Using SAAM II

Using Delays

Using 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 are part of the tutorial.

Data files: The data files for this tutorial are

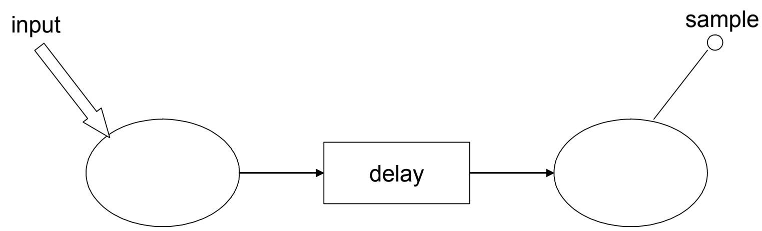
delay1.dat
delay3.dat

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.

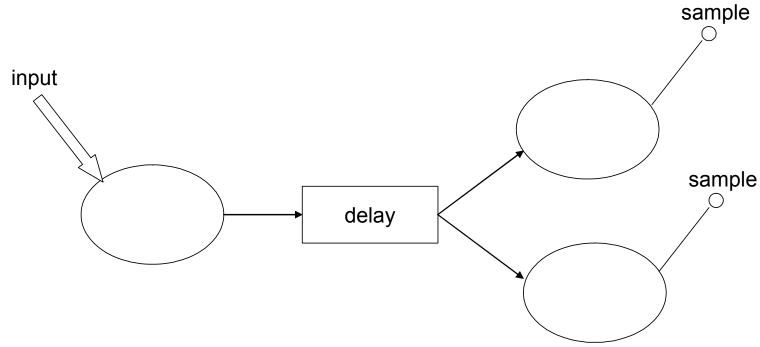
The **Delay** tool in the **SAAM II Compartmental** application creates delays automatically as a series of compartments. The larger the number of compartments specified for the delay in the **Delay Attributes** dialog box, the closer the delay will be to a true (absolute) delay, but the longer the computation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

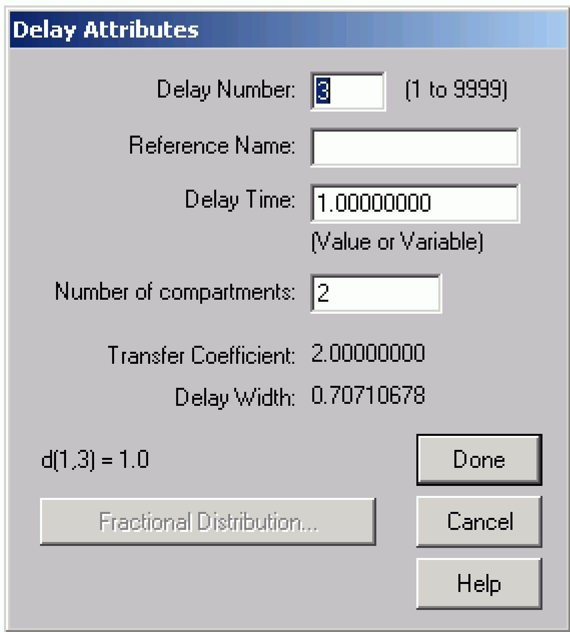
The situation above is one where the delay is between the input and the sample site. There are instances where material from the delay may actually pass to several compartments. An example would be the measurement of amino acid incorporation into several proteins. The situation for two outputs can be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



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

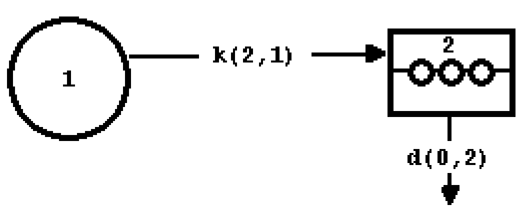
Delays implemented by a string of compartments actually represent a transfer function corresponding to a probability distribution function. The distribution function has a mean and a variance (standard deviation). The mean is the delay time, and the standard deviation is the delay width which is a measure 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:

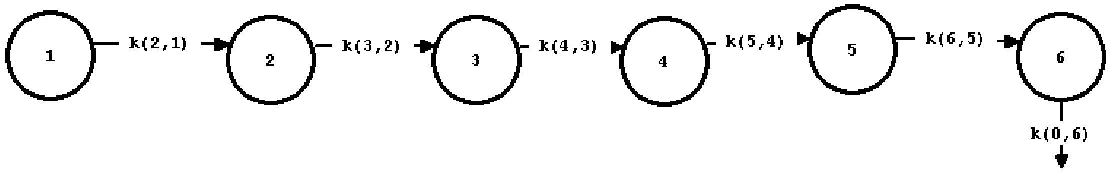


In this case, the delay number is "3". The default values for the delay time and the number of compartments in the delay are 1.0 and 2 respectively. Normally, as illustrated in this tutorial, the delay time is set equal to a parameter.

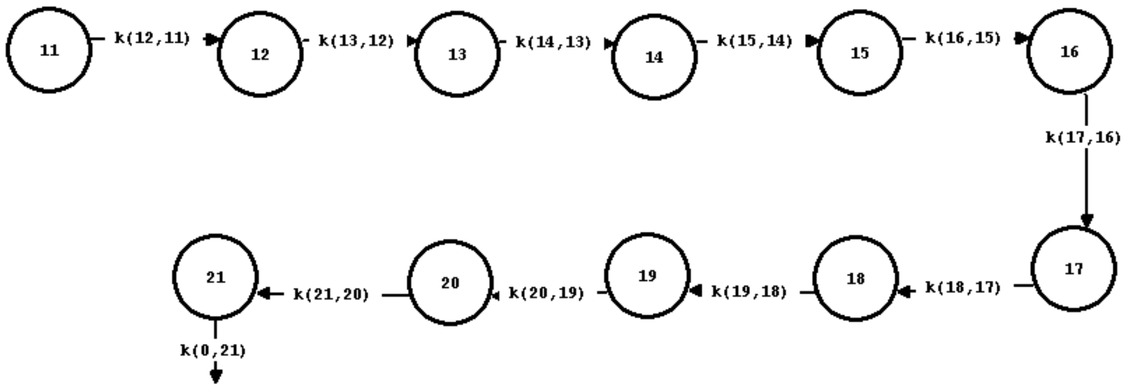
Consider the following example:



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:

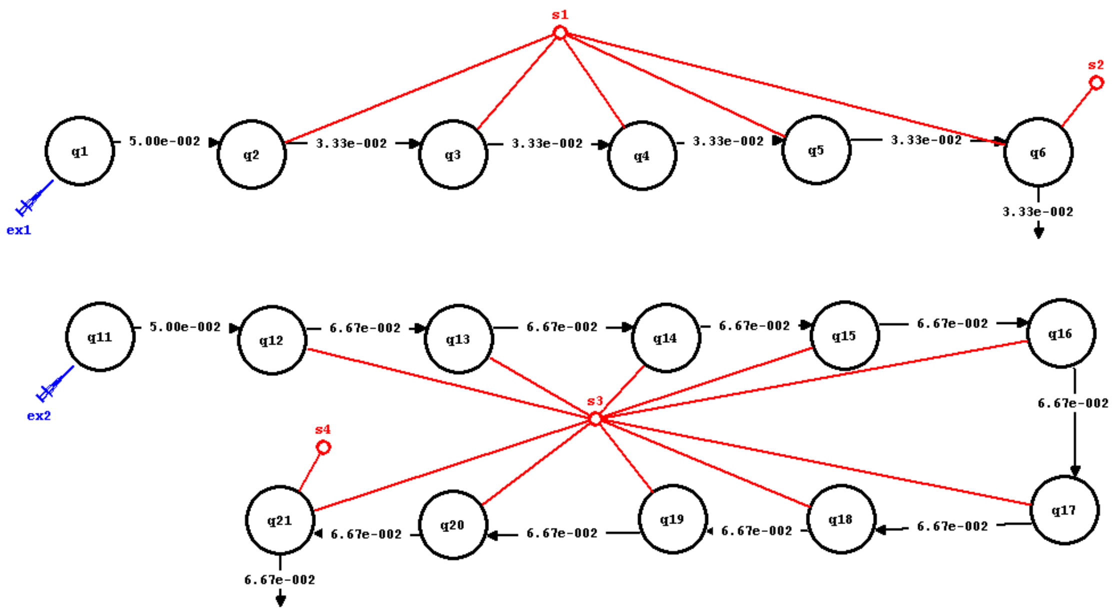


while if the number were set equal to 10, the model internally would appear:



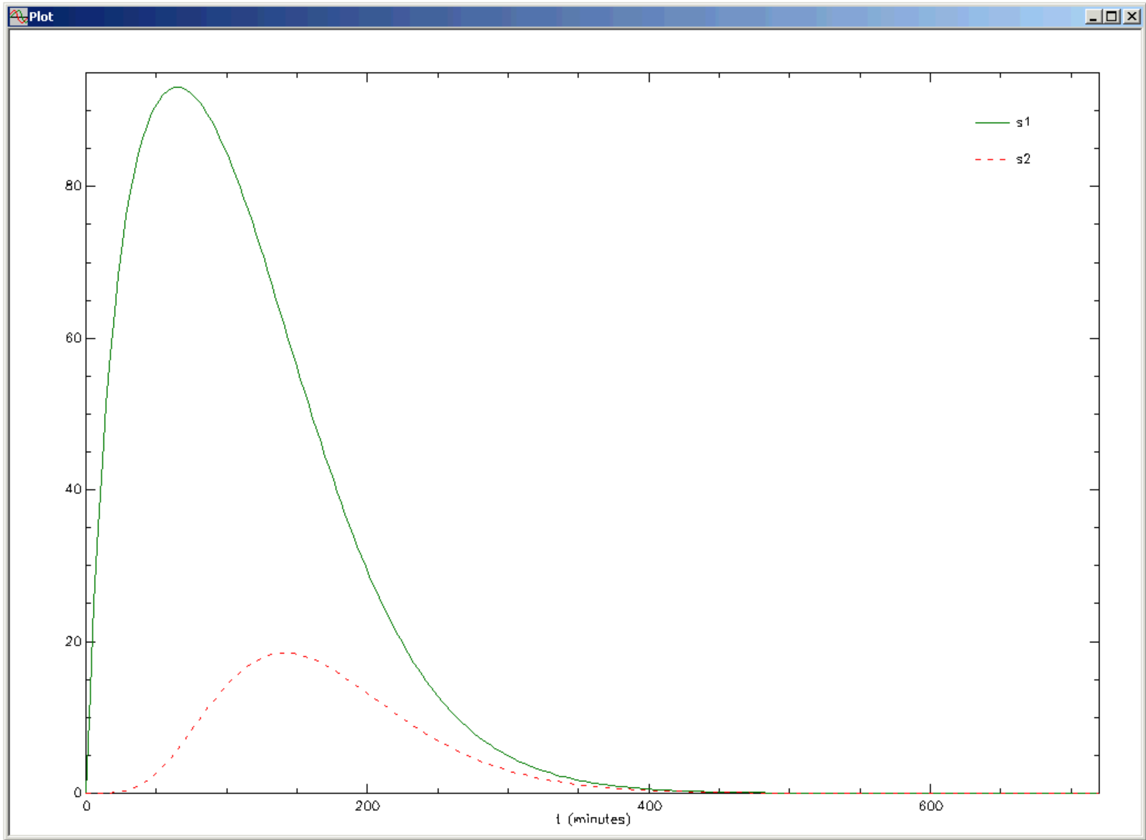
What is the difference, and what is the relationship between the delay time specified as part of the delay attribute, and the actual delay time that is desired? That is, the "delay time" as the transfer function mean, and the "delay time" actually required by the data may be different. This is a function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

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:

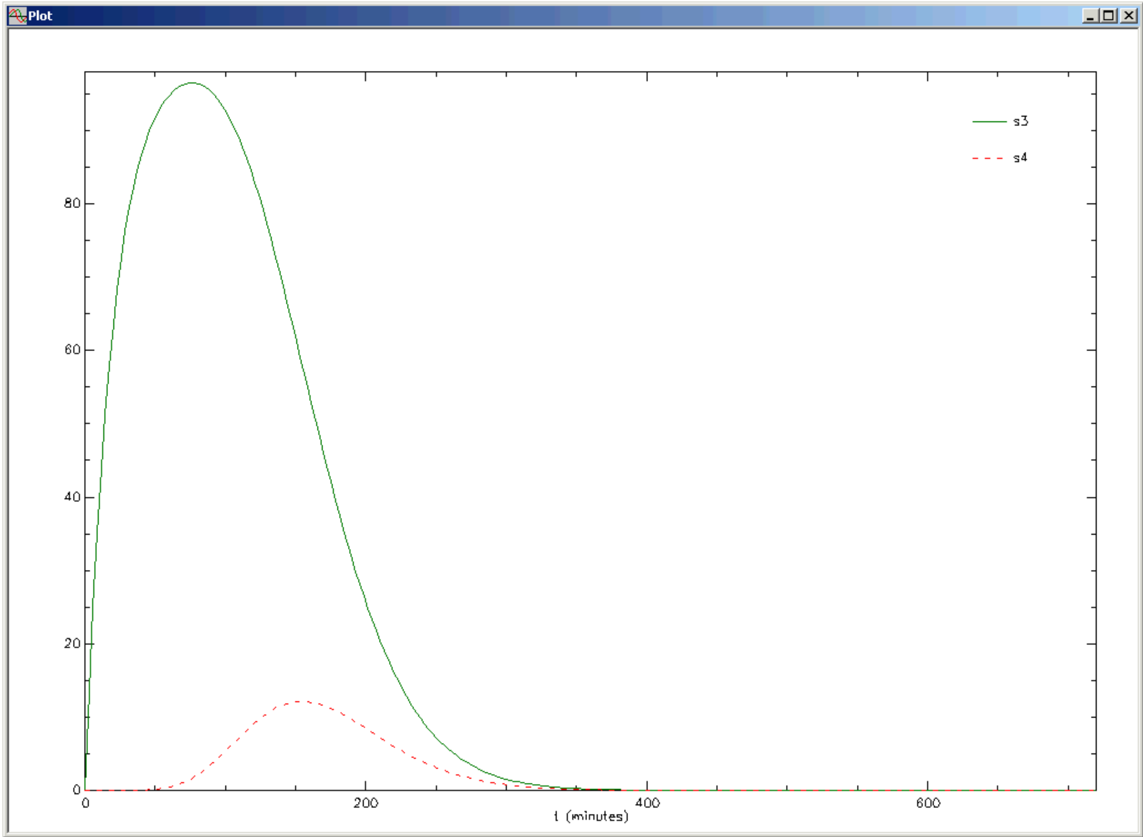


The actual delay is created by the material leaving the last compartment in the delay, **q6** and **q21** respectively.

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:

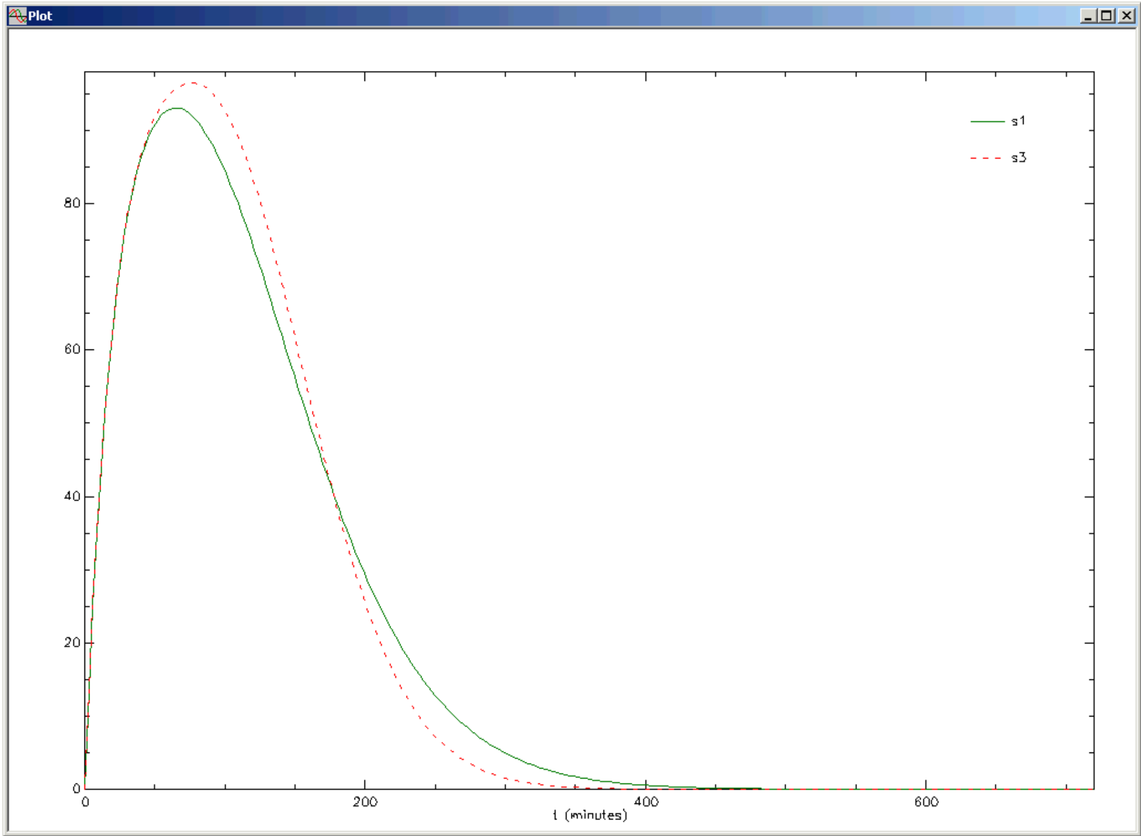


You can see that **s1** has a slightly skewed distribution with a mean around 150. You can also see that material starts to appear from Compartment **q6** (measured by **s2**) at around 30 minutes. Thus the "physiological" delay is about 30 minutes. The counterparts for the 10 compartment delay are shown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

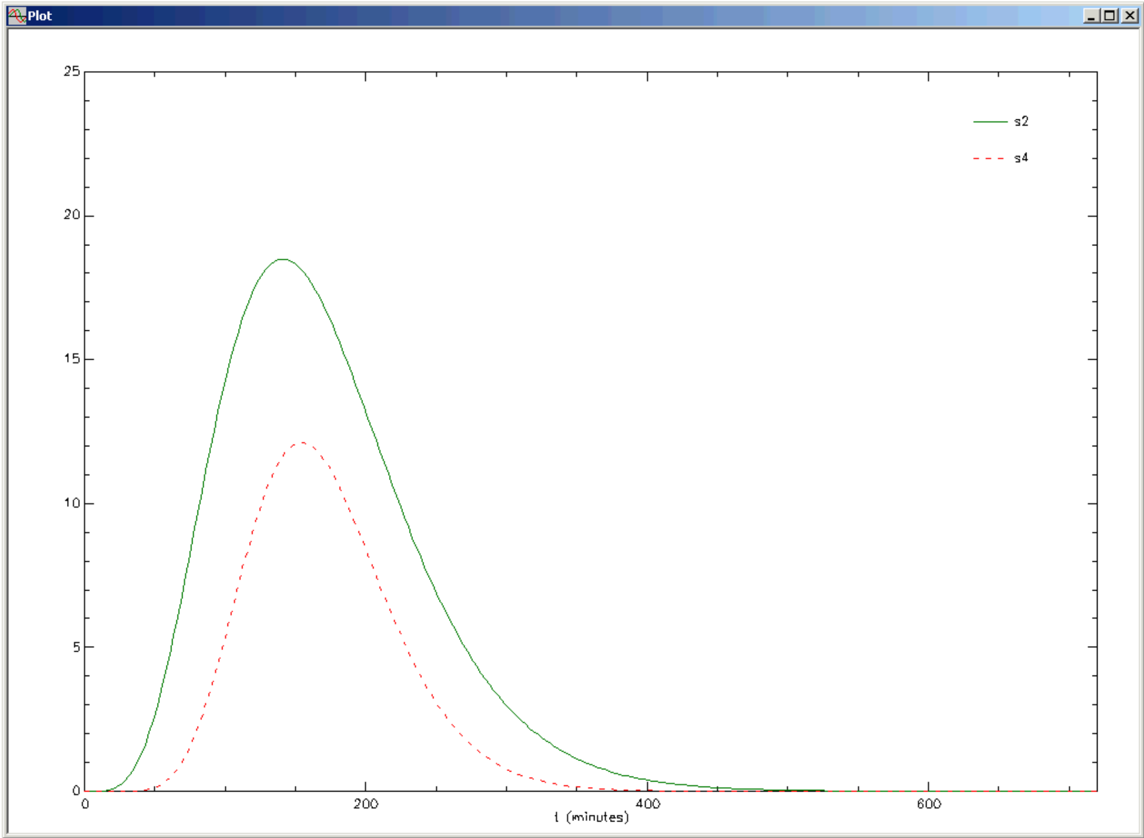


You can see the mean of the delay is again at 150, but now the width is smaller (as shown in the following figure). Material starts to appear from the last compartment in the delay (**s4**) at about 50 minutes.

