

Minimal Model of Cold Glucose Kinetics

Case Study

- How to work with IVGTT data
- How to create a forcing function for insulin concentration
- How to correct for baseline concentrations
- How to define the minimal model parameters

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The Minimal Model of Cold Glucose Kinetics

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 work with IVGTT data
- How to create a forcing function for insulin concentration
- How to correct for baseline concentrations
- How to define the minimal model parameters

Data Required

The data file for this case study is

IVGTT.dat

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

Introduction

The IVGTT results in glucose and insulin measurements obtained in plasma in a (human or animal) subject after an intravenous pulse dose of glucose. These data can be used to obtain estimates of insulin sensitivity and glucose effectiveness for this subject.

This case study will show you how to implement the minimal model of glucose disappearance in SAAM II. It also serves as an example of how to implement nonlinear differential equations and forcing functions. Some references and more about the minimal model are reported at the end of this case study (Modeling Notes).

The notation and minimal model differential equations are shown below. The first equation represents glucose kinetics, and the second represents insulin action.

$$\begin{aligned}
 \frac{dq(t)}{dt} &= -[S_G + x(t)]q(t) + S_G G_b & q(0) &= G_b + D \\
 \frac{dx(t)}{dt} &= -p_2 \{x(t) - S_I [I(t) - I_b]\} & x(0) &= 0 \\
 G(t) &= q(t) / V
 \end{aligned} \tag{1}$$

where, assuming time is expressed in minutes:

- $q(t)$ is glucose mass (mg/kg body weight) in plasma,
- $x(t)$ is insulin action (min^{-1}),
- p_2 is an insulin action parameter (min^{-1}),
- $I(t)$ is the measured plasma insulin concentration (U/ml),
- D is the exogenous glucose dose (mg/kg),
- V is the glucose volume of distribution (dl/kg body weight),
- $G(t)$ is the measured plasma glucose concentration (mg/dl),
- S_G is glucose effectiveness (units of inverse time, or min^{-1}),
- S_I is insulin sensitivity (units of inverse time per unit insulin concentration, or min^{-1} per U/ml),
- $q(0)$ is the initial condition in the glucose compartment,
- $x(0)$ is the initial condition in the insulin action compartment,
- G_b is basal glucose, and
- I_b is basal insulin.

Thus, in terms of SAAM II, there will be two models. One will describe the insulin action differential equation. The other will implement the glucose disappearance differential equation. The parameters to be estimated from data are: S_G , S_I , p_2 and V .

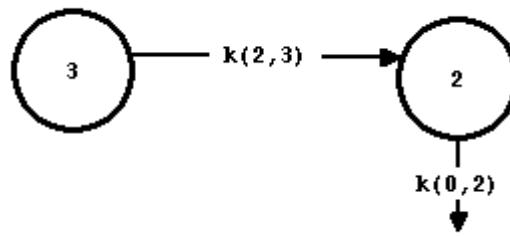
1. Bergman RN, Lovejoy J, Eds. The Minimal Model Approach and Determinants of Glucose Tolerance. Baton Rouge, LA: Louisiana State University Press, 1997.

Part 1. Create a two-compartment model in the SAAM II Compartmental application to implement the insulin action equation

This part of the case study will show you how to implement the insulin action equation

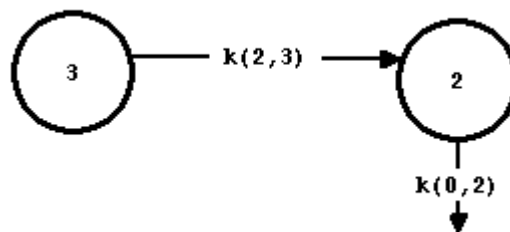
$$\frac{dx(t)}{dt} = -p_2 \{x(t) - S_I [I(t) - I_b]\} \quad (2)$$

by creating the following two-compartment model in the **SAAM II Compartmental** application:



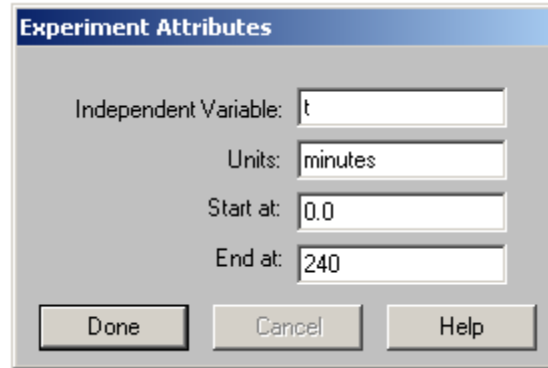
In implementing the insulin action equation in the context of this model, $k(0,2)$ will be used to describe the term $-p_2x(t)$ and compartment 3 will be specified as a forcing function to describe the term $-p_2S_I[I(t)-I_b]$.

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



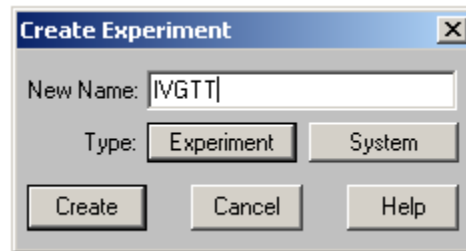
In creating this system model, you will need to renumber **Compartment 1**. Remember this is done by double-clicking on **Compartment 1** to open the **Compartment Attributes** dialog box, changing the **Compartment Number** from “1” to “3”, and clicking **Done**.

3. Create the experiment describing insulin action.
 - a. 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.
 - b. Be sure the entry in the **Units** box is minutes.
 - c. Enter “240” in the **End at** box. The **Experiment Attributes** dialog box will appear as follows:

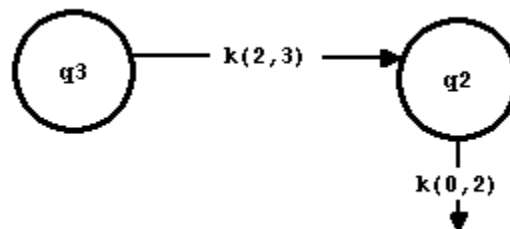



- a. Click **Done**.

