The Lewis B. Sheiner Lecturer Award
International Society of Pharmacometrics
November 8, 2021

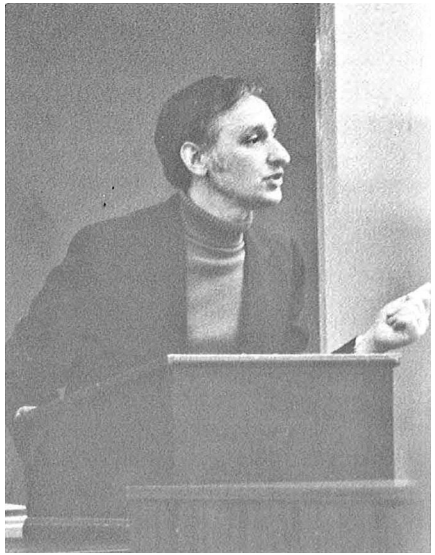
I’m a Bayesian and I’m OK:

Or How I Learned to Stop Worrying and Love Variability and Uncertainty

William R. Gillespie, Ph.D.
Metrum Research Group

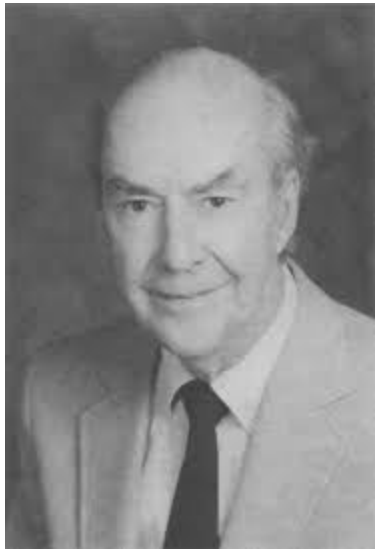
Acknowledgements

- Mentors



The Wayne Pharmic, 20(2), 1977.

Gerald E. Schumacher



H. A. Whitney Jr and J. G. Wagner. Seventy years in retrospect. DICP, 25(11):1265–1268, 1991.

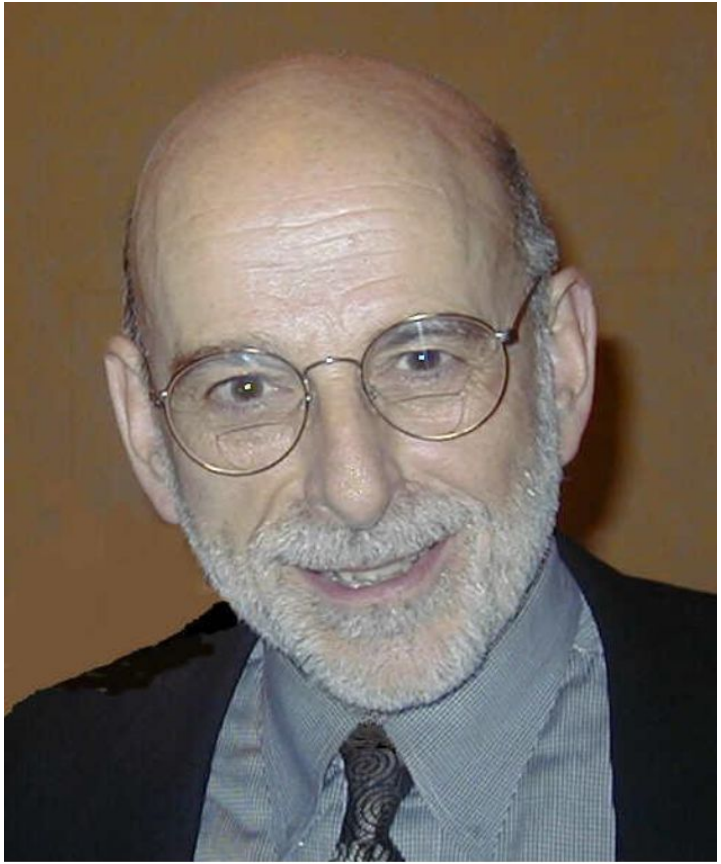
John G. Wagner

https://www.youtube.com/c/petervengpedersen

Peter Veng-Pedersen

- Colleagues & collaborators

Dr. Lewis B. Sheiner



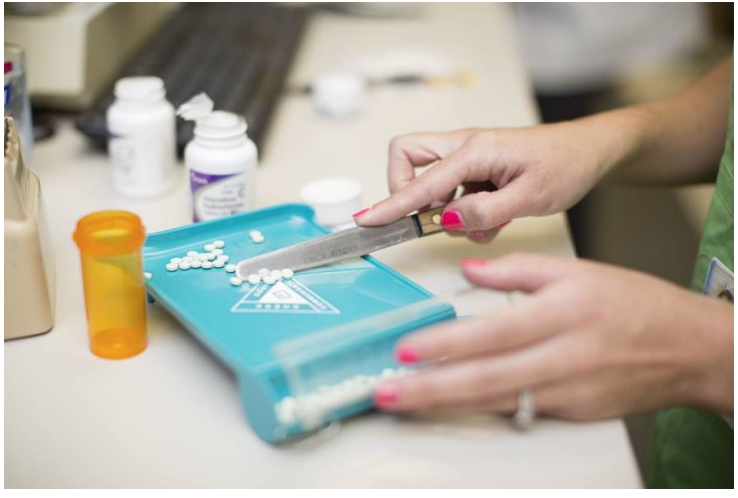
https://nonmem.iconplc.com/#/nonmem_history/NONMEM_history4.pdf

