Optimal Techniques and Sequences for Population Modeling of Bioavailability

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Why is Bioavailability Important? - Who really cares?

- Regulatory agencies - but really, why?
- The industry - but why again?
- The patient - he/she is the one who gets the drug - but again, why?
- The clinician - but why again?
- What about drugs with narrow safety margins?
- It is important for the patient, for optimal action (dosage regimens).

How to determine bioavailability?

- Compare AUC, IV vs PO, in a crossover study, with washout period.
- Parameter values may change between studies, therefore the crossover.
- Expensive.
- Study often done in volunteers, not in the patients really being treated.

Another method to determine bioavailability.

- Determine it **directly** from an **intermixed IV and PO dosage regimen**, in a single study.
- Much less chance for changing parameter values during a single study.
- Cheaper.
- Can study the patients really being treated.

The Nelder-Mead Simplex fitting algorithm

A SIMPLEX IS A GEOMETRICAL FIGURE

HAVING ONE MORE POINT OR VERTEX

THAN THE NUMBER OF PARAMETERS

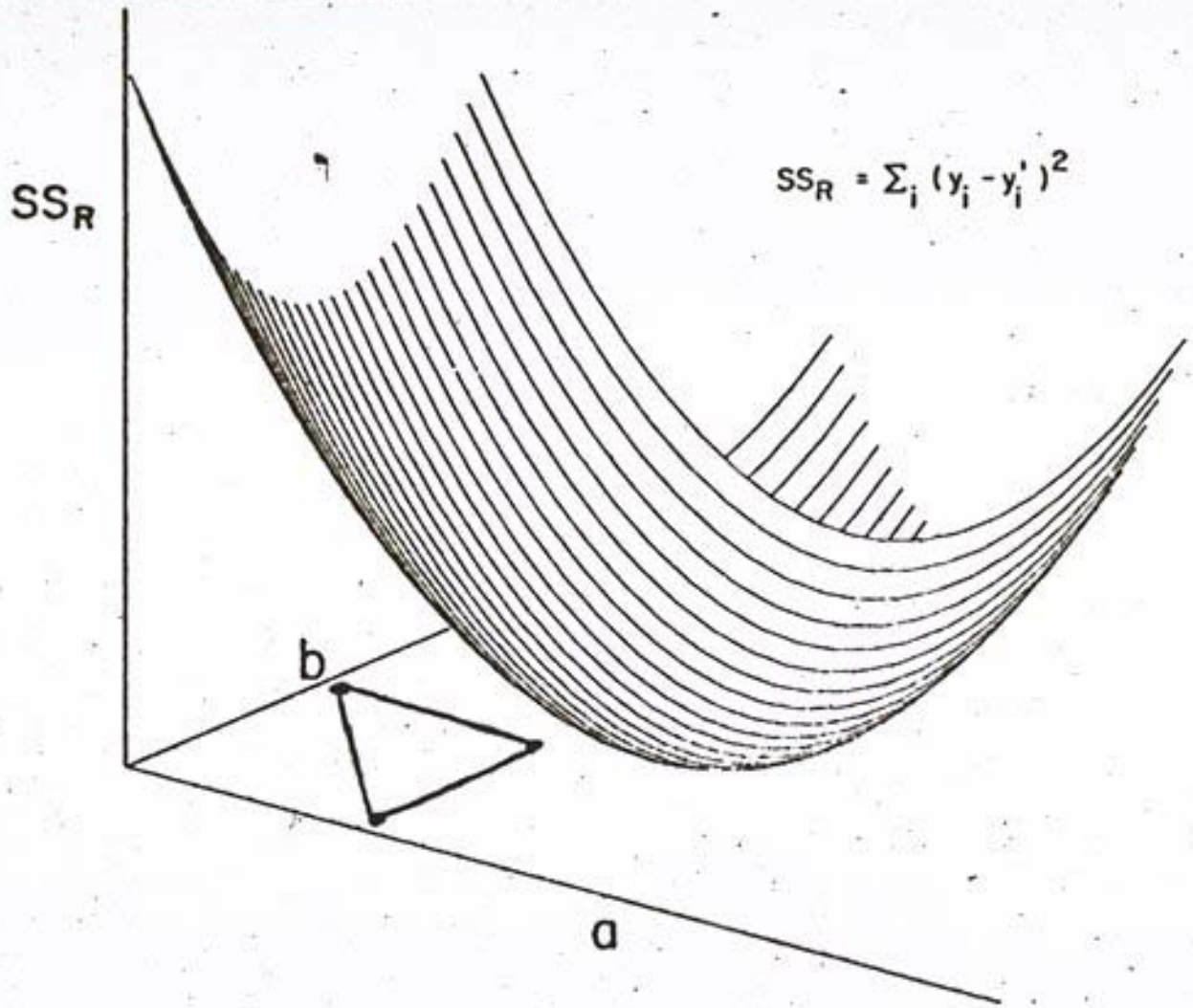


Figure 2: *Representation of the response surface,* SS_R *versus* a *and* b. *The best values for* a *and* b *are those where the* SS_R *value is the lowest. If you have poor* a *and* b *values, you will get large values for* SS_R.

