

# Nonlinear Parametric and Nonparametric Population Pharmacokinetic Modeling on a Supercomputer

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## Why Make Population Models?

- To describe and understand  
Drug PK/PD Behavior
- To use as Bayesian Prior for designing  
Goal-Oriented, Model-Based,  
individualized dosage regimens for patients

# Goal-Oriented, Model-Based Individualized Drug Dosage Regimens: the Structure

- Use Population Model as Bayesian Prior.
- Set specific target(s): Serum conc goal(s) at desired time(s), for example.
- Compute the regimen to achieve the goal(s).
- But: just how precisely will the regimen achieve the goal(s)? A good question!
- Even with feedback from serum levels, etc.

## Parametric Population PK/PD Models

- Assume shape (normal, etc,) of param distribs.
- Get Population Parameter Means, SD's, covariances, ranges.
- Separate “inter” from “intra” - individual from assay Variability
- But, only one value for each parameter, so
- Cannot evaluate expected therapeutic precision
- Can get confidence limits, do signif. tests.
- Not consistent.

## Inter-Individual Variability

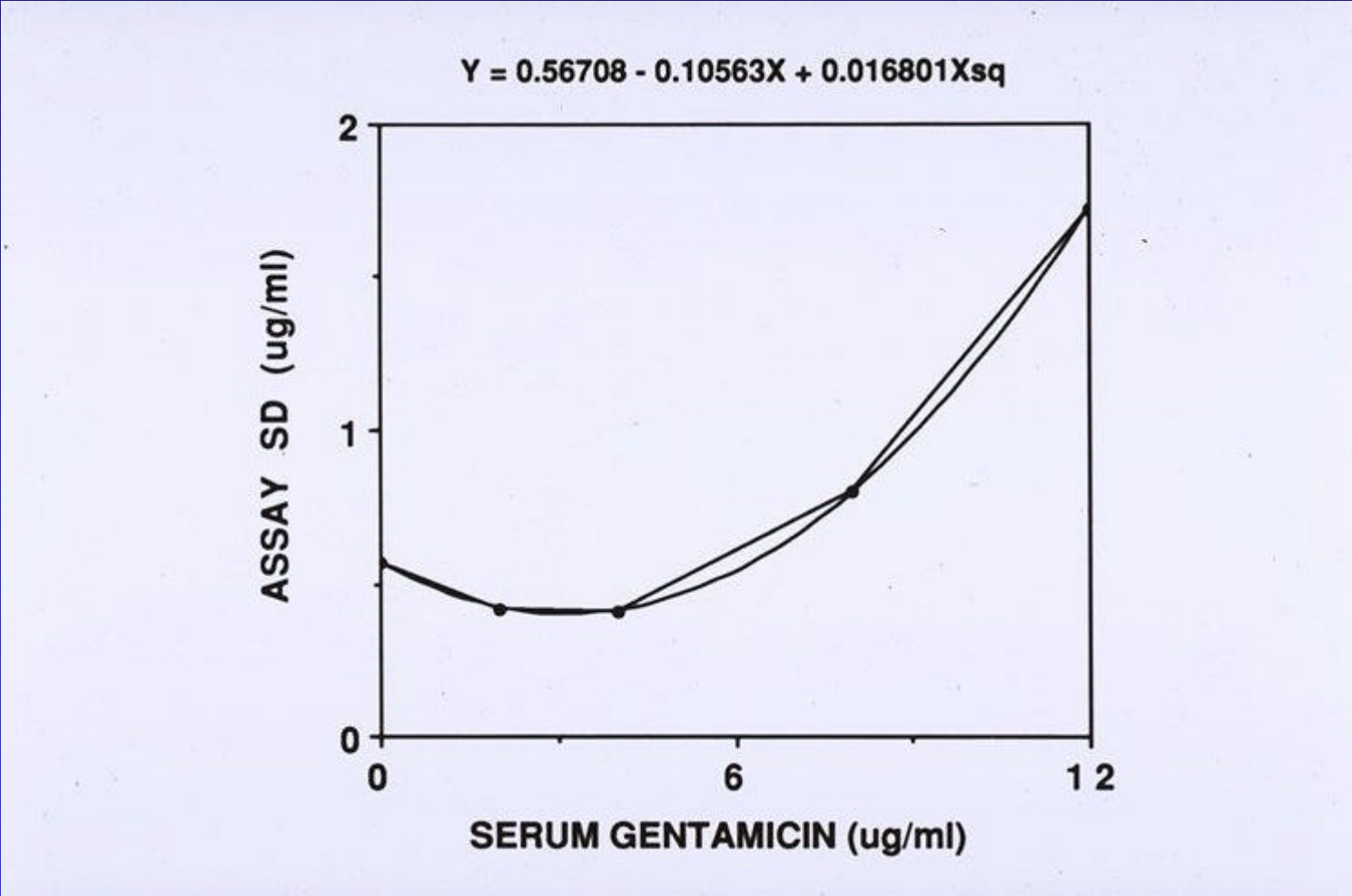
- A single number (SD, CV%) in parametric population models
- But there may be sub-populations
- eg, fast, slow, and medium acetylators
- How describe all this with one number?
- A good question!

