

Nonlinear Elimination with Bayesian Priors

Case Study

- Identifying nonlinear elimination
- Modeling nonlinear elimination
- Adding prior information about parameters

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Nonlinear Elimination with Bayesian Priors

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

- Identifying nonlinear elimination.
- Modeling nonlinear elimination.
- How to add prior information about parameters.

Data Required

The data file for this case study is

NLM

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

Introduction

The drug in this case study will be seen to exhibit nonlinear elimination kinetics of the Michaelis-Menten type. As an example, Phenytoin, a commonly used antiepileptic drug, shows this kind of pharmacokinetic behavior. The parameters considered in this case study are similar to those of Phenytoin. This case study uses prior available information about the pharmacokinetics of the drug to permit a more constrained estimation of one or more of the involved parameters. In this case, it is assumed information is available about both K_m (population mean of 6.0 mg/L, SD = 2.0) and V_{max} (population mean of 27.1 mg/h, SD = 5.0).

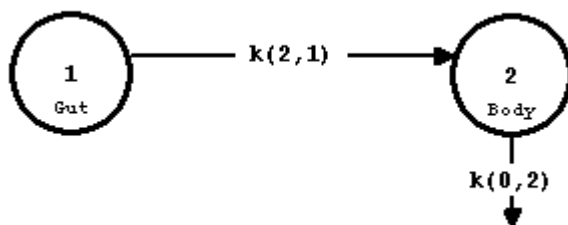
You will begin by modeling the data using the single-compartment model with absorption, and see that using first-order rate constants only, you cannot describe the data. With this knowledge, and the prior information from the literature, you will create a non-linear loss from the body compartment that exhibits Michaelis-Menten kinetics. The addition of the two new parameters will prohibit you from obtaining accurate parameter estimates, so you will use the Bayesian parameter feature in SAAM II to incorporate knowledge from the literature.

The dosing regimen is 300mg/day for 15 days (360 hours), and then 400 mg/day for an additional 15 days. Plasma concentrations are in mg/L.

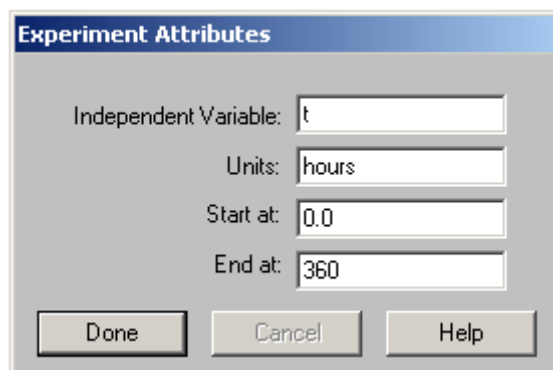
Part 1. Create the model for with first-order kinetics.

The first step will be to create the model for the drug kinetics, and to analyze the data for the first 360 hours using first-order kinetics.

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:

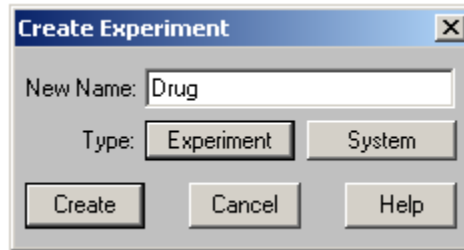


3. In the **SAAM II Toolbox**, click **Experiment**. Notice that the **Model** tools are unavailable and the **Experiment** tools are available. The **Experiment Attributes** dialog box will open.
 - a. Change the entry in the **Units** box to “hours”.
 - b. Enter “360” in the **End at** box. The **Experiment Attributes** dialog box will appear as follows:

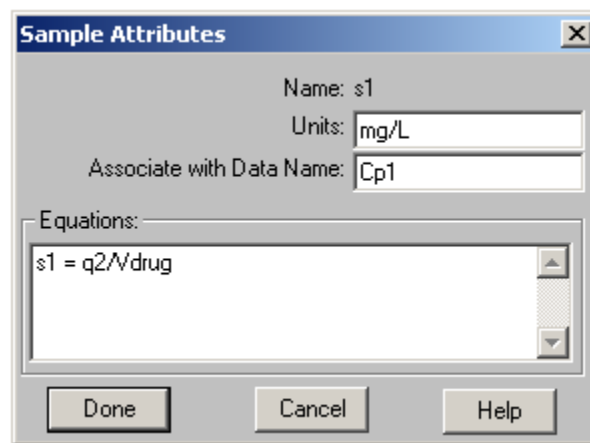


- c. Click **Done**.

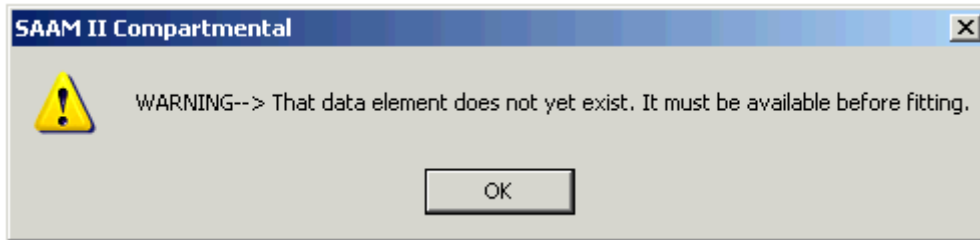
The **Create Experiment** dialog box will appear on the **Drawing Canvas**. Type “Drug” in the **New Name** box. The **Create Experiment** dialog box will appear as follows:



- d. Click **Create**. Notice “Drug” appears as the name under “Experiment” in the **SAAM II Toolbox**.
4. Create a sample.
- a. In the **SAAM II Toolbox**, click **Sample**.
 - b. Click Compartment **q2**, then click on the **Drawing Canvas**. The sample **s1** will appear.
 - c. Double-click **s1** to open the **Sample Attributes** dialog box.
 - d. Type “mg/L” in the **Units** box.
 - e. Type “Cp1” in the **Associate with Data Name** box.
 - f. Edit the sample equation “s1 = q2” to read “s1 = q2/Vdrug”. The **Sample Attributes** dialog box will appear as follows:



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



Remember the Warning message appears because you have not entered your data yet.

- h. Click **OK**.
5. Create an input.

Oral doses of 300 mg of the drug were given every 24 hours for 15 days (360 hours). Thus 15 doses were given. Starting on day 15, the dose was changed to 400mg; this will be examined later in the case study.

- In the **SAAM II Toolbox**, click **Input**
- Click Compartment **q1**, and then click on the **Drawing Canvas**. The input **ex1** will appear.
- Double-click **ex1** to open the **Exogenous Input** dialog box.
- Leave **Bolus** as the **Input Type**.
- Enter “300” in the **Initial Amount** box.
- Enter “0” in the **Event Start** box.
- Enter “24” in the **Repeat Every** box.
- Enter “14” in the **Nr. of Repeats** box (remember 14 repeats will give a total of 15 doses.)
- 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	300.000	-	0.000	-	24.000	14

Input Type:

Bolus
 Infusion
 Primed Infusion
 Equation

Initial Amount:

Constant Rate:

Event Start:

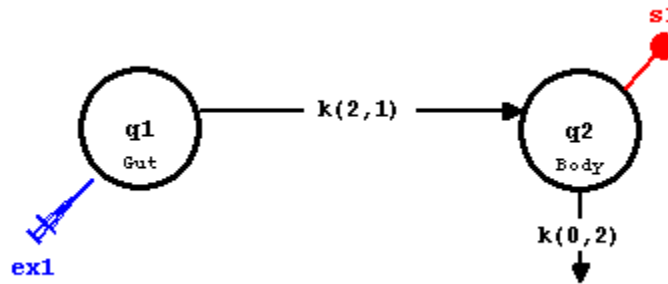
Event Stop:


Repeat Every:

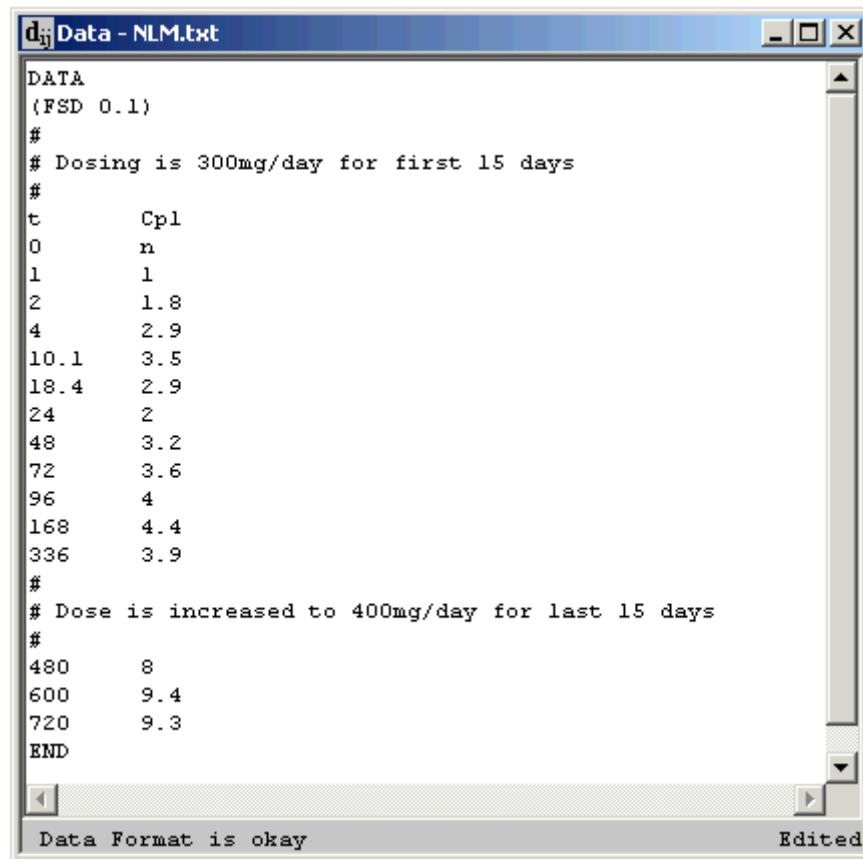
Nr. of Repeats:

