N-Acetylprocainamide (NAPA) Kinetics

Case Study

- How to analyze studies of bioavailability
- How to use Delays
- How to use Duplicate
- How to save results to a text file for report writing

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N-Acetylprocainamide (NAPA) Kinetics: Bioavailability Estimated by a Stable Isotope Method

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 will show you how to analyze the data from a study of absolute bioavailability in which an intravenous (iv) dose of stable isotope-labeled drug was injected at the same time as the conventional formulation was administered orally. You will learn how to deal with the time lag that occurs between the time of oral dose administration and its first appearance in plasma. This time lag reflects the time required for tablet dissolution and gastric emptying. You will learn:

- How to analyze data generated from studies of absolute bioavailability (simultaneously fitting iv and oral data).
- How to use the delay tool to model an absorption time lag.
- How to use the duplicate feature to duplicate a model structure.
- How to save results to a text file for report writing.

Data Required

The data file for this case study is

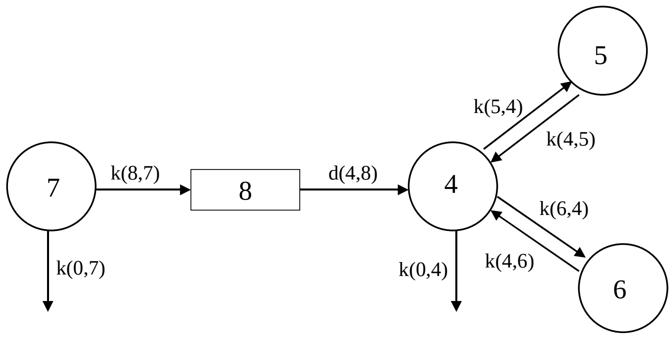
napa.dat

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

Introduction

Bioavailability is defined as the relative amount of a drug administered in a pharmaceutical product that enters the systemic circulation in an unchanged form, and the rate at which this occurs [1]. If the drug is administered iv, obviously 100% is absorbed. When the comparison is made between an oral (or other non-iv route of administration) and an iv dose, the absolute bioavailability of the drug is measured.

The situation can be described in the context of the following figure; this represents the model that will be developed in this case study.



In this model, Compartment **4** represents plasma; iv administration of a drug is into this compartment. Compartment **7** represents the first part of the gut. Since there is usually a time lag between the time a drug is taken orally and it appears in plasma, a delay, represented above by the box "8," is required in the model. In terms of bioavailability, one cannot tell the difference between a loss from Compartment **7** or the Delay **8**; it is usually modeled as a loss from Compartment **7** (this has no effect on estimation of bioavailability).

The fraction absorbed and the rate at which the drug is absorbed can be calculated from a knowledge of the rate constants *k(8,7)* and *k(0,7)*; this will be illustrated below.

Bioavailability cannot be estimated from an oral dose alone with only plasma samples. The reason is that the system model, represented by compartments 4, 5 and 6, cannot be estimated along with the absorption characteristics, compartment 7 and delay 8.

In most instances, absolute bioavailability is studied by administering iv and oral doses of a drug to a subject on two different occasions. In this way, one can determine the system model from the iv data and absorption by simultaneously analyzing the iv and oral data. This not only requires two separate studies and sets of blood samples, but requires the assumption that the pharmacokinetic parameters characterizing drug distribution and elimination have remained unchanged between the two studies. This assumption is particularly tenuous when bioavailability is being evaluated in the patient population for whom the drug is intended rather than in normal subjects.

This problem can be overcome by using a stable isotope labeled drug; in this way, the labeled drug can be administered iv and the conventional, unlabeled drug formulation can be administered orally [2]. Both compounds then can be measured simultaneously in plasma using a mass spectrometer coupled to either a gas chromatograph, as in this case, or to a high-performance liquid chromatograph. The data for this case study were taken from a study in patients who were candidates for therapy with this antiarrhythmic drug [3].

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1. Koch-Weser, J. “Bioavailability of drugs.” N Engl. J. Med. 1974, 291:233-7,503-6.

2. Strong, J. M., Dutcher, J. S., Lee, W-K., Atkinson, A. J., Jr. “Absolute bioavailability in man of N-acetylprocainamide in man determined by a novel stable isotope method.” Clin. Pharmacol. Ther 1975, 18: 613-22.

3. Atkinson, A. J. Jr., Ruo, T. I., Piergies, A. A., Breiter, H. C., Connelly, T. J., Sedek, G. S., Juan, D., Hubler, G. L., Hsieh, A-M. “Pharmacokinetics of N-acetylprocainamide in patients profiled with a stable isotope method”. Clin. Pharmacol. Ther. 1989, 46: 182-9.

Part 1. Analyze the data resulting from intravenous administration of NAPA-^{13}C.

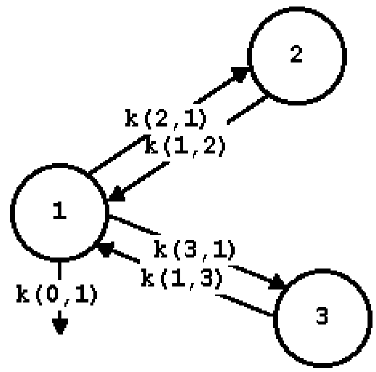
The first step will be to create a 3-compartment system model to describe the kinetics of the iv dose of stable isotope labeled NAPA. The data, NAPA_IV found in the data file **napa.dat**, are plasma samples following a 5-minute infusion of NAPA-^{13}C.

Which system model structure? The 3-compartment model is chosen here because *a priori* knowledge from the literature suggests this is the most appropriate. Using information from the literature can help you in the system model development process. You must be sure, however, that the experiment in the literature is similar to yours, especially the sample times. A richer set of samples will often indicate a more complex model.

If you are unsure of the model used in the literature, you should start first with the two-compartment model, and then move to the three- and four-compartment models to be sure the three-compartment model is in fact the most appropriate for your data. In this case, the central compartment had previously been shown to correspond to intravascular space, corrected for RBC/plasma partitioning. The slow and fast equilibrating peripheral compartments are primarily composed of splanchnic and somatic tissues, respectively.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open. In the **SAAM II Toolbox**, be sure the **Model** tools are available.

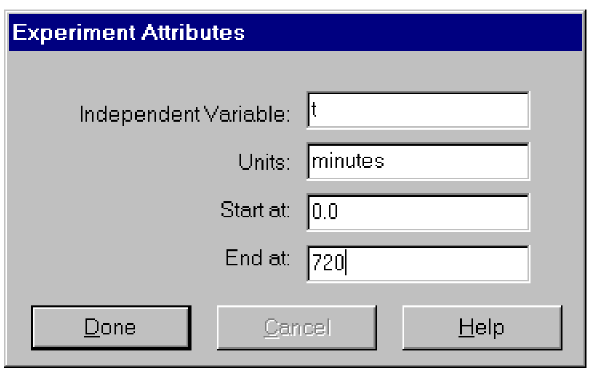
2. Create the following system model on the **Drawing Canvas**:



3. 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.

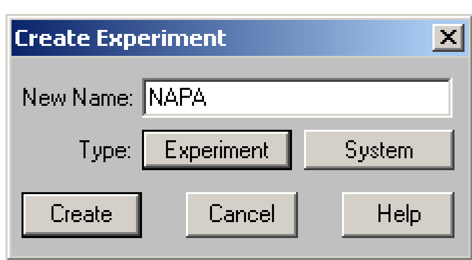
    a. Leave "minutes" in the **Units** box.

    b. Enter "720" in the **End at** box. The **Experiment Attributes** dialog box will appear as follows:



    c. Click **Done**.

The **Create Experiment** dialog box will appear on the **Drawing Canvas**. Type "NAPA" in the **New Name** box. The **Create Experiment** dialog box will appear as follows:



   d. Click **Create**. Notice "NAPA" appears as the name beneath "Experiment" in the **SAAM II Toolbox**.

4. Create a sample.

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

   b. Click compartment **q1**, then click on the **Drawing Canvas**. The sample **s1** will appear.

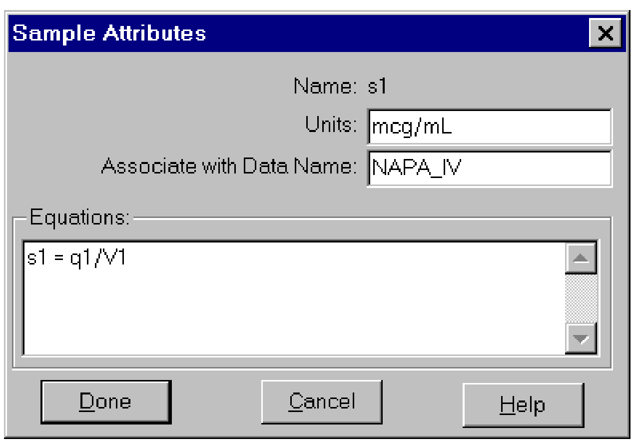
   c. Double-click **s1** to open the **Sample Attributes** dialog box.

   d. Type "mcg/mL" in the **Units** box.

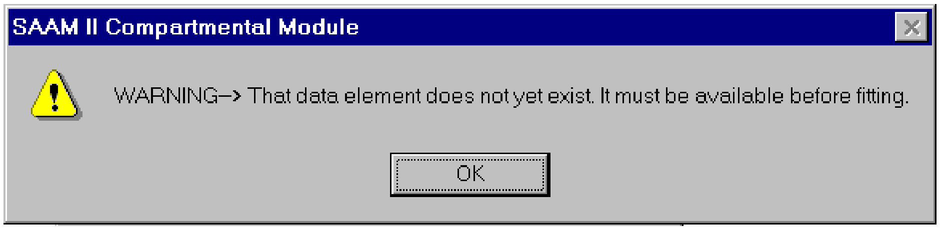
Units. The units of the data are micrograms/milliliter. Normally this would be written µg/ml or µg/mL. SAAM II does not accept µ for micro. Writing the units mg/ml would be normally interpreted as micrograms/ml. Thus writing the units mcg/mL is a convenient way to denote the microgram.

   e. Type "NAPA_IV" in the **Associate with Data Name** box.

   f. Edit the sample equation "s1 = q1" to read "s1 = q1/V1". The **Sample Attributes** dialog box will appear as follows:



   g. Click **Done**. The following Warning message will appear:



h. Click **OK**.

5. Create an input.

An intravenous dose of 271 mg of NAPA-^{13}C was infused over 5 minutes.

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

b. Click compartment **q1**, and then click on the **Drawing Canva**s. The input **ex1** will appear.

c. Double-click **ex1** to open the **Exogenous Input** dialog box.

