

# Getting Started with Numerical Tutorial

- How to use SAAM II Numerical
- How to view solutions
- How to create a sum of exponentials model
- How to enter data
- How to enter model parameters



## Getting Started with SAAM II Numerical

### Prerequisites

This tutorial has no prerequisites. It assumes you know the basics of the **Windows** operating system. It also assumes you have **SAAM II's Numerical** application installed on your computer, and that you know how to open the application.

### What you will learn in this tutorial

The basic operations of the **SAAM II Numerical** application:

- How to use a **SAAM II Numerical** study file.
- How to use **SAAM II Numerical** computational features.
- How to view solutions.
- How to create a Sum of Exponentials model.
- How to enter data, and associate data with the model.
- How to enter model parameters.

### Files Required

Study File:

**study\_0.nst**

This file is the same as **study\_0.nst** that is installed in the **SAAM II** program folder, and referred to in the **SAAM II** User Guide.

Data Files: The data file for this tutorial is

**study\_0.dat**

The data file is a text file. (This file is the same as **study\_0.dat** that is installed in the **SAAM II** program folder, and referred to in the **SAAM II** User Guide.)

### Introduction

This tutorial will show you how to perform the basic operations in the **SAAM II Numerical** application. It is intended to help the new user get started quickly with **SAAM II**.

This tutorial is divided into two parts. In the first part, you will load an existing **SAAM II** file. The purpose is to familiarize you with the basic computational operations, and how to view

information from solutions. In the second part, you will build a model. This will familiarize you with the tools used to build models and create experiments.



In this **SAAM II Numerical** tutorial, special information or notes to assist the user in the Numerical application are preceded by the **Numerical** symbol on the left and end with the small **Numerical** symbol.



### Part 1. Using a Numerical Application Study File

This part of the tutorial will show the key components of a numerical model specified by a sum of exponentials, the basic computational operations of **SAAM II**, and how to view information from solutions. You will work with the following sum of exponentials model:

$$y_a(t) = A_1 * \exp(-a_1 * t) + A_2 * \exp(-a_2 * t)$$

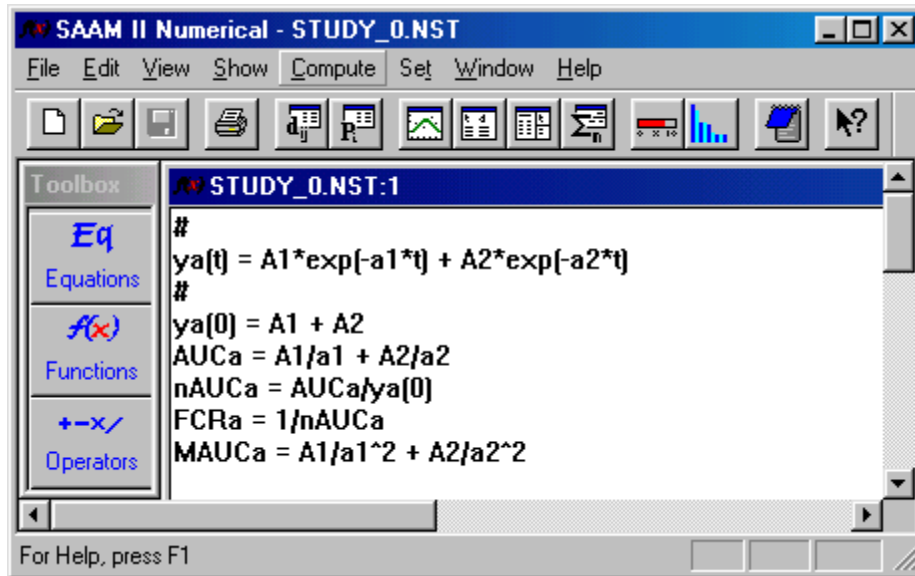
This model is appropriate to explain a decaying set of data following, for example, a bolus injection into plasma.

1. Start the **SAAM II Numerical** application.
2. Open the **SAAM II Numerical** study file **study\_0.nst**.

The file **study\_0.nst** should appear in the file list; if it does not, find the folder where you put this file.

In the **File** menu, click **Open**.

The **SAAM II Numerical** main window will open as follows:



The model is the **SAAM II Numerical** representation of a two-exponential model. The model is characterized by two coefficients,  $A1$  and  $A2$ , and two exponentials,  $a1$  and  $a2$ .

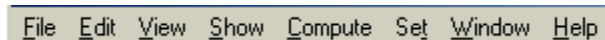


*Auxiliary equation.* **SAAM II** will automatically create auxiliary equations when the model is specified using the **SAAM II Toolbox**. In this case, the model is specified to explain data following a bolus injection into plasma. The auxiliary equations estimate the zero time value ( $ya(0)$ ), the area under the curve (AUC), the normalized area under the curve (nAUC), the fractional clearance rate (FCR), and the mean area under the curve (MAUC). These values can be used to calculate the noncompartmental parameters, especially in pharmacokinetic studies.



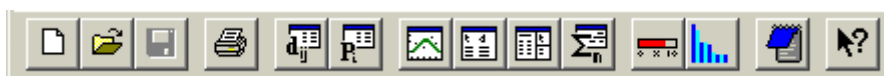
The **SAAM II Numerical** main window consists of four main areas:

The **Menu** bar:



This **menu** bar contains the **SAAM II** menu items.

Below the **Menu** bar is the **SAAM II Toolbar**:



This toolbar contains **SAAM II** specific tools such as "Solve" or "Fit." Most of the toolbar functions can also be found in the **Show** and **Compute** menus.

The **Equation area** is shown below:

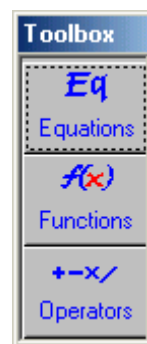
```

#
ya(t) = A1*exp[-a1*t] + A2*exp[-a2*t]
#
ya(0) = A1 + A2
AUCa = A1/a1 + A2/a2
nAUCa = AUCa/ya(0)
FCRa = 1/nAUCa
MAUCa = A1/a1^2 + A2/a2^2

```

The **Equation area** contains the area for writing algebraic equations.

The **SAAM II Toolbox**:



The **SAAM II Toolbox** contains various algebraic modeling tools. **Equations** lets you add predefined equations to the model. **Functions** lets you add standard mathematical functions to the model equations. **Operators** lets you add standard arithmetic, relational and miscellaneous operators to the equations. The **SAAM II Toolbox** will be discussed in detail in the next part of this tutorial.

Take a minute to examine the tools available on the **Numerical Toolbar** and in the **Toolbox**. Place the cursor on top of a **SAAM II** tool to show text describing the tool's function.

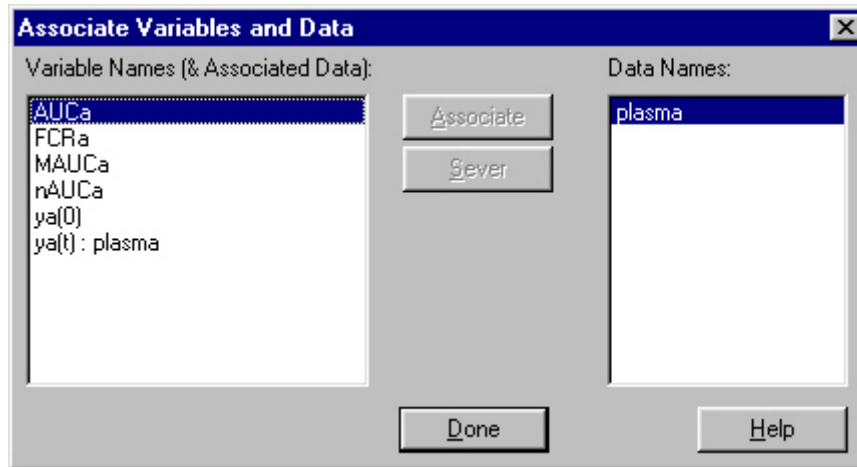


*The Numerical model:* In the **SAAM II Numerical** application, the model is specified by algebraic equations. There is no counterpart to the system model and experiment as described for the **SAAM II Compartmental** application. Thus there is no counterpart for an exogenous input or sample. However, the model must be

associated with data in a manner similar to associating a sample with data in SAAM II Compartmental.



