

Gentamicin Kinetics

A Simulation Case Study

- How to use simulations to examine toxicity differences between patients
- How to use simulations to analyze the impact of different dosing regimens
- How do flip-flop kinetics result from slow gentamicin distribution
- How to use the Duplicate command
- How to incorporate Michaelis-Menten kinetics in a transfer function

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Gentamicin Kinetics: A Simulation Exercise in Flip-Flop Kinetics and Toxicity

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

This case study will show you how to use heuristic simulations to understand interindividual differences in toxic response to gentamicin therapy and the impact of different dosing regimens on gentamicin toxicity. Overall it demonstrates the power of simulating the outcomes of different dosing regimens. You will learn:

- How to use simulations to understand how differences in gentamicin account for toxicity differences between patients.
- How to use simulations to analyze the impact of different drug dosing regimens on gentamicin toxicity.
- How "flip-flop" kinetics result from slow gentamicin distribution to a peripheral compartment.
- How to use the **Duplicate** feature of the **SAAM II** Compartmental application.
- How to incorporate Michaelis-Menten kinetics in a transfer function.

Data Required

No data files are required for this case study.

Introduction

In this case study, a number of simulations will be developed that are based on an actual analysis of gentamicin kinetics in patients who either tolerated intravenous therapy with this antibiotic without toxicity or developed significant nephrotoxicity [1]. Gentamicin owes its selective antibacterial action to the fact that it is unable to enter most mammalian cells but penetrates the cell walls of sensitive gram negative bacteria. Although gentamicin distributes primarily within the extracellular fluid (ECF) space, Schentag and co-workers demonstrated that it also distributes to a tissue compartment that they identified in autopsy studies as the kidney [2]. The mechanism for gentamicin uptake by renal tubular cells is thought to be receptor-mediated endocytosis. Gentamicin is eliminated from the body by glomerular filtration at a rate that approximates creatinine clearance. However, the distribution process is slow enough relative to the rate of gentamicin elimination that it accounts for the second rather than the first phase of

gentamicin's biphasic plasma level-vs.-time curve. This situation is referred to as “flip-flop” kinetics.

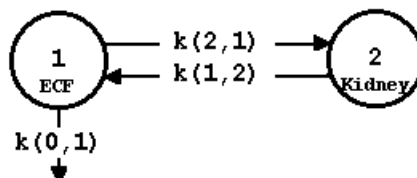
We will use simulations to compare gentamicin distribution in a non-toxic vs. a toxic patient after administration of 80 mg intravenous doses of this drug at 8-hour intervals, the standard administration regimen when these studies were done. Different dosing regimens also appear to have an impact on the incidence of gentamicin toxicity. Studies in dogs have shown that continuous intravenous infusion of gentamicin for several days results in much more nephrotoxicity than when the same total dose is divided into once-daily injections [3]. Therefore, we will use simulations in a heuristic fashion to compare the distribution of gentamicin after continuous infusion and after the once daily administration schedule that is the current standard.

1. Coburn, W. A., Schentag, J.J., Jusko, W.J., Gibaldi, M. “A model for the prospective identification of the prenefrotoxic state during gentamicin therapy.” *J. Pharmacokinet. Biopharm.* 1978, 6:179-86.
2. Schentag, J. J., Jusko, W. J., Vance, J. W., Cumbo, T. J., Abrutyn, E., DeLattre, M., Gerbracht, L. M. “Gentamicin disposition and tissue accumulation on multiple dosing.” *J. Pharmacokinet. Biopharm.* 1977, 5:559-77.
3. Reiner, N. E., Bloxham, D. D., Thompson, W. L. “Nephrotoxicity of gentamicin and tobramycin given once daily or continuously in dogs.” *J. Antimicrob. Chemother.* 1978, 4 (Suppl A):85-101.

Part 1. Investigate Gentamicin flip-flop kinetics in a non-toxic patient

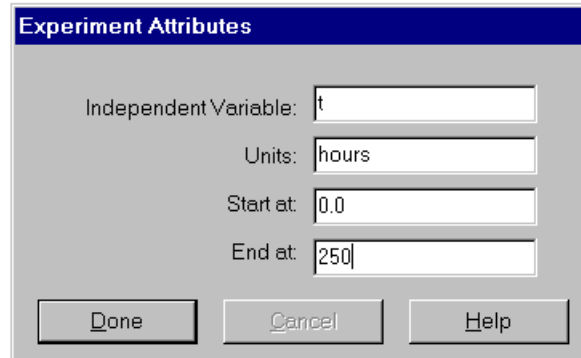
The first step will be to create the 2-compartment system model for a patient who tolerated an 8-day course of intravenous gentamicin therapy without toxicity.

1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open. In the **SAAM II Toolbox**, be sure the **Model** tools are available.
2. Create the following system model on the **Drawing Canvas**:



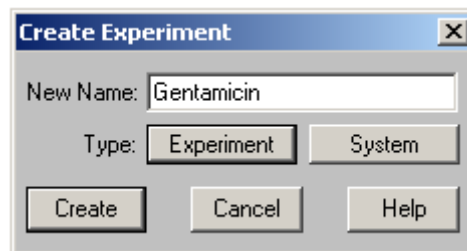
3. In the **SAAM II Toolbox**, click **Experiment**. Notice that the **Model** tools are unavailable and the **Experiment** tools are available. The **Experiment Attributes** dialog box will open.

- a. Change “minutes” to “hours” in the **Units** box.
- b. Enter “250” in the **End at** box. The **Experiment Attributes** dialog box will appear as follows:



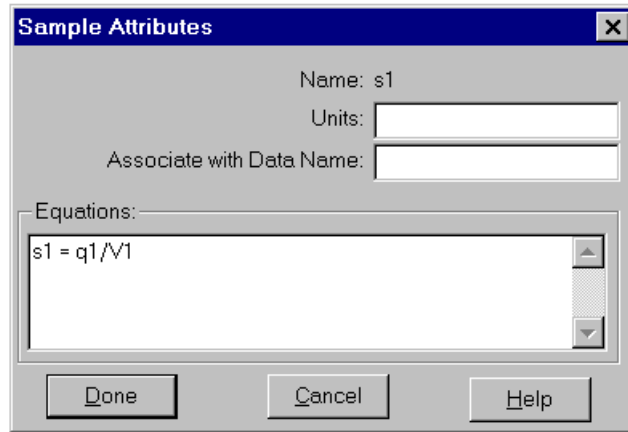
- c. Click **Done**.

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



- d. Click **Create**. Note the name “Gentamicin” appears under **Experiment** in the **SAAM II Toolbox**.
4. Create two samples.
 - a. In the **SAAM II Toolbox**, double-click **Sample** (this will lock the **Sample** tool so you can create multiple samples).
 - b. Click Compartment **q1**, then click on the **Drawing Canvas**. The sample **s1** will appear.
 - c. Click Compartment **q2**, then click on the **Drawing Canvas**. The sample **s2** will appear.
 - d. In the **SAAM II Toolbox**, click **Select** to unlock the **Sample** tool.

- e. Double-click **s1** to open the **Sample Attributes** dialog box.
- f. Edit the sample equation “ $s1 = q1$ ” to read “ $s1 = q1/V1$ ”. The **Sample Attributes** dialog box will appear as follows:



- g. Click **Done**.
 - h. Double-click **s2** to open the **Sample Attributes** dialog box.
 - i. Edit the sample equation “ $s2 = q2$ ” to read “ $s2 = q2/V2$ ”.
 - j. Click **Done**.
5. Create an input.

At the time of this study, gentamicin was routinely administered as an 80 mg intravenous infusion every 8 hours. The first simulation will be the response to a single administration of an 80 mg intravenous dose.

- 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. Select **Infusion** as the **Input Type**.
- e. Enter “80” in the **Constant Rate** box.
- f. Enter “0” in the **Event Start** box.
- g. Enter “1” in the **Event Stop** box.

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

Type	Initial	Constant	Start	Stop	Repeat Every	Nr. Repeats
Infusion	-	80.000	0.000	1.000	-	-

i. Click **Done**.

