

Insulin Effect on LDL Metabolism

Case Study

- How to model an experimental perturbation
- How to save solutions to compare solutions
- How to use change conditions
- How to unweight and reweight data for fitting purposes

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Prerequisites

The prerequisite for this case study is having worked through the SAAM II introductory tutorial, “Getting Started with SAAM II Compartmental.” It is recommended that you work through the Using SAAM II tutorial “Using Change Conditions.”

What you will learn in this case study

- How to model an experimental perturbation.
- How to save solutions to compare solutions.
- How to use change conditions.
- How to unweight and reweight data for fitting purposes.

Data Required

The data file for this case study is

LDL_TPN.dat

The contents of this file are included at the end of this case study.

Introduction

Low density lipoproteins (LDL) are particles in the plasma whose primary purpose is to transport cholesterol to cells in the periphery. It has long been known that insulin has an effect on the metabolism of these particles. Most of the evidence comes from cell culture studies. The problem in whole body studies is that most LDL kinetic studies last two weeks, and it is not possible to elevate insulin artificially for that period of time.

Total parenteral nutrition (TPN) is known to elevate insulin levels. This was used by Chait et al¹ to study insulin effect on LDL metabolism in humans. The study consisted of a typical LDL turnover study in which LDL was isolated, radioiodinated, purified and reinjected. Plasma and urine samples were collected for nine days at which point TPN was started. Plasma and urine samples were collected for another 10 days.

From a modeling point of view, the data presented several unique opportunities, the most important of which was how to deal with the perturbation caused by TPN. You will:

- First assume the perturbation caused no effect, and assess this hypothesis;

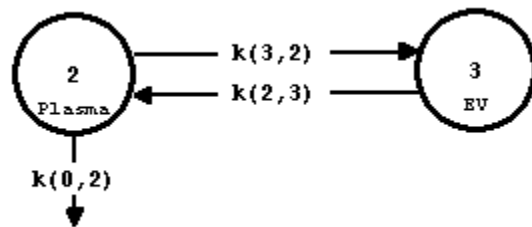
- Assume the perturbation caused an effect, and assess this hypothesis; and
- Postulate changes in the rate constants caused by the perturbation that will explain the data.

1. Chait, Alan, David Foster, Donald G. Miller and Edwin L. Bierman. Acceleration of LDL catabolism in man by total parenteral nutrition. Proc. Soc. Exper. Biol. Med. 168:97-104, 1981

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

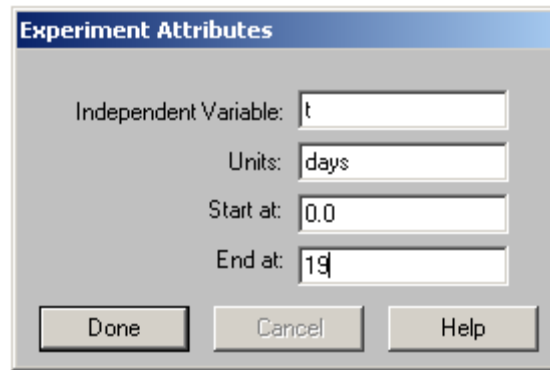
Low density lipoprotein kinetic described following a bolus injection of radioiodinated LDL is virtually always described by a two-compartment model. This will be the point at which we start the case study.

1. **Start the SAAM II Compartmental application.** The **SAAM II Compartmental** main window will open.
2. Create the following two-compartment model.



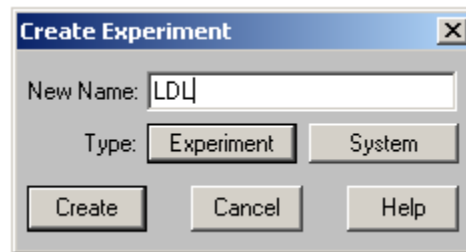
In creating this model, you compartment numbers will “1” and “2” to begin. You will have to renumber Compartment 2 to 3 first, and name it “EV” for extravascular. Then you can renumber and name Compartment 1. This is done by opening the **Compartment Attributes** dialog box associated with each compartment.

3. Create the experiment.
 - a. 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.
 - b. Change the entry in the **Units** box from “minutes” to “days.”
 - c. Enter “19” in the **End at** box. The **Experiment Attributes** dialog box will appear as follows:

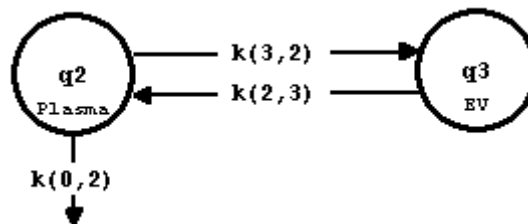


- d. Click **Done**.

The **Create Experiment** dialog box will appear on the **Drawing Canvas**. The choice of experiment **Types** is an **Experiment** or a **System**. **Experiment** is selected with the name “Exper”. Replace “Exper” with “LDL” by typing “LDL” in the **New Name** box. The **Create Experiment** dialog box will appear as follows:




- e. Click **Create**. The model will appear as follows:

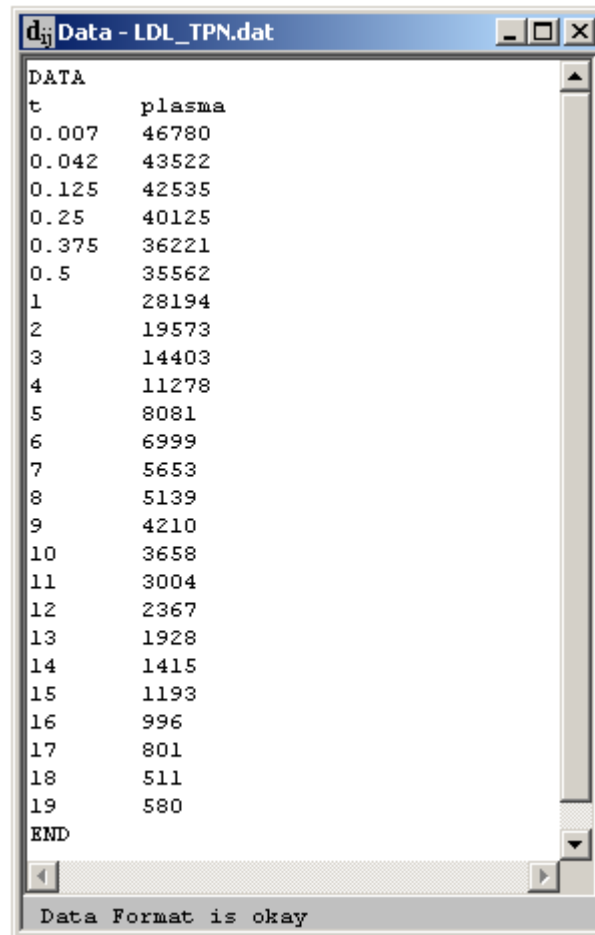


The name “LDL” will appear beneath **Experiment** in the **SAAM II Toolbox**.

4. Add 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 **LDL_TPN.dat** should appear in the list (if it does not, find the folder where you have installed this data file.)

- c. Double-click **LDL_TPN.dat**. The data will appear in the **Data** window as follows:

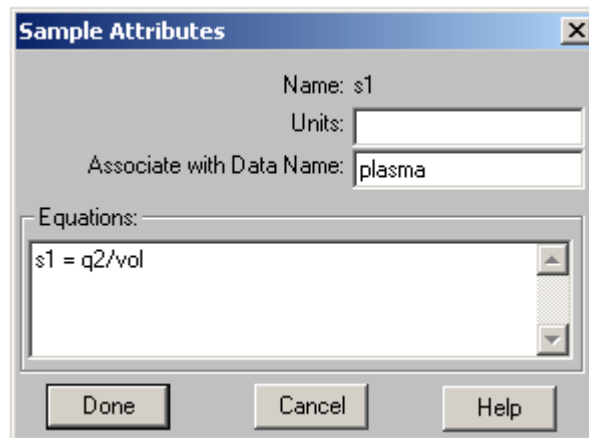


The screenshot shows a window titled "Data - LDL_TPN.dat" with a list of data points. The first column is labeled "t" and the second is labeled "plasma". The data points are as follows:

| t | plasma |
|-------|--------|
| 0.007 | 46780 |
| 0.042 | 43522 |
| 0.125 | 42535 |
| 0.25 | 40125 |
| 0.375 | 36221 |
| 0.5 | 35562 |
| 1 | 28194 |
| 2 | 19573 |
| 3 | 14403 |
| 4 | 11278 |
| 5 | 8081 |
| 6 | 6999 |
| 7 | 5653 |
| 8 | 5139 |
| 9 | 4210 |
| 10 | 3658 |
| 11 | 3004 |
| 12 | 2367 |
| 13 | 1928 |
| 14 | 1415 |
| 15 | 1193 |
| 16 | 996 |
| 17 | 801 |
| 18 | 511 |
| 19 | 580 |

The window also displays "END" at the bottom of the list and a status bar at the bottom that reads "Data Format is okay".

- d. Close the **Data** window.
5. Create the plasma sample.
- In the **SAAM II Toolbox**, click **Sample**.
 - Click Compartment **q2**, and then click on the **Drawing Canvas**. The sample **s1** will appear associated with Compartment **q2**.
 - Double-click **s1** to open the **Sample Attributes** dialog box.
 - In the **Associate with Data Name** box, type "plasma".
 - In the **Equations** box, edit the sample equation " $s1=q2$ " to read " $s1=q2/vol$ ". The **Sample Attributes** dialog box will appear as shown below:



- f. Click **Done**.
6. Create the experimental input
 - a. In the **SAAM II Toolbox**, click **Input**.
 - b. Click Compartment **q2**, and then click on the **Drawing Canvas**. An input arrow, **ex1**, will appear on the drawing canvas pointing to Compartment **q2**.
 - c. Double-click **ex1**. The **Exogenous Input** dialog box will open.
 - d. In the **Input Type** pane, be sure **Bolus** is selected.
 - e. Enter "1.04e+08" in the **Initial Amount** box.
 - f. 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 | 1.04e+8 | - | 0.000 | - | - | - |

Input Type:

Bolus
 Infusion
 Primed Infusion
 Equation

Initial Amount:

Constant Rate:

Event Start:

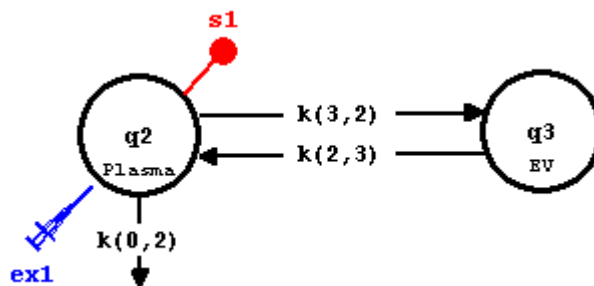
Event Stop:

Repeat Every:

Nr. of Repeats:

Equation:

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



Part 2. Analyze all the plasma data (to day19.)

We will first analyze all plasma data. The assumption is that TPN does not cause a change in LDL metabolism.

