Optimal design for trials with discrete longitudinal studies, with uncertainty on model and parameters

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DESIGNS IN NLMEM

- **Several methods/software for maximum likelihood estimation in Non Linear Mixed Effects Models (NLMEM) for analysis of longitudinal continuous or discrete data**

- **Problem beforehand: choice of design**
  - ➢ get precise estimates / adequate power
    - number of individuals?
    - number of sampling times/ individuals?
    - sampling times?
    - other design variables (doses, etc…)
  - ➢ Simulation (CTS): time consuming
  - ➢ Asymptotic theory: expected **Fisher Information Matrix**
    (Mentré, Mallet, Baccar, *Biometrika*, 1997)

Evaluation of Fisher matrix for discrete and time to event longitudinal data

- **Computation of the FIM for NLMEM for continuous or discrete longitudinal data without linearization of the model**

  1. Using Monte Carlo and Hamiltonian Monte Carlo (HMC) (Rivière, Ueckert, Mentré, *Biostatistics*, 2016)

  2. Using Monte Carlo and Adaptive Gaussian Procedure (Ueckert, Mentré, *CSDA*, 2017)

→ Both methods evaluated and compared to CTS

- 4 data types: continuous, binary, **count**, time to event

Extension for robust designs in NLMEM with discrete data

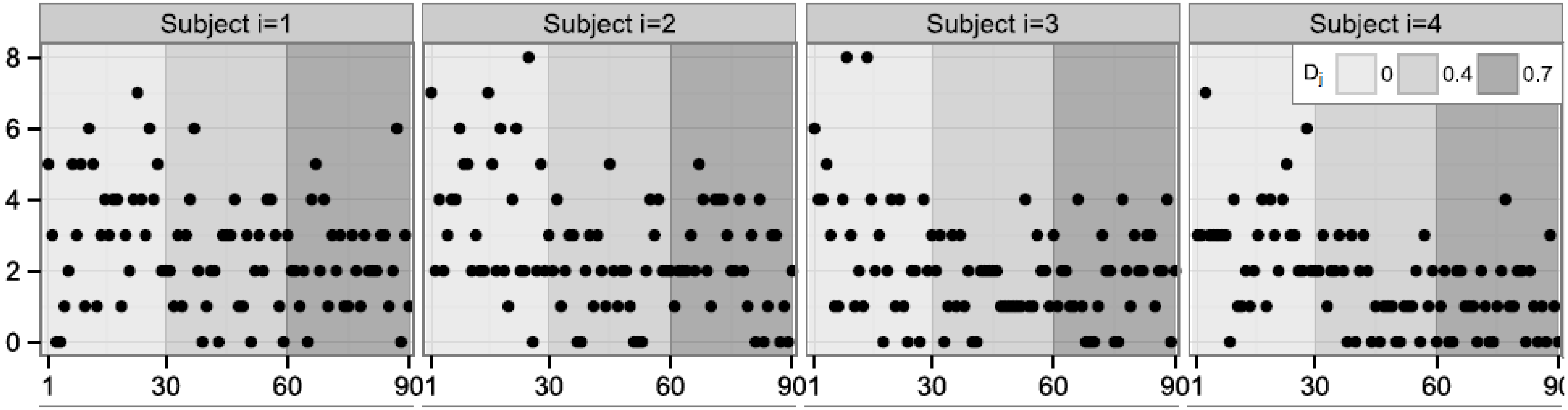
- **Optimal design depends on knowledge on model and parameters**
  - **Local planification**: model and a priori values for parameter are given
  - Widely used criterion: D-optimality (determinant of FIM)

- **Alternative: Robust designs**
  - Take into account uncertainty on parameters (prior distribution)
  - Over a set of candidate models (as in MCP-MOD)

