

Drug Interaction Between AZT and Probenecid

Case Study

- How to link models to reflect drug interaction
- How to incorporate a competitive inhibition model in drug metabolism
- How to obtain initial estimates of K_i from your data

This page is intentionally left blank

Drug Interaction Between AZT and Probenecid

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

- How to link models to reflect drug interaction.
- How to incorporate a competitive inhibition model in drug metabolism.
- How to obtain initial estimates of K_i from your data.

Data Required

The data file for this case study is

AZT_Probenecid.dat

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

Introduction

Probenecid (PBD) inhibits the metabolism of AZT competitively. In this Case Study, you are given plasma concentration-time data for AZT and probenecid, and are required to establish a model that characterizes the pharmacokinetics of both drugs, and the inhibition of AZT metabolism by Probenecid.

AZT is given in a dose of 200 mg every 6 hr orally for 144 hours. There are two components to the clearance of AZT from the body: renal and metabolic. The renal clearance of the drug (CL_r) may be fixed at 24 L/hr; it is assumed that probenecid has no effect on this clearance. Metabolic clearance is assumed to be first order, and is inhibited by probenecid by a competitive mechanism. Metabolic clearance will be written as:

$$CL_m = CL_{mo}/(1+(C_{pbd}/K_i))$$

where CL_{mo} is the baseline metabolic clearance of AZT (no probenecid present), C_{pbd} is the probenecid plasma concentration and K_i is the inhibition constant for the competitive inhibition interaction.

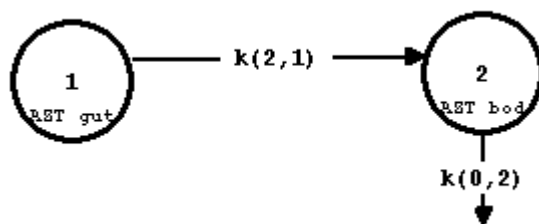
Although this is not really valid, we will assume complete bioavailability of the orally administered AZT. In addition, we will assume that the absorption rate for probenecid is first-order, and that the absorption rate constant is 0.30 per hr. The model you will use is the single-compartment model with absorption. In the model, there are 8 parameters, but two of them are fixed. The adjustable parameters are: 2 volume terms, 2 rate constants, the baseline metabolic clearance of AZT (CL_{mo}) and the K_i that describes the inhibition.

Probenecid dosing (500 mg q6h) begins at 24 hr (Day 2). Assume complete bioavailability of this drug also, and the single-compartment model with absorption. The units for both sets of data are mg/L.

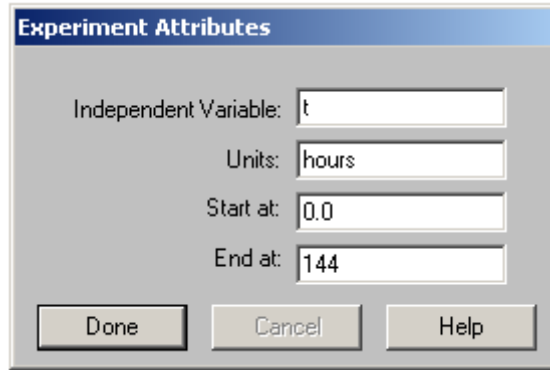
Part 1. Create the model for AZT and analyze the AZT data for the first 24 hours.

The first step will be to create the model for AZT kinetics, and to analyze the data for the first 24 hours (before treatment with Probenecid was started.)

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:

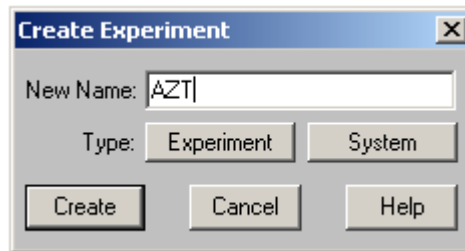


3. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open.
 - a. Change the entry in the **Units** box to “hours”.
 - b. Enter “144” in the **End at** box. The **Experiment Attributes** dialog box will appear as follows:

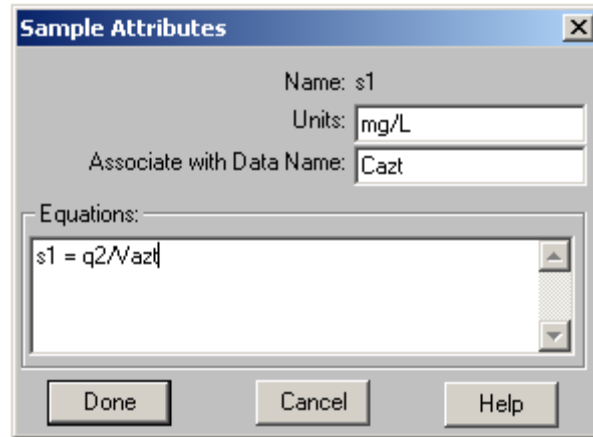


- c. Click **Done**.

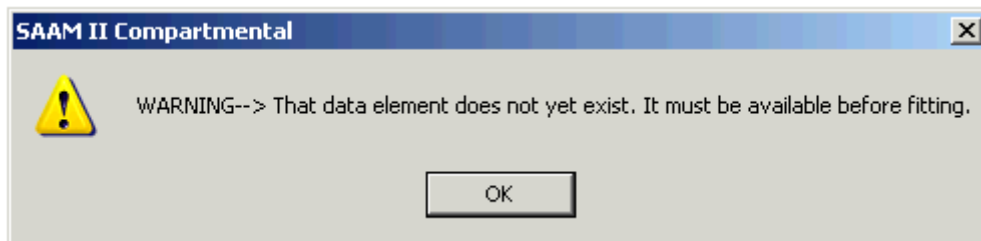
The **Create Experiment** dialog box will appear on the **Drawing Canvas**. Type “AZT” in the **New Name** box. The **Create Experiment** dialog box will appear as follows:



- d. Click **Create**. Notice “AZT” appears as the name under “Experiment” in the **SAAM II Toolbox**.
4. Create a sample.
- In the **SAAM II Toolbox**, click **Sample**.
 - Click Compartment **q2**, then click on the **Drawing Canvas**. The sample **s1** will appear.
 - Double-click **s1** to open the **Sample Attributes** dialog box.
 - Type “mg/L” in the **Units** box.
 - Type “Cazt” in the **Associate with Data Name** box.
 - Edit the sample equation “s1 = q2” to read “s1 = q2/Vazt”. 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 200 mg of AZT were given every 6 hours. Since the experiment lasted 144 hour, 23 doses were given.

- 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 "200" in the **Initial Amount** box.
- Enter "0" in the **Event Start** box.

- g. Enter "6" in the **Repeat Every** box.
- h. Enter "23" in the **Nr. of Repeats** 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	200.000	-	0.000	-	6.000	23


Input Type:

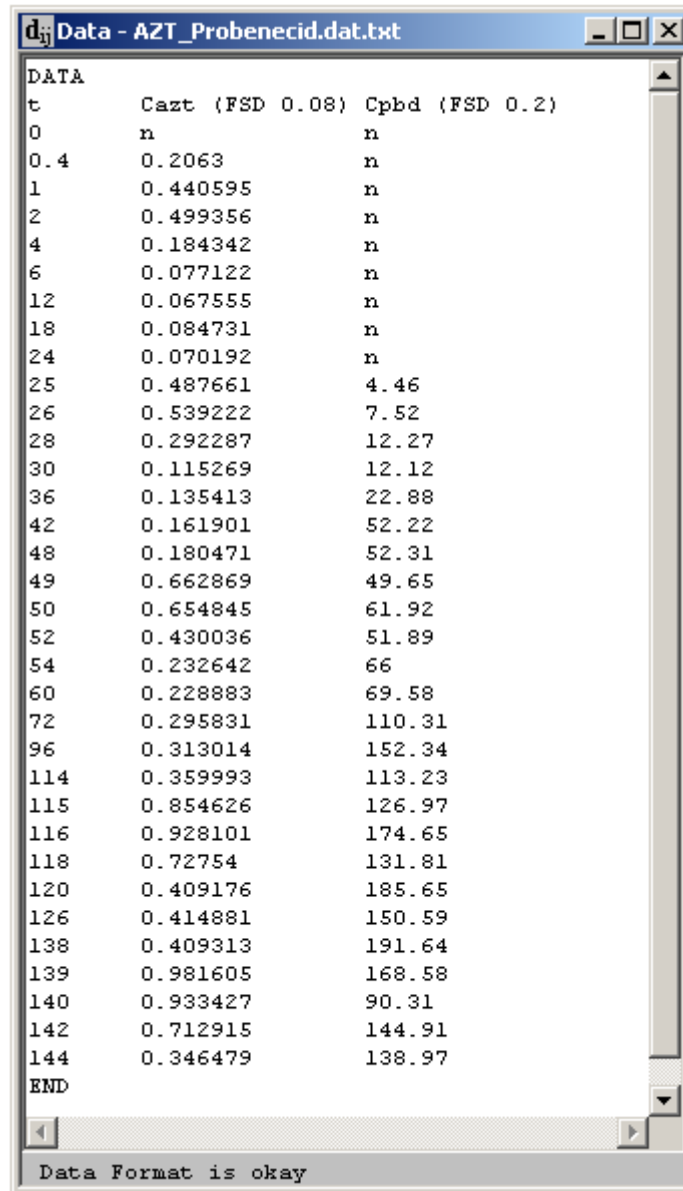
Bolus
 Infusion
 Primed Infusion
 Equation

