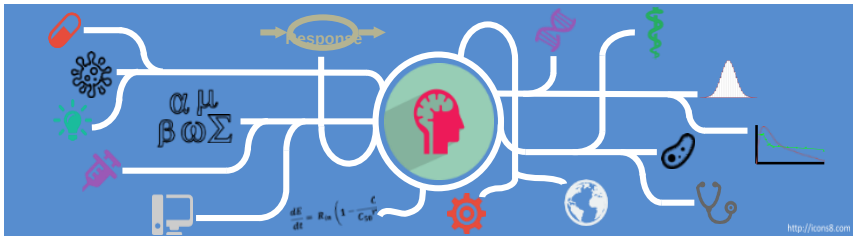

OPTIMAL DESIGNS FOR TRIALS WITH DISCRETE LONGITUDINAL DATA ANALYZED BY NONLINEAR MIXED EFFECT MODELS

France Mentré, Florence Loingeville, Jeremy Seurat, Thu Thuy Nguyen

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BIOSTATISTICAL MODELLING AND PHARMACOMETRICS

CIRM – May 2018

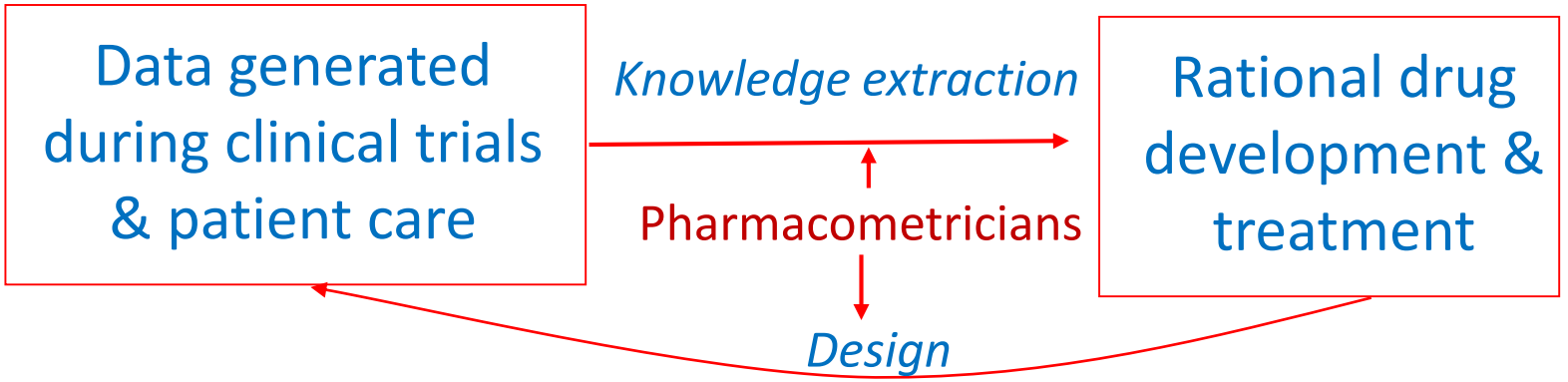
Outline

1. Design in pharmacometrics (PMX)
2. PODE
3. New method to compute FIM for discrete repeated data with model averaging
4. Two examples: count and binary repeated data
5. Conclusion

Pharmacometrics

- Clinical pharmacology = PK + PD + Disease Models

- Pharmacometrics: science of quantitative clinical pharmacology



- Analysis of longitudinal data in clinical trials and cohorts
- Model Informed Drug Discovery and Development
- Main statistical tool: Non-Linear Mixed Effect Models (NLMEM)

From PopPKPD to MID3

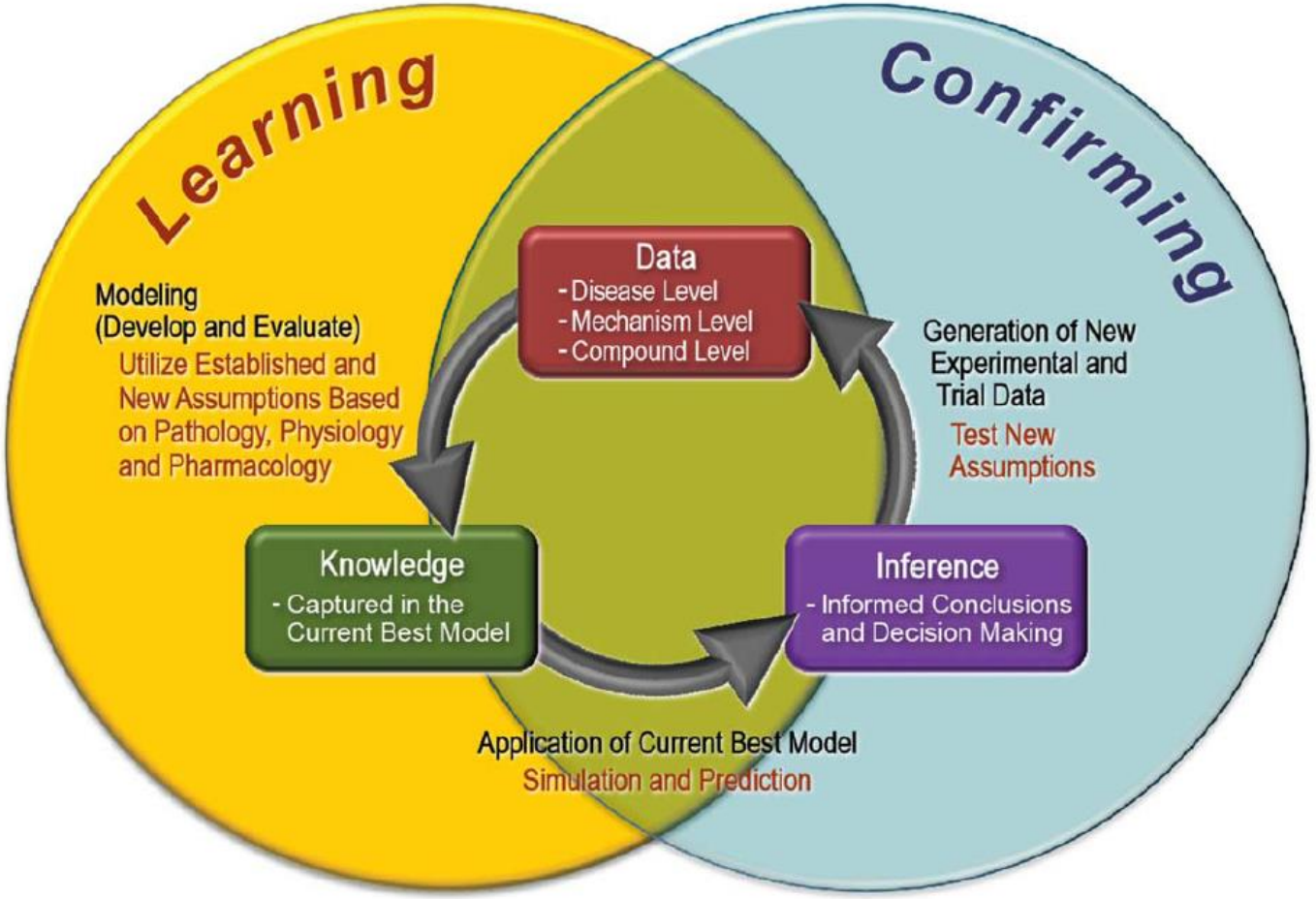
- Population pharmacokinetics /pharmacodynamics (Pop PKPD)
- Nonlinear mixed effect models (NONMEM, NLMEM)
- Modelling and Simulation (M&S)
- Pharmacometrics (PMX)
- Model Based Drug Development (MBDD)
- Model Informed Drug Development (MIDD)
- Model Informed Drug Discovery and Development (MID3)

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]



Population 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**

Evaluation of designs in NLMEM 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

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

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 day workshop
  - May 2006: London, University of London (B. Bogacka)
  - ➢ September 2017: Basel, Novartis → 100 participants

