

N-Acetylprocainamide (NAPA) Kinetics in a Hemodialysis Patient

Case Study

- How to analyze hemodialysis studies
- How to add equations to a model
- How to use the scaled data variance parameter
- How to use Change Conditions to initiate and terminate hemodialysis
- How to create a forcing function to model hemodialysis-associated perturbations in model parameters

This page is intentionally left blank

N-Acetylprocainamide (NAPA) Kinetics in a Hemodialysis Patient

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 that was conducted in a functionally anephric patient who received an intravenous (iv) dose of NAPA 24 hours before a regularly scheduled hemodialysis session. By analyzing NAPA concentrations measured in both plasma and dialysis bath fluid you will be able to deal with the physiological perturbations in drug distribution that occur during and after hemodialysis and will see why it is of paramount importance to estimate hemodialysis clearance by the *recovery method*. You will learn:

- How to analyze data generated from studies in functionally anephric patients that are receiving hemodialysis.
- How to use the transfer attributes box and the sample attributes box, as well as the equations window, to add equations to the model.
- How to use the change conditions tool to initiate and terminate dialysis clearance.
- How to create a forcing function using the input tool to model hemodialysis-associated alterations in model parameters.
- The importance of using the recovery method to calculate hemodialysis clearance.
- How to incorporate “venous” plasma concentrations in a hemodialysis model to estimate effective dialyzer blood flow and the fallacy of using plasma flow to calculate hemodialysis clearance by the A-V difference method.

Data Required

The data file for this case study is

dialysis.dat

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

Introduction

The conduct of pharmacokinetics studies in patients with impaired kidney function is of particular importance given that the clinical application of pharmacokinetics has perhaps had its greatest impact in estimating drug dosage in this patient group. For this reason, the

US Food and Drug Administration has provided detailed guidance for the conduct of these studies [1] and is continuing to evaluate optimal approaches for generating and presenting study results [2]. An underappreciated technical challenge is posed by the conduct of pharmacokinetic studies in functionally anephric patients who are receiving hemodialysis and may require dose supplementation for drugs that are removed by this procedure.

In this exercise, we will begin by analyzing pre-dialysis data from a functionally anephric patient who was given a single dose of N-acetylprocainamide (NAPA) 24 hours before a regularly scheduled hemodialysis session [3]. The elimination clearance of NAPA in functionally anephric patients corresponds to what would be predicted from non-renal clearance estimates in healthy subjects, so the dose-individualization approach first proposed by Luzius Dettli [4] is applicable. Because the elimination-phase half-life of this drug in functionally anephric patients is longer than 24 hours, it also is possible to obtain both pre-dialysis and hemodialysis study results after administration of a single NAPA dose.

From a pharmacokinetic standpoint, the hemodialyzer is an ideal eliminating organ because drug concentrations can be measured in blood entering and leaving the dialysis cartridge and in the spent dialysis bath fluid (Figure 1) [5].

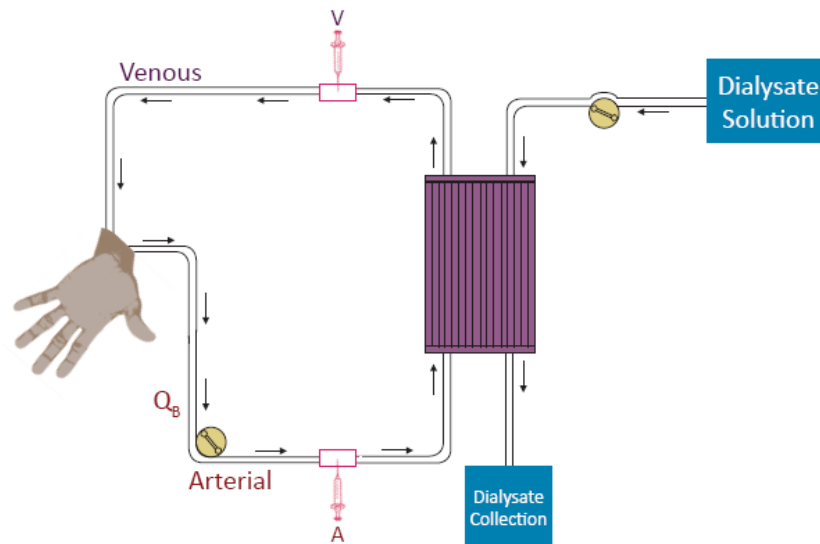


Figure 1. Sources of data for analysis of hemodialysis pharmacokinetics include drug concentration in blood or plasma entering (A) and leaving (V) the hemodialyzer, blood flow through the dialyzer (Q), and drug removed in the hemodialysis bath fluid.

In addition, blood flow through the dialyzer can be measured and drug partitioning between erythrocytes and plasma can be used to estimate the extent to which this partitioning enhances both effective plasma flow through the dialyzer and measured hemodialysis clearance. Finally, this study will illustrate how physiological changes occurring during and after hemodialysis have an important effect on plasma or blood drug concentrations measured during hemodialysis and in the extent of their post-dialysis

rebound. Most importantly, our accounting for these physiological changes in our pharmacokinetic model will demonstrate why measuring the amount of drug recovered in spent dialysis bath fluid to estimate hemodialysis clearance, the *recovery method*, is the “gold standard” for estimating hemodialysis clearance (CL_D) and why basing estimates of CL_D on the Fick Equation, which incorporates only plasma or blood concentration measurements and is termed the *A-V difference method*, is subject to error. The fundamental difference estimating CL_D by these two approaches is shown in the following equations:

Recovery method:

$$CL_D = \frac{C_D \cdot Vol_D}{\bar{A} \cdot t} \quad \text{Equation 1}$$

where the amount of drug recovered by dialysis is the product of the drug concentration in dialysate (C_D) and total volume of dialysate (Vol_D) collected during the dialysis time (t), and \bar{A} is the average concentration of drug in plasma entering the dialyzer. The product $\bar{A} \cdot t$ can be replaced by the area under the afferent blood or plasma concentration curve (AUC_A) during hemodialysis.

A-V difference method:

$$Cl_D = Q_B \left[\frac{A - V}{A} \right] \quad \text{Equation 2}$$

where the terms A, V, and Q_B are as shown in Figure 1.

1. US FDA CDER. “Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling.” 1998. (Internet at <http://www.fda.gov/cder/guidance>).
2. Huang, S.-M., Temple, R., Xiao, S., Zhang, L. Lesko, L.J. “When to conduct a renal impairment study during drug development: US Food and Drug Administration perspective.” *Clin Pharmacol Ther* 2009, 86: 475-9.
3. Stec GP, Atkinson AJ Jr, Nevin MJ, Thenot J-P, Ruo TI, Gibson TP, Ivanovich P, del Greco F. “N-Acetylprocainamide pharmacokinetics in functionally anephric patients before and after perturbation by hemodialysis.” *Clin Pharmacol Ther* 1979, 26: 618-28.
4. Dettli L. “Individualization of drug dosage in patients with renal disease.” *Med Clin North Am* 1974, 58: 977-85.
5. Atkinson AJ Jr, Umans JG. “Pharmacokinetic studies in hemodialysis patients.” *Clin Pharmacol Ther* 2009, 86: 548-52.

Part 1. Analyze the data resulting from intravenous administration of NAPA.

The first step will be to create a 3-compartment system model to describe the kinetics of the iv dose of NAPA. The data, NAPA found in the data file **dialysis.dat**, are plasma samples following a 30-minute infusion of a 15 mg/kg NAPA dose.

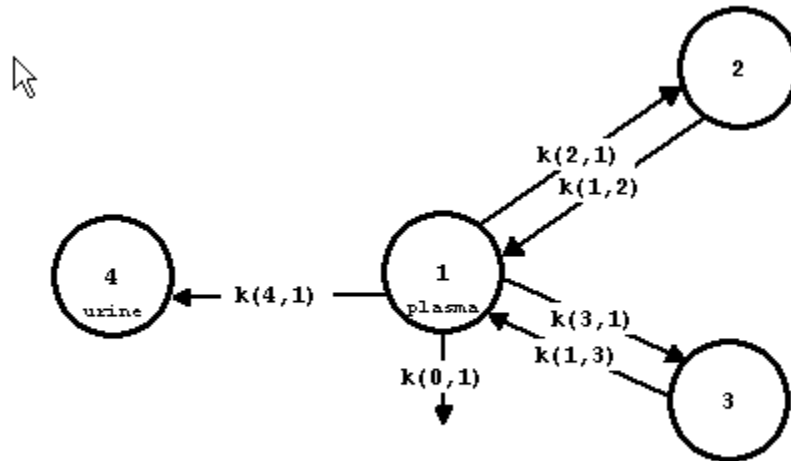


Which system model structure? The 3-compartment model is chosen here because *a priori* knowledge from the literature suggests this is the most appropriate. Using information from the literature can help you in the system model development process. You must be sure, however, that the experiment in the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

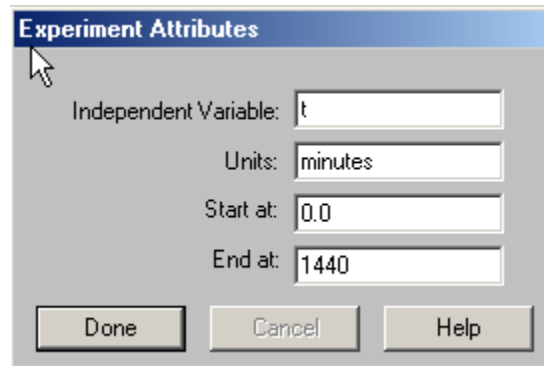
If you are unsure of the model used in the literature, you should start first with the two-compartment model, and then move to the three- and four-compartment models to be sure the three-compartment model is in fact the most appropriate for your data. In this case, the central compartment had previously 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. The importance of this will become apparent when we model the perturbation in NAPA distribution kinetics that occurs during hemodialysis.



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**: The fourth compartment represents renal excretion and is needed in this case because the patient retains some residual kidney function. Most NAPA elimination, represented by $k(0,1)$, reflects non-renal NAPA elimination.



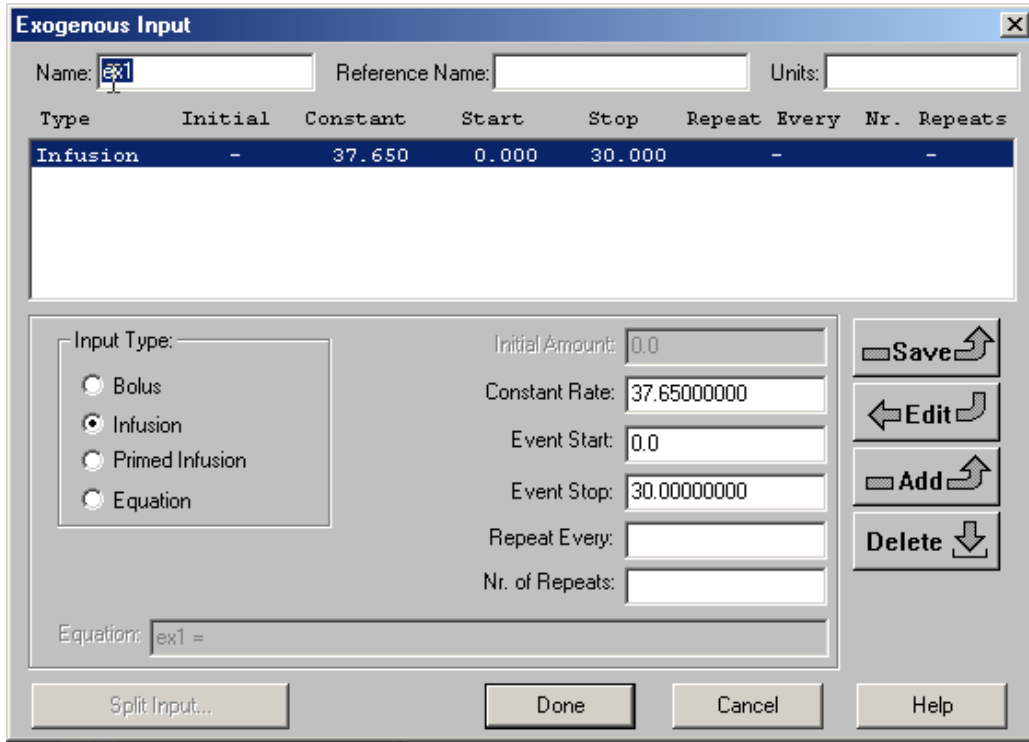
3. In the **SAAM II Toolbox**, click **Experiment**. Notice that the **Model** tools are unavailable and the **Experiment** tools are available. The **Experiment Attributes** dialog box will open.
 - a. Leave “minutes” in the **Units** box.
 - b. Enter “1440” in the **End at** box. The **Experiment Attributes** dialog box will appear as follows:



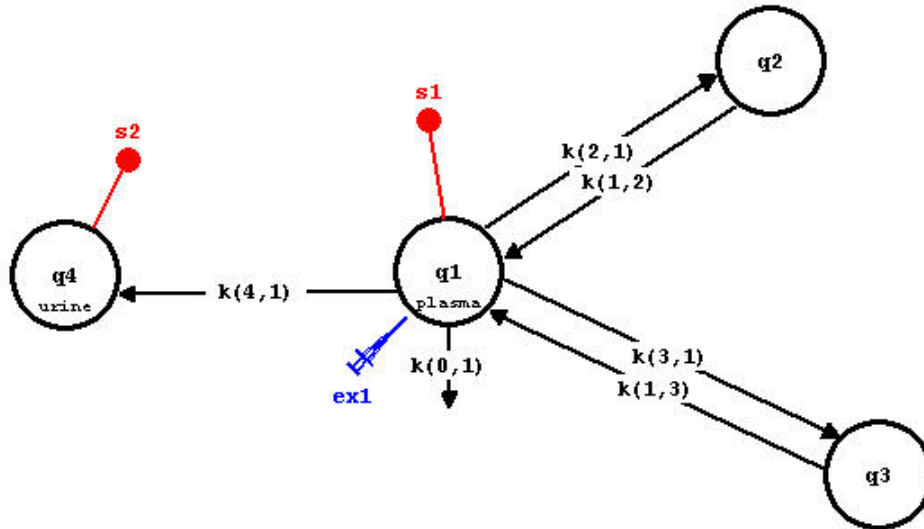
- c. Click **Done**.

