

Oral Theophylline Kinetics

Case Study

- How to create a one-compartment model with absorption
- How to obtain initial parameter estimates
- How to write the equations for the noncompartmental parameters
- How to identify two solutions that exist for this model
- How to use *a priori* knowledge

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Oral Theophylline Kinetics: The One-Compartment Model with Absorption

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 create the one-compartment model with absorption to analyze rising and falling data.
- How to obtain initial parameter estimates for the model.
- How to write the noncompartmental parameters for this model.
- How to identify the two solutions that exist for this model.
- How to select the solution to the model that is most appropriate using *a priori* knowledge of the system being studied.
- How to keep track of your modeling session using Notes.

Files Required

Data:

The data file for this case study is

theo_oral.dat

Introduction

This case study will show you how to create a one-compartment disposition model with absorption represented by a second compartment, and show that the model has two solutions. Based on modeling theory, this model is not *a priori* identifiable (see [1] for example), and one must decide which of the two solutions is most appropriate for the particular study. The data used in the case study come from a report in which plasma concentrations ($\mu\text{g/mL}$) were measured after oral administration of a 320 mg theophylline dose to healthy subjects [2].

Since the 1930's theophylline has been used as a bronchodilator to treat patients with bronchial asthma. It has a narrow therapeutic plasma concentration range. In addition, the pharmacokinetics varies widely among subjects, primarily because of differences in elimination clearance rather than distribution volume.

When theophylline is administered to humans by intravenous infusion, the drug exhibits a two-compartment or three-compartment pattern of distribution. When given orally with

typical blood sampling protocols, these compartments collapse into a single disposition compartment. In either case the distribution volume of theophylline, based on measurement of free + protein bound drug in plasma, is greater than extracellular fluid space but somewhat less than total body water because theophylline binds to plasma proteins [3].

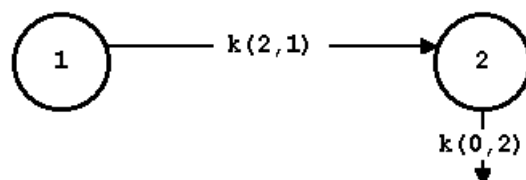
This case study will also discuss how to employ *a priori* identifiability to obtain the most appropriate solution to a model where more than one solution exists.

The problem addressed in this case study can be summarized briefly: I have performed a study to estimate the pharmacokinetic parameters of theophylline. Based on the data, I want to use a one-compartment disposition model with absorption to describe the kinetics and estimate the parameters. This is because the data rises and falls, and I believe that this compartmental model will be satisfactory. I have heard this model has more than one solution, and don't know what to do about it. What are my options?

1. Cobelli, C., Foster, D. and Toffolo, G. *Tracer Kinetics in Biomedical Research*. Kluwer Academic/Plenum Publishers. New York. 2000.
2. Upton, R. A., Thiercellin, J. F., Guentert, T. W., Wallace, S. M., Powell, J. R., Sansom, L., and Riegelman, S. "Intraindividual variability in theophylline pharmacokinetics: statistical verification in 39 of 60 healthy young adults." *J. Pharma. and Biopharma.* 1982, 10: 123-134.
3. Belknap, S.M. Nelson, J.E., Ruo, T.I., Frederiksen, M.C., Worwag, E.M., Shin, S.-G., Atkinson, A.J., Jr. "Theophylline distribution kinetics analyzed by reference to simultaneously injected urea and inulin". *J. Pharmacol. Exp. Ther.* 1987, 243: 963-969.

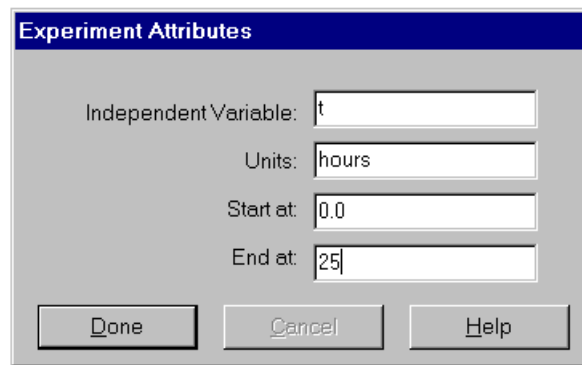
Part 1. Create the two-compartment model (one-compartment model with absorption).


1. **Start the SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.
2. In the **SAAM II Toolbox**, click **Model** to be sure these tools are available.
3. Create the following system model on the **Drawing Canvas**:

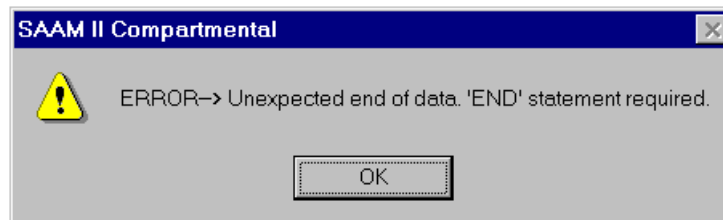


Part 2. Create the pharmacokinetic experiment on the model.

1. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open.
 - a. Enter “25” in the **End At** box.
 - b. Type “hours” in the **Units** box. The **Experimental Attributes** dialog box will appear as follows:



- c. Click **Done**. The **Create Experiment** dialog box will open.
 - d. Be sure “Experiment” as the **Type** is selected. Click **Create**.
2. 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 **theo_oral.dat** should appear in the list (if it does not, find the folder where you have put this data file).
 - c. Double-click **theo_oral.dat**. The data in this file will appear in the **Data** window. You may receive the following warning message. If you do, click **OK**. If you do not, the **Data** window will appear as shown below:





Warning messages. SAAM II will return warnings when it detects a problem with your model. In the case of the **Data** window, SAAM II expects no spaces at the end of the file. If you put your cursor at the end of the data file, you will see there may be spaces. Delete these spaces. To check that your data are okay, in the **Edit** menu, click **Check Data Format**. If the problem has not been fixed, a warning will appear. If it has been fixed, you will receive notification the data format are okay (message will appear at the lower left of the **Data** window.)



```

d Data - theo_oral.dat
DATA
#Dose: 320 mg Wt. 70.5kg
#Units: mcg/ml
(SD 1.0)
t      cp
0      0
0.27   4.4
0.58   6.9
1.02   8.2
2.02   7.8
3.62   7.5
5.08   6.2
7.07   5.3
9       4.9
12.15  3.7
24.17  1.05
END
#
# Equations for the noncompartmental parameters
#Tmax = log((k(2,1)/k(0,2)))/(k(2,1)-k(0,2))
#Cmax=(dose/vol)*exp(-k(0,2)*Tmax)
#Elim_t_half=log(2)/k(0,2)
#Abs_t_half=log(2)/k(2,1)
#AUC=dose/(vol*k(0,2))
#AUMC=dose/(vol*k(0,2)*k(0,2))
#MRT=AUMC/AUC
#MAT=1/k(2,1)
#Cl=vol*k(0,2)
#Vss=Cl*MRT
  
```

Data has been edited

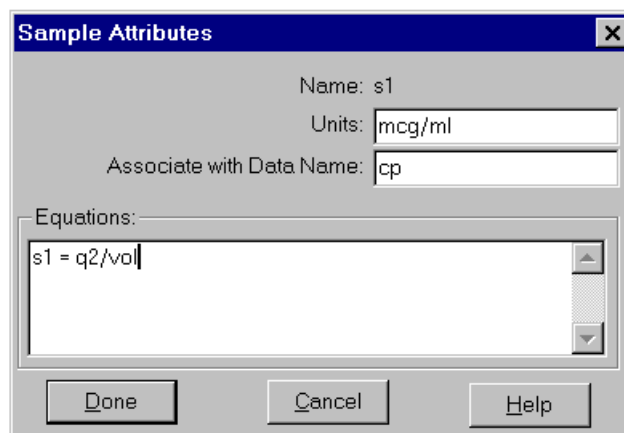
The weighting scheme is SD so you can leave the variance model set as the default data-relative.



