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A Hybrid Bayesian method to obtain Bayesian Posterior Parameter Distributions in Nonparametric Pharmacokinetic Models for Individual Patients.

By

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Abstract.

This laboratory has developed a new hybrid Bayesian method of analysis, combining the strengths of the maximum aposteriori probability (MAP) and the nonparametric Bayesian (NPB) approaches. It uses nonparametric (NP) population pharmacokinetic models. It has provided increased precision in estimation and fitting of data from therapeutic drug monitoring (TDM), and has provided good estimates of model parameter values and serum concentration data when a very unusual subject is far outside the bounds of the original population model.

Briefly, in the hybrid approach, a MAP estimate is made first, and a grid of extra support points is placed in the region of the MAP estimate. The grid and the original population model are then combined to form an augmented population model. Then an NPB analysis is done on the augmented model.

The hybrid analysis provides more support points when the patient is within the ranges of the population model parameter values, with more precise parameter estimates and estimates of the patient's measured serum concentrations. On the other hand, when the patient is quite unusual, with model parameter values far outside the ranges of the population model, one can obtain good fits to the data by adjusting the weights of the MAP prior downward, and revising the relative probabilities of the population model and the grid.

The capabilities of the hybrid Bayesian approach suggest that it may provide a means for managing drug therapy for patients such as children who do not yet have a good population model for them, by using a population model for adults and the hybrid analysis, until enough patients have been managed to permit a proper population model to be made for them. Once this is done, it may well be possible to use the population model for children to manage the care of newborns, and then to make a similar proper population model for them. This hybrid approach has been implemented in the MM-USCPACK clinical software for precise drug therapy [ref].

Introduction –

An overview of parametric and nonparametric (NP) population models.

Parametric modeling approaches assume normal, lognormal, or multimodal distributions, and have equations describing their assumed shape. The parametric approaches estimate these parameters, such as means, standard deviations (SD's), and covariances as point estimators of the assumed distributions.

One might ask what an ideal population model might be like. If one somehow had the ability to make a model and to observe each subject's model parameter values exactly, one would obtain a discrete collection of each subject's individual parameter values. If there were only two parameters, one could plot these as a scattergram. If more than two, they could be expressed as a matrix, in which each row, for example, would represent a patient, and each column would represent the various exactly known parameter values for each subject.

In reality, however, we must give doses of the drug, measure responses such as serum concentrations, and estimate the model parameter values. The nonparametric approach gives up the assumptions about the shape of the parameter distributions. They can be anything. Genetically polymorphic subpopulations such as fast and slow metabolizers can be easily seen.

Based on the theorems of Caratheodory, Lindsay, and Mallet [1-3], the most likely distribution out of all the infinity of parameter distributions is to be found in a discrete distribution, somewhat similar to the ideal one described above. The distribution consists of a multiple discrete support points, up to one per subject studied. Each point consists of an estimate of each model parameter value, plus an estimate of the probability of that point in the overall population. This is described in [4,5].

Strengths of nonparametric models.

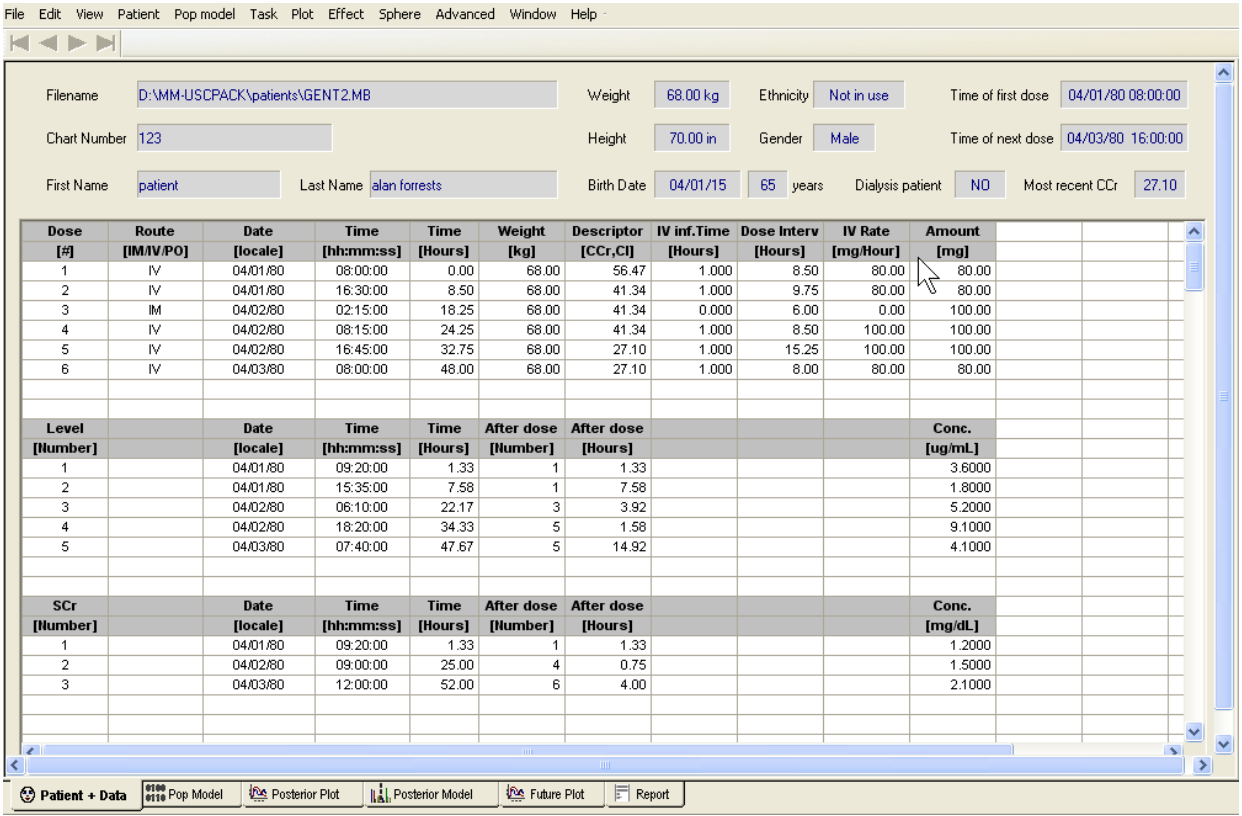
Nonparametric (NP) population pharmacokinetic/pharmacodynamic (PK/PD) models of drug behavior [3,4] have several important strengths over parametric models. Two important advantages are: 1) As stated above, no assumptions are made about the shape of the various parameter distributions. Instead of computing a point estimator of an assumed normal or lognormal distribution, for example, NP methods estimate the entire distribution itself. This distribution consists of a collection of discrete support points, up to one for each patient studied. Each support point contains an estimate of each model parameter value, as well as an estimate of the probability of that collection of estimates. 2) NP models are naturally suited for "multiple model" (MM) dosage design [6]. This method uses the multiple support points in the NP population model to make multiple predictions (each prediction weighted by the probability of the support point

generating that prediction) of responses (serum concentrations, for example) at the time one wishes to obtain the clinically selected therapeutic target goal. The weighted squared error of the failure of that regimen to hit the target is computed. This optimization process is iterated until the regimen which minimizes that error is found. Such dosage regimens therefore achieve target goals with maximum precision [6]. Such control approaches are used widely in the aerospace community for flight control and spacecraft guidance systems. This cannot be done with parametric models using single point parameter estimates, as there is no cost function to optimize.

Bayesian analysis using NP population models.

Here each population support point has its estimated probability. Those points that fit the patient's data well become more likely. Those that do not become less likely. In this way, while each population support point does not change its parameter values, its probability is revised based on the patient's data. In this way, the nonparametric Bayesian (NPB) posterior joint density is obtained for each individual patient [ref].

To begin our examination of Bayesian analyses, Figure 1 shows data of a patient, his doses of gentamicin, his serum concentrations, and his serum creatinine values.



Dose [#]	Route [IM/IV/PO]	Date [locale]	Time [hh:mm:ss]	Time [Hours]	Weight [kg]	Descriptor [CCr,Cl]	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	100.00
4	IV	04/02/80	08:15:00	24.25	68.00	41.34	1.000	8.50	100.00	100.00
5	IV	04/02/80	16:45:00	32.75	68.00	27.10	1.000	15.25	100.00	100.00
6	IV	04/03/80	08:00:00	48.00	68.00	27.10	1.000	8.00	80.00	80.00

Level [Number]		Date [locale]	Time [hh:mm:ss]	Time [Hours]	After dose [Number]	After dose [Hours]				Conc. [ug/mL]
1		04/01/80	09:20:00	1.33	1	1.33				3.6000
2		04/01/80	15:35:00	7.58	1	7.58				1.8000
3		04/02/80	06:10:00	22.17	3	3.92				5.2000
4		04/02/80	18:20:00	34.33	5	1.58				9.1000
5		04/03/80	07:40:00	47.67	5	14.92				4.1000

SCr [Number]		Date [locale]	Time [hh:mm:ss]	Time [Hours]	After dose [Number]	After dose [Hours]				Conc. [mg/dL]
1		04/01/80	09:20:00	1.33	1	1.33				1.2000
2		04/02/80	09:00:00	25.00	4	0.75				1.5000
3		04/03/80	12:00:00	52.00	6	4.00				2.1000

Fig 1. Data of doses, measured serum concentrations, serum creatinine, and the patient's age, gender, height and weight.

Figure 2 then shows the trajectory of the weighted average estimate of the serum concentrations based on the population model alone, without any fitting at all to his data. The relationship of the estimates to the measured data is very poor. The patient clearly is not an "average" patient.

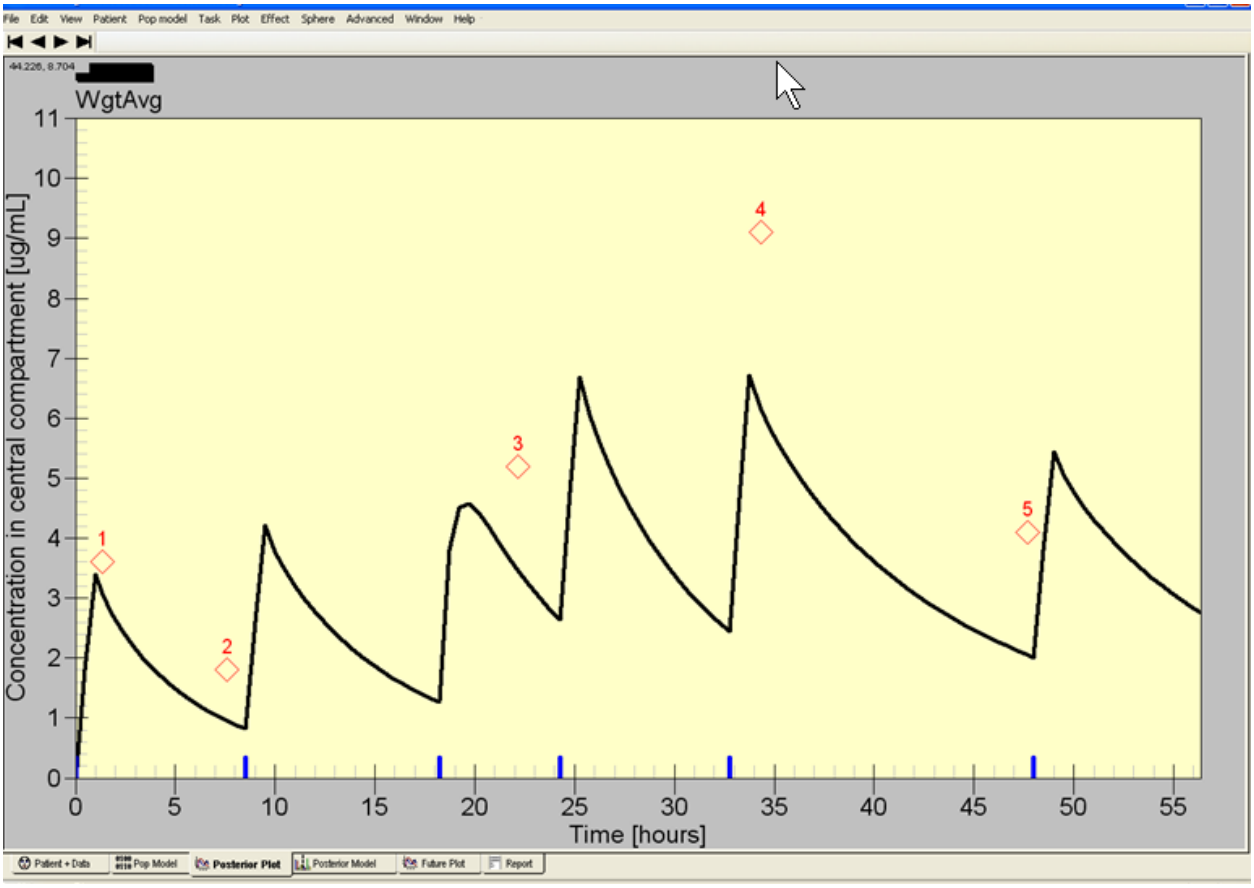


Figure 2 - weighted average estimates of the concentrations, using only the population model, without any fitting to his data yet. The measured serum concentrations are shown as numbered diamonds. The diamonds indicate that they have not been used in any fitting procedure.