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


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

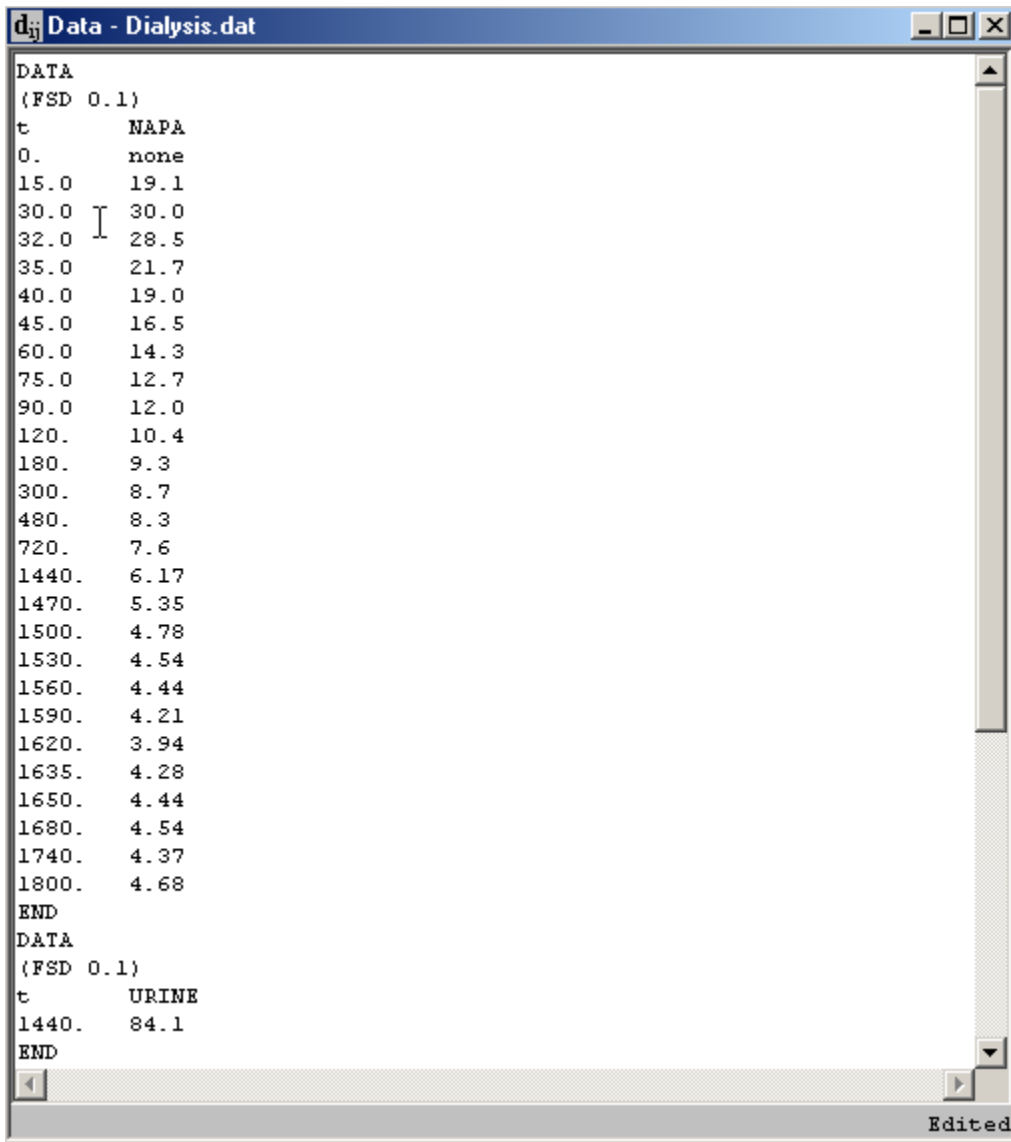


h. Click **Done**. Your model should appear approximately as follows:



7. 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 **dialysis.dat** should appear in the list (if it does not, find the folder where you have put this data file).
- c. Double-click **dialysis.dat**. The data file contains NAPA data obtained during the entire 30 hours of the experiment, and the cumulative amount of NAPA recovered in the urine during the 24 hours before dialysis. The **Data** window appears, in part, as follows:



```
DATA
(FSD 0.1)
t      NAPA
0.     none
15.0   19.1
30.0   30.0
32.0   28.5
35.0   21.7
40.0   19.0
45.0   16.5
60.0   14.3
75.0   12.7
90.0   12.0
120.   10.4
180.   9.3
300.   8.7
480.   8.3
720.   7.6
1440.  6.17
1470.  5.35
1500.  4.78
1530.  4.54
1560.  4.44
1590.  4.21
1620.  3.94
1635.  4.28
1650.  4.44
1680.  4.54
1740.  4.37
1800.  4.68
END
DATA
(FSD 0.1)
t      URINE
1440.  84.1
END
```

By scrolling down in this window you will see the “venous” NAPA concentrations in plasma returning to the patient from the dialyzer and the

total amount of NAPA recovered in the dialysate. By setting the end of the experiment at 1440 min in the **Experimental Attributes** box we confine this initial analysis to the pre-dialysis data. The data obtained during and after hemodialysis will be used in subsequent parts of this exercise. Note also there is only one datum for urine at 1440 minutes.


8. Enter derived model parameters.
 - a. At the bottom of the data file, you will find under the heading “Derived Anephric Model Parameters”, equations that calculate the clearances and peripheral compartment volumes for the model. These equations are preceded by the # sign so that they will not be interpreted as experimental data.
 - b. Highlight these equations and, using the **Edit** feature on the **Toolbar** of the SAAM program, copy these equations.
 - c. Close the **Data** window.
 - d. In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar**, click **Equations** . The **Equations** dialog box will open.
 - e. Using the **Edit** feature on the **Toolbar**, paste these equations into the **Equations Defined Here:** window in the **Equations** dialog box.
 - f. Remove the # sign before each of the equations but leave no spaces after the last equation. The **Equations** dialog box will appear as follows:

```

Eq Equations
-----
Equations Defined Elsewhere (read-only):
flux(2,1) = k(2,1) * q1
flux(1,2) = k(1,2) * q2
flux(3,1) = k(3,1) * q1
flux(1,3) = k(1,3) * q3
flux(4,1) = k(4,1) * q1
flux(0,1) = k(0,1) * q1
exl.bolus = 0.0
exl.infusion = 0.0
s2 = q4

Equations Defined Here:
#Derived Anephric Model Parameters
CLR = V1*k(4,1)
CLNR = V1*k(0,1)
CLF = V1*k(2,1)
CLS = V1*k(3,1)
V2 = CLF/k(1,2)
V3 = CLS/k(1,3)
VSS = V1+V2+V3

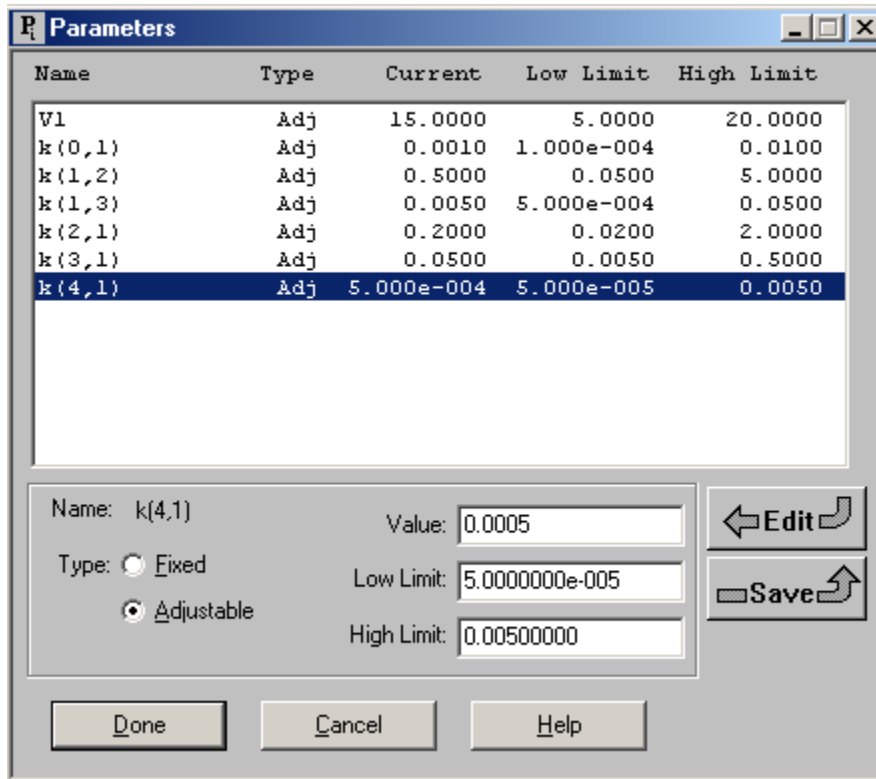
```

- g. Close the **Equations** dialog box.
9. 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 “15” in the **Value** box, “5” in the **Low Limit** box, “20” in the **High Limit** box, and click **Save**.
 - c. Double-click $k(0,1)$ to select it.
 - d. Enter “0.001” in the **Value** box, and click **Save**.
 - e. Double-click $k(1,2)$ to select it.
 - f. Enter “0.5” in the **Value** box, and click **Save**.
 - g. Double-click $k(1,3)$ to select it.
 - h. Enter “0.005” 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 “0.05” in the **Value** box, and click **Save**.
- m. Double-click $k(4,1)$ to select it.
- n. Enter “0.0005” in the **Value** box, and click **Save**

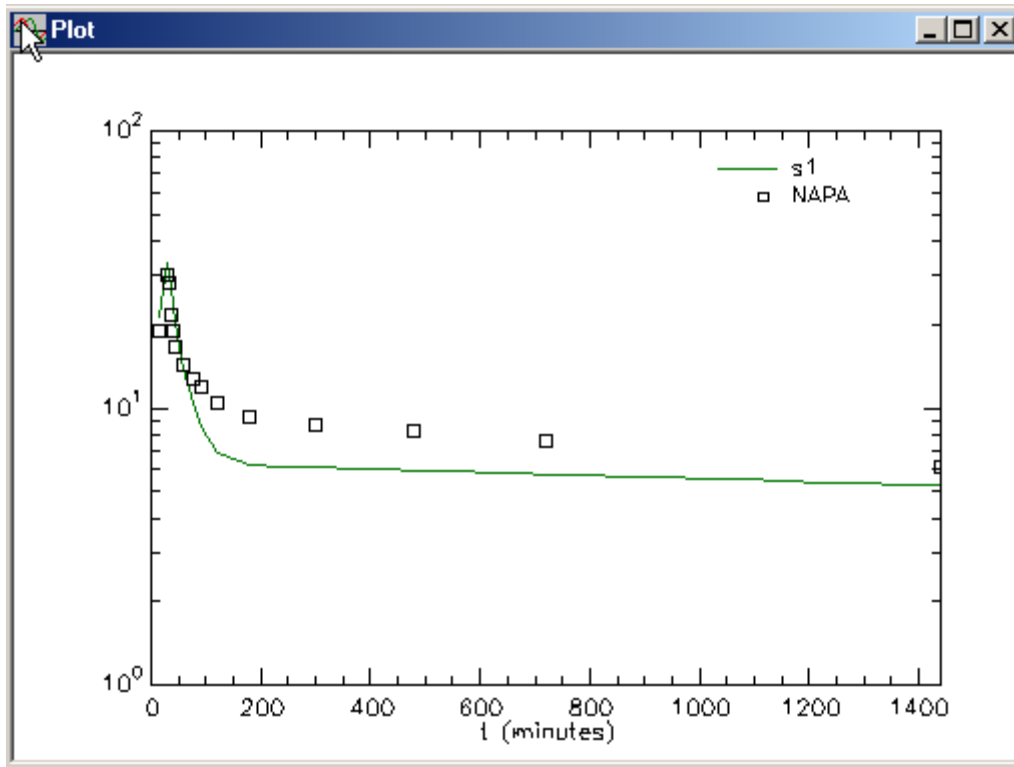
When you have finished, your **Parameters** dialog box should appear as follows:



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


Toolbar, click **Solve** .

