

Epsilon-aminocaproic Acid (EACA) Pharmacokinetics/Pharmacodynamics

Case Study

- How to use a biophase compartment to link PK and PD
- How to create an E_{\max} PD Model
- How to use SAAM II Bayesian

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Pharmacokinetics/Pharmacodynamics of Epsilon-aminocaproic Acid (EACA)

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 use a biophase compartment to link PK and PD.
- How to create an E_{\max} PD model.
- How to use the **Bayesian** feature of **SAAM II**.

Data Required

The data file for this case study is

EACA.dat

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

Introduction

This case study will show you how to analyze data from a study of EACA pharmacokinetics and antifibrinolytic or clot stabilizing effects in normal subjects. An E_{\max} model with a biophase or link compartment will be used for the PD analysis. The estimated PD parameters will be shown to be compatible with the proposed mechanism of EACA action.

EACA has been used to control hemorrhage in patients with a variety of bleeding problems. Lysis of fibrin in blood clots entails initial adsorption of plasminogen to fibrin, followed by cleavage of fibrin-bound plasminogen to plasmin, which results in fibrinolysis and clot dissolution. EACA is thought to act by binding to plasminogen, thereby altering its conformation and preventing or reversing its attachment to fibrin. An initial *in vitro* study found that EACA binds to the lysine binding sites of the A-chain of plasminogen with a dissociation constant of 0.55 mM or 72 $\mu\text{g/mL}$ [1]. It has since been shown that plasminogen has five different EACA binding sites, four with low affinity ($k_d = 5 \text{ mM}$) and one high affinity site ($k_d = 9 \text{ }\mu\text{M}$).

In this case study, data from a study of EACA PK/PD in a normal subject who received an intravenous dose of this drug will be analyzed [2]. Fibrinolytic activity was expressed as percent of total radioactivity released into the supernatant when trace amounts of ^{125}I -labeled fibrinogen were added to whole blood obtained before and at intervals after EACA administration, and the mixture incubated with bovine thrombin for three hours at 37°C [3]. The approach taken in this case study will be similar to that of Abiko et al. [1] in that only a single EACA binding site for plasminogen will be modeled.

1. Abiko, Y., Iwamoto, M., Tomikawa, M. "Plasminogen-plasmin system: V. A. stoichiometric equilibrium complex of plasminogen and a synthetic inhibitor." *Biochim. Biophys. Acta.* 1969, 185:424-431.
2. Frederiksen, M. C., Bowsher, D. J., Ruo, T. I., Henthorn, T. K., Ts'ao, C-H., Green, D., Atkinson, A. J., Jr. "Kinetics of epsilon-aminocaproic acid distribution, elimination, and antifibrinolytic effects in normal subjects." *Clin. Pharmacol. Ther.* 1984, 35:387-93.
3. Carroll, R. C., Gerrard, J. M., Gilliam, J. M. "Clot retraction facilitates clot lysis." *Blood.* 1981, 57:44-8.

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

The first step will be to create a 3-compartment system model to describe the kinetics of the EACA which was administered iv as a short infusion.



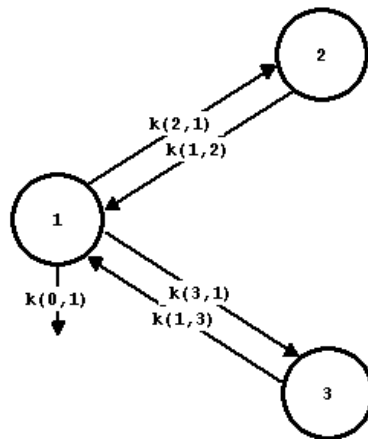
Which system model structure? The 3-compartment model is chosen here because a preliminary analysis showed a three exponential model was most appropriate for the data. The conclusion is supported by *a priori* knowledge from the literature which suggests this is the most appropriate model. Using information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

If you are unsure of the model used in the literature, you should start first with the two-compartment model, and then move to the three- and four-compartment models to be sure the three-compartment model is in fact the most appropriate for your data.

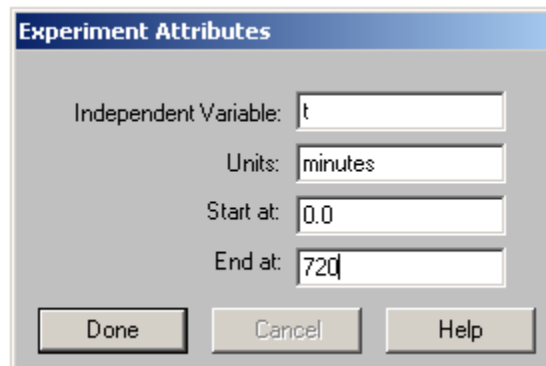


1. **Start the SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open. In the **SAAM II Toolbox**, be sure the **Model** tools are available.

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

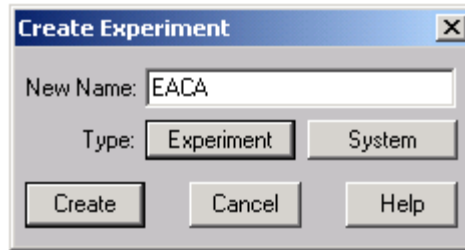


3. In the **SAAM II Toolbox**, click **Experiment**. Notice that the **Model** tools are unavailable and the **Experiment** tools are available. The **Experiment Attributes** dialog box will open.
- Leave “minutes” in the **Units** box.
 - Enter “720” in the **End at** box. The **Experiment Attributes** dialog box will appear as follows:



- Click **Done**.

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



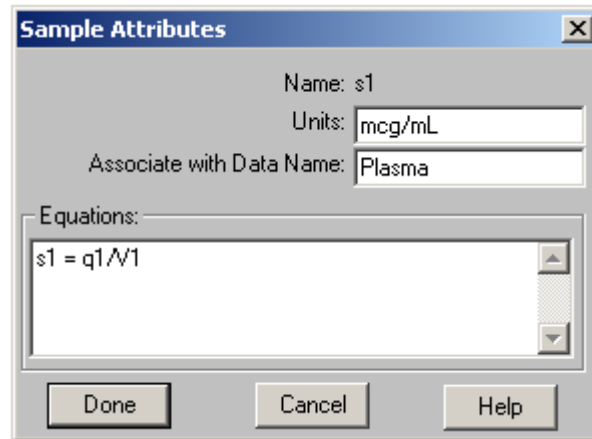
- d. Click **Create**. Notice “EACA” appears as the name under “Experiment” in the **SAAM II Toolbox**.
4. Create a sample.
 - a. In the **SAAM II Toolbox**, click **Sample**.
 - b. Click Compartment **q1**, then click on the **Drawing Canvas**. The sample **s1** will appear.
 - c. Double-click **s1** to open the **Sample Attributes** dialog box.
 - d. Type “mcg/mL” in the **Units** box.