1. Enter the parameter values as shown below:

| Name | Type | Current | Low Limit | High Limit |
|--------|------|-----------|-----------|------------|
| k(0,2) | Adj | 0.1000 | 0.0100 | 1.0000 |
| k(2,3) | Adj | 0.1000 | 0.0100 | 1.0000 |
| k(3,2) | Adj | 0.1000 | 0.0100 | 1.0000 |
| vol | Adj | 3000.0000 | 300.0000 | 30000.0000 |

Name: vol Value: 3000

Type: Fixed
 Adjustable

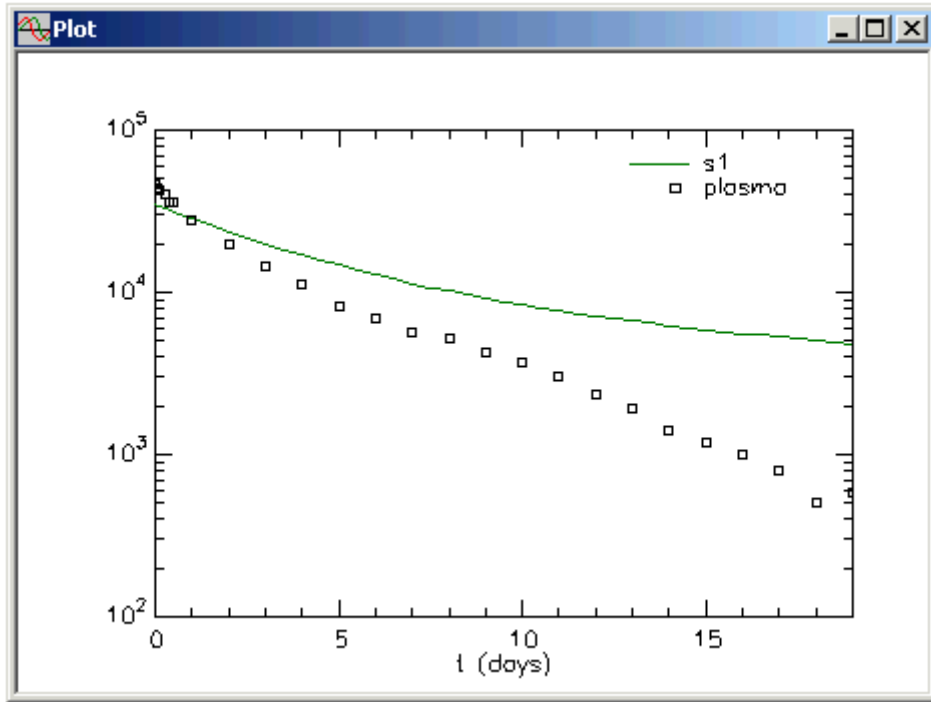
Low Limit: 300.00000000

High Limit: 30000.00000000

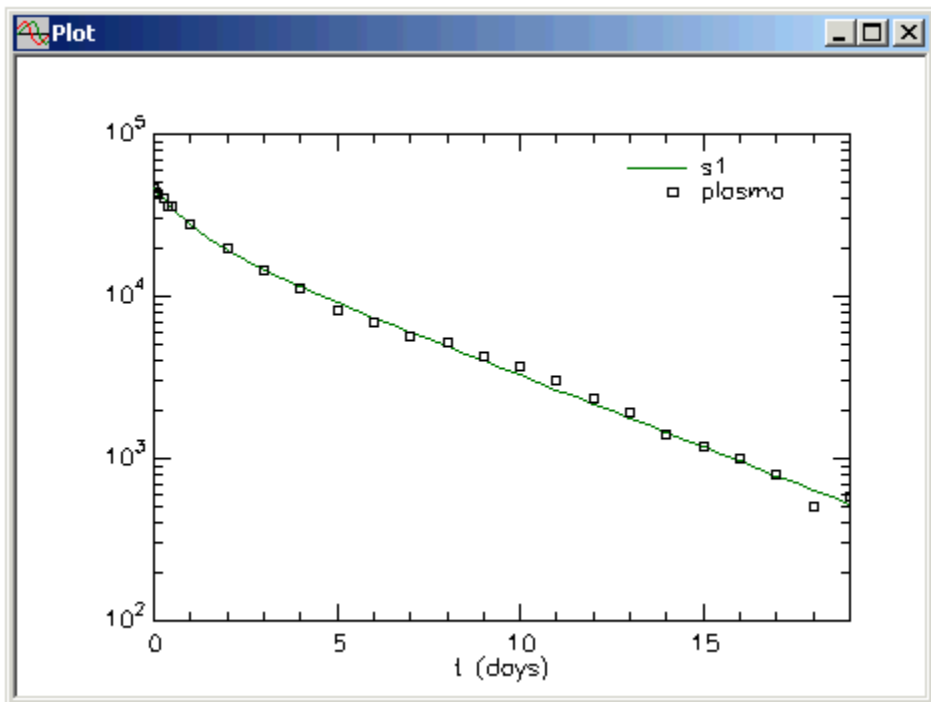
Buttons: Edit, Save, Done, Cancel, Help

How to obtain the initial parameter estimates is the subject of the case studies dealing with the two-compartment model.

2. Solve and view the solution. Your plot of the plasma data in semi-log mode will appear as follows:



3. Fit the model and view the solution. Your plot will be updated as follows:



The statistics associated with this Fit are shown as follows:

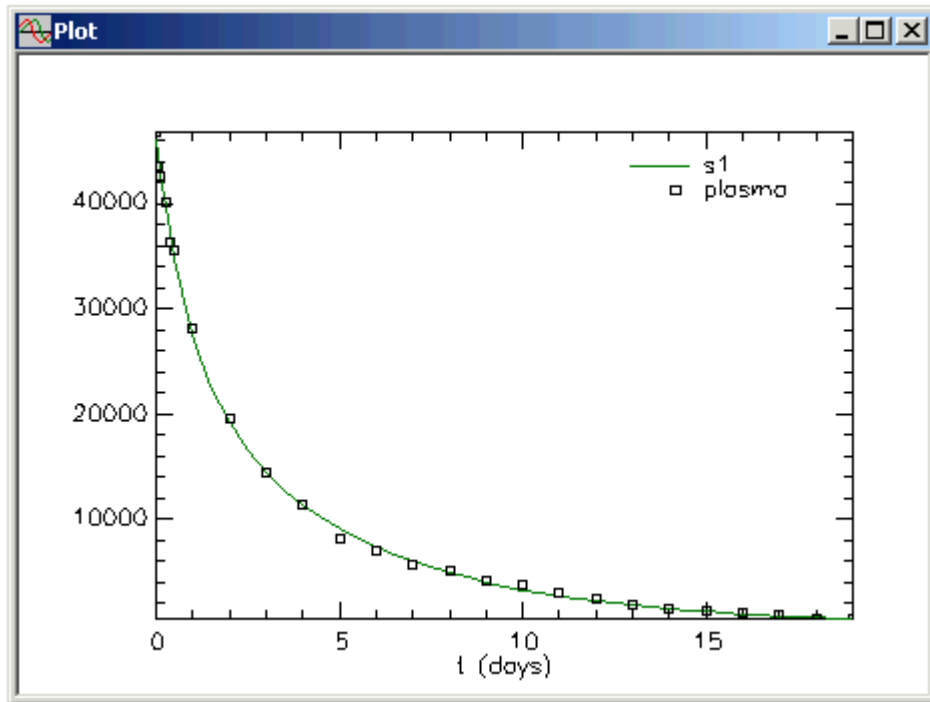
| Parameter/Variable | Value | Std.Dev. | Coef. of Var. | 95% Confidence Interval | |
|--------------------|------------|--------------|---------------|-------------------------|------------|
| k(0,2) | 0.32256 | 1.67863e-002 | 5.20411e+000 | 0.28765 | 0.35747 |
| k(2,3) | 0.67453 | 1.60509e-001 | 2.37957e+001 | 0.34073 | 1.00832 |
| k(3,2) | 0.27456 | 1.09778e-001 | 3.99835e+001 | 0.04626 | 0.50286 |
| vol | 2263.71700 | 1.03475e+002 | 4.57102e+000 | 2048.52937 | 2478.90464 |

| | Objective | Scaled Data Variance |
|-----------------|---------------|----------------------|
| sl : plasma | 1.331310e+001 | 6.976760e-001 |
| Total objective | 1.331310e+001 | |
| AIC | 7.775486e+000 | |
| BIC | 7.897374e+000 | |

While the statistics are reasonable, how would you assess the model Fit to the data? There are two points. First, there do appear to be systematic deviations between the data and model predicted values around day 10. Second, the datum on day 18 may be spurious.

Close the **Statistics** window; leave the **Plot** window open.

4. Assess the model Fit to the data.
 - a. Change your plot of the plasma data to the linear mode (in the **View** menu, click **Semilog**). The plot will appear as follows:



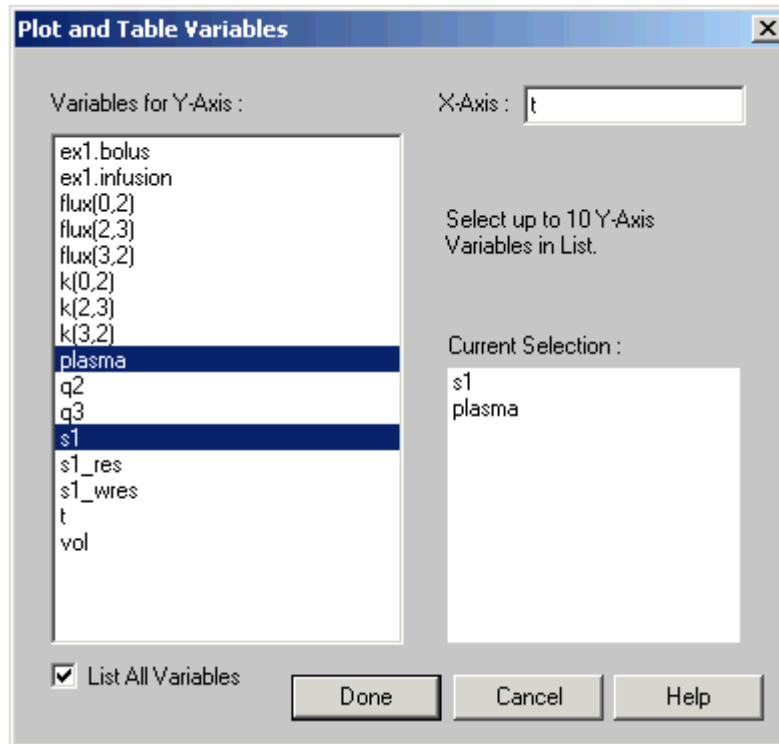
Because the semi-log plot tends to compress the data and model predictions, viewing the solution in linear mode can sometimes help resolve discrepancies. In this case, the deviations starting around day 5 to day 12 are more obvious. This can be seen much better if you plot the weighted residuals.

Leave the plot window open, and the plot in linear mode.

b. Plot the weighted residuals.

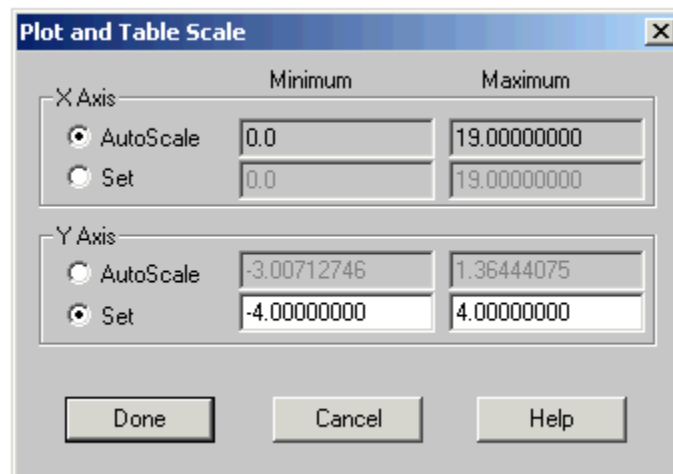
(1) Click in the **Plot** window to make it active. In the **Set** menu, click **Plot/Table Variables**. The **Plot and Table Variables** dialog box will open.

(2) Be sure the **List All Variables** box is selected. The **Plot and Table Variables** dialog box will appear as follows:

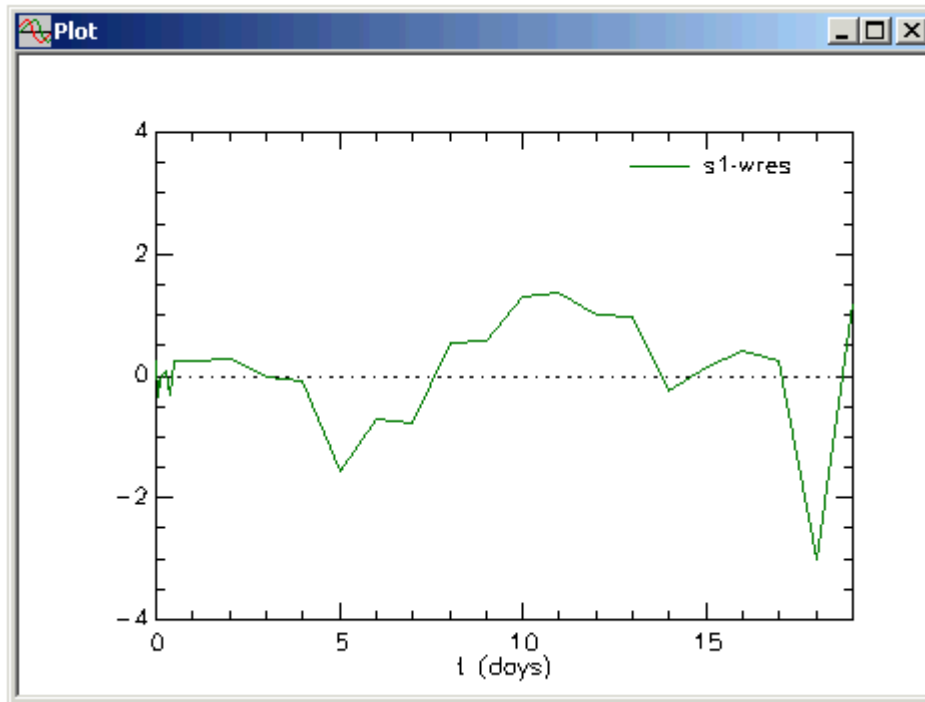


plasma and **s1** are selected because these are the variables for your current plot.

