Using Forcing Functions

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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:

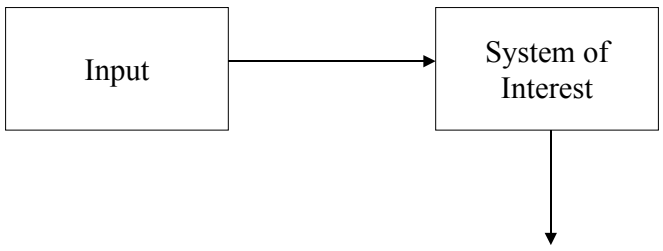
The data file for this tutorial is

ff_pre_pro.dat

Introduction

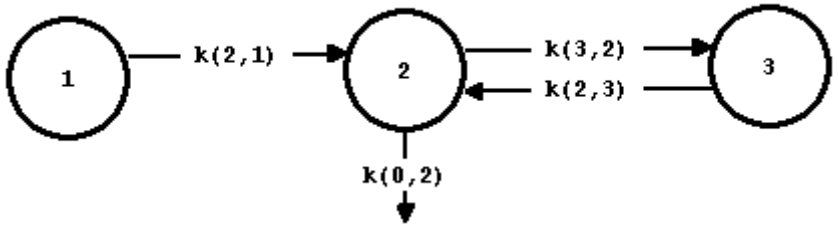
This tutorial will show you how to use forcing functions as a modeling tool in SAAM II.. They can be used for any precursor-product type system such as amino acid incorporation into a protein, drug absorption, or uptake from plasma by cells when data are available from imaging such as PET or MRI. Forcing functions can also be used as a model development and testing tool. This process is beyond the scope of this tutorial.

What are forcing functions, and how 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:

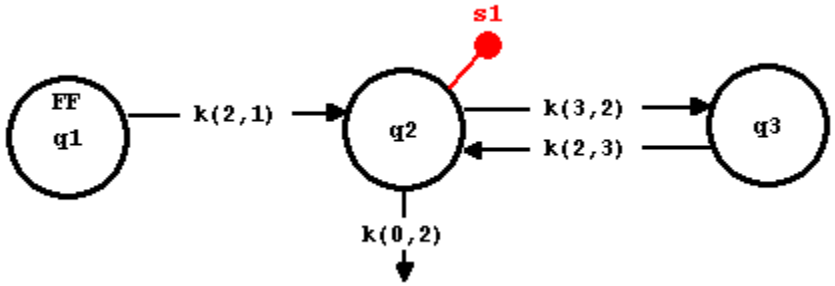


For this particular model, in the absence of the forcing function, SAAM II would create the following system of three differential equations:

$$\frac{dq1}{dt} = -k(2,1)q1$$
$$\frac{dq2}{dt} = -(k(3,2) + k(0,2))q2 + k(2,1)q1 + k(2,3)q3$$
$$\frac{dq3}{dt} = -k(2,3)q3 + k(3,2)q2$$

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.

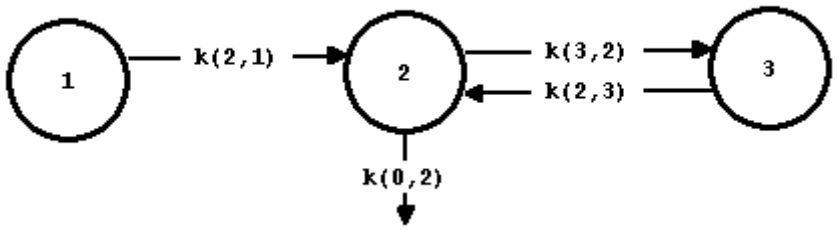
How are forcing functions defined? That is, how is **q1.FF** specified? There are two ways. One way is to write **q1.FF** as an equation such as a sum of exponentials. The other way is to connect sequential data points by a straight line. Both will be illustrated in this tutorial.

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:

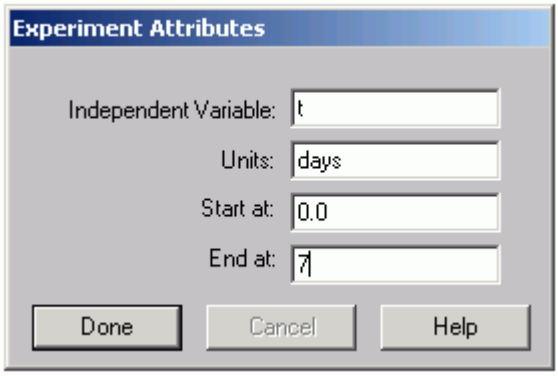


4. Create the experiment on the model

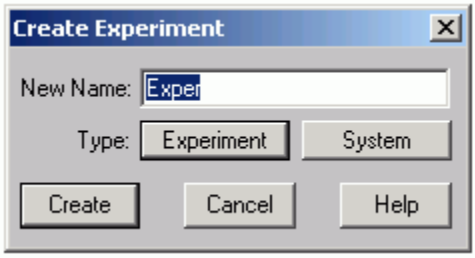
   a. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open.

   b. Type "days" in the **Units** box.

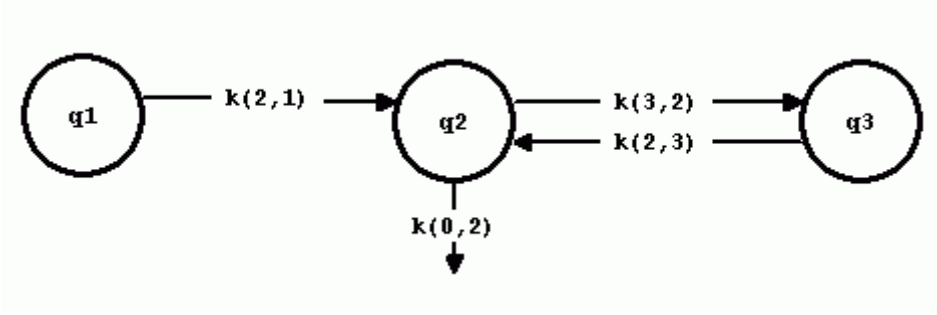
   c. Type "7" in the **End At** box. The Experiment Attributes dialog box will appear as follows:



   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)  ()       ()
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)    ()       ()
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
()       ()       ()
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:

Data - ff_pre_pro.dat

```
DATA
(FSD 0.1)
t        pre      pro
(/1440)  ()       ()
2        31.24    2.72
5        26.97    6.20
10       22.48    11.66
```

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:

Data - ff_pre_pro.dat

```
DATA
(FSD 0.1)
t        pre      pro
(/1440)  ()       ()
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)    ()       ()
1        4.14     31.94
1.5      2.23     34.84
2        1.69     36.20
```

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.

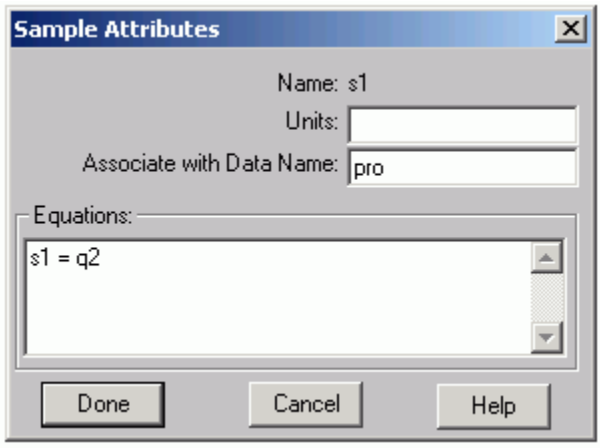
   a. In the **SAAM II Toolbox**, click **Sample**.

   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:

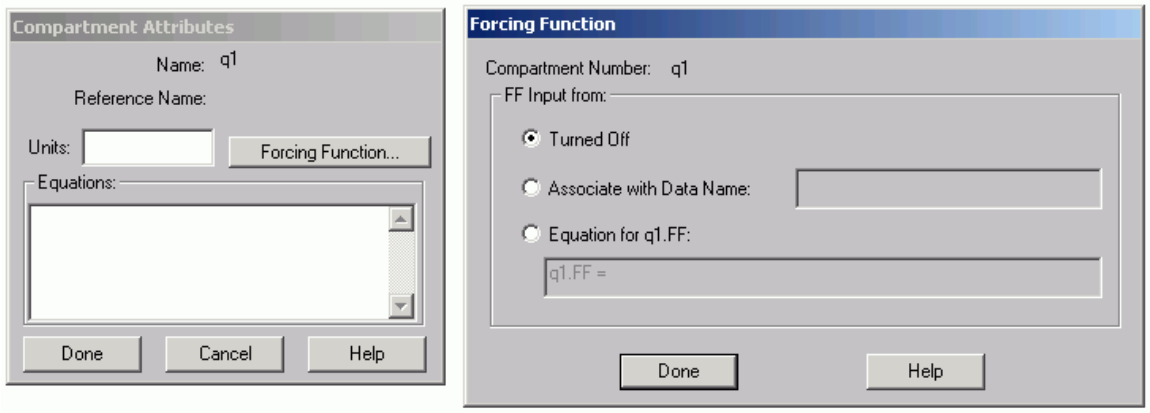


   f. Click **Done**. Noticed **s1** is now solid because it is associated with data.

7. Create a forcing function.

   a. Double-click Compartment **q1**, to open the **Compartment Attributes** dialog box.

