

SAAM II Version 2.2

Basic Tutorials

Working with Parameters – Basic

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Working with Parameters

Prerequisites

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

What you will learn in this tutorial

The purpose of this tutorial is to show you how to use the different options in SAAM II to define and use the most commonly used types of parameters. You will learn

- How to use the **Parameters** dialog box (Part 1a)
- How to hand-fit a model to data by individually adjusting parameters or by using the SAAM II slider bar (Part 1b)
- How to use the **Transfer** and **Loss Attributes** dialog boxes (Part 2)
- How to create nonlinear transfers (Part 3)

This tutorial is divided into parts to which you can refer individually for specific information. Once 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_Para.stu
study_0.stu

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** examples and tutorials. The file **study_0_Para.stu** is the same with the exception that the **Parameters** dialog box is empty.

Introduction

This tutorial is designed to show you how to use the different options available in SAAM II to work with the most commonly used types of parameters.

The first two tutorials explain how to use the different features in the **Parameters** dialog box by hand-fitting a model to data. The second explains how to use the features in the **Transfer** and **Loss Attributes** dialog boxes. Taken together, this information will cover most of what users will need to know about working with parameters in SAAM II.

The next tutorial explains how to create nonlinear parameters. The example used for the nonlinear parameters is Michaelis-Menten. SAAM II is not restricted only to this; any nonlinearity can be written using standard FORTRAN notation.

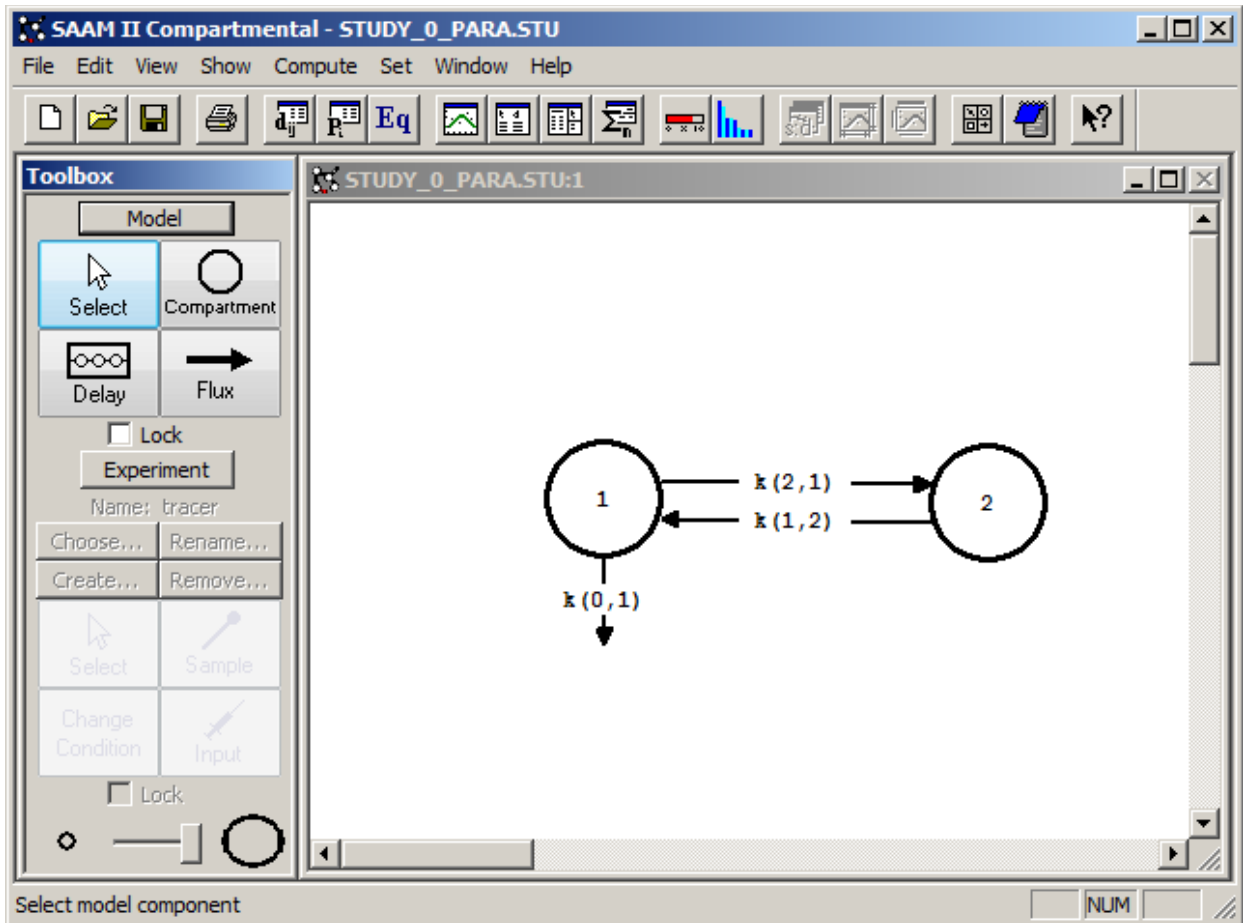
“Working with Parameters, Advanced” shows how to use the different additional options in SAAM II to define and use refined parameters. This will cover the following:

- 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.
- 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.
- Some models such as the commonly used two-compartment model can be re-parameterized based upon the desired secondary parameters.
- 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. 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.
- SAAM II has implemented a partial Bayesian option. 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.

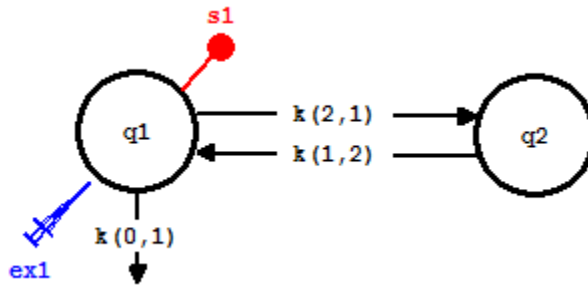
Part 1. a. Work with the Parameters dialog box

This part of the tutorial will illustrate the very basic operations of the **Parameters** dialog box.


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_Para**.
 - a. The file **study_0_Para.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.
 - a. In the **SAAM II Toolbox**, click **Experiment**. The model of the experiment will appear as follows:



This is the experimental model developed and used in the **Getting Started with Compartmental** tutorial. The difference is that no parameter values have been specified. If you examine the **Data** window, or the specifications for **ex1** or **s1**, you will find the study file is complete except for the parameter values. The sample equation is “ $s1=q1/vol$ ” so *vol* is a parameter.

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

Name	Type	Current	Low Limit	High Limit
k(0,1)	Adj			
k(1,2)	Adj			
k(2,1)	Adj			
vol	Adj			

Name: k(0,1) Value:

Type: Fixed Adjustable Low Limit:

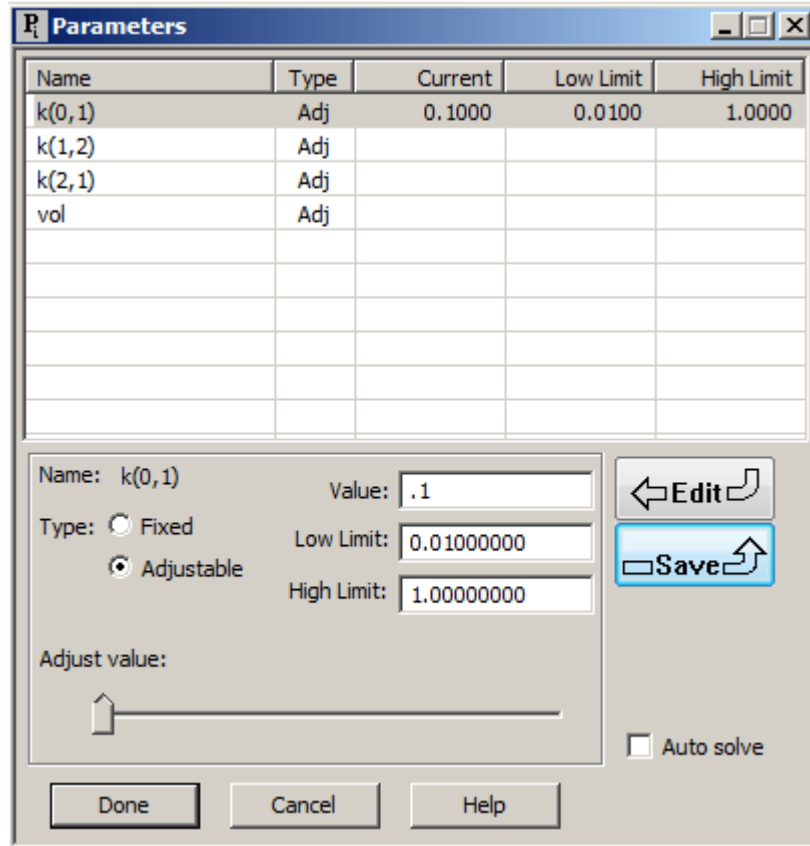
High Limit:

Adjust value:

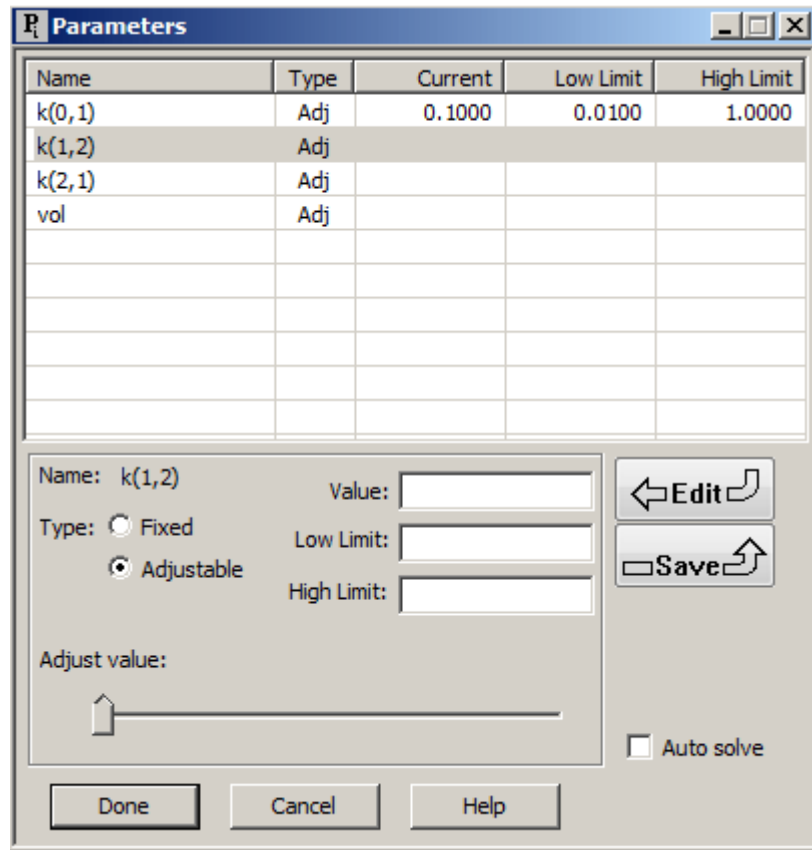
Auto solve

Notice that $k(0,1)$ is selected and that its type is **Adjustable**.

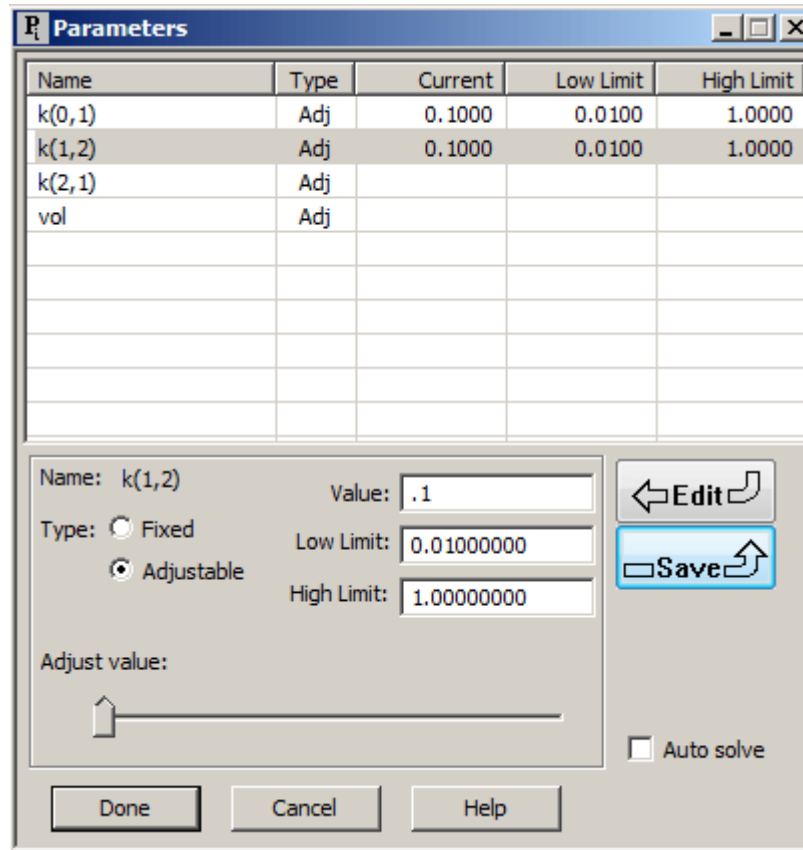
- a. Type “0.1” in the **Value** box, and click **Save**. SAAM II will automatically generate **Low** and **High** limits that are an order of magnitude smaller and larger than the initial value. The **Parameters** dialog box will appear as follows:



- b. Single-click $k(1,2)$ to select it. Notice $k(1,2)$ is highlighted, but the information in the pane beneath the **Parameters** window has not changed. The **Parameters** dialog box will appear as follows:



- c. Click **Save**. The values that you entered originally for $k(0,1)$ now appears as the values for $k(1,2)$. The **Parameters** dialog box will appear as follows:



- d. Double-click $k(2,1)$ to select it. Notice the name changes from $k(0,1)$ to $k(2,1)$ beneath the **Parameters** window, and that the **Value**, **Low Limit** and **High Limit** boxes have been cleared. The **Parameters** dialog box will appear as follows:

Parameters

Name	Type	Current	Low Limit	High Limit
k(0,1)	Adj	0.1000	0.0100	1.0000
k(1,2)	Adj	0.1000	0.0100	1.0000
k(2,1)	Adj			
vol	Adj			

Name: k(2,1) Value:

Type: Fixed Low Limit:

Adjustable High Limit:

Adjust value:

Auto solve

Done Cancel Help

← Edit ↩

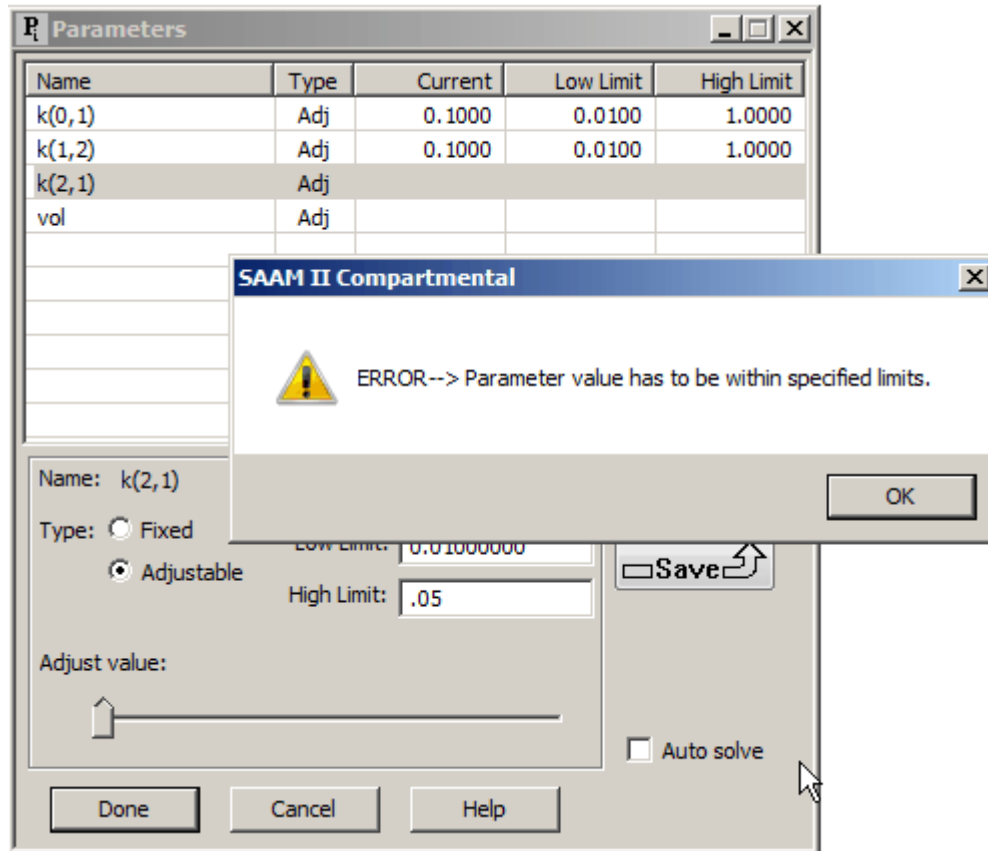
□ Save ↗



Single-clicking versus double-clicking parameters. There are occasions when you will be entering the same **Value**, **Low Limit** and **High Limit** for a number of parameters. If this is the case, then once you have entered the values for one parameter, you can single-click on each of the parameters to select them, and click **Save** to associate the current **Value**, **Low Limit** and **High Limit** with that parameter. Double-clicking a parameter will make it active and clear the **Value**, **Low Limit** and **High Limit** boxes so you can enter entirely new values.