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



- e. Click **Create**. Notice “IVGTT” now appears below **Experiment** in the **SAAM II Toolbox**. Your model will appear as follows:



4. Add the data to your model.
- In the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data** . The **Data** window will open.
 - In the **File** menu, click **Open**. The file **IVGTT.dat** should appear in the list (if it does not, find the folder where you put this data file).

- c. Double-click **IVGTT.dat**. The data in this file will appear in the **Data** window as follows:

```

d:\ Data - IVGTT.DAT
# Sample IVGTT data
DATA
t G (FSD 0.02) I
0 96 (-) 16
2 312 (-) 120
3 291 (-) 101
4 289 (-) 107
5 271 (-) 83
7 241 (-) 49
10 220 54
15 184 49
20 170 38
25 151 43
30 141 38
35 121 25
40 94 27
50 88 11
60 80 11
70 83 10
80 84 10
100 90 12
120 89 11
140 90 17
160 91 18
180 87 11
210 98 14
240 94 9
END
CONST Gb 93
CONST Ib 11.3
CONST D 305
Data Format is okay

```

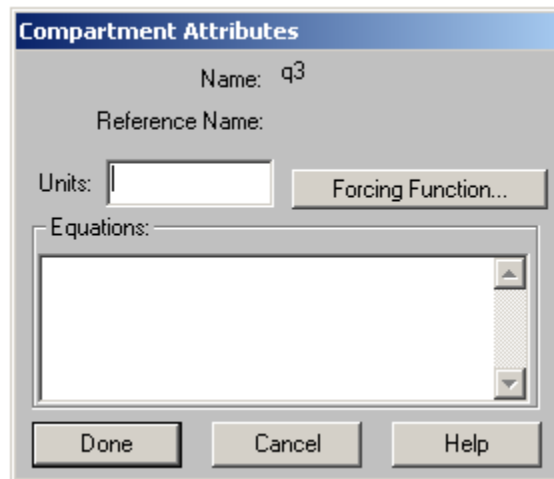


Entering constants in a Data file. The data file contains two columns of data. One is “G” for glucose and the other “I” for insulin. You will notice in the data file, following the END statement, the lines “CONST Gb 93”, “CONST Ib 11.3” and “CONST D 305.” These are respectively the baseline levels for glucose and insulin, and the dose. You can enter constants in your model using the CONST designator. Constants, so designated, must lie outside a data stream, i.e. streams between DATA and END. The “(-)” following the first few glucose data mean these data are unweighted. This will be explained later in the Case Study.

Notice also there are data at time zero. This is quite unusual in most experiments. However, to use the Forcing Function machinery in SAAM II as is done in this case study, a datum is required at time zero.



- d. Close the **Data** window.
5. Create the forcing function for Compartment **3**.
- a. Double-click Compartment **q3**. The **Compartment Attributes** dialog box will open as follows:



- b. Click **Forcing Function...**. The **Forcing Function** dialog box will open. The two dialog boxes will appear as follows:

The image shows two dialog boxes from a software interface. The top dialog box is titled "Compartment Attributes" and is for compartment "q3". It has fields for "Name: q3", "Reference Name:", "Units:" (with an empty text box), and "Equations:" (with an empty text area). There is a "Forcing Function..." button next to the Units field. At the bottom are "Done", "Cancel", and "Help" buttons. The bottom dialog box is titled "Forcing Function" and is for compartment "q3". It has a "Compartment Number: q3" field and an "FF Input from:" section with three radio button options: "Turned Off" (selected), "Associate with Data Name:" (with an empty text box), and "Equation for q3.FF:" (with a text box containing "q3.FF ="). At the bottom are "Done" and "Help" buttons.

- c. Select the **Equation for q3.FF** option.
- d. In the **Equation** box, type “q3.FF=lin(I)-Ib”. The **Forcing Function** dialog box will appear as follows:

Forcing Function

Compartment Number: q3

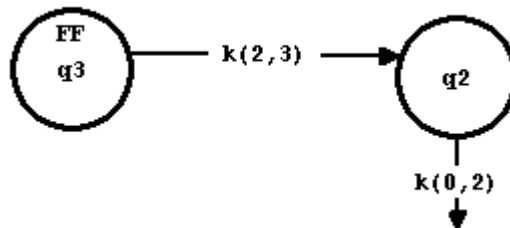
FF Input from:

Turned Off

Associate with Data Name:

Equation for q3.FF:

- e. Click **Done** to close the **Forcing Function** dialog box.
- f. Click **Done** to close the **Compartment Attributes** dialog box. Your model will appear as follows:



The forcing function equation. The forcing function equation illustrates two important features of SAAM II. First, “lin(name)” is an option in SAAM II which will create a function by linearly interpolating between sequential data in the “name” data column. In this case, it is the insulin data “I.” The same could be accomplished using the “Associate with Data Name” option except for one important thing. Basal insulin levels need to be subtracted from each datum. The basal insulin level, “Ib”, which is entered in the data file, is subtracted from “lin(I)” thus producing a forcing function due to the insulin increase above baseline.

Notice also the “FF” associated with Compartment **q3**; this shows the designation of this compartment as a forcing function.

In this particular situation, depending upon the “quality” of the data and the value for Ib, it is possible the numerical value for the forcing function could

be negative. Given the forcing function definition is using the “convenient” method, this is normally okay. However, if the data are quite noisy, or the function is negative over a large time span of the experiment, you should consider a functional description of FF which prevents the values from going negative.