Equation:

- j. Click **Done**. The model will appear as follows:



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 **NLM** should appear in the list (if it does not, find the folder where you put this data file).
 - c. Double-click **NLM**. The **Data** window should appear as follows:

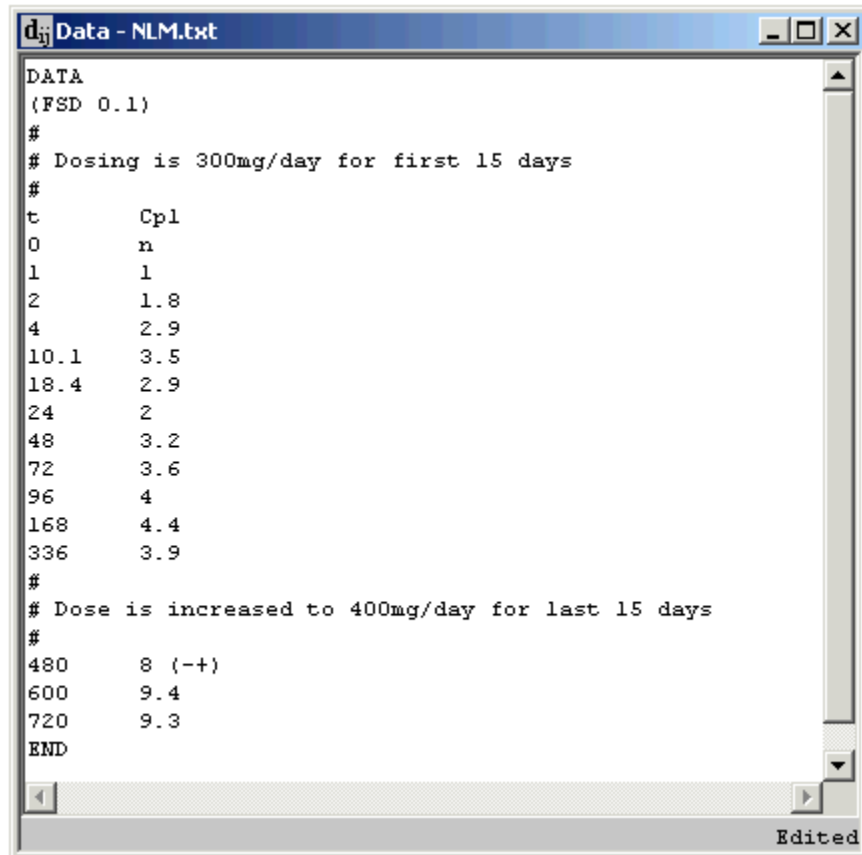


```
DATA
(FSD 0.1)
#
# Dosing is 300mg/day for first 15 days
#
t      Cp1
0      n
1      1
2      1.8
4      2.9
10.1   3.5
18.4   2.9
24     2
48     3.2
72     3.6
96     4
168    4.4
336    3.9
#
# Dose is increased to 400mg/day for last 15 days
#
480    8
600    9.4
720    9.3
END
```

Data Format is okay Edited

- d. Since the first part of the experiment up to 360 hours is being analyzed, the data following 360 hours need to be unweighted for purposes of fitting.

After the datum (“8”) at 480 hours, type “(-+)”. This will unweight this datum and all subsequent data. The **Data** window should appear as follows:



```
DATA
(FSD 0.1)
#
# Dosing is 300mg/day for first 15 days
#
t      Cp1
0      n
1      1
2      1.8
4      2.9
10.1   3.5
18.4   2.9
24     2
48     3.2
72     3.6
96     4
168    4.4
336    3.9
#
# Dose is increased to 400mg/day for last 15 days
#
480    8 {-+}
600    9.4
720    9.3
END
Edited
```

- e. Close the **Data** window.
7. Rename the parameters, obtain initial estimates and enter the estimates.
 - a. Rename the parameter values from $k(2,1)$ and $k(0,2)$ to k_a and k_e .
 - (1) Double-click $k(2,1)$ to open the **Transfer Attributes** dialog box.
 - (2) In the **Equations** pane, type “ $k(2,1) = k_a$ ”. The **Transfer Attributes** dialog box will appear as follows:

The screenshot shows the "Transfer Attributes" dialog box. It contains the following fields and controls:

- Transfer Coefficient: $k(2,1)$
- Reference Name:
- Flow Rate: $\text{flux}(2,1) = k(2,1) * q1$
- Flow Rate Units:
- Equations :
- Parameter Data:
k(2,1)
Type: Fixed Adjustable
Current Parameter Value:
Low Limit:
High Limit:
- Buttons: Done, Cancel, Help

(3) Click **Done**.


(4) Double-click $k(0,2)$ to open the **Loss Attributes** dialog box. In the **Equations** pane, type " $k(0,2) = k_e$ ". The **Loss Attributes** dialog box will appear as follows:

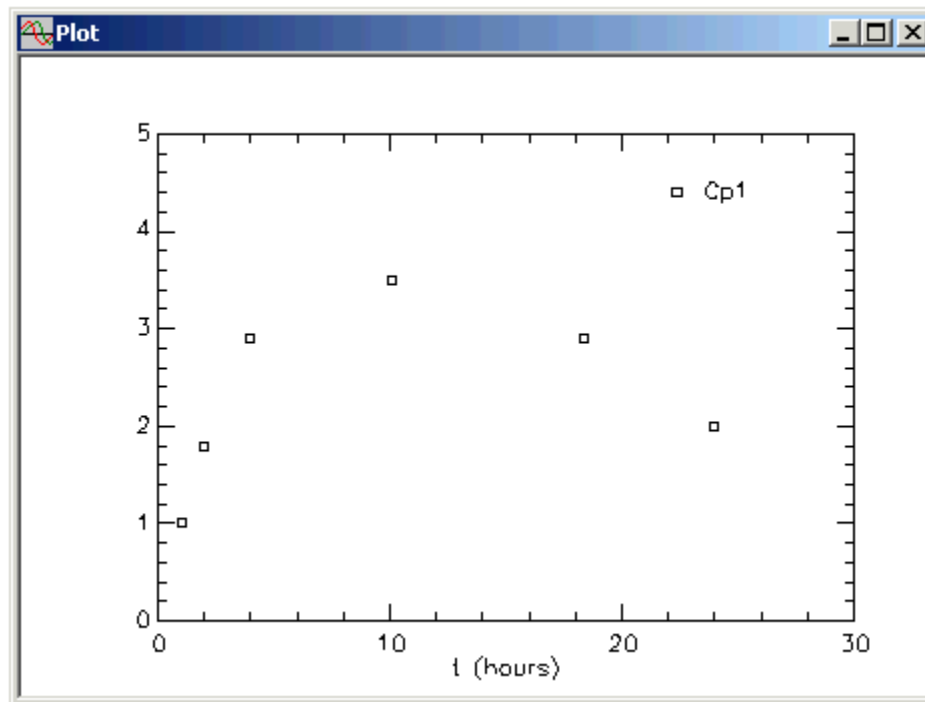
The screenshot shows the "Loss Attributes" dialog box. It contains the following fields and controls:

- Transfer Coefficient: $k(0,2)$
- Reference Name:
- Flow Rate: $\text{flux}(0,2) = k(0,2) * q2$
- Flow Rate Units:
- Equations :
- Parameter Data:
k(0,2)
Type: Fixed Adjustable
Current Parameter Value:
Low Limit:
High Limit:
- Buttons: Done, Cancel, Help

- (5) Click **Done**.
- b. Obtain initial parameter estimates.

To obtain initial parameter estimates, you will investigate the drug data during the first 24 hours.

- (1) In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is not selected.
- (2) Click **s1:Cp1** to move these to the **Current Selection** pane.
- (3) Click **Done**.
- (4) Reset the X – Axis minimum and maximum to 0 and 25; reset the Y – Axis minimum and maximum to 0 and 5. Your plot should appear as follows:



- (5) In obtaining initial estimates for k_a and k_e , it will be assumed that the drug exhibits rapid absorption and slow elimination, hence k_a will be larger than k_e . It will also be assumed that bioavailability, F , equals 1.