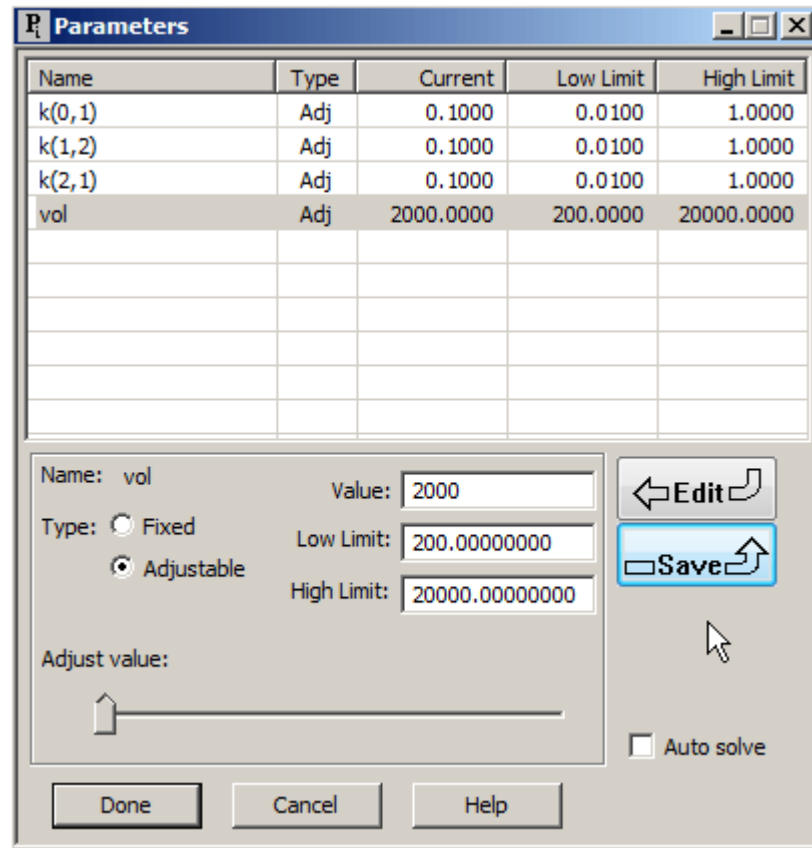
- e. For $k(1,2)$, enter “0.1” in the **Value** box, “0.01” in the **Low Limit** box and “0.05” in the **High Limit** box. Click **Save**. The following warning message will appear shown below superimposed on the **Parameters** dialog box:





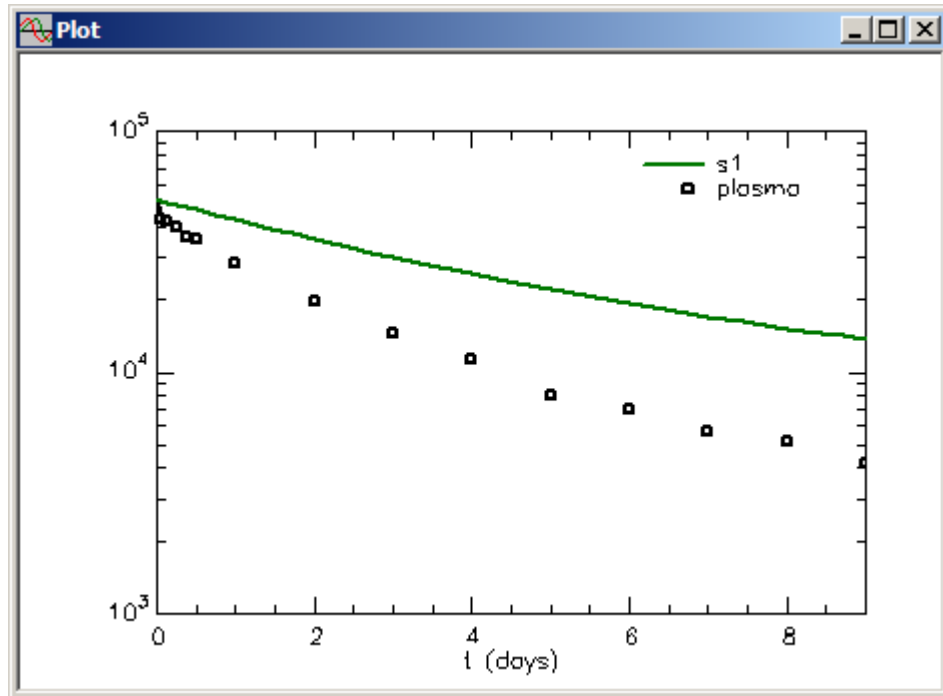
*Default low and high parameter limits. If you enter **Low Limit** and **High Limit** values directly, SAAM II will check to be sure that the **Value** that you entered for the parameter is within these limits.*



- f. To fix the problem, click “OK” in the warning message box. Then enter “1” in the **High Limit** box, and click **Save**.
- g. Double-click *vol* to select it. Type “2000” in the **Value** box, and click **Save**. The **Parameters** dialog box will appear as follows:



- h. Click **Done**.
5. 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:



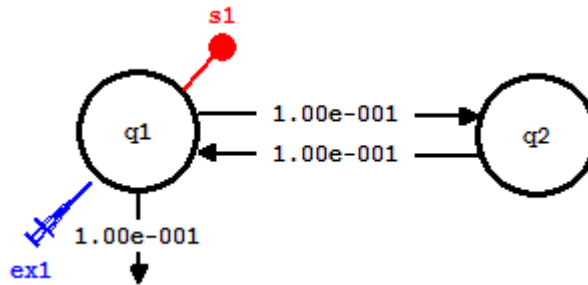
e. Close the **Plot** window.

You may continue to work with the **Parameters** dialog box in Part 1.b. of this tutorial. Here you will learn some of the steps involved in hand-fitting your model to the data. If you do not wish to continue working with the **Parameters** dialog box, you may **Quit** the **SAAM II Compartmental** application.

Part 1.b.1 Hand-fit the model to the data.

It is always a good idea to hand-fit the model to the data. In this way, you will learn which of the model parameters affect the different parts of the model solution. When you hand-fit your model to your data, you will change the values of the parameters in the **Parameters** dialog box.

1. In the **View** menu, click **Model Labels**, and then click **Values**. Your model will appear as follows:




The names of the transfer $k(i,j)$ have changed to their current numerical value.



Model labels. You have the option to have the current values for the parameters appear associated with your model. If the values, or name, do not appear, this is because your compartments are too close together. Move the compartments farther away from each other.



2. From the initial solution, it would appear that $k(0,1)$ needs to be increased.
 - a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar**, click **Parameters** . The **Parameters** dialog box will open.
 - b. Change the **Value** of $k(0,1)$ from “0.1” to “0.2”. There is no need to change the **Low** or **High Limits**. Click **Save**. The **Parameters** dialog box will appear as follows:

Name	Type	Current	Low Limit	High Limit
k(0,1)	Adj	0.2000	0.0100	1.0000
k(1,2)	Adj	0.1000	0.0100	1.0000
k(2,1)	Adj	0.1000	0.0100	1.0000
vol	Adj	2000.0000	200.0000	20000.0000

Name: k(0,1) Value: 0.2

Type: Fixed Low Limit: 0.01000000

Adjustable High Limit: 1.00000000

Adjust value:

_____↑_____

Auto solve

Done Cancel Help

← Edit ↩

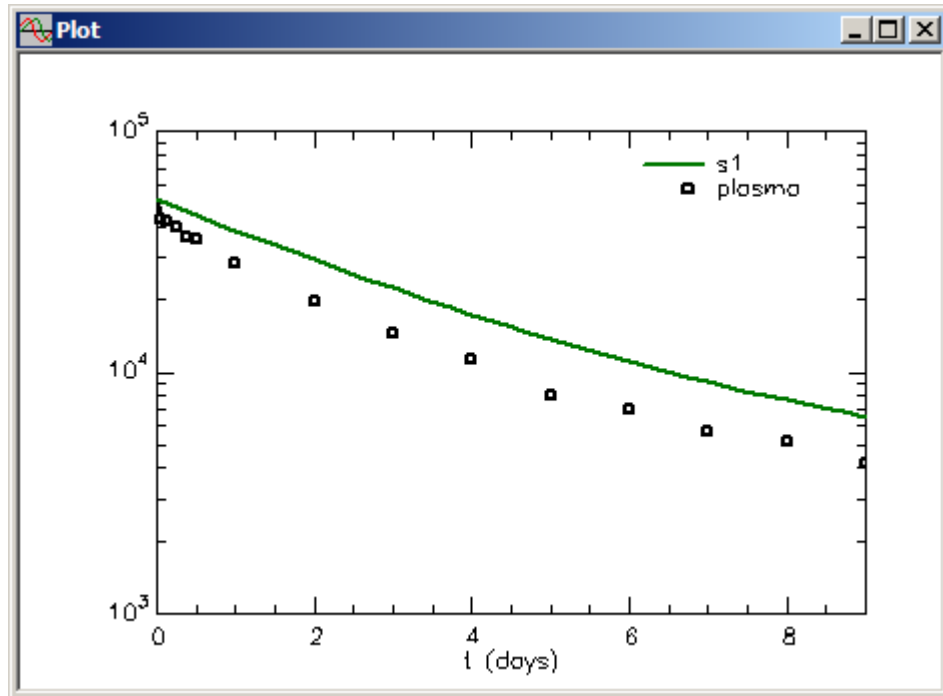
Save ↗



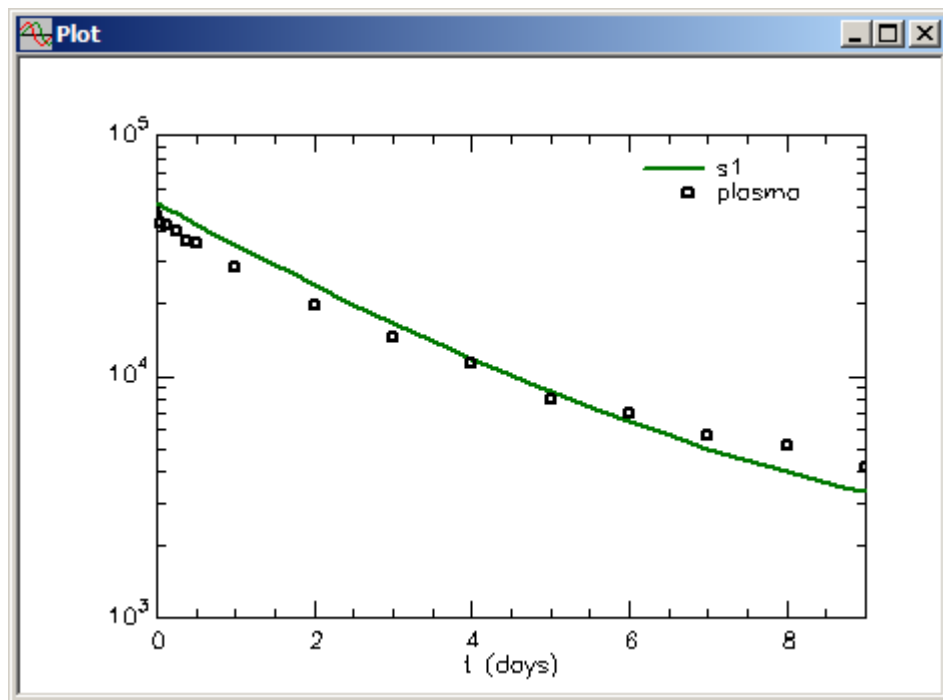
Hand-fitting. When you are hand-fitting your model to your data, you are changing the numerical values of your model parameters. In general, during this process, it is not necessary to adjust the **Low Limit** and/or **High Limit** each time you change a value. An exception is when you set a value of a parameter below the **Low Limit**, or above the **High Limit**; then you will need to change the appropriate value. You should also change these values if, after you hand-fit your model, a particular parameter value is near a limit, and you are proceeding to Fit your model to your data.



- c. Click **Done**.
3. Re-Solve the model and view the solution. The plot, in semilog mode, will appear as follows:

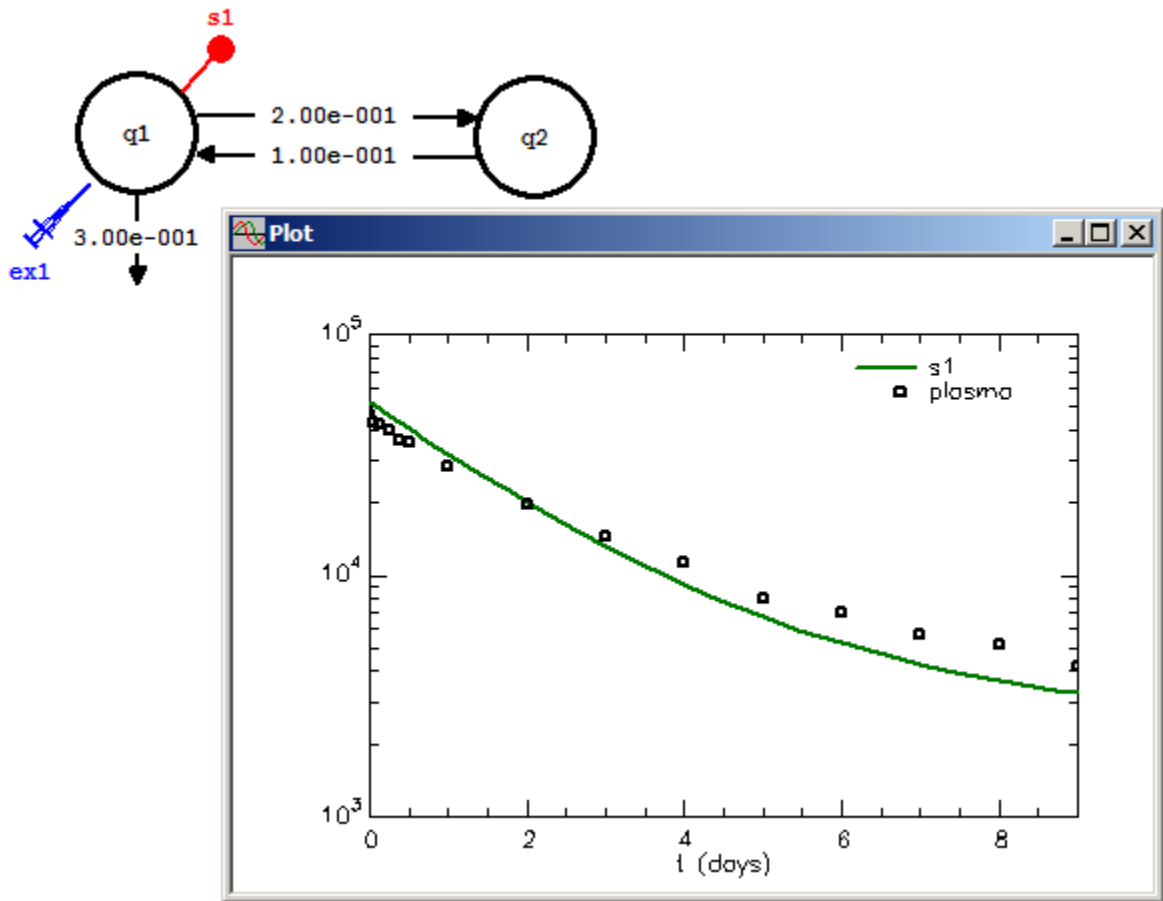


4. The model predicted value is still not decaying fast enough. Leave the **Plot** window open. Set the **Value** of $k(0,1)$ equal to "0.3". When you close the **Parameters** dialog box, the previous solution will disappear because the parameter values have changed. **Re-Solve** the model. The plot will appear as follows:



5. Leave the **Plot** window open. The initial decay is not fast enough. Yet if you increase $k(0,1)$ again, the model predicted values will decay faster than the data. Hence try

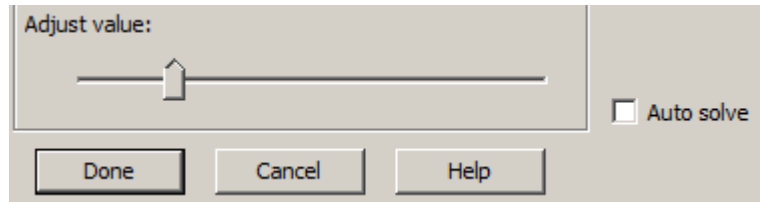
increasing $k(2,1)$ from “0.1” to “0.2”. When you Re-Solve the model, your model and plot will appear as follows:



6. You see that increasing $k(2,1)$ has accentuated the break in the model predicted curve. You should try adjusting $k(1,2)$ to see how this affects the model solution. Finally, you will note that the *vol* is a little off because the model predicted value at time zero is greater than the data. Thus *vol* needs to be increased a little, say to 2200 or 2300.
7. When you have finished your hand-fitting exercise, you may proceed **Quit** the **SAAM II Compartmental** application, or you can proceed to the next section to learn how to use the SAAM II parameter slider bar.

