We stand now at the turning point between two eras. Behind us is a past to which we can never return ...

Arthur C. Clarke

Exploration of Space (1952)

The Population Approach Identity Crisis

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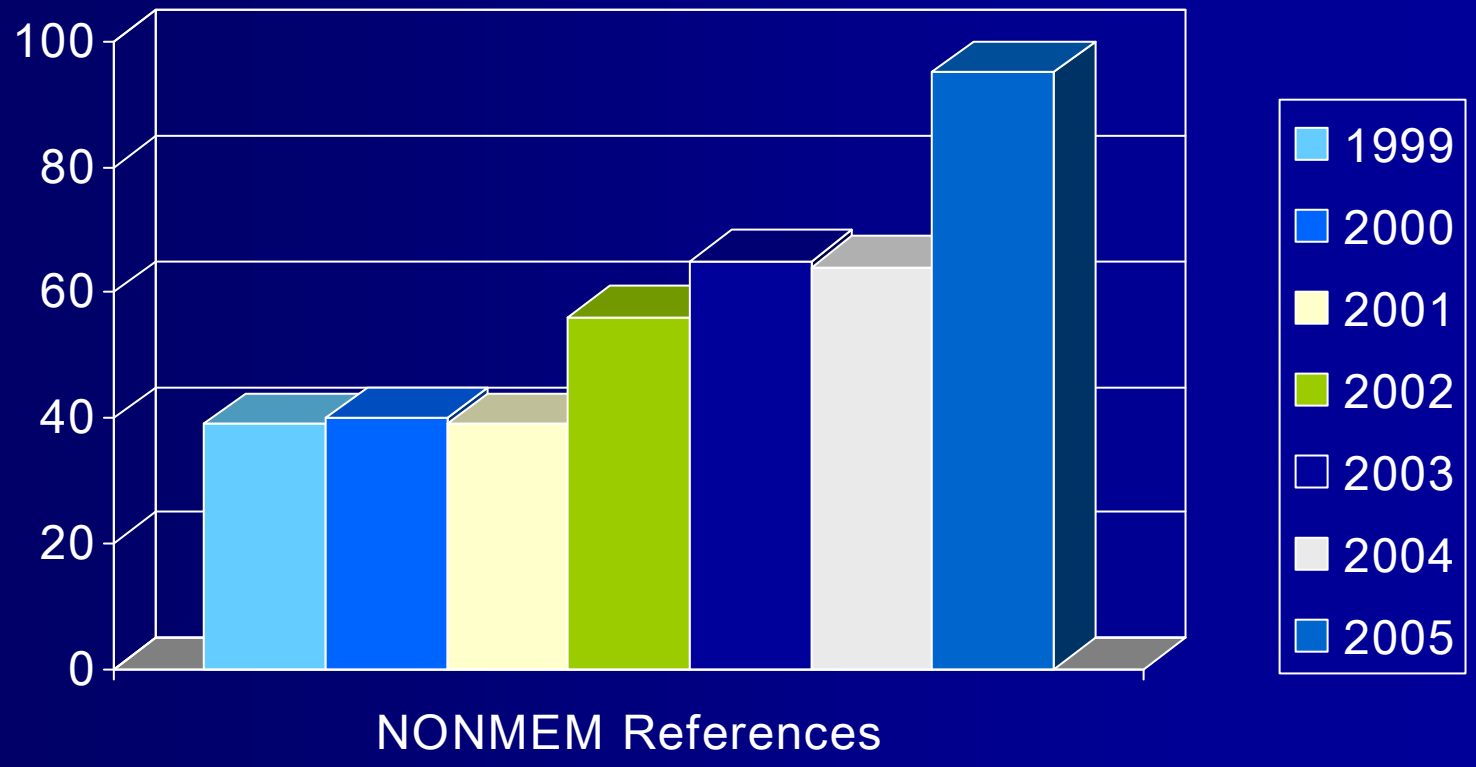
RFPK

NIBIB

NONMEM in PubMed



Data from Entrez PubMed abstract search
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=pubmed

Talk Overview

- Why population analysis?
- Asking new, different questions
- The roles of theory and software
- Tension between innovation/stagnation
- Pitfalls and user considerations
- Opportunities for future developments

Why Population Analysis?

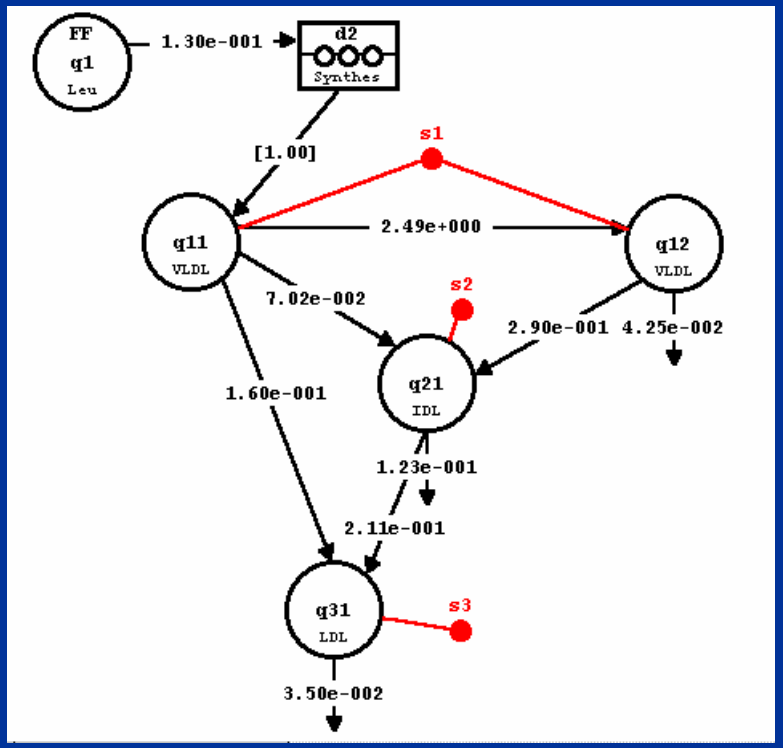
- It is widely recognized as an expedient methodology to estimate both trends and variability in clinical and preclinical response
- It has been immediately accompanied by software since the early days of its theoretical development (NONMEM)
- Very widely used and appreciated
- These are the usual answers – but is there more to it?

Individual and Population Information Content

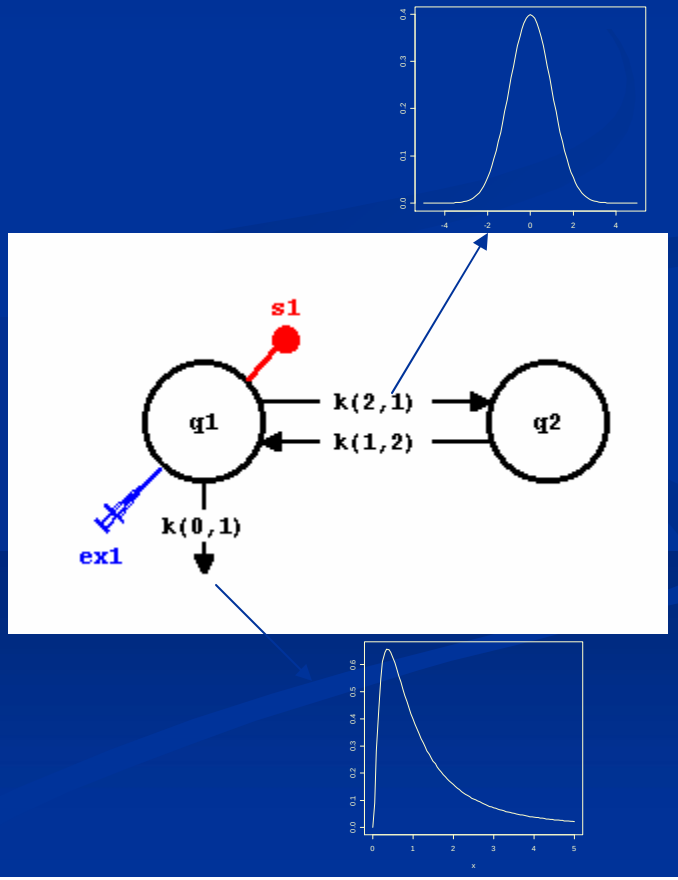
# of data per subject \ # of subjects available	Many	Few
Many	Both individual and population information are robust	Individual information is most robust
Few	Population information is most robust	Neither individual nor population information are robust

Modeling Philosophies

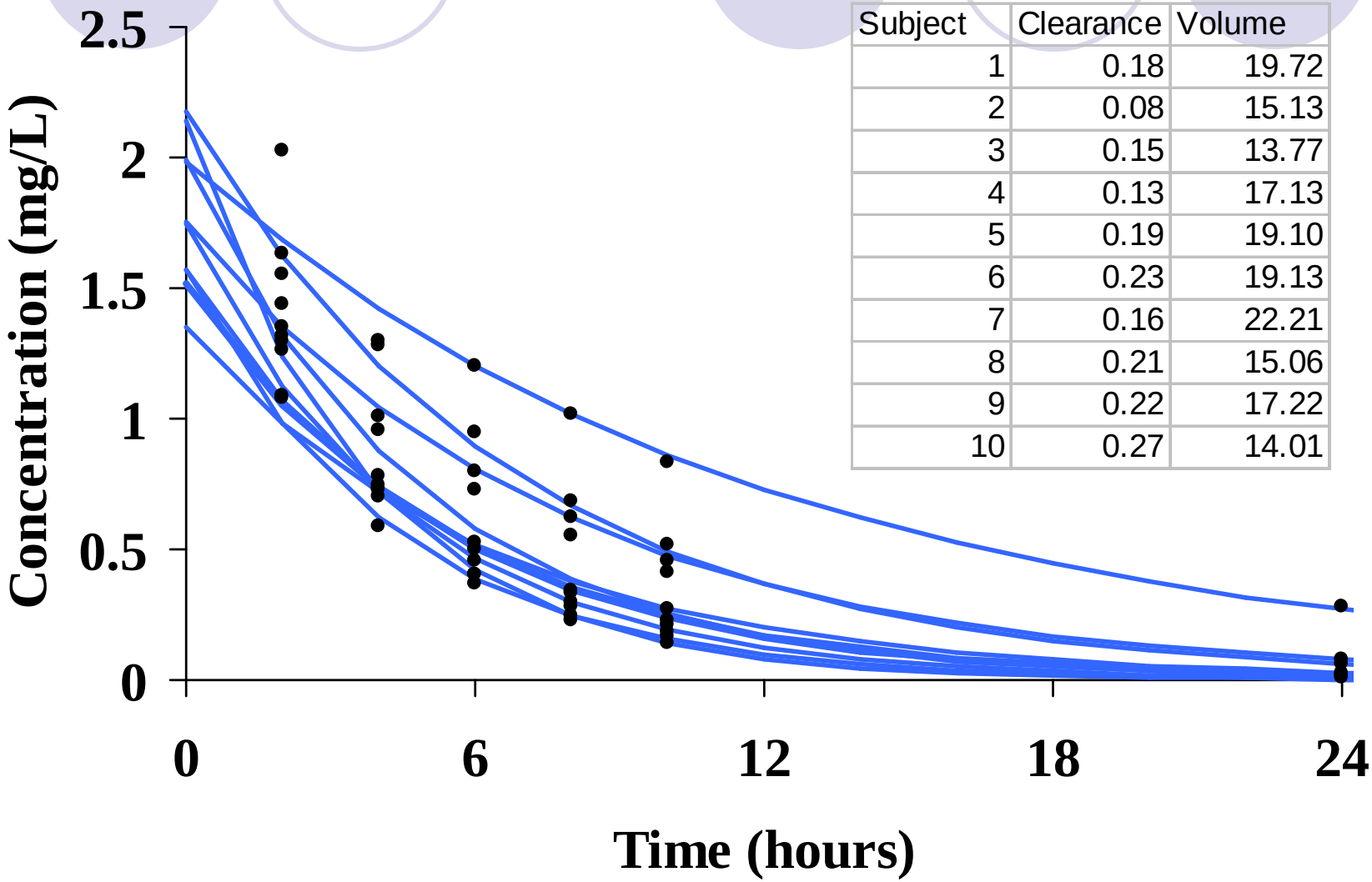
- Few subjects
- Rich data
- Individual models



- Many subjects
- Sparse data
- Population models



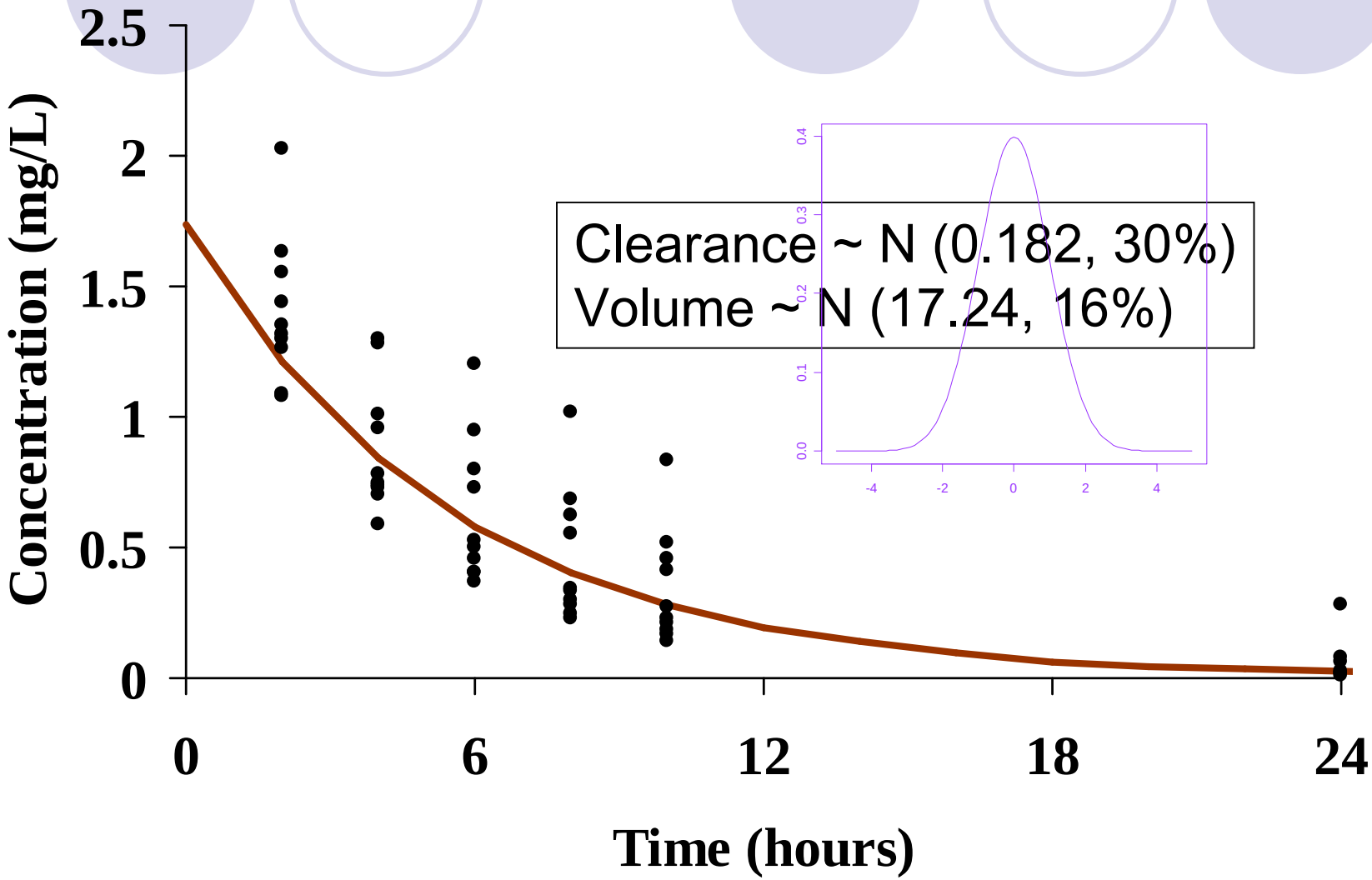
The Obvious Approach



Subject	Clearance	Volume
1	0.18	19.72
2	0.08	15.13
3	0.15	13.77
4	0.13	17.13
5	0.19	19.10
6	0.23	19.13
7	0.16	22.21
8	0.21	15.06
9	0.22	17.22
10	0.27	14.01