Entering comments in a Data file. You can enter comments in your data file if you precede each line with “#.” In this data file, comments are provided which give some information about the study. In addition, the equations for the noncompartmental parameters are entered as comments. This is for convenience; later in the case study, these will be pasted into the **Equations** window.



- d. Close the **Data** window.
3. Create the sample on the Compartment **2**.
 - a. In the **SAAM II Toolbox**, click **Sample**.
 - b. Click Compartment **q2**, and then click on the **Drawing Canvas**. The sample **s1** will appear.
 - c. Double-click **s1** to open the **Sample Attributes** dialog box.
 - d. Type “mcg/ml” in the **Units** box (mcg/ml is micrograms per ml.)
 - e. Type “cp” in the **Associate with Data Name** box. (Notice “cp” is in lower case.)
 - f. Edit the sample equation “s1=q2” to read “s1=q2/vol”. The **Samples Attributes** dialog box will appear as follows:



- g. Click **Done**.
4. Create an input into Compartment **1**.

The dose of theophylline was 320 mg. Since the units of the data are in $\mu\text{g}/\text{ml}$ (mcg/ml), the dose must be consistent with the data. Thus the dose is 320,000 μg .

- 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.
- Be sure bolus is selected as the input type and enter “320000” in the **Initial Amount** box.
- Click **Add**. The **Exogenous Input** dialog box will appear as follows:

The screenshot shows the 'Exogenous Input' dialog box. The 'Name' field is 'ex1'. The 'Type' is 'Bolus'. The 'Initial' value is '3.20e+5'. The 'Initial Amount' field is set to '320000'. The 'Input Type' section has 'Bolus' selected. The 'Equation' field contains 'ex1 ='. The 'Done' button is highlighted.

Type	Initial	Constant	Start	Stop	Repeat Every	Nr. Repeats
Bolus	3.20e+5	-	0.000	-	-	-

- Click **Done**.

Part 3. Defining Derived Variables (Noncompartmental parameters).

The parameters for your model are the rate constants $k(2,1)$, $k(0,2)$ and the volume vol . The rate constant $k(0,2)$ is a fractional measure of the elimination rate of the drug, and it has units of inverse time (in this case, 1/hour). It is usually of interest to calculate the elimination clearance of a drug. This is defined as the product of the elimination rate constant and the volume of the compartment from which the elimination rate constant exits. In other words:


$$Cl = k(0,2) * vol$$

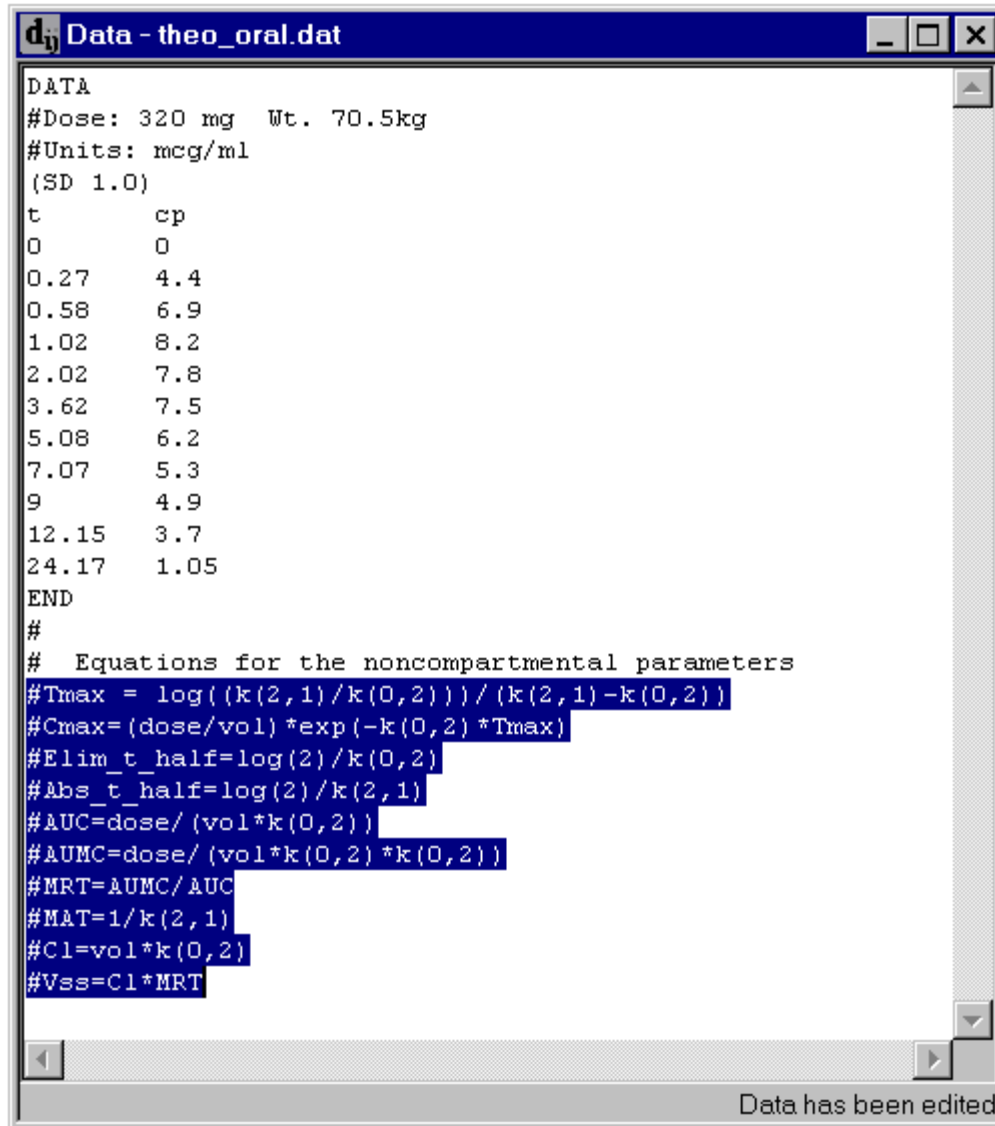
Although elimination clearance Cl is derived as a function of the primary parameters $k(0,2)$ and vol , it provides a volume-independent estimate of drug elimination. As you recall, parameters are variables that appear in the equations characterizing the model or experiment, but were not given numerical values. SAAM II automatically determines the model parameters. Following a successful “Fit,” the model parameters and the derived variables will appear in the **Statistics** window.

Besides clearance, there are a number of other noncompartmental pharmacokinetic parameters that can be estimated using the one-compartment model with absorption:

$$\begin{aligned}T_{max} &= \log((k(2,1)/k(0,2)))/(k(2,1)-k(0,2)) \\C_{max} &= (\text{dose}/vol) * \exp(-k(0,2) * T_{max}) \\Elim_t_half &= \log(2)/k(0,2) \\Abs_t_half &= \log(2)/k(2,1) \\AUC &= \text{dose}/(vol * k(0,2)) \\AUMC &= \text{dose}/(vol * k(0,2) * k(0,2)) \\MRT &= AUMC/AUC \\MAT &= 1/k(2,1) \\V_{ss} &= Cl * MRT\end{aligned}$$

You can enter these parameters directly. For convenience, they can be cut and pasted from the data file to the **Equations** dialog box as described below.