Initial Amount:
Constant Rate:
Event Start:
Event Stop:
Repeat Every:
Nr. of Repeats:

Equation:

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

- j. Click **Done**.
6. Add the data to your model.
 - a. In the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data** . The **Data** window will open.
 - b. In the **File** menu, click **Open**. The file **AZT_Probenecid.dat** should appear in the list (if it does not, find the folder where you put this data file).
 - c. Double-click **AZT_Probenecid.dat**. The data file contains the plasma AZT and Probenecid data following the oral dosing scheme. The **Data** window should appear as follows:



t	Cazt (FSD 0.08)	Cpbd (FSD 0.2)
0	n	n
0.4	0.2063	n
1	0.440595	n
2	0.499356	n
4	0.184342	n
6	0.077122	n
12	0.067555	n
18	0.084731	n
24	0.070192	n
25	0.487661	4.46
26	0.539222	7.52
28	0.292287	12.27
30	0.115269	12.12
36	0.135413	22.88
42	0.161901	52.22
48	0.180471	52.31
49	0.662869	49.65
50	0.654845	61.92
52	0.430036	51.89
54	0.232642	66
60	0.228883	69.58
72	0.295831	110.31
96	0.313014	152.34
114	0.359993	113.23
115	0.854626	126.97
116	0.928101	174.65
118	0.72754	131.81
120	0.409176	185.65
126	0.414881	150.59
138	0.409313	191.64
139	0.981605	168.58
140	0.933427	90.31
142	0.712915	144.91
144	0.346479	138.97

END

Data Format is okay

The weighting scheme is FSD. The AZT data are assumed to have an 8% coefficient of variation while that for probenecid is 20%. Note there are no probenecid data (Cpbd) until 25 hours; this is because the first dose of probenecid was 24 hours into the experiment.

- d. Close the **Data** window.
7. Enter the parameter values.

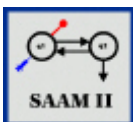


Parameter estimates for AZT. Although your interest is in characterizing the inhibition of AZT metabolism by probenecid, there are AZT data for the first 24 hours which can be analyzed first. This will allow you to estimate absorption and, knowing renal clearance is 24L/hr, you can estimate the metabolic clearance, CL_{mo} , as the difference between total cl and renal clearance. By fitting these data first, you can simulate the model predictions beyond 24 hours, and obtain a picture of how probenecid affects AZT metabolism. The first step will be to write $k(0,2)$ to incorporate the two clearance pathways.




- Double-click $k(0,2)$ to open the **Loss Attributes** dialog box. In the **Equations** pane, type “ $k(0,2) = (CL_r + CL_{mo})/V_{azt}$ ”. The **Loss Attributes** dialog box will appear as follows:

Click **Done**.



The loss parameter $k(0,2)$. For the initial analysis of the data, the inhibition due to Probenecid is not included. Thus the equation for $k(0,2)$ will need to be modified when all data are included in the modeling process.



- b. 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
CLmo	Adj			
CLr	Adj			
Vazt	Adj			
k(2,1)	Adj			

Name: CLmo Value:

Type: Fixed Low Limit:

Adjustable High Limit:

Buttons: Edit, Save, Done, Cancel, Help

Assume that the absorption rate for probenecid is first-order, and that the absorption rate constant is 0.30 per hr. Notice that there are 8 parameters, but two of these are fixed. The adjustable parameters are: 2 volume terms, 2 rate constants, the baseline metabolic clearance of AZT (CL_{mo}) and the K_i that describes the interaction. Make sure the Adjustable radio button is checked where appropriate. Enter initial values for each in turn, clicking Save after each entry.

Use appropriate values for the initial (Current) values of parameters. In order to obtain an initial estimate for CL_{mo}, consider the magnitude of the average steady-state plasma level of AZT (prior to the addition of probenecid to the regimen) from the data, and recognize that this is

$$C_{ss,av} = F \text{ Dose} / ((CL_{mo} + CL_r) * \tau)$$

where F is the bioavailability of AZT (assumed to be unity) and τ is the dosing interval (6 h).

An initial estimate of K_i can be obtained by examining the data file and noting how high the plasma concentration of AZT goes when PBD is added, and recognizing that:

$$CL_m/CL_{m0} = 1 + (s^2/K_i)$$

where s^2 is the plasma concentration of probenecid.

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

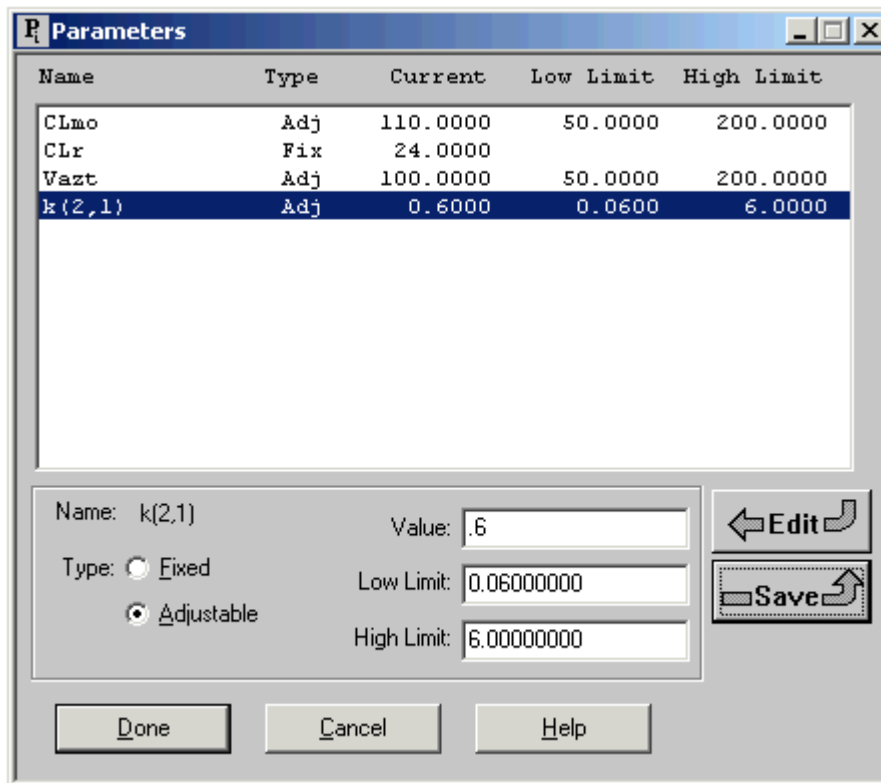
$CL_{m0} = 110$ (low limit 50, high limit 200)

$CL_r = 24$ (fixed)

$V_{azt} = 100$ (low limit 50, high limit 200)

$k(2,1) = .6$ (low limit .06, high limit 6)

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 dialog box titled "Parameters" with a table of parameters and a detailed view for the selected parameter $k(2,1)$.

Name	Type	Current	Low Limit	High Limit
CL_{m0}	Adj	110.0000	50.0000	200.0000
CL_r	Fix	24.0000		
V_{azt}	Adj	100.0000	50.0000	200.0000
$k(2,1)$	Adj	0.6000	0.0600	6.0000

Below the table, the detailed view for $k(2,1)$ is shown:

Name: $k(2,1)$ Value:

Type: Fixed Adjustable

Low Limit:


High Limit:

Buttons: Done, Cancel, Help, Edit, Save

- d. 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. In addition, because you are examining only the first 24 hours of the AZT data, you will want to unweight all data past 24 hours.