Population Optimum Design of Experiments

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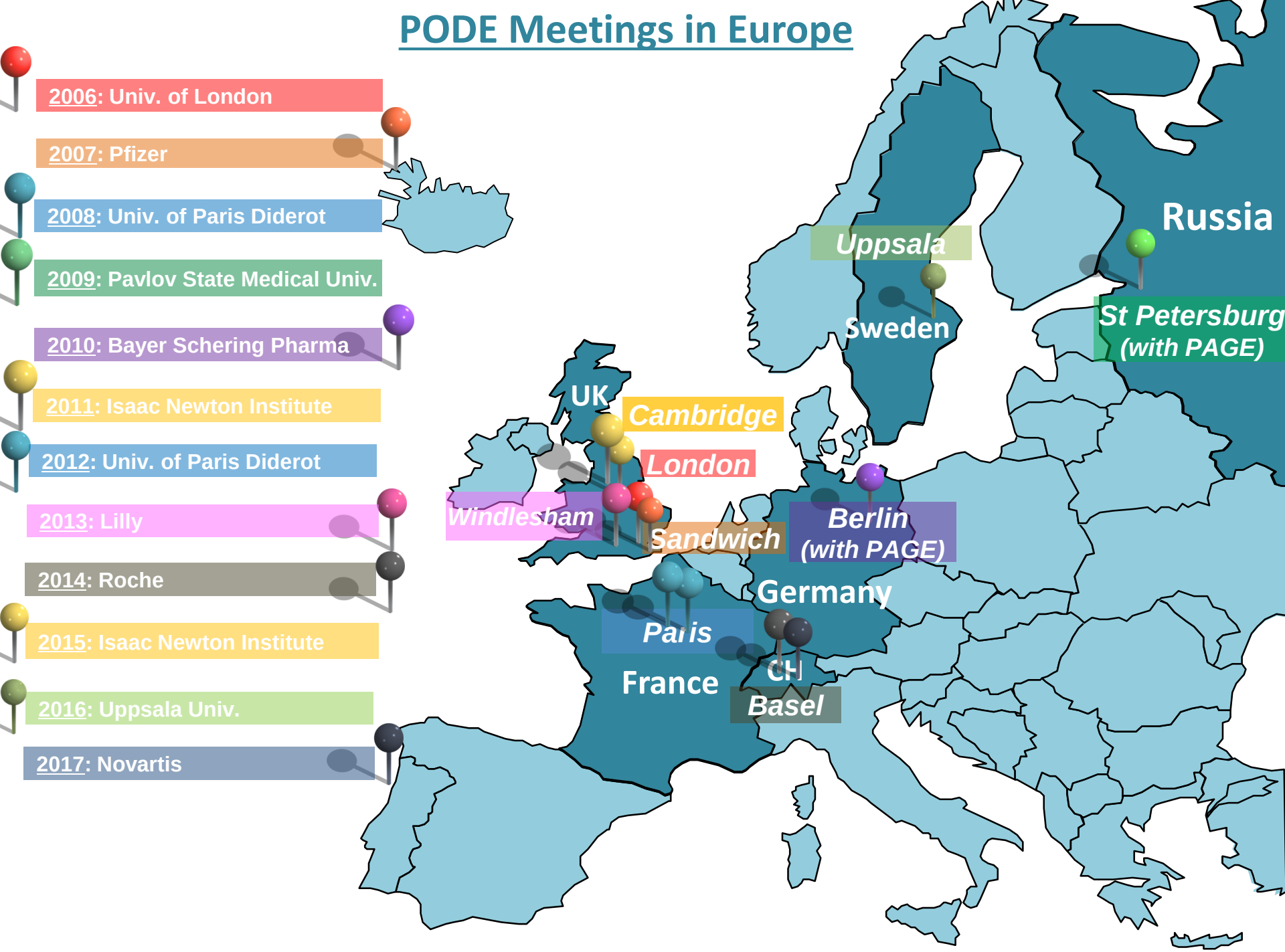
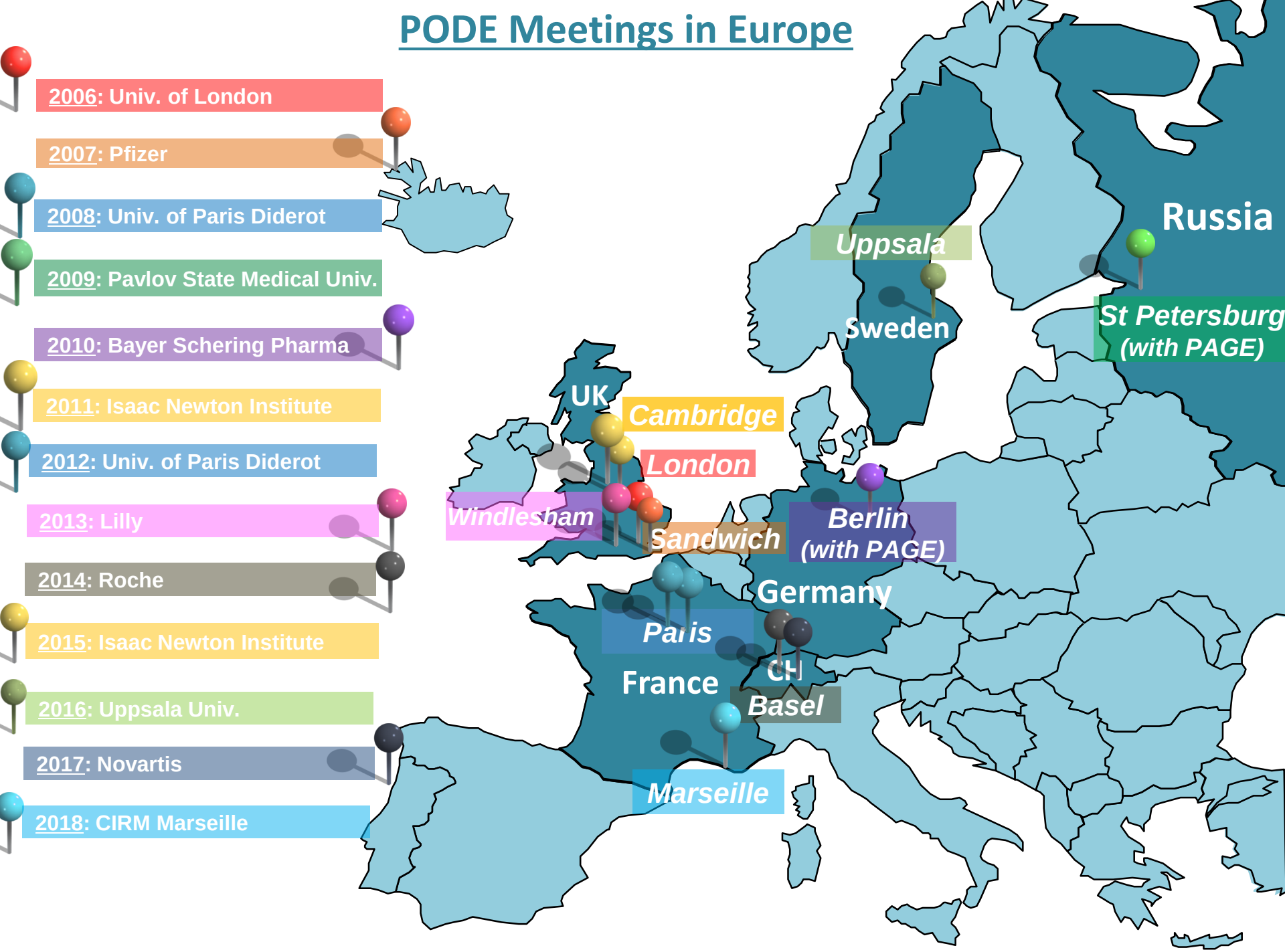
  - May 2006: London, University of London (B. Bogacka)
  - ➢ September 2017: Basel, Novartis → 100 participants
- Distribution list: PopDesign

  - organised by S. Duffull since 2007
  - to register: http://lists.otago.ac.nz/listinfo/popdesign
  - to send an email: popdesign@lists.otago.ac.nz
  - any questions/comments on design in NLMEM and software tools
  - answers by all members of PoDe