The core idea I want to communicate

Bayesian principles and methods

- make sense
- provide a flexible framework for
  - analyzing complex and heterogeneous collections of data, and
  - making statistical inferences that consider prior quantitative information.
- add value to the MIDD process

A scientific and professional journey



Torsten: A Pharmacokinetic/Pharmacodynamic Model Library for Stan

User's Guide
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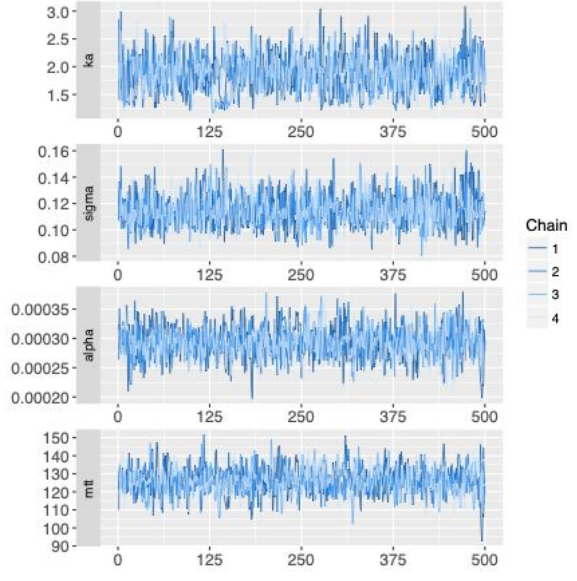
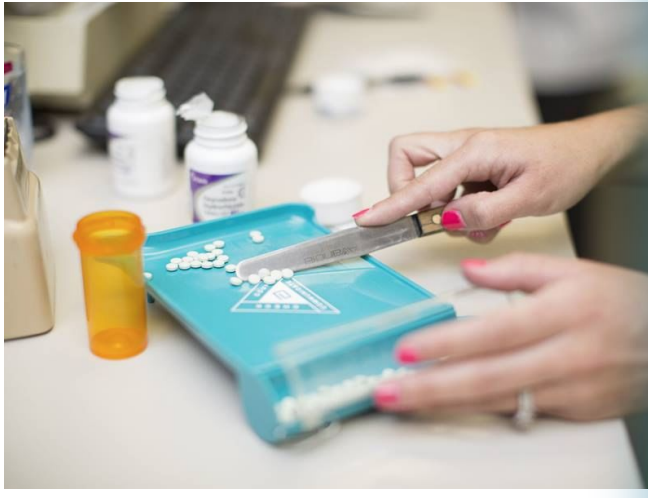
June 30, 2021



A scientific and professional journey



NONMEM Users Guide -- Part I

Users Basic Guide

November 1989

by

Stuart L. Beal

and

Lewis B. Sheiner

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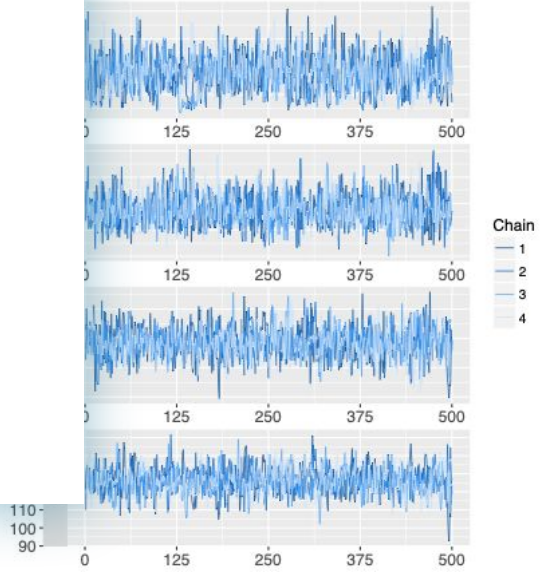

A scientific and professional journey

Relative Bioavailability of Commercially Available Ibuprofen Oral Dosage Forms in Humans

W. R. GILLESPIE, A. R. DiSANTO, R. E. MONOVICH, and K. S. ALBERT ˣ

Received August 20, 1981, from the *Clinical Biopharmaceutics Research Unit, The Upjohn Company*, publication December 1, 1981.