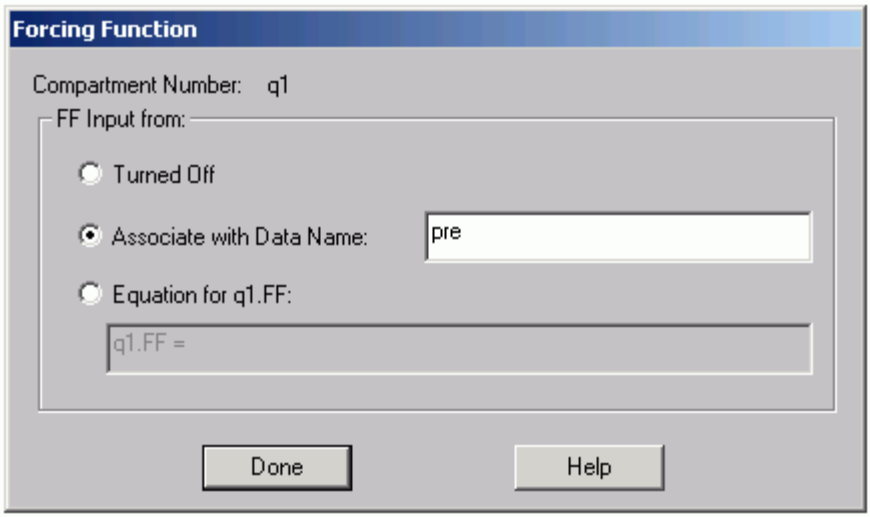
   b. Click **Forcing Function**. The **Forcing Function** dialog box will open as shown below (together with the **Compartments Attributes** dialog box):



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.

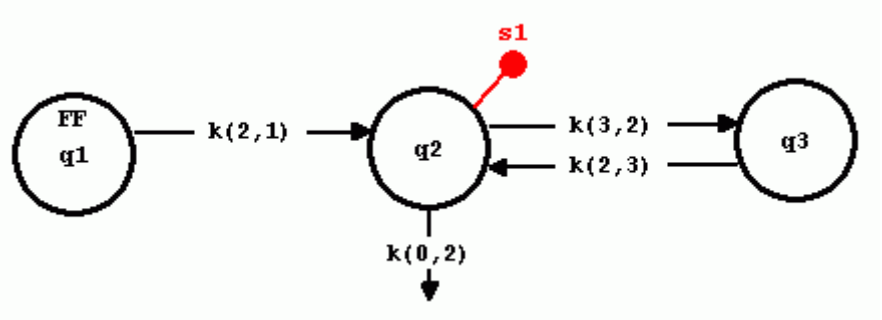
d. Type "pre" in the **Associate with Data Name** box. Your **Forcing Function** dialog box will appear as follows:



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.

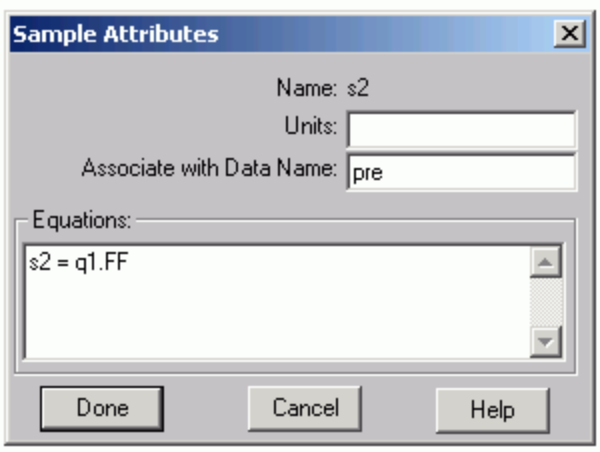
a. In the **SAAM II Toolbox**, click **Sample**.

b. Click Compartment **q1**, and then on the **Drawing Canvas**. The sample **s2** will appear.

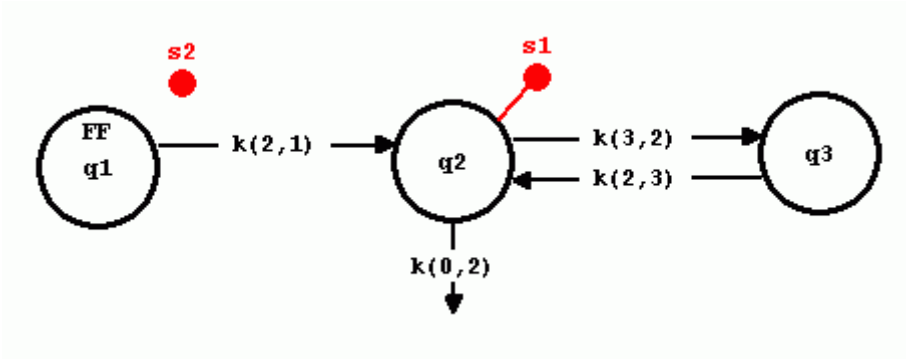
c. Double-click **s2** to open the **Sample Attributes** dialog box.

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.

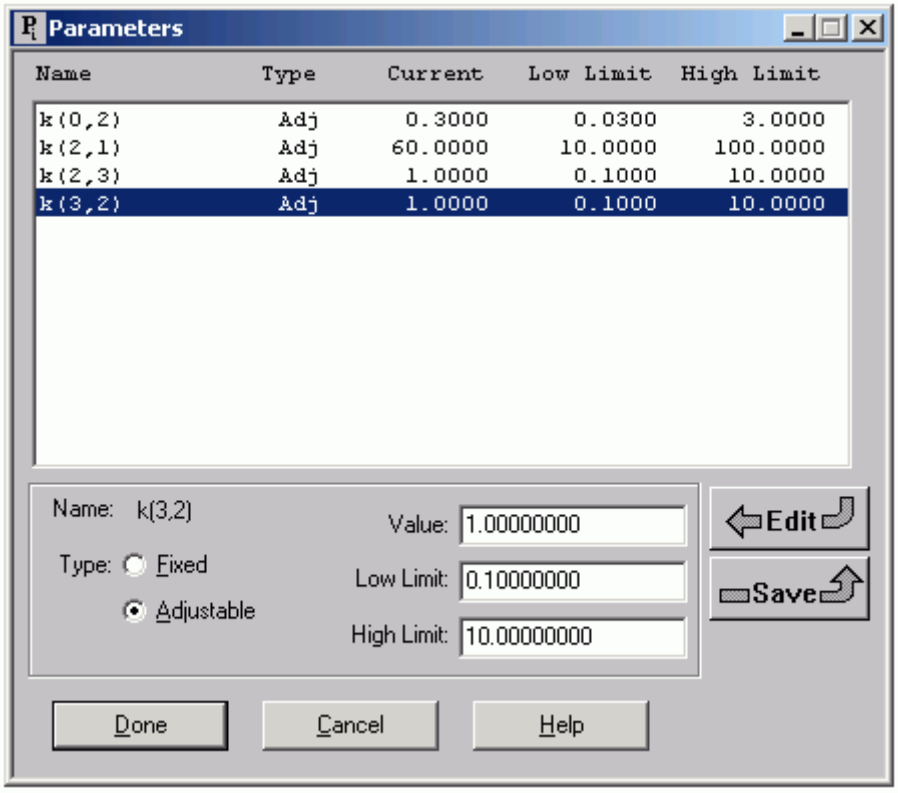


Samples. The Sample tool is a very powerful tool in SAAM II. Normally it is used to create samples that link a compartment, or compartments, with data. In this case, we are interested in viewing the forcing function. When we entered the equation "s2=q1.FF", **q1** no longer appeared in the sample equation, 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**.

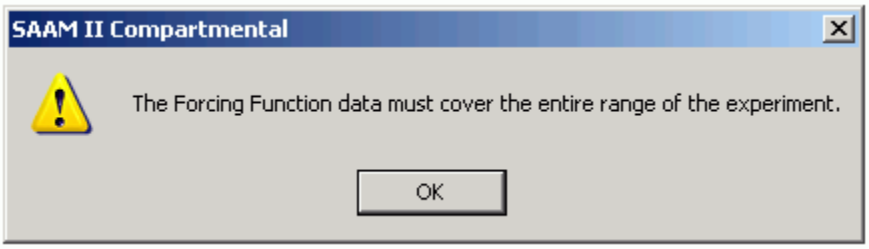
Volumes. Why was there no volume included in the sample **s1**? That is, normally when writing the sample equation we have usually included the volume term.