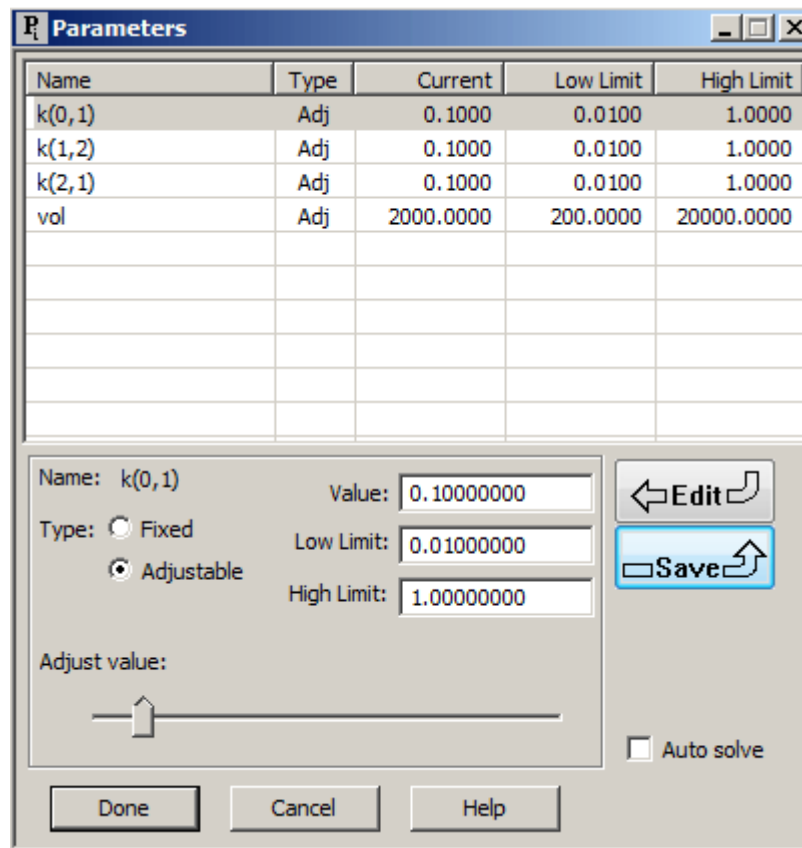
Part 1.b.2 Hand-fit the model to the data using the parameter slider bar

The parameter slider bar is another convenient way to hand fit your model to your data. The slider bar is in the lower part of the **Parameters** dialog box:

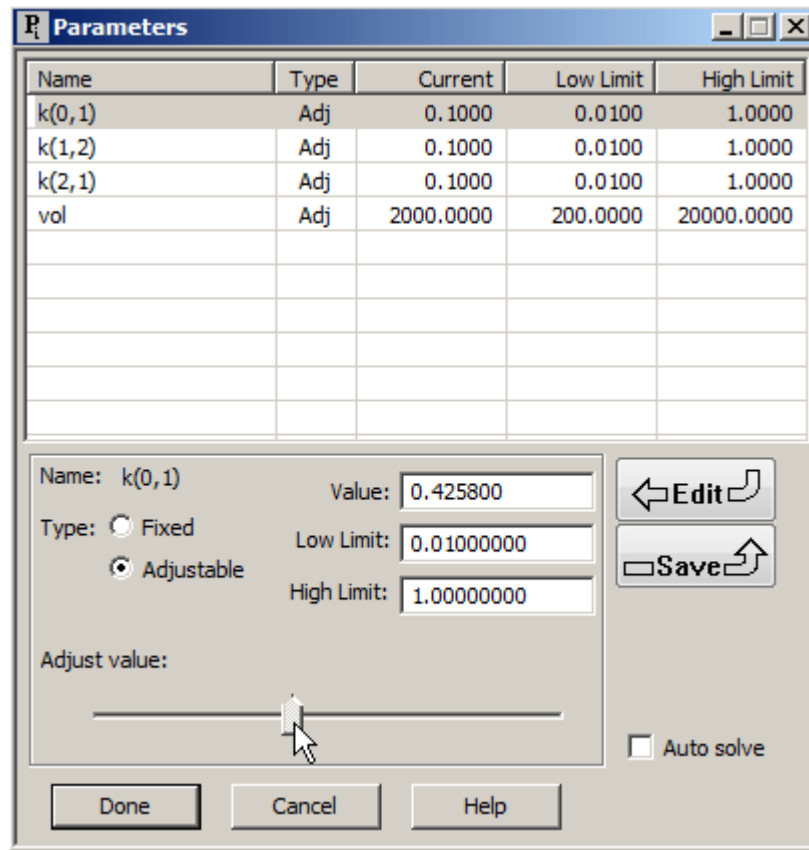


Moving the **adjustment tool**, you can change the value of the selected parameter between its **Low Limit** and **High Limit**. To solve with the new value, you can click **SOLVE** in the **Compute** menu. Alternatively, there is an **Auto solve** click box. If this box is checked, after you move the **adjustment tool** to the desired value and release the mouse, your model will solve and your plot, if open, will be updated.

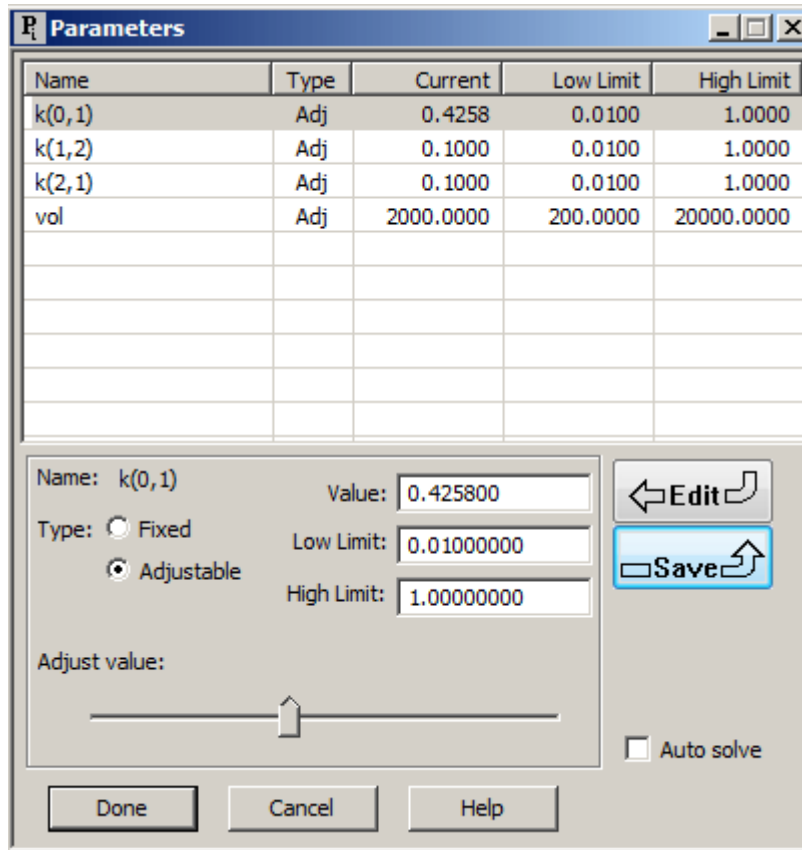
1. Reset your parameter values to the original starting values. The **Parameters** dialog box will appear:



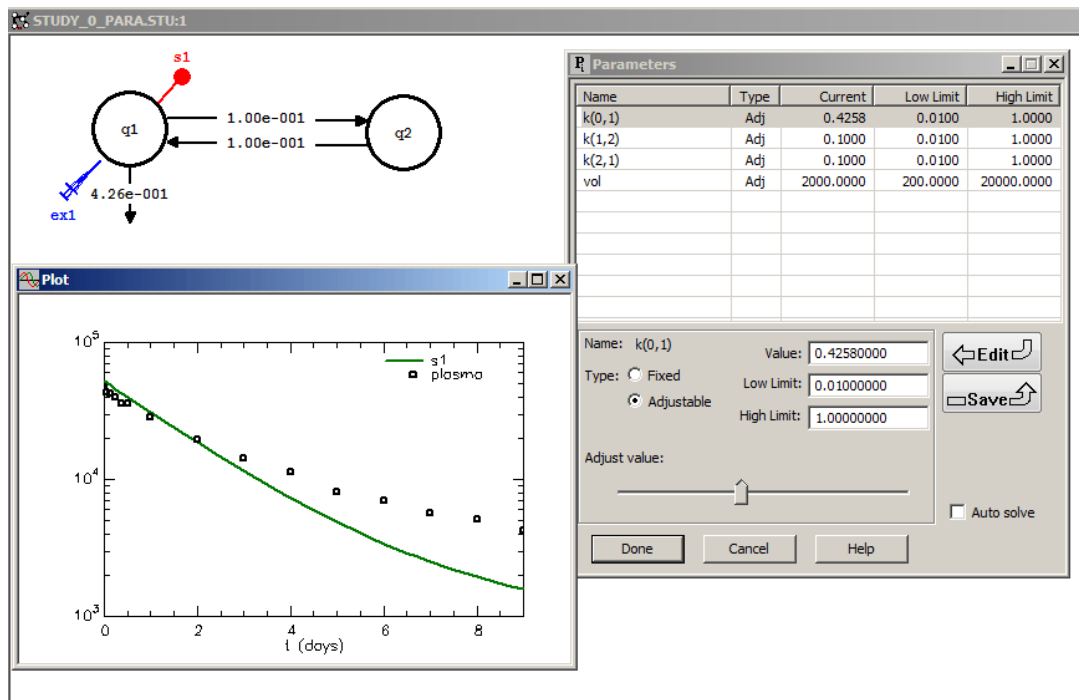
2. With $k(0,1)$ active, slide the **adjustment tool** to the right to increase the value. For example:



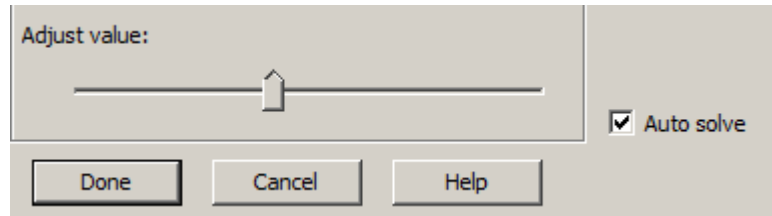
Notice the mouse is still on the **adjustment tool**, so while the value may be 0.4258 it has not been updated as the **Current** value for $k(0,1)$. Release the mouse, and click **Save**. The **Parameters** dialog box will appear:



3. Click **SOLVE**. Plot you solution. Your **Drawing Canvas** will appear, in part, as follows:

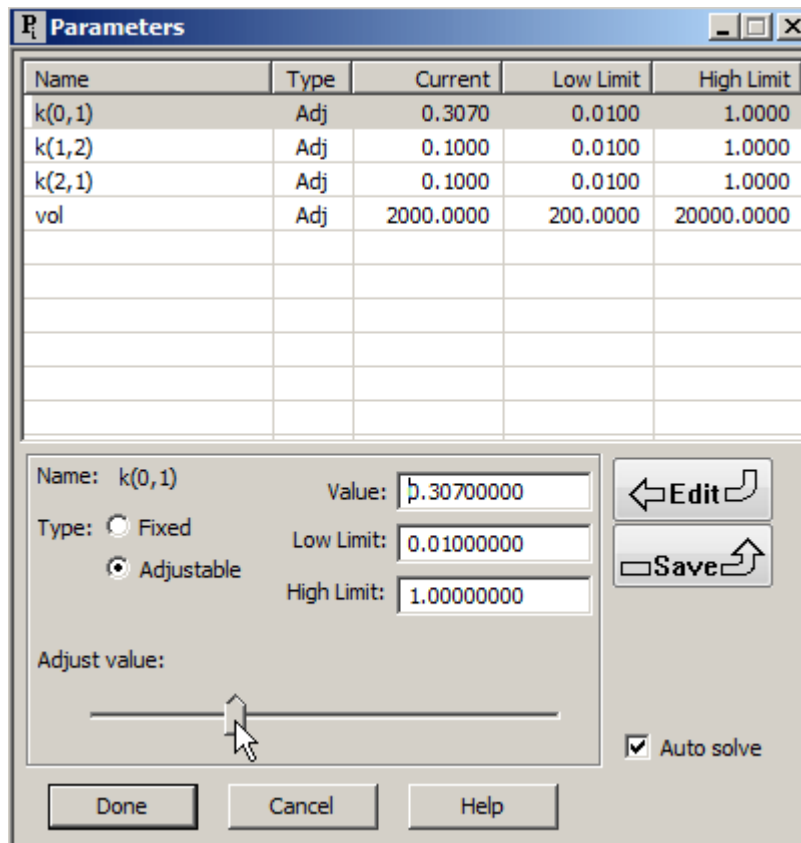


4. In the **Parameters** dialog box, click **Auto solve**. The **Parameters** dialog box will appear:



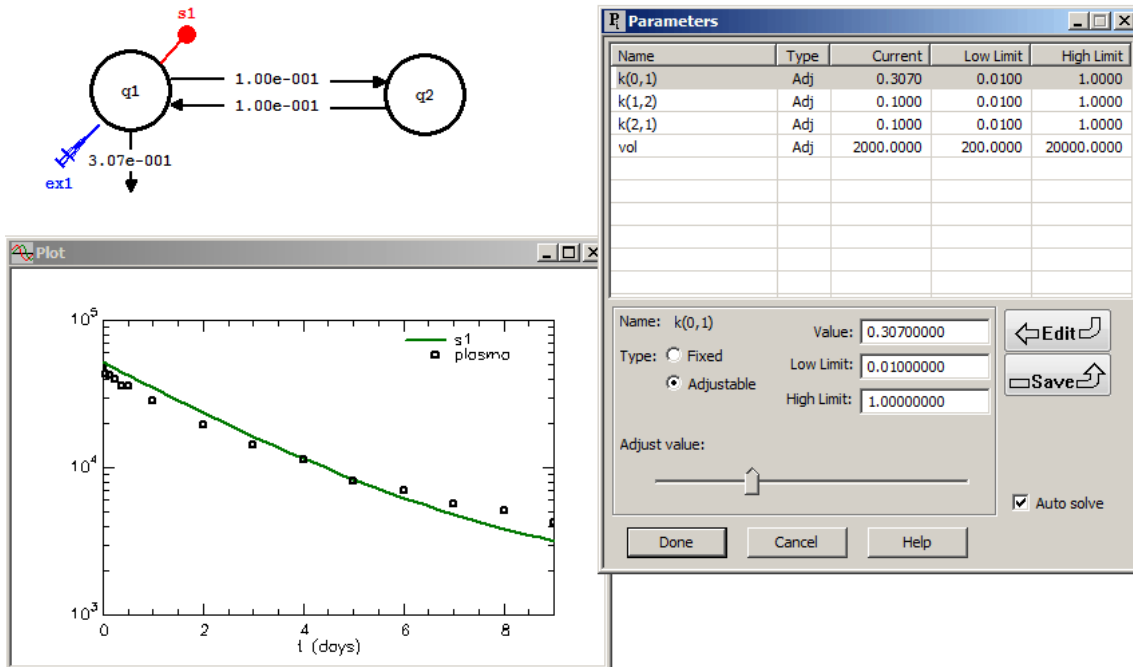
If you wish to have SAAM II re-**Solve** your model when you release the mouse from the **adjustment tool**, you activate **Auto solve**.

5. Move the **adjustment tool** left to a lower value for the parameter. For example:



Notice that the new value, as a result of **Auto solve** being checked, has been inserted as the **Current value** for $k(0,1)$.

6. Release the mouse. Your model will automatically **SOLVE**, and your **PLOT** will be updated as follows:

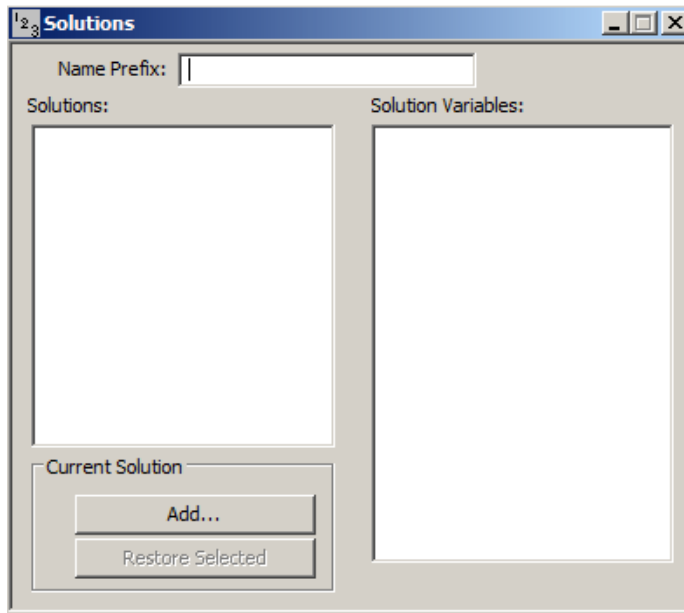


You can continue to explore the **Adjust value** slide bar. When you have finished, **Quit** the **SAAM II Compartmental** application. Do not save the changes to **study_0_Para** since, if you do, the **Parameters** dialog box will contain the last set of values you entered.

