Dynamic Contrast-Enhanced MRI Analysis of Tumor Data

Case Study

- How to create a forcing function for blood concentration
- How to define alternative model parameterizations
- How to write reports

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Dynamic Contrast-Enhances MRI Analysis of Tumor Data

Prerequisites

The prerequisite for this case study is having worked through the SAAM II introductory tutorial, "Getting Started with SAAM II Compartmental." It will be useful to have worked through the Using SAAM II tutorial "Using Forcing Functions."

What you will learn in this case study

You will learn how to define a model of capillary permeability and fit it to a set of data obtained during DEC-MRI.

- How to create a forcing function for blood concentration
- How to define alternative model parameterizations
- How to write reports

Data Required

The data file for this case study is

MRI.dat

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

Introduction

This case study will show you how to implement a model for dynamic contrast-enhanced MRI data in tumors. More specifically, it will deal with an experimental protocol in which signal intensity from a dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) protocol using Gd-DTPA albumin in an animal model of mammary tumors was carried out. Measurements have been made in blood and on the tumor rim. The goal will be to develop an integrated model that accounts for blood and the tumor rim, and permits estimation of parameters related to capillary permeability.

In terms of SAAM II, there will be two models. One will describe the blood data, and the other the tumor rim data. The blood data will be used as a forcing function to drive the tumor rim system.

The model equations which will be implemented in the SAAM II setting are given below.

Notation

- $q_1(t)$ is contrast agent concentration in blood (mg cc^{-1}),
- k_{01} the rate of disappearance of contrast agent concentration from blood (min^{-1}),
- ICB is the initial concentration pulse of contrast agent in blood (mg cc^{-1}),
- fBV is fractional blood volume (ml cc^{-1} of tissue)
- $q_2(t)$ is contrast agent concentration in plasma (mg cc^{-1}),
- $q_3(t)$ is contrast agent concentration in tumor tissue (mg cc^{-1} of tissue),
- $s_1(t)$ and $s_2(t)$ are measured contrast agent concentrations in blood and tissue respectively (mg cc^{-1} and mg cc^{-1} of tissue).

The blood model (time in minutes):

$$\frac{dq_1(t)}{dt} = -k_{01} \cdot q_1(t) + ICB\delta(t) \qquad (1)$$
$$s_1(t) = q_1(t)$$

In this model, q1 represents the blood compartment which decays monoexponentially following a bolus injection of contrast agent, and s1 is the sample equation.

The tumor rim model

$$q_2(t) = fBV \cdot q_1(t)$$
$$\frac{dq_3(t)}{dt} = k_{32} \cdot q_2(t) \qquad (2)$$
$$s_2(t) = q_2(t) + q_3(t)$$

In this model, you can see how q2 is defined from q1; this will be specified in SAAM II using the forcing function machinery. Compartment q3 represents the tumor rim which, because there is no loss, accumulates contrast agent during the experiment. Of interest is the measurement equation s2 which contains a term for blood and tissue.

Parameters to be estimated from data are *k(0,1)*, *fBV*, *ICB* and *k(3,2)*. An important derived parameter is permeability, calculated as PS=fBV(1-H) k(3,2), where H is the hematocrit. The produce fBV(1-H) is thus a measure of fractional plasma volume.

1. Daldrup H., Shames D., Wendland M., Okuhata Y., Link T., Rosenau W., Lu Y. and Brasch R.. Correlation of dynamic contrast-enhanced magnetic resonance imaging with histologic tumor grade: comparison of macromolecular and small-molecular contrast media. *Pediatr. Radiol*. 28: 67-78, 1998.

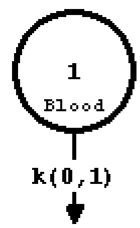
Part 1. Create a one-compartment model for the blood data using the SAAM II Compartmental application.

This part of the case study will show you how to implement the blood model

$$\frac{dq_1(t)}{dt} = -k_{01} \cdot q_1(t) + ICB\delta(t) \qquad (3)$$
$$s_1(t) = q_1(t)$$

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**.



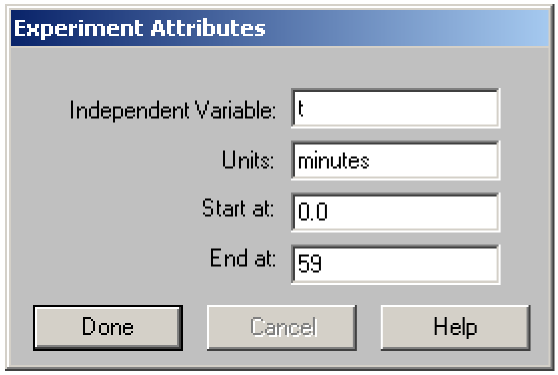
   In creating this model, you will need to open the **Compartment Attributes** dialog box by double-clicking on Compartment **1**, typing “Blood” in the **Reference Name** box, and clicking **Done**.

3. Create the experiment for the blood model.

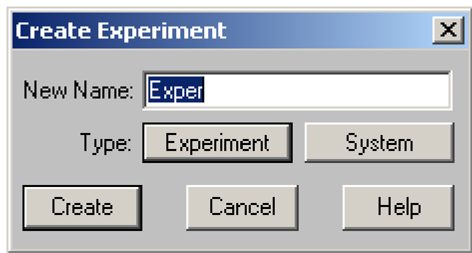
   a. In the **SAAM II Toolbox**, click **Experiment**. The **Experiment Attributes** dialog box will open.

   b. Be sure the entry in the **Units** box is minutes.

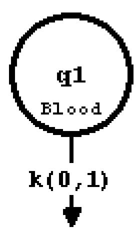
   c. Enter “59” in the **End At** box. The **Experiment Attributes** dialog box will appear as follows:



d. Click **Done**. The **Create Experiment** dialog box will open as follows:



e. Click **Create**. Your model will appear as follows:

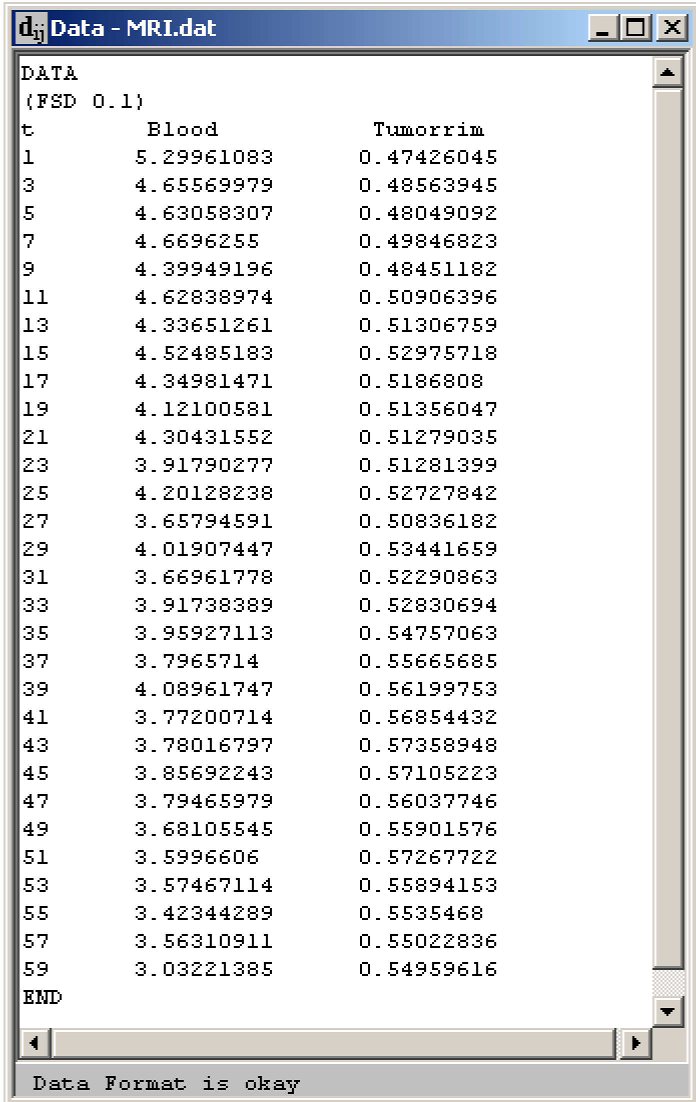


4. Add the data to your model.

a. On the **Show** menu, click **Data**, or alternatively click **Data**  on the **SAAM II Toolbar**. The **Data** window will open.

b. On the **File** menu, click **Open**. The file **MRI.dat** should appear in the list (if it does not, find the folder where you have installed this data file).