6. Enter the pharmacokinetic parameter equations.


You will now enter the following equations:

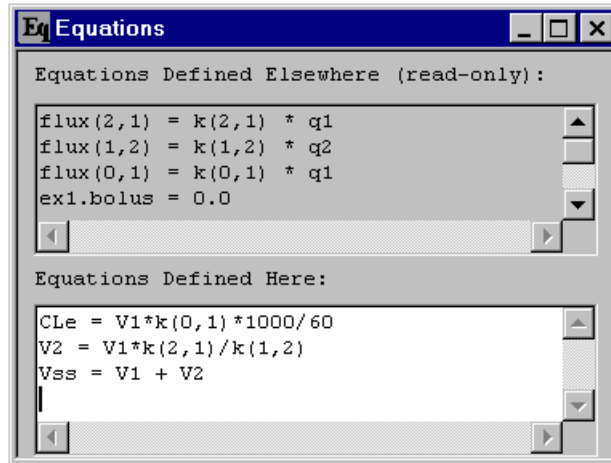
$$CL_e = V_1 * k_{(0,1)} * 1000/60$$


$$V_2 = V_1 * k_{(2,1)} / k_{(1,2)}$$

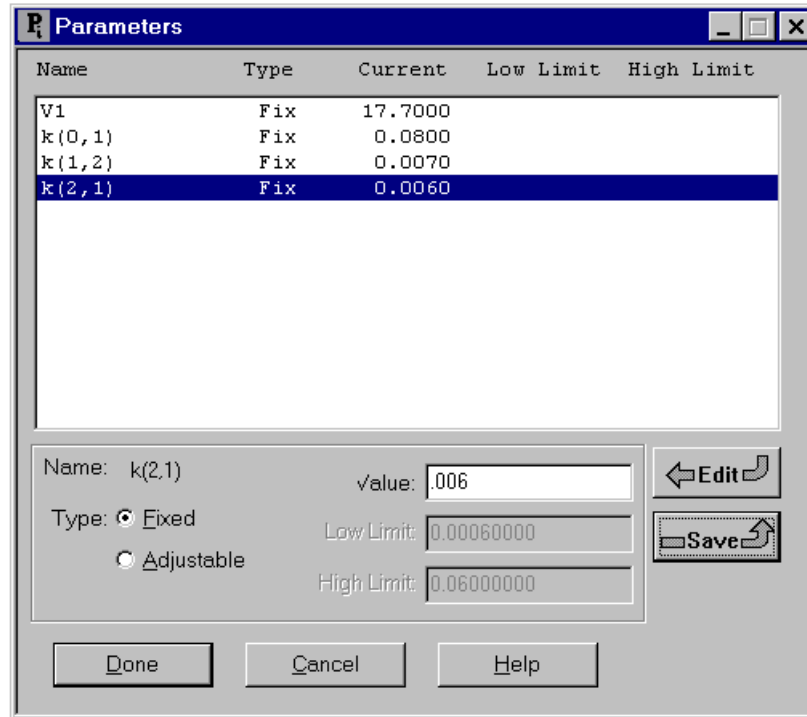
$$V_{ss} = V_1 + V_2$$

Multiplication by 1000/60 converts the units for clearance CL_e from L/hr to mL/min. The equation defining V_2 means V_2 is no longer a primary parameter that must be entered separately before you can solve.

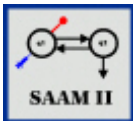
- In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar**, click **Equation** . The **Equations** dialog box will open.
- In the **Equations Defined Here** pane, type the above equations. The **Equations** dialog box will appear as follows:



- c. Close the **Equations** dialog box.
7. Enter the parameter values.
 - a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar**, click **Parameters** . The **Parameters** dialog box will open. If *V1* is not selected, double-click *V1* to select it.
 - b. Select **Fixed**. Enter “17.7” in the **Value** box, and click **Save**.
 - c. Double-click *k(0,1)*. Select **Fixed**. Enter “0.08” in the **Value** box, and click **Save**.
 - d. Double-click *k(1,2)*. Select **Fixed**. Enter “0.007” in the **Value** box, and click **Save**.
 - e. Double-click *k(2,1)*. Select **Fixed**. Enter “0.006” in the **Value** box, and click **Save**. The **Parameters Dialog** box will appear as follows:



- f. Click **Done**.
8. Solve your model and view the solution.
 - a. In the **Compute** menu, click **Settings**. The **Computational Settings** dialog box will open.
 - b. Enter “500” in the **Min. Nr. of Calculation Intervals** box. Click **Done**.



Minimum number of calculation intervals. The number of calculation intervals determines the resolution of your plots. Because this is a simulation study with no data, it is useful to set this number to its maximum of 500 in order to obtain better plots.





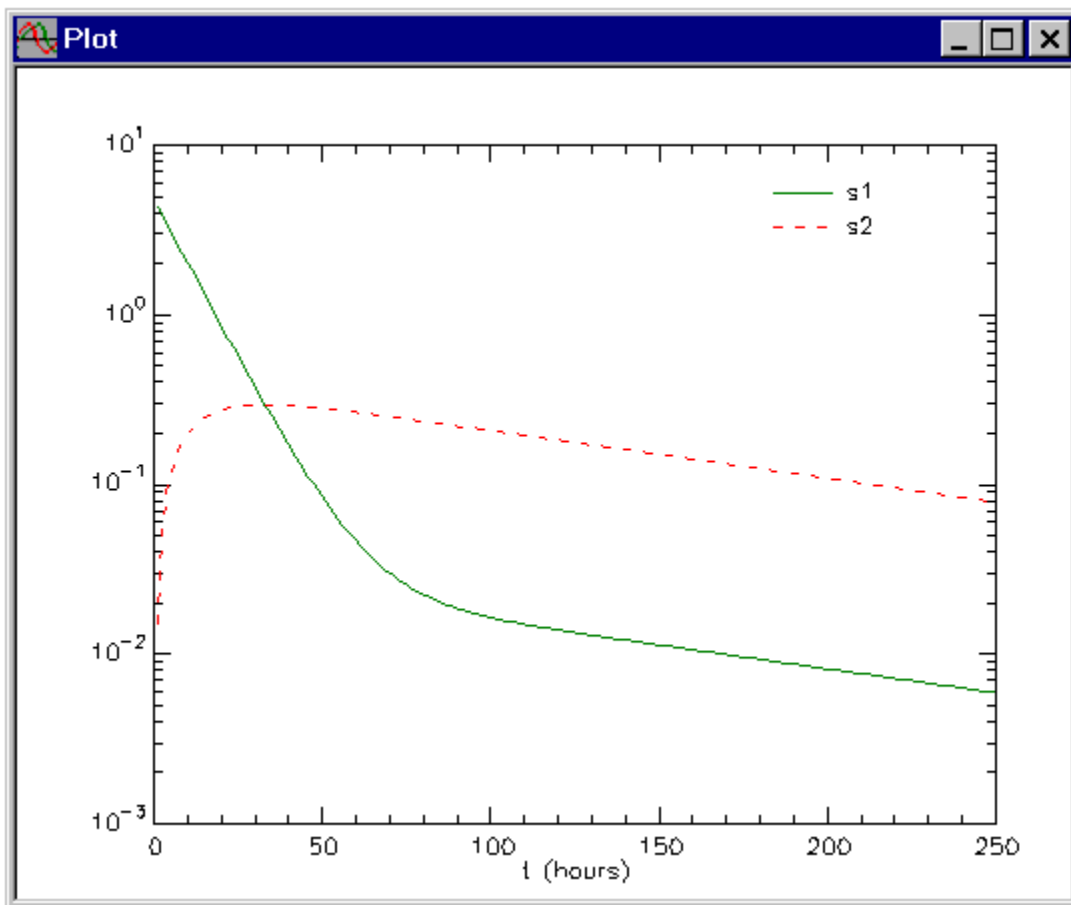
- c. In the **View** menu, select **Model Labels**, and click **Values**.



Model labels. When you select **Values** for your model labels, the current values of the parameters will appear associated with you model instead of the name $k(i,j)$.



- d. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar**, click **Solve** .
- e. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . The **Plot and Table Variables** dialog box will open.
- f. In the **Plot and Table Variables** dialog box, be sure the **List All Variables** is not selected so **s1** and **s2** will appear as your only choices.
- g. Click **s1** and **s2** to move these to the **Current Selection** pane.
- h. Click **Done**. The following plot will appear (if it does not appear in semilog mode, in the **View** menu click **Semilog**):



It can be seen that there is the expected biphasic plasma level-vs.-time curve and that the terminal phase is quite prolonged. We will demonstrate that this terminal phase represents slow re-distribution of gentamicin from the kidney to the ECF.

- i. Close the **Plot** window.

9. Create a duplicate model to illustrate flip-flop kinetics.

Flip-flop kinetics will now be illustrated by creating a second gentamicin model that is identical to the first model except for increased renal clearance of gentamicin.