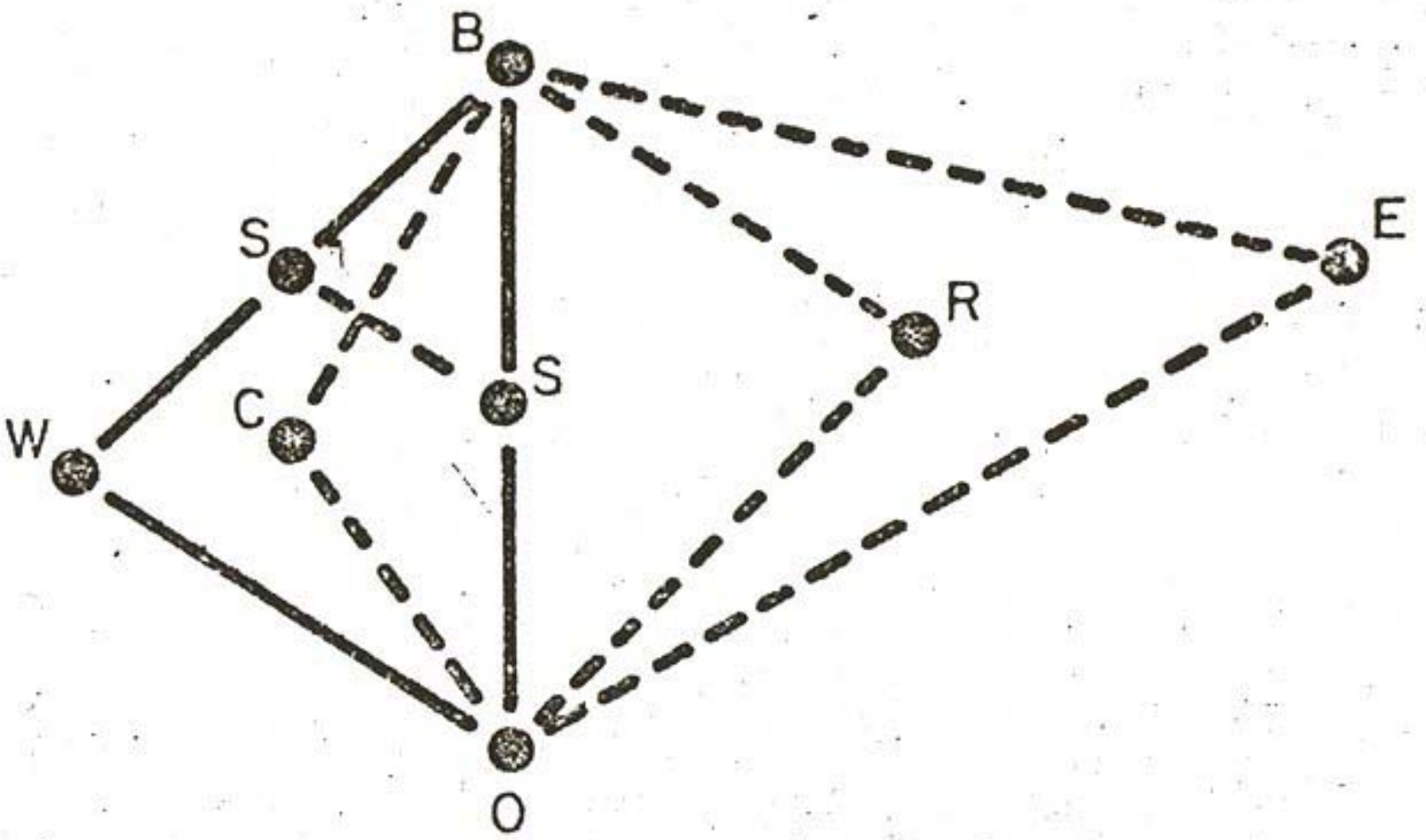


Figure 3: *Two-dimensional simplex BWO illustrating the four mechanisms of movement: reflection, expansion, contraction, shrinkage.* B = *vertex,* W = *worst vertex,* R = *reflected vertex,* E = *expanded vertex,* C = *contracted vertex, and* S = *shrunken vertexes.*

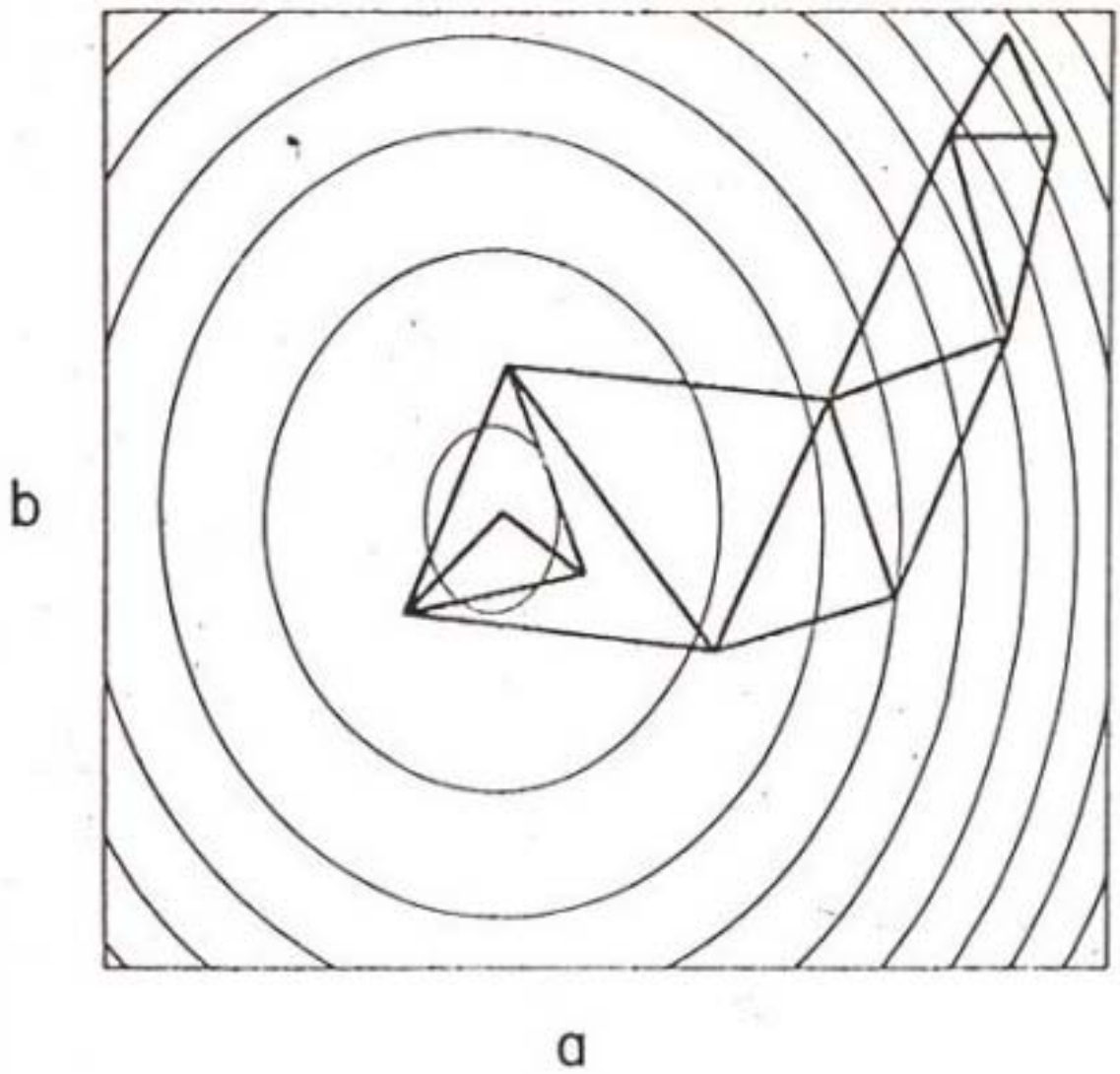


Figure 5: *An example of the simplex moving on the response surface's contour plot.*

Optimal Target-Oriented, Model-Based Individualized Drug Dosage Regimens.

- Use Population Model as Bayesian Prior.
- Set ***specific*** target(s): Serum conc(s) at desired time(s), for example.
- Plan the initial regimen to hit the target(s).
- But: just ***how precisely*** will the regimen do this? A good question!
- How to predict and optimize such precision ***in advance***?

What is the **IDEAL** Pop Model?