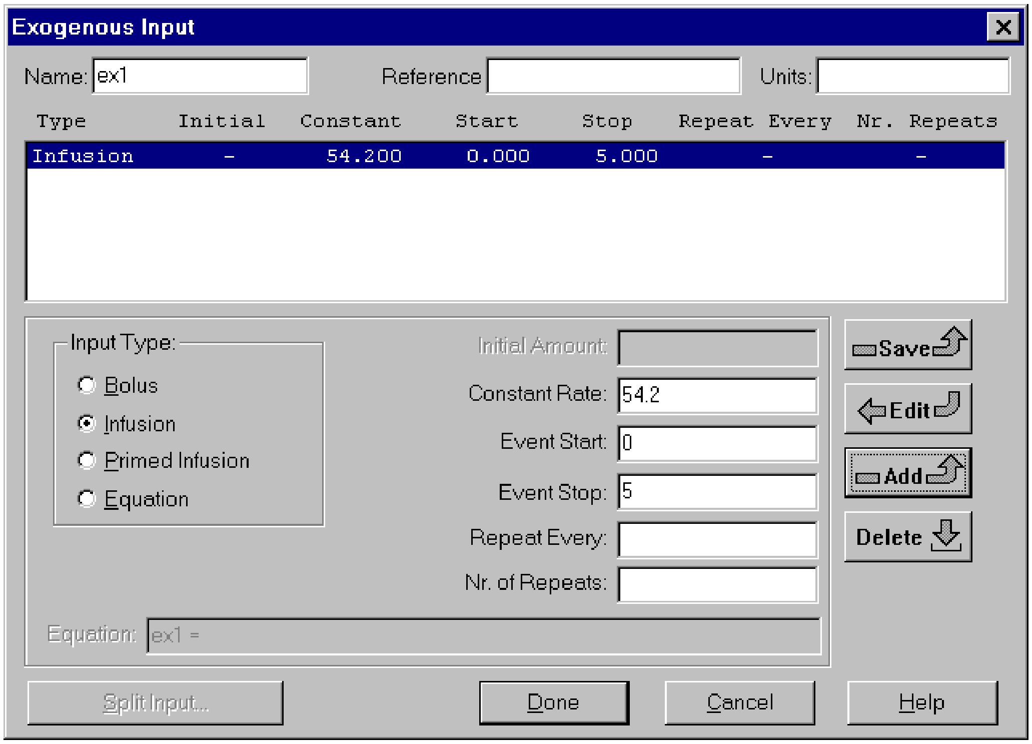
d. Select **Infusion** as the **Input Typ**e.

e. Enter “54.2” in the **Constant Rate** box.

f. Enter “0” in the **Event Start** box.

g. Enter “5” in the **Event Stop** box.

h. Click **Add**. The **Exogenous Input** dialog box will appear as follows:



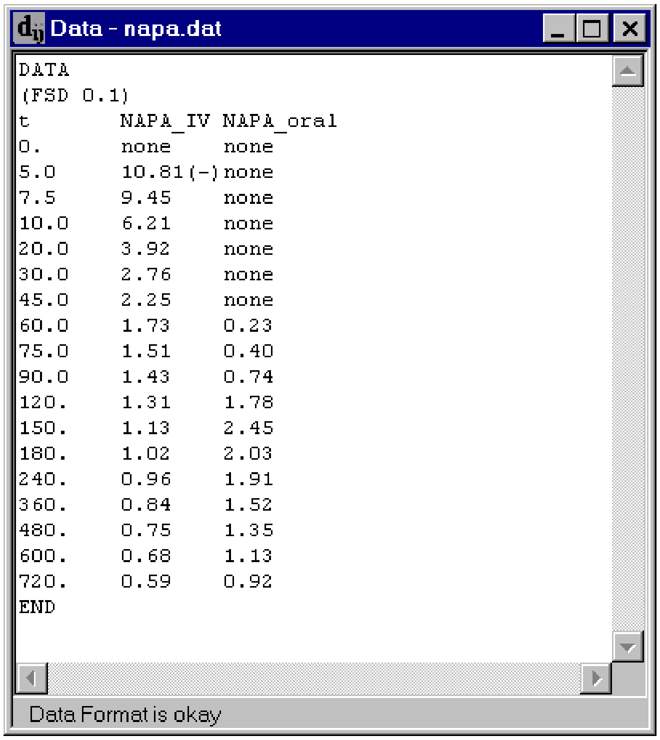
i. Click **Done**.

6. Add the data to your model.

a. In the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data** . The **Data** window will open.

b. In the **File** menu, click **Open**. The file **napa.dat** should appear in the list (if it does not, find the folder where you have put this data file).

c. Double-click **napa.dat**. The data file contains NAPA data following the 5 minute constant infusion, NAPA_IV, and following the oral administration, NAPA_oral. The oral data will be used later. The **Data** window appears as follows:


Data - napa.dat

```
DATA
(FSD 0.1)
t        NAPA_IV NAPA_oral
0.       none    none
5.0      10.81(-)none
7.5      9.45    none
10.0     6.21    none
20.0     3.92    none
30.0     2.76    none
45.0     2.25    none
60.0     1.73    0.23
75.0     1.51    0.40
90.0     1.43    0.74
120.     1.31    1.78
150.     1.13    2.45
180.     1.02    2.03
240.     0.96    1.91
360.     0.84    1.52
480.     0.75    1.35
600.     0.68    1.13
720.     0.59    0.92
END
```

Data Format is okay

The weighting scheme is FSD so you can leave the variance model set as the default data-relative. Note that the first NAPA_IV data point is followed by "(-)" to unweight it. The reason will be explained in more detail below. Note also that measurable NAPA from the oral dose first appears in plasma 60 minutes after the dose is administered. This will be modeled using the delay tool in Part 2 of this case study.

d. Close the **Data** window.

7. 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.

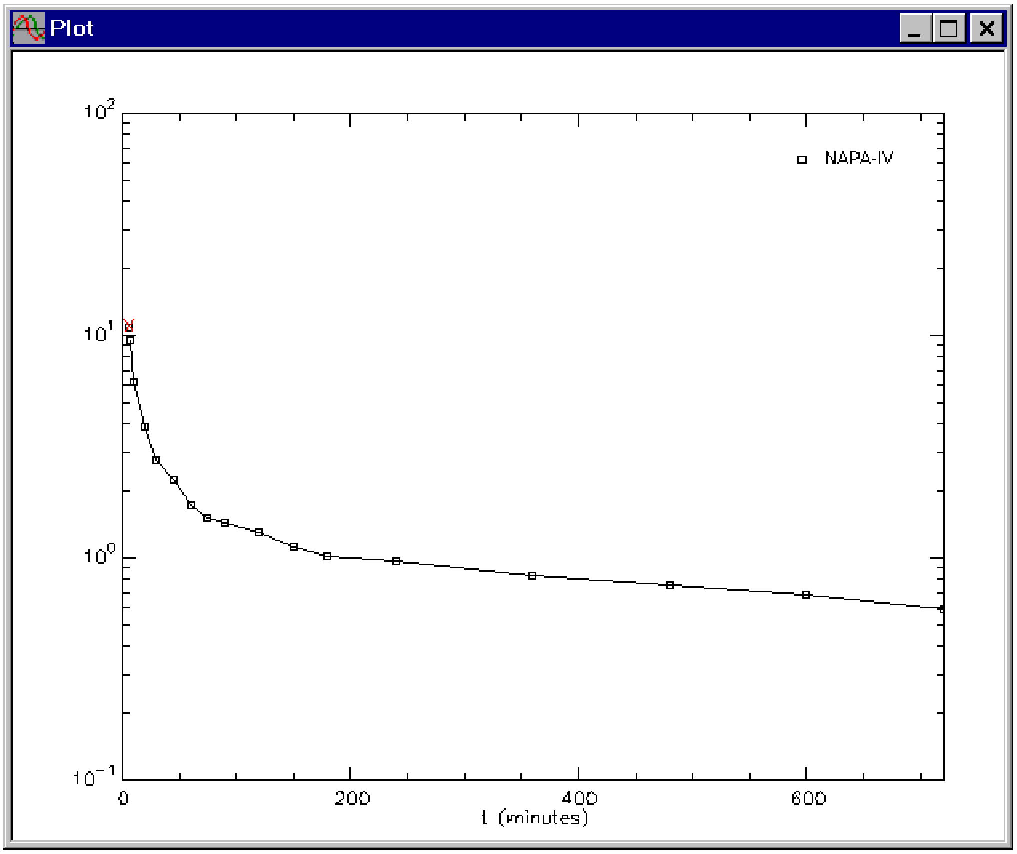
b. Be sure the **List All Variables** check box is selected. (Click this box if it is not selected).

c. Click **NAPA_IV** to move it to the **Current Selection** pane.

d. Click **Done**. A plot of your data will appear in the **Plot** window.

e. In the **View** menu, click **Line Plot**.

f. In the **View** menu, click **Semilog**. 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. However, three is more likely because the break in the curve is not “sharp” which would indicate a two-compartment model. Thus the three-compartment model discussed in the literature is probably appropriate.

g. Close the **Plot** window.

8. Enter parameter values.

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

The parameter *V1* should be selected. If it is not selected, double-click *V1*. Be sure the **Adjustable** option is selected.

b. Enter "5" in the **Value** box, "3" in the **Low Limit** box, "10" in the **High Limit** box, and click **Save**.

c. Double-click *k(0,1)* to select it.

d. Enter "0.02" in the **Value** box, and click **Save**.

e. Double-click *k(1,2)* to select it.

f. Enter "0.1" in the **Value** box, and click **Save**.

g. Double-click *k(1,3)* to select it.

h. Enter "0.007" in the **Value** box, and click **Save**.

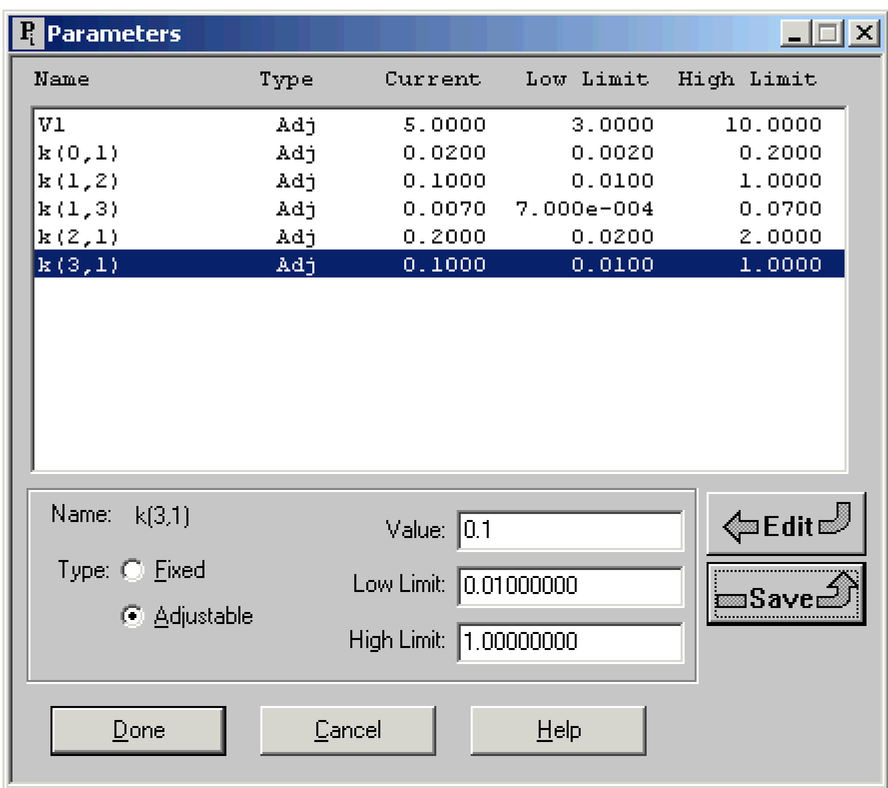
i. Double-click *k(2,1)* to select it.

j. Enter "0.2" in the **Value** box, and click **Save**.

k. Double-click *k(3,1)* to select it.

l. Enter "0.1" in the **Value** box, and click **Save**.

When you have finished, your **Parameters** dialog box should appear as follows:



m. Click **Done**.

9. Save your study file.

   a. In the **File** menu, click **Save As**.

   b. Type “napa_iv” in the **File Name** box.

   c. Select the folder where you wish to save the file in the **Save In** box.

   d. Click **Save**.

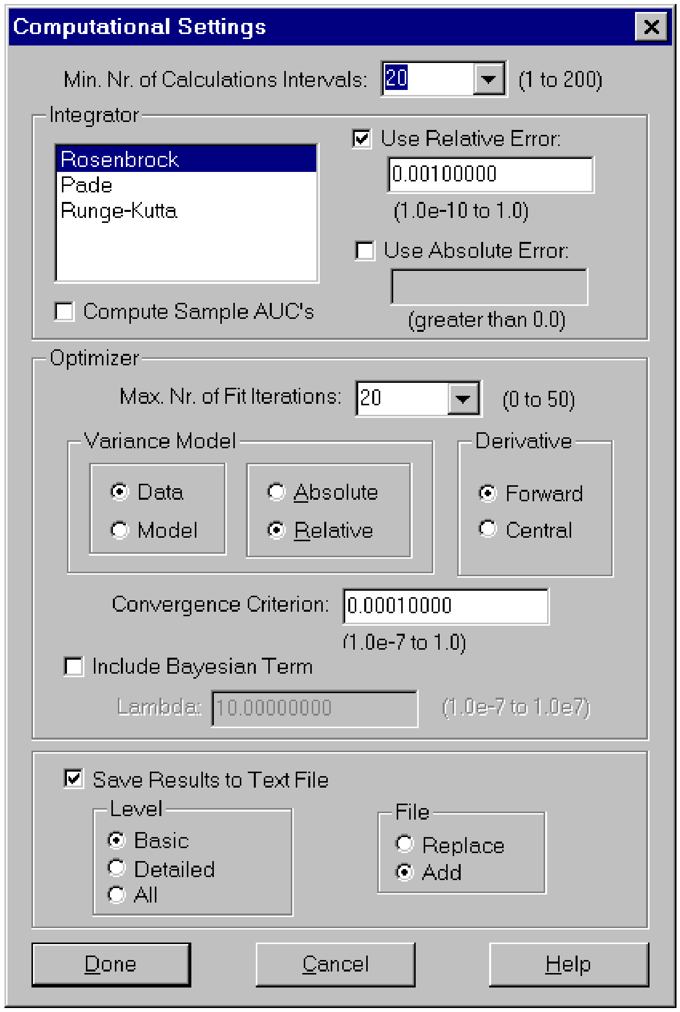
10. Prepare to save the results of your modeling session so you can write a report.

