

Using SAAM II

Creating Conditionals

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Creating Conditional Expressions

Prerequisites

The prerequisite for this tutorial is having worked through the **SAAM II** introductory tutorial, “Getting Started with **SAAM II Compartmental**.”

What you will learn in this tutorial

The purpose of this tutorial is to show you how to create conditional statements in your **SAAM II Compartmental** model. You will learn

- How to create “if-then-else” ((Part 1)
- How to create zero-order inputs (Part 2)
- How to create an input pump (Part 3)

Files Required

Study Files: The study files for this tutorial are

if_then_else.stu
zero_order.stu
pump_1.stu
pump_2.stu

Data Files: The data files for this tutorial are

if_then_else.dat
zero_order.dat
pump_1.dat

Introduction

There may be times in your modeling work when you need to create what is called a conditional. This means you are interrogating some variable in your model, and changing another variable or parameter in the model depending upon the “question” being asked.

Conditional statements

Conditional statements provide a mechanism for switching an execution path or the value assigned to one of more variables or parameters. Thus the conditional statement is a means by which to specify a switching mechanism. The most common example is the “if-then-else” statement. An example of the “if-then-else” statement is:

$$k(2,1) = \text{if (variable} > 0) \text{ then } 1 \text{ else } 2$$

In this situation if the variable you are interrogating is greater than zero, then the parameter $k(2,1) = 1$; otherwise it equals 2.

SAAM II regards conditionals as *explicit* or *implicit*. An explicit conditional statement is one where the time at which the switching occurs is known (can be predicted in advance). An implicit conditional statement is one where this time at which the switch occurs is not known until the condition itself is evaluated. Examples are:

Explicit:	$k(2,1) = \text{if (t ge 10) then } 1 \text{ else } 2$
Implicit:	$k(2,1) = \text{if (q1} < \text{q2) then } 1 \text{ else } 2$

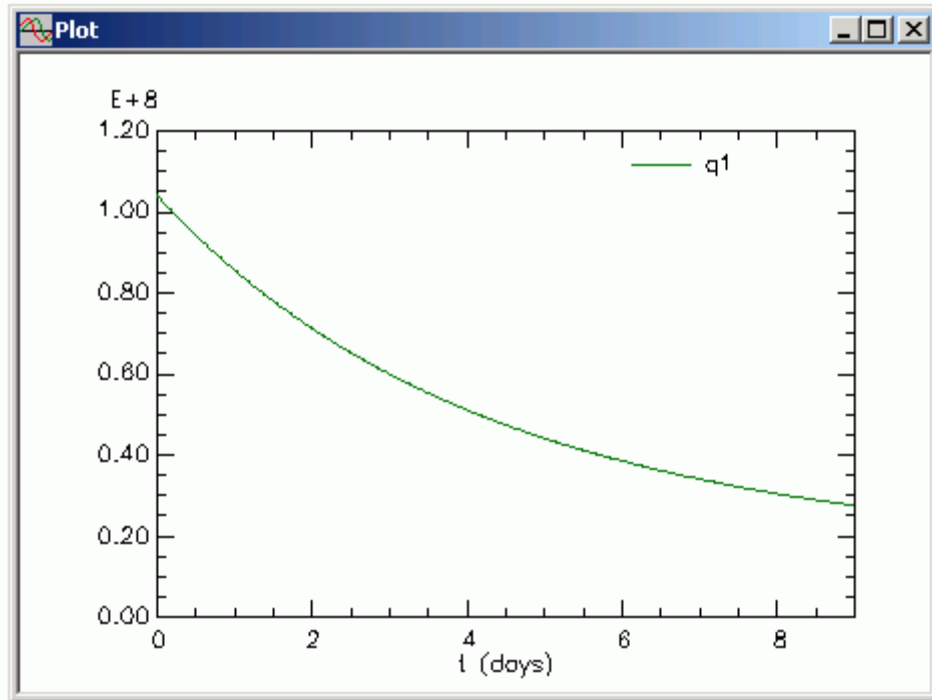
In these examples, “ge” is “greater than or equal to”, and **q1** and **q2** are the contents of Compartments **1** and **2** at time “t”.

In the explicit example, the time at which the switch occurs is known to equal 10. In the implicit case, there is no way to predict in advance when **q1** will be less than **q2**; values for **q1** and **q2** must be obtained at every integration step, and the test for “ $q1 < q2$.” performed.

Continuity and differentiability

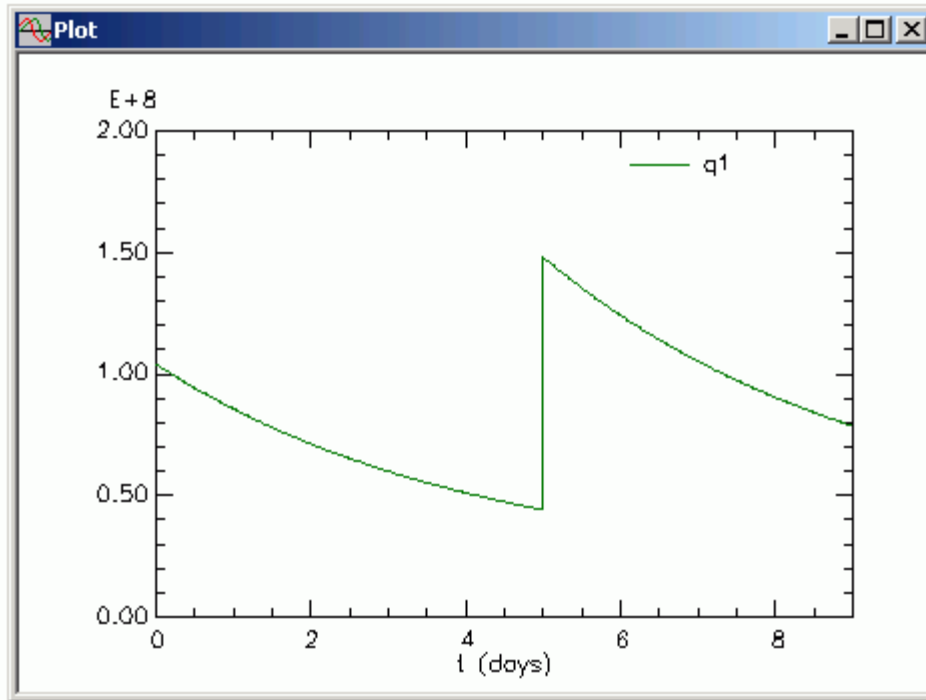
It is essential to understand the difference between continuity and differentiability because both are involved in how SAAM II “Solves” and “Fits”. During either a “Solve” or a “Fit”, SAAM II must perform numerical integration of the differential equations of your model. In order for the integrator to perform correctly, the functions (the q_i) must be both continuous and differentiable.

What do we mean by continuous and differentiable? Consider the following plot of **q1** from **study_0**:



This curve is “smooth”. That is, pick any point on the curve. Then start from a point on the curve to the left of this point. Move to the point along the curve. Then start from a point on the curve to the right of this point. Move to the point along the curve. You will reach the same final point no matter which side you start from and where. You can try this using the point at time equal to 5 days.

Now consider the following curve:



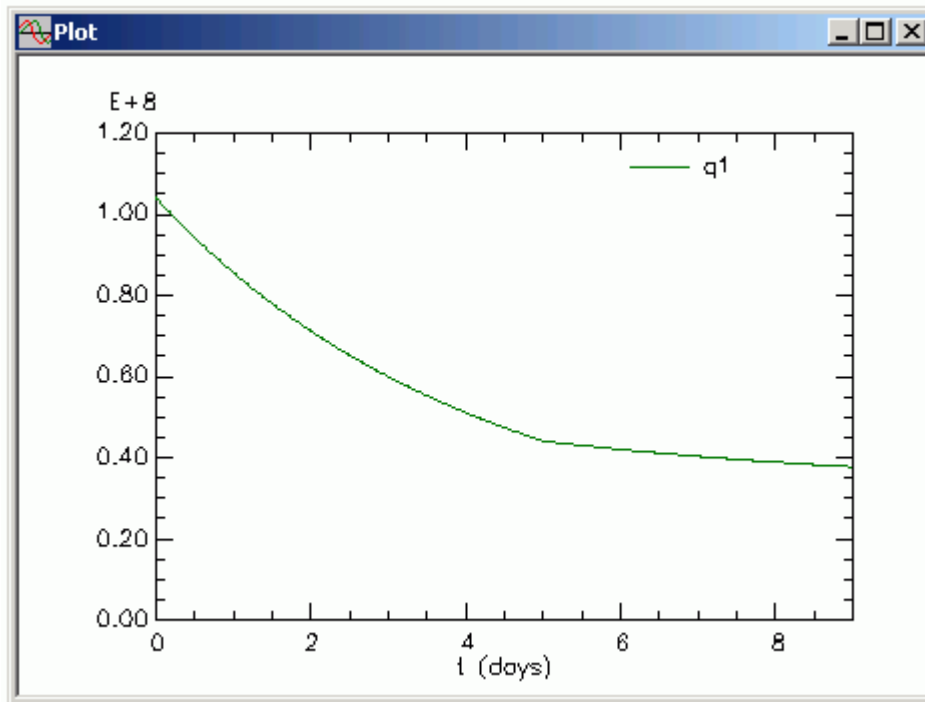
If you pick time equal to 5 days, and move to five days from the left (e.g. starting from 4) you will arrive at a different point than if you move to five days from the right (e.g. starting at 6). We say $q1$ is not continuous (or discontinuous, or has a discontinuity) when $t = 5$. You can see this even more clearly by looking at the table of values around $t = 5$:

t	q1
4.810	4.52824e+007
4.832	4.51364e+007
4.855	4.49911e+007
4.877	4.48466e+007
4.900	4.47028e+007
4.922	4.45598e+007
4.945	4.44175e+007
4.967	4.42760e+007
4.984	4.41742e+007
5.000	4.40728e+007
5.000	1.48073e+008
5.023	1.47466e+008
5.045	1.46863e+008
5.067	1.46263e+008
5.090	1.45667e+008
5.112	1.45074e+008
5.135	1.44484e+008
5.157	1.43897e+008
5.180	1.43313e+008

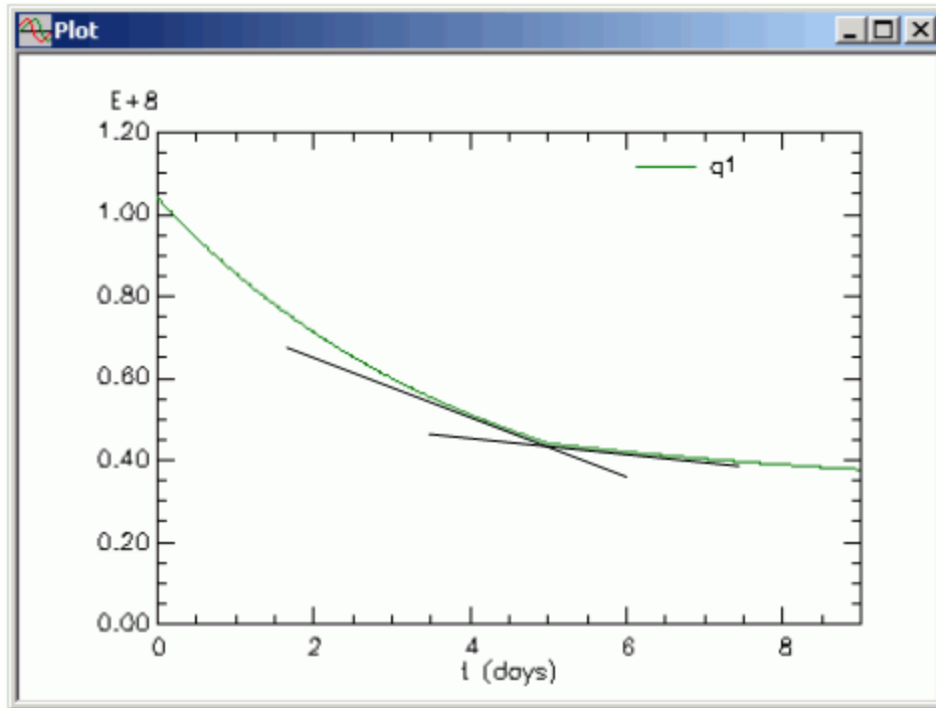
Moving in from a point less than time equal to 5 days you will end up at about 4.41×10^7 ; moving from a point to the right hand side of time equal to 5 days you will end up at 1.48×10^8 , two very different values. This also is why there are two values reported by SAAM II at time equal to 5 days since this simulation was set up using **Change Conditions**.

What about differentiable? Differentiable is similar to continuity but deals with tangent lines. In the solution of **q1** in study_0, pick an arbitrary point on the curve. Then move away from that point, and draw a tangent line to the curve. Then move the tangent line to the point you picked. You can see that no matter whether you start from the left or right side of your chosen point, you will end up with the same tangent line.

Now consider the following curve:



There is a break at day 5. The function is continuous, but, as shown in the figure below, you will end up with two different tangent lines at $t = 5$ depending on whether you start to the right or left of $t = 5$:



In this case, when the tangent lines do not coincide, we say the function is non-differentiable at that point. In this case, **q1** is not differentiable when $t = 5$.

Explicit and implicit conditionals.

An explicit conditional is allowed because the time at which it occurs is known. Integration can stop at the prescribed time, be reset, and continue. An implicit conditional can create either a discontinuity or non-differentiable function, or both. For this reason, implicit conditionals are not allowed in the **SAAMI II Compartmental** application.

Explicit conditionals are allowed in the **SAAM II Compartmental** application. They are implemented using the **Change Condition** tool in the **SAAM II Compartmental Toolbox**. When using Change Conditions, it is assumed that the time at which the change takes place is known exactly. For more information on the **Change Condition** tool, see the Using SAAM II tutorial “Working with Change Conditions.”

There is no equivalent to **Change Condition** in the **SAAM II Numerical** application. However, the explicit form of the “if-then-else” statement is allowed. An example is the following:

$$y(t) = \text{if } (t < 300) \text{ then } y_{\text{rise}}(t) \text{ else } y_{\text{wash}}(t)$$

This is an example of fitting a sum of exponentials to a constant infusion study where a washout phase was included starting at $t = 300$. Two functions, $y_{\text{rise}}(t)$ and $y_{\text{wash}}(t)$, are required. One describes the rise during the infusion and the other the washout. It is known that the infusion stops at “300.” The function that is fitted to the data, $y(t)$, then

equals $y_{rise}(t)$ for t less than 300, and equals $y_{wash}(t)$ when t is greater than or equal to 300.

Implicit conditionals and the Heaviside function

How can one deal with implicit conditionals in SAAM II? The “work-around” is to use the Heaviside function. The conditional statement specified by the Heaviside function approximates the desired switch by assuming a value of zero or 1 at a given point. While virtually instantaneous, the function is continuous and differentiable! Thus switches can be created using this function, and one does not need to worry during the “Solve” or “Fit” about the continuity and differentiability assumptions.

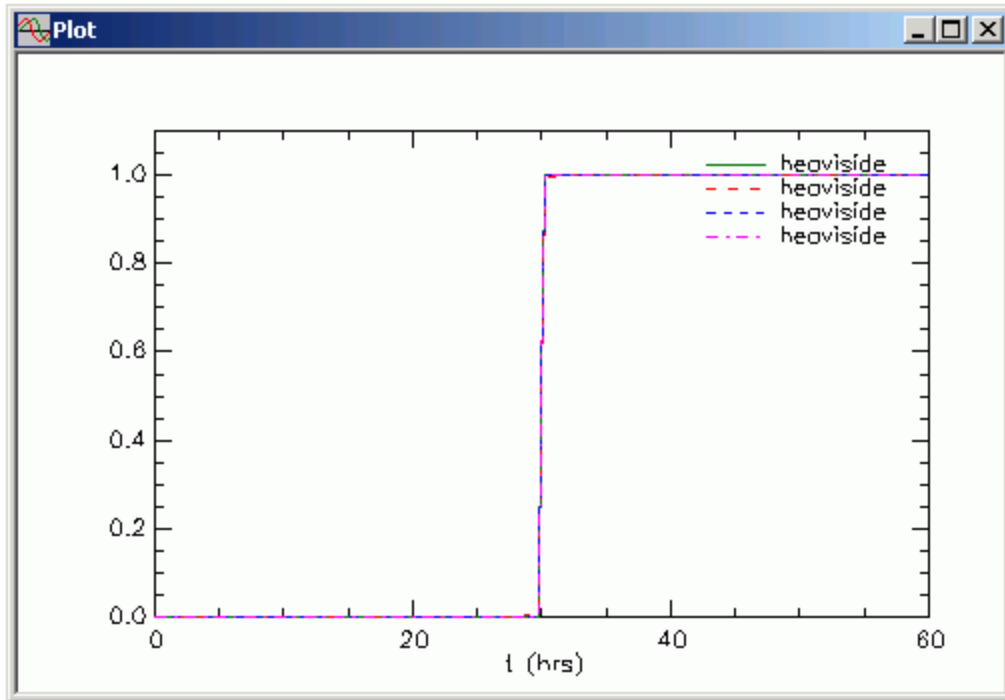
The Heaviside function is

$$\text{heaviside} = 0.5 * (1.0 + \text{atan}(\lambda * (x - x_{lag}))) * 2/3.141592653$$

