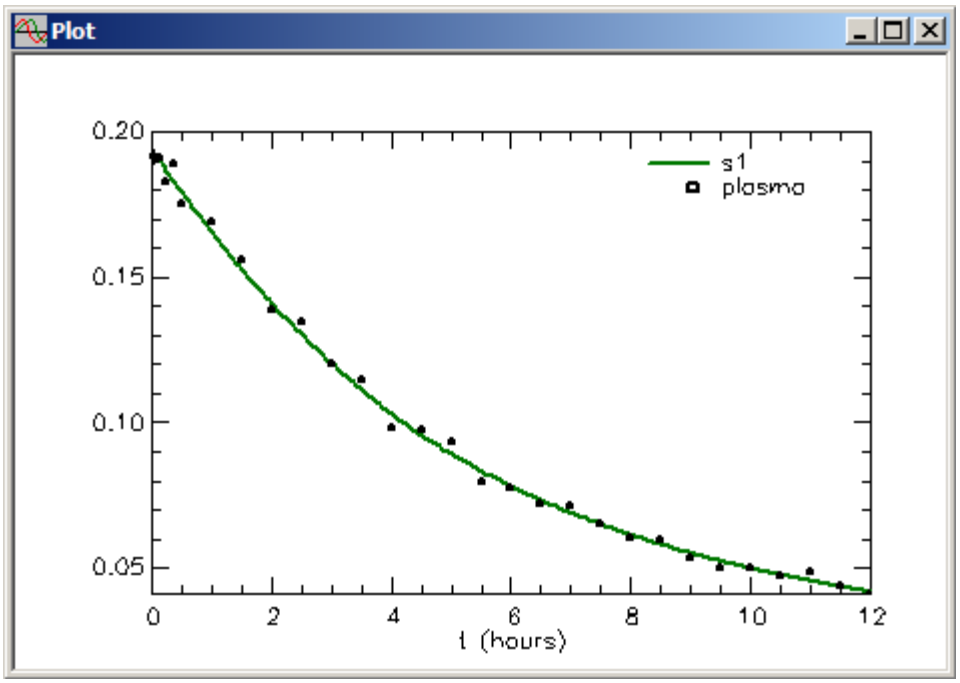
h. In the **Solution Variables** dialog box, click **Done**.

i. Close the **Solutions** dialog box.

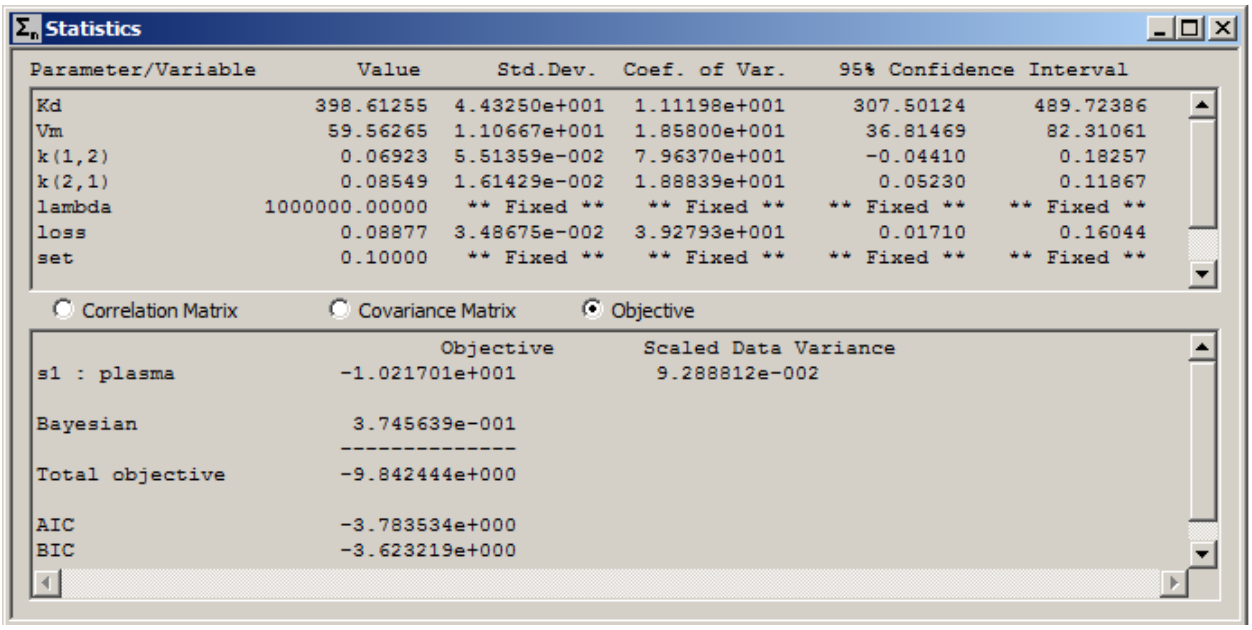
Tuning lambda. The parameter *lambda* is "tuned" by changing its value until there are no longer any significant changes in the adjustable parameters and their error estimates. To tune *lambda*, i.e. as you change the value, you must start from the same set of initial parameter estimates. This solution has been saved as that starting point. For more information on saving and restoring solutions, see the Using SAAM II tutorial "Saving and Restoring Solutions."

8. Fit the model to the data, view and record the solution.

a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar,** click **Fit** . The plot of **s1:plasma** will appear as shown below:



b. In the **Show** menu, click **Statistics**, or alternatively on the **SAAM II Toolbar** click **Statistics**  . The **Statistics** window will appear as follows:



c. Record the results as shown below:

lambda	1.00E+06	1.00E+07
Kd	399(11)	
Vm	59.6(19)	
k(1,2)	.069(80)	
k(2,1)	.085(19)	
loss	.089(39)	
vol	2060(1)	

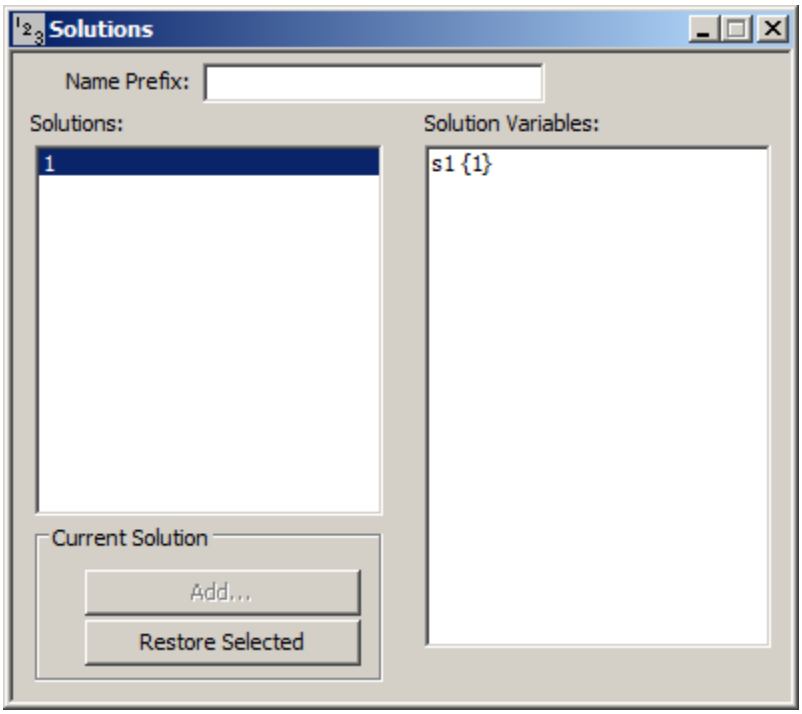
These are the values when *lambda* equals 1.00e+06. You can see *Kd* and *Vm* do not change much from their initial values meaning there is not much information in these data to help determine them. In addition, *k(1,2)* does not have very good precision.

d. Close all open windows and dialog boxes.

9. Restore the original solution, and refit the model to the data with *lambda* equal to 1.0e+07, and record the results.

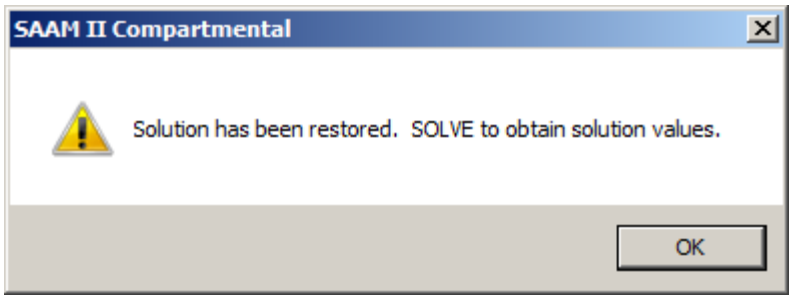
a. In the **Compute** menu, click **Solutions**. The **Solutions** dialog box will open.

b. Click "1" in the **Solutions** pane. The **Solutions** dialog box will appear as follows:



Notice **Restore Selected** is now available.

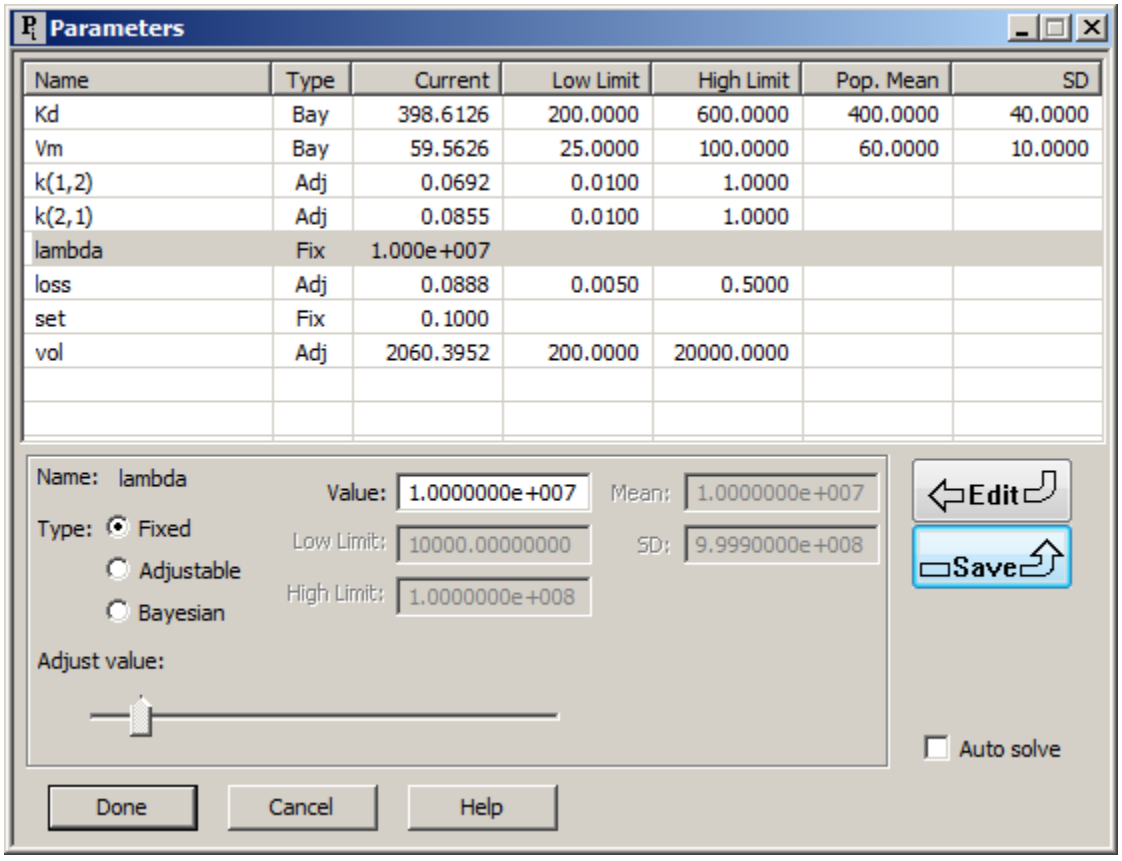
c. Click **Restore Selected**. The following message will appear:



d. Click **OK**, and close the **Solutions** dialog box.

e. Re-Solve the model. The original solution is now restored.

f. Change the value of *lambda* from 1.0e+06 to 1.0e+07. The **Parameters** dialog box will appear as follows:



Name	Type	Current	Low Limit	High Limit	Pop. Mean	SD
Kd	Bay	398.6126	200.0000	600.0000	400.0000	40.0000
Vm	Bay	59.5626	25.0000	100.0000	60.0000	10.0000
k(1,2)	Adj	0.0692	0.0100	1.0000		
k(2,1)	Adj	0.0855	0.0100	1.0000		
lambda	Fix	1.000e+007				
loss	Adj	0.0888	0.0050	0.5000		
set	Fix	0.1000				
vol	Adj	2060.3952	200.0000	20000.0000		

Close the **Parameters** dialog box.

g. Re-Fit the model to the data, and record the results. The results should appear as follows:

lambda	1.00E+06	1.00E+07
Kd	399(11)	399(11)
Vm	59.6(19)	59.6(19)
k(1,2)	.069(80)	.069(80)
k(2,1)	.085(19)	.085(19)
loss	.089(39)	.089(39)
vol	2060(1)	2060(1)

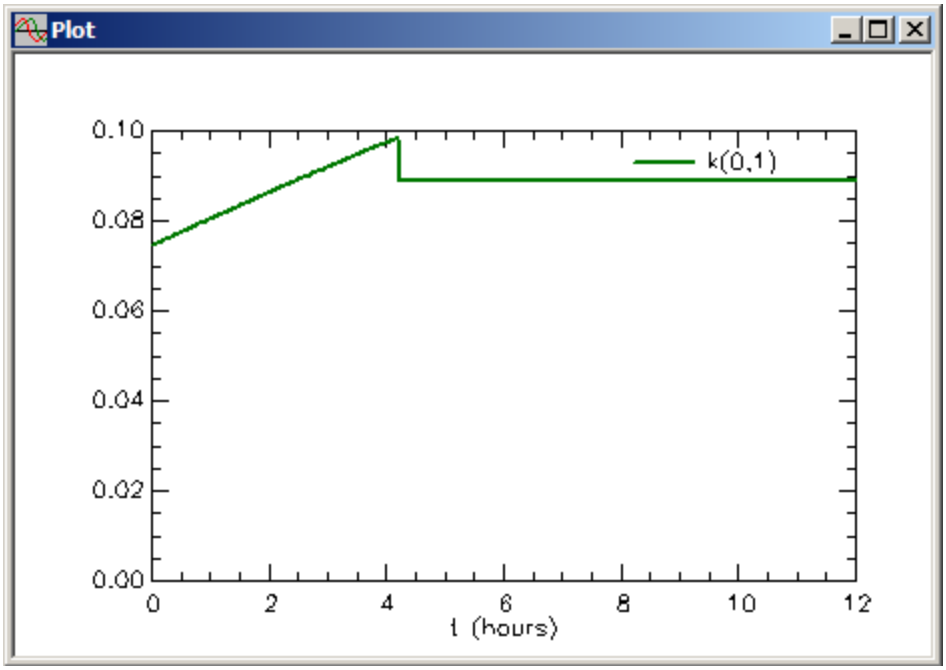
You can see there is no difference between *lambda* equaling 1.0e+06 and 1.0e+07, so you can regard *lambda* equal to 1.0e+06 as a well-tuned value.

You should also try different values for *lambda* such as 1.0e+05 and 1.0e+04 to see which parameters change, if any.

h. Close all open windows and dialog boxes.

Quit the **SAAM II Compartmental** application. Do not save the changes to **if_then_else**.

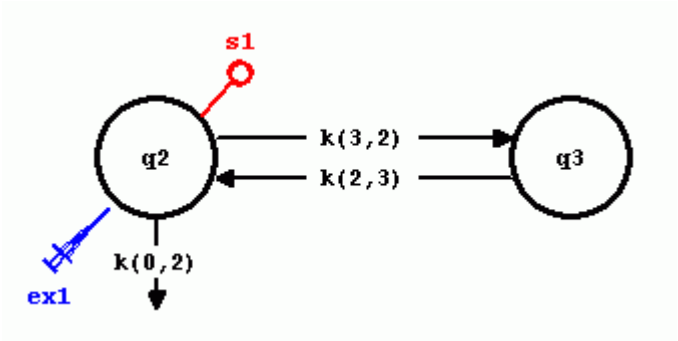
In this example, it is useful to examine *k(0,1)*. A plot of this parameter is shown below following the last "Fit":



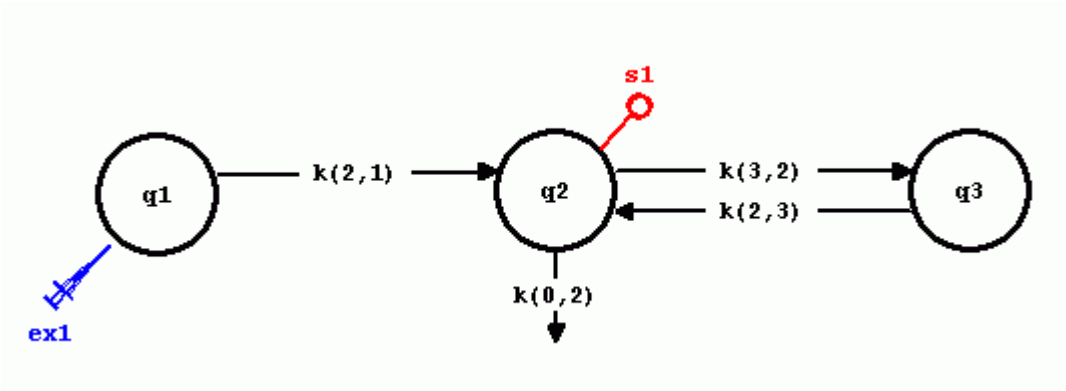
You can clearly see the value of *k(0,1)* rising during the initial decay phase of the data; the rise continues until around 4 hours at which point **s1** is less than *set*. However just before the switch defined by the conditional statement occurs, *k(0,1)* is actually greater than *loss* (the straight line portion parallel to the t-axis.) If one believes this should not be the case, then the value for *set* may be off a little.

Part 2. Creating a zero-order input of unknown duration

A zero-order input into a compartment is actually equivalent to a constant infusion. However, there are instances when specifying it in this manner is not appealing in terms of the physiology, or drug absorption, being studied. It is a difference between



and



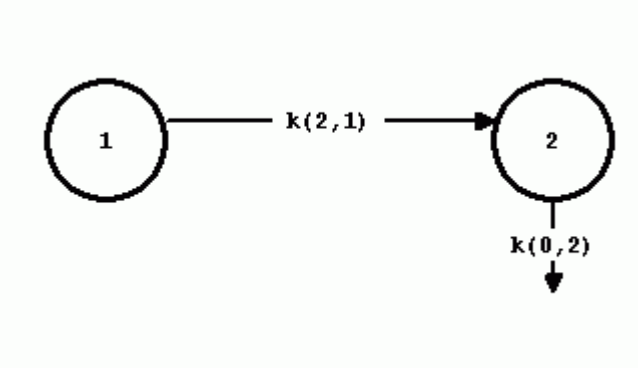
If one is dealing with absorption and believes that the absorptive process is zero-order, then either of these two model configurations can explain the kinetics. In the case of the second model, *k(2,1)* would be a zero-order rate constant. The first model will yield identical results, but the lack of a schematic for absorption is not appealing.

This part will explain how to create a zero-order absorption of an unknown amount for an unknown duration.

The experiment is one in which 100mg of the drug was given orally at the start of the experiment followed by several other doses sufficient to have drug mass levels high enough in Compartment **q1** for zero-order absorption to realistically take place. The hypothesis is that absorption is zero order of unknown amount for an unknown duration. The experiment lasts for 24 hours.

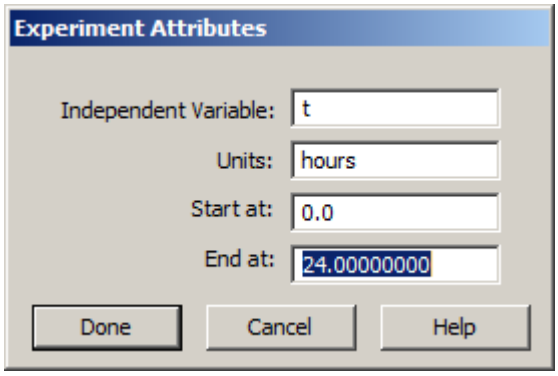
1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

2. Create the following system model:

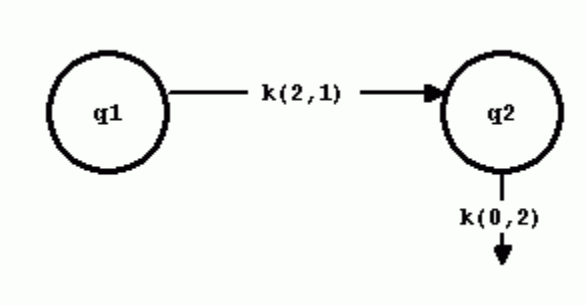


3. Create the experiment on the model.

   a. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open. Set the experimental attributes as follows:



   b. Click **Done**. The **Create Experiment** dialog box will open. Click **Create**. The model will appear as follows:

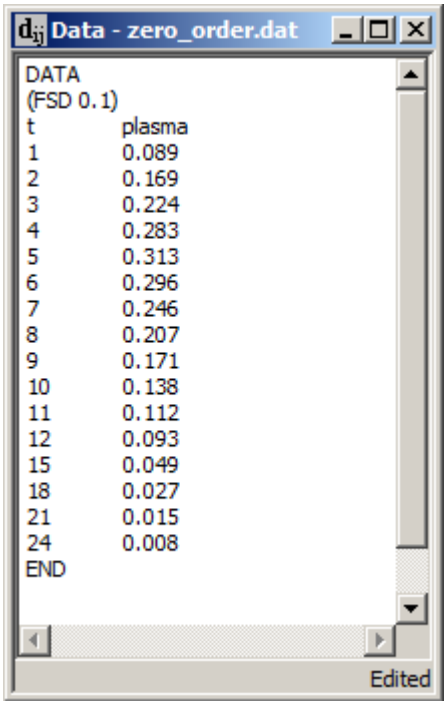


4. Add the data to the model.

   a. On the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data**  . The **Data** window will open.

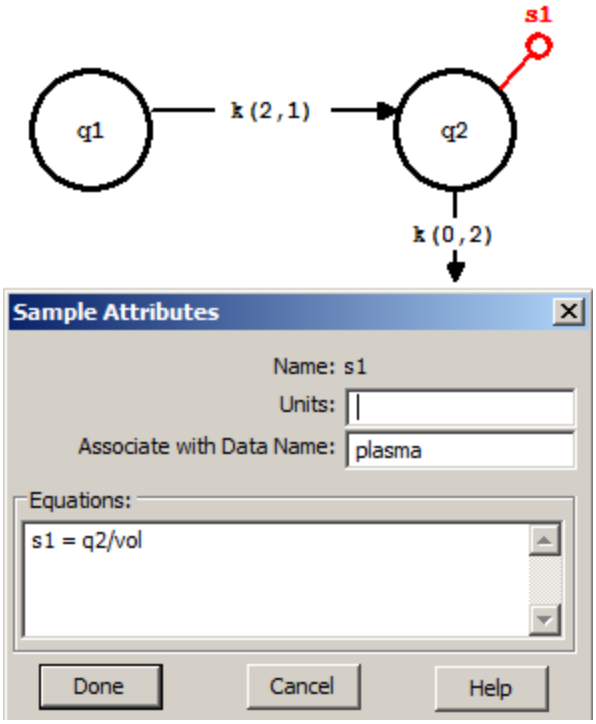
b. On the **File** menu, click **Open**. The file **zero_order.dat** should appear in the list (if it does not, find the folder where you put this data file).

c. Double-click **zero_order.dat**. The data in this file will appear in the **Data** window. The **Data** window should appear as follows:



d. Close the **Data** window.

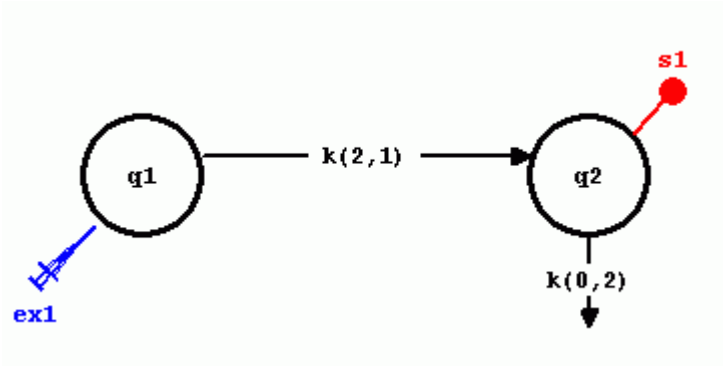
5. Create a sample on Compartment **q2**, associated with "plasma" and edit the sample equation to read "**s1=q2/vol**". The **Sample Attributes** dialog box should appear together with the model as follows:



Click **Done**. The sample **s1** will become filled.

6. Create an input into Compartment **q1**.

   a. Create the input into Compartment **q1**. The model should appear as follows:



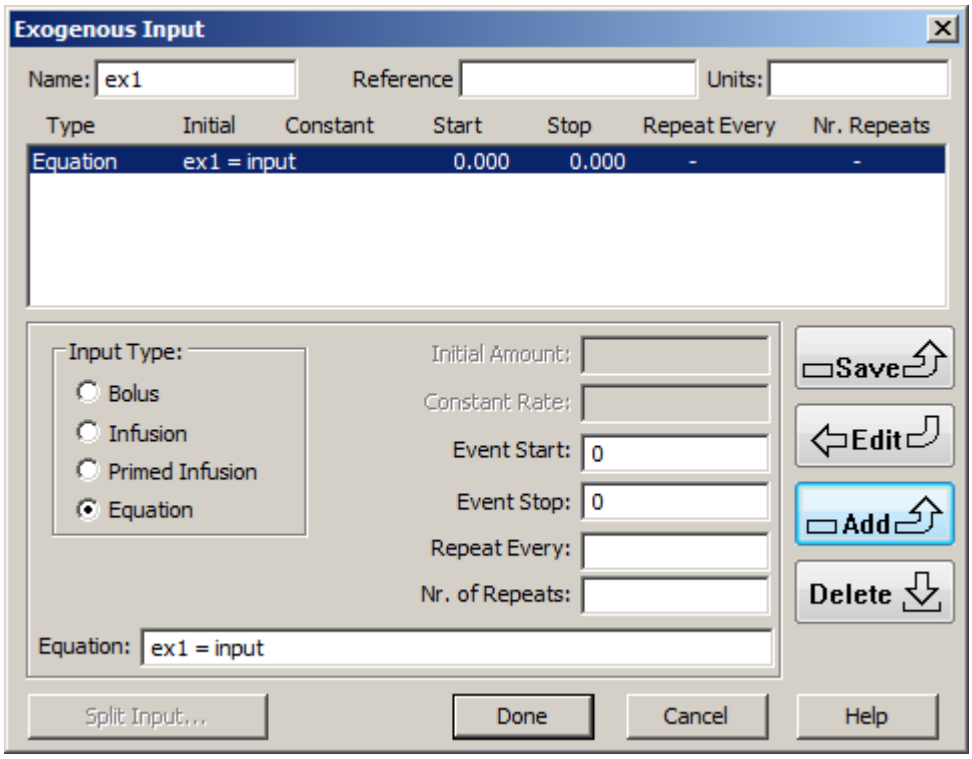
   b. Specify the input as a bolus equal to 100 using the equation format.

      (1) Double-click **ex1** to open the **Exogenous Input** dialog box.

      (2) Select **Equation** as the input type.

      (3) Set the **Start** and **Stop** time equal to zero.

(4) Write the input equation "ex1 = input". Click **Add**. The **Exogenous Input** dialog box should appear as follows:



(4) Click **Done**.

Exogenous input. Technically an exogenous input should not be needed in the case of zero-order absorption, . In this case, specifying the exogenous input as an equation "ex1 = input" will create *input* as a parameter; this allows for different studies to have different input values without having to go to the **Exogenous Input** dialog box first. The real reason why there needs to be an initial value at time zero is to prevent division by zero; this will be explained below.

7. Create the zero-order input.

   To create the zero order input, the parameter k(2,1) must be changed to zero order. To estimate the unknown time of the zero-order absorption, a Heaviside function must be created.

   a. In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar,** click **Equations** Eq. The **Equations** dialog box will open.

b. Create the Heaviside function. In the **Equations Defined Here** pane, type

"heaviside=0.5*(1+atan(lambda*(t-tlag))*2/3.141592653)"

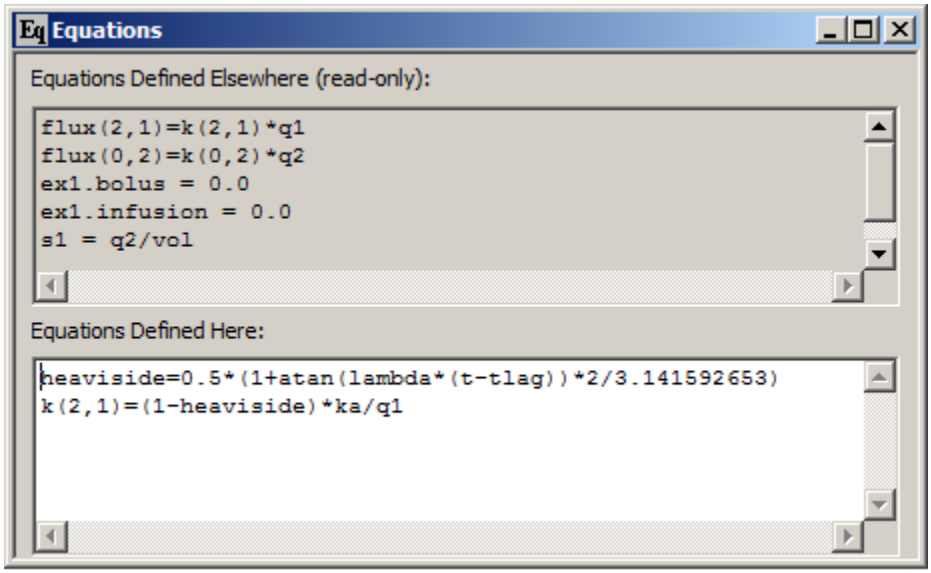
In this expression, for t less than the unknown parameter *tlag*, the value of the Heaviside function will be zero; otherwise it will equal 1. The parameter *tlag* will thus be the time when zero-order absorption stops.

c. Create the zero-order absorption parameter. In the **Equations Defined Here** pane, type

"k(2,1)=(1-heaviside)*ka/q1"

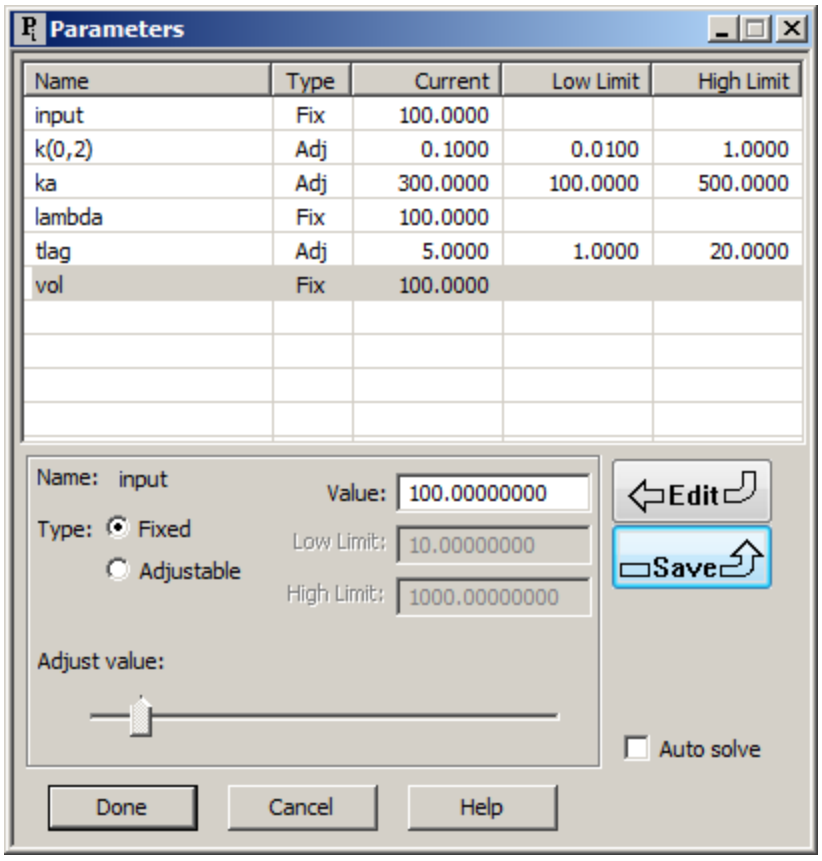
This equation specifies *k(2,1)* as a zero-order parameter because of the division by **q1**. It is this division that requires **q1** to have a value at time zero, otherwise you will receive a warning of division by zero. The absorption rate is the parameter **ka**. Up to time *tlag*, "1 – heaviside" will equal 1, and the zero-order absorptive process will occur. After time *tlag*, zero-order absorption will stop.

The **Equations** dialog box should appear as follows:



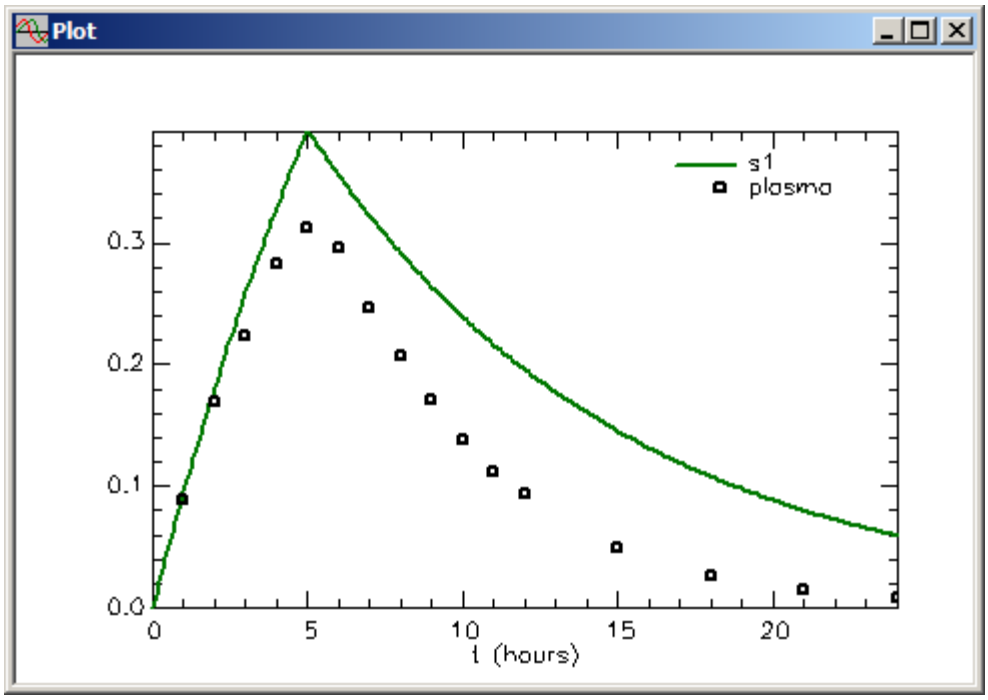
d. Close the **Equations** dialog box.

8. Enter the parameter values as shown below:



Of the parameters, *input* is the known initial dose; it is fixed. k(0,2) is the unknown loss from Compartment **2**. *ka* is the unknown zero-order absorption rate. *lambda* is the tuning parameter for the Heaviside function. *tlag* is the unknown duration of the zero-order absorption. The initial value of 100 is lower than the normally used 1.0e+06 for *lambda*. This value was picked by examining different values for *lambda* starting from 1.0e+06. Thus, choosing the initial value is also part of the tuning process. *vol* is the volume of Compartment 2. The volume is assumed to be known otherwise the amount of the zero-order absorption could not be estimated (if both were allowed to adjust, you will find they are perfectly correlated.)

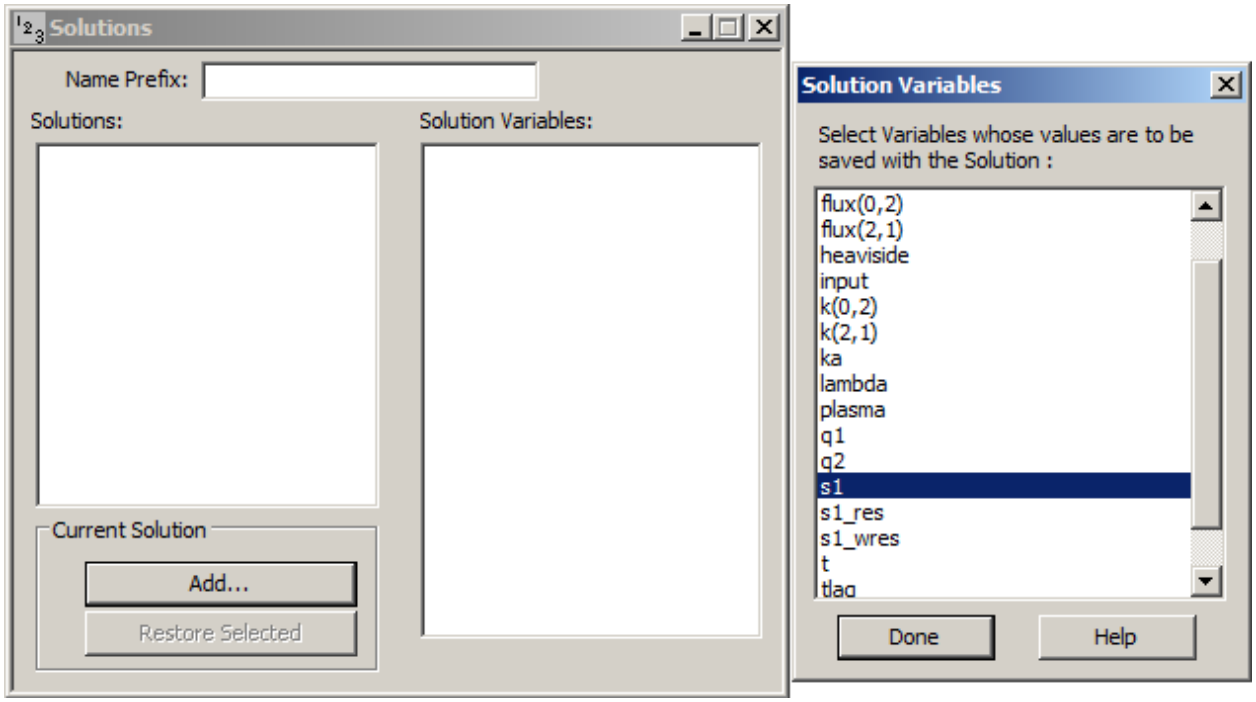
9. Solve the model, and view and save the solution. A plot of **s1** and **plasma** will appear as follows:



a. Close the **Plot** window.

b. In the **Compute** menu, click **Solutions**. The **Solutions** dialog box will open.

c. Click **Add**. The **Solution Variables** dialog box will open. Scroll through the variables and click **s1**. The two dialog boxes will appear as follows:



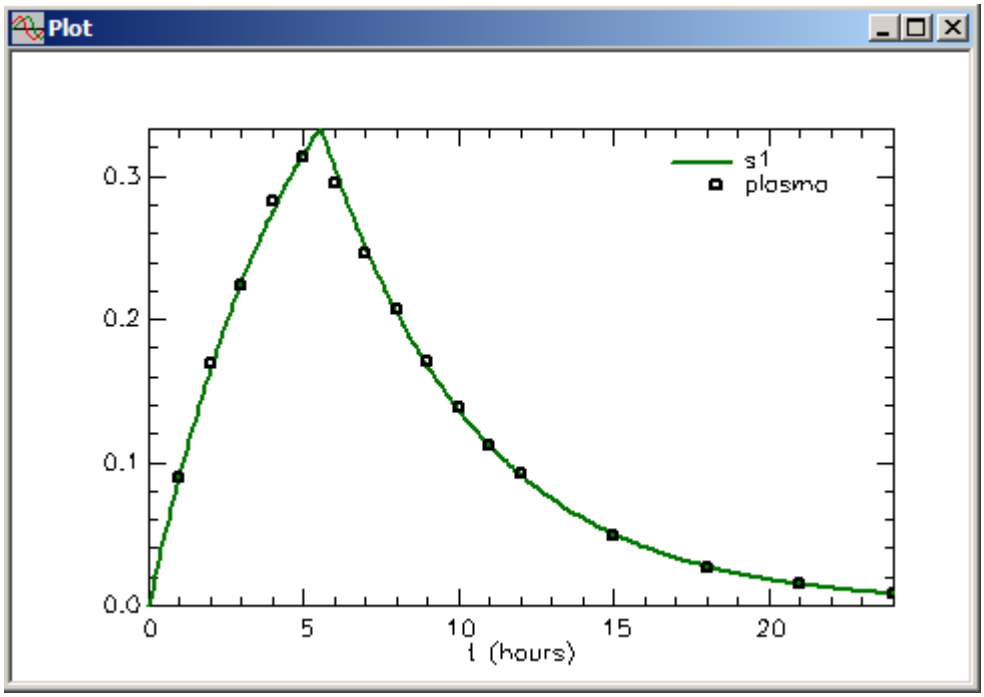
d. In the **Solution Variables** dialog box, click **Done**.

e. Close the **Solutions** dialog box.

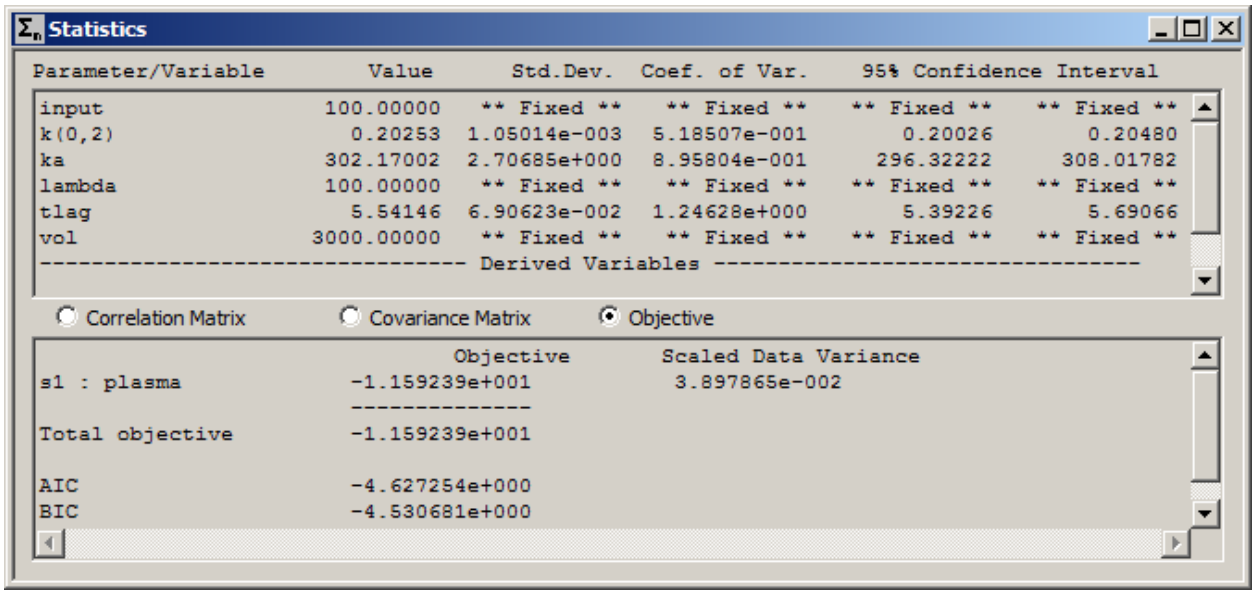
Tuning lambda. The parameter *lambda* is "tuned" by changing its value until there are no longer any significant changes in the adjustable parameters and their error estimates. To tune *lambda*, one must start from the same set of initial parameter estimates. This solution has been saved as that starting point. For more information on saving and restoring solutions, see the Using SAAM II tutorial "Saving and Restoring Solutions."

10. Fit the model to the data, view and record the solution.

a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar,** click **Fit**  . The plot of **s1:plasma** will appear as shown below:



b. In the **Show** menu, click **Statistics**, or alternatively on the **SAAM II Toolbar** click **Statistics**  . The **Statistics** window will appear as follows:



c. Record the results as shown below:

lambda	1.00E+02	1.00E+03
k(0,2)	0.203(0.52)	
ka	302(0.90)	
tlag	5.54(1.2)	

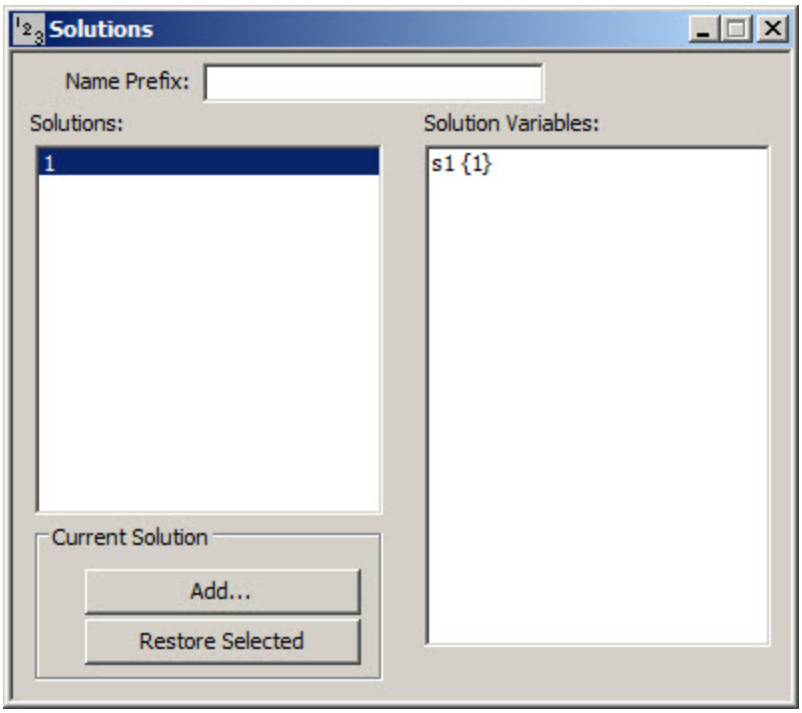
These are the values when *lambda* equals 100. The precision of all parameters is quite good.

d. Close all open windows and dialog boxes.

11. Restore the original solution, and refit the model to the data with *lambda* equal to 1000, and record the results.

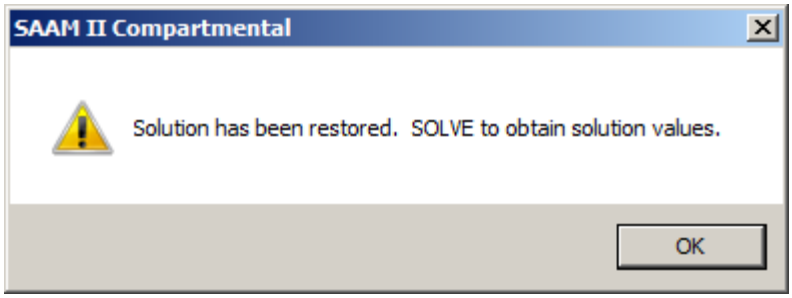
a. In the **Compute** menu, click **Solutions**. The **Solutions** dialog box will open.

b. Click "1" in the **Solutions** pane. The **Solutions** dialog box will appear as follows:



Notice **Restore Selected** is now available.

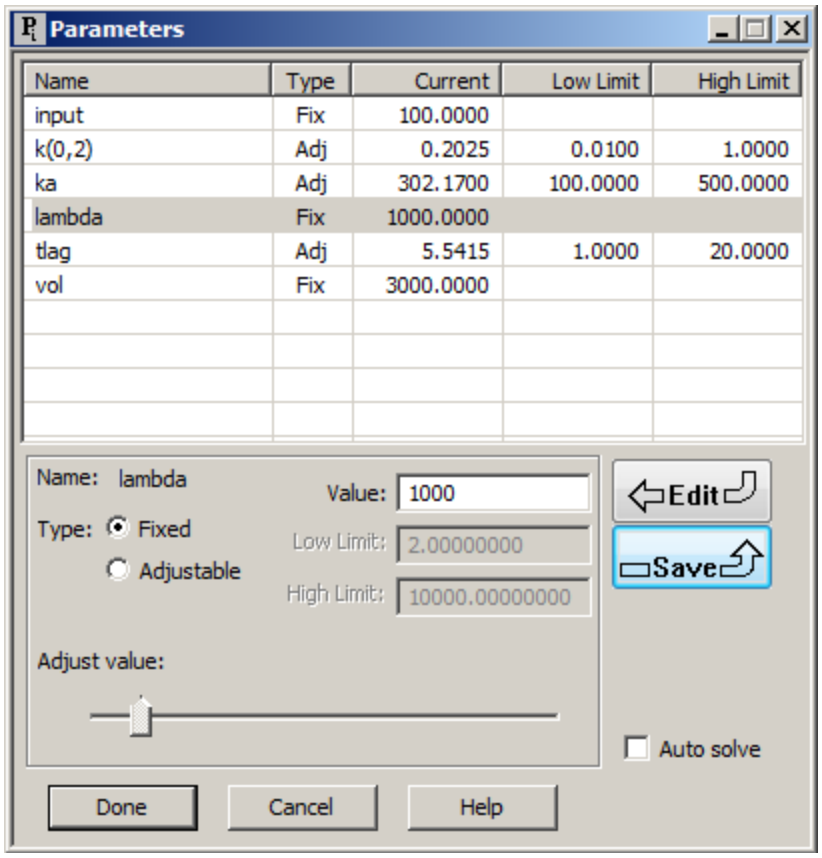
c. Click **Restore Selected**. The following message will appear:



d. Click **OK**, and close the **Solutions** dialog box.

e. Re-Solve the model. The original solution is now restored.

f. Change the value of *lambda* from 100 to 1000. The **Parameters** dialog box will appear as follows:



Close the **Parameters** dialog box.

g. Re-Fit the model to the data (you may have to click Fit twice), and record the results. The results should appear as follows:

lambda	1.00E+02	1.00E+03
k(0,2)	0.203(0.52)	0.202(0.51)
ka	302(0.90)	302(0.89)
tlag	5.54(1.2)	5.53(0.2)

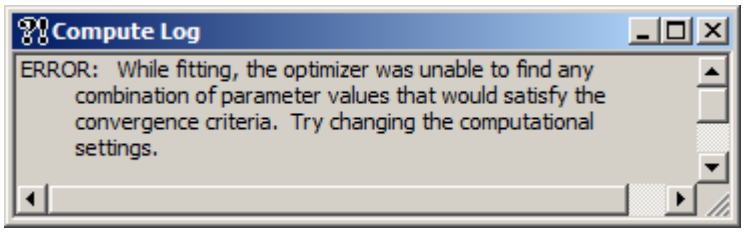
You can see there are some small differences in the values depending upon *lambda*. For the parameters, they are in the third digit. You can repeat the above setting *lambda* equal to 10000 if you wish. The results should be as follows:

lambda	1.00E+02	1.00E+03	1.00E+04
k(0,2)	0.203(0.52)	0.202(0.51)	0.202(0.51)
ka	302(0.90)	302(0.89)	302(0.89)
tlag	5.54(1.2)	5.53(0.2)	5.52(0.02)

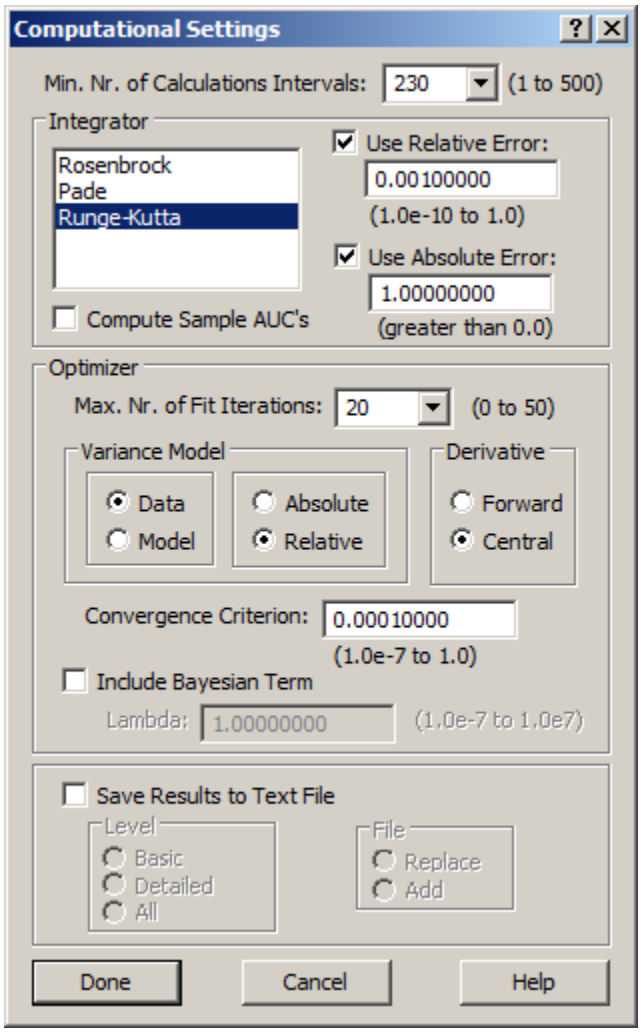
Now there are no differences in *k(0,2)* or *ka*; *tlag* is still fine-tuning slightly. If you wish, you can continue increasing *lambda* until there is no change in any of the parameters or their estimates; this should be the optimal value of *lambda* chosen. See below for more comments before increasing *lambda*.

h. Close all open windows and dialog boxes.

The last value of *lambda* was 1.0e+04. If you increase *lambda* to 1.0e+05, you will not be able to fit the model to the data. Instead, you will receive the following message:



When you are using the Heaviside function and this message appears, you need to change your computational settings. So far the default integrator and forward derivative methods have been used. You now need to ***try the Runge Kutta integrator and the central derivative method***. In the **Compute** menu, open the **Computational Settings** dialog box and make these changes. The **Computational Settings** dialog box will appear as follows:



Click **Done**. You will now be able to fit the model to the data with *lambda* equal to 1.0e+05. Changing *lambda* to 1.0e+06 will yield no changes in the parameters or their error estimates.

Thus for this problem, the above computational settings (i.e. Runge-Kutta integrator and the central derivative method) with *lambda* equal to 1.0e+05 is optimal.

Repeating all of the above calculations using Runge-Kutta integrator and the central derivative method yields the following:

lambda	1.00E+02	1.00E+03	1.00E+04	1.00E+05	1.00E+06
k(0,2)	0.203(0.52)	0.202(0.51)	0.202(0.51)	0.202(0.51)	0.202(0.51)
ka	302(0.90)	302(0.89)	302(0.89)	302(0.89)	302(0.89)
tlag	5.55(0.56)	5.55(0.18)	5.55(0.08)	5.55(0.01)	5.55(0.01)

Quit the **SAAM II Compartmental** application. You can save the study file if you wish. This study file is provided as **zero_order.stu** with the initial parameter values.

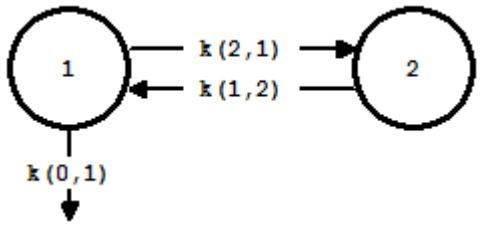
Part 3. Creating a pump to maintain plasma concentration.

There are several experimental protocols that use an infusion pump to maintain plasma concentration of a substance of interest at or near a specific level. The times at which the pump turns on or off are not known and need to be simulated. In this part, such a pump will be created and the results compared with a set of simulated data.

In this experiment, a pump capable of infusing at a rate of 100 mg/hr of drug is used. The experiment lasts for 24 hours. The desired concentration is maintained at approximately 0.06mg/ml.

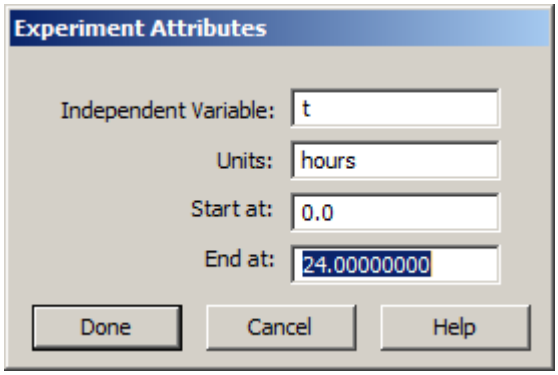
1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

2. Create the following system model:

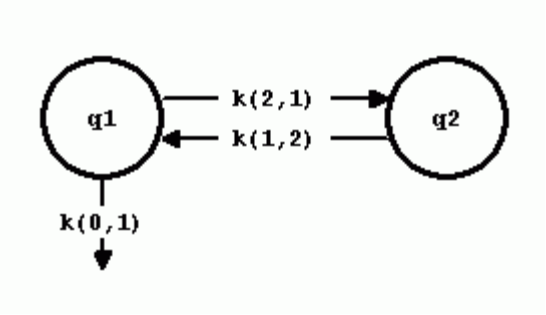


3. Create the experiment on the model.

   a. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open. Set the experimental attributes as follows:



   b. Click **Done**. The **Create Experiment** dialog box will open. Click **Create**. The model will appear as follows:

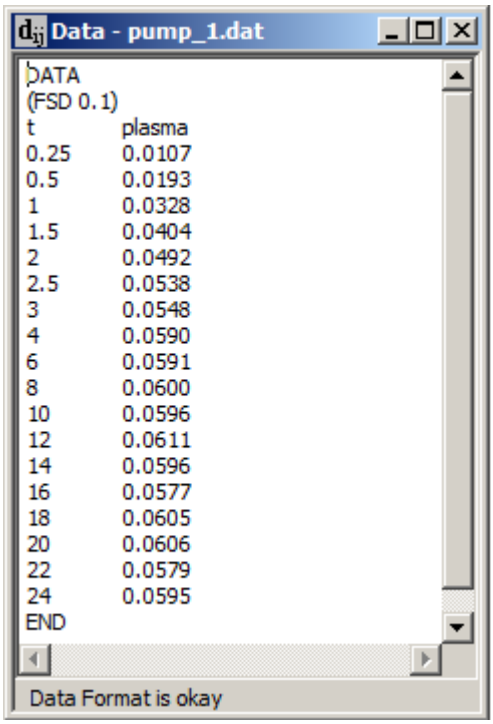


4. Add the data to the model.

   a. On the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data**  . The **Data** window will open.

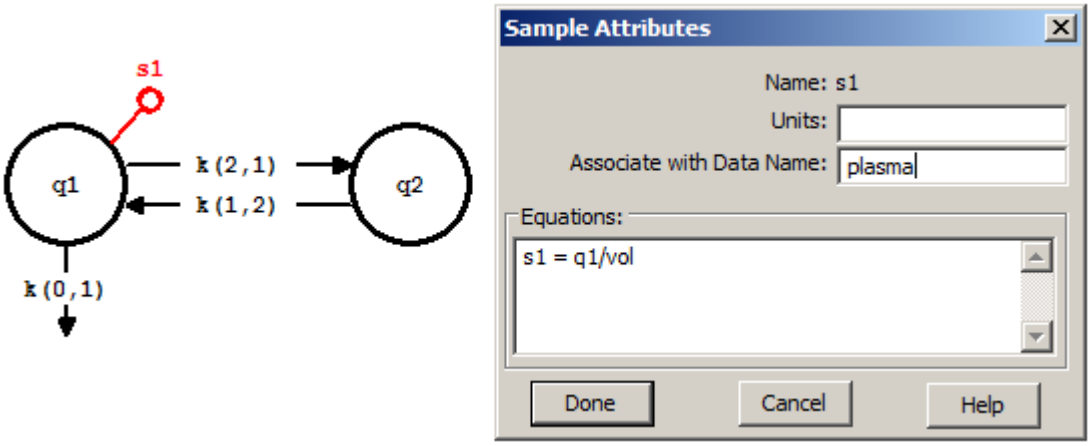
   b. On the **File** menu, click **Open**. The file **pump_1.dat** should appear in the list (if it does not, find the folder where you put this data file).

   c. Double-click **pump_1.dat**. The data in this file will appear in the **Data** window. The **Data** window should appear as follows:



   d. Close the **Data** window.

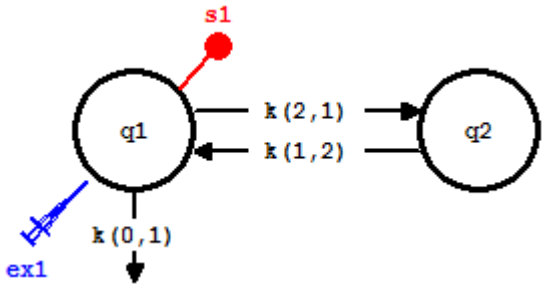
5. Create a sample on Compartment **q1**, associated with "plasma" and edit the sample equation to read "s1=q1/vol". The **Sample Attributes** dialog box should appear together with the model as follows:



Click **Done**. Notice that the circle at the top of the sample object is now filled as shown in the diagram below; this is because data are now associated with the sample.

6. Create an input into Compartment **q1**.

   a. Create the input into Compartment **q1**. The model should appear as follows:



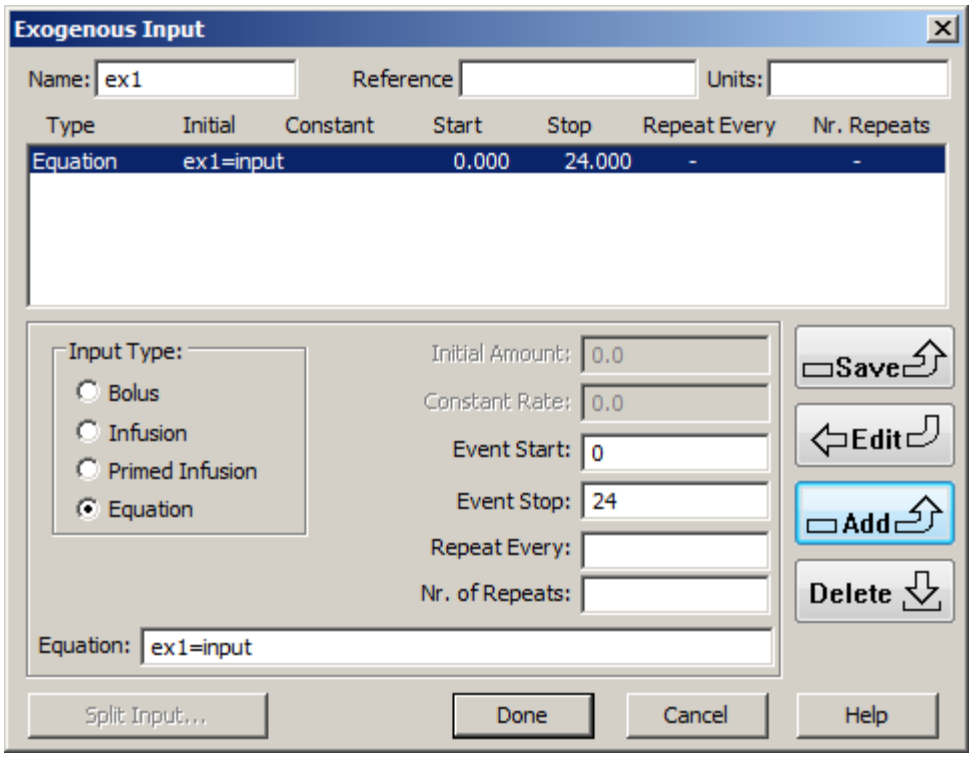
   b. Specify the input equation.

      (1) Double-click **ex1** to open the **Exogenous Input** dialog box.

      (2) Select **Equation** as the input type.

      (3) Set the **Start** equal to 0 and **Stop** time equal to 24.

      (4) Write the input equation "ex1 = input". Click **Add**. The **Exogenous Input** dialog box should appear as follows:



(4) Click **Done**.

Exogenous input. In this case, the input is defined by the equation "ex1 = input." The equation "input" will be defined using the Heaviside function which will be defined to turn on and off to maintain the plasma concentration of the drug at a specific level.

7. Create the input equation.

   The input equation "input" will be created using the Heaviside function, and will be defined to turn on or off depending upon whether **s1**, the plasma concentration, is below or above a certain set point, i.e. a concentration specified by the user. In this case, the set point concentration is 0.06 mg/ml.

   a. In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar,** click **Equations** Eq. The **Equations** dialog box will open.

   b. Create the conditional expression to define the switch. In the **Equations Defined Here** pane, type:

      "condition=0.06-s1"

"condition" will be positive when **s1** is less than 0.06, and will be negative when it is larger. This will be used as the switching mechanism in the Heaviside function.

c. Create the Heaviside function. In the **Equations Defined Here** pane, type

"heaviside=0.5*(1.0 + atan(lambda*condition)*2/3.141592653)"

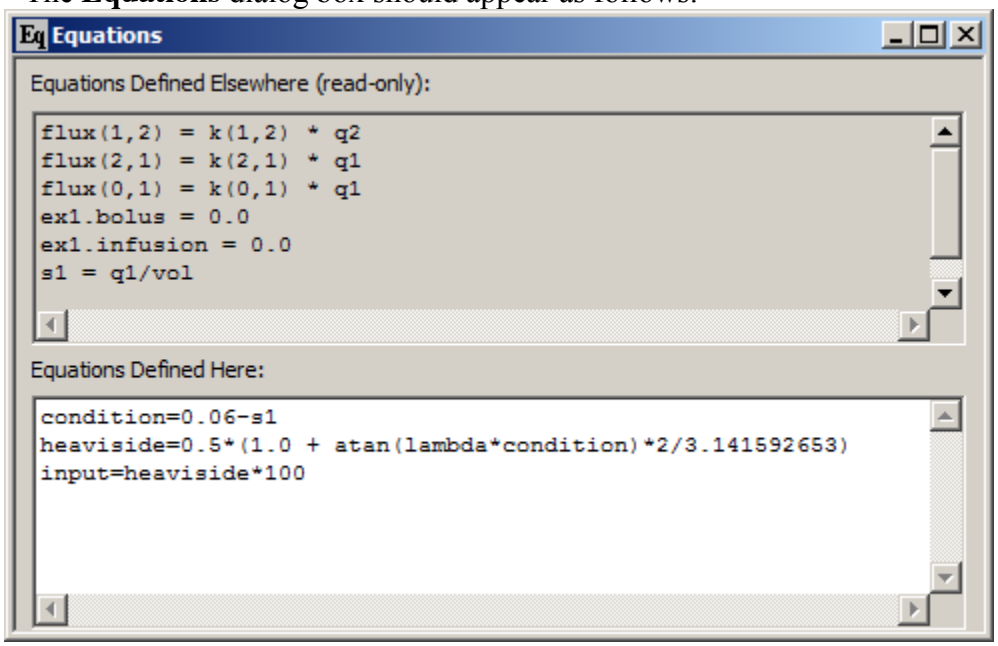
In this expression, when "condition" is negative, the value of the Heaviside function will be zero; otherwise it will equal 1. Values for **s1** will thus oscillate around 0.06.

d. Create the input equation. In the **Equations Defined Here** pane, type

"input=heaviside*100"

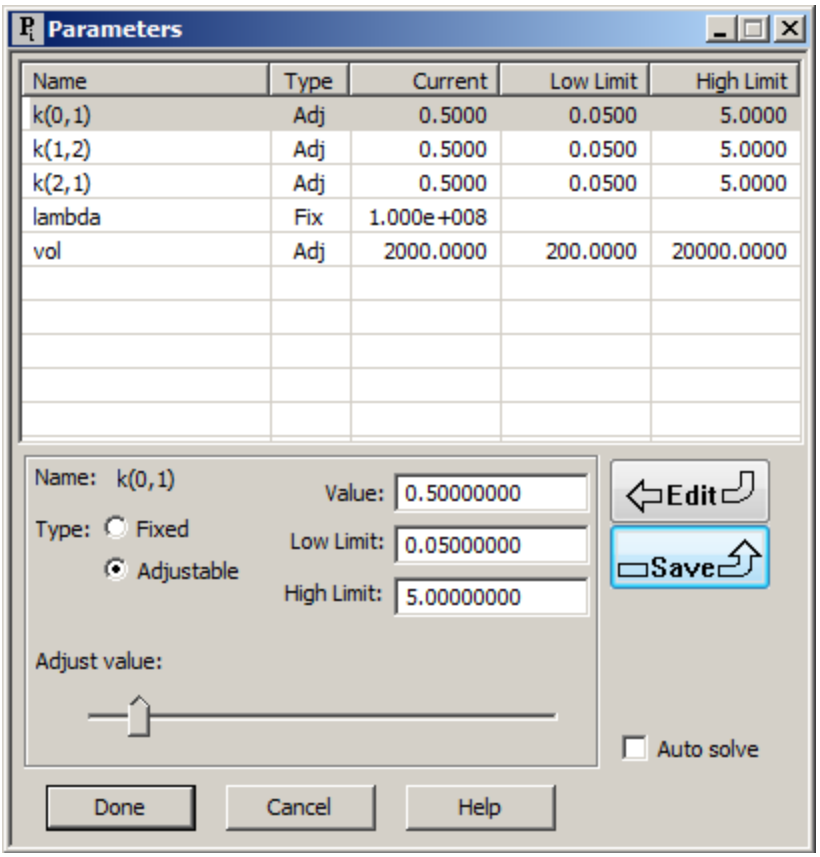
The infusion rate is 100mg/hr. When the value for the Heaviside function is 1, the infusion will be turned on; when it is zero, the infusion will be turned off.

The **Equations** dialog box should appear as follows:



e. Close the **Equations** dialog box.

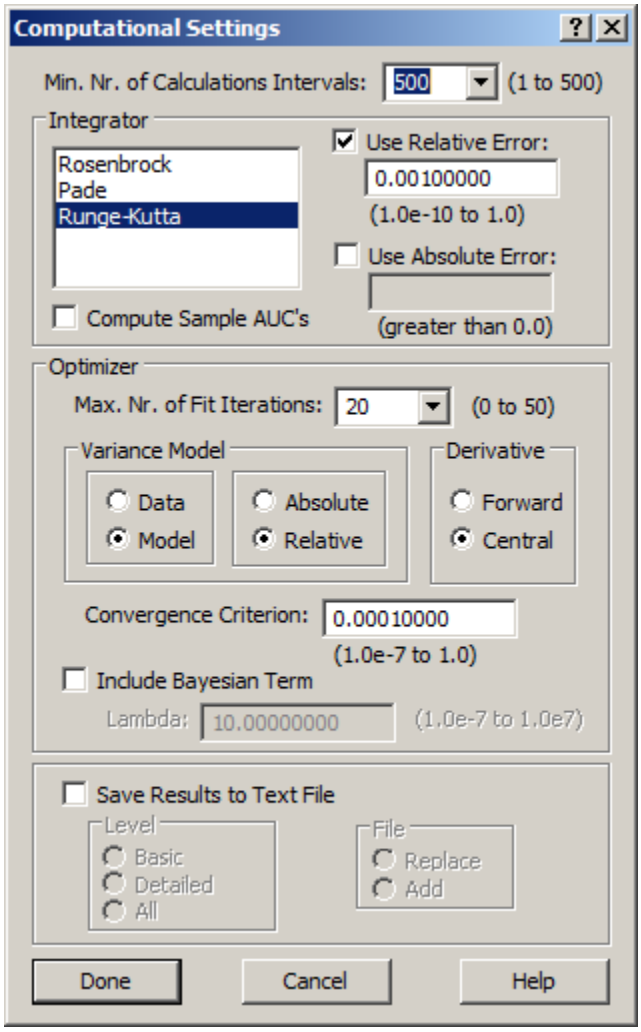
8. Enter the parameter values as shown below:



The parameters are those for the two-compartment model together with *lambda*, the "tuning" parameter for the Heaviside function. The initial value for *lambda* of 1.0e+08 was determined by initial tuning starting from 1.0e+06.

9. Solve the model and view the solution.

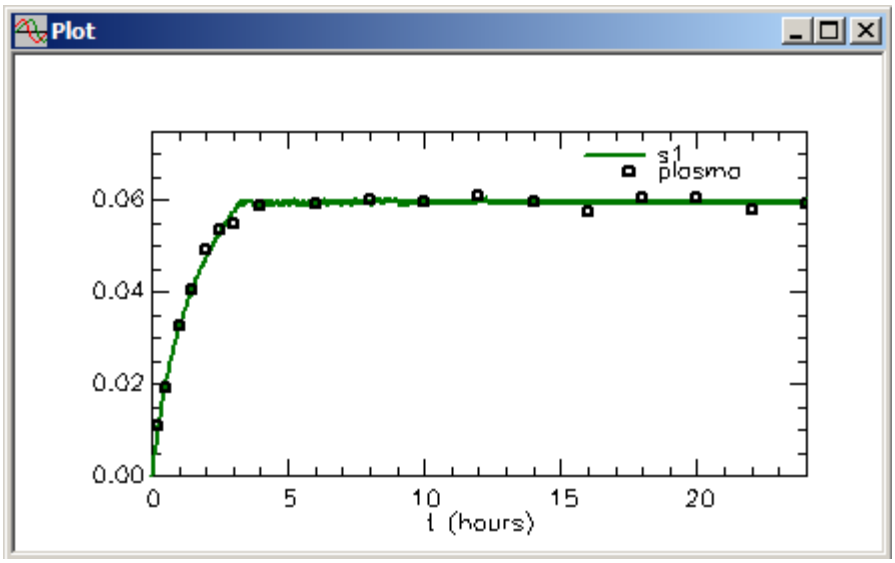
   a. Because the input will be turning off and on very rapidly, the Computational Settings are going to be changed as shown below:



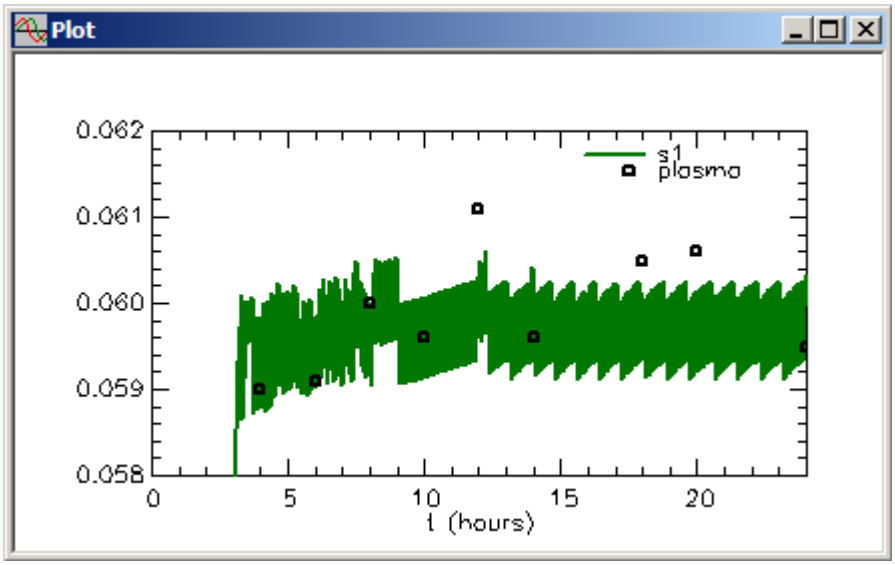
The **Min.Nr. of Calculation Intervals** is set to the maximum so you can visualize as much as possible the changes in the input function and **s1**. The integrator will be changed to the Runge-Kutta (you should compare results using the Rosenbrock if you are interested). The **Derivative** calculation is changed to **Central**.

When you have changed the settings, click **Done**.

b. Solve the model and view the solution. A plot of **s1** and **plasma** will appear as follows (the Y Axis maximum has been set equal to 0.075):

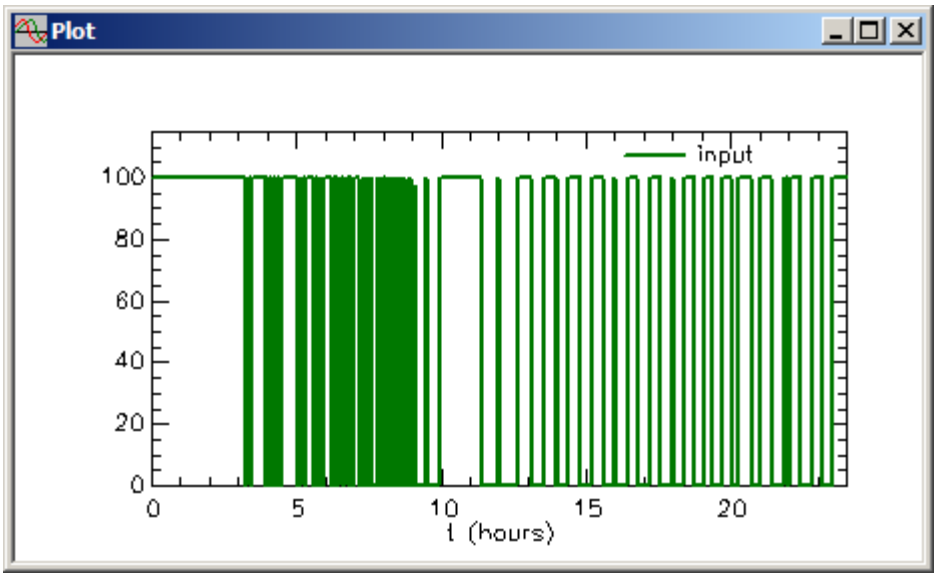


You can see the oscillations around 0.06. To visualize them better, change the **Plot/Table Scale** to a minimum and maximum respectively of 0.058 and 0.062. The plot will appear as follows:

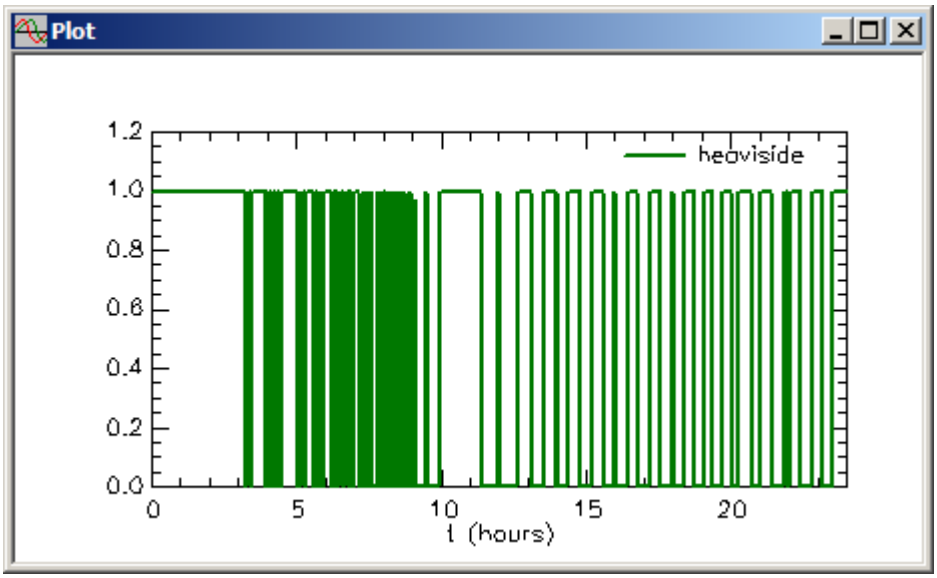


The rapidity of the oscillations indicates that you have to be very careful with the computational settings. You should try different options to be sure the same result is returned.

The plot of the input function "input" is shown below; again the rapidity of the input turning on and off is evident:



The calculation of the Heaviside function parallels that of the input function:



Notice the infusion is on until just after 3 hours when the concentration reaches the critical level for the infusion to turn off for the first time. Thereafter it turns off and on rapidly. The "gaps" after 3 hours are due to an insufficient number of calculation points for plotting purposes. You can tell from the plot of **s1** and **plasma** that the pump is still turning off and on.

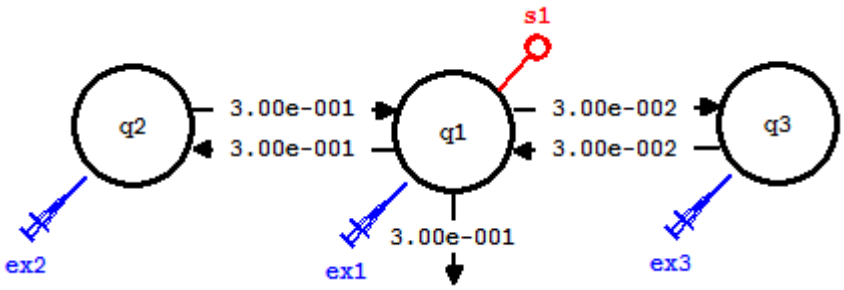
c. Close the **Plot** window and any remaining open dialog boxes.

The purpose of this part of the tutorial was to simulate a pump that is rapidly turning off and on. If you try to fit the model to the data, you will have problems with optimization because this example is not intended to illustrate fitting such pump models to data (there are insufficient data).

Quit the **SAAM II Compartmental** application. You can save the study file if you wish. This file is provided. **pump_1.stu** is the study file with the initial parameter values and computational settings.

The above example dealt with introducing material into the system for the first time. What about the situation where material is already in the system. For example, suppose you wished to infuse glucose to maintain glucose slightly above some basal level? The discussion below is based on the study file **pump_2.stu**. If you wish to follow the discussion, you can open **pump_2.stu** and click on **Experiment** in the **SAAM II Toolbox**.

The model of the experiment is shown in the figure below:



This is a typical 3-compartment model to explain glucose kinetics. The values of the rate constants, shown in the figure, are also typical.

Suppose you wanted to simulate a pump that elevates basal glucose concentration. Then you must first create the model of the experiment so that baseline conditions exist. This means you must specify masses in all compartments, and a rate of input that mirrors endogenous glucose production.

Suppose the baseline concentration is 100mg/ml and plasma volume is 3000ml. Then the mass in Compartment **1**, **Q1**, equals 300,000. Since *k(0,1)* equals 0.3, the loss flux is "k(0,1)*300000", or 90,000. To maintain a constant mass in Compartment **1**, therefore, you must specify a constant infusion of 90,000 during the experiment to simulate endogenous production.

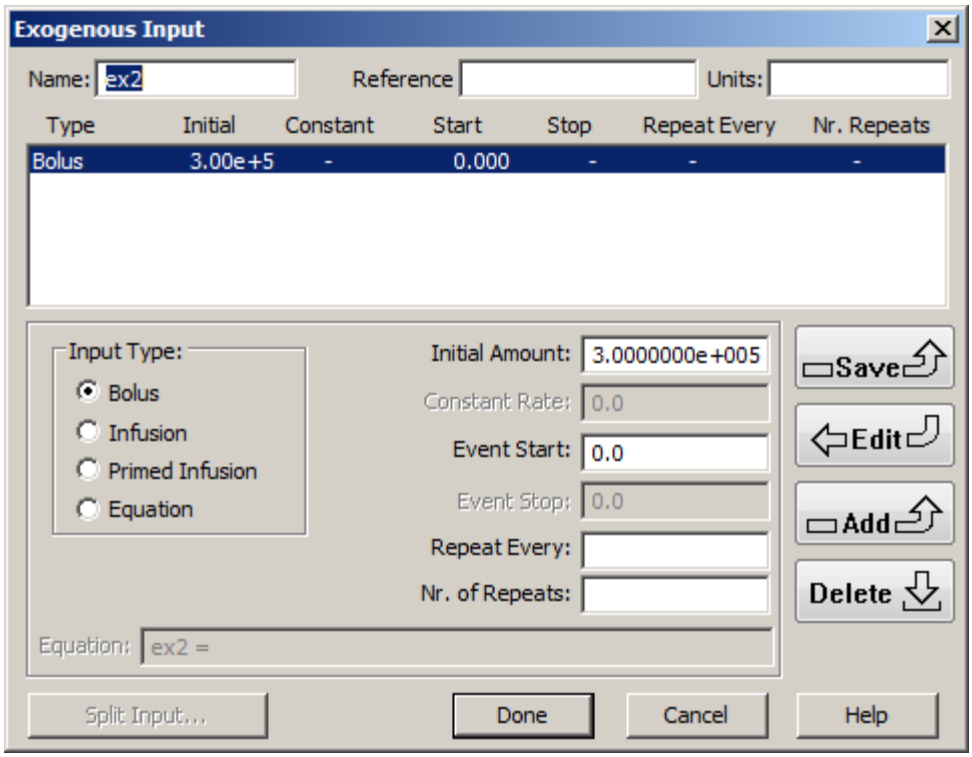
However there are masses to be described in Compartments **2** and **3**. Knowing the mass in Compartment **1**, these can easily be calculated since, for example,

$$k(2,1)*Q1 = k(1,2)*Q2$$

where **Q1** and **Q2** are respectively the masses in Compartments **1** and **2**. Since the corresponding exchange rate constants are equal, the mass in Compartments **2** and **3** are also equal to 300,000.

How is this information specified?

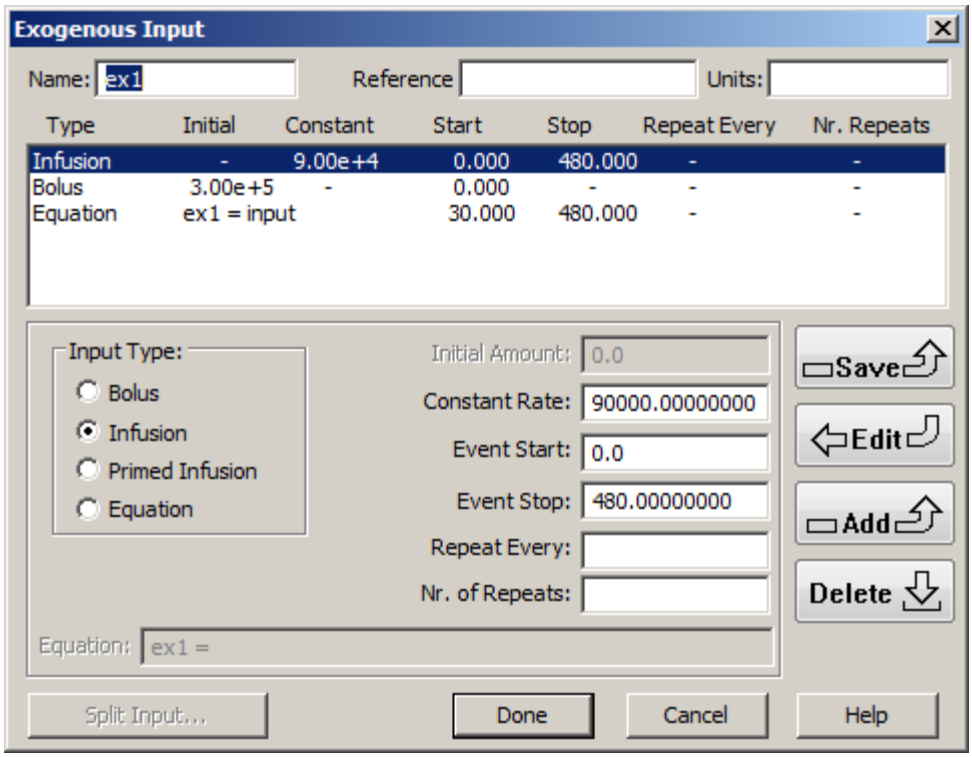
Double-click on **ex2** to open the **Exogenous Input** dialog box associated with Compartment **q2**. It will appear as follows:



Click **Done**.

The bolus injection of 300,000 will ensure the proper mass in Compartment **q2** at the start of the experiment. A parallel situation exists for Compartment **q3**.

Now double-click **ex1** to open the **Exogenous Input** dialog box associated with Compartment **q1**. It will appear as follows:

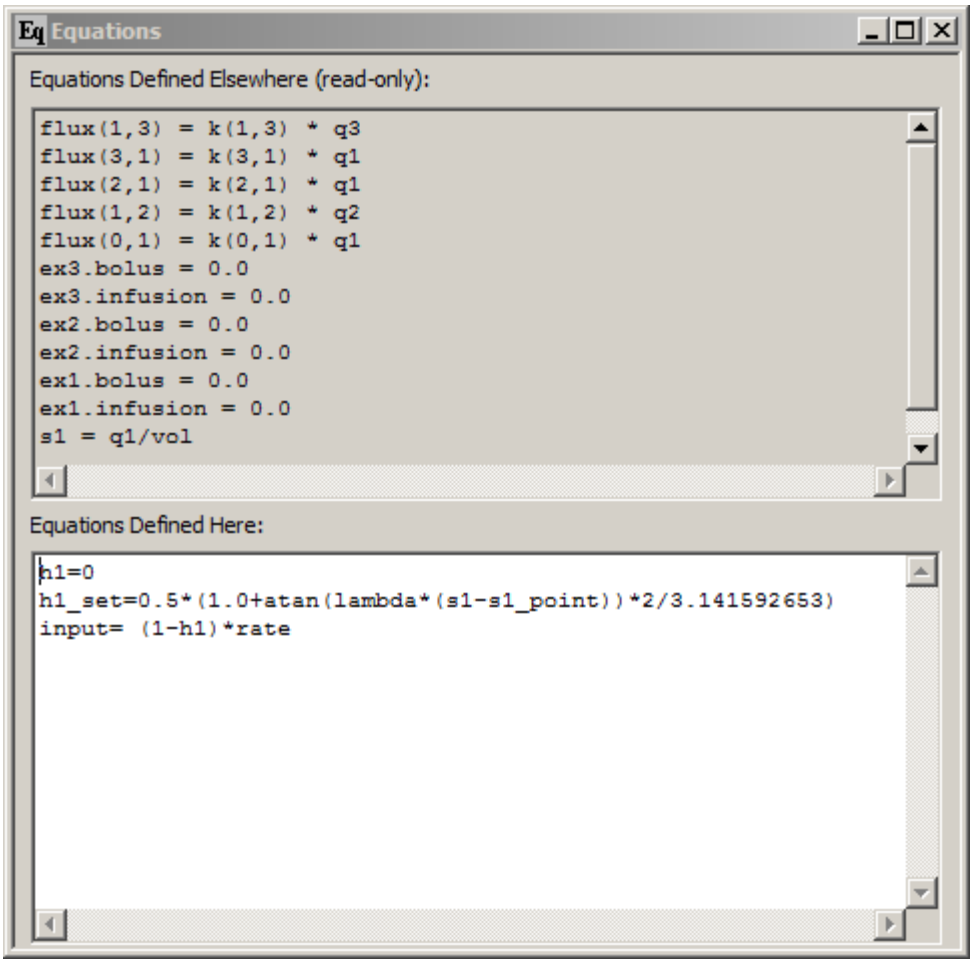


The first two inputs characterize the baseline state. Here the state variables (mass in the compartments) in the system, though dynamic in the sense that glucose is being metabolized, do not change. Input equals output. The bolus of 300,000 specifies the initial mass, and the infusion mimics endogenous glucose production.

The last equation input specifies the pump. The pump will start at 30 minutes. Thus for the first 30 minutes, the system will not change. With the pump turned on, the concentration in Compartment **q1** will rise to a new set point, and be maintained at that set point.

Click **Done**.

The pump input rate has been set in a manner similar to the previous tutorial. Open the **Equations** dialog box; it will appear as follows:



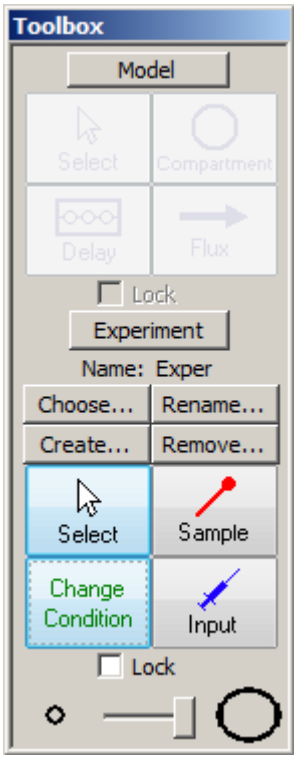
In the **Equations Defined Here** pane, the first two equations specify the Heaviside function. The function is zero (h1 = 0) up to the time the pump starts at 30 minutes. It then equals:

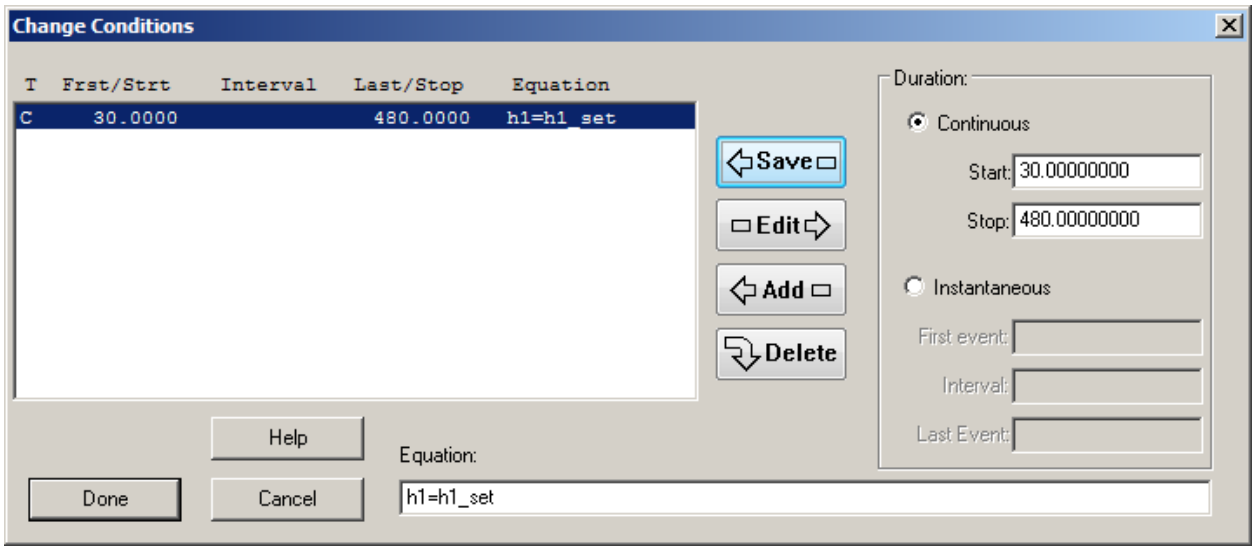
h1_set=0.5*(1.0+atan(lambda*(s1-s1_point))*2/3.141592653)

Thus *s1_point* will be specified in the **Parameters** dialog box as the new concentration to be maintained.

The last equation specifies the input rate. It will turn off and on according to the value of (1-h1). The magnitude, *rate*, will be a parameter specified in the **Parameters** dialog box.

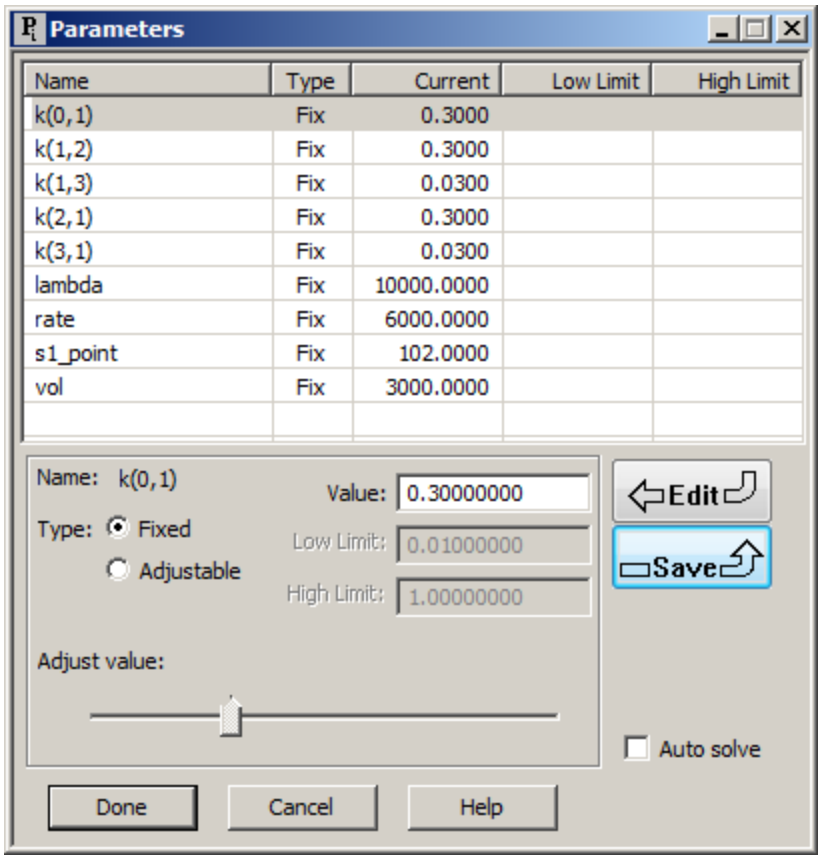
Close the **Equations** dialog box. Changing the value of h1 from zero to h1_set is done using **Change Conditions**. In the **SAAM II Toolbox**, click **Change Conditions**. The **Change Conditions** dialog box will open as follows:



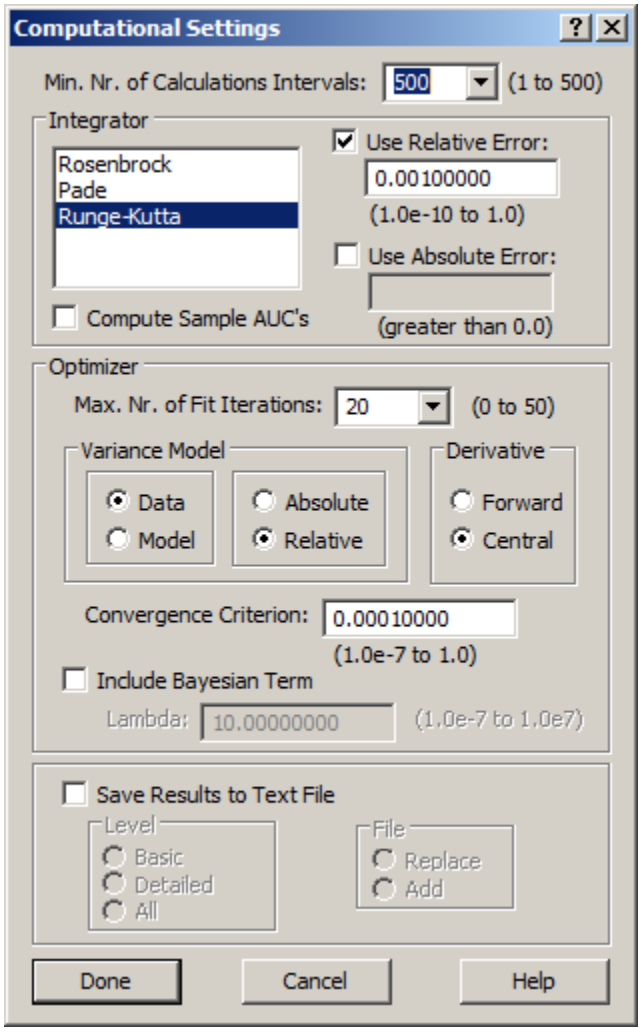


In the **Equations** dialog box, h1 was initially set equal to zero; here it changes to h1_set at 30 minutes and maintains this value for the duration of the experiment. Click **Done**.

Open the **Parameters** dialog box; it will appear as follows:

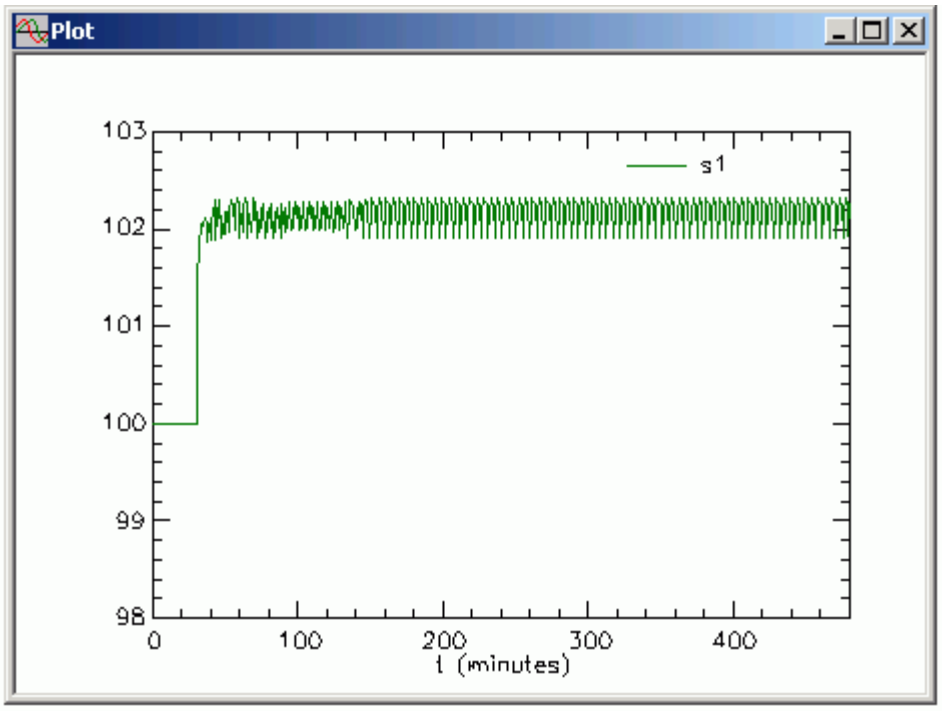


Since this exercise is a simulation, all parameters are fixed. Notice the value for *s1_point* is 102 meaning the pump will only slightly elevate the baseline concentration. Click **Done** to close the **Parameters** dialog box, and open the **Computational Settings** dialog box. It will appear as follows:

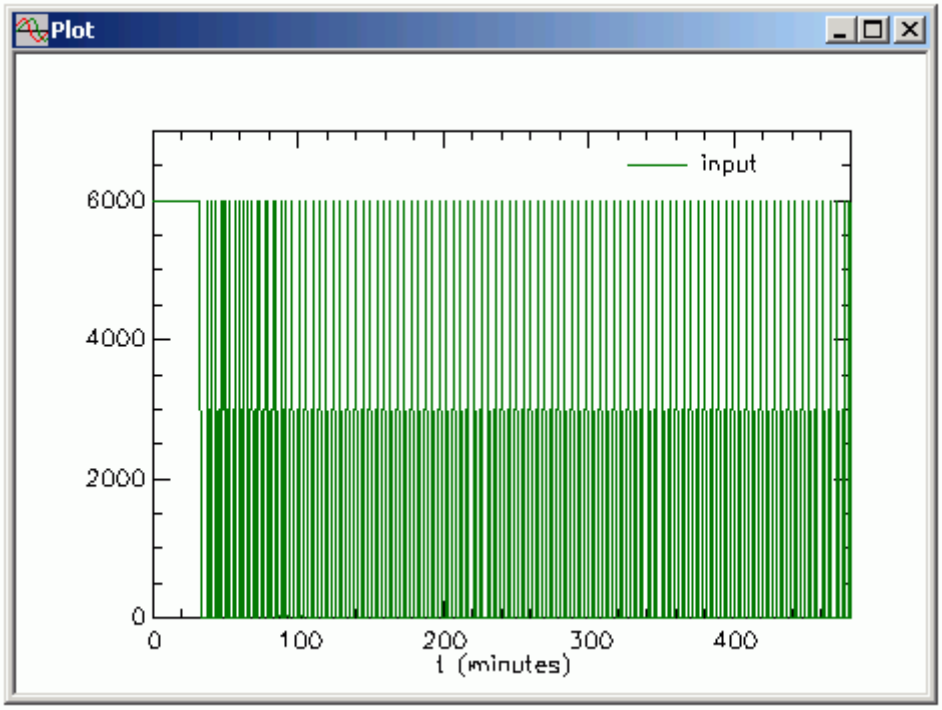


The **Minimum Number of Calculation Intervals** is set to its maximum value of 500. The integrator is the Runge-Kutta, and the derivative calculations are done using the Central mechanism. Click **Done**.

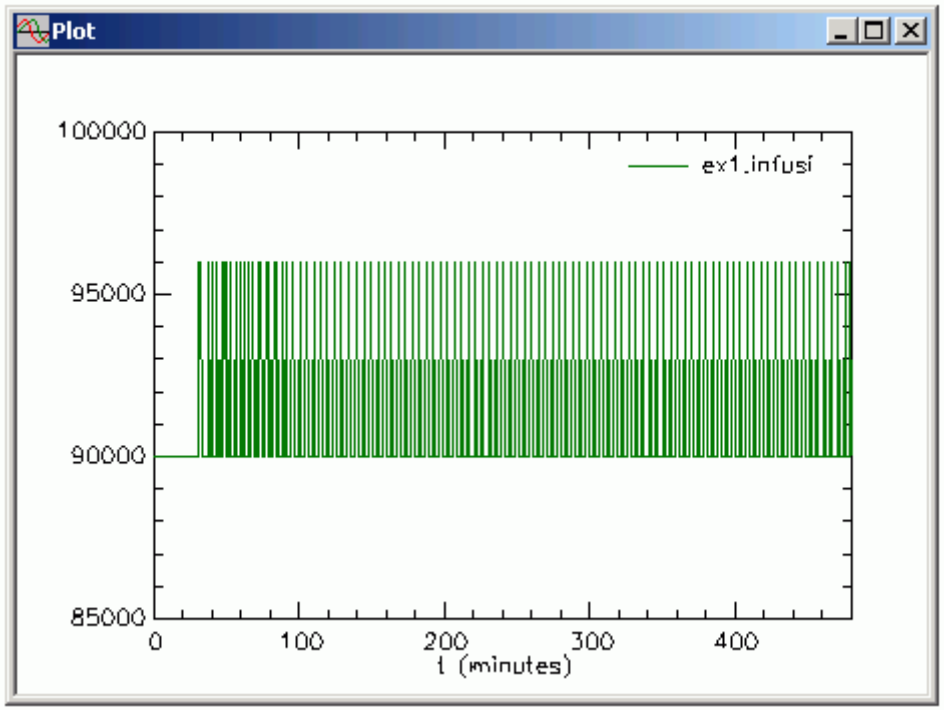
Solve the model and view the solution. A plot of **s1** (with the minimum and maximum values respectively set at 98 and 103) will appear in linear mode as follows:



You can clearly see that the basal state is maintained for the first 30 minutes after which the pump takes over. You can also see the switching mechanism maintains the new concentration very close to the desired 102. The input function will appear as follows:



Notice that input has a value during the first 30 minutes equal to 6000 (*rate*). However, input is not "seen" until 30 minutes as specified in the **Exogenous Input** dialog box. You can see this by plotting **ex1.infusion**, the infusion rate specified:



This is the actual infusion rate into Compartment **q1**. It equals the baseline up to time 30 after which time "input" is added to this baseline rate.

This study file is worth experimenting with to understand the behavior of such pumps. The parameters to change, and to see how these changes affect the solution, are *s1_point* and *rate*. Depending upon the magnitude of the changes, you may have to adjust *lambda*. You may also have to change some computational settings the most likely of which is value of the integrator relative error (you may need to reduce it).

Experimenting with this study file will give you a much better feeling to the strengths and limitations of trying to simulate pumps such as this.

Quit the **SAAM II Compartmental** application. Do not save any changes you made to **pump_2.stu**

SAAM II Version 2.1
Advanced Tutorials

Working with Change Conditions

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Working with Change Conditions

Prerequisites

The prerequisite for this tutorial is having worked through the SAAM II introductory tutorial, "Getting Started with **SAAM II Compartmental**."

What you will learn in this tutorial

The purpose of this tutorial is to show you how to use Change Conditions in SAAM II. You will learn

- How to create continuous changes in your model (Part 1)
- How to create instantaneous changes at different times in your model (Part 2)
- How to create instantaneous changes at an equal time interval in your model (Part 3)

Files Required

Study Files: The study files for this tutorial are

cc_cont.stu
cc_instInulin.stu
cc_instLDL

Data Files: The data files for this tutorial are:

cc.cont.dat
cc.instInulin.dat
cc.instLD.dat

These files are included as part of this tutorial.

Introduction

This tutorial will show you how to use Change Conditions, a tool in the **SAAM II Toolbox**. Change conditions allow you to describe experimental perturbations in your model. There are two kinds of perturbations – continuous and instantaneous.

An example of a continuous perturbation would be an experiment in which at some known time, something was done that altered the characteristics of the data. You might want to account for this by changing the value of one or more of your model parameters. The start would begin at some known time, and continue until the experiment ended, or another experimental perturbation occurred.

An example of an instantaneous perturbation would be urine collections. In the urine collection, the container holding the urine would be emptied at the time specified, and the collection for the next period would begin. You can model this by including a compartment for individual urine samples, and "emptying" it at the end of the collection period.

Two examples are presented. Inulin kinetics is a simpler model because inulin is represented by a single plasma compartment. The collections times, however, do not always coincide with a plasma measurement. LDL kinetics is a more complex model because plasma LDL exists in two plasma compartments. The collection times, however, are at 24 (daily) intervals.

Operationally when SAAM II detects a Change Condition, integration (simulation) will stop. The change or changes specified will be made, and integration (simulation) or optimization (fitting) will start again.

Part 1. A continuous Change Condition

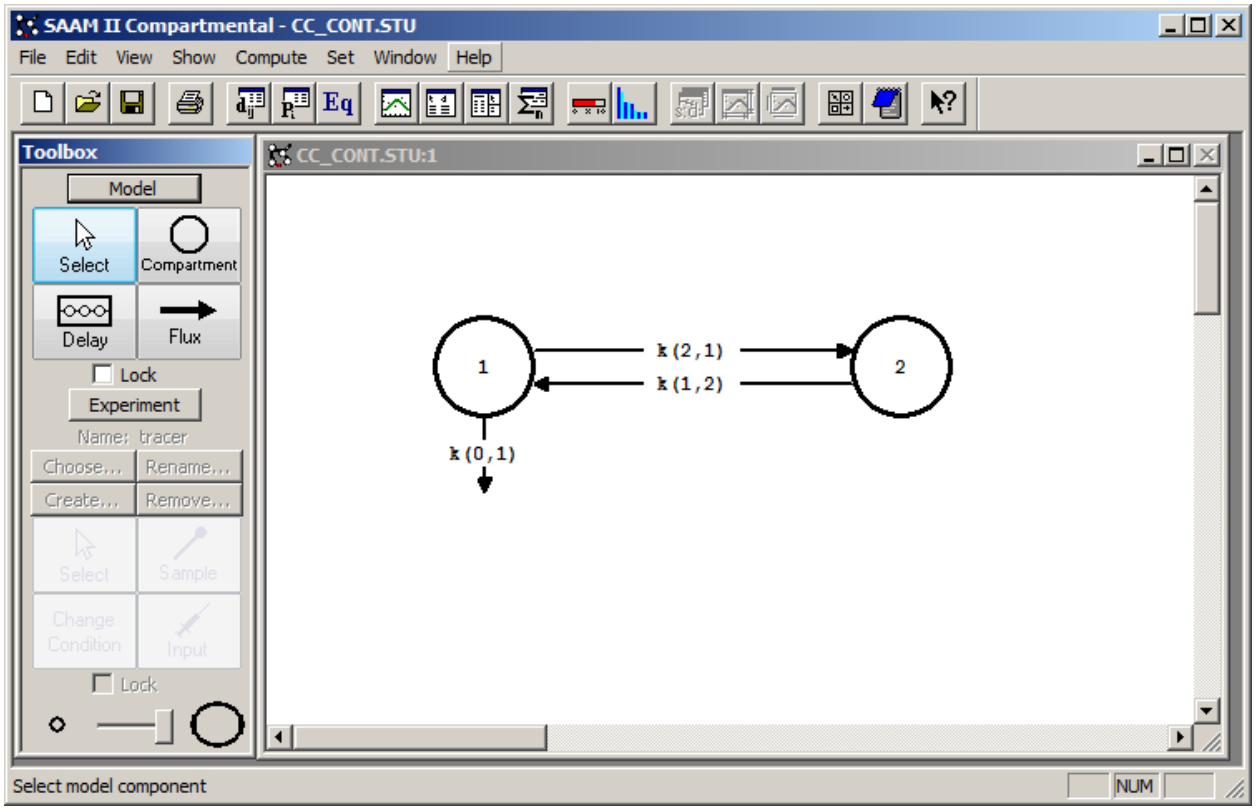
The following study investigated the effect of total parenteral nutrition (TPN) on the kinetics of low density lipoprotein (LDL) metabolism. Radioiodinated LDL was injected at time zero, and on day 9, TPN was commenced. The experiment lasted 19 days. The question asked was the following: Which of the model parameters change as a result of the TPN?

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

2. Open the **SAAM II Compartmental** study file **cc_cont**.

   a. The file **cc_cont.stu** should appear in the file list; if it does not, find the folder where you put this file.

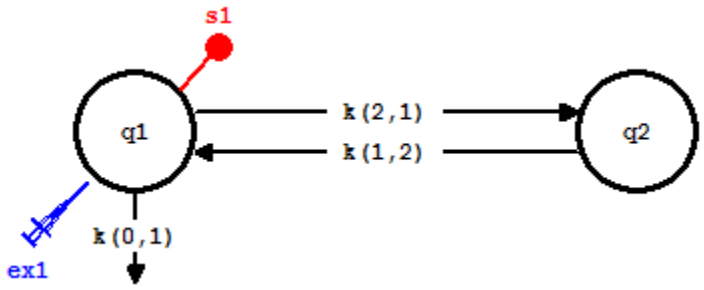
   b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as shown below:



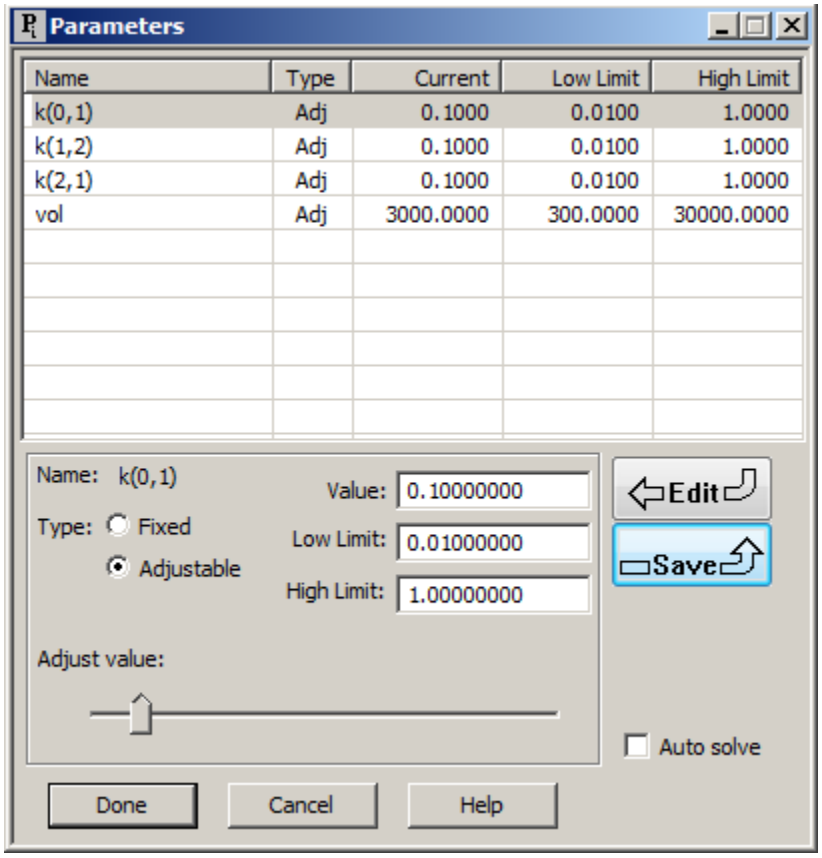
You may recognize this as the model used for **study_0**, the study file supplied with SAAM II. This is in fact the case. The data used for **study_0** are the first 9 days of the data used in this part of the tutorial.

3. View the model and the experiment on the model, and the parameters.

a. In the **SAAM II Toolbox**, click **Experiment**. The model of the experiment will appear on the **Drawing Canvas** as follows:



b. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters**  . The **Parameters** dialog box will open, as shown below:



These are the parameters for **study_0**. The question posed in this part of the tutorial is which of these parameters change following TPN starting on day 9.

c. Close the **Parameters** dialog box.

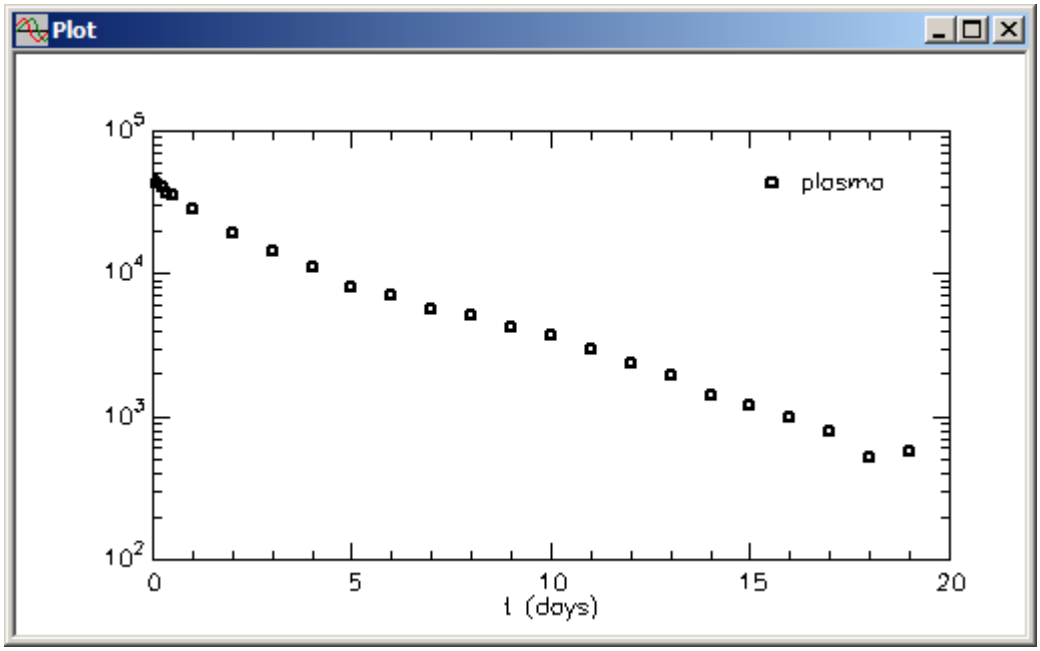
4. View the plasma data.

   An important part of deciding how to deal with a continuous change is to look at the raw data to see if a change is obvious.

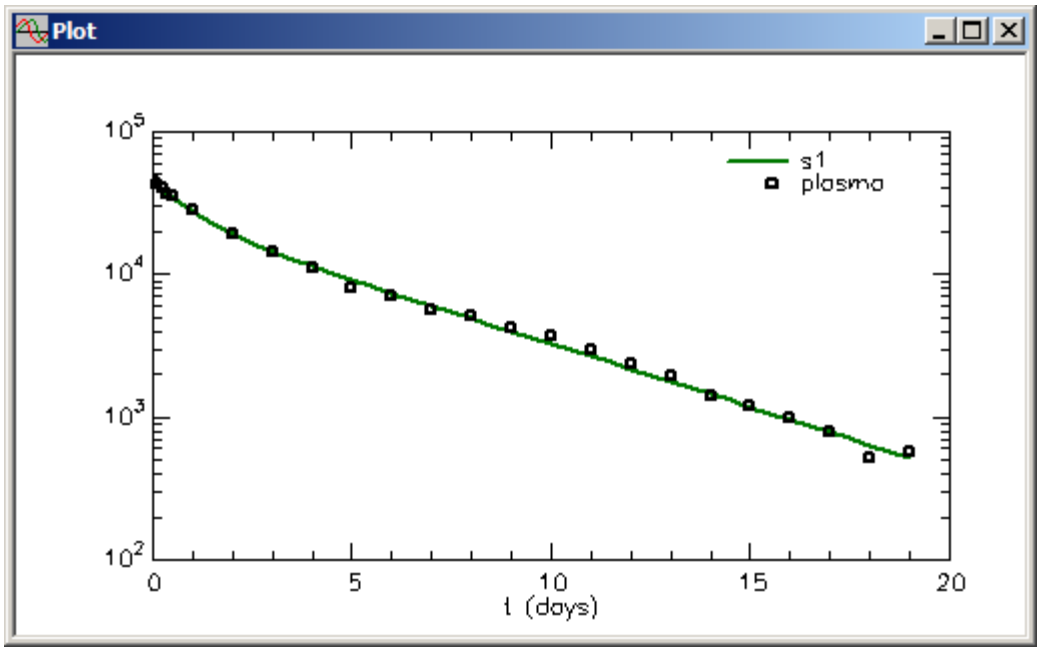
   a. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot**  . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is selected.

   b. Click **plasma** to move this to the **Current Selection** pane.

   c. Click **Done**. The plot of the plasma data will appear in semilog for as follows:



   You can see there appears to be a break in the curve at day 9. You can actually solve the model, and see how the model predicts the data. Fit the model to the data, and change the **Plot/Table Variables** to **s1:plasma**. You will obtain the following plot which only further supports a change at day 9:



d. Close the **Plot** window.

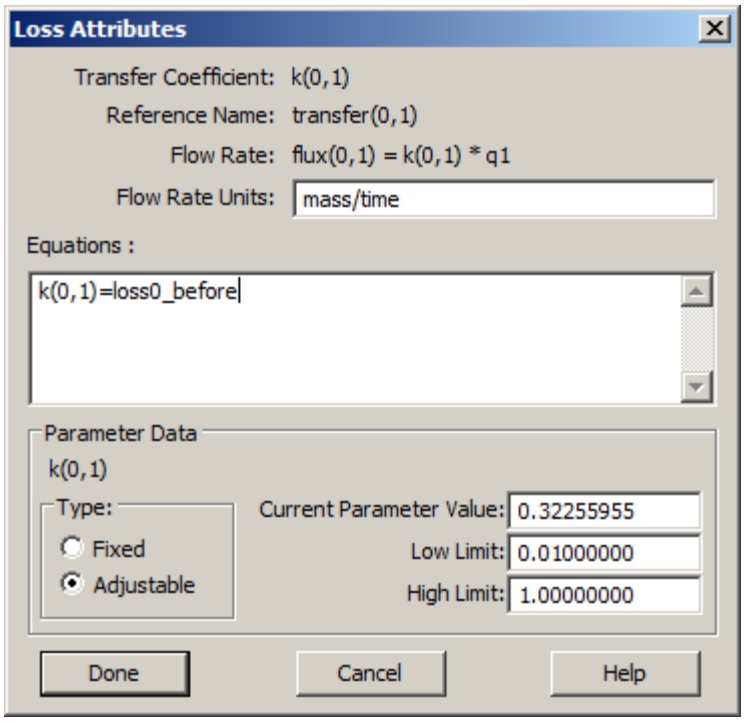
5. Change the value of *k(2,1)* and *k(0,1)* from day 9 to 19.