- The correct structural PK/PD Model.
- The collection of each subject's exactly known parameter values for that model.
- Therefore, multiple individual models, one for each subject.
- Usual statistical summaries can also be obtained, if desired, but usually lose info.

Parametric Population Models: IT2B, NONMEM, etc

- Assume shape (normal, etc,) of param distribs. (Describe params parametrically)
- Get the param param values = param means, SD's, covariances, correlations, etc.
- **Get bioavailability from intermixed IV+PO dosage**
- Get SEM's, confidence limits, signif tests.
- Separate "Inter -" from "Intra -" Individual from assay Variability
- Usually get only ***summary single values*** for parameter ***distributions***.
- Are not consistent. No guarantee of correct results

Inter-Individual Variability

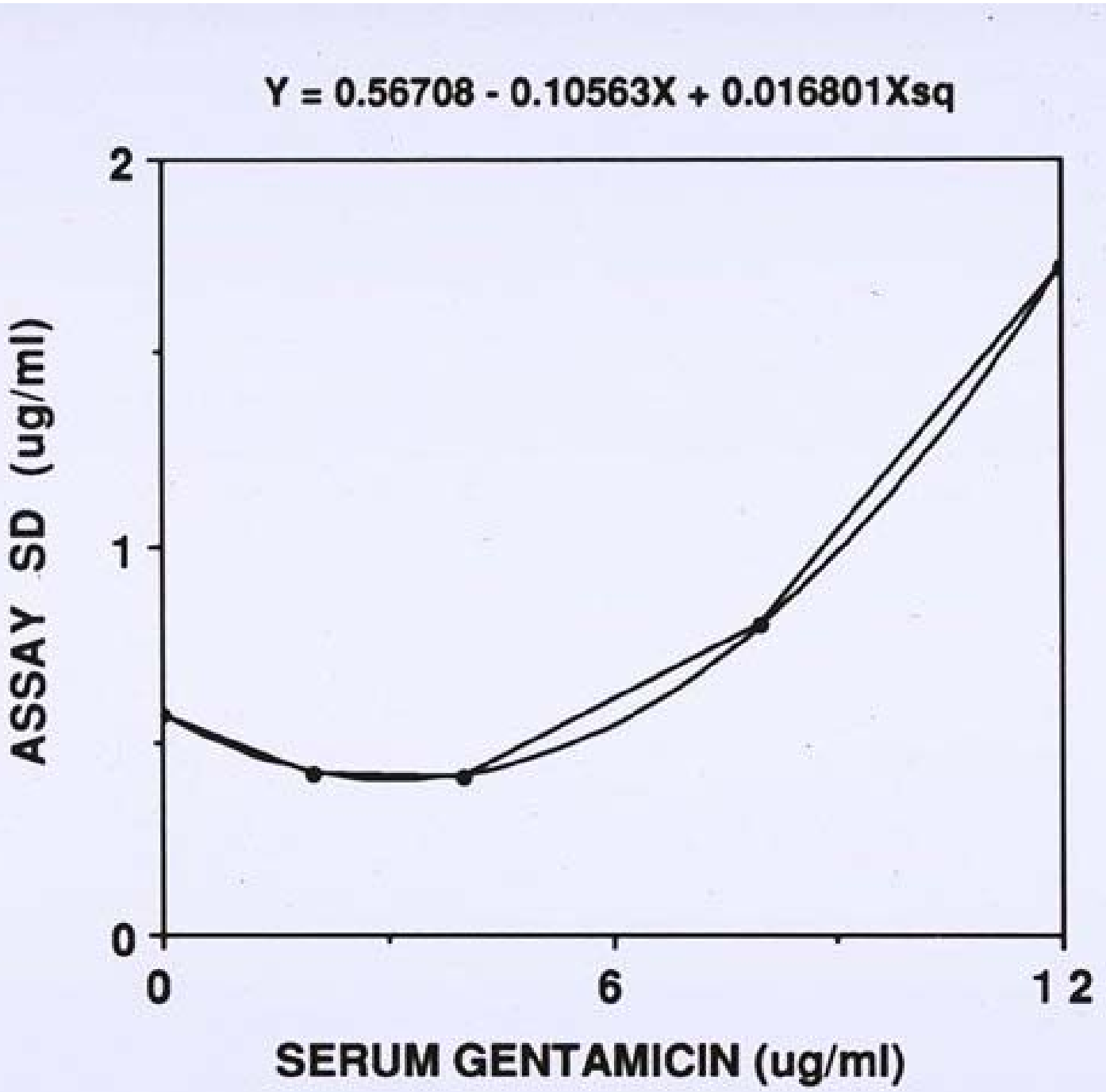
- Usually given as a single number (SD, CV%) in parametric pop models
- But there may be sub-populations
- eg, fast, slow metabolizers.
- How describe all this with one number?
- A good question!

Intra-Individual Variability

- Assay error pattern, plus
- Errors in Dosage Amounts prepared and given.
- Errors in Recording Dosage Times
- Errors in Recording Sampling Times
- Structural Model Mis-specification
- Changing parameter values with time
- Again, how describe all this with one number?