- (3) Click **s1_wres**, and then click **Done**. It will be convenient to set the **Plot and Table Scale** as follows:




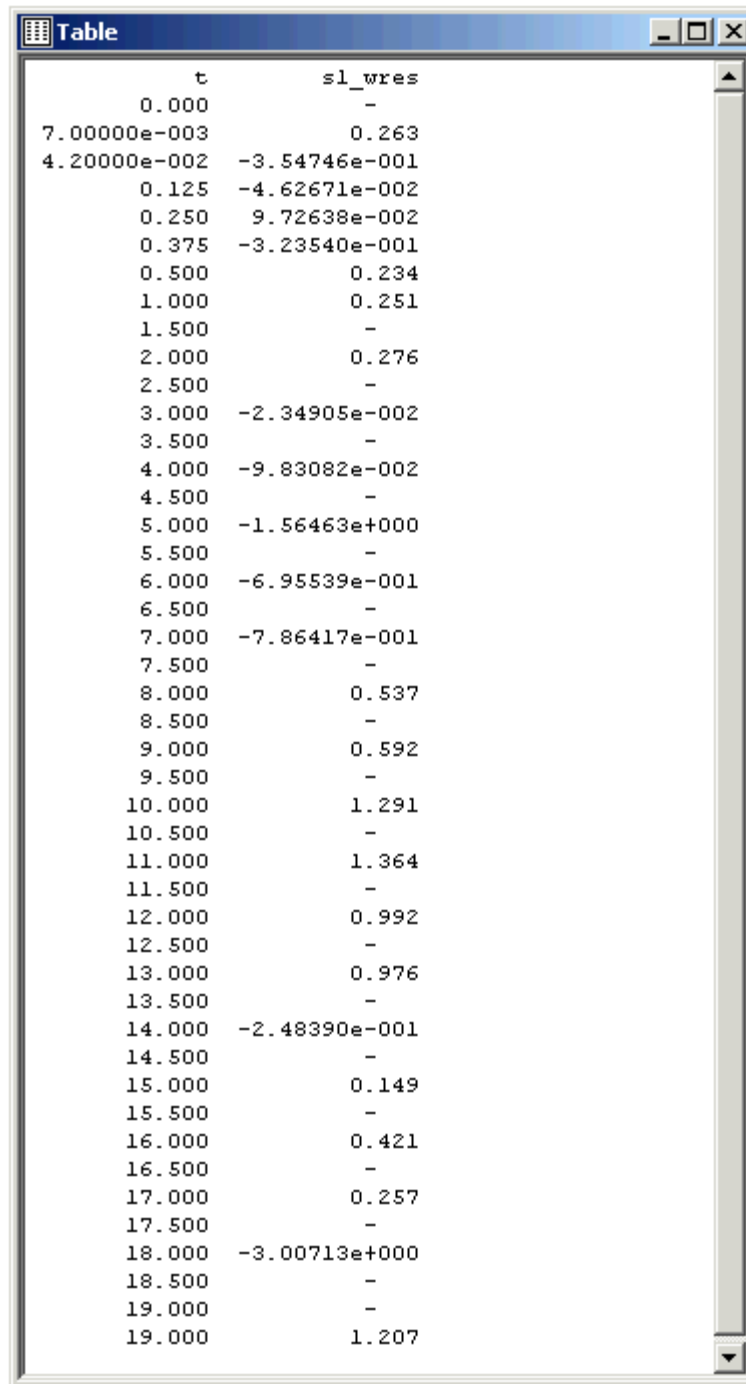
The plot of the weighted residuals will appear as follows:



It is clear there are systematic deviations among the weighted residuals. If you wish, you can perform the runs test for goodness-of-fit to reject this model. If you perform the runs test, and to visualize even better the systemic deviations, you can observe the table of weighted residuals.

(4) 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:



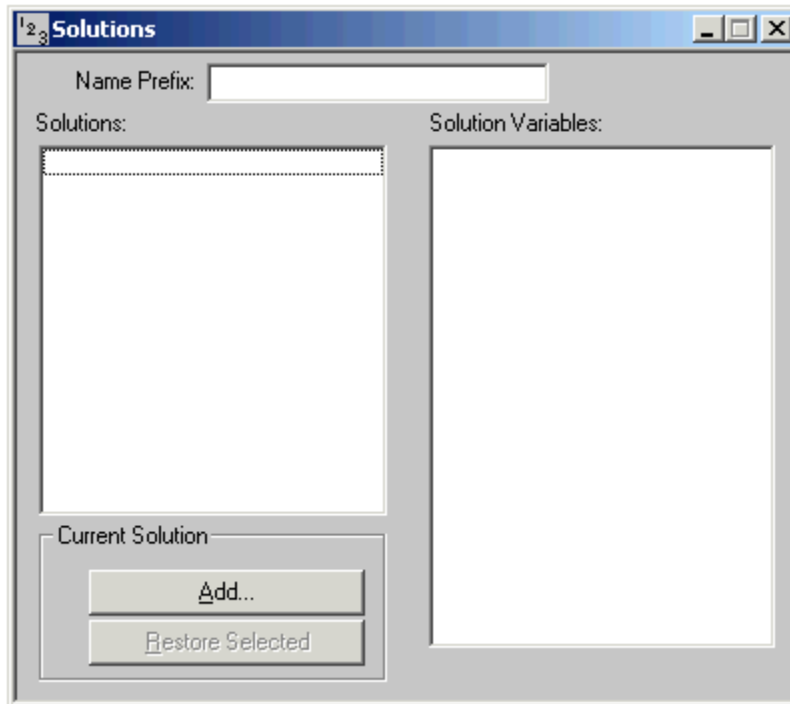
The screenshot shows a window titled "Table" with a scrollable list of data. The data consists of two columns: "t" (time) and "sl_wres" (plasma data). The values for "t" range from 0.000 to 19.000 in increments of 0.500. The values for "sl_wres" are mostly zero, with several non-zero values ranging from approximately -3.5 to 1.364.

| t | sl_wres |
|--------------|---------------|
| 0.000 | - |
| 7.00000e-003 | 0.263 |
| 4.20000e-002 | -3.54746e-001 |
| 0.125 | -4.62671e-002 |
| 0.250 | 9.72638e-002 |
| 0.375 | -3.23540e-001 |
| 0.500 | 0.234 |
| 1.000 | 0.251 |
| 1.500 | - |
| 2.000 | 0.276 |
| 2.500 | - |
| 3.000 | -2.34905e-002 |
| 3.500 | - |
| 4.000 | -9.83082e-002 |
| 4.500 | - |
| 5.000 | -1.56463e+000 |
| 5.500 | - |
| 6.000 | -6.95539e-001 |
| 6.500 | - |
| 7.000 | -7.86417e-001 |
| 7.500 | - |
| 8.000 | 0.537 |
| 8.500 | - |
| 9.000 | 0.592 |
| 9.500 | - |
| 10.000 | 1.291 |
| 10.500 | - |
| 11.000 | 1.364 |
| 11.500 | - |
| 12.000 | 0.992 |
| 12.500 | - |
| 13.000 | 0.976 |
| 13.500 | - |
| 14.000 | -2.48390e-001 |
| 14.500 | - |
| 15.000 | 0.149 |
| 15.500 | - |
| 16.000 | 0.421 |
| 16.500 | - |
| 17.000 | 0.257 |
| 17.500 | - |
| 18.000 | -3.00713e+000 |
| 18.500 | - |
| 19.000 | - |
| 19.000 | 1.207 |

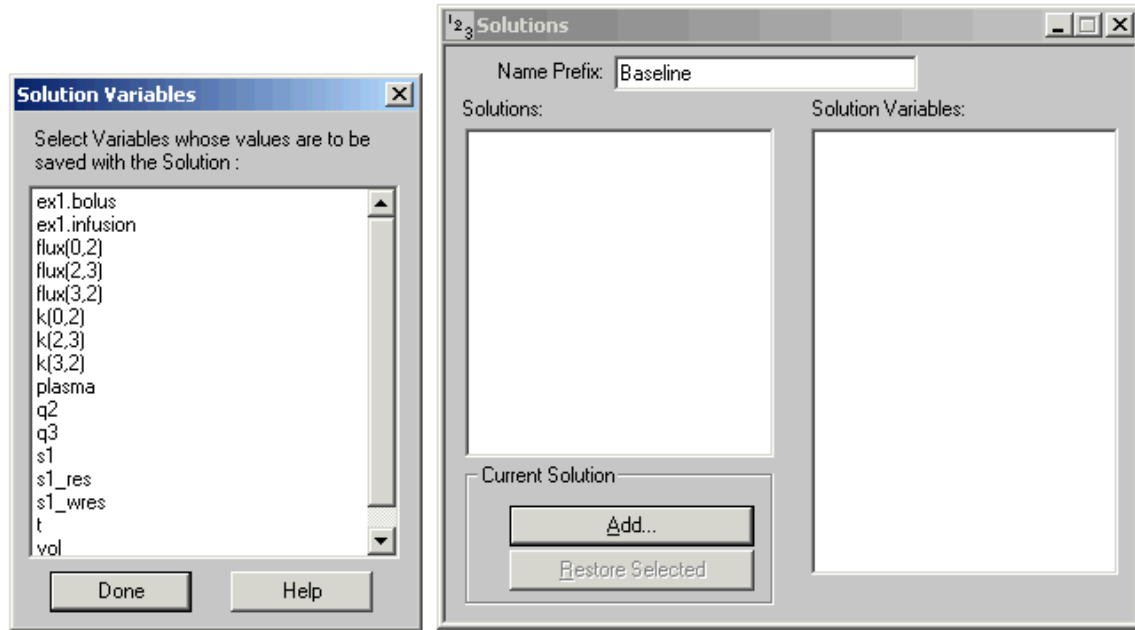
Close the **Table** window.

Restore the plot of the plasma data. To restore the plot of the plasma data, you will have to reset the **Plot and Table Variable**, and reset the **Plot and Table Scale** to **AutoScale**. Close the **Plot** window.

5. Save this solution as the baseline solution so that you can compare it with other potential model structures.
 - a. On the **Compute** menu, click **Solutions**. The **Solutions** dialog box will open as follows:



- b. Type “Baseline” in the **Name Prefix** box.
 - c. Click **Add**. The **Solution Variables** dialog box will open. The two boxes will appear as follows:



In the **Solution Variables** dialog box, click **s1**.



Saving solutions. When saving a solution, you can use the default (a number) or give it a name for reference purposes.

