

Glucose Kinetics: The Three-Compartment Model

Case Study

- How to create a two-compartment model
- How to obtain initial parameter estimates
- How to evaluate the “Fit”
- How to add a third compartment
- How to investigate different model structures (identifiability of the three-compartment model)

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Glucose Kinetics: The Three-Compartment Model

Prerequisites

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

What you will learn in this case study

This case study is a modeling exercise which will show you the steps to go through to develop a system model. As such, it will exercise many features of the SAAM II Compartmental application. You will learn:

- How to create a two-compartment system model.
- How to obtain initial parameter estimates.
- How to evaluate the “Fit” of the two-compartment model to the data.
- How to add a third compartment to the system model.
- How to obtain initial parameter estimates for the three-compartment model using information from the two-compartment model.
- How to evaluate the “Fit” of the three-compartment model to the data, and how to add a fourth compartment if desired.
- How to investigate different model structures (identifiability of the three-compartment model)

Data Required

The data file for this case study is

Glucose3Cpt.dat

This data file is a text file. The contents of this file are included at the end of this case study.

Introduction

In this case study, you will learn how to proceed in a step-wise fashion to develop a system model. It is based on an analysis of glucose kinetics in sheep using the data given in [1]. The glucose dose is administered intravenously as a bolus, and serial plasma samples were taken for 240 minutes.

We will begin with a two-compartment model, and then move to a three-compartment model. We will illustrate how to perform tests for goodness-of-fit, and how to use the Akaike and Schwartz criteria to aid in the selection between the two and three compartment model.

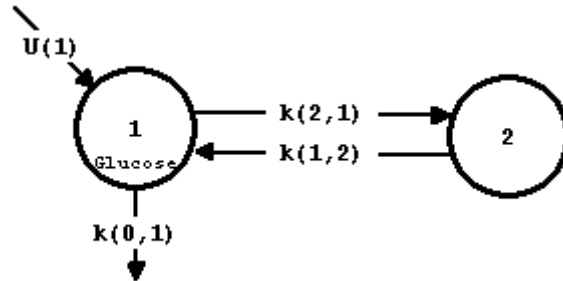
Although note required, it is highly recommended that you work through a case study on the two-compartment model. In these case studies, how to obtain initial parameter estimates for the two-compartment model is discussed. We will assume familiarity with these concepts in this case study.

If you are interested in the steady state solution, it will be helpful to have worked through the case study “Glucose Kinetics: The Two Compartment Model” since the effect of different model structures on the steady state variables is discussed in detail in this case study. We will not cover this in detail in this case study.

1. Gastaldelli, A. JM Schwarz, E Cavegion, LD Traber, DL Traber, J Rosenblatt, G Toffolo, C Cobelli and RR Wolfe. Glucose kinetics in interstitial fluid can be predicted by compartmental modeling. Am. J. Physiol. 272: E494-E505, 1997

Part 1. Create a two-compartment model in the SAAM II Compartmental application

1. **Start the SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.
2. Create the following system model on the **Drawing Canvas**:



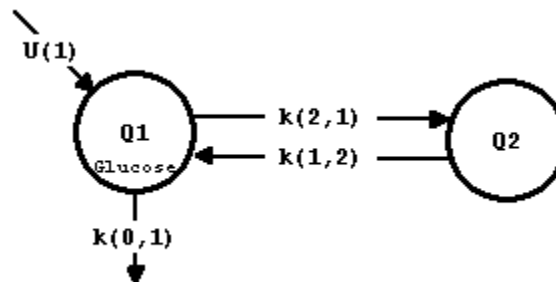
Remember to have “Glucose” appear in Compartment **1**, you will need to open the **Compartment Attributes** dialog box associated with that compartment.

Part 2. Create the system (tracee) model

1. In the **SAAM II Toolbox**, click **Experiment**. Notice that the **Model** tools are unavailable and the **Experiment** tools are available. The **Experiment Attributes** dialog box will open.
 - a. Enter “240” in the **End at** box. The **Experiment Attributes** dialog box will appear as shown below:

- b. Click **Done**. The **Create Experiment** dialog box will appear on the **Drawing Canvas**.
- c. Click **System** to activate this **Type**.
- d. Type “Glucose” in the **New Name** box. The **Create Experiment** dialog box will appear as follows:

- e. Click **Create**. Notice that “Glucose” now appears below **Experiment** in the **SAAM II Toolbox**. Your system model will appear as follows:



The compartment names have changed from **1** and **2** to **Q1** and **Q2**. SAAM II uses capital letters to name the compartments for the system experiment while it uses small letters to name the compartments for the “experiment” experiment.



Experiment vs. System. The **Create Experiment** dialog box is where you create your experiment. There are two types of experiments - “Experiment” and “System”.

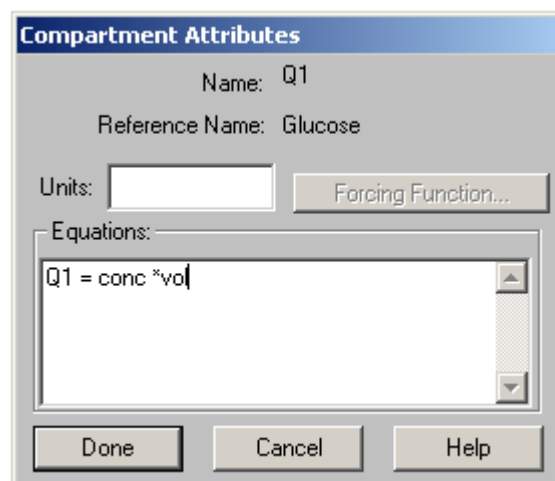
The **Experiment** type will invoke SAAM II’s differential equation machinery. When you create this type of experiment, your compartmental model will be interpreted by SAAM II as a system of differential equations. Once parameter values and inputs have been specified, SAAM II can Solve the system of differential equations, and can Fit your model to your data. This type of experiment is designed to deal with time dependent data following an experimental (exogenous) input into the system.

The **System** experiment creates a system of algebraic equations whose coefficients are the $k(i,j)$ of your compartmental model. The System model is used primarily in tracer-tracee experiments to describe the tracee data in the steady state. In this case study, it will be used to analyze steady state glucose kinetics.

The default **New Name** is “Exper”. This can be changed to a name of your choice.



2. Specify the steady state (tracee) information.
 - a. Double-click Compartment **Q1** to open the **Compartment Attributes** dialog box.
 - b. In the **Equation** pane, type “Q1 = conc * vol”. The **Compartment Attributes** dialog box will appear as follows:



Notice the experiment **Reference Name** appears in this dialog box.

- c. Click **Done**.



Specifying tracee masses in compartment. What is needed to solve the steady state problem is the tracee mass in either Compartment **Q1** or Compartment **Q2**. As written, we are solving for the mass **Q1**. What is known is the concentration, *conc*, of glucose in Compartment **Q1**, plasma. To obtain the mass, we need the volume, *vol*, of this compartment. The equation “ $Q1 = conc * vol$ ” thus introduces two parameters in your model, *conc* and *vol*. The parameter *conc* will be entered as a fixed parameter since it is measured and known as part of the experiment. The parameter *vol* will be estimated from the tracer data.


If *conc* is, for example, 100mg/ml, the equation could have been written “ $Q1 = 100 * vol$ ”. However, if you had several turnover studies you were analyzing, this equation would have to be edited for every study. By introducing the parameter, you need only enter the parameter and not worry about this defining equation

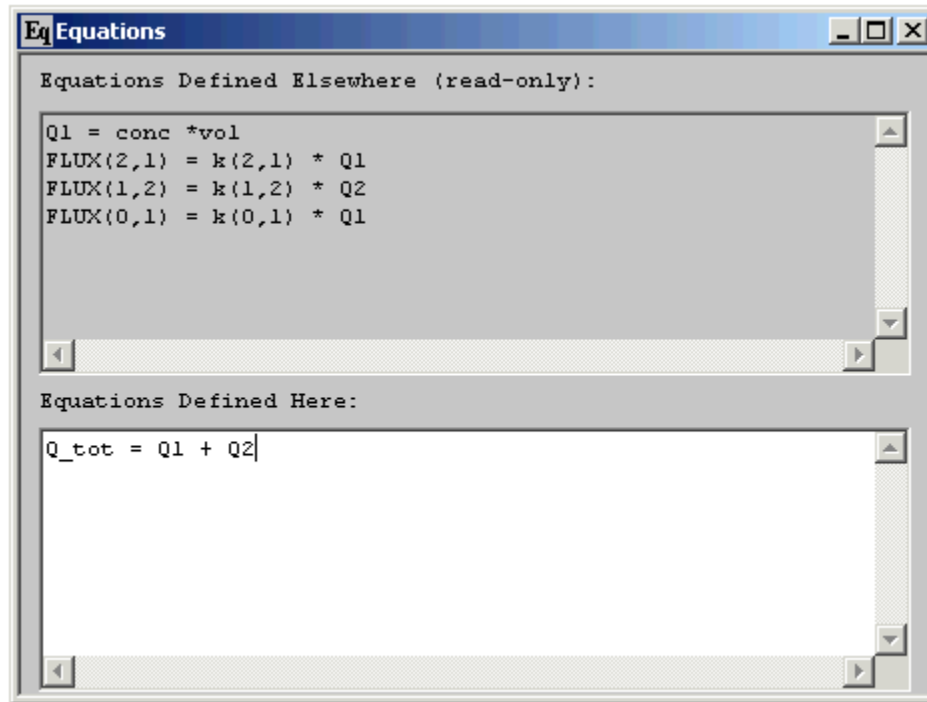
In writing the equations for the steady state, for every unknown **U(i)** there must be a known mass, and vice-versa. More specifically, it is not necessary to know the mass of a single compartment. If, in this case, the total glucose mass was known (total glucose mass would be **Q1 + Q2**), then the mass equation could be written: “ $Q1 = Total - Q2$ ”. Remember in SAAM II, you cannot write equations of the form “ $Q1 + Q2 = Total$ ”; there must be a single variable only on the left hand side of the equation.



3. Estimate total glucose mass in the system.

With **Q1** calculated, when the system model is solved, you will obtain an estimate for the mass **Q2** in Compartment **Q2**. You can thus calculate the total estimated glucose mass in the system as the sum of **Q1** and **Q2**.

- a. In the **Show** menu, click **Equations**, or alternatively, click the **Equations** tool  on the **SAAM II Toolbar**. The **Equations** dialog box will open.
- b. In the **Equations Defined Here** pane, type “ $Q_tot = Q1 + Q2$ ”. The **Equations** dialog box will appear as follows:

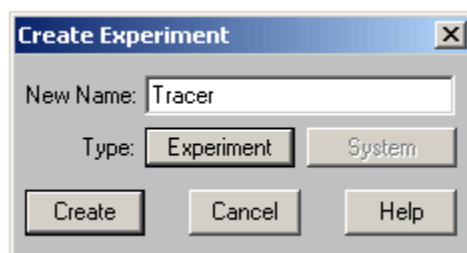


- c. Close the **Equations Dialog** box. **Q_tot** is now a variable that will be estimated when you solve or fit your model to the data.

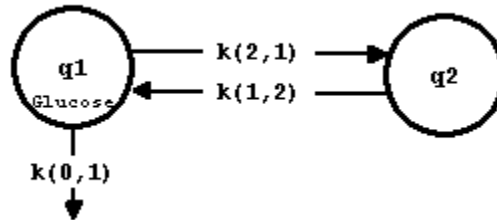
Part 3. Create the tracer kinetic experiment on the model

Remember the **Experiment** tools are active since you have been working with the system model.

1. Create the tracer experiment.
 - a. In the **SAAM II Toolbox**, click **Create**. The **Create Experiment** dialog box will open.
 - b. Be sure “Experiment” is the active **Type**. Type “Tracer” in the **New Name** box. The **Create Experiment** dialog box will appear as follows:



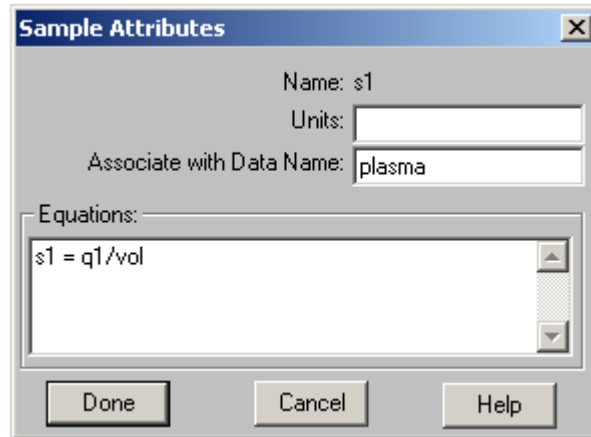
- c. Click **Create**. Notice that the name “Tracer” appears just under **Experiment** in the **SAAM II Toolbox**. The model will appear as follows:



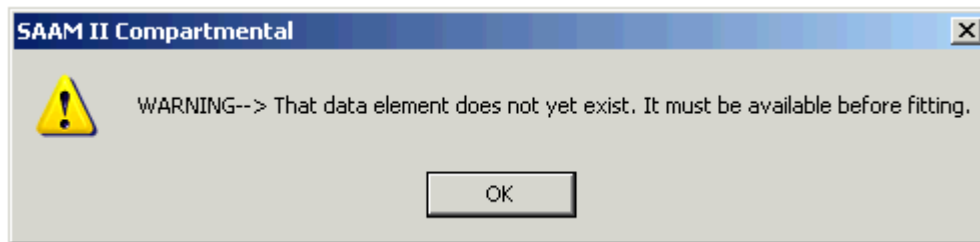
Naming experiments. When you create an experiment, you have the option of giving it names other than the default name. In this case, the system experiment was named “Glucose” and the tracer study was named “Tracer”. Depending upon whether you have the system or tracer model active on the **Drawing Canvas**, the appropriate name will appear under **Experiment** in the **SAAM II Toolbox**. This option is very useful especially when you performing multiple tracer experiments.



2. Create a sample on Compartment **1**.
 - a. In the **SAAM II Toolbox**, click **Sample**.
 - b. Click Compartment **q1**, and then click on the **Drawing Canvas**. The sample **s1** will appear.
 - c. Double-click **s1** to open the **Sample Attributes** dialog box.
 - d. Type “plasma” in the **Associate with Data Name** box. (Notice “plasma” is in lower case.)
 - e. Edit the sample equation “s1=q1” to read “s1=q1/vol” in the **Equations** box. The **Samples Attributes** dialog box will appear as follows:



f Click **Done**. The following warning message will appear:



The reason why this message appears is that the data have not been entered in the **Data** window. This will be done later.

- g. Click **OK**.
3. Create an input into Compartment **1**.

The dose of tracer glucose was $4.5 * 10^8$ dpm.

- In the **SAAM II Toolbox**, click **Input**.
- Click Compartment **q1**, and then click on the **Drawing Canvas**. The input **ex1** will appear.
- Double-click **ex1** to open the **Exogenous Input** dialog box.
- Enter “4.5e+08” in the **Initial Amount** box.
- Click **Add**. The **Exogenous Input** dialog box will appear as follows:

Exogenous Input

Name: Reference Name: Units:

Type	Initial	Constant	Start	Stop	Repeat Every	Nr. Repeats
Bolus	4.50e+8	-	0.000	-	-	-

Input Type:

Bolus
 Infusion
 Primed Infusion
 Equation

Initial Amount:

Constant Rate:

Event Start:

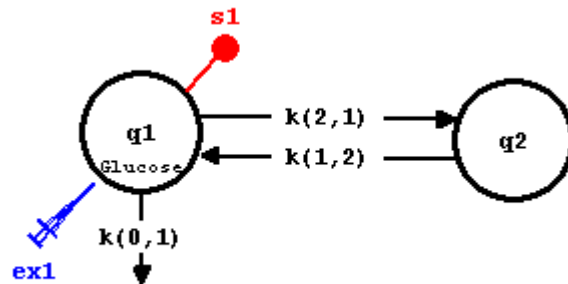
Event Stop:

Repeat Every:


Nr. of Repeats:

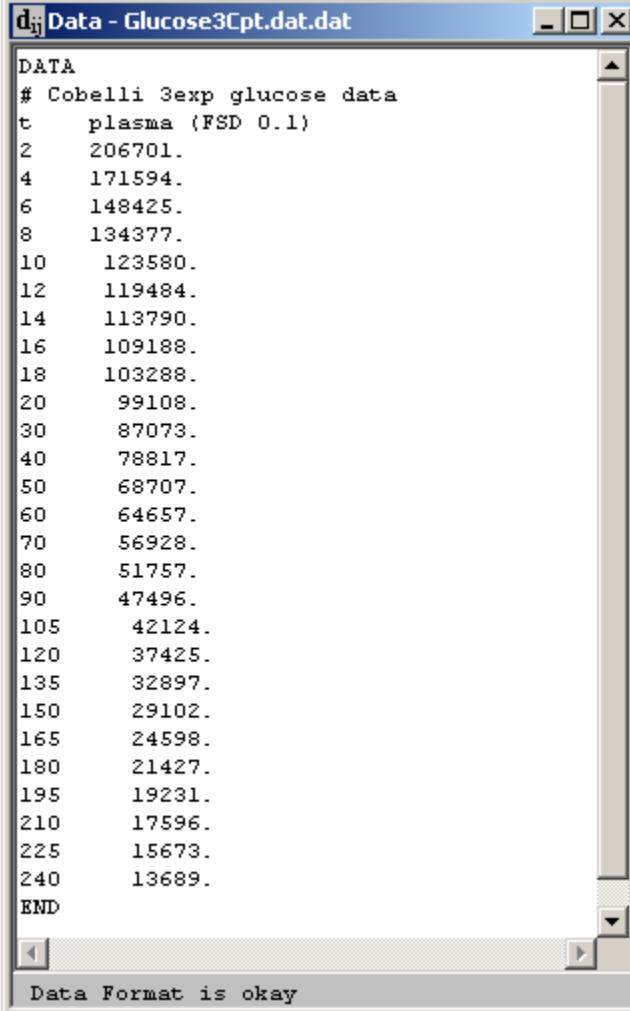
Equation:

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



4. Enter the data.

- In the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data** . The **Data** window will open.
- In the **File** menu, click **Open**. The file **Glucose3Cpt.dat** should appear in the list (if it does not, find the folder where you have put this data file).
- Double-click **Glucose3Cpt.dat**. The **Data** window will appear as follows:



```
DATA
# Cobelli 3exp glucose data
t      plasma (FSD 0.1)
2      206701.
4      171594.
6      148425.
8      134377.
10     123580.
12     119484.
14     113790.
16     109188.
18     103288.
20     99108.
30     87073.
40     78817.
50     68707.
60     64657.
70     56928.
80     51757.
90     47496.
105    42124.
120    37425.
135    32897.
150    29102.
165    24598.
180    21427.
195    19231.
210    17596.
225    15673.
240    13689.
END
Data Format is okay
```


The weighting scheme is FSD so you can leave the variance model set as the default, data-relative.

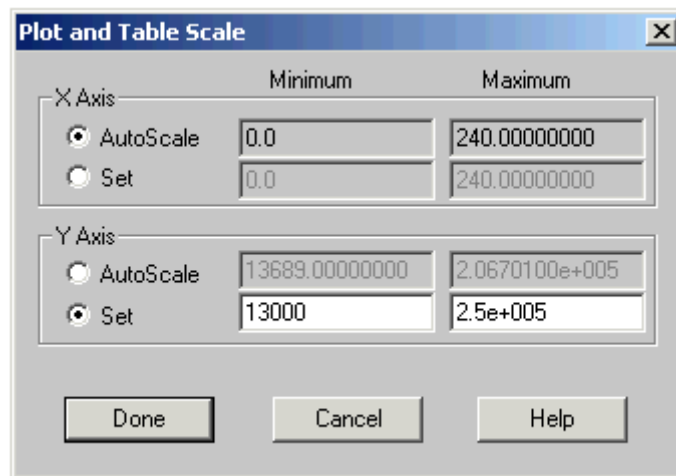
- d. Close the **Data** window.

Part 4. Enter the parameter values, solve the model, fit the model to data, view the solution and record the results.