Determining the Assay SD polynomial

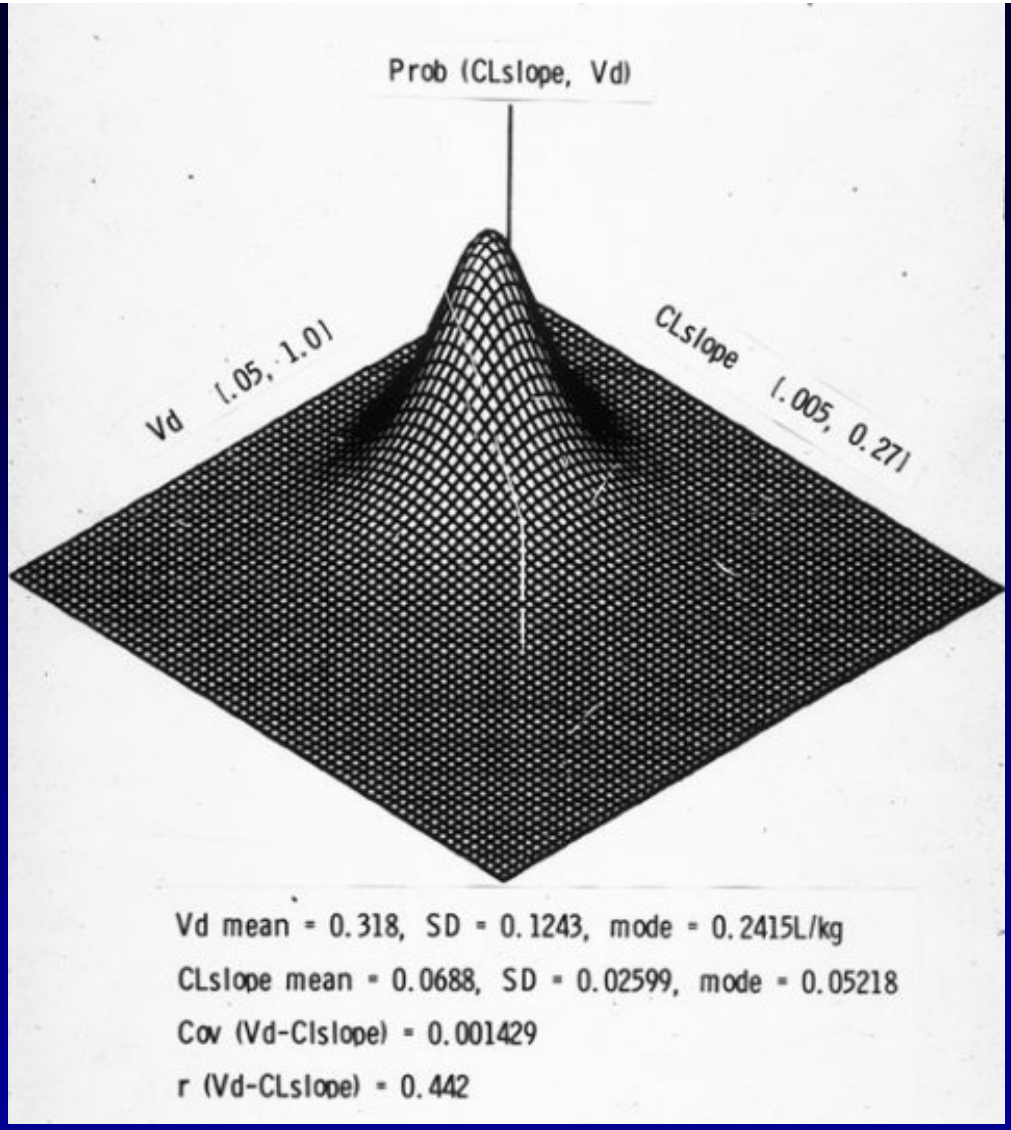
- Measure blank, low, medium, high, and very high samples in at least quadruplicate.
- Get mean + SD for each quadruplicate sample
- Fit a polynomial to the mean and SD data.
- $SD = A_0C^0 + A_1C^1 + A_2C^2 + A_3C^3$
- Then can weight each measurement by the reciprocal of its variance (Fisher Info)
- No lower detectable limit for PK work


Y = 0.56708 - 0.10563X + 0.016801Xsq
2
1
0
ASSAY SD (ug/ml)
0
6
12
SERUM GENTAMICIN (ug/ml)

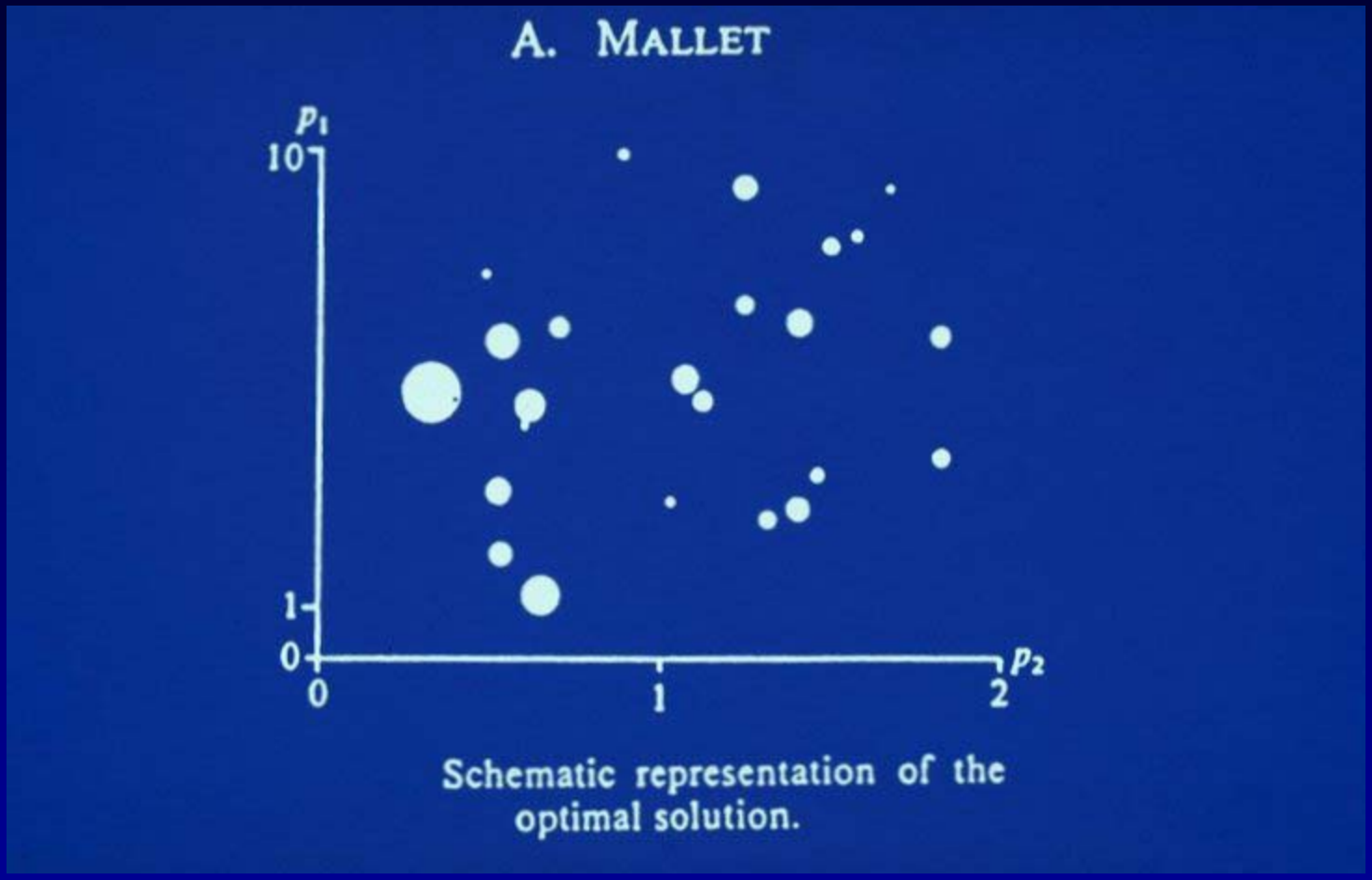
Intra - Individual Var (IIV) and Assay SD.