   It is hypothesized that these two parameters change following TPN. Such a change will be done using continuous Change Conditions.

   You must first provide values for these parameters up to day 9, and then provide values following TPN on day 9. This will be done as described below.

   a. Double-click *k(0,1)* to open the **Loss Attributes** dialog box.

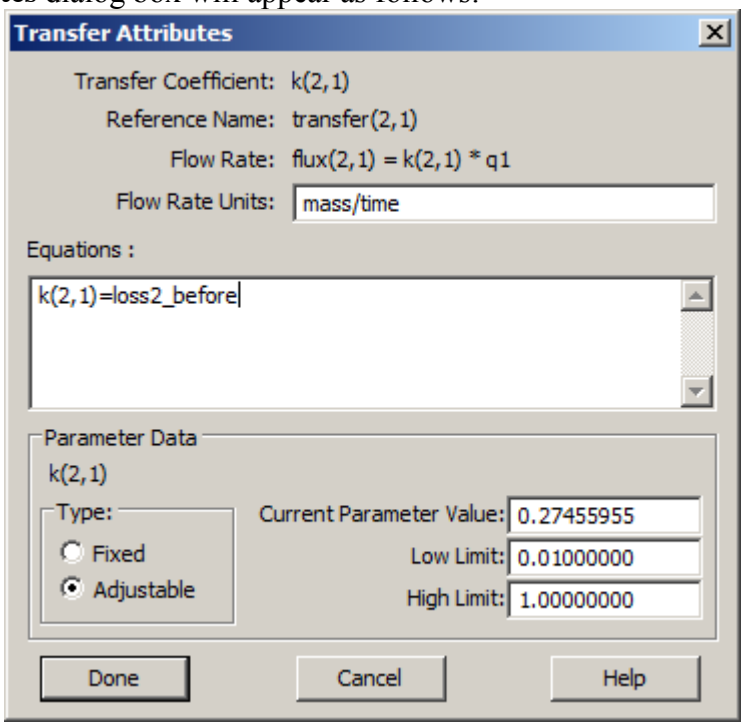
   b. In the **Equations** box, type the equation "k(0,1)=loss0_before". The **Loss Attributes** dialog box will appear as follows:



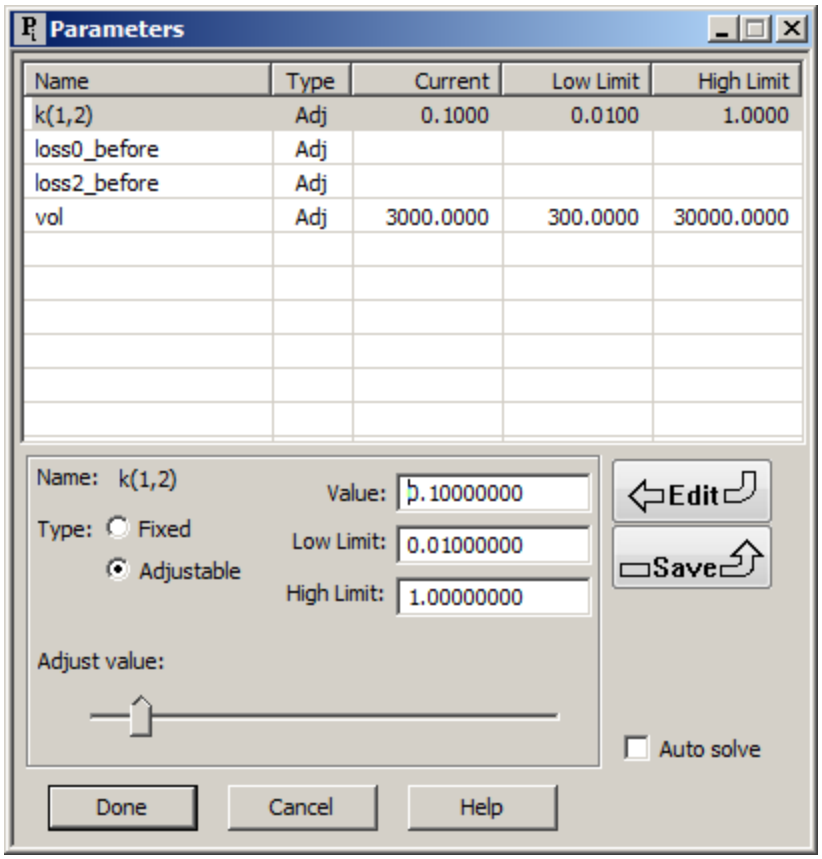
c. Click **Done**. The parameter *k(0,1)* is now defined by the equation, and *loss0_before* will appear as a parameter in the **Parameters** dialog box.

d. Double-click *k(2,1)* to open the **Transfer Attributes** dialog box.

e. In the **Equations** box, type the equation "k(2,1)=loss2_before". The **Transfer Attributes** dialog box will appear as follows:

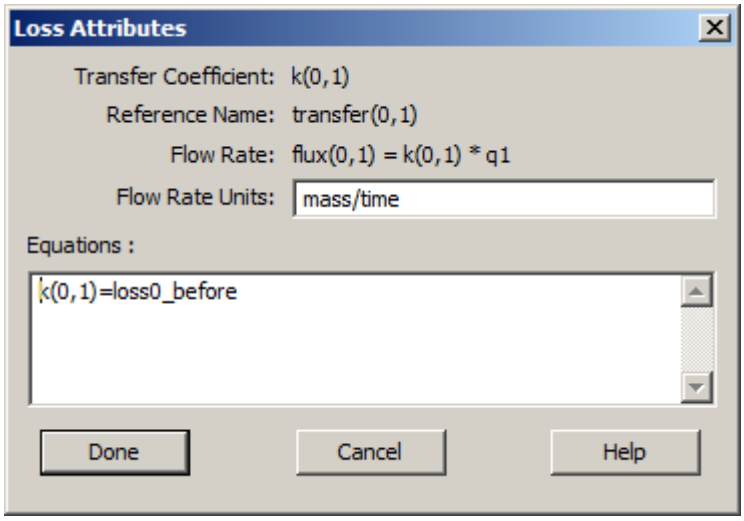


f. Click **Done**. The parameter *k(2,1)* is now defined by the equation, and *loss2_before* will appear as a parameter in the **Parameters** dialog box. If you open the **Parameters** dialog box, it will appear as follows:

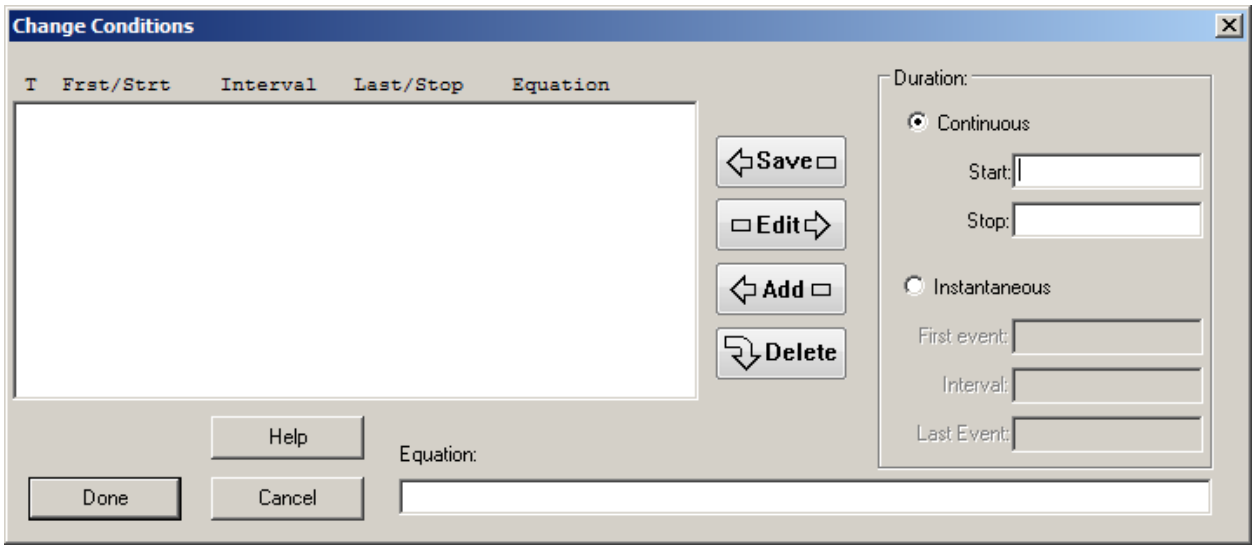


Close the **Parameters** dialog box.

Transfer and Loss Attributes dialog boxes. When you open either of these boxes, they will appear as shown above. However, once you define a parameter by an equation, the lower pane will not appear if you open them again. For example, if you double-click *k(0,1)* to open the **Loss Attributes** dialog box, it will appear as follows:



g. In the **SAAM II Toolbox**, click **Change Condition**. The **Change Conditions** dialog box will open as follows:



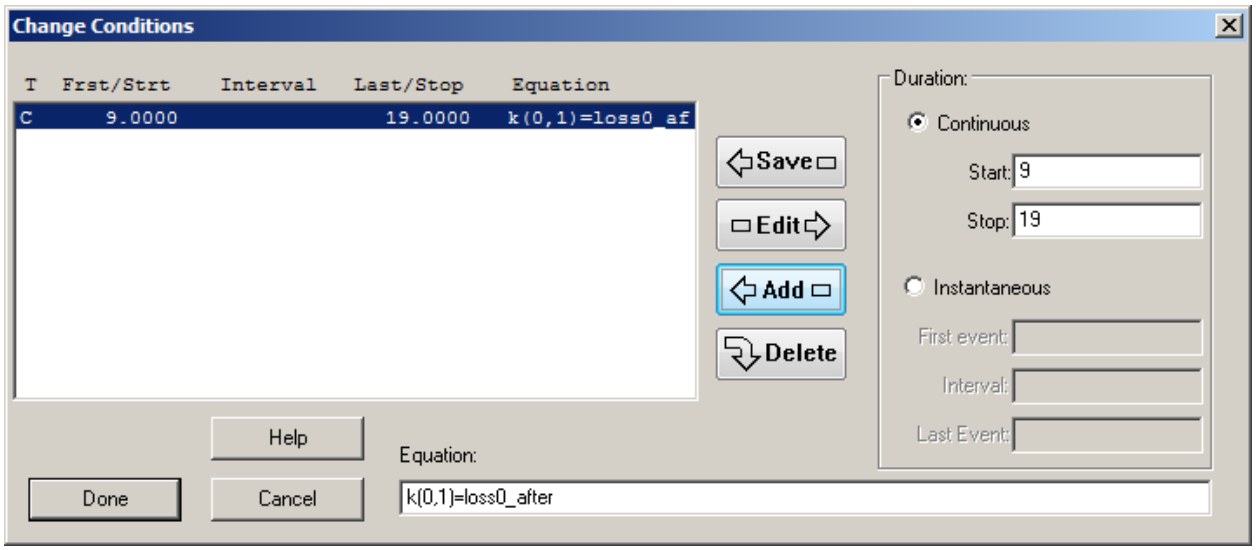
Change Conditions dialog box. The **Change Conditions** dialog box contains the **Duration** pane where you set the Change Condition to be **Continuous** (default) or **Instantaneous**. You set the **Start** and **Stop** times in the boxes below this pane. If the Change Condition is **Instantaneous**, the **First event**, **Interval**, and **Last Event** boxes will be active. You define the change in the **Equation** box.

h. In the **Start** box, type "9".

i. In the **Stop** box, type "19".

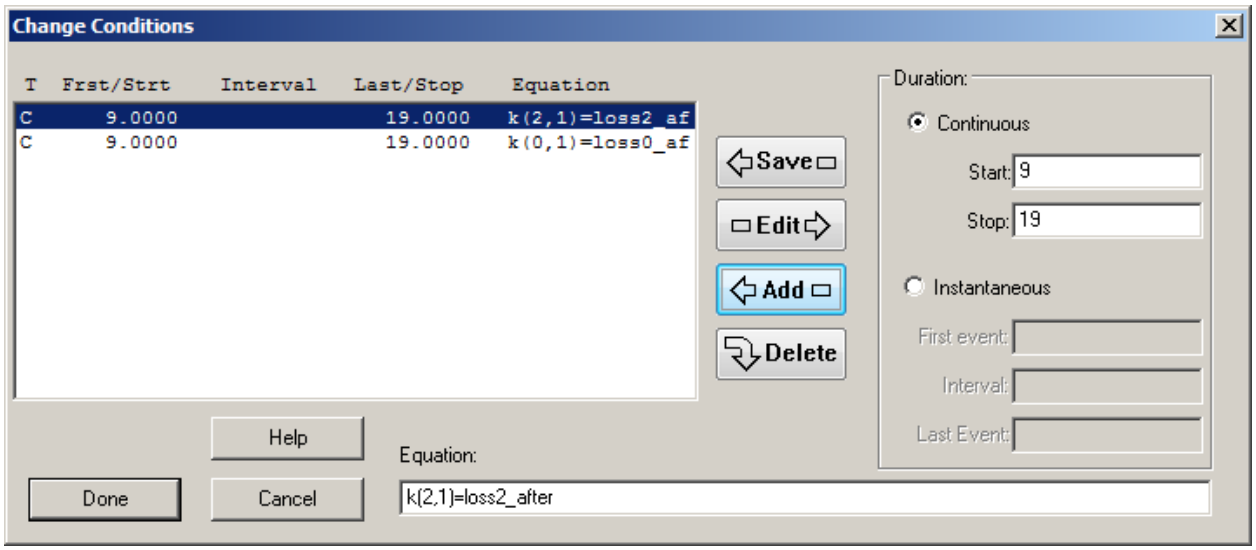
j. In the **Equation** box, type "k(0,1)=loss0_after"

k. Click **Add**. The **Change Conditions** dialog box will appear as follows:



l. Edit the equation to read "k(2,1)=loss2_after"

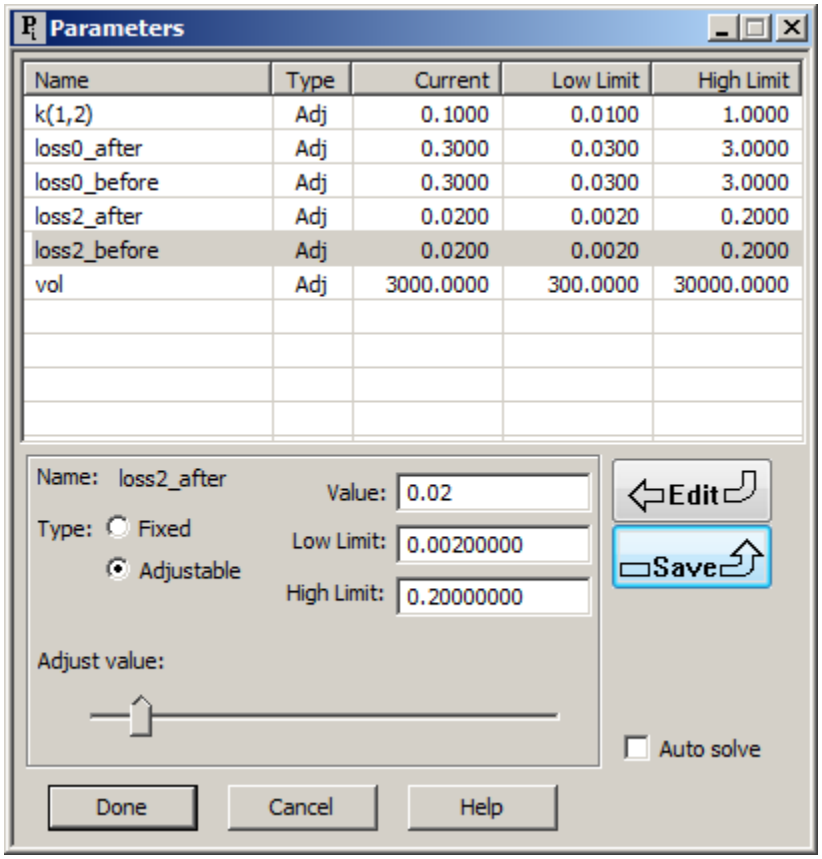
m. Click **Add**. The **Change Conditions** dialog box will appear as follows:



n. Click **Done**.

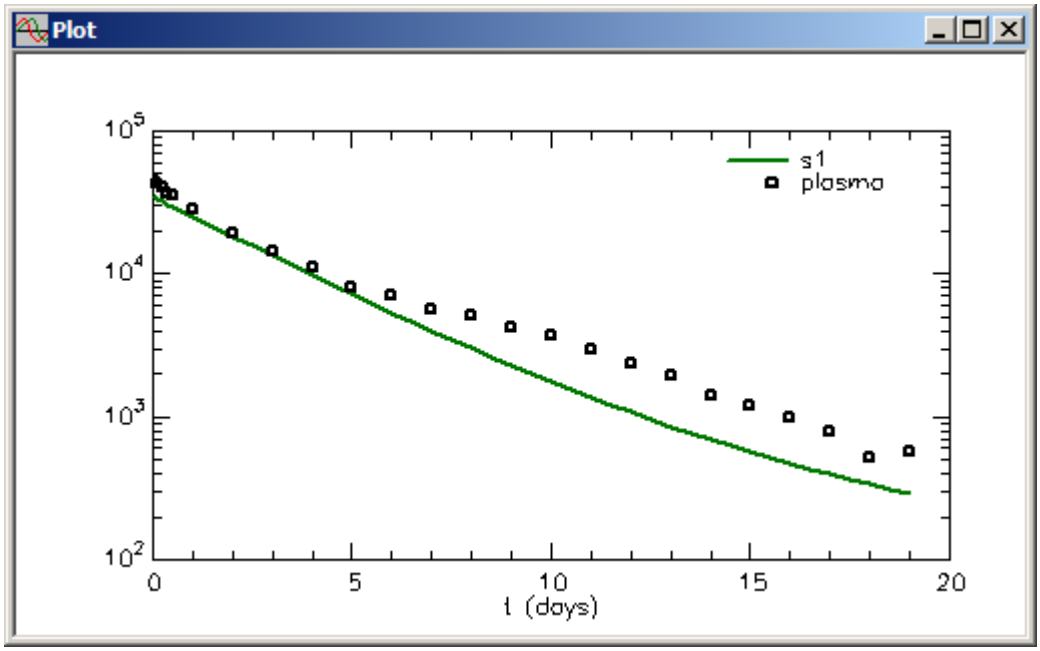
Using Change Conditions. While the above shows you how to change the value of one or more parameters, there are assumptions that must be made about the particular system being studied. In this case, the data are being analyzed using a constant coefficient model. The values of the two parameters *k(0,1)* and *k(2,1)* change instantaneously at day 9, and remain at the new value throughout the rest of the experiment. Is this realistic? That is, will the parameter values change that quickly? The assumption here is that, relative to the daily sampling, the change does occur that fast.

6. Add parameter values to the model as shown in the **Parameters** dialog box below:

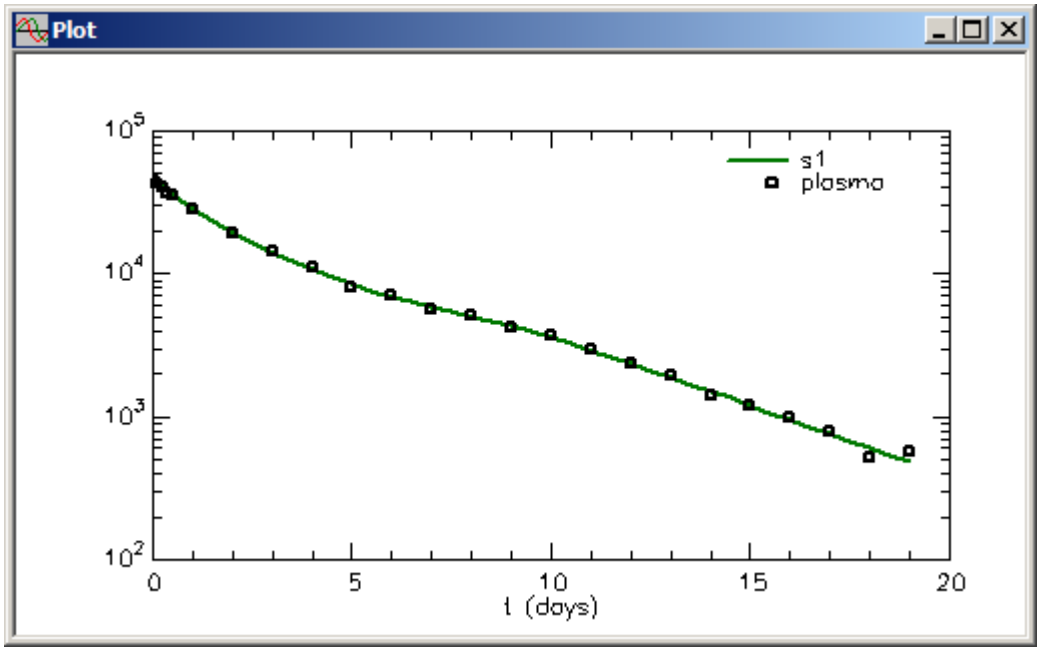


Notice the presence now of the values for the loss0 (*k(0,1)*) and loss2 (*k(2,1)*) before and after the perturbation. All values are the same; they will change when you fit the model to the data.

7. Solve the model and view the solution. The **Plot** window will appear as follows:

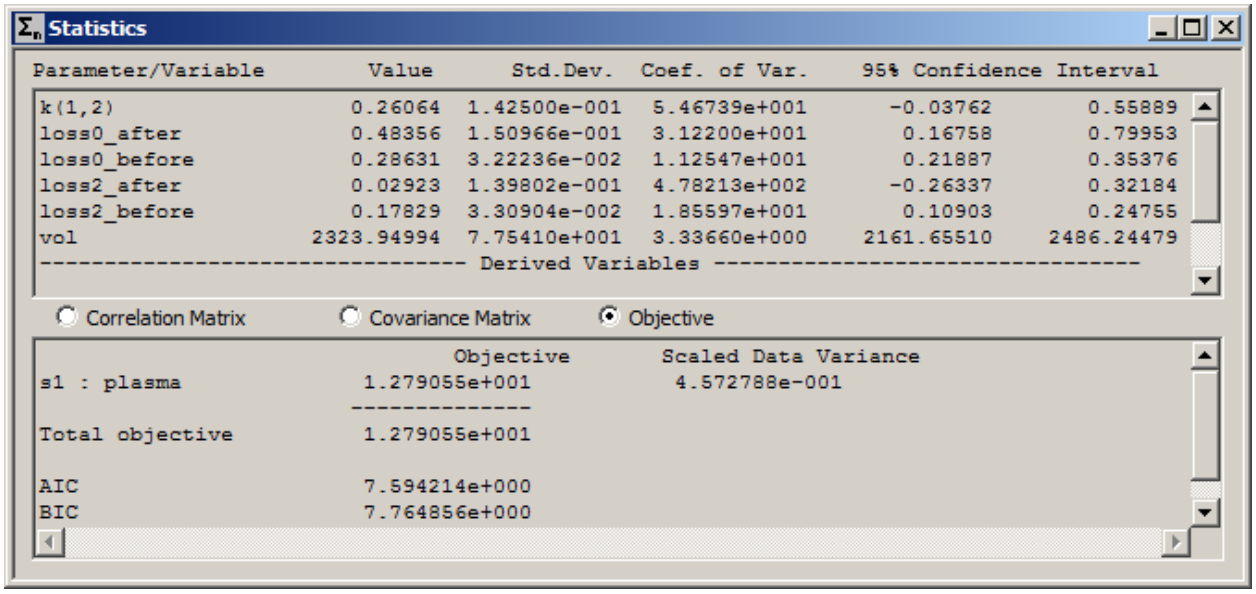


8. Fit the model to the data. The plot will be updated as follows:

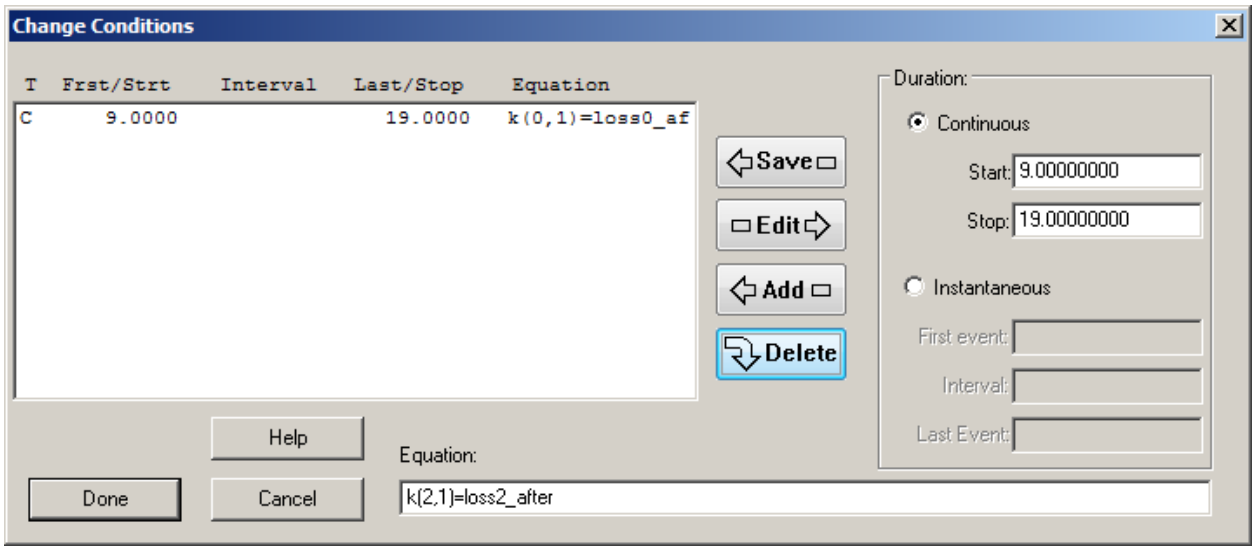


You can see that the parameter changes nicely describe the change starting at day 9.

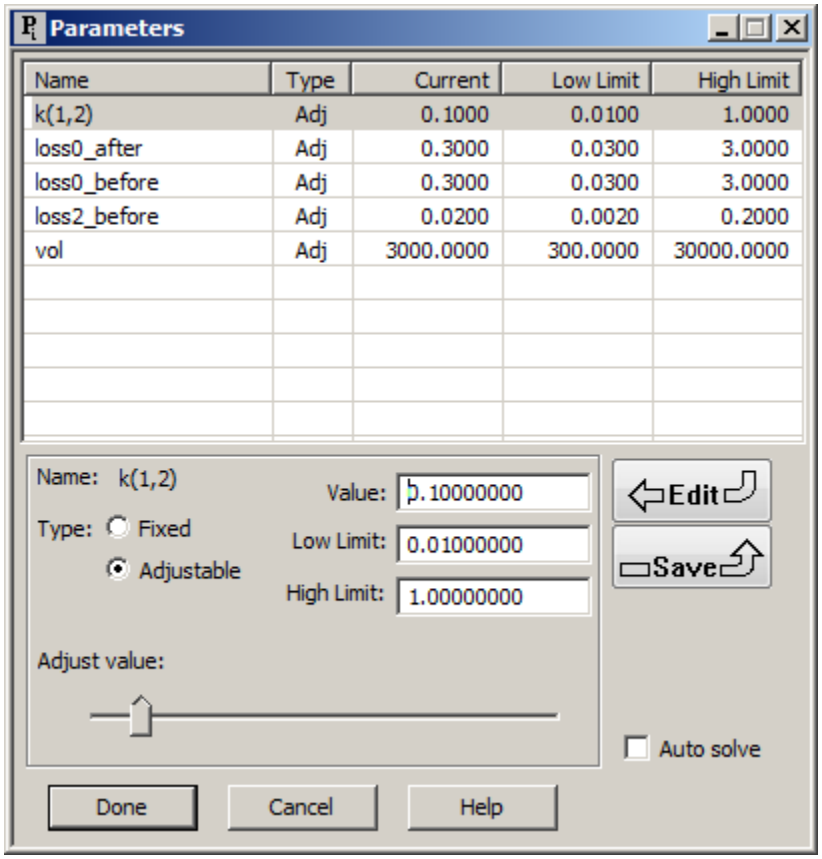
9. View the statistics. The **Statistics** window will appear as follows:



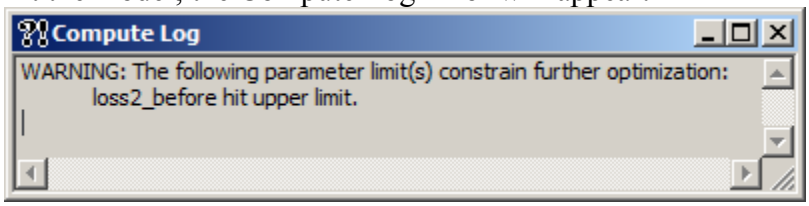
The statistics are reasonable except that *loss2_after* is not well defined, and hence its change is not supported by the data. Restore the initial values for the other parameters; Open the **Change Conditions** dialog box, and **delete the change** in *k(2,1)*.



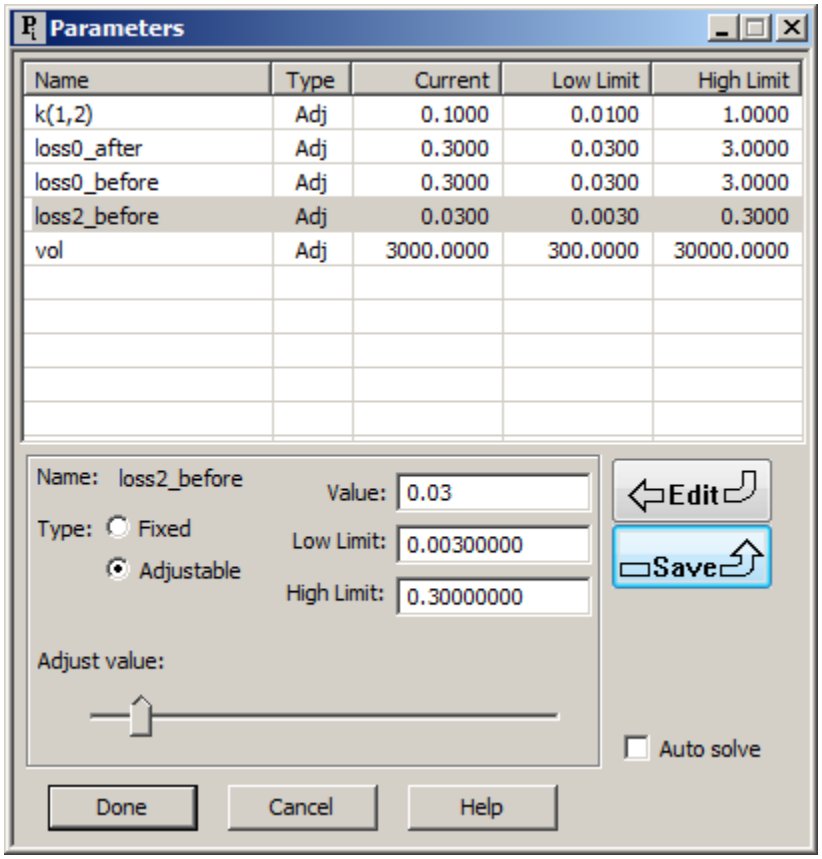
Restore the initial values for the other parameters;



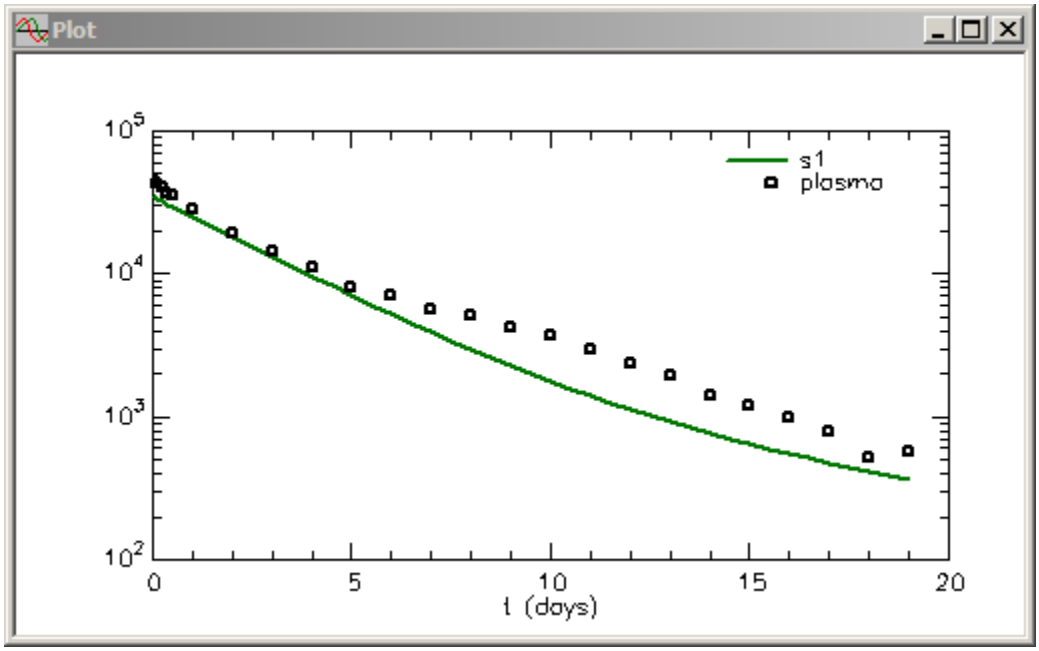
Fit the model; the Compute Log Error will appear:



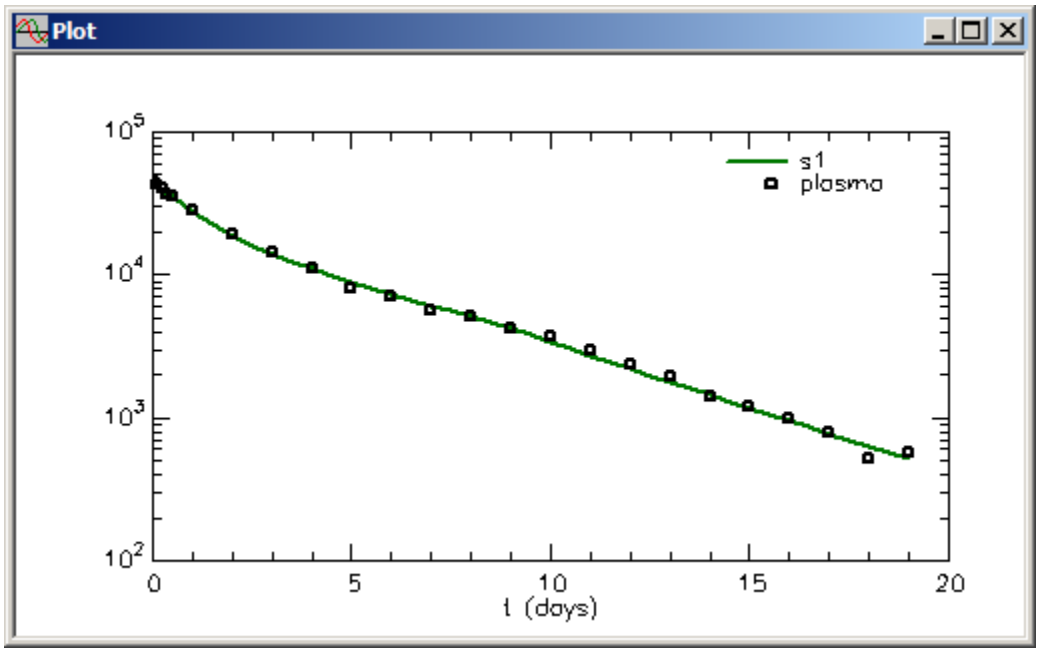
Modify the limits of *loss2_before* as shown below:



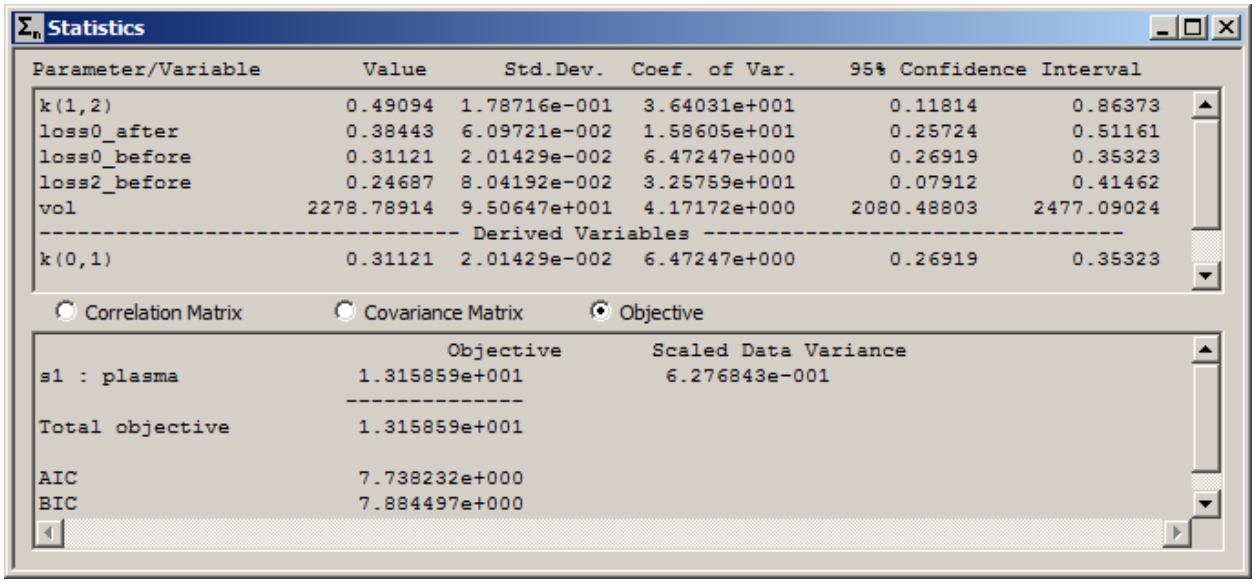
Solve the model;



Fit the model; the fit will be essentially the same as that shown above.



The statistics will change as follows:




```
k(1,2)                0.49094  1.78716e-001  3.64031e+001       0.11814       0.86373
loss0_after           0.38443  6.09721e-002  1.58605e+001       0.25724       0.51161
loss0_before          0.31121  2.01429e-002  6.47247e+000       0.26919       0.35323
loss2_before          0.24687  8.04192e-002  3.25759e+001       0.07912       0.41462
vol                2278.78914  9.50647e+001  4.17172e+000    2080.48803    2477.09024
--------------------------------- Derived Variables ---------------------------------
k(0,1)                0.31121  2.01429e-002  6.47247e+000       0.26919       0.35323
k(2,1)                0.24687  8.04192e-002  3.25759e+001       0.07912       0.41462
```

These are better, so a change in the loss is supported by the plasma data. In the actual experiment, urine data were also collected. When these are incorporated into the model, the change in the return is supported by the data.

Quit the **SAAM II Compartmental** application. Do not save the changes to **cont_cc**.

Part 2. An instantaneous Change Condition – inulin kinetics

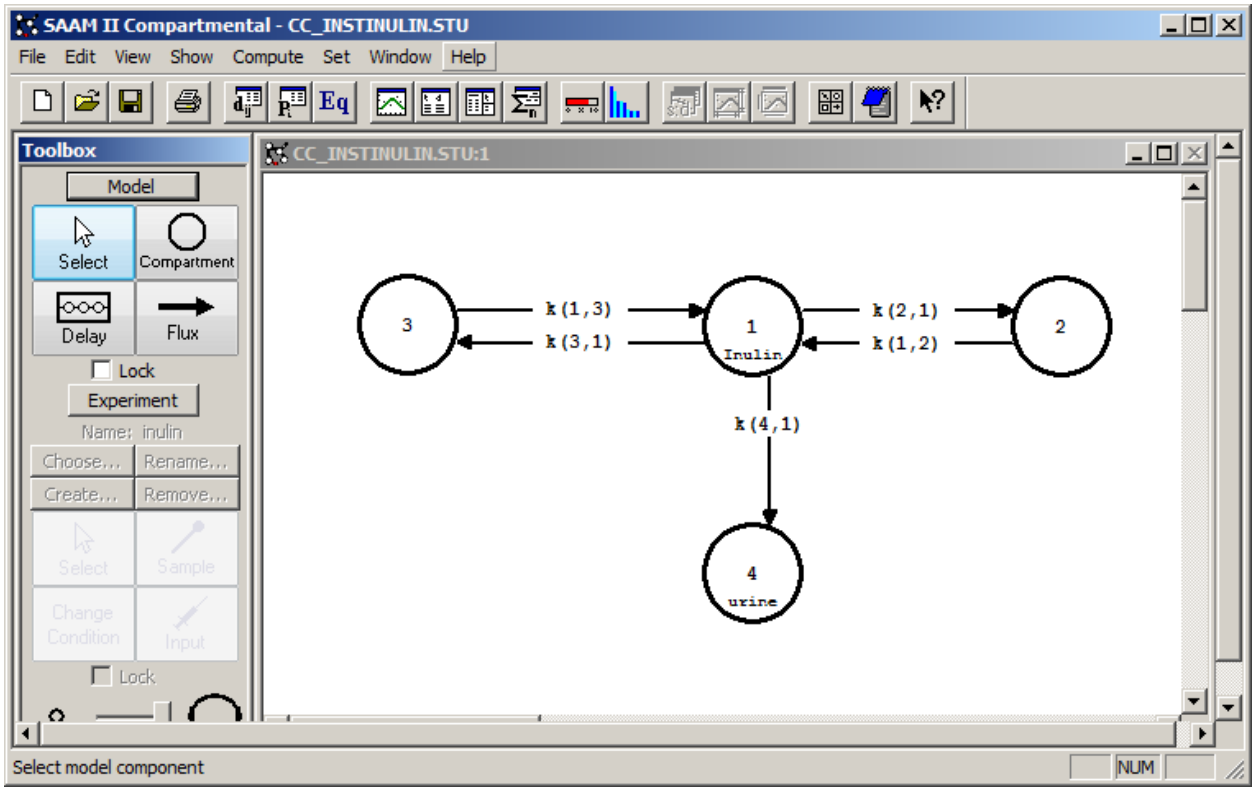
The following study investigated the metabolism of inulin. Inulin is known to be described by a three compartment model, and to be totally excreted in the urine. The experiment lasted 500 minutes. Plasma concentration is mg/L and urine measurements are mg.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

2. Open the **SAAM II Compartmental** study file **cc_instInulin**.

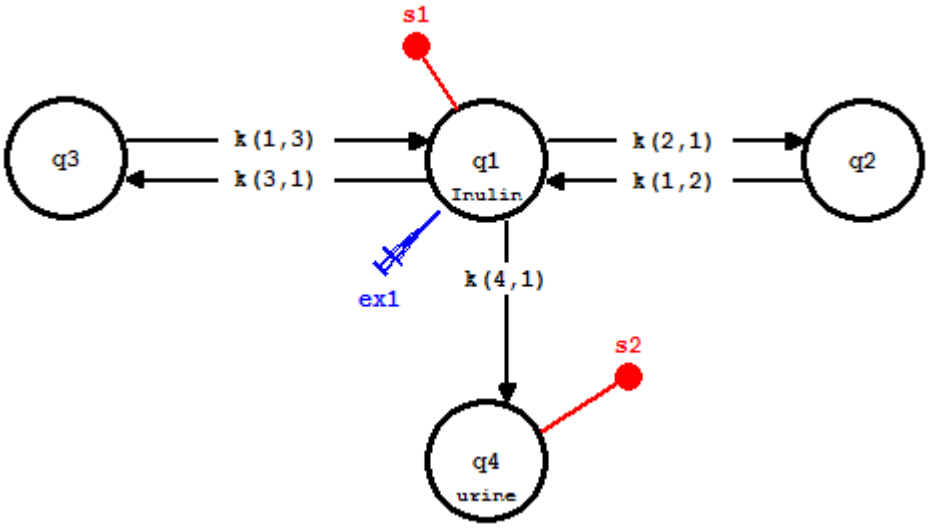
   a. The file **cc_instInulin.stu** should appear in the file list; if it does not, find the folder where you put this file.

   b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as shown below:



   The model is characterized by a central plasma compartment which exchanges with two peripheral compartments. Excretion in urine, Compartment **4**, is from the plasma compartment, Compartment **1**.

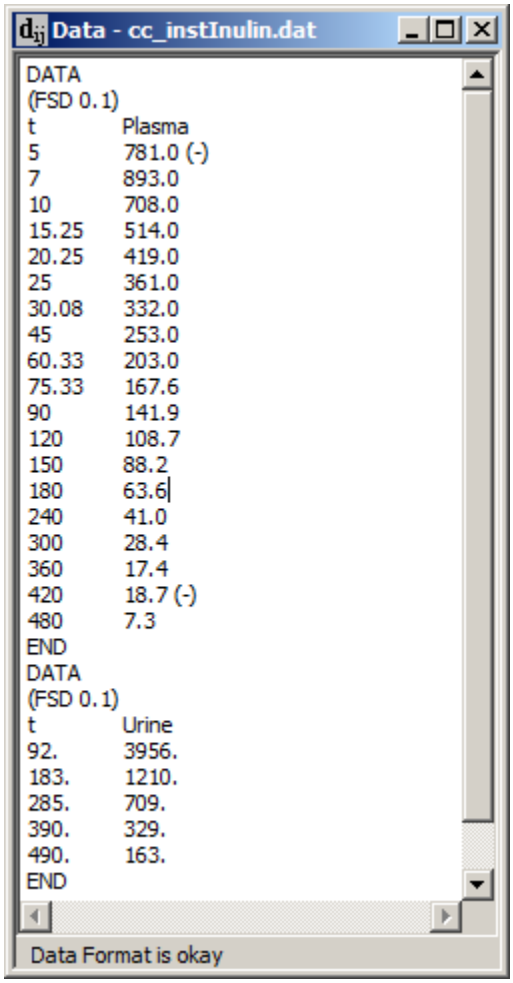
3. View the model and the experiment on the model. In the **SAAM II Toolbox**, click **Experiment**. The model of the experiment will appear on the **Drawing Canvas** as follows:



The plasma samples, **s1**, are the concentration of plasma inulin. Double-click **s1** to view the **Sample Attributes** dialog box. The compartment for the individual urine samples is Compartment **q4**. The sample **s2** links this compartment with the individual urine samples. Double-click **s2** to view the **Sample Attributes** dialog box.

The input is **ex1**. It is a bolus into plasma.

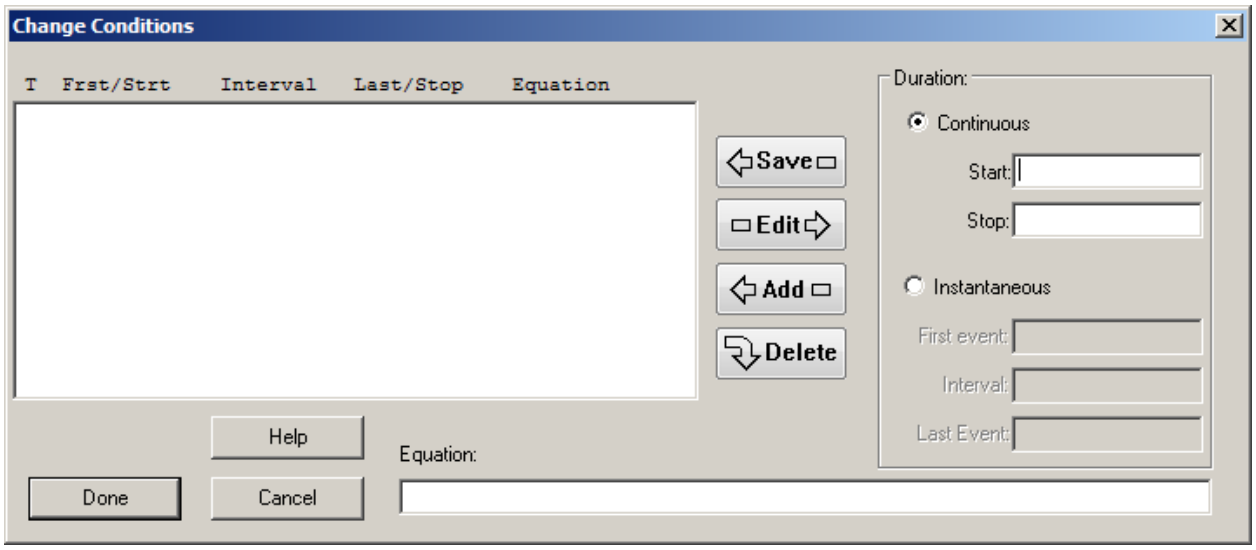
The data to be analyzed are shown in the **Data** window below:



The data are entered in two segments, one for plasma and one for the individual urine samples. Notice that the urine collection times do not coincide with the time of plasma samples.

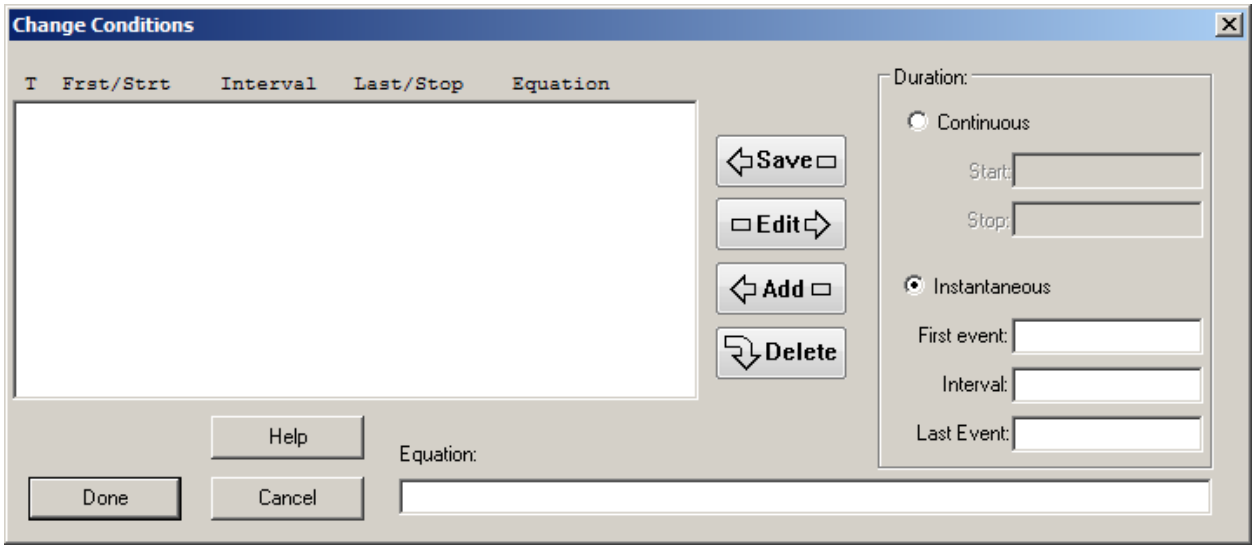
4. Use Change Conditions to model the individual urine collections.

   a. In the **SAAM II Toolbox**, click **Change Condition**. The **Change Conditions** dialog box will open as shown below:



Change Conditions dialog box. The **Change Conditions** dialog box contains the **Duration** pane. The **Duration** pane is where you set the Change Condition to be **Continuous** (default) or **Instantaneous**. You set the **Start** and **Stop** times in the boxes below this pane. If the Change Condition is **Instantaneous**, the **First event**, **Interval**, and **Last Event** boxes will be active. You define the change in the **Equation** box.

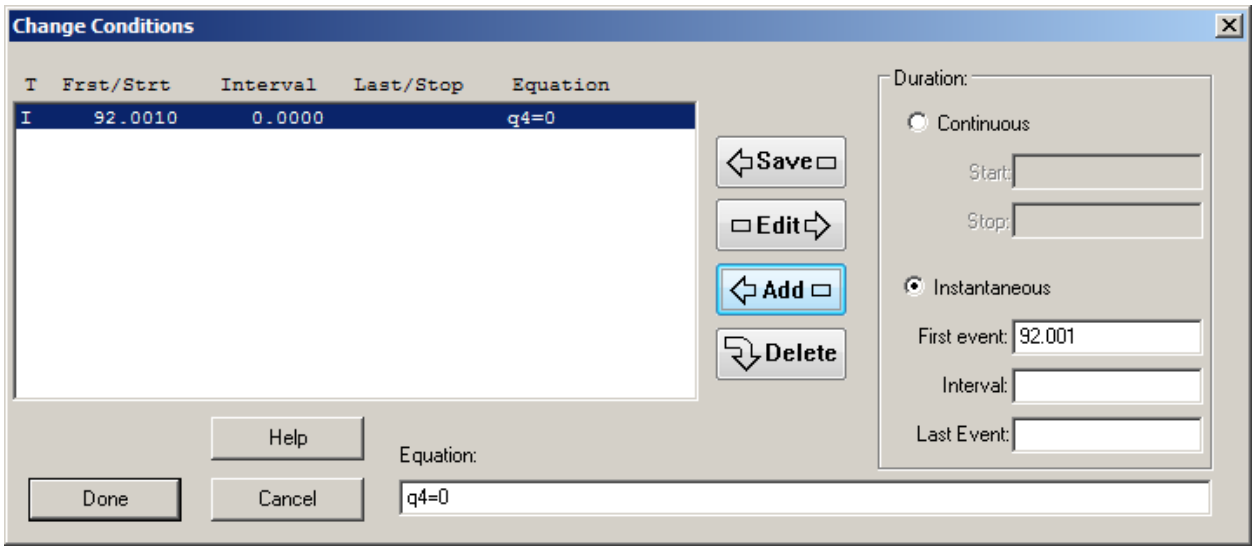
b. In the **Duration** pane, select **Instantaneous**. The **Change Conditions** dialog box will appear as follows:



c. In the **First event** box, type "92.001".

d. In the **Equation** box, type "q4=0".

e. Click **Add**. The **Change Conditions** dialog box will appear as follows:

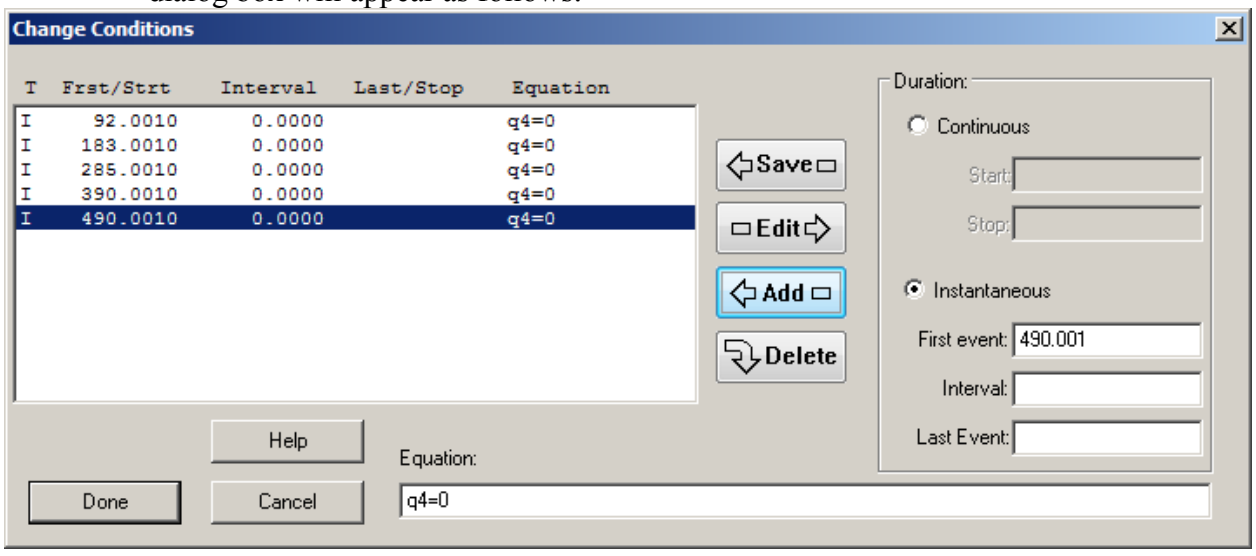


f. In the **First Event** box, type "183.001", and click **Add**.

g. In the **First Event** box, type "285.001", and click **Add**.

h. In the **First Event** box, type "390.001", and click **Add**.

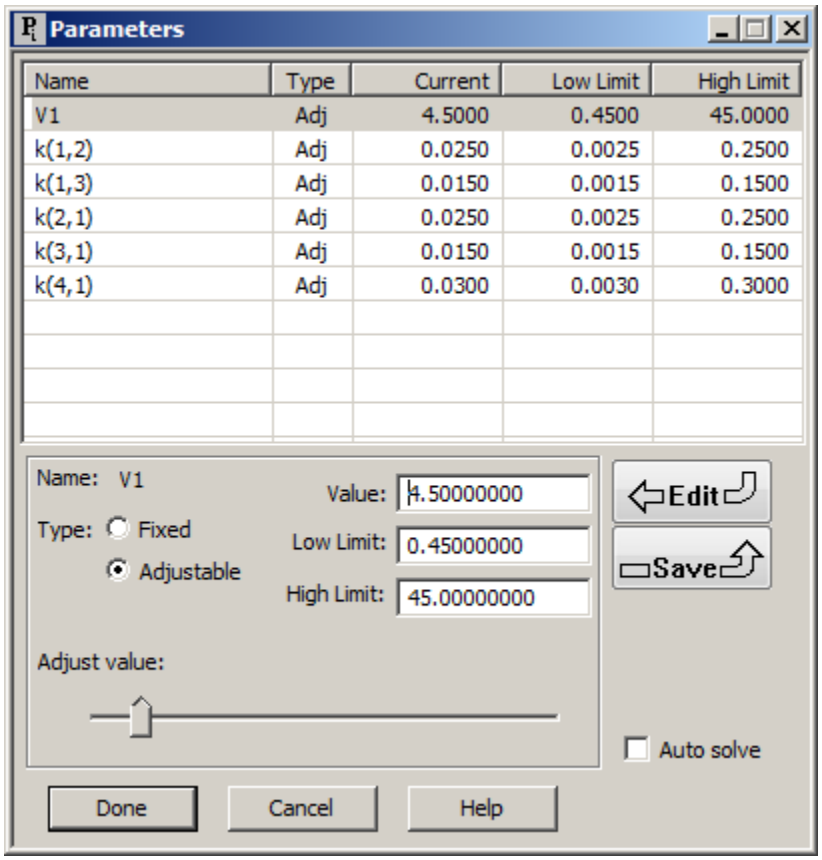
i. In the **First Event** box, type "490.001", and click **Add**. The **Change Conditions** dialog box will appear as follows:



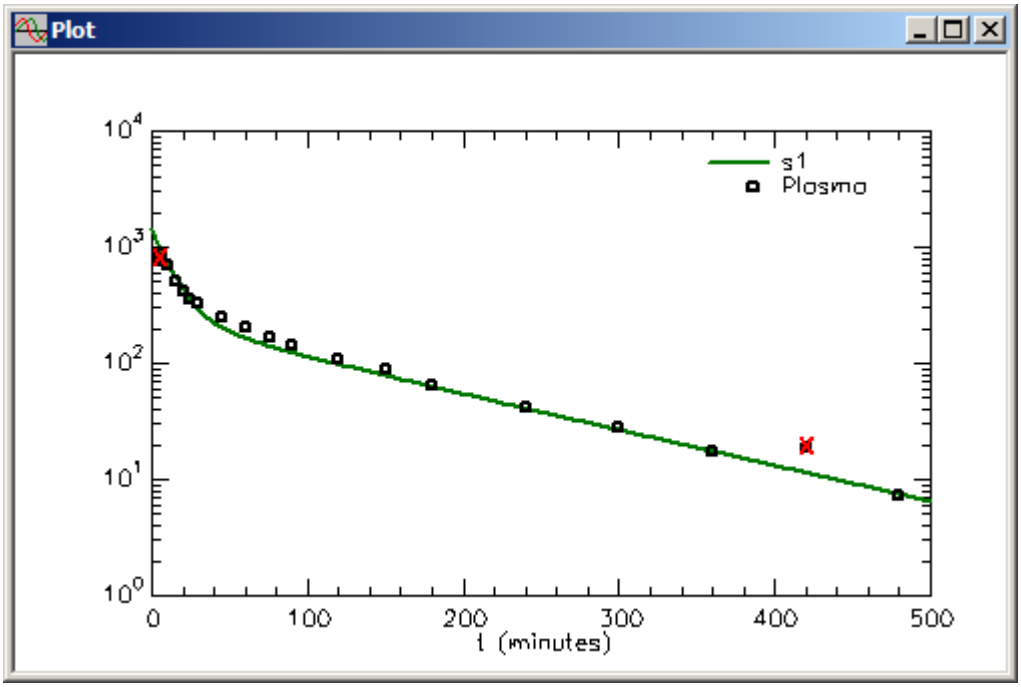
j. Click **Done**.

Instantaneous Change Conditions. Why do we enter the first event at 92.001? The reason is that the urine collections last for 92 hours. The container is emptied after the volume and concentration of inulin are made. Thus the actual event of emptying the container takes place slightly after the actual sample. Adding 0.001 to the time will accommodate this. The equation "q4 = 0" will resent the value of Compartment **q4** equal to zero at the specified time point. SAAM II will stop integration at, for example, 92.001, reset **q4** equal to zero, and continue integrating.

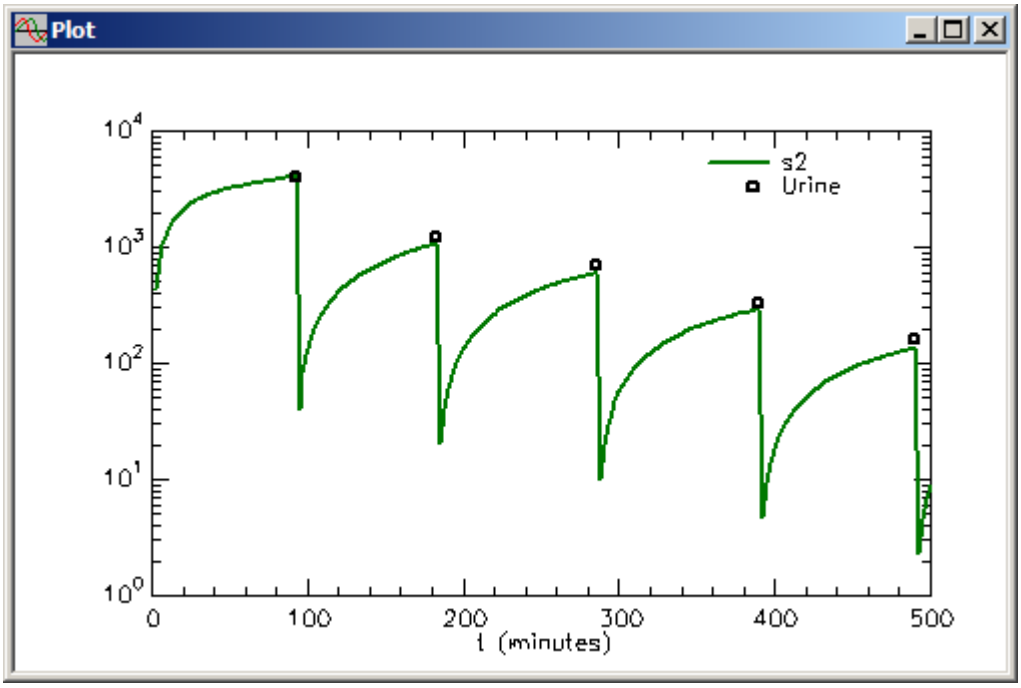
5. View the model parameters. The parameters have been entered as part of the study file. The **Parameters** dialog box is shown below:



6. Solve the model, and view the solution. The plot of **s1:Plasma** will appear as follows (in semi-log mode):



Notice the first datum and the datum at 420 are unweighted as indicated by the red x through them. The plot of **s2:Urine** will appear as follows:



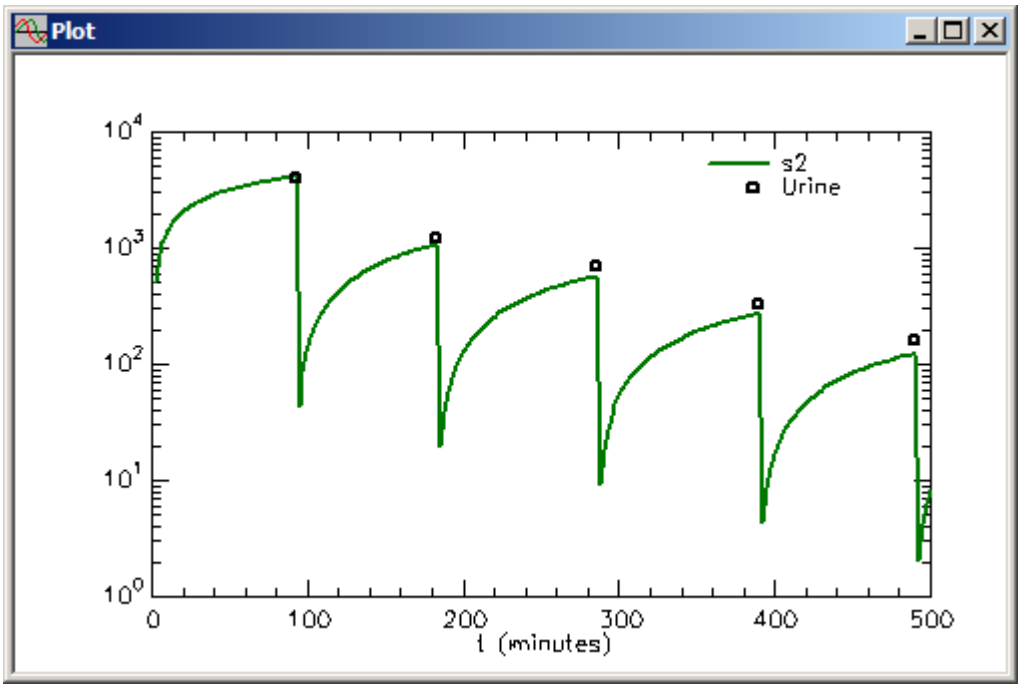
Viewing the individual urine samples. In viewing the individual urine samples, you can clearly see the effect of resetting **q4** equal to zero; this is produces the saw-tooth

curve. It is also important to note in these situations it is best to reset the **Minimum Number of Computation Intervals** equal to 200 to improve the resolution of the plot. This has been done in the study file. On the **Compute** menu, if you click **Settings**, the **Computational Settings** dialog box will open. You can see that the **Minimum Number of Computation Intervals** is set equal to 200. If you reduce this and resolve the model, you will loose some of the resolution of the plot.

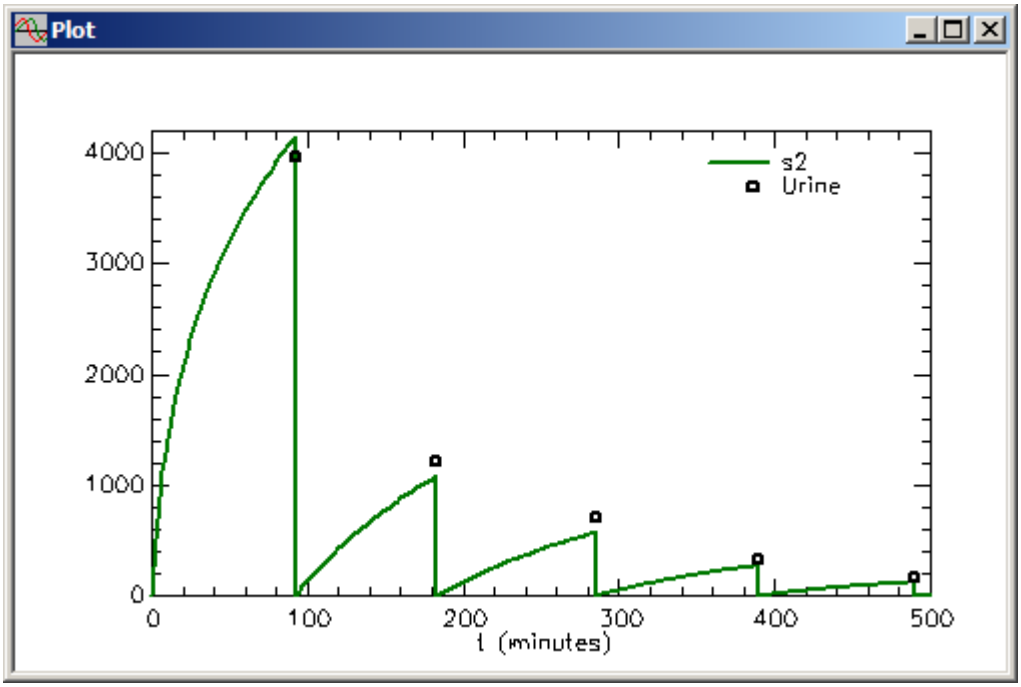
Leave the above plot of **s2:Urine** open.

7. Fit the model to the data, and view the solution.

   a. The plot of **s2:Urine** will be updated as follows:

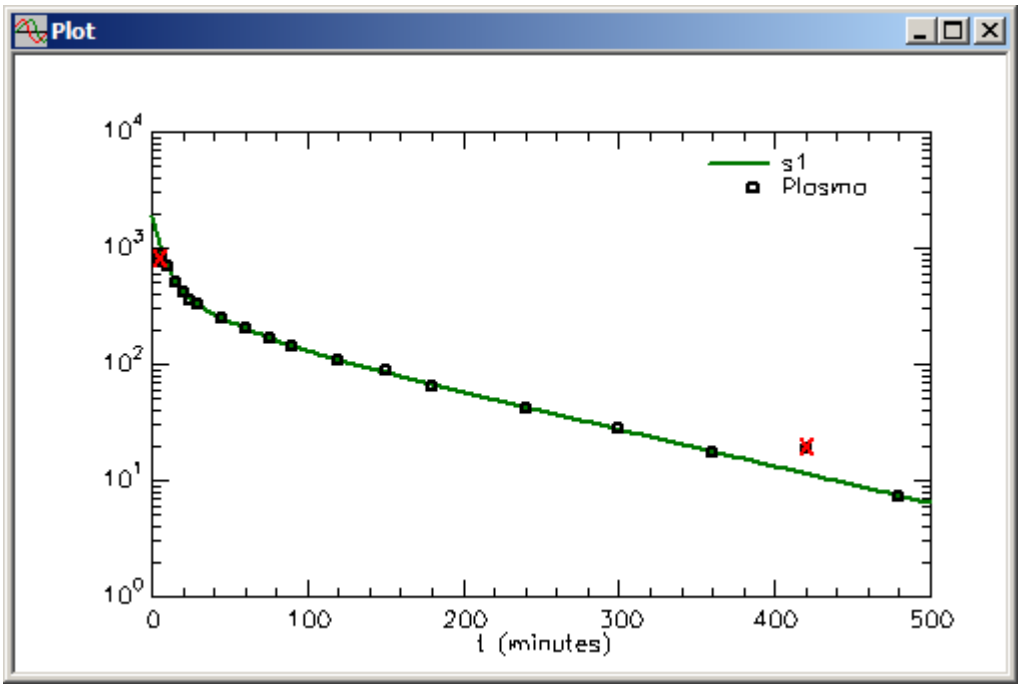


In the linear mode, the plot will appear (the **Y Axis** minimum should be set equal to zero to 4200):



Here you can see that **q4** has been reset to zero at the appropriate times.

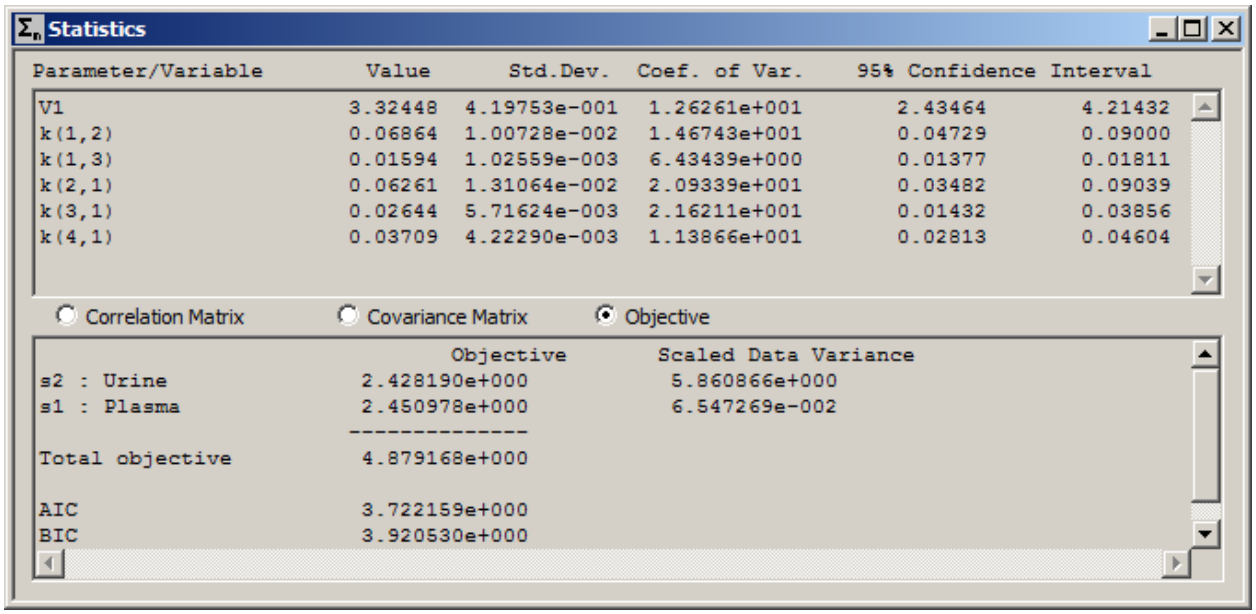
b. Plot **s1:Plasma**. The plot in semilog will appear as follows (the **Y Axis** scale should be set to autoscale):



You can see that the model describes the data reasonably well.

Close the **Plot** window.

c. View the statistics. The **Statistics** window will appear as follows:



The statistical information supports the model quite well also.

Close the **Statistics** window.

Quit the **SAAM II Compartmental** application. Do not save the changes to **cc_instInulin**.

Part 3. An instantaneous Change Condition – LDL kinetics

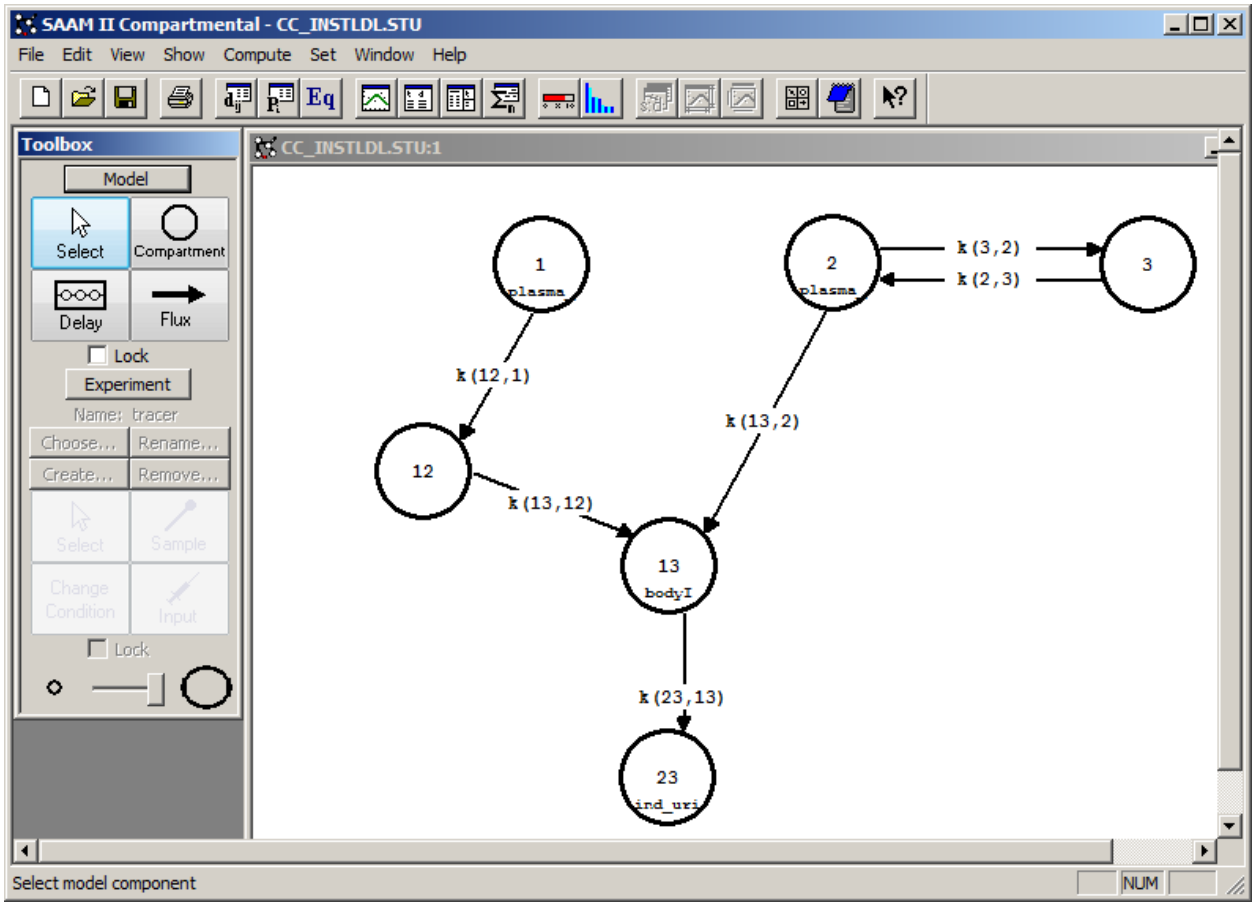
The following study investigated the metabolism of low density lipoproteins (LDL). Radioiodinated LDL was injected, and plasma and urinary radioactivity was determined. 24 hour urine collections were made. This part of the tutorial will show you have to model such collections using instantaneous change conditions.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

2. Open the **SAAM II Compartmental** study file **cc_instLDL**.

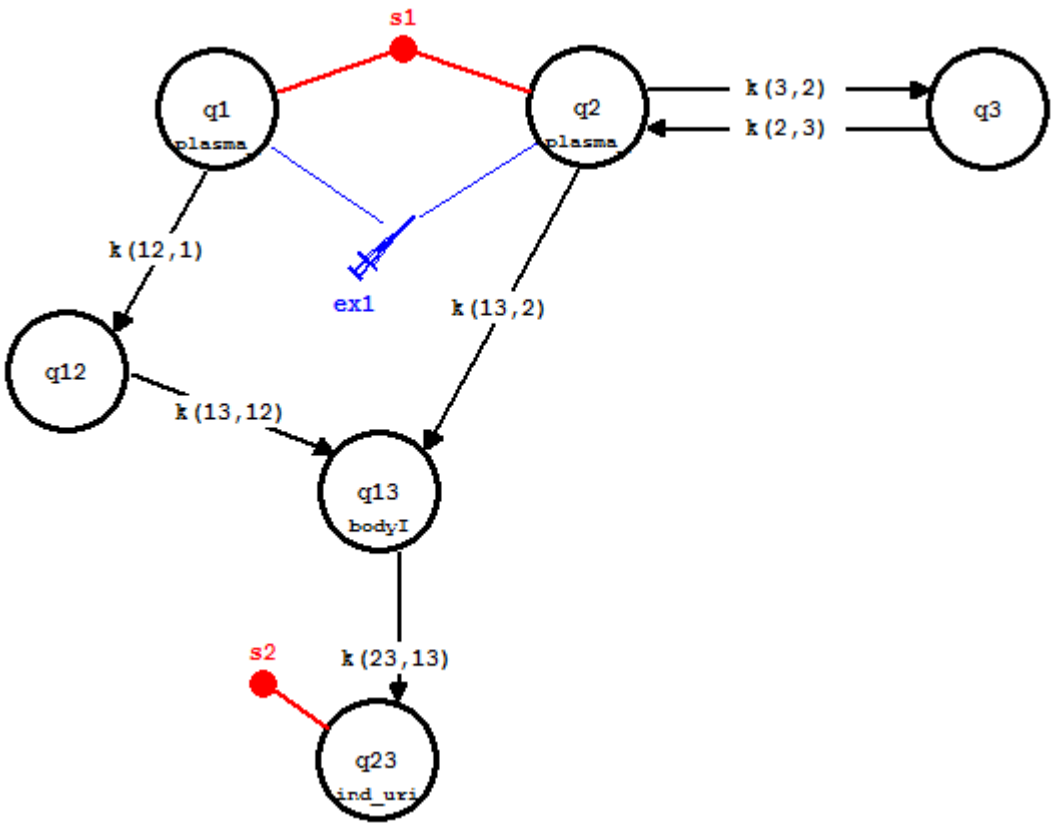
   a. The file **cc_instLDL.stu** should appear in the file list; if it does not, find the folder where you put this file.

   b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as shown below:

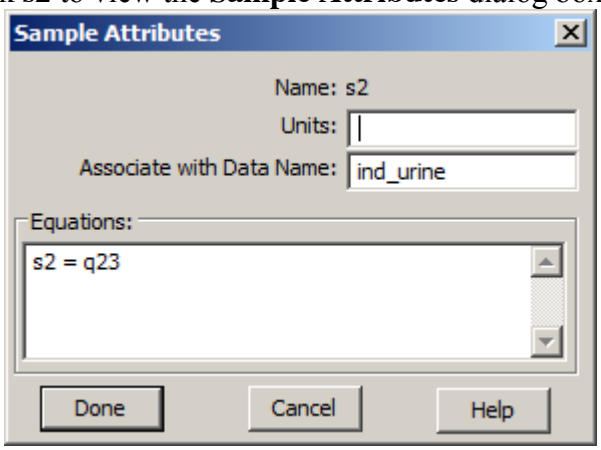


The model is characterized by two plasma pools representing two kinetically distinct subpopulations of LDL particles. Radioiodide leaves the LDL during the metabolic process and enters the total body iodide pool. It is excreted there into the urine.

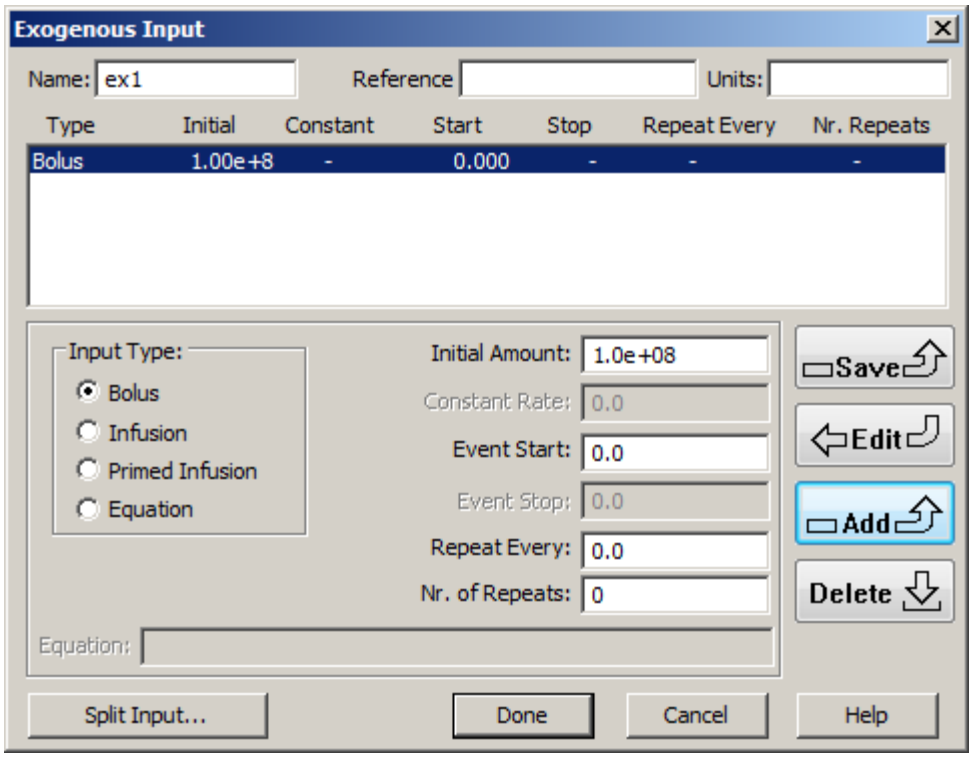
3. View the model and the experiment on the model. In the **SAAM II Toolbox**, click **Experiment**. The model of the experiment will appear on the **Drawing Canvas** as follows:



The plasma samples, **s1**, are a sum of the radioactivity in the two plasma compartments, **q1** and **q2**, divided by the plasma volume. Double-click **s1** to view the **Sample Attributes** dialog box. The compartment for the individual urine samples is Compartment **q23**. The sample **s2** links this compartment with the individual urine samples. Double-click **s2** to view the **Sample Attributes** dialog box.



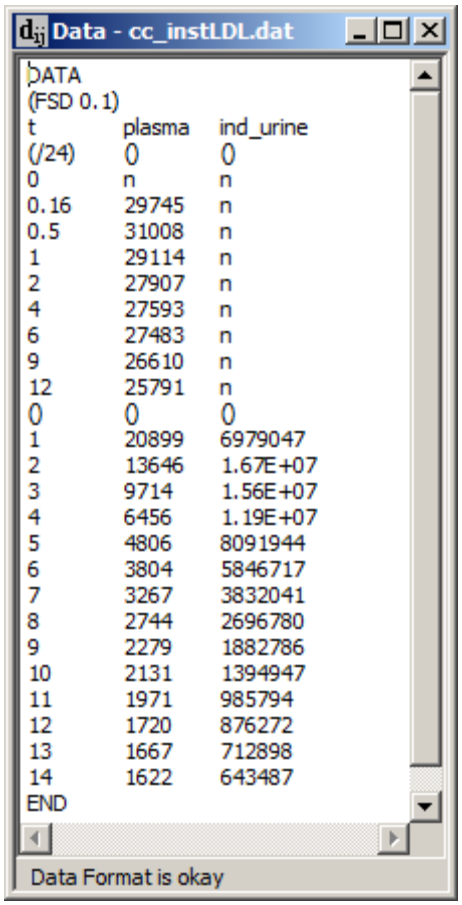
The input **ex1** is a split input. This is because the radiolabeled LDL is split between the two subpopulations of LDL represented by Compartments **q1** and **q2**. Double-click ex1 to open the **Exogenous Input** dialog box. Then click **Split Input**; the two dialog boxes will appear as follows:



The parameter *frac* will split the bolus dose between Compartments **q1** and **q2**. For more information on split inputs, see the Using SAAM II (Advanced) tutorial "Working with Experimental Inputs".

Close the two dialog boxes.

The data to be analyzed are shown in the **Data** window below:



The two columns of data are the plasma and the individual urine samples. The initial data were recorded in hours instead of days. The line in the data file

"(/24) () ()"

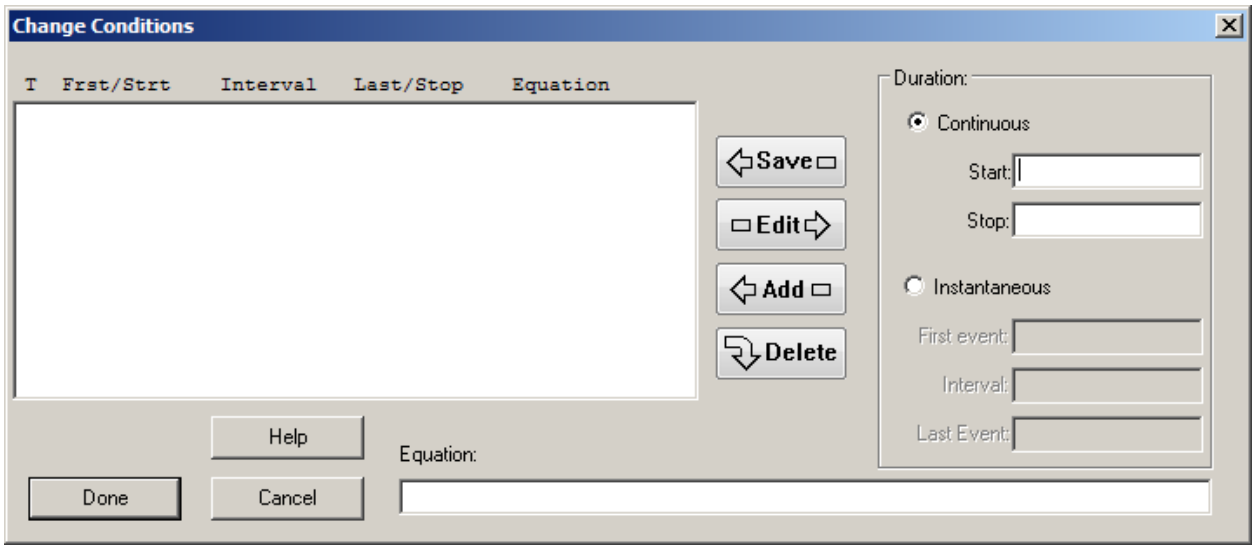
divides all samples up to 12 hours by 24 converting them to days. The line in the data file

() () ()

will stop the division by 24. The entries "n" in the "ind_urine" column means there are no urine data collected at these times.

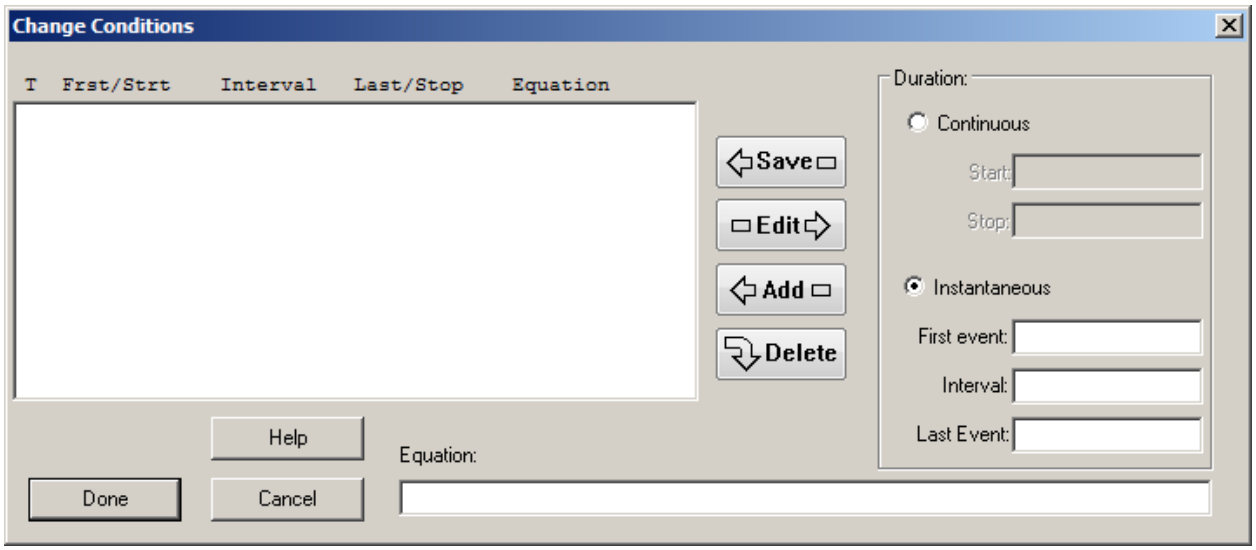
4. Use Change Conditions to model the 24 hour urine collections.

   a. In the **SAAM II Toolbox**, click **Change Condition**. The **Change Conditions** dialog box will open as shown below:



Change Conditions dialog box. The **Change Conditions** dialog box contains the **Duration** pane. The **Duration** pane is where you set the Change Condition to be **Continuous** (default) or **Instantaneous**. You set the **Start** and **Stop** times in the boxes below this pane. If the Change Condition is **Instantaneous**, the **First event**, **Interval**, and **Last Event** boxes will be active. You define the change in the **Equation** box.

b. In the **Duration** pane, select **Instantaneous**. The **Change Conditions** dialog box will appear as follows:



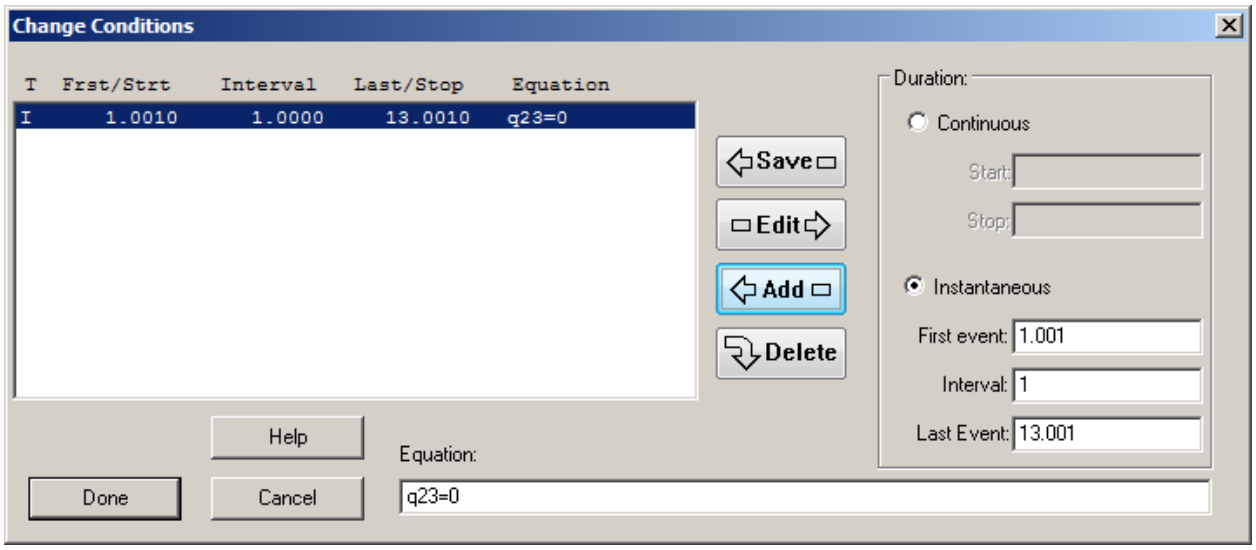
c. In the **First event** box, type "1.001".

d. In the **Interval** box, type "1".

e. In the **Last Event** box, type "13.001".

f. In the **Equation** box, type "q23=0".

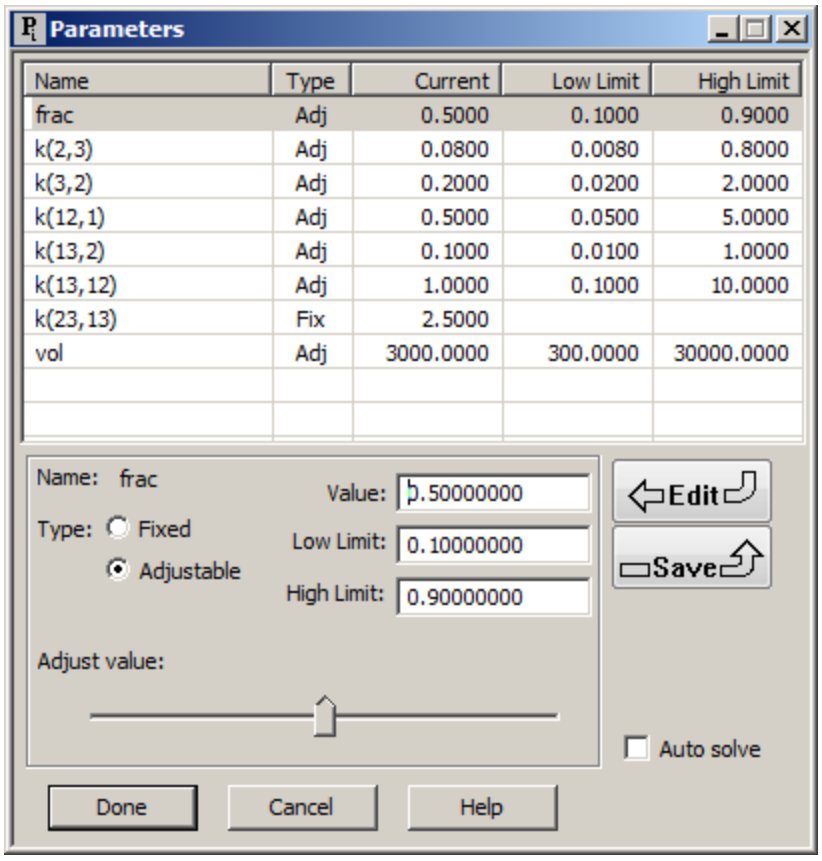
g. Click **Add**. The **Change Conditions** dialog box will appear as follows:



h. Click **Done**.

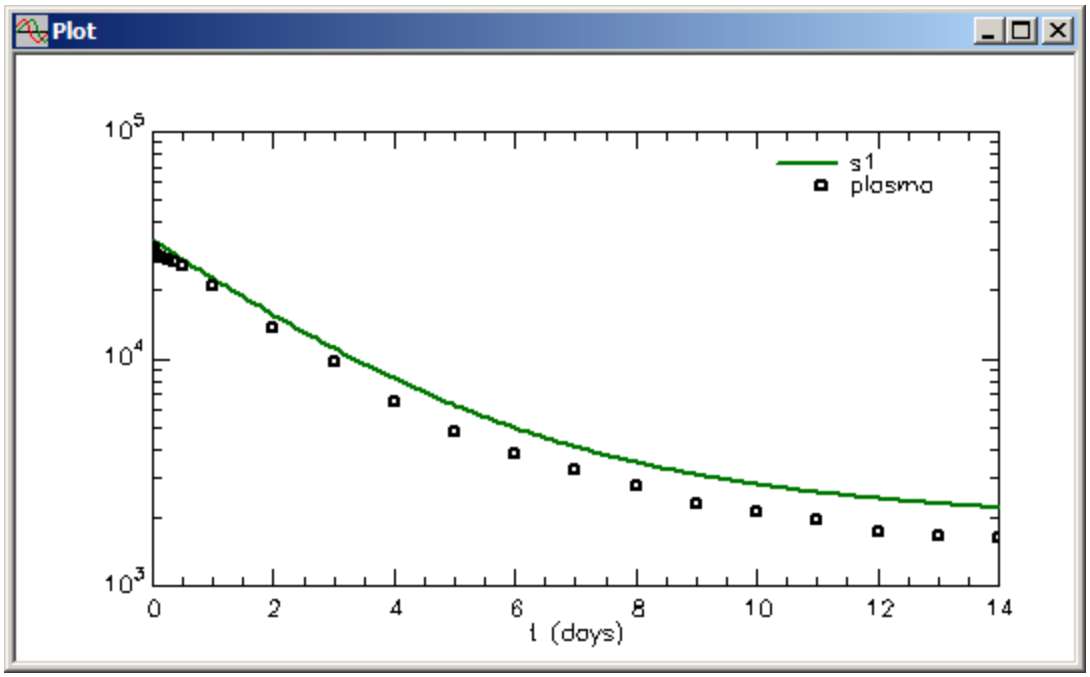
Instantaneous Change Conditions. Why do we enter the first event at 1.001? The reason is that the urine collections last for 24 hours, 1 day. The container is emptied after the volume and concentration of radioactivity are measured. Thus the actual event of emptying the container takes place slightly after the actual sample. Adding 0.001 to each day will accommodate this. The equation "q23 = 0" will reset the value of Compartment **q23** equal to zero at the specified time point. SAAM II will stop integration at, for example, 1.001, reset **q23** equal to zero, and continue integrating.

5. View the model parameters. The parameters have been entered as part of the study file. The **Parameters** dialog box is shown below:

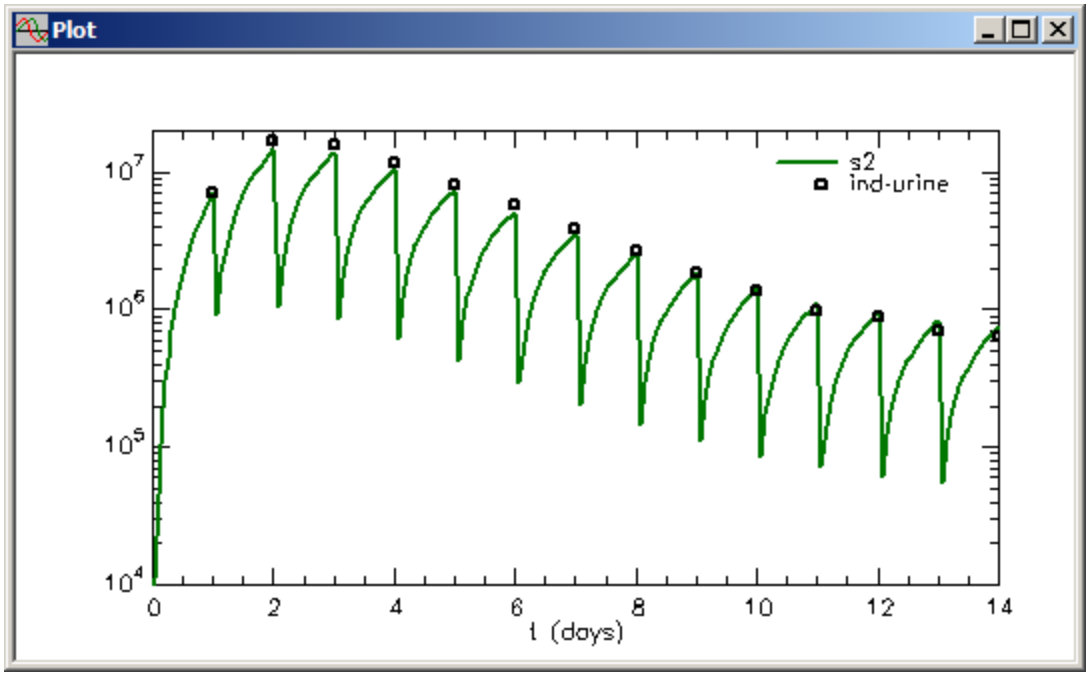


Of note in the **Parameters** dialog box is the fact that *frac*, the parameter that distributes the initial dose between the two plasma compartments, lies between 0.1 and 0.9; this parameter cannot be less than zero nor greater than 1. The parameter *k(23,13)* is fixed equal to 2.5. This is the fractional excretion rate from the body iodide pool, Compartment **q13**; this parameter cannot be determined from the data, and is taken from the literature where it is known that the total body iodide pool turns over at approximately 2.5/day.

6. Solve the model, and view the solution. The plot of **s1:plasma** will appear as follows (in semi-log mode):



The plot of **s2:ind_urine** will appear as follows (the **Y Axis** scale has been set with 10000 and 2.0e+07 as the minimum and maximum respectively):



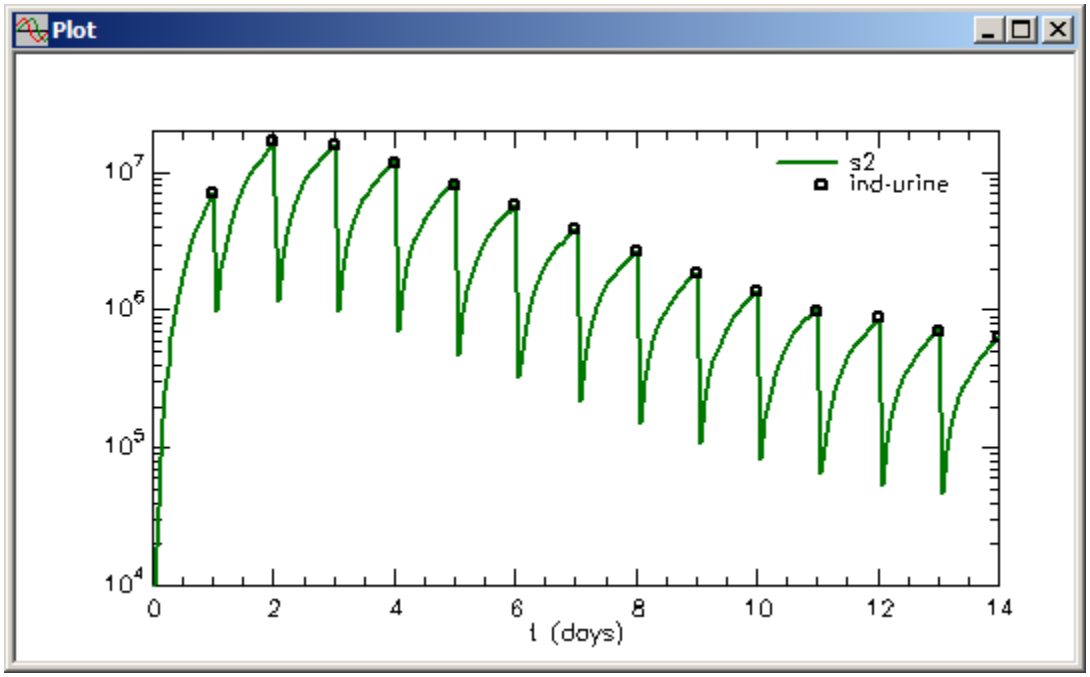
Viewing the individual urine samples. In viewing the individual urine samples, you can clearly see the effect of resetting **q23** equal to zero; this is what produces the saw-tooth curve. It is also important to note in these situations it is best to reset the

Minimum Number of Computation Intervals equal to 200 to improve the resolution of the plot. This has been done in the study file. On the **Compute** menu, if you click **Settings**, the **Computational Settings** dialog box will open. You can see that the **Minimum Number of Computation Intervals** is set equal to 200. If you reduce this and resolve the model, you will loose the resolution of the plot.

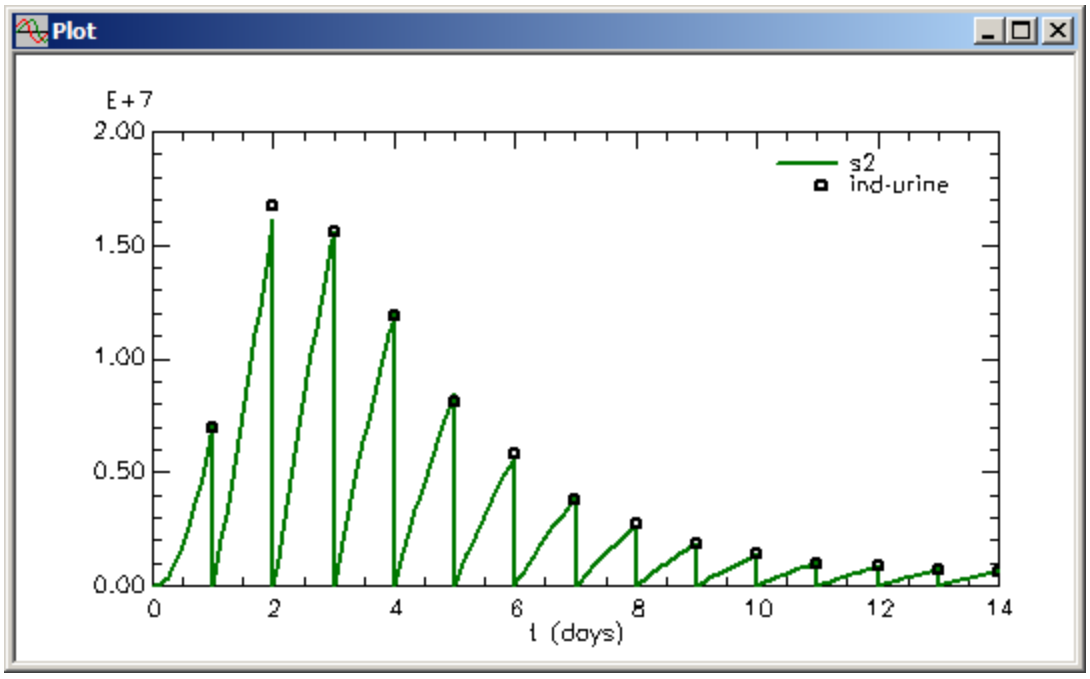
Leave the above plot of **s2:ind_urine** open.

7. Fit the model to the data, and view the solution.

   a. The plot of **s2:ind_urine** will be updated as follows:

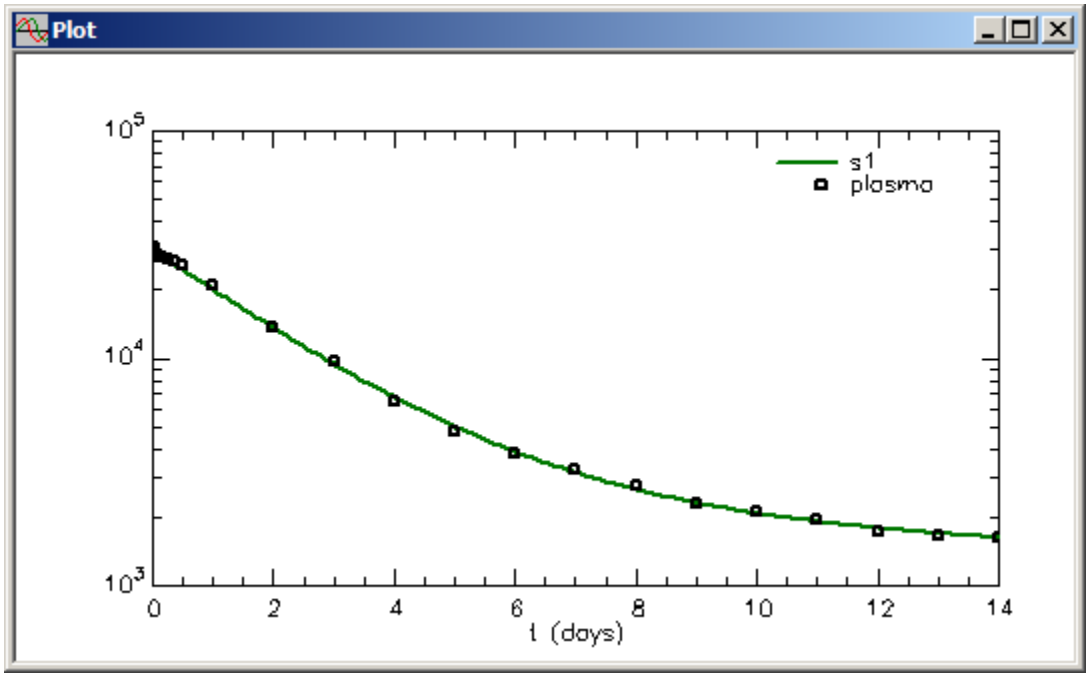


In the linear mode, the plot will appear (the **Y Axis** minimum has been set equal to zero):



Here you can see that **q23** has been reset to zero at the appropriate times.

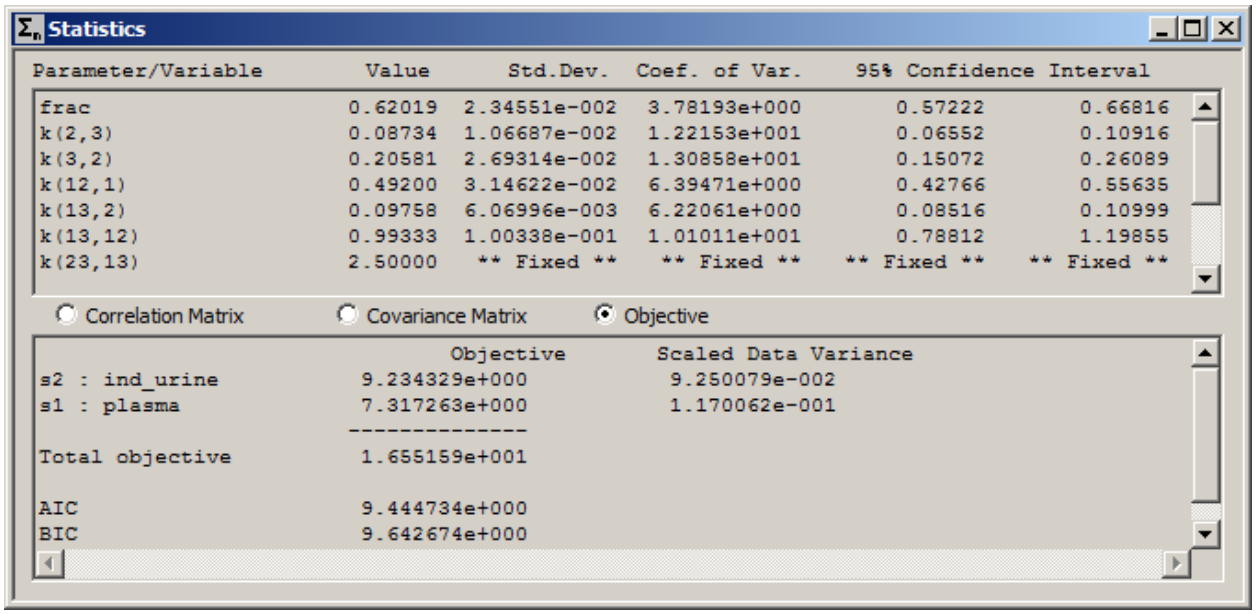
b. Plot **s1:plasma**. The plot will appear as follows (the **Y Axis** scale has been set to autoscale):



You can see that the model describes the data quite well.

Close the **Plot** window.

c. View the statistics. The **Statistics** window will appear as follows:



The statistical information supports the model quite well also.

Close the **Statistics** window.

Quit the **SAAM II Compartmental** application. Do not save the changes to **cc_instLDL.**

SAAM II Version 2.1
Advanced Tutorials

Working with Delays

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Working with Delays

Prerequisites

The prerequisite for this tutorial is having worked through the SAAM II introductory tutorial, "Getting Started with **SAAM II Compartmental**." It is recommended that you have worked through the **SAAM II** tutorial "**Saving and Restoring Solutions.**"

What you will learn in this tutorial

The purpose of this tutorial is to show you how to how to create delays in your compartment model. You will learn

- How to use the **Delay** tool in the **Model Toolbox** to create a delay (Part 1).
- How to use the **Delay** tool in the **Model Toolbox** to create a delay with split output (Part 2).
- How to create absolute delays (Part 3)

Files Required

Study Files: The study files for this tutorial are

delay1.stu
delay2.stu
delay3.stu

These file are included as part of this tutorial for convenience; you will actually create these study files as part of the tutorial.

Data files: The data files for this tutorial are

delay1.dat
delay3.dat

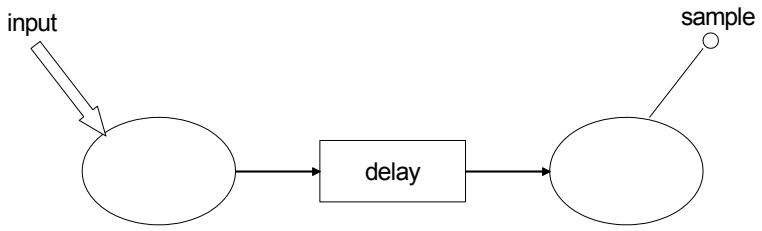
Introduction

This tutorial focuses on how to create delays in your compartment model. In the **SAAM II Compartmental** application, there are two ways delays can be created. One way is to use the **Delay** tool in the **SAAM II Toolbox**. The other way is to use a mathematical function called the Heaviside function. The latter is an advanced modeling technique that should be used only in specific instances when a nearly absolute delay is required; it is discussed in Part 3.

The **Delay** tool in the **SAAM II Compartmental** application creates delays automatically as a series of compartments. The larger the number of compartments specified for the delay in the **Delay Attributes** dialog box, the closer the delay will be to a true (absolute) delay, but the

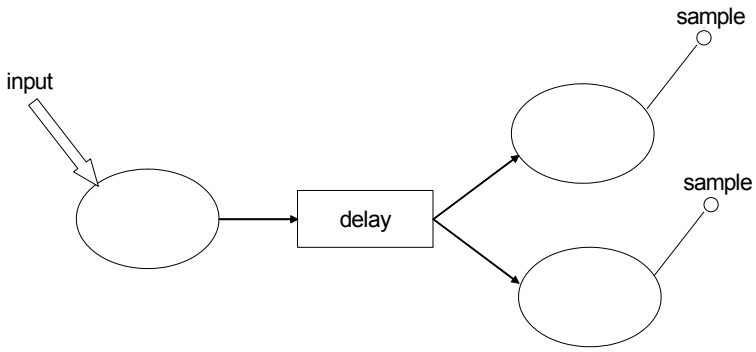
longer the computation time may be. The number of compartments in the delay is set by the user. The delay time can be either fixed, when the attributes associated with the delay are defined, or can be defined as a parameter that can be either fixed or adjustable.

Delays are usually required to describe physiological processes such as absorption, uptake across cell membranes, or amino acid incorporation into proteins. The situation can be represented schematically as follows:



There is an input "upstream" from where the experimental samples are taken. The delay is required when there is an actual delay in the appearance of the test substance in the compartment from which samples are taken. The delay usually represents a composite of metabolic activity, the details of which cannot be described from the actual data. This is why, in most instances, delays represented by a series of compartments is appropriate.

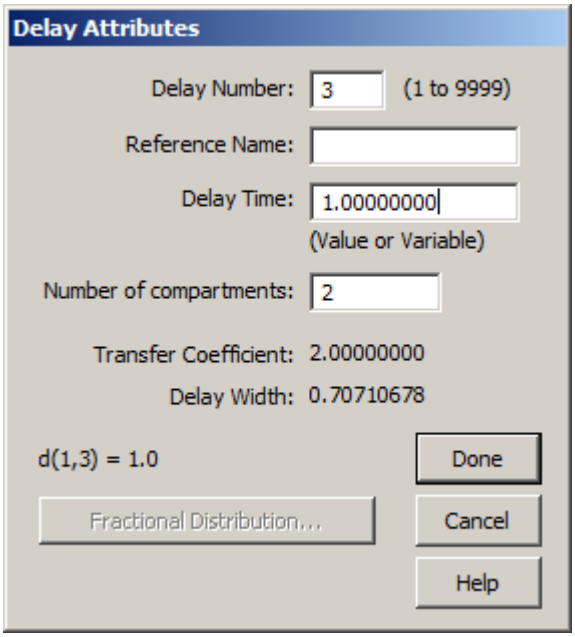
The situation above is one where the delay is between the input and the sample site. There are instances where material from the delay may actually pass to several compartments. An example would be the measurement of amino acid incorporation into several proteins. The situation for two outputs can be diagrammed as follows:



In this case, information on the split output must be provided; this is discussed in Part 2.

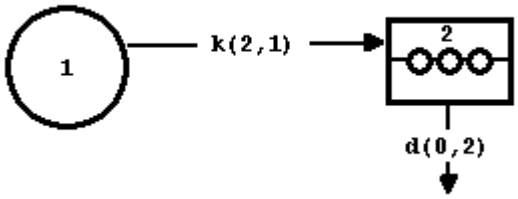
Delays implemented by a string of compartments actually represent a transfer function corresponding to a probability distribution function. The distribution function has a mean and a variance (standard deviation). The mean is the delay time, and the standard deviation is the delay width which is a measure of the "sharpness" of the delay. The transfer rate constant between compartments in the delay equals the number of compartments in the delay divided by the delay time.

What does this mean? The Delay Attributes dialog box associated with a delay in SAAM II appears as follows:

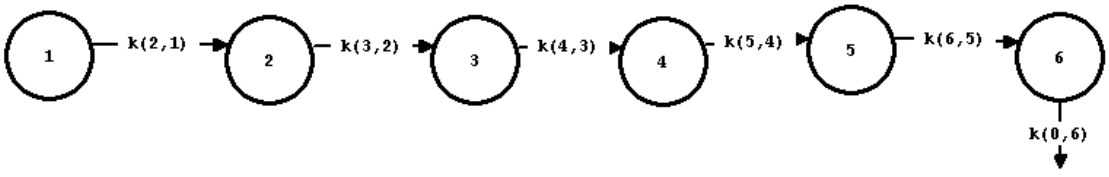


In this case, the delay number is "3". The default values for the delay time and the number of compartments in the delay are 1.0 and 2 respectively. Normally, as illustrated in this tutorial, the delay time is set equal to a parameter.