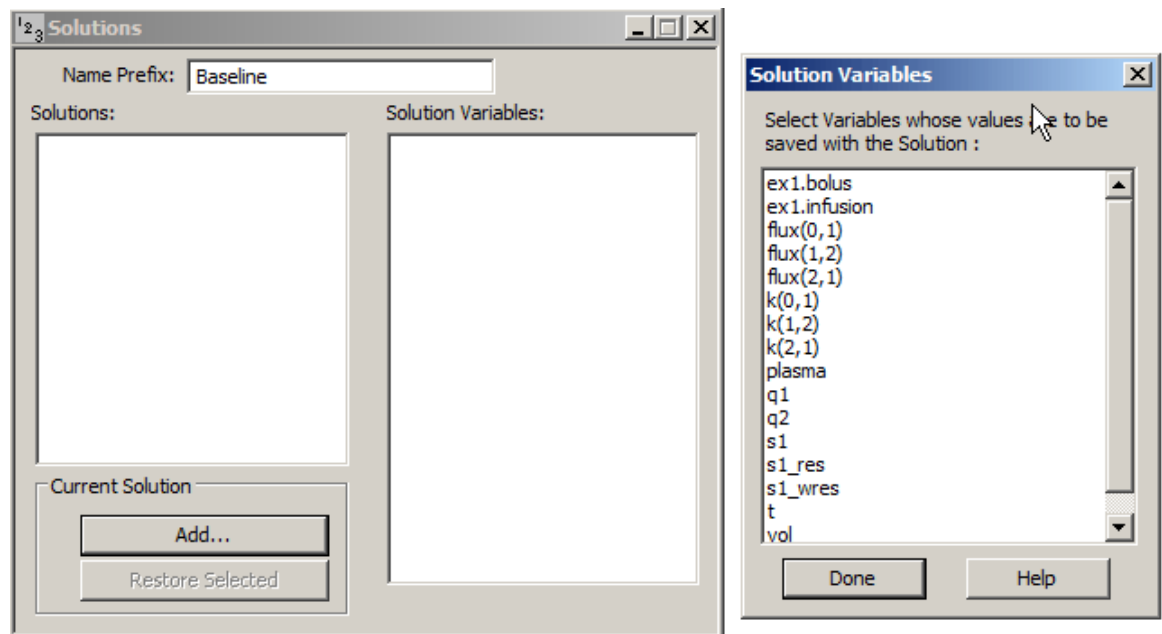
Part 1.b.c Hand-fit the model to the data using the parameter slider bar: comparing to a baseline solution

When hand-fitting a model to data, one often wants to compare a solution to a baseline solution. In SAAM II, this involves using **Solutions** in the Compute menu.

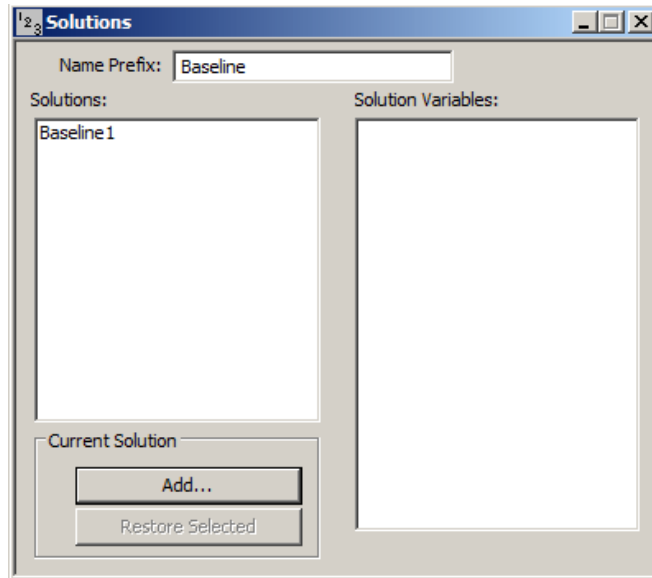
1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.
2. Open the **SAAM II Compartmental** study file **study**, and click on **Exper**. The Experiment will open.
3. **Solve** the model.
4. Click on the **Compute Menu**, and select **Solutions**. The **Solutions** dialog box will open (for more information on saving solutions, see the Tutorial on Saving Solutions):



Enter “Baseline” in the **Name Prefix** box. Click **Add**. The **Solutions Variables** dialog box will open.

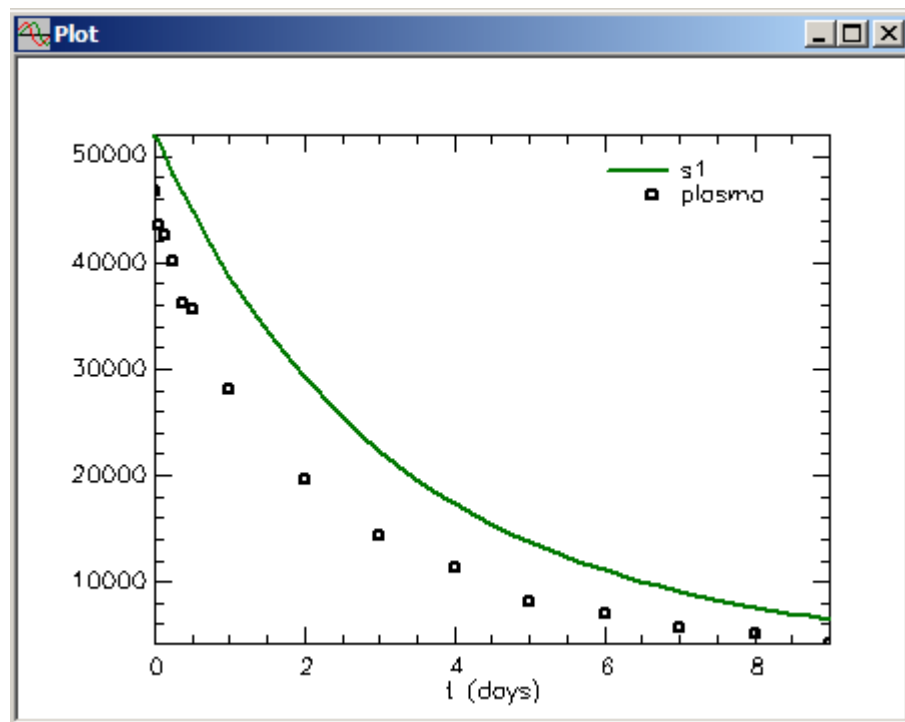


The baseline solution in which you are interested is *s1*. Click *s1*, and click **Done**. The **Solutions** dialog box will appear as follows:

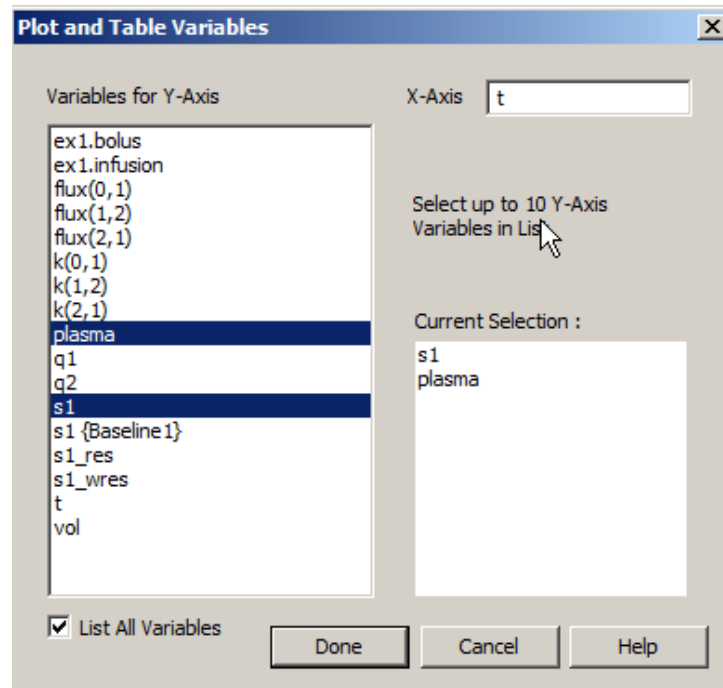


Close the **Solutions** dialog box.

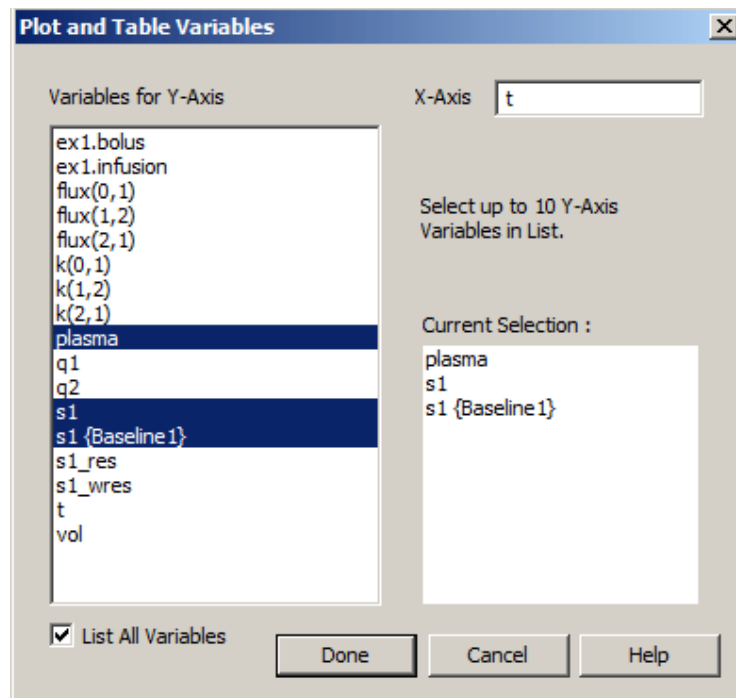
5. Change the value of, say $k(0,1)$ to 0.2, and SOLVE. Plot the solution; it will appear:



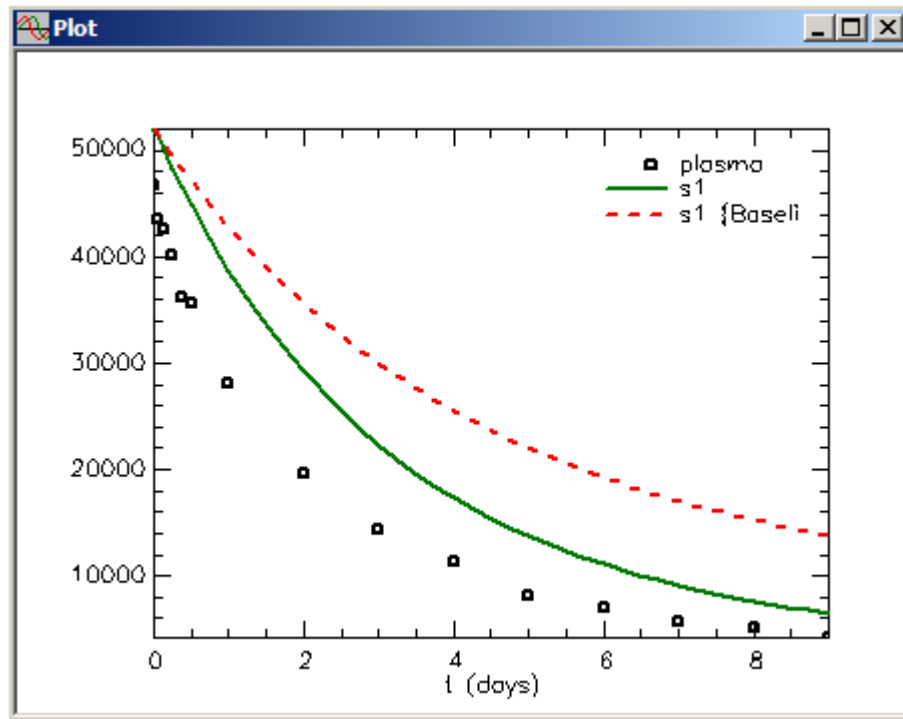
6. Compare this solution with the baseline solution.
 - a. Open the **PLOT AND TABLE VARIABLES** dialog box using either the **SET** menu or the **Select variables** tool in the **SAAM II Toolbox**. Check the **List All Variables** check box so all variables are listed:



- b. Notice *s1* and *plasma* are in the **Current Selection** pane. Hold the CTRL key down, and click *s1 {Baseline 1}*; this will now appear in the **Current Selection** pane:

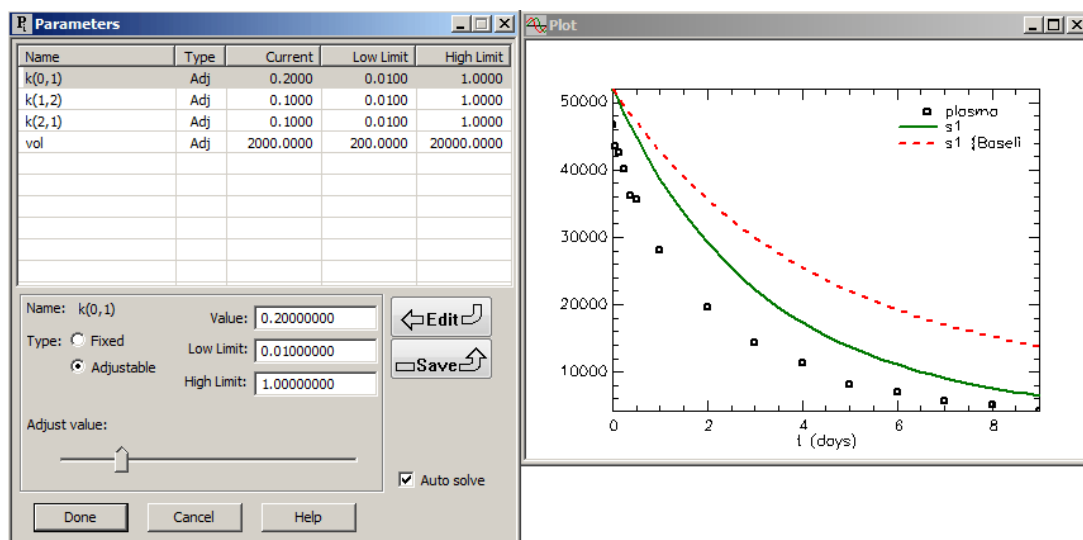


- c. Click Done. Your plot will appear:



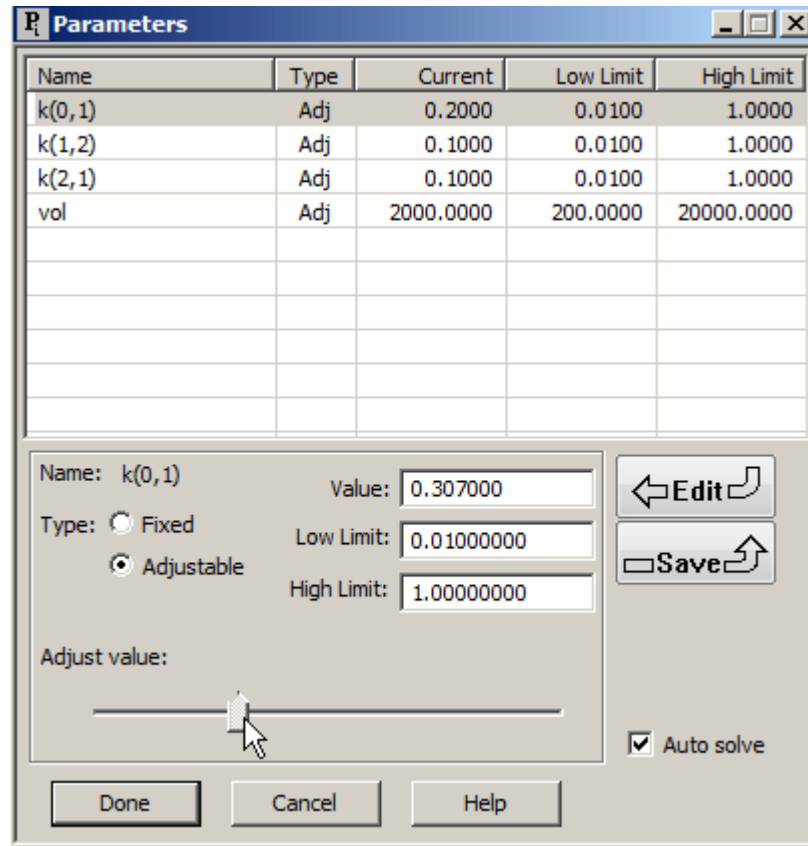
Be sure to leave this plot open on your **Drawing Canvas**.