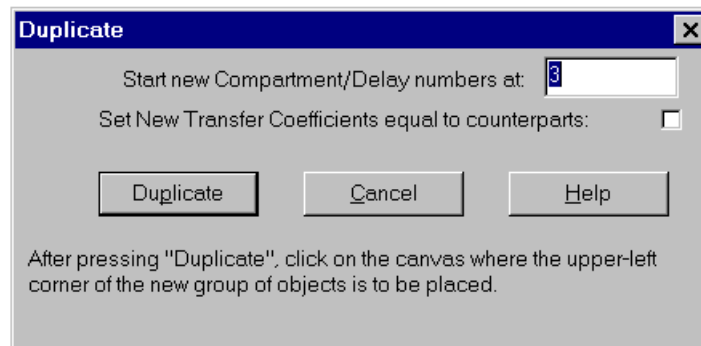
- a. While pressing the **CTRL** key, click in this precise order Compartments **q1** and **q2**, and **s2**, **s1** and **ex1**.



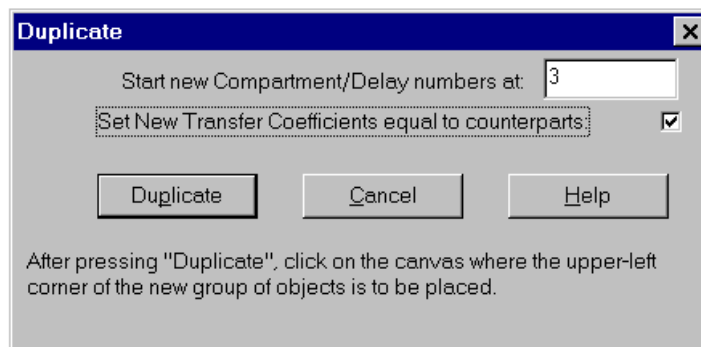
Model duplication. The precise order is necessary for the internal bookkeeping in SAAM II. If you follow this sequence, your model will appear as shown below. In general for duplication, you can simply select the model or portion of the model you want to duplicate, and proceed. When you do this, however, there may be occasions when you have to alter the model.



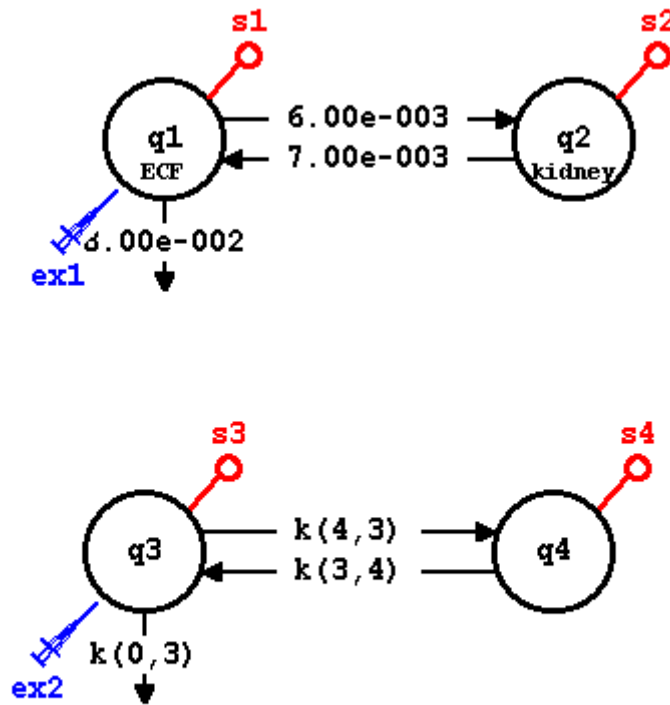
- b. In the **Edit** menu, click **Duplicate**. The **Duplicate** dialog box will open as follows:



- c. Select the **Set New Transfer Coefficients equal to counterparts** box. The **Duplicate** dialog box should appear as shown below:



- d. Click **Duplicate** and click the **Drawing Canvas** at the left margin below the initial system model. The following models should appear on the **Drawing Canvas** (you may need to move the duplicated model):

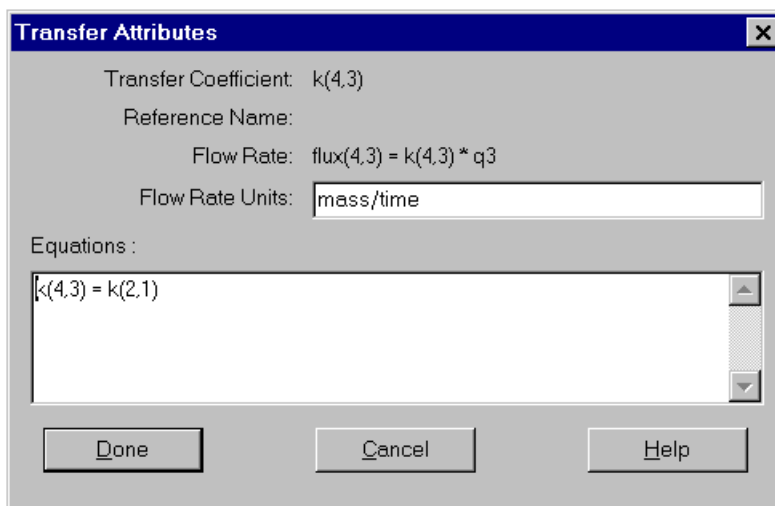


Notice in the figure that the top model has the parameter values while the lower model does not. This is because the lower model transfers are defined by equations.



Model duplication. The model duplication capability of the SAAM II Compartmental application is a convenient method by which several copies of a model can be created. In this case, the samples and inputs have been retained. However, the input specifications for **ex2** and the sample equations for **s3** and **s4** need to be written; these are not duplicated as part of the duplicate command. The precise order given in the instruction above was required in order for **s3** and **s4** to be attached to **q3** and **q4**. The effect of selecting the **Set New Parameters equal to counterparts** box is to predefine the rate constants of the second model equal to those of the first. For example,

if you double-click on $k(4,3)$, you will see the equation “ $k(4,3) = k(2,1)$ ”. This is shown in the **Transfer Attributes** dialog box:



- e. Double-click **s3** to open the **Sample Attributes** dialog box, and edit the sample equation “ $s3 = q3$ ” to read “ $s3 = q3/V3$ ”.
 - f. Click **Done**.
 - g. Double-click **s4** to open the **Sample Attributes** dialog box, and edit the sample equation “ $s4 = q4$ ” to read “ $s4 = q4/V4$ ”.
 - h. Click **Done**.
10. Create a duplicate input.
- a. Double-click **ex2** to open the **Exogenous Input** dialog box.
 - b. Select **Infusion** as the **Input Type**.
 - c. Enter “80” in the **Constant Rate** box.
 - d. Enter “0” in the **Event Start** box.
 - e. Enter “1” in the **Event Stop** box.
 - f. Click **Add**. The **Exogenous Input** dialog box will appear as follows:

Type	Initial	Constant	Start	Stop	Repeat Every	Nr. Repeats
Infusion	-	80.000	0.000	1.000	-	-

g. Click **Done**.

11. Modify the equations for the pharmacokinetic parameters.

You will now enter the following equations:

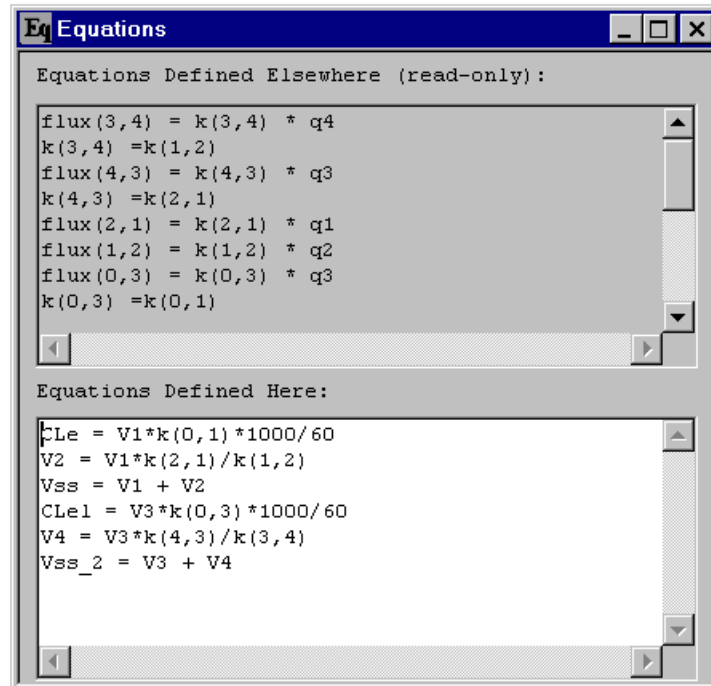
$$CL_{el} = V_3 * k_{(0,3)} * 1000/60$$

$$V_4 = V_3 * k_{(4,3)} / k_{(3,4)}$$


$$V_{ss_2} = V_3 + V_4$$

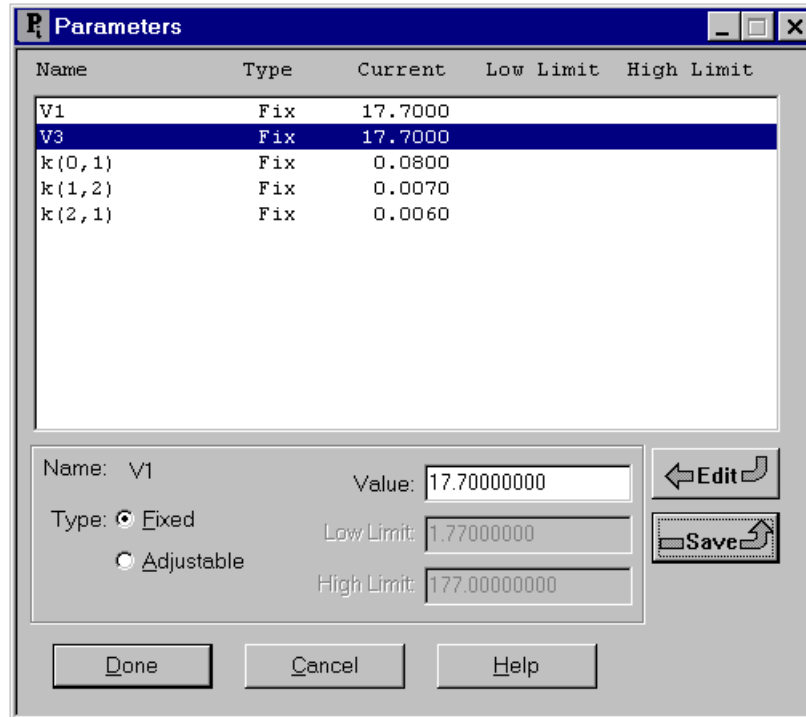
As before, multiplication by 1000/60 converts the units for CL_{el} from L/hr to mL/min. In addition, the equation for V_4 means V_4 is no longer a primary parameter that must be entered separately before you can solve.

- In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar**, click **Equation Eq**. The **Equations** dialog box will open.
- In the **Equations Defined Here** pane, type the above equations. The **Equations** dialog box will appear as follows:



Notice that in the **Equations Defined Elsewhere** pane, the equations making the rate constants of the duplicated model equal to their counterparts in the first model.

- c. Close the **Equations** dialog box.
12. Enter the new parameter values.
 - a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar**, click **Parameters** . The **Parameters** dialog box will open. If *V3* is not selected, double-click *V3* to select it (this is the only parameter that needs to be specified).
 - b. Select **Fixed**. Enter “17.7” in the **Value** box, and click **Save**. The **Parameters Dialog** box will appear as follows:



c. Click **Done**.

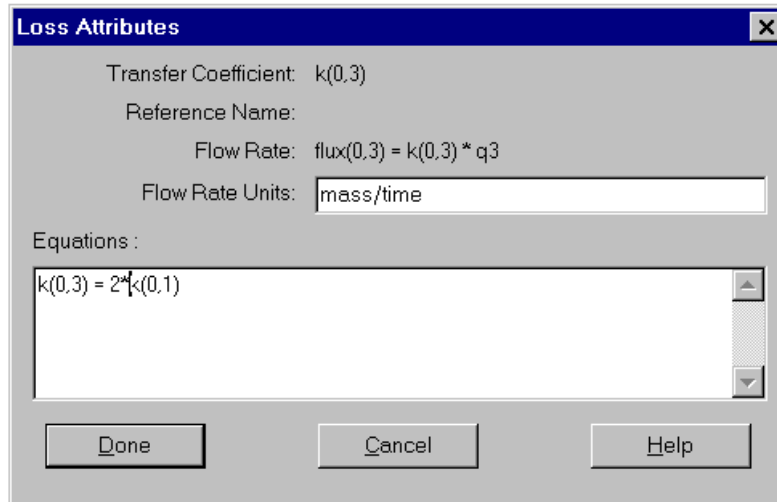
13. Save the study file.

This study file will be used in Part 3 of this case study. Thus it must be saved.

- In the **File** menu, click **Save As**.
- Enter “Gentamicin” in the **File name** box.
- Be sure you place the file in the proper **Save in** box.
- Click **Save**.



14. Double the loss from Compartment **q3**.

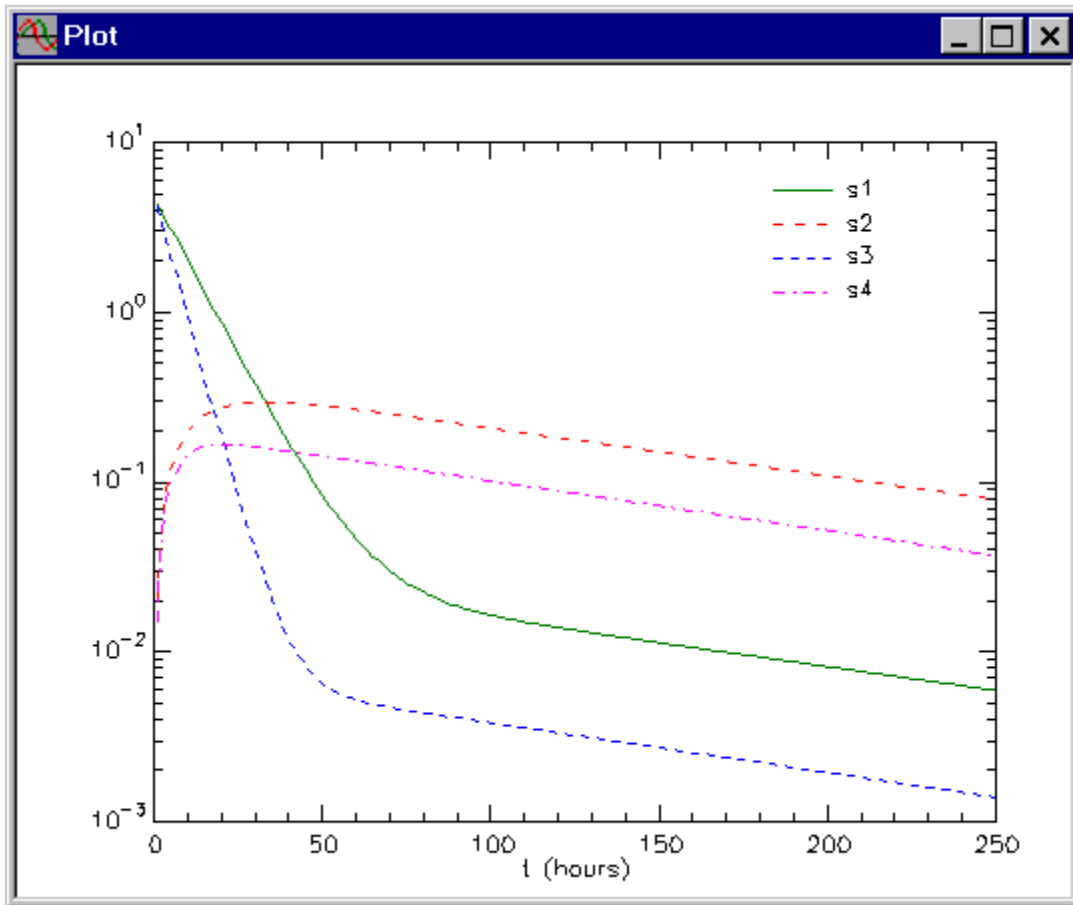
- Double-click $k(0,3)$. The **Loss Attributes** dialog box will open.
- Edit the equation “ $k(0,3) = k(0,1)$ ” to read “ $k(0,3) = 2*k(0,1)$ ”. The **Loss Attributes** dialog box will appear as follows:



- c. Click **Done**.

