Robust designs accounting for model uncertainty in longitudinal studies with binary outcomes

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Design in mixed effect models

- Nonlinear mixed effect models (NLMEMs)
  - Estimation of population parameters
    - Fixed effects (mean, covariate effects)
    - Variance of random effects (inter-individual variability)
  - Appropriate for exploiting the richness of longitudinal data
  - For both continuous and discrete data

- Problem beforehand: choice of population design
  - To obtain precise estimates / adequate power (Wald test)
  - Number of individuals ? Number and allocation of sampling times ? Dosing regimen ? …

Design and Fisher Information Matrix

- Design evaluation and optimization
  - Clinical trial simulation (CTS): time consuming
  - Fisher Information Matrix (FIM)
    - Inverse of FIM: lower bound of the variance-covariance matrix of any unbiased estimated parameters (Cramér-Rao)
- Computation of FIM
  - First order (FO) linearization of the model around the expectation of random effects[1]
    - Efficient in general but presents limitations with complex models and discrete data
  - New approaches for both continuous and discrete models
    - Monte Carlo/Hamiltonian Monte Carlo (MC/HMC)[2]
    - Monte Carlo/Adaptive Gaussian Quadrature (MC/AGQ)[3]

1: Mentré *et al.*, Biometrika, 1997
2: Riviere *et al.*, Biostatistics, 2016
3: Ueckert *et al.*, Comput Stat Data Anal, 2017

Model uncertainty in design

- Design evaluation and optimization require knowledge on model
- Local planification: given one model and its parameter values
- Alternative: Robust designs accounting for model uncertainty

Objectives

- To develop a FIM-based strategy to
  - Account for **model uncertainty** (robust designs)
  - Find a balance between the power of the Wald test and the precision of all the estimated parameters
- To illustrate this strategy with repeated binary data
- To evaluate this strategy by clinical trial simulations (CTS)

NLMEMs for discrete outcomes

- For a given model m, where the conditional probability for observation y_{ij} of individual i at sample j ($j = 1, \ldots, n_i$) is:

$$p(y_{ij}|b_i) = h_m\left(y_{ij}, \xi_i, g(\mu_m, b_i, z_i, \beta_m)\right),$$

with

h_m: structural model for m

ξ_i: elementary design for individual i

μ_m: vector of fixed effects for m

b_i: vector of random effects for individual i, $b_i \sim N\,(0, \Omega_m)$

z_i: vector of covariates

β_m: vector of covariate effects for m

ψ_m: population parameters $\{\mu_m, \beta_m, \Omega_m\}$

Fisher Information Matrix

- FIM $\mathcal{M}$ evaluation based on *Monte Carlo*/*Hamiltonian Monte Carlo* (R package *MIXFIM*[1])
  - Elementary FIM

$$\mathcal{M}(\psi, \xi) = E_{y}\left(\frac{\partial logL(y;\psi)}{\partial\psi}\frac{\partial logL(y;\psi)^{T}}{\partial\psi}\right)$$

  - Population FIM

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

with identical elementary design ξ in all N individuals

ψ: population parameters
ξ: elementary design
y: observations
L: likelihood
Ξ: population design

- Standard errors of parameters predicted from FIM
  - Power of the Wald test
- Design optimization: criteria based on FIM

1: Riviere MK. *et al.*, Biostatistics, 2016

Methods

Optimality criteria

Parameters of interest	Given model m	
All the parameters ψ_m	D-optimality[1] $\Phi_{\mathrm{D,m}}(\Xi) = Det(\mathcal{M}(\psi_m, \Xi))^{1/P_m}$	

Ξ: population design

ψ_m: vector of parameters of the model m (of size P_m), including parameters of interest $\psi_{S,m}$ (of size S_m) and other parameters $\psi_{\mathrm{T},m}$, $\mathcal{M}_T$: FIM on $\psi_{\mathrm{T},m}$

α_m: interest in the precision of estimation for $\psi_{S,m}$, $0 \leq \alpha_m \leq 1$

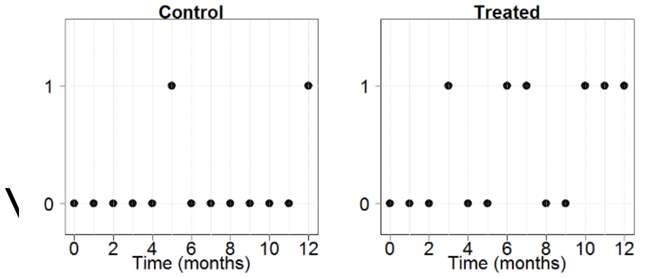
$$\sum_{m=1}^{M} w_m = 1$$

1: Atkinson AC. *et al.*, Optimum experimental designs, 2007

2: Atkinson AC. et *al.*, J Stat Plan inference, 2008

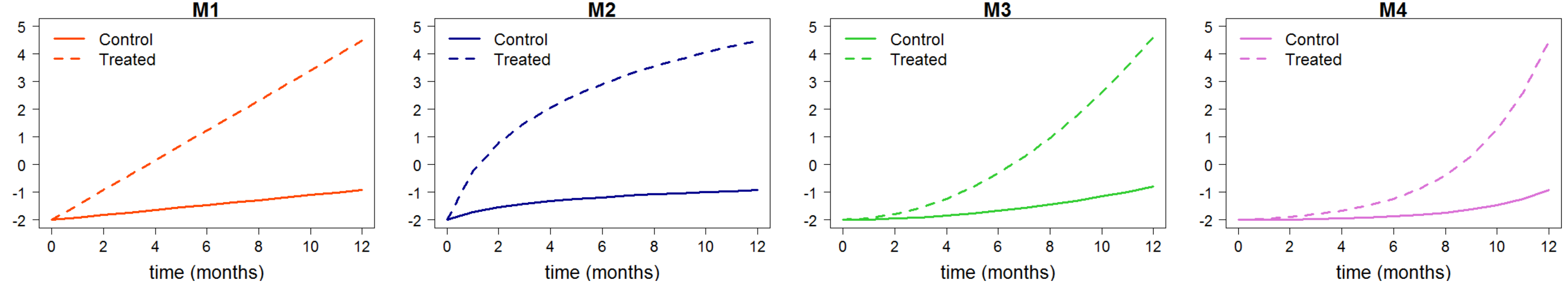
3: Nguyen TT. et *al.*, Pharm Stat, 2016