3. Associating model variables with data.
  - a. In the **Show** menu, click **Associations**. The **Associate Variables and Data** dialog box will open, as shown below:




*Associating variables and data dialog box:* The **Associate Variables and Data** dialog box consists of two panes. The **Variable Names** pane contains the variable names as specified in the **Equation Area**, and the **Data Names** pane contains the data names found in the data file. In the left pane, notice "ya(t):plasma." This shows that the variable ya(t) is associated with the data "plasma." During "Fitting," the parameters characterizing ya(t) will be adjusted to obtain a best "Fit" to the data, "plasma."

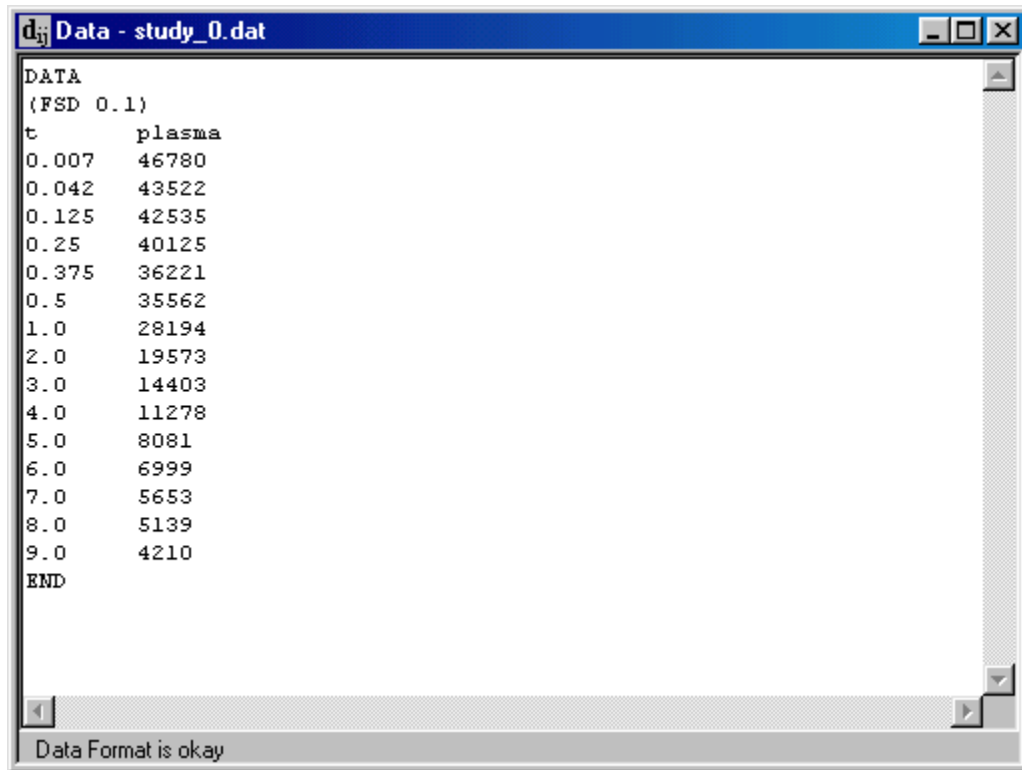
There are two operations the user can perform using this dialog box. One is **Associate** and the other is **Sever**. To associate a variable with a data name, click first on the variable, e.g. *AUCa*, then the data name, e.g. plasma, and then **Associate**. The variable name and data will appear in the left pane similar to "ya(t):plasma." To sever an association, click on the associated pair, and click, **Sever**. The variable name and data name will return to their respective panes in the dialog box.



- b. Click **Done** to close the dialog box.
4. View the data.

Data in SAAM II are entered as a text file where columns are space delimited. The data file for **study\_0.nst** can be viewed as follows:

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



```

DATA
(FSD 0.1)
t      plasma
0.007  46780
0.042  43522
0.125  42535
0.25   40125
0.375  36221
0.5    35562
1.0    28194
2.0    19573
3.0    14403
4.0    11278
5.0    8081
6.0    6999
7.0    5653
8.0    5139
9.0    4210
END

```

Data Format is okay

The first line of the data file is the word “DATA.” The next line, (FSD 0.1) specifies the weighting method assigned to the data. The first column in the data file is always the independent variable, usually time, denoted **t**. The columns representing data can be named whatever you wish; the name is case sensitive. The name of this column must be same as the name in the appropriate **Associate Variables and Data** dialog box.




*Data weighting.* Data weighting is used to provide a measurement of the user’s confidence in a particular datum and is used in the “Fitting” process. Data weights are calculated as the inverse of the data variance. **SAAM II** contains several variance models. If no method is explicitly specified, a fractional standard deviation of 0.1 (FSD 0.1) is assigned as the variance model to each datum.

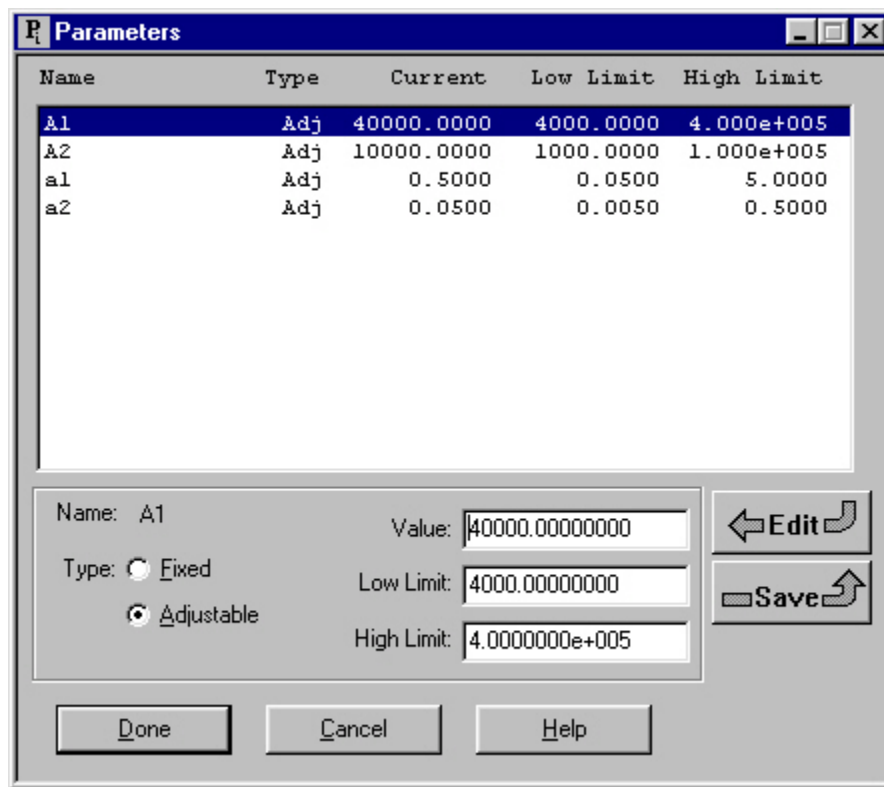
**SAAM II** calculates weight for each datum from the standard deviations you assign to your data. In the file above, the variance model, (FSD 0.1) means that a constant coefficient of variation (fractional standard deviation) of 10% is assigned to each datum. Therefore, for example, the standard deviation of the datum of 46780 is 4678.



