Multiple Model Dosage Design: Achieving Target Goals with Maximum Precision

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The Separation Principle

- Whenever you separate the process of controlling the behavior of a system into
- First, getting the best single point parameter estimates, and then…
- Second, using those point values to control the system to achieve target goals,
- The control is usually done **suboptimally**.
- No performance criterion is optimized.

The Way around the Separation Principle

- Use a multiple model discrete prior.
- Give a candidate regimen to each model.
- Predict results with each model.
- Compute weighted squared error of failure to hit target goal at target time.
- Find the regimen having the minimal weighted squared error. This is multiple model (MM) dosage design - the real reason for using nonparametric population models.

A Population Model, as made by Breugel

A Lidocaine MM Pop Model: $3^4 = 81$ Models

K_{10}	p_{10}	K_{12}	p_{12}	K_{21}	p_{21}	V	p_V
.018	.3085	.033	.4013	.019	.4013	13.72	.4013
.0225	.383	.066	.44	.038	.44	27.44	.44
.027	.3085	.132	.1587	.076	.1587	54.88	.1587

Here, the probabilities are listed next to each parameter value. The means and coefficients of variation CV can be computed for each of the parameters as follows,

	K_{10}	K_{12}	K_{21}	V
Mean	.0225	.0632	.0364	26.289
CV	15.7%	52.3%	52.3%	52.3%

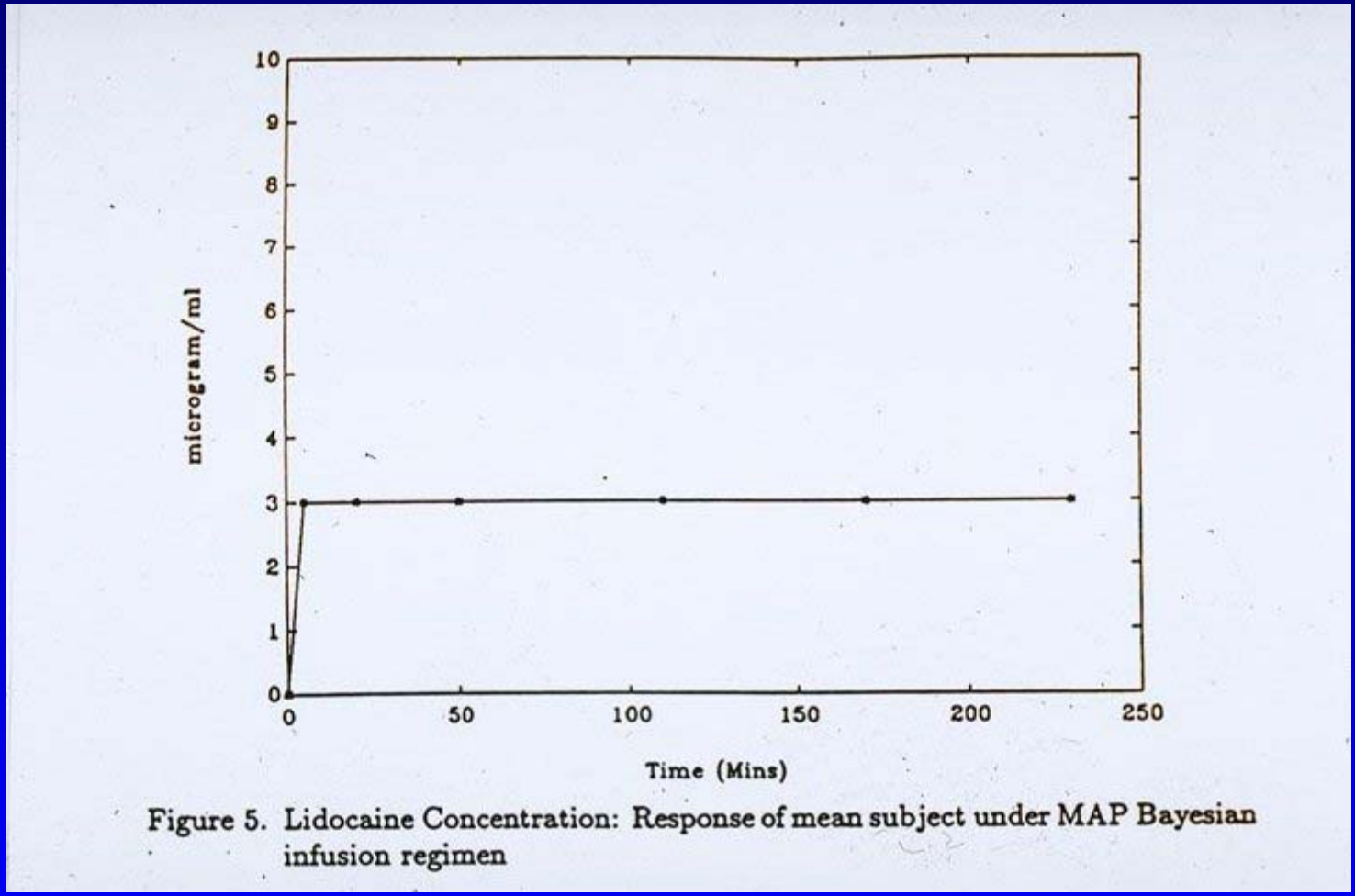

Figure 5. Lidocaine Concentration: Response of mean subject under MAP Bayesian infusion regimen

