

**A POPULATION MODEL OF GENTAMICIN MADE WITH A  
NEW NONPARAMETRIC EM ALGORITHM**

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### **ABSTRACT**

A nonparametric EM (NPEM) algorithm for population pharmacokinetic modeling has been implemented as a computer program for the IBM PC and compatible machines. It computes the joint probability density function (PDF) for a 1-compartment pharmacokinetic model with intravenous dosing. It can operate using data of only one serum level per patient.

The program utilizes patient data files from the USC\*PACK PC clinical programs (1). Output includes a 3D plot of the joint PDF, two marginal PDF plots, means, variances, modes, quartiles, skewness, kurtosis, and covariance and correlation coefficient between parameters. Results can be entered into population files for use with the USC\*PACK PC clinical programs.

The first clinical study with this algorithm, of patients receiving intravenous gentamicin, is described. Results are compared with the standard 2-stage algorithm. Various parameterizations and sparse data sets are analyzed. The NPEM PC computer program permits population pharmacokinetic modeling in community hospitals.

### **INTRODUCTION**

Interest in modeling the population pharmacokinetic behavior of a drug in a group of patients has been stimulated by the use of Bayesian approaches to the adaptive control of drug dosage regimens (2-7). Methods of making population models of drugs have been thoroughly reviewed (8). In that review, the standard 2-stage method is described.

Beal and Sheiner (9-11) made significant advances when they developed the nonlinear mixed-effects model with first order approximation (NONMEM). It is a true population model-maker. It considers simultaneously all data from all patients in a population. It can operate with as few serum level data points as one per patient. It provides estimates of the means, standard deviations, and covariances of the population distribution.

A different approach was developed by Mallet (12,13) in which the entire population distribution itself is estimated. From this estimated distribution, the means, standard deviations, and covariances can be derived along with any other statistics of the distribution such as percentiles. The Mallet approach is "nonparametric" in the statistical sense, as the population distribution to be estimated is not defined by any finite set of parameters such as means, standard deviations, covariances, and the like.

The approach of Mallet has recently been implemented in a different manner, using a nonparametric EM (NPEM) algorithm developed by Schumitzky (14, see also 15, 16). It has now been implemented as a computer program for the IBM PC and compatible machines (17).

The present report describes the first clinical use of the NPEM algorithm and computer program, to make a 1-compartment (2-parameter) pharmacokinetic model of gentamicin, based on data of 20 patients previously studied in our laboratory by Iglesias (18-20).

## METHODS

### The Patient Population

The patient population consisted of 12 men and 8 women. Their mean age was  $47 \pm 16$  (1 SD) years, and their mean weight was  $63 \pm 15$  kg. All patients had significant infections requiring gentamicin (18-20). Six patients had significant liver disease. Ten patients had highly unstable renal function during their therapy. The mean duration of therapy was  $7.3 \pm 4.7$  days, and ranged from 1 to 17 days. A total of 177 serum concentrations (mean=8.85, SD= 6.02, range = 3 to 21 per patient) had been obtained. The data of their doses, the 177 serum concentrations, their weight, and their often changing creatinine clearance (CCr) were the basis for this population model. Later on, to further examine the ability of this new algorithm to make a population model, all serum level data were deleted except the highest and the lowest one for each patient. In a random manner (coin flip), one serum level, the highest or the lowest one, was then discarded to make a population data base consisting of only a single serum level (a high or a low) for each patient. This extremely sparse data was also analysed by the program and the resulting population model was evaluated. Lastly, only the single lowest trough serum level was preserved from each patient's data, and the performance of the algorithm under these truly abusive conditions was also examined.