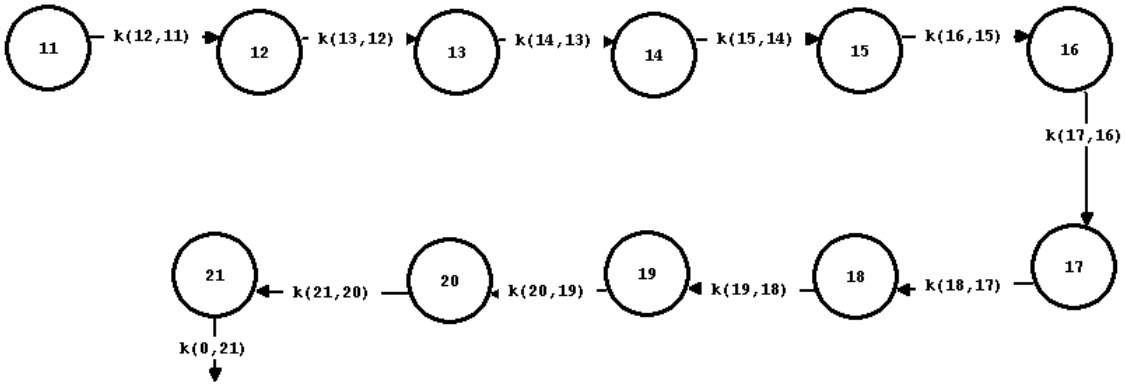
Consider the following example:



This could illustrate the first steps of absorption where Compartment **1** could be the stomach and Delay **2** could be the gut. If the number of compartments in the delay were set equal to 5, internally the model would appear:

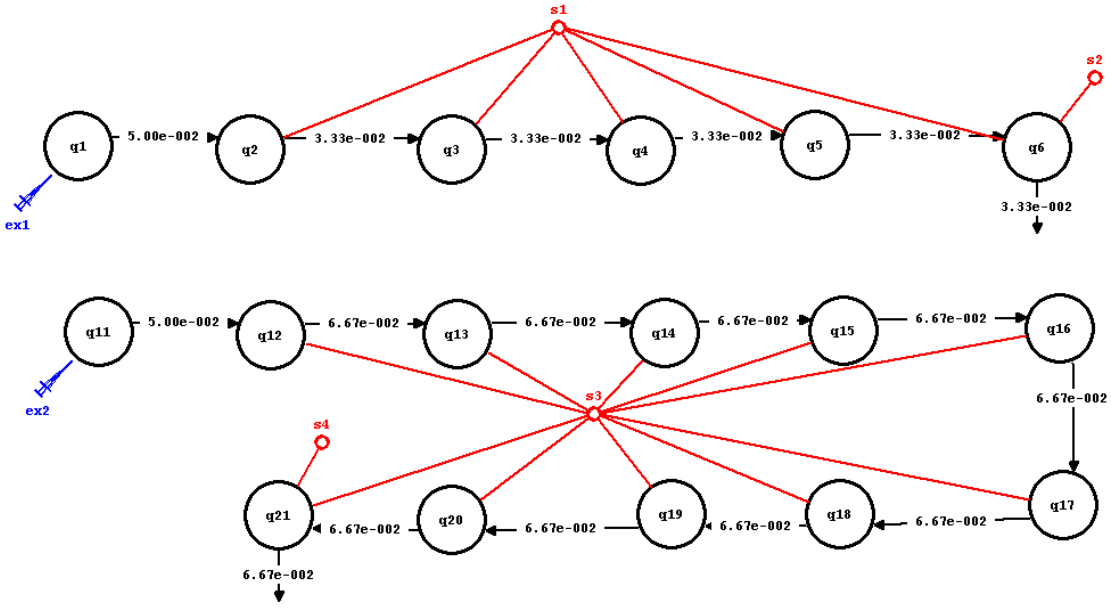


while if the number were set equal to 10, the model internally would appear:



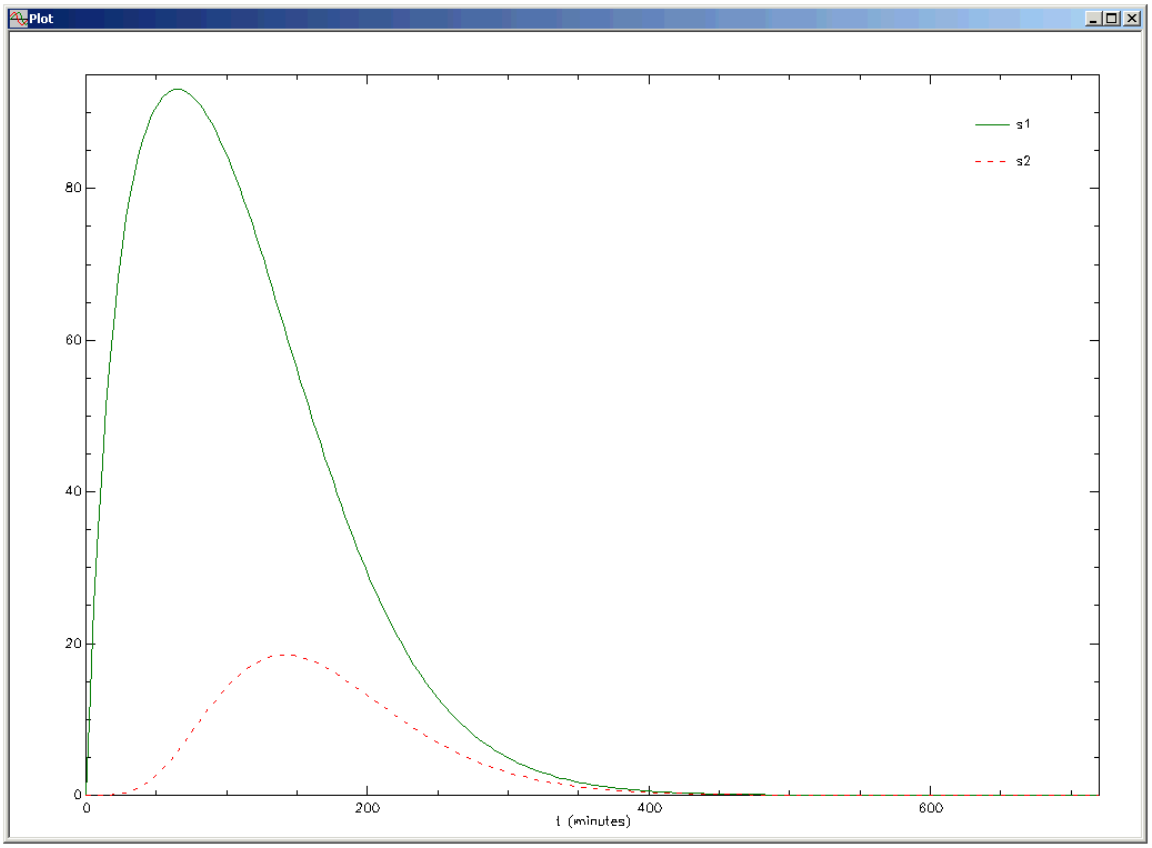
What is the difference, and what is the relationship between the delay time specified as part of the delay attribute, and the actual delay time that is desired? That is, the "delay time" as the transfer function mean, and the "delay time" actually required by the data may be different. This is a function of how a delay as a string of compartments works.

Consider an experiment on these two models where a bolus of "100" is given respectively into Compartments **1** and **11**. Suppose k(2,1)=k(12,11)=0.05, and the delay time is 150. Then for a the five compartment delay, the transfer rate constant equals 5/150, or .033 while for the 10 compartment delay, this is 10/150, or .0667. This is shown in the following figure:

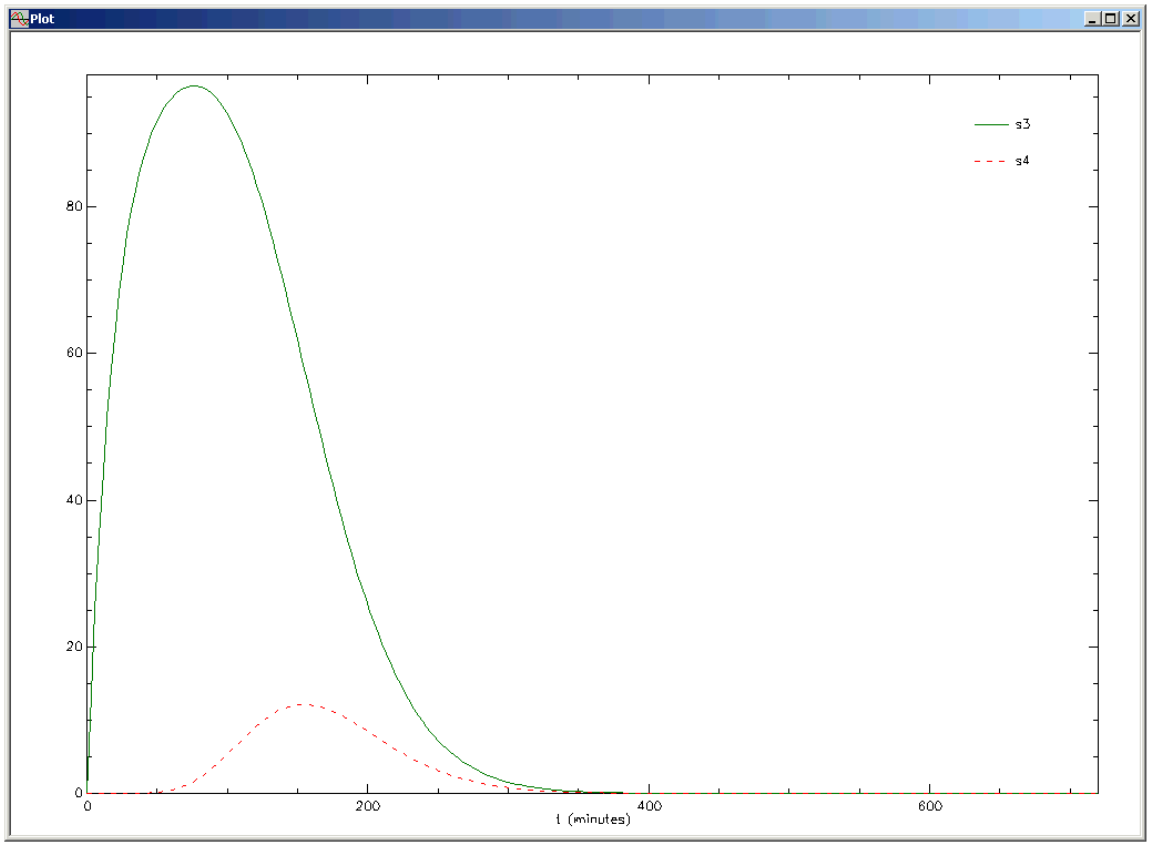


The actual delay is created by the material leaving the last compartment in the delay, **q6** and **q21** respectively.

For the five compartment delay, **s1** is the total mass in the delay as a function of time while **s2** is the amount in Compartment **q6**; it is this amount that will appear in the next compartment of interest in your model. A plot of the two is shown in the following figure:

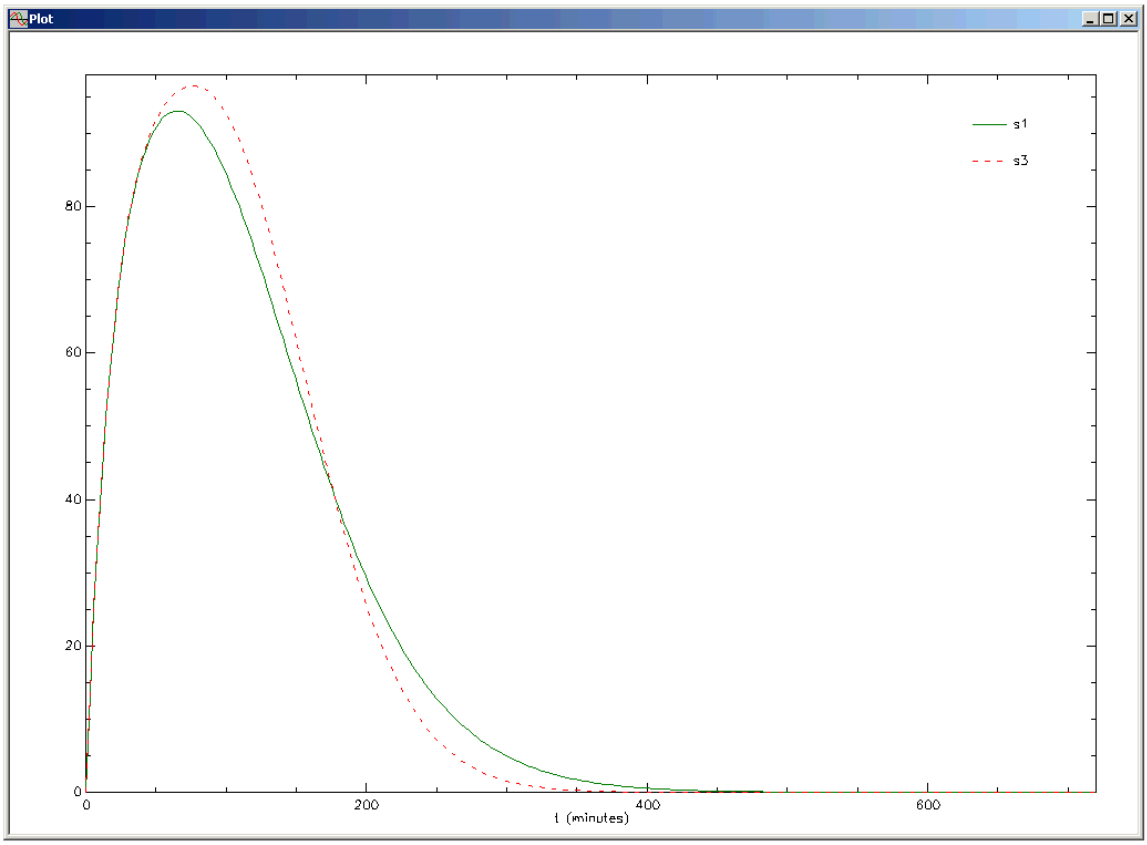


You can see that **s1** has a slightly skewed distribution with a mean around 150. You can also see that material starts to appear from Compartment **q6** (measured by **s2**) at around 30 minutes. Thus the "physiological" delay is about 30 minutes. The counterparts for the 10 compartment delay are shown in the following figure:

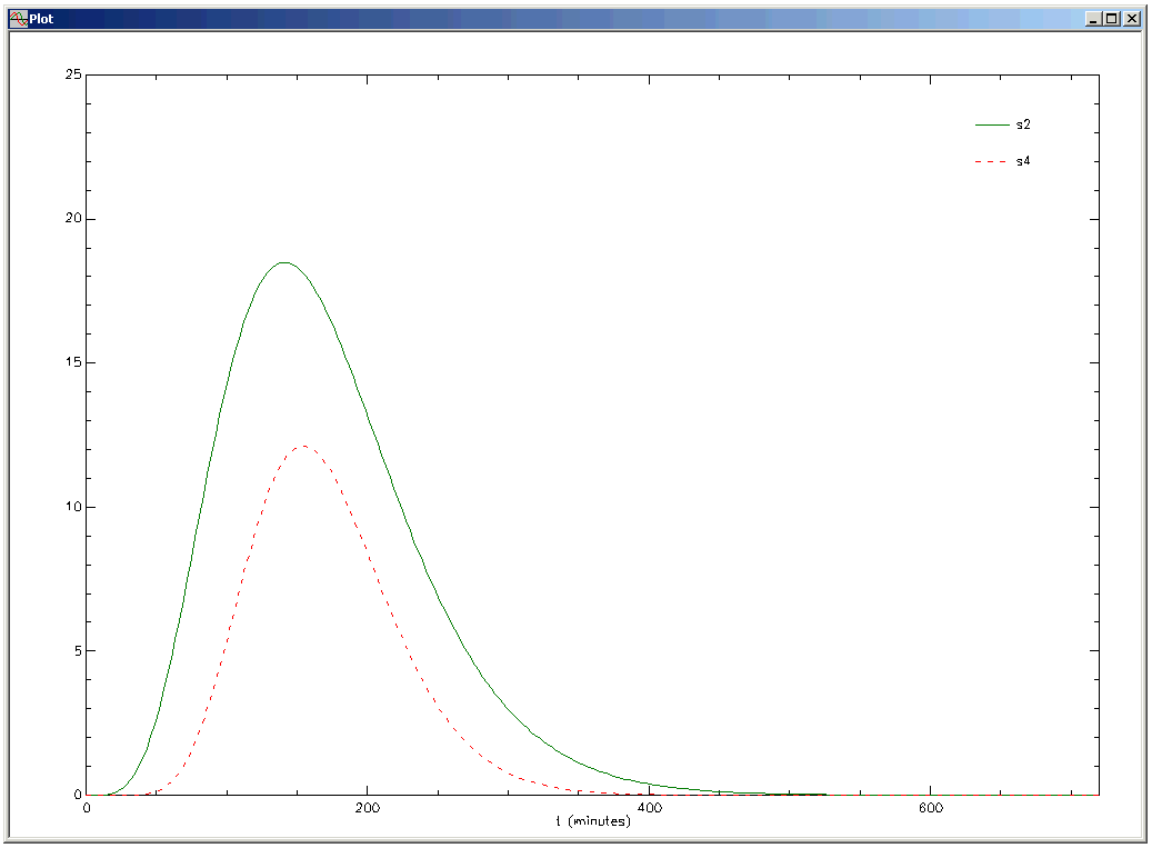


You can see the mean of the delay is again at 150, but now the width is smaller (as shown in the following figure). Material starts to appear from the last compartment in the delay (**s4**) at about 50 minutes.

Comparing the mass in the delay:



The 10 compartment delay, **s3**, has a slightly narrower distribution. Of interest is the effect on the "physiological" delay as shown in the following figure:

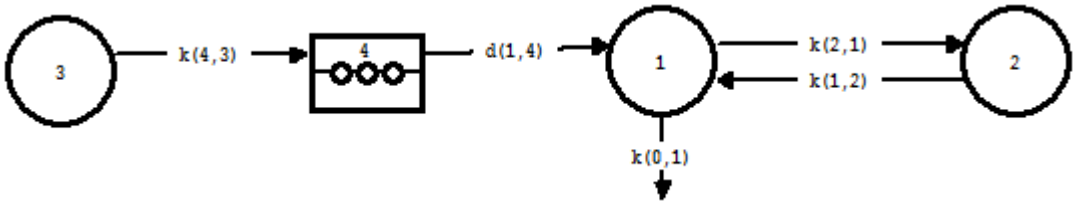


The difference in the appearance of material from the last compartment in the delay between the 5 and 10 compartment delay is quite dramatic.

In this tutorial, you will explore these phenomena in more detail so that you can better appreciate the nature of a string of compartments as a delay tool, and know better how to select the number of compartments.

Part 1. Working with the delay tool – Single output from the delay

In this part of the tutorial, you will create and work with the following model:

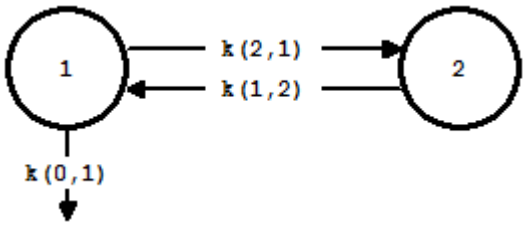


In the model shown above, Compartment **1** represents plasma and Compartment **2** represents an extra-plasma compartment. Thus, the "system" model, from the point of how the substance is metabolized in the body, is represented by these two compartments. Compartment **3** is the compartment into which the test substance, for example a drug, is administered. If the administration of the drug is oral, Compartment **3** can represent the first part of the gastrointestinal system. The Delay **4** represents passage and absorption of the drug through the gut. Since there is no loss from either Compartment **3** or Delay **4**, it is assumed that the drug is completely absorbed (100% absorption).

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

2. Create the model.

   a. Create the following part of the model.



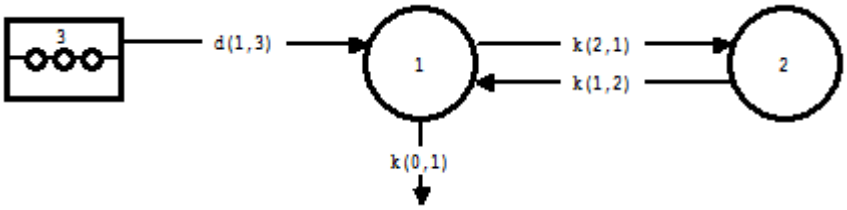
   b. Add the delay and transfer from the delay to Compartment **1**.

      (1) In the **SAAM II Toolbox**, click **Delay**.

      (2) Click on the **Drawing Canvas** where you would like the delay to be located.

      (3) In the **SAAM II Toolbox**, click **Flux**

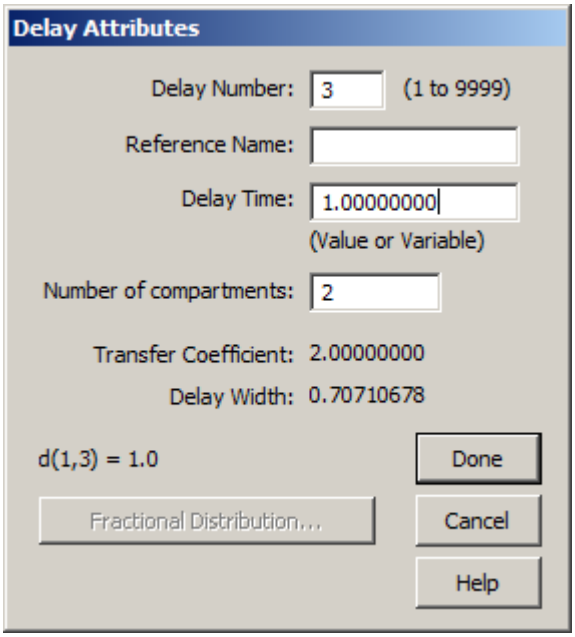
      (4) Click on Delay **3** and then Compartment **1**; the transfer *d(1,3)* will be created. Your model will appear as follows:



Transfers from delays. Transfers from delays are denoted by "*d(i,j)*" instead of "*k(i,j)*". The reason is that all material entering the delay eventually will leave the delay. Thus the *d(i,j)* represents a fraction of material moving along this pathway. In the model shown above, *d(1,3)* equals "1" because this is the only route by which material can leave the delay. If there were, for example, two routes by which material could leave the delay (as illustrated below in Part 2), the two *d(i,j)* would be numbers between 0 and 1, but the sum of the two would equal 1. An actual rate constant k(1,3) will be calculated internally by SAAM II; this value is available as output following a Solve or Fit. The value is the sum of the rate constants connecting the compartments in the chain representing the delay.

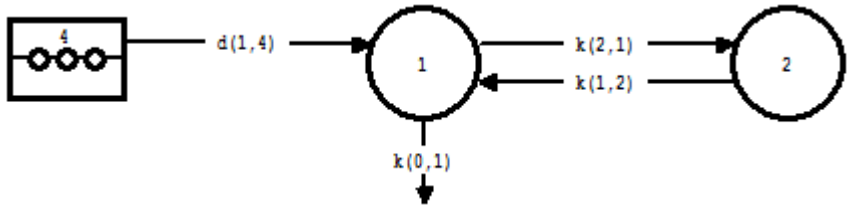
c. Change the number of the delay from "3" to "4".

(1) Double-click **Delay 3** to open the **Delay Attributes** dialog box. The dialog box will appear as follows:



(2) Change the **Delay Number** from "3" to "4".

(3) Click **Done**. Your model will appear as follows:



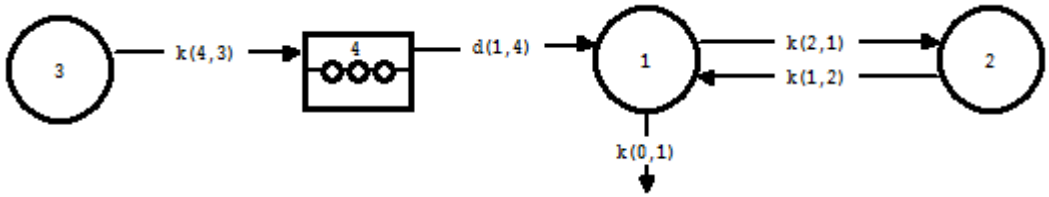
d. Add Compartment **3** and transfer *k(4,3)* to your model.

(1) In the **SAAM II Toolbox**, click **Compartment**.

(2) Click on the **Drawing Canvas** where you would like Compartment **3** located.

(3) In the **SAAM II Toolbox**, click **Flux**.

(4) Click on Compartment **3** and then Delay **4**. The transfer *k(4,3)* will be added to your model which should appear as follows:

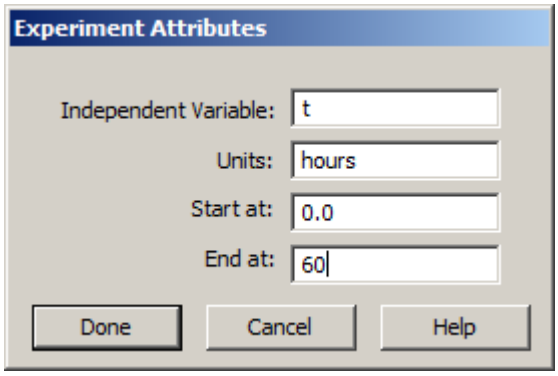


3. Create the experiment on the model.

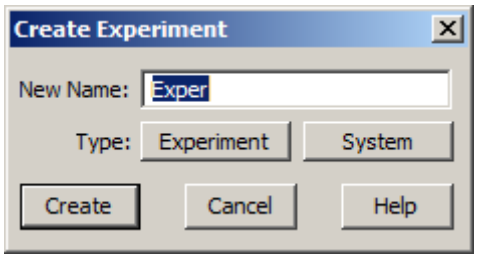
a. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open.

b. Change the entry in the **Units** box from "minutes" to "hours".

c. Type "60" in the **End At** box. The **Experiment Attributes** dialog box will appear as follows:

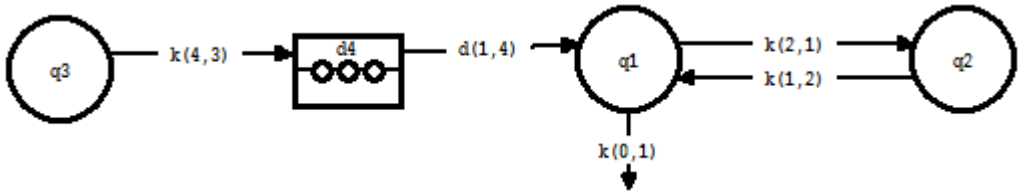


d. Click **Done**. The **Create Experiment** dialog box will open as shown below:



Be sure **Experiment** is selected (as indicated by "Exper" in the **New Name** box).

e. Click **Create**. Your model will appear as follows:

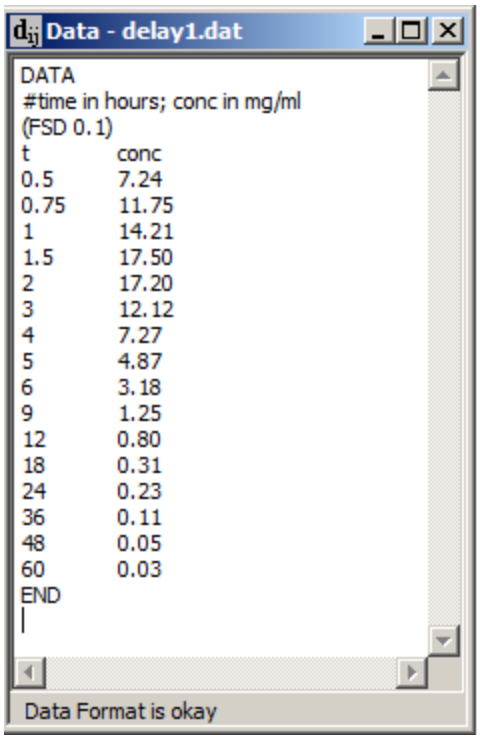


4. Add the data to the model

a. On the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data**  . The **Data** window will open.

b. On the **File** menu, click **Open**. The file **delay1.dat** should appear in the list (if it does not, find the folder where you put this data file).

c. Double-click **delay1.dat**. The data in this file will appear in the **Data** window as shown below:



d. Close the **Data** window.

5. Create the input and sample

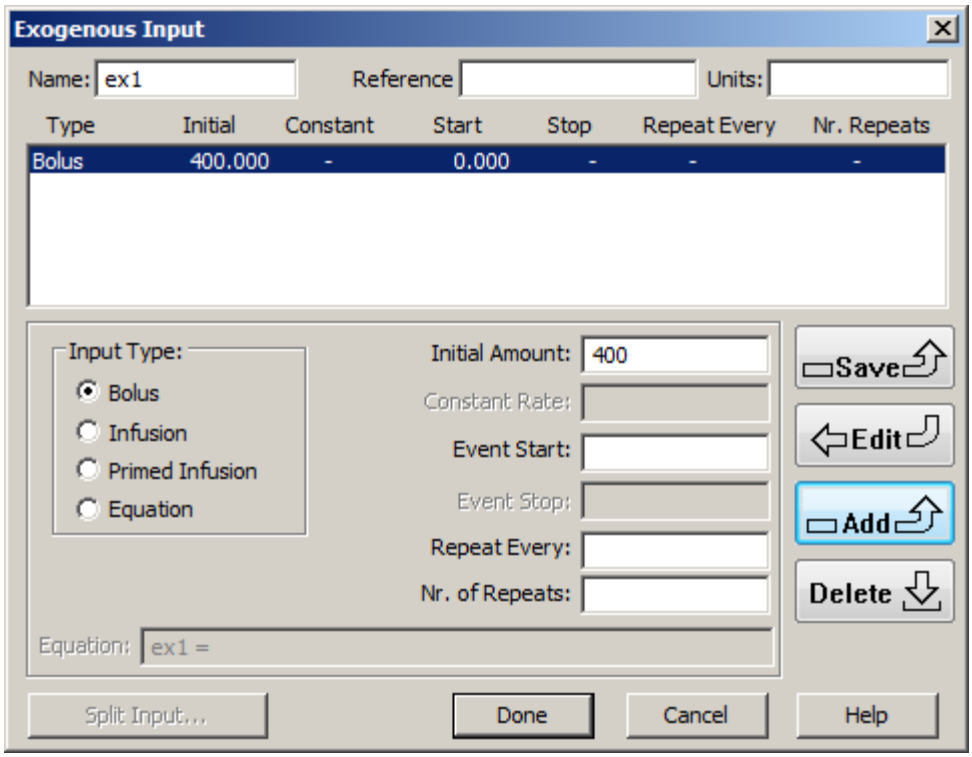
   a. In the **SAAM II Toolbox**, click **Input**.

   b. On the **Drawing Canvas**, click Compartment **q3**, and then click on the canvas. The input **ex1** will appear associated with your model.

   c. Double-click **ex1**. The **Exogenous Input** dialog box will open.

   d. Type "400" in the **Initial Amount** box.

   e. Click **Add**. The **Exogenous Input** dialog box should appear as follows:



f. Click **Done**.

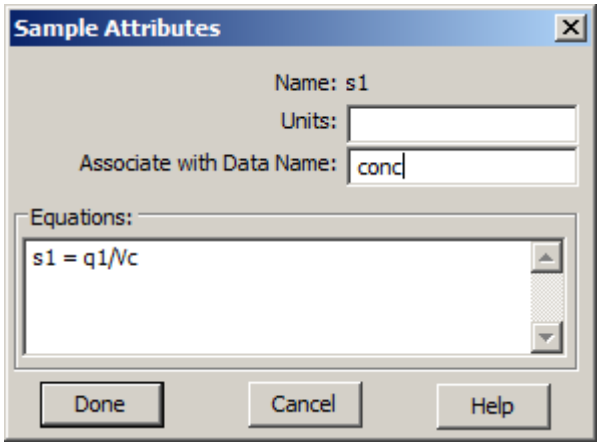
g. In the **SAAM II Toolbox**, click **Sample**.

h. On the **Drawing Canvas**, click Compartment **q1**, and then click on the canvas. The sample **s1** will appear associated with your model.

i. On the **Drawing Canvas**, double-click **s1** to open the **Sample Attributes** dialog box.

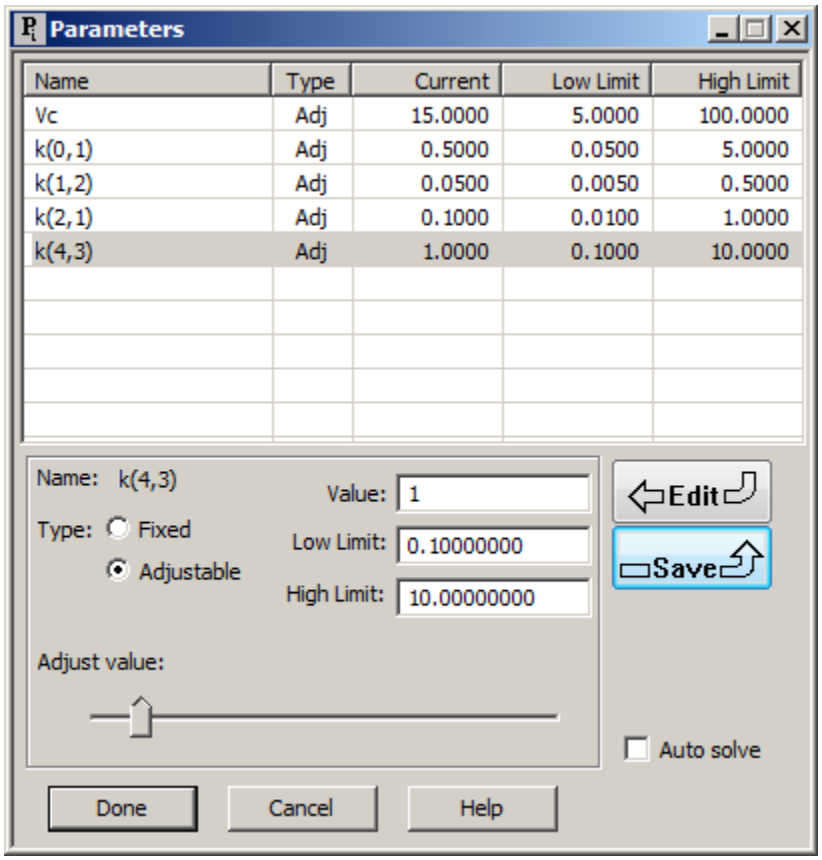
j. Type "conc" in the **Associate with Data Name** box.

k. Edit the sample equation to read "s1=q1/Vc" in the **Equation** box. The **Sample Attributes** dialog box will appear as follows:



l. Click **Done**.

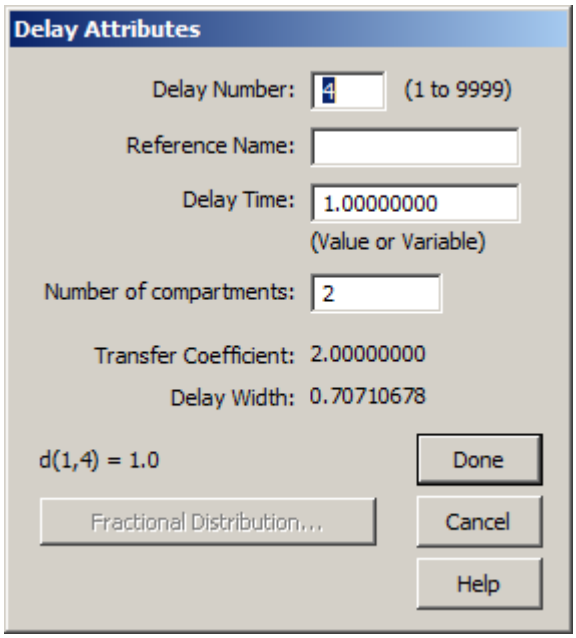
6. Enter the parameter values as shown below:



7. Work with the delay tool

At this point, your model is specified except for information about the delay. Information about the delay is specified in the **Delay Attributes** dialog box which is accessible only in the ***Model mode***.

The **Delay Attributes** dialog box is shown below:



The boxes in which information can be entered are:

Delay Number: Here you can specify the number you want associated with the delay.

Reference Name: You may add a reference name if you wish; this will appear associated with the delay in the same manner reference names appear with compartments.

Delay Time: The delay time can be specified here numerically if you know the exact time of the delay. It can also be specified as a parameter. For example, if you changed "1.0000000" to "deltime", deltime (delay time) would be interpreted by SAAM II as a parameter which would appear when you open the **Parameters** dialog box.

Number of Compartments: You can specify the number of compartments in the delay. The more compartments in the delay, the "sharper" the delay, but the more time it will take to solve your model.

Fractional Distribution: When there is only one pathway leaving the delay, this box is dimmed. If there is more than one pathway leaving the delay, the fractional delay is active. As described in Part 2, you must specify the characteristics of the split delay if there is more than one pathway leaving the delay.

Technical information about delays. The delay represents a transfer function corresponding to a probability distribution; the distribution has a mean and variance (standard deviation).

The mean is the delay time and the standard deviation is the delay width (measure of the sharpness of the delay).

The transfer coefficient equals the number of compartments in the delay divided by the delay time. In the above example, this is "2" divided by "1" which equals "2". Thus the transfer coefficient is reported as "2"

The delay width equals the square root of the delay time divided by the transfer coefficient. In the above example, this is the square root of ½ which equals 0.70710678.

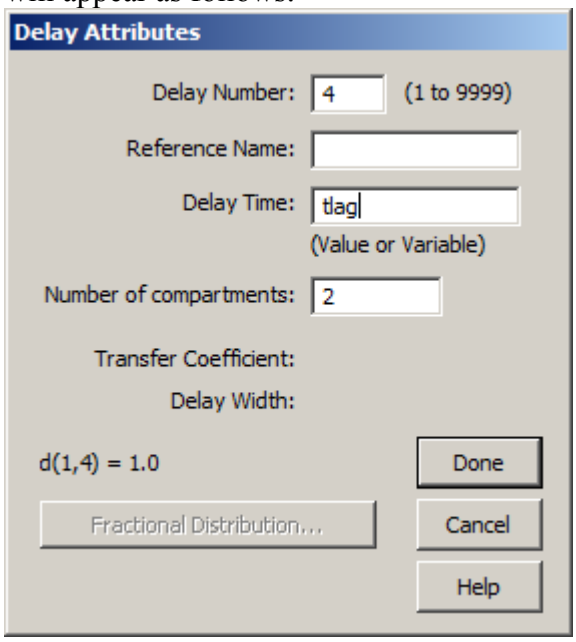
a. Set the time of the delay equal to a parameter.

This tutorial will not work with delays where the exact time value is known. If this were the case, simply enter the time of the delay in the **Delay Time** box, and enter the number of compartments in the delay in the **Number of compartments** box.

(1) In the **SAAM II Toolbox**, click **Model** to activate the Model tools.

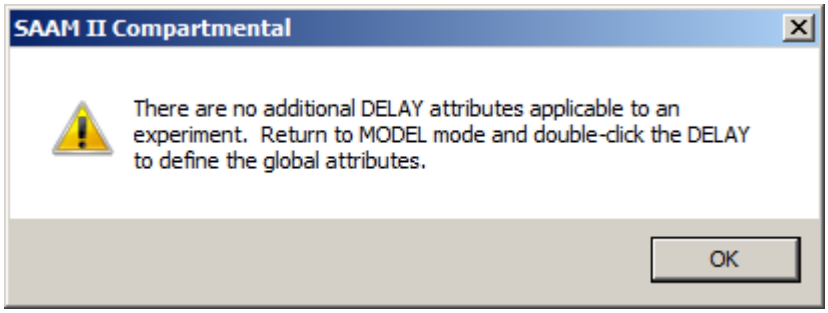
(2) Double-click Delay **4** to open the **Delay Attributes** dialog box.

(3) Change "1.0000000" to "tlag" in the **Delay Time** box. The **Delay Attributes** dialog box will appear as follows:



(4) Click **Done**.

The delay attributes dialog box. Remember the **Delay Attributes** dialog box can be opened only when you are in the **Model** mode. If you are in the **Experiment** mode and double-click on a delay, the following message will appear on the **Drawing Canvas**:



Click **OK**, and return to the **Model** mode.

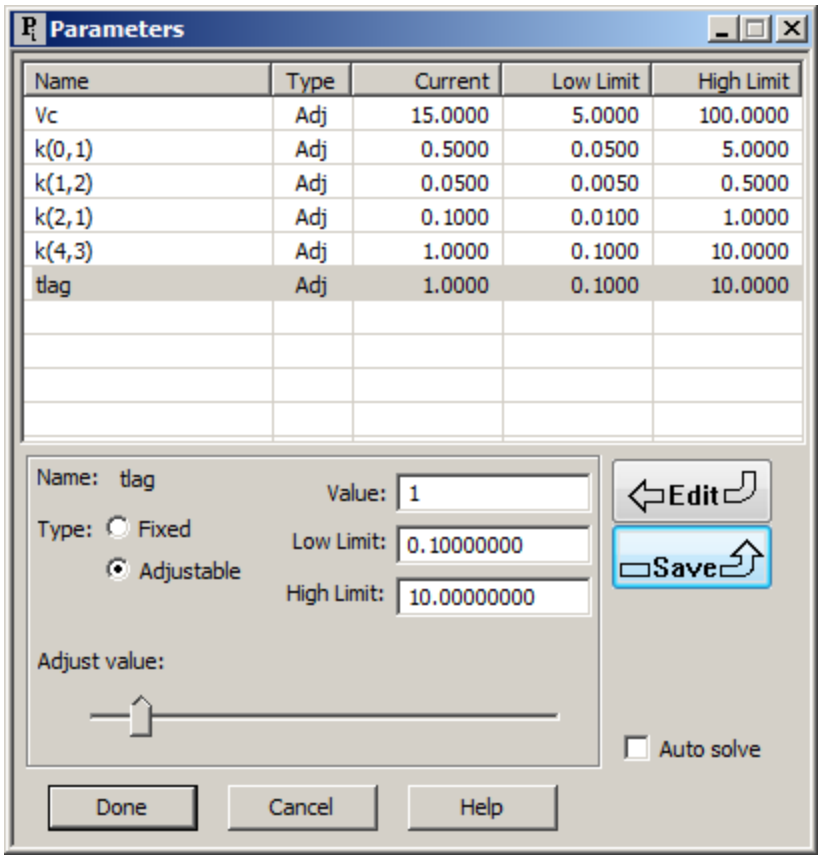
The delay time as a parameter. When you change the time of the delay from a number to a name, the name will appear as a parameter. In this case, *tlag* will appear when you open the **Parameters** dialog box. The time of a delay can be either a fixed or an adjustable parameter.

b. Work with the delay time.

In this part of the tutorial, three simulations will be run using different times for the delay. Remember the number of compartments in the delay is set at the default value "2". Each simulation will be saved, and a final plot comparing the three will be created.

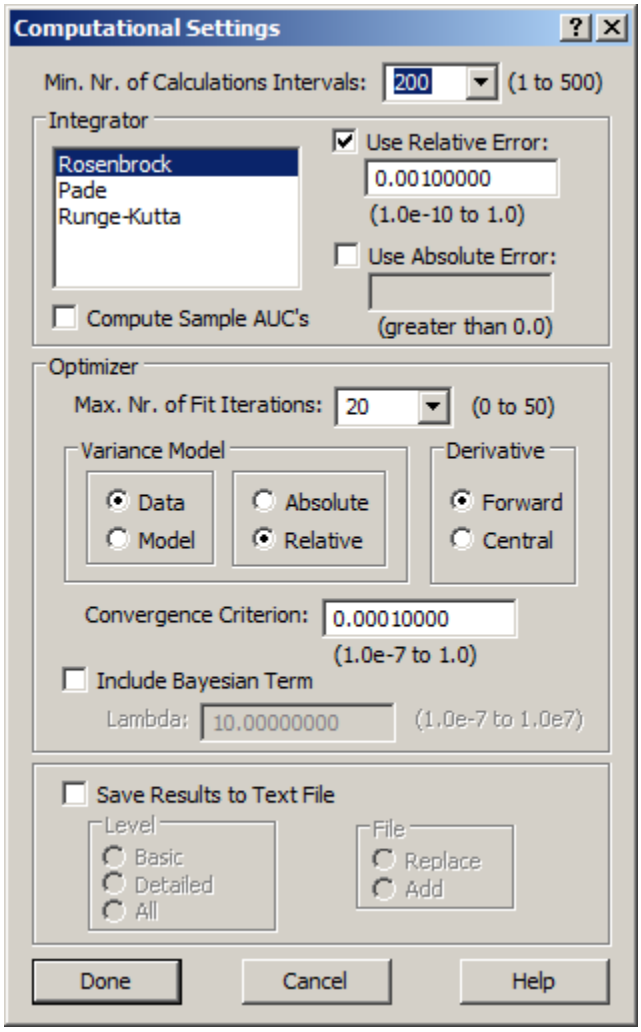
(1) In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters**  . The **Parameters** dialog box will open.

(2) Double-click *tlag* to select it. Type "1" in the value box, and click **Save**. The **Parameters** dialog box will appear as follows:



(3) Click **Done**.

(4) In the **Compute** menu, click **Settings**. The **Computational Settings** dialog box will open. In the **Min. Nr. of Calculation Intervals** box, change "20" to "200". The **Computational Settings** dialog box will appear as follows:



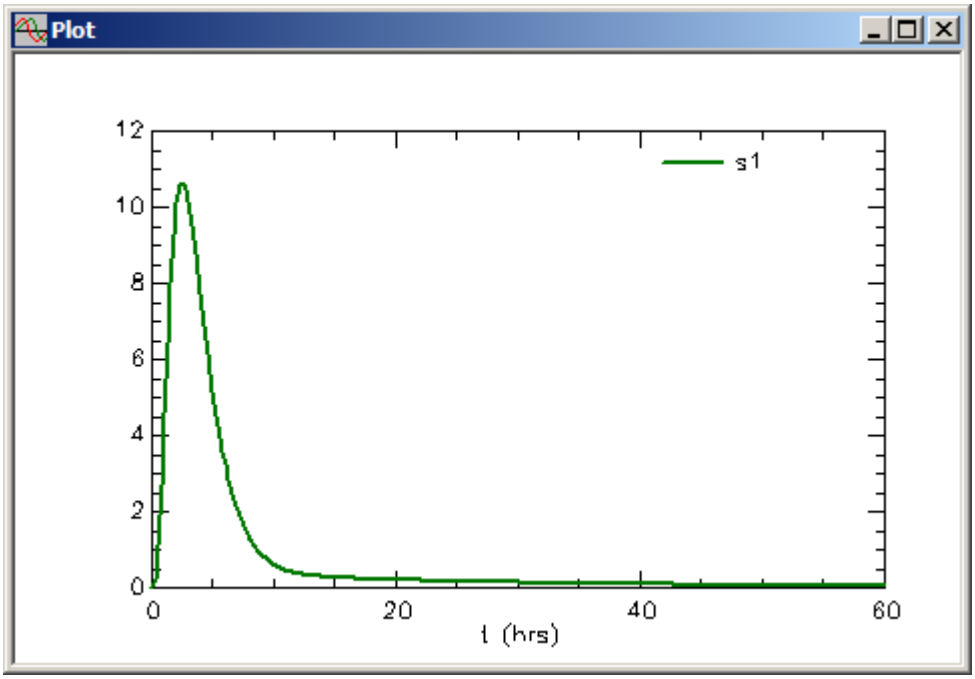
Click **Done**. (***Remember*** *increasing the calculation intervals will give better resolution to the plots*).

(5) In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve**  .

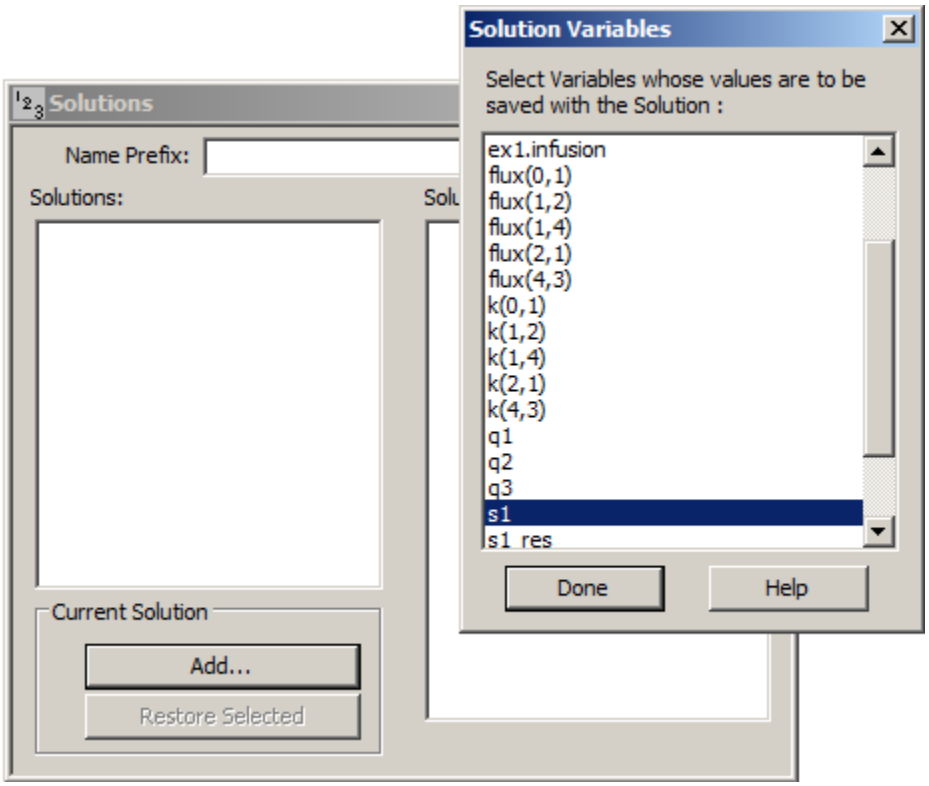
(6) In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot**  . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is selected.

(7) Click **s1** to move this to the **Current Selection** pane.

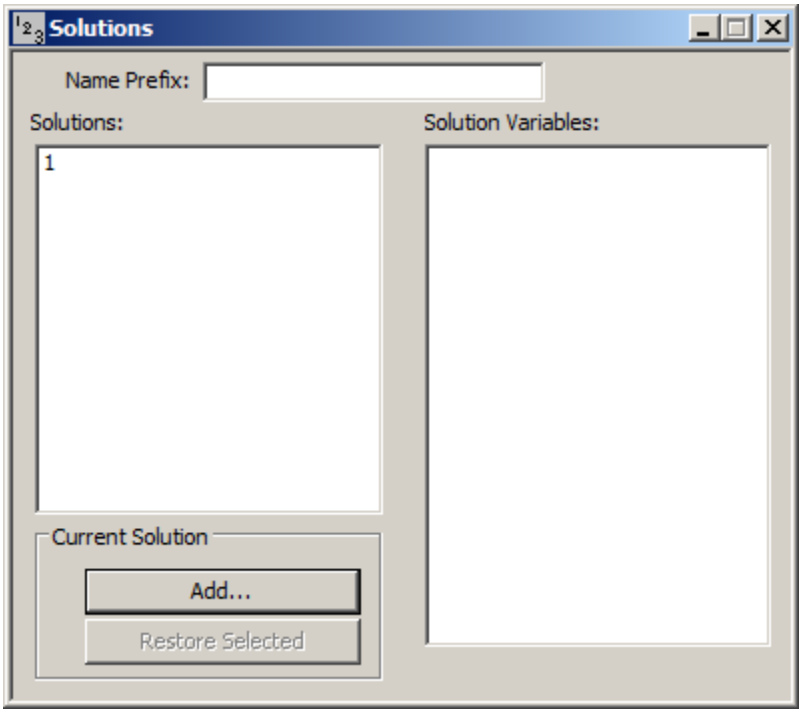
(8) Click **Done**. The plot will appear as follows (the maximum for the **Y Scale** has been set equal to "12")



(9) In the **Compute** menu click solutions. The **Solutions** dialog box will open. Click **Add**. The **Solutions Variables** dialog box will open. Scroll through the list, and select **s1**. The two dialog boxes will appear as follows:

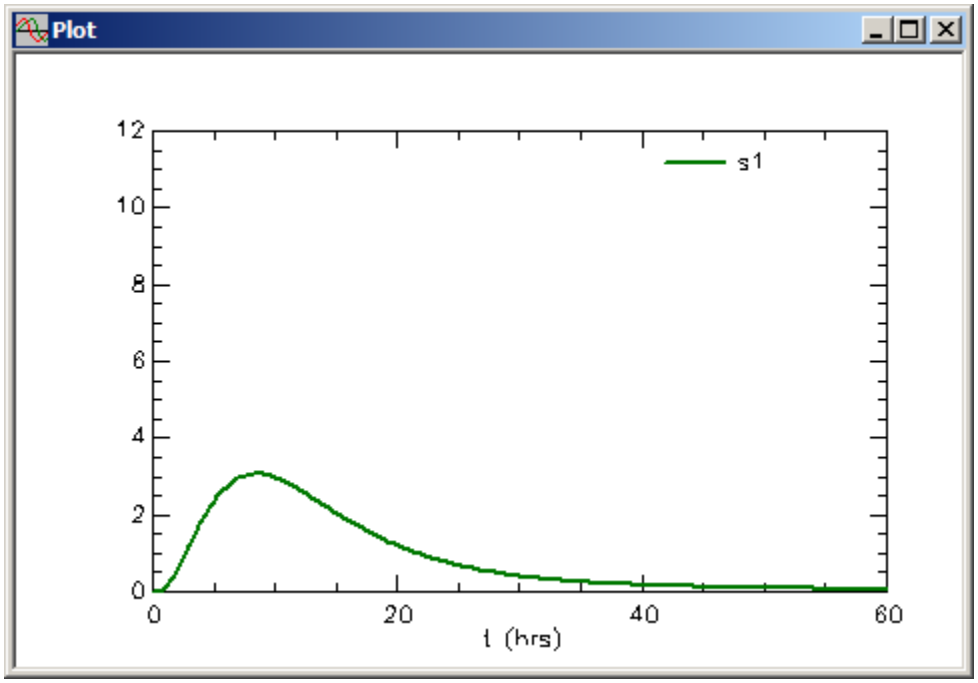


Click **Done**. The **Solutions** dialog box will appear as follows:



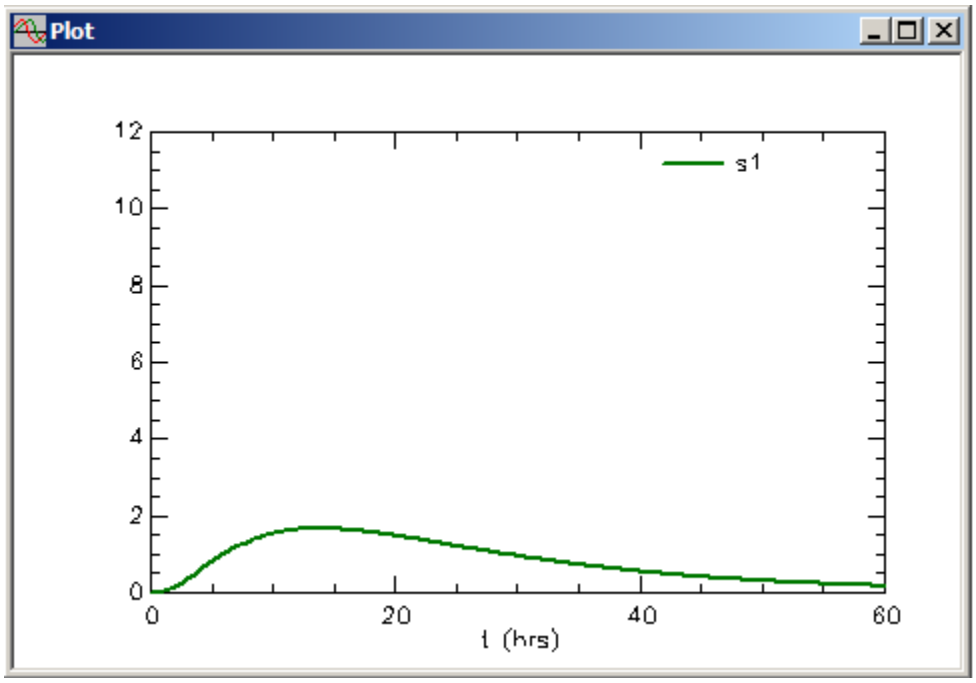
Close the **Solutions** dialog box.

(10) Set *tlag* equal to "10". Set the Upper Limit for tlag equal to "50". Repeat the above steps saving the solution as solution number "2". The plot will appear as follows:

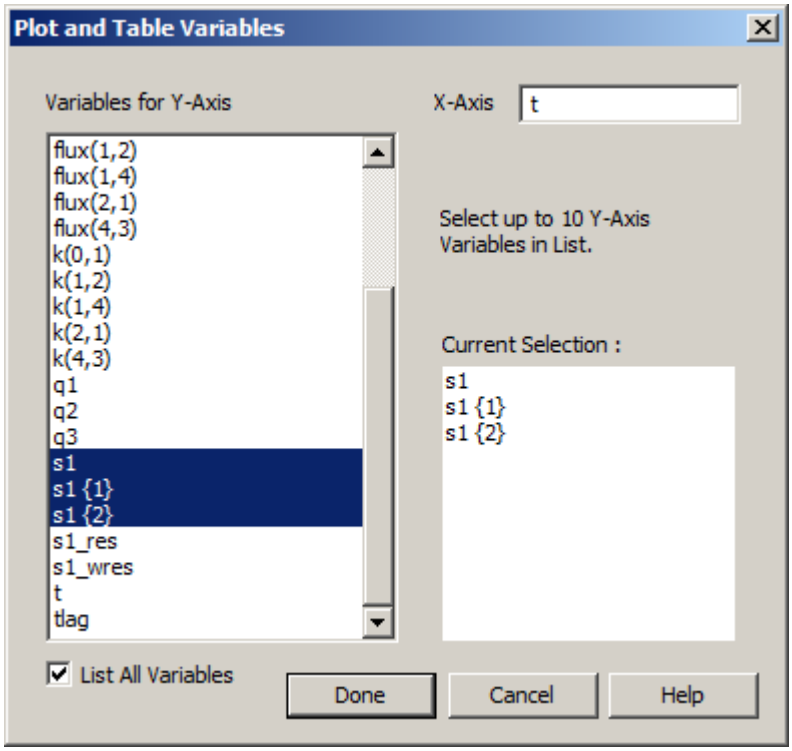


Notice the peak is not as high as when the delay was equal to "1". This is due to a combination of only two compartments in the delay, and the length of the delay time.

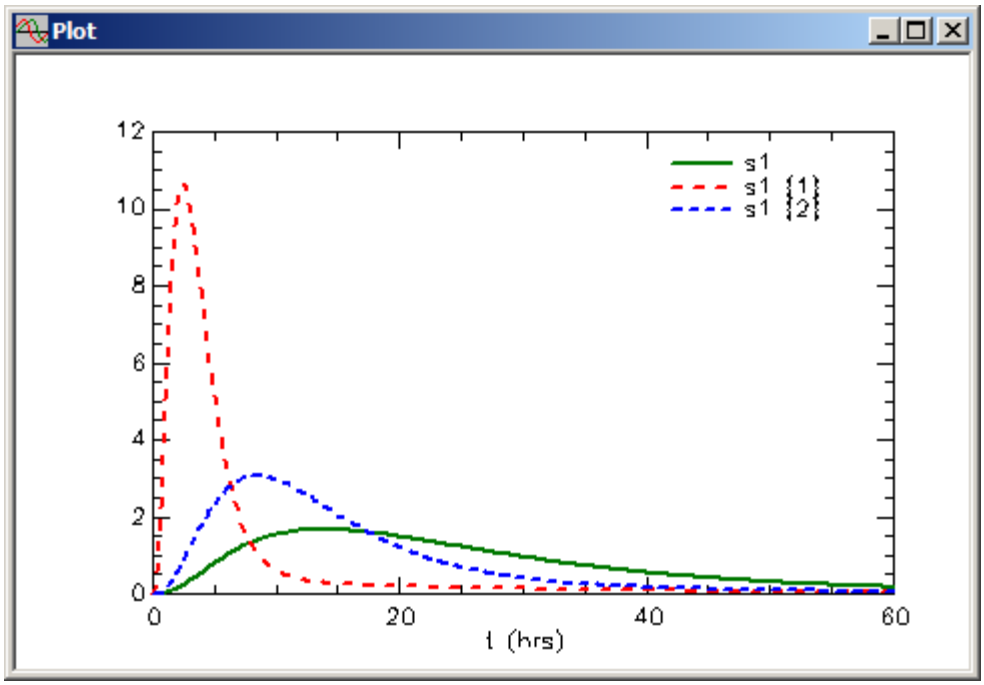
(10) Set *tlag* equal to "20", and repeat the above steps saving the solution as solution number "3". The plot will appear as follows:



(11) Plot all three simulations simultaneously. With the plot window open, in the **Set** menu, click **Plot/Tables Variables**; click the ***select variables button***  ; or ***right-click*** in the plot window and select ***variables***. The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is selected. Select **s1{1}**, **s1{2}** and **s1**; the **Plot and Table Variables** dialog box will appear as follows:



Click **Done**. The plot will appear as follows:



Close the **Plot** window.

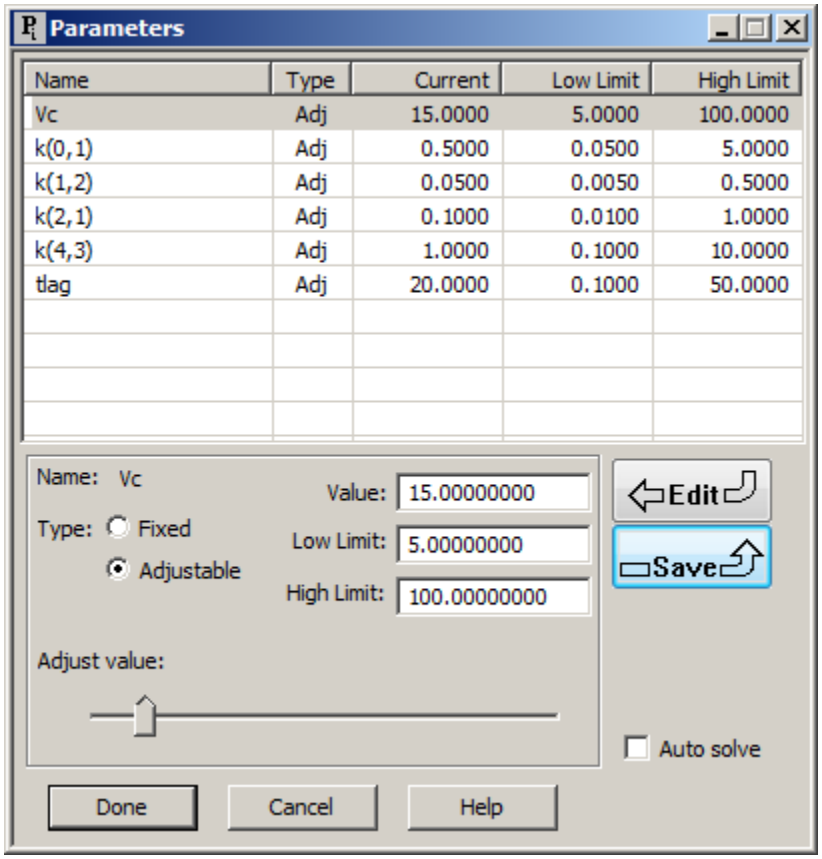
The delay time. For a given number of compartments in the delay, the longer the delay time, the less "pronounced" the delay will be. This is the result of the way the transfer between compartments in the delay is calculated.

The transfer coefficient equals the number of compartments in the delay divided by the delay time. In the above example, this is "2" divided by "1", "10" and "20" which equals "2", "0.2" and "0.01" respectively. The material is slower passing through the delay as the delay time increases.

The delay width equals the square root of the delay time divided by the transfer coefficient. This also increases as the delay time increases.

c. Work with the number of compartments in the delay.

In this part of the tutorial, the effect of the number of compartments in the delay will be investigated. Remember the number of compartments in the delay equals "2". Leave all parameters as set previously; leave *tlag* equal to "20". The **Parameters** dialog box should appear as follows:

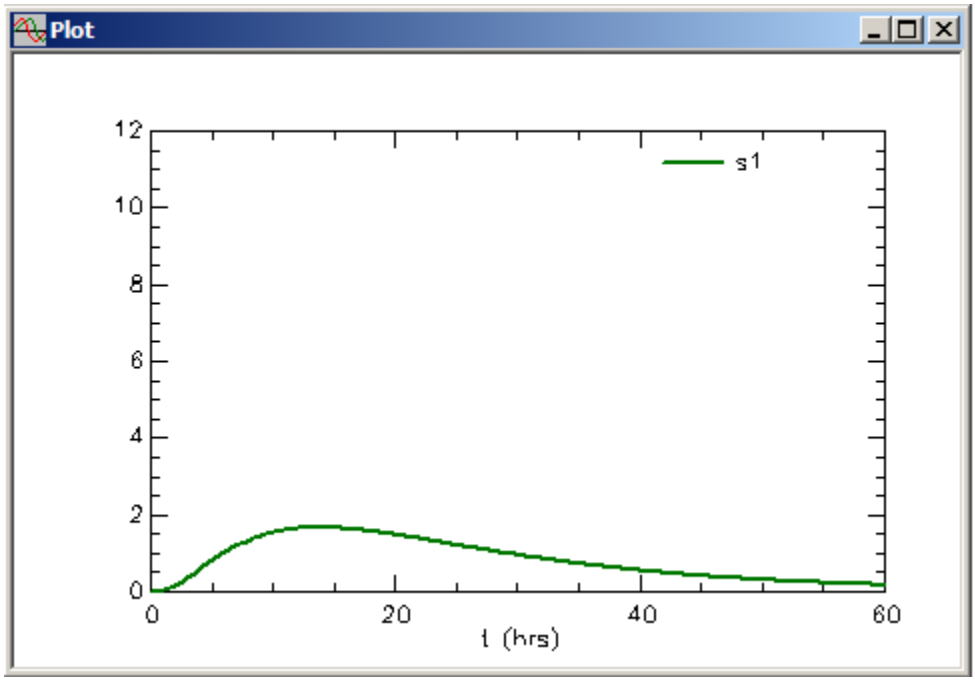


(1) In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve**  .

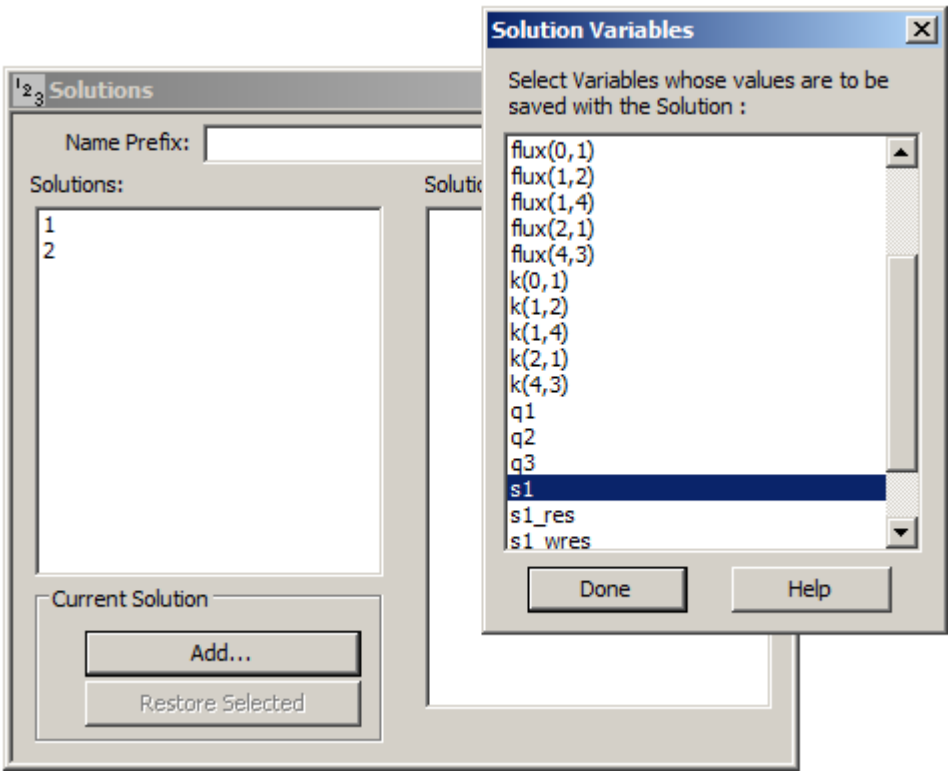
(2) In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot**  . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is selected.

(3) Click **s1** to move this to the **Current Selection** pane.

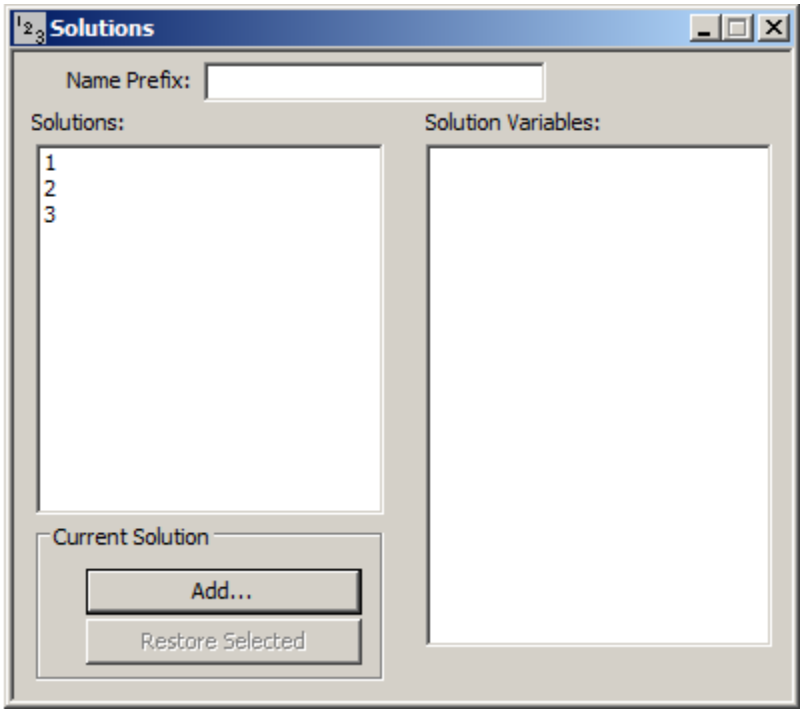
(4) Click **Done**. The plot will appear as follows (remember the maximum for the **Y Scale** has been set equal to "12")



(5) In the **Compute** menu click solutions. The **Solutions** dialog box will open. Click **Add**. The **Solutions Variables** dialog box will open. Scroll through the list, and select **s1**. The two dialog boxes will appear as follows (remember you already have saved solutions – this will be solution "3"):



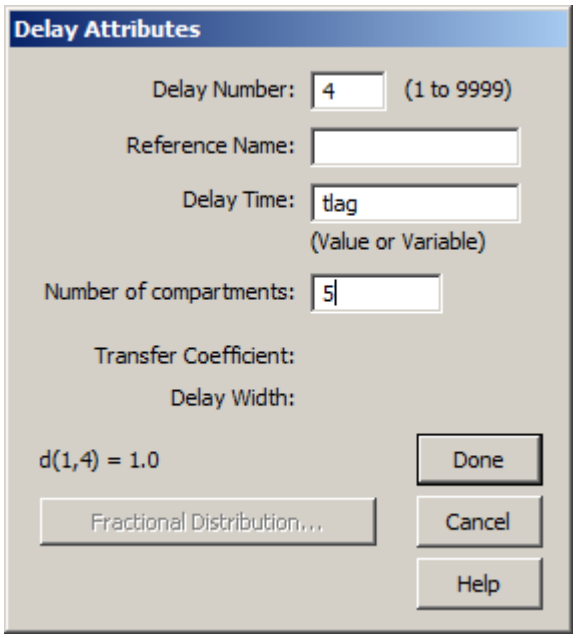
Click **Done**. The **Solutions** dialog box will appear as follows:



Close the **Solutions** dialog box.

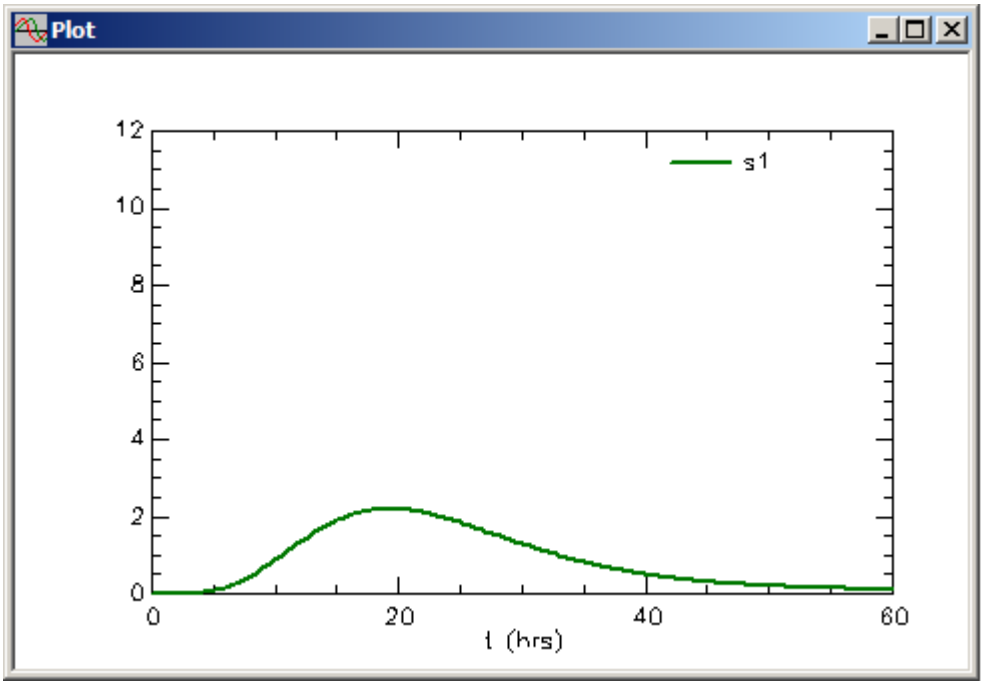
(7) In the **SAAM II Toolbox**, click **Model** to return to the **Model** mode.

(8) Double-click Delay **4** to open the **Delay Attributes** dialog box. Change the number of compartments in the delay from "2" to "5". The **Delay Attributes** dialog box will appear as follows:



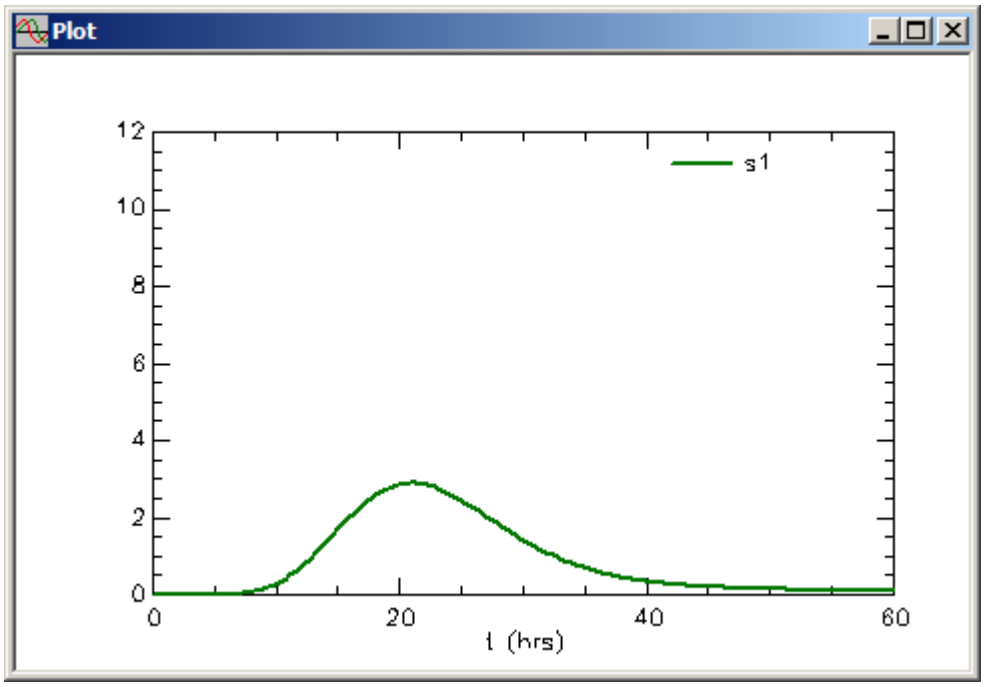
Click **Done**.

(9) Solve the model and view the solution. The plot will appear as follows:

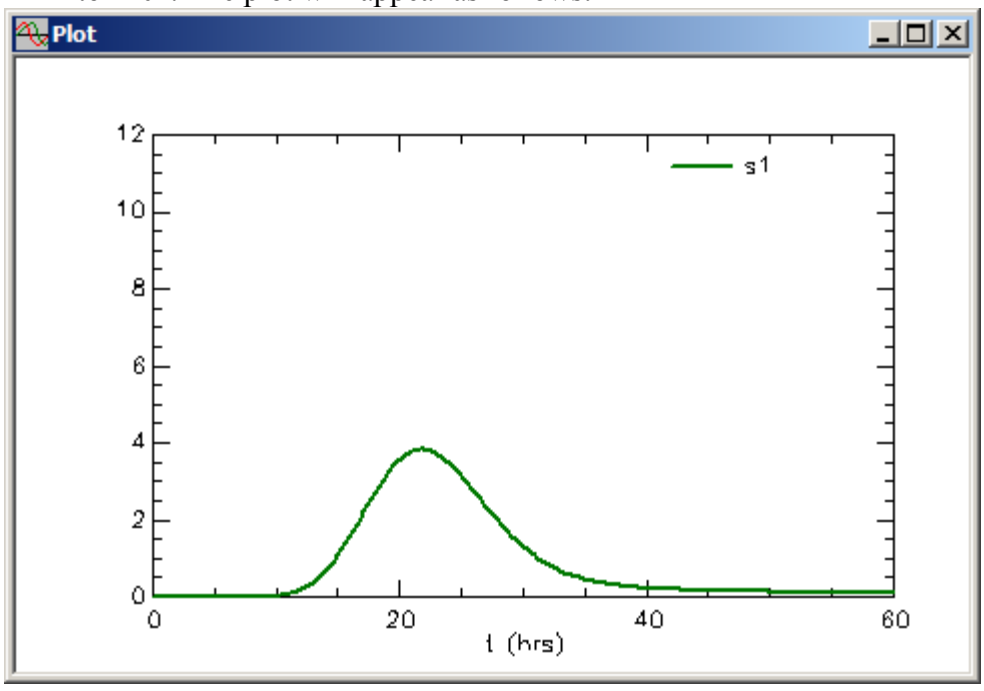


(10) Save **s1** as solution "4".

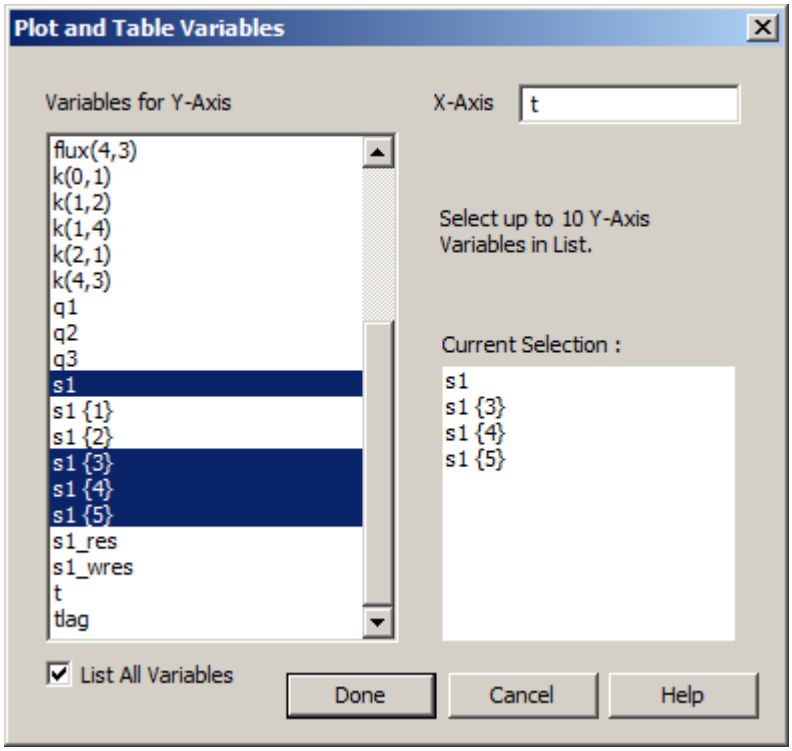
(11) Set the number of compartments in the delay equal to "10". Solve the model, view the solution, and save the solution as solution "5". The plot will appear as follows:



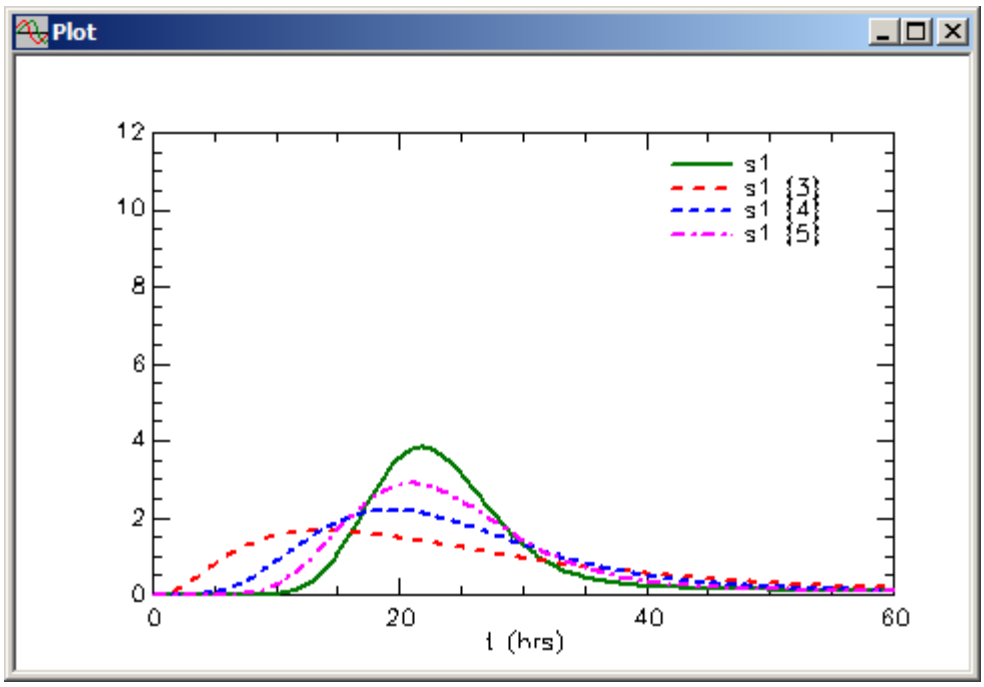
(12) Repeat the previous step with the number of compartments in the delay set equal to "20". The plot will appear as follows:



(13) Compare all four simulations. With the **Plot** window open, in the **Set** menu, click **Plot/Tables Variables**. In the **Plot and Table Variables** dialog box, select **s1{3}**, **s1{4}**, **s1{5}** and **s1**. The **Plot and Table Variables** dialog box will appear as follows:



Click **Done**. The plot will appear as follows:



The number of compartments in a delay. For a given delay time, the more compartments in the delay, the "sharper" the delay will become. This is the result of the way the transfer between compartments in the delay is calculated.

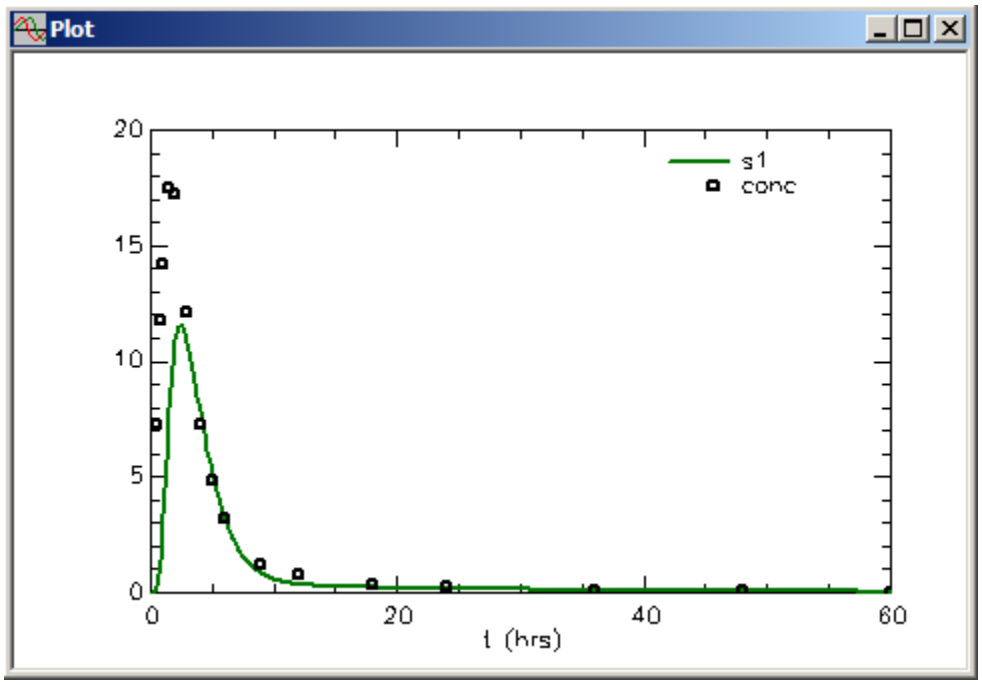
The transfer coefficient equals the number of compartments in the delay divided by the delay time. In the above example, this is "2", "5", "10" and "20" divided by "20". The material is faster passing through each compartment in the delay as the as the number of compartments increases.

d. Solve the model, and fit the model to the data.

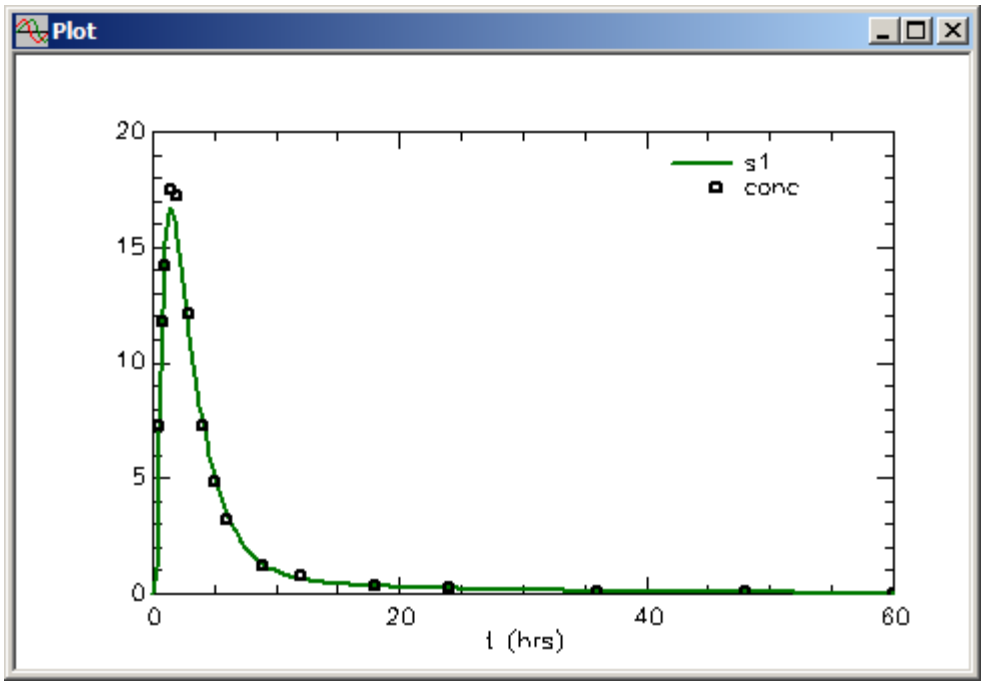
(1) Set the value for ***tlag*** equal to "1" with a minimum and maximum respectively equal to "0.1" and "10".

(2) Set the number of compartments in the delay equal to "5".

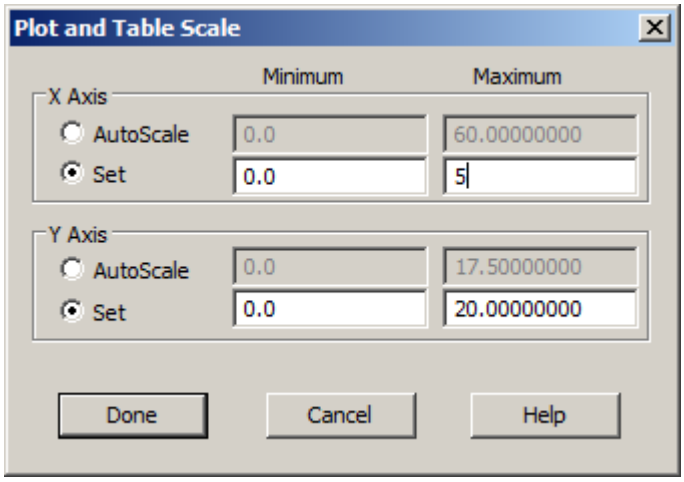
(3) Solve the model, and view the solution. The plot will appear as follows (the Y Scale maximum has been set equal to "20"):



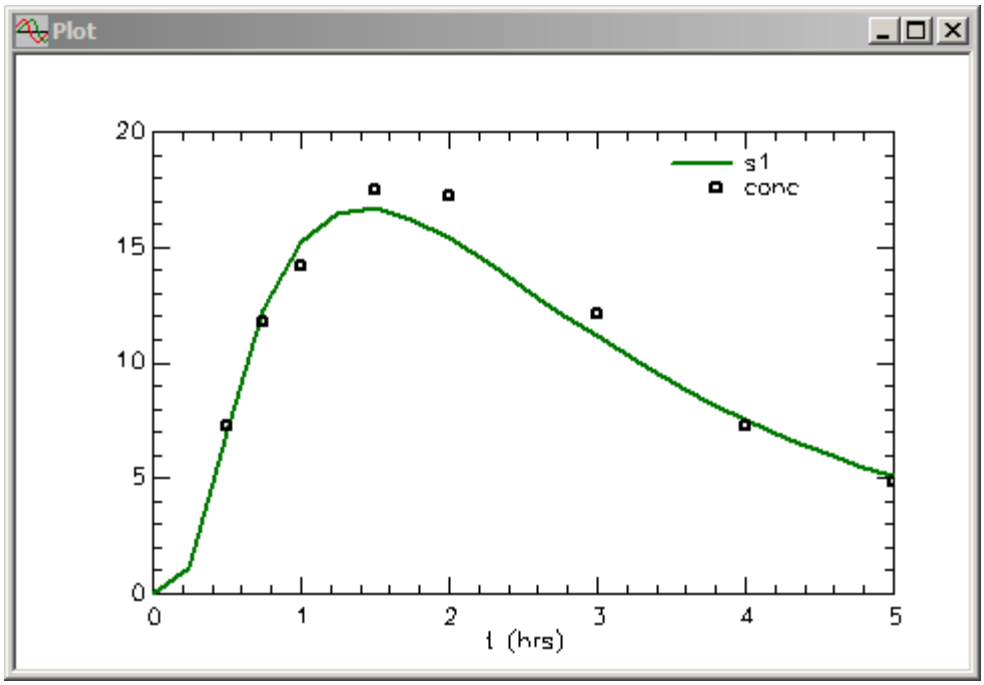
(4) In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar** click **Fit** . The plot will be updated as follows:



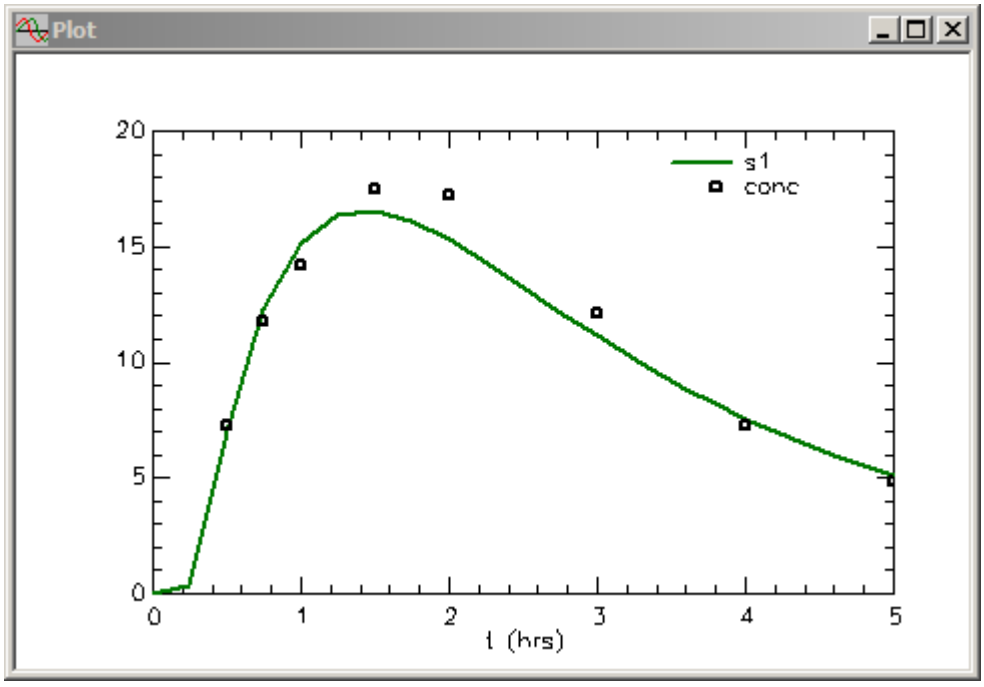
(5) View the details of the initial rise and fall. In the **Set** menu, click **Plot/Table Scale**. The **Plot and Table Scale** dialog box will open. Set the **X Axis** maximum equal to "5". The **Plot and Table Scale** dialog box will appear as follows:



Click **Done**. The plot will appear as follows:

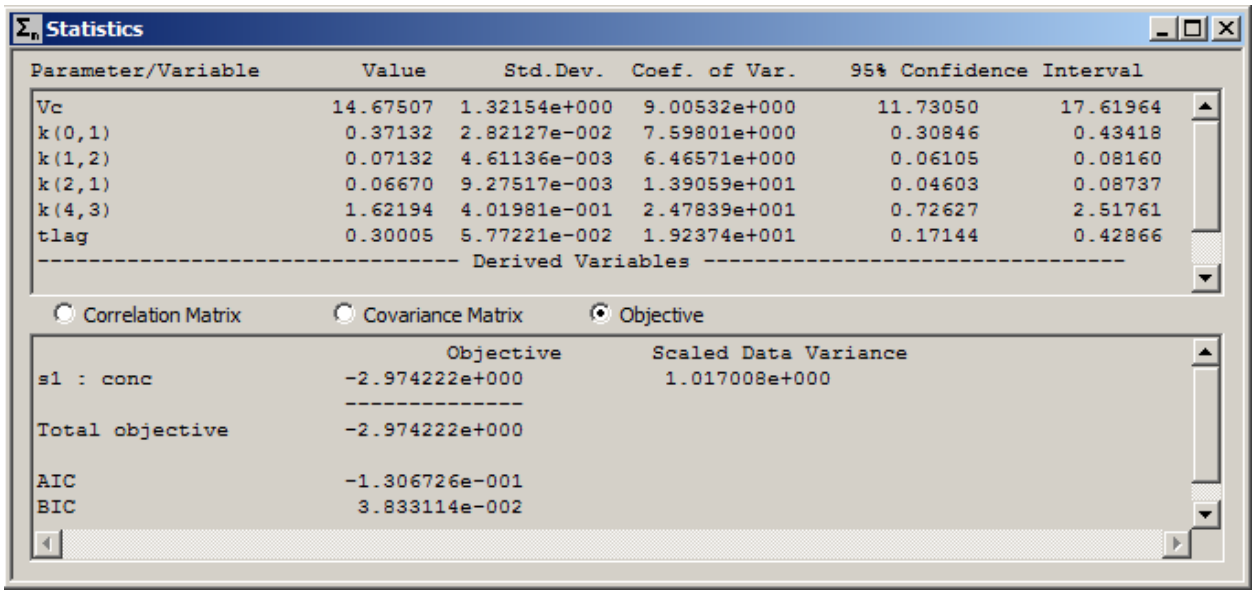


You can see the effect of the delay in the initial portion of the curve. What is the effect of the number of compartments in the delay in this situation? If you increase the number of compartments to "20", the plot will appear as follows:



The value for *tlag* is approximately 0.3, so you can see with the number of compartments equal to 20, the delay is approaching an absolute delay.

(6) View the statistics. In the **Show** menu, click **Statistics**, or alternatively on the **SAAM II Toolbar** click **Statistics**  . The **Statistics** window for the 5 delay compartment model will appear as follows:



Scrolling to reveal all of the values:

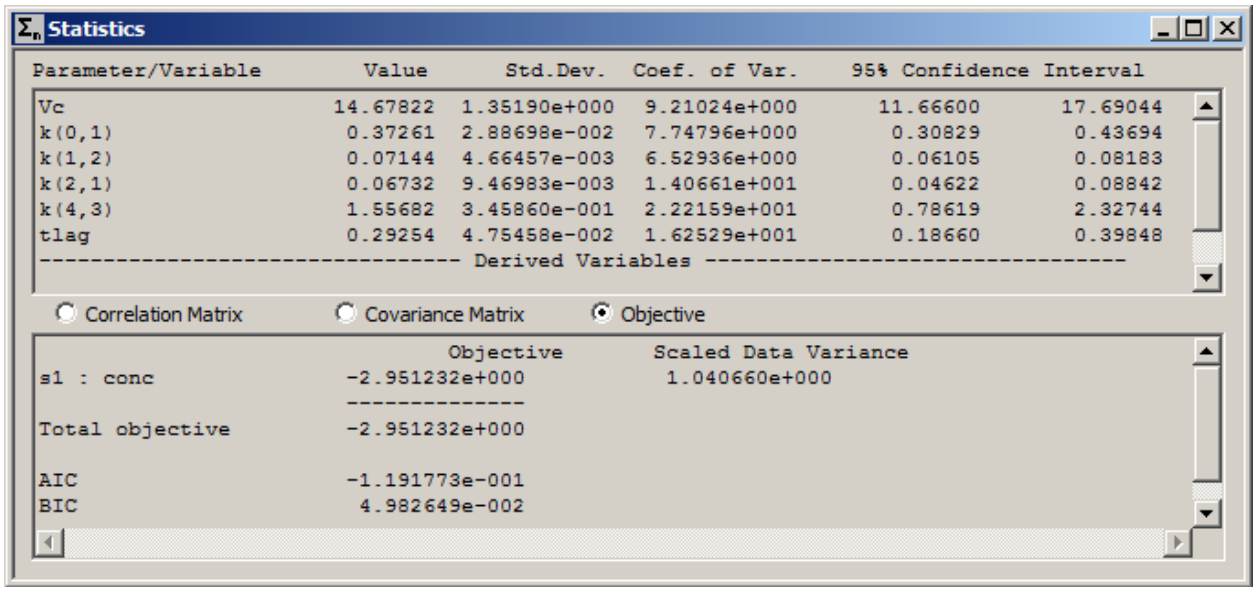
Vc	14.67507	1.32154e+000	9.00532e+000	11.73050	17.61964
k(0,1)	0.37132	2.82127e-002	7.59801e+000	0.30846	0.43418
k(1,2)	0.07132	4.61136e-003	6.46571e+000	0.06105	0.08160
k(2,1)	0.06670	9.27517e-003	1.39059e+001	0.04603	0.08737
k(4,3)	1.62194	4.01981e-001	2.47839e+001	0.72627	2.51761
tlag	0.30005	5.77221e-002	1.92374e+001	0.17144	0.42866
Derived Variables					
k(1,4)	16.66383	3.20572e+000	1.92376e+001	9.52103	23.80663

The statistics for the model and data are satisfactory since the largest coefficient of variation is just under 25%. Notice, however, the derived variable *k(1,4)*. There is no *k(1,4)* in the model; there is a *d(1,4)* for the delay. The value for *k(1,4)* is the value for the rate constants in the delay, and equal to the transfer rate constant from the last compartment in the delay to Compartment **1**.

It should be noted that the statistics will change a little if you change the number of compartments in the delay. The largest change will normally be in *k(1,4)* whose numerical value is a function of the number of compartments in the delay.

How many compartments in a delay. The number of compartments in a delay is an integer, and cannot be specified as an adjustable parameter. The number of compartments is set by the user, and can be determined by simulating which number

provides the most reasonable description of the data. You need to be sure that the number of compartments in the delay does not have a substantial effect on the model parameters. For example, in the above if the number of compartments in the delay is set at "20", the statistical information is:



Scrolling to reveal all of the values:

Vc	14.67822	1.35190e+000	9.21024e+000	11.66600	17.69044
k(0,1)	0.37261	2.88698e-002	7.74796e+000	0.30829	0.43694
k(1,2)	0.07144	4.66457e-003	6.52936e+000	0.06105	0.08183
k(2,1)	0.06732	9.46983e-003	1.40661e+001	0.04622	0.08842
k(4,3)	1.55682	3.45860e-001	2.22159e+001	0.78619	2.32744
tlag	0.29254	4.75458e-002	1.62529e+001	0.18660	0.39848
Derived Variables					
k(1,4)	68.36737	1.11118e+001	1.62531e+001	43.60868	93.12607

You can see there is essentially no difference **except** in the value of *k(1,4)* which, because the number of compartments is different, should be different.

(7) Close all open windows and dialog boxes.

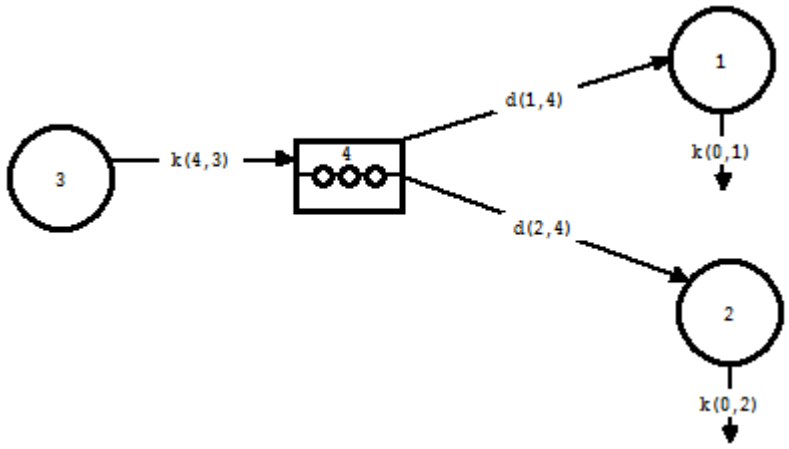
(8) **Quit** the **SAAM II Compartmental** application. You may save the study file if you wish. Note that it is provided as part of this tutorial as **delay1.stu**.

A Note about Solution Names:
Although the Solution # tacked onto the name prefix cannot be controlled, the user can ***specify the Name Prefix*** each time a solution is saved. An illustration of this use: In the previous example, the Solution names could have been specified as Lag1_1, Lag10_1, Lag20_1, C5_1, C10_1, C20_1, and the last two solutions could have been saved as FitC5_1 and FitC20_1.

Part 2. Working with the delay tool – Split output from the delay

This part of the tutorial assumes you have worked through Part 1, and hence are familiar with the role of delay time and the number of compartments in the delay.

In this part of the tutorial, you will create and work with the following model:

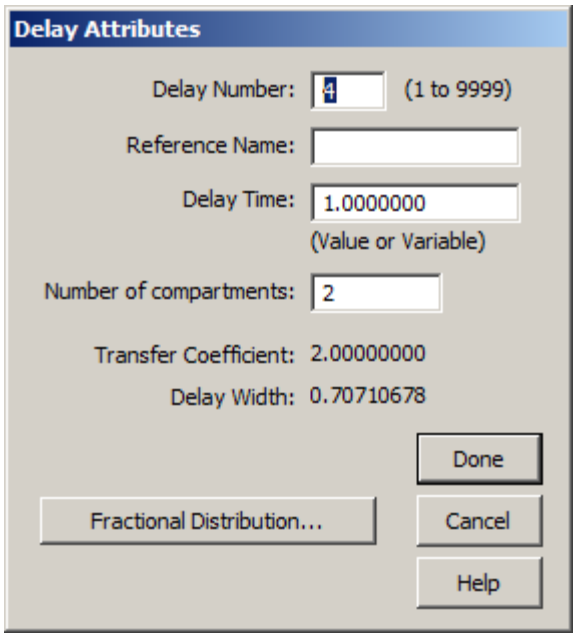


In the model shown above, Compartments **1** and **2** represent two distinct plasma compartments of the test substance introduced into the system. Thus, the "system" model, from the point of how the substance is metabolized in the body, is represented by these two compartments. Compartment **3** is the compartment into which the test substance, for example a drug, is administered. If the administration of the drug is oral, Compartment **3** can represent the first part of the gastrointestinal system. The Delay **4** represents passage and absorption of the drug through the gut. Since there is no loss from either Compartment **3** or Delay **4**, it is assumed that the drug is completely absorbed (100% absorption). The two plasma compartments in this situation could be interpreted as a drug and a metabolite of the drug where conversion takes place during the absorptive process.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

2. Create the **Model** shown above.

3. Double-click Delay **4** to open the **Delay Attributes** dialog box. The **Delay Attributes** dialog box will open as follows:



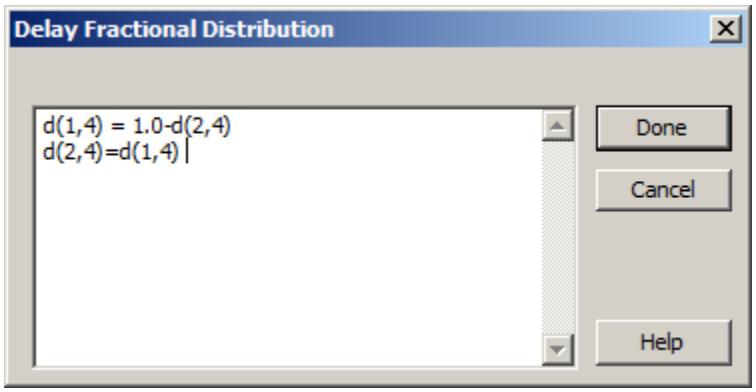
Notice unlike the situation in Part 1, the **Fractional Distribution** check box is active. This is because there are two outputs from Delay **4**.

4. Set the **Delay Attributes**.

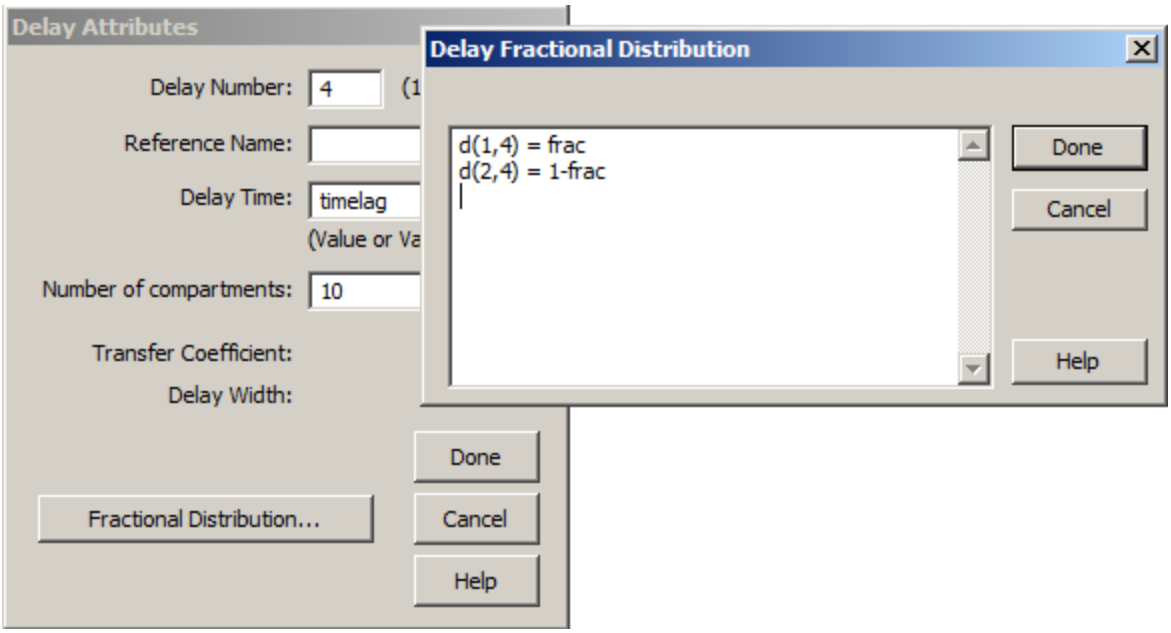
   a. Change the **Delay Time** from "1.000000" to "timelag"; *timelag* will become a model parameter.

   b. Change the **Number of compartments** from "2" to "10".

   c. Click the **Fractional Distribution** check box. The **Delay Fractional Distribution** dialog box will open as shown below:



Edit the equation "d(1,4) = 1.0-d(2,4)" to read "d(1,4) = frac". Edit the equation "d(2,4)=d(1,4)" to read "d(2,4)=1-frac". The **Delay Fractional Distribution** dialog box and the **Delay Attributes** dialog box will appear as follows:



d. Click **Done** in the **Delay Fractional Distribution** dialog box, and then click **Done** in the **Delay Attributes** dialog box.

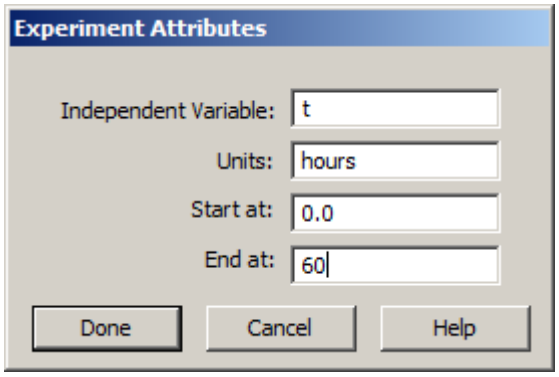
Fractional distribution from a delay. When there is more than one loss from a delay, you must specify the fractional distribution along each loss pathway. It is essential to remember that the total fractional loss must equal 1. Thus when you specify the fractional distribution, you must be sure the total equals 1. In the situation here, *d(2,4)* is defined as a parameter *frac*; this parameter will appear in the **Parameters** dialog box. The equation "d(1,4) = 1.0 – d(2,4)" will define *d(1,4)* in such a way that "d(1,4) + d(2,4) = 1." With two losses from a delay, making sure the sum of the fractional output equals "1" is easy; with more than two losses, it requires more bookkeeping.

5. Create the **Experiment** on the model.

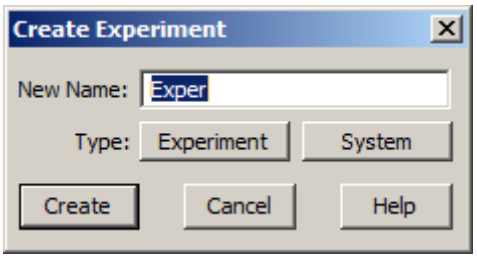
   a. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open.

   b. Change the entry in the **Units** box from "minutes" to "hours".

   c. Type "60" in the **End At** box. The **Experiment Attributes** dialog box will appear as follows:



d. Click **Done**. The **Create Experiment** dialog box will open as shown below:



Be sure **Experiment** is selected (as indicated by "Exper" in the **New Name** box).

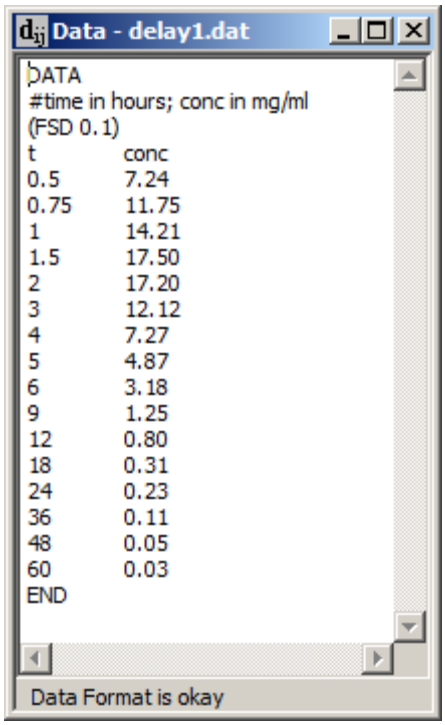
e. Click **Create**.

6. Add the **Data** to the model

a. On the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data**  . The **Data** window will open.

b. On the **File** menu, click **Open**. The file **delay1.dat** should appear in the list (if it does not, find the folder where you put this data file).

c. Double-click **delay1.dat**. The data in this file will appear in the **Data** window as shown below:



d. Close the **Data** window.

7. Create the **Input and Sample** in the **Experiment** window.

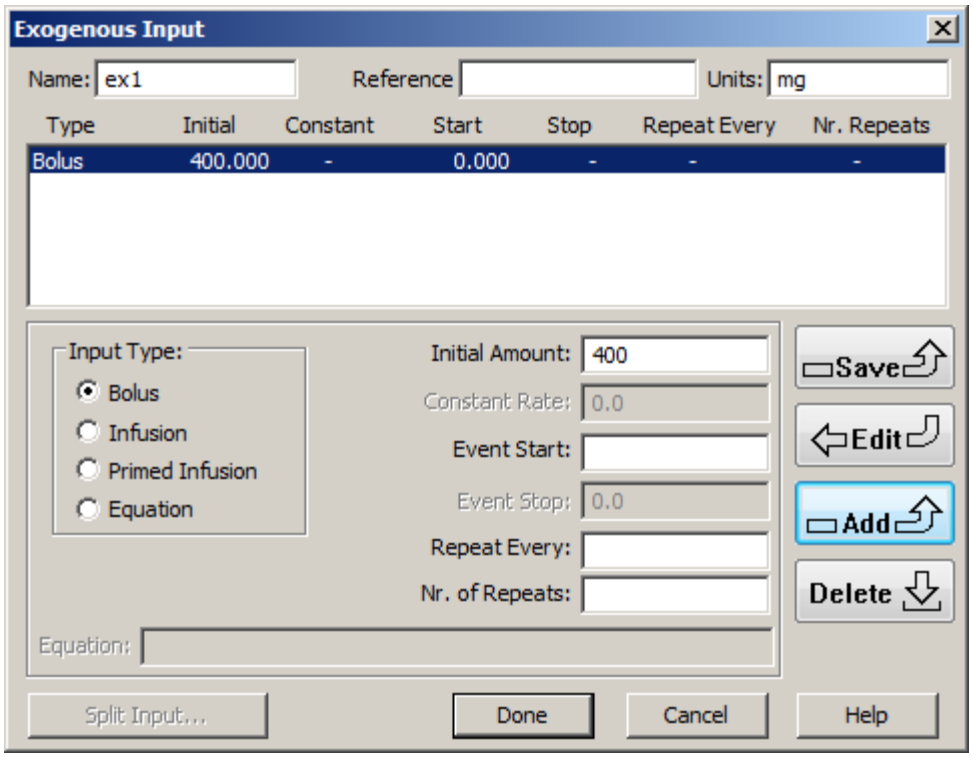
   a. In the **SAAM II Toolbox**, click **Input**.

   b. On the **Drawing Canvas**, click Compartment **q3**, and then click on the canvas. The input **ex1** will appear associated with your model.

   c. Double-click **ex1**. The **Exogenous Input** dialog box will open.

   d. Type "400" in the **Initial Amount** box.

   e. Click **Add**. The **Exogenous Input** dialog box should appear as follows:



f. Click **Done**.

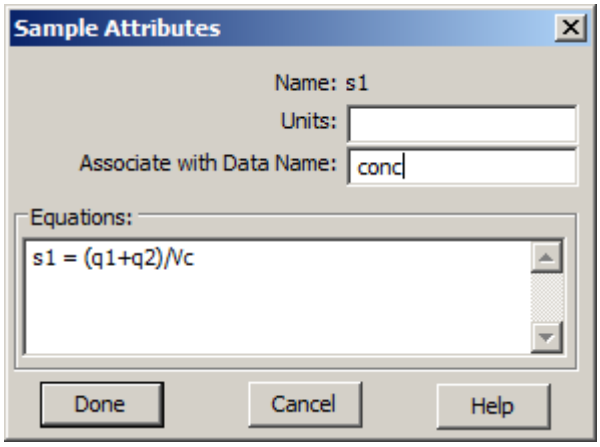
g. In the **SAAM II Toolbox**, click **Sample**.

h. On the **Drawing Canvas**, click Compartments **q1** and **q2**, and then click on the canvas. The sample **s1** will appear associated with your model.

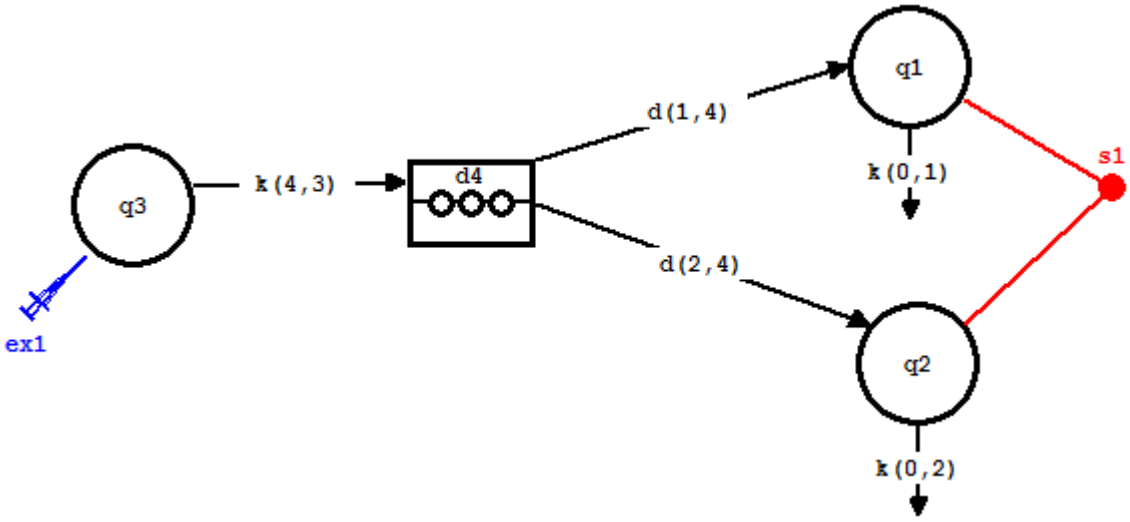
i. On the **Drawing Canvas**, double-click **s1** to open the **Sample Attributes** dialog box.

j. Type "conc" in the **Associate with Data Name** box.

k. Edit the sample equation to read "s1=(q1+q2)/Vc" in the **Equation** box. The **Sample Attributes** dialog box will appear as follows:

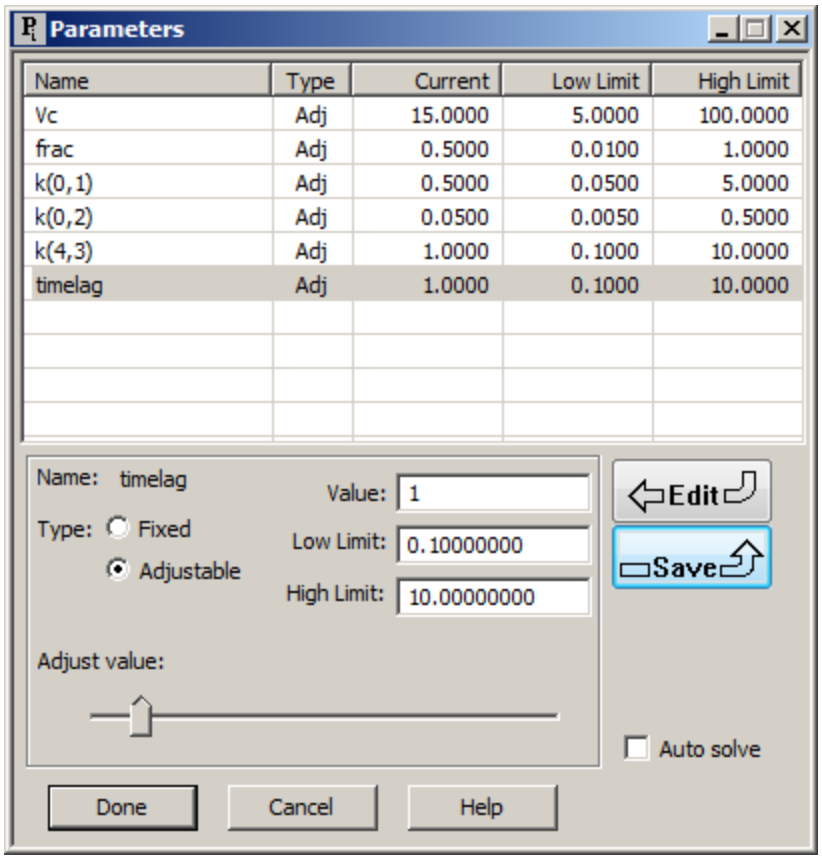


Click **Done**. The model will appear as follows:



8. Check the **Computational Settings**; the ***Minimum Number of Calculations Intervals*** should be at least 200 and the ***Minimum Number of Fit Iterations*** should be at least 20.

9. Enter the **Parameters** values as shown below:



It is important to notice the limits on the parameter *frac*; the value of this parameter cannot exceed "1", nor be less than zero.

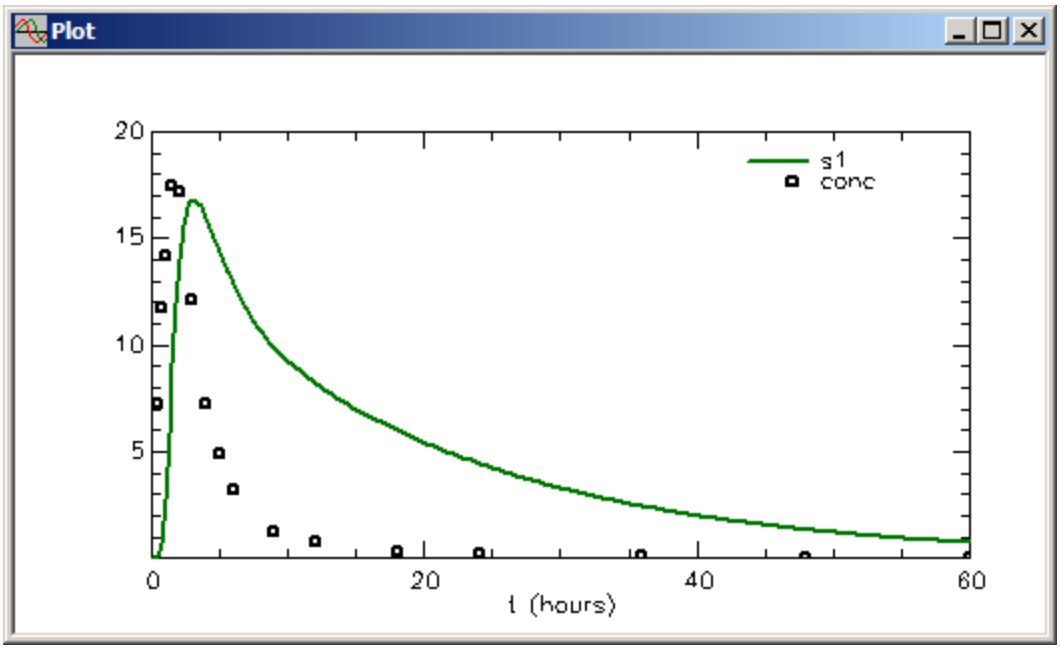
10. **Solve** the model and view the solution.

    a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve**  .

    b. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot**  or right-click in the plot window and select Variables. The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is not selected.