- 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.
- c. Click **Done**.
- d. In the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data** . The **Data** window will open.
- e. For each datum at 25 hours (for both AZT and Probenecid), type (-+). The **Data** window will appear as follows:



t	Cazt (FSD 0.08)	Cpbd (FSD 0.2)
0	n	n
0.4	0.2063	n
1	0.440595	n
2	0.499356	n
4	0.184342	n
6	0.077122	n
12	0.067555	n
18	0.084731	n
24	0.070192	n
25	0.487661 (-+)	4.46 (-+)
26	0.539222	7.52
28	0.292287	12.27
30	0.115269	12.12
36	0.135413	22.88
42	0.161901	52.22
48	0.180471	52.31
49	0.662869	49.65
50	0.654845	61.92
52	0.430036	51.89
54	0.232642	66
60	0.228883	69.58
72	0.295831	110.31
96	0.313014	152.34
114	0.359993	113.23
115	0.854626	126.97
116	0.928101	174.65
118	0.72754	131.81
120	0.409176	185.65
126	0.414881	150.59
138	0.409313	191.64
139	0.981605	168.58
140	0.933427	90.31
142	0.712915	144.91
144	0.346479	138.97
END		

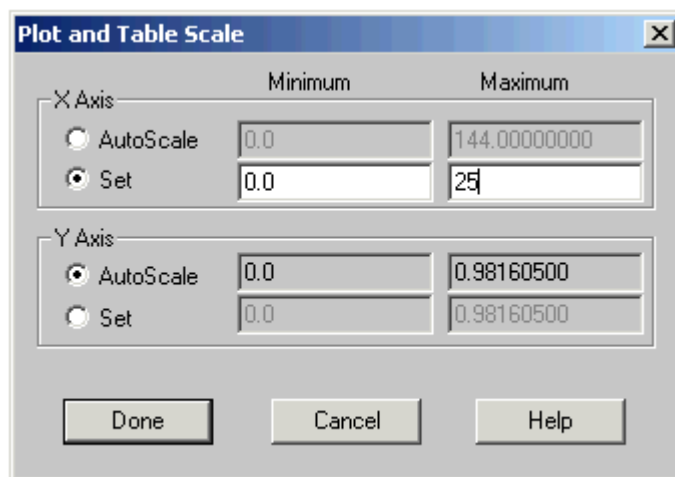


Unweighting data. Since the data after 24 hours results from the perturbation of introducing Probenecid, you do not want to include these in fitting the initial AZT data. Typing “(-)” following a single datum will unweight that datum in the fitting process. Typing “(-+)” will unweight that datum, and all data following.

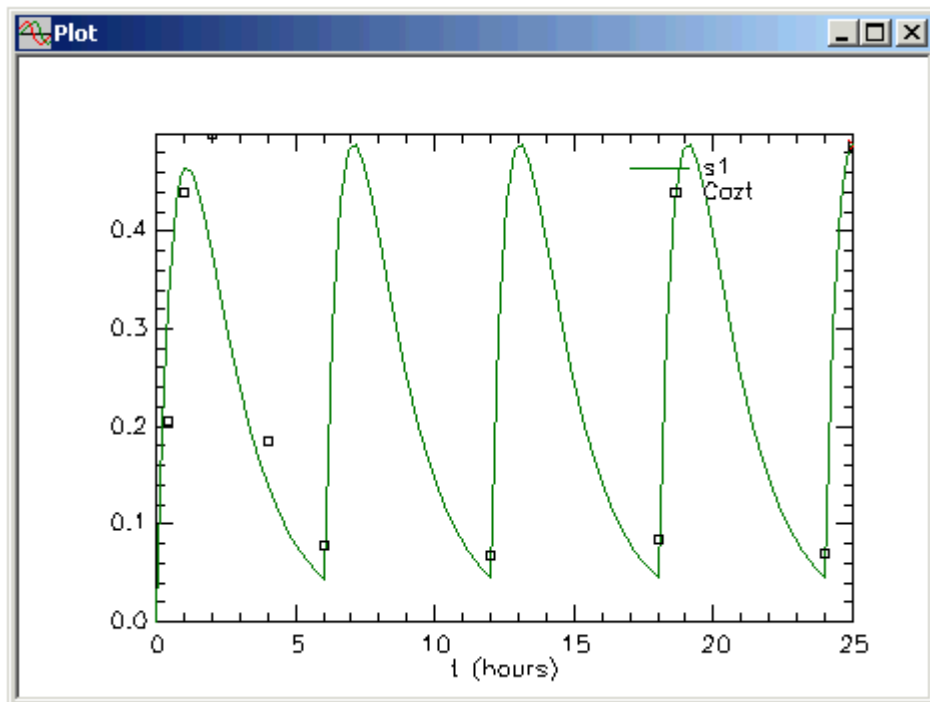


- f. Close the Data window.

- g. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar**, click **Solve** .
- h. 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.
- i. Click **s1:Cazt**; these will move to the **Current Selection** pane.
- j. Click **Done**. The plot for the full 144 hours will appear. You want to examine only the first 24 hours. In the **Set** menu, click **Plot and Table Scale**. The **Plot and Table Scale** dialog box will open. Change the X – Axis maximum to 25. The **Plot and Table Scale** dialog box will appear as follows:




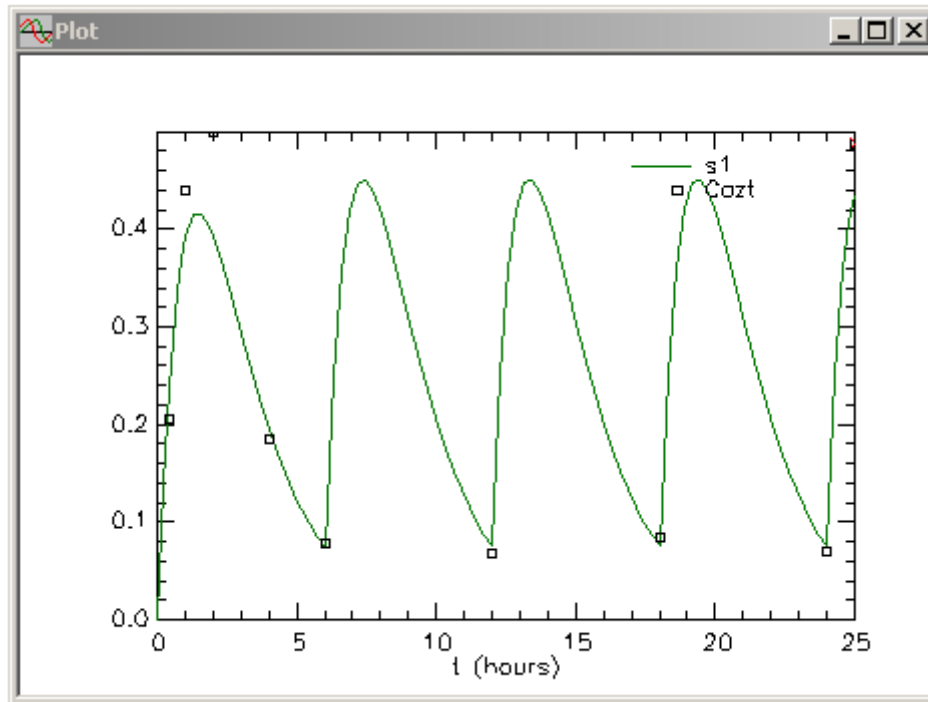
- k. Click **Done**. The following plot will appear:



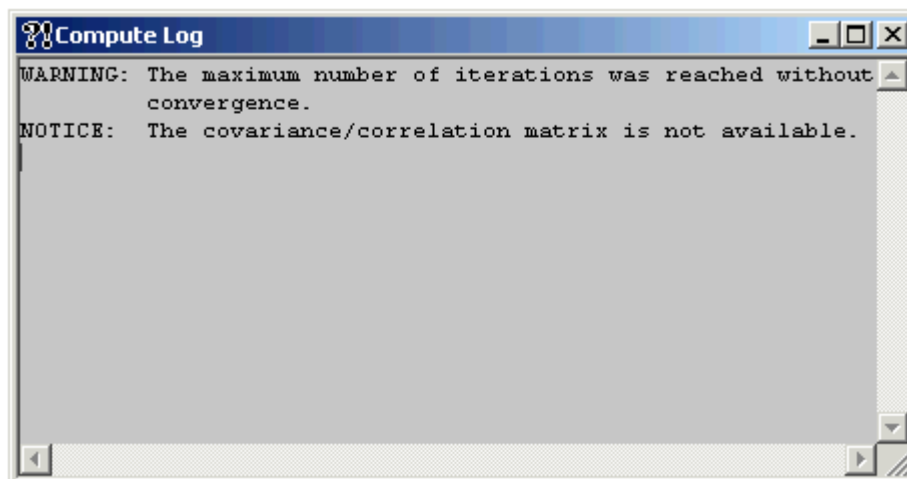
If you had not set the Minimum Number of Calculation Intervals equal to 500, you would not see the initial rise in the model predicted values. To check this, you can, if you wish, set the Minimum Number of Calculation Intervals equal to the default value of 20 and Re-Solve the model. You can also look at the plot in semi-log mode if you wish, or reset the Y-Axis scale.

