NONLINEAR PARAMETRIC AND NONPARAMETRIC POPULATION PHARMACOKINETIC MODELING ON A SUPERCOMPUTER.

Roger Jelliffe¹, Michael Van Guilder¹, Robert Leary², Alan Schumitzky¹, Xin Wang¹, and Alexander Vinks³.

¹ - Laboratory of Applied Pharmacokinetics, University of Southern California School of Medicine, 2250 Alcazar St (CSC-134-B) Los Angeles CA 90033. ² - San Diego Supercomputer Center, San Diego CA. ³ - The Hague Hospitals Central Pharmacy, The Hague, The Netherlands.

Email  jelliffe@hsc.usc.edu

Laboratory of Applied Pharmacokinetics
University of Southern California School of Medicine

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ABSTRACT

We extended our nonparametric EM (NPEM) PC software to include nonlinear systems, incorporating a differential equation (DE) solver and parallelization. The user either draws the model with the BOXES program or enters the DE's on the PC, and runs another PC program to enter instructions for the SDSC Cray T3E, and to specify subject data files.

The user then uses SSH to access the Cray, gets the files from his local FTP node, compiles the DE source code, and runs the program. Speedup is 24-fold for 32 nodes. Using 8 nodes, a 5-parameter Michaelis-Menten NPEM model of pipericillin, using 80,000 grid points, took 1/2 hr. The user FTP's the result files to his PC and examines them with local software and plots.

INTRODUCTION AND OVERVIEW

Pharmacokinetic population analysis is used to quantify the intersubject variability in pharmacokinetic studies. It is a necessary tool in model and noise parameters. The parameters are random variables with a common but unknown population distribution. Population analysis is the estimation of this population distribution based on the population data.

There are basically two approaches: parametric and nonparametric. In the parametric approach, the shape of the population distribution is assumed to be known except for the unknown population parameter values (e.g., normal with unknown means and covariances). The NONMEM system of Beal and Sheiner (1) is an example.

In the nonparametric approach, no such parametric assumptions about the form of the population parameter distributions are made. The entire distribution is estimated from the population data. It allows for non-normal and multimodal distributions such as occur, for example, in a population of fast and slow acetylators. This approach was developed by Mallet (3). A variation based on the nonparametric EM (NPEM) algorithm was developed by Schumitzky (4). Both approaches use two methods for the optimal estimates and their variability: maximum likelihood and Bayesian. The
Here we describe a Monte Carlo simulation study of the NPEM algorithm. We consider a one compartment model with bolus input applied to a population of 20 simulated subjects. The model for the $i^{th}$ subject is given by:

$$y_i = \left[ 20 \exp(-K_i t_j)/V_i \right] (1 + e_j);$$

$j=1,\ldots,M$, where
- $K_i$ = elimination rate constant
- $V_i$ = volume of distribution
- $M$ = # of measurements per subject
- $t_j$ = time of the $j^{th}$ measurement,
- $e_j$ = noise for $j^{th}$ measurement.

It is assumed that the $\{e_j\}$ are independent and $e_j \sim N(0, 0.04)$ where the notation $x \sim N(\mu, \sigma)$ means that the density of $x$ is normal with mean $= \mu$ and standard deviation $= \sigma$. In the Monte Carlo simulation, the random vectors $(K_i,V_i)$ are independent and identically distributed as a mixture of two normals so $K_i$ and $V_i$ are independent and $V_i \sim N(2.0, 0.2)$, and $K_i \sim 0.5 N(0.5, 0.05) + 0.5 * N(1.5, 0.15)$.

The true probability density of $(K, V)$ is graphed in Figure 1. Note that in Figures 1-5, the "x-axis" corresponds to $K$; the "y-axis" corresponds to $V$.

Figure 2, in which most of the mass is situated where in the true density there is no mass at all.

Fig. 2. Normal density of a random vector with same mean and covariance as $(K, V)$.

Two cases are considered: 5 and 2 levels per subject. Figure 3 shows the smoothed estimated density for the 5 levels case.

Figure 4 shows the smoothed estimated density $(K, V)$ for the 2 levels case. There is not much deterioration from the loss of measurements. The densities are actually discrete.
Fig. 4. Smooth estimated discrete density of \((K, V)\), 2 levels / subject

Figure 5 shows the similarly smoothed "empirical density" supported uniformly on the 20 actual points \((K_i, V_i)\) used in the Monte Carlo simulation. It resembles Figures 3 and 4.

Fig. 5. Smooth empirical discrete density of \((K, V)\), 20 subjects

Thus the NPEM algorithm can discover previously unsuspected subpopulations of patients, while parametric methods cannot, without further help and further information.

The "Big NPEM" now implemented on the SDSC Cray T3E has the following procedure for performing the analysis.

