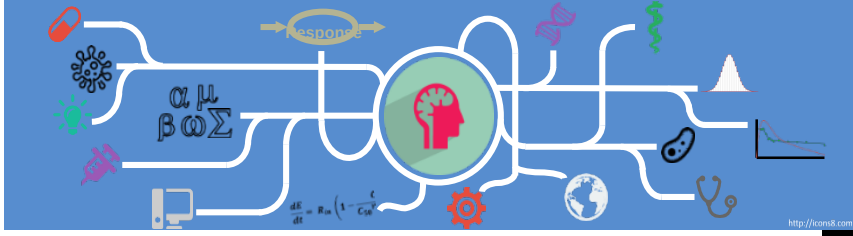


BRIDGING THE GAP BETWEEN PHARMACOMETRICIANS AND STATISTICIANS

PR FRANCE MENTRÉ, PHD, MD

UNIVERSITY PARIS DIDEROT – INSERM – IAME

BIOSTATISTICAL MODELLING AND PHARMACOMETRICS

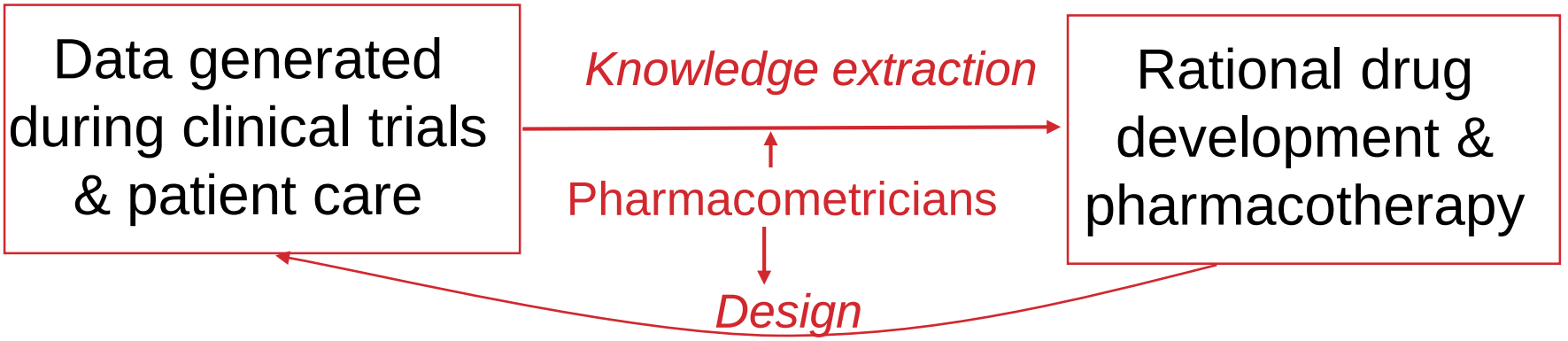
CES-ISBS Vienna 2017

Outline

1. **Pharmacometrics**
2. **Statisticians in pharmacometrics**
3. **Bridging the gap**

1. PHARMACOMETRICS

The science of quantitative clinical pharmacology



- Clinical pharmacology = PK + PD + **Disease progression**

- Analysis of longitudinal data
- Main statistical tool: Nonlinear Mixed Effect Models (NLMEM)

Started by Lew Sheiner

An impressive scientist who created a new discipline!

- **Web of Science**
  - 234 publications
  - 13,070 citations
  - H index = 59

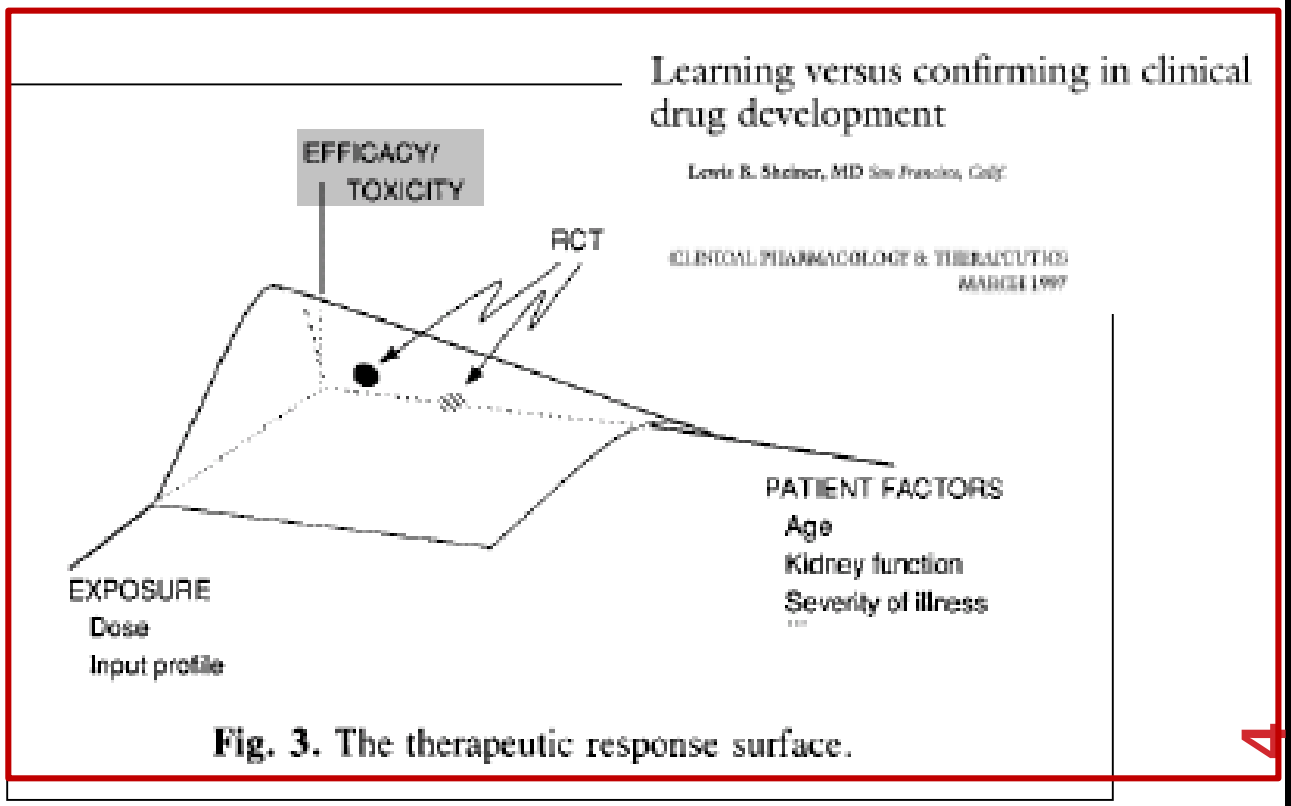


Fig. 3. The therapeutic response surface.