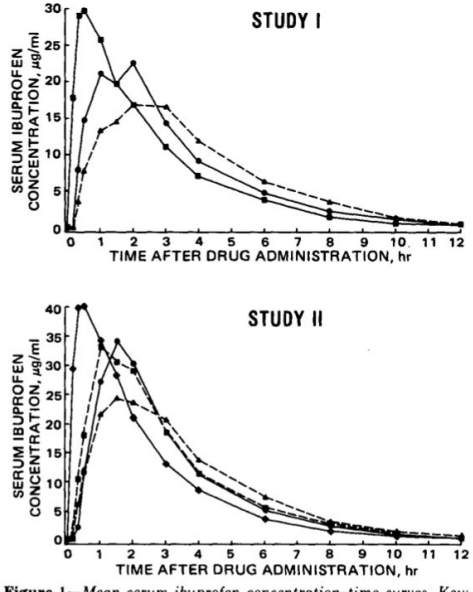

Figure 1—*Mean serum ibuprofen concentration–time curves. Key: Study I: (▲) 300-mg capsule (A); (●) 300-mg tablet (B); (■) oral solution (F); Study II: (▲) 400-mg capsule (C); (■) 200-mg capsule (D); (●) 400-mg tablet (E); (◆) oral solution (F).*

Combining patient-level and summary-level data for Alzheimer's disease modeling and simulation: a beta regression meta-analysis

James A. Rogers · Daniel Polhamus · William R. Gillespie · Kaori Ito · Klaus Romero · Ruolun Qiu · Diane Stephenson · Marc R. Gastonguay · Brian Corrigan

J Pharmacokinet Pharmacodyn (2012) 39:479–498

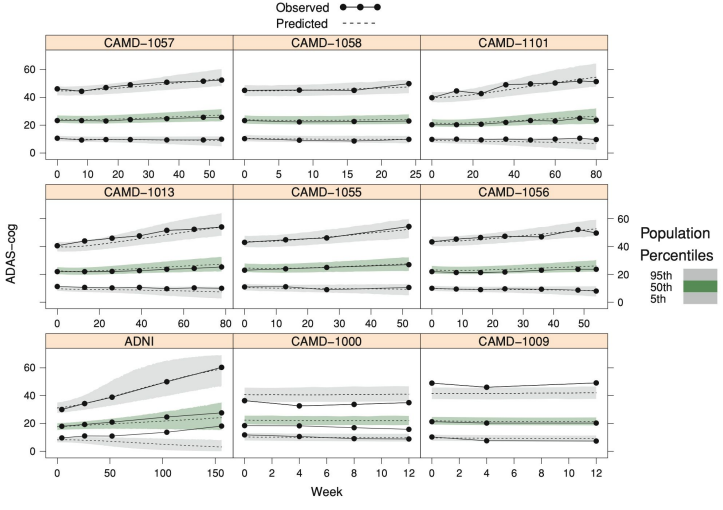

Fig. 7 Plot of unconditional predictive checks for sample population percentiles of ADNI and CAMD studies

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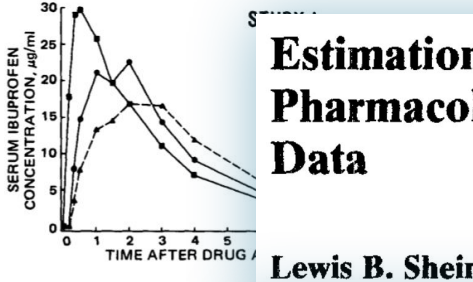

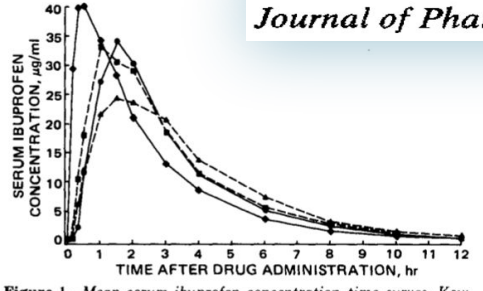

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Estimation of Population Characteristics of Pharmacokinetic Parameters from Routine Clinical Data

Lewis B. Sheiner,[1,4] Barr Rosenberg,[2] and Vinay V. Marathe[2,3]

Journal of Pharmacokinetics and Biopharmaceutics, Vol. 5, No. 5, 1977

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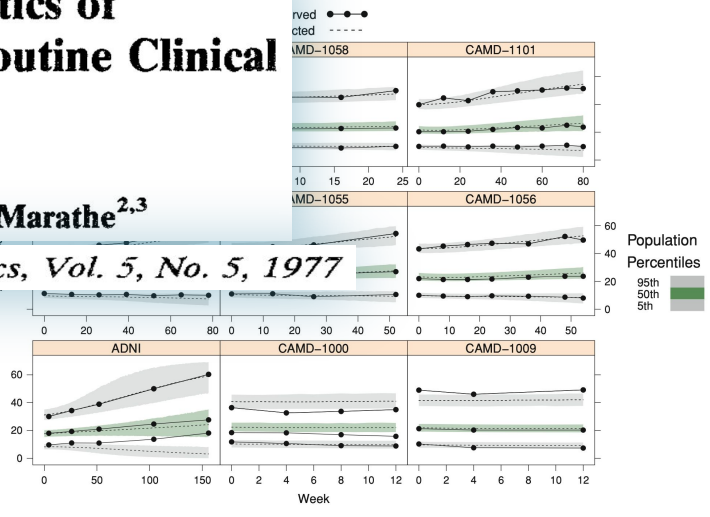


Fig. 7 Plot of unconditional predictive checks for sample population percentiles of ADNI and CAMD studies

A scientific and professional journey

Deconvolution Applied to the Kinetics of Extracorporal Drug Removal. Haemodialysis of Cefsulodin