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:

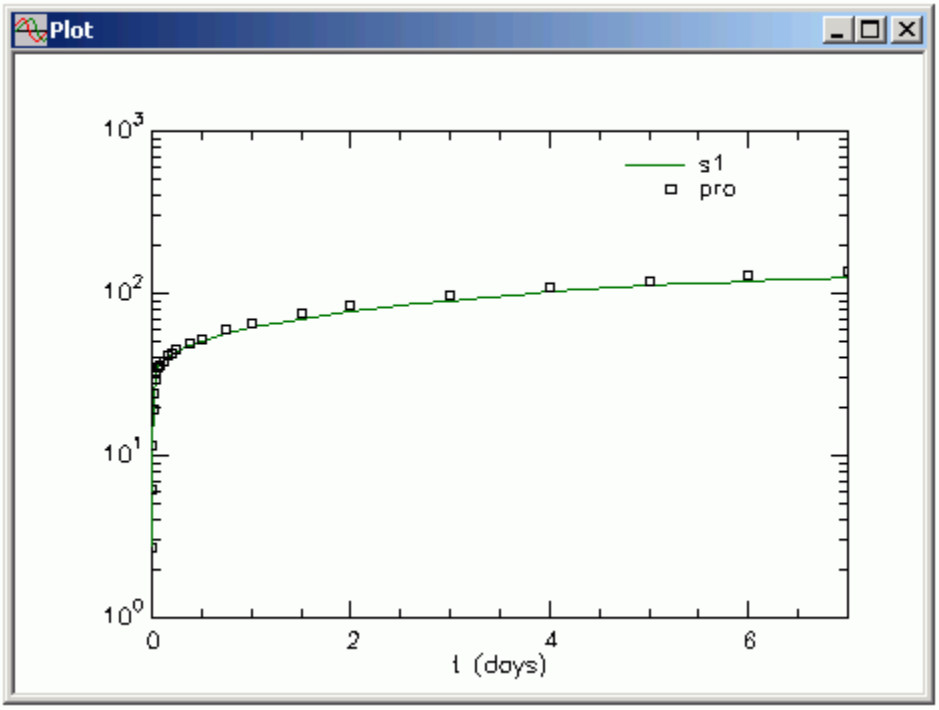
Data - ff_pre_pro.dat

```
DATA
(FSD 0.1)
t        pre      pro
(/1440)  ()       ()
0        35       n
2        31.24    2.72
5        26.97    6.20
```

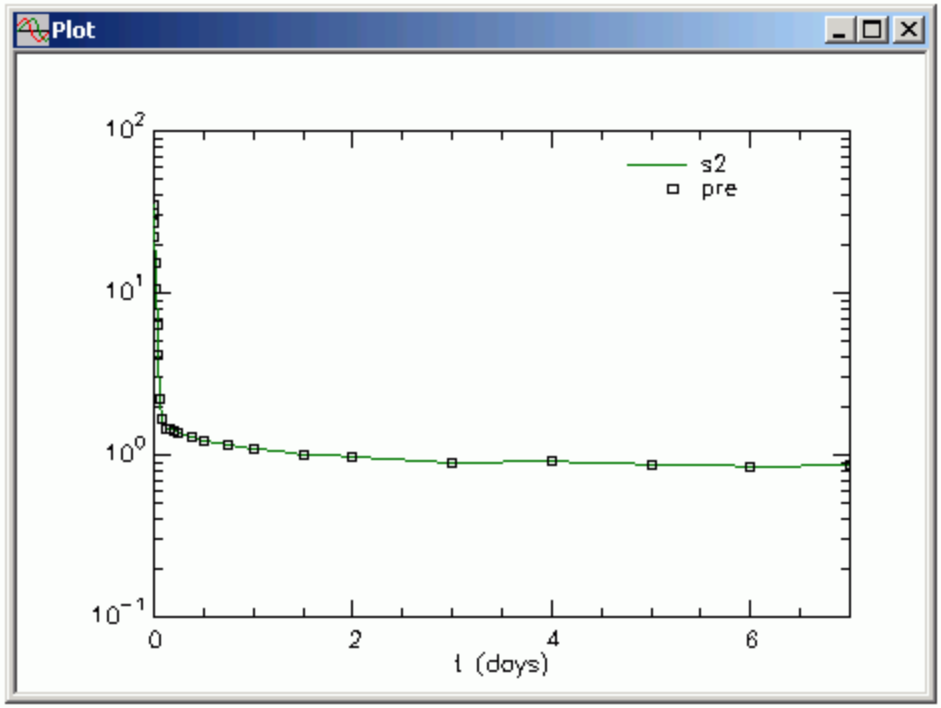
Data entry. Notice the "n" in the column for the pro. SAAM II expects an entry in each column for each time point. If there are no data, enter "n."

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:



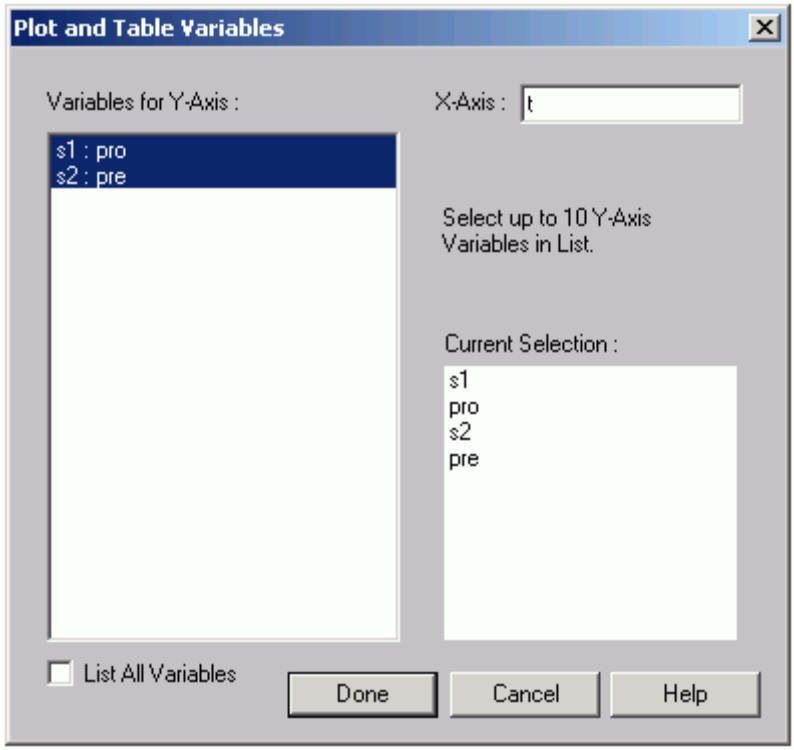
You can also plot **s2:pre**; it will appear as follows:



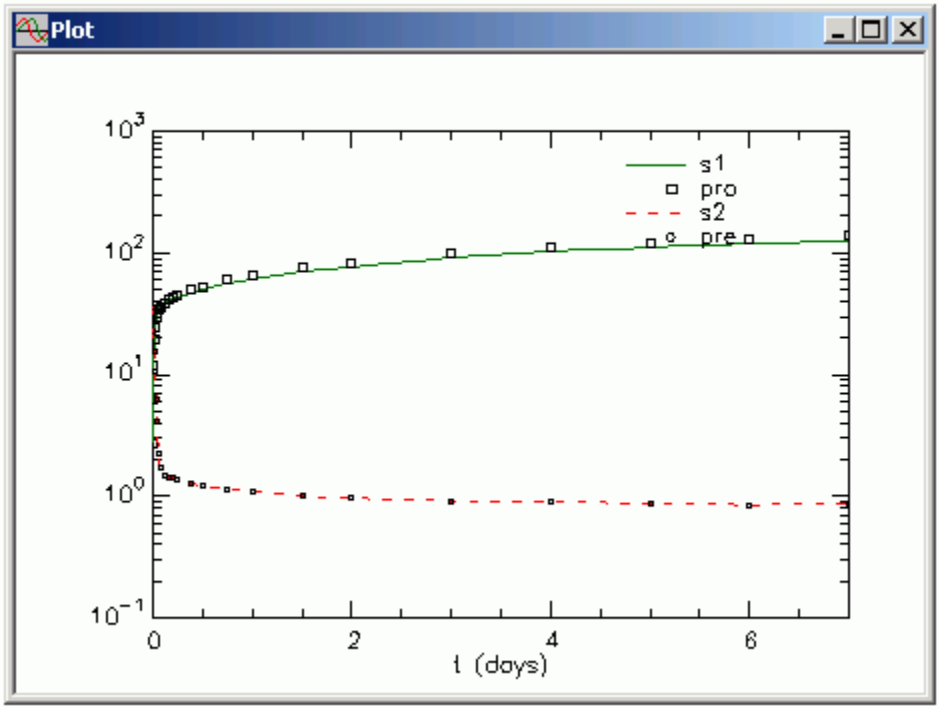
f. Plot **s2:pre** and **s1:pro** simultaneously.

(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:



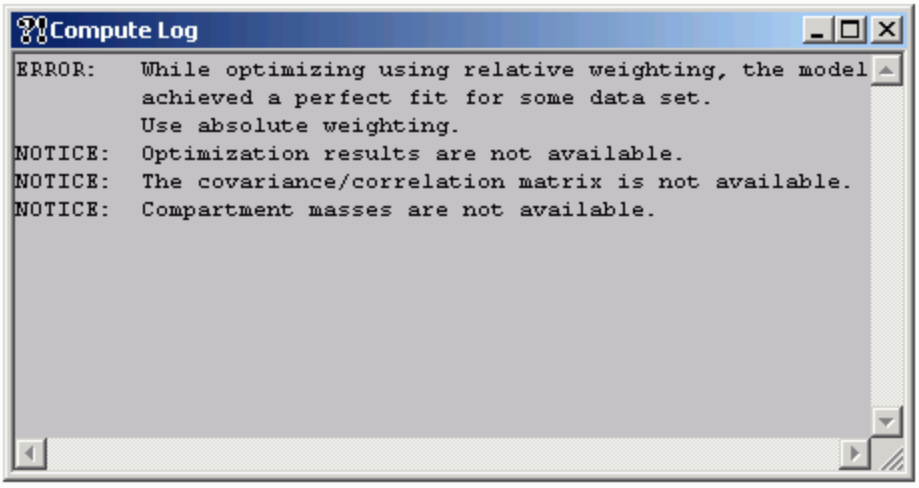
(3) Click **Done**. The **Plot** will appear as follows:



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.