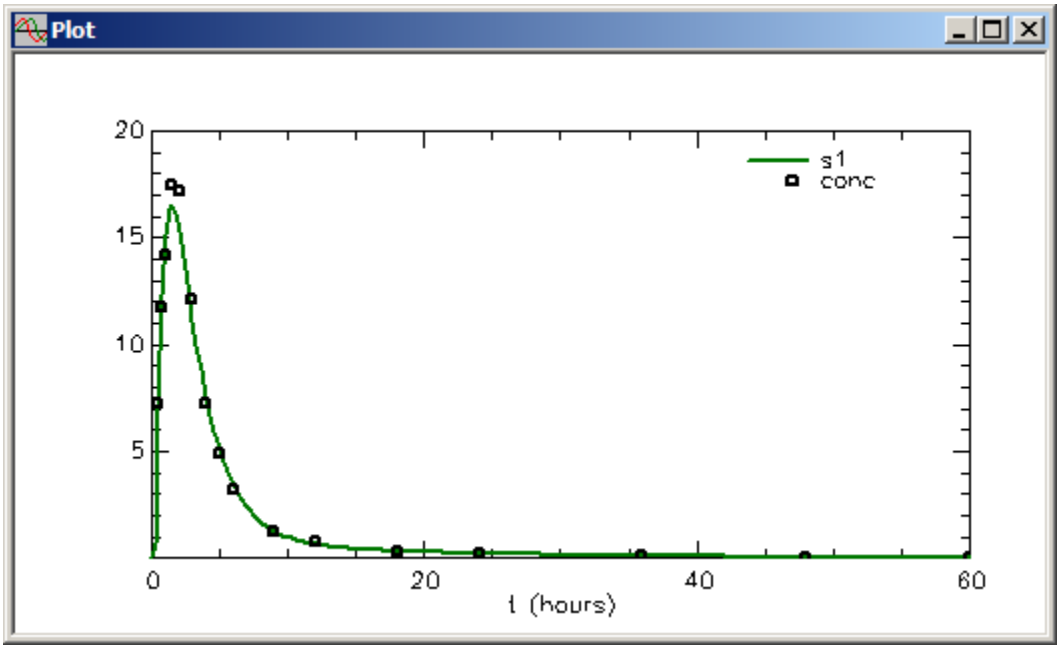
    c. Click **s1:conc** to move this to the **Current Selection** pane.

    d. Click **Done**. The plot will appear as follows (y-axis has been set to 20):

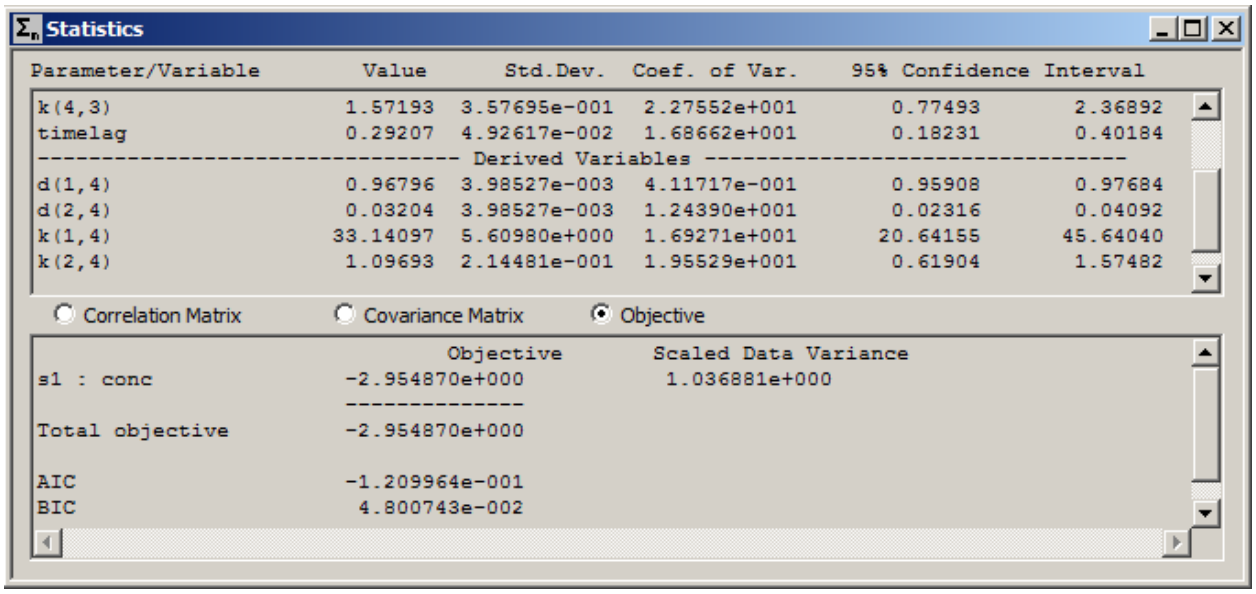


10. **Fit** the model to the data, and view the solution.

    a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar** click **Fit**  . The plot will be updated as follows:



    b. View the statistics. In the **Show** menu, click **Statistics**, or alternatively on the **SAAM II Toolbar** click **Statistics**  . The **Statistics** window will appear as follows:



To obtain this figure, *you must scroll down* thru the **Parameter/Variable** pane so that the derived variables are shown. The parameter *d(1,4)* equals *frac*; *d(2,4)* equals "1 – frac." The rate constants *k(1,4)* and *k(2,4)* are the rate constants from the last compartment in the delay to Compartment **1** and Compartment **2** respectively. The sum of these rate constants equals the rate constant connecting the other compartments in the delay.

Here is the entire Parameter/Variable Pane

Vc	14.68594	1.34445e+000	9.15467e+000	11.69032	17.68156
frac	0.96796	3.98527e-003	4.11717e-001	0.95908	0.97684
k(0,1)	0.45163	3.75993e-002	8.32516e+000	0.36786	0.53541
k(0,2)	0.05879	3.11748e-003	5.30273e+000	0.05184	0.06574
k(4,3)	1.57193	3.57695e-001	2.27552e+001	0.77493	2.36892
timelag	0.29207	4.92617e-002	1.68662e+001	0.18231	0.40184
Derived Variables					
d(1,4)	0.96796	3.98527e-003	4.11717e-001	0.95908	0.97684
d(2,4)	0.03204	3.98527e-003	1.24390e+001	0.02316	0.04092
k(1,4)	33.14097	5.60980e+000	1.69271e+001	20.64155	45.64040
k(2,4)	1.09693	2.14481e-001	1.95529e+001	0.61904	1.57482

11. Close all open windows and dialog boxes.

Quit the **SAAM II Compartmental** application. You may save the study file is you wish. It is provided as part of this tutorial as **delay2.stu**.

Part 3. Specifying a delay using the Heaviside function

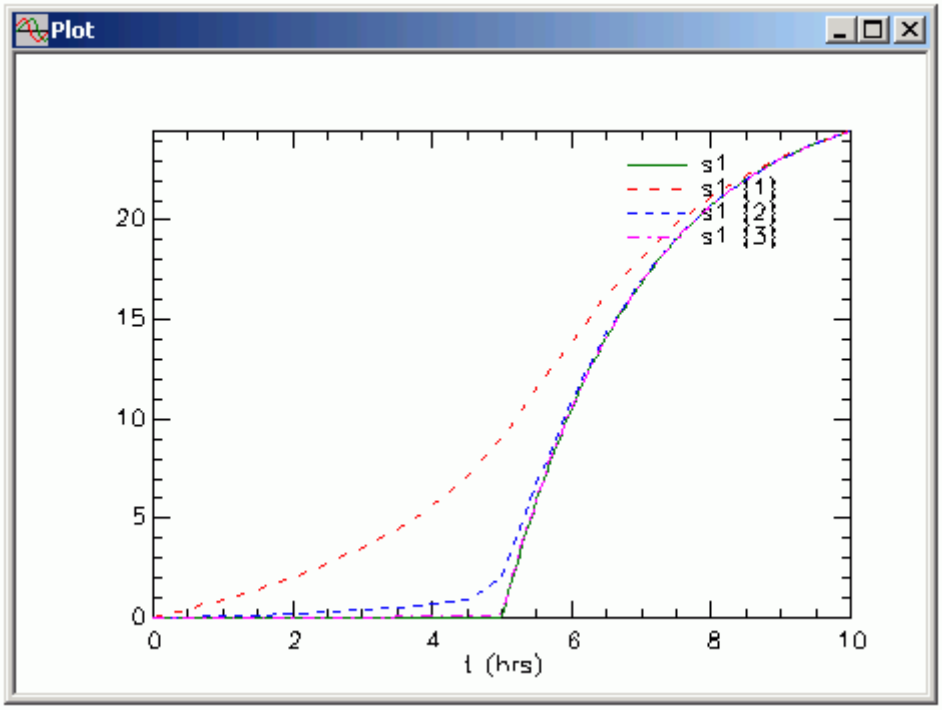
The Heaviside function

The Heaviside function is:

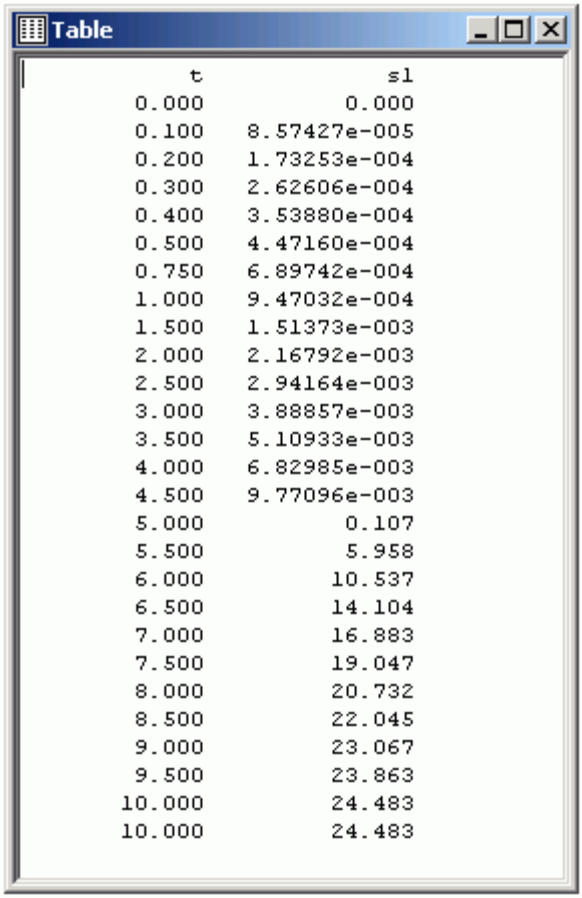
heaviside=0.5*(1.0+atan(lambda*(t - tlag))*2/3.141592653)

In this expression, "atan" is the arctangent function. The expression "t – tlag" acts as a switch. For values of "t" less than "tlag" the value of the Heaviside function equals zero. For values of "t" greater than "tlag", the value is non-zero. The values of the Heaviside function are between zero and 1. The parameter lambda controls the sharpness of the function, i.e. how close the values lie "exactly" between zero and 1.

The following shows a series of simulations with lambda equal to "1" (**s1{1}**), "10" (**s1{2}**), "100" (**s1{3}**) and "1000" (**s1**).



To see how the Heaviside function works, the following is the table of values when *lambda* equals 1000.



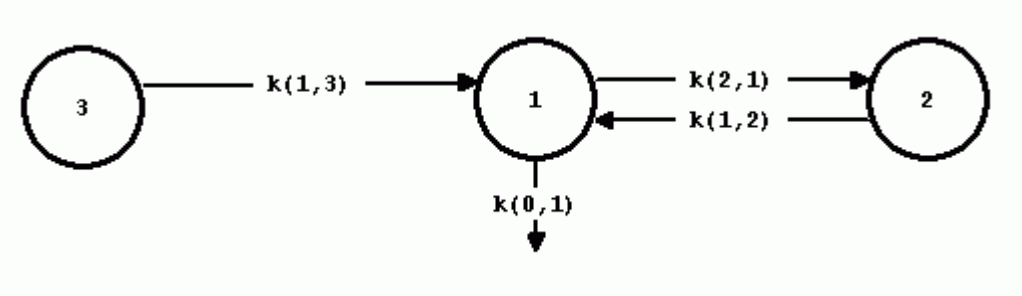
Table

t	s1
0.000	0.000
0.100	8.57427e-005
0.200	1.73253e-004
0.300	2.62606e-004
0.400	3.53880e-004
0.500	4.47160e-004
0.750	6.89742e-004
1.000	9.47032e-004
1.500	1.51373e-003
2.000	2.16792e-003
2.500	2.94164e-003
3.000	3.88857e-003
3.500	5.10933e-003
4.000	6.82985e-003
4.500	9.77096e-003
5.000	0.107
5.500	5.958
6.000	10.537
6.500	14.104
7.000	16.883
7.500	19.047
8.000	20.732
8.500	22.045
9.000	23.067
9.500	23.863
10.000	24.483
10.000	24.483

You can see up to time “5” the values of s1 are close to zero. After time “5”, they rise. This illustrates the essential point of the Heaviside function: it is continuous and differentiable! This is extremely important not so much for simulations (solving differential equations) but for fitting.

Suppose delays could be implemented using a conditional expression “if-then-else”. The problem here is the conditional can introduce a discontinuity in the model solution. Problems can arise when there is a datum near the discontinuity during optimization since the algorithm for optimization does not know on which side of the discontinuity the datum lays. When using conditionals, one needs to be very careful that incorrect solutions are not returned. This is why conditionals (e.g. “if-then-else” or the FORTRAN functions AMIN and AMAX) are not implemented in the **SAAM II Compartmental** application.

In this part of the tutorial, you will create and work with the following model:



The difference between this model and the model used in Part 1 is that the delay will be specified as part of the transfer *k(1,3)*.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

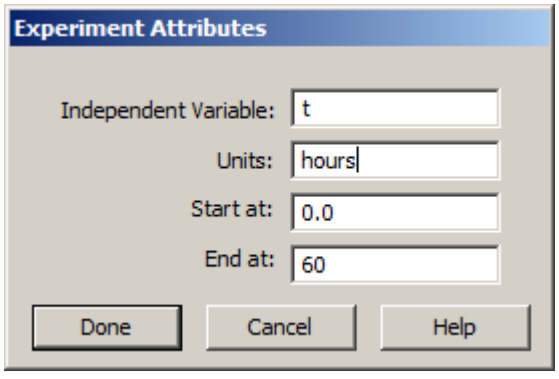
2. **Create the Model** shown above.

3. **Create the Experiment** on the model.

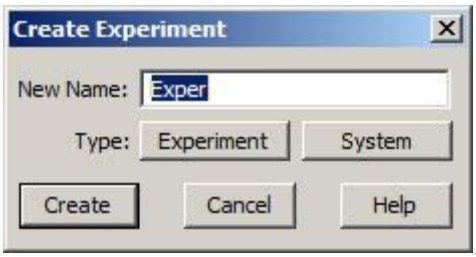
   a. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open.

   b. Change the entry in the **Units** box from "minutes" to "hours".

   c. Type "60" in the **End At** box. The **Experiment Attributes** dialog box will appear as follows:



   d. Click **Done**. The **Create Experiment** dialog box will open as shown below:



Be sure **Experiment** is selected (as indicated by "Exper" in the **New Name** box).

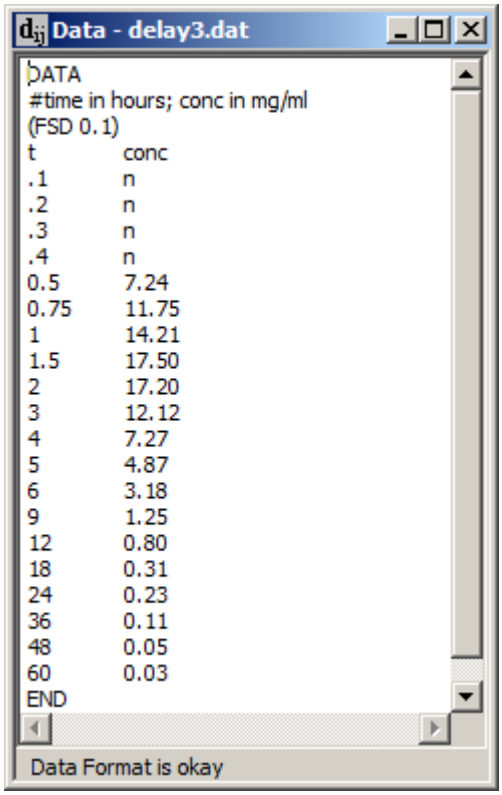
e. Click **Create**.

4. Add the **Data** to the model

   a. On the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data**  . The **Data** window will open.

   b. On the **File** menu, click **Open**. The file **delay3.dat** should appear in the list (if it does not, find the folder where you put this data file).

   c. Double-click **delay3.dat**. The data in this file will appear in the **Data** window as shown below:



   d. Close the **Data** window.

5. Create the **Input and Sample**

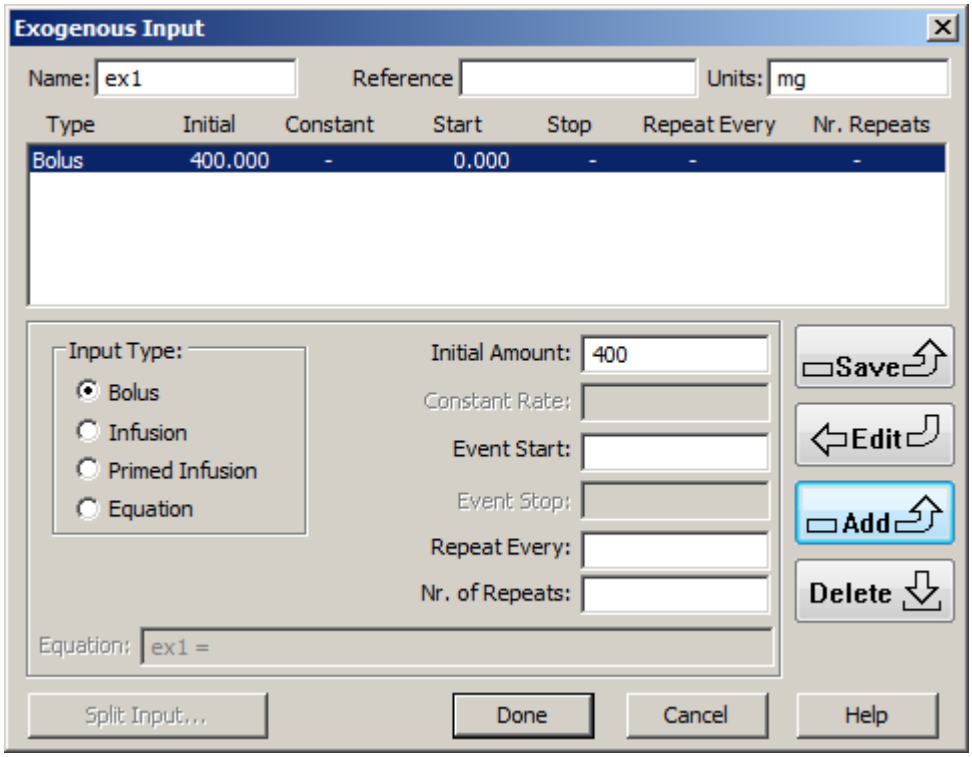
   a. In the **SAAM II Toolbox**, click **Input**.

   b. On the **Drawing Canvas**, click Compartment **q3**, and then click on the canvas. The input **ex1** will appear associated with your model.

   c. Double-click **ex1**. The **Exogenous Input** dialog box will open.

   d. Type "400" in the **Initial Amount** box.

   e. Click **Add**. The **Exogenous Input** dialog box should appear as follows:



   f. Click **Done**.

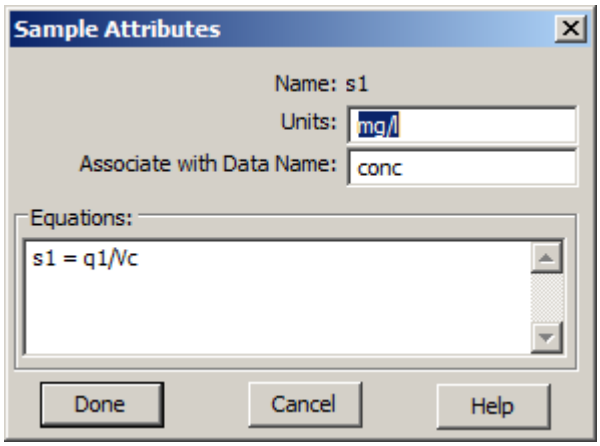
   g. In the **SAAM II Toolbox**, click **Sample**.

   h. On the **Drawing Canvas**, click Compartment **q1**, and then click on the canvas. The sample **s1** will appear associated with your model.

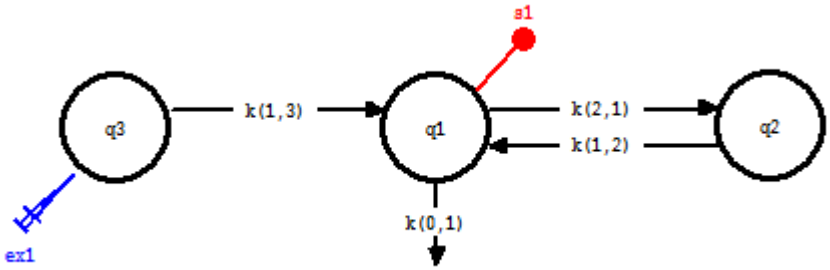
   i. On the **Drawing Canvas**, double-click **s1** to open the **Sample Attributes** dialog box.

   j. Type "conc" in the **Associate with Data Name** box.

k. Edit the sample equation to read "s1=q1/Vc" in the **Equation** box. The **Sample Attributes** dialog box will appear as follows:



l. Click **Done**. The model will appear as follows:



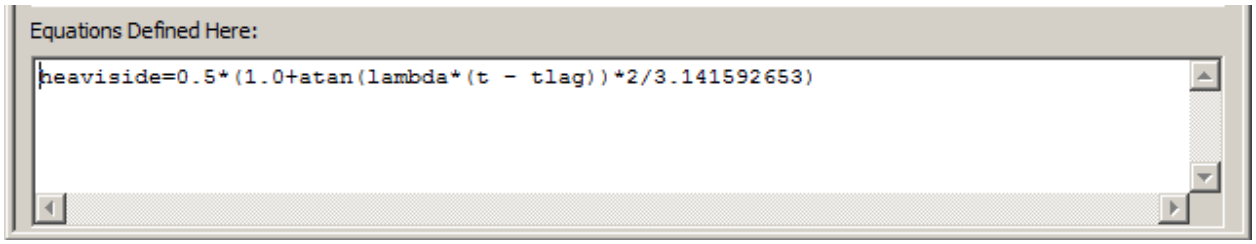
6. **Specify the Delay *k(1,3)***

a. In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar,** click **Equations** Eq. The **Equations** dialog box will open.

b. Type the following equation in the **Equations Defined Here** box:

heaviside=0.5*(1.0+atan(lambda*(t - tlag))*2/3.141592653)

The **Equations Defined Here** pane in the **Equations** dialog box will appear as follows:

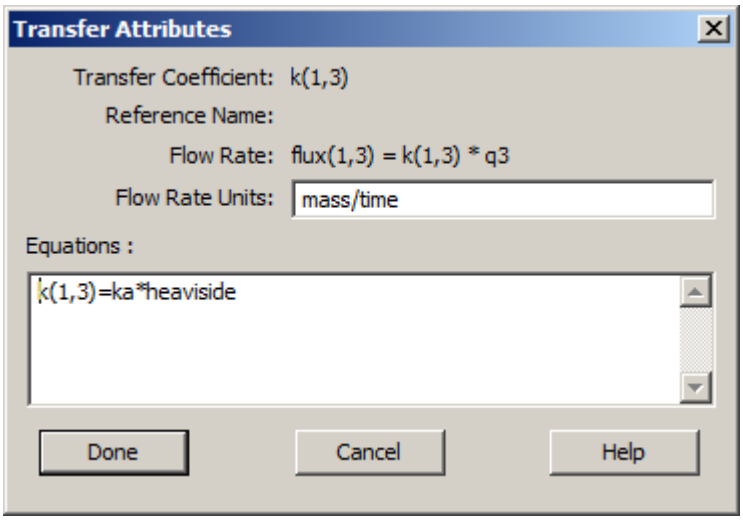


c. Close the **Equations** dialog box.

Using the Heaviside function. In the expression for the Heaviside function above, *tlag* will be an adjustable parameter which will equal the time of the delay. "t" is the name of the independent variable in the model. *lambda* is a parameter which will be hand tuned before fitting the model to the data.

d. Double-click *k(1,3)* to open the **Transfer Attributes** dialog box. The **Transfer Attributes** dialog box will open.

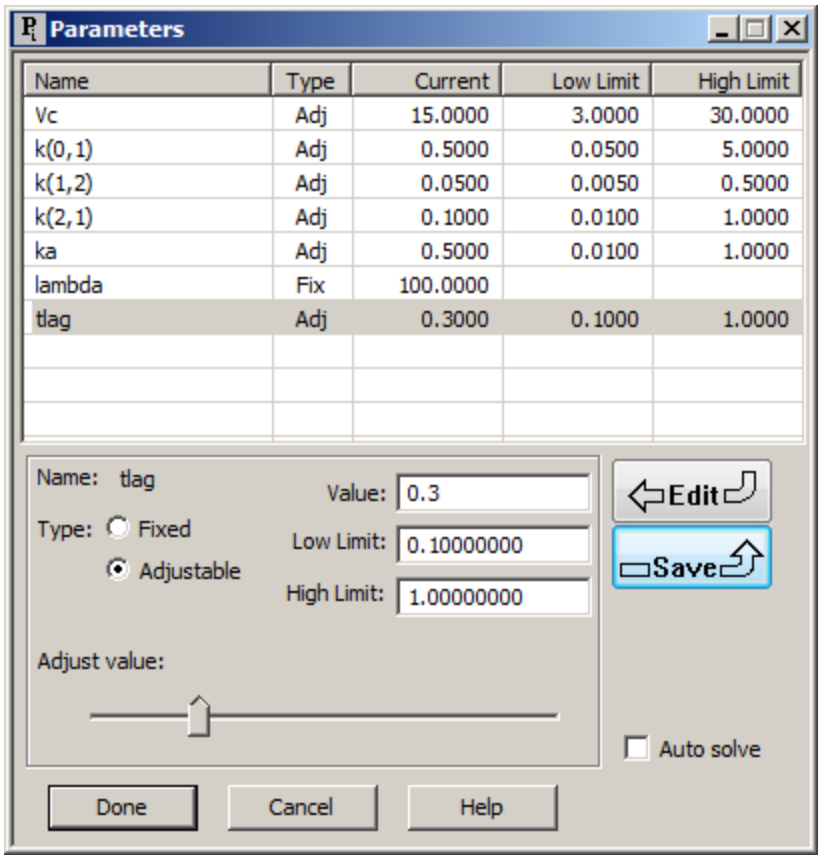
e. Type the equation "k(1,3)=ka*heaviside" in the **Equation** box. The **Transfer Attributes** dialog box will appear as follows:



This expression will result in *ka* being defined as a parameter.

f. Close the **Transfer Attributes** dialog box.

7. Enter the **Parameters** values as shown below:



8. **Solve** the model and view the solution.

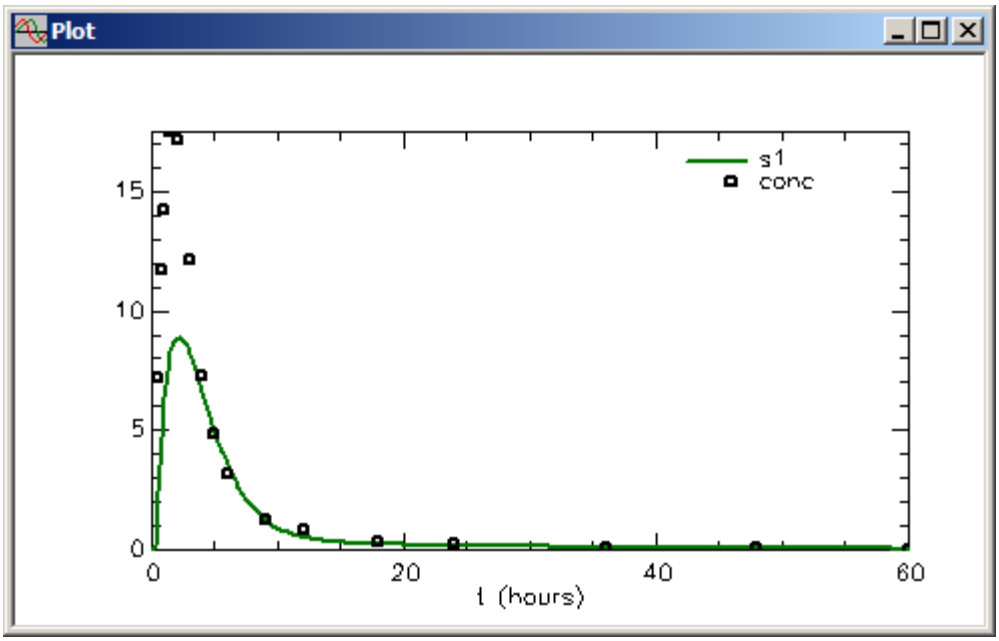
   a. In the **Compute** menu, click **Settings**. The **Computational Settings** dialog box will open. Change the **Min. Nr. of Calculation Intervals** from "20" to "200". This will improve the resolution of your plots.

   b. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve**  .

   c. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot**  . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is not selected.

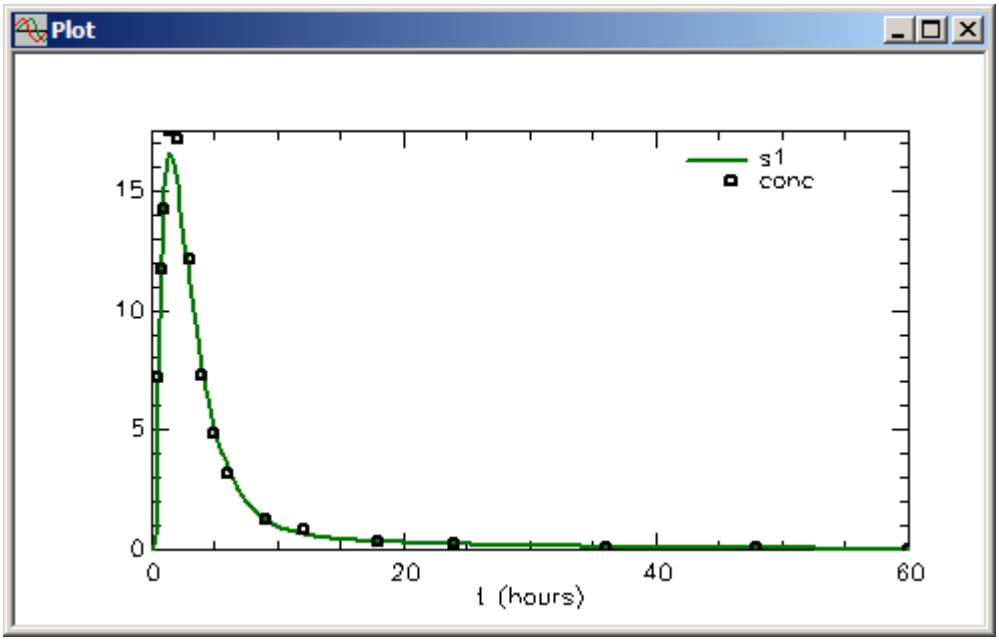
   d. Click **s1:conc** to move this to the **Current Selection** pane.

   e. Click **Done**. The plot will appear as follows:

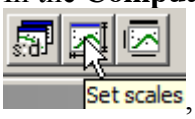


9. **Fit** the model to the data, and view the solution.

   a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar** click **Fit**  . The plot will be updated as follows:



   b. View the first 5 minutes of the solution.

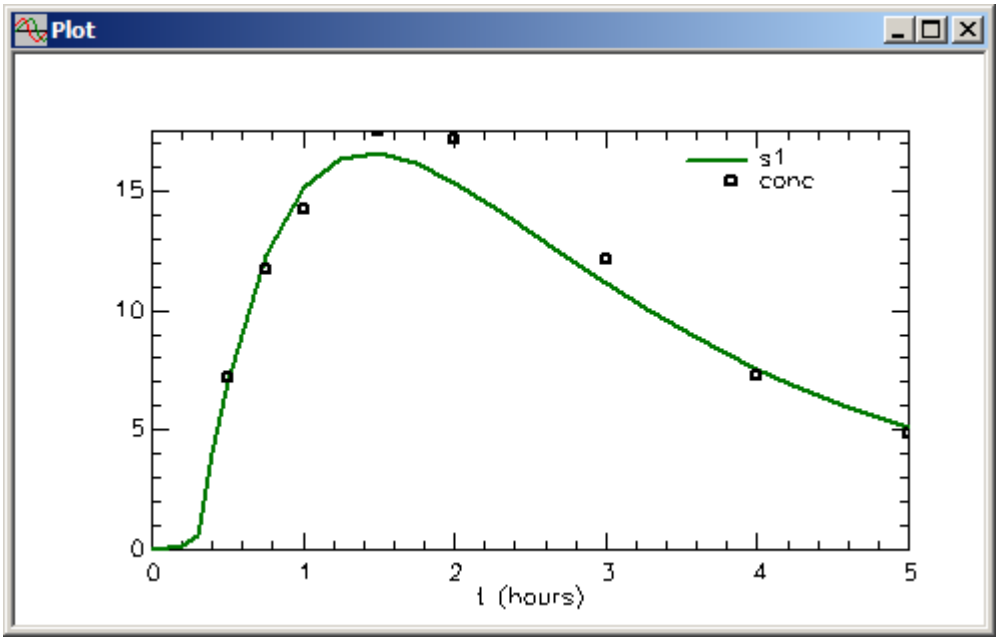
(1) In the **Compute** menu, click **Plot/Table Scale**, click the plot variables button 

, or right-click in the plot window and select Scale. The **Plot and Table Scale** dialog box will open.

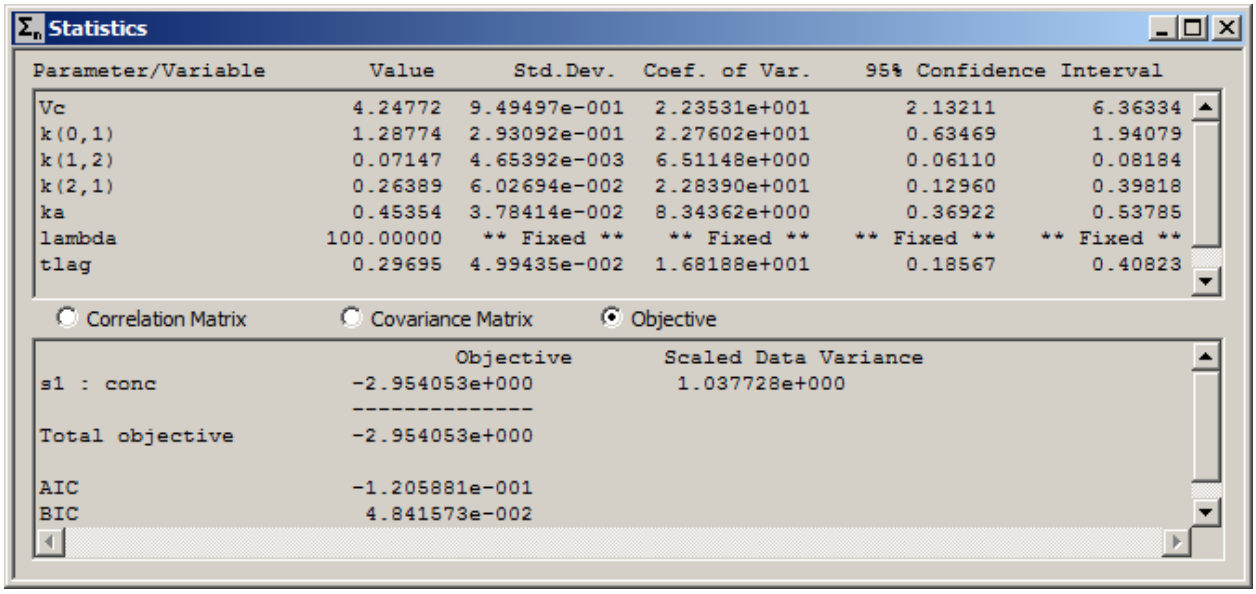
(2) In the **X Axis** pane, click **Set**.

(3) Type "5" in the **Maximum** box.

(4) Click **Done**. The plot will appear as follows:

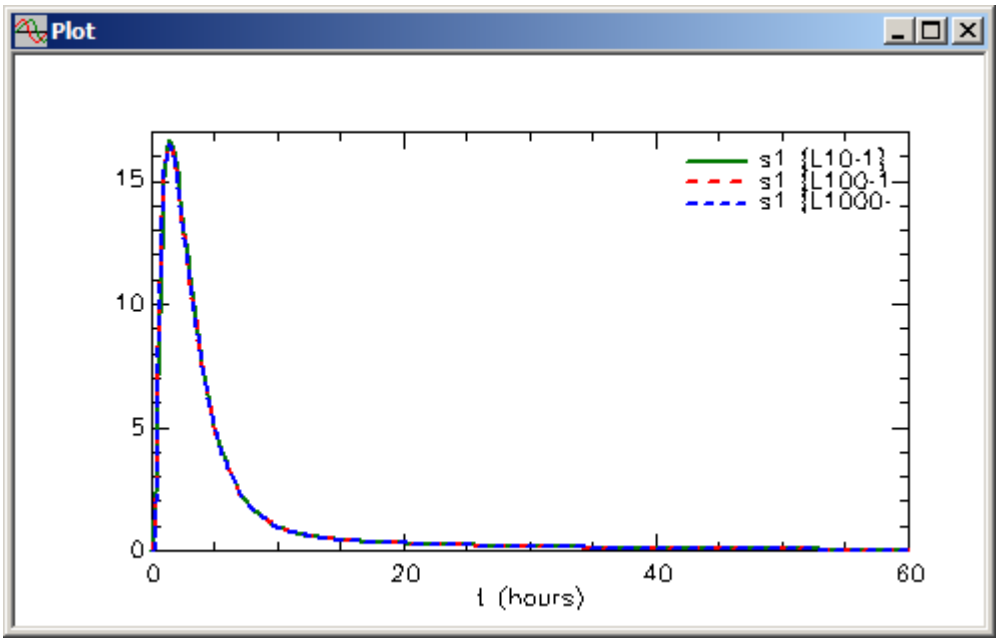


c. View the statistics. In the **Show** menu, click **Statistics**, or alternatively on the **SAAM II Toolbar** click **Statistics**  . The **Statistics** window will appear as follows:

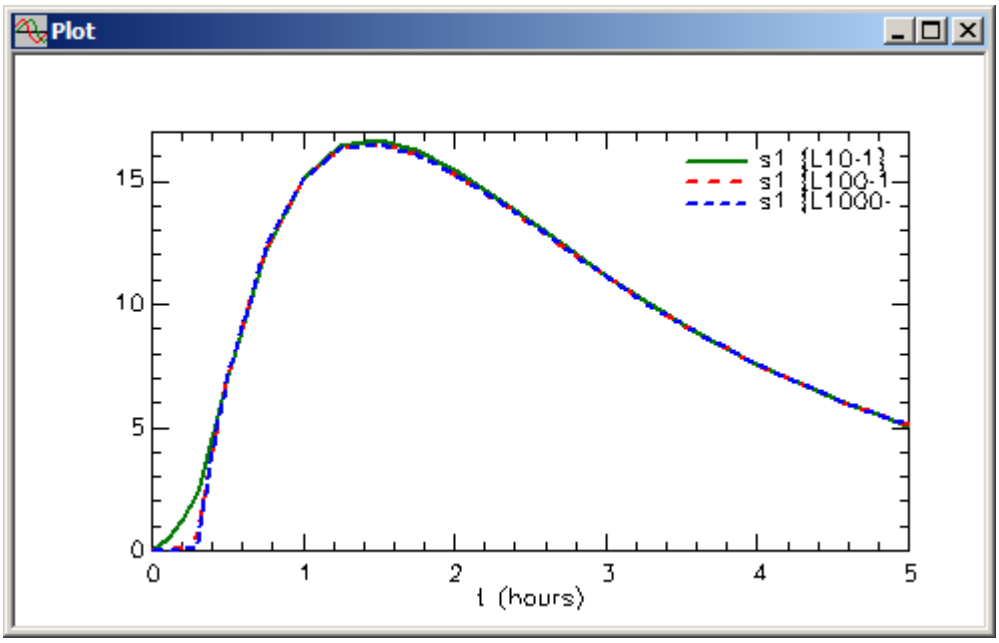


11. Close all open windows and dialog boxes.

lambda in the Heaviside function. In the above, lambda was set equal to 100. The following plot compares the best fit of the model to the data with *lambda* equal to 10 (**s1{L10_1}**), 100 (**s1{ L100_1}**) and 1000 (**L1000_1**).



The details of the initial rise are shown as follows:



You can see the differences in the initial rise caused by different values for *lambda*.

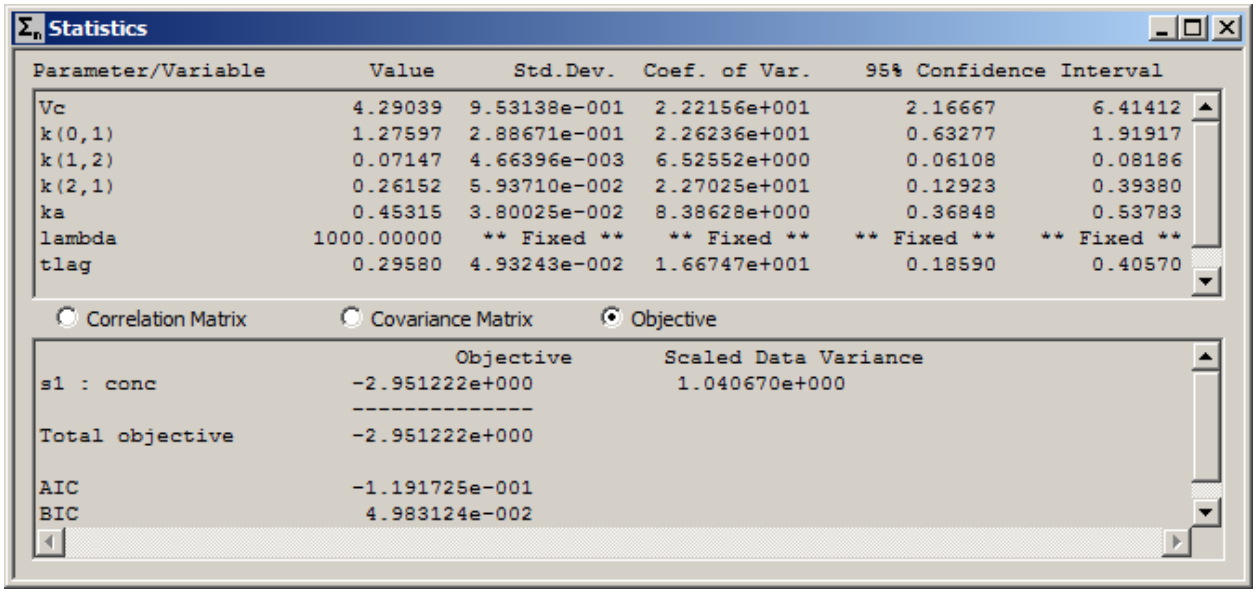
The statistics for the fit when *lambda* equal 10 and 1000 respectively are:

Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
Vc	3.79263	9.49826e-001	2.50440e+001	1.67628	5.90897
k(0,1)	1.43256	3.63476e-001	2.53724e+001	0.62269	2.24244
k(1,2)	0.07148	4.55455e-003	6.37170e+000	0.06133	0.08163
k(2,1)	0.29357	7.45433e-002	2.53920e+001	0.12748	0.45966
ka	0.45718	3.61985e-002	7.91782e+000	0.37652	0.53783
lambda	10.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
tlag	0.31942	6.12719e-002	1.91823e+001	0.18290	0.45594

Correlation Matrix Covariance Matrix Objective

	Objective	Scaled Data Variance
s1 : conc	-2.984151e+000	1.006960e+000
Total objective	-2.984151e+000	
AIC	-1.356369e-001	
BIC	3.336686e-002	



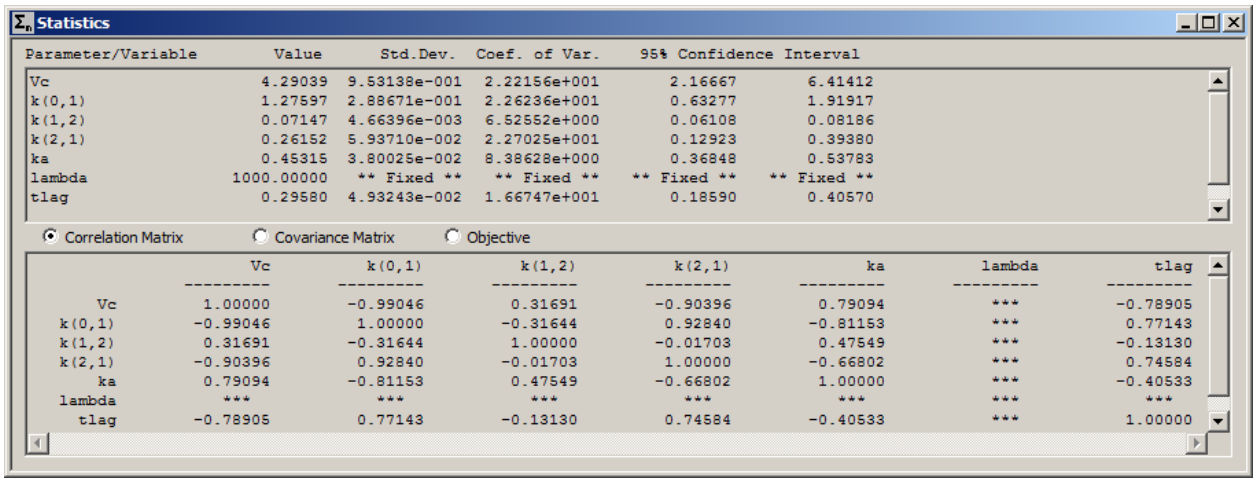
Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
Vc	4.29039	9.53138e-001	2.22156e+001	2.16667	6.41412
k(0,1)	1.27597	2.88671e-001	2.26236e+001	0.63277	1.91917
k(1,2)	0.07147	4.66396e-003	6.52552e+000	0.06108	0.08186
k(2,1)	0.26152	5.93710e-002	2.27025e+001	0.12923	0.39380
ka	0.45315	3.80025e-002	8.38628e+000	0.36848	0.53783
lambda	1000.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
tlag	0.29580	4.93243e-002	1.66747e+001	0.18590	0.40570

Correlation Matrix Covariance Matrix Objective

	Objective	Scaled Data Variance
s1 : conc	-2.951222e+000	1.040670e+000
Total objective	-2.951222e+000	
AIC	-1.191725e-001	
BIC	4.983124e-002	

You can see that, while the actual "Fits" are essentially the same, and the values for the Total objective function are essentially the same, there are differences in *Vc* and *k(0,1)*. The reason for these differences is the fact that these parameters are highly correlated as shown in the statistics below for the case *lambda* equals 1000:



Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
Vc	4.29039	9.53138e-001	2.22156e+001	2.16667	6.41412
k(0,1)	1.27597	2.88671e-001	2.26236e+001	0.63277	1.91917
k(1,2)	0.07147	4.66396e-003	6.52552e+000	0.06108	0.08186
k(2,1)	0.26152	5.93710e-002	2.27025e+001	0.12923	0.39380
ka	0.45315	3.80025e-002	8.38628e+000	0.36848	0.53783
lambda	1000.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
tlag	0.29580	4.93243e-002	1.66747e+001	0.18590	0.40570

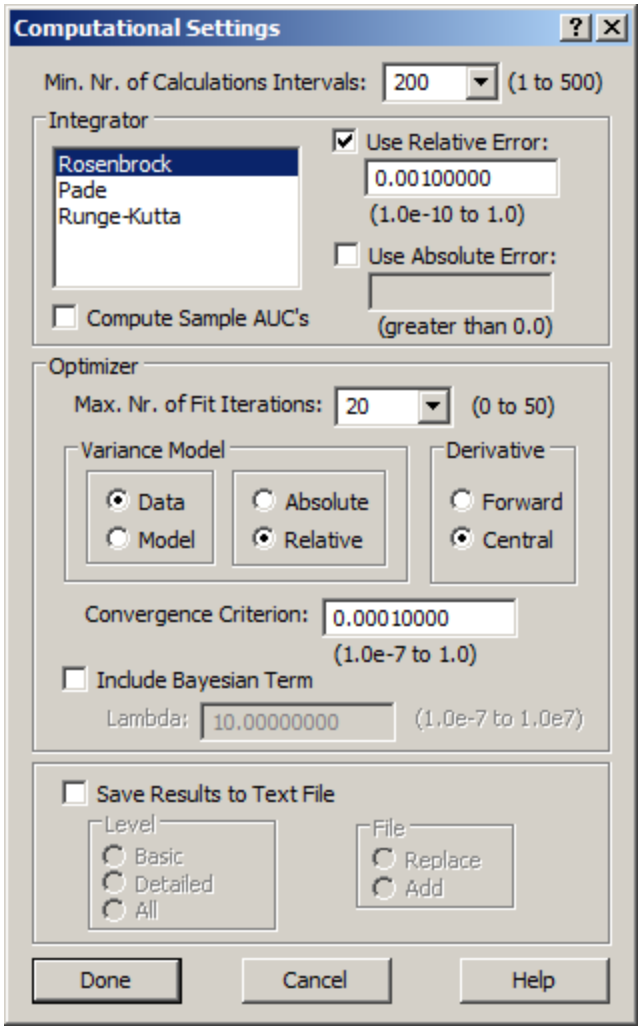
Correlation Matrix Covariance Matrix Objective

	Vc	k(0,1)	k(1,2)	k(2,1)	ka	lambda	tlag
Vc	1.00000	-0.99046	0.31691	-0.90396	0.79094	***	-0.78905
k(0,1)	-0.99046	1.00000	-0.31644	0.92840	-0.81153	***	0.77143
k(1,2)	0.31691	-0.31644	1.00000	-0.01703	0.47549	***	-0.13130
k(2,1)	-0.90396	0.92840	-0.01703	1.00000	-0.66802	***	0.74584
ka	0.79094	-0.81153	0.47549	-0.66802	1.00000	***	-0.40533
lambda	***	***	***	***	***	***	***
tlag	-0.78905	0.77143	-0.13130	0.74584	-0.40533	***	1.00000

With a correlation coefficient for *Vc* and k(0,1) equal to -0.99 it is not surprising there are differences for these parameters for different values of *lambda*. However all lie within the calculated 95% confidence intervals.

What is meant by "tuning *lambda*"? "Tuning *lambda*" is the process of adjusting lambda in increments until the model parameters become stable. Because of the nature of the Heaviside function, it is recommended tuning be done by increasing *lambda* by factors of 10 until the model parameters become stable (independent of the value of *lambda*). Note that the **Forward Difference Formula** was used in the previous fitting procedures. It is also recommended that in the fitting procedure the **central difference formula** be used for calculating the numerical derivatives. To **set**

the central difference, in the **Compute** menu, click **Settings**. The **Computational Settings** dialog box will open. In the **Derivative** pane in the **Optimizer** pane, click **Central**. The **Computational Settings** dialog box will appear as follows:



The following shows the results of fitting the model to the data for different values of *lambda* using these Computational Settings.

lambda	10	100	1000	10000	100000
Vc	3.793	4.248	4.295	4.292	4.295
k(0,1)	1.433	1.288	1.274	1.276	1.275

You can see that for *lambda* equal to 1,000 the parameters are stable. Thus in this tutorial a value of *lambda* equal to 1,000 or 10,000 would have been more appropriate than 100. If you wish, you can repeat this part of the tutorial using *lambda* equal to 100,000 and carefully compare the results with the case *lambda* equals 100.

When using the Heaviside function to create delays, you should go through the tuning process as described above to obtain an appropriate value of *lambda* for your particular modeling situation.

Quit the **SAAM II Compartmental** application. You may save the study file is you wish. It is provided as part of this tutorial as **delay3.stu**.

SAAM II Version 2.1
Advanced Tutorials

Working with Experimental Inputs

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Working with Experimental Inputs

Prerequisites

The prerequisite for this tutorial is having worked through the SAAM II introductory tutorial, "Getting Started with **SAAM II Compartmental**."

What you will learn in this tutorial

The purpose of this tutorial is to show you how to specify different input formats for your experiment in SAAM II. You will learn

- How to specify the amount of your input in a data file (Part 1)
- How to specify the amount of the input as an adjustable parameter (Part 2)
- How to specify split inputs (an input into more than one compartment (Part 3)
- How to perform parametric deconvolution (Part 4)

Files Required

Study Files: The study files for this tutorial are

ExpInp.stu
study_0.stu

These files are included as part of this tutorial. The file **ExpInp.stu** is the same as **study_0.stu** that is installed in the SAAM II program folder and referred to in the **SAAM II** User Guide with the exception there are no data in the **Data** window and the parameters have been set to "fixed."

Remember **study_0** is a study file for an experiment lasting 9 days. In this tutorial, the time of the experiment may be adjusted so specific points can be illustrated.

Data Files: The data files for this tutorial are

Paradecon.dat
study_0.dat

Introduction

This tutorial focuses on how to use the options in the **Exogenous Input** dialog box to specify less common or more advanced types of input dosage and to conduct parametric deconvolution. The tutorial covers

- Specifying the amount of a dose as a constant in the data file.
- Specifying the dose as an adjustable parameter.
- Split inputs (an input into more than one compartment)
- Parametric deconvolution

The most frequently used types of dosage inputs are covered in the tutorial Experimental Inputs, Basic**. These input types are the bolus, the constant infusion and the primed constant infusion and are predefined. The equation input allows the user to specify any input as long as the terms of the equation are recognized by** SAAM II.

Part 1. Specifying the amount of an input from the Data window

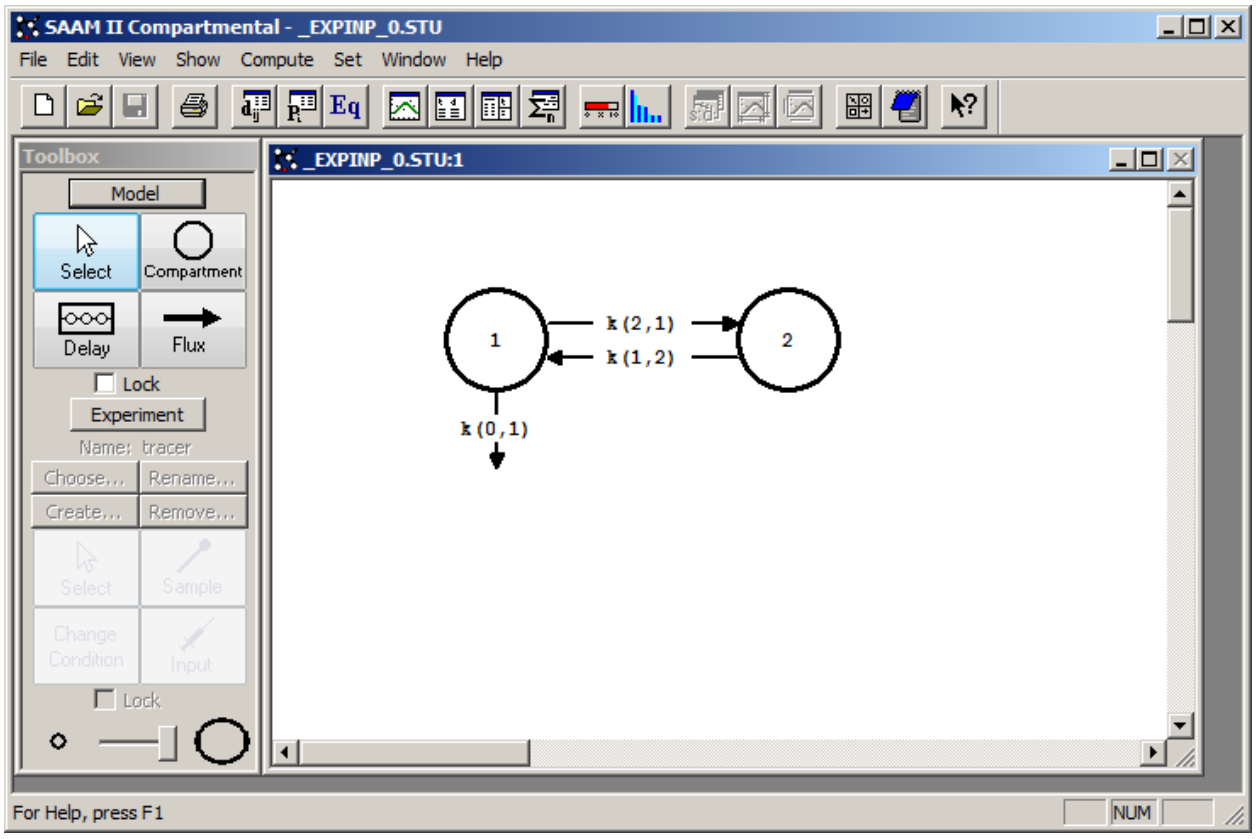
You can specify information about dosing from the data window. To do so, you use the equation input option in the **Exogenous Input** dialog box. This part of the tutorial will illustrate how to specify the amount of a bolus injection in the **Data** window.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

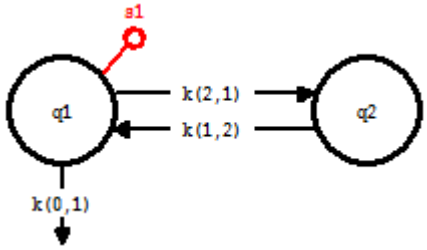
2. Open the **SAAM II Compartmental** study file **ExpInpUS**.

   a. The file **ExpInpUS.stu** should appear in the file list; if it does not, find the folder where you put this file.

   b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as shown below:



3. View the model and the experiment on the model. In the **SAAM II Toolbox**, click **Experiment**. The model of the experiment will appear on the **Drawing Canvas** as follows:



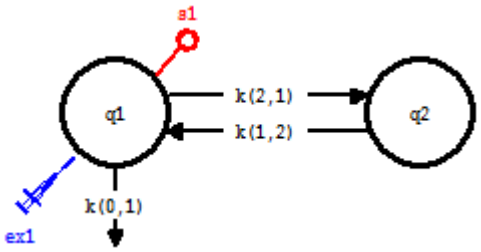
Notice the difference between this model and the experimental model developed and used in the **Getting Started with Compartmental** tutorial. Here there is no experimental input, **ex1**, and the sample circle, **s1**, is not filled because there are no data in the study file.

You may wish to review the **Parameters** dialog box and the **Samples Attributes** dialog box. The parameters are those from **study_0** except they have been fixed since this tutorial involves only simulations and no data fitting. The sample equation is "s1 = q1/vol".

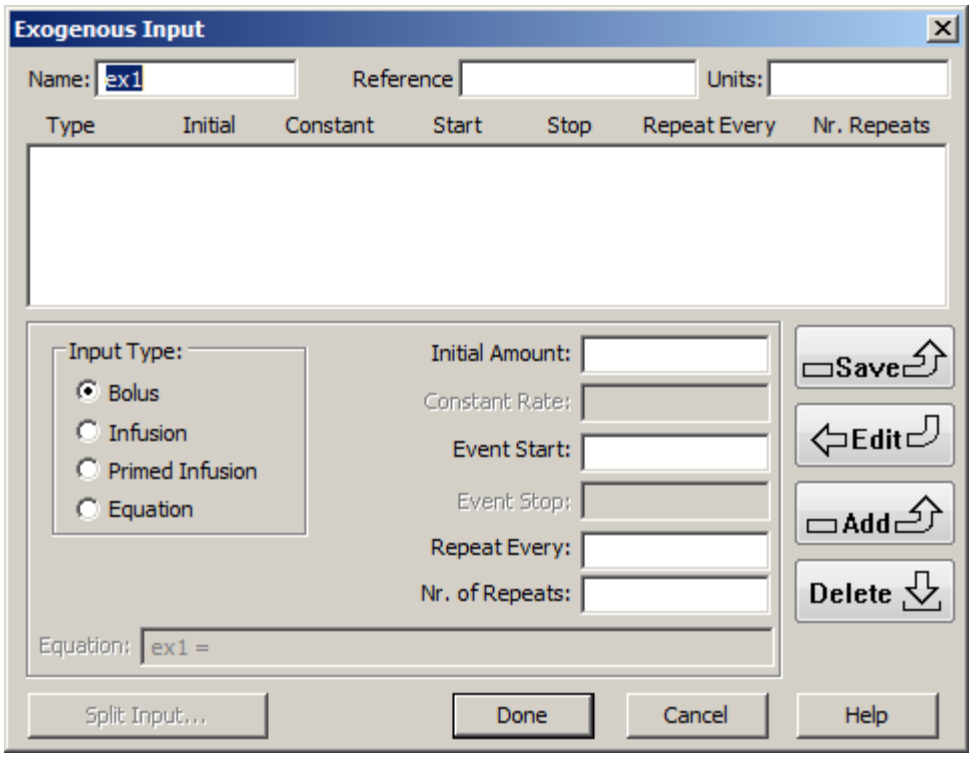
4. Create a bolus injection into Compartment **q1** where the amount of the bolus is specified in the **Data** window.

   a. In the **SAAM II Toolbox**, click **Input**.

   b. Click Compartment **q1** and then click on the **Drawing Canvas**. The experimental input **ex1** will appear associated with the model as shown below:



   c. Double-click **ex1** to open the **Exogenous Input** dialog box. The **Exogenous Input** dialog box will appear as follows:



Notice in the **Input Type** pane, **bolus** is selected.

d. Enter a bolus injection of "dose" specified by an equation.

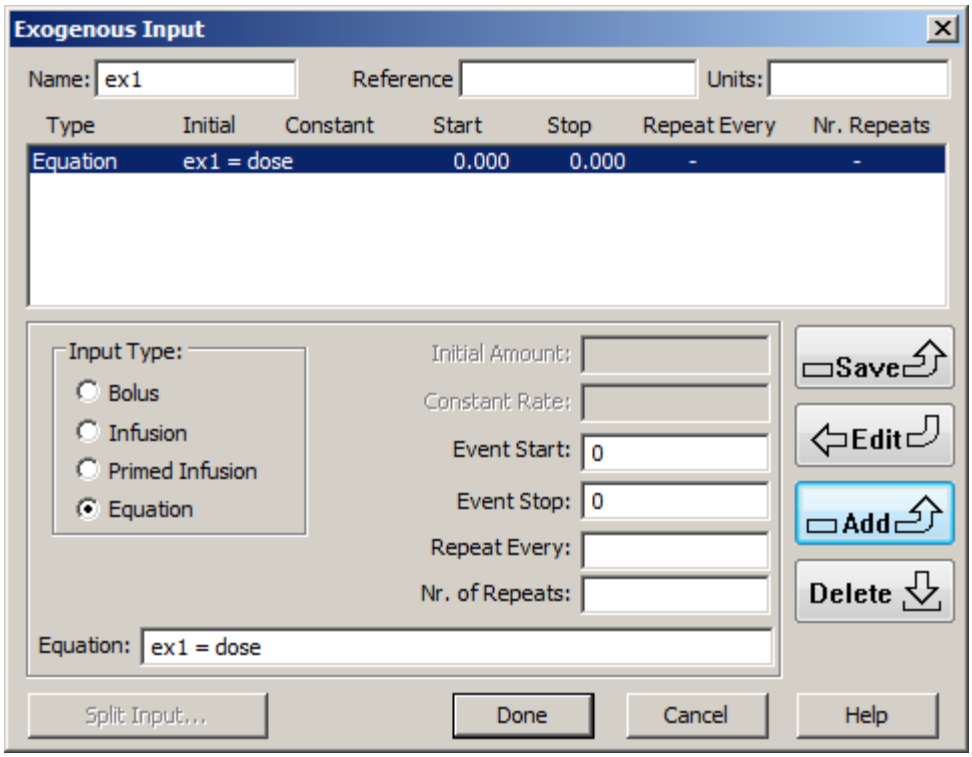
(1) In the **Input Type** pane, select **Equation**.

(2) In the **Equation** box, type "ex1 = dose".

(3) In the **Event Start** box, type "0".

(4) In the **Event Stop** box, type "0".

(5) Click **Add**. The **Exogenous Input** dialog box will appear as follows:



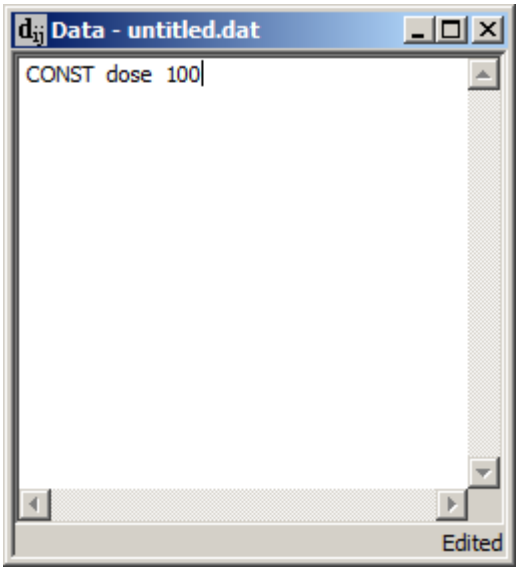
Specifying an equation as a bolus input. The effect of the above is the following. The equation is specified "ex1 = dose". However, the start and stop times being equal to zero, specifies the bolus. The result will be a bolus dose at time zero equal to an amount "dose". "dose" can either be entered as a parameter or in the **Data** window.

(6) Click **Done**.

e. Enter the amount of the dose in the **Data** window.

(1) In the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar** click **Data** . The **Data** window will open as blank since there are no data associated with this study file.

(2) In the **Data** window, type "CONST dose 100". The **Data** window will appear as follows:



*Specifying constants in the **Data** window*. You can specify constants in the data window using the **CONST** designator. In this case **CONST** is used to define the constant "dose" equal to "100."

(3) Close the **Data** window.

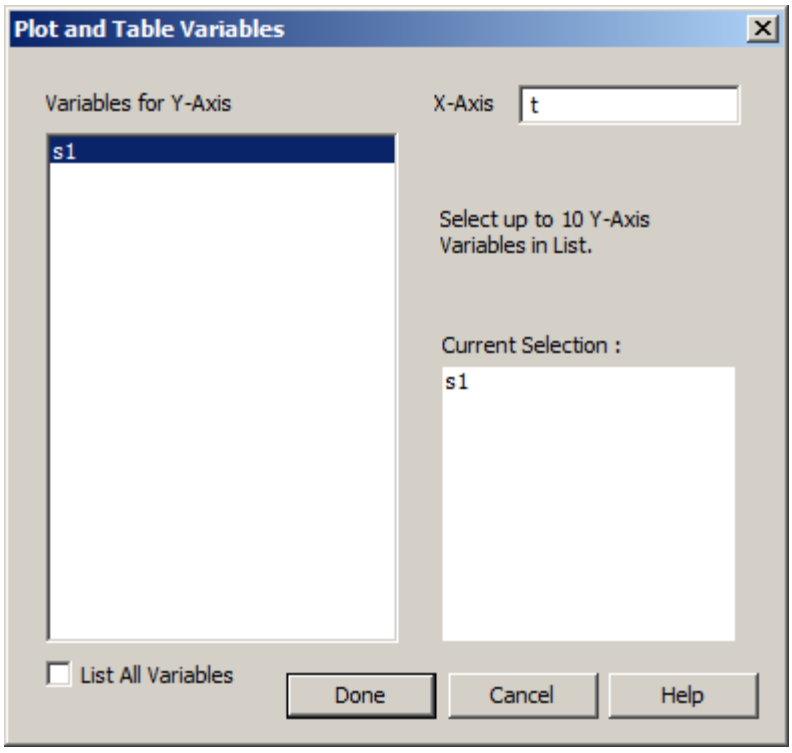
5. Solve the model and view the solution.

   a. It will be useful to increase the resolution of your plot. In the **Compute Menu**, click **Computational Settings**. Type "200" in the **Min. Nr. of Calculation Intervals** box. Click **Done**.

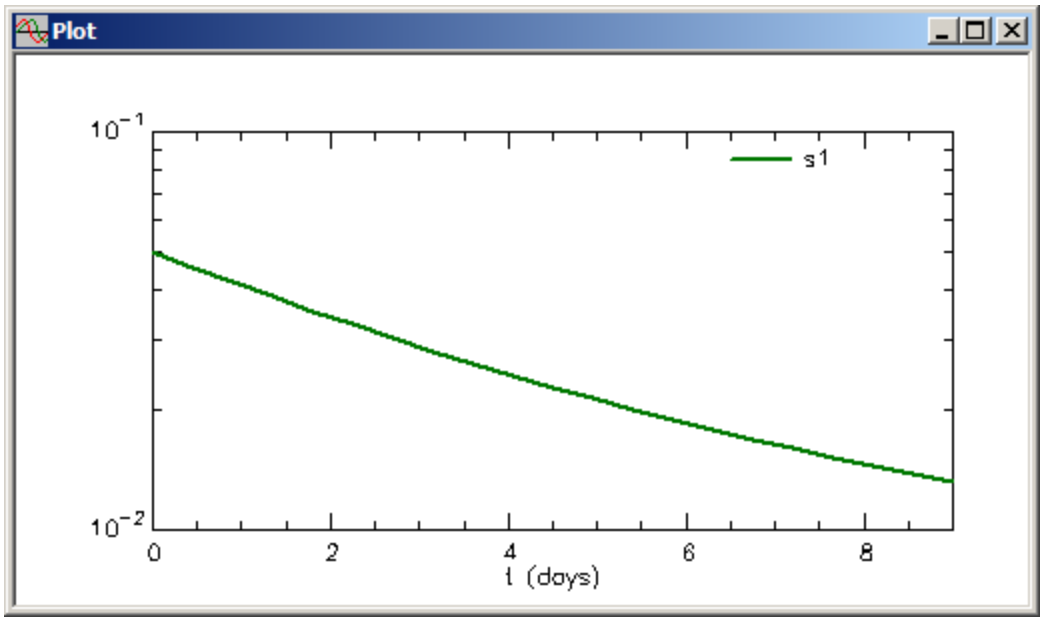
   b. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve** .

   c. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is not selected so **s1** is the only option in the **Variables for Y-Axis** pane.

   d. Click **s1** to add this to the **Current Selection** pane. The **Plot and Table Variables** dialog box will appear as shown below:



e. Click **Done**. A plot of **s1** will appear in semilog mode in the **Plot** window as shown below (if it is not in semilog mode, in the **View** menu, click **Semilog**):



f. Close the **Plot** window.

Quit the **SAAM II Compartmental** application. Do not save the changes to **study_0_ExpInp**.

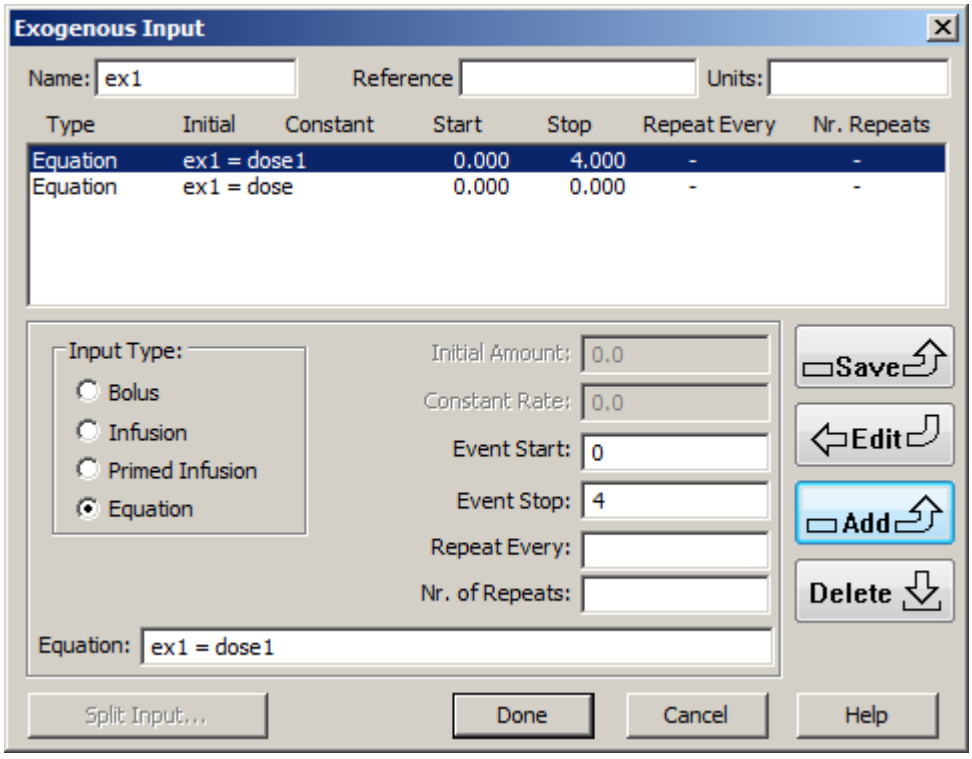
*Specifying the amount of an input in the **Data** window using the **Equation** type of **Exogenous Input***. The above is an example of how to specify the amount of a bolus injection where the amount of the bolus is specified in the Data window. It is clear that multiple boluses, constant infusions, multiple constant infusions and primed infusions can be specified similarly. It is simply a matter of how the equation input is specified. Suppose, for example, you wanted to specify a primed constant infusion where the priming dose was 100 and the infusion rate was 25 for a specified time interval. If in the Data window, there were two constants entered, for example

CONST dose 100

and

CONST dose1 25

were entered, the **Exogenous Input** dialog box could look as follows:



Here the bolus is specified equal to "dose" since it starts and stops at time zero. It is followed by a constant infusion equal to "dose1" starting at time 0 and ending at t=4.

Thus the **Equation** input type gives you great flexibility in specifying inputs where information about the input can be contained in the data file.

Part 2. Dose as an adjustable parameter

It is not often that the amount of material in the dose can be an adjustable parameter. This is because, under normal circumstances, the volume of the pool into which the test substance is administered needs to be estimated. To obtain an estimate of this volume, it is necessary to know the dose precisely.

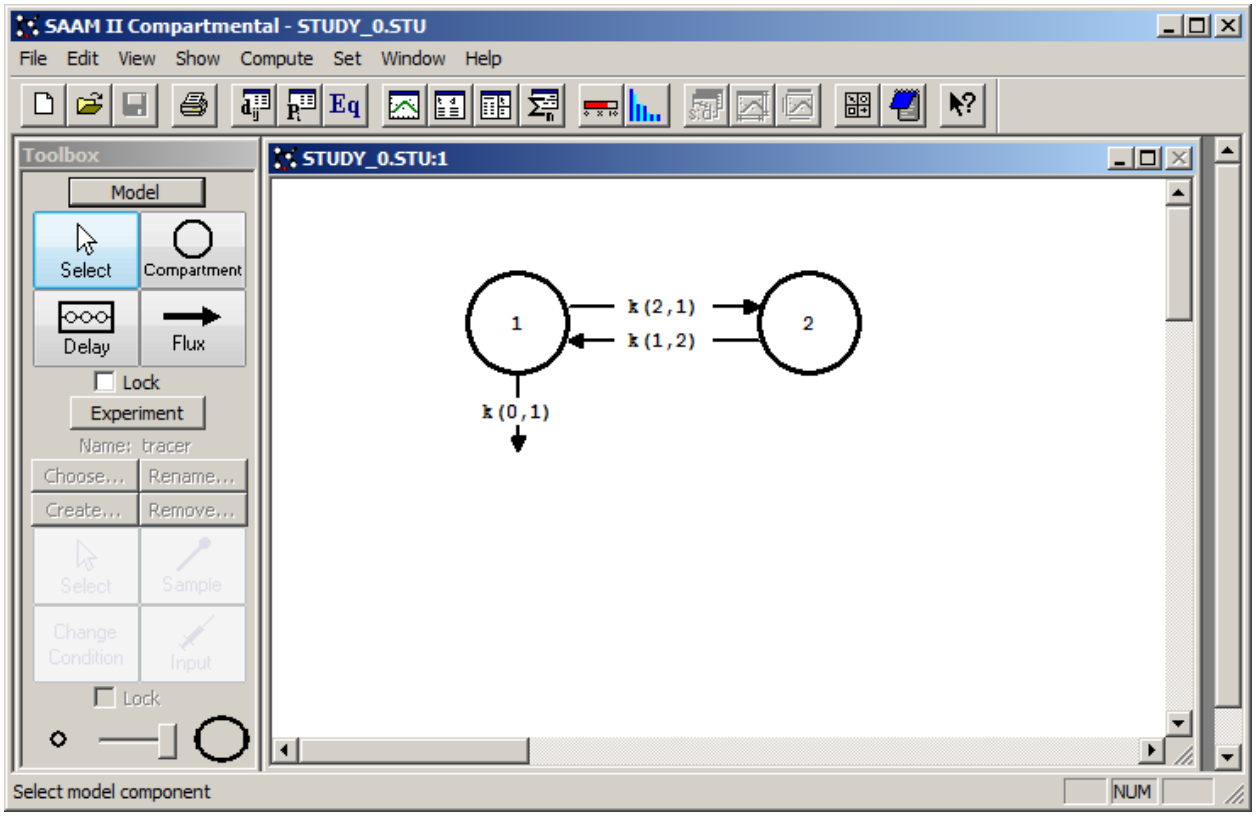
There are instances, however, when the amount of the dose can be an adjustable parameter. Normally this occurs when one has a single input-multiple output experimental design. An example would be a bolus injection into plasma with plasma and urine samples. Another example would be if volume were precisely known. This is the example that will be illustrated in this part of the tutorial.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

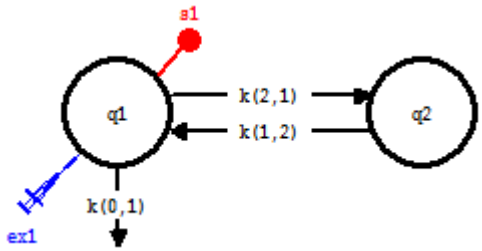
2. Open the **SAAM II Compartmental** study file **study_0**.

   a. The file **study_0.stu** should appear in the file list; if it does not, find the folder where you put this file.

   b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as shown below:



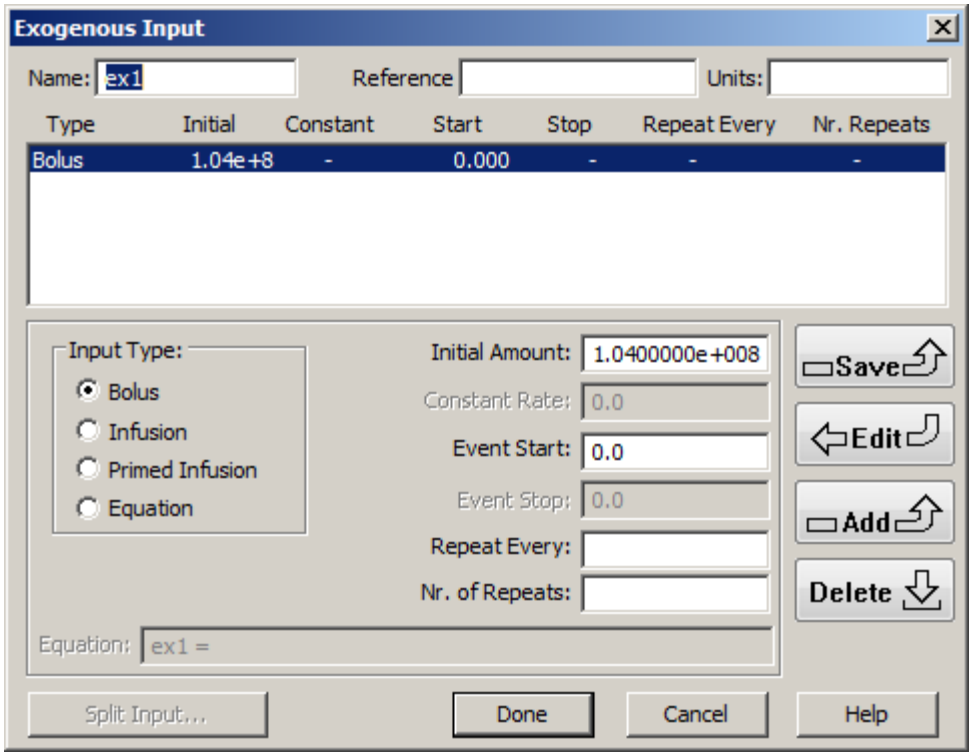
3. View the model and the experiment on the model. In the **SAAM II Toolbox**, click **Experiment**. The model of the experiment will appear on the **Drawing Canvas** as follows:



You may wish to review the **Parameters** dialog box and the **Samples Attributes** dialog box. The sample equation is "s1 = q1/vol".

4. Create a bolus injection into Compartment **q1** where the amount of the dose is an unknown parameter.

   a. Double-click **ex1** to open the **Exogenous Input** dialog box. The **Exogenous Input** dialog box will appear as follows:



This is the bolus input specified in **study_0**. It assumes the dose is known and the volume *vol* is unknown. In what follows, the situation will be reversed. The dose will be assumed unknown and the volume known.

b. Click **Delete** to remove the bolus injection.

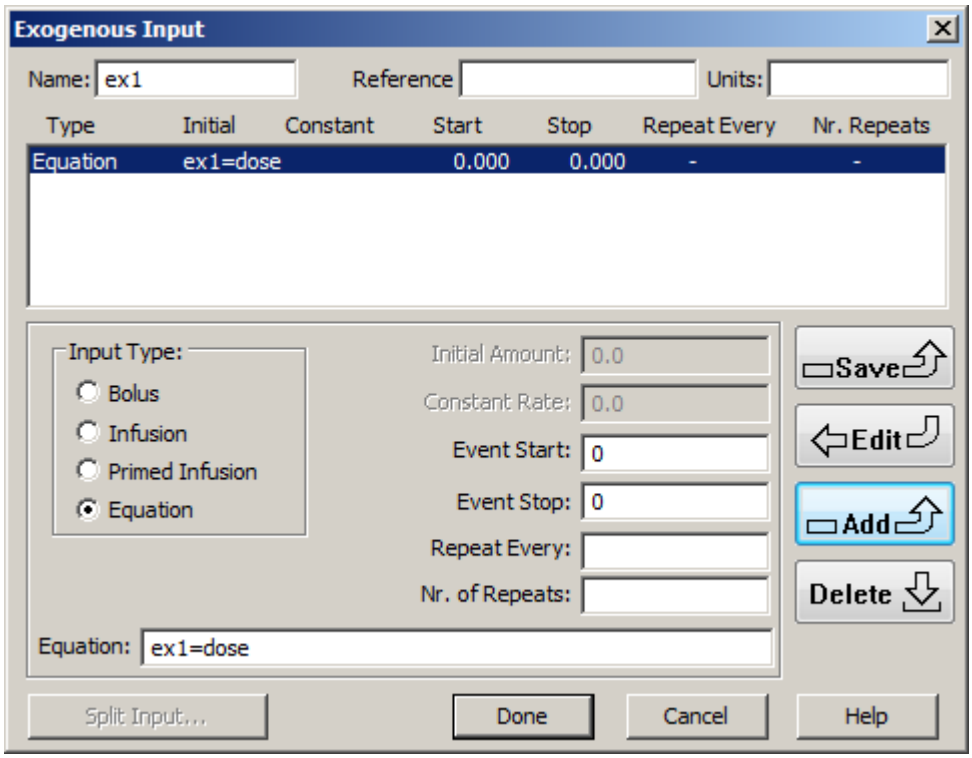
c. Create the input.

(1) In the **Input Type** pane, select **Equation**.

(2) In the **Equation** box, type "ex1 = dose".

(3) Be sure the **Event Start** and **Event Stop** times are set equal to zero.

(4) Click **Add**. The **Exogenous Input** dialog box will appear as follows:

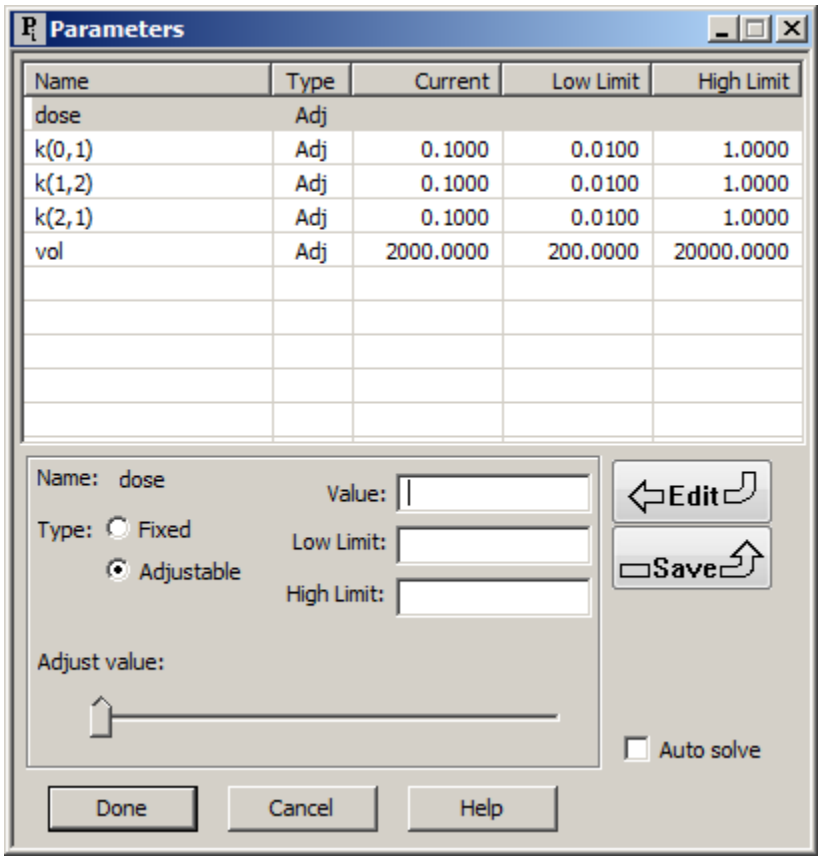


(5) Click **Done**.

The input now has been defined as an equation where the equation is a constant "dose". "dose" will appear as a parameter when you open the **Parameters** dialog box. The event start and stop times being zero specifies the equation as a bolus. Since a new parameter has been introduced, a value for it must be specified in the **Parameters** dialog box.

5. Specify the model parameters.

   a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters**  . The **Parameters** dialog box will open, as shown below:



   You can see *dose* now appears as a parameter. If you specify a value for the dose and leave all the other parameters adjustable, you will not be able to fit the model to the data because there are too many parameter values. In this example, it will be assumed that the volume *vol* is known, and equal to 2000 ml.

   b. Set the parameters are follows:

      (1) Double-click *dose* to select it.

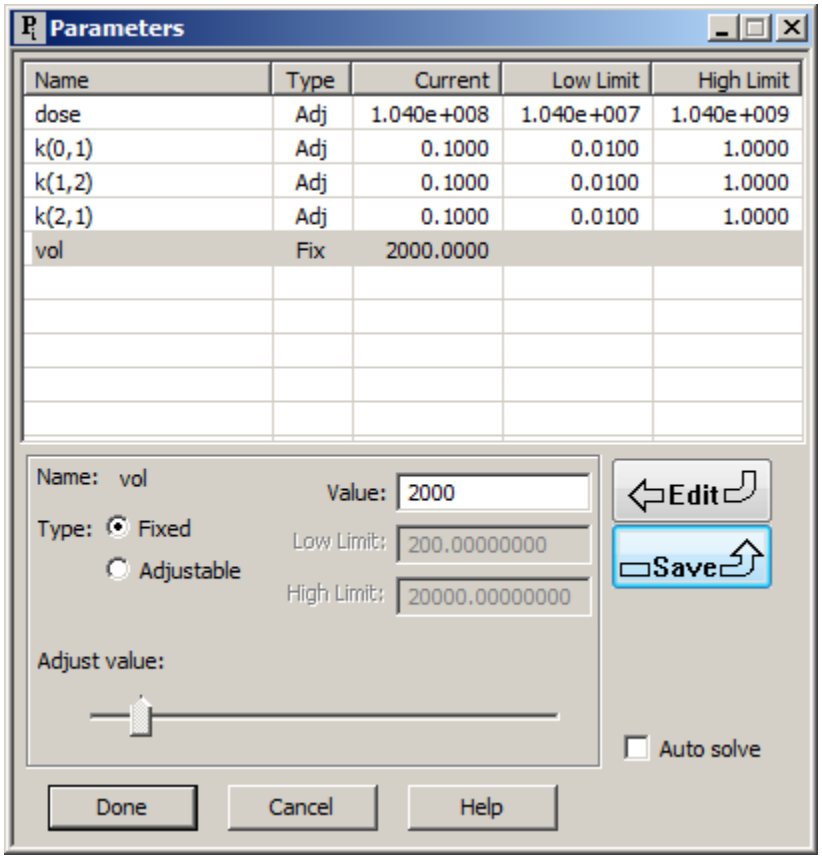
      (2) In the **Value** box, type "1.0e+08".

      (3) Click **Save**.

      (4) Double-click *vol* to select it.

      (5) Select **Fixed** as the **Type**.

(6) Click **Save**. The **Parameters** dialog box will appear as follows:



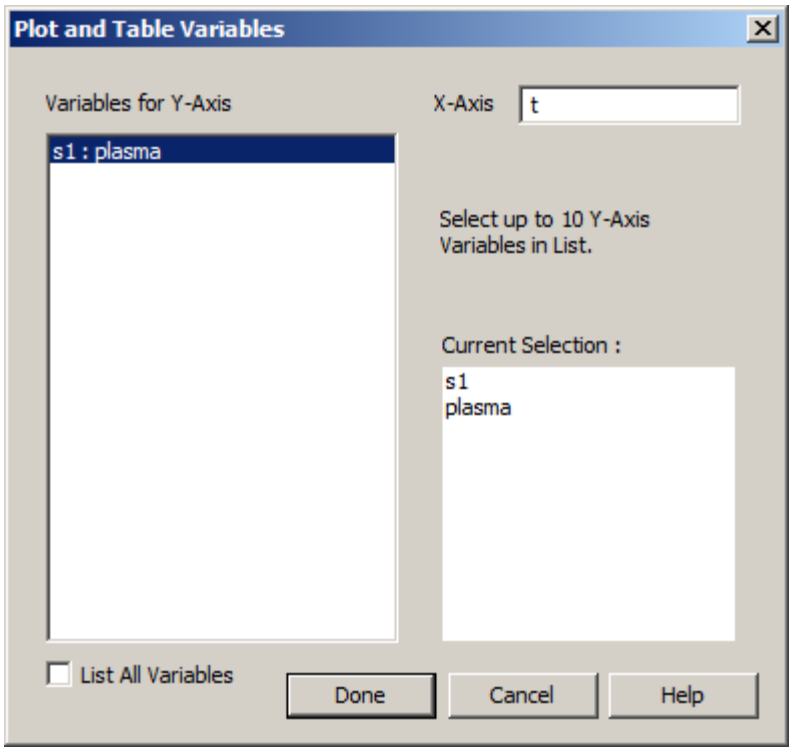
(7) Click **Done**.

6. Solve the model and view the solution.

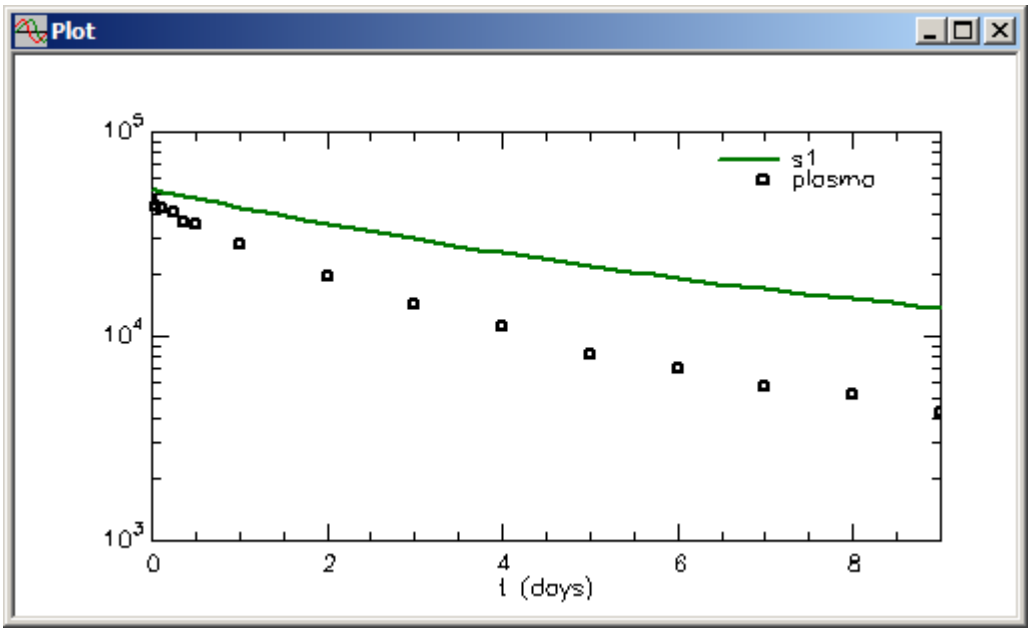
   a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve**  .

   b. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot**  . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is not selected so **s1:plasma** is the only option in the **Variables for Y-Axis** pane.

   c. Click **s1:plasma** to add this to the **Current Selection** pane. The **Plot and Table Variables** dialog box will appear as follows:



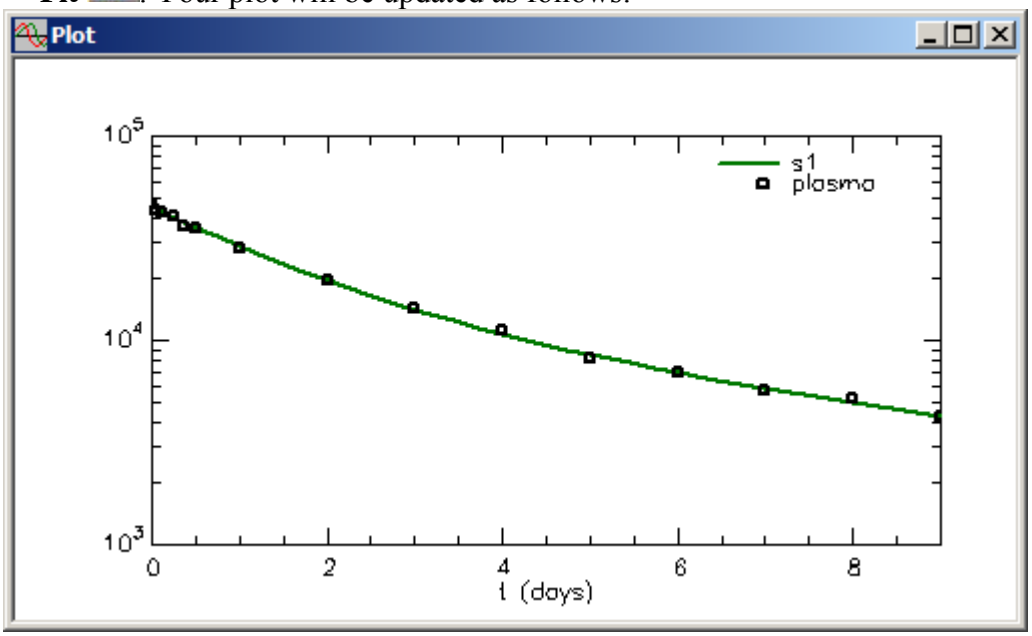
d. Click **Done**. A plot of **s1** and plasma will appear in semilog mode in the **Plot** window as shown below (if it is not in semilog mode, in the **View** menu, click **Semilog**):



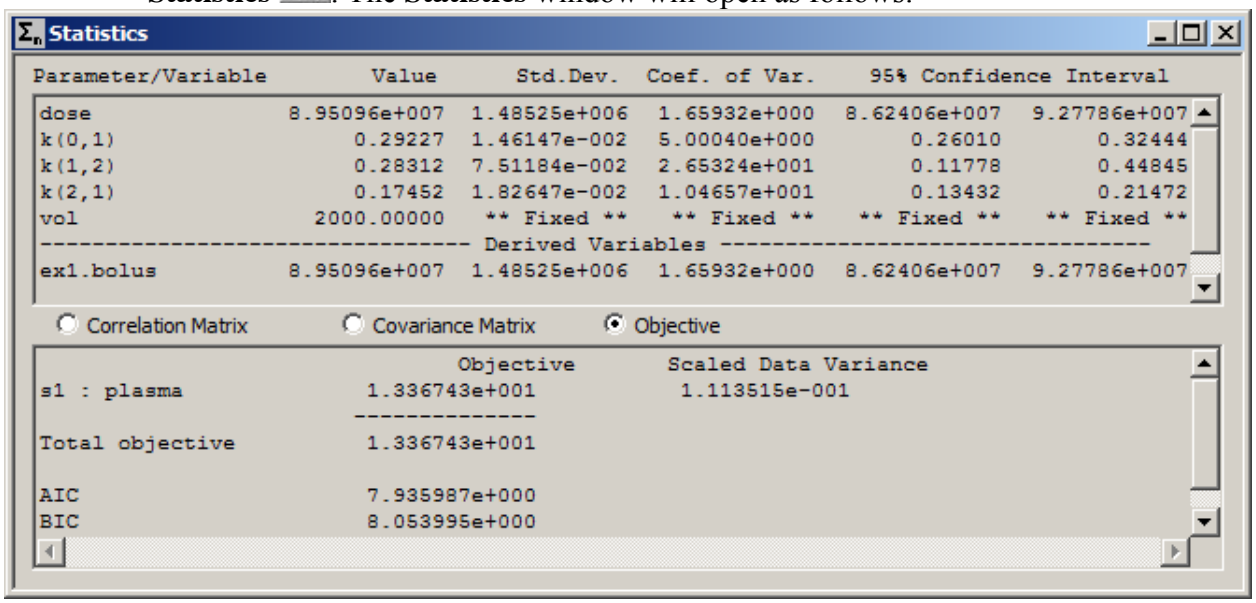
Leave the **Plot** window open.

7. Fit the model to the data and view the solution.

a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar,** click **Fit**  . Your plot will be updated as follows:



b. In the **Show** menu, click **Statistics**, or alternatively, on the **SAAM II Toolbar,** click **Statistics**  . The **Statistics** window will open as follows:



The model parameters are estimated with good precision. Notice, of course, *vol* is a fixed parameter. *ex1.bolus* appears as a derived parameter because of the specification of the input as an equation.

c. Close the **Statistics** and **Plot** windows.

Quit the **SAAM II Compartmental** application. Do not save the changes to **study_0**.

Part 3. Split inputs (an input into more than one compartment)

There may be occasion when your have an experimental input into more than one compartment, and you may not know how the input distributes among the compartments. One example is injecting radioiodinated low density lipoproteins (LDL) where the radioactive iodide distributes between two subpopulations of LDL particles. Another example would be an injected material with an unknown amount of contaminants where the material and contaminant have different kinetics. Thus what is known is the total amount of material administered; what may not be known is how it distributed. This situation is accommodated in SAAM II using the split input capability in the **Exogenous Input** dialog box.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

2. Create the following system model.

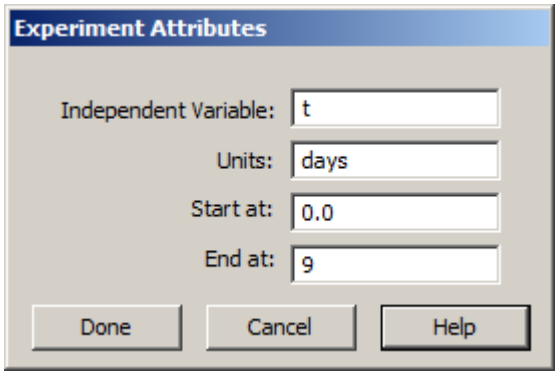
   Notice this is a two-compartment model where there is no interconnection between the two compartments; there is only a loss from each.

3. Create the experiment on the model.

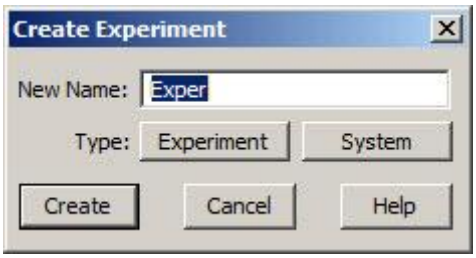
   a. In the **SAAM II Toolbox**, click **Experiment**. Notice that the **Model** tools are unavailable and the **Experiment** tools are available. The **Experiment Attributes** dialog box will open.

   b. Change the entry in the **Units** box from "minutes" to "days."

   c. Type "9" in the **End at** box. The **Experiment Attributes** dialog box will appear as shown below:



d. Click **Done**. The **Create Experiment** dialog box will appear on the **Drawing Canvas**. The choice is to create an **Experiment (Exper)** or **System** experiment. The **Exper** experiment is selected as follows:



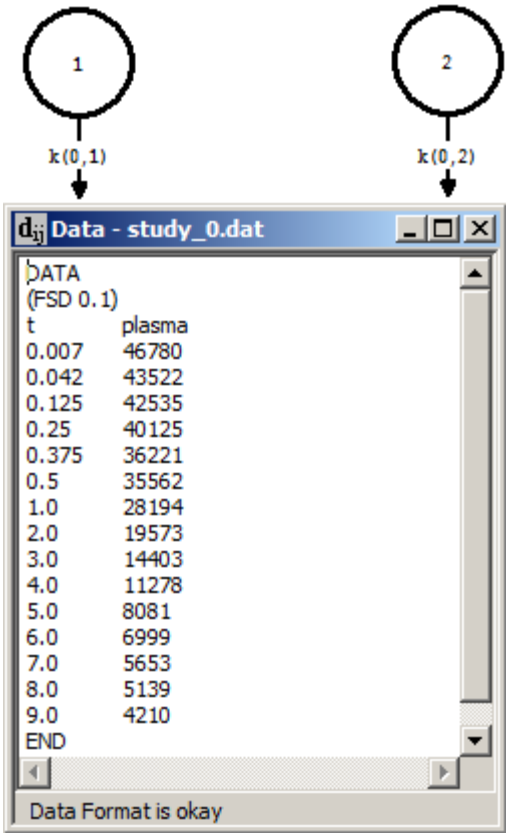
e. Click **Create** (since **Exper** is selected, and this is the type of experiment you want to create). Your model will appear as follows:

4. Add the data

a. On the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data**  . The **Data** window will open.

b. On the **File** menu, click **Open**. The file **study_0.dat** should appear in the list (if it does not, find the folder where you put this data file).

c. Double-click **study_0**. The data in this file will appear in the **Data** window. The model and the **Data** window should appear with the model on the **Drawing Canvas** as follows:



d. Close the **Data** window.

5. Create the sample on the model.

   a. In the **SAAM II Toolbox**, click **Sample**.

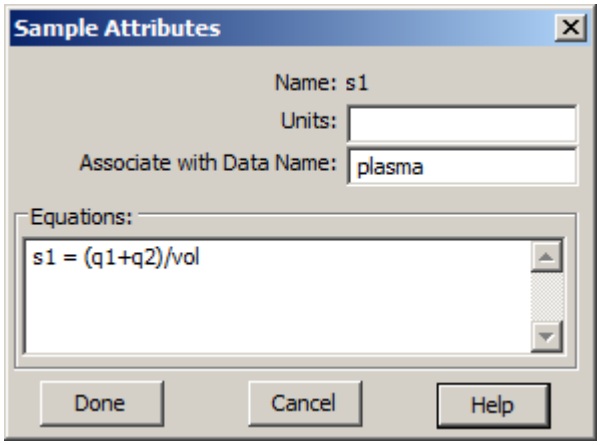
   b. Click Compartment **q1**, then Compartment **q2**, and then click on the **Drawing Canvas**.

      A sample object, **s1**, will appear on the **Drawing Canvas** attached to Compartments **q1** and **q2**. This means your sample was from plasma. Notice that the circle at the top of the sample object is an open circle; data have not yet been associated with the sample. The sample object can be moved on the **Drawing Canvas** to a location you desire.

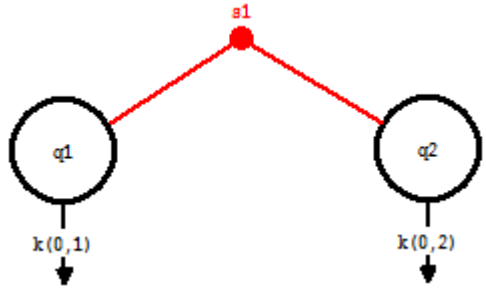
   c. Double-click **s1** to open the **Sample Attributes** dialog box.

   d. Type "plasma" in the **Associate with Data Name** box.

   e. Edit the sample equation "s1 = q1+q2" to read "s1 = (q1+q2)/vol" in the **Equations** pane. The **Sample Attributes** dialog box will appear as follows:



f. Click **Done**. The model will appear as follows:

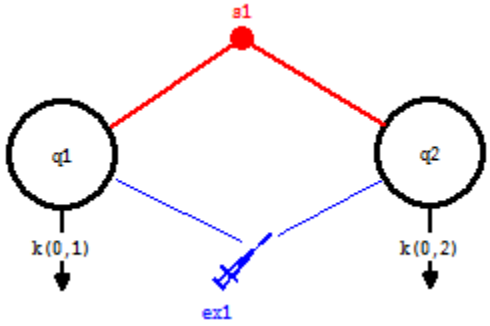


7. Create the experimental input

   a. In the **SAAM II Toolbox**, click **Input**.

   b. Click Compartment **q1**, then Compartment **q2**, and then click on the **Drawing Canvas**.

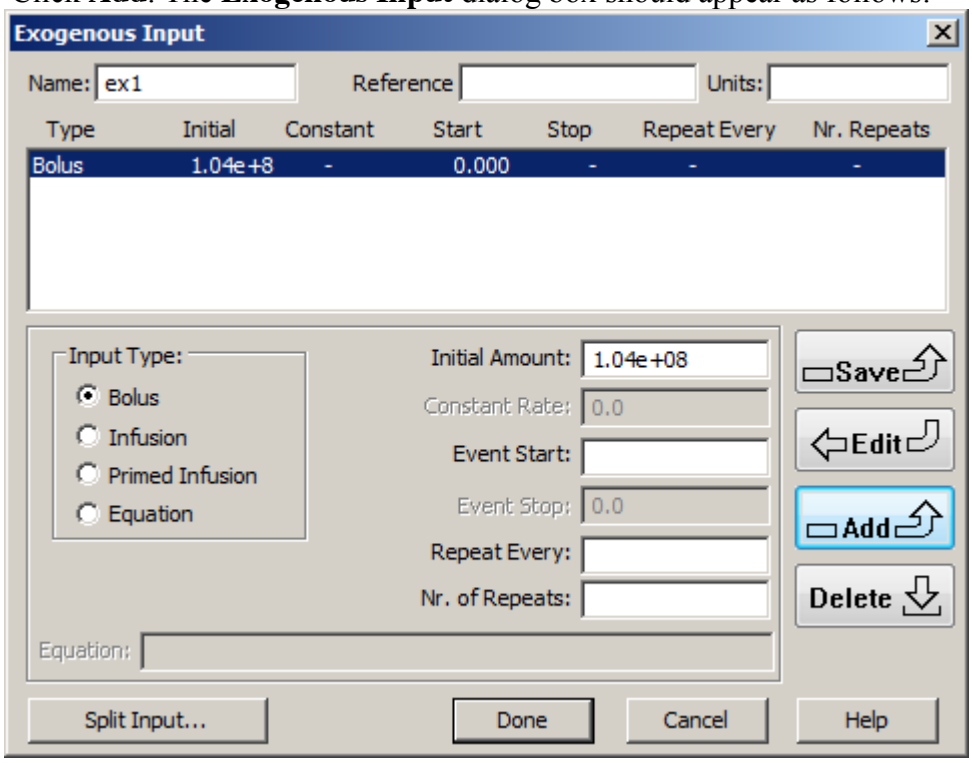
      An input arrow named **ex1** will appear on the **Drawing Canvas** attached to Compartments **q1** and **q2**. The input syringe can be moved to a desired location. The model will appear as follows:



   c. Double-click **ex1** to open the **Exogenous Input** dialog box.

   b. Type "1.04e+08" in the **Initial Amount** box.

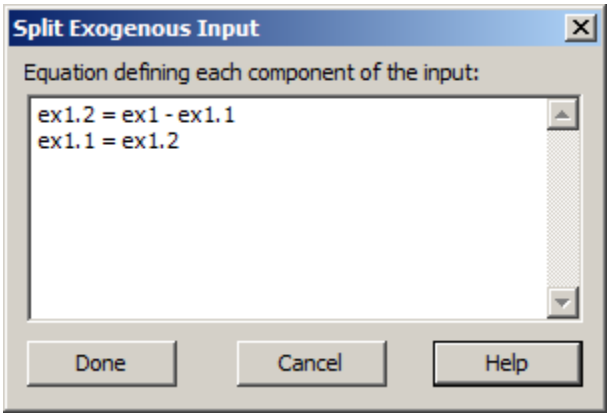
e. Click **Add**. The **Exogenous Input** dialog box should appear as follows:



Notice the **Split Input** button is active.

Split inputs. Split inputs occur when your injected test substance is not kinetically homogeneous, but kinetically heterogeneous. This means the input consists of two or more substances with different kinetics. This can be due to a variety of factors including contamination. It is important to be aware when this can happen, and incorporate it into your model.

f. In the **Exogenous Input** dialog box, click **Split Input**. The **Split Exogenous Input** dialog box will open as follows:

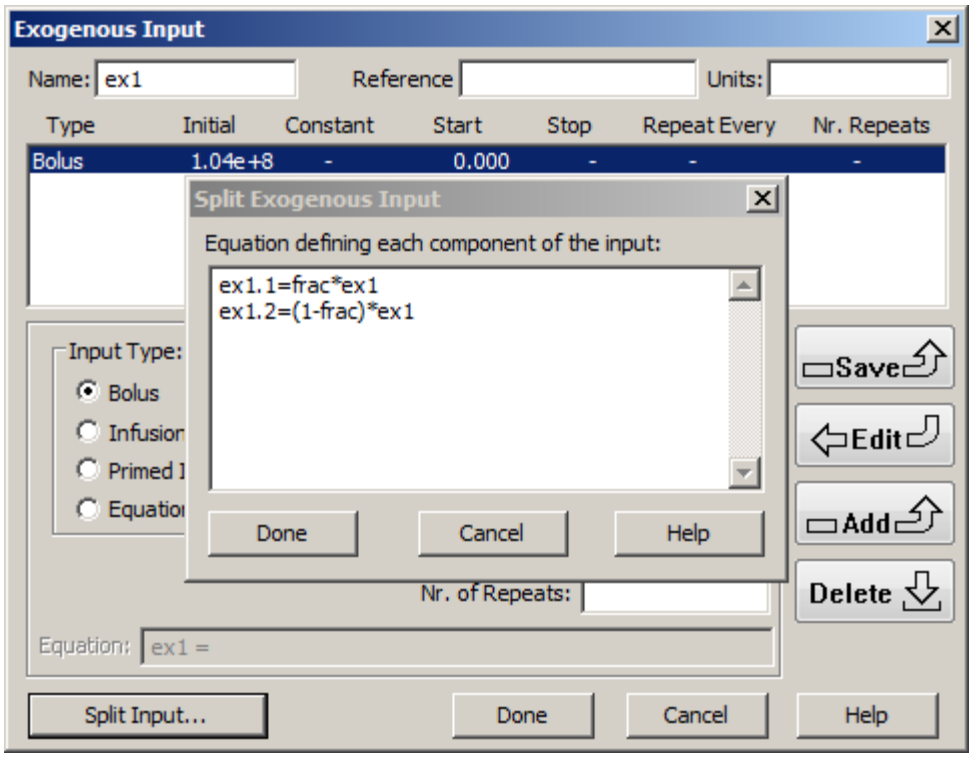


Split Exogenous Input. When you have a split input, you know the total amount of substance given, but you may not know how the substance distributes among different compartments. You must write equations which relate the amounts in the different compartments to the total. In this example where the input is a bolus, **ex1** is the total dose. The doses in Compartments **q1** and **q2** are respectively **ex1.1** and **ex1.2**.

g. In the **Equation** box in the **Split Exogenous Input** dialog box, edit the equations to read:

ex1.1 = frac*ex1
ex1.2 = (1-frac)*ex1

The **Split Exogenous Input** dialog box together with the **Exogenous Input** dialog box will appear as follows:



Split exogenous input. The above equations partition the total dose, **ex1**, into two fractions. *frac* will become a parameter whose value lies between 0 and 1. It will be the fraction of the total dose in Compartment **q1**. The value 1 – *frac* will be the total dose in Compartment **q2**.

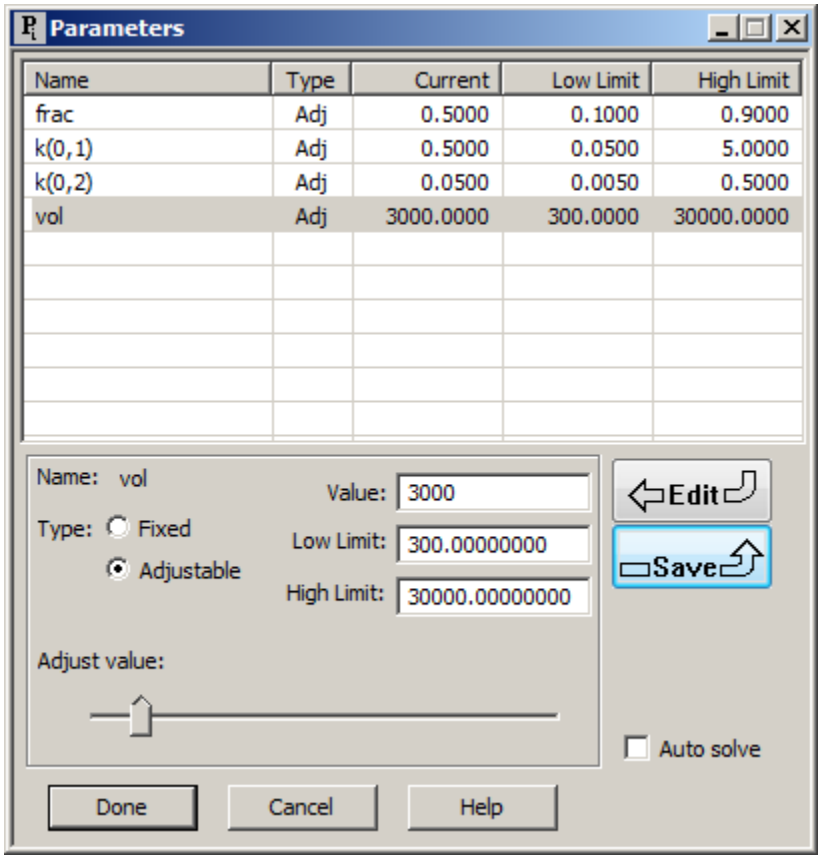
h. In the **Split Exogenous Input** dialog box, click **Done**. The **Exogenous Input** dialog box will remain as shown above. The only indication of the split input is the **Split Input** option is active.

i. In the **Exogenous Input** dialog box, click **Done**.

8. Add parameter values to the model.

a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters** . The **Parameters** dialog box will open.

b. Add the parameters as shown in the **Parameters** dialog box below:



Split exogenous input. In the above, *frac* is a parameter whose value lies between 0.1 and 0.9. Notice also there are four parameters to estimate, the two losses, the volume, and *frac*.

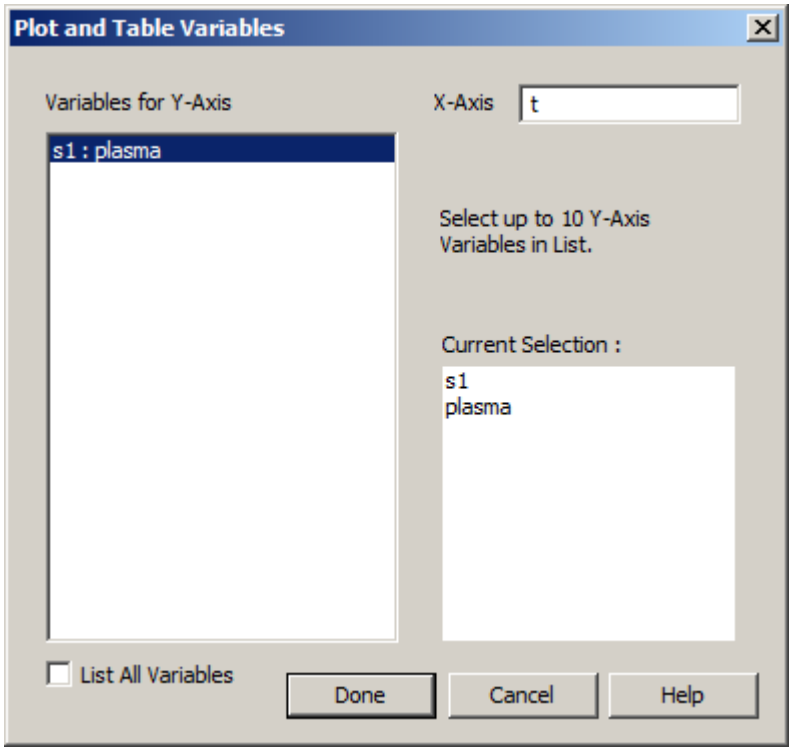
c. Click **Done**.

9. Solve the model, and view the solution.

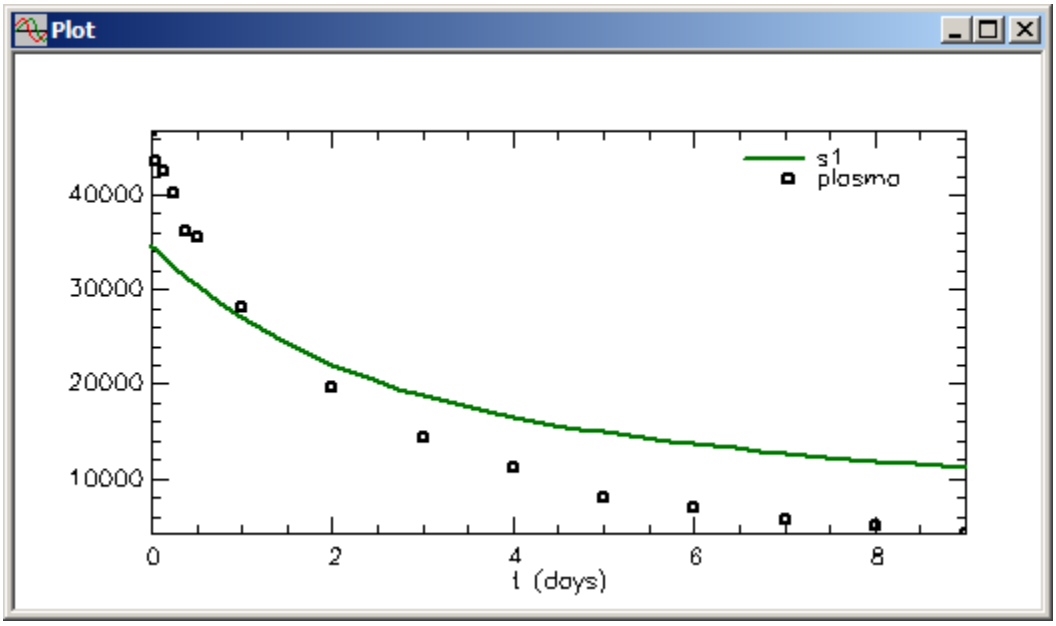
a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve**  .

b. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot**  . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is not selected so **s1:plasma** is the only option in the **Variables for Y-Axis** pane.

c. Click **s1:plasma** to add this to the **Current Selection** pane. The **Plot and Table Variables** dialog box will appear as follows:



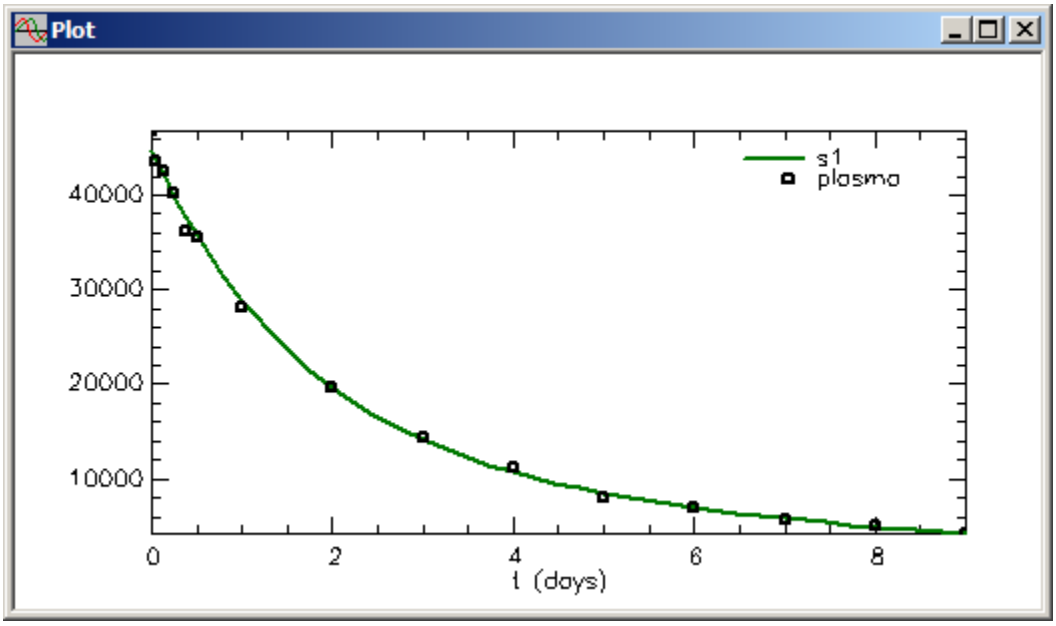
d. Click **Done**. A plot of **s1** and plasma will appear in semilog mode in the **Plot** window as shown below (if it is not in linear mode, in the **View** menu, click **Semilog**):



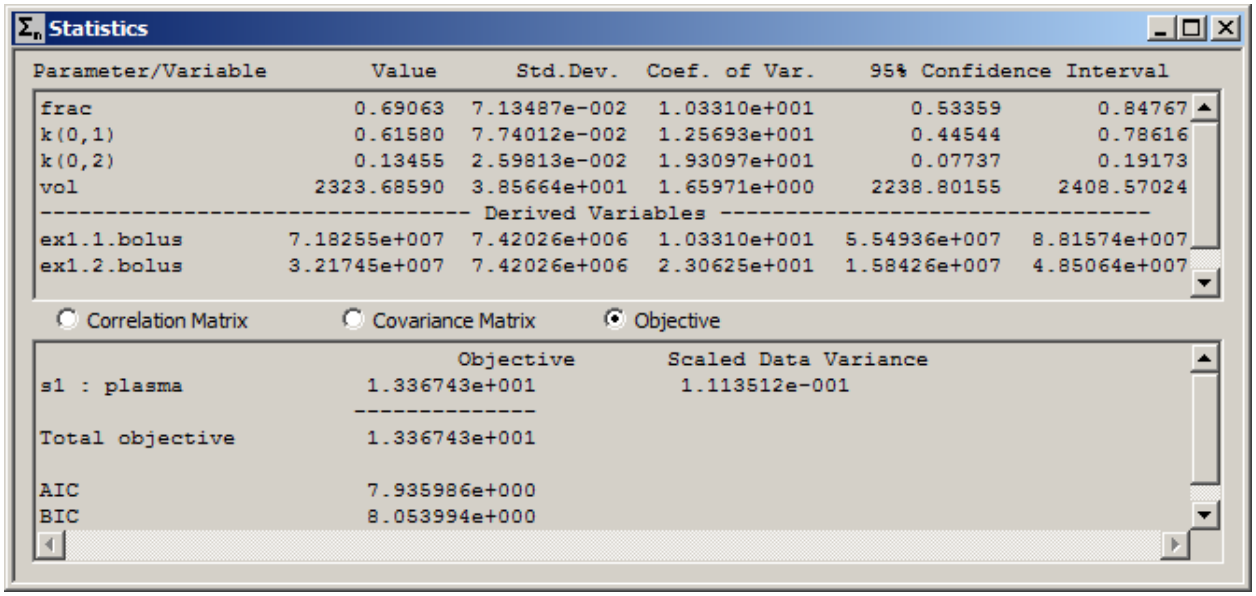
Leave the **Plot** window open.