Impact of the Pharmaceutical Sciences on Health Care: A Reflection over the Past 50 Years

Journal of Pharmaceutical Sciences, Vol. 101, 4075–4099 (2012)

MALCOLM ROWLAND,[1,2] CHRISTIAN R. NOE,[3] DENNIS A. SMITH,[4,5] G. T. TUCKER,[6,7] DAAN J. A. CROMMELIN,[8] CARL C. PECK,[2] MARIO L. ROCCI Jr.,[9] LUC BESANÇON,[10] VINOD P. SHAH[10]

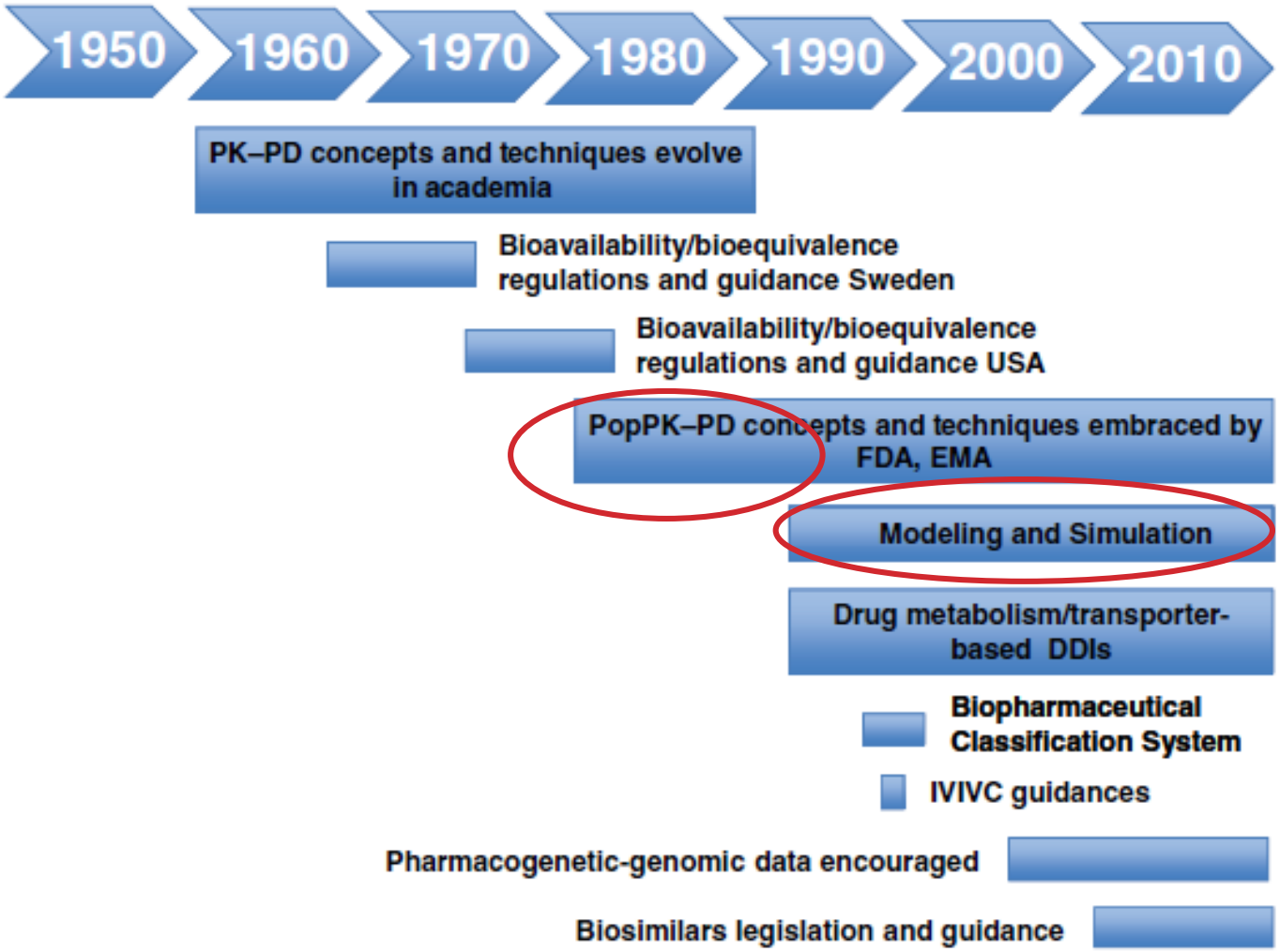
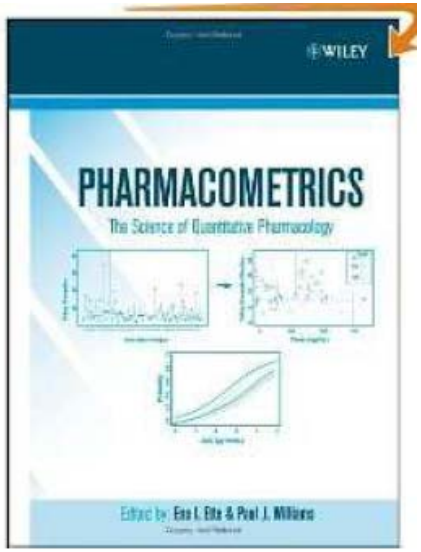


Figure 5. Timeline of introduction of some key developments and guidances in drug regulation.

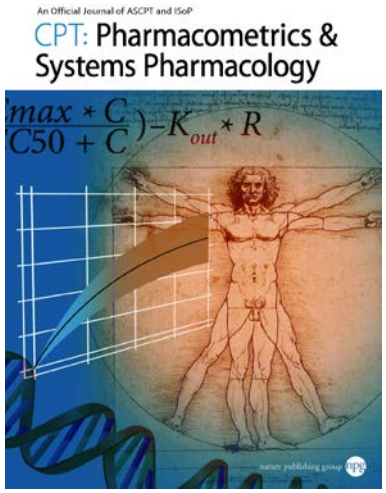
Pharmacometrics in the world

- **Conferences**
  - PAGE (1992-)
  - ACOP (2005-)
  - WCOP (2012-)

- **Book**
  - Pharmacometrics (2007)



- **Journal**
  - CPT: PSP (2012-)



- **Society**
  - ISOP (2012-)

From PopPK to MID3

- **Population pharmacokinetics (PopPK)**
- **Population pharmacokinetics /pharmacodynamics (Pop PKPD)**
- **Nonlinear mixed effect models (NONMEM, NLMEM)**
- **Modelling and Simulation (M&S)**
- **Pharmacometrics (PMX)**
- **Model Based Drug Development (MBDD)**
- **Model Informed Drug Development (MIDD)**
- **Model Informed Drug Discovery and Development (MID3)**