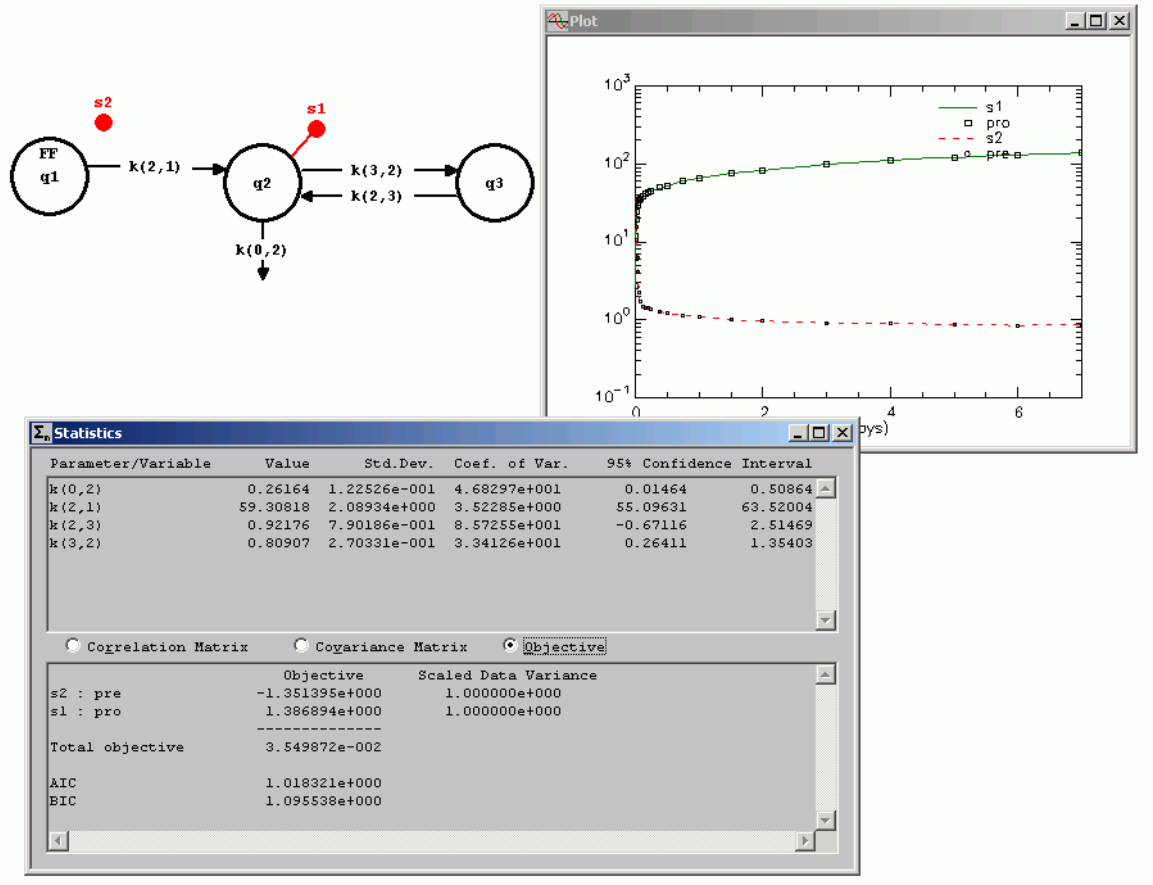
    (1) In the **Compute** menu, click **Settings**. The **Computational Settings** dialog box will open.

    (2) In the **Variance Model** pane, click **Absolute**. The **Variance Model** pane 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.

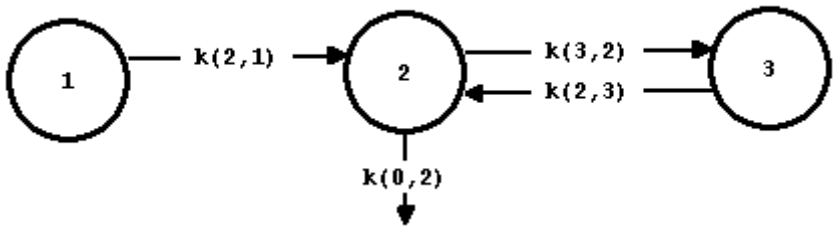
Quit the **SAAM II Compartmental** application. If you wish, you may save the study file for future use.

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:

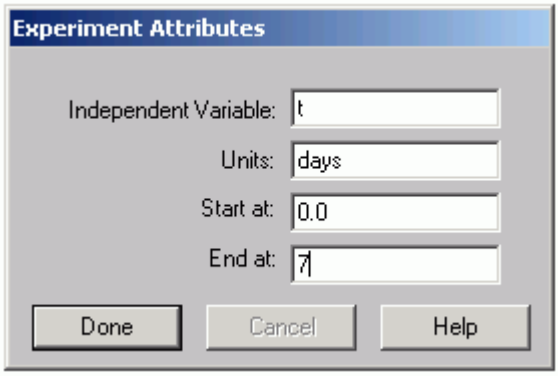


4. Create the experiment on the model

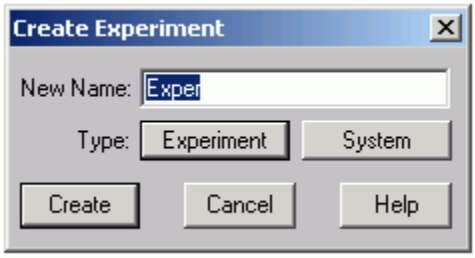
   a. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open.

   b. Type "days" in the **Units** box.

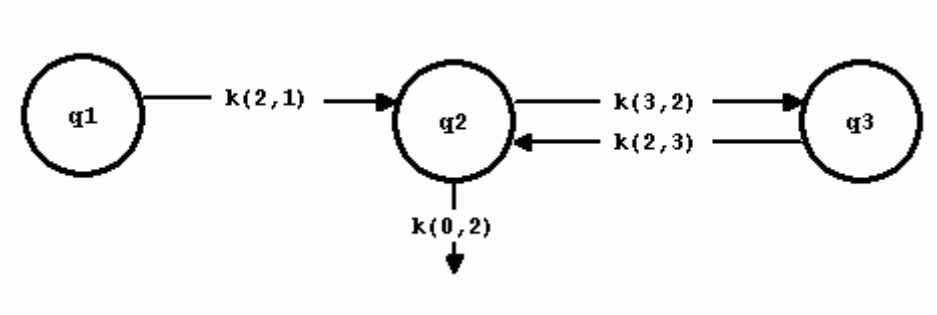
   c. Type "7" in the **End At** box. The **Experiment Attributes** dialog box will appear as follows:



   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)  ()       ()
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)    ()       ()
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
()       ()       ()
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:

Data - ff_pre_pro.dat

```
DATA
(FSD 0.1)
t         pre       pro
(/1440)   ()        ()
2         31.24     2.72
5         26.97     6.20
10        22.48     11.66
```

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:

Data - ff_pre_pro.dat

```
DATA
(FSD 0.1)
t         pre       pro
(/1440)   ()        ()
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)     ()        ()
1         4.14      31.94
1.5       2.23      34.84
2         1.69      36.20
```

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.

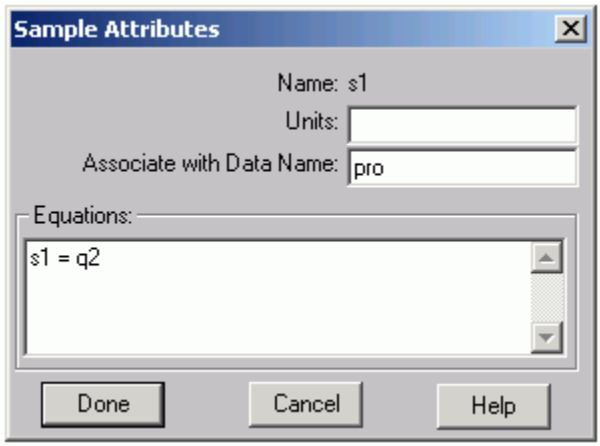
   a. In the **SAAM II Toolbox**, click **Sample**.

   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.