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:

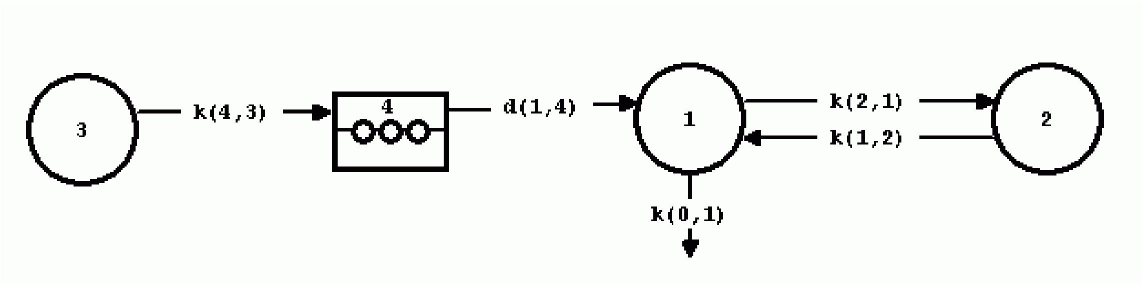


The difference in the appearance of material from the last compartment in the delay between the 5 and 10 compartment delay is quite dramatic.

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:

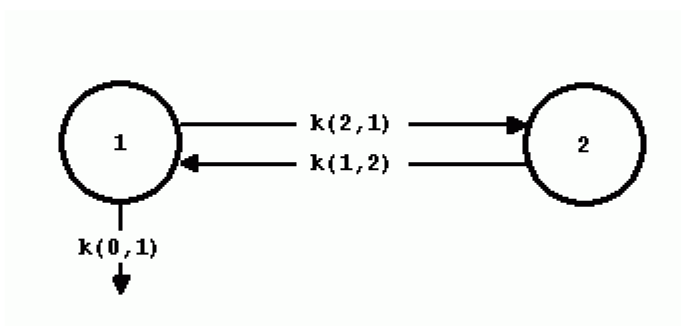


In the model shown above, Compartment **1** represents plasma and Compartment **2** represents an extra-plasma compartment. Thus, the "system" model, from the point of how the substance is metabolized in the body, is represented by these two compartments. Compartment **3** is the compartment into which 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.



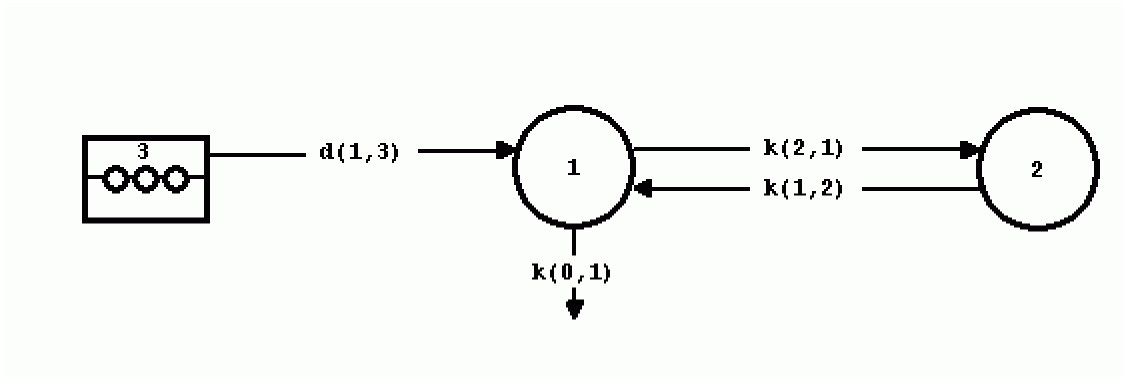
    b. Add the delay and transfer from the delay to Compartment **1**.

        (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**

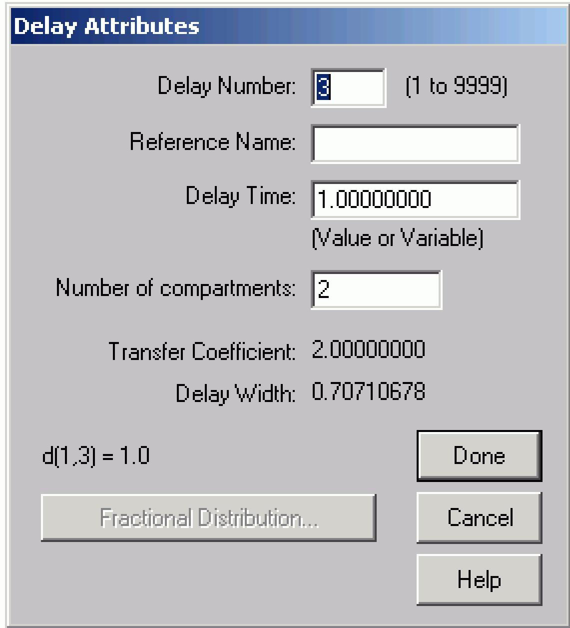
(4) Click on Delay **3** and then Compartment **1**; the transfer *d(1,3)* will be created. Your model will appear as follows:



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.

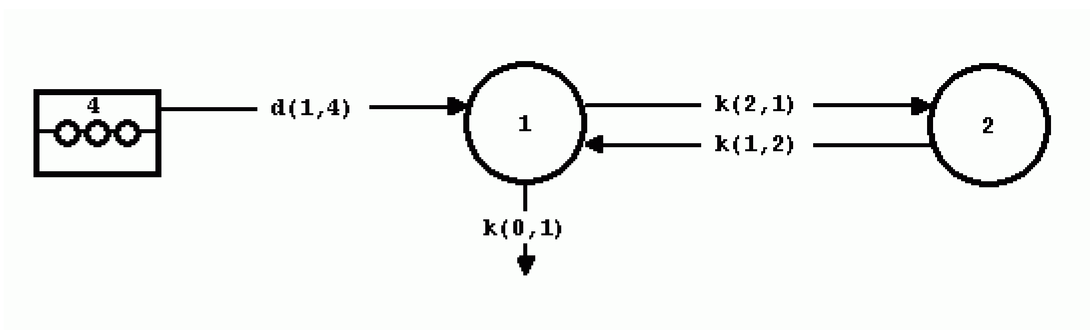
c. Change the number of the delay from "3" to "4".

(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:



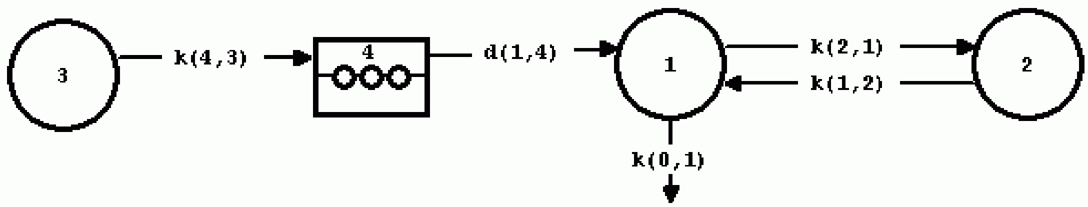
d. Add Compartment **3** and transfer *k(4,3)* to your model.

(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:

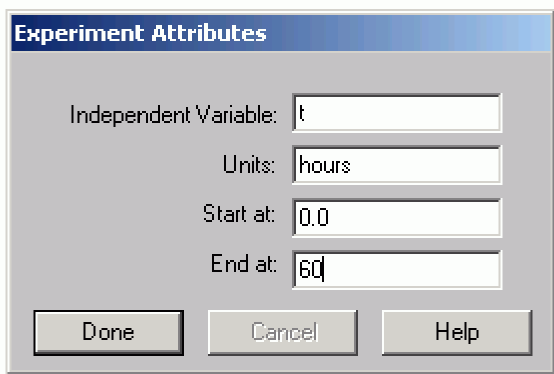


3. Create the experiment on the model.

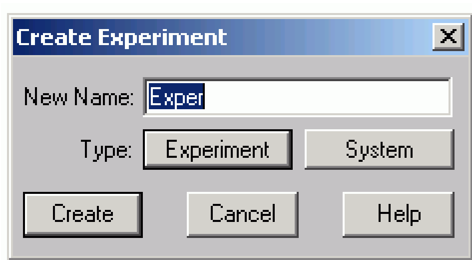
   a. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open.

   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:

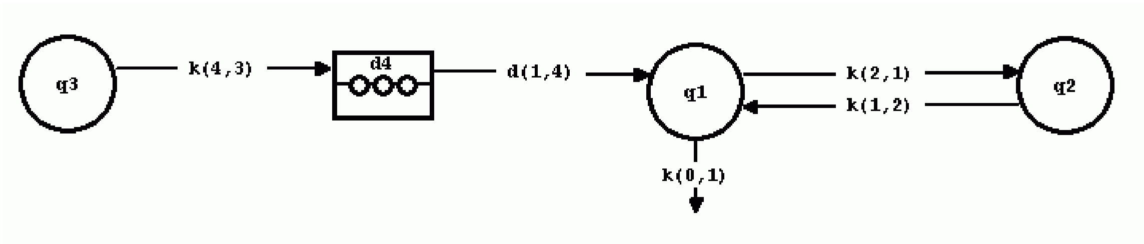


   d. Click **Done**. The **Create Experiment** dialog box will open as shown below:



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

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

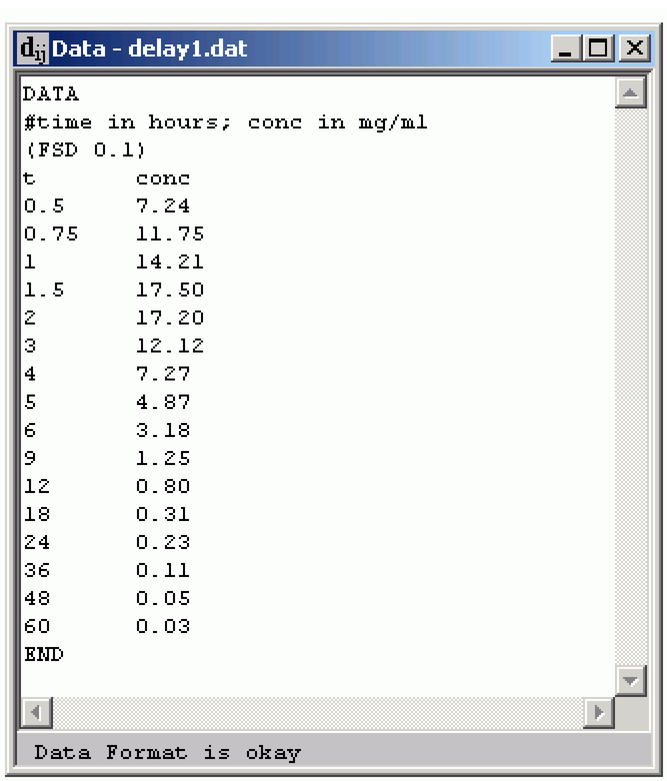


4. Add the data to the model

   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:




```
DATA
#time in hours; conc in mg/ml
(FSD 0.1)
t        conc
0.5      7.24
0.75     11.75
1        14.21
1.5      17.50
2        17.20
3        12.12
4        7.27
5        4.87
6        3.18
9        1.25
12       0.80
18       0.31
24       0.23
36       0.11
48       0.05
60       0.03
END
```


   d. Close the **Data** window.

5. Create the input and sample

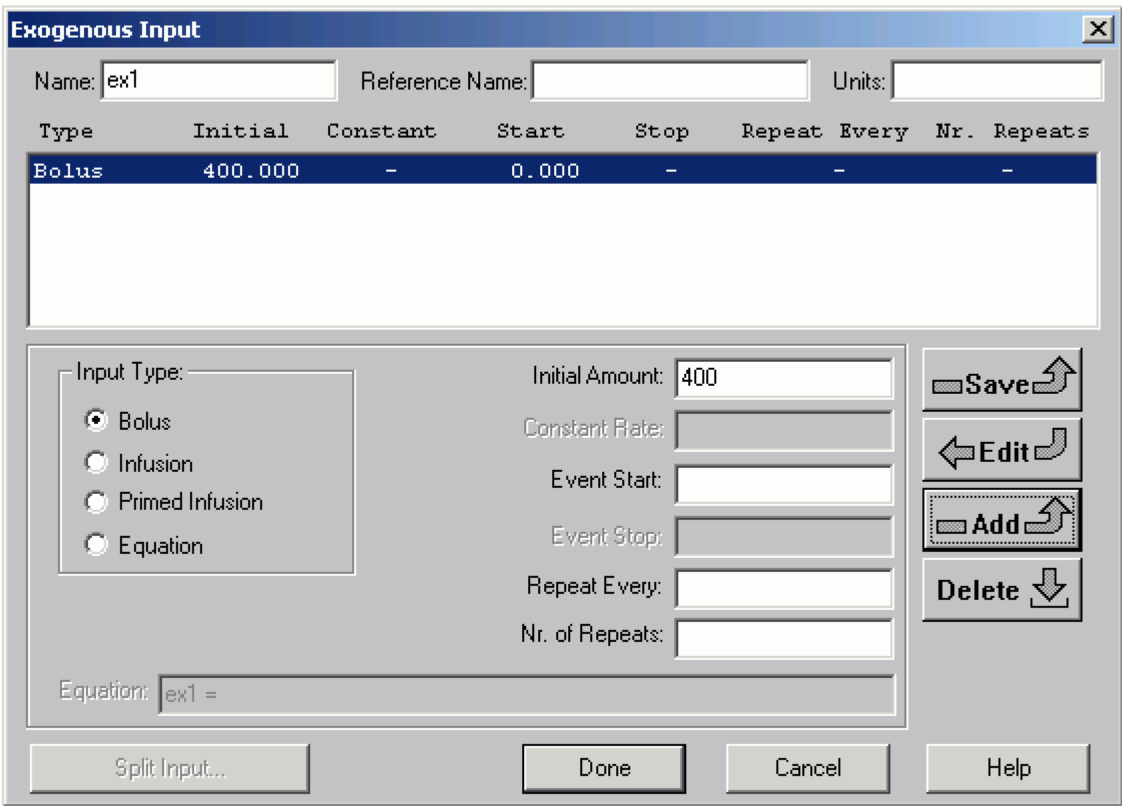
   a. In the **SAAM II Toolbox**, click **Input**.

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**.

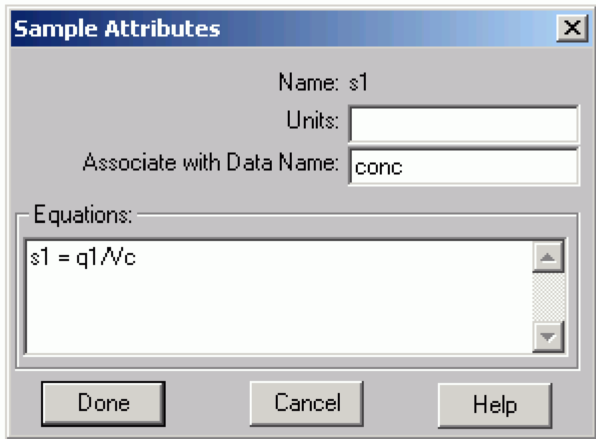
g. In the **SAAM II Toolbox**, click **Sample**.

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.

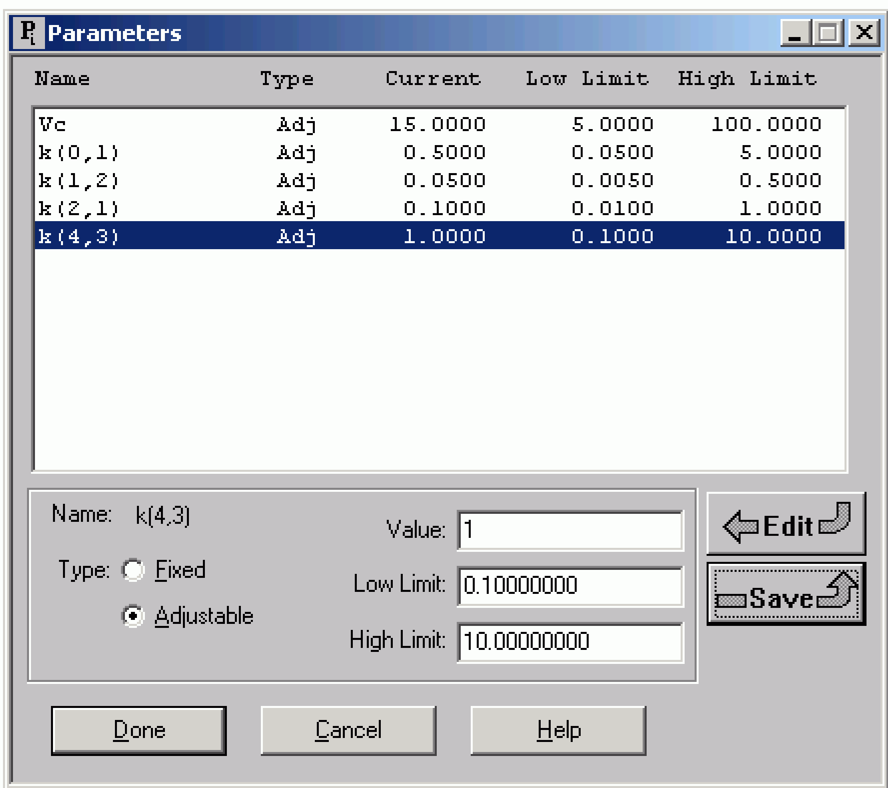
j. Type “conc” in the **Associate with Data Name** box.

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**.

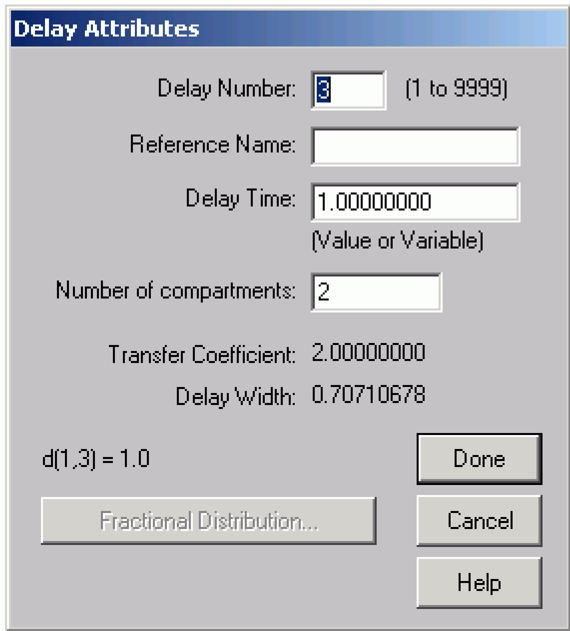
6. Enter the parameter values as shown below:



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.

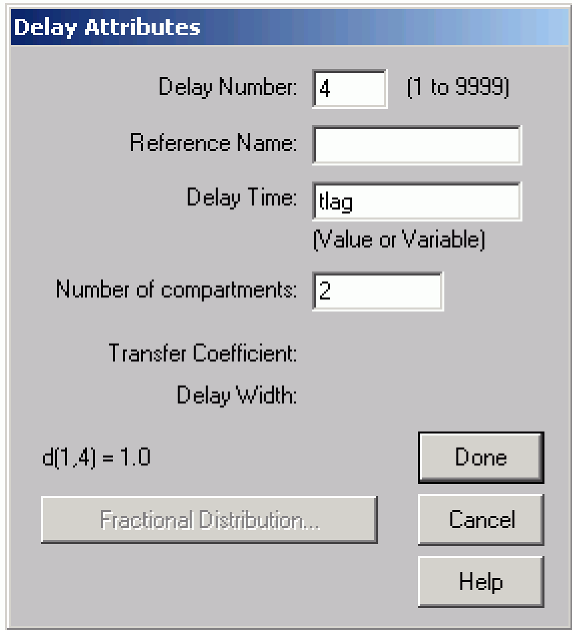
a. Set the time of the delay equal to a parameter.

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 active these tools.