Model Informed Drug Discovery and Development

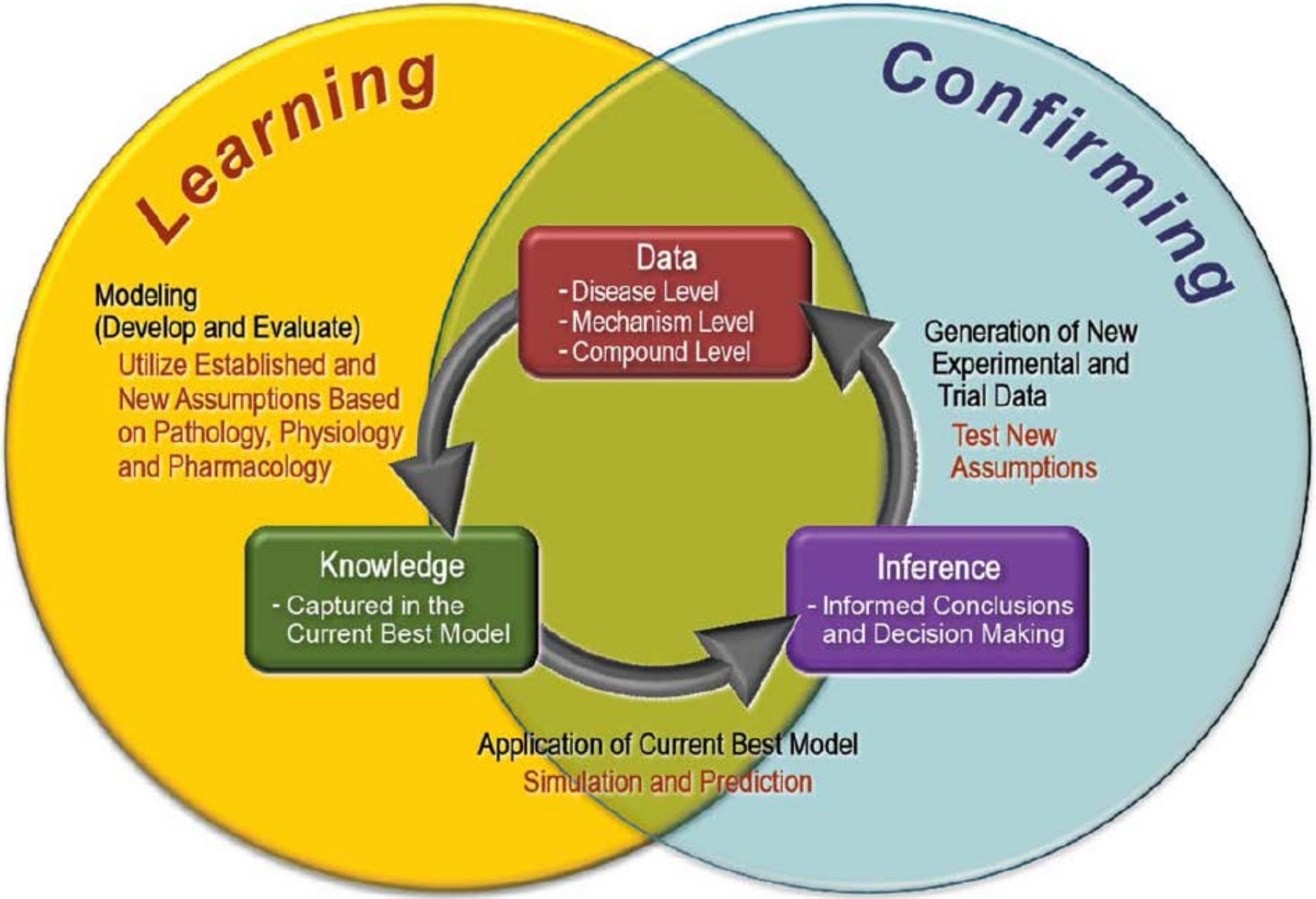
Citation: CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122; doi:10.1002/psp4.12049

WHITE PAPER

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

EFPIA MID3 Workgroup: SF Marshall[1]*, R Burghaus[2], V Cosson[3], SYA Cheung[4], M Chenel[5], O DellaPasqua[6], N Frey[3], B Hamrén[7], L Harnisch[1], F Ivanow[8], T Kerbusch[9], J Lippert[2], PA Milligan[1], S Rohou[10], A Staab[11], JL Steimer[12], C Tornøe[13] and SAG Visser[14]

This document was developed to enable greater consistency in the practice, application, and documentation of Model-Informed Drug Discovery and Development (MID3) across the pharmaceutical industry. A collection of ''good practice'' recommendations are assembled here in order to minimize the heterogeneity in both the quality and content of MID3 implementation and documentation. The three major objectives of this white paper are to: i) inform company decision makers how the strategic integration of MID3 can benefit R&D efficiency; ii) provide MID3 analysts with sufficient material to enhance the planning, rigor, and consistency of the application of MID3; and iii) provide regulatory authorities with substrate to develop MID3 related and/or MID3 enabled guidelines.


Learning
Confirming
Modeling
(Develop and Evaluate)
Utilize Established and
New Assumptions Based
on Pathology, Physiology
and Pharmacology
Data
- Disease Level
- Mechanism Level
- Compound Level
Generation of New
Experimental and
Trial Data
Test New
Assumptions
Knowledge
- Captured in the
Current Best Model
Inference
- Informed Conclusions
and Decision Making
Application of Current Best Model
Simulation and Prediction

Population PKPD: the beginning

- **Continuous variables**
- **Short time scale**
- **Exploratory studies**
- **Early phases in drug development**

➢ **Mainly learning**

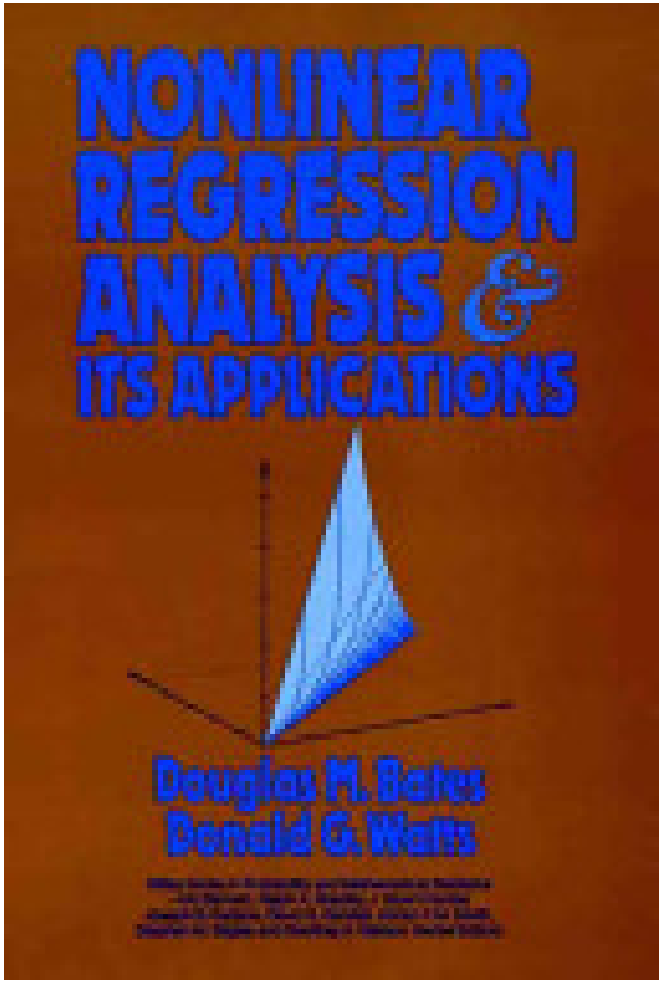
Pharmacometrics now

- **Clinical/ biomarker outcomes**
  - Longer time scale
  - Pivotal/confirming phases
  - Discrete variables and time to event
  - Disease progression
- **Results use for prediction / simulation**
  - Extrapolation
  - Planning / Design evaluation
  - Clinical trial simulation
  - Decision making…

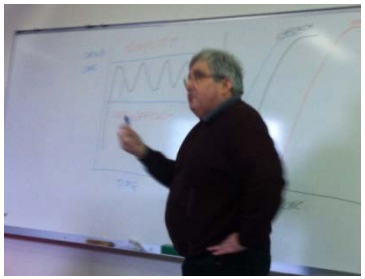
➢ **More attention to model building / estimation / uncertainties in inference**