The initial parameter estimates are reasonable. If you wish, you can try hand-fitting to improve the estimates. 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:



However, the Fit was not successful, and the following Compute Log will appear:



The problem is that there is not enough information in the data to 24 hours to estimate the three adjustable parameters. However, all you want is a set of parameter values which characterize these early data. This will allow you to investigate how, after the introduction of Probenecid, the data change as opposed to the model predictions with no perturbation. And it will give you a reliable set of initial parameter estimates for the AZT system.

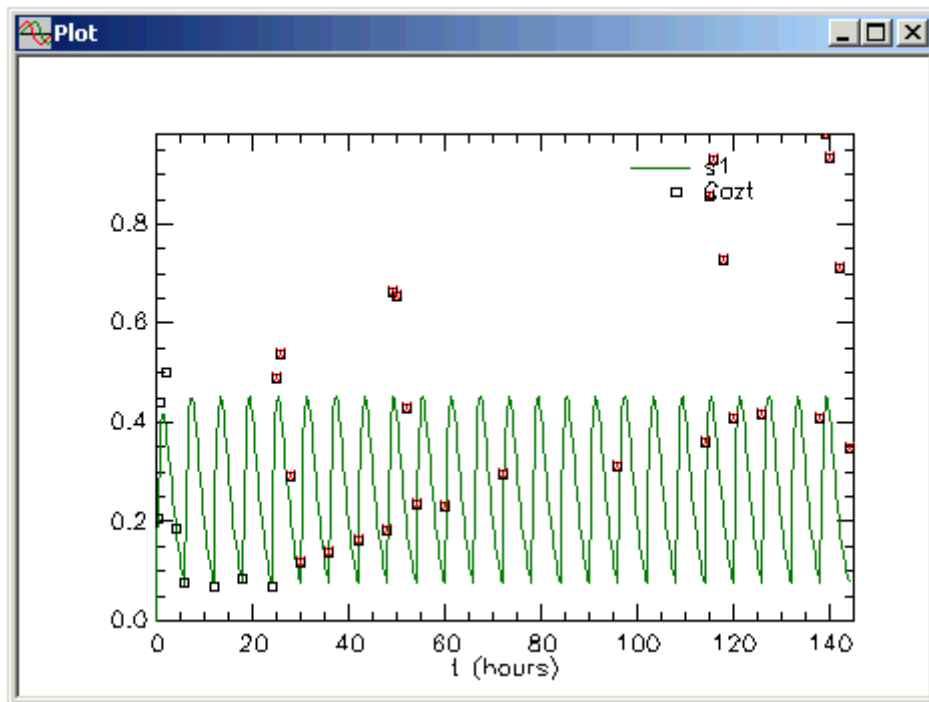
Close the **Compute Log**. Leave the **Plot** window open. Click on the window to be sure it is active.

b. Compare the model prediction with the actual data following Probenecid.

(1) In the **Set** menu, click **Plot and Table Scale**.

(2) Change the X – Axis maximum to 145.

(3) Click **Done**. Your plot will be updated as follows:



You can clearly see the effect of Probenecid. The AZT data following Probenecid (with the red “x” in them because they are unweighted) are slowly rising as a result of the inhibition which the model predicts, in the absence of Probenecid, a nadir of around 0.07mg/L.

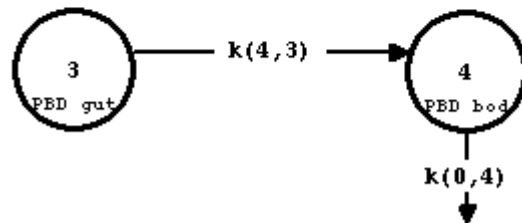
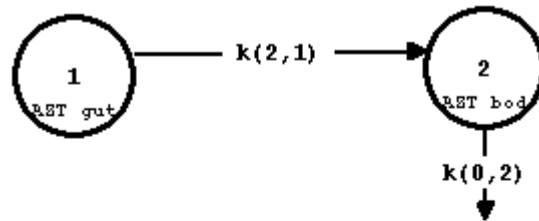
Your task now is to include the pharmacokinetic model for Probenecid, and to alter $k(0,2)$ to include inhibition.

Close all open windows.

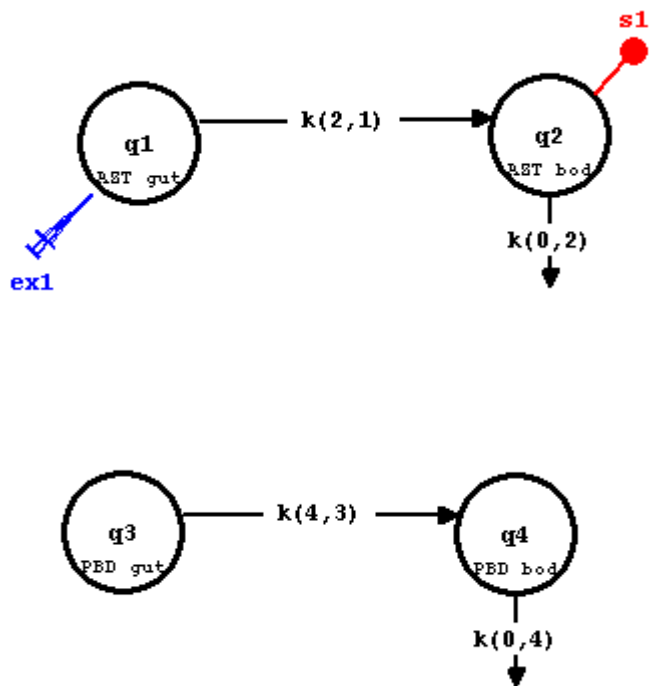
Part 2. Include Probenecid pharmacokinetics and inhibition of AZT metabolism by Probenecid in the model.

The next step in the case study will be to create the pharmacokinetic model for Probenecid, and use this to characterize the inhibition of AZT metabolism by Probenecid.

1. In the **SAAM II Toolbox**, click **Model** to be sure these tools are available.
2. Create the Probenecid pharmacokinetic model.
 - a. Add the following model to your **Drawing Canvas**:

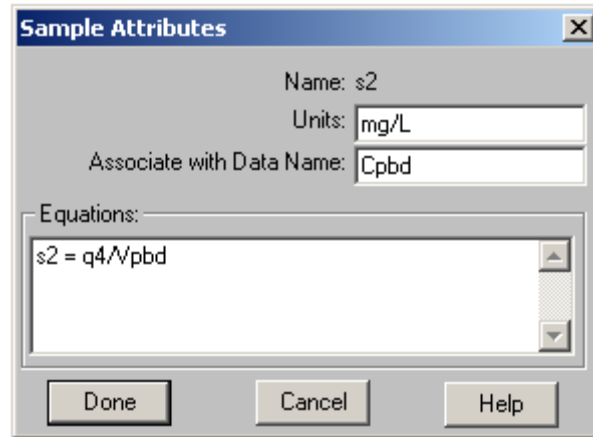


- b. In the **SAAM II Toolbox**, click **Experiment**. Your models will appear as follows:



Remember the experimental attributes have been set, and do not change as a result of including Probenecid in the model. But you need to specify the characteristics of the Probenecid experiment, and create the link with AZT kinetics.

3. Create a sample on Compartment 4.
 - a. In the **SAAM II Toolbox**, click **Experiment**. The **Experimental Attributes** dialog box will not open since the experimental attributes have been specified previously.
 - b. In the **SAAM II Toolbox**, click **Sample**.
 - c. Click Compartment **q4**, then click on the **Drawing Canvas**. The sample **s2** will appear.
 - d. Double-click **s2** to open the **Sample Attributes** dialog box.
 - e. Type “mg/L” in the **Units** box.
 - f. Type “Cpbd” in the **Associate with Data Name** box.
 - g. Edit the sample equation “s2 = q4” to read “s2 = q4/Vpbd”. The **Sample Attributes** dialog box will appear as follows:



- h. Click **Done**.
4. Create the input for Probenecid.
 - a. In the **SAAM II Toolbox**, click **Input**.
 - b. Click Compartment **q3**, then click on the **Drawing Canvas**. The input **ex2** will appear.
 - c. Double-click **ex2** to open the **Exogenous Input** dialog box. Leave **Bolus** as the **Input Type**.
 - d. Type “500” in the **Initial Amount** box.
 - e. Type “24” in the **Event Start** box.
 - f. Type “6” in the **Repeat Every** box.
 - g. Type “19” in the **Nr. of Repeats** box. 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	500.000	-	24.000	-	6.000	19

Input Type:

