Population Pharmacokinetic Models: Parametric and Nonparametric Approaches

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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 regimen to hit the target(s).
- But: just ***how precisely*** will the regimen do this? A good question!
- How to predict 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 may 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, etc.
- Get F 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***.
- They are not consistent.

Inter-Individual Variability

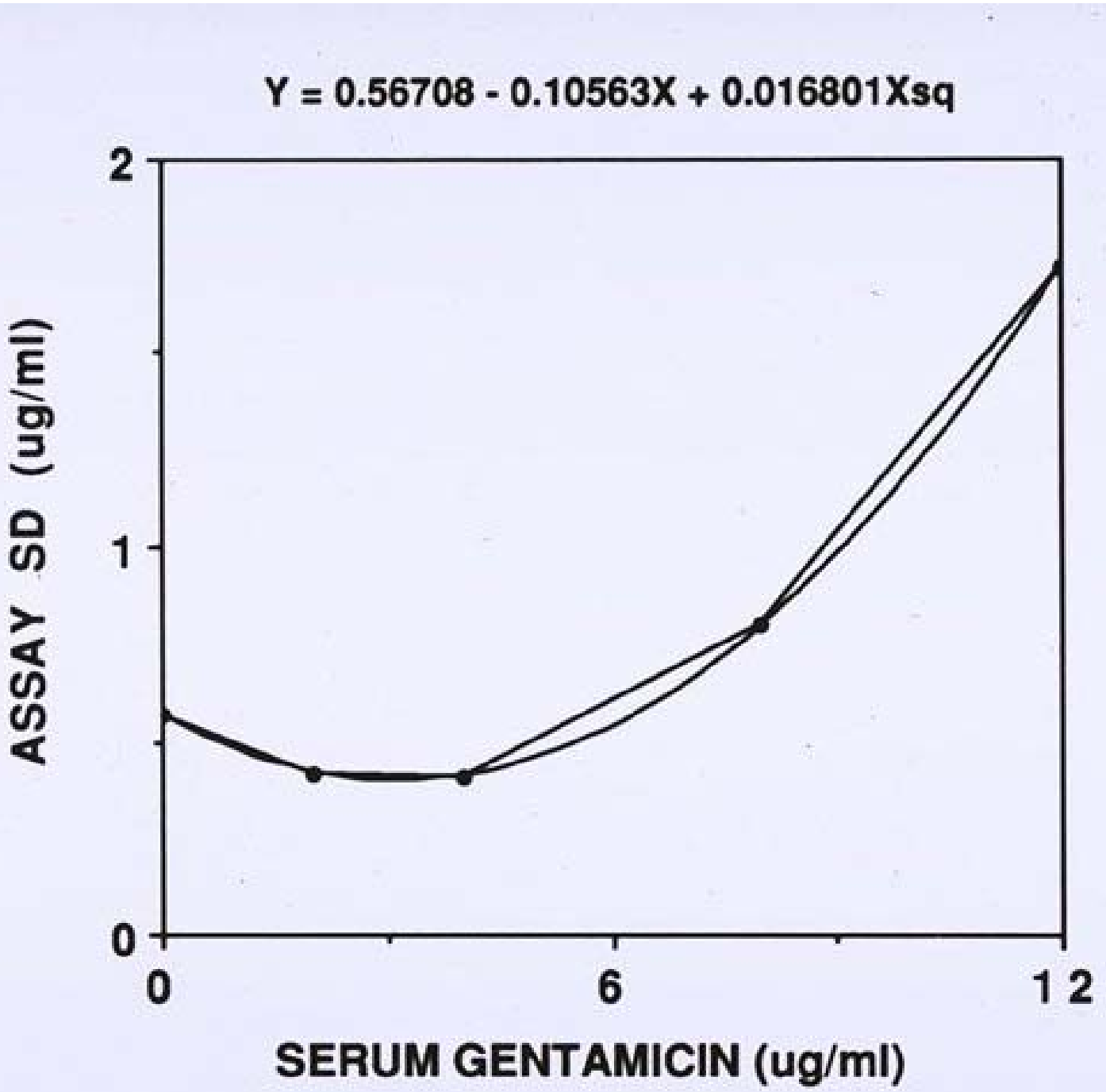
- Usually a single number (SD, CV%) in parametric population models
- But there may be sub-populations
- eg, fast, slow metabolizers.
- How describe all this with one number?
- A good question!