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

    b. Select the **Save Results to Text File** box.

    c. In the **Level** pane, select **Basic**.

    d. In the **File** pane, select **Add**. The **Computational Settings** dialog box will appear follows:

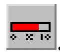


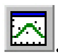
e. Click **Done**.

Report writing. SAAM II supports writing information to a text file which can then be used to write a report of your modeling session. There are three levels of information saved; they are basic, detailed and all. The difference between these options is explained in the Addendum to the SAAM II User Guide that accompanies version 1.2. In addition, you can “Replace” or “Add” to the text file. If you select the “Replace” option, when you save, the previous text file, **modelname.txt**, will be overwritten. If you choose “Add,” a new text file will be created but the original text file will be retained. In this case, “Add” is selected because the model development is step-wise and needs to be recorded.

When the “Add” option is chosen, each time you Solve or Fit, SAAM II will create a text file. Since you have saved your study file as **napa_iv** , the text files will be named "napa_iv" with a number after it so you can sequentially keep track of the order in which you "Solved" or "Fitted."

11. Solve your model and view the solution.

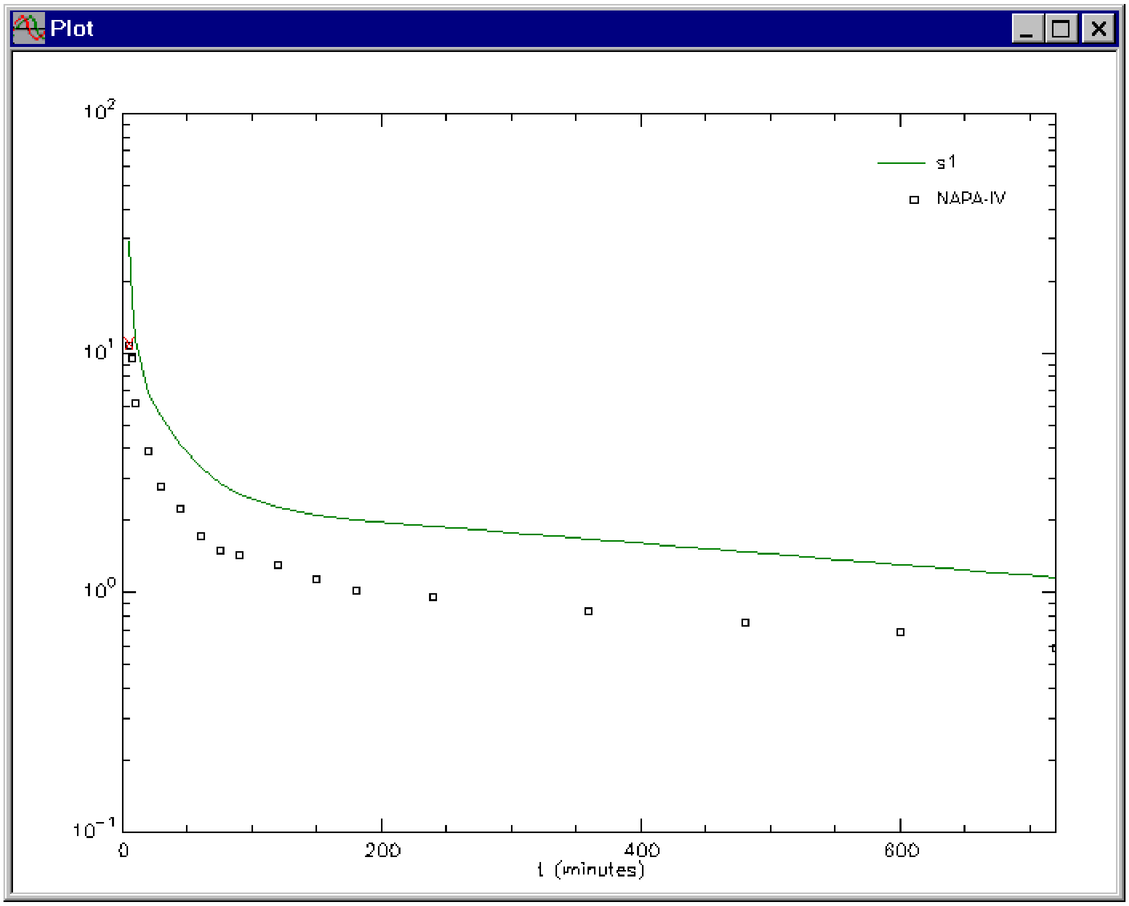
    a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve** .

    b. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot** . Since you had previously plotted your data, the **Plot** window will open. To plot the model solution, on the **Set** menu, click **Plot/Table Variables**. The **Plot and Table Variables** dialog box will open.

    c. In the **Plot and Table Variables** dialog box, clear the **List All Variables** check box to list only those variables associated with data.

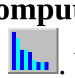
    d. Click **s1:NAPA_IV**; it will move to the **Current Selection** pane.

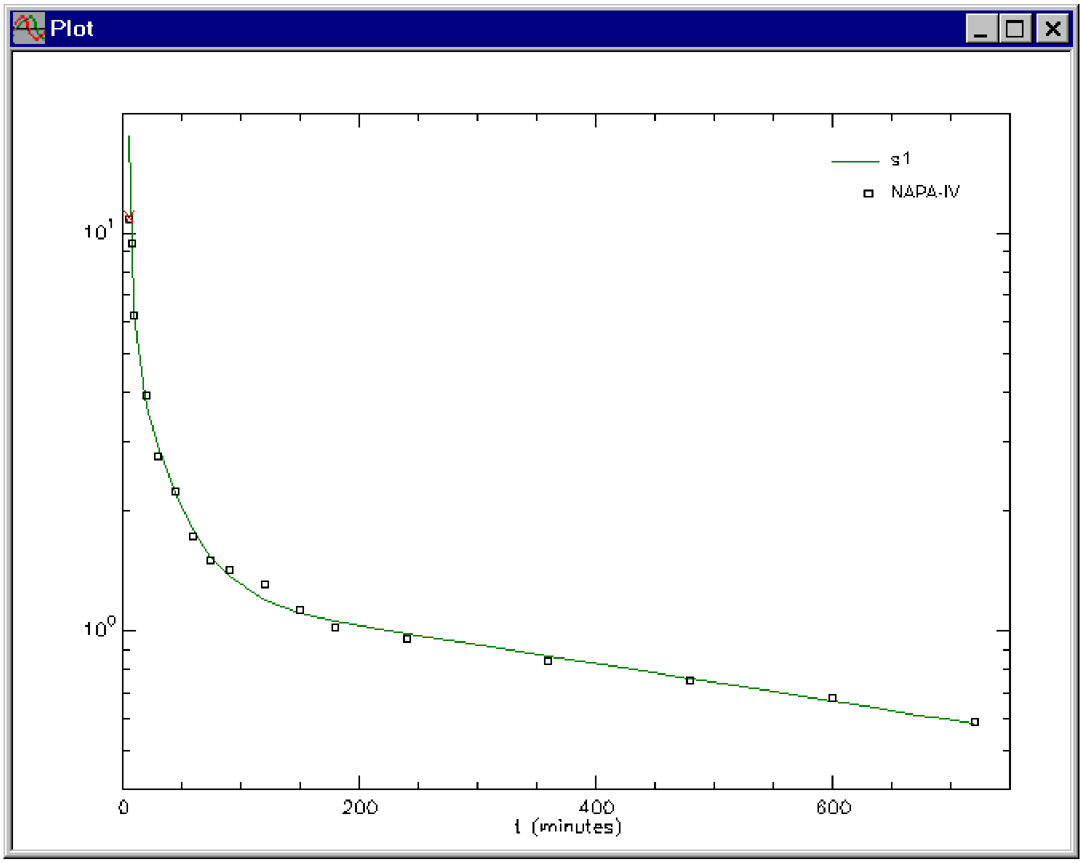
    e. Click **Done**. The following plot will appear (in semilog mode):



The initial estimates are reasonable in that the shape of the curve parallels the data. If you wish to hand-fit to improve the initial estimates, you should adjust the value for *V1* since this parameter acts as a linear scale factor. Leave the **Plot** window open.

12. 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 plot should appear as follows (the **Scale** has been changed for better visualization; the **X Axis** maximum is 750, and the **Y Axis** minimum and maximum are respectively 0.4 and 20):



Note that the first data point is marked with a red x because it was unweighted.

b. Close the **Plot** window.

c. View the results in tabular form.

(1) In the **Show** menu, click **Table**, or alternatively, on the **SAAM II Toolbar,** click **Table** . The **Plot and Table Variables** dialog box will not open since **s1:NAPA_IV** is already selected. The table will appear as follows:

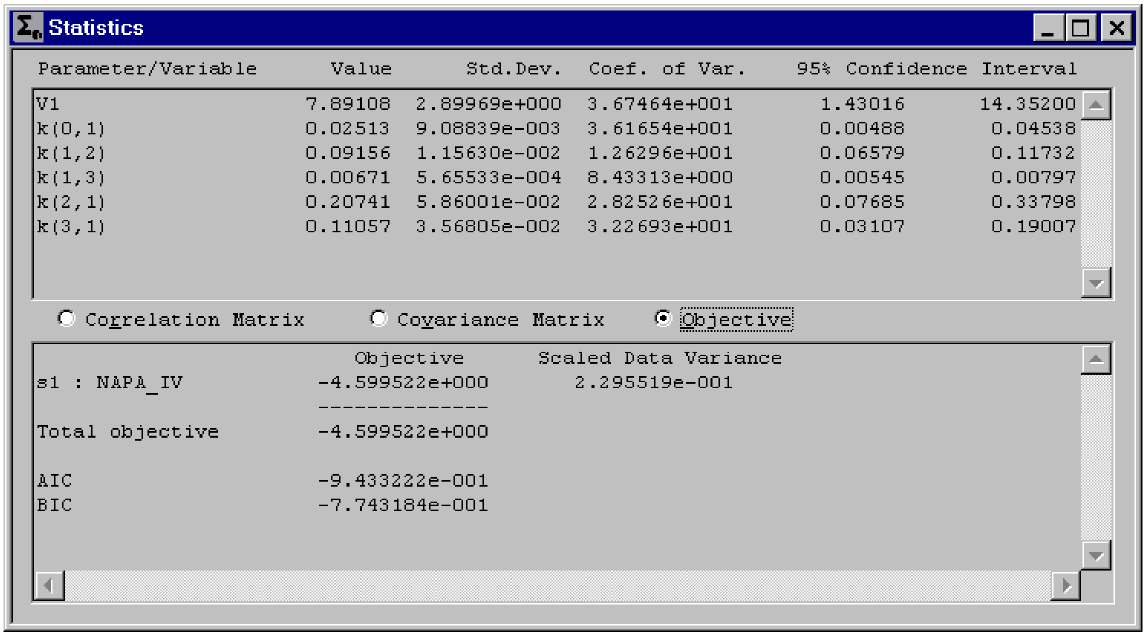
Table

t	s1	NAPA_IV
0.000	0.000	-
5.000	17.582	-
5.000	17.582	10.810
7.500	9.414	9.450
10.000	6.264	6.210
20.000	3.668	3.920
30.000	2.926	2.760
45.000	2.220	2.250
60.000	1.793	1.730
75.000	1.533	1.510
90.000	1.371	1.430
120.000	1.198	1.310
150.000	1.114	1.130
180.000	1.062	1.020
210.000	1.022	-
240.000	0.988	0.960
276.000	0.949	-
312.000	0.912	-
336.000	0.888	-
360.000	0.865	0.840
396.000	0.832	-
432.000	0.800	-
456.000	0.779	-
480.000	0.759	0.750
516.000	0.730	-
552.000	0.701	-
576.000	0.683	-
600.000	0.666	0.680
636.000	0.640	-
672.000	0.615	-
696.000	0.599	-
720.000	0.584	-
720.000	0.584	0.590

Note that the “Fit” to all but the first point is reasonably good. The concentration of the first data point is substantially below expected value for s1 because it was drawn immediately at the end of the infusion and intravascular mixing was incomplete. This mixing process usually requires 2 to 3 minutes. This is the rationale for unweighting this point.