Figure 3 shows the estimates of the patient's measured serum concentrations made from all 76 support points in the population model. Tremendous diversity is seen, with many very bad estimates of very low probability.

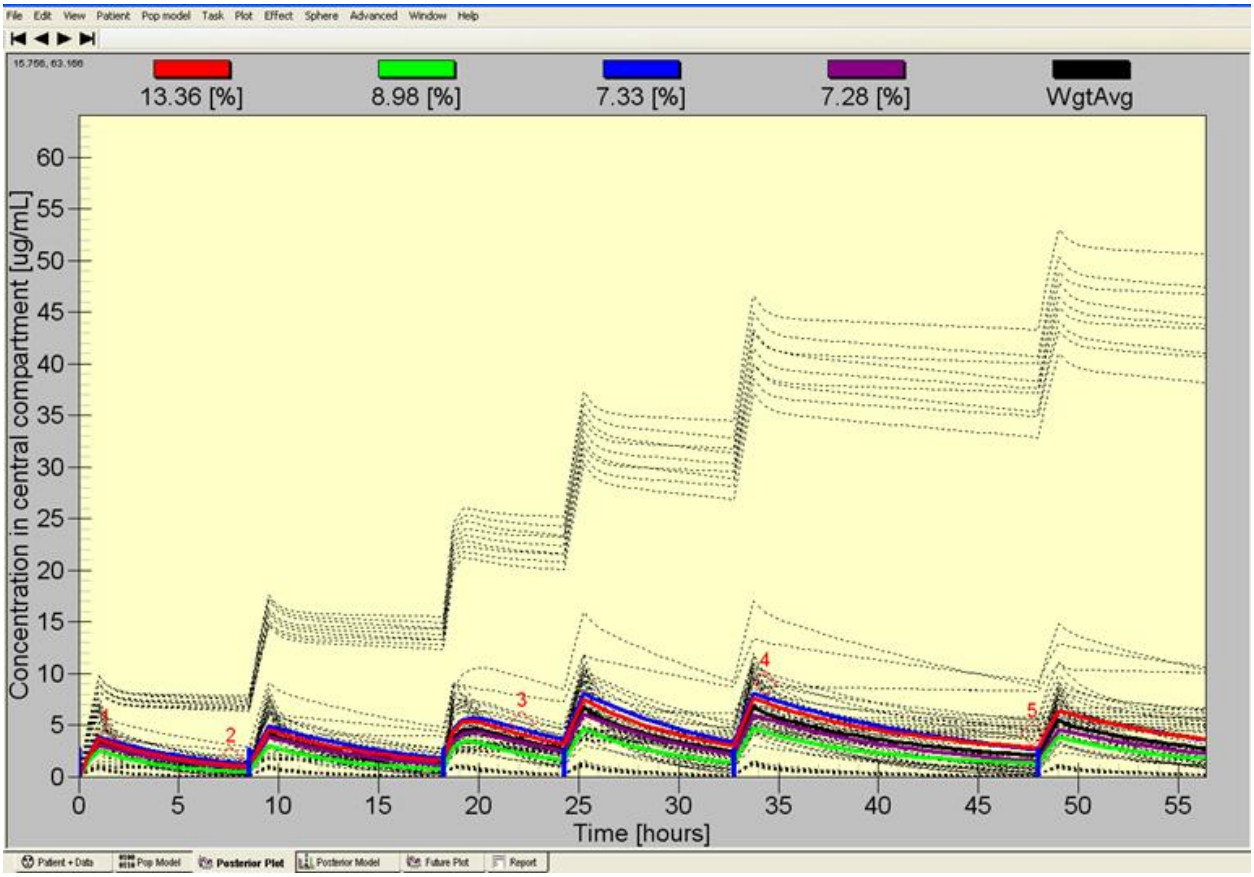


Figure 3 - trajectories of the 76 estimated of serum concentration based on the population model alone, without any fitting to his data yet. The five measured serum concentrations are numbered.

Figure 4 then shows the estimates of the patient's third measured serum concentration based on the population model alone. Again, great diversity in the estimate is seen, with many very high estimates of very low probability.

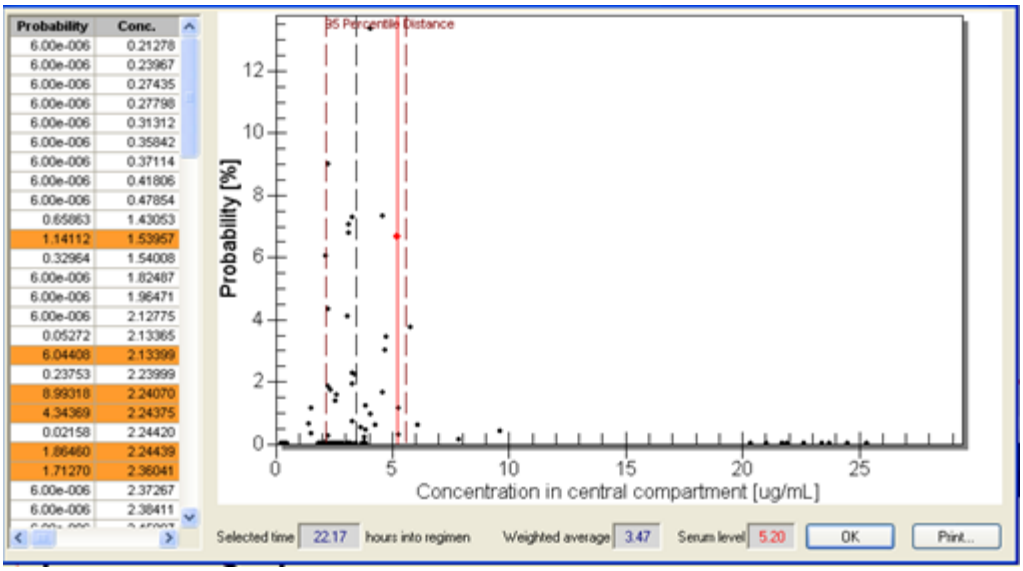


Figure 4 - estimates of the patient's third serum concentration, using only the population model. The measured concentration (solid vertical line with a dot) is very near the 95th percentile of the estimated distribution. Note the many estimates of very low probability from 20 to 25 ug/ml, corresponding to the numerous similar estimated trajectories at the time of this serum sample in Figure 2, above, at about 22 hours into the regimen.

NPB Bayesian Analysis.

The population model for gentamicin (the Bayesian prior) was based on data obtained from 634 patients studied by Dr. Pascal Maire and colleagues in seven different hospitals in France. To increase the speed of computation, the number of support points was reduced to 40 by increasing the apparent assay error. Thirty six extra points (nine at each corner of this plot) of very low probability (5 x 10-6 percent) were added later, as we began to encounter an occasional patient having parameter values outside the initial stated range of parameter values. That represented our first attempt to deal with the problem of unusual patients having model parameter values outside the range of the NP population model. As a result, there are 76 support points in the current population model.

Figure 5 shows a scattergram of the parameter distributions for VS1 (apparent volume of distribution of the central, serum concentration, compartment, on the horizontal, and KS1 (the increment of elimination rate constant per unit of estimated creatinine clearance) [7] on the vertical. Because this display looks down upon the parameters, the probability of the various support points in not seen. The region in the area of VS1 = 0.3 L/kg and KS1 = 0.0025 is reasonably well supplied with support points, but there are spaces between them. This is the area where this particular patient's Bayesian posteriors will be found to lie (see figure 10 below).

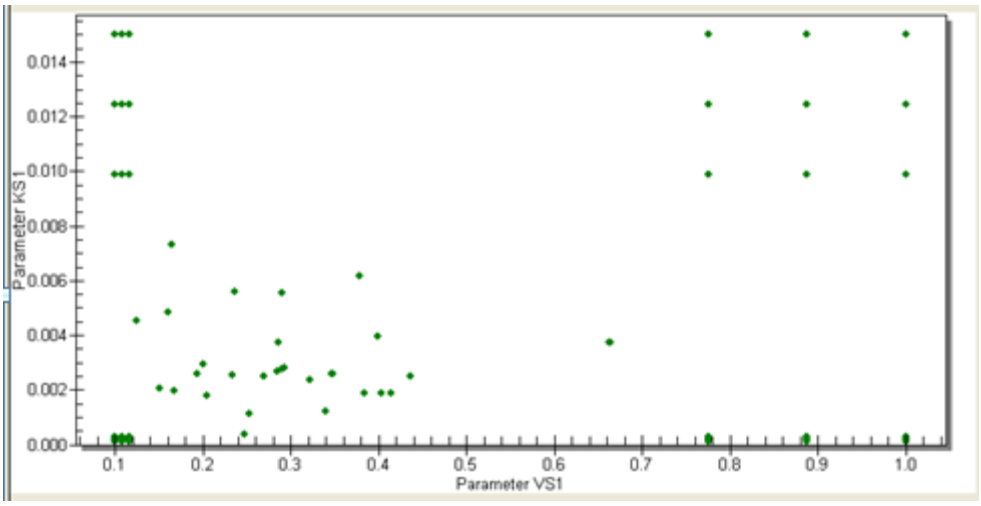


Figure 5. Scattergram of support points for VS1 and KS1 in the population model for gentamicin. Note the main area of somewhat random distribution (the 40 population support points) and the nine points at each corner, extending the model parameter ranges with points of very low probability.

As described earlier, the NPB posterior probability of each model support point is computed, based on that patient's data. The trajectory of the weighted average estimated serum concentration is shown below in Figure 6. Note that the fit is quite good despite the significant changes in the patient's renal function during the period of data analysis, because of our clinical method of tracking changing renal function [7].