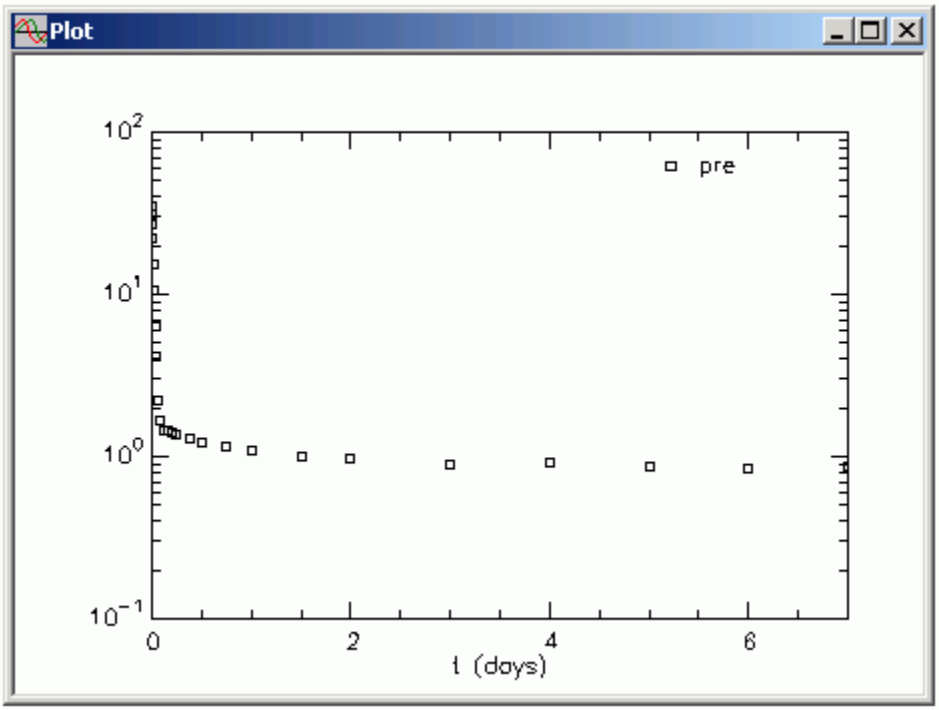
   You will be creating the forcing function by fitting "pre" by a sum of exponentials. Thus the first step will be to examine "pre" to estimate how many exponentials will be required, and to obtain initial estimates for the coefficients and exponentials.

   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.

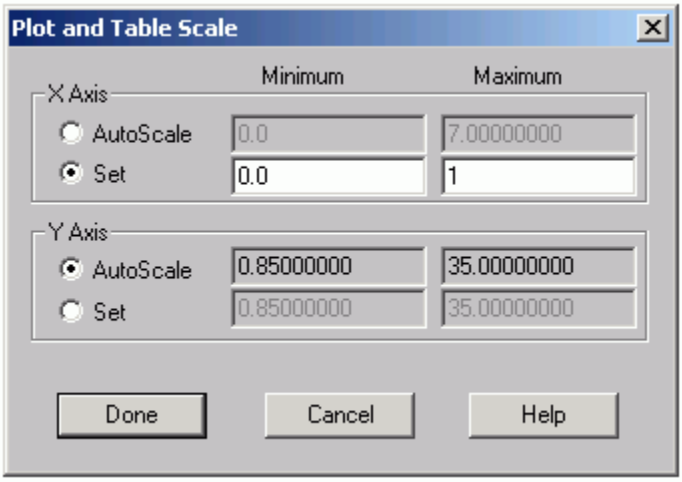
(3) Click **Done**. The plot of the **pre** will appear as follows.



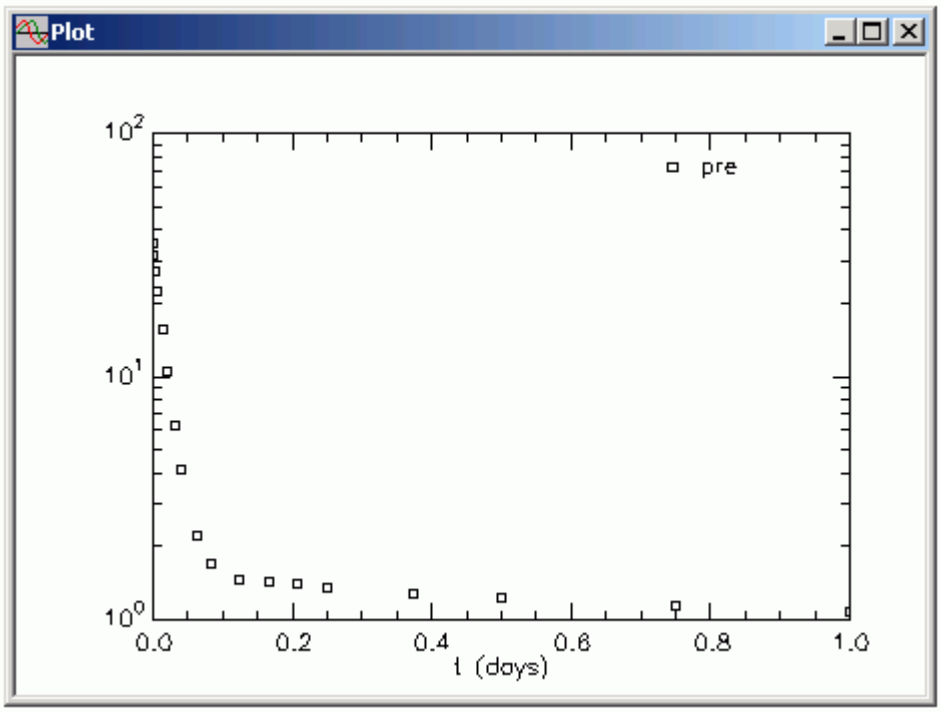
You can see there are an extremely rapid initial fall and a very slow final decay. To examine the characteristics of the initial decay, change the **Plot and Table Scale**.

(3) On the **Set** menu, click **Plot/Table Scale**. 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:

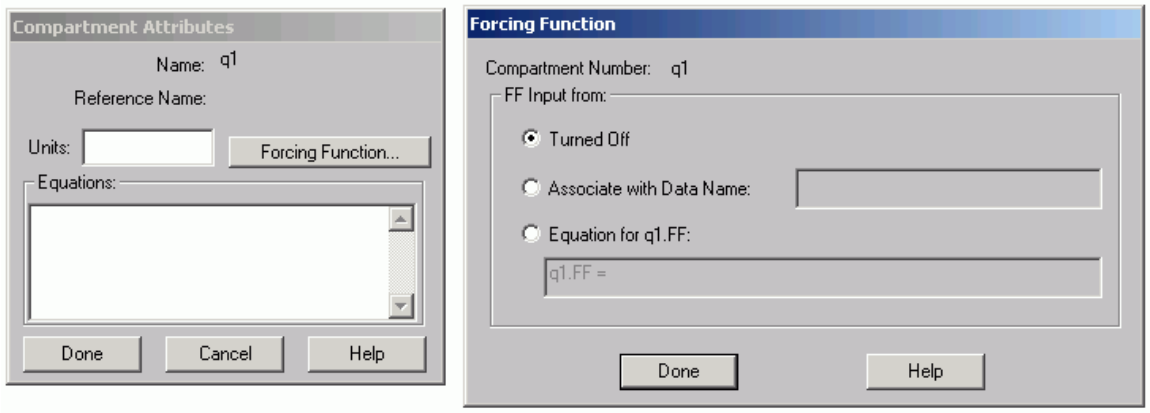
$$q1.FF = A1 * \exp(-a1 * t) + A2 * \exp(-a2 * t) + A3 * \exp(-a3 * t)$$

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.

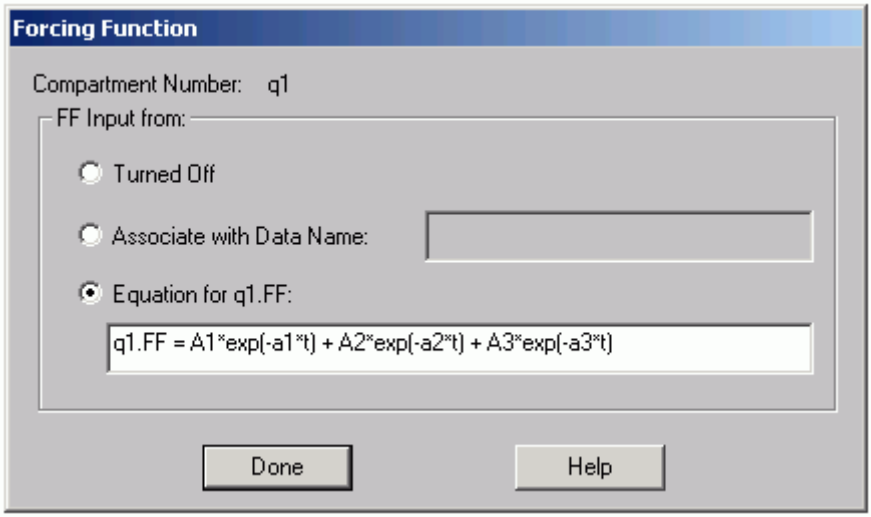
c. Click **Forcing Function**. The **Forcing Function** dialog box will open as shown below (together with the **Compartments Attributes** dialog box):



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:



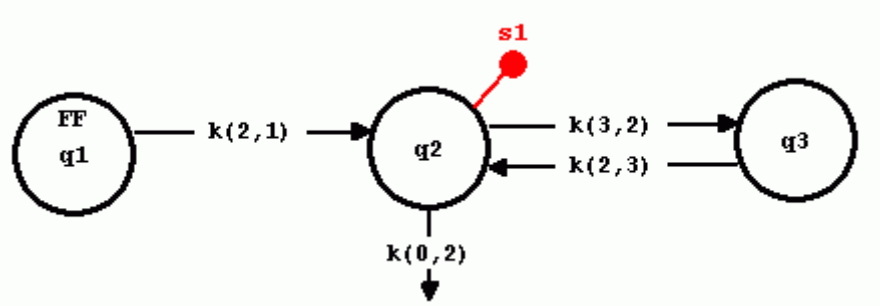
Creating Forcing Functions. When you choose the **Equation for q1.FF** option, you must enter a specific equation that will be used for the forcing

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.