7. Using the parameter slider bar with **Auto solve** selected to compare solutions.
 - a. Open the **Parameters** dialog box; the plot and dialog box will appear as shown below (be sure **Auto solve** is selected):

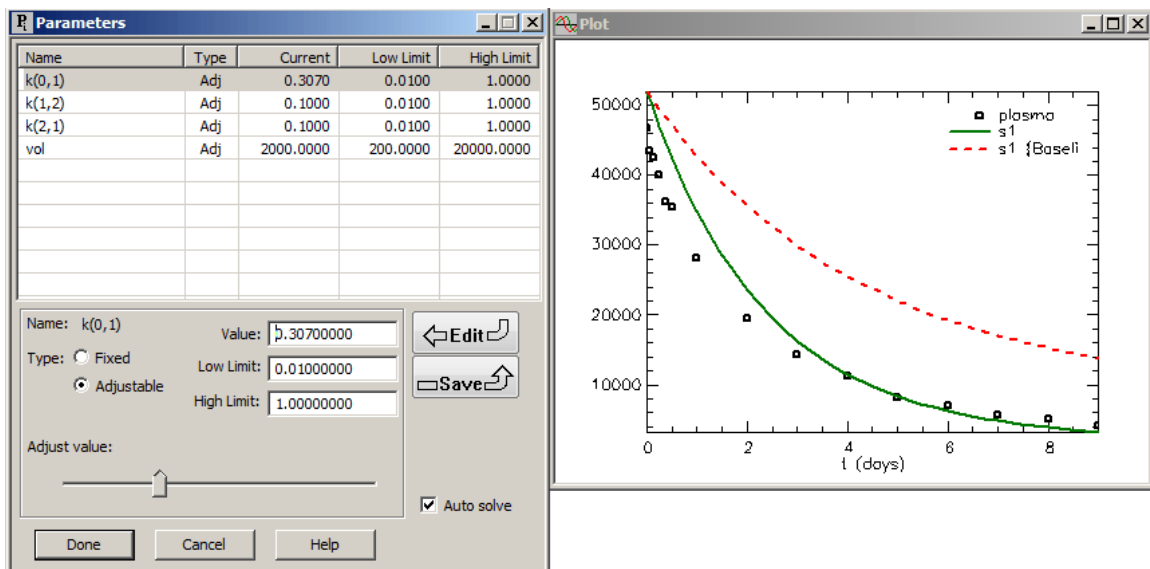


Remember the plot compares the current solution with $k(0,1)$ equal to 0.2 compared with the Baseline1 solution where $k(0,1)$ equals 0.1.

b. Move the slider bar to a value for $k(0,1)$ higher than 0.2; see below for example:



When you release the mouse, because **Auto solve** is selected, your model will solve with the new parameter value and your plot will be updated:

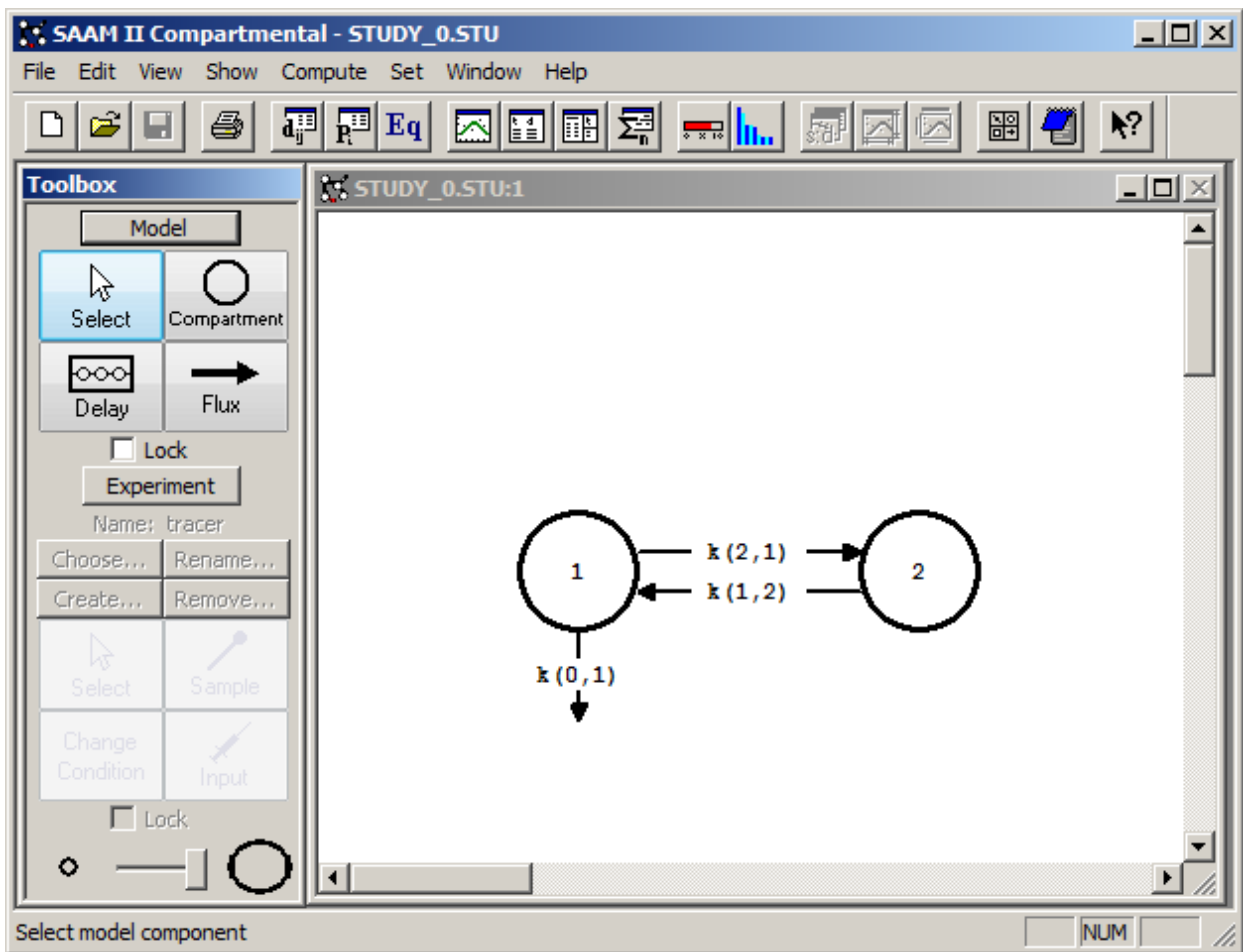


You can now scroll among different parameter values for $k(0, I)$, and compare the solution to the baseline solution. You can also change parameters to investigate, and, by using **Save Solutions**, create another “baseline” solution for comparison purposes. You may also fit your model and save the base solution; Use **Adjust value** and **Auto solve** to view the effect of changing parameters to the fitted solution. For more information about **Save Solutions**, see the Save Solutions tutorial.

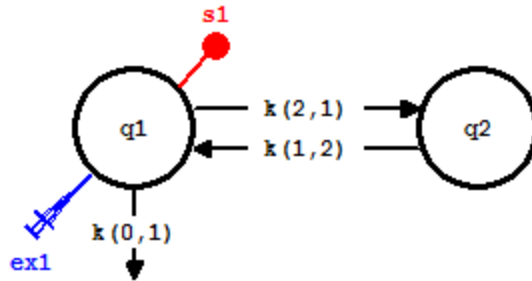
Quit the **SAAM II Compartmental** application. Do not save the changes to **study_0_Para** since, if you do, the **Parameters** dialog box will contain the last set of values you entered.

Part 2. Using Transfer and Loss Attributes dialog boxes.

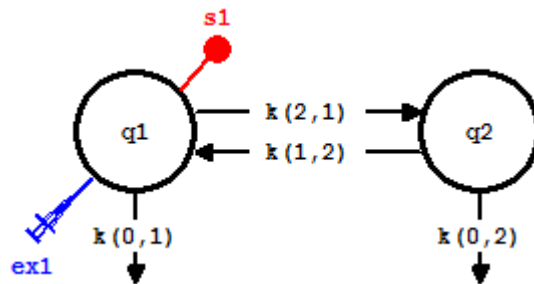
1. **Start the SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.
2. Open the **SAAM II Compartmental** study file **study_0**.
 - a. The file **study_0.stu** should appear in the file list; if it does not, find the folder where you put this file.
 - b. In the **File** 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. Enter the parameter values as shown in the following **Parameters** dialog box:

Parameters

Name	Type	Current	Low Limit	High Limit
k(0,1)	Adj	0.1000	0.0100	1.0000
k(0,2)	Adj	0.1000	0.0100	1.0000
k(1,2)	Adj	0.1000	0.0100	1.0000
k(2,1)	Adj	0.1000	0.0100	1.0000
vol	Adj	2000.0000	200.0000	20000.0000

Name: k(0,2) Value: .1

Type: Fixed Low Limit: 0.01000000

Adjustable High Limit: 1.00000000

Adjust value:

Auto solve

Done Cancel Help


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

- a. In the **View** menu, click **Model Labels**, and then click **Values**.

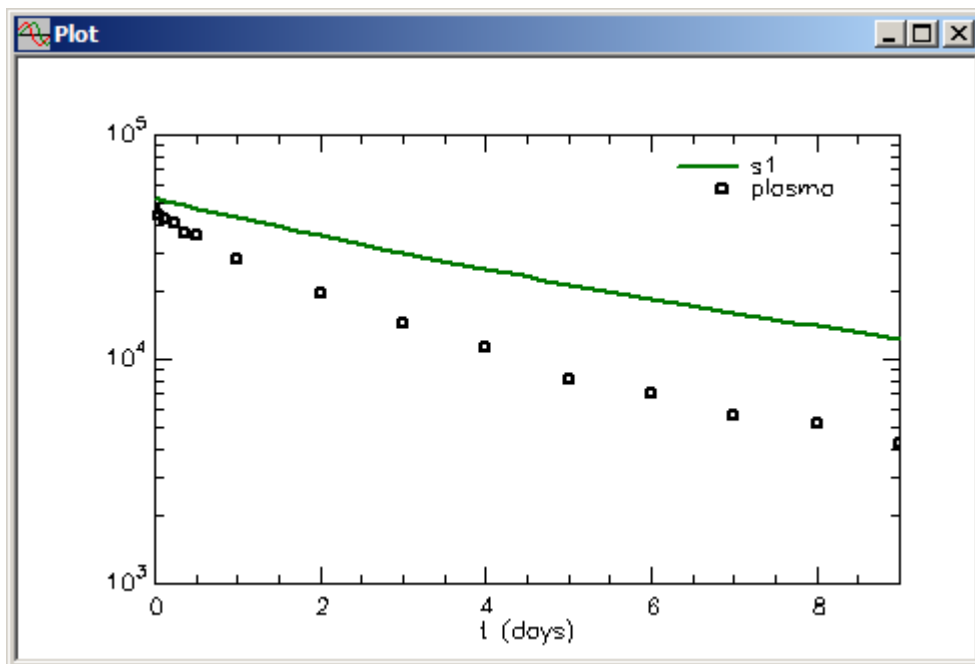


Model labels. You have the option to have the current values for the parameters appear associated with your model. If the values, or name, do not appear, this is because your compartments are too close together. Move the compartments farther away from each other.

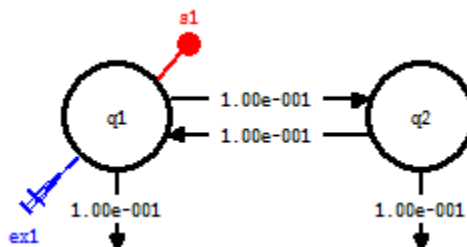


- b. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar**, click **Solve** .


- c. Plot the solution. The plot will appear as follows:

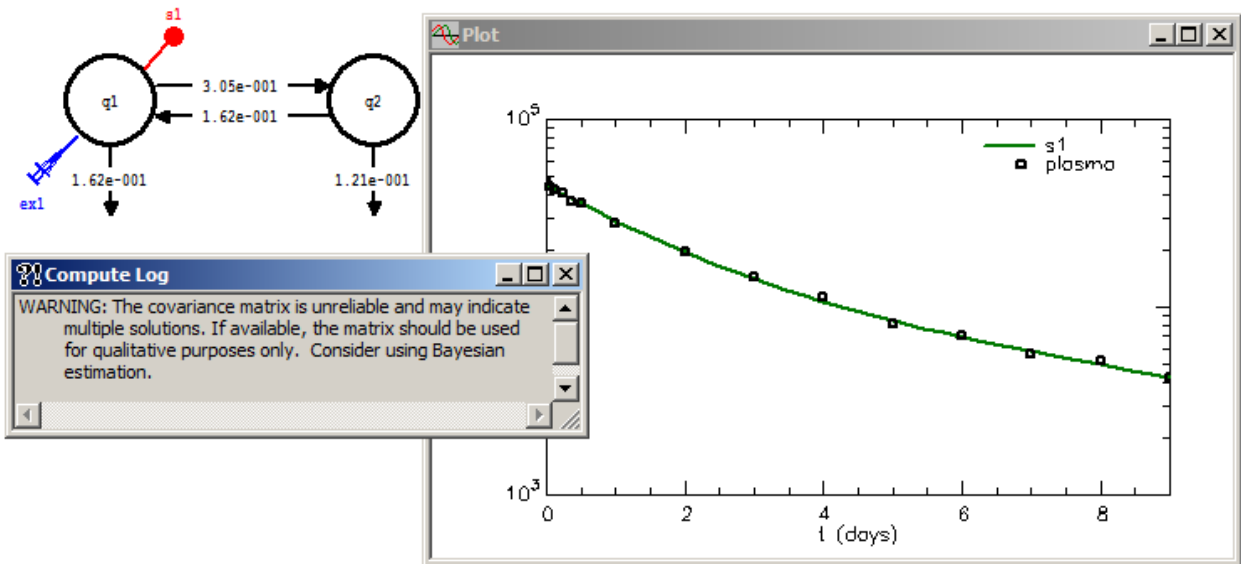


The model will appear as follows:



You can see the current values for the $k(i,j)$ appear associated with the transfer and loss arrows. Obviously the model solution is not very satisfactory, but the parameter estimates are still close enough to Fit the model to the data.


6. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar**, click **Fit** . The following warning message will appear together with the model and the plot:



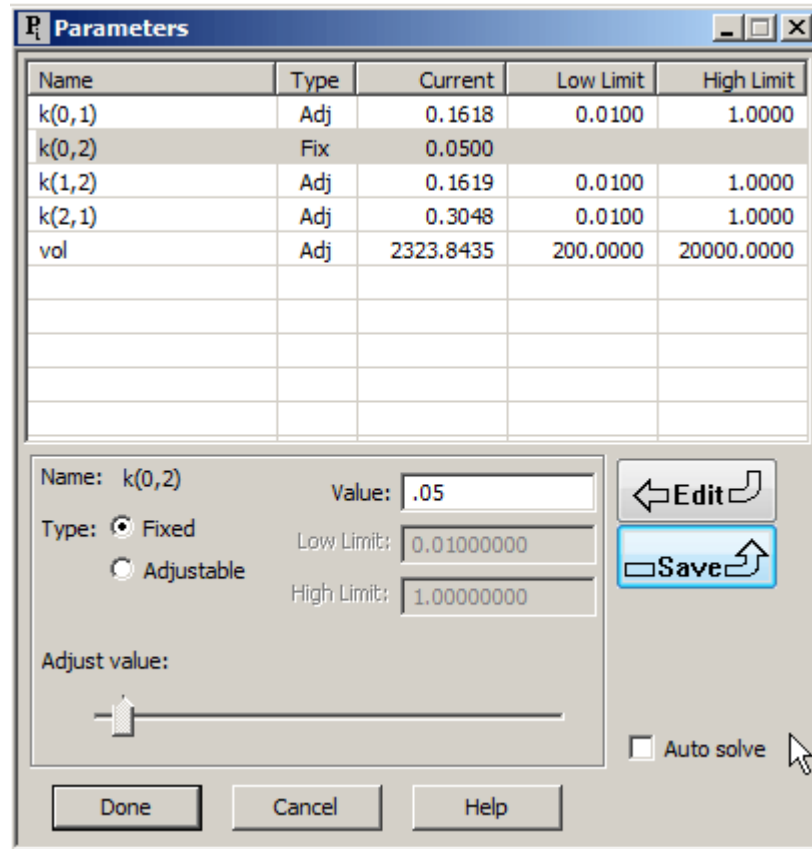
First you can see the numerical values of the parameters and the fact that a good fit of the model to the data has been obtained. However the warning message indicates that the covariance matrix is unreliable and may indicate multiple solutions. The covariance matrix unreliable message means that SAAM II is having problems fitting your model to your data. This, together with the warning there may be multiple solutions, usually means you have too many parameters in your model, i.e. there are more parameters in the model than can be estimated from the data. The last part of the warning message, consider using Bayesian estimation, will be considered in a later part of this tutorial.

The problem is how to reduce the number of parameters. There are several options which will be discussed below. The first will be fixing a specific parameter.

Close the **Compute Log** and **Plot** window.

7. Fix $k(0,2)$ to a specified value – method 1.
 - 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 $k(0,2)$ to select it.

- c. Select the **Fixed** option.
- d. Type “0.05” in the **Value** box. Click **Save**. The **Parameters** dialog box will appear as follows:



The screenshot shows the 'Parameters' dialog box with a table of parameters and configuration options for the selected parameter 'k(0,2)'. The table lists parameters with their types, current values, and limits. The configuration section shows 'k(0,2)' is set to 'Fixed' with a value of '.05'. The 'Auto solve' checkbox is unchecked.