15. Solve your models and compare the solutions.

- 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. If the previous plot of **s1** and **s2** appears, in the **Set** menu, click **Plot/Table Variables** to open the **Plot and Table Variables** dialog box.)
- c. In the **Plot and Table Variables** dialog box, be sure the **List All Variables** is not selected so **s1**, **s2**, **s3** and **s4** will appear as your only choices.
- d. Press the **CTRL** key and click **s1**, **s2**, **s3** and **s4** to move these variables to the **Current Selection** pane.
- e. Click **Done**. The following plot will appear (if it does not appear in semilog mode, in the **View** menu click **Semilog**):



Note that doubling the renal clearance of gentamicin increases the slope of the initial phase of the plasma level-vs.-time curve but does not affect the slope of the second phase. This is called “flip-flop kinetics” because the elimination phase precedes the distribution phase. Note also that gentamicin accumulation by the kidney is also predicted to vary inversely with the level of renal function. This would be expected if gentamicin doses were not adjusted downwards for patients with impaired renal function (see reference 2 cited above).

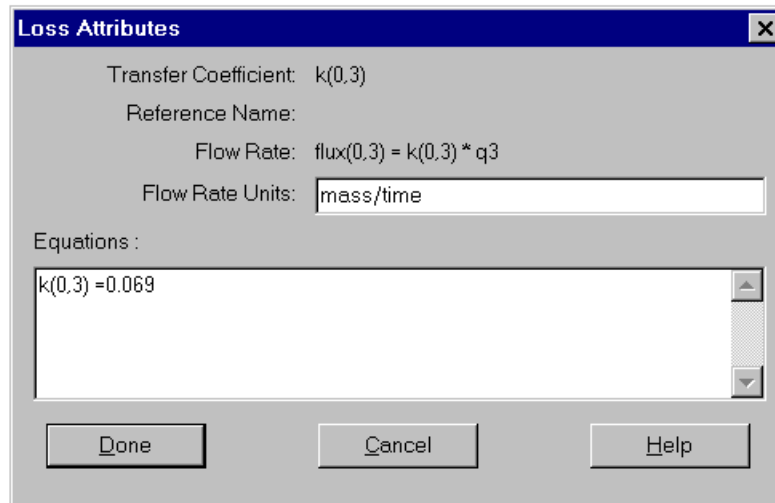
f. Close the **Plot** window.

Part 2. Pharmacokinetic basis for individual susceptibility to gentamicin nephrotoxicity.

In this part of the case study, we will compare renal accumulation of gentamicin in a patient who developed nephrotoxicity with that of our reference, non-toxic patient.

1. Enter parameter values characteristic of the toxic patient for the comparison with the nontoxic patient.

- a. Double-click $k(0,3)$ to open the **Loss Attributes** dialog box.
- b. Edit the equation “ $k(0,3) = 2*k(0,1)$ ” to “ $k(0,3) = 0.069$ ”. The **Loss Attributes** dialog box will appear as follows:




- c. Click **Done**.
- d. Double-click $k(4,3)$ to open the **Transfer Attributes** dialog box.
- e. Edit the equation “ $k(4,3) = k(2,1)$ ” to read “ $k(4,3) = 0.117$ ”.
- f. Click **Done**.
- g. Double-click $k(3,4)$ to open the **Transfer Attributes** dialog box.
- h. Edit the equation “ $k(3,4) = k(1,2)$ ” to read “ $k(3,4) = 0.014$ ”.
- i. Click **Done**.

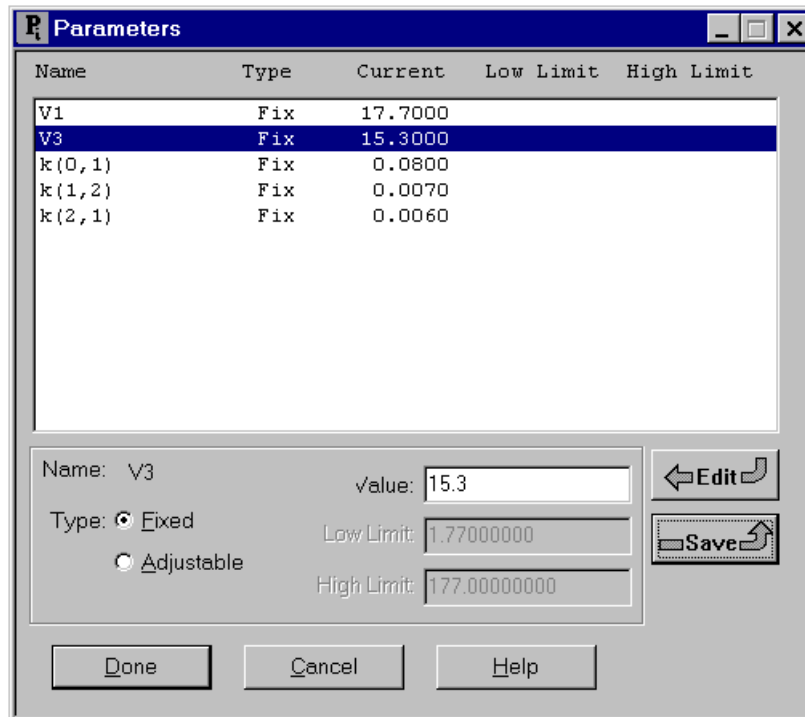




Equations for transfers and losses. The transfers $k(4,3)$ and $k(3,4)$, and the loss $k(0,3)$, are specified by equations. SAAM II will recognize this, and they will not appear in the **Parameters** window. Should you wish to change the values of any of these parameters, you will have to open the appropriate Transfer Attribute dialog box and manually change the value.

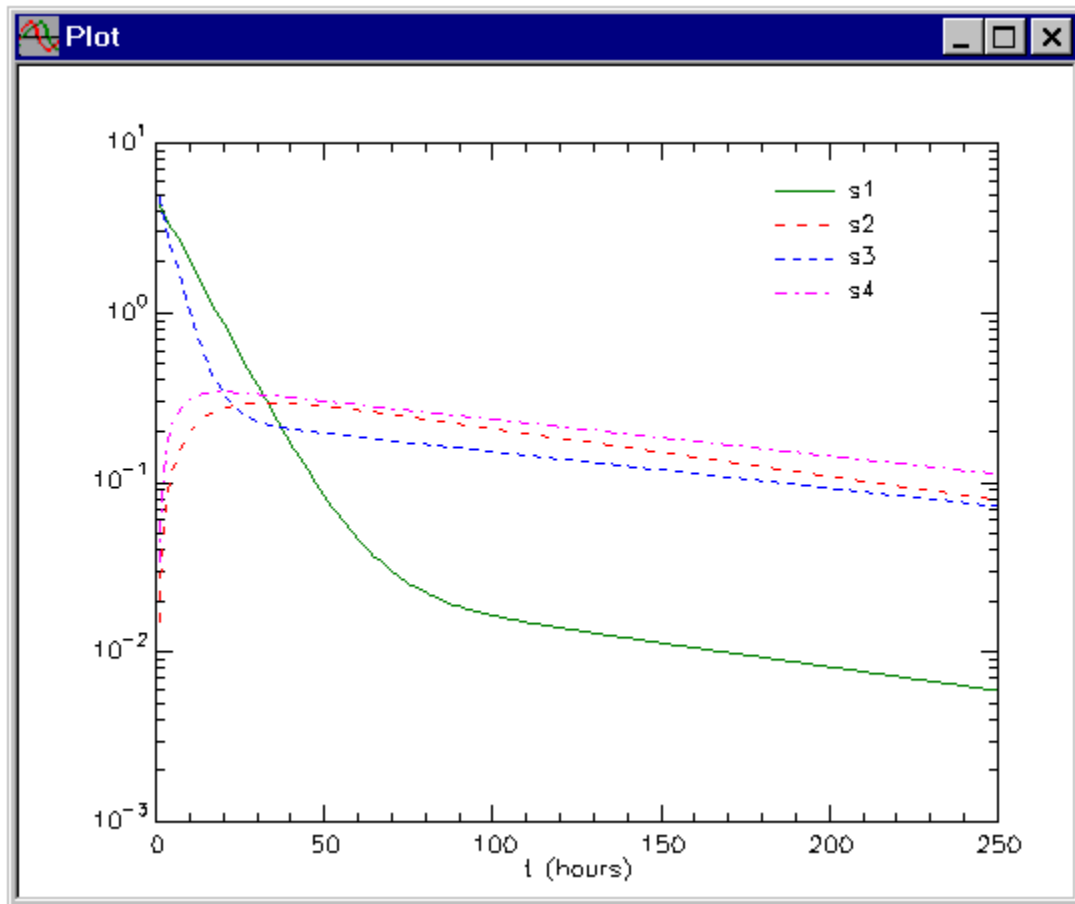


- j. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar**, click **Parameters** . The **Parameters** dialog box will open.