Bolus
 Infusion
 Primed Infusion
 Equation

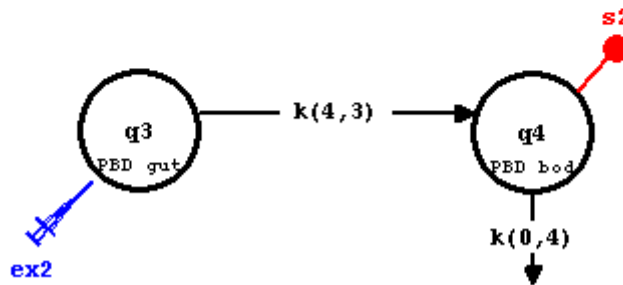
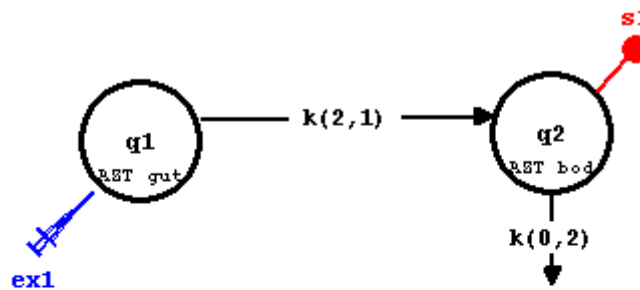
Initial Amount:
Constant Rate:
Event Start:
Event Stop:
Repeat Every:
Nr. of Repeats:

Equation:

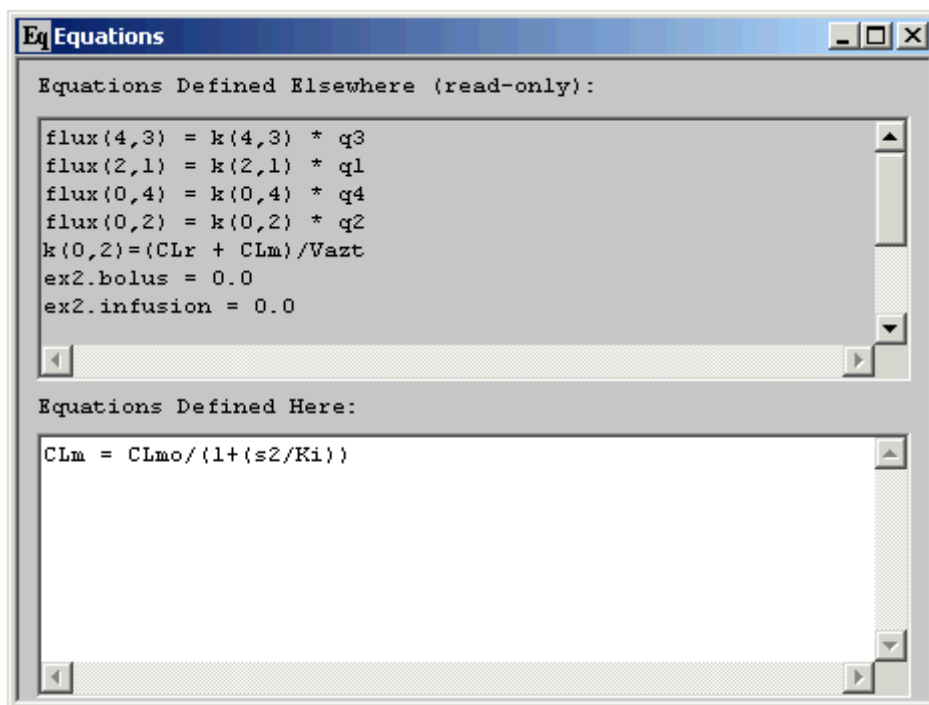
Buttons: Save, Edit, Add, Delete, Split Input..., Done, Cancel, Help

This input scheme will correctly introduce 500mg of Probenecid starting at 24 hours, with dosing every 6 hours until the experiment ends.

- h. Click **Done**. Your model will appear as follows:

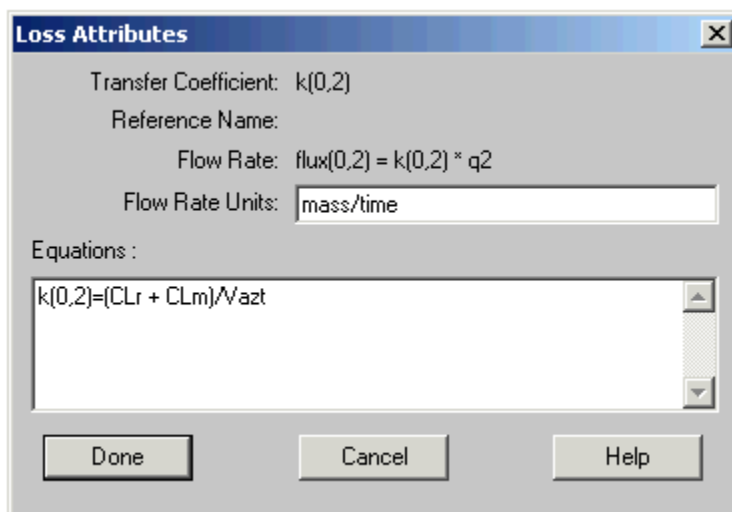


5. Create the inhibition equation for the metabolic clearance of AZT and change the characteristics of $k(0,2)$.
 - a. In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar**, click **Equations Eq**. The **Equations** dialog box will open.
 - b. In the **Equations Defined Here** pane, type “ $CL_m = CL_{m0}/(1+(s_2/K_i))$ ”. The **Equations** dialog box will appear as follows:



CLm is now the equation which describes the metabolic clearance of AZT. The basal clearance, $CLmo$ has been estimated from the first part of this case study. s_2 is the model predicted Probenecid concentration C_{pb} . The parameter characterizing inhibition, K_i , will be estimated from the model.

- c. Close the **Equations** dialog box.
- d. Double-click $k(0,2)$ to open the **Loss Attributes** dialog box.
- e. Edit the equation to read “ $k(0,2) = (CLr + CLm)/V_{azt}$ ”. The **Loss Attributes** dialog box will appear as follows:




- f. Click **Done**.
6. Enter the parameter values.

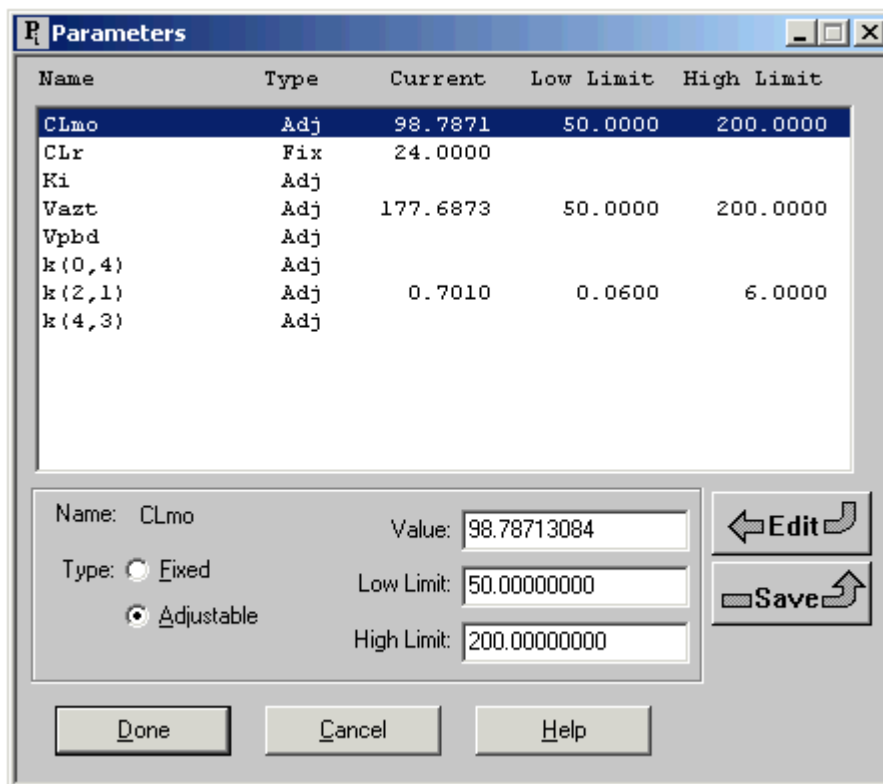
The new parameters added to the model are $k(4,3)$, $k(0,4)$, $Vpbd$ and Ki . Values for $k(4,3)$, $k(0,4)$ and $Vpbd$ will be taken from a knowledge of Probenecid kinetics. $k(4,3)$ will be assumed fixed and equal to 0.3/hr. Initial estimates for $k(0,4)$ and $Vpbd$ will be 0.02/hr and 25L.

An initial estimate for Ki can be obtained by recognizing

$$CL_{mo}/CL_m = 1 + (s^2/Ki)$$

where s^2 is the model-predicted Probenecid concentration. Of course CL_m is itself a function, but noting how rapidly the AZT concentration rises following the introduction of Probenecid, it can be assumed that CL_m is small compared to CL_{mo} .

