10 years of progress in population design methodology and applications
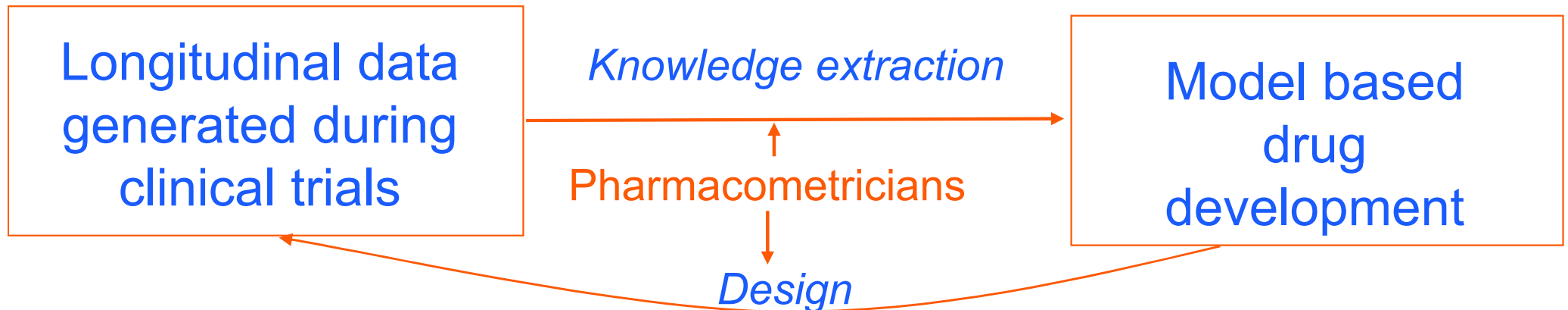
Pr. France Mentré

Team: **B**iostatistics, Clinical **I**nvestigation and **P**harmacometrics in **I**nfection **D**iseases

INSERM and University Paris Diderot,

Paris, France

PHARMACOMETRICS

The science of quantitative clinical pharmacology

| Longitudinal data generated during clinical trials | *Knowledge extraction* → | Model based drug development |

Pharmacometricians

Design

■ **Clinical pharmacology = PK + PD + Disease models**

Dose → *Pharmacokinetics* → Concentration → *Pharmacodynamics* → Effect

- Main statistical tool: Nonlinear Mixed Effect Models (NLMEM)
- Also called Population PKPD
- Increasingly used drug development

Design in pharmacometrics

- Several methods/software for maximum likelihood estimation of population parameters using NLMEM
  - Difficulties as no close form solution for the likelihood

- Problem beforehand: choice of 'population' design to get precise estimates
  - number of individuals?
  - number of sampling times/ individuals?
  - sampling times?
  - other design variables (doses, etc…)

  - Simulation (CTS)
  - Asymptotic theory: expected Fisher Information Matrix
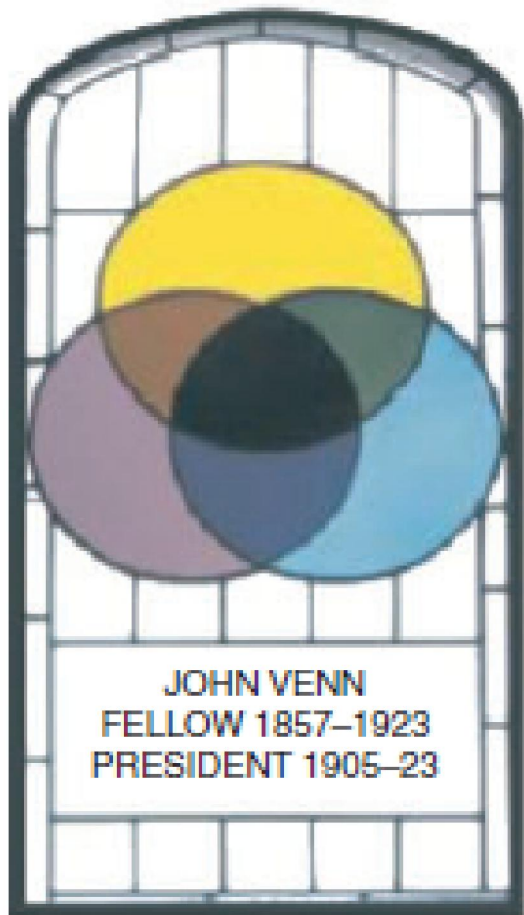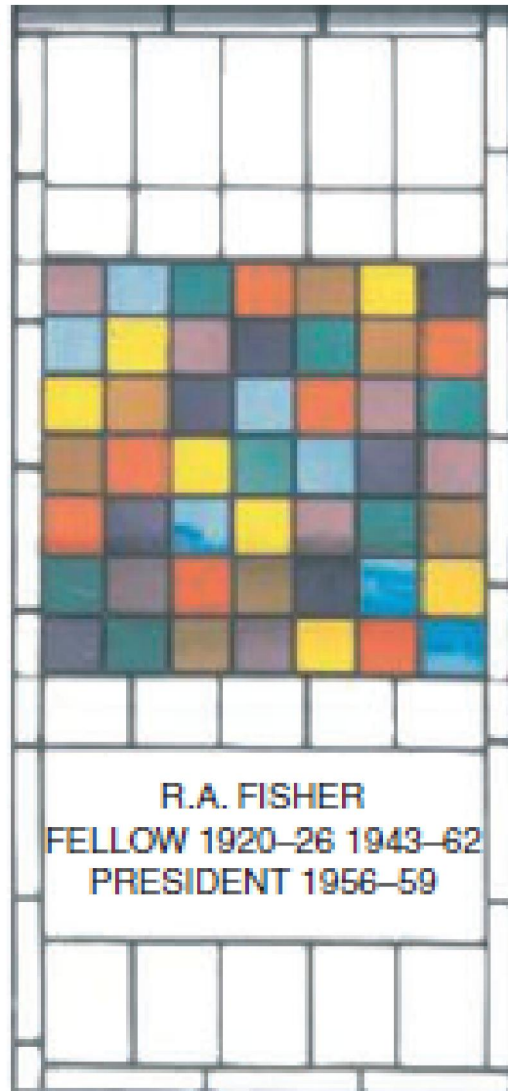
Fisher was elected Fellow of the Royal Society in 1929, and Balfour Professor of Genetics, Cambridge, 1943–57. He was knighted in 1952 and served as President of Caius 1957–9.

To consult the statistician after an experiment is finished is often merely to ask him to conduct a post mortem examination. He can perhaps say what the experiment died of

– R.A. Fisher [1]

1 Fisher R.A. Presidential address to the first Indian Statistical Congress. *Sankhya* 1938; 4: 14–7.

Figure 1 Stained glass windows in the Hall of Gonville and Caius College, Cambridge, commemorating (a) Venn (Fellow 1857–1923; a Venn diagram) and (b) Fisher (a Latin square).

From Pandit JJ , Anesthesia 2010

OUTLINE

1. 10 years of PODE
2. Evaluation of FIM for NLMEM
3. Recent Examples from Pharma industry
   - Novartis
   - Servier
   - Astra Zeneca
4. Conclusion

