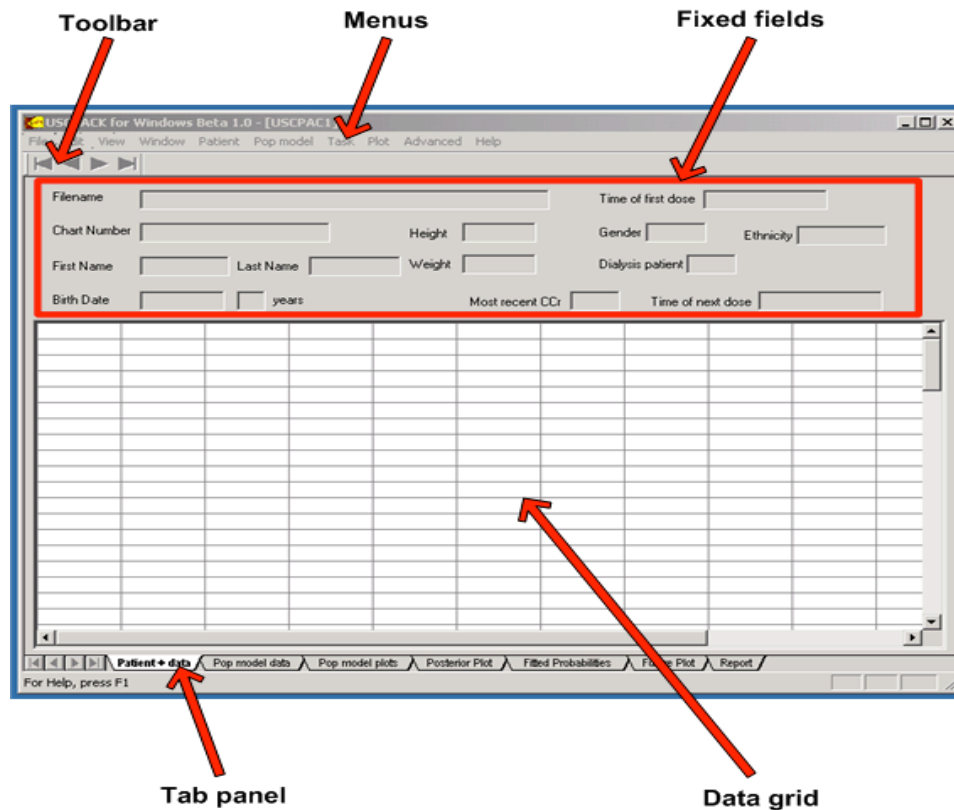


## Using RightDose

In this chapter we explain the structure and use of RightDose, with examples.

### General description

The image below shows the view you get when you start RightDose. The actual view is called the **Patient+data** view and will be explained in detail later.



The arrows in the **Toolbar** can be used when stepping through a series of plots over time. Pressing the leftmost triangle button when a time-series is displayed will take you to the start of the series. The rightmost button takes you to the end. The two middle buttons take you one step forward or backward in the time series.

You will have several **Menu** options available at any time. Use the menus to load new patients, select drug population models, change plots, and so on. The different menu options are in general connected to the various views you will get, and they will be explained in detail later.

The views may have **Fixed fields**, giving you information about the patient or the population model. You will not be able to edit these fields directly.

The different views available are shown in the **Tab panel**. The name of the view **Patient+data, Pop model data, Pop model plots, ...**, is shown on the tab. Pressing one of the tabs takes you to the corresponding view.

Some views may also have a **Data grid**. The grid is used to display time-dependent data, detailed information about the population model, and the suggested doses. Some data entry forms also use a **Data grid**. The grid can best be thought of as a spreadsheet. The fields in the **Data grid** can also easily be copied to the clipboard and into programs like Microsoft Excel. Simply select the desired fields and use **Copy** in the Edit menu.

## The Patient+data view

### The display

This view has two distinct parts, the fixed fields and a data grid. Go ahead and load a patient by selecting **Patient** and **Load patient** from the menu. The information displayed is either read directly from the file, or it is computed based on data read from the file. If you load the patient *SANCH.MB*, for example, the fixed fields of your patient view will look like this

Filename	C:\winUSCPACK\Patients\SANCH.MB			Time of first dose	08/01/85 00:00:00		
Chart Number	123	Height	69.00 in	Gender	Male	Ethnicity	Not in use
First Name	ed	Last Name	sanch	Weight	70.30 kg	Dialysis patient	NO
Birth Date	10/29/28	57	years	Most recent CCr	4.00	Time of next dose	08/23/85 10:00:00

The field label, to the left of each field, tells you what information is shown in each field. All dates will be shown in the format you have selected when installing your operating system. This means that if you selected the US locale dates will be given month/day/year, a European locale will show the dates as day/month/year.

Note that the **Ethnicity** field is not used at the moment. This field will be used when our model will take into account the ethnic group of the patient.

The data grid is filled with data if and only if the patient has a past history of drug doses and measured serum concentrations. The grid will be empty if the patient file contains no information. The patient we have loaded, *SANCH.MB*, has a past history.

Dose	Route	Date	Time	Time	Weight	Descriptor	IV inf.Time	Dose Interv	IV Rate	Amount
[#]	[IM/IV/PO]	[locale]	[hh:mm:ss]	[Hours]	[kg]	[CCr,Cl]	[Hours]	[Hours]	[mg/Hour]	[mg]
1	IV	08/01/85	00:00:00	0.00	70.30	3.00	0.500	19.33	200.00	100.0
2	IV	08/01/85	19:20:00	19.33	70.30	53.00	0.100	3.00	0.00	0.00
3	IV	08/01/85	22:20:00	22.33	70.30	3.00	0.100	1.00	0.00	0.00
4	IV	08/01/85	23:20:00	23.33	70.30	3.00	0.500	72.00	100.00	50.00
5	IV	08/04/85	23:20:00	95.33	70.30	3.00	0.500	14.77	220.00	110.0
6	IV	08/05/85	14:06:00	110.10	70.30	53.00	0.100	3.00	0.00	0.00
7	IV	08/05/85	17:06:00	113.10	70.30	3.00	0.100	5.50	0.00	0.00
8	IV	08/05/85	22:36:00	118.60	70.30	3.00	0.500	35.50	160.00	80.00
9	IV	08/07/85	10:06:00	154.10	70.30	53.00	0.100	3.00	0.00	0.00
10	IV	08/07/85	13:06:00	157.10	70.30	3.00	0.100	5.00	0.00	0.00
11	IV	08/07/85	18:06:00	162.10	70.30	3.00	0.500	38.00	200.00	100.0
12	IV	08/09/85	08:06:00	200.10	70.30	3.00	0.500	52.90	200.00	100.0
13	IV	08/11/85	13:00:00	253.00	70.30	53.00	0.100	3.00	0.00	0.00
14	IV	08/11/85	16:00:00	256.00	70.30	3.00	0.100	66.00	0.00	0.00
15	IV	08/14/85	10:00:00	322.00	70.30	53.00	0.100	4.00	0.00	0.00
16	IV	08/14/85	14:00:00	326.00	70.30	3.00	0.100	56.60	0.00	0.00
17	IV	08/16/85	22:36:00	382.60	70.30	3.00	0.500	39.40	200.00	100.0

The data shown in the grid consists of three sections: the doses given, the measured drug concentrations, and the serum creatinine. Use the scroll bar to the right to scroll up and down between the three sections.

The doses part consists of 11 columns

- 1 The dose number, starting at 1.
- 2 The route by which the dose was given, this can be one of PO, IM, or IV.
- 3 The date the dose was given, shown according to the selected locale.
- 4 The time the dose was given, shown hour:minutes:seconds
- 5 Time into the dosage regimen, starting at 0 hour for the start of the first dose
- 6 The weight of the patient at the time the dose was given
- 7 The creatinine clearance at the time the dose was given
- 8 The IV infusion time, the duration of the infusion if the dose was given IV. Doses given by other routes will have a 0 in this column.
- 9 The dose interval between the start of this dose to the start of the next.
- 10 The IV infusion rate. Doses given by other routes will have a 0 in this column.
- 11 The drug amount given.

Scrolling down to the serum levels, you should see something like this if your patient file has a record of serum levels;

Level	Date	Time	Time	After Do	After Dose	Level
[Num]	[locale]	[hh:mm:ss]	[Hours]	[Numbe	[Hours]	[mcg/ml]
1	08/05/85	00:48:00	96.80	5	1.47	5.00
2	08/05/85	12:18:00	108.30	5	12.97	3.00
3	08/05/85	22:24:00	118.40	7	5.30	1.90
4	08/06/85	00:04:00	120.07	8	1.47	5.30
5	08/06/85	22:36:00	142.60	8	24.00	2.90
6	08/10/85	13:36:00	229.60	12	29.50	2.40
7	08/18/85	16:00:00	424.00	19	0.50	1.20

There are 7 columns displaying information about the serum levels. Most of them correspond to the fields used for displaying the dosage information.

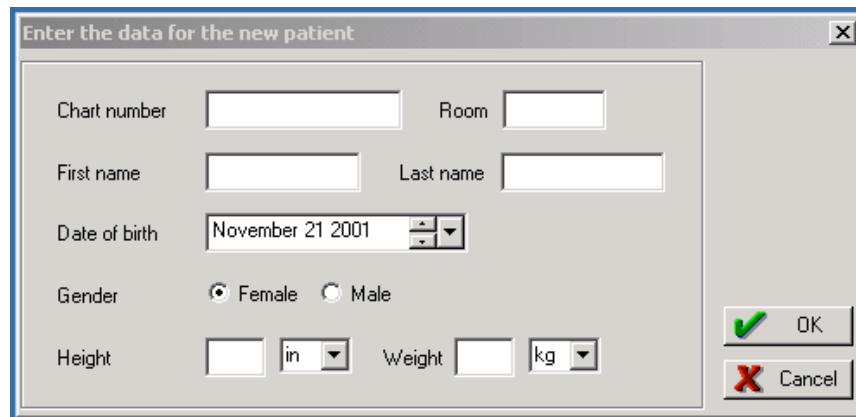
- 1 The serum level number, starting at 1.
- 2 The date the sample was obtained, shown according to the selected locale.
- 3 The time the sample was obtained, shown hour:minutes:seconds.
- 4 The time into the regimen, starting when the first dose was given.
- 5 The dose number just before this serum sample.
- 6 The time after the previous dose number.
- 7 The measured concentration.

## The controls

This section describes the menus and controls that can be used in combination with the patient view.

All options available for the patient view are accessible from the **Patient** menu option. By selecting this menu option the view will automatically switch to the **Patient+data** view. There are several options available for this menu selection, **New patient, Load patient**.... The options may be disabled based on your previous selections. You cannot save a patient's data if you have no patient loaded and so on.

Selection of the **New patient** option. You will be presented here with a dialog box allowing you to enter the information about your new patient.



The dialog box is titled "Enter the data for the new patient" and contains the following fields and controls:

- Chart number:
- Room:
- First name:
- Last name:
- Date of birth:  (calendar icon)
- Gender:  Female  Male
- Height:   (dropdown)
- Weight:   (dropdown)
- OK button:  (with green checkmark icon)
- Cancel button:  (with red X icon)

Some of the fields in this dialog box are optional. The ones you are required to fill in are the date of birth, the gender, the height, and weight. All of these values will be needed when analyzing data and/or computing a new dosage regimen. Click **OK** to use the patient data. The fixed field will now look like this. It even keeps the typo "FRank", which should be "Frank".

Filename	<input type="text"/>	Time of first dose	<input type="text"/>
Chart Number	<input type="text" value="X12345"/>	Height	<input type="text" value="180.00 cm"/>
Gender	<input type="text" value="Male"/>	Ethnicity	<input type="text" value="Not in use"/>
First Name	<input type="text" value="FRank"/>	Last Name	<input type="text" value="Hansen"/>
Weight	<input type="text" value="200.00 lb"/>	Dialysis patient	<input type="text" value="NO"/>
Birth Date	<input type="text" value="08/29/73"/>	<input type="text" value="28"/> years	Most recent CCr <input type="text"/>
		Time of next dose	<input type="text"/>

Any information previously present in the data grid will be removed. At this time a new patient file based on the information you entered in the dialog box has been created. Note that this patient only exists in the program. It has not yet been saved to a permanent file on disk.

The **Load patient** option allows you to load a patient from a file. The program recognizes three different patient types, the default file extensions are

- 1 **.MB**. This is an old format, and is a plain text file. It has been used in the previous DOS version of RightDose (USC\*PACK).
- 2 **.MB2**. This is an updated version of the old .MB format. The file is also a plain text file, but with additional fields.
- 3 **.USC**. This is a completely new format. .USC files are binary files that can contain information about multiple drugs given to the same patient. Note that even though this format is fully supported the current version of RightDose does not use the extended options provided by this format.

## The Pop model data view

### The display

The **Pop model data** view is very similar to the **Patient+data** view. They both have fixed fields and a data grid. This view will contain information about the selected drug population PK model. The top portion consists of a series of fixed fields.

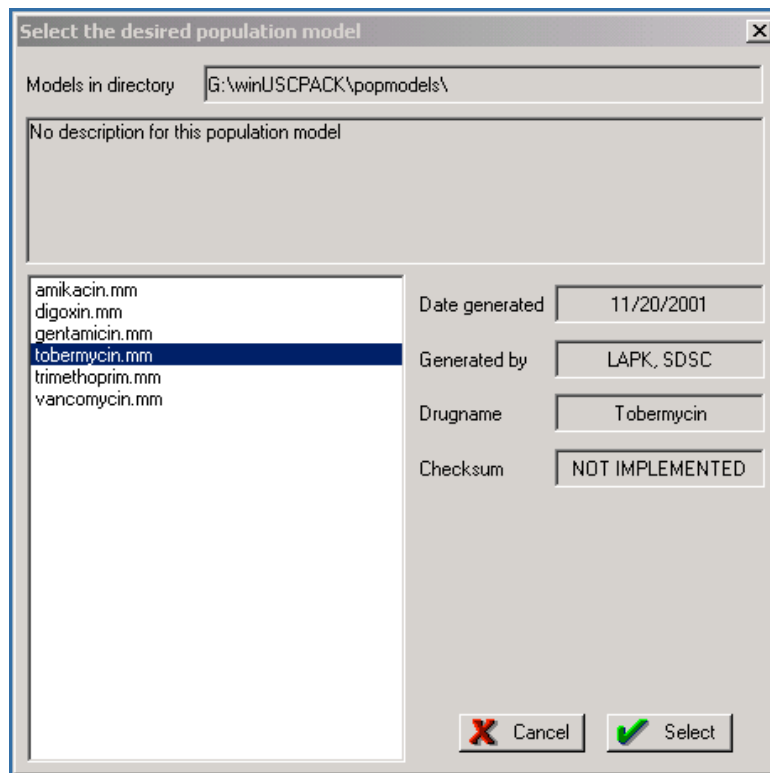
<b>General information</b>		<b>Model information</b>		<b>Ranges</b>											
Drugname	<input type="text"/>	Bioavailability	<input type="checkbox"/> %	<table border="1"> <tr> <td colspan="2">Usual ranges</td> </tr> <tr> <td>Peak (Central)</td> <td><input type="text"/> - <input type="text"/></td> </tr> <tr> <td>Trough (Central)</td> <td><input type="text"/> - <input type="text"/></td> </tr> <tr> <td>Peak (Peripheral)</td> <td><input type="text"/> - <input type="text"/></td> </tr> <tr> <td>Trough (Peripheral)</td> <td><input type="text"/> - <input type="text"/></td> </tr> </table>		Usual ranges		Peak (Central)	<input type="text"/> - <input type="text"/>	Trough (Central)	<input type="text"/> - <input type="text"/>	Peak (Peripheral)	<input type="text"/> - <input type="text"/>	Trough (Peripheral)	<input type="text"/> - <input type="text"/>
Usual ranges															
Peak (Central)	<input type="text"/> - <input type="text"/>														
Trough (Central)	<input type="text"/> - <input type="text"/>														
Peak (Peripheral)	<input type="text"/> - <input type="text"/>														
Trough (Peripheral)	<input type="text"/> - <input type="text"/>														
Provider	<input type="text"/>	Active salt fraction	<input type="text"/>												
Model file	<input type="text"/>														
				<table border="1"> <tr> <td colspan="2">Routes, compartments</td> </tr> <tr> <td>IV <input type="checkbox"/></td> <td>Peripheral <input type="checkbox"/></td> </tr> <tr> <td>IM <input type="checkbox"/></td> <td>Central <input type="checkbox"/></td> </tr> <tr> <td>PO <input type="checkbox"/></td> <td>Absorptive <input type="checkbox"/></td> </tr> </table>		Routes, compartments		IV <input type="checkbox"/>	Peripheral <input type="checkbox"/>	IM <input type="checkbox"/>	Central <input type="checkbox"/>	PO <input type="checkbox"/>	Absorptive <input type="checkbox"/>		
Routes, compartments															
IV <input type="checkbox"/>	Peripheral <input type="checkbox"/>														
IM <input type="checkbox"/>	Central <input type="checkbox"/>														
PO <input type="checkbox"/>	Absorptive <input type="checkbox"/>														

The fixed fields consist of three groups. The left gives **General information** about the population model: The name of the drug, the name of the group that made the population model, the bioavailability, and the active (salt) fraction. The center block, **Model information**, provides information about the compartments used in the model and the allowable routes. The target **Ranges** block displays the common ranges for the peak and trough goals usually used with this drug.

The data grid portion of this view will contain statistical information about the population model and the matrix containing the parameter description support points and their corresponding probabilities.

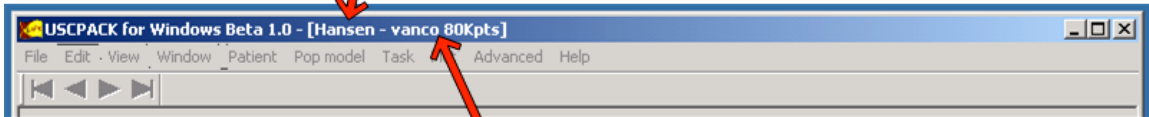
## The controls

Selecting **Pop model** on the menu bar will automatically switch the view to the **Pop model data**. The sub options for this menu are limited to one: **Load population model**. Select this option and you will get a dialog box asking you to select a drug population model.



Select the correct drug population model and press **OK**. If you selected Vancomycin, the **Pop model data** view should look like the one below. Take a look at the window frame at the top

Patient name



Population model

It now contains both the **Patient name**, we entered “FRank Hansen”, and the name of the **Population name** “vanco 80kpts”. The names shown in this frame are always up to date, so you can always take a look at it if you are uncertain about which patient or population model you are working on.

Statistical information

Name	Mean	Median	Mode	S.D.	Min	Max
KCP	1.13e+000	9.08e-001	9.08e-001	9.87e-001	0.00e+000	4.00e+000
KPC	4.69e-001	4.41e-001	4.41e-001	2.96e-001	0.00e+000	1.10e+000
KS	4.38e-003	3.71e-003	1.42e-003	3.03e-003	0.00e+000	1.50e-002
VS	2.68e-001	2.17e-001	1.35e-001	1.92e-001	0.00e+000	1.00e+000
KI	2.04e-003	2.04e-003	2.04e-003	0.0	2.04e-003	2.04e-003

Propability	KCP	KPC	KS	VS	KI
5.93e-002	9.30e-001	4.42e-001	6.10e-003	1.32e-001	2.04e-003
3.61e-002	1.69e-001	2.19e-001	6.02e-004	7.87e-001	2.04e-003
3.40e-002	2.92e-001	1.10e-001	1.36e-003	3.27e-001	2.04e-003
3.38e-002	2.63e-001	9.99e-002	1.13e-003	4.56e-001	2.04e-003
3.35e-002	5.13e-001	6.98e-001	1.36e-003	2.72e-001	2.04e-003
3.34e-002	1.65e-001	2.66e-001	1.38e-003	4.93e-001	2.04e-003
3.33e-002	3.35e+000	8.07e-001	7.4e-003	5.92e-002	2.04e-003
3.33e-002	4.46e-001	2.46e-001	2.85e-003	2.95e-001	2.04e-003
3.33e-002	5.63e-001	2.31e-001	5.17e-003	2.45e-001	2.04e-003
3.33e-002	1.45e+000	6.01e-001	8.80e-003	1.35e-001	2.04e-003
3.33e-002	1.43e-001	6.35e-001	5.05e-004	3.27e-001	2.04e-003

Full matrix

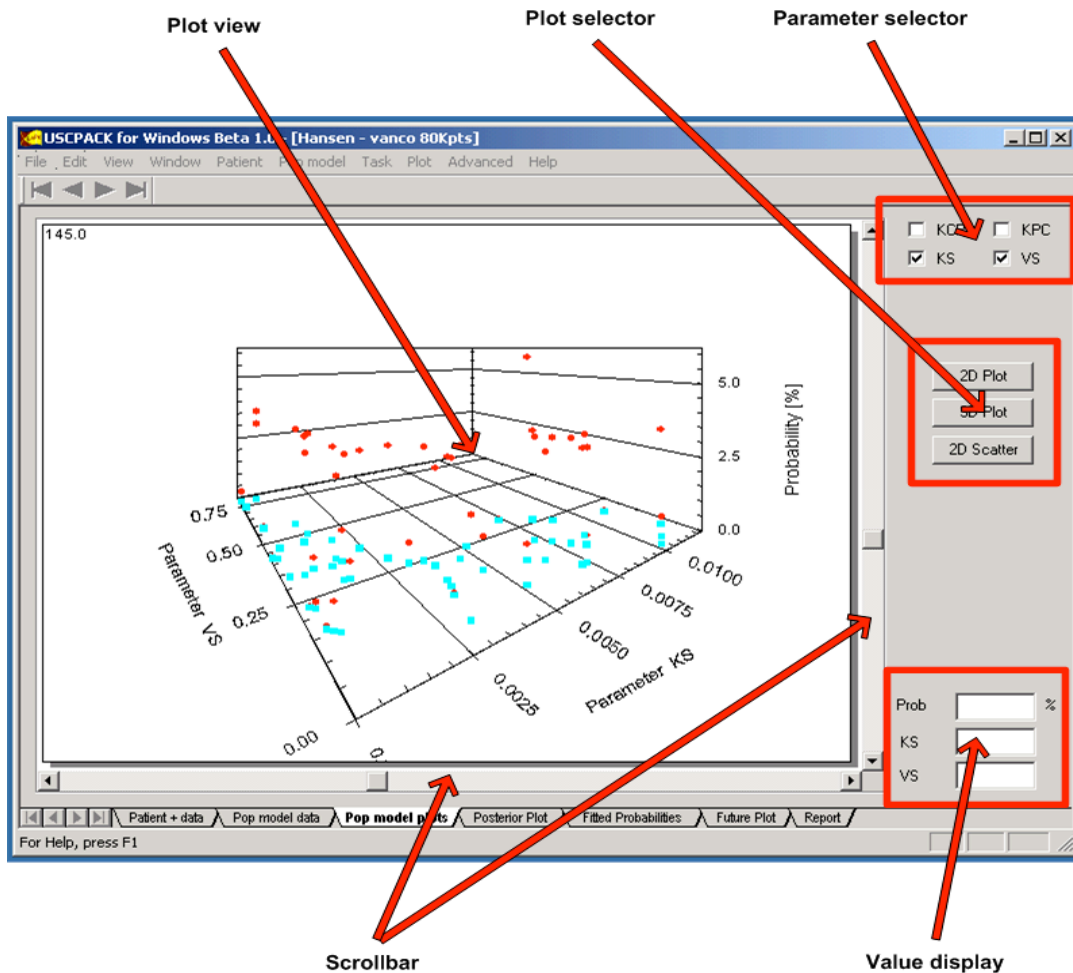
As mentioned the data grid for the **Pop model data** can be separated into two parts, one for the **Statistical information**, and one for the **Full matrix**.

## The Pop model plots view

This view is used to examine the data making up the population model in more detail. It will display the plots when you have selected a drug population model.

## The display

This is the first in a series of plots. When a population model is loaded and you switch to this tab, the default display is a 3D plot showing the parameters KS and VS if they are present in your population model. If they are not, the two first parameters will be selected and displayed.



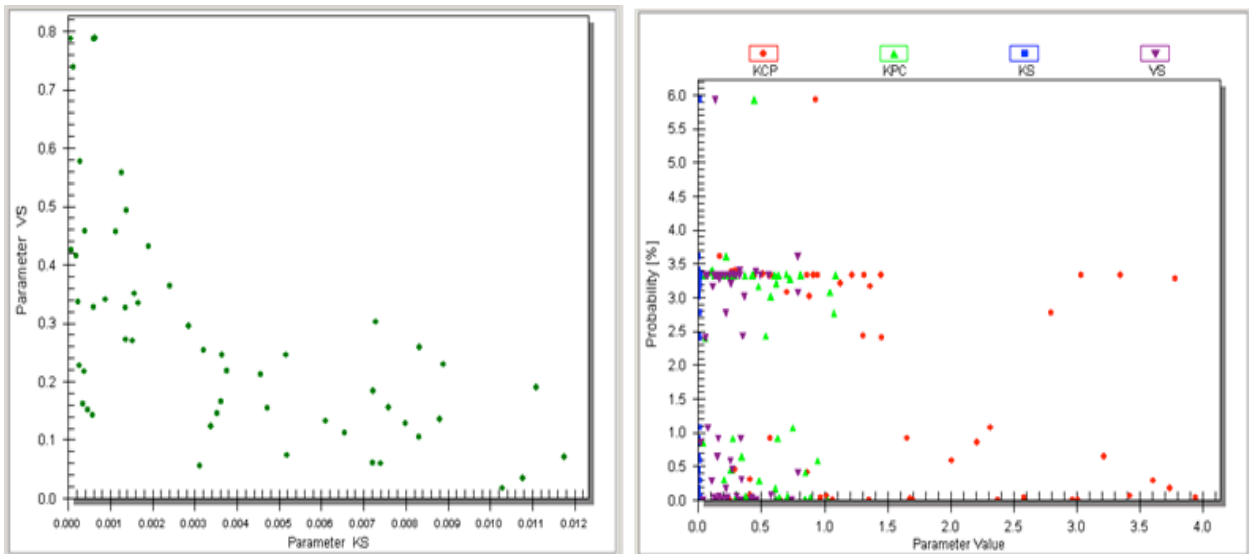
The **Plot view** is the main window in this view, all the plots will be displayed in this window. The plotting routines used in RightDose are quite extensive giving you a



multiple options. You can export the plot or the data making up the plot to your clipboard or printer. You can add a grid, change axis, and lots more. A detailed explanation of your options is given in Appendix A.

Use the **Parameter selector** to select the parameters to be plotted. You must select two parameters if you want the 3D plot or the 2D scatter plot. If present, KS and VS will be selected by default.

The **Plot selector** allows you to switch between the different plots mode. A 2D plot showing all parameters and the 2D scatter plot showing KS and VS is shown below.



If you move the arrow over one of the points in the plot, the numerical values for that plot will be displayed in the **Value display**. In the 3D plot, the values for the two parameters and their probability will be displayed. In the 2D plot, the probability and the parameter value will be displayed. Moving the arrow over one of the points in the 2D scatter plot, parameter value will be displayed.

## The controls

There are no menu options associated with this view.

## The Posterior plots view

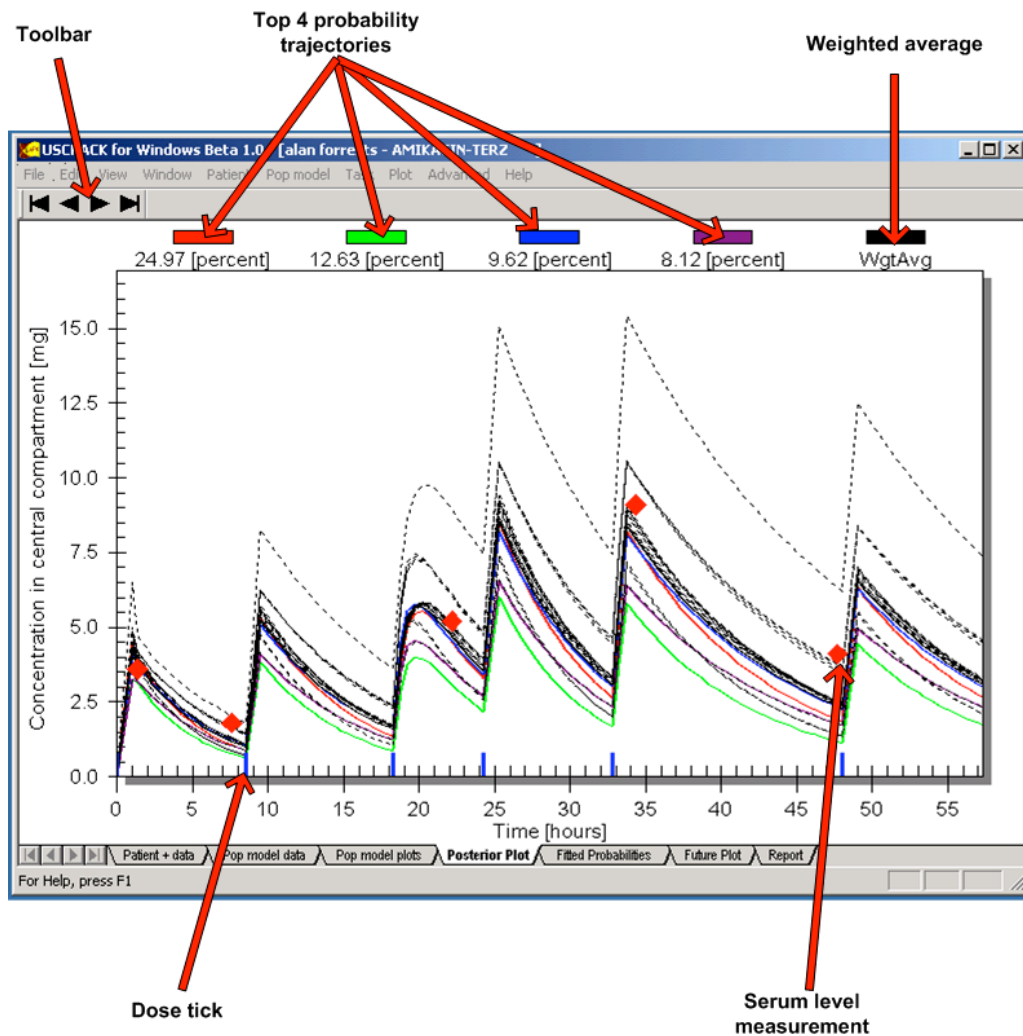
This view is will be shown when you have fitted a patient that has a past history, drug doses and serum concentrations measurements and a specific drug population model. To demonstrate this view we will load a patient and select the correct population model of the drug given to that patient. Pull down the **Patient** menu, select **Load patient**, and load

the “GENT2” file, for example. Pull down the **Pop model** menu, select **Load population model**, and select “Gentamicin”.

You will now fit the patient (provided by Alan Forrest) and a Gentamicin population model. This is simple. Pull down the **Task** menu and select **Fit model**. When the fitting has completed, you will be automatically transferred to the **Posterior plots** view.