(2) Close the **Table** window.

d. 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	
V1	7.89108	2.89969e+000	3.67464e+001	1.43016	14.35200
k(0,1)	0.02513	9.08839e-003	3.61654e+001	0.00488	0.04538
k(1,2)	0.09156	1.15630e-002	1.26296e+001	0.06579	0.11732
k(1,3)	0.00671	5.65533e-004	8.43313e+000	0.00545	0.00797
k(2,1)	0.20741	5.86001e-002	2.82526e+001	0.07685	0.33798
k(3,1)	0.11057	3.56805e-002	3.22693e+001	0.03107	0.19007

	Objective	Scaled Data Variance
s1 : NAPA_IV	-4.599522e+000	2.295519e-001

Total objective	-4.599522e+000	
AIC	-9.433222e-001	
BIC	-7.743184e-001	

It is apparent from the Coefficients of Variation in the **Statistics** window that the model parameters are moderately well determined.

e. Close the **Statistics** window.

Report writing (continued). You have performed two computational operations so far, one Solve and one Fit. Since you have selected the **Save Results to Text File** option in the **Computational Settings** window, SAAM II has automatically created two text files. You can view these text files by opening them (they are called napa_iv.txt and napa_iv_01.txt) in a text editor.

Part 2. Analyze the data resulting from oral administration of NAPA.

In the second part of this case study, a model describing the data following oral administration of NAPA will be postulated. The model will consist of two parts. The first part is the "system" model, i.e. a model describing the behavior of the drug once it enters plasma. The second part will describe how the drug is absorbed after oral administration. In postulating the "system" model, it is assumed that the disposition kinetics of NAPA-^{13}C administered as an iv infusion and NAPA administered orally are identical. That is, the system model is the same for both.

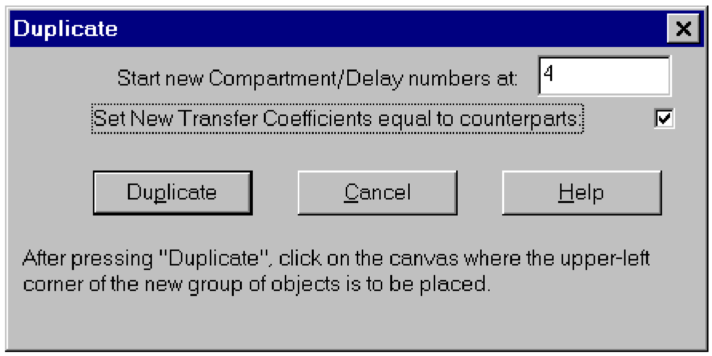
1. In the **SAAM II Toolbox**, be sure the **Experiment** tools are available. (You can **Duplicate** if either the **Model** or **Experiment** tools available. However, if only the **Model** tools are available, the samples will not be available for duplication.)

2. Duplicate the model for NAPA-^{13}C.

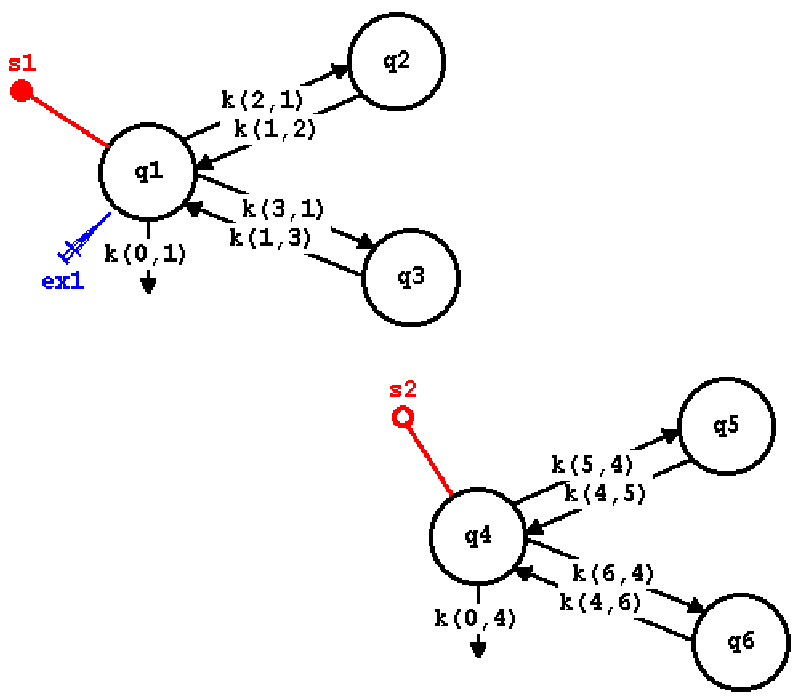
    a. While pressing the **CTRL** key, click compartments **q1**, **q2**, **q3** and **s1** ***in this specific order.***

    b. In the **Edit** menu, click **Duplicate**. The **Duplicate** dialog box will open.

    c. ***Important***: Check the **Set New Parameters Transfer Coefficients equal to counterparts** box. The **Duplicate** dialog box will appear as follows:



    d. Click **Duplicate** and click on the **Drawing Canvas** approximately where you would like the duplicated model to be inserted. The following two models (after rearrangement) will appear on the **Drawing Canvas** as follows:



Duplicating. There are occasions when you would like to have a duplicate copy of a model. In this case study, one model describes the intravenously administered drug. The other will describe oral absorption. The system model, i.e. the drug behavior in the body, is the same for either administration. Thus one would like to duplicate the model and have corresponding rate constants the same. As you will see, a structure to describe absorption will be added to the model consisting of Compartments **q4**, **q5** and **q6**.

The order in which the compartments and samples are clicked affects the restructuring of the duplicated model.

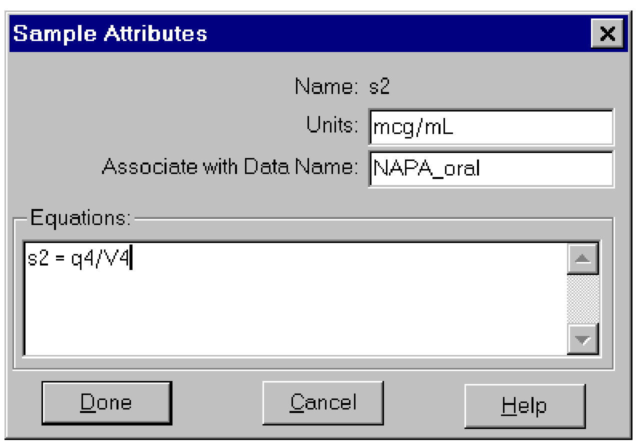
3. Modify the sample **s2**.

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

    b. Type “mcg/mL” in the **Units** box.

    c. Type “NAPA_oral” in the **Associated with Data Name** box.

    d. Edit the sample equation “s2 = q4” to read “s2 = q4/V4”. The **Samples Attributes** dialog box will appear as follows:



    e. Click **Done**.

4. Create the model for oral absorption.

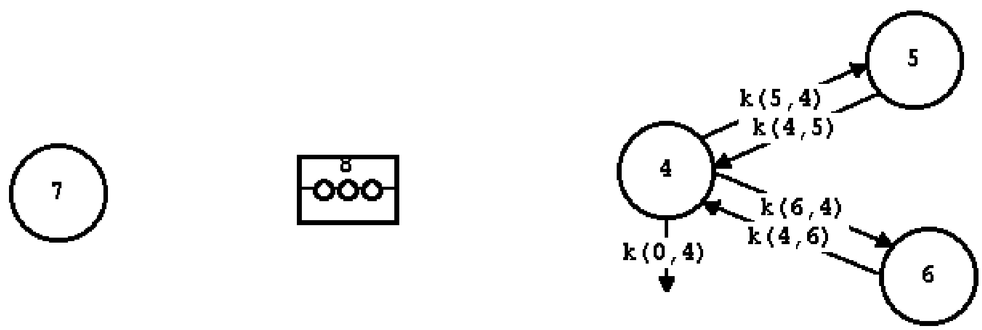
    a. In the **SAAM II Toolbox**, click **Model** to be sure these tools are available. These tools need to be available to define new transfer compartments, fluxes and delay attributes.

b. In the **SAAM II Toolbox**, click **Compartment**.

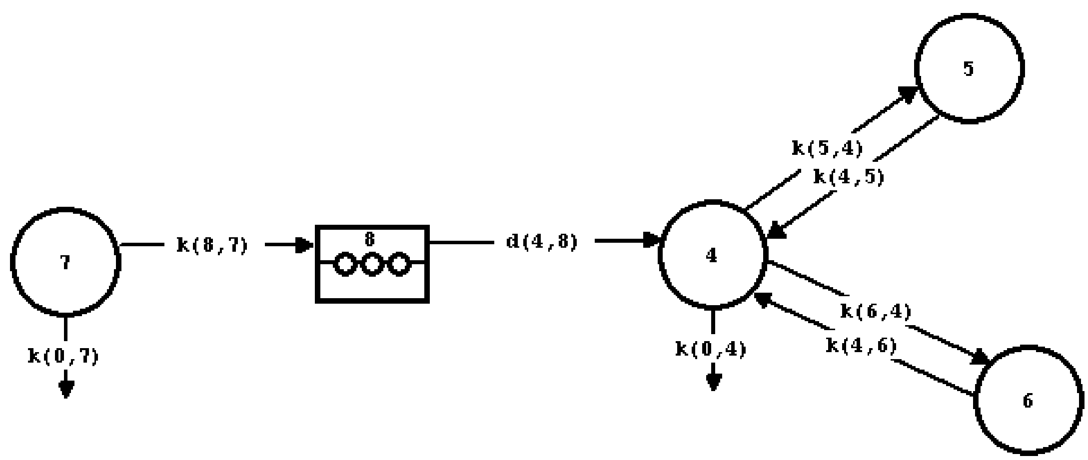
c. Click on the **Drawing** canvas where you would like Compartment **7** to be located. Place it near the left margin of the **Drawing Canvas** so that a delay and transfers can be added. Compartment 7 will appear on the **Drawing Canvas** as shown below.

d. In the **SAAM II Toolbox**, click **Delay**.

e. Click on the **Drawing Canvas** where you would like the delay to be located. Place it between Compartments **7** and **4**. Your model for the oral dose should appear as follows:



f. Add the fluxes *k(8,7)*, *k(0,7)* and *d(4,8)*. Your model for the oral dose should appear as follows:



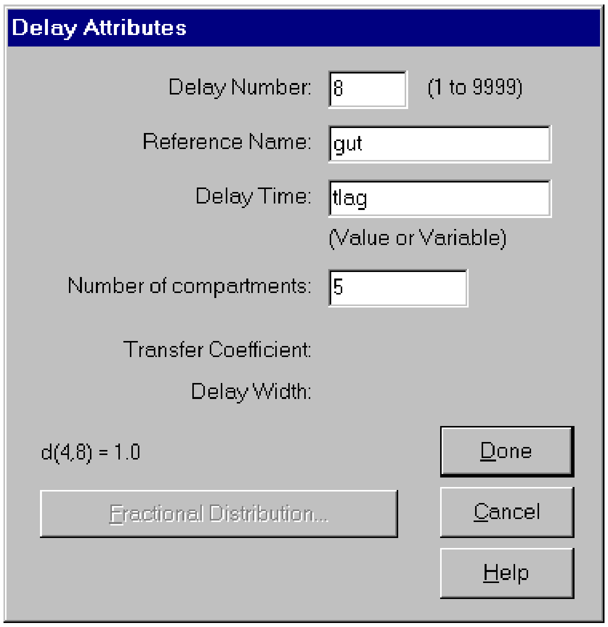
g. Define the delay attributes

(1) Double-click **Delay 8** to open the **Delay Attributes** dialog box.