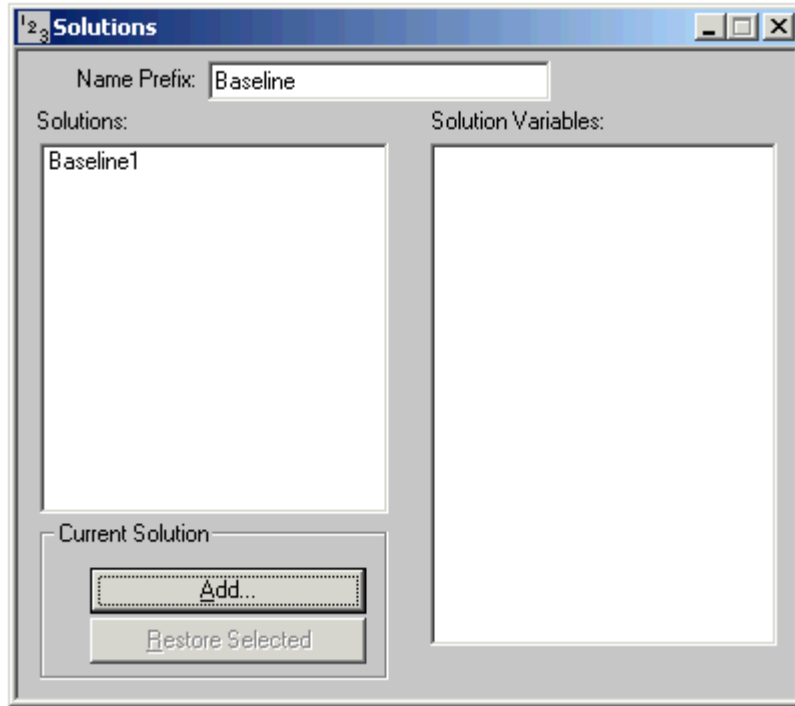
When you save a solution, you can save, associated with the **Name Prefix**, any of the variables in the **Solution Variables** dialog box.

If you wish only to compare solutions, then, as you did above, you can save only a particular solution, in this case **s1**.

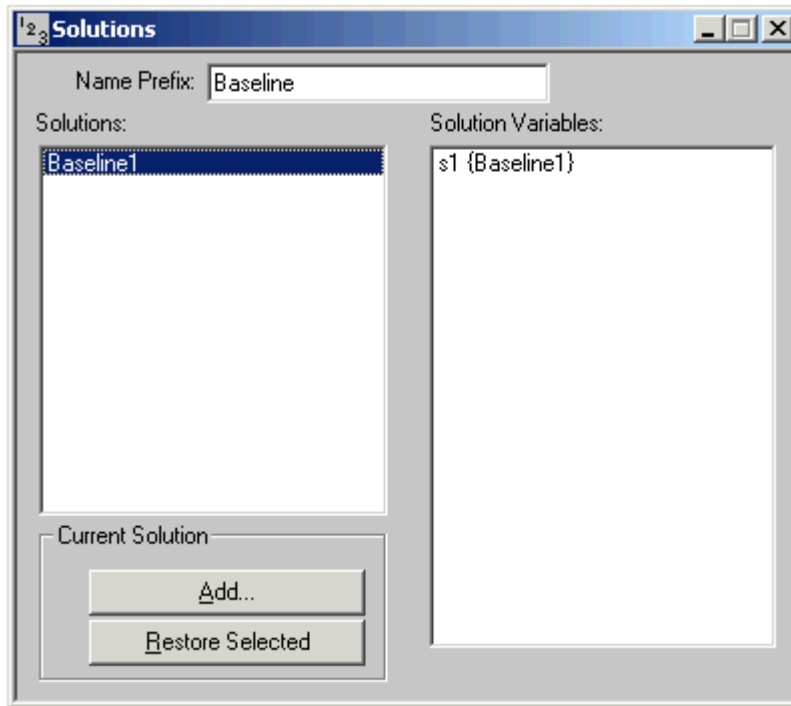
If, on the other hand, you wanted to be able to restore a solution, i.e. to recreate that solution, then you need to save all information that produced the solution. At a minimum, this would include the rate constants $k(i,j)$ and vol .



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



If you click on **Baseline1** in the **Solutions** pane, the **Solutions** dialog box will appear as follows:



If you click on a solution name in the **Solutions** pane, a list of the solution variables associated with a particular solution will appear in the **Solution Variables** pane.



Naming solutions. SAAM II will always put a number associated with a saved solution whether you give it your own name or not. In the above, “Baseline” appears as “Baseline1”. This gives you the option of saving another solution with the name “Baseline”; it would appear as “Baseline2”.



- e. Close the **Solutions** dialog box.
6. (Optional) Test to see if the datum at day 18 is spurious and affects the model Fit to the data.
 - a. Open the **Data** window, and scroll so that the datum at day 18 is visible.
 - b. After the datum on day 18, type “(-)”. The **Data** window will appear in part as follows:

```

15      1193
16      996
17      801
18      511 (-)
19      580
END

```

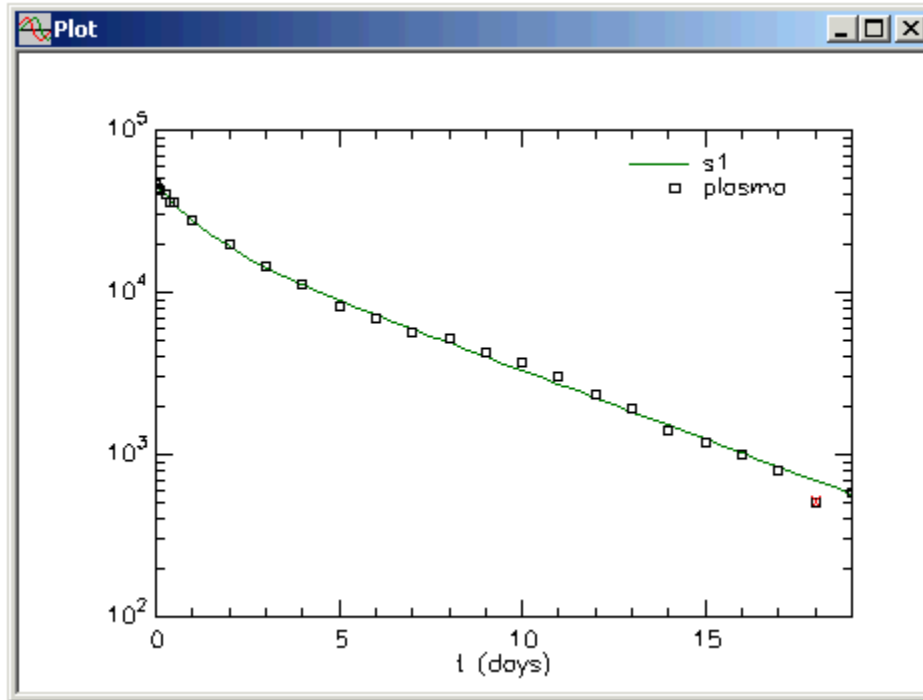
- c. Close the **Data** window.



Unweighting a datum. If you do not want to have a datum included in the fitting process, entering “(-)” after the datum will eliminate it from the fitting process. The datum will appear on your plots with a red “x” drawn through it.

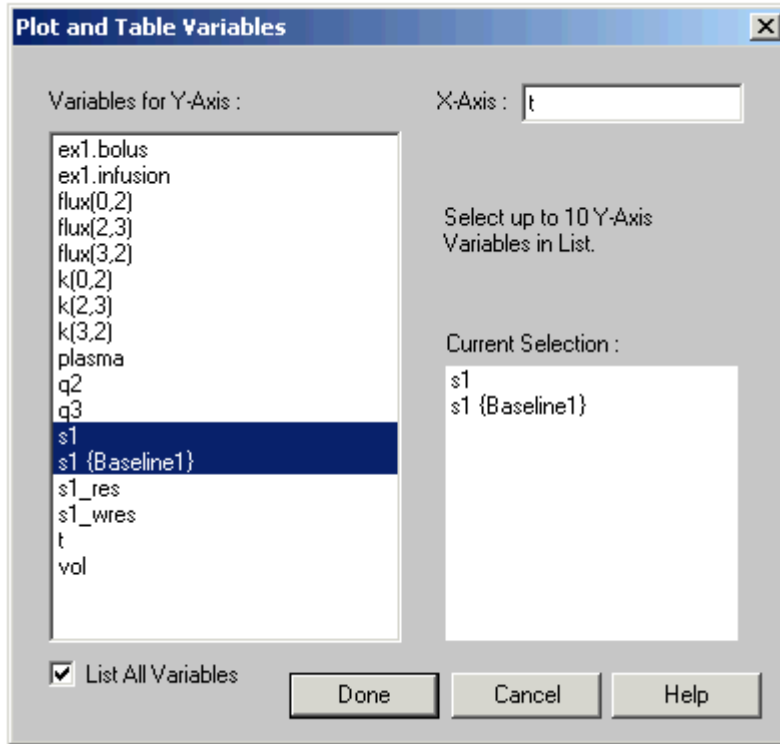


- d. Re-Fit the model to the data.
- e. View the solution. The plot of the plasma data, in semi-log mode, will appear as follows:

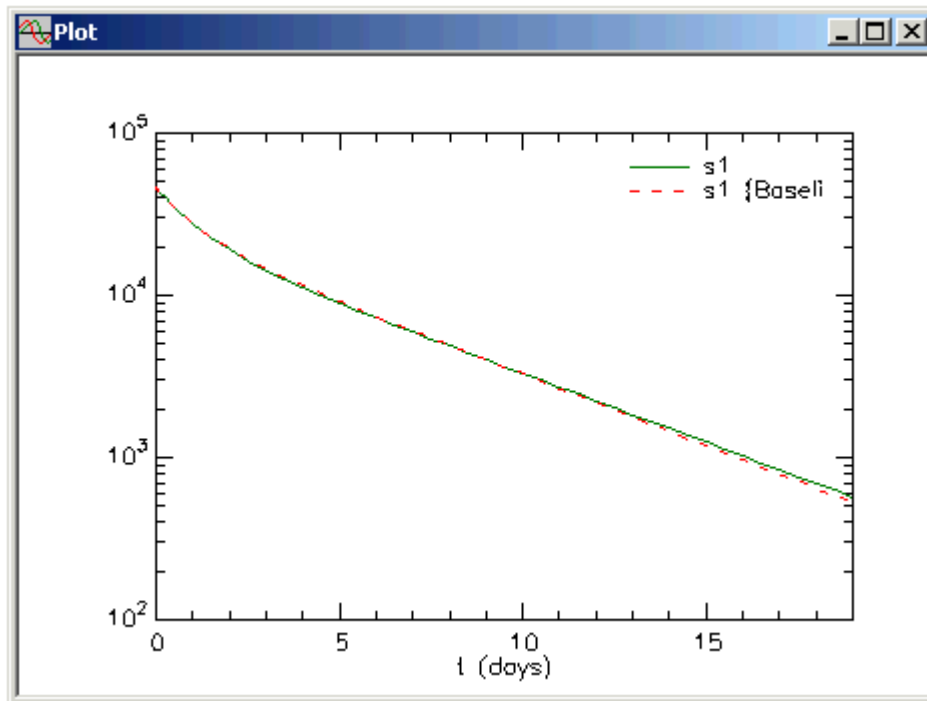


You can see unweighting the datum (with the red “x” through it) had little effect on the Fit.

- f. Compare this solution with the baseline solution.
 - (1) On the **Set** menu, click **Plot/Table Variables**.
 - (2) In the **Plot and Table Variables** dialog box, be sure **List All Variables** is selected.
 - (3) Press the **Ctrl** key, and click **s1** and **s1{Baseline1}** to move these variables to the **Current Selection** pane. The **Plot and Table Variables** dialog box will appear as follows:



(4) Click **Done**. Your plot will appear as follows:



You can see that unweighting this datum has virtually no effect on the Fit.

- g. Reweight the datum at day 18 (by opening the **Data** window and removing the “(-)” associated with it).
- h. Re-Fit the model (when you reweight the datum, the current solution will be lost) to restore the original solution.
- i. Plot **s1** and **plasma**.

You have now completed the analysis of the data to day 19 assuming there is no change in the metabolism of LDL as a result of TPN. Because the model could not describe the data, you can reject this hypothesis.

Part 3. Analyze the plasma data to day 9 using the two-compartment model.

To analyze the plasma data to day 9, we will simply repeat most of what we did in Part 2, but examine only the data for the first 9 days. We can compare the results with the results of the analysis of all of the data.

To begin, we must unweight all data starting at day 10.