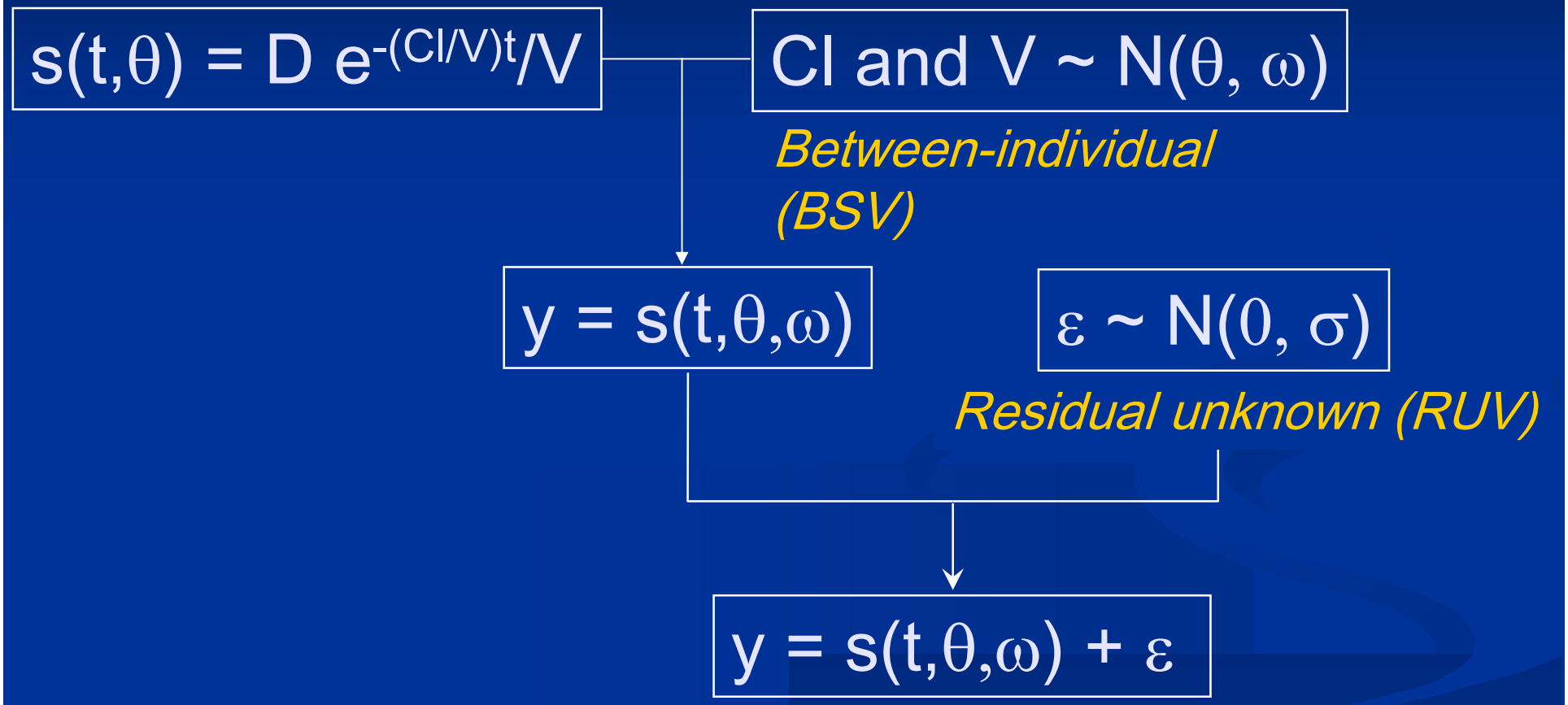
Data: cadralazine pharmacokinetics, from Wakefield, Racine-Poon et al, Applied Statistics 43,No 1, pp201-221,1994

The Population Approach



Data: cadralazine pharmacokinetics, from Wakefield, Racine-Poon et al, Applied Statistics 43,No 1, pp201-221,1994

Hierarchical Population Variability



- Simultaneous quantification of variability sources and their underlying statistics

A SWOT Analysis of the Population Approach

- Strengths
  - Increasingly used and accepted
- Weaknesses
  - Underlying theory not widely appreciated
- Opportunities
  - Rapidly widening areas of application
- Threats
  - Lack of innovation

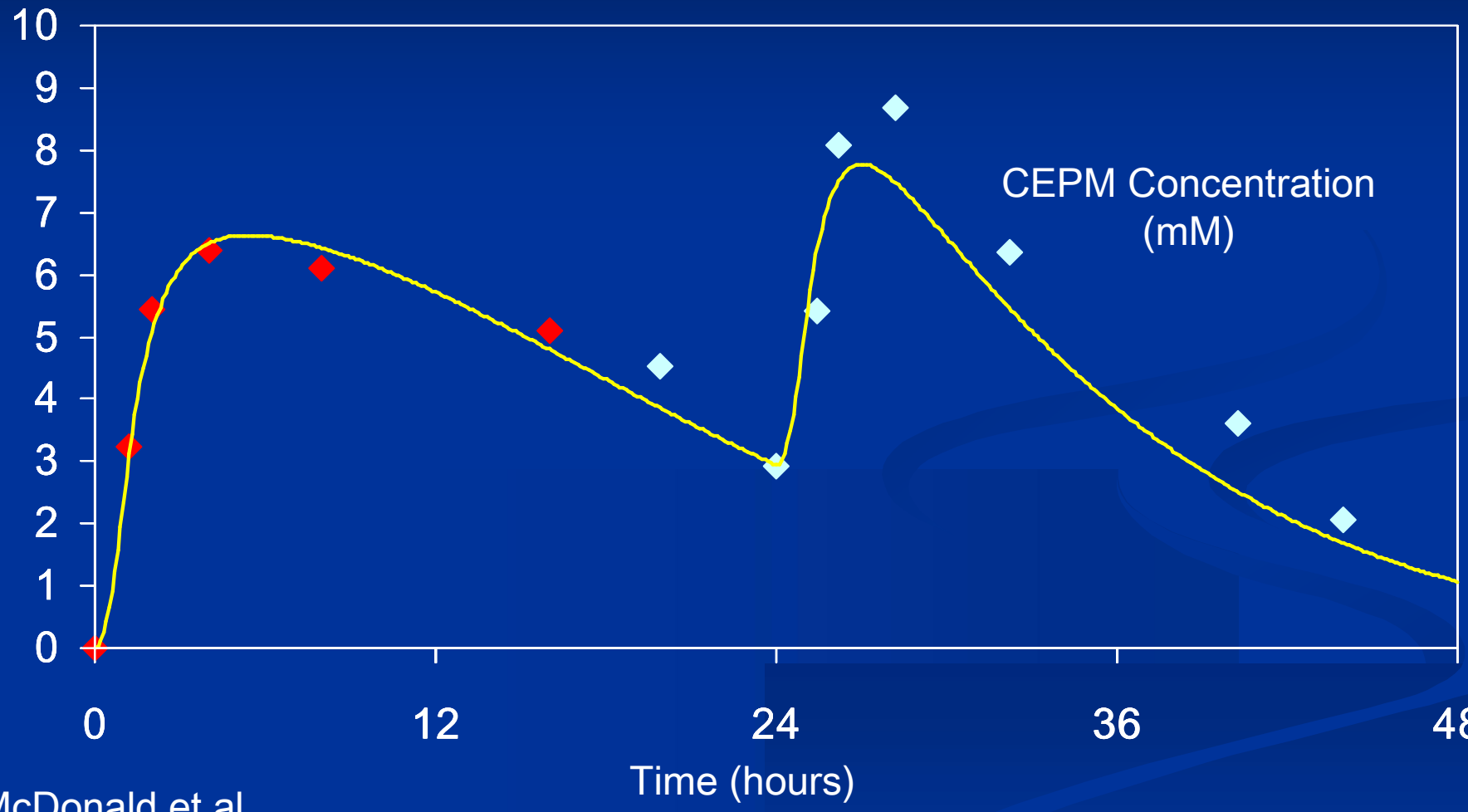
User Challenges

- The consequences of assumptions and model building are still poorly understood
- Model definition is often cumbersome and not very intuitive (elements of art and science)
- Model selection is in its infancy (more later)
- Novel methods (Bayesian) did not yet have the impact one would have expected
- The user needs to be trained on unintended consequences of common assumptions. *For example*

What Are the Real Advantages of Population Analysis?

- For parameter typical values (THETAs), naïve pooling is often adequate and may result in unbiased estimates
- What can be more accurately quantified are the *variances* (the OMEGA parameters – this has been shown already in Beal and Sheiner's original papers)
- However, this key characteristic of population analysis is often misunderstood

A Key Application: Individualized Drug Dosing

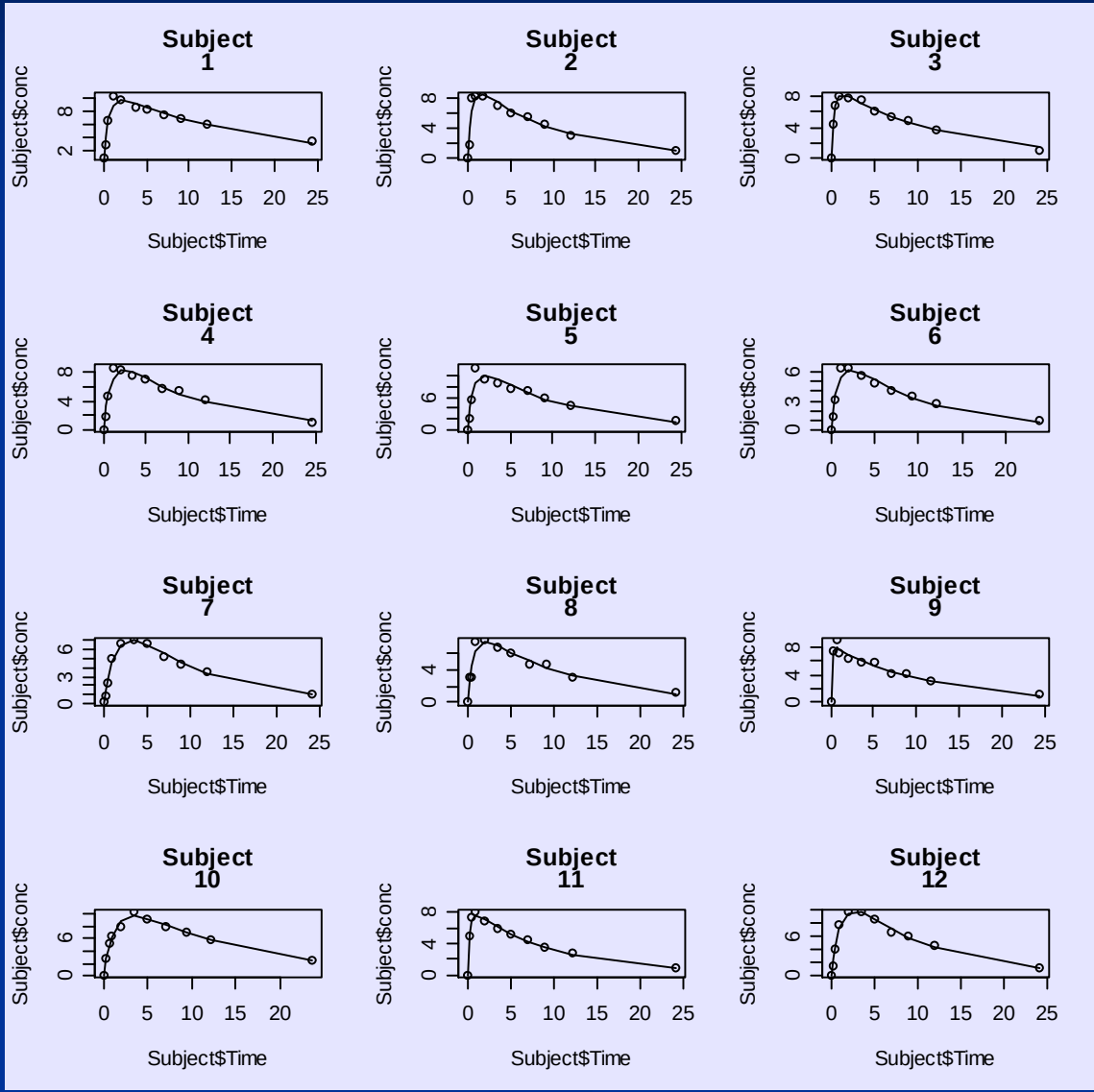


McDonald et al.
Metabolism-based cyclophosphamide dosing for hematopoietic cell transplant.
Clin Pharmacol Ther. 2005 Sep;78(3):298-308.

Why Variances?

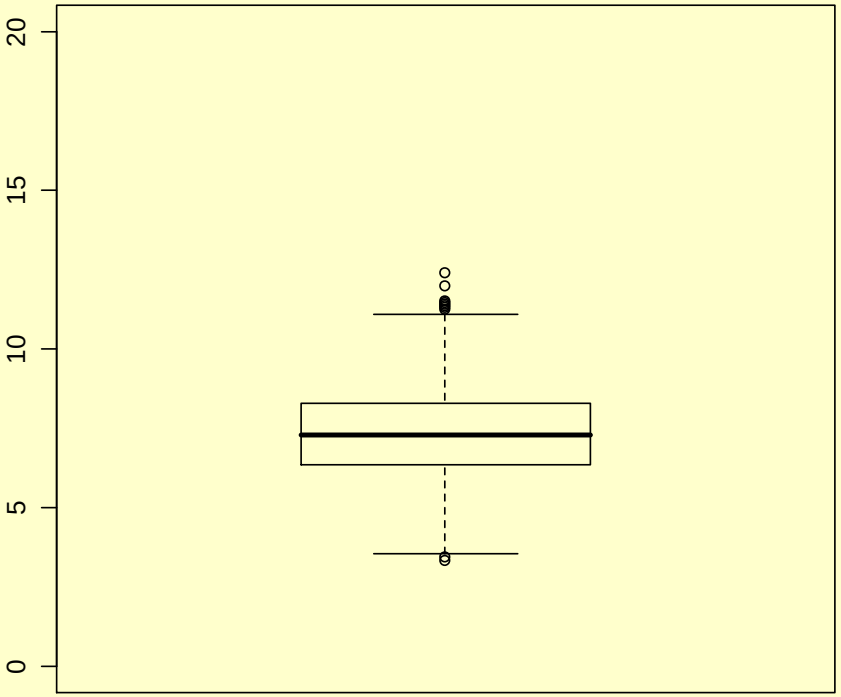
- Basically, to simulate and find covariates
- It can be said that *the entire mixed effects modeling analysis is an effort to estimate random effects variability in presence of sparse data at the individual level*
- Random effects estimates allow to correlate individual parameters with covariates and ultimately select a model
- What about *covariances*?