PODE Meetings in Europe



PODE Meetings in Europe



New method for computing FIM in NLMEM with discrete data

- **Analytical expression for FIM in NLMEM (in current design software programs)**
  - **first order linearisation** of model (FO)
  - limitations in case of complex nonlinear models and/or large variability
- **FIM for discrete longitudinal data**
  - Methods based on approximations

(Ogungbenro & Aarons. *J Pharmacokinet Pharmacodyn*, 2011 ; Waite & Woods, *Biometrika*, 2015)

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  - Methods based on approximations

(Ogungbenro & Aarons. *J Pharmacokinet Pharmacodyn*, 2011 ; Waite & Woods, *Biometrika*, 2015)

➢ **New approaches for computation of FIM without linearisation**

- Monte Carlo - Adaptive Gaussian Quadrature (MC-AGQ) (Ueckert & Mentré, *Comput Stat Data Anal*, 2017)
- Monte Carlo – Hamiltonian Monte Carlo (MC-HMC) (Riviere, Ueckert & Mentré, *Biostatistics*, 2016)

New method for computing FIM in NLMEM 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

Design and model

- $\mathcal{M}$ = Fisher information matrix (FIM)
- $\Xi = \{N, \xi\}$ = population design
  - N = number of individuals, ξ = elementary design

- M candidate models (m = 1,…,M)
  - w_m = weight quantifying prior belief between models

$$\sum_{m=1}^{M} w_m = 1$$

- y_i = vector of observations for individual i

$$p(y_i|b_i) = h_m\left(y_i, \xi, g(\mu_m, b_i, z_i, \beta_m)\right)$$

  - μ_m fixed effects, b_i random effects $\sim N\ (0, \Omega_m)$
  - z_i covariates, β_m covariate effects

- N patients (i = 1,…,N): $(y_i|b)$ are assumed independent
- ψ_m = population parameters vector of length P_m

$$(\mu_m, \Omega_m, \beta_m)$$

FIM and optimality criteria

$$\mathcal{M}(\psi_m, \Xi) = N \times \mathcal{M}(\psi_m, \xi)$$

$$\mathcal{M}(\psi_m, \xi) = E_y\left(\frac{\partial \log\left(L(y, \psi_m)\right)}{\partial \psi_m} \frac{\partial \log\left(L(y, \psi_m)\right)^T}{\partial \psi_m}\right)$$

$$L(y, \psi_m) = \int p(y|b, \psi_m)\, p(b|\psi_m)\, db$$

Two integrals to compute:

w.r.t *y* (using MC) and w.r.t *b* (using HMC)

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$$\mathcal{M}(\psi_m, \Xi) = N \times \mathcal{M}(\psi_m, \xi)$$

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$$L(y, \psi_m) = \int p(y|b, \psi_m)\, p(b|\psi_m)\, db$$

Two integrals to compute:

w.r.t *y* (using MC) and w.r.t *b* (using HMC)

→ D-optimality for model m

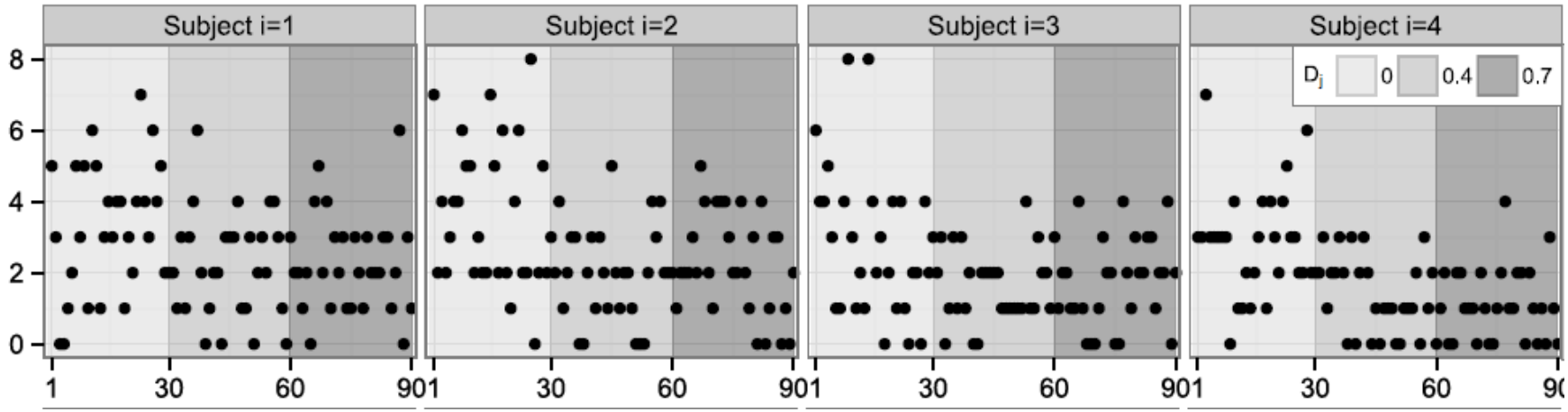
$$\Phi_{\mathrm{D,m}}(\Xi) = Det(\mathcal{M}(\psi_m, \Xi))^{\frac{1}{P_m}}$$

→ Compound D-optimality (Atkinson & Bogacka, 1997)

$$\Phi_{\mathrm{CD}}(\Xi) = \prod_{m=1}^{M} \Phi_{\mathrm{D,m}}(\Xi)^{w_m}$$

Example of repeated count data

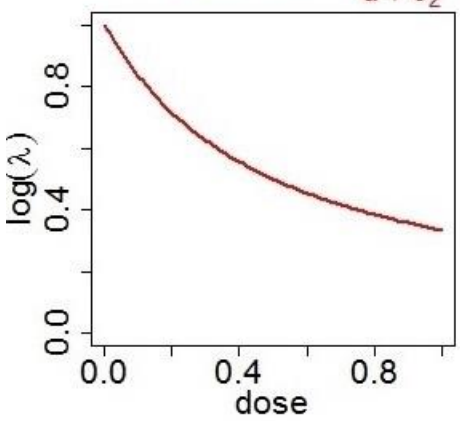

- Daily count of events that we want to prevent
- Poisson model for repeated count response data for each patient
  - $P(y = k|b) = \frac{\lambda^k e^{-\lambda}}{k!}$
  - Each patient observed at 3 dose levels (one placebo) during x days



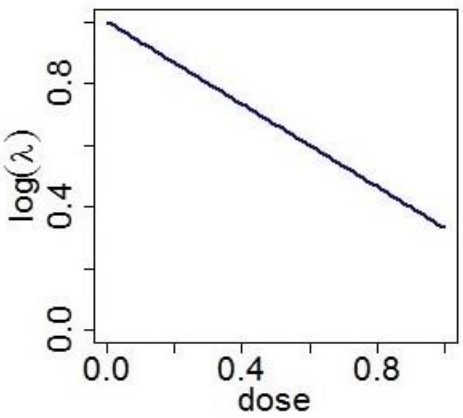
- Several candidate models for the link between log(λ) and dose
- λ: mean number of events / day in a patient

Five models of effect of dose on decreasing Poisson parameter

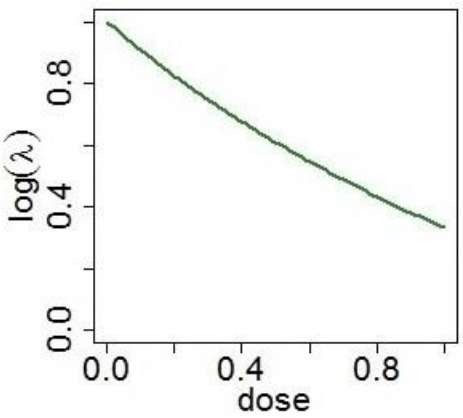
M1: $\log(\lambda)=\theta_1(1-\frac{d}{d+\theta_2})$