7. Fit the model to the data and view the solution.

   a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar,** click **Fit** . Your plot will be updated as follows:



   b. In the **Show** menu, click **Statistics**, or alternatively, on the **SAAM II Toolbar,** click **Statistics** . The **Statistics** window will open as follows:



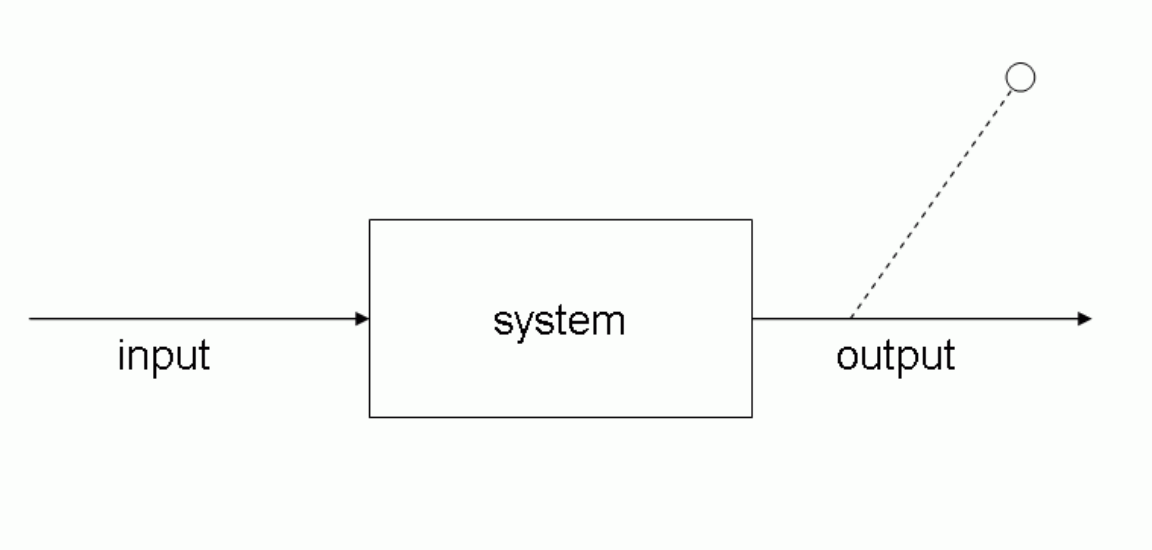
The model parameters are estimated with good precision. The value for *frac* is 0.69 which means 69% of the original injected dose is into Compartment **q1**. Under **Derived Variables**, you can see the exact amount of dose in each compartment predicted by the model.

c. Close the **Statistics** and **Plot** windows.

Quit the **SAAM II Compartmental** application. You may save the study file if you wish.

Part 4. Parametric deconvolution

Deconvolution is the technique used to address the following problem. There is a known system and a known output from an unknown input. The problem is to calculate the unknown input. The problem is shown diagrammatically as follows:



There are basically two ways to deal with this problem. One is called nonparametric deconvolution. This is an extremely difficult problem. The other is called parametric deconvolution.

In parametric deconvolution, the following are assumed:

- The exact specification of the system model (in terms of a compartmental model, this means the structure and all parameter values).
- There are output data.
- The specification of the input is known (in terms of the situation here, this means the equation for the input is known but the parameters of the equation are unknown and will be estimated from the data).

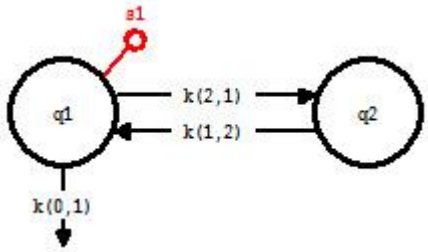
This part of the tutorial will illustrate how to perform parametric deconvolution using SAAM II.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open as shown below:

2. Open the **SAAM II Compartmental** study file **ExpInp_0**.

   a. The file **ExpInp_0.stu** should appear in the file list; if it does not, find the folder where you put this file.

b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear. In the **SAAM II Toolbox**, click **Experiment**. The model of the experiment for **ExpInp_0.stu** will appear on the **Drawing Canvas** as follows:

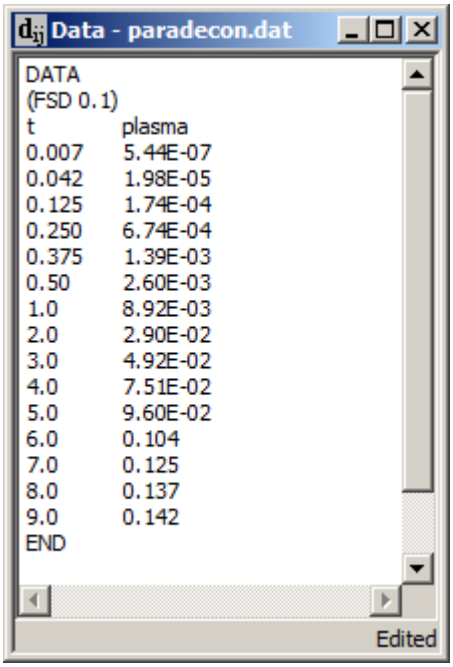


3. Enter and view the data.

a. In the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data**  . The **Data** window will open.

b. In the **File** menu, click **Open**. The file **paradecon.dat** should appear in the list (if it does not, find the folder where you put this data file).

c. Double-click **paradecon.dat**. The data in this file will appear in the **Data** window as follows:



These are simulated data obtained when an exponential input was specified and samples were created at the same time samples were taken in the data file **study_0.dat**.

d. Close the **Data** window.

e. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot**  . The **Plot and Table Variables** dialog box will open.

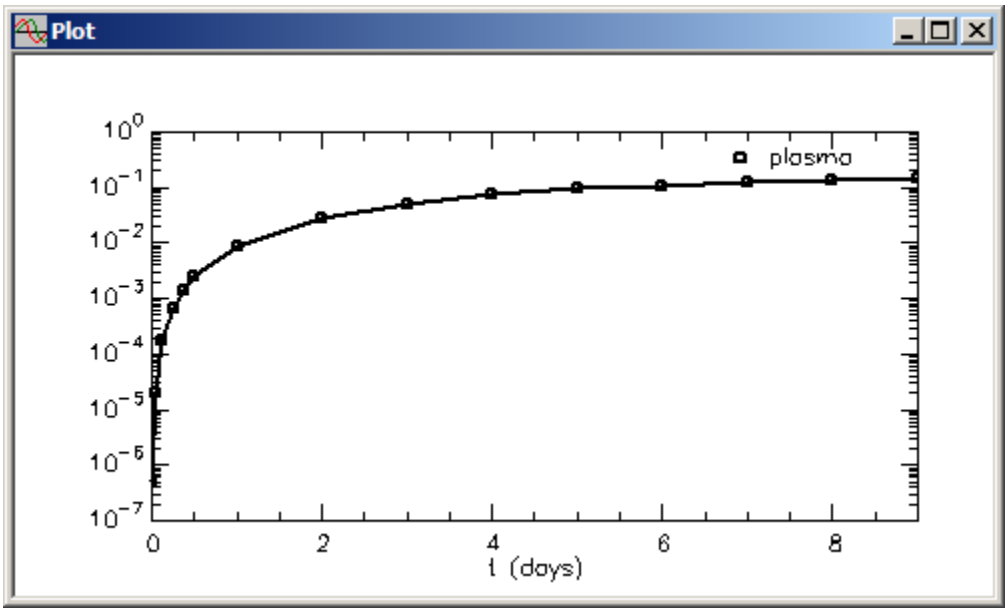
f. Be sure the **List All Variables** check box is selected. (Click this box if it is not selected).

g. Click **plasma** to move it to the **Current Selection** pane.

h. Click **Done**. A plot of the data will appear in the **Plot** window.

i. In the **View** menu or right-click in the plot window, click **Line Plot**.

j. In the **View** menu or right-click in the plot window, be sure **Semilog** is selected. Your plot will appear as follows:



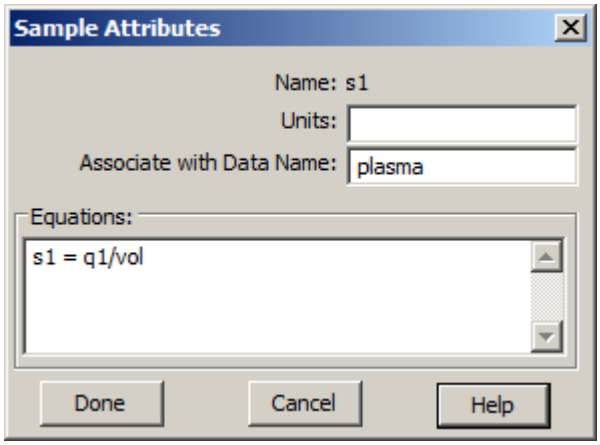
These are the output data. The problem is to specify an input function format, and to estimate the parameters of this input from the data.

k. Close the **Plot** window.

4. Associate the sample **s1** with the **plasma** data.

a. Double-click **s1** to open the **Sample Attributes** dialog box.

b. In the **Associate with Data Name** box, type "plasma". The **Sample Attributes** dialog box will appear as follows:



c. Click **Done**.

5. Specify and define the input function.

   In this example, the input function is assumed to be known, and to be equal to A*(exp(-a*t)-exp(-b*t)). This will be entered as equation input, and the parameters *A*, *a* and *b* estimated from the data.

   a. In the **SAAM II Toolbox**, click **Input**.

   b. Click on Compartment **q1** and then the **Drawing Canvas**. The input **ex1** will appear.

   c. Double-click **ex1** to open the **Exogenous Input** dialog box.

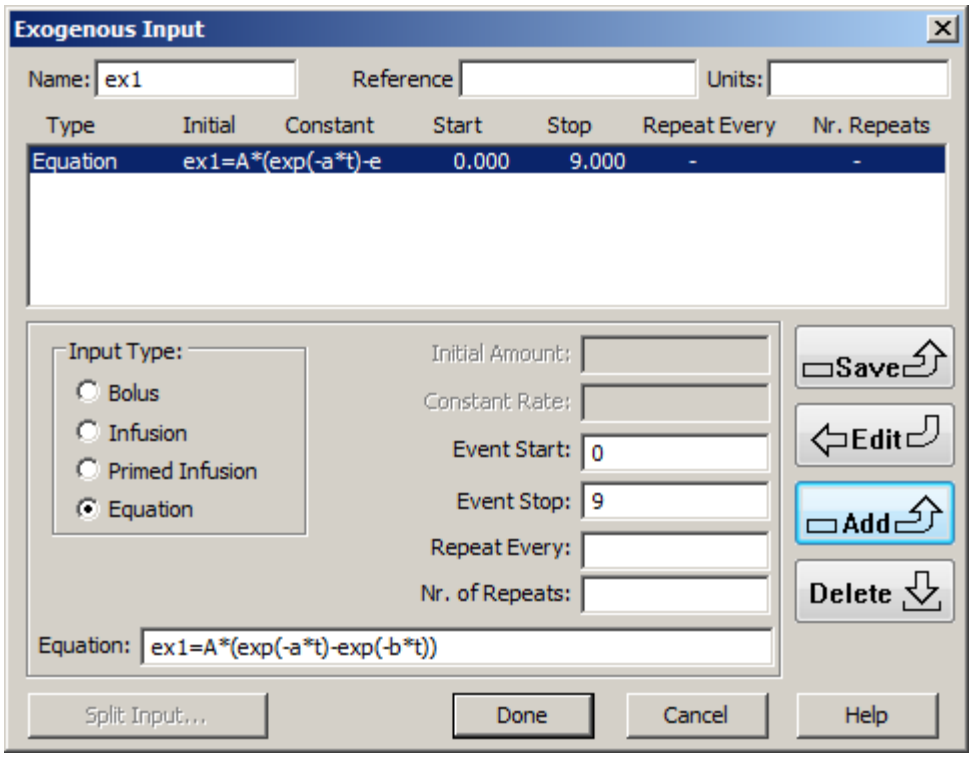
   d. Specify the equation input.

      (1) In the **Input Type** pane, select **Equation**

      (2) In the **Equation** box, type "ex1=A*(exp(-a*t)-exp(-b*t))".

      (3) In the **Event Start** box, type "0".

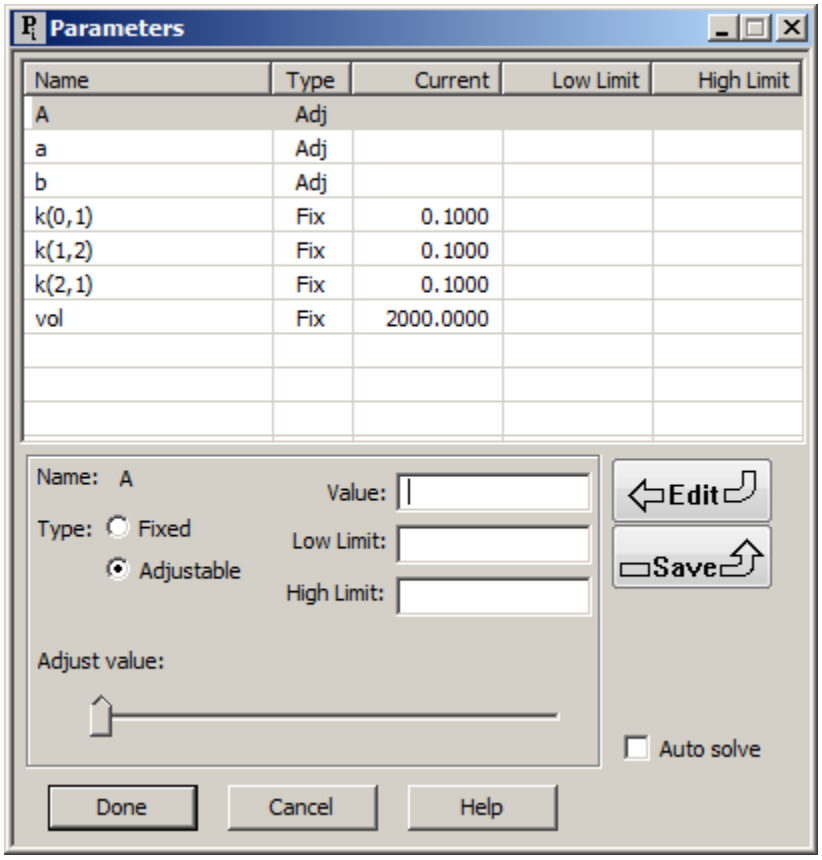
      (4) In the **Event Stop** box, type "9". (Remember the time of the experiment in **study_0** is 9 days). Click **Add**. The **Exogenous Input** dialog box will appear as follows:



(5) Click **Done**.

6. Specify the parameter values.

a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters**  . The **Parameters** dialog box will open, as shown below:



The ***model parameters*** are all present and fixed. These are the *k(i,j)* and *vol*. In parametric deconvolution, the model parameters are assumed to be known precisely, and hence must be fixed.

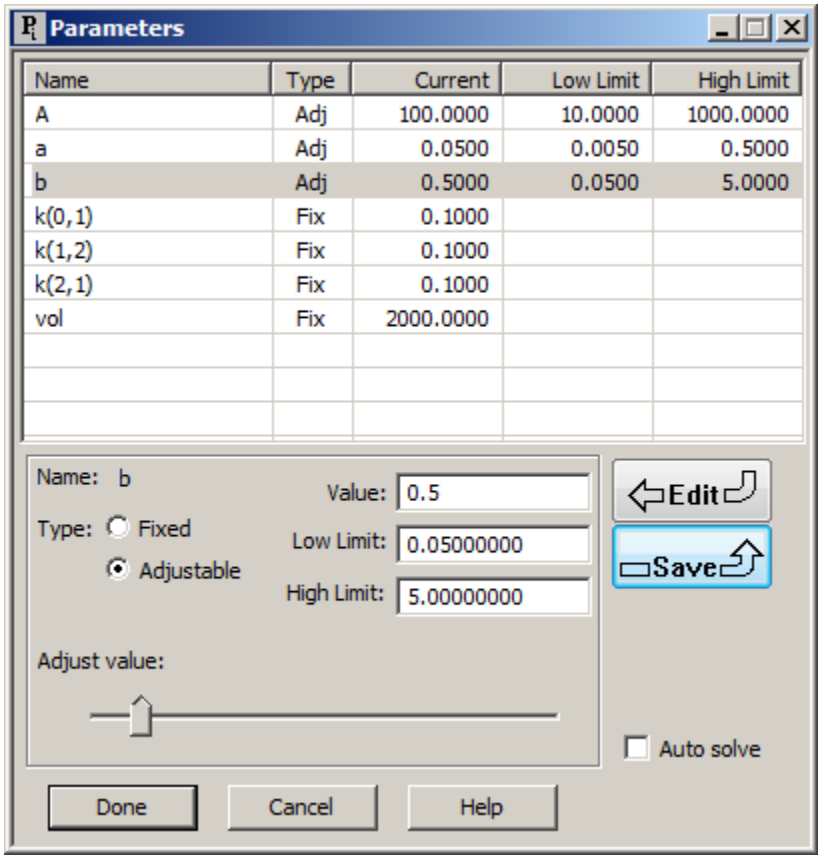
The ***unknown model parameters are those characterizing the input function***. In parametric deconvolution, the "type" of input function is assumed to be known but the parameters of the function are unknown.
In this case, these parameters are *A*, *a* and *b*.

b. Enter the parameter values.

(1) If *A* is not selected, double-click *A* to select it. Type "100" in the **Value** box, and click **Save**.

(2) Double-click *a* to select it. Type "0.05" in the **Value** box, and click **Save**.

(3) Double-click *b* to select it. Type "0.5" in the **Value** box, and click **Save**. The **Parameters** dialog box will appear as follows:



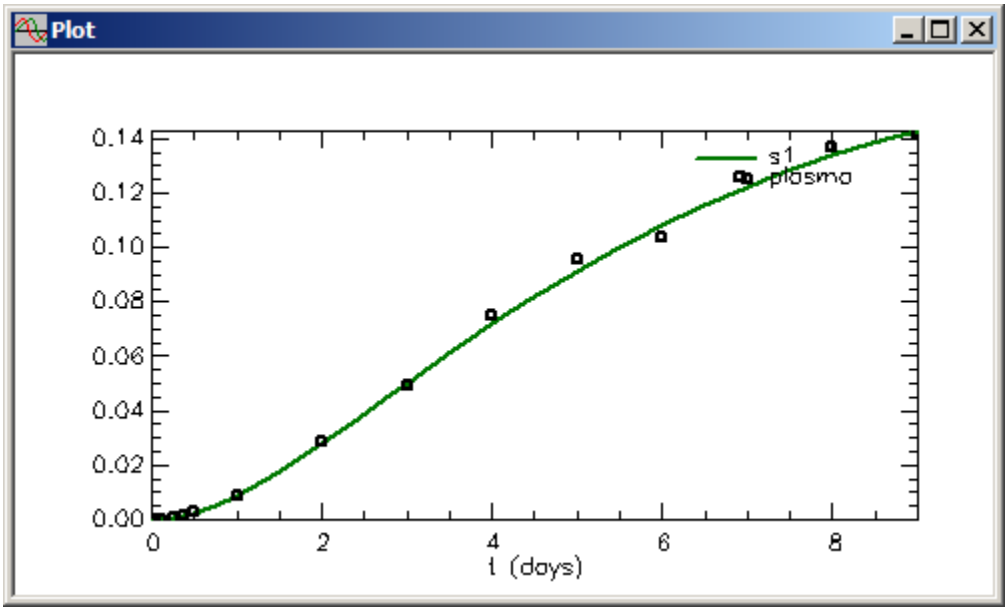
(4) Click **Done**.

7. Solve the model and view the solution.

   a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve**  .

   b. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot**  . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is not selected.

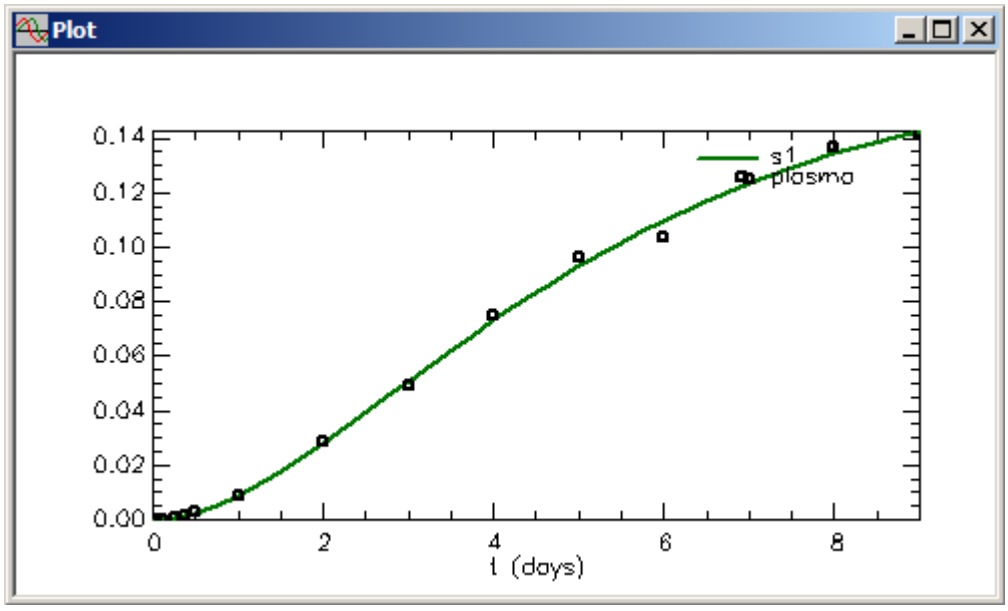
   c. Click **s1:plasma** to move this to the **Current Selection** pane. Your plot will appear as shown below (in linear mode).



Leave the **Plot** window open.

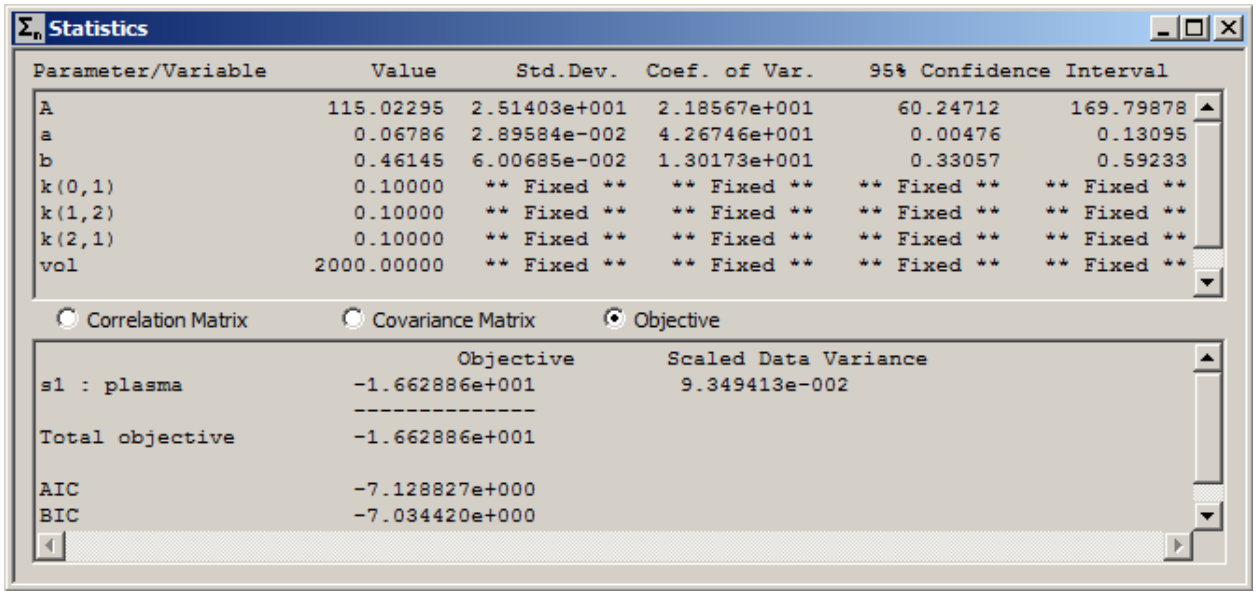
8. Fit the model to the data and view the results.

   a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar** click **Fit**  . The plot will be updated as follows:



Close the **Plot** window.

b. In the **Show** menu, click **Statistics**, or alternatively, on the **SAAM II Toolbar,** click **Statistics**  . The **Statistics** window will open as follows:



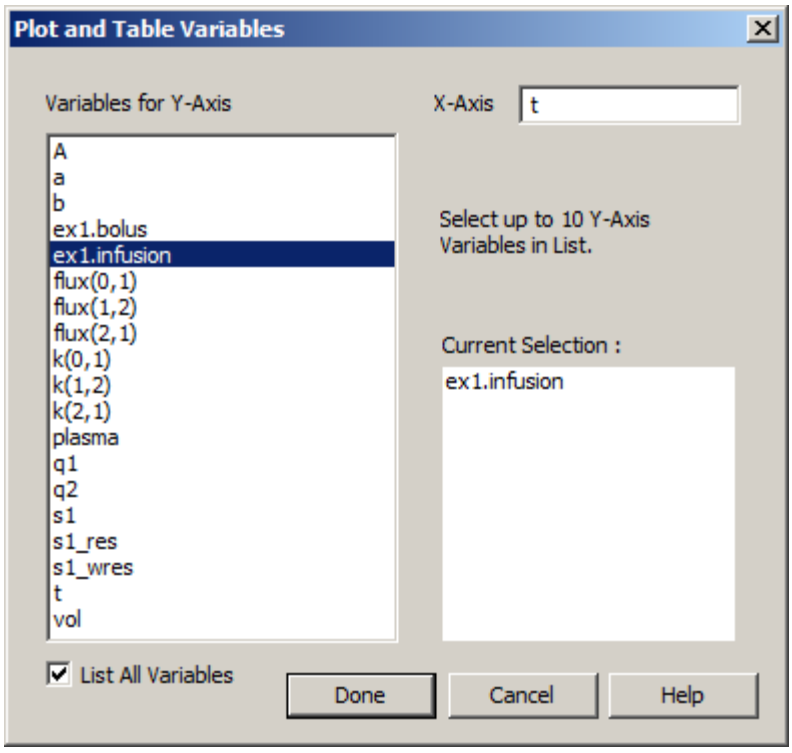
Close the **Statistics** window.

9. View the unknown input function.

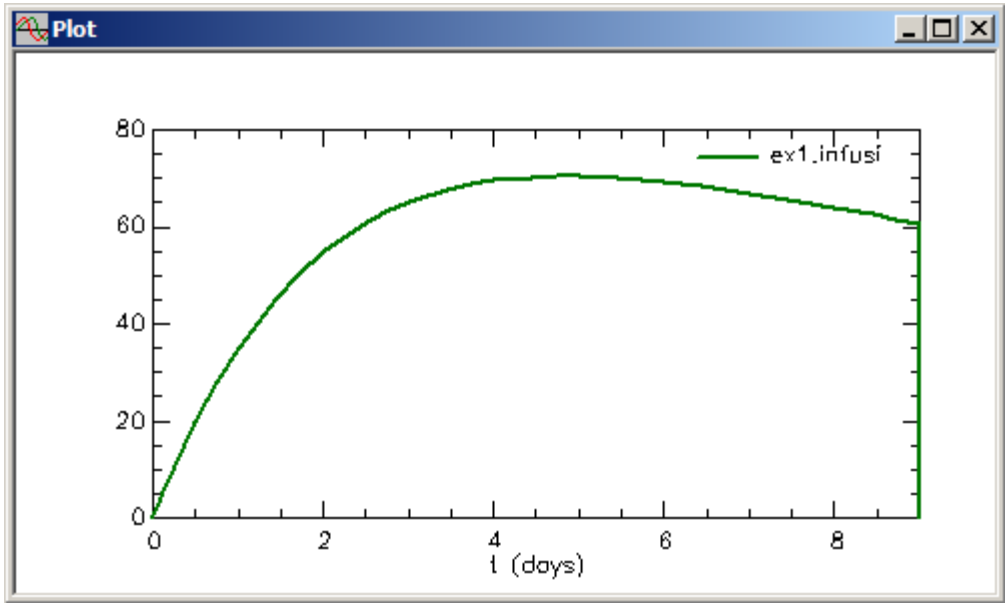
a. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot**  . Your previous plot should open.

b. In the **Set** menu, click **Plot/Table Variables**, or alternatively, on the **SAAM II Toolbar,** click **Plot**, or right-click in the plot window and select Variables. The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is selected.

c. Click **ex1.infusion** to move this to the **Current Selection** pane. The **Plot and Table Variables** dialog box will appear as follows:



d. Click **Done**. The plot of the unknown input function will appear as follows (the plot is in linear mode, and the **Y Axis maximum** has been set equal to 80):



e. Close the **Plot** window.

Quit the **SAAM II Compartmental** application. Do not save the changes to **study_0**.

SAAM II Version 2.1
Advanced Tutorials

Multiple Input-Output Experiments

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Multiple Input-Output Experiments

Prerequisites

The prerequisite for this tutorial is having worked through the **SAAM II** introductory tutorial, "Getting Started with **SAAM II Compartmental**." It will be helpful to have worked through the Using SAAM II Tutorial "Using Delays – Part 1."

What you will learn in this tutorial

The purpose of this tutorial is to show you have to deal with experiments with multiple inputs and multiple outputs. You will learn how to

- Create multiple input-output experiments using the **Duplicate** command (Part 1).
- Create multiple input-output experiments using **Create Experiment** in the **SAAM II Toolbox** (Part 2).

Files Required

Study Files: The study files for this tutorial are

io_duplicate.stu
io_expt.stu
io_expt_final.stu

The study file **io_duplicate.stu** is saved for convenience and can be used with Part 1. The study file **io_expt.stu** will be used for Part 2. The study file **io_expt_final.stu** is the study file created in Part 2.

Data File: The data file for this tutorial is

io.dat

This file is included as part of this tutorial.

Introduction

There are many instances when your experimental protocol may call for multiple inputs. Examples in metabolic kinetics come from multiple tracer studies. For example, carbon and hydrogen labeled glucose can be injected (two-inputs) and both tracers followed in plasma samples (two-outputs). In pharmacokinetic studies, an example would be the IV and oral administration of a drug in the same individual. Normally this is done at different times so the assumption has to be made that the subject is in the same "state" in both experiments. More recently, it has become possible to label a drug with a stable isotope. The drug and isotopically labeled drug can then be administered IV and orally (two-inputs), and plasma levels of drug and stable isotope followed (two-outputs). Finally, the increased use of tools such as MRI and PET is making multiple input-output studies more common. Multiple input-output studies will become more important especially in the pharmaceutical industry as the process of drug discovery and development becomes more sophisticated.

There are two ways multiple input-output studies can be created in SAAM II. One uses the model duplication command in the **Edit** menu. Here, as illustrated in Part 1, you can create a model, and then duplicate the model structure. You have the option of having corresponding rate constants set equal, or they can be different. In Part 1, you will see that you can create a model for the IV system. Then you can duplicate this model, and add to it components to describe absorption.

The other method uses the **Create Experiment** option in the **SAAM II Toolbox**. Here you first create the system model. In the system model, you can have inputs at different sites. SAAM II does the book keeping via the **Create Experiment** option. You create a different experiment for each input.

The most common experiment is the single input experiment. When you create your experiment, the compartment names change from, for example, **1** to **q1**. When you create multiple experiments, **q1** changes to, for example, **q1.1** for a second experiment, **q1.2** for a third experiment, etc. Using this option makes it much easier to keep track of the individual inputs and outputs.

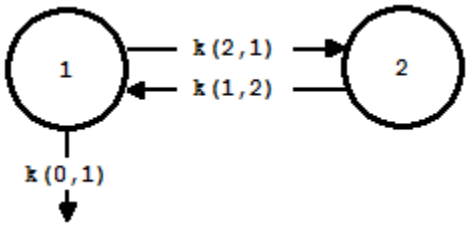
The data to be used in this tutorial come from a pharmacokinetic study in which a drug was first given IV, and then given later via a suspension into the upper GI tract.

Part 1. Creating a Multiple Input-Output Experiment Using the Duplicate Command

In this tutorial, you will simultaneously analyze data following an iv administration and oral suspension administration of a drug using the Duplicate command. In the IV experiment, the drug was infused for 20 minutes while in the suspension, it was given as a bolus.

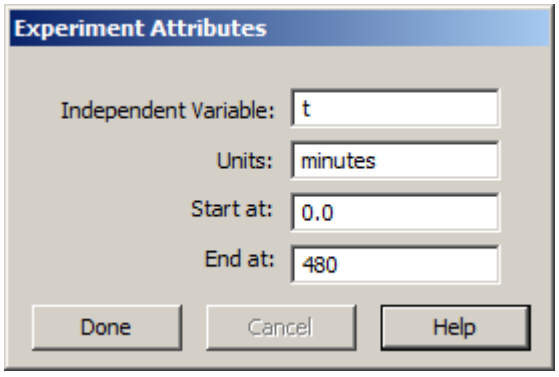
1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

2. Create the following system model for the IV data on the **Drawing Canvas**:

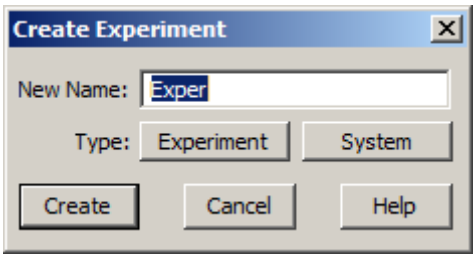


3. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open.

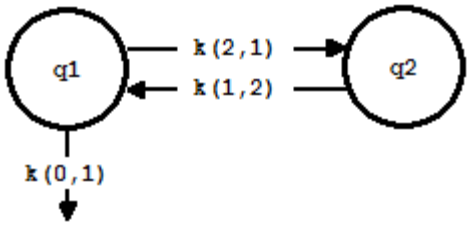
   a. Type "480" in the **End At** box. **The Experiment Attributes** dialog box should appear as follows:



   b. Click **Done**. The **Create Experiment** dialog box will open as follows:



   c. Click **Create**. The model will appear on the **Drawing Canvas** as follows:

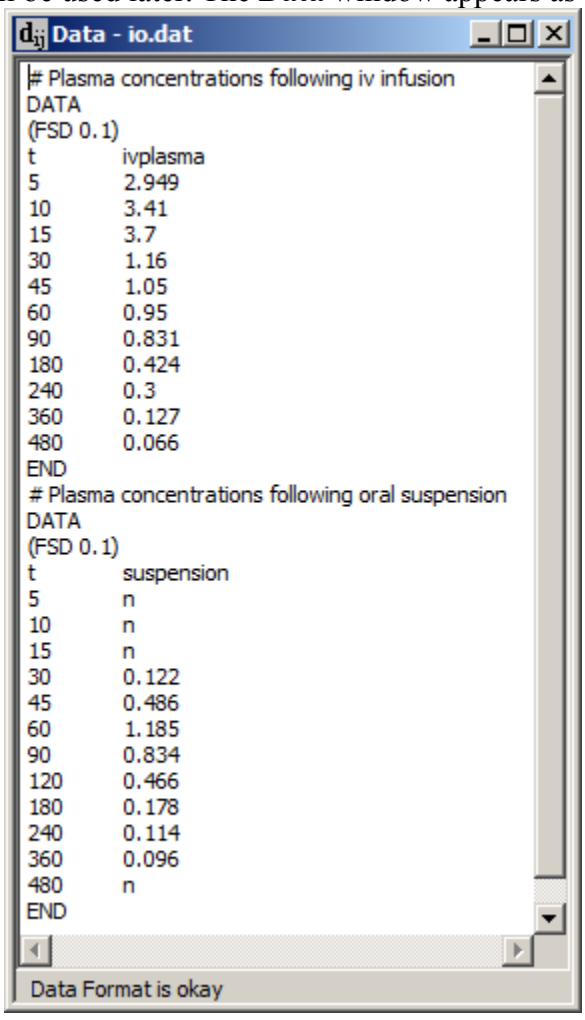


4. Add the data to your model.

   a. In the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data**  . The **Data** window will open.

   b. In the **File** menu, click **Open**. The file **io.dat** should appear in the list (if it does not, find the folder where you have put this data file).

   c. Double-click **io.dat**. The data file contains drug data following the 20 minute constant infusion, "ivplasma", and following the oral administration, "suspension." The oral data will be used later. The **Data** window appears as follows:



The weighting scheme is FSD; you can leave the variance model set as the default data-relative.

d. Close the **Data** window.

5. Create a sample and an input

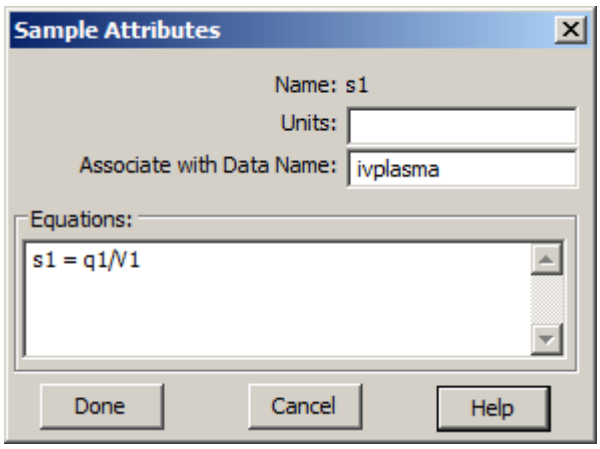
a. In the **SAAM II Toolbox**, click **Sample**.

b. Click Compartment **q1** and then the **Drawing Canvas**. The sample **s1** will appear associated with Compartment **q1**.

c. Double-click **s1** to open the **Sample Attributes** dialog box.

d. Type "ivplasma" in the **Associate with Data Name** box.

e. Edit the sample equation to read "s1=q1/V1". The **Sample Attributes** dialog box will appear as follows:



f. Click **Done**.

g. In the **SAAM II Toolbox**, click **Input**.

h. Click Compartment **q1** and then the **Drawing Canvas**. The input **ex1** will appear associated with Compartment **q1**.

i. Specify the 20 minute infusion.

(1) Double-click **ex1** to open the **Exogenous Input** dialog box.

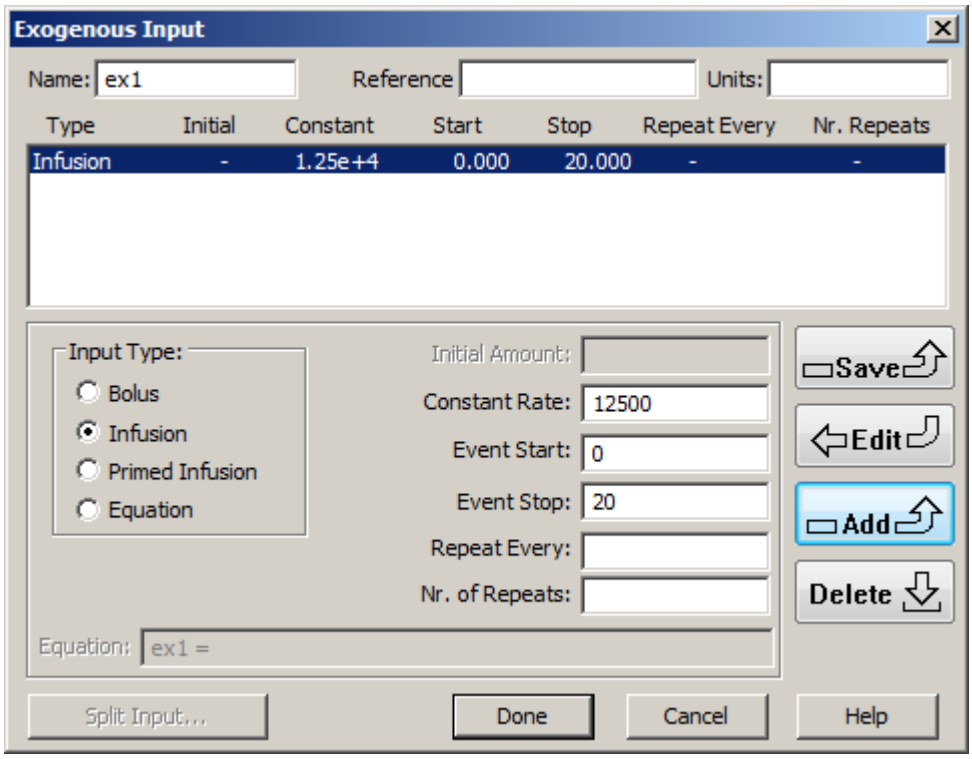
(2) Select **Infusion** in the **Input Type** pane.

(3) Type "12500" in the **Constant Rate** box.

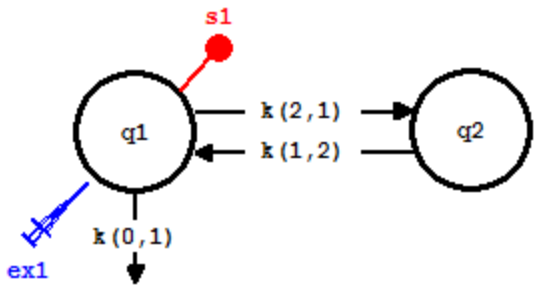
(4) Type "0" in the **Event Start** box.

(5) Type "20" in the **Event Stop** box.

(6) Click **Add**. The **Exogenous Input** dialog box should appear as follows:



(7) Click **Done**. The model will appear as follows:



6. Enter the parameter values.

   a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters**  . The **Parameters** dialog box will open.

   The parameter V1 should be selected. If it is not selected, double-click V1. Be sure the **Adjustable** option is selected.

b. Type "13000" in the **Value** box, "2000" in the **Low Limit** box, "20000" in the **High Limit** box, and click **Save**.

c. Double-click *k(0,1)* to select it.

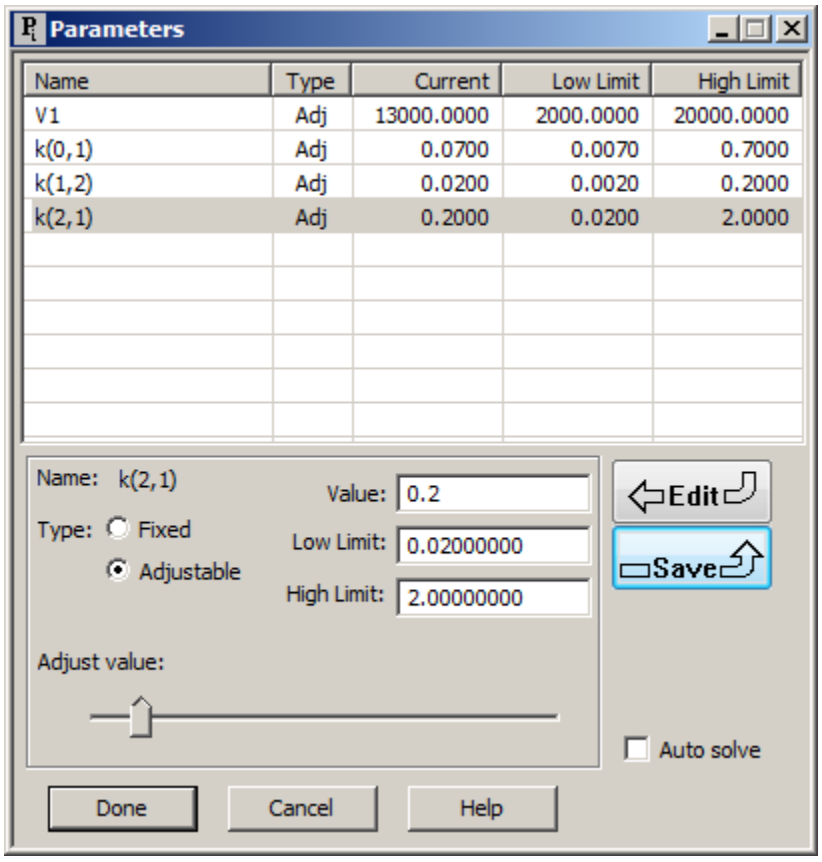
d. Type "0.07" in the **Value** box, and click **Save**.

e. Double-click *k(1,2)* to select it.

f. Type "0.02" in the **Value** box, and click **Save**.

g. Double-click *k(2,1)* to select it.

h. Type "0.2" in the **Value** box, and click **Save**. The **Parameters** dialog box should appear as follows:

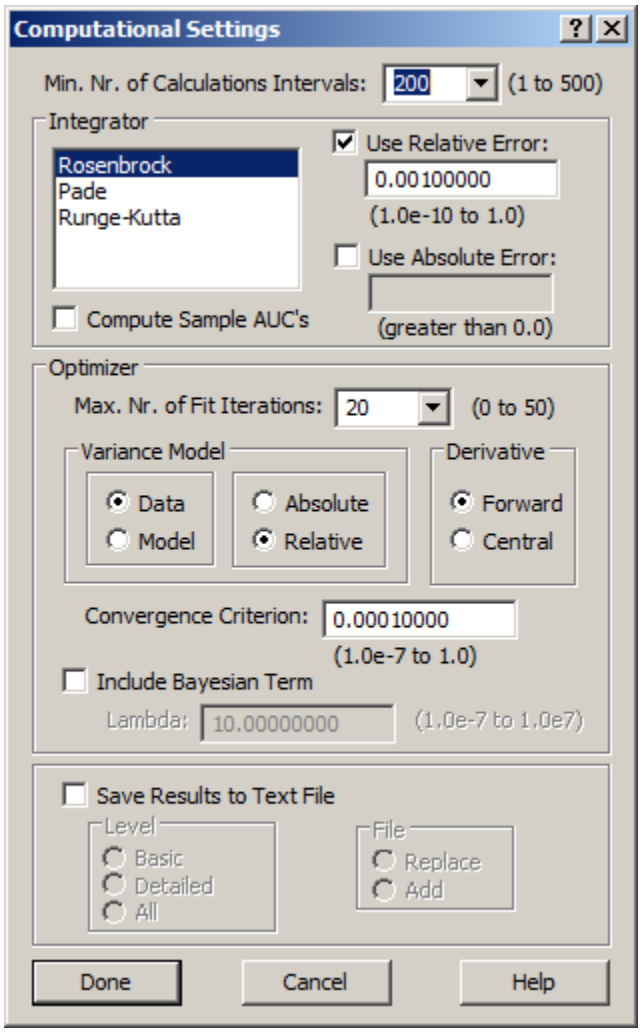


i. Click **Done**.

7. Solve the model and view the solution.

a. It will be helpful to have better resolution of your plots than the default. In the **Compute** menu, click **Settings**. The **Computational Settings** dialog box will open.

Change the entry in the **Min. Nr. of Calculation Intervals** from "20" to "200". The **Computational Settings** dialog box should appear as follows:



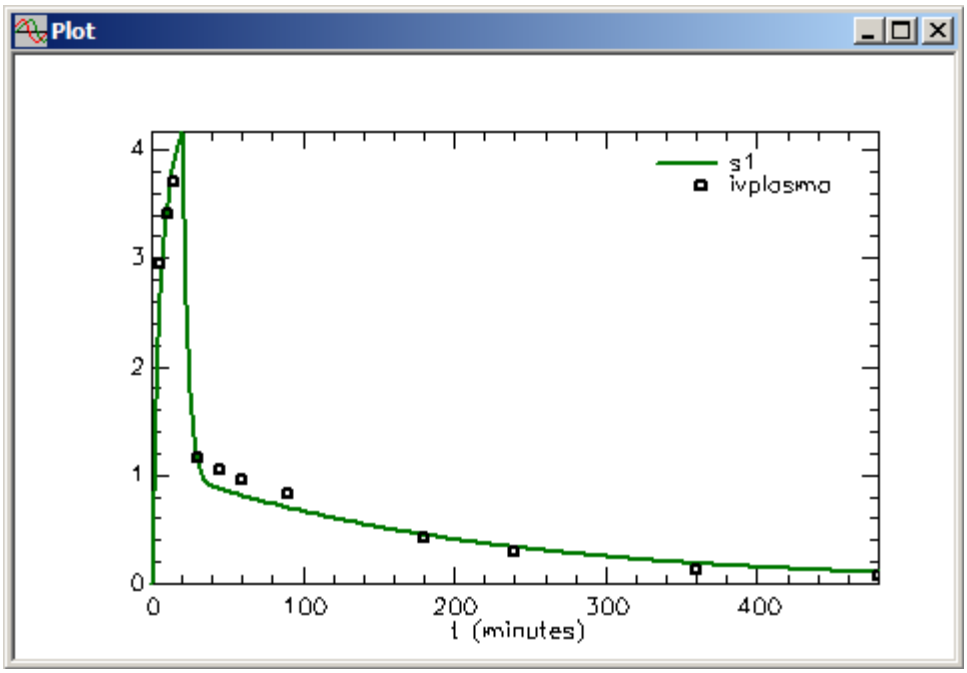
Click **Done**.

b. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve**  .

c. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot**  . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables check** box is not selected.

d. Click **s1:ivplasma**; it will move to the **Current Selection** pane.

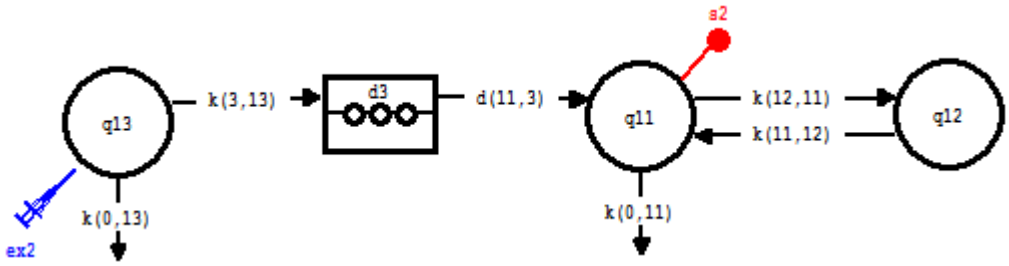
e. Click **Done**. The following plot will appear (in linear mode):



f. Close the **Plot** window.

You have now created the model which will be used to analyze the IV plasma data. The system model for the oral suspension data will now be created assuming once the drug enters plasma it behaves the same as the drug introduced using the IV infusion.

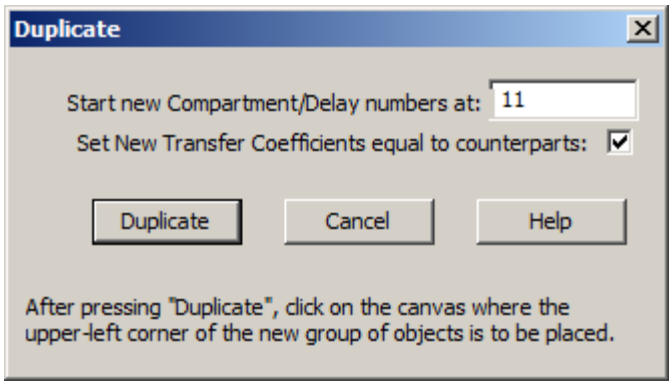
8. Create the following system model for the oral suspension data using the **Duplicate** command.



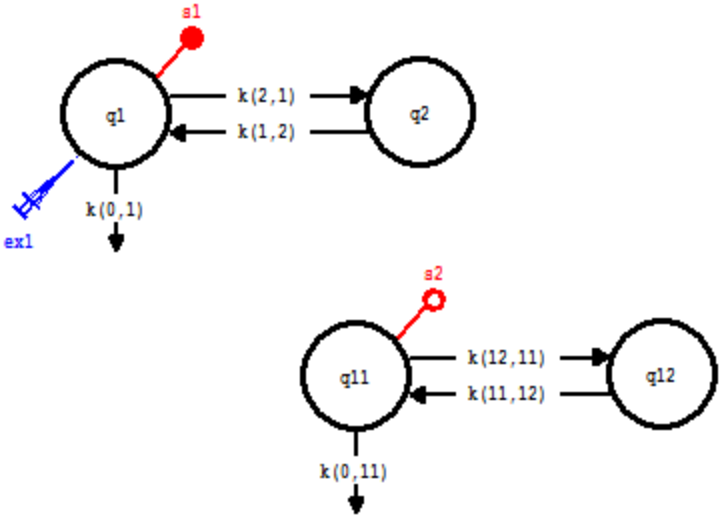
a. While pressing the **CTRL** key, click **q1**, **q2** and **s1**. Alternatively, use a crossing window, selecting all (you can delete the ex2 input later if necessary).

b. In the **Edit** menu, click **Duplicate**. The **Duplicate** dialog box will open.

c. Change the entry in the **Start new Compartment/Delay numbers at** box equal to "11". Select the **Set New Parameters Transfer Coefficients equal to counterparts** box. The **Duplicate** dialog box will appear as follows:



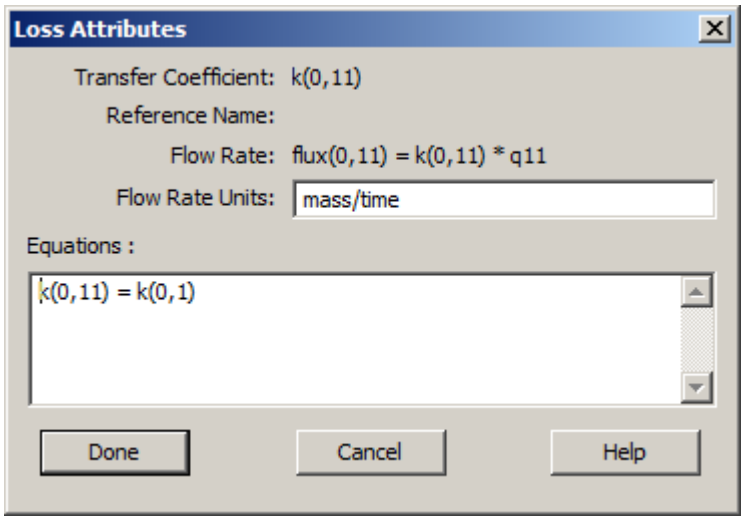
d. Click **Duplicate**. As instructed in the **Duplicate** dialog box, click on the Drawing Canvas approximately where you would like the duplicated model to appear. The following models will appear on the **Drawing Canvas** (after some rearrangement):



Duplicating. The **Duplicate** command allows you to duplicate a model, or a portion of a model. There are several features that are important.

- The duplicated sample **s2** will appear associated with Compartment **q11** (in this case). It is not, however, associated with data and hence the circle is open. In addition, the equation for the sample is "s2=q11", that is, the equation for sample **s1** does not carry over to **s2**.
- You have the option of setting the compartment number from where the duplicated model will start. For this reason, the order in which you click the compartments as you begin the duplication process can be important.
- You have the option of having the parameters of the duplicated model be different. In that case, the structure is preserved but the parameters, *k(0,11)*, *k(12,11)* and *k(11,12)* would appear in the **Parameters** dialog box. The other option, the one chosen here, is to set the new parameters' transfer coefficients equal to their counterparts.

To see how this works, double-click, for example, k(0,11). The **Loss Attributes** dialog box will appear as follows:



SAAM II has defined "k(0,11)=k(0,1" thus saving you the trouble of having to do this for every parameter in the duplicated model. (Of course, you can remove this equation if you wish in which case *k(0,11)* would appear as a parameter in the **Parameters** dialog box.)

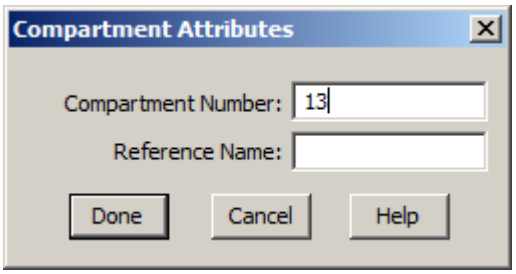
IMPORTANT If the option of setting the parameters equal to their counterparts is chosen, it is necessary to Solve the original model first in order for the model to be created internally in SAAM II.

e. Create the model for oral absorption.

(1) In the **SAAM II Toolbox**, click **Model**. The **Model** tools are now available.

(2) In the **SAAM II Toolbox**, click **Compartment**.

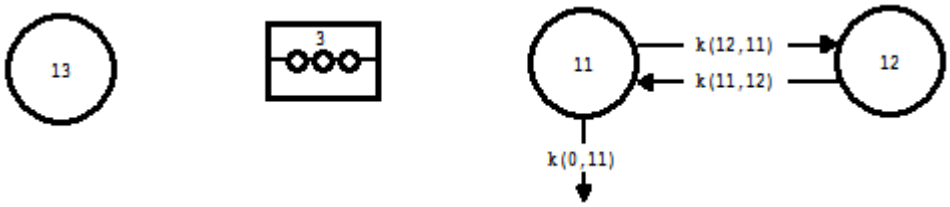
(3) Click on the **Drawing** canvas where you would like the new compartment to appear. Compartment **3** will appear. Double-click Compartment **3** to open the **Compartment Attributes** dialog box. Change the number of the compartment from "3" to "13". The **Compartment Attributes** dialog box will appear as follows:



Click **Done**.

(4) In the **SAAM II Toolbox**, click **Delay**.

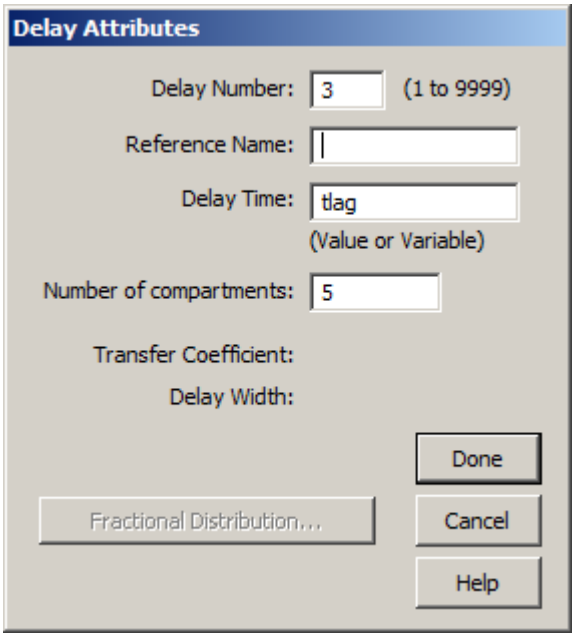
(5) Click on the **Drawing Canvas** where you would like the delay to be located. Place it between Compartments **13** and **11**. Your model for the oral dose should appear as follows:



(6) Double-click Delay **3**. The **Delay Attributes** dialog box will open.

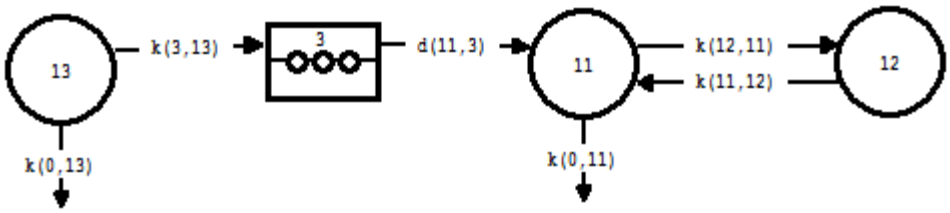
(7) Change the entry in the **Delay Time** box to "tlag". ***tlag*** will become an adjustable parameter equal to the delay time in absorption.

(8) Change the entry in the **Number of compartments** box to "5". The **Delay Attributes** dialog box should appear as follows:



(9) Click **Done**.

(10) Add the fluxes *k(0,13)*, *k(3,13)* and *d(11,3)*. The model will appear as follows:



Remember the output from the delay is denoted by "d" to signify the fraction of the material in the delay moving along this transfer pathway. In this case, *d(11,3)* is equal to 1.

9. Create an input into Compartment **q13**.

   a. In the **SAAM II Toolbox**, click **Experiment** to make these tools available.

   b. Click **Input**.

   c. Click Compartment **q13** and then the **Drawing Canvas**. The input **ex2** will appear associated with Compartment **q13**.

   d. Double-click **ex2** to open the **Exogenous Input** dialog box. Be sure "Bolus" is selected as the **Input Type**.

   e. In the **Initial Amount** box, type "2.5e+05".

   f. Click **Add**.

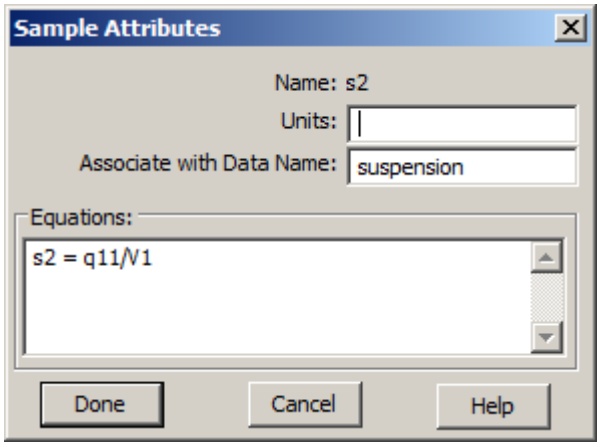
   g. Click **Done**.

10. Associate **s2** with the oral data, and change the sample equation.

   a. Double-click **s2** to open the **Sample Attributes** dialog box.

   b. Type "suspension" in the **Associate with Data Name** box.

   c. Edit the sample equation to read "s2=q11/V1" The **Sample Attributes** dialog box will appear as follows:



d. Click **Done**. Notice it is assumed that the volume of Compartments **q1** and **q11** are the same.

11. Specify the new parameter values.

There are three new parameters to specify, *tlag*, *k(0,13)* and *k(3,13)*. Compartment **q13** is the compartment into which the suspension is introduced, and hence is really a part of the delay which is the GT tract. Thus Compartment **q13** should turn over at approximately the same rate as the compartments in the delay. These turn over at the rate "tlag/5", i.e. the delay time divided by the number of compartments in the delay.

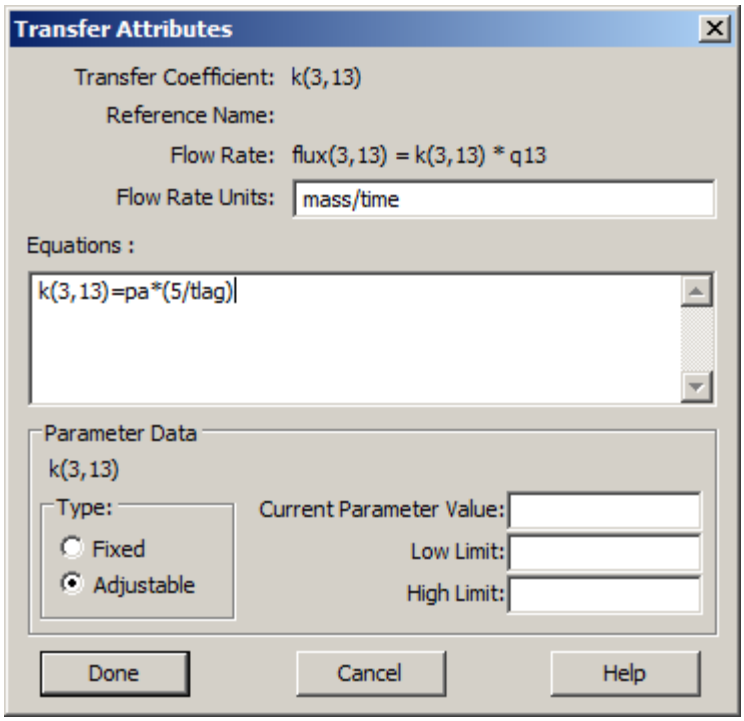
However not all of the suspension may be absorbed. Define a new parameter "pa" equal to the fraction absorbed. Then you can write:

k(3,13) = pa*(5/tlag)
k(0,13)=(1-pa)*(5/tlag)

This will allow you to estimate the fraction "pa", or percent "pa*100", of the drug in suspension absorbed.

a. Double-click *k(3,13)* to open the **Transfer Attributes** dialog box.

b. In the **Equation** pane, type the equation "k(3,13) = pa*(5/tlag)". The **Transfer Attributes** dialog box will appear as follows:



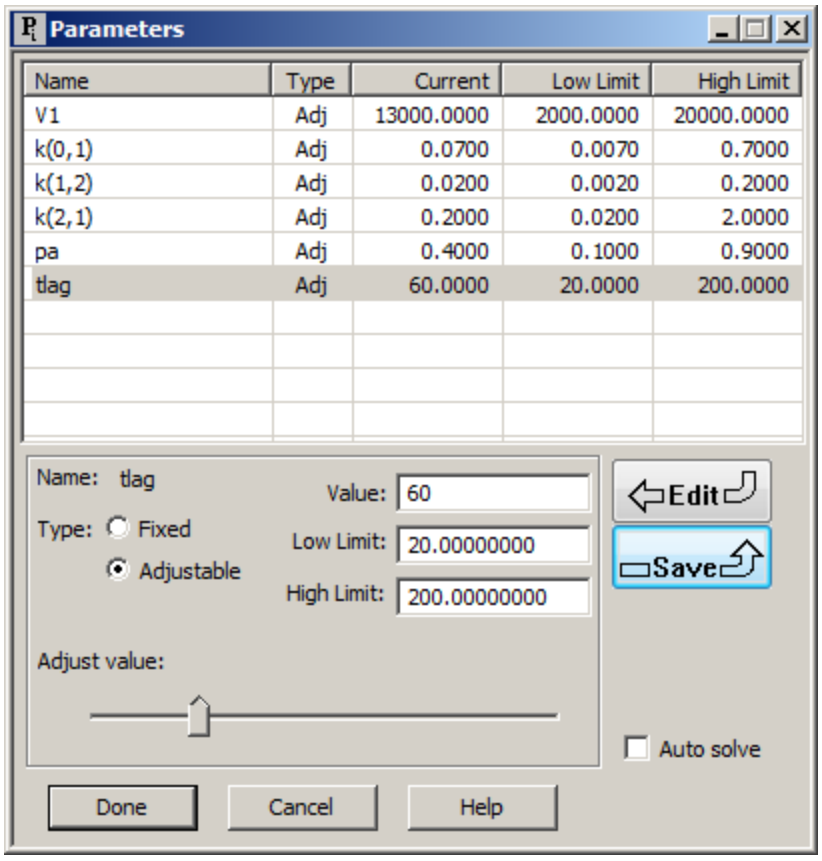
c. Click **Done**.

d. Double-click *k(0,13)* to open the **Loss Attributes** dialog box.

e. In the **Equation** pane, type the equation "k(0,13) = (1-pa)*(5/tlag)".

f. Click **Done**.

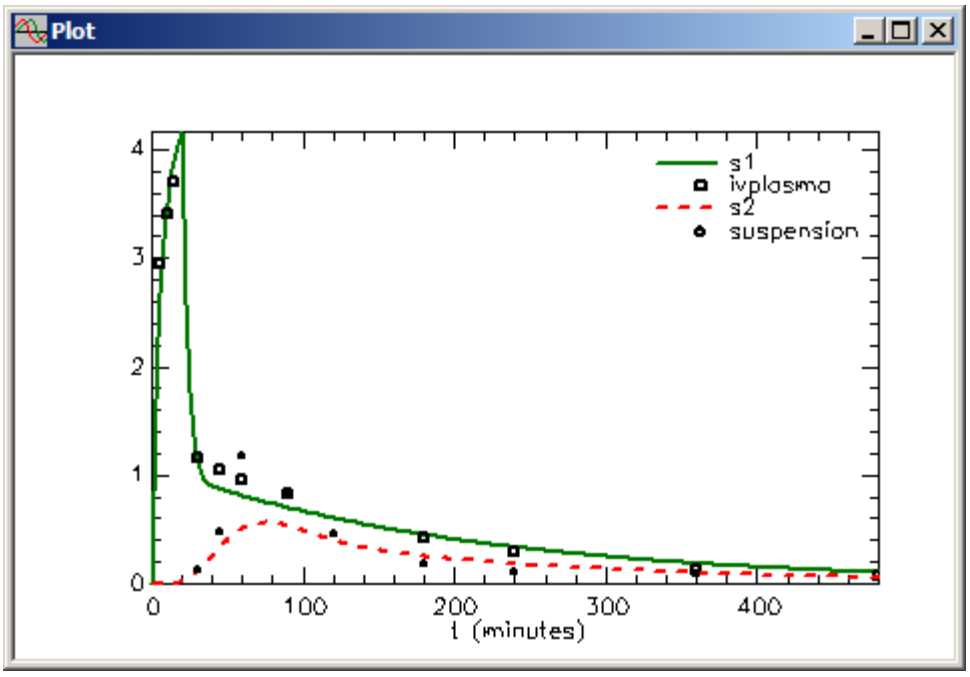
g. Open the **Parameters** dialog box, and enter values as shown below for *pa* and *tlag*.



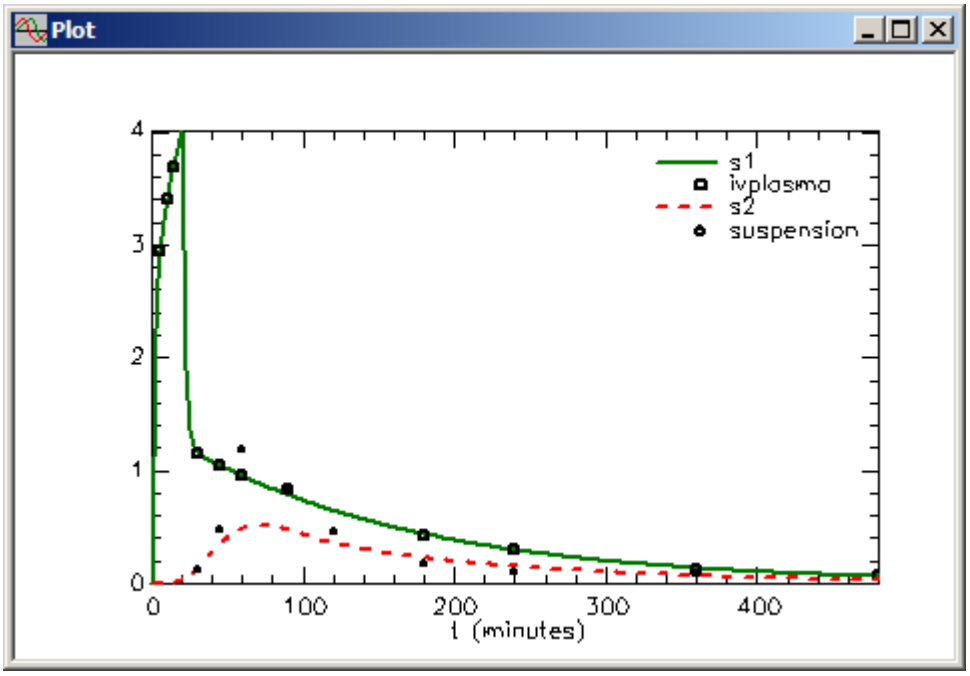
Notice the default **Low** and **High Limits** have not been used for *pa* or *tlag*. The reason for *pa* is that it is a fraction, and cannot exceed "1". The reason for *tlag* is that the lag time cannot be longer than the experiment itself.

h. Click **Done**.

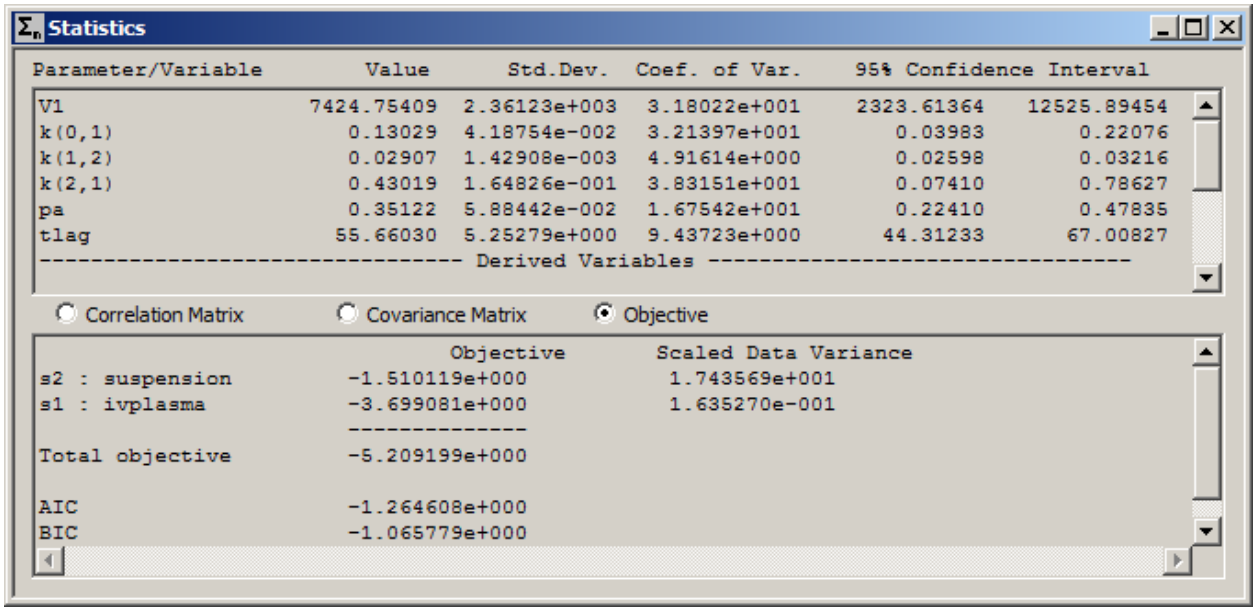
12. Solve the model and view the solution. The plot of **s1:ivplasma** and **s2:suspension** should appear as follows (in linear mode):



13. Fit the model to the data. The plot will be updated as follows:



The statistics will appear as follows:



Viewing all of the Parameter/Variable window:

V1	7424.75409	2.36123e+003	3.18022e+001	2323.61364	12525.89454
k(0,1)	0.13029	4.18754e-002	3.21397e+001	0.03983	0.22076
k(1,2)	0.02907	1.42908e-003	4.91614e+000	0.02598	0.03216
k(2,1)	0.43019	1.64826e-001	3.83151e+001	0.07410	0.78627
pa	0.35122	5.88442e-002	1.67542e+001	0.22410	0.47835
tlag	55.66030	5.25279e+000	9.43723e+000	44.31233	67.00827
Derived Variables					
k(0,11)	0.13029	4.18754e-002	3.21397e+001	0.03983	0.22076
k(0,13)	0.05828	8.81376e-003	1.51231e+001	0.03924	0.07732
k(3,13)	0.03155	5.12409e-003	1.62409e+001	0.02048	0.04262
k(11,3)	0.08983	8.47752e-003	9.43723e+000	0.07152	0.10815
k(11,12)	0.02907	1.42908e-003	4.91614e+000	0.02598	0.03216
k(12,11)	0.43019	1.64826e-001	3.83151e+001	0.07410	0.78627

Close the **Statistics** and **Plot** windows.

Quit the **SAAM II Compartmental** application. You may save this study file if you wish. The study file **io_duplicate.stu** is this study before the Fit.

Multiple input-output study. In studies such as this one where, on different occasions, a drug is administered iv and later orally (or in this case, as a suspension), there are two essential assumptions made when analyzing the data simultaneously:

Assumption 1: The subject is in the same "condition" during the two separate studies. That is, the determinants of how the drug is metabolized are the same on both days of the study.

Assumption 2: The metabolism of the drug that is absorbed into the systemic circulation is identical to that when the drug is introduced directly by IV.

For each such study, these assumptions must be considered if the "system model" is to be assumed identical for both studies.

Part 2. Creating a Multiple Input-Output Experiment Using Create Experiment

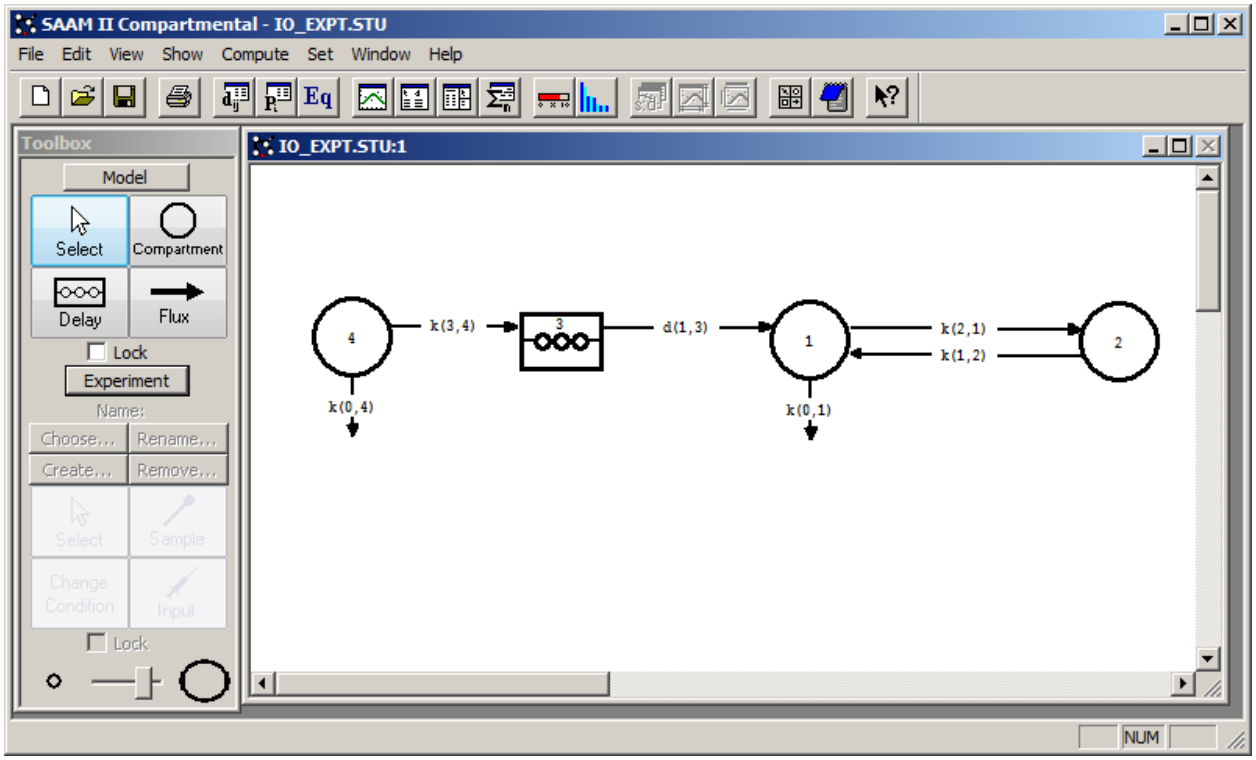
In this tutorial, you will simultaneously analyze data following an iv administration and oral suspension administration of a drug by creating two separate experiments. In the iv experiment, the drug was infused for 20 minutes while in the suspension, it was given as a bolus.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

2. Open the **SAAM II Compartmental** study file **io_expt.stu**.

   a. The file **io_expt.stu** should appear in the file list; if it does not, find the folder where you put this file.

   b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as shown below:



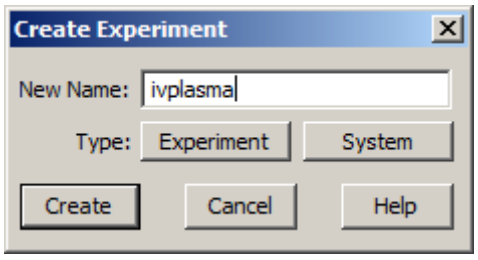
This is the system model which has been proposed to describe the drug data following an *IV* administration into plasma, Compartment **1**, and into the GI tract, Compartment **4**. Compartments **1** and **2** are proposed as the system model, i.e. to describe the drug kinetics in the body. Compartment **4** is proposed to be the upper end of the GI tract, the compartment into which the drug suspension is administered. The Delay **3** represents transit through the GI tract. The characteristics of the delay have been set in that the delay time is a parameter *tlag*, and the number of the compartments in the delay has been set equal to 5. You can confirm this by double-

clicking on Delay **3**, and examining the **Delay Attributes** dialog box. Also the time of the experiment has been set to 480 minutes. Thus when you click on **Experiment** in the **SAAM II Toolbox**, the **Experiment Attributes** dialog box will not open as is normally the case; the **Create Experiment** dialog box will open.

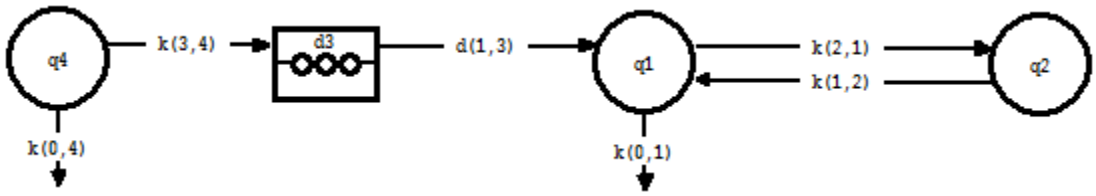
3. Create the iv experiment.

   a. In the **SAAM II Toolbox**, click **Experiment**. The **Create Experiment** dialog box will open.

   b. Change the name of the experiment from "Exper" to "ivplasma". The **Create Experiment** dialog box will appear as follows:



   c. Click **Create**. The model will appear as follows:



4. Create the experimental input and sample for the IV experiment.

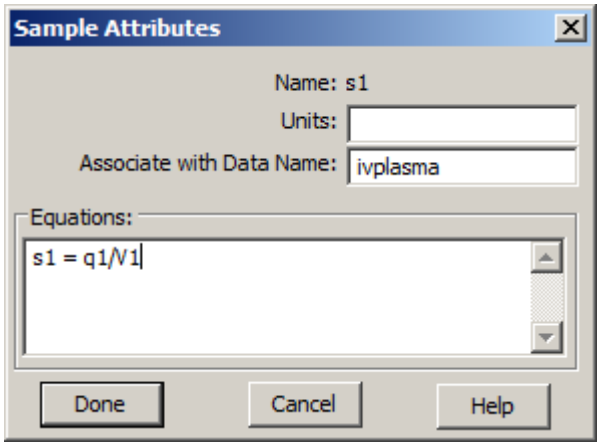
   a. In the **SAAM II Toolbox**, click **Sample**.

   b. Click Compartment **q1** and then the **Drawing Canvas**. The sample **s1** will appear associated with Compartment **q1**.

   c. Double-click **s1** to open the **Sample Attributes** dialog box.

   d. Type "ivplasma" in the **Associate with Data Name** box.

   e. Edit the sample equation to read "s1=q1/V1". The **Sample Attributes** dialog box will appear as follows:



f. Click **Done**.

g. In the **SAAM II Toolbox**, click **Input**.

h. Click Compartment **q1** and then the **Drawing Canvas**. The input **ex1** will appear associated with Compartment **q1**.

i. Specify the 20 minute infusion.

(1) Double-click **ex1** to open the **Exogenous Input** dialog box.

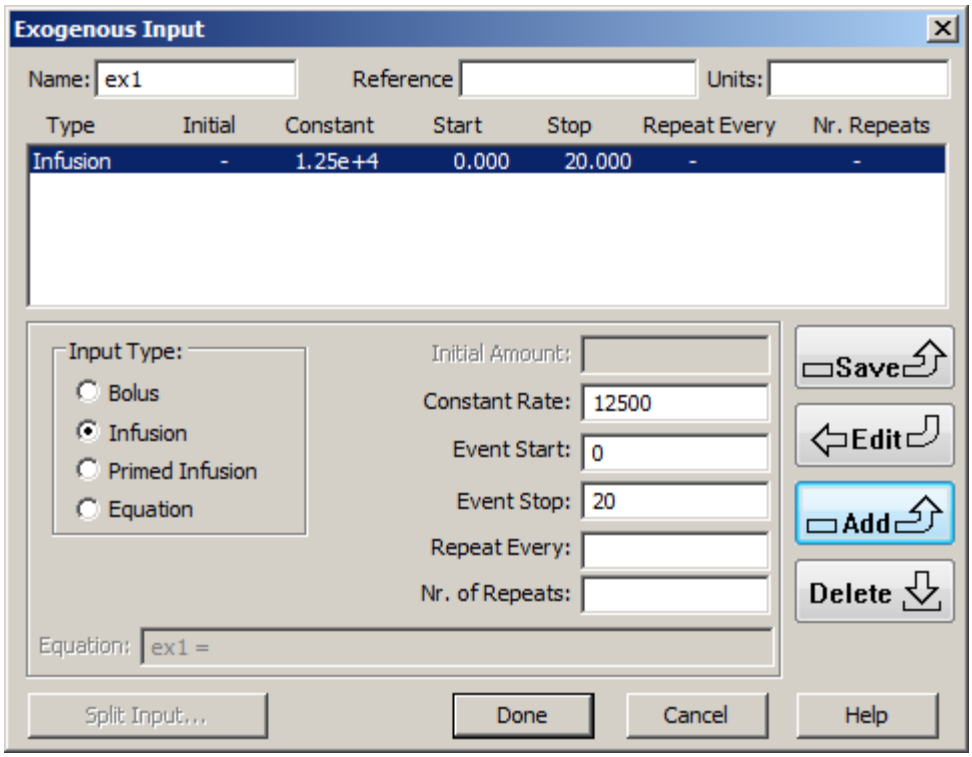
(2) Select **Infusion** in the **Input Type** pane.

(3) Type "12500" in the **Constant Rate** box.

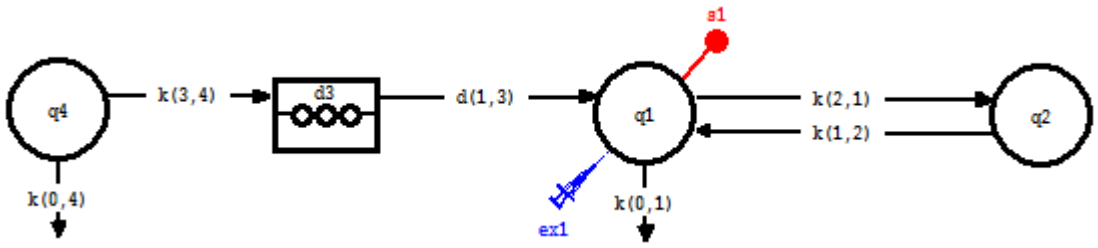
(4) Type "0" in the **Event Start** box.

(5) Type "20" in the **Event Stop** box.

(6) Click **Add**. The **Exogenous Input** dialog box should appear as follows:



(7) Click **Done**. The model will appear as follows:

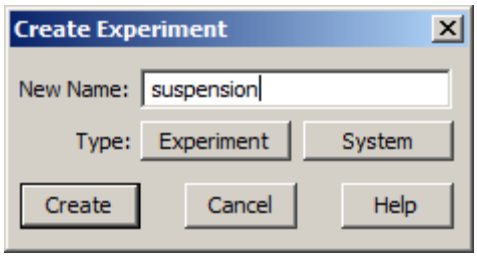


This is the model to describe the IV plasma data following the 20 minute constant infusion of drug. Notice that neither Compartment **q4** nor Delay **d3** will play any role whatsoever in describing the IV plasma data.

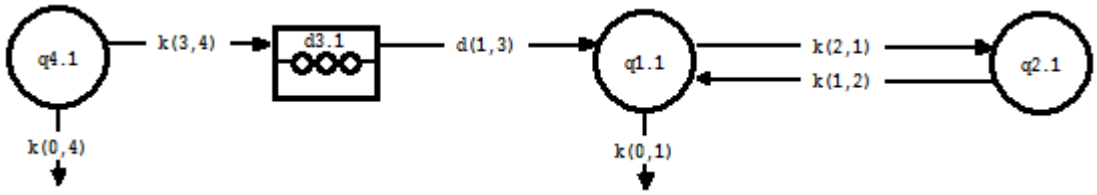
5. Create the experiment for introducing the drug in suspension.

   a. In the **SAAM II Toolbox**, click **Create**. The **Create Experiment** dialog box will open.

   b. Change the name of the experiment from "Exper" to "suspension". The **Create Experiment** dialog box will appear as follows:



c. Click **Create**. The model will appear as follows:



Notice the compartment numbers have changed from, for example, **q4** to **q4.1**. The ".1" means this is an experiment separate from the case where these is no such label. This is how SAAM II does its book keeping for multiple experiments.

6. Create the experimental input and sample for the suspension experiment.

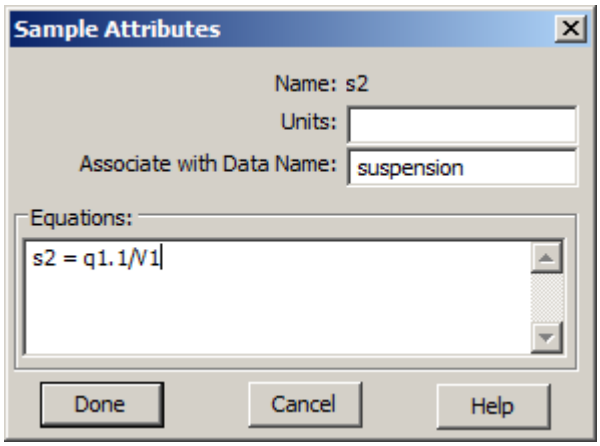
   a. In the **SAAM II Toolbox**, click **Sample**.

   b. Click Compartment **q1.1** and then the **Drawing Canvas**. The sample **s2** will appear associated with Compartment **q1.1**.

   c. Double-click **s2** to open the **Sample Attributes** dialog box.

   d. Type "suspension" in the **Associate with Data Name** box.

   e. Edit the sample equation to read "s2=q1.1/V1. The **Sample Attributes** dialog box will appear as follows



f. Click **Done**.

g. In the **SAAM II Toolbox**, click **Input**.

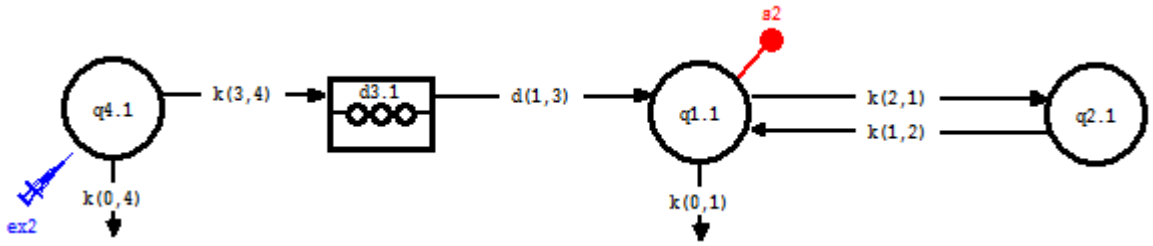
h. Click Compartment **q4.1** and then the **Drawing Canvas**. The input **ex2** will appear associated with Compartment **q4.1**.

i. Double-click **ex2** to open the **Exogenous Input** dialog box. Be sure "Bolus" is selected as the **Input Type**.

j. In the **Initial Amount** box, type "2.5e+05".

j. Click **Add**.

l. Click **Done**. The model will appear as follows:



This is the model to describe the suspension data following the bolus introduction of the drug as a suspension in the upper GI. Now both Compartment **q4** and Delay **d3** will play any role in describing the suspension data. The data can be analyzed together because the "iv" experiment will analyze these data while the above will analyze the suspension data. The parameters in common are *k(2,1)*, *k(1,2)*, *k(0,1)* and *V1*.

7. Enter the parameter values.

Besides the system model parameters *k(2,1)*, *k(1,2)*, *k(0,1)* and *V1*, there are the parameters describing absorption. These are *tlag*, the time of the delay, and *k(3,4)* and **k(0,4)**.

Compartment **4** is the compartment into which the suspension is introduced, and hence is really a part of the delay which is the GT tract. Thus Compartment **4** should turn over at approximately the same rate as the compartments in the delay. These turn over at the rate "tlag/5", i.e. the delay time divided by the number of compartments in the delay.

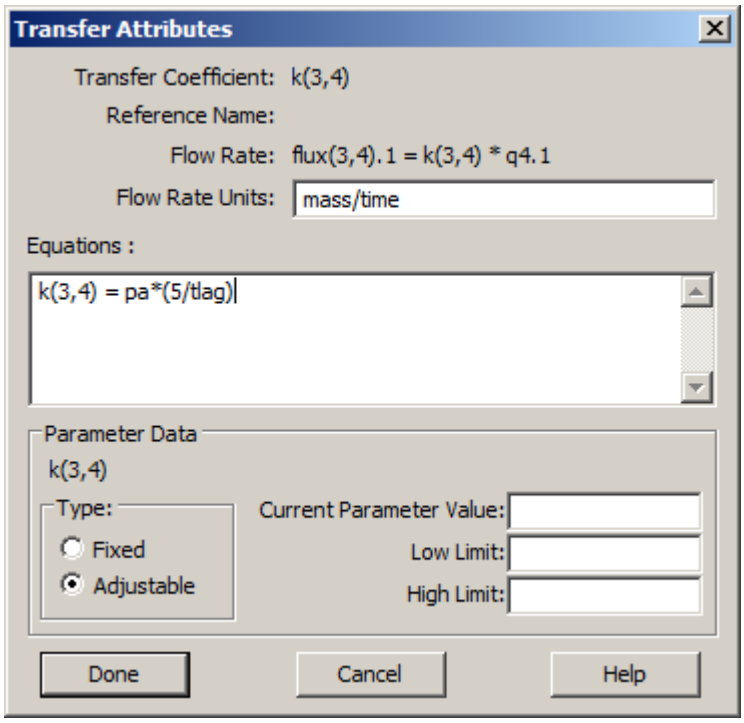
However not all of the suspension may be absorbed. Define a new parameter "pa" equal to the fraction absorbed. Then you can write the following equations in the respective Transfer Attributes dialog boxes:

k(3,4) = pa*(5/tlag)
k(0,4)=(1-pa)*(5/tlag)

This will allow you to estimate the fraction, or percent, of the drug in suspension absorbed.

a. Double-click *k(3,4)* to open the **Transfer Attributes** dialog box.

b. In the **Equation** pane, type the equation "k(3,4) = pa*(5/tlag)". The **Transfer Attributes** dialog box will appear as follows:



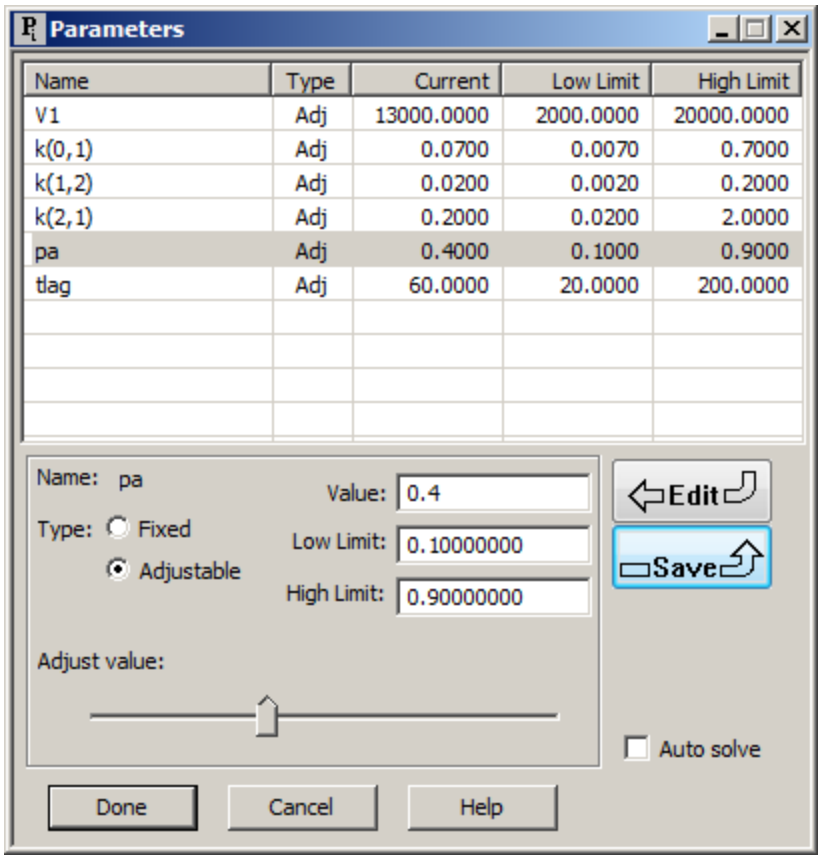
c. Click **Done**.

d. Double-click *k(0,4)* to open the **Loss Attributes** dialog box.

e. In the **Equation** pane, type the equation "k(0,4) = (1-pa)*(5/tlag)".

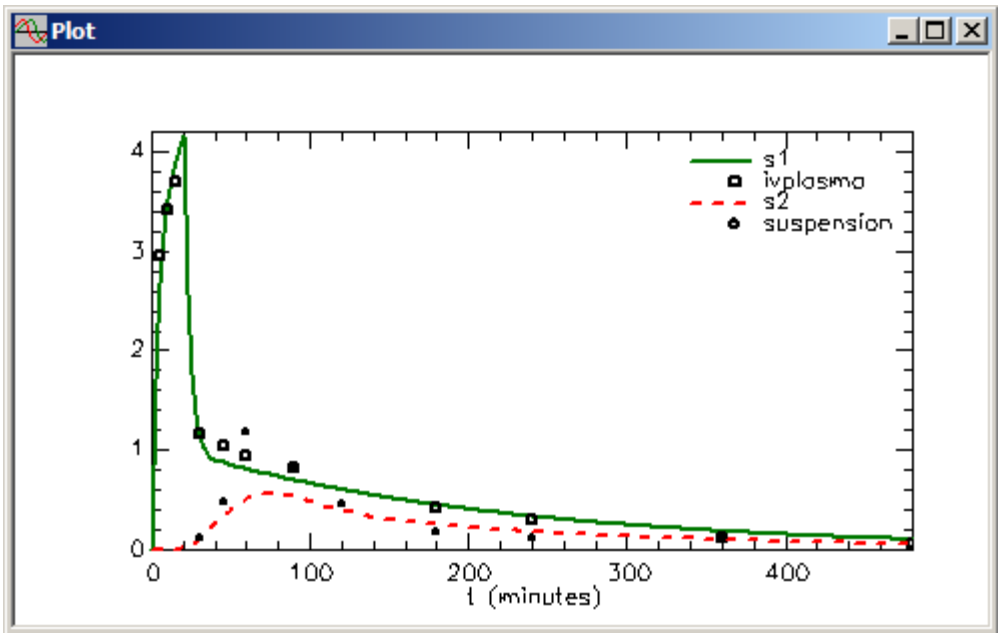
f. Click **Done**.

g. Open the **Parameters** dialog box. The value for *tlag* is already in the study file. Enter the remaining parameters as shown in the **Parameters** dialog box below:

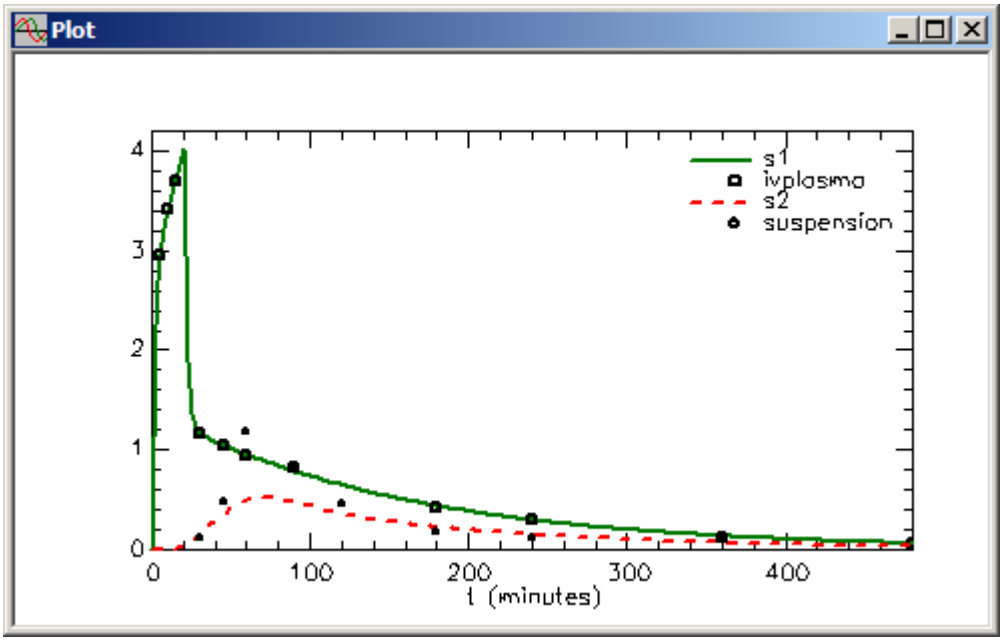


h. Click **Done**. Notice the default **Low** and **High Limits** have not been used for *V1*, *pa* or *tlag*. The reason for V1 is that it is known with more accuracy than the default **Low** and **High Limits** would indicate. The reason for *pa* is that it is a fraction, and cannot exceed "1". The reason for *tlag* is that the lag time cannot be longer than the experiment itself.

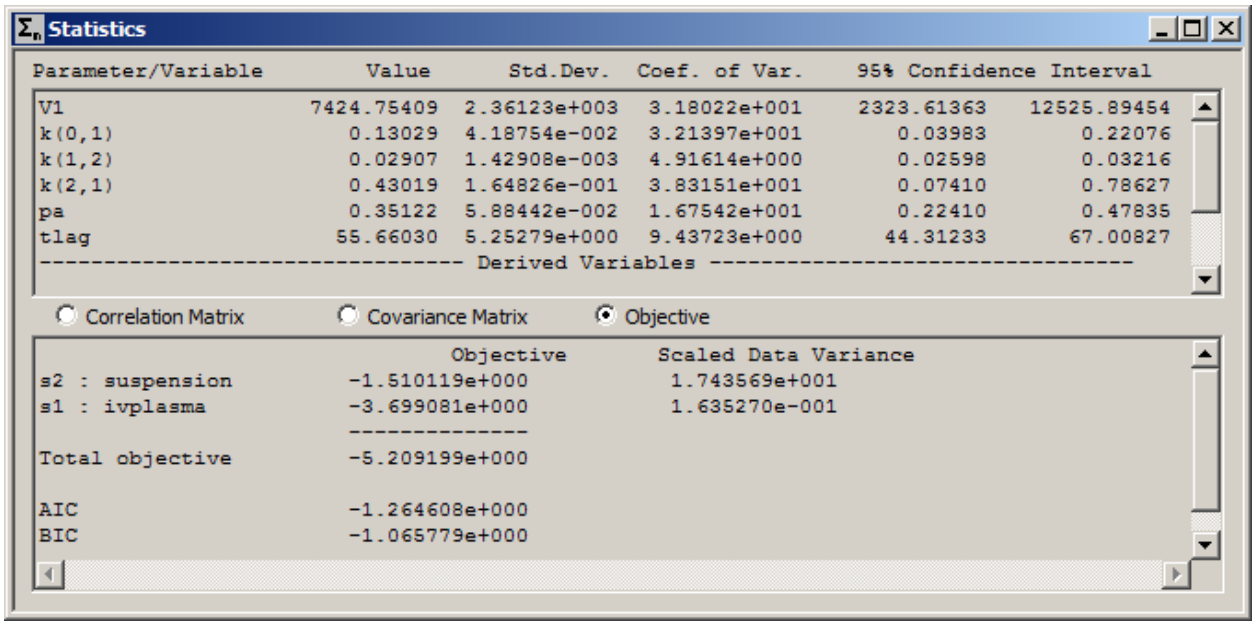
8. Solve the model and view the solution. The plot of **s1:ivplasma** and **s2:suspension** will appear as follows:



9. Fit the model to the data. The plot will be updated as follows:



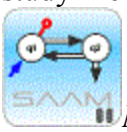
The statistics will appear as follows:



V1	7424.75409	2.36123e+003	3.18022e+001	2323.61363	12525.89454
k(0,1)	0.13029	4.18754e-002	3.21397e+001	0.03983	0.22076
k(1,2)	0.02907	1.42908e-003	4.91614e+000	0.02598	0.03216
k(2,1)	0.43019	1.64826e-001	3.83151e+001	0.07410	0.78627
pa	0.35122	5.88442e-002	1.67542e+001	0.22410	0.47835
tlag	55.66030	5.25279e+000	9.43723e+000	44.31233	67.00827
Derived Variables					
k(0,4)	0.05828	8.81376e-003	1.51231e+001	0.03924	0.07732
k(1,3)	0.08983	8.47752e-003	9.43723e+000	0.07152	0.10815
k(3,4)	0.03155	5.12409e-003	1.62409e+001	0.02048	0.04262

Close the **Plot** and **Statistics** windows.

Quit the **SAAM II Compartmental** application. Do not save the changes to **io_expt.stu**. The study file with the parameter values before the fit has been saved as **io_exp_final.stu**.



Multiple input-output study. In studies such as this one where, on different occasions, a drug is administered iv and later orally (or in this case, as a suspension), there are two essential assumptions made when analyzing the data simultaneously:

Assumption 1: The subject is in the same "condition" during the two separate studies. That is, the determinants of how the drug is metabolized are the same on both days of the study.

Assumption 2: The metabolism of the drug that is absorbed into the systemic circulation is identical to that when the drug is introduced directly by iv.

For each such study, these assumptions must be considered if the "system model" is to be assumed identical for both studies.

SAAM II Version 2.1
Advanced Tutorials

Working with Forcing Functions

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Using Forcing Functions

Prerequisites

The prerequisite for this tutorial is having worked through the SAAM II introductory tutorial, "Getting Started with **SAAM II Compartmental**."

What you will learn in this tutorial

- How to use forcing functions defined by linear interpolation of data (Part 1).
- How to use forcing functions defined by an equation (Part 2).

Files Required

Data:

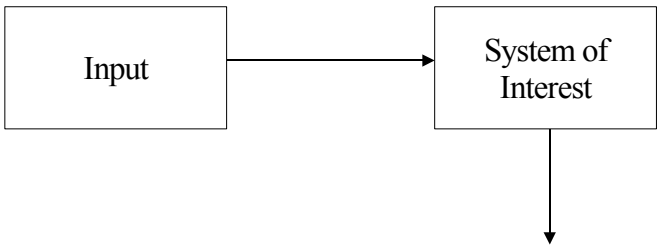
The data file for this tutorial is

ff_pre_pro.dat

Introduction

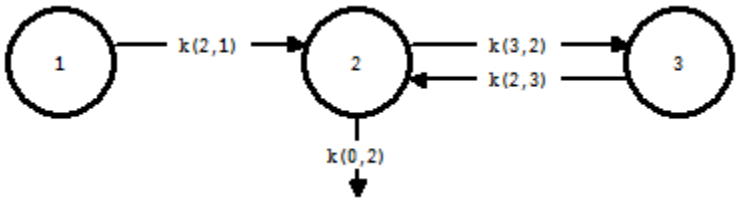
This tutorial will show you how to use forcing functions as a modeling tool in SAAM II.. They can be used for any precursor-product type system such as amino acid incorporation into a protein, drug absorption, or uptake from plasma by cells when data are available from imaging such as PET or MRI. Forcing functions can also be used as a model development and testing tool. That process is beyond the scope of this tutorial.

What are forcing functions, and how does SAAM II create and use them? Overall, the situation can be described as shown in the following diagram:



The input refers normally to a substance whose input is either extravascular in the case of drug uptake and metabolism, or a plasma born substances such as a metabolite whose uptake is in a tissue one is studying. The "System of Interest" refers to the details of the system one wants to model. It can thus describe absorption of the drug. It also can deal with a protein (amino acid incorporation into a protein), another metabolite (parent-metabolite system), or measurements taken by an external device such as PET or MRI (in which case the substance of interest is transported in blood and taken up where it can be metabolized in the tissue of interest one is studying).

To understand how forcing functions work, consider the model to be used in this tutorial:



For this particular model, in the absence of the forcing function, SAAM II would create the following system of three differential equations:

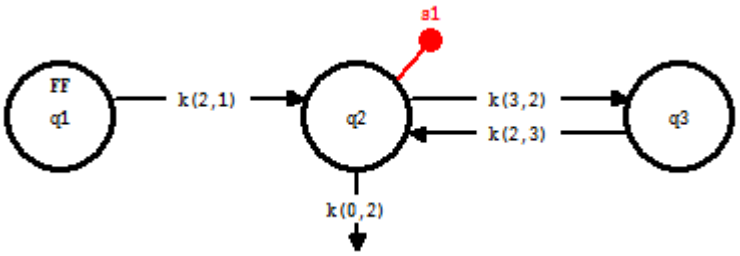
$$\frac{dq1}{dt} = -k(2,1)q1$$

$$\frac{dq2}{dt} = -(k(3,2) + k(0,2))q2 + k(2,1)q1 + k(2,3)q3$$

$$\frac{dq3}{dt} = -k(2,3)q3 + k(3,2)q2$$

In the case of the forcing function, Compartment **1** will be specified to represent the material that is "driving" the system. One has a choice either to develop a model for that system, or if one is not particularly interested in that system per se, to use a forcing function to describe Compartment **1**. The need to develop a model for the metabolism of material represented by Compartment **1** is eliminated.

Since this compartment will be used to drive the system, one needs a means by which to describe it. This is done by making Compartment **1** a forcing function, i.e. to force a known shape on the time course of **q1(t)**. This procedure will be explained in this tutorial. The model you will develop is shown below:



The difference in this figure is the presence of "FF" in Compartment **1** to indicate the compartment is now a "placeholder" for a forcing function. The equations SAAM II creates in this situation are

$$\frac{dq1}{dt} = -k(2,1)q1$$
$$\frac{dq2}{dt} = -(k(3,2)+k(0,2))q2 + k(2,1)q1.FF + k(2,3)q3$$
$$\frac{dq3}{dt} = -k(2,3)q3 + k(3,2)q2$$

The essential point to note and the key to the forcing function is that everywhere in the system of differential equations where **q1** appeared in the absence of the forcing function, when there is a forcing function, **q1** is replaced by **q1.FF** everywhere in the system except in the differential equation $\frac{dq1}{dt}$. Thus SAAM II does calculate a solution **q1**, but this has no effect on the other differential equations in the system.

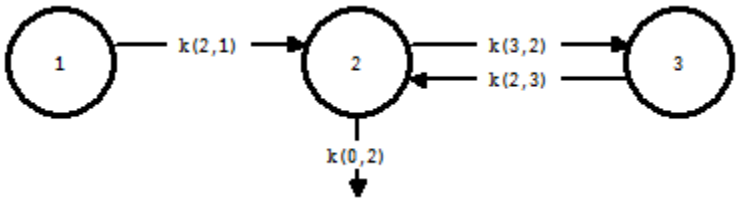
How are forcing functions defined? That is, how is **q1.FF** specified? There are two ways. One way is to write **q1.FF** as an equation such as a sum of exponentials. The other way is to connect sequential data points by a straight line. Both will be illustrated in this tutorial.

Part 1. Creating Forcing Functions by Data Interpolation.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

2. In the **SAAM II Toolbox**, click **Model** to be sure these tools are available.

3. Create the following model on the **Drawing** canvas:

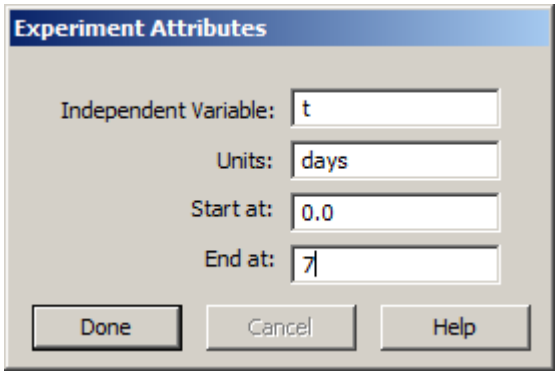


4. Create the experiment on the model

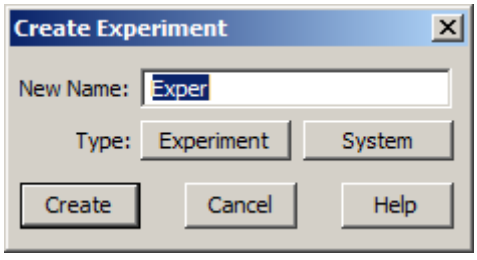
   a. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open.

   b. Type "days" in the **Units** box.

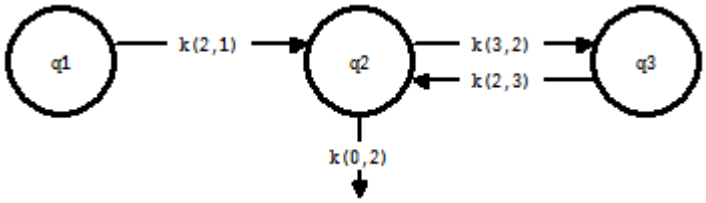
   c. Type "7" in the **End At** box. The Experiment Attributes dialog box will appear as follows:



   d. Click **Done**. The **Create Experiment** dialog box will open. Be sure **Exper** is selected. The **Create Experiment** dialog box will appear as follows:



e. Click **Create**. The model will appear on your drawing canvas as follows:



5. Add the data to the model.

a. In the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar,** click **Data**  . The **Data** window will open.

b. On the **File** menu, click **Open**. The file **ff_pre_pro.dat** should appear in the list (if it does not, find the folder where you have put this tutorial and data file).

c. Double-click **ff_pre_pro**. The data in this file will appear in the **Data** window as shown below.

Data - ff_pre_pro.dat

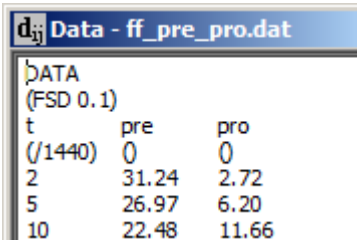
```
DATA
(FSD 0.1)
t          pre        pro
(/1440)    0          0
2          31.24      2.72
5          26.97      6.20
10         22.48      11.66
20         15.47      19.34
30         10.48      24.26
45         6.28       29.77
(/24)      0          0
1          4.14       31.94
1.5        2.23       34.84
2          1.69       36.20
3          1.46       38.47
4          1.43       40.85
5          1.40       43.03
6          1.36       44.93
9          1.28       49.36
12         1.23       52.68
18         1.15       60.25
0          0          0
1          1.08       64.50
1.5        1.01       75.43
2          0.97       83.39
3          0.90       97.27
4          0.91       109.00
5          0.87       120.00
6          0.85       131.00
7          0.86       137.00
END
```

Data Format is okay

There are some important features of this data file that we will describe below.

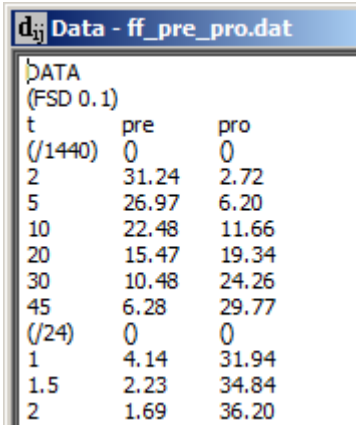
*Unit conversion in the **Data** window*. This data file illustrates several features of the SAAM II **Data** window. First, it illustrates that several columns of data can be used with a single independent variable, usually time "t". The column "pre" is the data driving the system; the column "pro" is the system whose characteristics will be modeled.

This data file also illustrates how to do unit conversion in the SAAM II **Data** window. The first few rows of the data file are shown below:



The three column names are "t" for time, "pre" for "precursor" and "pro" for "product". Under these are a line containing (/1440), (), and (). In the "t" column, the first data samples were recorded in minutes and not days, the units of the model. Thus, "(/1440)" divides all elements in the column by 1440 to convert minutes into days. This divisor is in effect until the next set of parentheses is encountered further down the column. There are no unit conversions for either "pre" or "pro"; the "()" must be included to indicate no conversion.

In the time column, the next unit conversion is shown below:



You can see after 45 minutes, the "t" changes to 1, 1.5, etc. These are hours, so the next few samples are in units of hours, not minutes or days. The division by 24 converts hours to days.

Finally, after 18 hours, you see in the time column () while () remains in both data columns. After 18 hours, the data are collected in days, and unit conversion is no longer necessary. The () tells SAAM II this is the point at which (/24) is no longer needed.

This is a very powerful way to use the SAAM II **Data** window to be sure all of your units are consistent.

d. Close the **Data** window.

6. Create a sample.

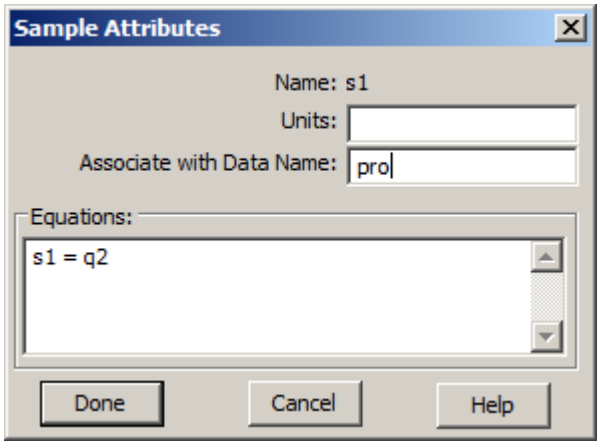
   a. In the **SAAM II Toolbox**, click **Sample**.

   b. Click compartment **q2**, and then click on the **Drawing Canvas**. The sample **s1** will appear.

   c. Double-click **s1** to open the **Sample Attributes** dialog box.

   d. Type "pro" in the **Associate with Data Name** box.

   e. There is no need to edit the sample equation. The **Sample Attributes** dialog box will appear as follows:

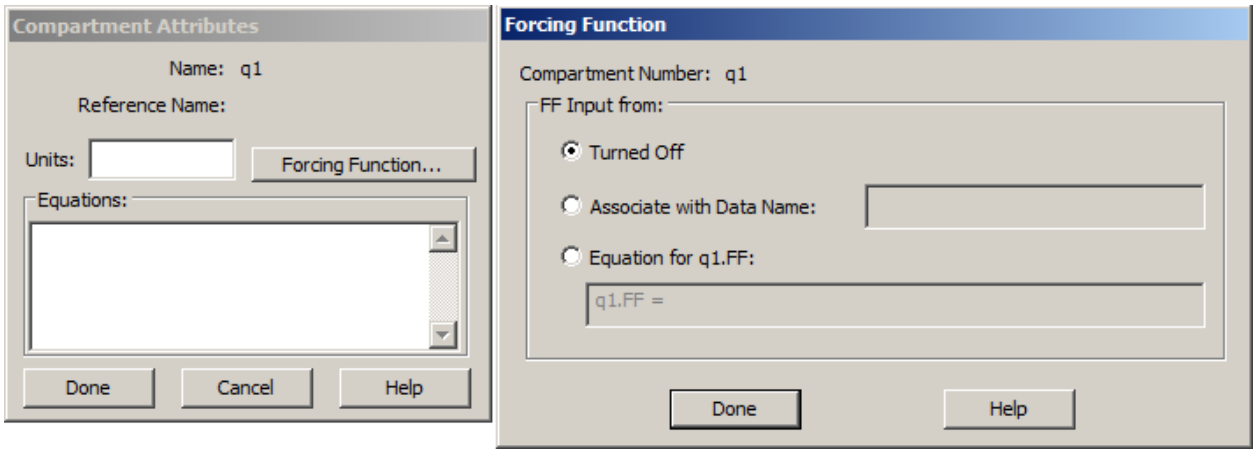


   f. Click **Done**. Noticed **s1** is now solid because it is associated with data.

7. Create a forcing function.

   a. Double-click Compartment **q1**, to open the **Compartment Attributes** dialog box.

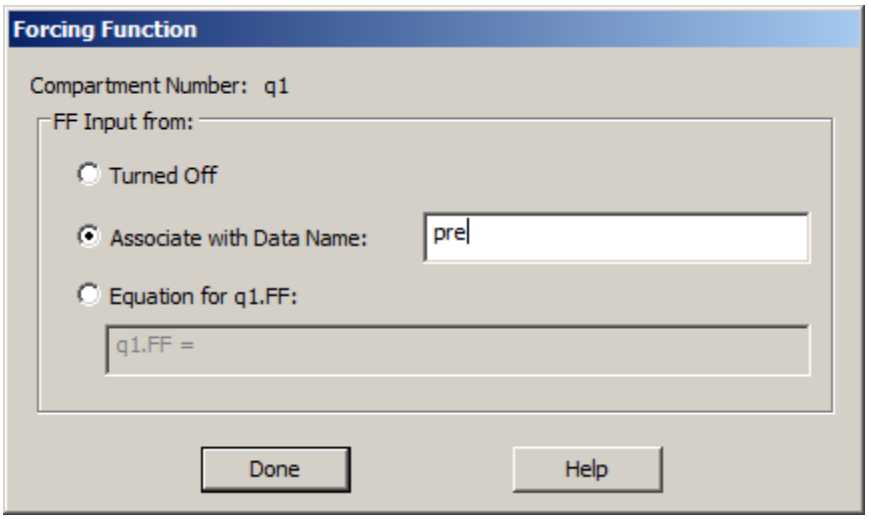
   b. Click **Forcing Function**. The **Forcing Function** dialog box will open as shown below (together with the **Compartments Attributes** dialog box):



There are three options in the **FF Input from** pane. The default option is **Turned Off** since no forcing function has been defined. The other two options are **Associate with Data Name** and **Equation for q1.FF**. If you select the **Associate with Data Name** option, the forcing function will be created by linear interpolation of sequential pairs of data. If you select the **Equation for q1.FF** option, you must specify an equation in the box provided.

c. Click **Associate with Data Name** in the **FF Input from** pane.

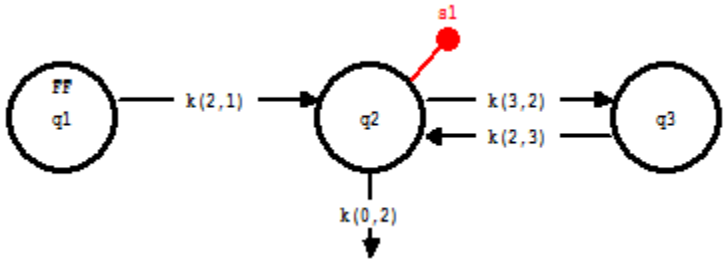
d. Type "pre" in the **Associate with Data Name** box. Your **Forcing Function** dialog box will appear as follows:



Creating Forcing Functions. When you choose the **Associate with Data Name** option, SAAM II will create a forcing function by linearly interpolating between sequential data.

e. Click **Done** in the **Forcing Function** dialog box.

f. Click **Done** in the **Compartment Attributes** dialog box. Your model will appear as follows:



Notice that "FF" appears in Compartment **q1**. This is to remind you that this compartment is now defining a forcing function.