W. R. Gillespie[1], P. Veng-Pedersen[1], and T. P. Gibson[2]*

[1]College of Pharmacy, The University of Iowa, Iowa City, Iowa, [2]Department of Medicine, Northwestern University Medical School, Northwestern Memorial Hospital and Veterans, Administration Lakeside Medical Center, Chicago, Illinois, USA

$$c(t) = \begin{cases} c_i(t), & t < t_1 \\ c_i(t) - \int_{t_1}^{t} r_e(u) c_\delta(t-u)\,du, & t_1 \leq t \leq t_2 \\ c_i(t) - \int_{t_1}^{t_2} r_e(u) c_\delta(t-u)\,du, & t > t_2 \end{cases}$$

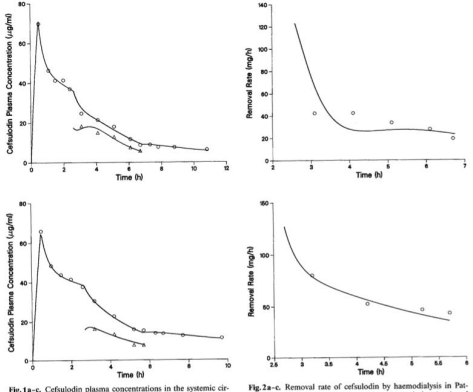
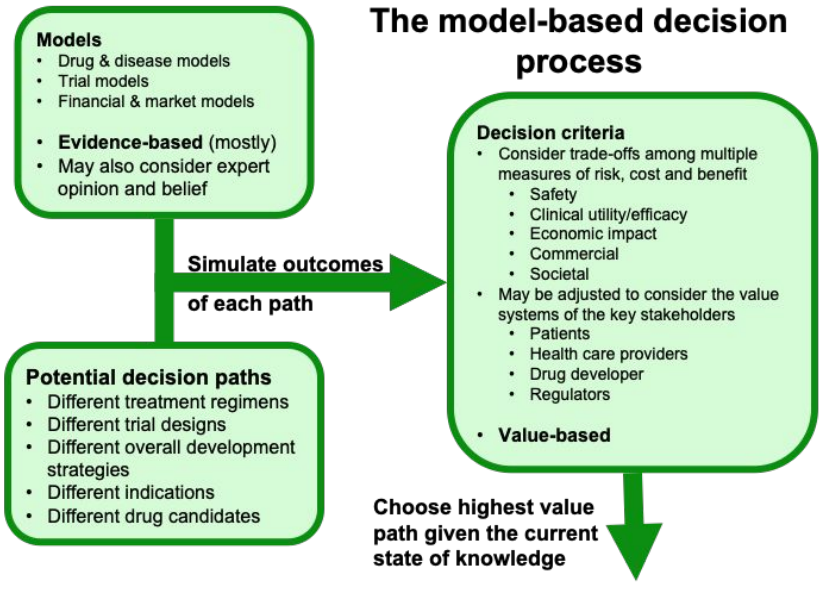


Fig. 1a–c. Cefsulodin plasma concentrations in the systemic circulation (0) and in the haemodialyzer effluent (Δ) of Patients 14 a, 15 b, and 17 c. The continuous curves represent polyexponential equations fit to the data

Fig. 2a–c. Removal rate of cefsulodin by haemodialysis in Patients 14 a, 15 b, and 17 c estimated by deconvolution (—) and mass balance (0) methods



WR Gillespie et al. PKUK 3-5 November 2010

A scientific and professional journey

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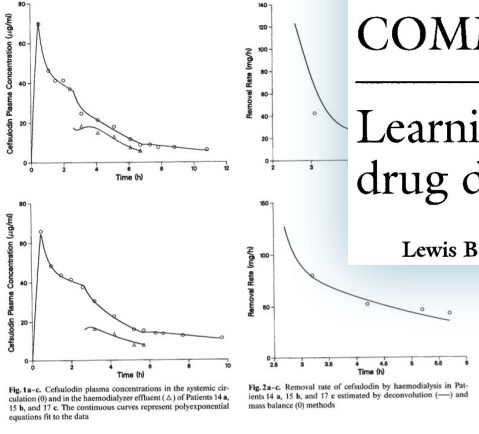

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CLINICAL PHARMACOLOGY & THERAPEUTICS
VOLUME 61 NUMBER 3 MARCH 1997

COMMENTARY

Learning versus confirming in clinical drug development

Lewis B. Sheiner, MD *San Francisco, Calif.*

Models
- Drug & disease models
- Trial models

The model-based decision process

Decision criteria
- Consider trade-offs among multiple measures of risk, cost and benefit
  - Safety
  - Clinical utility/efficacy
  - Economic impact
  - Commercial
  - Societal
- May be adjusted to consider the value systems of the key stakeholders
  - Patients
  - Health care providers
  - Drug developer
  - Regulators
- **Value-based**