- b. Close the **Data** window.
4. View the model parameters.

The model has four parameters:  $A1$ ,  $A2$ ,  $a1$  and  $a2$ . These parameters are entered in the **Parameters** dialog box.

- 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
A1	Adj	40000.0000	4000.0000	4.000e+005
A2	Adj	10000.0000	1000.0000	1.000e+005
a1	Adj	0.5000	0.0500	5.0000
a2	Adj	0.0500	0.0050	0.5000

Name: A1 Value: 40000.00000000

Type:  Fixed  Adjustable Low Limit: 4000.00000000 High Limit: 4.0000000e+005

Buttons: Edit, Save, Done, Cancel, Help



*Properties of parameters.* There are several important features of the **Parameters** dialog box.

- i. Each parameter has a "Type" that is either "fixed" or "adjustable." A fixed parameter is a parameter that is assumed to be known and does not change when the model is "Fitted" to the data. An adjustable parameter is adjusted when the model is "Fitted" to the data.

- ii. Each parameter, whether fixed or adjustable, has a "current" value; this is the value that will be used when you Solve or Fit the model.
- iii. Adjustable parameters have upper and lower limits. These are limits that cannot be exceeded when SAAM II Fits the model to the data. If SAAM II is Fitting the model to the data and a limit is reached, SAAM II will display a warning message.
- iv. To change a parameter value, double-click on the parameter name or click **Edit**. The parameter's current **Value**, and **Low** and **High** limits, if it is adjustable, can be changed. To save the changes, click **Save**.



- b. To close the **Parameters** dialog box, click **Done**.
5. Solve the model.

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

**Solve** 



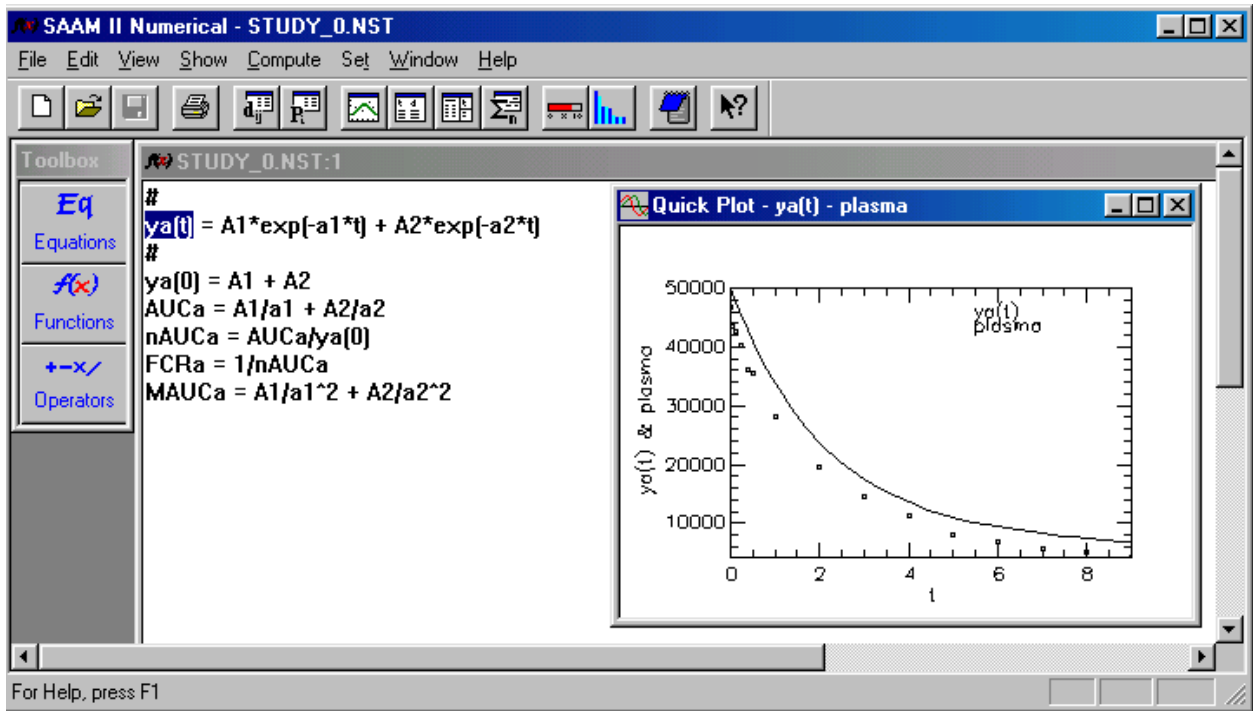
*Solve.* When you "Solve," SAAM II uses the current values of the parameters to solve the algebraic equations characterizing the model. It is important to note that no numerical integration is performed in SAAM II Numerical. This is because there are no differential equations as is the case with SAAM II Compartmental.

During a "solve," a **Solve Status** message will appear showing the status of the integration ("solving"). For small models such as this one, the message will appear and disappear extremely fast. For larger models, you can watch the progress. You can also choose to abort a "Solve."



6. View the solution to the model using **Quick Plot**.
- a. Highlight **ya(t)** in the **Equation** area to select it.
  - b. In the **View** menu, click **Quick Plot**.

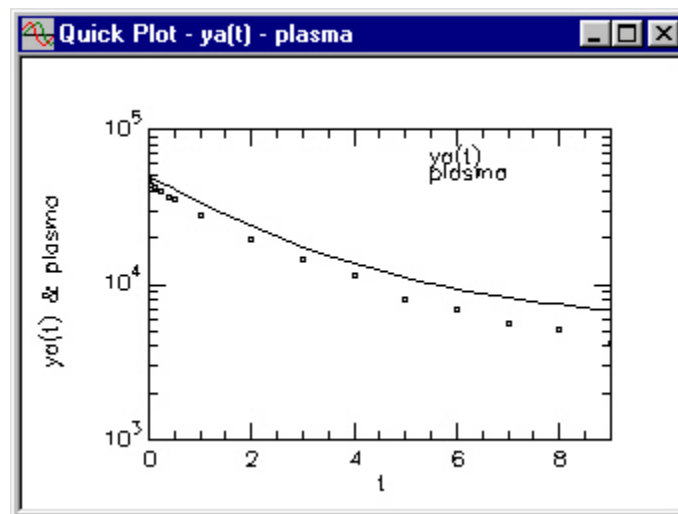
The **Quick Plot** will appear on the **Numerical Window** as follows (notice that it is a linear plot):