Candidate Models & Parameters



- Repeated binary data, 2 balanced groups : Control v
- Logistic models describing probability p of response y over times

$logit(p)$



Linear	Loglinear	Quadratic	Exponential
$\mathrm{logit(p)} = \theta_1 + \theta_2(1 + \beta \times 1_T)t$	$\mathrm{logit(p)} = \theta_1 + \theta_2(1 + \beta \times 1_T)\log(t+1)$	$\mathrm{logit(p)} = \theta_1 + \theta_2(1 + \beta \times 1_T)t^2$	$\mathrm{logit(p)} = \theta_1 + \theta_2(1 + \beta \times 1_T)[\exp(\theta_3 t) - 1]$

$\theta_p = \mu_p + b_p$ where $b_p \sim N\left(0, \omega_p^2\right)$, β: effect size of the treatment on θ_2

	ψ_1	ψ_2	ψ_3	ψ_4
μ_1	-2	-2	-2	-2
μ_2	0.09	0.42	0.0075	0.02015
μ_3	-	-	-	1/3
β	5	5	5	5
ω_1	0.7	0.7	0.7	0.7
ω_2	0.17	0.79	0.014	0.0379

Design optimisation accounting for model uncertainty

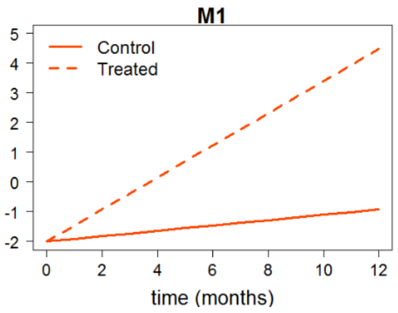
- Based on CDD_S-criterion Φ_{CDD_S}
  - Parameter of interest: β
  - Total model uncertainty: $w_1 = w_2 = w_3 = w_4 = 0.25$
- Constraints

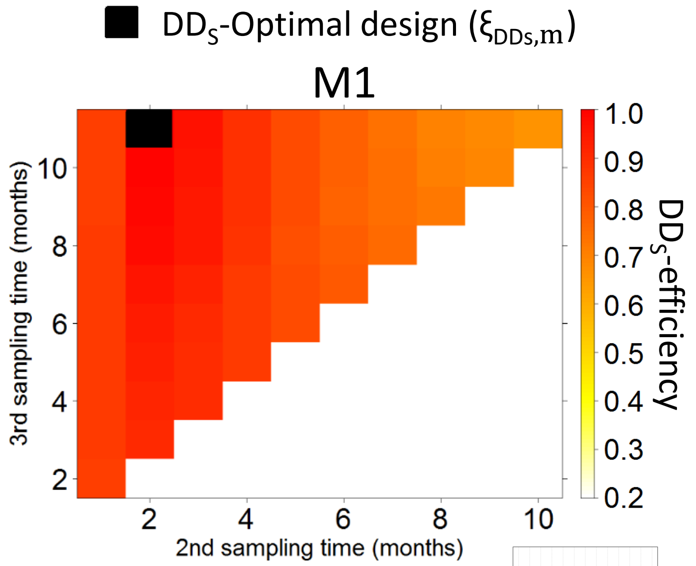
Measures / individual	n = 4 (among times from 0 to 12 months)
Measuring times $\xi=(t_1,t_2,t_3,t_4)$	t_1 = 0, t_4 = 12 months (fixed) **t_2, t_3 optimized among 11 times from 1 to 11**