Choose highest value path given the current state of knowledge

WR Gillespie et al. PKUK 3-5 November 2010

A path to Bayes

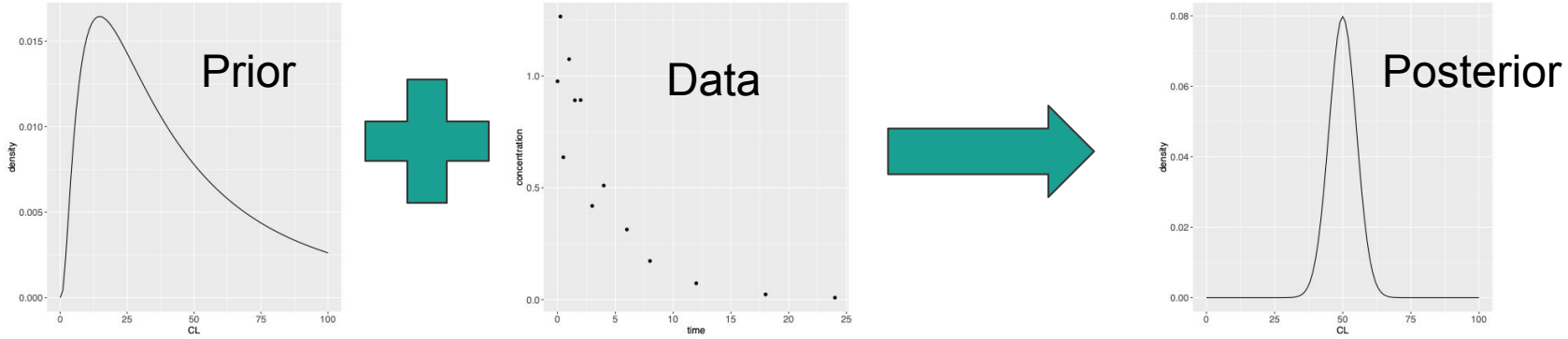
- Mathematical models to synthesize complicated collections of knowledge and data, and to help us understand how they interact in real systems.
- Maximum likelihood data analysis considers 2 knowledge types:
  - Data
  - Prior *qualitative* knowledge to inform model structure
- Bayesian data analysis extends this notion to also consider prior *quantitative* knowledge
  - Added to the model in the form of prior distributions.

Key components of Bayesian analysis

Your state of knowledge about an estimand such as a model parameter or a predicted outcome is described in terms of a probability distribution.

Bayes Rule is the basis for inference about model parameters (θ) given data (y) and prior knowledge about model parameters ($p(\theta)$):

$$p(\theta|y) = \frac{p(\theta)\,p(y|\theta)}{p(y)} = \frac{p(\theta)\,p(y|\theta)}{\int p(\theta)\,p(y|\theta)\,d\theta}$$
$$\propto p(\theta)\,p(y|\theta)$$



Potential added value of Bayesian methods

- Prior distributions to make inferences based on the combined evidence of new data and prior information
- Greater flexibility in experimental design and analysis
- Bayesian methods plus flexible PPLs make it easier to implement joint analysis of heterogeneous data

Prior distributions to make inferences based on the combined evidence of new data and prior information

Selective use of informative priors when analyzing sparse data from special populations

POPULATION PHARMACOKINETICS IN PEDIATRIC PATIENTS USING BAYESIAN APPROACHES WITH INFORMATIVE PRIOR DISTRIBUTIONS BASED ON ADULTS

Marc R. Gastonguay, PhD[1], William R. Gillespie, PhD[2], Leonid Gibiansky, PhD[1], Ko-Chin Khoo, MS[3], and the PPRU Network[4]

AAPS Annual Meeting, New Orleans, 1999

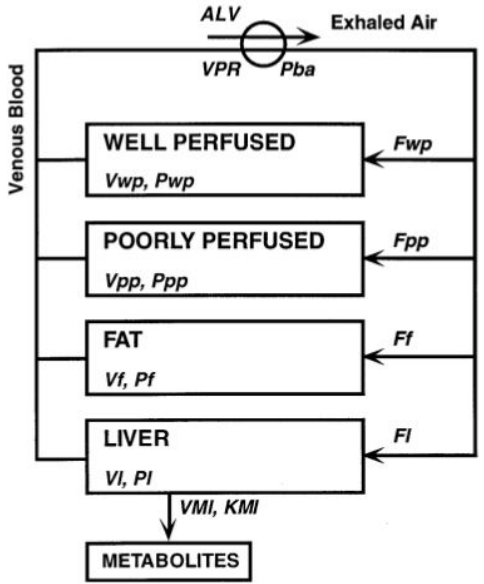
Bayesian PBPK modeling

Physiological Pharmacokinetic Analysis Using Population Modeling and Informative Prior Distributions

Andrew GELMAN, Frederic BOIS, and Jiming JIANG

Journal of the American Statistical Association, 91(436):1400–1412, 1996.