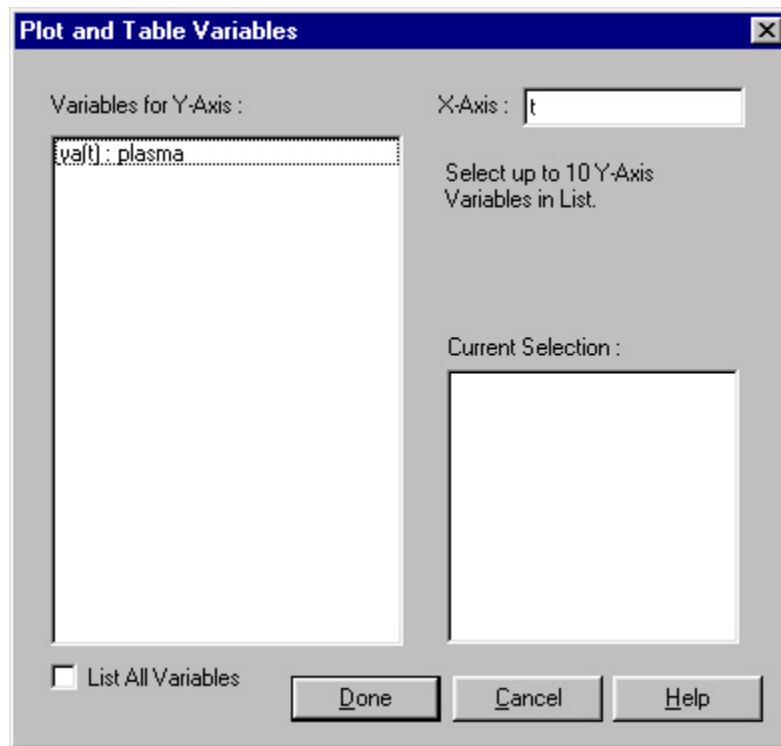
*Quick Plot.* **Quick Plot** has preset defaults that you cannot change. As you can see below, when you use the **Plot** command, you have more flexibility in what you can plot and how you can plot it.



- c. To view this plot in the semi-logarithmic mode, in the **View** menu, click **Semilog**. The following plot will appear:

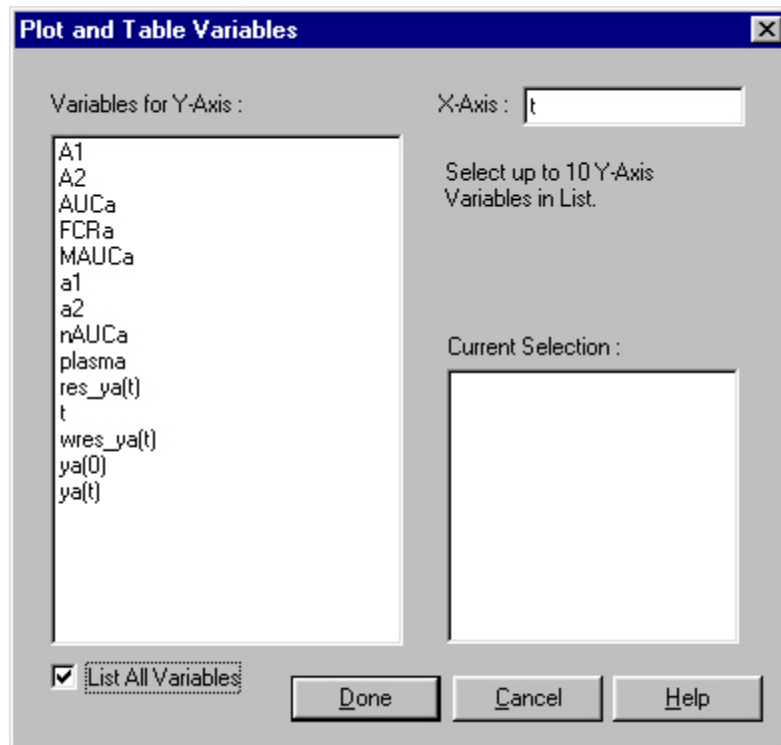


- d. Close the **Quick Plot** window.
7. View the solution to the model using the **Plot** command.
  - a. In the **Show** menu, click **Plot**, or alternatively on the **SAAM II Toolbar** click **Plot** . The **Plot and Table Variables** dialog box will open as shown below:



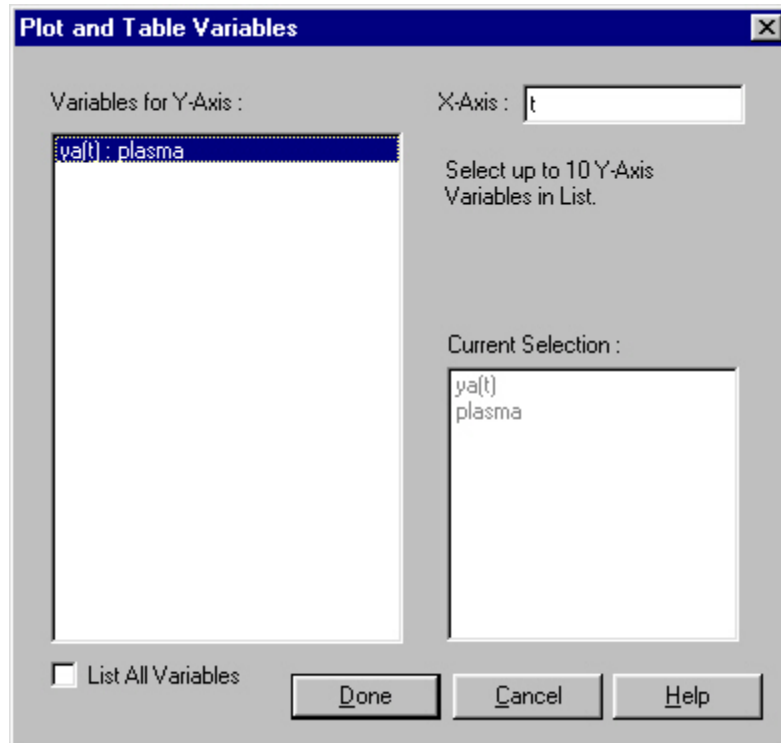
Only the variables that are associated with data will appear. However, you can plot any of the variables in the model.

- b. In the **Plot and Table Variables** dialog box, select the **List All Variables** check box. All the variables that can be plotted will appear as follows:



You can now select among the different variables for the Y-Axis for the plot.

- c. In the **Plot and Tables** dialog box, clear the **List All Variables** check box to clear all variables except **ya(t):plasma**.
- d. In the **Variables for Y-Axis** pane, click **ya(t):plasma**. The selection will move to the **Current Selection** pane as follows:



- e. Click **Done**.

A plot similar to the **Quick Plot** will appear.

8. Fit the model to the data and view the solution.



*Leaving the Plot window open.* The **Plot** window can remain open during the “Solve” and “Fit.” The plot will be updated after a successful “Solve” or “Fit.”