(2) Enter "gut" in the **Reference Name** box. The **Delay Attributes** dialog box will appear as follows:

(3). Type "tlag" in the **Delay Time** box. This will introduced a new parameter, *tlag*, into the model; it will represent the time of the delay in absorption of NAPA.

(4) Enter "5" in the **Number of Compartments** box



(5) Click **Done**. Notice the word "gut" now appears associated with Delay **8**.

5. Create the oral input

   a. In the **SAAM II Toolbox**, click **Experiment** to make these tools available.

   b. Click **Input** in the **SAAM II Toolbox**.

   c. Click Compartment **q7**, and then click on the **Drawing Canvas**. The input **ex2** will appear.

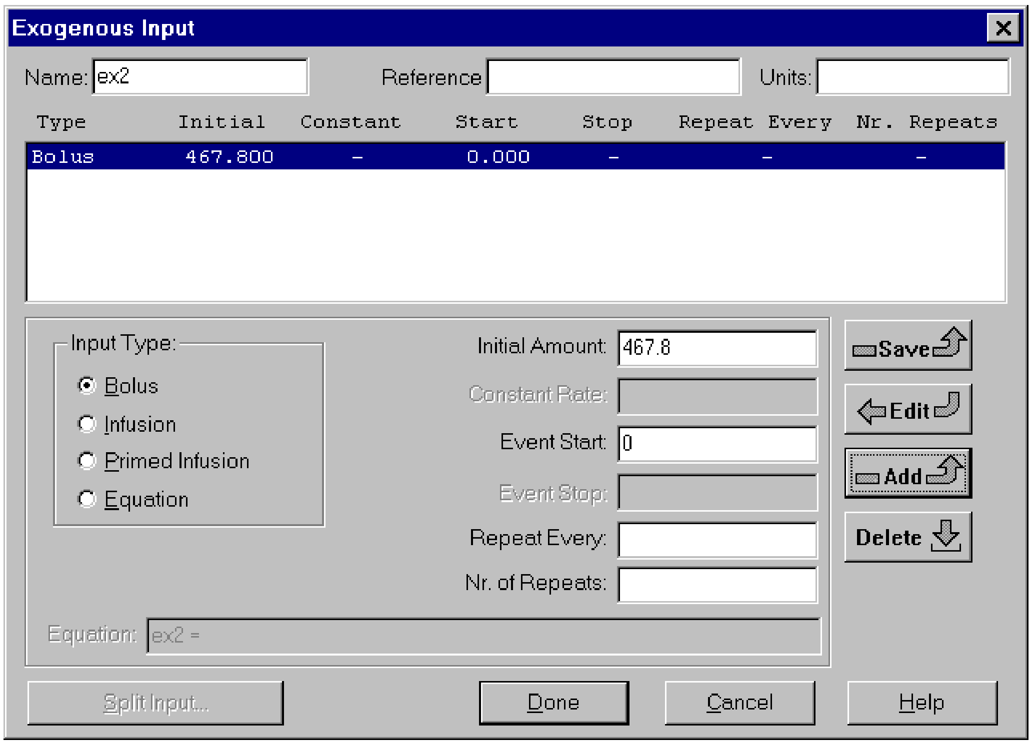
   d. Double-click **ex2** to open the **Exogenous Input** dialog box.

   e. Make sure that **Bolus** is selected as the **Input Type**.

f. Enter “467.8” in the **Initial Amount** box. This is the assayed amount of NAPA base in a 500 mg tablet of NAPA-HCl. (In general, the expected amount is 442.5 mg).

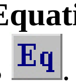
g. Enter “0” in the **Event Star**t box.

h. Click **Add**. The **Exogenous Input** dialog box will appear as follows:



i. Click **Done**.

6. Enter the following equations and parameters to complete the oral dose model.

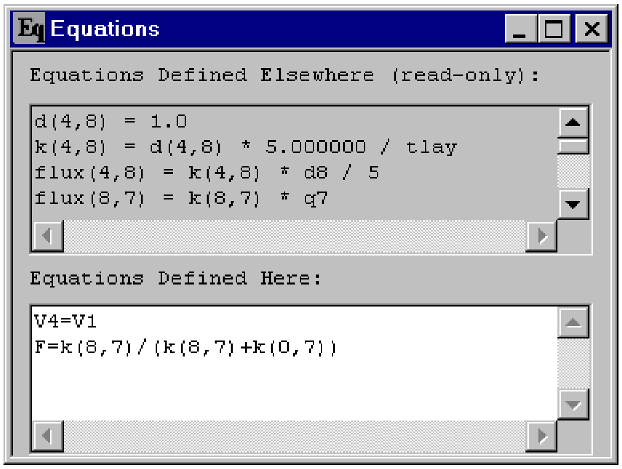
a. In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar**, click **Equations** 

. The **Equations** dialog box will open.

b. In the **Equations Defined Here** pane, type the following equations:

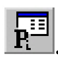
“V4 = V1”
“F = k(8,7)/(k(8,7) + k(0,7))”

The first equation makes the intravascular distribution volume for the iv and oral dose equal. This second equation defines the extent of drug absorption as the absorption rate constant divided by the sum of the rate constants describing absorption and non-absorptive loss from the intestine. The **Equations** dialog box should appear as follows:



c. Close the **Equations** dialog box.

7. Enter the parameter values.

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

b. Double-click *k(0,7)* to select it.

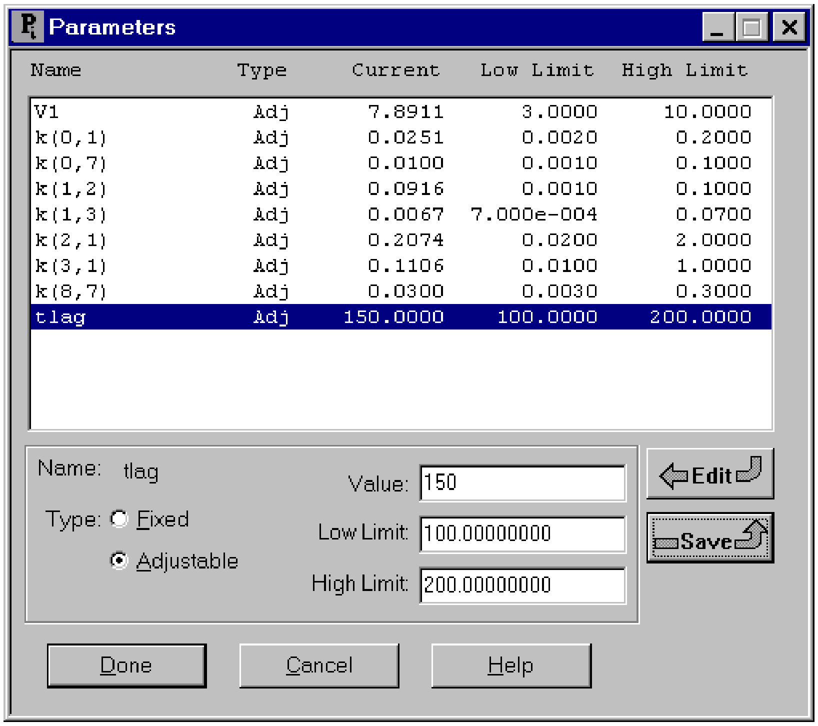
c. Enter “0.01” in the **Value** box, and click **Save**.

d. Double-click *k(8,7)* to select it.

e. Enter “0.03” in the **Value** box, and click **Save**.

f. Double-click *tlag* to select it.

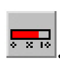
g. Enter “150” in the **Value** box, “100” in the **Low Limit** box, “200” in the **High Limit** box, and click **Save**. Your **Parameters** dialog box should appear as follows:



h. Click **Done**.

8. Save the study file as **napa_oral**.

9. Solve your model and view the solution.

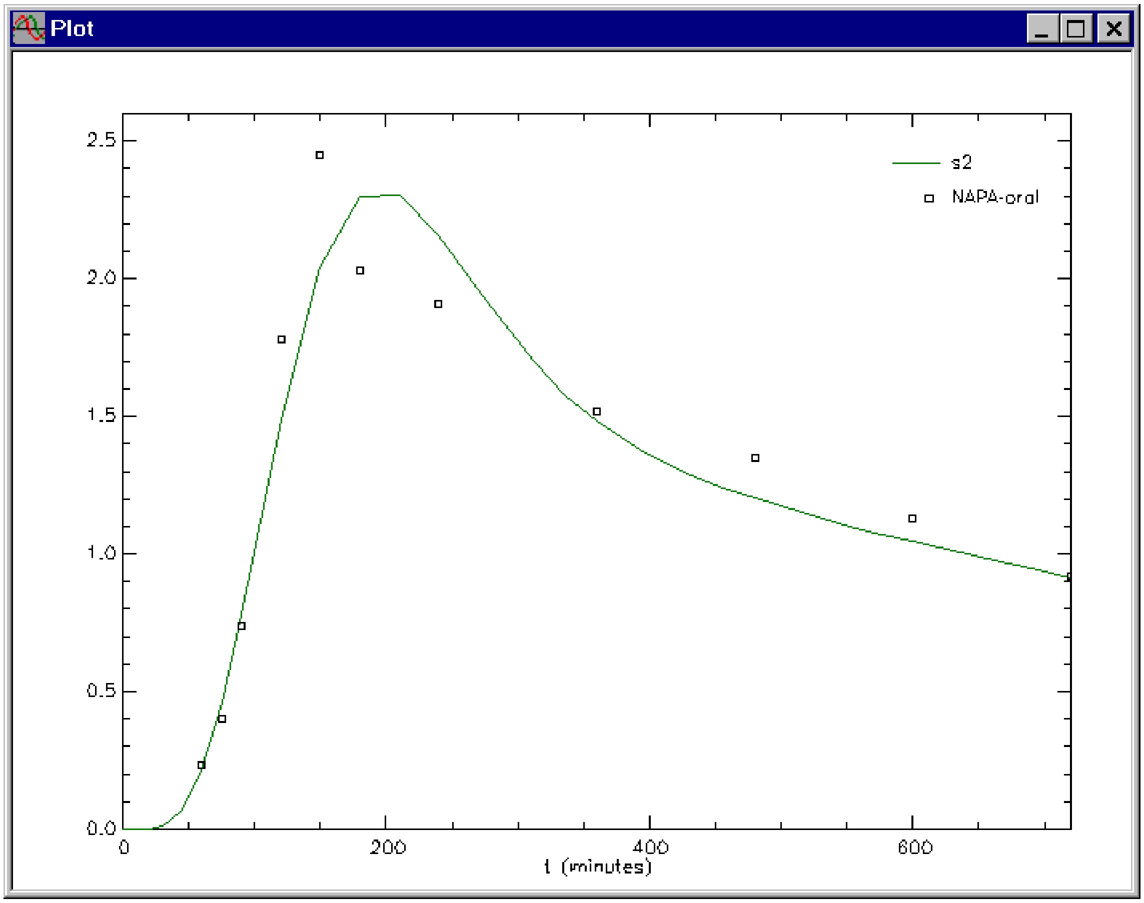
   a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar,** click **Solve** .

   b. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar,** click **Plot** . The **Plot and Table Variables** dialog box will open (if a previous plot appears, on the **Set** menu, click **Plot/Table Variables** to open the **Plot and Table Variables** dialog box.)

   c. In the **Plot and Table Variables** dialog box (Clear the **List All Variables** check box if checked to list only those variables associated with data.)