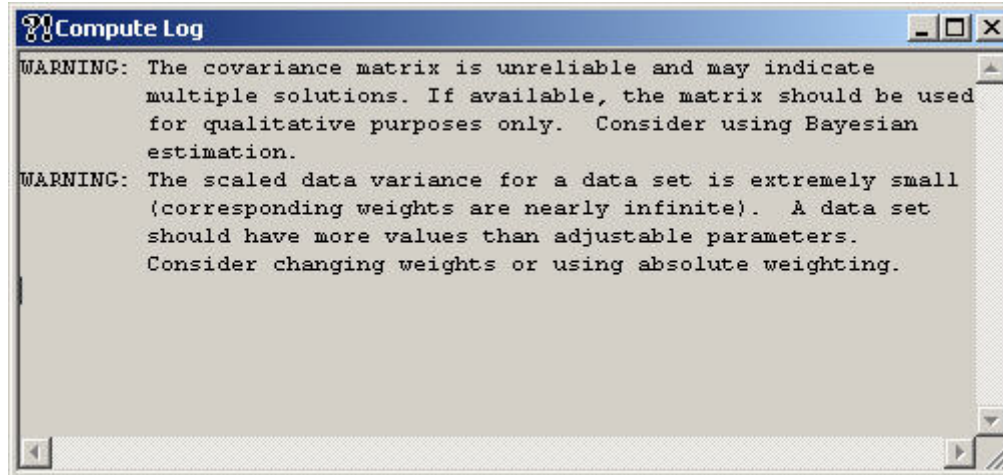
- b. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . The **Plot and Table Variables** dialog box will open.
- c. In the **Plot and Table Variables** dialog box, clear the **List All Variables** check box to list only those variables associated with data.
- d. Click **s1:NAPA**; it will move to the **Current Selection** pane.
- e. Click **Done**. The following plot will appear (in semilog mode):



The initial estimates are reasonably close, so proceed while the **Plot** window open.

11. Fit the model to the data and view the solution.

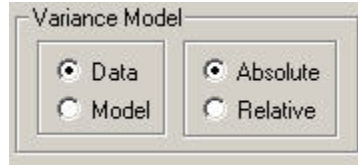
- a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar**, click **Fit** . While the **Fit** appears quite good, you will get the following **Warning message**:



What does this error message mean? The problem arises because of a problem with the scaled data variance. If you close the **Warning message** and open the **Statistics** window, you will see the scaled data variance for the urine data is 3.5e-013. In SAAM II the default weighting scheme is “data-relative” which means SAAM II will estimate a “best” numerical value for your assigned weight. However, to do this, SAAM II depends upon the residuals from the fit. When you have only one datum, the fit is perfect meaning the residual is zero. In this case, you have to change your weighting scheme from “data-relative” to “data-absolute”. However, there is useful information for the plasma data as the estimated scaled data variance, v , for plasma is 0.15. The “data-relative” calculates a weight for each plasma datum according to the formula “ $\text{var} = v \cdot (0.01) \cdot \text{datum}$ ”. With a FSD of 0.1, the variance becomes 0.01. Hence the “corrected” FSD for the plasma data is the square root of $0.15 \cdot 0.01$, or 0.04. The weight assigned to the plasma data will be changed in the data file.




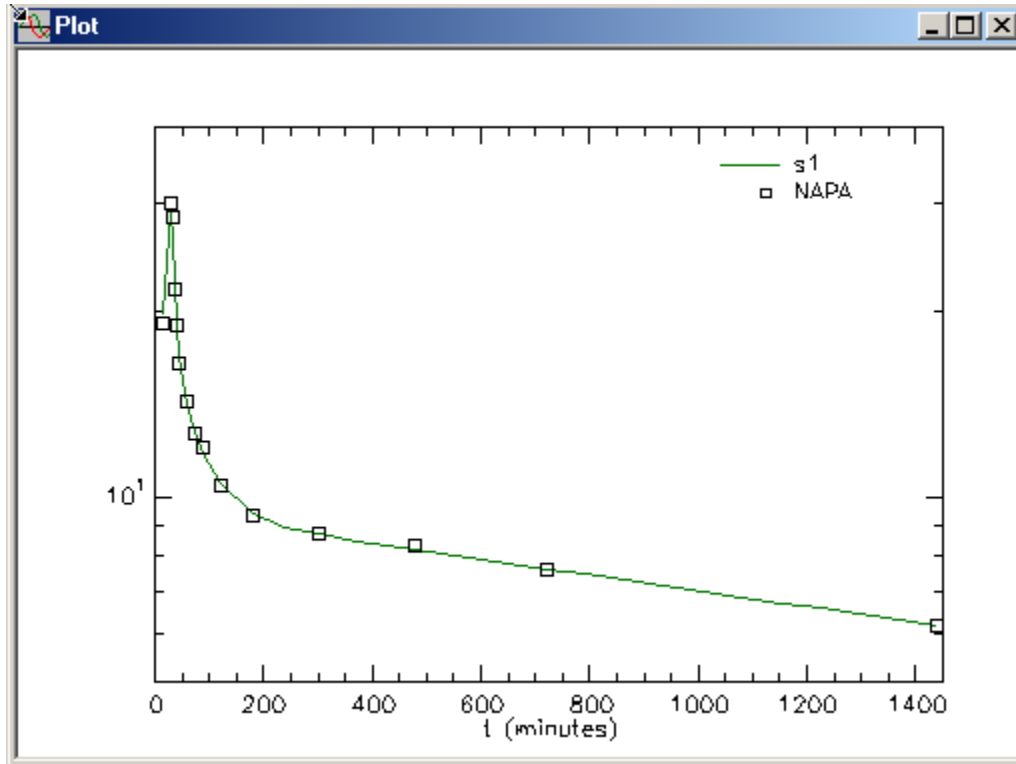
- b. Change the weighting scheme from “data-relative” to “data-absolute”.
 - (1) Close all open windows on the **Drawing Canvas**.
 - (2) In the **Compute Menu**, click **Settings**. The **Computational Settings** dialog box will open.
 - (3) Change the **Variance Model** to “data-absolute”. The **Variance Model** box in the **Computational Settings** dialog box will appear as follows:




- (4) Click **Done**.
- c. Change the FSD value assigned to the plasma data.
- (1) Open the **Data** window.
- (2) Change the FSD assigned to plasma from 0.1 to 0.04. The first few lines of the **Data** file will appear as follows:

```
DATA
(FSD 0.04)
t      NAPA
0.     none
15.0   19.1
30.0   30.0
```

- (3) Close the **Data** window.
- d. Refit the model to the data. This time no warning message will appear.
- e. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . The previous plot of the best fit will appear.
- f. Change the scale for better visualization. In the **Set** menu, click **Plot/Table Scale** and change the **X Axis** maximum to 1450 and the **Y Axis** minimum to 5 and maximum to 40. Your plot should appear as follows:




g. View the results in tabular form.

- (1) In the **Set Menu**, click the **Plot and Table Variables** dialog box. Click **s2:URINE** while holding down the **Ctrl** (control) key; it will move to the **Current Selection** pane. This will enable us to visualize the fit to both plasma and urine data in the table. Notice the plot of the predicted urine data is not informative due to the scale of the Y-axis.
- (2) Click **Done**.
- (3) In the **Show** menu, click **Table**, or alternatively, on the **SAAM II Toolbar**, click **Table** . The table will appear as follows:

t	s1	NAPA	s2	URINE
0.000	0.000	-	0.000	-
15.000	19.850	19.100	1.254	-
30.000	29.324	-	3.900	-
30.000	29.324	30.000	3.900	-
32.000	26.102	28.500	4.292	-
35.000	22.602	21.700	4.808	-
40.000	19.010	19.000	5.540	-
45.000	16.960	16.500	6.175	-
60.000	14.131	14.300	7.805	-
75.000	12.737	12.700	9.229	-
90.000	11.774	12.000	10.530	-
120.000	10.524	10.400	12.891	-
180.000	9.378	9.300	17.085	-
240.000	8.928	-	20.969	-
300.000	8.686	8.700	24.714	-
372.000	8.476	-	29.095	-
426.000	8.337	-	32.315	-
480.000	8.203	8.300	35.482	-
552.000	8.029	-	39.627	-
624.000	7.860	-	43.684	-
672.000	7.749	-	46.341	-
720.000	7.639	7.600	48.961	-
792.000	7.478	-	52.821	-
864.000	7.321	-	56.600	-
936.000	7.166	-	60.300	-
1008.000	7.015	-	63.921	-
1080.000	6.867	-	67.466	-
1152.000	6.722	-	70.936	-
1224.000	6.581	-	74.333	-
1296.000	6.442	-	77.658	-
1368.000	6.306	-	80.913	-
1440.000	6.173	-	84.100	-
1440.000	6.173	6.170	84.100	84.100

Note that the “Fit” to all the data points is reasonably good. The urine point fits exactly because $k(4,1)$ can adjust to any value that is less than the total rate of elimination from the central model compartment. This is what caused the problem with the “data-relative” weighting scheme.

(4) Close the **Table** window; if the **Plot** window is still open, close it also.

- h. 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	15.85373	2.02796e+000	1.27917e+001	11.26615 20.44131
k(0,1)	0.00173	3.70313e-004	2.14072e+001	8.92144e-004 0.00257
k(1,2)	0.05244	1.71880e-002	3.27739e+001	0.01356 0.09133
k(1,3)	0.00765	1.15589e-003	1.51183e+001	0.00503 0.01026
k(2,1)	0.06718	2.00848e-002	2.98991e+001	0.02174 0.11261
k(3,1)	0.03727	9.89728e-003	2.65552e+001	0.01488 0.05966
k(4,1)	4.47435e-004	7.23390e-005	1.61675e+001	2.83792e-004 6.11077e-004

	Objective	Scaled Data Variance
s2 : URINE	2.661777e-001	1.000000e+000
s1 : NAPA	-6.825259e-001	1.000000e+000
Total objective	-4.163482e-001	
AIC	1.148264e+000	
BIC	1.317268e+000	

It is apparent from the Coefficients of Variation in the **Statistics** window that the model parameters are reasonably well determined. Notice the value for the **Scaled Data Variance** is 1 for both NAPA and URINE; this is because the weighting scheme is now set to “data-absolute”.

- Scroll down in the **Statistics** window to view the **Derived Variables**. The **Statistics** window will appear as follows:

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval
----- Derived Variables -----				
CLF	1.06498	1.96978e-001	1.84960e+001	0.61938 1.51057
CLNR	0.02742	4.25714e-003	1.55231e+001	0.01779 0.03705
CLR	0.00709	7.18202e-004	1.01248e+001	0.00547 0.00872
CLS	0.59088	1.05737e-001	1.78949e+001	0.35168 0.83007
V2	20.30683	4.85509e+000	2.39087e+001	9.32383 31.28983
V3	77.28290	5.24168e+000	6.78246e+000	65.42537 89.14043
VSS	113.44346	4.61405e+000	4.06727e+000	103.00575 123.88117

The following table compares these results with those obtain in healthy subjects with normal renal function:

PARAMETER	HEALTHY SUBJECTS * (± SD)	ANEPHRIC PATIENT
CL _R (ml/min)	200 ± 56	7.1
CL _{NR} (ml/min)	34 ± 16	27.4

CL_F (L/min)	1.19 ± 0.32	1.07
CL_S (L/min)	0.83 ± 0.26	0.59
V_{SS} (L/kg)	1.46 ± 0.24	1.50

* Data from Atkinson AJ Jr, et al. Clin Pharmacol Ther 1989; 46; 182-9.

As expected, CL_R is markedly reduced but CL_{NR} is unaltered so the Dettli approach can be used to estimate NAPA dosing in this patient. The intercompartmental clearances and steady-state volume of distribution (patient weight = 75.6 kg) are similar to those of healthy subjects.



Can one datum separate $k(0,1)$ and $k(4,1)$? The user may be concerned that the single available urine measurement essentially dictates the difference between $k(0,1)$ and $k(4,1)$. Removal of the urine datum would make fitting the model impossible, however the level of noise in that single measurement would have a clear impact on the results of the analysis. In this case, it was assumed that residual renal function was quite minimal in a dialysis-dependent patient. Since the volume of urine produced is very small in these patients, collecting multiple samples would be subject to considerable error due to incomplete bladder emptying, etc. that would be substantially less in patients with normal renal function. Therefore, it was decided to minimize these collection errors by pooling the 24-hour urine sample - which is actually quite a common thing in some metabolic studies. This information allows to partition pre-dialysis drug elimination between renal and non-renal routes.



- j. Close the **Statistics** window, and close the **Plot** or **Table** windows if they are open.

Part 2. Analyze the dialysis data using a fixed distribution parameter model.