- 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:



Name	Type	Current	Low Limit	High Limit
CL _{mo}	Adj	98.7871	50.0000	200.0000
CL _r	Fix	24.0000		
K _i	Adj			
V _{azt}	Adj	177.6873	50.0000	200.0000
V _{pbd}	Adj			
k(0,4)	Adj			
k(2,1)	Adj	0.7010	0.0600	6.0000
k(4,3)	Adj			

Name: CL_{mo} Value: 98.78713084

Type: Fixed Adjustable

Low Limit: 50.00000000

High Limit: 200.00000000

Buttons: Done, Cancel, Help, Edit, Save

For the AZT model, you can leave the parameters as appear above.

Enter the following values for the remaining parameters:

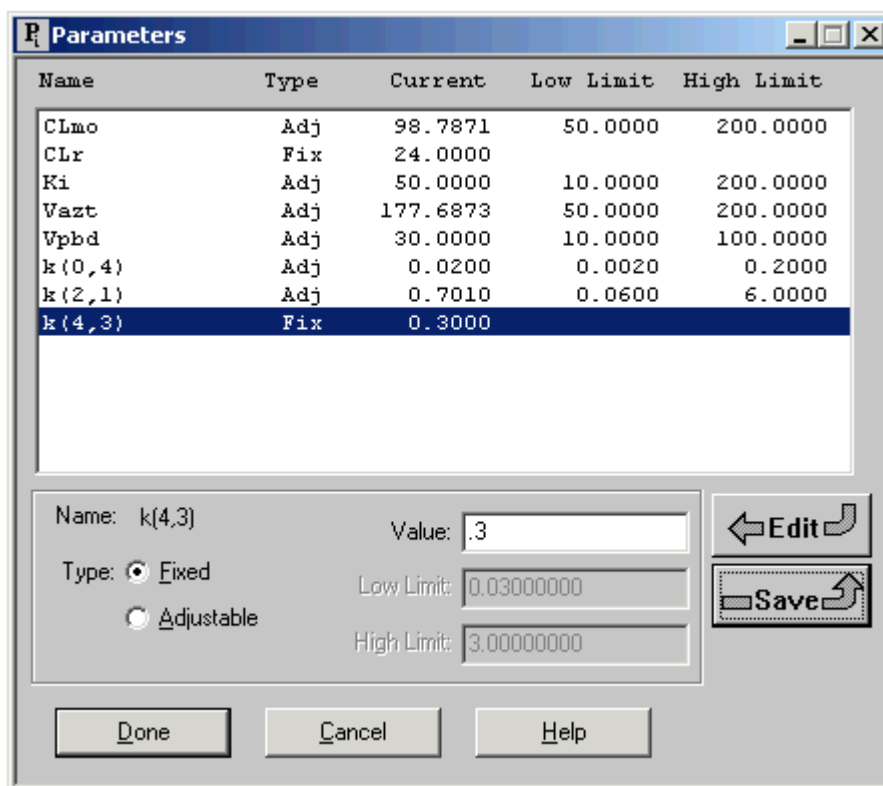
$K_i = 50$ (low limit 10, high limit 200)

$V_{pbd} = 30$ (low limit 10, high limit 100)

$k(0,4) = .02$ (low limit .002, high limit .2)

$k(4,3) = 0.3$ fixed.

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




b. Click **Done**.

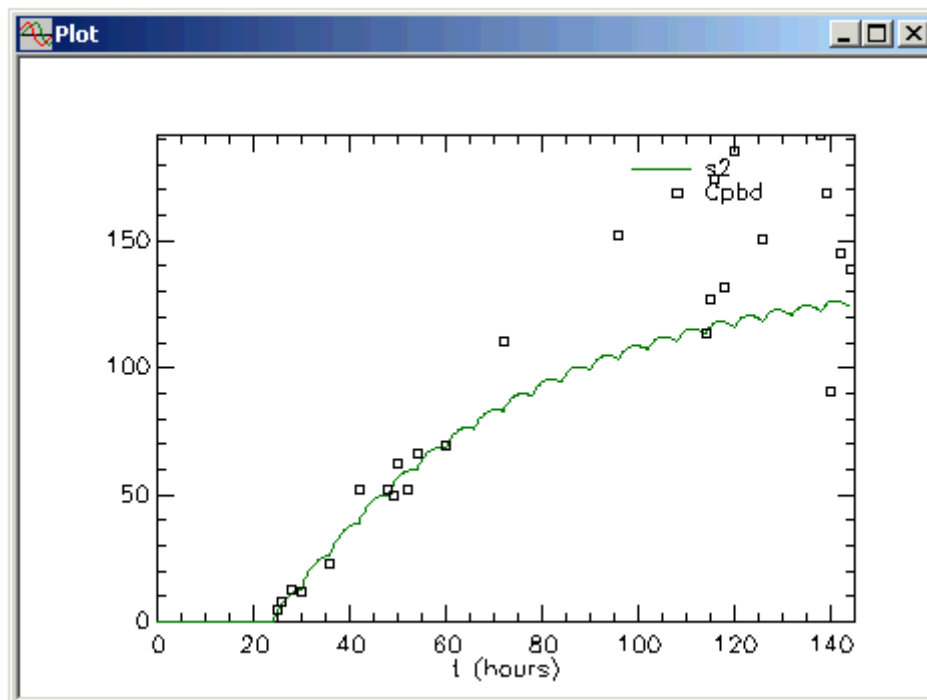
7. Solve your model and view the solution.

Before you work with this part of the case study, you need to reweight the data you unweighted in Part 1. Open the **Data** window, and remove the two “(-+)”. This will reweight all AZT data, and all Probenecid data.

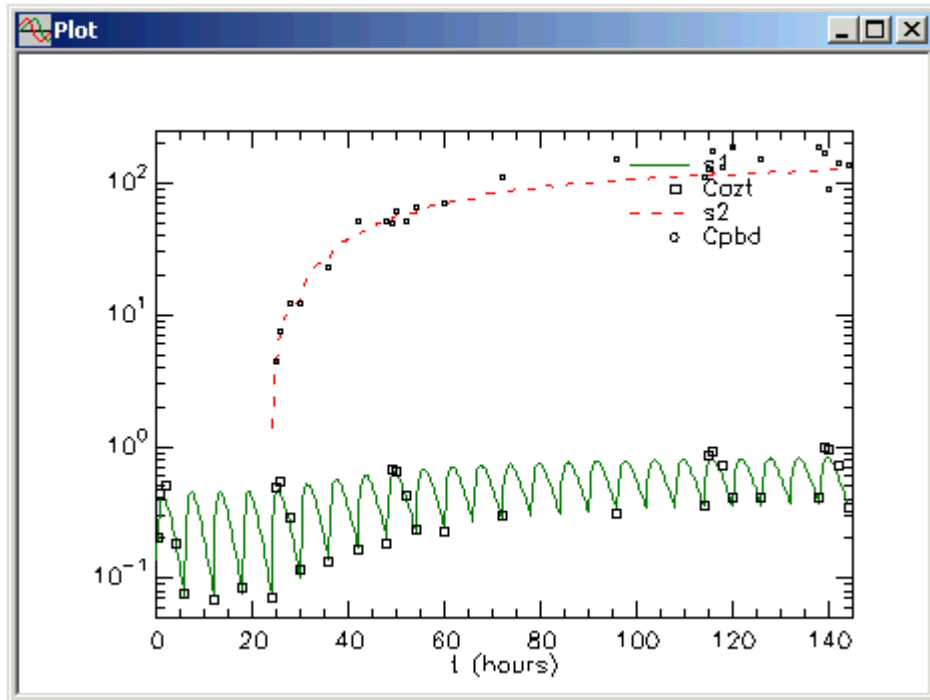
a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II**

Toolbar, click **Solve** .