## The display

Fitting the Alan Forrest’s patient to the amikacin population model produces this plot.

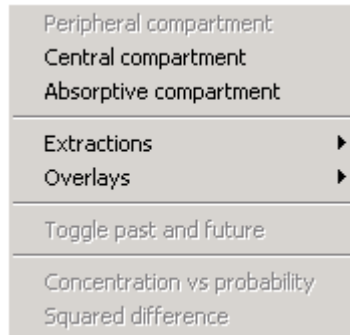


This plot shows all the trajectories produced by the fitting process. There will be one trajectory for each of the parameter/probabilities sets. The **Top 4 probability trajectories** will be shown in color. All others will be shown by dotted black lines. The probabilities of the 4 most probable trajectories and their corresponding color are shown at the top of the plot. The **Weighted average**, computed by adding up all trajectories and multiplying them by their corresponding probability, is shown in solid black.

The red diamonds show the measured **Serum concentrations**. In this case the trajectories are close to the measured values, a good thing. There are also some short blue bars just above the time axis. These **Dose tick** lines show when a dose was given by any route.

## The controls

This view can be altered using the **Plot** menu.



If you selected the amikacin population model your **Plot** menu will look like this. The “Peripheral compartment” will be dimmed because there is no peripheral compartment for this particular population model. The default plot for posterior fits is the central compartment, select the absorptive compartment and see what happens.

The plot now changed, showing the events in the absorptive compartment. If you selected Alan Forrest’s patient, you will see one spike at 18 hours (18.25 to be exact). This is the time when the IM dose was given. It might be a good time to spend some time looking at the patient, the population model, and the posterior fit views. Are the **Dose ticks** shown at the right times? Why are there no spikes in the absorptive compartment when doses are given IV? How many trajectories should there be in the plot?

In the above example the default posterior plot looks decent. This may not always be the case. If you have many diverse trajectories the plot may look cluttered, and the information shown may need to be reduced. If you want to only see the estimated **Weighted average** of all the trajectories, select the **Extractions** submenu, and select **Weighted average only**. You can also set a threshold level, showing you the trajectories making up a percent of the probabilities. Examine this by selecting **Set subsets** instead of **Weighted average only**. Enter 40 into the dialog that pops up, and you will get the two first trajectories (the first one has a probability of 24.97%, the second 12.63, making it a total of 37.6%), and the weighted average.

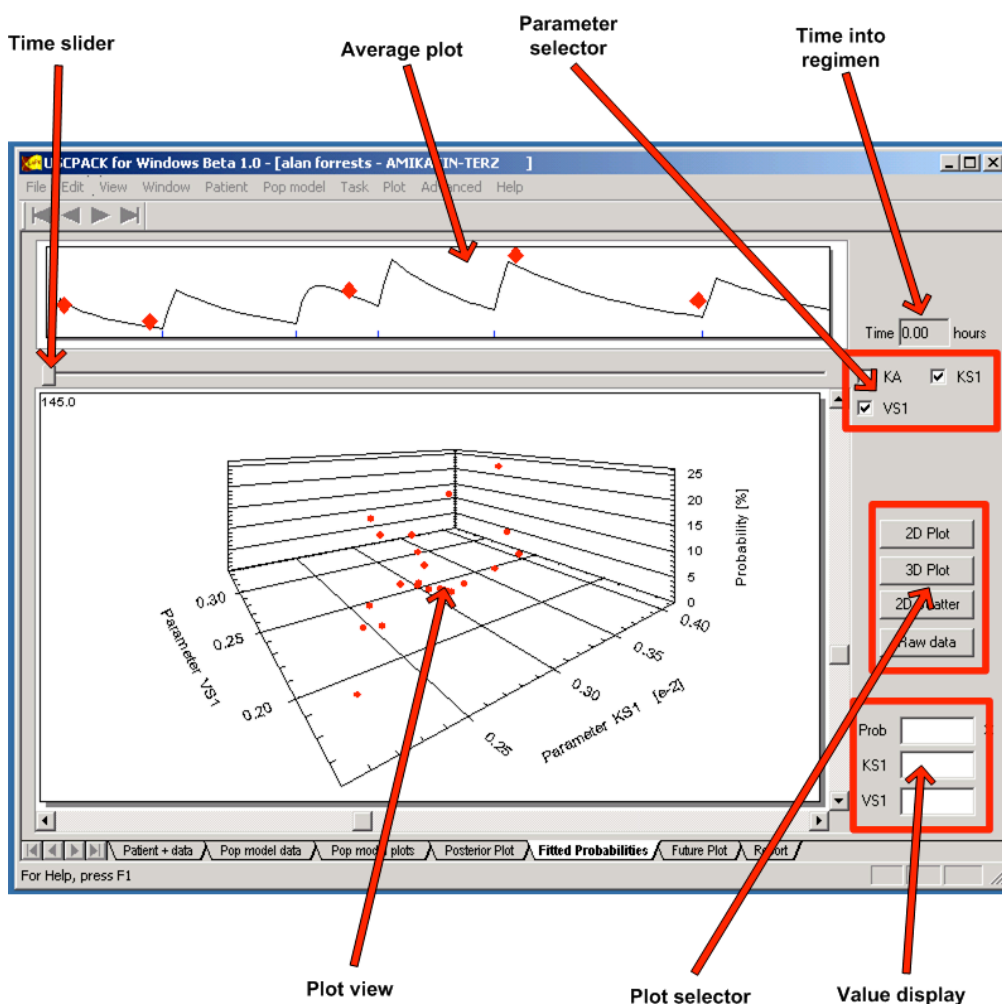
The subset selection will be active until you make a new selection or perform another fit. Selecting the absorptive compartment, the plot will show the two most probable trajectories. Return to the default display by selecting **Show all subsets**.

## The Fitted probabilities view

This view will give you useful information about a fitted model. It will only have data after you have fitted a model.

### The display

This display is very similar to the **Pop model data** view, and it does essentially provide the same information, but this time the probabilities are time dependent.



The main difference in this view is the weighted **Average plot**, and the **Time slider**. The average plot is the plot shown in the **Posterior plot** view when only the weighted average is plotted. The solid diamonds represent the serum level measurements. The blue ticks represent the doses given.

Select a time into the regimen, passing one or more of the serum level measurements. By dragging the **Time slider** to the right. See how the probabilities in the **Plot view** changes with each new sequential Bayesian posterior. New probabilities are computed each time there is a serum level measurements.

Select the **Raw data** button in the **Plot selector**, to see the most recent probabilities.

## **The controls**

There are no menu options associated with this view.

## ***The Report view***

Moving from left to right, the next option should be the future plot, but we will do the **Report view** first. The reason for this will become apparent in a few lines.

If you have followed this from top to bottom you will now have a patient that has been fitted in your program. If not, please perform the steps lined out at the start of the **Posterior plot** section.

You will now compute a future regimen for your patient. Start off by selecting **Future regimen** via the **Task** menu option. A dialog box will pop up, asking you to select the route and sub-option. The process of computing a new or future regimen will be explained in detail later. Accept the default route (IV option 1: Control peak and trough) by clicking on the **OK** button.

Select **Continue** when asked to use your fitted data with this regimen, and select **OK** to accept the body weight and creatinine clearance. The values suggested for body weight and creatinine clearance are the last known values recorded for your patient.

You must now select the target level goals for your patient. Enter values so that your dialog box looks like the one below

Enter the desired route information

IV option 1 - Control Peak and Trough, Select Dose Interval

Variable	Setting	Usual ranges
Peak goal	20 ug/mL	25.00 - 80.00
Trough goal	2 ug/mL	2.00 - 10.00
Infusion duration	1 hours	
Number of days in regimen	4 days	

Date of first planned dose: November 21 2001 09

Low bound: 6, High bound: 24

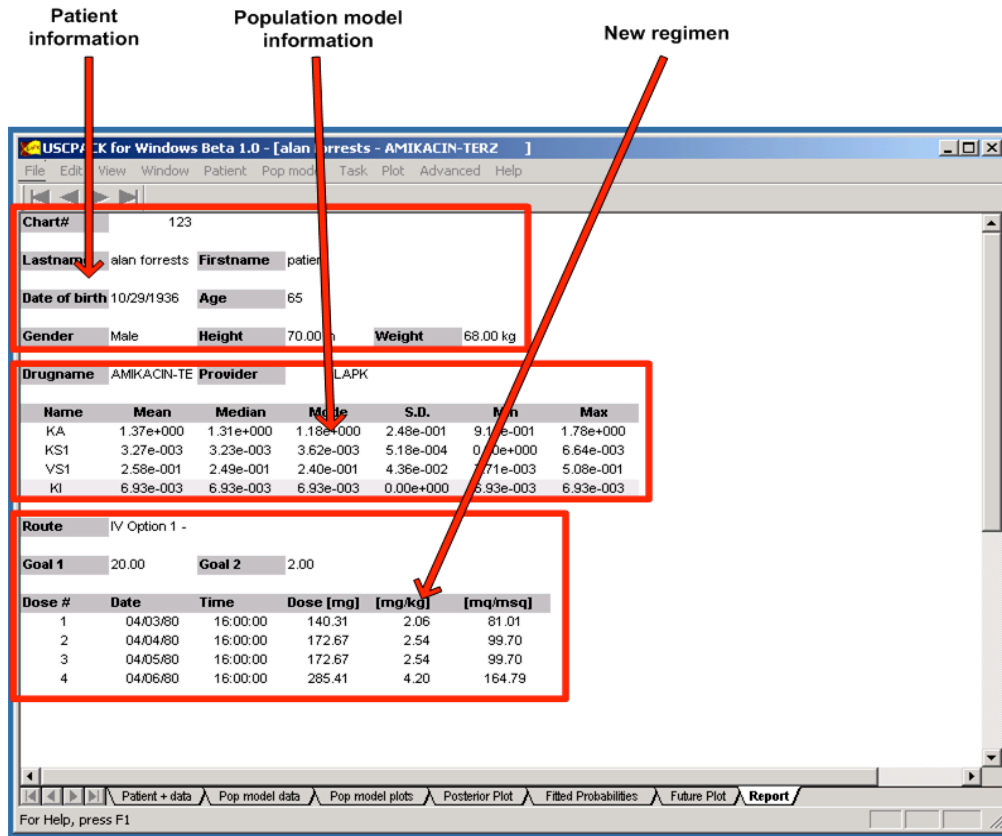
Dose interval: 6, 24

OK, Cancel

Select **OK**. The program now starts to compute this dosage regimen for several dose intervals. When it completed you will see a dialog box with a plot. Accept the selected dose interval of 24 hours by clicking on **OK**.

### The display

Voila, the doses for your patient have been computed, and the **Report** view is displayed.



This view consists of three sections. **Patient information** at the top, then **Population model information**, the route and the goals, and the **New suggested dosage regimen**.

You may switch to the **Report** view at any time. The information displayed will be based on your selected patient and population model. If you have no patient loaded, no patient information will be displayed, and so on.

## The controls

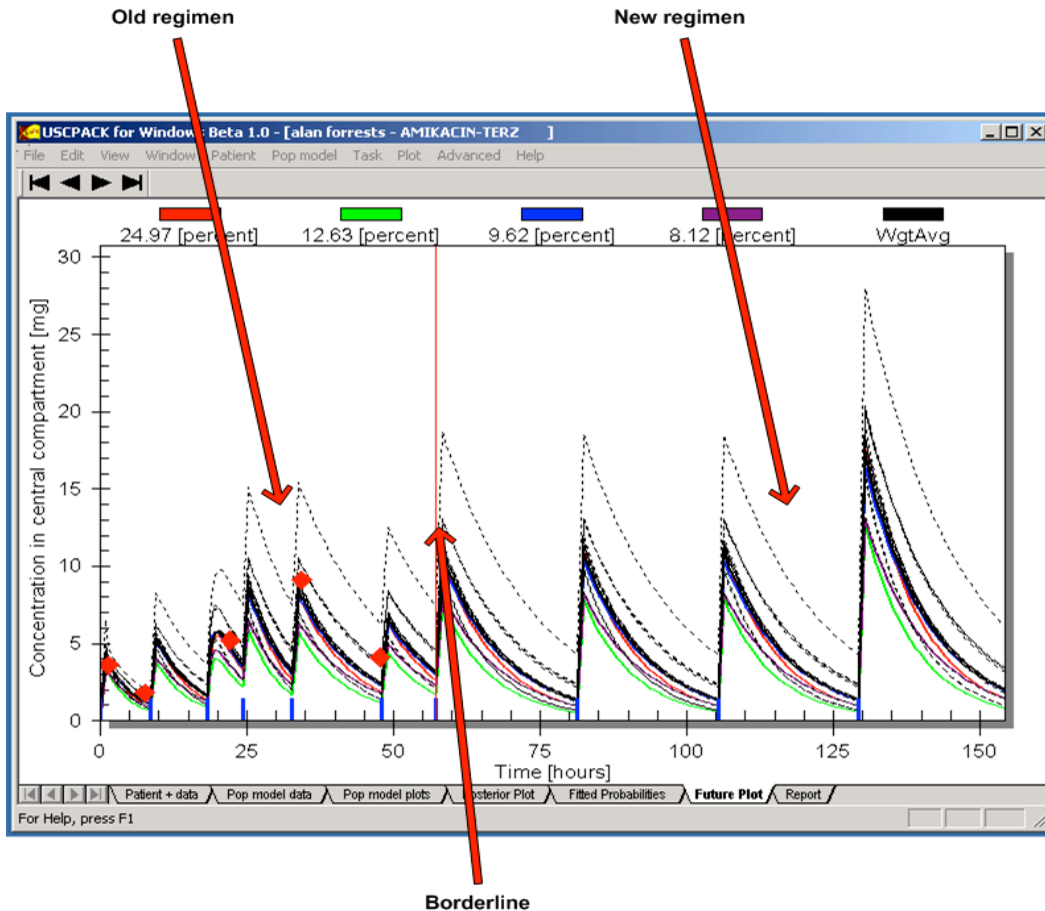
You can print this report by selecting **Print**, from the **File** menu.

## The Future plot view

Please complete the steps outlined for the **Report** view above, or develop your own future regimen.

## The display

Computing a new regimen takes you to the **Report** view. Then select the **Future plot** tab to see more detailed information about your new regimen.



Because we have based this new regimen on the fitted data, this view will also show the results on the **Old regimen**. The **Old regimen** has the diamonds indicating serum level measurement, and both plots have the blue lines showing where a dose was or will be given.

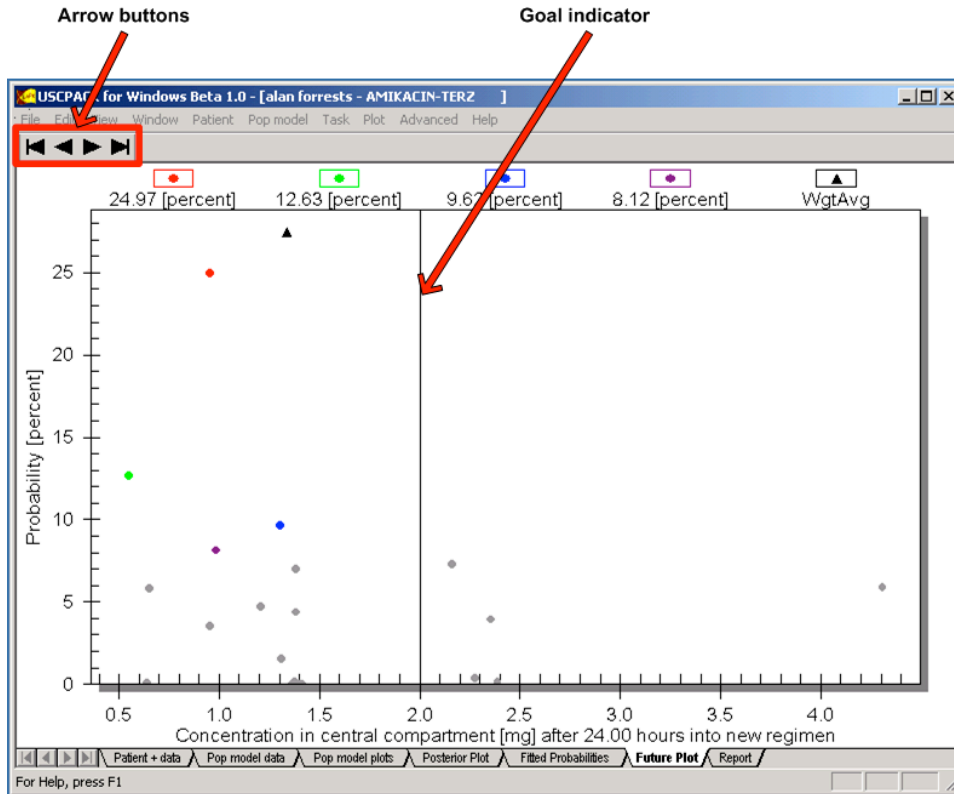
## The controls

The controls for this view are the same as with the **Posterior plot**, accessible from the **Plot** menu option. Note that you now have more options available for this menu selection.

You can remove the past plot by selecting **Toggle past and future**. Try it and watch the past disappear. Turn it back on using the same selection.

To get a completely different view, select the **Concentration vs. probability**. This will bring up the following display.

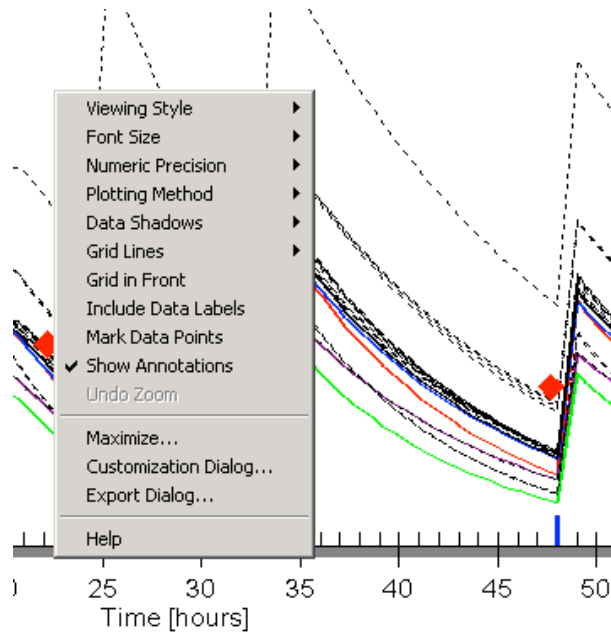




This is a scatter plot showing how well your new regimen is predicted to achieve your target goal values. Remember we selected to have a trough goal of 2.0. It seems like the values are a bit low at this time for this regimen. This plot is the situation after 24 hours. Use the **Arrow buttons** or the arrow keys on your keyboard to play forward in time to see if the new regimen improves. Note also how the **Goal indicator** changes back and forth between 2.0 and 20.0.

### ***Extended plotting options***

The plotting routine used in RightDose offers an extensive set of options. In this appendix we examine some of these options. All options are available by right-clicking inside a plot view. You will then get a menu providing the options.



As you can see there is also a **Help** option, offering detailed help for the various selections.

## Zooming

All plots in the program have been configured to allow for zooming. The process of zooming is simple. Press and hold the left mouse button when inside a plot. Move the mouse and you will see the zooming rectangle. When you then release the left mouse button, the plot will expand the selected region inside the zoom rectangle.

To return the plot to the original status simply right-click inside the plot and select **Undo zoom**.

## The customization dialog

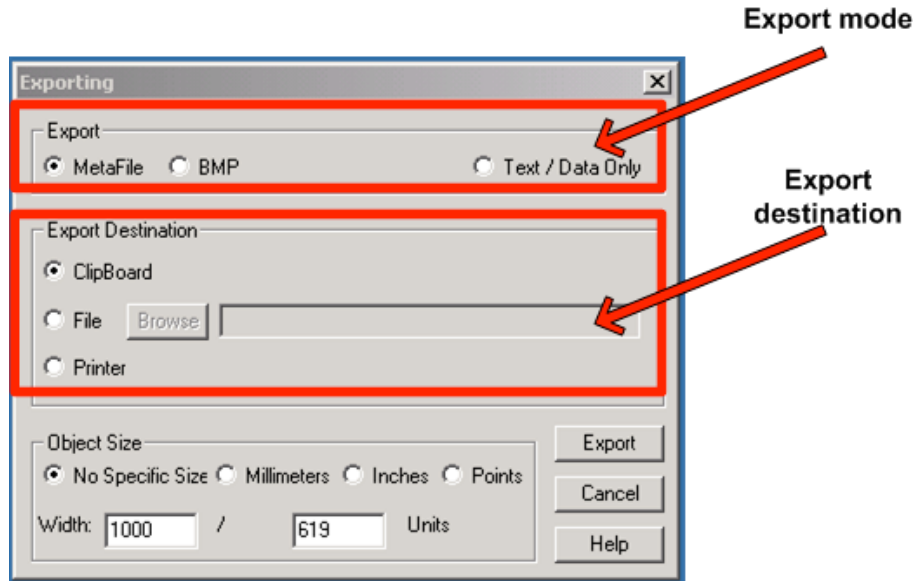
The customization dialog gives you many options for customizing your plot. It does essentially give you an entry point to all other options. Select the tabs to perform one or more of the following options

- You can add a title and subtitle for your plot.
- The plotting mode can be altered to show just the data points, to interpolate values between the plots, or to show the plot as a bar graph.
- Select the subsets to show.
- Adjust the axis range, and switch to logarithmic axes, if desired.
- Change the fonts used to display the axis labels and plot title.
- Change the colors used for the background and foreground for the desk and graph.

- Display the different trajectories using different symbols.

## Exporting plots

Several export options are provided for both data and plot images. Move the mouse pointer into a plot, right-click, and select the **Export Dialog**. You will then see the following dialog box.

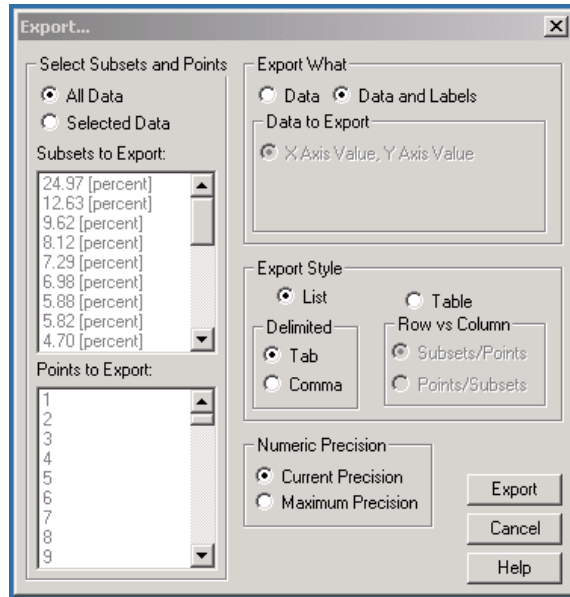


The **Export mode** section allows you to export the plot image, or the data making up the plot. Selecting **MetaFile**, or **BMP** will export the plot, **Text / Data Only** will export the plot as floating point data.

If you export as an image or as data you have several options about where you would like to export the data to (**BMP** cannot be exported to a printer). This can be determined using the **Export destination** section.

To copy a plot into a Microsoft Word document, simply select **MetaFile** in the **Export mode** panel, **Clipboard** as **Export destination**, and press or click **Export**. Go to the location in Word where you would like to have the plot and press Ctrl+v (Paste).

Exporting the actual data requires one more step. Select **Text / Data Only** in the **Export mode**, **Clipboard** in the **Export destination**, and click on **Export**. At this point, a new dialog box pops up, giving you an option to select which subset to export.



You can make multiple selections in the **Subsets to Export** and **Points to Export** by the keeping the Ctrl key pressed while selecting subsets or individual points.

To export the whole dataset into Microsoft Excel, select **Table** in the **Export Style** frame, and press **Export**. Select the cell in Excel where you want the upper left element of the table and press Ctrl+v (Paste).

## Removing the annotations

Annotations are used in three places, for the diamonds showing the serum concentration measurements, for the blue lines showing when the doses were or will be given, and for the red line separating the past and the future. You can toggle annotations on and off by selecting and deselecting the **Show Annotations** option.

## The data points

You have two options to get more information about the data points. Selecting the **Mark Data Points** option and the trajectories will have small black dots showing the locations of the actual data computed points. To get even more information about these points, select the **Include Data Labels** option. The plot will now display the X and Y values of the data plots. This option is usually only useful when used in combination with the zoom feature, as it tends to make the plot cluttered.

## **Enabling gridlines**

Gridlines can be enabled by selecting one of the options in the **Grid Lines** submenu. You can have gridlines in the X direction, Y direction, or both.

## **Maximize**

Select this option, and the plot will expand to occupy the whole area of your desktop. You can close this window by hitting the Esc key or by left-clicking on the top frame of the window.

## A Gentamicin case

In this chapter we give a detailed example on the use of RightDose using a gentamicin population model.

### Initial preparations

Start RightDose and load the GENT2.MB patient data file, and the gentamicin population model. A description on how to load patient data files and population models can be found in the **General usage** chapter.

### The initial view

After loading the patient and population model, the **Patient+data** display of RightDose will look like this

The screenshot shows the 'USCPACK for Windows Beta 1.0 - [alan forrests - Gentamicin]' window. The interface includes a menu bar (File, Edit, View, Window, Patient, Pop model, Task, Plot, Advanced, Help) and a toolbar with navigation arrows. The main area contains patient information fields:

- Filename: G:\Napk\USCPACK\Release\GENT2.MB
- Time of first dose: 04/01/80 08:00:00
- Chart Number: 123
- Height: 70.00 in
- Gender: Male
- Ethnicity: Not in use
- First Name: patient
- Last Name: alan forrests
- Weight: 68.00 kg
- Dialysis patient: NO
- Birth Date: 11/21/36
- Age: 43 years
- Most recent CCr: 27.10
- Time of next dose: 04/03/80 16:00:00

Below the fields are two tables:

Dose [#]	Route [IM/IV/PO]	Date [locale]	Time [hh:mm:ss]	Time [Hours]	Weight [kg]	Descriptor [CCr,CI]	IV inf.Time [Hours]	Dose Interv [Hours]	IV Rate [mg/Hour]	Amount [mg]
1	IV	04/01/80	08:00:00	0.00	68.00	56.47	1.000	8.50	80.00	80.00
2	IV	04/01/80	16:30:00	8.50	68.00	41.34	1.000	9.75	80.00	80.00
3	IM	04/02/80	02:15:00	18.25	68.00	41.34	0.000	6.00	0.00	100.0
4	IV	04/02/80	08:15:00	24.25	68.00	41.34	1.000	8.50	100.00	100.0
5	IV	04/02/80	16:45:00	32.75	68.00	27.10	1.000	15.25	100.00	100.0
6	IV	04/03/80	08:00:00	48.00	68.00	27.10	1.000	8.00	80.00	80.00

Level [Num]	Date [locale]	Time [hh:mm:ss]	Time [Hours]	After Dose [Number]	After Dose [Hours]	Level [mcg/ml]
1	04/01/80	09:20:00	1.33	1	1.33	3.60
2	04/01/80	15:35:00	7.58	1	7.58	1.80
3	04/02/80	06:10:00	22.17	3	3.92	5.20
4	04/02/80	18:20:00	34.33	5	1.58	9.10
5	04/03/80	07:40:00	47.67	5	14.92	4.10

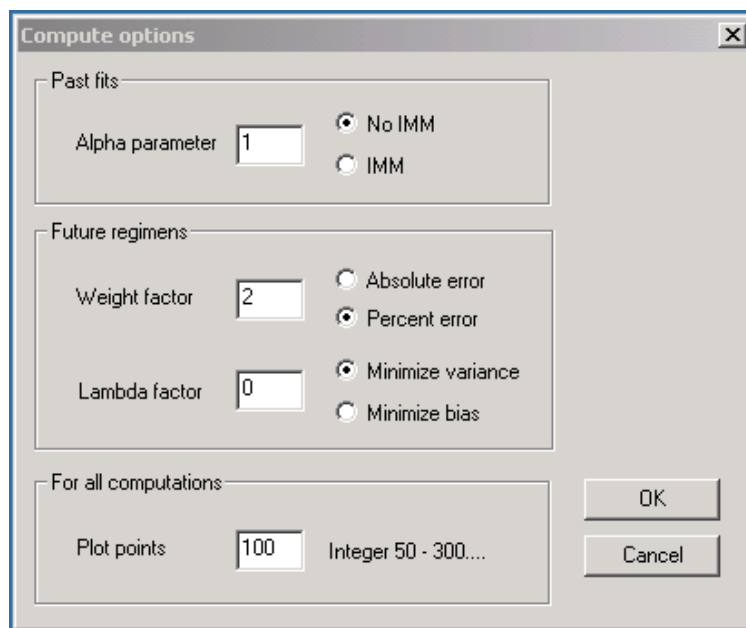
The bottom of the window features a tabbed interface with 'Patient + data' selected, and other tabs for 'Pop model data', 'Pop model plots', 'Posterior Plot', 'Fitted Probabilities', 'Future Plot', and 'Report'. A status bar at the very bottom indicates 'For Help, press F1'.

Note that the frame header displays the name of the patient and the name of the population model. The header display will be the same for all tabs making it easy to keep track of the current simulation.

### ***Fitting without IMM***

You will now fit the patient data to the population model, first without IMM. The settings controlling the use of IMM as well as other options can be found in the **Advanced** -> **Compute options** menu option.

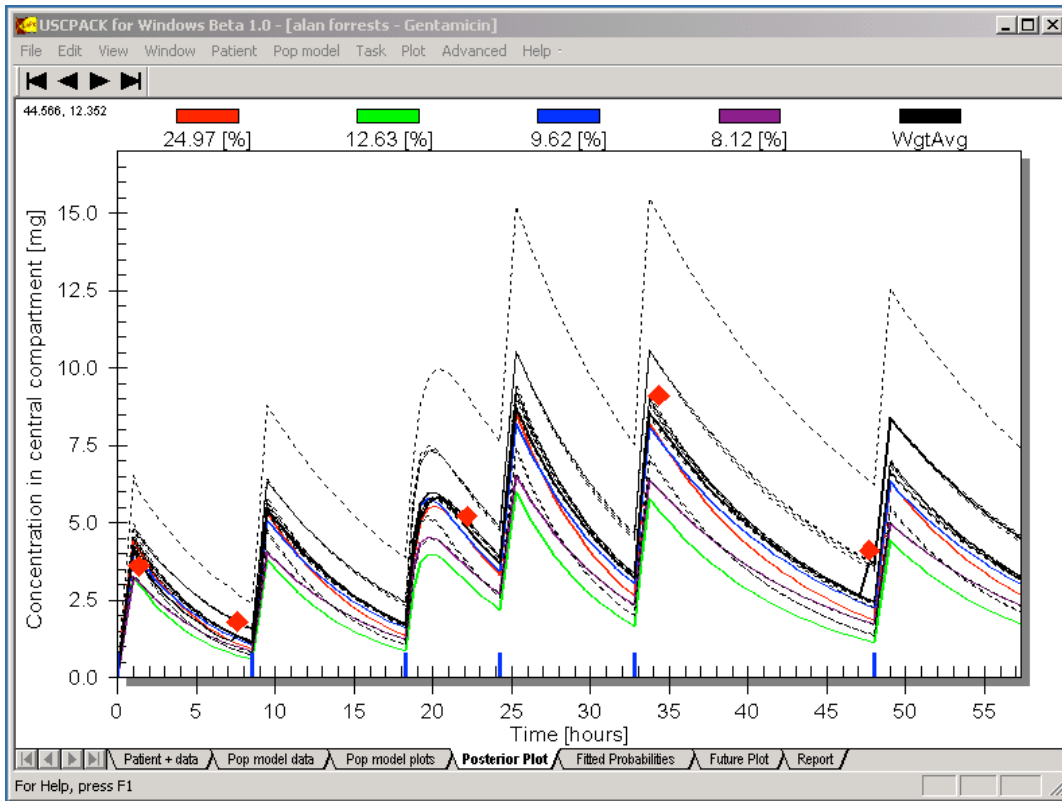
Turn IMM off by setting the Alpha parameter to 1. In this mode, the parameters that best fit the patient's data are assumed to be fixed and unchanging throughout the period of data analysis. This is a very conventional assumption. It underlies all our conventional practices of fitting data to find the best fit to it. In this case, the probabilities of the population parameter support points in the nonparametric joint density are recomputed, using Bayes' theorem. Those support points that predict the patient's measured serum concentrations well become more probable, and those that do not become less probable. In this way, the patient's individual Bayesian posterior joint parameter density is found.