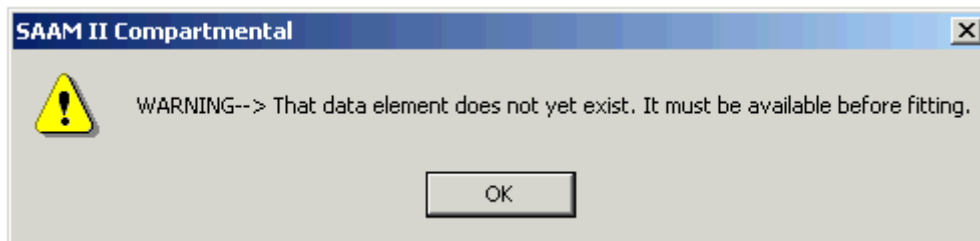
Units. The units of the data are micrograms/milliliter. Normally this would be written $\mu\text{g/ml}$ or $\mu\text{g/mL}$. SAAM II does not accept μ for micro. Writing the units mg/ml would be normally interpreted as milligrams/ml. Thus writing the units mcg/mL is an alternate way to denote micrograms/milliliter.



- e. Type “Plasma” in the **Associate with Data Name** box.
- f. Edit the sample equation “ $s1 = q1$ ” to read “ $s1 = q1/V1$ ”. The **Sample Attributes** dialog box will appear as follows:



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



- h. Click **OK**.
5. Create an input.
- An intravenous dose of 9900 mg of EACA was infused over 15 minutes.
- 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.
 - Select **Infusion** as the **Input Type**.
 - Enter "660" in the **Constant Rate** box.
 - Enter "0" in the **Event Start** box.
 - Enter "15" in the **Event Stop** box.
 - 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
Infusion	-	660.000	0.000	15.000	-	-

Input Type:

Bolus
 Infusion
 Primed Infusion
 Equation

Initial Amount:

Constant Rate:


Event Start:

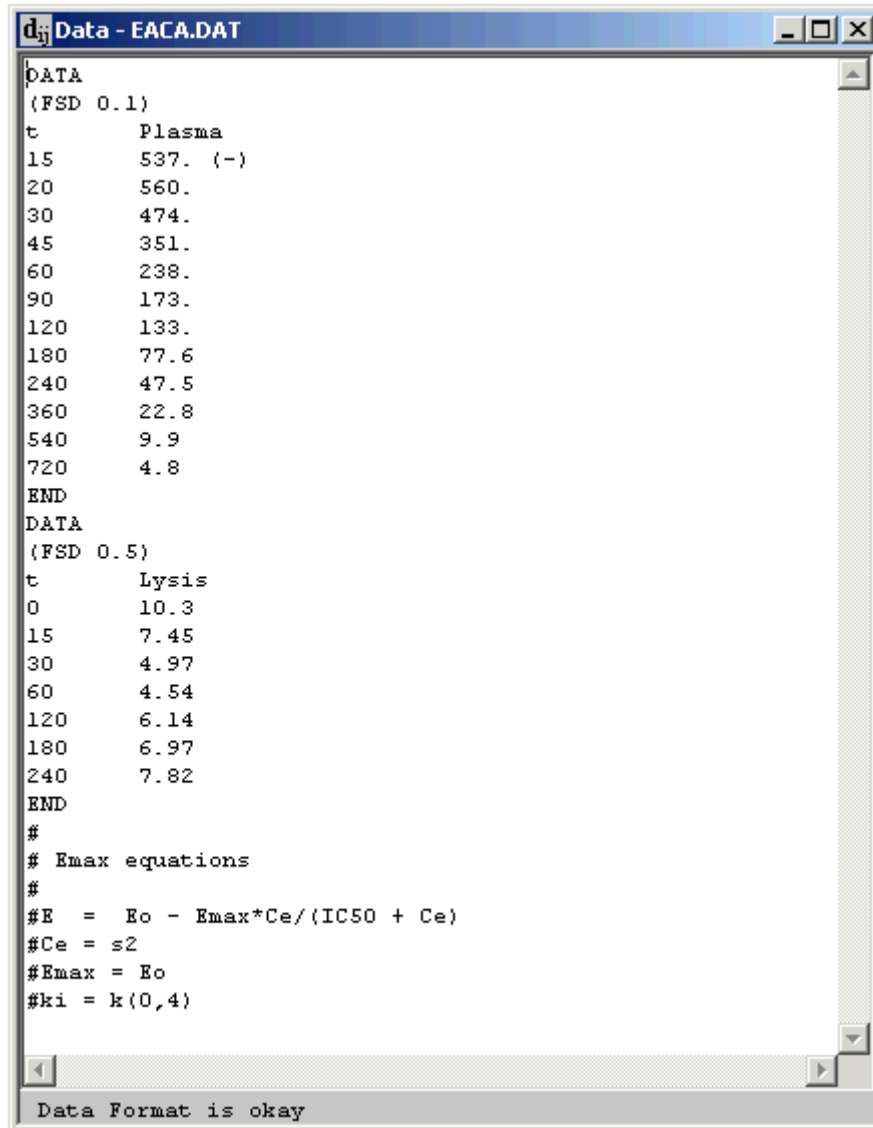
Event Stop:

Repeat Every:

Nr. of Repeats:

Equation:


- i. Click **Done**.
6. Add the data to your model.
 - a. In the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data** . The **Data** window will open.
 - b. In the **File** menu, click **Open**. The file **EACA.dat** should appear in the list (if it does not, find the folder where you put this data file).
 - c. Double-click **EACA.dat**. The data file contains the plasma EACA data following the 15-minute constant infusion, Plasma. It also includes a measure of clot lysis that will be used to assess EACA's antifibrinolytic effect. These data will be included in the model later in the case study. The **Data** window should appear as follows:



```
DATA
(FSD 0.1)
t      Plasma
15     537. (-)
20     560.
30     474.
45     351.
60     238.
90     173.
120    133.
180    77.6
240    47.5
360    22.8
540    9.9
720    4.8
END
DATA
(FSD 0.5)
t      Lysis
0      10.3
15     7.45
30     4.97
60     4.54
120    6.14
180    6.97
240    7.82
END
#
# Emax equations
#
#E = Eo - Emax*Ce/(IC50 + Ce)
#Ce = s2
#Emax = Eo
#ki = k(0,4)
```

Data Format is okay

The weighting scheme is FSD so you can leave the variance model set as the default data-relative. Note that the first Plasma data point is followed by “-“ to unweight it. This is because it was drawn immediately at the end of the infusion before intravascular mixing was complete. Notice also the equations for the Emax model are included; these will be pasted into the **Equations** window later.

