

POPULATION PHARMACOKINETIC MODELS: PARAMETRIC AND NONPARAMETRIC APPROACHES

R Jelliffe¹, A Schumitzky¹, M Van Guilder¹, X Wang¹, and R. Leary²

¹Laboratory of Applied Pharmacokinetics, USC School of Medicine, 2250 Alcazar St, Los Angeles, CA 90033, USA, (323)442-1300, jelliffe@hsc.usc.edu

²the San Diego Supercomputer Center, 9500 Gilman Drive, La Jolla CA 92093

ABSTRACT

Population modeling seeks to evaluate the contributions of interindividual and intraindividual variability, based on the raw subject data and the assay error, and to describe the findings in terms that are useful both for research and for optimal patient care. With parametric models, the probability distributions of each PK/PD parameter are described in terms of other parameters such as means and covariances which define the assumed shape of these distributions. Commonly used distributions are the normal or lognormal ones. The parameter values found are the single best estimates such as mean, median, or mode, which are felt to be the best estimators of the central tendency for each such distribution.

Nonparametric models have a different flavor. No such parametric assumptions are made about the assumed shape of a parameter distribution, nor is a single parameter value what is really sought. The approach proceeds rather from the point of view that the very best population model possible would be the correct structural model, plus the entire collection of each subject's exactly known parameter values, if it were somehow possible to know them. Nonparametric methods estimate essentially one set of parameter values for each subject, along with an estimated probability for each such set. The richness of the method is in the ability to obtain not simply a single estimate for the central tendency and one for the dispersion, but rather to estimate the entire population parameter joint density.

Optimal population modeling currently begins by determining the assay error pattern explicitly over its working range. One then uses a parametric population modeling approach to separate intra- from inter-individual variability. Having this information, one can then use a nonparametric approach to obtain the entire estimated population parameter joint density.

INTRODUCTION

Pharmacokinetic and dynamic population models provide the means to store past experience with the behavior of drugs, and to apply it to the care of future patients. They are used as the Bayesian prior to design the initial regimen for the next patient who appears to belong to the population in question.

As one makes a population pharmacokinetic model (see below) it is useful to search for relationships between the various parameters in the model and useful clinical covariates or descriptors, so that the model can then be reparameterized in terms of these descriptors, and dosage can be adjusted to this important and often changing clinical information. This provides the logical structure for precise dosage adjustment to body weight and renal function, for example, in order to achieve desired target serum or peripheral compartment concentrations. Using this approach, one then computes the regimen to achieve the desired target goals.

PARAMETRIC POPULATION MODELS

With parametric models, the various pharmacokinetic parameters themselves are described in terms of other single point parameter estimates such as measures of central tendency – means, medians, or modes, for example, and measures of dispersion - standard deviations or covariances. A traditional search has been for the best single point estimator of each parameter. Examples of such parametric population modeling approaches are the standard two-stage approach [1], the iterative two-stage Bayesian approach [2], the parametric EM method [3], nonlinear mixed effect modeling [4], and other variations on this approach [5,6]. Other population modeling approaches are the semi-nonparametric approach of Davidian and Gallant [7] and the hierarchical Bayesian approach of Wakefield and colleagues [8].

THE SEPARATION PRINCIPLE

The separation or heuristic certainty equivalence principle [9] describes control of a system when it is separated first, into obtaining single point parameter estimates for the model, and second, of using those single

point estimates to control the system. For most pharmacokinetic applications, controllers using this approach are suboptimal. This is a significant problem with current maximum a posteriori probability (MAP) Bayesian fitting and dosage design. The way around this problem is by incorporating improved approaches to dosage design which make use of the entire nonparametric population joint parameter density.

MORE ON PARAMETRIC POPULATION MODELS

In parametric population modeling, the probability distribution of the parameters is itself described by these other single-valued parameters such as means and covariances, for example. These other parameters impart an assumed shape to each pharmacokinetic parameter distribution, usually a Gaussian or lognormal distribution. In contrast, for nonparametric models, as we will see below, these parametric assumptions are relaxed. No assumptions at all are made about the shape of their probability distribution, except that it is the same for all subjects. This is what is meant by the terms parametric and nonparametric in this context.

An example of the parametric approach to population modeling is that of the iterative two-stage Bayesian (IT2B) method. One begins this approach by stating estimates of the initial means and standard deviations of the pharmacokinetic parameters. Based on these assumptions, the individual patient data are then examined, and each patient's MAP Bayesian posterior pharmacokinetic parameter values are determined as described above. This ends the first stage.

In the second stage, the population means and covariances are obtained from these individual subject parameter values [3]. These new population parameter means and standard deviations (SD's) are then used as the initial Bayesian priors, thus beginning a new iteration. Using these new priors, the MAP Bayesian posteriors are again found. Their population means and SD's are obtained. Again, these means and SD's are used as the Bayesian prior in still another iteration, and the MAP Bayesian posteriors are again found. This process continues iteratively until a convergence criterion is finally reached.