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




```
DATA
(FSD 0.1)
t          Blood            Tumorrim
1         5.29961083       0.47426045
3         4.65569979       0.48563945
5         4.63058307       0.48049092
7         4.6696255        0.49846823
9         4.39949196       0.48451182
11        4.62838974       0.50906396
13        4.33651261       0.51306759
15        4.52485183       0.52975718
17        4.34981471       0.5186808
19        4.12100581       0.51356047
21        4.30431552       0.51279035
23        3.91790277       0.51281399
25        4.20128238       0.52727842
27        3.65794591       0.50836182
29        4.01907447       0.53441659
31        3.66961778       0.52290863
33        3.91738389       0.52830694
35        3.95927113       0.54757063
37        3.7965714        0.55665685
39        4.08961747       0.56199753
41        3.77200714       0.56854432
43        3.78016797       0.57358948
45        3.85692243       0.57105223
47        3.79465979       0.56037746
49        3.68105545       0.55901576
51        3.5996606        0.57267722
53        3.57467114       0.55894153
55        3.42344289       0.5535468
57        3.56310911       0.55022836
59        3.03221385       0.54959616
END
```

Notice there are two columns of data, one for blood and the other for the tumor rim (tumorrim).

d. Close the **Data** window.

5. Create the blood sample.

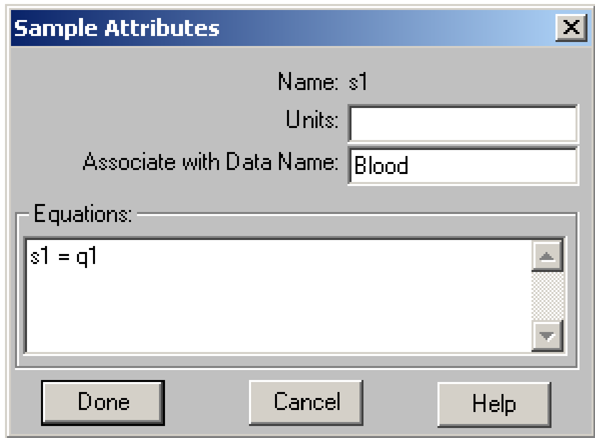
a. In the **SAAM II Toolbox**, click **Sample**.

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. Type “Blood” in the **Associate with Data Name** box.

e. Be sure the sample equation reads "s1=q1"; there should be no need to edit the sample equation. The **Sample Attributes** dialog box will appear as follows:



f. Click **Done**.

6. Create an input into Compartment **q1**.

a. In the **SAAM II Toolbox**, click **Input**.

b. Click compartment **q1**, and then click on the **Drawing Canvas**. The input **ex1** will appear.

c. Double-click **ex1** to open the **Exogenous Input** dialog box.

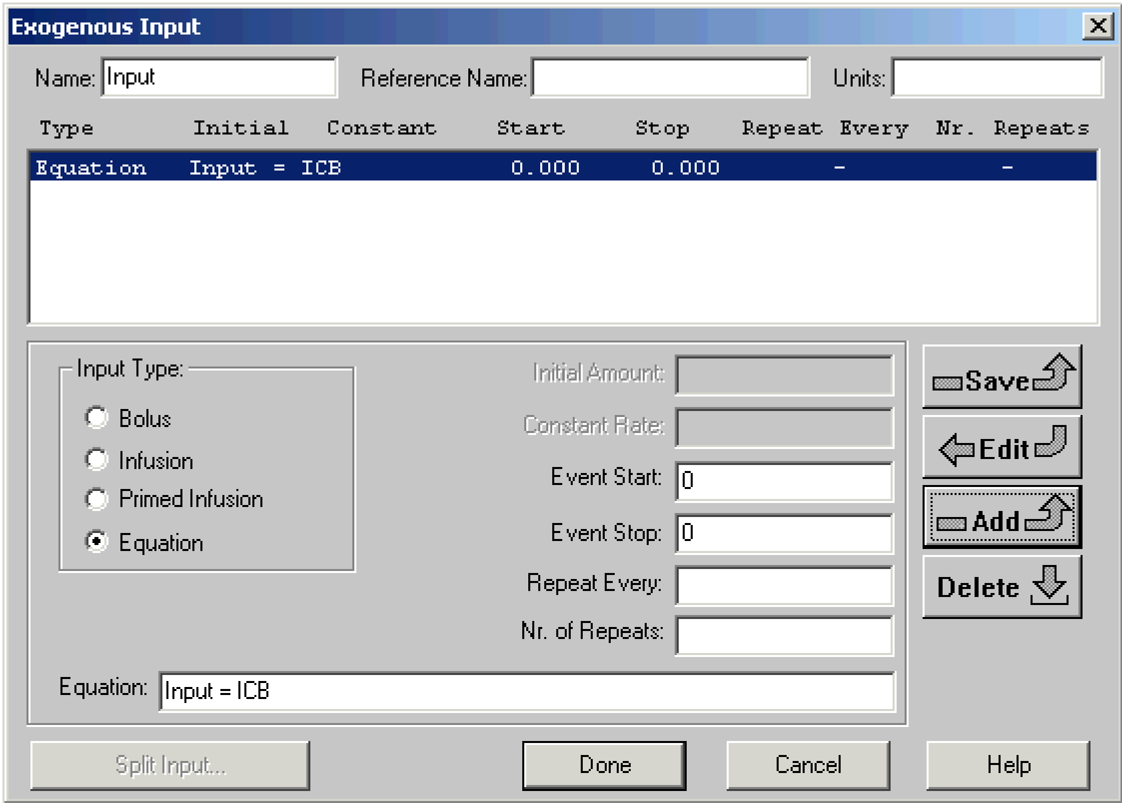
d. Type "Input" in the **Name** box.

e. In the **Input Type** pane, select **Equation**.

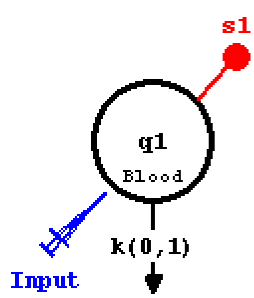
f. In the **Equation** box, type "Input=ICB".

g. Be sure "0" is entered in the **Event Start** and **Event Stop** boxes.

h. Click **Add**. The **Exogenous Input** dialog box will appear:



i. Click **Done**. Your model will appear as follows:



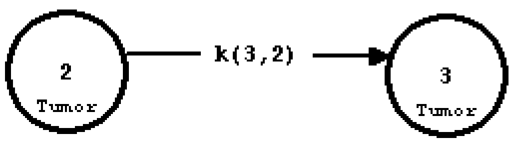
SAAM II *The equation input*. The experimental input in this case is an equation. By starting and stopping at time zero, it is essentially a bolus. "*ICB*" becomes a parameter which, in this case, will be estimated from the data. The equation input is what allows one to estimate the amount of material in a bolus injection. Because of the way the model is constructed, this will actually represent the amount of contrast agent injected that arrives in the tumor.