  - Combinatorial optimisation: 55 possible designs

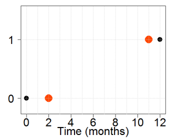
DD_S-efficiencies for each model

$$E_{DD_S,m}(\xi) = \frac{\Phi_{DDs,m}(\xi)}{\Phi_{DDs,m}(\xi_{DDs,m})}$$



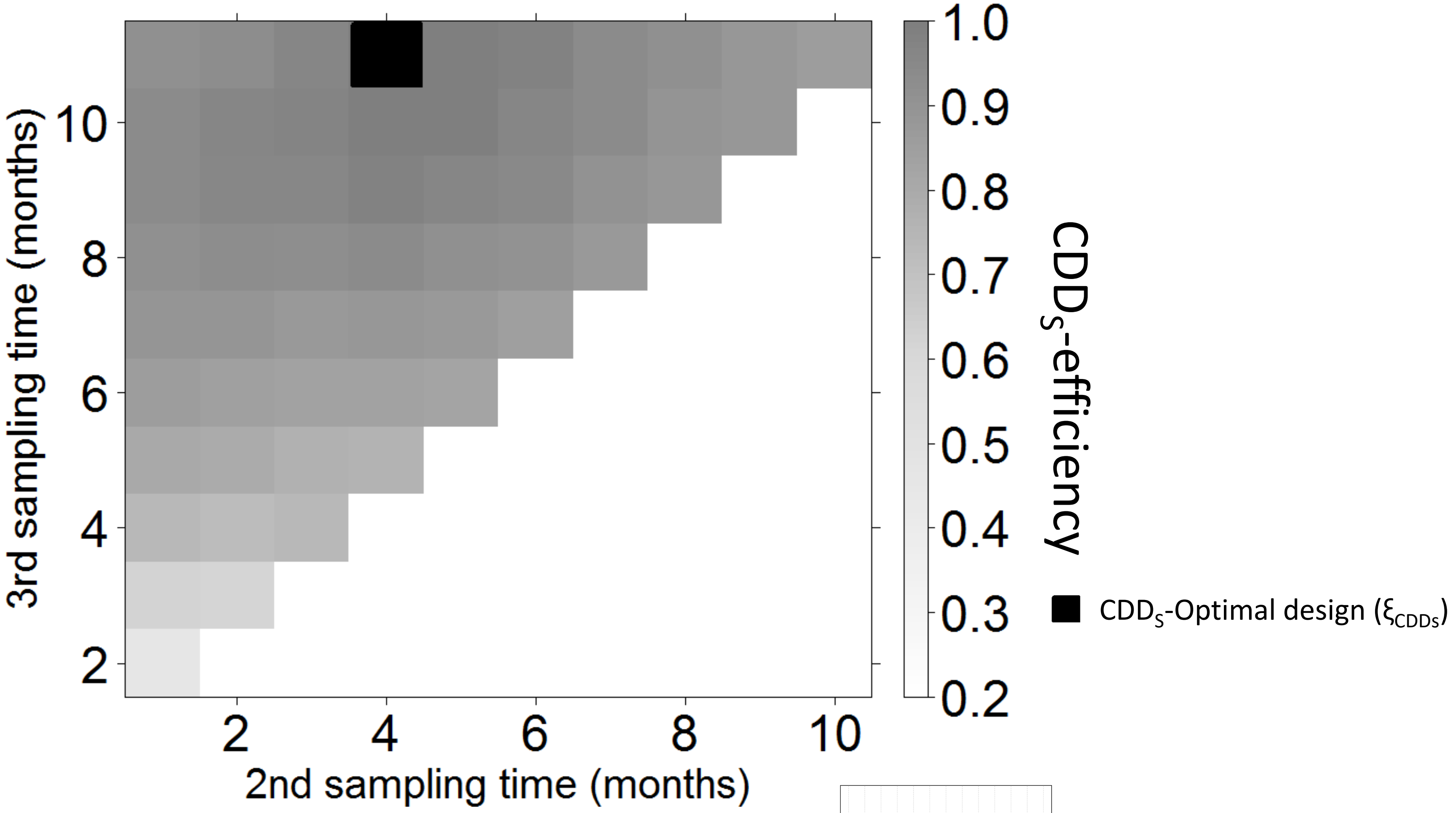


$\xi_{DDs,1}=(0,2,11,12)$

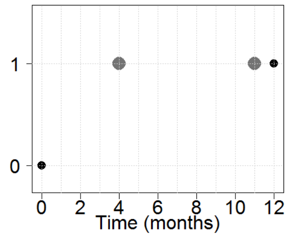


CDD_S-efficiencies

$$E_{CDD_S}(\xi) = \frac{\Phi_{CDDs}(\xi)}{\Phi_{CDDs}(\xi_{CDDs})}$$



ξ_{CDDs}= (**0**,4,11,**12**)