- **Using HMC in Stan**

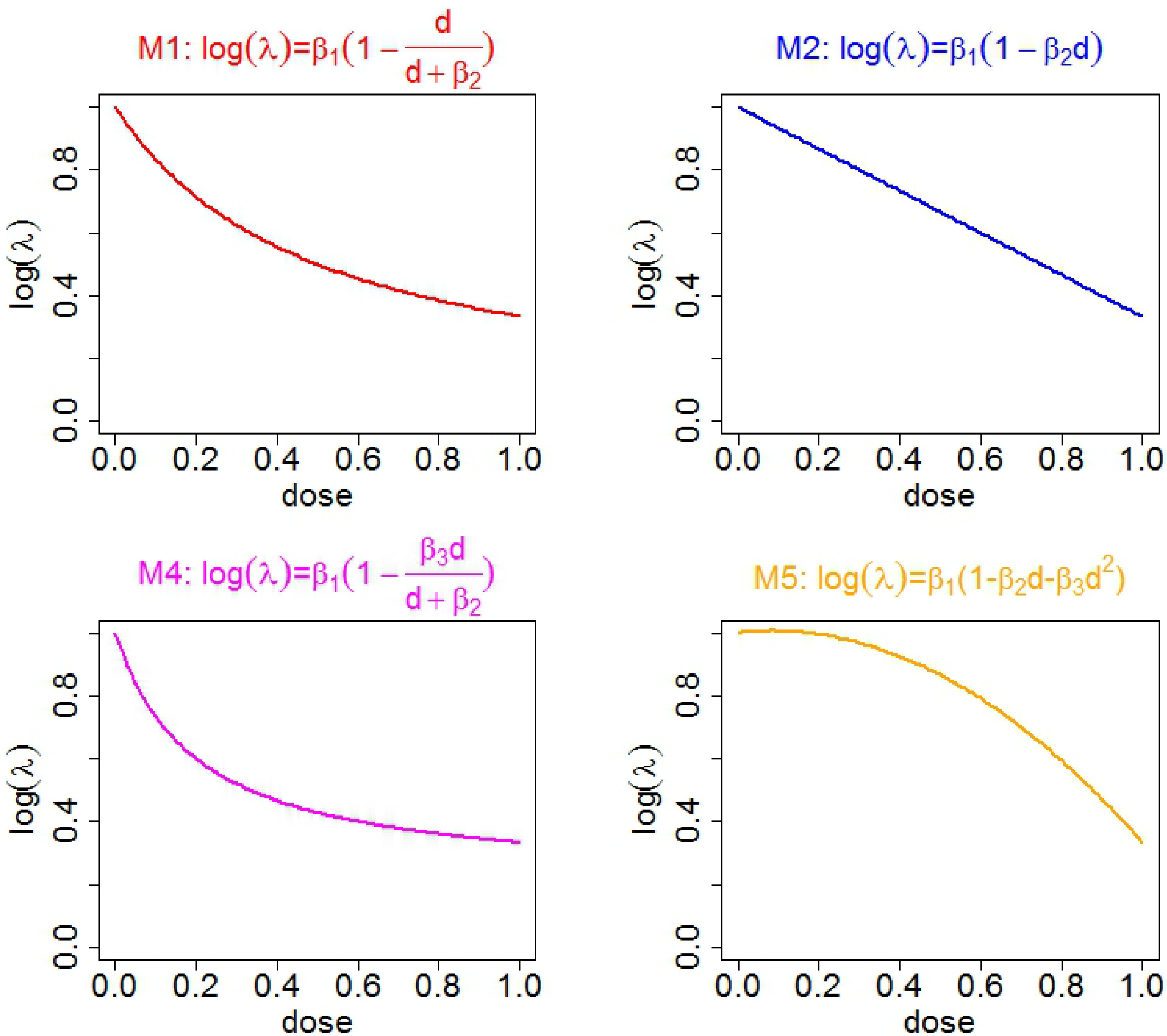
Application to robust designs for repeated count data

- Exemple: Daily count of events that we want to prevent
- Poisson model for repeated count response $P(\mathrm{y} = \mathrm{k}|\mathrm{b}) = \frac{\lambda^{\mathrm{k}}\, \mathrm{e}^{-\lambda}}{\mathrm{k}!}$
- 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