- Uses complex models with physiologically relevant parameters, e.g., tissue blood flows, tissue volumes, tissue/blood partition coefficients, etc.
- Prior distributions based on a combination of information sources:
  - Physiologic knowledge
  - Nonclinical data: animal & in vitro



Bois et al. Arch Toxicol (1996) 70: 347—355

Bayesian PBPK modeling

“Five key features, all of which work in combination:

1. a physiological model
2. a population model
3. prior information on the population physiological parameters
4. experimental data
5. Bayesian inference”

Bayesian PBPK modeling

"If any of these five features are missing, the model will not work:

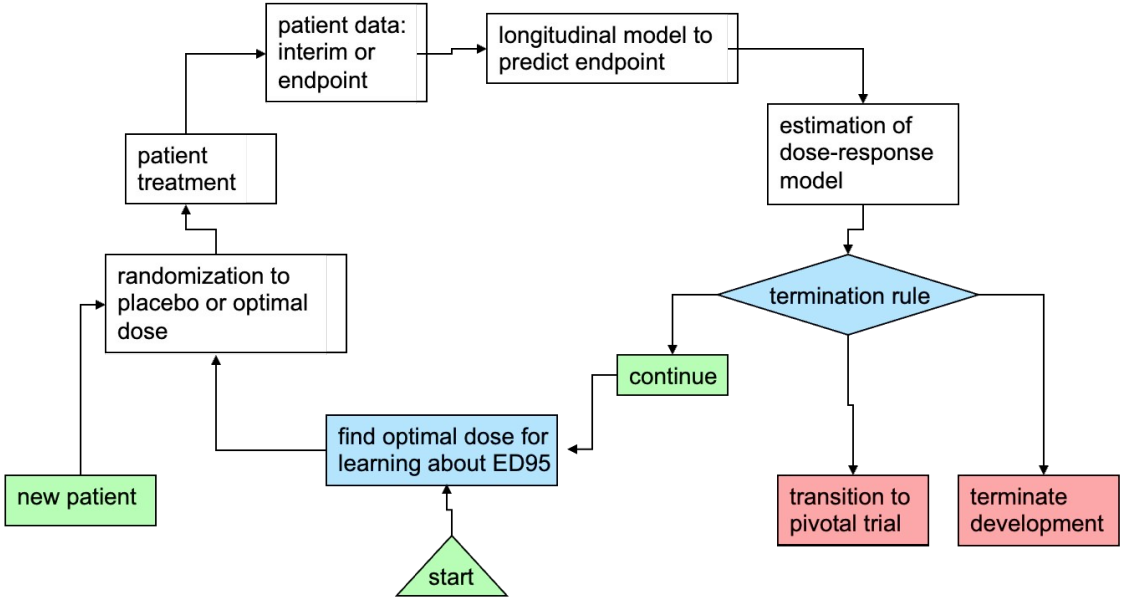
1. Without a physiological model, there is no good way to obtain prior information on the parameters;
2. Without a population model, there is not generally enough data to estimate the model independently on each individual;

3&4. The parameters of a multicompartment physiological model cannot be determined accurately by data or prior information alone;

5. Bayesian inference yields a distribution of parameters consistent with both prior information and data, if such agreement is possible."

Greater flexibility in experimental design & analysis

Dose-ranging trial design with Bayesian adaptive dose assignment and adaptive stopping: The ASTIN trial



Adapted from DA Berry et al. Case Studies in Bayesian Statistics, 5:99-157, 2002.

Bayesian methods plus flexible PPLs make it easier to implement joint analysis of heterogeneous data

Combining patient-level and summary-level data for Alzheimer's disease modeling and simulation: a beta regression meta-analysis

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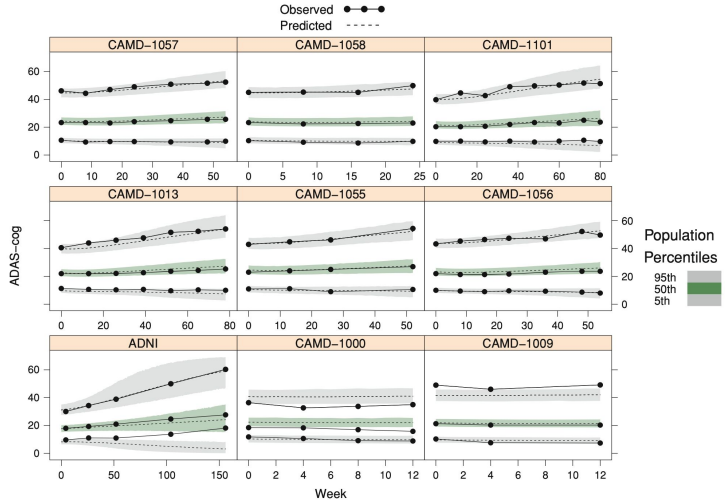


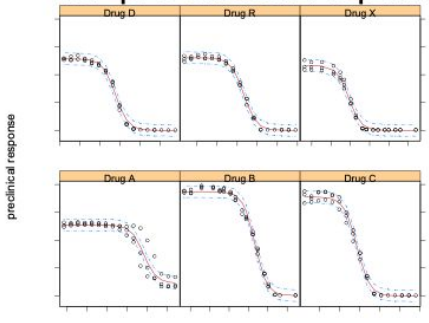
Fig. 7 Plot of unconditional predictive checks for sample population percentiles of ADNI and CAMD studies

"...a number of important innovations were also implemented:"

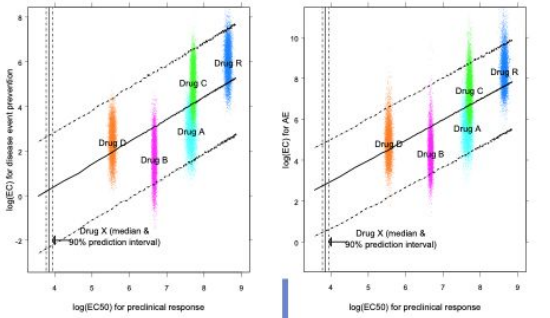
1. "A Bayesian implementation has been developed, allowing for a probabilistically correct synthesis of literature meta-data with patient-level data."
2. "The generalized logistic function for expected disease progression is used in conjunction with Beta-distributed residuals..."
3. "The covariance structure is extended to include inter- study variation..."
4. "The covariance structure is extended to include inter- study heterogeneity in variance components."