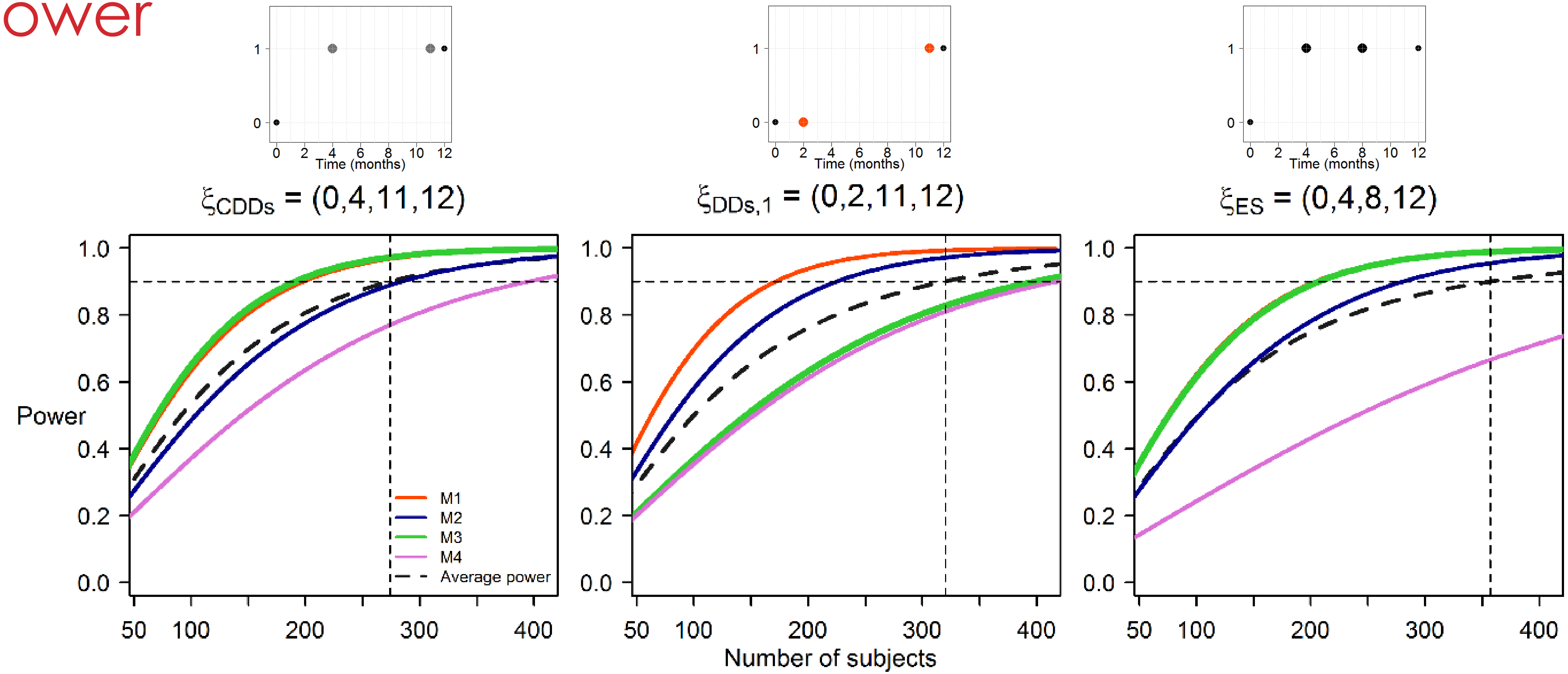


Predicted performances of different designs D-efficiencies

$$E_{D,m}(\xi) = \frac{\Phi_{D,m}(\xi)}{\Phi_{D,m}(\xi_{D,m})}$$

	Design \ Model	M1 Linear	M2 Loglinear	M3 Quadratic	M4 Exponential
Equi-spaced design	ξ_{ES}=(0,4,8,12)	0.908	0.926	0.975	0.869
DD_S-optimal design for M1	$\xi_{D,1}=\xi_{Ds,1}=\xi_{DDs,1}$=(0,2,11,12)	1	0.898	0.812	0.706
	$\xi_{D,2}$=(0,1,8,12)	0.932	1	0.875	0.787
	$\xi_{Ds,2}=\xi_{DDs,2}$=(0,1,11,12)	0.932	0.998	0.796	0.685
	$\xi_{D,3}$=(0,4,5,12)	0.916	0.839	1	0.646
	$\xi_{Ds,3}=\xi_{DDs,3}$=(0,5,11,12)	0.860	0.805	0.994	0.958
	$\xi_{D,4}$=(0,6,11,12)	0.829	0.802	0.960	1
	$\xi_{Ds,4}$=(0,10,11,12)	0.754	0.770	0.786	0.775
	$\xi_{DDs,4}$=(0,9,11,12)	0.771	0.777	0.813	0.864
	ξ_{CD}=(0,5,11,12)	0.860	0.805	0.994	0.958
Robust design	$\xi_{CDs}=\xi_{CDDs}$= (0,4,11,12)	**0.910**	**0.828**	**0.977**	**0.882**

Predicted performances of different designs
Power

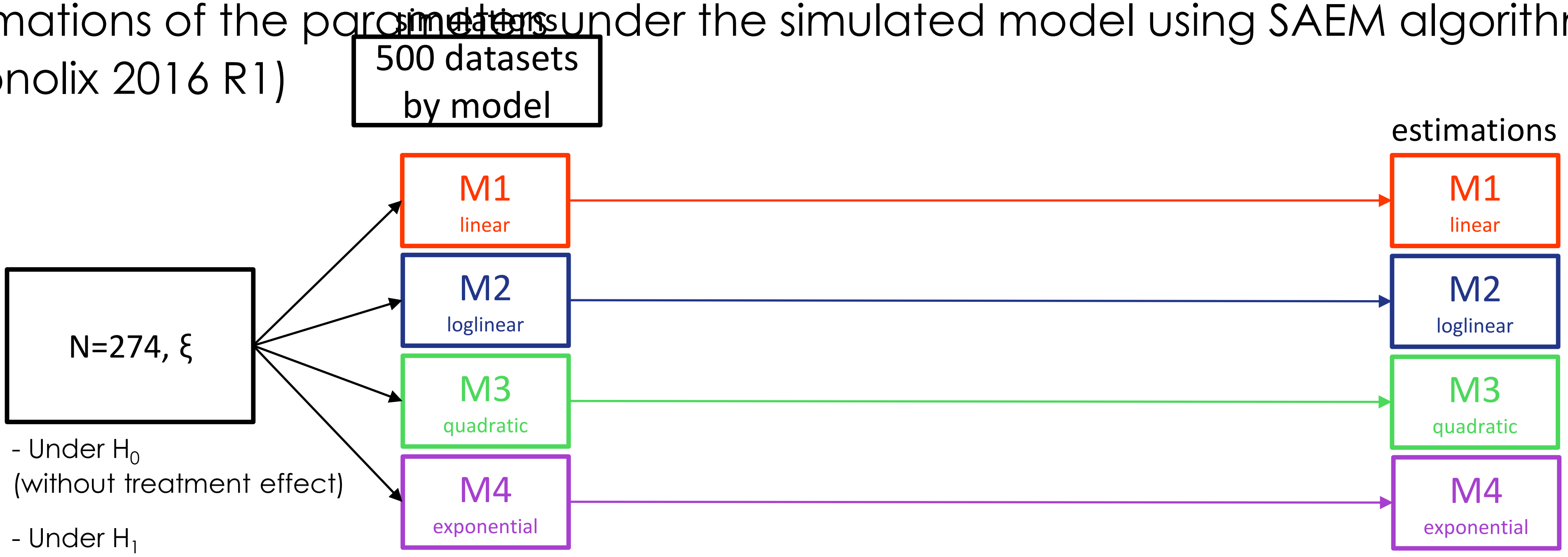


NSN to reach $\pi_{average}$ = 0.9	274	320	358

Average power: $\pi_{average}(\Xi) = \sum_{m=1}^{M} w_m \times \pi_m(\Xi)$

Clinical trial simulations (CTS)