8. Create a second sample to view the forcing function.

You may visualize the forcing function that is driving the system. To do this, you can create a sample, and write the sample equation equal to the forcing function as described below.

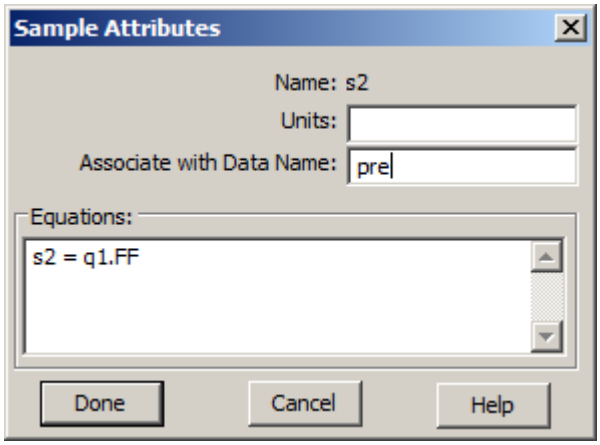
a. In the **SAAM II Toolbox**, click **Sample**.

b. Click Compartment **q1**, and then on the **Drawing Canvas**. The sample **s2** will appear.

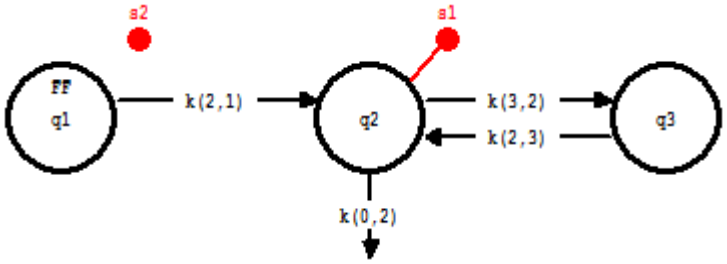
c. Double-click **s2** to open the **Sample Attributes** dialog box.

d. Type the sample equation "s2=q1.FF"

e. Type "pre" in the **Associate with Data Name** box. The **Sample Attributes** dialog box will appear as follows:



f. Click **Done**. You will notice that **s2** is solid, but no longer connected to Compartment **q1**. This is because the sample equation is no longer associated with a specific compartment in your model. This is a difference between **q1**, the differential equation in the model, and **q1.FF**, the forcing function. The model is shown below.

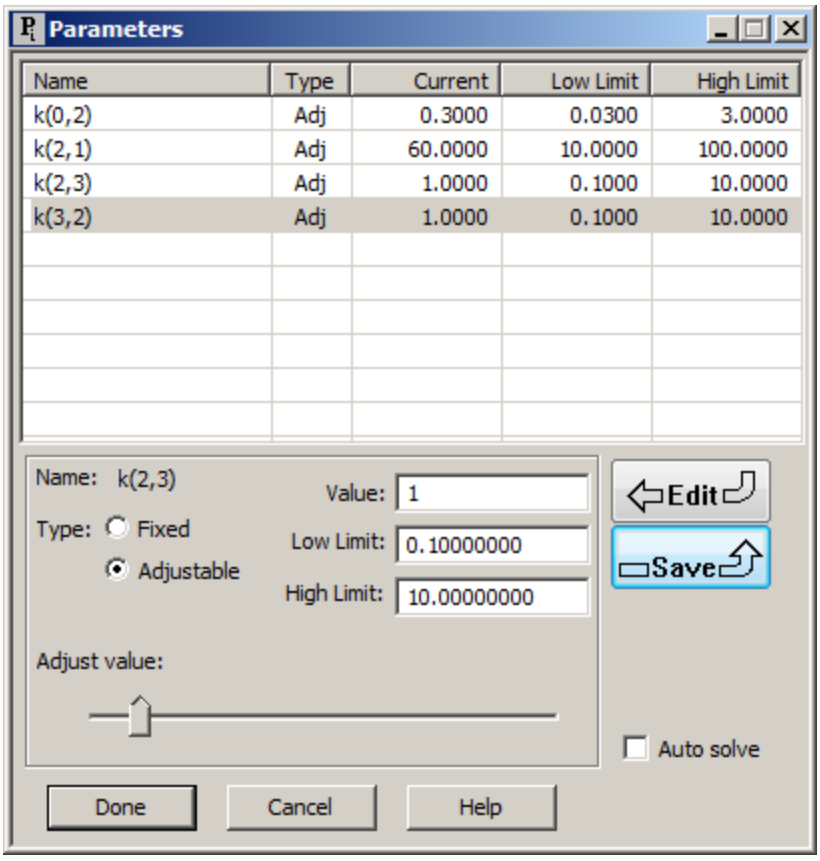


Samples. The Sample tool is a very powerful tool in SAAM II. Normally it is used to create samples that link a compartment, or compartments, with data. In this case, we are interested in viewing the forcing function. When we entered the equation "s2=q1.FF", **q1** no longer appeared in the sample equation, hence the line linking the sample to **q1** was severed.

Remember the name for the forcing function in SAAM II is cpt#.FF where cpt# is the number of the compartment with which the forcing function is associated.

9. Enter the parameter values.

Enter the parameter values as shown in the following **Parameters** dialog box:



a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameter**  . The **Parameters** dialog box will open.

b. Double-click *k(2,1)*. Type "60" in the **Value** box, "10" in the **Low Limit** box, "100" in the **High Limit** box, and click **Save**.

c. Double-click *k(0,2)*. Type "0.3" in the **Value** box, and click **Save**.

d. Double-click *k(3,2)*. Type "1" in the **Value** box, and click **Save**.

e. Double-click *k(2,3)*. Type "1" in the **Value** box, and click **Save**.

f. Click **Done**.

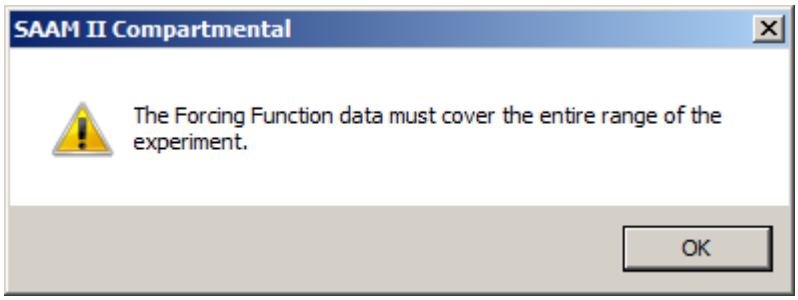
Volumes. Why was there no volume included in the sample **s1**? That is, normally when writing the sample equation we have usually included the volume term.

There is no volume here because the forcing function "pre" has units of µg/ml so the volume term is already built in. The units of "pro" are also µg/ml. It is assumed that

the "volume" for both "pre" and "pro" is the same. If the forcing function were in units of mass, then a volume term would be needed in **s1**.

10. Solve the model and view the solution.

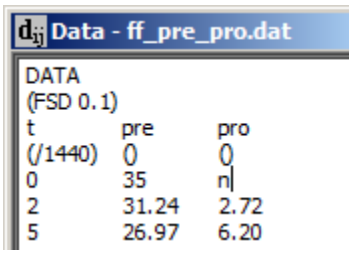
    a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve**. The following message will appear:



Forcing Functions. When you are using data to define a forcing function, the data must cover the entire range of the experiment. This means there must be a datum at time zero, and a datum at the last time of the experiment. Usually there is not a datum available at time zero, so you will have to add a dummy value, usually close to the first datum, so the solution can proceed.

    b. Click **OK**.

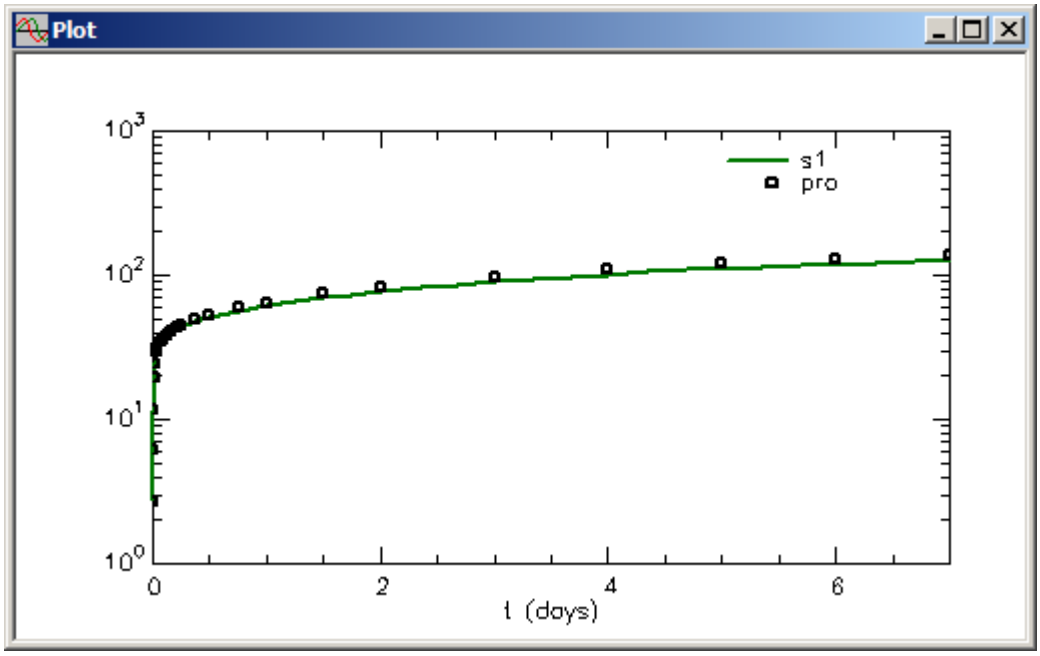
    c. Open the **Data** window. Enter a value for "pre" of 35 at time equals zero. Type "n" in the "pro" column at time equals zero. The first lines of your data file will appear as follows:



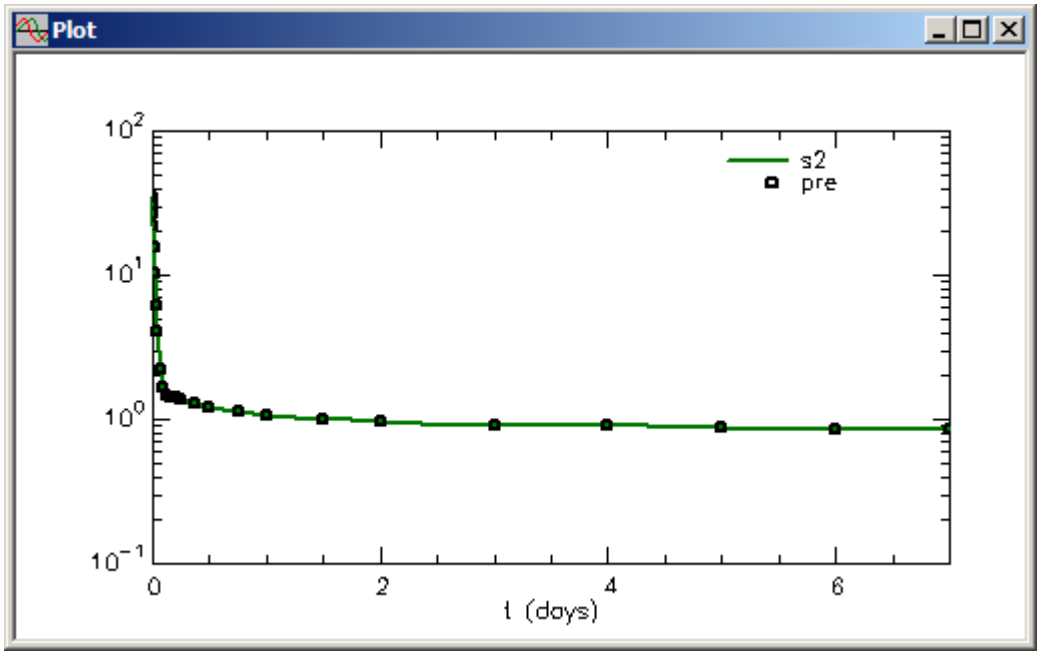
Data entry. Notice the "n" in the column for the pro. SAAM II expects an entry in each column for each time point. If there are no data, enter "n."

d. Close the **Data** window.

e. Re-Solve the model and view the solution in semilog. Your plot of **s1:pro** will appear as follows:



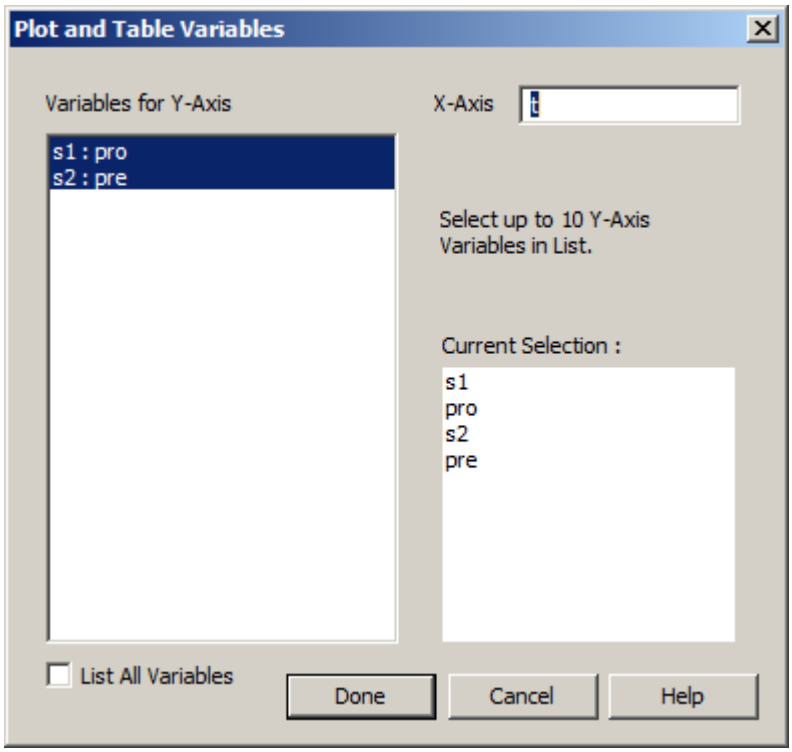
You can also plot **s2:pre**; it will appear as follows:



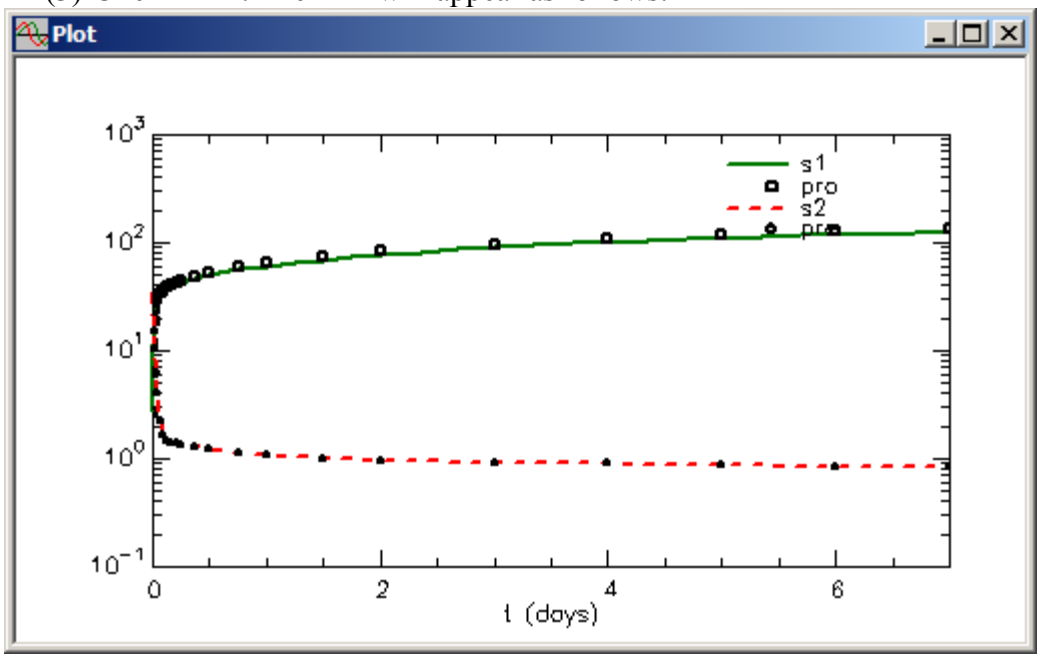
f. Plot **s2:pre** and **s1:pro** simultaneously.

(1) With the **Plot** window open, on the **Set** menu, click **Plot/Table Variables**. The **Plot and Table Variables** dialog box will open.

(2) Be sure the **List All Variables** check box is not selected. Click **s1:pro**. Press the **CTRL** key and click **s2:pre**. These will move to the **Current Selection** pane as shown below:



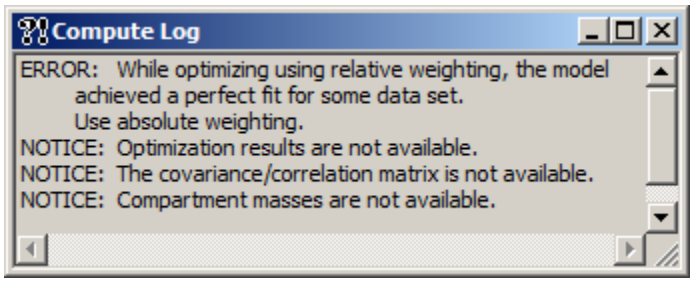
(3) Click **Done**. The **Plot** will appear as follows:



g. Close the **Plot** window.

11. Fit your model to your data and view the solution.

a. Fit your model to your data. On the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar,** click **Fit**  . The following message will appear:



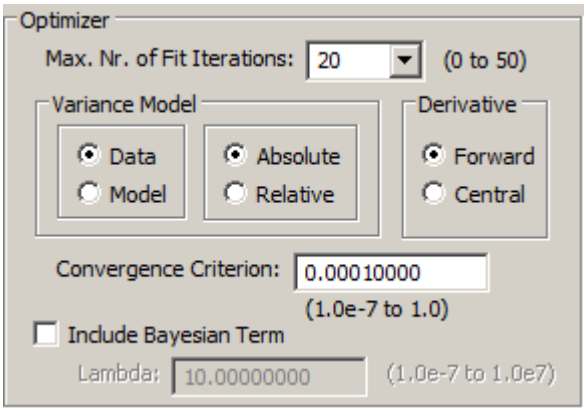
The message means that the data error model of "data-relative" is not appropriate for this model. We will follow the suggestion to set the error model to "data-absolute."

Close the **Compute Log** window.

b. Change the data error model.

(1) In the **Compute** menu, click **Settings**. The **Computational Settings** dialog box will open.

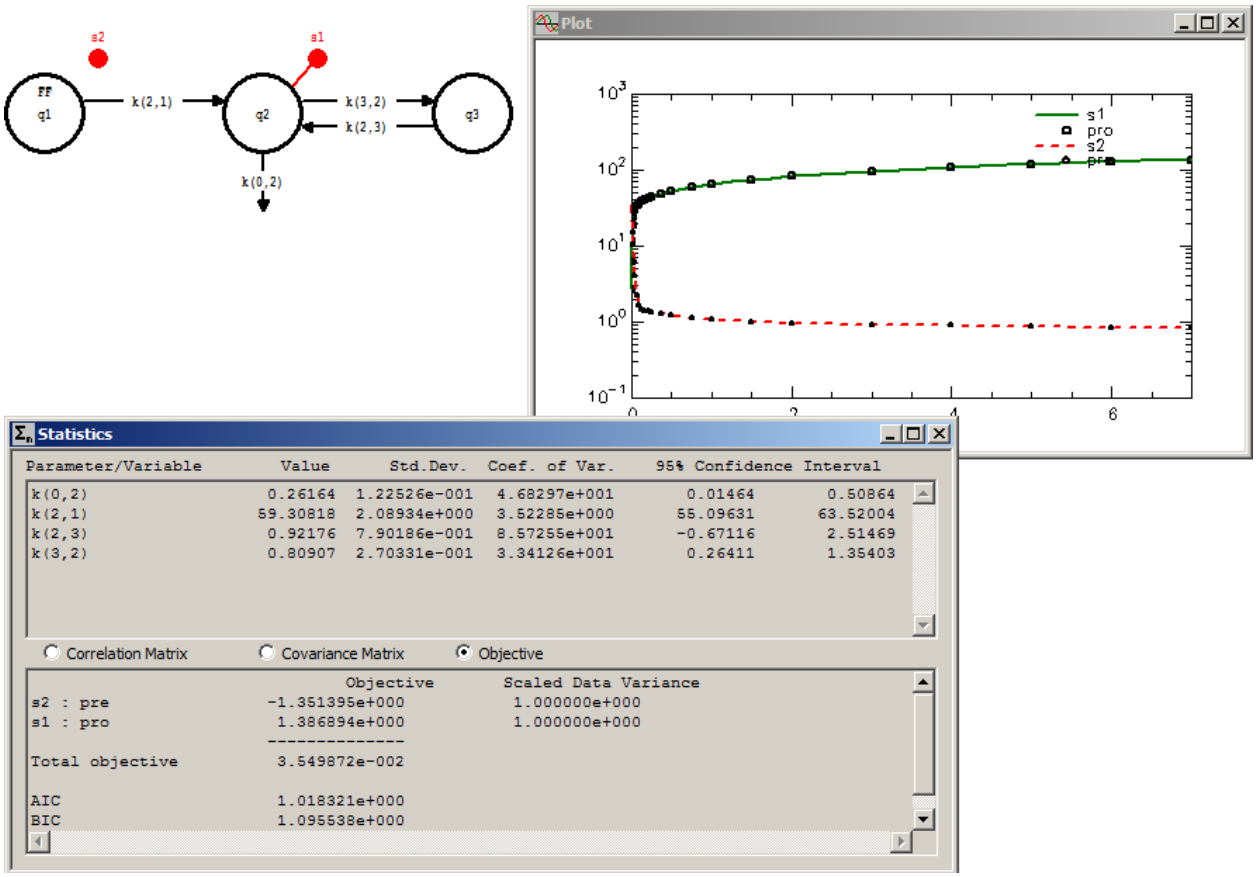
(2) In the **Variance Model** pane, click **Absolute**. The **Variance Model** pane inside the **Optimizer** pane will appear as follows:



(3) Click **Done**.

c. Re-Solve the model to activate the change in the variance model.
d. Re-Fit the model to the data. This time the fit is successful.
e. Open the **Plot** window and view the solution

f. On the **Show** menu, click **Statistics**, or alternatively, on the **SAAM II Toolbar**, click **Statistics**  . The **Statistics** and **Plot** windows along with the model will appear as follows:



g. Close the **Statistics** and **Plot** windows.

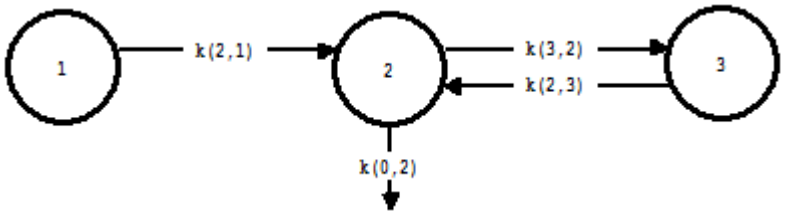
Quit the **SAAM II Compartmental** application. If you wish, you may save the study file for future use.

Part 2. Creating Forcing Functions Using an Equation.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

2. In the **SAAM II Toolbox**, click **Model** to be sure these tools are available.

3. Create the following model on the **Drawing** canvas:

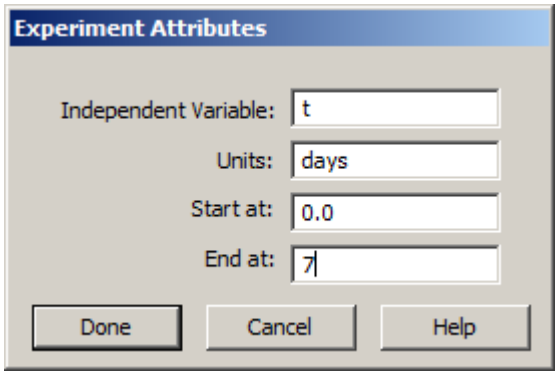


4. Create the experiment on the model

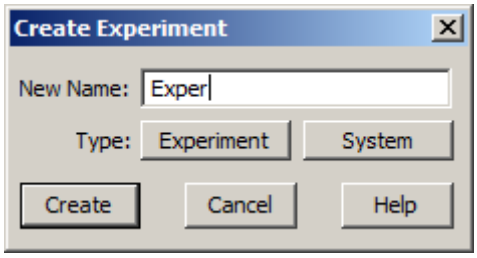
   a. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open.

   b. Type "days" in the **Units** box.

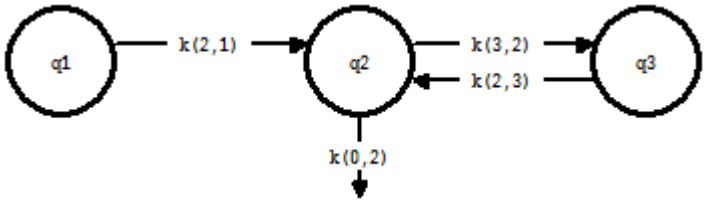
   c. Type "7" in the **End At** box. The **Experiment Attributes** dialog box will appear as follows:



   d. Click **Done**. The **Create Experiment** dialog box will open. Be sure **Exper** is selected. The **Create Experiment** dialog box will appear as follows:



e. Click **Create**. The model will appear on your drawing canvas as follows:



5. Add the data to the model.

a. In the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar,** click **Data**  . The **Data** window will open.

b. On the **File** menu, click **Open**. The file **ff_pre_pro.dat** should appear in the list (if it does not, find the folder where you have put this tutorial and data file).

c. Double-click **ff_pre_pro**. The data in this file will appear in the **Data** window as shown below.

Data - ff_pre_pro.dat

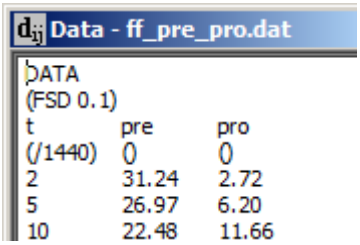
```
DATA
(FSD 0.1)
t          pre        pro
(/1440)    0          0
2          31.24      2.72
5          26.97      6.20
10         22.48      11.66
20         15.47      19.34
30         10.48      24.26
45         6.28       29.77
(/24)      0          0
1          4.14       31.94
1.5        2.23       34.84
2          1.69       36.20
3          1.46       38.47
4          1.43       40.85
5          1.40       43.03
6          1.36       44.93
9          1.28       49.36
12         1.23       52.68
18         1.15       60.25
0          0          0
1          1.08       64.50
1.5        1.01       75.43
2          0.97       83.39
3          0.90       97.27
4          0.91       109.00
5          0.87       120.00
6          0.85       131.00
7          0.86       137.00
END
```

Data Format is okay

There are some important features of this data file that we will describe below.

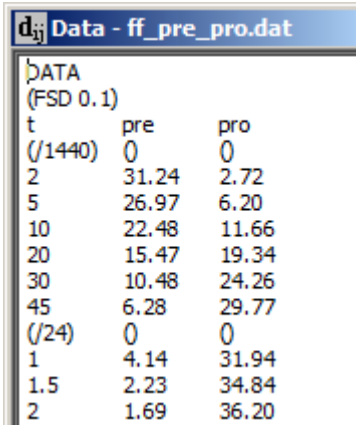
*Unit conversion in the **Data** window*. This data file illustrates several features of the SAAM II **Data** window. First, it illustrates that several columns of data can be used with a single independent variable, usually time "t". The column "pre" is the data driving the system; the column "pro" is the system whose characteristics will be modeled.

This data file also illustrates how to do unit conversion in the SAAM II **Data** window. The first few rows of the data file are shown below:



The three column names are "t" for time, "pre" for "precursor" and "pro" for "product". Under these are a line containing (/1440), (), and (). In the "t" column, the first data samples were recorded in minutes and not days, the units of the model. Thus, "(/1440)" divides all elements in the column by 1440 to convert minutes into days. This divisor is in effect until the next set of parentheses is encountered further down the column. There are no unit conversions for either "pre" or "pro"; the "()" must be include to indicate no conversion.

In the time column, the next unit conversion is shown below:



You can see after 45 minutes, the "t" changes to 1, 1.5, etc. These are hours, so the next few samples are in units of hours, not minutes or days. The division by 24 converts hours to days.

Finally, after 18 hours, you see in the time column () while () remains in both data columns. After 18 hours, the data are collected in days, and unit conversion is no longer necessary. The () tells SAAM II this is the point at which (/24) is no longer needed.

This is a very powerful way to use the SAAM II **Data** window to be sure all of your units are consistent.

d. Close the **Data** window.

6. Create a sample.

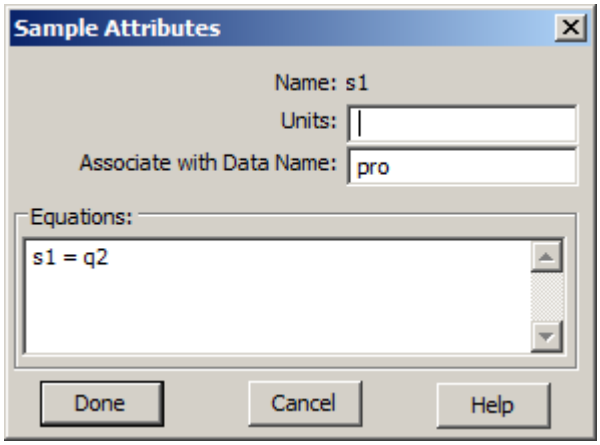
   a. In the **SAAM II Toolbox**, click **Sample**.

   b. Click compartment **q2**, and then click on the **Drawing Canvas**. The sample **s1** will appear.

   c. Double-click **s1** to open the **Sample Attributes** dialog box.

   d. Type "pro" in the **Associate with Data Name** box.

   e. There is no need to edit the sample equation. The **Sample Attributes** dialog box will appear as follows:



   f. Click **Done**. Noticed **s1** is now solid because it is associated with data.

7. Create a forcing function.

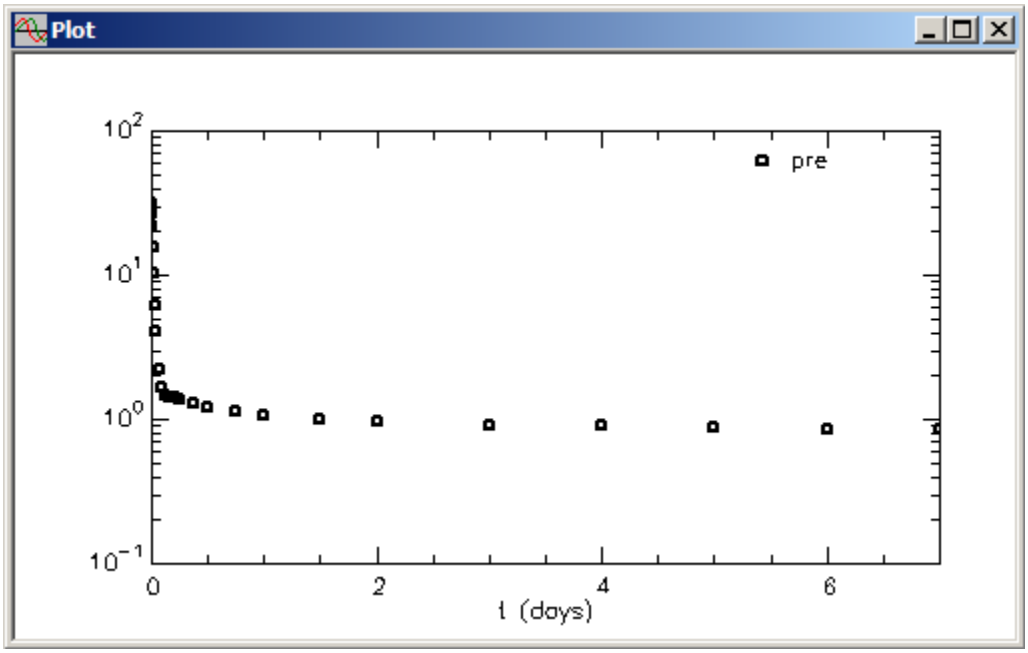
   You will be creating the forcing function by fitting "pre" by a sum of exponentials. Thus the first step will be to examine "pre" to estimate how many exponentials will be required, and to obtain initial estimates for the coefficients and exponentials.

a. Examine the "pre" data.

(1) In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar** click **Plot**  . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is selected.

(2) Click **pre** to move this to the **Current Selection** pane.

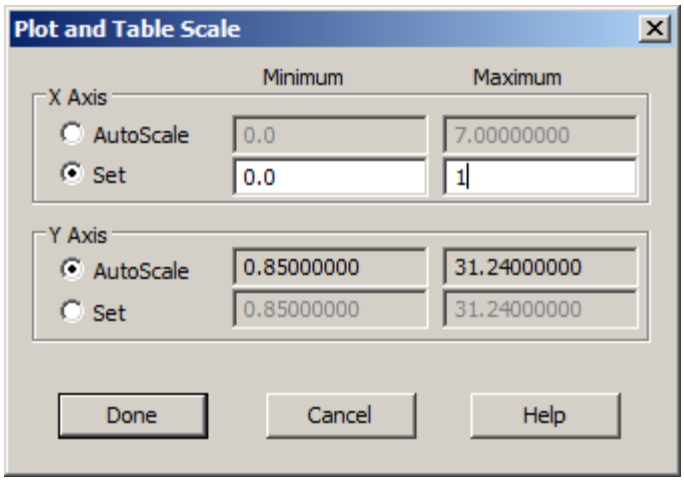
(3) Click **Done**. The plot of the **pre** will appear as follows.



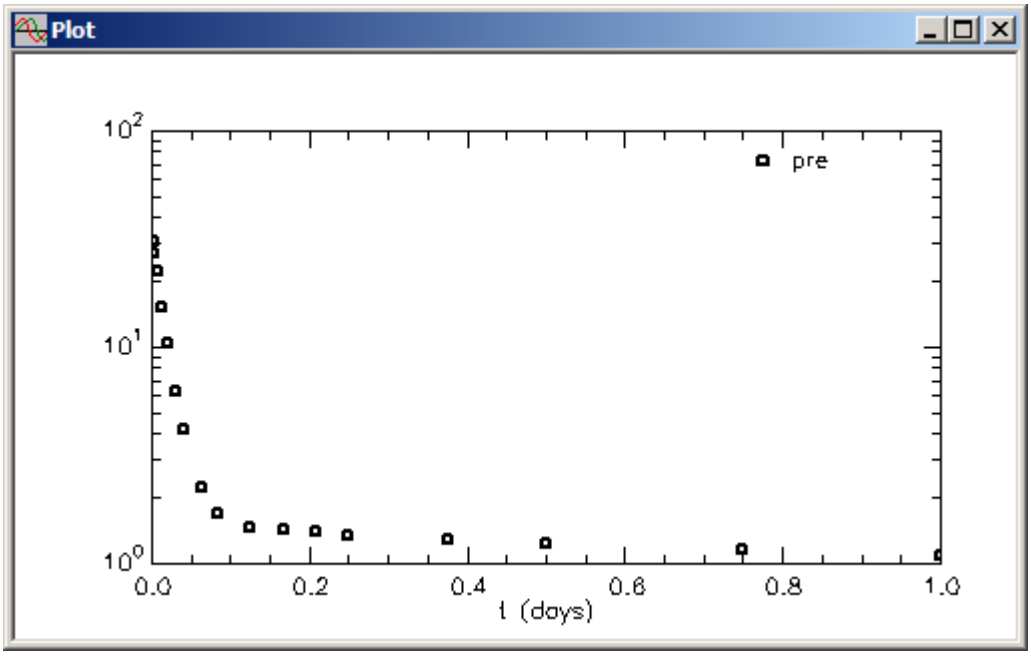
You can see there are an extremely rapid initial fall and a very slow final decay. To examine the characteristics of the initial decay, change the **Plot and Table Scale**.

(3) On the **Set** menu, click **Plot/Table Scale**. Alternatively, click the Set Scales Button  , or right-click in the plot window and select Scale… The **Plot and Table Scale** dialog box will open.

(4) In the **X Axis** pane, click **Set**. Type "1" in the **Maximum** box. The **Plot and Table Scale** dialog box will appear as follows:



(5) Click **Done**. The plot will appear as follows:



You can see there are probably three exponentials in these data, so the forcing function will be:

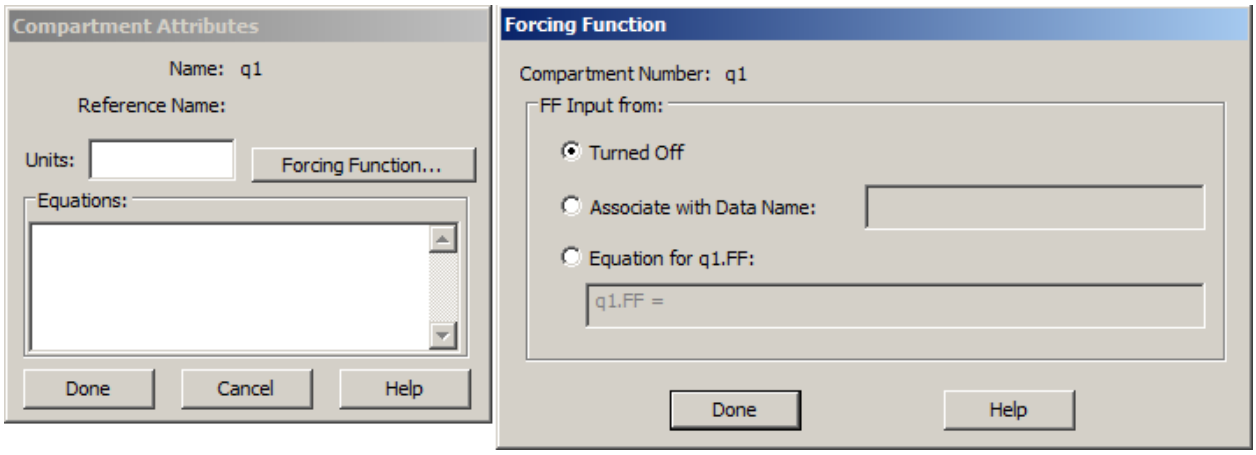
$$q1.FF = A1 * \exp(-a1 * t) + A2 * \exp(-a2 * t) + A3 * \exp(-a3 * t)$$

Estimates for *A1*, *A2* and *A3* respectively will be 30, 3 and 3. This comes from the zero time point being approximately 36, and most of the material disappears with the first exponential. This is the 30. The remaining two are half of the remaining. Since these are linear parameters, close estimates are not really required.

Estimates for *a1*, *a2* and *a3* respectively will be 75, 3 and .003. These estimates are obtained from a curve peeling method.

b. Double-click Compartment **q1**, to open the **Compartment Attributes** dialog box.

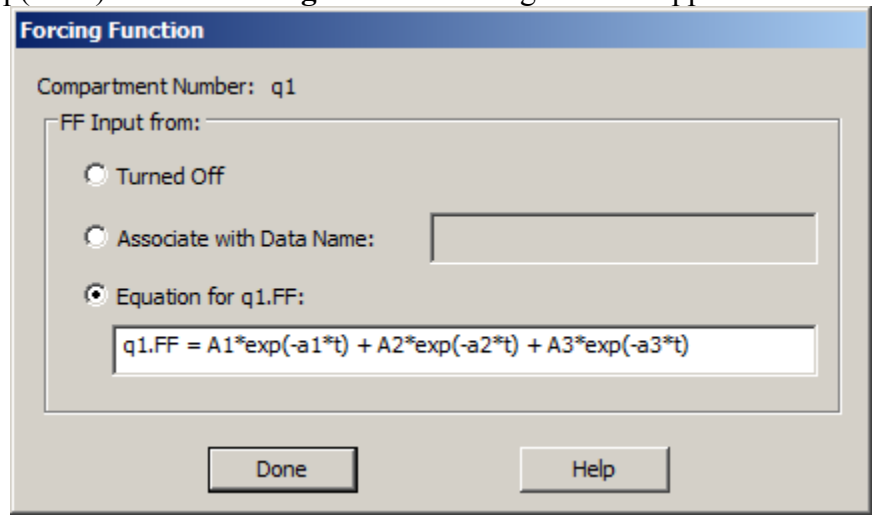
c. Click **Forcing Function**. The **Forcing Function** dialog box will open as shown below (together with the **Compartments Attributes** dialog box):



There are three options in the **FF Input from** pane. The default option is **Turned Off** since no forcing function has been defined. The other two options are **Associate with Data Name** and **Equation for q1.FF**. If you select the **Associate with Data Name** option, the forcing function will be created by linear interpolation of sequential pairs of data. If you select the **Equation for q1.FF** option, you must specify an equation in the box provided.

c. Click **Equation for q1.FF** in the **FF Input from** pane. The **Equation** box will become active.

d. In the **Equation** box, type the equation "q1.FF = A1*exp(-a1*t) + A2*exp(-a2*t) + A3*exp(-a3*t)". Your **Forcing Function** dialog box will appear as follows:

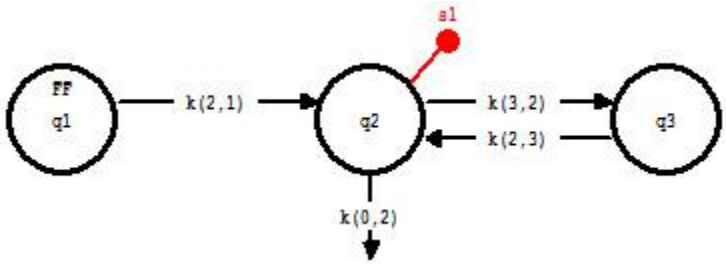


Creating Forcing Functions. When you choose the **Equation for q1.FF** option, you must enter a specific equation that will be used for the forcing function. In the above, you are using a sum of three exponentials meaning there are six parameters, *A1*, *A2*, *A3*, *a1*, *a2* and *a3*. These can be fixed or adjustable. In this case, they will be adjustable meaning the forcing function will be defined (fitted) as part of the modeling exercise.

The advantage here is that the forcing function can be determined simultaneously with examining the system model for "pro". Once the forcing function parameters are determined, they will be fixed before the final Fit to the "pro" data.

e. Click **Done** in the **Forcing Function** dialog box.

f. Click **Done** in the **Compartment Attributes** dialog box. Your model will appear as follows:



Notice that "FF" appears in Compartment **q1**. This is to remind you that this compartment is now defining a forcing function.

8. Create a second sample for the forcing function.

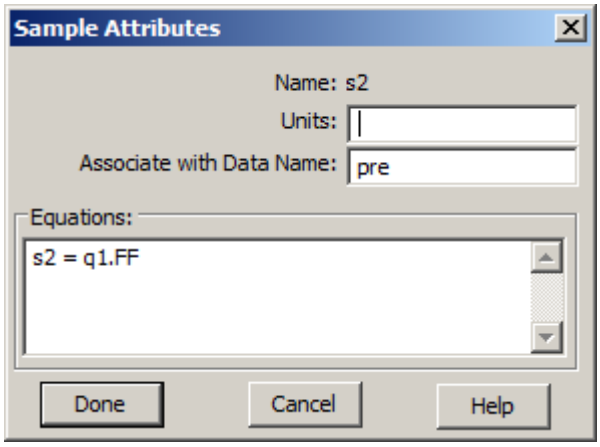
a. In the **SAAM II Toolbox**, click **Sample**.

b. Click Compartment **q1**, and then on the **Drawing Canvas**. The sample **s2** will appear.

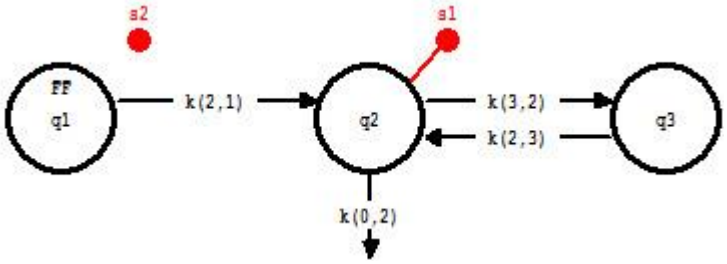
c. Double-click **s2** to open the **Sample Attributes** dialog box.

d. Type the sample equation "s2=q1.FF"

e. Type "pre" in the **Associate with Data Name** box. The **Sample Attributes** dialog box will appear as follows:



f. Click **Done**. You will notice that **s2** appears solid, but no longer connected to Compartment **q1**. This is because the sample equation is no longer associated with a specific compartment in your model. The model is shown below.

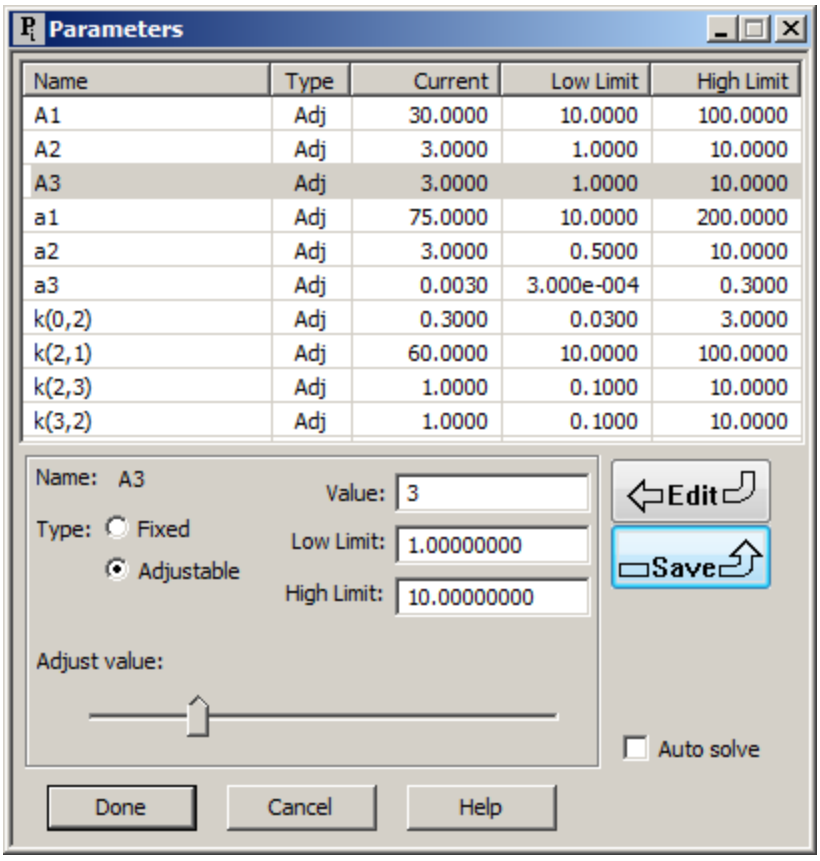


Samples. The Sample tool is a very powerful tool in SAAM II. Normally it is used to create samples that link a compartment, or compartments, with data. In this case, we are interested in viewing the forcing function. When we entered the equation "s2=q1.FF", **q1** no longer appeared in the sample equation, hence the line linking the sample to **q1** was severed.

Remember the name for the forcing function in SAAM II is cpt#.FF where cpt# is the number of the compartment with which the forcing function is associated.

9. Enter the parameter values.

Enter the parameter values as shown in the following **Parameters** dialog box:



Notice that some of the parameters do not use the default values for the **Low Limit** and/or **High Limit**.

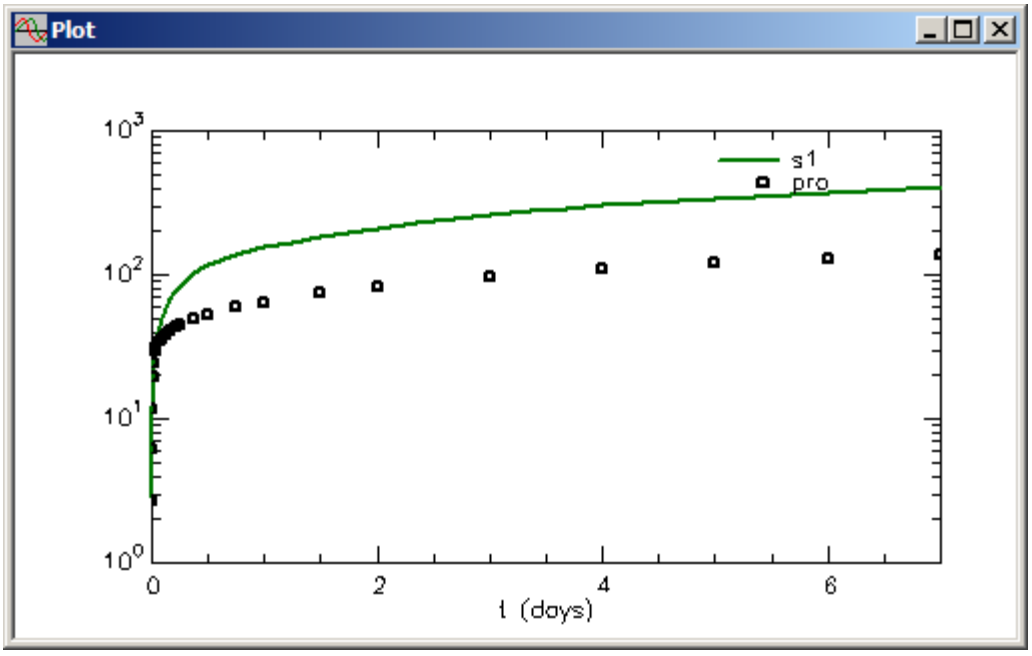
Volumes. Why was there no volume included in the sample **s1**? That is, normally when writing the sample equation we have usually included the volume term.

There is no volume here because the forcing function "pre" has units of µg/ml so the volume term is already built in. The units of "pro" are also µg/ml. It is assumed that the "volume" for both "pre" and "pro" is the same. If the forcing function were in units of mass, then a volume term would be needed in **s1**.

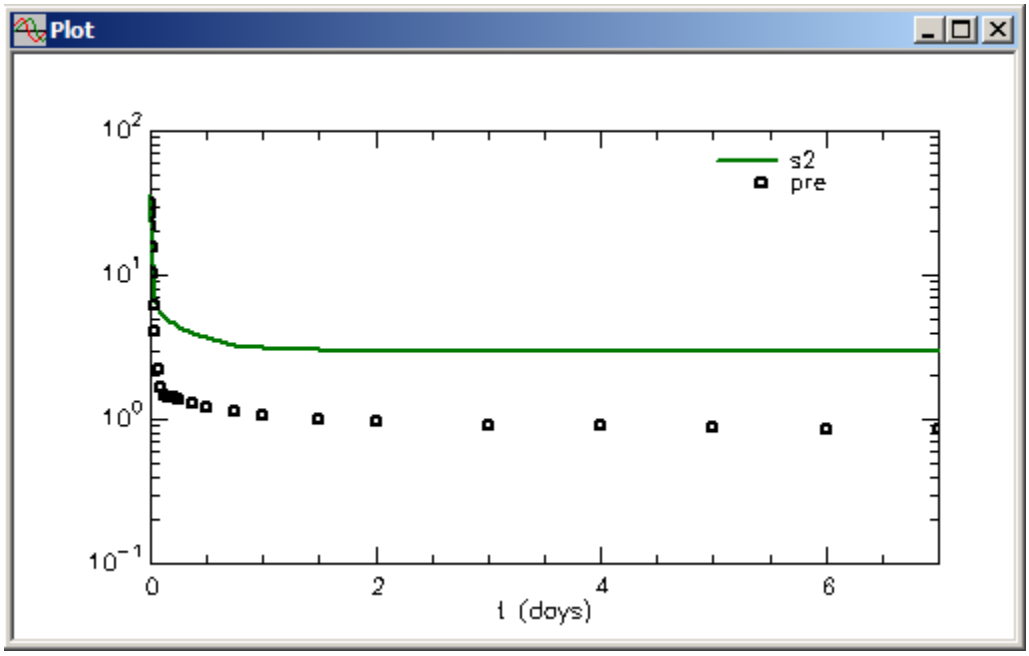
10. Solve the model and view the solution.

    a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve**  .

e. Plot **s1:pro**. Your plot of **s1:pro** will appear as follows (you may have to change the **Plot and Table Scale** resetting the **X Axis maximum** to "7"; you may also have to change the plot to the semilog shown below):



You can also plot **s2:pre**; it will appear as follows:

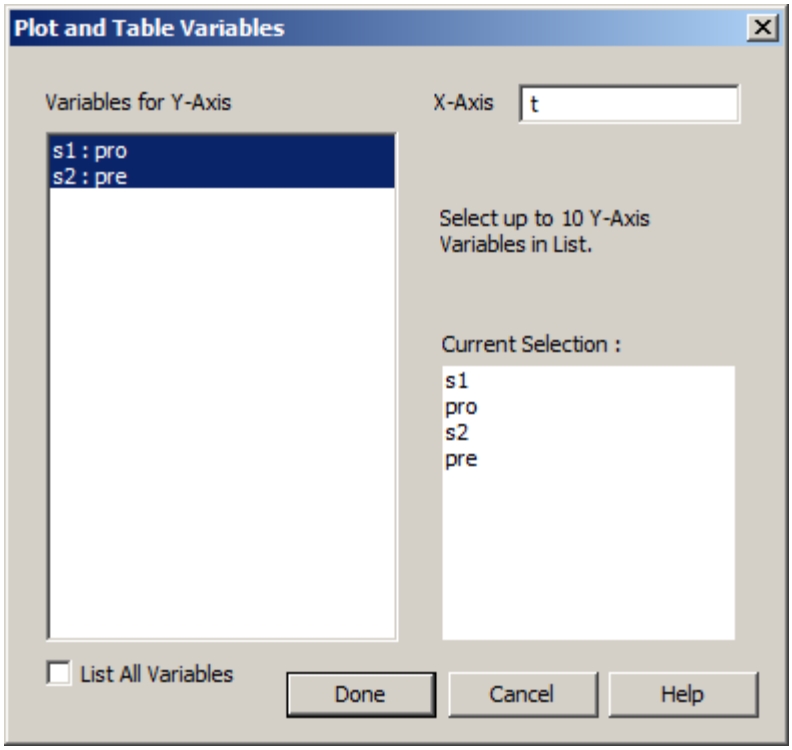


You can see that the estimates for the exponentials are reasonable, but the estimate for *A1* needs to be increased.

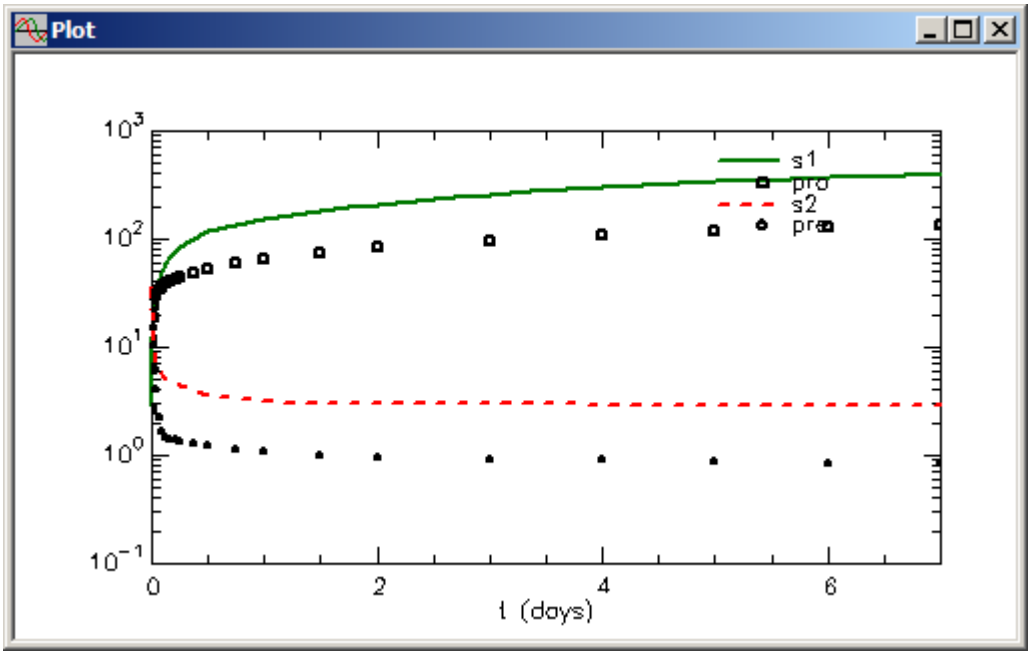
f. Plot **s2:pre** and **s1:pro** simultaneously.

(1) With the **Plot** window open, on the **Set** menu, click **Plot/Table Variables**. The **Plot and Table Variables** dialog box will open.

(2) Be sure the **List All Variables** check box is not selected. Click **s1:pro**. Press the **CTRL** key and click **s2:pre**. These will move to the **Current Selection** pane as shown below:



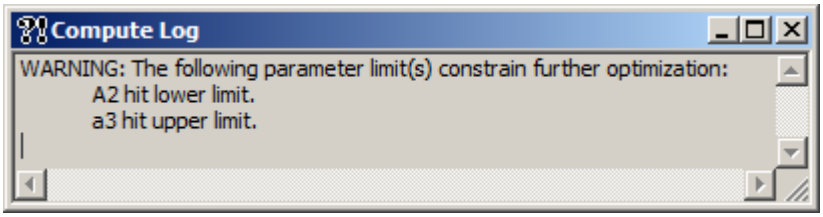
(3) Click **Done**. The **Plot** will appear as follows:



g. Leave the **Plot** window open.

11. Fit your model to your data and view the solution.

a. Fit your model to your data. On the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar,** click **Fit** . The following message will appear:



The message means that the limits on these parameters need to be changed. Remember, however, that what you want is a curve which has the characteristics of the data. The statistics on these parameters are thus not that important as they will be fixed before the final Fit.

Close the **Compute Log** window.

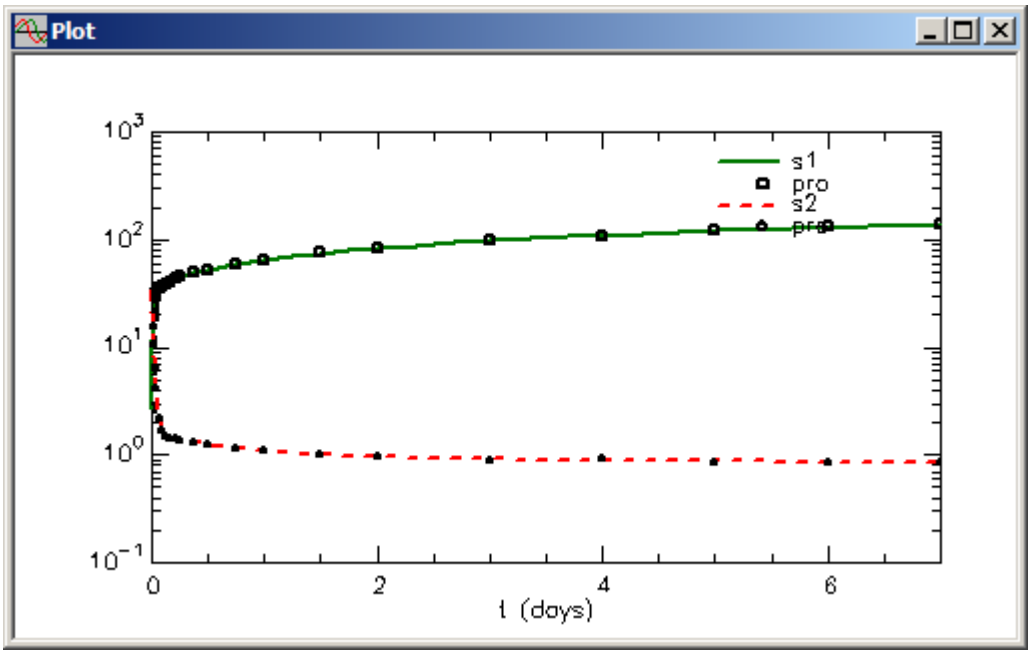
b. Change the limits on *A2* and *a3*.

(1) Change the **Low Limit** on *A2* to "0.5".

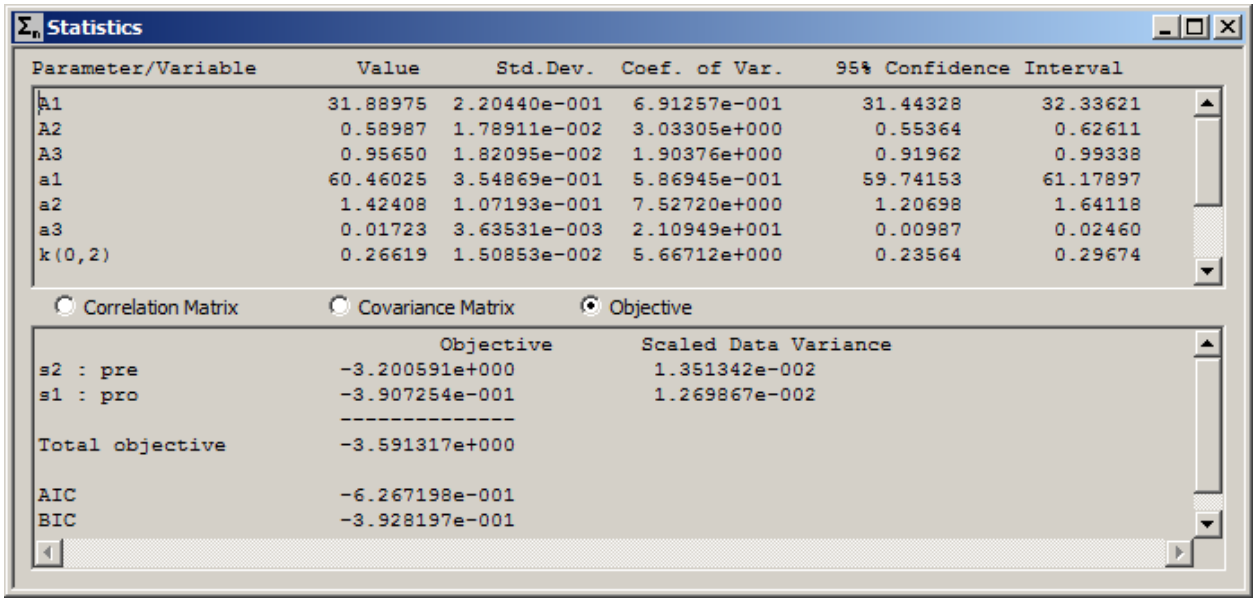
(2) Change the **High Limit** on *a3* to "0.3" respectively

c. Re-Fit the model. Another warning the "***A3* hit lower limit**" will appear. Change the **Low Limit** on *A3* to "0.5".

d. Refit the model to the data. This time the fit is successful. The plot of **s1:pro** and **s2:pre** will be updated as follows:



e. On the **Show** menu, click **Statistics**, or alternatively, on the **SAAM II Toolbar**, click **Statistics**  . The **Statistics** window will appear as follows:



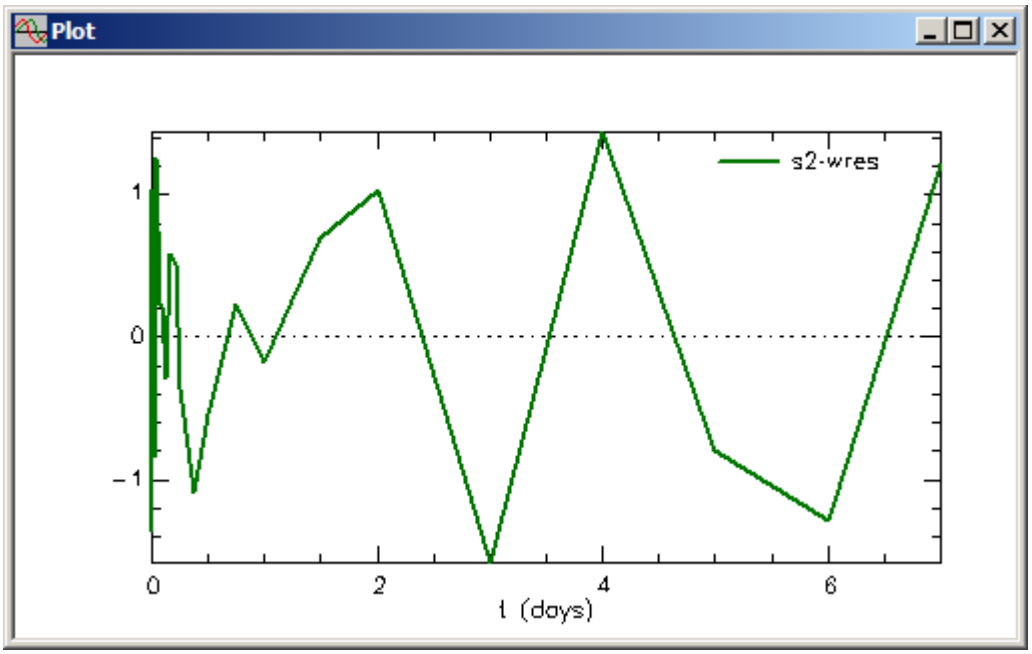
f. Close the **Statistics** windows. The **Plot** window is still open.

g. View the weighted residuals associated with the fit of **s2** to **pre**.

(1) On the **Set** menu, click **Plot/Table Variables**. Be sure the **List All Variables** check box is selected.

(2) Click **s2:wres** to move this to the **Current Selection** pane.

(3) Click **Done**. The plot of the weighted residuals, in linear mode, will appear as follows:

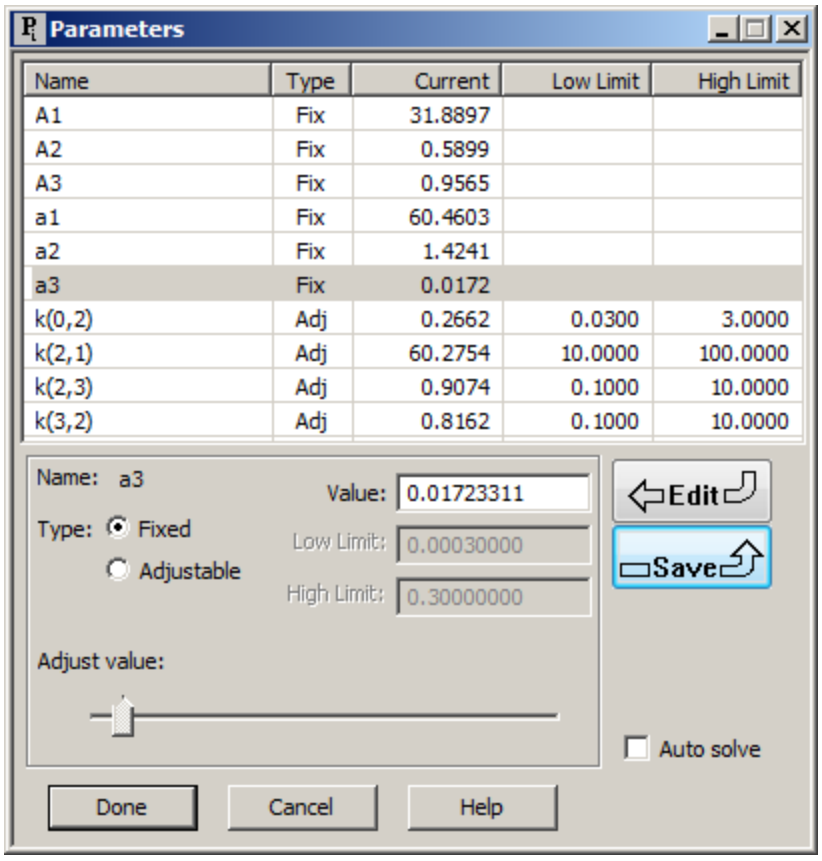


You can see the residuals are randomly distributed around zero and line in a band essentially between -1 and 1; thus the sum of three exponentials is providing a good description of the forcing function.

h. Re-Plot **s1:pro** in semilog mode.

12. Fix the parameters defining the forcing function, and fit the model to the data.

a. Open the **Parameters** dialog box, and fix all parameters associated with the forcing function. The **Parameters** dialog box will appear as follows:

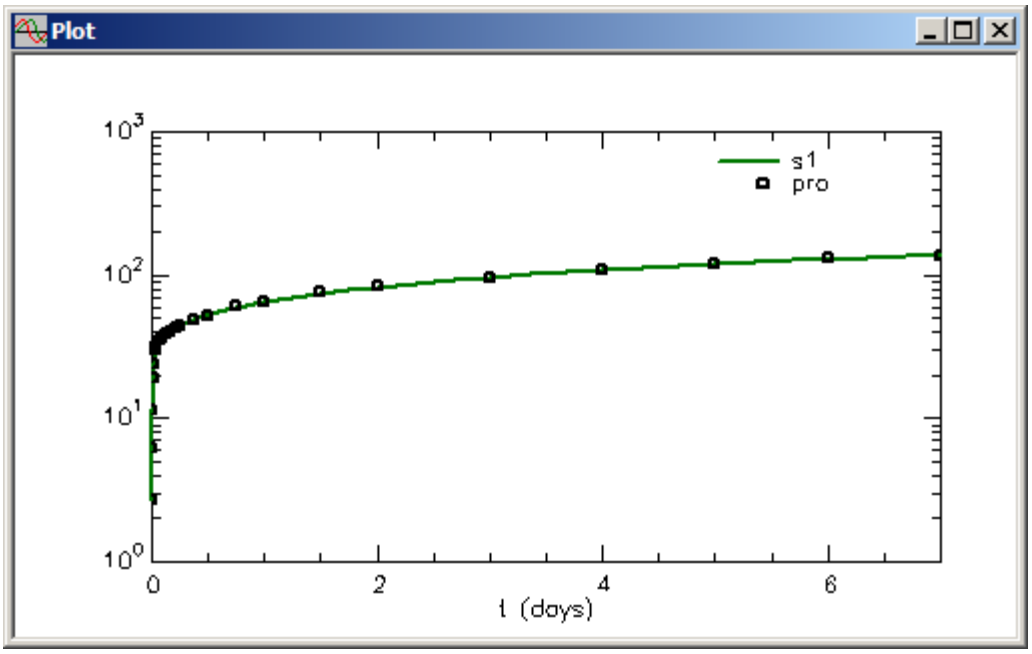


Fixing the parameters of the forcing function. The parameters of the forcing function should be fixed before performing a final fit of the system data, in this case the "pro". In this situation, the parameters of the forcing function could be estimated from the data. There will be situations when this is not the case. For example, you may have a situation when a sum of two exponentials has excellent statistics but does not describe the data. When you try three exponentials, you get an excellent description of the data but the statistics are not good.

What is important in this case is the shape of the forcing function. Thus even though a sum of three exponentials has bad statistics, because it has the correct shape, it should be used as the forcing function.

Finally, by fixing these parameters, the weights associated with the forcing function are not taken into account in the system model fit; this is what is desired when you are examining only the system model and using the forcing function simply to drive the system.

b. Fit the model to the data. The plot of **s1:pro** will appear as follows:



c. View the statistics. The **Statistics** window will appear as follows (after scrolling in the **Parameter/Variable** pane):

Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
a1	60.46025	** Fixed **	** Fixed **	** Fixed **	** Fixed **
a2	1.42408	** Fixed **	** Fixed **	** Fixed **	** Fixed **
a3	0.01723	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,2)	0.26619	1.31405e-002	4.93651e+000	0.23969	0.29269
k(2,1)	60.27537	2.22070e-001	3.68426e-001	59.82747	60.72327
k(2,3)	0.90738	8.12420e-002	8.95348e+000	0.74352	1.07124
k(3,2)	0.81617	2.80363e-002	3.43509e+000	0.75963	0.87272

Correlation Matrix Covariance Matrix Objective

	Objective	Scaled Data Variance
s2 : pre	-3.200591e+000	1.167068e-002
s1 : pro	-3.907254e-001	1.096703e-002
Total objective	-3.591317e+000	
AIC	-7.517198e-001	
BIC	-6.347697e-001	

You can see the parameters of the system model are quite well-determined.

d. Close the **Statistics** and **Plot** windows.

Quit the **SAAM II Compartmental** application. If you wish, you may save the study file for future use.

SAAM II Version 2.1
Advanced Tutorials

Working with Parameters (Advanced)

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Working with Parameters, Advanced

Prerequisites

The prerequisites for this tutorial are having worked through the SAAM II introductory tutorial, "Getting Started with **SAAM II Compartmental**" and the Basic Tutorial "Working with Parameters."

What you will learn in this tutorial

The Basic Tutorial, "Working With Parameters", showed you how to use the different options in SAAM II to define and use the most commonly used types of parameters. The purpose of this tutorial is to show you how to use the additional options in SAAM II to define and refine parameters. You will learn

- How to create zero order losses (Part 1)
- How to write parameters and variables in the **Equations** window (Part 2)
- How to re-parameterize the two-compartment model (Part 3)
- How to set parameter upper and lower limits (Part 4)
- How to use the Bayesian option (Part5)

This tutorial is divided into parts to which you can refer individually for specific information. Since you know how to enter parameters in the **Parameters** dialog box, you can proceed to any specific part of this tutorial without needing the information that preceded it.

Files Required

Study Files: The study files for this tutorial are

study_0.stu
Para_Limits.stu
Para_Limits.dat

These files are included as part of this tutorial. The file **study_0.**stu is the same as **study_0.stu** that is installed in the **SAAM II** program folder and referred to in the **SAAM II** Basic Tutorials.. The file **Para_Limits** is a one-compartment model with two parameters.

Introduction

This tutorial is designed to show you have to use the additional options available in SAAM II to work with parameters.

In general, most losses are first-order or nonlinear as covered in the basic tutorial, "Working with Parameters." There may be instances, when the loss is at a constant rate independent of the mass in the i^{th} compartment. In these cases, a zero-order loss is required. Part 1 of this tutorial shows how to create a zero-order loss. Zero-order inputs can also be created, but these are equivalent to constant infusions.

A multi-compartmental model in SAAM II is specified by the compartments, transfers and losses. The transfers *k(i,j)* and losses *k(0,i)* specify the terms in the different differential equations created internally by SAAM II. These are called the primary parameters. Often there are a number of parameters – volumes, clearances, absorptions – that are functions of these primary parameters. These parameters can be specified as variables in the **Equations** dialog box. This procedure is explained in Part 2 of this tutorial. Some models such as the commonly used two-compartment model can be re-parameterized based upon the desired secondary parameters; this is illustrated in Part 3 of this tutorial.

All adjustable parameters must have initial values specified with high and low limits. For an adjustable parameter, if you simply enter a value and click **Save**, SAAM II will create default high and low limits that are 10 times and 0.1 times the initial value. SAAM II actually uses the information in the limits as part of fitting. The information is a measure of how well you think you know your limits. As will be illustrated in Part 4 of this tutorial, if your limits are widely divergent from the initial value, you may have trouble fitting. This is because SAAM II thinks you don't know the parameter very well. On the other hand, if you know a parameter reasonably well, this information should be included when you set the limits.

Finally, SAAM II has implemented a partial Bayesian option. This is explained in Part 5 of this tutorial. The Bayesian option provides a means by which *a priori* information about a specific parameter, or parameters, can be entered in the **Parameters** dialog box.

Part 1. Creating a zero-order loss

In general, most losses are first-order or nonlinear. There may be instances, however, when a zero-order loss is required. The difference is the following. For the i[th] compartment, the loss is generally expressed (in terms of the differential equation):

$$\frac{dq_i}{dt} = -k(0,i) \cdot q_i(t) + \ldots$$

That is, the loss is proportional to the mass in the i[th] compartment. In the case of the zero-order loss, this is not the case:

$$\frac{dq_i}{dt} = -k(0,i) + \ldots$$

That is, the loss is at a constant rate independent of the mass in the i[th] compartment. This tutorial will explain how to create zero-order losses.

Incidentally, by the same logic, you can see why a zero-order input and a constant infusion are the same. If Compartment **1** transferred material to Compartment **2** via a zero-order process,

$$\frac{dq_2}{dt} = k(2,1) + \ldots$$

The parameter *k(2,1)* is simply a constant rate of input, and hence, in SAAM II notation, is equivalent to

$$\frac{dq_2}{dt} = ex(2) + \ldots$$

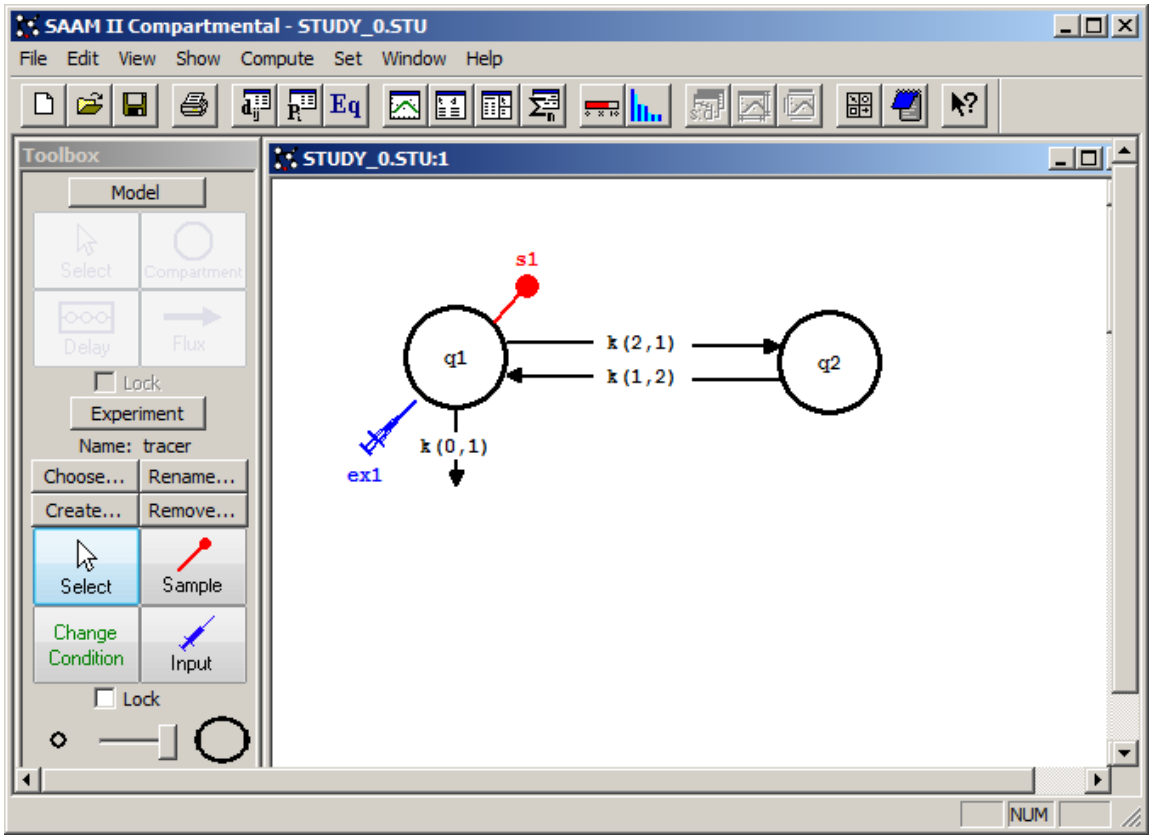
where **ex(2)** is specified as a constant infusion.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

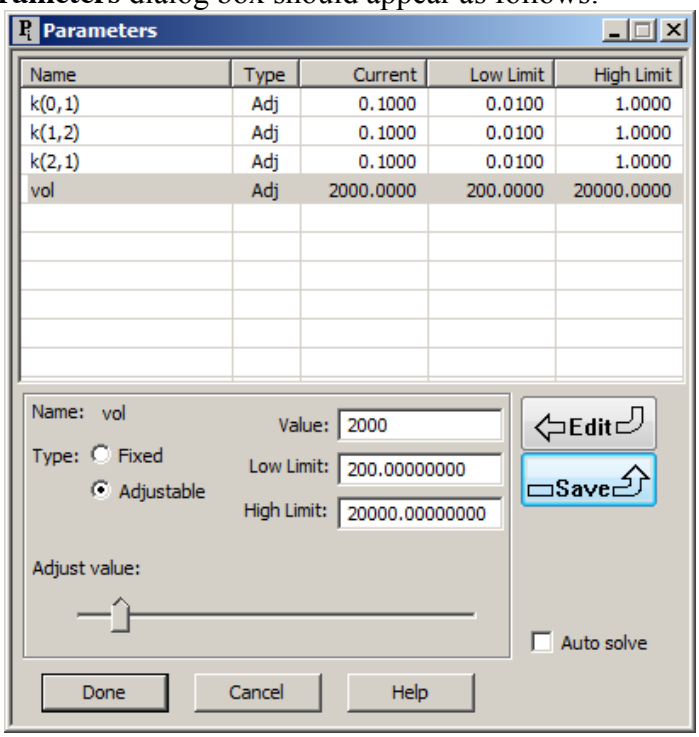
2. Open the **SAAM II Compartmental** study file **study_0**.

   a. The file **study_0.stu** should appear in the file list; if it does not, find the folder where you put this file.

   b. In the **File** menu, click **Open** and click **Experiment** in the **SAAM II Toolbox**. The **SAAM II Compartmental** main window will appear as shown below:



3. View the **Parameters** dialog box. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters**  . The **Parameters** dialog box will open. The **Parameters** dialog box should appear as follows:

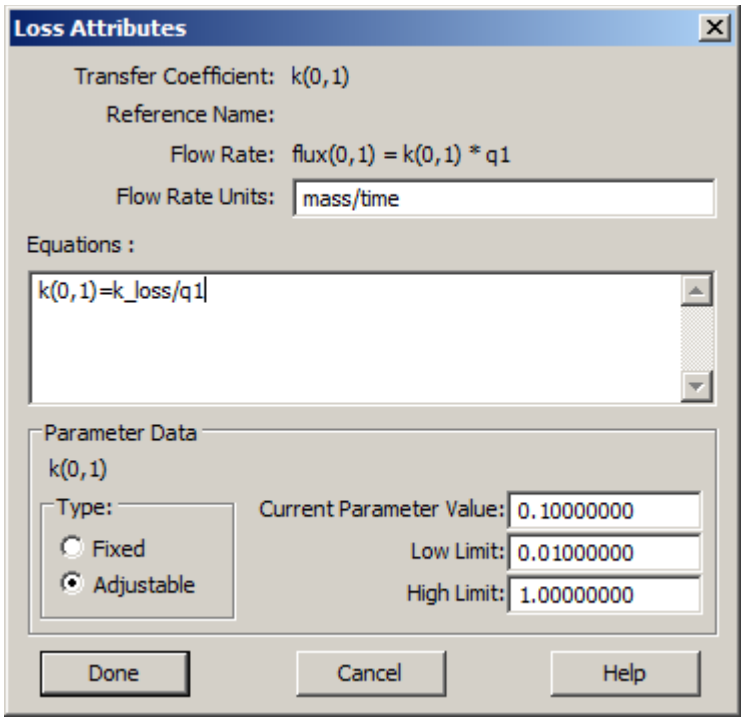


These are the parameters for **study_0.stu**.

4. Modify *k(0,1)* so that it is a zero-order loss.

   a. Double-click *k(0,1)* to open the **Loss Attributes** dialog box.

   b. In the **Equation** pane, type "k(0,1)=k_loss/q1". The **Loss Attributes** dialog box will appear as follows:



   c. Click **Done**.

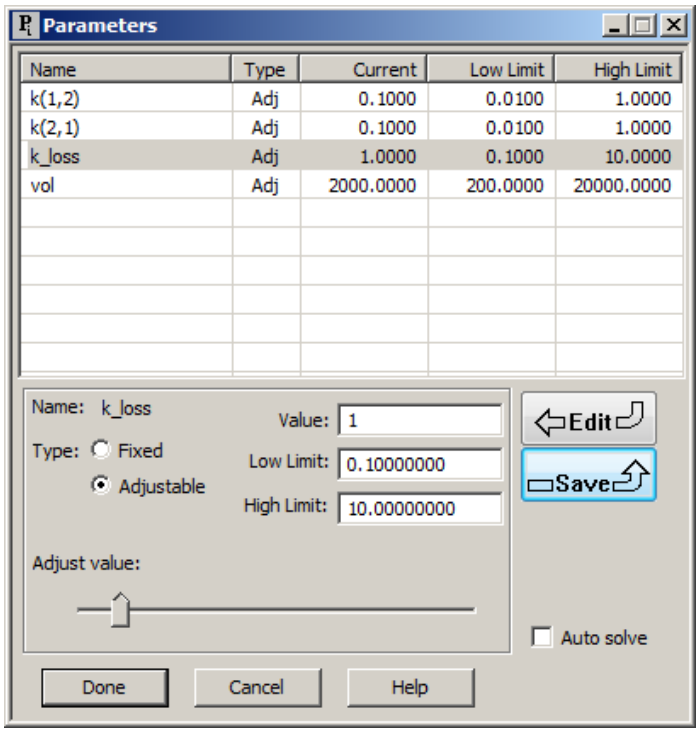
   The result is that *k(0,1)* is no longer a primary model parameter, but is a function of a new parameter, *k_loss*. In the differential equation for **q1**:

$$\frac{dq_1(t)}{dt} = -k(0,1)\cdot q1(t) + \cdots = \frac{k\_loss}{q1(t)}\cdot q1(t) + \cdots = -k\_loss + \cdots$$

   The result is now the loss from Compartment **q1** is zero-order, and specified by *k_loss*. A value for this parameter must be entered in the **Parameters** dialog box.

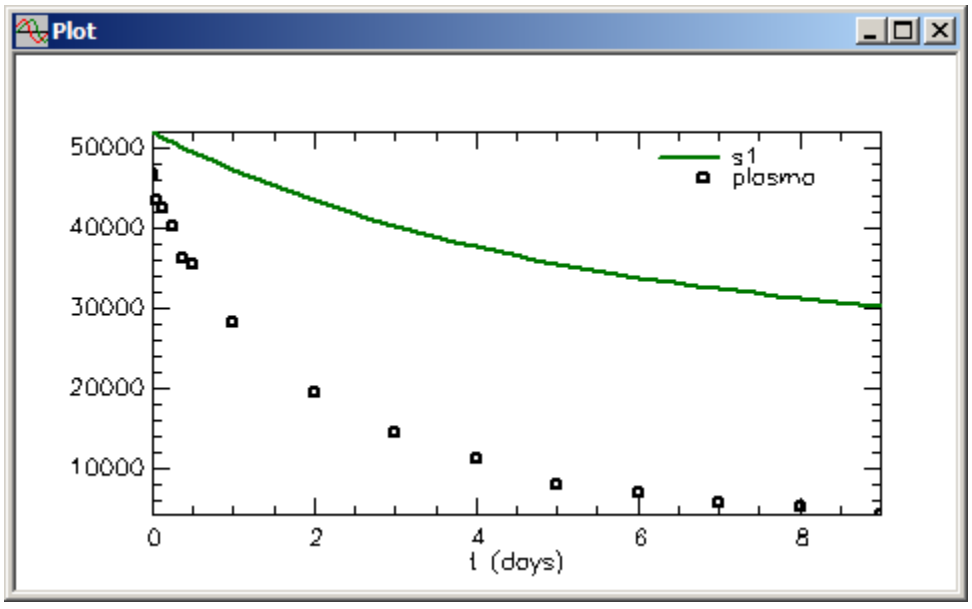
5. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters**  . The **Parameters** dialog box will open.

a. Type "1" as the **Value** for *k_loss*, and click **Save**. The **Parameters** dialog box will appear as follows:



b. Click **Done**.

6. Solve the model, and view the solution. A plot of the solution is shown as follows:

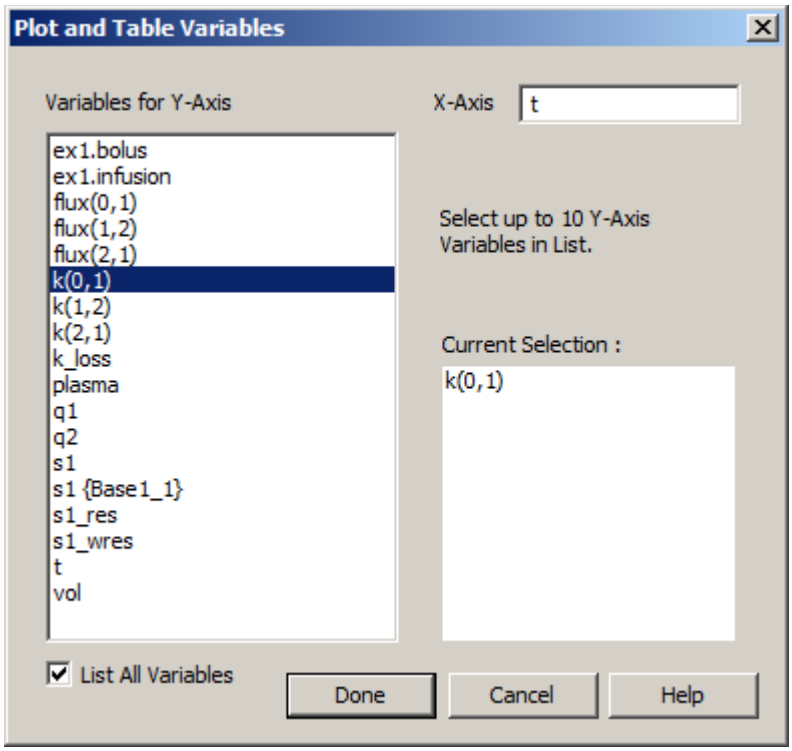


It is of interest, however, to plot *k(0,1)* which is no longer a constant but a function of time since **q1(t)** appears in the equation defining it. While this is the case, the rate of

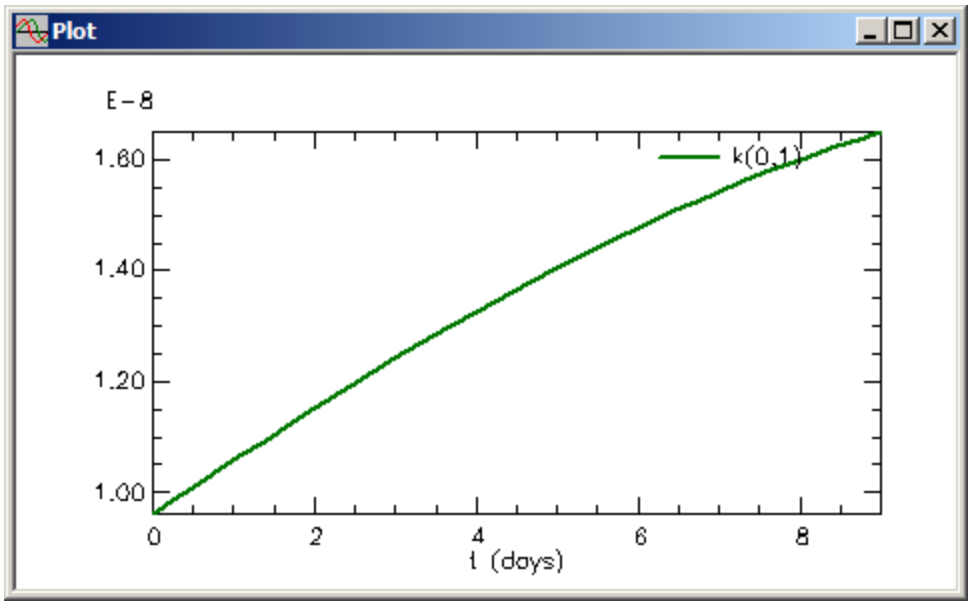
loss, **flux(0,1)**, should be constant. Both will be plotted. Be sure to keep your plot open so Plot is active.

a. Open the **Plot and Table Variables** dialog box, and be sure the **List All Variables** check box is selected. {Remember this can be accessed by right clicking on the plot, or using the **Select variables** tool on the **SAAM II Toolbar**.}

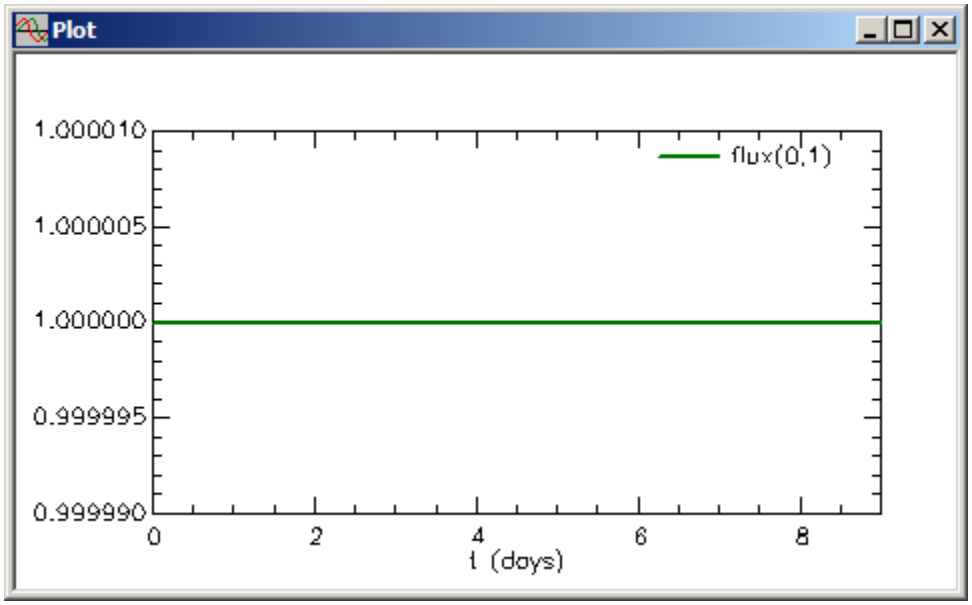
b. Click *k(0,1)* to move this to the **Current Selection** pane. The **Plot and Table Variables** box will appear as follows:



c. Click **Done**. The plot of *k(0,1)* will appear as follows (in linear mode):



d. Open the **Plot and Table Variables** dialog box, and select **flux(0,1)** as the **Current Selection**. When you click **Done**, the following plot of **flux(0,1)** should appear:



This is a constant indicative of the loss from Compartment **q1** being zero-order.

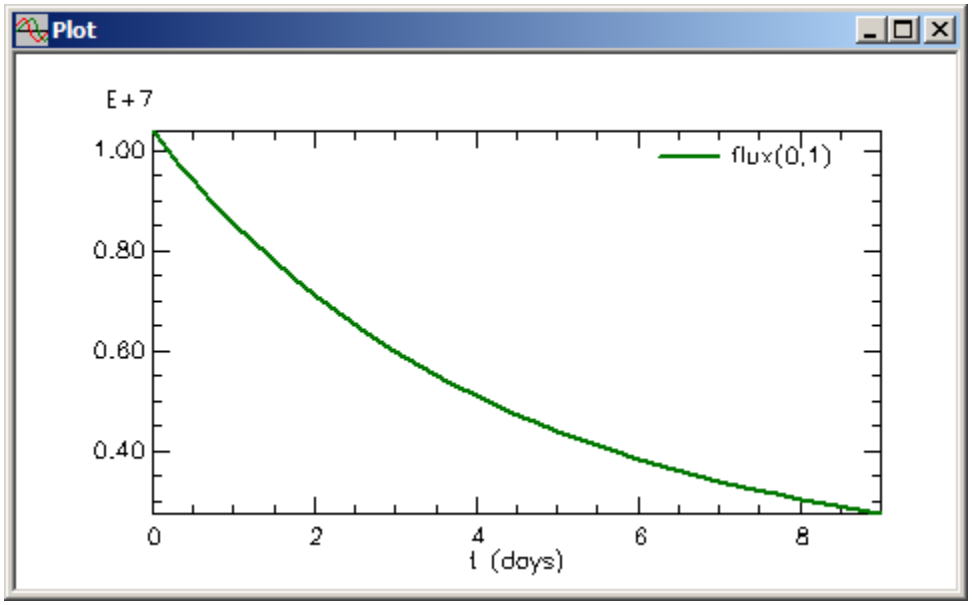
e. Close the **Plot** window.

7. Restore the original **study_0**.

a. Open the **Loss Attributes** dialog box associated with *k(0,1)*, and delete the equation "k(0,1)=k_loss/q1". Click Done.

b. Open the **Parameters** dialog box. Notice *k_loss* no longer appears; *k(0,1)* does. Select *k(0,1)*, and type "0.1" in the **Value** box. Click **Done**. This should restore the original settings in **study_0**.

c. Re-Solve the model. If you open the **Plot** window, since **flux(0,1)** was the previous plot, the **Plot** window will appear as follows:



The flux is no longer a constant since the loss is now a first-order process. If you wish, you can change the plot to **s1:plasma** to be sure you have restored the original solution for **study_0**.

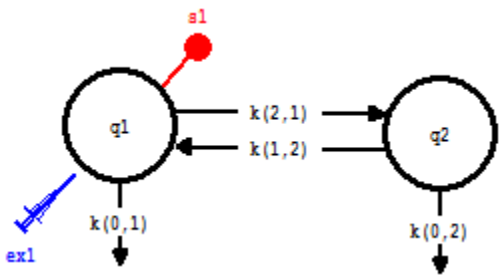
d. Close the **Plot** window.

8. Create a zero-order loss from Compartment **2**.

a. In the **SAAM II Toolbox**, click **Model**. The **Model** tools are now available.

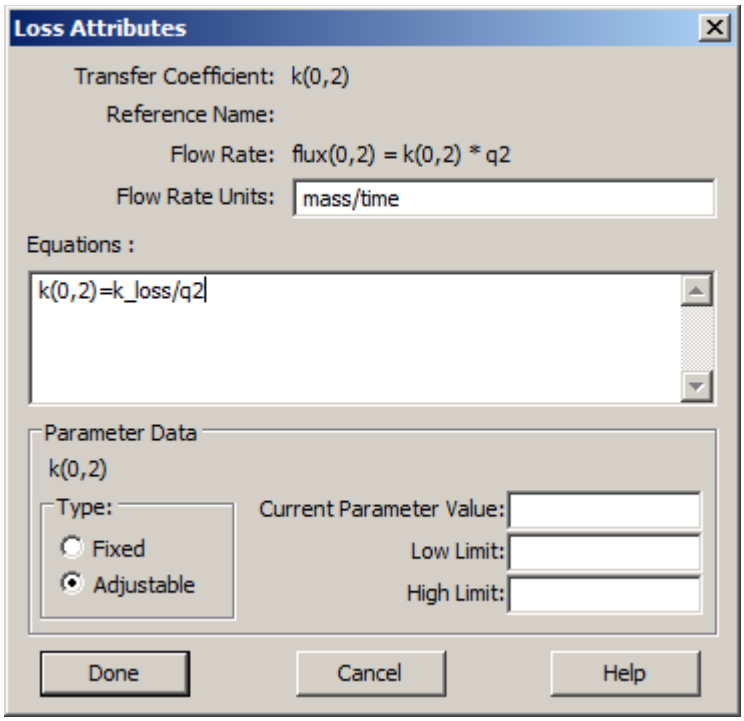
b. Create a loss *k(0,2)*.

c. In the **SAAM II Toolbox**, click **Experiment**. The model will appear as follows:



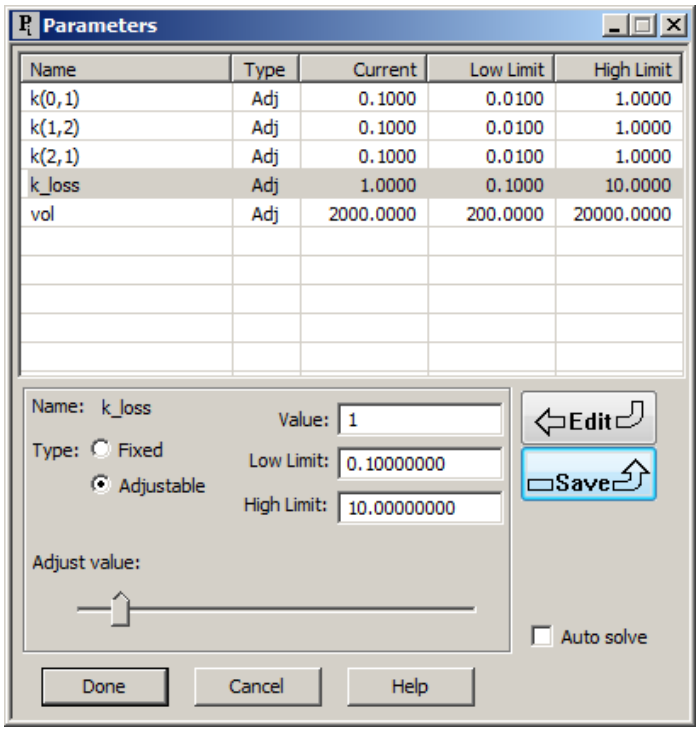
d. Double-click *k(0,2)* to open the **Loss Attributes** dialog box.

e. In the **Equation** pane, type "k(0,2)=k_loss/q2". The **Loss Attributes** dialog box will appear as follows:



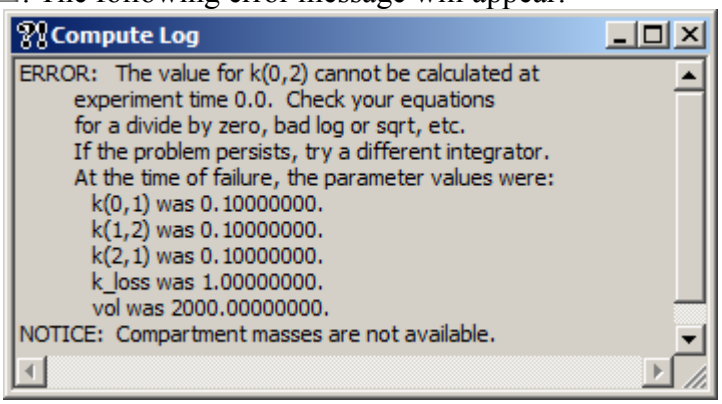
f. Click **Done**.

g. Open the **Parameters** dialog box, double-click *k_loss* to make it the current selection, and type "1" in the **Value** box. Click **Save**. The **Parameters** dialog box will appear as follows:



Click **Done**.

h. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve**  . The following error message will appear:



Close the **Compute Log**.

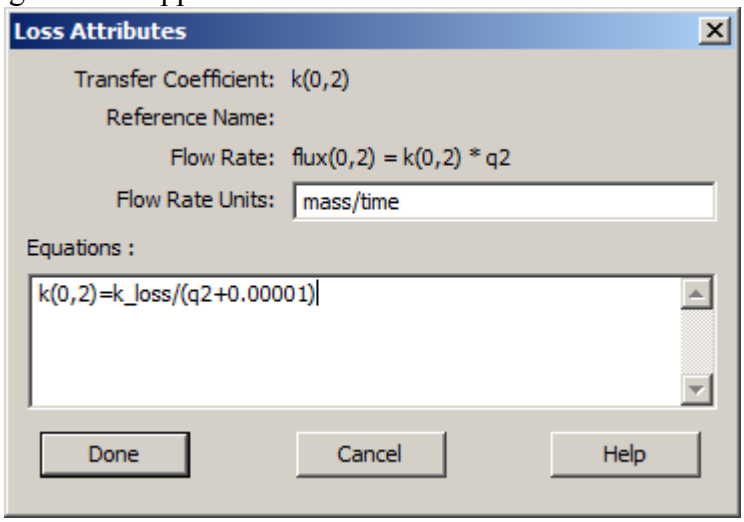
Division by zero. What is happening in this situation is that, at time zero, there is no mass in Compartment **q2**, i.e. q2(0) = 0. Remember *k(0,2)* has been defined by the equation k(0,2) = k_loss/q2. This cannot be evaluated at time zero. There are two solutions to this problem. The first solution is to change the equation for **k(0,2)** slightly. You know what the mass will be in the compartment because of the magnitude of the initial conditions in Compartment **q1**. Using a number much smaller, you can modify the equation for *k(0,2)* to, for example, k(0,2) =

k_loss/(q2+0.00001). The second solution is to introduce a very small bolus into Compartment **q2**, e.g. ex2 = 0.0001. Neither will have a significant effect on the solution.

i. Method 1: Modify the equation for *k(0,2)*.

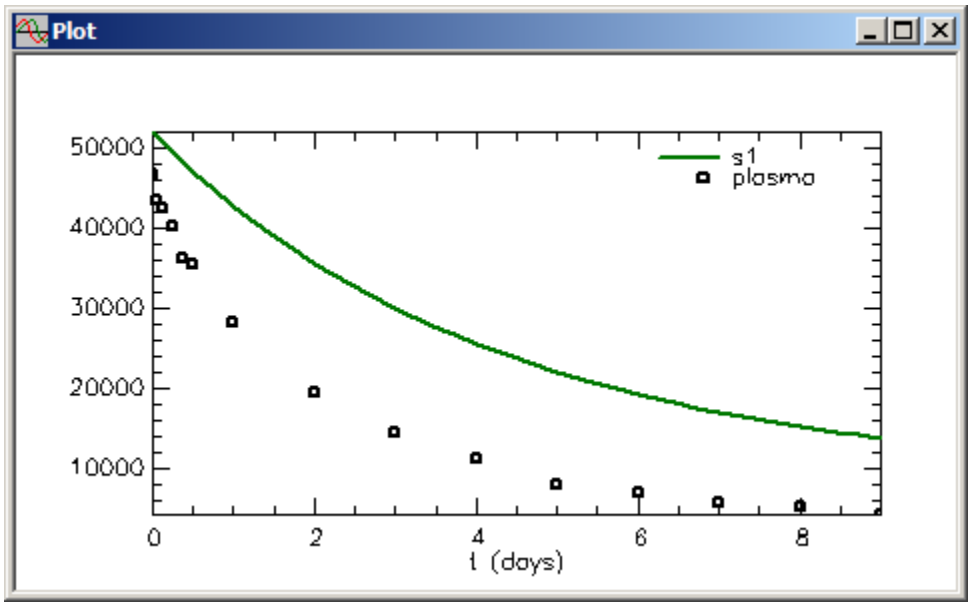
(1) Open the **Loss Attributes** dialog box associated with *k(0,2)*.

(2) Change the equation to read "k(0,2)=k_loss/(q2+0.00001). The **Loss Attributes** dialog box will appear as follows:



(3) Click Done.

(4) Re-Solve the model. This time, the solution will be successful, and a plot of **s1:plasma** will appear as follows:



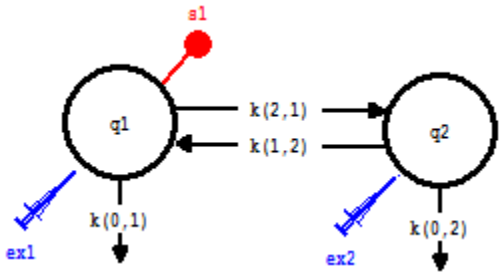
(5) Close the **Plot** window.

j. Method 2: Introduce a small bolus into Compartment **q2**.

(1) Open the **Loss Attributes** dialog box associated with *k(0,2)*, and re-enter the original equation "k(0,2)=k_loss/q2". Click **Done**.

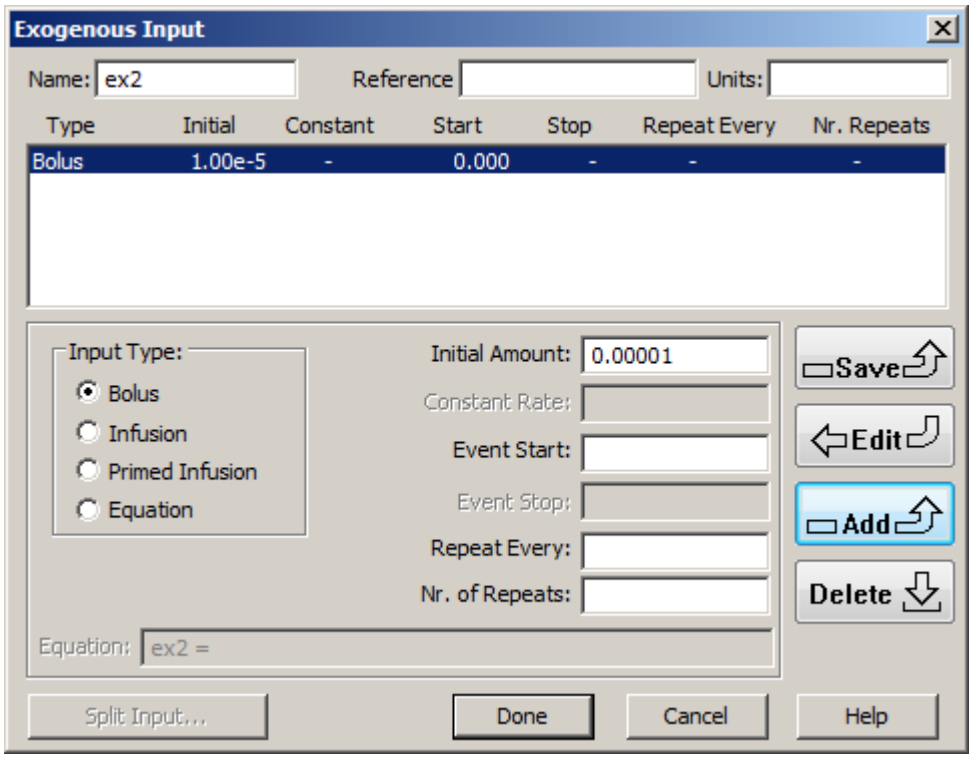
(2) In the **SAAM II Toolbox**, click **Input**.

(3) Click Compartment **q2** and then the **Drawing Canvas**. The input **ex2** will appear associated with Compartment **q2**. The model will appear as follows:



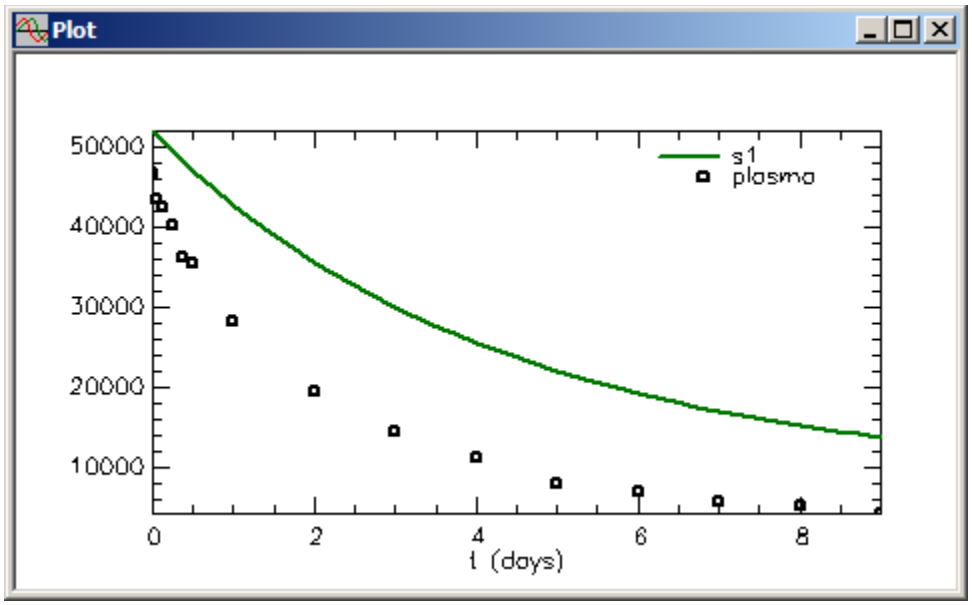
(4) Double-click **ex2** to open the **Exogenous Input** dialog box.

(5) Enter a bolus of 0.00001. The **Exogenous Input** dialog box should appear as follows:



(6) Click **Done**.

(7) Re-Solve the model. This time, the solution will be successful, and a plot of **s1:plasma** will appear as follows:



This plot is essentially identical with that obtained using the first method.

(8) Close the **Plot** window.

Zero-order losses. If you specify a zero-order loss from a compartment in your model where the initial conditions in that compartment are non-zero, the method described for *k(0,1)* is the method to use. If you specify a zero-order loss from a compartment whose initial conditions are zero, you must use either of the two methods described above to eliminate the problem of division by zero. Either method works fine – it is a matter of personal preference.

Quit the **SAAM II Compartmental** application. Do not save the changes to **study_0**.

Part 2. Specifying parameters and variables in the Equations window

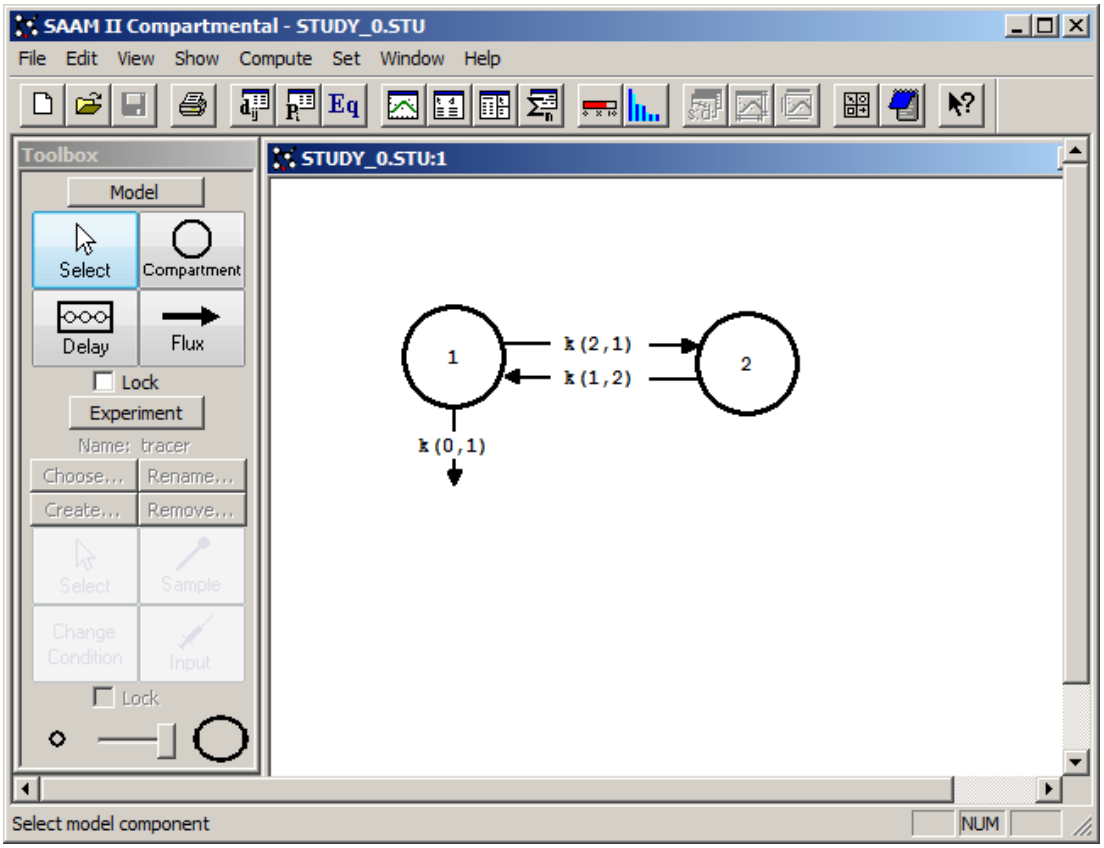
This part of the tutorial will show you have to specify parameters in the **Equations** window. You have seen how equations involving parameters can be written in the **Transfer** or **Loss Attributes** dialog boxes. Writing such equations in the **Equations** window is another option in SAAM II. In pharmacokinetic studies, this is how you would enter the pharmacokinetic parameters that are functions of the model parameters; examples are clearances and volumes.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

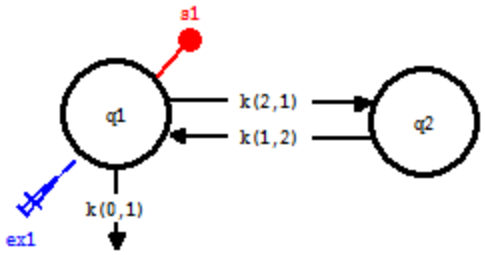
2. Open the **SAAM II Compartmental** study file **study_0**.

   a. The file **study_0.stu** should appear in the file list; if it does not, find the folder where you put this file.

   b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as shown below:



3. View the model and the experiment on the model. In the **SAAM II Toolbox**, click **Experiment**. The model of the experiment will appear as follows:



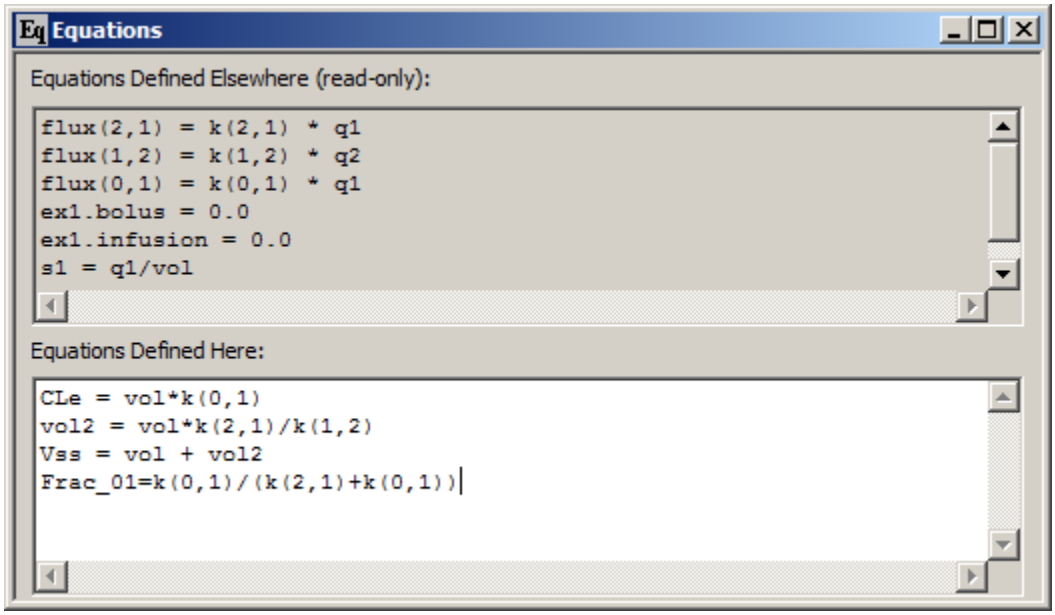
4. In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar,** click **Equations** Eq. The **Equations** dialog box will open.

   a. Enter the following equations in the **Equations Defined Here** pane:

   CLe = vol*k(0,1)
   vol2 = vol*k(2,1)/k(1,2)
   Vss = vol + vol2
   Frac_01=k(0,1)/(k(2,1)+k(0,1))

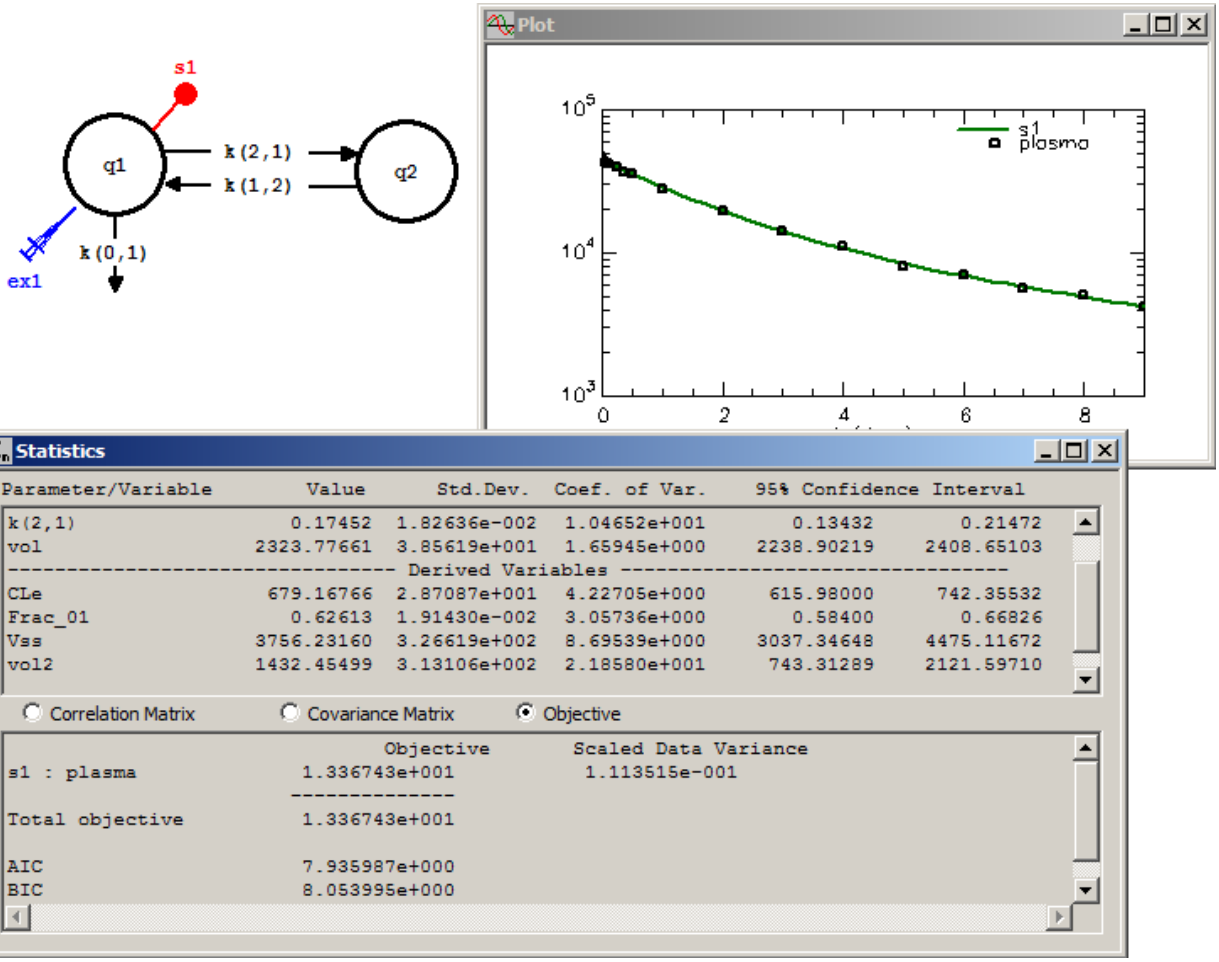
   CLe is the clearance of material from Compartment **2**. *vol2* is the volume of Compartment **2** assuming the concentrations in Compartments **1** and **2** are the same. *Vss* is the total system volume, or equivalent volume of distribution. *Frac_01* is the fraction of material in Compartment **1** that is irreversibly lost.

   When you have finished, the **Equations** dialog box should appear as follows:



   b Close the **Equations** dialog box.