- d. Close the **Data** window.
7. Enter the parameter values.
 - a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar**, click **Parameters** . The **Parameters** dialog box will open.

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

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

$V1 = 15$ (low limit 5, high limit 30)

$k(0,1) = .01$

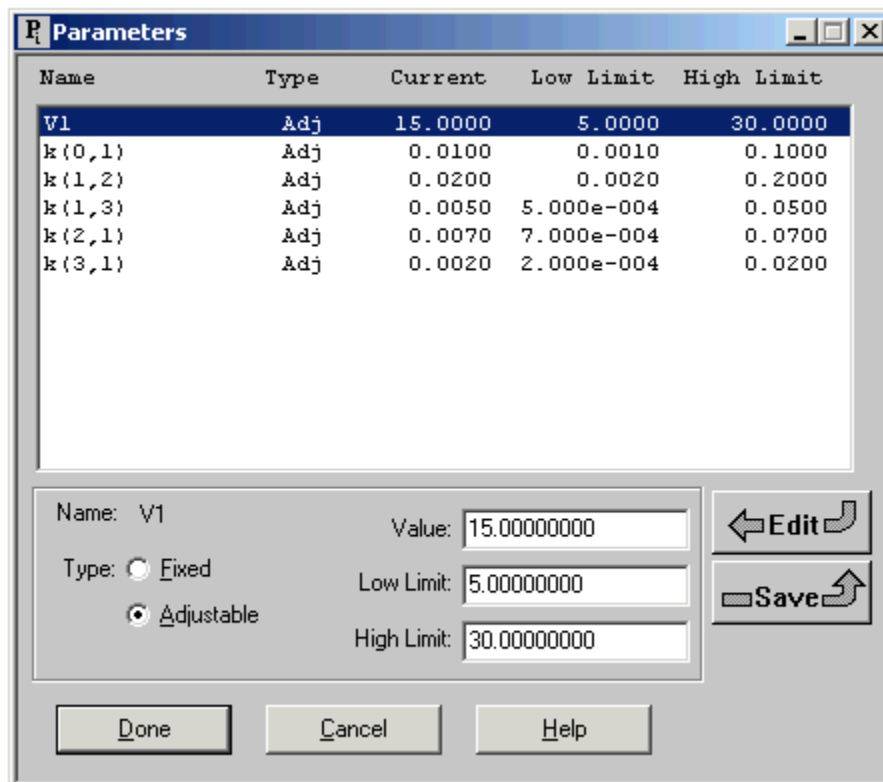
$k(1,2) = .02$

$k(1,3) = .005$

$k(2,1) = .007$

$k(3,1) = .002$

When you have finished, your **Parameters** dialog box should appear as follows (which parameter is highlighted will depend upon which one you entered last; it could be $k(3,1)$, for example):



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 parameter $V1$ is highlighted. Below the table, there are input fields for Name, Value, Type (Fixed or Adjustable), Low Limit, and High Limit. The "Adjustable" radio button is selected. There are also buttons for Edit, Save, Done, Cancel, and Help.

Name	Type	Current	Low Limit	High Limit
$V1$	Adj	15.0000	5.0000	30.0000
$k(0,1)$	Adj	0.0100	0.0010	0.1000
$k(1,2)$	Adj	0.0200	0.0020	0.2000
$k(1,3)$	Adj	0.0050	5.000e-004	0.0500
$k(2,1)$	Adj	0.0070	7.000e-004	0.0700
$k(3,1)$	Adj	0.0020	2.000e-004	0.0200

Name: $V1$ Value: 15.00000000
Type: Fixed Adjustable
Low Limit: 5.00000000 High Limit: 30.00000000



Buttons: Done, Cancel, Help, Edit, Save

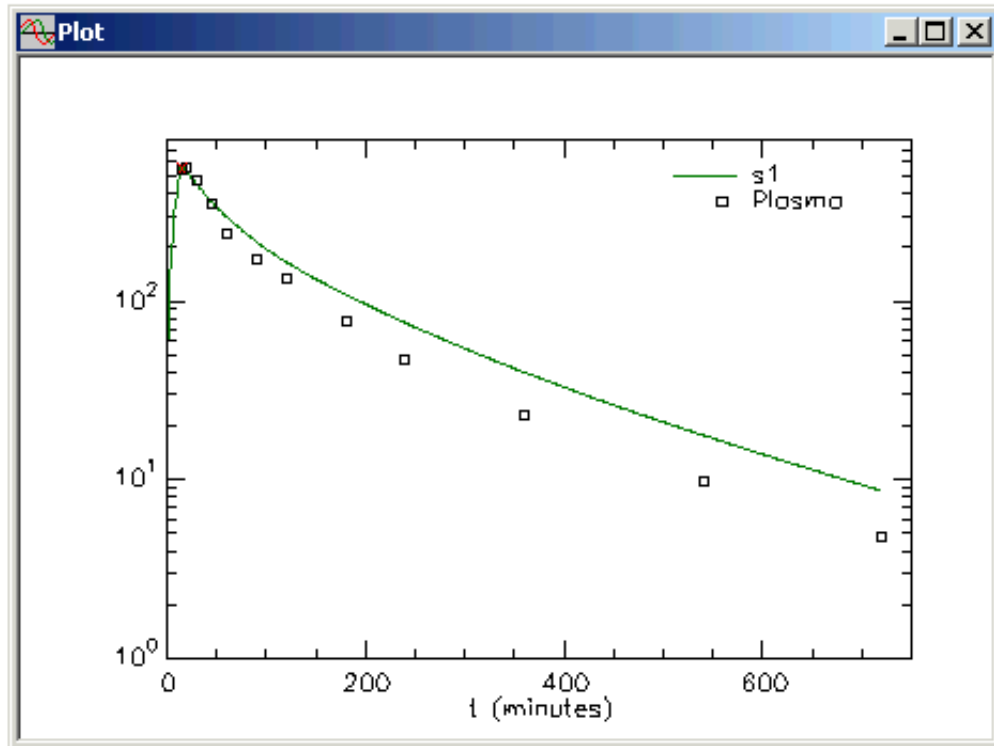
- c. Click **Done**.



Parameter estimates. The parameter estimates were taken from the literature. This is because a model from the literature is being used, and this can provide reasonable initial estimates. If such estimates were not available, one normally would start constructing the two, and then moving to the three-compartment model.