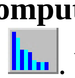
   d. Click **s2:NAPA_oral**; it will move to the **Current Selection** pane.

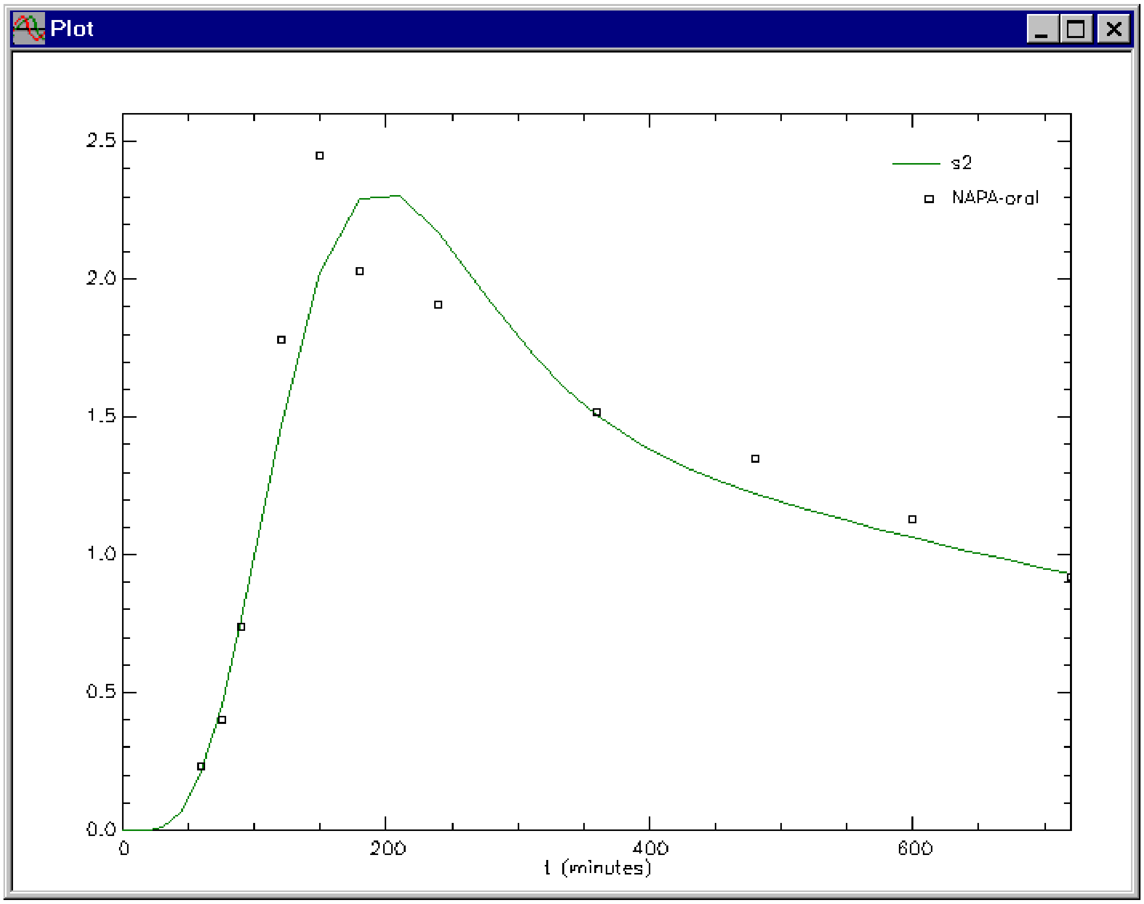
   e. Click **Done**. The following linear plot will appear (in this plot, the Y Axis maximum has been set to “2.6”):



Leave the **Plot** window open.

10. 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 plot should appear as follows:



Notice that this plot is in the linear mode; this helps you to see how the delay works during the first 50 minutes where there is a definite lag in the appearance of drug followed by a very gradual rise in plasma concentration. The steepness of this rise in concentration is determined by the number of compartments in the delay.

b. Plot both sets of data and model predictions.

(1) Be sure the **Plot** window is current. In the **Set** menu, click **Plot/Table Variables** to open the **Plot and Table Variables** dialog box.

(2) Select **s1:NAPA_IV** and **s2:NAPA_oral**.

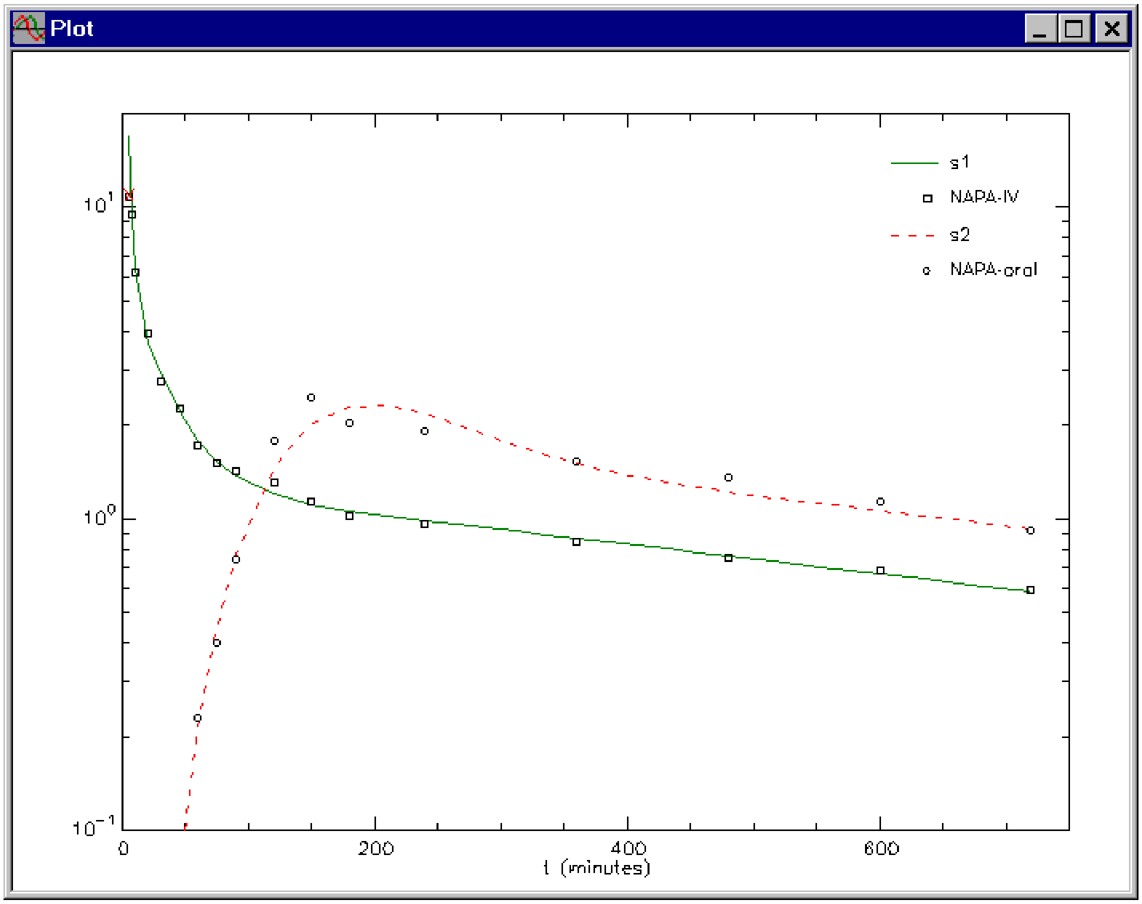
(3) Click **Done**.

(4) In the **Set** menu, click **Plot/Table Scale** to open the **Plot and Table Scale** dialog box.

(5) In the **X Axis** pane, select **Set**. Enter "750" in the **Maximum** box.

(6) In the **Y Axis** pane, select **Set**. Enter “0.1” in the **Minimum** box and “20” in the **Maximum** box.

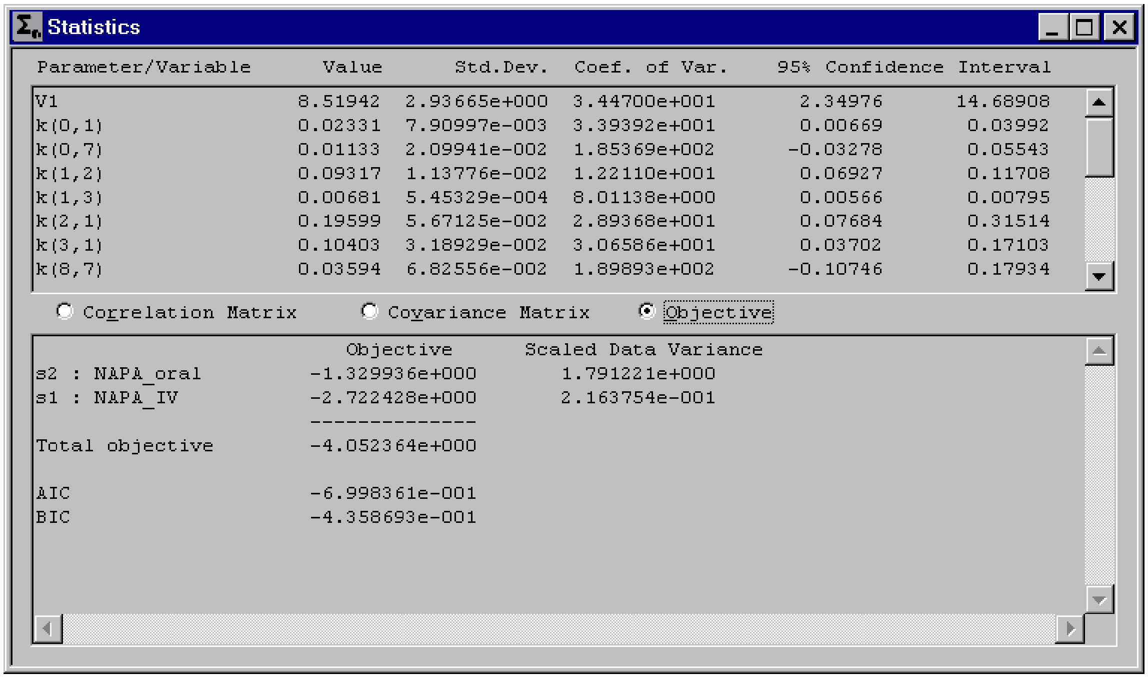
(7) Click **Done**. Your plot in semi-log mode should appear as follows:



As is usually the case, the model fits the data obtained after intravenous administration of NAPA-^{13}C better than that resulting from the oral NAPA dose.