5. Fit the model to the data, and view the solution and statistics. The results are summarized in the following:



The "Fit" is quite good as are the statistics. Note statistical information on the parameters you defined in the **Equations** dialog box appear as **Derived Variables** in the **Parameter/Variable** pane of the **Statistics** window.

5. Close the **Plot** and **Statistics** windows.

Quit the **SAAM II Compartmental** application. Do not save the changes to **study_0**.

Part 3. Re-parameterizing the two-compartment model

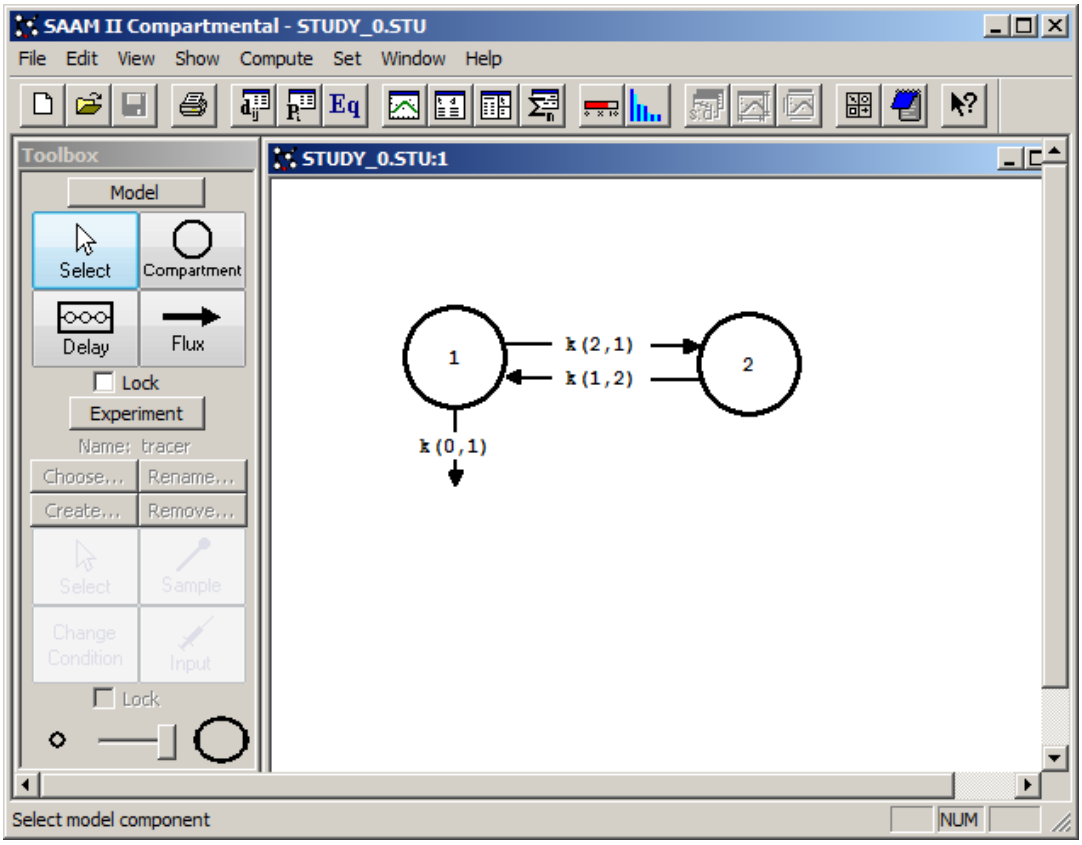
It is sometimes desirable to reparameterize a model so that the desired pharmacokinetic parameters become the model parameters. In this part of the tutorial, the two-compartment model with loss from the plasma compartment will be reparameterized.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

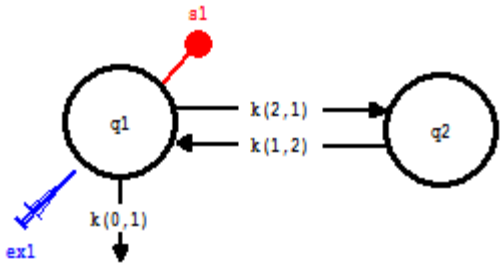
2. Open the **SAAM II Compartmental** study file **study_0**.

   a. The file **study_0.stu** should appear in the file list; if it does not, find the folder where you put this file.

   b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as shown below:



3. View the model and the experiment on the model. In the **SAAM II Toolbox**, click **Experiment**. The model of the experiment will appear as follows:



4. Re-specify the model parameters.

   The model parameters as the model is currently configured are *vol*, *k(2,1)*, *k(1,2)* and *k(0,1)*. The model will be reparameterized in terms of clearances. The equations which will be used are:

   CLe = vol*k(0,1)
   CLi = vol*k(2,1)
   vol2 = vol*k(2,1)/k(1,2)
   Vss = vol + vol2

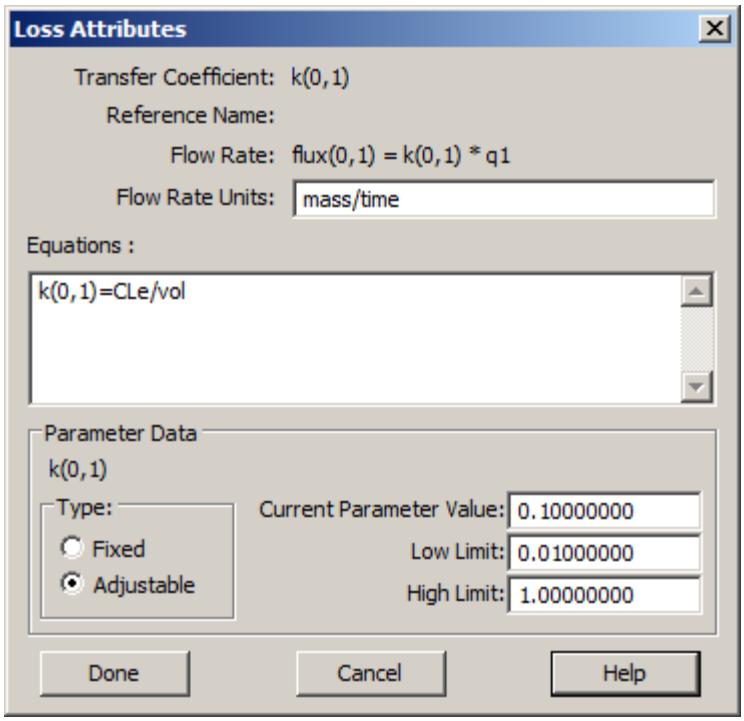
   In SAAM II, these will be rewritten:

   k(0,1) = CLe/vol
   k(2,1) = CLi/vol
   k(1,2) = CLi/vol2

   The result will be that the model parameters become *CLe*, *CLi*, *vol* and *vol2*.

   a. In the **Experiment**, double-click *k(0,1)* to open the **Loss Attributes** dialog box.

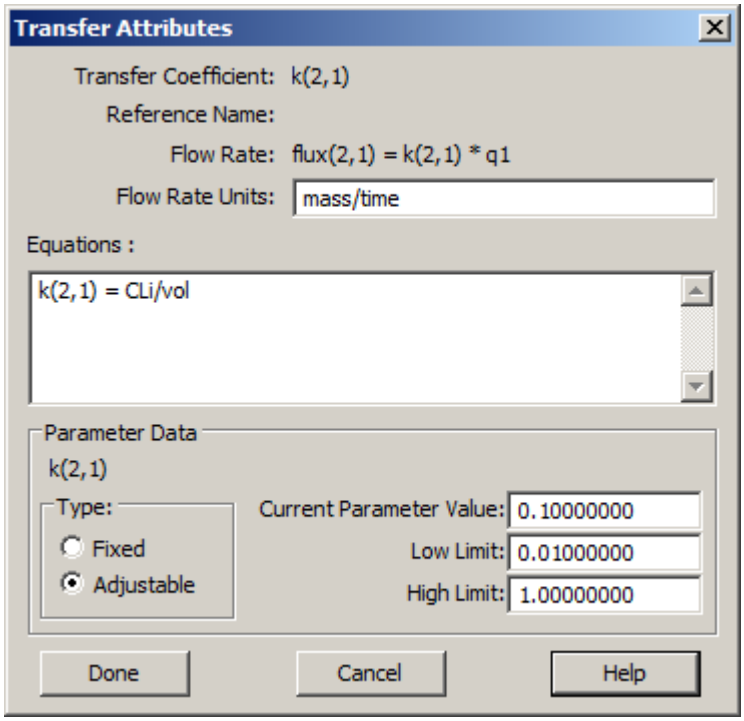
   b. In the **Equations** pane, type "k(0,1)=CLe/vol". The **Loss Attributes** dialog box will appear as follows:



c. Click **Done**.

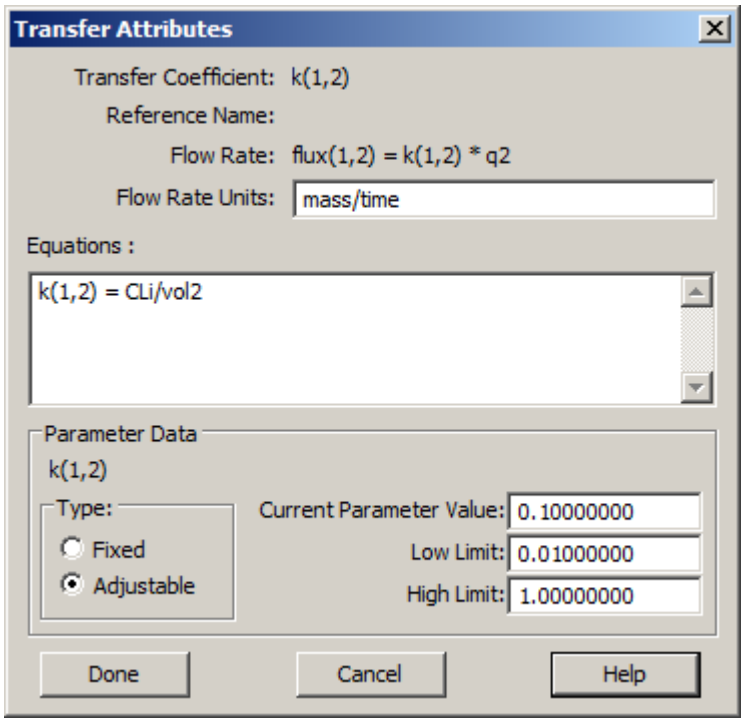
d. Double-click *k(2,1)* to open the **Transfer Attributes** dialog box.

e. In the **Equation** pane, type "k(2,1) = CLi/vol". The **Transfer Attributes** dialog box will appear as follows:



f. Click **Done**.

g. Double-click k(1,2) to open the **Transfer Attributes** dialog box. In the **Equations** pane, type "k(1,2) = CLi/vol2". The **Transfer Attributes** dialog box will appear as follows:

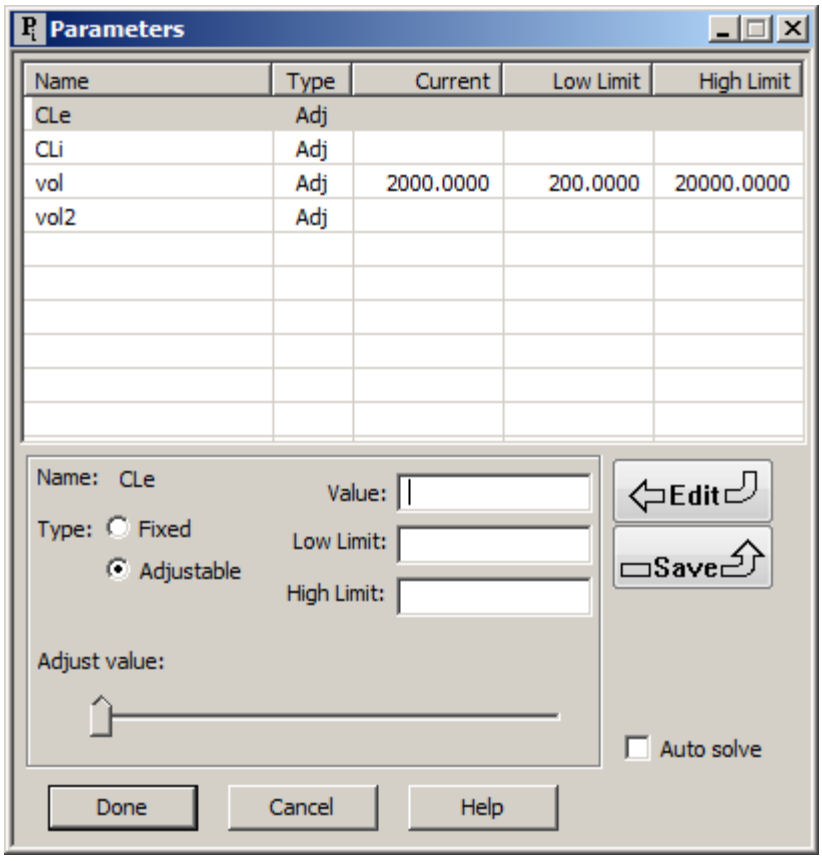


h. Click **Done**.

At this point, your model has been reparameterized.

4. Enter the parameter values.

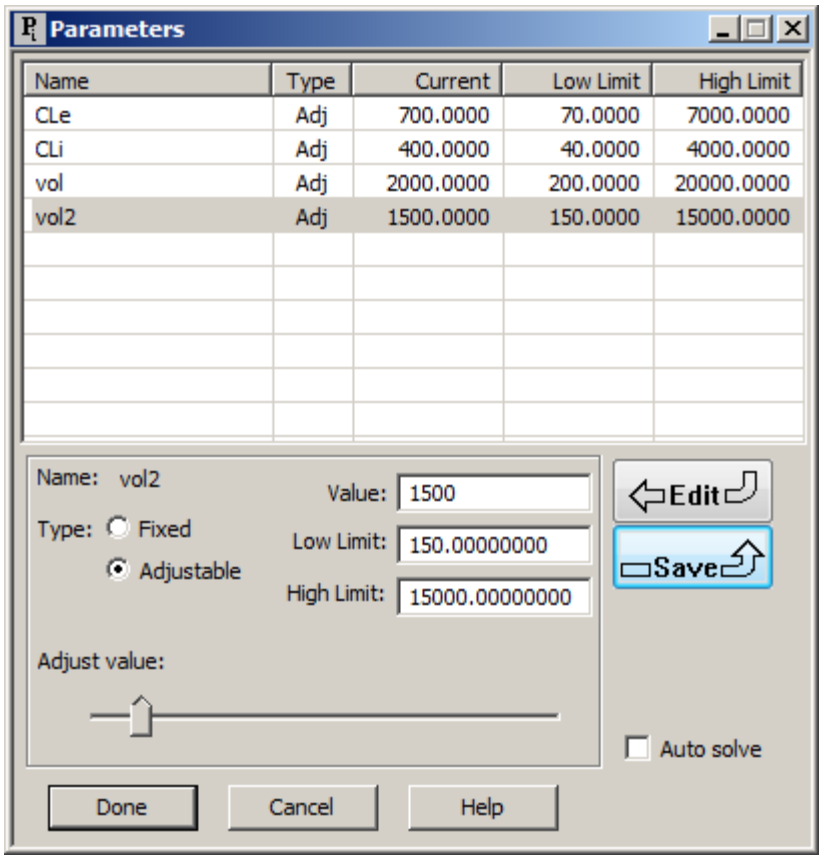
a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters**  . The **Parameters** dialog box will open as shown below:



You need to provide initial estimates for *CLe*, *CLi*, *vol* and *vol2*.

Note that *vol* is the only parameter that remains from the original setup and retains its initial estimate, change as appropriate.

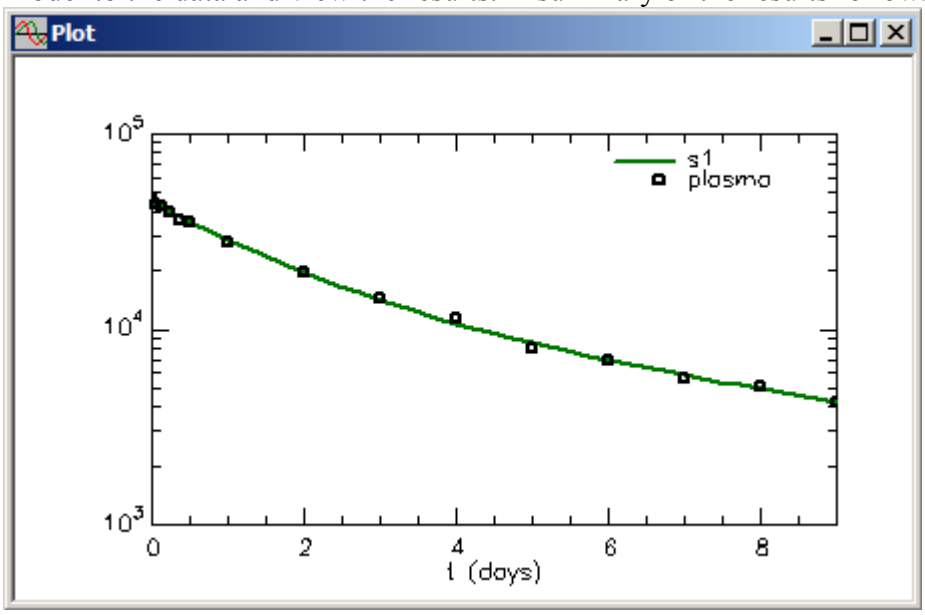
b. An initial estimate for *CLe* is 700, for *CLi* is 400, for *vol* is 2000 and *vol2* is 1500. When you enter these values, the **Parameters** dialog box should appear as follows:

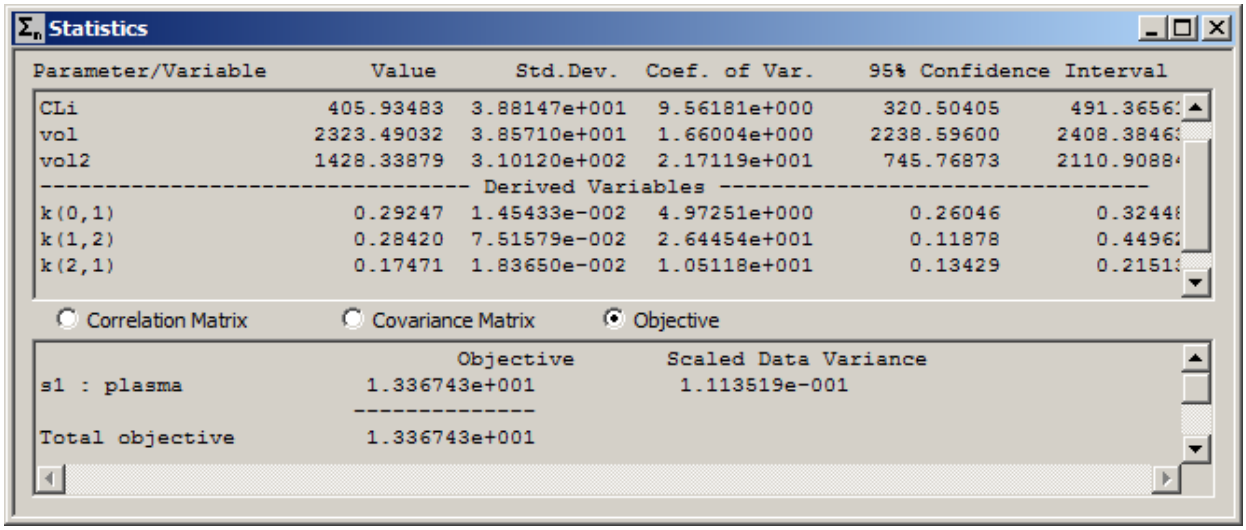


Click **Done** to close the **Parameters** dialog box.

6. Solve the model and view the solution. The initial parameter estimates are reasonable so you can proceed to Fit the model to the data.

7. Fit the model to the data and view the results. A summary of the results follows:





Model re-parameterization. In the above situation it is quite easy to parameterize the model in terms of the pharmacokinetic parameters. The results here should be essentially the same as the part in this tutorial where these parameters were defined in the Equations dialog box. Notice in this case the *k(i,j)* become the derived variables.

For the one-compartment model, the one-compartment model with absorption and the three-compartment model, re-parameterization is relatively straightforward. However, in instances when there is a single-input multiple-output study (e.g. plasma and urine samples), when the model has more than four compartments, or when the model is nonlinear, re-parameterization can be a very tricky bookkeeping exercise, and should be conducted with caution.

7. Close the **Plot** and **Statistics** window.

Quit the **SAAM II Compartmental** application. Do not save the changes to **study_0**.

Part 4. Work with parameter high and low limits

In the **Parameters** dialog box, for each adjustable parameter you must specify a **Low** and **High Limit**. SAAM II uses this information when you Fit your model to your data. It interprets the values for the **Low** and **High Limit** as a measure of the confidence you have in your knowledge of a particular parameter. SAAM II is very forgiving in these values, but if a particular limit strays too far from the **Value**, it can affect the statistical results following a Fit.

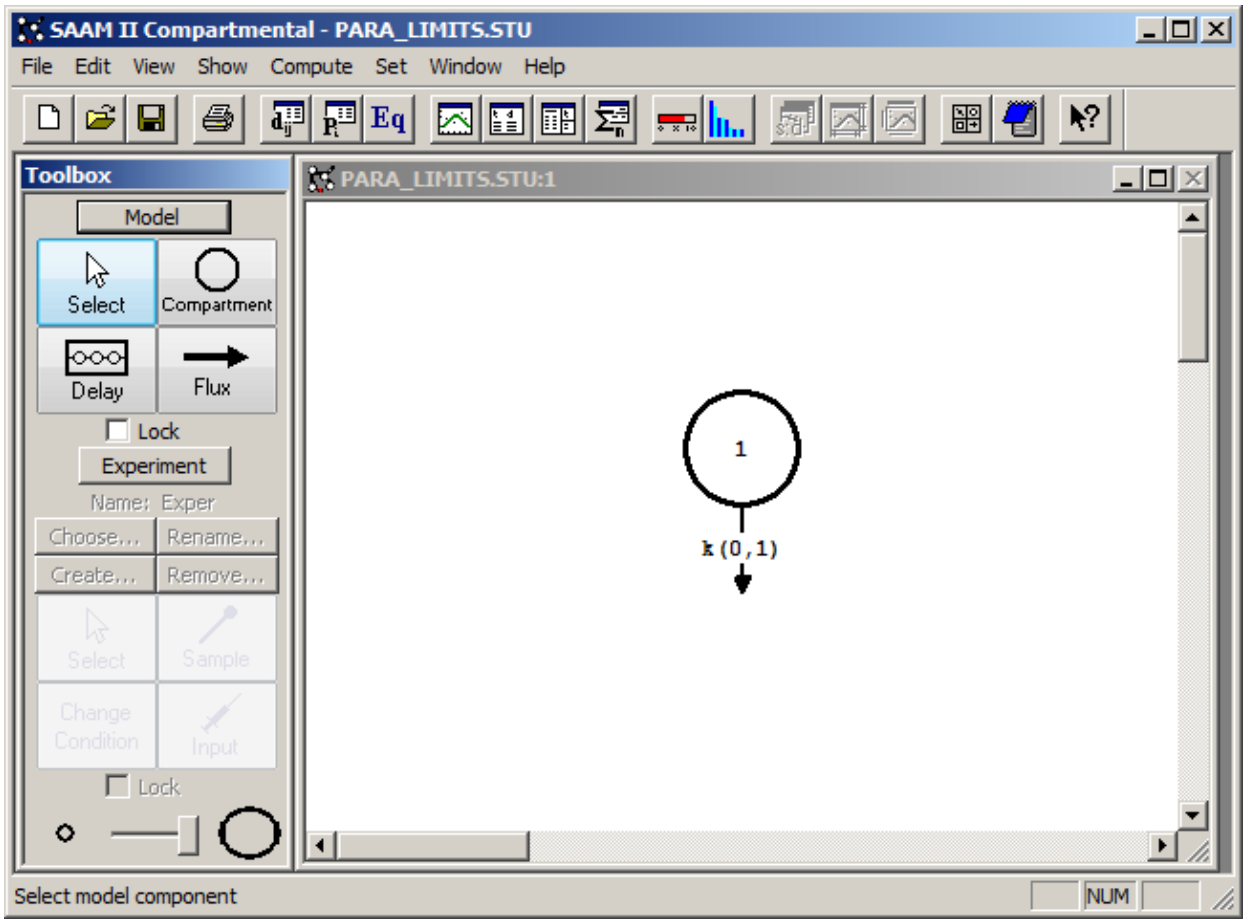
This tutorial will illustrate what can happen using a simple one-compartment model with two parameters, a loss *k(0,1)* and a volume parameter *vol*.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

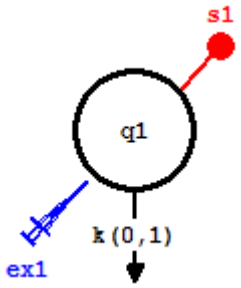
2. Open the **SAAM II Compartmental** study file **Para_Limits**.

   a. The file **Para_Limits.stu** should appear in the file list; if it does not, find the folder where you put this file.

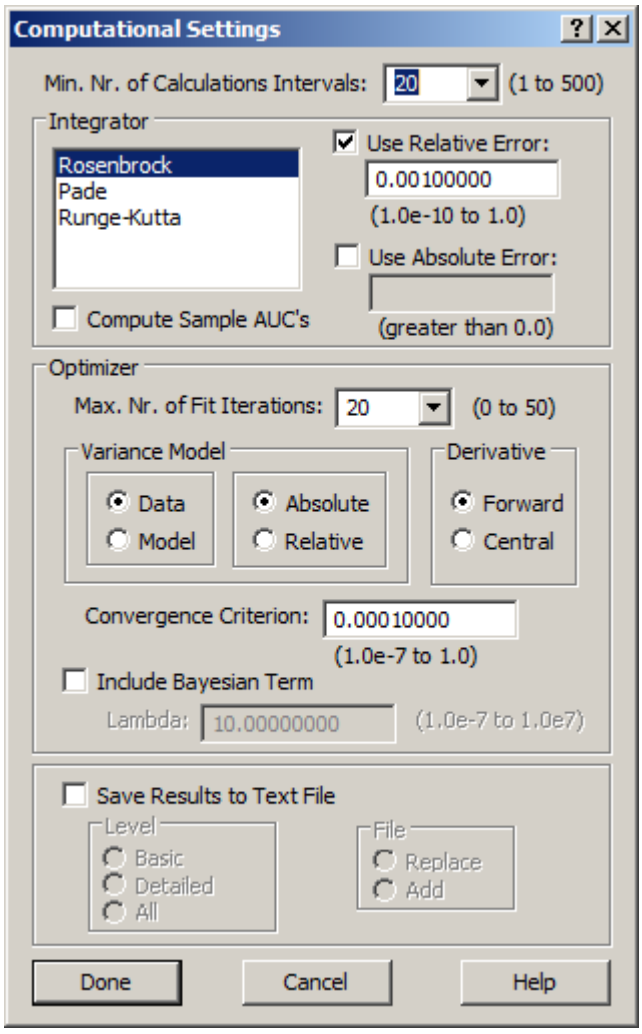
   b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as shown below:



3. View the model and the experiment on the model. In the **SAAM II Toolbox**, click **Experiment**. The model of the experiment will appear as follows:



This study file contains a set of monoexponentially decaying data. The default weighting value has been changed from the default "data-relative" to "data-absolute". This can be verified by viewing the **Computational Settings** dialog box which will as appear as shown below:



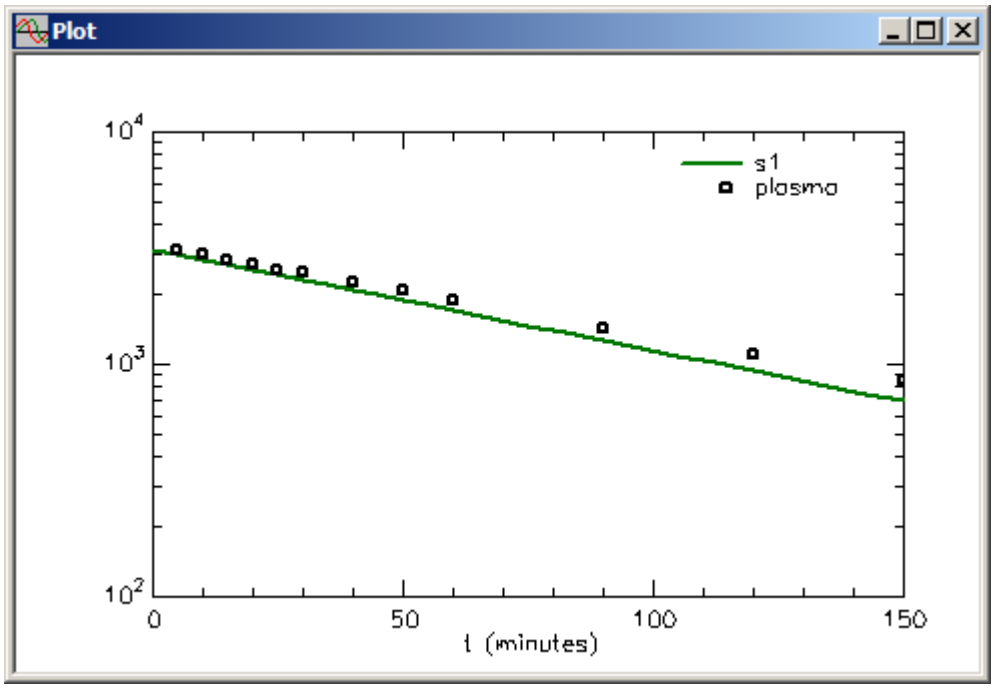
4. Solve the model and view the solution

a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve**  .

b. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot**  . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is not selected.

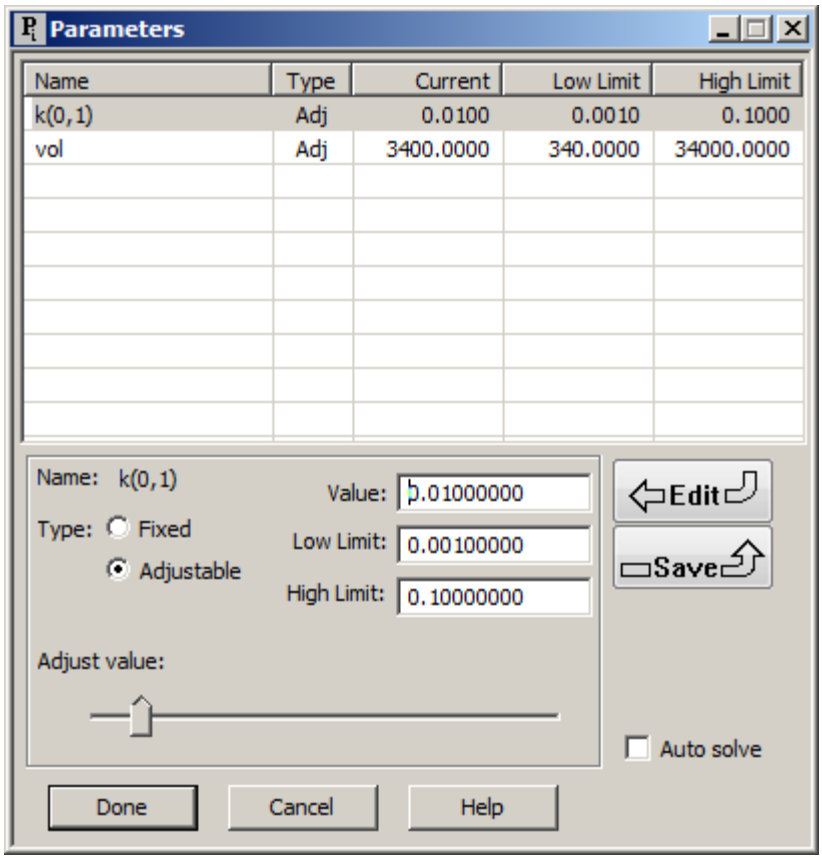
c. Click **s1:plasma** to move this to the **Current Selection** pane.

d. Click **Done**. If the plot is not in semilog, in the **View** menu, click **Semilog**. The plot will appear as follows:



e. Close the **Plot** window.

5. Perform a series of Fits with the **Low** and **High Limit** of *k(0,1)* set at different values. The **Low** and **High Limits** of the parameters in **Para_Limits** have been set using the default values in SAAM II. The **Parameters** dialog box will appear as follows:



Perform a series of Fits with the **Low** and **High Limit** of *k(0,1)* set at the values shown in the following table. The left-hand columns are the **Low** and **High Limit** for *k(0,1)*. The columns "k(0,1)(CoeffVar)" and "vol(CoeffVar)" are the final parameter values and coefficients of variations respectively. The column "Obj" is the value of the objective function following the Fit.

k(0,1) Limits	k(0,1)(CoeffVar)	vol(CoeffVar)	Obj
[0.001,0.1]			
[0.005,0.05]			
[0.0001,1.0]			
[1.0e-07,100]			
[0,1000]			
[0,0.1]			

You should fill in this table starting with the default **Low** and **High Limit** of *k(0,1)* respectively equal to 0.001 and 0.1. After the first fit, your table should appear as follows:

k(0,1) Limits	k(0,1)(CoeffVar)	vol(CoeffVar)	Obj
[0.001,0.1]	0.0089(7.4)	3288(4.4)	10.65
[0.005,0.05]			
[0.0001,1.0]			
[1.0e-07,100]			
[0,1000]			
[0,0.1]			

You should **reset the initial estimates** of the parameters to their original values of 0.01 and 3400 respectively, and set the **Low** and **High Limits** for *k(0,1)* equal to 0.005 and 0.05 respectively for the second Fit. You should continue in this fashion until you have completed the table which should appear approximately as follows:

k(0,1) Limits	k(0,1)(CoeffVar)	vol(CoeffVar)	Obj
[0.001,0.1]	0.0089(7.4)	3288(4.4)	10.65
[0.005,0.05]	0.0089(7.4)	3288(4.4)	10.65
[0.0001,1.0]	0.0089(7.4)	3288(4.4)	10.65
[1.0e-07,100]	0.0089(7.9)	3287(4.5)	10.65
[0,1000]	0.0089(14.2)	3288(5.3)	10.65
[0,0.1]	0.0089(7.4)	3288(4.4)	10.65

After each Fit, you can check the plot of **s1:plasma**. As expected, it will not change since the parameter values do not change, as noted above.

What you should observe in this exercise is that, when you can Fit successfully, the **Low** and **High Limits** will have little or no effect on the parameter estimates themselves, or the value of the objective function. What will be effected are the estimated coefficients of variations. However, in this instance, the limits have to move far away from the Value before this becomes noticeable. Thus SAAM II is, in general, robust.

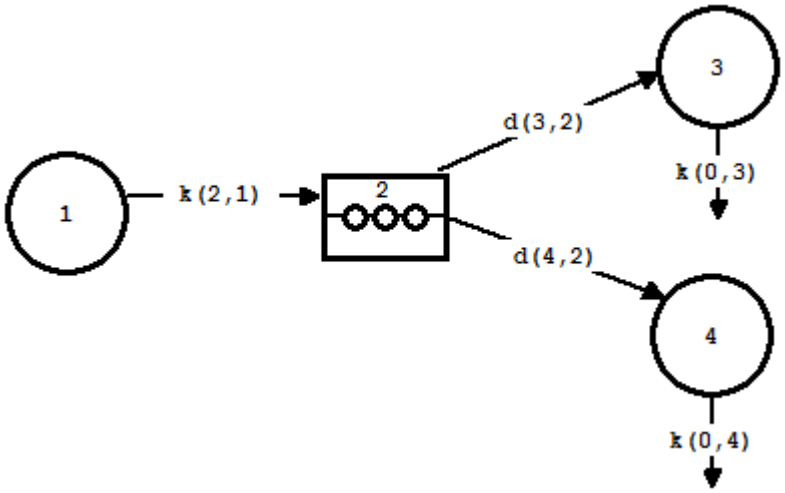
Understanding the effect of high and low parameter limits becomes crucial is when you have a large model with many parameters, some of which may be better estimated from the data than others. Here setting the **Low** and **High Limits** can have a dramatic effect on the final results.

Close all open windows and dialog boxes.

Quit the **SAAM II Compartmental** application. Do not save the changes to **Para_Limits**. Some additional comments on parameter limits are necessary.

The previous tutorial illustrated a simple case of setting the parameter limits on one parameter. In linear compartmental models, SAAM II is quite forgiving in setting these limits. There are instances when limits must be set, or instances when realistic limits must be set in order to achieve a successful fit of the model to the data.

An example of an instance in which a limit must be set rather than using the default value is the following. Suppose you have a delay in your model where there are two losses from the delay. This is illustrated in the following model:



There are two possible routes by which material can leave Delay **2**. Remember in SAAM II, loss from a delay is a fraction, i.e. a fraction of the material in the delay along the possible routes of loss. When there is only one loss, the fraction is 1. In this situation above, d(3,2) + d(4,2) = 1, and both *d(3,2)* and *d(4,2)* must lie between 0 and 1. A convenient way of doing the bookkeeping is the following. You can define

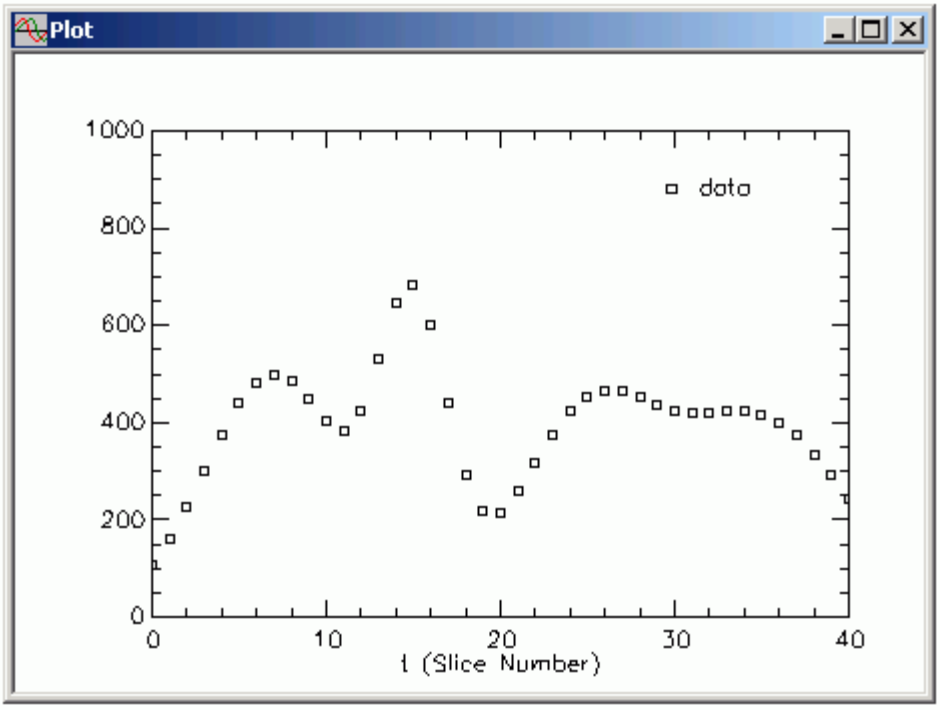
$$d(3,2) = frac$$

and

$$d(4,2) = 1 - frac$$

frac becomes a parameter for which a **Value**, **Low Limit** and **High Limit** must be specified. If you enter, for example, 0.5 in the **Value** box and use the default limits, the **Low Limit** will be 0.05 which is okay, but the **High Limit** will be 5 which is not okay since if in the process of fitting, *frac* goes above 1, *d(4,2)* will become negative and Conservation of Mass will be violated. Thus you must determine **Low** and **High** limits for *frac* that lie between 0 and 1.

Another example of where setting reasonable parameter limits rather than using the default values is the following example which will use the **SAAM II Numerical** application. The data to be analyzed are shown in the following plot:



These data are cholesterol concentrations in 40 subtractions of high density lipoprotein. The problem is to describe these data by a Sum of Gaussians using the **SAAM II Numerical** application.

A Gaussian is a function of the form

$$f(t)=\frac{1}{\sqrt{2\pi}\sigma}\exp\left[-\frac{1}{2}\left(\frac{t-\mu}{\sigma}\right)^2\right] \quad -\infty<t<\infty$$

where, in this expression, μ is called the mean and σ the standard deviation. It is known that the area under this so-called bell shaped curve is unity, i.e.

$$\int_{-\infty}^{\infty} f(t)dt=1.$$

The mean μ determines the location while the standard deviation σ provides a measure of the "sharpness" of the gaussian. That is, the smaller the σ, the narrower the peak.

A sum of four Gaussians will be used to describe these data. In SAAM II, a single Gaussian is written:

A1/(SA1*2.51)*exp(-((t-MA1)^2)/(2*SA1^2))

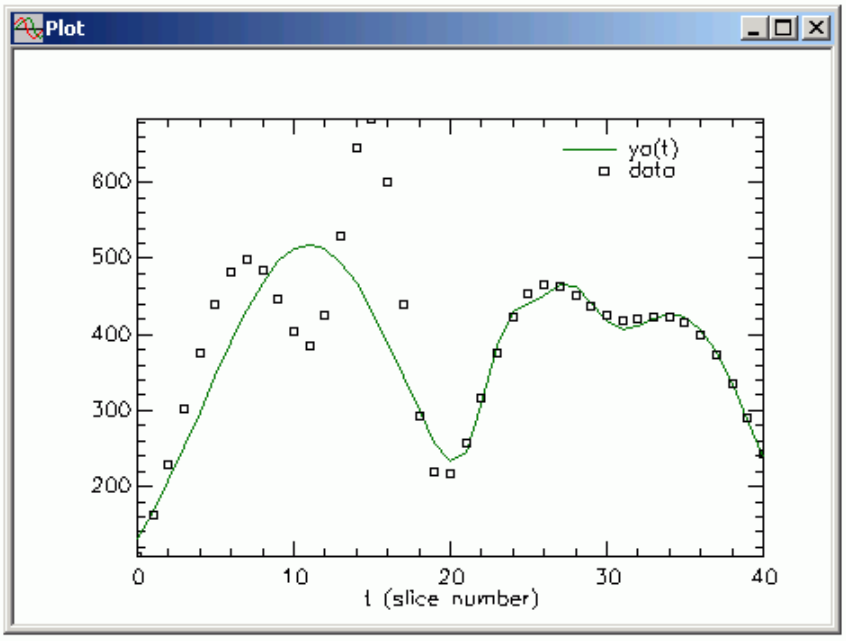
Where *A1* is a parameter characterizing the magnitude of the contribution of the Gaussian. *SA1* and *MA1* are the standard deviation and mean of the gaussian. 2.51 approximates $\sqrt{2\pi}$. Thus

the single Gaussian term has three parameters, *A1*, *SA1* and *MA1*. Thus in the sum of four Gaussians, there will be 12 parameters, and the expression will be:

ya(t) = A1/(SA1*2.51)*exp(-((t-MA1)^2)/(2*SA1^2)) + A2/(SA2*2.51)* exp(-((t-MA2)^2)/(2*SA2^2)) + A3/(SA3*2.51)*exp(-((t-MA3)^2)/(2*SA3^2)) + A4/(SA4*2.51)*exp(-((t-MA4)^2)/(2*SA4^2))

Initial estimates for the four means, *MA1*, *MA2*, *MA3* and *MA4* can be obtained by looking at the data and estimating where the peaks may lie. Similarly initial estimates for the four standard deviations can be obtained again just by looking at the sharpness of the peaks.

Initial estimates were obtained visually, and default values for the **Low** and **High Limits** have been used. When the model is fitted to the data (with the FSD option), the best fit is shown as follows:



Obviously this is not satisfactory. Neither are the statistics which are shown below:

Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
A1	8626.70801	4.16023e+002	4.82250e+000	7775.84498	9477.57104
A2	1771.89568	5.56438e+003	3.14035e+002	-9608.53487	13152.32624
A3	624.24291	3.21665e+003	5.15289e+002	-5954.55182	7203.03764
A4	5452.71015	3.37144e+003	6.18306e+001	-1442.66510	12348.08540
MA1	10.97825	3.87261e-001	3.52753e+000	10.18621	11.77029
MA2	26.78137	4.50542e+000	1.68230e+001	17.56675	35.99599
MA3	23.32592	2.22153e+000	9.52388e+000	18.78238	27.86946
MA4	34.50228	2.97499e+000	8.62259e+000	28.41774	40.58681

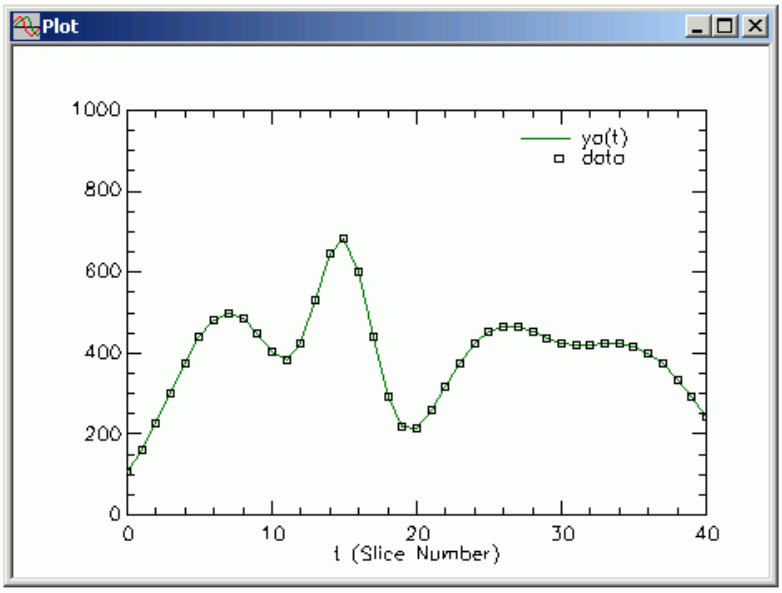
Correlation Matrix Covariance Matrix Objective

	Objective	Scaled Data Variance
ya(t) : data	9.043484e+000	3.159819e+000
Total objective	9.043484e+000	
AIC	5.757754e+000	
BIC	6.029418e+000	

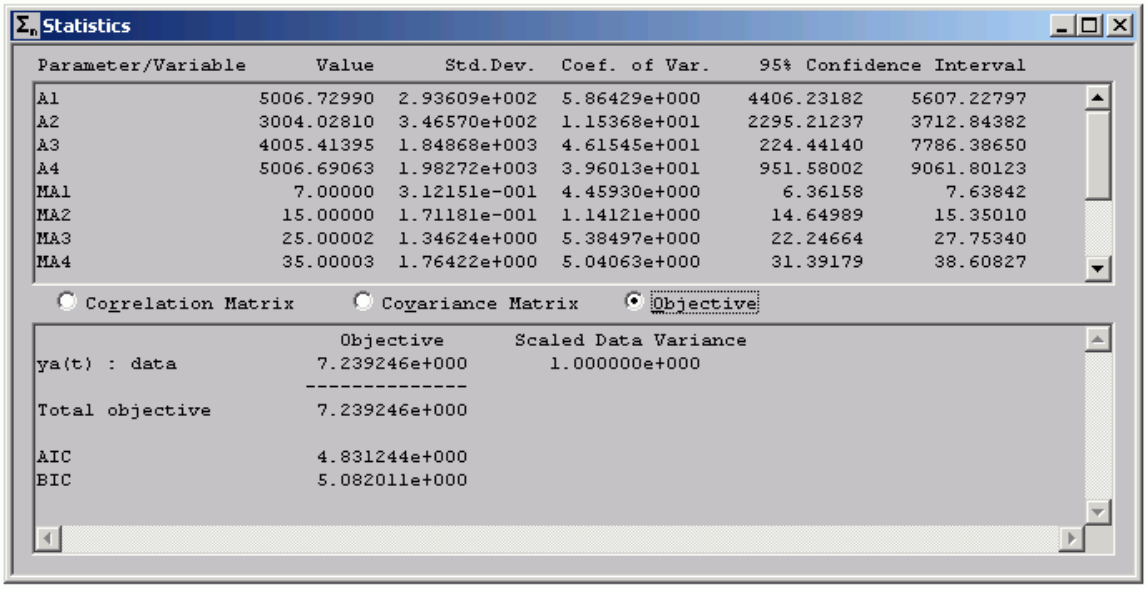
What is happening is that the limits set on the means and standard deviations are not realistic using the default values. For example, the **High Limits** for all the means are well beyond the data which end at "40". Visually, more realistic estimates for the **Low** and **High Limits** for both the means and standard deviations can be obtained visually.

You can see the limits for the means and standard deviations are much closer to their initial estimated **Values**. The default limits on the Ai are okay since these are linear parameters and are not that sensitive to the limits.

Using these initial estimates and limits, if you fit the model to the data (with the FSD option), you will obtain the following fit:



The statistics are also satisfactory:



This example thus illustrates the need to be aware of setting limits on your adjustable parameters, and to pay attention to how they may need to change as you go through your modeling exercise.

Part 5. Using the Bayesian option to incorporate prior knowledge

What happens if you have prior information about a parameter in your model? It may be the case, for example, a relationship between two parameters has been developed as a result of research conducted elsewhere. How can you incorporate this knowledge in your model?

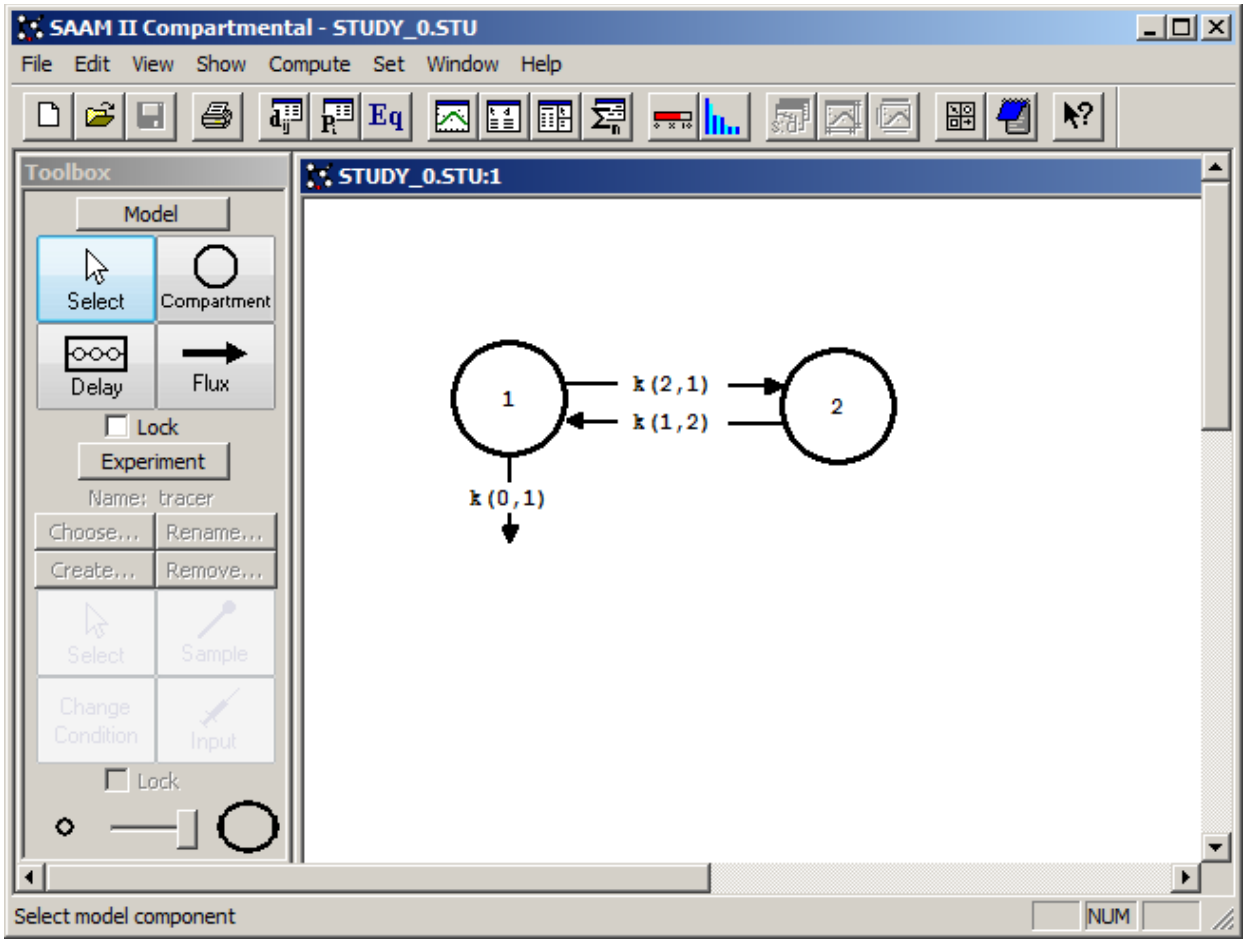
One way you can incorporate priori knowledge is to use the Bayesian option in SAAM II. This part of the tutorial will illustrate how this can be done.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

2. Open the **SAAM II Compartmental** study file **study_0**.

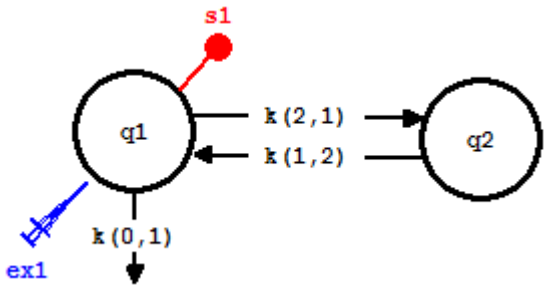
   a. The file **study_0.stu** should appear in the file list; if it does not, find the folder where you put this file.

   b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as shown below:

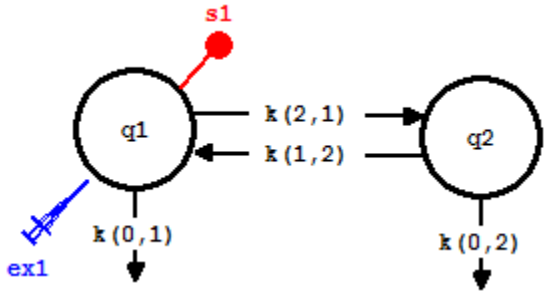


3. View the model and the experiment on the model, and change the model.

   a. In the **SAAM II Toolbox**, click **Experiment**. The model of the experiment will appear as follows:



   b. Modify the **model** by adding a loss from Compartment **2**. Your model for the **experiment** should appear as follows:

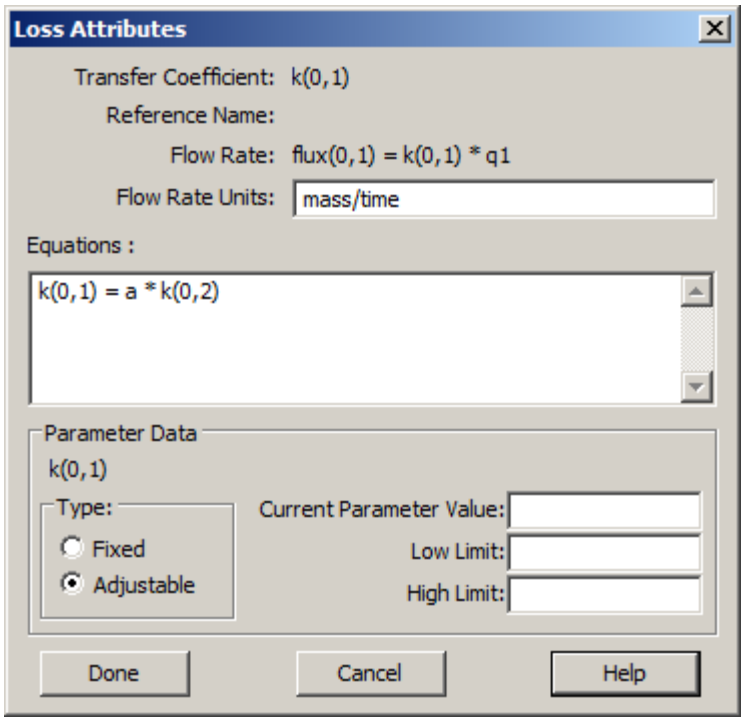


4. Specify a relationship between *k(0,1)* and *k(0,2)*.

   Suppose from the literature there is a known relationship between *k(0,1)* and *k(0,2)*. Suppose it is known that *k(0,1)* is approximately twice *k(0,2)*. How can this be incorporated in the model?

   a. Double-click *k(0,1)* to open the **Loss Attributes** dialog box.

   b. In the **Equations** pane, type "k(0,1) = a * k(0,2)". The **Loss Attributes** dialog box will appear as follows:



c. Click **Done**. A new parameter, *a*, has been added to the model.

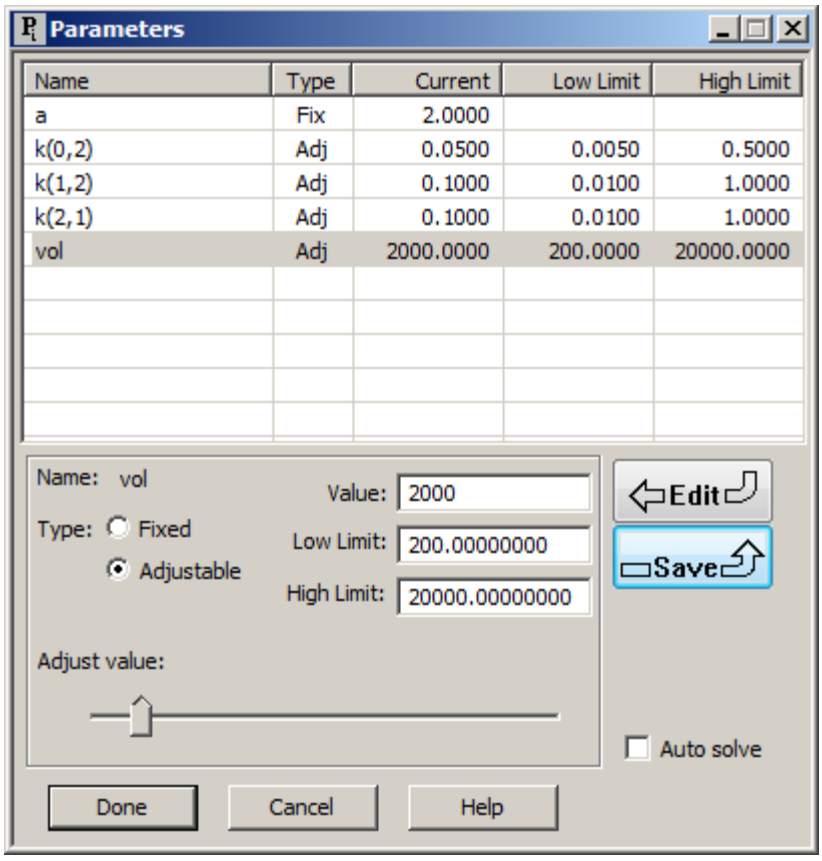
5. Enter parameter values, and Solve and Fit the model to the data.

   a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters**  . The **Parameters** dialog box will open.

   b. Be sure *a* is selected. Set *a* as a fixed parameter, type "2" in the **Value** box, and click **Save**.

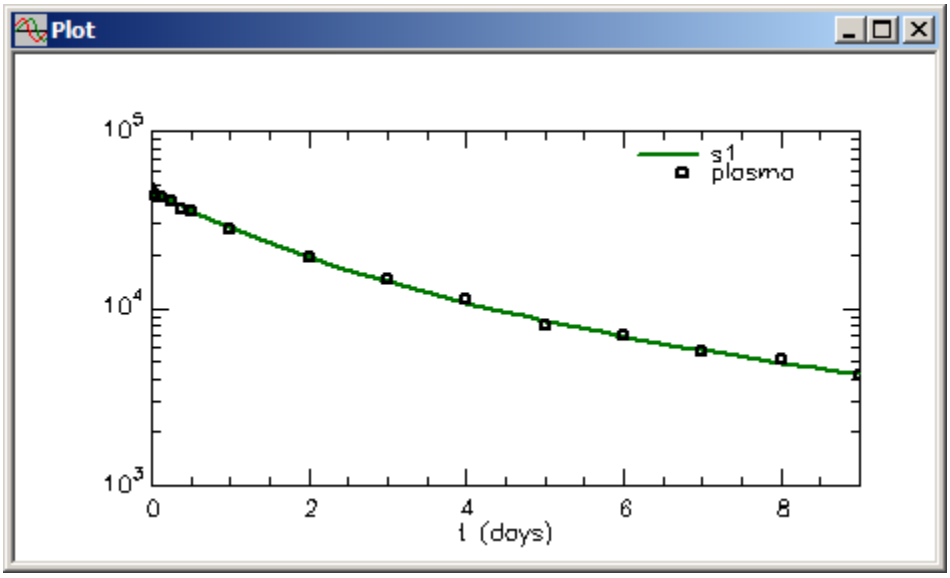
   c. Double-click *k(0,2)* to select it. Type "0.05" in the **Value** box, and click **Save**.

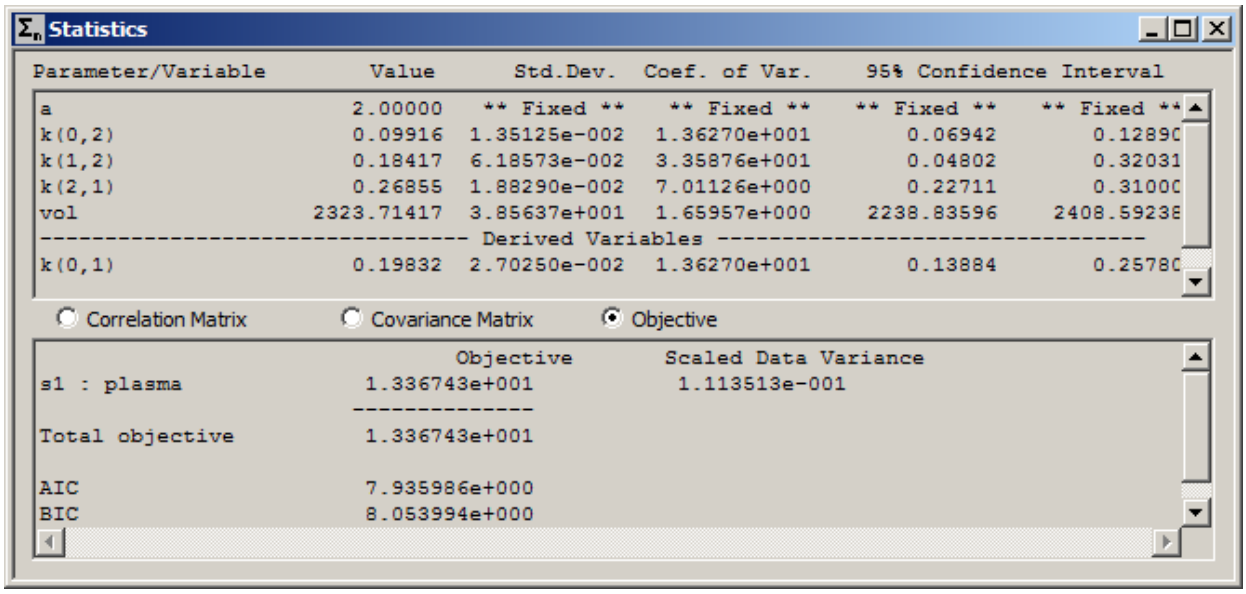
   d. Enter the other parameters as shown below: appear as follows:



d. Click **Done**.

6. Solve the model. The initial parameter value, while not great, are sufficient to proceed with a "Fit". Fit the model to the data and view the solution. A summary of the "Fit" is shown in the following:





Close the **Plot** and **Statistics** windows.

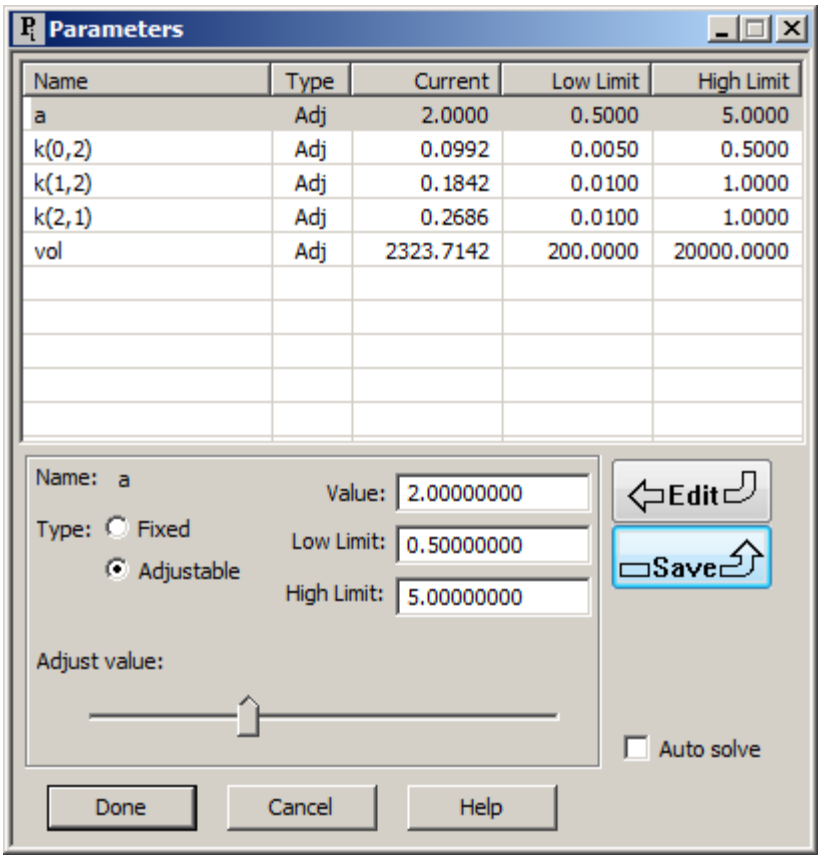
In this case, *a* was assumed to be known and equal to 2. The result is that there are four parameters to be estimated from the data, and the "Fit" was successful. What would happen if parameter *a* was adjustable?

7. Set *a* as an adjustable parameter.

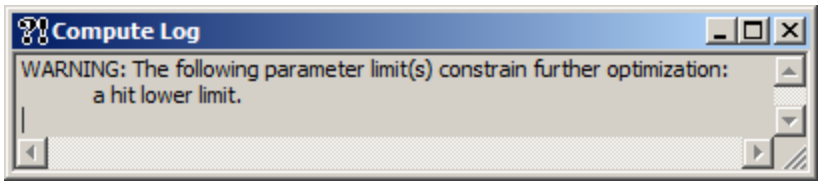
   a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters**  . The **Parameters** dialog box will open.

   b. Double-click ***a*** to select it.

   c. Set ***a*** as an adjustable parameter. Leave the initial **Value** equal to "2". Type "0.5" and "5" in the **Low Limit** and **High Limit** boxes respectively. The **Parameters** dialog box will appear as follows:



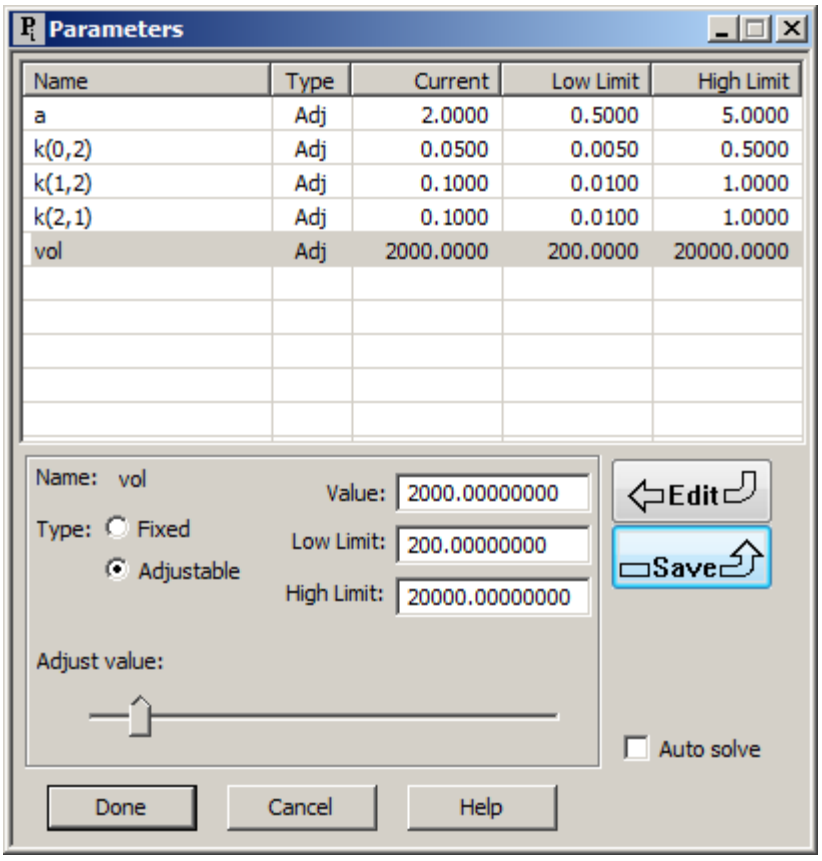
d. Fit the model to the data. The following warning message will appear:



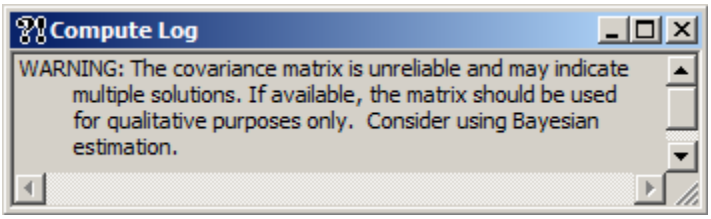
The warning is that *a* hit a lower limit. If you continue to adjust the **Low Limit**, *a* will continue to hit the lower limit. This means there are more parameters in the model than can be estimated from the data.

e. Close the **Compute Log** dialog box.

f. Note the effect of initial values. Set ***a*** as an adjustable value as noted above and restore all initial values of each parameter, the **Parameters** dialog box will appear as follows:



g. Fit the model to the data. The following warning message will appear:



The warning is that the covariance matrix is unreliable and suggests that the user consider using the Bayesian estimation.

However, you may note that incorporating the Bayesian option, as shown below, after receiving either one of these Compute Log Warnings, produces the same fitted solution.

h. Close the **Compute Log** dialog box.

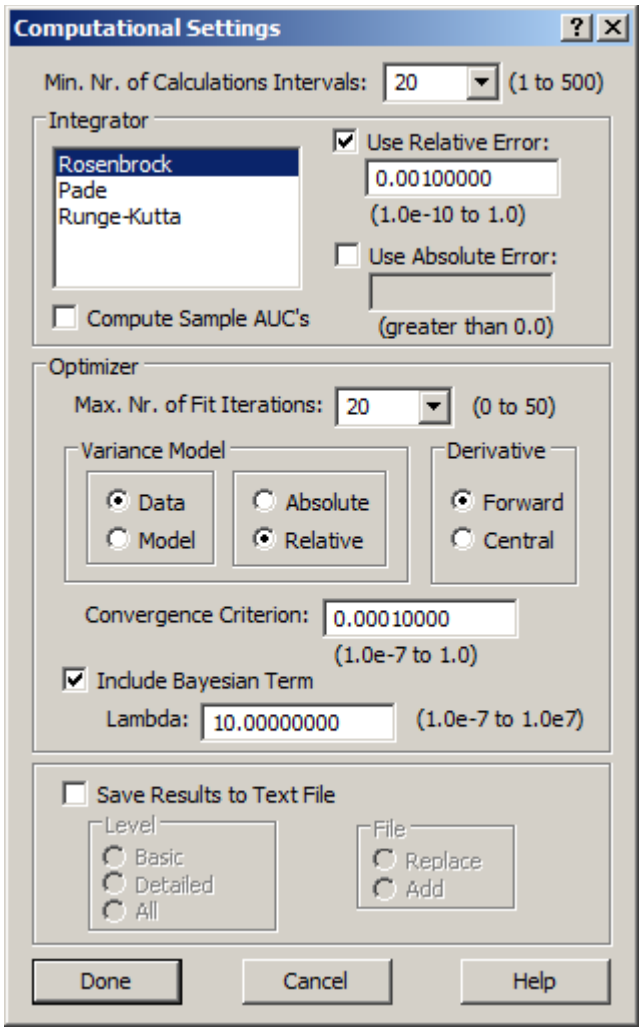
8. Incorporate prior knowledge about *a* into the model.

Suppose you really believed that *k(0,1)* was about twice *k(0,2)*. Suppose you had information on the value of *a* from another study. You can incorporate this knowledge

using the Bayesian option in SAAM II. Suppose you know from the literature that a value for *a* is "2" with a standard deviation of "0.05". In this part of the tutorial, this information will be incorporated into the model.

a. In the **Compute** menu, click **Settings**. The **Computational Settings** dialog box will open.

b. Select the **Include Bayesian Term** check box. The **Computational Settings** dialog box will appear as follows:



c. Click **Done**.

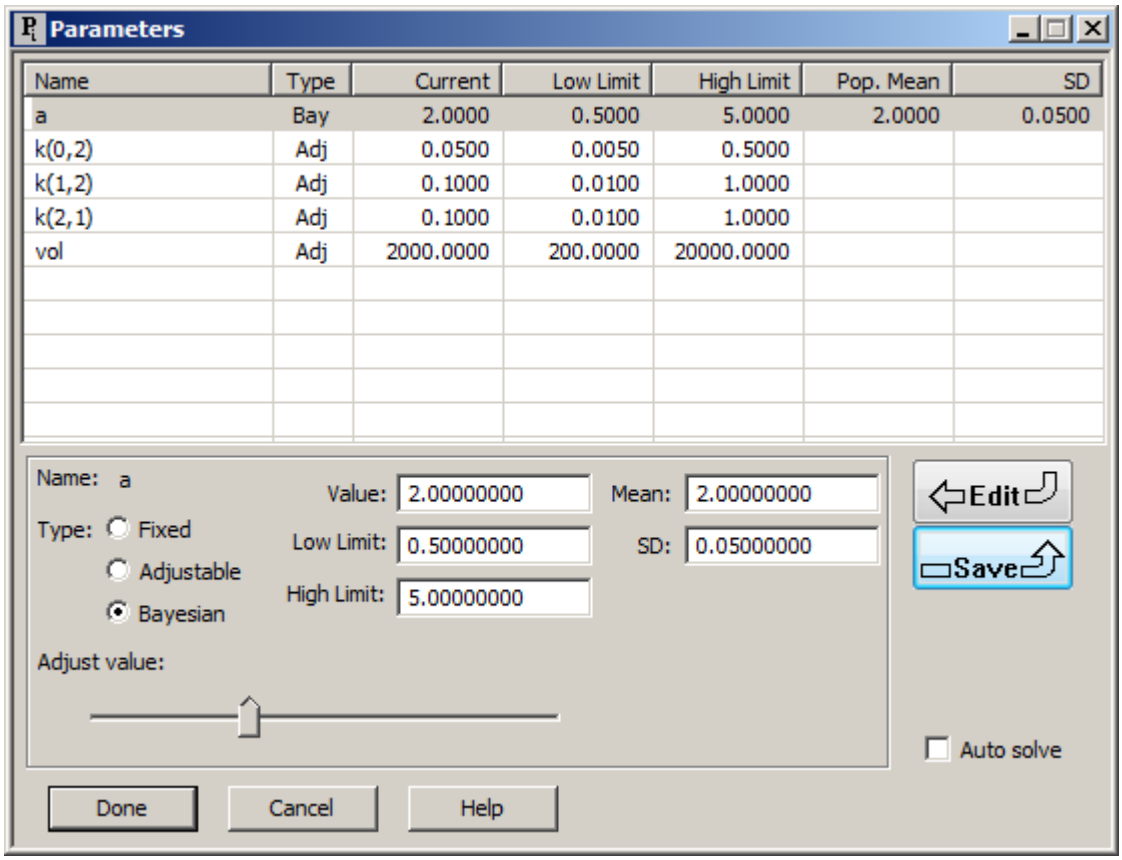
d. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters**  . The **Parameters** dialog box will open.

(1) Double-click *a* to select it.

(2) Select the type for *a* as Bayesian.

(3) Type "2" in the **Mean** box and "0.05" in the **SD** box.

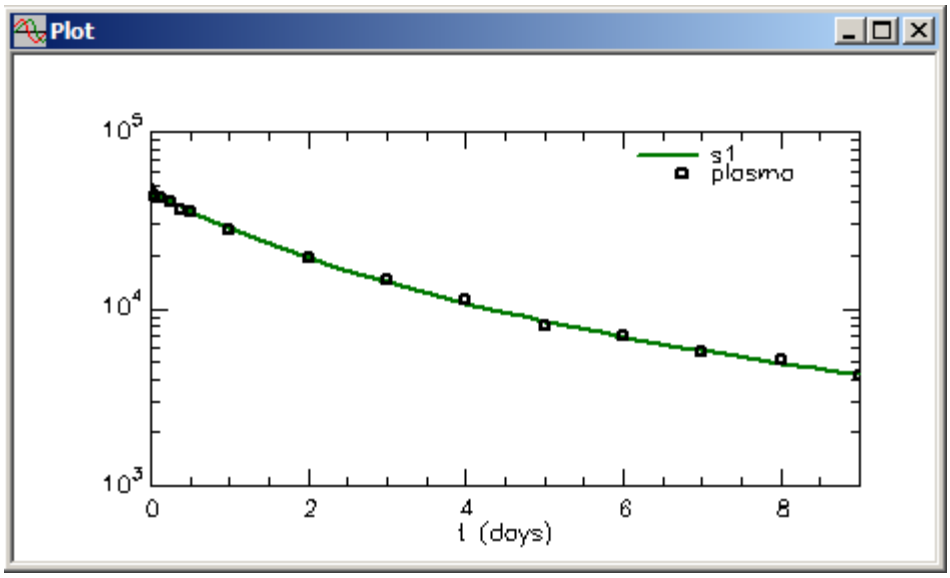
(4) Click **Save**. The **Parameters** dialog box will appear as follows:



(5) Click **Done**.

The Bayesian option. If you have information about the value of a model parameter from the literature, it is useful to include this in your model. When you have Bayesian parameters in your model and you fit your model to your data, SAAM II takes this information into account. If there is information in your data about a Bayesian parameter, SAAM II will adjust it from its mean value. If there is little or no information in your data about a Bayesian parameters, SAAM II will not adjust it from its mean value.

e. Fit the model to the data. A summary of the results is shown below:



Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
a	2.00000	6.03023e-002	3.01511e+000	1.86728	2.13272
k(0,2)	0.09916	1.40624e-002	1.41815e+001	0.06821	0.13011
k(1,2)	0.18417	6.39093e-002	3.47018e+001	0.04350	0.32483
k(2,1)	0.26855	1.96092e-002	7.30181e+000	0.22539	0.31171
vol	2323.71417	3.98284e+001	1.71400e+000	2236.05233	2411.37601
Derived Variables					
k(0,1)	0.19832	2.80250e-002	1.41312e+001	0.13664	0.26000

Correlation Matrix Covariance Matrix Objective

	Objective	Scaled Data Variance
s1 : plasma	1.253196e+001	1.187747e-001
Bayesian	-3.744665e-001	
Total objective	1.215750e+001	
AIC	7.372687e+000	
BIC	7.517547e+000	

Bayesian parameters. The Bayesian parameter option is a powerful way to incorporate prior information about a parameter in your model. In almost all cases if you use this option, you will achieve convergence. If your data do not contain much information about the Bayesian parameter, then the value you entered for the **Mean** and **SD** will not change much; if your data do contain information, they will change. In this case, the **Mean** didn't change; the **SD** changed a little.

You should note that the precision of the model parameters is not as good as the case, for example, when there were only four parameters to be estimated. This is because of the additional uncertainty added by the Bayesian parameter.

Using this option can also be useful as a modeling technique. If in the process of developing a model you cannot achieve a fit, you can sometimes use the Bayesian option on a specific parameter. You can then tell from the resulting statistical output which of the model parameters may be giving difficulty in achieving a "Fit." This can help identify where constraints on parameters or model simplification must be undertaken.

f. Close the **Plot** and **Statistics** windows.

Quit the **SAAM II Compartmental** application. Do not save the changes to **study_0**.

SAAM II Version 2.1
Advanced Tutorials

Working with Solutions
Saving and Restoring Solutions

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Saving and Restoring Solutions

Prerequisites

The prerequisite for this tutorial is having worked through the SAAM II introductory tutorial, "Getting Started with **SAAM II Compartmental**."

What you will learn in this tutorial

The purpose of this tutorial is to show you how save and restore solutions.

- How to save solutions and compare results among other solutions
- How to restore a specifically saved solution.

Files Required

Study Files: The study file for this tutorial is

study_0.stu

This file is included as part of this tutorial. This file is the same as **study_0.stu** that is installed in the SAAM II program folder and referred to in the **SAAM II** Basic Tutorials.

Introduction

SAAM II enables you to save and work with different solutions of the model you are using. When you save a solution you are, in effect, saving the state of the model (i.e., the current values of the model parameters). Additionally, you may save selected variables with their values as calculated during the last solve or fit. This can be used to compare results from other solutions.

When you ***restore a solution***, you are merely ***resetting the parameter values back to the saved state for that solution***. You are not resetting the values of any other variables. **You must solve to restore all other values**.

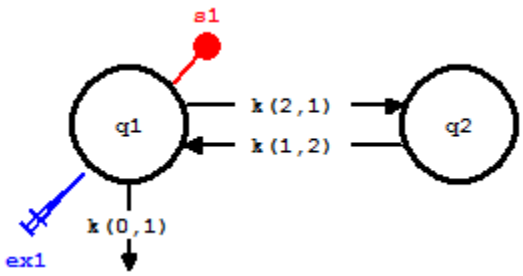
Part 1. Saving and restoring solutions

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

2. Open the **SAAM II Compartmental** study file **study_0**.

   a. The file **study_0.stu** should appear in the file list; if it does not, find the folder where you put this file.

   b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear. In the **SAAM II Toolbox**, click **Experiment**. The model of the experiment for **study_0.stu** will appear on the **Drawing Canvas** as follows:



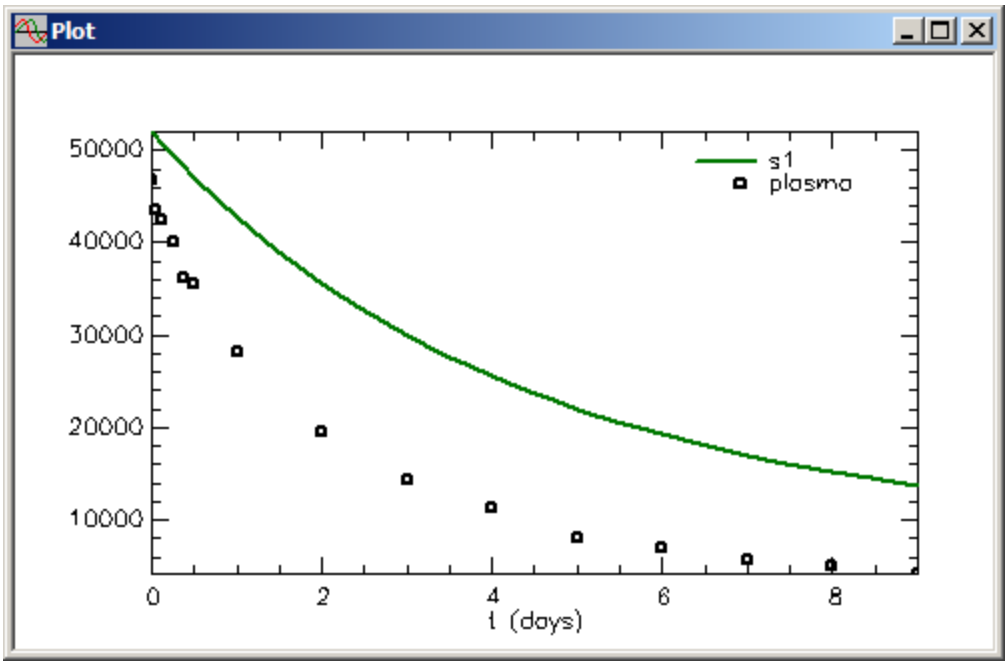
3. Solve the model and view the solution.

   a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve**  .

   b. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot**  . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is not selected.

   c. Click **s1:plasma** to move this to the **Current Selection** pane.

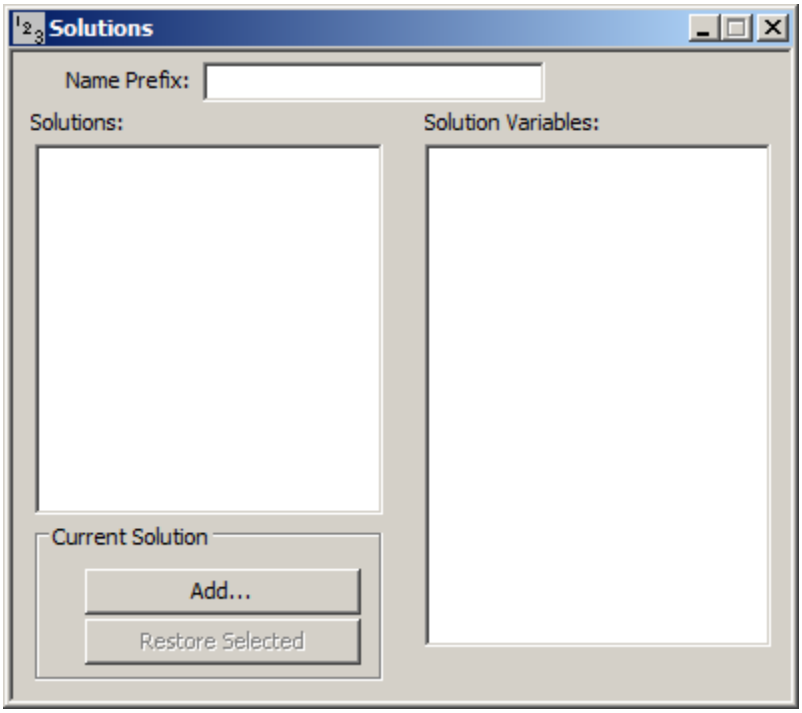
   d. Click **Done**. Your plot will appear as shown below (in linear mode):



Leave the **Plot** window open.

4. Save the solution.

   a. In the **Compute** menu, click **Solutions**. The **Solutions** dialog box will open as follows:



*The **Solutions** dialog box*. The **Solutions** dialog box contains

The **Name Prefix** box. Here you can type the name of the solution; the default name is "1." If you type, for example, "base", the solution will be saved with the name "base1"; thus a number is always added to your name. This allows you to create a sequence of solutions such as "base1", "base2", etc.

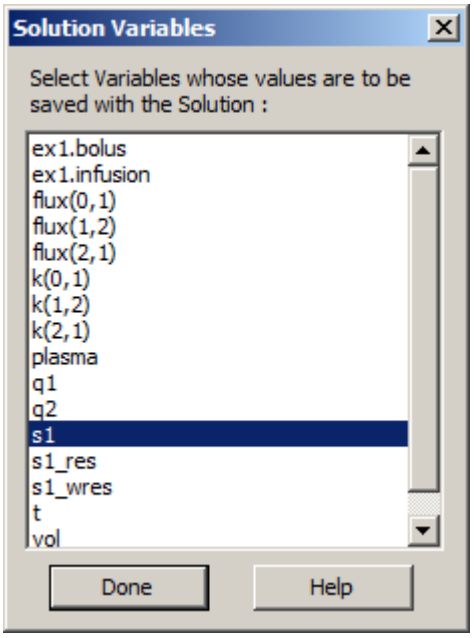
The **Solutions** pane listing the names of the saved solutions.

The **Solution Variables** pane with the names of the saved solutions variables for a given solution, Clicking on the name of a solution in the **Solutions** pane will produce a list of the variables saved in the **Solution Variables** pane.

The **Current Solution** pane providing you the option to **Add** a solution, or to **Restore Selected**, a selected solution.

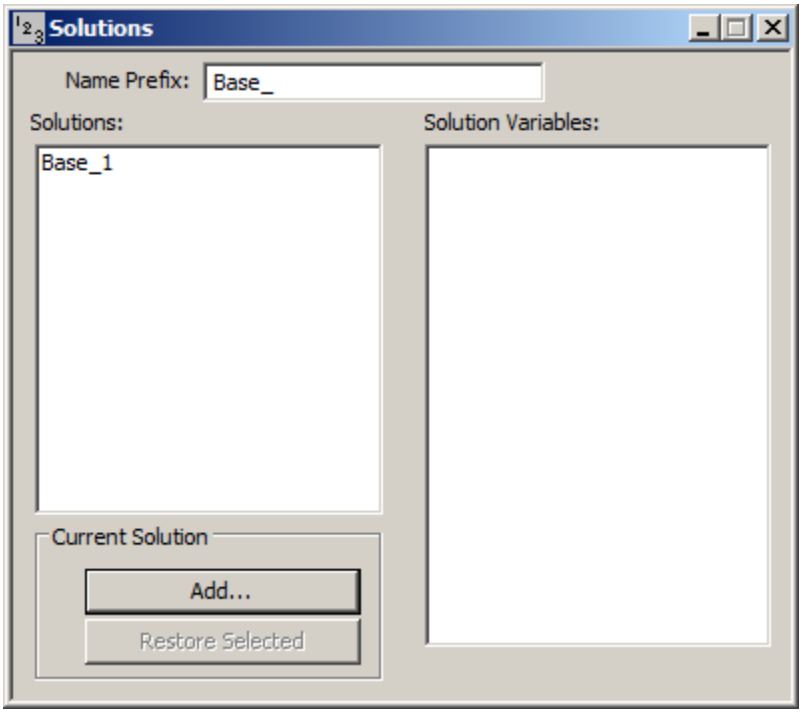
b. Type "Base_" in the **Name Prefix** box.

c. Click **Add** in the **Current Solution** pane. The **Solution Variables** dialog box will open as follows:

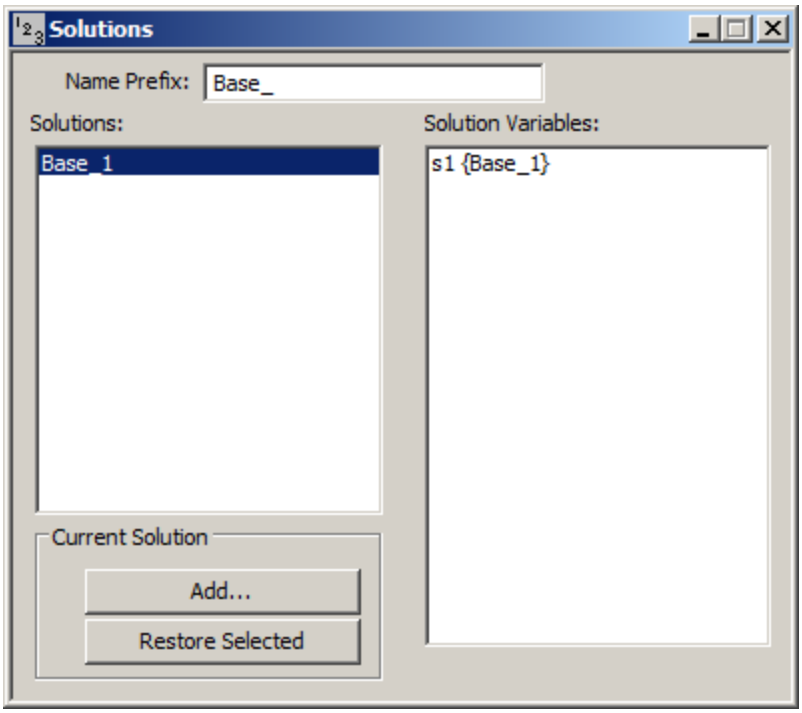


*The **Solution Variables** dialog box*. The **Solution Variables** dialog box contains the names of the model variables and/or parameters you may save with the solution. These saved variables can be accessed for plotting or tabular purposes. They will be saved with a suffix added to them. In this case, because the name of the saved solution is "Base_" hence saved as "Base_1", the variables will be saved with the name {Base_1} associated with them. For example, if you save **s1**, the name **s1{Base_1}** will appear in the **Plot and Table Variables** dialog box.

d. In the **Solution Variables** dialog box, click **s1** and then click **Done**. The **Solutions** dialog box will appear as follows:



e. In the **Solutions** pane, click "Base_1". The **Solutions** dialog box will appear as follows:



*The **Solutions** dialog box*. When you click the name of a solution in the **Solutions** dialog box, the variables and parameters saved with that solution will appear in the **Solution Variables** pane.

f. Close the **Solutions** dialog box.

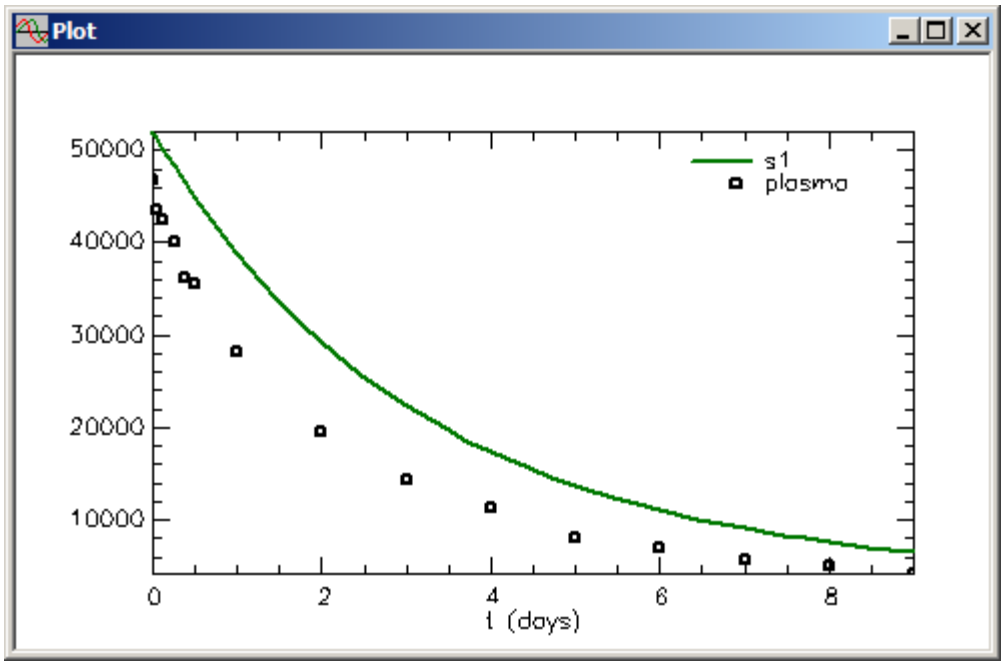
5. Change the value of *k(0,1)* and compare solutions.

   a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters** . The **Parameters** dialog box will open.

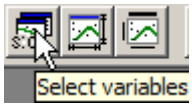
   b. Change the value of *k(0,1)* from "0.1" to "0.2".

   c. Close the **Parameters** dialog box.

   d. Solve the model. The plot will be updated as follows:

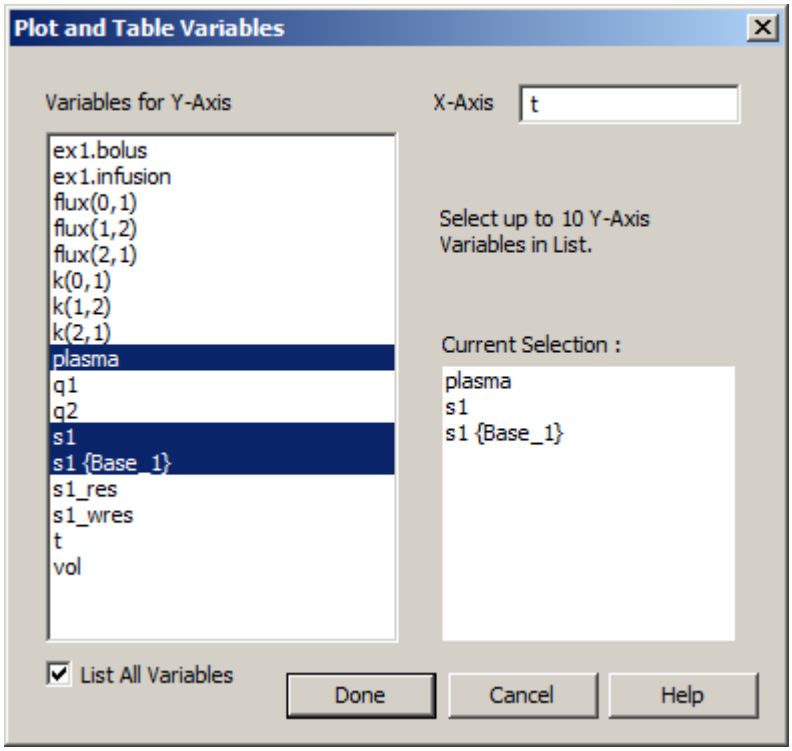


e. Compare this solution with the original base solution.

(1) In the **Set** menu, click **Plot/Table Variables**; use the 

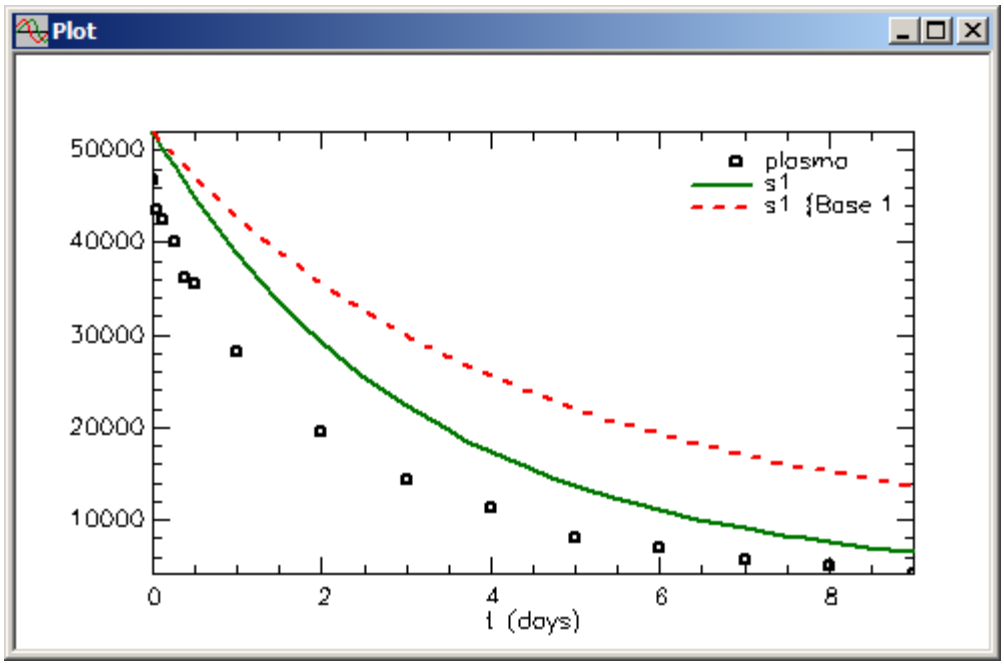
task bar button or right-click in the plot window. The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is selected.

(2) Press the **CTRL** key, and click **plasma**, **s1** and **s1{Base_1}**. The **Plot and Table Variables** dialog box will appear as follows:



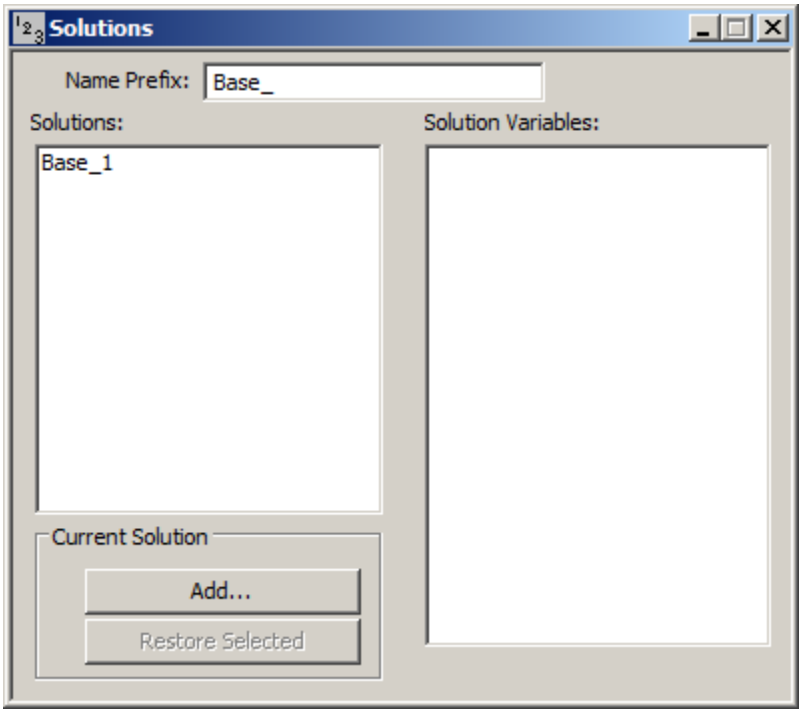
Saved variables and parameters. Notice in the **Variable for Y-Axis** pane the saved original solution **s1{Base_1}** appears. This is the only saved variable. If you had saved other variables or parameters, these would appear in this list followed by **{Base_1}**.

(3) Click **Done**. The plot will appear as follows:



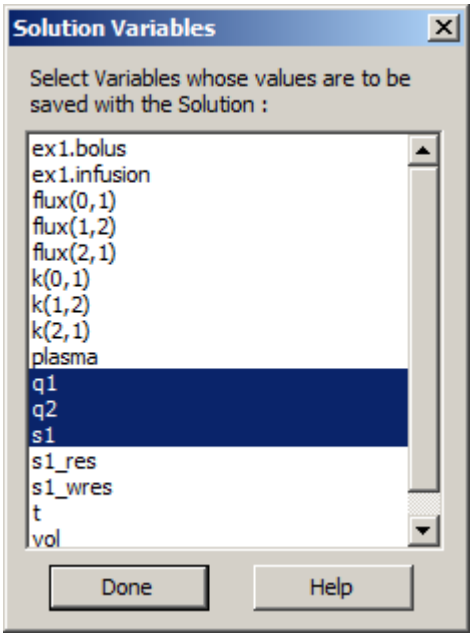
6. Save the solution.

   a. In the **Compute** menu, click **Solutions**. The **Solutions** dialog box will open as follows:

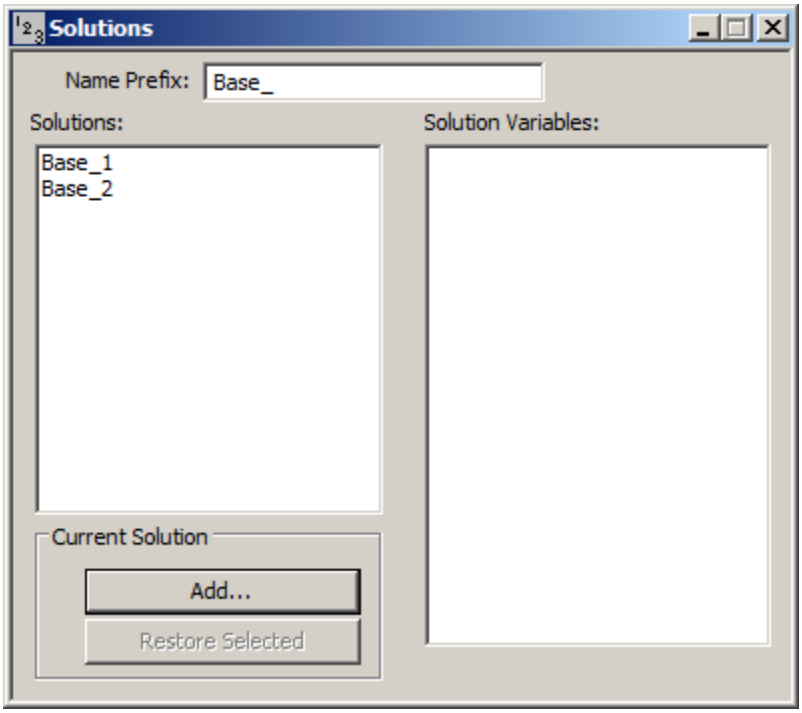


   Notice "Base_" appears in the **Name Prefix** box, and "Base_1" is the original saved solution. Leave the **Name Prefix** as "Base_".

b. Click **Add**. The **Solution Variables** dialog box will open. Clear the selected variables, press the **CTRL** key, and click **q1**, **q2** and **s1**. The **Solution Variables** dialog box will appear as follows:

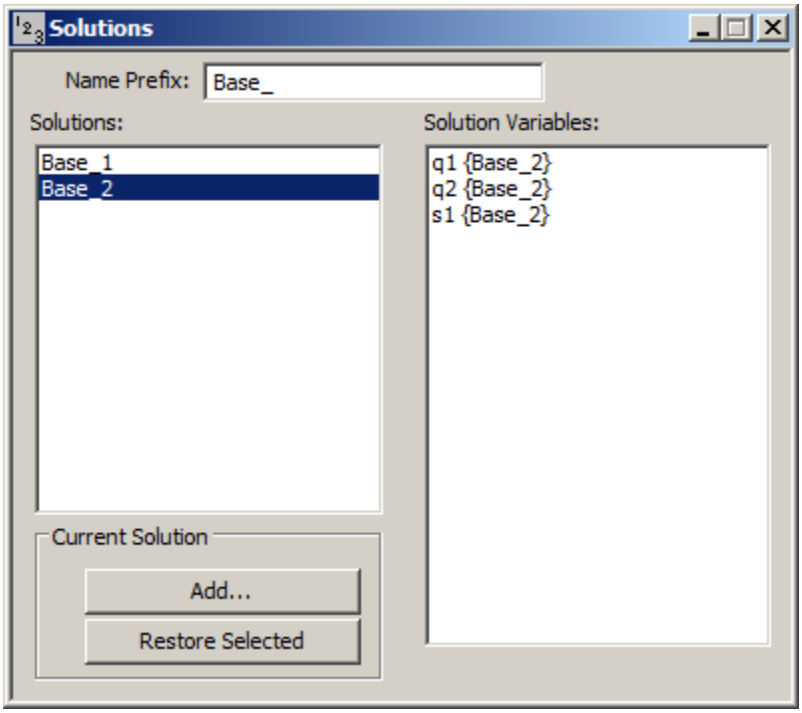


c. Click **Done**. The **Solutions** dialog box will appear as follows:



Notice the **Name Prefix** "Base_" remains, but the number "2" is added. Thus "Base_2" is the second "Base_" saved solution.

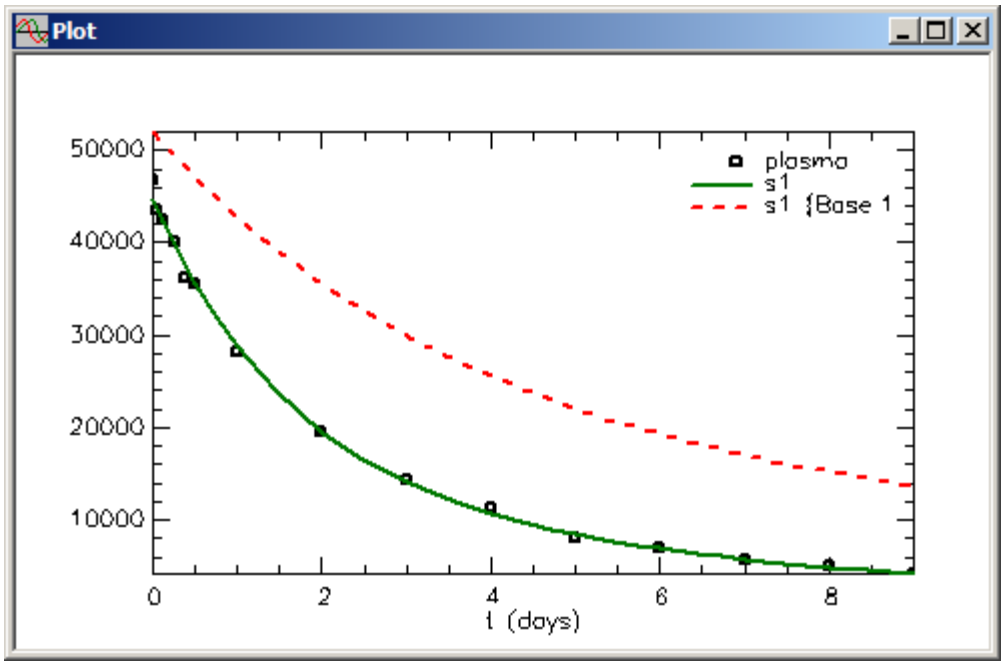
d. In the **Solutions** pane, click "base2". The **Solutions** dialog box will appear as follows:



The variables in the **Solution Variables** pane are those that you saved; they will appear as variables in the **Plot and Table Variables** dialog box.

e. Close the **Solutions** dialog box.

7. Fit the model to your data. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar** click **Fit**  . Since the **Plot** window was open during the "Fit", the **Plot** window will be updated as shown below:



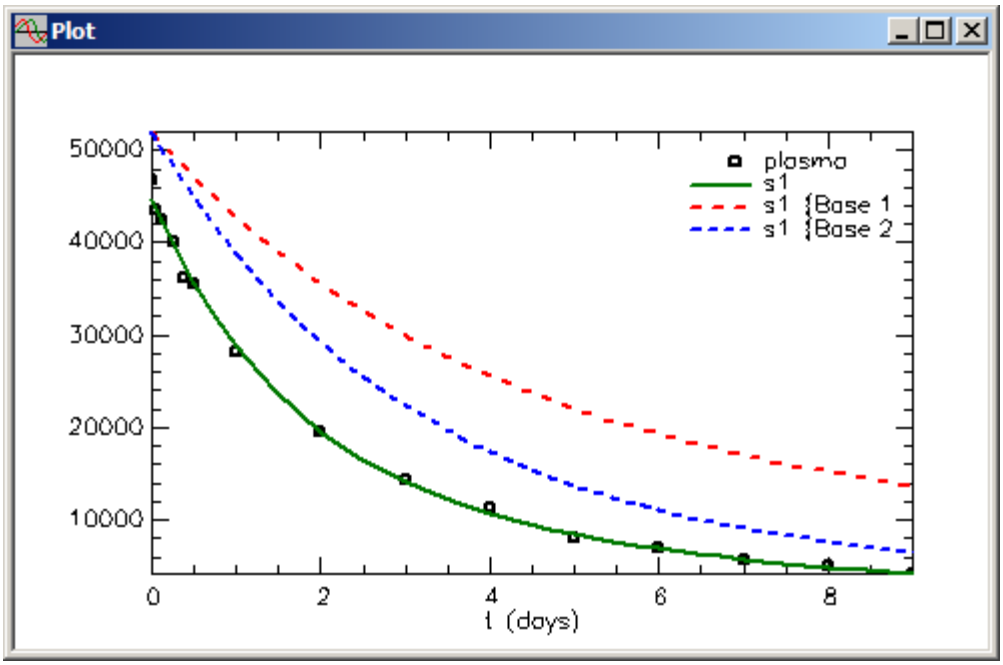
Remember your previous plot had **s1{base1}** as a variable in the **Current Selection** pane; thus this plot compares the best fit of the model to the data with the original solution.

8. Compare all three solutions.

   a. In the **Set** menu, click **Plot/Table Variables**; click the select variables button or right-click in the plot window and select Variables… The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is selected.

   b. Clear the selected variables, press the **CTRL** key, and click **plasma**, **s1**, **s1{Base_1}** and **s1{Base_2}** to move these variable to the **Current Selection** pane.

   c. Click **Done**. The plot will appear as follows:



d. Close the **Plot** window.

e. In the **Show** menu, click **Table**, or alternatively, on the **SAAM II Toolbar** click **Table**  . The following table will open.

Table

t	plasma	s1	s1 {Base_1}	s1 {Base_2}
0.000	-	44755.102	52000.000	52000.000
7.00000e-003	46780.000	44609.149	51927.264	51890.927
4.20000e-002	43522.000	43888.092	51565.485	51349.365
0.125	42535.000	42234.734	50720.094	50090.056
0.250	40125.000	39887.777	49479.518	48257.992
0.375	36221.000	37701.608	48277.014	46500.570
0.500	35562.000	35664.538	47111.365	44814.685
0.750	-	31995.176	44885.961	41645.749
1.000	28194.000	28802.293	42794.330	38728.842
1.450	-	24049.853	39340.009	34049.108
1.725	-	21664.290	37409.749	31512.801
2.000	19573.000	19600.851	35605.189	29195.561
2.450	-	16795.738	32901.059	25825.977
2.725	-	15368.731	31388.008	23997.303
3.000	14403.000	14120.793	29971.990	22324.748
3.450	-	12397.815	27846.960	19888.845
3.725	-	11506.125	26656.046	18564.604
4.000	11278.000	10715.574	25540.090	17351.718
4.450	-	9603.404	23862.412	15581.766
4.725	-	9016.148	22920.423	14617.450
5.000	8081.000	8487.371	22036.391	13732.649
5.450	-	7728.045	20704.602	12438.224
5.725	-	7318.557	19955.152	11731.041
6.000	6999.000	6944.012	19250.565	11080.723
6.450	-	6395.272	18186.512	10126.355
6.725	-	6093.436	17586.168	9603.172
7.000	5653.000	5813.407	17020.600	9120.734
7.450	-	5395.873	16164.076	8410.019
7.725	-	5162.344	15679.375	8018.784
8.000	5139.000	4943.155	15221.676	7656.819
8.450	-	4611.747	14526.287	7121.125
8.725	-	4423.988	14131.441	6824.776
9.000	-	4246.214	13757.604	6549.523
9.000	4210.000	4246.214	13757.604	6549.523

Because the previous plot had the Plot and Table Variables **plasma**, **s1**, **s1{base1}** and **s1{base2}** selected, these the variables will appear in the table. To change the variable, simply open the **Plot and Table Variables** dialog box, and select those variables you would like to view in tabular form.

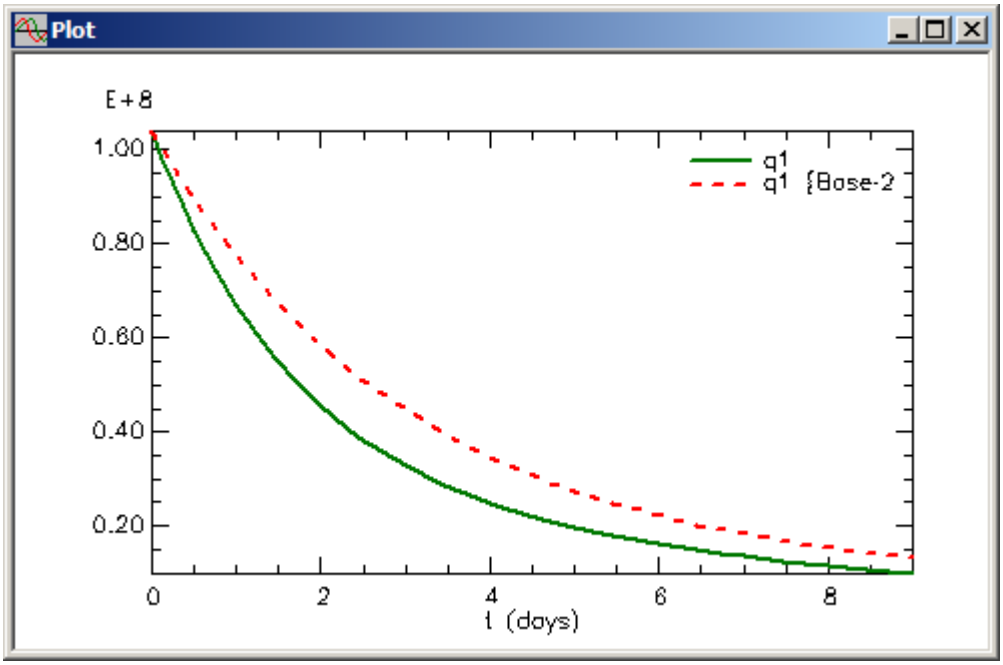
f. Close the **Table** window.

9. Compare **q1{base2}** with **q1** from the best fit.

a. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot**  . The previous plot will open.

b. In the **Set** menu, click **Plot/Table Variables**; click the select variables button or right-click in the plot window and select Variables… The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is selected.

c. Press the **CTRL** key, and click **q1** and **q1{base2}** to move these variables to the **Current Selection** pane. Notice there is no **q1{base1}**; this is because you did not save **q1** as a variable for base1. Click **Done**. The plot will appear as follows:



d. Close the **Plot** window.

10. Save the solution from the best fit.

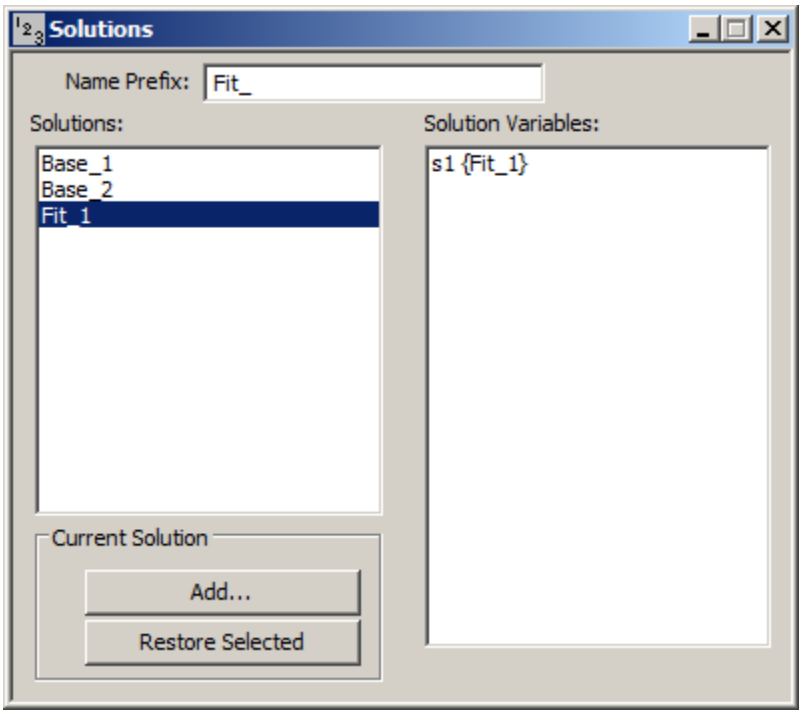
a. In the **Compute** menu, click **Solutions**. The **Solutions** dialog box will open.

b. Type "Fit_" in the **Name Prefix** box.

c. Click **Add**. The **Solutions Variables** dialog box will open.

d. Click **s1** and **Done**.

e. In the **Solutions** dialog box, click "Fit_1". The **Solutions** dialog box will appear as follows:

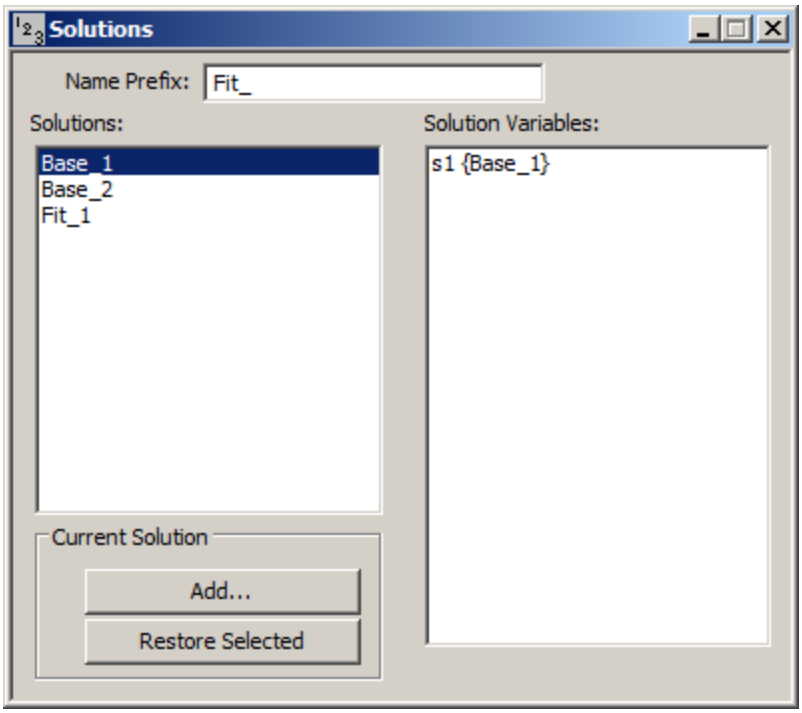


f. Close the Solutions dialog box.

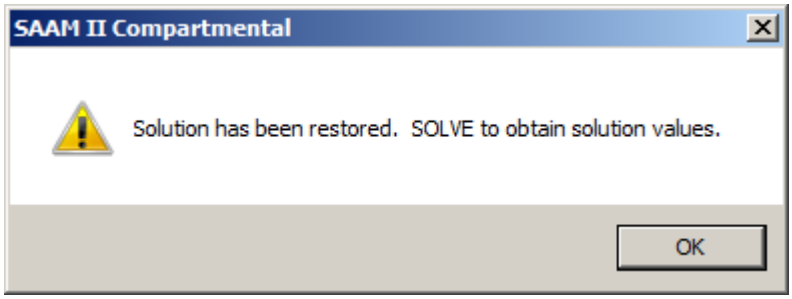
11. Restore the original solution {Base_1}.

a. In the **Compute** menu, click **Solutions**. The **Solutions** dialog box will open.

b. Click "Base_1". The saved variables for "Base_1" will appear in **the Solution Variables** pane as shown below. Notice also in the **Current Solution** pane, **Restore Selected** is active. You now have the option to restore this solution.



c. Click **Restore Selected**. The following message will appear:

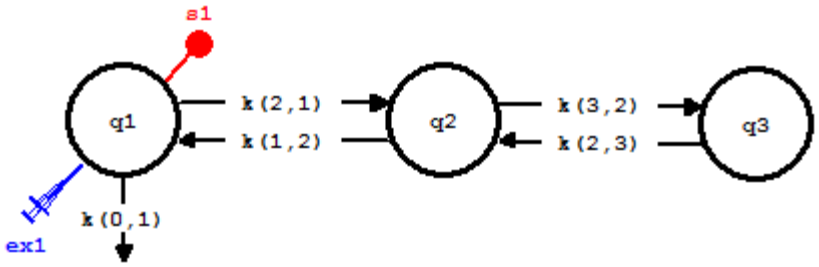


d. Click **OK**.

e. Solve the model and view the solution. You will see it is the original solution. You can confirm this by examining the parameter values. Close all open windows and dialog boxes.