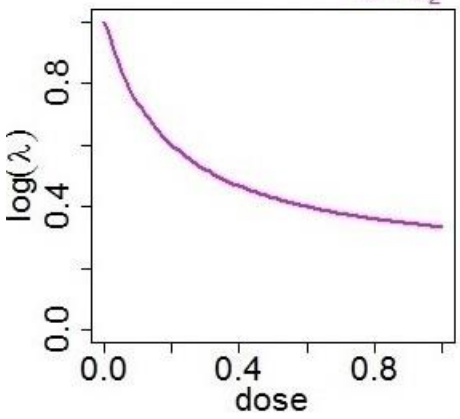
M2: $\log(\lambda)=\theta_1(1-\theta_2 d)$



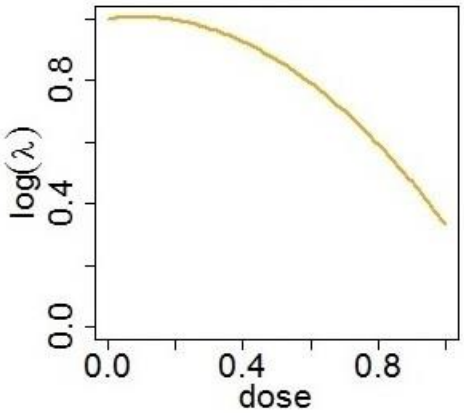
M3: $\log(\lambda)=\theta_1(1-\theta_2\log(d+1))$



M4: $\log(\lambda)=\theta_1(1-\frac{\theta_3 d}{d+\theta_2})$



M5: $\log(\lambda)=\theta_1(1-\theta_2 d-\theta_3 d^2)$



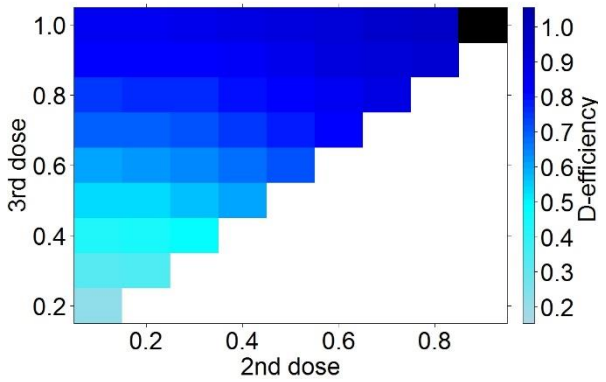
1. Full Imax
2. Linear
3. Log-Linear
4. Imax
5. Quadratic

$$\theta_p = \mu_p exp(b_p);\ b_p \sim \mathcal{N}(0, \omega_p^2)$$

Design optimisation

Methods		
Constraints	Number of subjects	N = 60
	Number of days	n = 10 days / dose
	Number of doses	3 doses / patients
	Choice of doses	d_1= 0 (placebo) → fixed d_2, d_3 optimized from 0.1 to 1 (step 0.1, no replication)
Combinatorial Optimization	Evaluation of FIM for all possible designs	5000 MC 200 HMC
	For each model	D-optimality
	Over 5 models	Compound D-optimality (averaging for uncertainty on model, w_m =1/5)

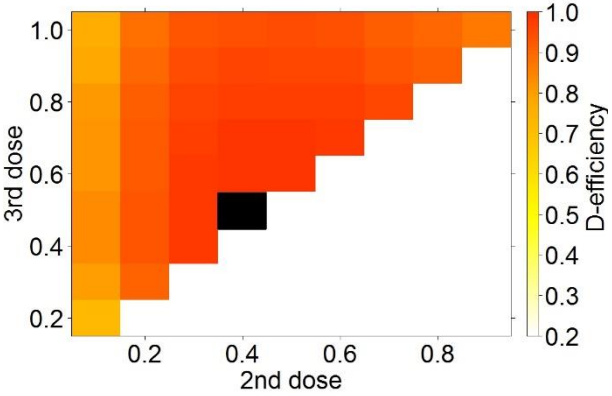
Results: D-optimal design for each model



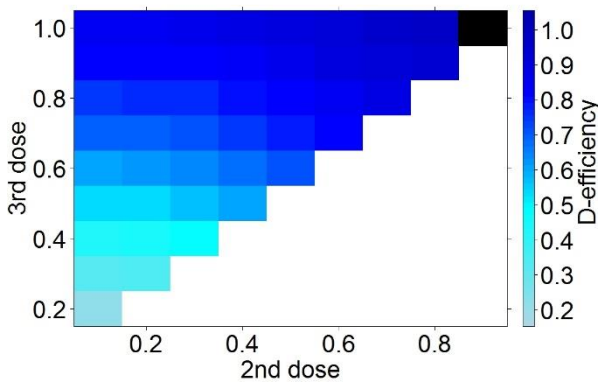
$\xi_{M2}=(0,\mathbf{0.9,1})$

1. Full Imax
2. Linear
3. Log-Linear
4. Imax
5. Quadratic

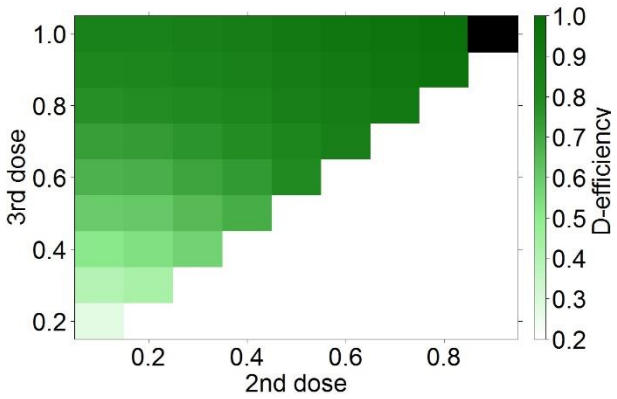
Results: D-optimal design for each model



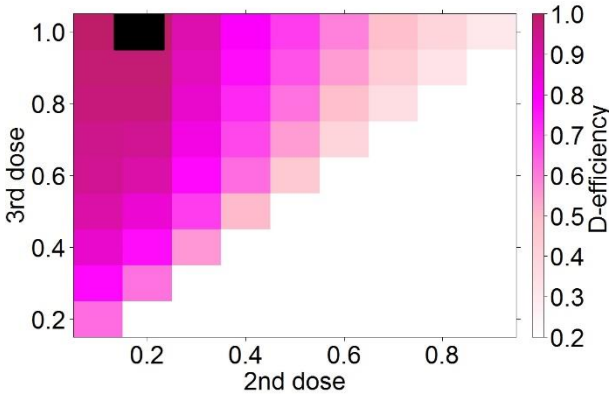
$\xi_{M1}=(0,\mathbf{0.4},\mathbf{0.5})$



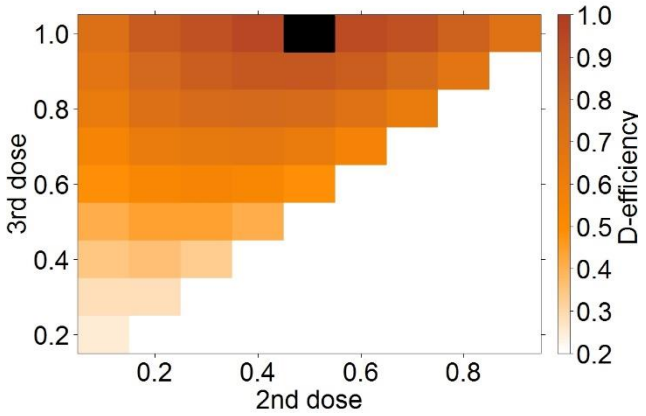
$\xi_{M2}=(0,\mathbf{0.9},\mathbf{1})$



$\xi_{M3}=(0,\mathbf{0.9},\mathbf{1})$



$\xi_{M4}=(0,\mathbf{0.2},\mathbf{1})$



$\xi_{M5}=(0,\mathbf{0.5},\mathbf{1})$

1. Full Imax
2. Linear
3. Log-Linear
4. Imax
5. Quadratic

Results: loss of efficiency if wrong model

	M1 Full Imax	M2 Linear	M3 Log-Linear	M4 Imax	M5 Quadratic
$\xi_{M1}=(0,0.4,0.5)$	100%	61%	69%	50%	**28%**
$\xi_{M2}=(0,0.9,1)$	87%	100%	100%	**31%**	67%
$\xi_{M3}=(0,0.9,1)$	87%	100%	100%	**31%**	67%
$\xi_{M4}=(0,0.2,1)$	88%	86%	85%	100%	86%
$\xi_{M5}=(0,0.5,1)$	95%	90%	92%	70%	100%