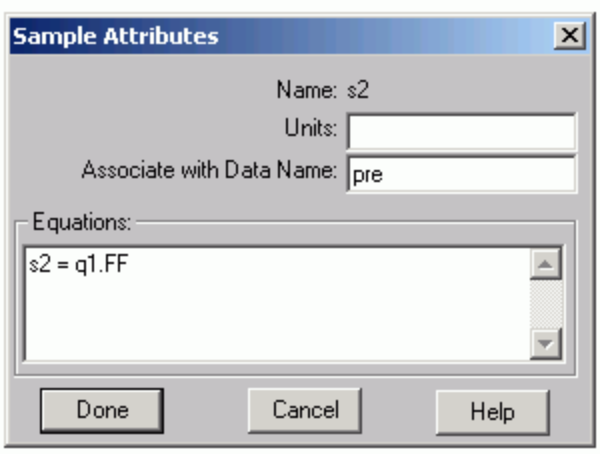
a. In the **SAAM II Toolbox**, click **Sample**.

b. Click Compartment **q1**, and then on the **Drawing Canvas**. The sample **s2** will appear.

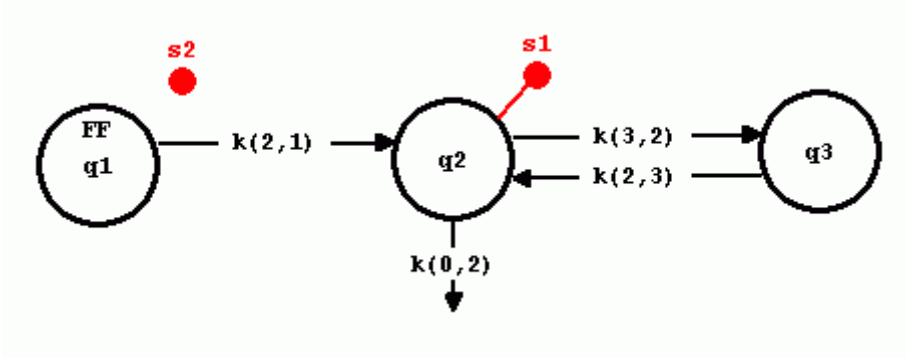
c. Double-click **s2** to open the **Sample Attributes** dialog box.

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.

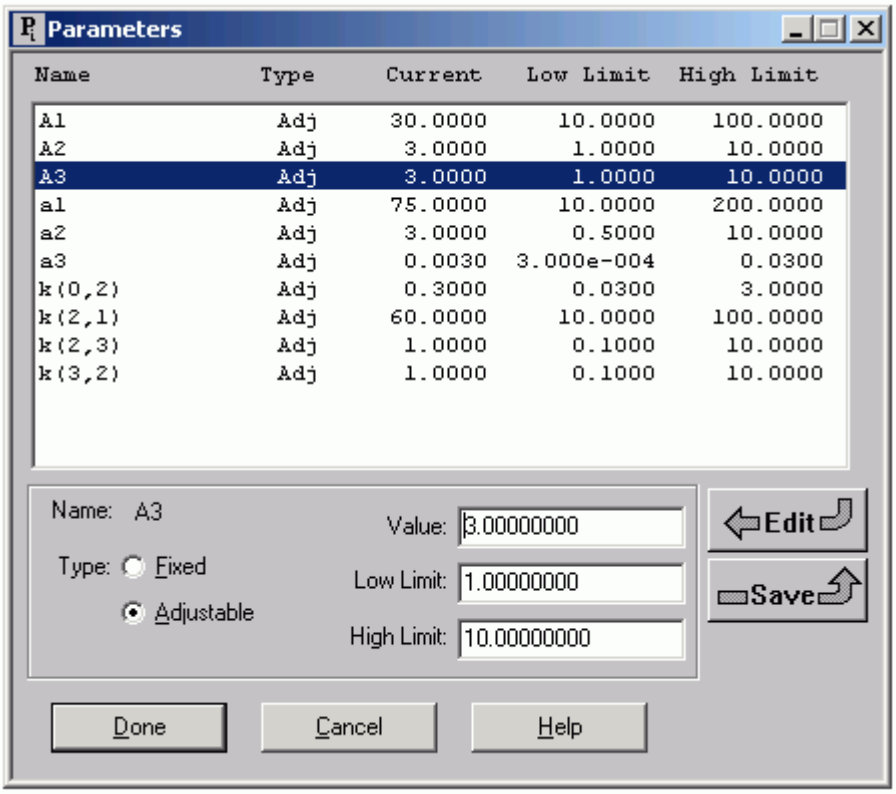


Samples. The Sample tool is a very powerful tool in SAAM II. Normally it is used to create samples that link a compartment, or compartments, with data. In this case, we are interested in viewing the forcing function. When we entered the equation "s2=q1.FF", **q1** no longer appeared in the sample equation, 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**.

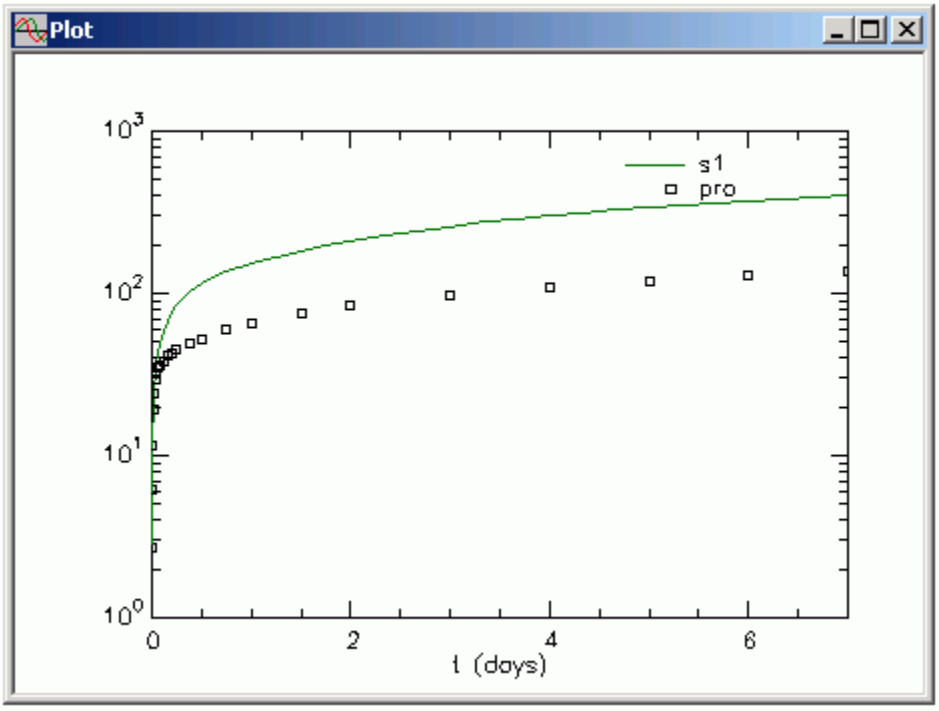
Volumes. Why was there no volume included in the sample **s1**? That is, normally when writing the sample equation we have usually included the volume term.

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**.

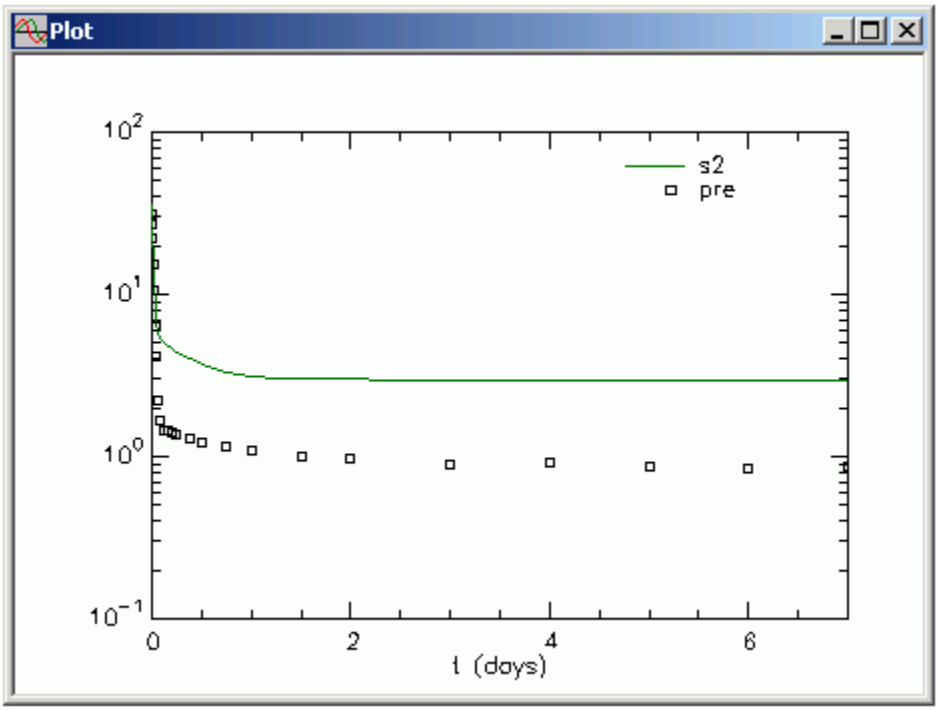
10. Solve the model and view the solution.