1. As a first step, we need to increase the duration of our analysis to access data obtained during hemodialysis.
 - a. In the **Set** menu, click **Experiment Attributes**. The **Experiment Attributes** dialog box will open. Leave “minutes” in the **Units** box.
 - b. Enter “1620” in the **End at** box. The **Experiment Attributes** dialog box will appear as follows:

Experiment Attributes

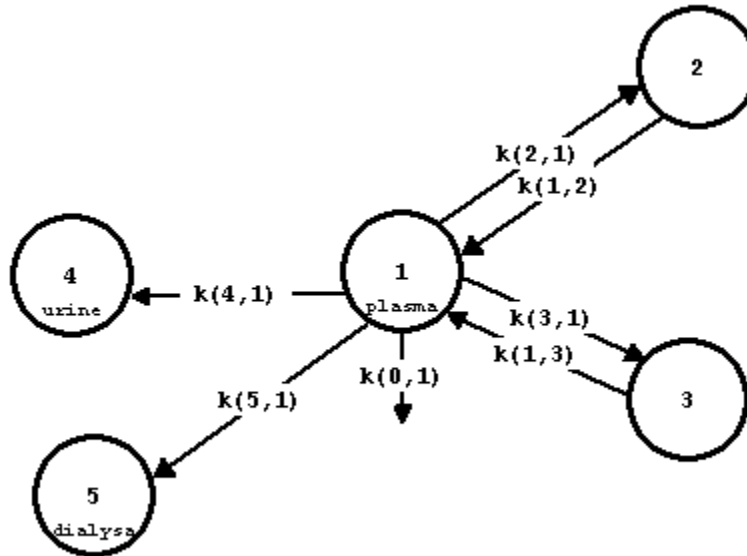
Independent Variable:

Units:

Start at:

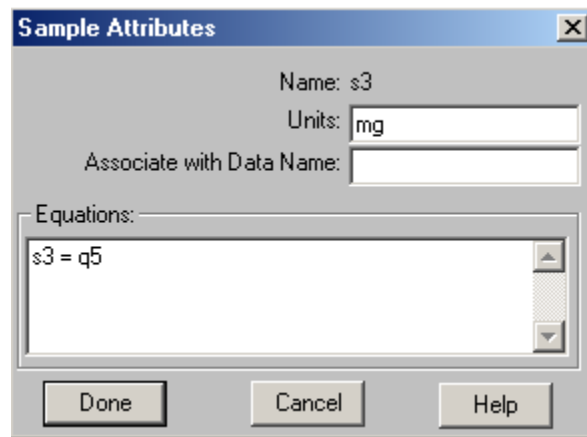
End at:

- c. Click **Done**
2. Add a compartment to the model to represent NAPA collected in the spent dialysis bath fluid.
 - a. In the **SAAM II Toolbox**, click **Model** and add a fifth compartment to the model. Label it “dialysate”
 - b. Add $k(5,1)$. The model should appear approximately as follows:

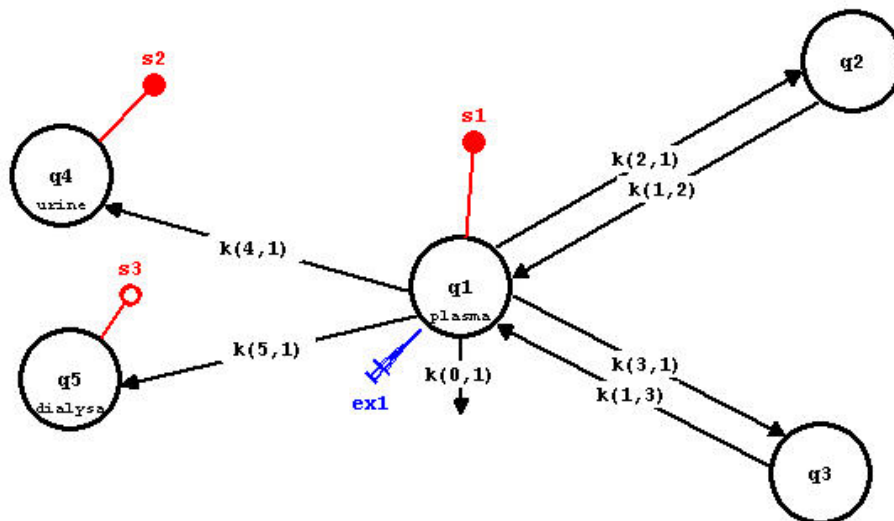


3. Create a sample for the dialysate data. At this time we will not associate it with the dialysis recovery result in the data file but will base our analysis only on plasma data.
 - a. In the **SAAM II Toolbox**, click **Experiment**, and then click **Sample**.

- b. Click compartment **q5**, then click on the **Drawing Canvas**. The sample **s3** will appear.
- c. Double-click **s3** to open the **Sample Attributes** dialog box.
- d. Type “mg” in the **Units** box. The **Sample Attributes** dialog box will appear as follows:



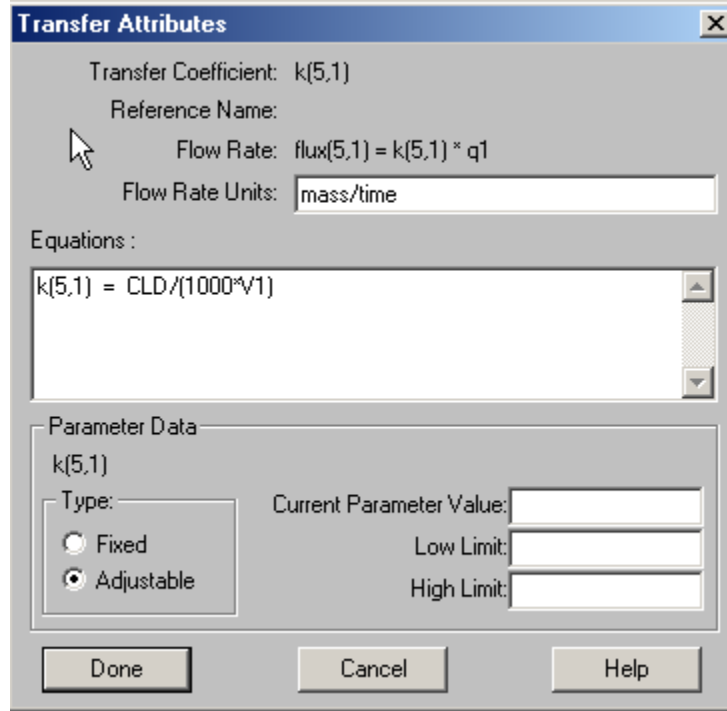
- e. Click **Done**. If the samples, compartments or transfers overlap, you can move them on the **Drawing Canvas** so they do not. For example:




4. Create CLD as a parameter.
 - a. Double click $k(5,1)$ to open the **Transfer Attributes** dialog box.
 - b. In the **Equation** box, type:

$$k(5,1) = CLD/(1000*V1)$$

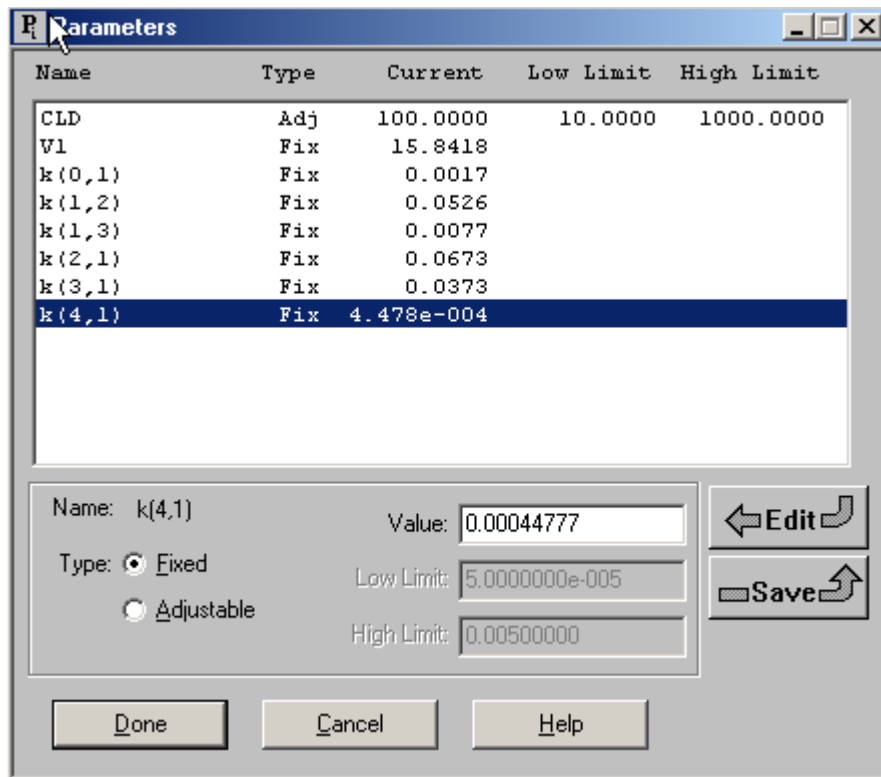
The **Transfer Attributes** dialog box will appear as follows:



- c. Click **Done**.
5. Enter a parameter value for *CLD* and hold the other parameters fixed.
 - a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar**, click **Parameters** . The **Parameters** dialog box will open.
The parameter *CLD* should be selected. If it is not selected, double-click *CLD*.
 - b. Enter 100. in the **Value** box, and click **Save**.
 - c. Double click *V1* to select it.
 - d. Click **Fixed**, then click **Save**.
 - e. Double-click *k(0,1)* to select it.
 - f. Click **Fixed**, then click **Save**.
 - g. Double-click *k(1,2)* to select it.

- h. Click **Fixed**, then click **Save**.
- i. Double-click $k(1,3)$ to select it.
- j. Click **Fixed**, then click **Save**.
- k. Double-click $k(2,1)$ to select it.
- l. Click **Edit**, click **Fixed**, then click **Save**.
- m. Double-click $k(3,1)$ to select it.
- n. Click **Fixed**, then click **Save**.
- o. Double-click $k(4,1)$ to select it.
- p. Click **Fixed**, then click **Save**.

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



The screenshot shows a dialog box titled "Parameters" with a table of parameters and a detailed view for the selected parameter $k(4,1)$.

Name	Type	Current	Low Limit	High Limit
CLD	Adj	100.0000	10.0000	1000.0000
V1	Fix	15.8418		
$k(0,1)$	Fix	0.0017		
$k(1,2)$	Fix	0.0526		
$k(1,3)$	Fix	0.0077		
$k(2,1)$	Fix	0.0673		
$k(3,1)$	Fix	0.0373		
$k(4,1)$	Fix	4.478e-004		

Below the table, the detailed view for $k(4,1)$ is shown:

Name: $k(4,1)$ Value: 0.00044777

Type: Fixed Adjustable

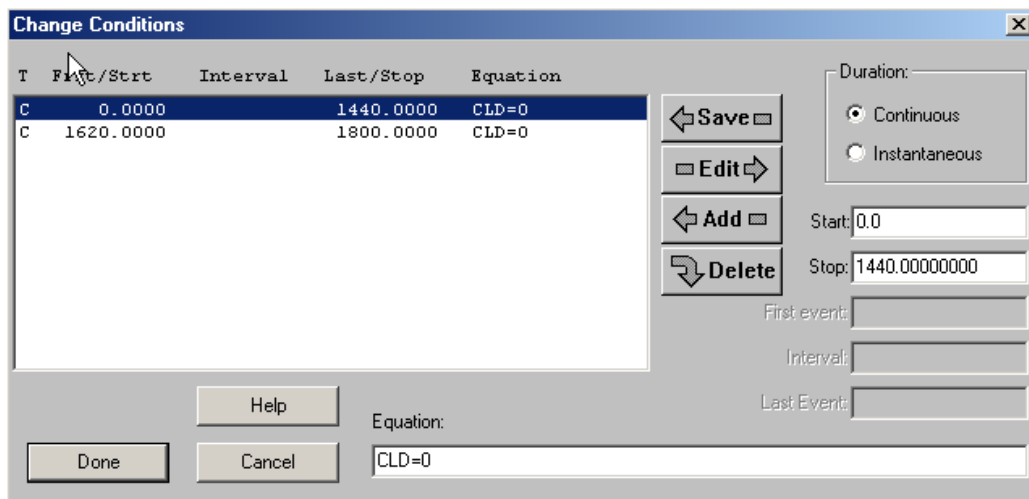
Low Limit: 5.0000000e-005


High Limit: 0.00500000


Buttons: Done, Cancel, Help, Edit, Save

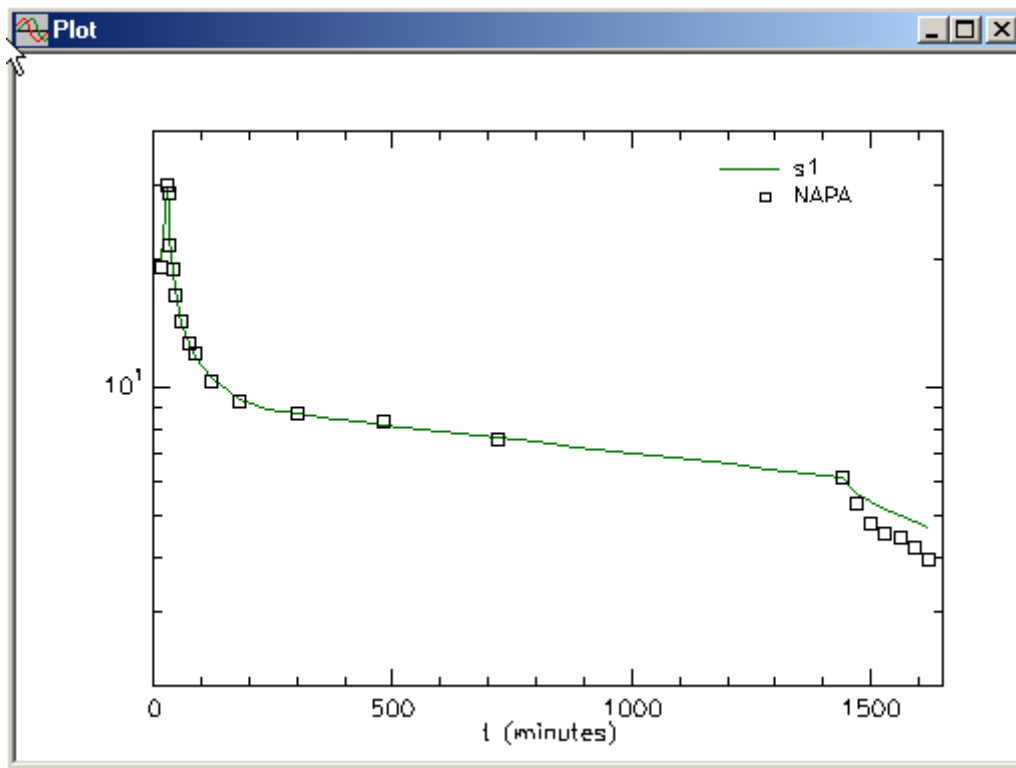
- q. Click **Done**.


