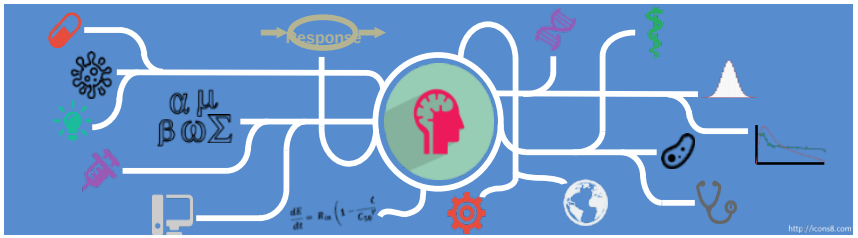


2018 SHEINER - BEAL PHARMACOMETRIC AWARD:

‘STANDING ON THE SHOULDER OF GIANTS’

PR FRANCE MENTRÉ

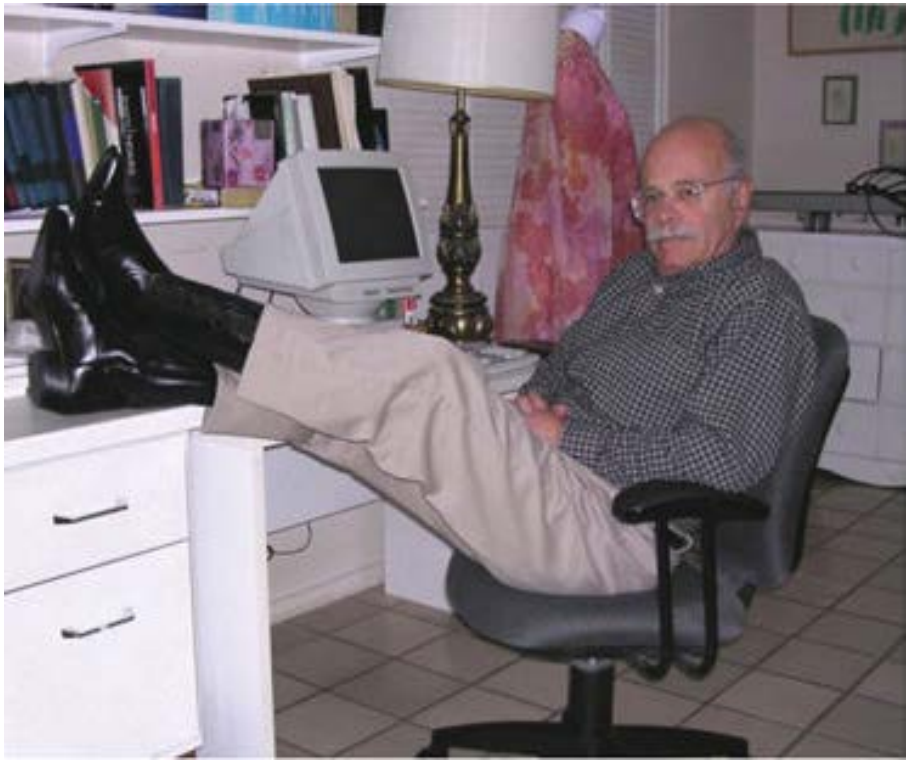
UNIVERSITY PARIS DIDEROT – INSERM – UMR 1137

BIOSTATISTICAL MODELLING AND PHARMACOMETRICS

ASCPT – March 2018

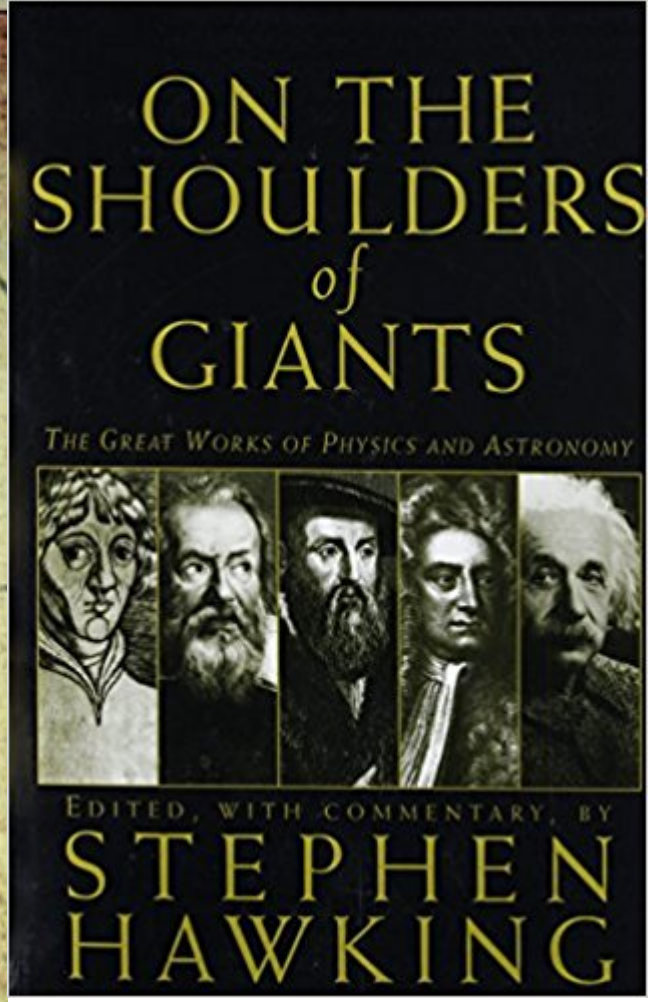
Lew Sheiner

Stuart Beal



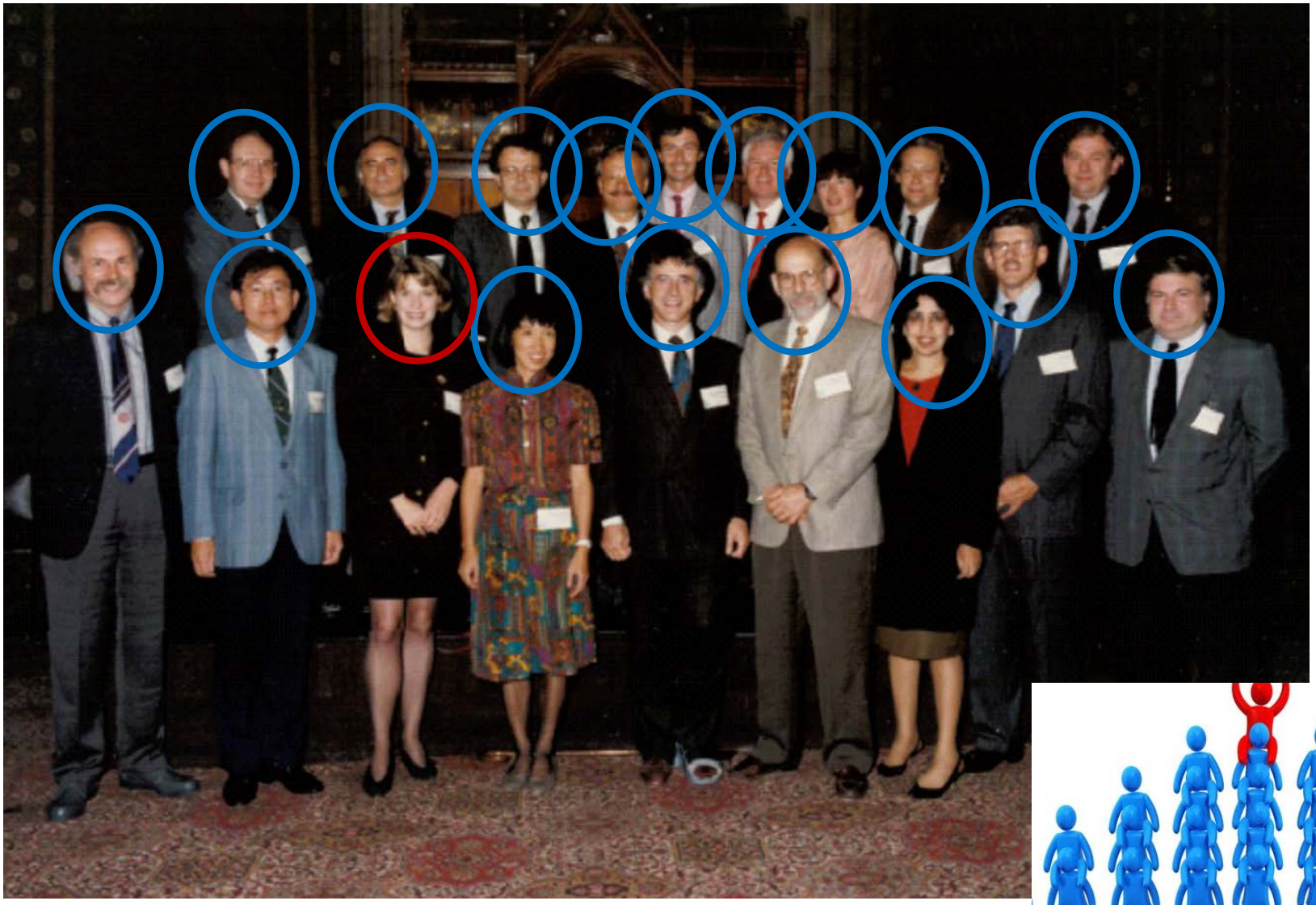
If I have seen further it is by standing on the shoulders of giants.

Isaac Newton



1942 - 2018

COST Meeting: New strategies in drug development and clinical evaluation (1991)



Past recipients of the ASCPT Sheiner-Beal pharmacometrics award:

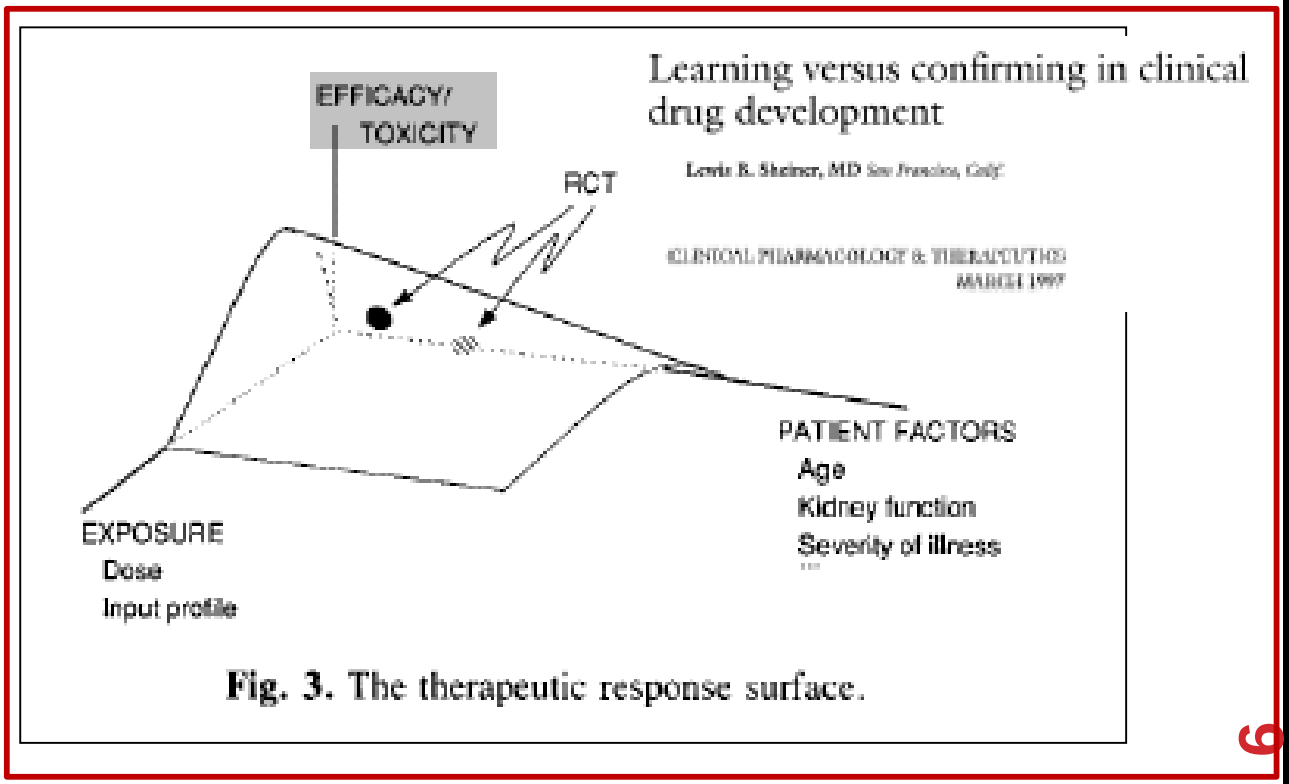
2017 Carl Peck
2015 Thomas M. Ludden
2014 Mats Karlsson
2013 William J. Jusko
2012 Malcolm Rowland
2011 Donald R. Stanski

Lew Sheiner

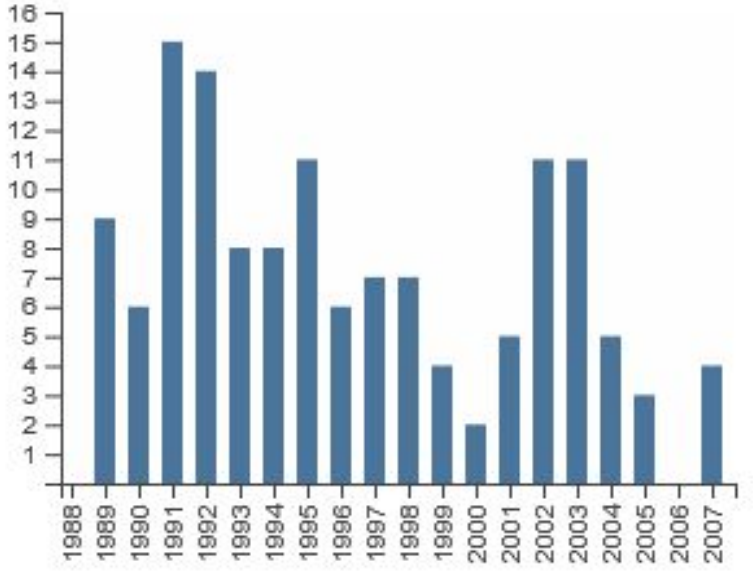
An impressive scientist who created a new discipline!