- IIV = Gamma($A_0C^0 + A_1C^1 + A_2C^2 + A_3C^3$)
- or, IIV = Gamma + ($A_0C^0 + A_1C^1 + A_2C^2 + A_3C^3$)
- or, IIV = ($A_0C^0 + A_1C^1 + A_2C^2 + A_3C^3$)
- Thus, IIV can be a single number
  - Just by itself, as often, where get A_0 above, (all other A's set to zero)
  - Or, an entire polynomial.
  - Or, best, Scaling or adding to the assay SD polynomial
- A summary index of quality of care given.
- Gamma often = < 2 to > 4

A Population Model, as made by Breugel



A Parametric Population Model
Joint Density



An NPML Population Joint Density, as made by Mallet

Nonparametric Population Models (1)

- Get the entire ML distribution, a Discrete Joint Density: one param set per subject, + its prob.
- Shape of distribution not determined by some equation, but only by the data itself.
- Multiple indiv models, one model set per subject.
- Can discover, locate, unsuspected subpopulations.
- ***Get bioavailability from intermixed IV+PO doses***.

Nonparametric Population Models (2)

- The multiple NP models permit multiple predictions.
- Can thus predict precision of goal achievement in advance by a regimen.
- Behavior is consistent. Proven correct results.
- Use IIV +/or assay SD, stated ranges.
- Same Gaussian signif tests. Bootstrap, coming soon.

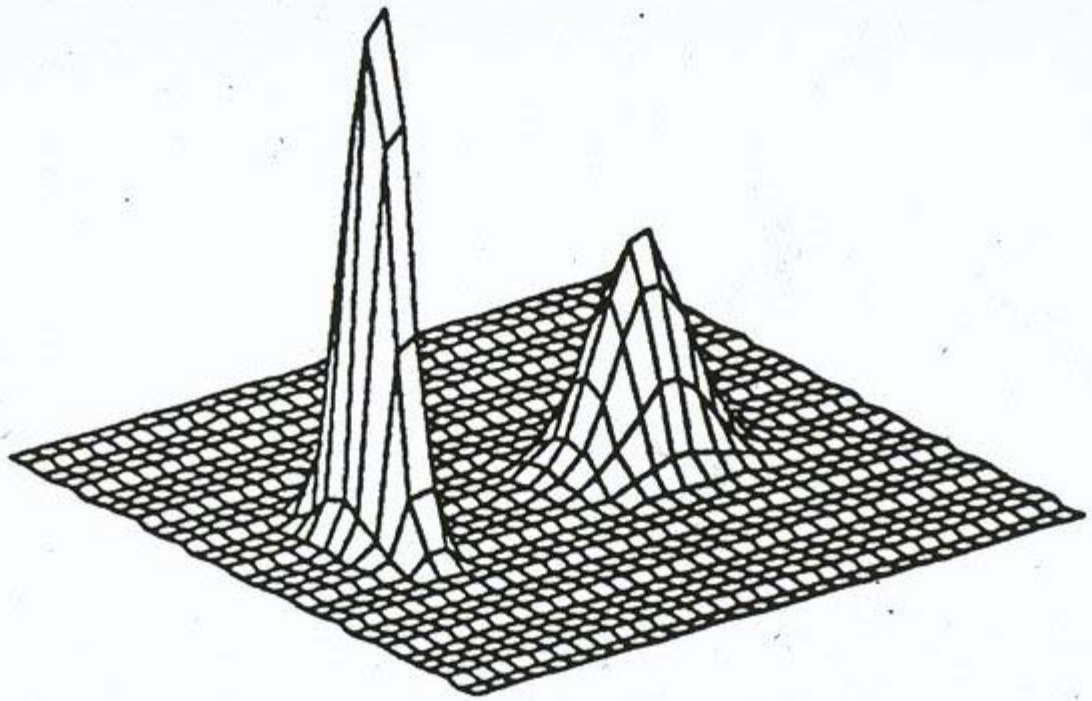


Fig. 1. True density of $\theta = (K, V)$.