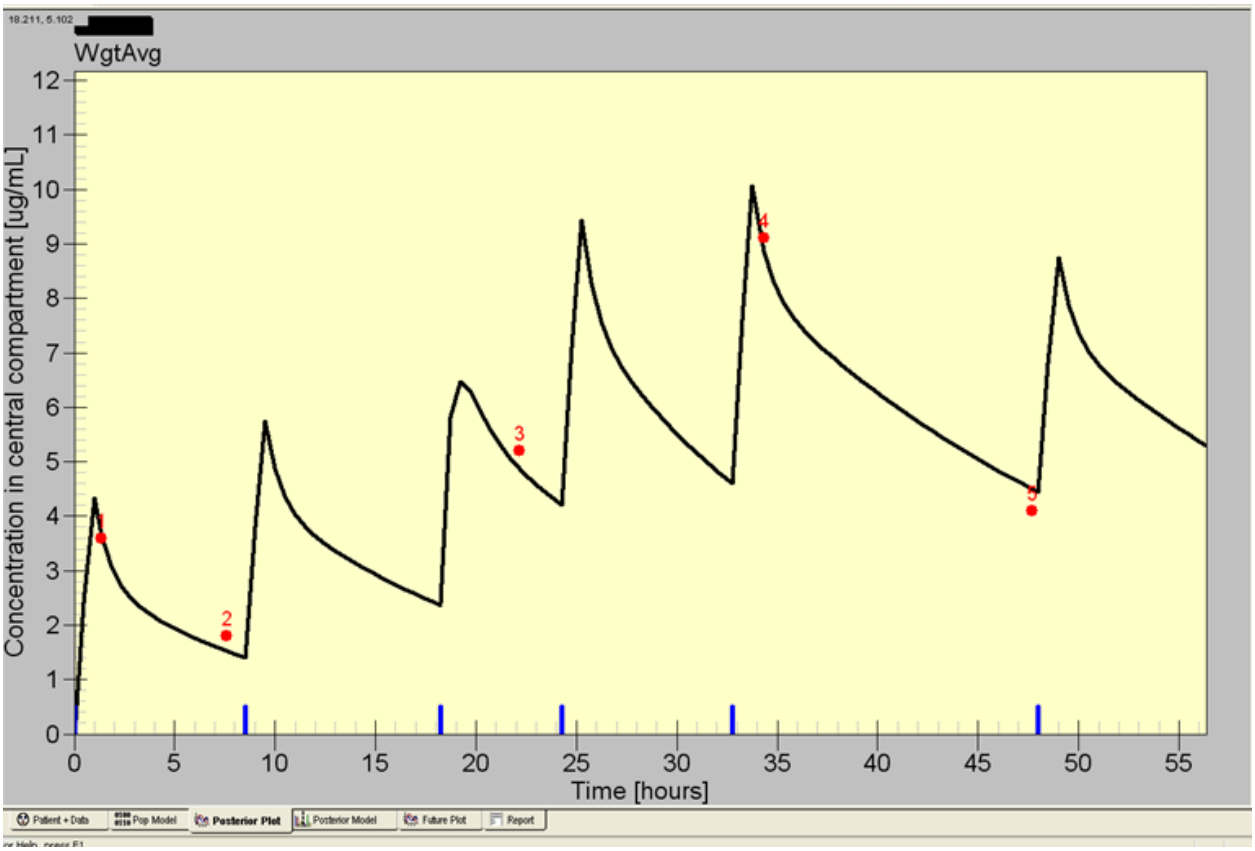


Figure 6. Trajectory of the weighted average estimate of the patient's serum gentamicin concentrations.

Figure 7 shows the NPB posterior model scattergram for this patient. Note that only five support points now have significant probability in the NPB analysis. They have a much narrower range than does the population model.

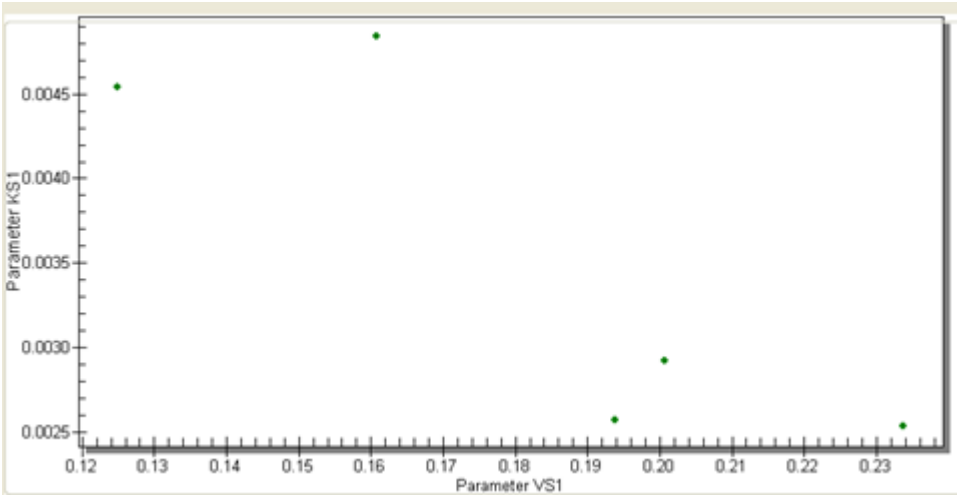


Figure 7. The patient's NPB Bayesian posterior joint parameter density. Only 5 points have probabilities over 0.1 % in the NPMM Bayesian analysis.

Figure 8 shows the trajectories of the estimated serum concentrations generated by those five NPB posterior estimates. Those support points that fitted the data well became much more probable, while those that did not became much less so. Here, only five support points had a Bayesian posterior probability over 0.1 %. Note the reduced bandwidth of these estimates compared to those from the population model, without any fitting, as shown in Figure 2, showing that the NPB analysis of the serum concentrations gave us more precise knowledge of the behavior of the drug in this patient.

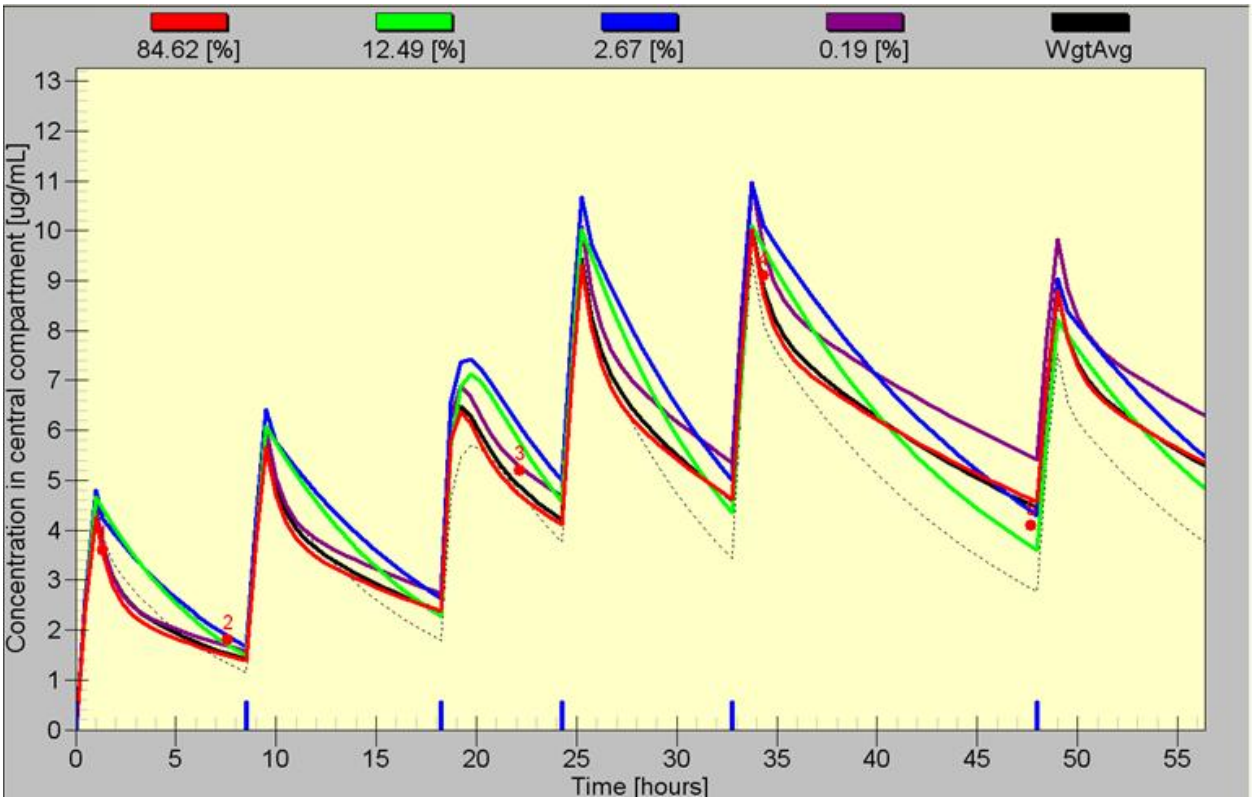


Figure 8. Trajectories of the serum concentration estimates from the five surviving Bayesian posterior support points. In contrast to the relatively low probabilities of the original 76 support points in the population model, note the much higher Bayesian posterior probabilities (up to 84%) in the five points shown here.

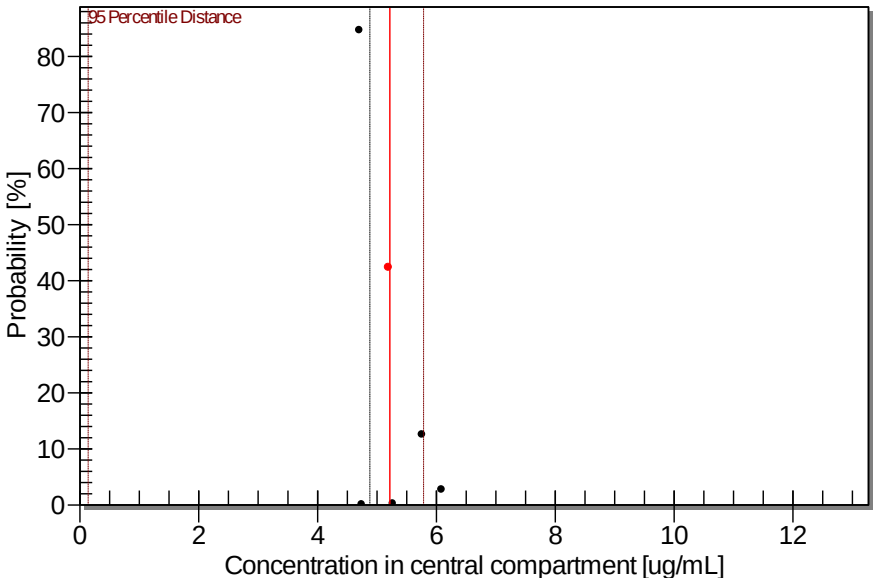


Figure 9 shows the estimates of the third serum concentration for this patient. The measured concentration is 5.2 ug/ml. The weighted average estimate is 4.89 ug/ml. However, the 2.5 percentile of the estimated distribution is very close to zero. The measured concentration is the vertical solid line with the dot halfway up. The other dots are the predictions, and their probabilities, of the surviving support points. The vertical dashed lines are the 95 percentile estimates of the distribution.

Figure 9 shows the much more precise estimates of the patient's 3rd serum concentration with the NPB analysis. However, it is noteworthy that the lower bound of the 95 percentile distance of the serum concentration estimate was far from the others. That is because one must draw a straight line from the estimated posterior probability of the lowest concentration (82%) down toward zero. Because of this, the 2.5 percentile estimate of the measured concentration is very close to zero. However, one can clearly see the increased precision with which this patient is known based of this analysis of his serum concentrations, compared to those made using only the population model. Here one can clearly see how much one has learned about the patient from the TDM one has done. However, having more support points in the area of the patient's Bayesian posterior might increase the precision of the estimate still further.

Problems with Bayesian Analysis using NP population models.

The strengths of NPB analysis are that 1) it estimates the entire Bayesian posterior parameter distribution given the data and the assay error pattern [roles of], permitting continued use of MM dosage design of the subsequent dosage regimen to hit the desired target goal once again, and each time, with maximum precision.