Lido Regimen based on Param means: Predicted response of “mean” patient

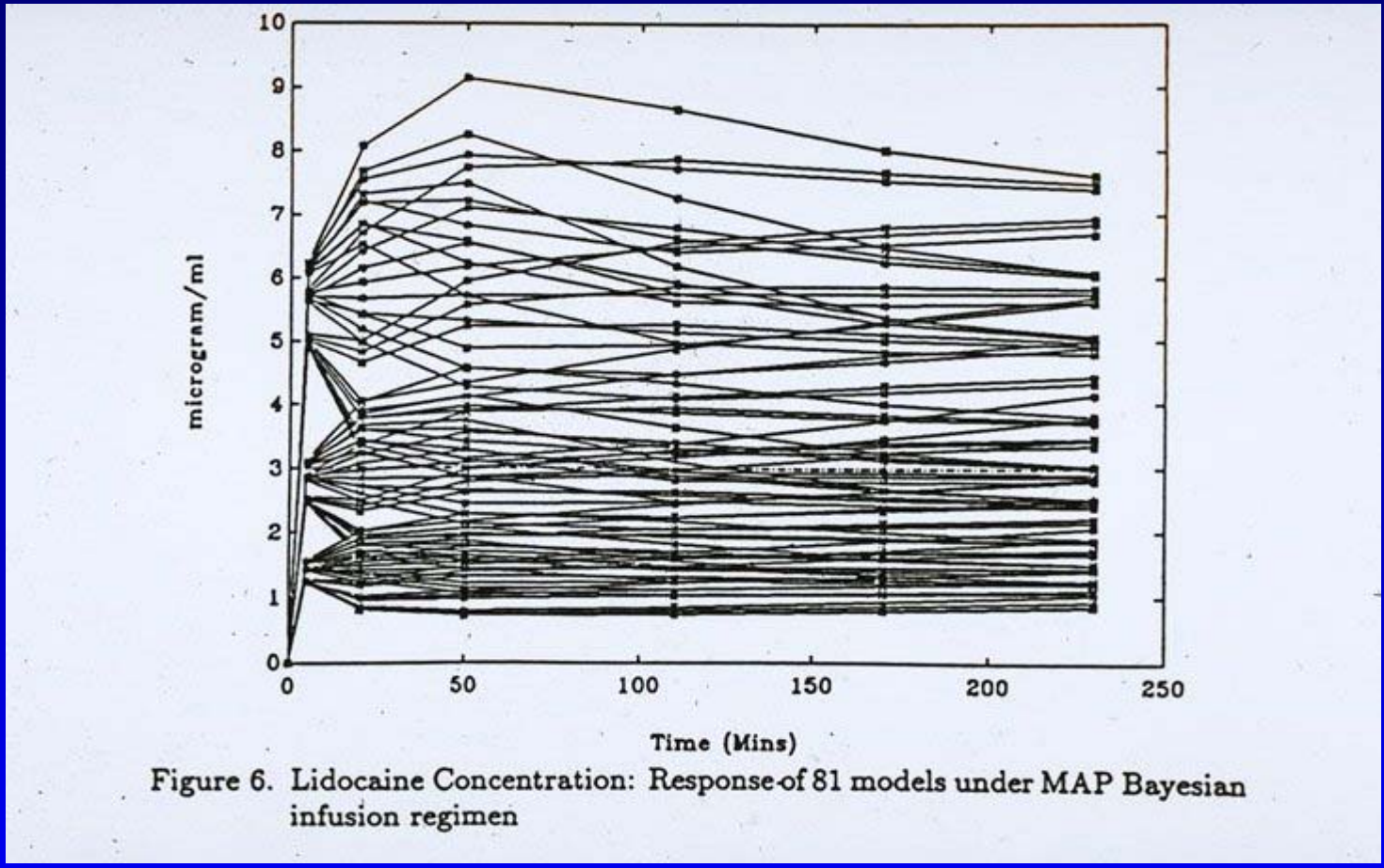

Figure 6. Lidocaine Concentration: Response of 81 models under MAP Bayesian infusion regimen