Part 2. Create the model of contrast agent tumor tissue kinetics in the SAAM II Compartmental application and define the permeability parameter

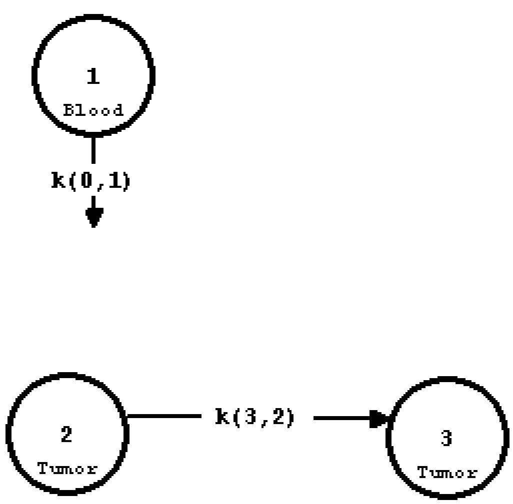
You have now specified the model for the blood data, the input and the measurement equation. We will now specify the model for the tumor rim equations:

$$\begin{aligned} q_2(t) &= fBV \cdot q_1(t) \\ \frac{dq_3(t)}{dt} &= k_{32} \cdot q_2(t) \\ s_2(t) &= q_2(t) + q_3(t) \end{aligned} \qquad (4)$$

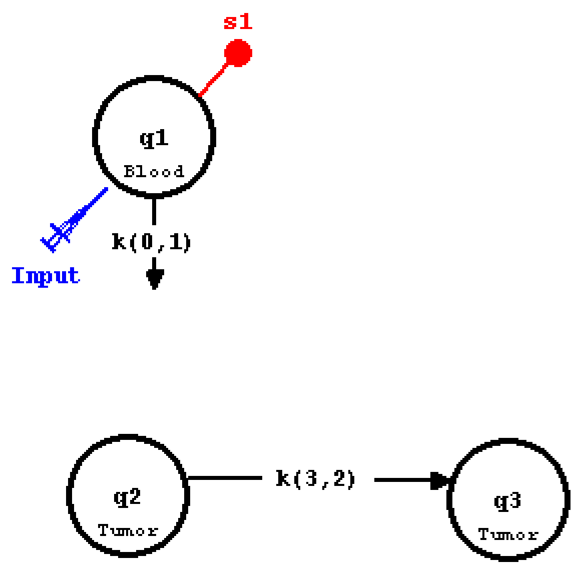
by creating the following two-compartment model:



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

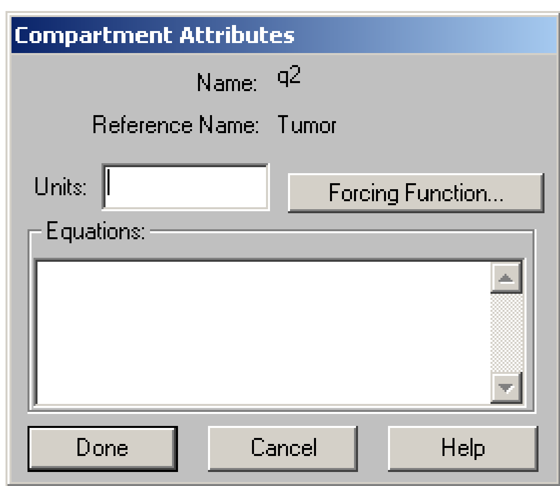


2. In the **SAAM II Toolbox**, click **Experiment**. Notice the **Experiment Attributes** dialog box does not open. This is because the attributes have already been defined. Your models will appear as follows:

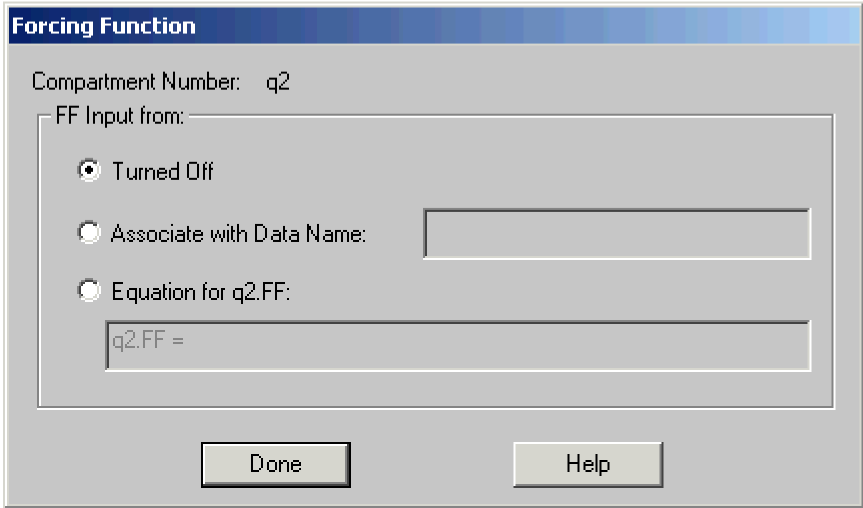


3. Create the forcing function for Compartment **q2**.

   a. Double-click Compartment **q2**. The **Compartment Attributes** dialog box will open as follows:

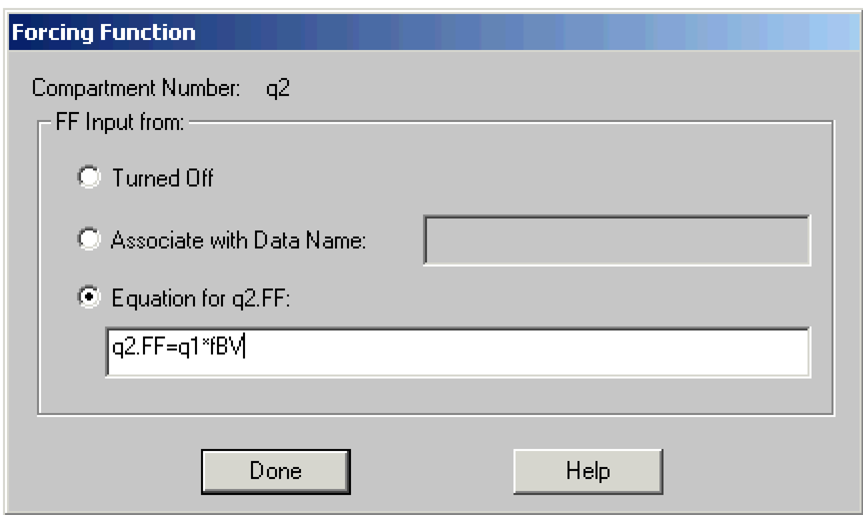


   b. Click **Forcing Function…**. The **Forcing Function** dialog box will open as shown below.



c. In the **FF Input from** pane, click **Equation for q2.FF**.

d. In the **Equation** box, type "q2.FF=q1*fBV". The **Forcing Function** dialog box will appear:



d. Click **Done** to close the **Forcing Function** dialog box.

e. Click **Done** to close the **Compartment Attributes** dialog box.