However, there are two weaknesses with this method. One is that the patient's individual model may lie in a region of parameter space where there are few support points, resulting in a loss of precision in estimating the model posterior parameter

distribution. The other is that the patient may be so unusual that his/her model parameter values may lie totally outside the stated range of the population parameter values. This was the problem that originally led us to add the extra points of low probability in the original gentamicin population model. We have now developed and implemented this new “hybrid” method of Bayesian analysis, described here, to overcome these problems. It is ad hoc, but useful.

Methods : The new Hybrid Bayesian method.

This new method begins with a standard maximum aposteriori probability (MAP) Bayesian estimation, based on the median population model parameter values, their standard deviations (SD’s), and the serum concentration measurements (or other measured responses) and their SD’s This MAP estimate is held back toward the population prior by the population model SD’s, which may be small or large. Because of this, MAP Bayesian estimation fails to discover the true patient optimally. This is called “shrinkage” in the field. However, the MAP estimate clearly goes well toward the patient’s true parameter values. It does not find the true patient, but instead finds the most likely compromise between the frequently conflicting information contained in the population model prior and that in the patient’s data.

Because of this problem of the conflict, we now add a number of extra support points to make a grid in the area of this MAP estimate. Since we know that this is the area in which the patient’s data is going to take the estimate, we know in advance that this region will have considerable probability. We therefore arbitrarily chose to give this grid 50% of the estimated probability, and to combine this grid with the original population model, which is also given 50% probability, to make an “augmented” population model. The grid currently has a total of 16 points, including the MAP estimate, but it can be any number, and it currently has a 5% change in value between the support points, but one can have any percent change.

The augmented population model is then used as the prior for NPB analysis. The resulting Hybrid Bayesian posterior joint density for that individual patient is used to compute the subsequent adjusted dosage regimen to most precisely achieve the desired clinical target goal at the new desired target time.

Hybrid Bayesian Model Augmentation

The process used to compute the Hybrid Bayesian method is shown in Figure 10 below. Here, individualized patient data is brought in at the top of the diagram, and used to compute a MAP estimate of the patient’s PK parameter values in the box marked “MAP Estimation”. The software allows for linear PK models having a central, peripheral, and an oral compartment.

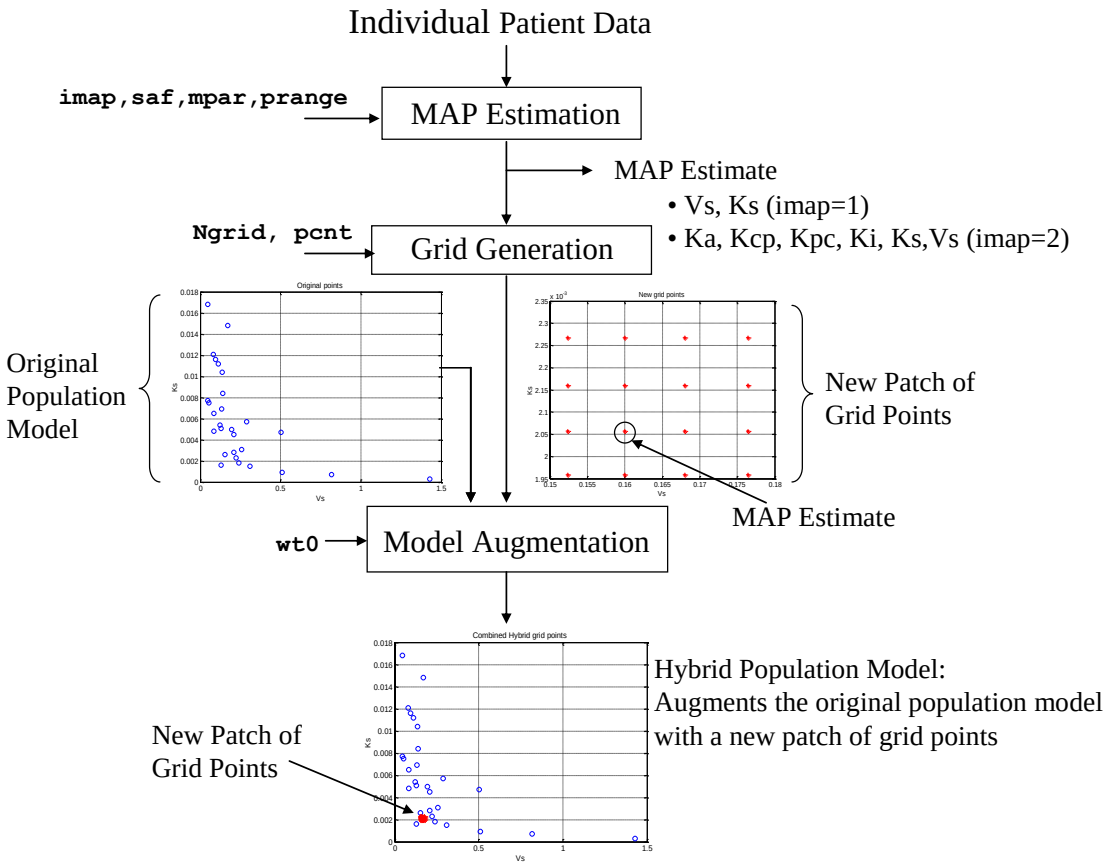


Figure 1: Process for computing the Hybrid Bayesian augmented population model

The process of computing the MAP estimate is guided by the quantities **`imap`**, **`saf`**, **`mpar`**, and **`prange`**, which are specified by the user. If **`imap=0`**, then only the volume VS1 and elimination constant KS1 are optimized in the MAP estimation process, with the remaining parameters held at their population median values. If **`imap=1`**, then all parameters of the PK model are optimized, for a total of 6 parameters in the case of a general 3 compartment linear PK model. The prior for the MAP estimate is given by the population median parameter values **`mpar`**, and the associated covariance P. The parameter **`saf`** is the sigma-augmentation-factor with a default value of 1, which is chosen by the user to either underweight (**`saf<1`**) or overweight (**`saf>1`**) the standard deviation of the prior in the determination of the MAP estimate. Internally, this is done by scaling the prior covariance P as **`saf^2`***P in computing the MAP estimate. The quantity **`prange`** gives hard upper and lower bounds on each of the optimized parameters to suitably constrain the MAP search process. For example, lower bounds on all PK parameters are typically zero since they are not allowed to become negative, and upper bounds can be specified based on practical experience.

The MAP estimate is input to the box marked “Grid Generation”, which is guided by the user-specified quantities **Ngrid**, and **pcnt**. Grid Generation generates an NxN grid in the region of parameter space surrounding the MAP estimate, such that the MAP estimate is one of the interior grid points. Here the value of N is specified by **Ngrid**, with a default value of **Ngrid=4**. The resulting 4x4 grid is shown in Figure 10, where the MAP estimate corresponds to the 10^{th} grid point (counting from left-to-right, top-to-bottom). The quantity **pcnt** specifies the spacing between grid points as fixed percentage offsets as a percent of the MAP estimate values. A default value of 5 percent is used for **pcnt**.

The last box marked “Model Augmentation” combines the original population model with the new patch of grid points to create the final augmented Hybrid model. Here, the user specifies the quantity **wt0** which weights the original population model points relative to the new patch of MAP grid points according to the formula

Hybrid Model = **wt0*** (original population model points) + (**1-wt0**)* (MAP grid points)

This form of the weights ensures that the total probability sums to unity. A default value for **wt0** is set to ½. A value of **wt0**>½, indicates that the original population model is to be trusted more than the MAP patch in treating the individual patient, while a value of **wt0**<½ indicates that the MAP patch is to be trusted more.

Example – a patient on Gentamicin. Putting more support points in the area.

Figure 11 shows a screen shot from our ClinMM clinical software [ref], of data from a patient receiving gentamicin. He had six doses given, and five serum concentrations measured. He also had quite significant changes in his renal function (serum creatinine) during this time, as shown. Because of this, his estimated creatinine clearance began at 56 ml/min/1.73m^2 body surface area, decreased to 41, and then to 27 (see the descriptor column).

The Hybrid Bayesian Approach. Putting more support points in the area.

Here the MAP Bayesian fit was done first, and the 4 by 4 grid applied. The population model was augmented by adding this grid, and is shown in Figure 12.

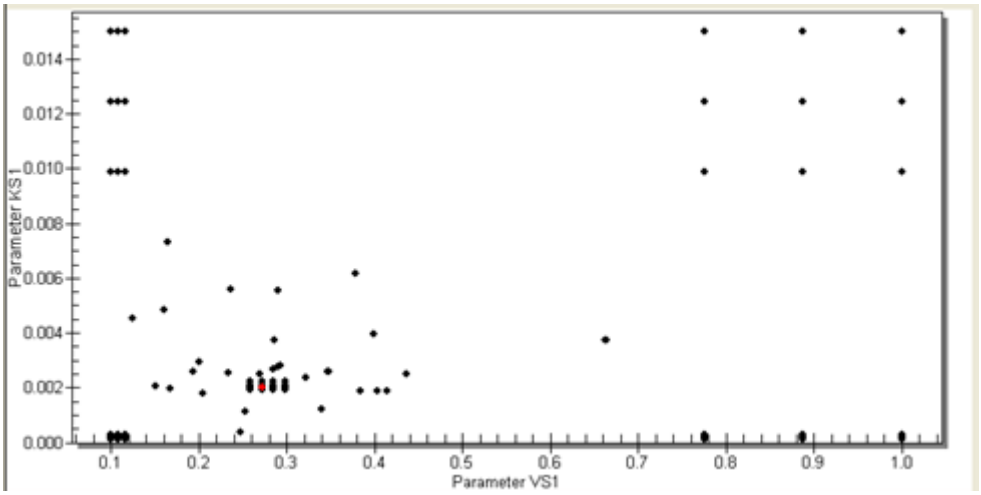


Figure 12. The augmented gentamicin population model for this patient. Note the 16 extra grid points added between about 0.25 and 0.3 for the VS1 horizontal axis and at about 0.002 for the vertical KS1 axis.

Now the NPB analysis was done on the augmented model, using this patient's data. Figure 13 shows the trajectory of the weighted average of the 17 Hybrid Bayesian estimates. A somewhat better fit is seen.

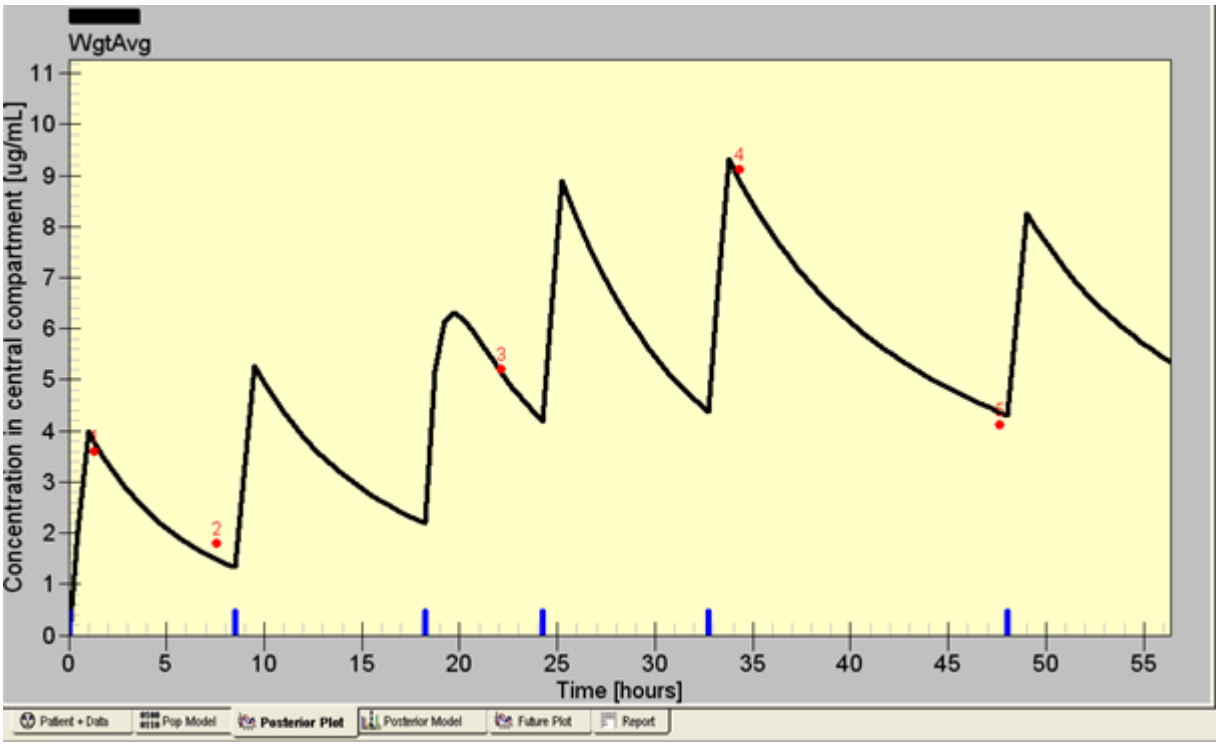


Figure 13. Trajectory of the weighted average estimate of the patient's serum concentrations using the Hybrid Bayesian analysis.