6. Define the transfer attributes for $k(2,3)$ and $k(0,2)$.

In what follows, the transfer attributes for $k(2,3)$ and $k(0,2)$ will be defined. How these relate to the differential equation for insulin action will be explained at the end of this section.

- Double-click $k(2,3)$ to open the **Transfer Attributes** dialog box.
- In the **Equation** pane, type “ $k(2,3)=SI*p2$ ”. The **Transfer Attributes** dialog box will appear as follows:

- Click **Done**.
- Double-click $k(0,2)$ to open the **Loss Attributes** dialog box.
- In the **Equation** pane, type “ $k(0,2)=p2$ ”. The **Loss Attributes** dialog box will appear as follows:

f. Click **Done**.



The minimum model second (insulin action) equation. At this point, you have successfully implemented the second equation of the minimal model. You can verify this simply writing the differential equation for q_2 and see that it is the same as that provided above for the time course of insulin action:

$$\frac{dx(t)}{dt} = -p_2 \{x(t) - S_I [I(t) - I_b]\} = -p_2 x(t) + p_2 S_I [I(t) - I_b].$$

Remembering that $q_2(t)$ plays the role of $x(t)$ in the equation, defining “ $k(0,2) = p_2$ ” will create the term $-p_2 * q_2(t)$ in the differential equation dq_2/dt . Now with q_3 defined as a forcing function, dq_2/dt will “see” q_3 .FF, not q_3 . Thus defining “ $k(3,2) = S_I * p_2$ ” will create the term $S_I * p_2 * (\ln(I) - I_b)$ in the differential equation for q_2 ; this is the equivalent of $p_2 S_I [I(t) - I_b]$.

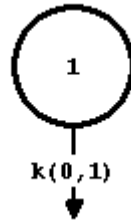


Part 2. Create a one-compartment model in the SAAM II Compartmental application to implement the glucose disappearance equation

This part of the case study will show you how to implement the glucose disappearance equation

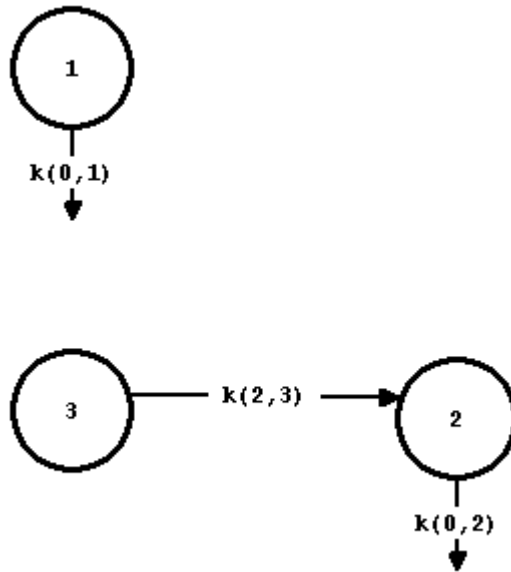
$$\frac{dq(t)}{dt} = -[S_G + x(t)]q(t) + S_G G_b \quad q(0) = G_b + D \quad (3)$$

by creating the following one-compartment model in the **SAAM II Compartmental** application:

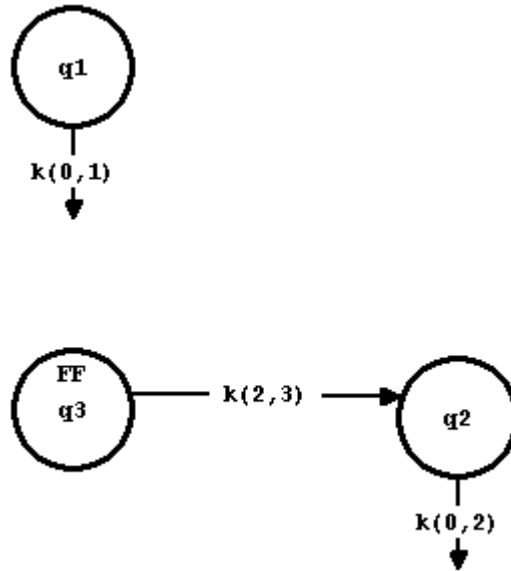


In implementing the glucose disappearance equation in the context of this model, $k(0,1)$ will be used to describe the term $-[S_G + x(t)]q(t)$ and the input into Compartment **q3** will be used to describe the term $S_G G_b$.

1. In the **SAAM II Toolbox**, click **Model** to make the **Model** tools available. Create the one-compartment model shown above. The two models (following some rearrangements) should appear on the **Drawing Canvas** as follows:



2. In the **SAAM II Toolbox**, click **Experiment**. Notice the **Experiment Attributes** dialog box does not open. This is because the attributes have already been defined. Your models will appear as follows:



3. Define the loss attributes for $k(0,1)$.
 - a. Double-click $k(0,1)$ to open the **Loss Attributes** dialog box.
 - b. In the **Equation** box, type “ $k(0,1)=SG+q2$ ”. The **Loss Attributes** dialog box will appear as follows:

Loss Attributes

Transfer Coefficient: $k(0,1)$

Reference Name:

Flow Rate: $\text{flux}(0,1) = k(0,1) * q1$

Flow Rate Units:

Equations :

Parameter Data

$k(0,1)$

Type: Fixed Adjustable

Current Parameter Value:

Low Limit:

High Limit:

- c. Click **Done**.

