# Using SAAM II

# Working with Parameters, Advanced

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**Prerequisites**

The prerequisites for this tutorial are having worked through the SAAM II introductory tutorial, "Getting Started with **SAAM II Compartmental**" and the tutorial "Working with Parameters, Basic."

**What you will learn in this tutorial**

The tutorial, "Working With Parameters, Basic", showed you how to use the different options in SAAM II to define and use the most commonly used types of parameters. The purpose of this tutorial is to show you how to use the additional options in SAAM II to define and refine parameters. You will learn

- How to create zero order losses (Part 1)
- How to write parameters and variables in the **Equations** window (Part 2)
- How to reparameterize the two-compartment model (Part 3)
- How to set parameter upper and lower limits (Part 4)
- How to use the Bayesian option (Part5)

This tutorial is divided into parts to which you can refer individually for specific information. Since you know how to enter parameters in the **Parameters** dialog box, you can proceed to any specific part of this tutorial without needing the information that preceded it.

**Files Required**

Study Files: The study files for this tutorial are

**study_0.stu**
**Para_Limits**

These files are included as part of this tutorial. The file **study_0.**stu is the same as **study_0.stu** that is installed in the **SAAM II** program folder and referred to in the **SAAM II** User Guide. The file **Para_Limits** is a one-compartment model with two parameters.

**Introduction**

This tutorial is designed to show you have to use the additional options available in SAAM II to work with parameters.

In general, most losses are first-order or nonlinear as covered in the tutorial, "Working with Parameters, Basic." There may be instances, when the loss is at a constant rate independent of the mass in the $i^{th}$ compartment. In these cases, a zero-order loss is required. Part 1 of this tutorial shows how to create a zero-order loss. Zero-order inputs can also be created, but these are equivalent to constant infusions.

A multicompartmental model in SAAM II is specified by the compartments, transfers and losses. The transfers *k(i,j)* and losses *k(0,i)* specify the terms in the different differential equations created internally by SAAM II. These are called the primary parameters. Often there are a number of parameters – volumes, clearances, absorptions – that are functions of these primary parameters. These parameters can be specified as variables in the **Equations** dialog box. This procedure is explained in the $5^{th}$ tutorial. Some models such as the commonly used two-compartment model can be reparameterized based upon the desired secondary parameters; this is illustrated in the $6^{th}$ tutorial.

All adjustable parameters must have initial values specified with high and low limits. For an adjustable parameter, if you simply enter a value and click **Save**, SAAM II will create default high and low limits that are 10 times and 0.1 times the initial value. SAAM II actually uses the information in the limits as part of fitting. The information is a measure of how well you think you know your limits. As will be illustrated in the $7^{th}$ tutorial, if your limits are widely divergent from the initial value, you may have trouble fitting. This is because SAAM II thinks you don't know the parameter very well. On the other hand, if you know a parameter reasonably well, this information should be included when you set the limits.

Finally, SAAM II has implemented a partial Bayesian option. This is explained in the $8^{th}$ tutorial. The Bayesian option provides a means by which *a priori* information about a specific parameter, or parameters, can be entered in the **Parameters** dialog box.

**Part 1. Creating a zero-order loss**

In general, most losses are first-order or nonlinear. There may be instances, however, when a zero-order loss is required. The difference is the following. For the i$^{th}$ compartment, the loss is generally expressed (in terms of the differential equation):

$$\frac{dq_i}{dt} = -k(0,i) \cdot q_i(t) + \dots$$

That is, the loss is proportional to the mass in the i$^{th}$ compartment. In the case of the zero-order loss, this is not the case:

$$\frac{dq_i}{dt} = -k(0,i) + \dots$$

That is, the loss is at a constant rate independent of the mass in the i$^{th}$ compartment. This tutorial will explain how to create zero-order losses.

Incidentally, by the same logic, you can see why a zero-order input and a constant infusion are the same. If Compartment **1** transferred material to Compartment **2** via a zero-order process,

$$\frac{dq_2}{dt} = k(2,1) + \dots$$

The parameter *k(2,1)* is simply a constant rate of input, and hence, in SAAM II notation, is equivalent to

$$\frac{dq_2}{dt} = ex(2) + \dots$$

where **ex(2)** is specified as a constant infusion.

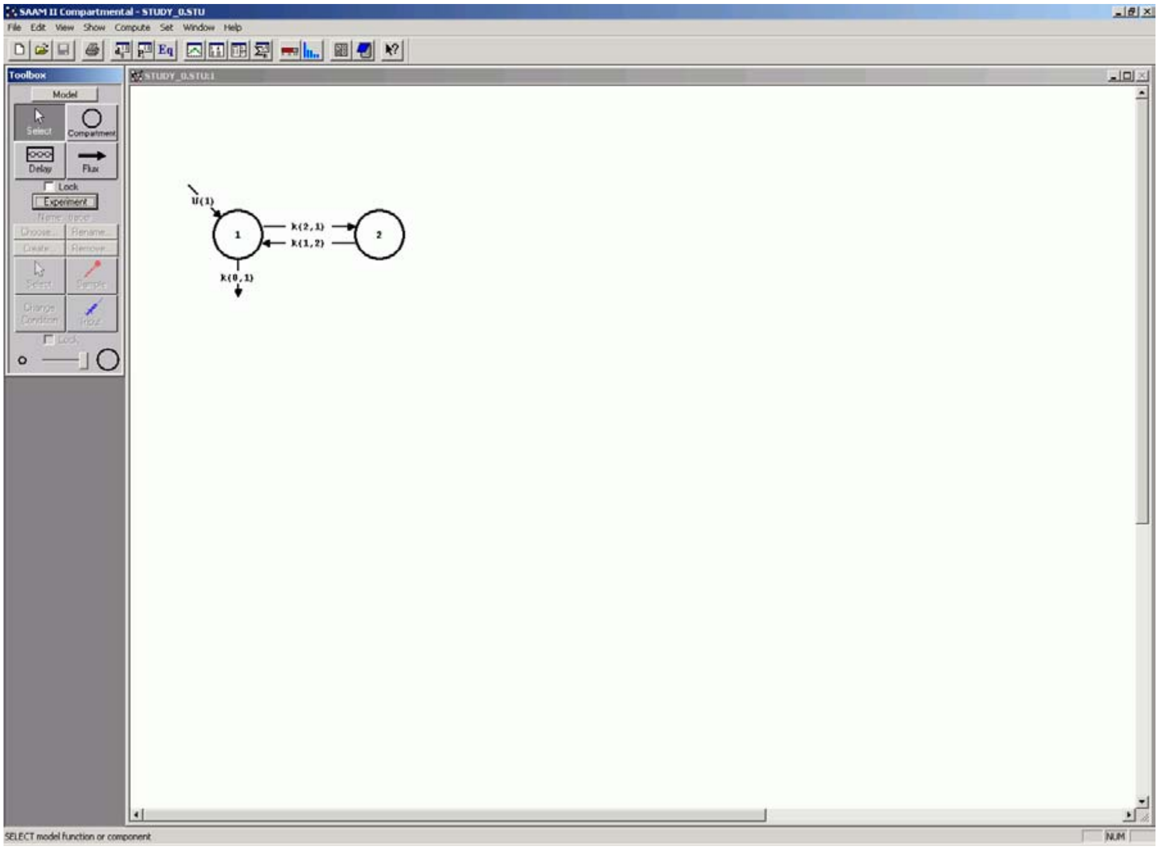
1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

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

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

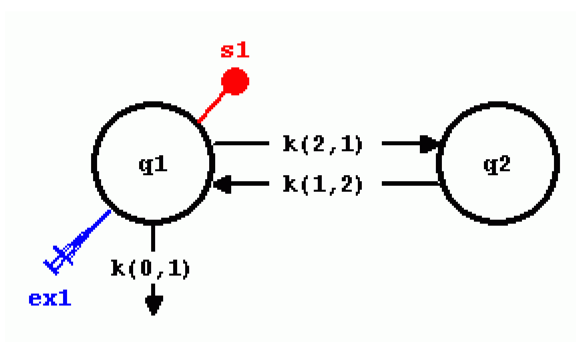
    b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as shown below:



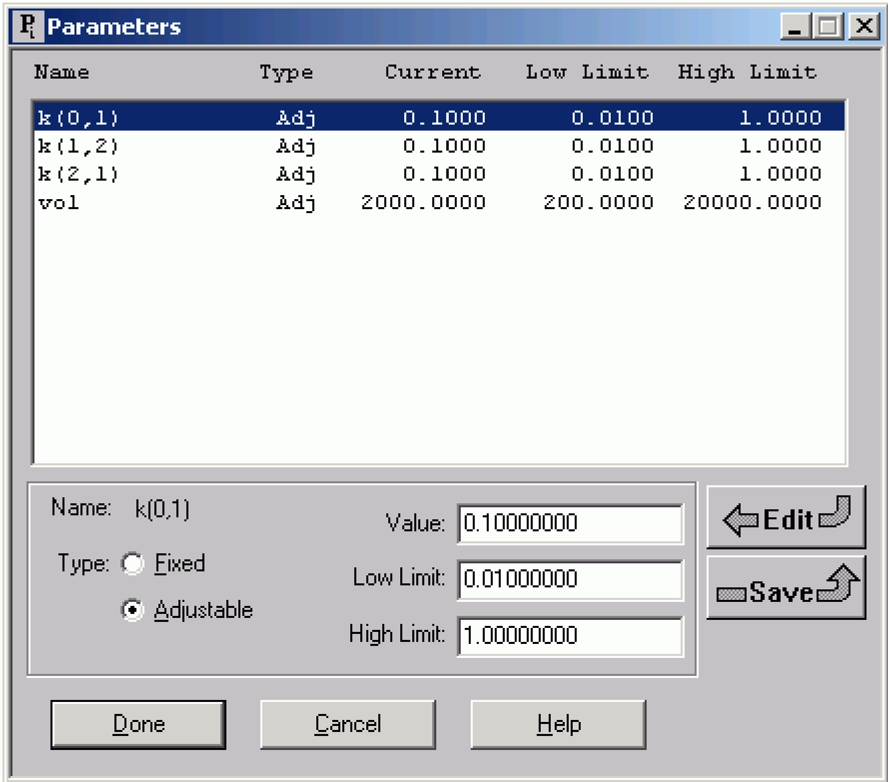

3. View the model and the experiment on the model, and the **Parameters** dialog box.

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




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



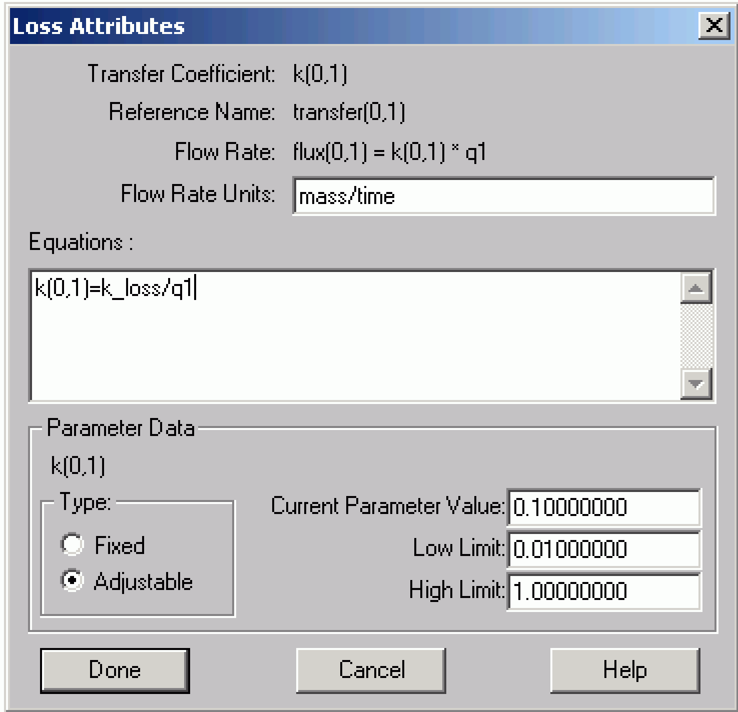

These are the parameters for **study_0.stu**.

4. Modify *k(0,1)* so that it is a zero-order loss.

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

   b. In the **Equation** pane, type "k(0,1)=k_loss/q1". The **Loss Attributes** dialog box will appear as follows:

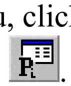



c. Click **Done**.

The result is that *k(0,1)* is no longer a primary model parameter, but is a function of a new parameter, *k_loss*. In the differential equation for **q1**:

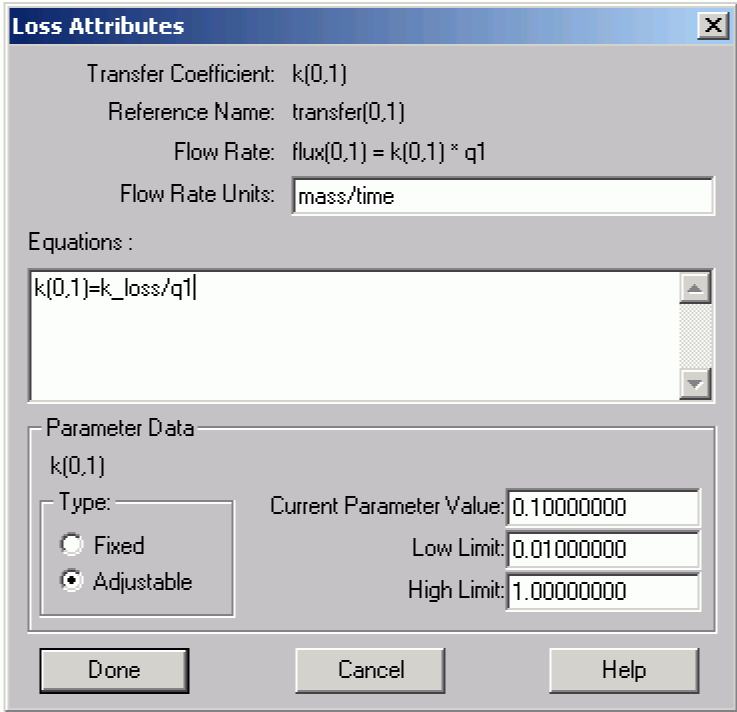
$$\frac{dq_1(t)}{dt} = -k(0,1)\cdot q1(t)+\cdots = \frac{k\_loss}{q1(t)}\cdot q1(t)+\cdots = -k\_loss+\cdots$$

The result is now the loss from Compartment **q1** is zero-order, and specified by *k_loss*. A value for this parameter must be entered in the **Parameters** dialog box.

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

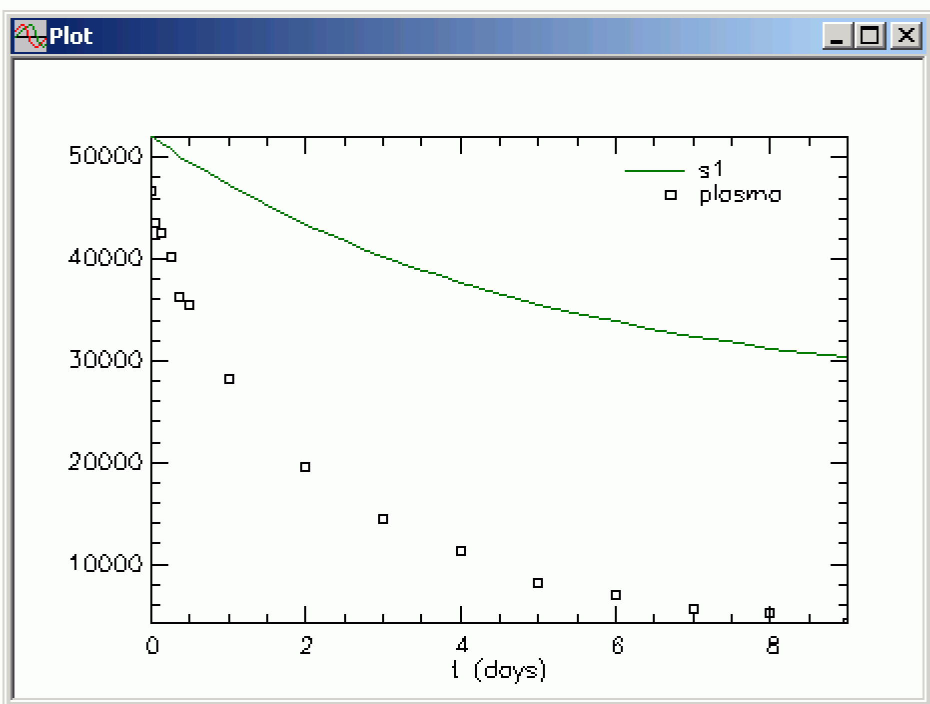
   a. Type "1" as the **Value** for *K_loss*, and click **Save**. The **Parameters** dialog box will appear as follows:



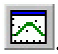

b. Click **Done**.