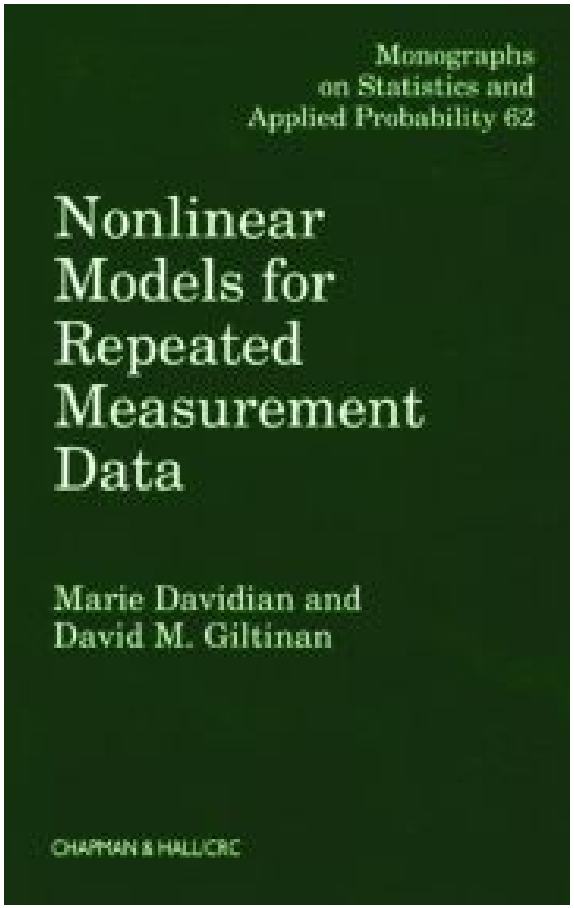
2. STATISTICIANS IN PHARMACOMETRICS

- **Estimation algorithms for NLMEM**
- **….**

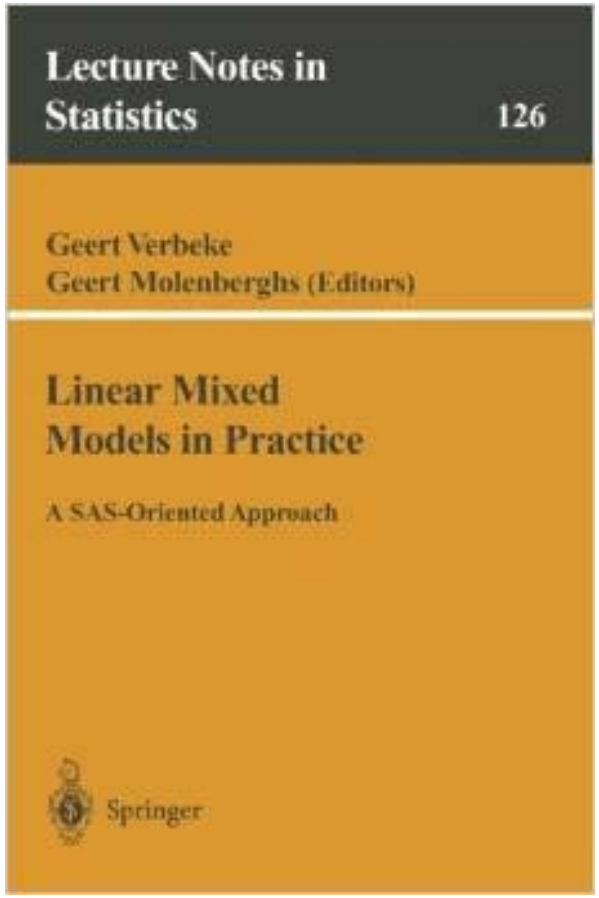

NONLINEAR
REGRESSION
ANALYSIS &
ITS APPLICATIONS
Douglas M. Bates
Donald G. Watts

1985

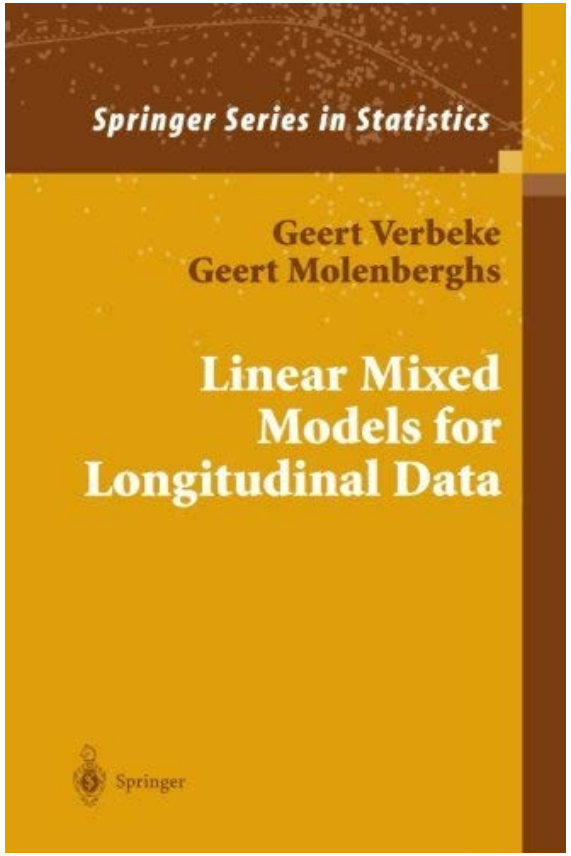


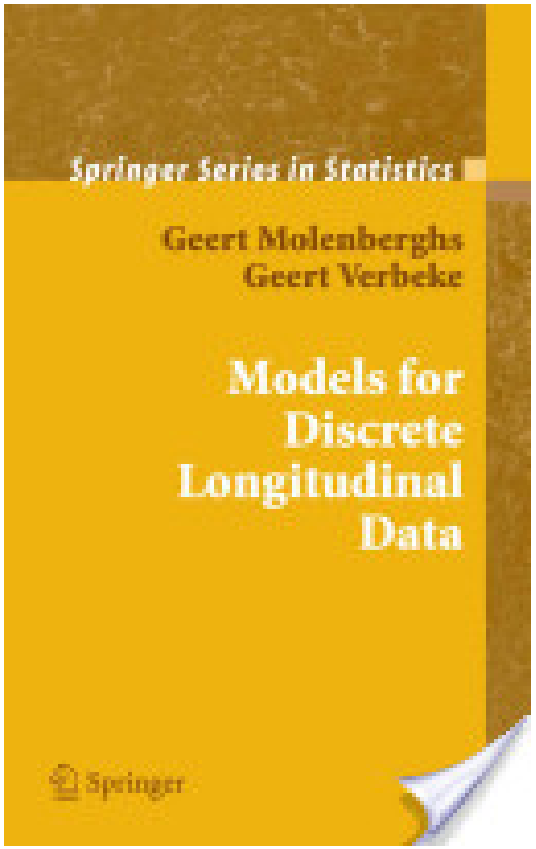

Monographs
on Statistics and
Applied Probability 62
Nonlinear
Models for
Repeated
Measurement
Data
Marie Davidian and
David M. Giltinan
CHAPMAN & HALL/CRC

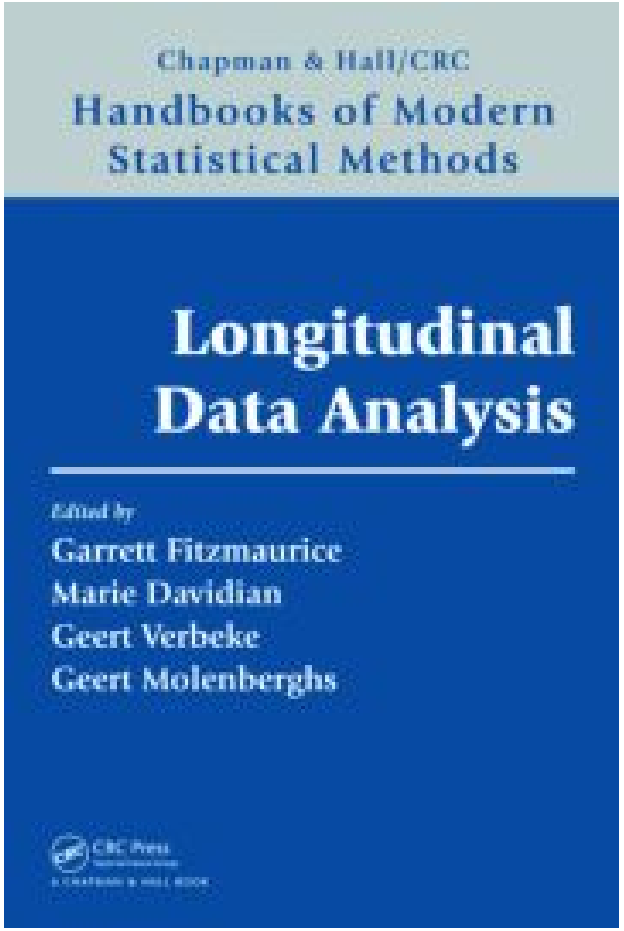
1995


Lecture Notes in
Statistics
126
Geert Verbeke
Geert Molenberghs (Editors)
Linear Mixed
Models in Practice
A SAS-Oriented Approach
Springer