4. Define the input into Compartment **q1**, the glucose system.
 - a. In the **SAAM II Toolbox**, click **Input**.
 - b. Click Compartment **q1**, and then click on the **Drawing Canvas**. An input arrow named **ex1** will appear on the drawing canvas pointing to Compartment **q1**.
 - c. Double-click **ex1**. The **Exogenous Input** dialog box will open.
 - d. In the **Name** box, type “IVGTT”.
 - e. In the **Input Type** box, select **Equation**.
 - f. In the **Equation** box, type “IVGTT=SG*Gb*V”.
 - g. In the **Event Start** box, enter “0”.
 - h. In the **Event Stop** box, enter “240”.
 - i. Click **Add**.
 - j. In the **Equation** box, type “IVGTT=Gb*V+D”.
 - k. In the **Event Start** box, enter “0”.
 - l. In the **Event Stop** box, enter “0”.
 - m. Click **Add**. The **Exogenous Input** dialog box will appear as follows:

Type	Initial	Constant	Start	Stop	Repeat	Every	Nr. Repeats
Equation	IVGTT = Gb*V+D		0.000	0.000	-	-	-
Equation	IVGTT = SG*Gb*V		0.000	240.000	-	-	-

- n. Click **Done**.

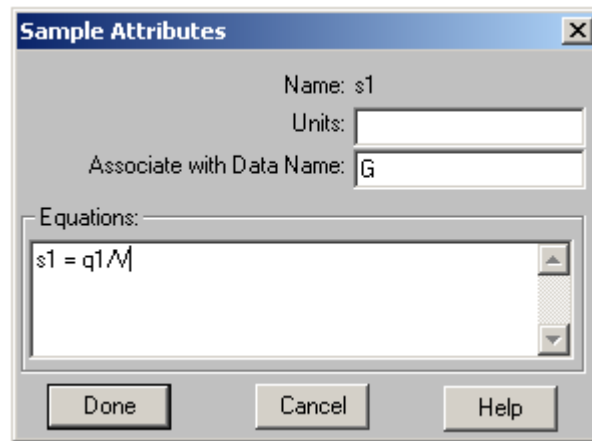


Naming the exogenous input. Because you entered the name “IVGTT” in the **Name** box in the **Exogenous Input** dialog box, the name “IVGTT” will appear associated with the input instead of the default “ex1”. In addition, the input equations are defined in terms of “IVGTT” instead of “ex1”. This is shown below.

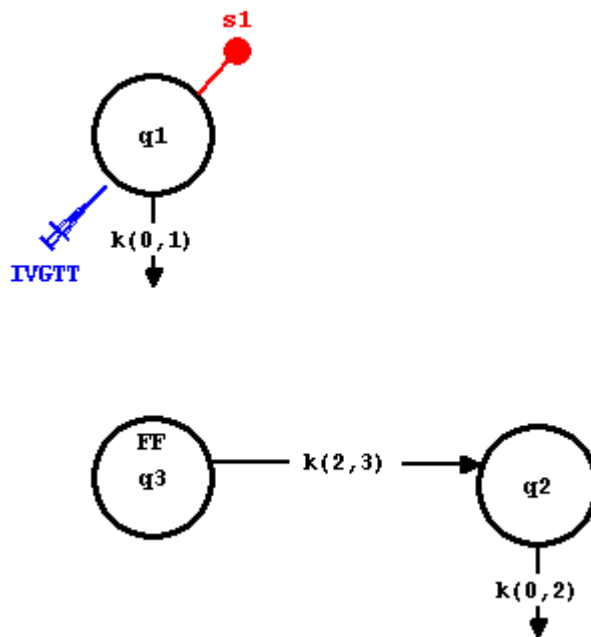


5. Create a sample and define the measurement equation.
 - a. In the **SAAM II Toolbox**, click **Sample**.
 - b. Click Compartment **q1** and then click on the **Drawing Canvas**. The sample **s1** will appear.
 - c. Double-click **s1** to open the **Sample Attributes** dialog box.
 - d. In the **Associate with Data Name** box, type “G”.

- e. In the **Equations** box, type “ $s1=q1/V$ ”. The **Sample Attributes** dialog box will appear:



- f. Click **Done**. Your models will appear as follows:

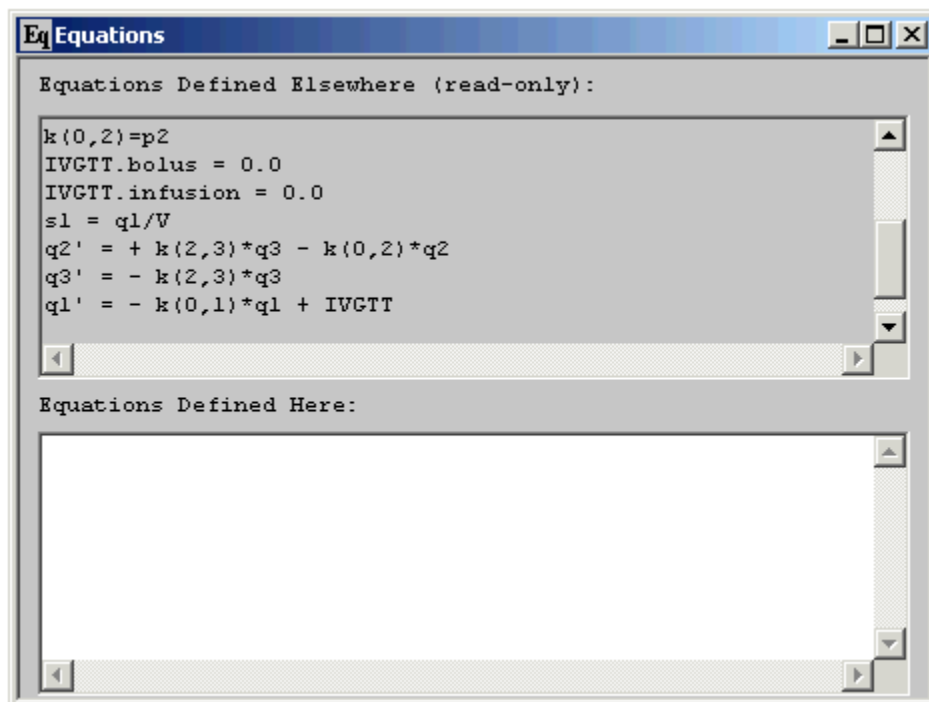


The minimum model first equation for glucose disappearance. At this point, you have successfully implemented the first equation of the minimal model describing glucose disappearance. Remember here that “ $q(t)$ ” in the first equation is “ $q1$ ” in the model, and that “ $x(t)$ ” in the first equation is “ $q2$ ” in

the model. Defining “ $k(0,1)=SG+q_2$ ” will create the term $-(SG+q_2)*q_1$ which is the first term in the first equation. The equation input $SG*Q_b*V$ will create the second term where Q_b*V will convert basal glucose concentration to basal glucose mass.