### The Model Parameterizations Examined

Four different parameterizations of the population model were examined. First, the elimination rate constant (K) and the total apparent volume of distribution (V) were examined. Second, the slope (KS) of the relationship between K and CCr, with the nonrenal intercept (KI) held fixed at a value of  $0.0069315 \text{ hr}^{-1}$  (corresponding to a half time of 100 hours in an anephric patient), and VS, the slope of the relationship between V and body weight, were examined. Third, the parameters of clearance (C)

and V were examined. Fourth, the parameters of the slope (CS) of the relationship between gentamicin clearance and CCr, (with the nonrenal clearance intercept (CI) being fixed at 0.00255044 units, again equivalent to a half-time of 100 hours), and the VS were examined.

Each of the 4 parameterizations was evaluated using all 177 serum levels. Finally the CS and VS parameterization was examined in the two sparse data sets, each using only a single level per patient.

In all cases, the joint probability density was described as a 30 by 30 point grid (900 points) whose boundaries were empirically defined by trial and error to cover the parameter space. In addition, the 3D plots (21) employed by the NPEM program were viewed from a specified height. It takes some trials at first to establish the parameter space and a useful height from which to view the 3D plots.

The program iteratively re-examines the population data set, patient by patient. Each re-examination obtains a better estimate of the log-likelihood function (16). All runs were set to go for 100 iterations or cycles, or until the log-likelihood function had a value less than 0.001 units from that of its previous cycle.

## RESULTS

### The K and V Parameterization

In this parameterization, a log-likelihood value of -338.388 was achieved on the 38th cycle. The 3D plot of the joint density and the 2D plots of the marginal densities of K and V are shown in Figure 1. The mean and standard deviation for K were  $0.1824 \pm 0.1149 \text{ hr}^{-1}$ , and the similar values for V were  $24.190 \pm 12.733 \text{ L}$ . The covariance between V and K was -.6449, and their correlation coefficient was -.4409. The mode, median, skewness and kurtosis of K were 0.1897, 0.1704, 1.3906, and 6.558, and for V were 18.974, 17.041, 2.1415, and 6.609 respectively.

### The KS and VS Parameterization

For this parameterization, the nonrenal component of K (Kint) was set at  $.0069315 \text{ hr}^{-1}$ , equivalent to a half time of 100 hr in a totally anephric patient. The parameter KS then reflected the slope of the relationship between K and the patient's often changing CCr (18-20,22). Similarly, VS reflected the slope between V and body weight, in L/kg.

In this examination, a log-likelihood value of -267.749 was reached on the 43rd cycle. The joint density and the marginal densities for KS and VS are shown in Figure 2. The mean and standard deviation for KS were  $0.002917 \pm .00122 \text{ (hr[ml/min/1.73M}^2\text{)]}^{-1}$ , and for VS were  $.36795 \pm .14004 \text{ L/kg}$ . Their covariance was -.1237 and their correlation coefficient was -.7260 respectively. The mode, median, skewness, and kurtosis of KS were .003236, .00300, .1243, and 2.33, and for VS were .2896, .2634, 1.1419, and 3.4774 respectively.

### The C and V Parameterization

For this parameterization, a log-likelihood value of -339.572 was reached on the 37th cycle. The joint and marginal densities are shown in Figure 3. The mean and standard deviation for the clearance (C) were  $3.8671 \pm 2.2223$  L/hr and for V were  $23.471 \pm 10.9537$  L respectively. Their covariance was -1.832 and their correlation coefficient was -.7524. The mode, median, skewness, and kurtosis for C were 4.147, 3.161, 1.4065, and 4.782, and for V were 17.377, 19.056, 1.939, and 6.156 respectively.

### The CS and VS Parameterization

Here CI, the nonrenal intercept of clearance, was set at 0.00255 L/hr, corresponding to a half-time of 100 hours in an anephric patient when  $KI=.0069315\text{hr}^{-1}$ . A log-likelihood value of -272.706 was reached on the 34th cycle. The joint density and the marginal densities are shown in Figure 4. The mean and standard deviation for CS (the slope of clearance with respect to creatinine clearance) were  $.06517 \pm .02312$  L/{kg[hr(ml/min/1.73M<sup>2</sup>)]}. The mean VS was  $.3728 \pm .1471$  L/kg. Their covariance and correlation coefficient were -.1544 and -.4538 respectively. The mode, median, skewness, and kurtosis for CS were .0378, .0527, .7158, and 2.683, and for VS were .2896, .3176, 1.228, and 4.042 respectively.