1. 10 YEARS OF PODE

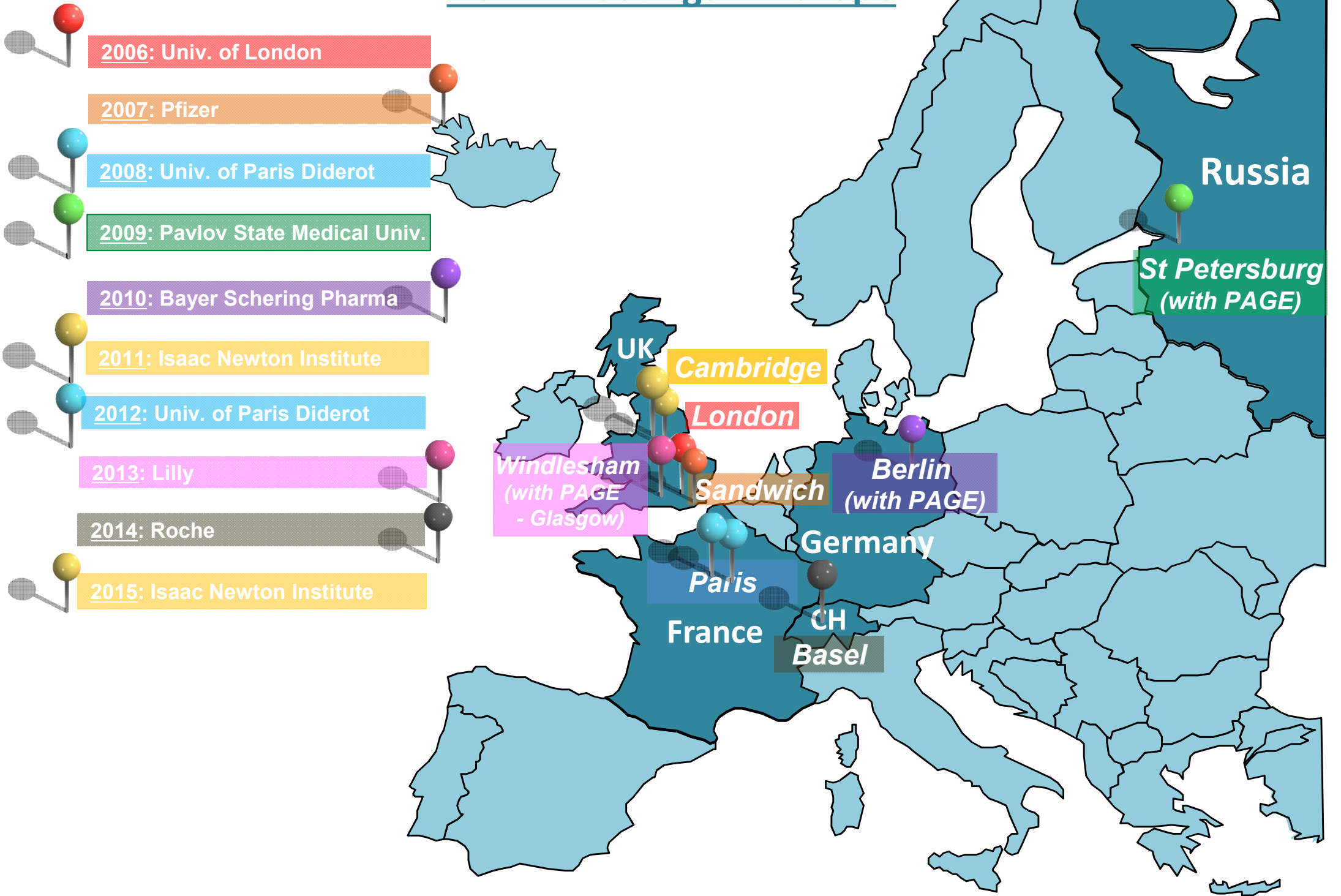# Population Optimum Design of Experiments (PODE)

■ **Workshop created in 2006**
- Multidisciplinary group
- initiated by Barbara Bogacka & France Mentré (PAGE 2005)
- discuss theory of optimum experimental design in NLMEM and their application in drug development

www.maths.qmul.ac.uk/~bb/PODE/PODE2015.htm

PODE Meetings in Europe

- 2006: Univ. of London
- 2007: Pfizer
- 2008: Univ. of Paris Diderot
- 2009: Pavlov State Medical Univ.
- 2010: Bayer Schering Pharma
- 2011: Isaac Newton Institute
- 2012: Univ. of Paris Diderot
- 2013: Lilly
- 2014: Roche
- 2015: Isaac Newton Institute

Russia

St Petersburg
(with PAGE)

UK

Cambridge

London

Windlesham
(with PAGE - Glasgow)

Sandwich

Berlin
(with PAGE)

Germany

Paris

France

CH

Basel

Population Optimum Design of Experiments (PODE)

- May 2006: London, University of London (B. Bogacka)

- May 2007: Sandwich, Pfizer (P. Johnson)

- June 2008: Paris, University Paris Diderot (F. Mentré)

- June 2009: St Petersburg, GSK (S. Leonov)

- June 2010: Berlin, Bayer (T. Schmelter & R. Schwabe)

- August 2011: Cambridge, IN Institute (B. Bogacka, S. Leonov)

- March 2012: Paris, University Paris Diderot (F. Mentré)

- June 2013: London, Eli Lilly (B. Bogacka & I. Gueorguieva)

- Sept 2014: Basel, Roche (S. Retout)

- July 2015: Cambridge, IN Institute (B. Bogacka)

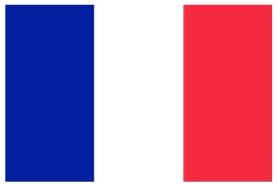# 88 talks: 68 from academia (77%)
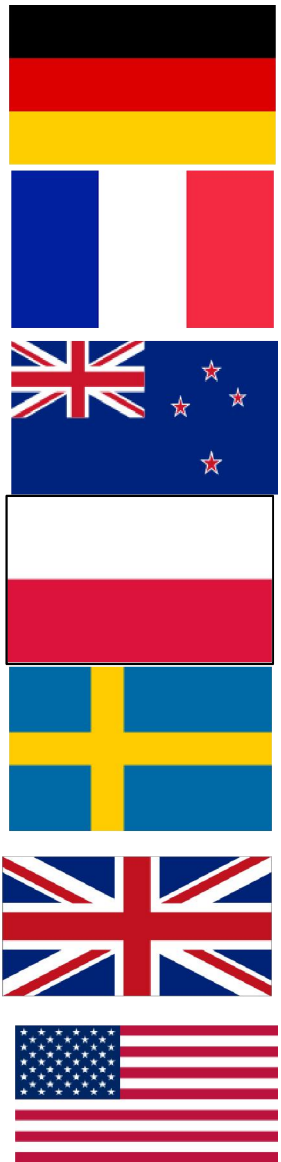
- 10 DE (University of Magdeburg)

- 16 FR (University Paris Diderot, Paris Descartes/ INSERM)

- 6 NZ (University of Otago)

- 2 PL (University of Zielona Gora)

- 16 SE (University of Uppsala)

- 12 UK (University of Cardiff, London, Manchester, Southampton)

- 6 US (USC, USCF, Univ Wisconsin, Anderson Cancer Research, Univ Iowa)

PODE 13 PhDs'

- **Tobias Mielke**, *Marina Prus*

- Sylvie Retout, Caroline Bazzoli, Thu Thuy Nguyen, François Combes, *Giulia Lestini*

- Le Kien Foo

- Joakym Nyberg, **Sebastian Ueckert**

- Aris Dokoumetzidis, Kay Ogungbenro, **Tim Waite**

88 talks: 20 from industry (23%)

PODE most talkative speakers (≥ 5 talks)
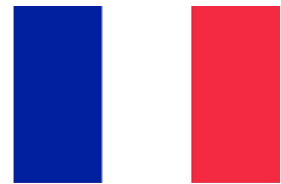
- France Mentré

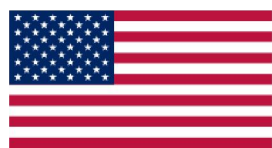- Steve Duffull

- Andy Hooker, Sebastian Ueckert

- Valerii Fedorov, Sergei Leonov

2. Evaluation of FIM for NLMEM

Various model linearisation for computing FIM in NLMEM

- FO: Simple First Order Approximation (FO)
  - "Reduced" or "Full" matrix

  A: block for fixed effects

  B: block for random components

$$FIM_{\text{Reduced}} = \begin{pmatrix} A & 0 \\ 0 & B \end{pmatrix}$$

$$FIM_{\text{Full}} = \begin{pmatrix} A^* & C \\ C & B \end{pmatrix}$$

$$A^* = A + \frac{1}{2} tr\left(\frac{\partial V}{\partial \theta} V^{-1} \frac{\partial V}{\partial \theta} V^{-1} \right)$$

- Other approximations: FOI (PkStaMP, PopDes), FOCEI / FOCE (PopED)

Software in population design

	PFIM	PFIM Int.	PkStaMP	PopDes	PopED	POPT
Authors	**Mentré** et al (Paris)	**Mentré** et al (Paris)	**Leonov** (US)	**Ogungbenro** (Manchester)	**Hooker** /Nyberg/Ueckert (Uppsala)	**Duffull** (Otago, NZ)
Language	R	R	Matlab CR	Matlab	Matlab and R	Matlab
Available on website	Yes	Yes	No	Yes	Yes	Yes
GUI	No	Yes	Yes	Yes	Yes	No
Library of models	Yes	Yes	Yes	Yes	Yes	Yes
User defined models	Yes	Yes	Yes	Yes	Yes	Yes

Comparison of software and linearisation approaches PODE07 to PODE12 Meetings

- **Comparison of software**
  - Overall summary of software at PODE 07, PAGE 2007
  - Updated at PODE 11