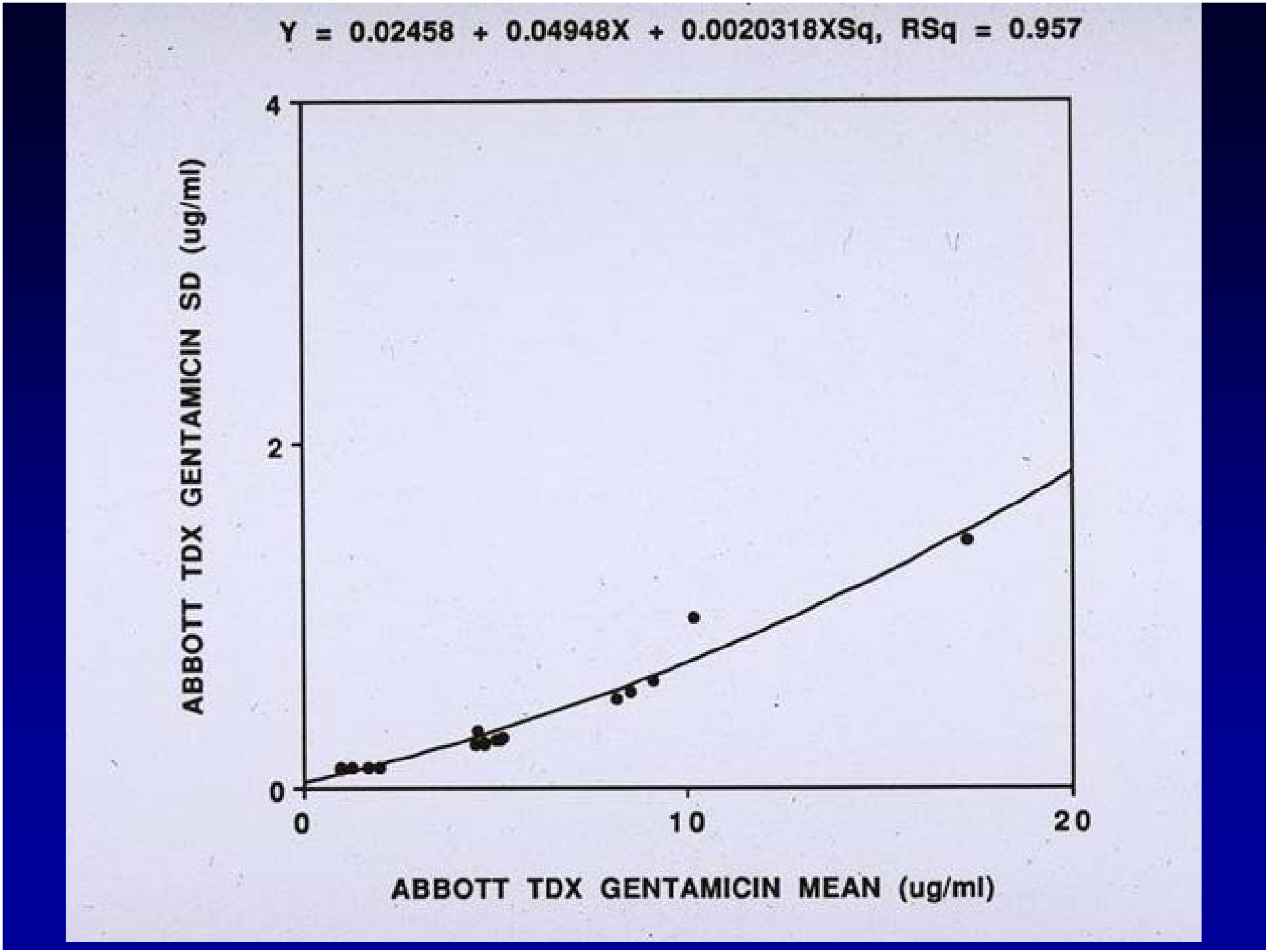
Intra-Individual Variability

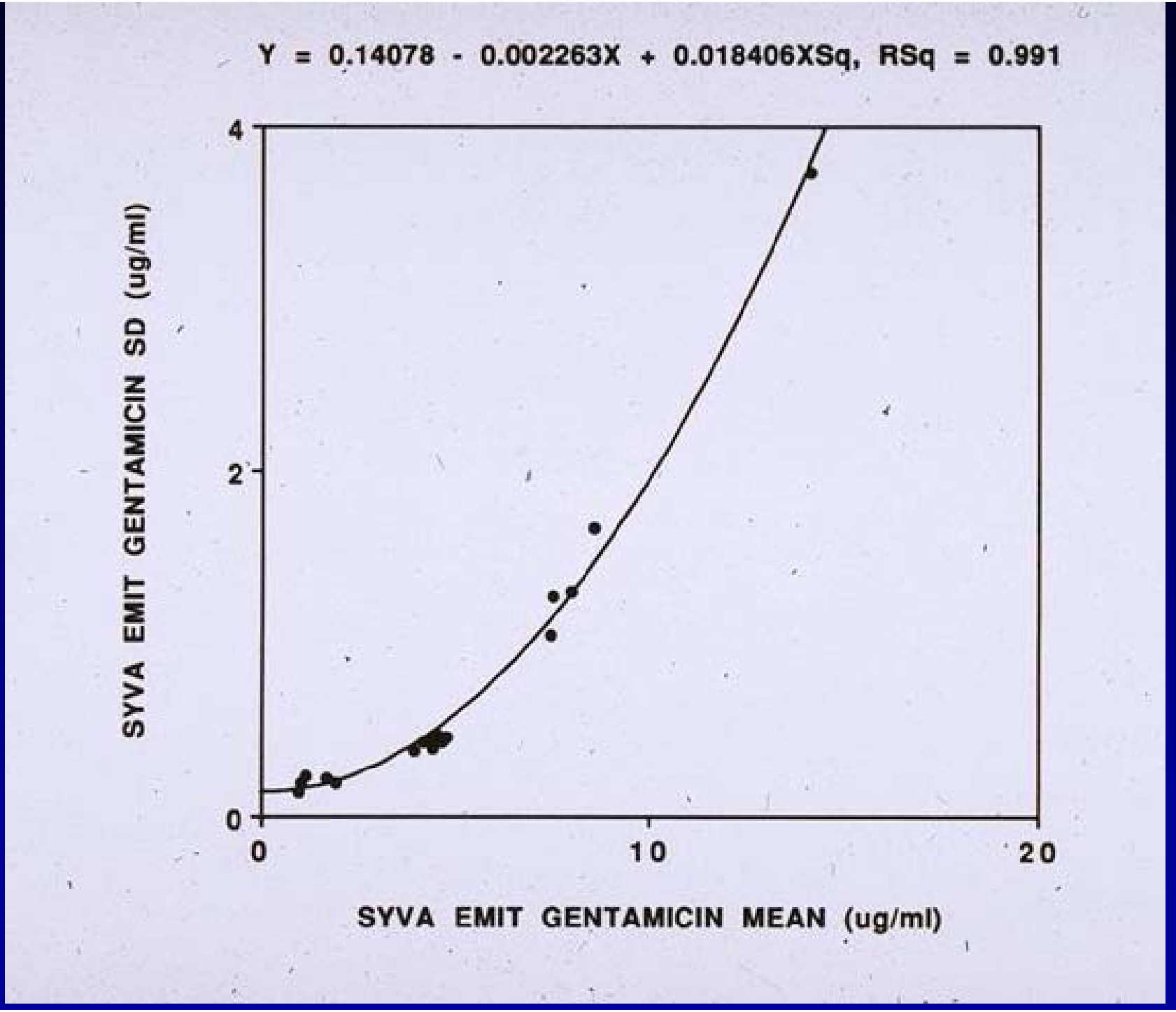
- Assay error pattern, plus
- Errors in Dosage Amounts
- Errors in Recording Dosage Times
- Errors in Recording Sampling Times
- Structural Model Mis-specification
- Changing parameter values with time

Determining the Assay SD polynomial

- Measure blank, low, medium, high, and very high samples in 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