## Intra-Individual Variability

- Assay error pattern
- Errors in Recording Sampling Times
- Errors in Dosage Prep and Admin
- Changing parameter values with time
- Structural Model Mis-specification
- However, all this is a mixture of
  - Measurement Noise, and
  - Process Noise (Noise in the DE's)

## Determine the Assay Variability

- As first suggested by Tom Gilman,
- Measure blank, low, medium, high, and very high samples at least in quadruplicate.
- Get mean + SD for each quadruplicate sample
- $SD = A_0C^0 + A_1C^1 + A_2C^2 + A_3C^3$
- Then can weight each measurement by the reciprocal of its variance (Fisher Info)
- No lower detectable limit!



## More on Intra - Individual Variability

- $\text{Var} = \text{Gamma} \times \text{assay SD}$
- or,  $\text{Var} = (A_0C^0 + A_1C^1 + A_2C^2 + A_3C^3)$
- Thus, Var can be a single number
  - Just by itself, as often, where get  $A_0$ , (all other A's set to zero)
  - Or, scaling the assay error polynomial
  - Or, an entire polynomial.
- A possible relative index of quality of care.

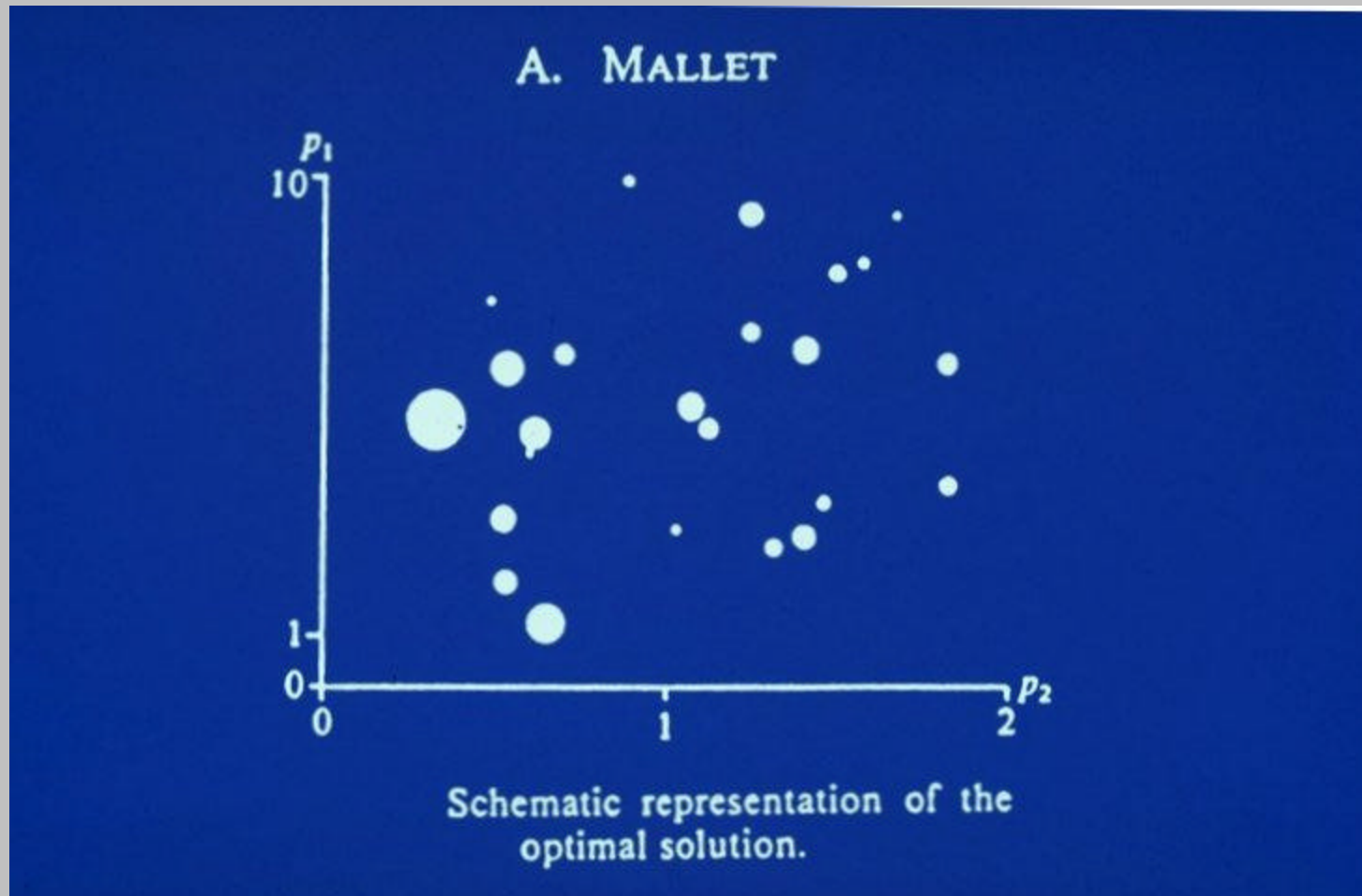
# Nonparametric Population Models

- Get not only means, SD's, etc, but also the entire distribution, a Discrete Joint Density.
- Can evaluate expected therapeutic precision.
- Can discover unsuspected subpopulations.
- Behavior is consistent.
- Use Var +/-or assay SD, stated ranges.
- No confidence limits or tests of signif yet.
  - Bootstrap, etc. in future.