1. In the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar** click **Data** . The **Data** window will open.
2. Select and copy the noncompartmental parameters. The selected information will appear in the **Data** window as follows:




```

Data - theo_oral.dat
DATA
#Dose: 320 mg Wt. 70.5kg
#Units: mcg/ml
(SD 1.0)
t      cp
0      0
0.27   4.4
0.58   6.9
1.02   8.2
2.02   7.8
3.62   7.5
5.08   6.2
7.07   5.3
9      4.9
12.15  3.7
24.17  1.05
END
#
# Equations for the noncompartmental parameters
#Tmax = log((k(2,1)/k(0,2)))/(k(2,1)-k(0,2))
#Cmax=(dose/vol)*exp(-k(0,2)*Tmax)
#Elim_t_half=log(2)/k(0,2)
#Abs_t_half=log(2)/k(2,1)
#AUC=dose/(vol*k(0,2))
#AUMC=dose/(vol*k(0,2)*k(0,2))
#MRT=AUMC/AUC
#MAT=1/k(2,1)
#Cl=vol*k(0,2)
#Vss=Cl*MRT

```

Data has been edited

3. Close the **Data** window.
4. In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar**, click **Equations** . The **Equations** dialog box will open.
5. Paste the equations in the **Equations Defined Here** pane in the **Equations** dialog box.
6. Remove the “#” from the beginning of each noncompartmental parameter equation. The **Equations** dialog box will appear as follows:

```

Eq Equations
Equations Defined Elsewhere (read-only):
flux(2,1) = k(2,1) * q1
flux(0,2) = k(0,2) * q2
ex1.bolus = 0.0
ex1.infusion = 0.0
s1 = q2/vol

Equations Defined Here:
Tmax = log((k(2,1)/k(0,2)) / (k(2,1)-k(0,2)))
Cmax = (dose/vol) * exp(-k(0,2) * Tmax)
Elim_t_half = log(2)/k(0,2)
Abs_t_half = log(2)/k(2,1)
AUC = dose / (vol * k(0,2))
AUMC = dose / (vol * k(0,2) * k(0,2))
MRT = AUMC / AUC
MAT = 1/k(2,1)
Cl = vol * k(0,2)
Vss = Cl * MRT

```



Equation syntax. There are two points to remember about equation syntax in SAAM II. First, while it may be appealing to define half time as $t_{1/2}$, this is improper syntax, and SAAM II will display an error message. The other point is that the natural log is “log”, not “ln.” If you define, for example, $t_{half} = \ln(2)/k(0,2)$, “ln(2)” will be interpreted as a parameter instead of an algebraic operation, and will appear as a parameter in the **Parameters** dialog box.




7. Close the **Equations** dialog box.

Part 4. Enter the parameter values, solve the model, fit the model to data, view the solution and record the results.

Before you can Solve (simulate) your model or Fit your model to your data, you must provide numerical estimates for the primary parameters of your model. These are the parameters that appear in the **Parameters** dialog box.

1. Enter the parameter values.

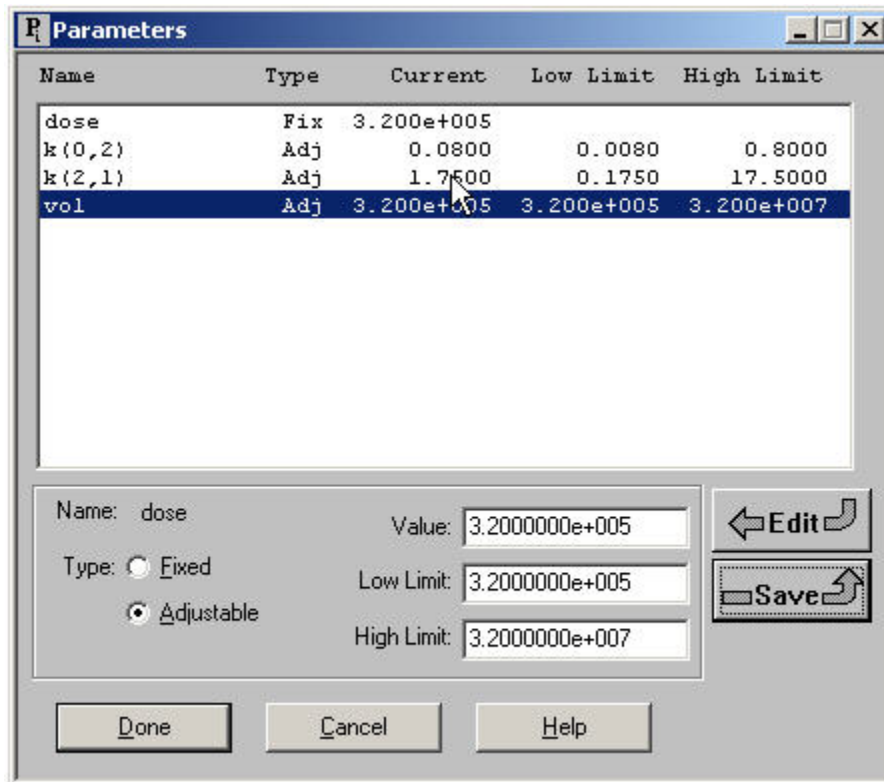
- a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar**, click **Parameter** . The **Parameters** dialog box will open. Notice that *dose* appears as a parameter. This is because *dose* is used in some of the calculations for the pharmacokinetic parameters.
- b. If *dose* is not selected, double-click *dose* to select it. Select the **Fixed** option. Enter “320000” in the **Value** box and click **Save**.



Dose as a parameter. In this case study, *dose* will be entered both as a parameter and in the **Exogenous Input** dialog box as the amount of the bolus injection. It is entered here as a fixed parameter because it is used in the calculation of some of the noncompartmental parameters. It should be noted that the bolus in the **Exogenous Input** dialog box could also be specified as an equation where, in this case, “ex1 = dose” with the starting and stopping times of zero.



- c. Double-click $k(0,2)$. Enter “0.08” in the **Value** box and click **Save**.
- d. Double-click $k(2,1)$. Enter “1.75” in the **Value** box and click **Save**.
- e. Double-click *vol*. Enter “300000” in the **Value** box and click **Save**. The **Parameters** dialog box will appear as follows:





- f. Click **Done**.

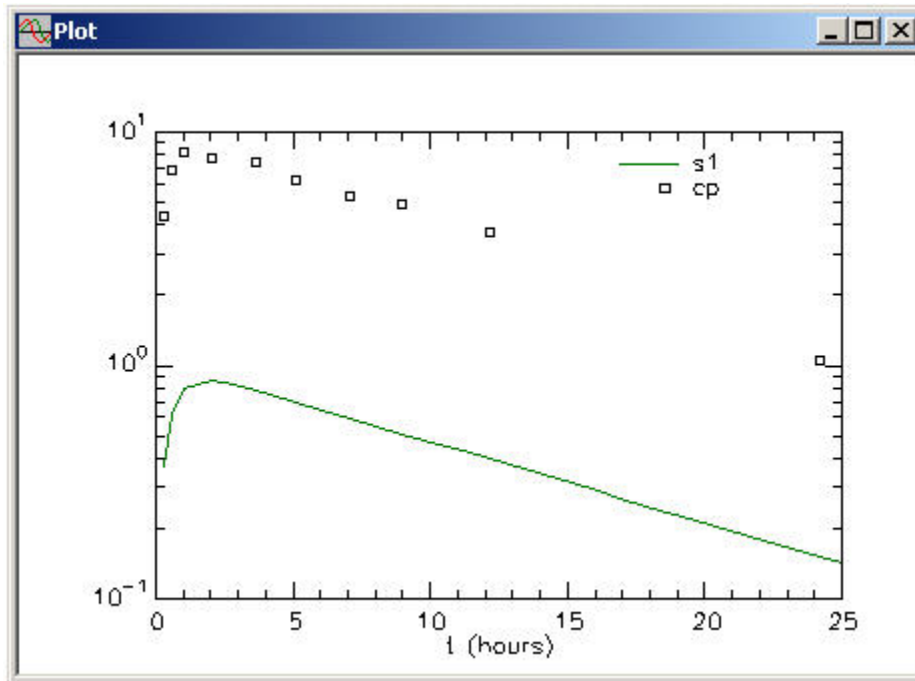


Initial parameter estimates. How the initial estimates for the parameters $k(2,1)$, $k(0,2)$ and vol are obtained is explained in the appendix to this case study. This approach can be applied to any experiment in which you are using the one-compartment model with absorption.