6. Solve the model, and view the solution. A plot of the solution is shown as follows:

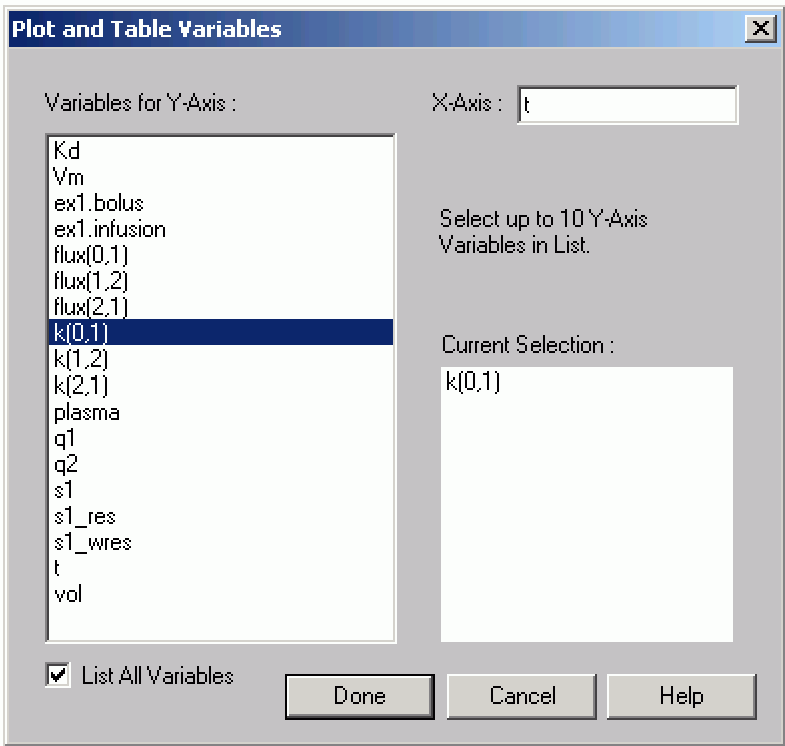


It is of interest, however, to plot *k(0,1)* which is no longer a constant but a function of time since **q1(t)** appears in the equation defining it. While this is the case, the rate of loss, **flux(0,1)**, should be constant. Both will be plotted.

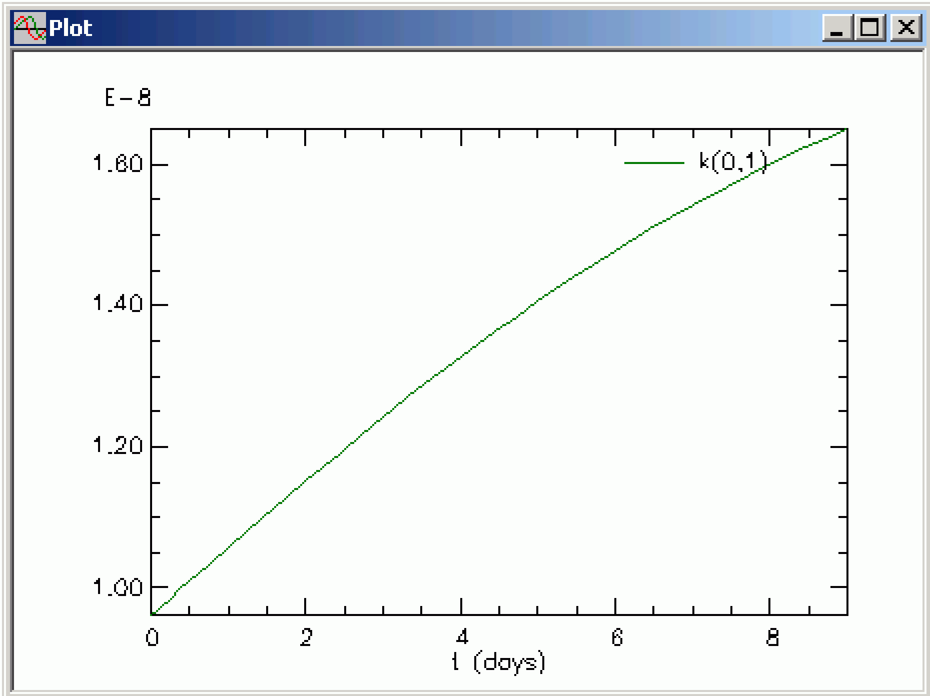
a. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot** . Open the **Plot and Table Variables** dialog box, and be sure the **List All Variables** check box is selected.

b. Click *k(0,1)* to move this to the **Current Selection** pane. The **Plot and Table Variables** box will appear as follows:

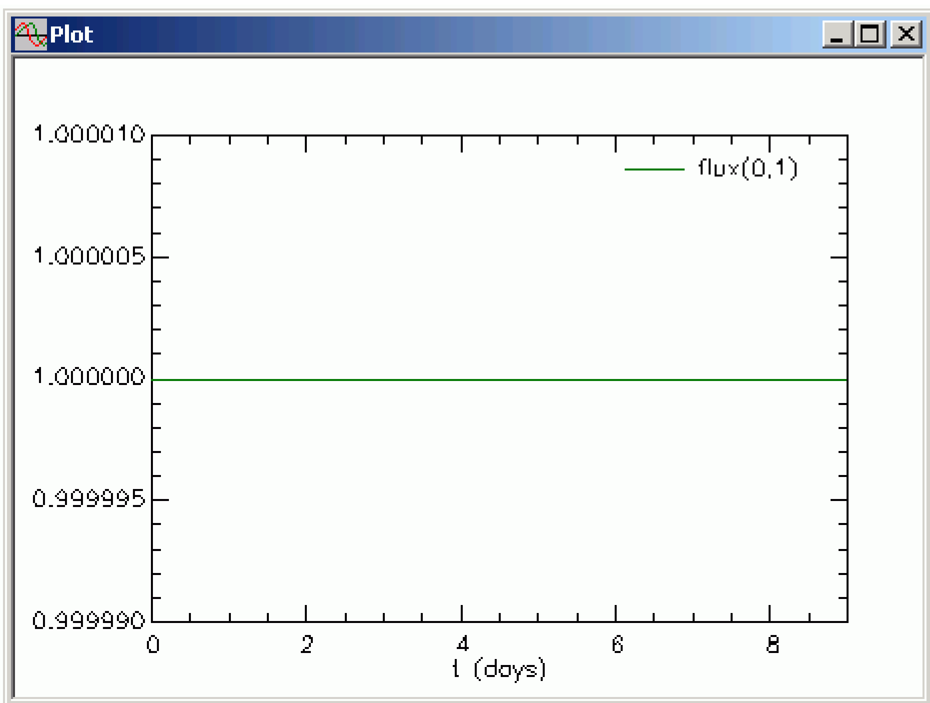



c. Click **Done**. The plot of *k(0,1)* will appear as follows (in linear mode):




d. Open the **Plot and Table Variables** dialog box, and select **flux(0,1)** as the **Current Selection**. When you click **Done**, the following plot of **flux(0,1)** should appear:




This is a constant indicative of the loss from Compartment **q1** being zero-order.

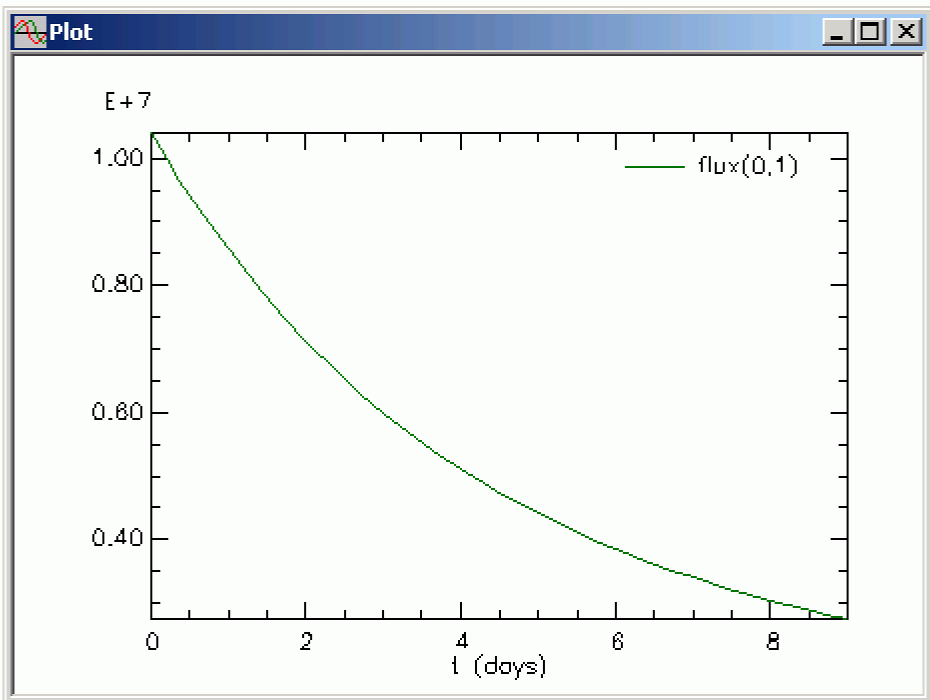
e. Close the **Plot** window.

7. Restore the original **study_0**.

   a. Open the **Loss Attributes** dialog box associated with *k(0,1)*, and delete the equation "k(0,1)=k_loss/q1". Click Done.

   b. Open the **Parameters** dialog box. Notice *k_loss* no longer appears; *k(0,1)* does. Select *k(0,1)*, and type "0.1" in the **Value** box. Click **Done**. This should restore the original settings in **study_0**.

   c. Re-Solve the model. If you open the **Plot** window, since **flux(0,1)** was the previous plot, the **Plot** window will appear as follows:




   The flux is no longer a constant since the loss is now a first-order process. If you wish, you can change the plot to **s1:plasma** to be sure you have restored the original solution for **study_0**.

   d. Close the **Plot** window.

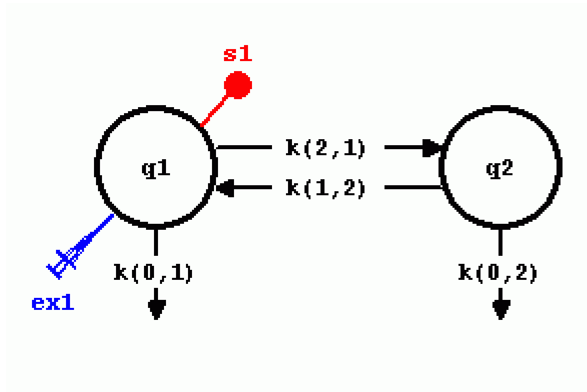
8. Create a zero-order loss from Compartment **2**.

   a. In the **SAAM II Toolbox**, click **Model**. The **Model** tools are now available.

   b. Create a loss *k(0,2)*.

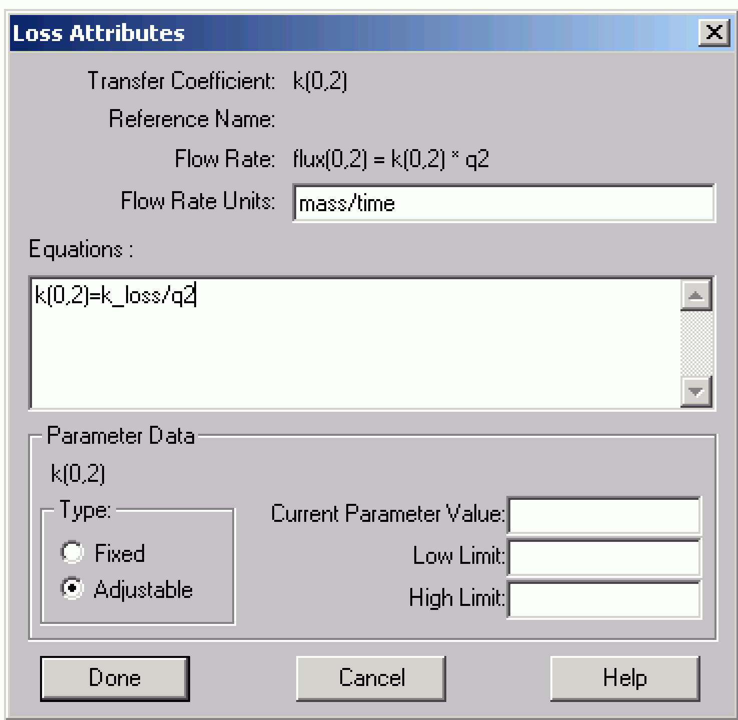
 

c. In the **SAAM II Toolbox**, click **Experiment**. The model will appear as follows:




d. Double-click *k(0,2)* to open the **Loss Attributes** dialog box.

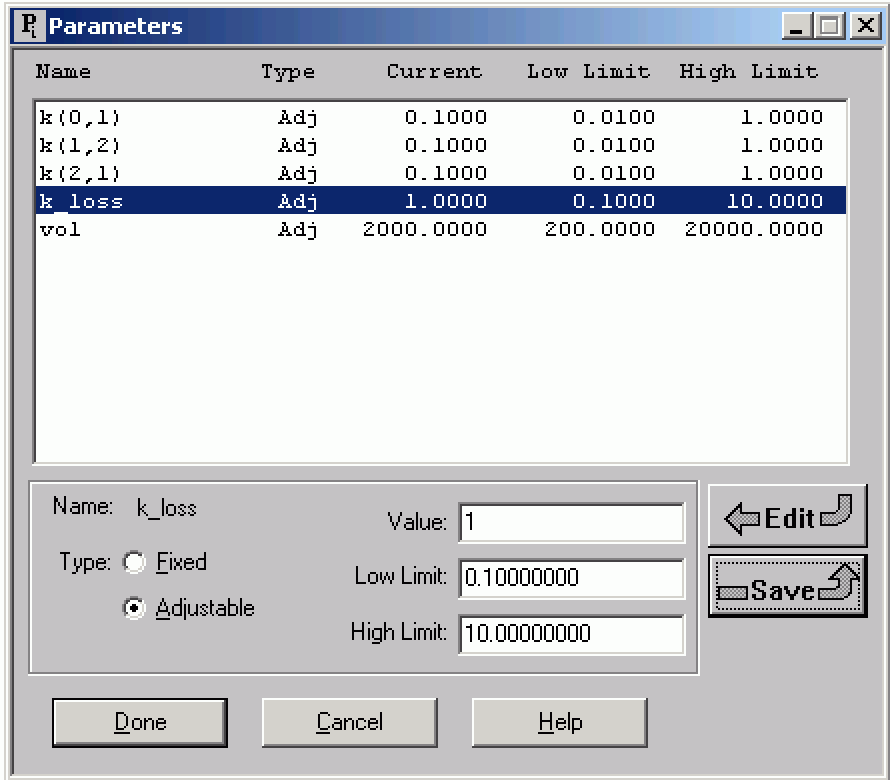
e. In the **Equation** pane, type "k(0,2)=k_loss/q2". The **Loss Attributes** dialog box will appear as follows:




f. Click **Done**.

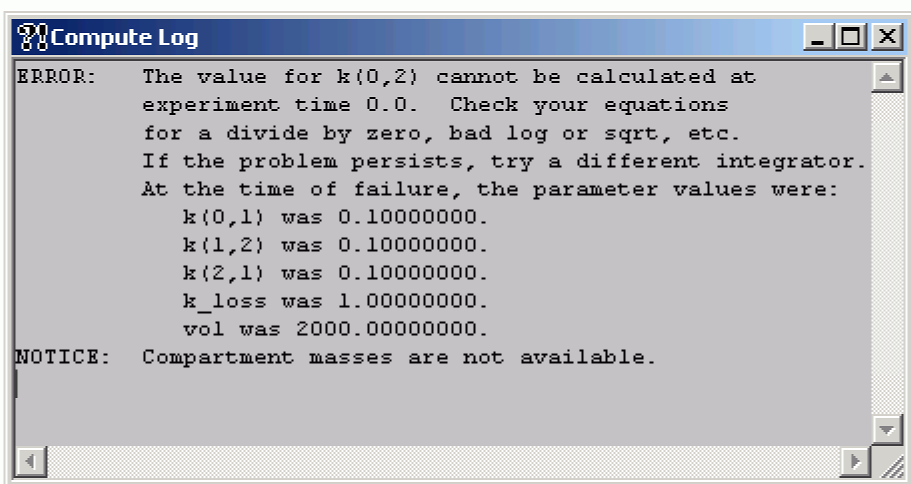
g. Open the **Parameters** dialog box, double-click *k_loss* to make it the current selection, and type "1" in the **Value** box. Click **Save**. The **Parameters** dialog box will appear as follows:




Click **Done**.

h. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve** . The following error message will appear:




Close the **Compute Log**.

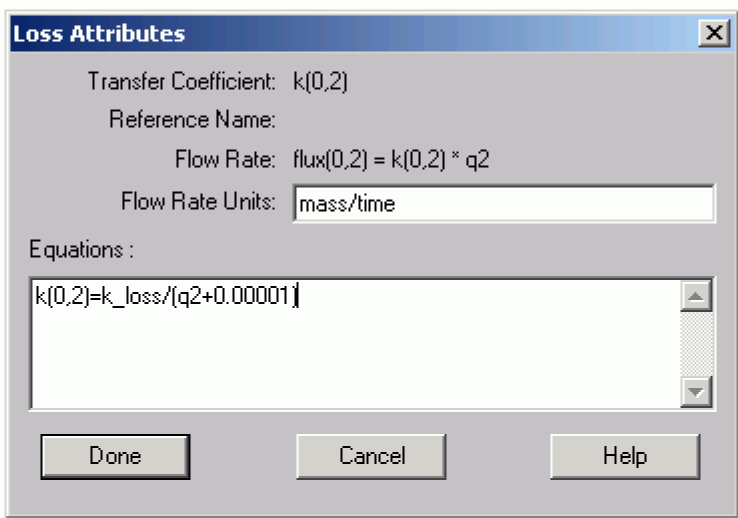
 

*Division by zero*. What is happening in this situation is that, at time zero, there is no mass in Compartment **q2**, i.e. q2(0) = 0. Remember *k(0,2)* has been defined by the equation k(0,2) = k_loss/q2. This cannot be evaluated at time zero. There are two solutions to this problem. The first solution is to change the equation for **k(0,2)** slightly. You know what the mass will be in the compartment because of the magnitude of the initial conditions in Compartment **q1**. Using a number much smaller, you can modify the equation for *k(0,2)* to, for example, k(0,2) = k_loss/(q2+0.00001). The second solution is to introduce a very small bolus into Compartment **q2**, e.g. ex2 = 0.0001. Neither will have a significant effect on the solution.

i. Method 1: Modify the equation for *k(0,2)*.