- b. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . Since the previous plot was **s1** and the AZT data, this plot will appear. The differences are that all data are now weighted meaning there are no more red “x”, and the calculation is different because the inhibition term is now included in $k(0,2)$.
- c. In the **Set** menu, click **Plot/Table Variables** to open the **Plot and Table Variables** dialog box. In the **Plot and Table Variables** dialog box, be sure the **List All Variables** check box is not selected.
- d. Click **s2:Cpbd**; these will move to the **Current Selection** pane.
- e. Click **Done**. The following plot will appear. This shows the initial parameter estimates for Probenecid are reliable. You can also see, because the maximum number of calculation intervals is set to 500, how the multiple dosing causes the model predicted curve to have humps and bumps:




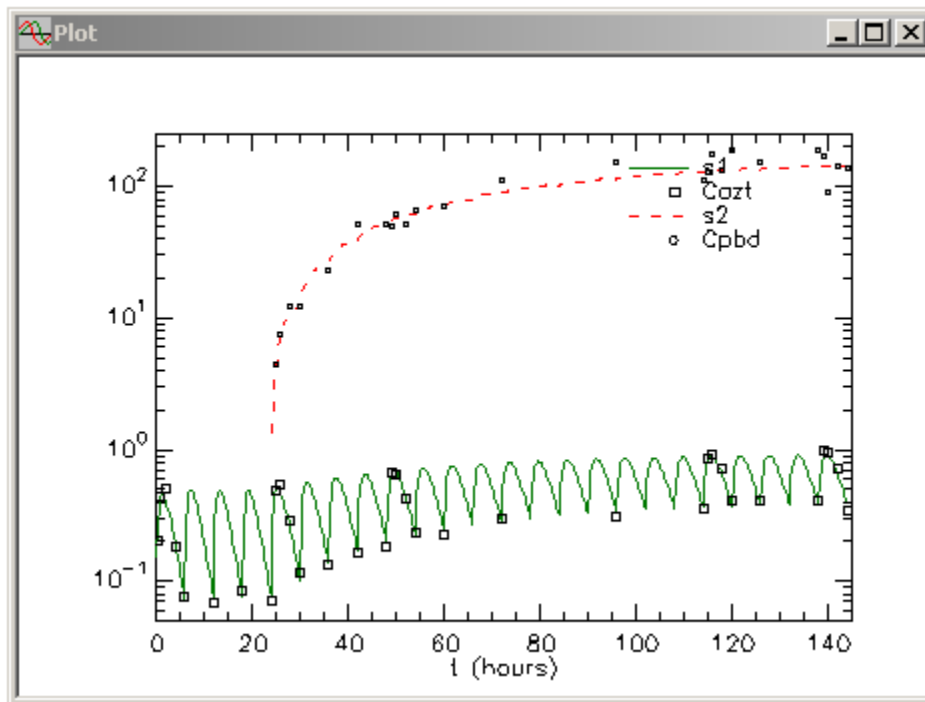
- f. Examine both sets of data by including **s1:Cazt** in the plot. The plot will appear as follows in semi-log :




In this plot, the Y – Axis minimum and maximum have been set to 0.05 and 250 respectively.

Leave the **Plot** window open.

8. Fit the model to the data and view the solution.
 - a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar**, click **Fit** . When you have “Fitted” your model to your data, your plot should appear as follow:



- 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	
CLmo	92.59499	4.59926e+000	4.96707e+000	83.35686	101.83312
CLr	24.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
Ki	48.63023	5.76644e+000	1.18577e+001	37.04769	60.21277
Vazt	133.56196	3.13905e+001	2.35025e+001	70.51070	196.61322
Vpbd	31.08083	2.02384e+000	6.51153e+000	27.01572	35.14593
k(0,4)	0.01554	2.15790e-003	1.38822e+001	0.01121	0.01988
k(2,1)	0.59312	1.25614e-001	2.11784e+001	0.34081	0.84543
k(4,3)	0.30000	** Fixed **	** Fixed **	** Fixed **	** Fixed **

Correlation Matrix
 Covariance Matrix
 Objective

	Objective	Scaled Data Variance
s2 : Cpbd	2.595967e+000	1.002583e+000
s1 : Cazt	-3.381493e+000	1.696997e+000

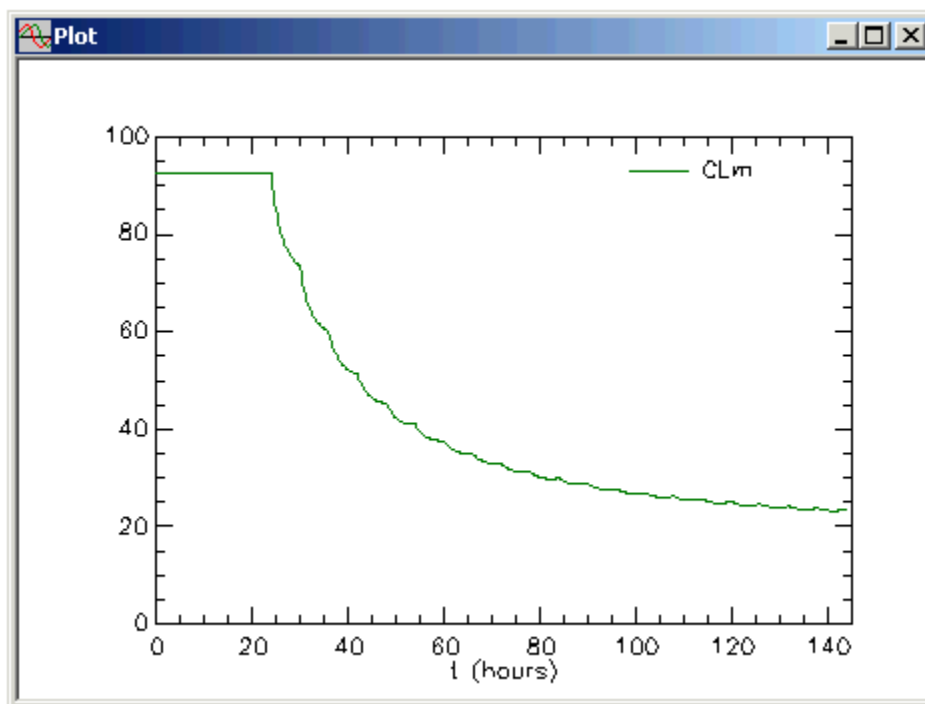
Total objective	-7.855259e-001	
AIC	6.641066e-001	
BIC	8.062061e-001	

All parameters are estimated with good precision. The scaled data variance, being close to one in both cases, indicates the weighting scheme for the data is very reasonable.

- c. Close the **Statistics** window. Leave the **Plot** window open.
9. View CL_m, the metabolic clearance.

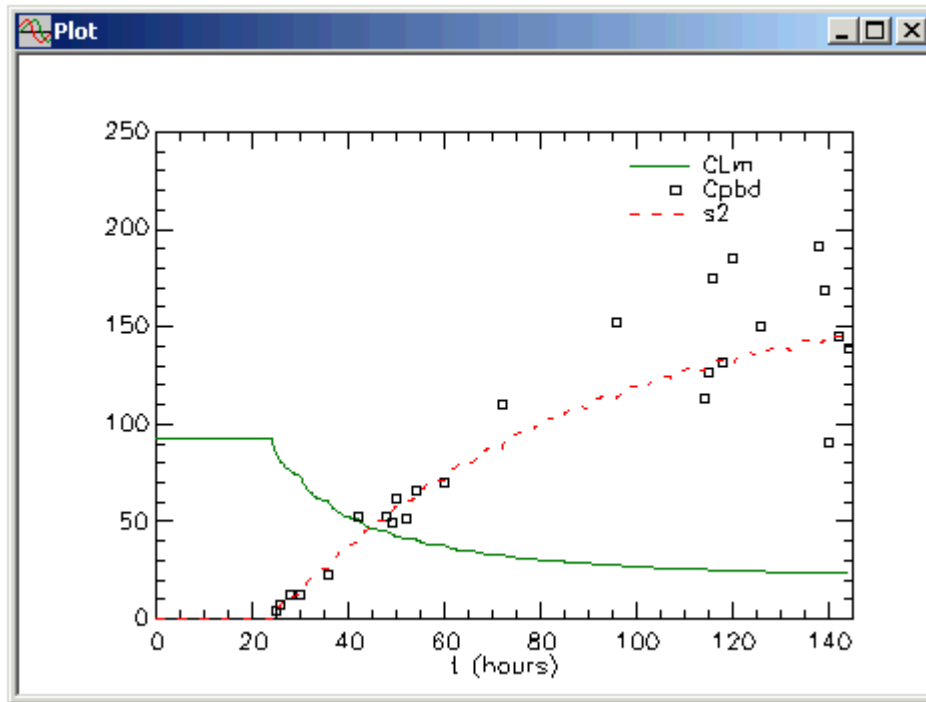
The point of this experiment was to understand how introducing Probenecid retarded the metabolic clearance of AZT. You can understand this better by examining a plot of CL_m.