    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:

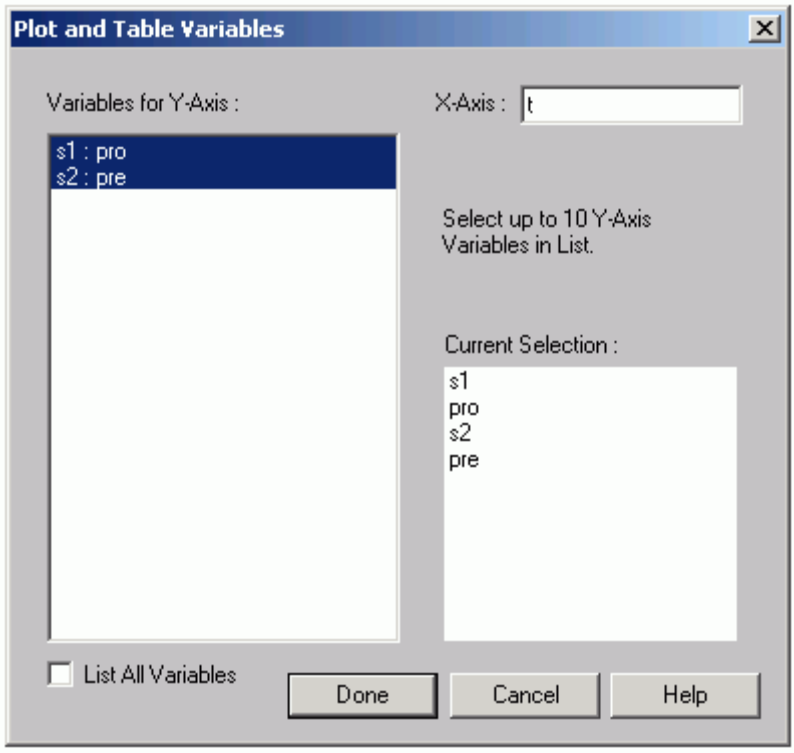


You can see that the estimates for the exponentials are reasonable, but the estimate for *A1* needs to be increased.

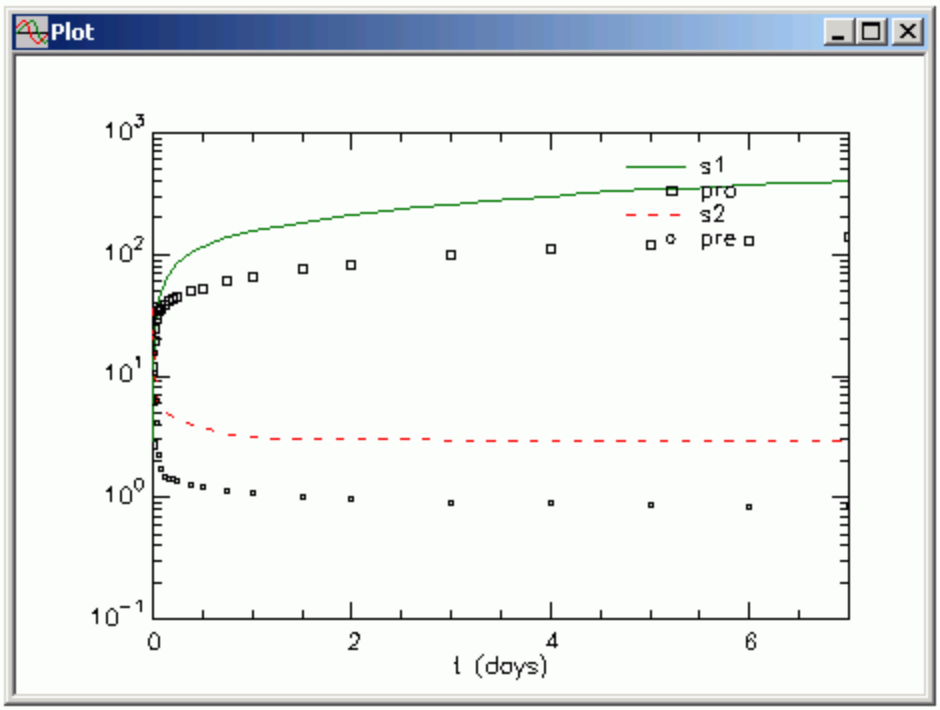
f. Plot **s2:pre** and **s1:pro** simultaneously.

(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:



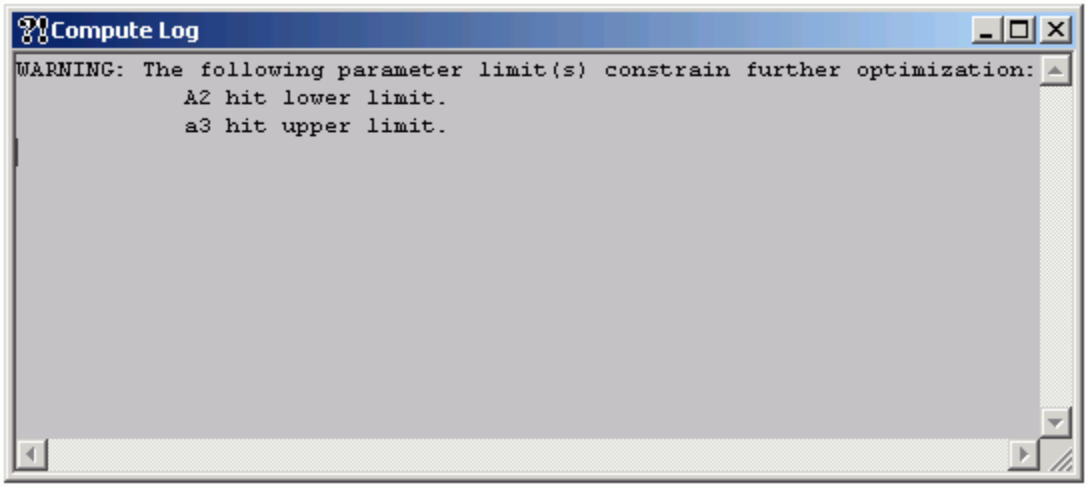
(3) Click **Done**. The **Plot** will appear as follows:



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.

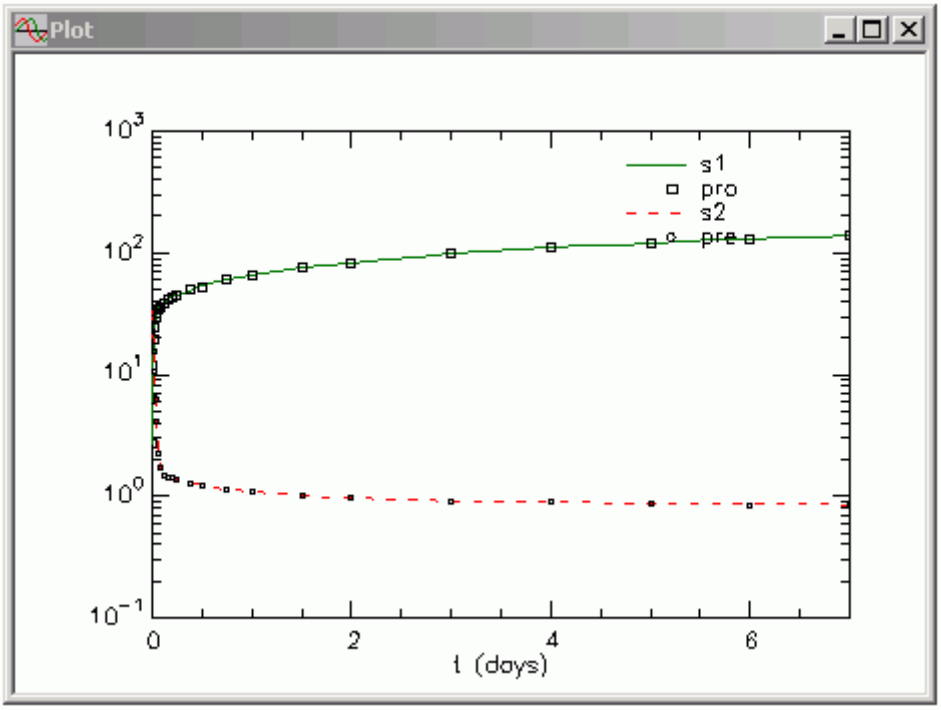
b. Change the limits on *A2* and *a3*.

(1) Change the **Low Limit** on *A2* to "0.5".