(1) Open the **Loss Attributes** dialog box associated with *k(0,2)*.

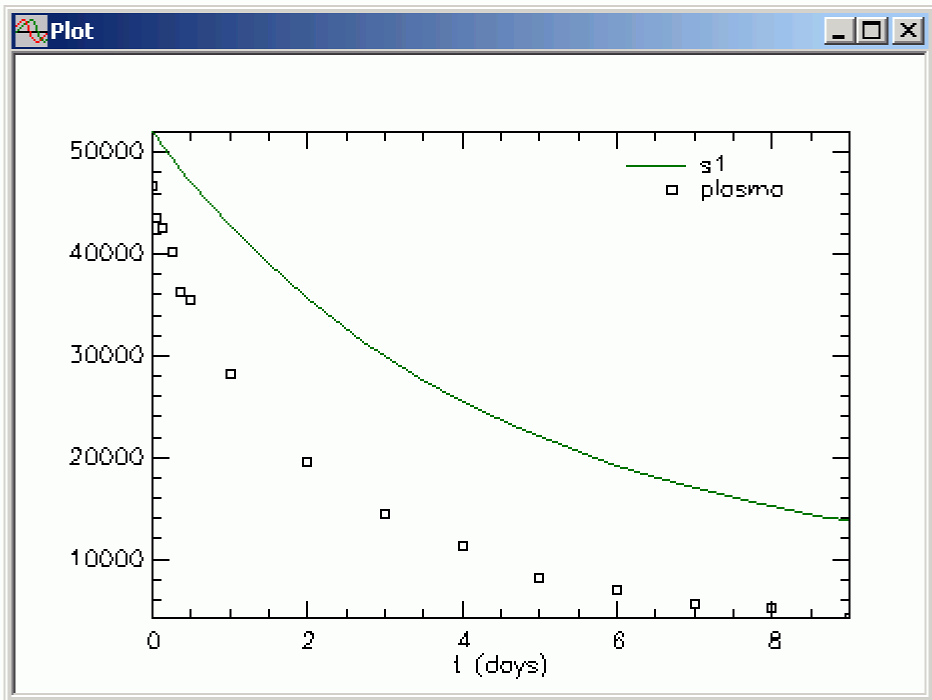
(2) Change the equation to read “k(0,2)=k_loss/(q2+0.00001). The **Loss Attributes** dialog box will appear as follows:




(3) Click Done.

(4) Re-Solve the model. This time, the solution will be successful, and a plot of **s1:plasma** will appear as follows:



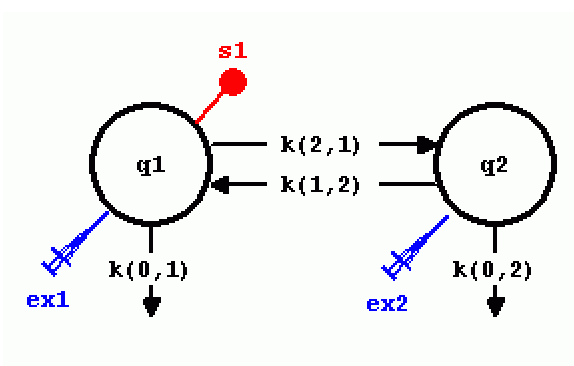

(5) Close the **Plot** window.

j. Method 2: Introduce a small bolus into Compartment **q2**.

(1) Open the **Loss Attributes** dialog box associated with *k(0,2)*, and re-enter the original equation "k(0,2)=k_loss/q2". Click **Done**.

(2) In the **SAAM II Toolbox**, click **Input**.

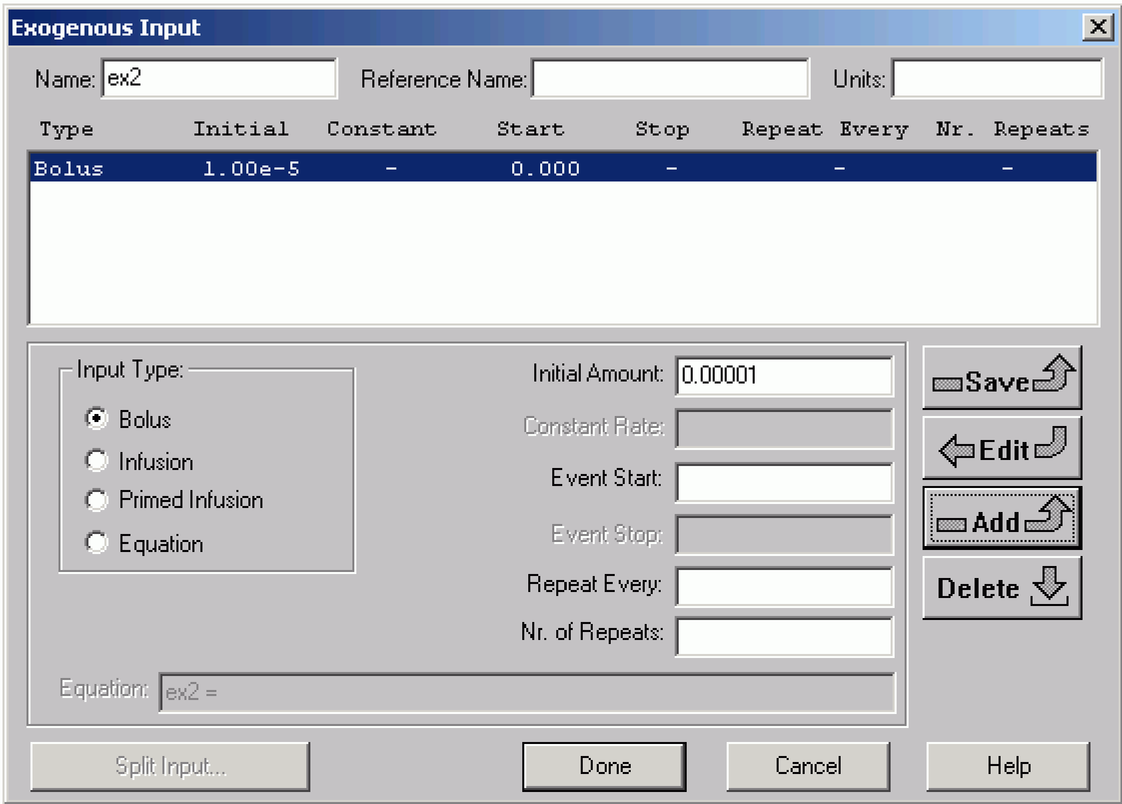
(3) Click Compartment **q2** and then the **Drawing Canvas**. The input **ex2** will appear associated with Compartment **q2**. The model will appear as follows:




(4) Double-click **ex2** to open the **Exogenous Input** dialog box.

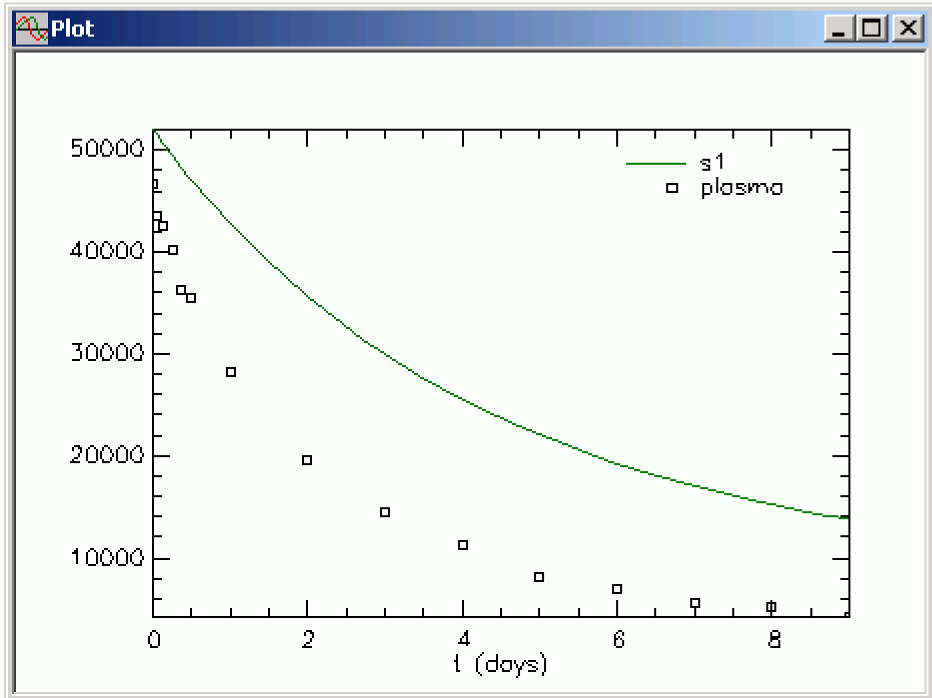
(5) Enter a bolus of 0.00001. The **Exogenous Input** dialog box should appear as follows:




(6) Click **Done**.

(7) Re-Solve the model. This time, the solution will be successful, and a plot of **s1:plasma** will appear as follows:




This plot is essentially identical with that obtained using the first method.

(8) Close the **Plot** window.


*Zero-order losses*. If you specify a zero-order loss from a compartment in your model where the initial conditions in that compartment are non-zero, the method described for *k(0,1)* is the method to use. If you specify a zero-order loss from a compartment whose initial conditions are zero, you must use either of the two methods described above to eliminate the problem of division by zero. Either method works fine – it is a matter of personal preference.

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

**Part 2. Specifying parameters and variables in the Equations window**

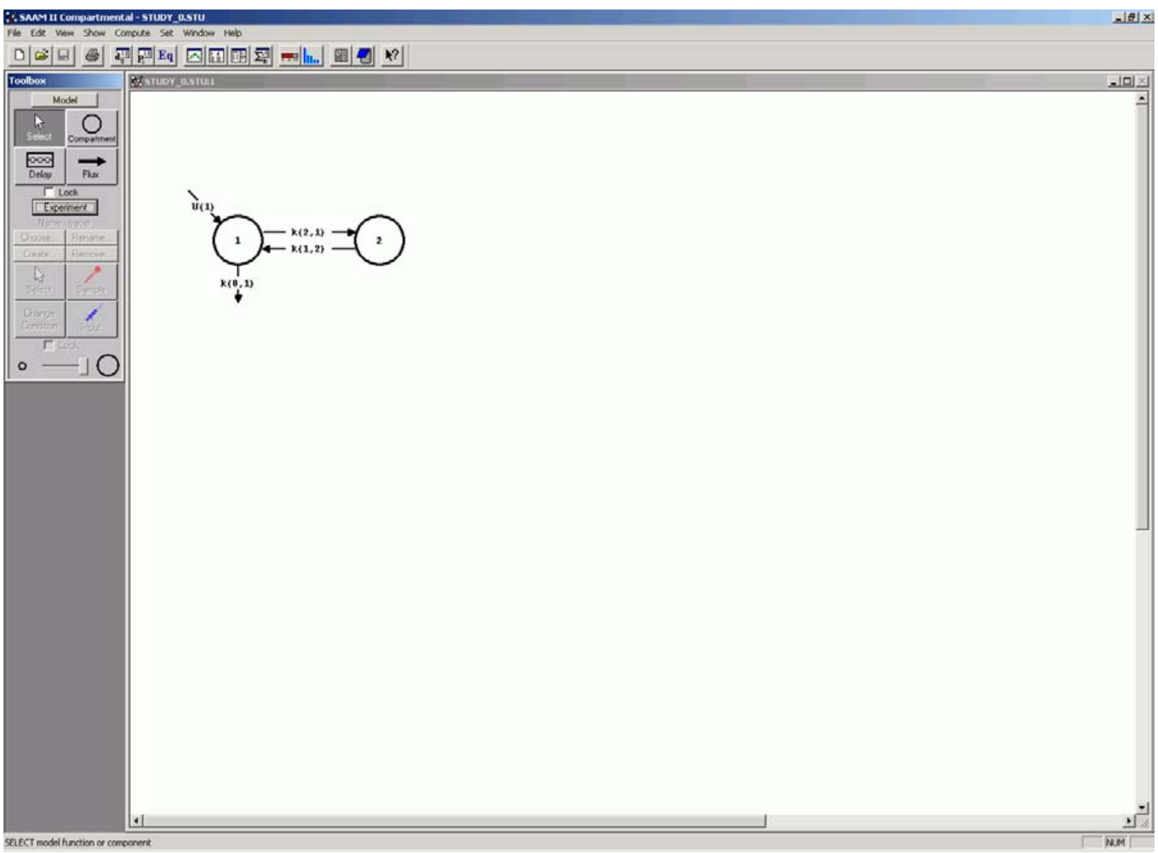
This part of the tutorial will show you have to specify parameters in the **Equations** window. You have seen how equations involving parameters can be written in the **Transfer** or **Loss Attributes** dialog boxes. Writing such equations in the **Equations** window is another option in SAAM II. In pharmacokinetic studies, this is how you would enter the pharmacokinetic parameters that are functions of the model parameters; examples are clearances and volumes.

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

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

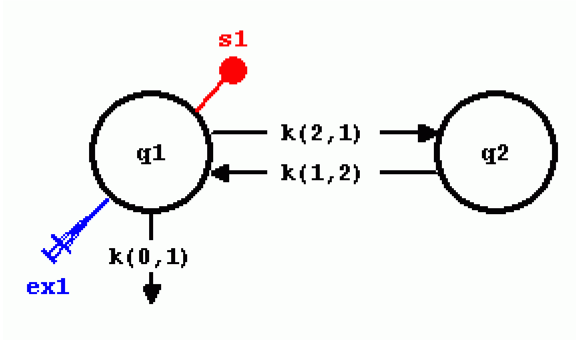
   a. The file **study_0.stu** should appear in the file list; if it does not, find the folder where you put this file.

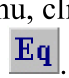
   b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as shown below:




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




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

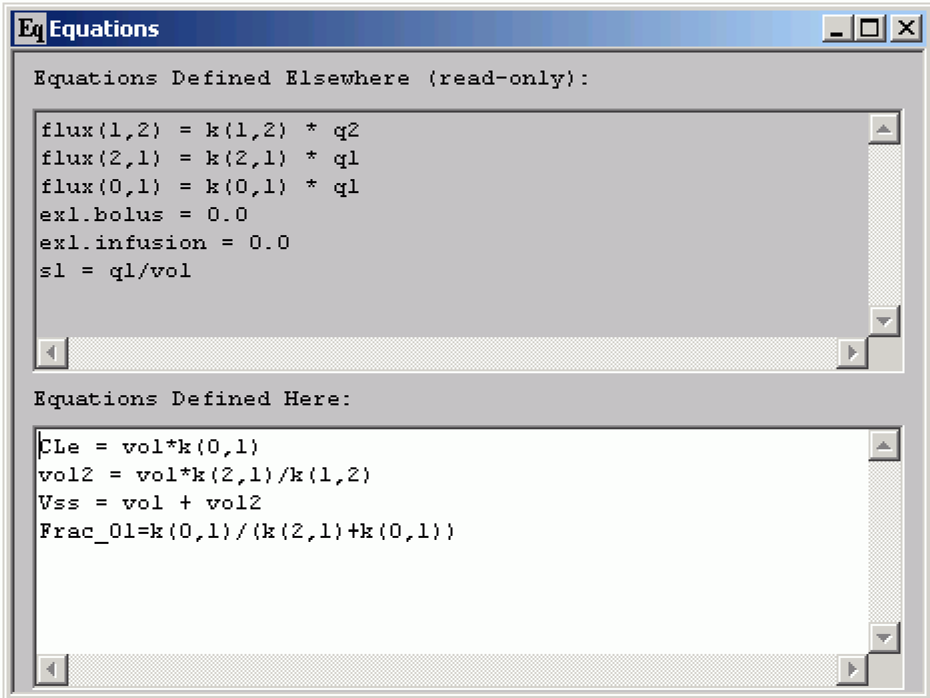
    a. Enter the following equations in the **Equations Defined Here** pane:

CLe = vol*k(0,1)
vol2 = vol*k(2,1)/k(1,2)
Vss = vol + vol2
Frac_01=k(0,1)/(k(2,1)+k(0,1))

*CLe* is the clearance of material from Compartment **2**. *vol2* is the volume of Compartment **2** assuming the concentrations in Compartments **1** and **2** are the same. *Vss* is the total system volume, or equivalent volume of distribution. *Frac_01* is the fraction of material in Compartment **1** that is irreversibly lost.