- 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 **CL_m**. Click CL_m to move it to the **Current Selection** pane. Click **Done**. The following linear plot will appear (the Y – Axis minimum and maximum have been set to 0 and 100 respectively):

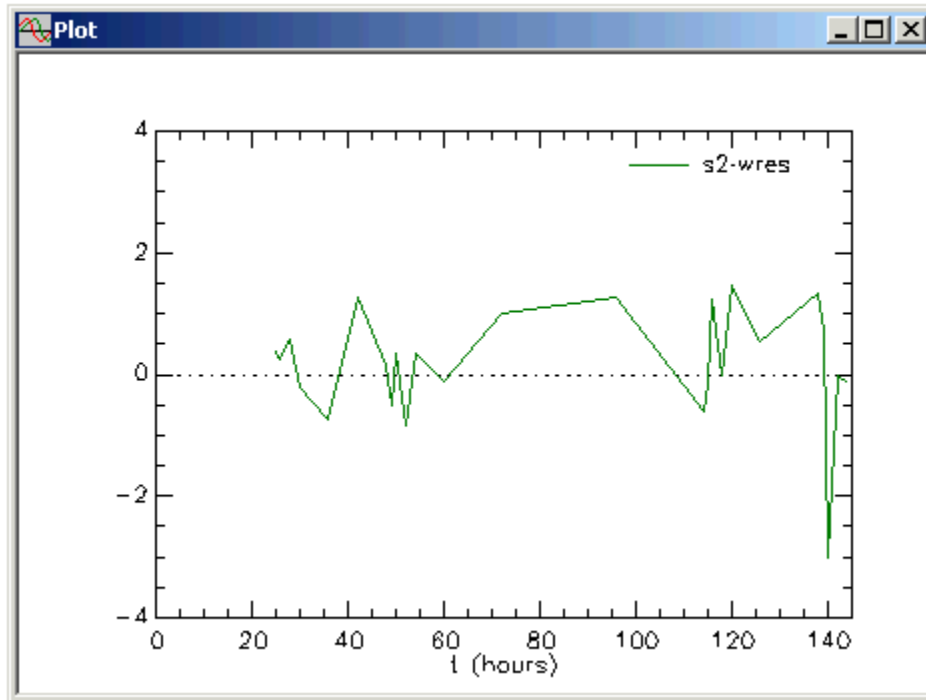


You can clearly see how this dosing of Probenecid decreases the metabolic clearance of AZT from a basal level of just over 90 to a value of around 23 L/hr.

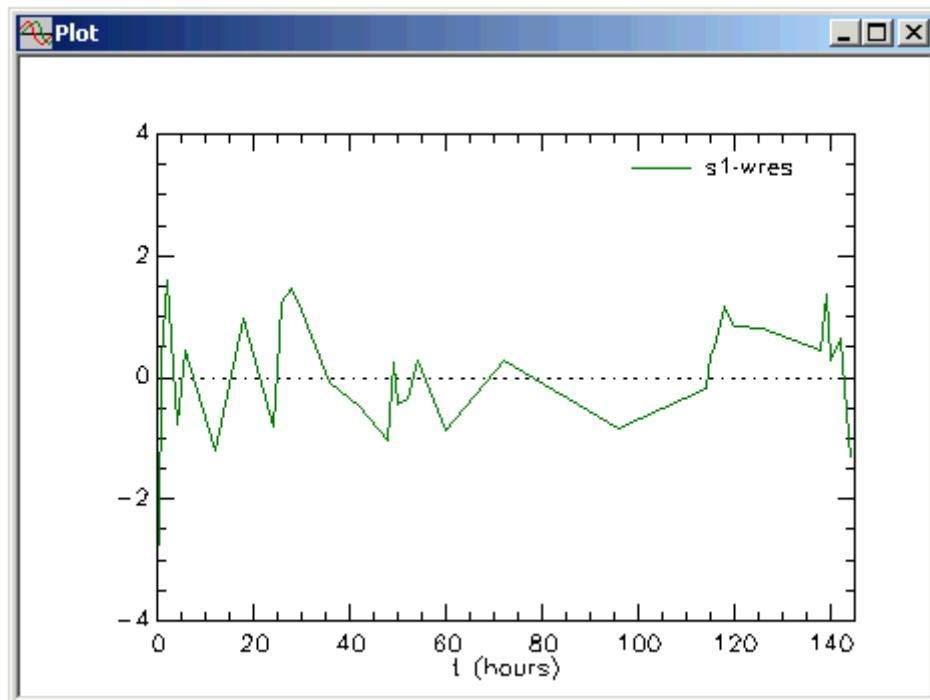
- c. You can now plot CL_m, s₂ and the Probenecid concentration C_{pbd}. The plot will appear as follows (the Y – Axis scale goes from 0 to 250):



- d. Close the **Plot** window.
10. Optional (you may continue the case study with the following steps. Or you may proceed to the end, and **Quit** the **SAAM II Compartmental** application.
 - a. In terms of assessing how “good” the model is, besides examining the statistics, you can examine the residuals or weighted residuals. Both should randomly scattered around zero. For the weighted residuals, they should lie in a band between -1 and 1. Tests for goodness-of-fit are available to help assess the residuals. For example, if you examine the weighted residuals for Probenecid, you will obtain:

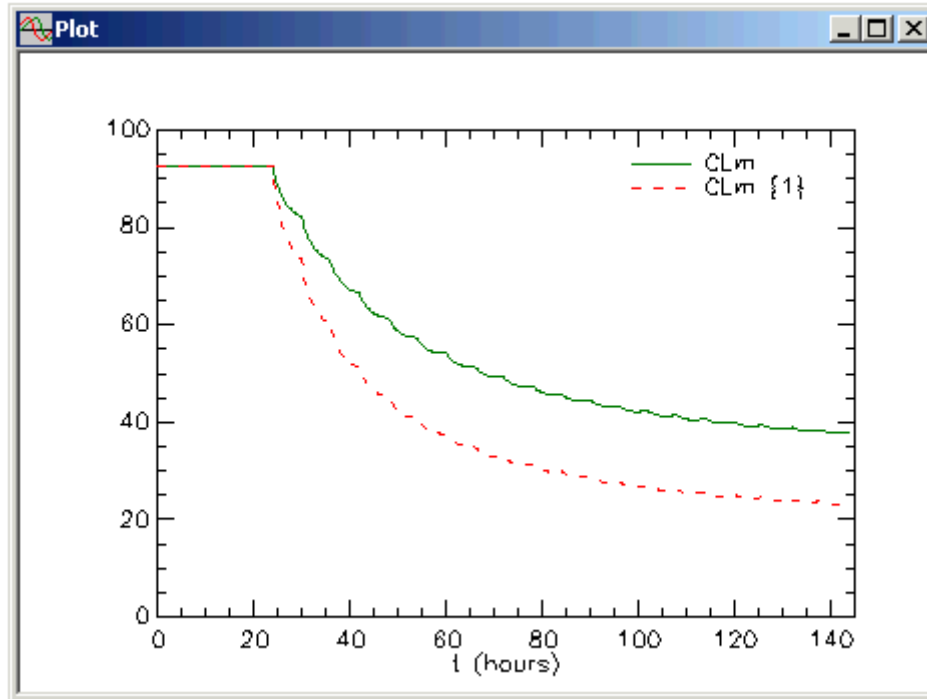


The Probenecid weighted residuals appear to be scattered with the possible exception of data towards the end of the study. Given the uncertainty of these data, this is not surprising. A plot of the AZT weighted residuals is more consistent with the lower coefficient of variation of error:



- b. To understand better how Probenecid inhibits the metabolic clearance of AZT, it is useful to perform some simulations. When you have finished, you may **Quit** the **SAAM II Compartmental** application.

- (1) Simulation 1. What happens if you increase K_i ? Does this make Probenecid a more or less potent inhibitor? For example, if K_i is doubled to 100, and compared with the original value of around 50, the plot of CL_m appears:



CL_m is the new value while $CL_m\{1\}$ is the original value. Doubling K_i has the effect of less inhibition.

- (2) Simulation 2. What would happen if the dosing schedule for Probenecid were different? For example, what would happen if the drug was given every 24 hours instead of every 6 hours? To perform this simulation, you will have to modify the characteristics of the **Exogenous Input**.

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

- When developing a system model during an experiment where there is a perturbation, you need to develop the model based upon data before the perturbation.
- When the model solution is changing rapidly, it is useful to increase the maximum number of calculation intervals to visualize the plot better.
- Multiple dosing experiments can easily be handled in SAAM II.
- Competitive inhibition can be easily handled in SAAM II.
- Simulating competitive inhibition can help you understand better drug-drug interaction.

Data for this case study

DATA

t	Cazt (FSD 0.08)	Cpbd (FSD 0.2)
0	n	n
0.4	0.2063	n
1	0.440595	n
2	0.499356	n
4	0.184342	n
6	0.077122	n
12	0.067555	n
18	0.084731	n
24	0.070192	n
25	0.487661	4.46
26	0.539222	7.52
28	0.292287	12.27
30	0.115269	12.12
36	0.135413	22.88
42	0.161901	52.22
48	0.180471	52.31
49	0.662869	49.65
50	0.654845	61.92
52	0.430036	51.89
54	0.232642	66
60	0.228883	69.58
72	0.295831	110.31
96	0.313014	152.34
114	0.359993	113.23
115	0.854626	126.97
116	0.928101	174.65
118	0.72754	131.81
120	0.409176	185.65
126	0.414881	150.59
138	0.409313	191.64
139	0.981605	168.58
140	0.933427	90.31
142	0.712915	144.91
144	0.346479	138.97

END