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

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



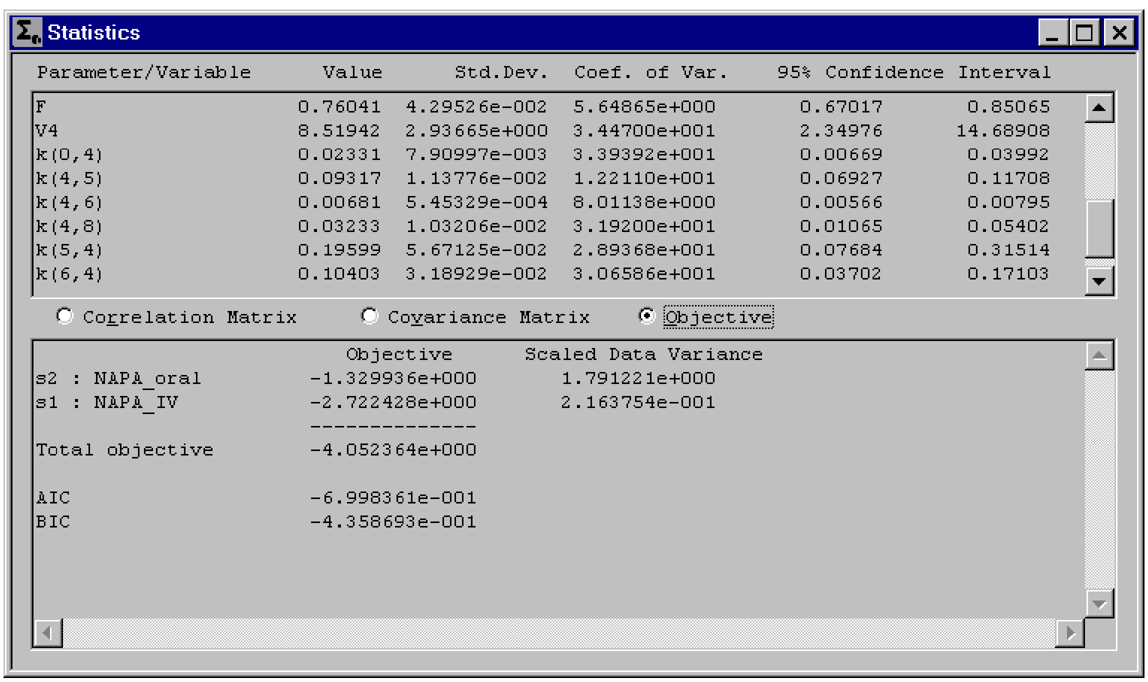
Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
V1	8.51942	2.93665e+000	3.44700e+001	2.34976	14.68908
k(0,1)	0.02331	7.90997e-003	3.39392e+001	0.00669	0.03992
k(0,7)	0.01133	2.09941e-002	1.85369e+002	-0.03278	0.05543
k(1,2)	0.09317	1.13776e-002	1.22110e+001	0.06927	0.11708
k(1,3)	0.00681	5.45329e-004	8.01138e+000	0.00566	0.00795
k(2,1)	0.19599	5.67125e-002	2.89368e+001	0.07684	0.31514
k(3,1)	0.10403	3.18929e-002	3.06586e+001	0.03702	0.17103
k(8,7)	0.03594	6.82556e-002	1.89893e+002	-0.10746	0.17934

Correlation Matrix   Covariance Matrix   Objective

	Objective	Scaled Data Variance
s2 : NAPA_oral	-1.329936e+000	1.791221e+000
s1 : NAPA_IV	-2.722428e+000	2.163754e-001
Total objective	-4.052364e+000	
AIC	-6.998361e-001	
BIC	-4.358693e-001	

The value for *tlag* is 154 with a 32% error and a 95% confidence interval of 51 to 258. Scroll to the bottom of the **Parameter/Variable** pane to see the remaining parameters:



Statistics

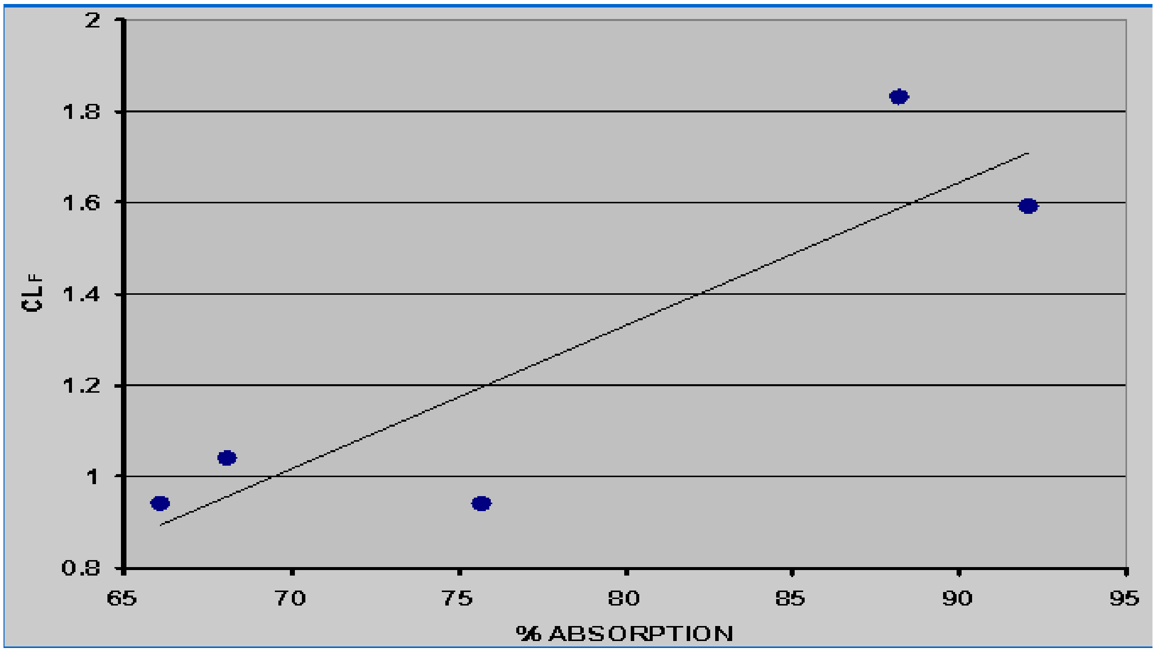
Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
F	0.76041	4.29526e-002	5.64865e+000	0.67017	0.85065
V4	8.51942	2.93665e+000	3.44700e+001	2.34976	14.68908
k(0,4)	0.02331	7.90997e-003	3.39392e+001	0.00669	0.03992
k(4,5)	0.09317	1.13776e-002	1.22110e+001	0.06927	0.11708
k(4,6)	0.00681	5.45329e-004	8.01138e+000	0.00566	0.00795
k(4,8)	0.03233	1.03206e-002	3.19200e+001	0.01065	0.05402
k(5,4)	0.19599	5.67125e-002	2.89368e+001	0.07684	0.31514
k(6,4)	0.10403	3.18929e-002	3.06586e+001	0.03702	0.17103

Correlation Matrix   Covariance Matrix   Objective

	Objective	Scaled Data Variance
s2 : NAPA_oral	-1.329936e+000	1.791221e+000
s1 : NAPA_IV	-2.722428e+000	2.163754e-001
Total objective	-4.052364e+000	
AIC	-6.998361e-001	
BIC	-4.358693e-001	

The value for **F** indicates that 76% of the oral NAPA dose was absorbed. The 95% confidence interval for this estimate is 67% - 85%. In the five patients that were studied it was found that **F** estimated in this way averaged 78.0% compared to 92% in the normal subjects that were studied initially.

Of particular interest is the fact that values for **F** in these five patients with cardiac disease were correlated with estimated intercompartmental clearance to the fast equilibrating peripheral compartment, that presumably includes splanchnic organs (r = 0.89, p = 0.045).



This suggests that splanchnic blood flow, which is decreased in patients with diminished cardiac output, is a determinant of the bioavailability for this, and probably a number of drugs that are commonly used.

SAAM II *Report writing (continued)*. You have performed two more computational operations so far, one "Solve" and one "Fit". Since you have selected the **Save Results to Text File** option with **Add**, SAAM II has automatically created two new text files, this time named **napa_oral.txt** since you saved your study file as **napa_oral**. You can view these text files my opening them in a text editor. The last, **napa_oral_01.txt**, is printed in the Appendix so you can see what the output looks like.

SAAM II *Dealing with poorly estimated parameters*. If you look at the statistics following this fit, you will see that the parameters *k(0,7)* and *k(8,7)* are poorly determined with errors in excess of 100%. This means they cannot be estimated with any degree of precision. However, bioavailability **F** which is a function of these two parameters can be estimated with good precision. This is an example frequently seen in the analysis of biological or pharmacokinetic data where specific parameters may not be well estimated, but function of them can be. If one is only interested in **F**, then it is probably safe to stop here.

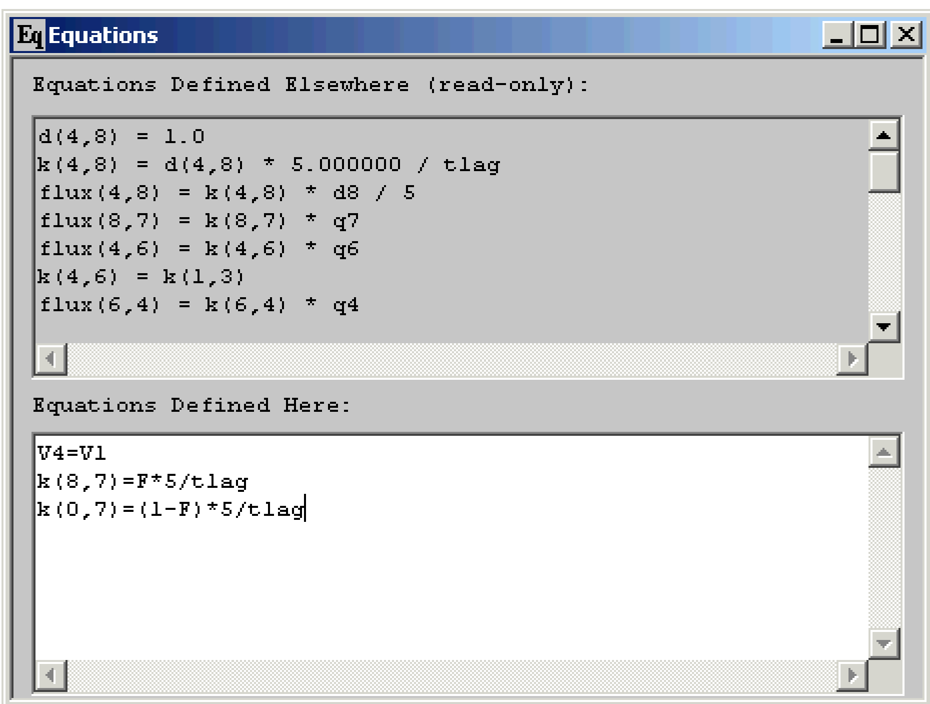
Is there a way to deal with this? The answer is "yes" if you are willing to introduce a constraint on the parameters to reduce the degrees of freedom in your model.

One way to do this is the following. The turnover for each compartment in the 5 compartment delay approximately equals 5/150 = 0.033. The total turnover for Compartment **7** is k(0,7) + k(8,7) = .046. One can thus regard Compartment **7** as another compartment in the delay, and fix it turnover equal to 0.033. **F** will become a parameter along with *tlag* (reducing the number of adjustable parameters from 3 to 2).

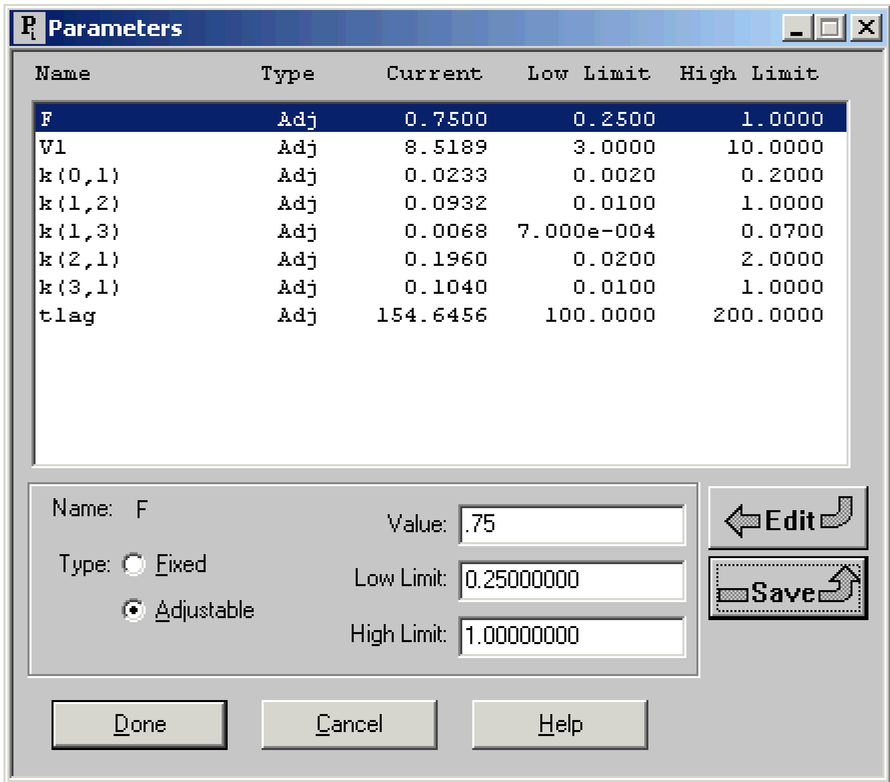
You need to define *k(0,7)* and *k(8,7)* as follows (this can be done in the **Equations** dialog box):