Name	Type	Current	Low Limit	High Limit
k(0,1)	Adj	0.1618	0.0100	1.0000
k(0,2)	Fix	0.0500		
k(1,2)	Adj	0.1619	0.0100	1.0000
k(2,1)	Adj	0.3048	0.0100	1.0000
vol	Adj	2323.8435	200.0000	20000.0000

Name: k(0,2) Value: .05

Type: Fixed Adjustable

Low Limits: 0.01000000

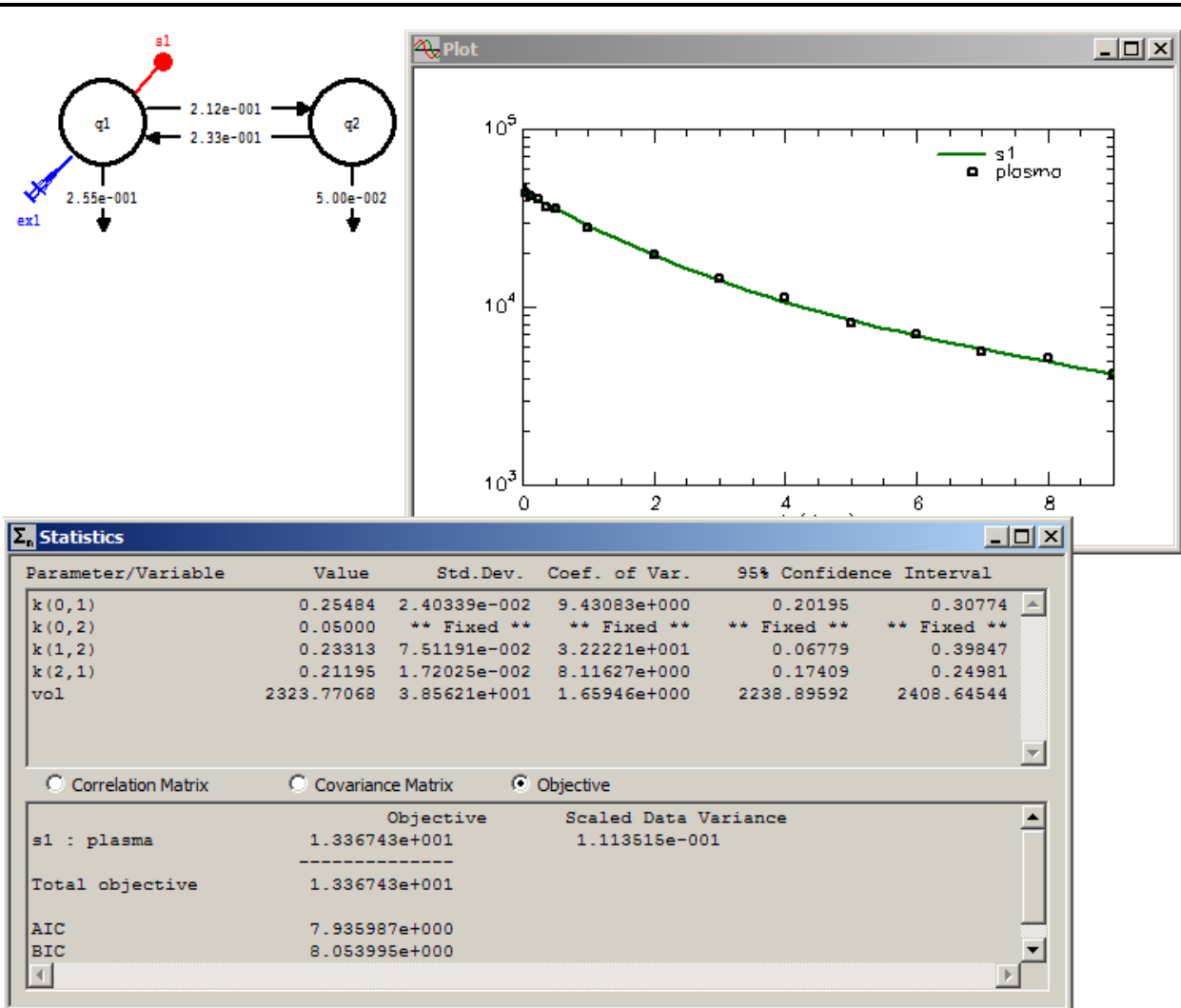
High Limits: 1.00000000

Adjust value:

Auto solve

Buttons: Done, Cancel, Help, Edit, Save

- e. Click **Done**.
- f. Re-**Fit** the model to the data. The results are summarized as follows:



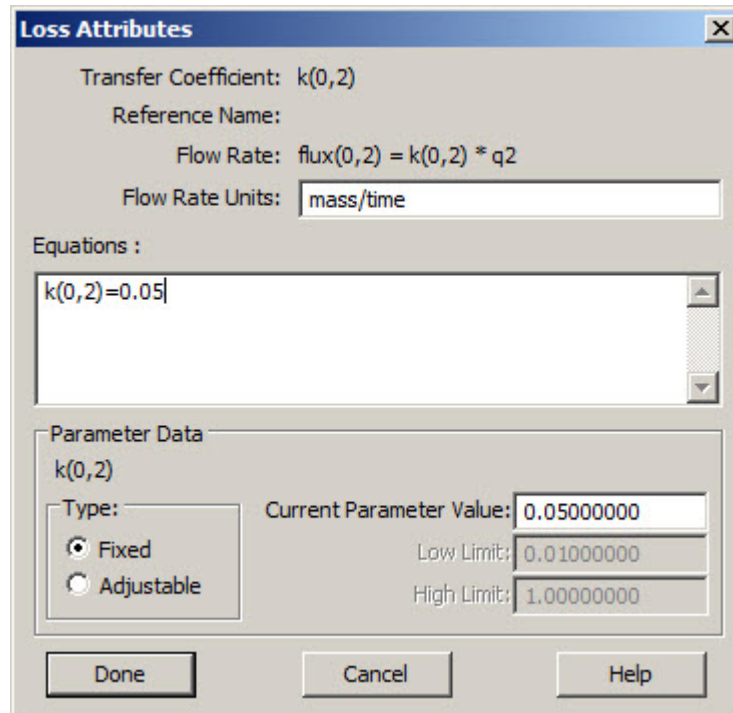
Fixed parameters. When you fix a parameter in the **Parameters** dialog box, it will appear in the dialog box with a **Value**, but no **Low Limit** or **High Limit**. When you “Fit” your model to the data, this parameter will not adjust. The value for the parameter will be displayed in the **Statistics** window following a “Fit”, but it will clearly be delineated as a fixed parameter.



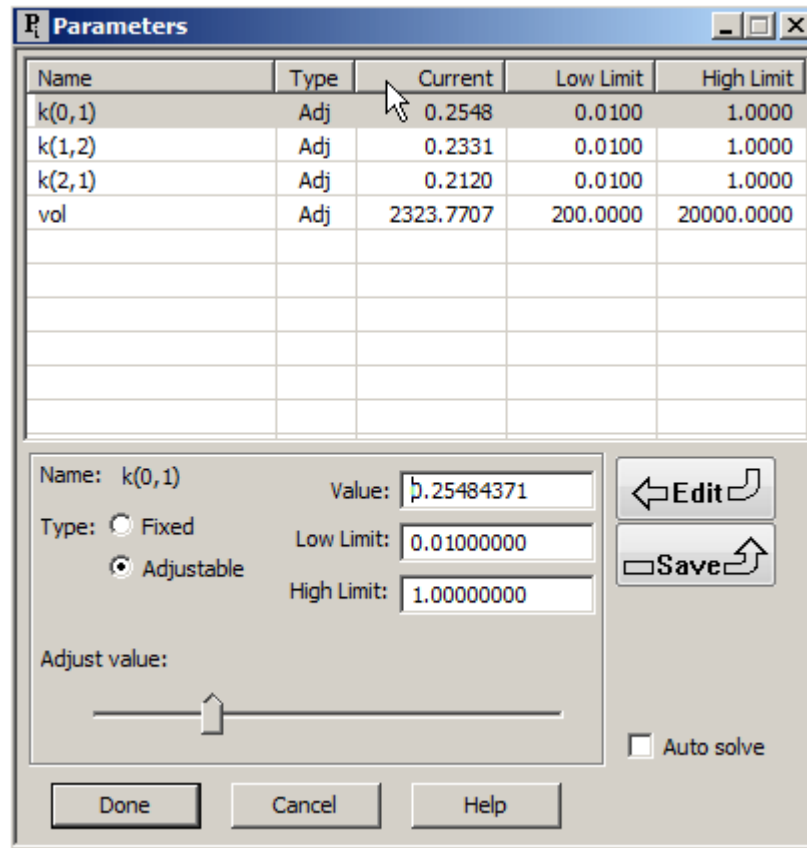
- g. Close the **Statistics** and **Plot** windows.
8. Fix $k(0,2)$ to a specified value – method 2.

There is another method to fix $k(0,2)$ to a specified value using the **Loss Attributes** dialog box.

-
- a. Double-click on the loss $k(0,2)$ from Compartment **q2** to open the **Loss Attributes** dialog box.
 - b. In the **Equations** pane, type “ $k(0,2) = 0.05$ ”. The **Loss Attributes** dialog box will appear as follows:



- c. Click **Done**. If you open the **Parameters** dialog box, it will appear as follows:



Notice $k(0,2)$ no longer appears as a parameter. The reason is that it has been defined as an equation in the **Loss Attributes** dialog box; SAAM II no longer recognizes it as a parameter to be listed in the **Parameters** dialog box.

- d. **Re-Fit** the model to the data. The results will be essentially identical to the above with the exception of the information in the **Statistics** window which, in this case, is shown as follows:

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
k(0,1)	0.25484	2.40339e-002	9.43083e+000	0.20195	0.30774
k(1,2)	0.23313	7.51191e-002	3.22221e+001	0.06779	0.39847
k(2,1)	0.21195	1.72025e-002	8.11627e+000	0.17409	0.24981
vol	2323.77068	3.85621e+001	1.65946e+000	2238.89592	2408.64544

	Objective	Scaled Data Variance
s1 : plasma	1.336743e+001	1.113515e-001

Total objective	1.336743e+001	
AIC	7.935987e+000	
BIC	8.053995e+000	

Notice $k(0,2)$ does not appear as a fixed parameter as it did previously. The reason is that it is now defined by an equation.



Parameters defined by an equation. What is the difference between this solution and the previous one? The difference is in the case above, $k(0,2)$ does not appear in the statistics window. In the first case, $k(0,2)$ is a parameter that appeared in the **Parameters** dialog box. It just happened to be a fixed parameter set to a specific value; this was reported in the **Statistics** window. In the case above, $k(0,2)$ is defined as an equation. It thus is no longer considered a parameter by SAAM II in terms of optimization.

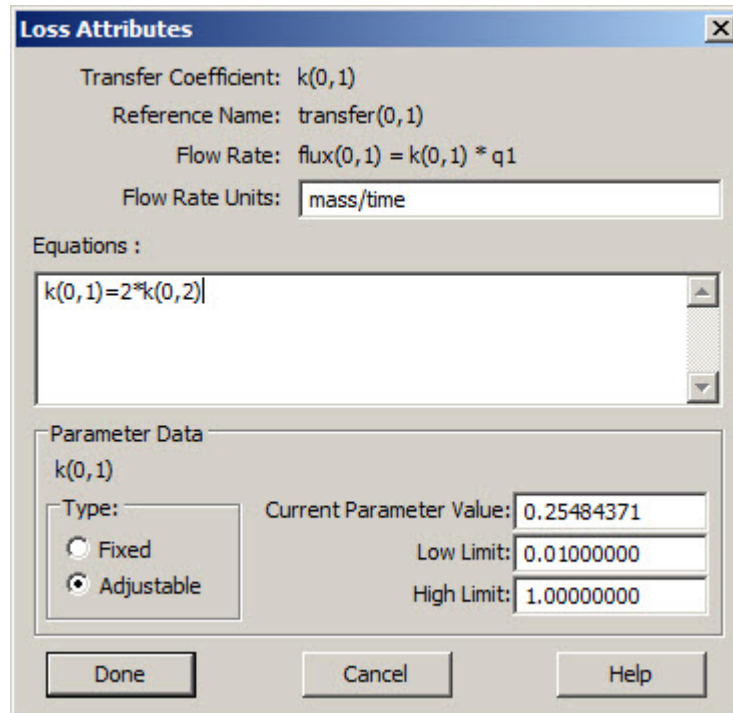


- e. Close the **Statistics** and **Plots** windows.
 - f. Open the **Loss Attributes** dialog box associated with $k(0,2)$, and delete the equation “ $k(0,2) = 0.05$ ”. Close the dialog box.
9. Write a constraint equation between $k(0,1)$ and $k(0,2)$.

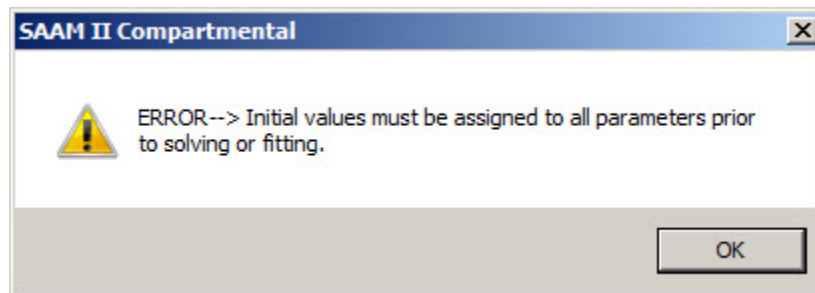
Suppose you know there is a relationship between $k(0,1)$ and $k(0,2)$. Suppose, for example, you knew that $k(0,1)$ was twice $k(0,2)$. How would you specify this in your model? This can be written “ $k(0,1) = 2*k(0,2)$ ”, or “ $k(0,2) = 0.5*k(0,1)$ ”. The former would be written in the **Loss Attributes** dialog box associated with $k(0,1)$; the latter with the **Loss Attributes** dialog box associated with $k(0,2)$.

- a. Double-click the loss $k(0,1)$ from Compartment **q1** to open the **Loss Attributes** dialog box.

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



- c. Click **Done**.
- d. Solve the model. The following warning message will appear:



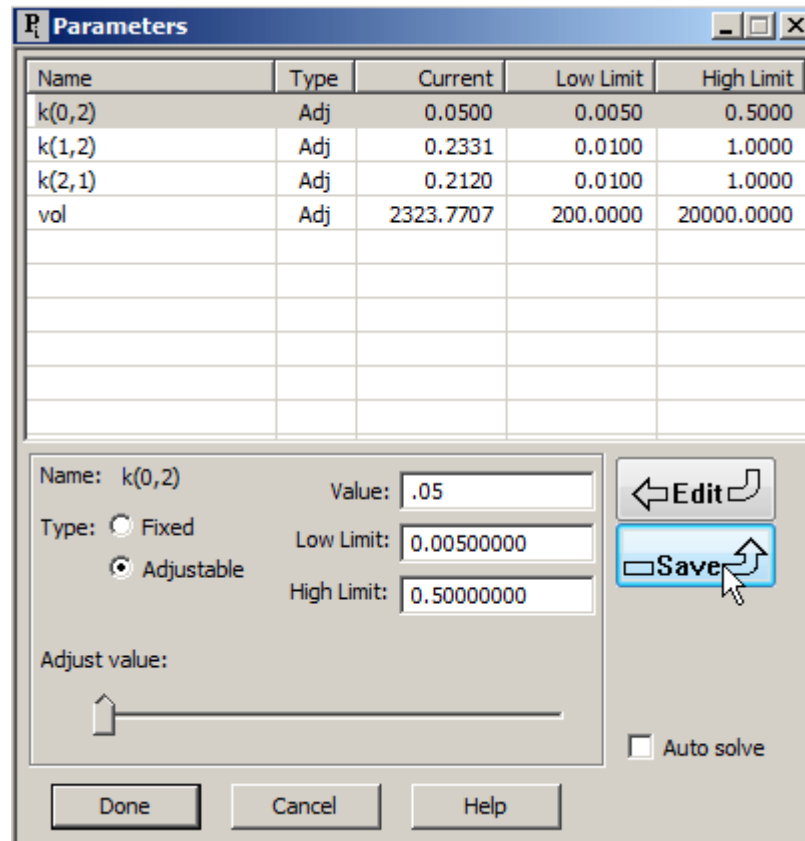
The warning message appears because a value for $k(0,2)$ has not been specified.

Click “OK”.

- e. Open the **Parameters** dialog box.
- (1) Double-click $k(0,2)$ to select it.
 - (2) Be sure $k(0,2)$ is set as an adjustable parameter.

(3) Type “0.05” in the **Value** box.