1997



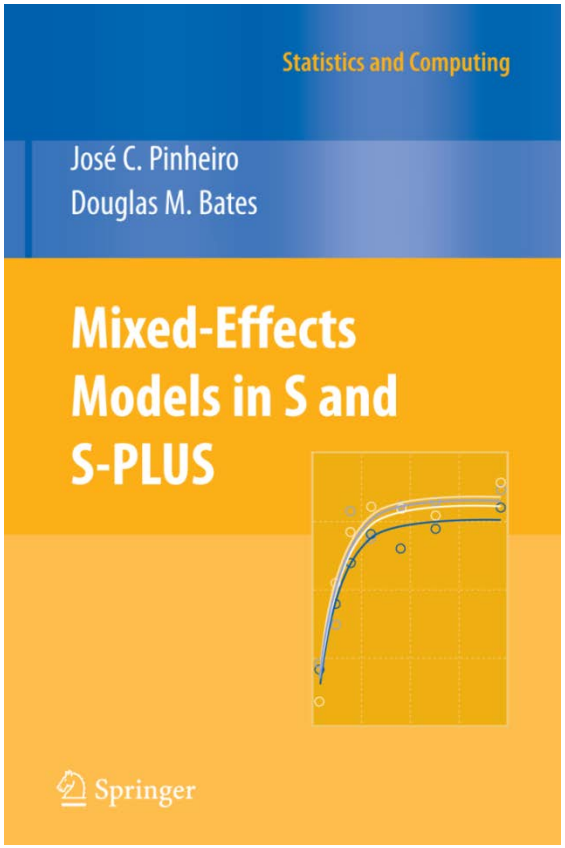


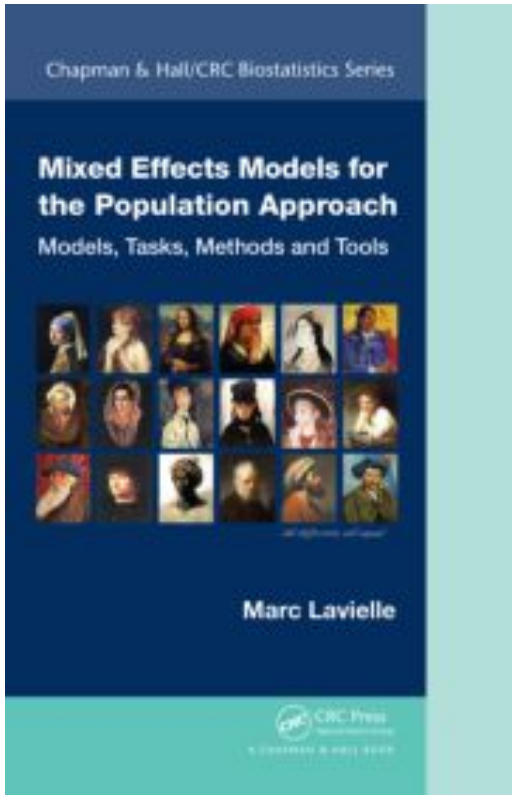


2000

2005

2008


Statistics and Computing
José C. Pinheiro
Douglas M. Bates
Mixed-Effects Models in S and S-PLUS
Springer


Chapman & Hall/CRC Biostatistics Series
Mixed Effects Models for the Population Approach
Models, Tasks, Methods and Tools
Marc Lavielle

2009

2014

Mould & Upton, **Basic concepts in population modeling, simulation and model-based drug development,** CPT: Pharmacomet Syst Pharmacol Pharm Sci 2012; 1:e6.

Table 4 Timeline for population modeling software development

Year	Event	Description
1972	Concept of "population pharmacokinetics"	The concept was published
1977	The first population pharmacokinetic analysis conducted	Application to digoxin data
1980	Announcement of NONMEM	An IBM-specific software for population pharmacokinetics
1984	NONMEM 77	A "portable" version of NONMEM
1989	NONMEM III	An improved user-interface with the NMTRAN front end. NONMEM Users Guide published
1989	BUGS software group forms	Different method: Markov chain Monte Carlo method
1991	USC*PACK	Different method: nonparametric population pharmacokinetic modeling (NPEM)
1992	NONMEM IV	New methods: FOCE

Mould & Upton, **Basic concepts in population modeling, simulation and model-based drug development,** CPT: Pharmacomet Syst Pharmacol Pharm Sci 2012; 1:e6.

Table 4 Timeline for population modeling software development

Year	Event	Description
1992	Publication with NPEM	First publication using NPEM method
1998	NONMEM V	New methods: mixture models
2001	Winbugs publication	First publication using Winbugs
2002	Publication with PKBUGs	Winbugs application designed for pharmacokinetic models
2003	Monolix Group Forms	Different method: stochastic approximation expectation maximization (SAEM)
2003	WinNonMix publication	Population modeling software with graphical user interface
2006	NONMEM VI	New methods: centering, HYBRID, nonparametric
2006	Monolix publications	First publications using Monolix
2009	Phoenix NLME	User-friendly GUI
2010	NONMEM 7	New methods: Bayes, SAEM, and others, parallel processing enabled
2012	Monolix 4.1	Full-script version (MLXTRAN, XML) and/or user-friendly GUI

Statisticians and estimation in NLMEM

Last decades

- **Development of good estimation methods and fast algorithms**

Present/ Future for estimation

- **More complex statistical models**
  - discrete data, RTTE, Markov model, joint models, dropouts, confounding, nonparametric, distributions, mixtures ….
- **More complex mechanistic models**
  - ODE, PDE, SDE….
- **Bayesian approaches** (HMC in STAN)
- **Better use of computers** (cloud, GPU,…)

➢ **Engineers, Computer scientists, Mathematicians, Statisticians….**

➢ **Enhanced (and new) software tools**

(Research) topics for statisticians for in pharmacomerics

- **Model evaluation**
- **Covariate model building**
- **Optimal design**
- **Joint models: prediction of event from biomarker evolution**
- **Uncertainty estimation and propagation**
- **Tests and inference for ‘small’ samples**
- **Model averaging**
- **Pooling data from various sources**
- **Multiplicity and type I error control**
- **…**

3. BRIDGING THE GAP

STATE OF THE ART

nature publishing group

Statisticians and Pharmacokineticists: What They Can Still Learn From Each Other

S Senn[1]

Examples are given of how the practice of statistics could be improved if statisticians showed a greater awareness of pharmacokinetic and pharmacodynamic modeling. Some examples are also given where a wider appreciation of statistical theory would improve current approaches to pharmacometrics. Areas in which the two disciplines are in agreement but have failed to have as much influence on others in drug development as they ought are also considered. It is concluded that there would be much benefit in increasing collaboration between these disciplines.