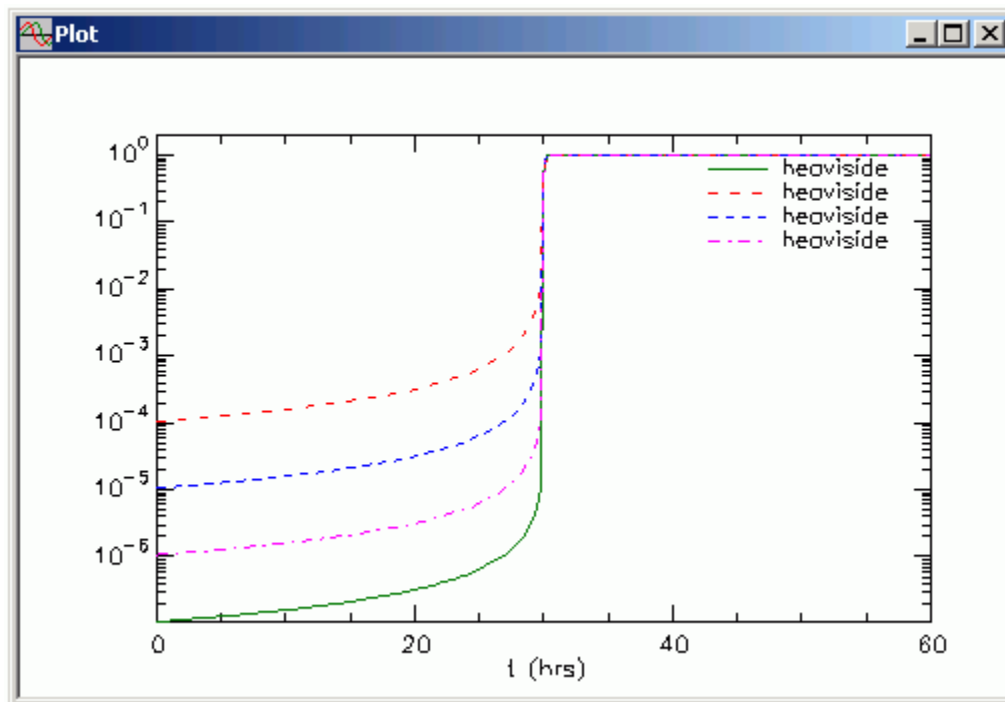
In this expression, “atan” is the arctangent function. The expression “ $x - x_{lag}$ ” creates the switch. “ x ” can be any function of “ t ”, and x_{lag} is the value at which the Heaviside function changes between 0 and 1. Normally “ x ” will be “ t ”, time, but the expression is general, and there may be time when “ x ” may equal one of the “ $q_i(t)$ ” in your model. For values of “ x ” less than “ x_{lag} ”, the value of the Heaviside function equals “zero.” For values of “ x ” greater than “ x_{lag} ”, the value is “one.” Thus the values of the Heaviside function are, for all practical purposes, either zero or 1. That is, the change from 0 to 1 is extremely rapid yet the function remains continuous and differentiable. The parameter, *lambda*, controls the sharpness of the function, i.e. how fast the values change between zero and 1. This can be seen in the following figure where the Heaviside function is calculated for *lambda* equal to 100, 1,000, 10,000 and 100,000 respectively where the Heaviside function is written

$$\text{heaviside} = 0.5 * (1.0 + \text{atan}(\lambda * (t - t_{lag}))) * 2/3.141592653$$

where “ t ” is the independent variable “time” and t_{lag} is set equal to 30. (In this example, then, “ x ” is specifically defined as “ t ”, time.) Thus when $t = 30$, the Heaviside function changes from zero to 1.



In the linear plot shown above, you can see how abrupt the change is; it almost looks discontinuous and nondifferentiable. To see what is really happening, and the role that λ plays, one must look at the plot in semilog mode:



In this figure, you can see the function is continuous and differentiable despite the “sharp” change from zero to “1.” As λ increases, the value of the Heaviside

function between zero and 30 becomes smaller, i.e. closer to zero, and the “sharpness” of the change from zero to 1 is increased. “Zero”, as you can see, is not true zero, but is arbitrarily small relative to the other values you are calculating so, for all practical purposes, it can be regarded as zero.

When you use the Heaviside function to create a conditional, you must set a value for *lambda*. Typical values for *lambda* are usually between 1,000 and 1.0e+08 depending upon the situation. But you need to “tune” *lambda* for your particular situation. What happens is the following. When you Fit your model to your data, the results may depend on the value of *lambda*. What you want to do, and this will be illustrated below, is change (usually increase) the value for *lambda* so that the final values for the adjustable parameters and their error estimates do not change. This will be a function of the sharpness of the Heaviside function mentioned above. It also depends upon the magnitude of “*x - xlag*”.

Example

Suppose you have a loss, $k(0, I)$ from your model which you believe, up to a certain unknown time, exhibits Michaelis-Menten behavior and thereafter is an unknown constant. If “*tlag*” is the unknown time at which the change occurs, you can write the Heaviside function as

$$\text{heaviside} = 0.5 * (1.0 + \text{atan}(\text{lambda} * (t - \text{tlag})) * 2 / 3.141592653)$$

in the **Equations** window of the **SAAM II Compartmental** application. *tlag* will be a parameter which will appear in the **Parameters** dialog box; it can be either fixed or adjustable. You can then write in the **Equations** window:

$$\text{Loss1} = V_m / (K_d + q_1)$$

The expression you would write for $k(0, I)$ is

$$k(0, I) = (1 - \text{heaviside}) * \text{Loss1} + \text{heaviside} * \text{Loss2}$$

Up to time *tlag*, “*t - tlag*” is negative hence “1-heaviside” equals 1, and $k(0, I)$ will equal *Loss1*, the Michaelis-Menten loss. For values of *t* greater than *tlag*, the Heaviside function will equal 1, and $k(0, I)$ will be equal to *Loss2*. *Loss2* will be recognized by SAAM II as a parameter which will appear in the **Parameters** dialog box; it can be either fixed or adjustable.

This is a specific example of the more general case when

$$\text{heaviside} = 0.5 * (1.0 + \text{atan}(\text{lambda} * (x - \text{xlag})) * 2 / 3.141592653)$$

i.e. you do not need “*t - tlag*”. One can then write

$$y = \text{heaviside} * \text{expression1} + (1 - \text{heaviside}) * \text{expression2}$$

For values of “ $x - x_{\text{lag}}$ ” that are positive, y will equal expression 1; when “ $x - x_{\text{lag}}$ ” is negative, y will equal expression 2. expression 1 and expression 2 can be a single value, parameter, a function such as “ q_1/vol ”, or the Michaelis-Menten expression used above.

Computational considerations

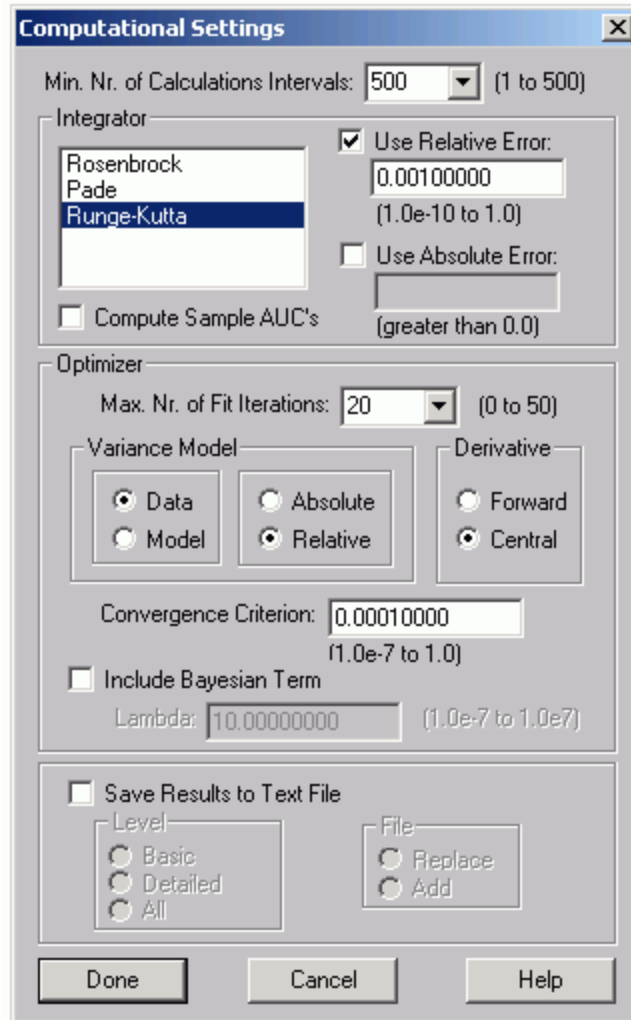
As you might expect, the Heaviside function, because of its sharpness, has the potential to create some problems when you Solve or Fit your model to your data. In general if there is only one conditional statement, the default **Computational Settings** will be sufficient although it is recommended you set the **Minimum Number of Calculation Intervals** equal to their maximum (500). You will see this is the case in the first two parts of this tutorial.

There may be other times when the switch specified by the conditional statement is active several times during the simulation of your experiment. An example is provided in Part 3 where an input pump is simulated to maintain plasma concentration at a certain level. In this case, the Heaviside function changes rapidly.

In this situation, the following Computational Settings are recommended:

- Set the **Minimum Number of Calculation Intervals** equal to 500.
- Change the **Integrator** to the “Runge-Kutta”.
- Set **Derivative** calculation to “Central”.

The **Computational Settings** dialog box will appear as follows:



Even with these settings, there are other adjustments you may need to make; most are suggested by SAAM II. As an example, you may need to change the value of the **Relative Error**. If you get such a warning message, first try decreasing this from 0.001 to 0.01.

The most important point is that when the switch specified by the conditional statement is rapidly turning on and off, you must be very careful that the software is operating correctly. This is why you should “tune” *lambda* until the solutions do not change.

Conclusion

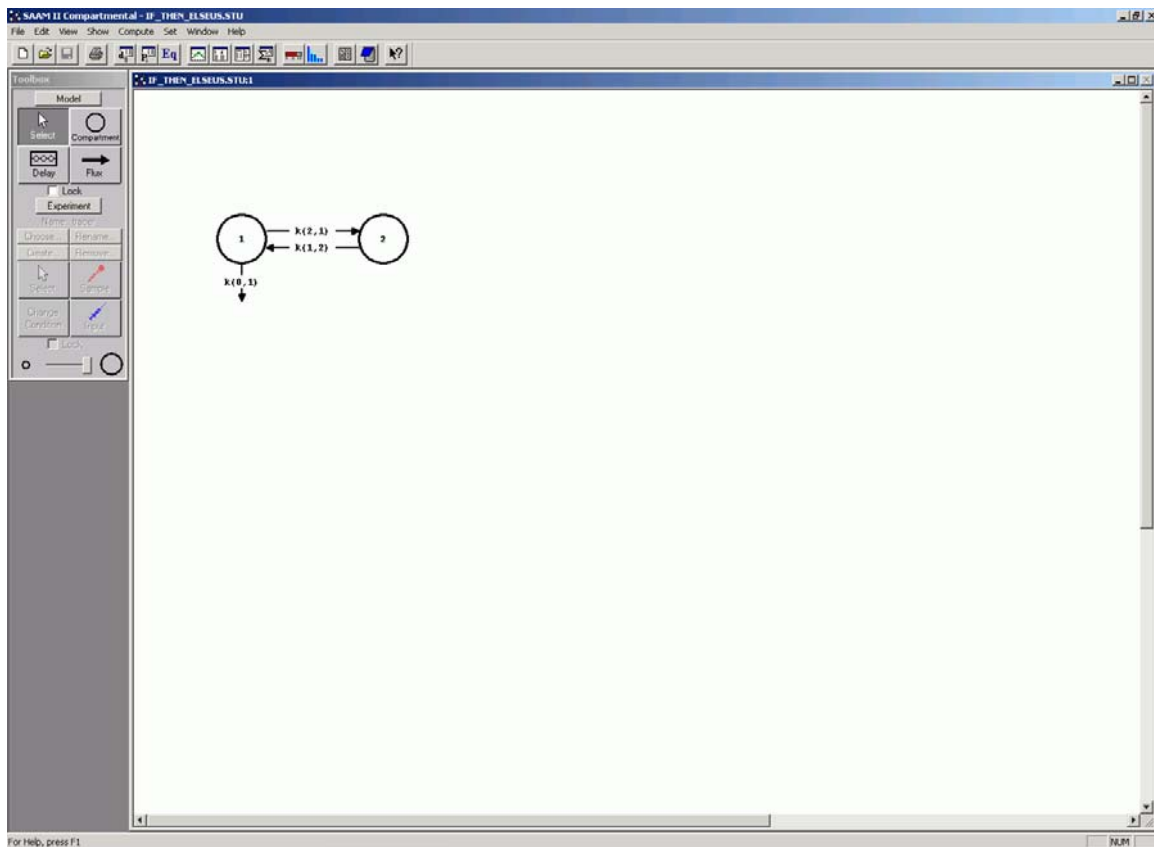
Finally, besides being used to specify implicit conditionals, the Heaviside function is used to create “absolute” delays. You can learn about “absolute” delays in the Using SAAM II tutorial “Working with Delays.”

Part 1. Creating a model with the conditional “if-then-else.”

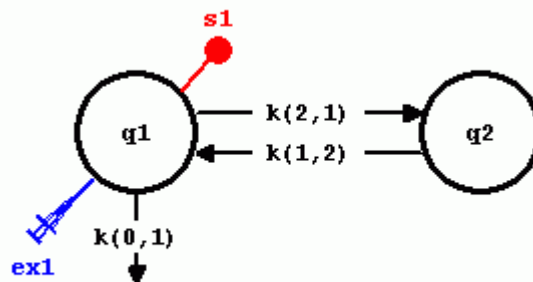
The example given below is a modification of the experiment in **study_0**. In the experiment described below, it is hypothesized that, for plasma concentration above a certain value, the loss from Compartment 1 exhibits Michaelis-Menten nonlinear behavior, and for concentration below this value, the loss is a constant rate. Information about the Michaelis-Menten constants, Vmax and Km, is available from the literature, so these parameters are entered using the SAAM II Bayesian option (for more information on this option, see the Using SAAM II tutorial “Working with Parameters.”)

You will use the study file **if_then_else**. This file has been created with the conditional expressed and the parameter values entered. The data file is included separately in case you would like to reconstruct the study file yourself. Each particular entry will be explained in detail.

1. **Start the SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.
2. Open the **SAAM II Compartmental** study file , **if_then_else**.
 - a. The file , **if_then_else** should appear in the file list; if it does not, find the folder where you put this file.
 - b. In the **File** menu, click **Open**. The **SAAM II Compartmental** main window will appear as follows:



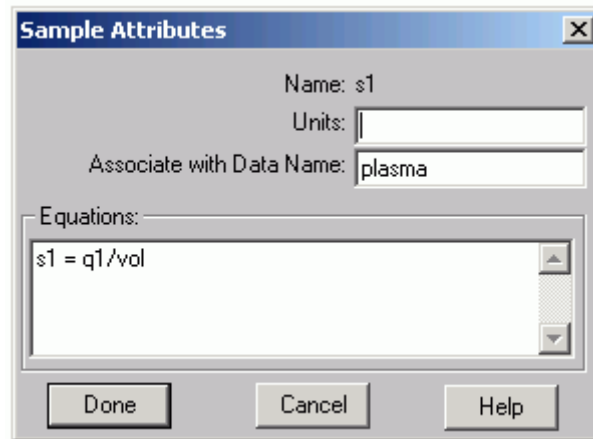
3. View the model and the experiment on the model, and change the model. In the **SAAM II Toolbox**, click **Experiment**. The experiment on the model will appear as follows:



The model of the experiment appears the same as the model of the experiment in study_0 structurally. The way in which the input and equations are specified in order to deal with the “if-then-else” makes the model different .

4. View the different components of the experiment on the model.
 - a. View the **Sample Attributes** dialog box associated with **s1**.

(1) Double-click **s1**. The **Sample Attributes** dialog box will open as follows:



The information in the **Sample Attributes** dialog box is standard in that the sample is associated with the **Data Name** “plasma”, and the sample equation “ $s1 = q1/vol$ ” will introduce the new parameter *vol*. You can open the **Data** window if you wish to view the “plasma” data.

(2) Click **Done**.

b. View the **Exogenous Input** dialog box associated with **ex1**.

(1) Double-click **ex1**. The **Exogenous Input** dialog box will open as follows:

Exogenous Input dialog box showing a single bolus input of 400 units.

Type	Initial	Constant	Start	Stop	Repeat Every	Nr. Repeats
Bolus	400.000	-	0.000	-	-	-

Input Type: Bolus, Infusion, Primed Infusion, Equation

Initial Amount: 400.00000000
 Constant Rate: 0.0
 Event Start: 0.0
 Event Stop: 0.0
 Repeat Every:
 Nr. of Repeats:
 Equation: ex1 =

The information in the **Exogenous Input** dialog box is standard in that the input is a single bolus of 400 units.


(2) Click **Done**.