**STEP 1.** Run BOXES on the PC. Output=PROG.FOR, a Fortran file containing source code defining the model, or type in the Fortran source code. The structural model is shown in Figure 6 below.

STEP 1. Run BOXES on the PC. Output=PROG.FOR, a Fortran file containing source code defining the model, or type in the Fortran source code. The structural model is shown in Figure 6 below.

![The Michaelis-Menten model of pipericillin](image)

**STEP 2.** Run M2_20 on the PC, in DOS.

**Input:** Choose Option 1: Prepare files for ‘BIG NPEM’
-PROG.FOR (Output from BOXES)
-Then one enters
  -Names and number of patient data files
  -Boundaries for random parameters
  -Assay Error Coefficients
  -Active or salt fraction
  -Number of grid points (from 2129 to about 20 million)
  -Max. number of cycles; stopping tolerance
STEP 3. Connect to SDSC Cray T3E, with Windows and SSH. Login to golden.sdsc.edu. Upload mod01.f and fi101.inp (ascii mode).

Execute comp.sh (compiles mod01.f, links it to BIG NPEM executable program.

Execute ‘BIG NPEM’: and state the no. of parallel cpu’s.

In background, may logout and login later; use qcat command to monitor progress.

In foreground--watch output. Download output files from run by FTP to the PC. Logout at end of run.

STEP 4. Run M2_20 on the PC
Input:-Choose Option 2: Examine files from’BIG NPEM’

-Enter names of output and density files, OUT0122, DEN0122, for example
-Select any or all of the 7 options to examine and plot results.

RESULTS

A partial display of the output for a Michaelis-Menten model of pipericillin, with IV input and both a central and a peripheral compartment is given below.

CYCLE NO. 4
THE TRUE (NUMERICAL) LOG-LIKELIHOOD (USING THE NUMBER THEORETIC INTEGRATION SCHEME) OF THE 8 SUBJECT VECTORS,
GIVEN THE PRIOR DENSITY, IS:

THE CORRESPONDING FIGURE FOR CYCLE 1 WAS 80014. SINCE IT IS NOW .62775, THIS ANALYSIS HAS GONE 80013. DIVIDED BY 80014. OR 99.99922 % OF THE WAY FROM THE APRIORI DENSITY TO THE MAXIMUM LIKELIHOOD ESTIMATE OF THE JOINT DENSITY.

THE NO. OF ACTIVE GRID POINTS IS NOW 29

THE FOLLOWING VALUES ARE FOR THE UPDATED DENSITY:

THE SCALED INFO FOR THIS CYCLE IS 98.91 %
THE ENTROPY FOR THIS CYCLE IS 2.1796

THE MEANS ARE:
VM MM 1-    KM MM 1-    V1 2195.214891    85.541580    13.224692
K12    K21 0.802670    0.57

THE STANDARD DEVIATIONS ARE, RESPECTIVELY:
VM MM 1-    KM MM 1-    V1 818.093945    60.553616    3.840690
K12    K21 0.627348    0.44

THE PERCENT COEFFICIENTS OF VARIATION ARE, ::
VM MM 1-    KM MM 1-    V1 37.267146    70.788518    29.041810
K12    K21 0.627348    0.44
Further graphics illustrate the correlation relationships between parameter pairs, as shown below. These graphics can be compared with the correlation coefficient matrix (not shown here, to save space).

The strong correlation between $V_m$ and $K_m$ is shown in Figure 12.
The relationship between $K_{12}$ and $K_{21}$ is shown below.

The scattergram of concentrations, this time estimated from the joint Bayesian posterior parameter medians is shown below.
The combination of these two methods for making large and nonlinear population PK/PD models is a strong one. The IT2B approach permits separation of variability associated with the assay error from that associated with the subject intraindividual variability. Parameter ranges are also easily estimated.

The above information is then usefully incorporated into the NPEM approach. The strength of the nonparametric approach is then that it leads directly to the new "multiple model" (MM) design of dosage regimens which are specifically designed to achieve desired target goals with maximal precision (minimal weighted squared error of the diverse predicted serum concentrations, approximately one per population subject) when the population model is used as the Bayesian prior for designing the initial dosage regimen (6).

Because of this, nonparametric population models and MM dosage regimens are useful for developing the optimal standard dosage regimen, especially when it must be used without feedback from measured serum concentrations. Whether one is searching for a standard dose for a population of subjects, as in cancer chemotherapy or therapy for AIDS, or whether one must treat a herd of cattle or flock of chickens, for example, the combination of a nonparametric population model and MM dosage design assures maximally precise achievement of desired target goals, whether they be serum concentrations or quantifiable effects.

The above IT2B and NPEM software has now become a research resource for such modeling of systems. The grid points have been increased from 80,000 on the PC to about 20 million to permit the larger models.

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REFERENCES