Estimates for k_a and k_e will be obtained by examining the half-time of absorption and elimination, and remembering the formulas

$$k_a = \ln(2)/\text{half time of absorption}$$

$$k_e = \ln(2)/\text{half time of elimination}$$

You can “guess” that the maximal concentration is around 4mg/L, and that this occurs around 8 hours. Half the maximal concentration, 2mg/L occurs at just after 2 hours, say 2.5 hours. An estimate for k_a can be obtained:

$$k_a = 0.693/2.5 = 0.28$$

For elimination, on the decreasing portion of the curve, 2mg/L (half the maximum) occurs at about 24 hours. The half-time is thus $24 - 2.5 = 21.5$, and an estimate for k_e can be obtained:

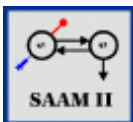
$$k_e = 0.693/21.5 = 0.03$$

An estimate for V_{drug} can be obtained by extrapolating the decaying portion of the data to time zero, and pretending the dose was administered as a bolus. The back extrapolation is approximately 5mg/L, so V_{drug} can be estimated:

$$V_{drug} = 300/5 = 60$$


While this will usually give a reasonable initial estimate for the volume, some hand fitting may be necessary depending upon the situation.

These values will be entered as the initial parameter estimates.



The half-time method for parameter estimation. The half-time method for parameter estimation is discussed in the case studies on Cadralazine and Hydromorphone. For the one-compartment model with absorption, it is discussed in the case study on Oral Theophylline.



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

Name	Type	Current	Low Limit	High Limit
Vdrug	Adj			
ka	Adj			
ke	Adj			

Name: Vdrug Value:

Type: Fixed Adjustable

Low Limit:

High Limit:

- d. Enter the following initial values for each of the model parameters:

Vdrug = 60 (low limit 25, high limit 150)

ka = .28 (low limit .028, high limit 2.8)

ke = .03 (low limit .003, high limit .3)

When you have finished, your **Parameters** dialog box should appear as follows (which parameter is highlighted will depend upon which one you entered last):

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

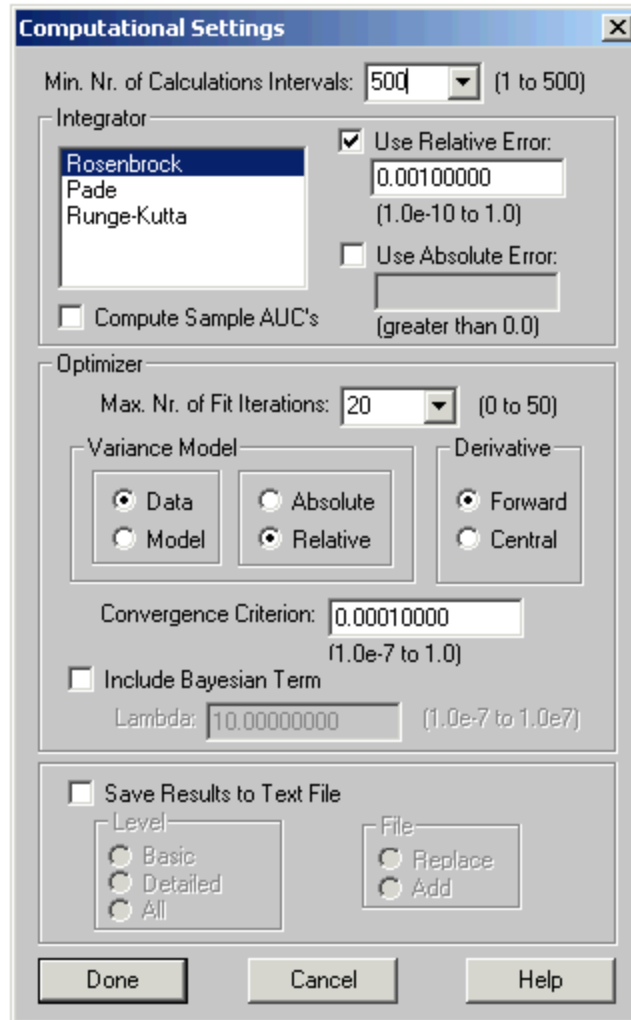
Name	Type	Current	Low Limit	High Limit
Vdrug	Adj	60.0000	25.0000	150.0000
ka	Adj	0.2800	0.0280	2.8000
ke	Adj	0.0300	0.0030	0.3000



Below the table, the 'ke' parameter is selected. The 'Name' field contains 'ke'. The 'Value' field contains '.03'. The 'Type' is set to 'Adjustable' (radio button selected). The 'Low Limit' field contains '0.00300000' and the 'High Limit' field contains '0.30000000'. There are 'Edit' and 'Save' buttons on the right, and 'Done', 'Cancel', and 'Help' buttons at the bottom.

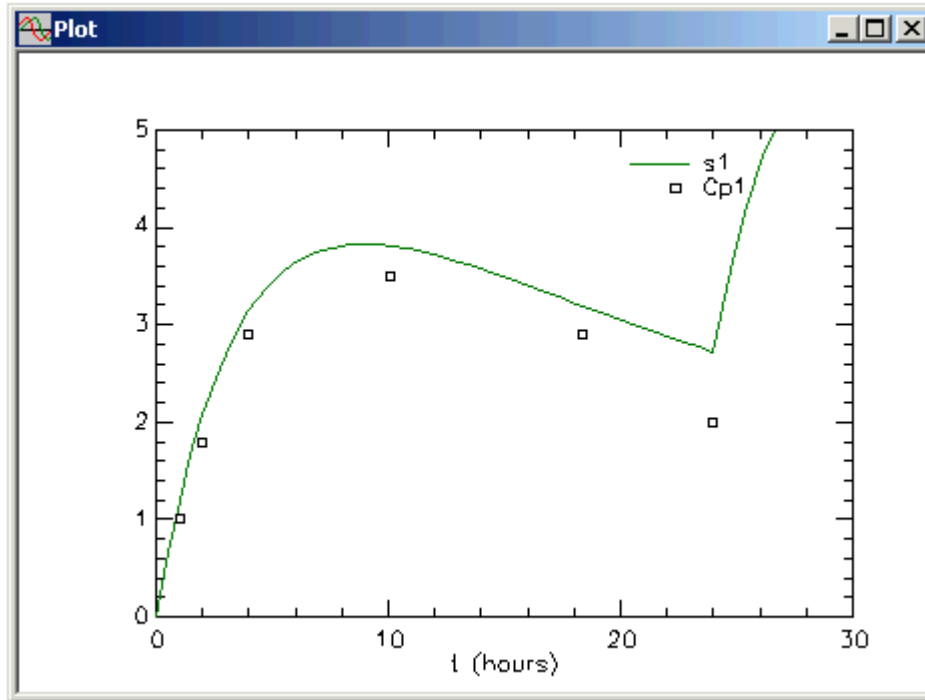
- e. Click **Done**.
8. Solve your model and view the solution.

Before Solving the model, you will want to increase the minimum number of calculation intervals; this will increase the resolution of your plots.

- a. In the **Compute** menu, click **Settings**. The **Computational Settings** dialog box will open.
- b. Enter "500" in the **Min. Nr. of Calculation Intervals** box. Remember this will improve the resolution of your plots. The Computational Settings dialog box will appear as follows:

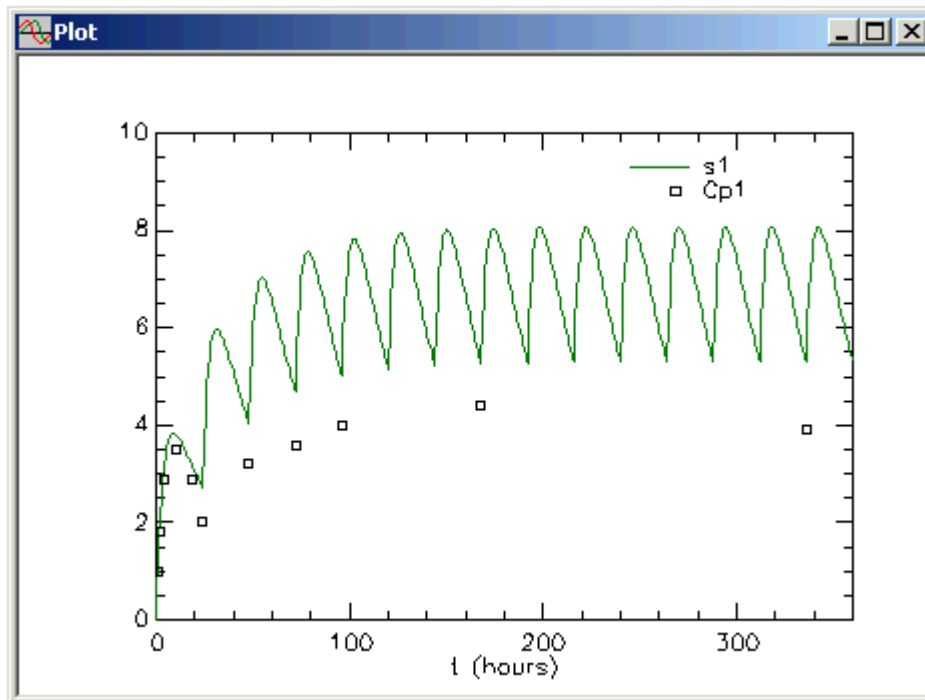


- c. Click **Done**.
- d. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar**, click **Solve** .
- e. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . Because you have plotted **s1:Cp1** previously to 24 hours, this plot will open as shown below:




You can see that the initial parameter estimates are quite reasonable.