When you have finished, the **Equations** dialog box should appear as follows:

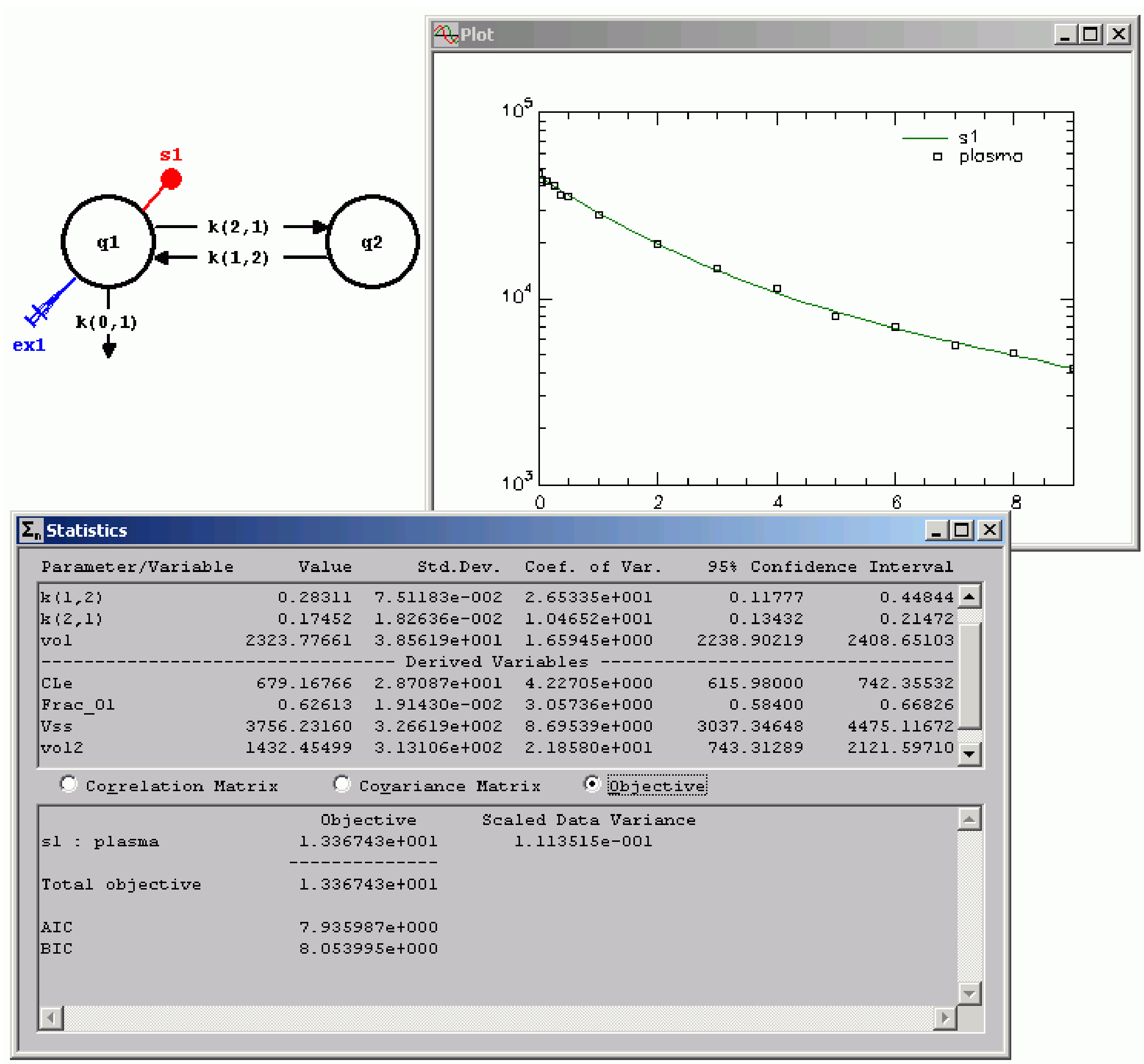
 




b Close the **Equations** dialog box.

5. Fit the model to the data, and view the solution and statistics. The results are summarized in the following:




The "Fit" is quite good as are the statistics. Note statistical information on the parameters you defined in the **Equations** dialog box appear as **Derived Variables** in the **Parameter/Variable** pane of the **Statistics** window.

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

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

**Part 3. Reparameterizing the two-compartment model**

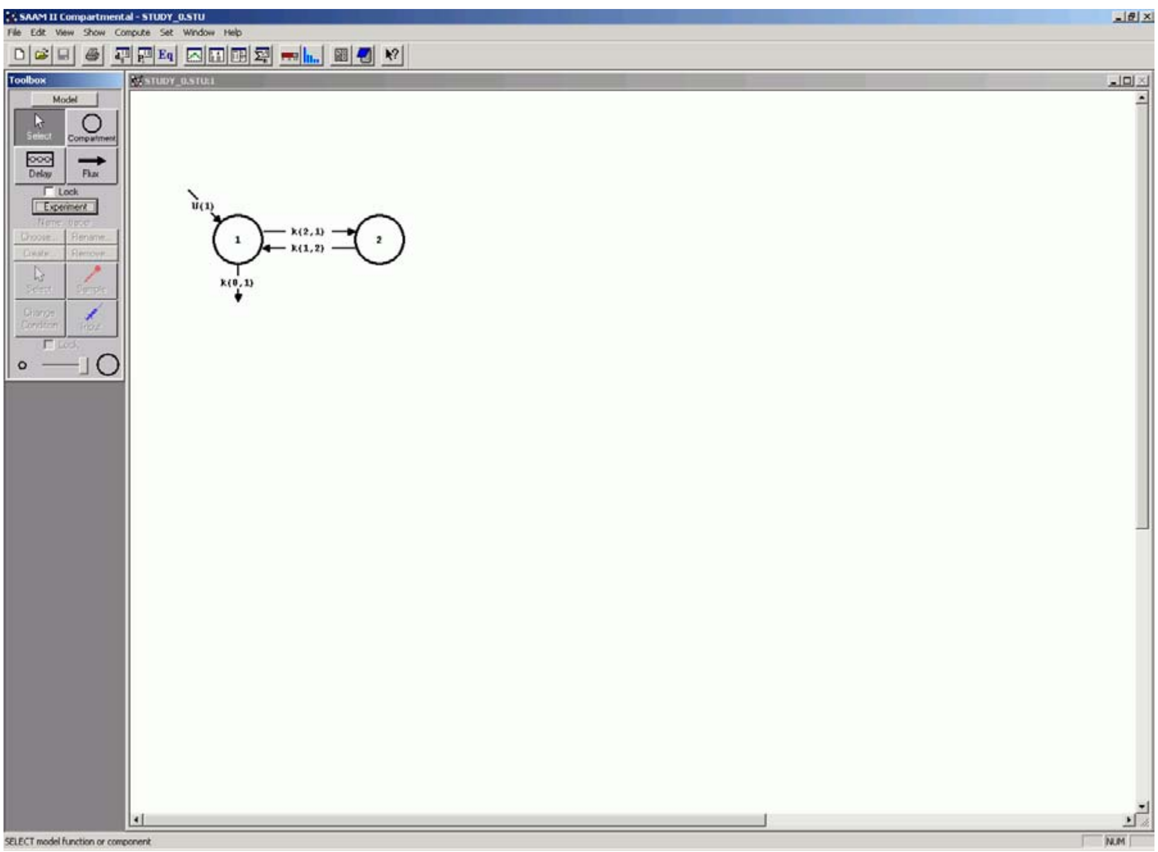
It is sometimes desirable to reparameterize a model so that the desired pharmacokinetic parameters become the model parameters. In this part of the tutorial, the two-compartment model with loss from the plasma compartment will be reparameterized.

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

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

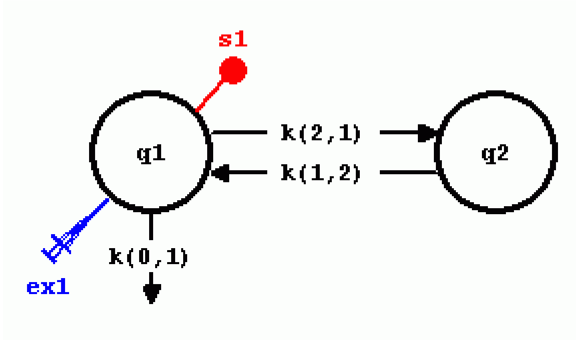
   a. The file **study_0.stu** should appear in the file list; if it does not, find the folder where you put this file.

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




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




4. Re-specify the model parameters.

   The model parameters as the model is currently configured are *vol, k(2,1), k(1,2)* and *k(0,1)*. The model will be reparameterized in terms of clearances. The equations which will be used are:

   CLe = vol*k(0,1)
   CLi = vol*k(2,1)
   vol2 = vol*k(2,1)/k(1,2)
   Vss = vol + vol2

   In SAAM II, these will be rewritten:

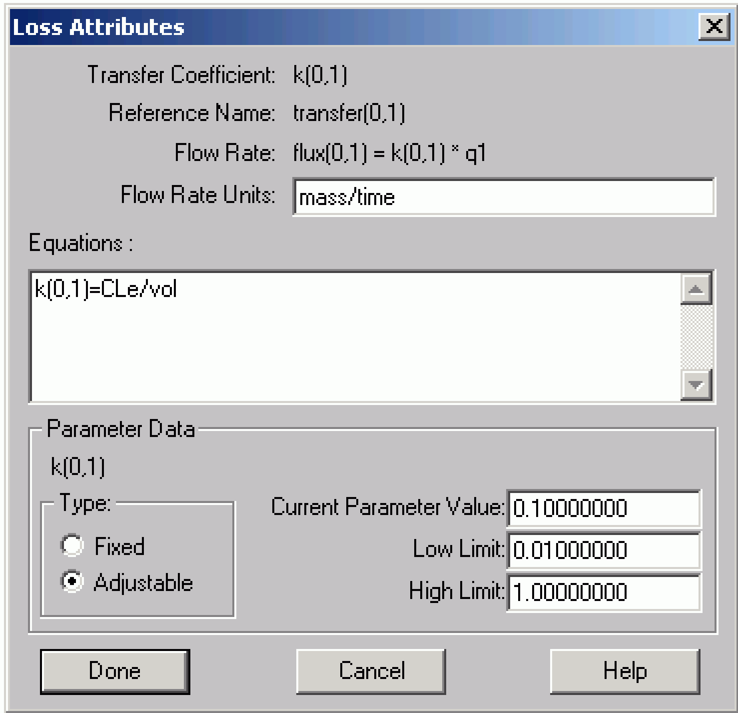
   k(0,1) = CLe/vol
   k(2,1) = CLi/vol
   k(1,2) = CLi/vol2

   The result will be that the model parameters become *CLe*, *CLi*, *vol* and *vol2*.

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

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

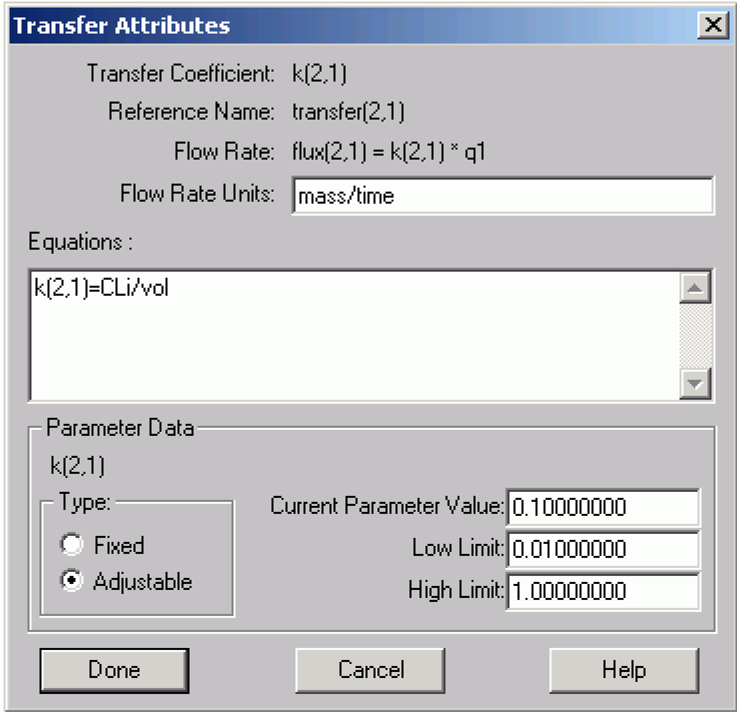



c. Click **Done**.

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

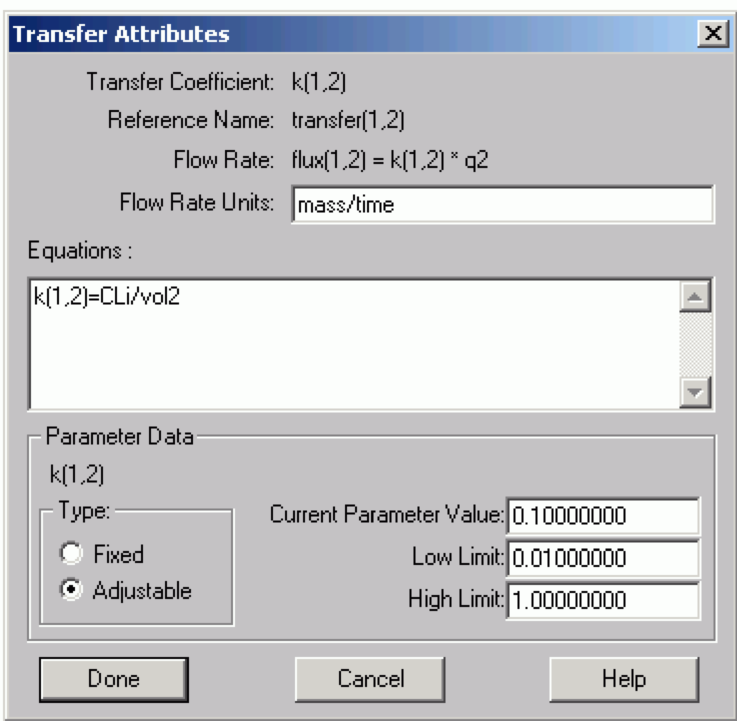
e. In the **Equation** pane, type "k(2,1) = CLi/vol". The **Transfer Attributes** dialog box will appear as follows:




f. Click **Done**.

g. Double-click k(1,2) to open the **Transfer Attributes** dialog box. In the **Equations** pane, type "k(1,2) = CLi/vol2". The **Transfer Attributes** dialog box will appear as follows:



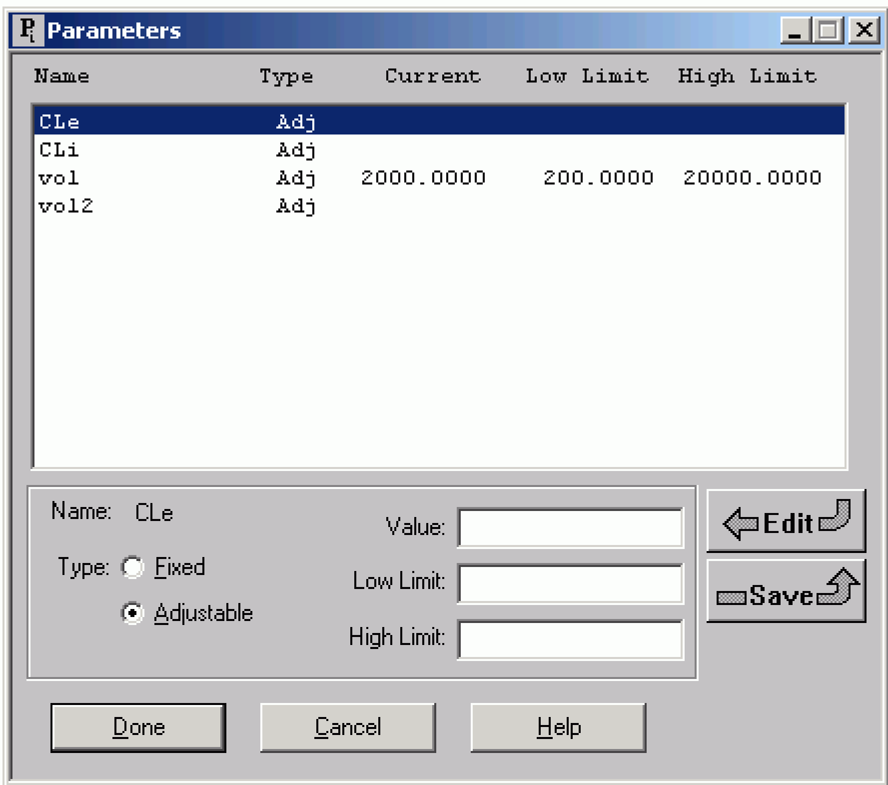

 

h. Click **Done**.

At this point, your model has been reparameterized.