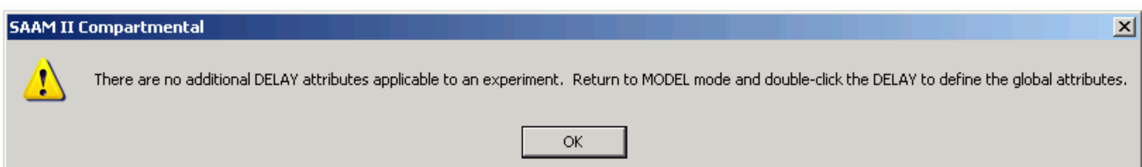
(2) Double-click Delay **4** to open the **Delay Attributes** dialog box.

(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.

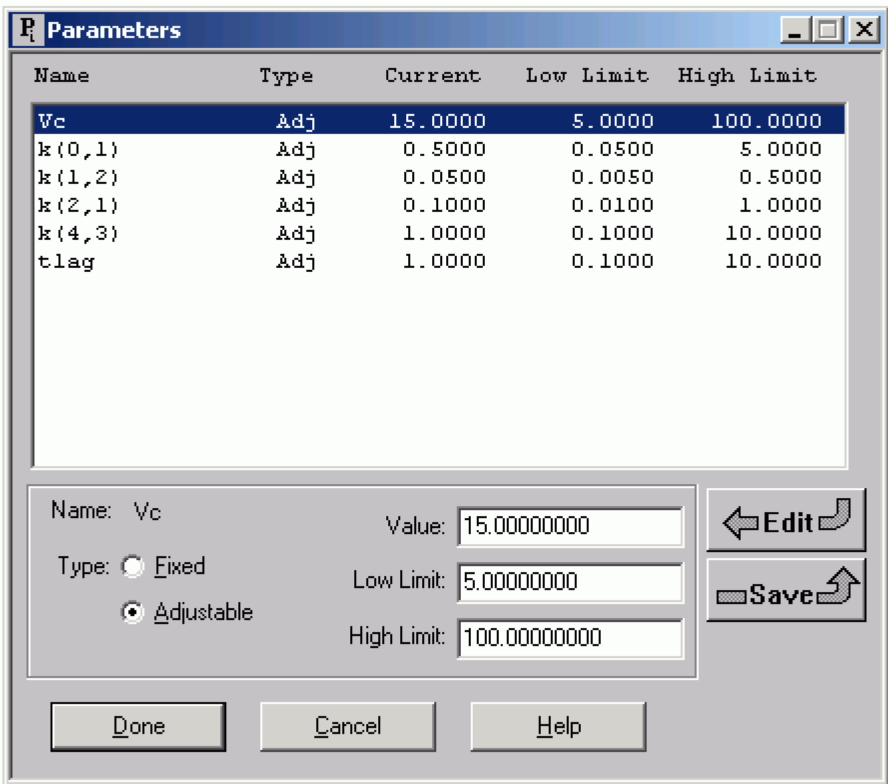
The delay time as a parameter. When you change the time of the delay from a number to a name, the name will appear as a parameter. In this case, *tlag* will appear when you open the **Parameters** dialog box. The time of a delay can be either a fixed or an adjustable parameter.

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.

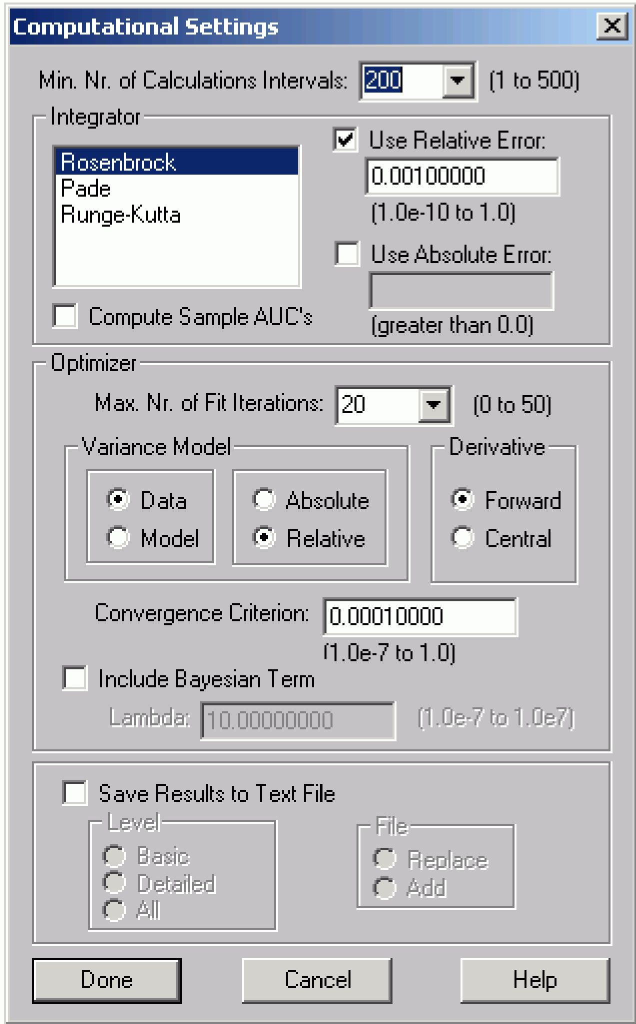
(1) In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters** . The **Parameters** dialog box will open.

(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 **Computational 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:



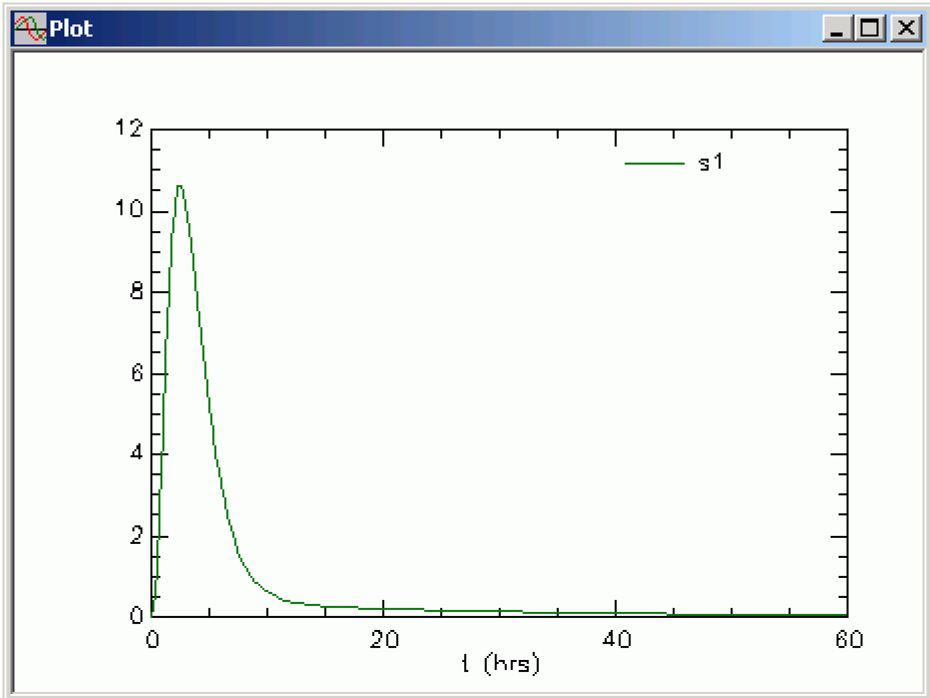
Click **Done**. (Remember increasing the calculation intervals will give better resolution to the plots).

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

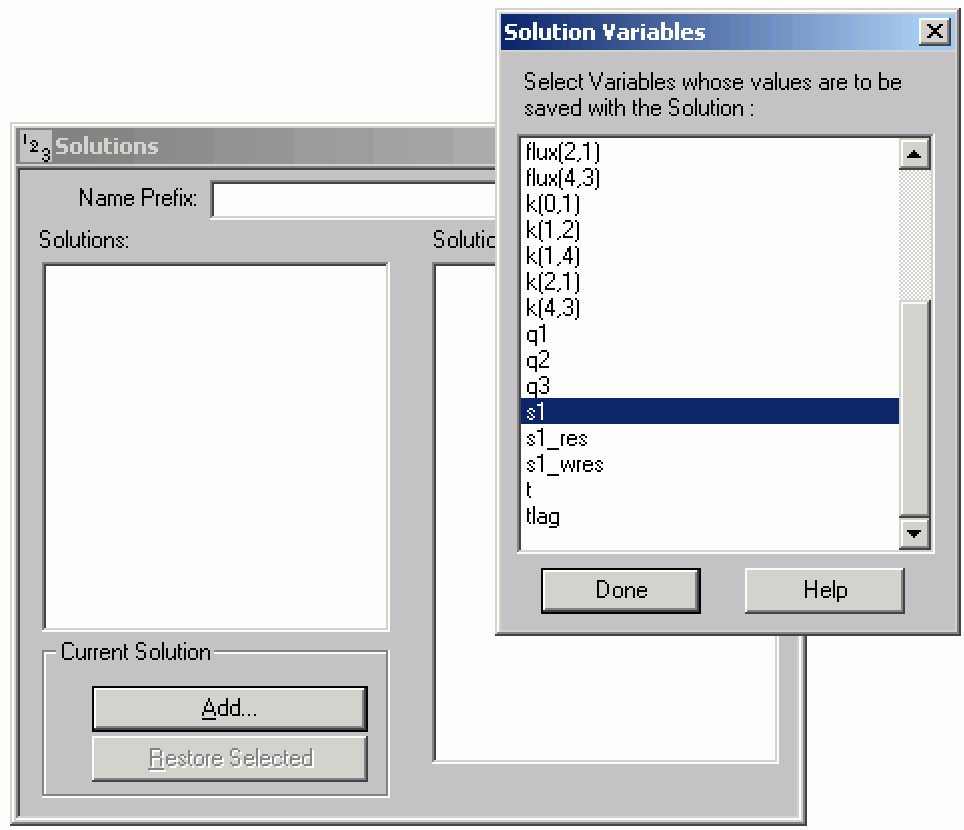
(6) In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot** . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is selected.

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

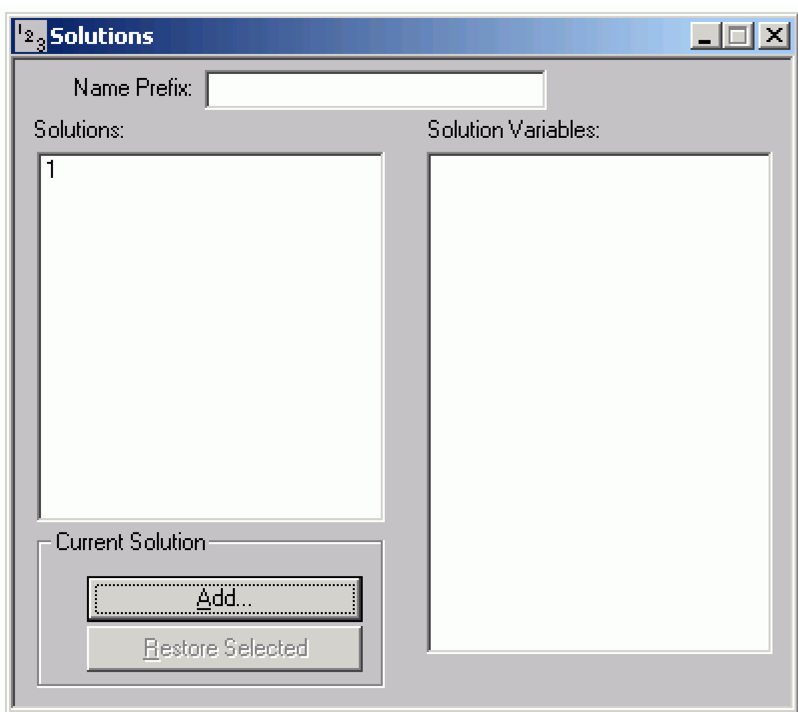
(8) Click **Done**. If the plot is not linear, in the **View** menu, click **Semilog**. The plot will appear as follows (the maximum for the **Y Scale** has been set equal to "12")



(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:

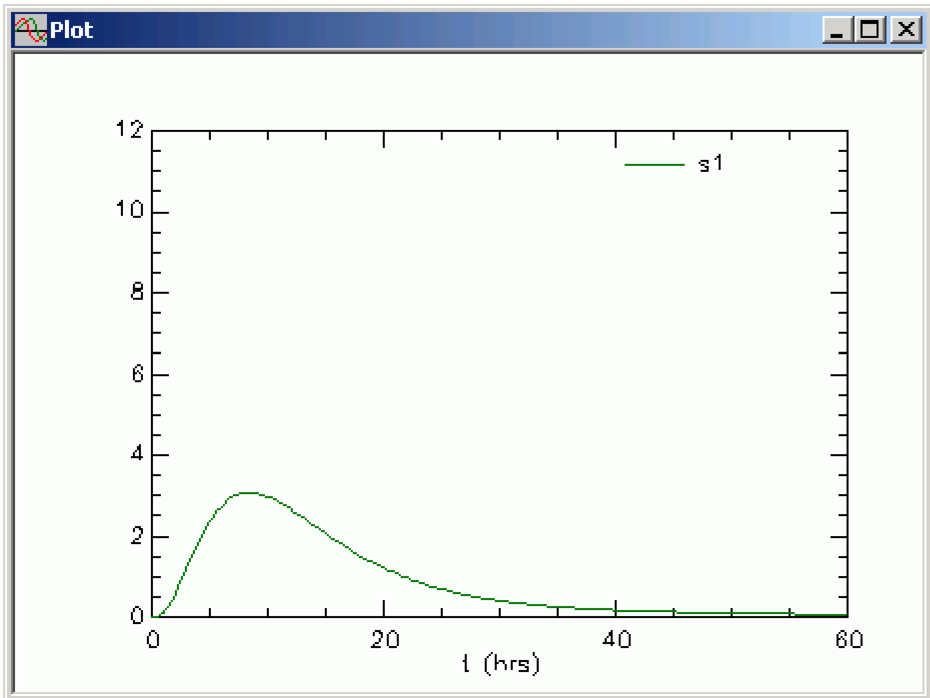


Click **Done**. The **Solutions** dialog box will appear as follows:



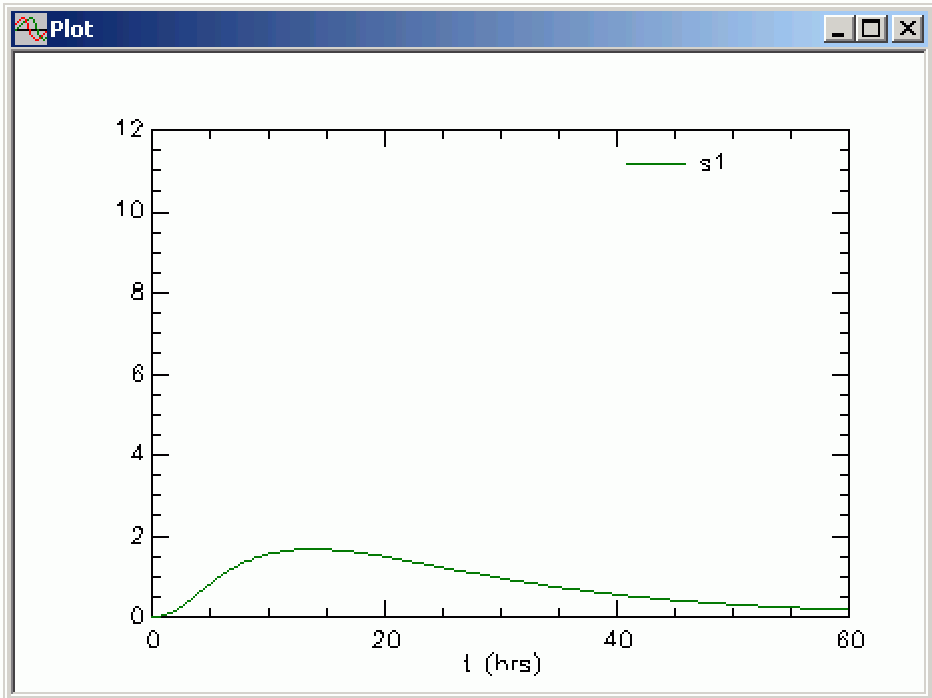
Close the **Solutions** dialog box.

(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:

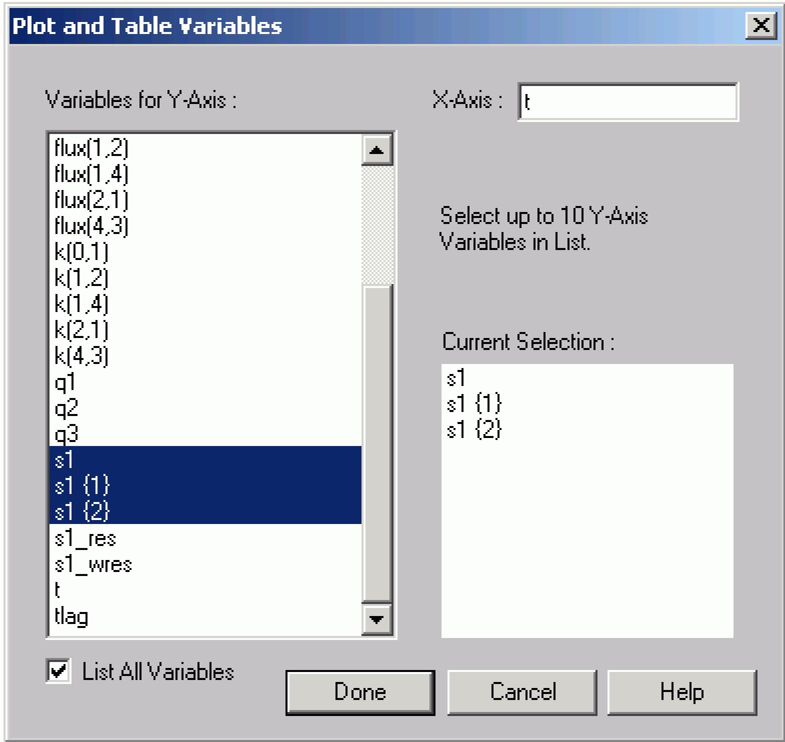


Notice the peak is not as high as when the delay was equal to "1". This is due to a combination of only two compartments in the delay, and the length of the delay time.

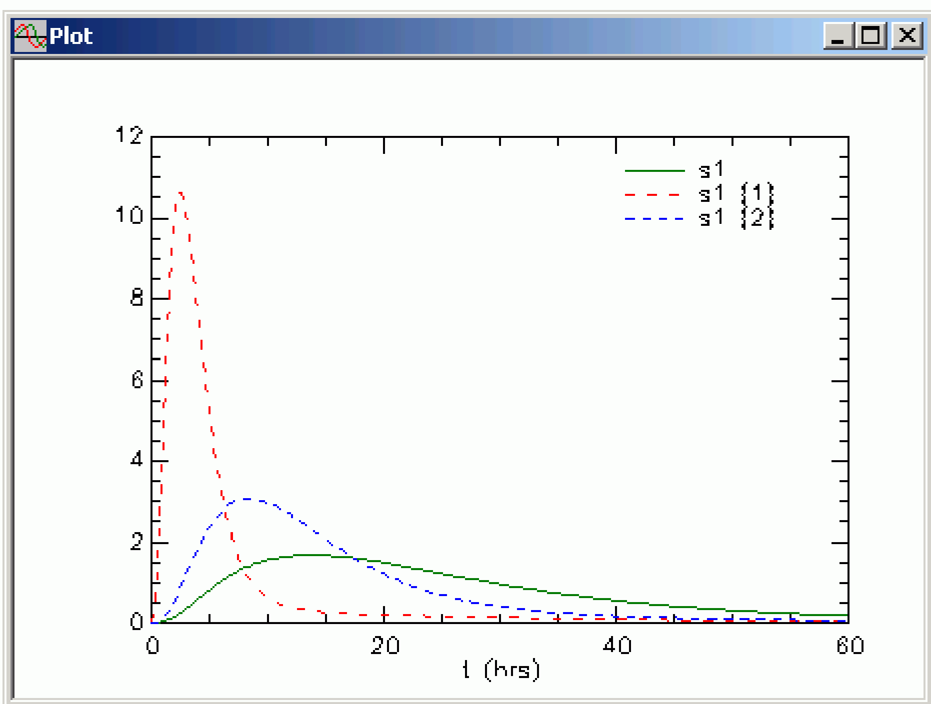
(10) Set *tlag* equal to "20", and repeat the above steps saving the solution as solution number "3". The plot will appear as follows:



(11) Plot all three simulations simultaneously. With the plot window open, in the **Set** menu, click **Plot/Tables Variables.** 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.