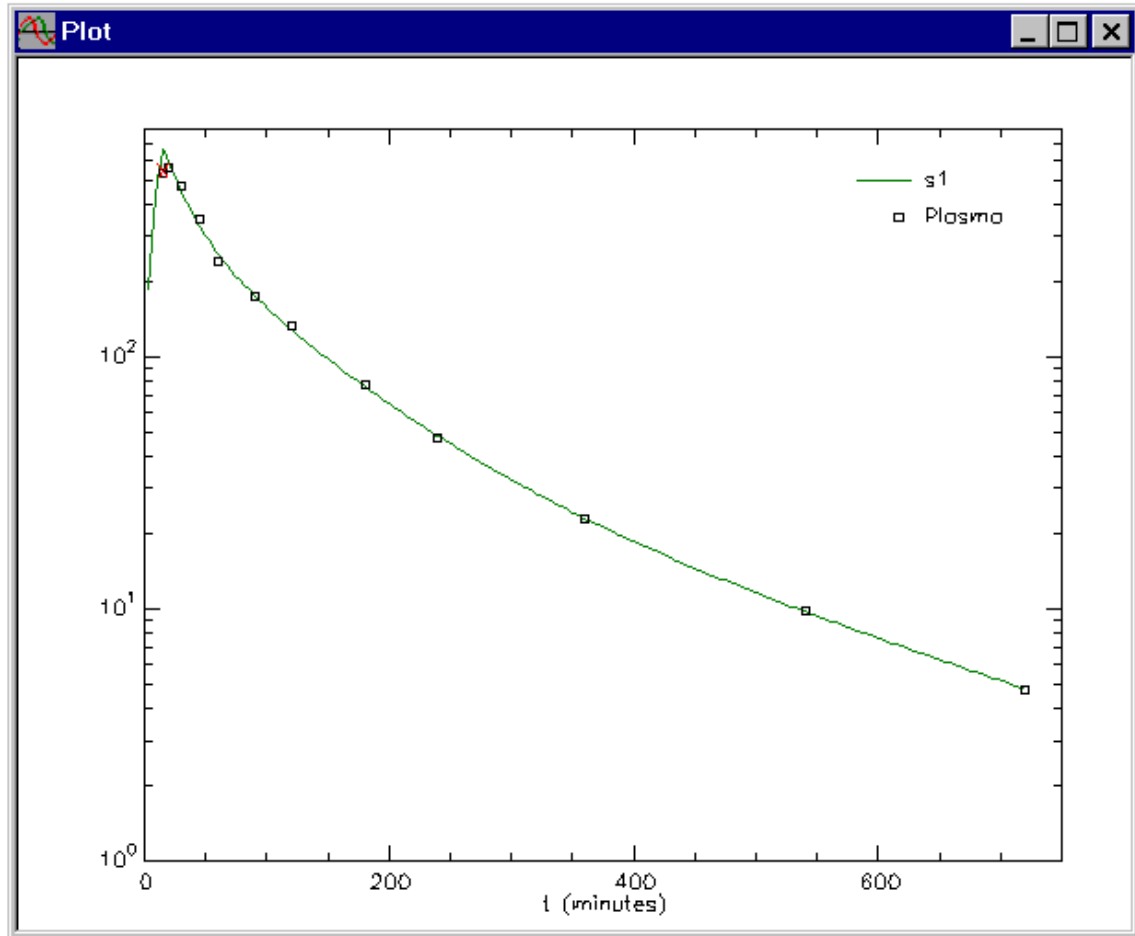
8. Solve your model and view the solution.
 - a. In the **Compute** menu, click **Settings**. The **Computational Settings** dialog box will open.
 - b. Enter “500” in the **Min. Nr. of Calculation Intervals** box. Remember this will improve the resolution of your plots.
 - c. Click **Done**.
 - d. In the **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** . The **Plot and Table Variables** dialog box will open.
 - f. Open the **Plot and Table Variables** dialog box. If the **List All Variables** box is checked, clear it to list only those variables associated with data.
 - g. Click **s1:Plasma**; it will move to the **Current Selection** pane.
 - h. Click **Done**. The following plot will appear (if it does not appear in semilog mode, in the **View** menu click **Semilog**). The **Plot/Table Scale** has been set as follows – X-Axis minimum and maximum are respectively 0 and 750; Y-Axis minimum and maximum are respectively 1 and 800:



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.

The initial estimates from the literature 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:



Note the "x" through the first datum which indicates it is unweighted.

b. View the statistics. The **Statistics** window will appear as follows:

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
V1	12.04754	1.40550e+000	1.16663e+001	8.43458	15.66050
k(0,1)	0.01536	1.65048e-003	1.07425e+001	0.01112	0.01961
k(1,2)	0.02707	1.10052e-002	4.06484e+001	-0.00122	0.05536
k(1,3)	0.00472	1.43091e-003	3.03342e+001	0.00104	0.00840
k(2,1)	0.01261	6.06331e-003	4.80966e+001	-0.00298	0.02819
k(3,1)	0.00299	1.30499e-003	4.36146e+001	-3.62484e-004	0.00635

	Objective	Scaled Data Variance
s1 : Plasma	3.344747e+000	3.064425e-001
Total objective	3.344747e+000	
AIC	3.227676e+000	
BIC	3.354279e+000	

It is apparent from the Coefficients of Variation in the **Statistics** window that some model parameters are better defined than others. The largest Coefficient of Variation is just under 50%. The central compartment volume and elimination are better determined than the exchange rate constants.



Parameter error estimates. This situation illustrates two phenomena that occur fairly often in the development of models and the analysis of kinetic data.

First, occasionally the lower limit of the 95% confidence interval is negative; this contradicts the constraint that none of the transfer rate constants can be negative. The other is that some parameters will have correlation coefficients well above 0.9 or below -0.9, yet have acceptable coefficients of variations.

The confidence limit situation is normally reflective of parameters with borderline to large coefficients of variation, and should be taken as a warning that the parameter, or parameters, in question may be suspect. One should be careful about reaching conclusions based upon these parameters. Normally, however, the negative portion will represent only a very small part of the interval.

The highly correlated parameters situation is more difficult to explain. It has to do with the “shape” of parameter space. You can think of it as a very narrow canyon running at, for example, a 45° angle to the x- and y-axes. The high correlation comes from the well-defined “canyon”. The correlation coefficients are calculated from the width of the canyon; if the canyon is very narrow, the distance along the x- and y-axes will be small meaning very low

coefficients of variation. As the width increases, the coefficients of variation will increase.

In the situation when parameters are highly correlated with very acceptable coefficients of variation, you should change the initial estimates of the parameters in question and refit your model to the data. If the parameters return to the same value, then you can conclude that, numerically, they are good. If they return to different values, even though the coefficients of variations are acceptable, then there is a problem with the model, and you may have to introduce parameter constraints to deal with the problem.