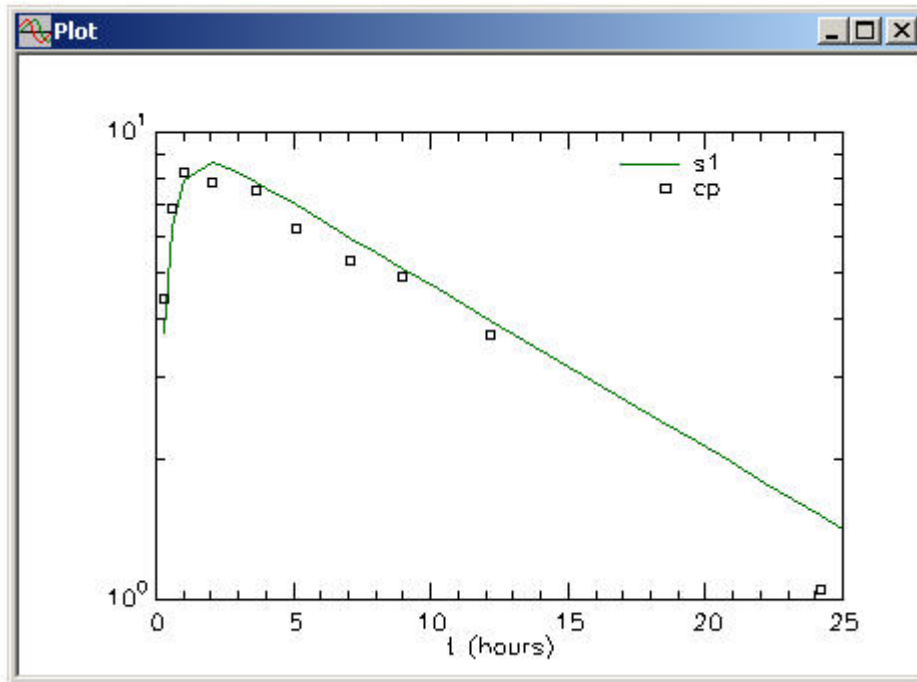
2. Solve the model and view the solution.
 - a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar**, click **Solve** .
 - b. Plot the data. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** .
 - c. In the **Set** menu, click **Plot/Table Variables**. The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** box is cleared.
 - d. Click “s1:cp” to move it to the **Current Selection** pane.

- e. Click **Done**. If your plot does not appear in semi-log mode, in the **View** menu, click **Semilog**. Your plot will appear as follows:




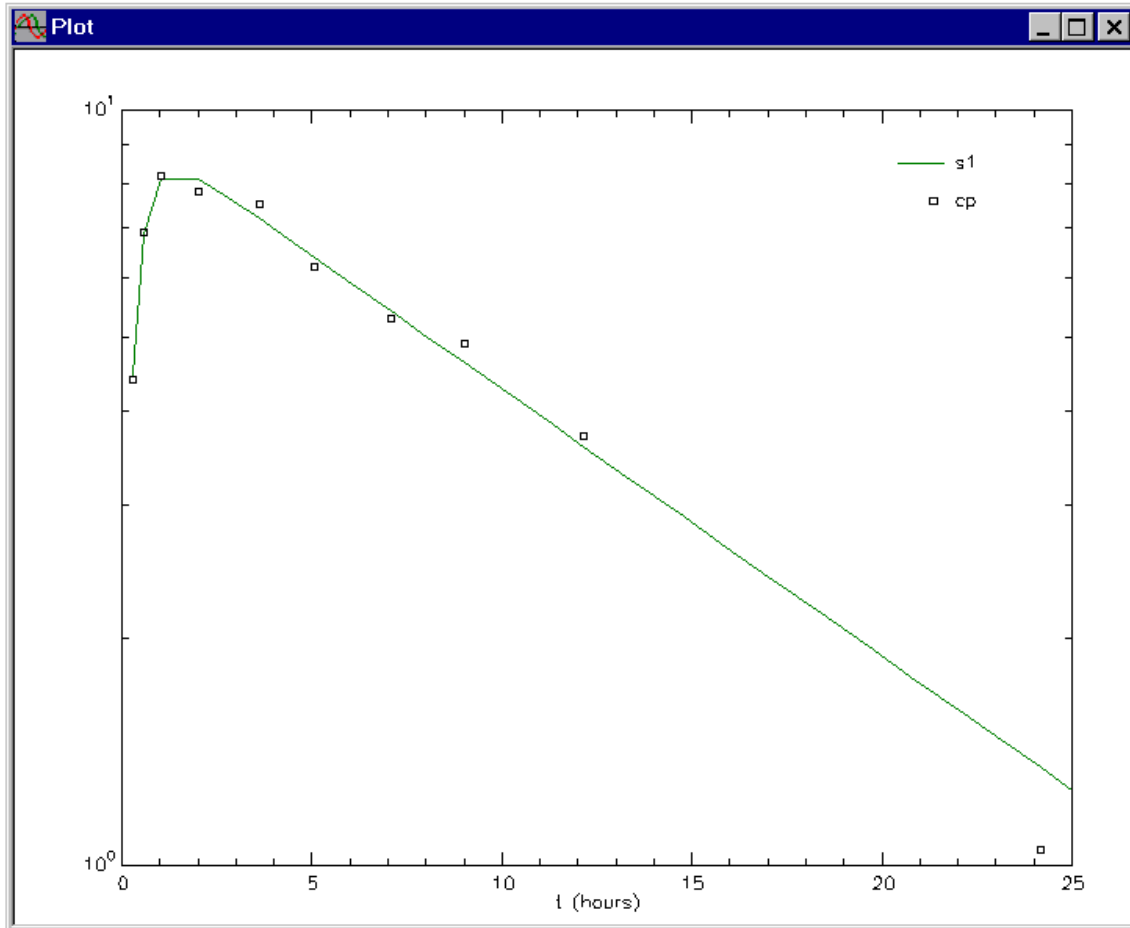
While the shape of the model predicted values follows the data fairly well meaning that the estimates for $k(2,1)$ and $k(0,2)$ are reasonable, you can see that the estimate for vol is off. This causes the model predicted values to lie below the data and means the estimate for vol is too large. Since the maximum difference between the data and model predicted values is about a factor of 10, you should reduce your estimate for vol by a factor of 10 from 300,000 to 30,000.

- f. Open the **Parameter** dialog box, set the initial estimate for vol equal to 30000 and reset the **Low** and **High** limits respectively of 3000 and 300000. Re-Solve the model. Your plot should appear as follows:




Now the model predicted values do not differ that much from the data. The initial rise is not fast enough meaning that the estimate for $k(2,1)$ is low. Should you wish to continue hand-fitting, you can increase this to see how the solution is affected. When you hand-fit your model to your data, a rule of thumb for increasing or decreasing rate constants is a factor of two. Thus if you increase a rate constant, multiply it by 2, and if you decrease it, multiply it by $\frac{1}{2}$.

- g. Leave the **Plot** window open.
3. Fit your model to your data, and view the solution and statistics.
 - a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar** click, **Fit** .
 - b. Since your **Plot** window is already open, your plot will appear as follows:



The “Fit” is satisfactory in that there are no obvious systematic deviations between the model predictions and the data with the possible exception of the final datum which appears to be low. Since this datum is at 24 hours which is 12 hours after the previous datum, it is possible that it is an outlier. It is also possible that the value is reaching the level at which the amount of drug in plasma cannot be quantitated with the same accuracy as the earlier data.

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


Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
dose	320000.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,2)	0.08141	4.56735e-003	5.60999e+000	0.07088	0.09195
k(2,1)	2.45364	1.70046e-001	6.93033e+000	2.06152	2.84577
vol	34322.21630	8.15610e+002	2.37633e+000	32441.41996	36203.01264
----- Derived Variables -----					
AUC	114.51772	4.54695e+000	3.97052e+000	104.03244	125.00299
AUMC	1406.60030	1.32569e+002	9.42478e+000	1100.89629	1712.30431
Abs_t_half	0.28250	1.95780e-002	6.93033e+000	0.23735	0.32764

	Objective	Scaled Data Variance
sl : cp	-2.227666e+000	5.451867e-002

Total objective	-2.227666e+000	
AIC	1.687420e-001	
BIC	2.410866e-001	

You can see that the statistics are quite reasonable in that no parameter has a large error. You will have to scroll through the **Parameter/Variable** pane to see all of the pharmacokinetic noncompartmental parameters.