### Analysis of Sparse Data Sets

The NPEM population program can utilize very sparse data consisting, for example, of only 1 serum data point per patient. To illustrate this point, the CS and VS parameterization was examined again as follows. First, all serum values were discarded except the highest and the lowest for each patient. Next, using a coin flip, the highest or the lowest data point was randomly discarded from each patient's data set until only a total of 20 data points, 10 high and 10 low, were present. Each patient's data set then consisted of only a single serum level data point, either a high one or a low one.

The NPEM program then examined this data set. The CI was again set at .00255044 L/hr. On the 58th cycle, a log-likelihood value of -25.0248 was reached. The joint and marginal densities are shown in Figure 5. The mean and standard deviations found for CS were  $.08238 \pm .02897$  L/{kg[hr(ml/min/1.73M<sup>2</sup>)]}, and for VS were  $.2193 \pm .0528$  L/kg. Their covariance and correlation coefficient were -.6322 and -.3745 respectively. The mode, median, skewness, and kurtosis for CS were .0604, .0534, .1844, and 1.414, and for VS were .2322, .2013, .01962, and 2.0727 respectively.

In a further study of this parameterization, only the single lowest serum data point was used for each of the 20 patients. This is an abusive, highly suboptimal "worst-case" scenario of a population study. CI was again fixed at .00255044. With this data set, a log-likelihood value of -21.74526 was reached on cycle 100, showing that the stopping criterion value of 0.001 had not yet been reached. The joint and marginal densities are shown in Figure 6. The marginal density for VS was not contained within the bounds of the grid, which had contained the densities when analyzing the other data sets. The mean and standard deviation found for CS were  $.09655 \pm .05596$  L/{kg[hr(ml/min/1.73M<sup>2</sup>)]}, and for VS were  $.6946 \pm .5836$  L/kg

respectively. Their covariance and correlation coefficient were .01929 and .5909 respectively. The mode, median, skewness and kurtosis were .06043, .05344, 1.554, and 5.124 for CS, and .30215, .26718, .97168, and 2.6004 for VS respectively.

### Comparison with the Standard Two -Stage Algorithm

The standard 2-stage algorithm was also used to examine the full data set of 177 serum levels, employing the K and V parameterization, using the MLS program in the USC\*PACK PC clinical collection (1). This uses the Nelder-Mead algorithm (23) to minimize the weighted least-squares function, where the serum level data points were weighted by the reciprocal of their variance, using the assay error pattern for the EMIT gentamicin assay in our center (24), as was done for the NPEM population program.

The frequency distribution of the values of K and V, and the scattergram of their relationship, are shown in Figure 7. The mean K was  $0.2002982 \pm .1357$  (1SD). The median, skewness and kurtosis were .1832, 1.392, and 4.865 respectively. The mode could not be calculated with the software used (25). The mean V was  $21.566 \pm 8.816$  L. Its median, skewness, and kurtosis were 18.914, 2.812, and 6.195 respectively. Their correlation coefficient was -0.435.

## DISCUSSION

A summary of the various results is presented in Table 1. First, the means, standard deviations, and correlations found for V and K are similar to those found using the standard 2-stage algorithm. They show the general correspondence of the two methods. Next, the coefficients of variation were smaller with the KS and VS parameterization than with the K and V parameterization, suggesting that using CCr and body weight as descriptors for K and V was useful. The result of this, however, was that KS and VS were better correlated and therefore perhaps less orthogonal.