- 500 simulated datasets under each candidate model and 3 different designs: ξ_{CDDs}, $\xi_{DDs,1}$, ξ_{ES}
- Estimations of the parameters under the simulated model using SAEM algorithm (Monolix 2016 R1)

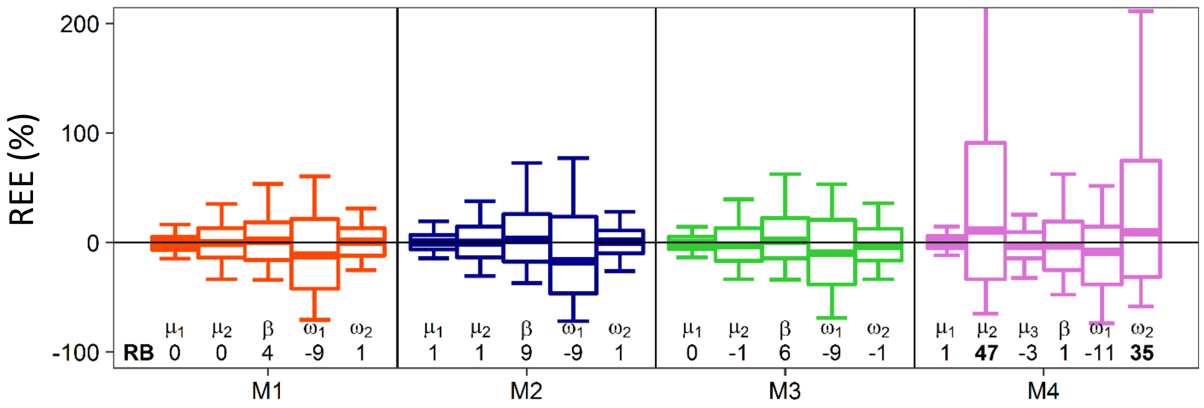


- Comparison of the performances of the robust design ξ_{CDDs} with $\xi_{DDs,1}$ and ξ_{ES}
- Adequation between FIM predictions and CTS results

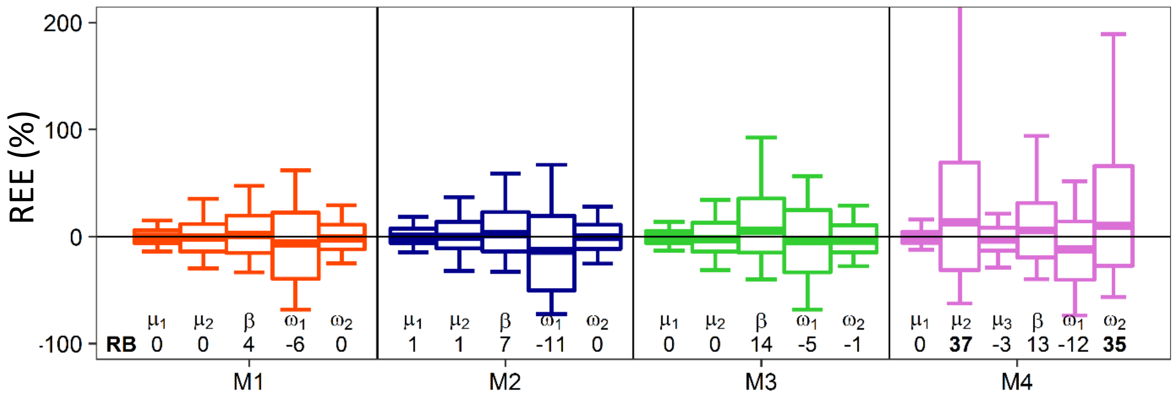
Relative estimation errors and bias

REE: Relative estimation error, in %
RB: Relative bias, in %

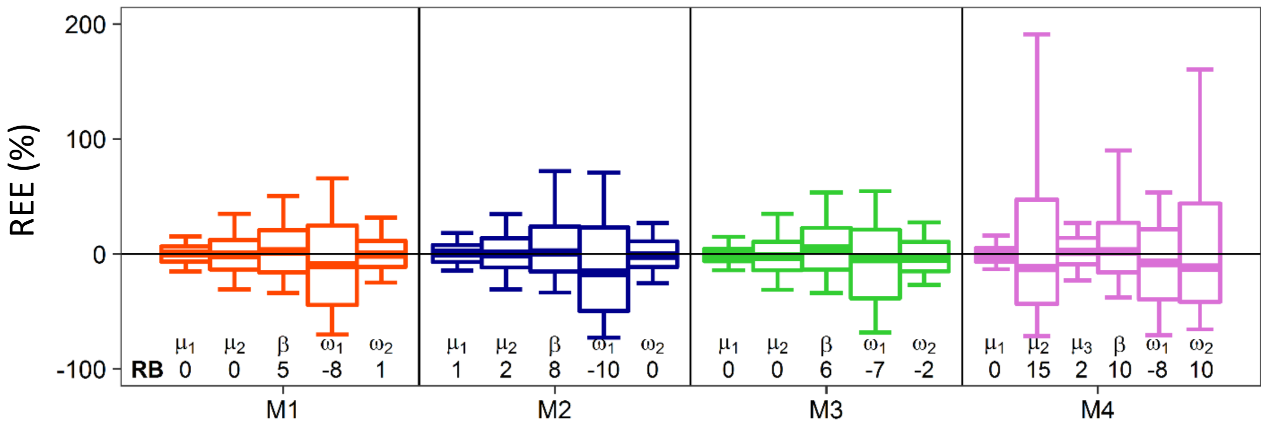
ξ_{ES} = (0,4,8,12)