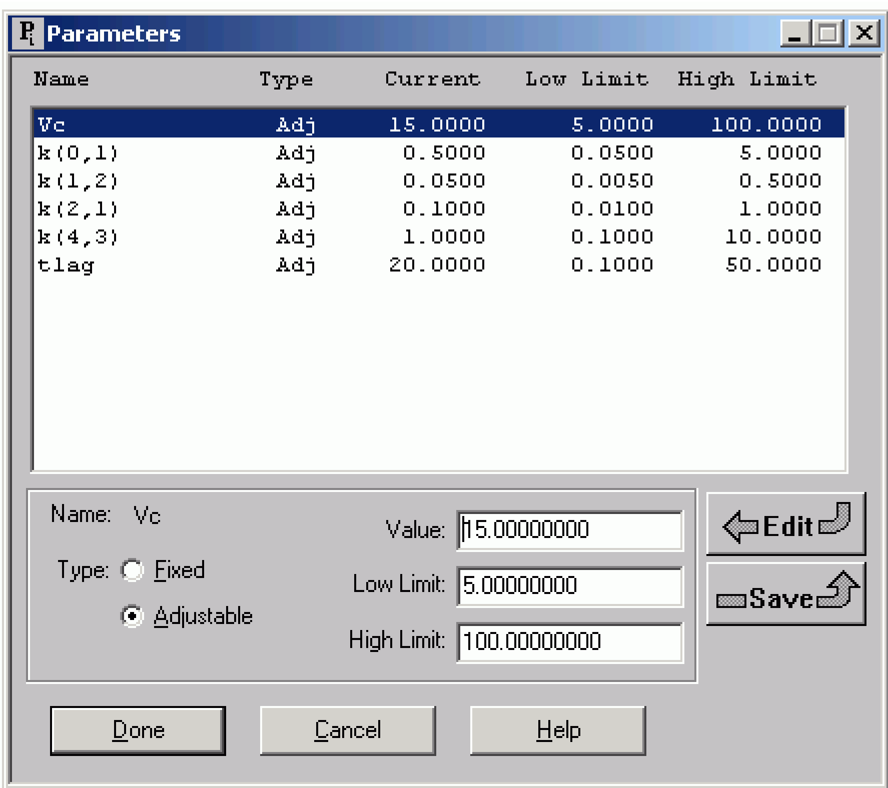
The delay time. For a given number of compartments in the delay, the longer the delay time, the less "pronounced" the delay will be. This is the result of the way the transfer between compartments in the delay is calculated.

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:

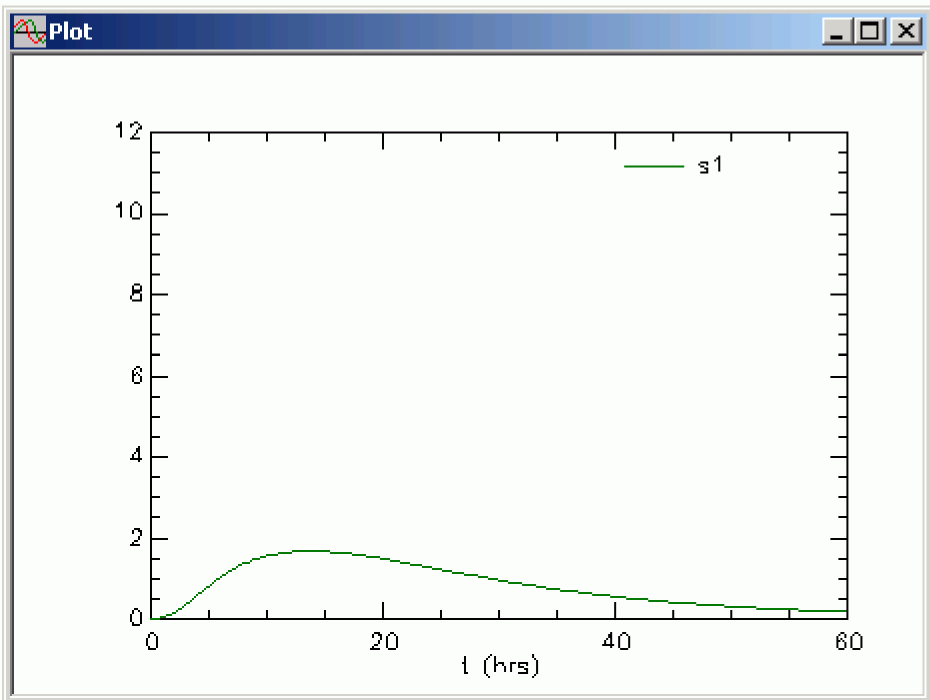


(1) In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve** .

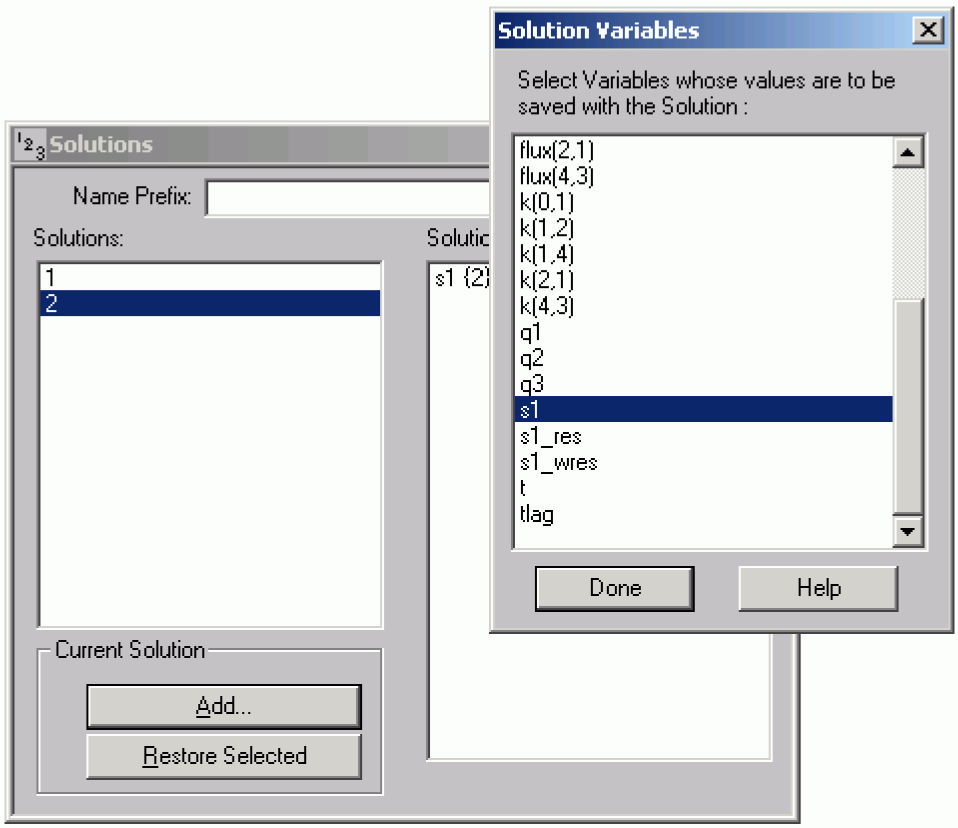
(2) In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot** . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is selected.

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

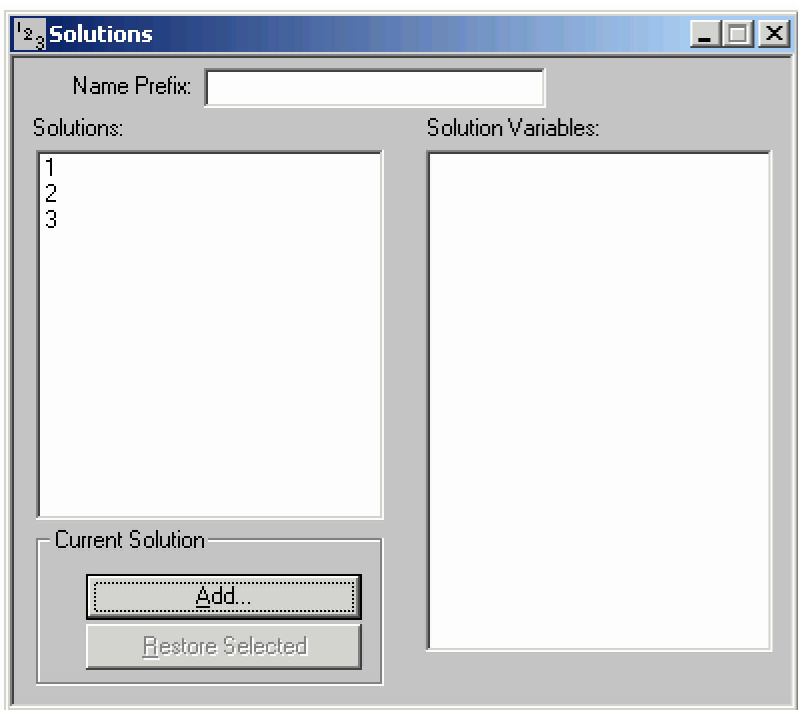
(4) Click **Done**. If the plot is not linear, in the **View** menu, click **Semilog**. The plot will appear as follows (remember the maximum for the **Y Scale** has been set equal to "12")



(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"):



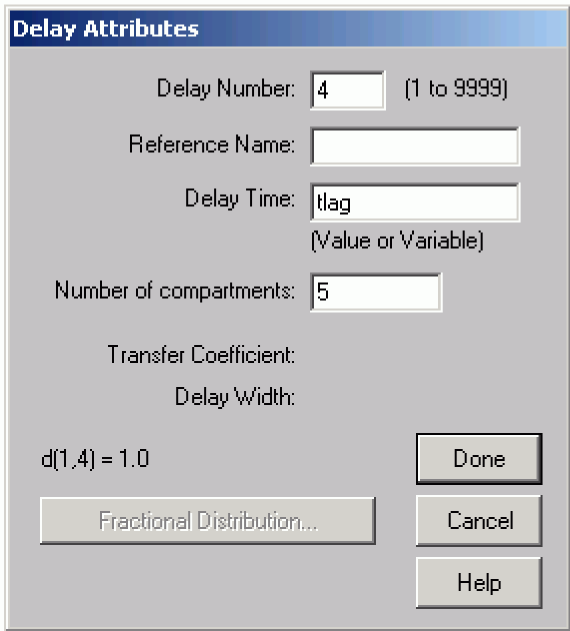
Click **Done**. The **Solutions** dialog box will appear as follows:



Close the **Solutions** dialog box.

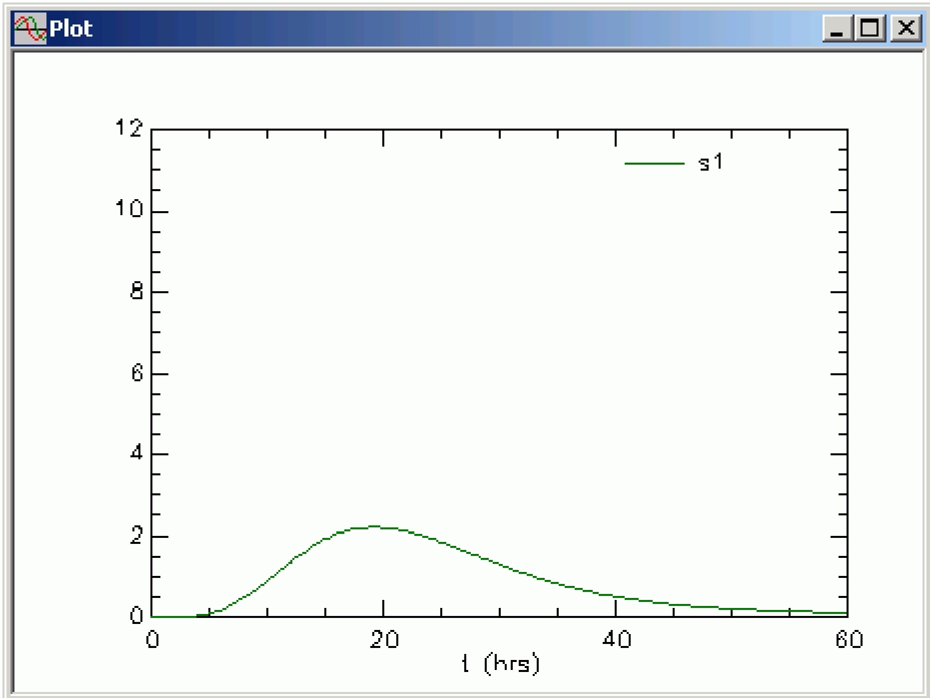
(7) In the **SAAM II Toolbox**, click **Model** to return to the **Model** mode.

(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:



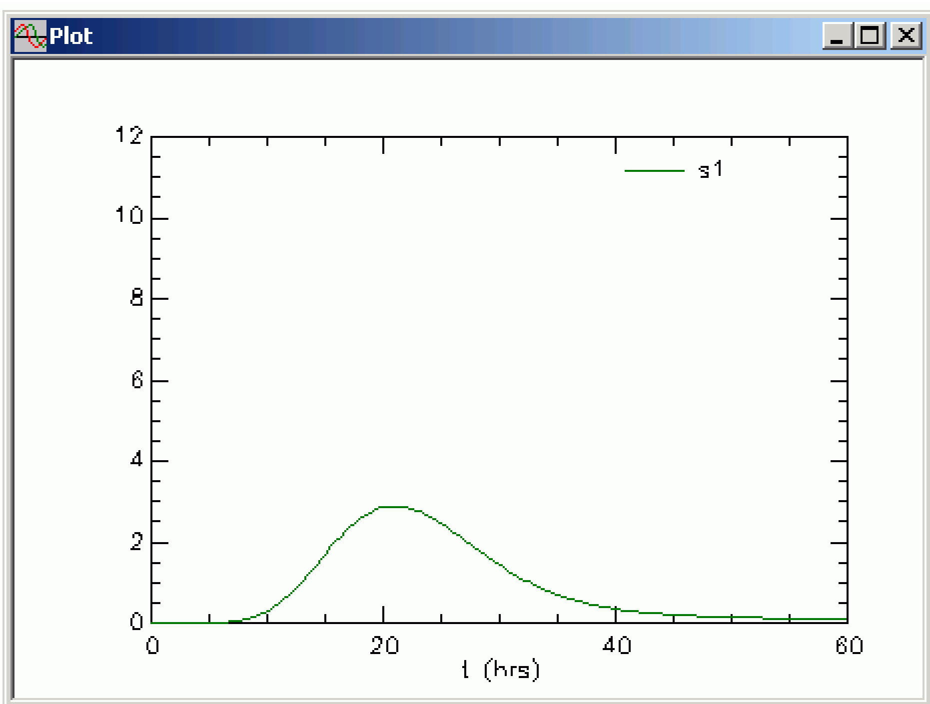
Click **Done**.

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

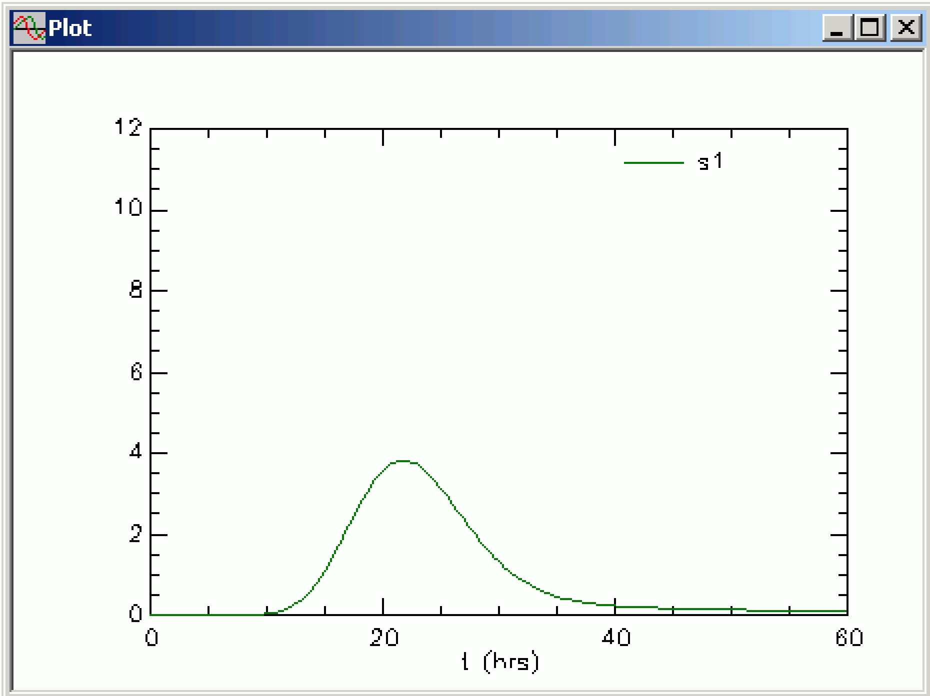


(10) Save **s1** as solution “4”.

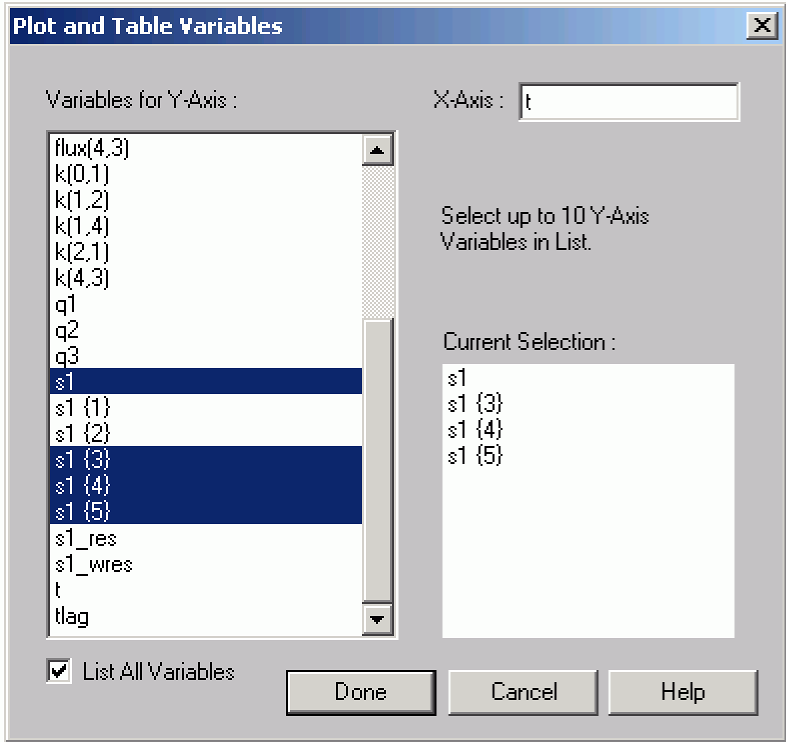
(11) Set the number of compartments in the delay equal to “10”. Solve the model, view the solution, and save the solution as solution “5”. The plot will appear as follows:



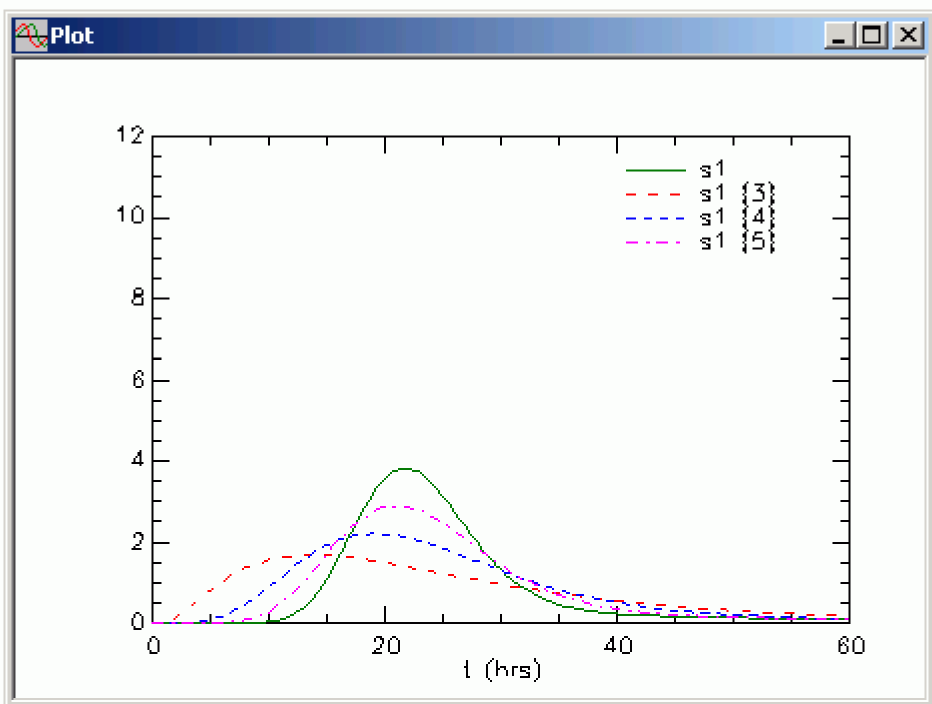
(12) Repeat the previous step with the number of compartments in the delay set equal to “20”. The plot will appear as follows:



(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.