The forcing function equation. The forcing function is the blood data as described by Compartment **q1**. The parameter *fBV* is the fraction of this compartment which actually "forces" the tumor rim model. This term is thus what drives the differential equation $q_2(t) = fBV \cdot q_1(t)$.

4. Define the second sample for the tumor rim.

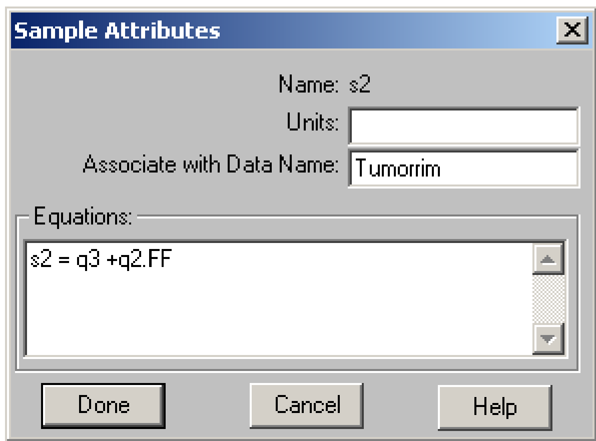
   a. In the **SAAM II Toolbox**, click **Sample**.

   b. Click compartment **q3**, and then click on the **Drawing Canvas**. The sample **s2** will appear.

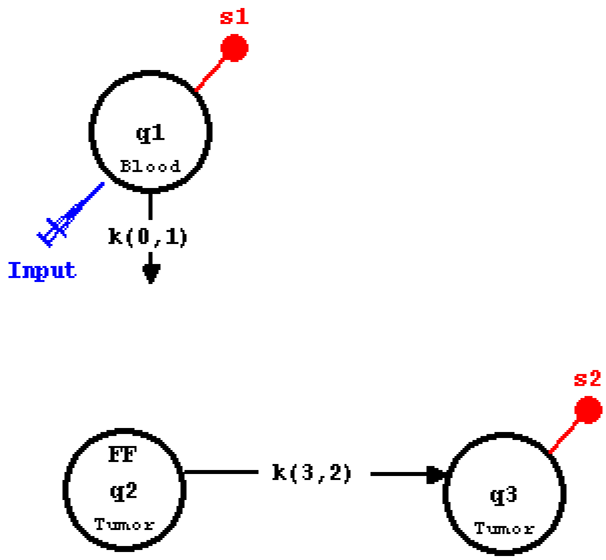
   c. Double-click **s2** to open the **Sample Attributes** dialog box.

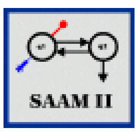
   d. Type "Tumorrim" in the **Associate with Data Name** box.

   e. Type "s2 = q3 + q2.FF" in the **Equations** box. The **Sample Attributes** dialog box will appear:



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



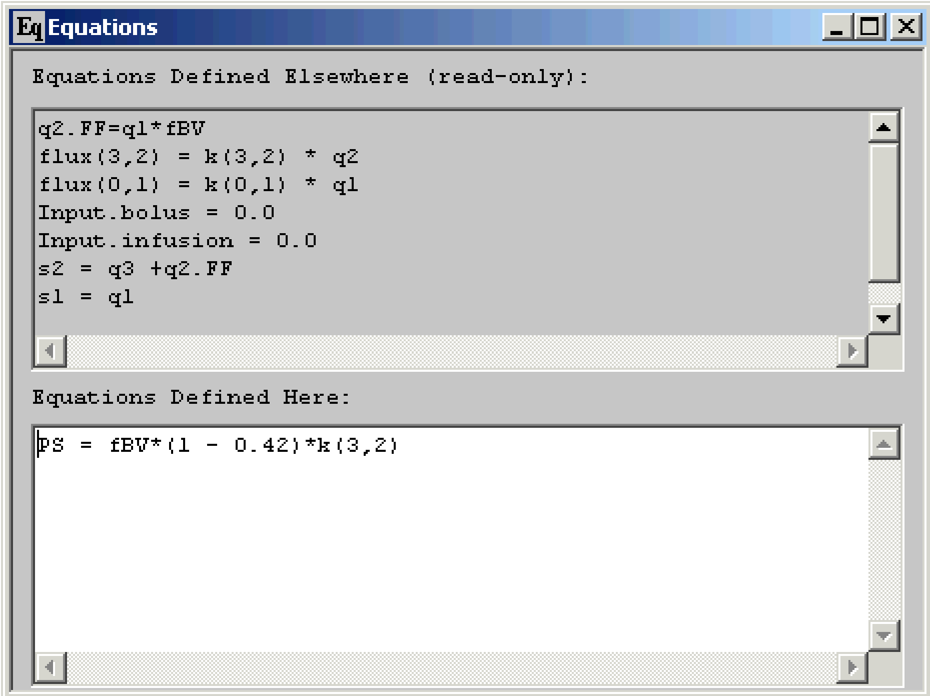


Samples. The sample for the tumor rim data includes both tissue and blood. The tissue is modeled by compartment **q3**. However blood is not compartment **q2**, but **q2.FF** which is the forcing function that describes the blood profile. Thus to calculate blood correctly, we must use the forcing function description.

Part 3. Define the permeability parameters.

1. On the **Show** menu, click **Equations**, or alternatively click **Equations** Eq on the **SAAM II Toolbar**. The **Equations** dialog box will open.

2. Type “PS=fBV*(1-.42)*k(3,2)” in the **Equations** box. The **Equations** dialog box will appear:



3. Close the **Equations** dialog box.

The permeability equation. The permeability equation is written as a fraction of plasma volume (fBV*(1-0.42)), where 0.42 is the hematocrit, times the rate constant k(3,2). This number is usually small, so it can be scaled by writing, for example, "fBV*(1-0.42)*k(3,2)*100" which will translate the units from "per cc" to "per 100cc".

Part 4. Enter the parameter values, Solve the model, Fit the model to the data and view the solution. Write a report describing the Fit.

1. Enter the initial parameter estimates. (These values are typical for an animal study.)

   a. On the **Show** menu, click **Parameters**, or alternatively click **Parameters** on the **SAAM II Toolbar**. The **Parameters** dialog box will open.

   b. Double-click *ICB*.

   c. Enter "5" in the **Value** box.

   d. Click **Save**.

e. Double-click *fBV*.

f. Enter “0.1” in the **Value** box.

g. Click **Save**.

h. Double-click *k(0,1)*.

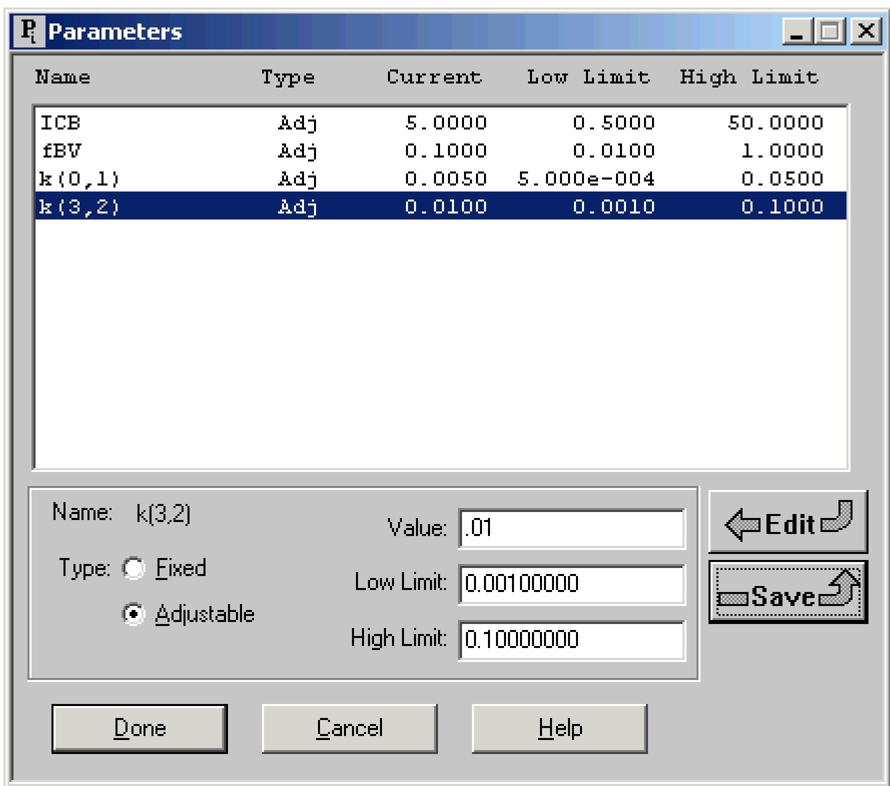
i. Enter “0.005” in the **Value** box.