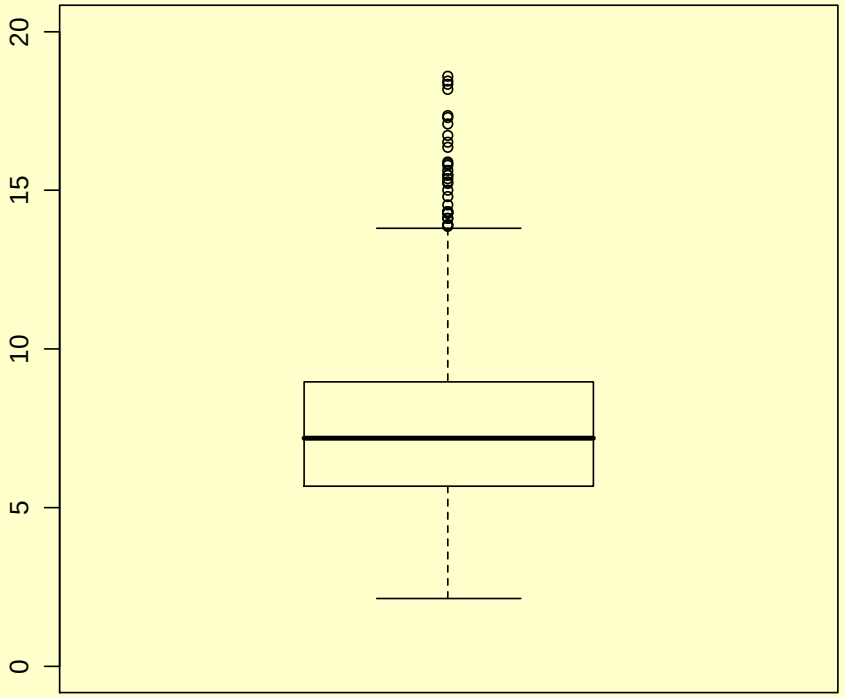
Example: Theophylline Dataset



Cmax Simulations (N=1000)

- Full Covariance
  - Median 7.34, SD 1.20
- Diagonal Covariance
  - Median 7.20, SD 2.69





Profile Simulations (N=1000)

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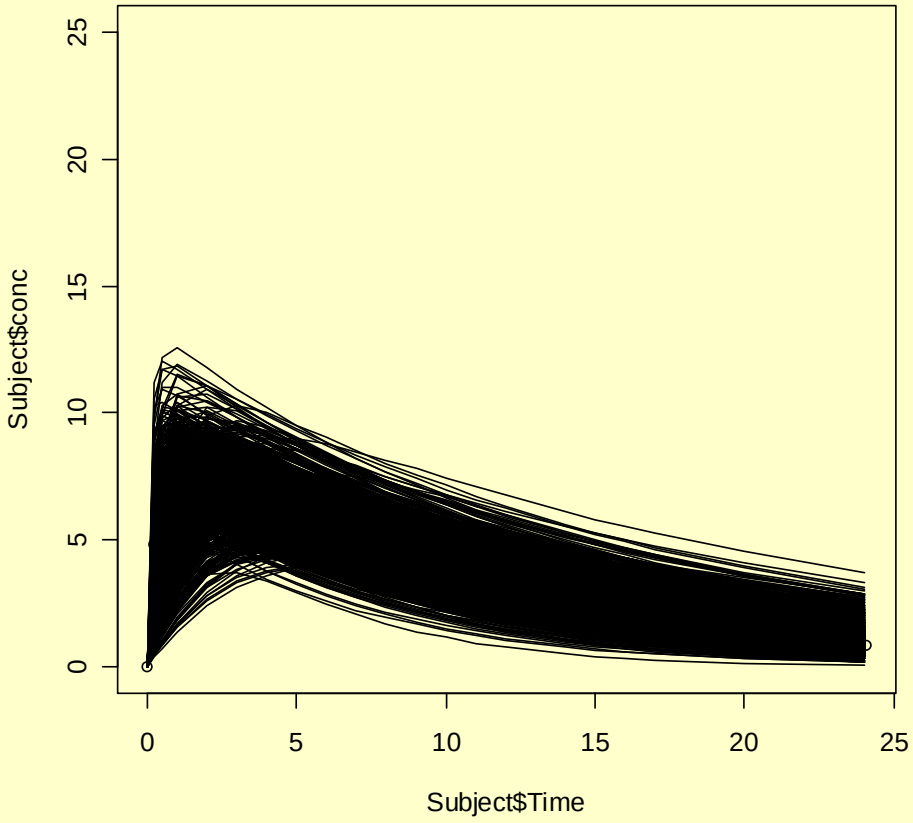
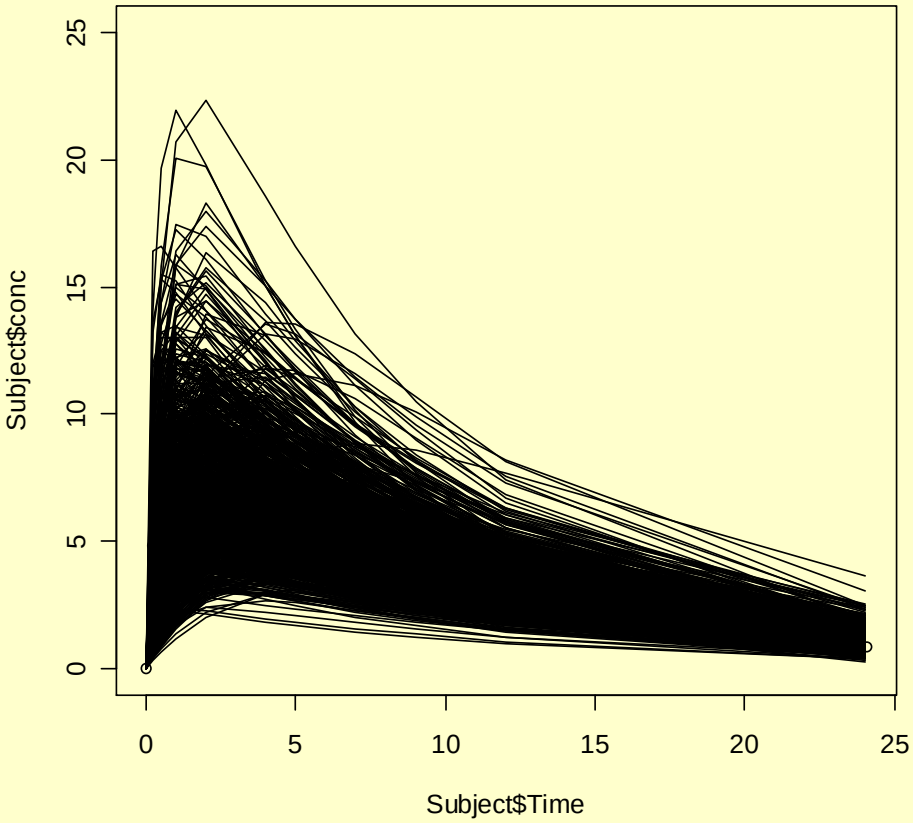
  - Median 7.34, SD 1.20
- Diagonal Covariance
  - Median 7.20, SD 2.69





The Role of Covariances

$$\omega = \begin{pmatrix} \mathrm{Var}[\eta_1] & \mathrm{Cov}[\eta_1, \eta_2] \\ \mathrm{Cov}[\eta_1, \eta_2] & \mathrm{Var}[\eta_2] \end{pmatrix} \quad \omega = \begin{pmatrix} \mathrm{Var}[\eta_1] & 0 \\ 0 & \mathrm{Var}[\eta_2] \end{pmatrix}$$

- Covariances (whether positive or negative) contribute to decreasing the variation in the simulations by generating correlated variates
- Simulations done in absence of covariance elements are bound to overestimate variation
- *But if it is so*: when was the last time you saw a population analysis where a full covariance was estimated?

An Alternative: Correlations

$$\text{CORRELATION} = \begin{pmatrix} 1.0 & \rho[\eta_1, \eta_2] \\ \rho[\eta_1, \eta_2] & 1.0 \end{pmatrix}$$

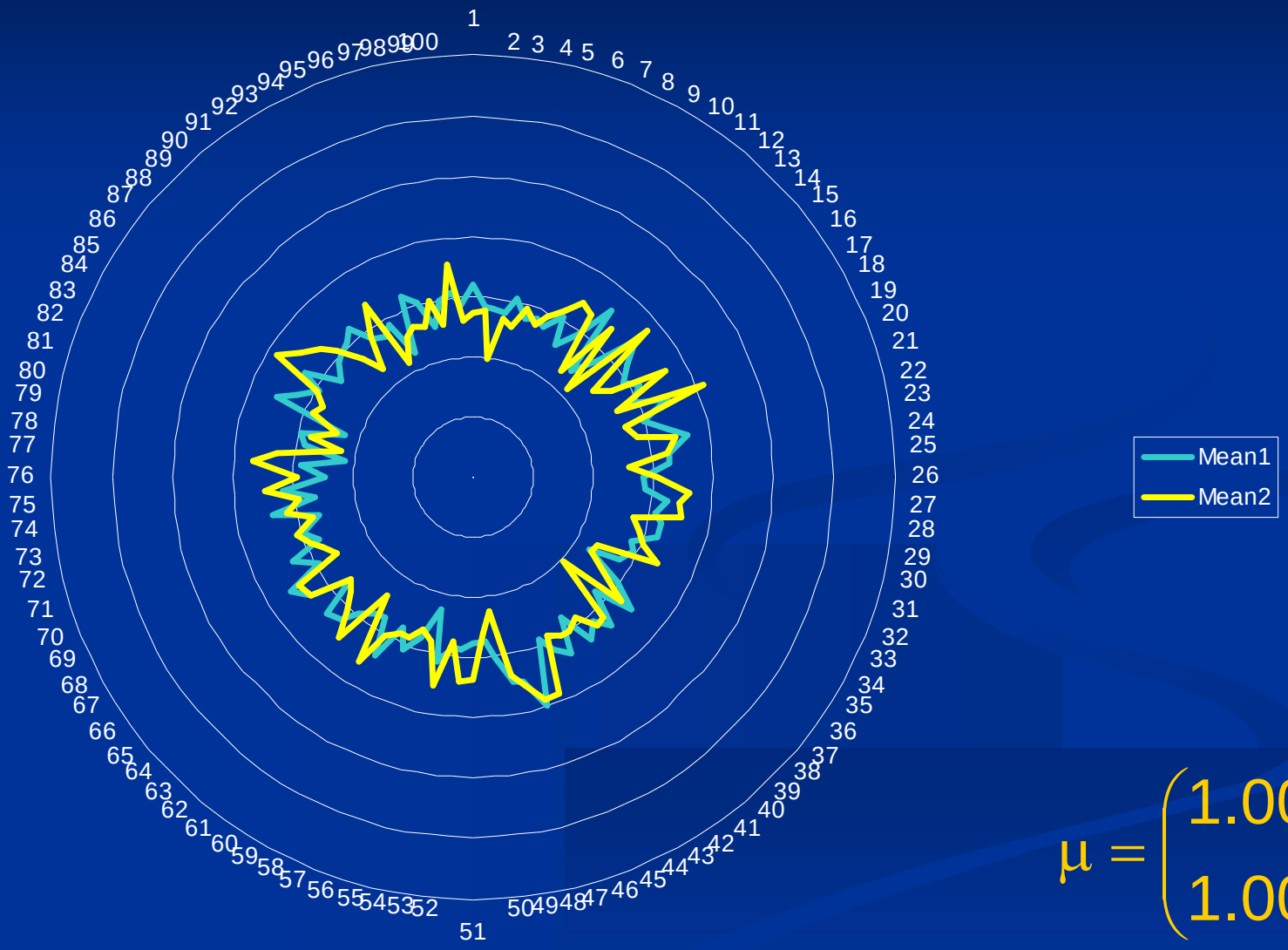
- The correlation matrix, together with the variance amounts, specifies completely the variation in the parameters
- It may be an alternative parameterization to the covariance matrix for mixed-effects modeling
- It also has the advantage of having no units (while the covariance matrix is harder to interpret)

But: How Can These Parameters Be Reliably Quantified?

- There are serious challenges in estimating reliably higher-order variation parameters
- We can do a little example to demonstrate it with reference to a covariance matrix
- We will generate a bivariate Gaussian and we will try and estimate its parameters by sample calculations with varying sample size Ns

$$\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} \sim N\left[\mu = \begin{pmatrix} 1.00 \\ 1.00 \end{pmatrix}, \omega = \begin{pmatrix} 1.00 & 0.50 \\ 0.50 & 2.00 \end{pmatrix}\right]$$