4. Enter the parameter values.

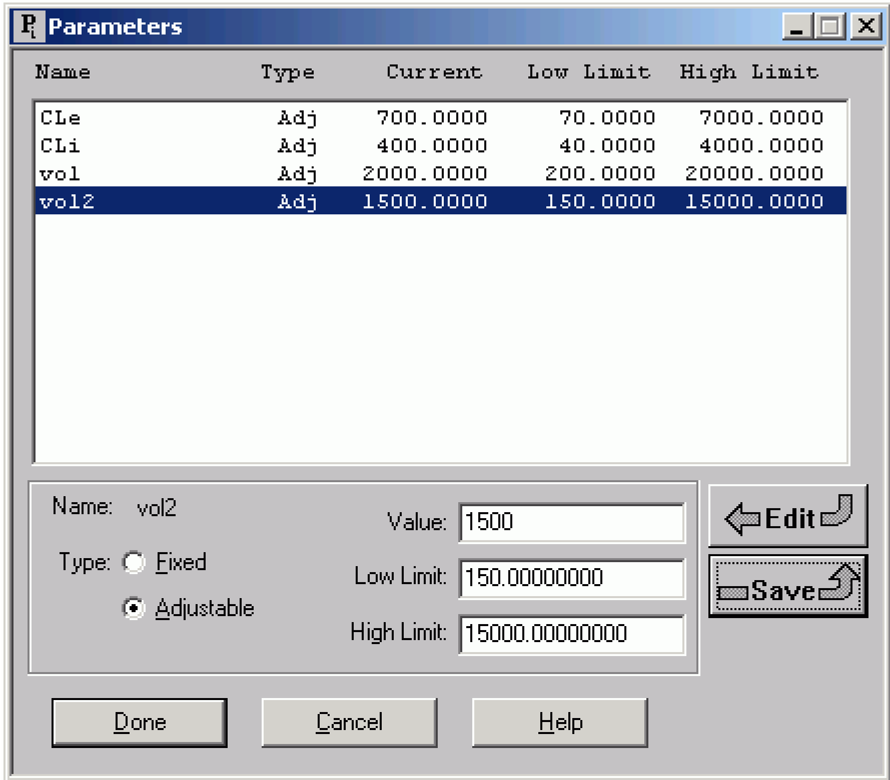
a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters** . The **Parameters** dialog box will open as shown below:




The estimate for *vol* can remain. You need to provide initial estimates for *CLe*, *CLi* and *vol2*.

b. An initial estimate for *CLe* is 700, for *CLi* is 400 and *vol2* is 1500. When you enter these values, the **Parameters** dialog box should appear as follows:

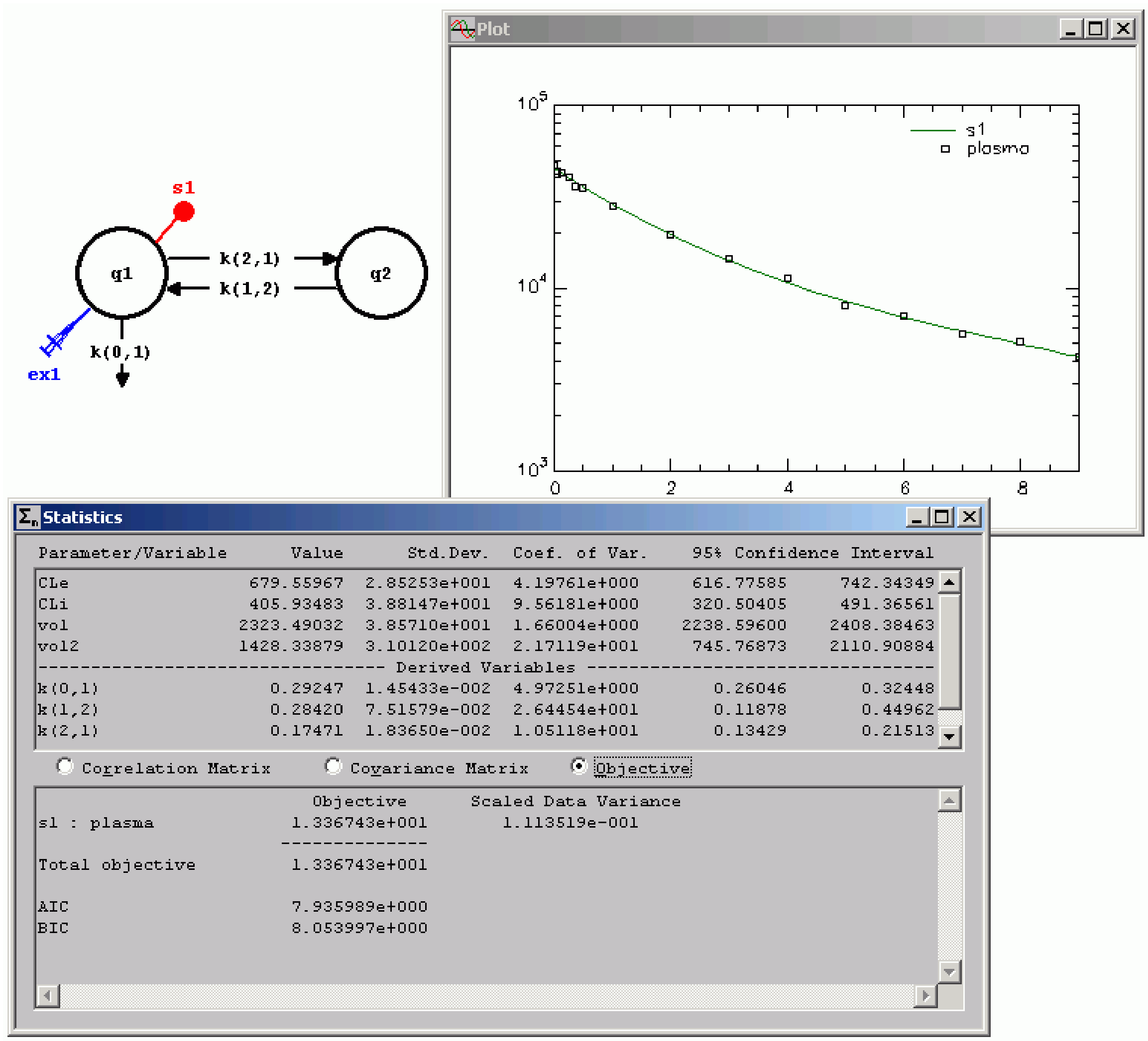



Click **Done** to close the **Parameters** dialog box.

6. Solve the model and view the solution. The initial parameter estimates are reasonable so you can proceed to Fit the model to the data.

7. Fit the model to the data and view the results. A summary of the results is shown as follows:




*Model reparameterization*. In the above situation it is quite easy to parameterize the model in terms of the pharmacokinetic parameters. The results here should be essentially the same as the part in this tutorial where these parameters were defined in the Equations dialog box. Notice in this case the *k(i,j)* become the derived variables.

For the one-compartment model, the one-compartment model with absorption and the three-compartment model, reparameterization is relatively straightforward. However, in instances when there is a single-input multiple-output study (e.g. plasma and urine samples), when the model has more than four compartments, or when the model is nonlinear, reparameterization can be a very tricky bookkeeping exercise, and should be conducted with caution.

7. Close the **Plot** and **Statistics** window.

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

**Part 4. Work with parameter high and low limits**

In the **Parameters** dialog box, for each adjustable parameter you must specify a **Low** and **High Limit**. SAAM II uses this information when you Fit your model to your data. It interprets the values for the **Low** and **High Limit** as a measure of the confidence you have in your knowledge of a particular parameter. SAAM II is very forgiving in these values, but if a particular limit strays too far from the **Value**, it can affect the statistical results following a Fit.

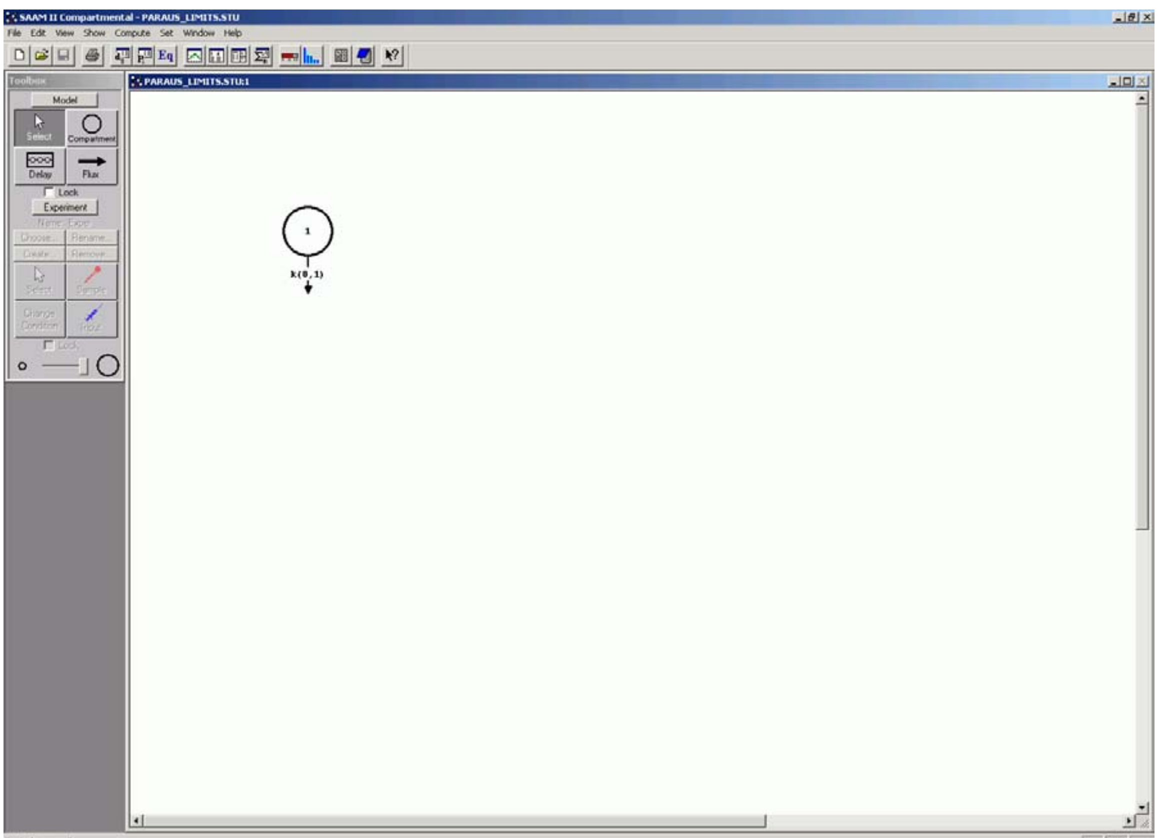
This tutorial will illustrate what can happen using a simple one-compartment model with two parameters, a loss *k(0,1)* and a volume parameter *vol*.

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

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

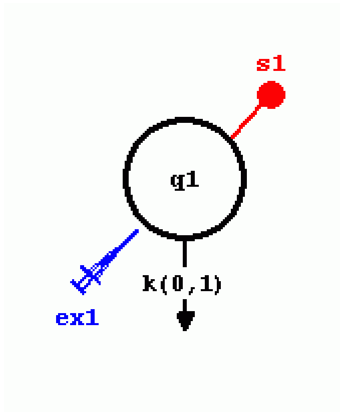
    a. The file **Para_Limits.stu** should appear in the file list; if it does not, find the folder where you put this file.

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



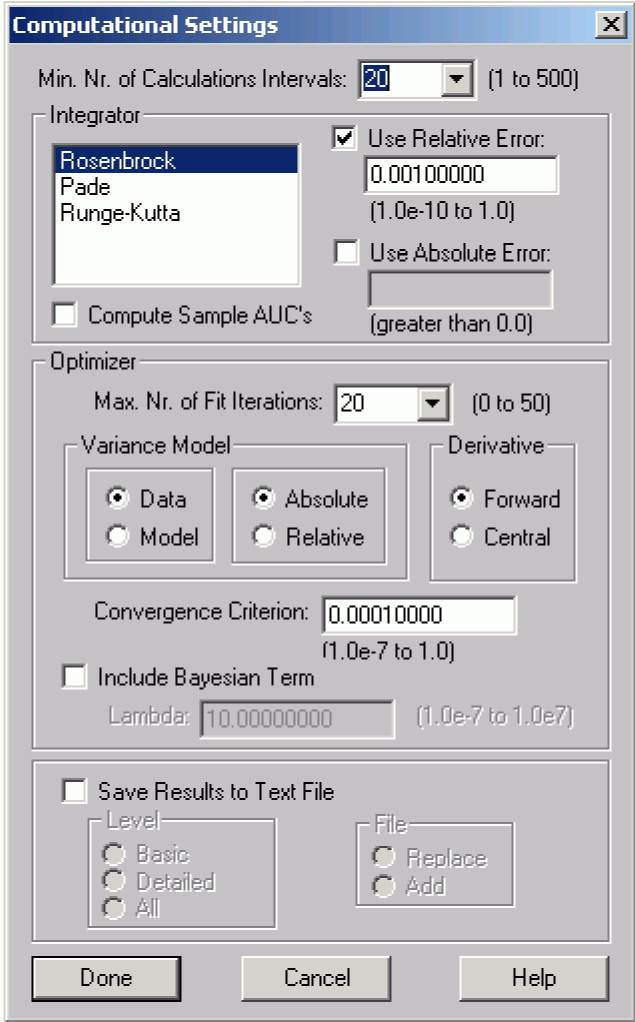

 

3. View the model and the experiment on the model. In the **SAAM II Toolbox**, click **Experiment**. The model of the experiment will appear as follows:




This study file contains a set of monoexponentially decaying data. The default weighting value has been changed from the default "data-relative" to "data-absolute". This can be verified by viewing the **Computational Settings** dialog box which will as appear as shown below:




4. Solve the model and view the solution

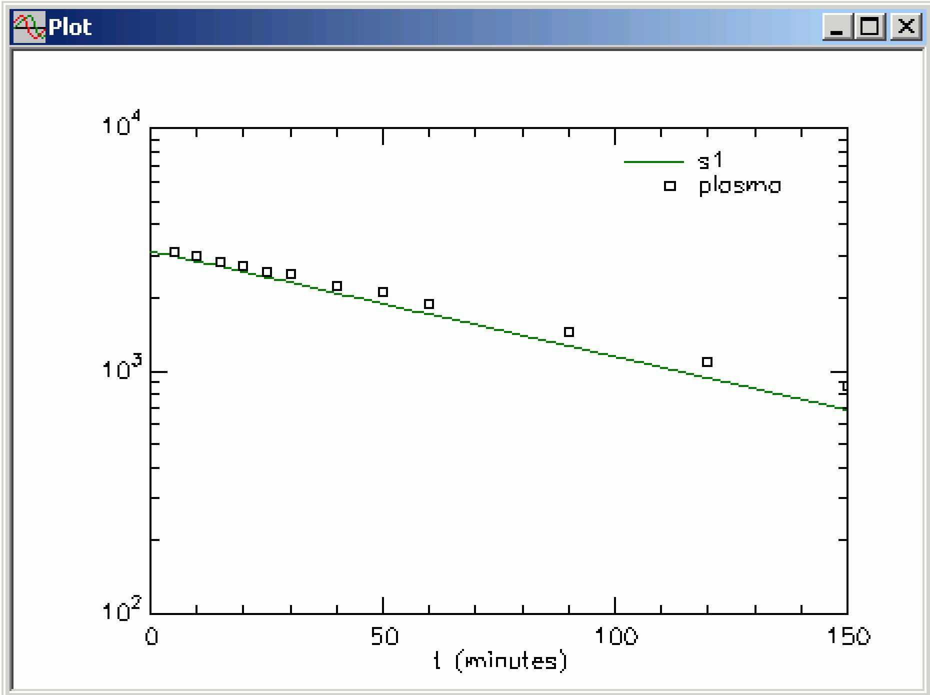
   a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve** .

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

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

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

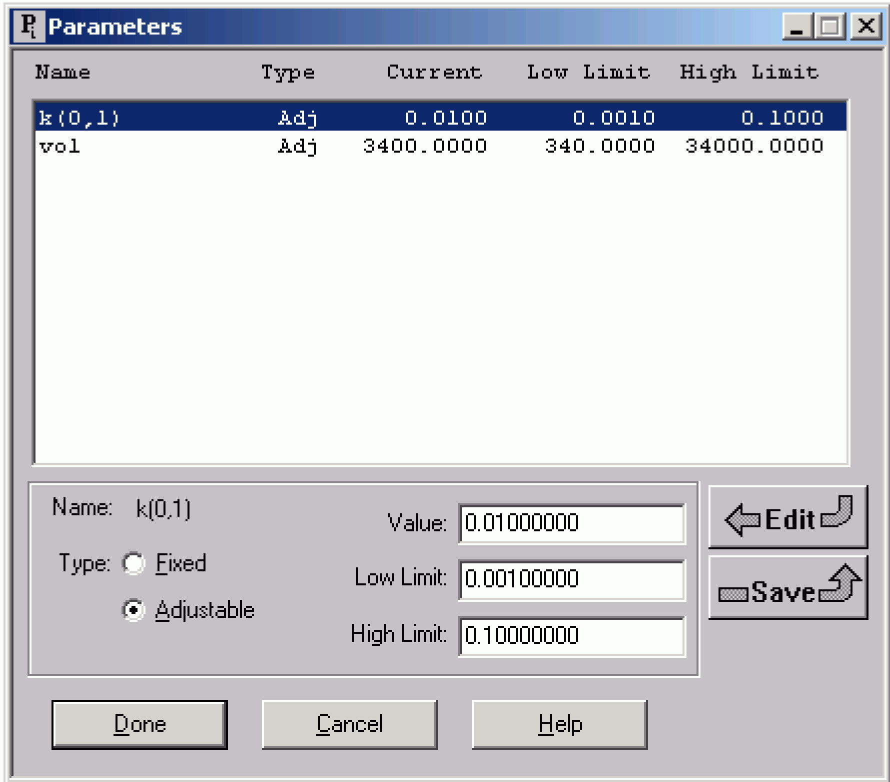
 




e. Close the **Plot** window.