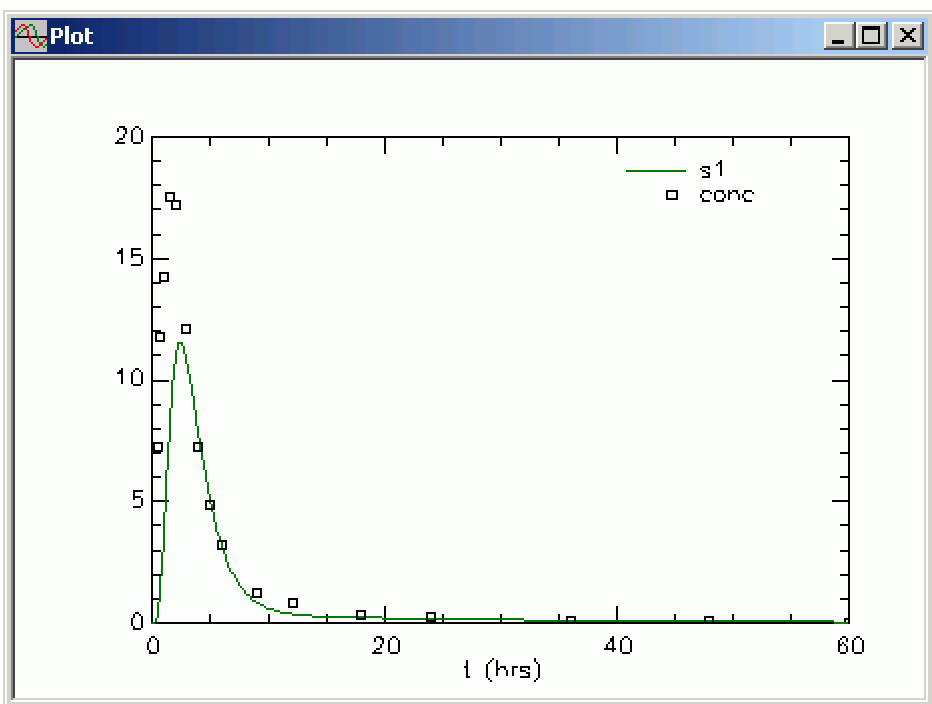
The transfer coefficient equals the number of compartments in the delay divided by the delay time. In the above example, this is "2", "5", "10" and "20" divided by "20". The material is faster passing through each compartment in the delay as the as the number of compartments increases.

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

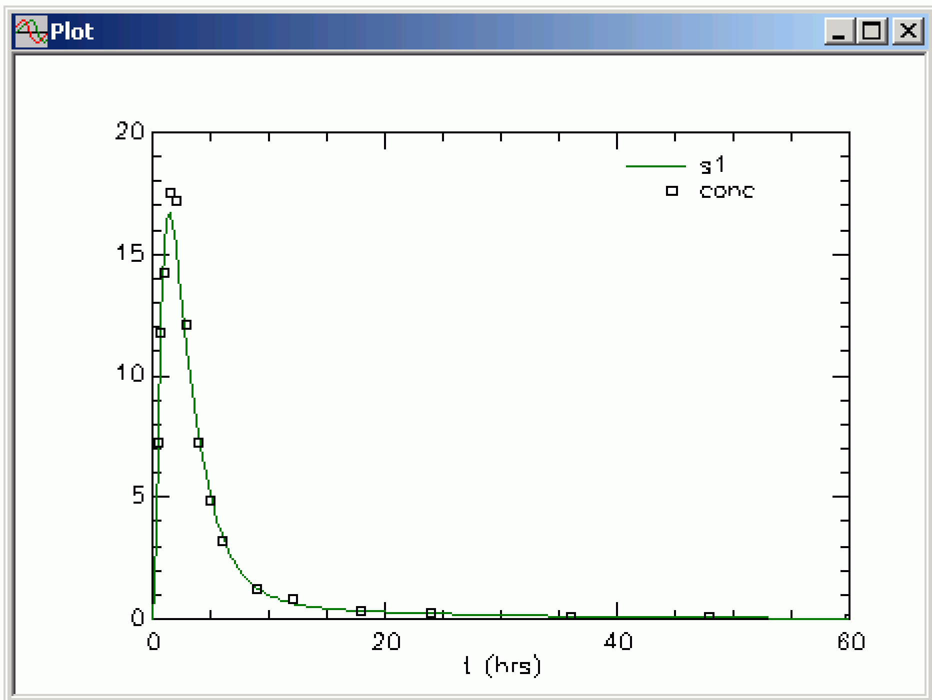
(1) Set the value for *tlag* equal to "1" with a minimum and maximum respectively equal to "0.1" and "10".

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

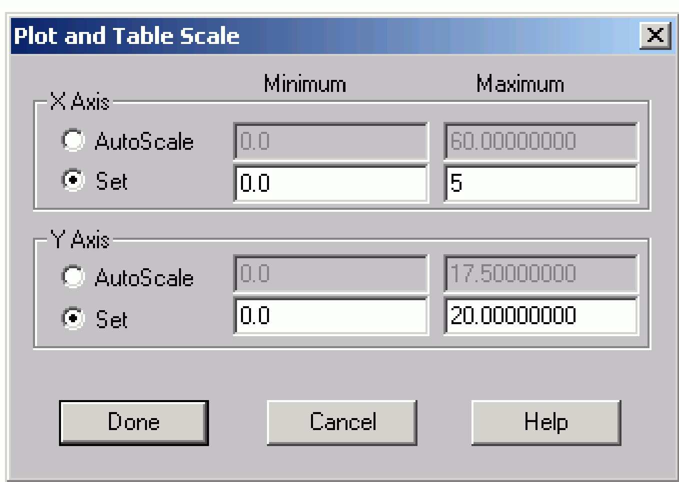
(3) Solve the model, and view the solution. The plot will appear as follows (the Y Scale maximum has been set equal to "20"):



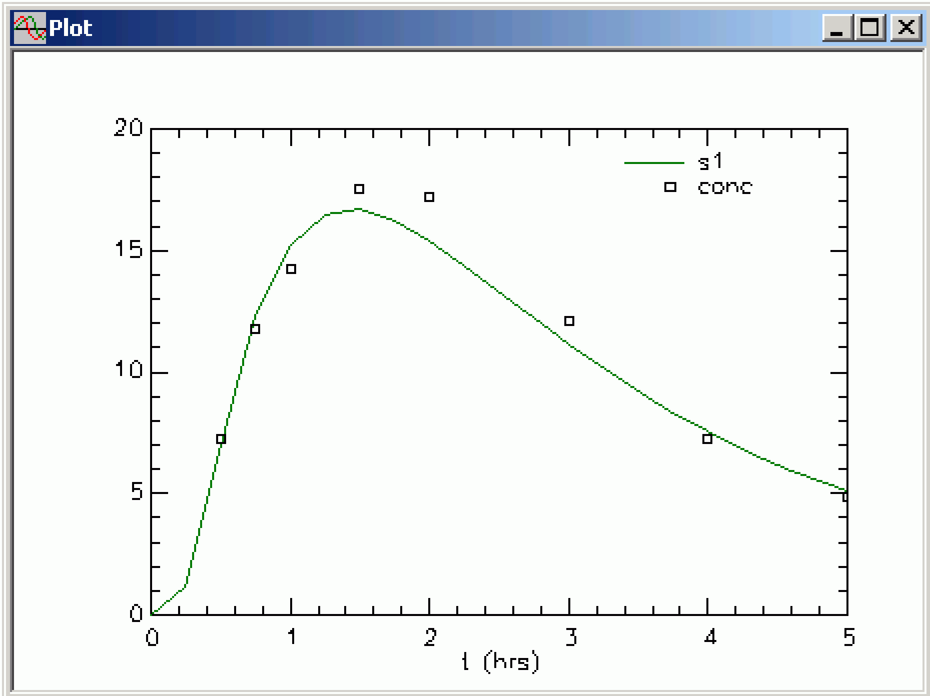
(4) In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar** click **Fit** . The plot will be updated as follows:



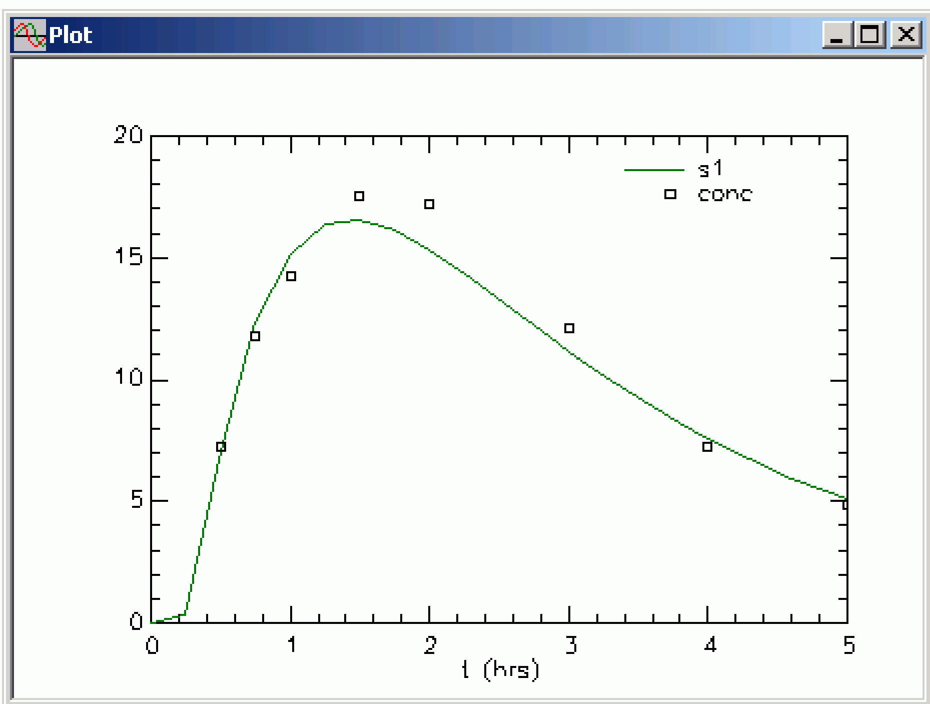
(5) View the details of the initial rise and fall. In the **Set** menu, click **Plot/Table Scale**. The **Plot and Table Scale** dialog box will open. Set the **X Axis** maximum equal to “5”. The **Plot and Table Scale** dialog box will appear as follows:



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

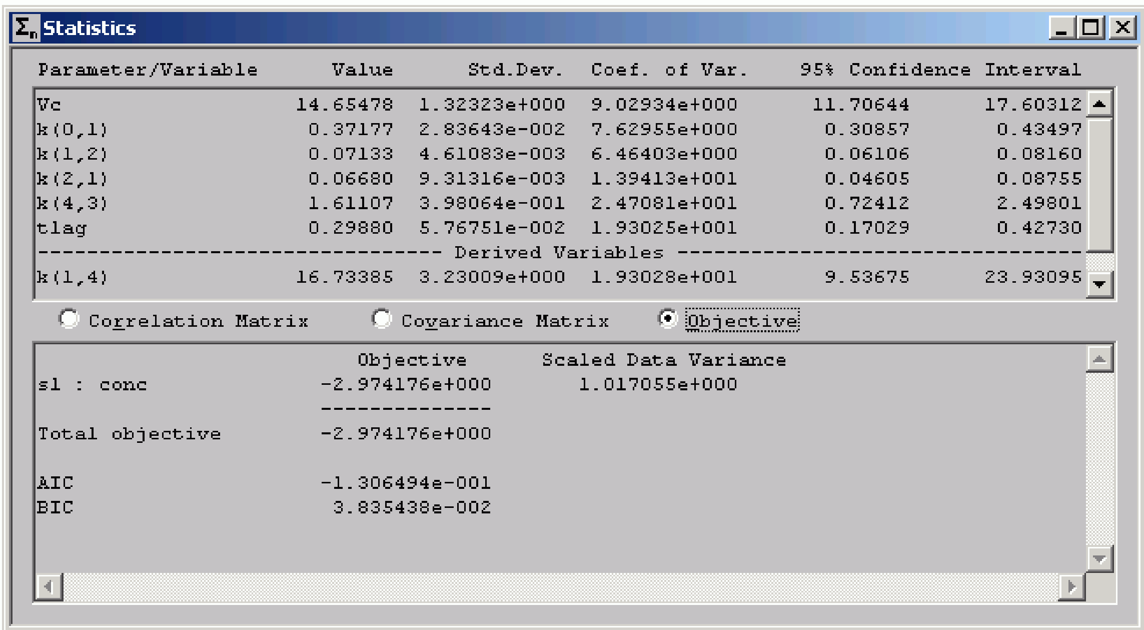


You can see the effect of the delay in the initial portion of the curve. What is the effect of the number of compartments in the delay in this situation? If you increase the number of compartments to "20", the plot will appear as follows:



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:



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.

8. Close all open windows and dialog boxes.

Quit the **SAAM II Compartmental** application. You may save the study file if you wish. It is provided as part of this tutorial as **delay1.stu**.

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:

Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
Vc	14.65964	1.35338e+000	9.23200e+000	11.64413	17.67516
k(0,1)	0.37304	2.90049e-002	7.77535e+000	0.30841	0.43766
k(1,2)	0.07146	4.66408e-003	6.52675e+000	0.06107	0.08185
k(2,1)	0.06744	9.50516e-003	1.40951e+001	0.04626	0.08861
k(4,3)	1.55001	3.44288e-001	2.22120e+001	0.78288	2.31713
tlag	0.29179	4.76814e-002	1.63410e+001	0.18555	0.39803
Derived Variables					
k(1,4)	68.54229	1.12006e+001	1.63412e+001	43.58577	93.49881

Correlation Matrix   Covariance Matrix   Objective

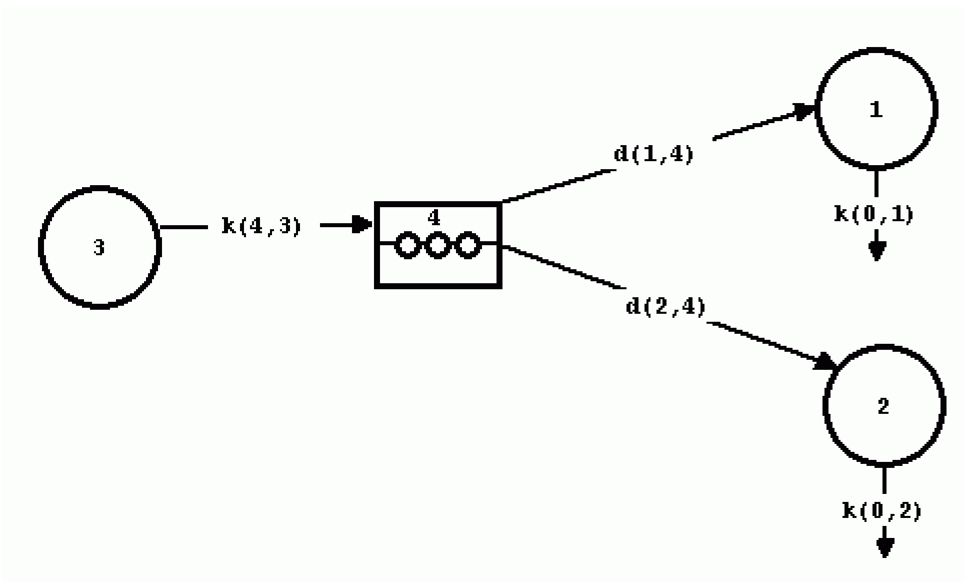
	Objective	Scaled Data Variance
s1 : conc	-2.951231e+000	1.040661e+000
Total objective	-2.951231e+000	
AIC	-1.191769e-001	
BIC	4.982684e-002	

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.

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:

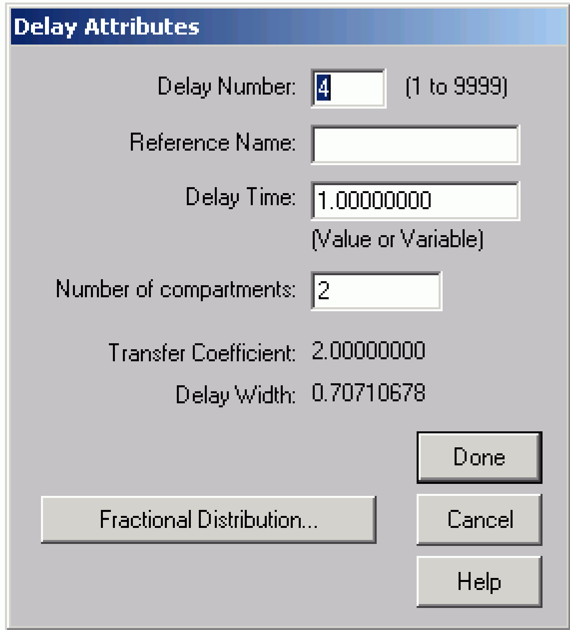


In the model shown above, Compartments **1** and **2** represent two distinct plasma compartments of the test substance introduced into the system. Thus, the "system" model, from the point of how the substance is metabolized in the body, is represented by these two compartments. Compartment **3** is 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:



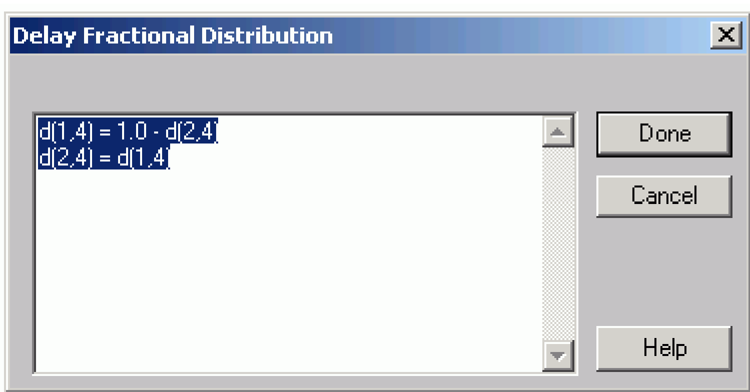
Notice unlike the situation in Part 1, the **Fractional Distribution** check box is active. This is because there are two outputs from Delay **4**.

4. Set the delay attributes.

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

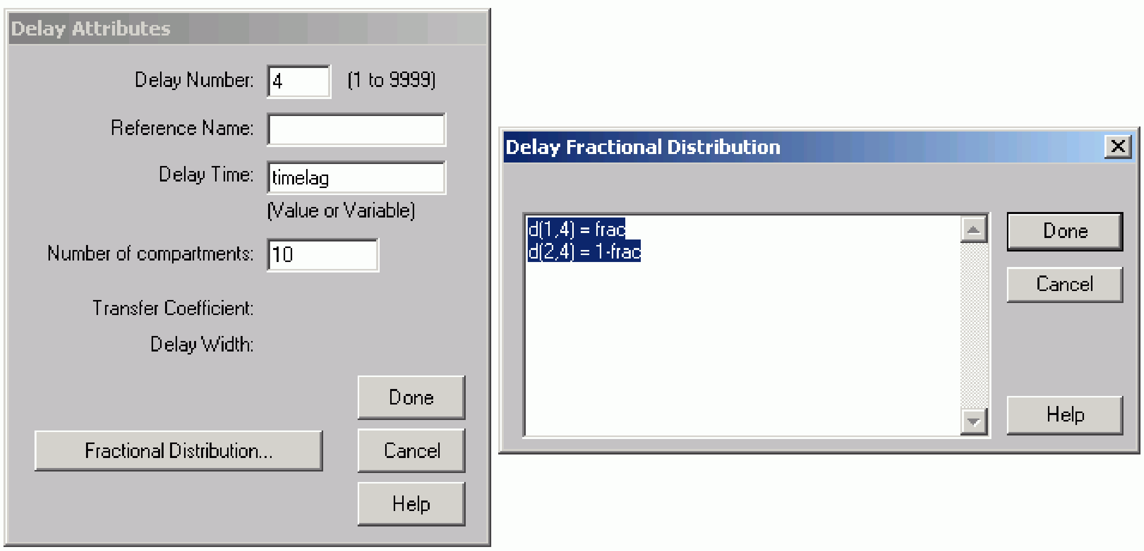
   b. Change the **Number of compartments** from "2" to "10".

   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.