6. Use the **Change Condition** feature to activate *CLD* only during the hemodialysis period.
 - a. Making sure that the **Experiment** options are highlighted. Click the **Change Condition** button. The **Change Conditions** dialog box will open. Be sure **Continuous** is checked in the **Duration** box.
 - b. Type “CLD = 0” in the **Equations** box.
 - c. Type “0” in the **Start** box.
 - d. Type “1440” in the **Stop** box. This keeps CL_D turned off until the start of hemodialysis at 1440 minutes.
 - e. Click the **Add** button.
 - f. Type “1620” in the **Start** box. This turns off CL_D when hemodialysis is discontinued at 1620 minutes.
 - g. Type “1800” in the **Stop** box.
 - h. Click the **Add** button. The **Change Condition** window should appear as follows:

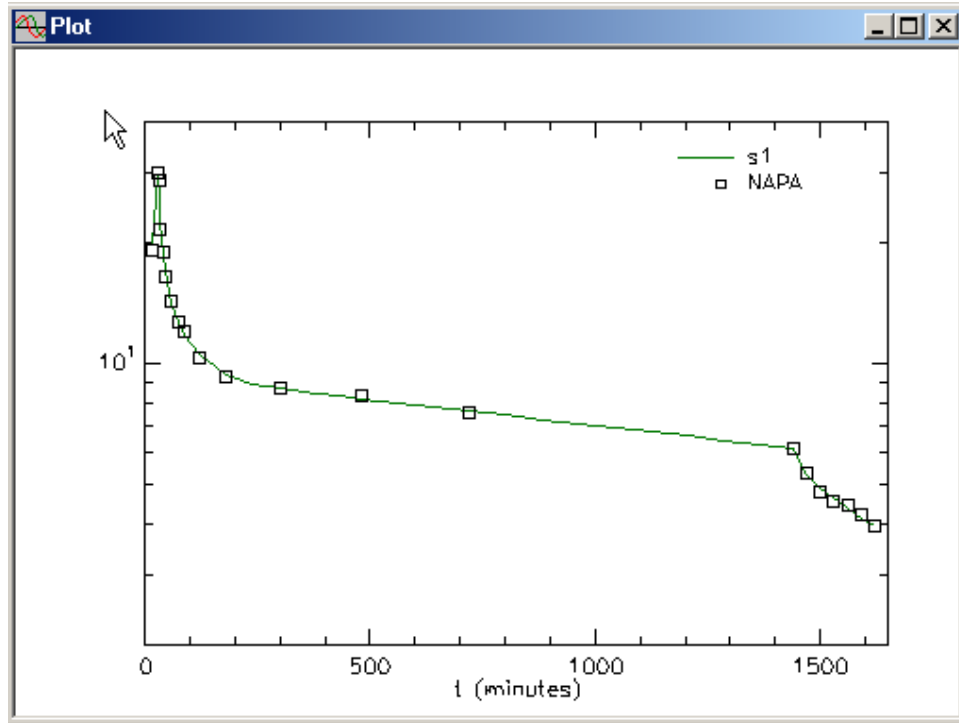




- i. Click **Done**.
7. Solve your model and view the solution.
 - a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar**, click **Solve** .

- 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.
- c. Click **s1:NAPA**; it will move to the **Current Selection** pane.
- d. Click **Done**.
- e. Select **Plot/Table Scale** in the **Set** menu and change the scale for better visualization so that the **X Axis** maximum is 1650 and the **Y Axis** minimum is 2 and maximum is 40. Your plot should appear as follows (in semilog mode):



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



9. We should further assess the results.
 - a. In the **Show** menu, click **Statistics**, or alternatively, on the **SAAM II Toolbar**, click **Statistics**  and examine the results. The dialysis clearance (CL_D) is estimated as 188 ml/min with a 6% coefficient of variation and represents a substantial increment over the pre-dialysis elimination clearance of 34.5 ml/min, representing the sum of $CL_R + CL_{NR}$. However, we have not compared the estimate of NAPA recovered in the dialysate with what was actually measured.
 - b. Close the **Statistics** window.
 - c. In the **Set** menu in the **Plot and Table Variables** dialog box, click **s3** while holding down the **Ctrl** key; it will move to the **Current Selection** pane. This will enable us to visualize the fit to both plasma and dialysate data in the table. The plot is not informative because of the scale, but we want to investigate the tabular results.
 - d. Click **Done**.
 - e. In the **Show** menu, click **Table**, or alternatively, on the **SAAM II Toolbar**, click **Table** . Adjust the **Table** window to obtain the following view:

t	s1	NAPA	s3
0.000	0.000	-	0.000
15.000	19.849	19.100	0.000
30.000	29.324	-	0.000
30.000	29.324	30.000	0.000
32.000	26.104	28.500	0.000
35.000	22.604	21.700	0.000
40.000	19.011	19.000	0.000
45.000	16.959	16.500	0.000
60.000	14.129	14.300	0.000
75.000	12.736	12.700	0.000
90.000	11.775	12.000	0.000
120.000	10.525	10.400	0.000
180.000	9.379	9.300	0.000
240.000	8.928	-	0.000
300.000	8.686	8.700	0.000
381.000	8.452	-	0.000
430.500	8.325	-	0.000
480.000	8.202	8.300	0.000
561.000	8.007	-	0.000
640.500	7.821	-	0.000
720.000	7.639	7.600	0.000
801.000	7.458	-	0.000
882.000	7.282	-	0.000
963.000	7.109	-	0.000
1044.000	6.941	-	0.000
1125.000	6.776	-	0.000
1206.000	6.616	-	0.000
1287.000	6.459	-	0.000
1363.500	6.315	-	0.000
1440.000	6.173	-	0.000
1440.000	6.173	6.170	0.000
1470.000	5.301	5.350	31.727
1500.000	4.928	4.780	60.532
1530.000	4.627	4.540	87.452
1560.000	4.372	4.440	112.816
1590.000	4.145	4.210	136.826
1620.000	3.937	-	159.610
1620.000	3.937	3.940	159.610

Inspection of these results confirms that the plasma data fit the model predictions reasonably well. But the value for dialysate recovery of NAPA (**s3**) is 159.6 mg, whereas the actual recovery was 80.9 mg (This data point is not shown in the **Table** because **s3** has not been associated with DIALYSATE).

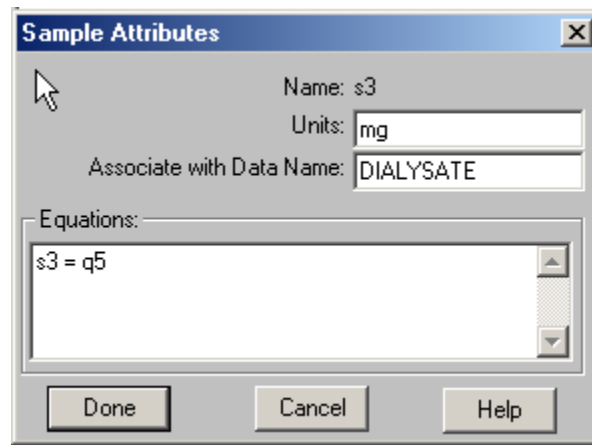
- f. Close the **Table** and **Plot** windows.

This part of the exercise illustrates how hemodialysis clearance can be significantly overestimated when only plasma data are obtained. The only single parameter change that can resolve this discrepancy in dialysate

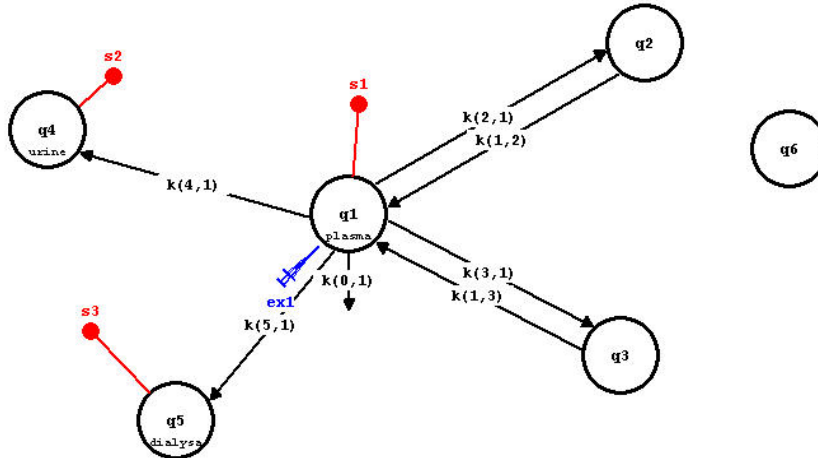
recovery estimates is a reduction in CL_S that starts with the beginning of hemodialysis.

Part 3. Analysis of dialysis data while allowing CL_S to decrease in order to fit dialysate recovery.

1. Associate dialysis recovery with **s3**
 - a. Double-click **s3** to open the **Sample Attributes** dialog box.
 - b. Type “DIALYSATE” in the **Associate with Data Name** box. The **Sample Attributes** dialog box will appear as follows:



- c. Click **Done**. If you check your **DATA** file, you will find only one datum for DIALYSATE so for fitting purposes, this could cause the same problem as the single datum for URINE.
2. Create a forcing function to adjust CL_S .
 - a. In the **SAAM II Toolbox**, click **Model** and add a sixth compartment to the model.
 - b. In the **SAAM II Toolbox**, click **Experiment**. Moving components of your model on the **Drawing Canvas**, you will have (approximately):



- c. In the **SAAM II Toolbox**, click **Sample**.
- d. Click compartment **q6**, then click on the **Drawing Canvas**. The sample **s4** will appear.
- e. Create a step function input for the forcing function.
 - (1) In the **SAAM II Toolbox**, click **Input**
 - (2) Click compartment **q6**, and then click on the **Drawing Canvas**. The input **ex2** will appear.
 - (3) Double-click **ex2** to open the **Exogenous Input** dialog box.
 - a. Select **Bolus** as the **Input Type**.
 - b. Enter “1” in the **Initial Amount** box.
 - c. Enter “0” in the **Event Start** box
 - d. Click **Add**
 - d. Select **Equation** as the **Input Type**.
 - f. Type “ex2 = Decrement” in the **Equation** Box.
 - g. Enter “1440” in the **Event Start** box.
 - h. Enter “1440” in the **Event Stop** box.
 - i. 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	1.000	-	0.000	-	-	-
Equation	ex2 = Decrement		1440.000	1440.000	-	-

Input Type:

Bolus
 Infusion
 Primed Infusion
 Equation

Initial Amount:

Constant Rate:

Event Start:

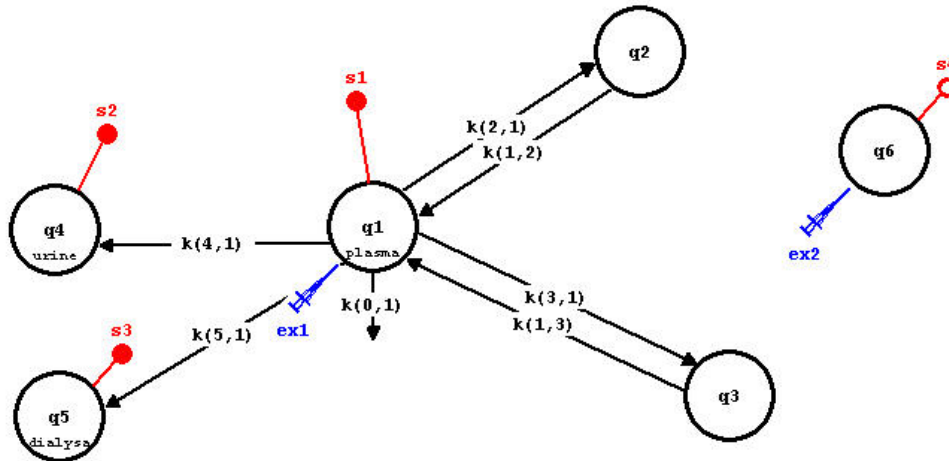
Event Stop:

Repeat Every:

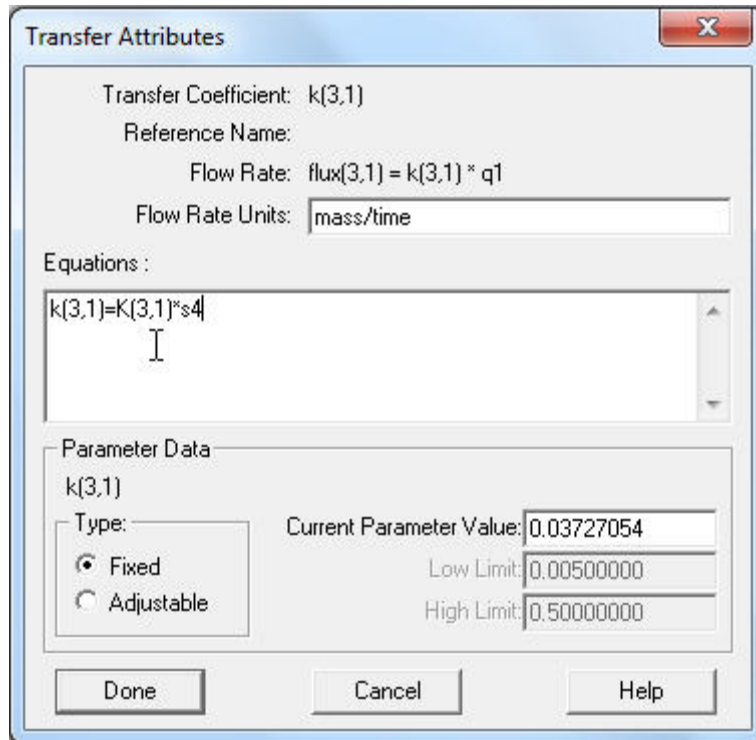
Nr. of Repeats:


Equation:

j. Click **Done**. The **Drawing Canvas** appears as follows:



3. Permit $k(3,1)$ and $k(1,3)$ to be perturbed (decremented) during the dialysis period.
 - a. Double-click rate constant $k(3,1)$ to open its **Transfer Attributes** dialog box.
 - b. In the **Equation Box**, type: $k(3,1) = K(3,1)*s4$. The **Transfer Attributes** dialog box appears as follows:



- c. Click **Done**.
 - d. Double Click rate constant $k(1,3)$ to open its **Transfer Attributes** dialog box.
 - e. In the **Equation Box**, type: $k(1,3) = K(1,3)*s4$.
 - f. Click **Done**.
3. Enter the new model parameters.
 - 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 *Decrement* to select it. Be sure the **Adjustable** option is selected.
 - c. Enter “-0.5” in the **Value** box and click **Save**.
 - d. Double-click $K(1,3)$ to select it.
 - e. Enter “.007652” in the **Value** box, click **Fixed**, and click **Save** (This is the same fixed parameter value that was used in the previous part of the exercise.)
 - f. Double-click $K(3,1)$ to select it.