Five models of effect of dose on decreasing Poisson parameter

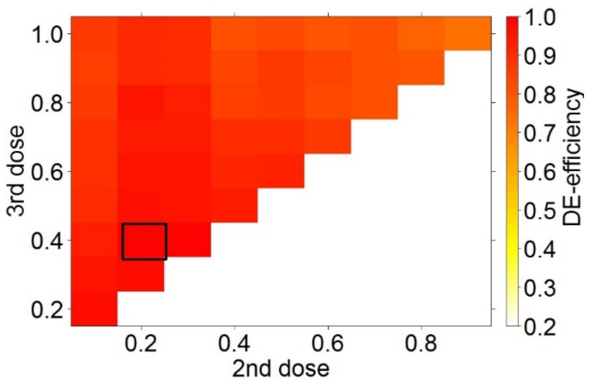


1. Full Emax
2. Linear
3. Log-Linear
4. Emax
5. Quadratic

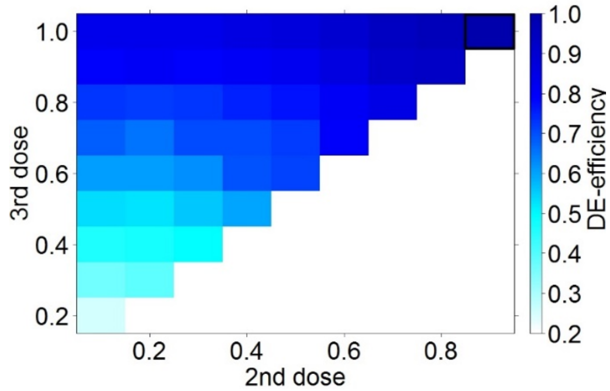
Design optimisation

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) d_2, d_3 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	DE-criterion on robust FIM (averaging for uncertainty on parameters)
	Over 5 models	Compound DE-criterion (averaging for uncertainty on models and parameters)

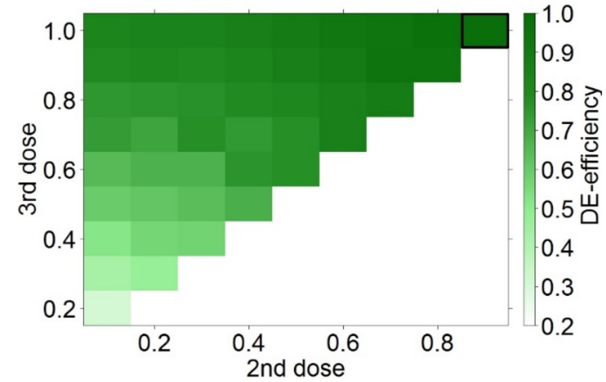
Results: robust optimal design for each model



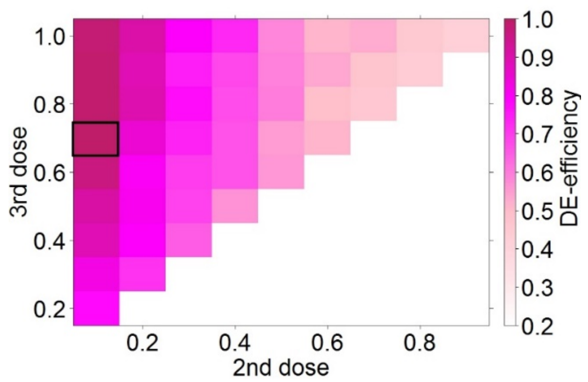
$\xi_{M1}=(0,\mathbf{0.2},\mathbf{0.4})$