$\xi_{DDs,1}$ = (0,2,11,12)

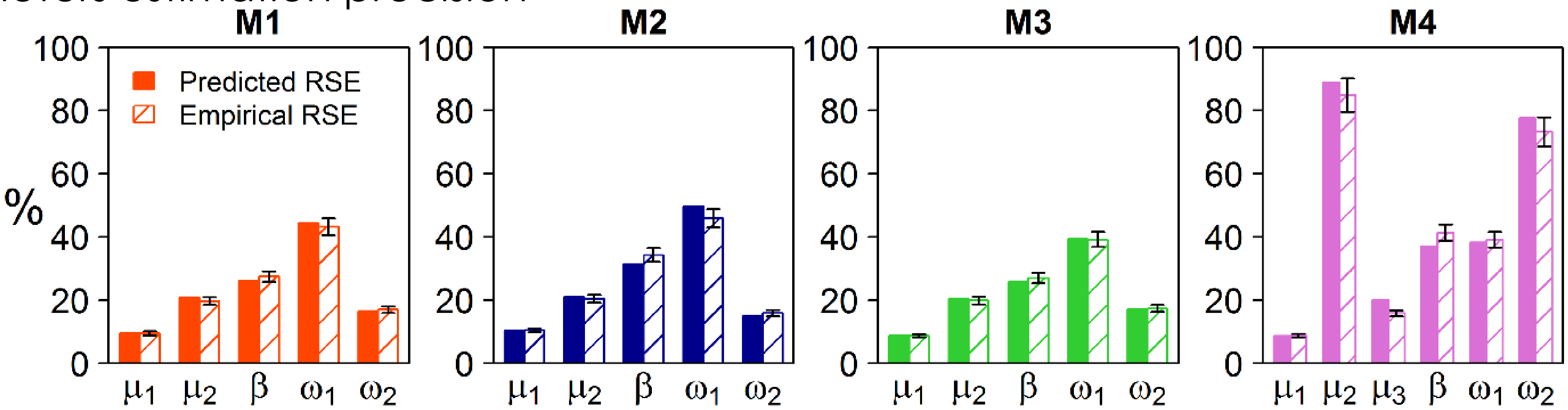


ξ_{CDDs} = (0,4,11,12)



Adequacy FIM predictions vs. CTS estimations (ξ_{CDDs}, N=274)

- Parameters estimation precision



- Type 1 error & Power of the Wald test on β

Under H_0				
Nominal type I error	0.05 [0.033,0.073]			
Observed type I error	0.048	0.060	0.068	0.036
Under H_1				
FIM predicted power	0.967 [0.949,0.982]	0.889 [0.859,0.916]	0.973 [0.959,0.986]	0.769 [0.731,0.792]
Observed power	0.988	0.988	0.996	0.860

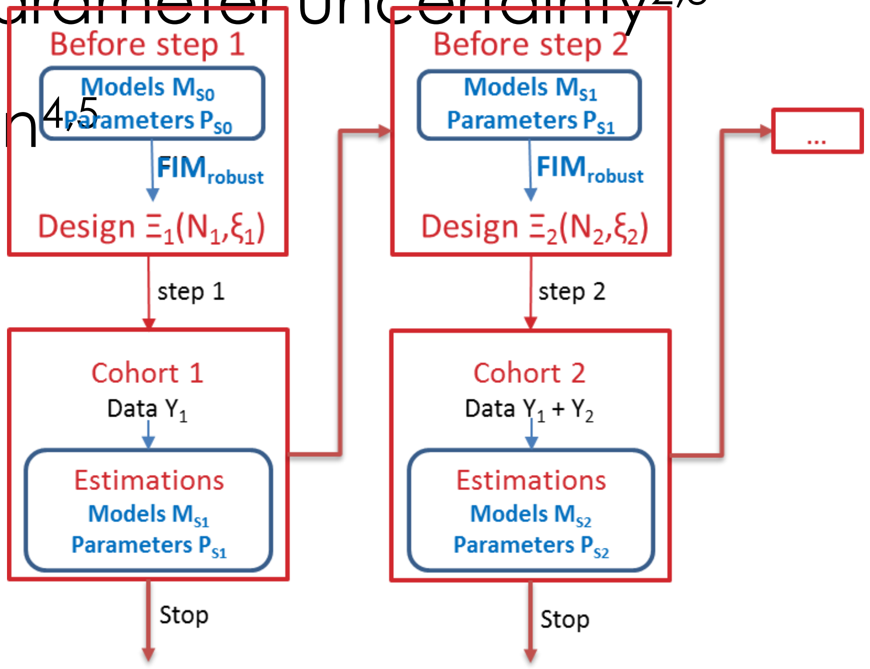
Discussion

- Method to design longitudinal studies with binary outcome accounting for model uncertainty
- Compromise between overall parameter precision and power of the Wald test
- Relevance of the approach evaluated by simulations

- MC-HMC method for computation of FIM enables applications to design optimization for discrete data but is computationally challenging (much slower than FO approach)

Perspectives

- Replacement of MC by more efficient approach: quasi-random sampling[1]
- Accounting for model and parameter uncertainty[2,3]
- Model based adaptive design[4,5]
  - model averaging[6]