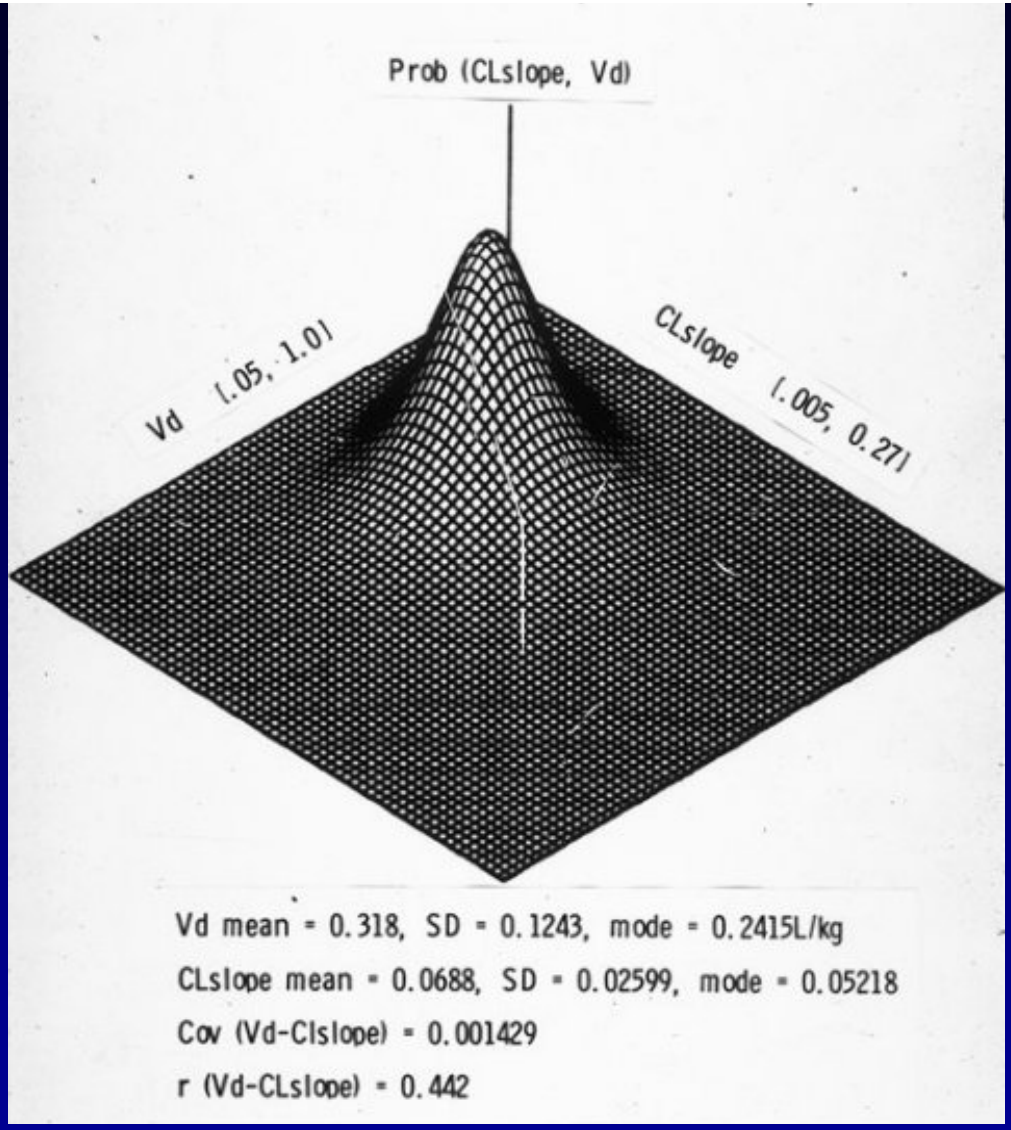

Y = 0.56708 - 0.10563X + 0.016801Xsq
2
1
0
ASSAY SD (ug/ml)
0
6
12
SERUM GENTAMICIN (ug/ml)


Y = 0.02458 + 0.04948X + 0.0020318XSq, RSq = 0.957
ABBOTT TDX GENTAMICIN SD (ug/ml)
4
2
0
0
10
20
ABBOTT TDX GENTAMICIN MEAN (ug/ml)


Y = 0.14078 - 0.002263X + 0.018406XSq, RSq = 0.991
SYVA EMIT GENTAMICIN SD (ug/ml)
4
2
0
0
10
20
SYVA EMIT GENTAMICIN MEAN (ug/ml)