### Comparison of the various Parameterizations

It is not clear what is the "best" way to parameterize a pharmacokinetic model, though many tend to favor C and V or CS and VS over K and V or KS and VS. This is often the case because C is often more clearly related to other descriptors (age, for example, with some drugs) than is either V or K. Also, C and V parameterizations are often less correlated, more orthogonal to each other, supposedly capturing more information from the data.

To our knowledge, the question of optimal parameterization of a pharmacokinetic model is still an unsettled one. Because of this, the various options have been provided in the NPEM program so they can easily be compared with each other, as in the results shown here.

The C and V parameterization had basically similar coefficients of variation as did the K and V parameterization, but a greater correlation than K and V, in contrast to what is often found. The most generally pleasing parameterization (the best?) was

the VS and CS one, as the joint PDF appeared to show the least correlation, the mass density points appeared not to have a grossly visible relation to each other, and the log-likelihood value for the two clearance parameterizations was less negative than the similar values found with the two K parameterizations. Each marginal PDF appeared to more closely approximate a normal or lognormal PDF than did their other counterparts. The correlation coefficient between CS and VS was among the lowest found, and the coefficients of variations of CS and VS were the lowest found with the full data set of all serum levels. Thus the CS and VS parameterization had the combination of the smallest coefficients of variation and the least correlation between parameters. These results suggest that it was useful to relate C and V to the descriptors of CCr and body weight respectively. CS and VS also had a more orthogonal relationship than did KS and VS. When KS was calculated from CS and VS, a value of .002776 was obtained, close to the mean KS of .002917 found with the KS and VS parameterization.

The marginal densities of V, as determined by both the K and V and by the C and V parameterizations (Figures 1 and 3) appeared generally similar in outline. There was a noticeable gap between the bulk of the density clustered between 13 and 35 L and a smaller mass of higher volume clustered between 50 and 60 L. In contrast, VS in both the VS and CS and the VS and KS parameterizations had a smaller gap between the main bulk of the density and the small mass of high outliers, as shown in Figures 2 and 4. This corresponds to the generally smaller coefficients of variation found in the VS parameter than in the V parameter, as shown in Table 1.

The marginal density of K in the K and V parameterization (Figure 1) appeared to be slightly more dispersed than did C in the C and V parameterization (Figure 3), although their respective coefficients of variation were not far apart, as shown in Table 1. Both marginal densities of KS and CS (Figures 2 and 4), were visibly less dispersed than were K and C, suggesting that incorporating the slope relationship of K and C to CCr was useful in this study. This is reinforced by the smaller coefficients of variation found with KS and CS compared to K and C, as shown in Table 1.

## Analysis of the Sparse Data Sets

The NPEM algorithm permitted the use of very sparse data sets of only 1 serum concentration data point per patient, permitting inclusion of such data, when present in clinical settings, when making population pharmacokinetic models. The standard two-stage method, in contrast, requires at least 1 data point for each parameter in the model, or at least two serum levels per patient for the population model evaluated here.

The results found with the two very sparse data sets were different from those found with the full 177 serum level data points. The results of the data set containing both high and low points were considerably closer to those found with the full data set than were those of the data set containing only trough levels. This is expected. What was not expected was that the NPEM algorithm would do as well as it did with the totally non-optimal "worst-case" data set of only the single lowest trough serum level from each patient.

The NPEM algorithm will also permit maximum information to be obtained from animal experiments where each animal must be sacrificed to obtain a single data point. Until now, the method of naive pooling (8) has had to be used, pooling all such data points into one large simulated animal. In contrast to such pooling, the NPEM algorithm, or the method of Mallet (12,13), permit proper population analysis of such data from multiple animals. An NPEM algorithm is under development for a 3 - compartment model, which should further facilitate such analyses.