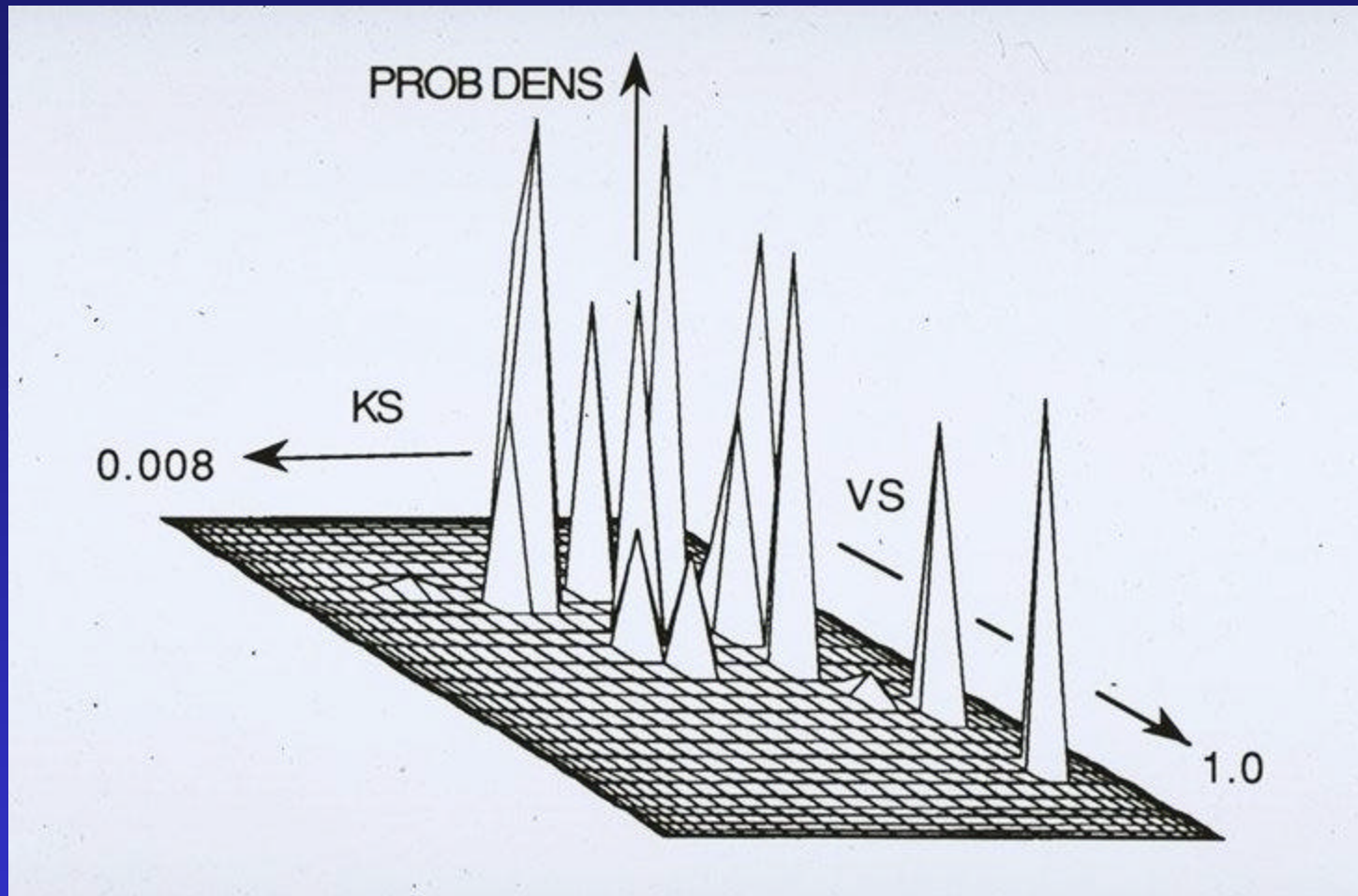


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