Lido Regimen based on Param means: Predicted response of full lido pop model

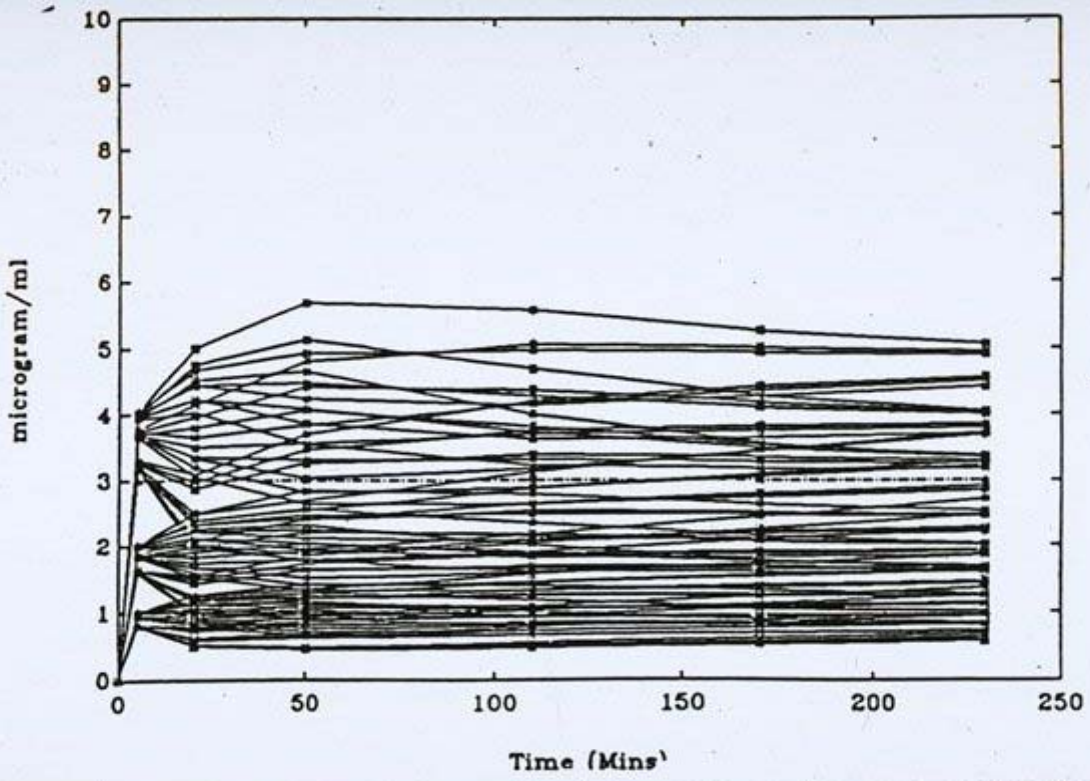

Figure 4. Lidocaine Concentration: Response of 81 models under MMLQ infusion regimen

Optimal MM lido regimen: Predicted response of full lido pop model

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

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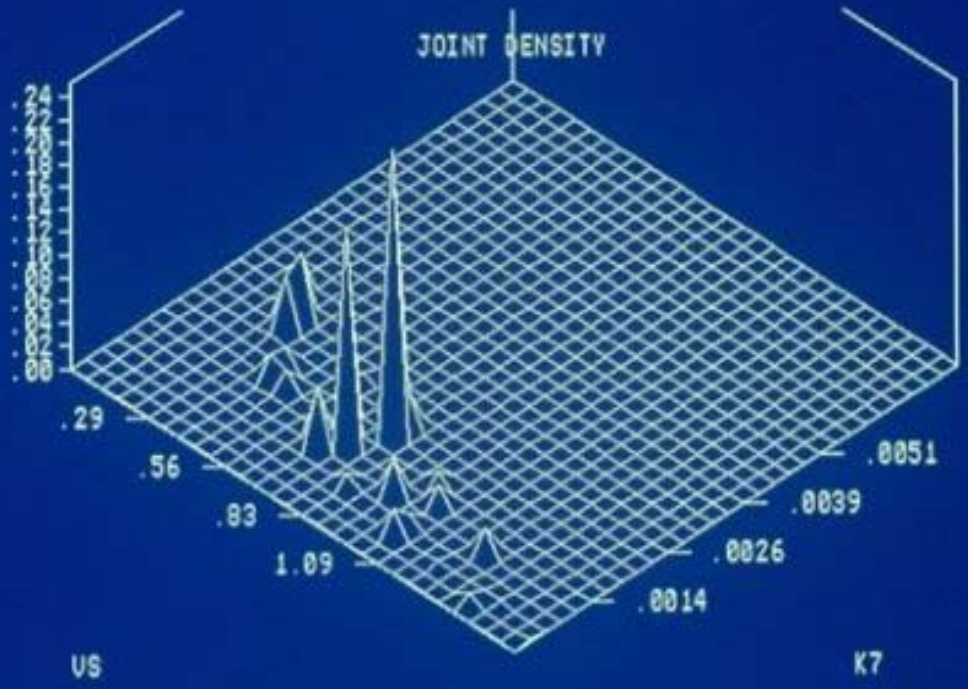
and Michael Van Guilder, Ph.D.