Results: loss of efficiency if wrong model

	M1 Full Imax	M2 Linear	M3 Log-Linear	M4 Imax	M5 Quadratic
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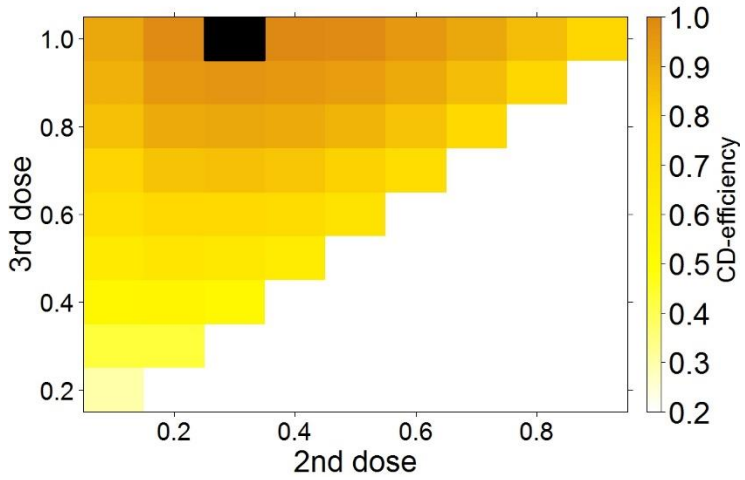

Optimal design over 5 models
$\xi_{all}=(0,\mathbf{0.3,1})$

Results: loss of efficiency if wrong model

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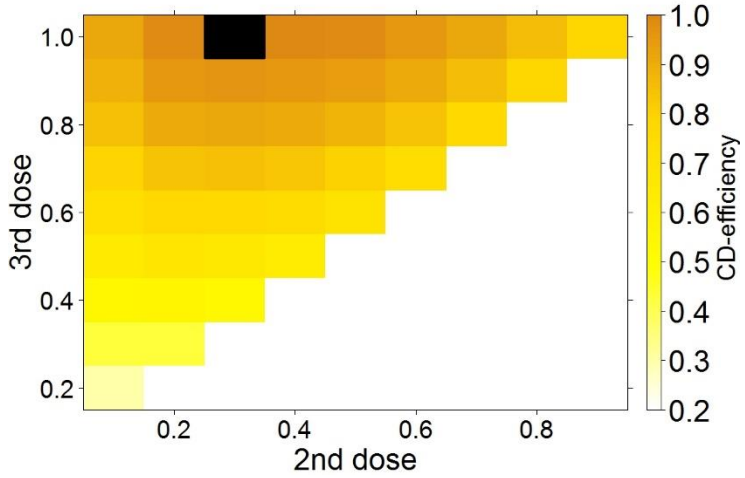
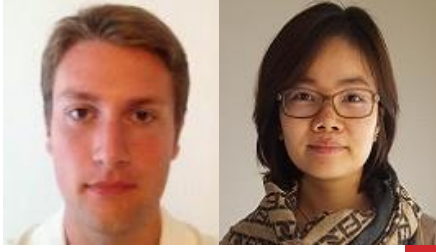
$\xi_{M5}=(0,0.5,1)$	95%	90%	92%	70%	100%
$\xi_{all}=(0,0.3,1)$	94%	88%	89%	80%	93%

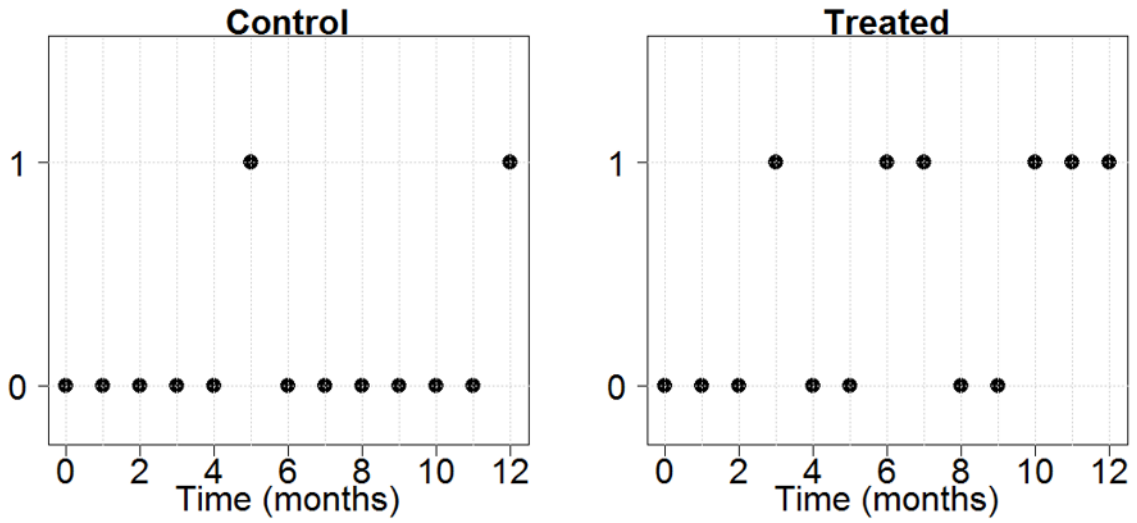
Efficiency greater than 80% for all models



Optimal design over 5 models
$\xi_{all}=(0,\mathbf{0.3,1})$

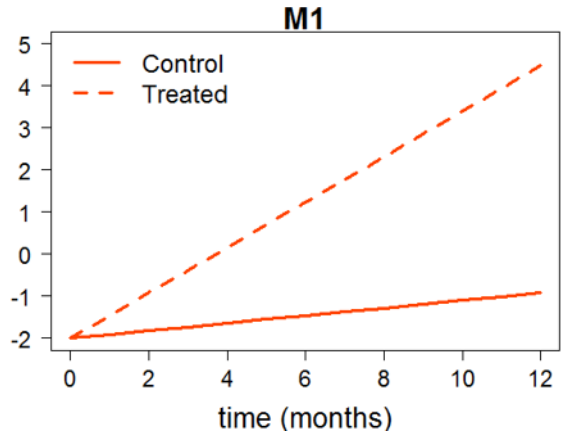
Example of repeated binary data: designing an RCT trial



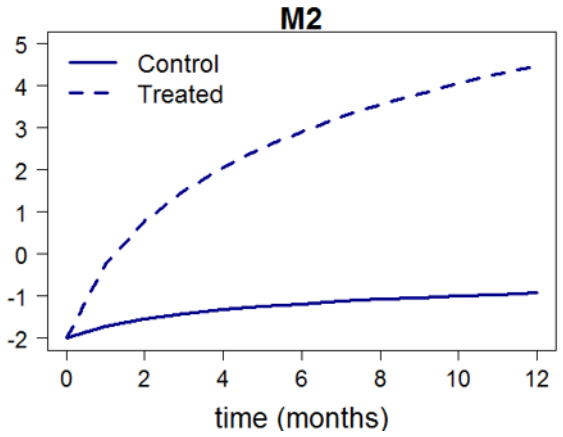


- P = probability of 1
- Logistic random effect models
- **Several candidate models for the link between $logit(P)$ and time**
- Treatment effect on 'slope' parameter

Four candidate models (placebo + drug effect)