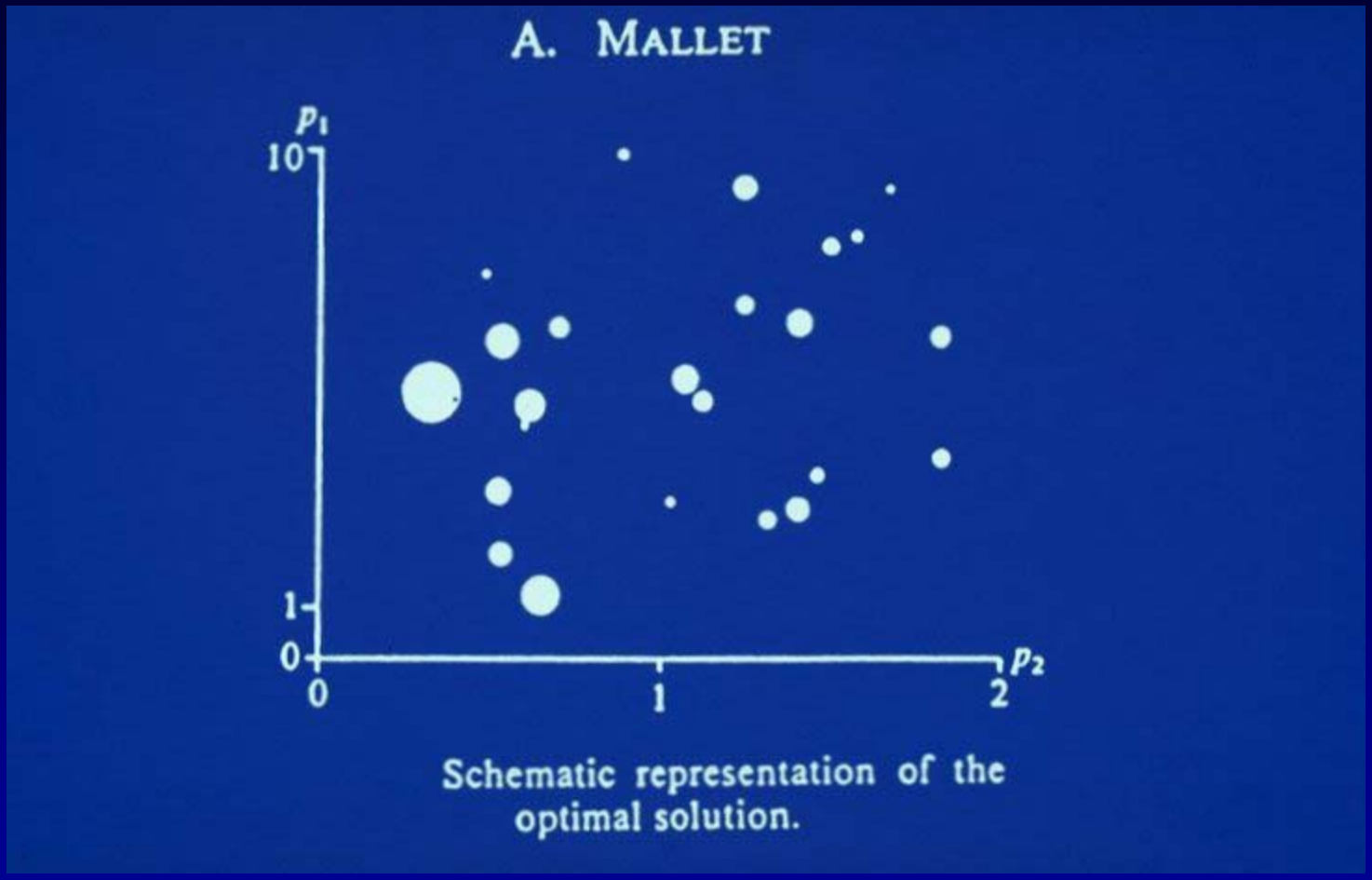
Intra - Individual Var (IIV) vs Assay SD.

- 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, (all other A's set to zero)
  - Or, an entire polynomial.
  - Or, best, Scaling the assay SD polynomial
- A summary index of quality of care given.
- Gamma often = < 2 to > 4



A Parametric Population Model
Joint Density

A Population Model, as made by Breugel



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 an equation, only by the data itself.
- Multiple indiv models, one model set per subject.
- Can discover, locate, unsuspected subpopulations.
- Get F from intermixed IV+PO dosage.