- g. Enter “.03734” in the **Value** box, click **Fixed**, and click **Save**. The **Parameters** dialog box appears as follows:

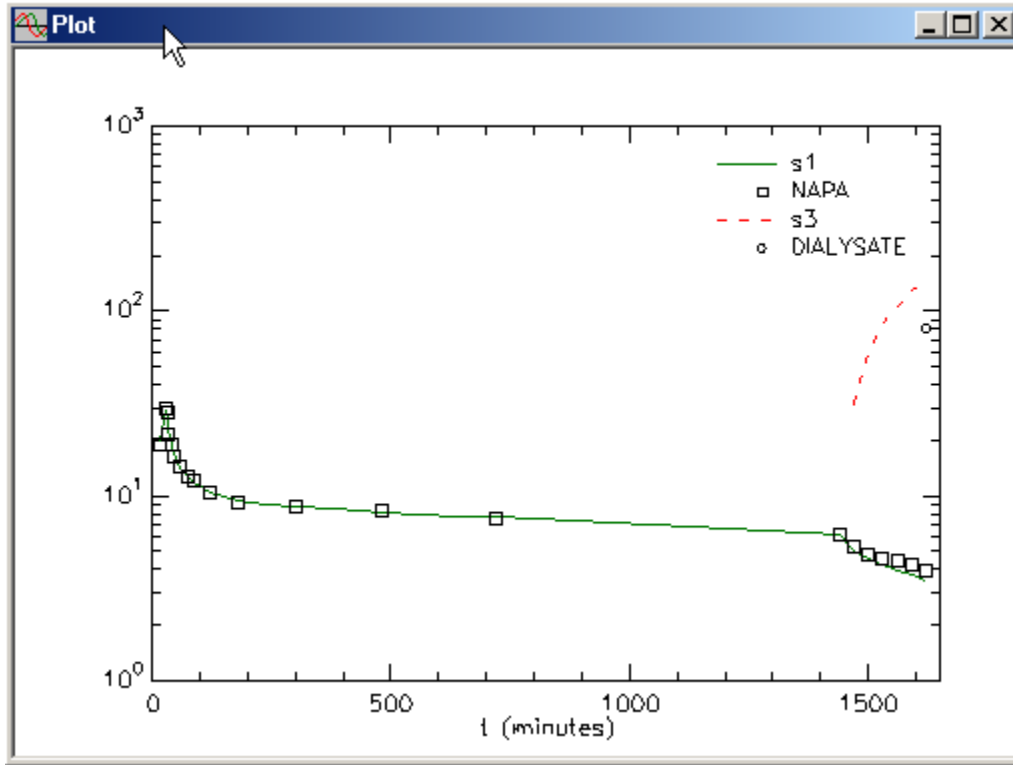
Name	Type	Current	Low Limit	High Limit
CLD	Adj	188.0074	10.0000	1000.0000
Decrement	Adj	-0.5000	-5.0000	-0.0500
K(1,3)	Fix	0.0077		
K(3,1)	Fix	0.0373		
V1	Fix	15.8537		
k(0,1)	Fix	0.0017		
k(1,2)	Fix	0.0524		
k(2,1)	Fix	0.0672		
k(4,1)	Fix	4.474e-004		

Below the table, the **Parameters** dialog box shows the following settings for the selected parameter **CLD**:


- Name: CLD
- Value: 188.00744500
- Type: Fixed, Adjustable
- Low Limit: 10.00000000
- High Limit: 1000.00000000

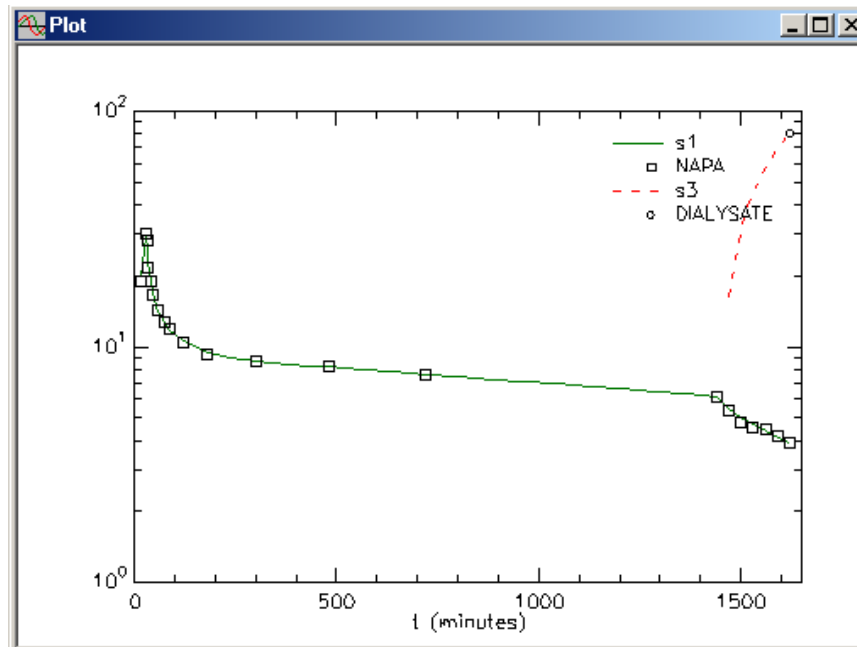
Buttons: Done, Cancel, Help, Edit, Save.

- h. Click **Done**.
5. Solve your model and view the solution.
- 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.
 - While pressing the **Ctrl** key click **s1:NAPA**; and **s3:DIALYSATE** to move these both to the **Current Selection** pane.
 - Click **Done**. Your plot should appear as follows (in semilog mode with **X Axis** set from 0 to 1650 minutes and **Y Axis** on **AutoScale**):




The discrepancy between the measured value and our initial estimate of NAPA recovery in the dialysate is now quite apparent.

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



The fit to both the “arterial” plasma data obtained during hemodialysis and dialysis recovery of NAPA now appears satisfactory.

7. In the **Show** menu, click **Statistics**, or alternatively, on the **SAAM II Toolbar**, click **Statistics**  and examine the results. Dialysis clearance (CL_D) of NAPA now is estimated as only 94 ml/min, substantially less than our previous estimate of 188 ml/min. But this improvement in results requires a hemodialysis-associated decrement in CL_S of 80%. This experiment provides no explanation for the mechanism behind this change. However, intercompartmental clearances (CL_I) of inulin and urea between plasma and splanchnic and somatic peripheral compartments can be analyzed with the following equation:

$$CL_I = Q (1 - e^{-P \cdot S/Q}) \quad \text{Equation 3}$$

where Q represents compartment blood flow rate and $P \cdot S$ represents the permeability coefficient-surface area product of the compartment’s capillary bed. Hemodialysis experiments with inulin and urea in dogs with intact kidneys demonstrated similar reductions in CL_S that reflected a 90% reduction in slow compartment blood flow but no reduction in $P \cdot S$.

This reduction in intercompartmental clearance also results in a marked reduction in apparent distribution volume calculated as follows from the amount of NAPA recovered in the dialysis bath fluid and the drop in plasma concentrations during hemodialysis:

$$V_D = \frac{\text{Amount Recovered}}{\Delta \text{Concentration}} = \frac{80.9 \text{ mg}}{6.17 - 3.94 \text{ mg/L}} = 36.3 \text{ L}$$

Because this value for V_D is substantially less than the value of 113.4 L calculated for V_{SS} before hemodialysis, calculating a dialysis replacement drug dose simply from the product of the pre-dialysis V_{SS} and the concentration drop would give a value of 252.9 mg that would represent a substantial drug overdose. This erroneous approach is sometimes advocated when therapeutic drug monitoring is available to measure predialysis and postdialysis drug concentrations.

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

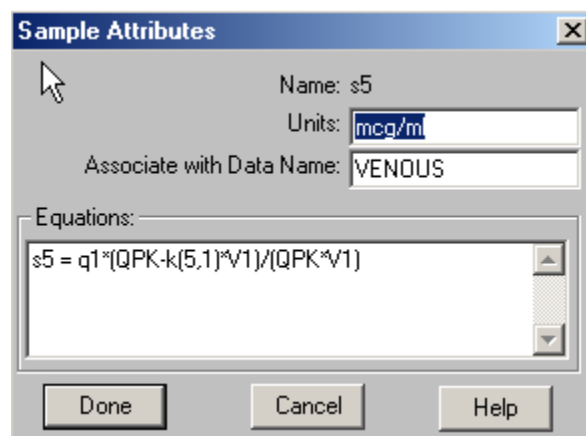
Part 4. Analysis of “venous” data in order to calculate pharmacokinetic flow through the dialyzer (Q_{PK}).

The relationship between “venous” (V) and “arterial” (A) plasma concentrations is obtained by re-arranging the Fick Equation (shown above as Equation 2) as follows:


$$V = A \left[\frac{Q_{PK} - CL_D}{Q_{PK}} \right] \quad \text{Equation 4}$$

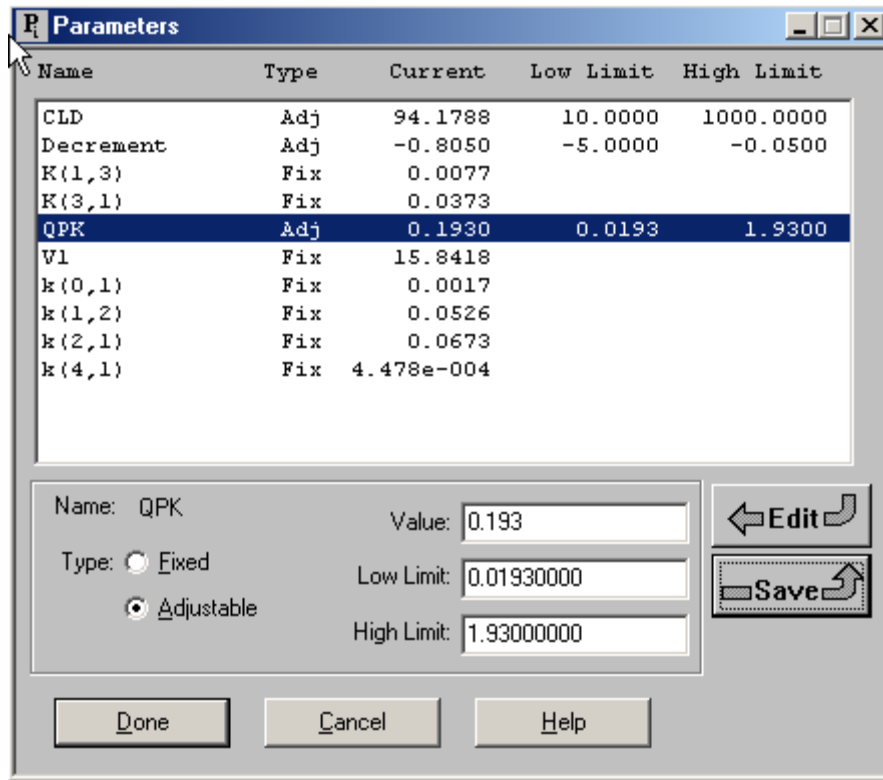
where Q_{PK} is the pharmacokinetically effective flow through the dialyzer. The relationship that Q_{PK} bears to measured blood flow through will depend on the extent to which the dialyzed drug partitions between plasma and erythrocytes and on the extent to which drug in erythrocytes is dialyzable. As a practical point, the constancy of this ratio provides a valuable check on the stability of the hemodialysis procedure (e.g. the constancy with which ultrafiltration affects CL_D).

1. Create a sample for the “venous” plasma data.
 - a. In the **SAAM II Toolbox**, click **Sample**.
 - b. Click compartment **q1**, then click on the **Drawing Canvas**. The sample **s5** will appear. You may want to move it on the **Drawing Canvas** for easier access.
 - c. Double-click **s5** to open the **Sample Attributes** dialog box.
 - d. Type “mcg/ml” in the **Units** box.
 - e. Type “VENOUS:” in the **Associate with Data Name** box.
 - f. Type “ $s5 = q1 * (QPK - k(5,1) * V1) / (QPK * V1)$ ” in the **Equations** box. The **Sample Attributes** dialog box will appear as follows:



- g. Click **Done**.
2. Enter parameter value for Q_{PK} .