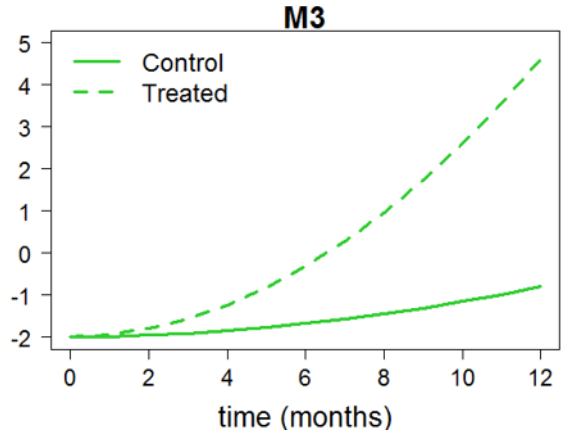


$logit(P) = \theta_1 + \theta_2(1 + \beta \times 1_T)t$

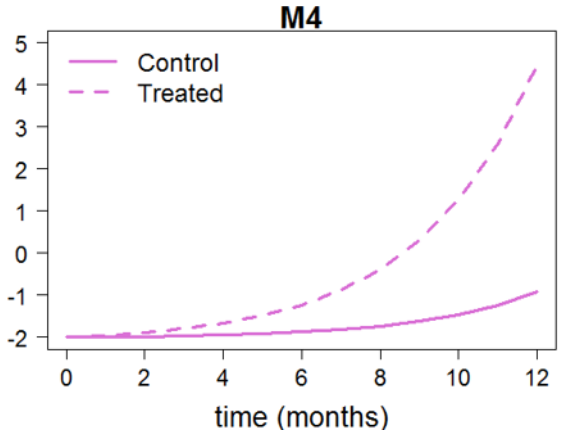


$logit(P) = \theta_1 + \theta_2(1 + \beta \times 1_T)\log(t+1)$

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



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



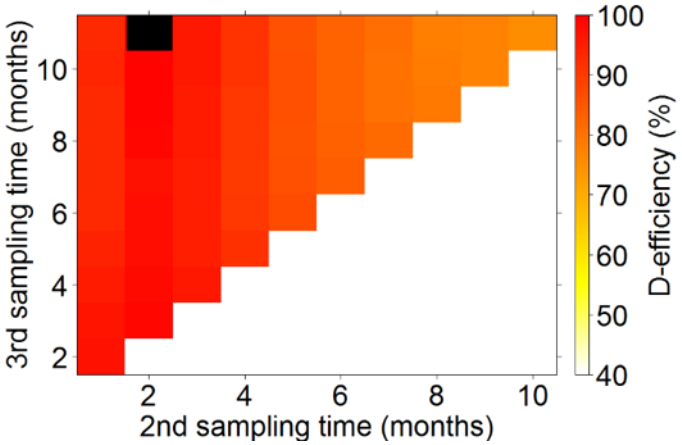
$logit(P) = \theta_1 + \theta_2(1 + \beta \times 1_T)[\exp(\theta_3 t) - 1]$

$$\theta_p = \mu_p exp(b_p);\ b_p \sim \mathcal{N}(0, \omega_p^2)$$

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-optimality
	Over 4 models	Compound D-optimality (averaging for uncertainty on models, w_m =1/4)

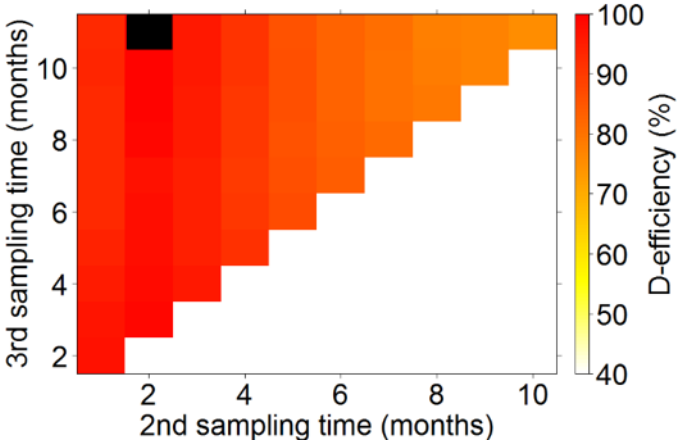
Results: D-optimal design for each model



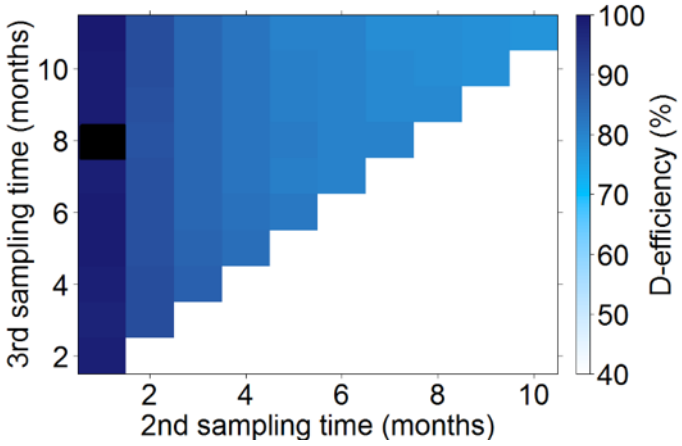
ξ_{M1}=(0,**2**,**11**,12)

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

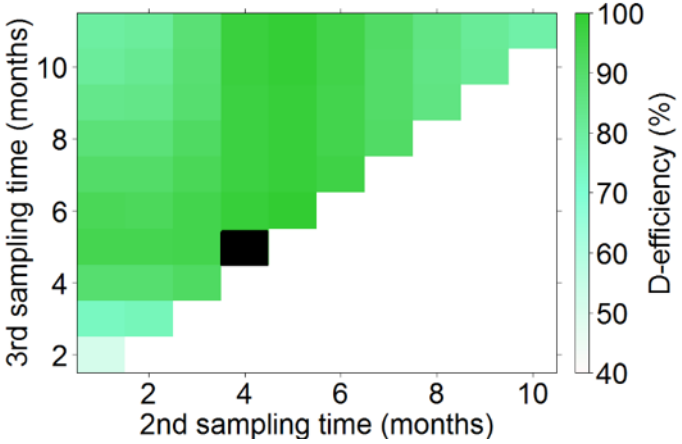
Results: D-optimal design for each model



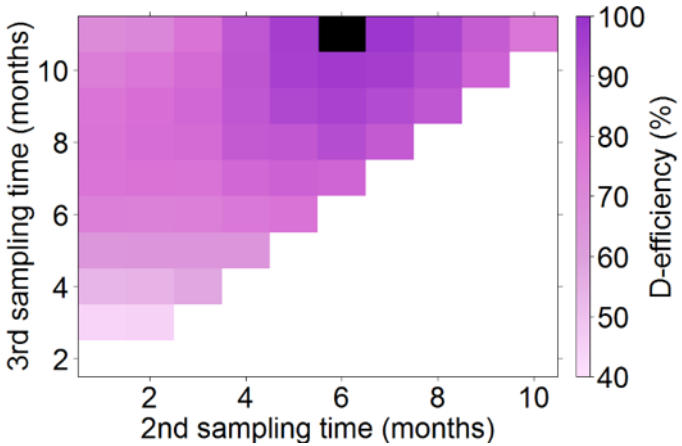
$\xi_{M1}=(0,\mathbf{2,11},12)$



$\xi_{M2}=(0,\mathbf{1,8},12)$



$\xi_{M3}=(0,\mathbf{4,5},12)$



$\xi_{M4}=(0,\mathbf{6,11},12)$

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%

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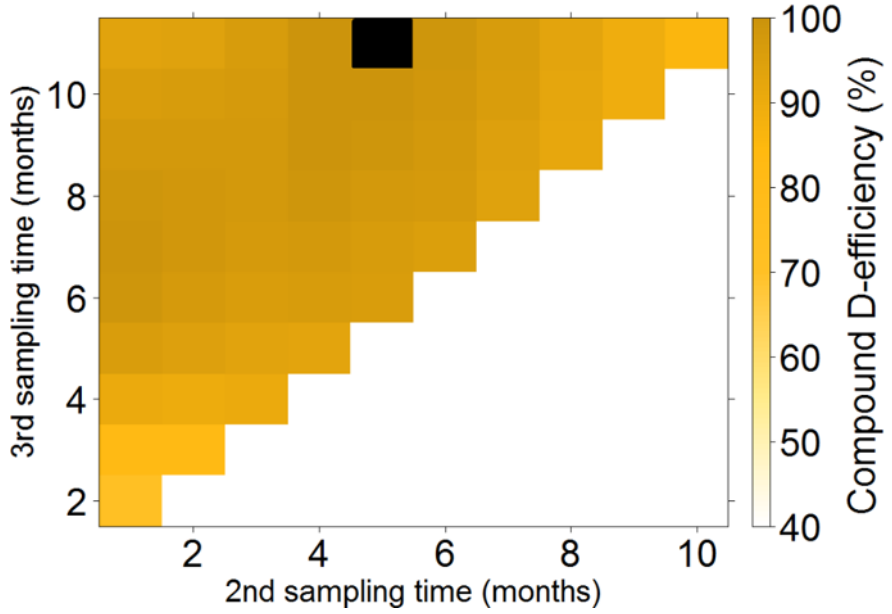