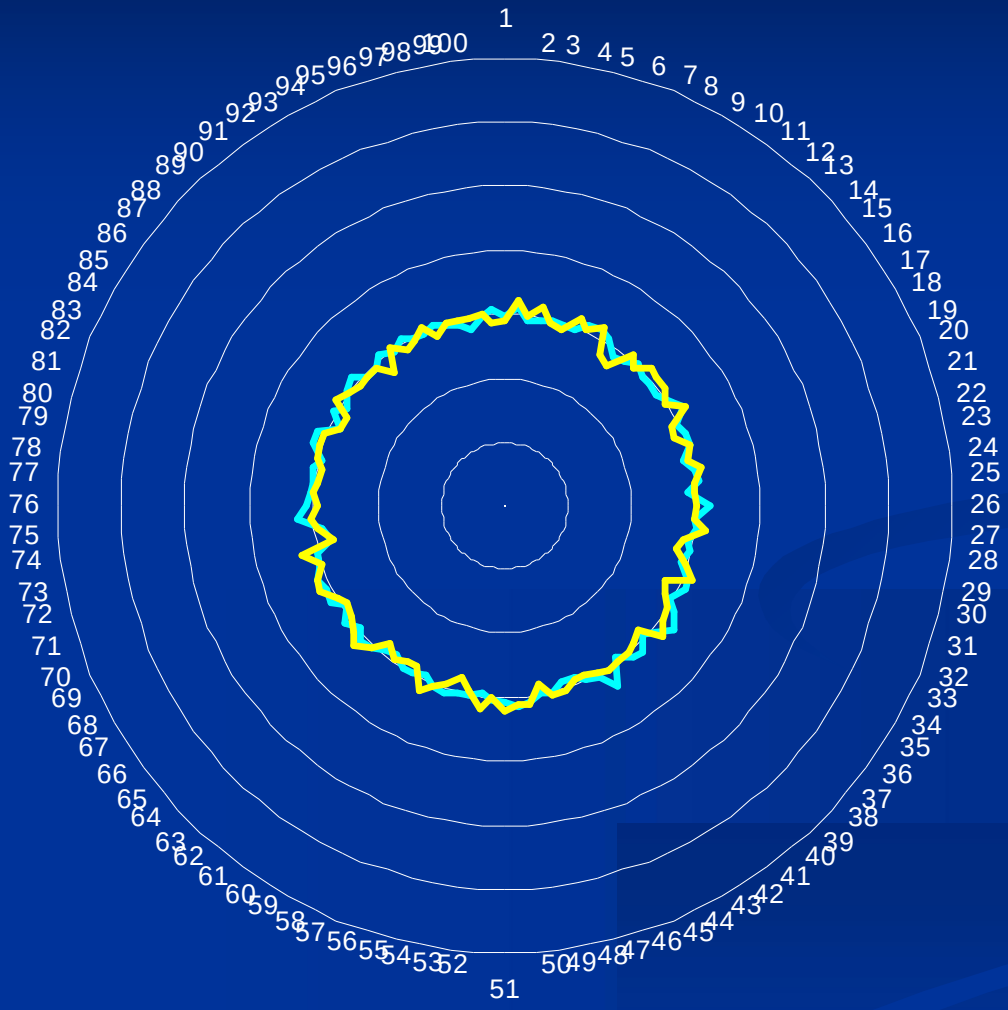
Mean Estimates – Ns=10



$$\mu = \begin{pmatrix} 1.00 \\ 1.00 \end{pmatrix}$$

Radar plot of 100 replicates

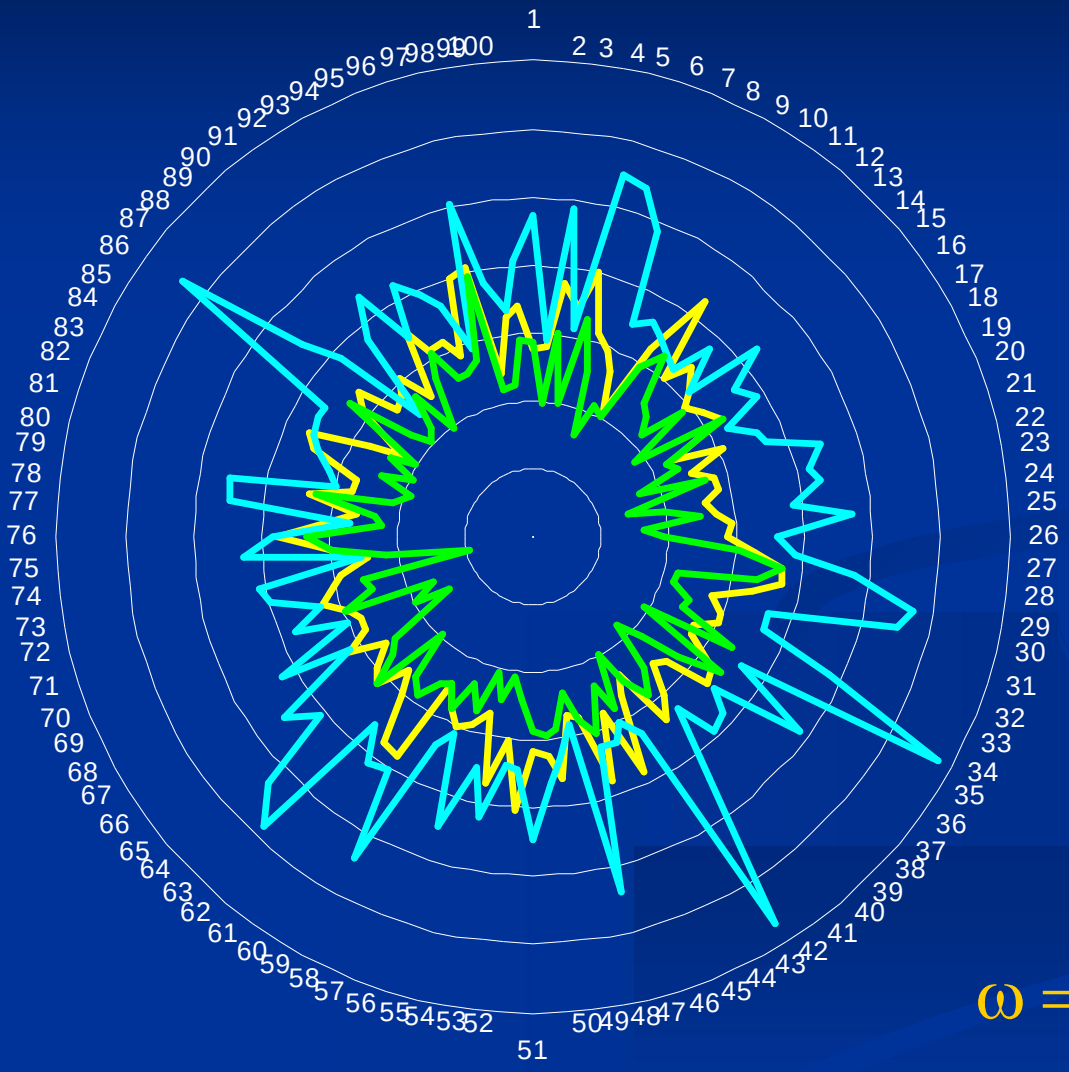
Mean Estimates – Ns=100



$$\mu = \begin{pmatrix} 1.00 \\ 1.00 \end{pmatrix}$$

Radar plot of 100 replicates

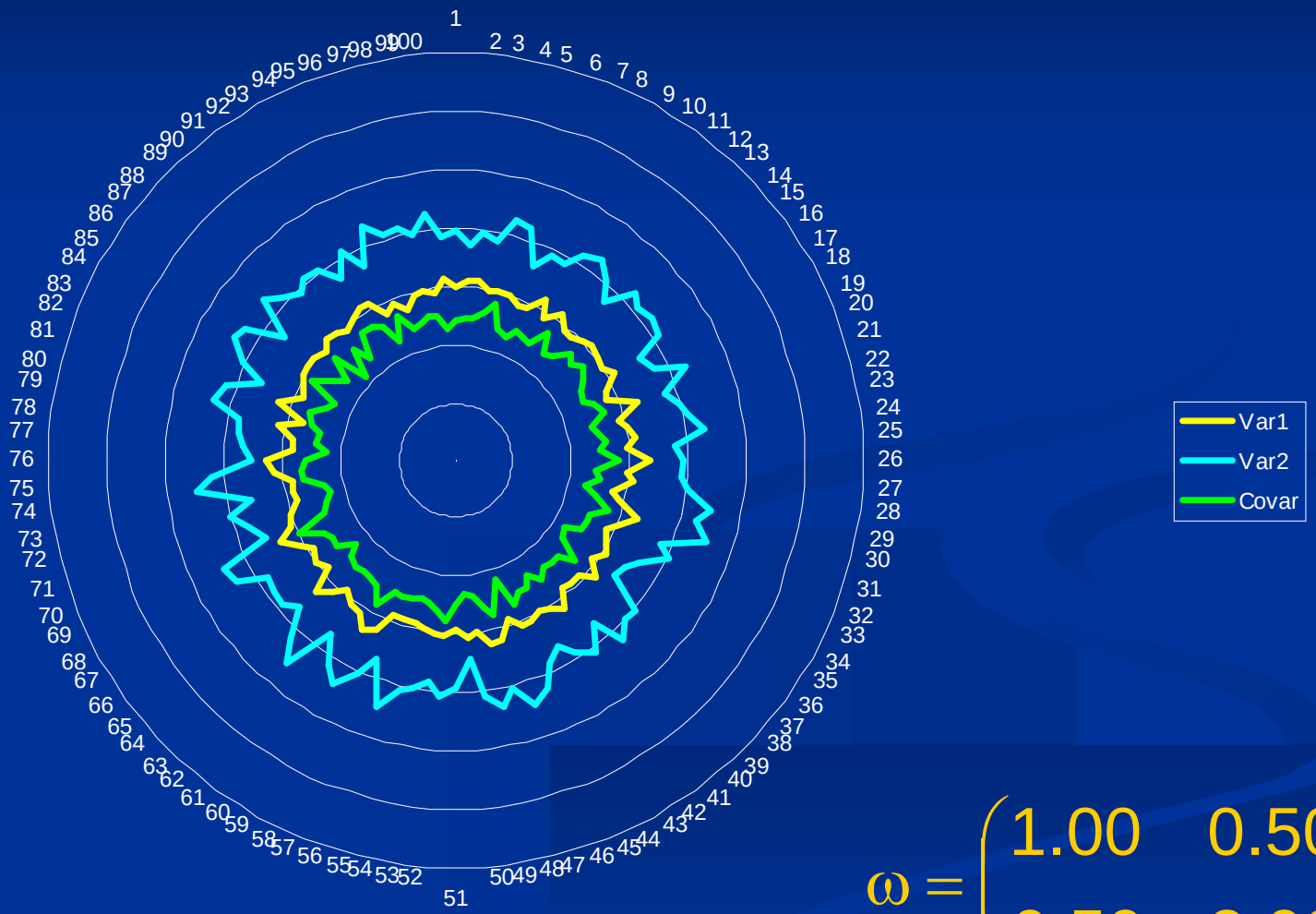
Variability Estimates – Ns=10



$$\omega = \begin{pmatrix} 1.00 & 0.50 \\ 0.50 & 2.00 \end{pmatrix}$$

Radar plot of 100 replicates

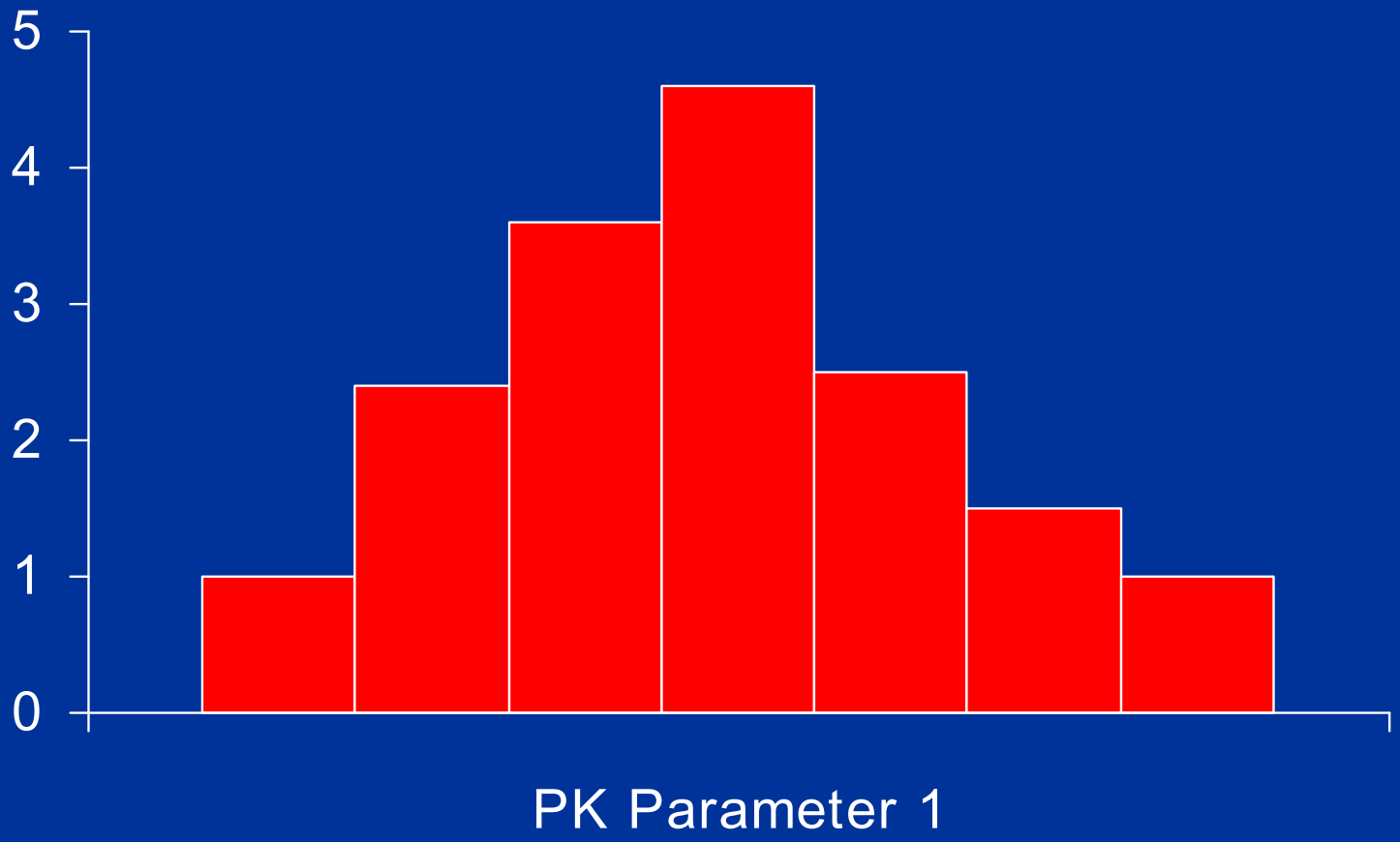
Variability Estimates – Ns=100



$$\omega = \begin{pmatrix} 1.00 & 0.50 \\ 0.50 & 2.00 \end{pmatrix}$$

Radar plot of 100 replicates

Which Measurements?