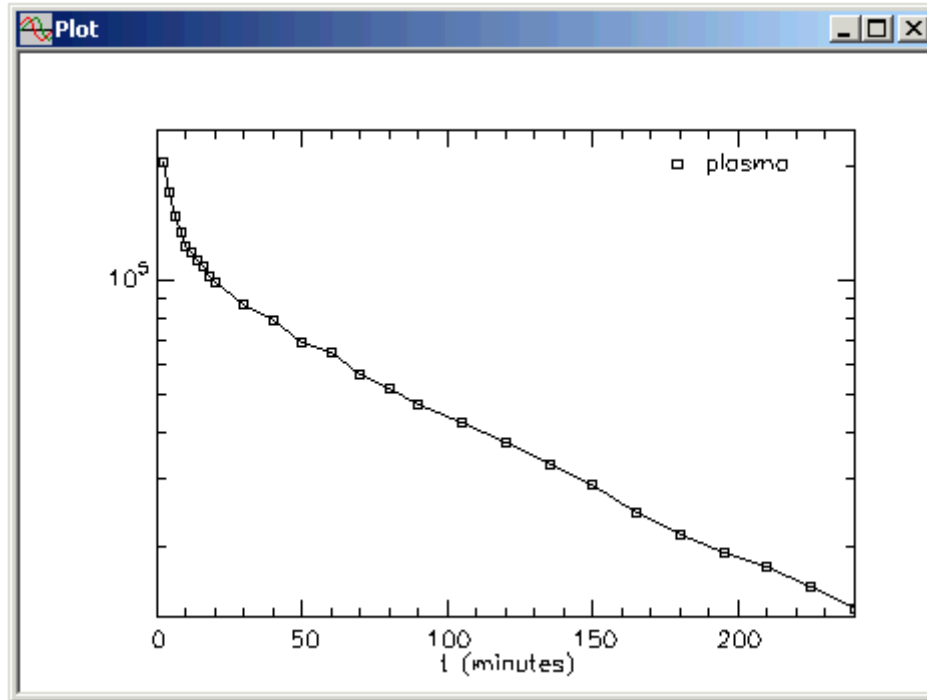
Before you can Solve (simulate) your model or Fit your model to your data, you must provide numerical estimates for the primary parameters of your model. These are the parameters that appear in the **Parameters** dialog box. First you need to obtain the initial parameter estimates.

1. View your data using a line plot.

- a. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . The **Plot and Table Variables** dialog box will open.
- b. Be sure the **List All Variables** check box is selected. (Click this box if it is not selected).
- c. Click **plasma** to move it to the **Current Selection** pane.
- d. Click **Done**. A plot of the data will appear in the **Plot** window.
- e. In the **View** menu, click **Line Plot**.
- f. In the **View** menu, click **Semilog**. Change the **Plot and Table Scale** as follows:



Your plot will appear as follows:




Line Plots. Using the line plot in semilog mode to connect your data can help you decide how many exponentials (compartments) will be needed for the model. In this case, it is clear that at least two exponentials, or compartments, will be needed.

Using the quick method to estimate the initial values for the three rate constants $k(i,j)$, we see the break in the curve appears to be around 15 minutes. We will thus use $1/15$ or 0.067 as initial estimates for the rate constants.

The first datum has a value of 206701. Knowing the dose is $4.5 * 10^8$, an estimate for vol will be obtained $4.5 * 10^8 / 206701$ which equals approximately 2200.



- g. Close the **Plot** window.
2. Enter the parameter values.
 - a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar**, click **Parameter** . The **Parameters** dialog box will open.

- b. If *conc* is not selected, double-click *conc* to select it. Select “Fixed” as the parameter **Type**. Enter “10” in the **Value** box, and click **Save**.
- c. Enter the remaining parameters as shown in the **Parameters** dialog box below:

Name	Type	Current	Low Limit	High Limit
conc	Fix	10.0000		
k(0,1)	Adj	0.0670	0.0067	0.6700
k(1,2)	Adj	0.0670	0.0067	0.6700
k(2,1)	Adj	0.0670	0.0067	0.6700
vol	Adj	2200.0000	220.0000	22000.0000

Name: vol Value: 2200

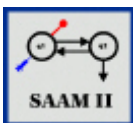
Type: Fixed Low Limit: 220.00000000

Adjustable High Limit: 22000.00000000

Buttons: Done, Cancel, Help, Edit, Save


- d. Click **Done**.

In the parameter dialog box, note *conc* is a fixed parameter. The measured concentration of glucose in this individual was 100mg%. Since the units of mass in the steady state model are mg, the concentration needs to be converted from mg% to mg/ml. Thus 100mg% is 10mg/ml.

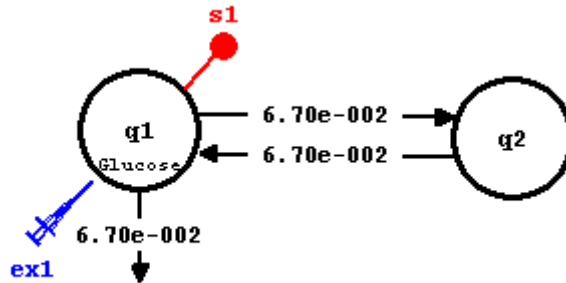


Initial parameter estimates. How to obtain the initial parameter estimates is described in one of the two-compartment case studies.




3. Solve the model and view the solution.
 - a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar**, click **Solve** .

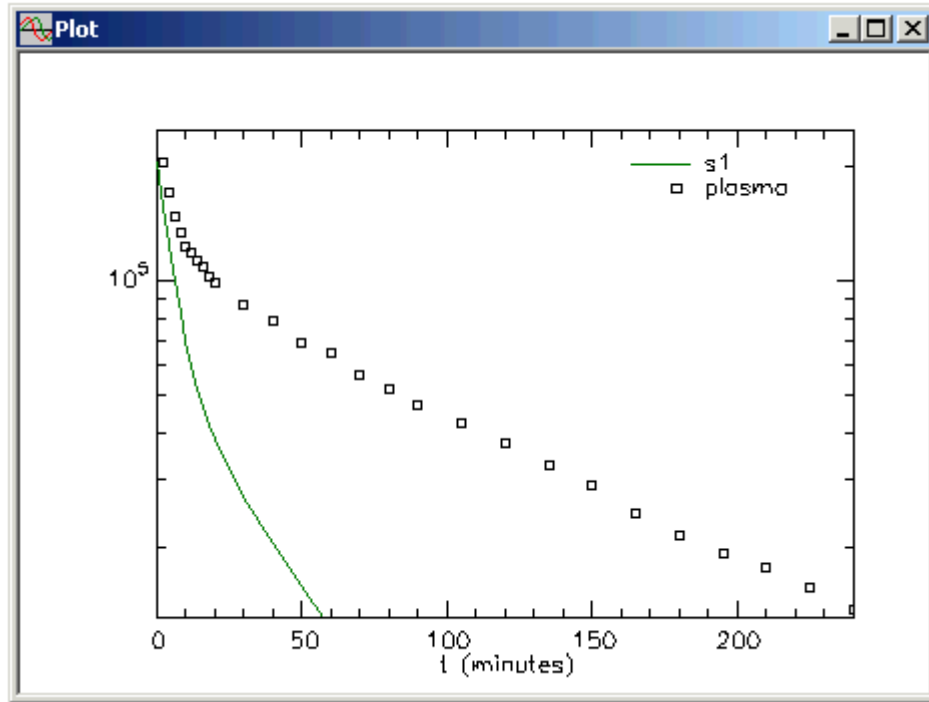
- b. In the **View** menu, select **Model Labels** and click **Values**. Your model will appear as follows:



Model labels. Model Labels gives you three options to label the transfers in your model. One is the name, $k(i,j)$ which is the default label. The other is **Values**; this labels the transfers with their current values. In the event that a transfer is non-linear, the current value is the zero time value. The final option is no label at all. Labeling with the parameter value is useful since it lets you know the current value of each parameter without having to open the **Parameters** dialog box.



- c. Plot the data. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . Since you have previously plotted the data, the plot of the data will appear.
- d. In the **Set** menu, click **Plot/Table Variables**. The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is cleared.
- e. Click **s1:plasma** to move these to the **Current Selection** pane.
- f. Click **Done**. If your plot does not appear in semi-log mode, in the **View** menu, click **Semilog**. Your plot will appear as follows:



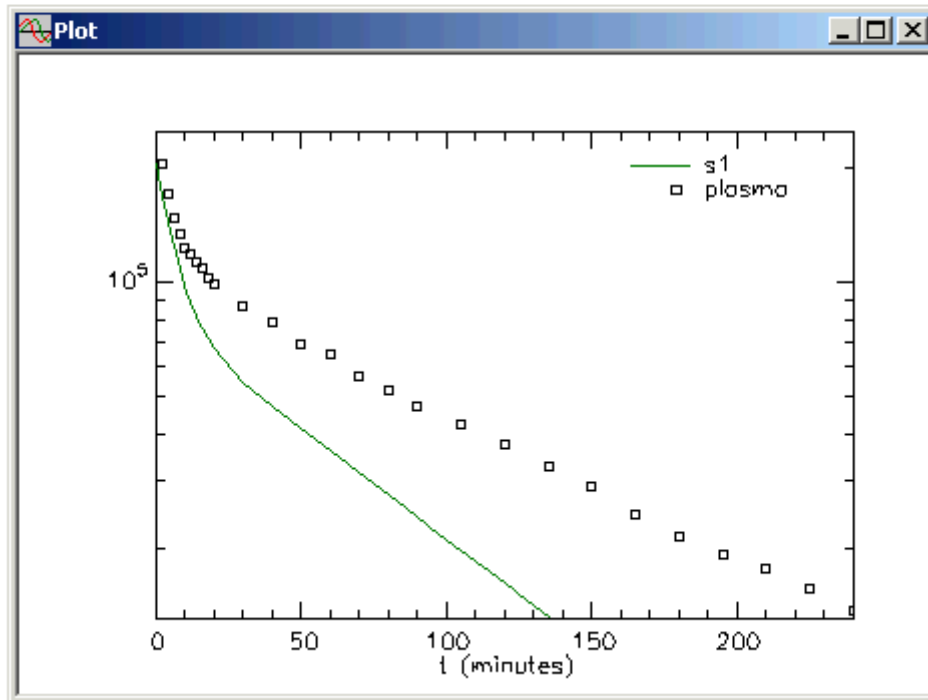
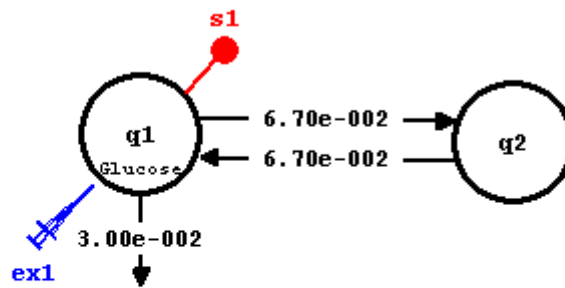
Remember you have set the **Plot and Table Scale** which is why the model predicted value disappears at approximately 60. If the scale has not been set but was on **Autoscale**, the plot would be very different as the model predicted value would appear to 240 minutes.

The initial estimates from the quick method are not quite right as the model predicted values are disappearing faster than the data. While this is actually close enough to Fit the model to the data, it is useful to hand-fit first.

In hand-fitting, we will choose one parameter at a time, and change its value by no more than twice or half. In this case, we will first reduce $k(0,1)$ by a factor of one-half to 0.03.

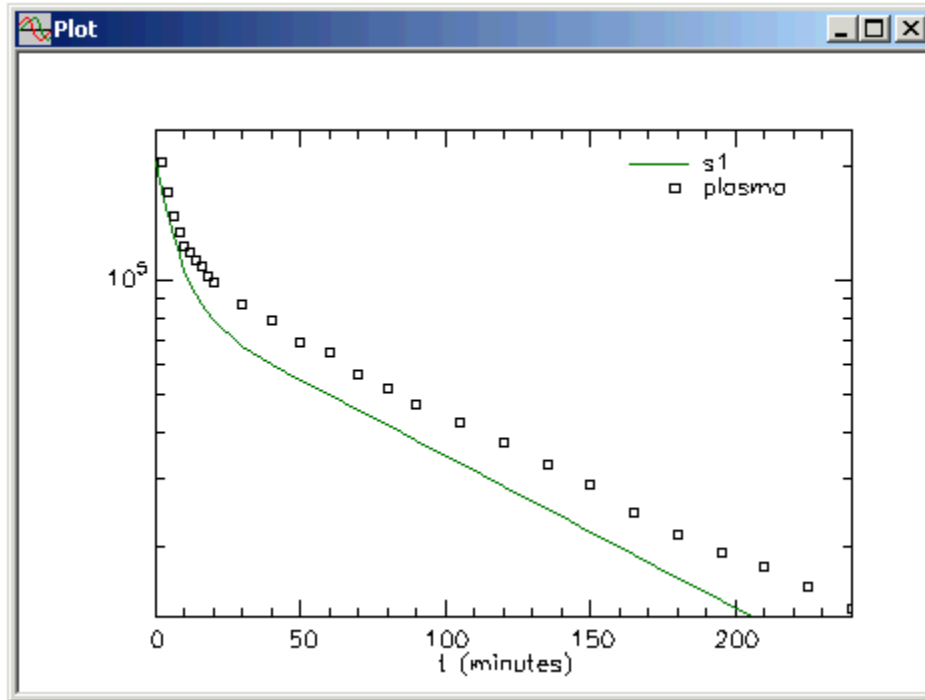
Leave the **Plot** window open.

- g. Open the **Parameter** dialog box, and change $k(0,1)$ to 0.03. Re-Solve the model. Your plot and model will be updated as follows:



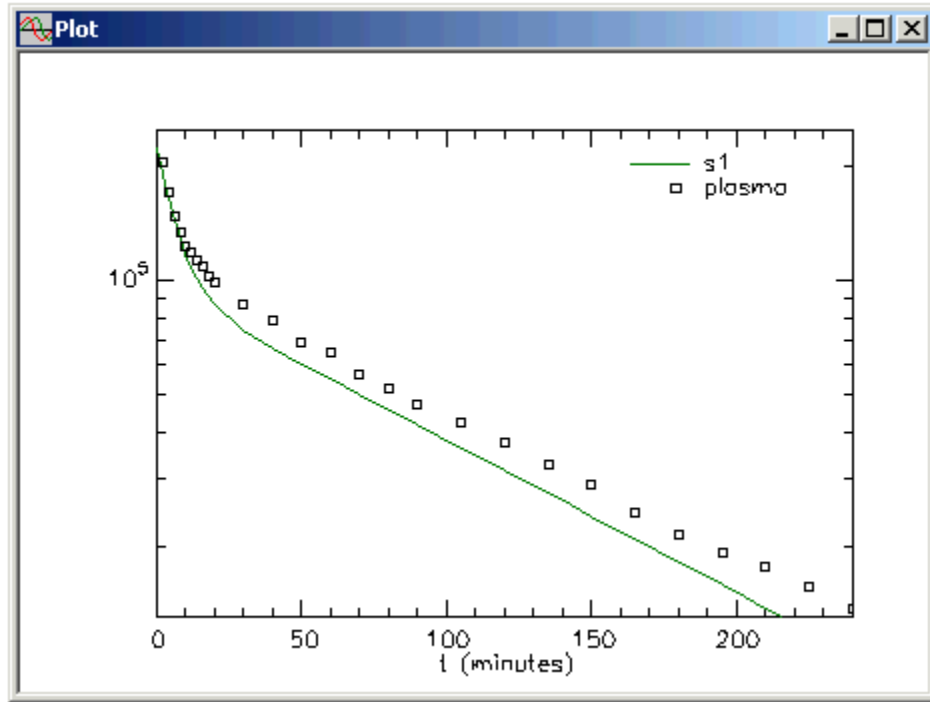
While this is better, $k(0,1)$ is still a little too large. We will reduce it again, but not by a factor of one-half since that will be too much. We will reduce it to 0.02.

- h. Open the **Parameter** dialog box, and change $k(0,1)$ to 0.02. Re-Solve the model. Your plot will be updated as follows:




This is much better, but you can see the initial points are not well estimated. This is because *vol* is a little off. Remember *vol* was estimated using the first datum which means it will be larger than the true estimated volume. We will reduce the estimate of *vol* to 2000.

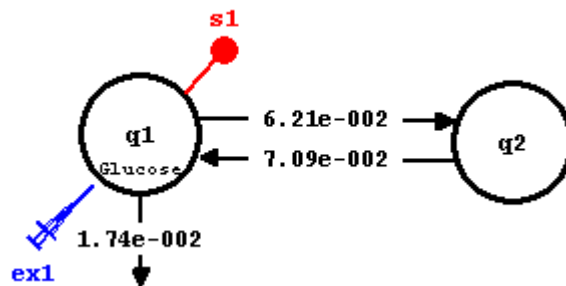
- i. Open the **Parameter** dialog box, and change *vol* to 2000. Re-Solve the model. Your plot and model will be updated as follows:



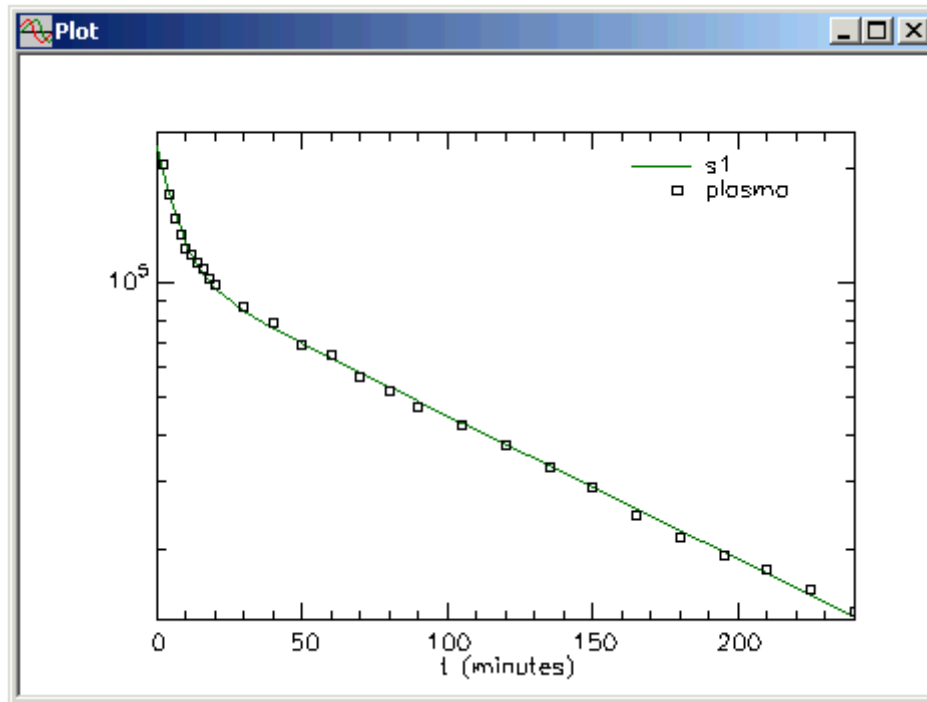
This is quite reasonable, and the parameter estimates were achieved using the quick method with just three hand adjustments to the parameters. This is certainly faster than formal curve peeling, or quick curve peeling.

Be sure to leave the **Plot** window open.