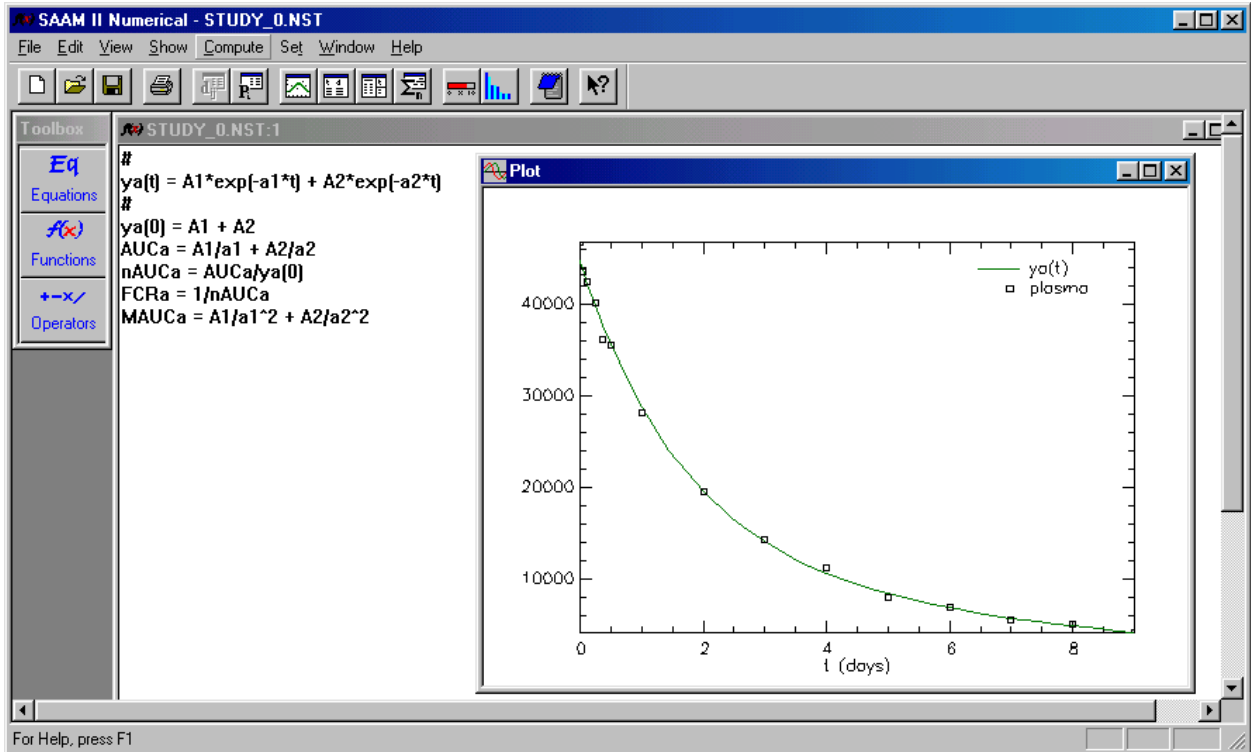
- a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar** click **Fit**




*Fit status.* During a “Fit,” a **Fit Status** message will appear (on a fast computer, you may just see a flash). This is the counterpart to the **Solution Status** message you saw when you solved the model originally. The **Fitting Status** bar gives information both on the integration part of the “Fitting” and on the number of iterations. You can abort the “Fit” by clicking **Abort**.

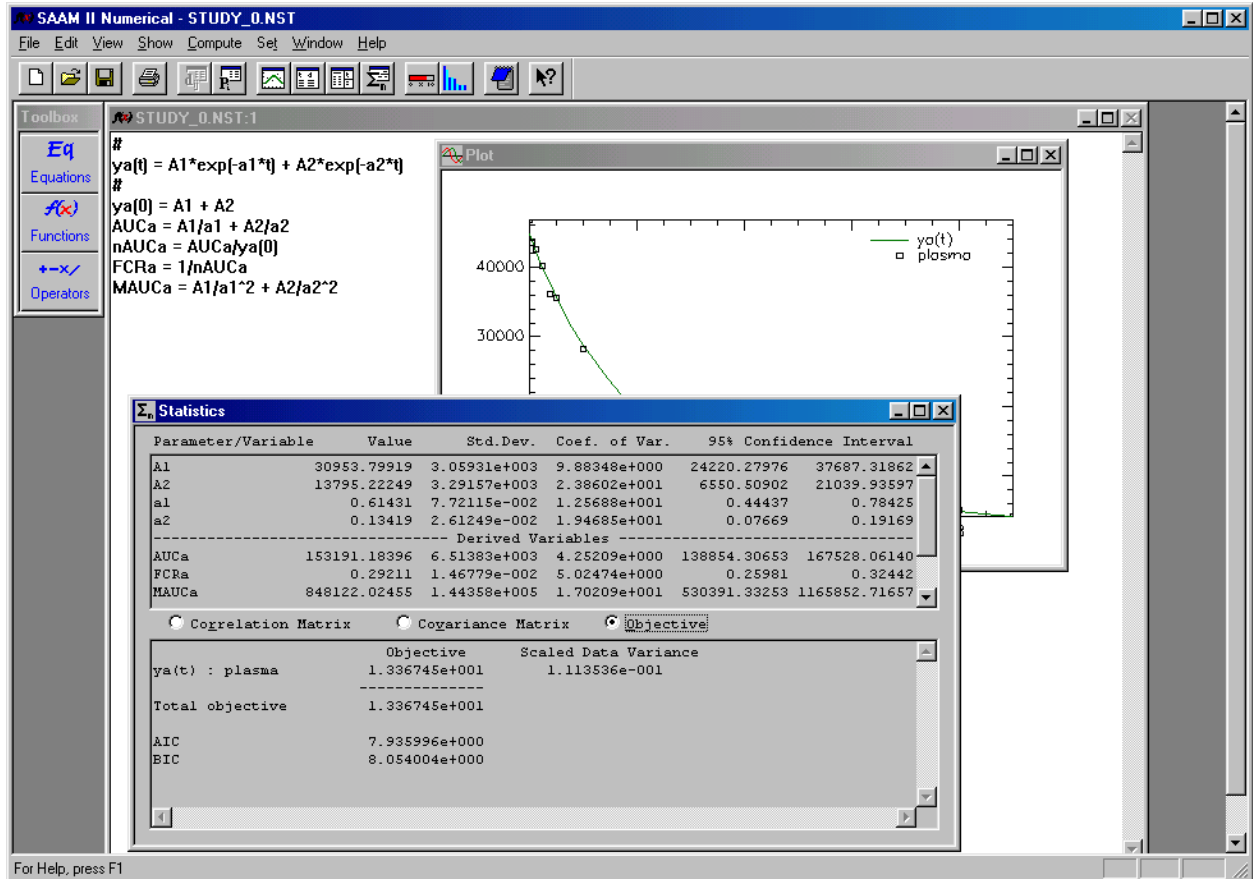


When you have “Fitted” the model to the data, the **SAAM II Numerical** main window with the **Plot** window should appear as follows:



The new parameter values will replace the original estimates in the **Parameters** window, and the best fit of the data appears in the plot. (You can change the plot to semi-logarithmic if you wish by clicking **Semilog** in the **View** menu - this is possible because the **Plot** window is open.)

9. View the statistics associated with the “Fit.”
  - a. In the **Show** menu, click **Statistics**, or alternatively, on the **SAAM II Toolbar** click **Statistics** . The **SAAM II Numerical** main window should appear with the **Statistics** window as follows:



Note that the statistics, plot and model all appear.



Statistical information following a successful “Fit.” The **Statistics** window contains information about the “Fit.” It includes

- i. the final values for the parameters, their estimated standard deviation, percent coefficient of variation, and 95% confidence interval.
- ii. the final values for the derived parameters (these are the auxiliary equations that are functions of the  $A1$ ,  $A2$ ,  $a1$  and  $a2$ ), percent coefficient of variation, and 95% confidence interval
- iii the final objective values:
  - Final value of the objective function (this is the function that is minimized during the fitting process)
  - Scaled data variance (this is a number that is estimated during the “Fitting” process when you use relative weighting – the default option in SAAM II)
  - Values for AIC and BIC; these values are used in the model development process to help assess which model structure best fits the data
- iv. the Covariance matrix.

- v. the Correlation matrix.

If, for example, you select the **Correlation Matrix** option in the **Statistics** window, the Correlation Matrix will appear in the lower half of the **Statistics** window. The Covariance Matrix or the values for the Objective will appear if you select one of the other options.

It is particularly important to note that the derived parameters such as the area under the curve have statistical information associated with them.