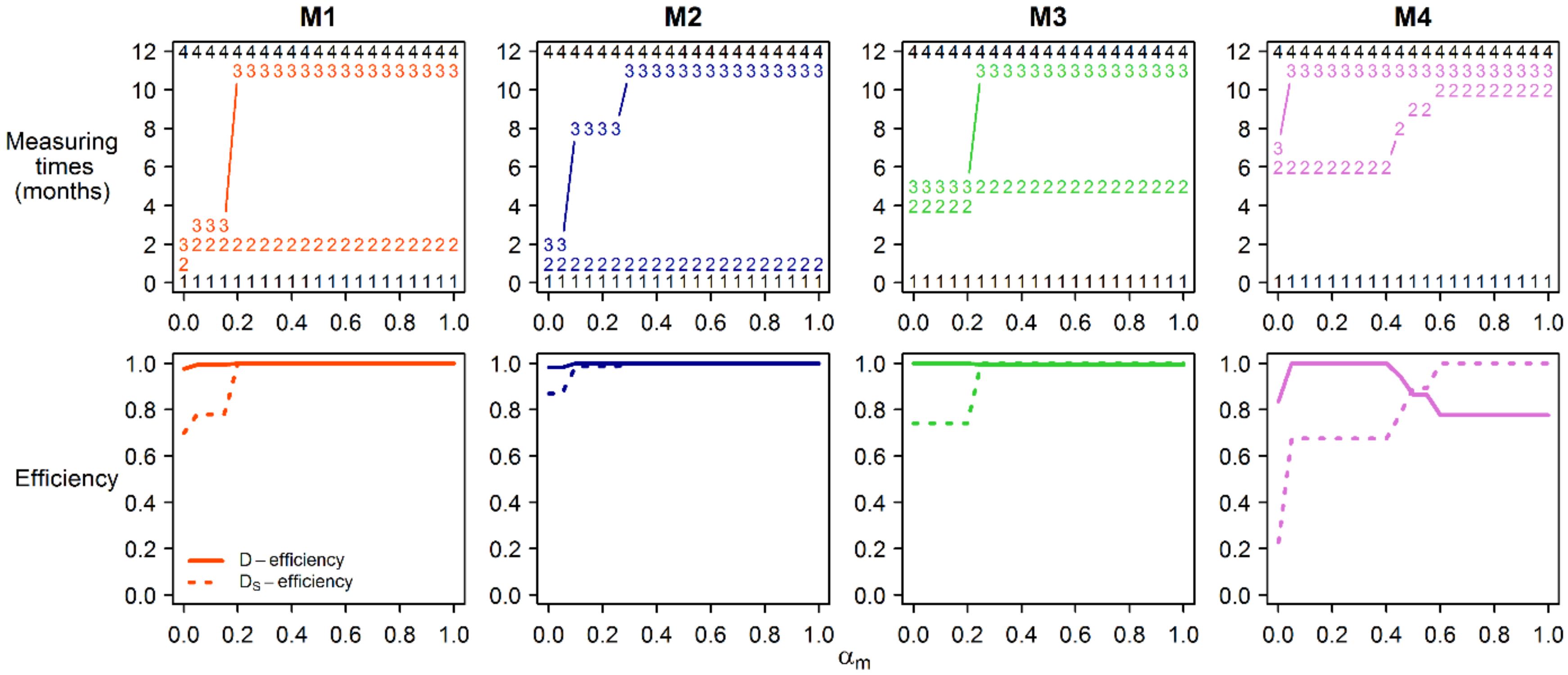
1: Ueckert S. *et al.*, CM Statistics Conference, UK, 2015
2: Foo LK. *et al.*, J Biopharm Stat, 2012
3: Loingeville F. *et al.*, PAGE meeting, 2017
4: Lestini G. *et al.*, Pharm Res., 2015
5: Strömberg EA. *et al.*, J Pharmacokinet Pharmacodyn, 2017
6: Buckland ST. *et al.*, Biometrics, 1997