- **Comparison of approximations**
  - discussed at PODE 09 & 10 for a simple PK model
  - presented at PAGE 2011 and PODE12 for a complex PKPD HCV model with two responses and ODE
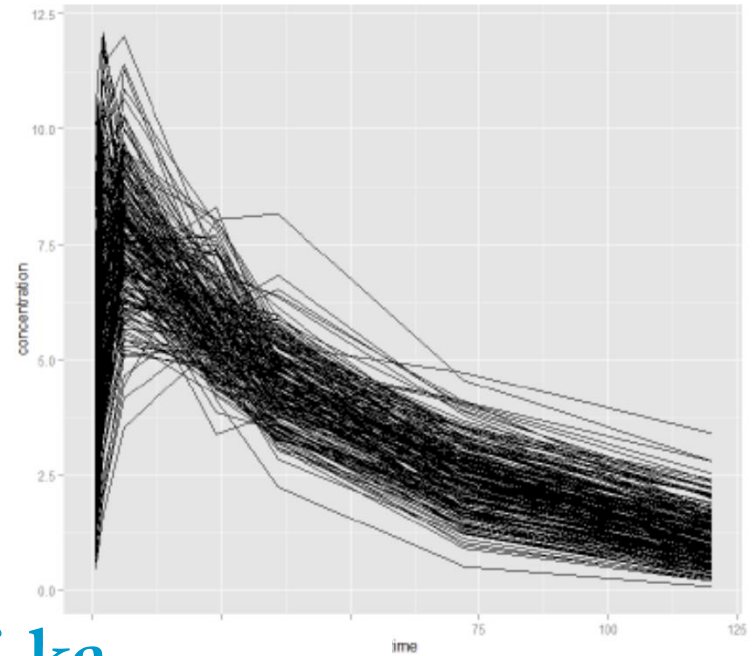
Objectives

To compare the **standard errors (SE)** and efficiency **criterion** provided by the different software for population designs on two examples:

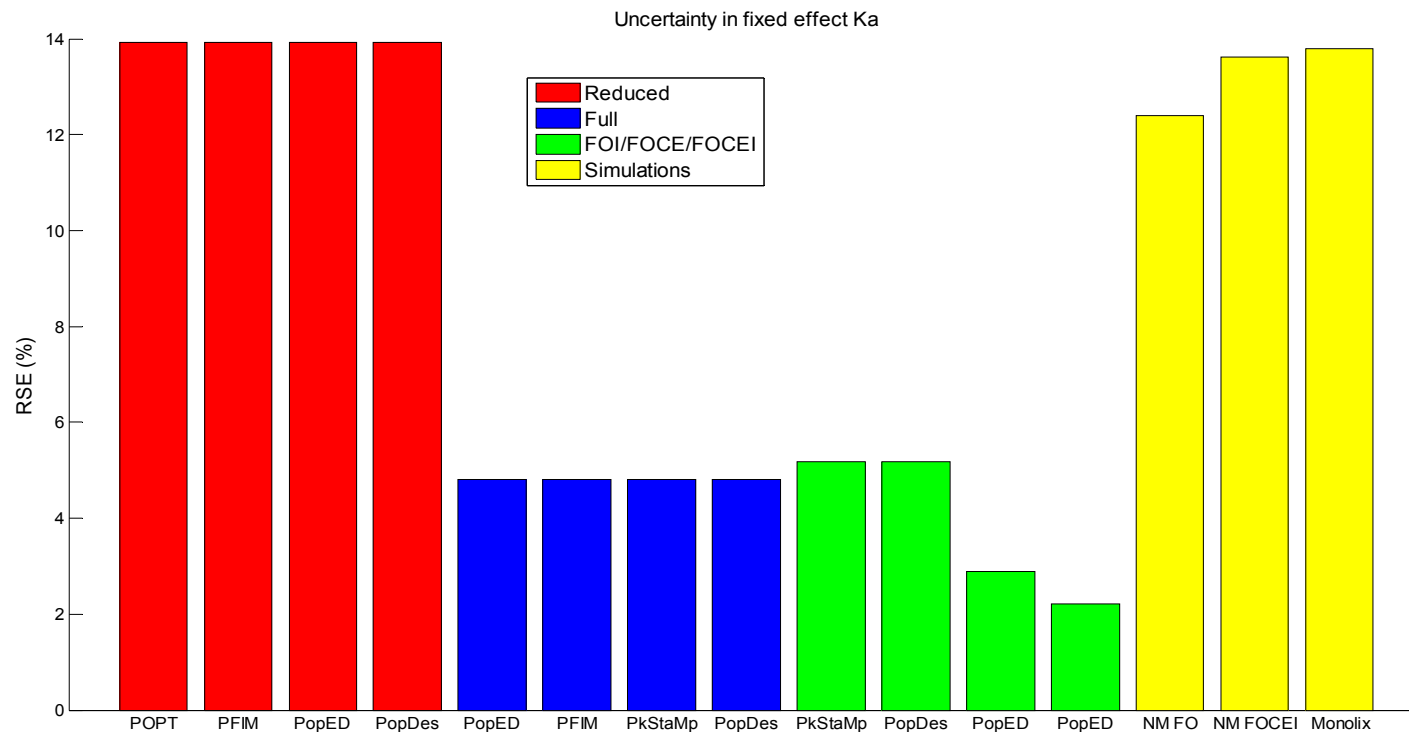1. a simple PK model of warfarin

2. a complex PKPD example for HCV

Gold standard: SE obtained from simulation

PK example

$$f(\phi = (k_a, V, CL), t) = \frac{70}{V} \frac{k_a}{k_a - \frac{CL}{V}} \left(e^{-\frac{CL}{V}t} - e^{-k_a t} \right)$$
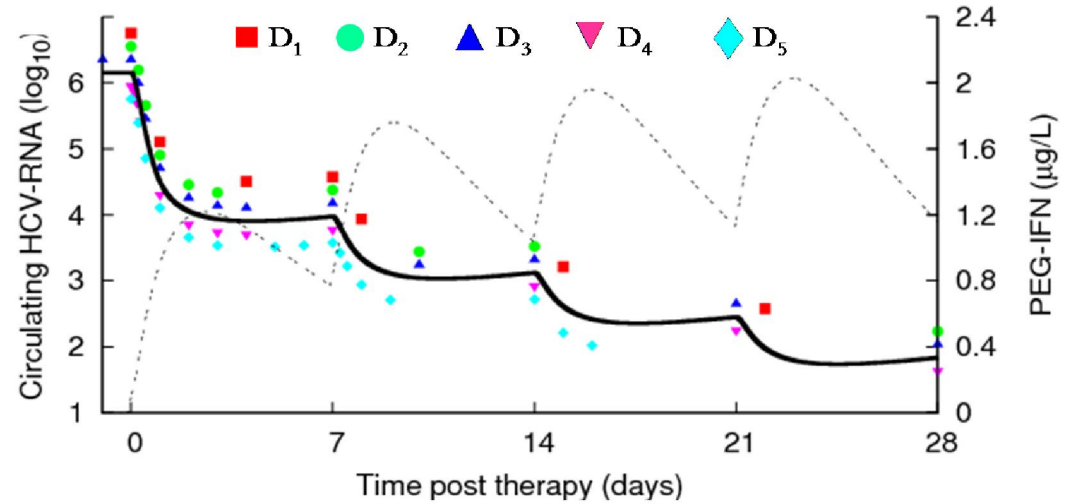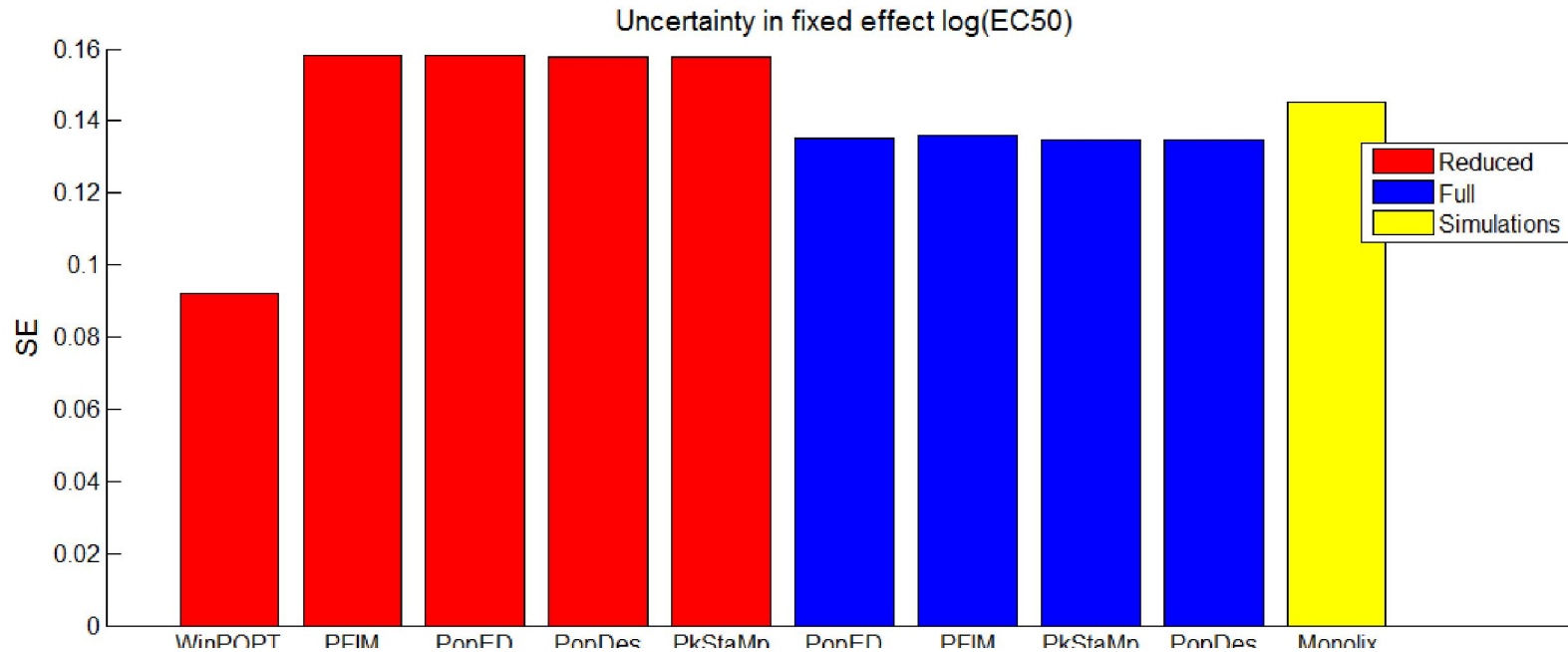