PHARMACOMETRICS

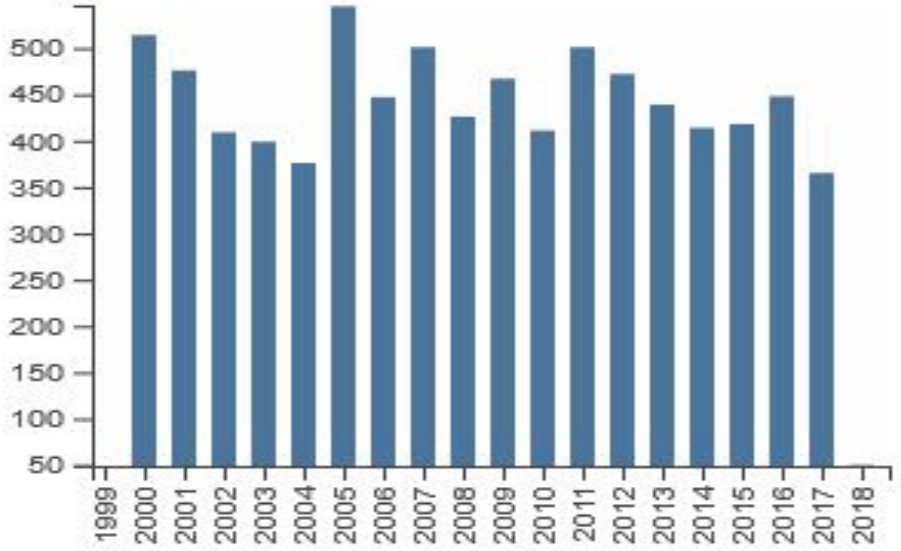
- **Web of Science**
  - 234 publications
  - 15,755 citations
  - H index = 62



Publications (N=234)



Citations (n=15,755 March 2018)



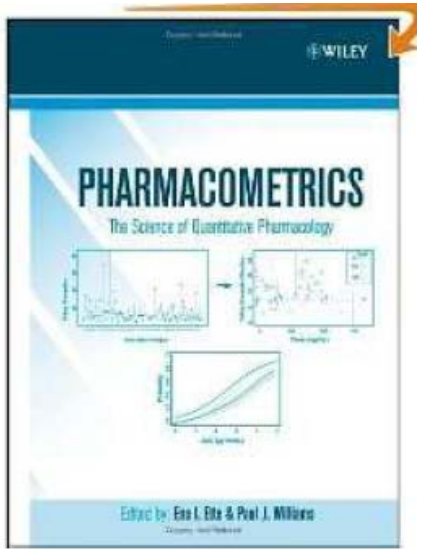
10 most cited papers
(March 2018)

SHEINER, LB; BEAL, SL	SOME SUGGESTIONS FOR MEASURING PREDICTIVE PERFORMANCE	JOURNAL OF PHARMACOKINETICS AND BIOPHARMACEUTICS	1981	1221
HOLFORD, NHG; SHEINER, LB	UNDERSTANDING THE DOSE-EFFECT RELATIONSHIP - CLINICAL-APPLICATION OF PHARMACOKINETIC-PHARMACODYNAMIC MODELS	CLINICAL PHARMACOKINETICS	1981	1023
SHEINER, LB; STANSKI, DR; VOZEH, S; MILLER, RD; HAM, J	SIMULTANEOUS MODELING OF PHARMACOKINETICS AND PHARMACODYNAMICS - APPLICATION TO D-TUBOCURARINE	CLINICAL PHARMACOLOGY & THERAPEUTICS	1979	997
SHEINER, LB; ROSENBERG, B; MARATHE, VV	ESTIMATION OF POPULATION CHARACTERISTICS OF PHARMACOKINETIC PARAMETERS FROM ROUTINE CLINICAL DATA	JOURNAL OF PHARMACOKINETICS AND BIOPHARMACEUTICS	1977	483
HOLFORD, NHG; SHEINER, LB	KINETICS OF PHARMACOLOGIC RESPONSE	PHARMACOLOGY & THERAPEUTICS	1982	377
MANDEMA, JW; VEROTTA, D; SHEINER, LB	BUILDING POPULATION PHARMACOKINETIC PHARMACODYNAMIC MODELS .1. MODELS FOR COVARIATE EFFECTS	JOURNAL OF PHARMACOKINETICS AND BIOPHARMACEUTICS	1992	358
SHEINER, LB; BEAL, S; ROSENBERG, B; MARATHE, VV	FORECASTING INDIVIDUAL PHARMACOKINETICS	CLINICAL PHARMACOLOGY & THERAPEUTICS	1979	343
SHEINER, LB; BEAL, SL	EVALUATION OF METHODS FOR ESTIMATING POPULATION PHARMACOKINETIC PARAMETERS .1. MICHAELIS-MENTEN MODEL - ROUTINE CLINICAL PHARMACOKINETIC DATA	JOURNAL OF PHARMACOKINETICS AND BIOPHARMACEUTICS	1980	327
KARLSSON, MO; SHEINER, LB	THE IMPORTANCE OF MODELING INTEROCCASION VARIABILITY IN POPULATION PHARMACOKINETIC ANALYSES	JOURNAL OF PHARMACOKINETICS AND BIOPHARMACEUTICS	1993	320
SHEINER, LB	LEARNING VERSUS CONFIRMING IN DRUG DEVELOPMENT	CLINICAL PHARMACOLOGY & THERAPEUTICS	1997	315

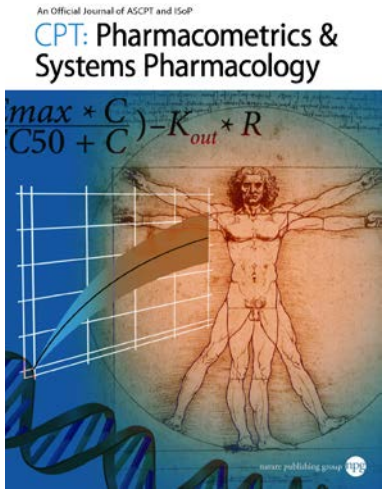
Pharmacometrics in the world

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

- **Book**
  - Pharmacometrics (2007)



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



From PopPKPD to MID3

- **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)**

Pop PKPD: the beginning

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

➢ **Mainly learning**

Pharmacometrics now

- **Clinical end points**
  - Longer time scale
  - Pivotal/confirming phases
  - Discrete variables and time to event
  - Disease progression
- **Results use for prediction / simulation & statistical inference**
  - Extrapolation
  - Planning / Design evaluation
  - Clinical trial simulation
  - Testing, Decision making…

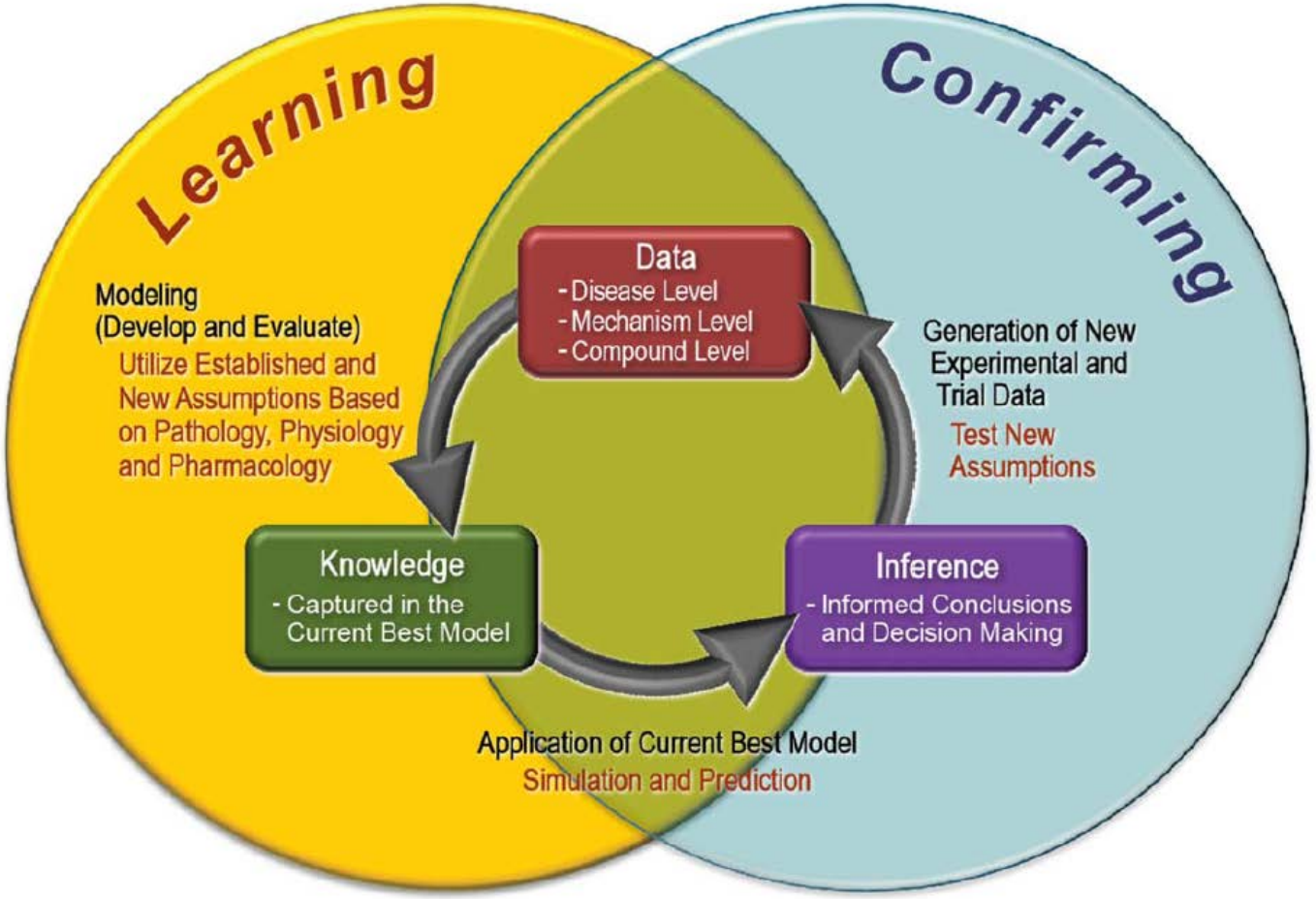
➢ **More attention to model building / estimation / uncertainties in inference**

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]



Statistical methods in NLMEM

1. **Estimation methods**
2. **Model evaluation**
3. **Design of experiments**

- **The impact of Lew Sheiner & Stuart Beal**
- **My contributions**
- **Future…**

1. ESTIMATION METHODS

- **1972: The concept and the FO method**

  Sheiner, Rosenberg, Melmon (1972). Modelling of individual pharmacokinetics for computer aided drug dosage. *Comput Biomed Res*, 5:441-59.

- **1977: The first case study**

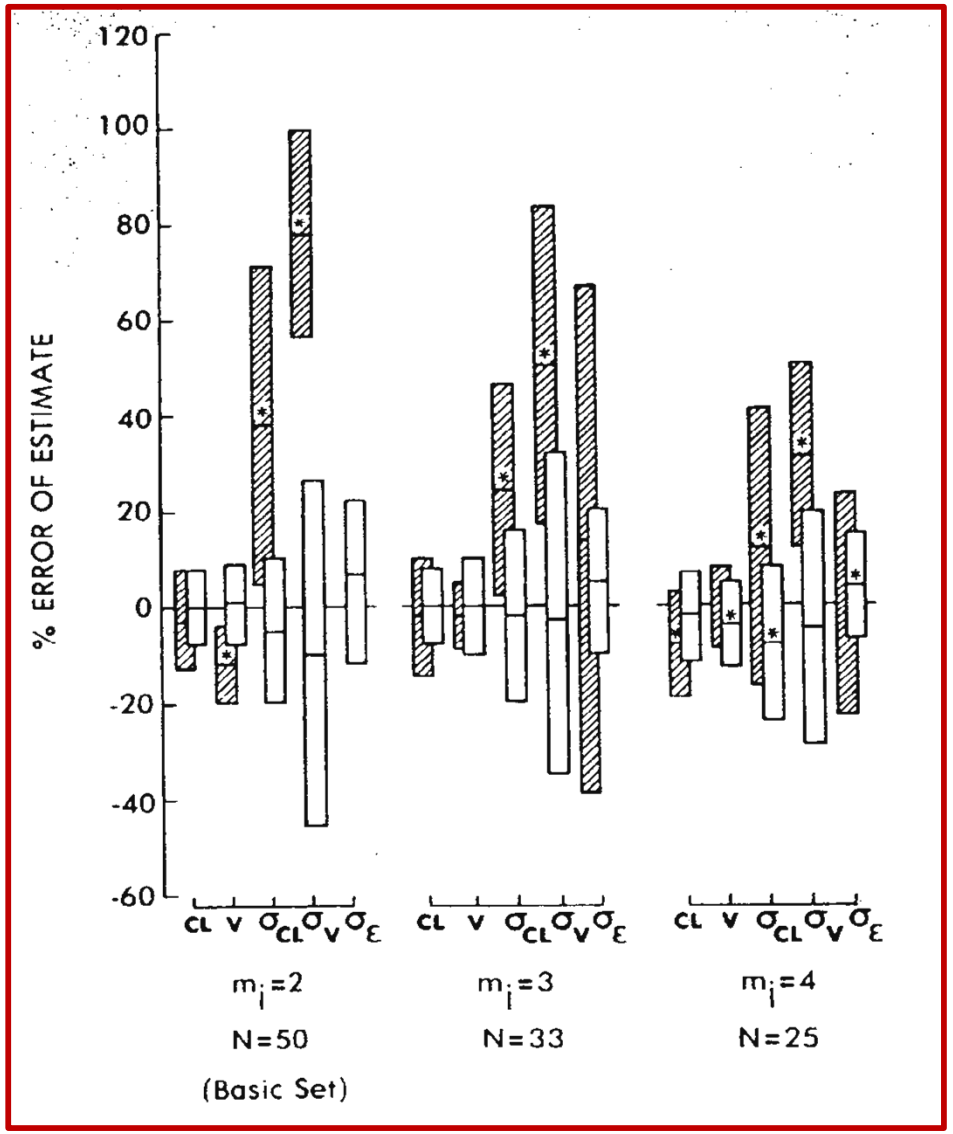
  Sheiner, Rosenberg, Marathe (1977). Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. *J Pharmacokin Biopharm*, 5: 445-479.

- **1980: NONMEM - An IBM-specific software**

  Beal, **Sheiner** (1980). The NONMEM system. *American Statistician, 34:118-19*.

  Beal, Sheiner (1982). Estimating population kinetics. *Crit Rev Biomed Eng*, 8:195-222.

Comparison of STS (shaded blocks) and NONMEM (white blocks) on simulated data sets



Sheiner, Beal. Evaluation of methods for estimating population pharmacokinetic parameters

J Pharmacokinet Biopharm,

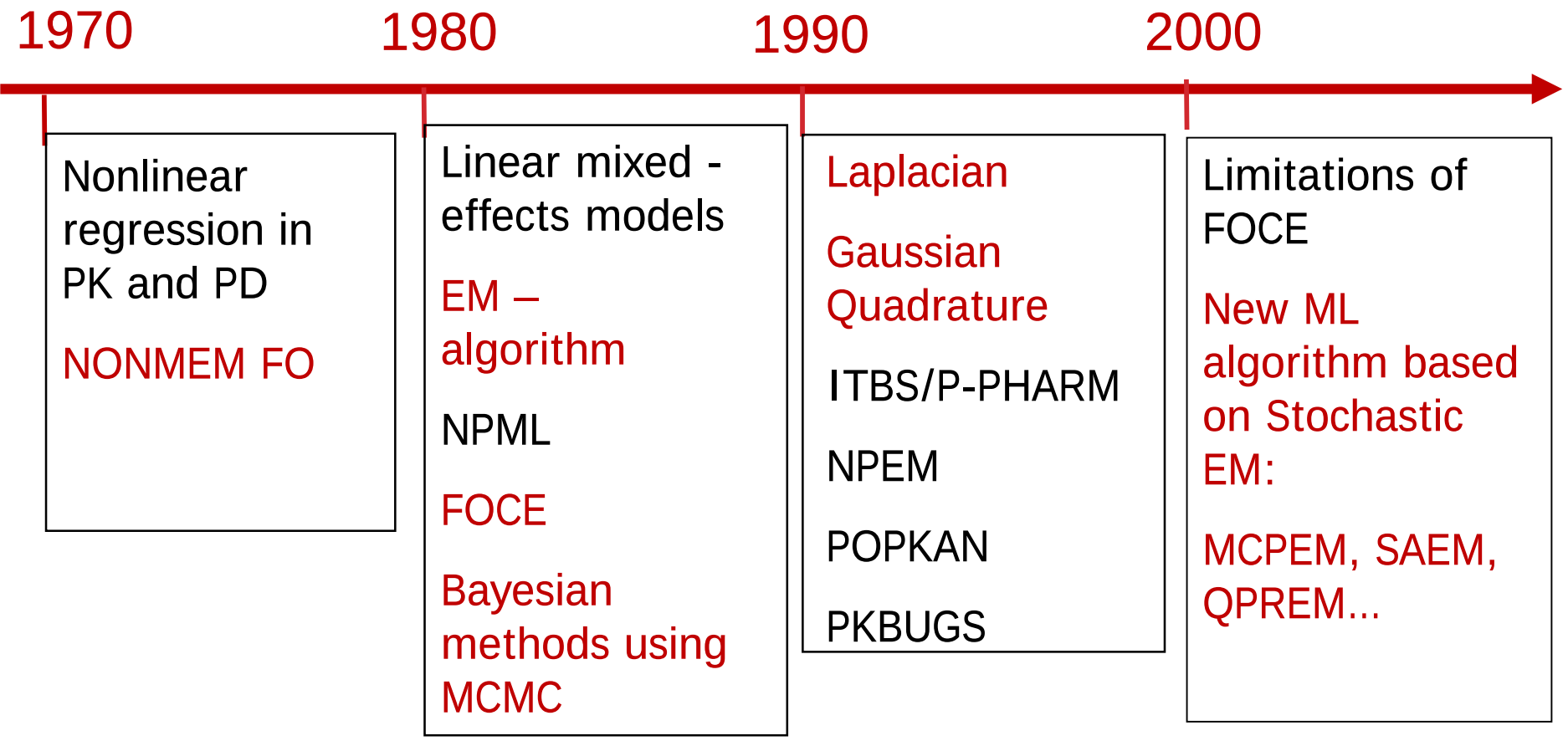
1. 1980
2. 1981
3. 1983

Discrete data

- **Sheiner**, **Beal**, Dunne (1997). Analysis of nonrandomly censored ordered categorical longitudinal data from analgesic trials. *J Am Stat Assoc*, *92*(440), 1235-1244.