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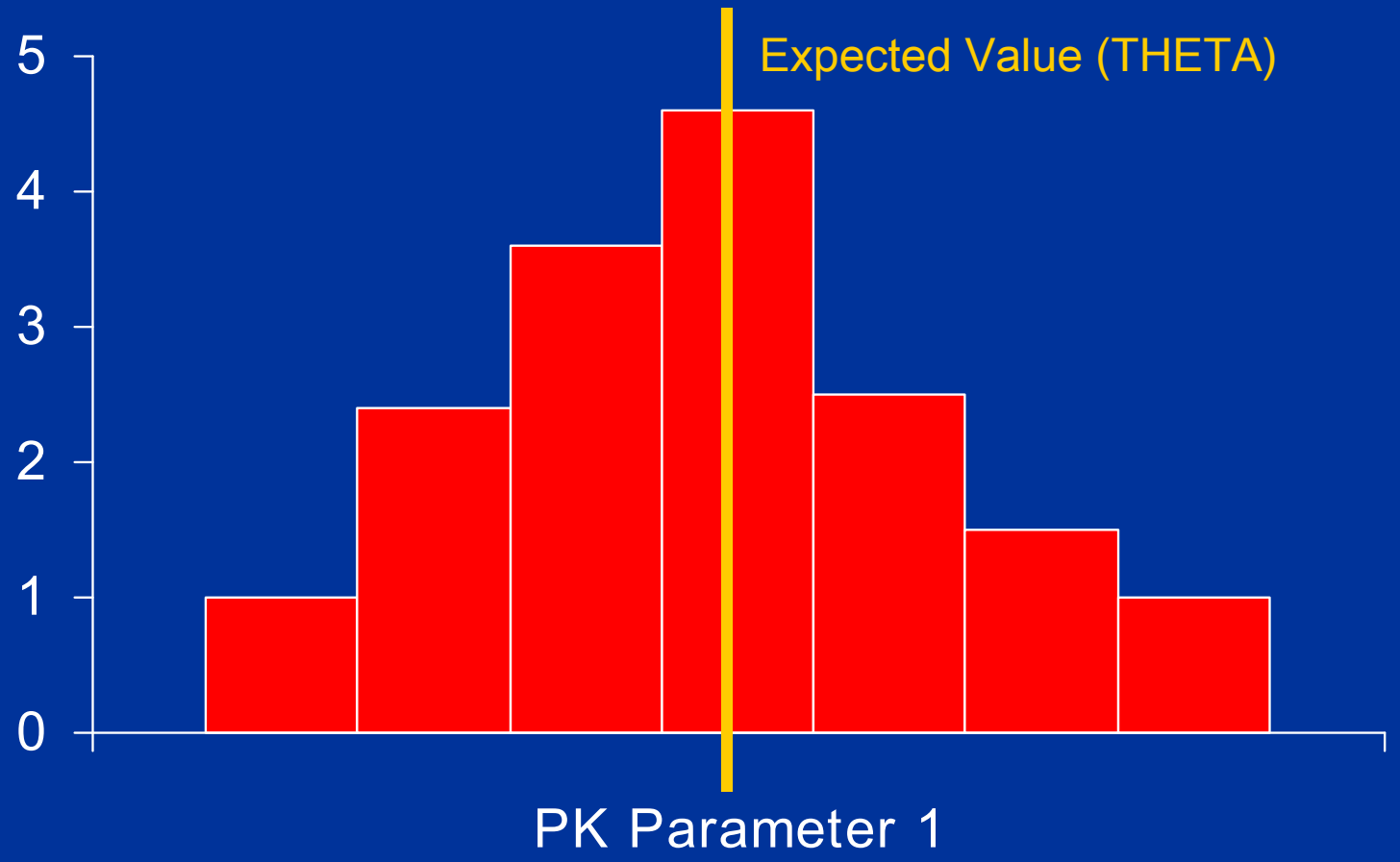
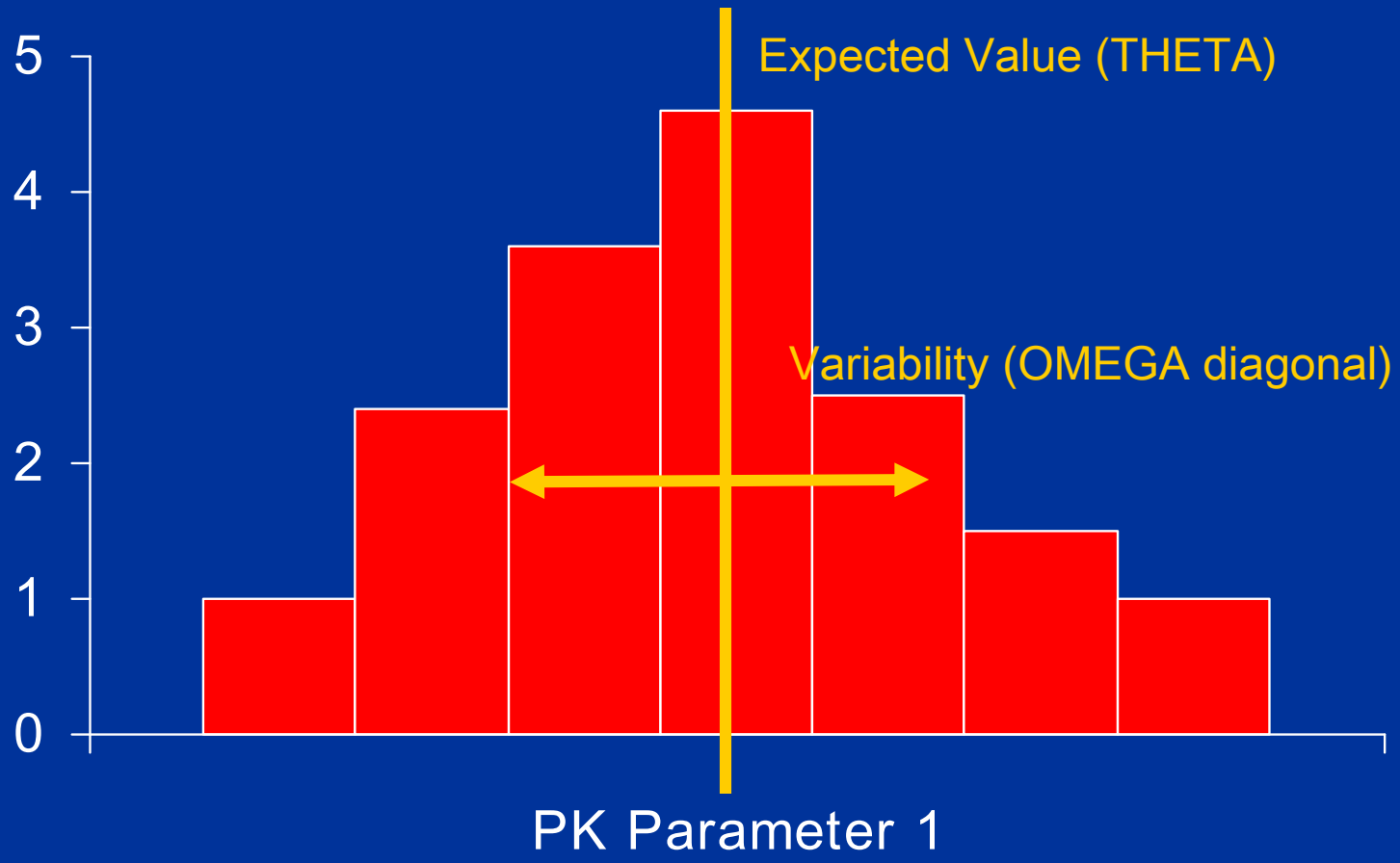


Which Measurements?



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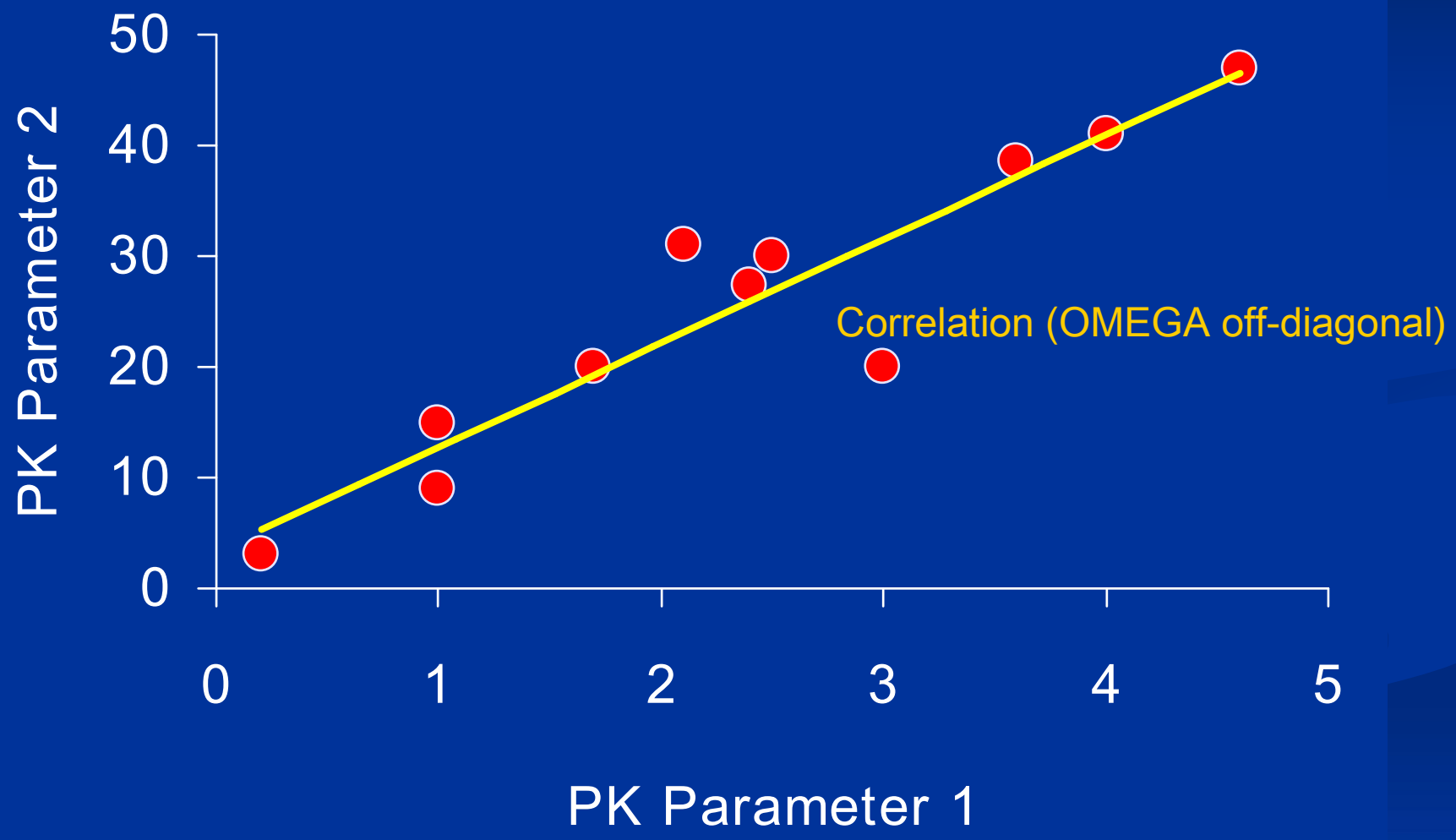
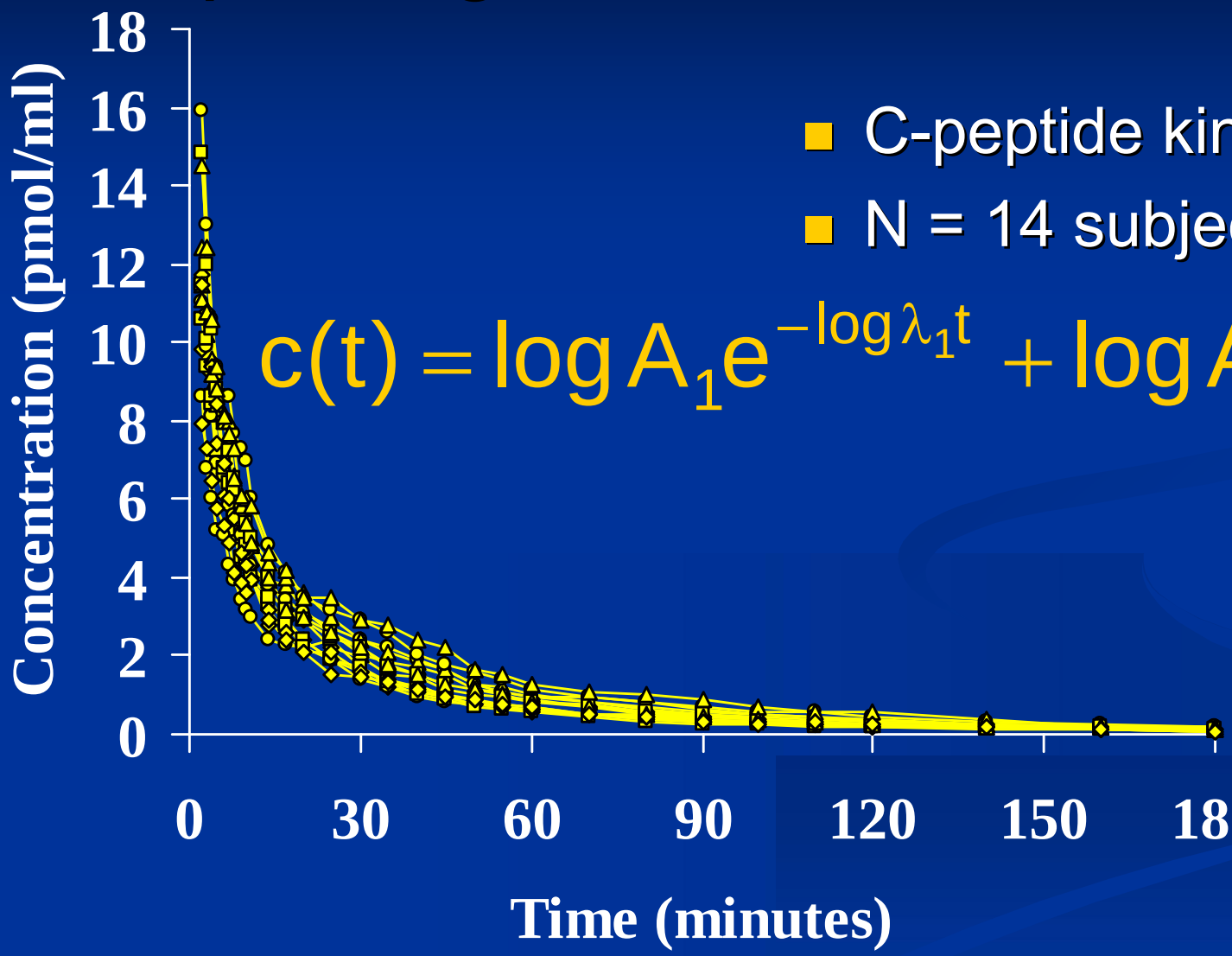


Improving Covariance Estimation



- C-peptide kinetics
- N = 14 subjects

$$c(t) = \log A_1 e^{-\log \lambda_1 t} + \log A_2 e^{-\log \lambda_2 t}$$

Data from IEEE Trans Biomed Eng. 2000 Jun;47(6):801-11

Population Models

- 14 subjects
- Population model with full random effects covariance
  - 4 THETAs
  - 4 OMEGAs
  - 1 SIGMA
- 9 parameters

- 14 subjects
- Population model with diagonal random effects covariance
  - 4 THETAs
  - 8 OMEGAs
  - 1 SIGMA
- 13 parameters

Role of Starting Values

FULL BSV (Minimum SPK Objective Function: 18.7376)

THETA(1)	2.44	(3)
THETA(2)	1.51	(5)
THETA(3)	-1.54	(3)
THETA(4)	-3.63	(1)

DIAGONAL BSV (Minimum SPK Objective Function: 23.5369)

THETA(1)	2.42	(2)
THETA(2)	1.49	(4)
THETA(3)	-1.54	(3)
THETA(4)	-3.64	(1)

Importance of Good Starting Values

- Diagonal BSV Covariance

$$\text{OMEGA} = \begin{bmatrix} 0.0483\,(29) & & & \\ & 0.0472\,(29) & & \\ & & 0.0191\,(42) & \\ & & & 0.0054\,(99) \end{bmatrix}$$

- Full BSV Covariance (seeded with STS)