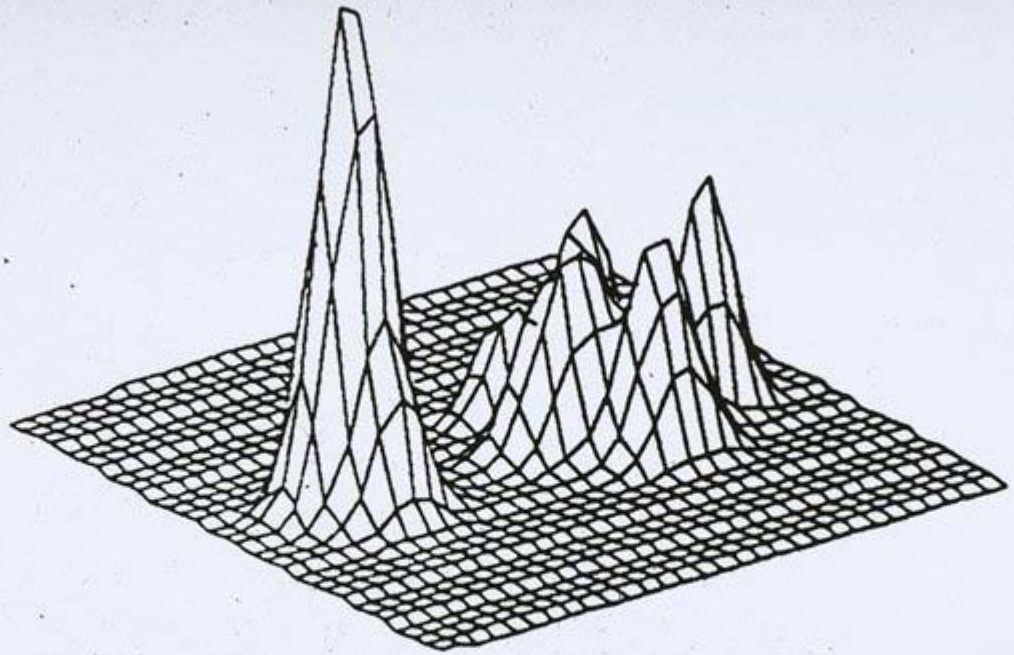


Fig. 6. Smooth empirical density of $\theta = (K, V)$. 20 subjects

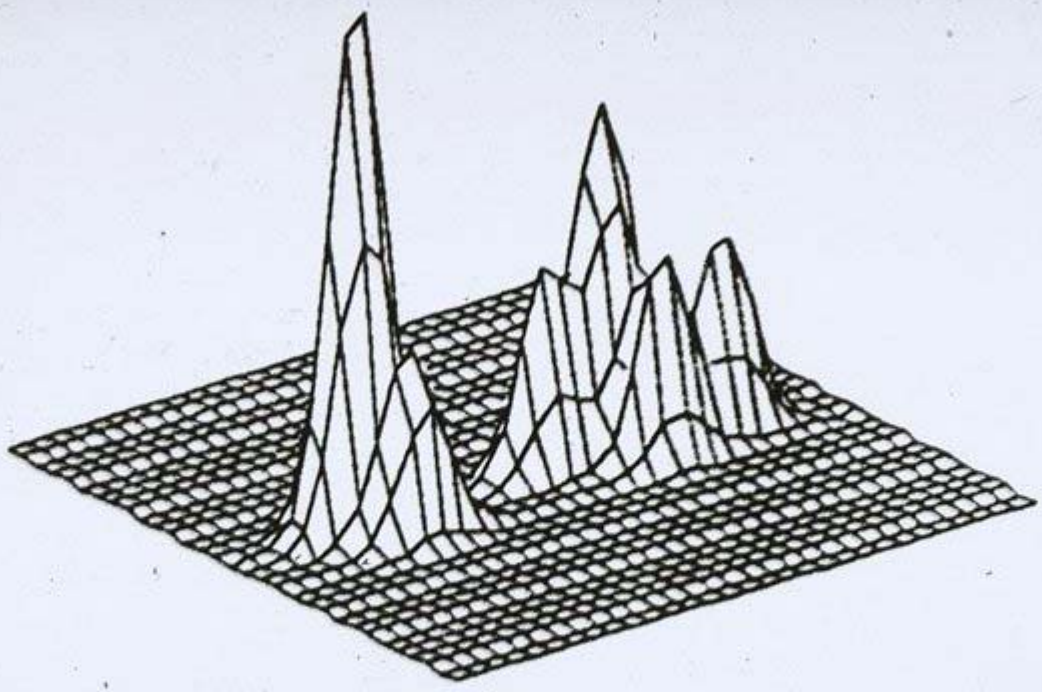


Fig. 4. Smooth estimated density of $\theta = (K, V)$.
5 levels / subject

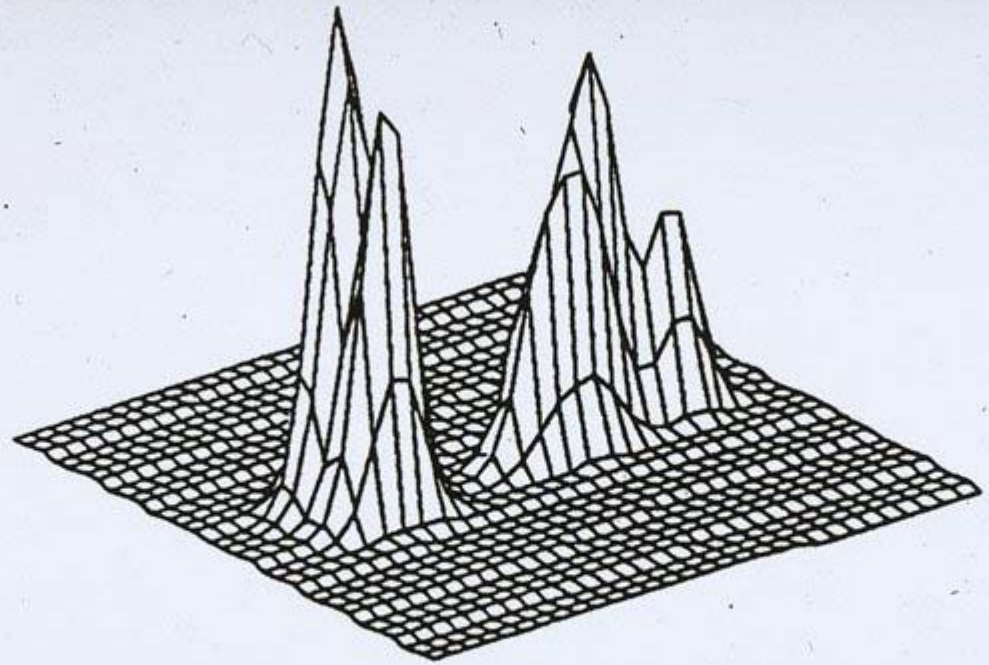


Fig. 5. Smooth estimated density of $\theta = (K, V)$.
2 levels / subject

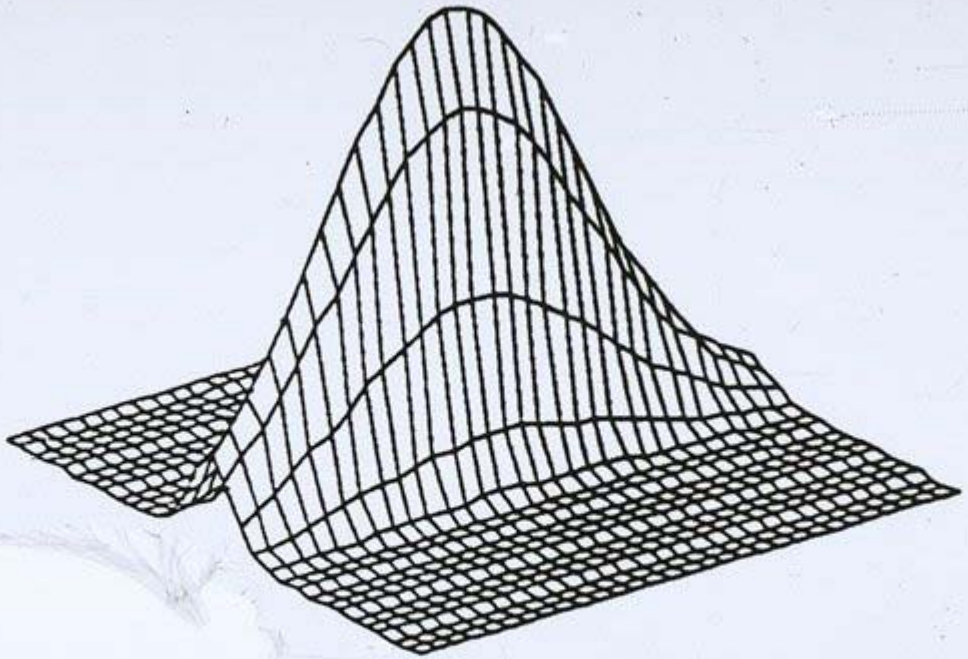


Fig. 2. Normal density of a random vector with same mean and covariance as $\theta = (K,V)$.

Larger + Nonlinear IT2B and NPEM Models

- Linear or Nonlinear Structural Models.
- May use BOXES to help make model.
- Responses are Serum Levels, Effects.
- Prepare Model + data on PC.
- Upload data files over the Web to SDSC resource, or our LAPK Dells.
- Do the analysis, get results.
- Download results back to PC, see them.