1. Unweight all data starting at day 10. Remember TPN was started following the sample on day 9.
 - a. Open the **Data** window.
 - b. Following the datum at day 10, type “(-+)”. The **Data** window will appear in part as follows:

```

9      4210
10     3658 (-+)
11     3004
12     2367
13     1928
14     1415
15     1193
16     996
17     801
18     511
19     580
END

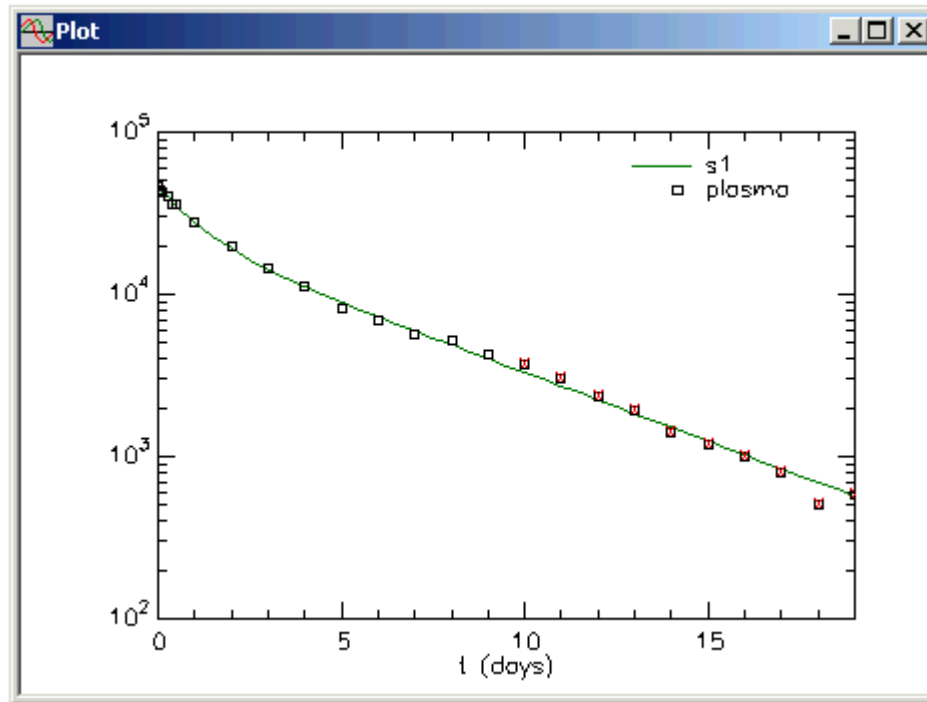
```



Unweighting a string of data. If you do not want to have a string of data included in the fitting process, entering “(-+)” after the first datum to be eliminated will eliminate all following data until the END, or until a “(+)” is encountered associated with a datum. The datum will appear on your plots with a red “x” drawn through it.

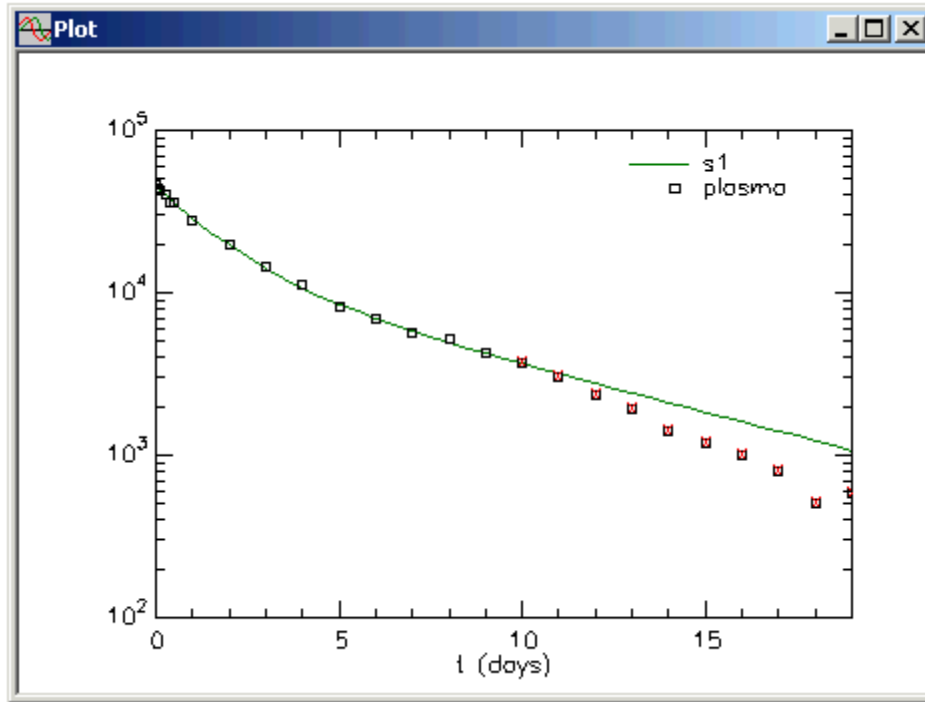


- c. Close the **Data** window.
2. Solve the model and view the solution. The **Plot** window should appear as follows (and should be your last plasma plot):

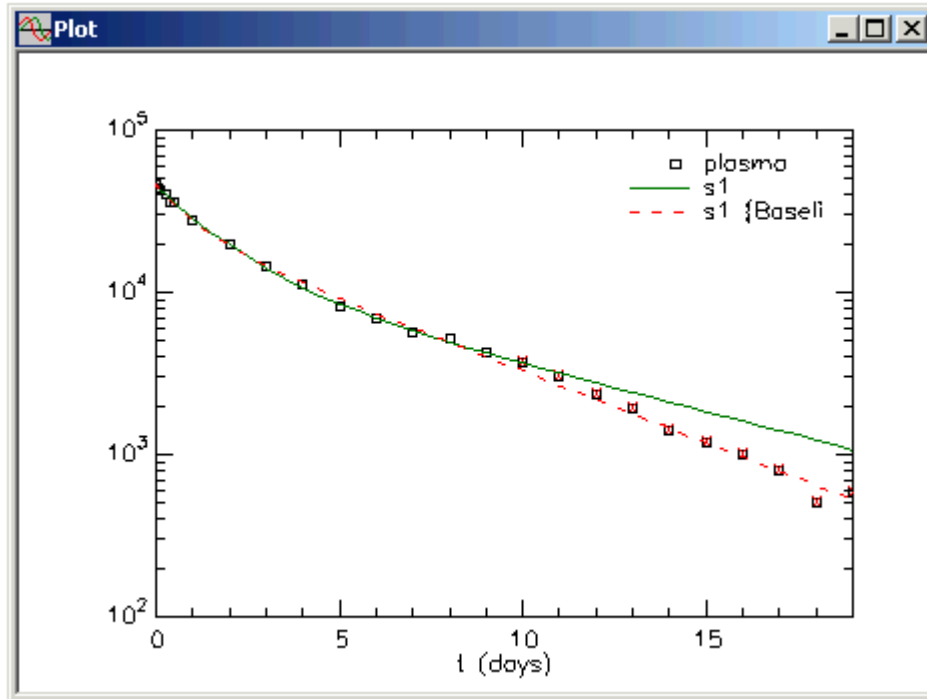


Notice now the red “x” through all the unweighted data. Leave the **Plot** window open.

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



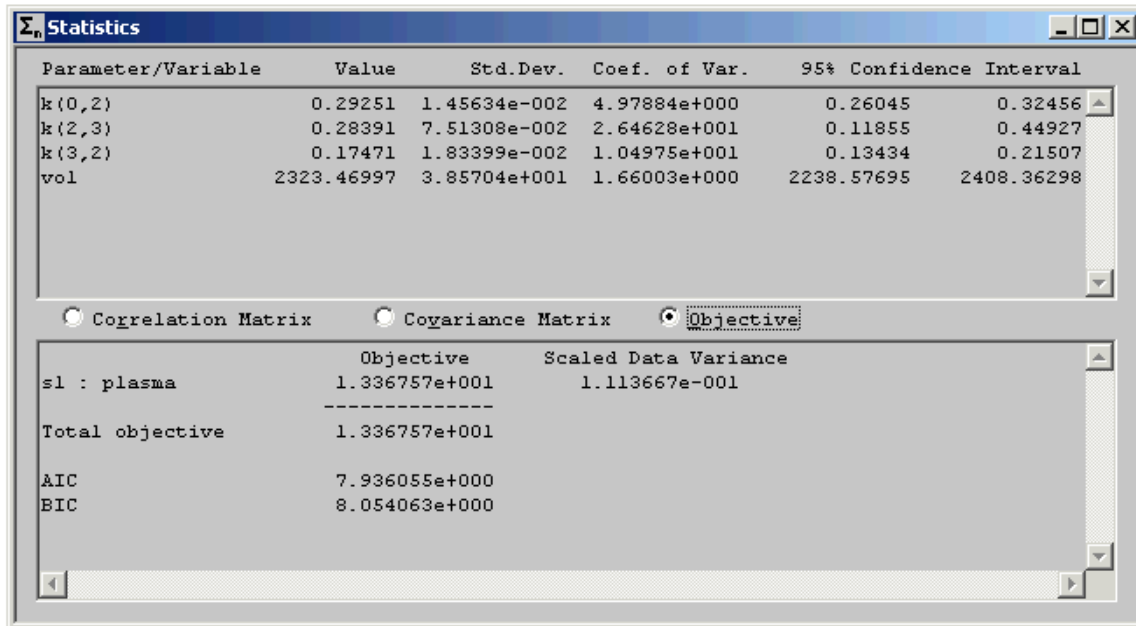
If you compare this plot with your Baseline1 plot, you will obtain:



Remember to visualize this plot, you need to open the **Plot and Table Variables** dialog box, and select **plasma**, **s1** and **s1{Baseline1}**. You can clearly see the

difference! The model adequately describes the data to day 9, the day on which TPN was started.

4. View the statistics associated with the fit. The **Statistics** window will appear as follows:



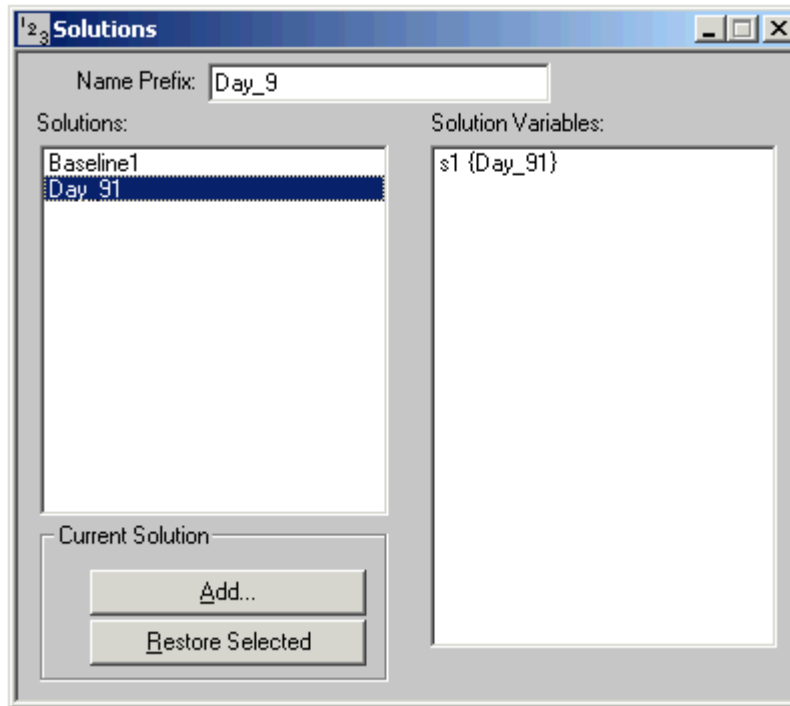
| Parameter/Variable | Value | Std.Dev. | Coef. of Var. | 95% Confidence Interval | |
|--------------------|------------|--------------|---------------|-------------------------|------------|
| k(0,2) | 0.29251 | 1.45634e-002 | 4.97884e+000 | 0.26045 | 0.32456 |
| k(2,3) | 0.28391 | 7.51308e-002 | 2.64628e+001 | 0.11855 | 0.44927 |
| k(3,2) | 0.17471 | 1.83399e-002 | 1.04975e+001 | 0.13434 | 0.21507 |
| vol | 2323.46997 | 3.85704e+001 | 1.66003e+000 | 2238.57695 | 2408.36298 |

| | Objective | Scaled Data Variance |
|-----------------|---------------|----------------------|
| s1 : plasma | 1.336757e+001 | 1.113667e-001 |
| Total objective | 1.336757e+001 | |
| AIC | 7.936055e+000 | |
| BIC | 8.054063e+000 | |

The statistics are clearly acceptable. Remember the value for $k(0,2)$ is 0.29; this will be used in the next part of this case study.