- 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 *QPK* to select it.
- c. The measured blood flow through the dialyzer was 193 ml/min, so type 0.193 in the **Value** box.
- d. Click **Save**. The **Parameters** dialog box will appear as follows:





Name	Type	Current	Low Limit	High Limit
CLD	Adj	94.1788	10.0000	1000.0000
Decrement	Adj	-0.8050	-5.0000	-0.0500
K(1,3)	Fix	0.0077		
K(3,1)	Fix	0.0373		
QPK	Adj	0.1930	0.0193	1.9300
V1	Fix	15.8418		
k(0,1)	Fix	0.0017		
k(1,2)	Fix	0.0526		
k(2,1)	Fix	0.0673		
k(4,1)	Fix	4.478e-004		

Name: QPK Value: 0.193

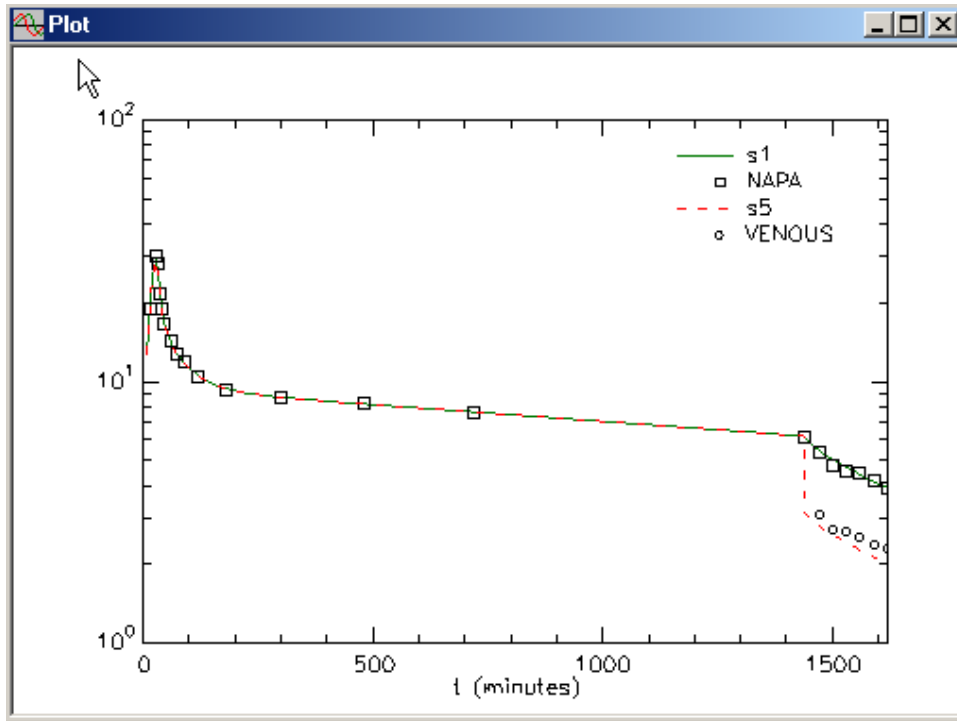
Type: Fixed Low Limit: 0.01930000


Adjustable High Limit: 1.93000000

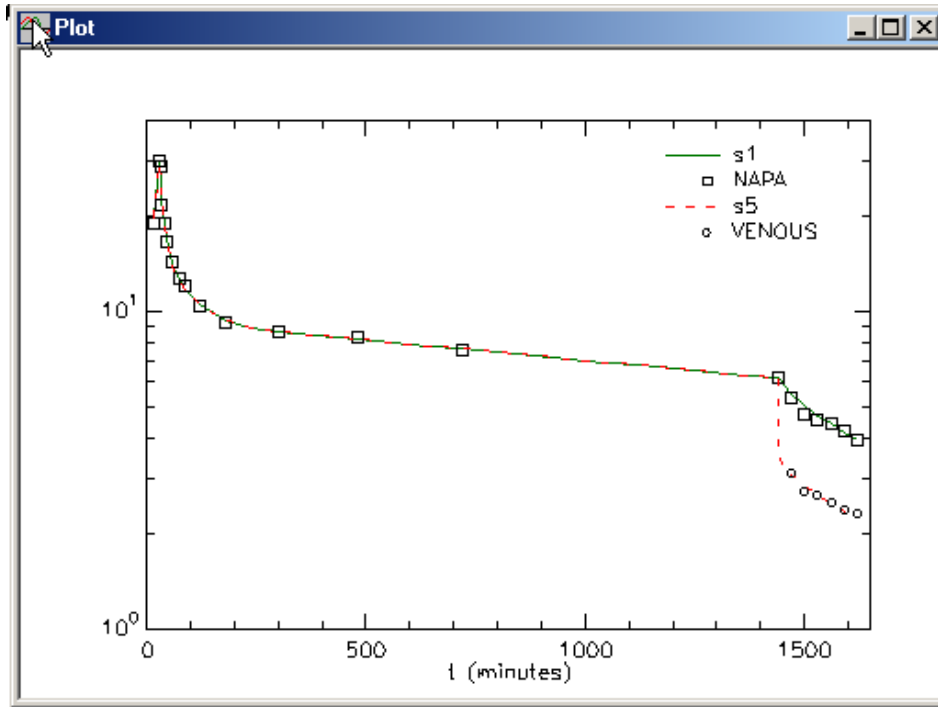
Buttons: Done, Cancel, Help, Edit, Save

- e. Click **Done**.
3. 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.
 - c. While pressing the **Ctrl** key click both **s1:NAPA** and **s5:Venous** it will move these to the **Current Selection** pane.


- d. Click **Done**.
- e. For better visualization make sure that the **X Axis** maximum is 1650 and the **Y Axis** minimum is 2 and maximum is 40. Your plot should appear as follows (in semilog mode):



4. 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** . The plot will be updated as follows:



The fit to both “arterial” and “venous” plasma concentrations is satisfactory.

- 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	
CLD	94.12461	1.42722e+000	1.51630e+000	91.19093	97.05830
Decrement	-0.80136	3.45380e-002	4.30992e+000	-0.87235	-0.73037
K(1,3)	0.00765	** Fixed **	** Fixed **	** Fixed **	** Fixed **
K(3,1)	0.03734	** Fixed **	** Fixed **	** Fixed **	** Fixed **
QPK	0.21735	1.34531e-002	6.18964e+000	0.18970	0.24500
V1	15.85373	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,1)	0.00173	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(1,2)	0.05244	** Fixed **	** Fixed **	** Fixed **	** Fixed **

	Objective	Scaled Data Variance
s5 : VENOUS	-5.400083e-001	1.000000e+000
s3 : DIALYSATE	-1.455050e-002	1.000000e+000
s2 : URINE	1.468577e-001	1.000000e+000
s1 : NAPA	-9.806949e-001	1.000000e+000

Total objective	-1.388396e+000	
AIC	3.281888e-001	
BIC	3.989110e-001	

The value for Q_{PK} is 0.215 L/min or 215 ml/min which is substantially higher than the measured blood flow (Q_{MEAS}) reading of 193 ml/min. This reflects the fact that NAPA partitions preferentially from plasma into erythrocytes (RBC), in this patient with an RBC/plasma partition ratio of 1.53. The expected effective blood flow (Q_{EFF}) through the dialyzer can be estimated as:

$$Q_{EFF} = [(1 - Hct/100) + (RBC/P \cdot Hct/100)] Q_{MEAS} \quad \text{Equation 5}$$

where Hct is the patient's hematocrit. Since this patient's Hct was 21.4%, the corresponding estimate for Q_{EFF} is 215 ml/min. This is similar to our estimate of 215 ml/min for Q_{PK} , indicating that NAPA within erythrocytes is fully dialyzable.

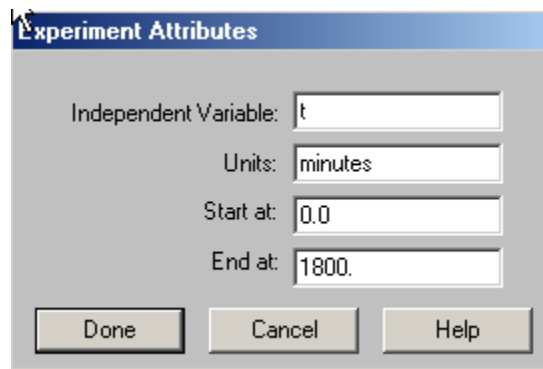
This part of the exercise illustrates the fallacy of the usual convention in which plasma flow is used to calculate CL_D by the A-V difference method.

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

Part 5. Analysis of post-dialysis rebound in NAPA concentrations.

At the conclusion of hemodialysis, redistribution of NAPA from peripheral compartments to the intravascular space results in an increase in NAPA plasma concentrations, termed a "rebound". As a final part of this exercise, we will proceed to analyze the post-dialysis data that was obtained in this patient.

1. Begin by increasing the duration of our analysis to access data obtained during hemodialysis.
 - a. In the **Set** menu, click **Experiment Attributes**. The **Experiment Attributes** dialog box will open.
 - b. Enter "1800" in the **End at** box. The **Experiment Attributes** dialog box will appear as follows:



- c. Click **Done**

2. Create a post-dialysis step function input for the forcing function.

- a. On the **Drawing Canvas**, double-click **ex2** to open the **Exogenous Input** dialog box for compartment **q6**.
- b. Select **Equation** as the **Input Type**.
- c. Type “ex2 = Increment” in the **Equation** Box.
- d. Enter “1620” in the **Event Start** box.
- e. Enter “1620” in the **Event Stop** 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	1.000	-	0.000	-	-	-
Equation	ex2 = Decrement		1440.000	1440.000	-	-
Equation	ex2 = Increment		1620.000	1620.000	-	-

Input Type:

Bolus
 Infusion
 Primed Infusion
 Equation

Initial Amount:

Constant Rate:

Event Start:


Event Stop:

Repeat Every:

Nr. of Repeats:

Equation:

Buttons: Save, Edit, Add, Delete, Split Input..., Done, Cancel, Help

- g. Click **Done**.
3. Enter an initial parameter value for “Increment”.
 - 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 *Decrement* to select it, click **Fixed**, then click **Save**.

- c. Double-click *Increment* to select it. Be sure the **Adjustable** option is selected.
- d. Enter “0.5” in the **Value** box and click **Save**. The **Parameters** dialog box should appear as follows.



Name	Type	Current	Low Limit	High Limit
CLD	Adj	94.1246	10.0000	1000.0000
Decrement	Fix	-0.8014		
Increment	Adj	0.5000	0.0500	5.0000
K(1,3)	Fix	0.0077		
K(3,1)	Fix	0.0373		
QPK	Adj	0.2173	0.0193	1.9300
V1	Fix	15.8537		
k(0,1)	Fix	0.0017		
k(1,2)	Fix	0.0524		
k(2,1)	Fix	0.0672		
k(4,1)	Fix	4.474e-004		