Notice that the estimated volume of Compartment 2 is 34,316 ml, or 34.32L. For a 70 kg individual, this is 0.49L/kg, or just under 50% of body weight.

4. (Optional) Record the results in the **Notes** window.
 - a. In the **Show** menu, click **Notes**, or alternatively, on the **SAAM II Toolbar** click **Notes** . The **Notes** window will open.
 - b. Type “First fit – rapid absorption and slow elimination.”
 - c. In the **Statistics** window, select all the information for all the parameters.
 - d. In the **Edit** menu, click **Copy**.
 - e. Click in the **Notes** window. In the **Edit** menu, click **Paste**.
 - f. In the **Statistics** window, select and copy the information for the objective function.
 - g. Click in the **Notes** window. Click below the statistical information. In the **Edit** menu, click **Copy**. Your **Notes** window will appear as follows:

Notes					
First fit - rapid absorption and slow elimination					
dose	320000.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,2)	0.08141	4.56735e-003	5.60999e+000	0.07088	0.09195
k(2,1)	2.45364	1.70046e-001	6.93033e+000	2.06152	2.84577
vol	34322.21630	8.15610e+002	2.37633e+000	32441.41996	36203.01264
----- Derived Variables -----					
AUC	114.51772	4.54695e+000	3.97052e+000	104.03244	125.00299
AUMC	1406.60030	1.32569e+002	9.42478e+000	1100.89629	1712.30431
Abs_t_half	0.28250	1.95780e-002	6.93033e+000	0.23735	0.32764
Cl	2794.32746	1.10952e+002	3.97063e+000	2538.47126	3050.18366
Cmax	8.29491	1.37041e-001	1.65210e+000	7.97890	8.61093
Elim_t_half	8.51380	4.77624e-001	5.60999e+000	7.41240	9.61520
MAT	0.40756	2.82451e-002	6.93033e+000	0.34242	0.47269
MRT	12.28282	6.89065e-001	5.60999e+000	10.69383	13.87180
Tmax	1.43569	6.40353e-002	4.46026e+000	1.28802	1.58335
Vss	34322.21630	8.15610e+002	2.37633e+000	32441.41996	36203.01264
		Objective	Scaled Data Variance		
sl : cp		-2.227666e+000	5.451867e-002		

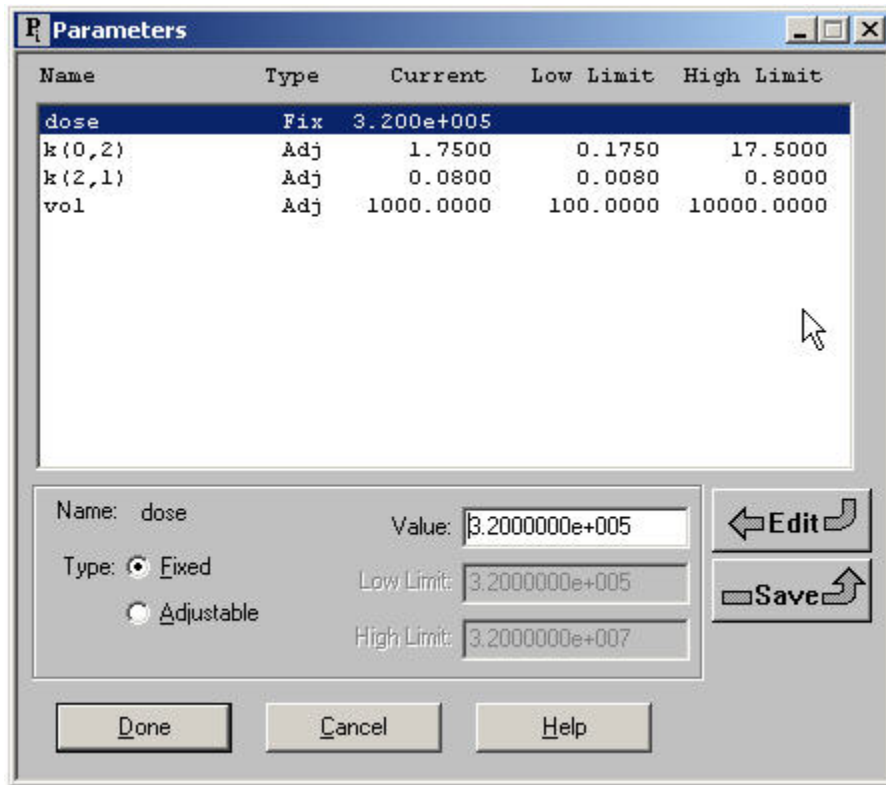
Total objective		-2.227666e+000			
AIC		1.687420e-001			
BIC		2.410866e-001			

h. Close the **Notes** window.

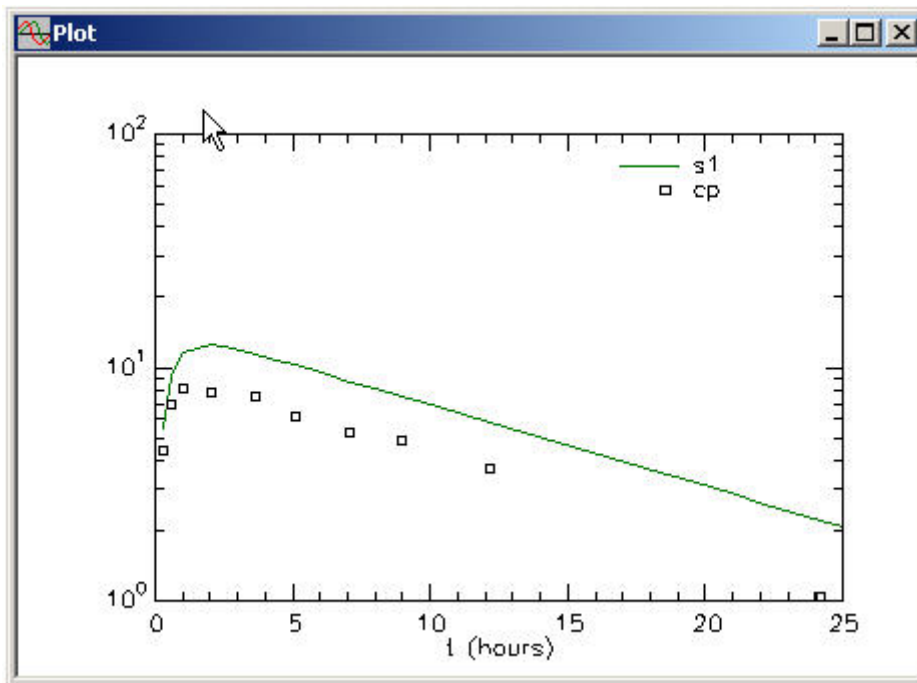
Part 5. Fit the model to data with another set of initial parameter estimates, view the solution and record the results.

The purpose of this part of the case study is to show that another set of initial parameter estimates will lead to an identical solution in terms of the fit but a different final set of parameter values. The difference here is slow absorption and rapid elimination, as opposed to the above where the absorption was rapid and elimination was slow. This is an example of so-called “flip-flop” kinetics that may be encountered when an extended release formulation of a drug is administered.