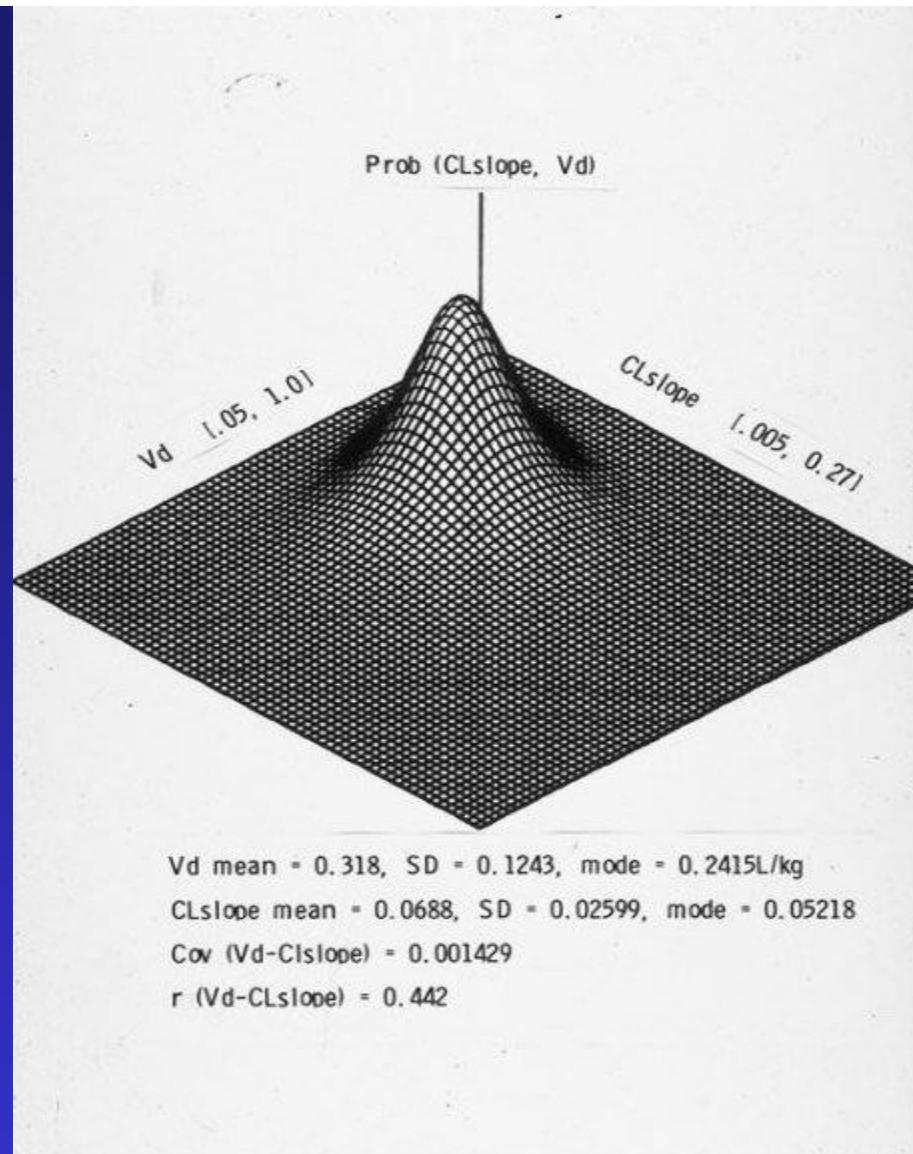
A Population Model, as made by Breugel!