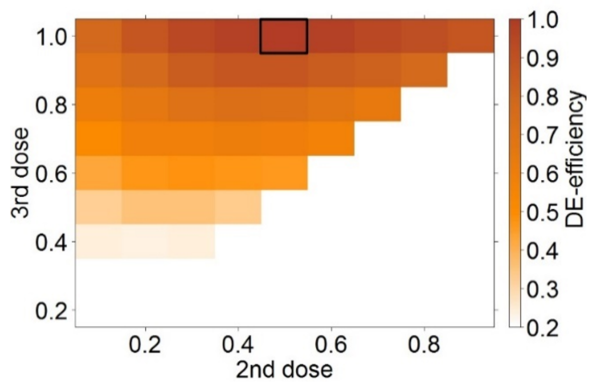
$\xi_{M2}=(0,\mathbf{0.9},\mathbf{1})$



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



$\xi_{M4}=(0,\mathbf{0.1},\mathbf{0.7})$



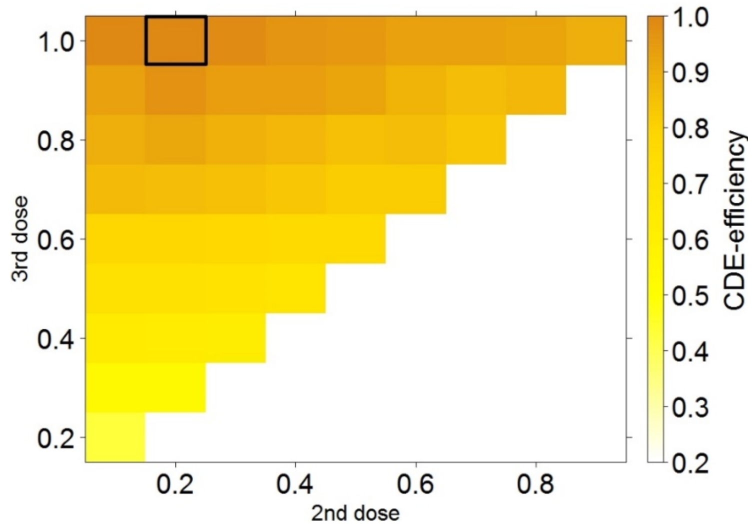
$\xi_{M5}=(0,\mathbf{0.5},\mathbf{1})$

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

Results: loss of efficiency if wrong model

	M1 Full Emax	M2 Linear	M3 Log-Linear	M4 Emax	M5 Quadratic
ξ_{M1}=(0,0.2,0.4)	100%	**47%**	57%	78%	**24%**
ξ_{M2}=(0,0.9,1)	73%	100%	100%	**44%**	87%
ξ_{M3}=(0,0.9,1)	73%	100%	100%	**44%**	87%
ξ_{M4}=(0,0.1,0.7)	89%	68%	74%	100%	51%
ξ_{M5}=(0,0.5,1)	83%	88%	90%	59%	100%
ξ_{all}=(0,0.2,1)	91%	84%	84%	85%	83%