4. Fit your model to your data and view the solution and the statistics.
 - a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar** click, **Fit** . Your model will be updated as follows:



Since your **Plot** window is already open, your plot will be updated and appear as follows:



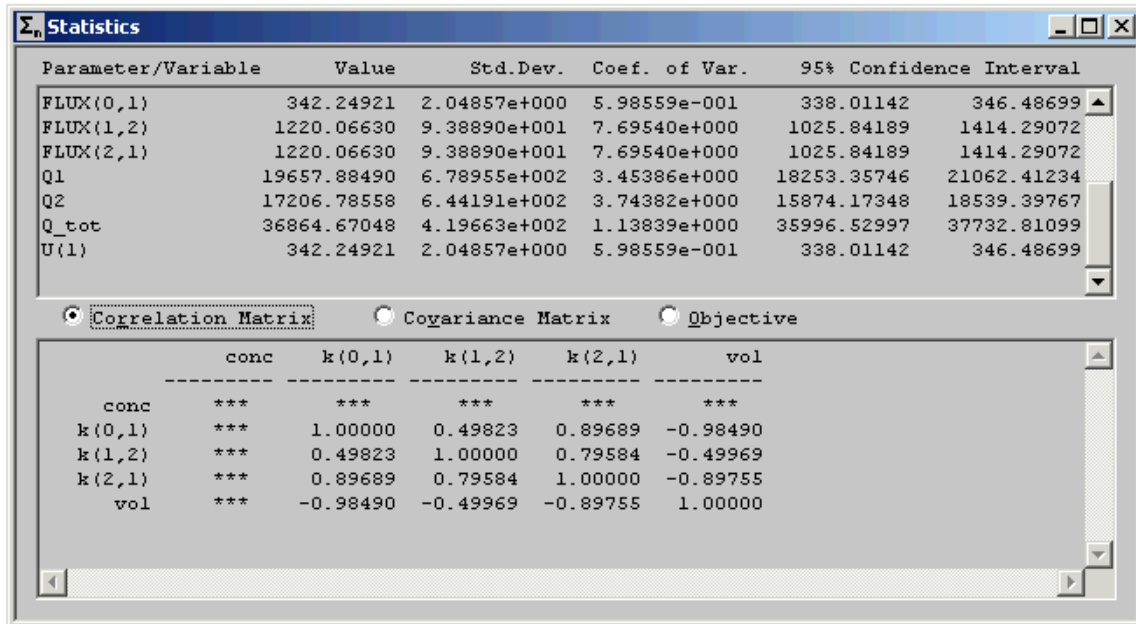
The “fit” appears to be reasonable.

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

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
conc	10.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,1)	0.01741	5.87854e-004	3.37647e+000	0.01619	0.01863
k(1,2)	0.07091	4.40428e-003	6.21143e+000	0.06180	0.08002
k(2,1)	0.06206	6.60573e-003	1.06432e+001	0.04840	0.07573
vol	1965.78849	6.78955e+001	3.45386e+000	1825.33575	2106.24123
----- Derived Variables -----					
FLUX(0,1)	342.24921	2.04857e+000	5.98559e-001	338.01142	346.48699
FLUX(1,2)	1220.06630	9.38890e+001	7.69540e+000	1025.84189	1414.29072
<input type="radio"/> Correlation Matrix <input type="radio"/> Covariance Matrix <input checked="" type="radio"/> Objective					
		Objective	Scaled Data Variance		
s1 : plasma		1.570677e+001	8.651187e-002		
Total objective		1.570677e+001			
AIC		8.957510e+000			
BIC		9.077495e+000			

You can see that the statistics are quite reasonable in that no parameter has a large error.

You will have to scroll through the **Parameter/Variable** pane to see the steady state values for **Q1**, **Q2**, **Q_tot** and **U(1)**. Remember the fluxes **FLUX(I,J)** are also calculated: “ $\text{FLUX(I,J)} = k(\text{I,J}) * Q(\text{J})$ ”. If you also select the **Correlation Matrix** option, the **Statistics** window will appear as follows:




- c. Record the results for the steady state variables and the parsimony criteria AIC and BIC. You will need this information when you compare the results of the two and three-compartment models.

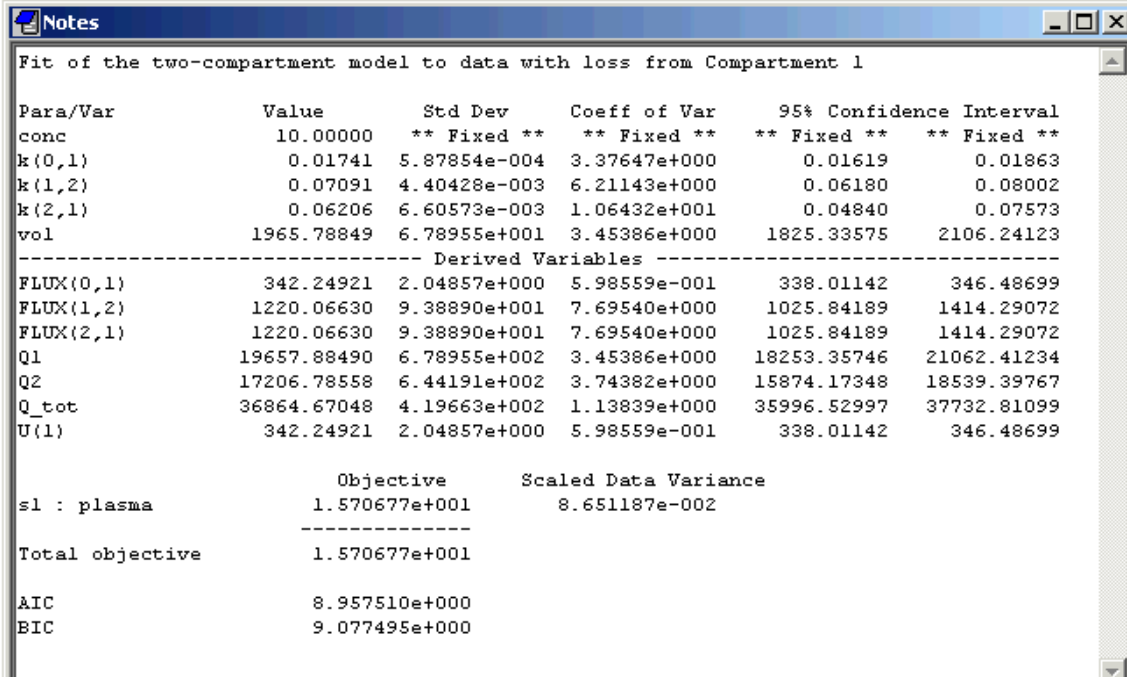
	Two Compartment	Three Compartment
Q1	19658	
Q2	17207	
Q3	0	
Q_tot	36865	
U(1)	342	
OBJ	15.71	
AIC	8.96	
BIC	9.08	

5. Record the results in the **Notes** window (optional).

You may record the results of your modeling exercise using the **Notes** window if you wish. You may also omit this part of the case study. The contents of the **Notes** window are included as Appendix 1.

If you do not do this part of the case study, close the **Statistics** and **Plot** windows and proceed to Step 6. If you do this part of the case study, leave these windows open.

- In the **Show** menu, click **Notes**, or alternatively, on the **SAAM II Toolbar** click **Notes** . The **Notes** window will open.
- Type the text “Fit of the two-compartment model to data with loss from Compartment 1.”
- In the **Statistics** window, select all the information for all the parameters and variables (top pane).
- In the **Edit** menu, click **Copy**.
- Click in the **Notes** window to make it the current window. In the **Edit** menu, click **Paste**. Add the titles to the columns (e.g. value, SD, Coeff of Var, etc.)
- In the **Statistics** window, select the information for the objective function (you may have to make this active if you previously selected the **Correlation Matrix** option).
- Click in the **Notes** window. Click below the statistical information. In the **Edit** menu, click **Copy**. Your **Notes** window should appear as follows:



Notes

Fit of the two-compartment model to data with loss from Compartment 1

Para/Var	Value	Std Dev	Coeff of Var	95% Confidence Interval	
conc	10.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,1)	0.01741	5.87854e-004	3.37647e+000	0.01619	0.01863
k(1,2)	0.07091	4.40428e-003	6.21143e+000	0.06180	0.08002
k(2,1)	0.06206	6.60573e-003	1.06432e+001	0.04840	0.07573
vol	1965.78849	6.78955e+001	3.45386e+000	1825.33575	2106.24123
----- Derived Variables -----					
FLUX(0,1)	342.24921	2.04857e+000	5.98559e-001	338.01142	346.48699
FLUX(1,2)	1220.06630	9.38890e+001	7.69540e+000	1025.84189	1414.29072
FLUX(2,1)	1220.06630	9.38890e+001	7.69540e+000	1025.84189	1414.29072
Q1	19657.88490	6.78955e+002	3.45386e+000	18253.35746	21062.41234
Q2	17206.78558	6.44191e+002	3.74382e+000	15874.17348	18539.39767
Q_tot	36864.67048	4.19663e+002	1.13839e+000	35996.52997	37732.81099
U(1)	342.24921	2.04857e+000	5.98559e-001	338.01142	346.48699


	Objective	Scaled Data Variance			
s1 : plasma	1.570677e+001	8.651187e-002			

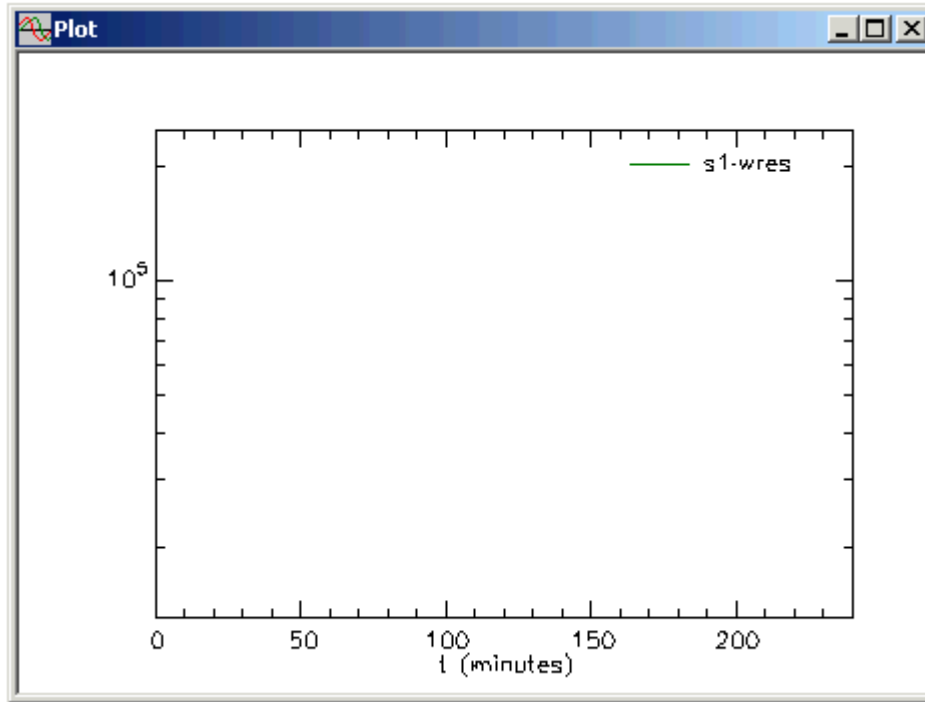
Total objective	1.570677e+001				
AIC	8.957510e+000				
BIC	9.077495e+000				



Two or three compartments? At this point, you have successfully fit the two-compartment model to your data, and estimated the primary parameters and the steady state parameters. How do you know the two-compartment model is the appropriate model? This will be addressed below. We will first examine the residuals from this Fit, and (optionally) perform the runs test for goodness-of-fit (described in Appendix 2). We will then add a third compartment to the model.

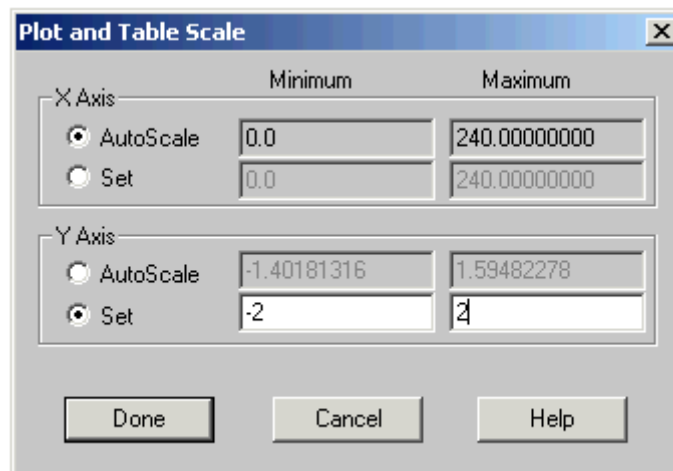


- h. Close the **Statistics** and **Notes** windows.
6. View the residuals.
- a. The **Plot** window should be open. If it is not, in the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . The previous plot of the bit fit of the model to the data will appear. Click on the **Plot** window to be sure it is the current window.
 - b. In the **Set** menu, click **Plot/Table Variables**. The **Plot and Table Variables** dialog box will open.
 - c. Select the **List All Variables** check box.
 - d. Click **s1_wres**. This variable will move to the **Current Selection** pane.
 - e. Click **Done**. The following plot will appear:

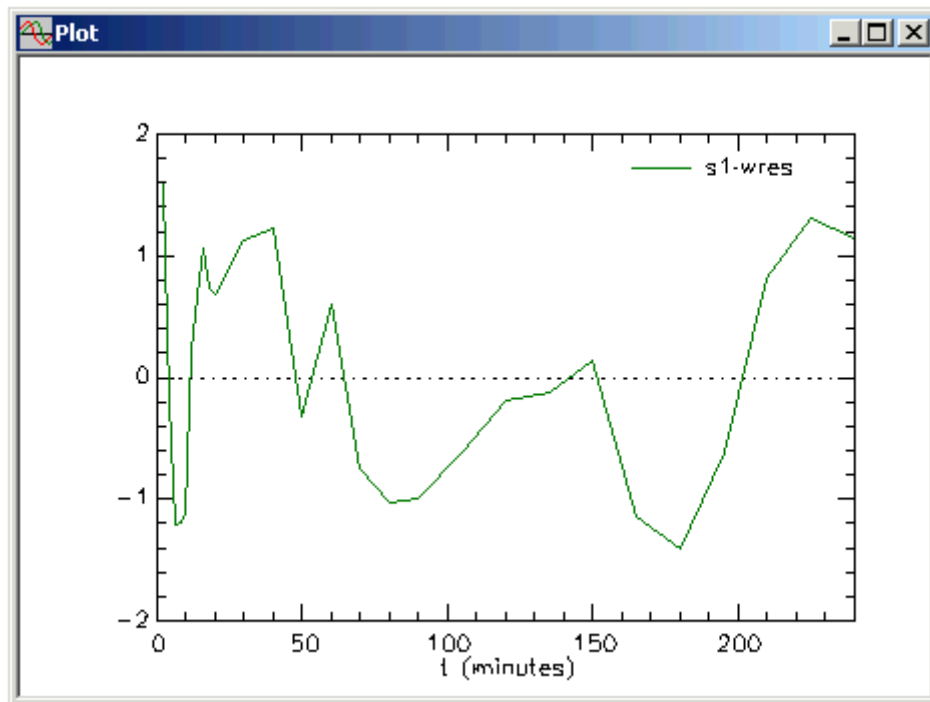


The plot is not informative for two reasons. First, you have previously set the scale; this plot retains that scale. Second the plot is in semi-log mode. This means that no negative residuals can be plotted. Both the scale and the semi-log mode will need to be changed.

- f. In the **View** menu, click **Semilog** to return to a linear plot.
- g. In the **Set** menu, click **Plot/Table Scale**. The **Plot and Table Scale** dialog box will open.
- h. In the **Y Axis** pane, select **Set**. Enter “-2” in the **Minimum** box, and “2” in the **Maximum** box. The **Plot and Table Scale** dialog box will appear as follows:




- i. Click **Done**. Your plot of the weighted residuals will appear as follows:

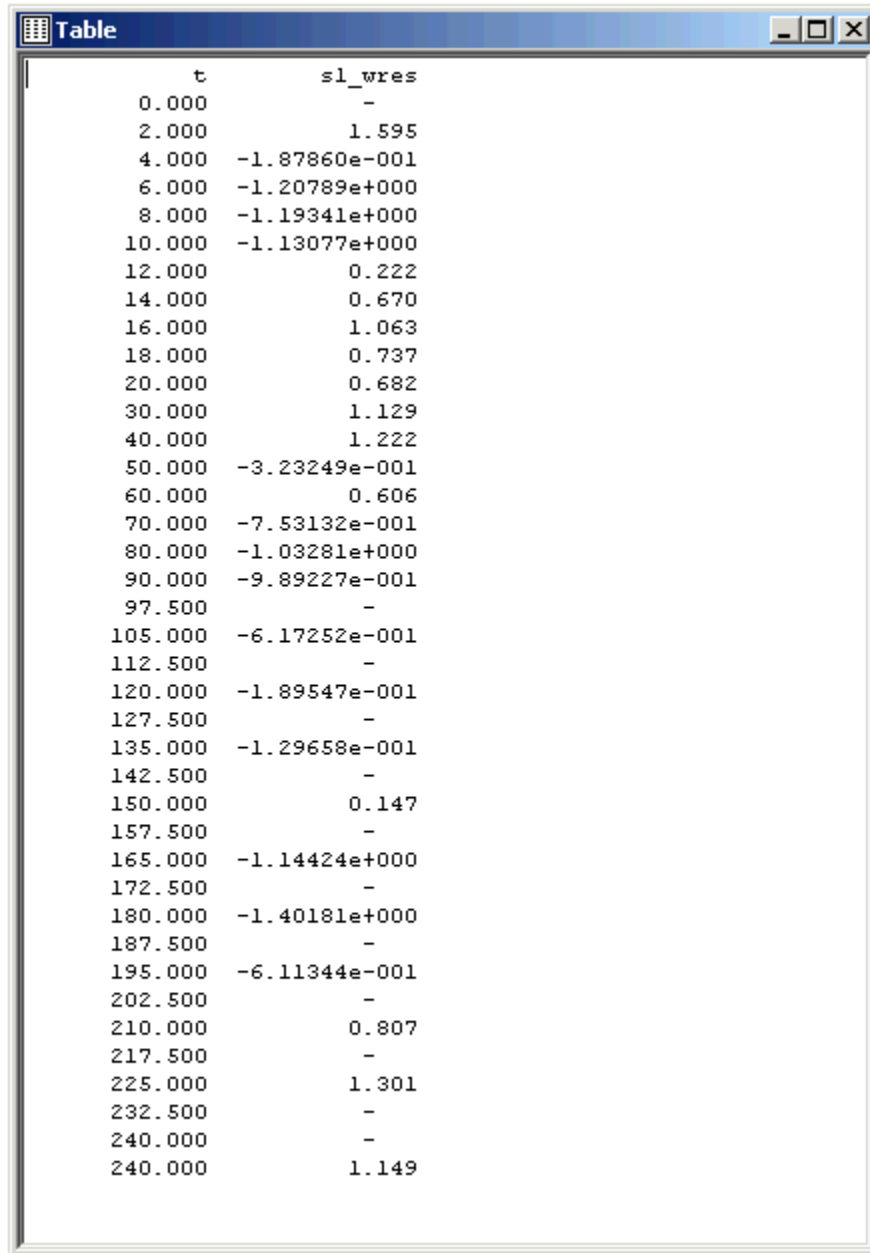


Residuals and weighted residuals. Plotting the residuals or weighted residuals can help you assess your goodness-of-fit; both contain the same information. The weighted residuals, however, should lie in a band between -1 and 1. In the above case, two features are immediately apparent. First, there are systematic deviations that are very clear because the residuals are not uniformly distributed about zero. This may not be immediately obvious by looking at the plot of the best fit of the model to the data.



To perform the runs test, it is useful to have the weighted residuals in tabular form.