An NPMML Population Joint Density,  
as made by Mallet



## An NPEM Pop Model by Schumitzky



## A Parametric Population joint density

# How to do Pop Modeling best?

## Use Both Methods

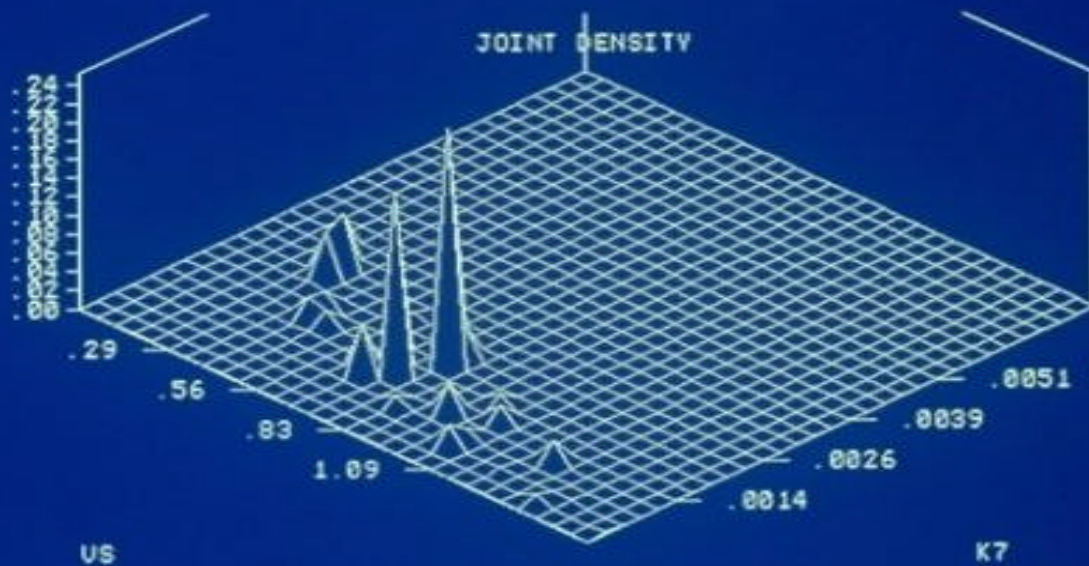
- Parametric: First, get assay errors, gamma, ranges, for assay and intraindividual variability.
- Nonparametric: Then, get the full discrete joint density
  - Find the best dose to achieve target goals.
  - Use Multiple Model Dosage design

## “Multiple Model” Dosage Design

- Start with multiple models in pop model
- e.g., each pop subject's indiv PK model.
- Give a regimen to each subject's model,
- Predict each subject's future levels,
- Compare each with chosen goal, get MSE.
- A better tool: use an NPEM joint density.
- Compute regimen having least weighted squared error in target goal achievement.