Summary: Parametric Population Models

- Single point parameter estimates only.
  - Only one (1) model.
  - Cannot discover unsuspected subpopulations
  - Cannot predict precision of goal achievement
  - Not consistent, but have SEM, confidence limits
  - Can get Parameter ranges
  - Can get Gamma
- **Can get Bioavailability directly**

Summary: Nonparametric Population Models

- Get the entire ML parameter joint density
  - Use stated ranges. Will get Gamma soon.
  - Get multiple parameter sets, one per subject
  - Discover, locate, subpopulations
  - Predict precision of goal achievement
  - Consistent. Same Gaussian signif tests.
    Bootstrap coming soon.
- **Can get Bioavailability directly.**
- **NP models can consider BA clusters.**

How to do Pop Modeling best? Use Both Methods for now, NP soon.

- First, determine the assay SD polynomial.
- Second, Parametric: get the ranges, gamma.
- Third, Nonparametric: get the full discrete joint density. Multiple models.
- Get bioavailability directly.
  - Predict precision of goal achievement
  - Find the best dose to achieve target goals with maximum precision.
  - Multiple Model Dosage design

Action: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.

Action: 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 with the minimal weighted squared error. This is multiple model (MM) dosage design - the real reason for using nonparametric population models.

Multiple Model Dosage Design: Achieving Target Goals with Maximum Precision

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%

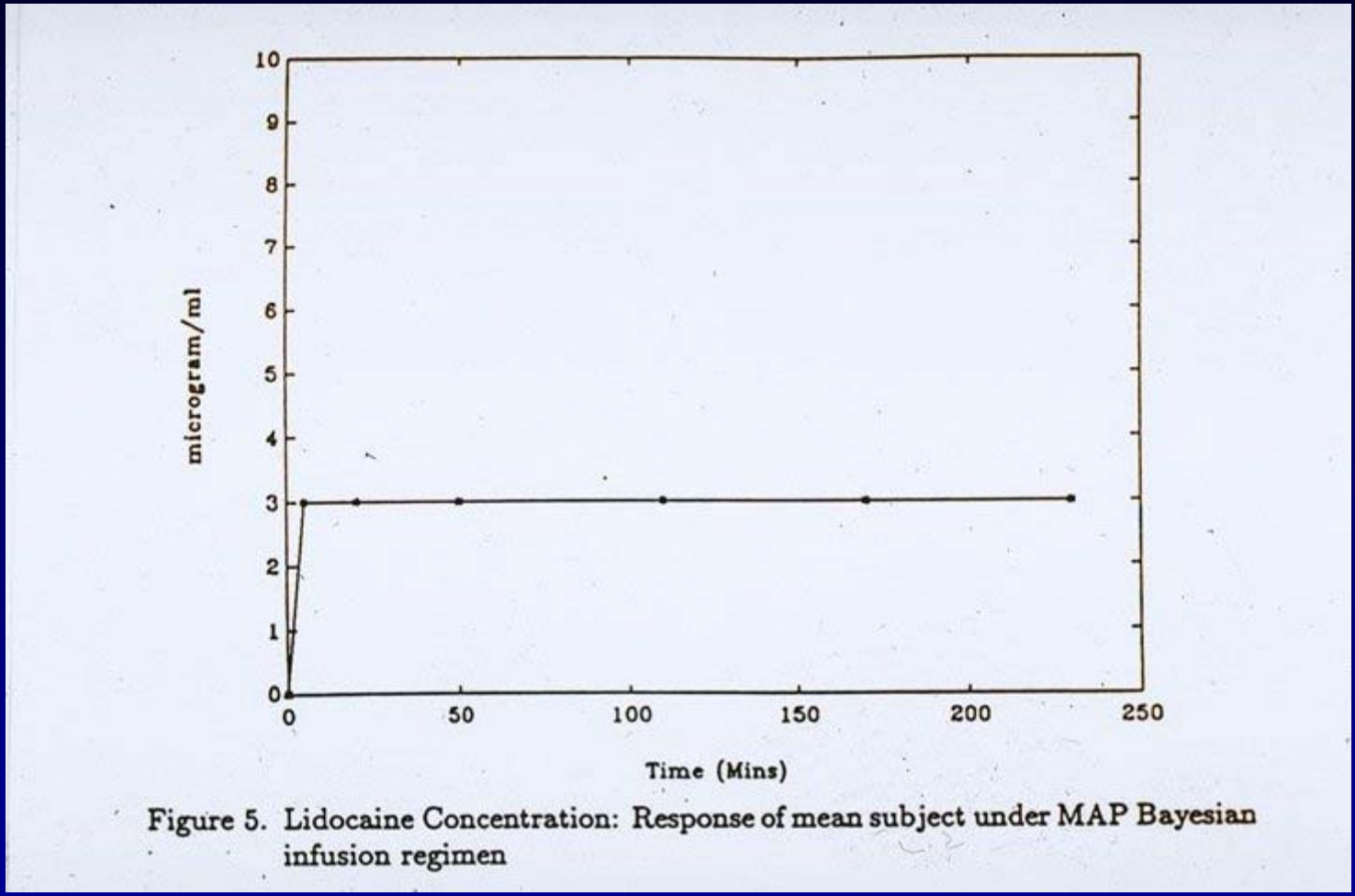


Figure 5. Lidocaine Concentration: Response of mean subject under MAP Bayesian infusion regimen