6. View the differential equations created by SAAM II.
 - a. In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar** click **Equation Eq**. The **Equations** dialog box will open.
 - b. In the **View** menu, click **Diff. Eq.** The **Equations** dialog box will appear as follows (you will have to scroll in the **Equations Defined Elsewhere** box to see the differential equations):




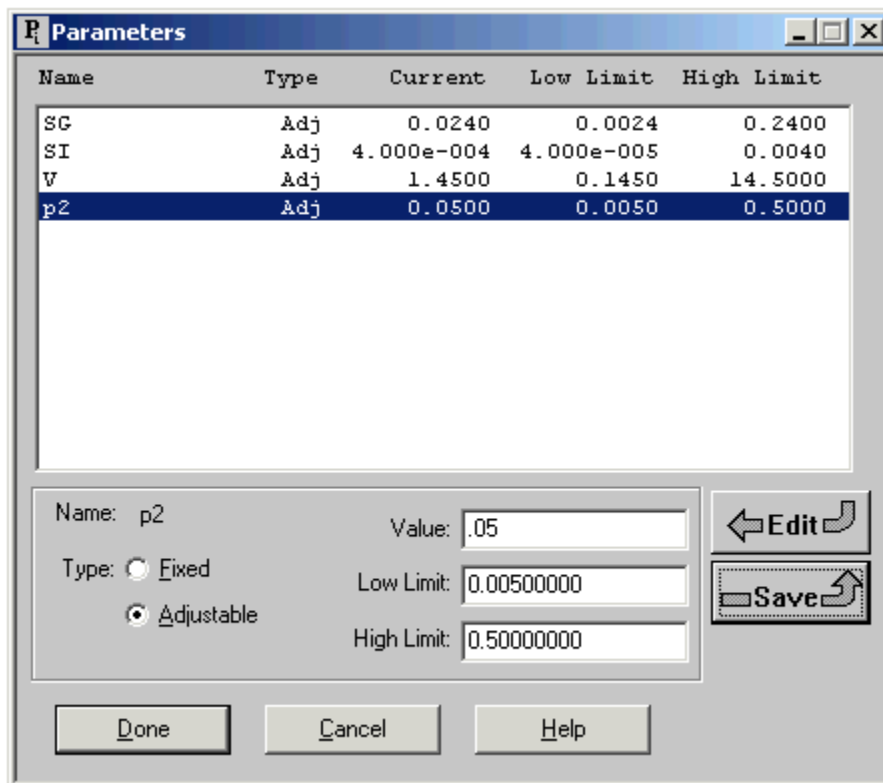
- c. Close the **Equations** dialog box.

Part 3. Enter the parameter values, Solve the model, Fit the model to the data and view the solution.



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

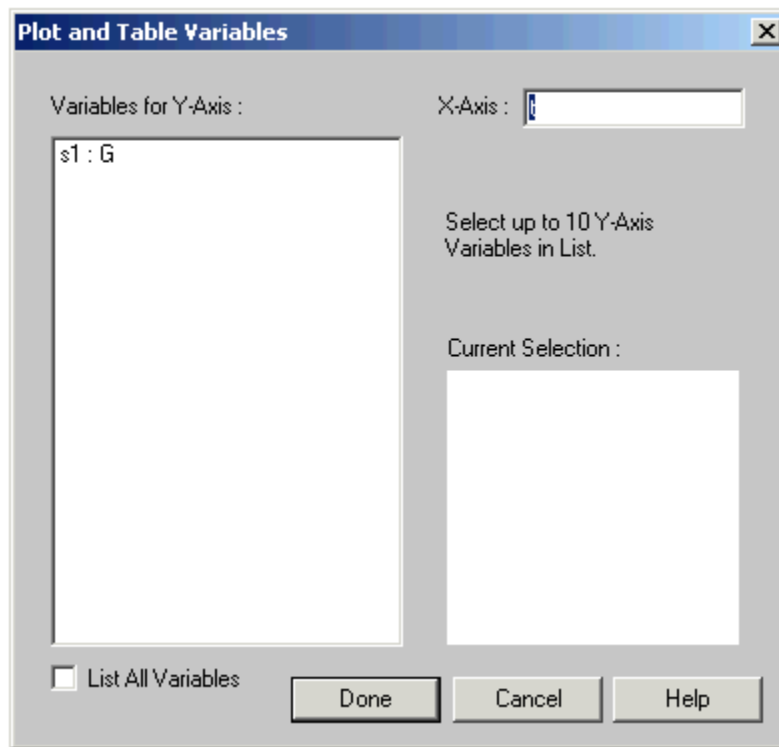
1. Enter the parameter values.