1. Open the **Parameters** dialog box, and change the values as follows:

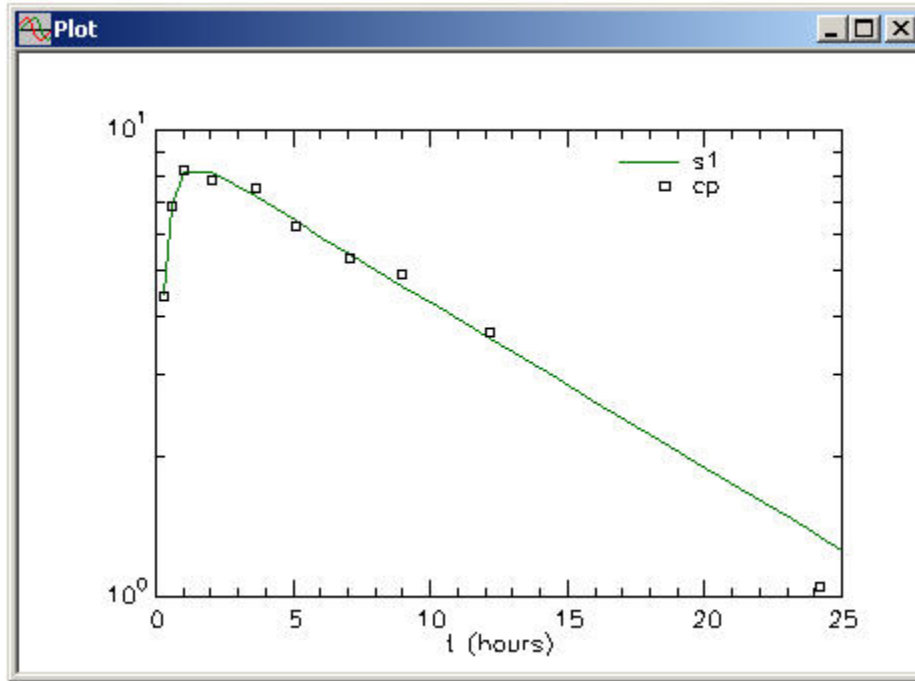



2. Solve the model, and view the solution. Your plot will appear as follows:



3. Fit the model to the data, and view the solution and statistics.

- a. Fit the model to the data. The plot will appear as shown below (Notice that this “Fit” is identical to the previous “Fit”):



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


Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
dose	320000.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,2)	2.45233	1.69913e-001	6.92864e+000	2.06051	2.84415
k(2,1)	0.08142	4.56643e-003	5.60872e+000	0.07089	0.09195
vol	1139.14423	1.05225e+002	9.23719e+000	896.49564	1381.79282
----- Derived Variables -----					
AUC	114.54944	4.54869e+000	3.97094e+000	104.06015	125.03873
AUMC	46.71052	3.03522e+000	6.49794e+000	39.71129	53.70974
Abs_t_half	8.51360	4.77504e-001	5.60873e+000	7.41247	9.61472

		Objective		Scaled Data Variance	
s1 : cp		-2.227552e+000		5.452490e-002	

Total objective		-2.227552e+000			
AIC		1.687991e-001			
BIC		2.411437e-001			

You can see that the statistics are equivalent to those of the previous “Fit” and that the value of the objective function is the same. In addition, the precision of the model parameter estimates is similar.

What about the pharmacokinetic parameters? It is interesting to see which are different. Those that remain the same, C_{max} , T_{max} , AUC and Cl , are expected. However, the two model solutions resulting from the different initial values of the parameter have a dramatic effect on parameters characterizing absorption and elimination.

4. (Optional) Record the results in the **Notes** window.
 - a. In the **Show** menu, click **Notes**, or alternatively, on the **SAAM II Toolbar**, click **Notes** . The **Notes** window will open.
 - b. Under the information from the first “fit”, type “Second “Fit” – slow absorption and rapid elimination.”
 - c. In the **Statistics** window, select all the information for all the parameters.
 - d. On the **Edit** menu, click **Copy**.
 - e. Click in the **Notes** window. In the **Edit** menu, click **Paste**.
 - f. In the **Statistics** window, select and copy the information for the objective function.
 - g. Click in the **Notes** window. In the **Edit** menu, click **Paste**. Your **Notes** window will appear in part as follows:

SAAM II Compartmental - [Notes]

File Edit View Show Compute Set Window Help

First fit - rapid absorption and slow elimination

Parameter	Value	Fixed	Fixed	Fixed	Fixed
dose	320000.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,2)	0.08141	4.56735e-003	5.60999e+000	0.07088	0.09195
k(2,1)	2.45364	1.70046e-001	6.93033e+000	2.06152	2.84577
vol	34322.21630	8.15610e+002	2.37633e+000	32441.41996	36203.01264

----- Derived Variables -----

Variable	Value	Fixed	Fixed	Fixed	Fixed
AUC	114.51772	4.54695e+000	3.97052e+000	104.03244	125.00299
AUMC	1406.60030	1.32569e+002	9.42478e+000	1100.89629	1712.30431
Abs_t_half	0.28250	1.95780e-002	6.93033e+000	0.23735	0.32764
Cl	2794.32746	1.10952e+002	3.97063e+000	2538.47126	3050.18366
Cmax	8.29491	1.37041e-001	1.65210e+000	7.97890	8.61093
Elim_t_half	8.51380	4.77624e-001	5.60999e+000	7.41240	9.61520
M&T	0.40756	2.82451e-002	6.93033e+000	0.34242	0.47269
MRT	12.28282	6.89065e-001	5.60999e+000	10.69383	13.87180
Tmax	1.43569	6.40353e-002	4.46026e+000	1.28802	1.58335
Vss	34322.21630	8.15610e+002	2.37633e+000	32441.41996	36203.01264

Objective Scaled Data Variance

sl : cp -2.227666e+000 5.451867e-002

Total objective -2.227666e+000

AIC 1.687420e-001

BIC 2.410866e-001

Second fit - slow absorption and fast elimination

Parameter	Value	Fixed	Fixed	Fixed	Fixed
dose	320000.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,2)	2.45233	1.69913e-001	6.92864e+000	2.06051	2.84415
k(2,1)	0.08142	4.56643e-003	5.60872e+000	0.07089	0.09195
vol	1139.14423	1.05225e+002	9.23719e+000	896.49564	1381.79282

----- Derived Variables -----

Variable	Value	Fixed	Fixed	Fixed	Fixed
AUC	114.54944	4.54869e+000	3.97094e+000	104.06015	125.03873
AUMC	46.71052	3.03522e+000	6.49794e+000	39.71129	53.70974
Abs_t_half	8.51360	4.77504e-001	5.60873e+000	7.41247	9.61472
Cl	2793.55365	1.10930e+002	3.97094e+000	2537.74823	3049.35907
Cmax	8.29701	1.36846e-001	1.64934e+000	7.98144	8.61257
Elim_t_half	0.28265	1.95837e-002	6.92864e+000	0.23749	0.32781
M&T	12.28252	6.88893e-001	5.60873e+000	10.69393	13.87111
MRT	0.40778	2.82533e-002	6.92864e+000	0.34262	0.47293
Tmax	1.43625	6.40393e-002	4.45879e+000	1.28857	1.58392
Vss	1139.14423	1.05225e+002	9.23719e+000	896.49564	1381.79282

Objective Scaled Data Variance

sl : cp -2.227552e+000 5.452490e-002

h. Close the **Notes** window.



Flip-flop kinetics. When you use this model to analyze your data, you must be aware that there are two solutions that give the same “Fit” to the data. Which solution you achieve will depend upon your choice of initial parameter

estimates. The difference in the two solutions is rapid absorption and slow elimination versus slow absorption and rapid elimination.

One can often choose the “correct” model based on the volume parameter. One may know, *a priori*, that the volume of distribution for a particular drug should be some known percentage of body weight, for example. There are cases when the choice for the volume may not be so obvious. This could happen in studies at the organ or cellular level.

In this case study, the volume of 34.3 L or 0.49 L/kg obtained for compartment 2 when absorption rate is more rapid than elimination agrees with the expected distribution volume of 0.5 L/kg expected for theophylline (see tables in the Goodman and Gilman text). On the other hand, the second volume of 11.39 L or 0.16 L/kg for compartment 2 resulting from slow absorption and rapid elimination is unrealistic, so the correct choice would be the model with rapid absorption and slow elimination.



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

- This very simple one-compartment model with absorption used to explain the kinetics of a drug administered orally has two solutions.
- If your model has more than one solution, when you fit your model to your data, the solution that you obtain depends upon how you choose your initial parameter estimates.
- If you use this model, then you must choose the “correct” solution based upon additional information about the system you are studying.
- In this case study we have assumed that the oral dose is completely absorbed ($F = 1.0$ where F is the parameter for fraction absorbed). If this is not the case, we can only estimate relative clearance and distribution volume as CL/F and V/F . The fact that expected value for the volume of compartment 2 was obtained with the rapid absorption model not only supports this model choice but indicates that the oral absorption of this theophylline formulation is essentially complete.