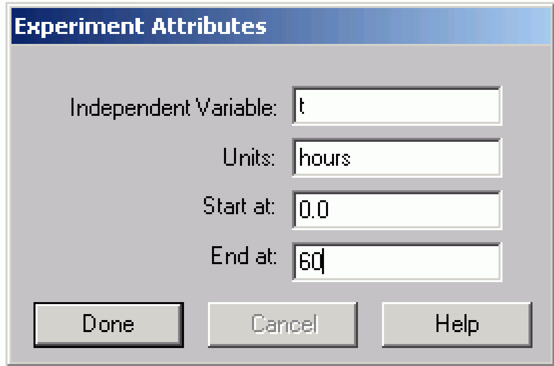
Fractional distribution from a delay. When there is more than one loss from a delay, you must specify the fractional distribution along each loss pathway. It is essential to remember that the total fractional loss must equal 1. Thus when you specify the fractional distribution, you must be sure the total 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:

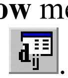


d. Click **Done**. The **Create Experiment** dialog box will open as shown below:

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

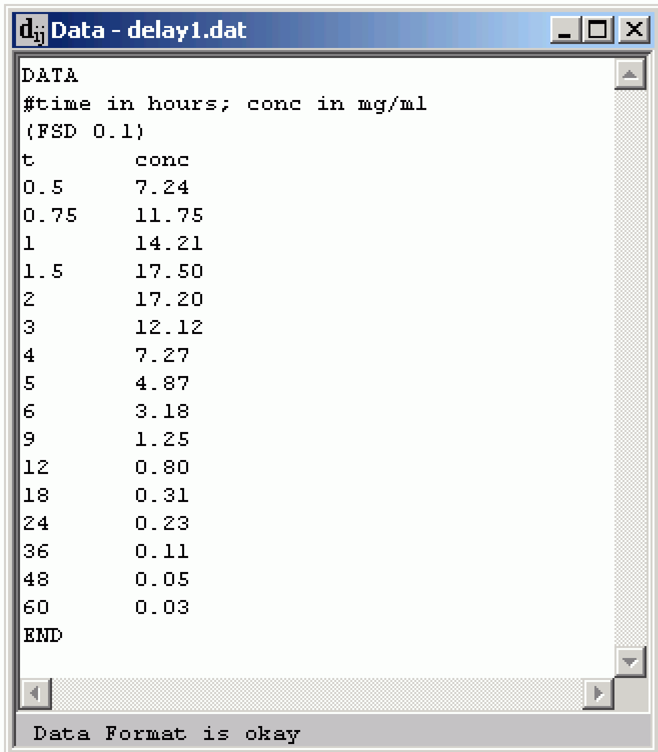
e. Click **Create**.

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:



```
DATA
#time in hours; conc in mg/ml
(FSD 0.1)
t       conc
0.5     7.24
0.75    11.75
1       14.21
1.5     17.50
2       17.20
3       12.12
4       7.27
5       4.87
6       3.18
9       1.25
12      0.80
18      0.31
24      0.23
36      0.11
48      0.05
60      0.03
END
```


d. Close the **Data** window.

7. Create the input and sample

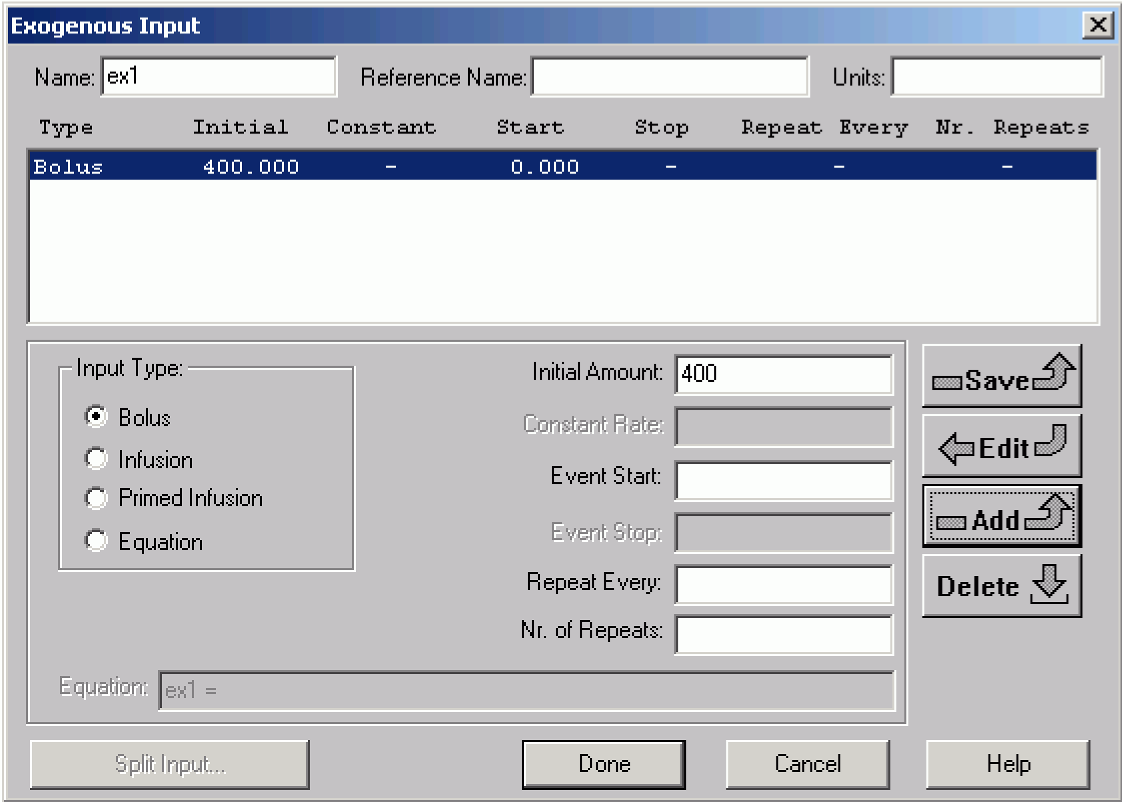
a. In the **SAAM II Toolbox**, click **Input**.

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**.

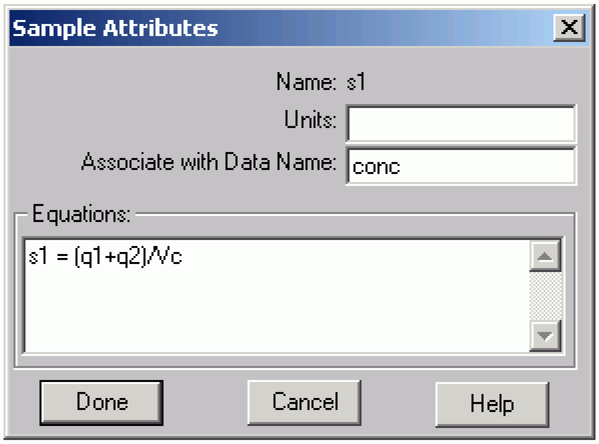
g. In the **SAAM II Toolbox**, click **Sample**.

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

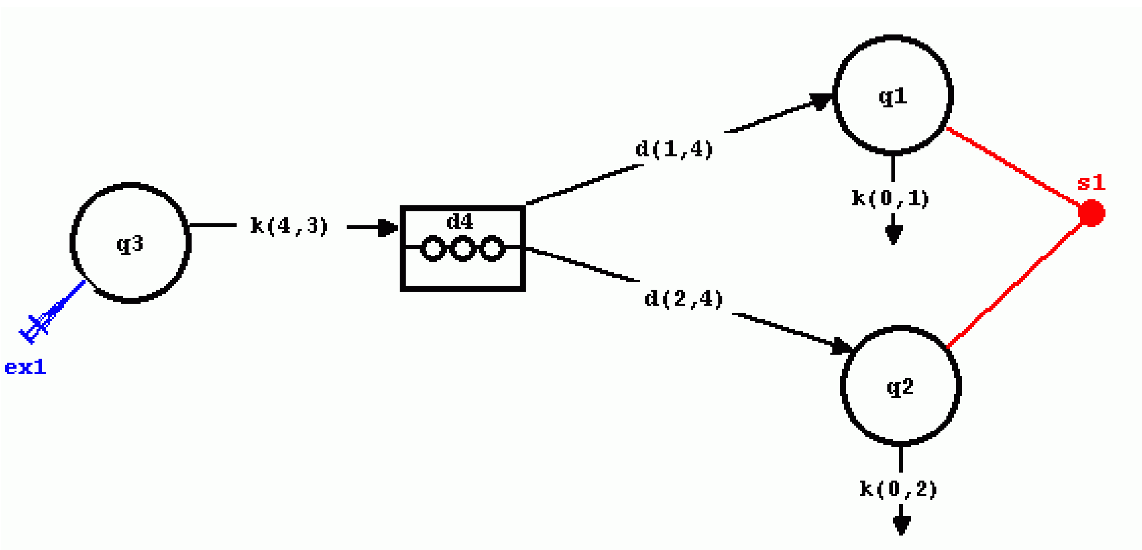
i. On the **Drawing Canvas**, double-click **s1** to open the **Sample Attributes** dialog box.

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

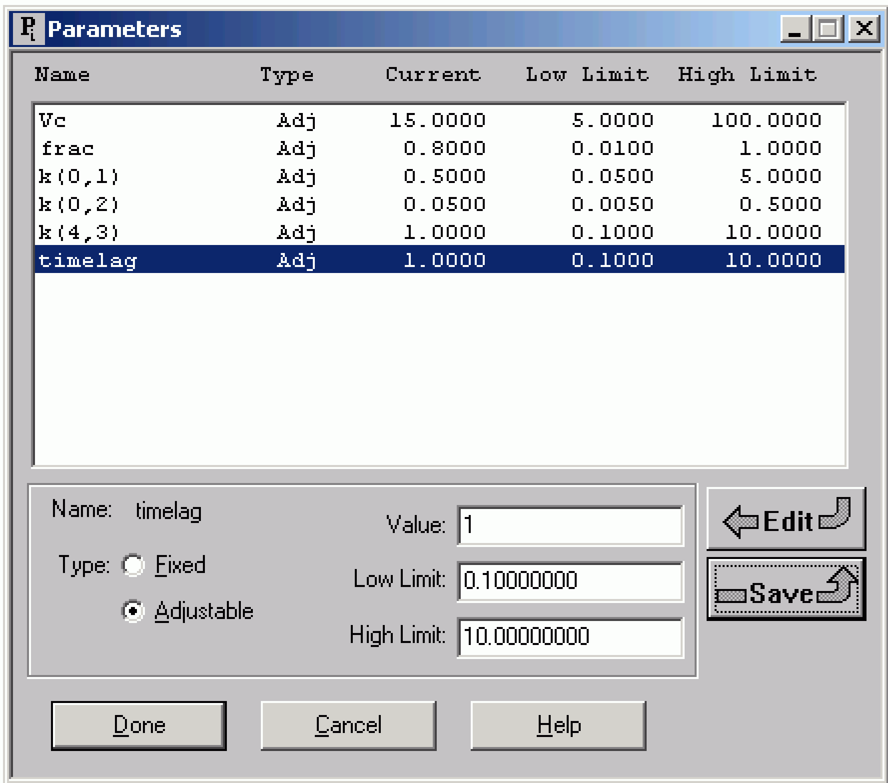
k. Edit the sample equation to read “s1=(q1+q2)/Vc” in the **Equation** box. The **Sample Attributes** dialog box will appear as follows:



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



8. Enter the parameter 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.

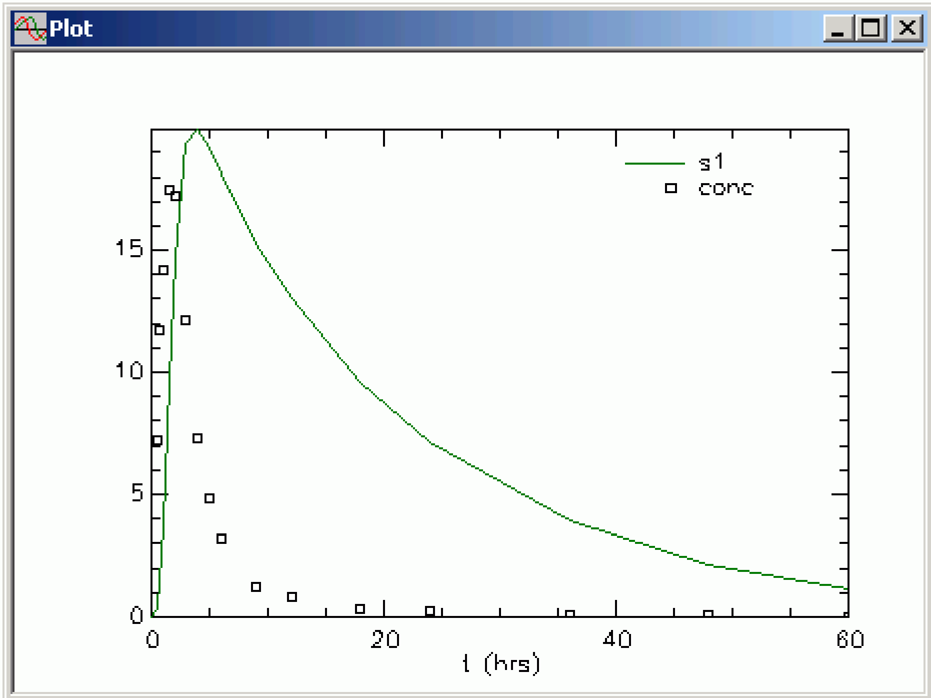
9. Solve the model and view the solution.

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

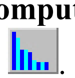
   b. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot** . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is not selected.

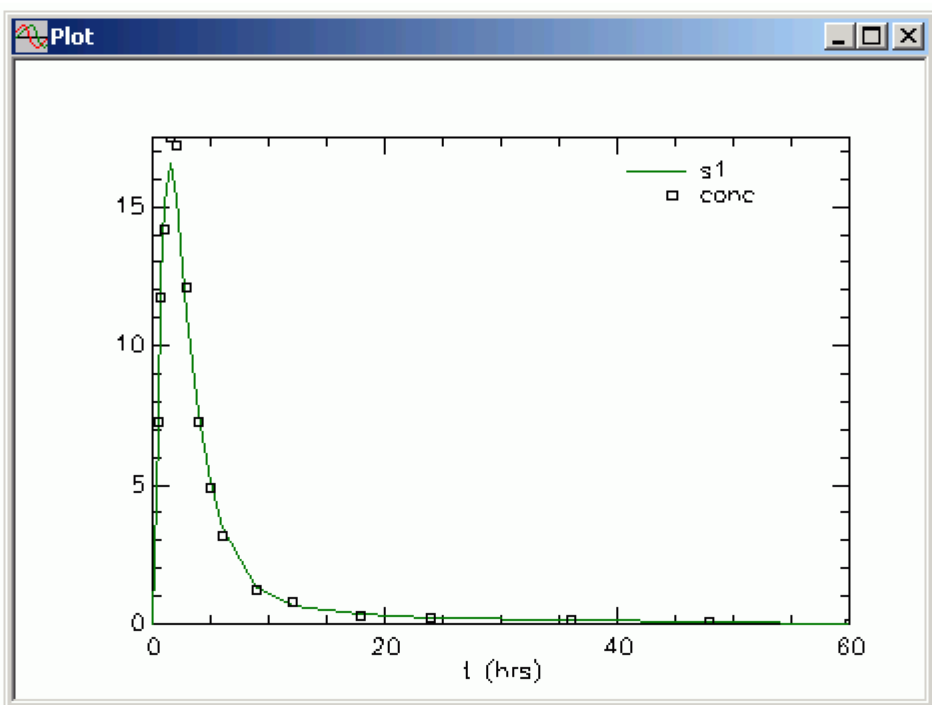
   c. Click **s1:conc** to move this to the **Current Selection** pane.

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

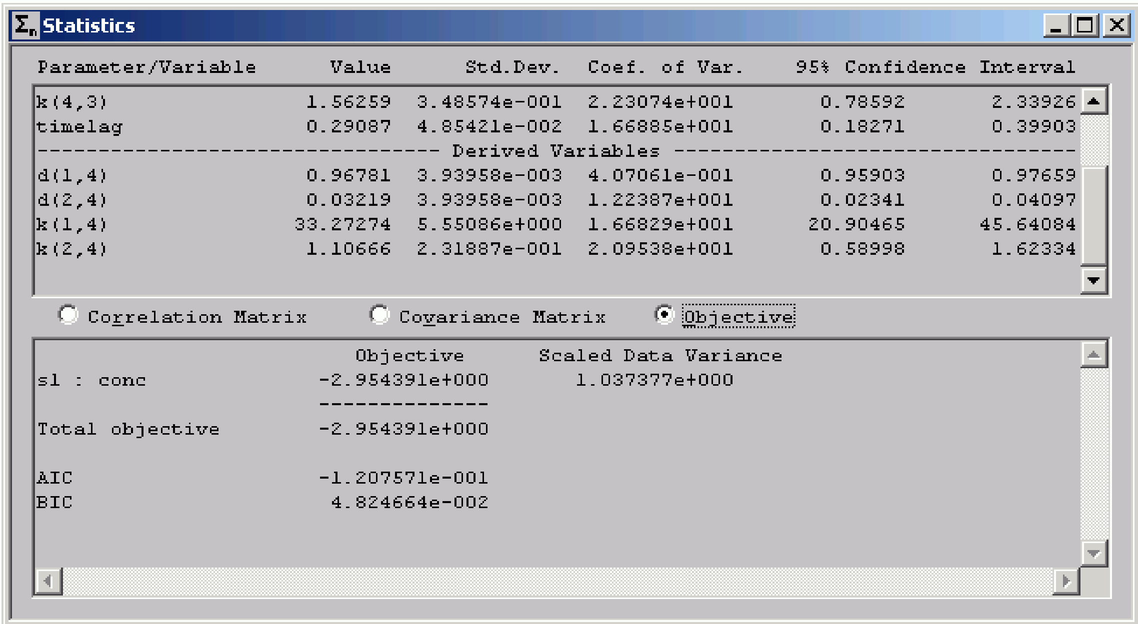


10. Fit the model to the data, and view the solution.

   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.

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

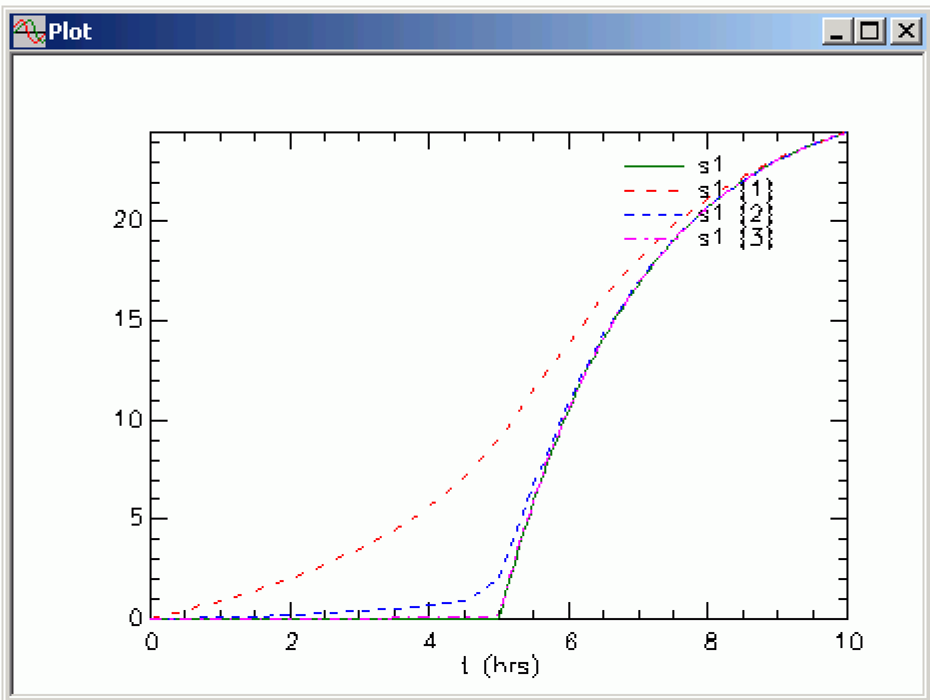
The Heaviside function

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.