- a. In the **Show** menu, click **Parameters**, or alternatively, in the **SAAM II Toolbar** click **Parameters** . The **Parameters** dialog box will open.
- b. If *SG* is not selected, double-click *SG* to select it. Be sure the **Adjustable** option is selected.
- c. Enter “0.024” in the **Value** box, and click **Save**.
- d. Double-click *SI* to select it.
- e. Enter “0.0004” in the **Value** box, and click **Save**.
- f. Double-click *V* to select it.
- g. Enter “1.45” in the **Value** box, and click **Save**.
- h. Double-click *p2* to select it.
- i. Enter “0.05” in the **Value** box, and click **Save**. The **Parameters** dialog box will appear as follows:

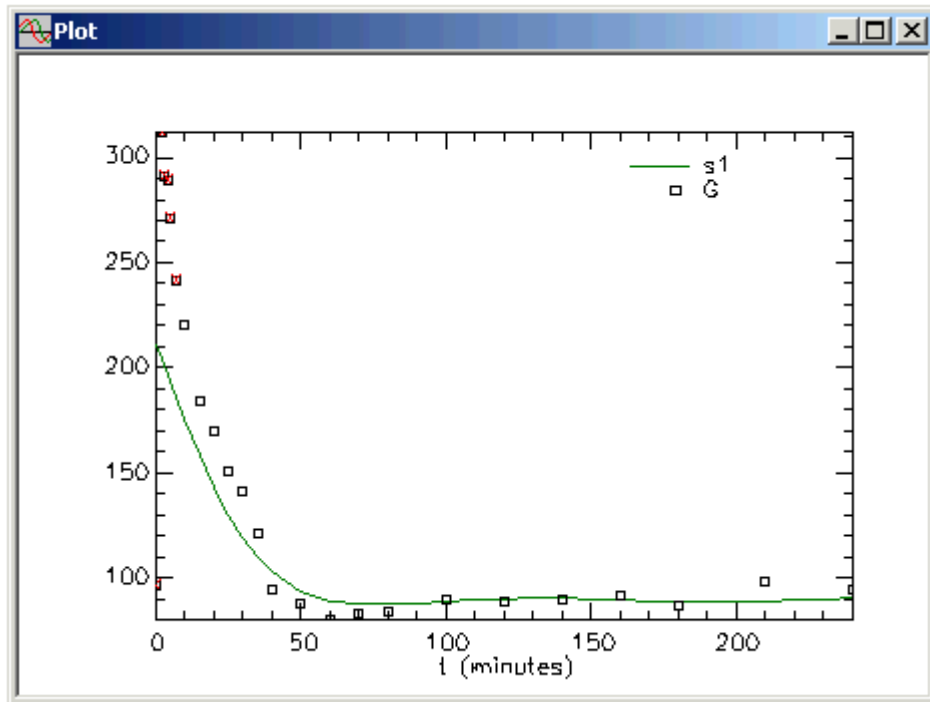


- j. Click **Done**.

2. Solve your model and view 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 Tables Variables** dialog box will open as follows (if does not open as shown below, be sure the **List All Variables** check box is not selected).



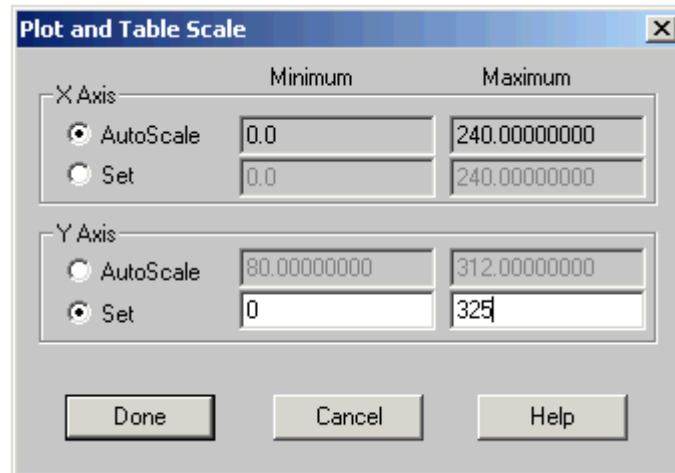
- b. Click **s1:G**; these variables will move to the **Current Selection** pane.
- c. Click **Done**. The plot of **s1** and **G** will appear as follows (in linear mode):



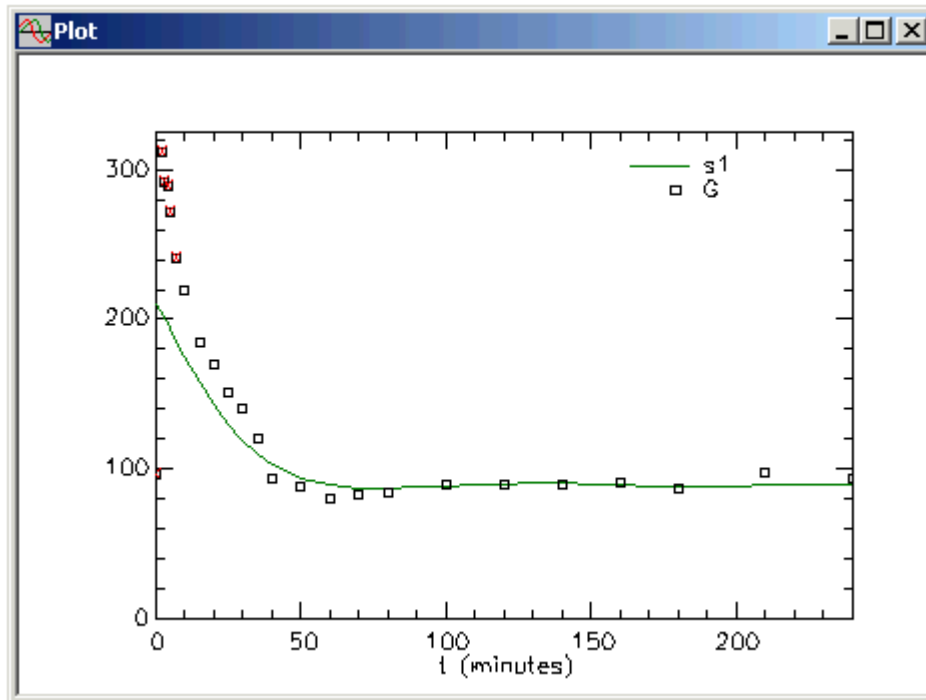
Unweighting data. Notice in the plot the red “x” through the first few data; this signifies these data do not have weights associated with them, and will not be used in the fitting process. This is typical for the IVGTT glucose minimal model, i.e. the data up to 10 minutes are unweighted, that is, they will not be used when you Fit your model to your data.