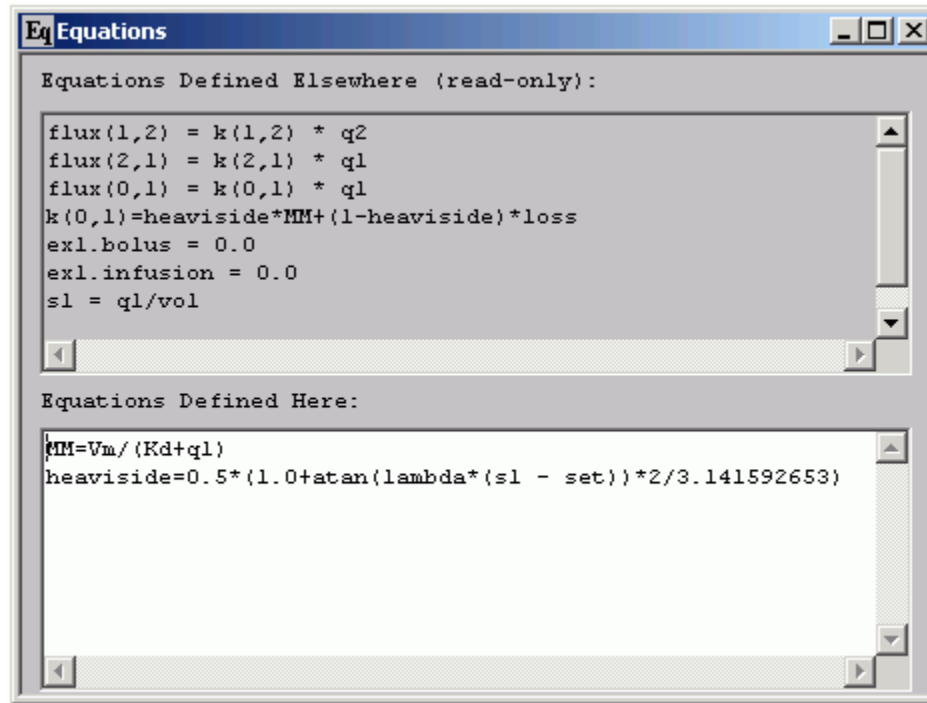
5. Creating the conditional.

As stated above, it is hypothesized that for plasma concentrations above a certain, known level, the loss $k(0, I)$ exhibits Michaelis-Menten kinetics while below that level, the loss rate is a constant. The plasma concentration ranges from approximately 0.2mg/ml to 0.04mg/ml. The concentration at which the loss changes from Michaelis-Menten to a constant is known to be 0.1mg/ml, but the exact time at which this occurs is unknown.

The following describes how to specify $k(0, I)$ equal to a Michaelis-Menten expression for values of **s1** greater than 0.1 and equal to a constant for values of **s1** less than 0.1.

- View the equations setting up the Michaelis-Menten loss and the conditional expression to create the switch.

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

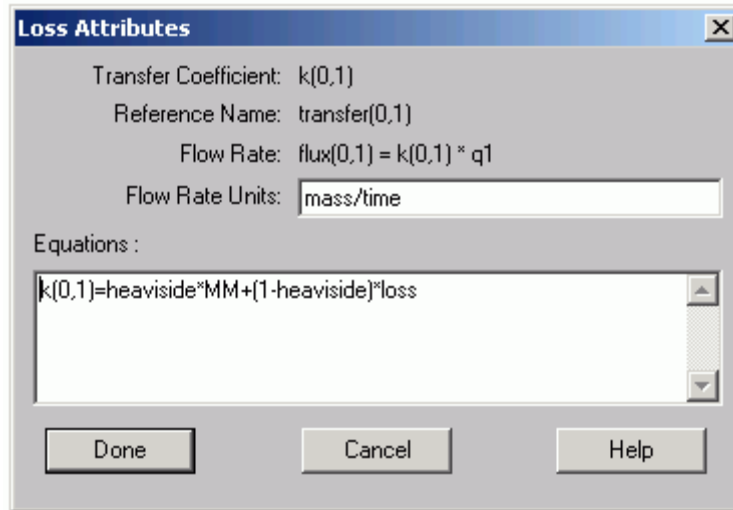


There are two equations in the **Equations Defined Here** pane.

The equation “MM” defines the Michaelis-Menten term which will be used to defined $k(0,1)$. This will introduce two new parameters in the model, V_m and K_d .

The second equation is the Heaviside equation. In this equation, the concentration s_1 is being compared to the parameter set . s_1 is the model calculated value for the concentration, and set will be entered as a fixed parameter, in this case equal to 0.1. When s_1 is greater than or equal to set , the value of heaviside will equal 1, otherwise it will equal zero.

- (2) Close the **Equations** dialog box.
- b. View the definition of $k(0,1)$.
- (1) Double-click $k(0,1)$. The **Loss Attributes** dialog box will appear as follows:



The equation specifying $k(0,1)$ now is the key to understand how the conditional expression is working. The expression is:

$$k(0,1)=\text{heaviside}*\text{MM}+(1-\text{heaviside})*\text{loss}$$

When the Heaviside function equals 1, i.e. when **s1** is greater than or equal to *set*, $k(0,1)$ will equal “MM”. Otherwise it will equal “loss”; “loss” will be recognized by SAAM II as a parameter appearing in the **Parameters** window. Thus this expression is equivalent to

$$k(0,1) = \text{if}(s1 \geq \text{set}) \text{ then MM else loss.}$$



If-then-else and the Heaviside function. The Heaviside function can be used to create if-then-else statement by recognizing that the “then” part of the statement occurs when the value of the Heaviside function is 1, and the “else” part of the statement occurs when the value of the Heaviside function is zero.




(2) Click Done.


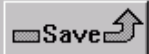
At this point, the model is fully specified. It remains to examine the **Parameters** window. Then you can proceed to Solve and Fit the model to the data.

6. View the **Parameters** window.



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:

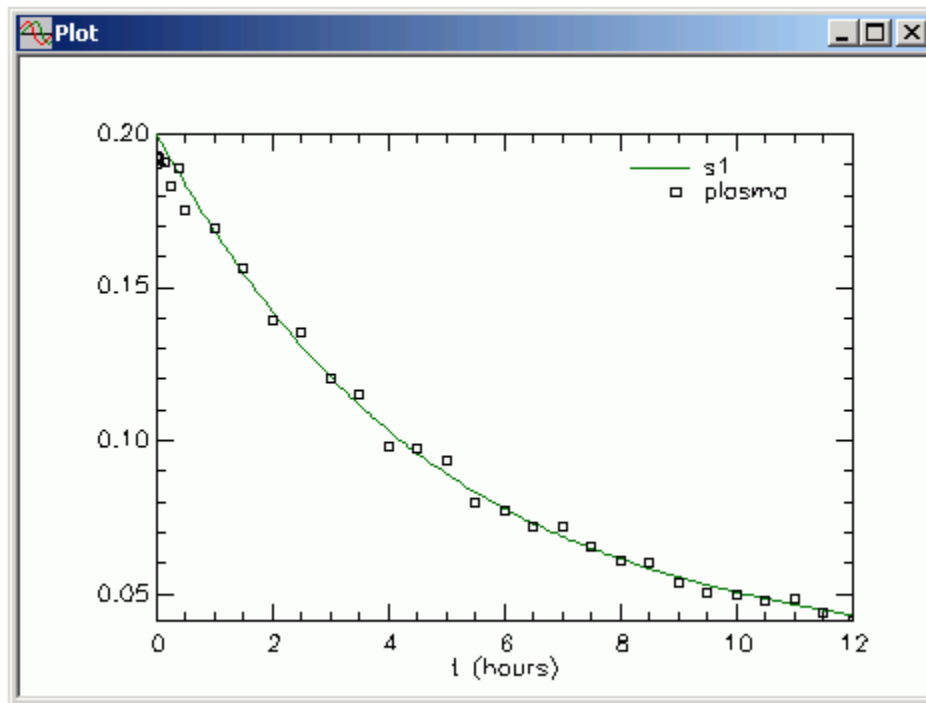
Name	Type	Current	Low Limit	High Limit	Pop. Mean	SD
Kd	Bay	400.0000	200.0000	600.0000	400.0000	40.0000
Vm	Bay	60.0000	25.0000	100.0000	60.0000	10.0000
k(1,2)	Adj	0.1000	0.0100	1.0000		
k(2,1)	Adj	0.1000	0.0100	1.0000		
lambda	Fix	1.000e+006				
loss	Adj	0.1000	0.0050	0.5000		
set	Fix	0.1000				
vol	Adj	2000.0000	200.0000	20000.0000		

Name: Kd	Value: 400.00000000	Mean: 400.00000000	
Type: <input type="radio"/> Fixed	Low Limit: 200.00000000	SD: 40.00000000	
<input type="radio"/> Adjustable	High Limit: 600.00000000		
<input checked="" type="radio"/> Bayesian			

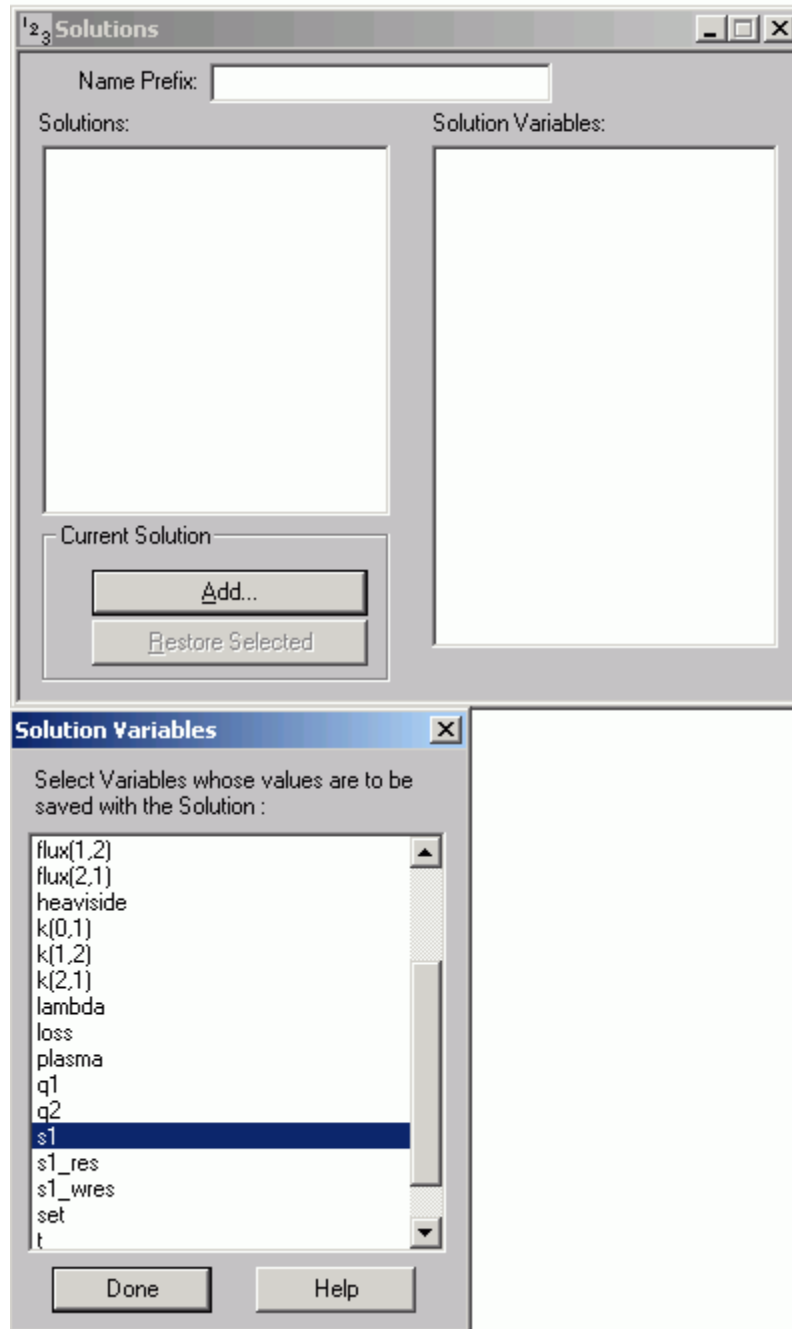
The first two parameters, Kd and Vm , are the Michaelis-Menten parameters. Since prior information is available about these parameters, they are entered as Bayesian (for more information on SAAM II Bayesian parameters, see the Using SAAM II tutorial “Working with Parameters.” The next two parameters, $k(2,1)$ and $k(1,2)$, are the exchange rate constants. The parameter $lambda$ is fixed; it is part of the Heaviside function. The “tuning” of $lambda$ will be explained below. The initial value of $1.0e+06$ is usually a reliable starting point; it can be changed during the tuning process. The parameter $loss$ is the constant rate of loss once $s1$ falls below set , the concentration at which $k(0,1)$ changes from Michaelis-Menten to a constant. vol is just the volume of Compartment 1.

- b. Click **Done**.
7. Solve the model and save the solution.
 - a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar**, click **Solve** .
 - b. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . The **Plot and Table Variables** dialog box will open. Be sure the **List All Variables** check box is not selected.
 - c. Click **s1:plasma** to move this to the **Current Selection** pane.

- d. Click **Done**. If the plot is not in semilog, in the **View** menu, click **Semilog**. The plot will appear as follows:



- e. Close the **Plot** window.
- f. In the **Compute** menu, click **Solutions**. The **Solutions** dialog box will open.
- g. Click **Add**. The **Solution Variables** dialog box will open. Scroll through the variables and click **s1**. The two dialog boxes will appear as follows:




- h. In the **Solution Variables** dialog box, click **Done**.
- i. Close the **Solutions** dialog box.

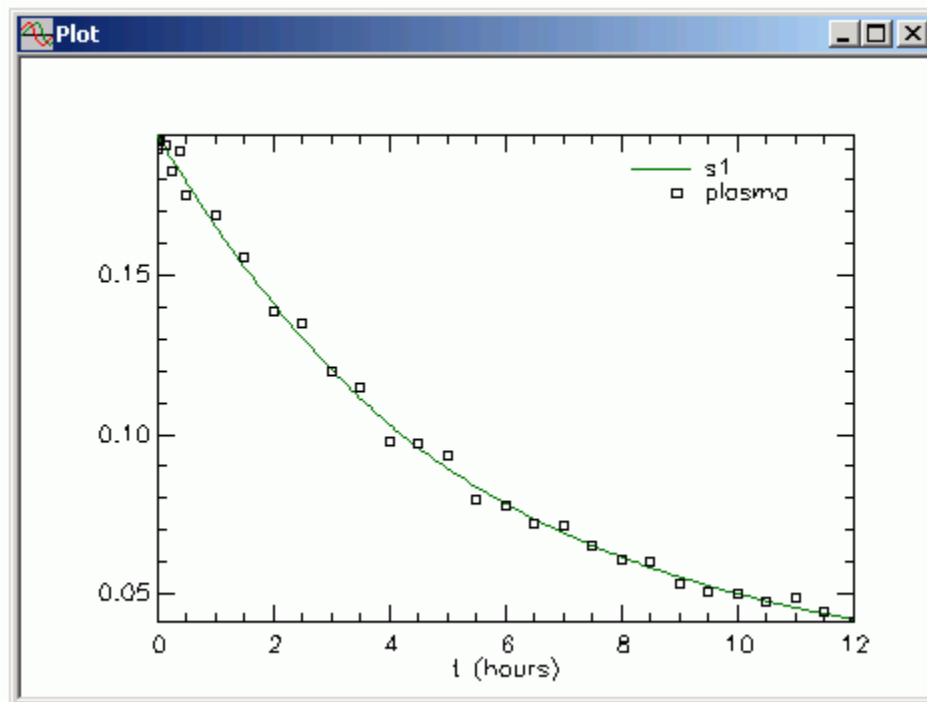



Tuning lambda. The parameter *lambda* is “tuned” by changing its value until there are no longer any significant changes in the adjustable parameters and their error estimates. To tune *lambda*, i.e. as you change the value, you must

start from the same set of initial parameter estimates. This solution has been saved as that starting point. For more information on saving and restoring solutions, see the Using SAAM II tutorial “Saving and Restoring Solutions.”



8. Fit the model to the data, view and record the solution.
 - a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar**, click **Fit** . The plot of **s1:plasma** will appear as shown below:



- 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	
Kd	398.61255	4.43250e+001	1.11198e+001	307.50125	489.72386
Vm	59.56265	1.10667e+001	1.85800e+001	36.81469	82.31061
k(1,2)	0.06923	5.51359e-002	7.96370e+001	-0.04410	0.18257
k(2,1)	0.08549	1.61429e-002	1.88839e+001	0.05230	0.11867
lambda	1000000.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
loss	0.08877	3.48675e-002	3.92793e+001	0.01710	0.16044
set	0.10000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
vol	2060.39520	2.25511e+001	1.09450e+000	2014.04080	2106.74960

	Objective	Scaled Data Variance
s1 : plasma	-1.021701e+001	9.288812e-002
Bayesian	3.745639e-001	

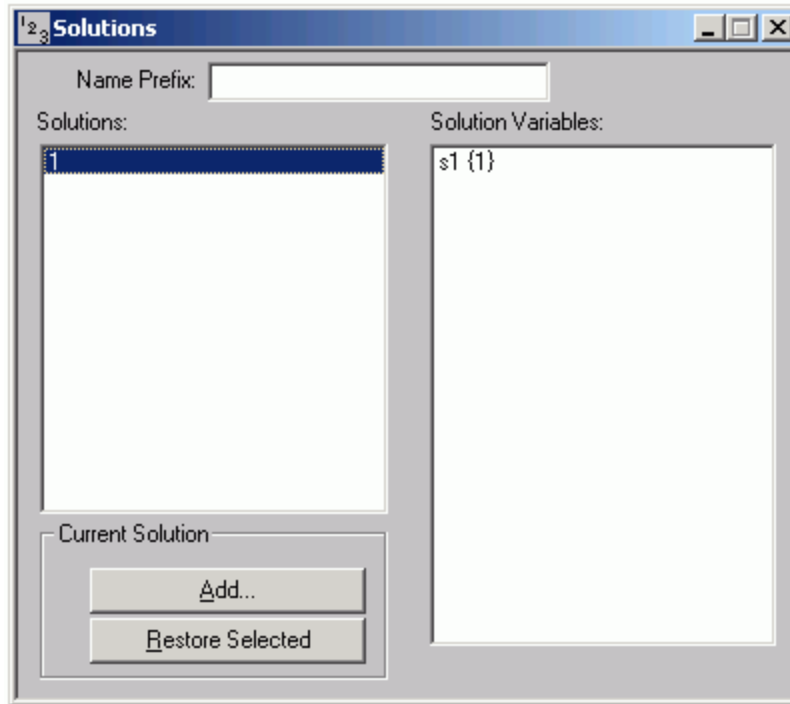
Total objective	-9.842444e+000	
AIC	-3.783534e+000	
BIC	-3.623219e+000	

- c. Record the results as shown below:

lambda	1.00E+06	1.00E+07
Kd	399(11)	
Vm	59.6(19)	
k(1,2)	.069(80)	
k(2,1)	.085(19)	
loss	.089(39)	
vol	2060(1)	

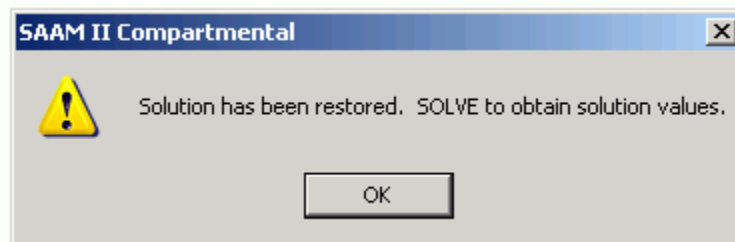
These are the values when $lambda$ equals $1.00e+06$. You can see Kd and Vm do not change much from their initial values meaning there is not much information in these data to help determine them. In addition, $k(1,2)$ does not have very good precision.