## Comparison with the Standard Two - Stage Method

The population model made with the NPEM algorithm appeared similar to that made using the standard two-stage procedure. The frequency distribution of K and V made with the standard 2 - stage algorithm and shown in Figure 7 are similar to the marginal PDF's of K and V found with the NPEM algorithm, as shown in Figure 1. The scatterplot of the 2 - stage K and V in Figure 7 is similar to the joint PDF of K and V shown in Figure 1. This similarity is especially striking if one turns K and V around in the opposite direction, for example, using the transformations  $0.7 - K$  and  $80 - V$ , as shown in Figure 8. In that figure, both K and V were scaled and directionally oriented to highlight the similarity of K and V found with the 2 - stage procedure to the joint PDF of K and V found with the NPEM algorithm and shown in Figure 1.

In addition to the fact that the NPEM population algorithm is more efficient in extracting information from clinical data than the 2 - stage method, one does not have the problem of selecting the proper initial conditions from which to start the nonlinear least squares fitting procedure. Even when fitting only two parameters, the choice of initial conditions can make a significant difference in fitting a 1 - compartment model to serum level data. For example, of 31 patients examined in another study by two of us independently (RJ and PG), significantly different parameter values were found in 2 of the 31 patients. This was because we had started with slightly different, but surprisingly close, initial conditions in the fitting procedure. This highlights the problems of choosing proper initial conditions and having to verify the parameter

values found by showing that they are found repeatedly, starting from a wide variety of initial conditions, even in such a small, 2 parameter, model.

The great similarity found between the PDF of the NPEM algorithm and the scatterplot of the 2 - stage method also illustrates the utility of that traditional method. However, the NPEM algorithm not only is mathematically superior and can include sparse data sets which the 2 - stage method cannot handle, it is also easier to use. There is no repetitive labor. One can simply start the analysis by indicating the proper patient data files, direct the output to the printer using the DOS Control-Printscreen command, and come back later to see the finished results, which are ready well before they would have been using the standard 2 - stage method.

### Relationship to Other Population Modeling Algorithms

The NPEM algorithm is a population modeling algorithm along with that of NONMEM (9-11) and the method of Mallet (12,13). However the NPEM algorithm computes the entire joint PDF of the parameters, which the NONMEM one does not. In addition, the NONMEM algorithm of first-order approximation has been found to give results which have varied from known pharmacokinetic parameter values in a careful simulation study (26). Preliminary data (27) suggest that the NPEM program gives results generally similar to those found using the nonparametric maximum likelihood method and program of Mallet (12,13), which currently runs on larger machines.

The NPEM computer program runs on an IBM PC or compatible machine with a math coprocessor, 640 K of memory, and a CGA, EGA or VGA monitor. It accepts routine clinical data entered into patient files in the USC\*PACK PC clinical programs. Its output is shown as the joint PDF in a 3D plot. The marginal PDF's are also shown, as shown in Figures 1 through 6. The means, SD's, and correlation coefficient between parameters can be entered into the USC\*PACK PC clinical programs for use as population priors for Bayesian adaptive control of drug dosage regimens for use with patients similar to those in the population studied.

Most clinical pharmacokinetic software does not take into account the extra information provided by the correlation coefficient between parameters, simply assuming instead that  $r=0$ . However, the USC\*PACK PC clinical programs, to which the NPEM program relates, accept and utilize the correlation coefficient in their Bayesian fitting procedure, revising the population model according to the information contained in a particular patient's serum level data to make an individual pharmacokinetic model (the Bayesian posterior) for that particular patient.

The NPEM program using this algorithm has now been added to the USC\*PACK PC collection of research and clinical resources for use in both University and community hospital settings. It permits pharmacokinetically oriented personnel to make population models for their own patients in their own center, also incorporating data of the error pattern of their own center's laboratory assay of the serum concentrations of the drug (24).