VOLUME 88 NUMBER 3 | SEPTEMBER 2010 | www.nature.com/cpt

‘The battle lines were clear’

On the one side were the forces of light:

those who liked models used biological insights, generally welcomed data from disparate sources and were not afraid to try various bold and ingenious strategies for putting models and data together

Bridging the gap

On the other side were the forces of darkness:

a bunch of dice throwers and hypothesis testers with an inane obsession with intention to treat

Statisticians and Pharmacokineticists: What They Can Still Learn From Each Other, S Senn, Clinical Pharmacology and Therapeutics (2010) 88: 328–334

Pitfalls in pharmacometrics

- **Handling of data (per protocol, ITT, missing, dropout)**
  - problem especially in confirmatory analysis
- **Multiple testing in model building, covariates analysis …**
  - Lack of control of type I error
- **Model evaluation, checking assumptions**
- **Often lacking model based analysis plan**
- **Design / sample size (uncertainty…)**

MODEL EVALUATION: A CORE SET OF GRAPHS

Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 87–109; doi:10.1002/psp4.12161

TUTORIAL

Model Evaluation of Continuous Data Pharmacometric Models: Metrics and Graphics

THT Nguyen[1], M-S Mouksassi[2], N Holford[3], N Al-Huniti[4], I Freedman[5], AC Hooker[6], J John[7], MO Karlsson[6], DR Mould[8], JJ Pérez Ruixo[9], EL Plan[10], R Savic[11], JGC van Hasselt[12], B Weber[13], C Zhou[14], E Comets[1,15] and F Mentré[1]*
for the Model Evaluation Group of the International Society of Pharmacometrics (ISoP) Best Practice Committee

This article represents the first in a series of tutorials on model evaluation in nonlinear mixed effect models (NLMEMs), from the International Society of Pharmacometrics (ISoP) Model Evaluation Group. Numerous tools are available for evaluation of NLMEM, with a particular emphasis on visual assessment. This first basic tutorial focuses on presenting graphical evaluation tools of NLMEM for continuous data. It illustrates graphs for correct or misspecified models, discusses their pros and cons, and recalls the definition of metrics used.
CPT Pharmacometrics Syst. Pharmacol. (2017) **6**, 87–109; doi:10.1002/psp4.12161; published online 24 November 2016.

[1]INSERM, IAME, UMR 1137, Paris, France, Université Paris Diderot, Sorbonne Paris Cité, Paris, France; [2]Certara Strategic Consulting, Montréal, Canada; [3]Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand; [4]Quantitative Clinical Pharmacology, AstraZeneca, Waltham, Massachusetts, USA; [5]Dr Immanuel Freedman Inc., Harleysville, Pennsylvania, USA; [6]Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; [7]Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Washington, DC, USA; [8]Projections Research Inc., Phoenixville, Pennsylvania, USA; [9]The Janssen Pharmaceutical Companies of Johnson & Johnson, Belgium; [10]Pharmetheus, Uppsala, Sweden; [11]Department of Bioengineering and Therapeutic Sciences, University of California – San Francisco, San Francisco, California, USA; [12]Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, Netherlands; [13]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, USA; [14]Genentech, San Francisco, California, USA; [15]INSERM CIC 1414, Rennes, France, University Rennes-1, Rennes, France. *Correspondence: F Mentré (france.mentre@inserm.fr)

Pitfalls in biostatistics

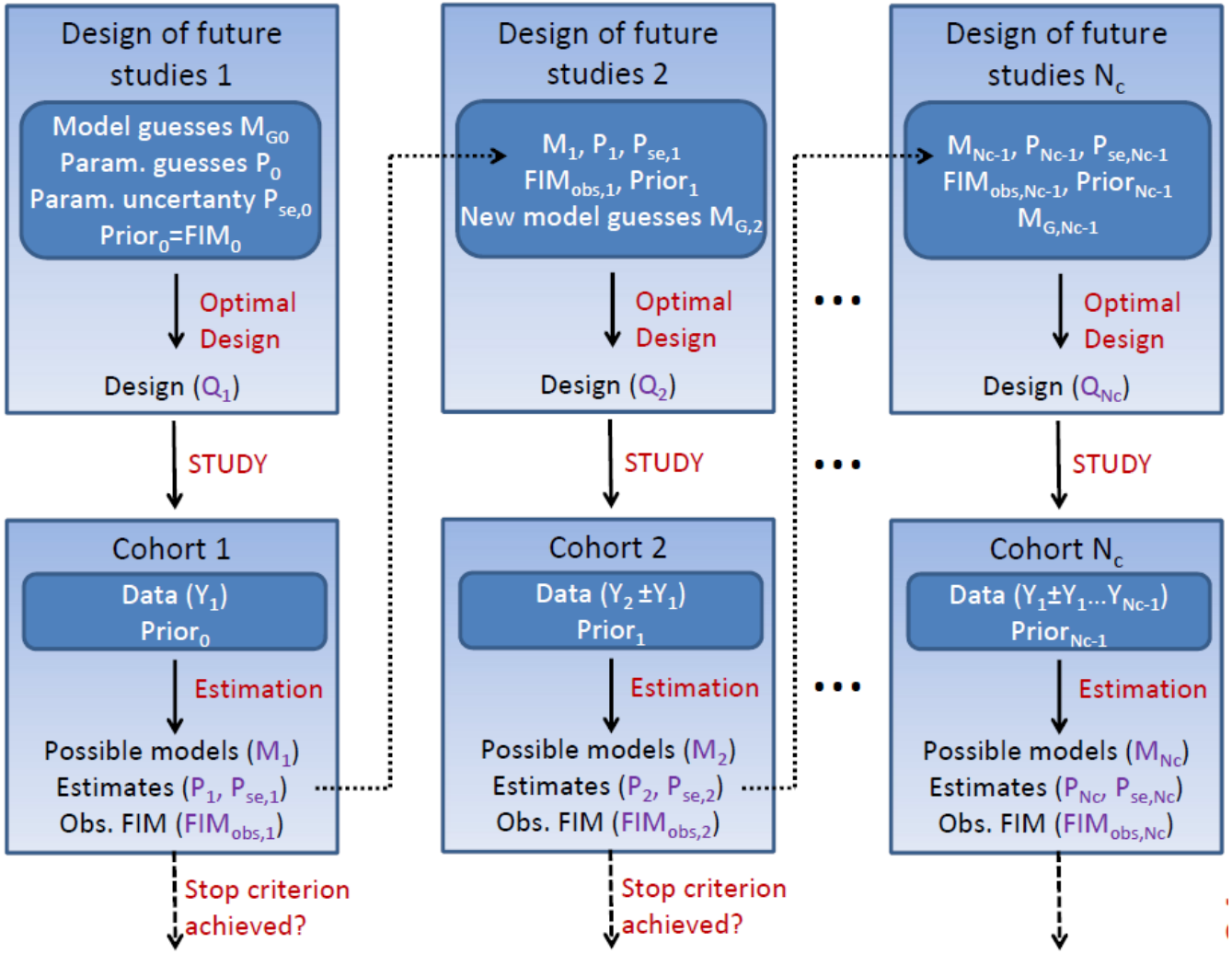
- **‘Stuck’ to standard linear or standard empirical models for end of trial data**
- **Like few assumption models**
  - whereas PKPD based on centuries of physiology in pharmacology
- **Reluctance to use new software/ tools, and not totally pre-specified analysis**
  - ‘fear’ for NLMEM or long

Benefits: evolution of both groups

- **More standardization in pharmacometrics**
- **More modelling in biostatistics (analysis of longitudinal data in clinical trials)**

➢ **Education and teaching**

Model based adaptive design: a common ground?