4. Change the scale of your plot.
 - a. In the **Set** menu, click **Plot/Table** scale. The **Plot and Table Scale** dialog box will open.
 - b. In the **Y Axis** box, click **Set**.
 - c. In the **Minimum** box, enter “0”. In the **Maximum** box, enter “325”. The **Plot and Table Scale** dialog box will appear as follows:

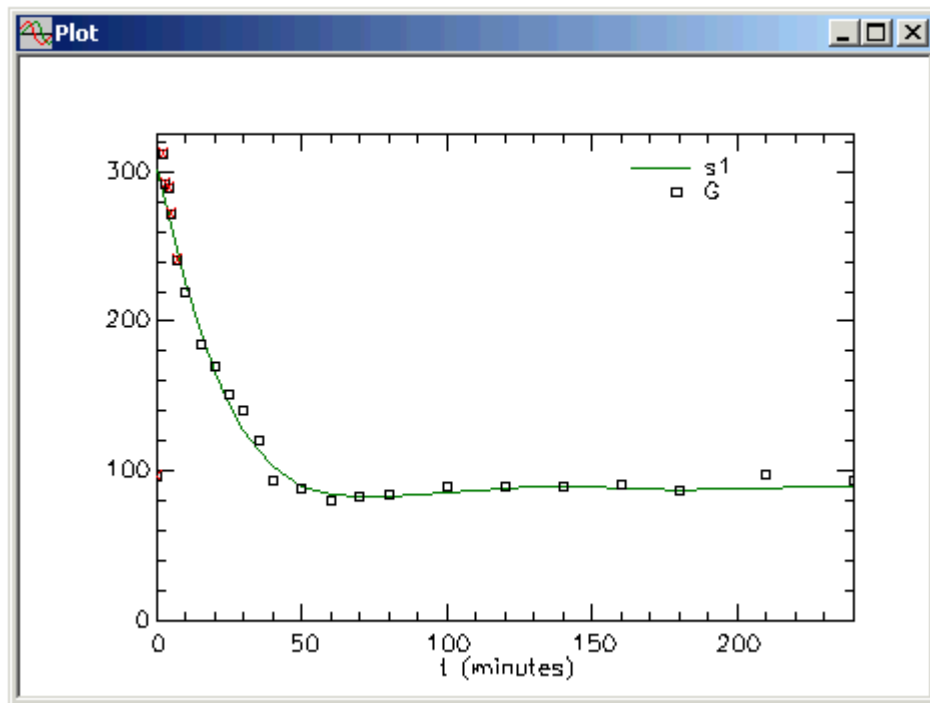



d. Click **Done**. The plot will now appear (in linear mode) as follows:



Changing the plot scale allows you to better visualize the initial decaying portion of the glucose data.

5. With the **Plot** window open, 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 follows:



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

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
SG	0.03291	1.99773e-002	6.07094e+001	-0.00994	0.07575
SI	5.81696e-004	7.38531e-005	1.26962e+001	4.23296e-004	7.40095e-004
V	1.01536	1.11557e-001	1.09869e+001	0.77610	1.25463
p2	0.04167	3.45758e-002	8.29764e+001	-0.03249	0.11583
----- Derived Variables -----					
IVGTT.bolus	305.03341	1.72649e-002	5.66000e-003	304.99638	305.07044
IVGTT.infusion	3.10732	1.60564e+000	5.16728e+001	-0.33644	6.55107
k(0,2)	0.04167	3.45758e-002	8.29764e+001	-0.03249	0.11583


		<input type="radio"/> Correlation Matrix	<input type="radio"/> Covariance Matrix	<input checked="" type="radio"/> Objective	
		Objective	Scaled Data Variance		
s1 : G	4.426329e+000	8.408708e+000			

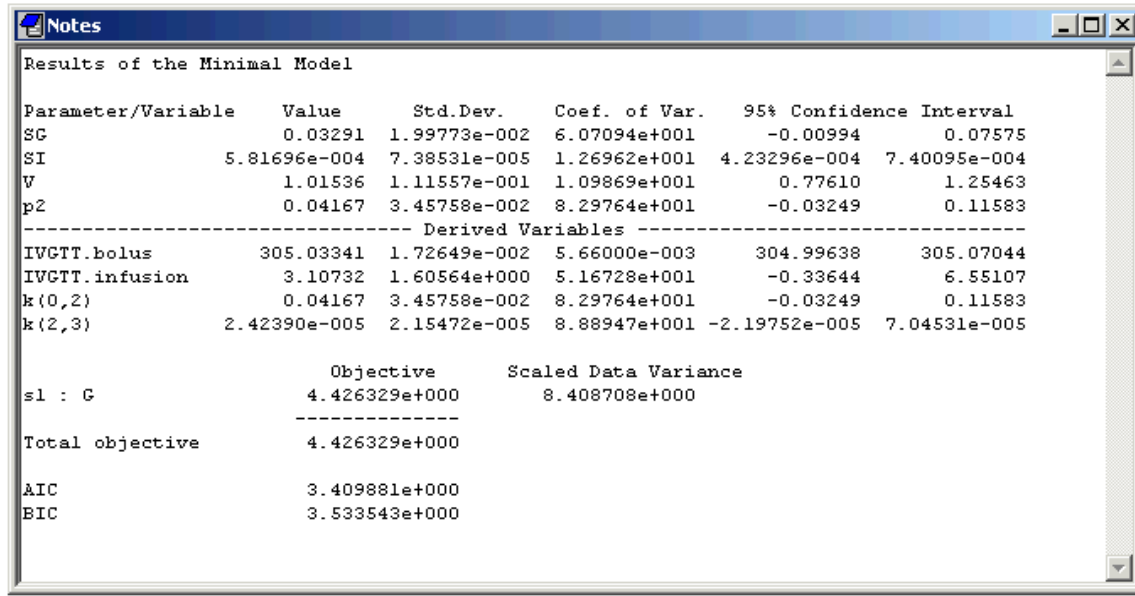
Total objective	4.426329e+000				
AIC	3.409881e+000				
BIC	3.533543e+000				