11. Add a compartment to the model.

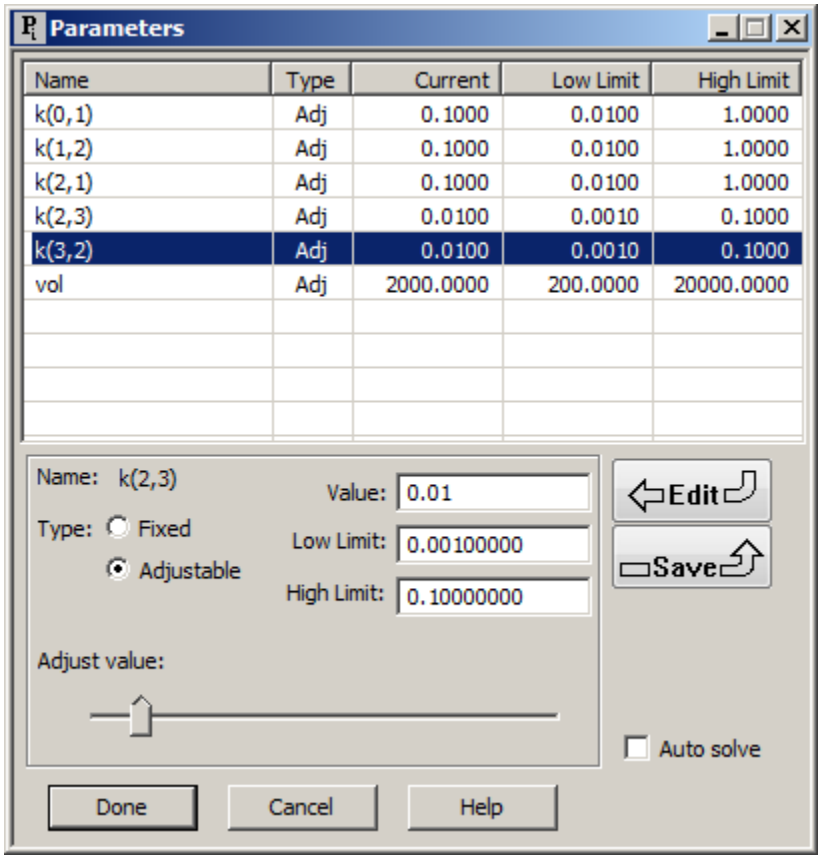
a. Add a third compartment to your model. The new model should appear as follows:



b. Add parameter values to your model.

(1) In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters**  . The **Parameters** dialog box will open. Notice the values for *k(2,1)*, *k(1,2)*, *k(0,1)* and *vol* are those for **study_0**.

(2) Double-click *k(3,2)* to make it active. Type "0.01" in the **Value** box, and click **Save**. Repeat the process for *k(2,3)*. The **Parameters** dialog box will appear as follows:



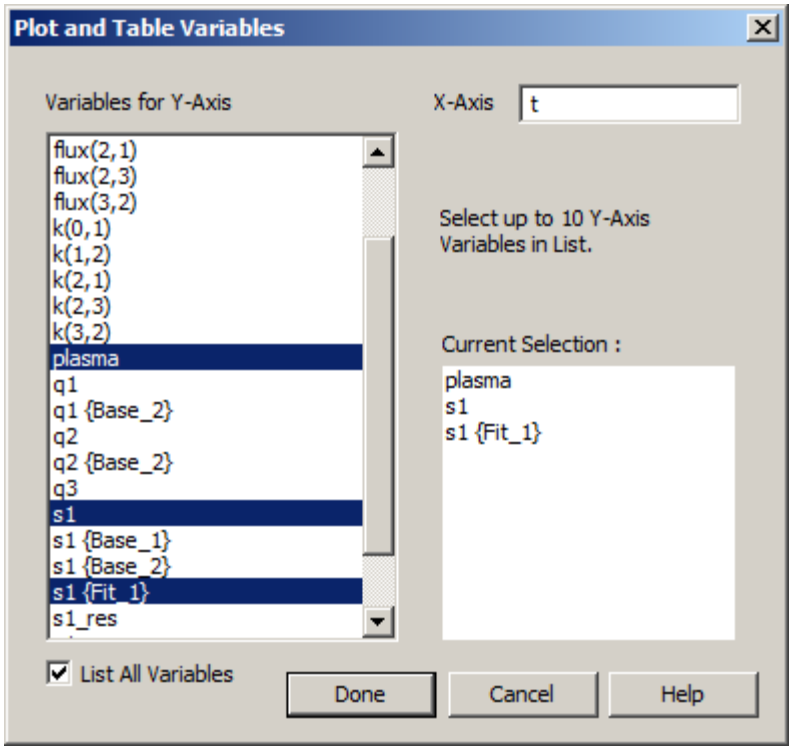
(3) Click **Done**.

c. Solve the model, and compare the solution with the best fit to a two-compartment model solution.

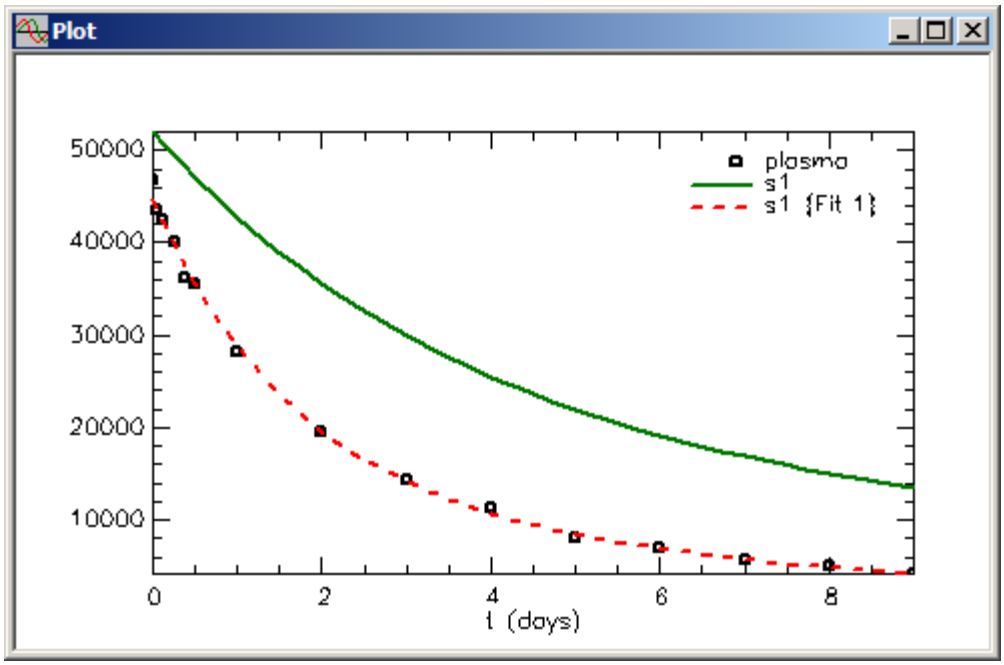
(1) In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve**  .

(2) In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot**  . A plot of the current solution s1 and the plasma data may appear. If a plot opens, in the **Set** menu, click **Plot/Table Variables**; click the select variables button or right-click in the plot window and select Variables… The **Plot and Table Variables** dialog box will open. If a plot does not open, the **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is selected.

(3) Press the **CTRL** key, and click **plasma**, **s1** and **s1{fit1}**. The **Plot and Table Variables** dialog box will appear as follows:

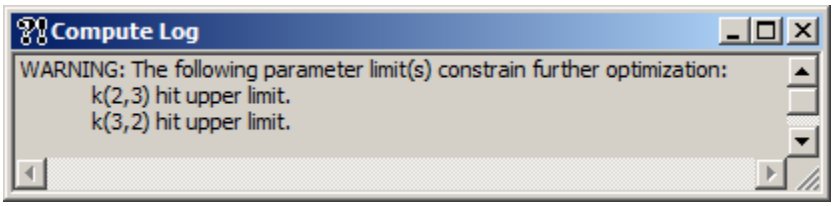


(4) Click **Done**. The Plot window will appear as follows:

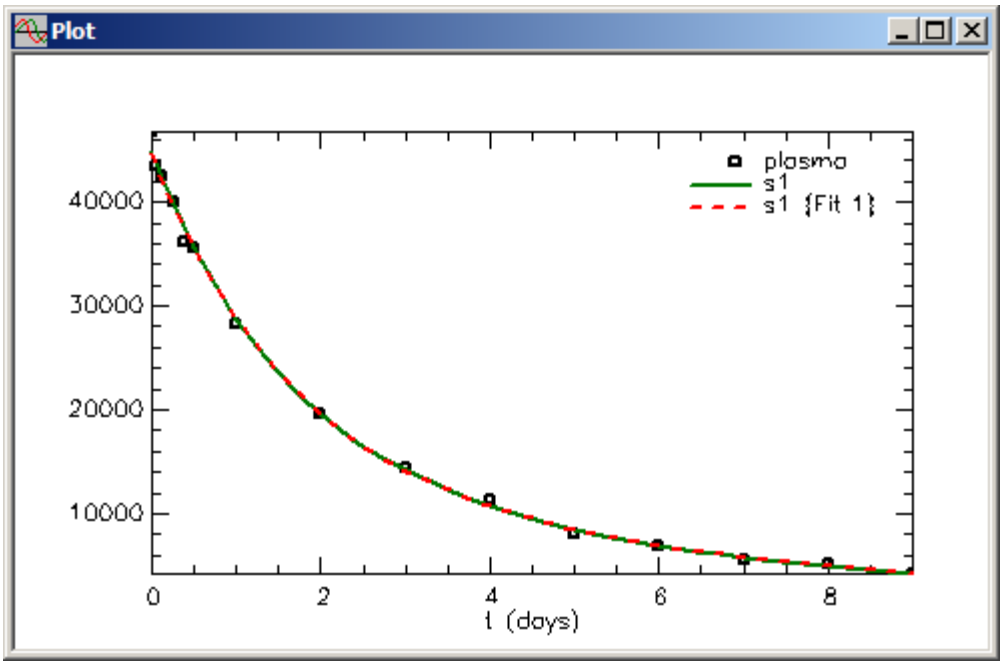


Saved solutions. It is important to know that, even though you changed the model structure by adding a third compartment, the solutions saved for the two-compartment model remain, and can be compared with your work on the third compartment.

d. Fit the model to the data. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar** click **Fit**  . The following warning message will appear:



The **Plot** window will be updated as follows:



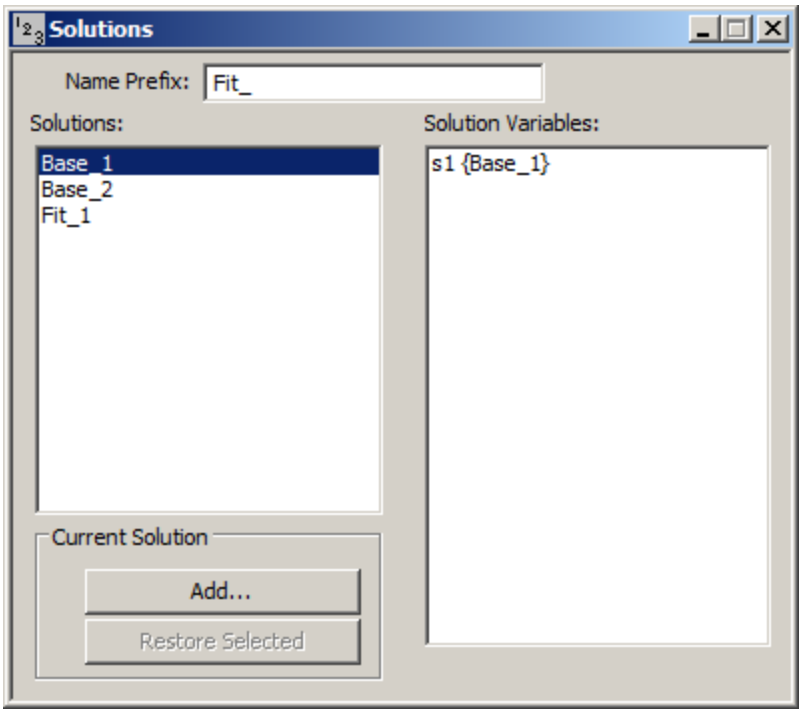
NOTE: The combination of the warning message and the identical fit of the model to the data indicate a third compartment is not supported by the data.

e. Close the **Compute Log** window and the **Plot** window.

12. Restoring the original two-compartment model

a. In the **Compute** menu, click **Solutions**. The **Solutions** dialog box will open.

b. In the **Solutions** pane, click "Base_1". The **Solutions** dialog box will appear as follows:



Although "Base_1" is active, the **Restore Selected** option in the **Current Solution** pane is dimmed.

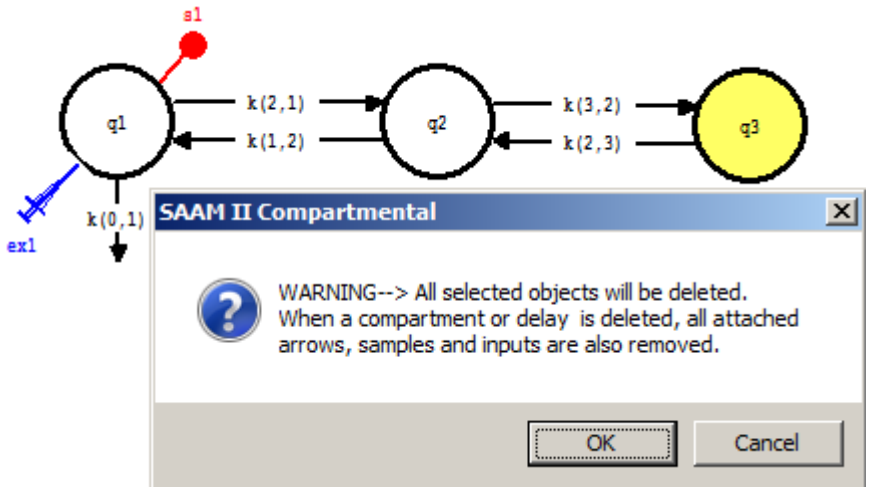
Restoring solutions. When you restore a solution, the model on the drawing canvas must be the same structural model as the saved solution. In the above case, the current model is a three-compartment model while the saved "base1" solution is a two-compartment model. Thus it cannot be restored.

c. Close the **Solutions** dialog box.

d. Delete Compartment **3** from the model.

(1) Click Compartment **q3** to make it active.

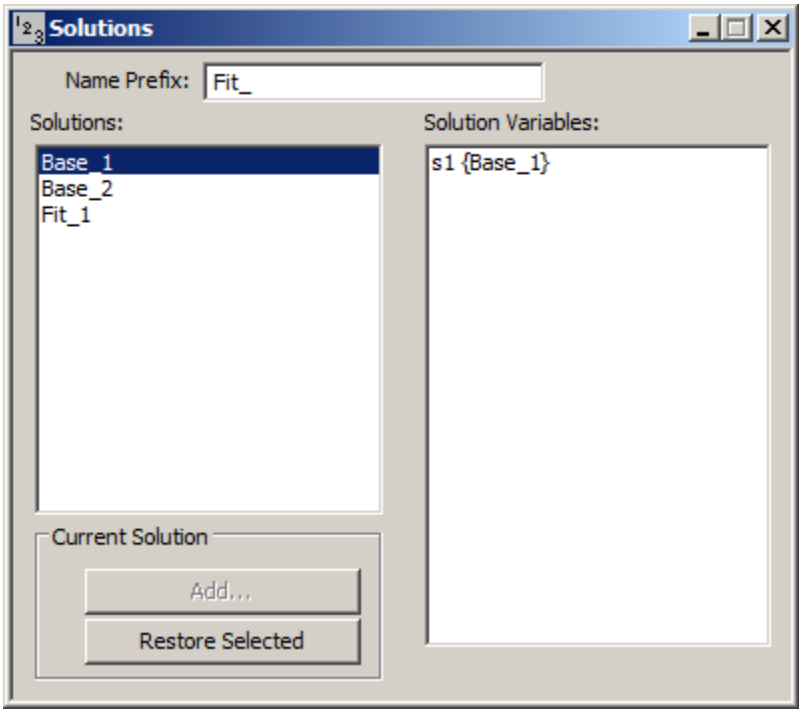
(2) Press the **Delete** key. The model and a warning message will appear as follows:



(3) Click **OK**. The original two-compartment model will appear on the **Drawing Canvas**.

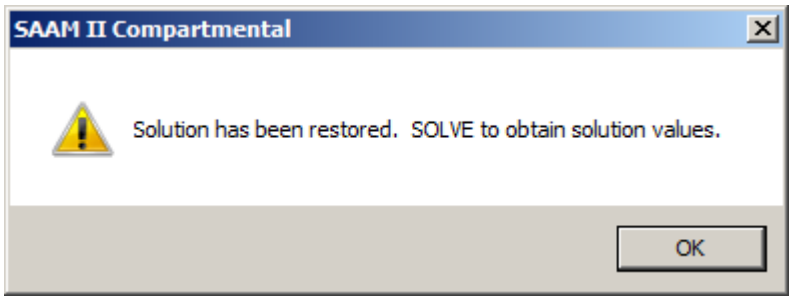
e. In the **Compute** window, click **Solutions**. The **Solutions** dialog box will open.

f. In the **Solutions** pane, click "Base_1". The **Solutions** dialog box will appear as follows:



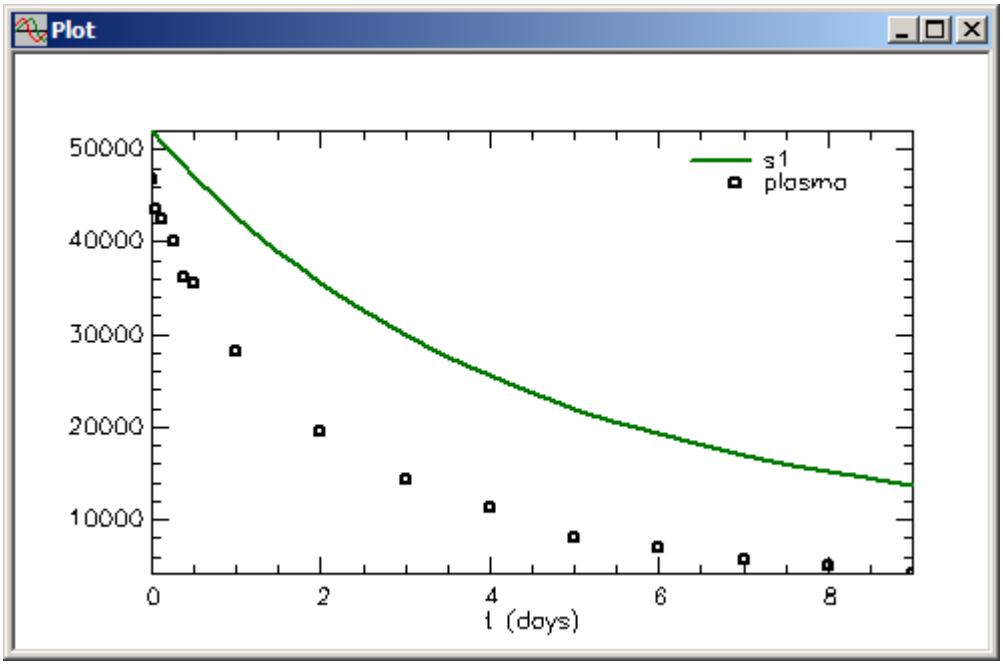
Now because the model on the **Drawing Canvas** is the same as the original saved model, the **Restored Selected** option is available in the **Current Solution** pane.

g. Click **Restored Selected**. The following message will appear:



h. Click **OK**, and close the **Solutions** dialog box.

i. Solve the model, and view the solution. In the Plot Variables dialogue box, uncheck the 'List All Variables' box. Double-clicking 's1:plasma' will clear the 'Current Selection' replacing it with s1 and plasma. The original solution will appear as indicated by the following plot.



j. Close all open windows and dialog boxes.

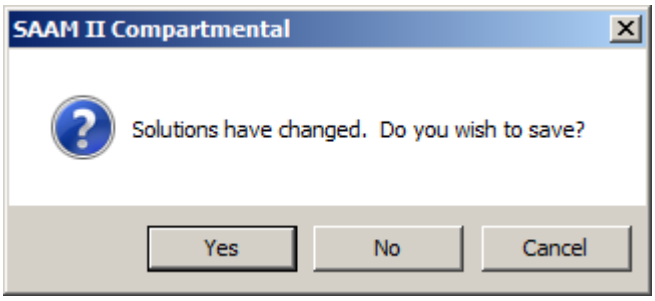
13. Save this study file and its solutions.

a. In the **File** menu, click **Save As**. The **Save As** dialog box will open.

b. Type "solutions" in the **File Name** box.

c. Click **Save**.

14. **Quit** the **SAAM II Compartmental** application. In the **File** menu, click **Exit**. The following message will appear:



If you click **Yes**, a file called **solutions.sol**. containing the solutions will be created. The ".sol" indicates a **SAAM II** solutions file. When you open **solutions.stu**, the solutions saved will be available in the **Solutions** dialog box. If you click **No**, the solutions will not be saved.

Click **Yes**. Now when you open **solutions.stu**, your solutions will be available.

Restoring solutions.
In order to restore a solution, ***the model on the drawing canvas must be the same structural model as the saved solution***. Otherwise, 'Restore Selected' will be greyed out in the Solutions dialog box
When you restore a solution, ***the Minimum Number of Calculations Intervals in the Computational Settings must be the same as the saved solution***. Otherwise, 'Restore Selected' will be greyed out in the Solutions dialog box

SAAM II Version 2.1
Advanced Tutorials

Simulating Data

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Simulating Data

Prerequisites

The prerequisite for this tutorial is having worked through the SAAM II introductory basic tutorial, "**Getting Started with Compartmental SAAM II**." It will be helpful to have worked through the Advanced SAAM II tutorial "**Working with Change Conditions**."

What you will learn in this tutorial

The purpose of this tutorial is to show you how to simulate experimental data given a model. You will learn

- How to create plasma data (a single input-single output experiment) (Part 1)
- How to create plasma and 24 hour urine collections (a single input-two output experiment) (Part 2)

Files Required

Study File: The study file for this tutorial is

study_0.stu

This file is included as part of this tutorial. This file is the same as **study_0.stu** that is installed in the SAAM II program folder and referred to in the **SAAM II** tutorials.

Data File: The data file for this tutorial is

SimPlasUrine.dat

Introduction

This tutorial will show you how to simulate experimental data for a single subject given a model and an experiment on the model. The simulated data are generated using the FORTRAN function RAND(). RAND() is a random number generator that will generate random numbers between zero and 1.

The way the RAND() function will be used is the following. If RAND() generates a random number between zero and 1, then

$RAND() - 0.5$ - will generate a random number between -0.5 and 0.5. Thus
$2*(RAND() - 0.5)$ - will generate a random number between -1 and 1.

Consider now, for example, Compartment **q1**. q1(t) is the solution of the differential equation q1'(t); its values are calculated at the times samples were collected. The sample **s1**, for example, is a function of q1(t) such as "s1=q1/vol."

To create simulated data, a new sample on the desired compartment will be created. In the **Equation** dialog box, a function "error" will be created as follows:

$$error = 2*(RAND() - 0.5)$$

The new sample equation, if the sample is in terms of concentration, will be written:

s2 = (q1 + (wt*error)*q1)/vol

What is the effect of this equation? The key is in the term "wt*error". "wt" will be the weight assigned. Thus the product "wt*error*q1" will produce a random error term equal to "wt" associated with q1(t). If "wt" is a fractional standard deviation of 10%, then this would be written:

s2 = (q1 + (0.1*error)*q1)/vol

You can assign any error structure you want as long as it falls in the general equation supported by SAAM II:

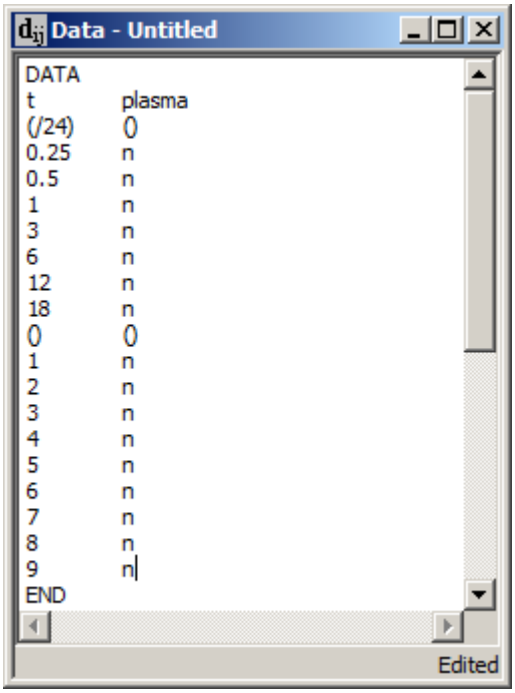
wt = A + B*q1(t)^C

The simulated data can be used in the **DATA** window for analytical purposes, or can be used to create a table which can be exported to a spreadsheet.

Part 1. Simulating plasma data

Suppose you had one or two prototype experiments and you were developing a model of the system. Simulating data sets will allow you to examine the robustness of your model and can be used to suggest changes in the experimental protocol, particularly when samples should be drawn.

In creating simulated plasma data, one can start from a model (with parameters and experimental design) and no data. To create the simulated data, one must create a data file containing the desired data (sample) points. For example, one could have a model and create the following data file:



This will result in simulated plasma samples at 15 and 30 minutes, 1, 3, 6, 12 and 18 hours, and then daily to 9 days. The "n" in the plasma column is simply a placeholder for "plasma".

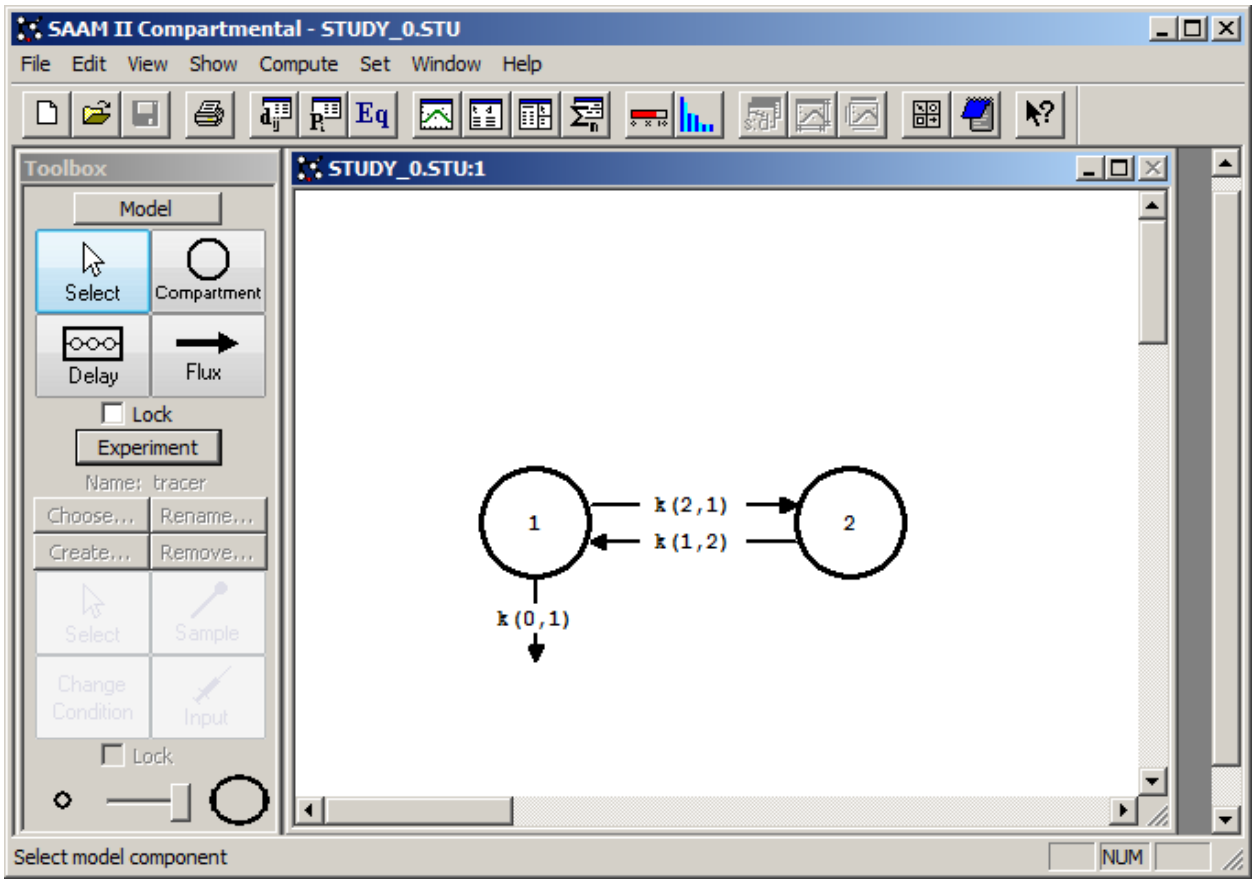
The alternative is to use an existing study file that contains data. This part of the tutorial will use the study file **study_0**, which already contains a data set. What you will learn is how to create a new data set that parallels the existing data

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

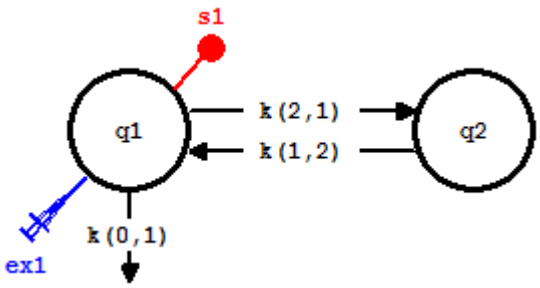
2. Open the **SAAM II Compartmental** study file **study_0**.

    a. The file **study_0.stu** should appear in the file list; if it does not, find the folder where you put this tutorial.

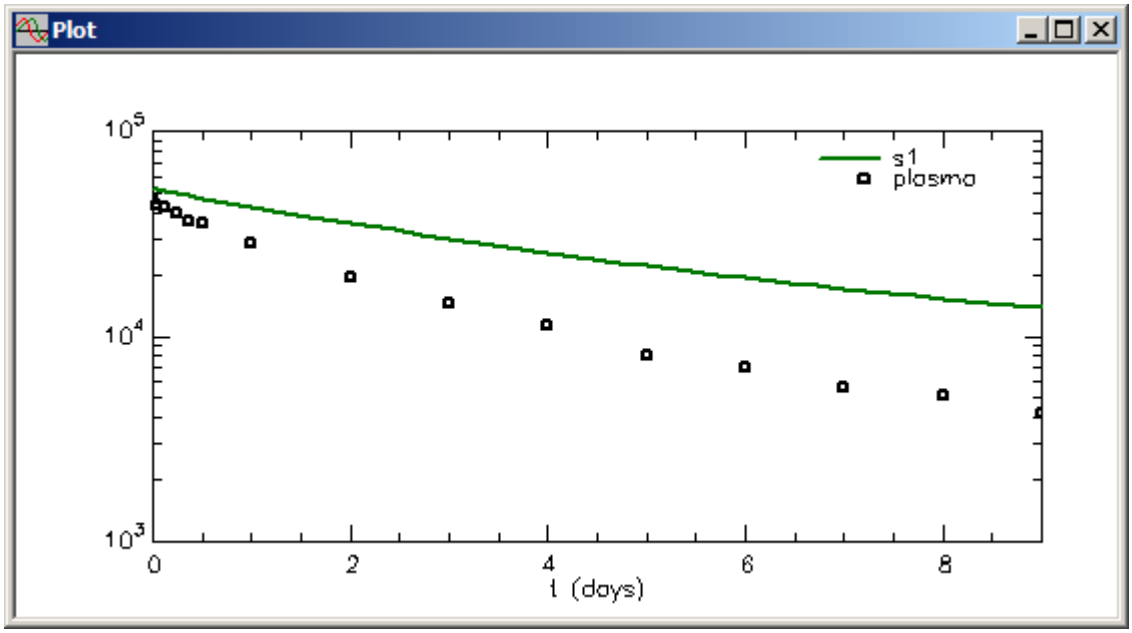
b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as shown below:



3. View the model and the experiment on the model. In the **SAAM II Toolbox**, click **Experiment**. The model of the experiment will appear on the **Drawing Canvas** as follows:



4. Solve the model and view the solution. The plot of **s1:plasma** will appear as follows (in semi-log mode):



Close the **Plot** window.

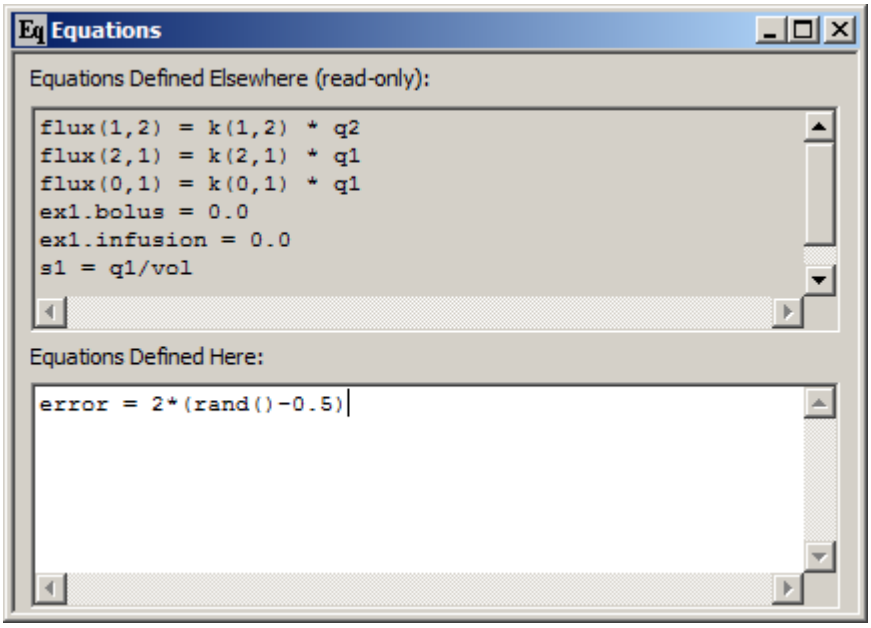
5. Create the error function.

   a. In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar,** click **Equations** Eq. The **Equations** dialog box will open.

   b. Type the following equation in the **Equations Defined Here** box:

   error = 2*(rand()-0.5)

   The **Equations** dialog box will appear as follows:



c. Close the **Equations** dialog box.

6. Create the sample to generate the simulated data.

   a. In the **SAAM II Toolbox**, click **Sample**.

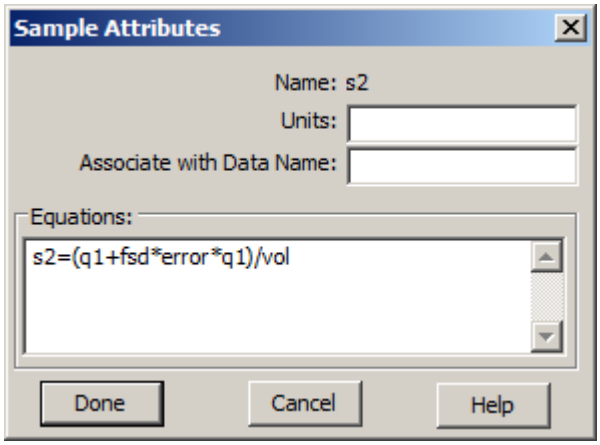
   b. Click Compartment **q1** and then click on the **Drawing Canvas**. The sample **s2** will appear associated with **q1**.

   c. Double-click **s2** to open the **Sample Attributes** dialog box.

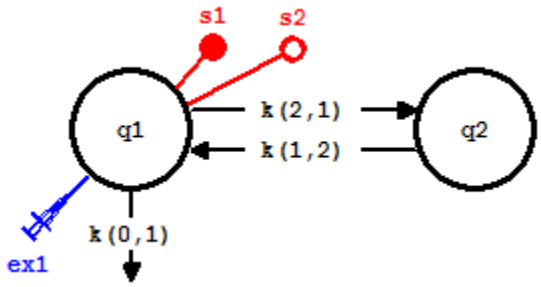
   d. Change the equation for **s2** to read:

      s2=(q1+fsd*error*q1)/vol

      The **Sample Attributes** dialog box will appear as follows:



The model will appear as follows:



Samples and simulated data. Notice the original sample **s1** remains associated with the original plasma data. Sample **s2** will be used to generate simulated data. Keeping both samples will let one compare the original and simulated data.

e. In the **Sample Attributes** dialog box, click **Done**.

Creating simulated data. As explained in the Introduction to this tutorial, the function "error" will generate a random number between -1 and 1. The effect of the "fsd*error*q1" part of the sample equation is the following. In this example, the error associated with the simulated data will be fractional standard deviation. An actual value could be used in the equation instead of "fsd" if you know exactly what the percent error should be. Writing the equation in this way will result in "fsd" becoming a parameter, *fsd*, which will appear when you open the **Parameters** dialog box. In this way you can adjust the percent error to a value which will generate simulated data in line with the kinds of real data you anticipate generating in a real

experiment. Thus the term "fsd*error" will be a random number not between -1 and 1, but between –fsd and fsd. This, when multiplied by the model solution q1(t) will give a random error equal to the assigned "fsd". When added to q1(t), it will produce a datum with a random "fsd" error.

7. View the **Parameters** dialog box, and enter a value for *fsd*.

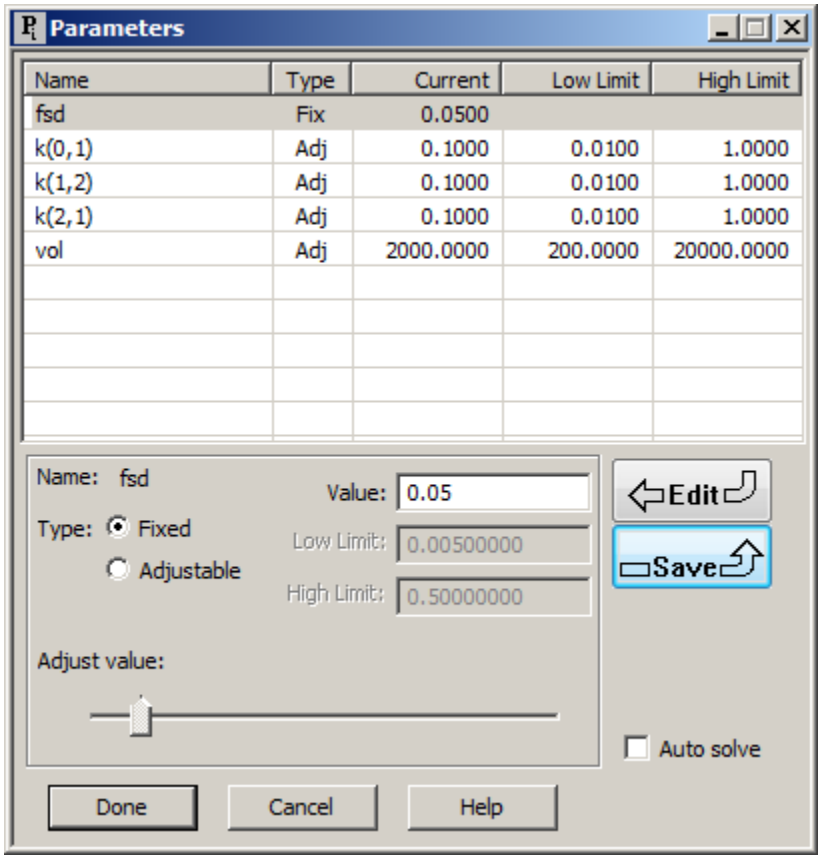
   a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters**  . The **Parameters** dialog box will open.

   b. Double-click *fsd* to make this the active parameter.

   c. In the **Value** box, type "0.05".

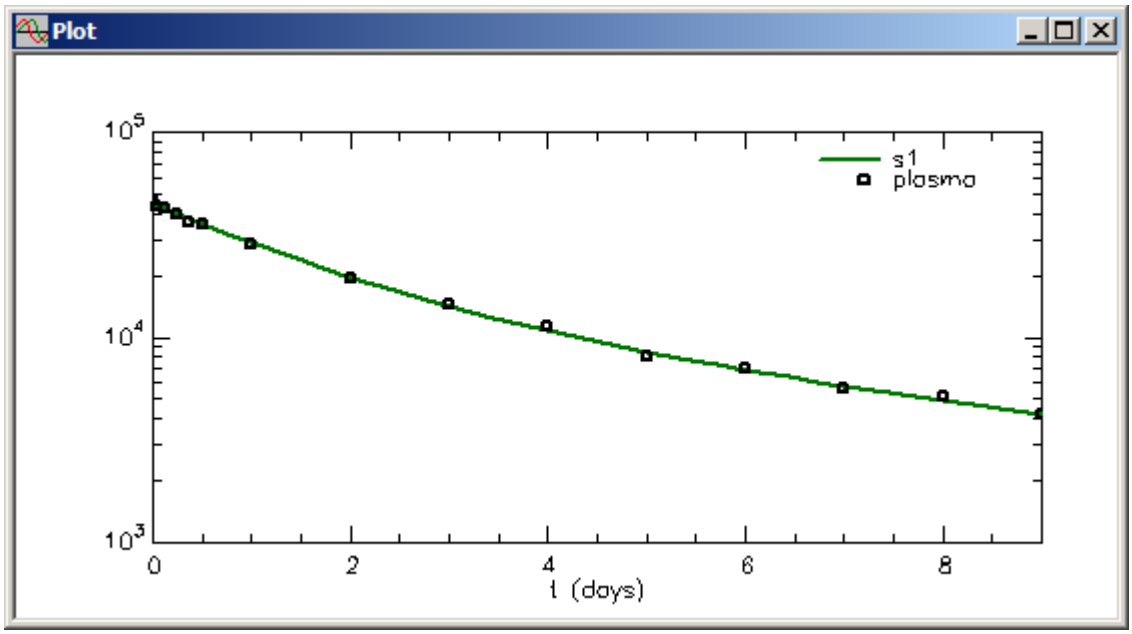
   d. Select **Fixed** as the **Parameter** type.

   e. Click **Save**. The **Parameters** dialog box will appear as follows:



f. Click **Done**.

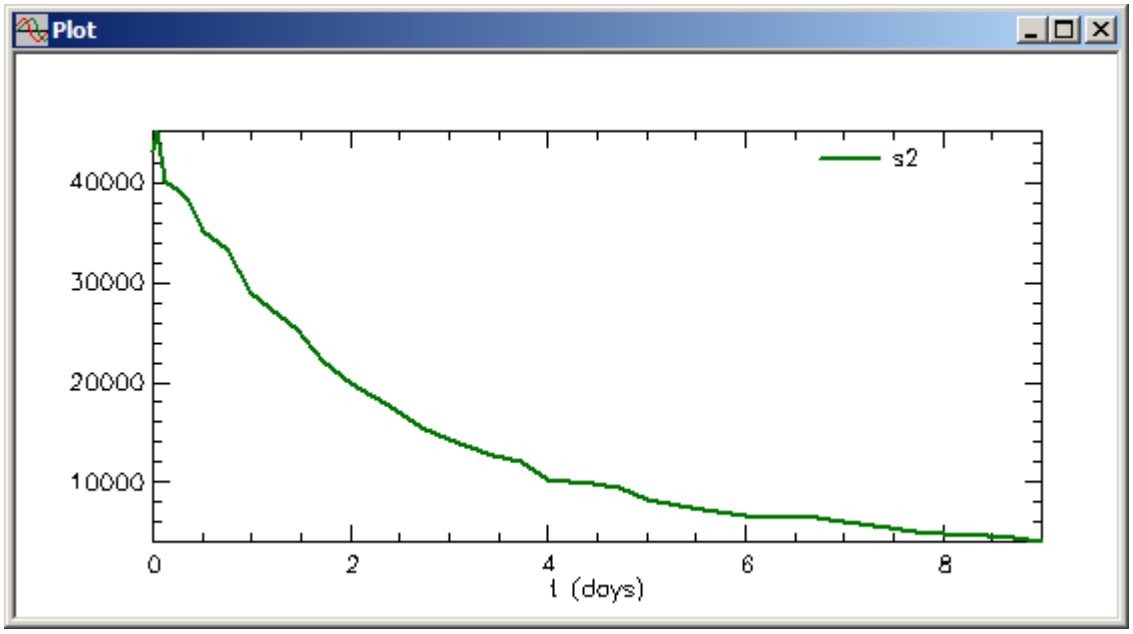
8. Fit the model to the data. The plot of **s1:plasma** will appear as follows:



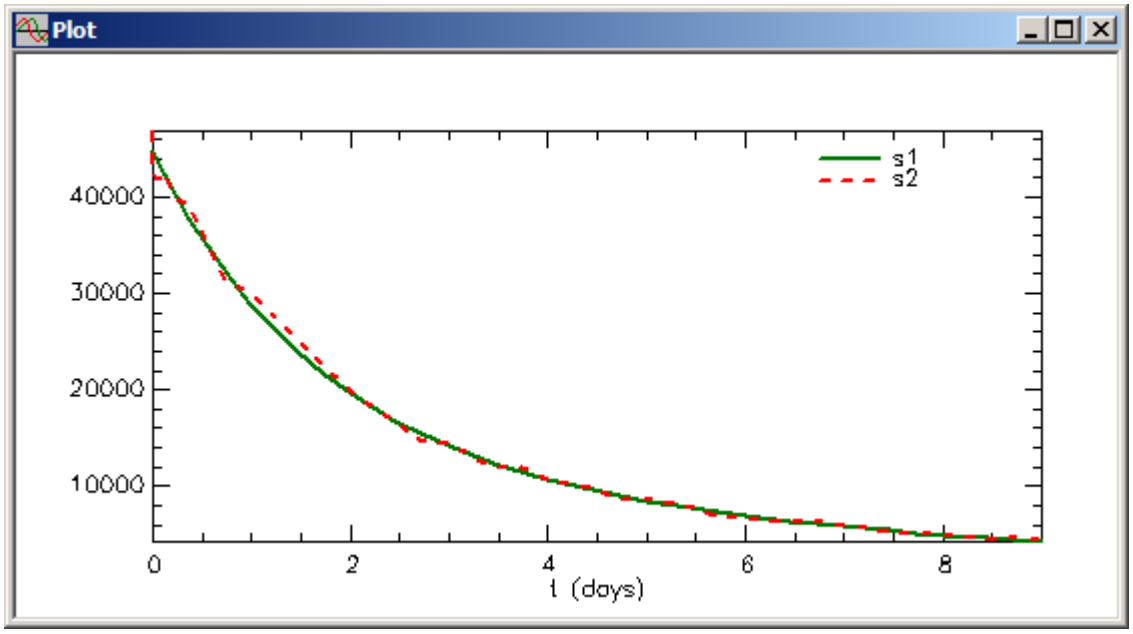
Parameters and simulated data. The strategy in simulating data in this situation is to simulate data comparable to the original data. In this case, you want to simulate data similar to that in **study_0.dat**. Thus you need to Fit the model to the data since the simulated data are based upon the model, and you need a good model description of the original data as a starting point. Once the Fit is performed, you will only be solving to generate new simulated data sets. Of course *fsd* must be a fixed parameter.

9. View the simulated data.

   As part of the fitting process, you solve the model so you will have generated a set of simulated data. A plot of **s2** in linear mode will appear approximately as follows:



A plot of the solution **s1** compared with **s2** in linear mode will appear as follows:



There are two points that need to be made.

The word "approximately" is used because each time you Solve, you will obtain a new set of simulated data. Thus your simulated set may not look exactly like these.

The second is **s2** not smooth while **s1** is smooth? The answer is that **s1** contains the solution **q1** which is a smooth, continuous function. On the other hand, **s2** contains the solution **q1** to which error has been added. At each SAAM II calculation point, a value

of **s2** which contains this error is calculated, and plotted. This is why **s2** is not smooth. In this case, *fsd* is 0.05 or only a 5% error. If you increase the value of *fsd*, the **s2** will exhibit much more variability when compared with **s1**.

Close the **Plot** window.

10. Modify the format for the simulated data.

    a. View the simulated data in tabular format. In the **Show** menu, click **Table**, or alternatively, on the **SAAM II Toolbar,** click **Table**  . Since the **Plot** window was previously opened with **s1** and **s2**, the **Table** window will open as follows:

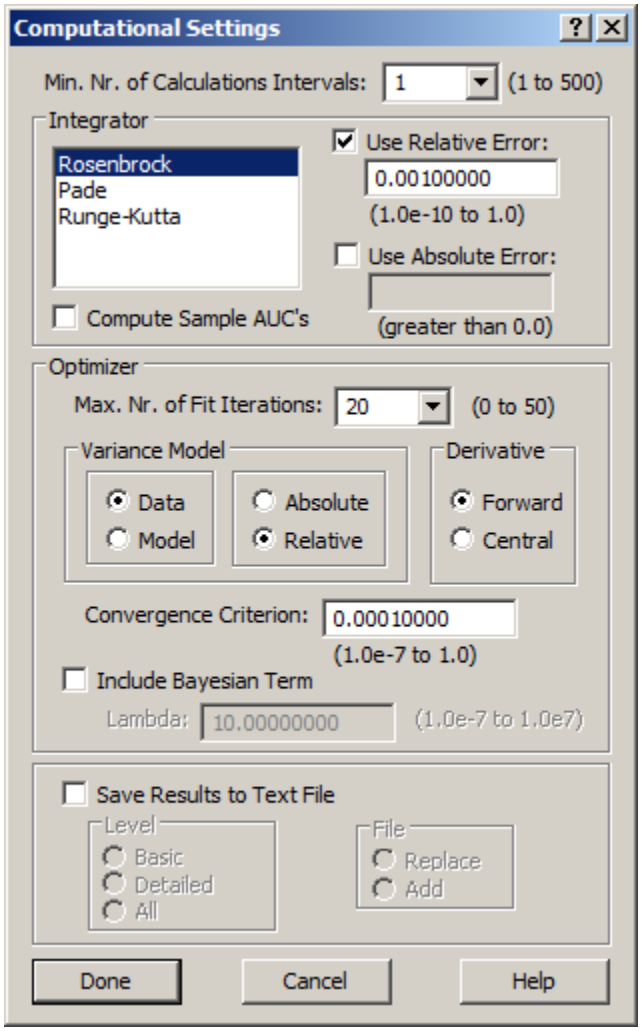
Table

t	s1	s2
0.000	44754.732	46846.460
7.00000e-003	44608.789	42992.338
4.20000e-002	43887.777	41900.994
0.125	42234.517	42398.147
0.250	39887.687	39718.298
0.375	37701.625	39056.166
0.500	35664.642	36262.028
0.750	31995.409	31160.298
1.000	28802.603	30029.661
1.450	24050.218	25228.874
1.725	21664.652	22604.873
2.000	19601.193	19915.457
2.450	16796.027	16641.764
2.725	15368.982	14724.688
3.000	14121.006	14437.691
3.450	12397.968	11878.034
3.725	11506.245	11895.306
4.000	10715.665	10742.171
4.450	9603.457	9863.817
4.725	9016.183	8622.993
5.000	8487.392	8688.976
5.450	7728.050	7818.368
5.725	7318.556	7033.057
6.000	6944.009	6765.413
6.450	6395.269	6390.087
6.725	6093.436	6306.428
7.000	5813.411	5997.685
7.450	5395.888	5249.484
7.725	5162.366	5031.436
8.000	4943.185	4869.227
8.450	4611.791	4528.927
8.725	4424.042	4558.685
9.000	4246.276	4438.063
9.000	4246.276	4403.165

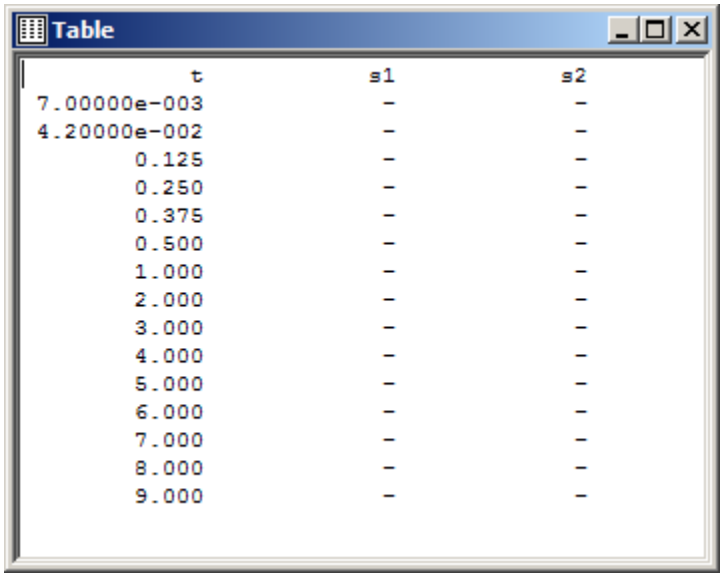
This allows you to compare the simulated solution **s1** with the new simulated data set **s2**. There are many more simulated data than in your original data file because SAAM II will calculate a simulated datum at each calculation point. How to deal with this will be explained below.

b. In the **Compute** menu, click **Settings**. The **Computational Settings** dialog box will open.

c. Type "1" in the **Min. Nr. of Calculation Intervals** box. The **Computational Settings** dialog box will appear as follows:



d. Click **Done**. Notice the **Table** window changes as follows:

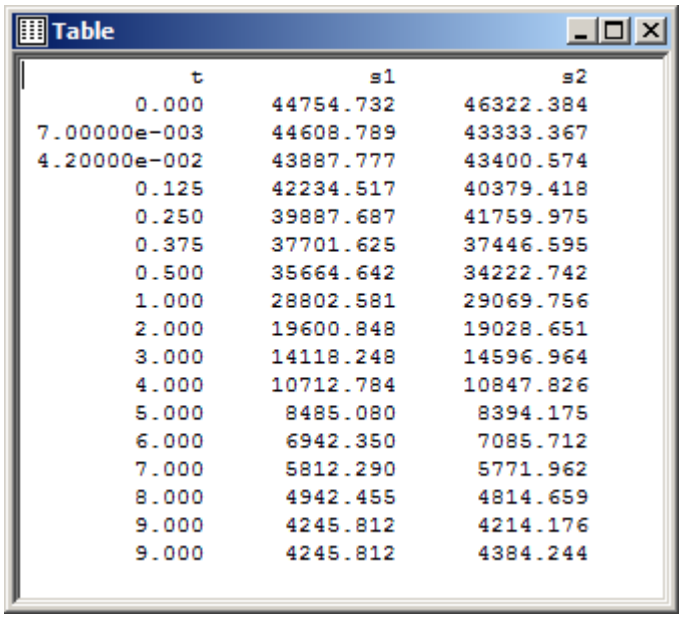


Table

t	s1	s2
7.00000e-003	-	-
4.20000e-002	-	-
0.125	-	-
0.250	-	-
0.375	-	-
0.500	-	-
1.000	-	-
2.000	-	-
3.000	-	-
4.000	-	-
5.000	-	-
6.000	-	-
7.000	-	-
8.000	-	-
9.000	-	-

This now has the sample times in agreement with the original data file because the minimum number of calculation intervals has been set equal to 1. Notice there are no values for **s1** or **s2**; this is because the computational settings have been changed. To obtain values, you must Re-Solve.

e. Re-Solve the model. The **Table** will be updated as follows:



Table

t	s1	s2
0.000	44754.732	46322.384
7.00000e-003	44608.789	43333.367
4.20000e-002	43887.777	43400.574
0.125	42234.517	40379.418
0.250	39887.687	41759.975
0.375	37701.625	37446.595
0.500	35664.642	34222.742
1.000	28802.581	29069.756
2.000	19600.848	19028.651
3.000	14118.248	14596.964
4.000	10712.784	10847.826
5.000	8485.080	8394.175
6.000	6942.350	7085.712
7.000	5812.290	5771.962
8.000	4942.455	4814.659
9.000	4245.812	4214.176
9.000	4245.812	4384.244

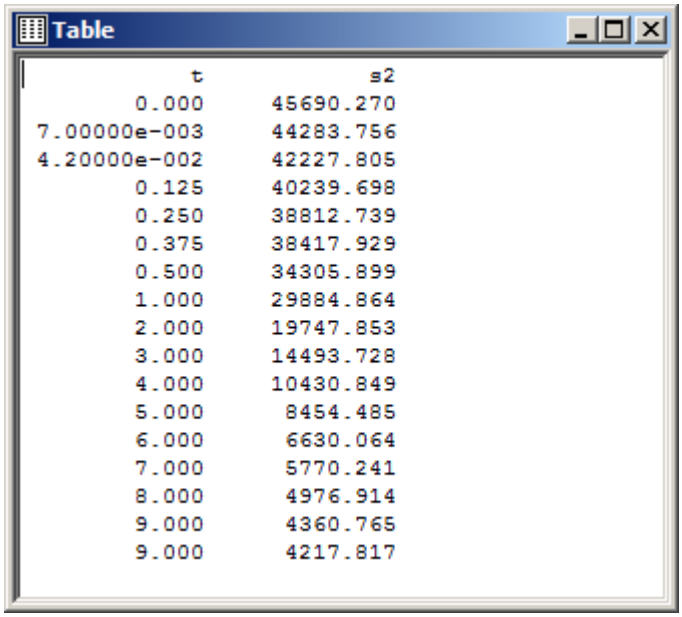
Notice there are two values at day 9. SAAM II always calculated two values at the last sample point. You can simply delete one of them when you continue your work.

Solving and simulated data. Every time you Solve, you will generate a new set of simulated data. This is because, in this case, **s2** gets calculated with each Solve. Thus if you compare the data set generated above with the original set of simulated data, there will be differences. This is useful if you are generating several sets of simulated data. You can simply Solve, save the data as described in Step 10, Re-Solve and continue.

10. Use the simulated data.

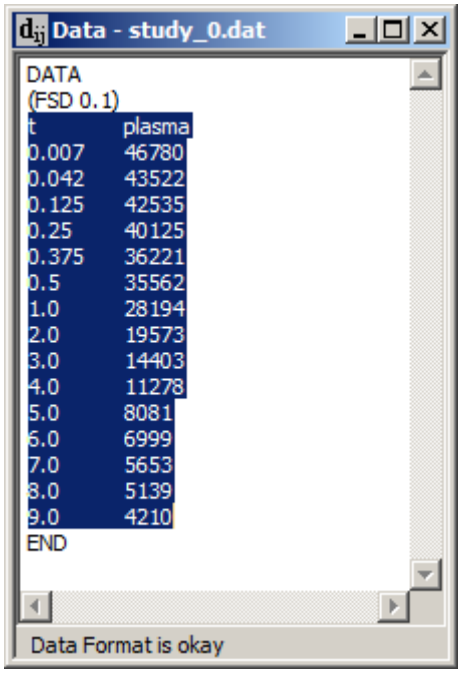
    There are many ways you can use the simulated data. One is to cut and paste the data to a spread sheet. Another way, cutting and pasting directly into the **Data** window, and fitting the model to the data will be illustrated how.

    a. In the **Set** menu, click **Plot/Table** variables. The **Plot and Table Variables** dialog box will open. Click **s2** to move this (as the only variable) to the **Current Selection** pane. Click **Done**. The **Table** window will appear as follows:



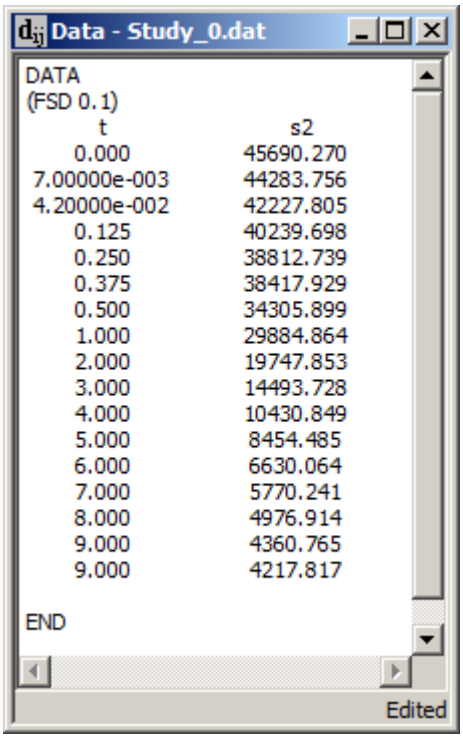
    b. ***Select and copy the data*** in the **Table** window. Close the **Table** window.

    c. Open the **Data** window, and select the contents of this window as shown below:



Notice the first two and last lines have not been selected.

c. In the **Edit** menu, click **Paste**. The **Data** window will appear as follows:



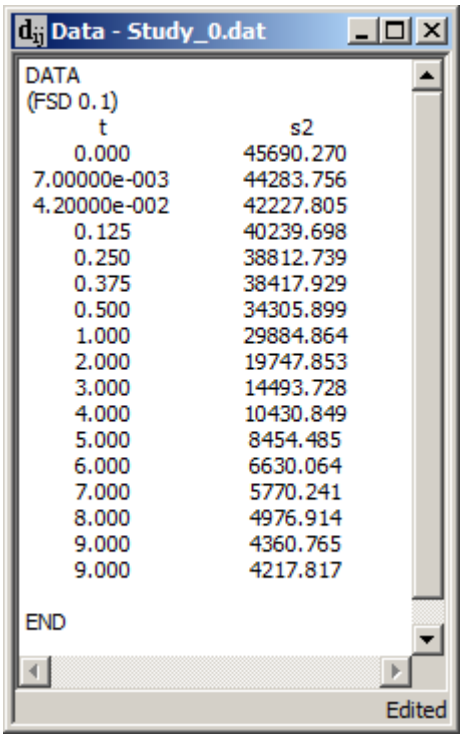
d. In the **Data** window:

(1) Change "s2" to "plasma".

(2) Remove the zero time value. Remove the second datum at day 9.

(3) Remove any spaces before the "END" statement.

(4) In the **Edit** menu, click **Check Data Format**. Correct any errors if there are any. The **Data** window should appear as follows:



(5) Close the **Data** window.

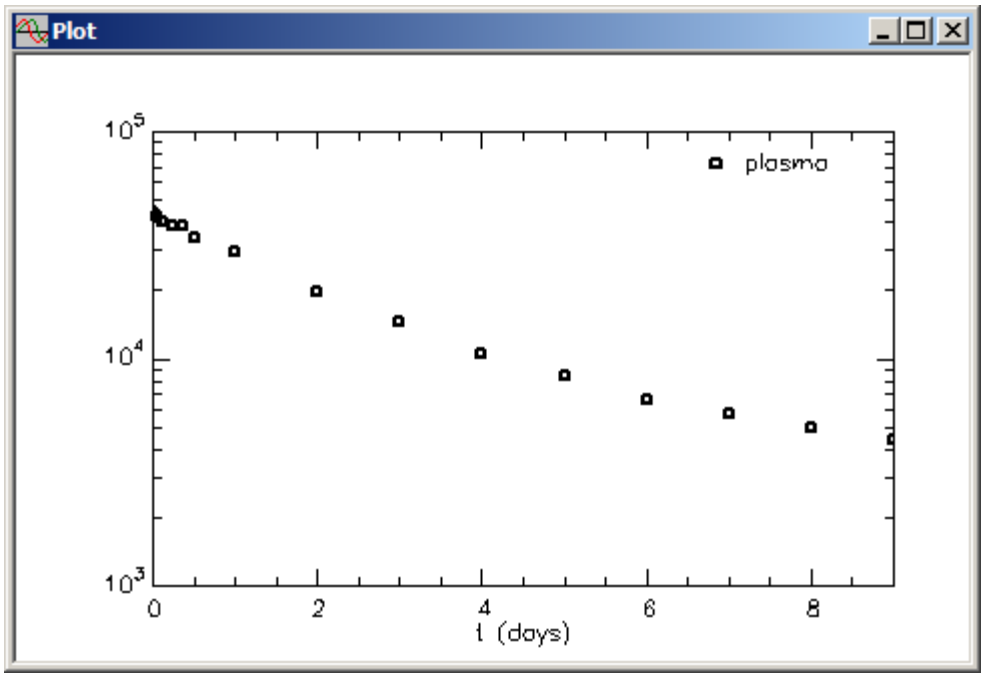
e. Save the study file with the new data.

Since these data are not those in **study_0.dat**, if you want to work with this new set of data, you should save the study file with a new name.

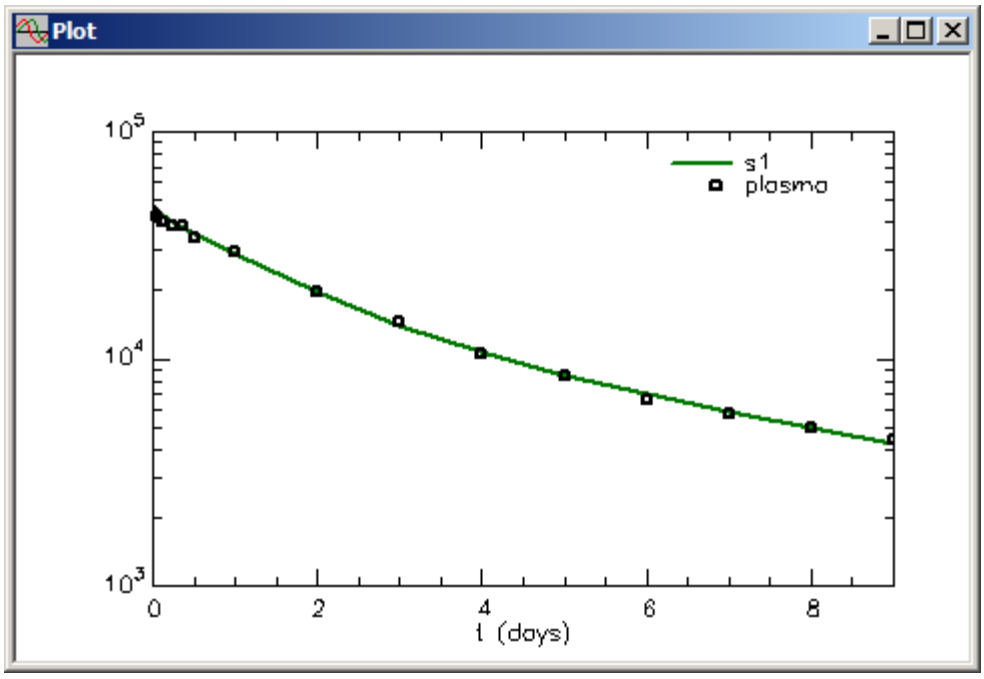
(1) In the **File** menu, click **Save As**.

(2) In the **File Name** box, type the desired new file name (e.g. Simulate_1).

(3) Click **Save**. You can now use this file to continue your analyses. For example, a plot of the simulated data is shown as follows:



and a plot of the solution (remember using the initial parameter estimates for **study_0**) is shown below:



Close the **Plot** window if you created these plots.

Quit the **SAAM II Compartmental** application. You may want to check to be sure there are no changes to **study_0**.

Part 2. Simulating plasma data and 24 hour urine collections

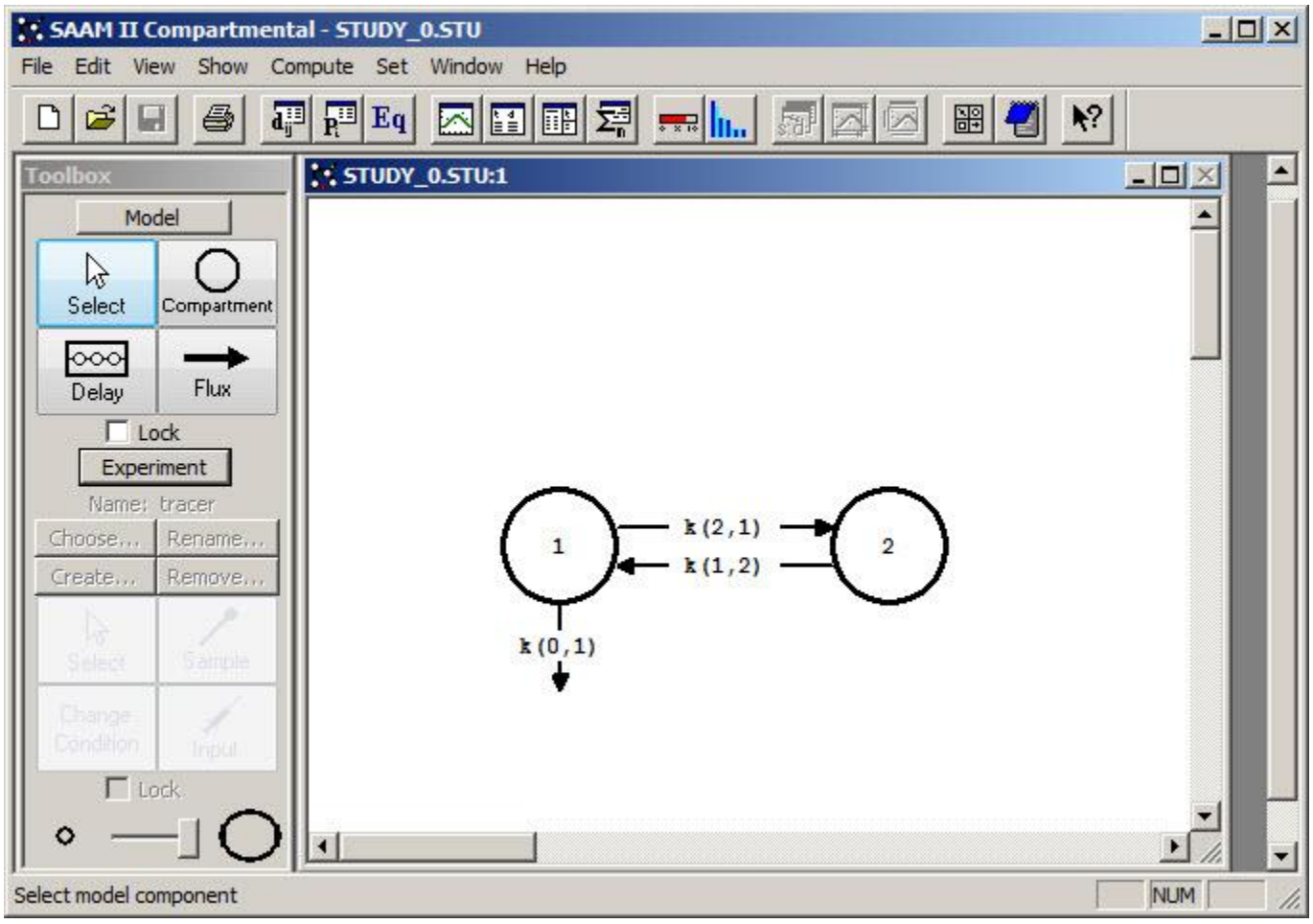
This part of the tutorial will use the study file **study_0**. **study_0** already contains a data set. You will change the experimental protocol for one lasting 14 days instead of 9, and use a data file which contains only the times at which you wish samples. Such a strategy can be used in establishing experimental protocols when you want to determine, for example, an optimal, practical sampling schedule. Thus this is an example of using an existing system model, and modifying it as part of an experimental design process.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

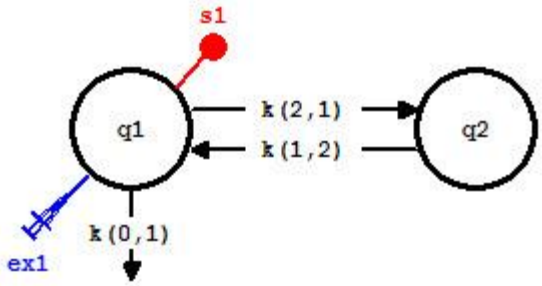
2. Open the **SAAM II Compartmental** study file **study_0**.

   a. The file **study_0.stu** should appear in the file list; if it does not, find the folder where you put this tutorial.

   b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as shown below:



3. View the model and the experiment on the model. In the **SAAM II Toolbox**, click **Experiment**. The model of the experiment will appear on the **Drawing Canvas** as follows:

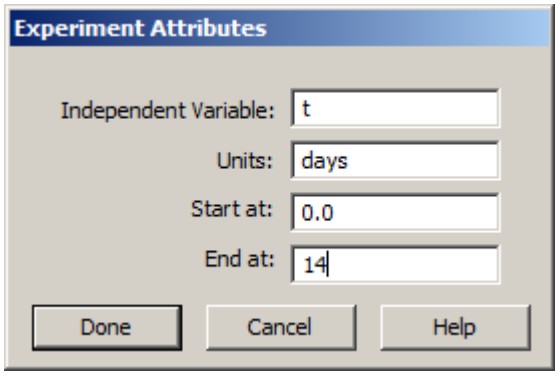


4. Modify the experiment in **study_0**.

   a. Change the time of the experiment from 9 to 14 days.

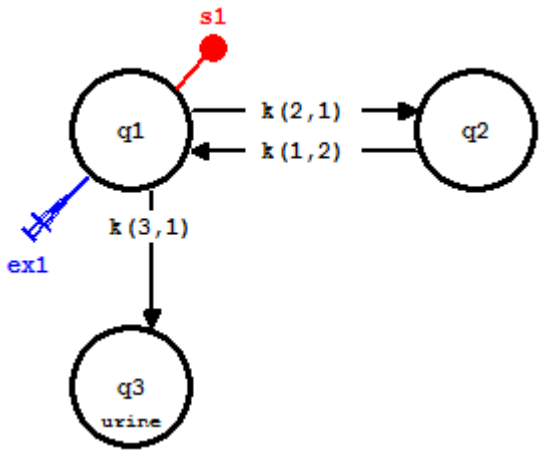
      (1) In the **Set** menu, click **Experimental Attributes**. The **Experimental Attributes** dialog box will open.

      (2) Change the value in the **End At** box from "9" to "14". The **Experimental Attributes** dialog box will appear as follows:



      (3) Click **Done**.

   b. Add a compartment to the model for urine. Modify the model to the following:

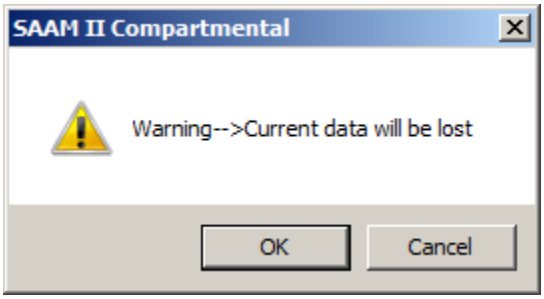


Compartment **q3** will be used to simulate the 24 hour urine collections.

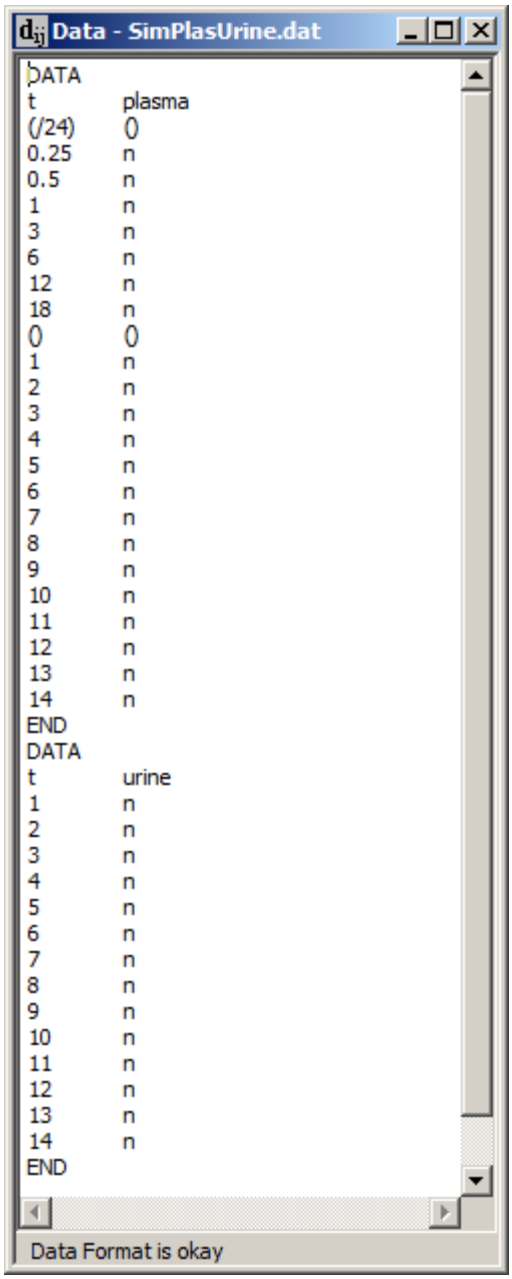
c. Change the data in the **Data** window.

(1) Open the **Data** window (the original data for **study_0** will appear).

(2) Replace these data with **SimPlasUrine.dat**. Open the **Data** window. In the **File** menu, click **Open**. Double-click **SimPlasUrine.dat** to replace the data in **study_0**. A Warning will be appear:



Click on OK. The **Data** window should appear as follows.



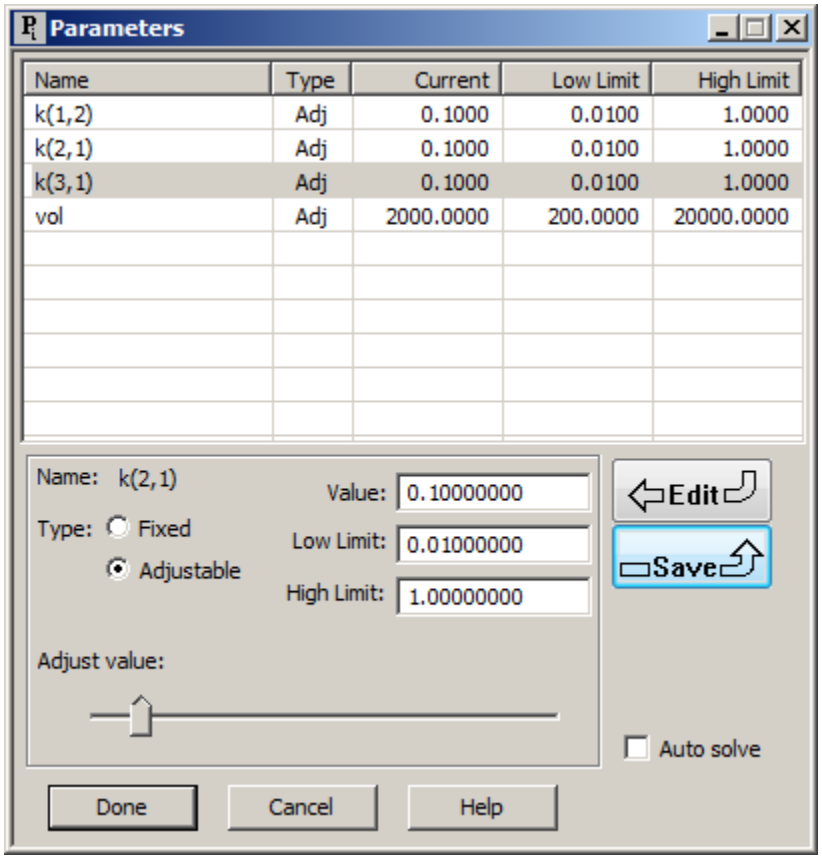
Notice in the **Data** window the first few samples are in hours. Division by 24, which is invoked by (/24), will convert these times to days. There are separate data segments for plasma and urine since urine and plasma sample times do not always coincide.

This **Data** window is different from Part 1 of the tutorial. In Part 1, you were starting from a given set of data, and generating new data. In this part of the tutorial, the **Data** window contains only the time points at which you want to produce simulated data.

(3) Close the **Data** window.

d. Reset the parameter values.

When you eliminated *k(0,1)* and introduced Compartment **q3**, essentially *k(0,1)* was replaced by *k(3,1)*. Open the **Parameters** dialog box, and type "0.1" in the **Value** box for *k(3,1)*. Click **Save**. The **Parameters** dialog box should appear as follows:



Close the **Parameters** dialog box.

e. Create the mechanism for the 24 hour urine collections.

To create the 24 hour urine collections, the contents of Compartment **q3** will be reset to zero using **Change Conditions**.

(1) In the **SAAM II Toolbox**, click **Change Conditions**. The **Change Conditions** dialog box will open.

(2) In the **Duration** pane, select **Instantaneous**.

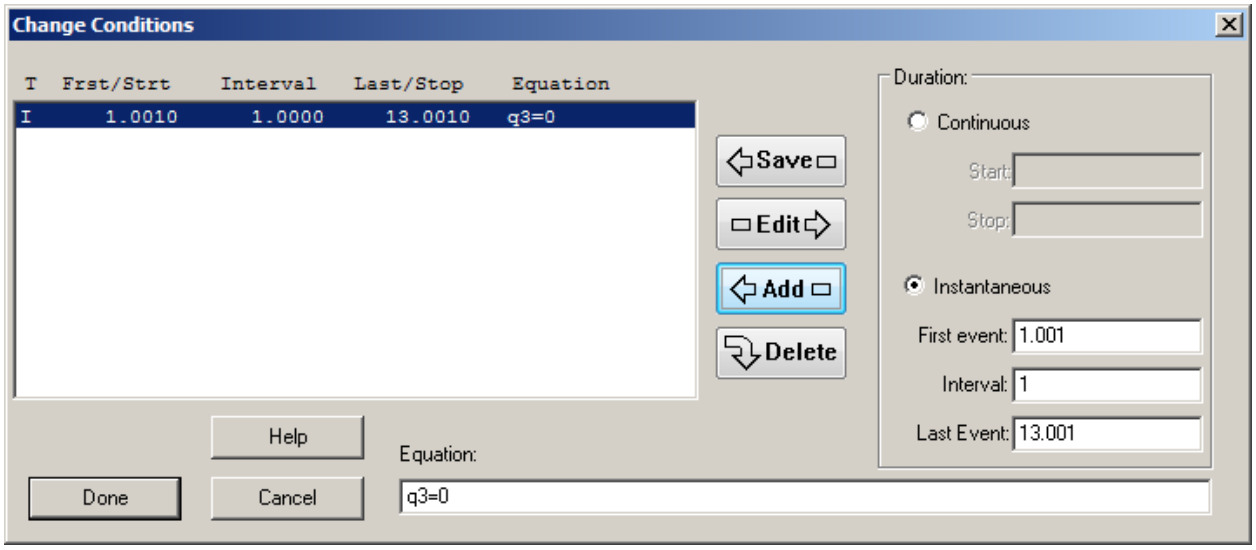
(3) In the **First Event** box, type "1.001".

(4) In the **Interval** box, type "1".

(5) In the **Last Event** box, type "13.001"

(6) In the **Equation** box, type "q3=0".

(7) Click **Add**. The **Change Conditions** dialog box will appear as follows:



Remember the purpose of setting the value of Compartment q3 equal to zero at 1.001, 2.001, etc. is because the actual sample is at 1, 2, etc, and the container is emptied just after the sample. Adding "0.001" to the time accommodates this.

(8) Click **Done**.

f. Save the study file as **SimPlasUrine** (this to ensure you do not over write **study_0**.)

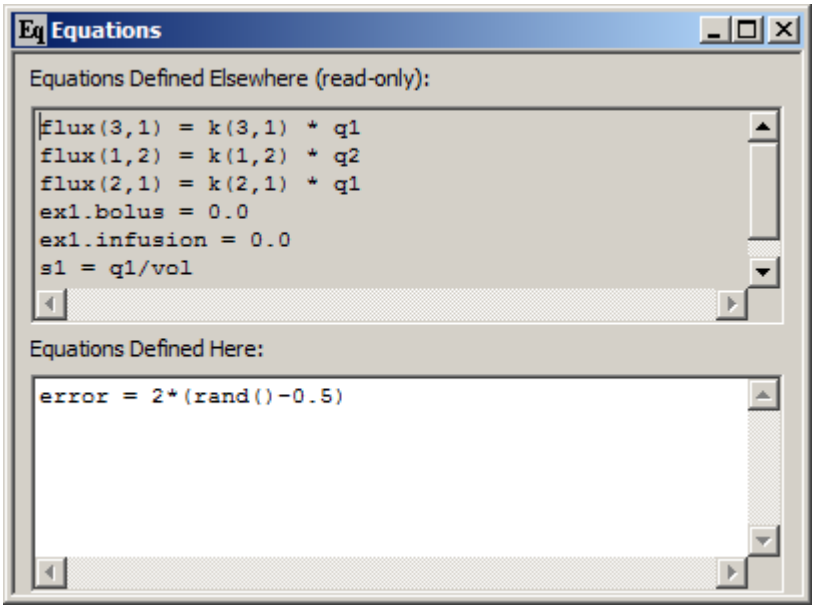
5. Create the error function.

a. In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar,** click **Equations** Eq. The **Equations** dialog box will open.

b. Type the following equation in the **Equations Defined Here** box:

error = 2*(rand()-0.5)

The **Equations** dialog box will appear as follows:



c. Close the **Equations** dialog box.

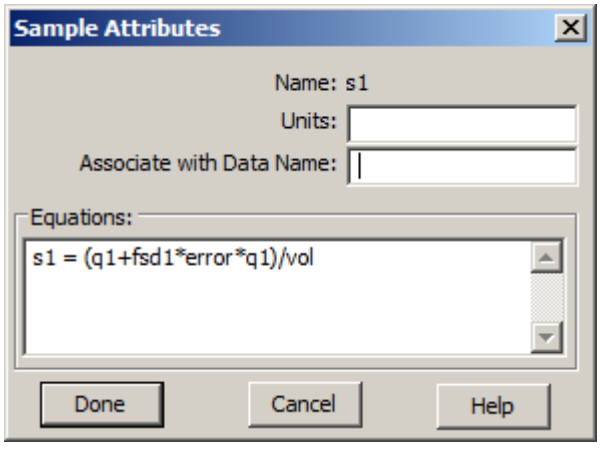
6. Create the samples to generate the simulated data.

   a. Double-click **s1** to open the **Sample Attributes** dialog box.

   b. Edit the sample equation to read:

$$s1 = (q1+fsd1*error*q1)/vol$$

   c. Remove "plasma" from the **Associate with Data Name** box. The **Sample Attributes** dialog box should appear as follows:



   d. Click **Done**.

   e. In the **SAAM II Toolbox**, click **Sample**.

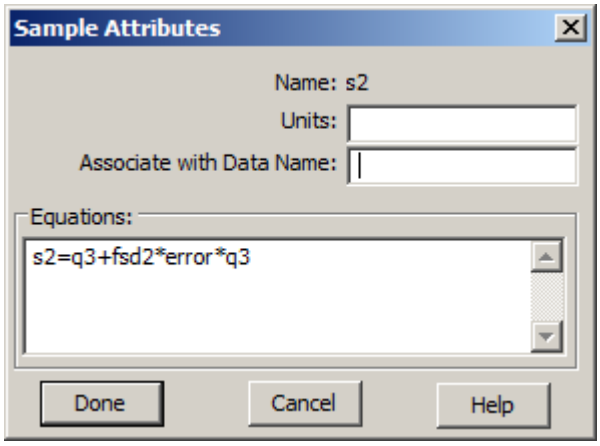
f. Click Compartment **q3** and then click on the **Drawing Canvas**. The sample **s2** will appear associated with **q3**.

g. Double-click **s2** to open the **Sample Attributes** dialog box.

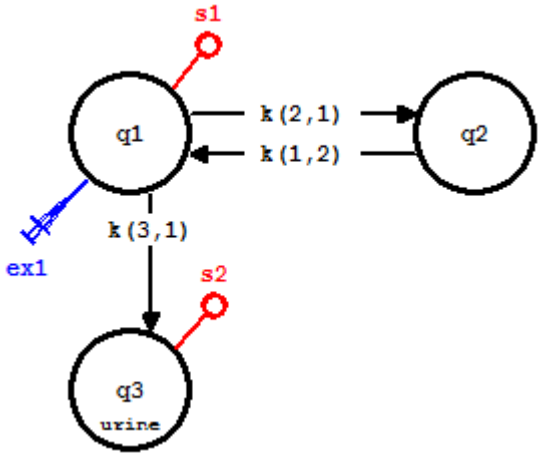
h. Change the equation for **s2** to read:

s2=q3+fsd2*error*q3

The **Sample Attributes** dialog box will appear as follows:



The model will appear as follows:



i. In the **Sample Attributes** dialog box, click **Done**.

Creating simulated data. As explained in the Introduction to this tutorial, the function "error" will generate a random number between -1 and 1. The effect of the "fsd1*error*q1" part of the sample equation is the following. In this example, the error associated with the simulated data will be fractional standard deviation. An actual value could be used in the equation instead of "fsd1" if you know exactly what the percent error should be. Writing the equation in this way will result in "fsd1" becoming a parameter, *fsd1*, which will appear when you open the **Parameters** dialog box. In this way you can adjust the percent error to a value which will generate simulated data in line with the kinds of real data you anticipate generating in a real experiment. Thus the term "fsd1*error" will be a random number not between -1 and 1, but between –fsd1 and fsd1. This, when multiplied by the model solution q1(t) will give a random error equal to the assigned "fsd1". When added to q1(t), it will produce a datum with a random "fsd1" error. Similarly for the urine, except "fsd2" is used in the expression. This will permit the possibility of the plasma and urine simulated data having different coefficients of variation.

7. View the **Parameters** dialog box, and enter a value for *fsd1* and *fsd2*.

   a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters**  . The **Parameters** dialog box will open.

   b. Double-click *fsd1* to make this the active parameter.

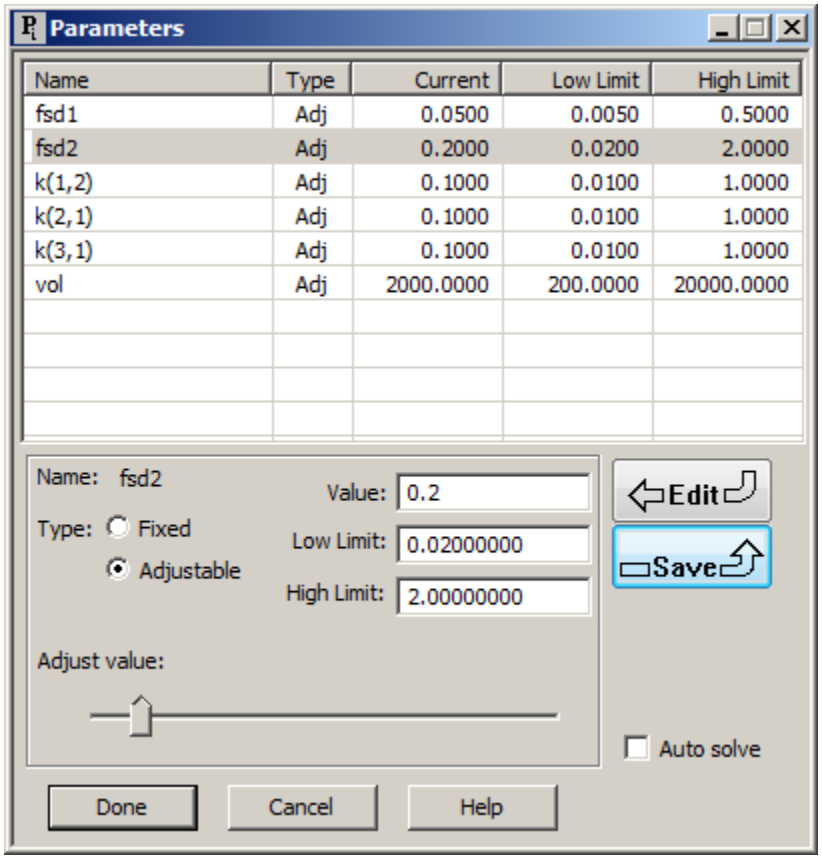
   c. In the **Value** box, type "0.05".

   d. Click **Save**.

   e. Double-click *fsd2* to make this the active parameter.

   f. In the **Value** box, type "0.2".

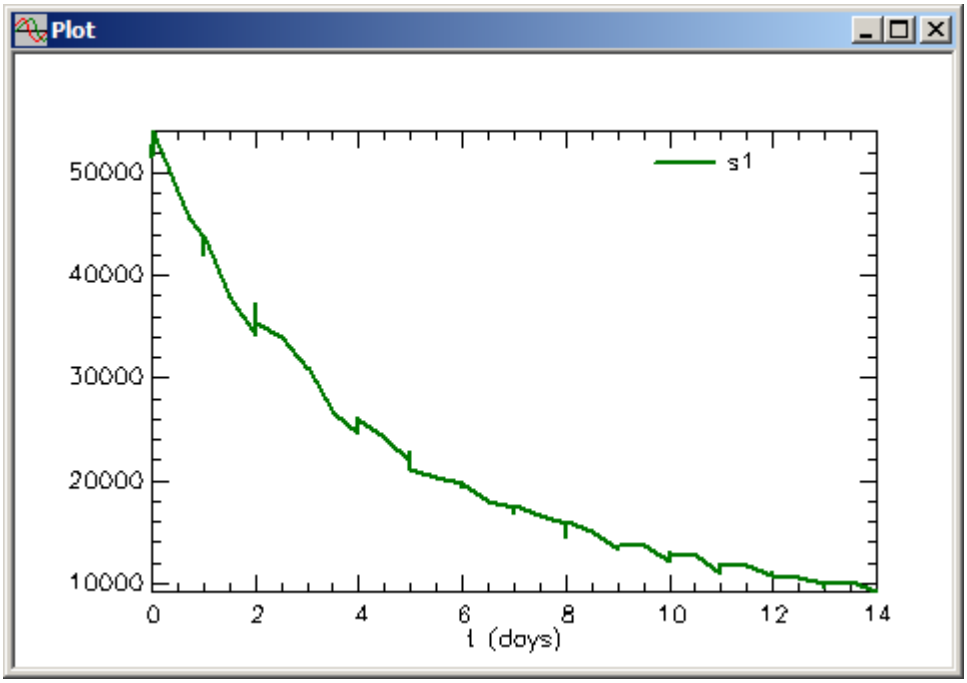
   h. Click **Save**. The **Parameters** dialog box will appear as follows:



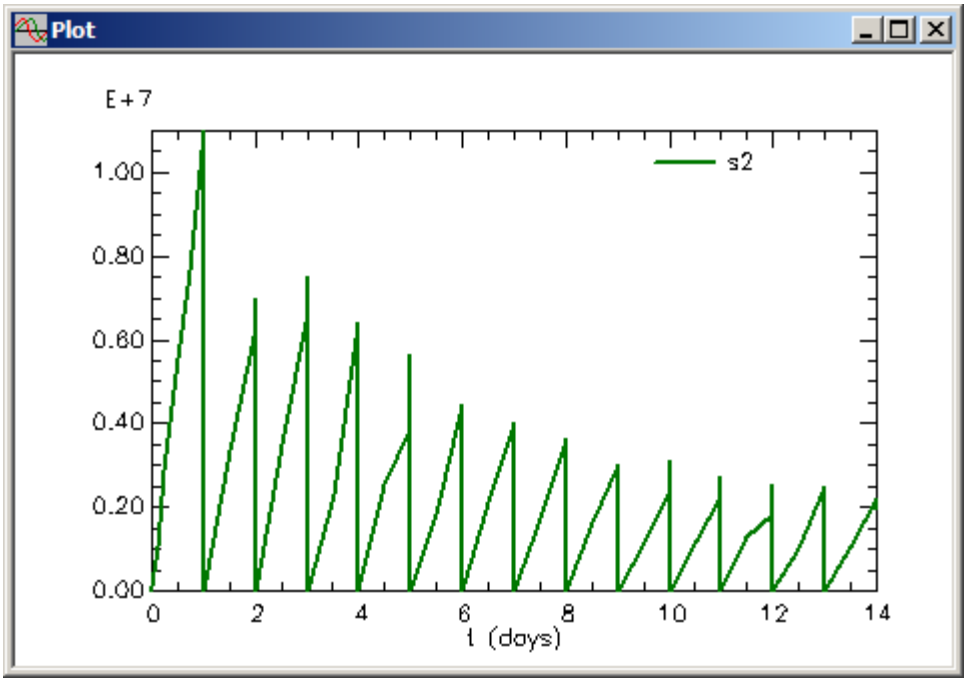
Parameters and simulated data. Even though the parameters in **study_0** are adjustable, only simulations will be performed when simulating data. Thus the parameters can be regarded as fixed.

i. Click **Done**.

8. Solve the model and view the simulated data **s1** and **s2**. The plot of **s1** in linear mode will appear (approximately) as follows:



The plot of **s2** will appear in linear mode as follows:



There are two points that need to be made.

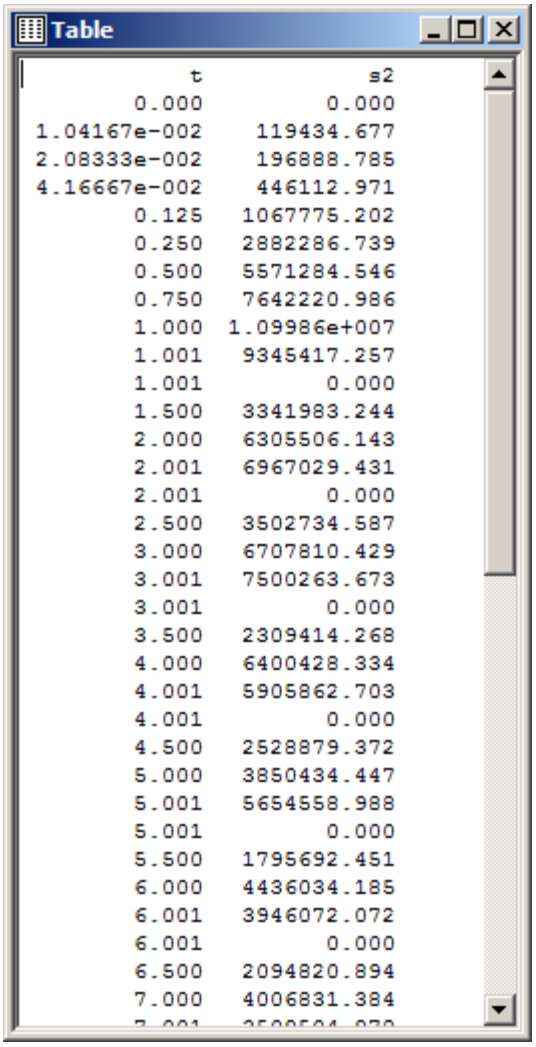
The word “approximately” is used because each time you Solve, you will obtain a new set of simulated data. Thus your simulated set may not look exactly like these.

The second is neither **s1** nor **s2** are smooth. Why? The answer is that both contain the solutions **q1** and **q3** respectively which are smooth, continuous functions. At each SAAM II calculation point, the values of **s1** and **s2** contain the errors, i.e. the errors are calculated and added to **q1** and **q3** respectively. This is what is plotted. Obviously it is not as noticeable in **s2** because these are simulated 24 hour urine collections.

Close the **Plot** window.

9. Modify the format for the simulated data.

   a. View the simulated data in tabular format. In the **Show** menu, click **Table**, or alternatively, on the **SAAM II Toolbar,** click **Table**  . Since the **Plot** window was previously opened with **s2**, the **Table** window will open (in part) as follows:

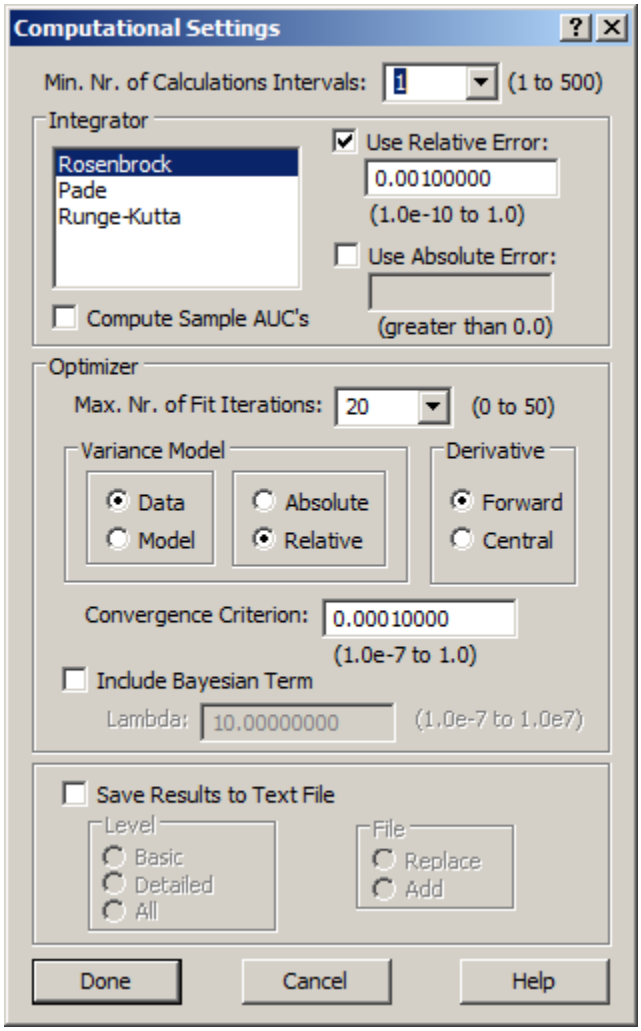


There are many more simulated data than in your original data file. This is because SAAM II will calculate a simulated datum at each calculation point. How to deal with this will be explained below.

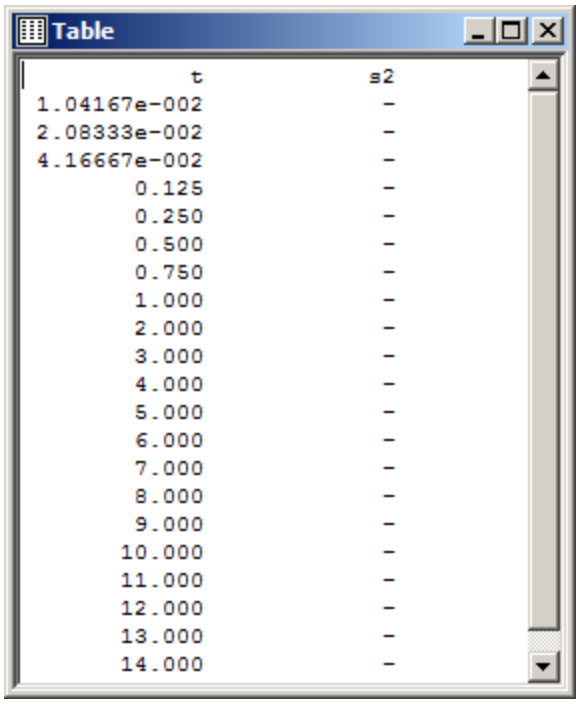
Leave the **Table** window open.

b. In the **Compute** menu, click **Settings**. The **Computational Settings** dialog box will open.

c. Type "1" in the **Min. Nr. of Calculation Intervals** box. The **Computational Settings** dialog box will appear as follows:



d. Click **Done**. Notice the **Table** window changes as follows:



This now has the sample times in agreement with the original data file because the minimum number of calculation intervals has been set equal to 1. As before, there are no calculated values for **s2** as the computational settings have changed.

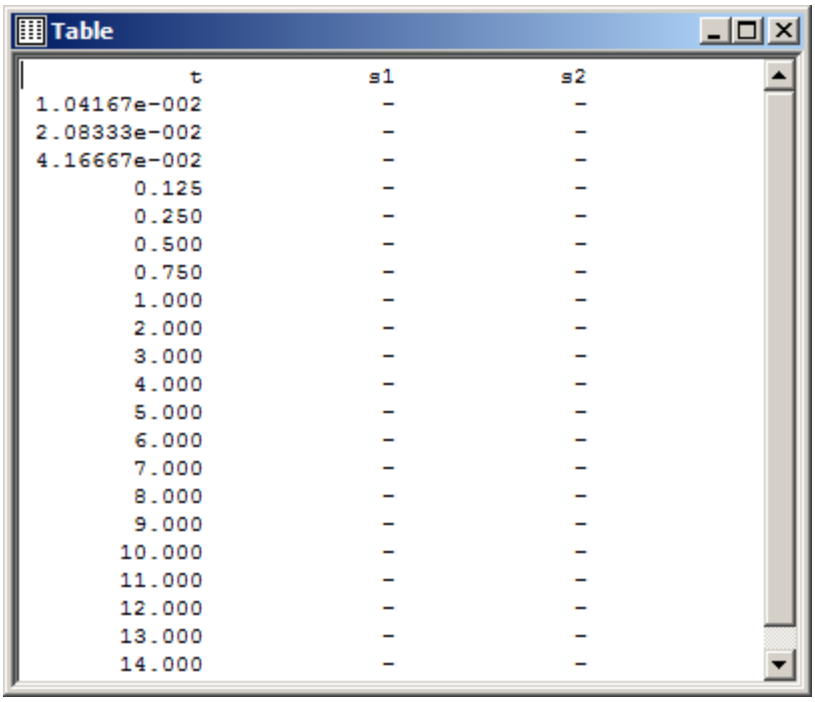
e. Include **s1** in the table.

(1) In the **Set** menu, click **Plot/Table** variables; or select the Plot/Table Variables button 

. The **Plot and Table Variables** dialog box will open.

(2) Include **s1** in the **Current Selection** pane.

(3) Click **Done**. The **Table** window will appear as follows:



f. Re-Solve the model. The **Table** will be updated as follows:

Table

t	s1	s2
0.000	49427.931	0.000
1.04167e-002	50520.595	96781.906
2.08333e-002	51623.094	213530.433
4.16667e-002	49342.215	357001.003
0.125	51525.081	1365426.924
0.250	48827.558	2402653.865
0.500	46445.750	4670717.431
0.750	46430.538	8247750.464
1.000	40977.461	7837960.798
1.001	43405.483	9996961.678
1.001	43513.209	0.000
2.000	34987.159	7260315.693
2.001	36906.068	8956174.409
2.001	34153.941	0.000
3.000	29146.511	5809036.867
3.001	30933.531	7377179.560
3.001	29337.929	0.000
4.000	26595.351	6441605.039
4.001	24351.894	4506738.316
4.001	26762.632	0.000
5.000	22778.473	5377672.913
5.001	22729.934	5343645.744
5.001	22885.396	0.000
6.000	18636.624	3589298.525
6.001	19597.751	4417169.673
6.001	19870.311	0.000
7.000	17165.794	3738766.609
7.001	17679.725	4181100.808
7.001	16612.363	0.000
8.000	15442.192	3401029.945
8.001	15129.347	3141089.095
8.001	15002.729	0.000
9.000	14129.724	3202862.894
9.001	13506.329	2682687.435
9.001	14410.438	0.000
10.000	12693.515	2741256.418
10.001	12999.653	3001080.266
10.001	12241.851	0.000
11.000	11462.801	2329244.045
11.001	11083.144	2015762.047
11.001	11307.673	0.000
12.000	10537.056	2075547.191
12.001	10188.721	1788886.210
12.001	11138.626	0.000
13.000	10389.810	2390727.637
13.001	9763.891	1875430.160
13.001	10117.592	0.000
14.000	9838.630	2310772.917
14.000	9402.499	1951056.412

Change conditions and simulated data. The table is different from the table with no calculated values. This is because when SAAM II calculates a solution in a model

that includes Change Conditions, it will calculate and report the model calculated value at the Change condition time (e.g. 1.001); it will then report the value after the Change Condition has occurred. Thus for the time point 1.001 at which a Change Condition occurred, you see a value followed by a second value of zero. This is a check to let you know the calculations are being performed correctly. SAAM II also calculates two values for the end of experiment time. You will simply remove one of these as you work with this table.

Solving and simulated data. Every time you Solve, you will generate a new set of simulated data. This is because, in this case, **s1** and **s2** get calculated with each Solve. Since the error term is included and is random, it also is calculated producing different values for **s1** and **s2** with each solve.

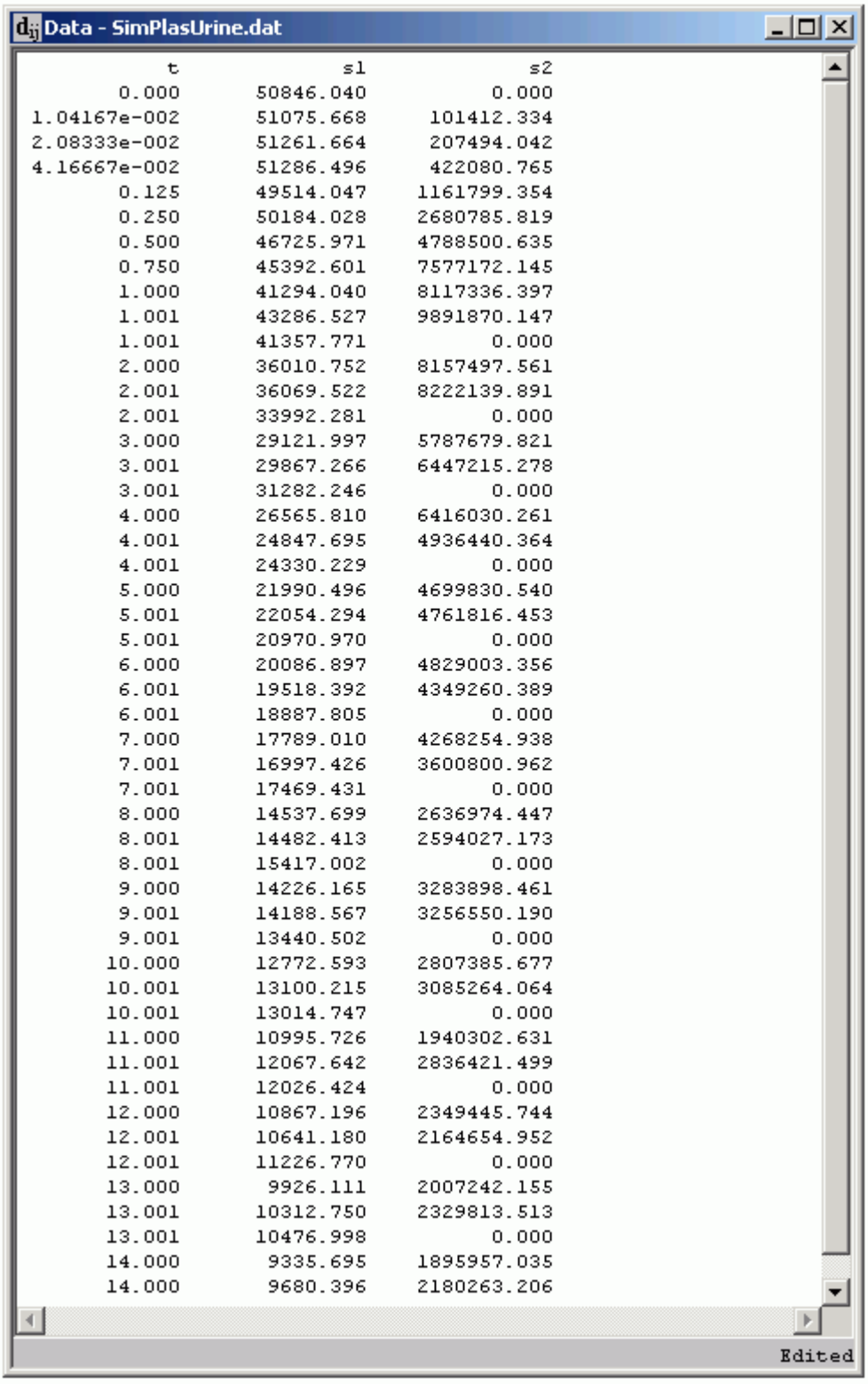
10. Use the simulated data.

    There are many ways in which you can use the simulated data. One is to cut and paste the data to a spread sheet. Another way, cutting and pasting directly into the **Data** window, and fitting the model to the data will be illustrated how.

    a. Select and copy the data in the **Table** window. Close the **Table** window.

    b. Open the **Data** window, and select all the contents of this window.

    c. In the **Edit** menu, click **Paste**. The **Data** window will appear as follows:



Data - SimPlasUrine.dat

t	s1	s2
0.000	50846.040	0.000
1.04167e-002	51075.668	101412.334
2.08333e-002	51261.664	207494.042
4.16667e-002	51286.496	422080.765
0.125	49514.047	1161799.354
0.250	50184.028	2680785.819
0.500	46725.971	4788500.635
0.750	45392.601	7577172.145
1.000	41294.040	8117336.397
1.001	43286.527	9891870.147
1.001	41357.771	0.000
2.000	36010.752	8157497.561
2.001	36069.522	8222139.891
2.001	33992.281	0.000
3.000	29121.997	5787679.821
3.001	29867.266	6447215.278
3.001	31282.246	0.000
4.000	26565.810	6416030.261
4.001	24847.695	4936440.364
4.001	24330.229	0.000
5.000	21990.496	4699830.540
5.001	22054.294	4761816.453
5.001	20970.970	0.000
6.000	20086.897	4829003.356
6.001	19518.392	4349260.389
6.001	18887.805	0.000
7.000	17789.010	4268254.938
7.001	16997.426	3600800.962
7.001	17469.431	0.000
8.000	14537.699	2636974.447
8.001	14482.413	2594027.173
8.001	15417.002	0.000
9.000	14226.165	3283898.461
9.001	14188.567	3256550.190
9.001	13440.502	0.000
10.000	12772.593	2807385.677
10.001	13100.215	3085264.064
10.001	13014.747	0.000
11.000	10995.726	1940302.631
11.001	12067.642	2836421.499
11.001	12026.424	0.000
12.000	10867.196	2349445.744
12.001	10641.180	2164654.952
12.001	11226.770	0.000
13.000	9926.111	2007242.155
13.001	10312.750	2329813.513
13.001	10476.998	0.000
14.000	9335.695	1895957.035
14.000	9680.396	2180263.206

Edited

d. In the **Data** window:

(1) Add the first two lines "DATA" and "(FSD 0.1)"; add the last line "END"

(2) Change "s1" to "plasma" and "s2" to "urine".

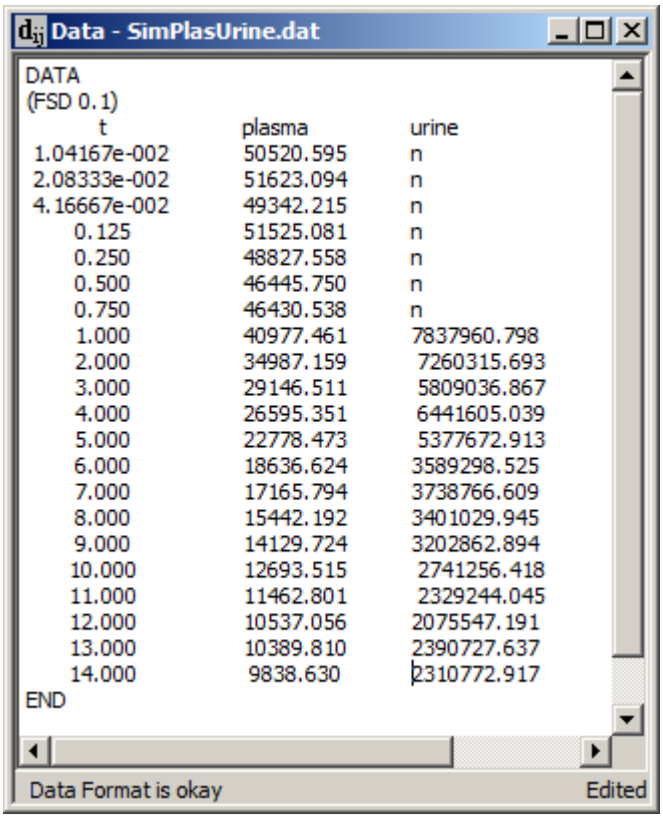
(3) Remove the zero time value.

(4) Remove all values at time points with ".001".

(5) Replace all simulated urine samples up to day 1 with "n".

(6) Remove the second datum at day 14.

(7) In the **Edit** menu, click **Check Data Format**. Correct any errors if there are any. The **Data** window should appear as follows:



Remember the data were simulated with an FSD equal to 0.1 and 0.2 respectively for plasma and urine. In the above, FSD equal to 0.1 applies to both sets of data. If you wish, you can modify the first lines in the **Data** window to reflect the weighting scheme used to simulate the data. The line (FSD 0.1) can be removed, and the three columns can be headed:

t plasma (FSD 0.1) urine (FSD 0.2)

(8) Close the **Data** window.

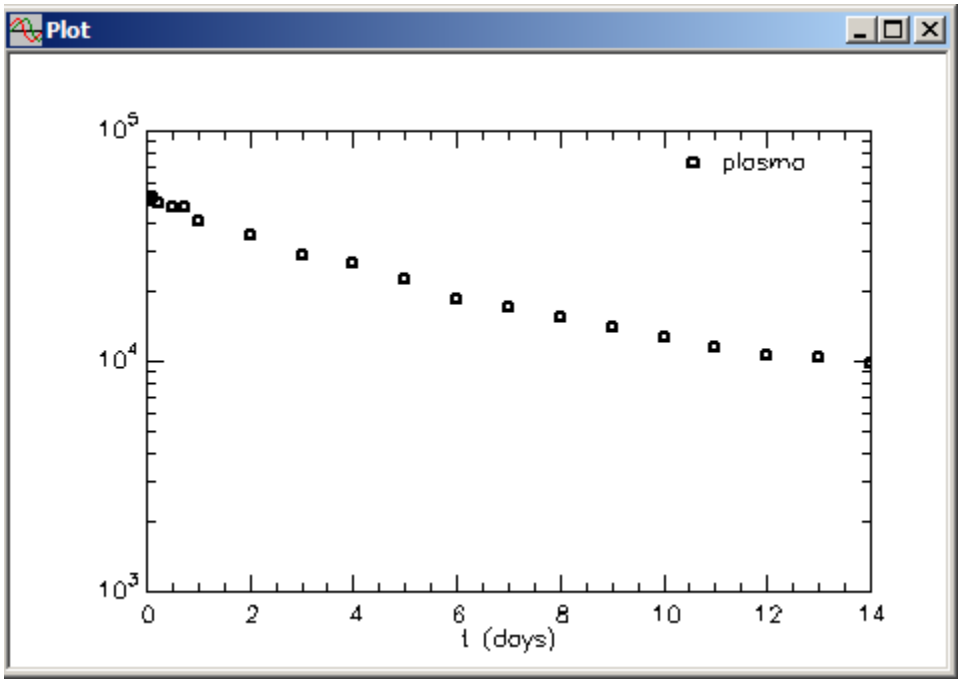
e. Save the study file with the new data.

Since these data are not those in **SimPlasUrine.stu**, if you want to work with this new set of data, you should save the study file with a new name.

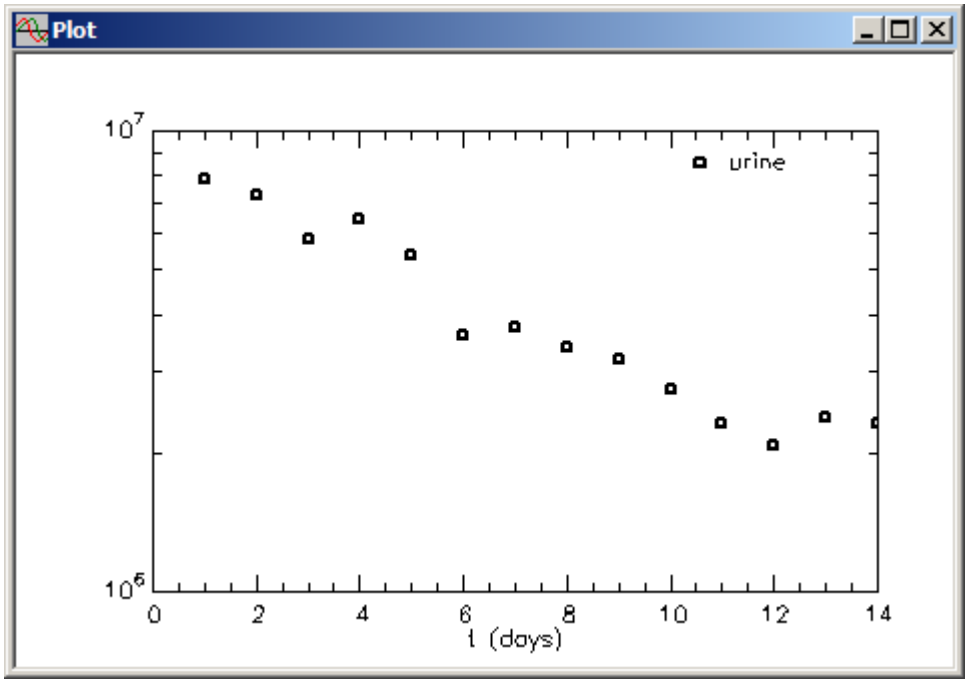
(1) In the **File** menu, click **Save As**.

(2) In the **File Name** box, type the desired new file name (e.g. SimPlasUrine_1).

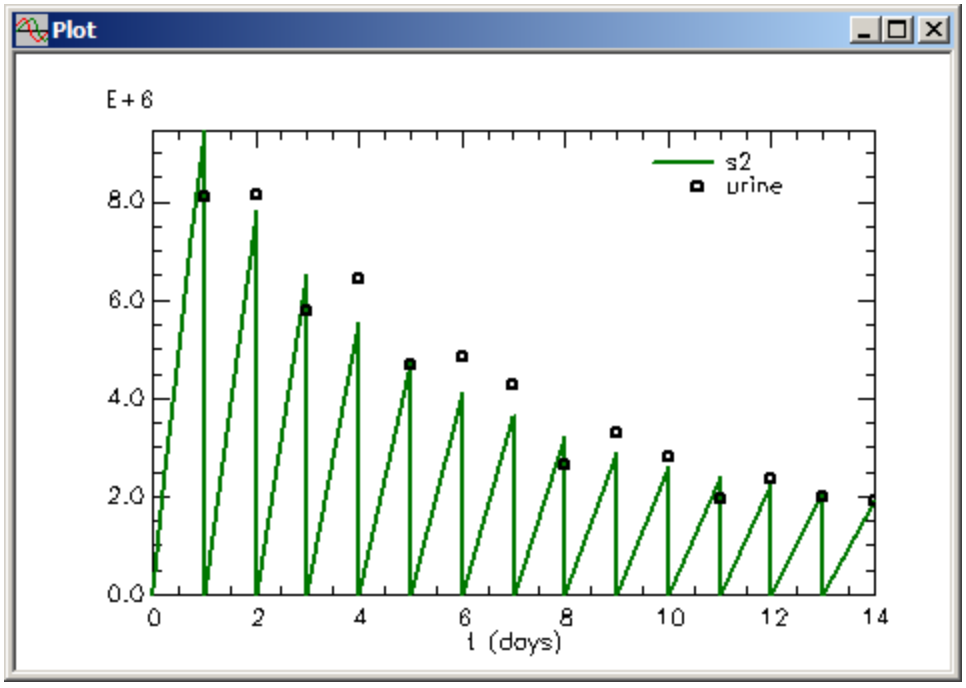
(3) Click **Save**. You can now use this file to continue your analyses. For example, a plot of the simulated plasma data is shown as follows:



A plot of the simulated urine data is shown as follows:



A plot of the solution using the model parameters to generate the simulated data is shown as follows:



You can now work with these simulated data as you would with a set of experimental data.

Quit the **SAAM II Compartmental** application.