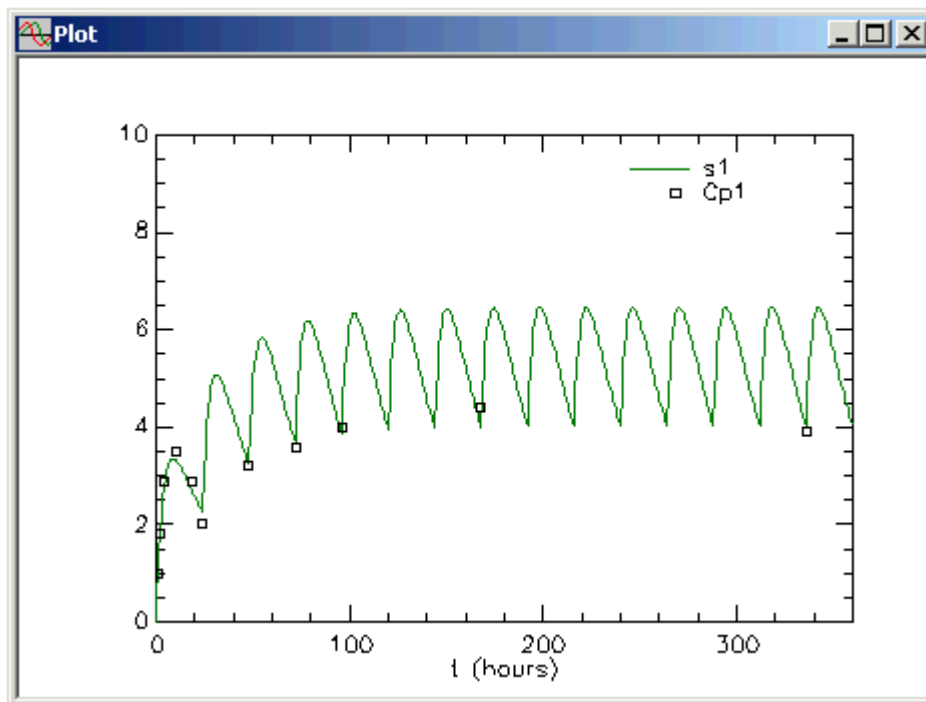
- f. View all data by setting the X – Axis scale maximum to 360, and the Y – Axis minimum and maximum to 0 and 10 respectively. Your plot will appear as follows:



You can see that, while the initial estimates are reasonable, there is a constant over prediction of the data. The extent to which this over prediction occurs is an initial indication that there may not be enough “movement” in the two parameters k_a and k_e to permit a description of the data, and that another strategy will have to be employed. First, however, you can Fit the model to the data.

Leave the **Plot** window open.

9. 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 will be updated as follows:



The Fit actually appears quite reasonable. The statistics associated with the fit are shown below:

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval
Vdrug	66.32769	4.59842e+000	6.93289e+000	55.72372 76.93166
ka	0.26783	2.78469e-002	1.03971e+001	0.20362 0.33205
ke	0.03448	2.76677e-003	8.02372e+000	0.02810 0.04086
----- Derived Variables -----				
k(0,2)	0.03448	2.76677e-003	8.02372e+000	0.02810 0.04086
k(2,1)	0.26783	2.78469e-002	1.03971e+001	0.20362 0.33205

	Objective	Scaled Data Variance
s1 : Cpl	-2.574591e+000	4.906265e-001

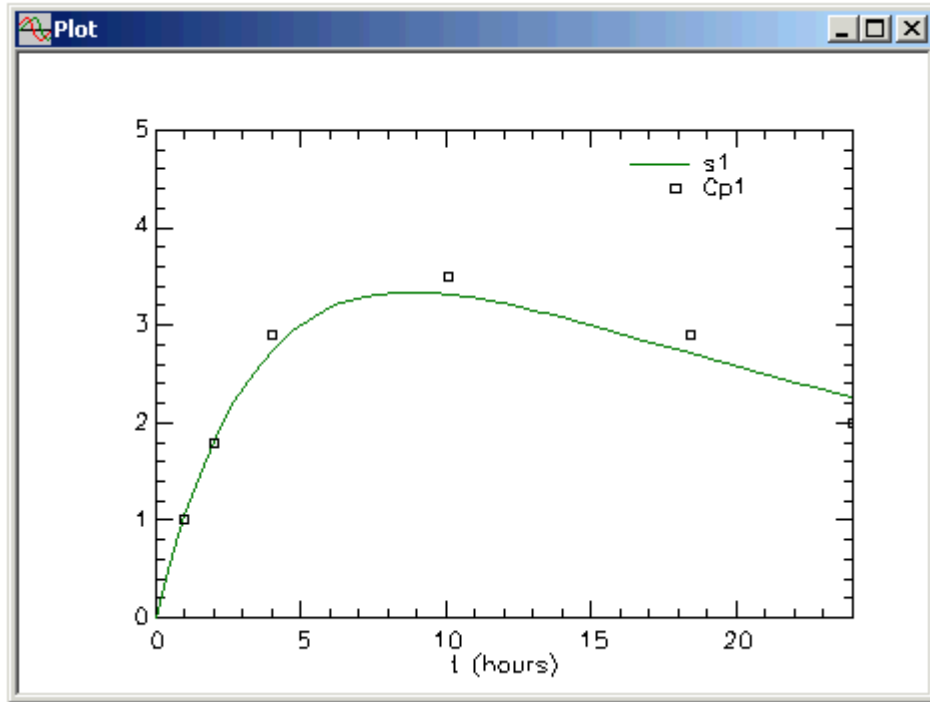
Total objective	-2.574591e+000	
AIC	-4.720529e-003	
BIC	6.762407e-002	

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

- b. View the model predictions to 24 hours.

While the Fit of all data appears reasonable, you should examine the data during the first 24 hours. Other data are collected infrequently meaning there is not much transient information about the drug kinetics; this information is available only when samples are frequent.

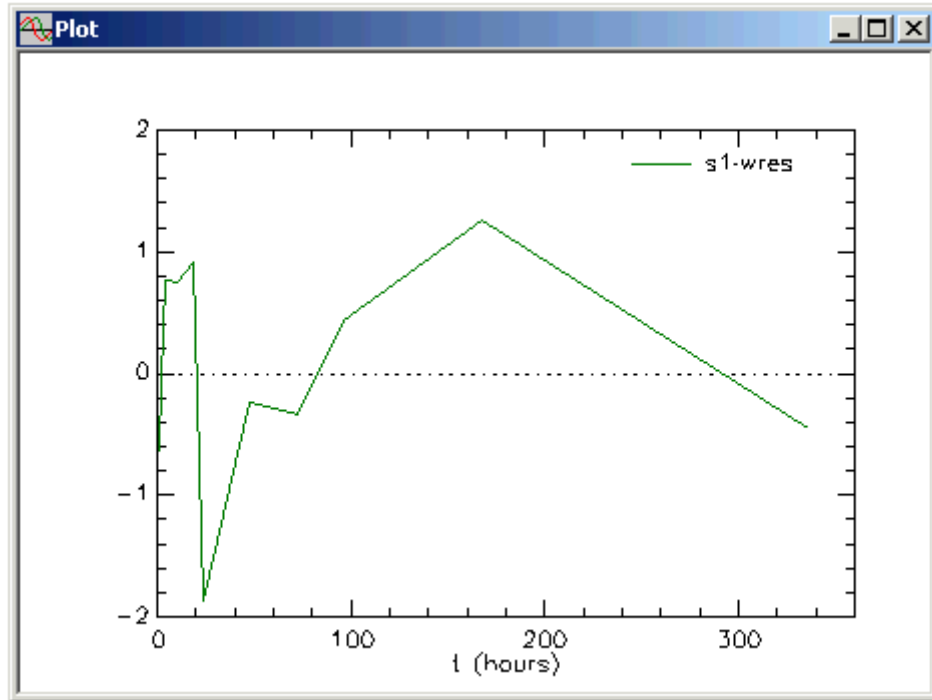
A plot of the data to 24 hours (X – Axis maximum is 24 hours, Y – Axis minimum and maximum are 0 and 5 respectively) is shown below:



You can see that the model, while predicting nicely the first two data, under predict the next three, and then over predict the data.

- c. View the weighted residuals.

The best way to visualize the potential problems with this model fit are to examine the weighted residuals (**s1_wres**). If you plot these (X – Axis maximum of 360, Y – Axis minimum and maximum of -2 and 2 respectively), you will obtain the following plot:



Here the systematic deviations around zero are obvious, and as a result, you must modify your model by incorporating a new strategy.


Close all open windows.