Note - in the present version, it is the numbers given that are used. The radio buttons have no effect.

Select **OK** to continue using the selected settings. These settings will be valid until they are changed or until RightDose is restarted.

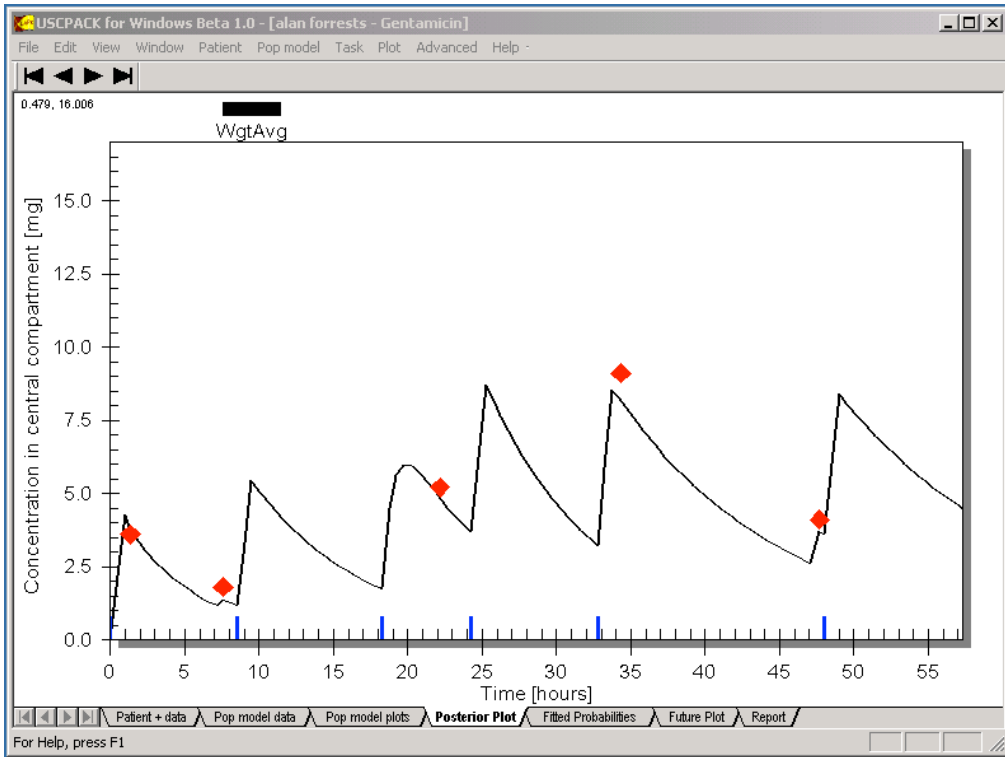
Start the fitting process by selecting **Fit model** from the **Task** menu bar. After a few seconds, the new **Posterior plot** will be displayed, as shown below.



The Blue vertical bars along the horizontal time axis show when doses were given. The red diamonds show the measured serum levels and their times.

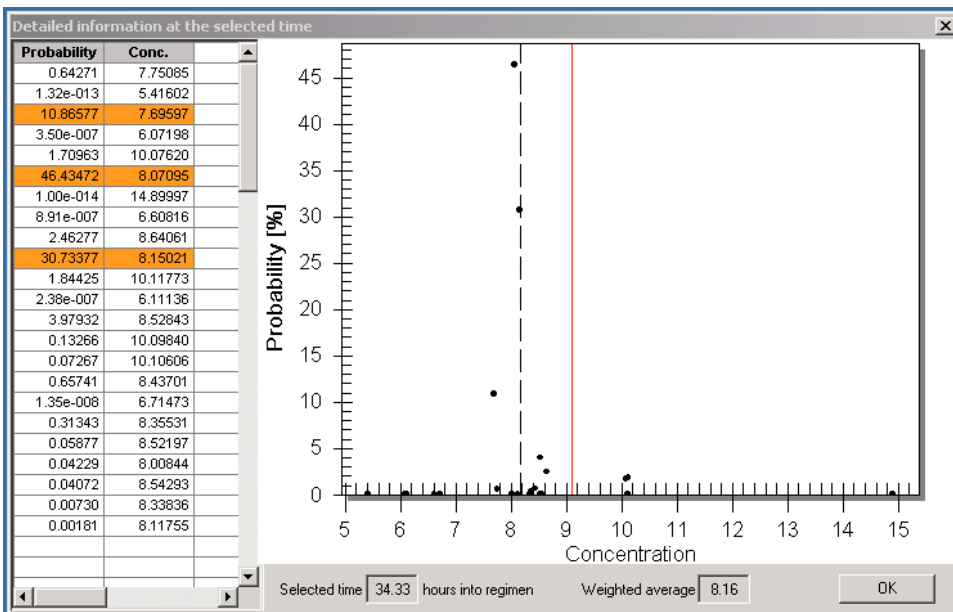
The information in these plots can be overwhelming due to the number of trajectories. If you wish to see only the central tendency of the Bayesian posterior fits, **Select subsets - > Weighted average only** from the **Plot** menu, as shown below.





As you can see there is a decent correlation between the weighted average trajectory and the serum level measurements.

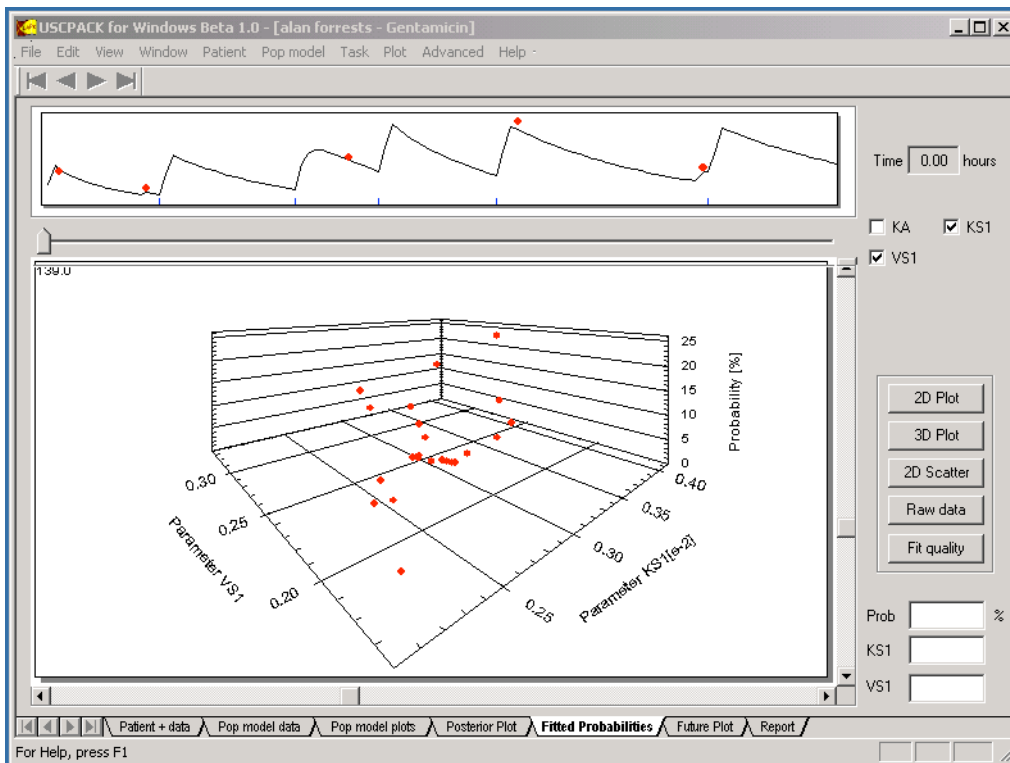
You can get more information about the correlation between the trajectories and the serum levels by left-clicking on one of the red diamonds.



The dotted vertical line shows the value of the weighted average trajectory. The solid red line shows the value of the serum level at that time. The table to the right shows the concentrations and their corresponding probability. The concentrations that have a probability of more than 10% are shown having a different background.

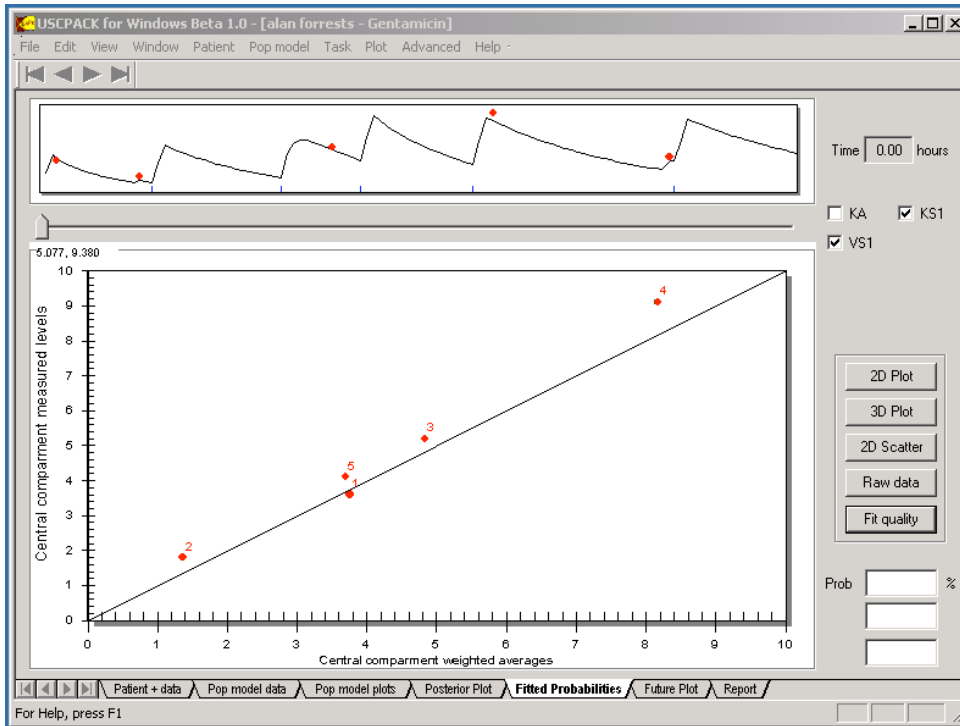
You can left-click on any plot point to see a similar display, but only the times that have a serum level measurement will have the red solid vertical line.

More information about the fit you just made can be found in the **Fitted probabilities** tab. The information accessible in this tab is similar to the **Pop model** data tab, and the default plot for this tab is a 3D scatter plot.



As with the **Posterior plot** tab you can left-click on the diamonds in the upper window to control the time slice shown in the lower window.

Select the **Fit quality** button to get a look at how good your fit was.



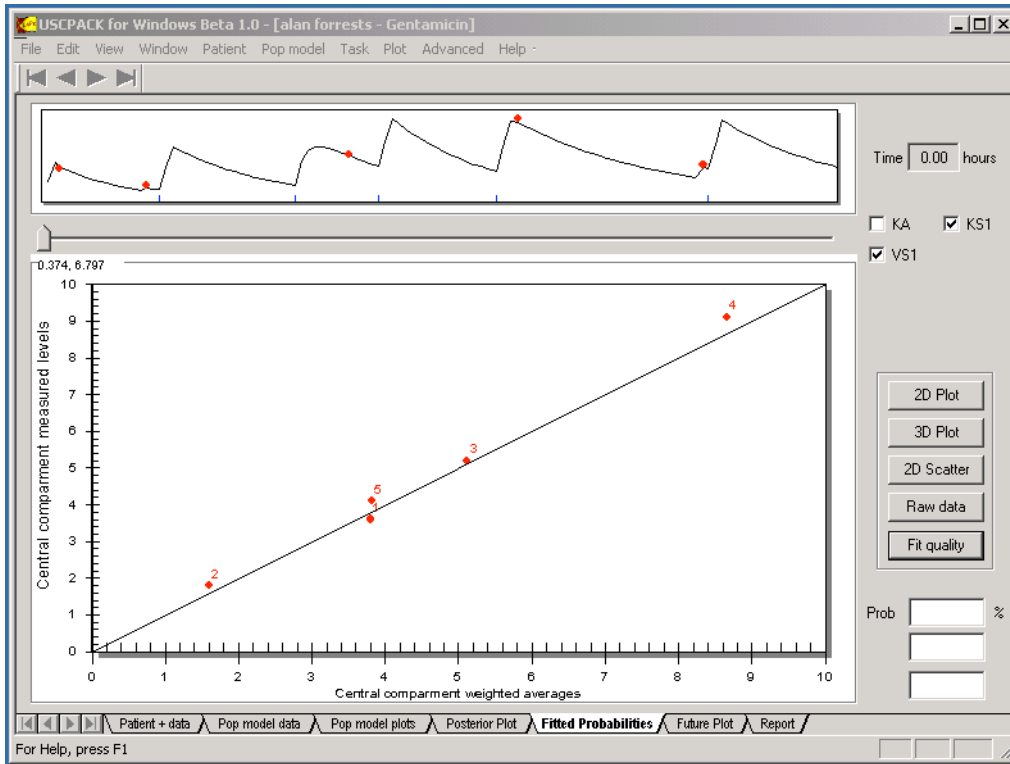
This plot shows the correlation between the serum levels and the weighted average trajectory. The red dots are marked with numbers indicating the serum level number as shown in the **Patient+data** tab. The closer the red dots are to the diagonal line, the better the fit.

Again this shows that the fit you just made was not too bad.

### ***Fitting with IMM***

Lets us see what happens when we enable IMM. Select **Compute options** under the **Advanced** menu, set the Alpha parameter to 0.999, and press **OK**.

Make a fit using the new value for the Alpha parameter by selecting **Fit model** under the **Task** menu. The **Fit quality** should now look like this



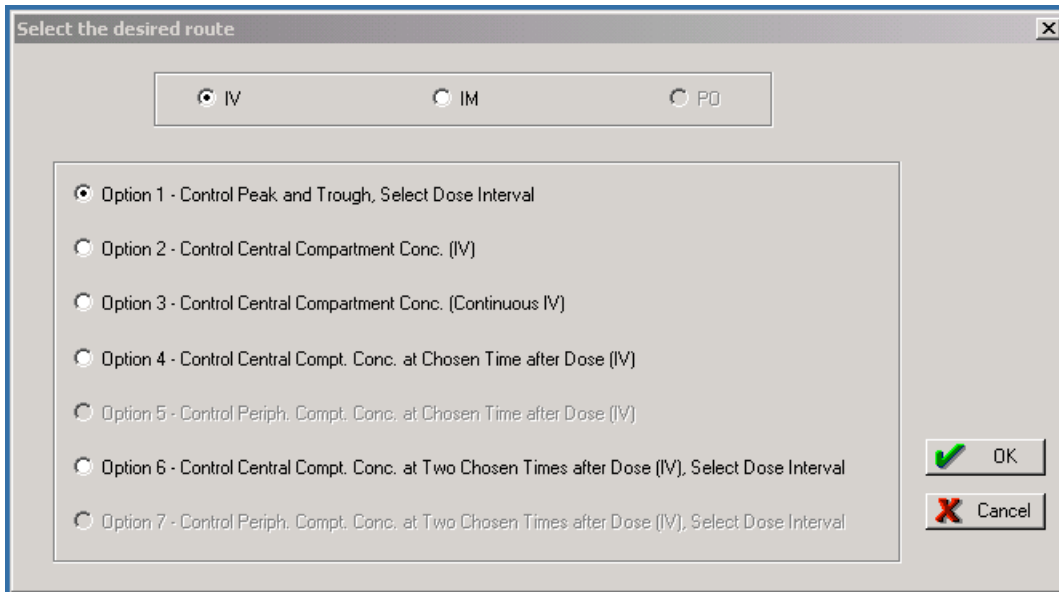
As you can see there is a slight improvement in the fit for serum level number 3, the rest is roughly the same as with no IMM.

Let us accept this fit and move on to developing a future regimen for this patient using the information we have obtained by making the fit.

## ***Designing a future regimen***

### **Using Minimized variance**

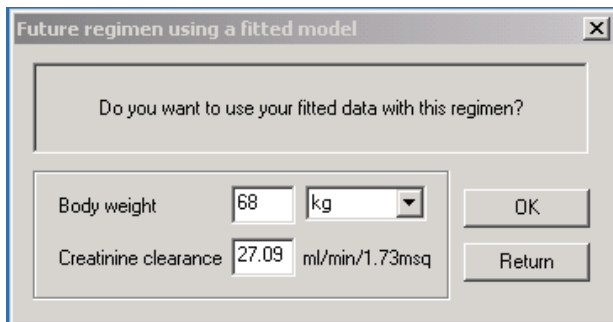
First we design a future regimen using minimized variance. Select the **Future regimen** under the **Task** menu option.



You control the main route using one of the three radio buttons at the top, and the sub-route using one of the 7 vertical buttons. As you can see there the PO route is not allowed for this model, also there is no peripheral compartment for this population model.

Accept the default selection, IV option 1 – Control peak and trough, select dose interval, and press **OK**.

As we have performed a fit for the current patient and population model the program already has knowledge about the weight and creatinine clearance for this patient.



The latest recorded weight for this patient was 68 kg, and the most recent computed creatinine clearance was 27.09 ml/min/1.73msq. Accept these values by pressing **OK**.

Fill in the data for IV option 1 so that your dialog box looks like the one below.

Enter the desired route information

IV option 1 - Control Peak and Trough, Select Dose Interval

Variable	Setting	Usual ranges
Peak goal	12 ug/mL	6.00 - 25.00
Trough goal	1 ug/mL	0.20 - 1.50
Infusion duration	0.5 hours	
Number of days in regimen	4 days	

Date of first planned dose: April 03 1980 16

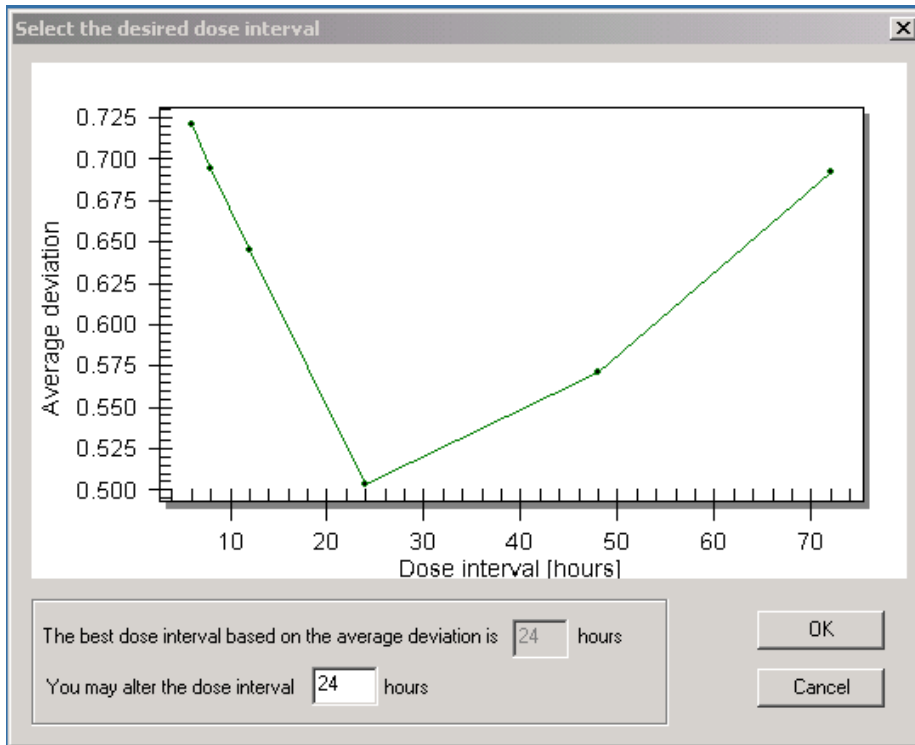
Low bound: 6 High bound: 72

Dose interval: 6

OK Cancel

Note that you can select a dose outside the usual ranges, and moving too far outside these ranges will result in a warning. For now, press **OK** to continue.

The program now computes the cost of using the different dose intervals. You control the ranges examined by altering the low and high bound options in the previous dialog box. After a few seconds this dialog box appears



The dots in the graph indicate that a cost has been computed for that dosage interval. The graph shows that the optimal dose interval is 24 hours. Select **OK** to continue.

The new regimen is now computed, an operation that will take a few seconds. When completed RightDose will switch to the **Report** tab.

USCPACK for Windows Beta 1.0 - [alan forrests - Gentamicin]

File Edit View Window Patient Pop model Task Plot Advanced Help

**Lastname** alan forrests **Firstname** patient  
**Date of birth** 11/21/1936 **Age** 65 **BSA** 1.84  
**Gender** Male **Height** 70.00 in **Weight** 68.00 kg  
**Drugname** Gentamicin **Provider** LAPK, SDSC

Name	Mean	Median	Mode	S.D.	Min	Max
KA	0.069148	1.306860	0.00e+000	0.164049	0.946229	1.768180
KS1	0.000110	0.003099	0.00e+000	0.000259	0.002099	0.004059
VS1	0.009727	0.242018	0.00e+000	0.023233	0.169692	0.329628
KI	0.006932	0.006932	0.006932	0.0	0.006932	0.006932

**Route** IV Option 1 - Control Peak and Trough, Select Dose Interval

**Goal 1** 12.00 **Goal 2** 1.00  
**Time 1** -1.00 **Time 2** -1.00

**Cost** 0.347280 **AUC** 322.872901

Dose #	Date	Time	Dose [mg]	[mg/kg]	[mq/msq]
1	04/03/80	16:00:00	39.22	0.58	21.33
2	04/04/80	16:00:00	88.92	1.31	48.36
3	04/05/80	16:00:00	88.96	1.31	48.38
4	04/06/80	16:00:00	92.97	1.37	50.56

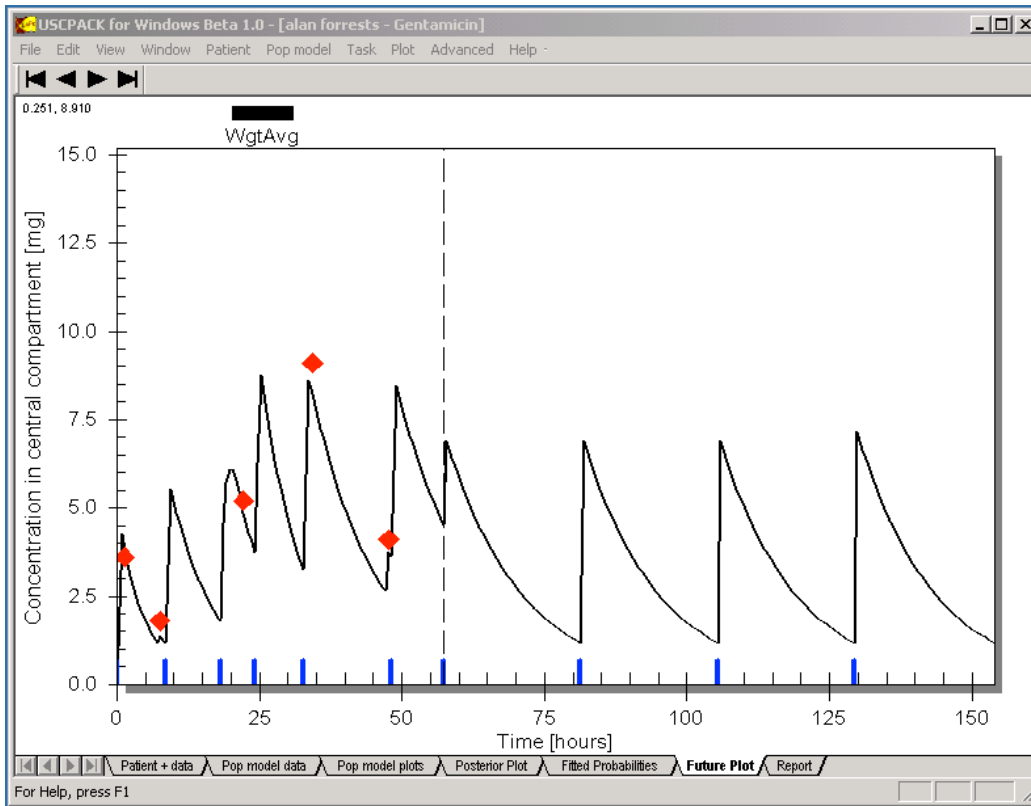
Patient + data | Pop model data | Pop model plots | Posterior Plot | Fitted Probabilities | Future Plot | **Report**

For Help, press F1

The lower portion of the report show the cost, the area under the curve (AUC), and the 4 computed doses. You can print this report by selecting **Print** under the **File** menu or by pressing Ctrl+p.

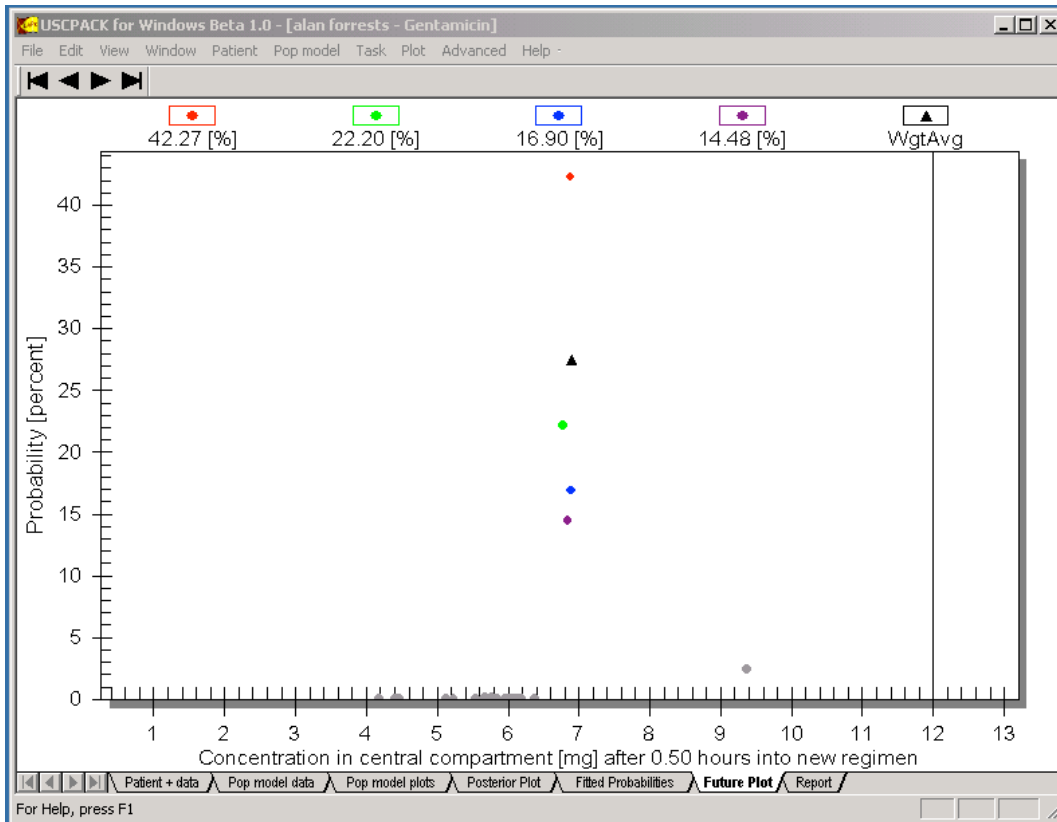
Switch to the **Future plot** tab to see more visual information about the new regimen. Change the plot to only show the weighted average.





This plot show the weighted average serum concentration in the central compartment. The past history is show to the left of the dotted vertical line, the future regimen to the right.

Enable all subset again, and select the **Concentration vs probability** under the **Plot** menu.



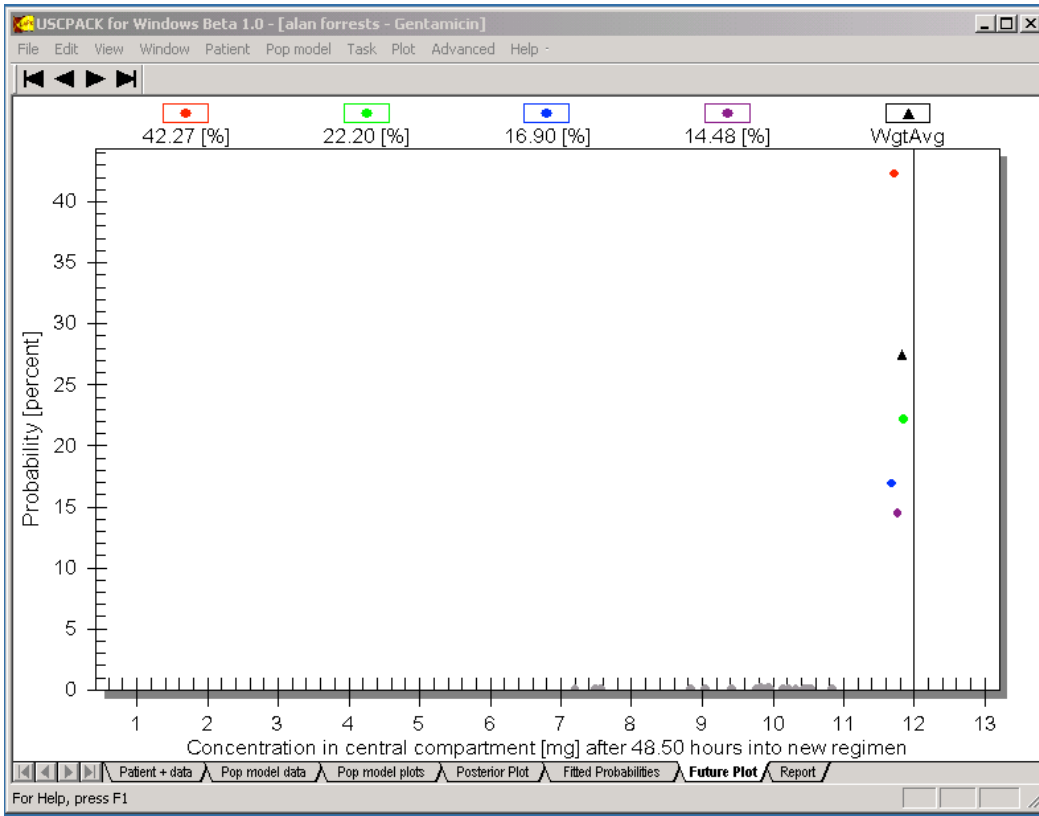
This plot shows the concentration along the x-axis and the probability along the y-axis for the first goal time, a goal of 12 0.5 hours into the regimen. The most probably set of support points, or trajectory, is again indicated by a solid red dot. It has a probability of 42.27% and this time it has a value of out 7. This is below your selected goal indicated by the solid vertical line. The black triangle shows the weighted average.