RSE(%) for fixed effect of ka

HCV example

$$\begin{cases} \dfrac{dX}{dt} = D - k_a X \\[2mm] \dfrac{dA}{dt} = k_a X - k_e A \\[2mm] \boxed{C(t) = \dfrac{A(t)}{V_d}} \\[2mm] \dfrac{dT}{dt} = s - \beta(1-\eta)VT - dT \\[2mm] \dfrac{dI}{dt} = \beta(1-\eta)VT - \delta I \\[2mm] \boxed{\dfrac{dV}{dt}} = p\left(1 - \dfrac{C(t)^n}{C(t)^n + EC_{50}^{\,n}}\right)I - cV \end{cases}$$

SE for fixed effect of log(EC50)

Uncertainty in fixed effect log(EC50)

Legend: Reduced, Full, Simulations

WinPOPT, PFIM, PopED, PopDes, PkStaMp, PopED, PFIM, PkStaMp, PopDes, Monolix

Conclusion on Examples

- Good prediction of SE of all PKPD parameters even with FO, using the block matrix

- Numerical issues to solve across software

- Computing time for HCV example
  - Simulation = 5 days
  - design evaluation with software = 5 min

➢ Nyberg, Bazzoli, Ogungbenro, Aliev, **Leonov**, Duffull, **Hooker, Mentré**. Methods and software tools for design evaluation for population pharmacokinetics-pharmacodynamics studies. *Br J Clin Pharmacol,* 2015 Jan;79(1):6-17

➢ Continue working on better approximation of the FIM

➢ Compare software for design optimisation

New dose response example

$$f(\phi = (E_0, E_{max}, ED_{50}, \gamma), d) = E_0 + \frac{E_{max}d^\gamma}{ED_{50}^\gamma + d^\gamma}$$
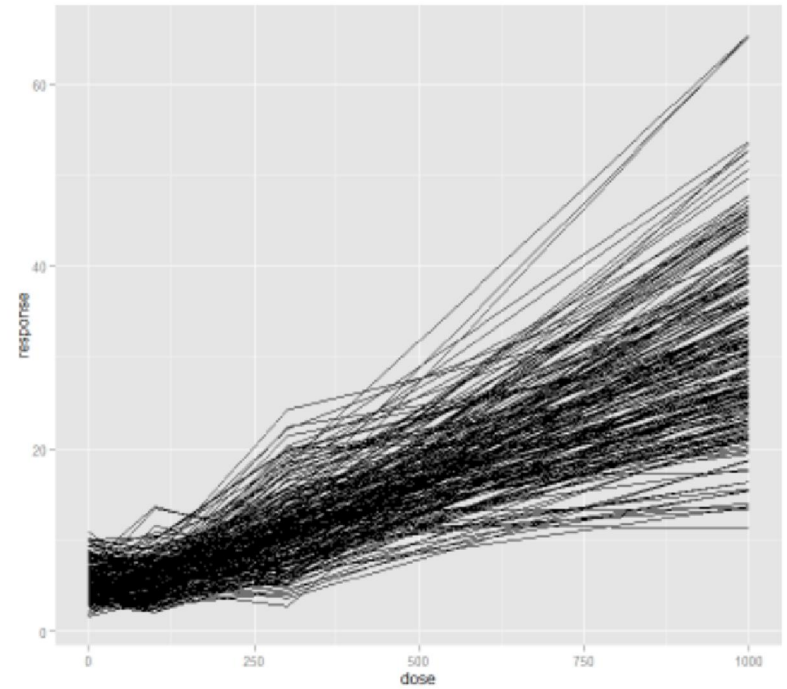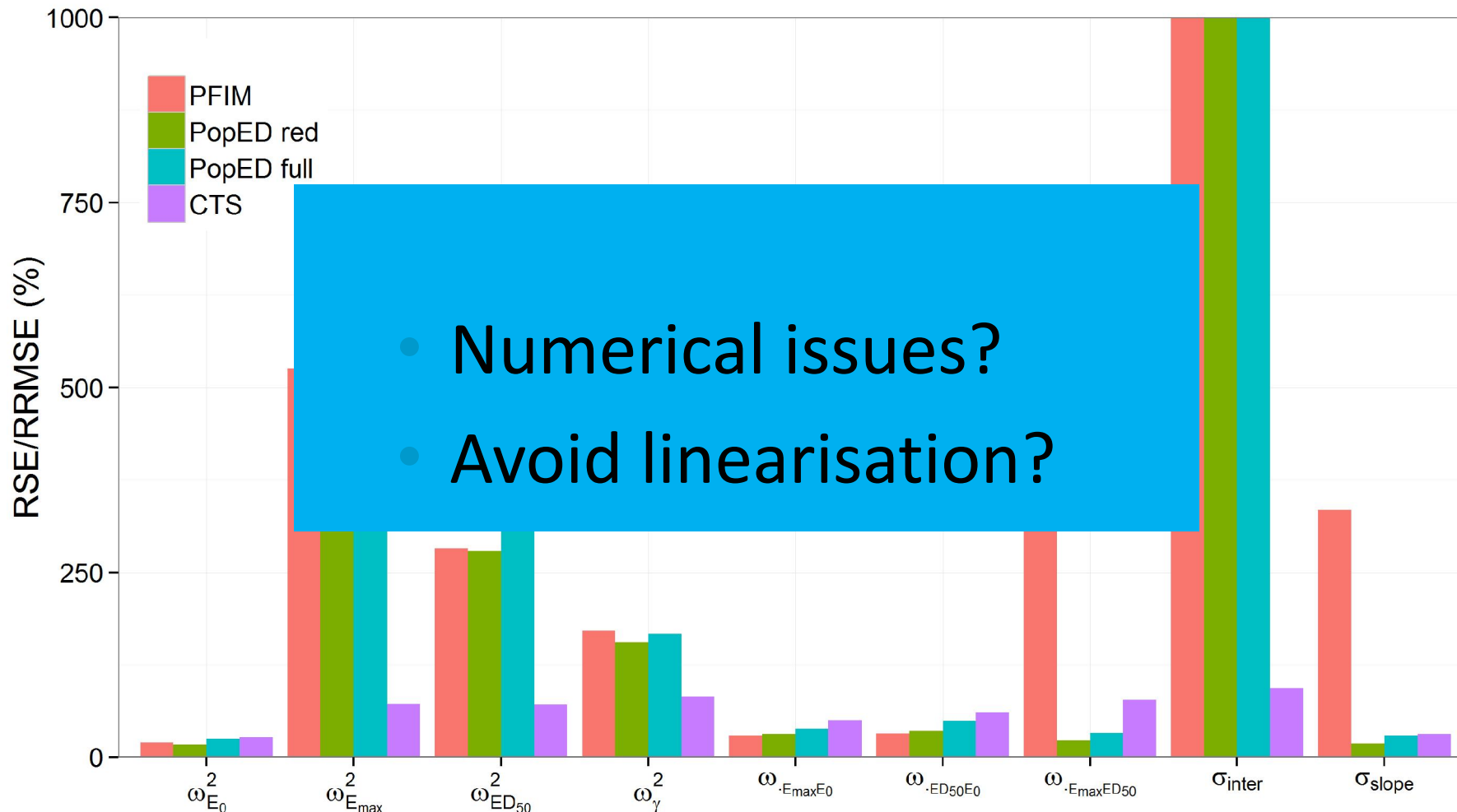
RSE for fixed effects
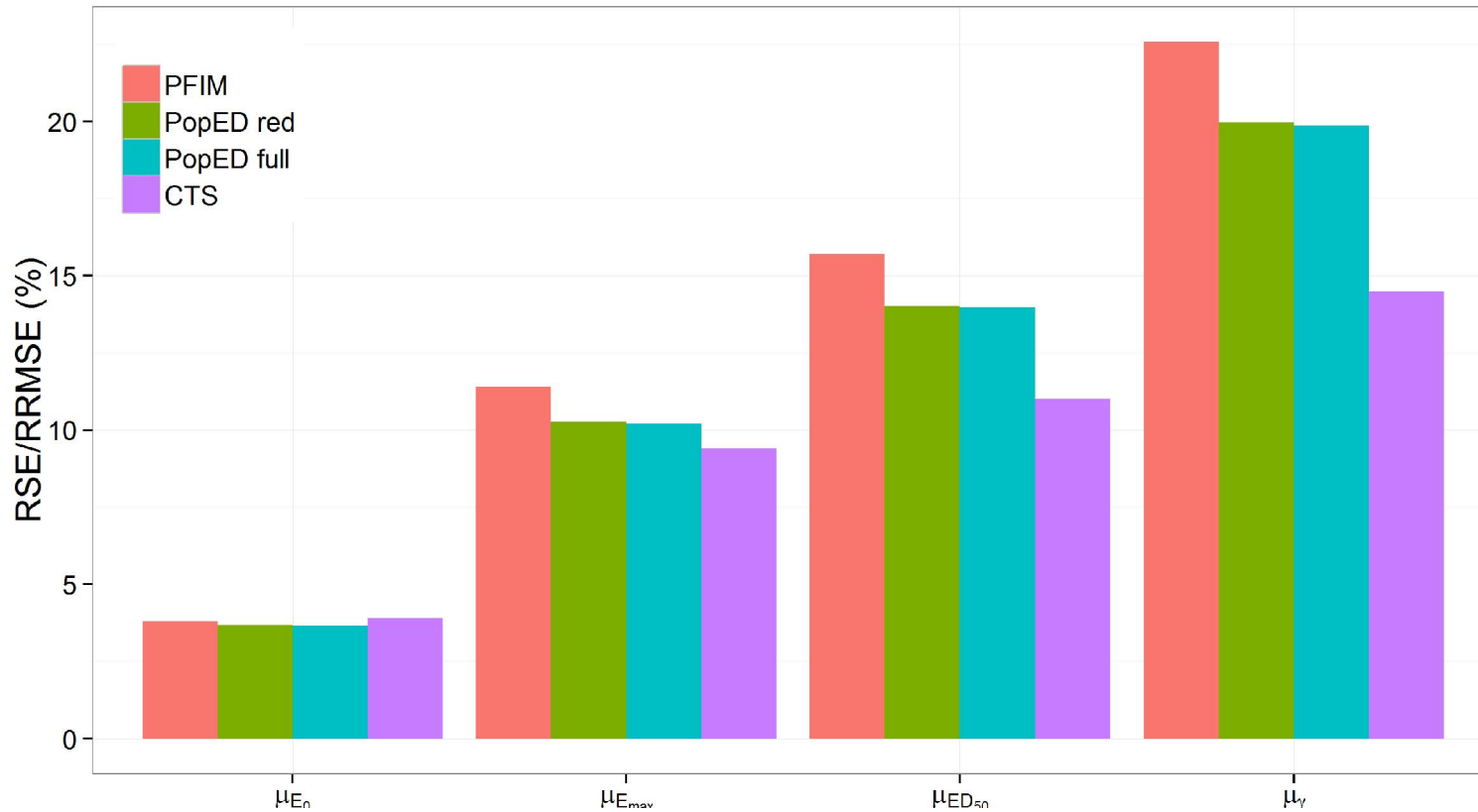
New dose response example