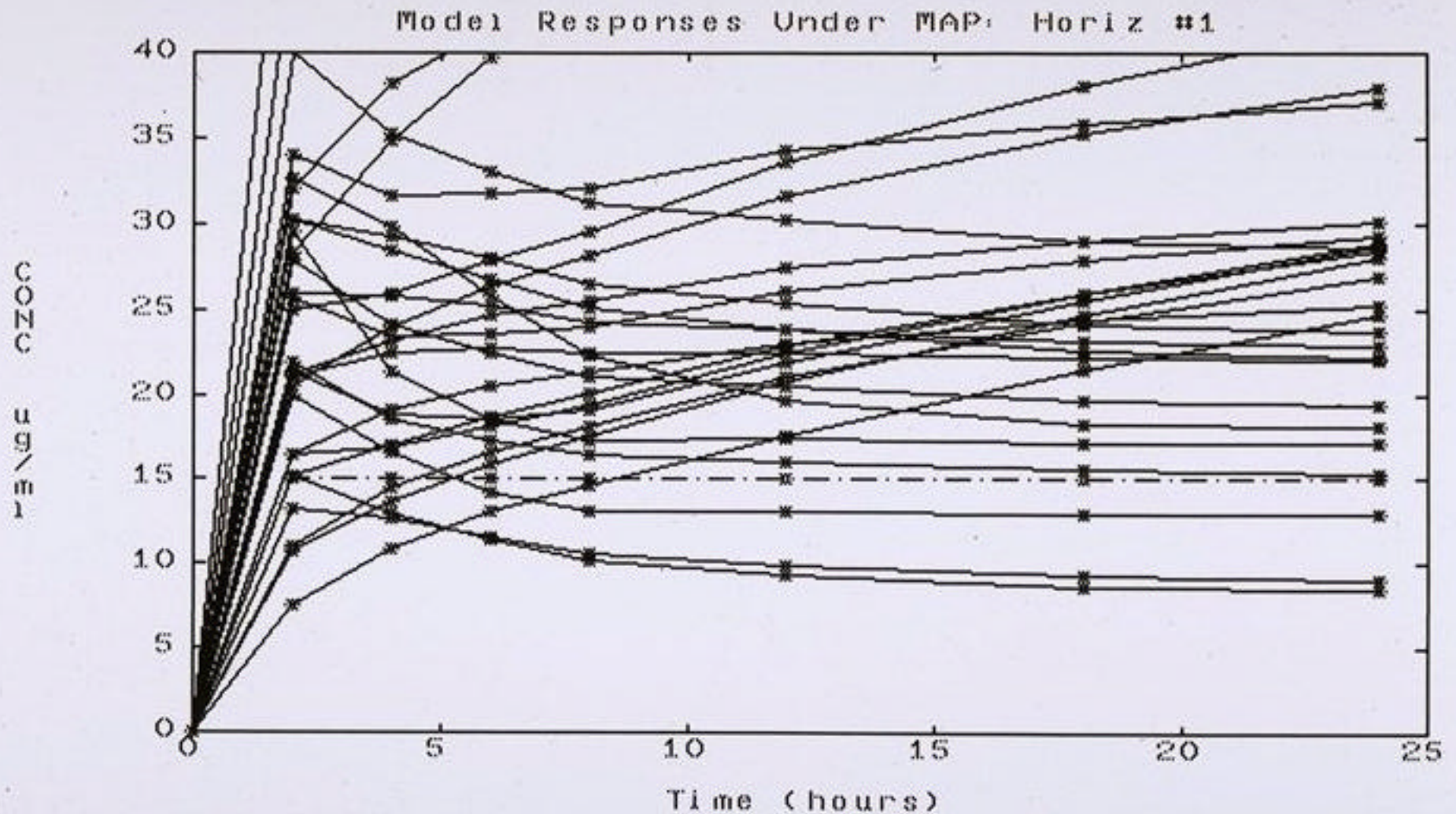
**User Manual  
for  
The Non-Parametric EM Program for  
Population Pharmacokinetic Modeling  
Version 3.0, August 26, 1995.**