j. Click **Save**.

k. Double-click *k(3,2)*.

l. Enter “0.01” in the **Value** box.

m. Click **Save**. The **Parameters** dialog box will appear:



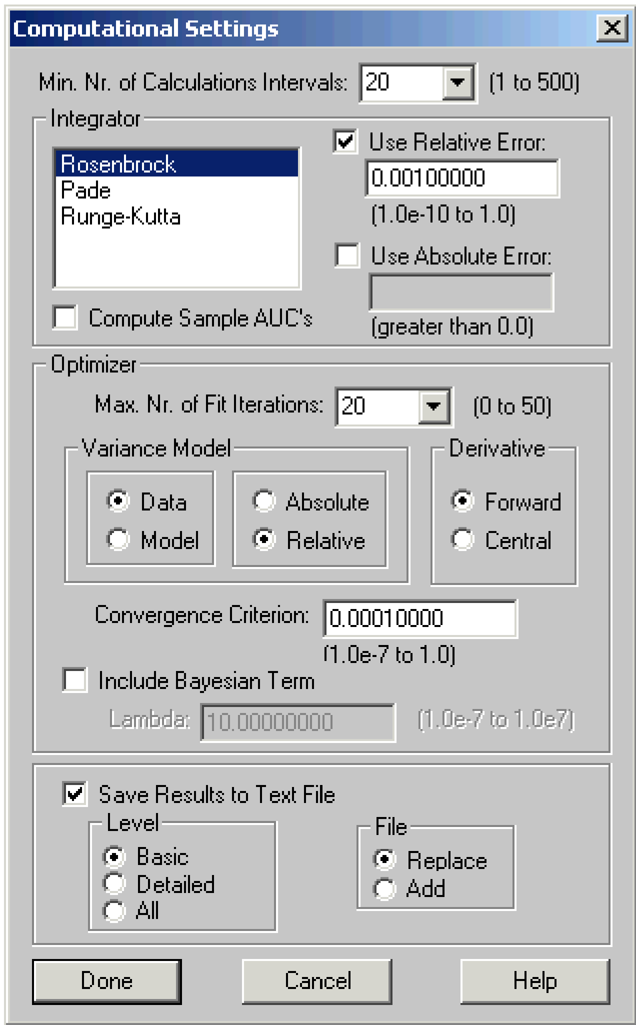
n. Click **Done**.

2. Prepare to write a final report.

a. On the **Compute** menu, click **Computational Settings**. The **Computational Settings** dialog box will open.

b. Select **Save Results to Text File** box.

c. In the **Level** pane, be sure **Basic** is selected. In the **File** pane, be sure **Replace** is selected. The **Computational Settings** dialog box will appear:



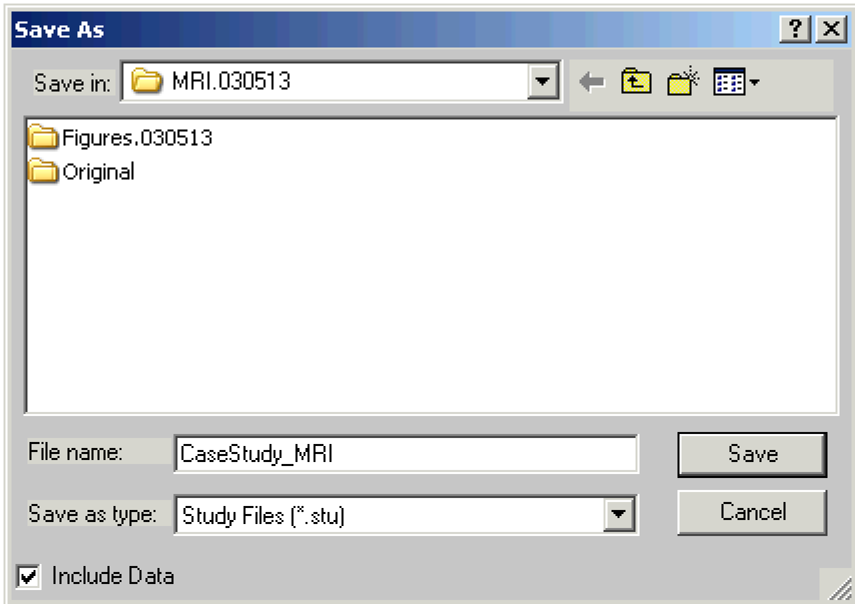
d. Click **Done**.

e. Save the study file. Since report writing relies on the file name of your study file, you need to save this **SAAM II Compartmental** study file.

(1) On the **File** menu, click **Save As**. The **Save As** dialog box will open.

(2) Navigate to where you would like to save the file.

(3) In the **File Name** box, type “CaseStudy_MRI”. An example of the **Save As** dialog box is shown below:



(4) Click **Save**.

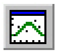
Report writing. SAAM II provides the capability to write the results from your modeling session to a text file which can then be used in report writing. When you have selected this option, SAAM II will create a text file whose name is the same as the study file; in this case, the text file will be named CaseStudy_MRI.

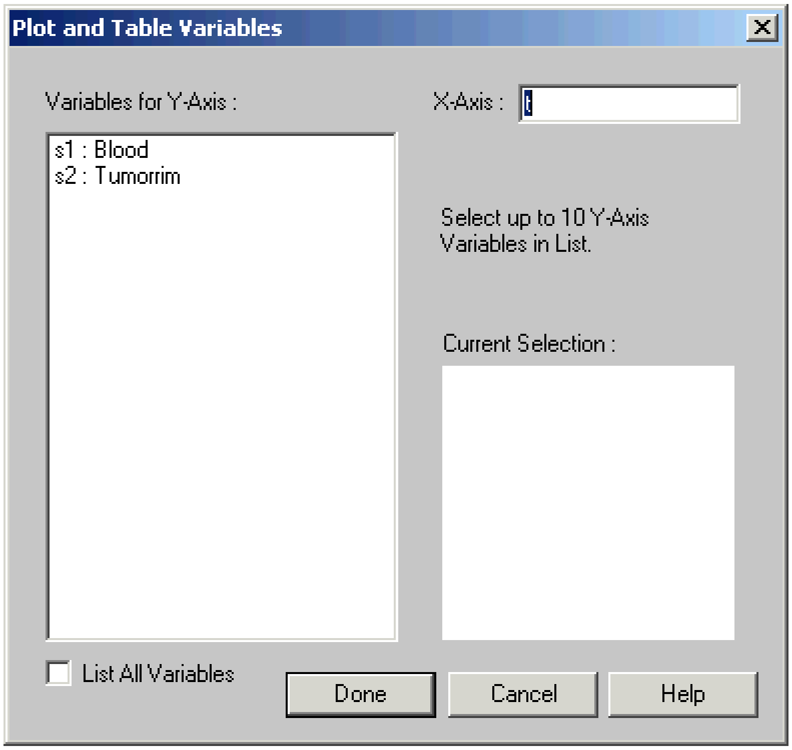
There are three levels depending upon the amount, or detail, of information you require.