Use the black arrows to move forward/backward in time to look at next/previous goals.

## Using minimize bias

Select the **Compute options** under the **Advanced** menu option, change the lambda factor to 1 and the weighting factor to 0 (absolute error). Repeat the steps above to compute a new future regimen.

Select the **Concentration vs probability** under the **Plot** menu.



Note how the serum levels are much closer to the goal.

## Appendix A

Publications related to the MM-USCPACK program.

The following publications can be found in this appendix:

- POPULATION PK/PD MODELING: PARAMETRIC AND NONPARAMETRIC METHODS.
- ESTIMATION OF CREATININE CLEARANCE IN PATIENTS WITH UNSTABLE RENAL FUNCTION, WITHOUT A URINE SPECIMEN.
- ACHIEVING TARGET GOALS MOST PRECISELY USING NONPARAMETRIC COMPARTMENTAL MODELS AND "MULTIPLE MODEL" DESIGN OF DOSAGE REGIMENS.
- MULTIPLE MODEL (MM) DOSAGE DESIGN: ACHIEVING TARGET GOALS WITH MAXIMUM PRECISION.
- A NEW METHOD TO UPDATE BAYESIAN POSTERIORES FOR PHARMACOKINETIC MODELS WITH CHANGING PARAMETER VALUES. (*Abstract*)

## **POPULATION PK/PD MODELING: PARAMETRIC AND NONPARAMETRIC METHODS.**

Roger Jelliffe, Alan Schumitzky, and Michael Van Guilder. Laboratory of Applied Pharmacokinetics, USC School of Medicine.

As we acquire experience with the clinical and pharmacokinetic behavior of a drug, it is usually optimal to store this experience in the form of a population pharmacokinetic model, and then to relate the behavior of the model to the clinical effects of the drug or to a linked pharmacodynamic model. The role of population modeling is thus to describe and store our experience with the behavior of a drug in a certain group or population of patients or subjects.

The traditional method of Naive Pooling has been used for population modeling when experiments are performed on animals, for example, which must be sacrificed to obtain a single data point per subject. Data from all subjects is then pooled as if it came from one single subject. One can estimate pharmacokinetic parameter values, but cannot estimate any of the variability that exists between the various subjects making up the population.

### **Parametric Methods for Population Modeling**

A good review of parametric population modeling methods is given in [1]. These methods obtain means and standard deviations (SD's) for the pharmacokinetic parameters, and correlations (and covariances) between them. Only a few of these will be described, and quite briefly, here.

1. In the **Standard Two-Stage** (S2S) approach, one begins by using a method such as weighted nonlinear least squares to obtain pharmacokinetic parameter estimates for each patient, and their correlations and covariances between parameters. The second and final stage consists of obtaining the population mean and SD of the various individual parameter values. To do this, one needs at least one serum concentration data point for each parameter to be estimated. One can also examine the frequency distributions of the individual parameter values.

The **Iterative Two-stage Bayesian** (IT2B) method begins by using an initial estimate of the mean parameter values. They may be obtained, for example, by the two stage procedure, as above. On the other hand, one can use any reasonable initial estimate of the population mean parameter values and their SD's. These are then used as the Bayesian priors. The IT2B method uses these priors and examines each individual patient's data to obtain the individual maximum a posteriori probability (MAP) Bayesian posterior parameter values for each subject, using the MAP Bayesian procedure in current wide use

[2]. One then finds the population means and SD's of those individual posterior parameter values.

One can then turn around and use these new population values as the MAP Bayesian priors, and can once again obtain each patient's MAP Bayesian posterior values. This process can continue iteratively indefinitely. The procedure ends when a convergence criterion is reached. The IT2B method is much less prone to the problems often found with fitting data by least squares. In addition, it does not require nearly as many serum concentration data points per patient, and can function with as few data points as only one per patient.

The Global Two Stage (G2S) method is a further refinement of the S2S and the IT2B in which the covariance and correlations between the parameters are also estimated. Each of these methods, and all those below, require software to implement them.

3. In the **parametric EM** method, the letters EM stand for the two steps in each iteration, of 1) computing a conditional expectation and 2) of maximizing a conditional likelihood, to obtain a set of parameter values which are more likely than in the previous iteration. The process continues until a convergence criterion is met. The results are given in terms of the parameter means, SD's, and correlations, or means, variances, and covariances [3].

4. The **nonlinear mixed-effect modeling** (NONMEM) method, developed by Beal and Sheiner [4-6], was the first true population modeling program. The method can function with as few samples as one per patient. However, this very popular algorithm lacks the desirable property of mathematical consistency [7-9]. Early versions of it have at times given results which differed considerably from other approaches [10,11]. Later improvements have shown more consistent behavior. Other variations on this approach are those of Lindstrom and Bates [12], and Vonesh and Carter [13].

In analyzing any data set, it is usually optimal to assign a measure of credibility to each data point. In the IT2B program of the USC\*PACK collection, for example, one is encouraged to determine the error pattern of the assay quite specifically before beginning the analysis, by determining several representative data points in at least quadruplicate, and to find the standard deviation (SD) of each of these points. One can measure, in at least quadruplicate, a blank sample, a low one, an intermediate one, a high one, and a very high one. One can then find the relationship between the serum concentration (or other response) and the SD with which it has been measured, so that one can compute the Fisher information, for example, as a good measure of credibility, so that each serum level can be evaluated in the fitting process by a good measure of its credibility. This has been discussed more fully in another paper in this collection, and in other communications [14,15].

In addition, gamma, a further measure of overall intra-individual variability, can also be computed by the IT2B program, but not by the nonparametric methods. It is used in the USC\*PACK IT2B program as a multiplier of all the coefficients of the assay error

polynomial as determined above. Because of this, its nominal value is 1.0, indicating that there is no other source of variability than the assay error pattern itself. Gamma is thus usually greater than 1.0. It not only includes the various environmental errors such as those present in preparing and administering the doses, errors in recording the timing of the serum samples, and also errors in which the structural model used fails to describe the events fully (model misspecification), but also any changes in various parameter values over time. It is an overall measure of all the other sources of intraindividual variability besides that of the assay. However, most of these other sources are not really sources of measurement noise, but are rather of noise in the differential equations describing the behavior of the drug, and are best described as process noise [16]. The problem is that it is difficult to estimate process noise, as it requires stochastic differential equations, and no software for this exists at present in the pharmacokinetic field, to our knowledge.

Furthermore, the IT2B program can also be used to search for estimates of the various assay error pattern coefficients, if one has absolutely no idea what the assay error pattern is, or if the measurement is one which it is impossible to replicate. In this case, gamma is not determined, but is implied in all the various other coefficients.

The following results are taken from a representative run of the IT2B program. The original patient data files were made using the USC\*PACK clinical software. The program, like the NPEM program, reads those files and writes out working copies of them in another format. The following illustrative results are taken from a subset of data obtained by Dr. Dmiter Terziivanov in Sofia, Bulgaria [17], on 10 patients who received intramuscular Amikacin, 1000 mg, every 24 hours for 5 or 6 days. In each patient, two clusters of serum levels were measured, one on the first day and one on the 5th or 6th day, approximately 5 levels in each cluster. Creatinine clearance was estimated from data of age, gender, serum creatinine, height and weight, as described in another paper in this issue. Serum concentrations were measured by a bioassay method. The assay error pattern was described by a polynomial in which the assay SD =  $0.12834 + 0.045645C$ , where C is the serum concentration. The assay SD of a blank was therefore 0.12834 ug/ml, and the subsequent coefficient of variation was 4.5645%. In this particular analysis, gamma was not computed, but was held fixed at 1.0. The following results were obtained with the USC\*PACK IT2B program.

The initial very first parameter estimates, and their SD's, were:  $K_a$  (the absorption rate constant) =  $1.5 \pm 1.5 \text{ hr}^{-1}$ ,  $K_s$  (the increment of elimination rate constant per unit of creatinine clearance in  $\text{ml}/\text{min} / 1.73\text{M}^2$ ) =  $0.005 \pm 0.005 \text{ hr}^{-1}$ , and  $V_s$  (the apparent central volume of distribution) =  $0.6 \pm 0.6 \text{ l}/\text{kg}$ . The nonrenal intercept of the elimination rate constant ( $K_i$ ) was held fixed at  $0.0069315 \text{ hr}^{-1}$ , so that the elimination rate constant =  $K_i + K_s \times \text{creatinine clearance}$ .

The IT2B program converged, in this analysis, on the 8th iteration. The population mean values for the parameters  $K_a$ ,  $K_s$ , and  $V_s$  found were  $1.45 \text{ hr}^{-1}$ ,  $0.0033 \text{ hr}^{-1}$ , and  $0.257 \text{ L}/\text{kg}$  respectively. The medians were  $1.42 \text{ hr}^{-1}$ ,  $0.0035 \text{ hr}^{-1}$ , and  $0.252 \text{ L}/\text{kg}$  respectively. The population standard deviations were  $0.341 \text{ hr}^{-1}$ ,  $0.000693 \text{ hr}^{-1}$ ,

and 0.0479 L/kg respectively, yielding coefficients of variation of 24, 21, and 19 percent respectively.

The empirical distributions of  $K_a$ ,  $K_s$ , and  $V_s$  are shown in Figures 1 through 3. The joint distribution of  $K_s$  and  $V_s$  is shown in Figure 4, which shows a visible positive correlation between the two parameters, consistent with their population correlation coefficient of 0.671.

The entropy (a measure of randomness) was 3.57. This value is 81.6% of the distance from the high initial entropy associated with the uninformed initial grid in which all possible parameter values had equal probability, to the theoretical least possible entropy which would result if each subject's parameter values could be known exactly. The value of the scaled information of 81.6% indicates that a good deal of information was obtained from this analysis.

Figures 5 and 6 are scattergrams of predicted versus measured serum concentrations. Figure 5 shows the predictions based on the population parameter medians and the doses each subject received. In contrast, Figure 6 shows the predictions made using each subject's individual MAP Bayesian posterior parameter values to predict only his/her own measured serum concentrations. The improved predictions in Figure 6 are due to the removal of the population interindividual variability, as perceived by the IT2B program. The remaining smaller scatter is due to the intraindividual variability resulting not only from the assay error, but also to the other sources of noise in the system, such as the errors in preparation and administration of the various doses, errors in recording the times the doses were given and the serum samples drawn, and the misspecification of the pharmacokinetic model used. The results shown in Figure 6 show that the study was done with reasonable precision.

The IT2B method of population modeling is a useful one, and is based on the widely used and robust strategy of MAP Bayesian individualization of pharmacokinetic models. Its weaknesses, like those of any parametric method, are that it only perceives population parameter values in terms of their means, medians, variances, and correlations. The actual parameter distributions are usually not of this type. Lognormal assumptions have often been made, but the actual parameter distributions are frequently not of that form either.

### **Larger and Nonlinear IT2B Population Models**

Similar software for IT2B population modeling of large and nonlinear PK/PD models has now been implemented, on the Cray T3E parallel computer at the San Diego Supercomputer Center (SDSC), as a research resource for such work. The user uses a PC program in the USC\*PACK collection to specify the data files to be analyzed and the instructions for the analysis. One also either writes the differential equations for the structural PK/PD model to be used, or employs the BOXES program in the USC\*PACK collection, placing boxes on the screen for the compartments and connecting them with



arrows to represent the various types of pathways involved. The model equations are then generated automatically and stored in a model file.

These two files are then sent to the SDSC Cray by a secure protocol. The model source code file is compiled and linked. The analysis is performed using the desired number of processors. A differential equation solver is employed. The results are then sent back to the user's PC where they are examined just as in the various figures shown above. Thus one can now make large and nonlinear models of a drug, with multiple responses such as serum concentrations and various drug effects [18]. This resource is now in use by researchers.

### **Strengths and Weaknesses of Parametric Population Modeling**

The major strength of the parametric population modeling approaches is their ability to separate interindividual variability in the population from intraindividual variability in the individual subjects (gamma, for example), and from variability due to the assay error. Because of this, it seems best, for the present, to begin making a population model by using a parametric method such as the IT2B. First, one should estimate the assay error pattern explicitly, obtaining the assay error polynomial as described in an earlier paper in this collection, and elsewhere [14,15]. Then, having that assay error polynomial, one can use a parametric method such as IT2B to find gamma, and to determine the overall intraindividual variability, and to know what fraction of that is due to the assay itself. Then, one is in a position to overcome the weaknesses of these approaches by using this information in making a nonparametric population model (see below).

One weakness of the parametric methods is that they generally lack the desirable property of mathematical consistency, which is present in the nonparametric methods [7-9]. However, the major weakness of the parametric methods is that they make parametric assumptions about the shape of the parameter distributions, and cannot perceive the entire shape of the parameter distributions, as the nonparametric methods do [19,20].

The major weakness of the parametric approaches is that they only obtain such single point estimates of parameter distributions. Much discussion has taken place about which is the optimal estimate of a parameter distribution— the mean, median, or mode, for example. When one acts on such single point information to develop a dosage regimen to achieve a desired target goal at a desired target time, the regimen that is computed is simply the one which will hit the target exactly. There is no way to estimate the degree to which the regimen may fail to hit the target, as there is only a single model, with each parameter having only a best single point parameter estimate.

### **The Separation Principle**

The separation or heuristic certainty equivalence principle states that whenever the behavior of a system is controlled by separating the control process into: Getting the best single point parameter estimates, and then:

Using those single point estimates to control the system,

that the task of control is inevitably done suboptimally [21], as there is no performance criterion which is optimized. This is the major weakness of parametric population models, that when their single point parameter estimates are used to design dosage regimens, that the target goals are inevitably achieved with a precision that is not specifically evaluated, and which is suboptimal. One may ask why we make models – to simply report such single point estimates, or to take some useful action based on the information obtained from the modeling process? That is why it is useful to supplement the knowledge of the assay error, empirically determined before starting the modeling, with information about the intraindividual variability obtained from a parametric population model. Having this information, one can then proceed to make a nonparametric population model which can overcome the difficulties presented by the separation principle stated above.

### **Nonparametric Methods for Population Modeling**

Until recently, we have become accustomed to obtaining certain types of statistical summaries of past experience. We know there is great variability among patients with regard to their pharmacokinetic parameter values. Nevertheless, we have become accustomed to using selected single numbers to describe such diverse behavior. For example, we have usually used the population mean or median parameter values as the best single number to describe the central tendencies of their distributions, and the standard deviation (SD) to describe the dispersion of values about such a central tendency. It has been customary to focus on such single numbers as summaries of experience, rather than to consider the complexities of the entire collection of the many and varied individual experiences themselves. In this section we discuss newer and more powerful nonparametric methods which can give us richer and more likely information from the raw data, which can then be applied to patient care more optimally than by using models having only single values for the various parameters.

What is meant here by the word nonparametric? Most of the time, when we gather data and summarize it statistically, we are accustomed to obtaining a single parameter value for the central tendency of a distribution such as the mean, median, or mode, and another single parameter value to describe the dispersion about this central tendency, such as the standard deviation (SD). The usual reason for this is that so many events in statistics have a normal or Gaussian distribution, and that the mean and the SD are the two parameters in the equation of a Gaussian distribution which define the shape of that distribution explicitly. Because of this, describing a distribution parametrically, in terms of its own parameters, the mean and SD, is very common. Indeed, the entire concept of analysis of variance is based on the assumption that the shape of the parameter distributions in the system are best described by their own other parameters of mean and SD or covariance. A great body of experience has been brought to bear to describe pharmacokinetic models parametrically, in this way. Much of this is described in an excellent review [1].

On the other hand, if each individual subject's pharmacokinetic parameter values in a given population could somehow be truly and exactly known, and if we were examining two typical parameters such as volume of distribution ( $V$ , in L, or  $V_{\text{slope}}$ , in L/kg) and elimination rate constant ( $K$ , in  $\text{hr}^{-1}$ , or  $K_{\text{slope}}$ , in  $\text{hr}^{-1}$ /unit of its descriptor, such as creatinine clearance), then the truly optimal joint population distribution of these parameter values would actually be the entire collection of each patient's individual parameter values. All subpopulations, and those in between, would be truly known as well - not merely classified, but truly quantified.

However, these values can never be known exactly, but must be estimated from data of doses given and serum concentrations measured, and in a setting of environmental uncertainty, with errors in preparation and administration of the doses, and errors in recording the times when doses are given and serum samples obtained. In the nonparametric approach, one obtains discrete spikes, approximately one per subject. The location of each spike reflects its set of estimated values, usually for a given subject data set. The height represents the estimated probability of that individual parameter set. No other summary parameters such as mean or SD will be any more likely, given the data of dosage and serum concentrations, than the actual estimated collection of all the individual discrete points, each one having certain parameter values such as  $V_d$  and  $K_{el}$ , for example, and the estimated probability associated with each combined point of  $V_d$  and  $K_{el}$ . This is what is meant by the word nonparametric in this sense. No specific parameters such as means and SD's are used or needed to describe the distribution of parameter values within a population. The shape of the discrete distribution is totally determined only by the raw data of the individual subjects studied in the population.

Many patient populations actually are made up of clusters of unsuspected subpopulations. For example, there may be fast and slow metabolizers of a drug, and those in between. The relative proportions of fast, in between, and slow subjects may vary from one population (Caucasian people, for example) to another (Asian people, for example) [22]. Describing such a distribution of clusters optimally is not possible with any parametric method.

Since one obviously cannot know each patient's values exactly in real life, we must study a sample of patients requiring therapy with a drug by giving it to them and measuring the serum levels and/or other responses. Lindsay [23], and Mallet [19], were the first to show that the optimal solution to the population modeling problem is actually a discrete (not continuous), spiky (not smooth) probability distribution in which no preconceived parametric assumptions (such as Gaussian, lognormal, multimodal, or other) are made about its shape [19,20,24].

The nonparametric maximum likelihood (NPML) estimate of the population joint density or distribution is analogous to the entire collection of each patient's exactly known parameter values described above. Whatever its shape or distribution turns out to be, it does not matter. The distribution is determined and supported by up to  $N$  discrete points for the  $N$  patients in the population studied. Each point consists of the estimated

single numbered parameter values, one for each parameter such as Vd, Kel, etc., along with an estimate of the associated probability of each of these discrete points.

The NPML method of Mallet [19], like the parametric NONMEM method, can also function with only one sample per patient. In contrast to parametric methods, however, no parametric assumptions about the shape of the parameter distributions (Gaussian, etc.) need to be made. The distribution is totally flexible, and depends only on the actual subject data. The mean, SD, and other common statistical summary parameters can easily be obtained later, from the entire discrete distribution, if desired. The only assumption made about the shape of the discrete parameter distribution is that the shape, whatever it is, is the same for all subjects studied in the population. The method therefore can discover, in the population itself, unsuspected subpopulations of subjects such as fast, intermediate, and slow metabolizers, without recourse to other descriptors or covariates, and without recourse to individual Bayesian posterior parameter estimates [19]. That cannot be done with parametric methods.

A nonparametric EM (NPEM) method has been developed by Schumitzky [20,24]. Like the NPML method, it also can work with only one sample per patient and does not have to make any approximating parametric assumptions about the shape of the joint probability distribution. It also obtains the entire discrete joint density or distribution of points. In contrast to the NPML method, though, the NPEM method obtains a continuous (although very spiky) distribution, which then becomes discrete in the limit, after an infinite number of iterations. With each iteration, the NPEM method examines the patient data and develops a more and more spiky joint distribution. The spikes eventually become the approximately N discrete support points for the population distribution of parameter values, just as with the NPML method. Both the NPML and the NPEM methods converge to essentially the same results [11]. Both the NPML and the NPEM methods are proven under suitable hypotheses to have the desirable property of mathematical consistency [7-9].

Figures 7 through 9 illustrate the ability of the nonparametric approach, as shown by the NPEM algorithm, to discover unsuspected subpopulations [20]. The NPML method of Mallet has similar capability. Figure 7 shows a carefully constructed simulated population of patients. This population is actually a bimodal distribution consisting of two subpopulations. Half are "fast" and half are "slow" metabolizers of a drug. They all have the same volume of distribution, but two different elimination rate constants. There was no correlation between the two parameters.

From this defined population, twenty simulated patients were sampled at random. Figure 8 shows these sampled patients' exactly known parameter values, smoothed and graphed as in Figure 7. Figure 8 thus shows the true empirical population parameter distribution that NPEM, or any other population modeling method, must now discover.

These twenty simulated patients each received a simulated single short infusion of a drug having one compartment behavior. Five simulated serum samples were drawn at uniformly spaced times. The assay SD was defined as  $\pm 0.4$  concentration units. The

resulting data of serum concentrations over time was presented to the NPEM algorithm and computer program [20,24], and also to a parametric population modeling method such as NONMEM or IT2B.

Figure 9 shows the NPEM results, again graphed as in Figure 7. The NPEM method clearly discovered the two subpopulations of patients, and closely described the shape of the known empirical original population joint distribution shown in Figure 8.

Figure 10 shows the very different perception of the population when a parametric method such as IT2B, the parametric EM, or NONMEM is used to study the population shown in Figure 8. The second order density in the figure is the one obtained by a parametric method. Note that the mean is actually where there are no subjects at all! Parametric methods cannot discover subpopulations without additional aid. They give an entirely different impression of the population behavior of the drug. Figure 10 also gives an impression of much greater variability within the population than actually existed among the two fairly tightly grouped subpopulations, as shown in Figures 8 and 9.

Figure 11 describes an NPEM population model of Vancomycin made by Hurst et al. [25]. It shows the relationship between the volume of distribution (VS, in L/kg) and the slope (K7) of the elimination rate constant ( $\text{hr}^{-1}$ ) per unit of creatinine clearance. The many discrete spikes are seen in this now unsmoothed plot of this pair of parameters. The multiple spikes and their various probabilities provide a much more optimal Bayesian prior, permitting “multiple model” design of a dosage regimen to achieve a selected target goal with optimal precision [26-31].

Some representative results from the NPEM program are shown below, from the same data set as in the IT2B analysis of the 10 patients receiving intramuscular Amikacin, 1000 mg every 24 hours for 5 or 6 days [17]. It obtains somewhat similar, but more likely, results than IT2B. A total of 10,007 possible points for the overall parameter space constituted the grid of available discrete points.

There are two methods by which the NPEM iterative analysis is accelerated. One is that whenever the estimated probability of a grid point in the parameter space is less than  $10^{-10}$ , it never returns as an active or significant point again. For this reason, such points can be omitted from further analysis. This is why the number of active grid points gets less with almost every cycle.

Another acceleration technique consists of jumping forward 10, 50, or 70 cycles into the future, based on the change in probability for each grid point in the present cycle from the cycle before. Based on such a change in probability per cycle, the new density is found, the subject data is then analyzed, and the new density and its likelihood is found. It is more likely than the one before, then further extrapolations are performed to 50 or 70 cycles in the future. These two acceleration techniques have increased the speed of NPEM analysis by 30 to 50 times over previous versions of NPEM.

The results of this analysis, which converged on Cycle 39, are shown in Table 1, and in the figures below. The population mean parameter values for  $K_a$ ,  $K_s$ , and  $V_s$  were 1.53 hr<sup>-1</sup>, 0.0033 hr<sup>-1</sup>, and 0.255 L/kg respectively, very similar to the values obtained by the IT2B program in the previous paper. The correlation coefficient between  $K_s$  and  $V_s$  was 0.513, similar to 0.671 obtained with the IT2B program. However, the entropy was less, 2.2998 (versus 3.57), and the scaled information was 100.04 % (versus 81.6 %). The fact that this information value was greater than 100 % suggests that more grid points than the 10,007 used might be considered if the run was to be repeated. Usually the more grid points, the better, up to the current maximum of 80,000 on the PC.

### **Larger and Nonlinear Nonparametric Population Models**

Large and nonlinear nonparametric population modeling software has now been implemented on the Cray T3E parallel machine at the San Diego Supercomputer Center (SDSC), as a research resource for such work. The user specifies the structural model and pathways using PC software now in the USC\*PACK collection. The model file, the patient data files, and the instructions are sent to the SDSC machine, the analysis is done using the desired number of processors, and the results are sent back to the user's PC, where they are examined just as with the NPEM program described herein [18]. For these larger models, up to several million grid points may be used to define the parameter space. This resource is now available and in use by researchers to make such models.

### **Weaknesses and Strengths of Nonparametric Methods**

The main weakness of the nonparametric population modeling approach is that there is no feature to separate the various sources of variability into their respective components – the interindividual variability due to the diversity among the subjects in the ways they handle the drug, and the intraindividual variability due to the errors in preparing and giving the doses, recording the times at which responses such as serum concentrations were obtained, structural model misspecification, changing parameter values during the study period, and the assay error itself. Nonparametric methods do not resolve these things. That, however, is what the parametric methods do very well, as described earlier.

The strengths of nonparametric approaches are many. First, they have the desirable property of mathematical consistency, as described [7-9]. Second, no assumptions about the shape of the parameter distributions need to be made. Because of this, nonparametric methods can detect, without additional aid from covariates or descriptors, previously unsuspected subpopulations of patients, as shown in Figures 7 through 9. Third, instead of obtaining only single-point parameter estimates, one gets multiple estimates, basically one for each subject studied. This is why the nonparametric approach is mathematically optimal, as it comes the closest to the ideal of the best that can ever be done, namely to obtain the collection of each subject's exactly known parameter values, without bothering with other parametric statistical summaries, though these are easily obtained as well. Fourth, the multiple sets of parameter values provide a tool to circumvent the separation principle [21], and to predict the precision (weighted

squared error, for example) with which a candidate dosage regimen will hit a desired target serum concentration, or other response, at a desired time. The nonparametric population models thus permit “multiple model” design of dosage regimens to optimize a specific performance criterion [26-31]. The development of such optimally precise dosage regimens, using such nonparametric population models, will be discussed in a separate paper.

### **Other Methods of Population Modeling**

Besides the nonparametric approaches, there are the hierarchical Bayesian, or Gibbs sampling approaches of Wakefield et al [32], and the Semi-Nonparametric approach of Davidian and Gallant [33]. The first method describes another Bayesian strategy of sampling and Bayesian inference. The second method is nonparametric, but with certain restraints to smooth the distributions. These approaches are active and interesting areas of further investigation at the present time.

### **Optimal Strategies in Population Modeling**

The optimal strategy for making clinically useful population PK/PD models currently appears to be:

Determine the assay error pattern explicitly and obtain the assay error polynomial.  
Use a parametric population modeling program such as IT2B. Obtain gamma.  
Having both of the above, then use a nonparametric population modeling program to obtain the entire discrete joint parameter distribution.

This sequence of steps currently appears to make optimal use of the information about the assay error, often 1/3 to 1/2 of the overall intraindividual variability, and the raw data present in the population studied, to obtain the most probable parameter distribution. It appears to provide optimal tools to develop dosage regimens which achieve desired target goals with maximum precision.

### ACKNOWLEDGMENTS

Supported by US Government grants LM 05401, RR11526, and RR 01629, and by the Stella Slutsky Kunin Research Fund.

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Table 1. Text output of the NPEM program. Results of the population analysis of 10 subjects receiving intramuscular Amikacin [17].

CYCLE NO. 39  
TODAY IS 01/26/98; THE TIME IS 18:58:54

THE TRUE (NUMERICAL) LOG-LIKELIHOOD (USING THE NUMBER  
THEORETIC INTEGRATION SCHEME) OF THE 10 SUBJECT VECTORS,  
GIVEN THE PRIOR DENSITY, IS:  
-484.380880981189

(Note: compare this value with that of -494.234411 found with the IT2B program).

THE DIFFERENCE BETWEEN THE LIKELIHOOD OF THE  
THE MAXIMUM LIKELIHOOD ESTIMATE OF THE DENSITY AND THE  
LIKELIHOOD OF THIS CYCLE IS LESS THAN THE FOLLOWING NUMBER:  
0.895388311240986D-002

THE CORRESPONDING FIGURE FOR CYCLE 1 WAS 10374. .  
SINCE IT IS NOW .89539E-02, THIS ANALYSIS HAS GONE 10374.  
DIVIDED BY 10374. OR 99.99992 % OF THE WAY FROM THE  
APRIORI DENSITY TO THE MAXIMUM LIKELIHOOD ESTIMATE OF THE  
JOINT DENSITY.

THE NO. OF ACTIVE GRID POINTS IS NOW 11  
THE INITIAL NO. OF GRID POINTS WAS 10007

THE FOLLOWING VALUES ARE FOR THE UPDATED DENSITY:  
THE SCALED INFO FOR THIS CYCLE IS 100.04 %  
THE ENTROPY FOR THIS CYCLE IS 2.2998

THE MEANS ARE:

KA	KS1	VS1
1.537113	0.003339	0.255431

THE COV MATRIX IS, IN LOWER TRI FORM:

KA	KS1	VS1
0.191390		
-0.000096	0.000000	
0.000483	0.000017	0.002320

THE STANDARD DEVIATIONS ARE, RESPECTIVELY:

KA	KS1	VS1
0.437481	0.000681	0.048166

THE PERCENT COEFFICIENTS OF VARIATION ARE, RESP.:

KA	KS1	VS1
28.461229	20.395316	18.856982

THE CORR. MATRIX IS, IN LOWER TRIANGULAR FORM:

KA	KS1	VS1
1.000000		
-0.321800	1.000000	
0.022907	0.513156	1.000000

THE 3 SETS OF LINES BELOW WILL GIVE ADDITIONAL STATISTICS FOR THE VARIABLES. FOR EACH SET:

THE 1ST LINE WILL GIVE THE MODE, THE SKEWNESS, THE KURTOSIS, AND THE 2.5 %-TILE VALUE OF THE DISTRIBUTION.

THE 2ND LINE WILL GIVE THE 25, 50, 75, AND 97.5 %-TILE VALUES OF THE DISTRIBUTION.

THE 3RD LINE WILL GIVE THREE ADDITIONAL AD-HOC ESTIMATES OF THE STANDARD DEVIATION FOR THAT MARGINAL DENSITY.