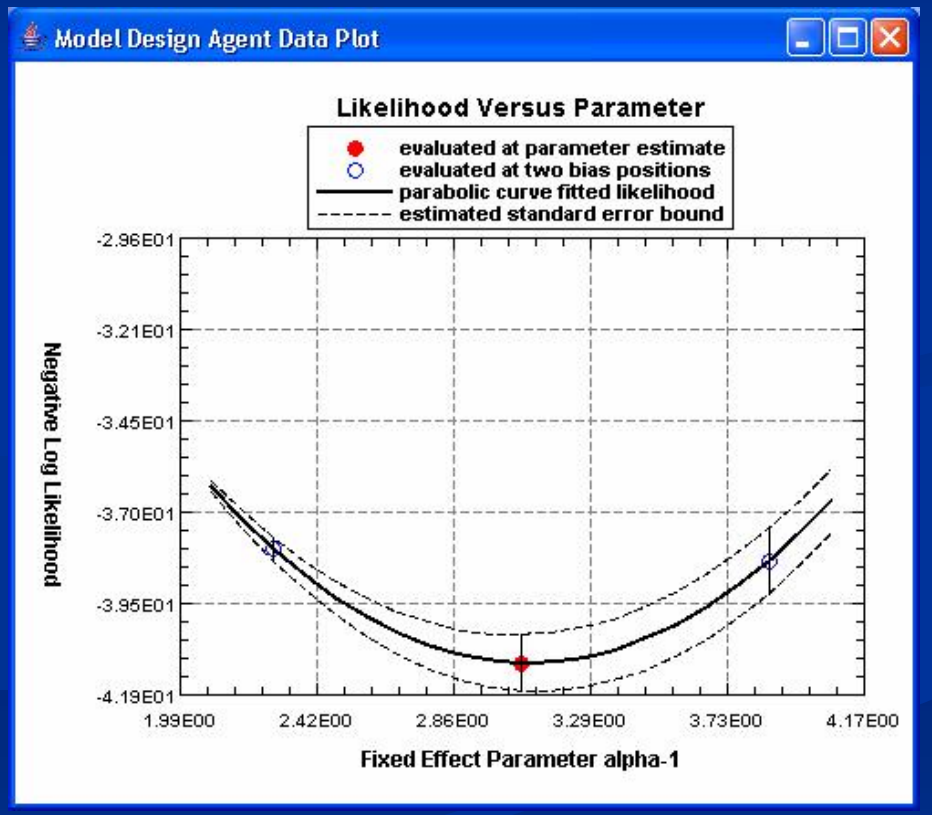
$$\text{OMEGA} = \begin{bmatrix} 0.0483\,(28) & 0.0239\,(55) & 0.0148\,(53) & 0.0092\,(44) \\ & 0.0442\,(34) & 0.0142\,(62) & -0.0051\,(117) \\ & & 0.0226\,(28) & 0.0025\,(169) \\ & & & 0.0052\,(93) \end{bmatrix}$$

Estimate Reliability

- While nonlinear mixed effects models work well for noisy and sparse data, they will not estimate everything reliably
- Some key parameters may be out of reach of this methodology, *even with extremely large data sets*
- Solutions (Bayesian?) may have to employ novel techniques to detect weak signals and/or uncertain estimates

Proposed Model Diagnostic: Monte Carlo Likelihood

- The "true" marginal likelihood can be evaluated at and near a parameter estimate, *however obtained*
- This enables us to compare the relative performance of methods that optimize *different approximations* to the marginal likelihood

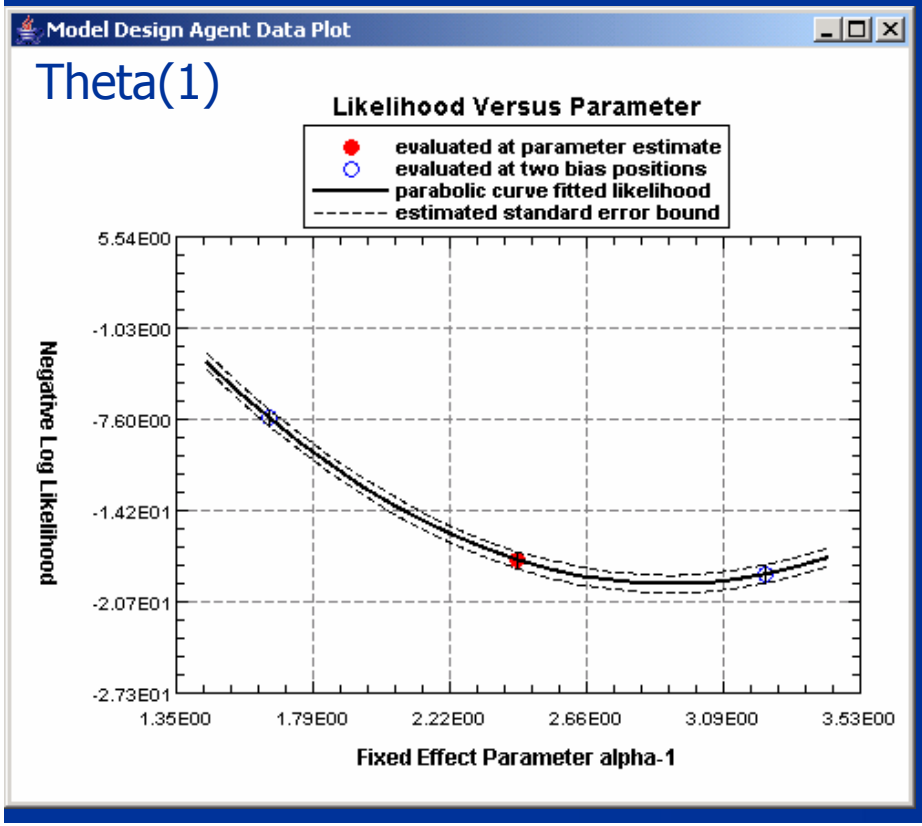


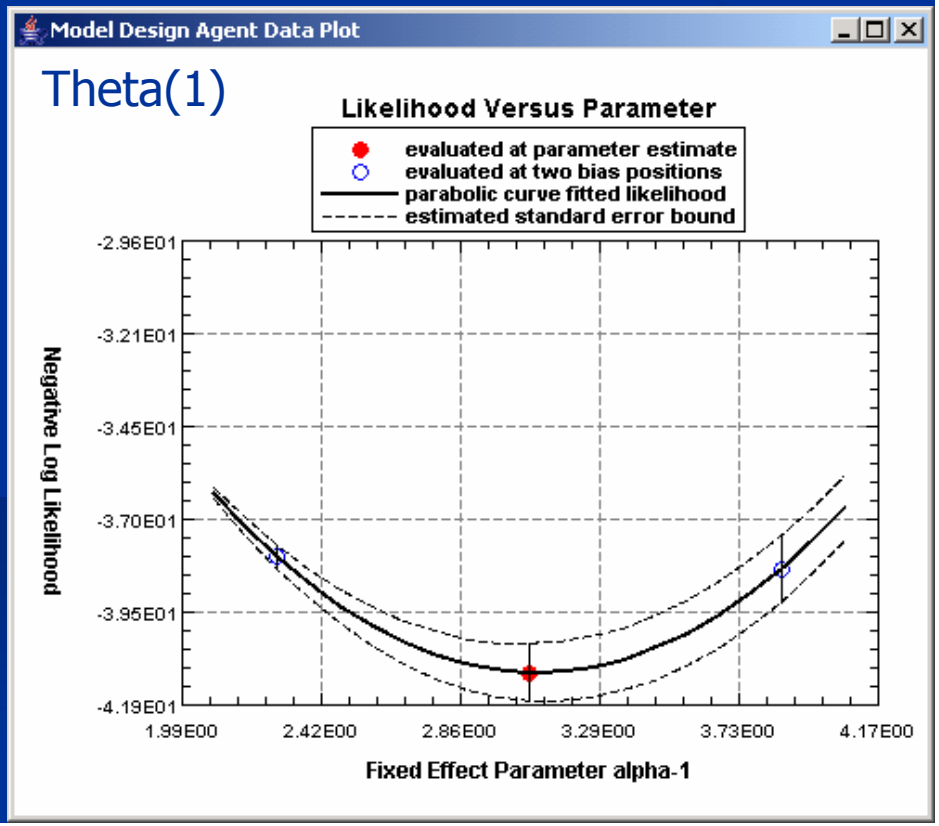
Post-Optimality Check

(Cadralazine Data, One-Compartment CL,V Model)

- First Order OF:
  - –43.9216
- Grid Likelihood:
  - –17.824±0.621

- Expected Hessian OF:
  - –39.5094
- Grid Likelihood:
  - –41.089±0.748





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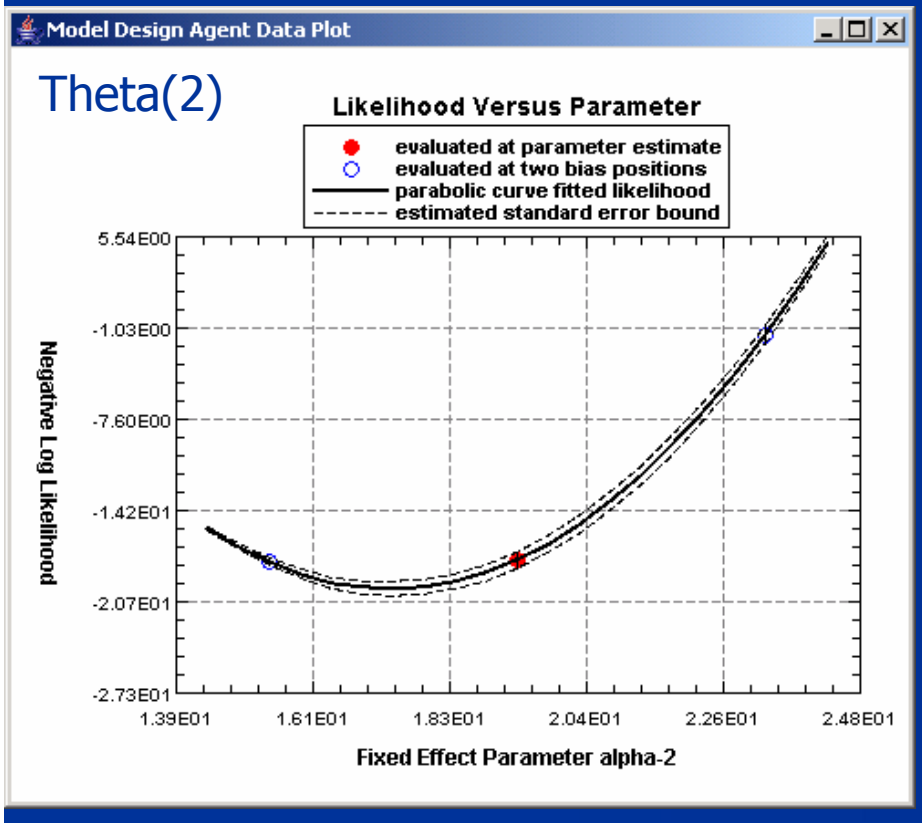

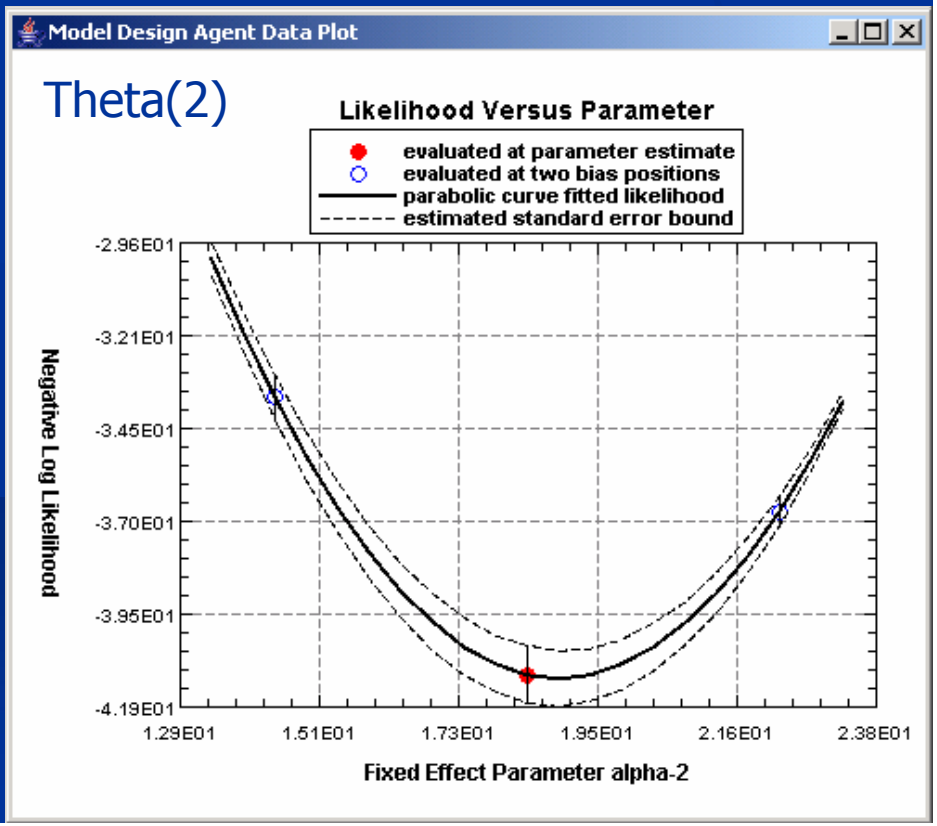

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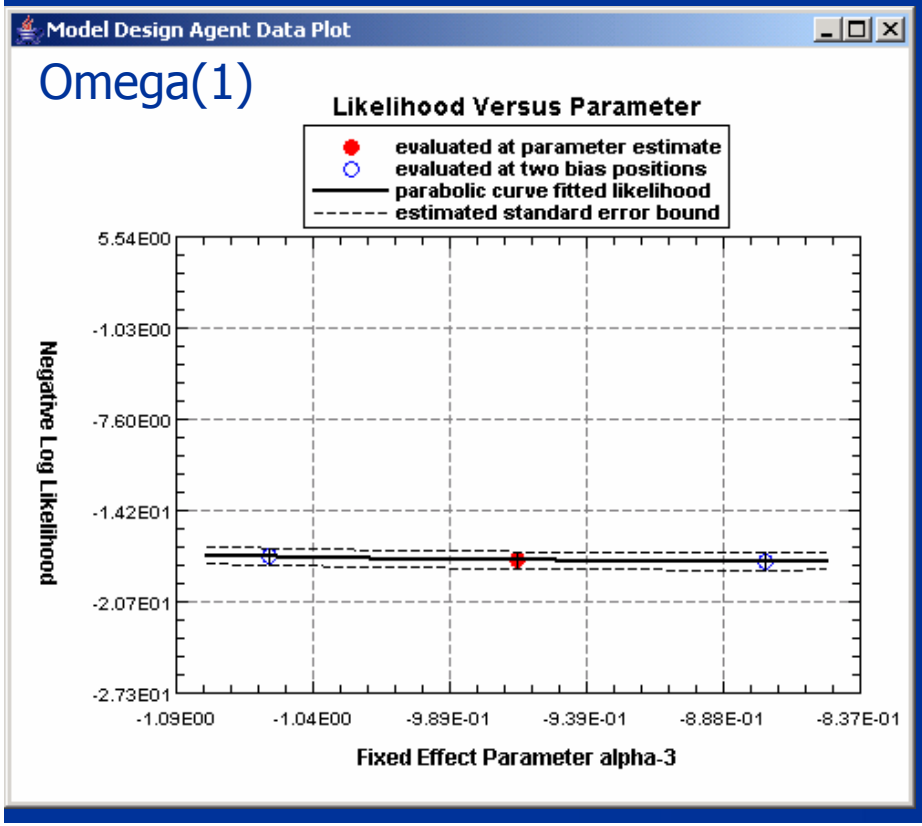