- Cox, Veyrat-Follet, Beal, Fuseau, Kenkare, **Sheiner** (1999). A population pharmacokinetic-pharmacodynamic analysis of repeated measures time-to-event pharmacodynamic responses: the antiemetic effect of ondansetron. *J Pharmacokinet Biopharm.* 27(6):625-44

Development of estimation methods



Pillai, **Mentré**, Steimer (2005). Non-linear mixed effects modeling - from methodology and software development to driving implementation in drug development science. *J Pharmacokin Pharmacodyn*, 32:161-83.

Contribution to estimation methods (1)

Jean Louis Steimer (1982)

Alain Mallet (1984)

Mentré, Mallet, Steimer (1988). Hyperparameter estimation using stochastic approximation with application to population pharmacokinetics. *Biometrics.* 44(3):673-83.

Mallet, **Mentré** , Steimer , Lokiec (1988). Nonparametric maximum likelihood estimation for population pharmacokinetics, with application to cyclosporine. *J Pharmacokinet Biopharm.* 16(3):311-27.

- **NPML**

Contribution to estimation methods (2)

Mentré, Gomeni (1995). A two-step iterative algorithm for estimation in nonlinear mixed-effect models with an evaluation in population pharmacokinetics. *J Biopharm Stat.* 5(2):141-58.

Gomeni, Pineau**,** **Mentré** (1994). Population kinetics and conditional assessment of the optimal dosage regimen using the P-PHARM software package. *Anticancer Res*. 14(6A):2321-6.

- **ITS, P-PHARM**

Contribution to estimation methods (3)

Marc Lavielle (2003)

Lew Sheiner (2001)

Serge Guzy (2001)

MCPEM??

SAEM??

Adeline Samson (2003)

Lavielle, **Mentré** (2007). Estimation of population pharmacokinetic parameters of saquinavir in HIV patients with the MONOLIX software. *J Pharmacokinet Pharmacodyn.* 34(2):229-49.

Samson, Lavielle, **Mentré** (2007). The **SAEM** algorithm for group comparison tests in longitudinal data analysis based on non-linear mixed-effects model. *Stat Med*. 26(27):4860-75.

- **MONOLIX, in NONMEM, R: saemix, nlmixr**

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

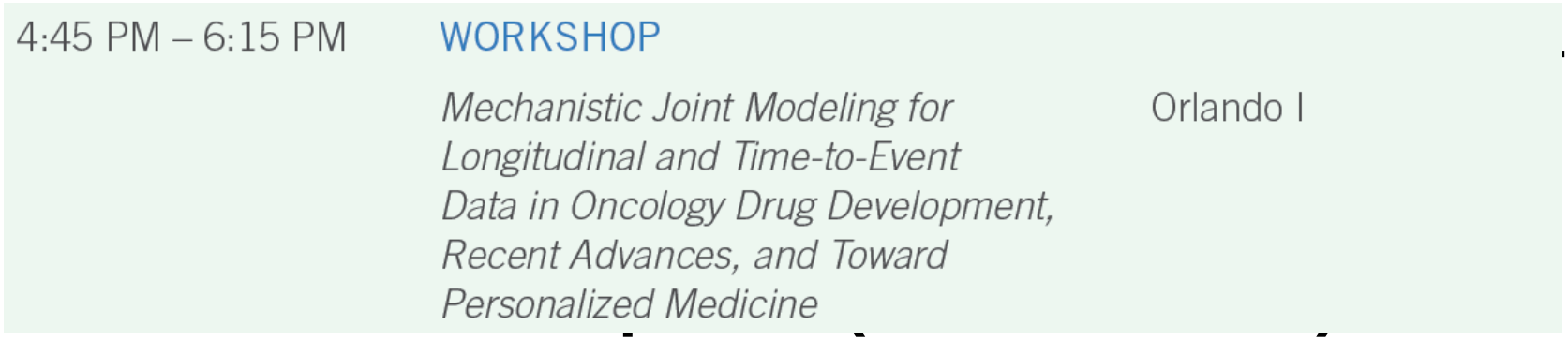
Mould & Upton, **Basic concepts in population modeling, simulation and model-based drug development,** CPT: Pharmacomet Syst Pharmacol Pharm Sci 2012; 1:e6.

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

Future….

- **Good estimation methods and fast algorithms**
- **More complex statistical models**
  - discrete data, RTTE, Markov models, IRT,
  - joint models , dropouts, confounding,



- **Better statistical inferences (uncertainty)**

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

➢ **Enhanced software tools**

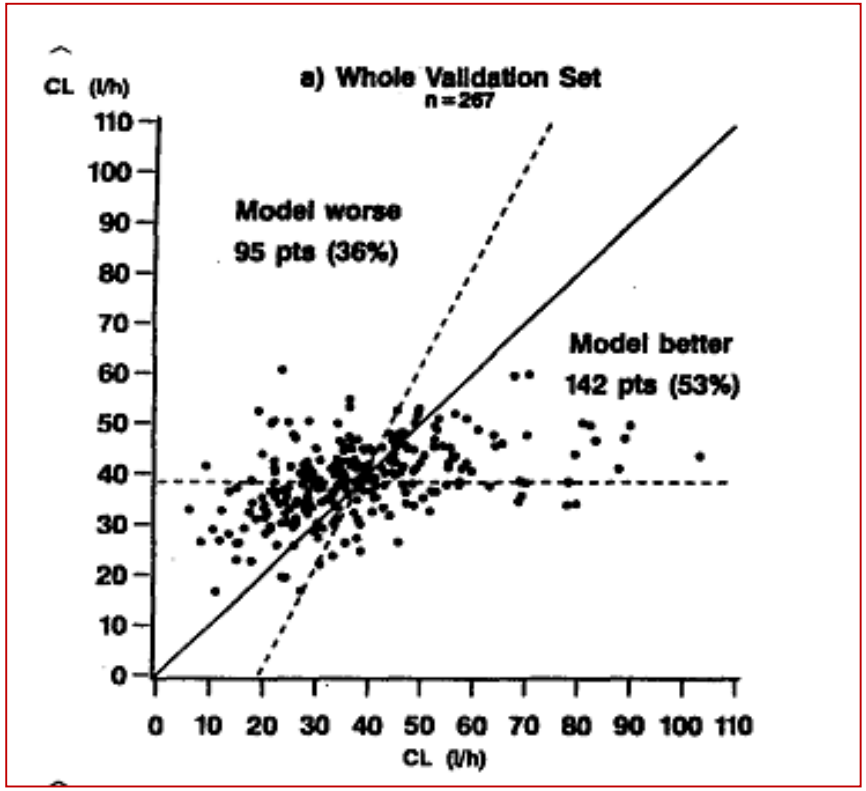
➢ **Greater Interoperability**

Drug Disease Model Resources ddmore

2. MODEL EVALUATION

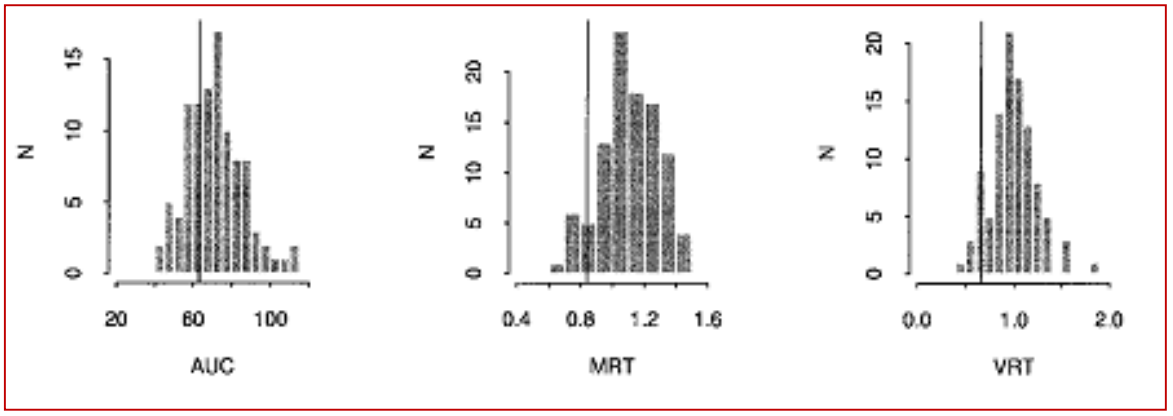
- **Sheiner**, **Beal** (1981). Some suggestions for measuring predictive performance. *J Pharmacokinet Biopharm*. 9(4):503-12
- Bruno, Vivier, Vergniol, De Phillips, Montay, **Sheiner** (1996). A population pharmacokinetic model for docetaxel (Taxotere): model building and validation. *J Pharmacokinet Biopharm*. 24(2):153-72.
- Yano, **Beal, Sheiner** (2001). Evaluating PKPD models using the posterior predictive check. *J Pharmacokinet Pharmacodyn.* 28(2):171-92.

➢ **Simulation-based model evaluation methods**



Bruno et al., JPB 1986

- External validation data set
- Prediction errors
- Evaluation of covariate model



Yano et al., JPKPD 2001

- Simulation based diagnostic
- PPC

Contribution to methods for model evaluation

Jean Louis Steimer (1996)

Lew Sheiner (2000)

Emmanuelle Comets (2000)

Karl Brendel (2006)

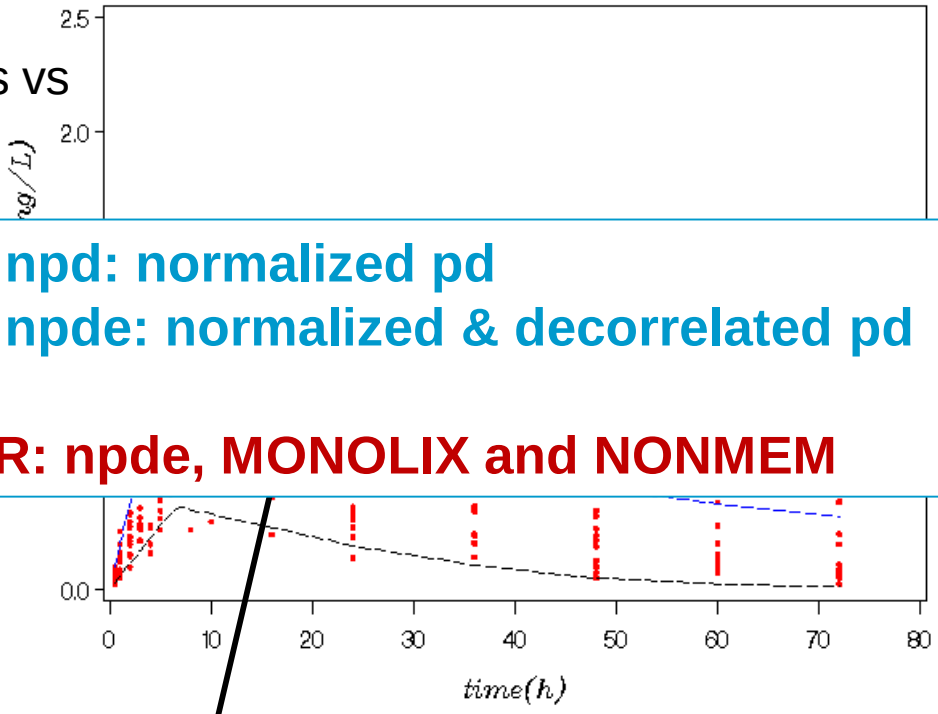
pseudo-residuals ➔ prediction discrepancies

- **Mentré**, Escolano (2006). Prediction discrepancies for the evaluation of nonlinear mixed-effects models. *J Pharmacokinet Pharmacodyn*. Jun;33:345-67.

- Comets , Brendel, **Mentré** (2008). Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: the npde add-on package for R. *Comput Methods Programs Biomed*. 90(2):154-66.

Prediction Discrepancies (PD)

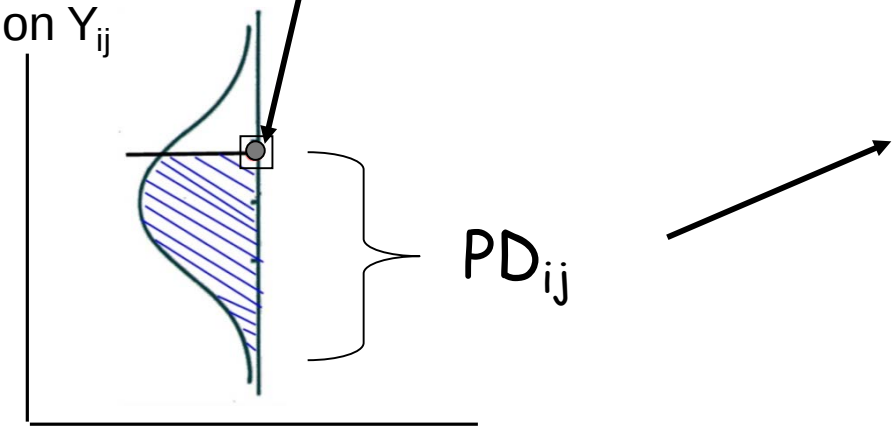
Observations vs time



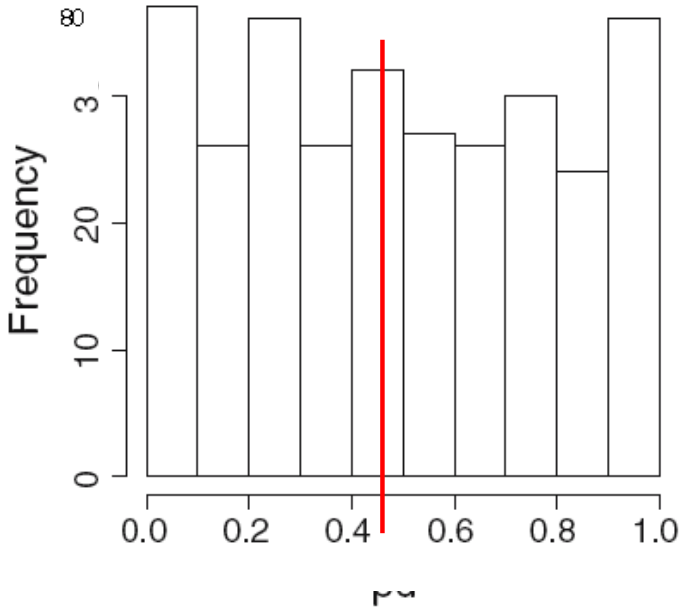
- **npd: normalized pd**
- **npde: normalized & decorrelated pd**

➢ **R: npde, MONOLIX and NONMEM**

Predicted distribution of observation Y_{ij}



Distribution of PD



npde for PK example with 3 doses: no splitting

npde: Normalised prediction distribution errors for nonlinear mixed-effect models

Routines to compute normalised prediction distribution errors, a metric designed to evaluate non-linear mixed effect models such as those used in pharmacokinetics and pharmacodynamics

Version:	2.0
Depends:	methods, mclust
Imports:	graphics, stats
Published:	2012-10-15
Author:	Emmanuelle Comets, Karl Brendel, Thi Huyen Tram Nguyen, France Mentre.
Maintainer:	Emmanuelle Comets <emmanuelle.comets at inserm.fr>
License:	GPL-2 | GPL-3 [expanded from: GPL (≥ 2)]
NeedsCompilation:	no
In views:	Distributions
CRAN checks:	npde results

```
-------------------------------------------
Distribution of npde :
      nb of obs: 600
           mean= 0.04471    (SE= 0.04 )
       variance= 0.9422    (SE= 0.054 )
       skewness= 0.00646
       kurtosis= -0.01451
-------------------------------------------

Statistical tests
  t-test                      : 0.26
  Fisher variance test        : 0.317
  SW test of normality        : 0.872
Global adjusted p-value       : 0.779
---
Signif. codes:  '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
-------------------------------------------
```

J Pharmacokinet Pharmacodyn (2012) 39:499–518
DOI 10.1007/s10928-012-9264-2

ORIGINAL PAPER

Extension of NPDE for evaluation of nonlinear mixed effect models in presence of data below the quantification limit with applications to HIV dynamic model