- d. Close all open windows and dialog boxes.
9. Restore the original solution, and refit the model to the data with $lambda$ equal to $1.0e+07$, and record the results.
- In the **Compute** menu, click **Solutions**. The **Solutions** dialog box will open.
 - Click “1” in the **Solutions** pane. The **Solutions** dialog box will appear as follows:



Notice **Restore Selected** is now available.

- c. Click **Restore Selected**. The following message will appear:



- d. Click **OK**, and close the **Solutions** dialog box.
- e. Re-Solve the model. The original solution is now restored.
- f. Change the value of *lambda* from 1.0e+06 to 1.0e+07. The **Parameters** dialog box will appear as follows:

Name	Type	Current	Low Limit	High Limit	Pop. Mean	SD
Kd	Bay	400.0000	200.0000	600.0000	400.0000	40.0000
Vm	Bay	60.0000	25.0000	100.0000	60.0000	10.0000
k(1,2)	Adj	0.1000	0.0100	1.0000		
k(2,1)	Adj	0.1000	0.0100	1.0000		
lambda	Fix	1.000e+007				
loss	Adj	0.1000	0.0050	0.5000		
set	Fix	0.1000				
vol	Adj	2000.0000	200.0000	20000.0000		

Name: lambda Value: 1.0000000e+007 Mean: 1.0000000e+006

Type: Fixed Low Limit: 10000.00000000 SD: 9.9000000e+006

Adjustable High Limit: 1.0000000e+008

Bayesian

Buttons: Edit, Save, Done, Cancel, Help

Close the **Parameters** dialog box.

- g. Re-Fit the model to the data, and record the results. The results should appear as follows:

lambda	1.00E+06	1.00E+07
Kd	399(11)	399(11)
Vm	59.6(19)	59.6(19)
k(1,2)	.069(80)	.069(80)
k(2,1)	.085(19)	.085(19)
loss	.089(39)	.089(39)
vol	2060(1)	2060(1)

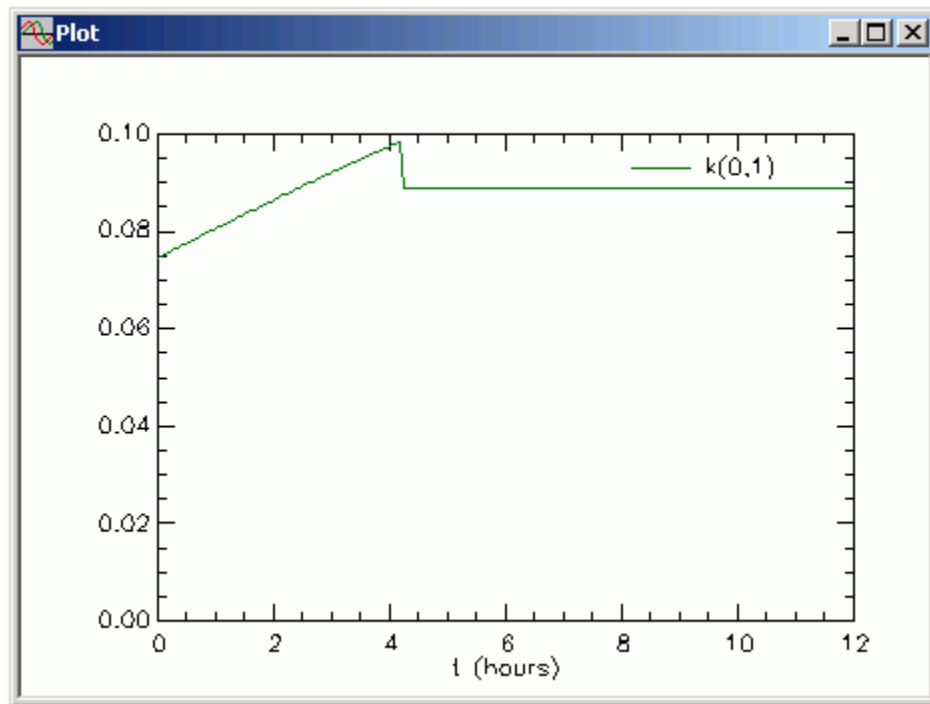
You can see there is no difference between *lambda* equaling 1.0e+06 and 1.0e+07, so you can regard *lambda* equal to 1.0e+06 as a well-tuned value.

You should also try different values for *lambda* such as 1.0e+05 and 1.0e+04 to see which parameters change, if any.

- h. Close all open windows and dialog boxes.

Quit the SAAM II Compartmental application. Do not save the changes to if_then_else.

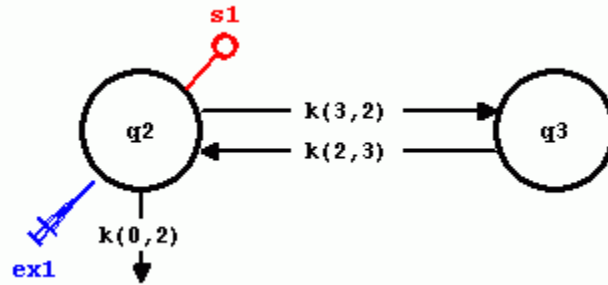
In this example, it is useful to examine $k(0,1)$. A plot of this parameter is shown below following the last “Fit”:



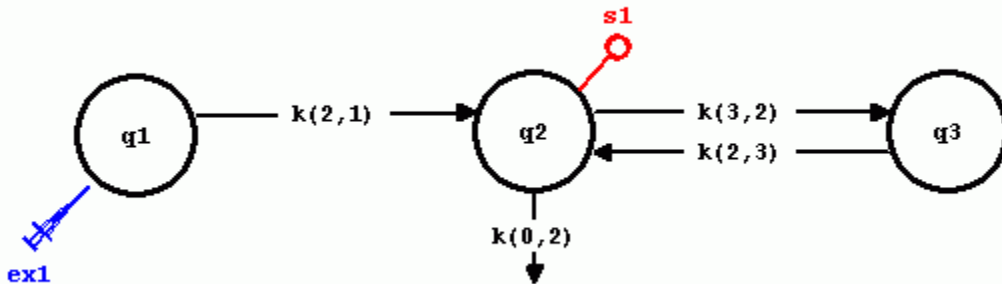
You can clearly see the value of $k(0,1)$ rising during the initial decay phase of the data; the rise continues until around 4 hours at which point $s1$ is less than set . However just before the switch defined by the conditional statement occurs, $k(0,1)$ is actually greater than $loss$ (the straight line portion parallel to the t-axis.) If one believes this should not be the case, then the value for set may be off a little.

Part 2. Creating a zero-order input of unknown duration

A zero-order input into a compartment is actually equivalent to a constant infusion. However, there are instances when specifying it in this manner is not appealing in terms of the physiology, or drug absorption, being studied. It is a difference between



and



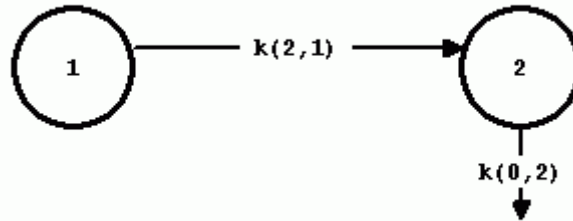
If one is dealing with absorption and believes that the absorptive process is zero-order, then either of these two model configurations can explain the kinetics. In the case of the second model, $k(2,1)$ would be a zero-order rate constant. The first model will yield identical results, but the lack of a schematic for absorption is not appealing.

This part will explain how to create a zero-order absorption of an unknown amount for an unknown duration.

The experiment is one in which 100mg of the drug was given orally at the start of the experiment followed by several other doses sufficient to have drug mass levels high enough in Compartment **q1** for zero-order absorption to realistically take place. The hypothesis is that absorption is zero order of unknown amount for an unknown duration. The experiment lasts for 24 hours.

1. **Start the SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.

2. Create the following system model:



3. Create the experiment on the model.
 - a. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open. Set the experimental attributes as follows:

Experiment Attributes

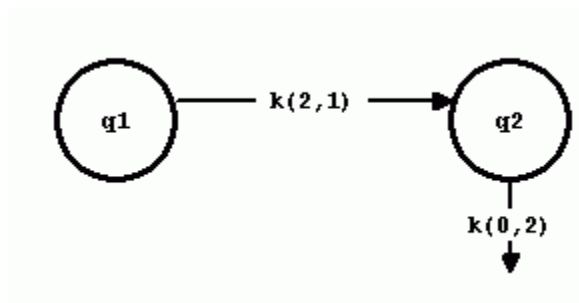
Independent Variable:

Units:


Start at:

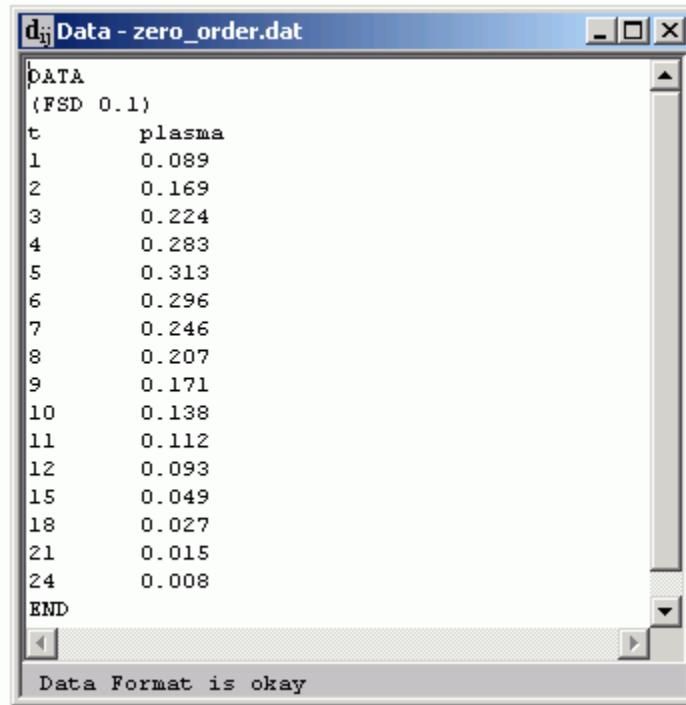
End at:

- b. Click **Done**. The **Create Experiment** dialog box will open. Click **Create**. The model will appear as follows:

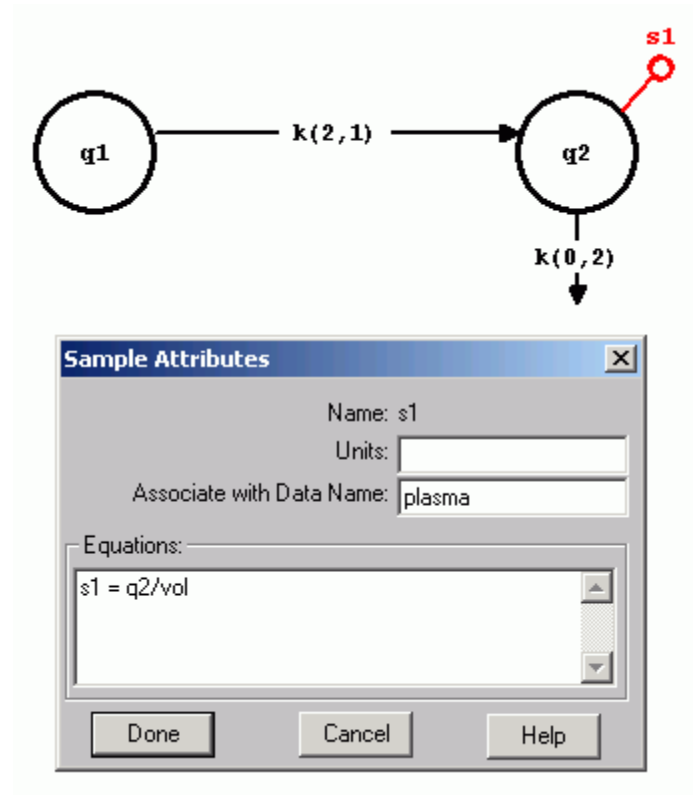


4. Add the data to the model.

- a. On the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data** . The **Data** window will open.
- b. On the **File** menu, click **Open**. The file **zero_order.dat** should appear in the list (if it does not, find the folder where you put this data file).
- c. Double-click **zero_order.dat**. The data in this file will appear in the **Data** window. The **Data** window should appear as follows:

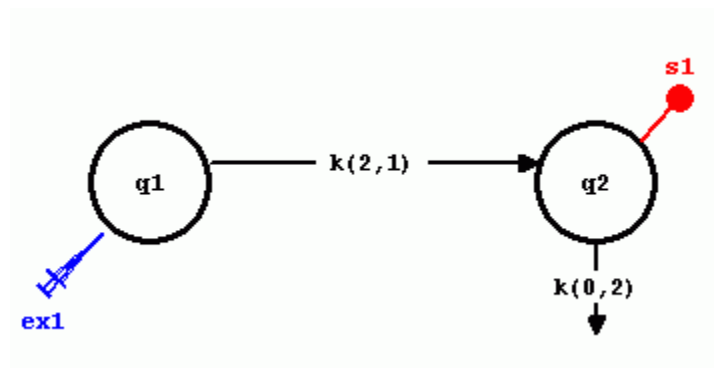


- d. Close the **Data** window.
5. Create a sample on Compartment **q2**, associated with “plasma” and edit the sample equation to read “ $s1=q1/vol$ ”. The **Sample Attributes** dialog box should appear together with the model as follows:



Click **Done**. The sample **s1** will become filled.

6. Create an input into Compartment **q1**.
 - a. Create the input into Compartment **q1**. The model should appear as follows:

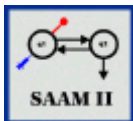


- b. Specify the input as a bolus equal to 100 using the equation format.
 - (1) Double-click **ex1** to open the **Exogenous Input** dialog box.
 - (2) Select **Equation** as the input type.
 - (3) Set the **Start** and **Stop** time equal to zero.

- (4) Write the input equation “ex1 = input”. Click **Add**. The **Exogenous Input** dialog box should appear as follows:

Type	Initial	Constant	Start	Stop	Repeat Every	Nr. Repeats
Equation	ex1 = input	0.000	0.000	-	-	-

- (4) Click **Done**.




Exogenous input. Technically an exogenous input should not be needed in the case of zero-order absorption, . In this case, specifying the exogenous input as an equation “ex1 = input” will create *input* as a parameter; this allows for different studies to have different input values without having to go to the **Exogenous Input** dialog box first. The real reason why there needs to be an initial value at time zero is to prevent division by zero; this will be explained below.



7. Create the zero-order input.

To create the zero order input, the parameter k(2,1) must be changed to zero order. To estimate the unknown time of the zero-order absorption, a Heaviside function must be created.

- a. In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar**, click **Equations** . The **Equations** dialog box will open.
- b. Create the Heaviside function. In the **Equations Defined Here** pane, type

```
“heaviside=0.5*(1+atan(lambda*(t-tlag))*2/3.141592653)”
```

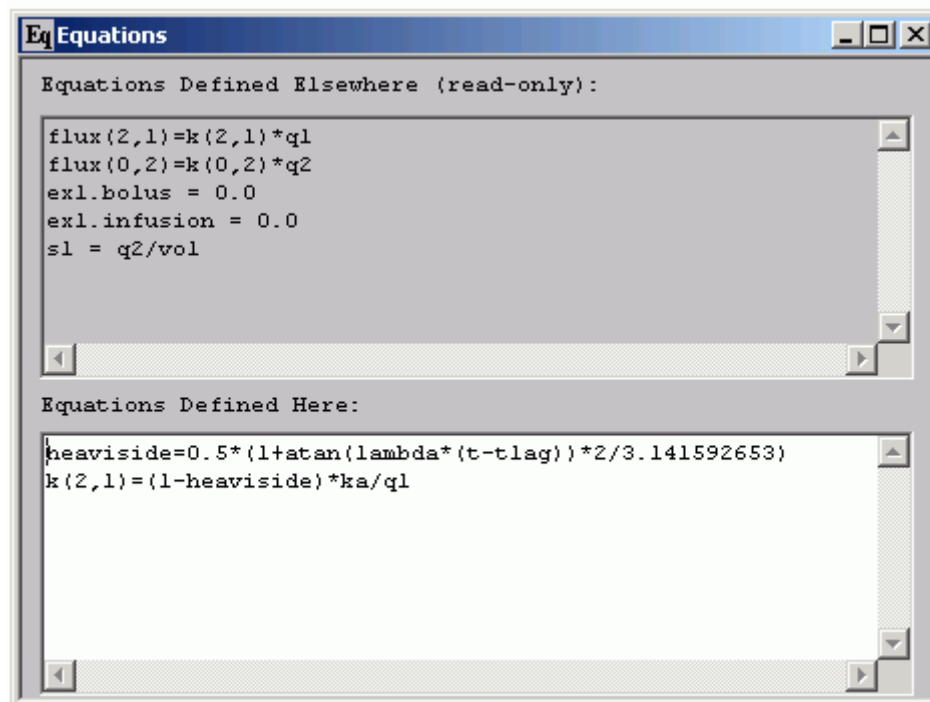
In this expression, for t less than the unknown parameter $tlag$, the value of the Heaviside function will be zero; otherwise it will equal 1. The parameter $tlag$ will thus be the time when zero-order absorption stops.