Optimal design over 4 models
$\xi_{all}=(0, 5,11,12)$

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%
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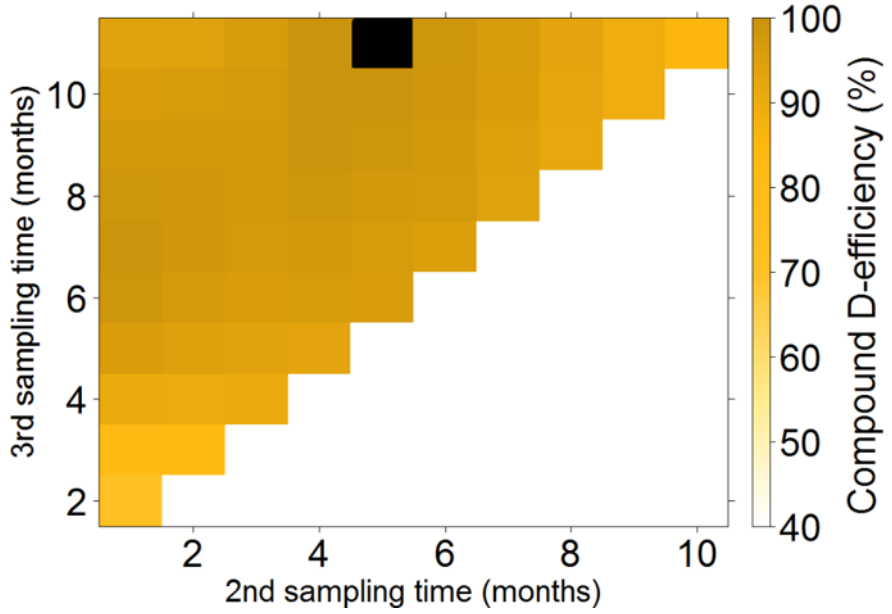
$\xi_{M4}=(0,6,11,12)$	83%	80%	96%	100%
$\xi_{all}=(0,5,11,12)$	86%	81%	99%	96%

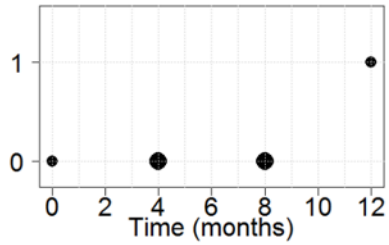
Efficiency greater than 80% for all models

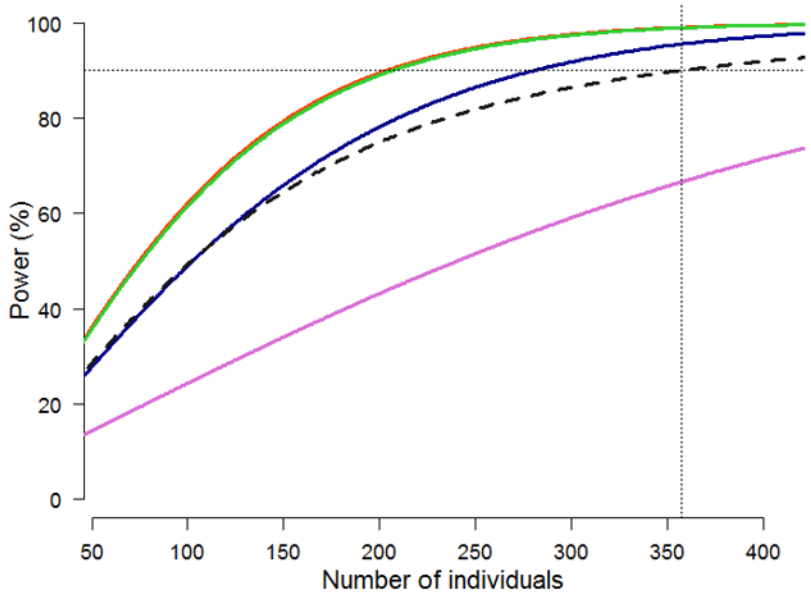


Optimal design over 4 models
$\xi_{all}=(0, 5,11,12)$

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

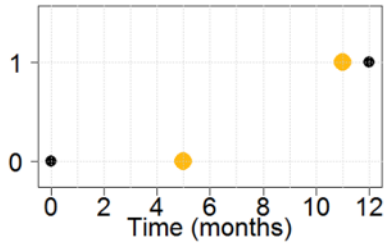
$\xi_{equi\text{-}spaced}=(0,4,8,12)$

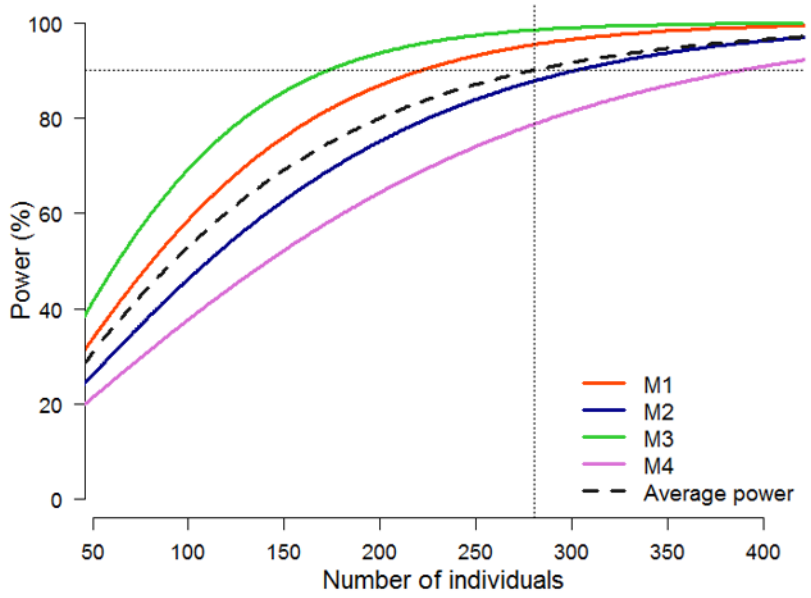




$NSN_{average}\ (\xi_{equi\text{-}spaced}) = \mathbf{358}$

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





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

Discussion

- MC-HMC method for computation of FIM without linearization enables applications to design optimization for NLMEM with discrete data
- Extension of this method to propose robust optimal designs accounting for uncertainty w.r.t. models (and parameters)
- Computationally challenging

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- Computationally challenging