k(8,7) = F*5/tlag
k(0,7)=(1-F)*5/tlag

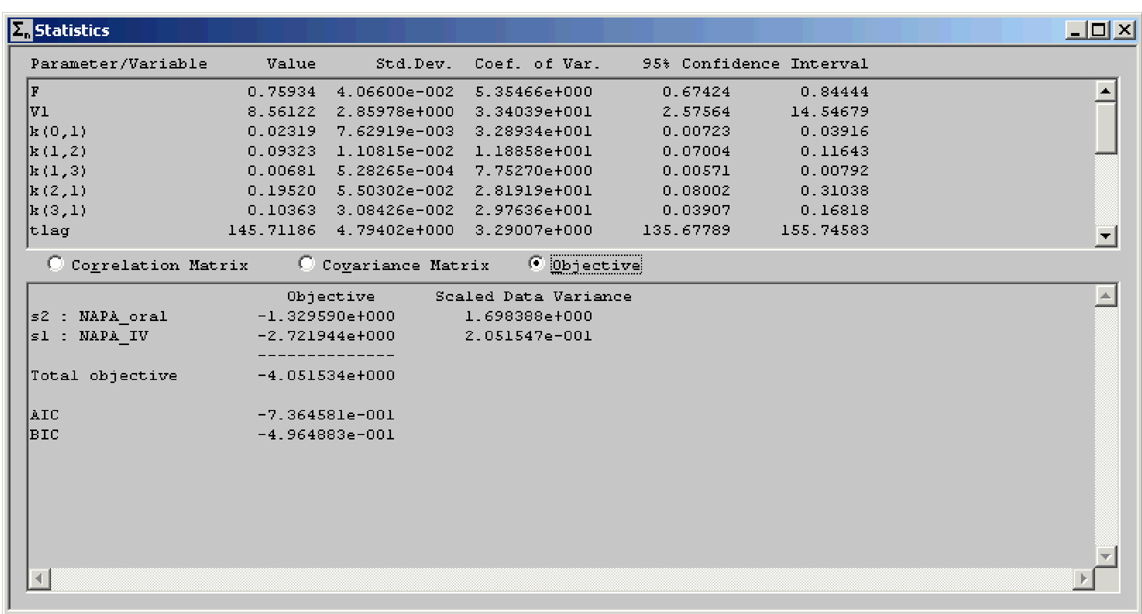
The **Equations** dialog box will appear as follows:



Notice the previous equation defining **F** has been removed. You also need to enter an initial estimate for **F** in the **Parameters** dialog box; you can use 0.75. The **Parameters** dialog box will appear as shown below:



If you now **Fit** the model to the data, you will obtain the following results:



You can see that the parameter estimates are much better with this added constraint, and that the value of **F** remains virtually unchanged.

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

Essential Points to Remember

- It is convenient to use the duplicate feature of SAAM II to analyze data from absolute bioavailability studies.
- The delay tool of SAAM II is often required to model the lag time between administration of an oral drug dose and its appearance in plasma.
- The report writing option provides a convenient way of documenting data analysis procedures and results.
- Sometimes the parameter of interest can be well-determined even if other model parameters cannot. When other model parameters cannot be well-determined, one must seek constraints on the parameters to reduce the degrees of freedom in the model.

Appendix: Text File Output "napa_oral_01.txt"

Study Name: napa_oral.stu
Basic Summary Output
Date: 01:32 PM, Saturday, July 06, 2002
Application: Compartmental
Type of Calculation: Fit

Computational Settings

Integrator: Rosenbrock
Relative Integrator Error: 1.0000e-003
Variance Model: Data, Relative
Derivative: Forward

Values at t = 0.0 minutes

F	0.760475
NAPA_IV	-
NAPA_oral	-
V1	8.524599
V4	8.524599
d(4,8)	1.000000
d8	0.000000
ex1.bolus	0.000000
ex1.infusion	54.200000
ex2.bolus	467.800000
ex2.infusion	0.000000
flux(0,1)	0.000000
flux(0,4)	0.000000
flux(0,7)	5.255014
flux(1,2)	0.000000
flux(1,3)	0.000000
flux(2,1)	0.000000
flux(3,1)	0.000000
flux(4,5)	0.000000
flux(4,6)	0.000000
flux(4,8)	0.000000
flux(5,4)	0.000000
flux(6,4)	0.000000
flux(8,7)	16.684298
k(0,1)	0.023293
k(0,4)	0.023293
k(0,7)	0.011233
k(1,2)	0.093163
k(1,3)	0.006807
k(2,1)	0.195874
k(3,1)	0.103970
k(4,5)	0.093163
k(4,6)	0.006807
k(4,8)	0.032362

k(5,4)	0.195874
k(6,4)	0.103970
k(8,7)	0.035665
q1	0.000000
q2	0.000000
q3	0.000000
q4	0.000000
q5	0.000000
q6	0.000000
q7	467.800000
s1	0.000000
s1_res	-
s1_wres	-
s2	0.000000
s2_res	-
s2_wres	-
t	0.000000
tlag	154.500310

Calculated Sample Values and Data

t	NAPA_oral	Weight	s2	s2_wres
0.000e+000	-	-	0.000e+000	-
5.000e+000	-	-	1.054e-006	-
5.000e+000	-	-	1.054e-006	-
7.500e+000	-	-	1.019e-005	-
1.000e+001	-	-	4.894e-005	-
2.000e+001	-	-	1.777e-003	-
3.000e+001	-	-	1.226e-002	-
4.500e+001	-	-	7.092e-002	-
6.000e+001	2.300e-001	1.055e+003	2.136e-001	5.320e-001
7.500e+001	4.000e-001	3.489e+002	4.524e-001	-9.783e-001
9.000e+001	7.400e-001	1.019e+002	7.684e-001	-2.867e-001
1.200e+002	1.780e+000	1.762e+001	1.473e+000	1.289e+000
1.500e+002	2.450e+000	9.301e+000	2.026e+000	1.294e+000
1.800e+002	2.030e+000	1.355e+001	2.292e+000	-9.634e-001
2.100e+002	-	-	2.305e+000	-
2.400e+002	1.910e+000	1.530e+001	2.169e+000	-1.015e+000
2.760e+002	-	-	1.939e+000	-
3.120e+002	-	-	1.723e+000	-
3.360e+002	-	-	1.604e+000	-
3.600e+002	1.520e+000	2.416e+001	1.506e+000	7.062e-002
3.960e+002	-	-	1.392e+000	-
4.320e+002	-	-	1.308e+000	-
4.560e+002	-	-	1.262e+000	-
4.800e+002	1.350e+000	3.063e+001	1.222e+000	7.089e-001
5.160e+002	-	-	1.169e+000	-
5.520e+002	-	-	1.121e+000	-
5.760e+002	-	-	1.091e+000	-
6.000e+002	1.130e+000	4.372e+001	1.062e+000	4.508e-001
6.360e+002	-	-	1.020e+000	-
6.720e+002	-	-	9.809e-001	-
6.960e+002	-	-	9.554e-001	-

7.200e+002	-	-	9.307e-001	-
7.200e+002	9.200e-001	6.596e+001	9.307e-001	-8.677e-002

t	NAPA_IV	Weight	s1	s1_wres
0.000e+000	-	-	0.000e+000	-
5.000e+000	-	-	1.684e+001	-
5.000e+000	1.081e+001	Excluded	1.684e+001	-
7.500e+000	9.450e+000	5.175e+000	9.338e+000	2.545e-001
1.000e+001	6.210e+000	1.198e+001	6.305e+000	-3.284e-001
2.000e+001	3.920e+000	3.007e+001	3.665e+000	1.398e+000
3.000e+001	2.760e+000	6.067e+001	2.917e+000	-1.226e+000
4.500e+001	2.250e+000	9.129e+001	2.214e+000	3.459e-001
6.000e+001	1.730e+000	1.544e+002	1.790e+000	-7.411e-001
7.500e+001	1.510e+000	2.027e+002	1.531e+000	-2.944e-001
9.000e+001	1.430e+000	2.260e+002	1.370e+000	9.068e-001
1.200e+002	1.310e+000	2.693e+002	1.198e+000	1.830e+000
1.500e+002	1.130e+000	3.619e+002	1.115e+000	2.797e-001
1.800e+002	1.020e+000	4.442e+002	1.064e+000	-9.215e-001
2.100e+002	-	-	1.024e+000	-
2.400e+002	9.600e-001	5.015e+002	9.890e-001	-6.498e-001
2.760e+002	-	-	9.501e-001	-
3.120e+002	-	-	9.133e-001	-
3.360e+002	-	-	8.896e-001	-
3.600e+002	8.400e-001	6.550e+002	8.666e-001	-6.799e-001
3.960e+002	-	-	8.331e-001	-
4.320e+002	-	-	8.010e-001	-
4.560e+002	-	-	7.803e-001	-
4.800e+002	7.500e-001	8.216e+002	7.601e-001	-2.889e-001
5.160e+002	-	-	7.308e-001	-
5.520e+002	-	-	7.026e-001	-
5.760e+002	-	-	6.844e-001	-
6.000e+002	6.800e-001	9.994e+002	6.667e-001	4.209e-001
6.360e+002	-	-	6.410e-001	-
6.720e+002	-	-	6.163e-001	-
6.960e+002	-	-	6.003e-001	-
7.200e+002	-	-	5.848e-001	-
7.200e+002	5.900e-001	1.328e+003	5.848e-001	1.905e-001

Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
V1	8.52460	2.93733e+000	3.44571e+001	2.35351	14.69569
k(0,1)	0.02329	7.90278e-003	3.39273e+001	0.00669	0.03990
k(0,7)	0.01123	2.11982e-002	1.88706e+002	-0.03330	0.05577
k(1,2)	0.09316	1.13753e-002	1.22101e+001	0.06926	0.11706
k(1,3)	0.00681	5.45327e-004	8.01107e+000	0.00566	0.00795
k(2,1)	0.19587	5.66938e-002	2.89440e+001	0.07677	0.31498
k(3,1)	0.10397	3.18669e-002	3.06500e+001	0.03702	0.17092
k(8,7)	0.03567	6.89233e-002	1.93249e+002	-0.10914	0.18047
tlag	154.50031	5.04022e+001	3.26227e+001	48.60935	260.39127
--------------------------------- Derived Variables ---------------------------------					
F	0.76047	4.29565e-002	5.64864e+000	0.67023	0.85072

V4	8.52460	2.93733e+000	3.44571e+001	2.35351	14.69569
k(0,4)	0.02329	7.90278e-003	3.39273e+001	0.00669	0.03990
k(4,5)	0.09316	1.13753e-002	1.22101e+001	0.06926	0.11706
k(4,6)	0.00681	5.45327e-004	8.01107e+000	0.00566	0.00795
k(4,8)	0.03236	1.05575e-002	3.26227e+001	0.01018	0.05454
k(5,4)	0.19587	5.66938e-002	2.89440e+001	0.07677	0.31498
k(6,4)	0.10397	3.18669e-002	3.06500e+001	0.03702	0.17092

	Objective	Scaled Data Variance
s2 : NAPA_oral	-1.329932e+000	1.791237e+000
s1 : NAPA_IV	-2.722407e+000	2.163830e-001

Total objective	-4.052340e+000	

AIC -6.998239e-001
BIC -4.358571e-001

Number of Iterations Required to Fit: 3

Data for this Case Study

DATA
(FSD 0.1)

t	NAPA_IV	NAPA_oral
0.	none	none
5.0	10.81(-)	none
7.5	9.45	none
10.0	6.21	none
20.0	3.92	none
30.0	2.76	none
45.0	2.25	none
60.0	1.73	0.23
75.0	1.51	0.40
90.0	1.43	0.74
120.	1.31	1.78
150.	1.13	2.45
180.	1.02	2.03
240.	0.96	1.91
360.	0.84	1.52
480.	0.75	1.35
600.	0.68	1.13
720.	0.59	0.92

END

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