One would prefer to have more than twenty patients when describing the population pharmacokinetic behavior of a drug. Nevertheless, patients with highly unstable renal function during therapy, who are acutely and severely ill, are a distinct subset of patients receiving gentamicin therapy (18-20). They are distinctly different from general medical patients (28), having a greater volume of distribution and a somewhat lower  $K_{slope}$ , and are quite different from young people with gangrenous or perforated appendicitis (29). It is because of these differences that the population PDF's are reported in these patients and compared with results obtained with earlier methods.

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TABLE 1. SUMMARY OF RESULTS

METHOD	LOG-LIK	V(mean, SD, CV)	K(mean, SD, CV)	r
NPEM	-338.388	26.190 ± 12.733 (53%)	.1824 ± .1149 (63%)	-.441
STS	-	23.566 ± 8.816 (41%)	.2203 ± .1367 (68%)	-.435
	LOG-LIK	VS(mean, SD, CV)	KS(mean, SD, CV)	r
NPEM	-267.749	.36795 ± .14004 (38%)	.00292 ± .001217 (47%) (KI fixed at 0.00693)	-.726
	LOG-LIK	V(mean, SD, CV)	C(mean, SD, CV)	r
NPEM	-339.572	25.471 ± 10.953 (47%)	3.8671 ± 2.2423 (57%)	-.752
	LOG-LIK	VS(mean, SD, CV)	CS(mean, SD, CV)	r
NPEM, all levels .454	-272.706	.37278 ± 14714 (39%)	.06519 ± .02312 (35%)	-
NPEM, 1 high or low	-27.025	.21927 ± .05288 (27%)	.08238 ± .02897 (35%)	-.375
NPEM, only 1 lowest	-21.745	.69465 ± .58356 (84%)	.09655 ± .05596 (58%) (CI fixed at 0.00255)	+.591

NPEM = nonparametric EM algorithm

STS = standard two-stage algorithm

## TABLE LEGEND

Table 1. Summary of results found with the NPEM algorithm, using various parameterizations and on various data sets, and those found with the standard two-stage algorithm. See text for discussion.

## FIGURE LEGENDS

Figure 1. 3D plot of the population joint PDF found using the K and V parameterization (middle), and 2D plots of the marginal PDF's of K and V (top and bottom respectively). Data from all 177 serum samples in the 20 patients.

Figure 2. 3D plot of the population joint PDF found using the KS and VS parameterization (middle), and 2D plots of the marginal PDF's of KS and VS (top and bottom respectively). Data from all 177 serum samples in the 20 patients.

Figure 3. 3D plot of the population joint PDF found using the C and V parameterization (middle), and 2D plots of the marginal PDF's of C and V (top and bottom respectively). Data from all 177 serum samples in the 20 patients.

Figure 4. 3D plot of the population joint PDF found using the CS and VS parameterization (middle), and 2D plots of the marginal PDF's of CS and VS (top and bottom respectively). Data from all 177 serum samples in the 20 patients.

Figure 5. 3D plot of the population joint PDF found using the CS and VS parameterization (middle), and 2D plots of the marginal PDF's of CS and VS (top and bottom respectively). Sparse data set of only 1 serum sample per patient, the highest (10 patients) or the lowest (10 patients), from each of the 20 patients.

Figure 6. 3D plot of the population joint PDF found using the CS and VS parameterization (middle), and 2D plots of the marginal PDF's of CS and VS (top and bottom respectively). Sparse data set of only 1 serum sample per patient, the lowest trough sample from each of the 20 patients.

Figure 7. Results found with the Standard two-stage algorithm. Data from all 177 serum samples in the 20 patients. Top: frequency distribution of K. Middle: Scatterplot of K and V. Bottom: Frequency distribution of V. Note similarity of the frequency distributions to the marginal PDF's of K and V shown in Figure 1, and the similarity of the scatterplot of K and V with the population joint PDF of K and V in Figure 1.

Figure 8. Transformation of results of the scatterplot in Figure 7 to more closely resemble the scale and direction of the population joint PDF shown in Figure 1, middle. The resemblance between the two is highlighted by the transformation.