Close the **Statistics** window. Re-Plot **s1** and **plasma**; close the **Plot** window.

5. Save the solution.
 - a. On the **Compute** menu, click **Solutions**. The **Solutions** dialog box will open.
 - b. Type "Day_9" in the **Name Prefix** box.
 - c. Click **Add**. The **Solution Variables** dialog box will open.
 - d. In the **Solution Variables** dialog box, click **s1**, and then click **Done**.
 - e. Click **Add**.
 - f. If you click on **Day_91** (remember SAAM II will add the "1" to Day_9) in the **Solutions** pane, the **Solutions** dialog box will appear as follows:



- g. Close the **Solutions** dialog box.



Study0. The above part of the case study is equivalent to Study0. That is, the data to day 9 used above is the data found in Study0.dat.



Perturbations. Some experimental protocols call for perturbations during the experiment. These can cause changes in the kinetics of the data. In the case of this case study, the perturbation is TPN. What the above shows is that TPN does appear to cause a change in the kinetics of LDL metabolism. The question now is how can one deal with this. One way is to say there is a change, and leave it at that. The other is to try to postulate a change in the model that will account for this observed change.



Part 4. Test for changes in the rate constants that can explain the perturbation.

It is clear that, following TPN, LDL is being metabolized more rapidly than before. Thus a logical place to start would be to change $k(0,2)$. We will do this using **Change Conditions**.

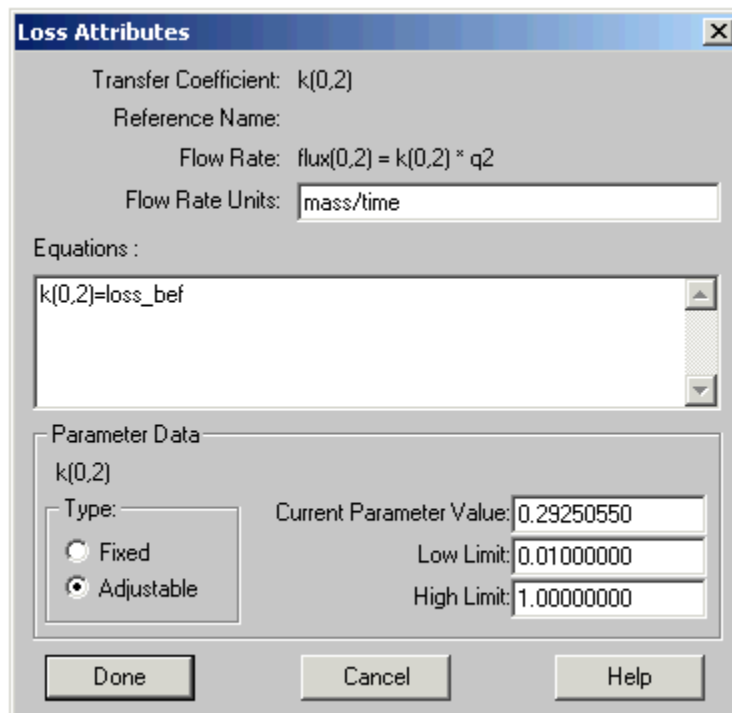
In the following strategy, a physiological assumption has to be made. The assumption is that the change in LDL metabolism as a result of TPN is very rapid compared to the daily sampling schedule. This means that a new steady-state has been achieved rapidly, and that we can assume the transfers in the model are constant.

When using this strategy to analyze any perturbation study, one must be careful to delineate the physiological consequences of any modeling assumption.

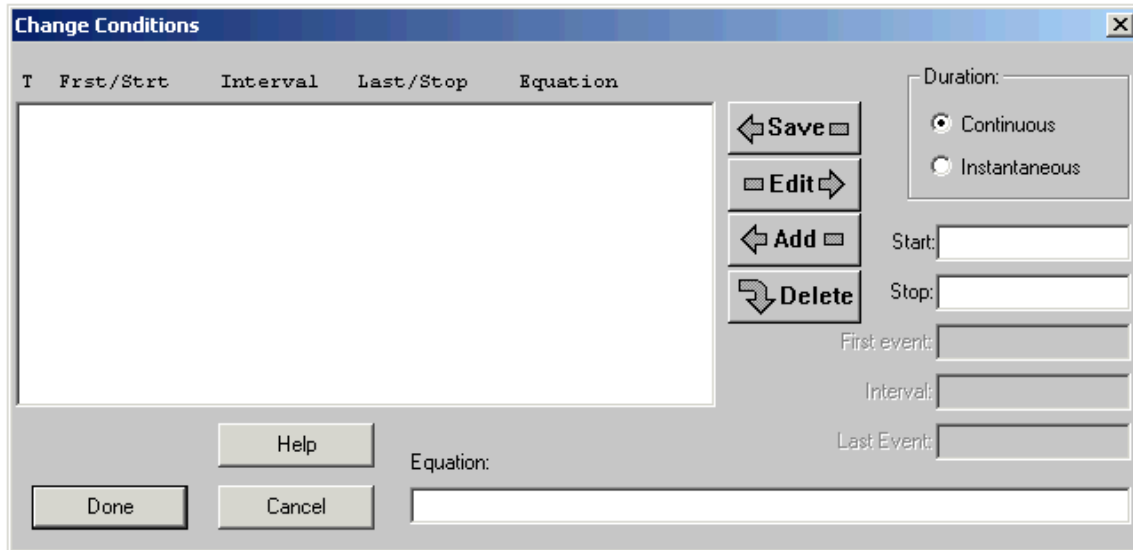
1. Reweight all data.

Open the **Data** window, and remove the “(-+)” following the datum at day 10. Close the **Data** window.

2. Use the **Change Conditions** tool to introduce a change in $k(0,2)$ at day 9.
 - a. Double-click $k(0,2)$ to open the **Loss Attributes** dialog box.
 - b. In the **Equation** pane, type the equation “ $k(0,2)=\text{loss_bef}$ ”. The **Loss Attributes** dialog box will appear:



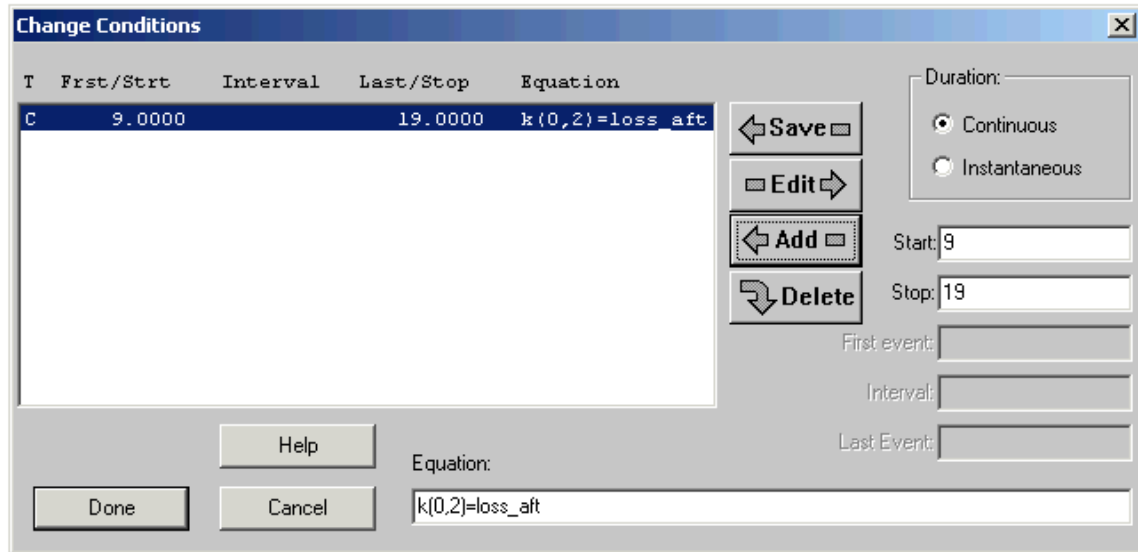
- c. Click **Done**. Remember the value 0.29 for $k(0,2)$ from the initial part of the case study; this will be the initial value for the new parameter $loss_bef$.
- d. In the **SAAM II Toolbox**, click **Change Conditions**. The **Change Conditions** dialog box will open as shown below:



Change conditions. The **Change Conditions** tool allows you to make a change to any component in your model. The changes can be continuous, i.e. over a period of time, or instantaneous. Continuous changes could be changes in a rate constant that will last over a period of time; this will be illustrated below. Instantaneous changes could be when you want to change a state variable such as a **qi** at some point in time.



- e. Be sure the **Continuous** is selected in the **Duration** box.
- f. In the **Equation** pane, type “ $k(0,2)=loss_aft$ ”.
- g. In the **Start** box, enter “9”
- h. In the **Stop** box, enter “19”.
- i. Click **Add**. The **Change Conditions** dialog box will appear:



- j. Click **Done**.



Change conditions for $k(0,2)$. As a result of defining $k(0,2)=\text{loss_bef}$ from time 0 to day 9, and $k(0,2)=\text{loss_aft}$ from day 9 to 19, we have introduced two new parameters in the model: loss_bef and loss_aft . The parameter $k(0,2)$ will no longer appear in the **Parameters** list because of this. In terms of solving your model, up to day 9, $k(0,2)$ will equal loss_bef , and after day 9, it will equal loss_aft . The question is: is this change sufficient to explain the change in the data?



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

The image shows a 'Parameters' dialog box with a table of parameters and a detailed view for the selected parameter 'loss_aft'.

| Name | Type | Current | Low Limit | High Limit |
|----------|------|-----------|-----------|------------|
| k(2,3) | Adj | 0.2839 | 0.0100 | 1.0000 |
| k(3,2) | Adj | 0.1747 | 0.0100 | 1.0000 |
| loss_aft | Adj | 0.4000 | 0.0400 | 4.0000 |
| loss_bef | Adj | 0.2900 | 0.0290 | 2.9000 |
| vol | Adj | 2323.4700 | 300.0000 | 30000.0000 |

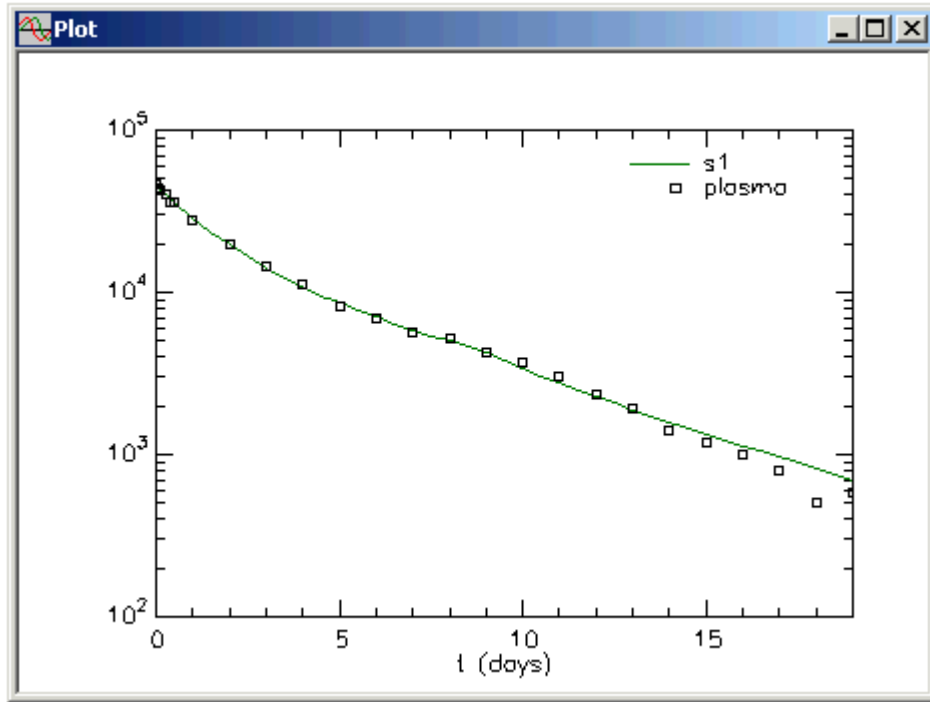
Below the table, the 'loss_aft' parameter is detailed:

Name: loss_aft
Value: .4
Type: Fixed Adjustable
Low Limit: 0.04000000
High Limit: 4.00000000

Buttons: Done, Cancel, Help, Edit, Save

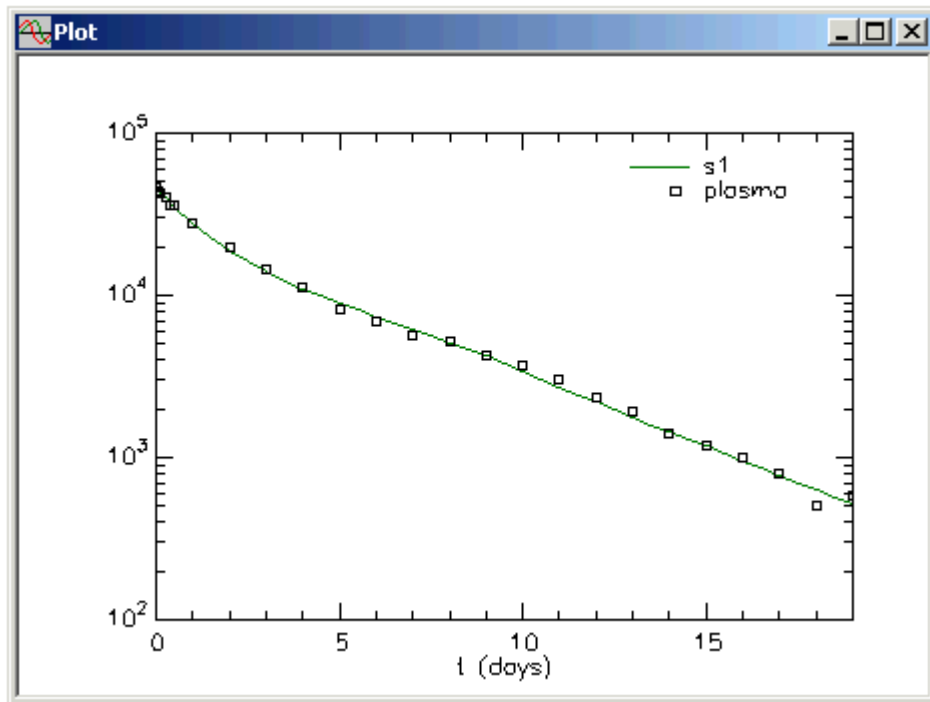
With the exception of *loss_aft*, these values are those from the best fit of the model to day 9. The initial **Value** for *loss_aft* has been increased to take into account the more rapid metabolism of LDL after day 9.

4. Solve the model, and view the solution. The plot of the plasma data will appear as follows:

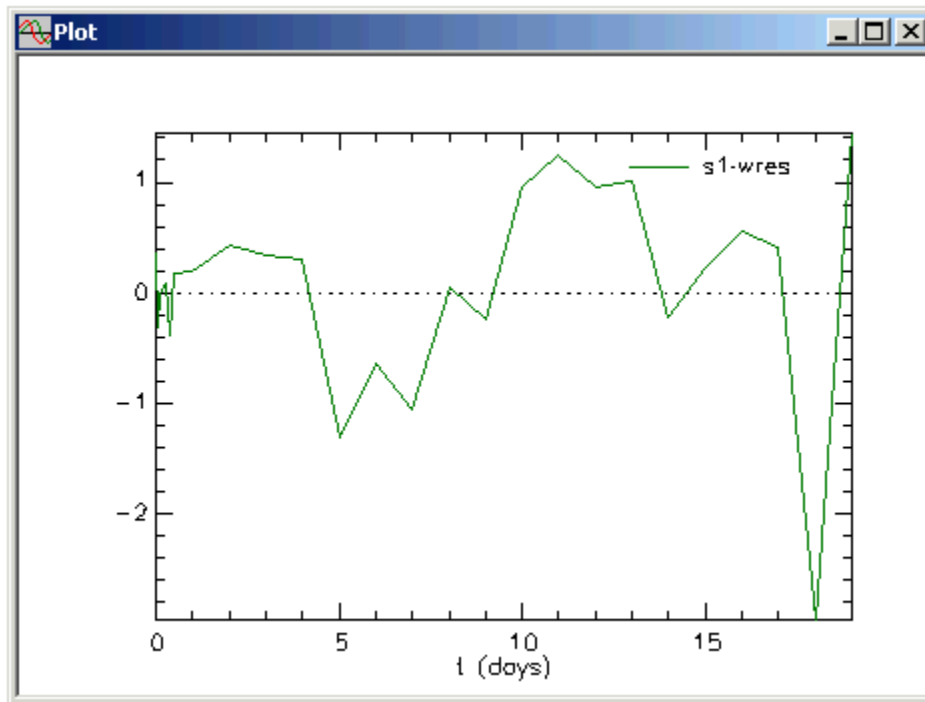


Leave the **Plot** window open.

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



To help assess the solution, plot the weighted residuals. They will appear as follows:



While the strategy of increase $k(0,2)$ following TPN appears to be working, there still appear to be systematic deviations in the model predicted values. You can perform a runs test for goodness-of-fit if you wish to assess the weighted residuals.

If you open the **Statistics** window, it will appear as follows:

| Parameter/Variable | Value | Std.Dev. | Coef. of Var. | 95% Confidence Interval |
|-------------------------------|------------|--------------|---------------|-------------------------|
| k(2,3) | 0.48807 | 1.76752e-001 | 3.62142e+001 | 0.11938 0.85677 |
| k(3,2) | 0.24623 | 7.95397e-002 | 3.23035e+001 | 0.08031 0.41214 |
| loss_aft | 0.38543 | 6.13009e-002 | 1.59044e+001 | 0.25756 0.51330 |
| loss_bef | 0.31100 | 2.01301e-002 | 6.47275e+000 | 0.26901 0.35299 |
| vol | 2278.86349 | 9.48731e+001 | 4.16318e+000 | 2080.96197 2476.76502 |
| ----- Derived Variables ----- | | | | |
| k(0,2) | 0.31100 | 2.01301e-002 | 6.47275e+000 | 0.26901 0.35299 |

| | Objective | Scaled Data Variance |
|-----------------|---------------|----------------------|
| s1 : plasma | 1.315861e+001 | 6.276988e-001 |
| Total objective | 1.315861e+001 | |
| AIC | 7.738244e+000 | |
| BIC | 7.884509e+000 | |

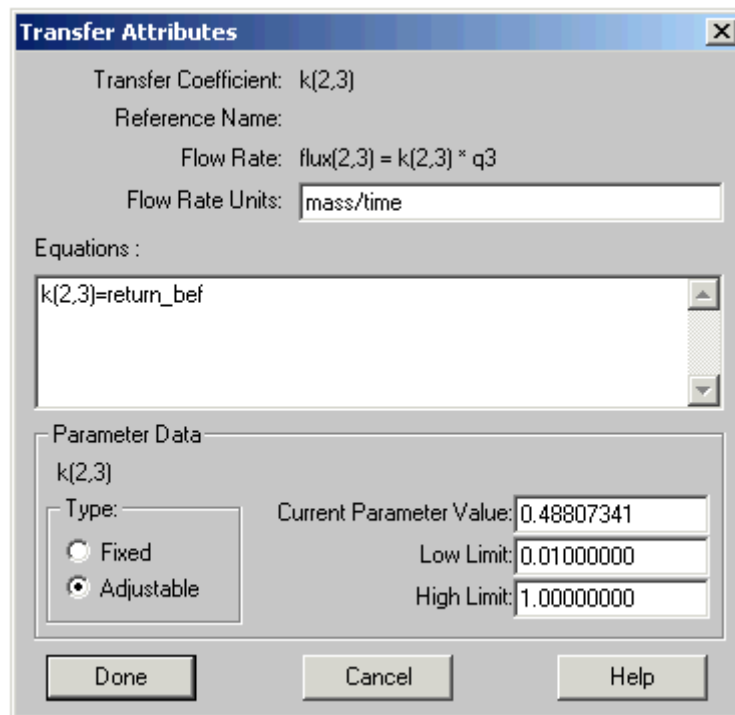
Thus even with the increased model complexity, i.e. adding a new parameter to describe the loss from plasma following TPN, the statistics are reasonable.

Close all open windows.

6. Use the **Change Conditions** tool to introduce a change in $k(2,3)$ at day 9.

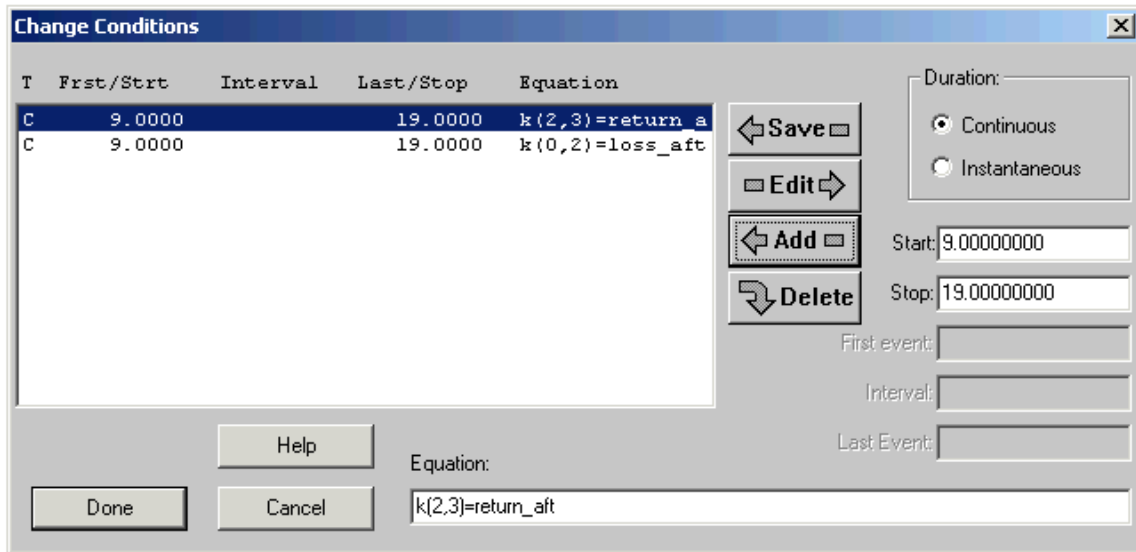
The logic in testing this change is again based upon physiology. It is clear that TPN causes an increase in the metabolism of LDL, and that an increased loss rate is probably not sufficient to explain the change. If the hyperinsulinemia caused by TPN is increasing the rate of metabolism by, for example, increasing the receptor sites on cells where LDL can exit the cell, than an increase in $k(2,3)$ as well as $k(0,2)$ is reasonable. This hypothesis will now be tested.

- a. Double-click $k(2,3)$ to open the **Transfer Attributes** dialog box.
- b. In the **Equation** pane, type the equation “ $k(2,3)=\text{return_bef}$ ”. The **Transfer Attributes** dialog box will appear as follows:



- c. Click **Done**.
- d. On the **SAAM II Toolbox**, click **Change Conditions**. The **Change Conditions** dialog box will open.
- e. In the **Equation** pane, type “ $k(2,3)=\text{return_aft}$ ”.

- f. Click **Add**. The **Change Conditions** dialog box will appear as shown below:



Notice because of the first change condition you added, the **Continuous** radio button was selected, and the entries in the **Start** and **Stop** box were correctly set.