STRENGTHS OF PARAMETRIC MODELS

Parametric population modeling methods can separate variability between the various subjects from variability within the individual subjects. This is their main strength - the ability to separate inter- from intra-individual subject variability. If the inter-individual variability is large, there is significant diversity in the population with respect to the parameter values. If the intra-individual variability is large, it suggests that the patients were unstable or that significant noise and uncertainty existed in their therapeutic environment.

DETERMINE THE ASSAY ERROR EXPLICITLY

Frequently, assumptions are made about the shape of the assay error pattern, but relatively little attention is paid specifically to determining the magnitude of the true laboratory assay error pattern itself, over its entire working range. It is frequently assumed that the assay error is only a small part of all the other environmental errors and uncertainties. These other errors are due, for example, to errors in the amounts of the doses given, errors in recording when they were given, errors in recording when the serum samples were obtained, errors due to misspecification of the structural model, and errors due to changes in the pharmacokinetic parameter values during the study period.

However, it is not difficult at all to determine the assay error pattern specifically, over its entire working range, by measuring representative samples in replicate. For example, the blank sample always has a certain error. The assay may become somewhat more precise at low to middle concentrations, and then usually less so at higher concentrations. The form of the relationship between the measured concentration and the assay SD is nonlinear, and a polynomial has been a useful way to capture the nonlinearity in this relationship [10]. Use of such a polynomial to describe the assay SD permits each serum concentration data point be fitted by its Fisher information, the reciprocal of its variance.

START WITH A PARAMETRIC POPULATION MODEL

Once the assay error pattern and its polynomial has been carefully determined over the entire working range of the assay, a parametric population modeling method such as IT2B can be used. The remaining intra-individual variability can be described as a scaling factor with respect to the assay error. One can then determine what fraction of the total overall intra-individual variability is due to the assay error itself. This is very useful information. In the USC*PACK IT2B population modeling program, this factor of intra-individual variability is

called gamma. If gamma is 1.0, then there is no other source of error than the assay error itself. Usually gamma is larger, and ranges from about 2 to 4, showing that the assay error often ranges from about 1/2 to 1/4 of the overall intra-individual variability, a significant fraction.

A significant limitation is that most parametric population modeling methods in current use do not have the desirable property of statistical consistency. Consistency means that as the number of subjects becomes arbitrarily large, the population parameter estimates approach the true population parameter values [11]. Furthermore, parametric population models are often used only to provide a single value for each population parameter when developing dosage regimens for patients. Because of the separation principle, such regimens are usually suboptimal.

NONPARAMETRIC POPULATION MODELS

The nonparametric approach to population modeling was first introduced independently by Lindsay [12] and by Mallet [13]. They showed that the most likely parameter estimates are actually found to be in a discrete, not continuous, collection of sets of individual parameter values, each of which has a single value for each parameter, along with an estimate of the probability of that particular set of values. There is usually about one significant support point (set of parameter values) for each subject studied in the population. This approach makes no parametric assumptions (such as normality or unimodality) about the actual shape of the population parameter distribution. The shape of the distribution is determined solely by the population raw data itself. Means and covariances can easily be obtained. Nonparametric methods such as the nonparametric maximum likelihood (NPML) method of Mallet [13] and the nonparametric expectation-maximization (NPEM) method of Schumitzky [14,15] can discover, without additional help from covariates, unsuspected clusters or subpopulations such as fast and slow metabolizers of a drug. The nonparametric discrete collections of parameter values and their estimated probabilities reflects the fact that the ideal theoretical population model would simply be the entire collection of each subject's exactly known parameter values, if one could somehow know them.

In an examination of the capability of the nonparametric method, Figure 1 shows a carefully defined simulated population in which there was only one distribution for the volume of distribution (V) but two for the elimination rate constant (K), such as occurs for fast and slow metabolizers of a drug [15]. There was no correlation between the two parameters.

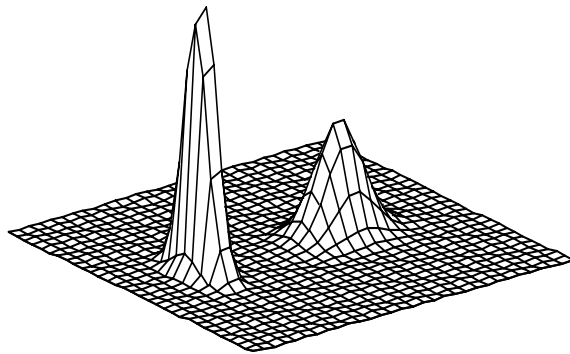


Figure 1. True population joint density of V and K. If the bottom corner is "home plate", then the axis toward third base is that of V, and the axis toward first base is that of K. Note that there are two subpopulations with respect to K, but only one for V. The vertical axis is the probability of a parameter pair v,k.