THE 1ST S.D. ESTIMATE IS THE STANDARD DEVIATION OF A NORMAL DISTRIBUTION HAVING THE SAME [25, 75] %-TILE RANGE AS THAT VARIABLE.

THE 2ND ESTIMATE IS THE STANDARD DEVIATION OF A NORMAL DIST. HAVING THE SAME [2.5, 97.5] %-TILE RANGE AS THAT VARIABLE.

THE 3RD ESTIMATE IS THE AVERAGE OF THE FIRST TWO.

THE 4TH VALUE IN THE LINE IS THE % SCALED INFO FOR THAT MARGINAL DENS.

KA	:			
		1.36500000	0.96735293	2.99978849
		1.18500000	1.37326197	1.90500000
		0.53372870	0.37883033	0.45627951
				100.12102914

KS1	:			
		0.00405000	-0.40887166	1.62823861
		0.00275000	0.00380000	0.00397895
		0.00091101	0.00050104	0.00070603
				112.25082665

VS1	:			
		0.23400001	0.12716226	1.85668144
		0.20998806	0.25200001	0.30600001
		0.07117268	0.04407568	0.05762418
				106.38472260

## Figures and Legends

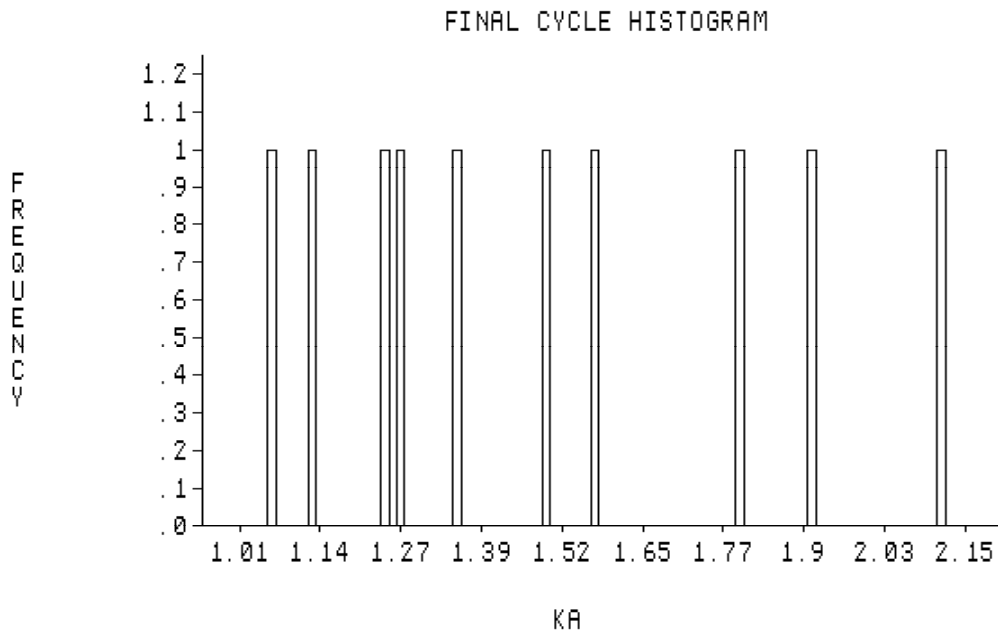


Figure 1. Showing the values of the  $K_a$ , the absorptive rate constant, in the population.

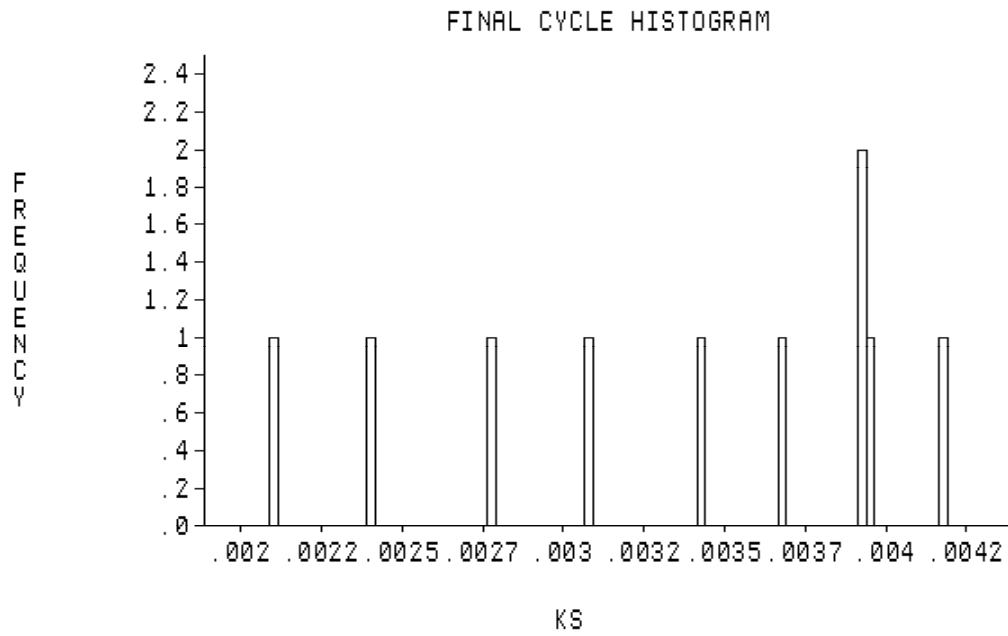


Figure 2. Showing the values of the  $K_s$ , the increment of  $K_{el}$  (the elimination rate constant, per unit of creatinine clearance), in the population.

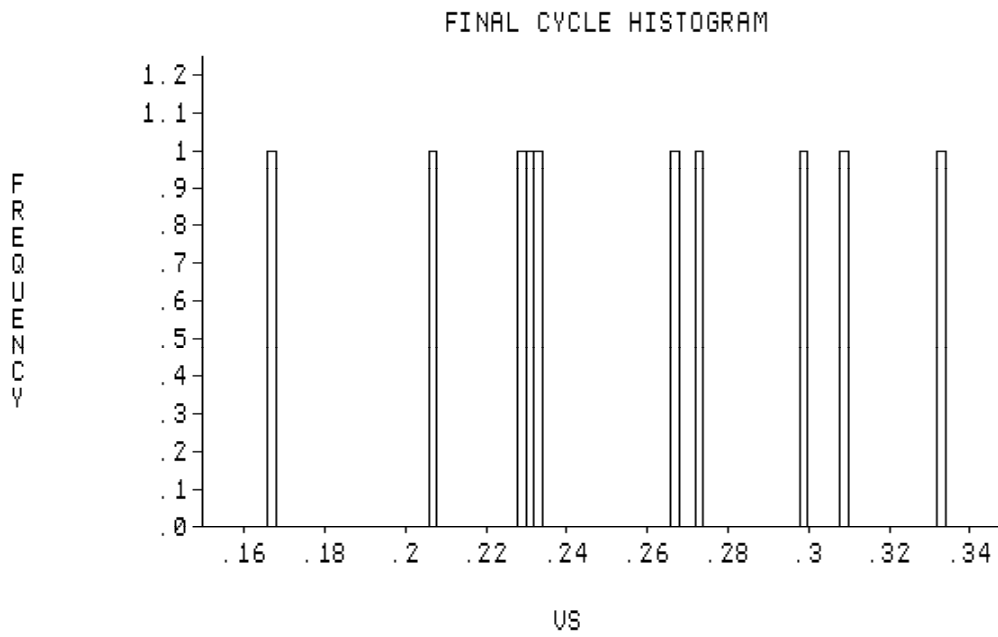


Figure 3. Showing the values of the  $V_s$ , the increment of the apparent volume of distribution per unit of body weight, in the population.

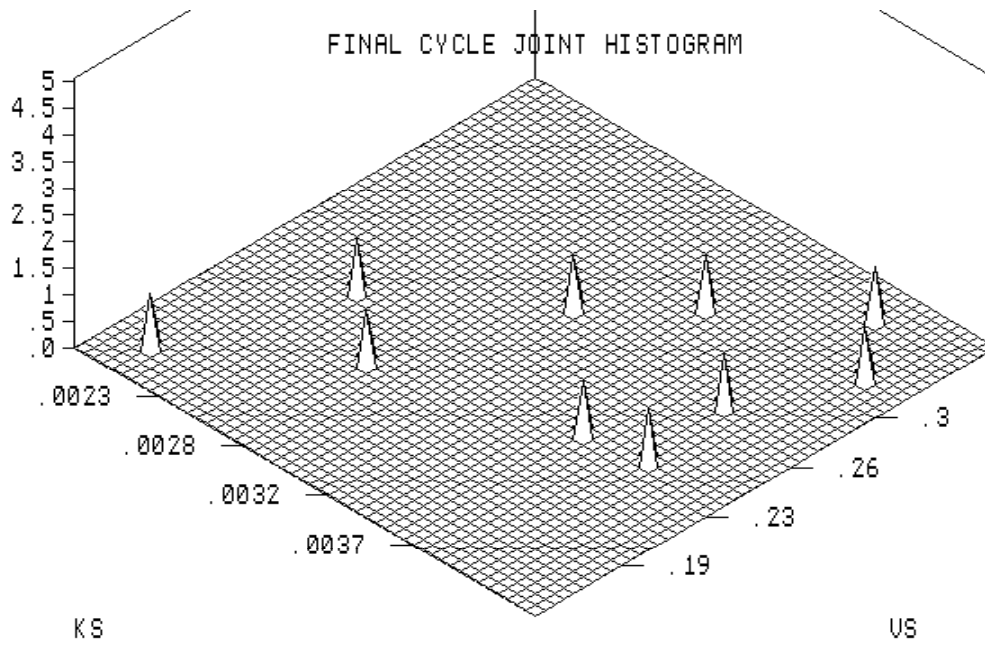


Figure 4. Showing the joint values of the Ks and Vs, in the population.



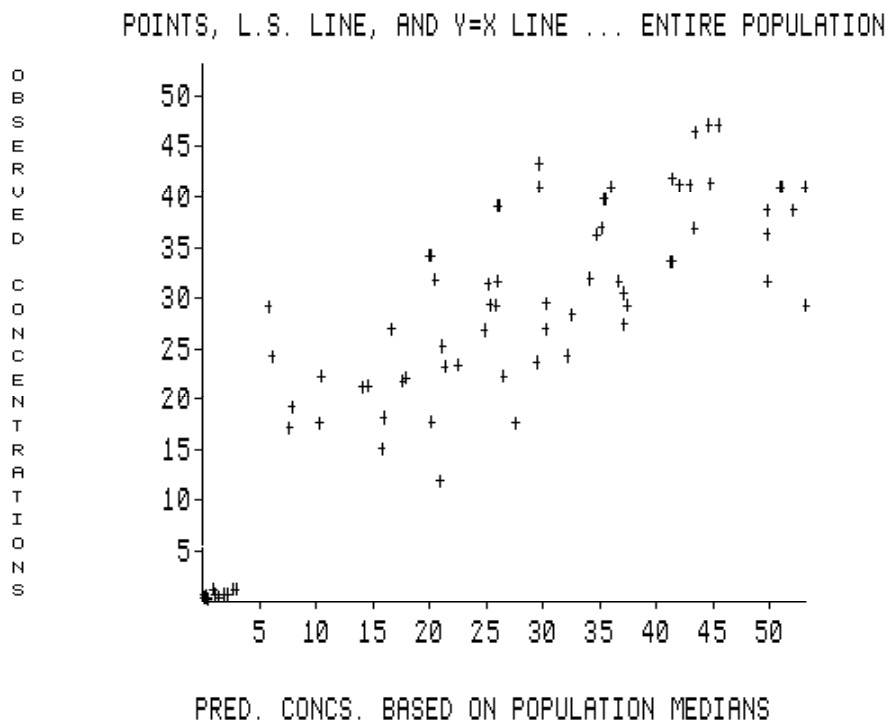


Figure 5. Showing the predicted values of the serum concentrations, using the population median values of  $K_a$ ,  $K_s$ , and  $V_s$ , in the population.

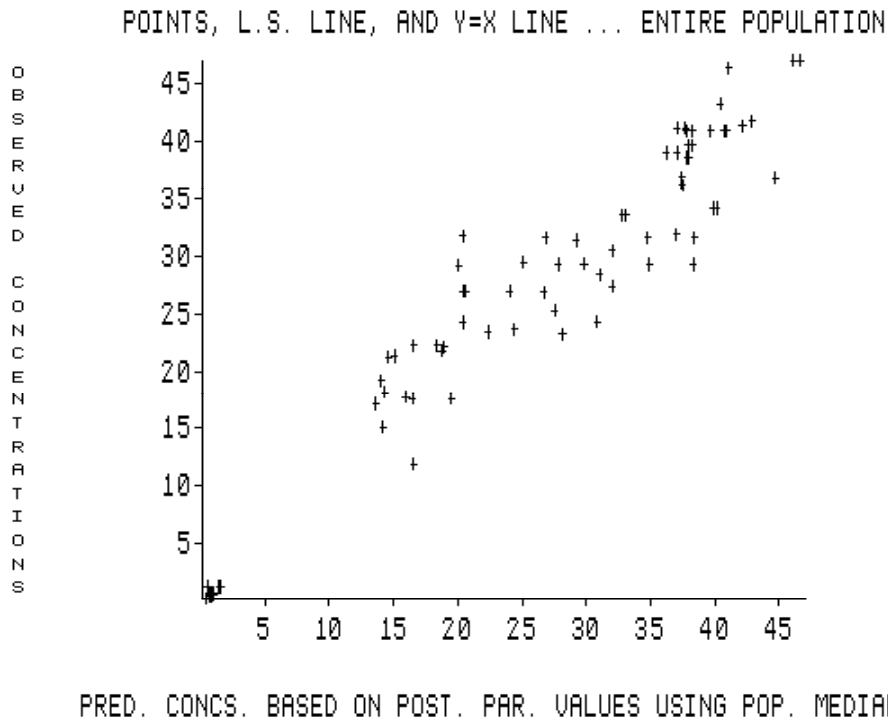


Figure 6. Showing the predicted values of the serum concentrations, using the individual MAP Bayesian posterior parameter values of  $K_a$ ,  $K_s$ , and  $V_s$ , based on using the population median parameter values and their SD's as the MAP Bayesian prior, in the population.

### True Density

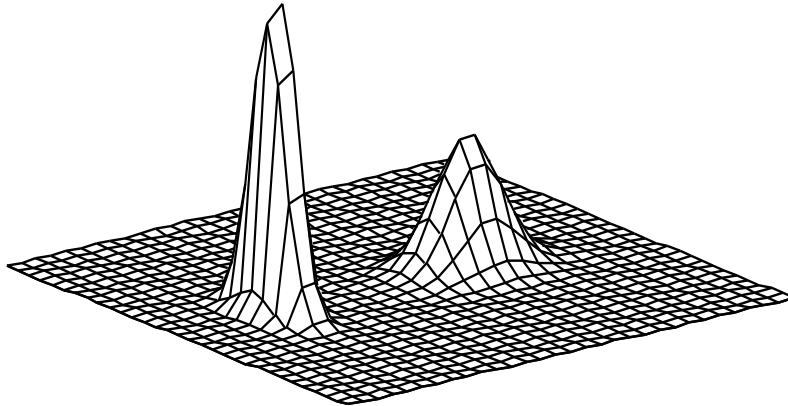


Figure 7. The true pharmacokinetic population joint density from which the 20 samples were taken. If the bottom (or 0.0,0.0) corner is "Home plate", then the axis toward third base is that of the volume of distribution  $V$ , while that toward first base is the elimination rate constant  $K$ . Note that there are actually two subpopulations, with two clusters of distributions for  $K$ .  $V$  and  $K$  are uncorrelated.

Smoothed Sample Density

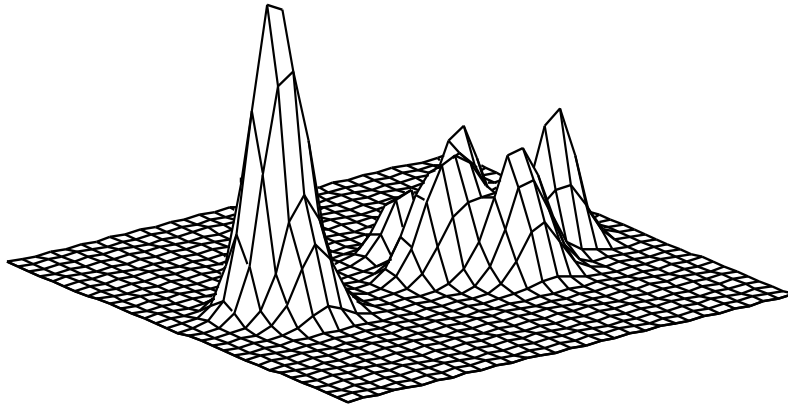


Figure 8. Graph, smoothed as in Figure 7, of the actual parameter values in the twenty sampled patients. The axes are as in Figure 7. This is the distribution that NPEM should discover.

Smoothed Estimated Density -- 5 Levels/Subject

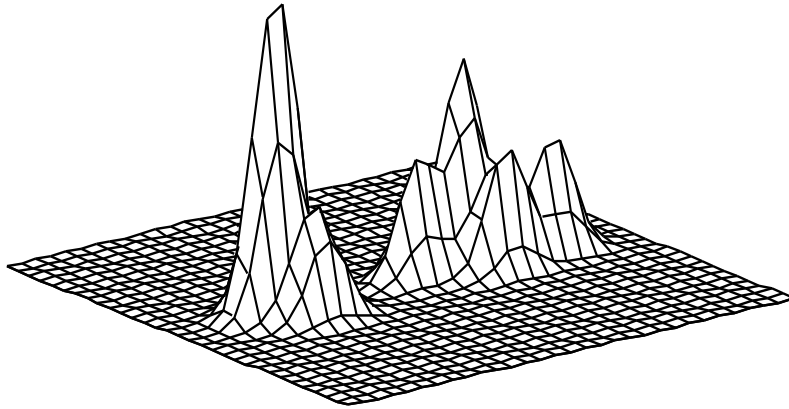


Figure 9. Smoothed estimated population joint density obtained with NPEM, using all five serum levels. Axes as in Figure 7. Compare this figure with Figure 8.

### Second Order Density

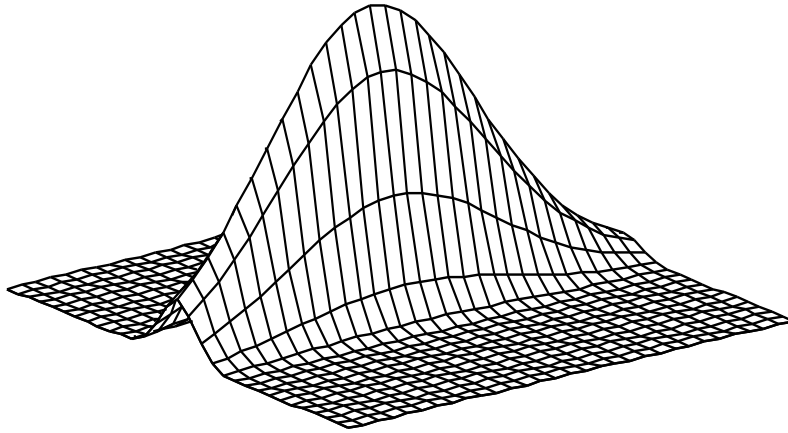
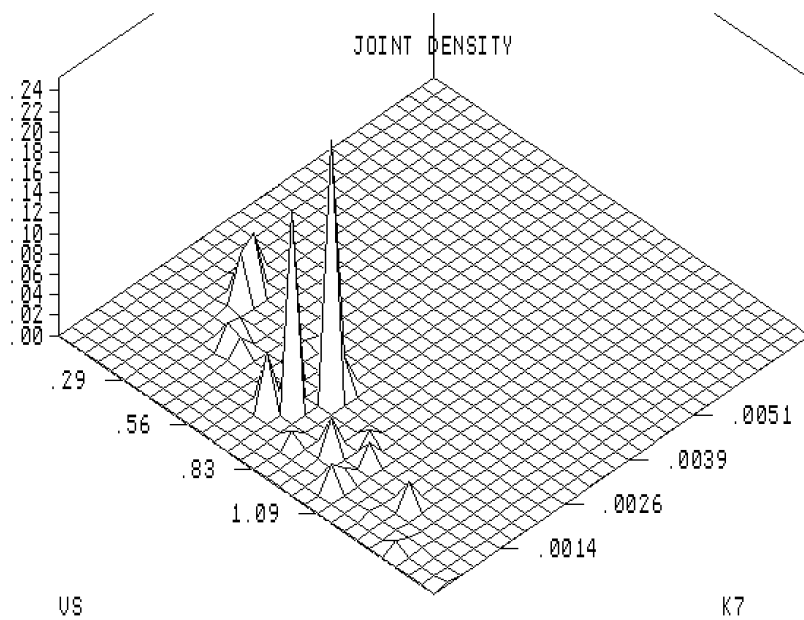


Figure 10. Plot of the population density (the second order density) as perceived by a theoretically optimal parametric method. Axes as in Figure 7. Compare this figure with Figures 8 and 9. The two subpopulations are not discovered here. The true parameter distributions are perceived with great error by this method.



**Figure 11.** Population joint density of Vancomycin as studied by Hurst, et al. VS = volume of distribution of the central (serum) compartment, in L/kg. K7 = increment of elimination constant per unit of creatinine clearance.

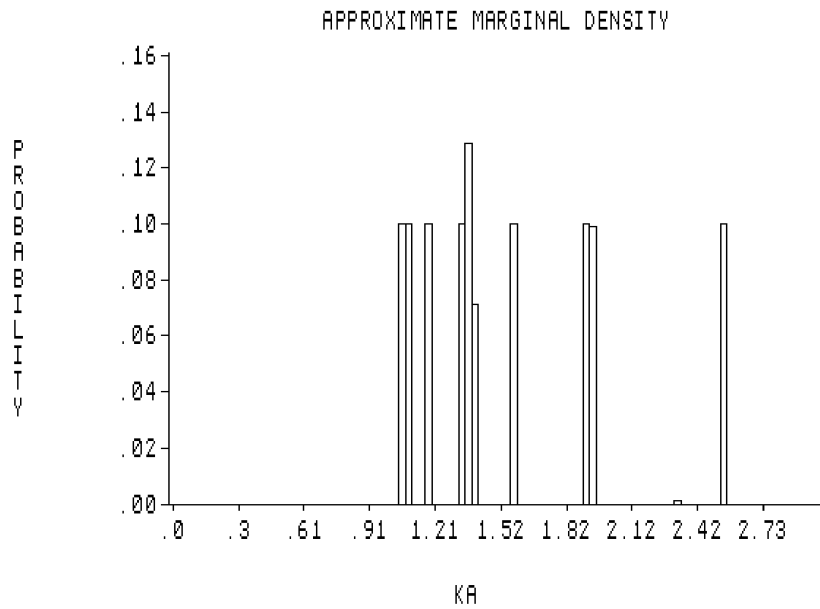


Figure 12. NPEM marginal distribution for the rate constant  $K_a$ . Note that there are 10 major points here, each with its own estimated probability. Another quite minor point is also shown. In this plot, there are 100 divisions in which such points can exist.



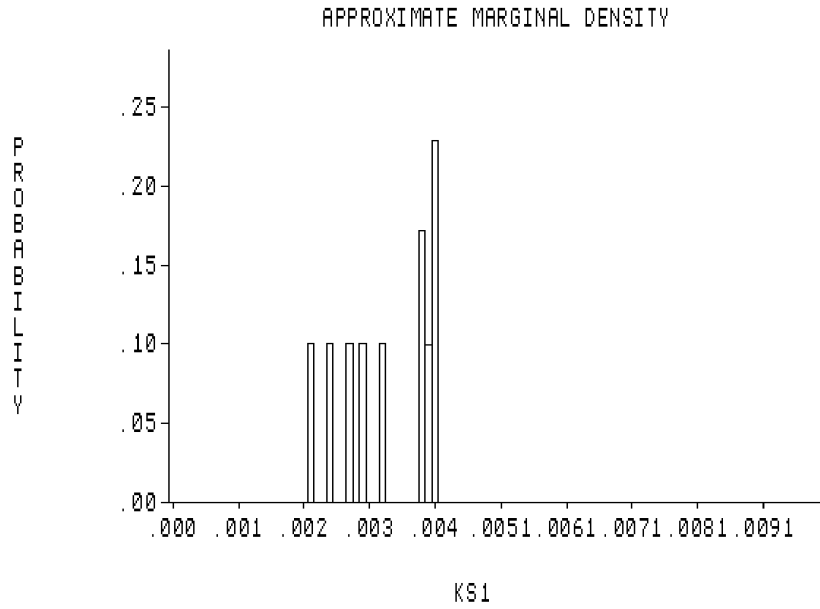


Figure 13. NPEM marginal distribution for the rate constant  $K_{s1}$ , the increment of elimination rate constant per unit of creatinine clearance. Note that there are 9 major points here, each with its own estimated probability. One point corresponds to approximately two subjects. Two points correspond to approximately two subjects each. In this plot, there are 100 divisions in which points can exist.

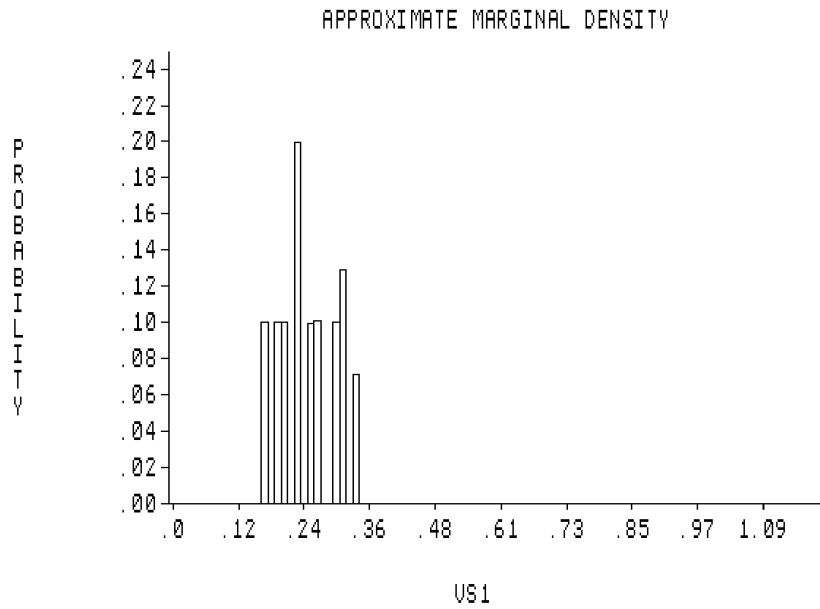


Figure 14. NPEM marginal distribution for the apparent volume of distribution per unit of body weight,  $V_{s1}$ . Note that there are 10 major points here, each with its own estimated probability. In this plot, there are 100 divisions in which points can exist.

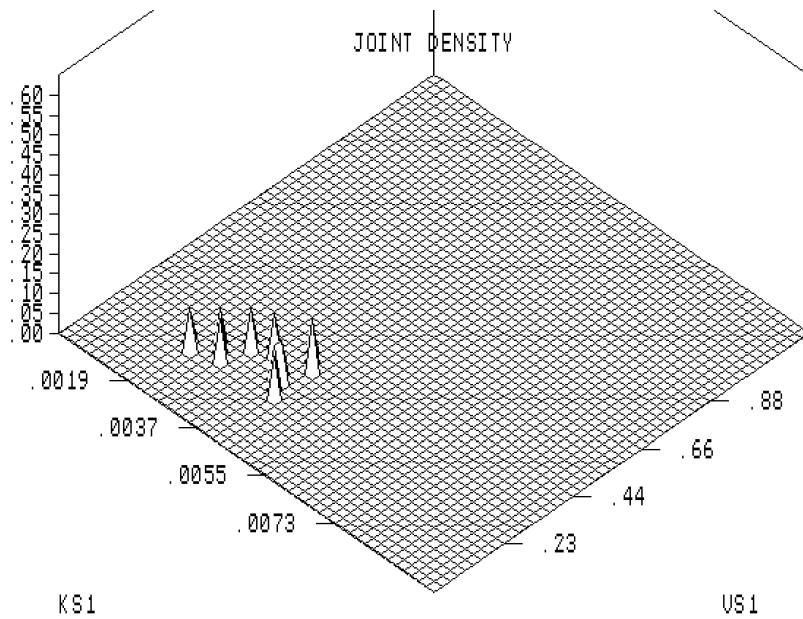


Figure 15. NPEM joint marginal distribution for the parameters  $K_{s1}$ , the increment of elimination rate constant per unit of creatinine clearance, and  $V_{s1}$ , the apparent volume of distribution per unit of body weight. There are actually 10 major points here, each with its own estimated probability, but some are difficult to see. One can check this by looking at Figures 13 and 14, which show each single marginal density in better detail. In this frequency plot, there are 50 x 50 divisions in which points can exist.

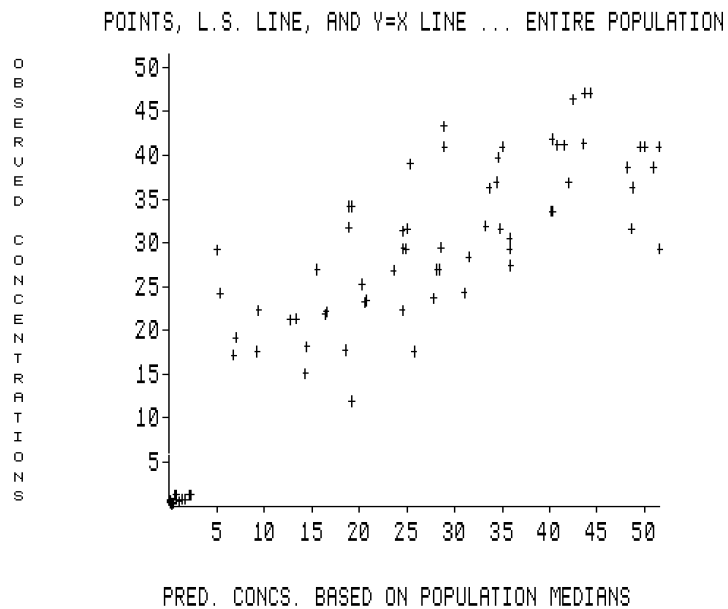


Figure 16. Scatterplot of serum concentrations predicted using the population median parameter values. Predicted concentrations are on the horizontal axis, measured ones on the vertical.