Nonparametric Population Models (2)

- The multiple models permit multiple predictions.
- Can predict precision of goal achievement by a dosage regimen.
- Behavior is consistent.
- Use IIV +/or assay SD, stated ranges.
- No signif tests yet. Bootstrap, etc. in future

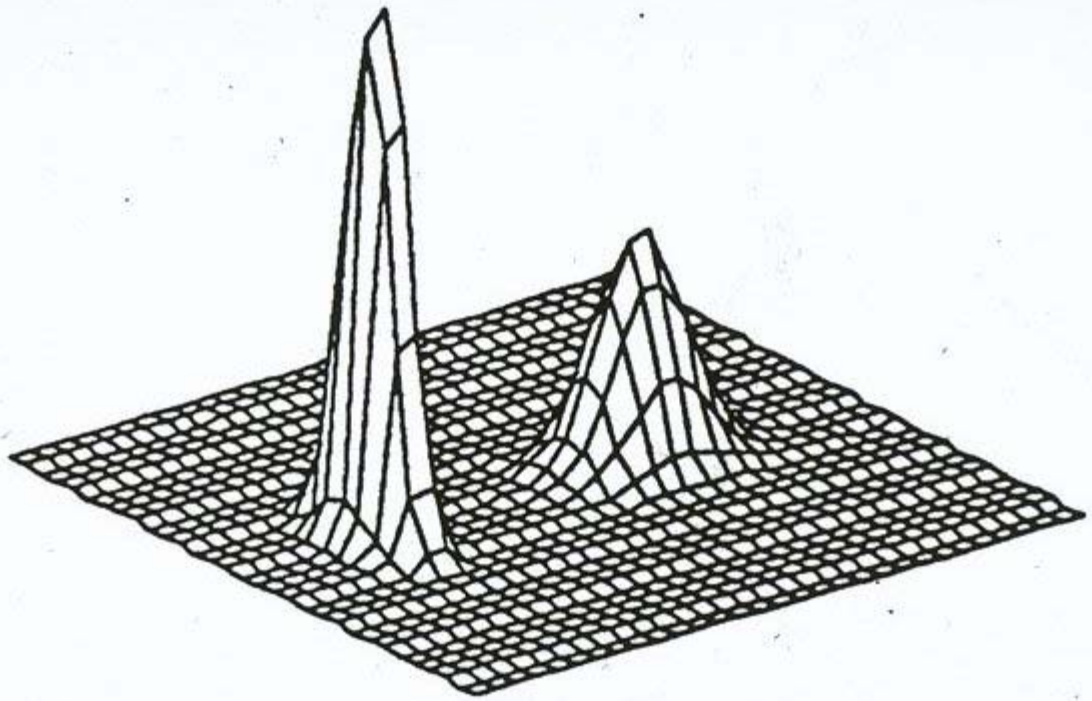


Fig. 1. True density of $\theta = (K, V)$.