- j. In the **Show** menu, click **Table**, or alternatively, on the **SAAM II Toolbar**, click **Table** . Since the **Plot** window is already open with a plot of the weighted residuals, a table of the weighted residuals will open as shown in the following:



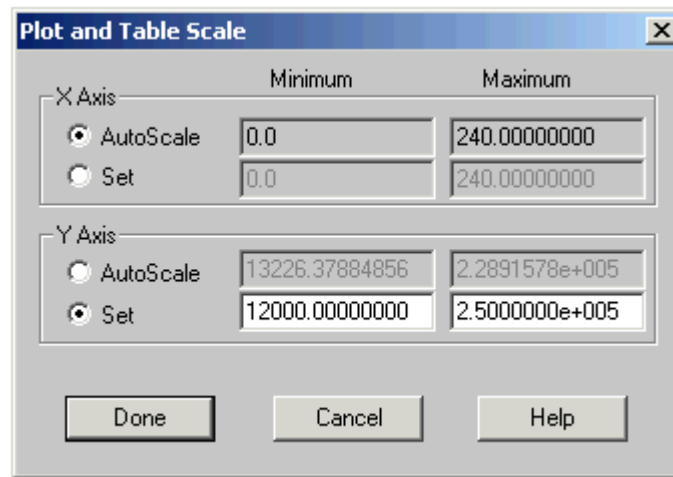
t	s1_wres
0.000	-
2.000	1.595
4.000	-1.87860e-001
6.000	-1.20789e+000
8.000	-1.19341e+000
10.000	-1.13077e+000
12.000	0.222
14.000	0.670
16.000	1.063
18.000	0.737
20.000	0.682
30.000	1.129
40.000	1.222
50.000	-3.23249e-001
60.000	0.606
70.000	-7.53132e-001
80.000	-1.03281e+000
90.000	-9.89227e-001
97.500	-
105.000	-6.17252e-001
112.500	-
120.000	-1.89547e-001
127.500	-
135.000	-1.29658e-001
142.500	-
150.000	0.147
157.500	-
165.000	-1.14424e+000
172.500	-
180.000	-1.40181e+000
187.500	-
195.000	-6.11344e-001
202.500	-
210.000	0.807
217.500	-
225.000	1.301
232.500	-
240.000	-
240.000	1.149

Now the systematic deviations are quite clear. How to perform the runs test is described in Appendix 2.

Close the **Table** window (you can print the contents of this window if you wish to help with the runs test).

- k. Return to your plot of **s1:plasma**. (To return to this plot, you will have to open the **Plot and Table Variables** dialog box, and select **s1:plasma**. You will then have to open the **Plot and Table Scale** dialog box, and reset the scale for the Y Axis. You can either select the AutoScale option, or set your own high and low limits. The reason the scale needs to be reset is that it was

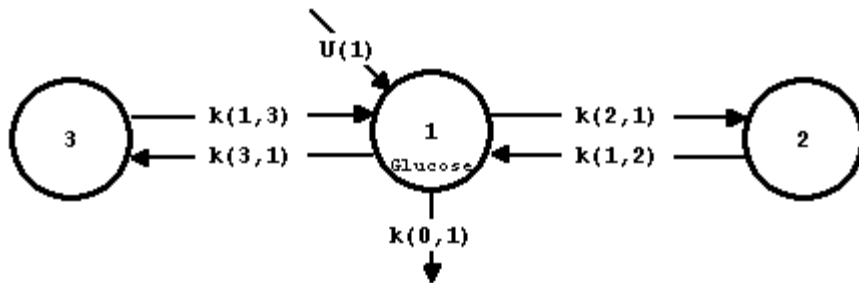
set manually for the plot of the weighted residuals.) An example of resetting the scale is shown in the following:



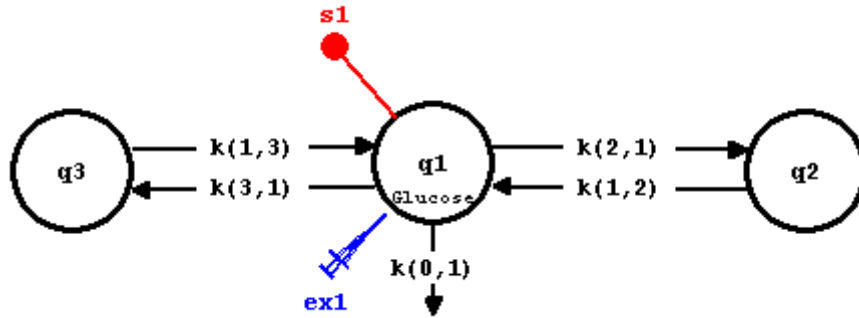
1. Close the **Plot** window.

Part 5. Create a three-compartment model in the SAAM II Compartmental application

1. In the **SAAM II Toolbox**, click **Model** to make these tools available.
2. Modify your system model on the **Drawing Canvas** by adding a third compartment and associated fluxes as follows:



3. In the **SAAM II Toolbox**, click **Experiment**. Notice that the **Model** tools are unavailable and the **Experiment** tools are available. Notice also that the **Experiment Attributes** dialog box, unlike the previous situation, will not open. This is because the experiment attributes have already been specified. The model (of the experiment) will appear as follows (you may need to move the sample or input):

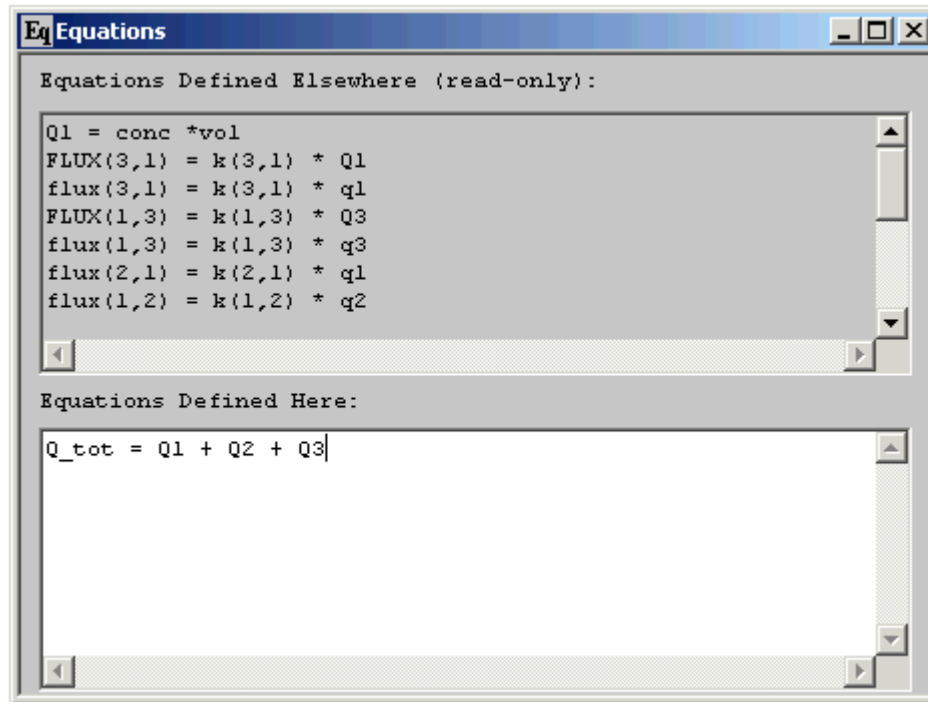


Modifying a system model. Suppose you have created your system model, and your experiment on the model. That is, you have specified your experiment attributes (in this case for both the system and tracer models). In addition, if you have edited your data file, the information will remain. That is, if you have unweighted any data, they will remain unweighted. When you modify your system model by adding more compartments or transfers, your experiment attributes do not change. What will change is the information required to solve your model, or fit your model to your data. When you add additional transfers, you must specify the initial values and limits (if they are adjustable). In this case, you have added a third compartment, Compartment **3**, and two transfers, $k(3,1)$ and $k(1,3)$. Thus to solve the model, you need only provide initial estimates and the limits for these parameters.



4. Change the equation for **Q_tot**.

Since you have added a new Compartment **3** to the model, the equation for **Q_tot** will change. Open the **Equations** dialog box, and modify the equation as shown in the following:



Close the **Equations** dialog box.

5. Enter the parameter values.




Obtaining initial parameter estimates. When you build your model structure as we are doing in the case study, you need to provide initial estimates for your new parameters, in this situation, $k(3,1)$ and $k(1,3)$. You can use the best estimates from your two-compartment model as follows to obtain these estimates. In the case of the two-compartment model, the best estimates are $vol = 1970$, $k(0,1) = 0.017$, $k(2,1) = 0.062$ and $k(1,2) = 0.071$. You now need initial estimates for vol , $k(2,1)$, $k(1,2)$, $k(3,1)$, $k(1,3)$ and $k(0,1)$ for the three-compartment model. Let us assume Compartment **2** is the rapidly turning over compartment.

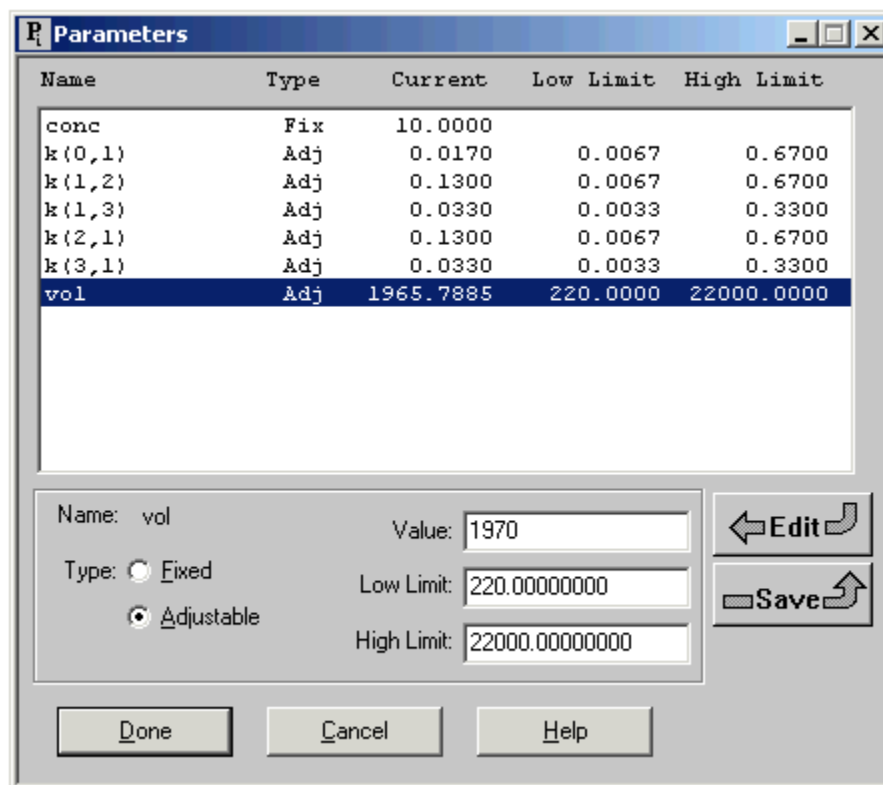
- i. Initial estimates for $k(2,1)$ and $k(1,2)$. Initial estimates for $k(2,1)$ and $k(1,2)$ for the three-compartment model can be obtained by doubling the average of $k(2,1)$ and $k(1,2)$ from the best fit of the two-compartment model. This number is about 0.133.
- ii. Initial estimates for $k(3,1)$ and $k(1,3)$. Initial estimates for $k(3,1)$ and $k(1,3)$ can be obtained by halving the average of $k(2,1)$ and $k(1,2)$ from the best fit of the two-compartment model. This number is about 0.033.

- iii. Initial estimates for vol and $k(0,1)$. Initial estimates for vol and $k(0,1)$ can be obtained by using the best fit values for the two-compartment model. These are 1966 and 0.017 respectively.

This rule of thumb in terms of obtaining initial parameter estimates works most of the time. When it does not, you may need to hand-fit to adjust some of the initial estimates.



- a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar**, click **Parameters** . The **Parameters** dialog box will open. Enter the parameter value as shown in the following:




Name	Type	Current	Low Limit	High Limit
conc	Fix	10.0000		
k(0,1)	Adj	0.0170	0.0067	0.6700
k(1,2)	Adj	0.1300	0.0067	0.6700
k(1,3)	Adj	0.0330	0.0033	0.3300
k(2,1)	Adj	0.1300	0.0067	0.6700
k(3,1)	Adj	0.0330	0.0033	0.3300
vol	Adj	1965.7885	220.0000	22000.0000


Name: vol Value: 1970

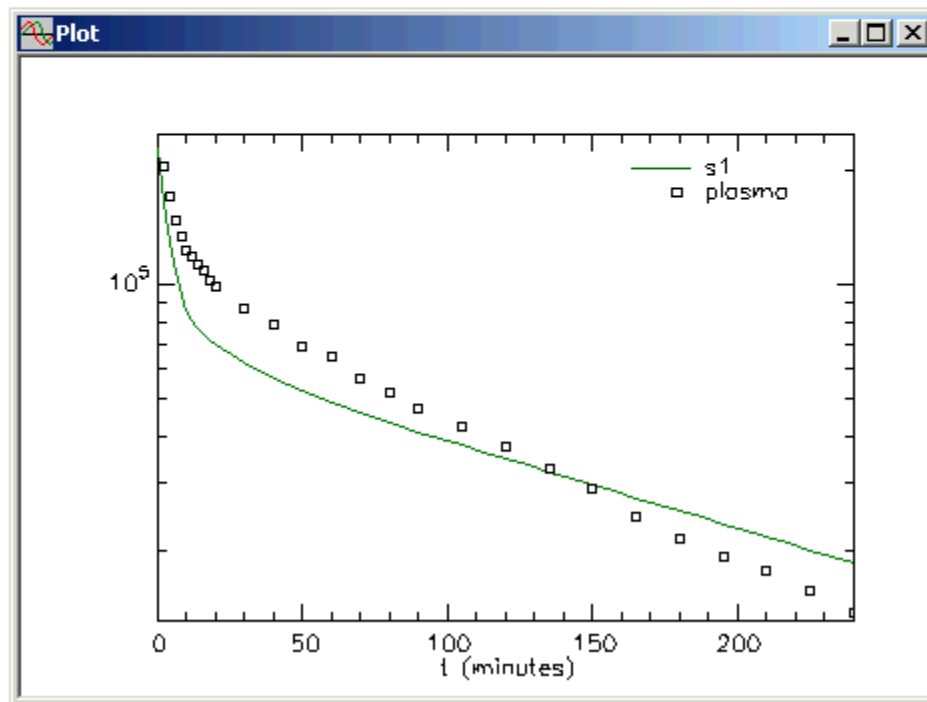
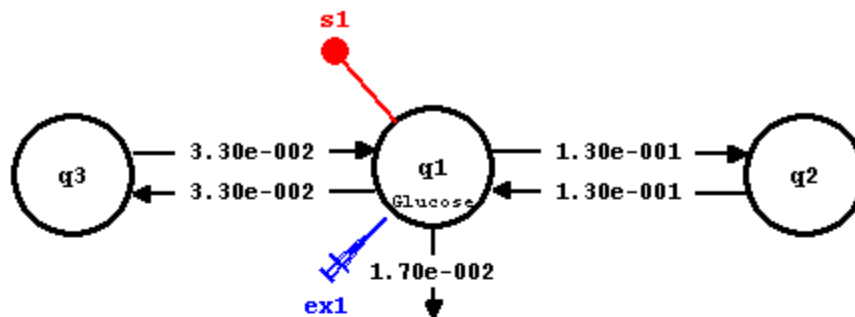
Type: Fixed Low Limit: 220.00000000

Adjustable High Limit: 22000.00000000


Buttons: Edit, Save, Done, Cancel, Help

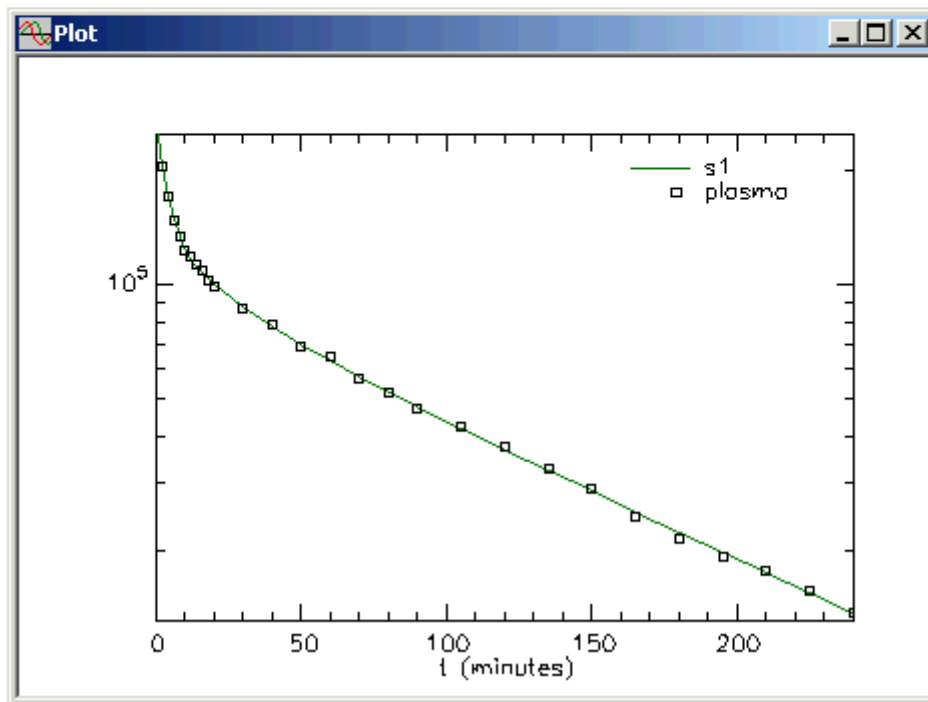
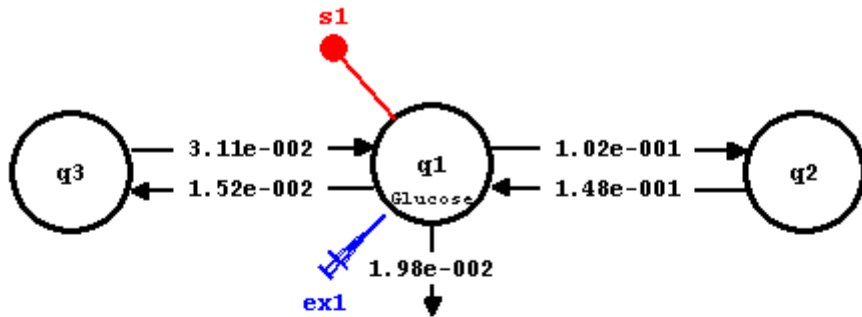
- b. Click **Done**.
6. Solve your model and view the solution.
- a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar**, click **Solve** .


- In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . The **Plot and Table Variables** dialog box will open. (It is possible that a plot of **s1** and **plasma** will appear; if this is the case, you can view the solution, and skip to Part 7.)
- In the **Plot and Table Variables** dialog box, be sure the **List All Variables** check box is cleared to list only those variables associated with data.
- Click **s1:plasma**; it will move to the **Current Selection** pane.
- Click **Done**. The following plot with the model will appear (you will probably have to reset the **Plot and Table Scale**; the following has a **Y Axis minimum** and **maximum** of 13000 and 2.5×10^5 respectively):



The initial parameter estimates are sufficient so that we can proceed to fit the model to the data. Leave the **Plot** window open.

7. Fit the model to the data and view the solution.
- a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar**, click **Fit** . When you have “Fitted” your model to your data, your model and plot will be updated as follows:



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

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
conc	10.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,1)	0.01976	8.03991e-004	4.06944e+000	0.01808	0.02143
k(1,2)	0.14757	2.15374e-002	1.45947e+001	0.10278	0.19236
k(1,3)	0.03109	6.16671e-003	1.98327e+001	0.01827	0.04392
k(2,1)	0.10162	1.40911e-002	1.38658e+001	0.07232	0.13093
k(3,1)	0.01520	5.70681e-003	3.75339e+001	0.00334	0.02707
vol	1710.79501	6.96405e+001	4.07065e+000	1565.96986	1855.62016

----- Derived Variables -----

Correlation Matrix Covariance Matrix Objective

	Objective	Scaled Data Variance
s1 : plasma	1.459865e+001	3.128476e-002

Total objective	1.459865e+001	
AIC	8.477523e+000	
BIC	8.645502e+000	

The statistics appear reasonable with the largest coefficient of variation being about 38%.