Statistics window. The **Statistics** window contains information about the “Fit.” Notice that information about the input IVGTT appears in the “Derived Variables” in the **Parameter/Variable** pane. The reason why is that the model parameters SG and V appear in the equation for IVGTT.



6. (Optional) Record you results in the **Notes** window. If you do not do this part of the Case Study, close the **Statistics** and **Plot** windows. Quit the **SAAM II Compartmental** application. You may save this file for future reference if you wish.
 - a. Close the **Plot** window.
 - b. In the **Statistics** window, in the **Parameter/Variable** pane, select the parameters and derived variables.
 - c. In the **Edit** menu, click **Copy**.
 - d. In the **Show** menu, click **Notes**, or alternatively, on the **SAAM II Toolbar**, click **Notes** . The **Notes** window will open.
 - e. In the **Notes** window, type “Results of the Minimal Model.”
 - f. In the **Edit** menu, click **Paste**. The statistical information will be pasted into the **Notes** window. The titles of the columns in the statistics window will not be copied, so you will have to title the columns (as shown below).
 - g. In the **Statistics** window, select and copy the information about the fit in the lower pane. Paste this in the **Notes** window. The **Notes** window will appear as follows:



Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
SG	0.03291	1.99773e-002	6.07094e+001	-0.00994	0.07575
SI	5.81696e-004	7.38531e-005	1.26962e+001	4.23296e-004	7.40095e-004
V	1.01536	1.11557e-001	1.09869e+001	0.77610	1.25463
p2	0.04167	3.45758e-002	8.29764e+001	-0.03249	0.11583
----- Derived Variables -----					
IVGTT.bolus	305.03341	1.72649e-002	5.66000e-003	304.99638	305.07044
IVGTT.infusion	3.10732	1.60564e+000	5.16728e+001	-0.33644	6.55107
k(0,2)	0.04167	3.45758e-002	8.29764e+001	-0.03249	0.11583
k(2,3)	2.42390e-005	2.15472e-005	8.88947e+001	-2.19752e-005	7.04531e-005

	Objective	Scaled Data Variance			
s1 : G	4.426329e+000	8.408708e+000			

Total objective	4.426329e+000				
AIC	3.409881e+000				
BIC	3.533543e+000				



Notes. The **Notes** window allows you to keep track of what you did during your modeling exercise. If you save the study file, the notes are saved as part of the file so you can return to them when you run the study file another time.



h. Close the **Notes** and **Statistics** windows.

You may save your study file if you wish for future use.

Quit the **SAAM II Compartmental** application.

Modeling Notes:

- More details on the minimal model method, its realm of applicability and various case studies can be found in the text: Bergman RN, Lovejoy J, Eds. *The Minimal Model Approach and Determinants of Glucose Tolerance*. Baton Rouge, LA: Louisiana State University Press, 1997.
- An implementation of the minimal model is also suggested in the SAAM II reference, Barrett PH, Bell BM, Cobelli C, Golde H, Schumitzky A, Vicini P, Foster DM. SAAM II: Simulation, Analysis, and Modeling Software for tracer and pharmacokinetic studies. *Metabolism* 47: 484-492, 1998.

Essential Points to Remember

- The minimal model exercises two of the tools that SAAM II makes available: the forcing function (through the definition of insulin action on glucose disappearance, $x(t)$) and nonlinear equations (through the definition of the time-varying rate of glucose disposal, $SG + x(t)$).
- Usually, data up to 8 minutes after the glucose bolus are unweighted so that glucose disappearance can be described by a single compartment.
- Baseline values of glucose and insulin are chosen in one of two ways: as the average of the pre-test values (usually, three values taken 30 minutes before the glucose bolus), or as the average of the end-test values (usually, of the values at 180, 210 and 240 minutes). In healthy volunteers, this choice is almost always irrelevant, but in pathologies it may make a difference. Consult the published literature about the most common strategy.
- Although the SAAM II implementation may appear cumbersome, it makes use of simple mass balance principles.
- While the parameters we have used here are for healthy volunteers, their values can change considerably in various disease states. Reference values can be found in the literature.
- The **Notes** window provides a convenient way to keep track of your modeling exercise.
- This model can serve as a template for the cold minimal model for an IVGTT glucose tolerance test.

Data for this case study

Sample IVGTT data

DATA

t G (FSD 0.02) I

0	96 (-)	16
2	312 (-)	120
3	291 (-)	101
4	289 (-)	107
5	271 (-)	83
7	241 (-)	49
10	220	54
15	184	49
20	170	38
25	151	43
30	141	38
35	121	25
40	94	27
50	88	11
60	80	11
70	83	10
80	84	10
100	90	12
120	89	11
140	90	17
160	91	18
180	87	11
210	98	14
240	94	9

END

CONST Gb 93

CONST Ib 11.3

CONST D 305

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