If the parameters are highly correlated and the coefficients of variation are marginal, then you need to investigate your experimental design or model more closely. For example, you may have either to simplify your model, or introduce parameter constraints. In this case, the experiment was not carried out long enough to accurately define the terminal exponential phase of the plasma level vs. time curve shown in the plot. The use of even shorter experiment times in some earlier pharmacokinetic studies of this drug led to substantial underestimation of EACA's distribution volume.

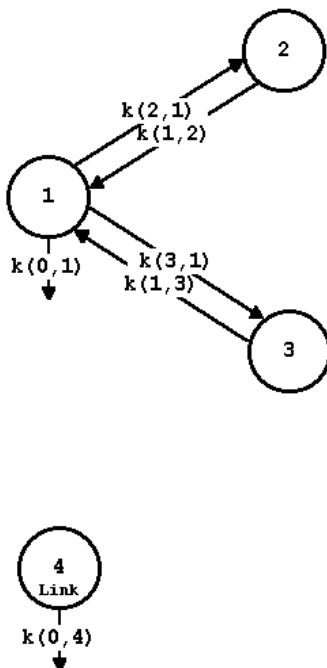


- c. Close the **Statistics** and **Plot** windows.

Part 2. Analyze the antifibrinolytic effect data.

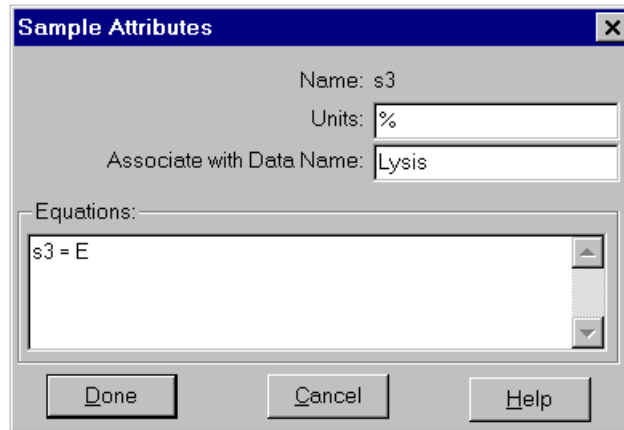
The next step in the case study will be to create a biophase or link compartment and a fibrinolysis effect sample.

1. In the **SAAM II Toolbox**, click **Model** to be sure these tools are available.
2. Create the biophase or link compartment.
 - a. Click **Compartment** in the **SAAM II Toolbox** and then click on the **Drawing Canvas** below Compartment 1 and $k(0,1)$. This will create Compartment 4.
 - b. Double-click on Compartment 4 to open the **Compartment Attributes** dialog box. Type "link" in the **Reference Name** box. Click **Done**.
 - c. Click **Flux** in the **SAAM II Toolbox**.
 - d. Click on compartment 4 and then on the **Drawing Canvas**. This will create $k(0,4)$. Your model will appear as follows:



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. Edit the sample equation “ $s2 = q4$ ” to read “ $s2 = q4/V4$ ”.
 - f. Click **Done**.
4. Create the sample for the pharmacodynamic (lysis inhibition) effect.
 - a. In the **SAAM II Toolbox**, click **Sample**.
 - b. Click Compartment **q4**, then click on the **Drawing Canvas**. The sample **s3** will appear.
 - c. Double-click **s3** to open the **Sample Attributes** dialog box.
 - d. Type “%” in the **Units** box.

- e. Type “Lysis” in the **Associate with Data Name** box.
- f. Edit the sample equation “s3 = q3” to read “s3 = E”. The **Sample Attributes** dialog box will appear as follows:



- g. Click **Done**.



Samples not linked to compartments. You will notice that after you click done that the sample **s3** is no longer has a line connecting it to compartment **q4**. The reason is that q4 no longer appears in the sample equation. Samples and sample equations thus have great flexibility in that they do not have to be associated with a specific compartment or compartments. Notice also that the circle is closed; this is because the sample is associated with data.



5. Create an input for the link compartment.
 - a. In the **SAAM II Toolbox**, click **Input**
 - b. Click Compartment **q4**, and then click on the **Drawing Canvas**. The input **ex2** will appear.
 - c. Double-click **ex2** to open the **Exogenous Input** dialog box.
 - (1) Select **Equation** as the **Input Type**.
 - (2) Enter “0” in the **Event Start** box.
 - (3) Enter “720” in the **Event Stop** box.

(4) Type “ $ex2 = ki*s1$ ” in the **Equation** box. Because **s1** is entered in the equation rather than **q1**, this defines the new parameter *ki* as an intercompartmental clearance.

(5) Click **Add**. The **Exogenous Input** dialog box will appear as follows:

Name	Reference	Units	Type	Initial	Constant	Start	Stop	Repeat Every	Nr. Repeats
ex2			Equation	ex2 = ki*s1		0.000	720.000	-	-

Input Type:

Bolus

Infusion

Primed Infusion

Equation

Initial Amount: 0.0

Constant Rate: 0.0

Event Start: 0.0

Event Stop: 720.00000000

Repeat Every:

Nr. of Repeats:

Equation: ex2 = ki*s1

Save

Edit

Add

Delete

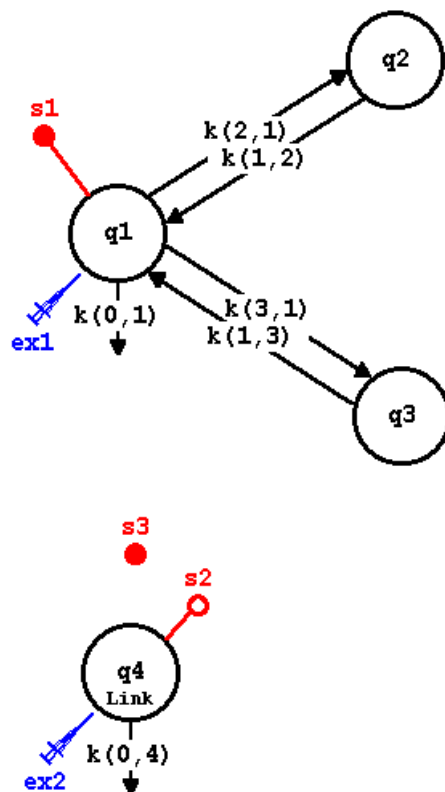
Split Input...