Thi Huyen Tram Nguyen · Emmanuelle Comets · France Mentré

Pharmaceutical Research (2018) 35: 30
https://doi.org/10.1007/s11095-017-2291-3

RESEARCH PAPER

CrossMark

Development and performance of npde for the evaluation of time-to-event models

M. Cerou[1,2,3,4,5] · M. Lavielle[6] · K. Brendel[5] · M. Chenel[5] · E. Comets[1,2,3,4]

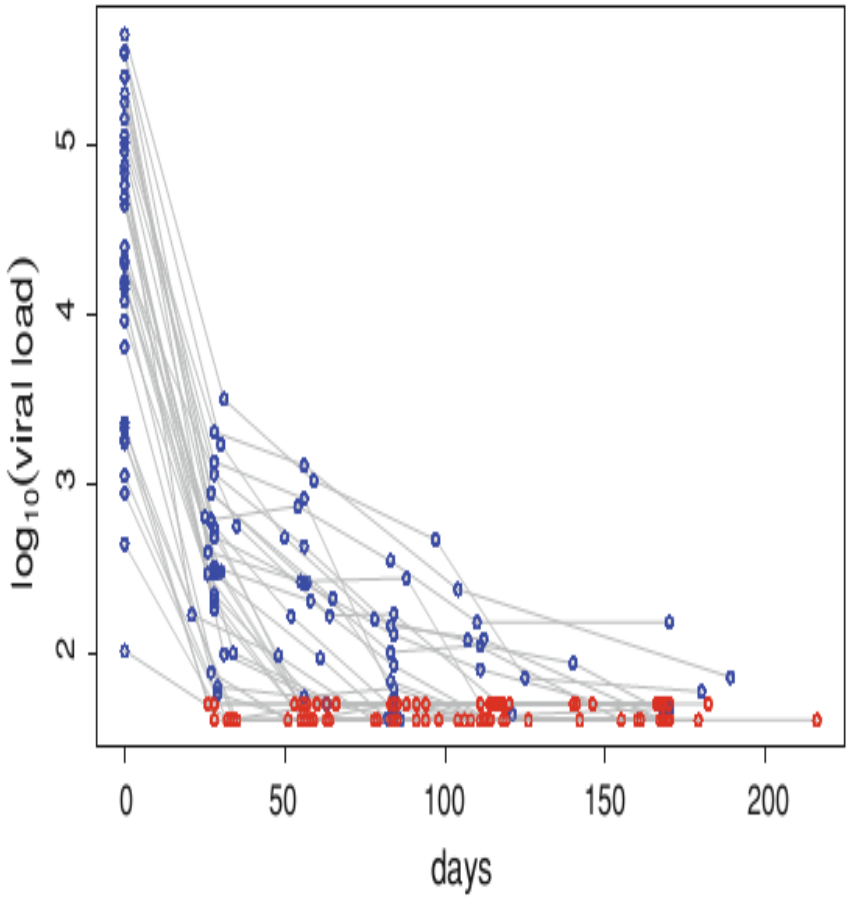
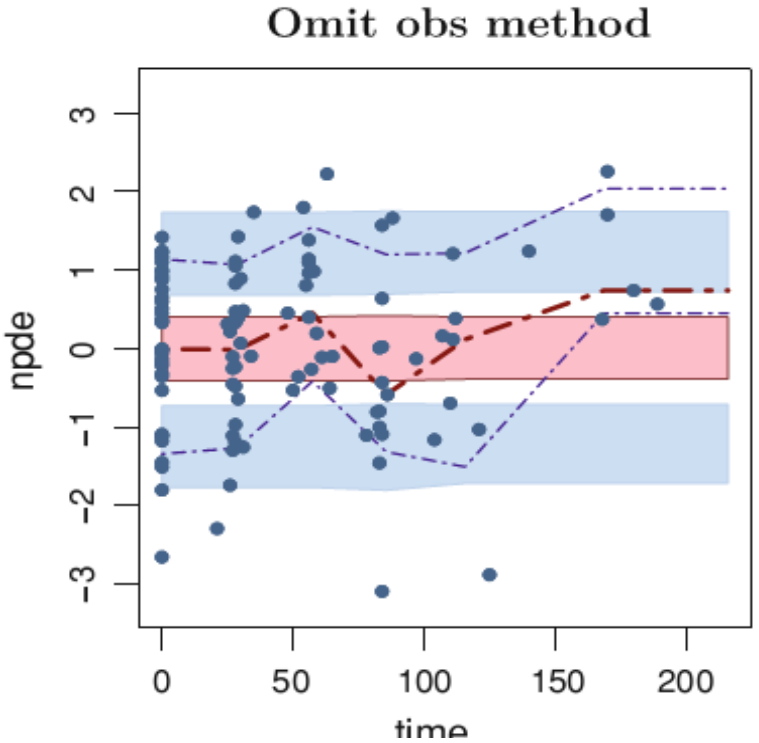
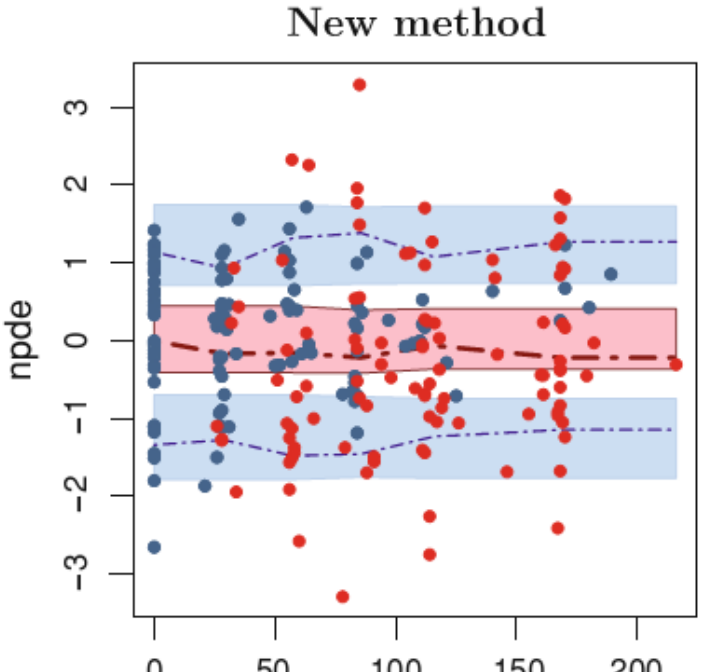


Fig. 1 Spaghetti plot of viral load in logarithmic scale versus time from COPHAR 3-ANRS 134 trial. Data above LOQ are presented as *blue circles*, data below LOQ are imputed at LOQ in this graph and presented as *red circles* (Color figure online)





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)

- **ISOP best practice committee** has initiated a ‘Model Evaluation Group’ (chair France Mentré)
- **Series of tutorials** to provide detailed guidance for model evaluation in pharmacometrics
- **First tutorial:** Model evaluation for continuous data pharmacometric models
  - Target audience: beginner modellers
  - Focus on graphical uses of evaluation tools
  - Define metrics and graphs
  - Propose a core set of graphs
- **Two tutorials in preparation**
  - for discrete data
  - time-to-event data

First tutorial: developed by an international group of experienced pharmacometricians from various backgrounds

Started October 2014 (ACOP), published online November 2016

1. Academia

Paris: **France Mentré**, **Emmanuelle Comets**, **Tram Nguyen**
Uppsala: **Mats Karlsson**, **Andy Hooker**
Auckland: **Nick Holford**
Netherlands Cancer Institute: **Coen Van Hasselt**
San Francisco : **Rada Savic**
Basel: Marc Pfister
Buffalo: Don Mager
INRIA: Marc Lavielle

2. Regulatory agencies

FDA: **Jyothy John**
EMA : Flora Musuamba Tshinanu

3. Software developers

Phoenix: Bob Leary

4. Pharmaceutical industries

Boehringer-ingelheim: **Benjamin Weber**
GSK: **Immanuel Freedman**
Genetech: **Norman Zhou**
JNJ: Chuanpu Hu, **Juan Jose Perez Ruixo**
Astra Zeneca: **Nidal Al-Huniti**
Merck : Malidi Ahamadi
Pfizer: Byon Wonkyung, Brian Corrigan, Peter Milligan
Novonordisk: Rune Overgaard

5. Consulting companies

Certara: **Samer Mouksassi**, Rene Bruno
Projection Research: **Diane Mould**
Pharmatheus : **Elodie Plan**
PKPD systems: Richard Upton
Qpharmetra: Kevin Dykstra

Participants: authors - commented first outline

GRAPHS FOR EVALUATION OF CONTINOUS NLMEM

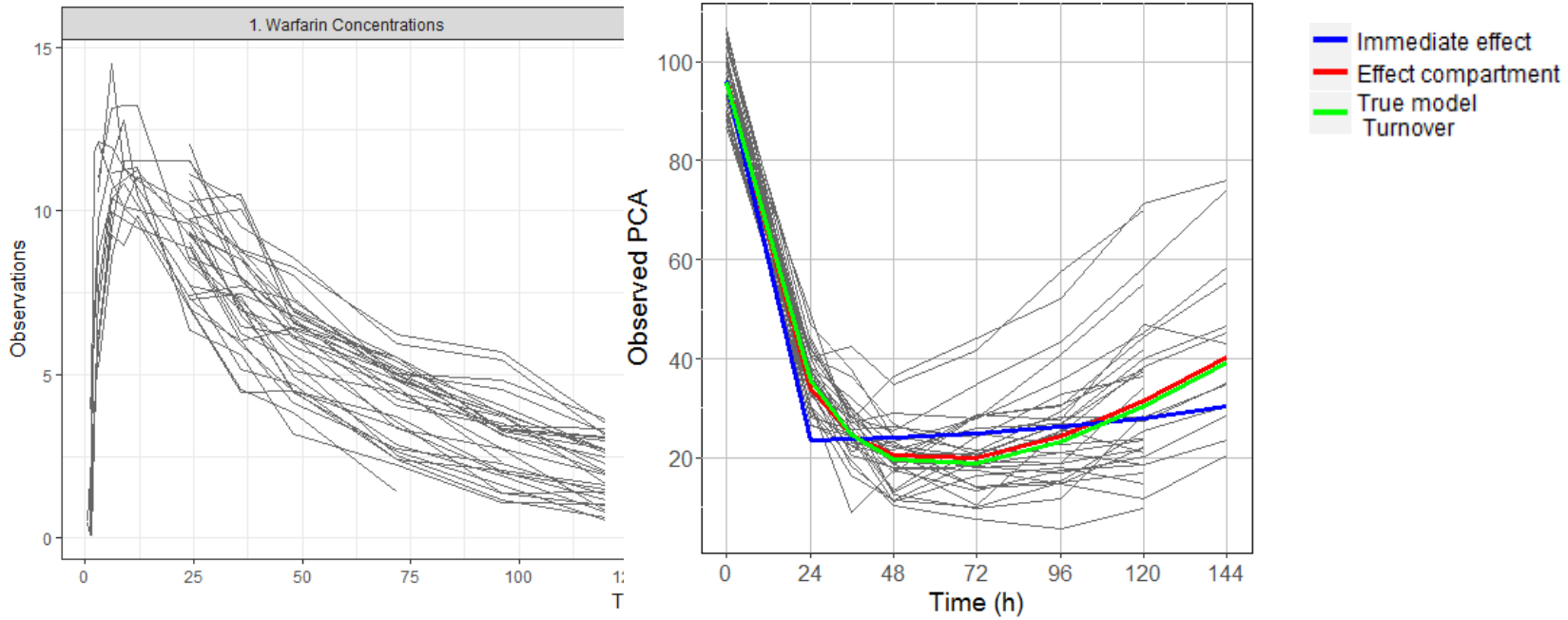
Table 1 Various evaluation graphs in nonlinear mixed effect model[a] and proposal for a core set of evaluation graphs

Graphs	In core set	What to expect if the model is correct?	What to do if the graph does not fulfill the requirements?
Evaluation graphs	**In core set**	**What to expect if the model is correct?**	**What to do if the graph does not fulfill the requirements?**
a. Basic goodness-of-fit plots	✓		
OBS vs xPRED, (x=C, P, I)	✓		
xWRES vs Time or xPRED	✓		
b. Individual fits	✓		
c. EBE-based graphs	✓		
d. Simulation-based graphs	✓		
VPC	✓		
NPD vs Time or PPRED	✓		

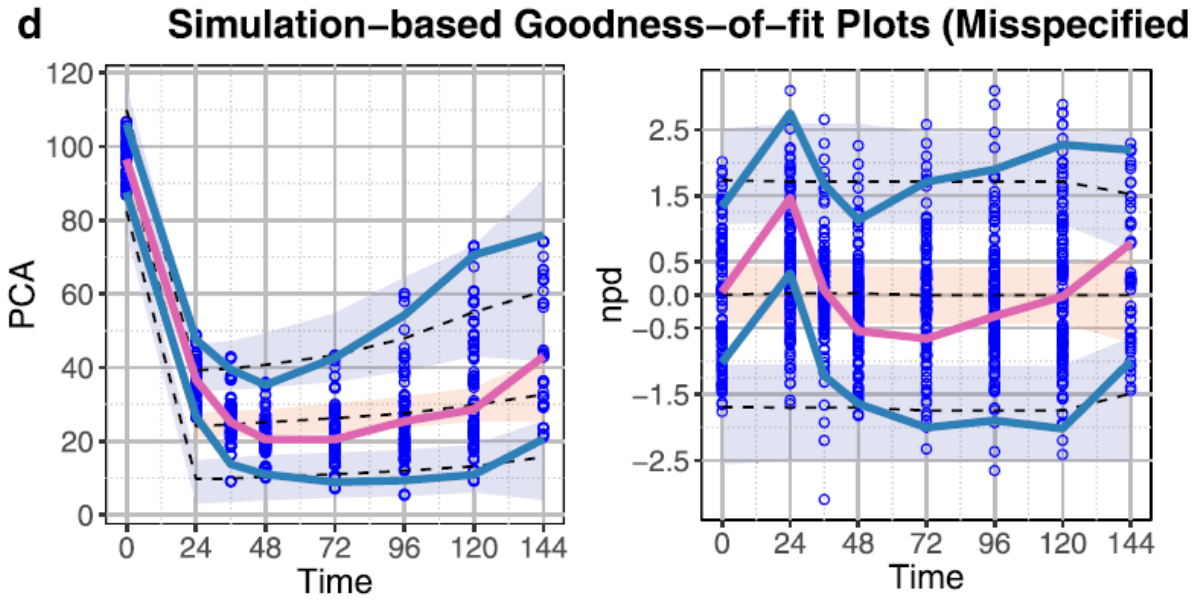
- Population predictions/ residuals: CPRED/CWRES or PPRED/PWRES
- Individual predictions/residuals: IPRED/IWRES
- EBE: Empirical Bayes estimates

MOTIVATING EXAMPLE: 3 MODELS FOR PKPD OF WARFARIN

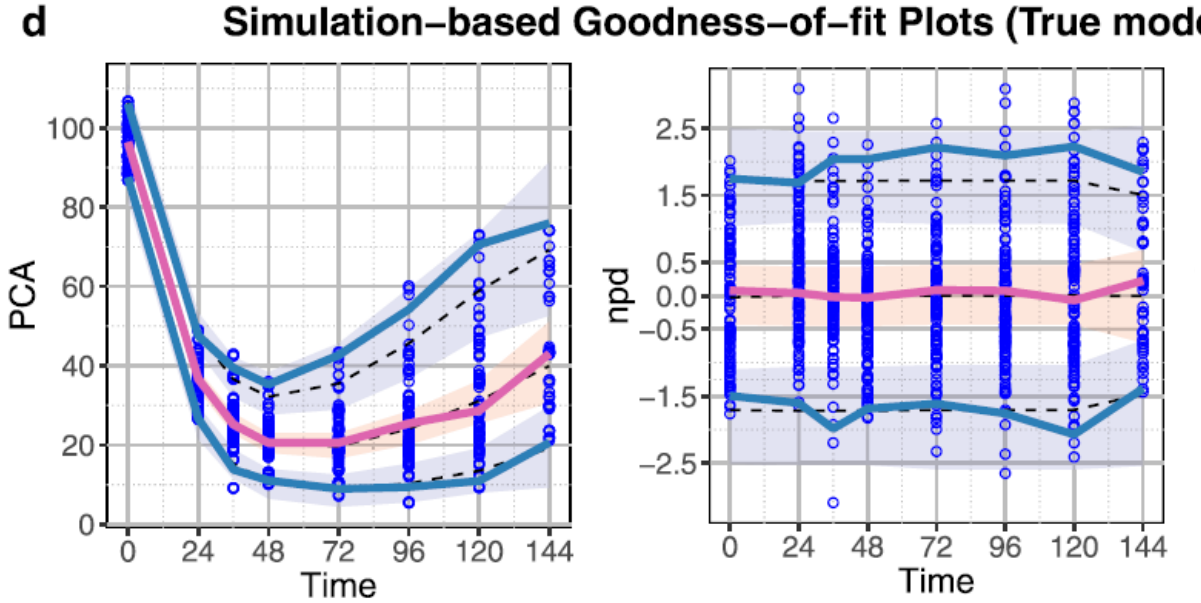
- **PK model: One compartment model**
- **PD Model for PCA**
  - Misspecified: Immediate effect model
  - True: Turnover model



SIMULATION-BASED GRAPHS



Immediate effect model



Turnover model

Future….