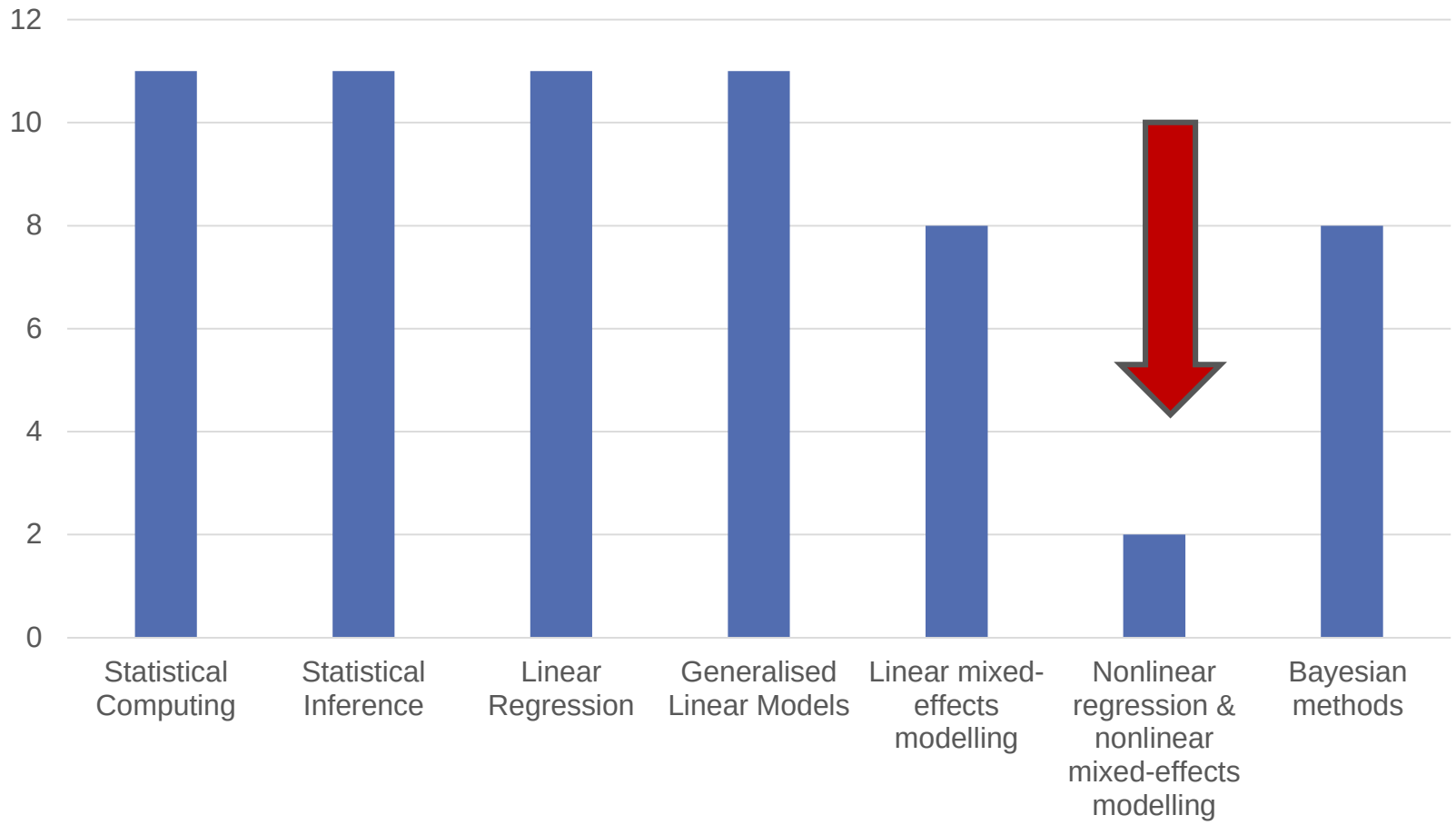
- **MBAOD prototype in R** (developed by Andrew Hooker, Uppsala University)

Masters in top 16 universities for Clinical, Pre-clinical and Health 2015-16

Rank	Institution	Country	Master of Biostatistics	Master of Pharmacometrics	Master of Computational Biology
1	University of Oxford	UK	√ (MSc Applied Stats)	X	X
2	Harvard University	USA	√	X	√
3	University of Cambridge	UK	X	X	√
4	University College London	UK	√	X	X
=5	University of California, Berkeley	USA	√	X	√ (1st year PhD)
=5	Imperial College London	UK	X	X	X
7	Stanford University	USA	√ (1st year PhD)	X	√ (1st year PhD)
8	King's College London	UK	X	X	X
9	Johns Hopkins University	USA	√	X	X
10	Columbia University	USA	√	X	X
11	University of Toronto	Canada	√	X	X (undergraduate training)
12	University of Edinburgh	UK	X	X	X
13	Karolinksa Institute	Sweden	X	X	X
14	Duke University	USA	√	X	√ (1st year PhD)
=15	University of California, Los Angeles	USA	√	X	√ (MSc Biomathematics)
=15	University of Melbourne	Australia	√	X	X

From Julie Simpson (University of Melbourne), WCoP 2016

Master of Biostatistics (11 Universities): Skill set for PK-PD modelling?



ASA Statistics and Pharmacometrics Interest Group (SxP)

AMERICAN STATISTICAL ASSOCIATION
Promoting the Practice and Profession of Statistics®

ISOP INTERNATIONAL SOCIETY OF PHARMACOMETRICS

- SxP: Special Interest Group created in 2016

➢ Promote collaboration between Statisticians and Pharmacometricians

- to enable each discipline to learn and grow from the other
- to develop innovative approaches to model informed drug development

- Steering Committee
  - Co-chairs: Bret Musser (Merck) & Matt Rotelli (Lilly)
  - Fred Balch (U Utah), Rob Bies (U Buffalo), Brian Corrigan (Pfizer), Kevin Dykstra (qPhametra), Manolis Efthymios (EMA), Jonathan French (Metrum), Lena Friberg (U Uppsala), Alan Hartford (Abbvie), France Mentre (U Paris Diderot & INSERM), Jose Pinheiro (J&J), Dionne Price (FDA), Garry Rosner (Johns Hopkins), Vikram Sinha (FDA), Brian Smith (Novartis), Jing Su (Merck), Neelima Thaneer (BMS), Jingtao Wu (Takeda)

- Membership open to everyone
- Join http://community.amstat.org/sxp/home

SxP organizes sessions in both statistics & pharmacometrics conferences

- **PAGE (June 2016):** First announcement of SxP
- **ACOP7 (Oct 2016):** Meet the ASA/ISoP Stat SIG
- **Joint Statistical Meeting (July 2016):** A mixer on SxP SIG

- **WCoP 2016 (August 2016)**

  Session: Bridging the gap between pharmacometricians and statisticians
- **ASA/FDA Regulatory-Industry Statistics Workshop (Sept 2016)**

  Panel session: Moving pharmacometrics and statistics beyond a marriage of convenience - Improving discipline synergy and drug development decision making
- **ASCPT (March 2017)**

  Symposium: Using biomarkers to predict registration endpoints: a look inside the crystal ball
- **Joint Statistical Meeting (July 2017)**

  Session: Pharmacometric Programming
- **Joint Conference on Biometrics & Biopharmaceutical Statistics (August 2017)**

  Session: Collaboration space between statistics and pharmacometrics: Opportunity and Challenges
- **ACOP8 (Oct 2017)**

  Symposium: Integrating quantitative disciplines - Making model-informed discovery and drug development (MID3) work in practice
- .....