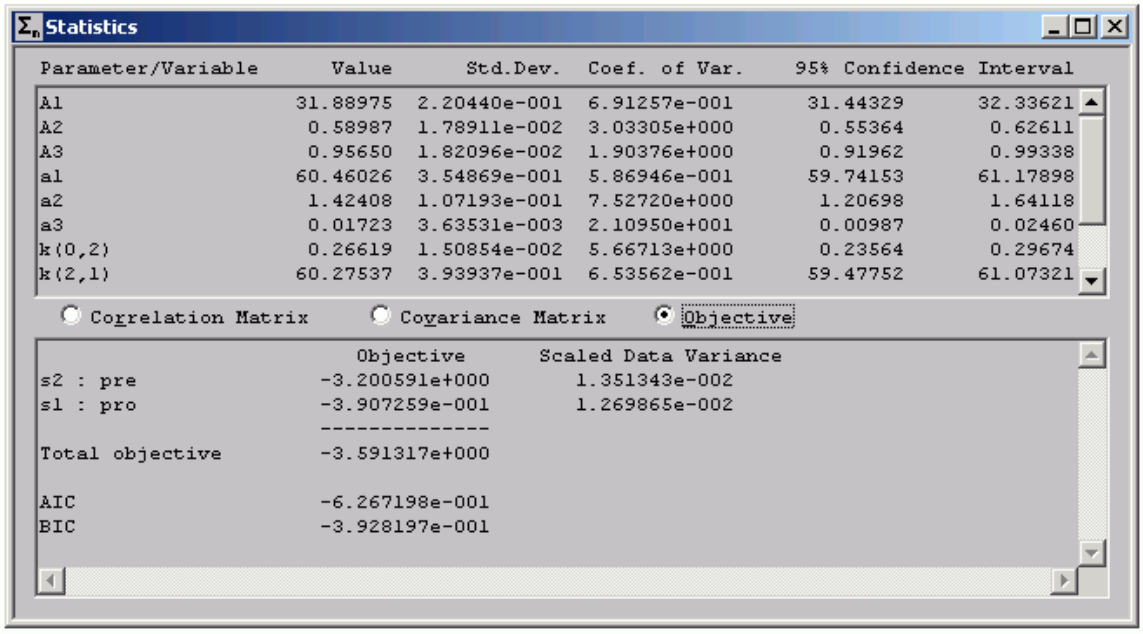
(2) Change the **High Limit** on *a3* to "0.3" respectively

c. Re-Fit the model. A warning the *A3* hit a low 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:



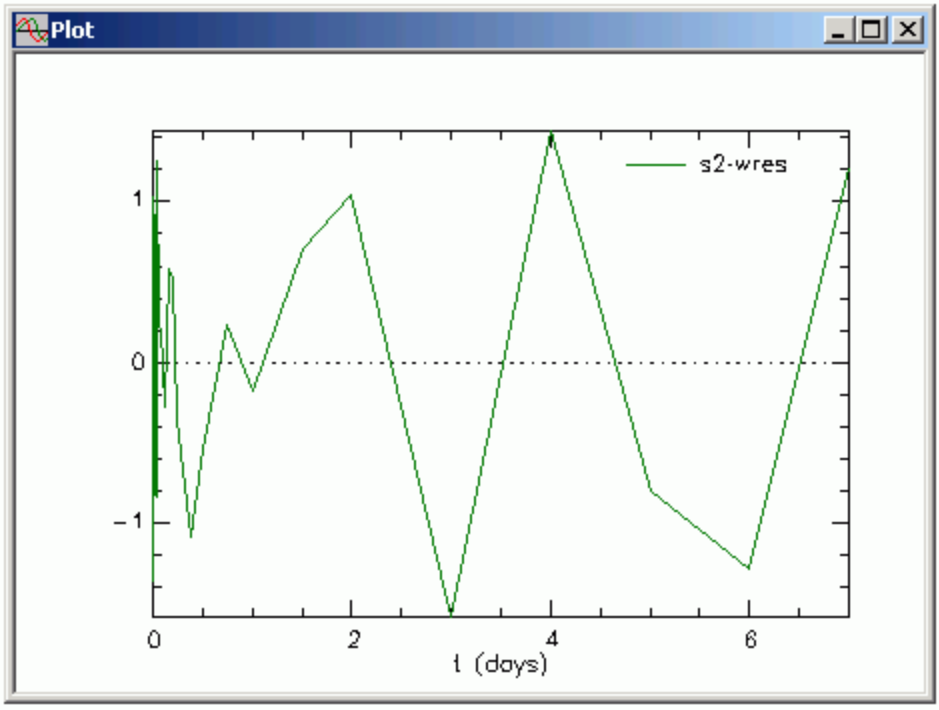
f. Close the **Statistics** windows. The **Plot** window is still open.

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:

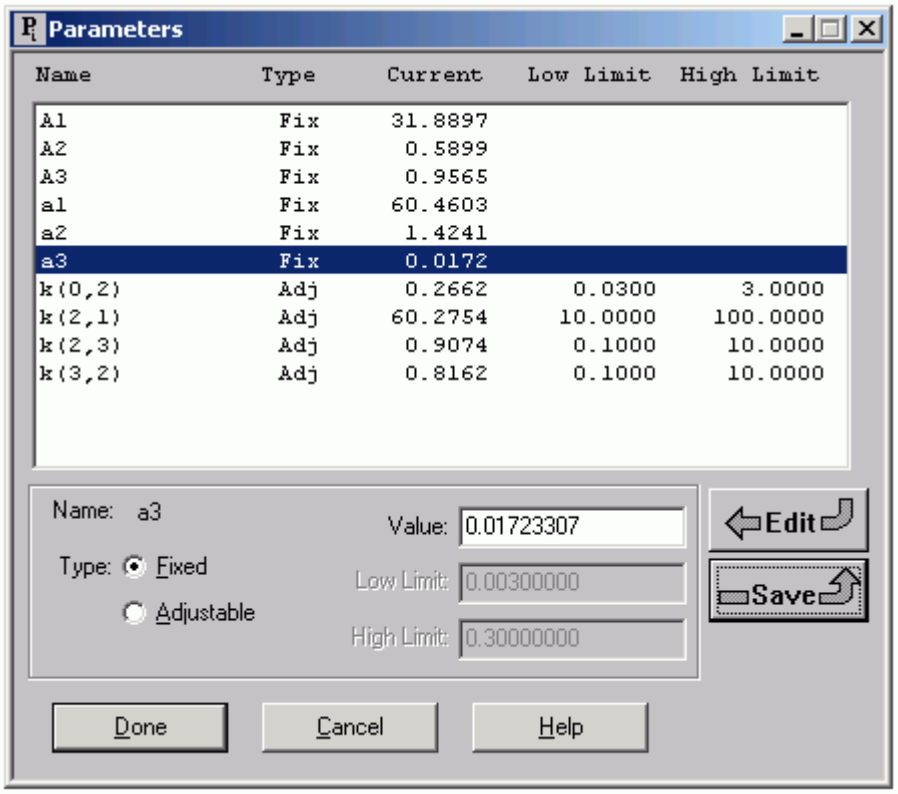


You can see the residuals are randomly distributed around zero and line in a band essentially between -1 and 1; thus the sum of three exponentials is providing a good description of the forcing function.

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:

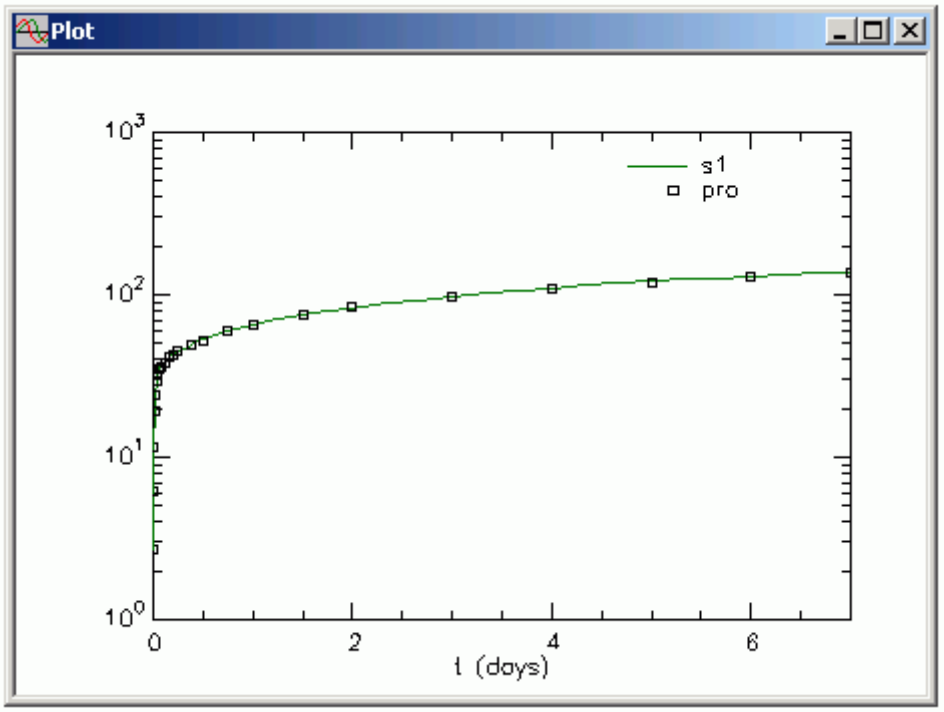


Fixing the parameters of the forcing function. The parameters of the forcing function should be fixed before performing a final fit of the system data, in this case the "pro". In this situation, the parameters of the forcing function could be estimated from the data. There will be situations when this 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	
A3	0.95650	** Fixed **	** Fixed **	** Fixed **	** Fixed **
a1	60.46026	** Fixed **	** Fixed **	** Fixed **	** Fixed **
a2	1.42408	** Fixed **	** Fixed **	** Fixed **	** Fixed **
a3	0.01723	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,2)	0.26619	1.31406e-002	4.93652e+000	0.23969	0.29269
k(2,1)	60.27537	2.22070e-001	3.68425e-001	59.82747	60.72326
k(2,3)	0.90738	8.12418e-002	8.95348e+000	0.74352	1.07124
k(3,2)	0.81617	2.80362e-002	3.43508e+000	0.75963	0.87272

Correlation Matrix Covariance Matrix Objective

	Objective	Scaled Data Variance
s2 : pre	-3.200591e+000	1.167069e-002
s1 : pro	-3.907259e-001	1.096702e-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.