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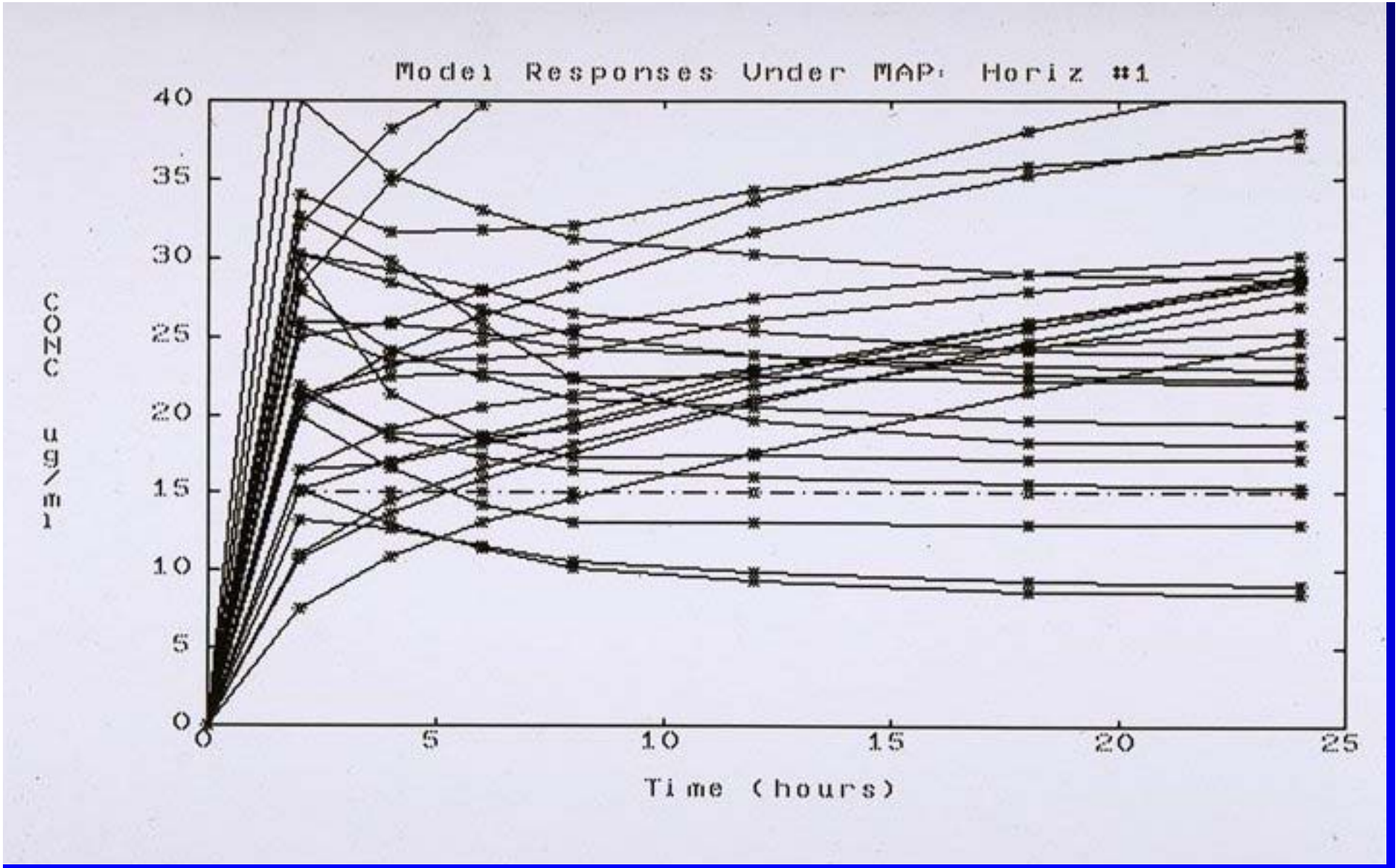
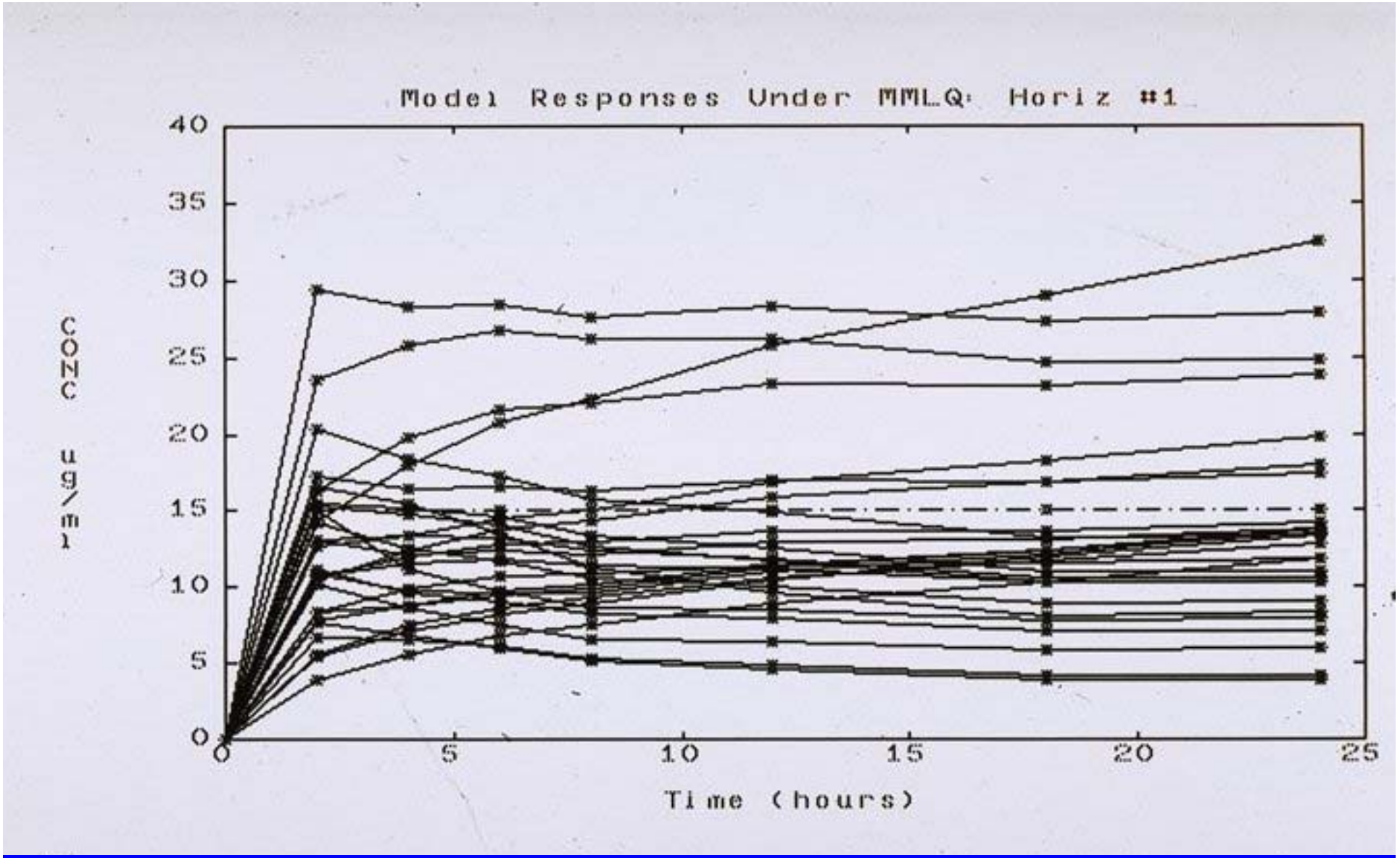