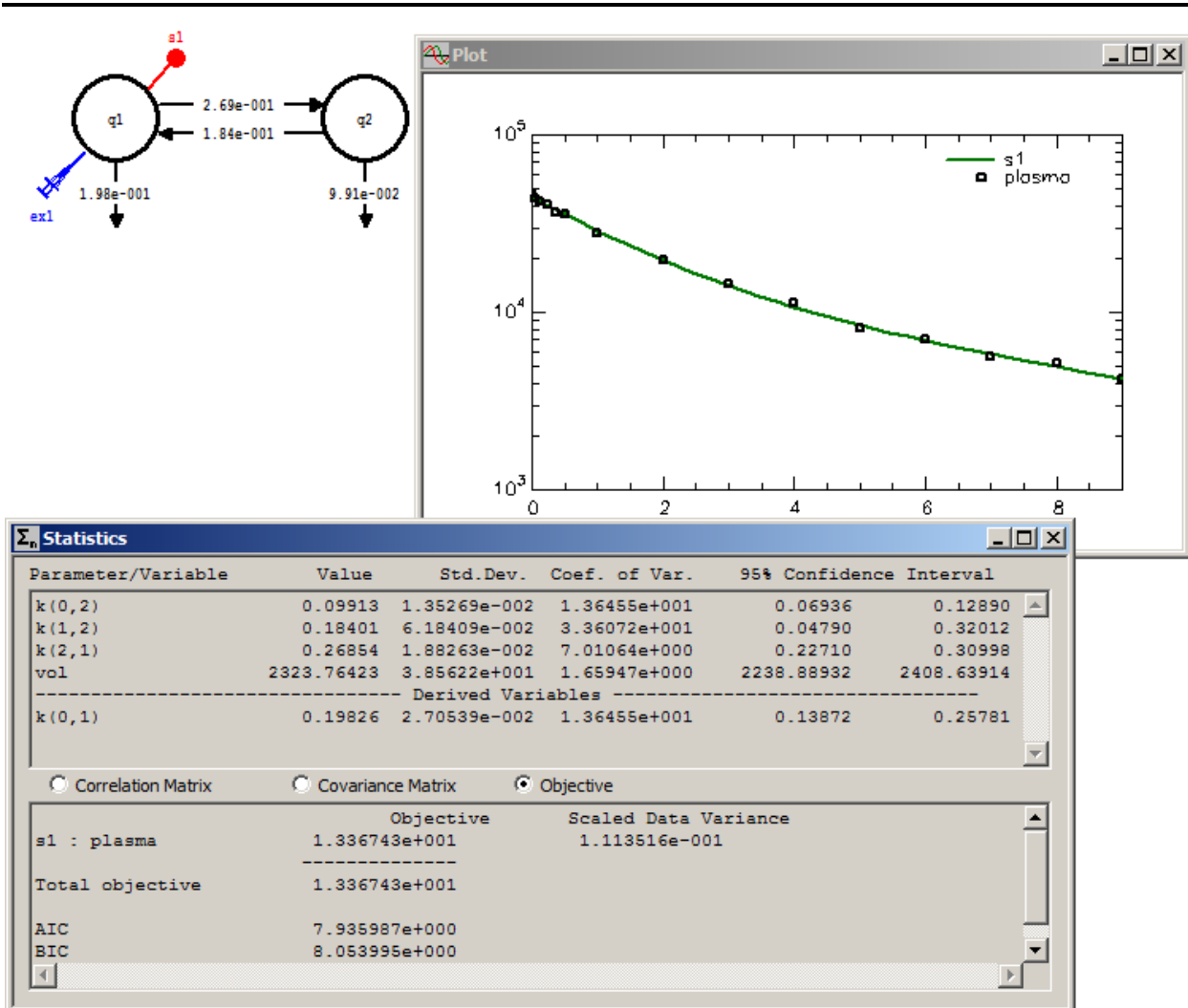
(4) Click **Save**. The **Parameters** dialog box will appear as follows:



(5) Click **Done**.

f. Re-Solve the model. The model will now solve because all parameter values have been specified.

h. Fit the model to the data. The results are summarized as follows:



The “Fit” is essentially the same as the previous ones. Now, however, $k(0,1)$ appears as a derived variable. It is a function of $k(0,2)$ defined by the equation “ $k(0,1) = 2 * k(0,2)$ ”. The statistical information on $k(0,2)$ carries over to $k(0,1)$. It is important to note the difference between defining a parameter as a function of another parameter versus as an equation with a specified value. That is, you should compare this situation with the situation where $k(0,2)$ was defined by the equation “ $k(0,2) = 0.05$ ”. In this case, $k(0,1)$ and $k(0,2)$ adjust to accommodate the relationship “ $k(0,1) = 2 * k(0,2)$ ”. In the former case, $k(0,1)$ adjusts to accommodate $k(0,2)$ being fixed equal to 0.05.



Constrained parameters. Constrained parameters are parameters that are functions of other parameters. Constraining parameters reduces the number of parameters to be estimated from the data, and hence can improve the statistical information. However, there must be a rationale for such constraints. Constrained parameters are still model

parameters, but appear as **Derived Variables** in the **Statistics** window since they are functions of the model parameters.

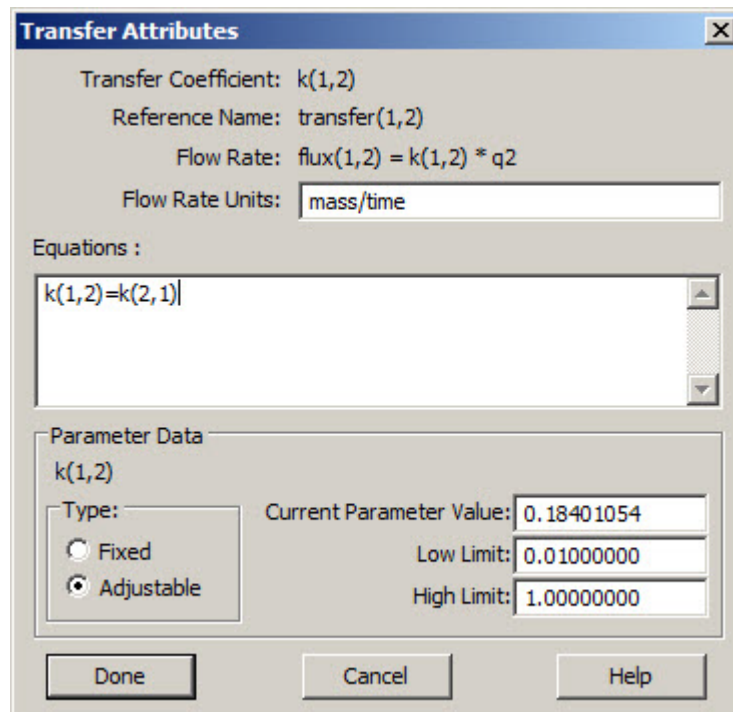


- g. Close the **Statistics** and **Plot** windows. Open the **Loss Attributes** dialog box associated with $k(0,1)$, and delete the equation “ $k(0,1) = 2*k(0,2)$ ”.

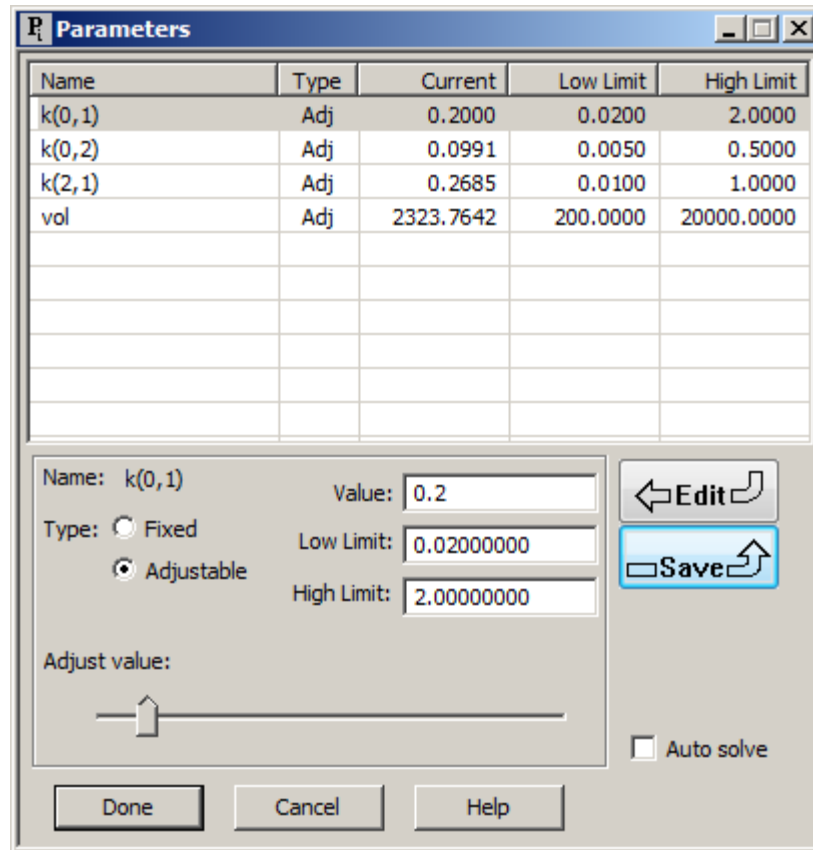
10. (Optional) Write a constraint between $k(1,2)$ and $k(2,1)$.

Suppose it is known that $k(2,1)$ and $k(1,2)$ are equal. How can this be specified in the model?

- a. Double-click the transfer $k(1,2)$ to open the **Transfer Attributes** dialog box.
- b. In the **Equation** pane, type “ $k(1,2) = k(2,1)$ ”. The **Transfer Attributes** dialog box will appear as follows:

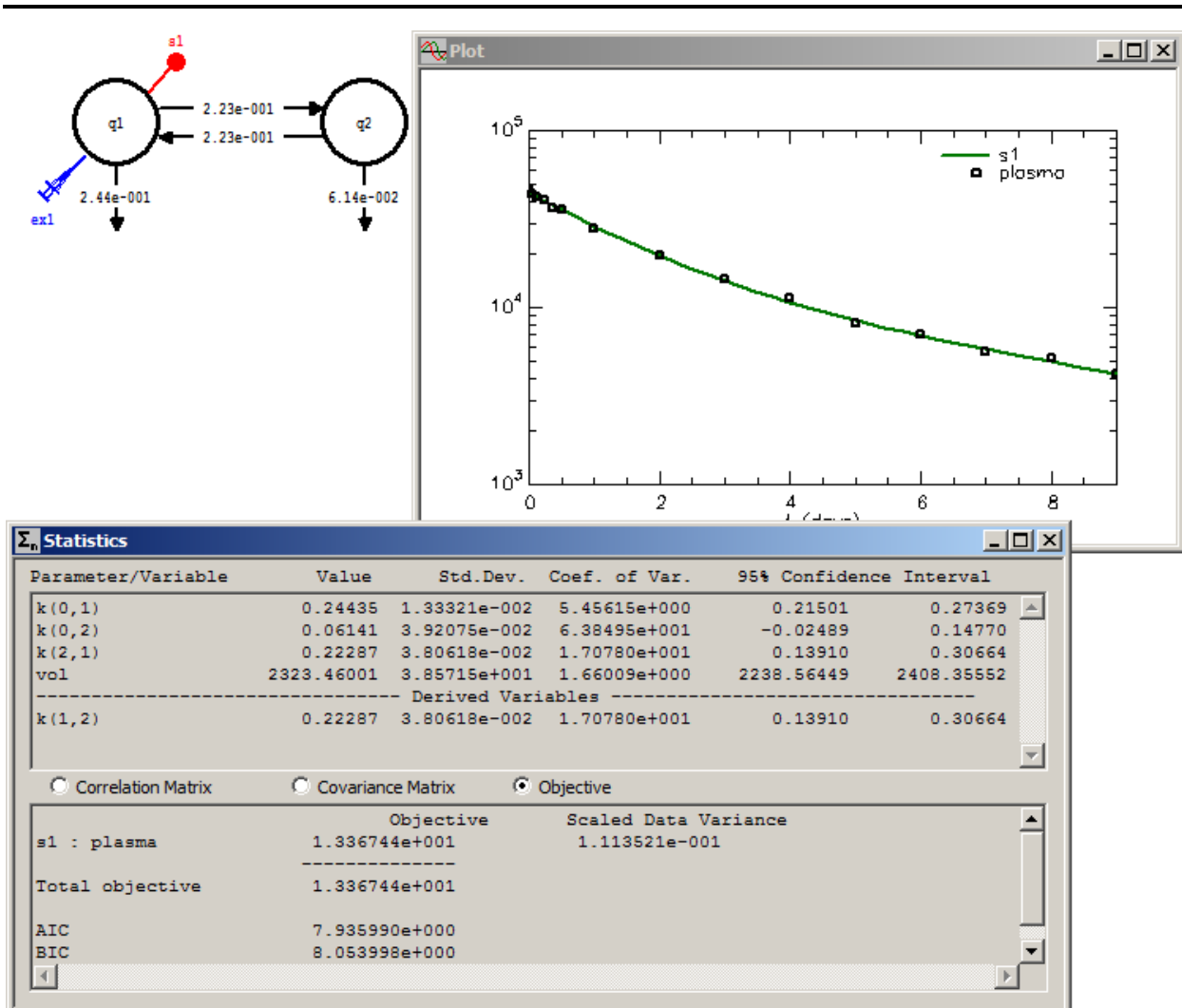


- c. Click **Done**.
- d. Open the **Parameters** dialog box, and enter the parameter values as shown below:



Notice $k(1,2)$ does not appear in the list of parameters. The reason is it is constrained to equal $k(2,1)$.

- e. Solve the model and view the solution. The solution is reasonable, so you can proceed to Fit the model to the data.
- f. Fit the model to the data. The results are summarized as follows:



Again the results are satisfactory and compare favorably with the other “Fits” in this part of the tutorial.



Transfer and Loss attributes. The attribute dialog boxes associated with transfers and losses in the model give you great flexibility in specifying relationships among parameters. In each of the cases above, an equation of constraint was specified which reduced the number of parameters to be estimated from 5 (the four $k(i,j)$ and vol) to 4. In the next part of the tutorial, you will learn how to use these dialog boxes to specify nonlinear parameters.



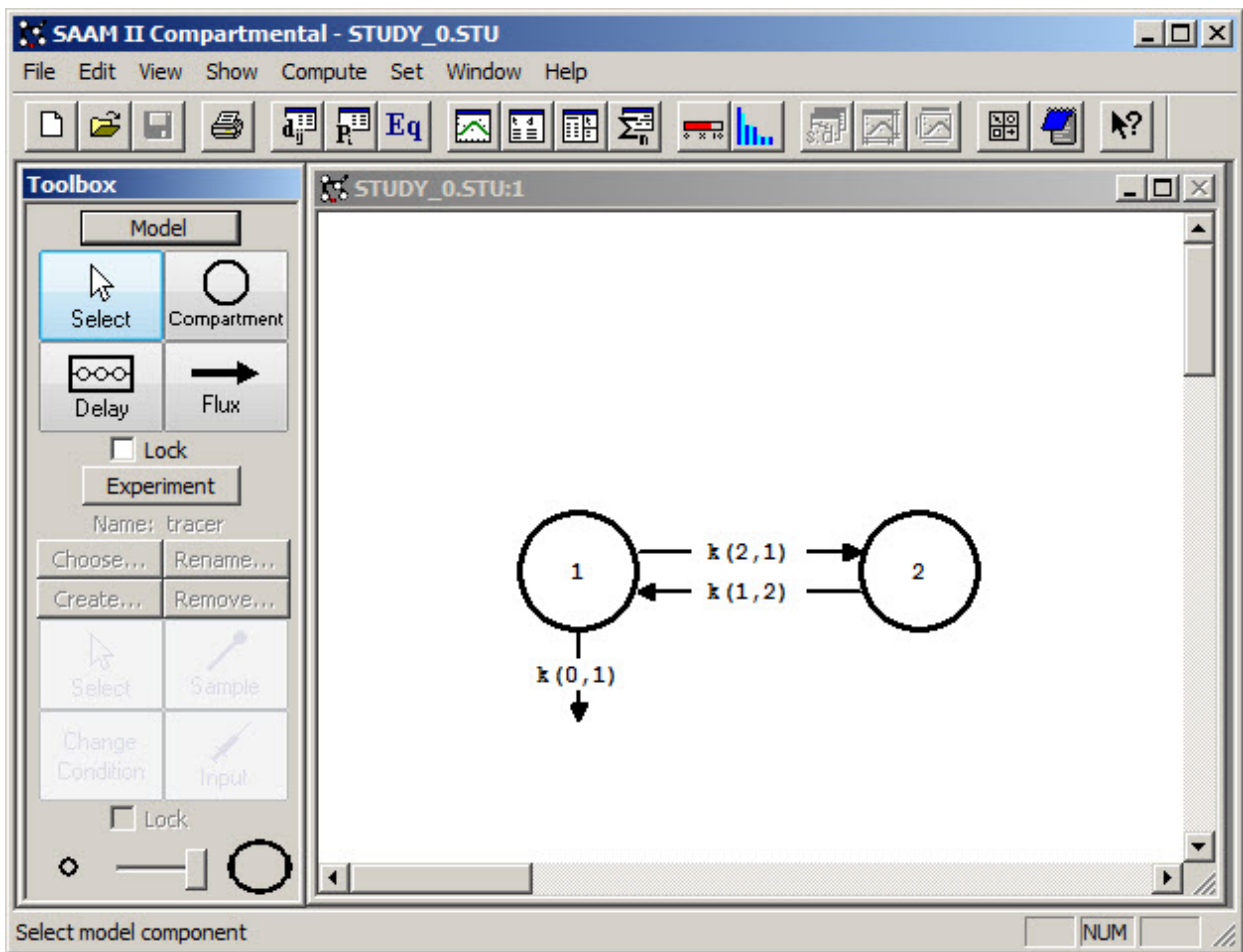
g. Close the **Plot** and **Statistics** windows.