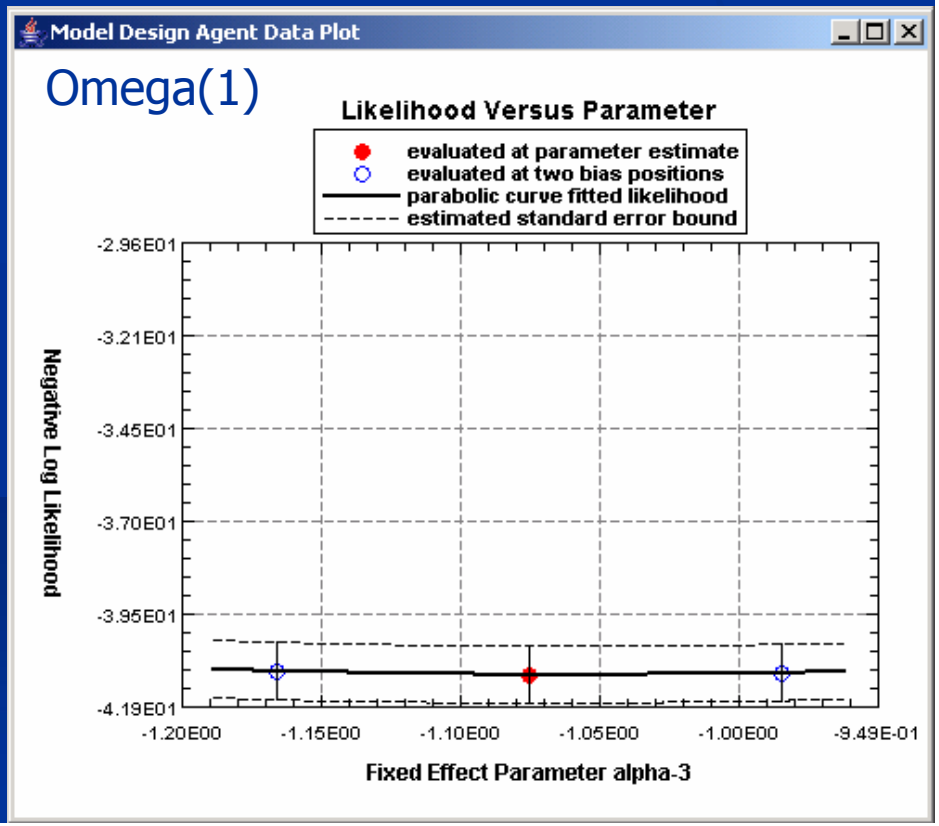

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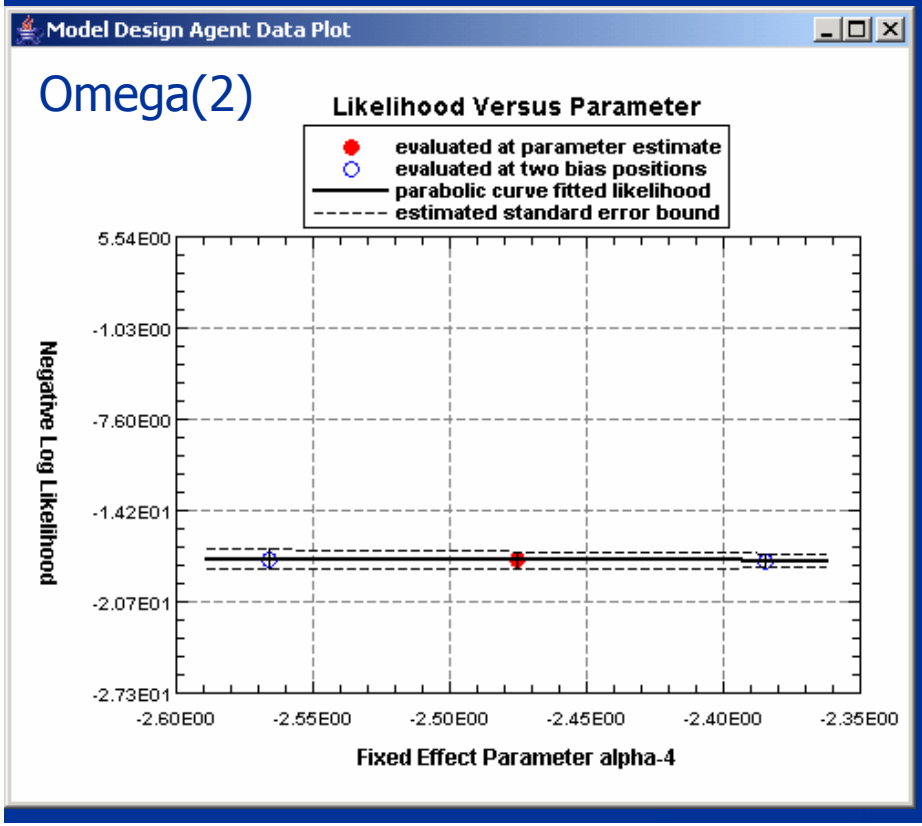

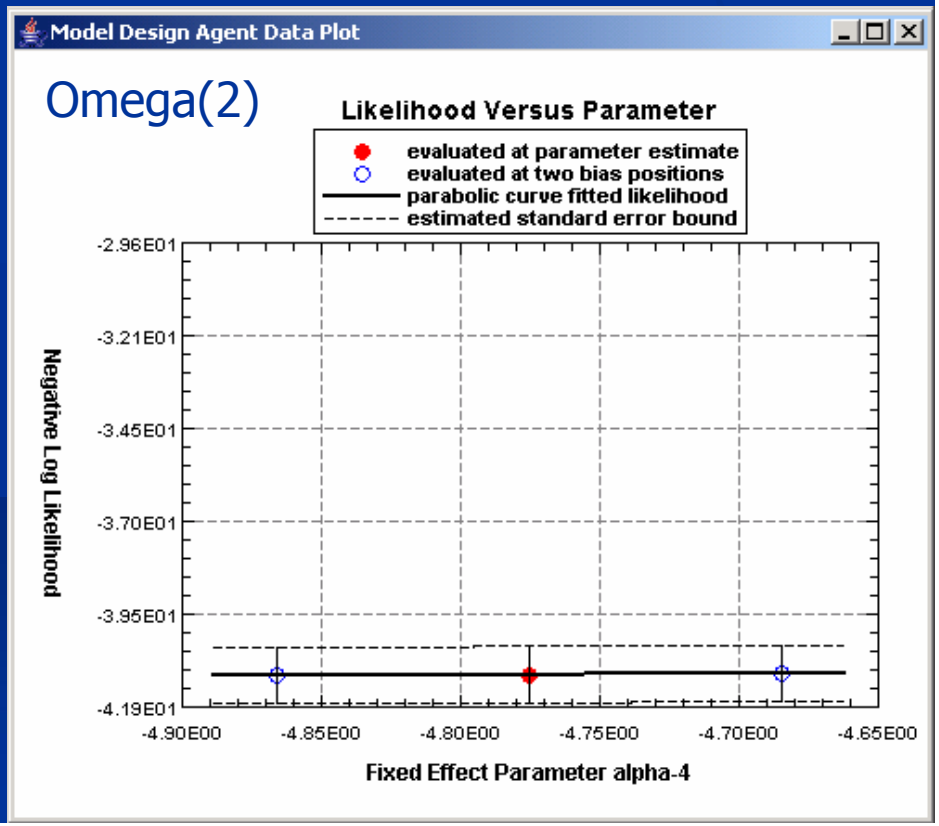

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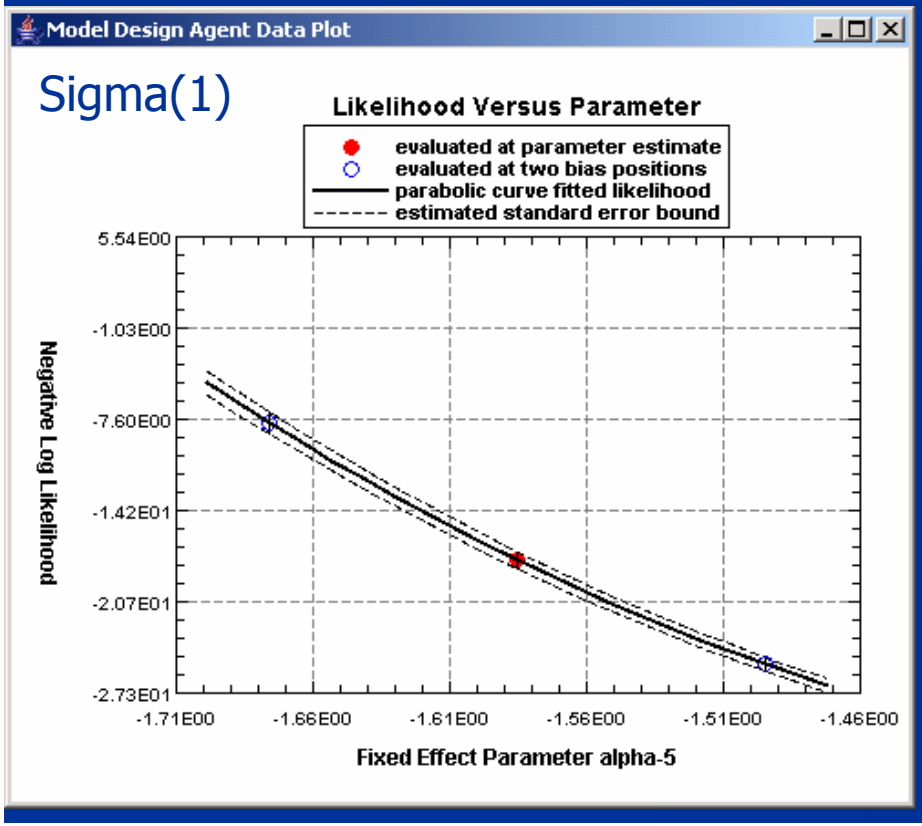
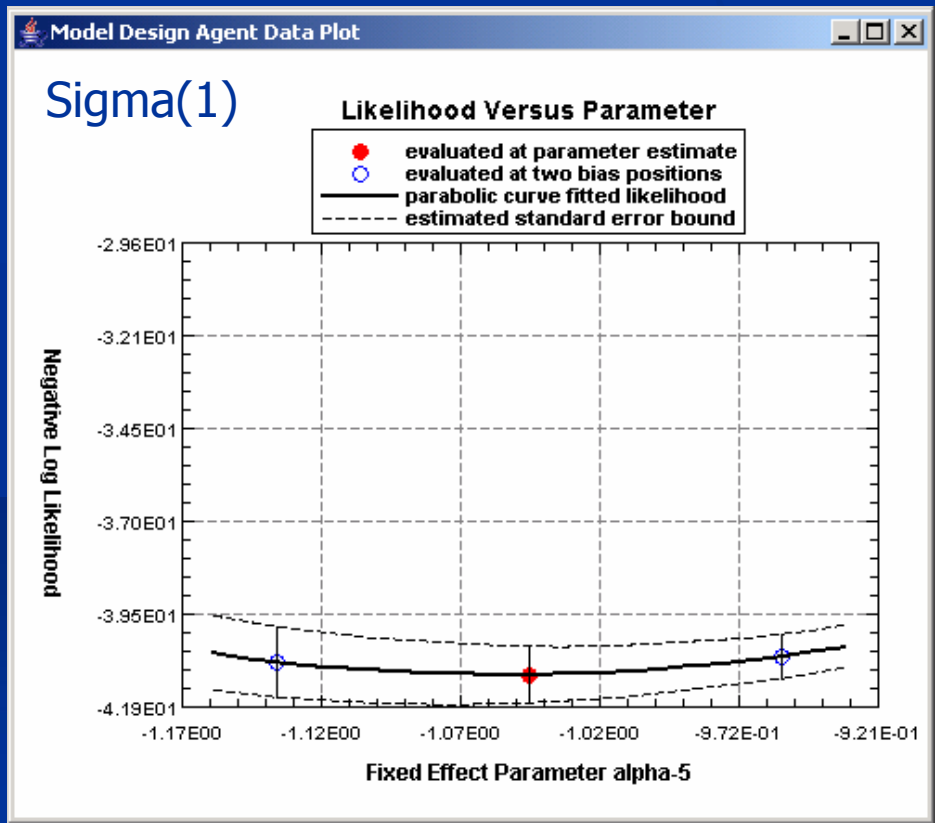




The Future: Hybrid Methods?

- Ultimate purpose: Model selection
- Example: optimization theory
  - Global and local optimization methods
    - Global (stochastic): provide global optimum
    - Local (deterministic): speed and precision
  - Lately: hybrid approaches (best of both)
- Hybrid methods in population analysis
  - Global searches and local minimizations
  - Approximate likelihood methods
  - Exact diagnostics (likelihood value, gradient and Hessian)

How Can the Population Approach Be Improved Upon?

- Improve user understanding
- Provide more guidance to the community
- Be wary of “cookie-cutter” approaches
- Clarify the consequences of assumptions
- Help users diagnose method failure
- Exploit advances in computer sciences
- Improve upon and develop new software
- In a word, *innovate…*

What Is Innovation?

- There are challenges in defining innovation in the context of a modeling and simulation package
- Theory and methodology?
  - Already solidly developed in the 70-80s
- User interface and diagnostics?
  - Have not changed in a long time
- New areas of application?
  - Do not constitute innovation *per se*

Judging Innovation

- National Institutes of Health review criteria
  - Significance
  - Approach
  - Innovation
  - Investigators
  - Environment
- Proposing innovative endeavors is at the root of modern US biomedical research

http://www.niaid.nih.gov/ncn/grants/write/write_c1.htm

Example Open Question: Model Selection

- Conditioning inference on a specific model
- Stepwise approaches
  - Addition-deletion, Leave one out, AIC stepwise selection
- Novel approaches
  - Genetic algorithm (Bies et al., JPKPD 2006 33: 195-221)
- Latest approaches
  - What model selection?