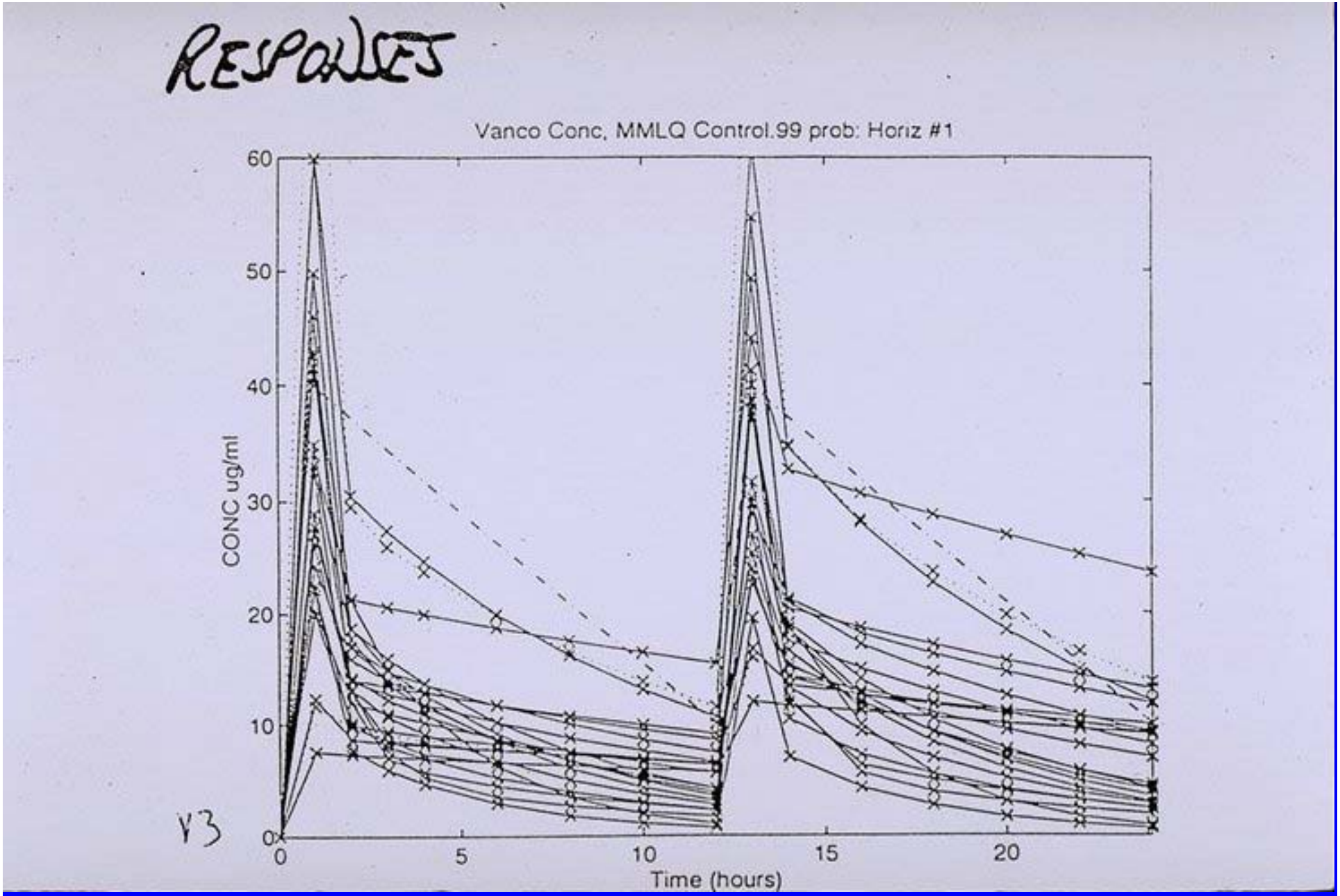
Supported by NIH Grant LM 05401
and by the Stella Slutzky Kunin Memorial Research Fund