Done

Cancel

Help

(6) Click **Done**. Your model will appear (after you move the sample objects) as follows:



6. Create the pharmacodynamic equation.

a. The following equations will be entered in the **Equations Defined Here** pane:

$$"E = E_0 - E_{max} * C_e / (IC_{50} + C_e)"$$

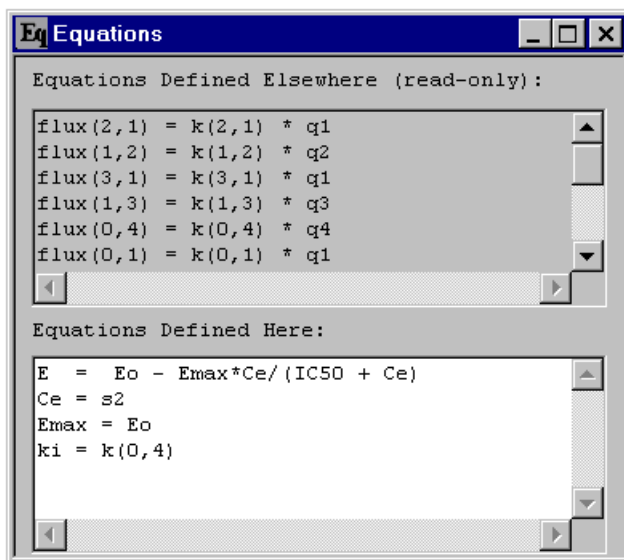
$$"C_e = s_2"$$

$$"E_{max} = E_0"$$

$$"k_i = k(0,4)"$$

The first equation describes the relationship between the observed effect, **E**, the initial measurement of fibrinolysis, E_0 , the concentration of EACA in the link compartment, C_e , and the constants of the Emax model, E_{max} and IC_{50} . The second equation specifies C_e as equal to s_2 . The third equation specifies that that maximum antifibrinolytic effect, E_{max} , would simply consist of a complete reversal of the fibrinolysis that was initially observed, E_0 . In the last equation $k(0,4)$ is defined as a clearance that is equal to k_i . In the $k_i * s_1$ input to Compartment **q4**, k_i is equivalent to an intercompartmental clearance between **q1** and **q4**. However, the system model is structured without actual mass transfer between the pharmacokinetic model and the effect compartment. This allows the effect kinetic data to be analyzed without perturbing the pharmacokinetic "Fit."

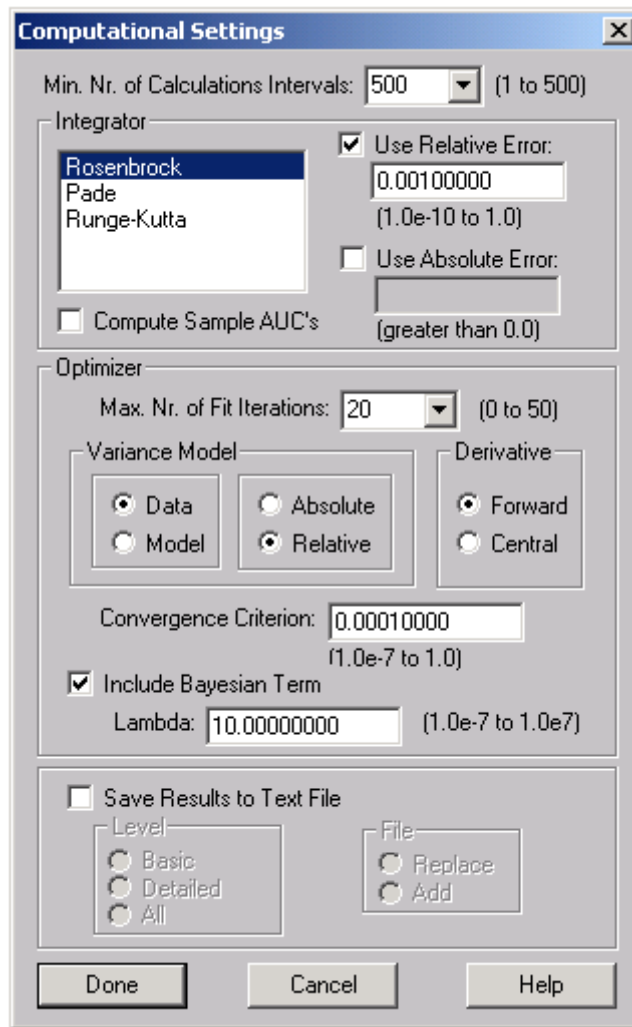
- (1) Open the **Data** window. Select and copy the Emax equations that appear at the end of the file. Close the **Data** window.
- (2) Open the **Equations** dialog box. Paste the equations in the **Equations Defined Here** pane.
- (3) Remove the “#” from the beginning of each line. The **Equations** dialog box should appear as follows:




- b. Close the **Equations** dialog box.
7. Enter the parameter values.

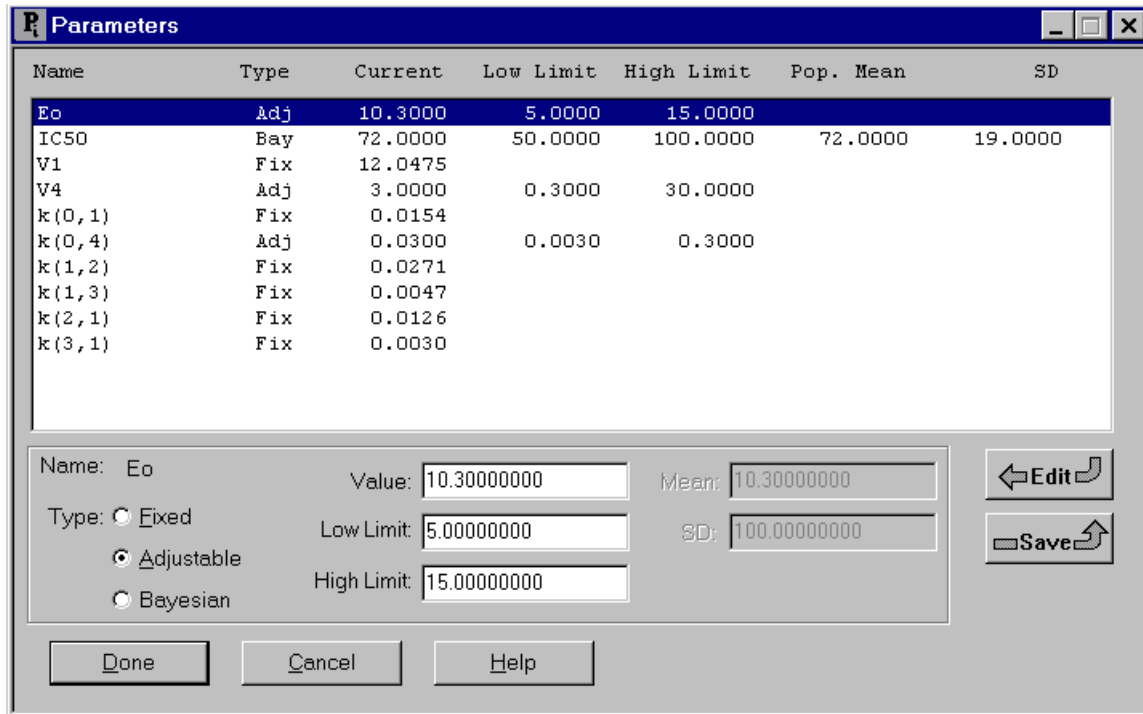
Estimates for the pharmacodynamics parameters E_o and IC_{50} together with V_4 and $k(0,4)$ need to be entered. Because the pharmacokinetic and pharmacodynamics analyses are independent, the pharmacokinetic parameters will be fixed at their present values. In this case, from *in vitro* studies, it is known that the expected value for IC_{50} is 72 mcg/ml. To incorporate this information, IC_{50} will be entered as a Bayesian parameter.