Thanks to

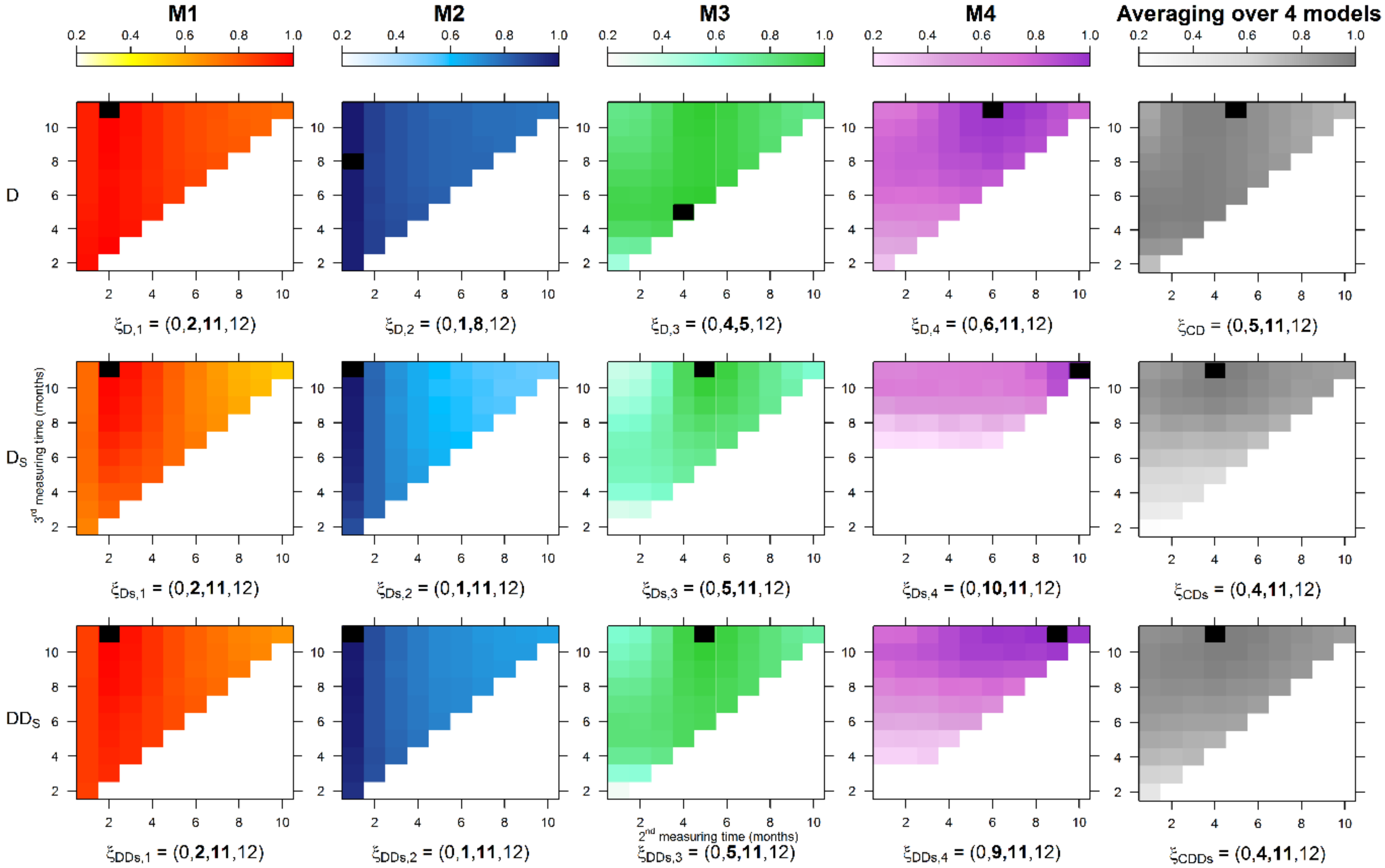
- You for listening
- The organizing committee
- IAME

Backup

α_m choice



Heatmaps


M1
M2
M3
M4
Averaging over 4 models
D
Ds
DDs
3rd measuring time (months)
2nd measuring time (months)
ξD,1 = (0,2,11,12)
ξD,2 = (0,1,8,12)
ξD,3 = (0,4,5,12)
ξD,4 = (0,6,11,12)
ξCD = (0,5,11,12)
ξDs,1 = (0,2,11,12)
ξDs,2 = (0,1,11,12)
ξDs,3 = (0,5,11,12)
ξDs,4 = (0,10,11,12)
ξCDs = (0,4,11,12)
ξDDs,1 = (0,2,11,12)
ξDDs,2 = (0,1,11,12)
ξDDs,3 = (0,5,11,12)
ξDDs,4 = (0,9,11,12)
ξCDDs = (0,4,11,12)

Predicted Power Wald test for N=100

Protocole \ Modèle final	M1 Linéaire	M2 Loglinéaire	M3 Quadratique	M4 Exp	AVERAGE
$\xi_{D,1}$=(0,2,11,12)	**69.7%**	58.0%	36.9%	35.4%	50.0%
$\xi_{D,2}$=(0,1,8,12)	58.0%	66.7%	47.5%	20.3%	48.1%
$\xi_{D,3}$=(0,4,5,12)	60.0%	50.6%	56.3%	8.7%	43.9%
$\xi_{D,4}$=(0,6,11,12)	54.6%	45.0%	67.6%	38.1%	51.3%
$\xi_{Ds,1}$=(0,2,11,12)	**69.7%**	58.0%	36.9%	35.4%	50.0%
$\xi_{Ds,2}$=(0,1,11,12)	57.4%	**67.3%**	33.6%	35.8%	48.5%
$\xi_{Ds,3}$=(0,5,11,12)	58.6%	46.3%	**69.3%**	37.7%	53.0%
$\xi_{Ds,4}$=(0,10,11,12)	43.6%	41.1%	48.6%	**52.2%**	46.4%
$\xi_{DDs,1}$=(0,2,11,12)	**69.7%**	58.0%	36.9%	35.4%	50.0%
$\xi_{DDs,2}$=(0,1,11,12)	57.4%	67.3%	33.6%	35.8%	48.5%
$\xi_{DDs,3}$=(0,5,11,12)	58.6%	46.3%	**69.3%**	37.7%	53.0%
$\xi_{DDs,4}$=(0,9,11,12)	45.6%	41.7%	52.6%	47.8%	46.9%
ξ_{CD}=(0,5,11,12)	58.6%	46.3%	**69.3%**	37.7%	53.0%
ξ_{CDs}=(0,4,11,12)	63.4%	48.5%	65.0%	37.1%	**53.5%**
ξ_{CDDs}=(0,4,11,12)	63.4%	48.5%	65.0%	37.1%	**53.5%**
ξ_{ES}=(0,4,8,12)	62.2%	49.0%	61.5%	24.4%	49.3%

N274

Observed D-efficiencies

	M1	**M2**	**M3**	**M4**
$\xi_{\mathrm{CDD\,S}}$: *reference*	*1*	*1*	*1*	*1*
$\xi_{\mathrm{DD\,S},1}$	1.11	1.06	0.79	0.74
ξ_{ES}	0.98	0.94	0.98	0.84

	M1	**M2**	**M3**	**M4**
FIM predicted power	0.968	0.889	0.973	0.77
CTS observed power	0.988	0.988	0.996	0.86
CTS observed power using simulated β	0.976	0.914	0.992	0.746