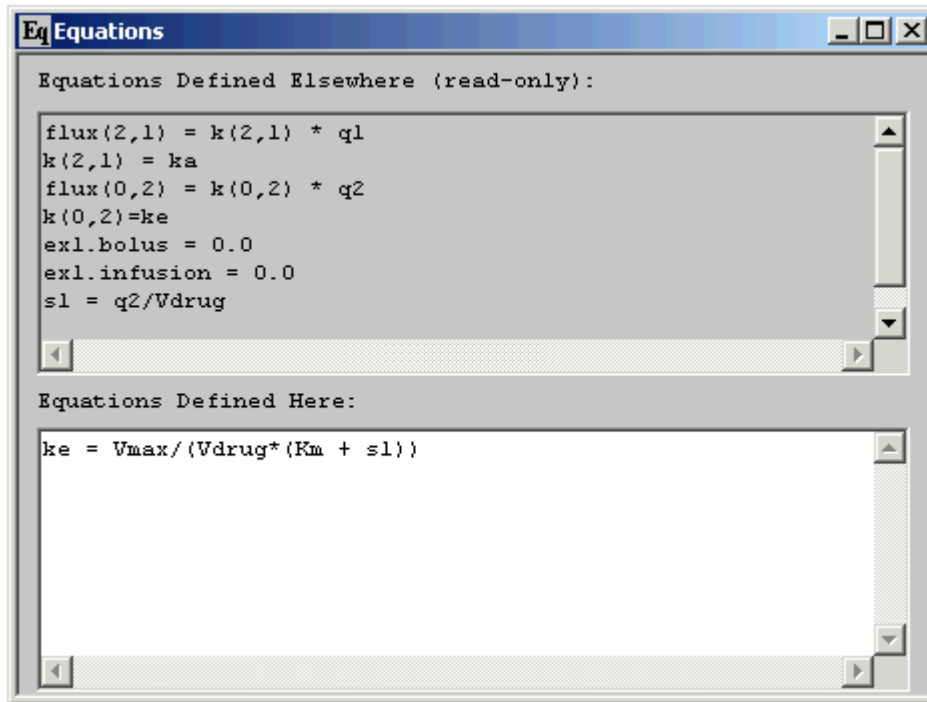
Part 2. Introduce a nonlinear loss from Compartment 2.

In this part of the Case Study, you will create a non-linear elimination with Michaelis-Menten characteristics; you are doing this because literature information indicates this type of elimination for the drug under study. The equation will be:

$$k_e = V_{\max}/(V_{\text{drug}}*(K_m + s_1))$$

where **s1** is the model predicted concentration of the drug.


1. Create a nonlinear k_e .
 - 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 “ $k_e = V_{\max}/(V_{\text{drug}}*(K_m + s_1))$ ”. The **Equations** dialog box will appear as follows:

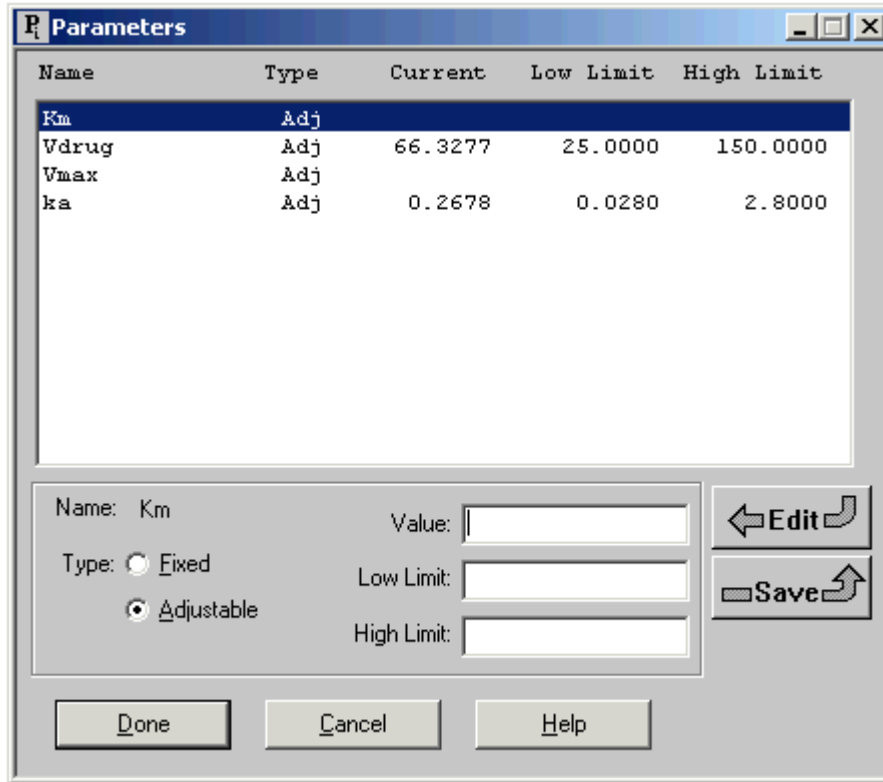


This introduces two new parameters in your model, V_{max} and K_m .

- c. Close the **Equations** dialog box.
2. Enter the parameter values.

From the literature, you can use 25 and 6 as initial estimates for V_{max} and K_m respectively.

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



The screenshot shows a dialog box titled "Parameters" with a table of parameters and their settings. The table has columns for Name, Type, Current, Low Limit, and High Limit. The parameters listed are Km, Vdrug, Vmax, and ka. Below the table, there are input fields for Name, Value, Type (Fixed or Adjustable), Low Limit, and High Limit. There are also buttons for Edit, Save, Done, Cancel, and Help.

Name	Type	Current	Low Limit	High Limit
Km	Adj			
Vdrug	Adj	66.3277	25.0000	150.0000
Vmax	Adj			
ka	Adj	0.2678	0.0280	2.8000

Name: Km Value:

Type: Fixed Adjustable

Low Limit:

High Limit:

Buttons: Edit, Save, Done, Cancel, Help

Initial estimates for V_{drug} and ka can be those from the previous best fit.

Enter the following values for the remaining parameters:

$V_{max} = 25$ (low limit 5, high limit 200)

$Km = 6$ (low limit 1, high limit 20)

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



Name	Type	Current	Low Limit	High Limit
Km	Adj	6.0000	1.0000	20.0000
Vdrug	Adj	66.3277	25.0000	150.0000
Vmax	Adj	25.0000	5.0000	100.0000
ka	Adj	0.2678	0.0280	2.8000