- c. Create the zero-order absorption parameter. In the **Equations Defined Here** pane, type

```
“k(2,1)=(1-heaviside)*ka/q1”
```

This equation specifies $k(2,1)$ as a zero-order parameter because of the division by $q1$. It is this division that requires $q1$ to have a value at time zero, otherwise you will receive a warning of division by zero. The absorption rate is the parameter ka . Up to time $tlag$, “1 – heaviside” will equal 1, and the zero-order absorptive process will occur. After time $tlag$, zero-order absorption will stop.

The **Equations** dialog box should appear as follows:



- d. Close the **Equations** dialog box.
8. Enter the parameter values as shown below:

Name	Type	Current	Low Limit	High Limit
input	Fix	100.0000		
k(0,2)	Adj	0.1000	0.0100	1.0000
ka	Adj	300.0000	100.0000	500.0000
lambda	Fix	100.0000		
tlag	Adj	5.0000	1.0000	20.0000
vol	Fix	3000.0000		

Name: input Value: 100.00000000

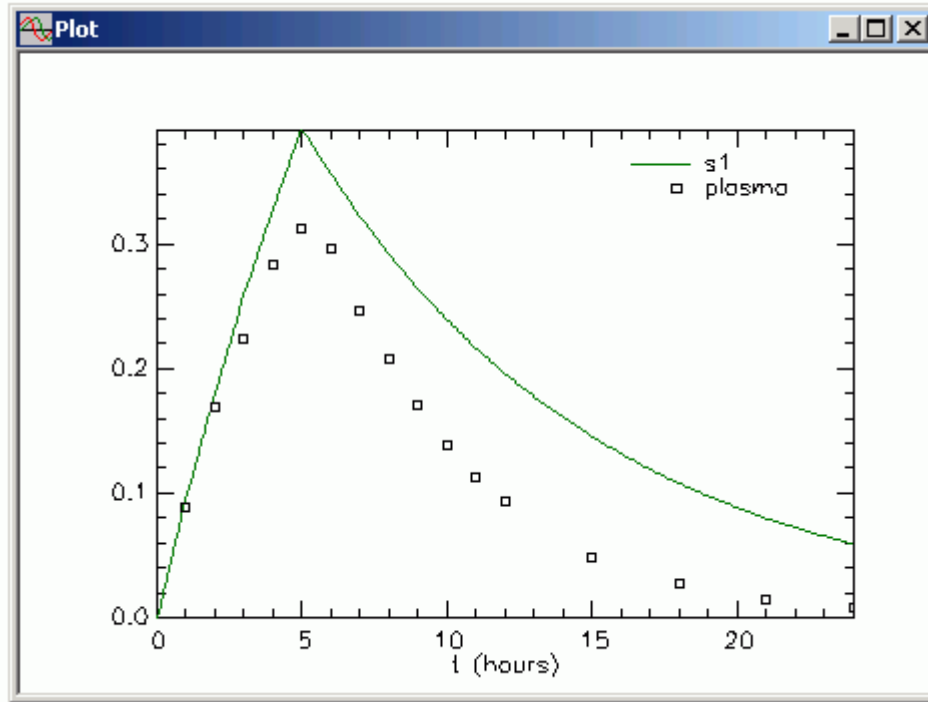
Type: Fixed Low Limit: 10.00000000

Adjustable High Limit: 1000.00000000

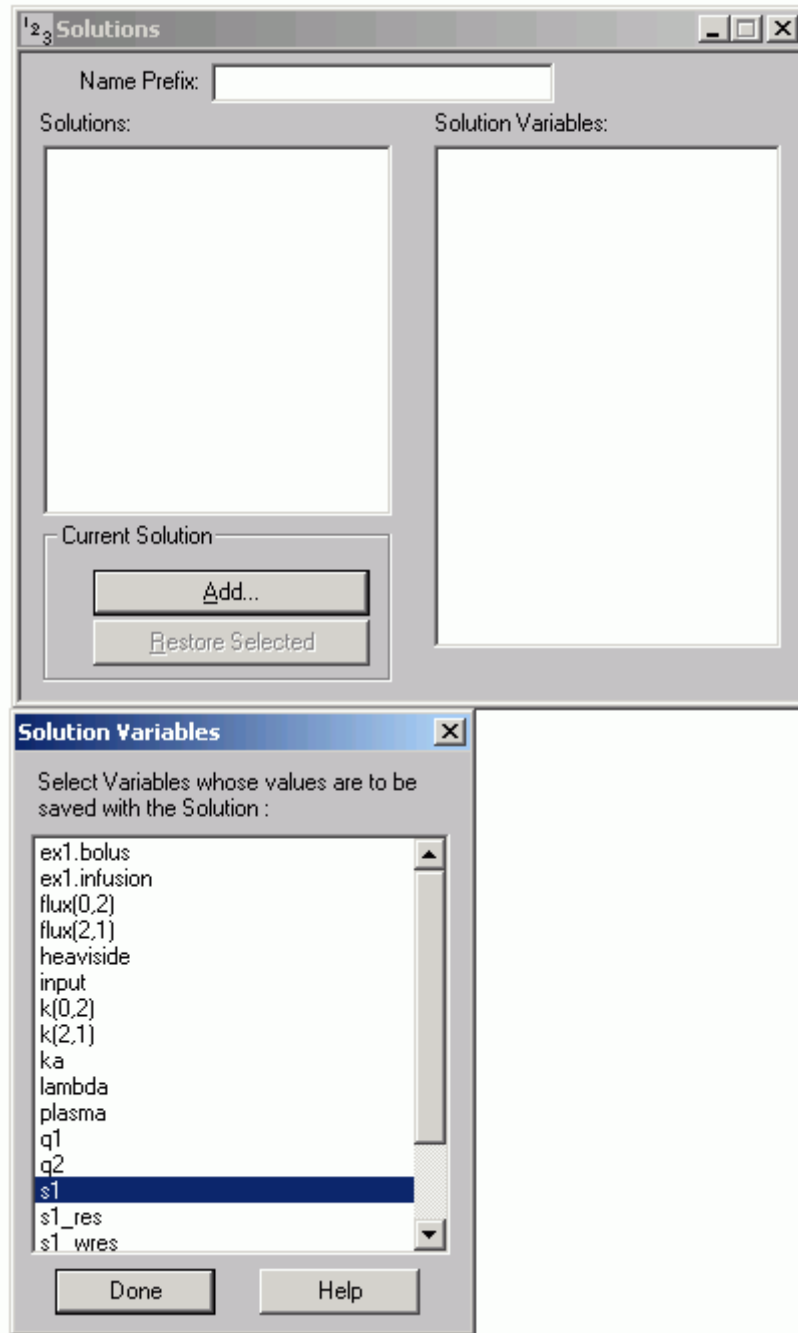
Buttons: Done, Cancel, Help, Edit, Save

Of the parameters, *input* is the known initial dose; it is fixed. *k(0,2)* is the unknown loss from Compartment 2. *ka* is the unknown zero-order absorption rate. *lambda* is the tuning parameter for the Heaviside function. *tlag* is the unknown duration of the zero-order absorption. The initial value of 100 is lower than the normally used $1.0e+06$ for *lambda*. This value was picked by examining different values for *lambda* starting from $1.0e+06$. Thus, choosing the initial value is also part of the tuning process. *vol* is the volume of Compartment 2. The volume is assumed to be known otherwise the amount of the zero-order absorption could not be estimated (if both were allowed to adjust, you will find they are perfectly correlated.)

9. Solve the model, and view and save the solution. A plot of **s1** and **plasma** will appear as follows:



- Close the **Plot** window.
- In the **Compute** menu, click **Solutions**. The **Solutions** dialog box will open.
- Click **Add**. The **Solution Variables** dialog box will open. Scroll through the variables and click **s1**. The two dialog boxes will appear as follows:



- d. In the **Solution Variables** dialog box, click **Done**.
- e. Close the **Solutions** dialog box.




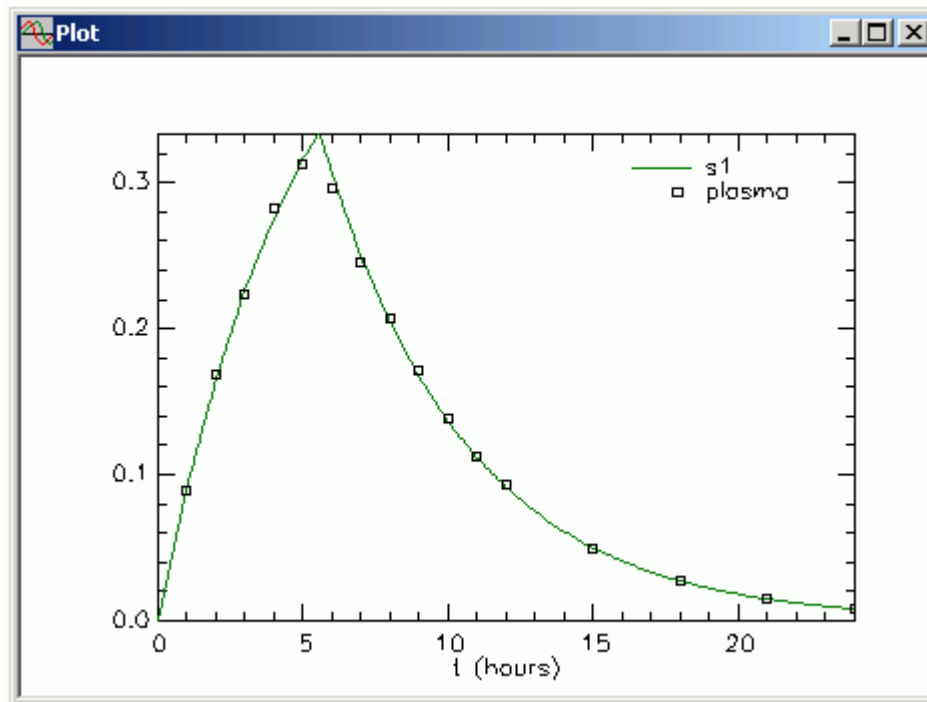
Tuning lambda. The parameter *lambda* is “tuned” by changing its value until there are no longer any significant changes in the adjustable parameters and


their error estimates. To tune λ , one must start from the same set of initial parameter estimates. This solution has been saved as that starting point. For more information on saving and restoring solutions, see the Using SAAM II tutorial “Saving and Restoring Solutions.”



10. Fit the model to the data, view and record the solution.

- a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar**, click **Fit** . The plot of **s1:plasma** will appear as shown below:



- 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	
input	100.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
k(0,2)	0.20253	1.05014e-003	5.18506e-001	0.20026	0.20480
ka	302.17009	2.70685e+000	8.95804e-001	296.32228	308.01789
lambda	100.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
tlag	5.54145	6.90178e-002	1.24548e+000	5.39234	5.69055
vol	3000.00000	** Fixed **	** Fixed **	** Fixed **	** Fixed **
----- Derived Variables -----					
exl.bolus	100.00000	0.00000e+000	0.00000e+000	100.00000	100.00000

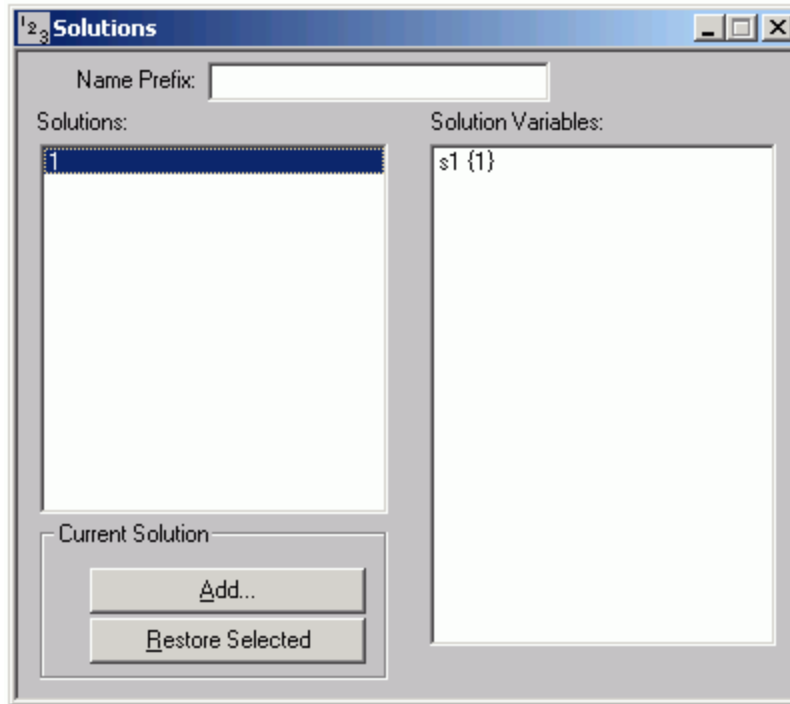
	Objective	Scaled Data Variance
s1 : plasma	-1.159239e+001	3.897866e-002
Total objective	-1.159239e+001	
AIC	-4.627254e+000	
BIC	-4.530681e+000	

- c. Record the results as shown below:

lambda	1.00E+02	1.00E+03
k(0,2)	.203(5.2)	
ka	302(9.0)	
tlag	5.54(1.2)	

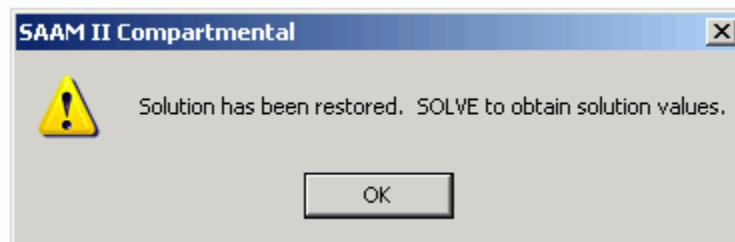
These are the values when $lambda$ equals 100. The precision of all parameters is quite good.

- d. Close all open windows and dialog boxes.
11. Restore the original solution, and refit the model to the data with $lambda$ equal to 1000, and record the results.
- In the **Compute** menu, click **Solutions**. The **Solutions** dialog box will open.
 - Click "1" in the **Solutions** pane. The **Solutions** dialog box will appear as follows:

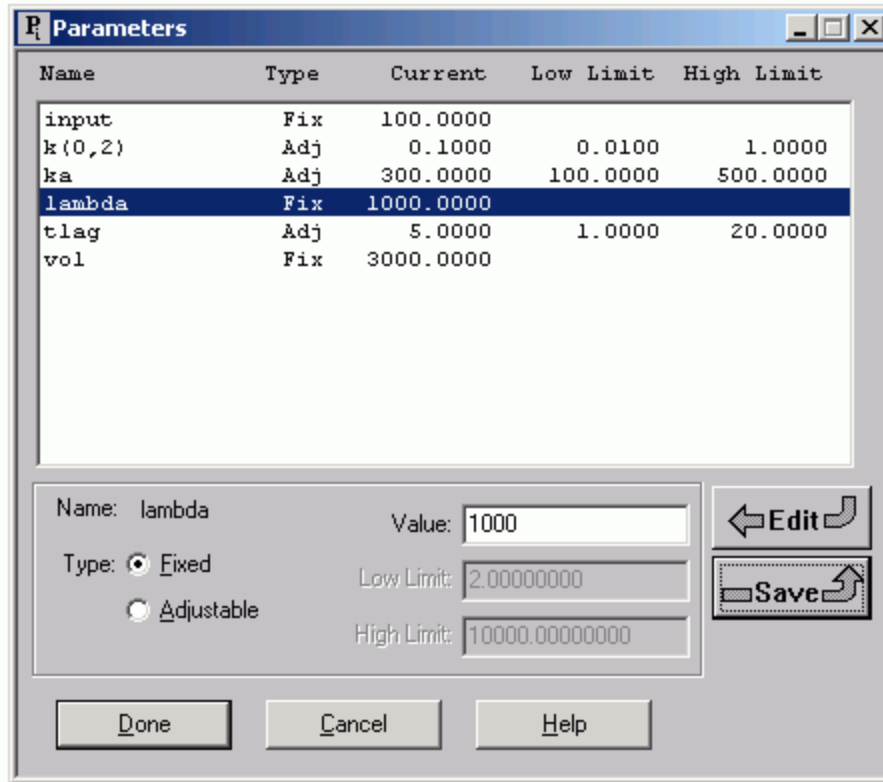


Notice **Restore Selected** is now available.