The add or replace option has the following consequence. If you select the add option, every time you solve or fit your model to your data, the results are written to the text file. If you select the replace option, every time you solve or fit your model to your data, the results will overwrite what was written previously.

3. Solve the model and view the solution.

   a. On the **Compute** menu, click **Solve**, or alternatively click **Solve**  on the **SAAM II Toolbar**.

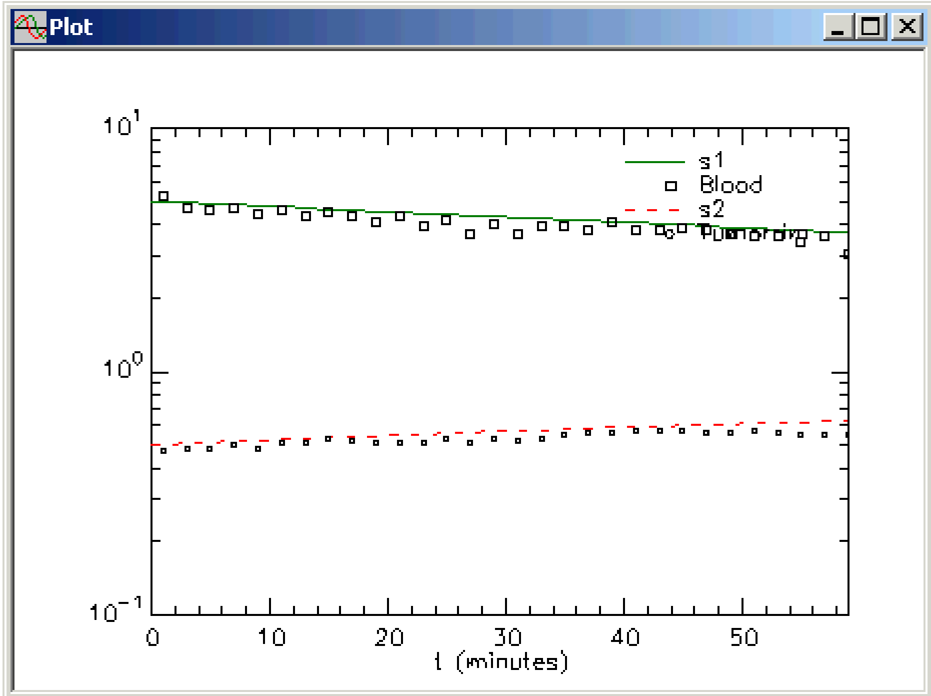
b. On the **Show** menu, click **Plot**, or alternatively click **Plot**  on the **SAAM II Toolbar**. The **Plot and Table Variables** dialog box will open as follows:



c. Click **s1:Blood** and **s2:Tumorrim** to move them to the **Current Selection** pane.

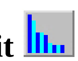
d. Click **Done**. The plot should appear in linear mode.

e. On the **View** menu, click **Semilog**. Your plot will appear:



Leave the **Plot** window open.

4. Fit the model and view the statistics.

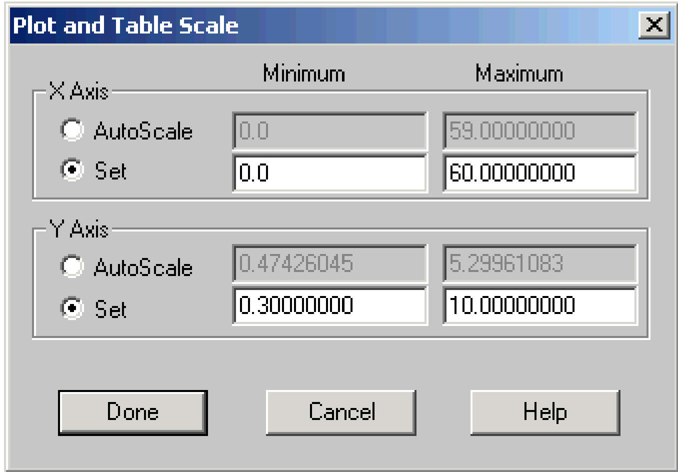
   a. On the **Compute** menu, click **Fit**, or alternatively click **Fit**  on the **SAAM II Toolbar**.

   b. The model should successfully converge. However, it is difficult to visualize the plot.

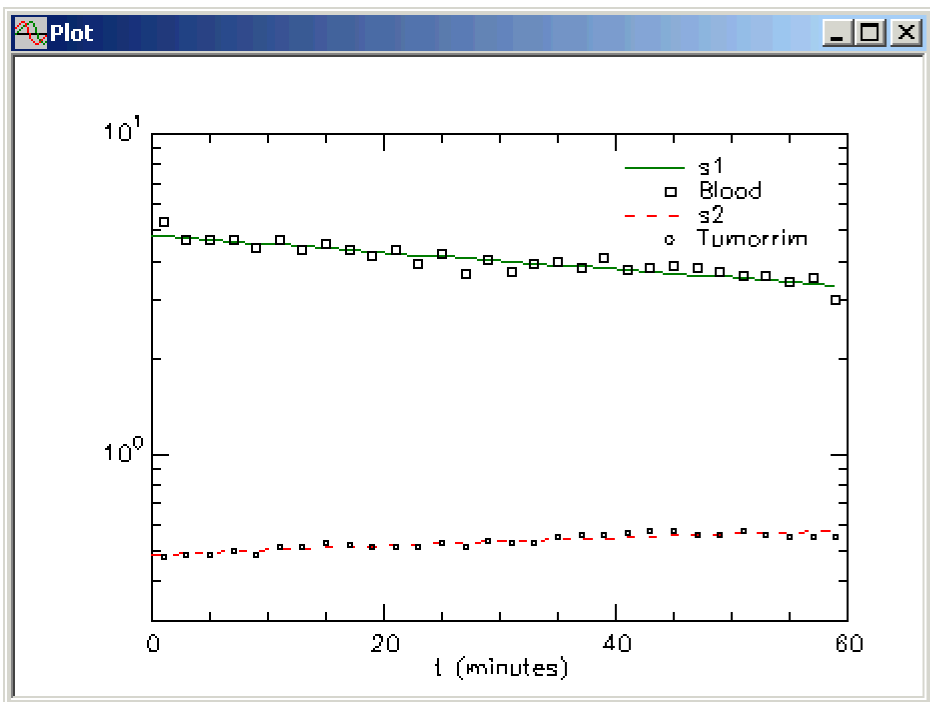
      (1) On the **Set** menu, click **Plot/Table Scale**. The **Plot and Table Scale** dialog box will open.

      (2) In the **X Axis** pane, click **Set**. In the **Maximum** box, enter “60”.