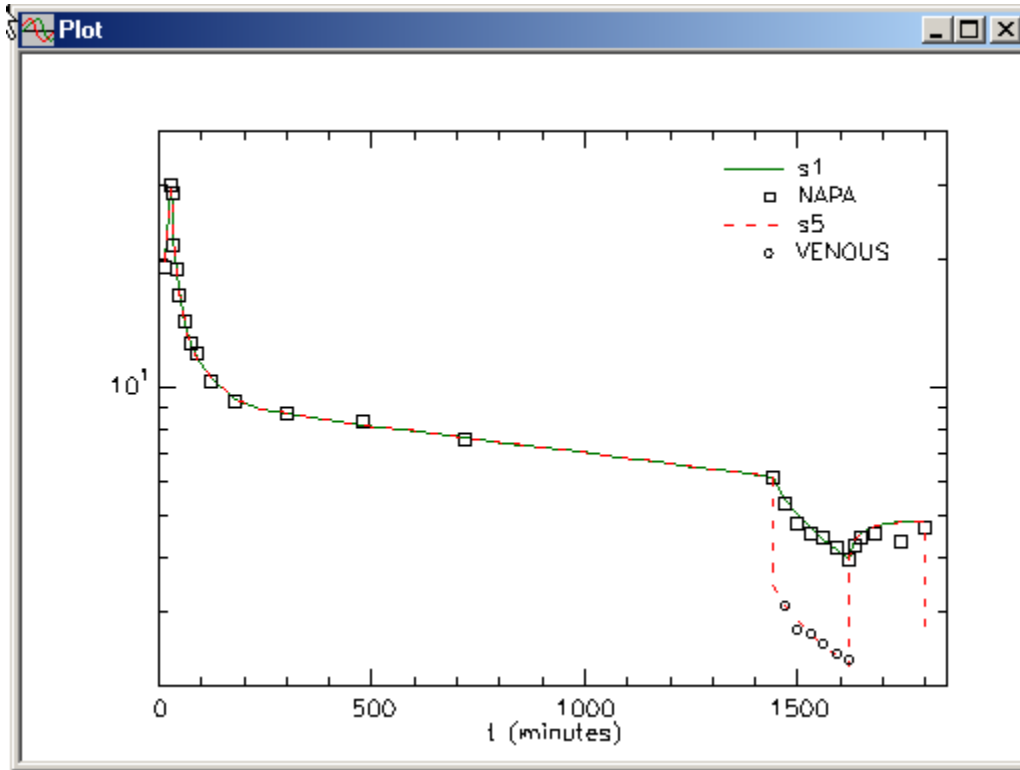
Name: Increment Value: .5


Type: Fixed
 Adjustable

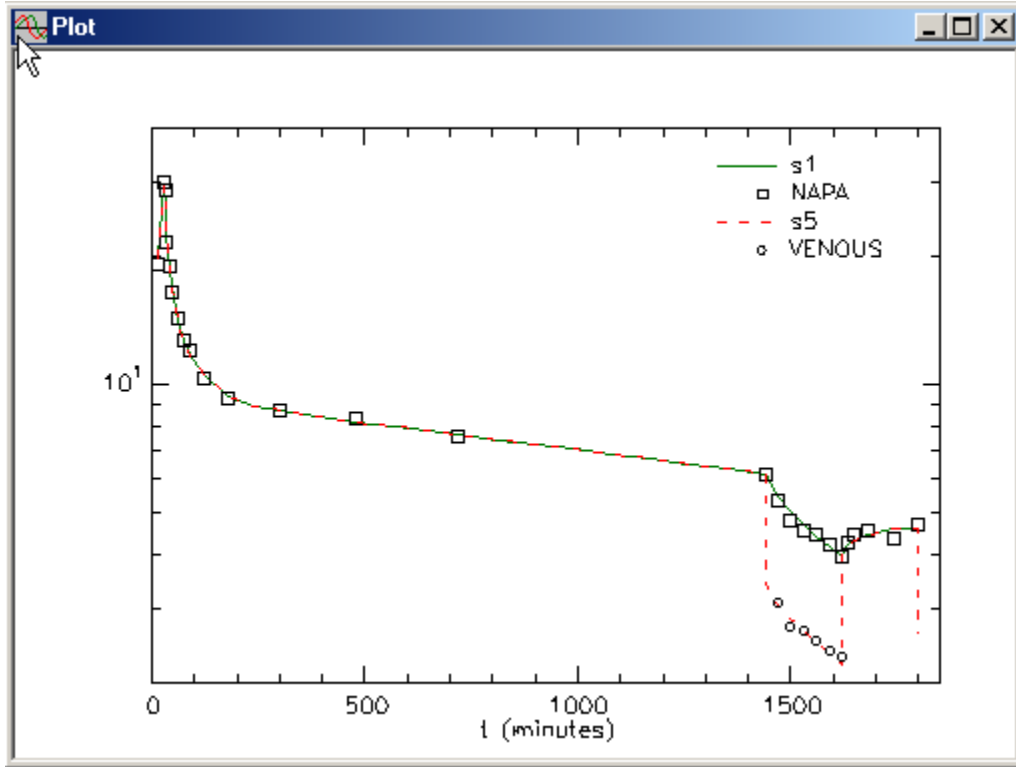
Low Limit: 0.05000000
High Limit: 5.00000000

Buttons: Edit, Save, Done, Cancel, Help


- e. Click **Done**.
4. 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** . Both s1:NAPA and s4:venous data should be displayed. (If not, open the **Plot and Table Variables** dialog box and while pressing the Ctrl key click both **s1:NAPA** and **s4:Venous** it will move these to the **Current Selection** pane. Then click **Done**.)
 - c. To visualize the post-dialysis rebound in plasma NAPA concentrations, set the **X Axis** maximum to 1850 and make sure the **Y Axis** minimum is 2 and maximum is 40. Your plot should appear as follows (in semilog mode):



5. Proceed to fit the model to the post-dialysis data.
 - a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar**, click **Fit** . The plot should be updated as follows:



The fit to the rebound plasma concentrations is reasonable.

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

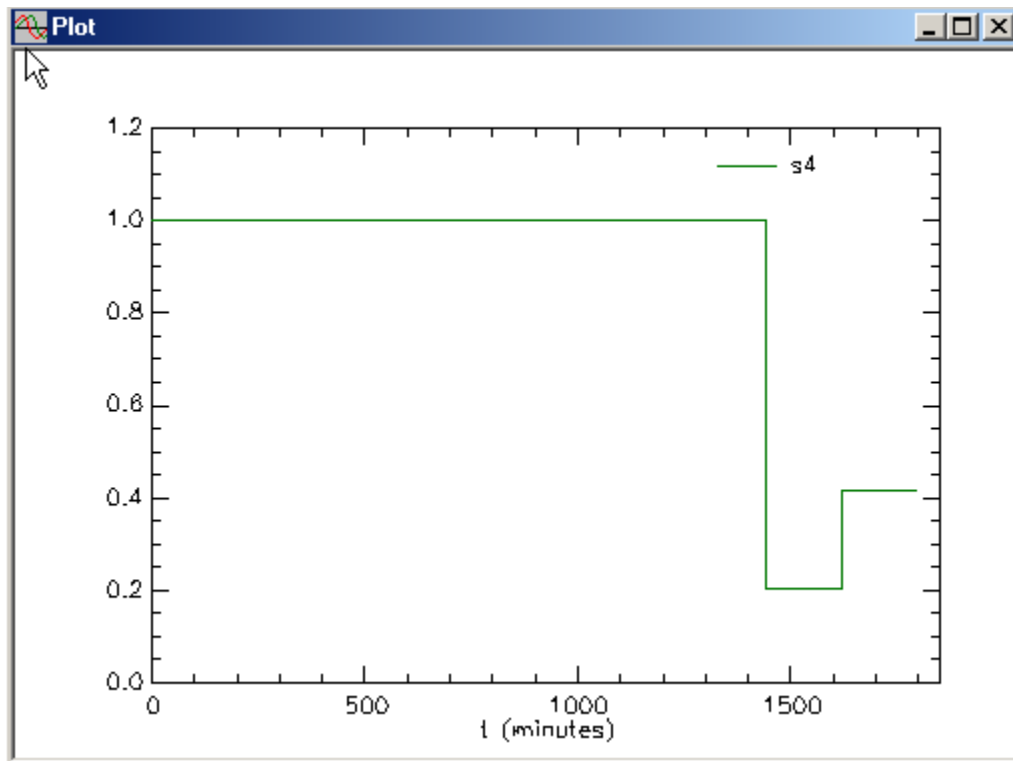
Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence	Interval
CLD	94.57344	1.12994e+000	1.19478e+000	92.26819	96.87869
Decrement	-0.80136	** Fixed **	** Fixed **	** Fixed **	** Fixed **
Increment	0.21885	7.63891e-002	3.49047e+001	0.06301	0.37470
K(1,3)	0.00765	** Fixed **	** Fixed **	** Fixed **	** Fixed **
K(3,1)	0.03734	** Fixed **	** Fixed **	** Fixed **	** Fixed **
QPK	0.21661	1.29181e-002	5.96382e+000	0.19025	0.24296
V1	15.85373	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,1)	0.00173	** Fixed **	** Fixed **	** Fixed **	** Fixed **

	Objective	Scaled Data Variance
s5 : VENOUS	9.473950e-001	1.000000e+000
s3 : DIALYSATE	-6.915775e-003	1.000000e+000
s2 : URINE	1.252610e-001	1.000000e+000
s1 : NAPA	-1.261770e+000	1.000000e+000

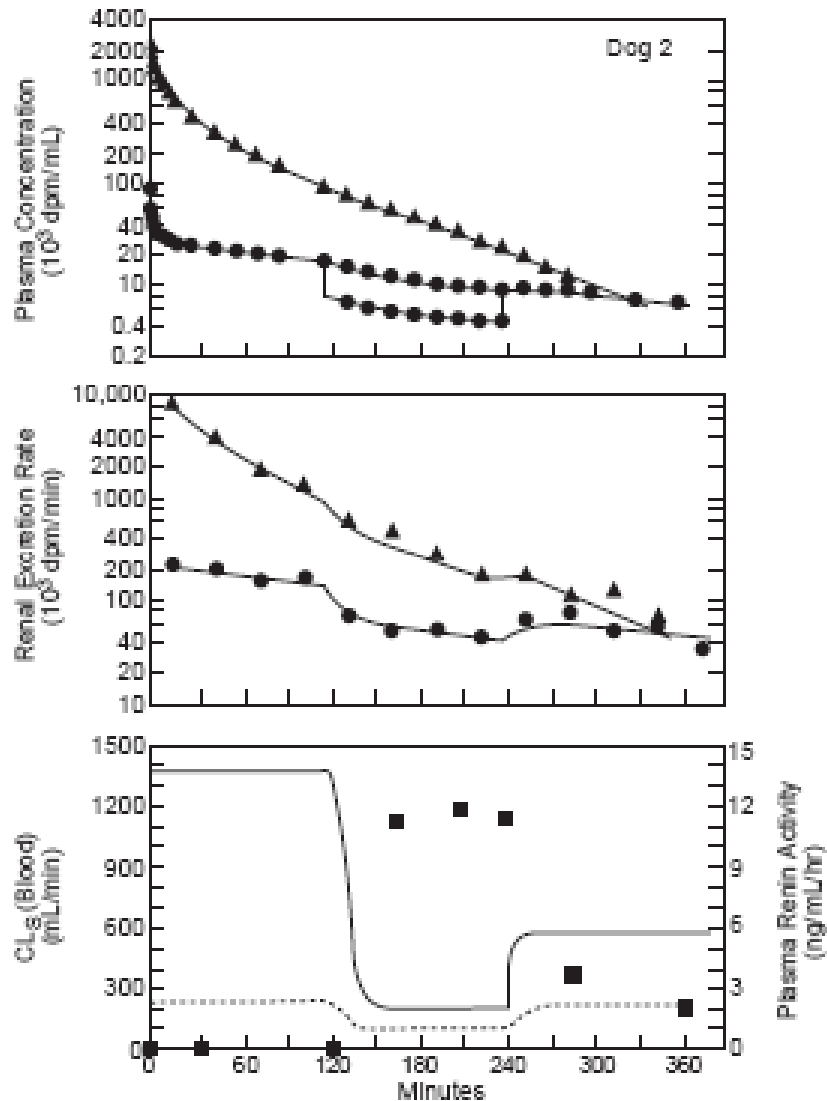
Total objective	-1.960296e-001	
AIC	9.091590e-001	
BIC	9.764984e-001	

Since there was an 80% dialysis associated decrement in CL_S and the post-dialysis increment is only 21% of its pre-dialysis value, it is apparent that CL_S does not return to pre-dialysis values immediately after hemodialysis is terminated. We can visualize these changes in CL_S as follows:

- c. Close the **Statistics** window. The **Plot** window should remain open.
- d. In the **Set** menu, select **Plot/Table Variables**.
- e. Click **s4**, then **Done**.
- f. Open the **Plot/Table Scale** window and set the **Y Axis** minimum to 0 and maximum to 1.2.
- g. In the **View** menu, de-select **Semilog** so the plot is linear. The plot should appear as follows:



In patients, the basis of this hemodialysis-associated decrease in CL_S is not clear. However, when dogs with intact kidneys are dialyzed after receiving intravenous injections of urea and inulin, similar reductions in CL_S occur and result from a 90% reduction in slow compartment blood flow that is accompanied by activation of the renin-angiotensin system, as shown in the figure below.



Kinetic analysis of urea ¹⁴C (●) and inulin ³H (▲) plasma concentrations (*upper panel*) and renal excretion rates (*middle panel*) before, during and after dialysis of a dog with intact kidneys. Inulin was not dialyzable but urea concentrations entering and leaving the dialyzer are both shown. The *lower panel* shows CL_s estimates for urea (—) and inulin (---), and measured plasma renin activity (■). (Reproduced from Bowsher DJ, Krejcie TC, Avram MJ, Chow MJ del Greco F, Atkinson AJ Jr. *J Lab Clin Med* 1985;105:489-97.)



If you wish, you may save the study file for future use. You can use this study file as a template for other sets of data you wish to analyze using the one-compartment model with absorption.

Quit the SAAM II Compartmental application.

Essential Points to Remember

- Realistic models of physiologic systems can be constructed using forcing functions to model physiologic changes that occur during a pharmacokinetic study
- Partitioning of drug into erythrocytes and physiologic changes that occur during hemodialysis make it a “best practice” to calculate hemodialysis clearance by the “recovery method”
- Pharmacokinetic analysis of hemodialysis studies can incorporate both pre-dialyzer (“arterial”) and post-dialyzer (“venous”) drug concentrations and provide an estimate of flow through the dialyzer that is pharmacokinetically effective in removing drug from the patient.
- Changes to a model, such as the addition of hemodialysis clearance, can be incorporated in the analysis using the change conditions tool.
- Equations can be added to a model using the transfer attributes box, as well as the equations window.

Data for this Case Study

DATA

(FSD 0.1)

t NAPA

0. none

15.0 19.1

30.0 30.0

32.0 28.5

35.0 21.7

40.0 19.0

45.0 16.5

60.0 14.3

75.0 12.7

90.0 12.0

120. 10.4

180. 9.3

300. 8.7

480. 8.3

720. 7.6

1440. 6.17

1470. 5.35

1500. 4.78

1530. 4.54

1560. 4.44

1590. 4.21

1620. 3.94

1635. 4.28

1650. 4.44

1680. 4.54

1740. 4.37

1800. 4.68

END

DATA

(FSD 0.1)

t URINE

1440. 84.1

END

DATA

(FSD 0.1)

t VENOUS

1470. 3.09

1500. 2.70

1530. 2.65

1560. 2.52

```
1590. 2.38
1620. 2.31
END
DATA
(FSD 0.01)
t      DIALYSATE
1620. 80.9
END
#Derived Anephric Model Parameters
#CLR = V1*k(4,1)
#CLNR = V1*k(0,1)
#CLF = V1*k(2,1)
#CLS = V1*k(3,1)
#V2 = CLF/k(1,2)
#V3 = CLS/k(1,3)
#VSS = V1+V2+V3
```