- c. Click **Restore Selected**. The following message will appear:



- d. Click **OK**, and close the **Solutions** dialog box.
- e. Re-Solve the model. The original solution is now restored.
- f. Change the value of *lambda* from 100 to 1000. The **Parameters** dialog box will appear as follows:



Close the **Parameters** dialog box.

- g. Re-Fit the model to the data (you may have to click Fit twice), and record the results. The results should appear as follows:

lambda	1.00E+02	1.00E+03
k(0,2)	.203(5.2)	.202(5.1)
ka	302(9.0)	302(8.9)
tlag	5.54(1.2)	5.53(1.5)

You can see there are some small differences in the values depending upon *lambda*. For the parameters, they are in the third digit. You can repeat the above setting *lambda* equal to 10000 if you wish. The results should be as follows:

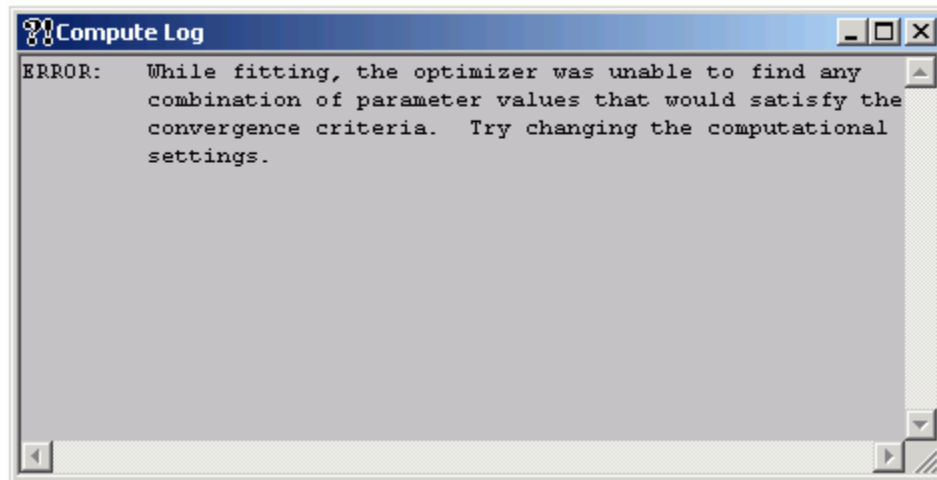
lambda	1.00E+02	1.00E+03	1.00E+04
k(0,2)	.203(5.2)	.202(5.1)	.202(5.1)
ka	302(9.0)	302(8.9)	302(8.9)
tlag	5.54(1.2)	5.53(1.5)	5.52(0.2)

Now there are no differences in $k(0,2)$ or ka ; $tlag$ is still fine-tuning slightly. If you wish, you can continue increasing *lambda* until there is no change in any of the parameters or their estimates; this should be the optimal value of *lambda* chosen. See below for more comments before increasing *lambda*.

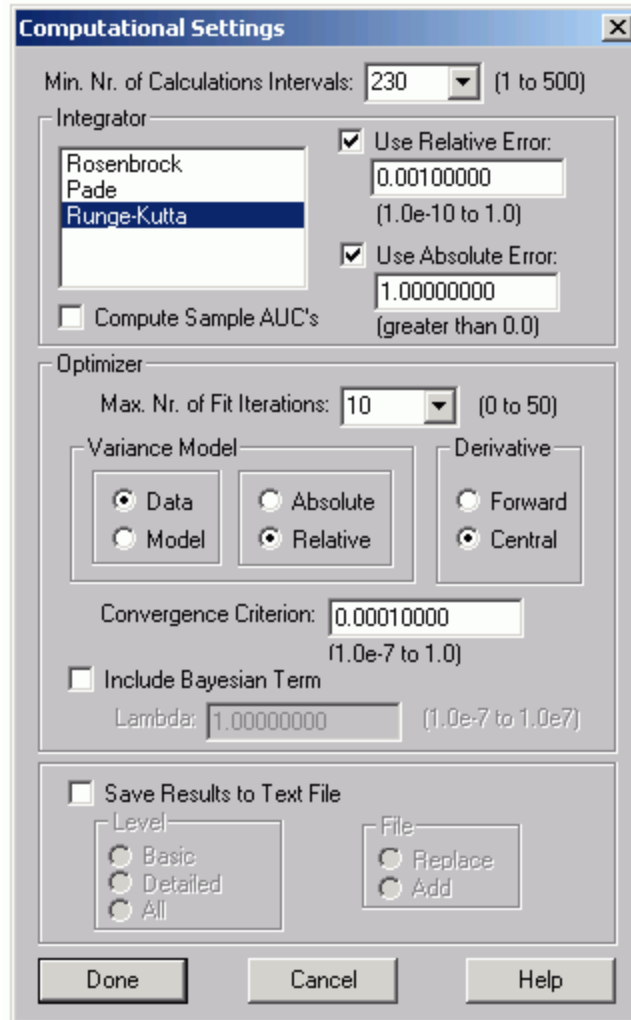
- h. Close all open windows and dialog boxes.

Quit the **SAAM II Compartmental** application. You can save the study file if you wish. **zero_order.stu** is the study file with the initial parameter values.

The last value of *lambda* was $1.0e+04$. If you increase *lambda* to $1.0e+05$, you will not be able to fit the model to the data. Instead, you will receive the following message:



When you are using the Heaviside function and this message appears, you need to change your computational settings. So far the default integrator and forward derivative methods have been used. You now need to try the Runge Kutta integrator and the central derivative method. In the **Compute** menu, open the **Computational Settings** dialog box and make these changes. The **Computational Settings** dialog box will appear as follows:



Click **Done**. You will now be able to fit the model to the data with λ equal to 1.0×10^5 . Changing λ to 1.0×10^6 will yield no changes in the parameters or their error estimates.

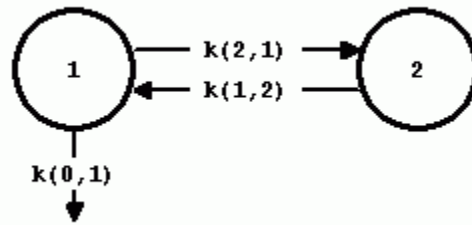
Thus for this problem, the above computational settings (i.e. Runge-Kutta integrator and the central derivative method) with λ equal to 1.0×10^5 is optimal.

Part 3. Creating a pump to maintain plasma concentration.

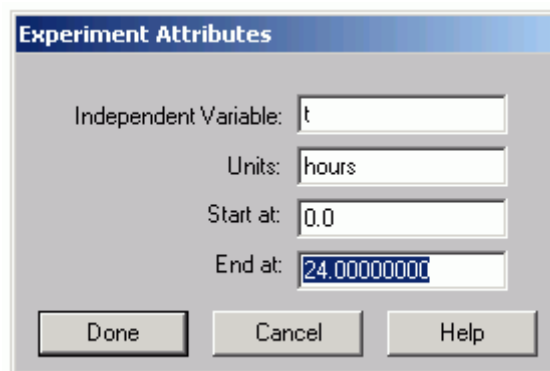
There are several experimental protocols that use an infusion pump to maintain plasma concentration of a substance of interest at or near a specific level. The times at which the pump turns on or off are not known and need to be simulated. In this part, such a pump will be created and the results compared with a set of simulated data.

In this experiment, a pump capable of infusing at a rate of 100mg/hr of drug is used. The experiment lasts for 24 hours. The desired concentration is maintained at approximately 0.06mg/ml.

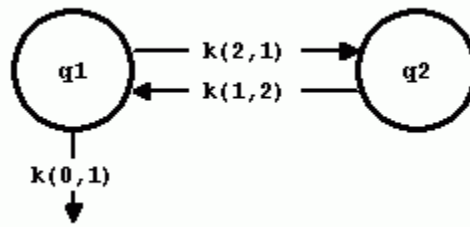
1. **Start the SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open.
2. Create the following system model:




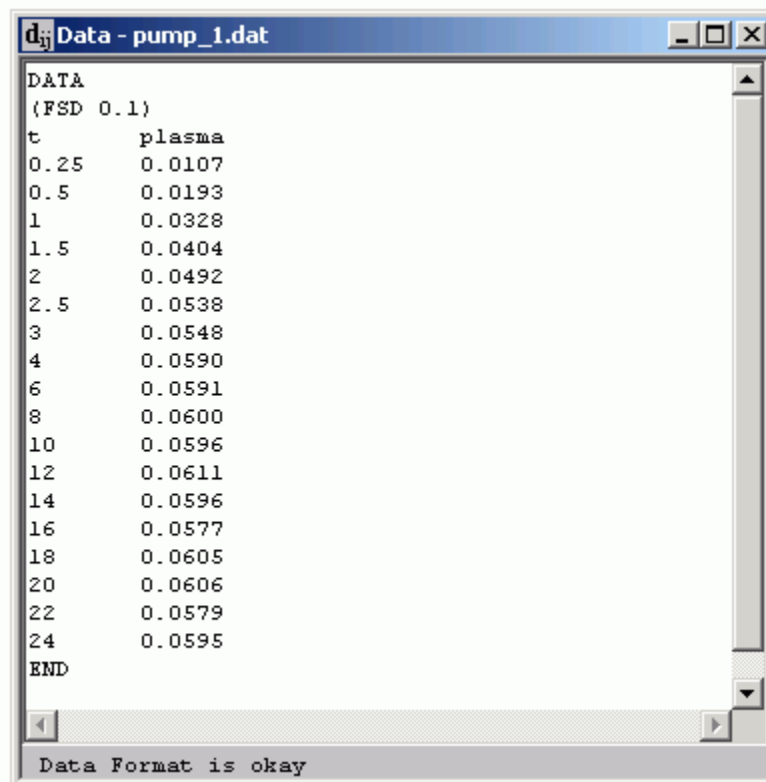
3. Create the experiment on the model.
 - a. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open. Set the experimental attributes as follows:



- b. Click **Done**. The **Create Experiment** dialog box will open. Click **Create**. The model will appear as follows:

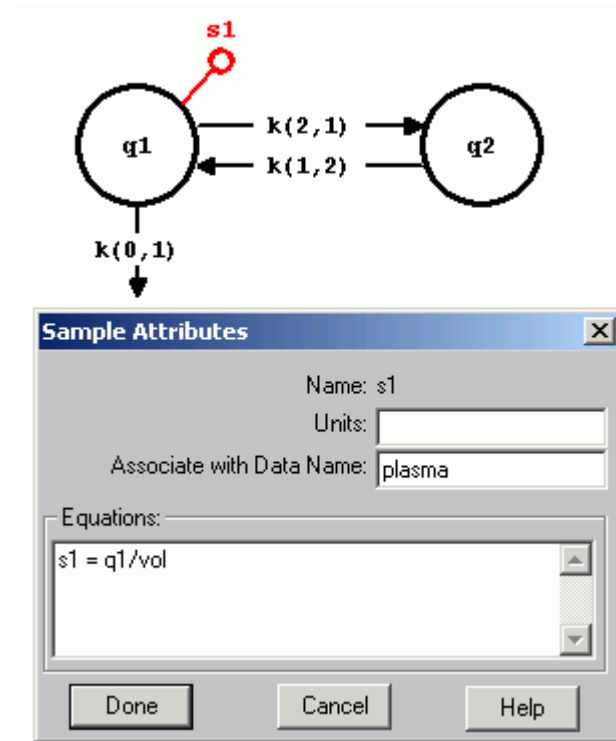


4. Add the data to the model.
 - a. On the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data** . The **Data** window will open.
 - b. On the **File** menu, click **Open**. The file **pump_1.dat** should appear in the list (if it does not, find the folder where you put this data file).
 - c. Double-click **pump_1.dat**. The data in this file will appear in the **Data** window. The **Data** window should appear as follows:



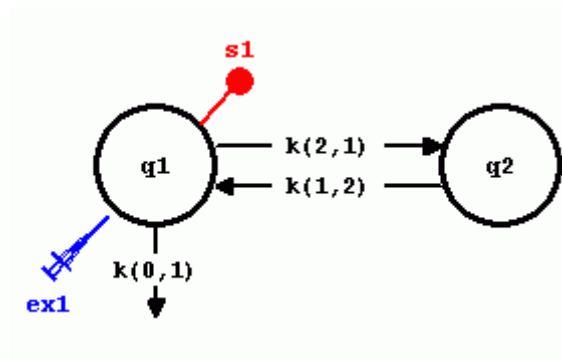
- d. Close the **Data** window.

5. Create a sample on Compartment **q1**, associated with “plasma” and edit the sample equation to read “ $s1=q1/vol$ ”. The **Sample Attributes** dialog box should appear together with the model as follows:



Click **Done**. Notice that the circle at the top of the sample object is now filled as shown in the diagram below; this is because data are now associated with the sample.

6. Create an input into Compartment **q1**.
 - a. Create the input into Compartment **q1**. The model should appear as follows:



- b. Specify the input equation.

- (1) Double-click **ex1** to open the **Exogenous Input** dialog box.
- (2) Select **Equation** as the input type.
- (3) Set the **Start** equal to 0 and **Stop** time equal to 24.
- (4) Write the input equation “ex1 = input”. Click **Add**. The **Exogenous Input** dialog box should appear as follows:

- (4) Click **Done**.




Exogenous input. In this case, the input is defined by the equation “ex1 = input.” The equation “input” will be defined using the Heaviside function which will be defined to turn on and off to maintain the plasma concentration of the drug at a specific level.



7. Create the input equation.

The input equation “input” will be created using the Heaviside function, and will be defined to turn on or off depending upon whether **s1**, the plasma concentration,

is below or above a certain set point, i.e. a concentration specified by the user. In this case, the set point concentration is 0.06mg/ml.

- a. In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar**, click **Equations** . The **Equations** dialog box will open.
- b. Create the conditional expression to define the switch. In the **Equations Defined Here** pane, type:

“condition=0.06-s1”

“condition” will be positive when **s1** is less than 0.06, and will be negative when it is larger. This will be used as the switching mechanism in the Heaviside function.

- c. Create the Heaviside function. In the **Equations Defined Here** pane, type

“heaviside=0.5*(1.0 + atan(lambda*condition)*2/3.141592653)”

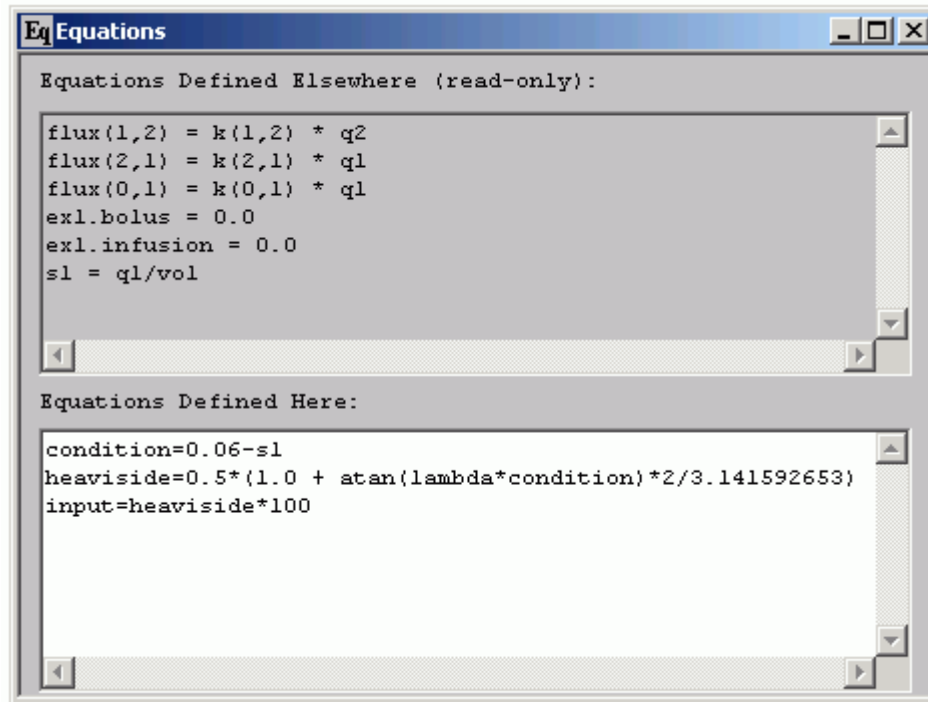
In this expression, when “condition” is negative, the value of the Heaviside function will be zero; otherwise it will equal 1. Values for **s1** will thus oscillate around 0.06.

