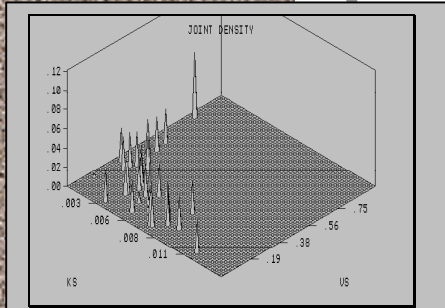
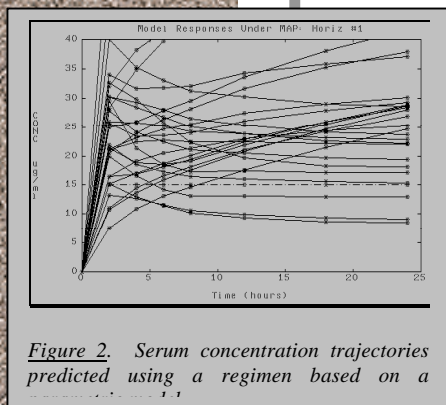


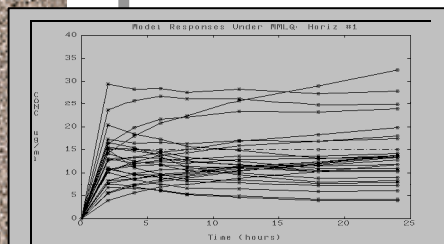
# MATHEMATICAL OPTIMIZATION OF DRUG THERAPY



*Figure 1. Population joint density of the drug Vancomycin. KS and VS are model parameters.*



*Figure 2. Serum concentration trajectories predicted using a regimen based on a*



*Figure 3 Serum concentration trajectories predicted using the MM regimen based on the NPEM model.*

**P**opulation drug models store experience with drug therapy, to optimize dosage for the next patient. In the past, parametric methods obtained single values for the central tendency and dispersion of a distribution of drug parameter values, which were assumed to have a Gaussian shape. However, in most populations, parameter distributions are not Gaussian. Subpopulations (fast or slow metabolizers) may also be present.

A nonparametric EM (NPEM) population modeling method has been developed by CAMS faculty (Schumitzky) in collaboration with Dr. Roger Jelliffe and colleagues in the Laboratory of Applied Pharmacokinetics (LAPK) at the USC School of Medicine. No assumptions about the shape of the parameter distributions are made. Using this method as a PC program for linear drug models, one obtains multiple discrete spikes, the location and height of which reflect the collection of estimated individual parameter values in the population, and their probability, as shown in Figure 1 for the drug Vancomycin.

The NPEM software also runs on large parallel supercomputers, in collaboration with the LAPK and the San Diego Supercomputer Center. It is available over the internet as a research resource for larger and nonlinear drug models.

Especially important, the multiple spikes in the NPEM model provide an improved Bayesian prior for the new "multiple model" (MM) design of dosage regimens, to achieve selected target therapeutic goals (serum concentrations, etc.) with optimal precision (least predicted weighted squared error).

Figure 2 shows great diversity in predicted serum drug concentrations when a conventional regimen based on mean population parameter values is given to the support points of the population model, as shown in Figure 1.

In contrast, Figure 3 shows the much smaller diversity in predicted serum concentrations when the MM regimen is given.

MM regimens based on NPEM models obtain greater precision in drug therapy than conventional regimens using parametric models. A user - friendly clinical version of the MM program is now in development, in collaboration with Dr. Jelliffe and colleagues at the LAPK.