Modeling Notes

What happens in this situation? There are ways to choose one set of parameter values over another, but this relies on additional information about the drug and subjects being studied.

You can see why there are two solutions to this model by performing an *a priori* identifiability analysis on the model. You can do this by solving the system of differential equations that the model represents.

Remember that the data in this case study can be “Fitted” to the two-exponential model,

$$y(t) = A(\exp(-a \cdot t) - \exp(-b \cdot t))$$

If d is the amount of the bolus injection, then the solution for $q_2(t)$ for the differential equation represented by Compartment **q2** is

$$q_2(t) = \frac{d \cdot k(2,1)}{(k(0,2) - k(2,1))} (\exp(-k(2,1) \cdot t) - \exp(-k(0,2) \cdot t))$$

Using the measurement equation $s1 = q2/vol$, one has

$$s1 = \frac{q_2(t)}{vol} = \frac{d \cdot k(2,1)}{vol \cdot (k(0,2) - k(2,1))} (\exp(-k(2,1) \cdot t) - \exp(-k(0,2) \cdot t))$$

The relationship between $s1$ and $y(t)$ will show why there are two solutions for this model. Since they both describe the same set of data, $s1 = y(t)$! This means the coefficients for the sum of exponentials must be the same, and the exponentials and rate constants $k(i,j)$ are the same.

More specifically, if the exponential has been “Fitted” to the data, then

$$\frac{d \cdot k(2,1)}{vol \cdot (k(0,2) - k(2,1))} = A$$

from which vol can be found.

It is easy to see that $k(2,1)$ and $k(0,2)$ play interchangeable roles as you observed in the “Fitting” exercise above. That is, since the data in this case study can be “Fitted” to the two-exponential model,

$$y(t) = A(\exp(-a \cdot t) - \exp(-b \cdot t))$$

you can interchange “a” and “b”, and write

$$\frac{d \cdot k(2,1)}{vol \cdot (k(2,1) - k(0,2))} (\exp(-k(0,2) \cdot t) - \exp(-k(2,1) \cdot t)) = A \cdot (\exp(-a \cdot t) - \exp(-b \cdot t))$$

from which you have

$$\frac{d \cdot k(2,1)}{vol \cdot (k(2,1) - k(0,2))} = A$$

The two cases you observed during the two “Fitting” processes can now be explained. In case 1, $k(2,1) = a$ and $k(0,2) = b$, and you can solve for vol . In case 2, $k(2,1) = b$ and $k(0,2) = a$, and you can solve for vol .

Data for this case study

DATA

#Dose: 320 mg/kg Wt. 70.5kg

#Units: mcg/ml

(SD 1.0)

t cp

0 0

0.27 4.4

0.58 6.9

1.02 8.2

2.02 7.8

3.62 7.5

5.08 6.2

7.07 5.3

9 4.9

12.15 3.7

24.17 1.05

END

#

Equations for the noncompartmental parameters

#Tmax = $\log((k(2,1)/k(0,2)))/(k(2,1)-k(0,2))$

#Cmax=(dose/vol)*exp(-k(0,2)*Tmax)

#Elim_t_half=log(2)/k(0,2)

#Abs_t_half=log(2)/k(2,1)

#AUC=dose/(vol*k(0,2))

#AUMC=dose/(vol*k(0,2)*k(0,2))

#MRT=AUMC/AUC

#MAT=1/k(2,1)

#Cl=vol*k(0,2)

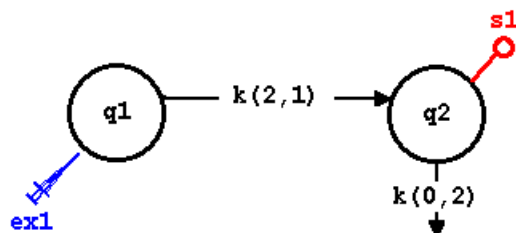
#Vss=Cl*MRT

**Appendix: Obtaining Initial Parameter Estimates for a
Two-Compartment Model with Input into One Compartment and
Samples from the Second Compartment
(the One-Compartment Model with Absorption)**

The situation described in this appendix is one in which data, normally plasma, are rising and falling following a bolus injection of drug, normally into a compartment other than plasma. The typical situation is oral administration of a drug as a tablet with plasma samples; it is the so-called one compartment model with absorption.

This appendix assumes you are familiar with the notion of half-life, and how it is used to estimate the rate constant of the one-compartment model following a bolus injection or constant infusion. This is explained in the Appendix to the case study on cadralazine kinetics.

The two-compartment model is the following:

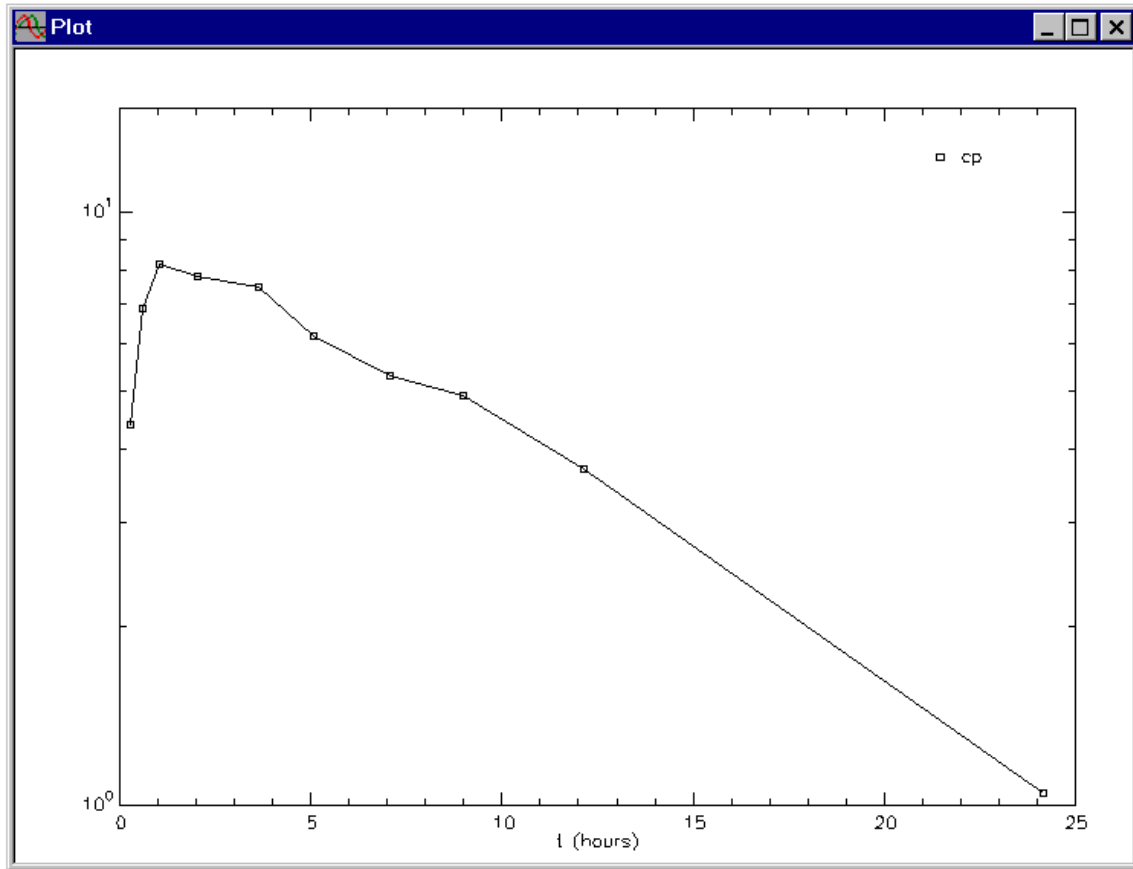


The rate constants to be estimated are $k(2,1)$ and $k(0,2)$ together with the volume term, vol , if the sample equation is $s1=q1/vol$. The exponential model for this situation is

$$y(t) = A_1 \cdot e^{-\alpha t} + A_2 \cdot e^{-\alpha_2 t} \quad A_1 + A_2 = 0 \quad (1)$$