5. Perform a series of Fits with the **Low** and **High Limit** of *k(0,1)* set at different values. The **Low** and **High Limits** of the parameters in **Para_Limits** have been set using the default values in SAAM II. The **Parameters** dialog box will appear as follows:




Perform a series of Fits with the **Low** and **High Limit** of *k(0,1)* set at the values shown in the following table. The left-hand columns are the **Low** and **High Limit** for *k(0,1)*. The columns "k(0,1)(CoeffVar)" and "vol(CoeffVar)" are the final parameter values and coefficients of variations respectively. The column "Obj" is the value of the objective function following the Fit.

| k(0,1) Limits | k(0,1)(CoeffVar) | vol(CoeffVar) | Obj |
|---|---|---|---|
| [0.001,0.1] | | | |
| [0.005,0.05] | | | |
| [0.0001,1.0] | | | |
| [1.0e-07,100] | | | |
| [0,1000] | | | |
| [0,0.1] | | | |

You should fill in this table starting with the default **Low** and **High Limit** of *k(0,1)* respectively equal to 0.001 and 0.1. After the first fit, your table should appear as follows:

| k(0,1) Limits | k(0,1)(CoeffVar) | vol(CoeffVar) | Obj |
|---|---|---|---|
| [0.001,0.1] | 0.0089(7.4) | 3288(4.4) | 10.65 |
| [0.005,0.05] | | | |
| [0.0001,1.0] | | | |
| [1.0e-07,100] | | | |
| [0,1000] | | | |
| [0,0.1] | | | |

You should reset the initial estimates of the parameters to their original values of 0.01 and 3400 respectively, and set the **Low** and **High Limits** for *k(0,1)* equal to 0.005 and 0.05 respectively for the second Fit. You should continue in this fashion until you have completed the table which should appear approximately as follows:

| k(0,1) Limits | k(0,1)(CoeffVar) | vol(CoeffVar) | Obj |
|---|---|---|---|
| [0.001,0.1] | 0.0089(7.4) | 3288(4.4) | 10.65 |
| [0.005,0.05] | 0.0089(7.4) | 3288(4.4) | 10.65 |
| [0.0001,1.0] | 0.0089(7.4) | 3288(4.4) | 10.65 |
| [1.0e-07,100] | 0.0089(7.9) | 3288(4.5) | 10.65 |
| [0,1000] | 0.0089(14.2) | 3288(5.3) | 10.65 |
| [0,0.1] | 0.0089(7.4) | 3288(4.4) | 10.65 |

After each Fit, you can check the plot of **s1:plasma**. As expected, it will not change since the parameter values do not change, as noted above.

What you should observe in this exercise is that, when you can Fit successfully, the **Low** and **High Limits** will have little or no effect on the parameter estimates themselves, or the value of the objective function. What will be effected are the estimated coefficients of variations. However, in this instance, the limits have to move far away from the Value before this becomes noticeable. Thus SAAM II is, in general, robust.

Understanding the effect of high and low parameter limits becomes crucial is when you have a large model with many parameters, some of which may be better estimated from the data than others. Here setting the **Low** and **High Limits** can have a dramatic effect on the final results.

Close all open windows and dialog boxes.

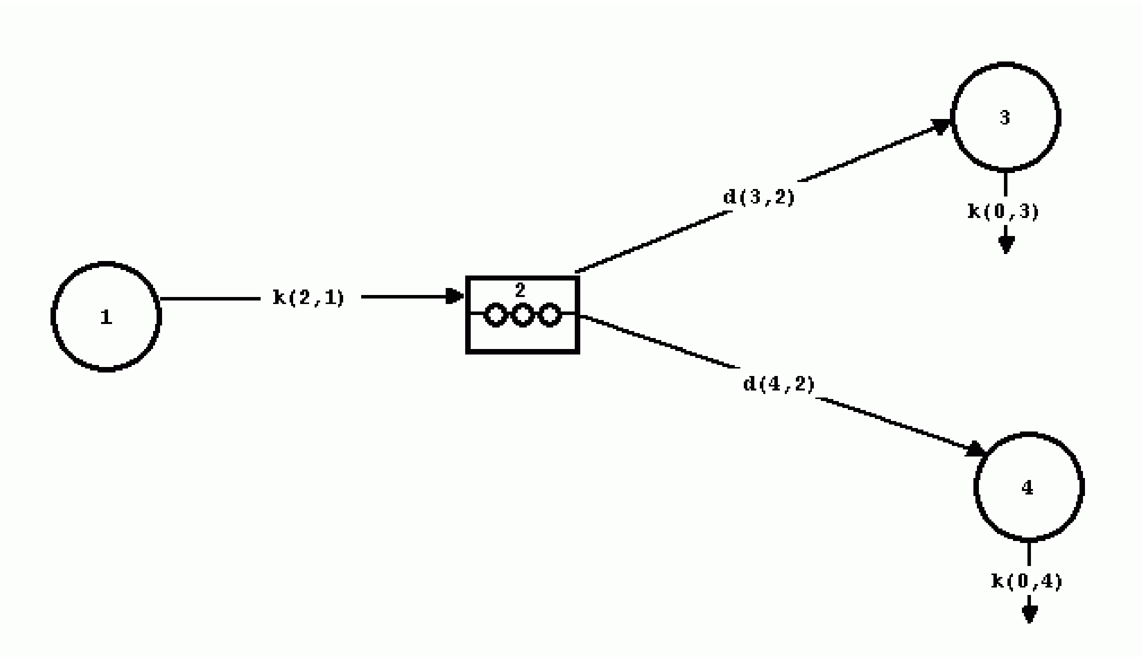
**Quit** the **SAAM II Compartmental** application. Do not save the changes to **Para_Limits**.

Some additional comments on parameter limits are necessary.

The previous tutorial illustrated a simple case of setting the parameter limits on one parameter. In linear compartmental models, SAAM II is quite forgiving in setting these limits. There are instances when limits must be set, or instances when realistic limits must be set in order to achieve a successful fit of the model to the data.

An example of an instance in which a limit must be set rather than using the default value is the following. Suppose you have a delay in your model where there are two losses from the delay. This is illustrated in the following model:




There are two possible routes by which material can leave Delay **2**. Remember in SAAM II, loss from a delay is a fraction, i.e. a fraction of the material in the delay along the possible routes of loss. When there is only one loss, the fraction is 1. In this situation above, d(3,2) + d(4,2) = 1, and both *d(3,2)* and *d(4,2)* must lie between 0 and 1. A convenient way of doing the bookkeeping is the following. You can define

$$d(3,2) = \text{frac}$$

and

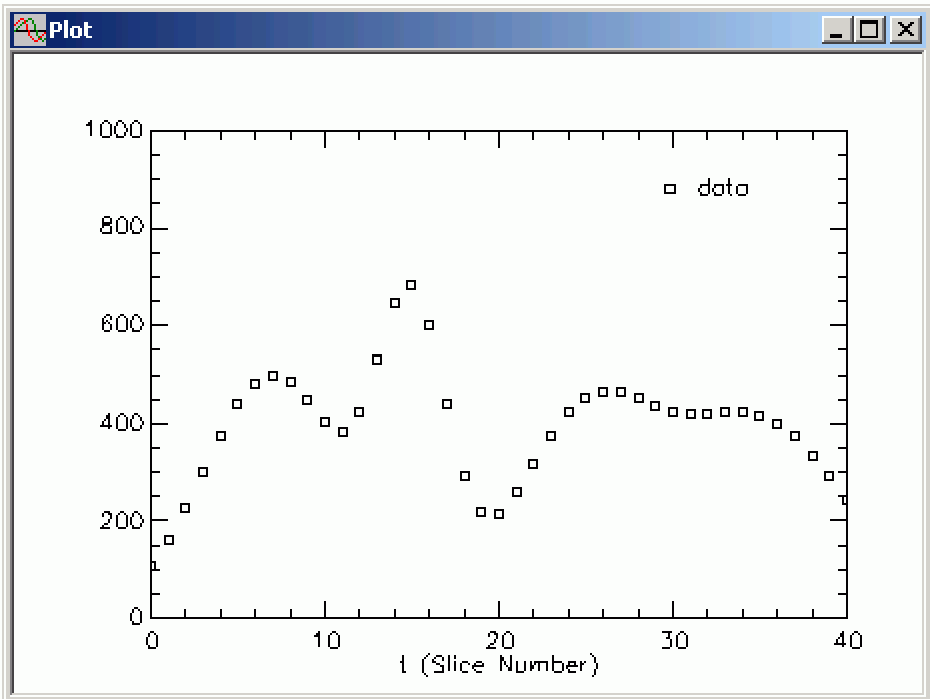
$$d(4,2) = 1 - \text{frac}$$

*frac* becomes a parameter for which a **Value**, **Low Limit** and **High Limit** must be specified. If you enter, for example, 0.5 in the **Value** box and use the default limits, the **Low Limit** will be 0.05 which is okay, but the **High Limit** will be 5 which is not okay since if in the process of fitting, *frac* goes above 1, *d(4,2)* will become negative and

Conservation of Mass will be violated. Thus you must determine **Low** and **High** limits for *frac* that lie between 0 and 1.

Another example of where setting reasonable parameter limits rather than using the default values is the following example which will use the **SAAM II Numerical** application. The data to be analyzed are shown in the following plot:




These data are cholesterol concentrations in 40 subtractions of high density lipoprotein. The problem is to describe these data by a Sum of Gaussians using the **SAAM II Numerical** application.

A Gaussian is a function of the form

$$f(t) = \frac{1}{\sqrt{2\pi}\sigma}\exp\left[-\frac{1}{2}\left(\frac{t-\mu}{\sigma}\right)^2\right] \quad -\infty < t < \infty$$

where, in this expression, $\mu$ is called the mean and $\sigma$ the standard deviation. It is known that the area under this so-called bell shaped curve is unity, i.e.

$$\int_{-\infty}^{\infty} f(t)dt = 1 .$$

The mean $\mu$ determines the location while the standard deviation $\sigma$ provides a measure of the "sharpness" of the gaussian. That is, the smaller the $\sigma$, the narrower the peak.

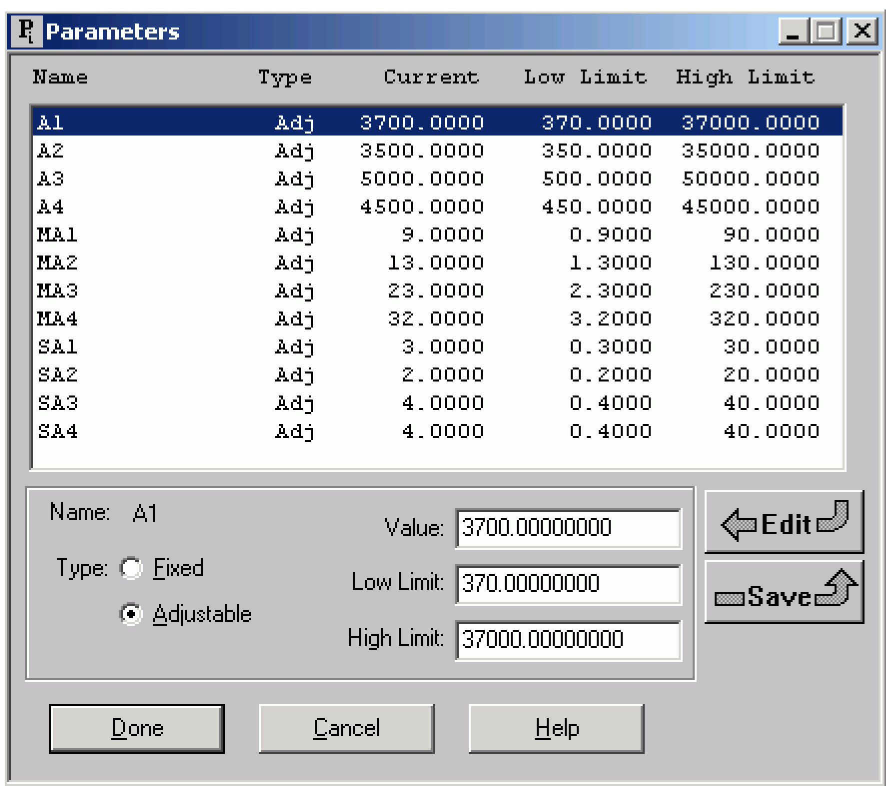
A sum of four Gaussians will be used to describe these data. In SAAM II, a single Gaussian is written:

A1/(SA1*2.51)*exp(-((t-MA1)^2)/(2*SA1^2))

Where *A1* is a parameter characterizing the magnitude of the contribution of the Gaussian. *SA1* and *MA1* are the standard deviation and mean of the gaussian. 2.51 approximates $\sqrt{2\pi}$ . Thus the single Gaussian term has three parameters, *A1*, *SA1* and *MA1*. Thus in the sum of four Gaussians, there will be 12 parameters, and the expression will be:

ya(t) = A1/(SA1*2.51)*exp(-((t-MA1)^2)/(2*SA1^2)) + A2/(SA2*2.51)*
exp(-((t-MA2)^2)/(2*SA2^2)) + A3/(SA3*2.51)*exp(-((t-MA3)^2)/(2*SA3^2)) +
A4/(SA4*2.51)*exp(-((t-MA4)^2)/(2*SA4^2))

Initial estimates for the four means, *MA1, MA2, MA3* and *MA4* can be obtained by looking at the data and estimating where the peaks may lie. Similarly initial estimates for the four standard deviations can be obtained again just by looking at the sharpness of the peaks. The **Parameters** dialog box could appear as follows:

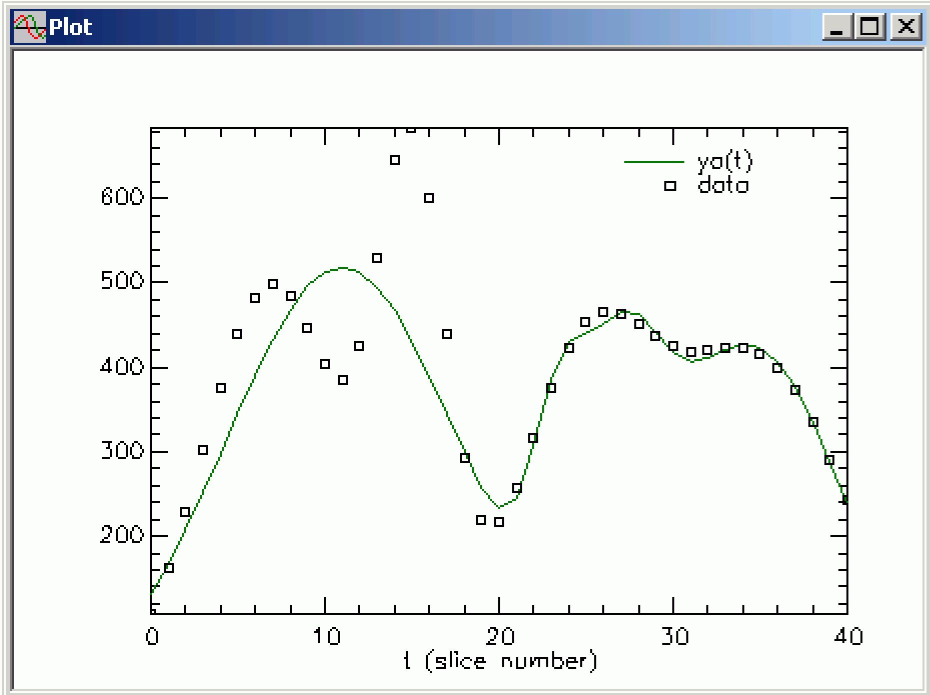


| Name | Type | Current | Low Limit | High Limit |
|---|---|---|---|---|
| A1 | Adj | 3700.0000 | 370.0000 | 37000.0000 |
| A2 | Adj | 3500.0000 | 350.0000 | 35000.0000 |
| A3 | Adj | 5000.0000 | 500.0000 | 50000.0000 |
| A4 | Adj | 4500.0000 | 450.0000 | 45000.0000 |
| MA1 | Adj | 9.0000 | 0.9000 | 90.0000 |
| MA2 | Adj | 13.0000 | 1.3000 | 130.0000 |
| MA3 | Adj | 23.0000 | 2.3000 | 230.0000 |
| MA4 | Adj | 32.0000 | 3.2000 | 320.0000 |
| SA1 | Adj | 3.0000 | 0.3000 | 30.0000 |
| SA2 | Adj | 2.0000 | 0.2000 | 20.0000 |
| SA3 | Adj | 4.0000 | 0.4000 | 40.0000 |
| SA4 | Adj | 4.0000 | 0.4000 | 40.0000 |



Initial estimates were obtained visually, and default values for the **Low** and **High Limits** have been used. When the model are fitted to the data (with the FSD option), the best fit is shown as follows:




Obviously this is not satisfactory. Neither are the statistics which are shown below:

Statistics

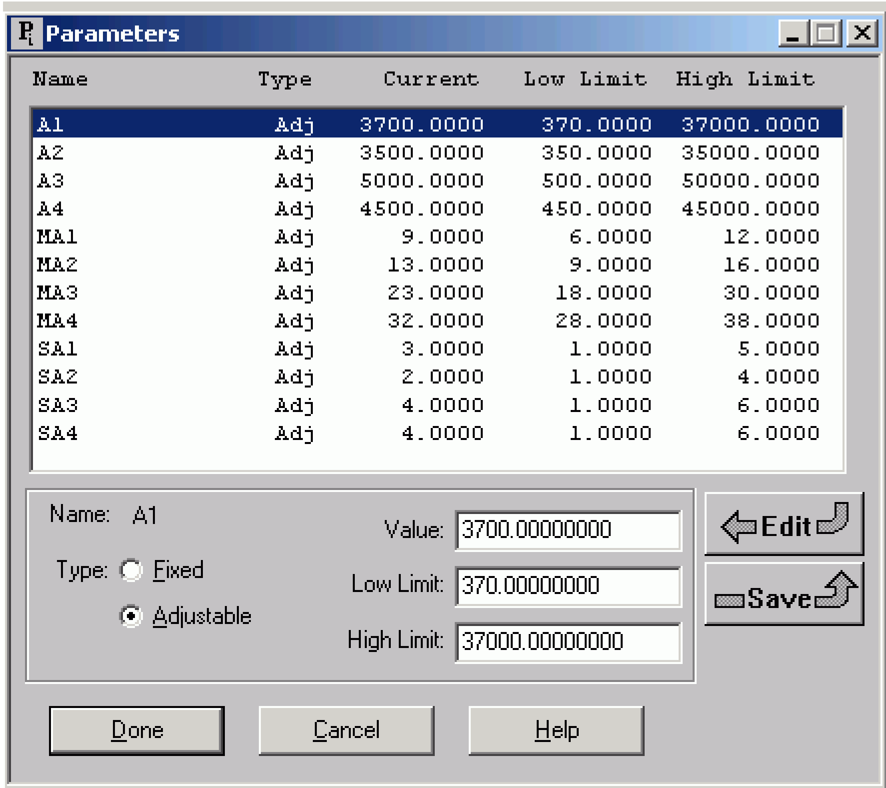
| Parameter/Variable | Value | Std.Dev. | Coef. of Var. | 95% Confidence Interval | |
|---|---|---|---|---|---|
| A1 | 8626.70801 | 4.16023e+002 | 4.82250e+000 | 7775.84498 | 9477.57104 |
| A2 | 1771.89568 | 5.56438e+003 | 3.14035e+002 | -9608.53487 | 13152.32624 |
| A3 | 624.24291 | 3.21665e+003 | 5.15289e+002 | -5954.55182 | 7203.03764 |
| A4 | 5452.71015 | 3.37144e+003 | 6.18306e+001 | -1442.66510 | 12348.08540 |
| MA1 | 10.97825 | 3.87261e-001 | 3.52753e+000 | 10.18621 | 11.77029 |
| MA2 | 26.78137 | 4.50542e+000 | 1.68230e+001 | 17.56675 | 35.99599 |
| MA3 | 23.32592 | 2.22153e+000 | 9.52388e+000 | 18.78238 | 27.86946 |
| MA4 | 34.50228 | 2.97499e+000 | 8.62259e+000 | 28.41774 | 40.58681 |