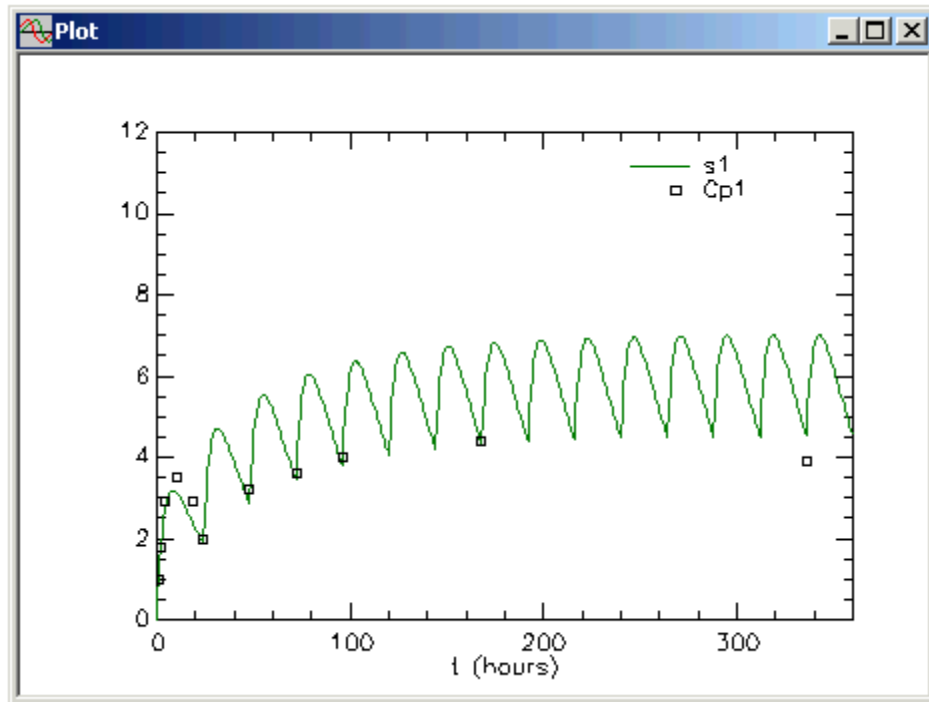
Name: Vmax Value: 25

Type: Fixed Adjustable

Low Limit: 5.00000000 High Limit: 100.00000000


Buttons: Done, Cancel, Help, Edit, Save

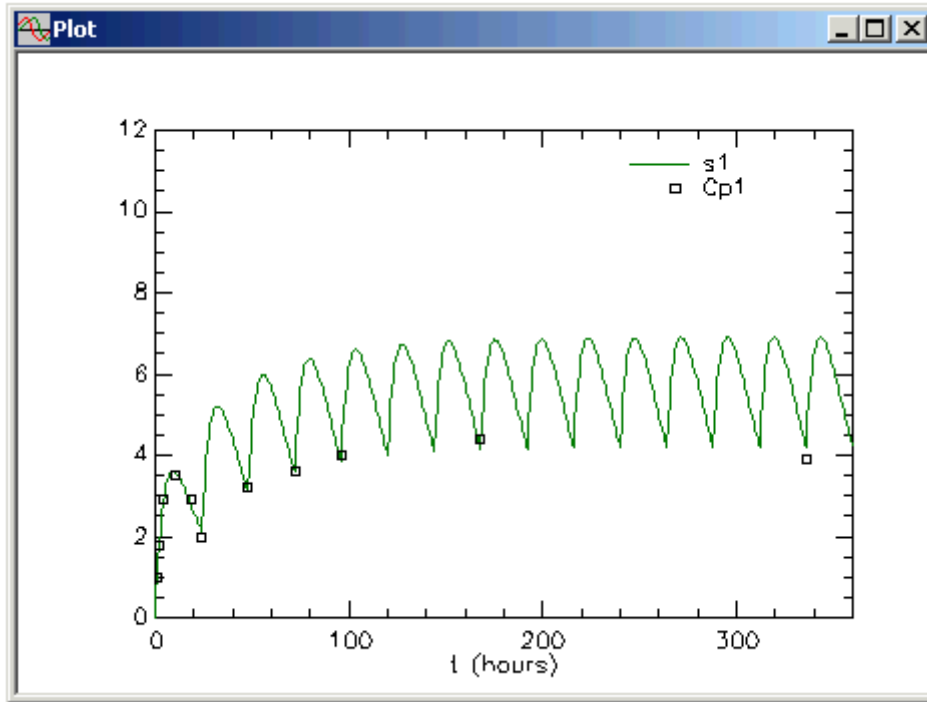
- b. Click **Done**.
3. Solve your model and view the solution.
 - a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar**, click **Solve** .
 - b. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . Depending upon your previous plot, you will probably need to change the variables in the **Current Selection** pane in the **Plot and Table Variables** dialog box to **s1** and **Cp1**, and change the Y – Axis minimum and maximum to 0 and 10 respectively. Your plot should appear as follows:



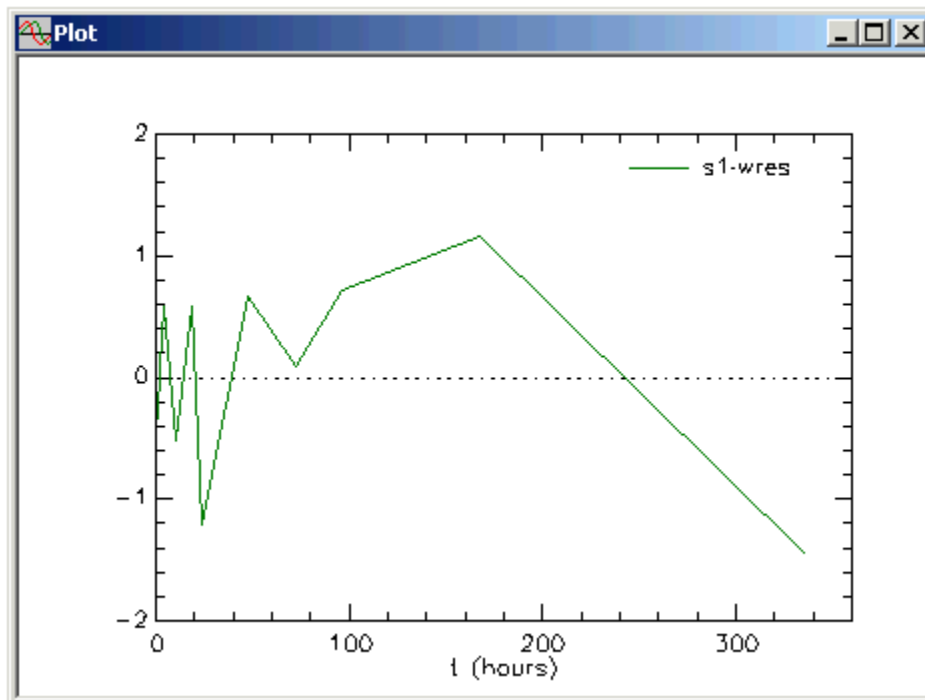
You can see that the initial parameter estimates are quite reasonable.

Leave the **Plot** window open.

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** . When you have “Fitted” your model to your data, your plot should be updated as follow:




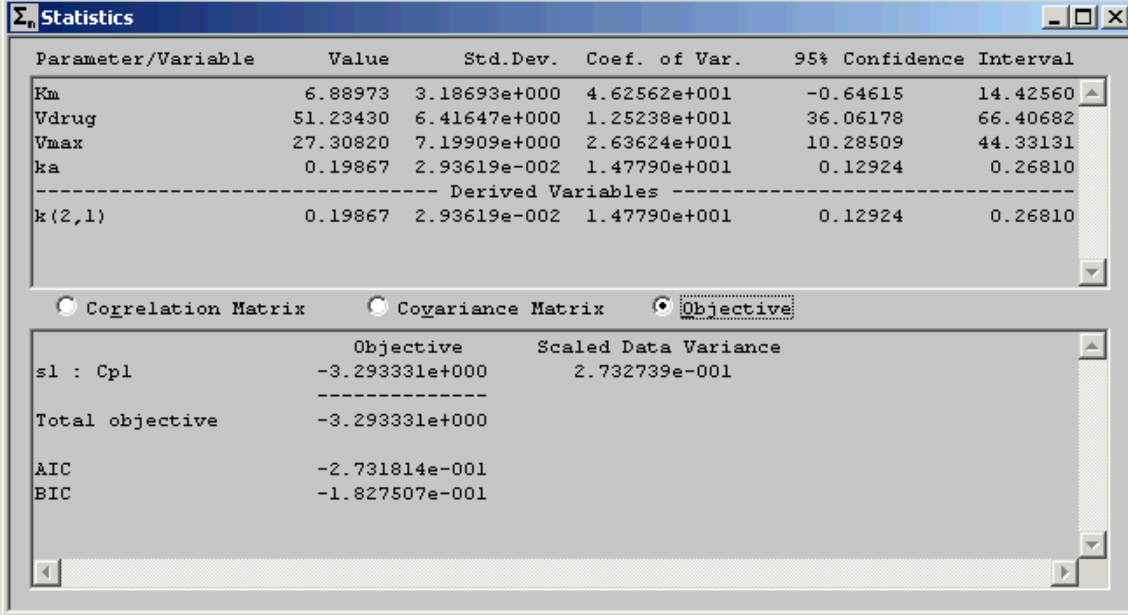
If you view the weighted residuals, you will obtain:



The random scatter around zero has improved from the previous fit.

Return to a plot of **s1** and **Cp1**.

- 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
K_m	6.88973	3.18693e+000	4.62562e+001	-0.64615 14.42560
V_{drug}	51.23430	6.41647e+000	1.25238e+001	36.06178 66.40682
V_{max}	27.30820	7.19909e+000	2.63624e+001	10.28509 44.33131
k_a	0.19867	2.93619e-002	1.47790e+001	0.12924 0.26810
----- Derived Variables -----				
$k(2,1)$	0.19867	2.93619e-002	1.47790e+001	0.12924 0.26810

	Objective	Scaled Data Variance
s1 : Cpl	-3.293331e+000	2.732739e-001

Total objective	-3.293331e+000	
AIC	-2.731814e-001	
BIC	-1.827507e-001	

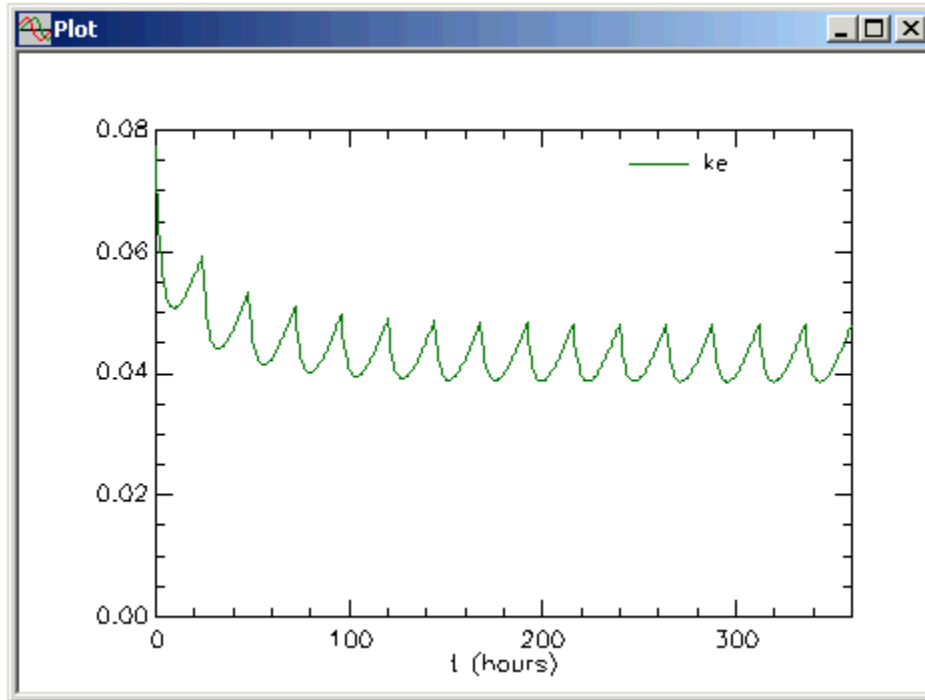
All parameters are estimated with good precision. The negative value for the 95% confidence interval for K_m , however, is troubling. To deal with this, you will include the population information from the literature for V_{max} and K_m .

- c. Close the **Statistics** window. Leave the **Plot** window open.