- **External Validation vs Cross-Validation vs …**
- **(pc)VPC vs (t)npd(e) vs….**
- **Evaluation methods for**
  - complex data (discrete, RTTE, joint…)
  - complex designs (adaptive, dropouts…)
- **Quantification of predictability (‘C-statistics’?)**

We do not like to ask , ‘Is our model true or false ?’, since probability models in most data analyses will not be perfectly true. The most relevant question is, ‘Does the model’s deficiencies have a noticeable effect on substantive inferences ?’

Gelman et al., 1995

3. DESIGN OF EXPERIMENTS

- **Sheiner**, **Beal**, Sambol (1989). Study designs for dose-ranging. *Clin Pharmacol Ther.* 46(1):63-77
- **Sheiner**, Hashimoto, **Beal** (1991). A simulation study comparing designs for dose ranging. *Stat Med.* 199110(3):303-21.
- Hashimoto**, Sheiner** (1991). Designs for population pharmacodynamics: value of pharmacokinetic data and population analysis. *J Pharmacokinet Biopharm*. 19(3):333-53.

Good designs in biomedical research

nature human behaviour

PERSPECTIVE

PUBLISHED: 10 JANUARY 2017 | VOLUME: 1 | ARTICLE NUMBER: 0021

OPEN

A manifesto for reproducible science

Marcus R. Munafò[1,2*], Brian A. Nosek[3,4], Dorothy V. M. Bishop[5], Katherine S. Button[6], Christopher D. Chambers[7], Nathalie Percie du Sert[8], Uri Simonsohn[9], Eric-Jan Wagenmakers[10], Jennifer J. Ware[11] and John P. A. Ioannidis[12,13,14]

Improving the reliability and efficiency of scientific research will increase the credibility of the published scientific literature and accelerate discovery. Here we argue for the adoption of measures to optimize key elements of the scientific process: methods, reporting and dissemination, reproducibility, evaluation and incentives. There is some evidence from both simulations and empirical studies supporting the likely effectiveness of these measures, but their broad adoption by researchers, institutions, funders and journals will require iterative evaluation and improvement. We discuss the goals of these measures, and how they can be implemented, in the hope that this will facilitate action toward improving the transparency, reproducibility and efficiency of scientific research.

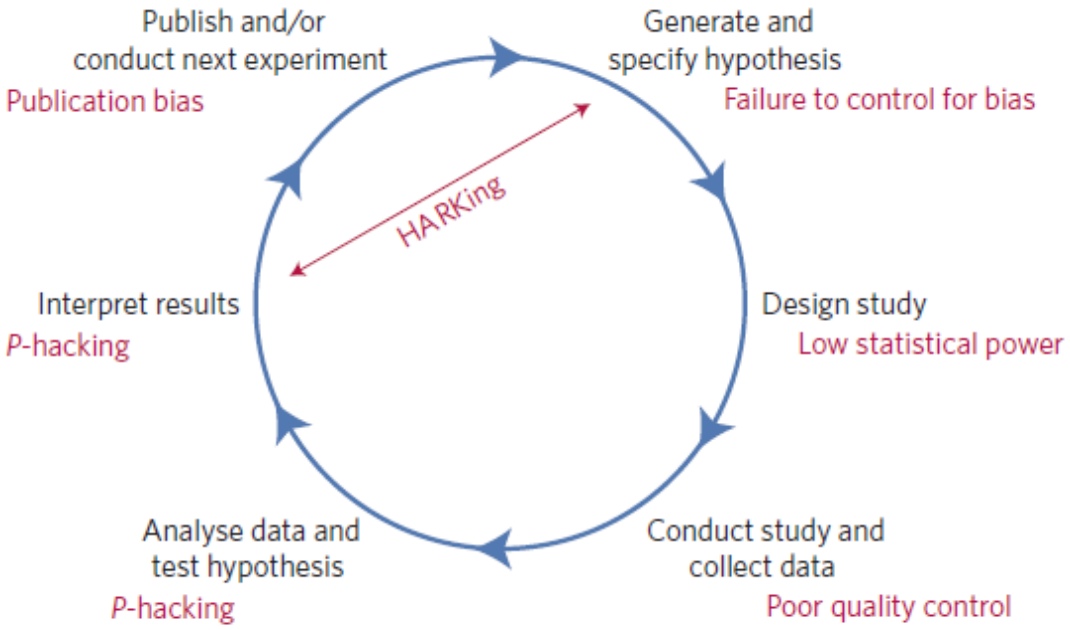


Figure 1 | Threats to reproducible science. An idealized version of the hypothetico-deductive model of the scientific method is shown. Various potential threats to this model exist (indicated in red), including lack of replication[5], hypothesizing after the results are known (HARKing)[7], poor study design, low statistical power[2], analytical flexibility[51], *P*-hacking[4], publication bias[3] and lack of data sharing[6]. Together these will serve to undermine the robustness of published research, and may also impact on the ability of science to self-correct.

Shortlisted for the BBC Samuel Johnson Prize for Non-Fiction

Bad Science

Ben Goldacre

'A fine lesson in how to skewer the enemies of reason and the peddlers of cant and half-truths' The Economist

"You'll laugh your head off, then throw all those expensive health foods in the bin' Observer, Book of the Year

Half a million copies sold worldwide

A Rough Guide to

SPOTTING BAD SCIENCE

Being able to evaluate the evidence behind a scientific claim is important. Being able to recognise bad science reporting, or faults in scientific studies, is equally important. These 12 points will help you separate the science from the pseudoscience.

1. SENSATIONALISED HEADLINES

Aa

Article headlines are commonly designed to entice viewers into clicking on and reading the article. At times, they can over-simplify the findings of scientific research. At worst, they sensationalise and misrepresent them.

2. MISINTERPRETED RESULTS

News articles can distort or misinterpret the findings of research for the sake of a good story, whether intentionally or otherwise. If possible, try to read the original research, rather than relying on the article based on it for information.

3. CONFLICTS OF INTEREST

Many companies will employ scientists to carry out and publish research - whilst this doesn't necessarily invalidate the research, it should be analysed with this in mind. Research can also be misrepresented for personal or financial gain.

4. CORRELATION & CAUSATION

Be wary of any confusion of correlation and causation. A correlation between variables doesn't always mean one causes the other. Global warming increased since the 1800s, and pirate numbers decreased, but lack of pirates doesn't cause global warming.

5. UNSUPPORTED CONCLUSIONS

Speculation can often help to drive science forward. However, studies should be clear on the facts their study proves, and which conclusions are as yet unsupported ones. A statement framed by speculative language may require further evidence to confirm.

6. PROBLEMS WITH SAMPLE SIZE

In trials, the smaller a sample size, the lower the confidence in the results from that sample. Conclusions drawn can still be valid, and in some cases small samples are unavoidable, but larger samples often give more representative results.

7. UNREPRESENTATIVE SAMPLES USED

In human trials, subjects are selected that are representative of a larger population. If the sample is different from the population as a whole, then the conclusions from the trial may be biased towards a particular outcome.

8. NO CONTROL GROUP USED

In clinical trials, results from test subjects should be compared to a 'control group' not given the substance being tested. Groups should also be allocated randomly. In general experiments, a control test should be used where all variables are controlled.

9. NO BLIND TESTING USED

To try and prevent bias, subjects should not know if they are in the test or the control group. In 'double blind' testing, even researchers don't know which group subjects are in until after testing. Note, blind testing isn't always feasible, or ethical.

10. SELECTIVE REPORTING OF DATA

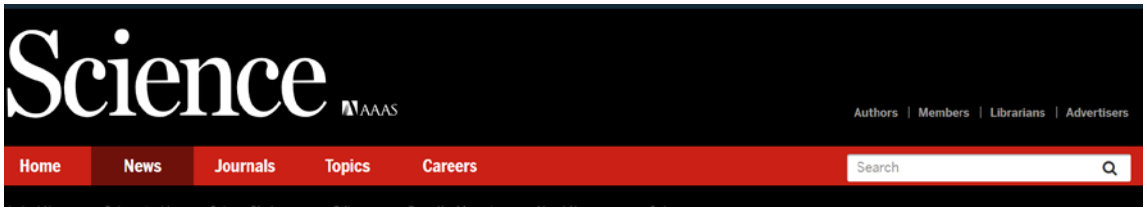
Also known as 'cherry picking', this involves selecting data from results which supports the conclusion of the research, whilst ignoring those that do not. If a research paper draws conclusions from a selection of its results, not all, it may be guilty of this.

11. UNREPLICABLE RESULTS

Results should be replicable by independent research, and tested over a wide range of conditions (where possible) to ensure they are consistent. Extraordinary claims require extraordinary evidence - that is, much more than one independent study!

12. NON-PEER REVIEWED MATERIAL

Peer review is an important part of the scientific process. Other scientists appraise and critique studies, before publication in a journal. Research that has not gone through this process is not as reputable, and may be flawed.



NIH aims to beef up clinical trial design as part of new data sharing rules

By Jocelyn Kaiser | Sep. 16, 2016 , 12:00 PM

Drug companies and academic researchers will have to step up their public reporting of clinical trial results under new federal policies released today. The National Institutes of Health (NIH) in Bethesda, Maryland, also laid out a new plan for submitting clinical trial proposals that aims to beef up the rigor of the studies.

Researchers can no longer submit an unsolicited idea, but must respond to a request for applications that will include specific design requirements. The goal is to cut down on the number of "small crappy studies," that don't include sufficient numbers of patients or veer off from the original study plan, NIH staffers say. The agency wants to "reengineer the process by which clinical investigators develop ideas for new trials," NIH officials explain in a **commentary today in *The Journal of the American Medical Association*** (*JAMA*).

Evaluation of designs by clinical trial simulation

- Several published studies
  - Hashimoto & Sheiner, *J Pharmacokin Biopharm*, 1991
  - Jonsson, Wade & Karlsson, *J Pharmacokin Biopharm*, 1996
  - …
- Evaluation of with respect to
  - number of patients (N), number of samples per patient (n)
  - sampling times
  - number of occasions per patient, number of samples per occasion
- Main limitation
  - very time consuming
  - only limited number of designs evaluated

➢ Approach for design evaluation without simulation based on Fisher Information matrix (FIM)

Contribution to design of experiments

Alain Mallet (1983)

David D'Argenio (1990)

Valerii Fedorov (1998)

Luc Pronzato (1989)

Elliot Landaw (1990)

Kathryn Chaloner (1998)

Biometrika (1997), **84,** 2, *pp.* 429–442
Printed in Great Britain

Optimal design in random-effects regression models

BY FRANCE MENTRÉ, ALAIN MALLET AND DOHA BACCAR

INSERM U 436, Département de Biomathématiques, CHU Pitié-Salpêtrière, 91 Boulevard de l'Hôpital, 75013 Paris, France

e-mail: fm@biomath.jussieu.fr ama@biomath.jussieu.fr dba@biomath.jussieu.fr

SUMMARY

An approach is proposed to optimal design of experiments for estimating random-effects regression models. The population designs are defined by the number of subjects and the individual designs to be performed. Cost functions associated with individual designs are incorporated. For a given maximal cost, an algorithm is proposed for finding the statistical population design that maximises the determinant of the Fisher information matrix of the population parameters. The Fisher information matrix is formulated for linear models and normal distributions. The approach is applied to the design of an optimal experiment in toxicokinetics using a first-order linearisation of the model. Several cost functions and designs of various orders are studied. An example illustrates the optimal population designs and the increased efficiency of some optimal designs over more standard designs.

Some key words: Fisher information matrix; Optimal design; Population parameter; Random-effects model; Regression models.

Doc & Post Doc on design at INSERM/ University Paris Diderot

Sylvie Retout (PhD 2003)

Published articles since 1997

- **Stat Journals:** 19
- **Pharma Journals:**13

ançois Combes (PhD 2014)

Giulia Lestini (PhD 2016)

Sebastian Ueckert (PostDoc 2014-2015)

Marie-Karelle Riviere (PostDoc 2015)

Florence Loingeville (PostDoc 2016-2018)

Jérémy Seurat (*PhD 2017- …*)

PFIM and PFIM interface

- R package for design evaluation and optimisation in NLMEM
- Developed initially by Sylvie Retout & France Mentré

Computer Methods and Programs in Biomedicine 156 (2018) 217–229

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Computer Methods and Programs in Biomedicine

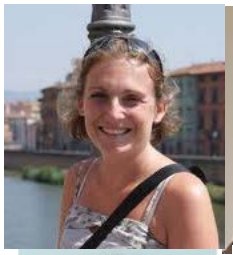
journal homepage: www.elsevier.com/locate/cmpb

PFIM 4.0, an extended R program for design evaluation and optimization in nonlinear mixed-effect models

Cyrielle Dumont[a,b], Giulia Lestini[a], Hervé Le Nagard[a], France Mentré[a], Emmanuelle Comets[a], Thu Thuy Nguyen[a,*], for the PFIM group[a]

[a] IAME, UMR 1137, INSERM and University Paris Diderot, Sorbonne Paris Cité, Paris, F-75018, France
[b] University of Lille, EA 2694, Public Health: Epidemiology and Healthcare Quality, ILIS, Lille, F-59000, France

Emmanuelle
ulia Lestini,






  - April 2014: PFIM 4.0
  - May 2015: PFIM interface 4.0

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12352

Methods in Clinical Pharmacology Series

Methods and software tools for design evaluation in population pharmacokinetics–pharmacodynamics studies

Joakim Nyberg,[1] Caroline Bazzoli,[2] Kay Ogungbenro,[3] Alexander Aliev,[4] Sergei Leonov,[5] Stephen Duffull,[6] Andrew C. Hooker[1] & France Mentré[7]

[1]Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, [2]Laboratoire Jean Kuntzmann, Département Statistique, University of Grenoble, Grenoble, France, [3]Centre for Applied Pharmacokinetic Research, School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, UK, [4]Institute for Systems Analysis, Russian Academy of Sciences, Moscow, Russia, [5]AstraZeneca, Wilmington, DE, USA, [6]School of Pharmacy, University of Otago, Dunedin, New Zealand and [7]INSERM U738 and University Paris Diderot, Paris, France

Correspondence
Professor France Mentré PhD, MD, Université Paris Diderot, INSERM, Paris 75018, France.
Tel.: +33 1 57 27 77 59
Fax: + 33 1 57 27 75 21
E-mail: france.mentre@inserm.fr

Keywords
Fisher information matrix, nonlinear mixed effect models, optimal design, population design, population pharmacokinetics–pharmacodynamics

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Accepted Article Published Online
18 February 2014