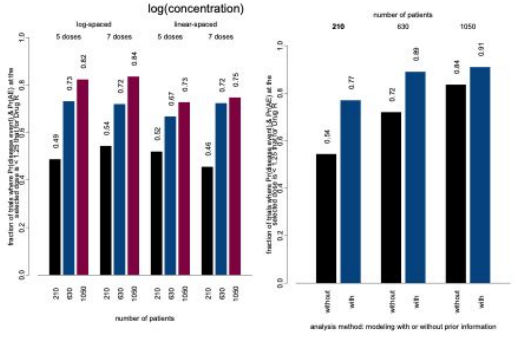
Bayesian methods plus flexible PPLs make it easier to implement joint analysis of heterogeneous data

Model concentration-response for pre-clinical response

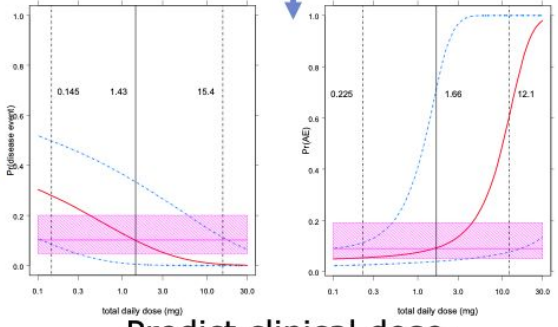


Model relationships between pre-clinical & clinical potencies





Optimize trial design and analysis via clinical trial simulations



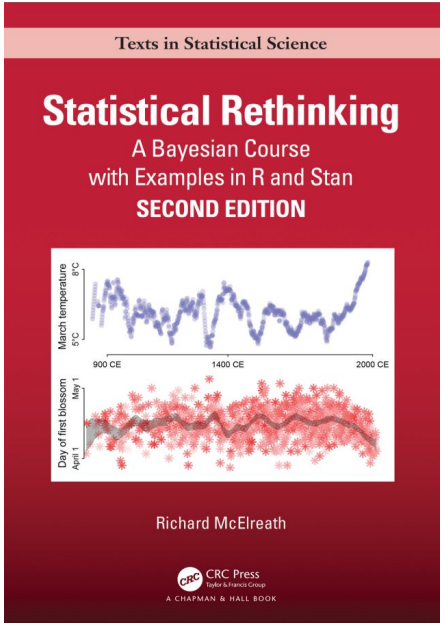
Predict clinical dose-response of drug X

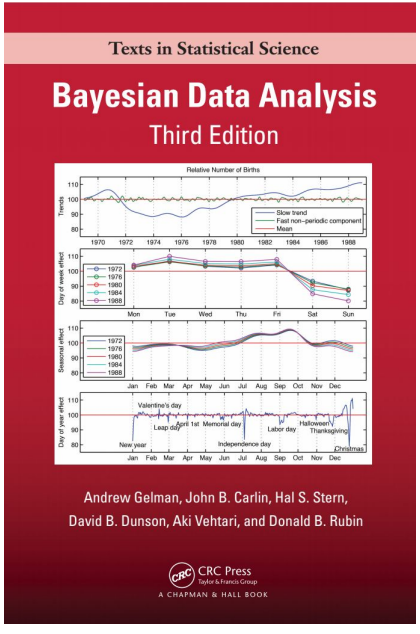
Joint model of pre-clinical response, and frequency of clinical efficacy and AE events

WR Gillespie. ACCP Annual Meeting, Philadelphia, 2008

Getting started: Learning the ropes

Reading for self-study & reference





Online workshops
https://www.metrumrg.com/courses/

A Brief Introduction to Bayesian Modeling Using Stan

This introduction to Stan provides a brief primer to Bayesian modeling and the practical use... See More

LEARN MORE

Advanced Use of Stan, RStan and Torsten for Pharmacometric Applications

These videos capture most of a one day workshop presented at the PAGE 2018 meeting... See More