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

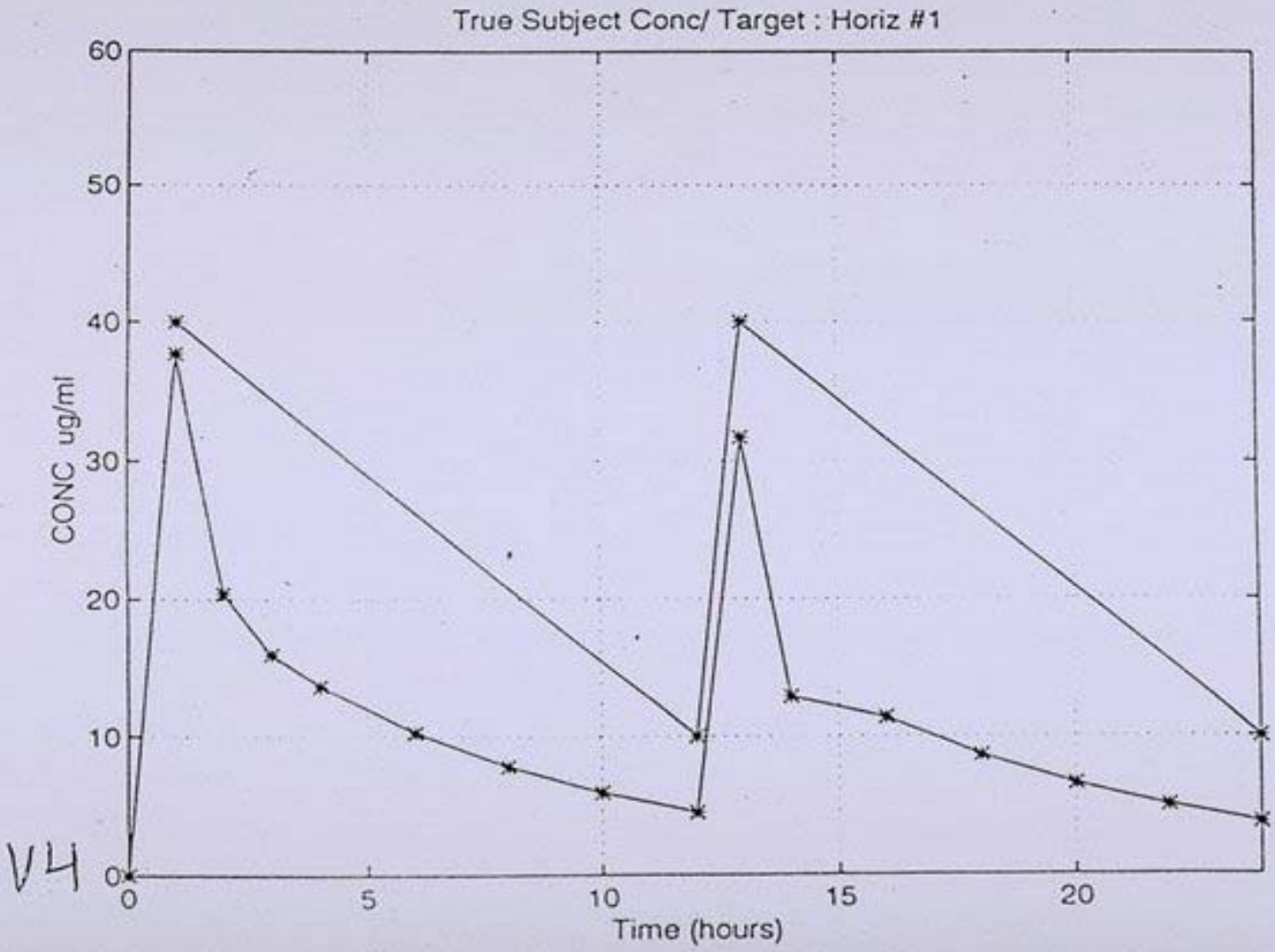


Vanco, continuous IV. Predictions from MM regimen



Vanco, 95% and 99% predictions

TRUE SUBJECT

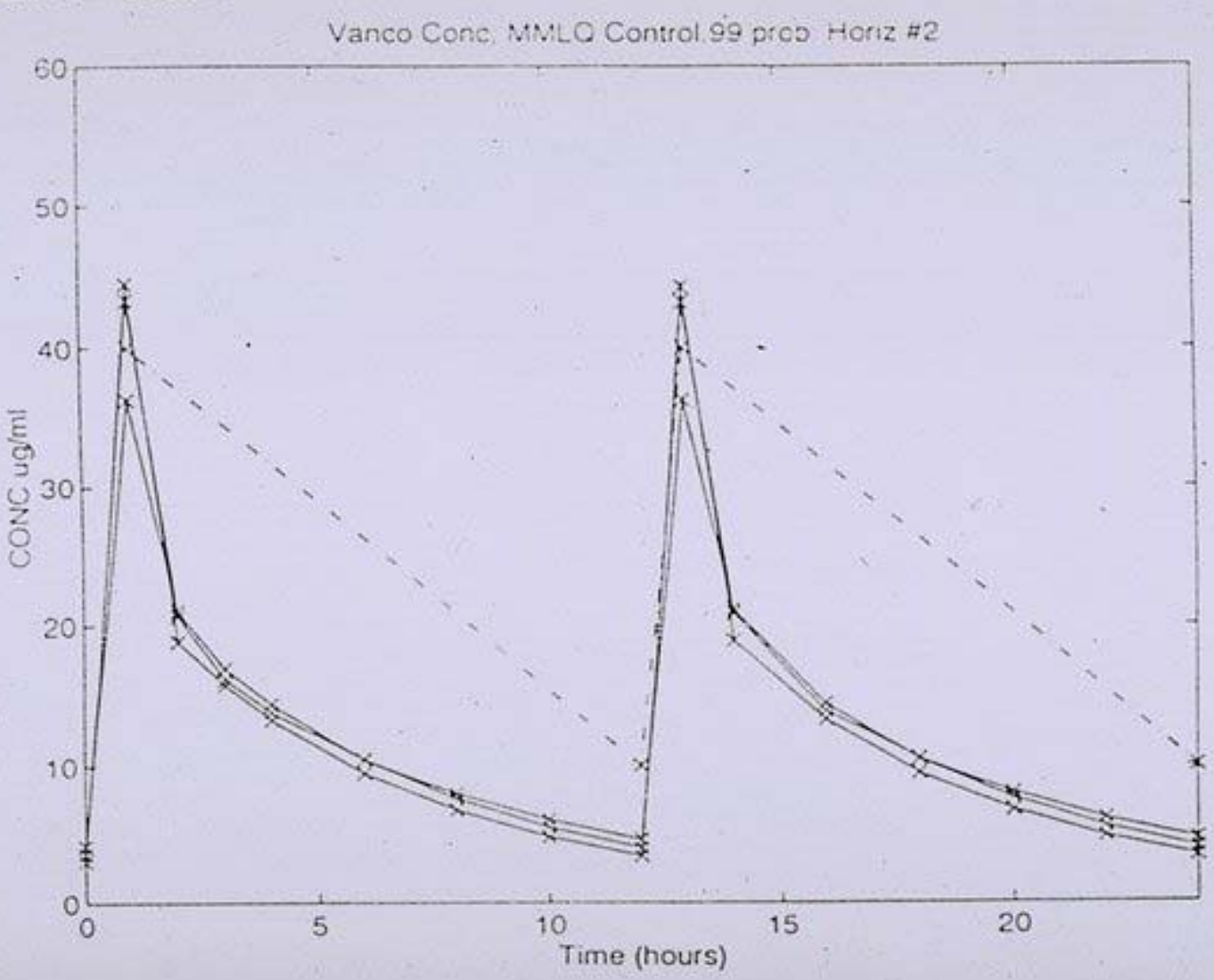


True Patient, Day 1

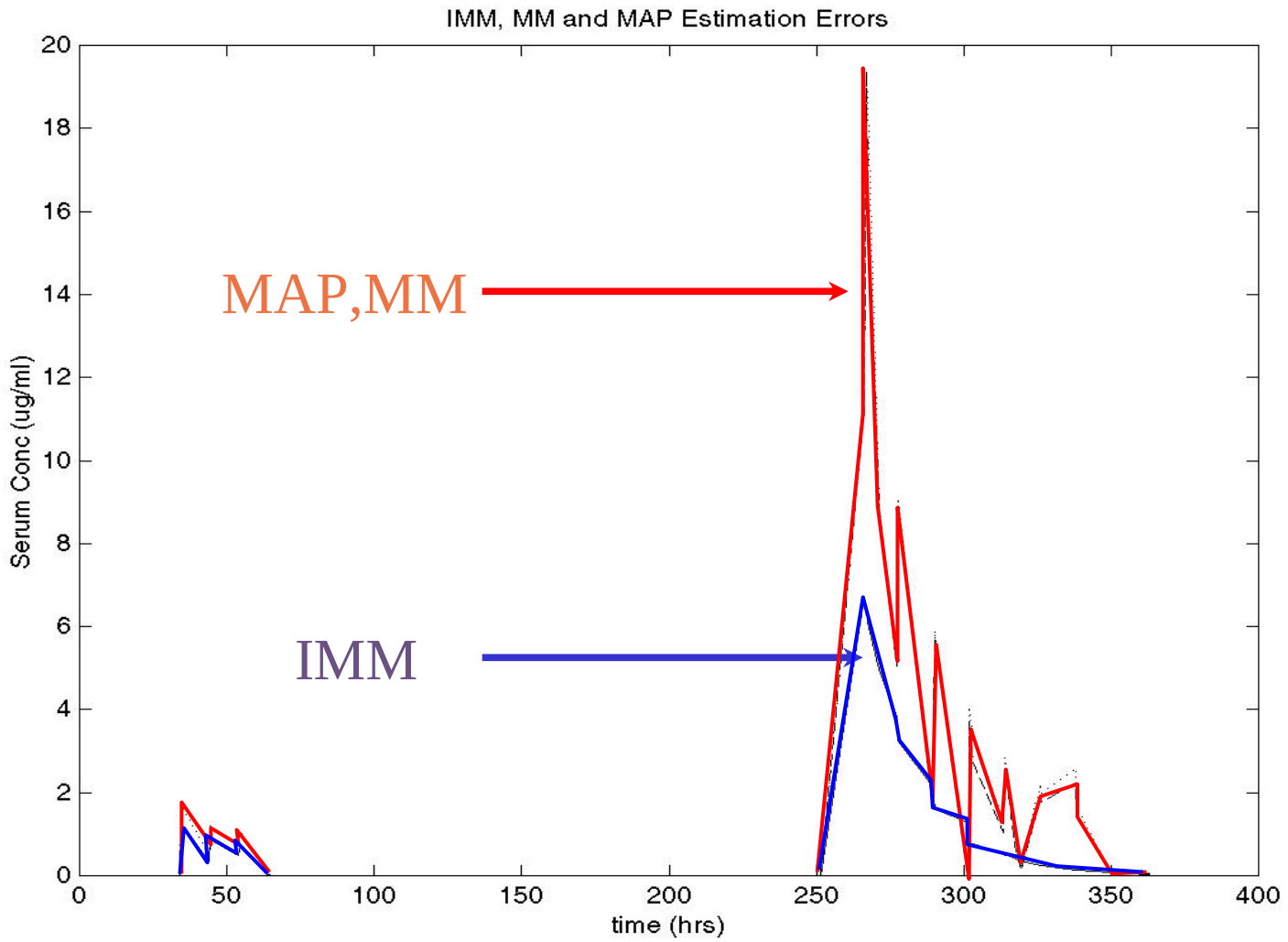
Getting Individual Nonparametric Bayesian Posteriors from Serum Levels

- Start with Population discrete joint density
- Use the patient's measured serum levels
- Recompute Bayesian posterior probability of each discrete support point (model, parameter value set) given that patient's own measured levels.
- Interacting MM (IMM) sequential Bayesian posteriors now permit detection of changing parameter values during the analysis.

RESPONSES



Vanco: 95% and 99% predictions for Day 2



Errors in tracking serum conc: Sequential MAP, MM, and IMM Bayesian posteriors

MM Optimal Dosage Regimens:

- Show the quantitative effect of outliers.
- A simulated clinical trial with each regimen.
- Achieve target goals with max precision.
- Get the best overall “standard dose”.
- Best for Vet use, without feedback.
- Best for Patient use, with or without feedback - cancer, AIDS, inf. Disease, CV disease.
- Best combination regimens in future.