Andrew Hooker

PopED

Joakim Nyberg

PopED

Kay Ogungbenro

PopDes

Sergei Leonov

PkStaMP

Stephen Duffull

POPT

Caroline Bazzoli

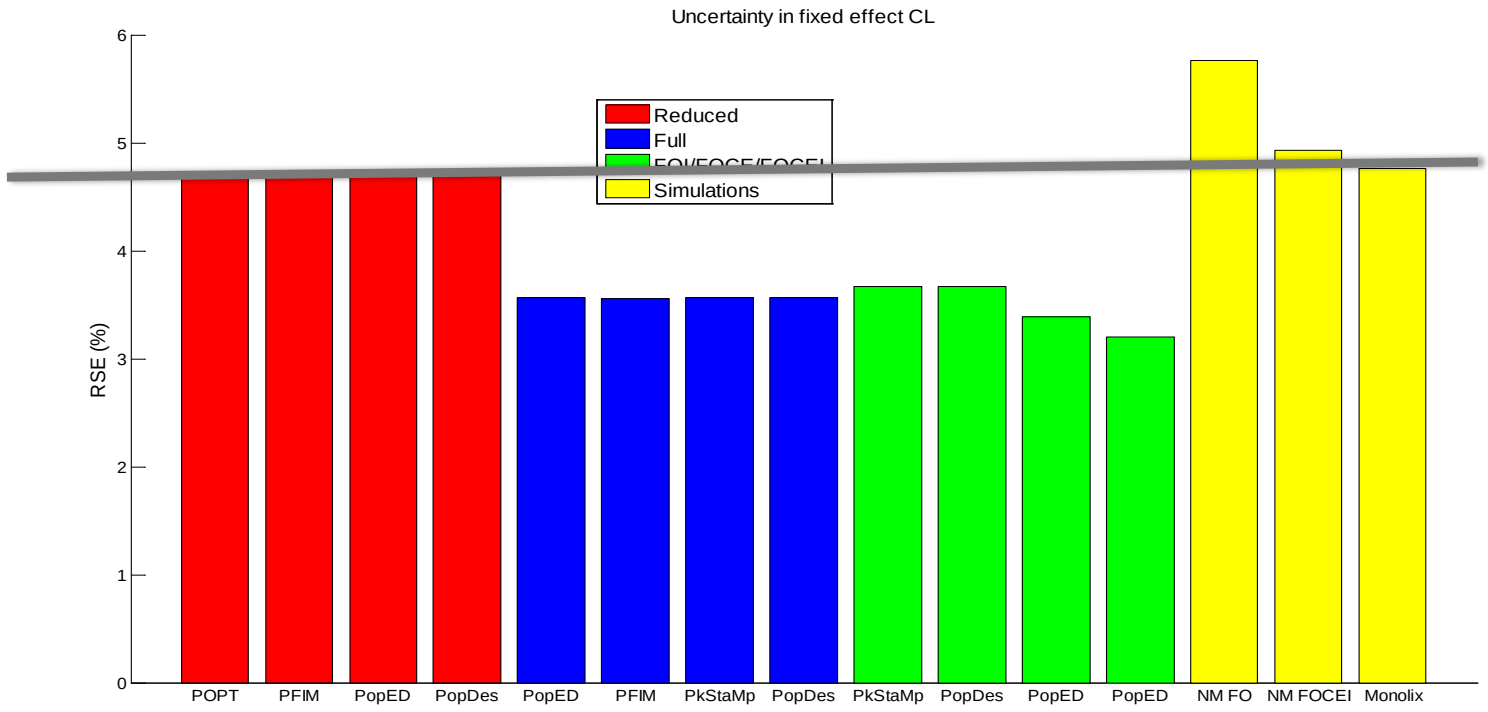
PFIM

France Mentré

PFIM

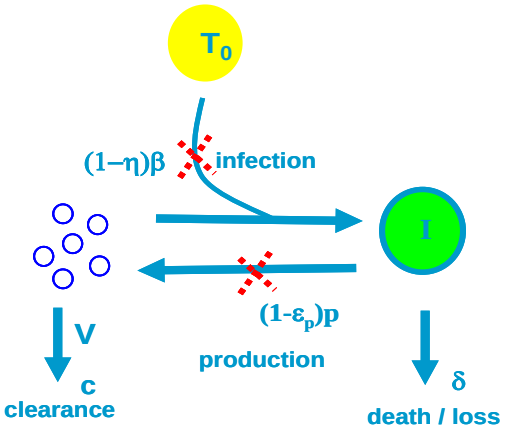
Simple PK example

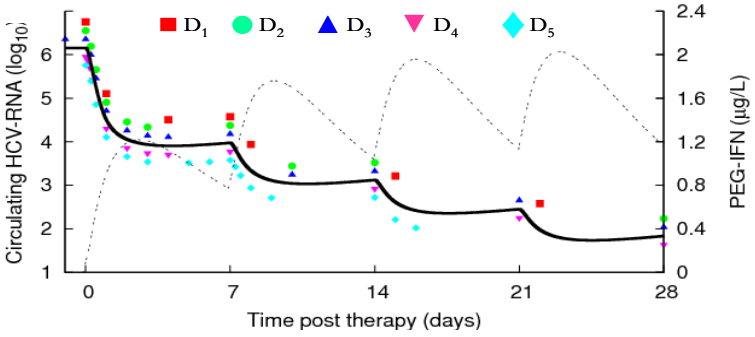
RSE(%) for fixed effect of CL/F

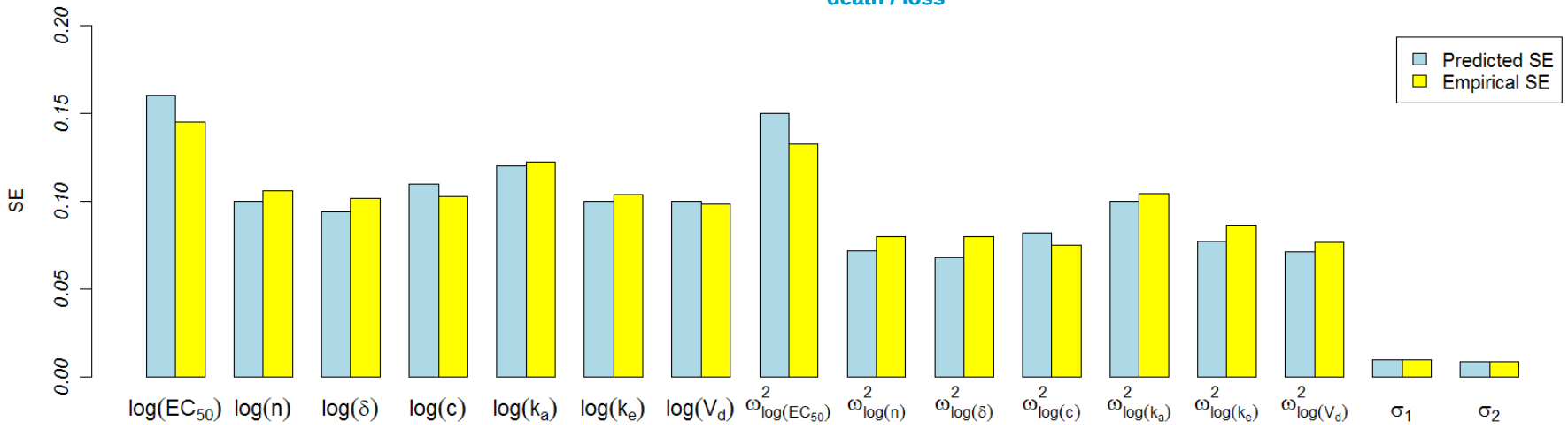


PKPD example in HCV

$$\begin{cases} \frac{dX}{dt} = D - k_a X \\ \frac{dA}{dt} = k_a X - k_e A \\ C(t) = \frac{A(t)}{V_d} \\ \frac{dT}{dt} = s - \beta(1-\eta)VT - dT \\ \frac{dI}{dt} = \beta(1-\eta)VT - \delta I \\ \frac{dV}{dt} = p\left(1 - \frac{C(t)^n}{C(t)^n + EC_{50}^n}\right) I - cV \end{cases}$$







- Good prediction of SE of all PKPD parameters
- Computing time
  - CTS = 5 days
  - Design evaluation with PFIM = 5 mins!

(Guedj, Bazzoli, Neumann, Mentré, *Stat Med,* 2011)

Population Optimum Design of Experiments

- Multidisciplinary group: **PODE**
  - initiated by Barbara Bogacka & France Mentré in 2006
  - discuss theory of optimum experimental design in NLMEM and their application in drug development
  - www.maths.qmul.ac.uk/~bb/PODE/PODE2017.html
- One
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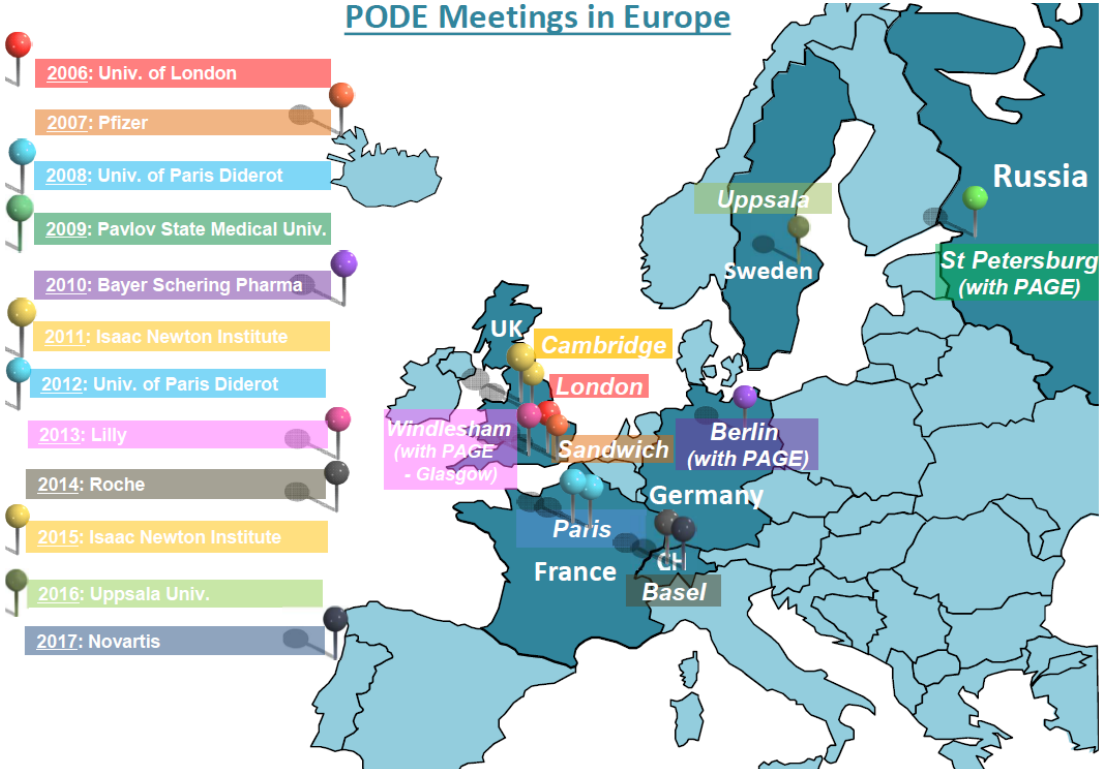


ACoP 8
October 15 – 18, 2017
Fort Lauderdale, FL

Optimal design: just nerdy or useful?

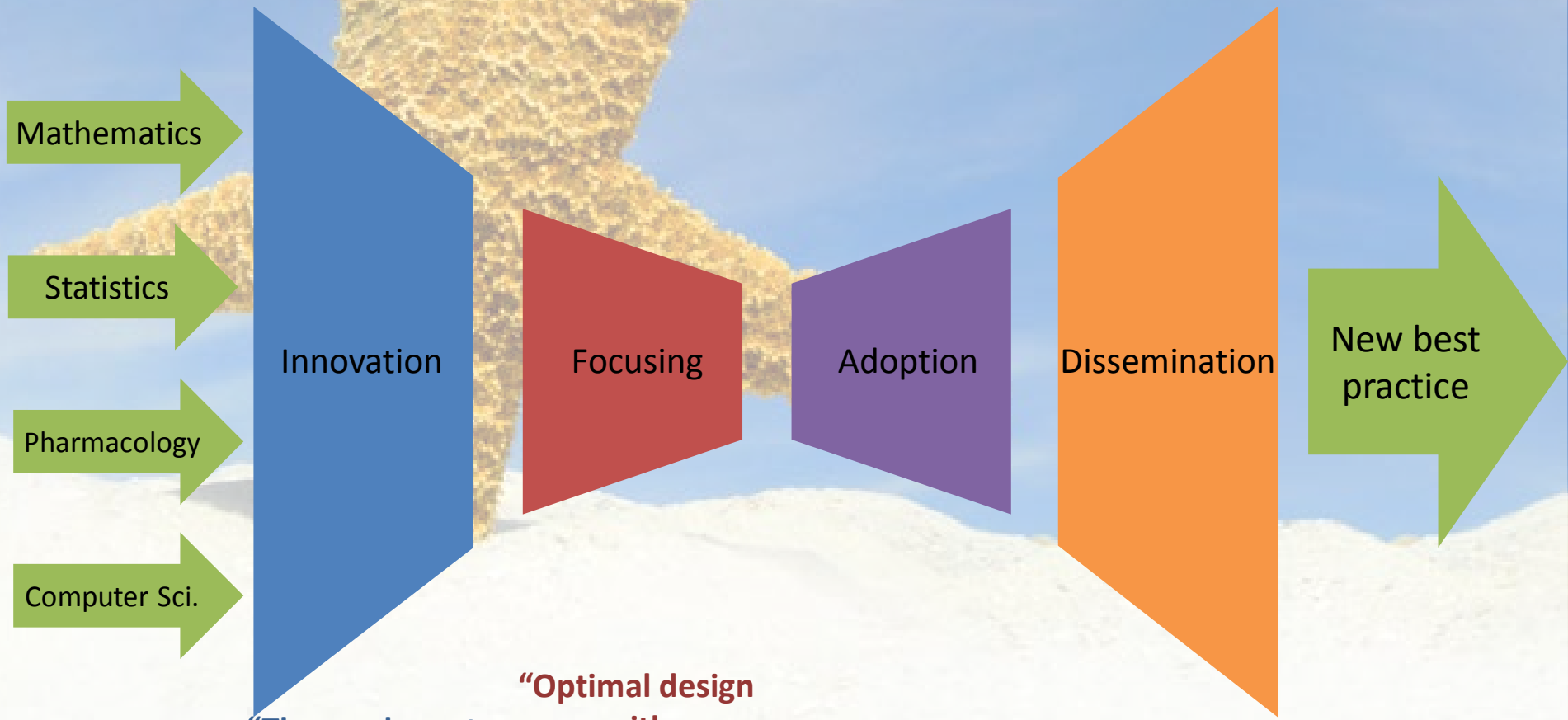
Session Chairs:

Elodie Plan (Pharmetheus)

Steve Duffull (University of Otago)

ACoP 8 AMERICAN CONFERENCE ON PHARMACOMETRICS

“Pharmacometric innovation funnel”



“The nerdy part made simple”
S Ueckert (Uppsala U)

“Optimal design with pharmacometric models”
J Nyberg (Pharmetheus)

“Challenges within Industry?”
M Chenel (Servier)

Panel discussion
F Mentré (Paris Diderot U)
A Hooker (Uppsala U)
T Waterhouse (Lilly)
Y Wang (FDA)

ACoP8 AMERICAN CONFERENCE ON PHARMACOMETRICS

New method for computing FIM with discrete data

Computational Statistics and Data Analysis 111 (2017) 203–219

Contents lists available at ScienceDirect

Computational Statistics and Data Analysis

journal homepage: www.elsevier.com/locate/csda

A new method for evaluation of the Fisher information matrix for discrete mixed effect models using Monte Carlo sampling and adaptive Gaussian quadrature

Sebastian Ueckert *, France Mentré

Biostatistics (2016), **17**, 4, *pp.* 737–750
doi:10.1093/biostatistics/kxw020
Advance Access publication on May 10, 2016

An MCMC method for the evaluation of the Fisher information matrix for non-linear mixed effect models

MARIE-KARELLE RIVIERE*, SEBASTIAN UECKERT, FRANCE MENTRÉ
INSERM, IAME, UMR 1137, F-75018 Paris, France and Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France
marie-karelle.riviere@inserm.fr

Model averaging for robust designs

- **Design evaluation requires knowledge on model and parameters**
  - Local optimal design: given a model and a priori values for population parameter → D-optimal design

- **Alternative: Robust designs**
  - Take into account uncertainty on parameters (ED-optimal design)
  - **Over a set of candidate models** (model averaging as in **MCP-MOD**)

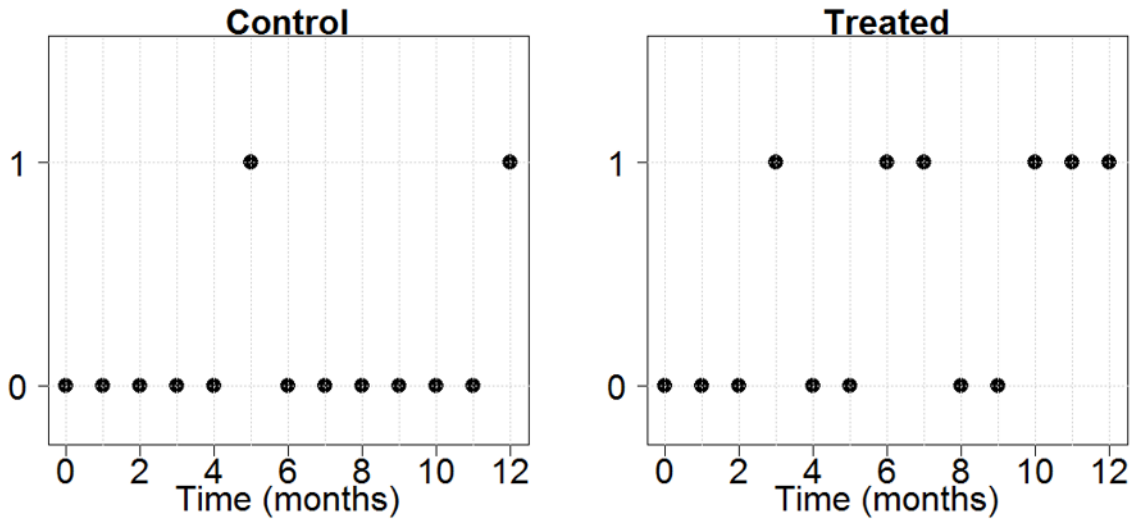
- **FIM computed using MC-HMC in R-package MXFIM calling RStan**

MIXFIM: Evaluation of the FIM in NLMEMs using MCMC

Evaluation and optimization of the Fisher Information Matrix in NonLinear Mixed Effect Models using Markov Chains Monte Carlo for continuous and discrete data.