You will have to scroll through the **Parameter/Variable** pane to see the steady state values for **Q1**, **Q2**, **Q_tot** and **U(1)**. Remember the fluxes **FLUX(I,J)** are also calculated: “ $FLUX(I,J) = k(I,J) \cdot Q(J)$ ”. If you also select the **Correlation Matrix** option, the **Statistics** window will appear as follows:

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
FLUX(2,1)	1738.59059	1.78363e+002	1.02591e+001	1367.66424	2109.51695
FLUX(3,1)	260.11603	9.29184e+001	3.57219e+001	66.88201	453.35005
Q1	17107.95011	6.96405e+002	4.07065e+000	15659.69859	18556.20164
Q2	11781.44018	1.38546e+003	1.17597e+001	8900.22188	14662.65849
Q3	8365.55709	1.44013e+003	1.72149e+001	5370.65799	11360.45620
Q_tot	37254.94739	3.52395e+002	9.45901e-001	36522.10368	37987.79110
U(1)	337.99836	1.67995e+000	4.97029e-001	334.50472	341.49201

Correlation Matrix Covariance Matrix Objective

	conc	k(0,1)	k(1,2)	k(1,3)	k(2,1)	k(3,1)	vol
conc	***	***	***	***	***	***	***
k(0,1)	***	1.00000	0.69290	0.39209	0.89763	0.55423	-0.99254
k(1,2)	***	0.69290	1.00000	0.74778	0.63643	0.87774	-0.65328
k(1,3)	***	0.39209	0.74778	1.00000	0.11756	0.95632	-0.31422
k(2,1)	***	0.89763	0.63643	0.11756	1.00000	0.31065	-0.91758
k(3,1)	***	0.55423	0.87774	0.95632	0.31065	1.00000	-0.48863
vol	***	-0.99254	-0.65328	-0.31422	-0.91758	-0.48863	1.00000

- c. Record the results for the steady state variables and the parsimony criteria AIC and BIC. You will need this information when you compare the results of the two and three-compartment models.

	Two Compartment	Three Compartment Mammillary
Q1	19658	17108
Q2	17207	11781
Q3	0	8366
Q_tot	36865	37255
U(1)	342	338
OBJ	15.71	14.60
AIC	8.96	8.48
BIC	9.08	8.65

We will say more about which model is more appropriate in a moment.

What are the differences between the two- and three-compartment models? The mass in Compartment **Q1** has changed. The reason why is not that the measured concentration changed, but, because the three-compartment model describes the initial decay of the data better, there are differences in the estimated volume *vol* between the two models. For the two-compartment model, *vol* was 1966 while for the three-compartment model, it is 1710.


It is of interests that neither the total mass **Q_tot** nor the synthesis **U(1)** changes very much between the two models. This is because both models provide a reasonable description of the data as indicated by comparing the values of the objective functions, and the parsimony criteria AIC and BIC.

Still, as will be seen below, the three-compartment model can be judged to provide a better description of the data than the two-compartment model.

8. Record the results in the **Notes** window (optional).

You may record the results of your modeling exercise using the **Notes** window if you wish. You may also omit this part of the case study. The contents of the **Notes** window are included as Appendix 1.

If you do not do this part of the case study, close the **Statistics** and **Plot** windows and proceed to Step 9. If you do this part of the case study, leave these windows open.

- In the **Show** menu, click **Notes**, or alternatively, on the **SAAM II Toolbar** click **Notes** . The **Notes** window will open.
- Type the text “Fit of the three-compartment mammillary model to data with loss from Compartment 1.”

- c. In the **Statistics** window, select all the information for all the parameters.
- d. In the **Edit** menu, click **Copy**.
- e. Click in the **Notes** window to make it the current window. In the **Edit** menu, click **Paste**.
- f. In the **Statistics** window, select the information for the objective function (you may have to make this active if you previously selected the **Correlation Matrix** option).
- g. Click in the **Notes** window. Click below the statistical information. In the **Edit** menu, click **Copy**. Your **Notes** window should appear in part as follows:

```

Fit of the three-compartment mammillary model to data with loss from Compartment 1

```

conc	10.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,1)	0.01976	8.03991e-004	4.06944e+000	0.01808	0.02143
k(1,2)	0.14757	2.15374e-002	1.45947e+001	0.10278	0.19236
k(1,3)	0.03109	6.16671e-003	1.98327e+001	0.01827	0.04392
k(2,1)	0.10162	1.40911e-002	1.38658e+001	0.07232	0.13093
k(3,1)	0.01520	5.70681e-003	3.75339e+001	0.00334	0.02707
vol	1710.79501	6.96405e+001	4.07065e+000	1565.96986	1855.62016
----- Derived Variables -----					
FLUX(0,1)	337.99836	1.67995e+000	4.97029e-001	334.50472	341.49200
FLUX(1,2)	1738.59059	1.78363e+002	1.02591e+001	1367.66423	2109.51694
FLUX(1,3)	260.11603	9.29184e+001	3.57219e+001	66.88201	453.35005
FLUX(2,1)	1738.59059	1.78363e+002	1.02591e+001	1367.66423	2109.51694
FLUX(3,1)	260.11603	9.29184e+001	3.57219e+001	66.88201	453.35005
Q1	17107.95010	6.96405e+002	4.07065e+000	15659.69858	18556.20162
Q2	11781.44015	1.38546e+003	1.17597e+001	8900.22185	14662.65846
Q3	8365.55710	1.44013e+003	1.72149e+001	5370.65800	11360.45621
Q_tot	37254.94736	3.52395e+002	9.45901e-001	36522.10365	37987.79107
U(1)	337.99836	1.67995e+000	4.97029e-001	334.50472	341.49200


		Objective	Scaled Data Variance		
sl : plasma		1.459865e+001	3.128476e-002		

Total objective		1.459865e+001			

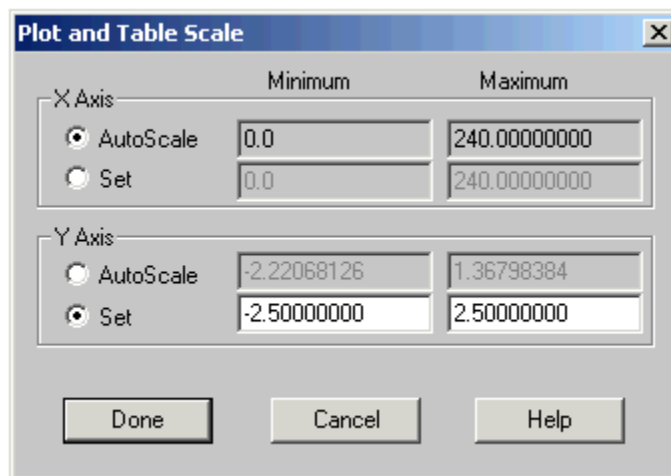
AIC		8.477523e+000			
BIC		8.645502e+000			

- h. Close the **Statistics** and **Notes** windows. Leave the **Plot** window open.

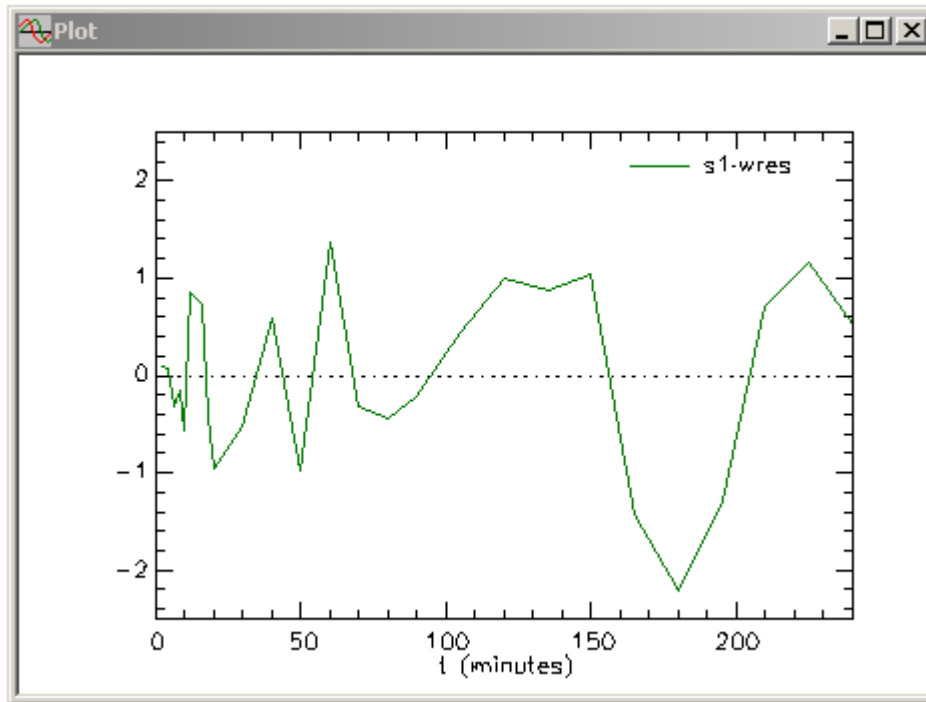
9. View the residuals.

- a. The **Plot** window should be open. If it is not, in the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . The previous plot of the fit of the model to the data will appear. Click on the **Plot** window to be sure it is the current window.
- b. In the **Set** menu, click **Plot/Table Variables**. The **Plot and Table Variables** dialog box will open.


- c. Select the **List All Variables** check box.
- d. Click **s1_wres**. This variable will move to the **Current Selection** pane.
- e. Click **Done**. As before, the plot is not informative. Remember you have previously set the scale; this plot retains that scale. Second the plot is in semi-log mode. This means that no negative residuals can be plotted. Both the scale and the semi-log mode will need to be changed.
- e. In the **View** menu, click **Semilog** to return to a linear plot.
- f. In the **Set** menu, click **Plot/Table Scale**. The **Plot and Table Scale** dialog box will open.
- g. In the **Y Axis** pane, select **Set**. Enter “-2.5” in the **Minimum** box, and “2.5” in the **Maximum** box. The **Plot and Table Scale** dialog box will appear as follows:

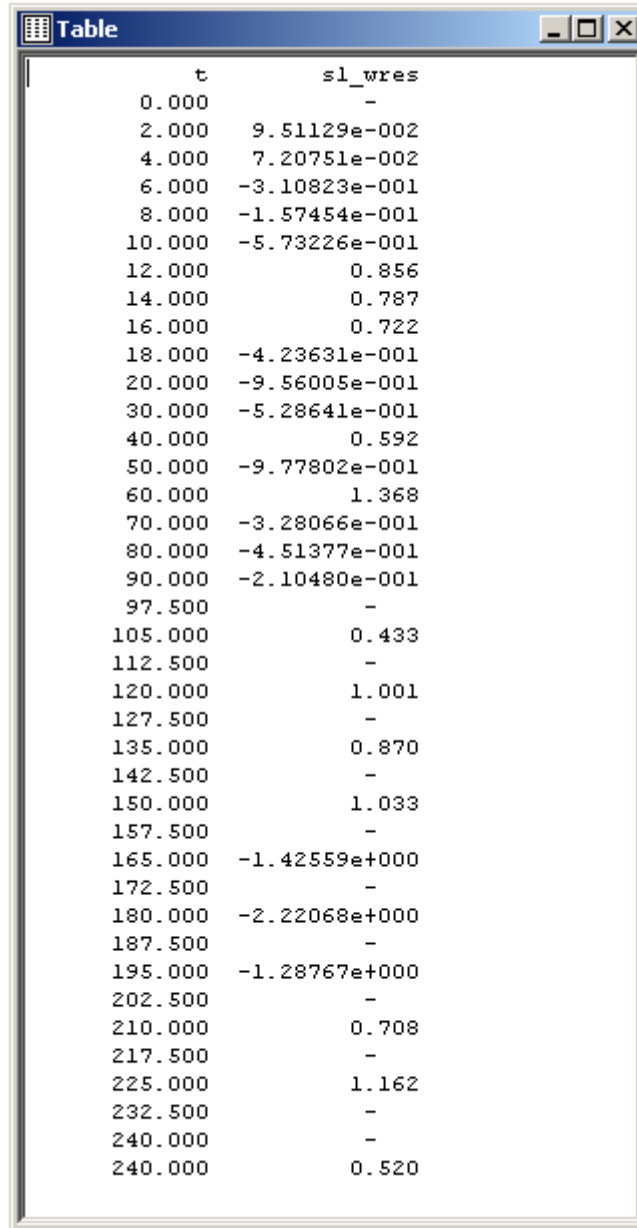


- h. Click **Done**. Your plot of the weighted residuals will appear as follows:



To perform the runs test, it is useful to have the weighted residuals in tabular form. This will also help to show that the residuals are more randomly distributed for the three-compartment model when compared to the two-compartment model.

- i. In the **Show** menu, click **Table**, or alternatively, on the **SAAM II Toolbar**, click **Table** . Since the **Plot** window is already open with a plot of the weighted residuals, a table of the weighted residuals will open as shown in the following:



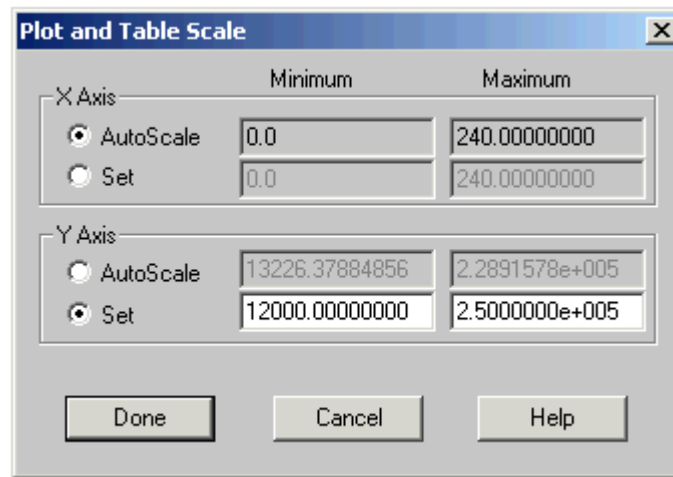
t	s1_wres
0.000	-
2.000	9.51129e-002
4.000	7.20751e-002
6.000	-3.10823e-001
8.000	-1.57454e-001
10.000	-5.73226e-001
12.000	0.856
14.000	0.787
16.000	0.722
18.000	-4.23631e-001
20.000	-9.56005e-001
30.000	-5.28641e-001
40.000	0.592
50.000	-9.77802e-001
60.000	1.368
70.000	-3.28066e-001
80.000	-4.51377e-001
90.000	-2.10480e-001
97.500	-
105.000	0.433
112.500	-
120.000	1.001
127.500	-
135.000	0.870
142.500	-
150.000	1.033
157.500	-
165.000	-1.42559e+000
172.500	-
180.000	-2.22068e+000
187.500	-
195.000	-1.28767e+000
202.500	-
210.000	0.708
217.500	-
225.000	1.162
232.500	-
240.000	-
240.000	0.520

You can use the information in this table to perform the runs test. How to perform the runs test is described in Appendix 2. You can see the systematic deviations present in the two-compartment model are not as evident here.

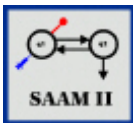
Close the **Table** window (you can print the contents of this window if you wish to help with the runs test).

- j. Return to your plot of **s1:plasma**. (To return to this plot, you will have to open the **Plot and Table Variables** dialog box, and select **s1:plasma**. You will then have to open the **Plot and Table Scale** dialog box, and reset the scale for the Y Axis. You can either select the AutoScale option, or set your own high and low limits. The reason the scale needs to be reset is that it was

set manually for the plot of the weighted residuals.) An example of resetting the scale is shown in the following:



- k. Close the **Plot** window.



Which model is best? You have two pieces of information to help determine which of the two or three-compartment model is most appropriate to describe the glucose data. These are the residuals and the parsimony parameters. The residuals in the case of the three-compartment model are better because they do not have systematic deviations. If you have performed a runs test, this observation can be confirmed. Second you have the parsimony parameters, AIC and BIC. Because those for the three-compartment are smaller than those for the two-compartment model, we choose the three-compartment model as the model best describing the plasma glucose data

To complete the exercise, you should try a four-compartment model. If you do (following the above rules for obtaining initial parameter estimates), in most cases you will have problems fitting with different parameter values hitting lower limits. In the event that you choose a set of initial values where you actually fit, you will find that some of your parameters have error estimates greater than 100%, and that the values for AIC and BIC for the four-compartment model are larger than those for the three-compartment model.

Thus you can safely choose the three-compartment model for glucose kinetics.

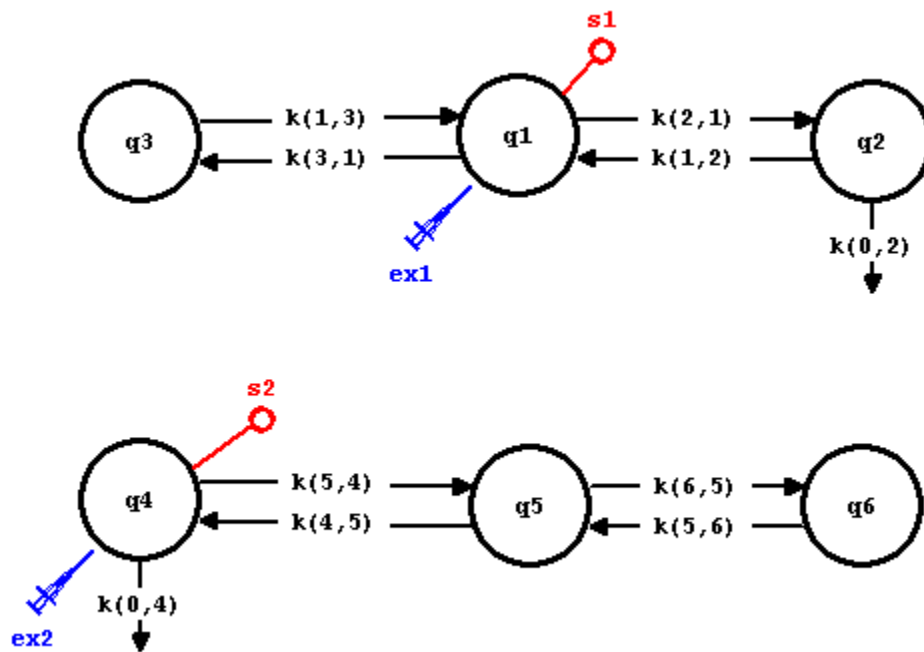


Part 6. Investigate the a priori identifiability of the three-compartment model (optional)

This part of the case study will investigate the a priori identifiability of the three-compartment model.

If you do not wish to work through this part of the case study, you may **Quit** the **SAAM II Compartmental** application. You can save your study file for future reference if you wish.

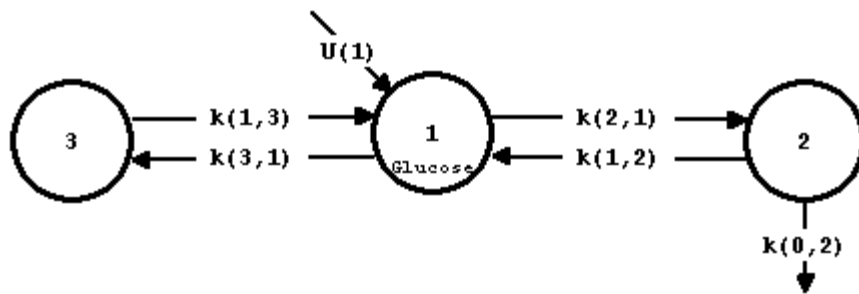
There are actually 18 basic model structures for the three-compartment model making the situation much more complex than the situation for the two-compartment model. In this part of the case study, we will investigate the following two model structures:



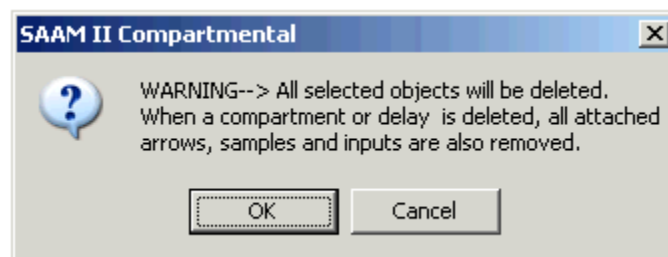
The first is the mammillary model but with the loss from a peripheral compartment rather than the central compartment. We will see this model is not a priori identifiable, but has two solutions. The second model, called a catenary model, is a priori identifiable. But when compared to the mammillary model, it has a different physiological interpretation.