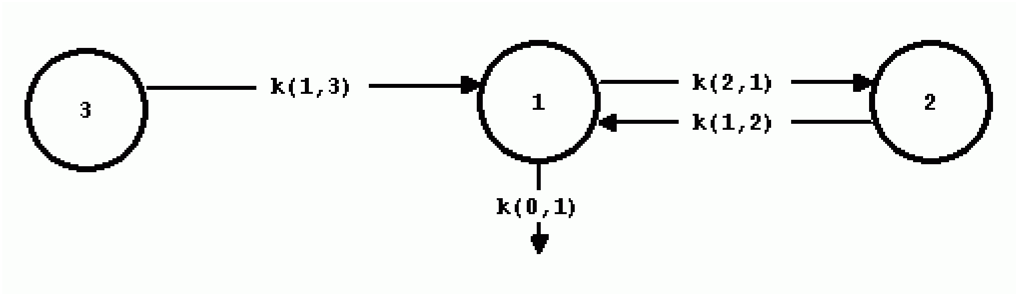
Table

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.

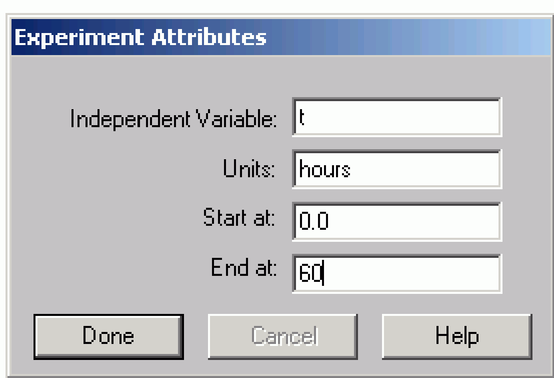
2. Create the model shown above.

3. Create the experiment on the model.

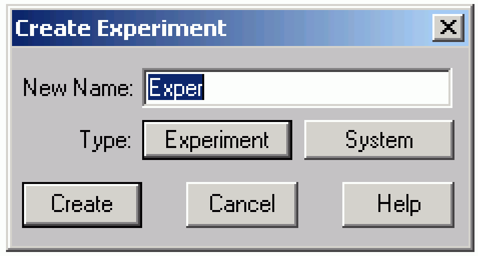
   a. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open.

   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:



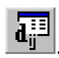
   d. Click **Done**. The **Create Experiment** dialog box will open as shown below:



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

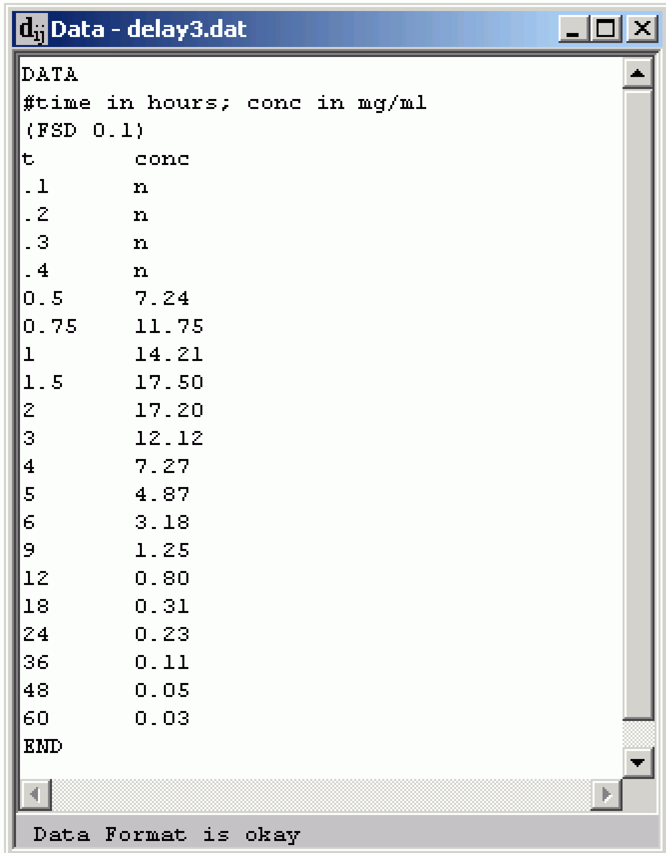
e. Click **Create**.

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

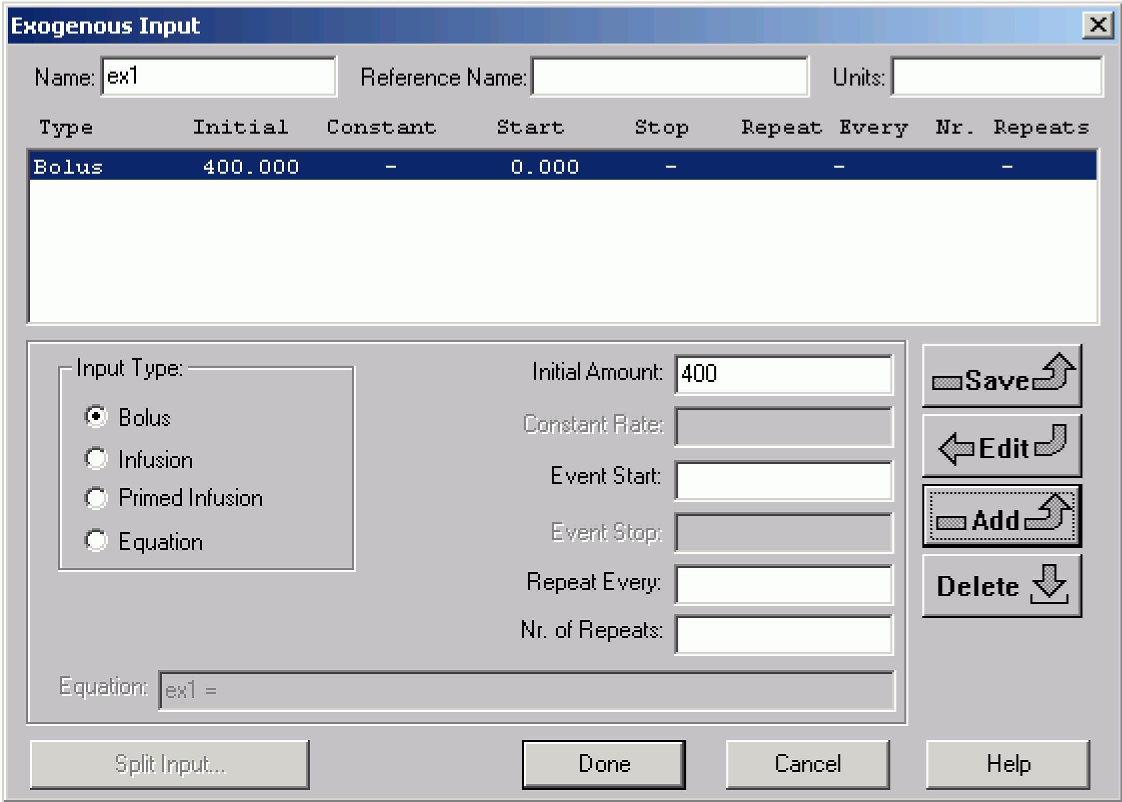
a. In the **SAAM II Toolbox**, click **Input**.

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**.

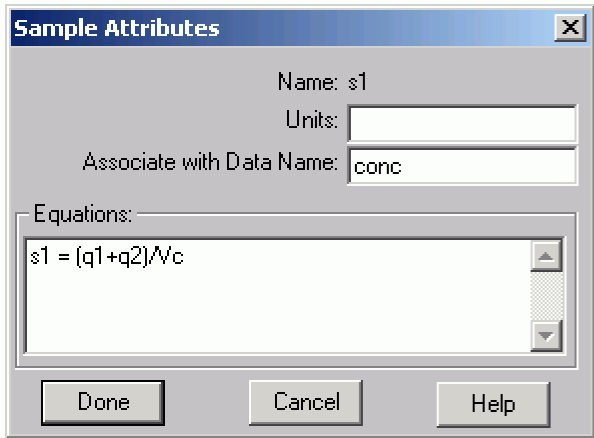
g. In the **SAAM II Toolbox**, click **Sample**.

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

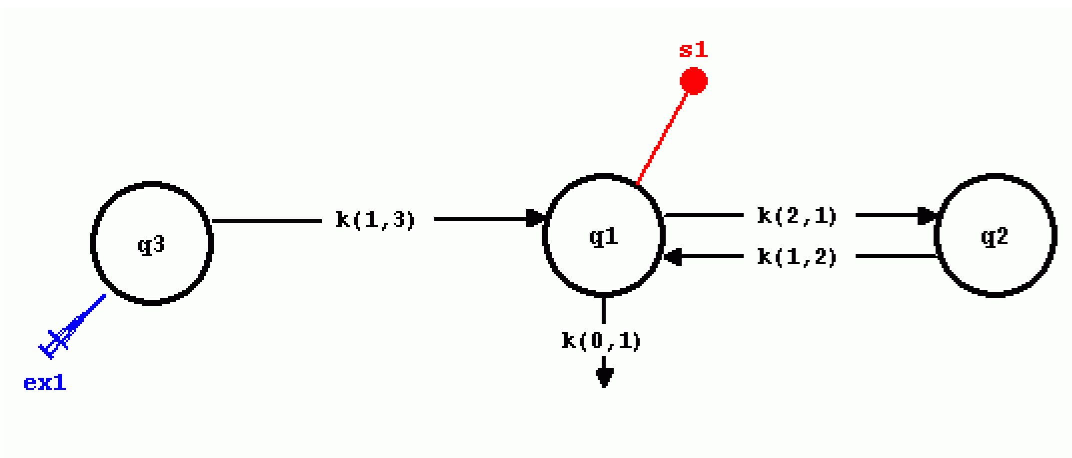
i. On the **Drawing Canvas**, double-click **s1** to open the **Sample Attributes** dialog box.

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:



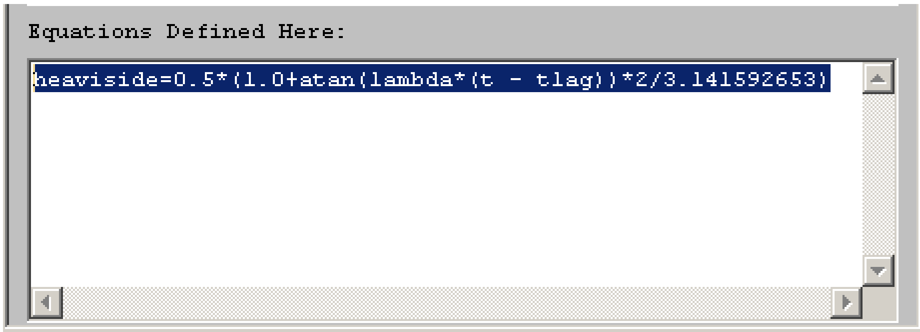
6. Specify the delay *k(1,3)*.

   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:

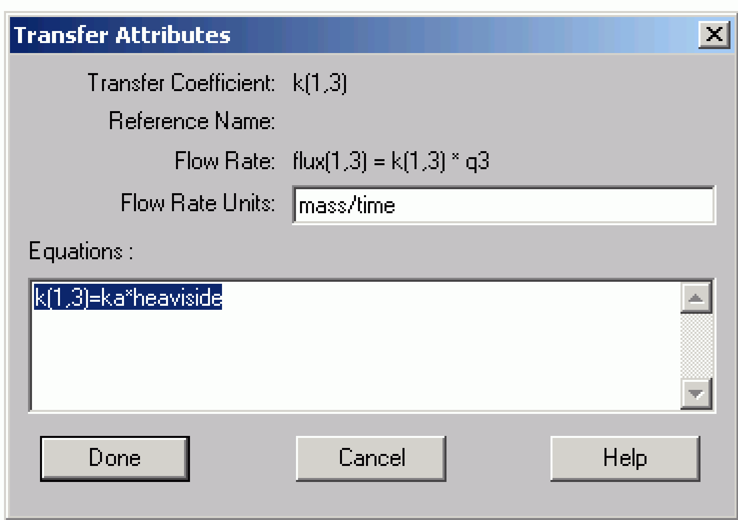


c. Close the **Equations** dialog box.

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.

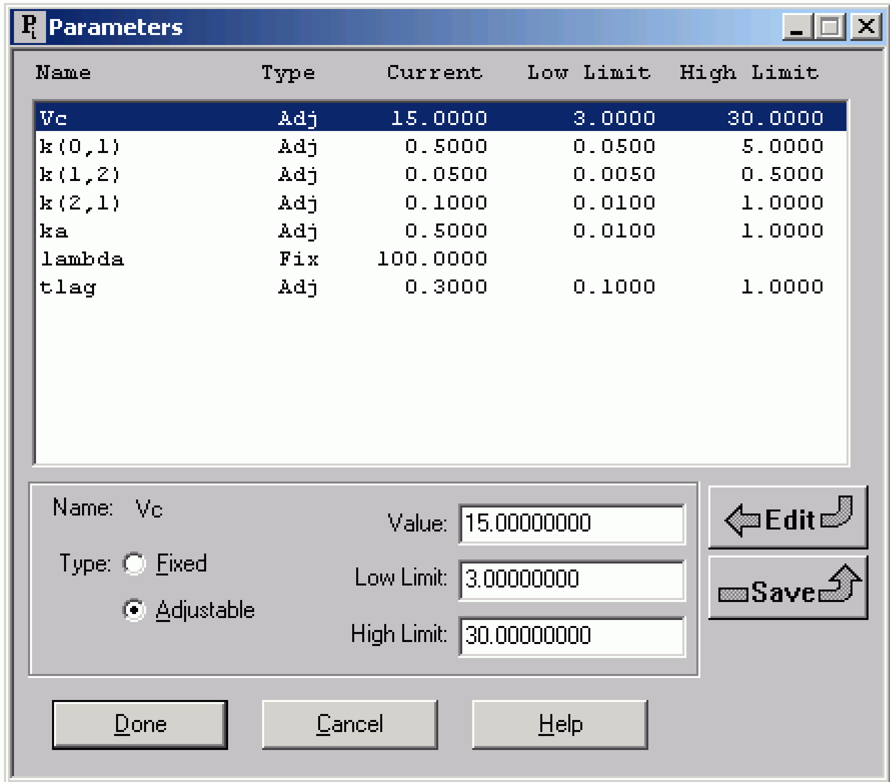
e. Type the equation "k(1,3)=ka*heaviside" in the **Equation** box. The **Transfer Attributes** dialog box will appear as follows:



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

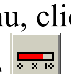
f. Close the **Transfer Attributes** dialog box.

7. Enter the parameter values as shown below:



8. Solve the model and view the solution.

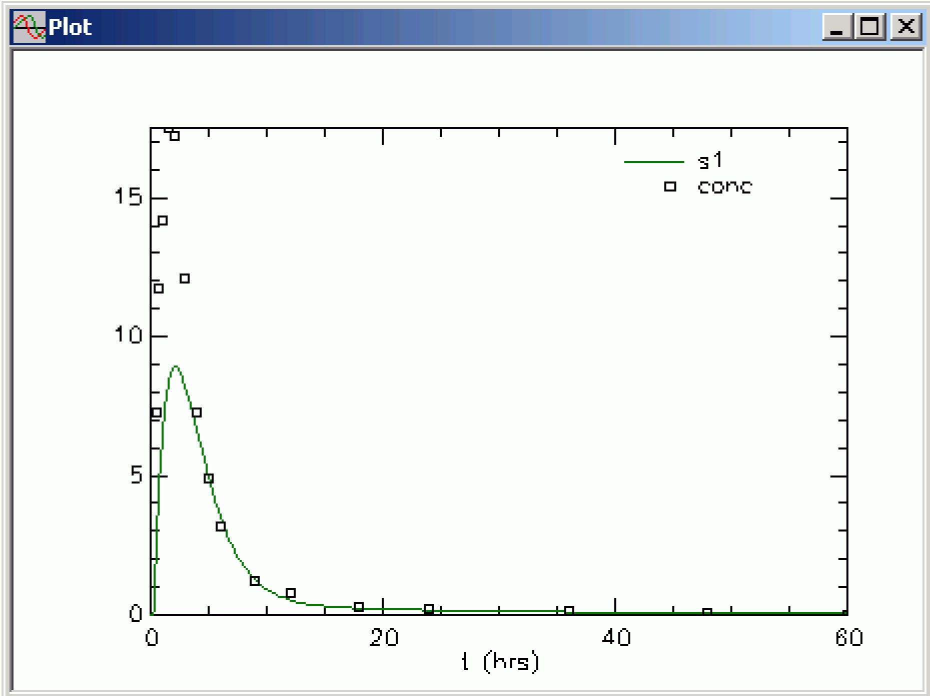
   a. In the **Compute** menu, click **Settings**. The **Computational Settings** dialog box will open. Change the **Min. Nr. of Calculation Intervals** from “20” to “200”. This will improve the resolution of your plots.

   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.

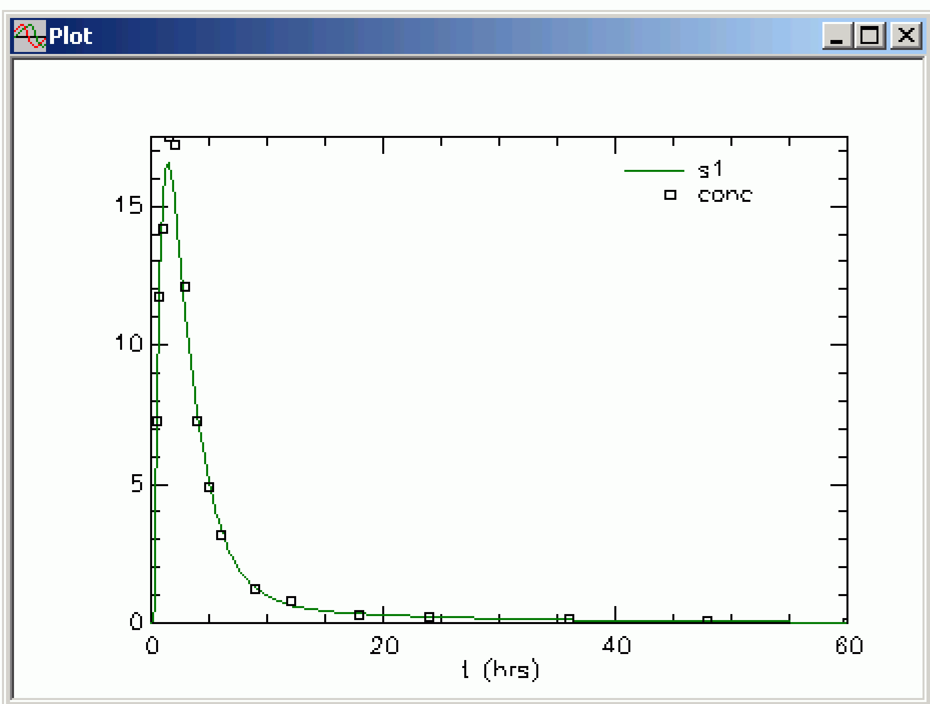
   d. Click **s1:conc** to move this to the **Current Selection** pane.

   e. Click **Done**. If the plot is not linear, in the **View** menu, click **Semilog**. 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:



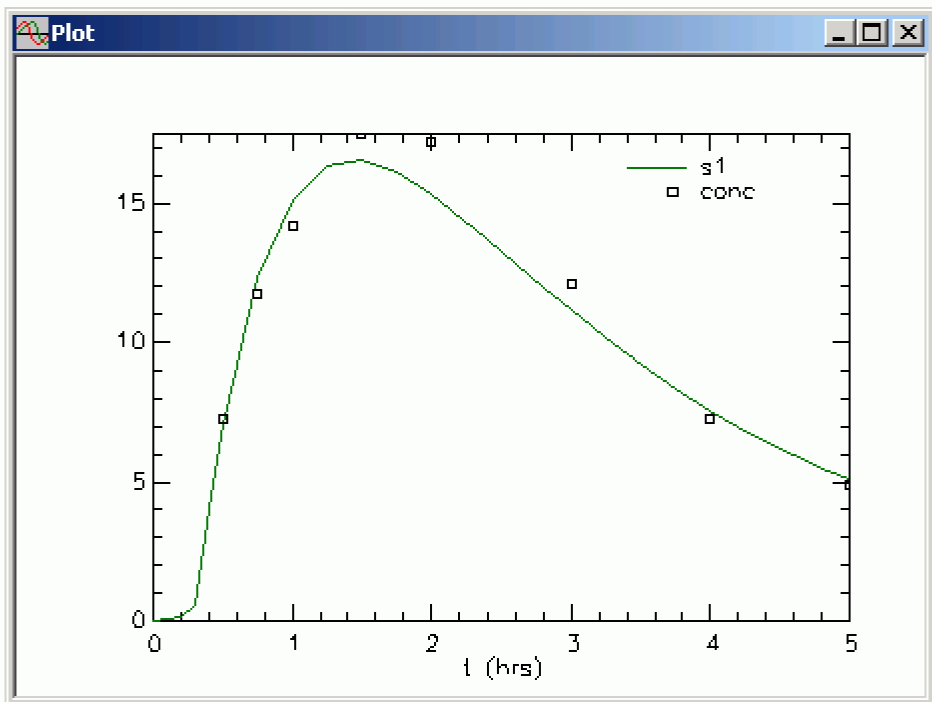
b. View the first 5 minutes of the solution.