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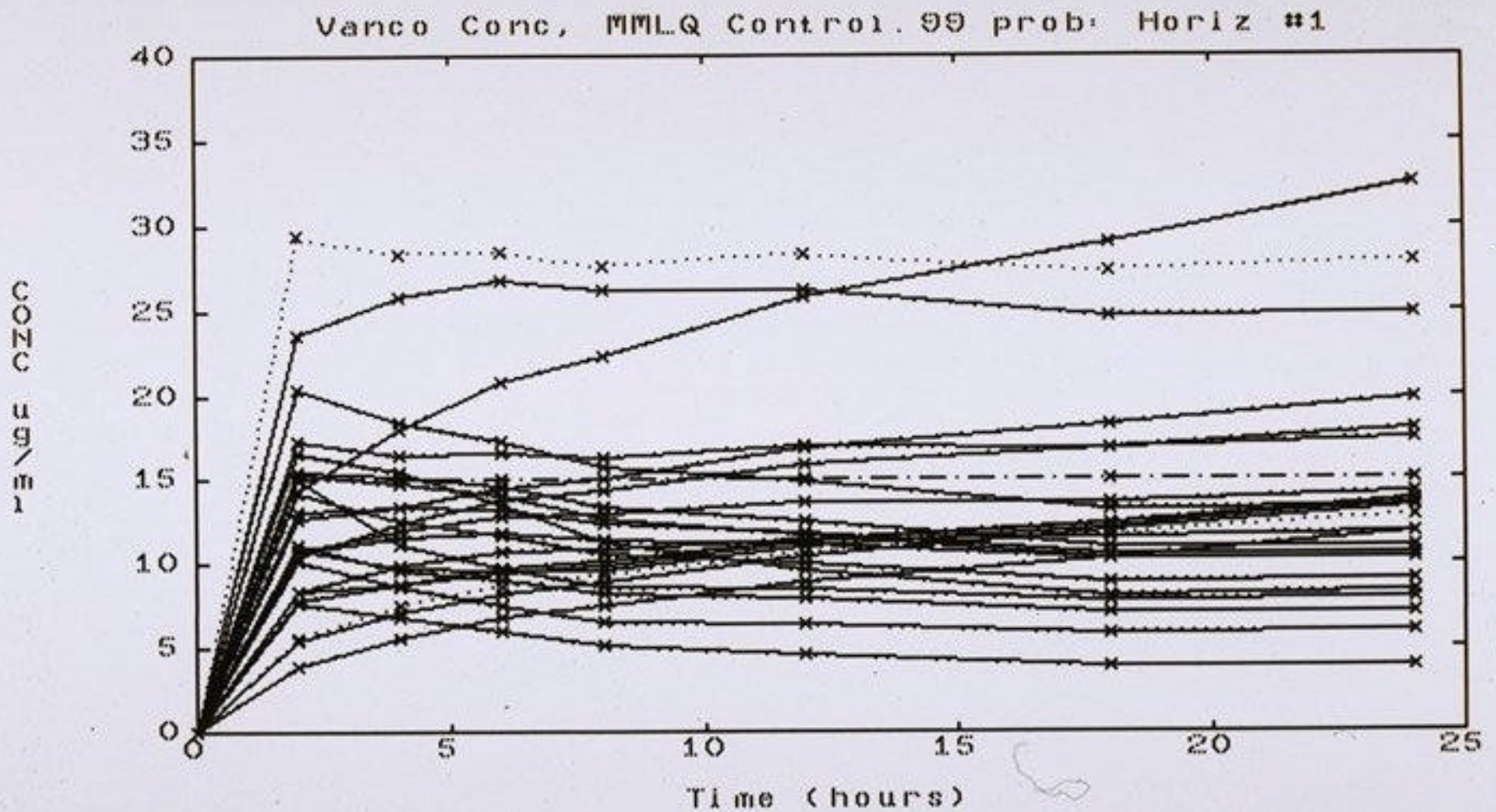


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Supported by NIH Grant LM 05401  
and by the Stella Slutzky Kunin Memorial Research Fund



Continuous IV Vanco. Predictions when regimen based on means is given to all subjects



Continuous IV MM Vanco regimen, Day 1.