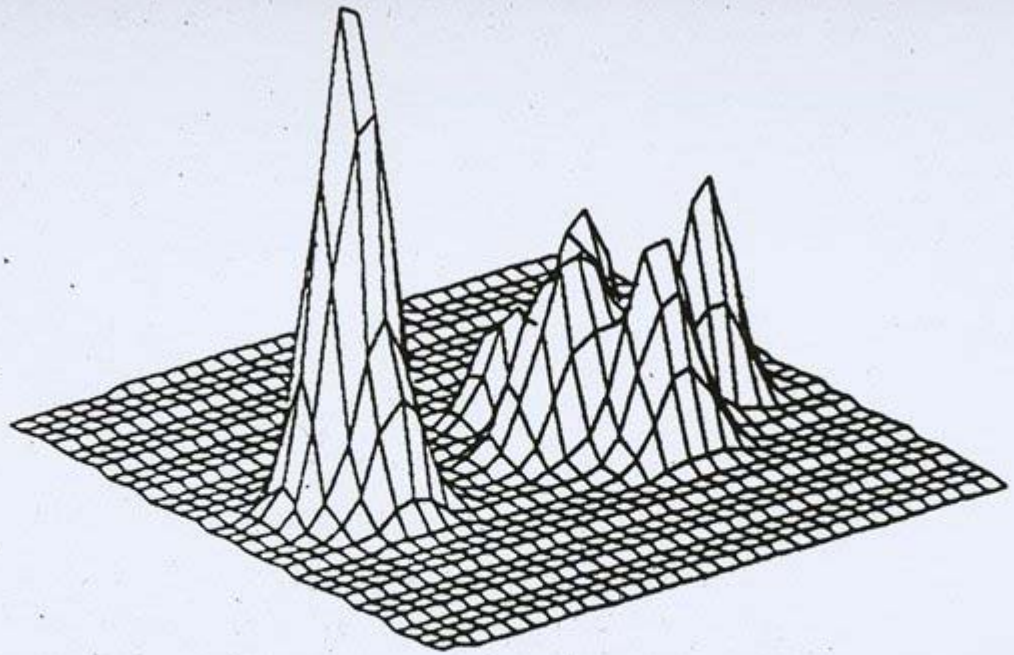


Fig. 6. Smooth empirical density of $\theta = (K, V)$. 20 subjects

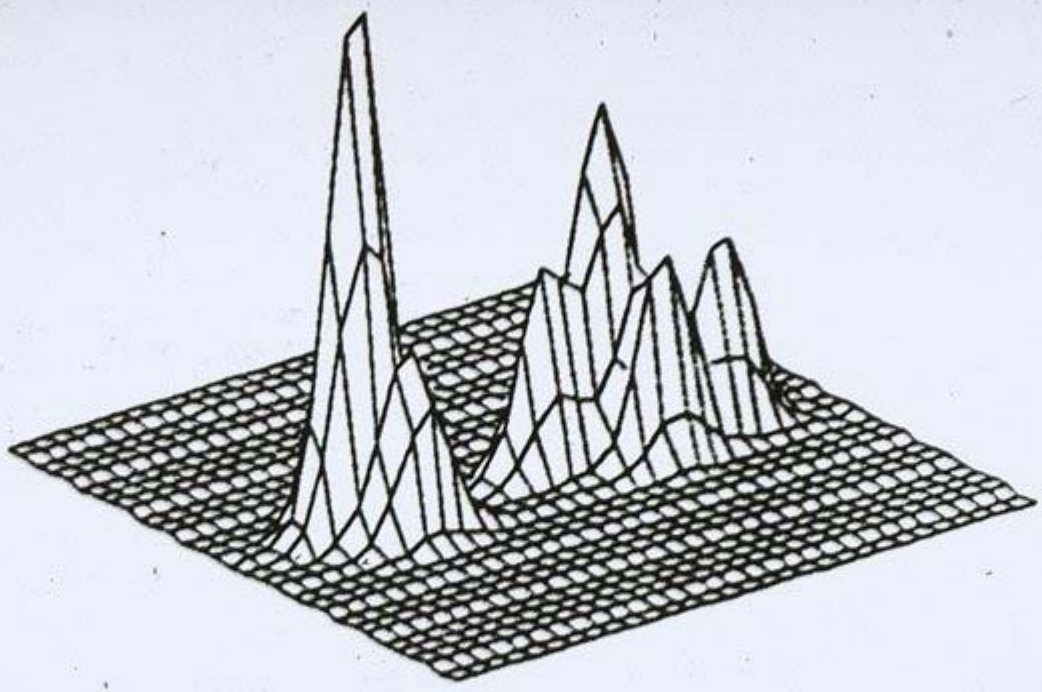


Fig. 4. Smooth estimated density of $\theta = (K, V)$.
5 levels / subject

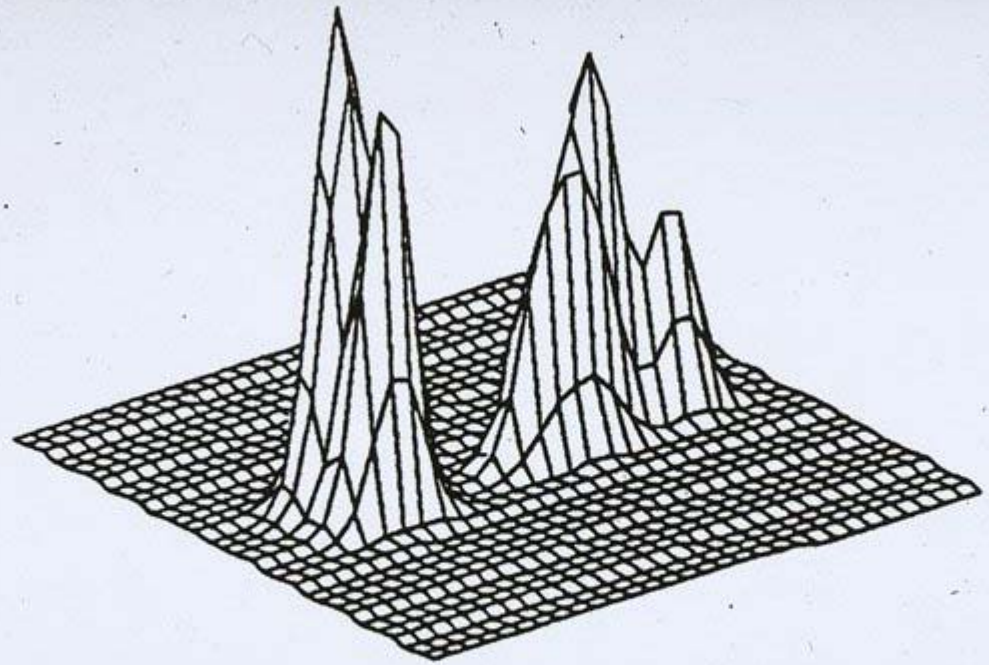


Fig. 5. Smooth estimated density of $\theta = (K, V)$.
2 levels / subject

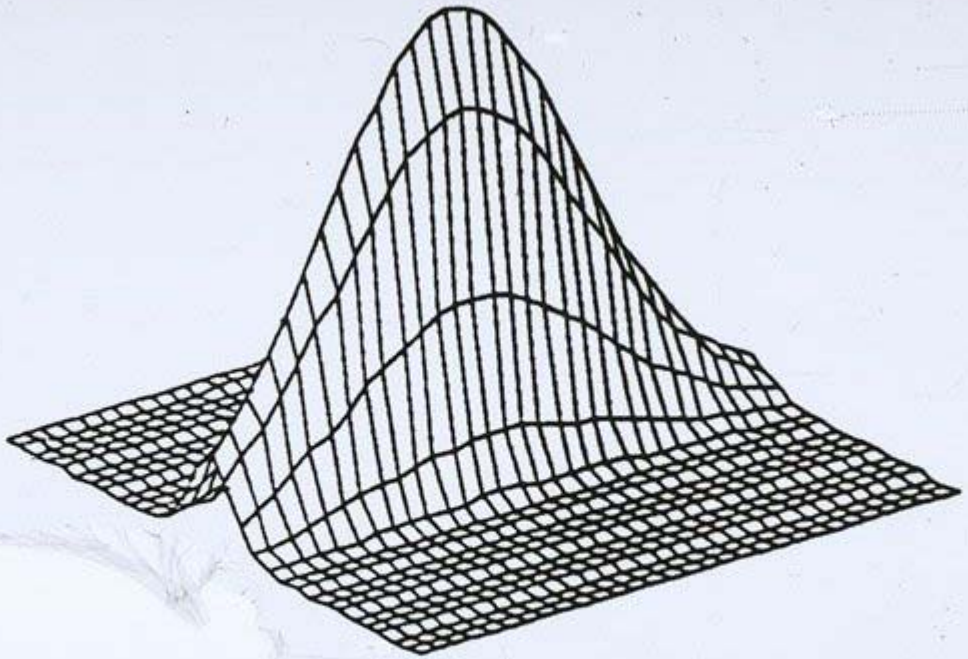


Fig. 2. Normal density of a random vector with same mean and covariance as $\theta = (K,V)$.

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.
- Use the Internet.
- SSH to SDSC Cray T3E, FTP data.
- Do the analysis, get results and density.
- FTP results back to PC, see them there.

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

Nonparametric Population Models

- Get the entire ML parameter joint density
  - Use stated ranges. Use Gamma.
  - Get multiple parameter sets, one per subject
  - Discover, locate, subpopulations
  - Can predict precision of goal achievement
  - Consistent. No signif tests yet. Bootstrap in future.

How to do Pop Modeling best?
Use Both Methods

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

Our LAPK group