- g. Click **Done**.
7. Enter the new parameter values.
- Open the **Parameters** dialog box. Notice there are the two new parameters, *return_bef* and *return_aft*, for which values must be supplied in order to solve your model.
 - In the **Value** box for *return_bef* and *return_aft*, enter “0.5” and “0.7” respectively. The **Parameter** dialog box will appear:

| Name | Type | Current | Low Limit | High Limit |
|------------|------|-----------|-----------|------------|
| k(3,2) | Adj | 0.2460 | 0.0100 | 1.0000 |
| loss_aft | Adj | 0.3852 | 0.0400 | 4.0000 |
| loss_bef | Adj | 0.3110 | 0.0290 | 2.9000 |
| return_aft | Adj | 0.7000 | 0.0700 | 7.0000 |
| return_bef | Adj | 0.5000 | 0.0500 | 5.0000 |
| vol | Adj | 2279.2736 | 300.0000 | 30000.0000 |

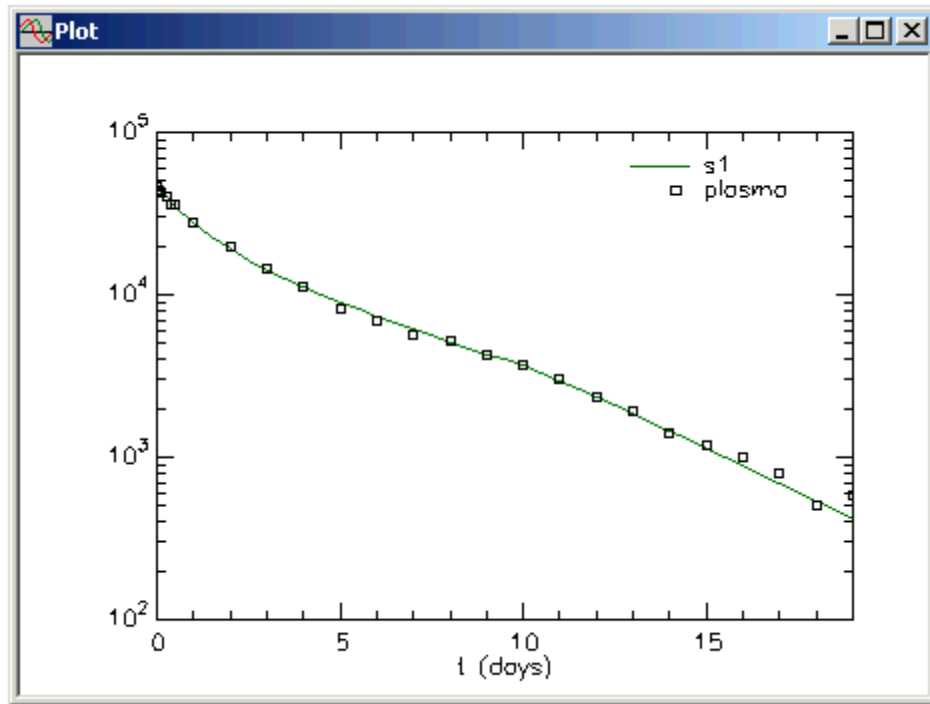
Name: return_bef Value: 0.5

Type: Fixed Adjustable

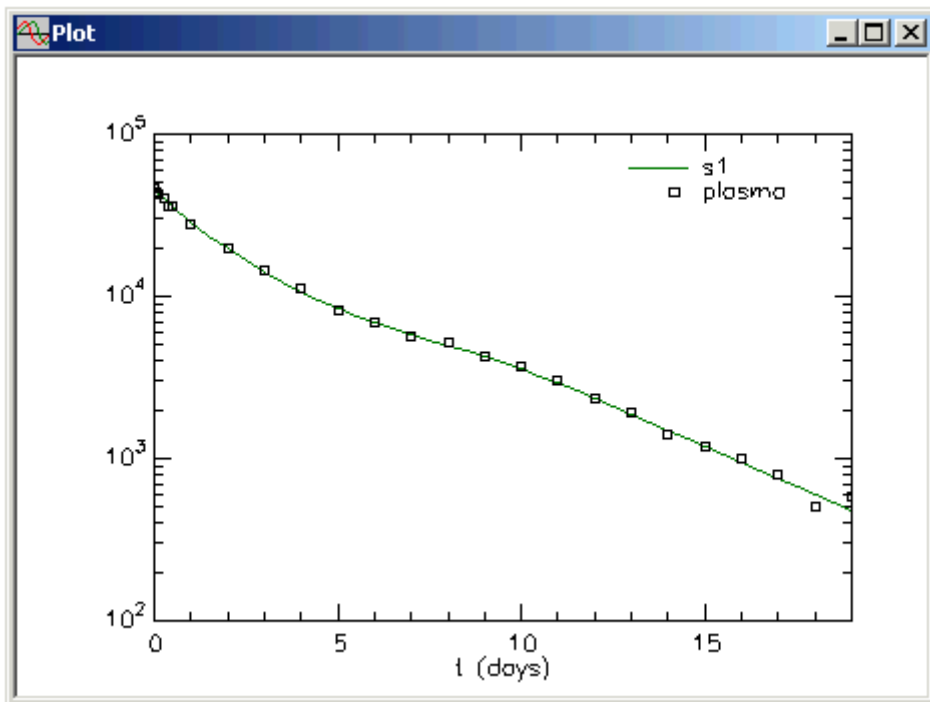
Low Limit: 0.05000000 High Limit: 5.00000000

Buttons: Done, Cancel, Help, Edit, Save

- c. Click **Done**.
8. Solve the model and view the solution. The plot of the plasma data will appear as follows:



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



a. View the statistical information. The **Statistics** window will appear as shown below:

| Parameter/Variable | Value | Std.Dev. | Coef. of Var. | 95% Confidence Interval | |
|-----------------------------------------------------------------------------------------------------------------------------|------------|---------------|----------------------|-------------------------|------------|
| k(3,2) | 0.17558 | 3.30876e-002 | 1.88452e+001 | 0.10632 | 0.24483 |
| loss_aft | 0.47378 | 1.47562e-001 | 3.11458e+001 | 0.16493 | 0.78263 |
| loss_bef | 0.28739 | 3.16857e-002 | 1.10253e+001 | 0.22107 | 0.35371 |
| return_aft | 0.39604 | 1.21745e-001 | 3.07409e+001 | 0.14122 | 0.65085 |
| return_bef | 0.26231 | 1.43233e-001 | 5.46055e+001 | -0.03748 | 0.56210 |
| vol | 2325.44733 | 7.69406e+001 | 3.30864e+000 | 2164.40914 | 2486.48551 |
| ----- Derived Variables ----- | | | | | |
| k(0,2) | 0.28739 | 3.16857e-002 | 1.10253e+001 | 0.22107 | 0.35371 |
| <input type="radio"/> Correlation Matrix <input type="radio"/> Covariance Matrix <input checked="" type="radio"/> Objective | | | | | |
| | | Objective | Scaled Data Variance | | |
| s1 : plasma | | 1.277287e+001 | 4.492636e-001 | | |
| Total objective | | 1.277287e+001 | | | |
| AIC | | 7.585372e+000 | | | |
| BIC | | 7.756015e+000 | | | |

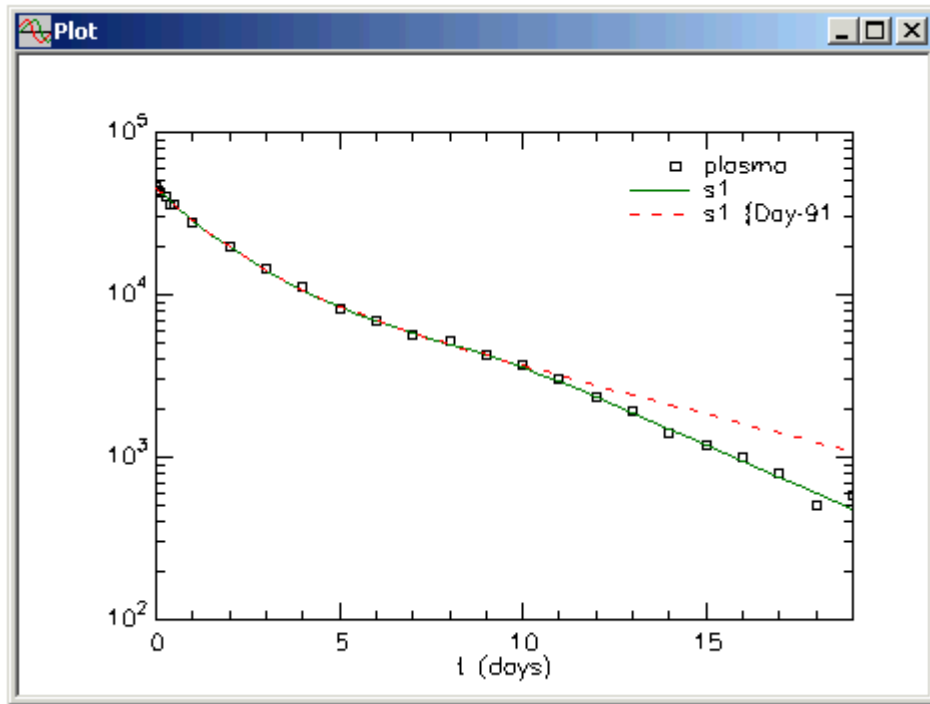


Parameters estimated from data. Notice in going through this case study that you started with four adjustable parameters and ended up estimating with satisfactory precision six. The reason why is that there is enough information in the data. When you fitted the data to day 9, you say there was enough information to estimate the four parameters quite well. When the perturbation was introduced and the shape of the curve changed, there was enough information to estimate the remaining two parameters. The statistics are reasonable with the possible exception of *return_bef* whose coefficient of variation is larger than 50%.



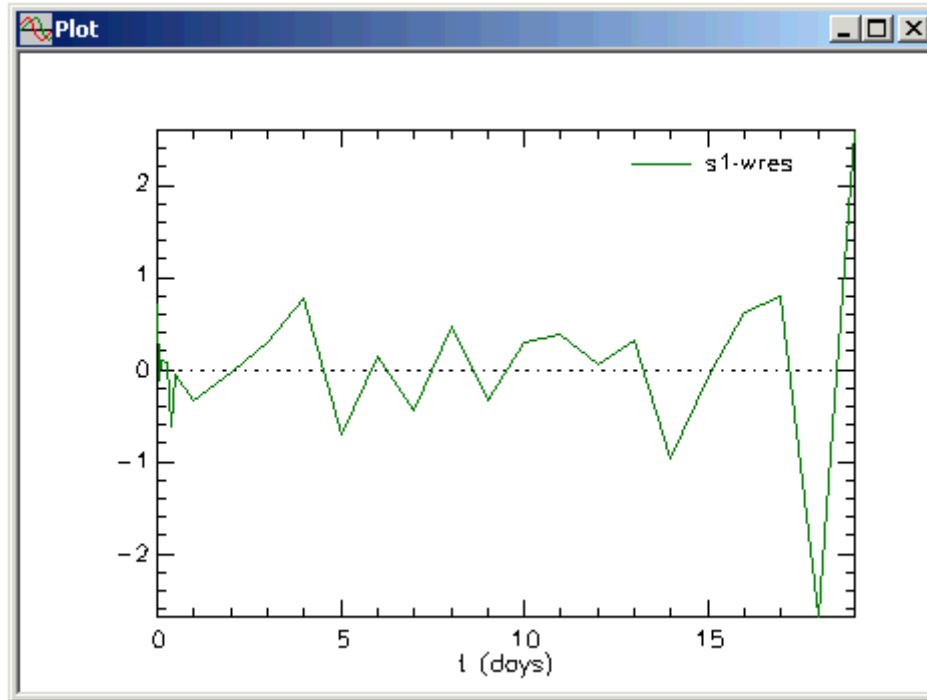
Close the **Statistics** window.

- b. Plot **s1, plasma** and **s1{Day91}**. The plot will appear as follows:



You can see the model which permits changes in $k(0,2)$ and $k(2,3)$ describes the data very well; the difference caused by the introduction of TPN can be observed by comparing the solution with the solution when only data to day 9 were fitted.

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



The weighted residuals are randomly distributed, and lie, with the exception of the datum at day 18, in a band between -1 and 1.

10. Close all open windows.

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

Essential Points to Remember

- Change conditions is a power tool in SAAM II to model experimental perturbations.
- Saving solutions can help in the model development process by permitting comparisons among competing model structures.
- Unweighting and reweighting data can be an important component of the model development and testing process.
- In assessing different model structures, it is necessary to examine both the model solution and the weighted residuals.

Data for this case study

DATA
t plasma
0.007 46780
0.042 43522
0.125 42535
0.25 40125
0.375 36221
0.5 35562
1 28194
2 19573
3 14403
4 11278
5 8081
6 6999
7 5653
8 5139
9 4210
10 3658
11 3004
12 2367
13 1928
14 1415
15 1193
16 996
17 801
18 511
19 580
END

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