From this overall population, twenty subjects first were drawn at random. They constituted the sample population under study. Figure 2 shows the actual true distribution of these 20 subject parameter values. The task of any population analysis now is to discover this distribution optimally.

Figure 3 now shows the above true sample parameter distributions as estimated by the NPEM program. The NPML approach of Mallet is entirely similar. Two distinct and fairly tight groups of parameter values are seen. In contrast, Figure 4 shows these same true subject parameter distributions as estimated by a parametric population modeling method. A totally different, and erroneous, understanding of what is going on in the population is obtained by the parametric method. Where the mean value for the elimination rate constant actually exists, there are actually no subjects at all, as shown in Figures 1-3. The two groups of subjects were well

detected by the NPEM method, but were not detected at all by the parametric method. In addition, the nonparametric methods have the desirable property of mathematical consistency [11].

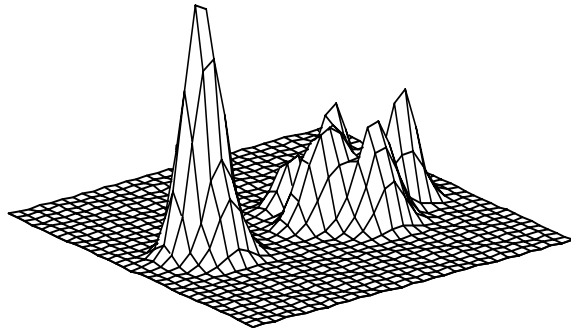


Figure 2. Graph, somewhat smoothed as in Figure 1, of the actual parameter values in the 20 sampled subjects. Axes as in Figure 1.

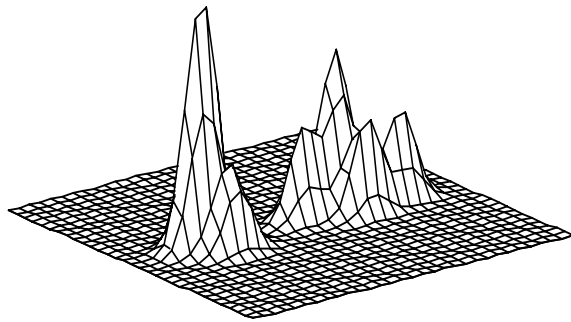


Figure 3. Estimated joint density obtained with NPEM. Axes as in Figure 1.

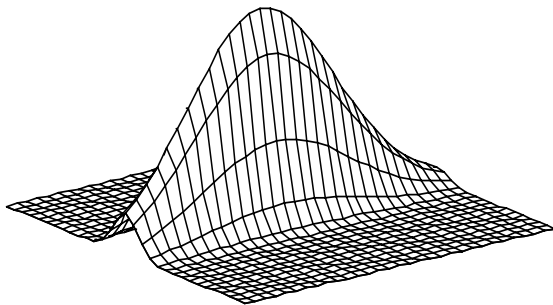


Figure 4. Estimated joint density obtained by an optimal parametric method. Axes as in Figure 1.

The nonparametric methods specifically obtain the single most likely distribution of parameter values for the population studied. This distribution is a multivalued distribution, and has a number of support points, or individual models, approximately equal to the number of subjects studied. The nonparametric approaches are superior to parametric methods in this respect, as they obtain the most likely representation of the entire population parameter distribution, while those based on parametric assumptions do not [13-15]. However, the nonparametric methods also have drawbacks. They cannot separate inter- from intra-individual sources of

variability. Further, they do not have confidence limits for the discrete distributions they obtain. Bootstrap methods are under consideration for developing such confidence limits.

CONCLUSION: USE BOTH METHODS SEQUENTIALLY

It currently seems that the best approach to population modeling is to make use of both methods to take advantage of each of their individual strengths. First, it seems best to determine the specific assay error pattern and polynomial well, by itself, before beginning any analysis. If a multicenter study is being done, where different assays are being used in different settings, then each center should and can have its own assay error polynomial so that the subject data from each center can be analyzed correctly, each according to its own credibility. Next, gamma can be computed, using a parametric method such as the IT2B. In this way, one has obtained good knowledge of the intra-individual variability and of the assay error variability itself. Confidence limits on the parametric parameter distributions can also be obtained.

This information can then be used by the nonparametric approaches to obtain the entire, and most likely, discrete joint population parameter density. Software for IT2B and NP\EM population modeling approaches is available from our laboratory on PC's for 3 compartment linear models, and can also access the Cray T3E at the San Diego Supercomputer Center for larger and nonlinear models.

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