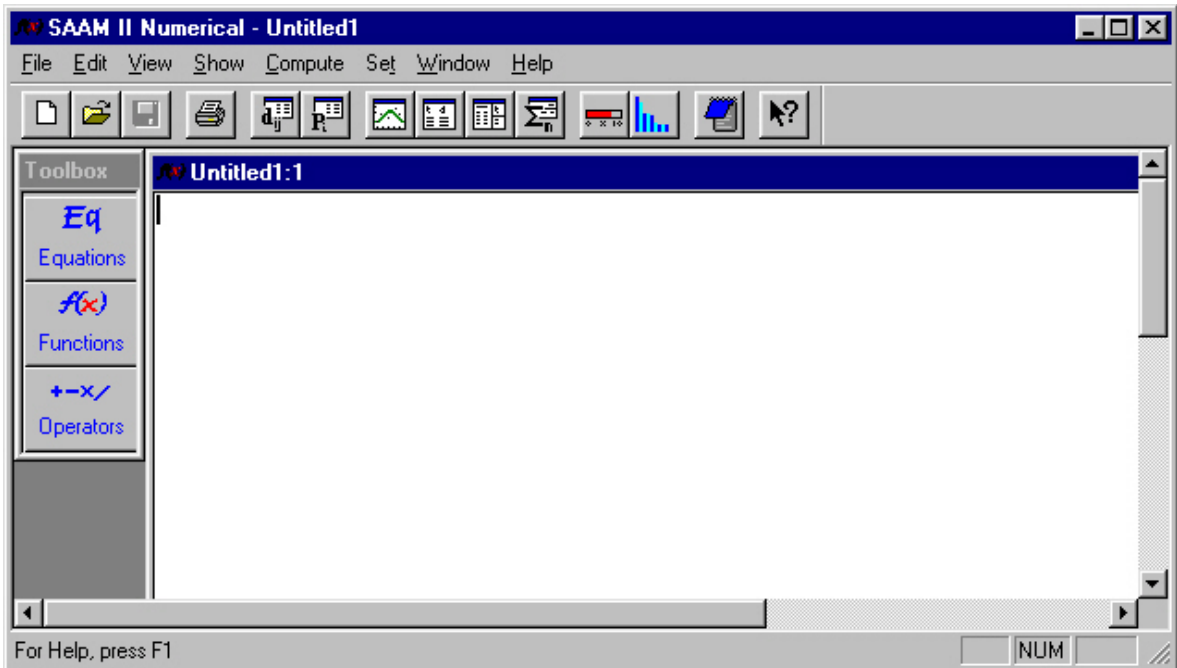


- b. Close the **Statistics** window.
  - c. Close the **Plot** window.
10. **Quit** the **SAAM II Numerical** application
    - a. In the **File** menu, click **Exit**.
    - b. Click **No** (you do not wish to save the file).

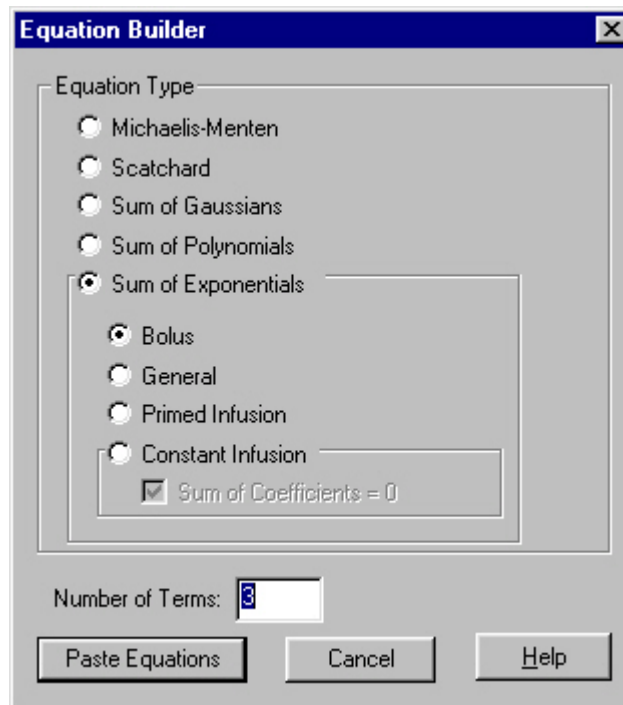
## Part 2. Building models in the SAAM II Numerical Application

This part of the tutorial will show you how to create the sum of two exponentials model used in Part 1. This part of the tutorial will show you how to use the tools in the **SAAM II Toolbox** to build models.

1. Start the **SAAM II Numerical** application. The **SAAM II Numerical** main window will open as follows:



2. Create the sum of two exponentials model.
  - a. In the SAAM II Toolbox, click **Equations**. The **Equation Builder** dialog box will open as shown below:



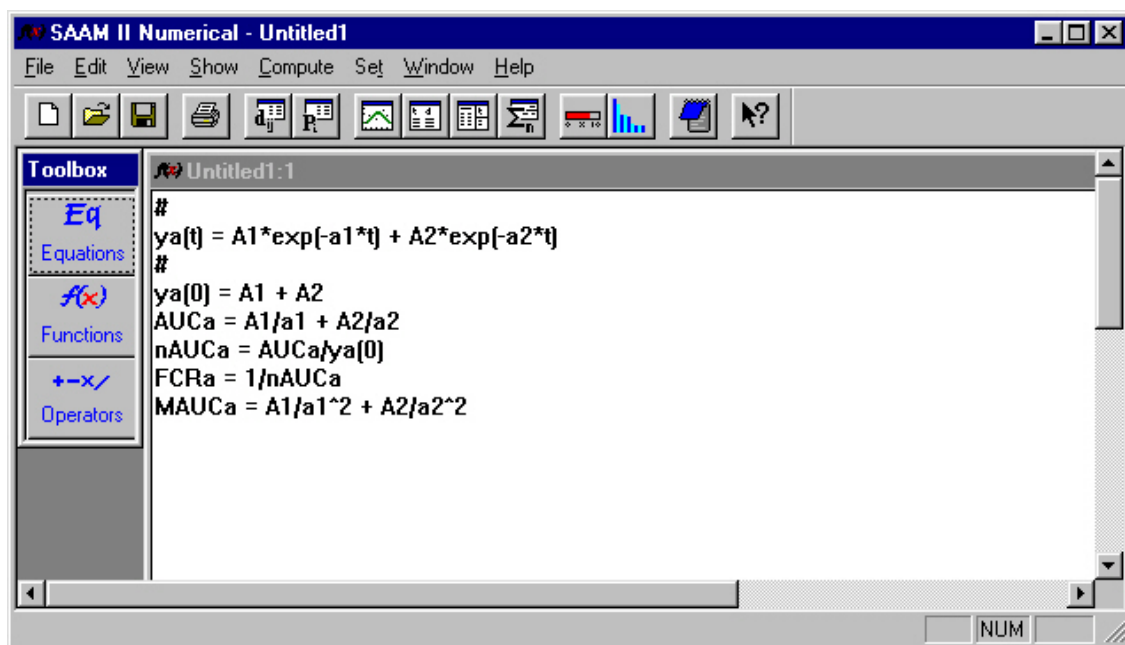


*The Equation Builder.* The **Equation Builder** dialog box contains a number of model building options to make your modeling with **SAAM II Numerical** easier. The predefined equations are Michaelis-Menten, Scatchard, Sum of Gaussians, Polynomials, and Sum of Exponentials. Sum of Exponentials are further subdivided to help you model data following a bolus injection, a primed or constant infusion, or an input described by a general equation.