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



- c. Click **Done**.
- d. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar**, click **Parameters** . The **Parameters** dialog box will open.
 - (1) If *E_o* is not selected, double-click *E_o* to select it. Enter “10.3”, the measured value, in the **Value** box, “5” in the **Low Limit** box and “15” in the **High Limit** box. Click **Save**.
 - (2) Double-click *IC₅₀* and select the **Bayesian** option. Enter “72” in the **Value** box, “50” in the **Low Limit** box, and “100” in the **High Limit** box. Enter “72” in the **Mean** box, “19” in the **SD** box, and click **Save**.
 - (3) Double-click *V₄*. Enter “3” in the **Value** box and click **Save**.
 - (4) Double-click *k(0,4)*. Enter “.03” in the **Value** box and click **Save**.

- (5) Select *V1*. Click **Edit**, select **Fixed**, and click **Save**.
- (6) Fix the following parameters: $k(0,1)$, $k(1,2)$, $k(1,3)$, $k(2,1)$ and $k(3,1)$ as you did in step (5). When you have finished, the **Parameters Dialog** box should appear as follows:



Name	Type	Current	Low Limit	High Limit	Pop. Mean	SD
Eo	Adj	10.3000	5.0000	15.0000		
IC50	Bay	72.0000	50.0000	100.0000	72.0000	19.0000
V1	Fix	12.0475				
V4	Adj	3.0000	0.3000	30.0000		
k(0,1)	Fix	0.0154				
k(0,4)	Adj	0.0300	0.0030	0.3000		
k(1,2)	Fix	0.0271				
k(1,3)	Fix	0.0047				
k(2,1)	Fix	0.0126				
k(3,1)	Fix	0.0030				

Name: Eo Value: 10.30000000 Mean: 10.30000000



Type: Fixed Low Limit: 5.00000000 SD: 100.00000000

Adjustable High Limit: 15.00000000

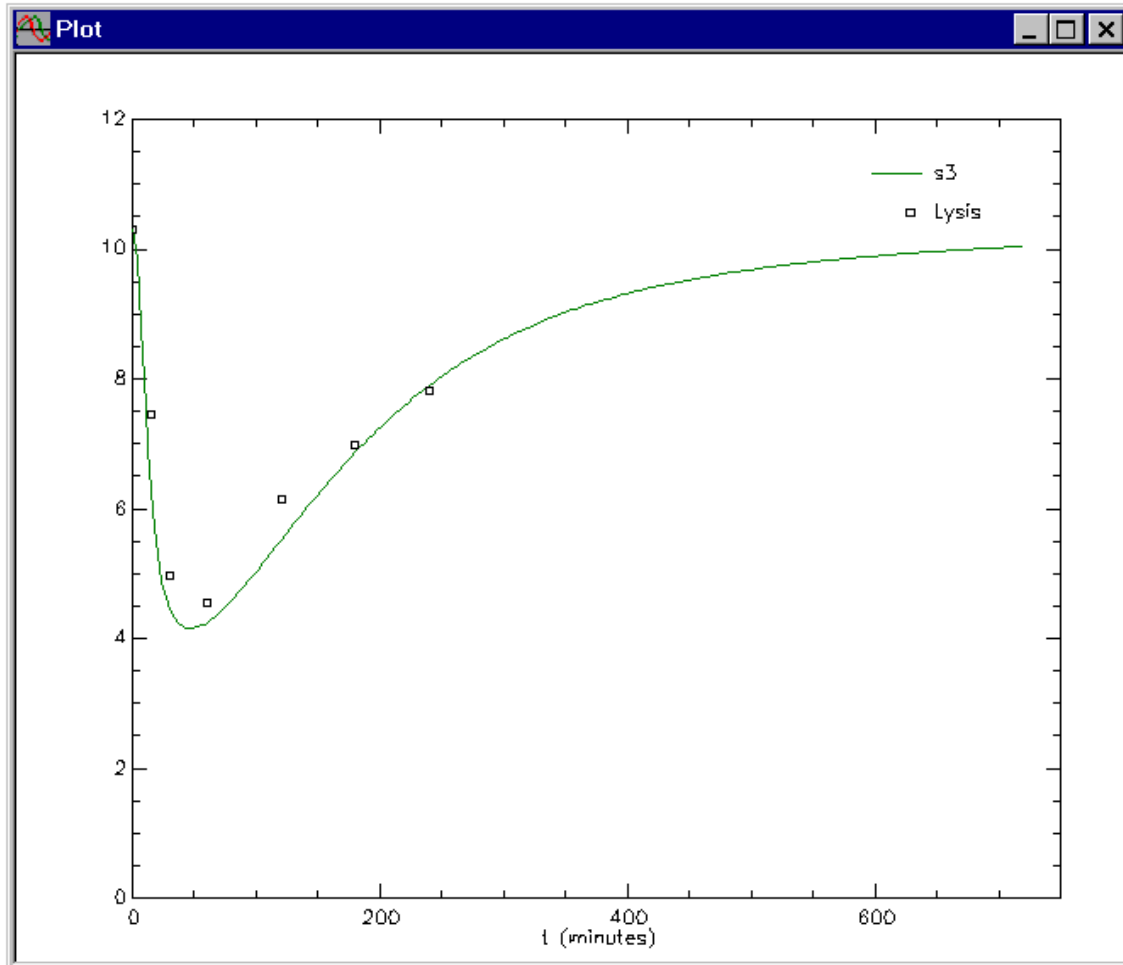
Bayesian

Buttons: Done, Cancel, Help, Edit, Save


(7) Click **Done**.