5. View ke .

It is useful to see how nonlinear elimination is characterized by viewing the function ke (remember this is now a function with Michaelis-Menten characteristics, and not a constant as was the case in Part 1.)

- a. With the **Plot** window active (click in the **Plot** window), in the **Set** menu, click **Plot and Table Variables**. The **Plot and Table Variables** dialog box will open.
- b. Select the **List All Variables** check box. A list of all variables that can be plotted will appear. Scroll through the list until you find **ke**. Click **ke** to move it to the **Current Selection** pane. Click **Done**. The following plot will appear (the Y – Axis minimum and maximum have been set to 0 and 0.08 respectively):



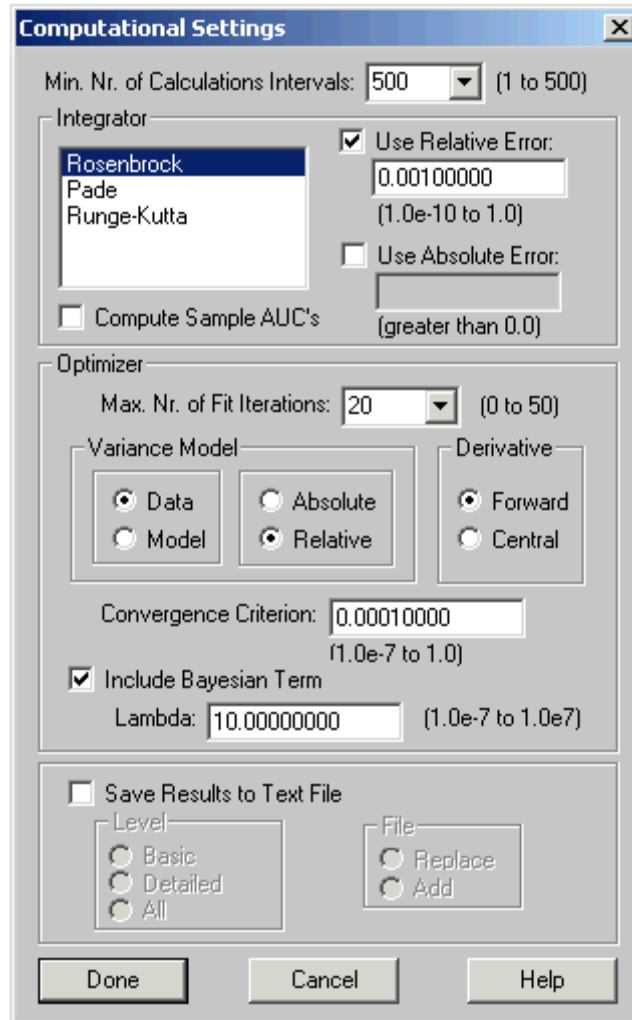
You can clearly see how elimination changes with changing drug concentration.


- c. Return to a plot of **Cp1** and **s1**. Close the **Plot** window.

Part 3. Add prior information on V_{max} and K_m .

In this part of the case study, you will take advantage of the fact that from the literature, values for V_{max} and K_m are known to be 27.1 mg/hr (SD = 5.0) and 6.0 mg/L (SD 2.0). These are incorporated into your model using SAAM II's Bayesian feature.

1. In the **Compute** menu, click **Computational Settings**. The **Computational Settings** dialog box will open.
2. Select the **Include Bayesian Term** check box. The **Computational Settings** dialog box will appear as follows:



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

Name	Type	Current	Low Limit	High Limit	Pop. Mean	SD
Km	Adj	6.8897	1.0000	20.0000		
Vdrug	Adj	51.2343	25.0000	150.0000		
Vmax	Adj	27.3082	5.0000	100.0000		
ka	Adj	0.1987	0.0280	2.8000		

Name: Km

Value: Mean:

Type: Fixed Adjustable Bayesian

Low Limit: SD:

High Limit:

Notice there is now a third option for each parameter, “Bayesian”. For those parameters whose Type is Bayesian, you can enter a population mean and standard deviation.

5. Be sure *Km* is the active parameter. Click on the **Bayesian** radio button, and type “6” and “2” in the **Mean** and **SD** boxes respectively. Click **Save**.
6. Click *Vmax* to make it the active parameter. Click on the **Bayesian** radio button, and type “27.1” and “5” in the **Mean** and **SD** boxes respectively. Click **Save**. The **Parameters** dialog box will appear as follows:

Name	Type	Current	Low Limit	High Limit	Pop. Mean	SD
Km	Bay	6.8897	1.0000	20.0000	6.0000	2.0000
Vdrug	Adj	51.2343	25.0000	150.0000		
Vmax	Bay	27.3082	5.0000	100.0000	27.1000	5.0000
ka	Adj	0.1987	0.0280	2.8000		

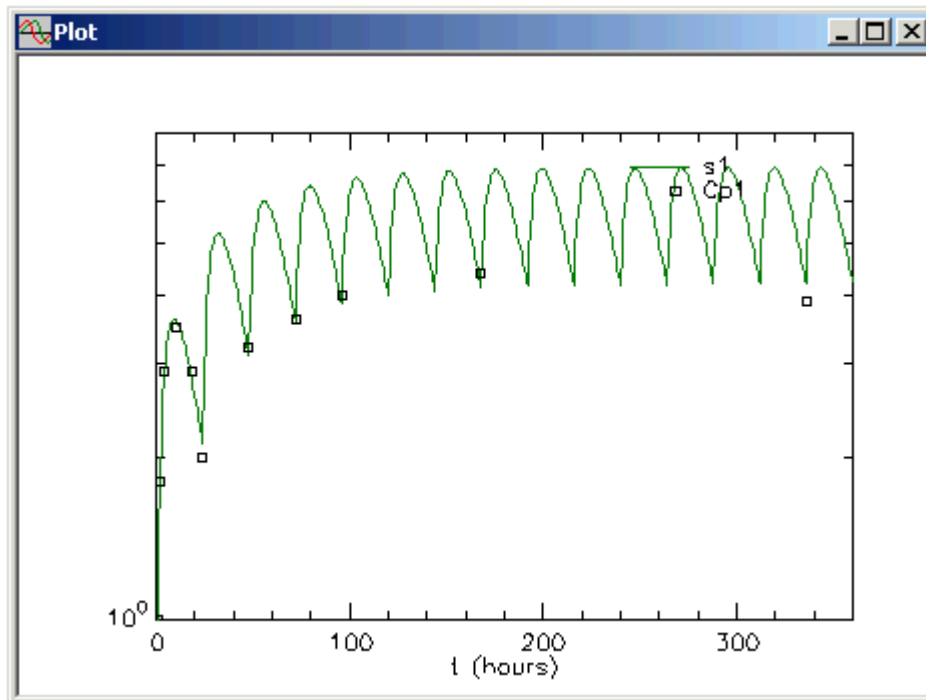
Name: Km Value: 6.88972797 Mean: 6.00000000

Type: Fixed Low Limit: 1.00000000 SD: 2.00000000

Adjustable

Bayesian High Limit: 20.00000000

- Click **Done**.
- Solve your model, and view **s1** and **Cp1**; the plot will appear as follows (semi-log with Y – Axis minimum and maximum are respectively 0 and 8):



The solution is the same as the best fit from Part 1; this is because the initial parameter values in the **Parameters** dialog box are those following the best fit. Leave the **Plot** window open.

- Fit the model, and view the solution. The plot will be updated, but does not change from above. Open the **Statistics** window; it will appear as follows:

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval
Km	6.50061	1.50365e+000	2.31309e+001	3.09912 9.90210
Vdrug	50.49447	4.24792e+000	8.41264e+000	40.88500 60.10394
Vmax	26.43345	3.39408e+000	1.28401e+001	18.75551 34.11140
ka	0.19544	2.02759e-002	1.03745e+001	0.14957 0.24131
----- Derived Variables -----				
k(2,1)	0.19544	2.02759e-002	1.03745e+001	0.14957 0.24131

	Objective	Scaled Data Variance
sl : Cpl	-2.784955e+000	2.516991e-001
Bayesian	3.604303e-001	
Total objective	-2.424525e+000	
AIC	9.129143e-002	
BIC	1.999355e-001	

You can see there are some small changes in the values for the parameters. The big changes come in the error estimates. Notice in particular that the 95% confidence interval for Km is much improved.

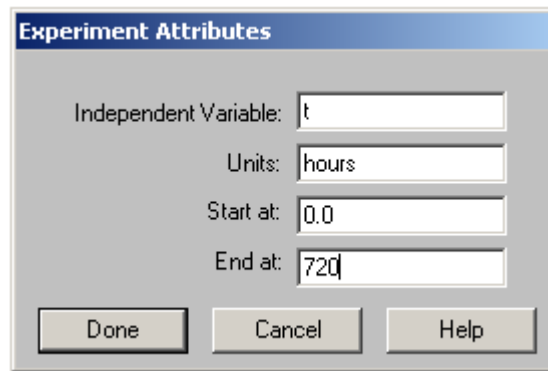
The Vmax and Km parameter estimates here are obtained by means of Bayesian estimation. Where the data from the individual are “sparse” (few in number), many individual-specific parameters approximate the estimates for the typical individual given by the population model (determined by “prior” information, usually expressed as the mean and SD of the parameter in the *same* population). This is because as the amount of information (data) decreases, individual-specific parameter Bayesian estimates become increasingly constrained by the “Bayes penalty term” in the Bayes objective function to be “close to” the typical individual parameter estimates. As the amount of data per individual increases (approaching a “rich data” scenario), the Bayesian term becomes less influential in the objective function, and the individual’s parameter estimate is less constrained, and therefore allowed to “drift” further from the typical value in the population.