Thus, while both the mammillary model (with loss from the central compartment) and the catenary model are a priori identifiable, they had different physiological interpretations, and will have different estimates for the steady state variables.

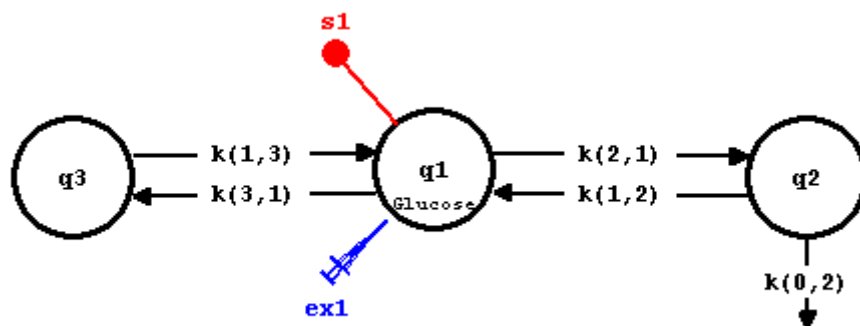
1. Work with the following model:



- In the **SAAM II Toolbox**, click **Model** to return to the system model and activate these tools.
- Click on $k(0,1)$, and then press **Delete**. (If you have the values option active, $k(0,1)$ will appear with its current numerical value.) The following warning message will appear:



- Click **OK**.
- Click the **Flux** tool, and then click on Compartment **2** and the **Drawing Canvas** to create $k(0,2)$.
- In the **SAAM II Toolbox**, click **Experiment**. Your model will appear as follows:



Remember all **Experiment Attributes** have been set.



Loss from a peripheral compartment. In the first three-compartment model studied, the loss was from the central compartment (plasma). This model can be shown to be *a priori* identifiable; equations similar to those written for the two-compartment model can be produced (see the Case Study on the two-compartment model). In the case when the loss is from a peripheral compartment, we will see that there are in fact two solutions that minimize the objective function. The reason why is that one of the peripheral compartments turns over more rapidly than the second. Thus the loss can occur from either the rapid one, or the slow one.



- f. Enter the parameter values as shown in the following **Parameters** dialog box.

Name	Type	Current	Low Limit	High Limit
conc	Fix	10.0000		
k(0,2)	Adj	0.0200	0.0020	0.2000
k(1,2)	Adj	0.1000	0.0100	1.0000
k(1,3)	Adj	0.0200	0.0020	2.0000
k(2,1)	Adj	0.1000	0.0100	1.0000
k(3,1)	Adj	0.0200	0.0020	2.0000
vol	Adj	1800.0000	180.0000	18000.0000

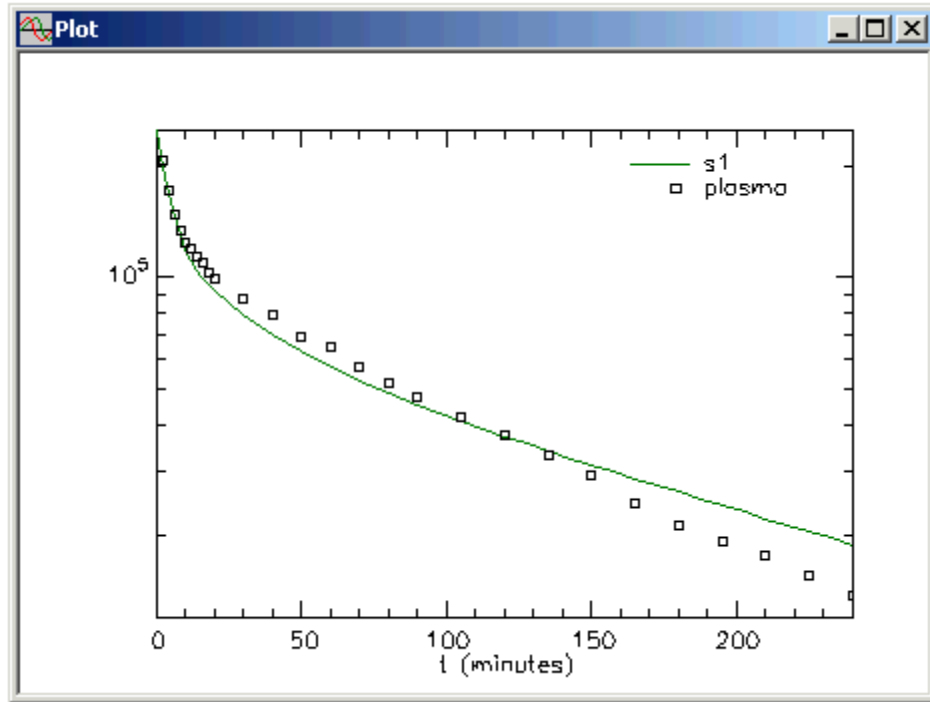
Name: vol Value: 1800

Type: Fixed Low Limit: 180.00000000

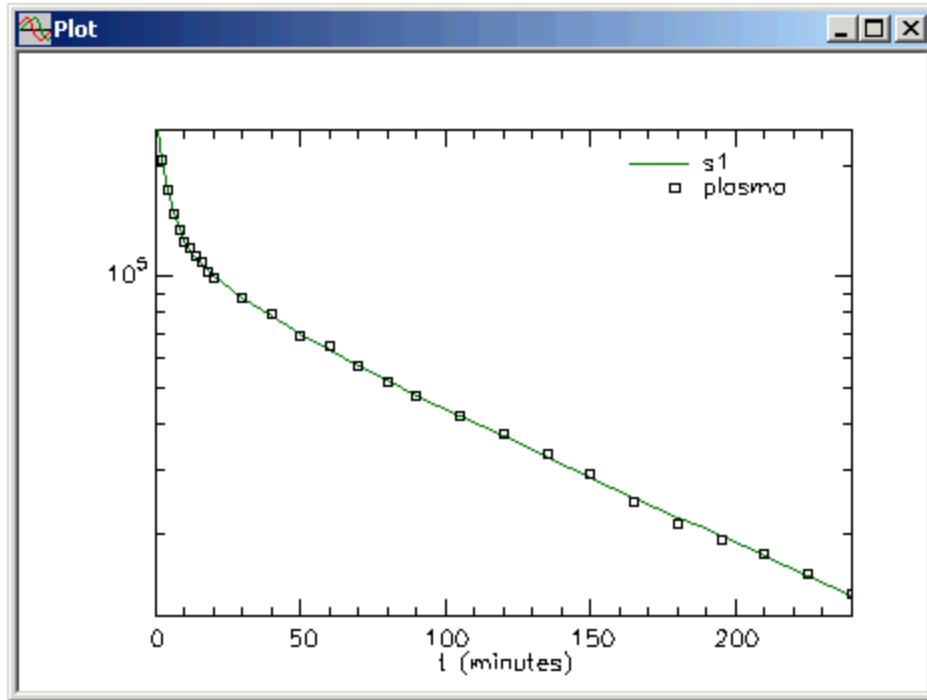
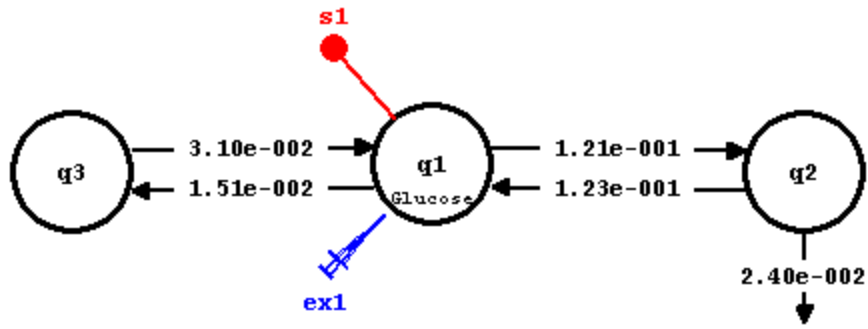
Adjustable High Limit: 18000.00000000

Buttons: Done, Cancel, Help, Edit, Save

- g. Solve the model and view the solution. The plot will appear as follows:



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



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

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
conc	10.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,2)	0.02398	2.85003e-003	1.18827e+001	0.01806	0.02991
k(1,2)	0.12331	1.92456e-002	1.56073e+001	0.08329	0.16333
k(1,3)	0.03102	6.17412e-003	1.99050e+001	0.01818	0.04386
k(2,1)	0.12129	1.47749e-002	1.21813e+001	0.09057	0.15202
k(3,1)	0.01513	5.69048e-003	3.76154e+001	0.00329	0.02696
vol	1711.32508	6.95487e+001	4.06402e+000	1566.69098	1855.95919

----- Derived Variables -----

Correlation Matrix
 Covariance Matrix
 Objective

	Objective	Scaled Data Variance
s1 : plasma	1.459868e+001	3.128570e-002
Total objective	1.459868e+001	
AIC	8.477538e+000	
BIC	8.645517e+000	

Scroll to see the steady state variables.

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
FLUX(2,1)	2075.69087	1.77559e+002	8.55423e+000	1706.43646	2444.94528
FLUX(3,1)	258.89027	9.27011e+001	3.58071e+001	66.10817	451.67237
Q1	17113.25084	6.95487e+002	4.06402e+000	15666.90982	18559.59186
Q2	14091.93639	1.63519e+003	1.16037e+001	10691.37681	17492.49596
Q3	8346.45513	1.43843e+003	1.72340e+001	5355.08540	11337.82485
Q_tot	39551.64236	5.79938e+002	1.46628e+000	38345.59667	40757.68805
U(1)	337.99163	1.68227e+000	4.97725e-001	334.49316	341.49009

Correlation Matrix
 Covariance Matrix
 Objective

	Objective	Scaled Data Variance
s1 : plasma	1.459868e+001	3.128570e-002
Total objective	1.459868e+001	
AIC	8.477538e+000	
BIC	8.645517e+000	

- j. Record the results for the steady state variables and fitting information. An example follows:

	Two Compartment	Three Compartment Mammillary	Three Compartment Loss from Fast
Q1	19658	17108	17113
Q2	17207	11781	14092
Q3	0	8366	8347
Q_tot	36865	37255	39552
U(1)	342	338	338
OBJ	15.71	14.60	14.60
AIC	8.96	8.48	8.48
BIC	9.08	8.65	8.65

- k. Record the results as you have done previously in the **Notes** window (Optional). This part of the **Notes** window will appear (approximately) as follows:

```

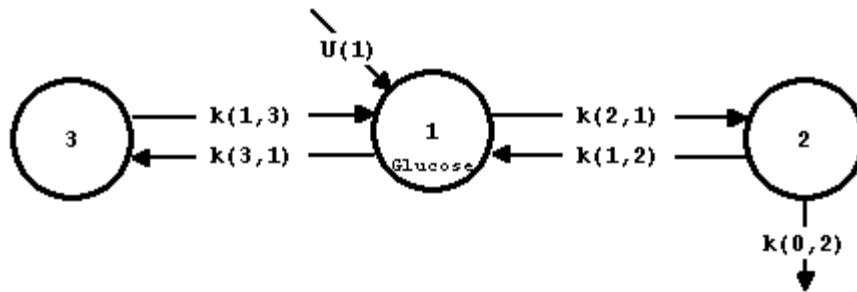
Fit of the three-compartment mammillary model to data with loss from Compartment 2 where
Compartment 2 is the rapidly turning over peripheral compartment

conc          10.00000  ** Fixed **  ** Fixed **  ** Fixed **  ** Fixed **
k(0,2)        0.02403  2.86077e-003  1.19068e+001  0.01808  0.02998
k(1,2)        0.12360  1.93290e-002  1.56389e+001  0.08340  0.16379
k(1,3)        0.03111  6.16729e-003  1.98251e+001  0.01828  0.04393
k(2,1)        0.12140  1.48247e-002  1.22118e+001  0.09057  0.15223
k(3,1)        0.01522  5.71124e-003  3.75270e+001  0.00334  0.02710
vol           1710.70119  6.96578e+001  4.07188e+000  1565.84019  1855.56218
----- Derived Variables -----
FLUX(0,2)     338.00217  1.68010e+000  4.97067e-001  334.50823  341.49612
FLUX(1,2)    1738.74205  1.78454e+002  1.02634e+001  1367.62675  2109.85736
FLUX(1,3)     260.35165  9.29830e+001  3.57144e+001  66.98329  453.72001
FLUX(2,1)    2076.74423  1.78127e+002  8.57723e+000  1706.30930  2447.17915
FLUX(3,1)     260.35165  9.29830e+001  3.57144e+001  66.98329  453.72001
Q1            17107.01186  6.96578e+002  4.07188e+000  15658.40195  18555.62177
Q2            14067.96930  1.63587e+003  1.16283e+001  10666.00677  17469.93183
Q3            8369.16306  1.44065e+003  1.72138e+001  5373.17288  11365.15323
Q_tot         39544.14421  5.78599e+002  1.46317e+000  38340.88458  40747.40385
U(1)          338.00217  1.68010e+000  4.97067e-001  334.50823  341.49612

Objective      Scaled Data Variance
s1 : plasma    1.459865e+001      3.128463e-002
-----
Total objective 1.459865e+001
AIC            8.477521e+000
BIC            8.645500e+000

```

- Close all open windows.
- Work with the following model (continued):



In the above, we assumed Compartment 2 was the rapidly turning over peripheral compartment. We will now assume it is the slowly turning over peripheral compartment.

- a. Enter the parameter values as shown in the following **Parameters** dialog box.

Name	Type	Current	Low Limit	High Limit
conc	Fix	10.0000		
k(0,2)	Adj	0.0200	0.0020	0.2000
k(1,2)	Adj	0.0300	0.0030	0.3000
k(1,3)	Adj	0.1000	0.0100	1.0000
k(2,1)	Adj	0.0300	0.0030	0.3000
k(3,1)	Adj	0.1000	0.0100	1.0000
vol	Adj	1800.0000	180.0000	18000.0000

Name: vol Value: 1800

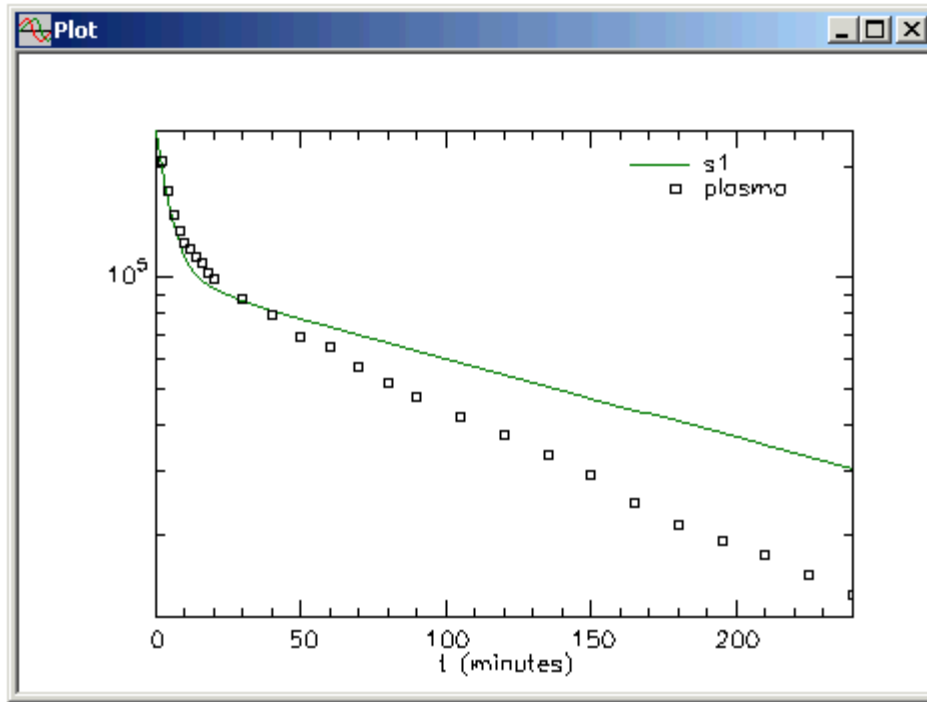
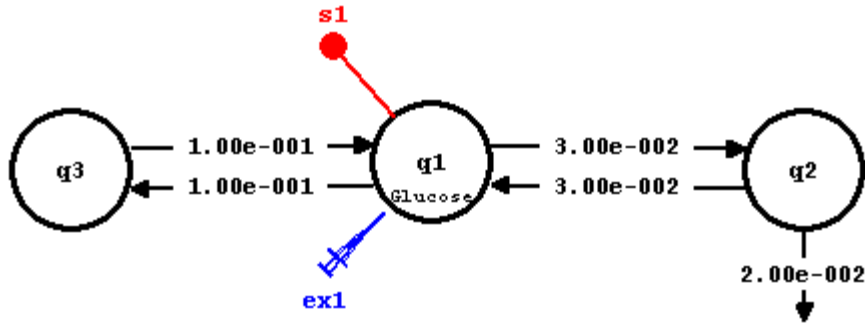
Type: Fixed Low Limit: 180.00000000

Adjustable High Limit: 18000.00000000

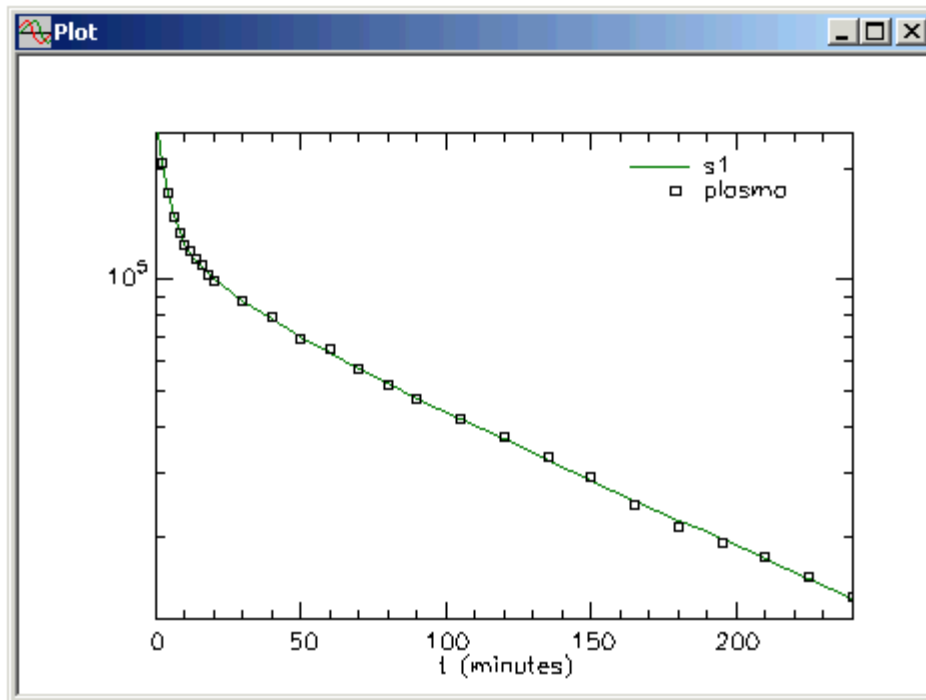
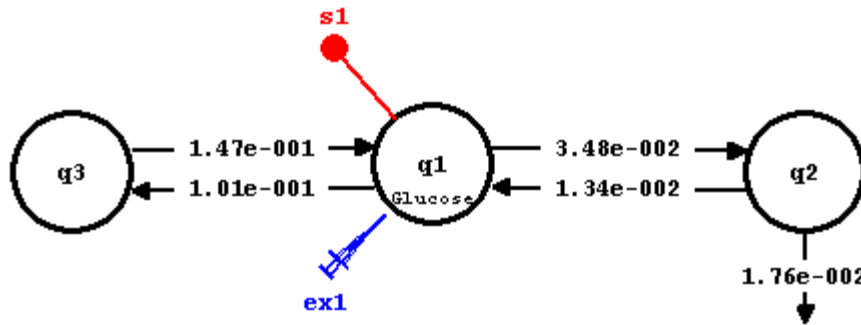
Buttons: Edit, Save, Done, Cancel, Help

Notice in setting these parameter estimates, the roles of $k(2,1)$ and $k(1,2)$ are interchanged from the initial solution from $k(3,1)$ and $k(1,3)$.