In this situation, we are dealing with a sum of two exponentials following a bolus injection. Notice by default the options for **Sum of Exponentials** and **Bolus** input are selected.

- b. Change the entry in the **Number of Terms** box from “3” to “2.”
- c. Click **Paste Equations**. The following equations will appear in the **Equation Area** of the **SAAM II Numerical** main window:



*Auxiliary equations.* **SAAM II** will automatically create auxiliary equations when the model is specified using the **SAAM II Toolbox**. In this case, the model is specified to explain data following a bolus injection into plasma. The auxiliary equations estimate the zero time value ( $ya(0)$ ), the area under the curve (AUC), the normalized area under the curve (nAUC), the fractional clearance rate (FCR), and the mean area under

the curve (MAUC). These values can be used to calculate the noncompartmental parameters, especially in pharmacokinetic studies.



3. Define the experiment.
  - a. In the **Set** menu, click **Experiment Attributes**. The **Experiment Attributes** dialog box will open as shown below:

The screenshot shows the 'Experiment Attributes' dialog box with the following fields and values:

- Independent Variable: t
- Units: minutes
- Start at: 0.0
- End at: (empty)

Buttons: Done, Cancel, Help

- b. Change the entry in the **Units** box from “minutes” to “days.”
  - c. Enter “9” in the **End at** box. The **Experiment Attributes** dialog box will appear as follows:

The screenshot shows the 'Experiment Attributes' dialog box with the following fields and values:

- Independent Variable: t
- Units: days
- Start at: 0.0
- End at: 9

Buttons: Done, Cancel, Help




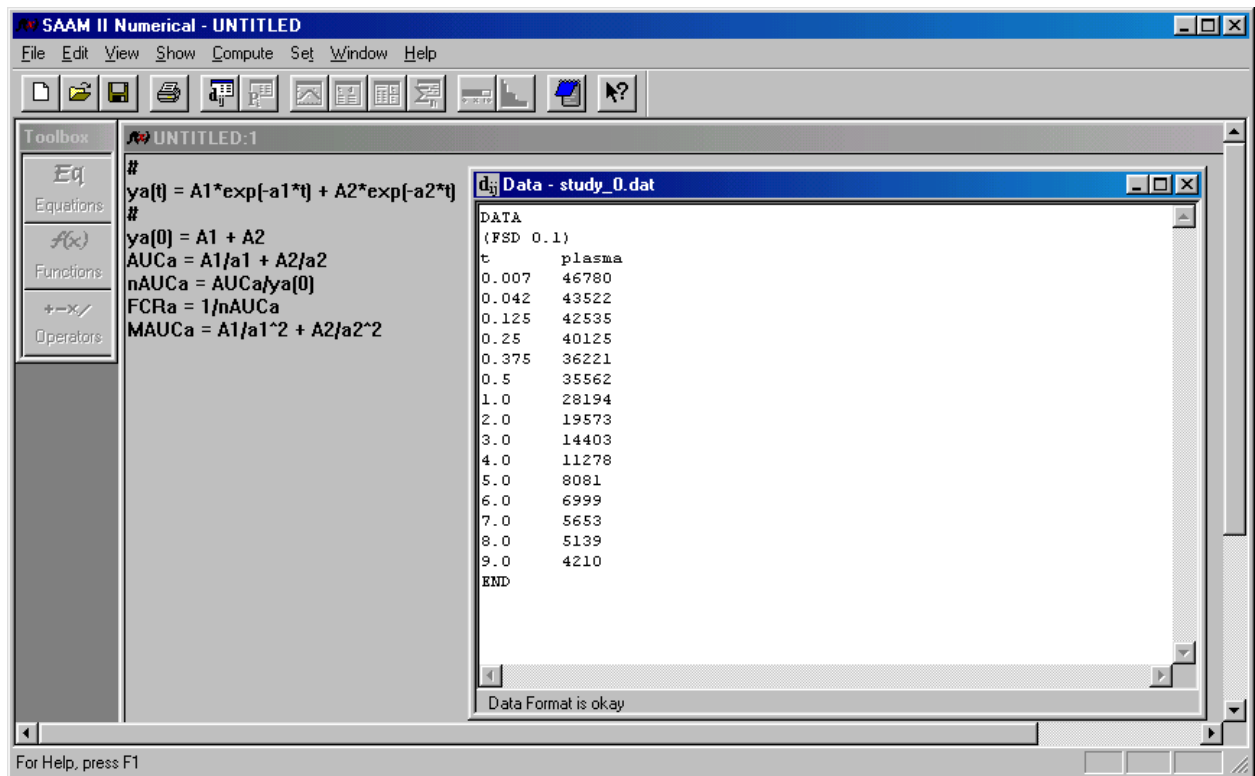
*Experiment Attributes*. The **Experiment Attributes** dialog box is normally where you set the ending time of the experiment. **Units** are for convenience only. **Start at** is normally zero which is the time of the first test input. **End at** is normally the time at which the experiment ends. There are, however, occasions when you may wish to set **End at** to a larger value.



- d. Click **Done**.
4. Add the data to the **SAAM II Numerical** model.

The data you will use are in the data file **study\_0.dat**.

- 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 **study\_0.dat** should appear in the list (if it does not, find the folder where you put this data file).
- c. Double-click **study\_0.dat**. The data in this file will appear in the **Data** window. The **SAAM II Numerical** main window should appear with the **Data** window as follows:



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

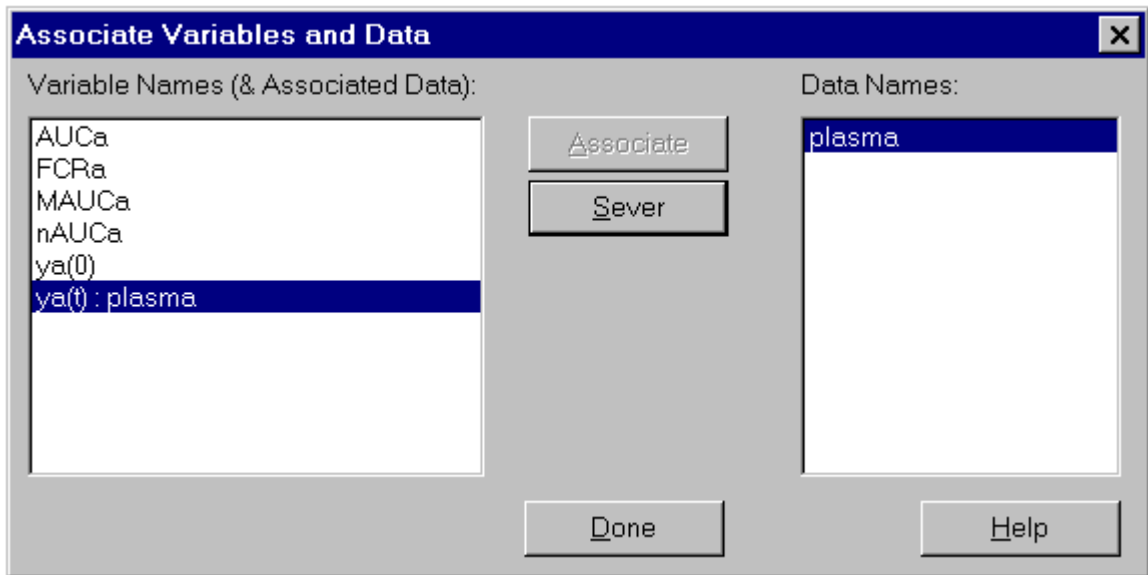


*Error structure of the data.* For this introductory tutorial, the errors in the data are assumed to be a constant coefficient of variation; this is denoted in the data file by (*FSD 0.1*).