The patient's Hybrid Bayesian posterior model is shown in Figure 14 below. Note that 14 of the 16 support points in the grid had probabilities over 0.1% after the analysis, as did 3 points from the original population model, compared to only 5 with the routine NPMM analysis. Thus there are now 17 support points from which to predict the various serum concentrations.

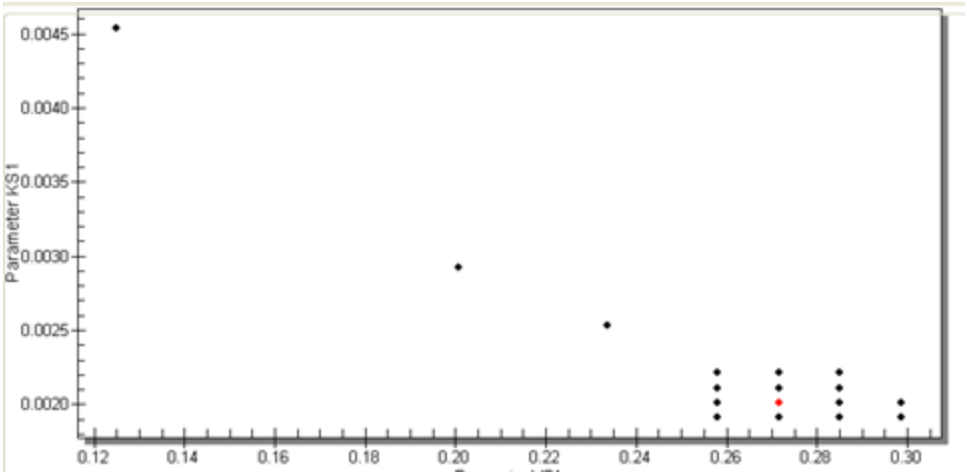


Figure 14. Scattergram of the patient's Hybrid Bayesian posterior joint density.

Figure 15 shows the trajectories of the seventeen Hybrid posterior estimates. The bandwidth of these estimates is less than that shown in Figure 8, using the regular NPB analysis, which had only five support points

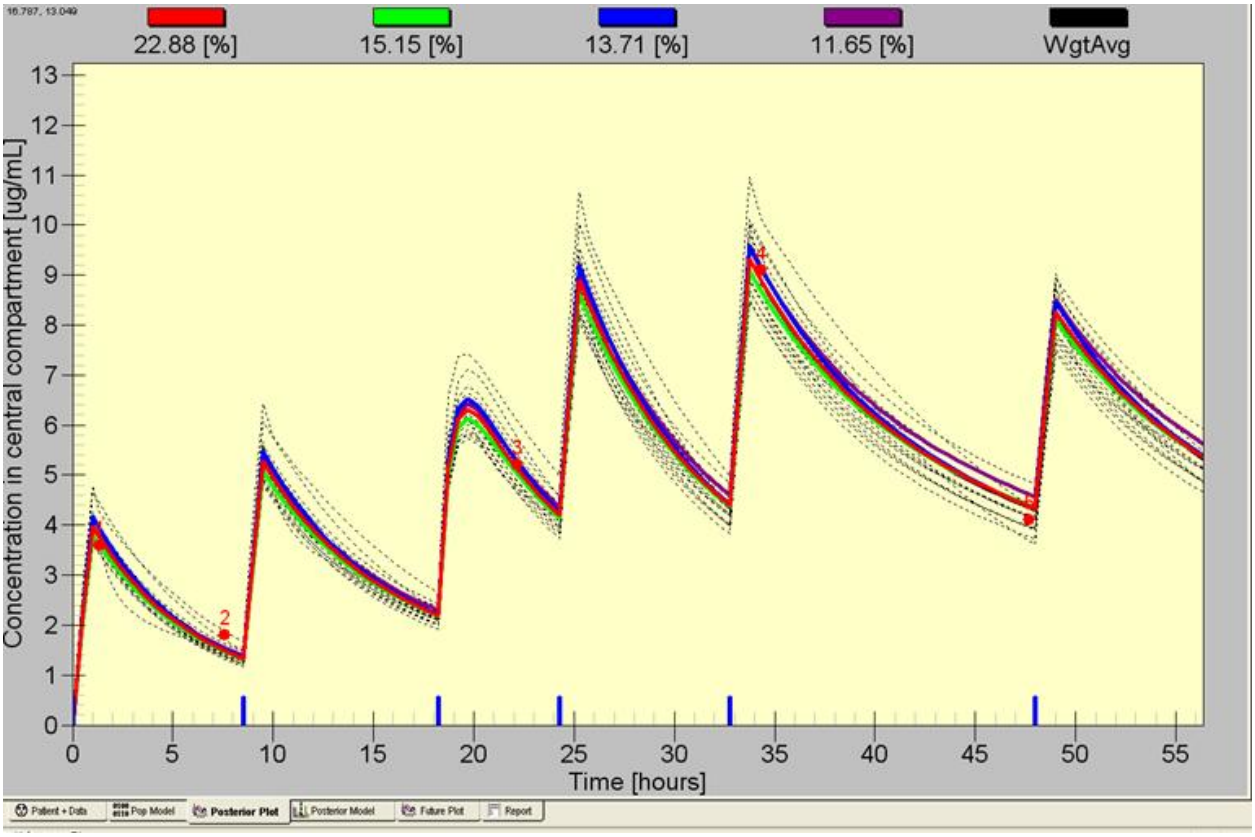


Figure 15: Trajectories of the seventeen hybrid Bayesian posterior estimates.

Figure 16 now shows the predictions of the patient's third serum concentration, using the hybrid Bayesian analysis. Note the significant increase in precision and the greatly reduced bandwidth of predictions compared to those shown in Figure 9.

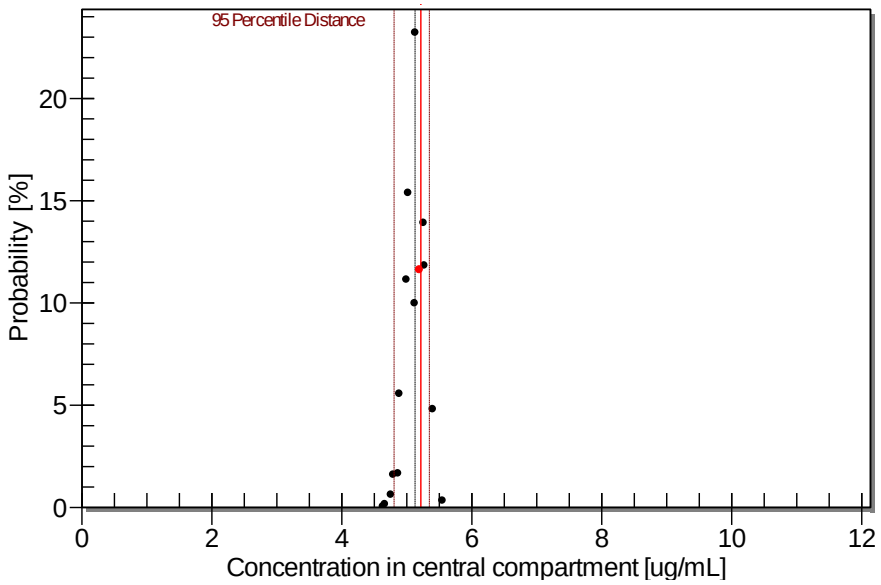


Figure 16. Estimates of the patient's third serum concentration using the Hybrid Bayesian analysis. The measured concentration is the vertical solid line with the dot halfway up. The other dots are the predictions, and their probabilities, of the surviving support points. The vertical dashed lines are the 95 percentile estimates of the distribution.

The Hybrid when the subject is outside the stated NP population model parameter ranges,

In contrast to the above patient whose parameter values were well within the stated ranges of the population model, sometimes a very unusual patient is encountered, whose model parameter values are outside the stated ranges of those of the NP population model. This raises a real problem in getting Bayesian posteriors for such patients, as in NP models it is not possible to have parameter values outside these ranges, Very poor fits result.

Let us now turn to our population model of digoxin, which was developed in adults based on the data of Reuning, Sams, and Notari [8]. This is an unusual model, as it was not developed from raw data. Instead, it was developed based on the parameter values reported by the above authors. It was converted to an NP model by a method to create discrete joint parameter densities using a method of maximum entropy [9]. The resulting scattergram of VS1 and KS1 appears to show only four support points, one at each corner of the model. The model parameters are Ka, the oral absorptive rate constant (hr^{-1}), Vs1 (L/kg), Ki (the nonrenal rate constant of elimination (hr^{-1}), KS1, the renal component of elimination (hr^{-1}per unit of creatinine clearance, in ml/min/1.73 M^2 body surface area), Kcp, the rate constant from central to peripheral compartment (hr^{-1}, and Kpc, the rate constant from peripheral back to the central compartment (hr^{-1}). What appears in the plot to be four points, one at each corner of the model, are actually 64 points, with 16 at each corner, each with its own probability. These are not seen in the scatterplot, as it is viewed entirely from above.

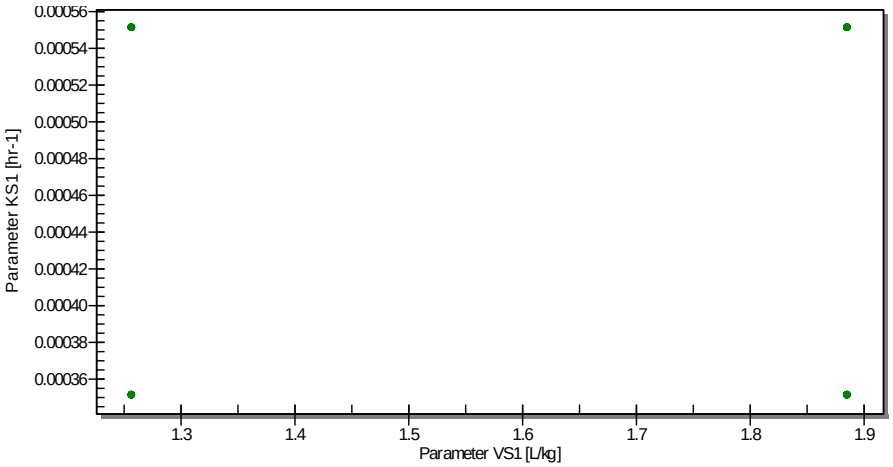


Figure 17. Scatterplot of the population model for digoxin in adult human patients. Horizontal, VS1 (L/kg), vertical, KS1,(hr^{-1}), Each point shown here actually consists of 16 points having the same parameter values, but having different probabilities, so that the entire distribution matches closely the parameter values found by Reuning, Sams,and Notari [8]. This was done using the method of maximum entropy to create discrete distributions from data of parameter means, SD's, correlations, and ranges [9].