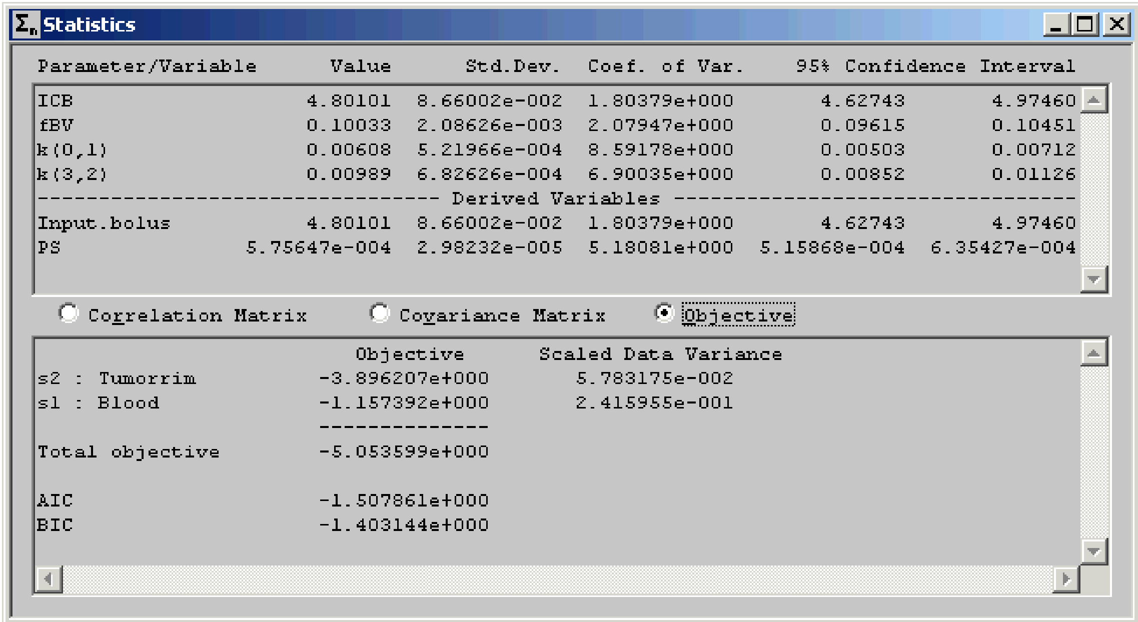
      (3) In the **Y Axis** pane, click **Set**. In the **Minimum** box, enter “0.3”. In the **Maximum** box, enter “10”. The **Plot and Table Scale** dialog box will appear:



(4) Click **Done**. Your plot will appear as follows:



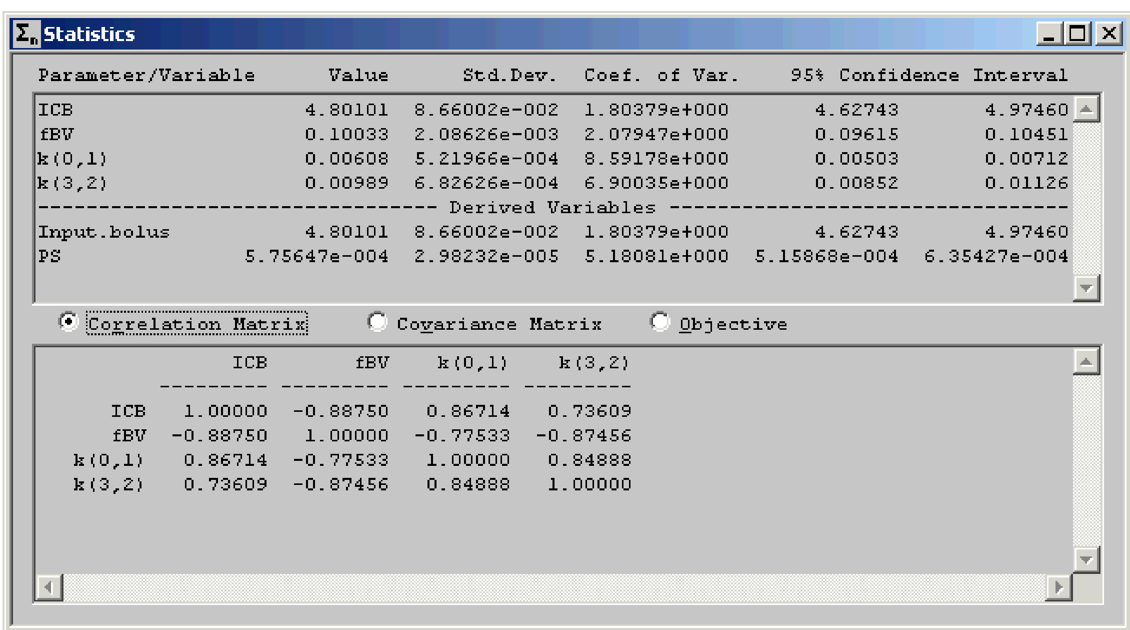
c. View the statistics. On the **Show** menu, click **Statistics**, or alternatively click **Statistics**  on the **SAAM II Toolbar**. Your **Statistics** window will appear as follows:



The parameter precision is quite good with the largest coefficient of variation being just under 10%. Notice also the input bolus and the permeability parameter appear as derived variables which also have their own error estimates.

d. View the Correlation matrix

(1) In the **Statistics** window, select **Correlation Matrix**. The **Statistics** window will appear:



The correlation matrix is also reasonable with the “highest” correlation being 0.89 between *ICB* and *fBV*.

(2) Close the **Statistics** window.

e. If you wish, you can investigate the weighted residuals to see how well your model describes your data. These can be used to test for goodness-of-fit using the runs test.

f. Close all open windows and dialog boxes.

Quit the **SAAM II Compartmental** application. Remember you have saved this file already, so you can use it again.

Essential points to remember

- The model is fit to two curves simultaneously, the blood and tumor tissue time courses of macromolecular contrast agent. The relevant parameter here is permeability, i.e. the rate at which contrast agent escapes the vasculature. Permeability is thought to be related to tumor malignancy.
- In this model, permeability is a derived parameter.

Modeling notes

This modeling approach is described in detail in the reference: Daldrup H., Shames D., Wendland M., Okuhata Y., Link T., Rosenau W., Lu Y. and Brasch R.. Correlation of dynamic contrast-enhanced magnetic resonance imaging with histologic tumor grade: comparison of macromolecular and small-molecular contrast media. *Pediatr. Radiol*. 28: 67-78, 1998.

Report Writing

When you activate SAAM II's report writing capability, SAAM II will create text files which you can use to follow what you did every time you Solve or Fit. Below is the basic file created following the Fit. Navigate first to where you saved CaseStudy_MRT. There you will find a file entitled CaseStudy_MRT.txt. The contents of this file are shown below. You can cut and paste parts or all of this file into any application such as Word.