Lido Regimen based on ***Param means***: Predicted response of "mean" patient

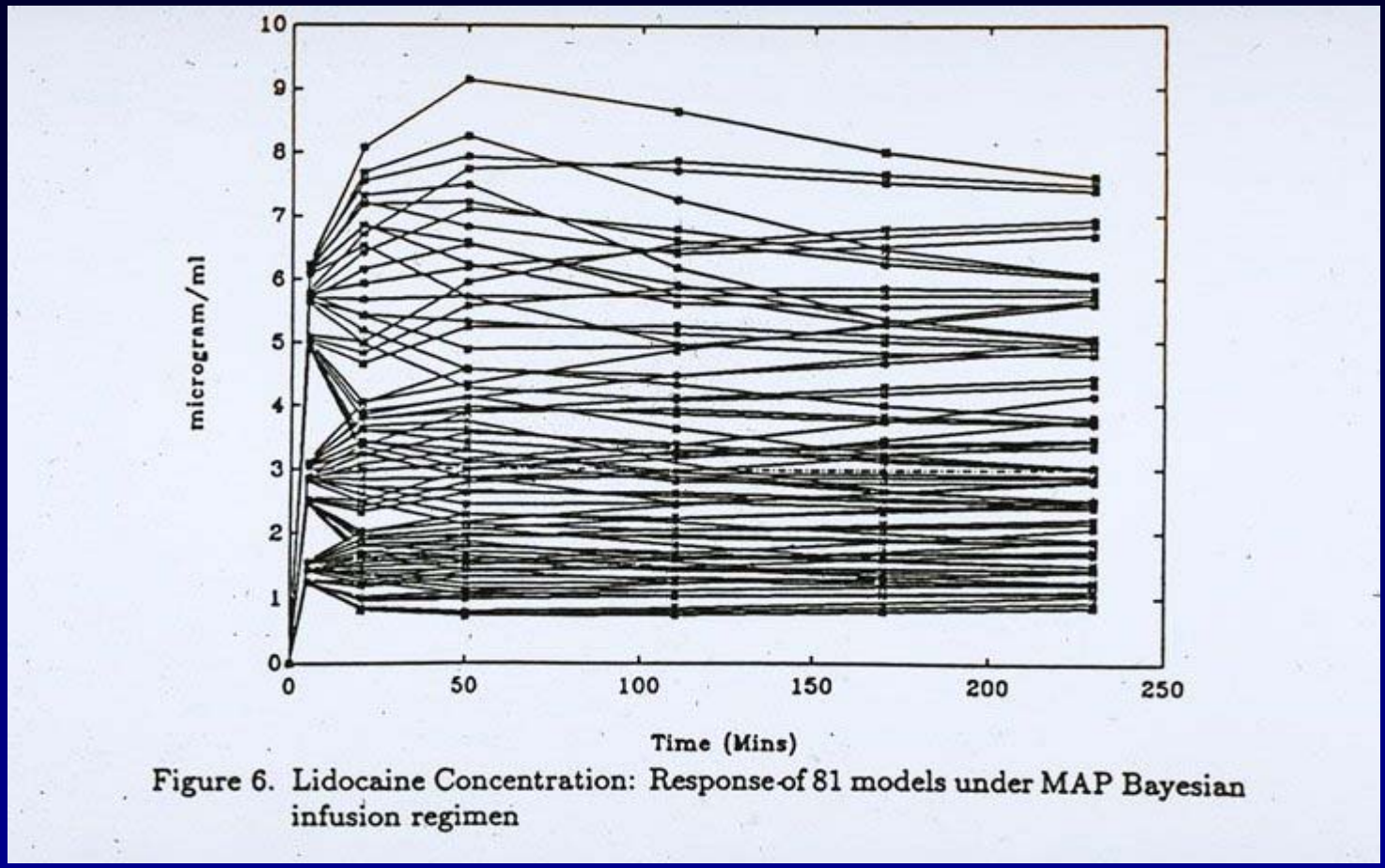


Figure 6. Lidocaine Concentration: Response of 81 models under MAP Bayesian infusion regimen

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

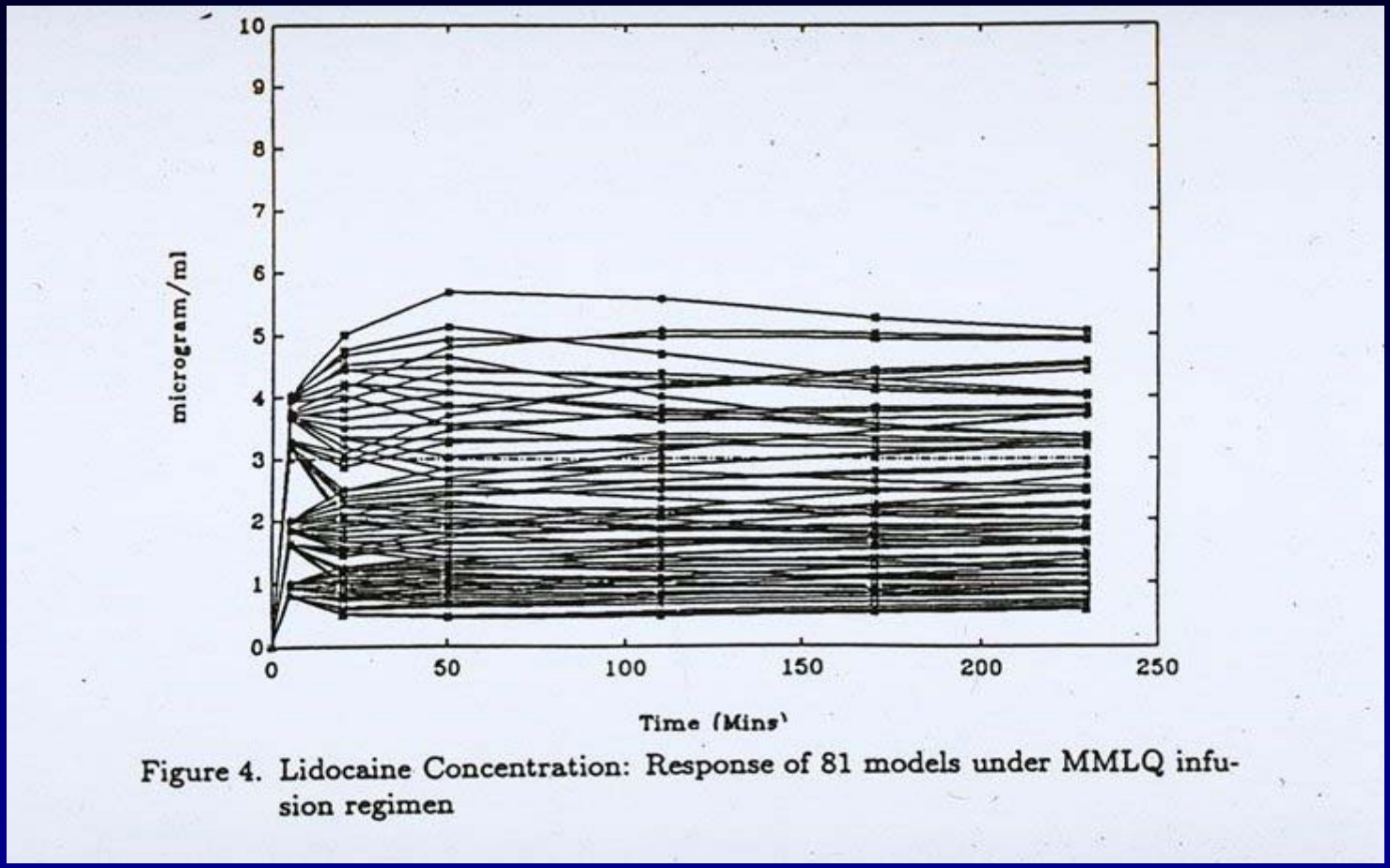


Figure 4. Lidocaine Concentration: Response of 81 models under MMLQ infusion regimen

Optimally precise MM lido regimen:
Predicted response of full lido pop model

MM Optimal Dosage Regimens:

- Show the quantitative effects of outliers.
- **Act optimally on bioavailability data**.
- A simulated clinical trial with each regimen.
- Achieve target goals with max precision.
- Get the best overall “standard dose”.
- Best for Patient or Vet use, with or without feedback - cancer, AIDS, inf. Disease, CV disease.
- Optimally coordinated combination dosage regimens coming.

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