Now let us analyze an unusual subject whose data lie far beyond the stated ranges of this adult human population model of digoxin. Let us look at data of a small dog who weighs only 9.1 kg. These data were generously made available by Dr. Marilyn Martinez of the FDA Center for Veterinary Medicine. The data are described by Whittem et.al. [11], with many thanks to them for sharing them with us.

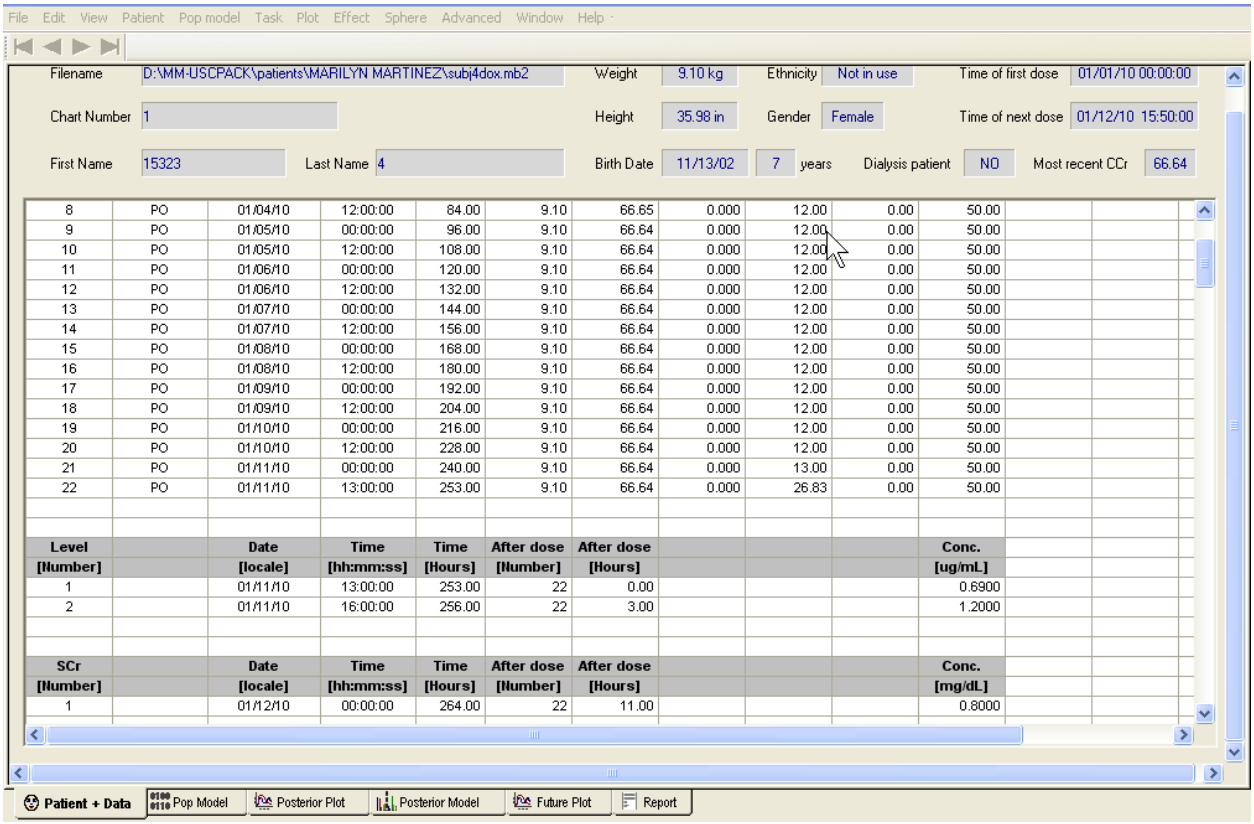


Figure 18. Data of doses and serum concentrations in a 9.1 kg dog. The values in this data set are far from those which would be expected in adult patients, whose average body weight usually is about 70 kg.

Figure 19 shows the very poor fit obtained using the human adult digoxin population model, with no fitting at all to the data. The weighted average of the estimated serum concentrations is quite far from the measured ones.

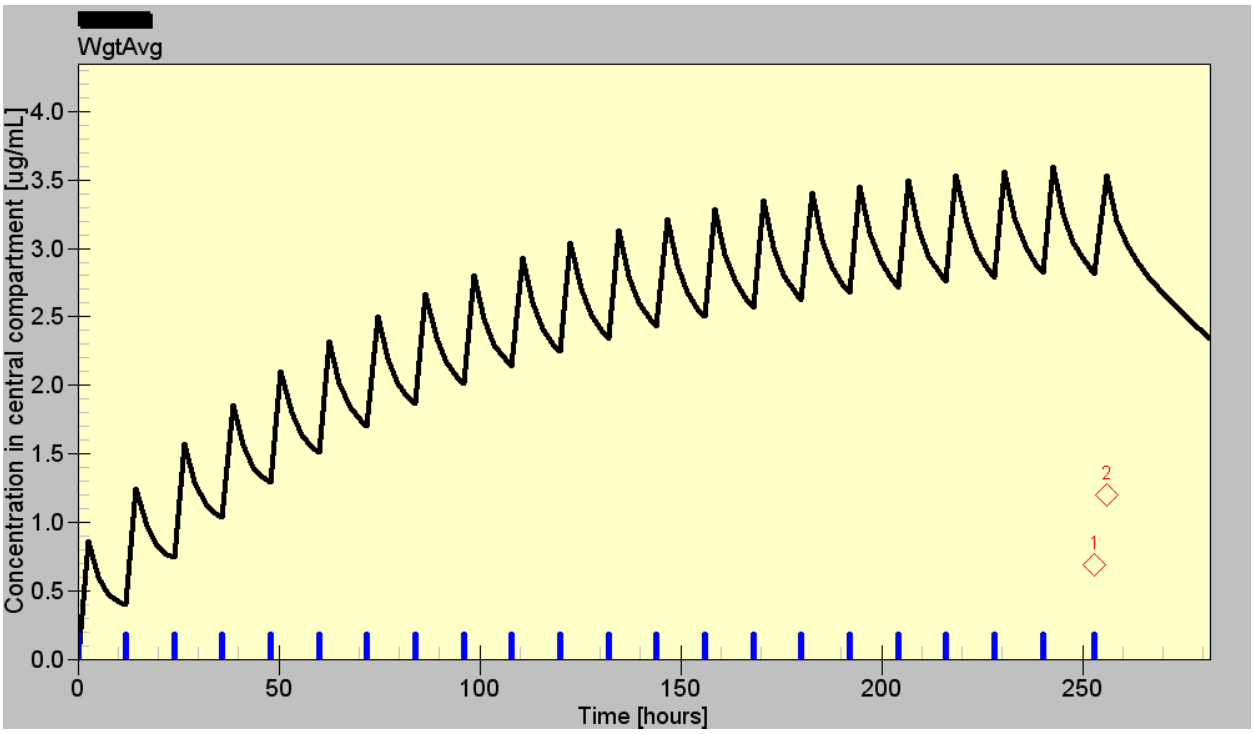


Figure 19. Estimation of the weighted average serum concentrations in this dog, using only the adult population model.

Figure 20 shows the diversity in the estimates from the 64 support points in the adult human digoxin population model.

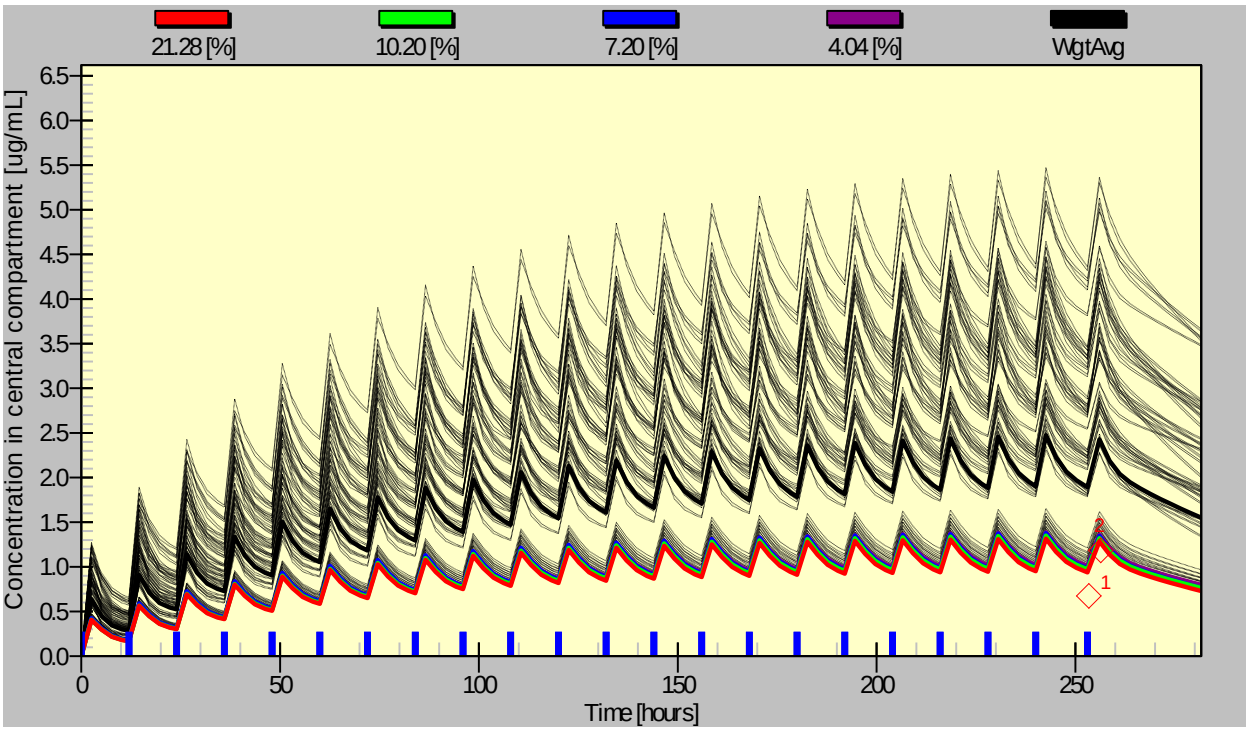


Figure 20. Diversity of the estimates using the population model, from all 64 support points.

Next, the NPB Bayesian analysis was used. The results are shown in Figure 21 below, for the weighted average of the NPB Bayesian posterior estimates. The fit is extremely poor, and not at all useful.