Statistics and Pharmacometrics - Why I care

By Matthew D. Rotelli posted 10 days ago

1 Recommend

I'm a statistician and a pharmacometrician. Some people think I'm better as one than the other; some don't think I'm very good at either. I've been a statistician longer, but I've been a pharmacometrician for the last six years. Personally, I'd like to excel at both. Then I would be able to do a better job of capturing what I have learned and observed in experiments through models. I could use those models to improve my next design. I could use the new data to refine my models, and so on. By the end of development, I could use what I have learned from my experiments and models to provide stronger evidence and better information about the safe and efficacious use of the drugs. I'd be able to use the data that subjects and patient volunteers have taken the time and had the courage to provide to drive better decisions about whether and how a drug should be developed. I could get the drugs that are safe and effective to the broader patient population more quickly. That's the main reason most of us got into the pharmaceutical area; so I definitely wish I could do it better. Then, maybe the more efficient approach to development (quicker abandonment of bad molecules, higher probabilities of success for good molecules, and more efficient designs) will lead to reductions in spending on medicines and, through better outcomes, the even more important reductions in the overall spend on healthcare. That's a side effect I could tolerate!

But try as I might, I just can't seem to learn everything I need to know about statistics and pharmacometrics. So I need to lean on the expertise of my colleagues in both those fields. Fortunately, there are some statisticians who have a great understanding of pharmacometrics, and some pharmacometricians who have a great understanding of statistics. More likely, on any given project, I encounter a really good statistician and a really good pharmacometrician. It's amazing when they work together really well. However, too often, whether due to organizational structure or workload, they don't spend enough time interacting. It is often difficult to understand the other's approach, particularly when seeing it for the first time. It can be frustrating when either one objects to the conclusions drawn by the other. My experience has been that it is very rare that one is right and the other is wrong. They each apply different philosophies, they often are seeking to answer different questions, they use different terminology, and they almost always start with different assumptions. I'm hoping I can use my combined background to facilitate bridging the two disciplines. It's not as convenient as being able to do it all myself of course, but it's much more feasible. It should also be a great relief to those that don't think I'm very good at either!

When the different approaches do result in the same conclusions, that's great! We can be more confident in what we have learned. The data is clear, the signal is strong, and we have a good understanding of the underlying processes. It's when the different approaches don't agree that there is a great opportunity for learning and improvement. Something unexpected has happened, or there is a gap in our knowledge. Often, the in-depth discussion of the different approaches can lead to good hypotheses which can be subsequently evaluated. Sometimes, it highlights the need for more data or additional experiments. Either way, our knowledge and certainty will improve or we can highlight the uncertainties remaining.

To achieve the vision of efficient drug development, we must realize the synergies between statistical and pharmacometric approaches. We need to take the time to explain our models, understand the differences in approaches, understand what it implies if conclusions are similar or if they're not, and leverage each approach to continually inform and improve the other. I may never be as good at either discipline as I'd like to be, but at least my experience has taught me the value of both. I hope we continue to find ways to work together to bring better medicines to patients faster.

All Time

Topic	Users	Replies	Views	Activity
What are the sticking points between statistics and pharmacometrics?		9	625	Apr 20
Optimal PK sampling shedule		5	540	Mar 13
When is a result worth noting? A quick thought on pharmacometrics and multiplicity		5	687	Mar 15
My Career as a Pharmacometrician and Commentary on the Overlap Between Statistics and Pharmacometrics in Drug Development		0	705	Feb '16
Survey to Help in Planning		0	142	Mar 10
Announcing SxP (Statistics and Pharmacometrics Interest Group)		0	460	Jun '16
Variability, Uncertainty, and Error		4	428	Mar 29
2016 ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop		0	254	Oct '16
Statistics and Pharmacometrics Blog		1	59	1d
Symposium on Dose Selection for Cancer Treatment Drugs		0	121	Apr 24

Personal perspectives & hopes ....

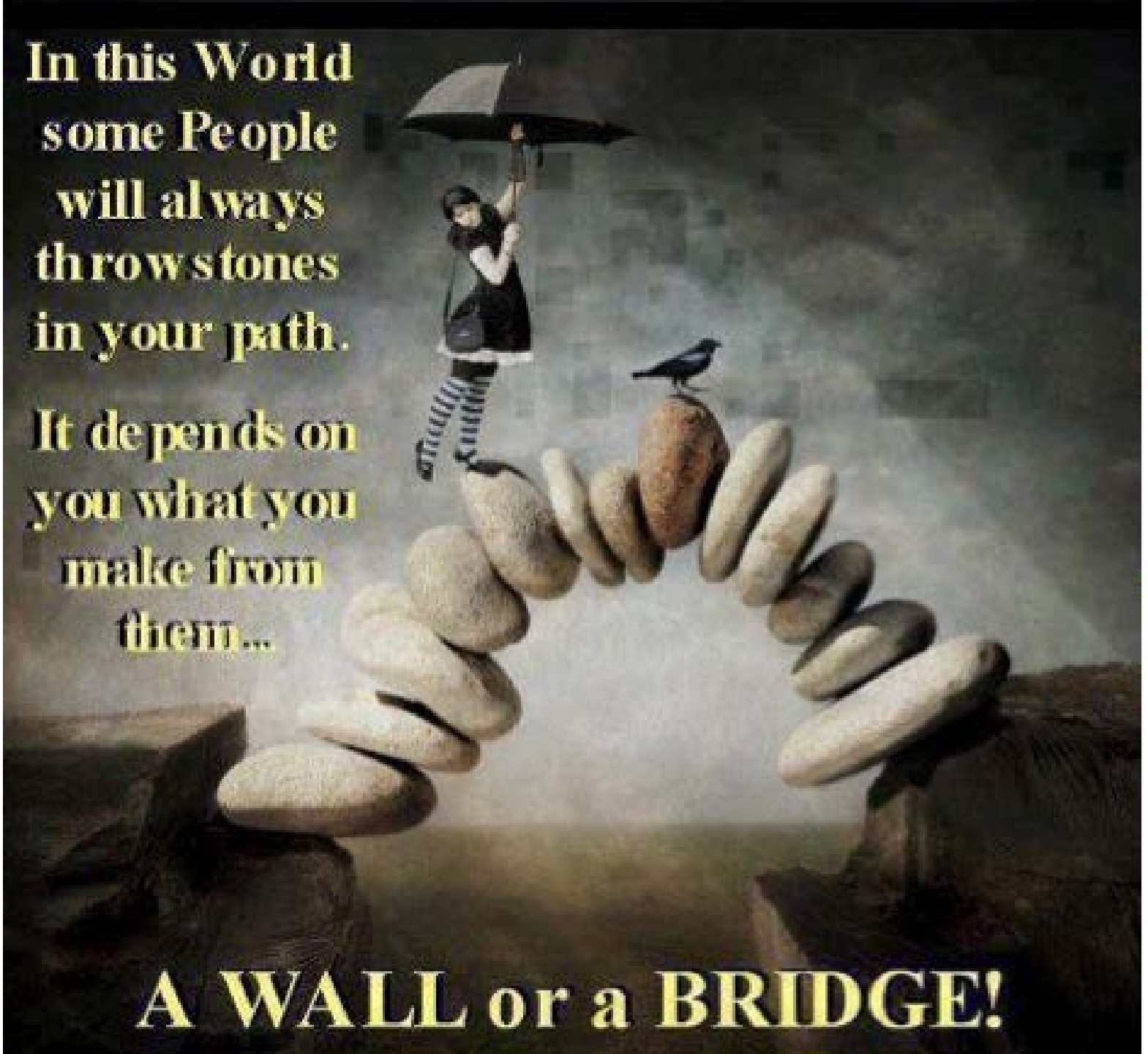
1. **Model-based analysis of pivotal trials in drug development and academic research**
2. **Model-based treatment personalization**
3. **Model-based evaluation of treatments in the developing world**

Pharmacometricians AND

(Bio)Statisticians

➢ **Help decrease disease burden in the world**

- better drugs/ treatments
- better targeted to each patient


In this World some People will always throw stones in your path.
It depends on you what you make from them...
A WALL or a BRIDGE!


We build too many walls
and not enough bridges.
~ Isaac Newton