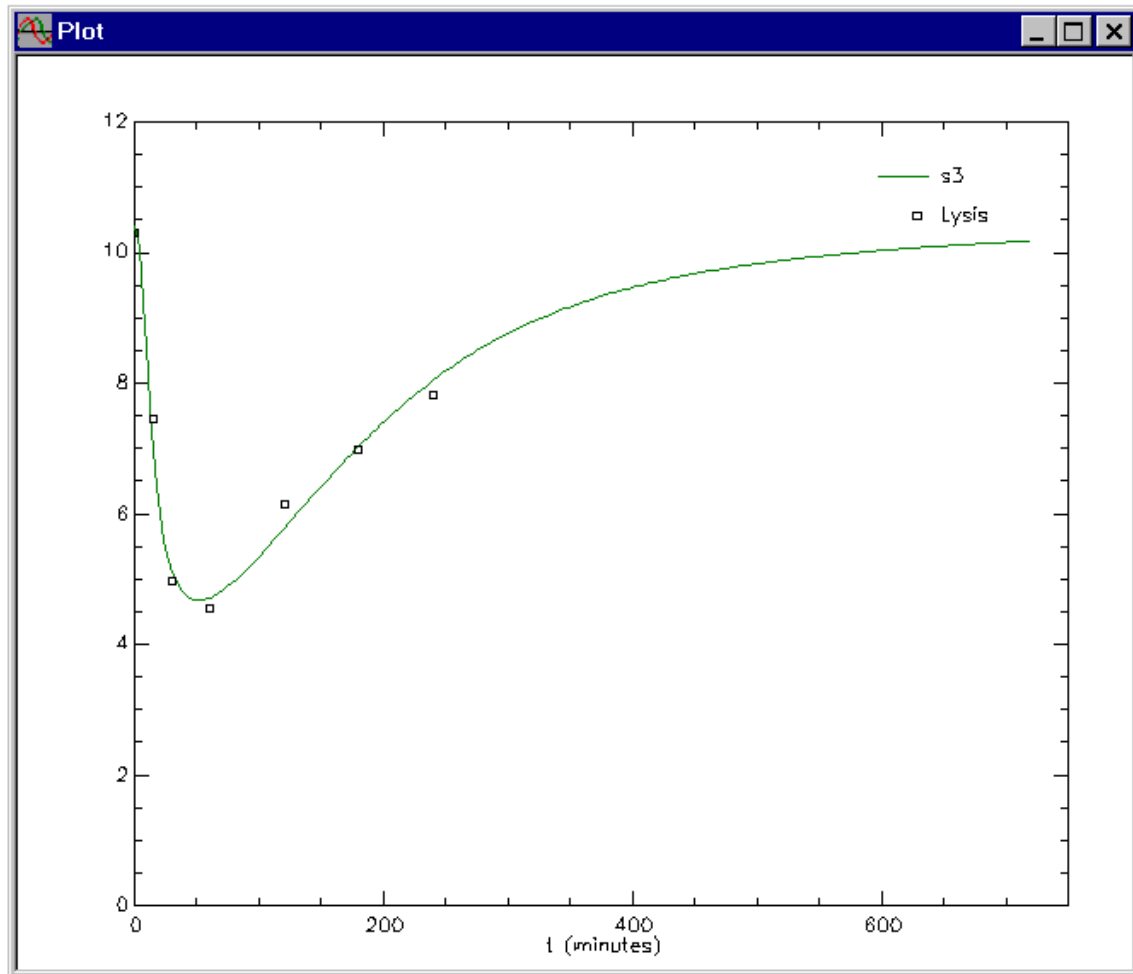
8. Solve your model and view the solution.
- In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar**, click **Solve** .
 - In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . The previous plot should open. In the **Set** menu, click **Plot/Table Variables** to open the **Plot and Table Variables** dialog box.
 - In the **Plot and Table Variables** dialog box, clear the **List All Variables** check box to list only those variables associated with data.
 - Click **s3:Lysis**; it will move to the **Current Selection** pane.


- e. Click **Done**. The following plot will appear in the linear mode (the **Plot/Table scale** has been set as follows: X-Axis minimum and maximum are respectively 0 and 750; Y-Axis minimum and maximum are respectively 0 and 12):



The initial estimates from the literature are reasonable. 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 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	
Eo	10.41539	3.90770e-001	3.75186e+000	9.58248	11.24829
IC50	72.00087	2.13838e+001	2.96994e+001	26.42238	117.57936
V1	12.04754	** Fixed **	** Fixed **	** Fixed **	** Fixed **
V4	3.33607	1.05482e+000	3.16188e+001	1.08776	5.58437
k(0,1)	0.01536	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,4)	0.02505	2.59131e-003	1.03436e+001	0.01953	0.03058
k(1,2)	0.02707	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(1,3)	0.00472	** Fixed **	** Fixed **	** Fixed **	** Fixed **

	Objective	Scaled Data Variance
s3 : Lysis	-6.229081e-001	7.754769e-003
s1 : Plasma	1.936433e+000	1.764366e-001
Bayesian	3.099409e-001	
Total objective	1.623466e+000	
AIC	2.046461e+000	

The value for E_o is consistent with what was measured initially and the pharmacodynamic parameters are reasonably well determined. This is a reflection of the use of the **Bayesian** feature in estimating the value for IC_{50} which remains unchanged from the initial estimate that was based on *in vitro* results of EACA binding to plasminogen.

Had this study been carried out during the early clinical development of EACA, it would have provided a useful “proof of concept” by demonstrating that the *in vivo* IC_{50} was consistent with *in vitro* results. Unfortunately, few PK/PD studies lend themselves to this type of *in vivo-in vitro* correlation.

- c. Close the **Statistics** window.

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 **Equations Dialog** feature of **SAAM II** can be used to set up the commonly used PK-PD models (linear, Emax and sigmoidal Emax).
- Although early PK-PD applications required actual mass transfer between the PK model and the link compartment, the input feature **SAAM II** allows the PD analysis to be conducted independently without affecting PK parameter estimates.
- Selected *in vitro* results (e.g. IC50 estimates) can be incorporated in the PK-PD model using the Bayesian feature and can enhance the information from the analysis.
- PK-PD modeling has the potential to provide in vivo-in vitro correlations and “proof of concept” during the early phases of drug development.

Data for this case study

DATA

(FSD 0.1)

t Plasma

15 537.(-)

20 560.

30 474.

45 351.

60 238.

90 173.

120 133.

180 77.6

240 47.5

360 22.8

540 9.9

720 4.8

END

DATA

(FSD 0.5)

t Lysis

0 10.3

15 7.45

30 4.97

60 4.54

120 6.14

180 6.97

240 7.82

END

#

Emax equations

#

#E = Eo - Emax*Ce/(IC50 + Ce)

#Ce = s2

#Emax = Eo

#ki = k(0,4)

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