- b. Solve the model and view the solution. The model and plot will appear as follows:



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



You can see visually that this Fit is identical with the previous fit. The difference, however, is in the values for the rate constants. In the first Fit, Compartment **q2** was the rapidly turning over compartment while in this case, it is the slowly turning over compartment.

If you were not aware that two solutions existed for this model configuration, then you could reach erroneous conclusions from your model since the best-fit values of the parameters depend upon your initial estimates.

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

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
conc	10.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,2)	0.01756	1.12028e-003	6.38119e+000	0.01523	0.01989
k(1,2)	0.01338	5.32240e-003	3.97910e+001	0.00231	0.02444
k(1,3)	0.14699	2.13619e-002	1.45329e+001	0.10257	0.19141
k(2,1)	0.03478	6.14085e-003	1.76541e+001	0.02201	0.04755
k(3,1)	0.10145	1.40067e-002	1.38059e+001	0.07233	0.13058
vol	1711.89851	6.94404e+001	4.05634e+000	1567.48948	1856.30755

	Objective	Scaled Data Variance
s1 : plasma	1.459873e+001	3.128715e-002
Total objective	1.459873e+001	
AIC	8.477562e+000	
BIC	8.645540e+000	

Scroll to see the steady state variables.

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
FLUX(2,1)	595.46973	9.32411e+001	1.56584e+001	401.56469	789.37477
FLUX(3,1)	1736.78589	1.77367e+002	1.02124e+001	1367.93179	2105.63998
Q1	17118.98514	6.94404e+002	4.05634e+000	15674.89478	18563.07551
Q2	19250.95486	1.16884e+003	6.07159e+000	16820.22385	21681.68587
Q3	11815.65809	1.38248e+003	1.17004e+001	8940.63330	14690.68287
Q_tot	48185.59809	2.39006e+003	4.96012e+000	43215.19874	53155.99743
U(1)	337.97084	1.68921e+000	4.99811e-001	334.45794	341.48375

	Objective	Scaled Data Variance
s1 : plasma	1.459873e+001	3.128715e-002
Total objective	1.459873e+001	
AIC	8.477562e+000	
BIC	8.645540e+000	

- e. Record the results for the steady state variables and fitting information. An example follows:

	Two Compartment	Three Compartment Mammillary	Three Compartment Loss from Fast
Q1	19658	17108	17113
Q2	17207	11781	14092
Q3	0	8366	8347
Q_tot	36865	37255	39552
U(1)	342	338	338
OBJ	15.71	14.60	14.60
AIC	8.96	8.48	8.48
BIC	9.08	8.65	8.65

	Three Compartment Loss from Slow
Q1	17119
Q2	19251
Q3	11816
Q_tot	48186
U(1)	338
OBJ	14.60
AIC	8.48
BIC	8.65

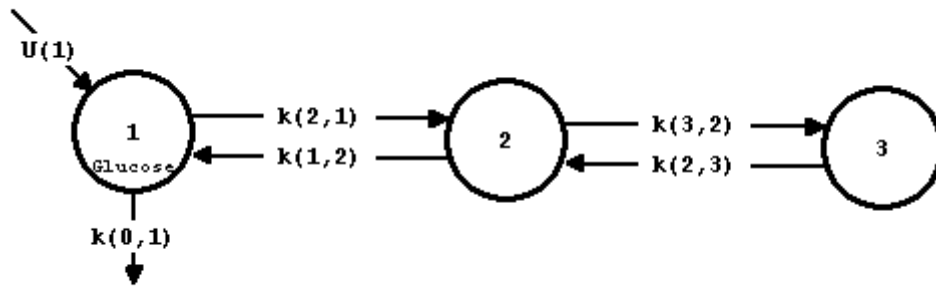


Steady state variables and model configuration. You can now compare the results of the three-compartment mammillary model. Production **U(1)** changes little. The reason is that production is always in the central compartment. You should experiment (as you did with the two-compartment model) changing **U(1)** to **U(2)**, i.e. production into Compartment **2**. If you do this, you will find significant difference, especially in the two situations we have just investigated.

Thus when using this model to interpret your data including steady state data, it is important to think carefully about the compartment into which production will occur.



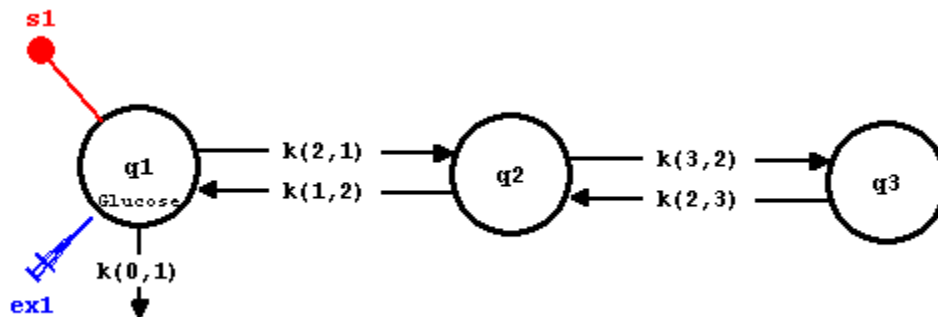
- f. Record the results as you have done previously in the **Notes** window (Optional). (The results are shown in Appendix 1.)
 - g. Close all open windows.
3. Work with the following model:



To create this model, you will have to delete Compartment **3** from the mammillary model, and you will have to delete $k(0,2)$ from the previous model. You will then need to add Compartment **3** again, and create the fluxes $k(3,2)$, $k(2,3)$ and $k(0,1)$. This model is called the catenary three-compartment model.

In addition, because you deleted Compartment **3** from your model, it will be removed from the equation for Q_{tot} . Thus you will also need to open the **Equations** dialog box, and redefine Q_{tot} as the sum of $Q1$, $Q2$ and $Q3$.

When you click on **Experiment** in the **SAAM II Toolbox**, the model will appear as follows:



Remember the **Experiment Attributes** remain set.

- a. Obtain the parameter estimates.

It is useful to explain how the initial parameter estimates are obtained for this three-compartment model configuration. When we worked with the mammillary model, we saw how to move from the two- to the three-compartment model. The situation is exactly the same here, as explained in the following.



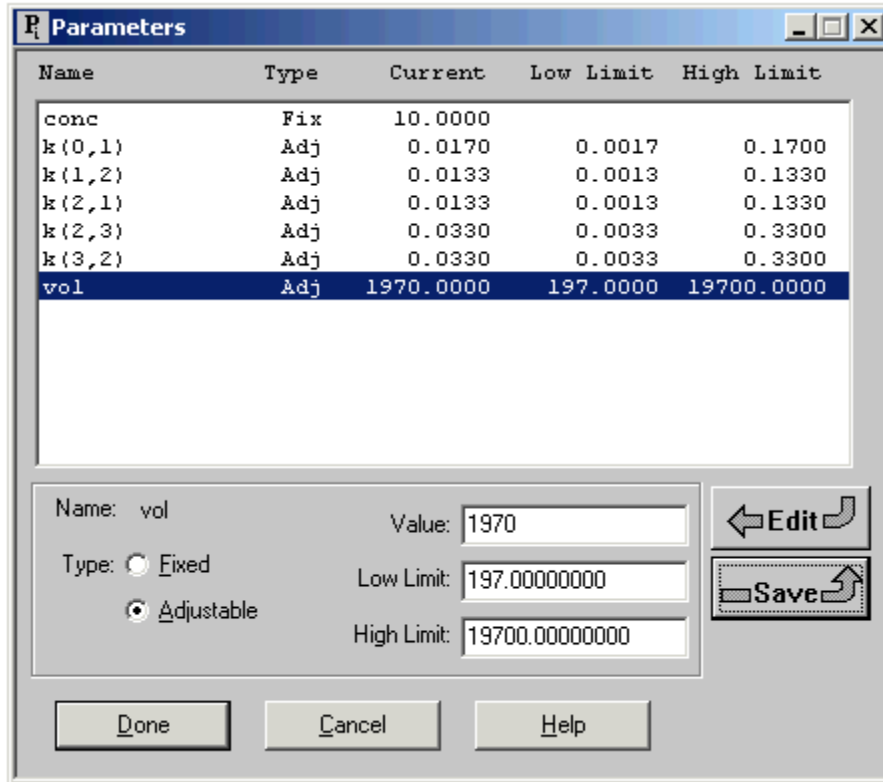
Obtaining initial parameter estimates. When you build your model structure as we are doing in the case study, you need to provide initial estimates for your new parameters, in this situation, $k(3,2)$ and $k(2,3)$. You can use the best estimates from your two-compartment model as follows to obtain these estimates. In the case of the two-compartment model, the best estimates are $vol = 1970$, $k(0,1) = 0.017$, $k(2,1) = 0.062$ and $k(1,2) = 0.071$. You now need initial estimates for vol , $k(2,1)$, $k(1,2)$, $k(3,2)$, $k(2,3)$ and $k(0,1)$ for the three-compartment model.

- i. Initial estimates for $k(2,1)$ and $k(1,2)$. Initial estimates for $k(2,1)$ and $k(1,2)$ for the three-compartment model can be obtained by doubling the average of $k(2,1)$ and $k(1,2)$ from the best fit of the two-compartment model. This number is about 0.133.
- ii. Initial estimates for $k(3,2)$ and $k(2,3)$. Initial estimates for $k(3,2)$ and $k(2,3)$ can be obtained by halving the average of $k(2,1)$ and $k(1,2)$ from the best fit of the two-compartment model. This number is about 0.033.
- iii. Initial estimates for vol and $k(0,1)$. Initial estimates for vol and $k(0,1)$ can be obtained by using the best fit values for the two-compartment model. These are 1970 and 0.017 respectively.

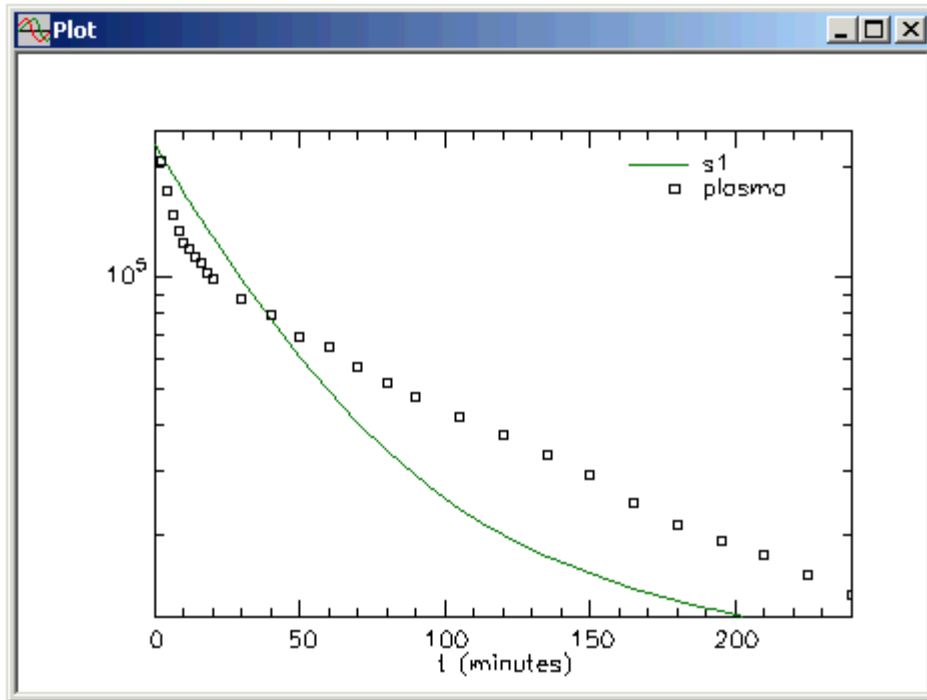
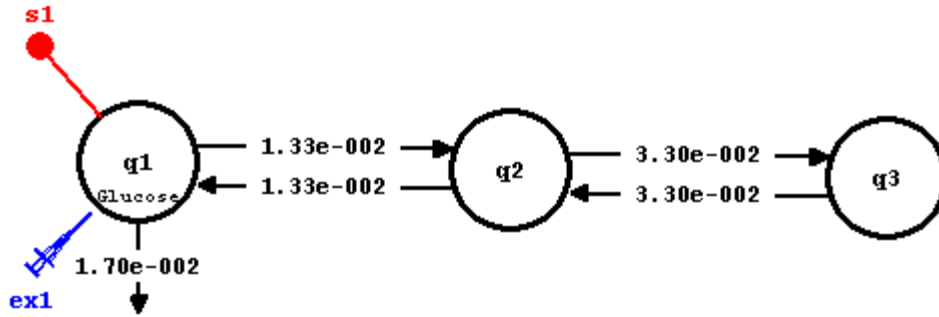
This rule of thumb in terms of obtaining initial parameter estimates works most of the time. When it does not, you may need to hand-fit to adjust some of the initial estimates.



- b. Enter the parameter values as shown in the following **Parameters** dialog box:

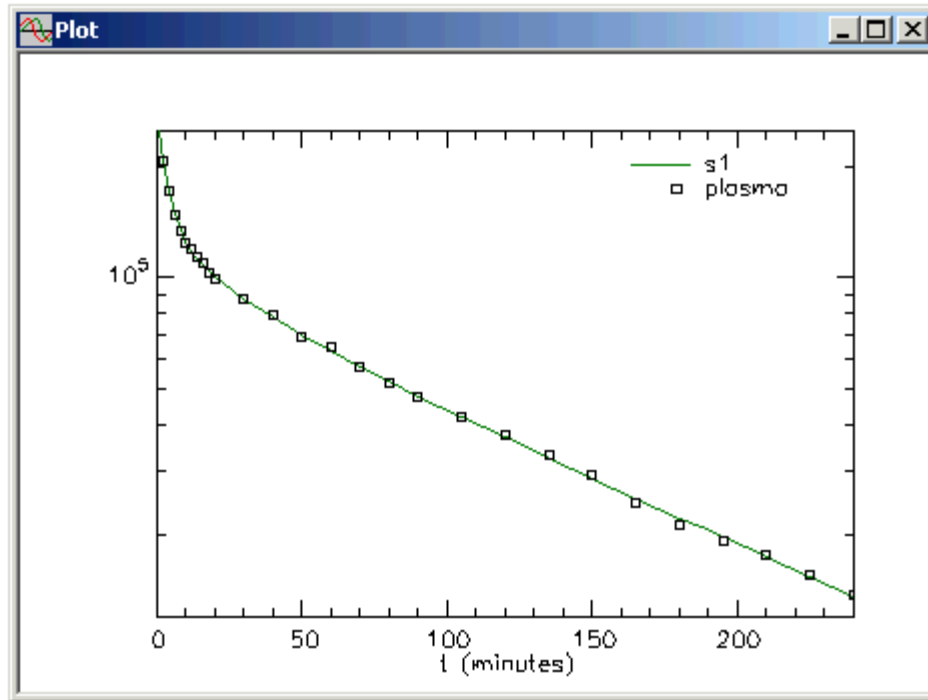
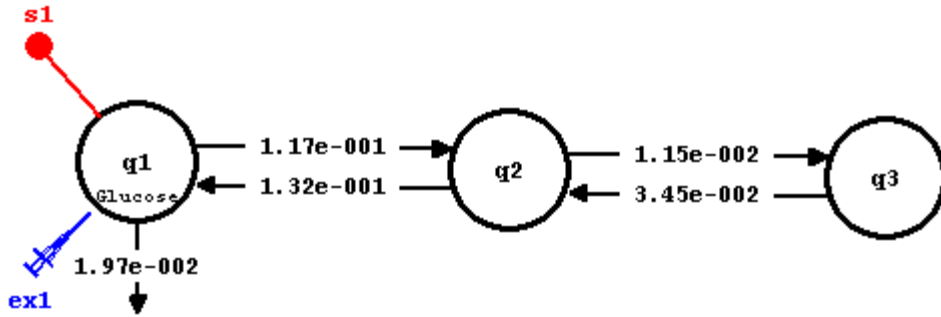


- c. Solve the model and view the solution. The model and plot will appear as follows:



The solution, while not perfect, is certainly close enough that we can proceed to Fit the model to the data.

- d. Fit the model to the data. The model and plot will be updated as follows:



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

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
conc	10.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,2)	0.01756	1.12028e-003	6.38119e+000	0.01523	0.01989
k(1,2)	0.01338	5.32240e-003	3.97910e+001	0.00231	0.02444
k(1,3)	0.14699	2.13619e-002	1.45329e+001	0.10257	0.19141
k(2,1)	0.03478	6.14085e-003	1.76541e+001	0.02201	0.04755
k(3,1)	0.10145	1.40067e-002	1.38059e+001	0.07233	0.13058
vol	1711.89851	6.94404e+001	4.05634e+000	1567.48948	1856.30755

----- Derived Variables -----

Correlation Matrix
 Covariance Matrix
 Objective

	Objective	Scaled Data Variance
s1 : plasma	1.459873e+001	3.128715e-002
Total objective	1.459873e+001	
AIC	8.477562e+000	
BIC	8.645540e+000	

Scroll to see the steady state variables.

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
FLUX(2,3)	173.56516	6.00286e+001	3.45856e+001	48.72905	298.40127
FLUX(3,2)	173.56516	6.00286e+001	3.45856e+001	48.72905	298.40127
Q1	17118.42662	6.94541e+002	4.05727e+000	15674.05288	18562.80036
Q2	15105.40148	6.77866e+002	4.48758e+000	13695.70373	16515.09923
Q3	5034.52011	8.02103e+002	1.59321e+001	3366.45875	6702.58148
Q_tot	37258.34821	3.53885e+002	9.49815e-001	36522.40479	37994.29163
U(1)	337.97689	1.68575e+000	4.98776e-001	334.47119	341.48259

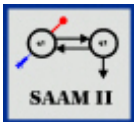
Correlation Matrix
 Covariance Matrix
 Objective

	Objective	Scaled Data Variance
s1 : plasma	1.459872e+001	3.128678e-002
Total objective	1.459872e+001	
AIC	8.477556e+000	
BIC	8.645534e+000	

- f. Record the results for the steady state variables and fitting information. An example follows:

	Two Compartment	Three Compartment Mammillary	Three Compartment Loss from Fast
Q1	19658	17108	17113
Q2	17207	11781	14092
Q3	0	8366	8347
Q_tot	36865	37255	39552
U(1)	342	338	338
OBJ	15.71	14.60	14.60
AIC	8.96	8.48	8.48
BIC	9.08	8.65	8.65

	Three Compartment Loss from Slow	Three Compartment Catenary
Q1	17119	17118
Q2	19251	15105
Q3	11816	5045
Q_tot	48186	37258
U(1)	338	338
OBJ	14.60	14.60
AIC	8.48	8.48
BIC	8.65	8.65



Steady state variables and model configuration. You can now compare the results of the mammillary and catenary models. As with the mammillary models, **U(1)** does not change. However, production will change if it occurs in a non-plasma compartment. If you wish, you can remove **U(1)** and add a **U(2)** or **U(3)** to see how the variables in the steady state change.



- g. Record the results as you have done previously in the **Notes** window (Optional). (The results are shown in Appendix 1.)
- h. Close all open windows.

Quit the **SAAM II Compartmental** application. You can save your study file for future reference if you wish.

Essential Points to Remember

You now have four models that describe your kinetic data equally well. In the mammillary model, one has the loss from the central compartment, and the other two have the loss from a peripheral compartment, one that turns over rapidly and the other more slowly. Each model has a different physiological interpretation. The first is that all irreversible loss occurs from the central compartment while in the latter two, loss is from a peripheral compartment.

In the mammillary model, the interpretation would be that the central compartment exchanges with two distinct peripheral compartments. In the case of glucose, one might be the brain and the other the remaining tissues – muscle, liver, etc. In the catenary model, the assumption is that the first peripheral compartment exchanges with a more slowly turning over “deeper” compartment. Here an interpretation could be the first compartment represents membrane bound substance and the second compartment substance that has been internalized.

You thus need to think carefully when using the three-compartment model to interpret data from a single input-single output study. Besides just the structural interpretation, you should look at the results of the model predicted steady state variables. What is different and what does not change? The changes are due to the different model configurations.