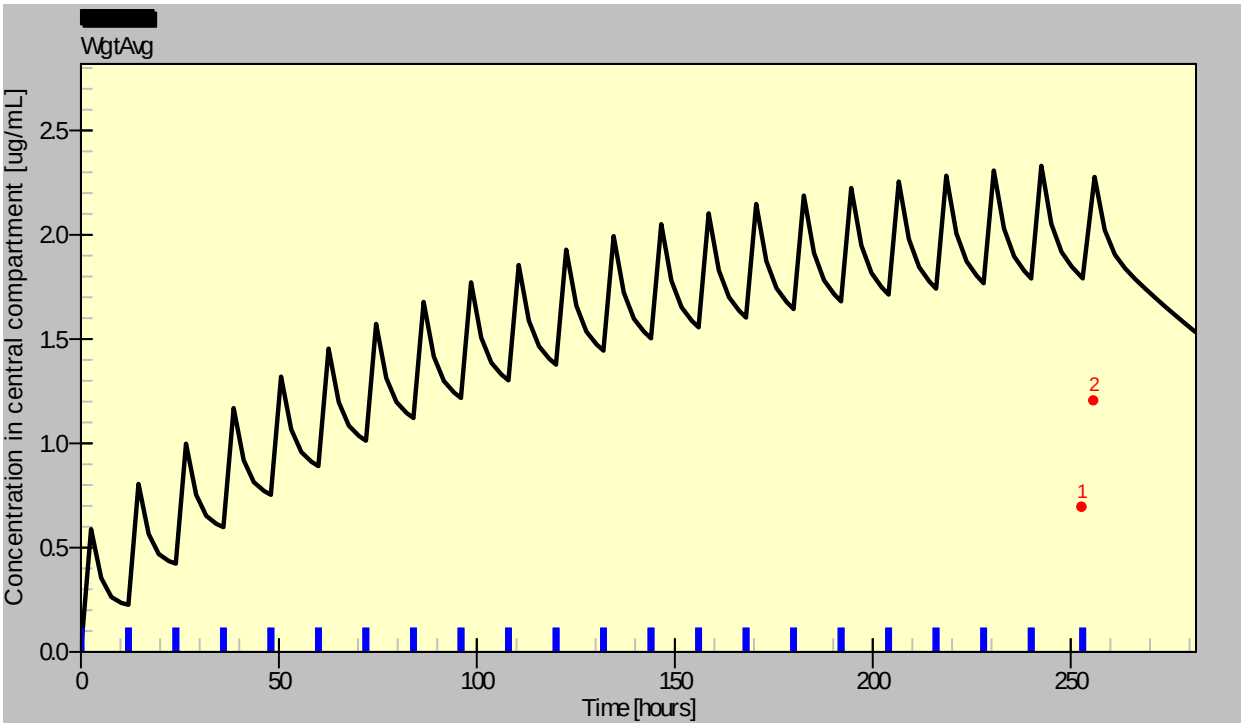


Figure 21. Weighted average Bayesian posterior estimates of the serum concentrations.

Figure 22 shows the estimates from the two significant support points in the NPB posterior model. It looks almost identical to Figure 21, but there are actually two support points, very close together.

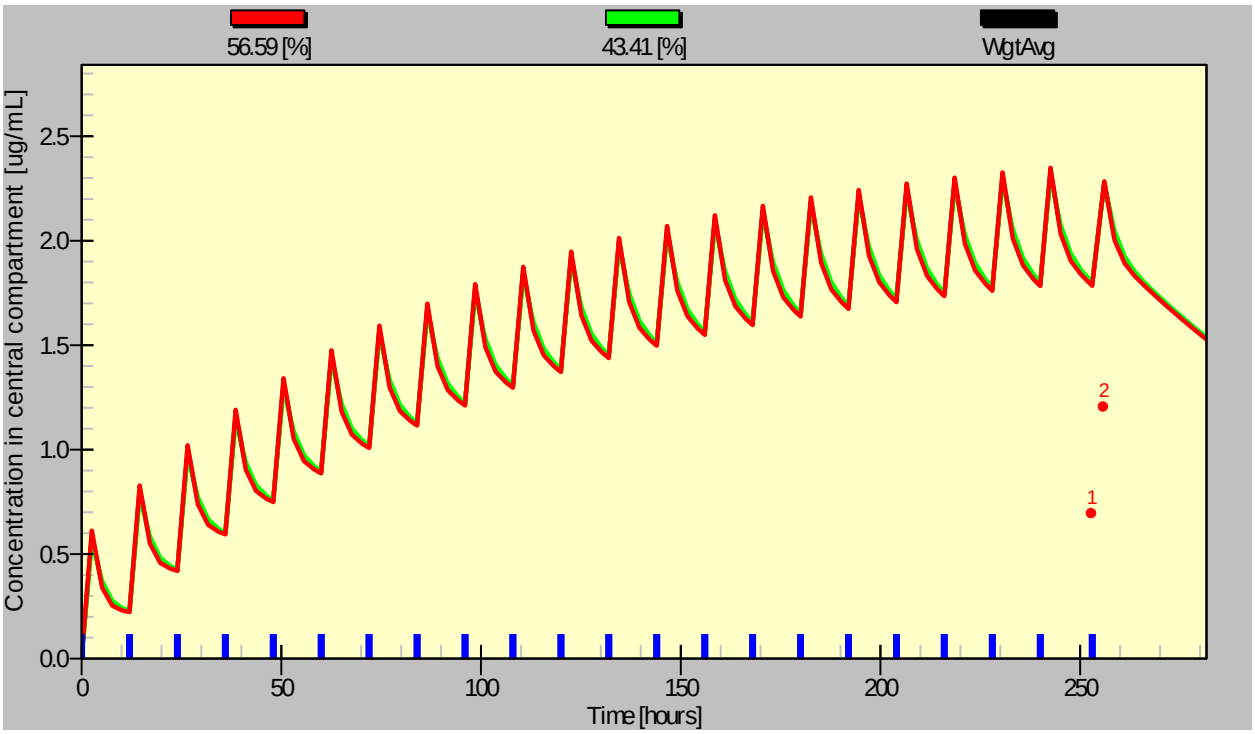


Figure 22. The estimates of the two surviving support points in the NPB Bayesian posterior model. The fit is not useful at all.

Next, the hybrid Bayesian analysis was used to analyze this dog's data. The peak serum concentration was reached in the fit, but not the trough. The resulting fit is still not satisfactory.

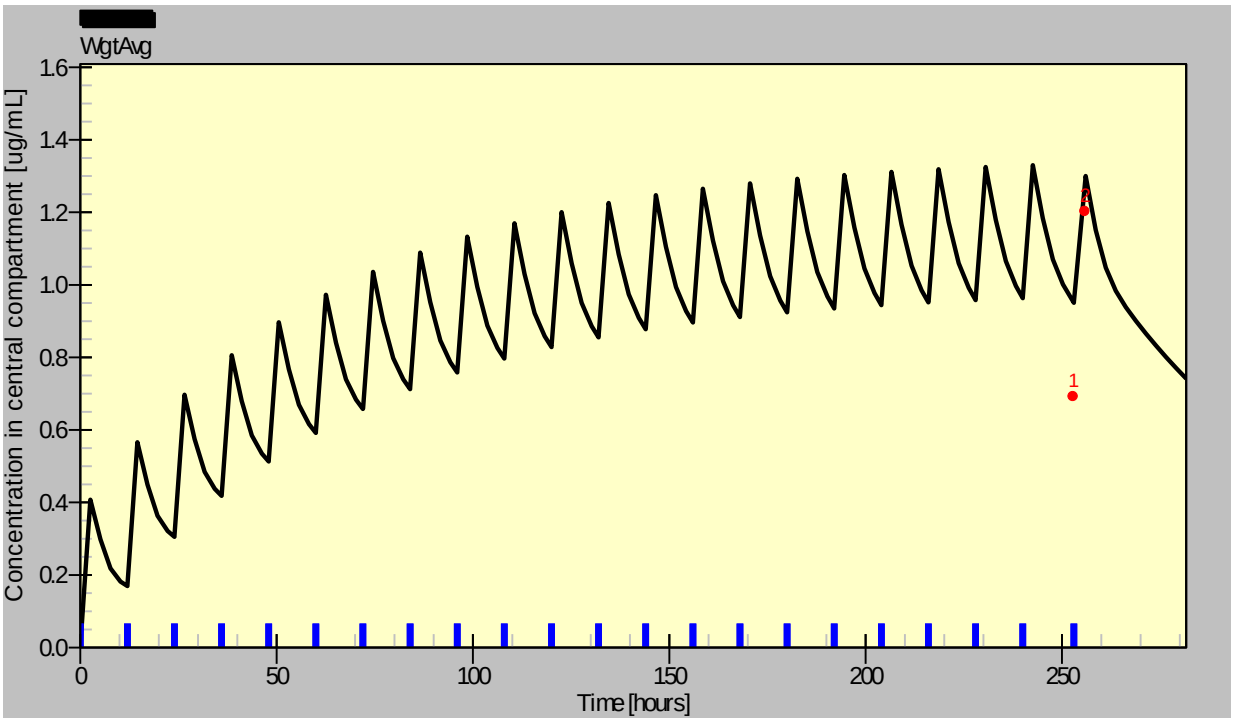


Figure 23. Better but still poor fit using the hybrid Bayesian analysis. Weighted average of the surviving trajectories of the estimated serum concentrations.

Now, there are still several options. One can downweight the prior, and can restate the relative probabilities of the population model and the MAP Bayesian estimate and its grid (see appendix for details). As one explores these downweighting options, the fit is drawn more and more to the data itself, and less and less back toward the population model. Figure 24 below shows the good fit obtained by exploring these options by increasing the standard deviation of the MAP Bayesian mean parameter value by a factor of 25, significantly decreasing its weight in the MAP Bayesian estimation, and by decreasing the probability of the original population model from 50% down to 25%, making the probability of the grid rise to 75%. This hybrid Bayesian analysis and the options for downweighting has been incorporated into the MM-USCPACK clinical software [10]. It is available for evaluation and use from www.lapk.org/software/downloads.

The result is shown in Figure 24 below, for the weighted average of the estimates. A good fit is seen.

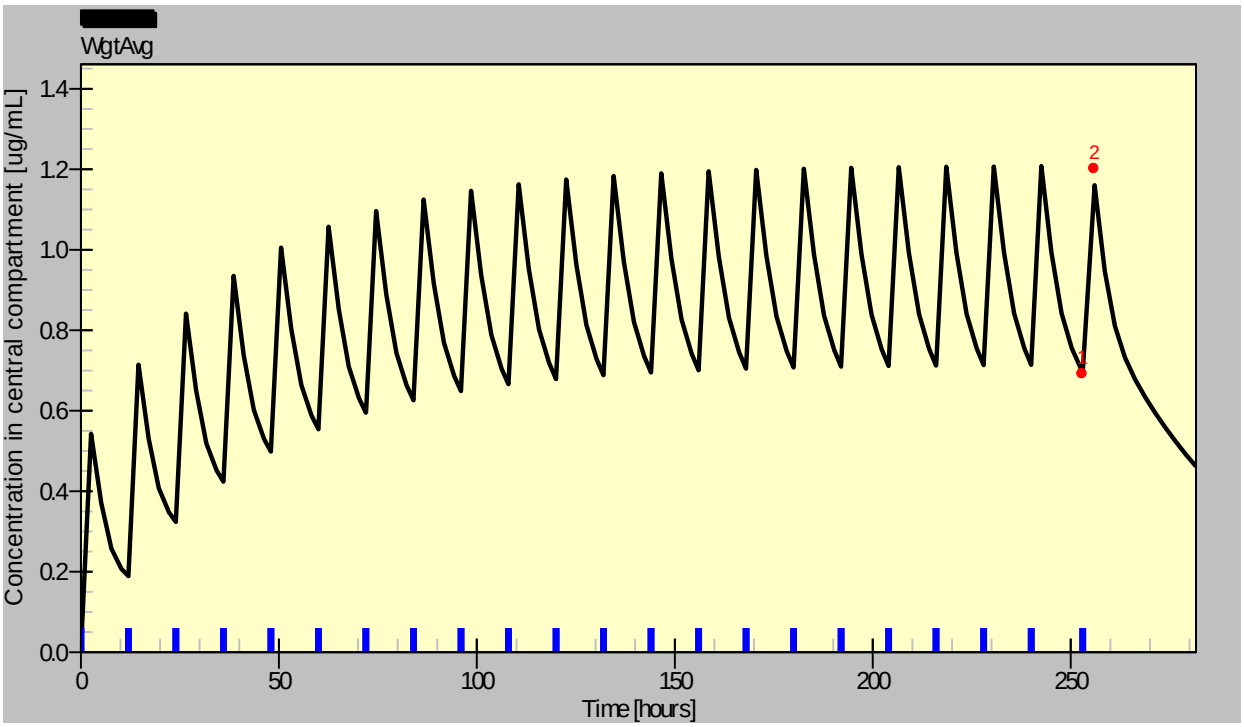


Figure 24. Weighted average estimates using the Hybrid, with downweighting of the prior as explained in the text and the appendix.