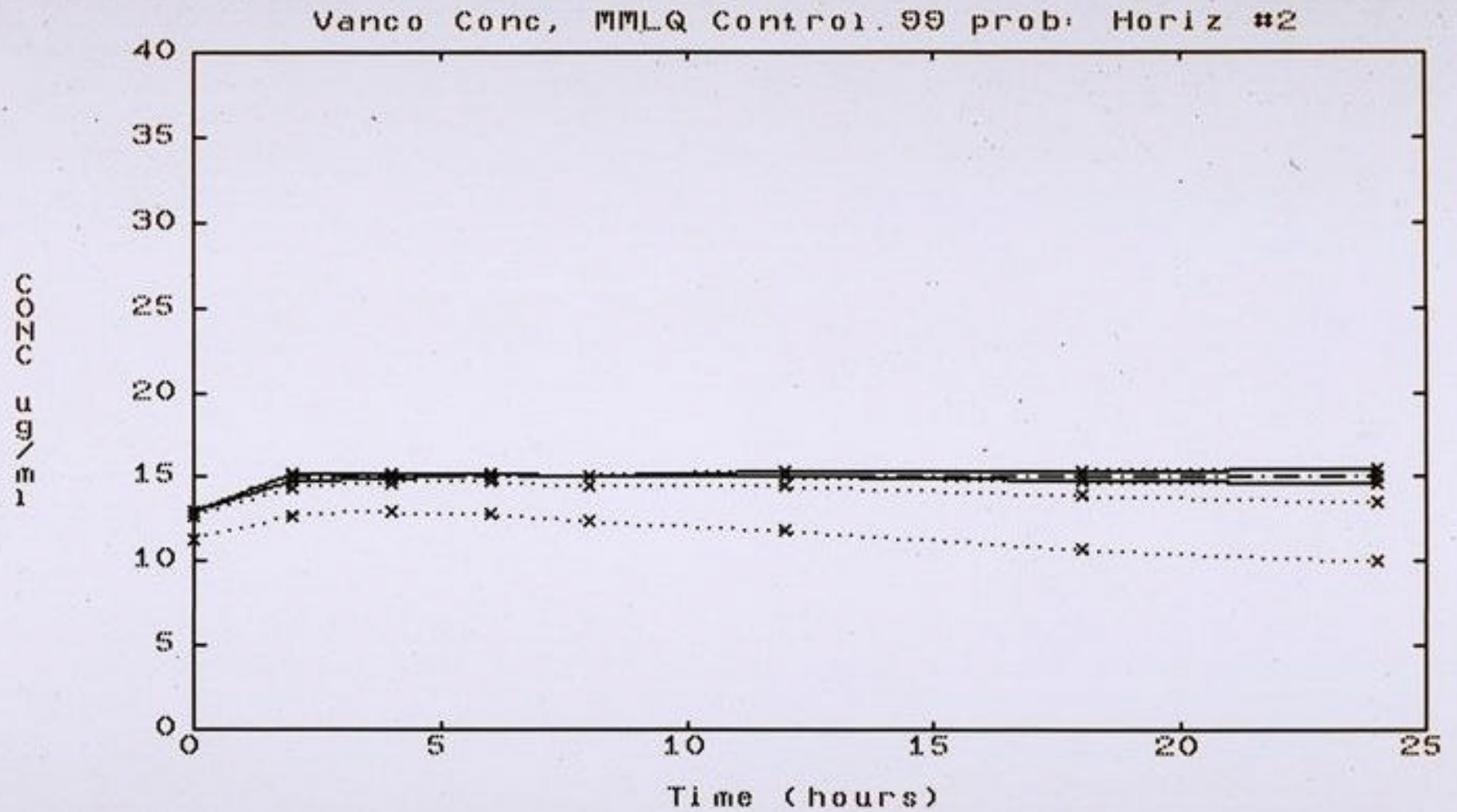
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95% and 99% most likely predictions.

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## Getting Nonparametric Bayesian Posteriors with Serum Level Feedback

- Start with Population discrete joint density
- Use the patient's measured serum levels
- Recompute probability of each pop model, given the patient's measured levels.



Continuous IV Vanco, Day 2. 95% and 99%

# Larger + Nonlinear IT2B and NPEM Models

- Linear or Nonlinear Structural Models
- Serum Levels +/- Effects
- Available over the Internet
- Prepare Model + data on PC
- SSH to SDSC Cray T3E, FTP data.
- Do the analysis, get results and density.
- FTP back to PC, see them there

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(Supported in part by LM05419 and RR11526)

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