Study Name: CaseStudy_MRI.stu
Basic Summary Output
Date: 05:35 PM, Tuesday, May 13, 2003
Application: Compartmental
Type of Calculation: Fit

Computational Settings

Integrator: Rosenbrock
Relative Integrator Error: 1.0000e-003
Variance Model: Data, Relative
Derivative: Forward

Values at t = 0.0 minutes

Blood	-
ICB	4.801012
Input.bolus	4.801012
Input.infusion	0.000000
PS	0.000576
Tumorrim	-
fBV	0.100327
flux(0,1)	0.029167
flux(3,2)	0.000000
k(0,1)	0.006075
k(3,2)	0.009893
q1	4.801012
q2	0.000000
q2.FF	0.481670
q3	0.000000
s1	4.801012
s1_res	-
s1_wres	-
s2	0.481670

s2_res -
s2_wres -
t 0.000000

Calculated Sample Values and Data

t	Tumorrim	Weight	s2	s2_wres
0.000e+000	-	-	4.817e-001	-
1.000e+000	4.743e-001	7.688e+003	4.835e-001	-8.104e-001
3.000e+000	4.856e-001	7.332e+003	4.871e-001	-1.282e-001
5.000e+000	4.805e-001	7.490e+003	4.907e-001	-8.858e-001
7.000e+000	4.985e-001	6.959e+003	4.943e-001	3.501e-001
9.000e+000	4.845e-001	7.366e+003	4.978e-001	-1.138e+000
1.100e+001	5.091e-001	6.673e+003	5.012e-001	6.395e-001
1.300e+001	5.131e-001	6.569e+003	5.047e-001	6.819e-001
1.500e+001	5.298e-001	6.161e+003	5.080e-001	1.705e+000
1.700e+001	5.187e-001	6.427e+003	5.114e-001	5.862e-001
1.900e+001	5.136e-001	6.556e+003	5.147e-001	-8.949e-002
2.100e+001	5.128e-001	6.576e+003	5.179e-001	-4.162e-001
2.300e+001	5.128e-001	6.575e+003	5.211e-001	-6.751e-001
2.500e+001	5.273e-001	6.219e+003	5.243e-001	2.334e-001
2.700e+001	5.084e-001	6.691e+003	5.275e-001	-1.562e+000
2.900e+001	5.344e-001	6.054e+003	5.306e-001	3.000e-001
3.100e+001	5.229e-001	6.324e+003	5.336e-001	-8.523e-001
3.300e+001	5.283e-001	6.195e+003	5.367e-001	-6.570e-001
3.500e+001	5.476e-001	5.767e+003	5.396e-001	6.019e-001
3.700e+001	5.567e-001	5.580e+003	5.426e-001	1.050e+000
3.900e+001	5.620e-001	5.475e+003	5.455e-001	1.219e+000
4.100e+001	5.685e-001	5.349e+003	5.484e-001	1.473e+000
4.300e+001	5.736e-001	5.256e+003	5.513e-001	1.619e+000
4.500e+001	5.711e-001	5.303e+003	5.541e-001	1.237e+000
4.700e+001	5.604e-001	5.506e+003	5.568e-001	2.619e-001
4.900e+001	5.590e-001	5.533e+003	5.596e-001	-4.316e-002
5.100e+001	5.727e-001	5.272e+003	5.623e-001	7.528e-001
5.300e+001	5.589e-001	5.535e+003	5.650e-001	-4.501e-001
5.500e+001	5.535e-001	5.643e+003	5.676e-001	-1.059e+000
5.700e+001	5.502e-001	5.711e+003	5.703e-001	-1.514e+000
5.900e+001	-	-	5.728e-001	-
5.900e+001	5.496e-001	5.725e+003	5.728e-001	-1.759e+000

t	Blood	Weight	s1	s1_wres
0.000e+000	-	-	4.801e+000	-

1.000e+000	5.300e+000	1.474e+001	4.772e+000	2.026e+000
3.000e+000	4.656e+000	1.910e+001	4.714e+000	-2.561e-001
5.000e+000	4.631e+000	1.930e+001	4.657e+000	-1.177e-001
7.000e+000	4.670e+000	1.898e+001	4.601e+000	2.985e-001
9.000e+000	4.399e+000	2.138e+001	4.546e+000	-6.755e-001
1.100e+001	4.628e+000	1.932e+001	4.491e+000	6.054e-001
1.300e+001	4.337e+000	2.201e+001	4.436e+000	-4.688e-001
1.500e+001	4.525e+000	2.022e+001	4.383e+000	6.385e-001
1.700e+001	4.350e+000	2.188e+001	4.330e+000	9.306e-002
1.900e+001	4.121e+000	2.437e+001	4.278e+000	-7.732e-001
2.100e+001	4.304e+000	2.234e+001	4.226e+000	3.703e-001
2.300e+001	3.918e+000	2.697e+001	4.175e+000	-1.335e+000
2.500e+001	4.201e+000	2.345e+001	4.125e+000	3.718e-001
2.700e+001	3.658e+000	3.093e+001	4.075e+000	-2.318e+000
2.900e+001	4.019e+000	2.562e+001	4.025e+000	-3.248e-002
3.100e+001	3.670e+000	3.074e+001	3.977e+000	-1.703e+000
3.300e+001	3.917e+000	2.697e+001	3.929e+000	-5.953e-002
3.500e+001	3.959e+000	2.640e+001	3.881e+000	4.001e-001
3.700e+001	3.797e+000	2.872e+001	3.835e+000	-2.034e-001
3.900e+001	4.090e+000	2.475e+001	3.788e+000	1.499e+000
4.100e+001	3.772e+000	2.909e+001	3.742e+000	1.593e-001
4.300e+001	3.780e+000	2.897e+001	3.697e+000	4.462e-001
4.500e+001	3.857e+000	2.782e+001	3.653e+000	1.078e+000
4.700e+001	3.795e+000	2.875e+001	3.609e+000	9.981e-001
4.900e+001	3.681e+000	3.055e+001	3.565e+000	6.418e-001
5.100e+001	3.600e+000	3.194e+001	3.522e+000	4.396e-001
5.300e+001	3.575e+000	3.239e+001	3.479e+000	5.426e-001
5.500e+001	3.423e+000	3.532e+001	3.437e+000	-8.247e-002
5.700e+001	3.563e+000	3.260e+001	3.396e+000	9.553e-001
5.900e+001	-	-	3.355e+000	-
5.900e+001	3.032e+000	4.502e+001	3.355e+000	-2.164e+000

Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
ICB	4.80101	8.66002e-002	1.80379e+000	4.62743	4.97460
fBV	0.10033	2.08626e-003	2.07947e+000	0.09615	0.10451
k(0,1)	0.00608	5.21966e-004	8.59178e+000	0.00503	0.00712
k(3,2)	0.00989	6.82626e-004	6.90035e+000	0.00852	0.01126
------------ Derived Variables ------------					
Input.bolus	4.80101	8.66002e-002	1.80379e+000	4.62743	4.97460
PS	5.75647e-004	2.98232e-005	5.18081e+000	5.15868e-004	6.35427e-004

	Objective	Scaled Data Variance
s2 : Tumorrim	-3.896207e+000	5.783175e-002
s1 : Blood	-1.157392e+000	2.415955e-001

Total objective	-5.053599e+000	

AIC	-1.507861e+000
BIC	-1.403144e+000

Number of Iterations Required to Fit: 2

Data for this tutorial

```
# Sample DCE-MRI data
DATA
(FSD 0.1)
  t     Blood        Tumorrim
1       5.29961083   0.47426045
3       4.65569979   0.48563945
5       4.63058307   0.48049092
7       4.6696255    0.49846823
9       4.39949196   0.48451182
11      4.62838974   0.50906396
13      4.33651261   0.51306759
15      4.52485183   0.52975718
17      4.34981471   0.5186808
19      4.12100581   0.51356047
21      4.30431552   0.51279035
23      3.91790277   0.51281399
25      4.20128238   0.52727842
27      3.65794591   0.50836182
29      4.01907447   0.53441659
31      3.66961778   0.52290863
33      3.91738389   0.52830694
35      3.95927113   0.54757063
37      3.7965714    0.55665685
39      4.08961747   0.56199753
41      3.77200714   0.56854432
43      3.78016797   0.57358948
45      3.85692243   0.57105223
47      3.79465979   0.56037746
49      3.68105545   0.55901576
51      3.5996606    0.57267722
53      3.57467114   0.55894153
55      3.42344289   0.5535468
57      3.56310911   0.55022836
59      3.03221385   0.54959616
END
```