RSE for variance components

- Numerical issues?
- Avoid linearisation?

3. RECENT EXAMPLES from Pharma INDUSTRY

Novartis

Servier

Astra Zeneca

DDMoRe: an evolutionary step in model building and sharing

Lutz Harnisch, Pfizer, UK

Mats Karlsson, Uppsala University, Sweden

Participants

From industry formation of model builders, model users, software developers and teachers

DDMoRe – The Vision

Drug Disease Model Resources
ddmore

Standards for describing models, data and designs

Model Definition Language

Modelling Library
Shared knowledge

Specific disease models
Examples from high priority areas

Modelling Framework
A modular platform for integrating and reusing models; shortening timelines by removing barriers

System interchange standards
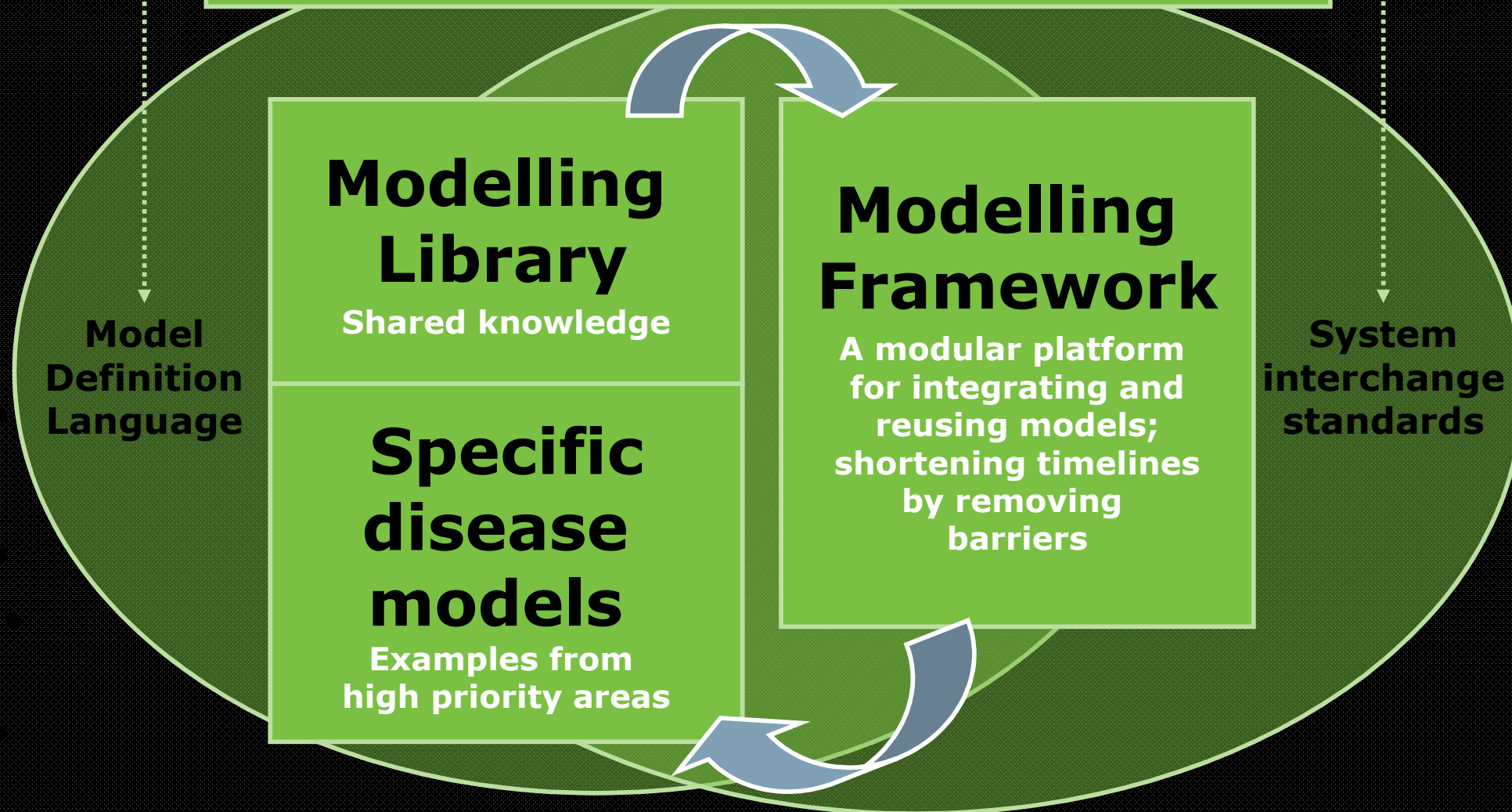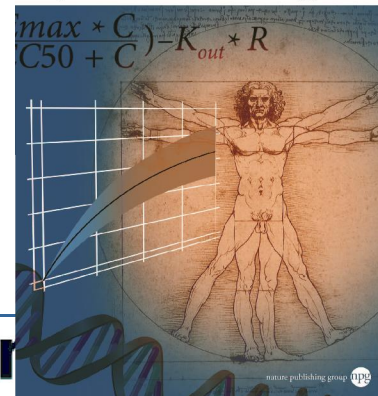
Survey on use of design software tools in pharmacometrics

PERSPECTIVE

Current Use and Developments Needed for Optimal Design in Pharmacometrics: A Study Performed Among DDMoRe's European Federation of Pharmaceutical Industries and Associations Members