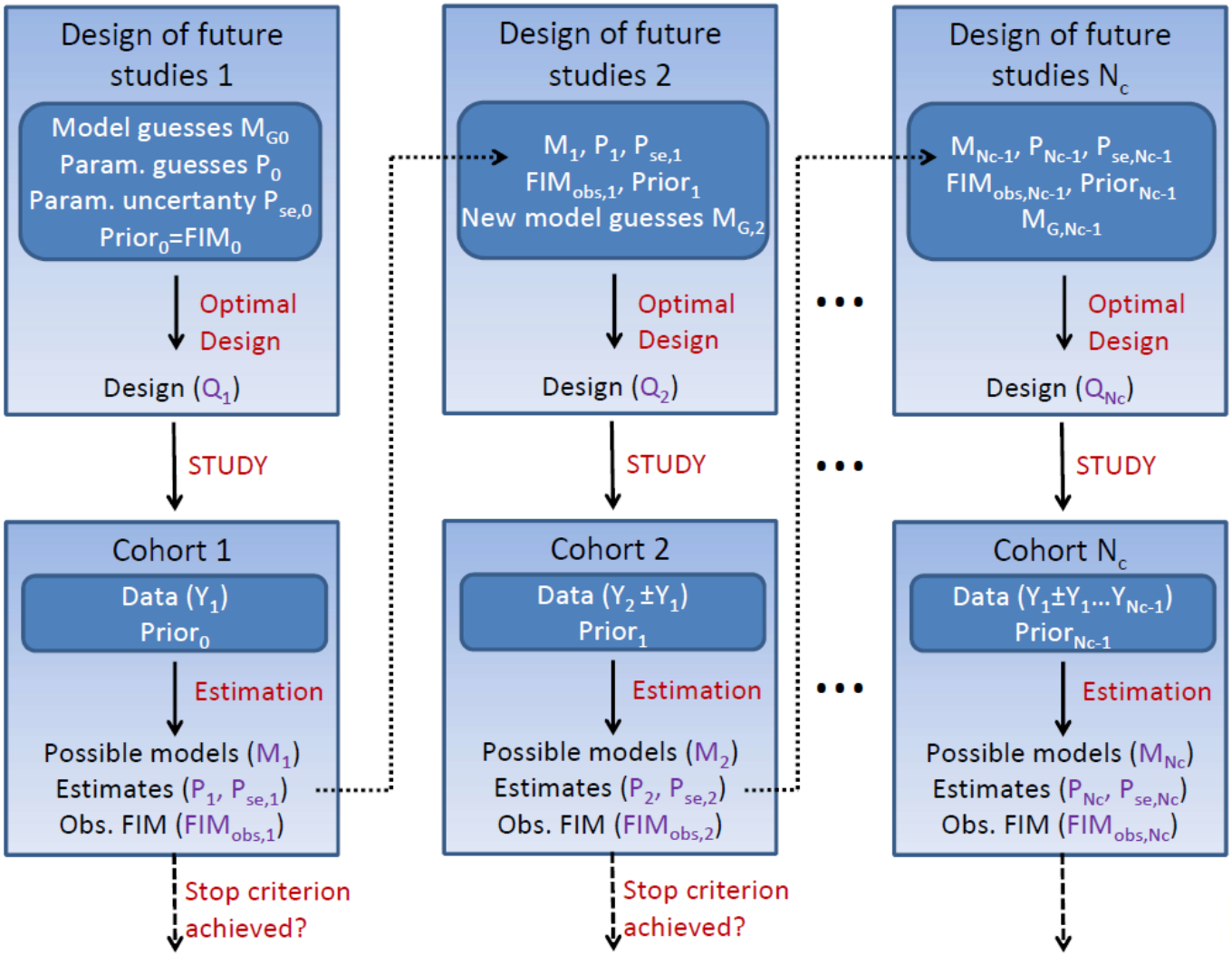
Perspectives

- Replacement of MC by more efficient approach: quasi-random sampling
- Application to continuous data, to other type of discrete data and to multivariate models
- Optimization algorithm (PSO?)
- Different elementary design across patients
- Adaptive designs

Future of optimal design in PMX….

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

MBAOD prototype in R (Andrew Hooker, Uppsala University)



➢ 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** (2018). 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 of optimal design in PMX….

- **Ongoing work by statisticians & pharmacometricians**
  - Model based adaptive designs
  - Fisher matrix for repeated discrete/count data and TTE
  - Model averaging for designing and analysing experiments
  - Design and identifiability of complex models
  - Bayesian design
  - ...

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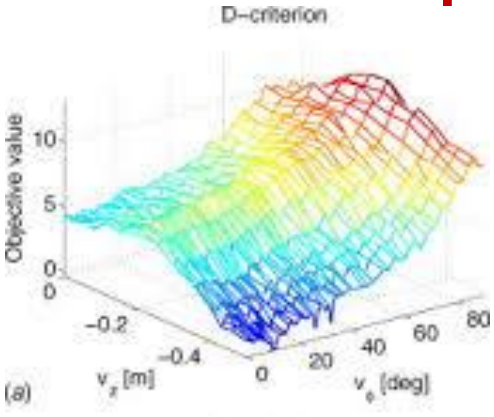
➢ **More collaboration between pharmacometricians and statisticians / computer scientists**



- 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

American Conference on Pharmacometrics
October 15 – 18, 2017
Fort Lauderdale, FL

Optimal design: just nerdy or useful?

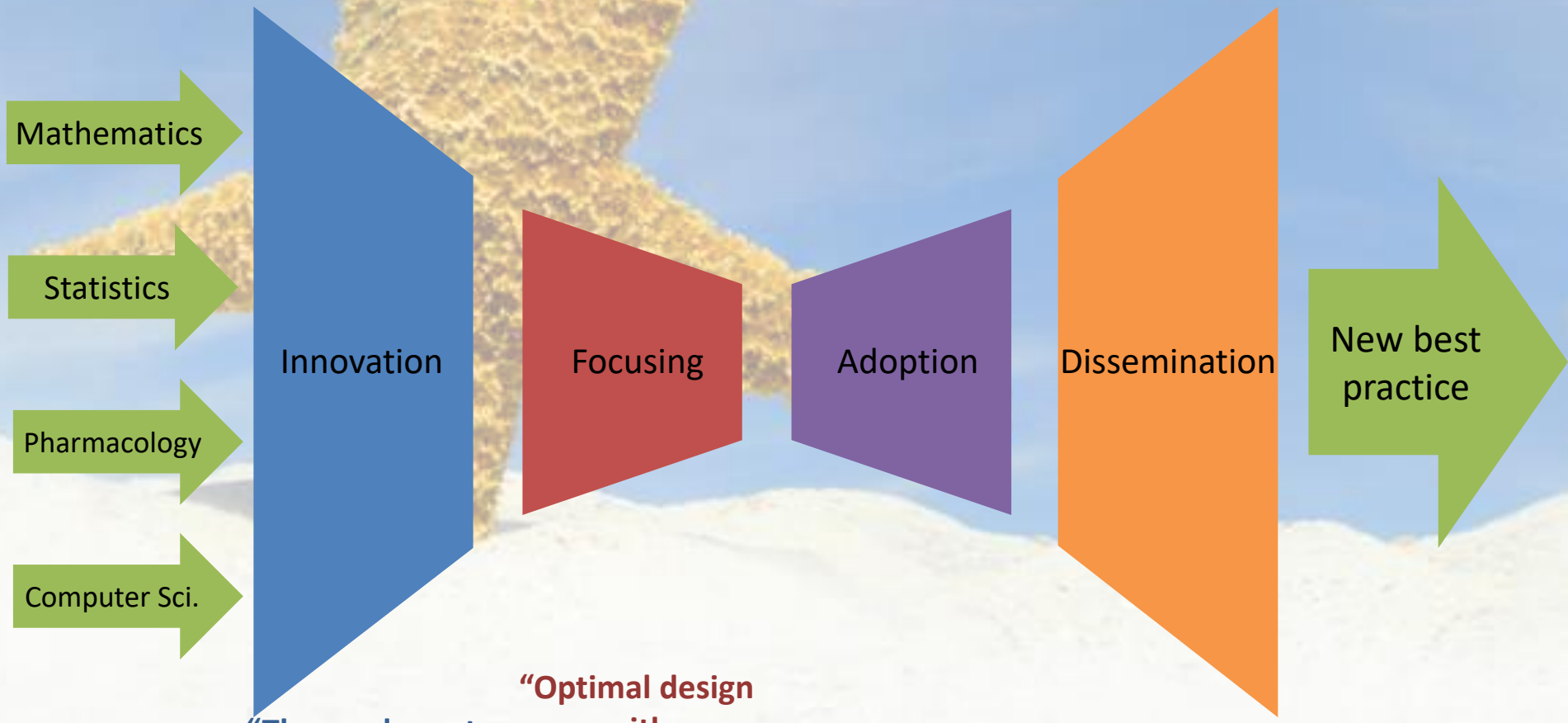
Session Chairs:

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

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