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

Part 3. Creating a nonlinear parameter

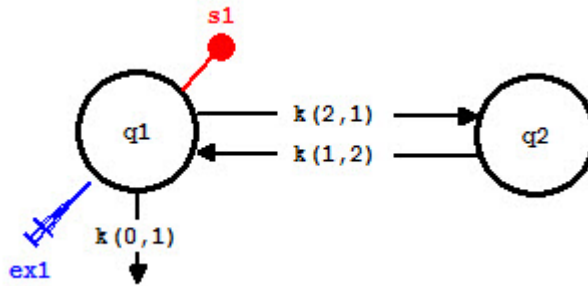
SAAM II can deal easily with nonlinear compartmental models. One simply needs to decide which of the model parameters is nonlinear, and then write an equation defining the nonlinearity. In this part of the tutorial, the loss $k(0,1)$ will be defined to have Michaelis-Menten characteristics.


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:

Name	Type	Current	Low Limit	High Limit
k(0,1)	Adj	0.1000	0.0100	1.0000
k(1,2)	Adj	0.1000	0.0100	1.0000
k(2,1)	Adj	0.1000	0.0100	1.0000
vol	Adj	2000.0000	200.0000	20000.0000

Name: k(0,1) Value: 0.10000000

Type: Fixed Adjustable

Low Limit: 0.01000000 High Limit: 1.00000000

Adjust value:

Auto solve

Buttons: Done, Cancel, Help, Edit, Save

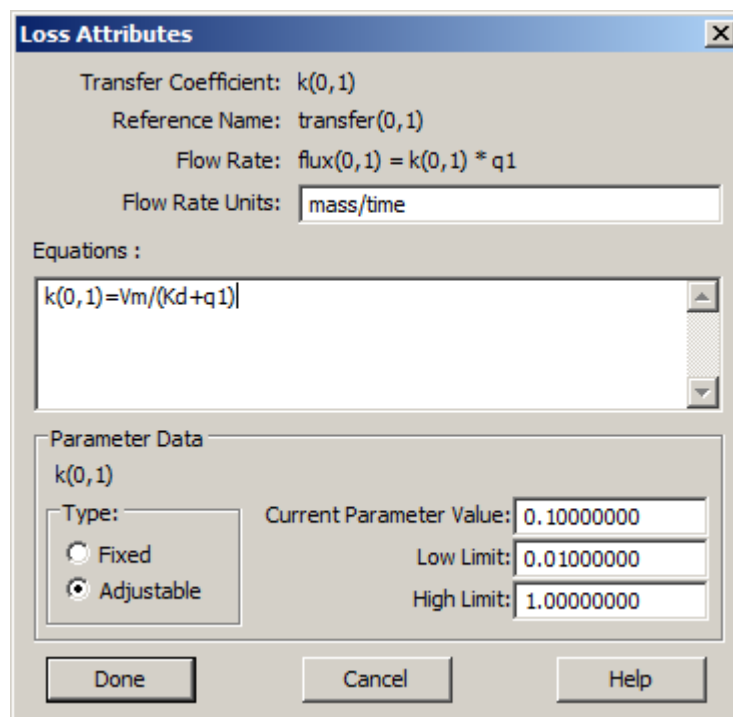
These are the parameters for **study_0.stu**.

4. Modify $k(0,1)$ so that it is a nonlinear parameter with Michaelis-Menten saturation kinetics.

Suppose you cannot fit your data to a model with constant $k(i,j)$. This situation usually arises when no combination of parameter values, or adding components to the model, can account for the characteristics in the data. It is up to the modeler to decide which of the model parameters are nonlinear, and how to specify the nonlinearity.


In what follows, $k(0,1)$ will be changed to a nonlinear parameter with Michaelis-Menten saturation kinetics.

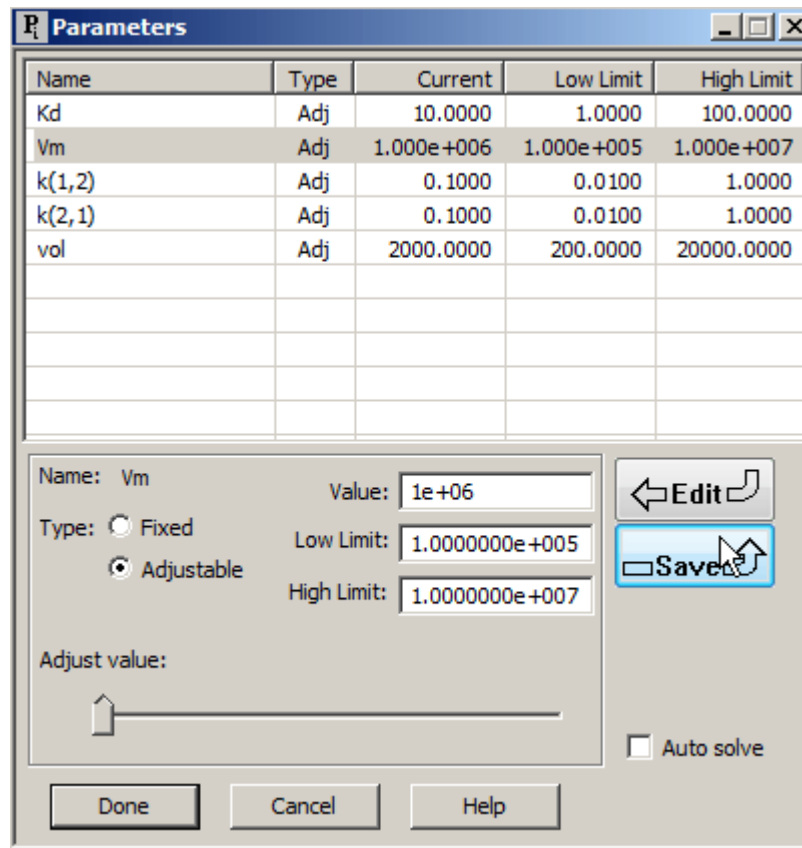
- a. Double-click $k(0,1)$ to open the **Loss Attributes** dialog box.
- b. In the **Equation** pane, type “ $k(0,1)=V_m/(K_d+q_1)$ ”. The **Loss Attributes** dialog box will appear as follows:



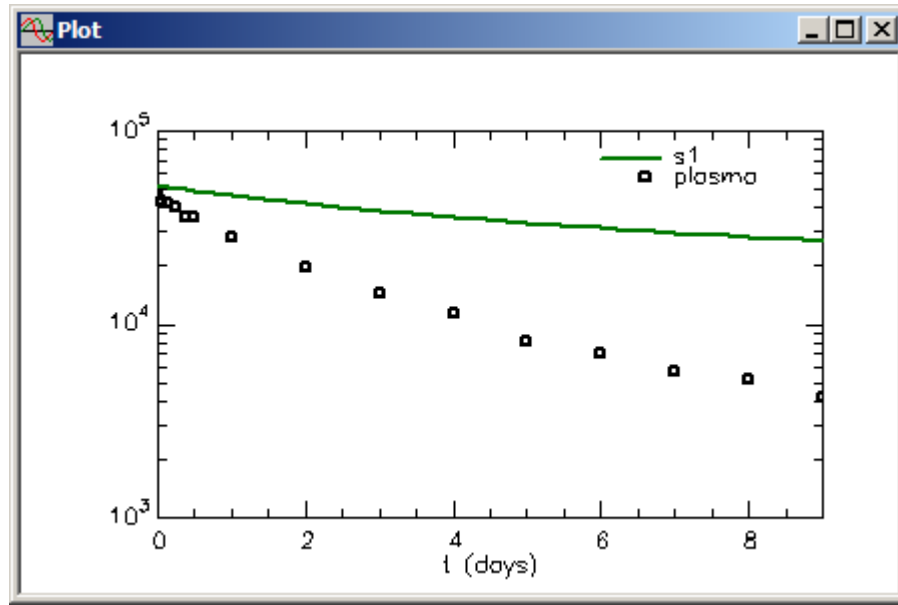
- c. Click **Done**.

The result is that $k(0,1)$ is no longer a primary model parameter, but is a function of two new parameters, V_m and K_d . Thus $k(0,1)$ will no longer appear in the **Parameters** dialog box; V_m and K_d will.


5. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar**, click **Parameters** . The **Parameters** dialog box will open.
 - a. Type “10” as the **Value** for K_d , and click **Save**.
 - b. Type “1e+06” as the **Value** for V_m , and click **Save**. The **Parameters** dialog box will appear as follows:

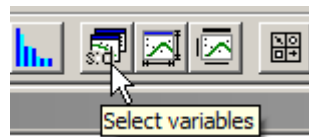


- c. Click **Done**.
6. Solve the model, and view the solution. The solution, of course, is not particularly good since the data do not display nonlinear features. A plot of the solution is shown as follows:



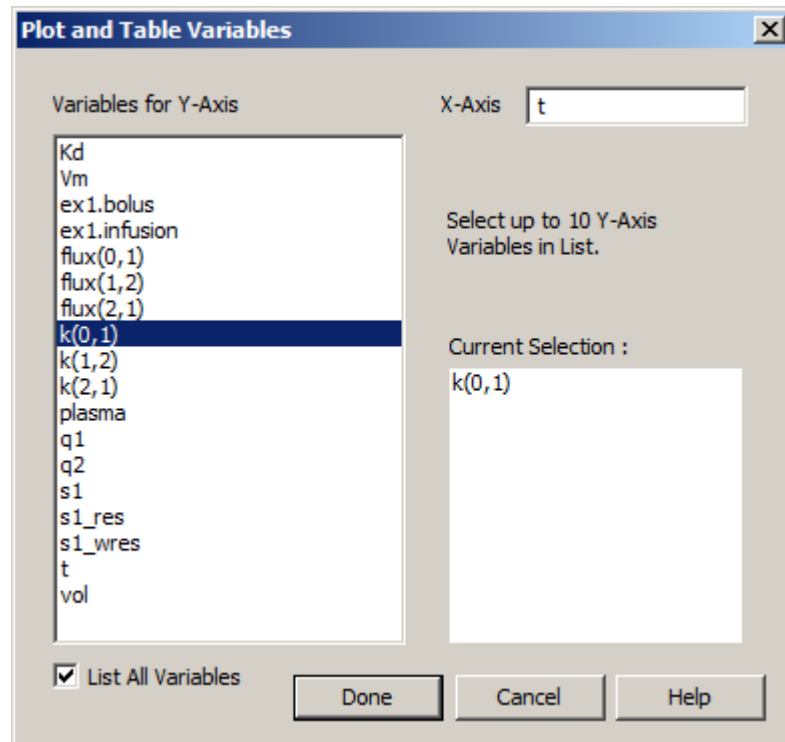
It is of interest, however, to plot $k(0,1)$ which is no longer a constant but a function of time since $\mathbf{q1}(t)$ appears in the equation defining it. More specifically, if you introduce a nonlinear parameter in your model, since it is no longer constant, you should plot the transfer to see how it changes over the course of the solution.

- a. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** , or alternatively click the **Select variables** tool in the **SAAM II Toolbar**:

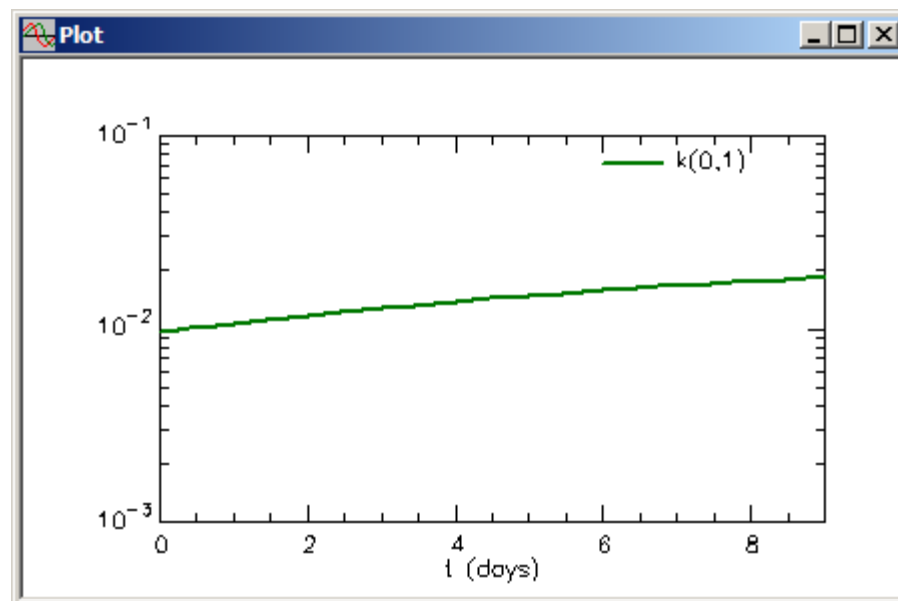


The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is selected.

- 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 with the Y axis scale set from 0 to 0.02):

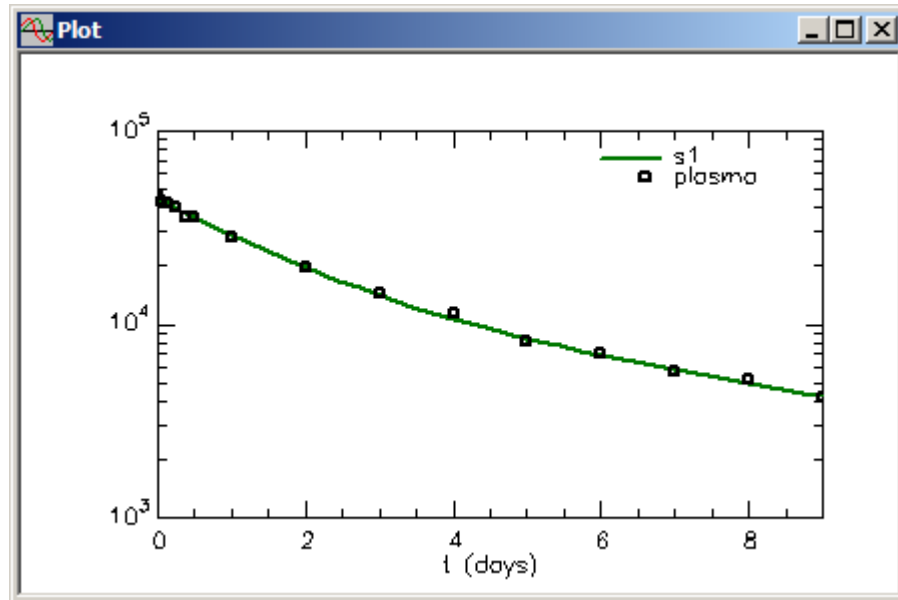


- d. Close the **Plot** window.

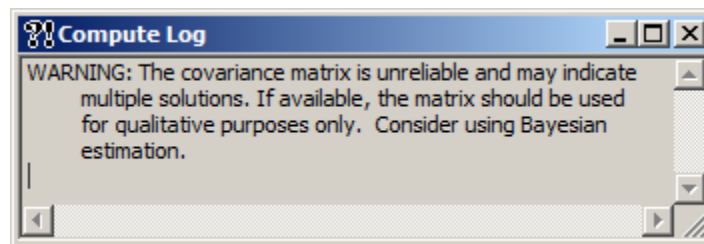
If you plot any other of the model parameters, since they are constant, the plot will appear as a straight line parallel to the x-axis. In the example here, $k(0,1)$ is slowly increasing during the solution.

Thus it is very easy to create nonlinear models in SAAM II. It is also easy to see how a nonlinear parameter behaves; in this case, it is slowly rising.

You can Fit the model to the data if you wish. However, despite the fit shown in the following plot, this is not a situation when nonlinearity is supported by the data.



If you Fit the model to the data, a warning message as shown below will appear that indicates there are more parameters in the model than can be estimated from the data.



Thus while there will appear to be a good “Fit”, the statistics will appear as shown below:

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
Kd	100.00000	3.43893e+007	3.43893e+007	-7.66240e+007	7.66242e+007
Vm	4799552.22112	1.88374e+007	3.92483e+002	-3.71729e+007	4.67720e+007
k(1,2)	0.14192	2.94452e-001	2.07470e+002	-0.51416	0.79800
k(2,1)	0.40468	1.28450e-001	3.17410e+001	0.11848	0.69089
vol	2333.32426	4.38114e+001	1.87764e+000	2235.70633	2430.94220

	Objective	Scaled Data Variance
s1 : plasma	1.341130e+001	1.279800e-001
Total objective	1.341130e+001	
AIC	8.024590e+000	
BIC	8.166200e+000	

Clearly the statistics are not satisfactory. If you were considering the possibility in this particular situation that the model might be nonlinear, you can safely conclude that, if it is nonlinear, $k(0,1)$ cannot display Michaelis-Menten kinetics.

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