Version:	1.0
Depends:	R (≥ 3.0.2), rstan (≥ 2.7.0-1), mvtnorm (≥ 1.0-2), ggplot2 (≥ 1.0.1)
Published:	2015-08-31
Author:	Marie-Karelle Riviere-Jourdan and France Mentre
Maintainer:	Marie-Karelle Riviere-Jourdan <eldamjh at gmail.com>
License:	GPL-3
Copyright:	All files are copyright Institut National de la Sante Et de la Recherche Medicale.
NeedsCompilation:	no
CRAN checks:	MIXFIM results

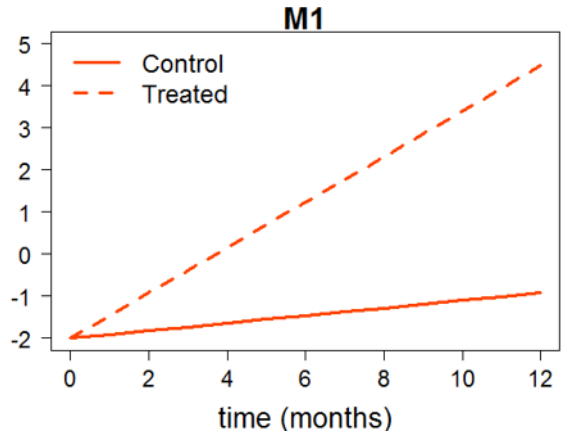
Example: designing an RCT trial with repeated binary data



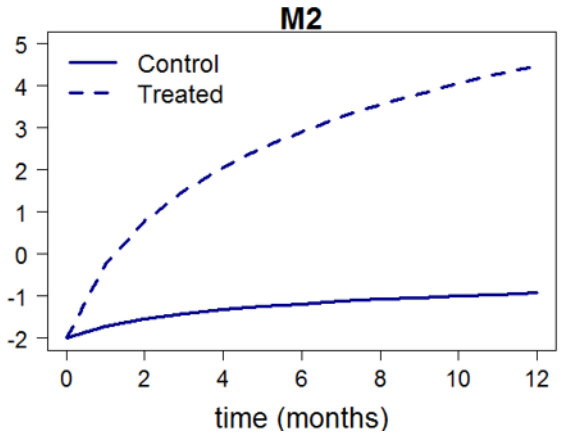
- P = probability of 1
- Logistic random effect models
- **Several candidate models for the link between $logit(P)$ and time**

Seurat, **Mentré**, Nguyen, PODE 2017

Four candidate models (placebo + drug effect)

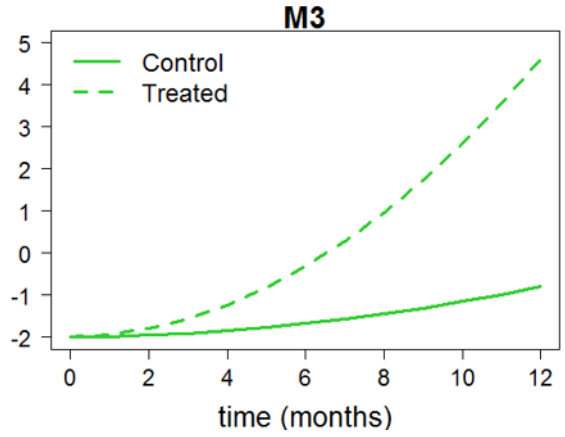


$logit(P) = \theta_1 + \theta_2(1 + \beta \times 1_T)t$

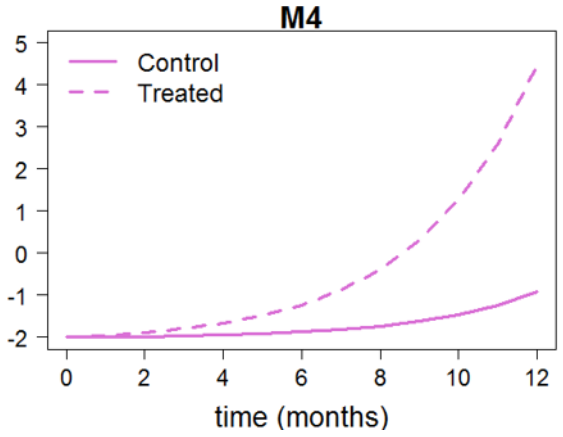


$logit(P) = \theta_1 + \theta_2(1 + \beta \times 1_T)\log(t + 1)$

1. Linear
2. Log-Linear
3. Quadratic
4. Exponential



$logit(P) = \theta_1 + \theta_2(1 + \beta \times 1_T)t^2$

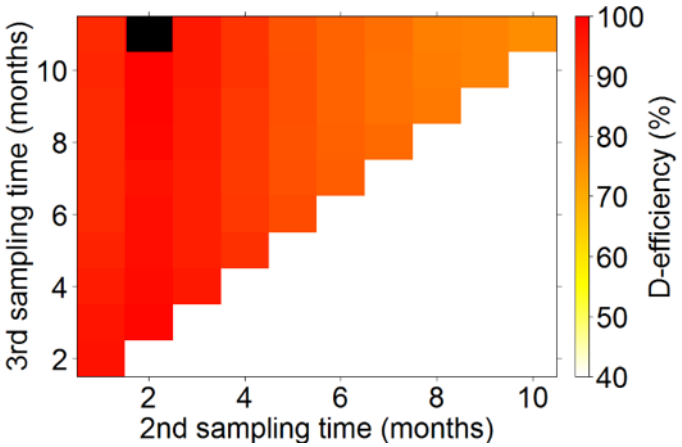


$logit(P) = \theta_1 + \theta_2(1 + \beta \times 1_T)[\exp(\theta_3 t) - 1]$

Design optimisation

Methods		
Constraints	Number of subjects	N = 100 (50 per treatment group)
	Number of samples	n = 4 per individual (from 0 to 12 months)
	Sampling times	➢ t_1 = 0, t_4 = 12 months (fixed) ➢ t_2 and t_3 optimized from 1 to 11 months no replication)
Combinatorial Optimization	Evaluation of FIM for all possible designs	5000 MC 200 HMC
	For each model	D-criterion on FIM
	Over 4 models	Compound D-criterion (averaging for uncertainty on models)

Results: D-optimal design for each model



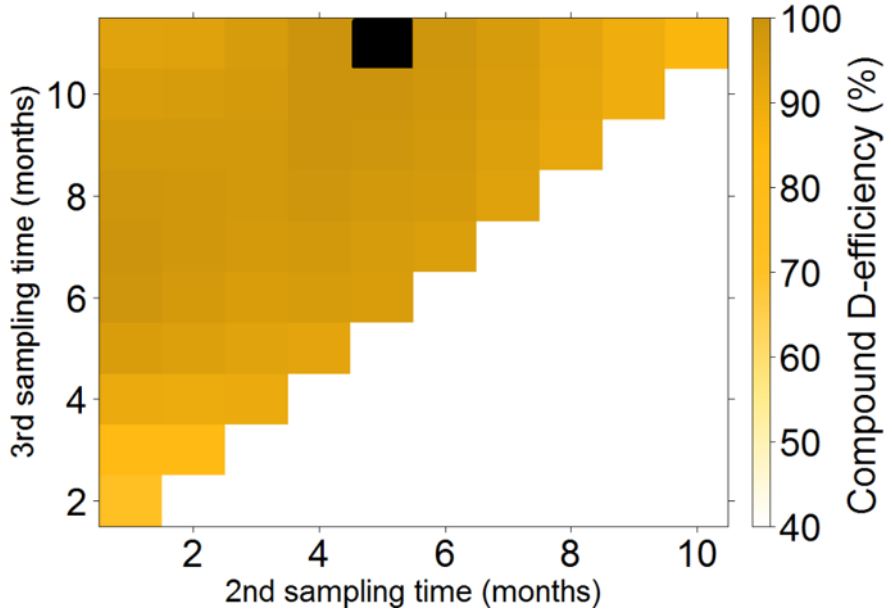
ξ_{M1}=(0,**2**,**11**,12)

1. Linear
2. Log-Linear
3. Quadratic
4. Exponential

Results: loss of efficiency if wrong model

	M1 Linear	M2 Log-Linear	M3 Quadratic	M4 Exponential
$\xi_{M1}=(0,2,11,12)$	100%	90%	81%	71%
$\xi_{M2}=(0,1,8,11)$	93%	100%	88%	79%
$\xi_{M3}=(0,4,5,11)$	92%	84%	100%	**65%**
$\xi_{M4}=(0,6,11,12)$	83%	80%	96%	100%
$\xi_{all}=(0,5,11,12)$	86%	81%	99%	96%

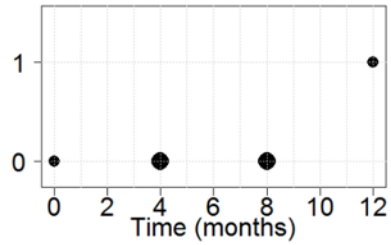
Efficiency greater than 80% for all models

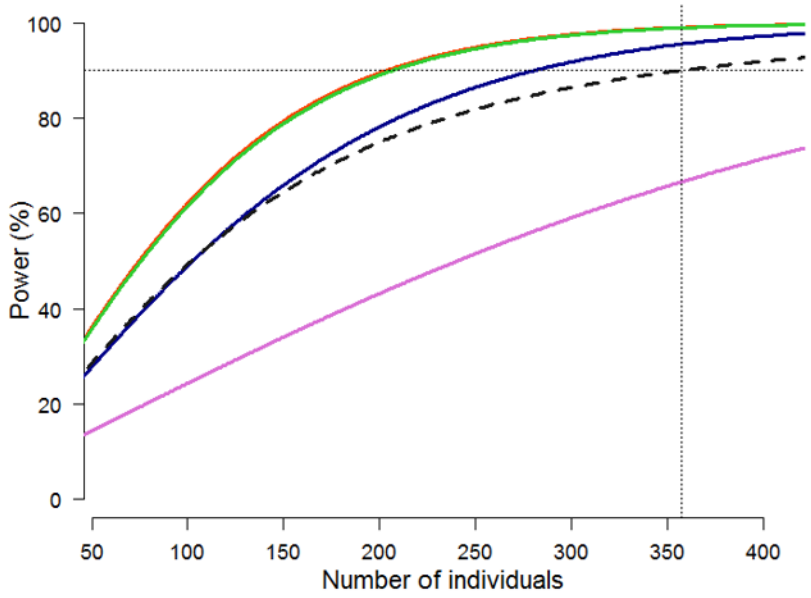


Optimal design over 4 models
$\xi_{all}=(0, 5,11,12)$

Results: NSN for average power of 90% smaller with optimal design

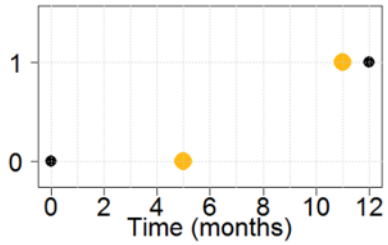
$\xi_{equi\text{-}spaced}=(0,4,8,12)$

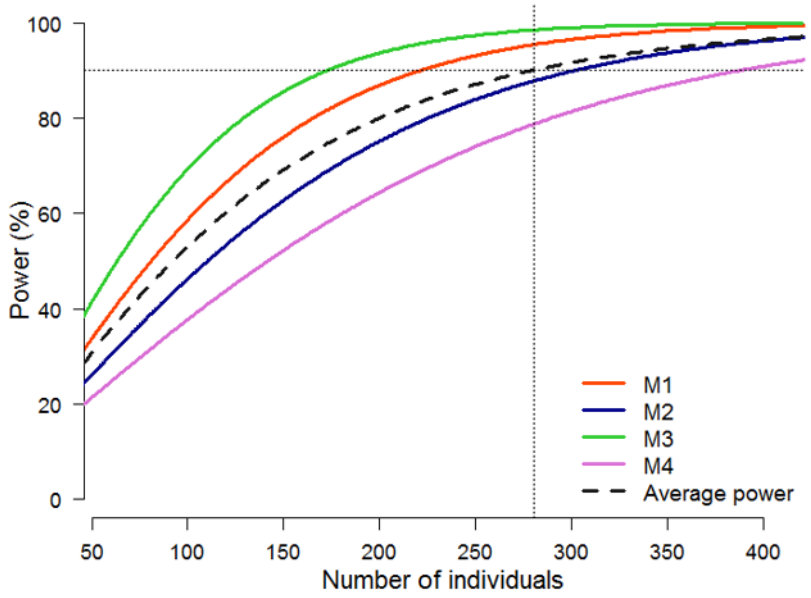




$NSN_{average}(\xi_{equi\text{-}spaced}) = \mathbf{358}$

$\xi_{all}=(0,5,11,12)$





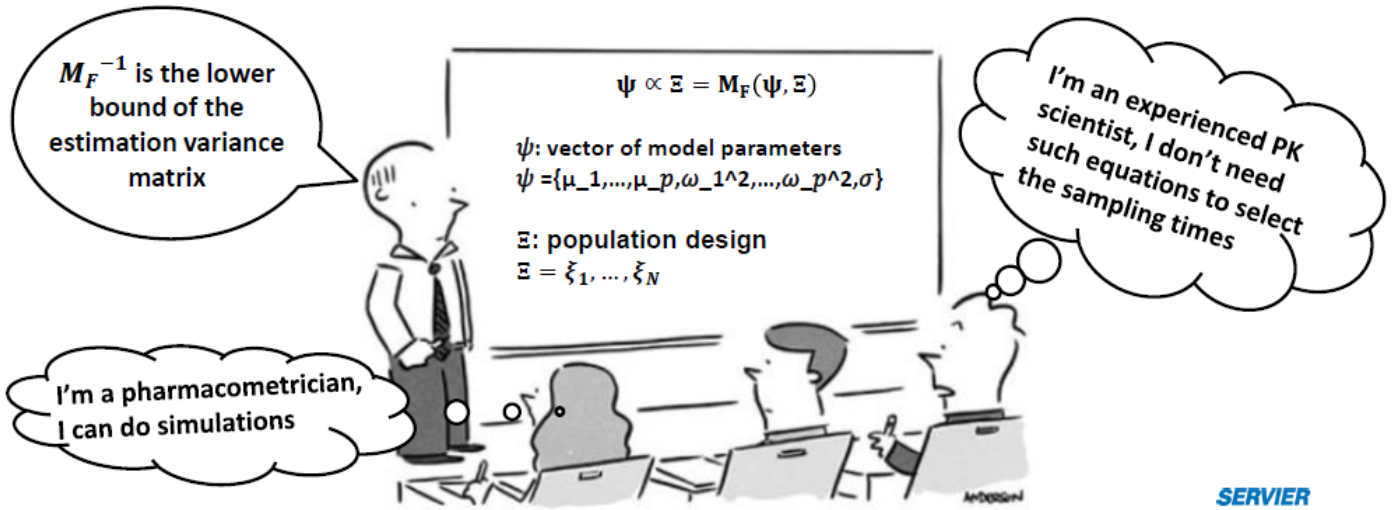
$NSN_{average}(\xi_{all}) = \mathbf{274}$

Seurat, **Mentré**, Nguyen, PODE 2017

Optimal design: challenges within industry?