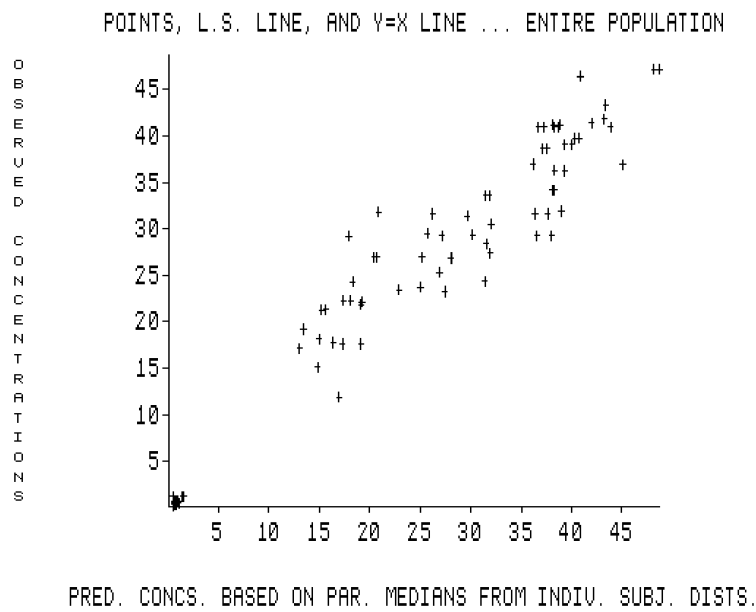


Figure 17. Scatterplot of serum concentrations predicted using the median values of the Bayesian posterior parameter density for each subject. Predicted concentrations are on the horizontal axis, measured ones on the vertical.

# **ESTIMATION OF CREATININE CLEARANCE IN PATIENTS WITH UNSTABLE RENAL FUNCTION, WITHOUT A URINE SPECIMEN.**

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Running title: Estimation of Unstable Creatinine Clearance

Keywords: Creatinine Clearance, Renal Function

## **Abstract**

**Background:** There is a significant need to estimate creatinine clearance easily in acutely ill patients with unstable renal function, who have changing serum creatinine values and who need careful individualization of drug dosage, without the difficulty of having to collect a traditional timed urine specimen. **Method:** The daily change in the total amount of creatinine is the difference between its production and excretion. Production is estimated based on studies by others employing many carefully timed urine specimens. It is related both to age and to the degree of chronic uremia. Urinary excretion of creatinine is equal to creatinine clearance times the average of a pair of timed serum creatinine concentrations, times the duration of the collection (usually 24 hours). **Results:** Good correlation was found between measured creatinine clearance and the estimated values, with precision essentially equal to that of the traditional method. **Conclusions:** In this way, one can estimate the creatinine clearance which makes serum creatinine change from an initial concentration at one stated time to another one at another stated time, for a patient of a stated age, gender, height, and weight. This method has been incorporated into software to perform the calculations easily and rapidly, and has been integrated into the USC\*PACK PC programs for planning, monitoring, and adjusting individualized dosage regimens of drugs.

## **Introduction**

Especially for purposes of providing guidance for dosage with renally excreted drugs that are potentially toxic, estimation of creatinine clearance (CCr) has long been a problem in sick and unstable patients, largely because of difficulty in collecting a

carefully timed urine specimen in unstable and critically ill patients. A number of years ago, several methods were developed to estimate CCr without a urine specimen [1-4]. However, those approaches only considered the situation where serum creatinine was stable. To overcome this problem, a dynamic approach to the problem was developed.

### **A Model of Creatinine Kinetics**

The dynamic model [5] first used the relationship that the daily change in the total amount of creatinine in a patient's body is the difference between creatinine production (P) and excretion (E) during that day. This was described by

$$V(C_2 - C_1) = P - E \quad (1)$$

where V is the apparent volume of distribution of serum creatinine (in hundreds of ml), C<sub>1</sub> and C<sub>2</sub> are the first and second serum creatinine values taken typically one day apart (in mg/dL), and P and E are production and excretion in mg. Since V is somewhat less than total body water, it was empirically approximated as 40 % of the patient's total body weight (in hundreds of grams).

### **Calculation of Daily Creatinine Production**

#### The Effect of Age.

The data of Siersbaek-Nielsen et al. [2] of the effect of age upon the carefully measured 24 hour urinary creatinine excretion, in hospitalized patients who were clinically free of any renal disease, was shown to be described by

$$E = 29.305 - 0.203A \quad (2)$$

where E is the measured urinary creatinine excretion (in mg/kg/day) and A is the age (in years). Since the patients were all quite stable, and in a steady state,

$$E = P. \quad (3)$$

In this way, one can use this carefully measured data of excretion to estimate daily creatinine production. This estimate can be further refined as described below. It should also be noted that in these patients, the average serum creatinine their patients was 1.1 mg/dL [2]. This will be useful below.

#### The Effect of Degree of Uremia.

It was shown by Goldman [6] that uremic patients also have a decreased excretion (and therefore production) of creatinine. Using data from that report, creatinine production (P, in mg /day for an average size patient) is related to serum creatinine (C, in mg/dL) by

$$P = 1344.4 - 43.76C \quad (4)$$

Based on this, one can now adjust the first estimate of creatinine production for age as given in Eqn (2) to the average value ( $C_{avg}$ ) of the patient's  $C_1$  and  $C_2$  by the ratio  $R$ , where

$$P_1 = 1344.4 - 43.76 \times C_{avg}, \quad (5)$$

and

$$P_2 = 1344.4 - 43.76 \times 1.1, \quad (6)$$

where 1.1 = the average serum creatinine in Siersbaek-Nielsen's patients, in each age group, as described above. Then,

$$R = P_1 / P_2, \text{ and} \quad (7)$$

$$\text{the adjusted } P, \text{ or } P_{adj} = P \times R \quad (8)$$

In our work, the best empirical correlation between measured and estimated CCr was finally found by taking 95% of  $P_{adj}$ . In this way, daily creatinine production can be estimated for men, based on many careful measurements of 24 hour urinary creatinine excretion, and adjusted to the patient's age, weight, and degree of uremia [6]. In further adjustments, 90% of the value for men was then taken if the patient was female, and, finally, 85% of that was taken for both men and women. This gave the best correlations between estimated and measured CCr when renal function was severely impaired.

However, the 15% reduction led to underestimations of about 15 % when renal function was close to normal [5]. Because of this, we have now modified the original algorithm to apply the above 15 % reduction only for patients who have severely impaired renal function and who are on hemodialysis or peritoneal dialysis. Removal of the 15 % restriction results in the improved estimates shown in Figure 1, which are less biased than those found with the previous procedure [5].

Further, if a patient's muscle mass is clearly above or below normal, as may be the case with very muscular patients, or conversely in cirrhotic patients or those with AIDS, for example, one can simply make a rough clinical estimate of the patient's body (muscle) mass as a percent of normal, if desired, to make a further final adjustment of  $P$ . There are no specific rules for this – only that one might make a rough clinical estimate based on findings on physical examination. The adjustment for body mass was not done either in the original study [5] or in the present one. However, it provides an additional degree of freedom to protect against overestimation of CCr in cachectic patients, or underestimation in very muscular patients. The range currently permitted in these estimates is from 70 to 130 percent of normal.

### **Calculation of Daily Creatinine Excretion**



In the traditional calculation of creatinine clearance,

$$C = UV/P, \quad (9)$$

where U is the urinary creatinine concentration, V is the 24 hour urine volume, P is the plasma or serum creatinine concentration, and C is creatinine clearance. This can be rearranged to show that what comes out of the body is equal to what was cleared from the body. Thus

$$PC = UV. \quad (10)$$

Because they are numerically equal, PC can therefore be substituted for UV, the measured 24 hour excretion. Thus

$$E = UV = PC, \text{ and}$$

$$E = PC = C_{\text{avg}} \times (CCr/100) \times 1440, \quad (11)$$

where E is expressed in mg/day,  $C_{\text{avg}}$  is in mg/dL, CCr is in ml/min, and 1440 represents the number of minutes in one day.

### **The Final Overall Algorithm**

The final overall algorithm to calculate creatinine clearance from unstable serum creatinine values, and without requiring a urine specimen, may now be written as

$$0.4W(C_2 - C_1) = P_{\text{adj}} - C_{\text{avg}} \times CCr/100 \times 1440 \quad (12)$$

Where W is body weight in hundreds of grams, and  $C_1$  and  $C_2$  are serum creatinine in grams/100 ml. One can simply rearrange the equation and solve it for CCr. After this, the raw creatinine clearance above can be corrected for body surface area to that of an average patient having a body surface area of 1.73 square meters.

The above equation thus represents a dynamic model of creatinine kinetics, and permits estimation of CCr from routine clinical data of age, gender, height, weight, and either a pair of unstable and changing serum creatinine levels or a single stable serum creatinine, all without having to collect a urine specimen, which is an extremely difficult and unreliable procedure in all but research situations, especially for acutely ill patients in intensive care units.

### **Comparison of Estimated with Measured Creatinine Clearance**

In a first set of 128 observations on 15 patients in the renal transplant unit of the Los Angeles County – USC Medical Center [5], the algorithm was shown to have an accuracy essentially equal to that of Jadry [1]. In an additional set of 250 observations on a group of 14 patients who had just undergone renal transplantation, the standard error of the estimate ( $\pm 14.9$  ml/min) was slightly more precise than the equations of Jadry ( $\pm 16.6$  ml/min), with an overall scatter of about  $\pm 25\%$  between the estimated and the measured values, as shown in Figure 1.

As a control, one must consider the traditional determination of CCr, and the errors present in its estimation. If one can measure a serum creatinine level with a coefficient of variation of 5%, as is the case with many common autoanalyzer methods, and if one measures urinary creatinine concentrations with a coefficient of variation of 8%, as is also common, then if one can collect a 24 hour urine specimen with a coefficient of variation of 5%, these errors will propagate so that the resulting value of the traditionally measured creatinine clearance will have a coefficient of variation of 11%. The resulting 95% confidence limit is therefore  $\pm 22\%$ . This error closely corresponds to the scatter found between the estimated and measured CCr values shown in Figure 1. Because of this, it is likely that this method of estimating CCr has a precision about equal to the classical measurement of it. In addition, it is practical in clinical situations. It is also probably better at sensing changes in renal function in response to sudden changes in serum creatinine than are the more simple formulas of Jadry [1], Jelliffe [3], or Cockcroft and Gault [4], which were designed only for use when serum creatinine is stable, as serum creatinine usually requires about one week to stabilize following a change in renal function.

### **The Question of Ideal Body Weight**

It would seem logical to correct the estimate of creatinine production and muscle mass by using some estimate of ideal body weight. However, in anecdotal examinations of this question in several morbidly obese patients, somewhat more precise estimates of CCr were actually obtained using total body weight than with various estimates of ideal body weight. Because of this, we have continued to use total body weight in preference to an estimate of ideal body weight. It would be interesting to study this question further in another study.

### **Conclusion**

The method described here for estimating CCr in acutely ill and unstable patients provides a useful tool for evaluation of a patient's renal function in a practical manner when serum creatinine concentrations are unstable, changing from day to day. It also permits linkage of this information about rapidly changing renal function in patients to track the pharmacokinetic and dynamic behavior of drugs in such patients, thus permitting improved understanding of drug behavior and improved individualization of drug dosage regimens in such patients.

### **ACKNOWLEDGMENTS**

Supported by US Government grants LM 05401 and RR 01629, and by the Stella Slutzky Kunin Research Fund.

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Figure legend

Figure 1. Comparison of Estimated CCr as described herein, with measured CCr.

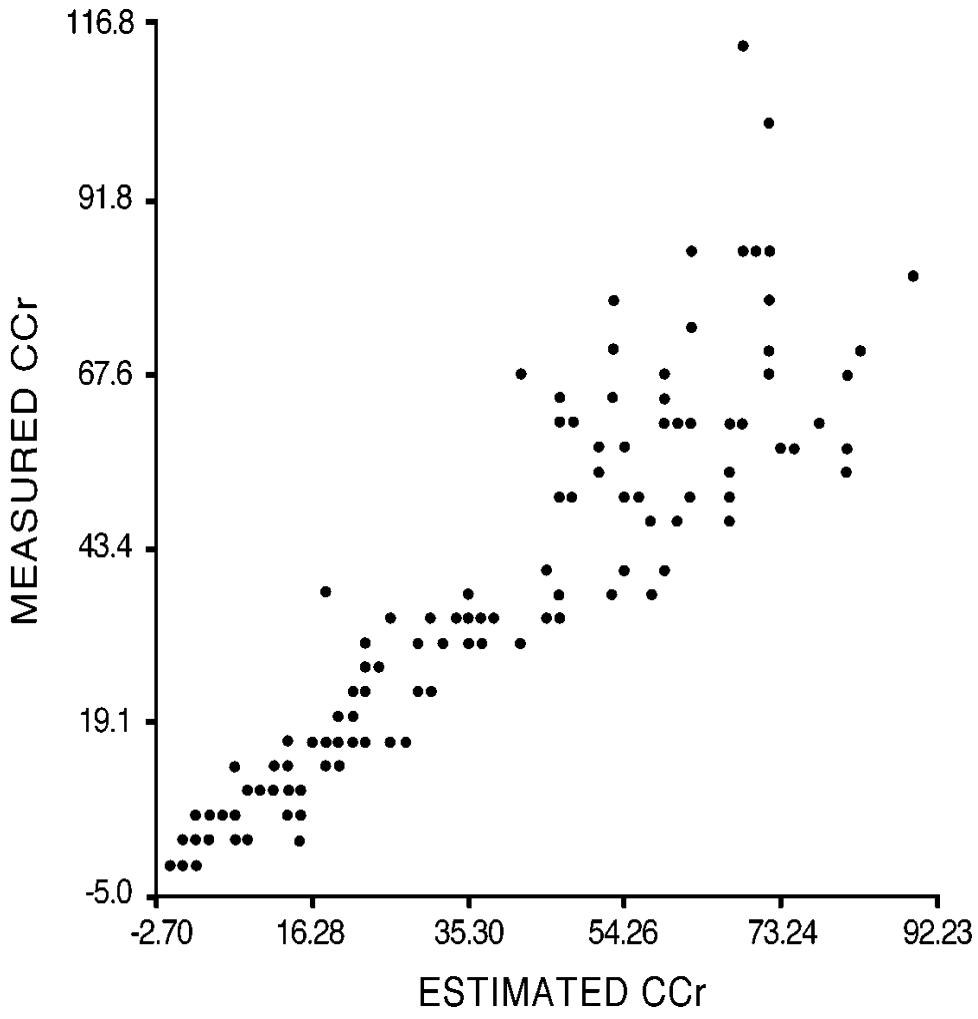


Figure 1. Comparison of Estimated CCr as described herein, with measured CCr.

# **ACHIEVING TARGET GOALS MOST PRECISELY USING NONPARAMETRIC COMPARTMENTAL MODELS AND "MULTIPLE MODEL" DESIGN OF DOSAGE REGIMENS.**

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## **ABSTRACT**

Multiple model (MM) design and stochastic control of dosage regimens permits essentially full use of all the information contained in either a Bayesian prior nonparametric EM (NPEM) population pharmacokinetic model or in an MM Bayesian posterior updated parameter set, to achieve and maintain selected therapeutic goals with optimal precision (least predicted weighted squared error). The regimens are visibly more precise in the achievement of desired target goals than are current methods using mean or median population parameter values. Bayesian feedback has now also been incorporated into the MM software. An evaluation of MM dosage design using an NPEM population model versus dosage design based on conventional mean population parameter values is presented, using a population model of Vancomycin. Further feedback control was also evaluated, incorporating realistic simulated uncertainties in the clinical environment such as those in the preparation and administration of doses.

## **INTRODUCTION**

Previous work from this laboratory has shown the utility of nonparametric population pharmacokinetic modeling, resulting in a discrete number of support points for the entire population joint probability density function, compared to that using conventional single point parameter estimates such as means and variances, as are obtained from parametric population models [1]. These multiple discrete support points become multiple contending population parameter estimates, instead of the conventional single point summary parameter estimates, to use in planing the initial dosage regimen for a new patient who appears to belong to that population.

Figure 1 shows an example of the multiple support points for the joint probability density for a population pharmacokinetic model of Vancomycin. There are a total of 28 such support points, derived from the population of 30 patients studied. Each support point has a discrete value for each of the 4 pharmacokinetic parameter values - the central compartment apparent volume of distribution ( $V_d$ ), the increment of elimination rate constant per unit of creatinine clearance ( $K_{slope}$ ), and the rate constants from the central to the peripheral compartment ( $K_{cp}$ ) and back from it ( $K_{pc}$ ). Each discrete support point is a collection of the estimated values for each parameter, along with an estimate of the probability for that parameter set. The collection of all such points (28 in the present case) constitutes the nonparametric estimate of the discrete joint probability density for the population. It is made without using any parametric assumptions (normal, lognormal, etc.) about the overall shape of that distribution. The nonparametric population model is

thus represented not simply by a single best parameter estimate such as mean or standard deviation (SD), but rather by a matrix of rows and columns. The 5 columns here represent the discrete values of the 4 parameters  $V_d$ ,  $K_{slope}$ ,  $K_{cp}$  and  $K_{pc}$ , and of the probability associated with that set of parameter values which constitute each support point.

In the present model, there were 28 rows of 5 columns each. The 28 rows provided 28 possible versions of the next patient for whom the population model might serve as the Bayesian prior for the optimal design of the initial dosage regimen to achieve a clinically selected individualized target goal. The selection of such individualized target goals has been discussed in another paper in this collection. These multiple discrete support points are shown graphically in Figure 1, for the parameters of  $V_d$  and  $K_{slope}$ . A similar 3D plot can be made for  $K_{cp}$  and  $K_{pc}$ , and for any desired pair of parameters.

This report further describes a comparison of the results achieved using the nonparametric population model versus results obtained using the traditional method based on the mean Vancomycin population parameter values, with respect to the ability of each regimen to achieve and maintain the chosen serum level goal(s) precisely. Note that the MM regimen is specifically computed to minimize the expected value of the total weighted squared error in the achievement of the goal(s), while the traditional regimen, using single point parameter estimates, cannot do this.

The MM software has now been extended to incorporate feedback as well. This report describes a realistic simulation of vancomycin therapy in which common errors are present in the preparation of the doses and in their timing, as well as in the measurement of the serum levels. These mean clinical error values are also known to the MM controller for designing the dosage regimen with appropriate skepticism.

The natural link between nonparametric population modeling and optimal (maximally precise) drug therapy is MM dosage design. In contrast, the limiting factor in parametric population modeling is that there is only one single possible value for each parameter. Using parametric population models, after the therapeutic goal is clinically selected, there is only one regimen to compute, that which achieves the target goal for the single chosen version or model of the patient, using the mean, median, or modal parameter values, exactly. There is no opportunity to consider the fact that the patient actually might not have that exact model of the behavior of the drug.

In contrast, when one uses nonparametric population models as the Bayesian prior for designing the initial dosage regimen, there are many (multiple) possible models or versions of the patient which one can use, one for each support point in the discrete probability joint density or distribution. Each support point has its own probability of representing the patient. A candidate regimen can be given to each support point, with its own individual parameter values and the probability associated with that point. Multiple future serum concentrations can be predicted, using the parameter values for each support point, and its probability. In this way, an entire family of serum concentrations can be predicted into the future. At the time for which the chosen goal is desired, it can be

compared with the many serum concentrations predicted to occur at that time (one from each support point), and the weighted squared error with which the goal fails to be achieved can be computed. Other candidate regimens can also be examined.

The optimal regimen is the one which specifically minimizes the weighted squared error in the achievement of the goal. In this way, the MM regimen has the new feature of being specifically designed to achieve target goal(s) with the greatest possible precision for any set of population raw data (doses and serum levels) available up to that time, because it considers all the many possible versions or models of the patient, using the NPEM population model, and the many different predicted serum concentrations, one from each support point, as shown below in Figures 2 and 3, instead of making only one prediction using a population model having only the single most likely value for each parameter [2].

Later on, as data of serum concentrations become available for feedback, Bayes' theorem is used to appropriately increase the probability of those support points or models that predicted the patient's measured levels well, and to decrease the probability of those that did not. The revised Bayesian posterior joint distribution, usually consisting of fewer significant support points, is then used to reconstruct the family of serum level trajectories taking place during the past [3,4].

The bandwidth or diversity of these predicted trajectories reflects the confidence with which the joint distribution is known, and the degree of learning about the patient provided by feedback from any serum levels obtained. As always, the plot based on the past trajectories of serum levels is compared with the clinical behavior of the patient, the patient's sensitivity to the serum drug concentrations is reassessed, the target goal is re-evaluated, and a new regimen is again computed to achieve the goal, always with the greatest possible precision for all the information in the population model and the individual patient data which is available up to that time.

## **THE POPULATION PHARMACOKINETIC MODEL OF VANCOMYCIN**

This 2 compartment model [5] was developed using the NPEM2 program in the USC\*PACK PC clinical collection. Its parameters were  $V_c$ , the apparent volume of the central (serum level) compartment, in L/kg;  $K_{cp}$ , the rate constant from the central to the peripheral compartment;  $K_{pc}$ , the rate constant in the reverse direction, and  $K_{slope}$ , the increment of the elimination rate constant ( $K_{el}$ ) for each unit of creatinine clearance ( $CCr$ ), all in  $hr^{-1}$ . A nonrenal component,  $K_{int}$ , was fixed at  $0.002043 hr^{-1}$ . Thus the overall  $K_{el} = K_{int} + (K_{slope} \times CCr)$ .

Data of 30 patients receiving Vancomycin were analyzed. The file containing the population joint probability density values (the 28 rows of parameter values and their probabilities) was read into the program for MM design of dosage regimens [3,4]. Table 1 shows the summary values of the various population parameters.



There were 28 support points for the population joint parameters. Each support point had a value for each parameter, representing a candidate model for the patient, and a computed probability. The graphical plot of the values for  $V_c$  and  $K_{slope}$  is shown in Figure 1.

### **THE SIMULATED CLINICAL SCENARIO FOR INITIAL THERAPY (DAY 1)**

A therapeutic goal of a stable serum vancomycin concentration of 15 ug/ml, to be achieved by continuous series of continuous stepwise intravenous infusions at various rates, was chosen for this simulated study. While it is common to give vancomycin by intermittent IV infusion and to select a trough goal of 10 ug/ml, with peaks about 35 to 45 ug/ml, the stable goal of 15 ug/ml was selected here as a reasonable alternative goal, to be achieved at the end of an initial 2 hr loading infusion, again at the end of 2 subsequent 2 hr infusions during the distribution phase of this 2-compartment drug, and at the end of 3 further infusions of 6 hrs each, to complete Day 1 of therapy. Thus the vancomycin was given by continuous IV in 3 infusion steps of 2 hrs each, followed by 3 steps of 6 hrs each, to achieve the goal of 15 ug/ml at the end of each infusion step during Day 1 of therapy.

### **THE TWO INITIAL REGIMENS COMPARED**

Two types of dosage regimen to achieve a target goal of 15 ug/ml were developed and compared. One, the traditional regimen, was developed using the single point mean population NPEM parameter values shown in Table 1. It was designed to achieve the goal exactly, as there was only one exact value for each parameter to consider. No consideration of any therapeutic error is possible with this current widely used method of dosage design.

The other regimen, the MM regimen, used all the 28 support points of the NPEM Vancomycin population model in designing the regimen. It therefore took into account all these different models of the patient, each with its probability of "being" the new patient, to receive the initial regimen. The MM dosage designer thus faces the fact that what may be a correct regimen for a particular support point set of parameter values (such as the means), will inevitably be incorrect for all other parameter values in the population, and develops the regimen which minimizes the overall error in the failure to achieve the desired target goal. It thus does a simulated clinical trial in which the most precise dosage regimen is found.

If the regimen based on the mean parameter values is given to each of the 28 support points or "multiple models" of the patient, each model will have its own predicted trajectory of serum levels over time, and each of these will contribute its increment of weighted squared error in the overall failure of the regimen to achieve the target goal.

Figure 2 shows the multiple predicted serum concentration trajectories when the regimen based on the population mean parameter values was given to all the individual

28 support points or models of the patient that generated those mean values. Many predicted serum concentrations were very high, as the distribution of the Vd was not at all Gaussian, but was skewed to the right. As shown in Table 1, the mean Vd was actually close to the 75th percentile. Due to all the variability in the various combinations of population parameter values, the variability in the serum level response was great.

In contrast, the MM regimen was specifically designed to minimize the expected value of the total weighted squared error in achievement of the goal, taking into account all the individual predicted 28 MM trajectories, each of which was weighted by its probability. Figure 3 shows the results achieved using the MM regimen. The trajectories are much less variable, and are much better centered about the chosen goal of 15 ug/ml.

### **INCORPORATION OF CLINICAL ENVIRONMENTAL NOISE TERMS AND MM SERUM LEVEL FEEDBACK**

The MM therapeutic scenario has now been carried further, incorporating serum level feedback, with Bayesian posterior updating of the probabilities (but not the parameter values) of the 28 population model support points.

The capabilities of this control strategy were evaluated by a Monte Carlo simulation of a realistic clinical scenario which also contained stated sources of simulated clinical environmental errors in the preparation of the doses and the timing of their administration, as well as in the laboratory assay error. Each ideal computed dose was assumed to be prepared with a random Gaussian error having a standard deviation (SD) of 10% of the dose. That erroneous dose was then what was "given". Further, the times of switching from one IV infusion rate to another were assumed to have a random Gaussian error having a SD of 6 min for the start of the first 2 hr infusion step, and of 12 min for the switch to each of the other infusion steps.

Three days of such simulated therapy were analyzed. Serum levels were assumed to be drawn exactly at 2, 4, and 8 hours into the regimen for each day. Their assay error was introduced as a random Gaussian error having the SD of the Abbott TDx assay used in our laboratory to make the original population model. This heteroschedastic random Gaussian assay error (see [6]) had an SD represented by the polynomial

$$SD = 0.30752 + 0.024864C + 0.00027637C^2,$$

where C is the true serum level of a simulated "true patient" (randomly chosen as support point number 15 of the 28 in the model set) "drawn" at the various sampled times.

Thus two things were going on in this scenario. On the one hand, the MM stochastic controller was designing the MM stepwise infusion regimen to most precisely achieve the goal of 15 ug/ml at 2, 4, 6, 12, 18, and 24 hours during the first day of therapy. On the other hand, this ideal dosage regimen was being corrupted by the Monte Carlo simulator, incorporating the clinical errors stated above. The MM controller also takes these stated errors into account in designing the dosage regimen.

Figure 4 shows the computed 99% most probable trajectories of the serum levels for Day 1 of MM therapy, before any feedback. The variability is close to that shown in Figure 3. The solid lines represent the 95% most probable trajectories, and the dotted lines represent the next most probable 4%. This represents the clinical situation as much as it is knowable to the clinician until the serum level results come back.

Further, in a way that is never knowable clinically, the time course of the computed serum concentrations for a simulated "true patient" (here represented by support point #15, chosen randomly), is shown in Figure 5. Clearly there was visible error in the initial achievement of the therapeutic goals, as the true patient had parameter values different from those of the population means.

The true patient's serum level results at 2, 4, and 8 hrs into the regimen, corrupted by their assay errors, were made available at the end of Day 1. Based on these results, Bayesian updating of the multiple models was done, revising their probabilities, given the "observed" serum concentration data, using Bayes theorem. Instead of the 28 original support points, only four support points now had significant probabilities. The rest had negligible ones.

The simulated events of therapy days 2 and 3 repeated the same format as in Day 1. The goals again were 15 ug/ml, to be achieved at 2, 4, 6, 12, 18, and 24 hrs into each day's regimen. The same continuous infusion format of 3 steps of 2 hrs, followed by 3 steps of 6 hrs was used. Serum levels were again "obtained" at 2, 4, and 8 hrs into each day, with results available at the end of each day for revising the model probabilities and planning the next day's regimen.

Based on this, the regimen for day 2 was then computed and (with the corrupting clinical environmental errors) was given. Figure 6 shows the 99% most probable serum level trajectories predicted for day 2 (horizon #2). As shown by the much narrower bandwidth of predicted serum concentrations for Day 2, one has learned a lot about the patient from the first set of serum levels. In addition, the response of the "true patient" was predicted to be quite precisely controlled for Day 2, as shown in Figure 7.

At the end of Day 2, when the 3 new serum levels came back during Day 2, the model probabilities were further updated. Only three significant support points now were present. These revised probabilities were used to plan the regimen for Day 3, which was computed and given. Figure 8 shows the 99% most probable predicted serum level trajectories. The controller (and thus the clinician) thinks it is doing just great. However, life is never quite so kind. Because of the stated errors in the clinical environment, the response of the "true patient" departed slightly from the predicted response on this day, as shown in Figure 9..

Finally, after the three new simulated measured serum levels came back from Day 3, the "true patient" was found. Furthermore, in other preliminary (as yet unpublished)

studies in which the true patient was not a member of the original model set, the MM controller was also able to perform its MM adaptive control function quite acceptably.

## **DISCUSSION AND CONCLUSION**

The MM dosage designer developed regimens which were the result of many simulated clinical trials with each virtual subject who was studied to make the population model used as the Bayesian prior. Its dosage regimen achieved the therapeutic goals with visibly greater precision than did the regimen based on traditional single point mean population pharmacokinetic parameter values. Further, the MM controller appeared to learn well from the feedback provided by the serum levels, and to achieve the target goals for the simulated patient with increasing precision as therapy progressed from one feedback cycle (therapy day, or event horizon) to another. The MM regimen thus permits visibly greater precision in achievement of desired therapeutic target goals compared to conventional control based on single mean pharmacokinetic parameter values, which is employed today by all maximum a posteriori probability (MAP) Bayesian software in current wide use. A user - friendly clinical version of the MM program is now in development.

## ACKNOWLEDGMENTS

Supported by US Government grants LM 05401, RR 11526 and RR 01629, and by the Stella Slutzky Kunin Research Fund.

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TABLE 1. SUMMARY of VANCOMYCIN POPULATION PARAMETER VALUES\*

<u>Attribute</u>	<u>Vc (L/kg)</u>	<u>Kcp#</u>	<u>Kpc#</u>	<u>Kslope#</u>
MEAN	0.2278	2.2532	0.8147	0.0063
MODE	0.1275	2.425	0.8775	0.0051
25th %ile	0.0946	1.0832	0.5487	0.0023
(MEDIAN)	0.1427	2.1594	0.8743	0.0051
75th %ile	0.2348	3.3032	1.0467	0.0105

\* Kint was held fixed at 0.002043 hr<sup>-1</sup> throughout.