Correlation Matrix    Covariance Matrix    Objective

| | Objective | Scaled Data Variance |
|---|---|---|
| ya(t) : data | 9.043484e+000 | 3.159819e+000 |
| | -------------- | |
| Total objective | 9.043484e+000 | |
| AIC | 5.757754e+000 | |
| BIC | 6.029418e+000 | |

What is happening is that the limits set on the means and standard deviations are not realistic using the default values. For example, the **High Limits** for all the means are well beyond the data which end at "40". Visually, more realistic estimates for the **Low** and **High Limits** for both the means and standard deviations can be obtained visually. Below is the Parameters dialog box with just such a set of more reasonable estimates:

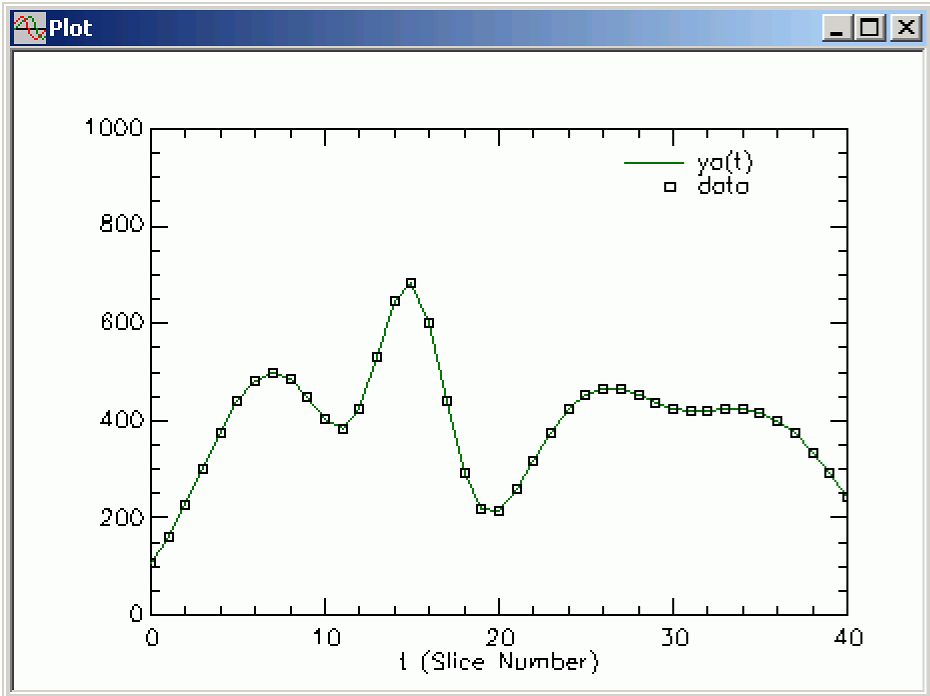
 




You can see the limits for the means and standard deviations are much closer to their initial estimated **Values**. The default limits on the Ai are okay since these are linear parameters and are not that sensitive to the limits.

Using these initial estimates and limits, if you fit the model to the data (with the FSD option), you will obtain the following fit:




The statistics are also satisfactory:

**Statistics**

| Parameter/Variable | Value | Std.Dev. | Coef. of Var. | 95% Confidence Interval | |
|---|---|---|---|---|---|
| A1 | 5006.72990 | 2.93609e+002 | 5.86429e+000 | 4406.23182 | 5607.22797 |
| A2 | 3004.02810 | 3.46570e+002 | 1.15368e+001 | 2295.21237 | 3712.84382 |
| A3 | 4005.41395 | 1.84868e+003 | 4.61545e+001 | 224.44140 | 7786.38650 |
| A4 | 5006.69063 | 1.98272e+003 | 3.96013e+001 | 951.58002 | 9061.80123 |
| MA1 | 7.00000 | 3.12151e-001 | 4.45930e+000 | 6.36158 | 7.63842 |
| MA2 | 15.00000 | 1.71181e-001 | 1.14121e+000 | 14.64989 | 15.35010 |
| MA3 | 25.00002 | 1.34624e+000 | 5.38497e+000 | 22.24664 | 27.75340 |
| MA4 | 35.00003 | 1.76422e+000 | 5.04063e+000 | 31.39179 | 38.60827 |

○ Correlation Matrix ○ Covariance Matrix ◉ Objective

| | Objective | Scaled Data Variance |
|---|---|---|
| ya(t) : data | 7.239246e+000 | 1.000000e+000 |
| | -------------- | |
| Total objective | 7.239246e+000 | |
| AIC | 4.831244e+000 | |
| BIC | 5.082011e+000 | |

This example thus illustrates the need to be aware of setting limits on your adjustable parameters, and to pay attention to how they may need to change as you go through your modeling exercise.

**Part 5. Using the Bayesian option to incorporate prior knowledge**

What happens if you have prior information about a parameter in your model? It may be the case, for example, a relationship between two parameters has been developed as a result of research conducted elsewhere. How can you incorporate this knowledge in your model?

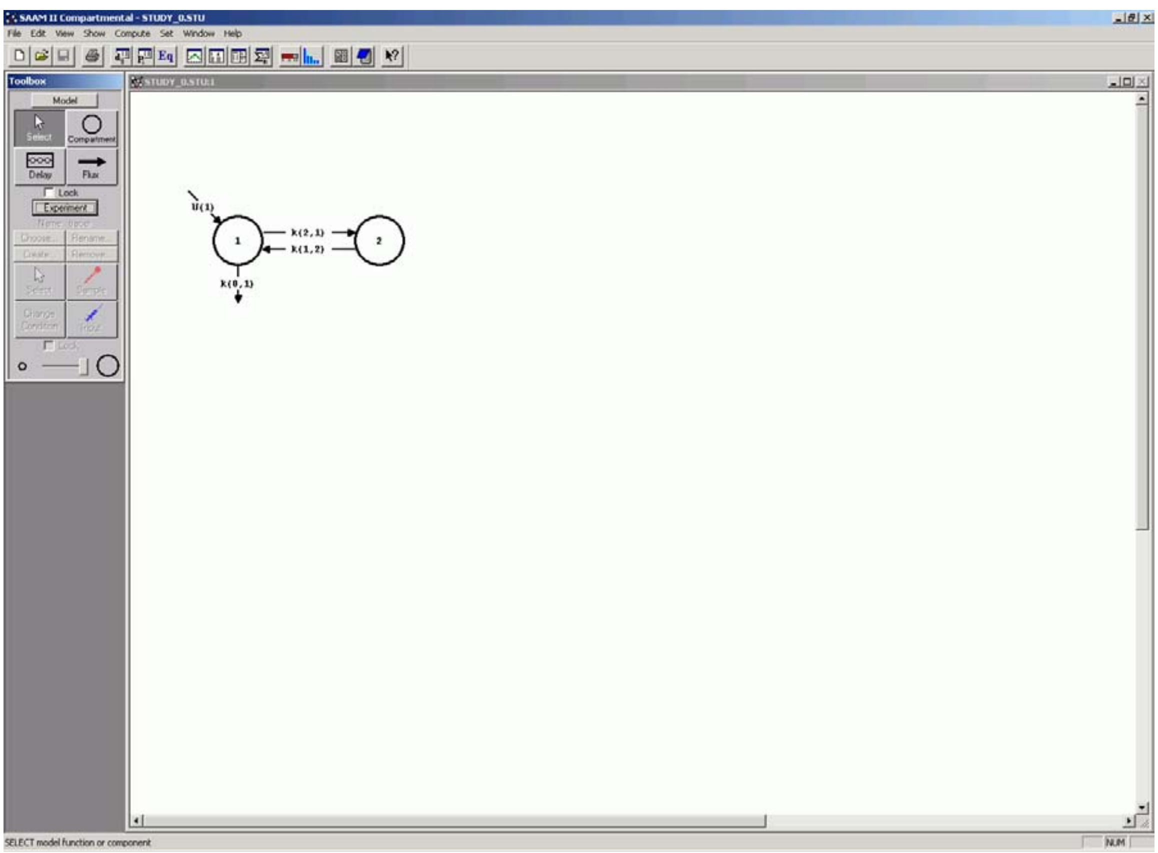
One way you can incorporate priori knowledge is to use the Bayesian option in SAAM II. This part of the tutorial will illustrate how this can be done.

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

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

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

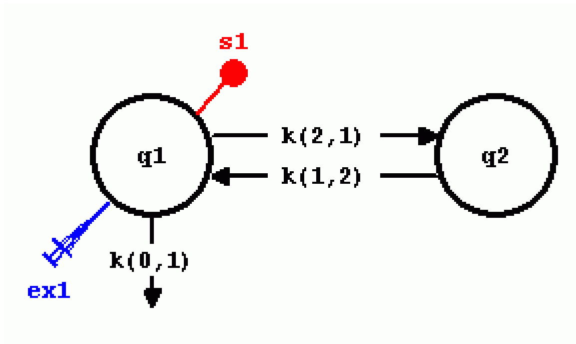
    b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as shown below:



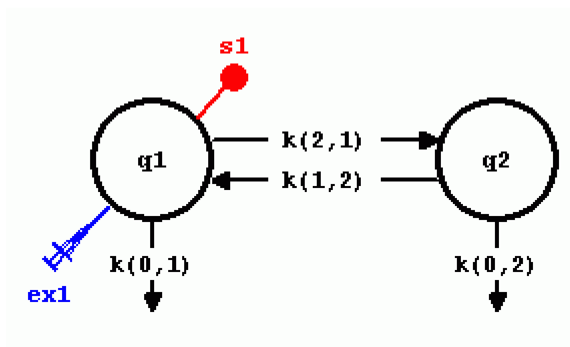

3. View the model and the experiment on the model, and change the model.

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




b. Modify the model by adding a loss from Compartment **2**. Your model for the experiment should appear as follows:



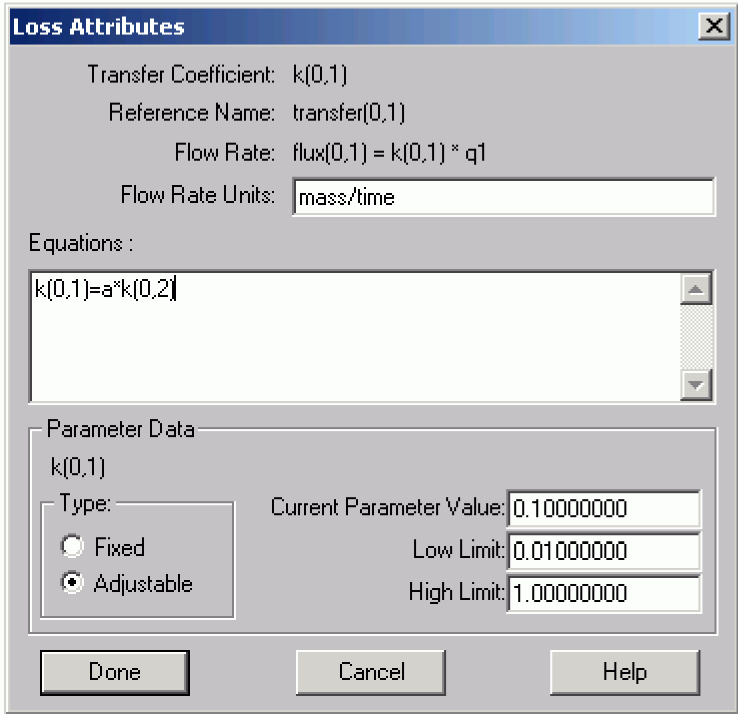

4. Specify a relationship between *k(0,1)* and *k(0,2)*.

   Suppose from the literature there is a known relationship between *k(0,1)* and *k(0,2)*. Suppose it is known that *k(0,1)* is approximately twice *k(0,2)*. How can this be incorporated in the model?

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

   b. In the **Equations** pane, type “k(0,1) = a * k(0,2)”. The **Loss Attributes** dialog box will appear as follows:




c. Click **Done**. A new parameter, *a*, has been added to the model.

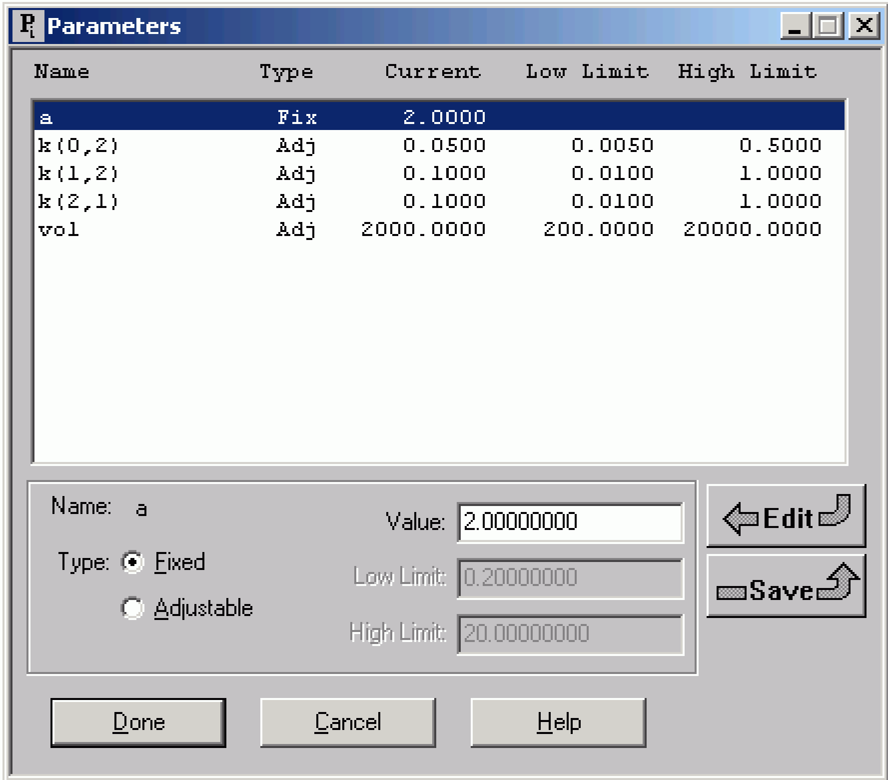
5. Enter a value for *a*, and Solve and Fit the model to the data.