- k. Change the **Value** of V3 from “17.7” to “15.3”. The **Parameters** dialog box will appear as follows:

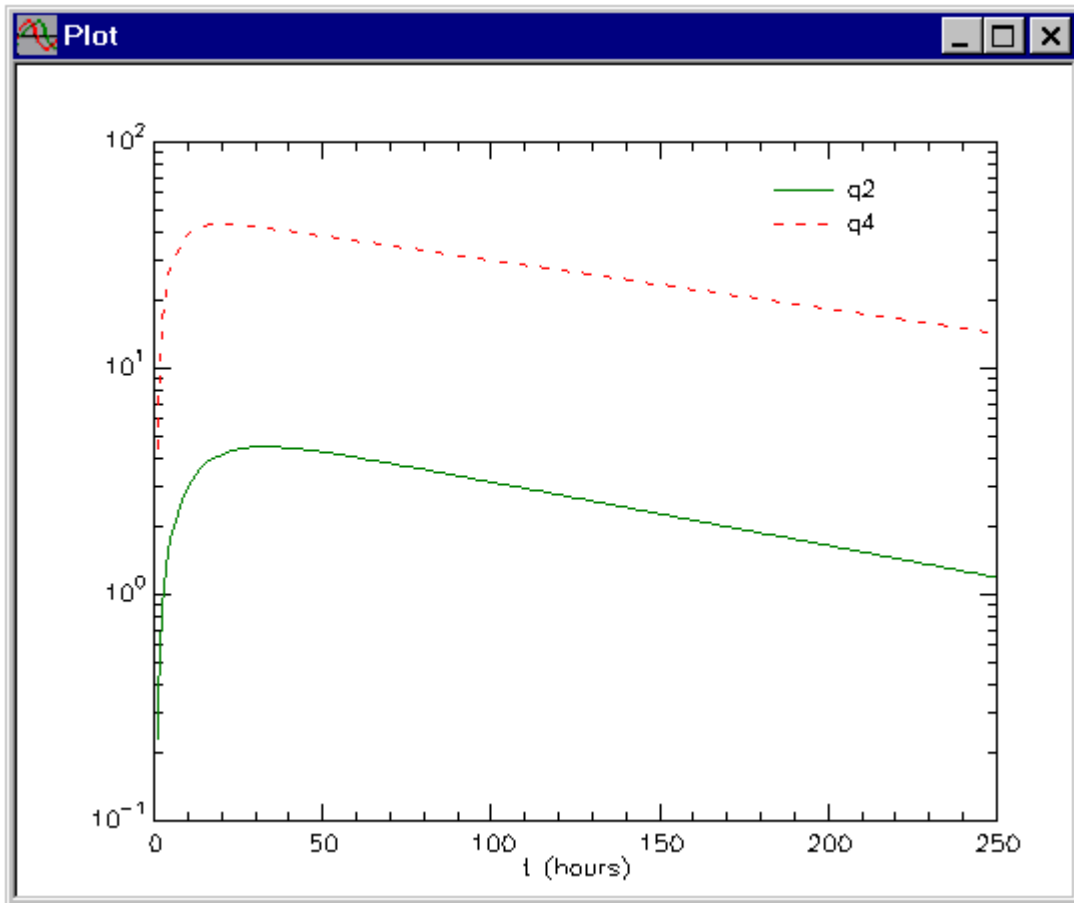


1. Click **Done**.
2. Solve your models and compare the solutions.
 - a. In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar**, click **Solve** .
 - b. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . The **Plot and Table Variables** dialog box will open. (If the previous plot of **s1**, **s2**, **s3** and **s4** appears, you may skip the next steps and go immediately to the plot below.)
 - c. In the **Plot and Table Variables** dialog box, be sure the **List All Variables** is not selected so **s1**, **s2**, **s4** and **s4** appear as your only choices.
 - d. Press the **CTRL** key and click **s1**, **s2**, **s3** and **s4** to move these to the **Current Selection** pane.
 - e. Click **Done**. The following plot will appear (if it does not appear in semilog mode, in the **View** menu click **Semilog**):



It is apparent that the toxic patient is maintaining much higher central compartment levels of gentamicin than the non-toxic patient, even though both received the same dose. The toxic patient also demonstrates slightly higher tissue concentrations of gentamicin. However, nephrotoxicity is presumably related to net kidney uptake of gentamicin. Proceed as follows to compare kidney uptake in the two patients:

- f. In the **Set** menu click **Plot/Table Variables**. The **Plot and Table Variables** dialog box will open.
- g. Select the **List All Variables** box.
- h. Click **q2**; this will replace the previous selections. Then press the **CTRL** key and click **q4** to move these to the **Current Selection** box.
- i. Click **Done**. The following plot should appear:



It is apparent since **q4** is larger than **q2** that there is far greater accumulation of gentamicin in the patient with nephrotoxicity than in the non-toxic patient. Note that the coefficient for gentamicin transfer from the ECF to the kidney is almost 20 times greater in the toxic than in the non-toxic patient.

- j. Close the **Plot** window.

Part 3. Impact of gentamicin dosing regimen on nephrotoxicity.

In this part of the case study, a comparison of the impact of different gentamicin dosing regimens on the renal accumulation of this drug will be made. The reference, non-toxic patient for these simulations, saved in *Gentamicin.stu*, will be used as the study file.

1. Open the SAAM II study file "**Gentamicin.stu**." Be sure the maximum number of calculation intervals is set at 500. If it is not, set it equal to 500.
2. Modify the inputs **ex1** and **ex2**.

A 7-day course of gentamicin therapy for both patients will be simulated. The reference patient will receive a 1-hour intravenous infusion of 240 mg every day; this is the dose-frequency regimen that was used in the study cited in reference 3

and that is used most frequently at this time. The comparison patient will receive a continuous infusion at a rate of 10 mg/hr.

- Double-click **ex1** to open the **Exogenous Input** dialog box for the reference patient.
- Enter “240” in the **Constant Rate** box (replacing “80”).
- Enter “24” in the **Repeat Every** box.
- Enter “6” in the **Nr. of Repeats** box.
- Click **Save**. The **Exogenous Input** dialog box will appear as follows:

Exogenous Input

Name: Reference: Units:

Type	Initial	Constant	Start	Stop	Repeat Every	Nr. Repeats
Infusion	-	240.000	0.000	1.000	24.000	6

Input Type:

Bolus

Infusion

Primed Infusion

Equation

Equation:

Initial Amount:

Constant Rate:

Event Start:

Event Stop:

Repeat Every:

Nr. of Repeats:

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

- Click **Done**.
- Double-click **ex2** to open the **Exogenous Input** dialog box for the comparison patient.
- Enter “10” the **Constant Rate** box.
- Enter “168” in the **Event Stop** box.
- Click **Save**. The **Exogenous Input** dialog box will appear as follows:

Exogenous Input

Name: Reference: Units:

Type	Initial	Constant	Start	Stop	Repeat Every	Nr. Repeats
Infusion	-	10.000	0.000	168.000	-	-

Input Type:

Bolus
 Infusion
 Primed Infusion
 Equation

Initial Amount:

Constant Rate:



Event Start:

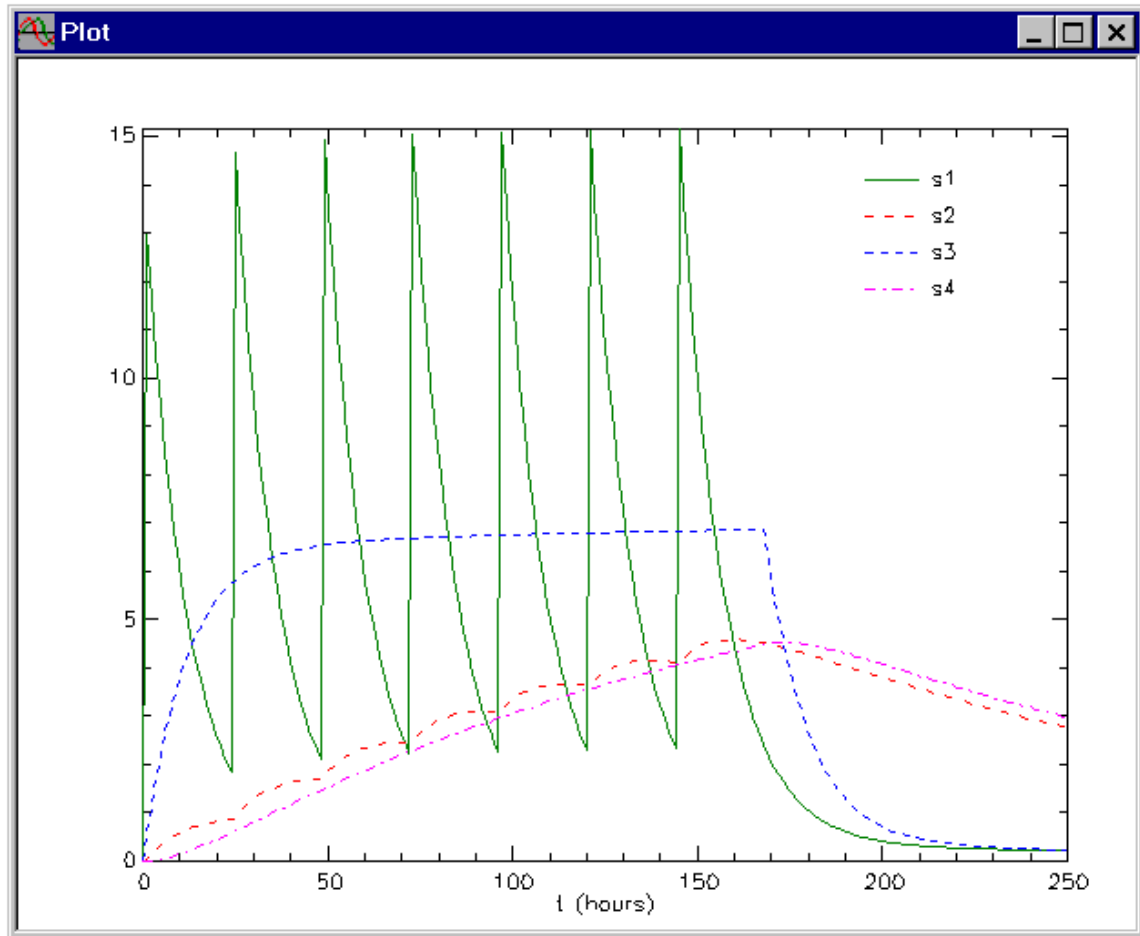
Event Stop:

Repeat Every:

Nr. of Repeats:

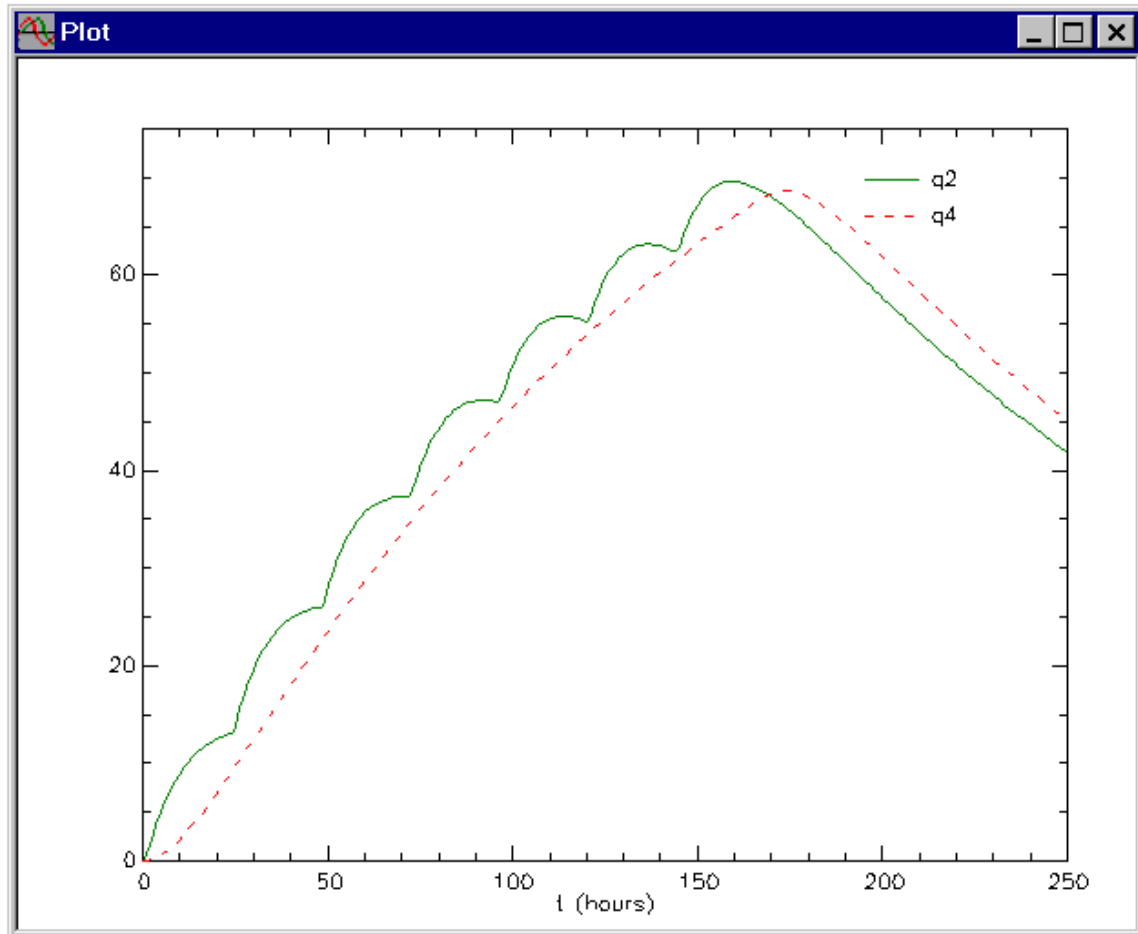
Equation:

- k. Click **Done**.
3. Solve your models and compare the solutions.
 - 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** . If a previous plot opens, in the **Set** menu, click **Plot/Table Variables** to open the **Plot and Table Variables**.
 - c. In the **Plot and Table Variables** dialog box, be sure the **List All Variables** is not selected so **s1**, **s2**, **s3** and **s4** will appear as your only choices.
 - d. Press the **CTRL** key and click **s1**, **s2**, **s3** and **s4** to move these to the **Current Selection** pane.
 - e. Click **Done**. The following plot will appear (if it does not appear in linear mode, in the **View** menu click **Semilog**):



It appears that apparent kidney *concentrations* of gentamicin are somewhat higher with intermittent than with continuous infusion therapy. However, toxicity in this case is most like the result of the total *amount* of gentamicin taken up by renal tubular cells. This can be evaluated as follows:

- f. In the **Set** menu click **Plot/Table Variables**. The **Plot and Table Variables** dialog box will open.
- g. Select the **List All Variables** box.
- h. Click **q2**. Then press the **CTRL** key and click **q4** to move these to the **Current Selection** pane.
- i. Click **Done**. The following plot should appear (the scale for the Y Axis maximum has been changed to "75"):



There is certainly no evidence that the continuous infusion of gentamicin results in less renal accumulation of this drug than when the same dose is given intermittently. Hence the pharmacokinetic model needs revision because it fails to account for this important experimental observation.

A likely explanation for this shortcoming of the model is that receptor mediated endocytotic uptake of gentamicin by renal tubule cells is saturable at high gentamicin concentrations. This could explain why intermittent dosing results in less renal tubule cell gentamicin uptake and consequent nephrotoxicity. .

To explore this possibility, we must move from a linear to a nonlinear model by writing the rate constants $k(2,1)$ and $k(4,3)$ to display Michaelis-Menten kinetics.

- j. **Close** the Plot window.