F Mentré[1], M Chenel[2], E Comets[1], J Grevel[3], A Hooker[4], MO Karlsson[4], M Lavielle[5] and I Gueorguieva[6]
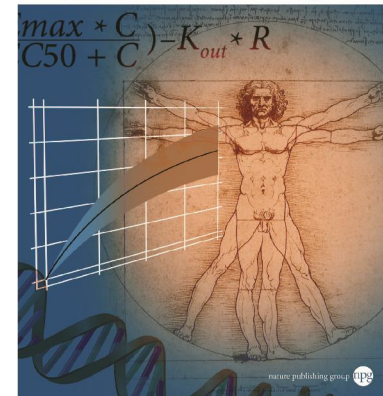
Table 1 Current use of optimal design software tools for the $n = 9$ European Federation of Pharmaceutical Industries and Associations companies, out of the 10 of DDMoRe, presently using this approach

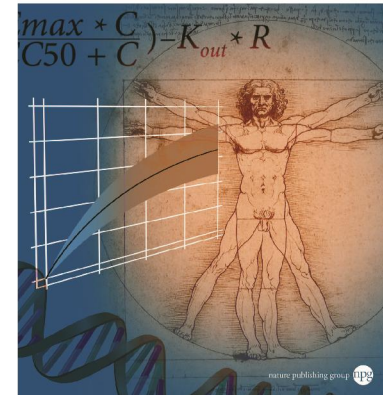|	Yes
Type of investigations	
Design evaluation	7
Design optimization	8
Power evaluation	6
Complexity of designs	
Dose/input optimization	6
Sampling windows in designs	7
Several group of elementary designs	7
Bayesian/robust approaches	5
Complex error models	3
Interoccasion variability	3
Covariates	5
Multiresponse models	4

Table 2 Expectations of $n = 10$ European Federation of Pharmaceutical Industries and Associations companies of DDMoRe regarding the capabilities of a new optimal design software

	Median	Range
Accepts continuous covariates	5	3–5
Handles data below quantification limit	4	2–5
Handles robustness across models	4	2–5
Handles discrete data	4	1–5
Handles jointly continuous and discrete data	4	1–5
Handles repeated time-to-event (RTTE) data	3	1–5
Predicts shrinkage	3	1–5
Provides standard errors for individual parameters	3	1–5
Provides choice of several optimality criteria	3	1–5
Handles jointly continuous and RTTE data	3	1–3

Scale from 0 to 5.
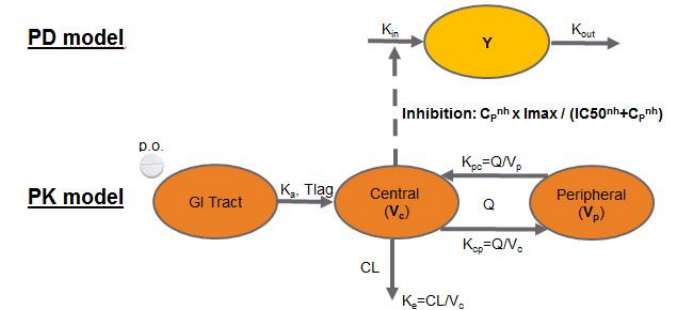
Optimal design at Novartis
Two examples (by Martin Fink, Etienne Pigeolet & Björn Bornkamp)

- **Used at the design stage to quickly evaluate different design options**
  - Often: Ranking of different „logistically-feasible" design-options
  - Almost never: Exact implementation of a calculated optimal design

- **Used primarily in early stage trials**
  - Two examples
  1. PK-PD modelling (dose-exposure-response modelling over time)
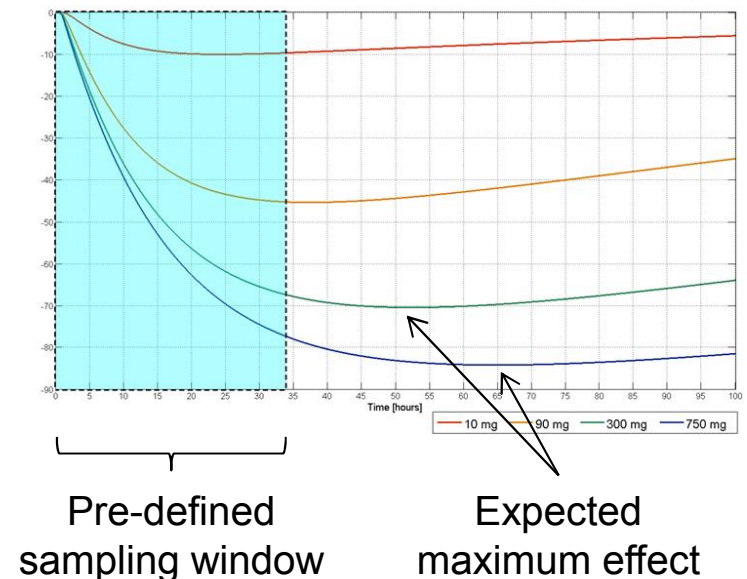 2. Dose-finding studies (modelling population dose-response curve)

NOVARTIS

Example 1: PK-PD modelling
Choosing sampling times in Phase I

- **Ongoing Phase I study**
  - 4 cohorts conducted, 2 cohorts to be designed
  - PK two-comp, PD turnover model
  - Challenging measurement: in cerebrospinal fluid
  - Maximum effect of higher doses likely after the end of predefined sampling window
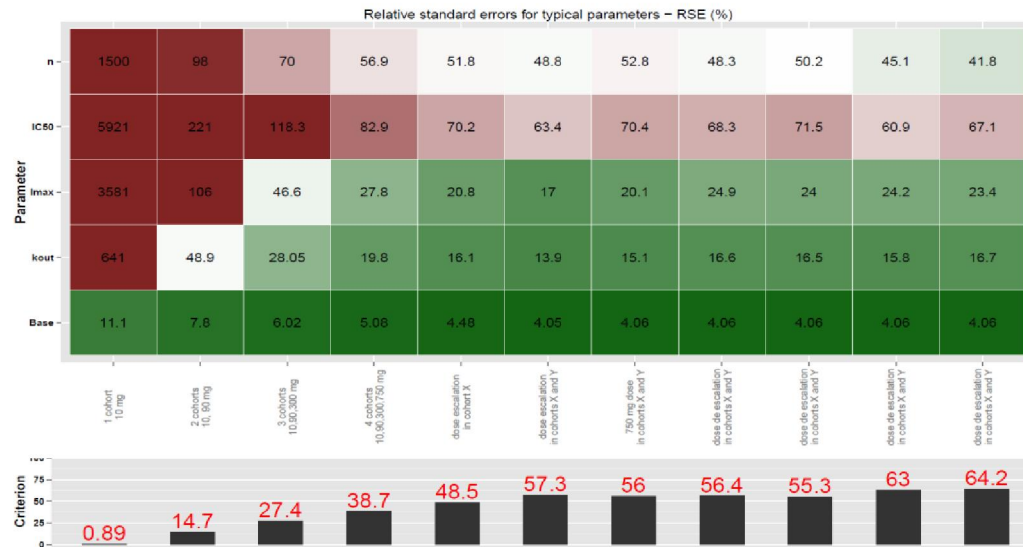

- **Two options**
  - Option 1: Do not change sampling window (only doses)
  - Option 2: Change of sampling window & doses
  - Compare designs based on Fisher information as well as relative standard error for population model parameters

Pre-defined sampling window   Expected maximum effect

NOVARTIS
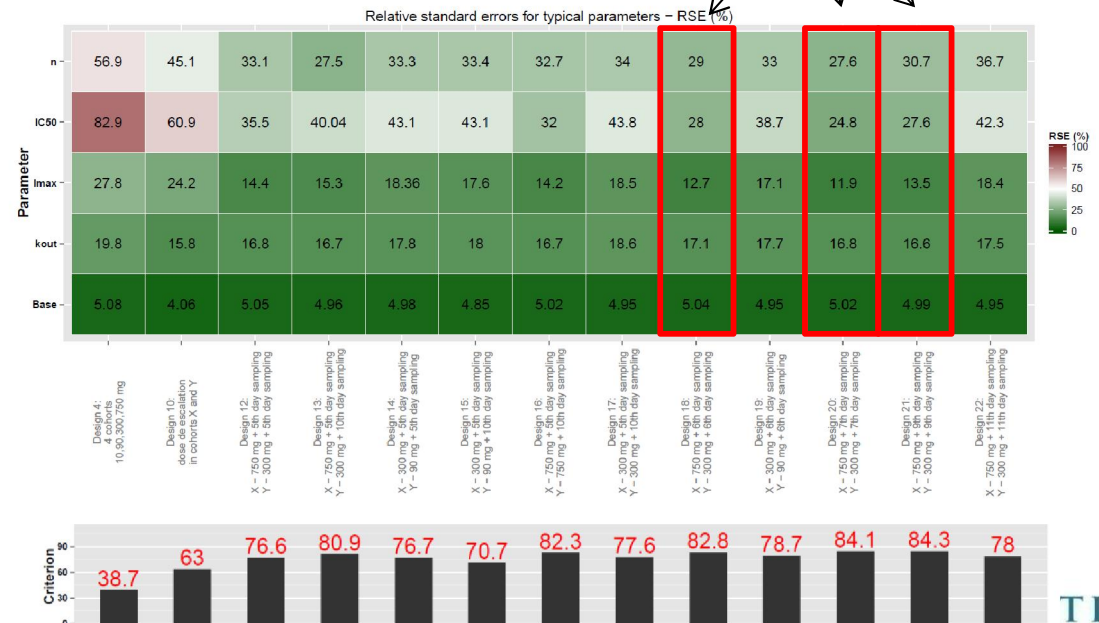
Information content based on calculations using PFIM 4.0