# all in units of hr<sup>-1</sup>

## FIGURES AND FIGURE LEGENDS

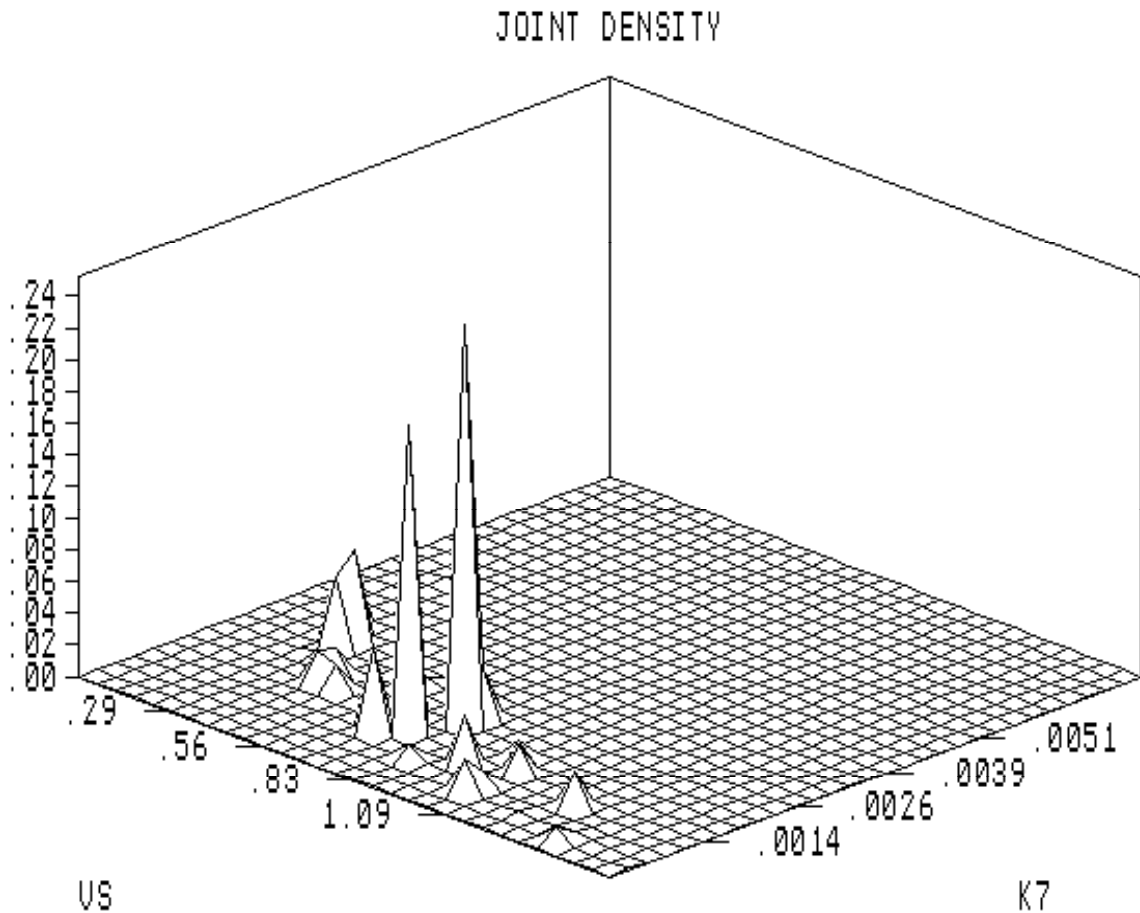


Figure 1. 3D plot of a Vancomycin population marginal joint density.  $V_s$  = slope of volume with respect to body weight.  $K_7$  = slope of  $K_{el}$  with respect to creatinine clearance. The other parameters  $K_{cp}$  and  $K_{pc}$ , which describe exchange out to and back from the peripheral (nonserum) compartment, are not shown here, but can be similarly displayed, as can any selected pair of parameters.

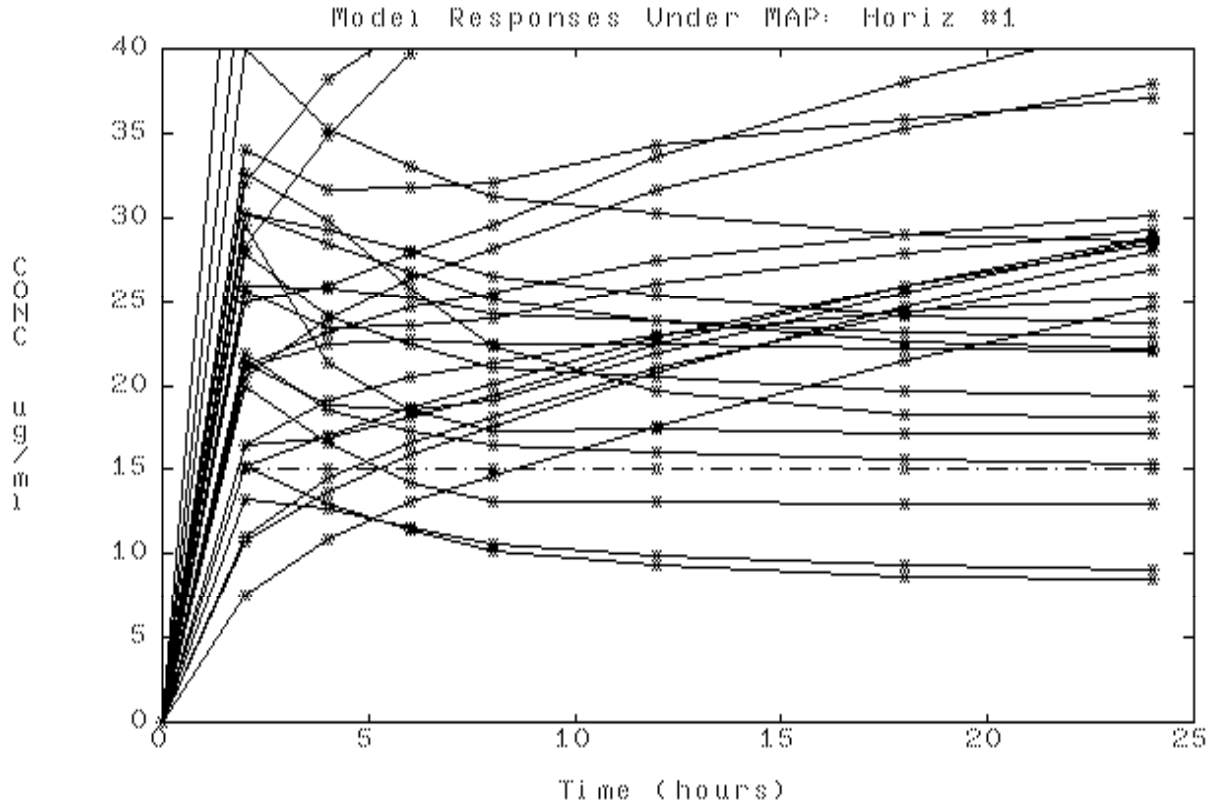
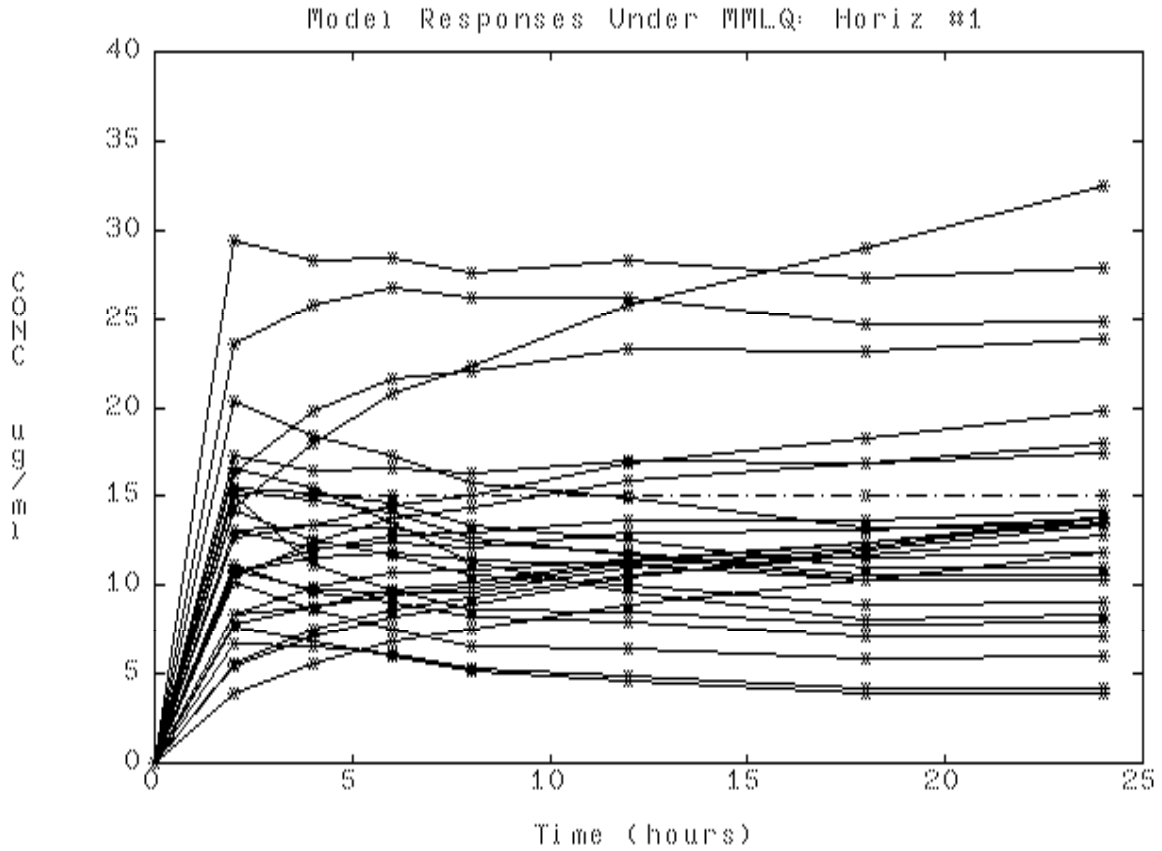


Figure 2. Serum concentration trajectories predicted when the regimen to control the mean value of each parameter in the Vancomycin nonparametric population model is given to all many support points which constitute the model. The horizontal dashed line is the 15 ug/ml therapeutic goal. Great diversity in predicted serum concentrations is seen, due to the diversity of patients in the population model.



**Figure 3.** Serum level trajectories predicted when the MM regimen is given to all support points in the nonparametric population model. The horizontal dashed line is the 15 ug/ml therapeutic goal. Much less diversity in predicted serum concentrations is seen, due to the fact that the MM regimen is specifically designed to achieve the desired goal with the least possible weighted squared error over the course of that day.



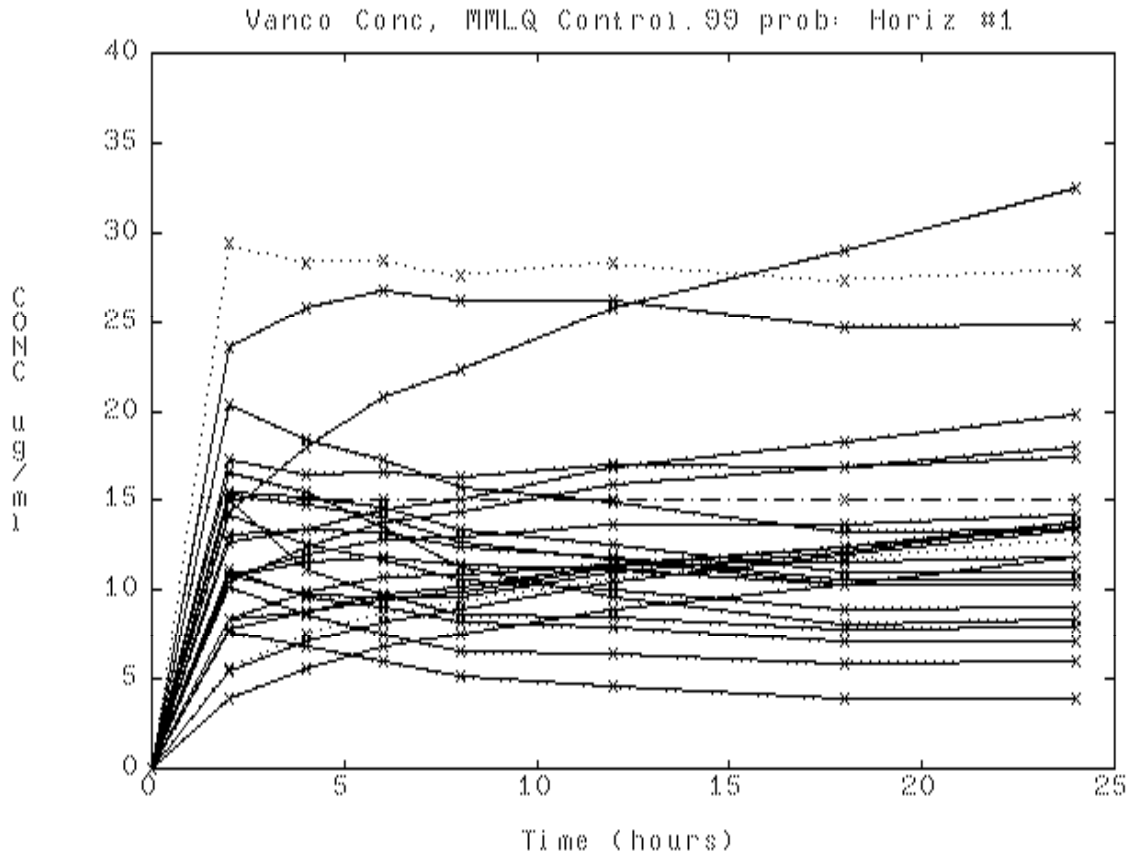


Figure 4. Trajectories of the 99% most probable predicted serum level responses during Day 1 of therapy, before feedback. Solid lines: the 95% most probable trajectories. Dotted lines: the next most likely 4%, for the total of 99%. The horizontal dashed line is the 15 ug/ml therapeutic goal.

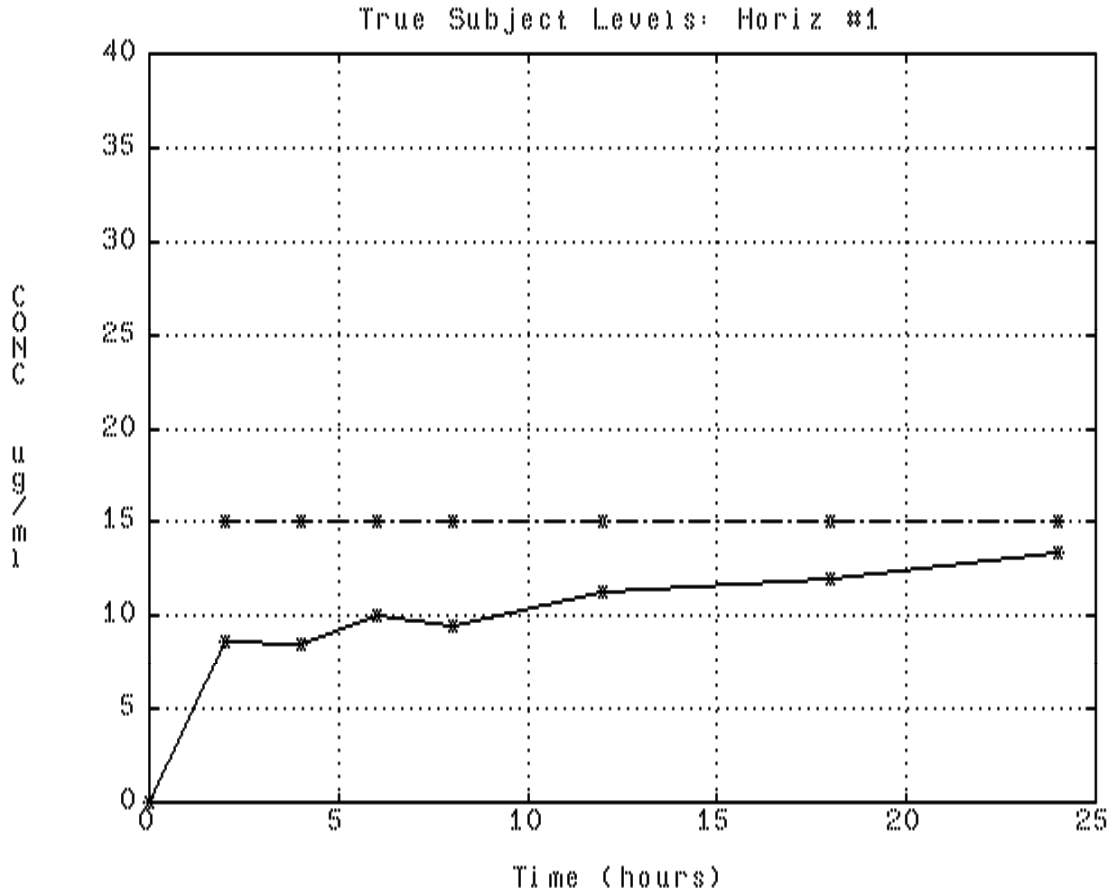


Figure 5. Serum level response of the "true patient" during therapy day 1 (horizon 1). Horizontal dashed line: the desired goal of 15 ug/ml at 2, 4, 6, 12, 18, and 24 hrs. Solid line: true serum concentrations in the simulated true patient.

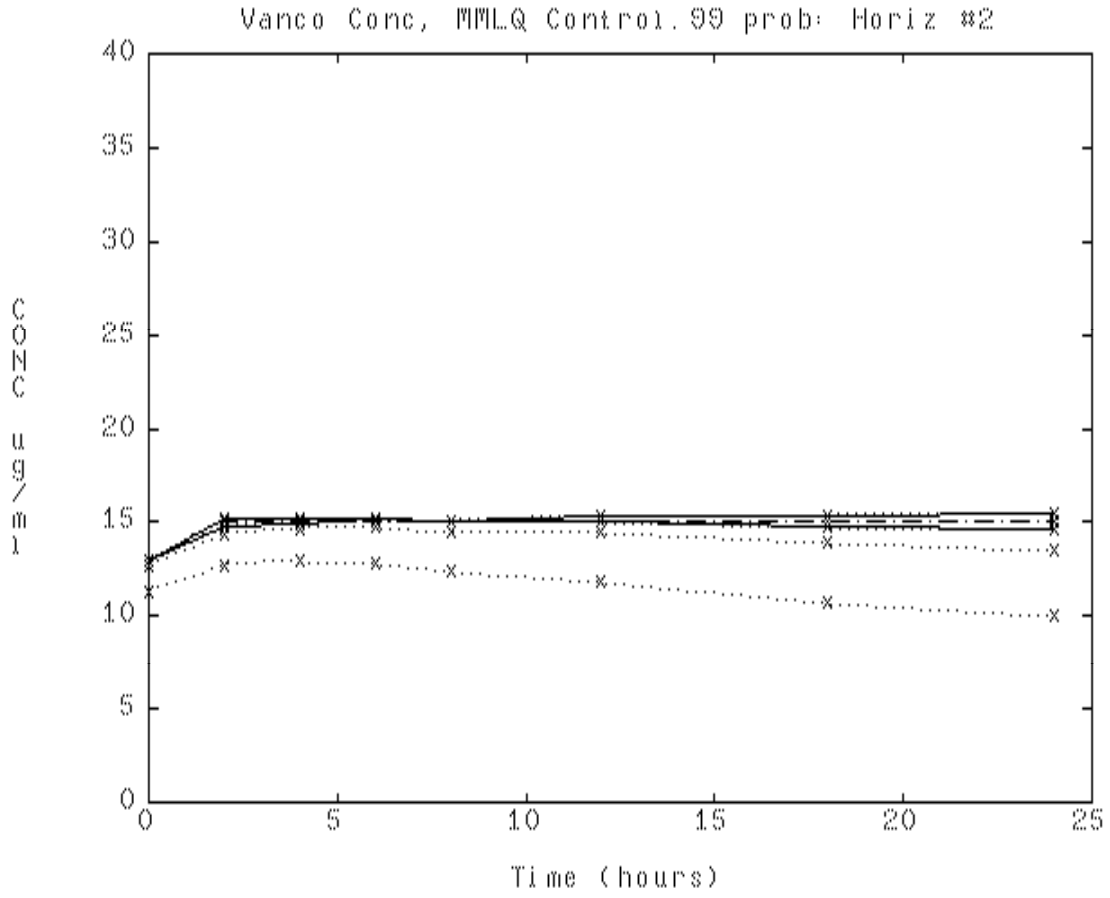


Figure 6. The 99% most probable serum level trajectories predicted for Day 2 of therapy (event horizon #2). The horizontal dashed line is the 15 ug/ml therapeutic goal.

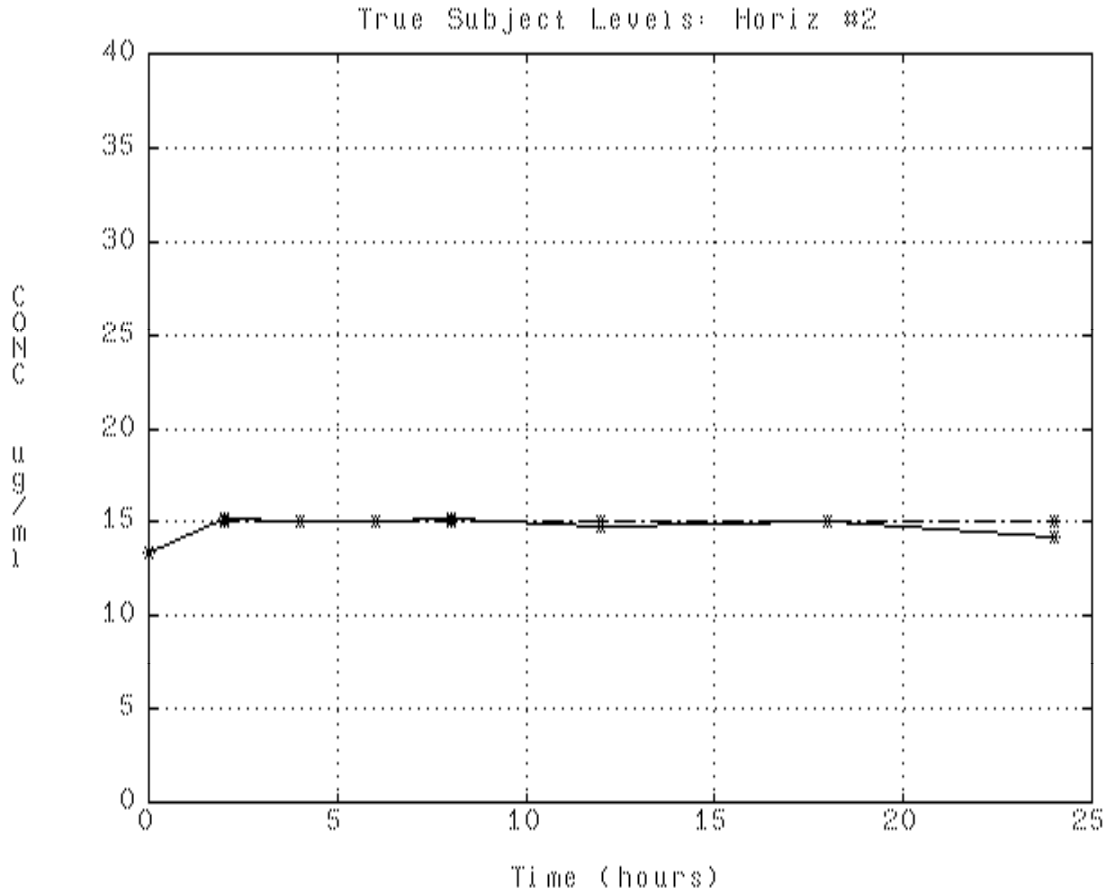


Figure 7. Serum level responses of the "true patient" during therapy day (event horizon) #2. The horizontal dashed line is the 15 ug/ml therapeutic goal.

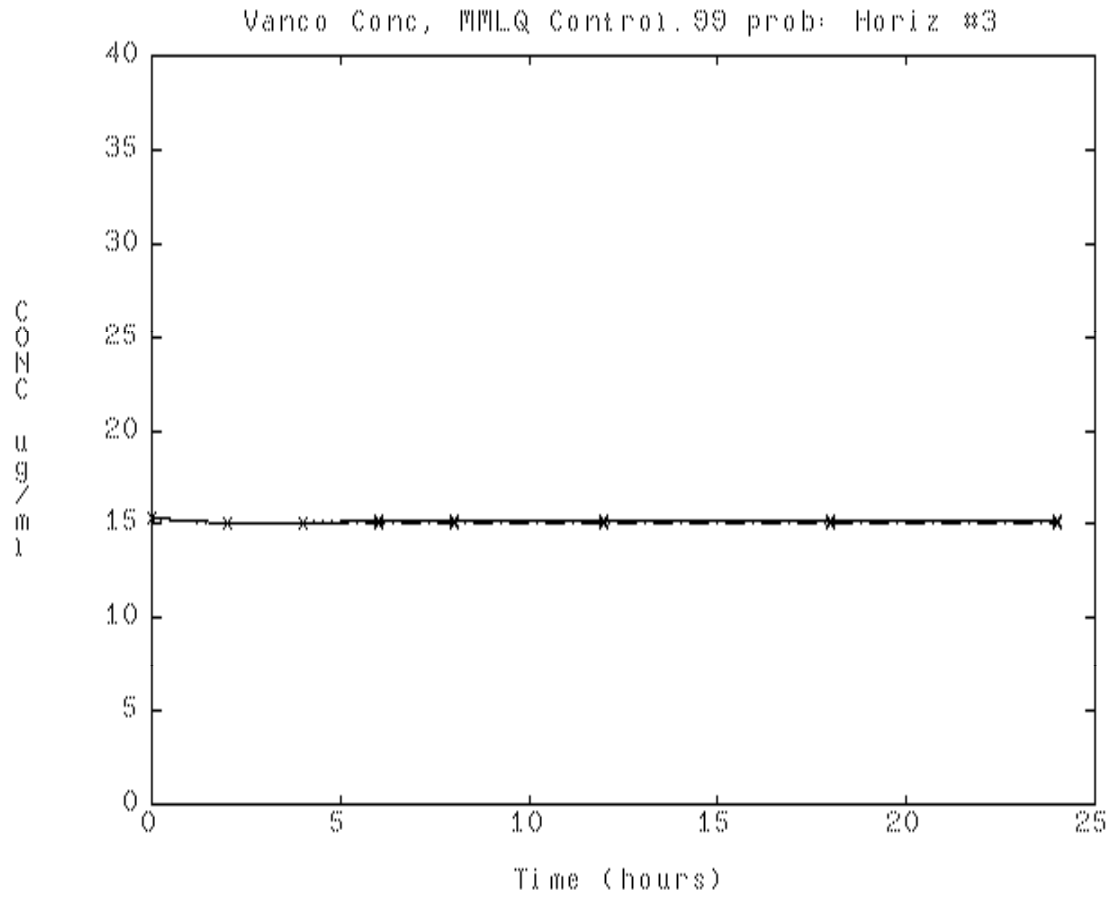


Figure 8. The 99% most probable serum level trajectories predicted for Day 3 of therapy (event horizon #3). The horizontal dashed line is the 15 ug/ml therapeutic goal.

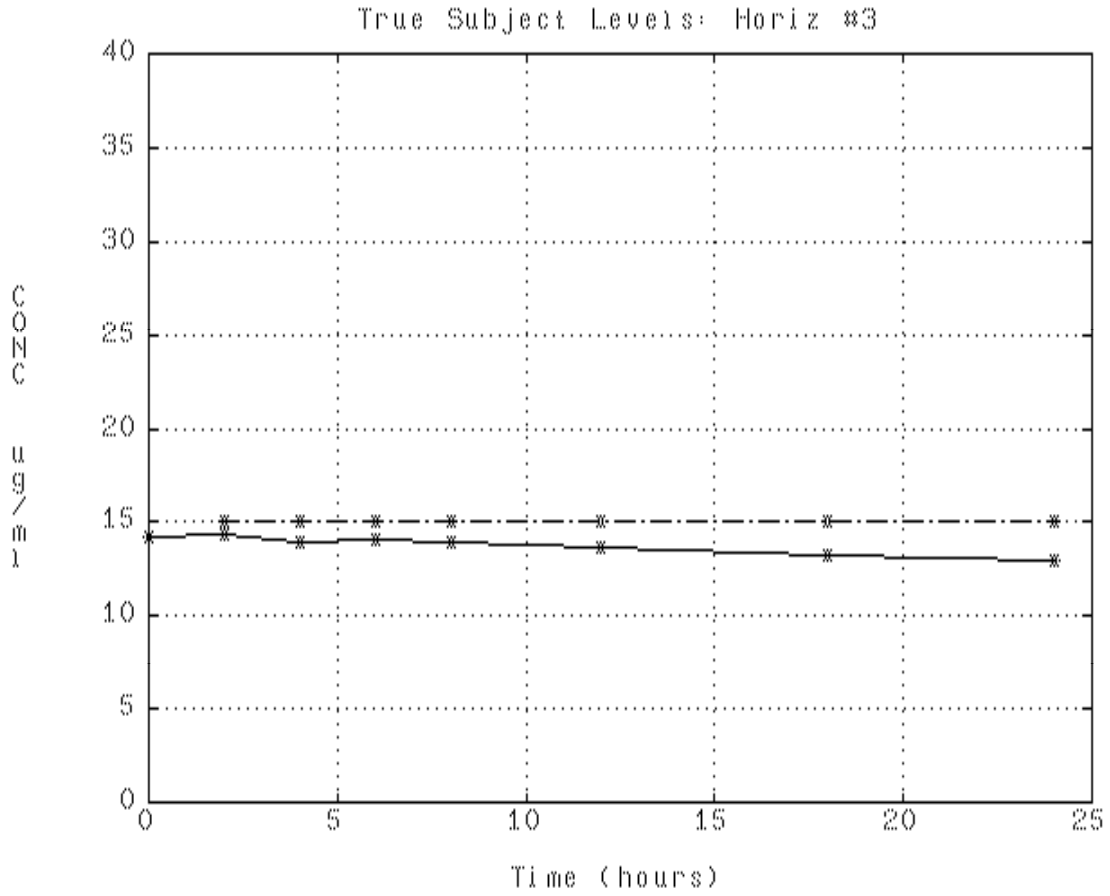


Figure 9. Response of the "true patient" during day (event horizon) #3. The horizontal dashed line is the 15 ug/ml therapeutic goal.



## **MULTIPLE MODEL (MM) DOSAGE DESIGN: ACHIEVING TARGET GOALS WITH MAXIMUM PRECISION.**

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### **ABSTRACT**

Most dosage regimens based on parametric population models as the Bayesian prior, including most Bayesian approaches of adaptive feedback control, use a single parameter value to describe the central tendency of each parameter distribution. Because of this, when a target goal is selected, the regimen to achieve it assumes that it does so exactly. However, the separation or heuristic certainty equivalence principle states that whenever a system is controlled, first, by obtaining single point parameter values, and then by using those values to control the system, the control achieved is usually suboptimal. In contrast, Multiple Model dosage design is based on nonparametric population models which have essentially one set of parameter values for each subject in the population. With this more likely Bayesian prior, multiple predictions are possible. Using these nonparametric models, one can compute the dosage regimen which specifically minimizes the predicted weighted squared error with which a desired target goal can be achieved. Other cost functions can also be employed.

As Bayesian feedback from serum concentrations is obtained, each set of parameter values in the nonparametric prior has its probability recomputed. Using this individualized nonparametric Bayesian posterior joint density, the new regimen to achieve the target with maximum precision is computed. In addition, a new Interacting Multiple Model (IMM) sequential Bayesian method has been developed to estimate such posterior densities when parameter values have been changing, as in unstable patients, during the time of analysis. A clinical software package implementing these approaches is in development.