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

b. Be sure *a* is selected. Set *a* as a fixed parameter, type “2” in the **Value** box, and click **Save**.

c. Double-click *k(0,2)* to select it. Type “0.05” in the **Value** box, and click **Save**. The **Parameters** dialog box will appear as follows:

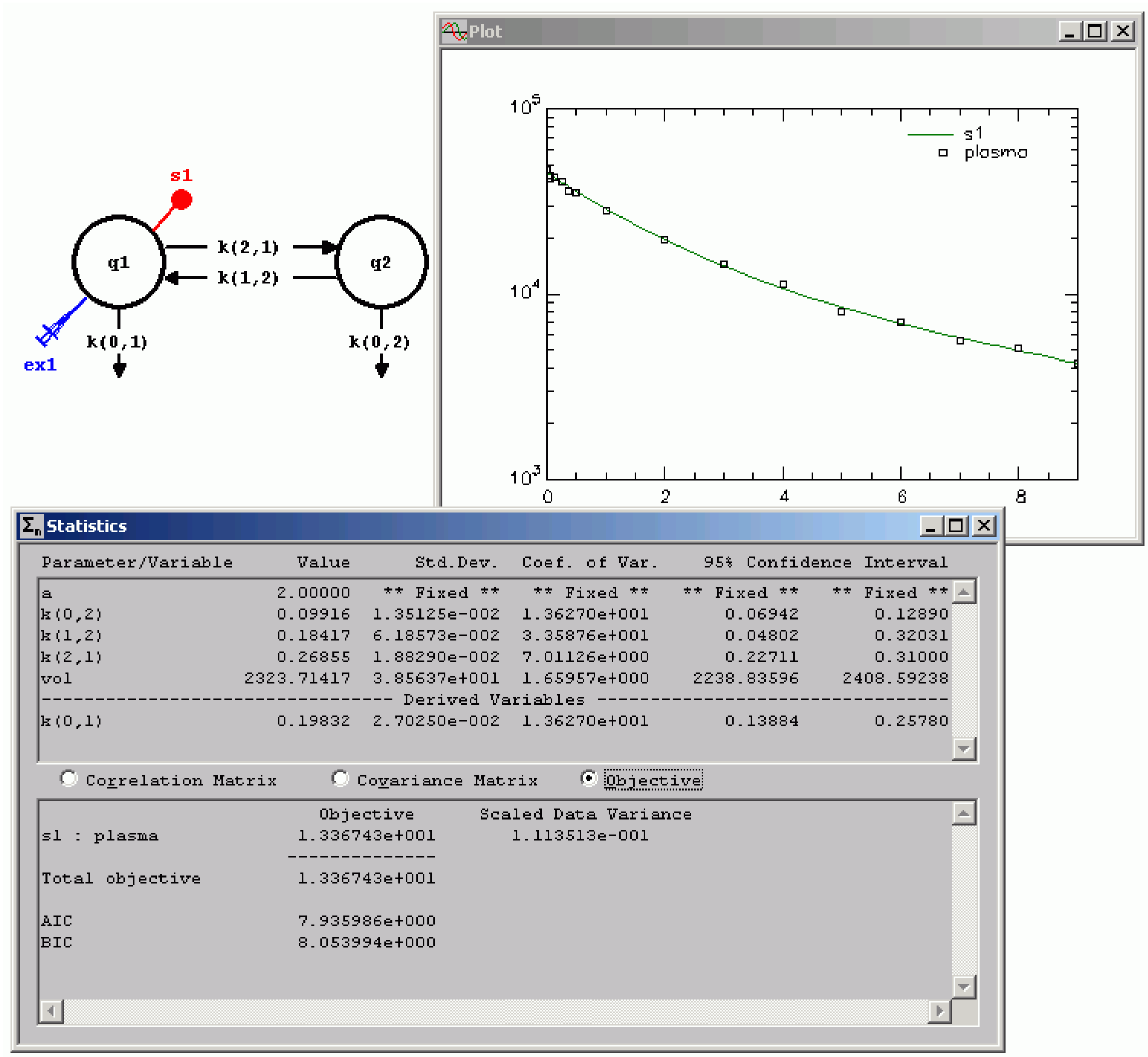
 




   d. Click **Done**.

6. Solve the model. The initial parameter value, while not great, are sufficient to proceed with a "Fit". Fit the model to the data and view the solution. A summary of the "Fit" is shown in the following:




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

In this case, *a* was assumed to be known and equal to 2. The result is that there are four parameters to be estimated from the data, and the "Fit" was successful. What would happen is *a* was adjustable?

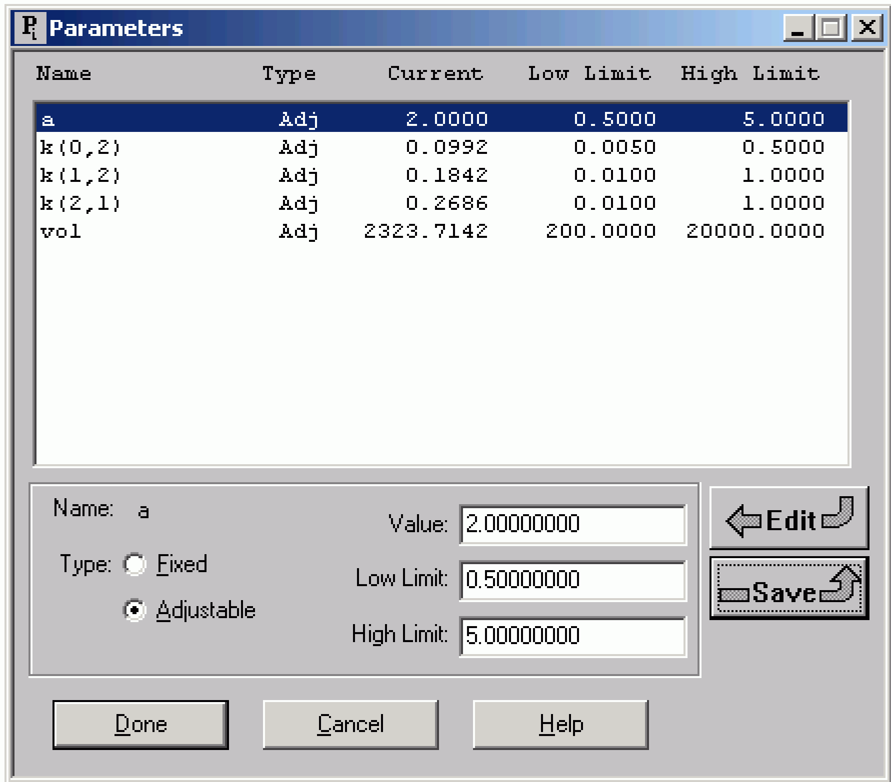
7. Set *a* as an adjustable parameter.

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

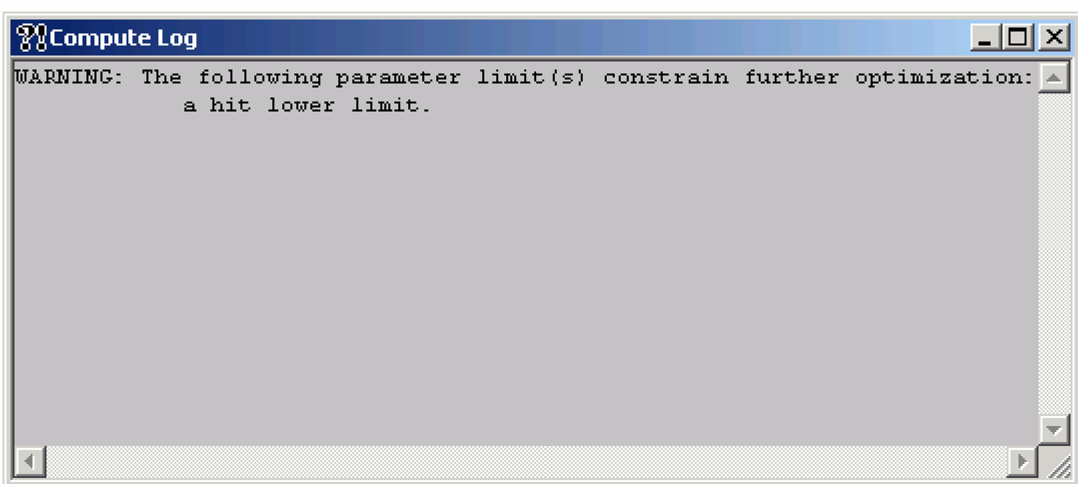
   b. Double-click *a* to select it.

   c. Set a as an adjustable parameter. Leave the initial **Value** equal to "2". Type "0.5" and "5" in the **Low Limit** and **High Limit** boxes respectively. The **Parameters** dialog box will appear as follows:




d. Fit the model to the data. The following warning message will appear:




The warning is that *a* hit a lower limit. If you continue to adjust the **Low Limit**, *a* will continue to hit the lower limit. This means there are more parameters in the model than can be estimated from the data.

e. Close the **Compute Log** dialog box.

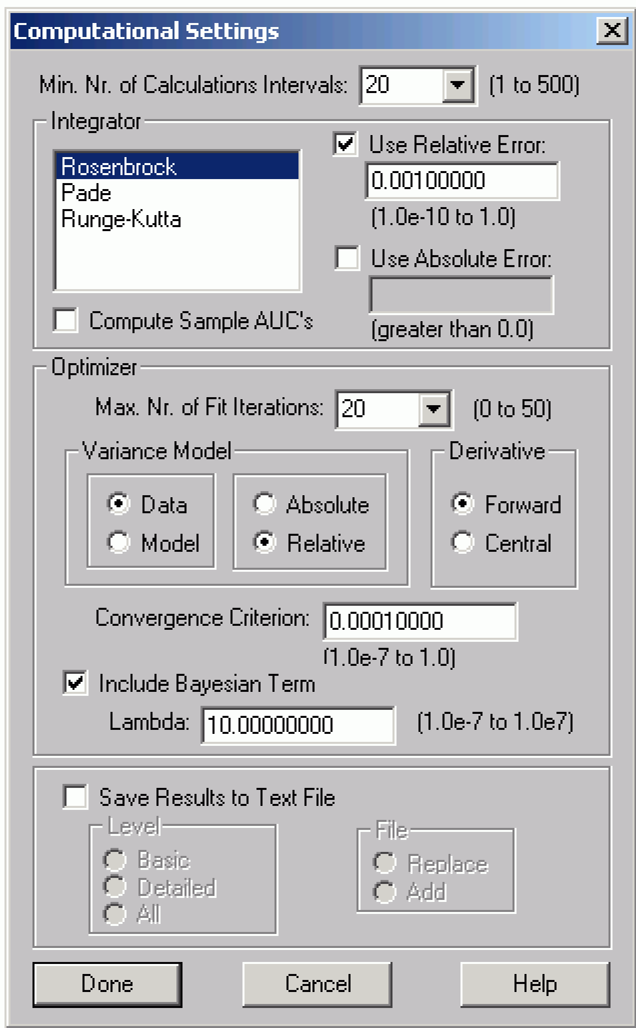
 

8. Incorporate prior knowledge about *a* into the model.

Suppose you really believed that *k(0,1)* was about twice *k(0,2)*. Suppose you had information on the value of *a* from another study. You can incorporate this knowledge using the Bayesian option in SAAM II. Suppose you know from the literature that a value for *a* is "2" with a standard deviation of "0.05". In this part of the tutorial, this information will be incorporated into the model.

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

b. Select the **Include Bayesian Term** check box. The **Computational Settings** dialog box will appear as follows:




c. Click **Done**.

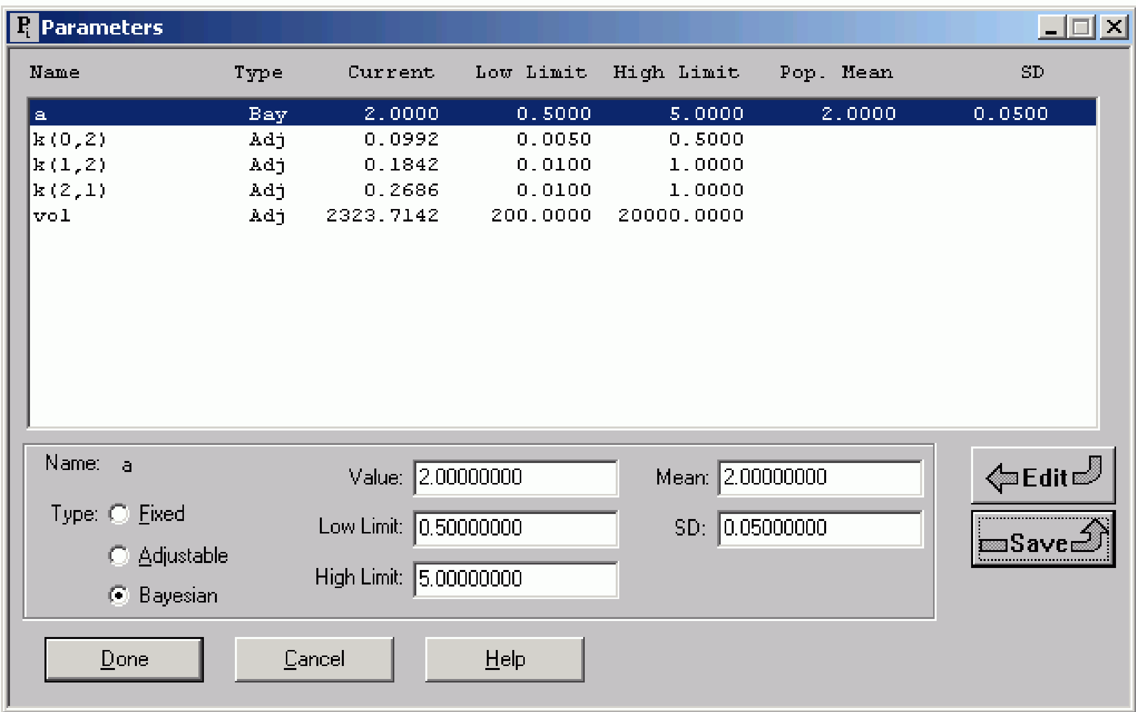
d. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar,** click **Parameters** . The **Parameters** dialog box will open.

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

(2) Select the type for *a* as Bayesian.

(3) Type “2” in the **Mean** box and “0.05” in the **SD** box.

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

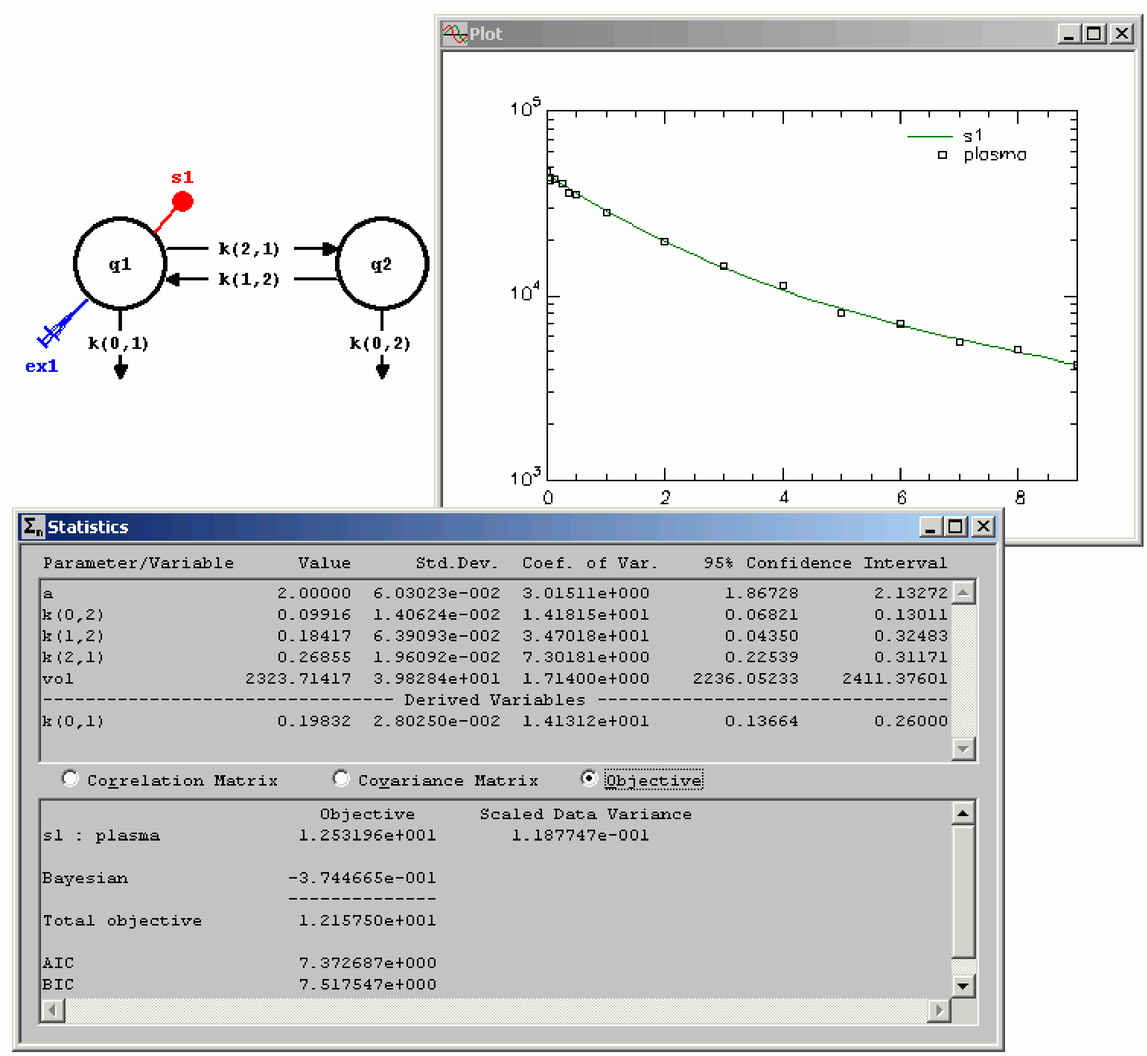



(5) Click **Done**.

*The Bayesian option*. If you have information about the value of a model parameter from the literature, it is useful to include this in your model. When you have Bayesian parameters in your model and you fit your model to your data, SAAM II takes this information into account. If there is information in your data about a Bayesian parameters, SAAM II will adjust it from its mean value. If there is little or no information in your data about a Bayesian parameters, SAAM II will not adjust it from its mean value.

e. Fit the model to the data. A summary of the results is shown below:




*Bayesian parameters*. The Bayesian parameter option is a powerful way to incorporate prior information about a parameter in your model. In almost all cases if you use this option, you will achieve convergence. If your data do not contain much information about the Bayesian parameter, then the value you entered for the **Mean** and **SD** will not change much; if your data do contain information, they will change. In this case, the **Mean** didn't change; the **SD** changed a little.

You should note that the precision of the model parameters is not as good as the case, for example, when there were only four parameters to be estimated. This is because of the additional uncertainty added by the Bayesian parameter.

Using this option can also be useful as a modeling technique. If in the process of developing a model you cannot achieve a fit, you can sometimes use the Bayesian option on a specific parameter. You can then tell from the resulting statistical output which of the model parameters may be giving difficulty in achieving a “Fit.” This can help identify where constraints on parameters or model simplification must be undertaken.

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

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