**Option 1
Using dose-
adjustments only
is sub-optimal!**

Several options
to discuss with the team

**Option 2
Dose-adjustments and
new sampling times**

Choosing doses for a Phase IIb study (using DoseFinding R package)

- **Usage of MCP-Mod methodology**
  - Limited information on dose-response curve
  - → Broad candidate set of monotonic shapes
  - Use of robust D-optimal design weighting candidate shapes equally („Bayes design")
    - Calculated design impossible to implement logistically
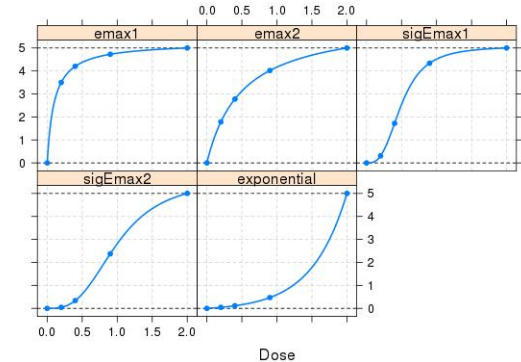
Logistically feasible candidate designs (balanced allocations)

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
equally spaced	0.00	0.50	1.00	1.50	2.00
equally spaced in log	0.00	0.20	0.40	0.90	2.00
compromise 1	0.00	0.20	0.60	1.20	2.00
compromise 2	0.00	0.20	0.80	1.40	2.00
compromise 3	0.00	0.40	0.90	1.50	2.00

Efficiency vs averaged optimal design

```
##                         Efficiency
## equally spaced                0.85
## equally spaced log            0.87
## compromise 1                  0.94
## compromise 2                  0.92
## compromise 3                  0.91
```

Efficiencies under each scenario and worst case

```
##                    emax1 emax2 sigEmax1 sigEmax2 exponential  Worst case eff.
## equally spaced      0.46  0.77     0.67     0.89        0.82             0.46
## equally spaced log  0.71  0.85     0.85     0.70        0.54             0.54
## compromise 1        0.72  0.83     0.73     0.92        0.71             0.71
## compromise 2        0.73  0.81     0.63     0.83        0.81             0.63
## compromise 3        0.53  0.81     0.81     0.83        0.82             0.53
```

NOVARTIS

Using optimal design approaches in industry

Servier's experience

Contributors: Marylore Chenel and the Servier pharmacometrics group

Context

Pharmacometrics at Servier:
    8 PK & PKPD modellers (various backgrounds) + PBPK modelling group
    Preclinical & clinical context (from stB to post-market)
    Variable individual experience in FIM-based software
    Team interest in optimal design techniques (collaboration (PhD funding) with
    Uppsala & Paris groups, involvement in ddmore WP6,…)

Over the last year (July 2014 – June 2015), optimal-design software (PFIM) were used for:
    2 * Optimisation of PK samples of an *in vivo* pharmacology experiment
    1 * Optimisation of PK samples of a clinical trial
    2 * Model identifiability investigation
   1 * Power calculation through design evaluation

Context: Phase III clinical trial, limited samples
PK data is planned to be analysed through a Bayesian approach
Existing population PK model
PK sampling design to be defined

Aim of the work: to collect enough information for the estimation of individual parameters (= to limit the shrinkage)

Method: Using Bayesian FIM, exploration of the relation between the number of samples per patient and the shrinkage on each parameter in order to choose the number of samples

Figure 1: Pixantrone PPK structural model

6 samples -> low expected shrinkage
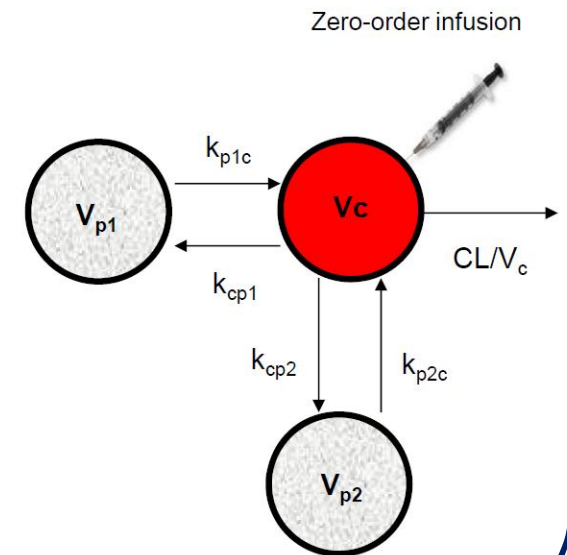
Shrinkage vs Nsamples(/subjects)
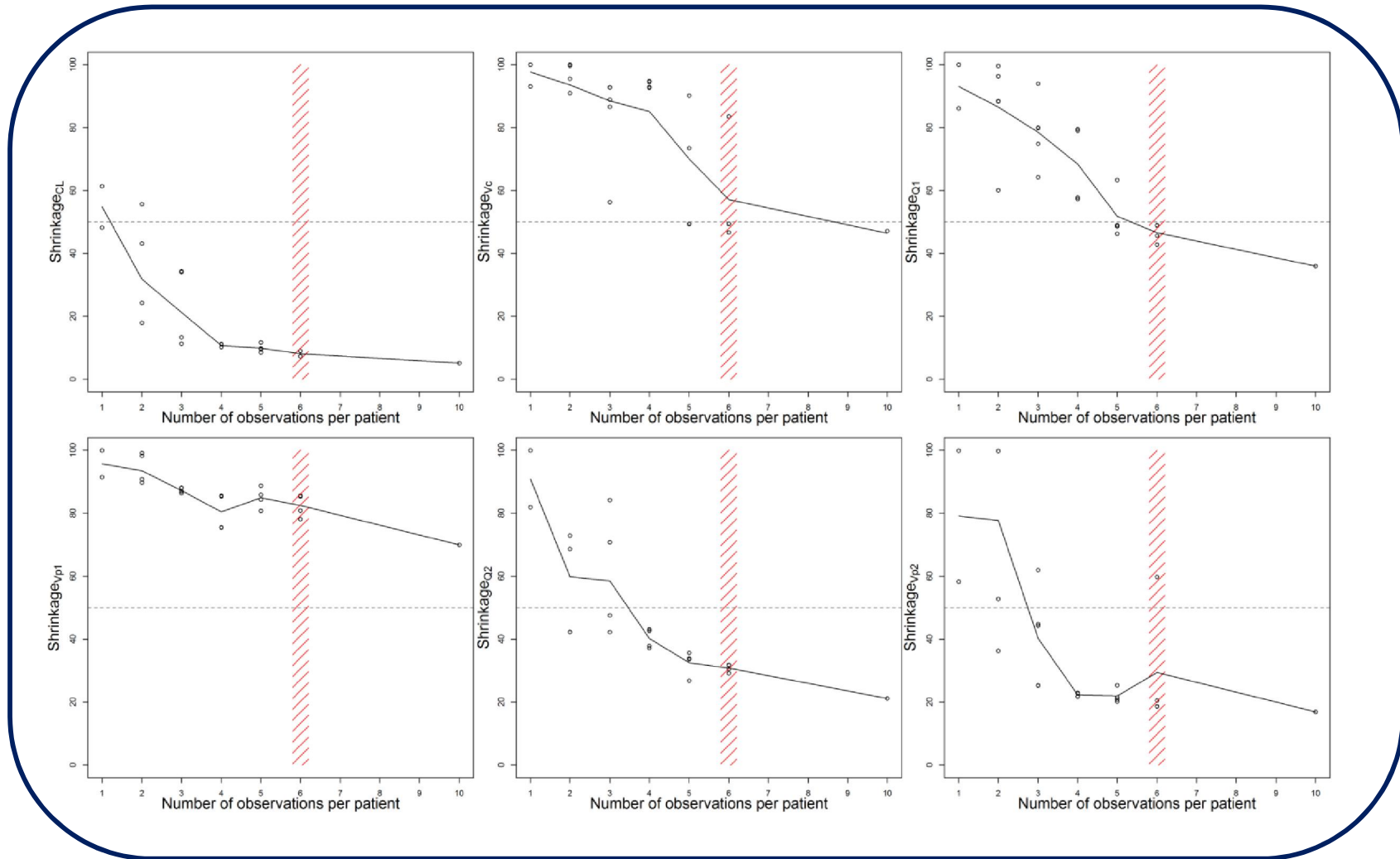
(+high sensitivity of shrinkage with regards to initial values for simplex algorithm)