- d. Create the input equation. In the **Equations Defined Here** pane, type

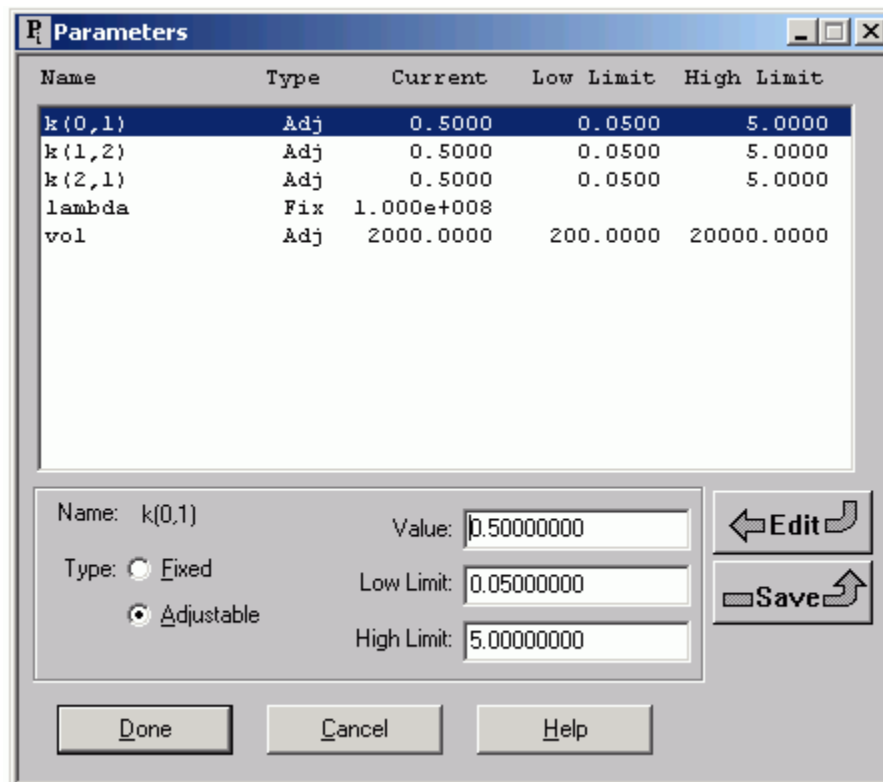
“input=heaviside*100”

The infusion rate is 100mg/hr. When the value for the Heaviside function is 1, the infusion will be turned on; when it is zero, the infusion will be turned off.

The **Equations** dialog box should appear as follows:

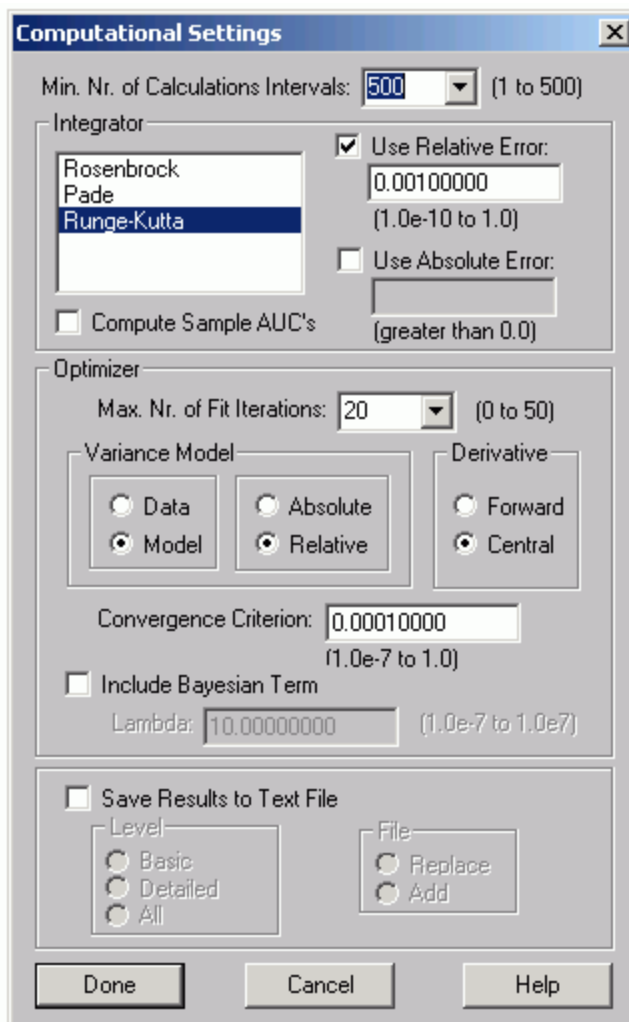


- e. Close the **Equations** dialog box.
8. Enter the parameter values as shown below:



The parameters are those for the two-compartment model together with λ , the “tuning” parameter for the Heaviside function. The initial value for λ of $1.0e+08$ was determined by initial tuning starting from $1.0e+06$.

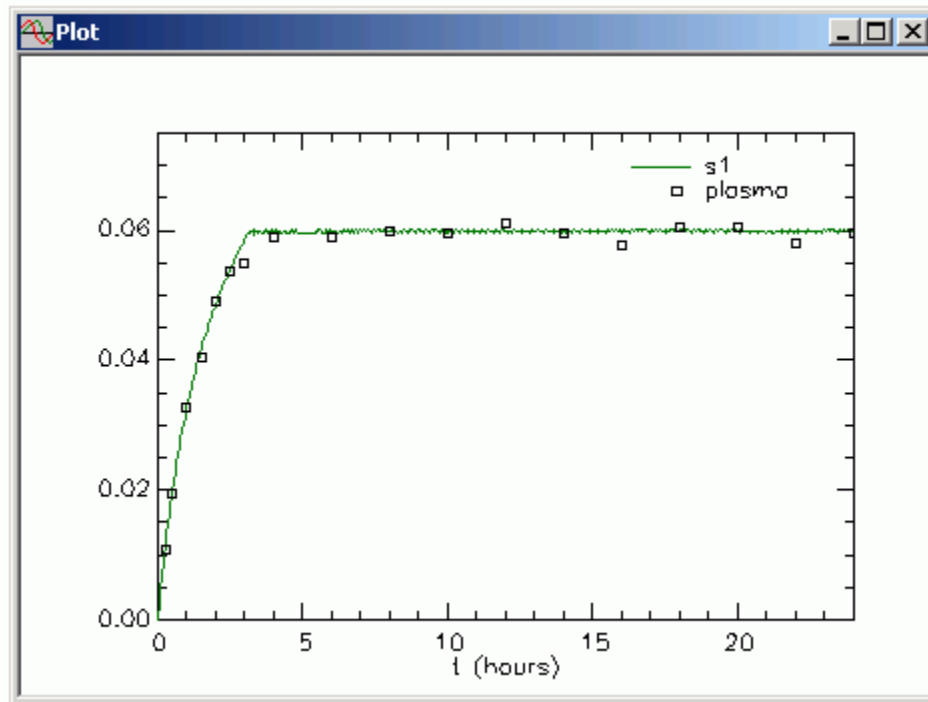
9. Solve the model and view the solution.
 - a. Because the input will be turning off and on very rapidly, the Computational Settings are going to be changed as shown below:



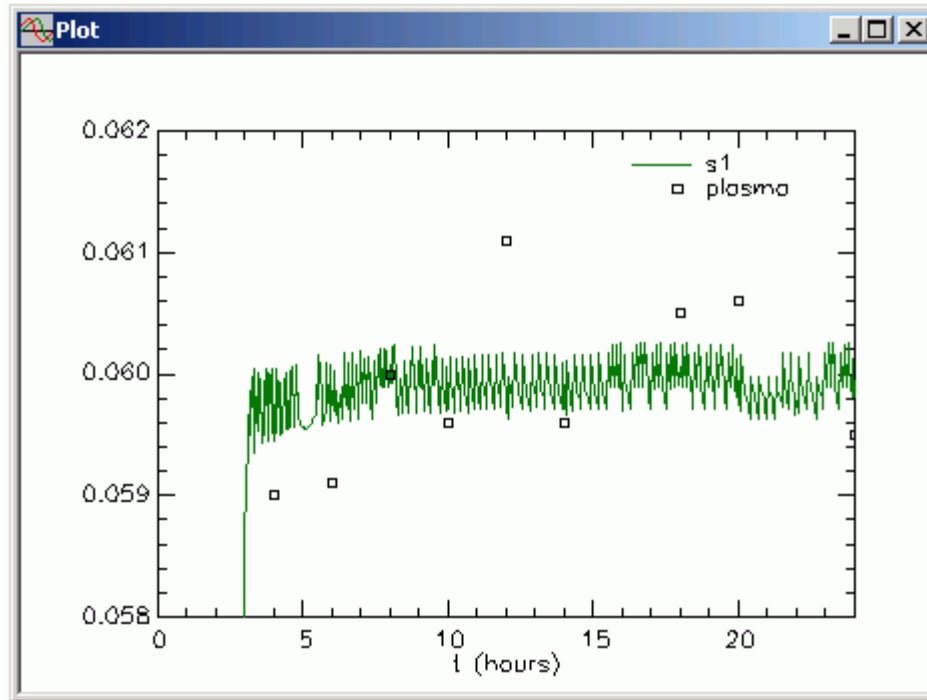
The **Min.Nr. of Calculation Intervals** is set to the maximum so you can visualize as much as possible the changes in the input function and s_1 . The integrator will be changed to the Runge-Kutta (you should compare results using the Rosenbrock if you are interested). The **Derivative** calculation is changed to **Central**.

When you have changed the settings, click **Done**.

- b. Solve the model and view the solution. A plot of **s1** and **plasma** will appear as follows (the Y Axis maximum has been set equal to 0.075):

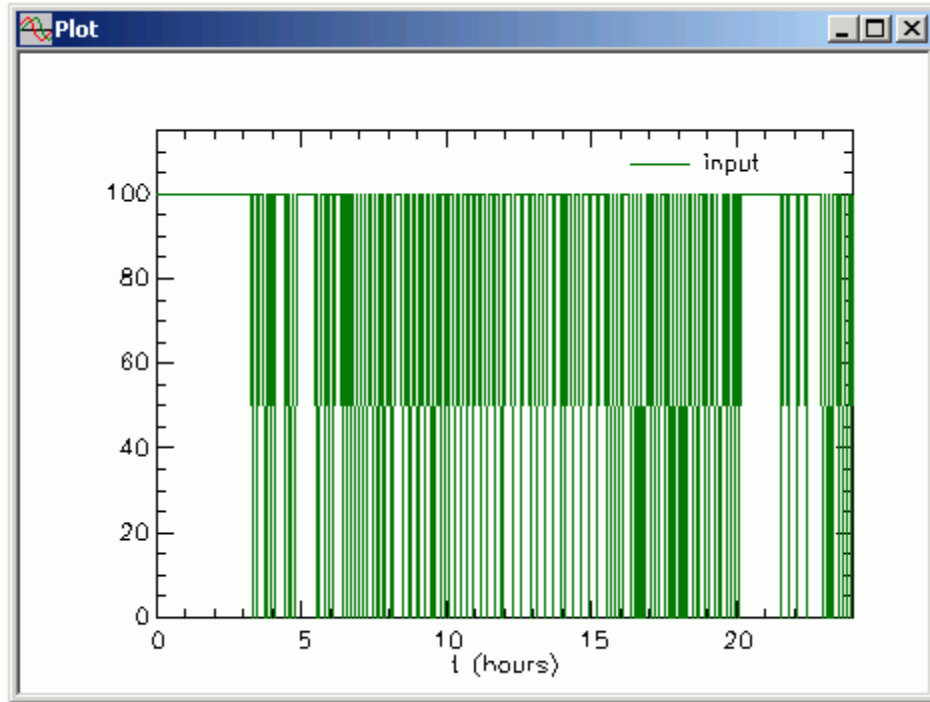


You can see the oscillations around 0.06. To visualize them better, change the **Plot/Table Scale** to a minimum and maximum respectively of 0.058 and 0.052. The plot will appear as follows:

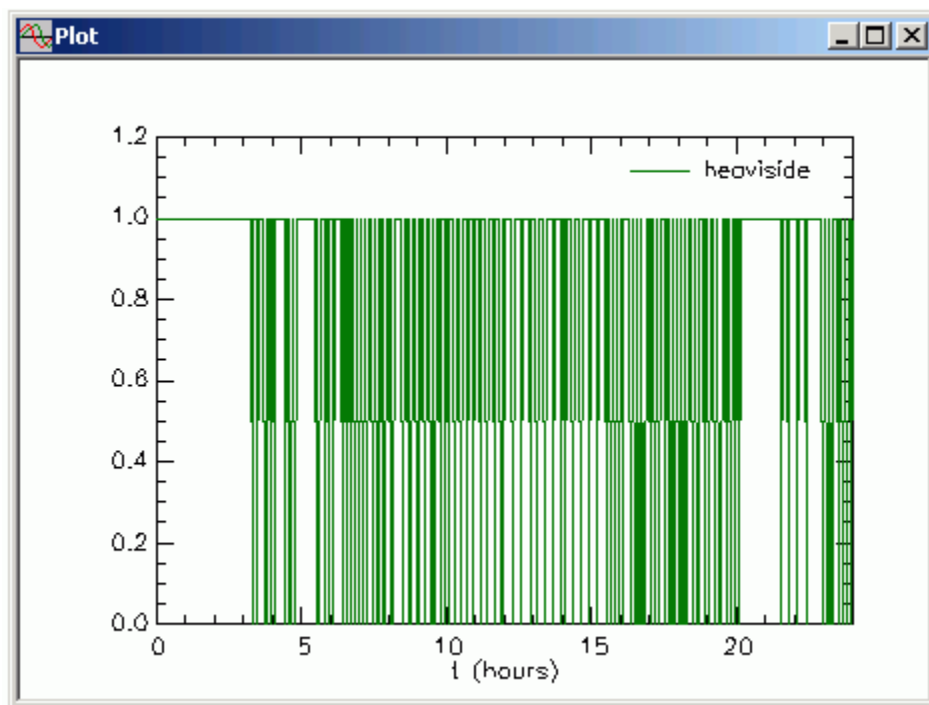


The rapidity of the oscillations indicates that you have to be very careful with the computational settings. You should try different options to be sure the same result is returned.

The plot of the input function “input” is shown below; again the rapidity of the input turning on and off is evident:



The calculation of the Heaviside function parallels that of the input function:



Notice the infusion is on until just after 3 hours when the concentration reaches the critical level for the infusion to turn off for the first time. Thereafter it turns off and on rapidly. The "gaps" after 3 hours are due to an

insufficient number of calculation points for plotting purposes. You can tell from the plot of **s1** and **plasma** that the pump is still turning off and on.

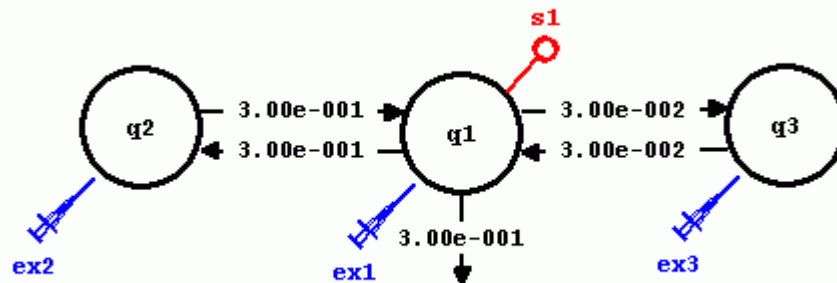
- c. Close the **Plot** window and any remaining open dialog boxes.

The purpose of this part of the tutorial was to simulate a pump that is rapidly turning off and on. If you try to fit the model to the data, you will have problems with optimization because this example is not intended to illustrate fitting such pump models to data (there are insufficient data).

Quit the **SAAM II Compartmental** application. You can save the study file if you wish. **pump_1.stu** is the study file with the initial parameter values and computational settings.

The above example dealt with introducing material into the system for the first time. What about the situation where material is already in the system. For example, suppose you wished to infuse glucose to maintain glucose slightly above some basal level? The discussion below is based on the study file **pump_2.stu**. If you wish to follow the discussion, you can open **pump_2.stu** and click on **Experiment** in the **SAAM II Toolbox**.

The model of the experiment is shown in the figure below:



This is a typical 3-compartment model to explain glucose kinetics. The values of the rate constants, shown in the figure, are also typical.

Suppose you wanted to simulate a pump that elevates basal glucose concentration. Then you must first create the model of the experiment so that baseline conditions exist. This means you must specify masses in all compartments, and a rate of input that mirrors endogenous glucose production.

Suppose the baseline concentration is 100mg/ml and plasma volume is 3000ml. Then the mass in Compartment **1**, **Q1**, equals 300,000. Since $k(0,1)$ equals 0.3, the loss flux is “ $k(0,1)*300000$ ”, or 90,000. To maintain a constant mass in Compartment **1**, therefore,

you must specify a constant infusion of 90,000 during the experiment to simulate endogenous production.

However there are masses to be described in Compartments **2** and **3**. Knowing the mass in Compartment **1**, these can easily be calculated since, for example,

$$k(2,1)*Q1 = k(1,2)*Q2$$

where **Q1** and **Q2** are respectively the masses in Compartments **1** and **2**. Since the corresponding exchange rate constants are equal, the mass in Compartments **2** and **3** are also equal to 300,000.

How is this information specified?

Double-click on **ex2** to open the **Exogenous Input** dialog box associated with Compartment **q2**. It will appear as follows:

Type	Initial	Constant	Start	Stop	Repeat Every	Nr. Repeats
Bolus	3.00e+5	-	0.000	-	-	-

Click **Done**.

The bolus injection of 300,000 will ensure the proper mass in Compartment **q2** at the start of the experiment. A parallel situation exists for Compartment **q3**.