5. Associate the variable **ya(t)** with the plasma data.
  - a. In the **Show** menu, click **Associations**.
  - b. Click **ya(t)** in the **Variable Names** pane, and then click **plasma** in the **Data Names** pane.
  - c. Click **Associate**.

The **Associate Variables Name and Data** dialog box should appear as shown below:




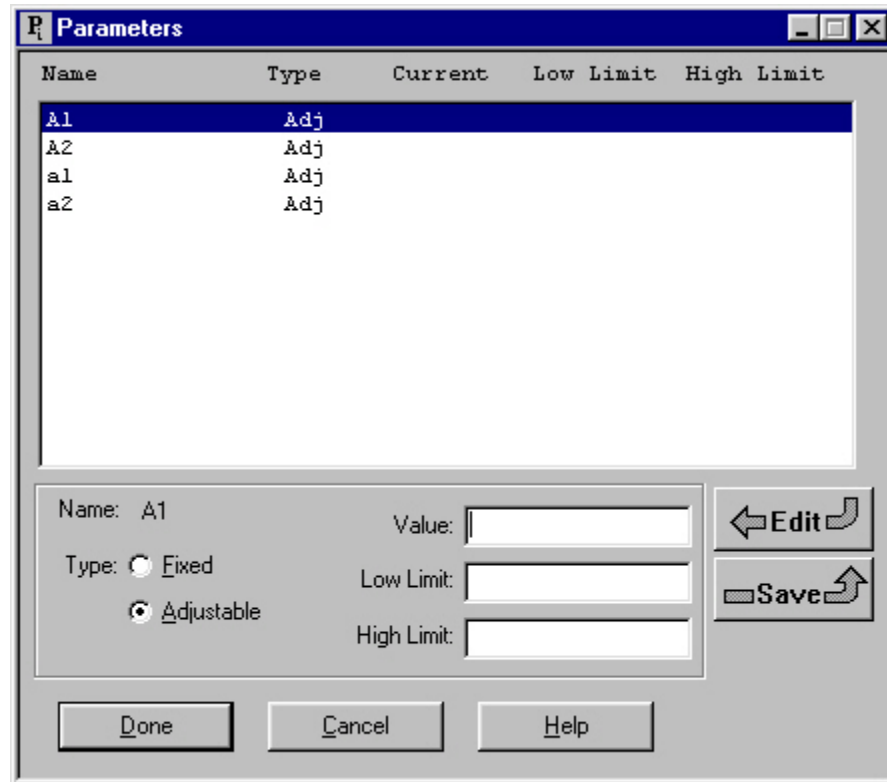
Associating a variable with data. A successful association is indicated by the "ya(t):plasma" pairing in the **Variable Names** pane.



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

The parameters for the model are  $A1$ ,  $A2$ ,  $a1$  and  $a2$ .

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



The parameter *A1* should be selected. If it is not selected, double-click *A1* to select it. Be sure the **Adjustable** option is selected.

- b. Enter "40,000" in the **Value** box, and click **Save**.



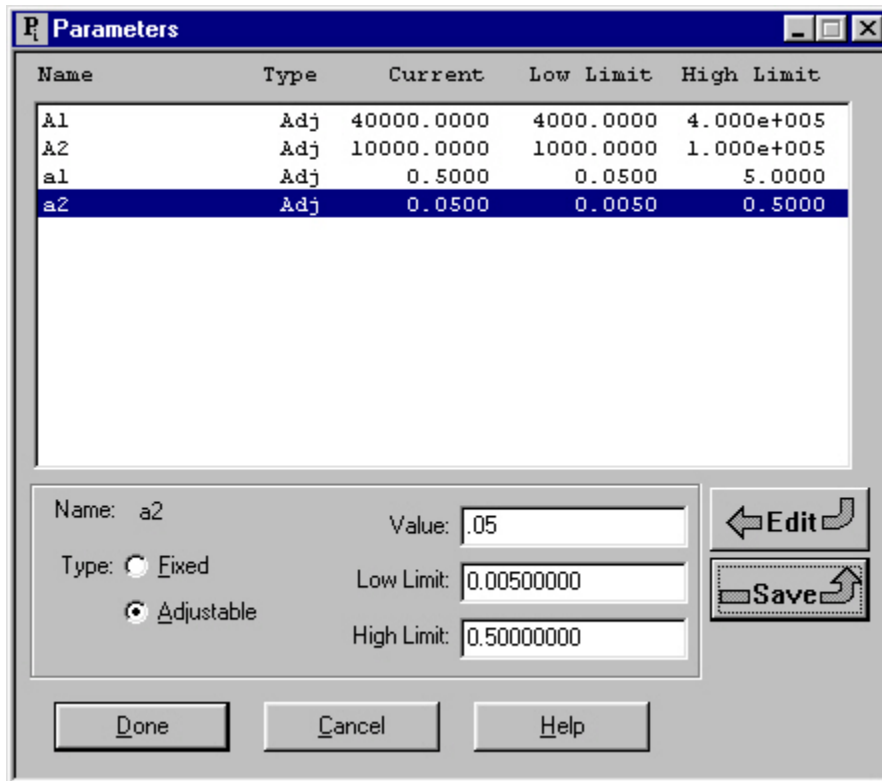
*Default low and high parameter limits.* Notice that when a value is entered in the **Value** box and nothing is entered in the **Low Limit** or **High Limit** boxes, the default low and high limits of one tenth of the value and ten times the value respectively are automatically entered when the value is saved.



- c. Double-click *A2* to select it.
- d. Enter "10,000" in the **Value** box, and click **Save**.
- e. Double-click *a1* to select it.
- f. Enter "0.5" in the **Value** box, and click **Save**.
- g. Double-click *a2* to select it.

- h. Enter "0.05" in the **Value** box, and click **Save**.

When you have finished, the **Parameters** dialog box should appear as follows:



- i. To close the **Parameters** dialog box, click **Done**.



Single or double-clicking a parameter in the **Parameters** dialog box. When the **Parameters** dialog box is open, there is always a current parameter. Its name appears in **Name:** in the lower pane. The **Value**, **Low Limit** and **High Limit** boxes will either contain the values associated with the current parameter or be empty if no values have been entered.

If you single-click on another parameter, the **Name** of the current parameter will not change nor will the entries in the **Value**, **Low Limit** and **High Limit** boxes. However, if you click **Save**, the current **Value**, **Low Limit** and **High Limit** shown in the boxes will be saved for the new parameter. This makes it easy to enter the same values for more than one parameter.

If you double-click on another parameter, the name of the new parameter will appear in **Name:**. The **Value**, **Low Limit** and **High Limit** boxes will change to the values

associated with this parameter. If no values were entered for this parameter, these boxes will be cleared, and you can enter the new values for this parameter.



At this point, you have successfully created the study file **study\_o.nst** that was used in Part 1 of this tutorial. If you wish, you can repeat Part 1 (we recommend you start at Step 5 with “solving”). If you wish to quit the **SAAM II Numerical** application:

7. **Quit** the **SAAM II Numerical** application, or repeat the steps in Part 1.
  - a. In the **File** menu, click **Exit**.
  - b. Click **No**.

**Data for this tutorial**

```
DATA
(FSD 0.1)
t      plasma
0.007 46780
0.042 43522
0.125 42535
0.25  40125
0.375 36221
0.5   35562
1.0   28194
2.0   19573
3.0   14403
4.0   11278
5.0   8081
6.0   6999
7.0   5653
8.0   5139
9.0   4210
END
```