Use of model based dose response in phase 2b to improve efficiency and dose selection for hyperphosphatemia in ESRD patients

Magnus Åstrand
Quantitative Clinical Pharmacology, January 2014

Tina Rydén-Bergsten (Project Leader)
Tomas Andersson, Christof Bischoff, Björn Carlsson, Klaus Christensen, Colette Clarke, Martin Billger, Marie Elebring, Peter Greasley, Lizzie Grosset, Johanna Husmark, Johan Holmberg, Monique Isgaard, Camilla Jansson, Susanne Johansson, Mikael Knutsson, Maria Leonsson-Zachrisson, Richard Ogborne, Bergur Stefansson, Constanze Wartenberg, Martin Wikberg

AstraZeneca

Model based dose response Ph2B design for hyperphosphatemia in ESRD patients

Background

A Ph2B study evaluating the efficacy and safety of AZ compound to treat hyperphosphatemia in End-Stage Renal Disease (ESRD) patients is planned.

Study design elements
- 2 week washout period, current treatment removed
- 4 week randomized treatment period, active or placebo
- Weekly recordings of serum phosphate in each patient.

Expected time course of serum phopshate

$$Kin = Kin0 * (1 - \frac{Emax}{1 + ED50/Dose})$$
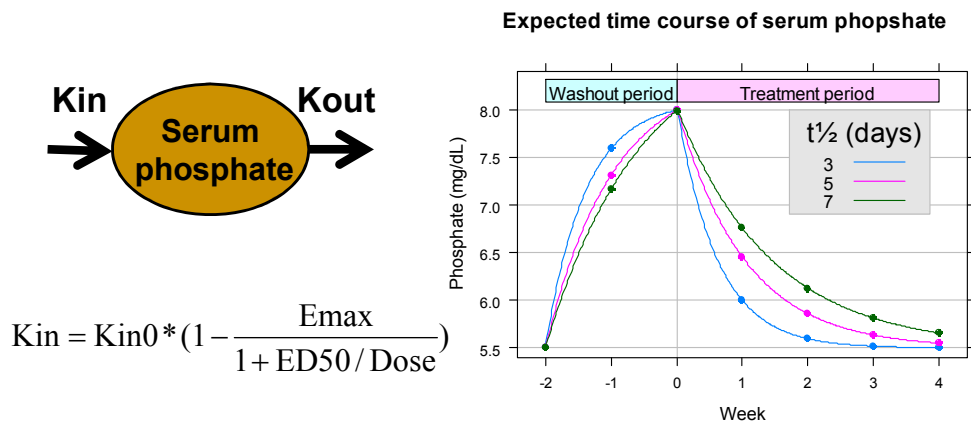
A indirect response model for serum phosphate

A indirect response model was selected for evaluation:
- Natural choice with a mechanistic interpretation
- Kin represents absorption of phosphate from the gut
- Kout is the rate at which phosphate is eliminated from serum. A continuous elimination approximates the piece-wise elimination during hemodialysis
- The compound reduces the phosphate absorption (kin)

Methods

Design and analysis approach was evaluated by clinical trial simulations.
Longitudinal dose-response was compared with a traditional statistical analysis approach; pair-wise change from baseline to and of treatment
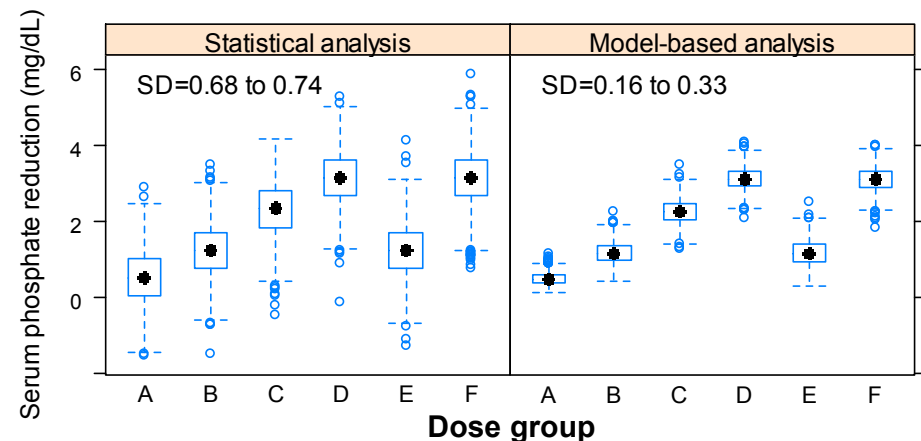
Results

~50% reduced uncertainty on dose response understanding
~50% reduced risk of selecting non efficacious dose for Ph3
A conventional statistical analysis requires 4 times more patients to match performance of the model based approach
75% reduced costs and faster progress to Ph3

Estimated treatment effects in clinical trial simulations

Magnus Åstrand, Principal Clinical Pharmacometrician, Ph.D. Innovative Medicines | Quantitative Clinical Pharmacology

4. CONCLUSION

Conclusion (1)

- **NLMEM increasingly used in drug development**
  - ➤ Need fo informative studies with small estimation error

  SPARSE-SAMPLING DESIGN = BEST INFORMATION NEEDED

COMPLEX MODELS = DIFFICULT TO 'GUESS' GOOD DESIGNS

- **Several statistical extensions for design in mixed models**
- **Several software tools available**
  - define good population designs (ethical/financial reasons)
  - anticipate 'fatal' population designs
  - Careful: lower bound (nonlinearity, small sample size)
    - Clinical trial simulation for important designs

- **Local planification: relies on a priori information**
  - perform sensitivity analysis of parameters and models
  - define compromise design, sampling windows…
  - use robust approach, adaptive design….

Conclusion (2)

(Ongoing) work for stasticians

- Better Approximation of the FIM
- FIM for joint models
- Prediction of power: Wald / LRT
- Correction for small samples
- Model averaging
- Model based adaptive designs (MBAOD)
- Better optimisation algorithms
- …

(Ongoing) work for pharmacometricians

- Increase use of model based design at all steps of drug development

10 years
and *growing stronger*

➤ **10 MORE YEARS FOR PODE**

Celebrating

20 years

PoDE 2015

Isaac Newton Institute for Mathematical Sciences, Cambridge

7 July 2015

Time	Session
9.30 - 10.00	**Registration**
10.00 - 10.05	**Welcome**
10.05 - 11.00	**France Mentre**, INSERM, Paris *10 years of progress in population design methodology and applications.* **Sergei Leonov, Tobias Mielke**, ICON Clinical Research *Optimal design and parameter estimation for population PK/PD models.*
11.00 - 11.30	**TEA/COFFEE**
11.30 - 12.30	**Marie-Karelle Riviere**, INSERM, Paris *Evaluation of the Fisher information matrix in nonlinear mixed effects models using Monte Carlo Markov Chains.* **Sebastian Ueckert**, INSERM, Paris *Computation of the Fisher information matrix for discrete nonlinear mixed effects models.*
12.30 - 14.00	**LUNCH**
14.00 - 15.30	**Tim Waite**, University of Southampton *Design for generalized linear models with random block effects.* **Steve Gilmour**, University of Southampton *Design and analysis of in-vitro pharmacokinetic experiments.* **Moreno Ursino**, INSERM, Paris *Incorporating pharmacokinetic information in phase I studies in small populations.*
15.30 - 16.00	**TEA/COFFEE**
16.00 - 17.00	**Andy Hooker**, Uppsala University *Model based adaptive optimal designs of adult to children bridging studies using FDA proposed stopping criteria.* **Valerii Fedorov**, Innovation Center, ICON plc. *Cost constrained optimal design for regression models with random parameters.*
17.00 - 17.30	**Discussion**

« Notes for France » (V. Fedorov, INI 2011)

RESEARCH PAPER

Prediction of Shrinkage of Individual Parameters Using the Bayesian Information Matrix in Non-Linear Mixed Effect Models with Evaluation in Pharmacokinetics

François Pierre Combes • Sylvie Retout • Nicolas Frey • France Mentré

ORIGINAL ARTICLE

Powers of the Likelihood Ratio Test and the Correlation Test Using Empirical Bayes Estimates for Various Shrinkages in Population Pharmacokinetics

FP Combes[1,2,3,4], S Retout[3,4], N Frey[4] and F Mentré[1,2]

DIDEROT