Efficiency greater than 80% for all models

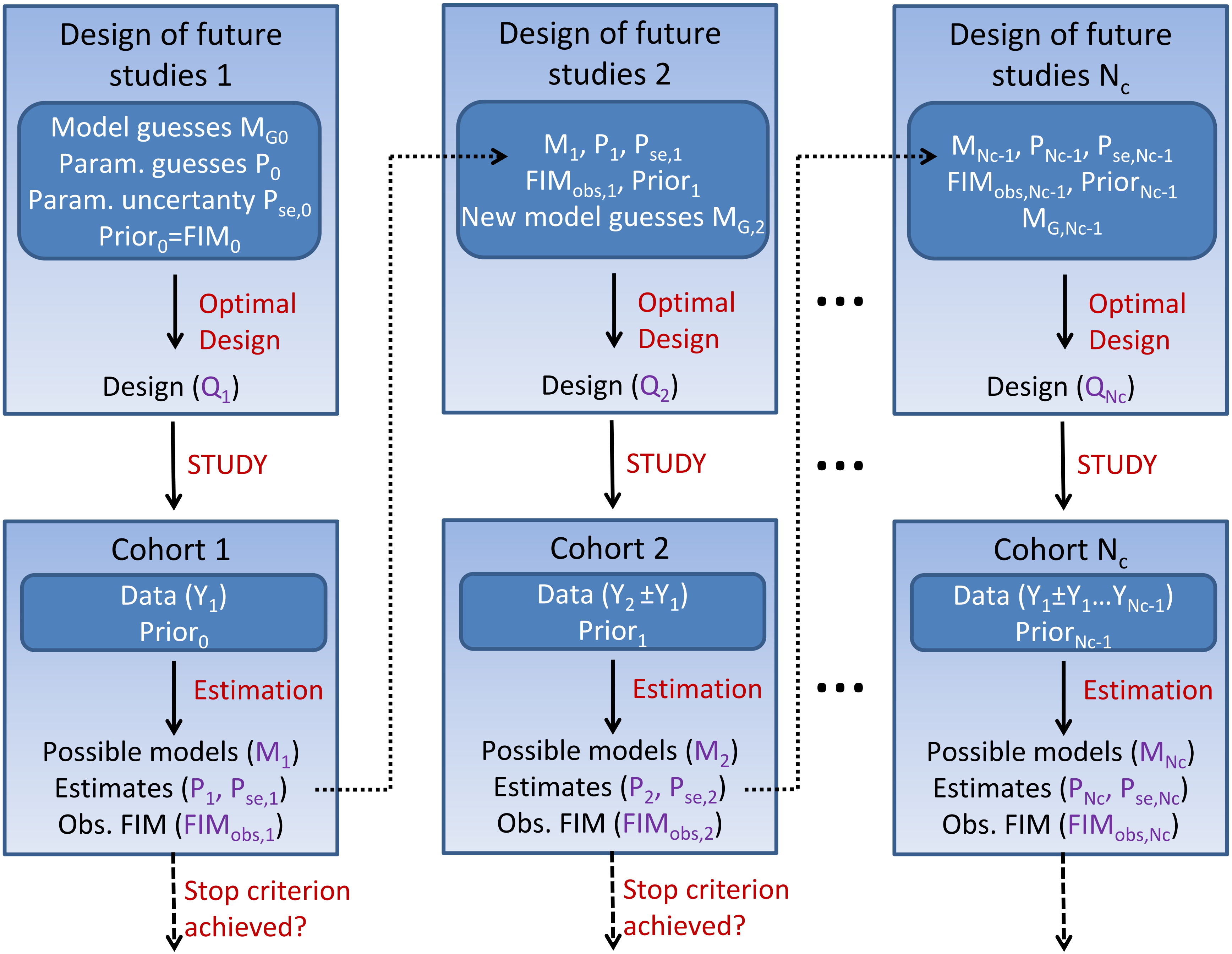


Optimal design over 5 models ξ_{all}=(0,**0.2**,**1**)

Discussion

- **Example on count data**
  - Important loss of efficiency when the model is not correctly pre-specified
  - Good performance of the compound DE-optimal design (robust on parameters and models)
- **New methods for Robust designs**
  - Extension of R package *MIXFIM* to compute the robust FIM using HMC (connexion with Rstan)
  - Compound optimality criterion to combine several candidate models
- **Perspectives**
  - Model based adaptive optimal designs (MBAOD)
  - With or without uncertainty during first cohort(s)

➢ Design trials where analysis of longitudinal data is pre-specified



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

Model parameters

	Prior guess: ψ*					A priori distribution: p(ψ)				
	μ_1^*	μ_2^*	μ_3^*	ω_1^*	ω_2^*	μ_1	$\boldsymbol{\mu_2}$	μ_3	ω_1	$\boldsymbol{\omega_2}$
M1	1	0.5		0.3	0.3	1	**LN(-0.89,0.63)**		0.3	**LN(-1.50,0.77)**
M2	1	0.67		0.3	0.3	1	**LN(-0.60,0.63)**		0.3	**LN(-1.50,0.77)**
M3	1	0.96		0.3	0.3	1	**LN(-0.24,0.63)**		0.3	**LN(-1.50,0.77)**
M4	1	0.2	0.8	0.3	0.3	1	**LN(-1.81,0.63)**	0.8	0.3	**LN(-1.50,0.77)**
M5	1	0.8	0.13	0.3	0.3	1	**LN(-0.60,0.63)**	0.13	0.3	**LN(-1.50,0.77)**

$E(\mu_2)=\mu_2^*$; $E(\omega_2)= \omega_2^*$

$CV(\mu_2)=70\%$; $CV(\omega_2)=90\%$

Using MCMC for robust designs in NLMEM

Robustness w.r.t. a set of *M* candidate models

- D-criterion for optimization of design $\Xi_{D,m}$

$$\Phi_{D,m}(\Xi) = \det\left(\mathrm{M}(\psi_m^*, \Xi)\right)^{1/P_m}$$

P_m: number of population parameters of model *m*

- Compound D-criterion[1,2] for common optimal design Ξ_{CD}

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

α_m: weight quantifying the balance between the *M* models: $\sum_m \alpha_m = 1$

Robustness w.r.t. parameters and models

- Compound DE-criterion for common optimal design Ξ_{CDE}

$$\Phi_{CDE}(\Xi) = \prod_{m=1}^{M} \Phi_{DE,m}(\Xi)^{\alpha_m}$$

$\Phi_{DE,m}$: DE-criterion evaluated for each model *m*

⇒ Extension of R package *MIXFIM*

[1] Atkinson et al. *J Stat Plan Inference*, 2008.
[2] Nguyen et al. *Pharm Stat*, 2016.