Figure 25 shows the augmented population model used for the hybrid Bayesian analysis. Note how the MAP Bayesian estimate provides a good estimate of where the dog's model parameter values lie far outside the stated population model parameter ranges. It provides a good guide for placement of the grid.

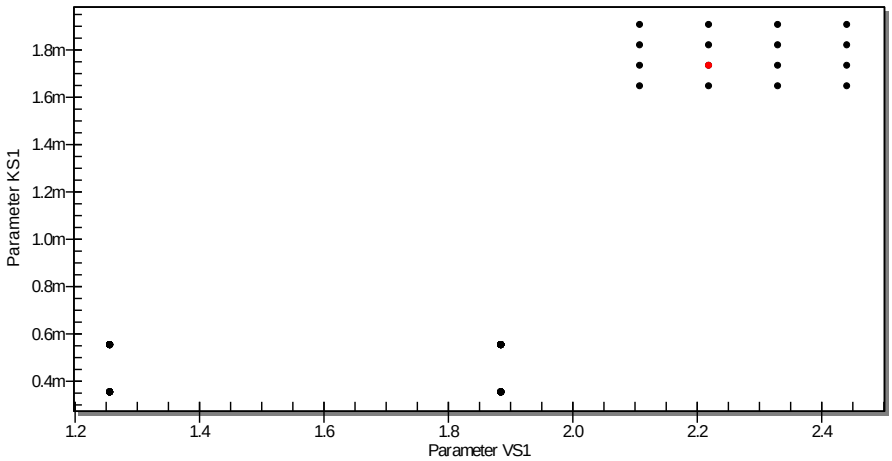


Fig 25. The augmented population model for this dog. Note that the grid is now far outside the ranges of the population parameter values.

Figure 26 shows the hybrid Bayesian posterior joint density for this dog.

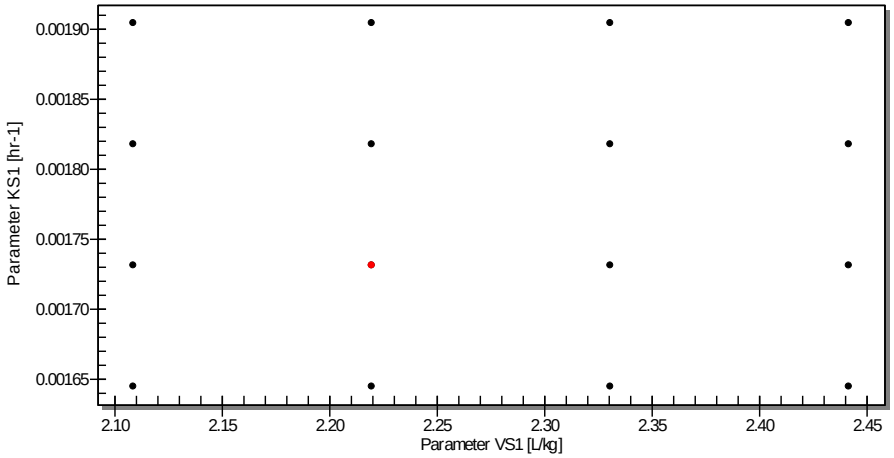


Figure 26. Hybrid Bayesian posterior joint density for this dog.

Figure 27 shows the Bayesian posterior estimates from all sixteen Bayesian posterior support points.

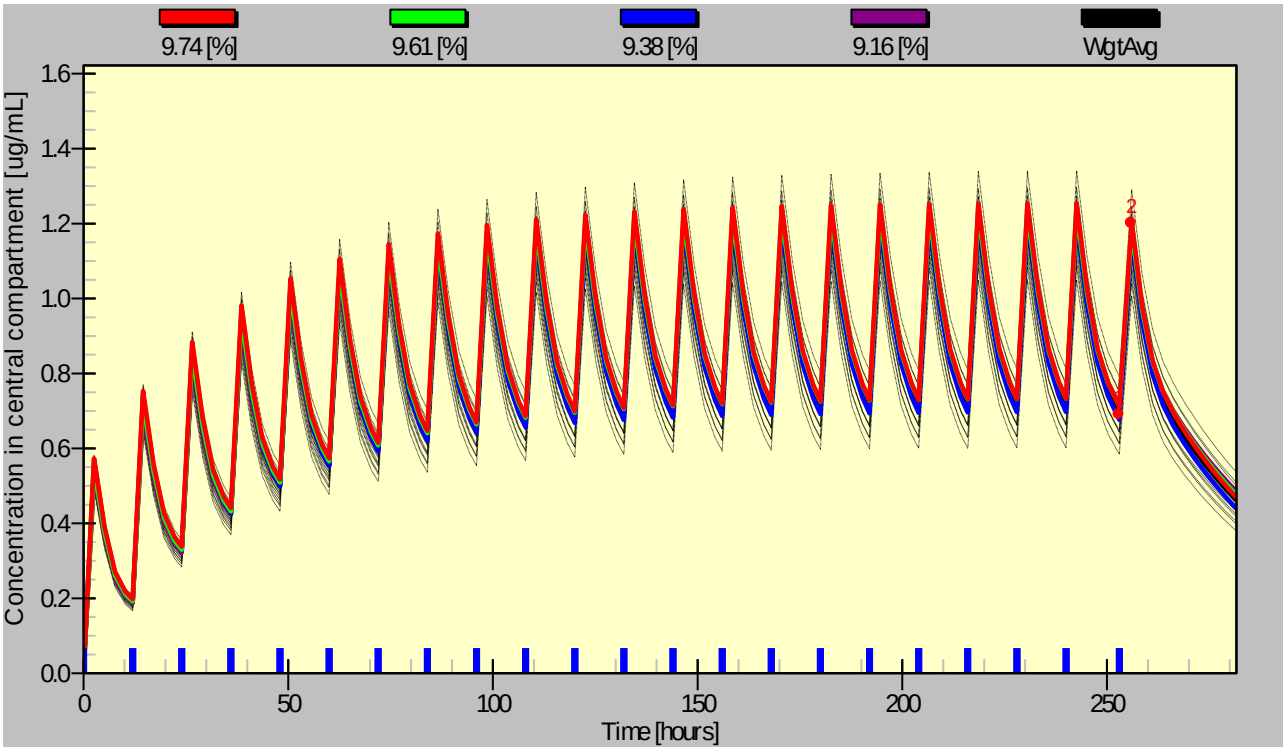


Figure 27. Plot of all surviving support points in the Hybrid Bayesian analysis with downweighted prior.

A further example is the estimation of that troublesome trough serum sample. It is well estimated now, as shown in Figure 28.

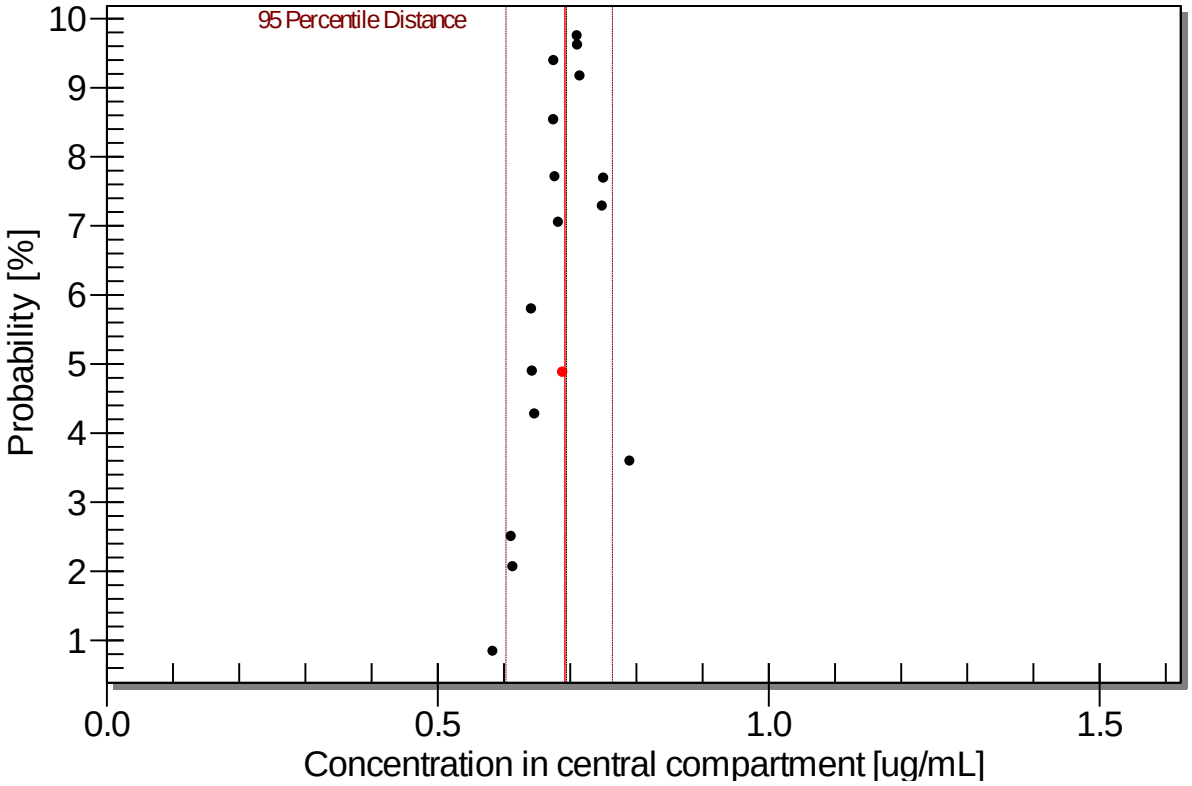


Figure 28. Estimation of the trough serum concentration in this 9.1 kg dog, using the hybrid Bayesian analysis with downweighted prior. The measured concentration is the vertical solid line with the dot halfway up. The other dots are the predictions, and their probabilities, of the surviving support points. The vertical dashed lines are the 95 percentile estimates of the distribution.

Implications for Therapy

The hybrid Bayesian analysis described above was effective in obtaining good estimates of model posterior parameter distributions in these two clinical settings. For the first patient, it provided more support points (a richer collection of points) in the area of the patient's parameter values, resulting in better estimation of those distributions, more precise estimation of that patient's third serum concentration, and therefore more precise dosage regimens to hit desired target goals, using multiple model (MM) dosage design [ref].

In the second setting, that of subjects clearly outside the stated ranges of the model parameter values, we were able to fit 19 out of 22 such dogs. Their weights ranged from 70 kg down to as low as 3 kg, The three dogs whose data could not be fitted were all less than 6 kg in weight. It was also interesting to see that after fitting, if one set a therapeutic target goal at the each dog's steady state trough concentration,

the dosage regimen suggested for the future was almost exactly that which they had received in the past.

These findings raise interesting possibilities. For example, for children who have no population model of a drug, it may well be possible to use an adult population model and the hybrid Bayesian analysis, perhaps with downweighting, as described here, to manage their dosage regimens. After enough children have been cared for in this way, then a proper population model can be made for them. Next, the process may employ such a population model for children to manage the care of newborn infants, and then again to make a population model for them. Thus the hybrid Bayesian approach for individual patients may make it easier to care for new patients outside the range of a particular population model, and then, later on, to make a population model for these new patients.

Conclusions.

We have described a new method of Bayesian analysis which combines the strengths of both the MAP and the NPB approaches. It permits dosage regimens to be developed to hit desired therapeutic target goals with maximum precision (minimum expected weighted squared error) when NP population model support points are relatively few. It can also be especially effective when treating patients who have very unusual model parameter values beyond the ranges of the particular population model, as in case of the small dog, for example

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