### **INTRODUCTION: SET INDIVIDUALIZED TARGET GOALS FOR EACH PATIENT**

The concept of a therapeutic range of serum drug concentrations is a generalization. It is an overall range in which most patients, but certainly not all, do well. One must always check each individual patient to see if he or she is doing not only well, but optimally, whatever the serum concentration is found to be. Figure 1 shows the usual means by which such therapeutic ranges are obtained. First, there is an increased incidence of therapeutic effects with increasing serum drug concentrations. Later on the incidence of toxic effects becomes significant. The eye is drawn to the upward bends in each line, and the classification of the therapeutic range is developed. However, this procedure does not deal with the need to develop a gentle dosage regimen for a patient who needs only a gentle touch, and a more aggressive one for a patient who really needs his dosage "pushed".



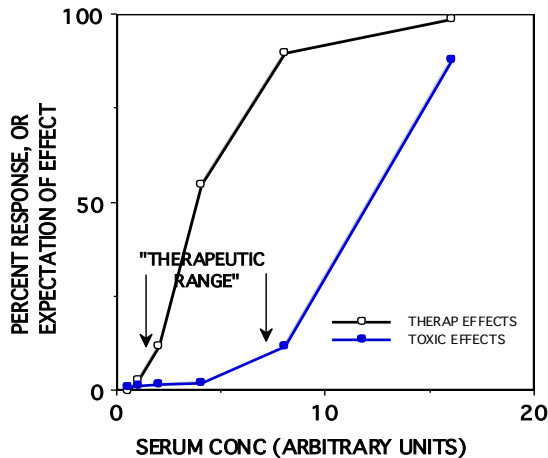


Figure 1. General relationships usually found between serum drug concentrations and the incidence of therapeutic and toxic effects. The eye is drawn to the bends in the curves, and the therapeutic range is classified in relation to these bends. This qualitative procedure of classification discards the important quantitative relationship of the incidence of toxic effects versus serum concentration.

Another approach is one in which the clinician evaluates each patient's individual clinical need for the drug in question, and selects an estimated risk of toxicity which is felt on clinical grounds to be justified by the patient's need. One then selects a target serum concentration goal to be achieved. One does not want the patient to run any greater risk of toxicity than is justified by the patient's clinical need. Within that constraint, however, one wants to give the patient as much drug as possible, to get the maximum benefit. This approach provides the rationale for selecting a specific target serum concentration goal, rather than a wider window, and then to attempt to achieve that target goal with the greatest possible precision, just as if one were shooting at any other target. Individualized drug therapy therefore begins by setting such specific individualized target goals. Without specific target goals, there can be no individualized precise drug therapy. The task of the clinician is to select, and then to hit, the desired target goal as precisely as possible. As the initial regimen is given, the clinical task is to observe the patient's response, and to reevaluate whether the target goal was hit precisely or not, was correctly chosen or not, or if it should be changed and a new dosage regimen developed.

## THE NEED FOR MODELS

Pharmacokinetic and dynamic models provide the means to store past experience with the behavior of drugs, and the tool to apply that past experience to the care of future patients. This experience is usually stored in the form of a population pharmacokinetic model which is used as the Bayesian prior to design the initial regimen for the next patient who appears to belong to that population. The dosage regimen to achieve the target goal is computed and given. The patient is then monitored both clinically and by measuring serum concentrations. The serum concentrations are used not only to note if they are within a therapeutic range, but also to make a specific model of the behavior of the drug in that individual patient. One can see what the probable serum concentrations were at all other times when they were not measured. One can also see the computed concentrations of drugs in a peripheral nonserum compartment or in various effect compartments. These cannot be seen or inferred at all without such models. By

comparing the clinical behavior of the patient with the behavior of the patient's model, one can evaluate the patient's clinical sensitivity to the drug, and can adjust the target goal appropriately. For digoxin, for example, the inotropic effect of the drug correlates best with the behavior of the drug in the peripheral compartment rather than with the serum concentrations. The excellent model made by Reuning and colleagues for digoxin [1] has been highly useful clinically [2].

## CURRENT BAYESIAN INDIVIDUALIZATION OF DRUG DOSAGE REGIMENS

The Maximum A posteriori Probability (MAP) Bayesian approach to individualization of drug dosage regimens was introduced to the pharmacokinetic community by Sheiner et al. [3]. In this approach, parametric population models are used as the Bayesian priors. The credibility of these population models (their parameter variances) is then evaluated in relationship to those of the measured serum concentrations as they are obtained. The contribution of these two types of data and their variances to the MAP Bayesian posterior individualized patient model is shown in the objective function used, as shown below (1).

$$\frac{\sum (C_{obs} - C_{mod})^2}{\text{Var}(C_{obs})} + \frac{\sum (P_{pop} - P_{mod})^2}{\text{Var}(P_{pop})} \quad (1)$$

where  $C_{obs}$  is the collection of observed serum concentrations,  $\text{Var}(C_{obs})$  is the collection of their respective variances, and  $C_{mod}$  is the model estimate of each serum concentration at the time it was obtained. Similarly,  $P_{pop}$  is the collection of the various population model parameter values,  $\text{Var}(P_{pop})$  is the collection of their respective variances, and  $P_{mod}$  is the collection of the Bayesian posterior model parameter values. Each data point is given a weight according to its Fisher information, the reciprocal of its variance. Population models in which there is greater diversity, and therefore greater variance, contribute less to the individualized model than do more uniform models having smaller variances. Similarly, a precise assay will draw the fitting procedure more closely to the observed concentrations, and a less precise assay will do the opposite. The more serum data are obtained, the more that information dominates the determination of the MAP Bayesian posterior parameter values ( $P_{mod}$ ) in the patient's individualized pharmacokinetic model.

Having made the patient's individualized model, one then uses it to reconstruct the past behavior of the drug in the patient during his therapy to date. One can examine a plot of the behavior of this model over the duration of the past therapy. One can thus evaluate the clinical sensitivity of the patient to the drug, by looking at the patient clinically and comparing the patient's clinical behavior with that of the patient's individualized pharmacokinetic model. In that way, one can evaluate whether the initial target goal was well chosen or not. One can choose a different goal if needed, and once again one can compute the dosage regimen to achieve it. In this way, the model can be individualized and dosage can continue to be adjusted to the patient's body weight, renal function, and available serum concentrations, for example, to achieve the desired target goal, usually with increasing precision.

## CRITIQUE OF THE MAP BAYESIAN APPROACH

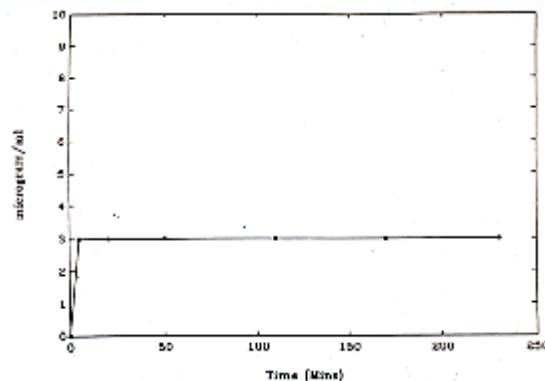
The weakness of the MAP Bayesian procedure is that the models it uses have only single point estimates of the various pharmacokinetic parameters. Because of that, there is only one version of either the individualized model, or of the population model itself. The regimen developed to achieve the target goal is simply assumed to do so exactly.

## THE SEPARATION PRINCIPLE

The separation or heuristic certainty equivalence principle [4] states that whenever control of a system is separated first, into obtaining single point parameter estimates for the model, and second, of using those single point estimates to control the system, the task is often achieved in a suboptimal manner. This is a significant problem with MAP Bayesian fitting and dosage design. The way around this problem is by incorporating improved nonparametric approaches to population pharmacokinetic modeling, and in using them specifically to design maximally precise dosage regimens.

## USE OF POPULATION MODELS IN CLINICAL THERAPEUTICS

When a parametric population model is used as the Bayesian prior to design an initial dosage regimen for the next patient one encounters, one usually has only a single estimated value for each parameter. Because of this, only one prediction of future



concentrations can be made. The dosage regimen is simply assumed to achieve the target goal exactly, as shown in Figure 2.

*Figure 2. Using lidocaine population mean parameter values, an infusion regimen designed to achieve and maintain a target goal of 3 ug/ml does so exactly when the patient, as here, has exactly the mean population parameter values.*

Figure 2 shows the results of an infusion regimen of lidocaine, based on the mean population parameter values for that drug, which was designed to achieve and maintain a target serum concentration of 3 ug/ml. As shown, this regimen, based on the single mean population parameter values, hits the target exactly, but only when the patient has parameter values which are exactly the population mean values. However, as shown in Figure 3, when the regimen used in Figure 2 was given to the combination of the actual 81 diverse nonparametric population support points from which the mean values were obtained, an extremely wide distribution of predicted serum concentrations was seen, due to the diversity in the nonparametric population support

points from which the mean parameter values were obtained. The predicted serum concentrations actually covered much more than the usual therapeutic range of 2 to 6 ug/ml.

In contrast, if one has a nonparametric population model [5-8], with its multiple sets of model parameter values (81 in this case), one can make multiple predictions, instead of only one, forward into the future from any candidate dosage regimen which is "given" to all the models in the population discrete joint density. The richer and more likely population parameter joint density reflects better the actual diversity among the subjects studied in the past population. Based on these multiple models in the population (the discrete joint density), one can compute

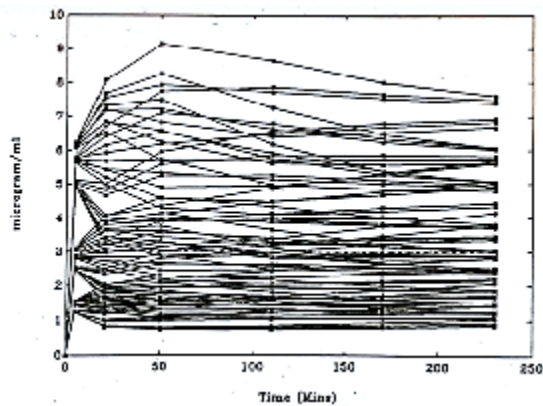


Figure 3. Result when the above lidocaine infusion based on population mean parameter values is given to the 81 diverse support points from which the population mean values were obtained. Great diversity in the predicted responses is seen.

the weighted squared error with which any candidate regimen is predicted to fail to achieve the desired target goal at a target time. Other regimens can then be considered, and the optimal regimen can be found which is specifically designed to achieve the desired target goal with the least weighted squared error [9-11].

This approach, using the multiple models of the patient provided by the nonparametric population model, avoids much of the limitations of the separation principle. This is the real strength of the combination of nonparametric population models coupled with "multiple model" dosage design [9-11].

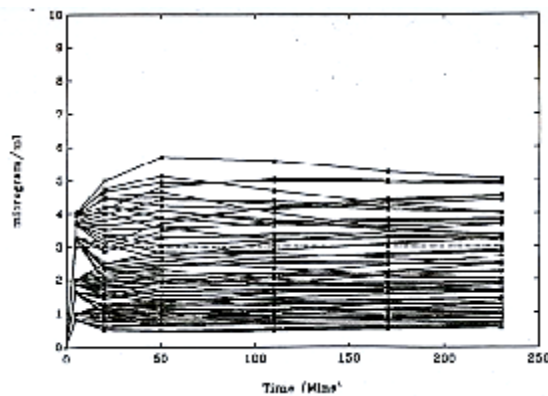


Figure 4. Predicted response of the 81 support points (models) when the regimen obtained by multiple model dosage design is given. The target is achieved with visibly greater, and optimal, precision.

As shown in Figure 4, the multiple model (MM) dosage regimen, based on the same nonparametric population model with its 81 support points, obtained a much more precise achievement of the target goal, because it was specially designed to do so. The error in the achievement of the therapeutic target goal is much less, and the dispersion of predicted serum concentrations about the target goal is much less. Other cost functions can also be used [13,14].

## OBTAINING MULTIPLE MODEL BAYESIAN POSTERIOR JOINT DENSITIES

With the MAP Bayesian approach to posterior parameter values, the single most likely value for each parameter is obtained when they altogether minimize the objective function shown in equation (1). In contrast, the MM Bayesian approach, using the nonparametric joint densities, preserves the multiple sets of population parameter values, but specifically recomputes their Bayesian posterior probability, based upon the serum concentrations obtained. Those combinations of parameter values that predicted the measured concentrations well become more probable. Those that predicted them less well become less so. In this way, the probabilities of all the nonparametric population support points become revised, using Bayes' theorem [10-11]. A smaller number of significant points, or perhaps even only one, is usually obtained. When the regimen for the next cycle is developed, these revised models, containing their revised MM Bayesian posterior probabilities, are used to develop it. The regimen is again specifically designed to achieve the desired target goal with maximum precision (minimum weighted squared error).

## OTHER BAYESIAN APPROACHES

Three other Bayesian approaches have been used by us to incorporate feedback from measured serum concentration data. The first is the sequential MAP Bayesian approach, in which the MAP posterior parameter values are sequentially updated after each serum concentration data point is obtained. This procedure improves the tracking of the behavior of the drug through each data set. However, at the end of each full feedback cycle, (after each new full cluster of data points), at the time the next regimen is to be developed, this method has learned no more with respect to developing the next new dosage regimen, than if it had fitted all the data together at once, even though it tracks the changing MAP Bayesian parameter values better sequentially.

The second approach is the sequential MM Bayesian one [9-11]. Here the MM Bayesian posterior joint density is also sequentially updated after each data point. Still, at the end of each feedback cycle, this procedure similarly has learned no more with respect to developing the next dosage regimen than if all the data in that cluster were fitted simultaneously. The procedure is still looking for a hypothetical single model (support point, set of parameter values) which best describes all the data. When this fails to be the case, combinations of support points are found which fit best. Still, the procedure is looking for a fixed and unchanging single model, or combination of models, which best fit the data, even though the posteriors are fitted sequentially.

A third approach is the interacting multiple model (IMM) approach [12]. This method permits the true patient being sought for actually to jump from one model or

support point to another during the sequential Bayesian analysis. Because of this the IMM method, originally designed to track missiles and aircraft taking evasive action, permits detection of changing pharmacokinetic parameter densities during the sequential analysis procedure. It thus provides an improved method to track the changing parameter densities and behavior of a patient during the evolution of his clinical therapy. For example, it permits an improved ability to detect and to quantify changes in the volume of distribution of aminoglycoside drugs during changes in a patient's clinical status which are not captured by the use of conventional clinical descriptors. Using carefully simulated models in which the true parameter values changed during the data collection, the integrated total error in tracking a simulated patient was very similar with the sequential MAP and sequential MM Bayesian procedures. However, the integrated total error of the sequential IMM procedure was only about one half that of the other two [12].

## CLINICAL APPLICATIONS

Nonparametric population parameter joint densities, MM dosage design and IMM Bayesian posterior joint densities appear to offer significant improvements in the ability to track the behavior of drugs in patients during their care, especially when the patients are unstable and have changing parameter values. These approaches also develop dosage regimens which are specifically designed to achieve target goals with maximum precision. These methods make optimal use of all information contained in the past population data, coupled with whatever current data of feedback may be available about a particular patient up to that point, to develop that patient's most precise dosage regimen. A clinical version of this software, which runs on PC's in Windows, is now in development.

**Acknowledgements:** Supported by NIH grants LM 05401 and RR 11526.

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## **A NEW METHOD TO UPDATE BAYESIAN POSTERIOBS FOR PHARMACOKINETIC MODELS WITH CHANGING PARAMETER VALUES.**

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**Purpose:** to improve the quality of Bayesian posterior densities for pharmacokinetic models of drugs when the patient's parameter values change significantly during the period of the data analysis.

**Methods:** the prior probability was assumed to be a nonparametric population model discrete joint density. Parameter changes were modeled as "jumps" from one discrete support point in the density to another. Given such discrete priors, previous work in our laboratory showed that the multiple model (MM) estimator works well when the patient's parameters are unknown but constant. However, both it and the MAP Bayesian method work less well where the patient's parameter values change. The interactive multiple model (IMM) algorithm is an effective method in the aerospace community for tracking maneuvering targets. We implemented the IMM sequential Bayesian algorithm in pharmacokinetic software, and compared its performance with the MM and MAP sequential Bayesian estimation methods, using both simulated and real clinical data for Tobramycin therapy.

**Results:** in a simulation of changing parameter values taking place at a stated time, the IMM approach tracked the drug with about half the integrated total error found with the MM and MAP methods. Further, in examining data from a real patient whose parameter values changed significantly during therapy, the IMM approach tracked the patient's data much better than the sequential MM or MAP Bayesian approaches.

**Conclusions:** the IMM approach can detect and quantify changing parameter values in unstable patients, and should permit more informed dosage regimens, especially for drugs having narrow margins of safety. Supported in part by NIH grants LM 05401 and RR 11526



## Appendix C

A description of the .mb patient file format. The description comments are given below the patient file sample.

### The file description

-110 (or -11)

This is a General File Flag: If the first digit is not equal to the minus sign "-", then the file is of much older format. If the 4th character is 1, there is a steady state input.

John Doe 2989

Last name (20 characters), first name (20 characters), and chart number (10 characters).

20 76.000000F 64.17163.002

If the second character of File flag is not equal to '1', then read ward (10 characters), patient age (Floating point F5.1), patient sex (1 character, M or F), patient height in inches (F5.1), height in cm (F5.1), flag for displaying height in other units (usually in cm) (Integer 1 digit) where: height flag = 1: height input in inches; height flag = 2: height in cm.

If the second digit of File flag equal '1' Then read (10 characters), patient age (Floating point F10.6), patient sex (1 character, M or F), patient height in inches (F6.2), height in cm (F6.2), flag for displaying height in other units (usually cm) (Integer 1 digit) where: height flag = 1: height input in inches; height flag = 2: height in cm. The difference here is in the formats of age and height.

6 6 94

Read Month (4 Digits), Day (4 Digits), and Year (4 Digits) of Therapy Day .

CCR ML/MIN/ 0.00 150.00

Read the Elimination Descriptor Name (4 Characters), its Units(8 Characters), Minimum(Floating point F7.2), Maximum (Floating point F7.2)

HOURS MG MG/HR MCG/ML KG MG/DL 60.00

Read the units: Time units (8 Characters), amount units (8 Characters), rate units (8 Characters), level units (8 Characters), weight units (8 Characters), Serum Creatinine units (8 Characters), and mpertu (F7.2), where: 'MPerTU' is Minutes PER Time Unit

being used. Compute minutes since midnight on day of each PO or IV dose, or start of IV infusion.

5

Read the number of doses (4 digits)

IM	1 540	0.00000000	0.00000000	1000.00000000	38.33874000
IM	2 540	0.00000000	0.00000000	1000.00000000	38.33874000
IM	3 540	0.00000000	0.00000000	1000.00000000	38.33874000
IM	4 540	0.00000000	0.00000000	1000.00000000	39.66926000
IM	5 540	0.00000000	0.00000000	1000.00000000	39.66926000

If second digit of File flag is not equal to '1' Then read (do loop until last dose (in this case repeat 5 times), route name (4 chars), day of therapy (4 digits), minutes into the day when dose was given (4 digits), infusion rate (F13.8), infusion time (F13.8), dose amount (F13.8), genval, the value of the elimination descriptor, usually CCr (F13.8).

If second digit of File flag is equal to '1' then read (do loop until last dose (in this case repeat 5 times) route name (4 chars), day of therapy (4 digits), minutes into the day when the dose was given (4 digits), infusion rate (F15.8), infusion time (it, F15.8), dose amount

263.00000000

The last dose interval (in hours). If the second digit of File Flag is not 1, then format F7.2, else Format F15.8

8

Read how many serum levels (4 digits)

1	600	40.97
1	720	38.64
1	960	26.96
2	510	1.25
5	600	40.97
5	720	29.29
5	960	26.96
6	510	1.25

Do loop until last dose, in this case repeat 8 times. Read therapy day # (4 digits), min into the day that level was obtained (4 digits), the level (F7.2)

2

Read how many weights (4 digit integer)

1	480	54.00
5	480	54.00

Do loop until last weight, in this case repeat 2 times. Read therapy day # (4 digits), mins into day that weight was obtained (4 digits), the Weight (F7.2)

3

Read how many serum creatinines (4 digit integer)

1	480	1.1900
4	480	1.2600
15	480	1.2000

Do loop until last serum creatinine, in this case repeat 3 times If the third digit of general file flag is not equal to '1', Then read therapy day (4 digits), minutes into day serum creatinine obtained (4 digits), serum creatinine (F7.2)

If the third digit of general file flag is equal to '1', Then read therapy day (4 digits), minutes into day serum creatinine obtained (4 digits), serum creatinine (F9.4). The difference here is in the Floating point format, which was made more precise in the newer version

100.00

Read muscle mass as percent of normal (F7.2)

0

Read Flag for Dialysis Patient status (1 digit integer) if Flag equal to 1 then this is a DIALYSIS PATIENT. If Flag equal to 0 then this is NOT A DIALYSIS PATIENT

1

Read MIC Flag (1 digit integer) MIC Flag=0: no MIC; MIC Flag=1: with MIC Flag is initialized as 0 here, it is set to be 1 in the drug initialization routine where it is needed (e.g. Ginit for Gentamicin)

1

Read SC/CCr Flag SC/CCR Flag = 1 for SC entries followed by calculation of CCr, SC/CCR Flag = 2 for direct entry of CCr, in the PASTRX.EXE program

8.00000

if (MIC Flag is equal to 1) MIC Flag = conc of MIC entered (0-150) Read MIC (F10.5), else do not read anything here, but simply go directly to the next line

1

Read CCr Flag (ikpccr 1 digit integer).If ikpccr = 0: recompute CCr; if ikpccr= 1 : keep current CCr. This is used in the edit portion of PASTRX.EXE

1 1

If the second digit of General File Flag (see first line) is equal to '1' Then read these two age and weight unit flags (2 digit integer, 2 spaces, 2 digit integer)

## An example of a population model file

The file shown below is the patient data file GENT2.MB

```
-1
alan forrests      patient      123
8E      65.000000M 70.00 70.001
  4  1  80
CCR ML/MIN/      0.00 150.00
HOURS  MG      MG/HR      MCG/ML KG      MG/DL      60.00
  6
IV  1 480      80.00000000      1.00000000      80.00000000      56.46828000
IV  1 990      80.00000000      1.00000000      80.00000000      41.34090000
IM  2 135      0.00000000      0.00000000      100.00000000      41.34090000
IV  2 495      100.00000000      1.00000000      100.00000000      41.34090000
IV  21005      100.00000000      1.00000000      100.00000000      27.09849000
IV  3 480      80.00000000      1.00000000      80.00000000      27.09849000
      8.00000000
  5
  1 560      3.60
  1 935      1.80
  2 370      5.20
  21100      9.10
  3 460      4.10
  1
  1 480      68.00
  3
  1 560      1.20
  2 540      1.50
  3 720      2.10
100.00
0
1
1
  2.00000
1
1  1
```

## Appendix C

A description of the .mm population model file format. The description comments are given below the population model sample.

### The file description

```
#-BEGIN-FILE-----
```

This indicates the beginning of the file

```
#
# USCPACK for Windows population model file
# File revision 1.0
#
```

The header section, the current file revision is 1.0.

```
#-BEGIN-LOCKED-SECTION-----
#
# The drug modeled           : Trimethoprim
# Date file was generated    : 11/14/2001
# File generated by program   : bignpem v4.3
# Location where file was generated : LAPK, SDSC
# File authorized by         : Roger Jelliffe, LAPK
# File lock code             : 1
#
#-END-LOCKED-SECTION-(15937389753495)-----
```

This section is to be considered locked. When the population model file is read by RightDose the program computes a checksum from the section between the –BEGIN-LOCKED-SECTION and –END-LOCKED-SECTION. This checksum must match the number given (in this case 15937389753495). If the file lock code is 3 or higher RightDose will consider this population model to be invalid and it will not be used.

```
#
# File update list
#
# 11/14/2001 - Andreas Botnen
#           Manually converted from old file
#
```

The file update list where updates to the file is entered. Note that altering a file with file lock code of 3 or higher without updating the checksums will invalidate the file.

```
# START DESCRIPTION
No description for this population model
# END DESCRIPTION
```

A general description of the population model can be entered between the lines START DESCRIPTION and END DESCRIPTION.

```
# The drug used in this analysis was  
Trimethoprim
```

The drug modeled

```
# The units to be used with this drug is  
mg
```

The most common units for the drug

```
# The molecular weight is  
-1.0
```

The molecular weight of the drug

```
# The active salt fraction is  
0.90
```

The active salt fraction

```
# The bioavailability is  
1.0
```

The bioavailability

```
# The valid routes are  
IV    PO
```

The routes that can be used with this population model.

```
# The ranges for the central compartment (peak and trough)  
# use the value -1 if this selection is not valid for this model  
# Usual ranges (peak min, peak max, trough min, trough max)  
8.0  12.0  4.0  7.0  
# Not to exceede ranges (peak min, peak max, trough min, trough max)  
4.0  18.0  1.0  9.0
```

RightDose operates with two sets of ranges. When computing future or initial regimens the usual ranges are displayed. The users can select to give a dose outside these ranges, if the selected dose is also outside the not to exceed range the user will get a warning.

```
# The ranges for the peripheral compartment (peak and trough)  
# use the value -1 if this selection is not valid for this model  
# Usual ranges (peak min, peak max, trough min, trough max)  
-1.0 -1.0 -1.0 -1.0  
# Not to exceede ranges (peak min, peak max, trough min, trough max)  
-1.0 -1.0 -1.0 -1.0
```

The same as above but for the peripheral compartment.

```
# The assay polynomial (as1, as2, as3, as4)
0.322720 0.0183650 0.00120510 0.0
```

The coefficients in the assay polynomial, where as1 is the zero-order coefficient, as2 the first order and so on. The assay polynomial will in general depend on both the population model and the apparatus used to measure the serum level.

```
# The process noise (wsqrt, de1, de2, de3, de4, terr)
0.000010 0.0 0.000010 0.0 0.0 0.000010
```

TBD.

```
# The number of random parameters
4
```

The number of random parameters in the model.

```
# The random parameters used was
KA      KS1      VS1      FA
3       7       16      20
```

The names of the random parameters and their corresponding coefficients.

```
# The number of fixed parameters
1
```

The number of fixed parameters in the model.

```
# The fixed parameters used was
KI
6
```

The names of the fixed parameters and their corresponding coefficients.

```
# The values of the fixed parameters
0.115500E-01
```

The values of the fixed parameters

```
# The number of probability points
13
```

The number of support points for this model

```
# The probability matrix
PROBABILITY  KA      KS1      VS1      FA
0.3078591  0.3361750  0.0010866  1.0126800  0.9998090
0.2048287  0.8304400  0.0014187  1.0063800  0.9998580
0.0865280  0.0762225  0.0006258  1.2360500  0.8043380
0.0729067  0.8320020  0.0014187  1.0073500  0.9998580
0.0667204  0.5291610  0.0021567  0.6420140  0.9998340
0.0550678  0.0966272  0.0009847  0.8849330  0.8272260
0.0374097  0.0962025  0.0005925  1.4900300  0.9265490
```

```
0.0336980 0.3529200 0.0014854 0.6441420 0.8660140
0.0324623 1.9477200 0.0002237 3.1675500 0.9999600
0.0303316 0.0002172 0.0000721 3.5082600 0.0000668
0.0289079 3.5189700 0.0011616 1.7157800 0.9102320
0.0285714 0.0003410 0.0081684 0.7570980 0.2779230
0.0147084 0.0962025 0.0005925 1.4910000 0.9273300
```

The support point matrix

```
#-END-FILE---- (43597657865846357819) -----
```

An end of file indicator and the checksum for the whole file.

## An example of a population model file

The file shown below is the population model for Amikacin

```
#-BEGIN-FILE-----
#
# USCPACK for Windows population model file
# File revision 1.0
#
#-BEGIN-LOCKED-SECTION-----
#
# The drug modeled           : Amikacin
# Date file was generated    : 11/14/2001
# File generated by program   : bignpem v4.3
# Location where file was generated : LAPK, SDSC
# File authorized by         : Roger Jelliffe, LAPK
# File lock code             : 1
#
#-END-LOCKED-SECTION-(15937389753495)-----
#
# File update list
#
# 11/14/2001 - Andreas Botnen
#           Manually converted from old file
#
# START DESCRIPTION
No description for this population model
# END DESCRIPTION

# The drug used in this analysis was
Amikacin

# The units to be used with this drug is
mg

# The molecular weight is
-1.0

# The active salt fraction is
1.0

# The bioavailability is
1.0
```



```

# The valid routes are
IV      IM

# The ranges for the central compartment (peak and trough)
# use the value -1 if this selection is not valid for this model
# Usual ranges (peak min, peak max, trough min, trough max)
25.0  80.0  2.0  10.0
# Not to exceede ranges (peak min, peak max, trough min, trough max)
15.0  90.0  1.0  20.0

# The ranges for the peripheral compartment (peak and trough)
# use the value -1 if this selection is not valid for this model
# Usual ranges (peak min, peak max, trough min, trough max)
4.0  10.0  1.5  8.0
# Not to exceede ranges (peak min, peak max, trough min, trough max)
1.0  20.0  1.0  15.0

# The assay polynomial (as1, as2, as3, as4)
0.322720 0.0183650 0.00120510 0.0
# The process noise (wsqrt, de1, de2, de3, de4, terr)
0.000010 0.0 0.000010 0.0 0.0 0.000010

# The number of random parameters
3

# The random parameters used was
KA  KS1  VS1
3   7    16

# The number of fixed parameters
1

# The fixed parameters used was
KI
6

# The values of the fixed parameters
0.693150E-02

# The number of probability points
23

# The probability matrix
PROBABILITY  KA  KS1  VS1
0.2496989  1.1795200  0.0036028  0.2388060
0.1263305  1.3131900  0.0039525  0.3238900
0.0962309  1.6597200  0.0030496  0.2638510
0.0811791  1.6189300  0.0031278  0.3296280
0.0729027  1.7663000  0.0026310  0.2194260
0.0697936  1.2892600  0.0030204  0.2536460
0.0588230  1.0618300  0.0020986  0.1696920
0.0581757  1.7362900  0.0039970  0.2631730
0.0469558  0.9462290  0.0033766  0.2230620
0.0434977  1.2468700  0.0030408  0.2502980
0.0392361  1.5365300  0.0024865  0.2260670
0.0350195  1.4554400  0.0031884  0.3242060
0.0151405  0.9678660  0.0032120  0.2325450
0.0035417  1.6529700  0.0025439  0.2233810
0.0011343  1.5475700  0.0024586  0.2277910
0.0010446  1.0119700  0.0031067  0.2394870
0.0005267  1.7681800  0.0040594  0.2567400
0.0004898  1.0578300  0.0030989  0.2420180
0.0001036  1.0153500  0.0031186  0.2365600

```

0.0000838	1.3316000	0.0030331	0.2549090
0.0000819	1.0049000	0.0031339	0.2353480
0.0000073	1.1392600	0.0030355	0.2451820
0.0000022	1.3068600	0.0030058	0.2528610

#-END-FILE---- (43597657865846357819) -----