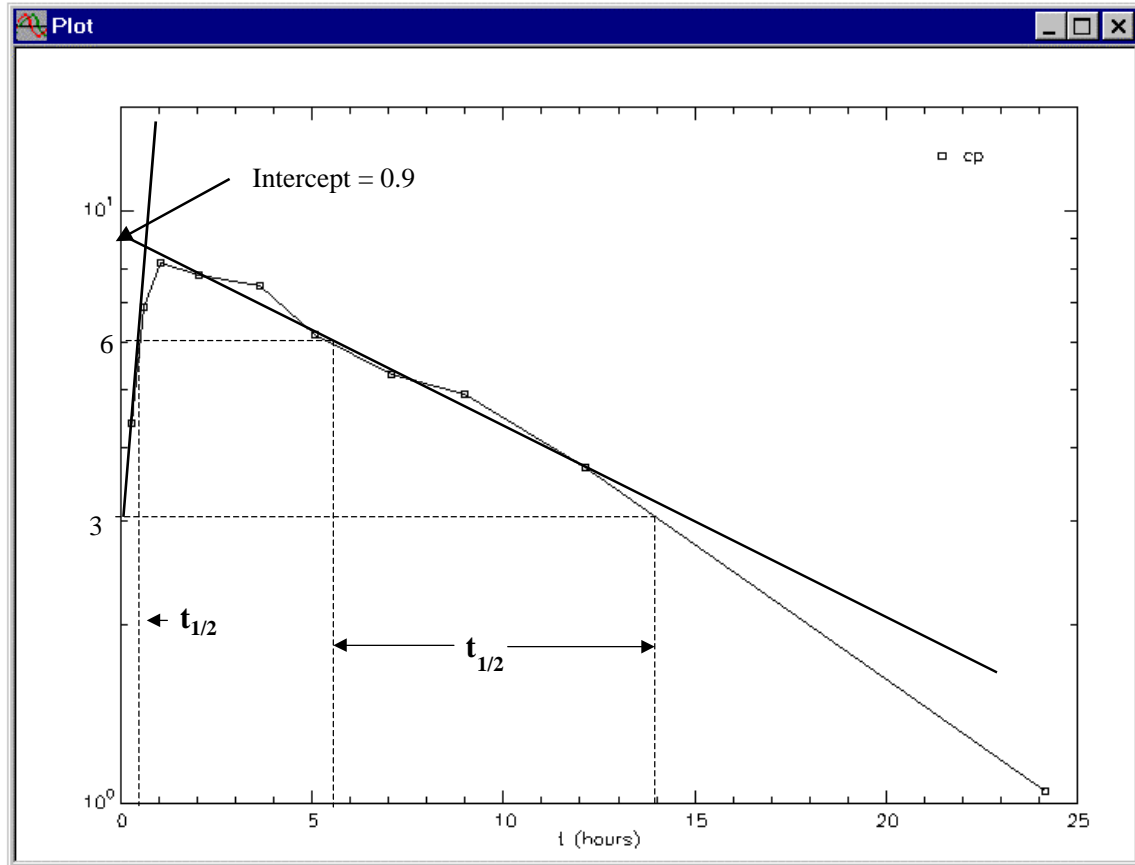
In this appendix, you will learn how to obtain the initial estimates for both the compartmental and exponential model.

If you plot the data in **theo_oral.dat** in semi-log form, connect the data using the **Line-Plot** option in the **View** menu, and set the **Plot/Table Scale Y axis** from 1.0 to 15, you will obtain



These data are classical rising and falling data. The falling portion of the curve appears to be decaying monoexponentially.

How can you use the notion of half-life to obtain initial parameter estimates? It is clear for the decaying portion of the data, that you can simply draw a straight line through the data and estimate the half-life as you did for the one-compartment model following the bolus injection. To obtain the second parameter estimate, you can simply draw a tangent line to the rising portion of the curve as you did for the one compartment model following a constant infusion. This is illustrated in the following figure:



For the terminal slope, the time it takes to go from “6” to “3” is about 8.5 hours for a half-life of $\ln(2)/8.5$, or .08. For the initial rise, the time to go from “3” to “6” is about 0.4 hours for a half-life of $\ln(2)/0.4$, or 1.75. Estimates for $k(2,1)$ and $k(0,2)$ are thus 1.75 and 0.08. Obviously this supports rapid absorption and slow elimination.

There are no set rules for obtaining an estimate for the volume vol , but the following rule of thumb often works (it may require some hand adjusting). Remember that the dose is 320 mg and the units of the data are $\mu\text{g/ml}$. An estimate for vol can be obtained by dividing the dose, in this case 320 mg or 320,000 μg , by the point where the decaying slope intersects the y-axis, in this case 0.9 $\mu\text{g/ml}$. An estimate for vol is thus 300,000/0.9 which is about 300,000 ml. This is obviously too high and will require some hand-fitting.

The other way to estimate vol is to take advantage of knowing the subject’s body weight. Extracellular fluid space is approximately 16% of body weight, and total body water is about 65% of body weight. The subject here weights 70.5 kg, so expected extracellular fluid space and total body water are respectively 11,300 ml and 45,825 ml, or 11.3 L and 45.8 L. For theophylline we can expect that vol will lie somewhere between the expected volumes for extracellular fluid space and total body water (for further explanation see reference 3 above).

In summary, the steps in obtaining the initial estimates for the one-compartment model with absorption are:

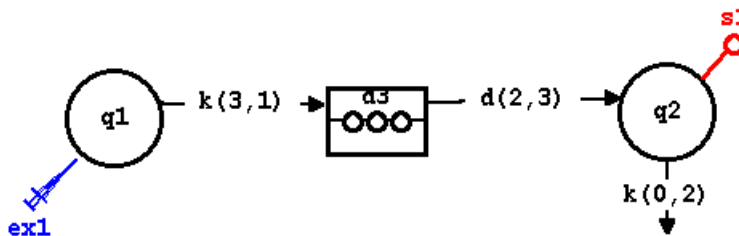
- Plot the data on semi-log paper.
- Draw a straight line through the decaying data; extend the line to intersect with the y-axis.
- Calculate the half-life $t_{1/2}$ as described above; this provides an estimate for $k(0,2)$.
- Note where the line intersects the y-axis. Dividing the dose by this number provides an estimate for VI (remember to keep the units consistent.)
- Draw a straight line through the rising data.
- Calculate the half-life $t_{1/2}$ as described above; this provides an estimate for $k(2,1)$.

If you are fitting (1) to the data (written again for convenience below as (2))

$$y(t) = A_1 \cdot e^{-\alpha_1 t} + A_2 \cdot e^{-\alpha_2 t} \quad A_1 + A_2 = 0 \quad (2)$$

estimates for A_2 and α_2 are obtained by analyzing the decaying data. The estimate for α_2 is 0.08 and A_2 is the intercept with the y-axis, 0.9. The estimate for α_1 comes from the rising portion of the data and hence is 0.35. Since $A_1 + A_2 = 0$, an estimate for A_1 is $-A_2$, or -0.9. Because of the constraint equation $A_1 + A_2 = 0$, one needs to estimate only A_1 or A_2 .

An important point to note is the following: Suppose there is a delay in the appearance of drug in plasma. The model changes to



How is this handled? Exactly the same as above with the exception of the delay. You extend the initial rising portion to intersect with the x-axis; where it intersects will give you an initial estimate of the delay, call it $tlag$. To obtain estimates of the rate constant and volumes, or α_1 and α_2 , proceed directly as described above. Equation (1), however, has to change to accommodate the delay:

$$y(t) = \begin{cases} 0 & 0 \leq t \leq tlag \\ A_1 \cdot e^{-\alpha_1(t-tlag)} + A_2 \cdot e^{-\alpha_2(t-tlag)} & tlag < t \end{cases} \quad A_1 + A_2 = 0 \quad (3)$$