(1) In the **Compute** menu, click **Plot/Table Scale**. The **Plot and Table Scale** dialog box will open.

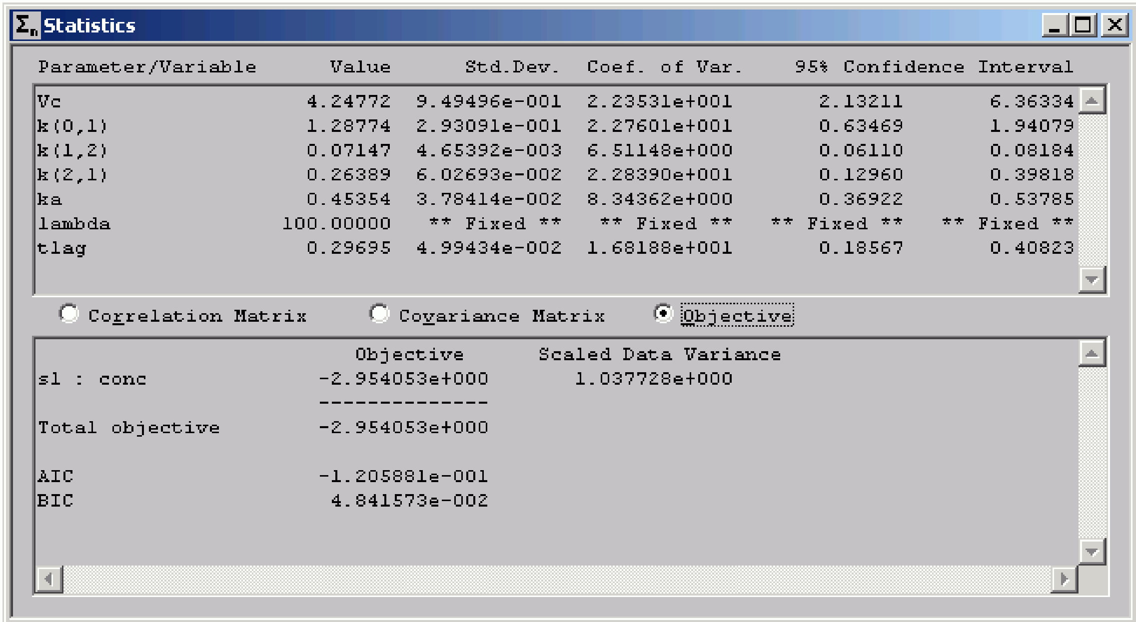
(2) In the **X Axis** pane, click **Set**.

(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:



Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
Vc	4.24772	9.49496e-001	2.23531e+001	2.13211	6.36334
k(0,1)	1.28774	2.93091e-001	2.27601e+001	0.63469	1.94079
k(1,2)	0.07147	4.65392e-003	6.51148e+000	0.06110	0.08184
k(2,1)	0.26389	6.02693e-002	2.28390e+001	0.12960	0.39818
ka	0.45354	3.78414e-002	8.34362e+000	0.36922	0.53785
lambda	100.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
tlag	0.29695	4.99434e-002	1.68188e+001	0.18567	0.40823

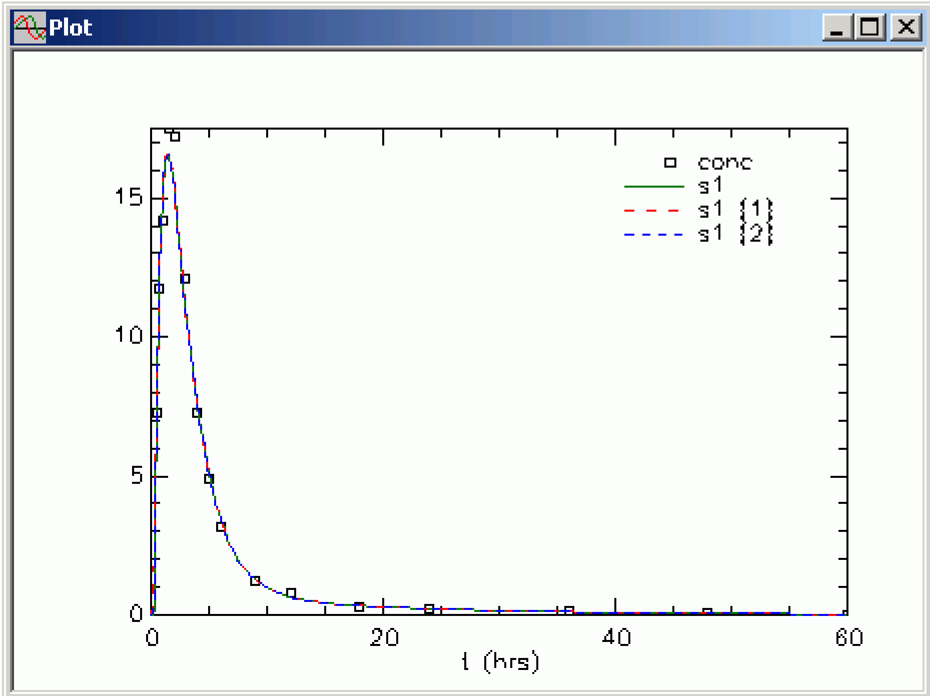
Correlation Matrix Covariance Matrix Objective

	Objective	Scaled Data Variance
s1 : conc	-2.954053e+000	1.037728e+000

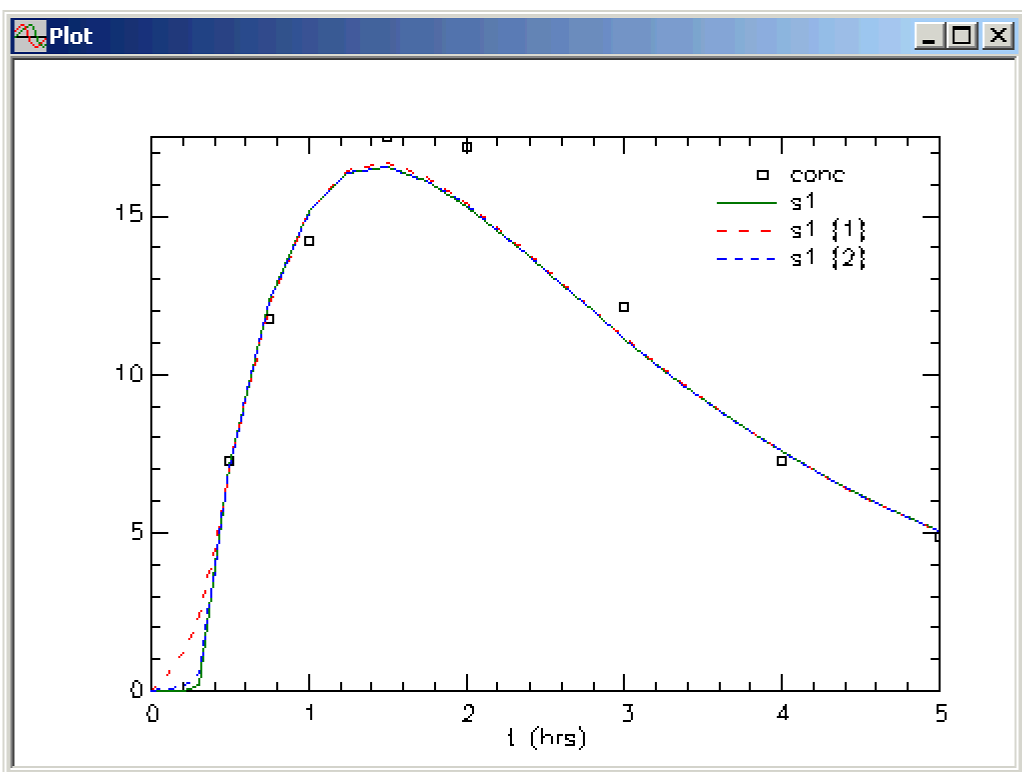
Total objective	-2.954053e+000	
AIC	-1.205881e-001	
BIC	4.841573e-002	

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{1}**), 100 (**s1{2}**) and 1000 (**s1**).

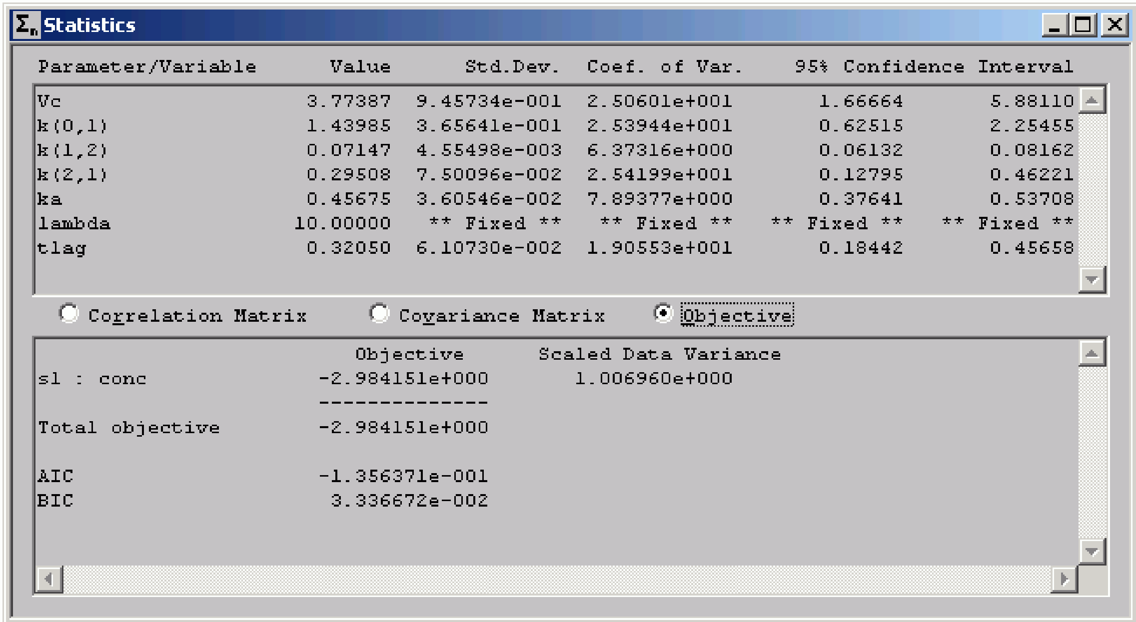


The details of the initial rise are shown as follows:



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:

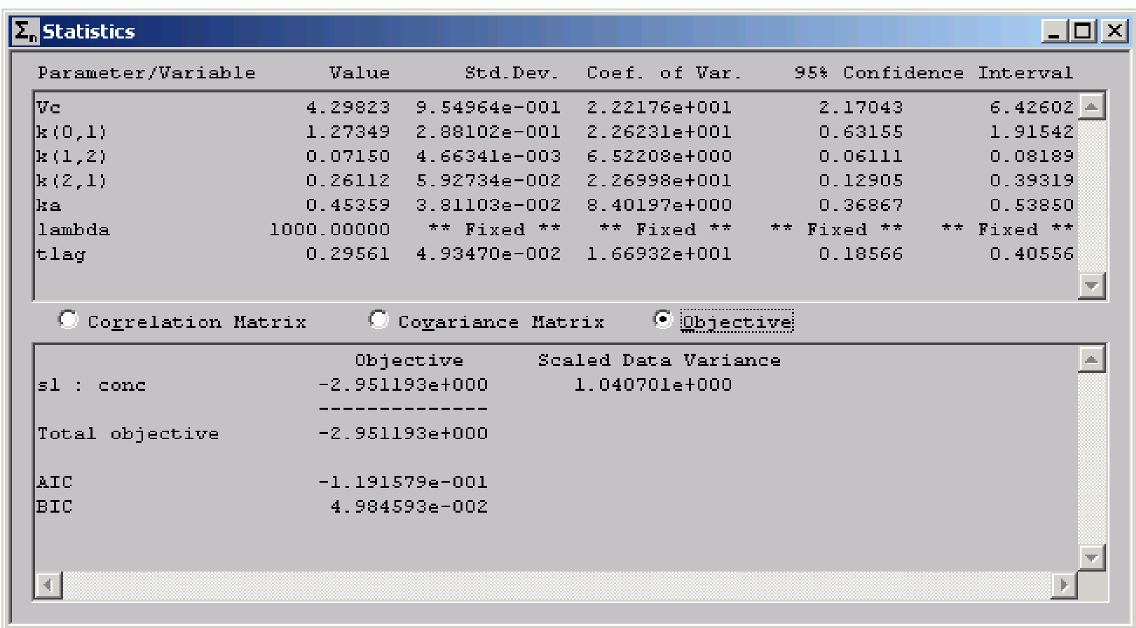


Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
Vc	3.77387	9.45734e-001	2.50601e+001	1.66664	5.88110
k(0,1)	1.43985	3.65641e-001	2.53944e+001	0.62515	2.25455
k(1,2)	0.07147	4.55498e-003	6.37316e+000	0.06132	0.08162
k(2,1)	0.29508	7.50096e-002	2.54199e+001	0.12795	0.46221
ka	0.45675	3.60546e-002	7.89377e+000	0.37641	0.53708
lambda	10.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
tlag	0.32050	6.10730e-002	1.90553e+001	0.18442	0.45658

Correlation Matrix   Covariance Matrix   Objective

	Objective	Scaled Data Variance
s1 : conc	-2.984151e+000	1.006960e+000
Total objective	-2.984151e+000	
AIC	-1.356371e-001	
BIC	3.336672e-002	



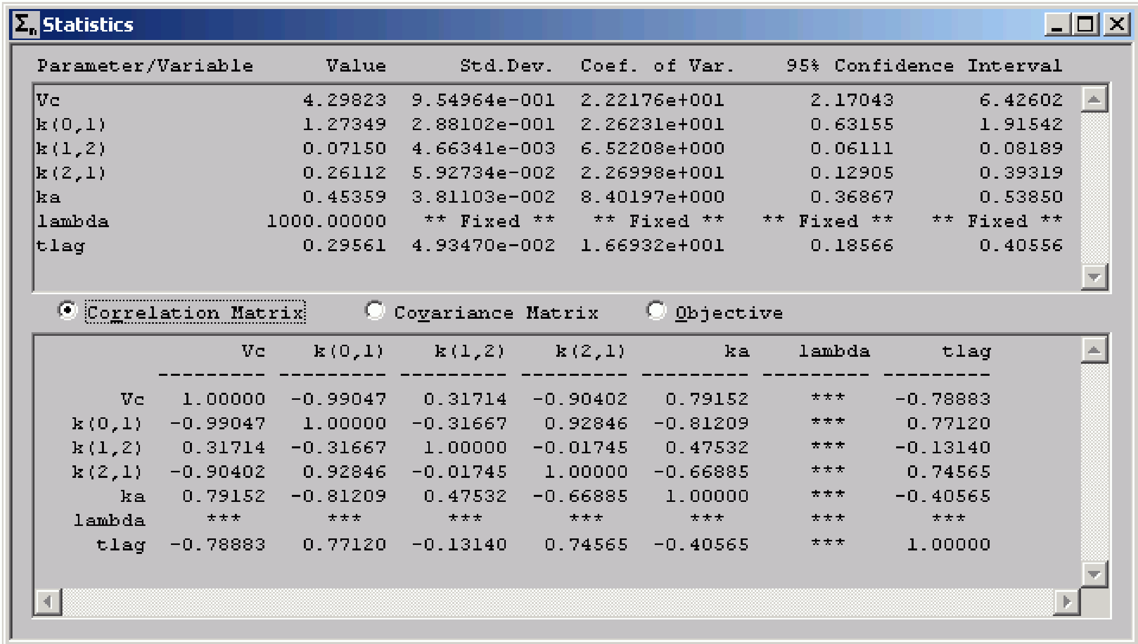
Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
Vc	4.29823	9.54964e-001	2.22176e+001	2.17043	6.42602
k(0,1)	1.27349	2.88102e-001	2.26231e+001	0.63155	1.91542
k(1,2)	0.07150	4.66341e-003	6.52208e+000	0.06111	0.08189
k(2,1)	0.26112	5.92734e-002	2.26998e+001	0.12905	0.39319
ka	0.45359	3.81103e-002	8.40197e+000	0.36867	0.53850
lambda	1000.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
tlag	0.29561	4.93470e-002	1.66932e+001	0.18566	0.40556

Correlation Matrix   Covariance Matrix   Objective

	Objective	Scaled Data Variance
s1 : conc	-2.951193e+000	1.040701e+000
Total objective	-2.951193e+000	
AIC	-1.191579e-001	
BIC	4.984593e-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

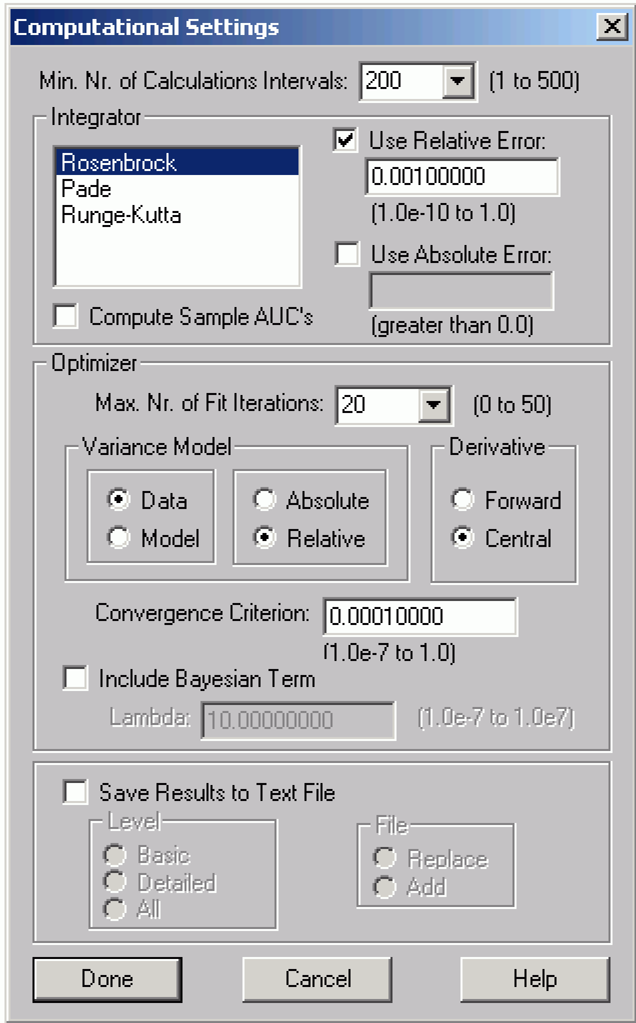
Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
Vc	4.29823	9.54964e-001	2.22176e+001	2.17043	6.42602
k(0,1)	1.27349	2.88102e-001	2.26231e+001	0.63155	1.91542
k(1,2)	0.07150	4.66341e-003	6.52208e+000	0.06111	0.08189
k(2,1)	0.26112	5.92734e-002	2.26998e+001	0.12905	0.39319
ka	0.45359	3.81103e-002	8.40197e+000	0.36867	0.53850
lambda	1000.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
tlag	0.29561	4.93470e-002	1.66932e+001	0.18566	0.40556

Correlation Matrix   Covariance Matrix   Objective

	Vc	k(0,1)	k(1,2)	k(2,1)	ka	lambda	tlag
Vc	1.00000	-0.99047	0.31714	-0.90402	0.79152	***	-0.78883
k(0,1)	-0.99047	1.00000	-0.31667	0.92846	-0.81209	***	0.77120
k(1,2)	0.31714	-0.31667	1.00000	-0.01745	0.47532	***	-0.13140
k(2,1)	-0.90402	0.92846	-0.01745	1.00000	-0.66885	***	0.74565
ka	0.79152	-0.81209	0.47532	-0.66885	1.00000	***	-0.40565
lambda	***	***	***	***	***	***	***
tlag	-0.78883	0.77120	-0.13140	0.74565	-0.40565	***	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*). 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*:

lambda	10	100	1000	10000	100000
Vc	3.774	4.247	4.298	4.298	4.298
k(0,1)	1.44	1.288	1.274	1.274	1.274

You can see that for *lambda* equal to 1000 the parameters are stable. Thus in this tutorial a value of *lambda* equal to 1000 or 10000 would have been more appropriate than 100. If you wish, you can repeat this part of the tutorial using *lambda* equal to 10000 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**.