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

Part 4 (Optional). Include all data.

In this part of the case study, you will add the data following the dose increase to 400mg/day. The length of the study will now run to 30 days, or 720 hours. If you do not wish to do this part of the case study, you may now **Quit** the **SAAM II Compartmental** application. You may save the study file for future reference if you wish.

1. Change the time of the experiment.
 - a. In the **Set** window, click **Experimental Attributes**. The **Experimental Attributes** box will open.
 - b. Change the “End At” time from “360” to “720”. The **Experimental Attributes** dialog box will appear as follows:



- c. Click **Done**.
 2. Add the new dosing schedule.
 - a. Double-click **ex1** to open the **Exogenous Input** dialog box.
 - b. Type “400” in the **Initial Amount** box.
 - c. Type “360” in the **Event Start** box.
 - d. 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	300.000	-	0.000	-	24.000	14
Bolus	400.000	-	360.000	-	24.000	14

Input Type:

Bolus
 Infusion
 Primed Infusion
 Equation

Initial Amount:

Constant Rate:

Event Start:

Event Stop:

Repeat Every:

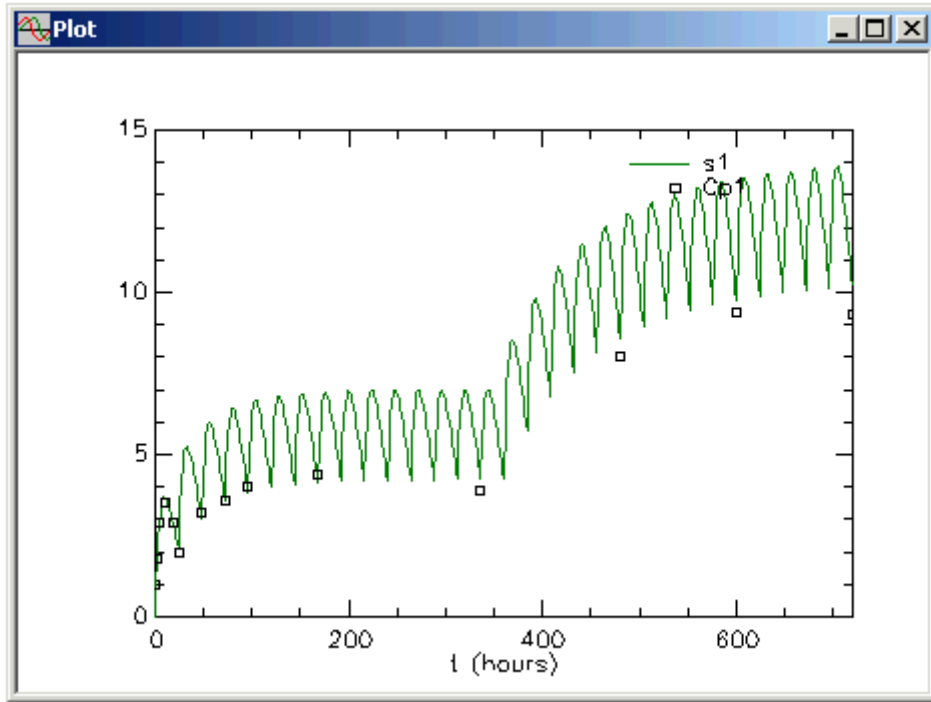
Nr. of Repeats:

Equation:

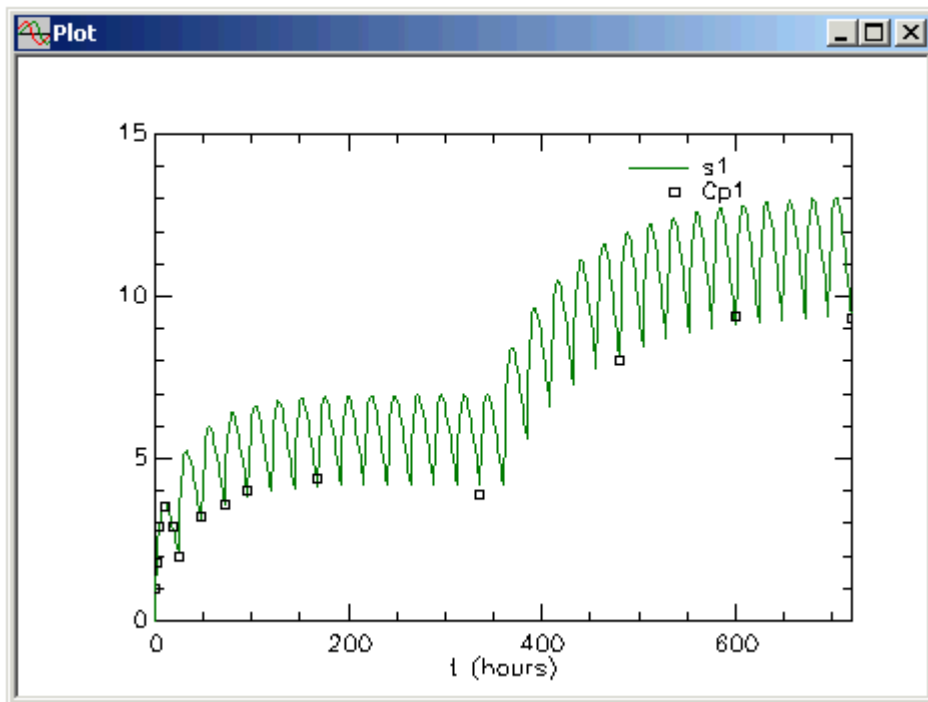
- e. Click **Done**.
3. You will want to start this part of the exercise not using the Bayesian priors to see if the additional information will help in your parameter estimates, i.e. will any of the 95% confidence intervals go negative.

In the **Computational Settings** dialog box, click the **Include Bayesian Term** check box to deactivate this option.

4. You need to reweight all data. In the **Data** window, and remove “(-+)” from the datum at 480 hours.
5. You can check if you wish the **Parameters** dialog box; you can use these values as a starting point. Solve the model, and view the solution. The plot of **s1** and **Cp1** will appear as follows (linear with Y – Axis minimum and maximum equal to 0 and 15 respectively):



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



Open the **Statistics** window. It will appear as follows:

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
Km	5.83802	4.25585e-001	7.28989e+000	4.88976	6.78628
Vdrug	49.14028	3.16495e+000	6.44064e+000	42.08832	56.19223
Vmax	24.93731	7.99628e-001	3.20655e+000	23.15562	26.71899
ka	0.18964	1.56768e-002	8.26647e+000	0.15471	0.22457
----- Derived Variables -----					
k(2,1)	0.18964	1.56768e-002	8.26647e+000	0.15471	0.22457

	Objective	Scaled Data Variance
s1 : Cpl	-2.946893e+000	2.100460e-001

Total objective	-2.946893e+000	
AIC	-1.973653e-001	
BIC	-8.324795e-002	

Notice the addition of the three additional data resulted in excellent parameter estimates with acceptable 95% confidence intervals.

Suppose you now re-introduce the Bayesian option and include the prior information on V_{max} and K_m . The plot will not change appreciably; the statistics will appear as follows:

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
Km	5.86664	4.09267e-001	6.97618e+000	4.97492	6.75835
Vdrug	49.24902	3.07031e+000	6.23425e+000	42.55940	55.93864
Vmax	24.99200	7.69664e-001	3.07964e+000	23.31505	26.66895
ka	0.19015	1.52384e-002	8.01397e+000	0.15695	0.22335
----- Derived Variables -----					
k(2,1)	0.19015	1.52384e-002	8.01397e+000	0.15695	0.22335

	Objective	Scaled Data Variance
s1 : Cpl	-2.578258e+000	2.001064e-001
Bayesian	2.992102e-001	

Total objective	-2.279048e+000	
AIC	9.191465e-002	
BIC	2.126316e-001	

This illustrates that, in this case, there is enough information in the data to estimate all parameters with precision, and the inclusion of the prior information does not contribute very much to the overall results.

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

- The introduction of prior information about parameters in your model can increase the accuracy of the estimates, and their errors.
- The contribution of this information results in a balance between the information content in the data themselves, and the priors.
- When there is enough information in the data to estimate the parameters and their precision, the priors contribute less information.

Data for this case study

DATA

(FSD 0.1)

#

Dosing is 300mg/day for first 15 days

#

t	Cp1
---	-----

0	n
---	---

1	1
---	---

2	1.8
---	-----

4	2.9
---	-----

10.1	3.5
------	-----

18.4	2.9
------	-----

24	2
----	---

48	3.2
----	-----

72	3.6
----	-----

96	4
----	---

168	4.4
-----	-----

336	3.9
-----	-----

#

Dose is increased to 400mg/day for last 15 days

#

480	8
-----	---

600	9.4
-----	-----

720	9.3
-----	-----

END