LEARN MORE

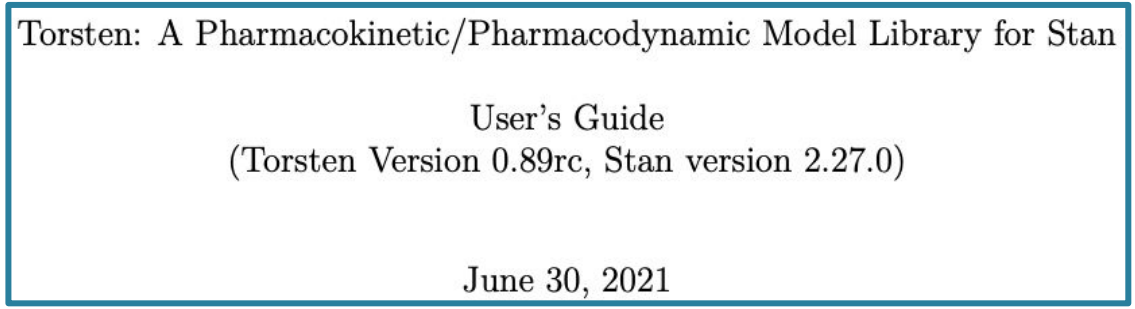
Getting started

Selected tools for Bayesian PMX modeling

- Commercial PMX s/w
  - NONMEM
  - PUMAS
- More flexible open source PPLs
  - WinBUGS/OpenBUGS/JAGS
  - Stan / Torsten
  - Turing

Torsten / Stan

- Stan is an open source PPL for Bayesian data analysis.
  - Primary inference engine is NUTS, an adaptive HMC sampler.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- Torsten is a collection of Stan functions to facilitate analysis of PMX data---analogous to PREDPP.
  - Models and data format are based on NONMEM/NMTRAN/PREDPP conventions.
  - https://github.com/metrumresearchgroup/Torsten

Torsten Teorell

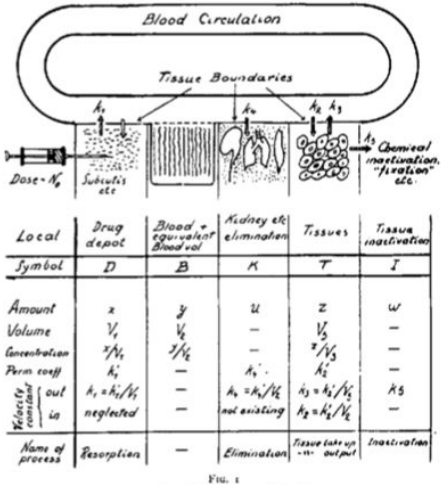

FIG. 1

Scheme of the Concept of Drug Distribution used in this paper. Instead the *injection* pictured in the figure, the administration of the drug depot can be made *per os, per rectum, by inhalation*, etc.

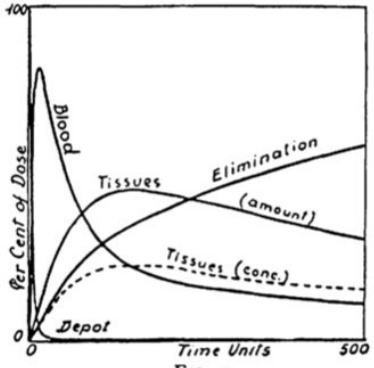

FIG. 3

Typical Case of Extravascular Administration in the absence of tissue inactivation.

($k_1 = 0.2$; $k_2 = 0.01$; $k_3 = 0.005$; i.e. "blood" volume/"tissue" volume is 1 : 2; $k_4 = 0.005$; $k_5 = 0$).

T. Teorell. Kinetics of distribution of substances administered to the body. I. The extravascular modes of administration. Arch Int Pharmacodyn et Ther 57: 205-225, 1937.

Bayesian modeling in perspective

- MIDD contributes huge value without using Bayesian approaches.

- OTOH, Bayesian methods can provide substantial added value, particularly where data is limited and prior information is available to inform inferences and decisions.

Add Bayesian approaches to your modeling tool kit

When considering a potential modeling application, assess the pros and cons of applying a Bayesian approach.

- Will use of quantitative prior information add value?
- Will joint analysis of heterogeneous data types add value?
- Do you want to make probabilistic inferences about parameter values or predictions?
- Do you want to evaluate potential decision paths based on quantitative optimization of risk-benefit trade-offs?
- Is the added value sufficient to offset the additional time and effort?

Caution

- Bayesian modeling is not a magic bullet that solves all your data analysis and statistical inference problems.
  - It is just a particularly flexible and coherent approach.
  - Study design still matters as do issues like causality and multiplicity.
- Posterior sampling methods like MCMC require new skills, or in the words of the WinBUGS/OpenBUGS manuals:

Beware: MCMC sampling can be dangerous!

Think Bayesian; act pragmatically

- Conceptualize a modeling & simulation project in Bayesian terms.
- Then assess whether you can execute the project with fully Bayesian methods within the time available to add value.
- It not, compromise using methods that attempt to approximate the Bayesian ideal.
  - Use approximate Bayesian methods like MAP Bayes.
  - Compromise on the model structure to permit use of standard tools like NONMEM.

Future of Bayesian methods in PMX and MIDD

- Continuing improvements in h/w and s/w will make Bayesian computations faster and more accessible.
  - Improvements in posterior sampling algorithms including better exploitation of parallel computation.
  - Simplified user interfaces to facilitate more rapid PMX model development and shorten the learning curve.
  - Bayesian calibration of large scale QSP models will become increasingly feasible.
  - As will Bayesian analysis of very large data sets.

Dr. Lewis B. Sheiner

Be curious; be creative

Grow the science by sharing what you learn

Learn from other disciplines and adapt it to extend the range of PMX

Apply your hard-earned knowledge and skills to real world problems

In particular, apply them for the benefit of our ultimate stakeholders—patients