4. Write the transfer for renal uptake of gentamicin as a Michaelis-Menten process.
 - a. Double-click $k(2,1)$ to open the **Transfer Attributes** dialog box.
 - b. Type the equation “ $k(2,1)=V_{max}/(K_m+s_1)$ ” in the **Equation** pane. The **Transfer Attributes** dialog box will appear as follows:

Transfer Attributes

Transfer Coefficient: $k(2,1)$

Reference Name:

Flow Rate: $\text{flux}(2,1) = k(2,1) * q_1$

Flow Rate Units:

Equations :

Parameter Data

$k(2,1)$

Type:


Fixed

Adjustable

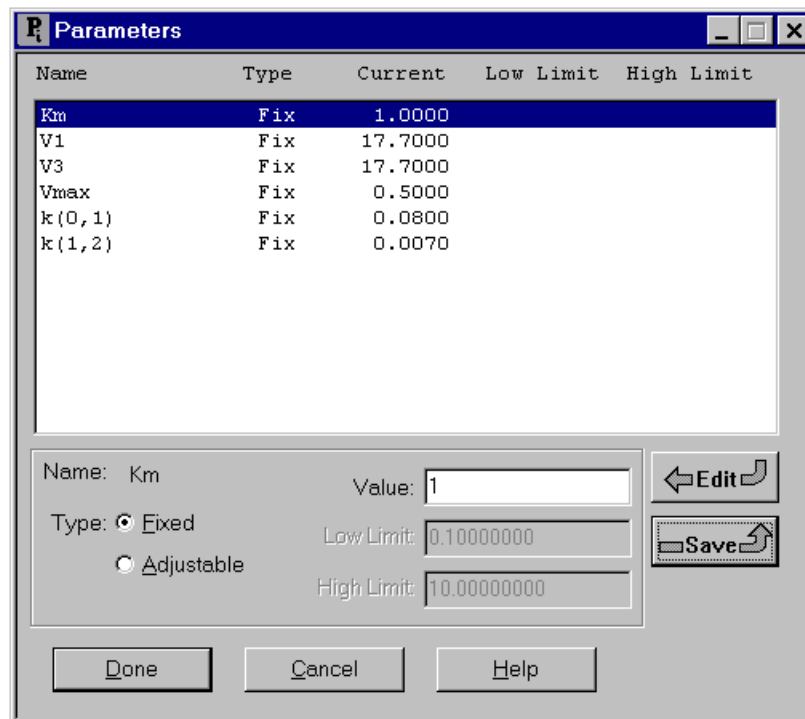
Current Parameter Value:


Low Limit:


High Limit:

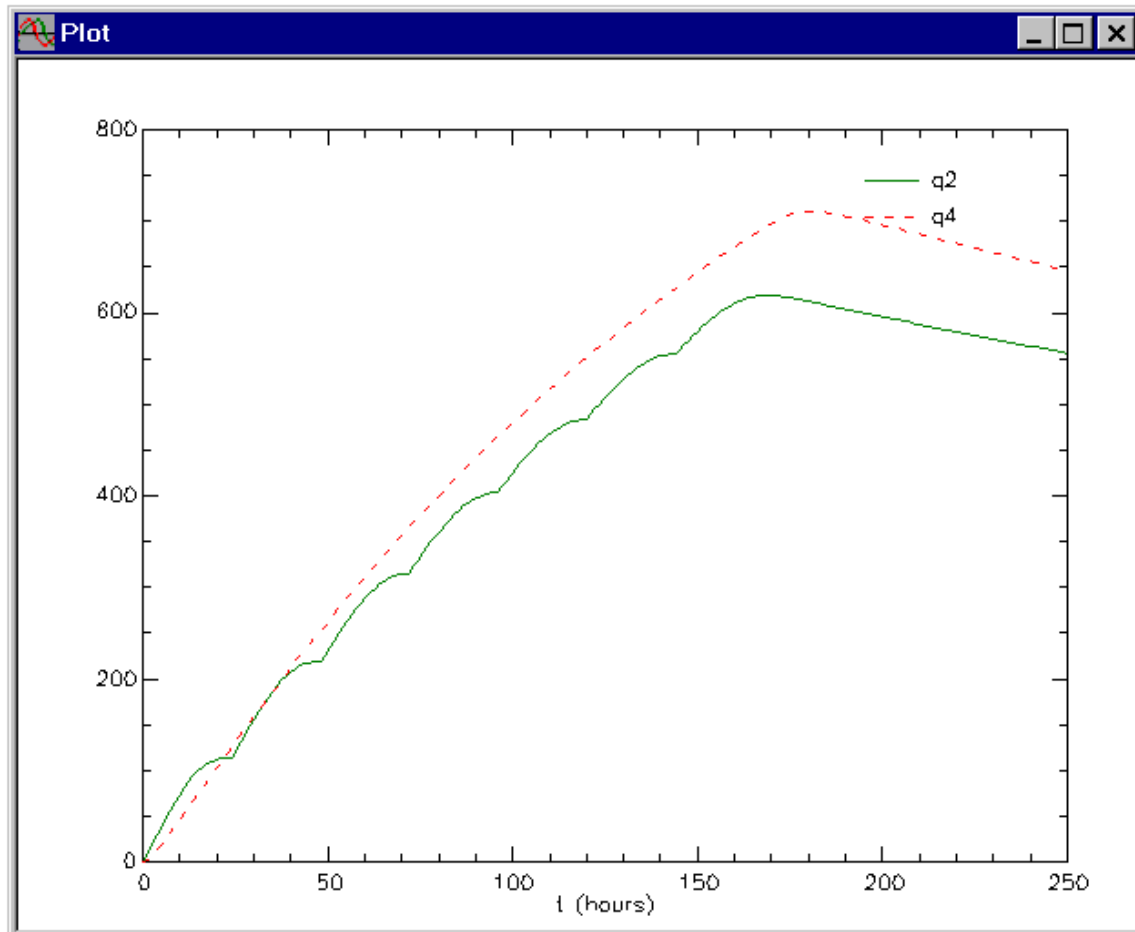
- c. Click **Done**.
 - d. Double-click $k(4,3)$ to open the **Transfer Attributes** dialog box.
 - e. Type the equation “ $k(4,3)=V_{max}/(K_m+s_3)$ ” in the **Equation** pane.
 - f. Click **Done**.
5. Enter the values for the Michaelis-Menten parameters V_{max} and K_m .
 - a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar**, click **Parameters** . The **Parameters** dialog box will open.

- b. Double-click K_m to select it.
- (1) Select the **Fixed** option.
 - (2) Enter “1” in the **Value** box.
 - (3) Click **Save**.
- c. Double-click V_{max} to select it.
- (1) Select the **Fixed** option.
 - (2) Enter “0.5” in the **Value** box.
 - (3) Click **Save**. The **Parameters** dialog box will appear as follows:



- d. Click **Done**.
5. Solve your models and compare the solutions.
- 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** . Since your last plot was of **q2** and **q4**, this plot should appear (in linear mode). If it does not, open the **Plot and Table Variables** dialog box, and select **q2** and **q4**. In the following plot the Y Axis maximum has been set to “800”.



Although the parameter estimates are arbitrary, this plot is consistent with experimental observations in that renal accumulation of equal administered gentamicin doses is greater when the drug is given by continuous intravenous infusion than when it is administered intermittently.

Examples of *dose-regiment dependency* in clinical medicine are not numerous and in most cases, including this one, their basis is poorly understood. This exercise is of heuristic value because it demonstrates that the observed dependence of nephrotoxicity on gentamicin dose regimen would not occur were it not for the fact that the renal tubular uptake of this drug is mediated by a saturable process.

Since this exercise was created, Lui and Bendayan have in fact demonstrated that gentamicin uptake by cultured renal epithelial cells is saturable with a V_{max} of 289 pmol/min-mg and a K_m of 1.26 mM. However, incorporation of these results into a more realistic model would require additional data, for example specification of actual gentamicin concentrations in renal tubular lumina. These concentrations can be expected to be considerably higher than the plasma concentrations used in this simulation exercise.

Liu, E. C.-C., Bendayan, R. "Gentamicin uptake by LLC_{PK}₁ cells: effect of intracellular and extracellular pH changes." Can. J. Physiol. Pharmacol. 1998,76:155-60.

You may now **Quit** the **SAAM II Compartmental** application. You may save the study file for future reference if you wish.

Essential Points to Remember

- Simulations can provide important insight in understanding pharmacokinetic systems and the therapeutic implications of different pharmacokinetic results and drug dosage regimens. The simulations in this case are particularly helpful in providing a pharmacokinetic rationale for clinical observations that gentamicin nephrotoxicity is dose-regimen dependent.
- The model duplication feature in SAAM II is a powerful tool that can be used in conducting comparisons of different simulated results.
- Flip-flop kinetics can reflect a slow drug distribution rate as well as slow absorption, e.g. from an extended release formulation.
- Michaelis Menten kinetics can be incorporated in drug intercompartmental transfer processes as well as in modeling drug elimination.