- There are different commonly used structures for the three-compartment model. One can have two solutions and hence is not *a priori* identifiable.
- When comparing the different solutions, although the model parameter values change depending upon the site of loss, the value of the objective function is the same.
- Your derived parameters (in this case the steady state parameters but it can also be pharmacokinetic parameters) will depend upon which model structure is chosen.
- It is important to know, *a priori*, if your model parameters can be estimated. In this case, with the loss from the peripheral compartment, which minimum is achieved depends upon your initial values.
- Statistical methods can be used to decide on the number of distribution compartments that are optimal for pharmacokinetic analysis but, in some cases, an understanding of relevant physiology can also be brought to bear.
- You can use information on the parameters in a “simpler” model to obtain initial parameter estimates in a more “complex” model; the case illustrated here was moving from a two to a three-compartment model.
- The **Notes** window can be valuable in keeping track of your modeling session. The **Notes** window is printed in the Appendix 1.

Modeling Notes

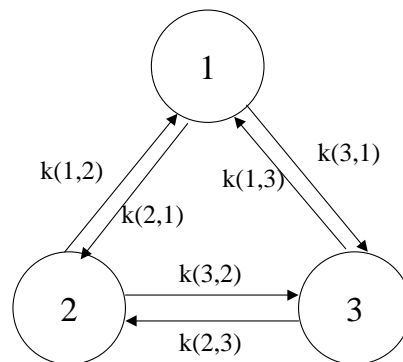
There is an intuitive reason why there are two solutions for this model. For the mammillary (loss from the central compartment) three-compartment model, one compartment exchanges rapidly with the central (plasma) compartment while the second exchanges more slowly. The choice for the two solutions comes from the two options of having the loss from the rapidly or slowly exchanging compartment. This is what was illustrated in this case study, and is an example of “flip-flop” kinetics.

The three-compartment configuration where there is a bolus injection into the accessible pool has a solution that is a sum of three exponentials. Thus s_1 , the concentration in Compartment 1, can be written

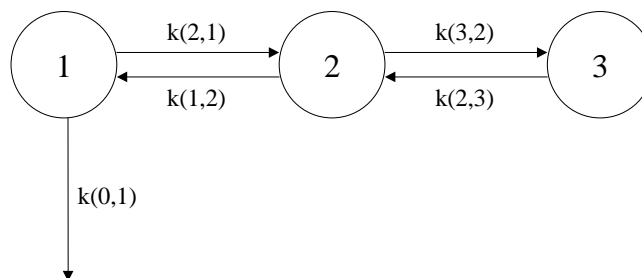
$$s_1 = A_1 * \exp(-a_1 * t) + A_2 * \exp(-a_2 * t) + A_3 * \exp(-a_3 * t)$$

There are thus six parameters that can be determined, the three coefficients A_1 , A_2 and A_3 , and the three exponentials a_1 , a_2 and a_3 .

The general three-compartment, without losses indicated, can be diagrammed:



Assuming input and samples from Compartment 1, you can see immediately the various possibilities for the $k(i,j)$. The models used in this case study, of course, did not have $k(3,2)$ and $k(2,3)$. If these parameters were present, and $k(3,1)$ and $k(1,3)$ were not present, one would have the catenary (chain) model:



To grasp the nature of the difficulty, you should contemplate writing a set of equations similar to those that we derived in the identifiability analysis of the general two-compartment model.

If you are interested, you can try to develop them. Alternatively, they are derived in Cobelli, Foster and Toffolo Tracer Kinetics in Biomedical Research: From Data to Models (Kluwer Academic/Plenum Publishers, New York, 2000).

Data for this Case Study

```
DATA
# Cobelli 3exp glucose data
t plasma (FSD 0.1)
2 206701.
4 171594.
6 148425.
8 134377.
10 123580.
12 119484.
14 113790.
16 109188.
18 103288.
20 99108.
30 87073.
40 78817.
50 68707.
60 64657.
70 56928.
80 51757.
90 47496.
105 42124.
120 37425.
135 32897.
150 29102.
165 24598.
180 21427.
195 19231.
210 17596.
225 15673.
240 13689.
END
```

Appendix 1: Contents of the Notes window

Fit of the two-compartment model to data with loss from Compartment 1

Para/Var	Value	Std Dev	Coeff of Var	95% Confidence Interval	
conc	10.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,1)	0.01741	5.87854e-004	3.37647e+000	0.01619	0.01863
k(1,2)	0.07091	4.40428e-003	6.21143e+000	0.06180	0.08002
k(2,1)	0.06206	6.60573e-003	1.06432e+001	0.04840	0.07573
vol	1965.78849	6.78955e+001	3.45386e+000	1825.33575	2106.24123
----- Derived Variables -----					
FLUX(0,1)	342.24921	2.04857e+000	5.98559e-001	338.01142	346.48699
FLUX(1,2)	1220.06630	9.38890e+001	7.69540e+000	1025.84189	1414.29072
FLUX(2,1)	1220.06630	9.38890e+001	7.69540e+000	1025.84189	1414.29072
Q1	19657.88490	6.78955e+002	3.45386e+000	18253.35746	21062.41234
Q2	17206.78558	6.44191e+002	3.74382e+000	15874.17348	18539.39767
Q_tot	36864.67048	4.19663e+002	1.13839e+000	35996.52997	37732.81099
U(1)	342.24921	2.04857e+000	5.98559e-001	338.01142	346.48699

	Objective	Scaled Data Variance			
s1 : plasma	1.570677e+001	8.651187e-002			

Total objective	1.570677e+001				
AIC	8.957510e+000				
BIC	9.077495e+000				

Fit of the three-compartment mammillary model to data with loss from Compartment 1

conc	10.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,1)	0.01976	8.03991e-004	4.06944e+000	0.01808	0.02143
k(1,2)	0.14757	2.15374e-002	1.45947e+001	0.10278	0.19236
k(1,3)	0.03109	6.16671e-003	1.98327e+001	0.01827	0.04392
k(2,1)	0.10162	1.40911e-002	1.38658e+001	0.07232	0.13093
k(3,1)	0.01520	5.70681e-003	3.75339e+001	0.00334	0.02707
vol	1710.79501	6.96405e+001	4.07065e+000	1565.96986	1855.62016
----- Derived Variables -----					
FLUX(0,1)	337.99836	1.67995e+000	4.97029e-001	334.50472	341.49200
FLUX(1,2)	1738.59059	1.78363e+002	1.02591e+001	1367.66423	2109.51694
FLUX(1,3)	260.11603	9.29184e+001	3.57219e+001	66.88201	453.35005
FLUX(2,1)	1738.59059	1.78363e+002	1.02591e+001	1367.66423	2109.51694
FLUX(3,1)	260.11603	9.29184e+001	3.57219e+001	66.88201	453.35005
Q1	17107.95010	6.96405e+002	4.07065e+000	15659.69858	18556.20162
Q2	11781.44015	1.38546e+003	1.17597e+001	8900.22185	14662.65846
Q3	8365.55710	1.44013e+003	1.72149e+001	5370.65800	11360.45621
Q_tot	37254.94736	3.52395e+002	9.45901e-001	36522.10365	37987.79107
U(1)	337.99836	1.67995e+000	4.97029e-001	334.50472	341.49200

	Objective	Scaled Data Variance			
s1 : plasma	1.459865e+001	3.128476e-002			

Total objective	1.459865e+001				
AIC	8.477523e+000				

BIC 8.645502e+000

Fit of the three-compartment mammillary model to data with loss from Compartment 2 where Compartment 2 is the rapidly turning over peripheral compartment

conc	10.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,2)	0.02403	2.86077e-003	1.19068e+001	0.01808	0.02998
k(1,2)	0.12360	1.93290e-002	1.56389e+001	0.08340	0.16379
k(1,3)	0.03111	6.16729e-003	1.98251e+001	0.01828	0.04393
k(2,1)	0.12140	1.48247e-002	1.22118e+001	0.09057	0.15223
k(3,1)	0.01522	5.71124e-003	3.75270e+001	0.00334	0.02710
vol	1710.70119	6.96578e+001	4.07188e+000	1565.84019	1855.56218
----- Derived Variables -----					
FLUX(0,2)	338.00217	1.68010e+000	4.97067e-001	334.50823	341.49612
FLUX(1,2)	1738.74205	1.78454e+002	1.02634e+001	1367.62675	2109.85736
FLUX(1,3)	260.35165	9.29830e+001	3.57144e+001	66.98329	453.72001
FLUX(2,1)	2076.74423	1.78127e+002	8.57723e+000	1706.30930	2447.17915
FLUX(3,1)	260.35165	9.29830e+001	3.57144e+001	66.98329	453.72001
Q1	17107.01186	6.96578e+002	4.07188e+000	15658.40195	18555.62177
Q2	14067.96930	1.63587e+003	1.16283e+001	10666.00677	17469.93183
Q3	8369.16306	1.44065e+003	1.72138e+001	5373.17288	11365.15323
Q_tot	39544.14421	5.78599e+002	1.46317e+000	38340.88458	40747.40385
U(1)	338.00217	1.68010e+000	4.97067e-001	334.50823	341.49612
	Objective	Scaled Data		Variance	
s1 : plasma	1.459865e+001	3.128463e-002			

Total objective	1.459865e+001				
AIC	8.477521e+000				
BIC	8.645500e+000				

Fit of the three-compartment mammillary model to data with loss from Compartment 2 where Compartment 2 is the slowly turning over peripheral compartment

conc	10.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,2)	0.01756	1.12028e-003	6.38119e+000	0.01523	0.01989
k(1,2)	0.01338	5.32240e-003	3.97910e+001	0.00231	0.02444
k(1,3)	0.14699	2.13619e-002	1.45329e+001	0.10257	0.19141
k(2,1)	0.03478	6.14085e-003	1.76541e+001	0.02201	0.04755
k(3,1)	0.10145	1.40067e-002	1.38059e+001	0.07233	0.13058
vol	1711.89851	6.94404e+001	4.05634e+000	1567.48948	1856.30755
----- Derived Variables -----					
FLUX(0,2)	337.97084	1.68921e+000	4.99811e-001	334.45794	341.48375
FLUX(1,2)	257.49888	9.22615e+001	3.58299e+001	65.63098	449.36679
FLUX(1,3)	1736.78589	1.77367e+002	1.02124e+001	1367.93179	2105.63998
FLUX(2,1)	595.46973	9.32411e+001	1.56584e+001	401.56469	789.37477
FLUX(3,1)	1736.78589	1.77367e+002	1.02124e+001	1367.93179	2105.63998
Q1	17118.98514	6.94404e+002	4.05634e+000	15674.89478	18563.07551
Q2	19250.95486	1.16884e+003	6.07159e+000	16820.22385	21681.68587
Q3	11815.65809	1.38248e+003	1.17004e+001	8940.63330	14690.68287
Q_tot	48185.59809	2.39006e+003	4.96012e+000	43215.19874	53155.99743
U(1)	337.97084	1.68921e+000	4.99811e-001	334.45794	341.48375

	Objective	Scaled Data Variance
s1 : plasma	1.459873e+001	3.128715e-002

 Total objective 1.459873e+001

AIC 8.477562e+000

BIC 8.645540e+000

Fit of the three-compartment catenary model with input and loss from the plasma compartment

conc	10.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,1)	0.01974	8.00787e-004	4.05596e+000	0.01808	0.02141
k(1,2)	0.13205	1.63255e-002	1.23635e+001	0.09810	0.16600
k(2,1)	0.11652	1.66671e-002	1.43042e+001	0.08186	0.15118
k(2,3)	0.03448	7.95379e-003	2.30712e+001	0.01793	0.05102
k(3,2)	0.01149	4.36855e-003	3.80195e+001	0.00241	0.02058
vol	1711.84266	6.94541e+001	4.05727e+000	1567.40529	1856.28004

----- Derived Variables -----

FLUX(0,1)	337.97689	1.68575e+000	4.98776e-001	334.47119	341.48259
FLUX(1,2)	1994.61249	2.11349e+002	1.05960e+001	1555.08924	2434.13574
FLUX(2,1)	1994.61249	2.11349e+002	1.05960e+001	1555.08924	2434.13574
FLUX(2,3)	173.56516	6.00286e+001	3.45856e+001	48.72905	298.40127
FLUX(3,2)	173.56516	6.00286e+001	3.45856e+001	48.72905	298.40127
Q1	17118.42662	6.94541e+002	4.05727e+000	15674.05288	18562.80036
Q2	15105.40148	6.77866e+002	4.48758e+000	13695.70373	16515.09923
Q3	5034.52011	8.02103e+002	1.59321e+001	3366.45875	6702.58148
Q_tot	37258.34821	3.53885e+002	9.49815e-001	36522.40479	37994.29163
U(1)	337.97689	1.68575e+000	4.98776e-001	334.47119	341.48259

	Objective	Scaled Data Variance
s1 : plasma	1.459872e+001	3.128678e-002

 Total objective 1.459872e+001

AIC 8.477556e+000

BIC 8.645534e+000

Appendix 2: The Runs Test for Goodness-of-Fit

The runs test for the two-compartment model is performed as described below. If you do not know how to perform or interpret the runs test, please consult any standard book on statistics or biostatistics.

It is assumed you have visualized the weighted residuals for both the two- and three-compartment models. The table of the residuals is reproduced in the following for convenience.

1. The table of weighted residuals for the two-compartment model is shown in the following:

t	sl_wres
0.000	-
2.000	1.595
4.000	-1.87860e-001
6.000	-1.20789e+000
8.000	-1.19341e+000
10.000	-1.13077e+000
12.000	0.222
14.000	0.670
16.000	1.063
18.000	0.737
20.000	0.682
30.000	1.129
40.000	1.222
50.000	-3.23249e-001
60.000	0.606
70.000	-7.53132e-001
80.000	-1.03281e+000
90.000	-9.89227e-001
97.500	-
105.000	-6.17252e-001
112.500	-
120.000	-1.89547e-001
127.500	-
135.000	-1.29658e-001
142.500	-
150.000	0.147
157.500	-
165.000	-1.14424e+000
172.500	-
180.000	-1.40181e+000
187.500	-
195.000	-6.11344e-001
202.500	-
210.000	0.807
217.500	-
225.000	1.301
232.500	-
240.000	-
240.000	1.149

From the table, there are 27 (weighted) data points used in the “Fit”; thus for the runs test, $N = 27$. Notice “240.000” appears twice; SAAM II prints out the final experiment time twice. Also notice there are some time values for which there are no weighted residuals. In your **Computational Settings** dialog box, the **Minimum Number of Calculation Intervals** is the default 20. Thus there will be solution values that are saved at time where there are no data. If you wish to remove this, you can set the **Minimum Number of Calculation Intervals** equal to 1.

2. Calculate the Z variable.

- a. N , the number of data, is 27.
- b. The number of positive and negative residuals, n^+ and n^- , is respectively 13 and 14.
- c. The number of runs R equals 9. (Remember a run is a sequence of positive or negative residuals; a run can consist of only one, or several, positive or negative residuals).
- d. Estimate the mean, variance and standard deviation from the formulas shown below:

$$\mu = \frac{2n^+n^-}{N} + 1 = 14.48 \quad \sigma^2 = \frac{2n^+n^-(2n^+n^- - N)}{(N-1)N^2} = 6.47 \quad \sigma = 2.54$$

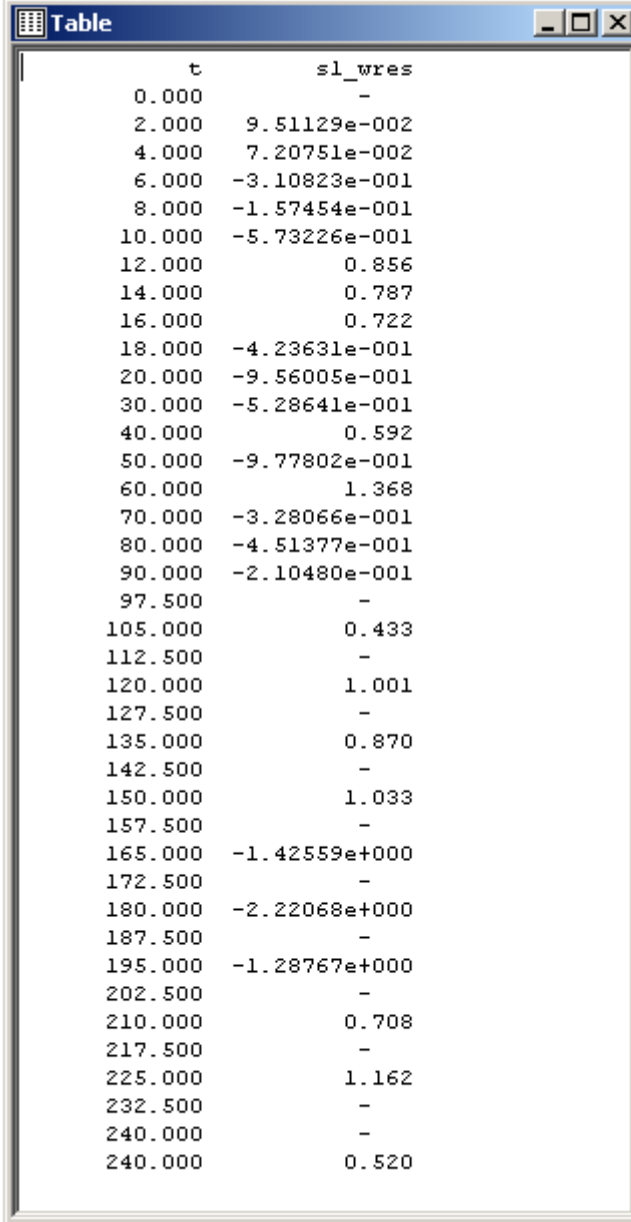
- e. Calculate the Z variable:

$$Z = \frac{9 - 14.48}{2.54} = -2.12$$

For a 5% significance level to see whether the “Fit” should be accepted or not, Z should be in the interval $[-1.96, 1.96]$. Since it is not, the test for goodness-of-fit indicates that the “Fit” cannot be accepted.

The runs test for the three-compartment model is performed as described below.

3. The table of weighted residuals for the three-compartment model is shown in the following:



t	sl_wres
0.000	-
2.000	9.51129e-002
4.000	7.20751e-002
6.000	-3.10823e-001
8.000	-1.57454e-001
10.000	-5.73226e-001
12.000	0.856
14.000	0.787
16.000	0.722
18.000	-4.23631e-001
20.000	-9.56005e-001
30.000	-5.28641e-001
40.000	0.592
50.000	-9.77802e-001
60.000	1.368
70.000	-3.28066e-001
80.000	-4.51377e-001
90.000	-2.10480e-001
97.500	-
105.000	0.433
112.500	-
120.000	1.001
127.500	-
135.000	0.870
142.500	-
150.000	1.033
157.500	-
165.000	-1.42559e+000
172.500	-
180.000	-2.22068e+000
187.500	-
195.000	-1.28767e+000
202.500	-
210.000	0.708
217.500	-
225.000	1.162
232.500	-
240.000	-
240.000	0.520

As above, $N = 27$.

4. Calculate the Z variable.
 - a. N , the number of data, is 27.
 - b. The number of positive and negative residuals, n^+ and n^- , is respectively 14 and 13.
 - c. The number of runs R equals 11. (Remember a run is a sequence of positive or negative residuals; a run can consist of only one, or several, positive or negative residuals).

- d. Estimate the mean, variance and standard deviation from the formulas:

$$\mu = \frac{2n^+n^-}{N} + 1 = 14.48 \quad \sigma^2 = \frac{2n^+n^-(2n^+n^- - N)}{(N-1)N^2} = 6.48 \quad \sigma = 2.54$$

- e. Calculate the Z variable

$$Z = \frac{11 - 14.48}{2.54} = -1.37$$

For a 5% significance level to see whether the fit should be accepted or not, Z should be in the interval [-1.96,1.96]. Since it is, the test for goodness-of-fit indicates the fit can be accepted.

The conclusion, based upon the goodness-of-fit test, is that the three-compartment model provides a satisfactory fit to the data. Acceptance of this model comes from the fact that the parsimony parameters, AIC and BIC, are less for the three- than the two-compartment models.

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