Talk of Marylore Chenel at ACOP October 17, 2 017

- Study design is essential to collect informative data during drug discovery and development (EFPIA MID3, CPT:PSP 2016)
- **Non informative studies represent cost and time loss**
- **Non informative studies are non ethical**: optimal design approaches are not limited to vulnerable patients and should be applied for any study involving animals, volunteers and patients



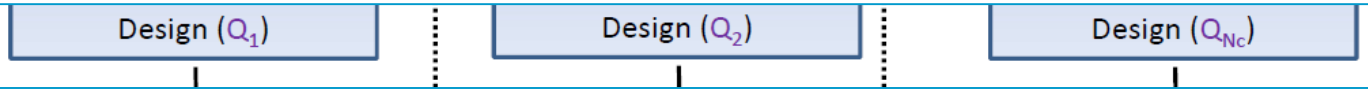
Future....

- **Ongoing work by statisticians & pharmacometricians**
  - Model based adaptive designs (MBAOD)

➢ MBAOD prototype in R (Andrew Hooker, Uppsala University)

- Pierrillas, Fouliard, Chenel, Hooker, Friberg, Karlsson (2018). Model-based adaptive optimal design (MBAOD) improves combination dose finding designs: an example in oncology. *AAPS J*. 20(2):39.

- Ryeznik, Sverdlov, Hooker (2017). Adaptive optimal designs for dose-finding studies with time-to-event outcomes. *AAPS J*. 20(1):24.



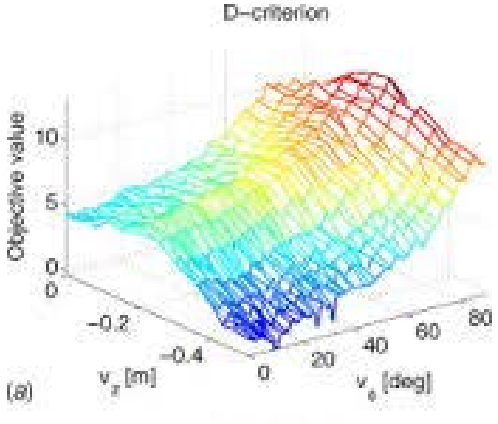
- Dumont, Chenel, **Mentré** (2016). Two-stage adaptive designs in nonlinear mixed effects models: application to pharmacokinetics in children. *Communications in Statistics - Simulation and Computation,* 45: 1511

- Lestini, Dumont, **Mentré** (2015). Influence of the size of cohorts in adaptive design for nonlinear mixed effects models: an evaluation by simulation for a pharmacokinetic and pharmacodynamic model for a biomarker in oncology. *Pharm Res.* 32:3159

Future....

- **Ongoing work by statisticians & pharmacometricians**
  - Model based adaptive designs
- Fisher matrix for repeated discrete/count data and TTE
- Model averaging for designing experiments
- Design and identifiability of complex models
- ‘Optimal’ design for individual predictions

➢ **More collaboration between pharmacometricians and statisticians / computer scientists**



CONCLUSION

BRIDGING THE GAP between Pharmacometricians & Biostatisticians

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

Pitfalls in pharmacometrics

- Handling of data (per protocol, missing, dropout)
- Multiple testing in model building, covariates analysis
- Model evaluation, checking assumptions
- Often lacking model based analysis plan
- Design / sample size (uncertainty…)

Pitfalls in biostatistics

- ‘Stuck’ to standard linear or standard empirical models for end of trial data
- Like ‘few-assumptions’ 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

Evolution of both groups needed

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

Bridging the gap

- **Education and teaching**
- **Collaborations**

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 (new one since 2018)
  - Co-chairs: Bret Musser (Regeneron) & France Mentré (U Paris Diderot & INSERM)
  - Fred Balch (U Utah), Rob Bies (U Buffalo), Kevin Dykstra (qPhametra), Manolis Efthymios (EMA), Jonathan French (Metrum), Lena Friberg (U Uppsala), Vijay Ivaturi (U Maryland), Jose Pinheiro (J&J), Dionne Price (FDA), Gary Rosner (Johns Hopkins), Matt Rotelli (Merck), Mike Smith (Pfizer), Jing Su (Merck), Stacey Tannenbaum (Astellas Pharma), Neelima Thaneer (BMS), Jingtao Wu (Takeda), Yaning Wang (FDA)
  - ISoP board liason: Siv Jonsson (U Uppsala)

- Membership open to everyone http://community.amstat.org/sxp/home
- During ASCPT 2018: **Meet us at ISoP booth 505**

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**

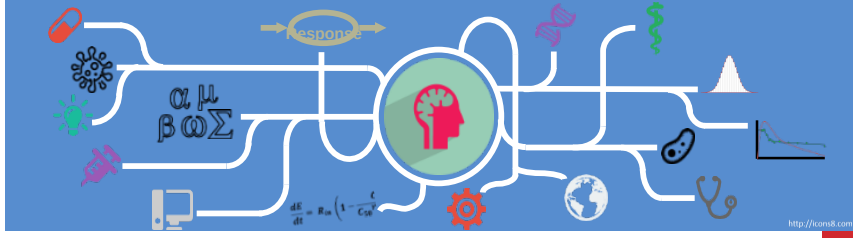
- better drugs/ treatments
- better targeted to each patient

Thanks to Lew and Malcolm

Advanced Workshop in PKPD (... -1999-2004)

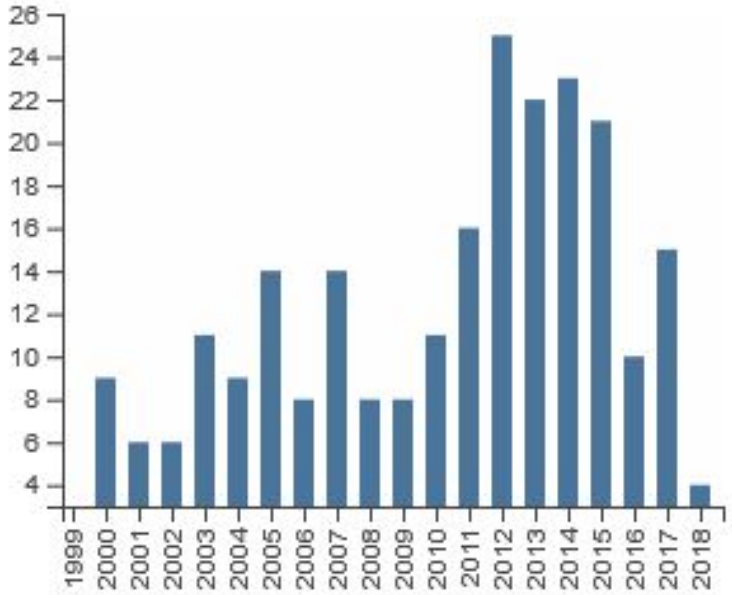
Thanks to
my colleagues and friends

THE SHEINER/ROWLAND ADVANCED COURSE IN PKPD- Silsmaria 2012

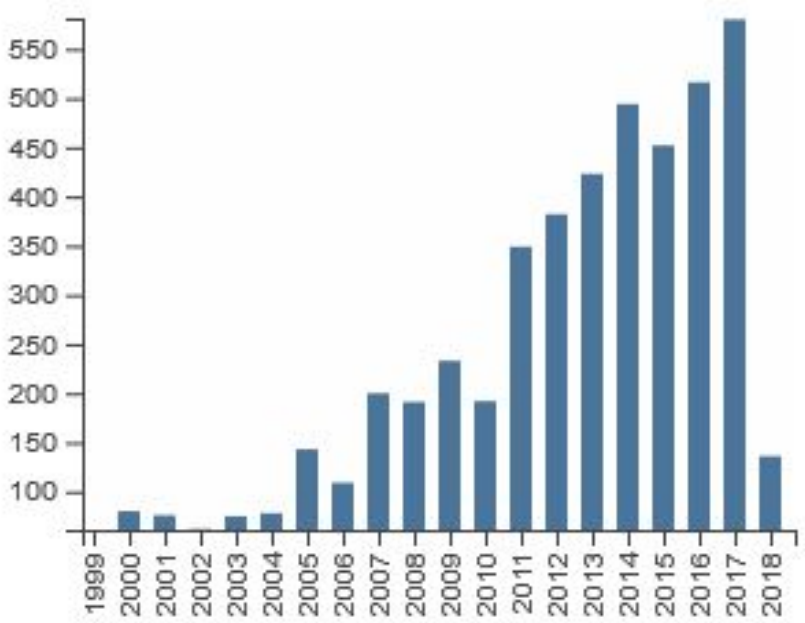


Thanks to Paris research team & PhD students

Publications (N=286)



Citations (n_{tot}=5,083 March 2018)

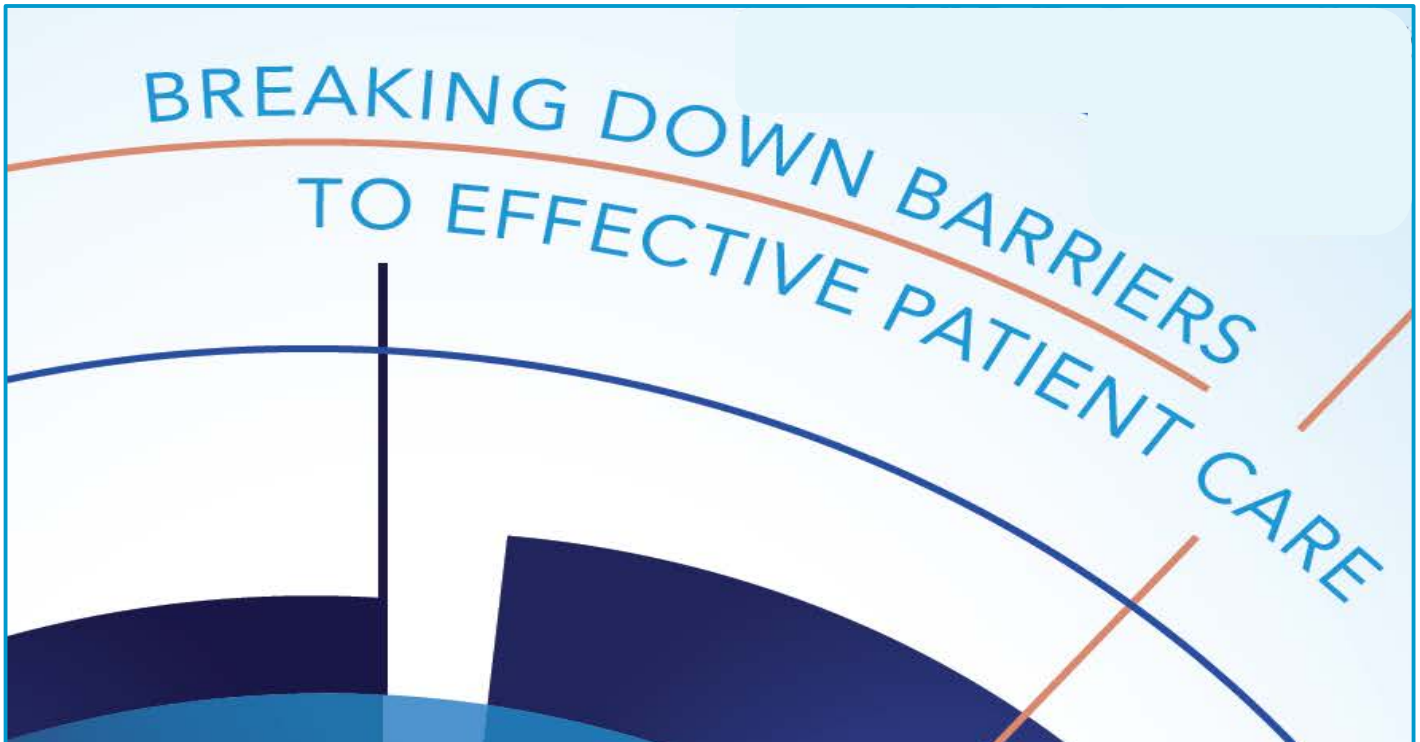


10 most cited papers
(March 2018)

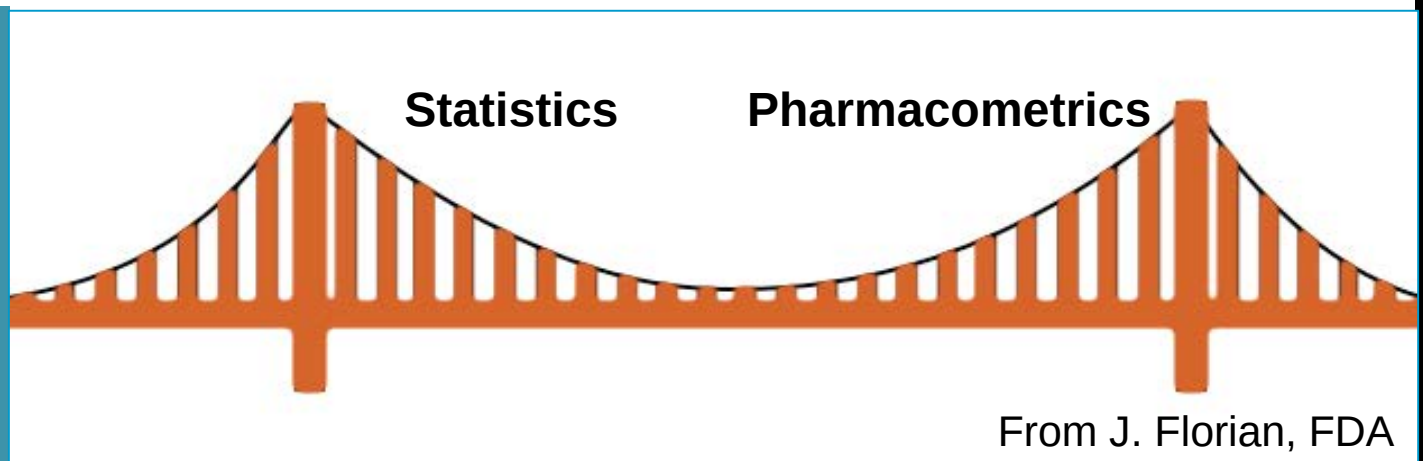
Comets, E; Brendel, K; Mentre F	Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: The npde add-on package for R	COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE	**2008**	**193**
Brendel, K; Comets, E; Laffont, C; Laveille, C; Mentre, F	Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide	PHARMACEUTICAL RESEARCH	**2006**	**170**
Mentre, F; Mallet, A; Baccar, D	Optimal design in random-effects regression models	BIOMETRIKA	**1997**	**170**
Maubec, E; Petrow, P; ...; Mentre, F; Avril, MF	Phase II Study of Cetuximab As First-Line Single-Drug Therapy in Patients With Unresectable Squamous Cell Carcinoma of the Skin	JOURNAL OF CLINICAL ONCOLOGY	**2011**	**107**
Retout, S; Duffull, S; Mentre, F	Development and implementation of the population Fisher information matrix for the evaluation of population pharmacokinetic designs	COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE	**2001**	**103**
Brendel, K; Dartois, C; Comets, E; Lemenuel-Diot, A; Laveille, C; Tranchand, B; Girard, P; Laffont, C; Mentre, F	Are population pharmacokinetic and/or pharmacodynamic models adequately evaluated? A survey of the literature from 2002 to 2004	CLINICAL PHARMACOKINETICS	**2007**	**97**
Vozeh, S; Steimer, JL; Rowland, M; Morselli, P; Mentre, F; Balant, LP; Aarons, L	The use of population pharmacokinetics in drug development	CLINICAL PHARMACOKINETICS	**1996**	**91**
Sissoko, D; Laouenan, C; …; Mentre, F; Anglaret, X; Malvy, D	Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of-Concept Trial in Guinea	PLOS MEDICINE	**2016**	**90**
Bazzoli, C; Jullien, V; Le Tiec, C; Rey, E; Mentre, F; Taburet, AM	Intracellular Pharmacokinetics of Antiretroviral Drugs in HIV-Infected Patients, and their Correlation with Drug Action	CLINICAL PHARMACOKINETICS	**2010**	**86**
Lavielle, M; Mentre, F	Estimation of population pharmacokinetic parameters of saquinavir in HIV patients with the MONOLIX software	JOURNAL OF PHARMACOKINETICS AND PHARMACODYNAMICS	**2007**	**72**

Thanks to ASCPT for this award

ASCPT American Society for Clinical Pharmacology & Therapeutics



Thank you Lew



From J. Florian, FDA


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