Model Uncertainty

- Model selection implies conditioning on a single model, the *best* model by some [set of] criteria
- The user runs the risk to ignore model uncertainty
- Inferences based on this inappropriate conditioning are falsely optimistic, e.g. confidence intervals are narrower

Bayesian Model Melding

- α ~ the quantities of interest
- D ~ the data
- $\mathcal{M}$ ~ the model space

$$p(\alpha \mid D) = \sum_{k \in \mathcal{M}} p(\alpha \mid M_k, D) p(M_k \mid D)$$

Hoeting et al. *Statistical Science* 1999, Vol. 14, No. 4, 382–417

Posterior Model Probability

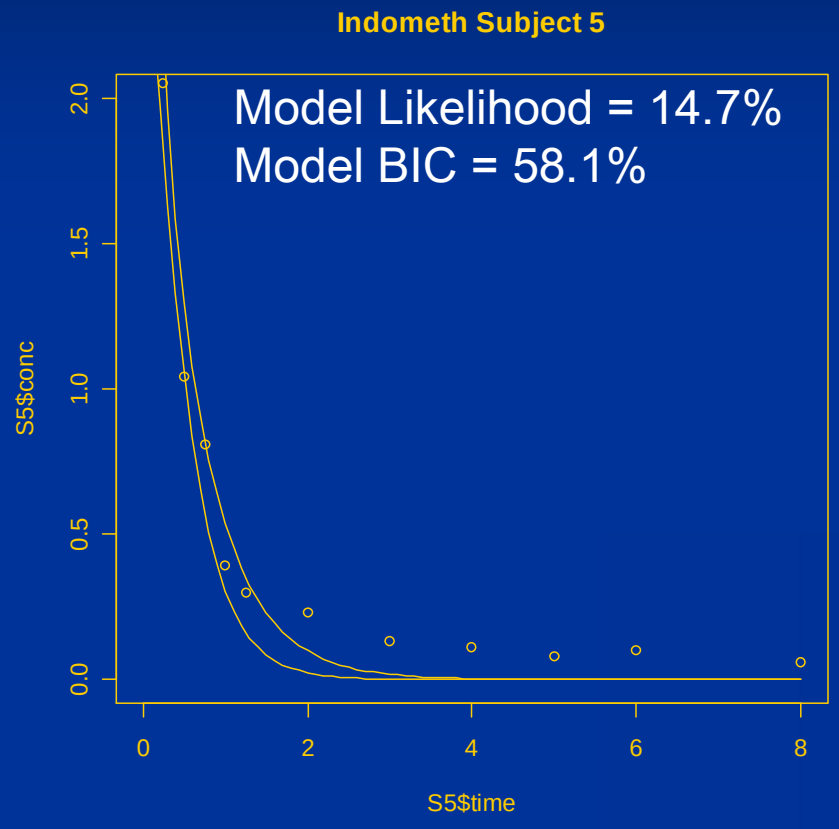
- α ~ the quantities of interest
- D ~ the data
- $\mathcal{M}$ ~ the model space

$$p(M_k \mid D) = \frac{p(D \mid M_k)p(M_k)}{\sum_{k \in \mathcal{M}} p(D \mid M_s)p(M_s)}$$

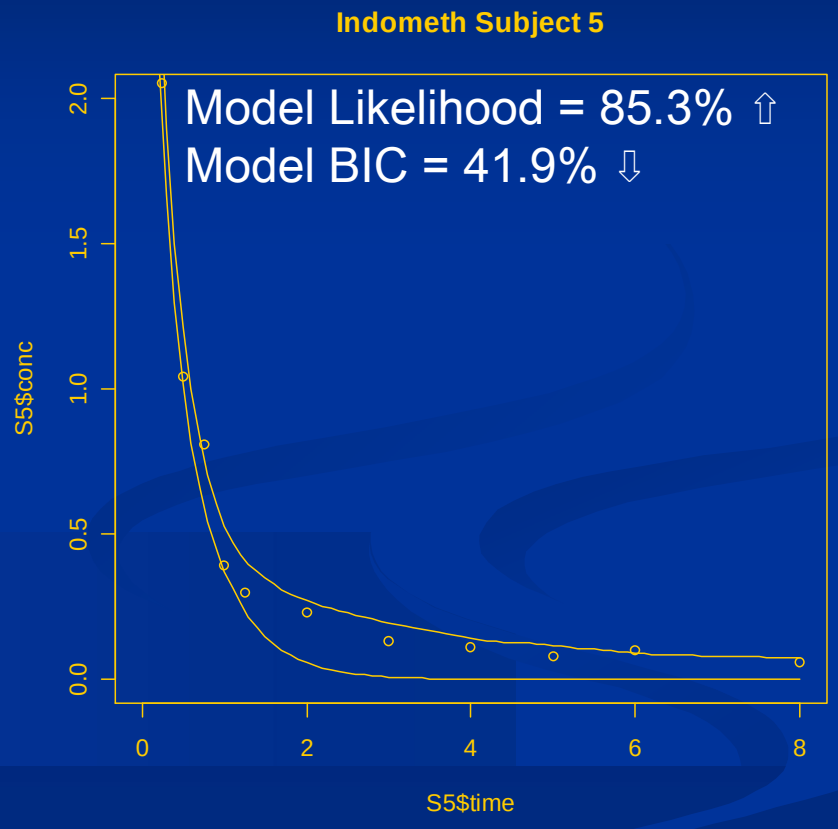
- Probability of each model given the data

Hoeting et al. *Statistical Science* 1999, Vol. 14, No. 4, 382–417

What Could It Look Like



$$c(t) = Ae^{-\lambda t}$$

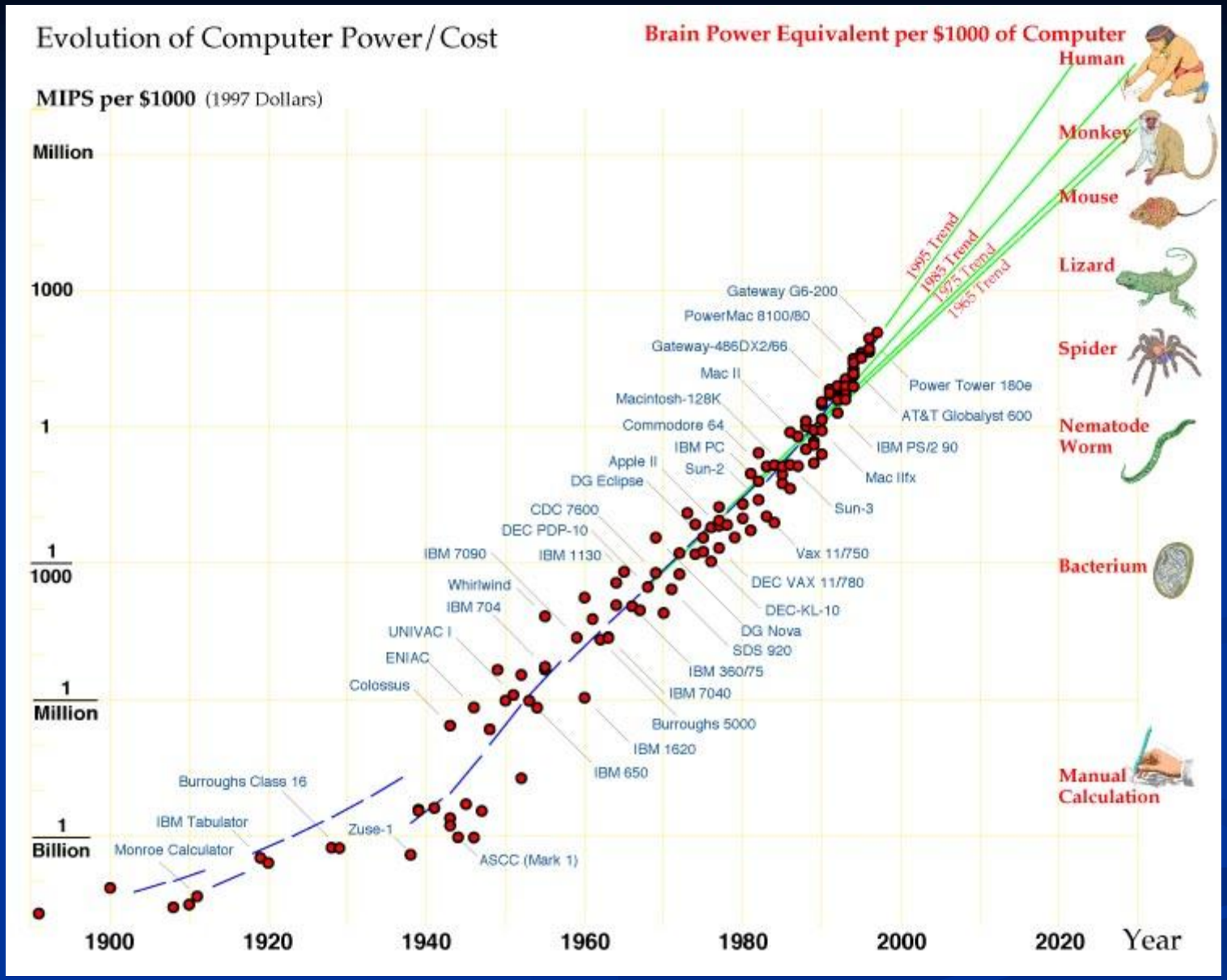


$$c(t) = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t}$$

Difficulties

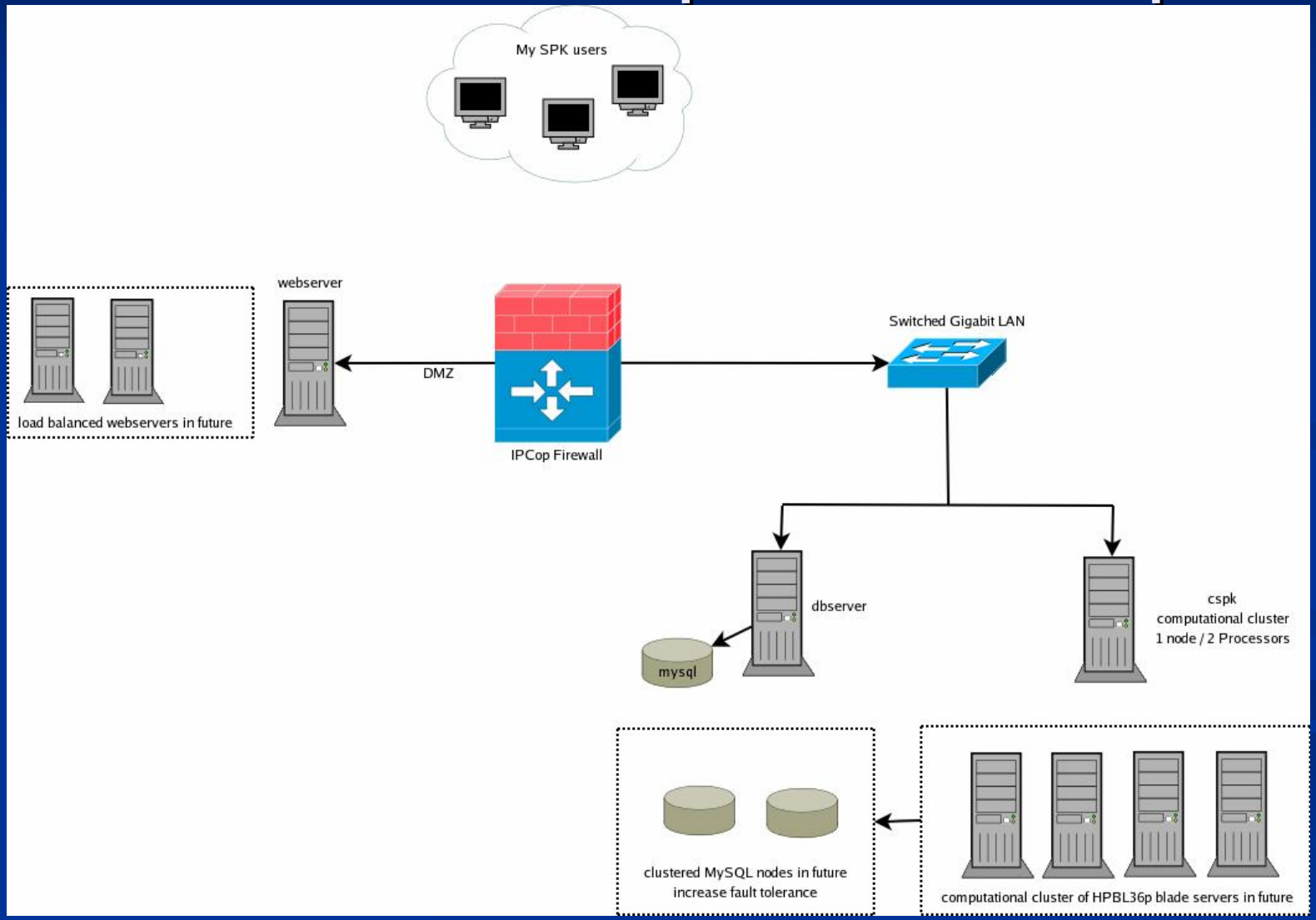
- The required integrals can be difficult to compute or approximate
- Specification of a prior distribution on $\mathcal{M}$ is challenging: choosing the model class is still a fundamental scientific task
- The number of elements in $\mathcal{M}$ can be enormous, rendering the necessary computations infeasible. However…

Hoeting et al. *Statistical Science* 1999, Vol. 14, No. 4, 382–417



http://jeffsutherland.org/objwld98/future.html,
see also http://en.wikipedia.org/wiki/Million_instructions_per_second

Our Own Approach: Web Service Ubiquitous Computing



Courtesy Andrew Ernst
http://www.rfpk.washington.edu

What's Next?

Strengths

- Population analysis is responsive to some key questions that are being asked today:
  - *In vivo* pharmacology is essential for drug discovery and development
  - Microdialysis and imaging facilitate *in vivo* data collection
  - [Pharmaco]genomics development accelerate the demand for integration strategies and applications

Preusch PC. Integrative and organ systems pharmacology: a new initiative from the national institute of general medical sciences. Mol Interv. 2004 Apr;4(2):72-3.

Weaknesses

- Academic infrastructure is inadequate to meet training demand
- The success enjoyed by molecular and cellular reductionism has come at the expense of integrative disciplines
- The cost of *in vivo* and preclinical research has increased
- New training paradigms are needed

Preusch PC. Integrative and organ systems pharmacology: a new initiative from the national institute of general medical sciences. Mol Interv. 2004 Apr;4(2):72-3.

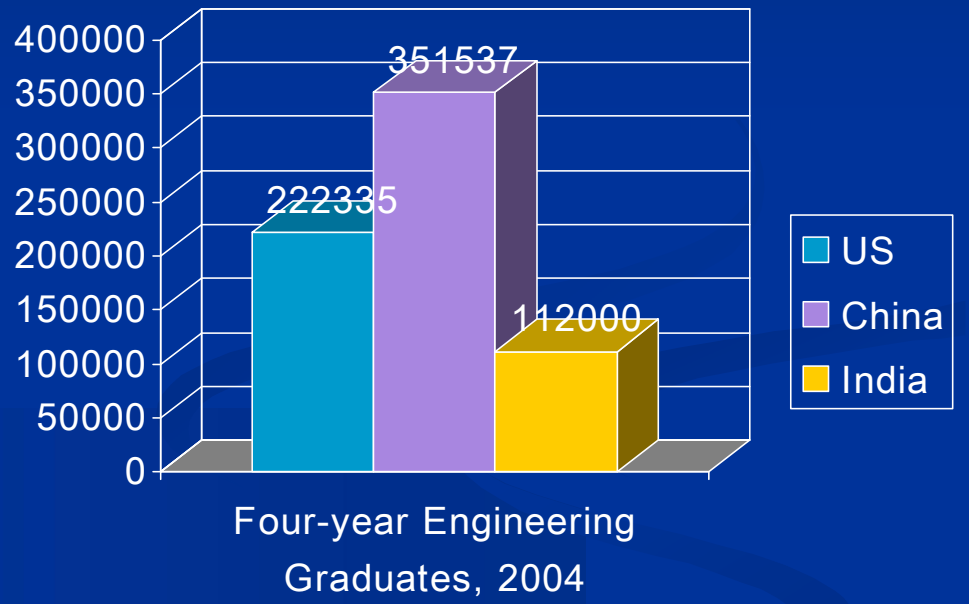
Opportunities

- Requirements/ingredients:
  - Statistics
  - Engineering (differential equations)
  - Simulation
  - Data display and synthesis
  - (Pharmaco)kinetics
- The marketplace of ideas is now global
- Pharmacometricians may come from non-traditional disciplines (bioengineering)

Threats

- “In engineering, the scarcity of geniuses is compensated by a formal language that successfully unites many efforts. In biology, we use several arguments to convince ourselves that problems that require calculus can be solved with arithmetic if one tries hard enough and does another series of experiments.”

Y. Lazebnik, in Cancer Cell. 2002 Sep;2(3):179-82



Four-year Engineering Graduates, 2004

Graduate data from Business Week Online December 13, 2005
http://businessweek.com/smallbiz/content/dec2005/sb20051212_623922.htm

To be productive, scientists need to keep their eye on the ball, on the problem, which is understanding the subject matter better or teaching students better.
Then everything else falls out; they become successful as a researcher, or successful as a teacher, and get the rewards. But they should not keep the rewards in mind as the reason for it.

(ATN) Clinical Trials: Asking the Right Questions - Interview with Lewis Sheiner, MD. AIDS Treatment News #142, Jan 7, 1992

John S. James