Now double-click **ex1** to open the **Exogenous Input** dialog box associated with Compartment **q1**. It will appear as follows:

Type	Initial	Constant	Start	Stop	Repeat Every	Nr. Repeats
Infusion	-	9.00e+4	0.000	480.000	-	-
Bolus	3.00e+5	-	0.000	-	-	-
Equation	ex1 = input		30.000	480.000	-	-

Input Type:

Bolus
 Infusion
 Primed Infusion
 Equation

Initial Amount: 0.0

Constant Rate: 90000.00000000

Event Start: 0.0

Event Stop: 480.00000000

Repeat Every:

Nr. of Repeats:

Equation: ex1 =

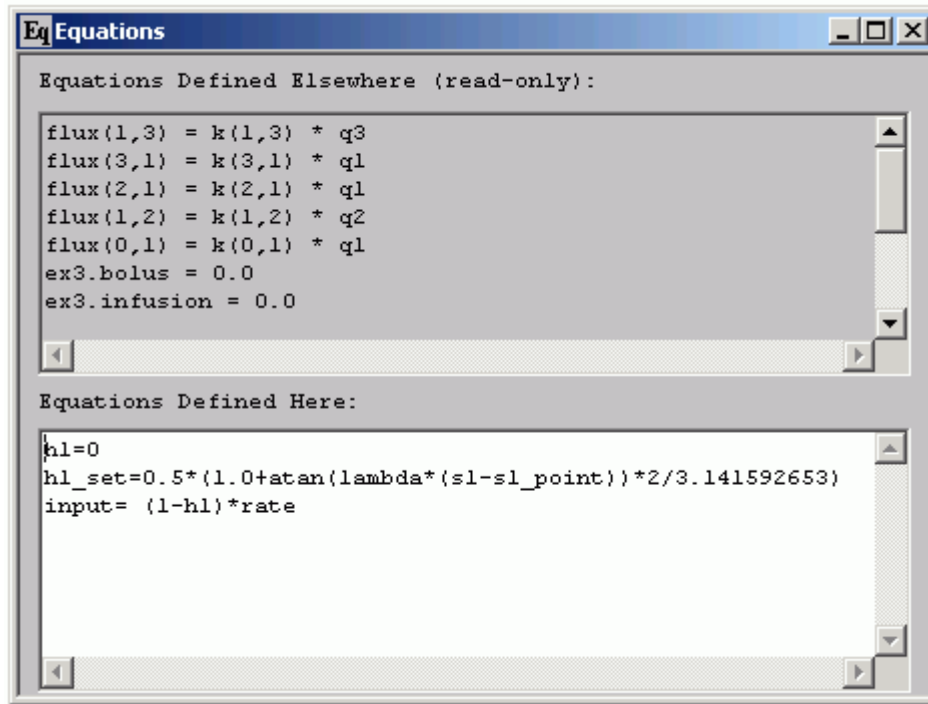
Buttons: Save, Edit, Add, Delete, Split Input..., Done, Cancel, Help

The first two inputs characterize the baseline state. Here the state variables (mass in the compartments) in the system, though dynamic in the sense that glucose is being metabolized, do not change. Input equals output. The bolus of 300,000 specifies the initial mass, and the infusion mimics endogenous glucose production.

The last equation input specifies the pump. The pump will start at 30 minutes. Thus for the first 30 minutes, the system will not change. With the pump turns on, the concentration in Compartment **q1** will rise to a new set point, and be maintained at that point.

Click **Done**.

The pump input rate has been set in a manner similar to the previous tutorial. Open the **Equations** dialog box; it will appear as follows:



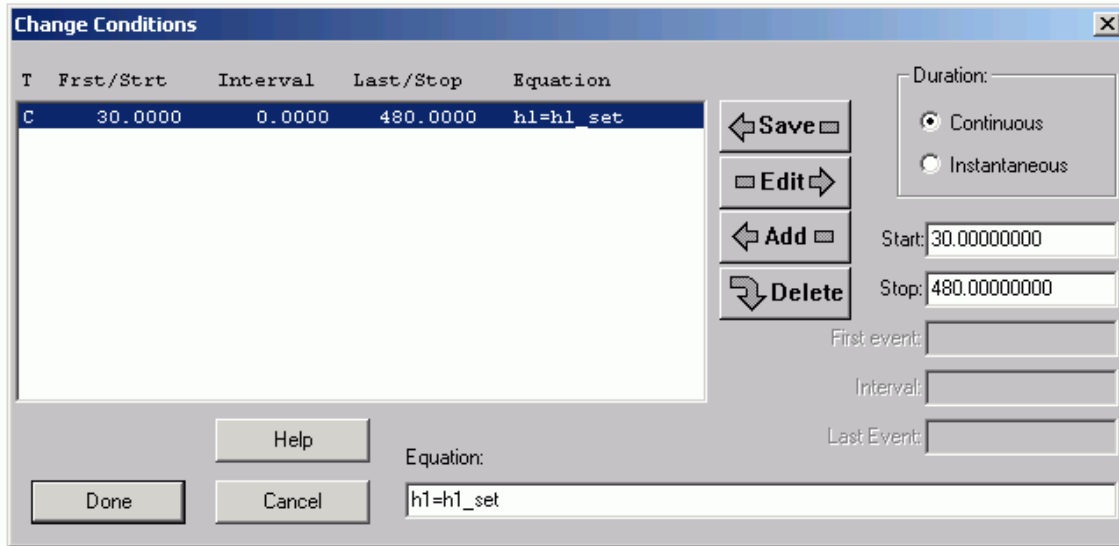
In the **Equations Defined Here** pane, the first two equations specify the Heaviside function. The function is zero ($h1 = 0$) up to the time the pump starts at 30 minutes. It then equals:

$$h1_set=0.5*(1.0+\text{atan}(\text{lambda}*(s1-s1_point))*2/3.141592653)$$

Thus $s1_point$ will be specified in the **Parameters** dialog box as the new concentration to be maintained.

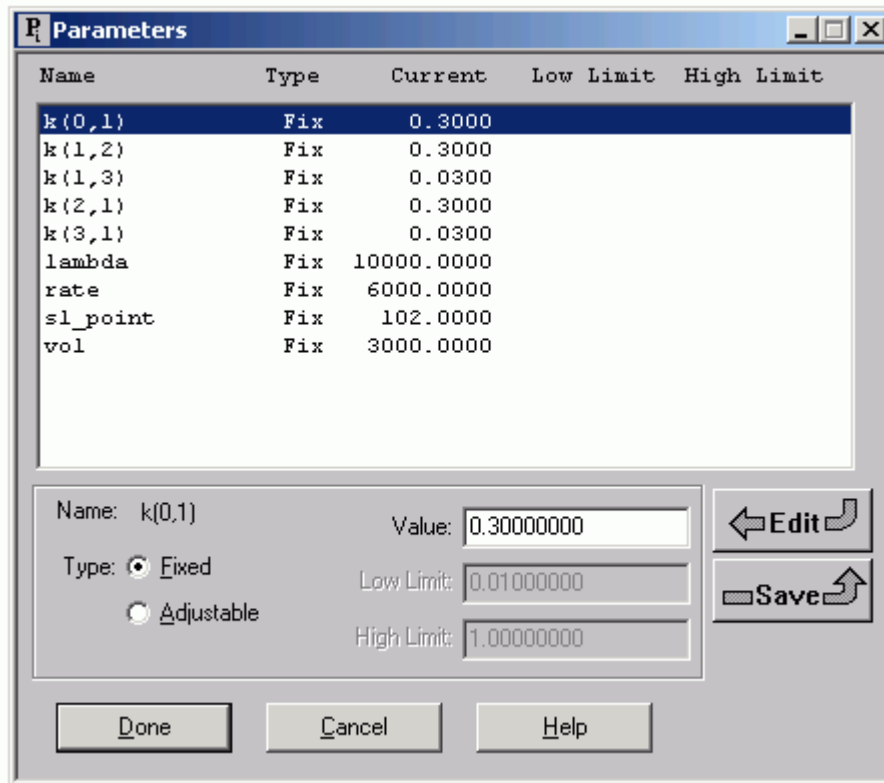
The last equation specifies the input rate. It will turn off and on according to the value of $(1-h1)$. The magnitude, $rate$, will be a parameter specified in the **Parameters** dialog box.

Close the **Equations** dialog box. Changing the value of $h1$ from zero to $h1_set$ is done using **Change Conditions**. In the **SAAM II Toolbox**, click **Change Conditions**. The **Change Conditions** dialog box will open as follows:



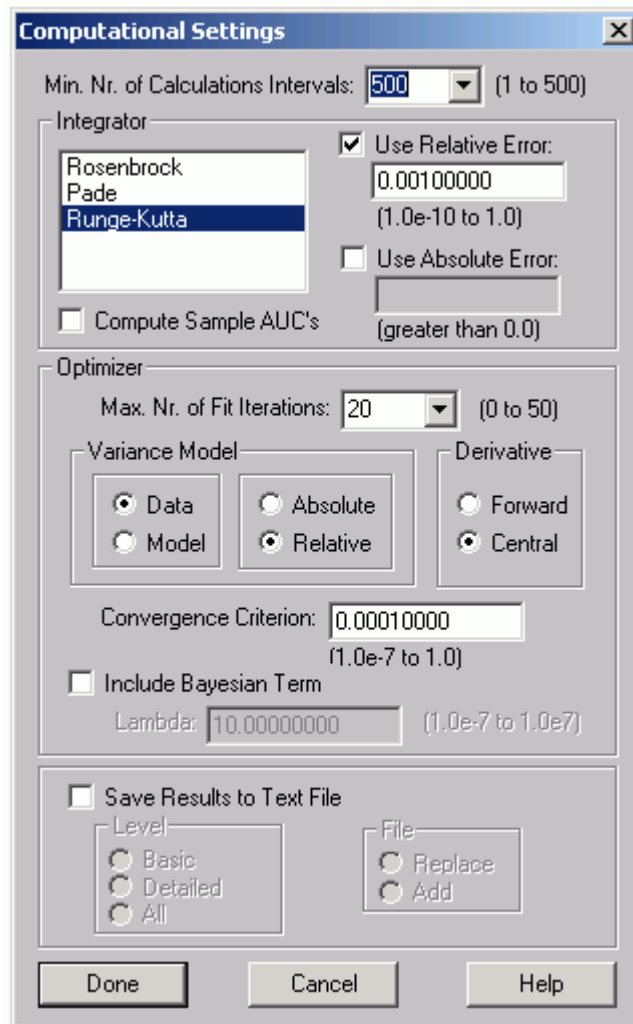
In the **Equations** dialog box, h1 was initially set equal to zero; here it changes to h1_set at 30 minutes and maintains this value for the duration of the experiment. Click **Done**.

Open the **Parameters** dialog box; it will appear as follows:



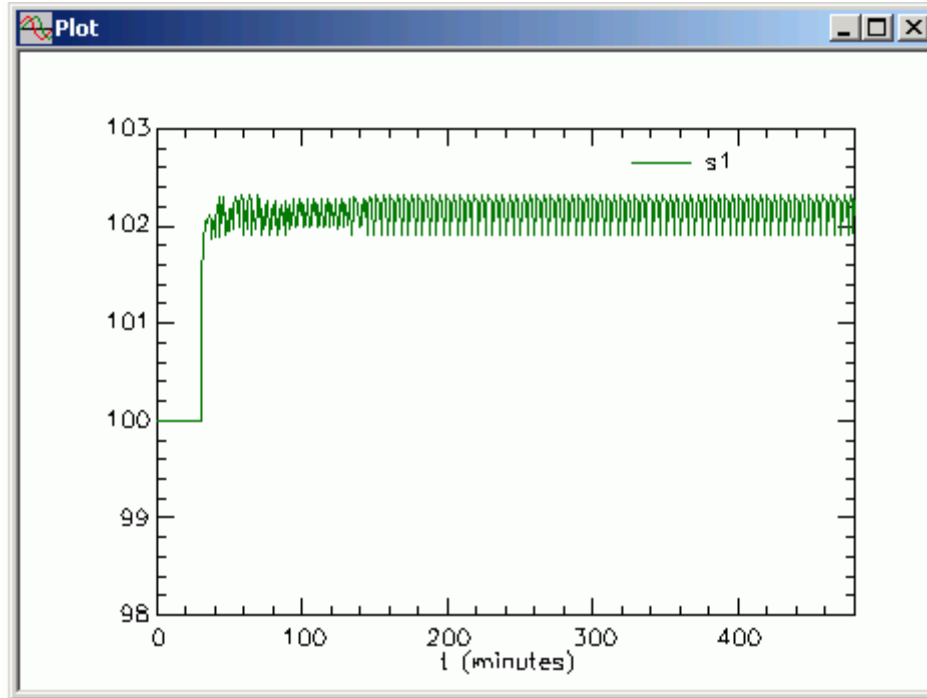
Since this exercise is a simulation, all parameters are fixed. Notice the value for *sl_point* is 102 meaning the pump will only slightly elevate the baseline concentration. Click

Done to close the **Parameters** dialog box, and open the **Computational Settings** dialog box. It will appear as follows:

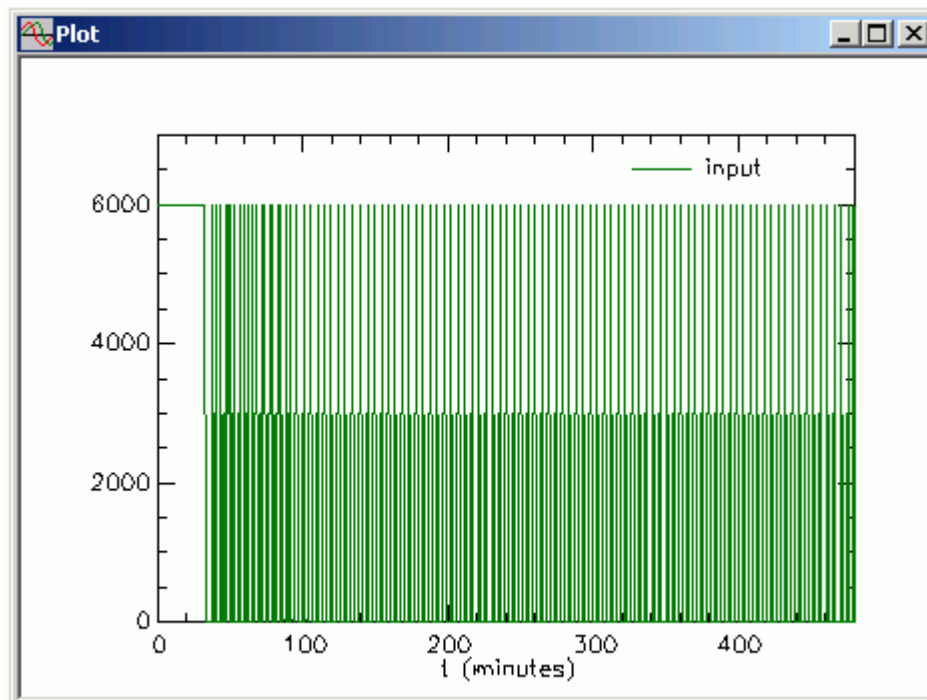


The **Minimum Number of Calculation Intervals** is set to its maximum value of 500. The integrator is the Runge-Kutta, and the derivative calculations are done using the Central mechanism. Click **Done**.

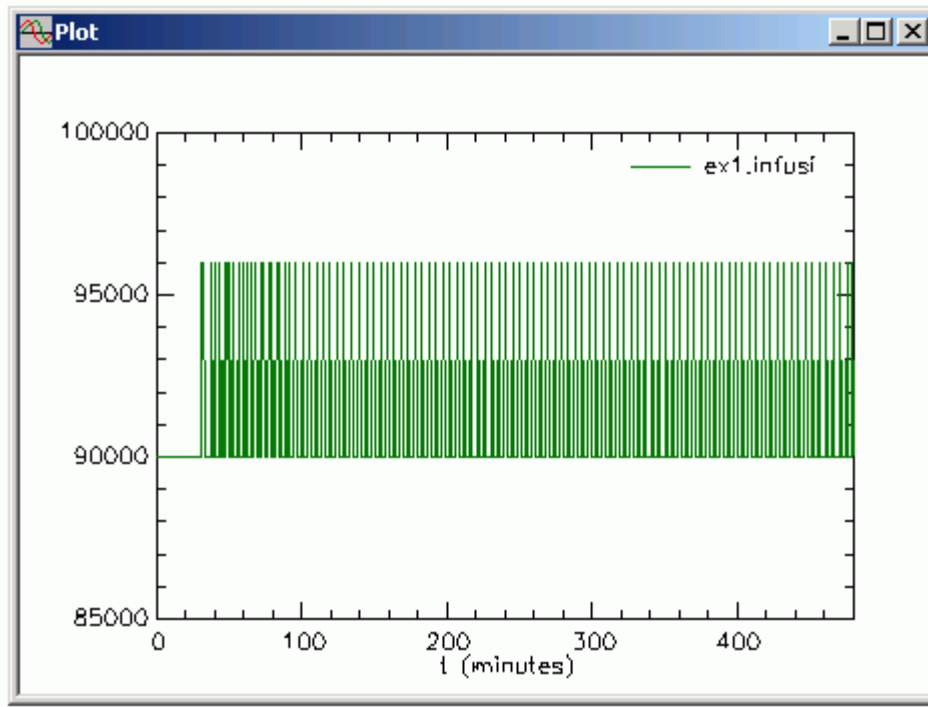
Solve the model and view the solution. A plot of **s1** (with the minimum and maximum values respectively set at 98 and 103) will appear in linear mode as follows:



You can clearly see that the basal state is maintained for the first 30 minutes after which the pump takes over. You can also see the switching mechanism maintains the new concentration very close to the desired 102. The input function will appear as follows:



Notice that input has a value during the first 30 minutes equal to 6000 (*rate*). However, input is not “seen” until 30 minutes as specified in the **Exogenous Input** dialog box. You can see this by plotting **ex1.infusion**, the infusion rate specified:



This is the actual infusion rate into Compartment **q1**. It equals the baseline up to time 30 after which time “input” is added to this baseline rate.

This study file is worth experimenting with to understand the behavior of such pumps. The parameters to change, and to see how these changes affect the solution, are *sl_point* and *rate*. Depending upon the magnitude of the changes, you may have to adjust *lambda*. You may also have to change some computational settings the most likely of which is value of the integrator relative error (you may need to reduce it).

Experimenting with this study file will give you a much better feeling to the strengths and limitations of trying to simulate pumps such as this.

Quit the SAAM II Compartmental application. Do not save any changes you made to **pump_2.stu**