

Introduction

Background

- Clinical trials with longitudinal data should be analyzed by nonlinear mixed effect models (NLMEMs). Design evaluation and/or optimisation of these trials relies on the Fisher Information Matrix (FIM)
- A method evaluating the FIM without linearisation was proposed [1], based on Monte Carlo/Hamiltonian Monte Carlo (MC/HMC) & implemented in the R package *MIXFIM* [2]
- This approach however requires a priori knowledge in model, which may lead to non-informative designs if the guessed model is inaccurate

Objectives

- To develop a method to find robust designs: i) accounting for model uncertainty and ii) ensuring a compromise between the overall precision of parameters and the power of the Wald test to detect a treatment effect
- To illustrate and evaluate the proposed method by Clinical Trial Simulations (CTS), through an example of a longitudinal trial with repeated binary outcome

Methods

Notations

\mathcal{M} = Fisher information matrix (FIM), $\Xi = \{N, \xi\}$ = population design, N = number of individuals, ξ = elementary design
 M candidate models ($m = 1, \dots, M$), w_m = weight quantifying the balance between M models, $0 \leq w_m \leq 1$, $\sum_{m=1}^M w_m = 1$
 y = vector of observations for one individual, using NLMEM:

$$p(y|b) = h_m(y, \xi, g(\mu, b, z, \beta)) \text{ with the function } h_m \text{ describing the probability of } y \text{ given: } \mu \text{ the fixed effects, } b \text{ the random effects } (b \sim N(0, \Omega)), z \text{ the covariates and } \beta \text{ the covariate effects}$$

ψ_m = population parameters vector of length P_m containing μ_m, Ω_m and β_m for model m

$\psi_{S,m}$ = subset of parameters of interest of length S_m , \mathcal{M}_t : truncated FIM with information on $\psi_{t,m}$ ($\psi_{t,m} = \psi_m \setminus \psi_{S,m}$)

α_m = weight quantifying the interest for $\psi_{S,m}$, $0 \leq \alpha \leq 1$

FIM evaluation by MC/HMC

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

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

with the likelihood $L(y, \psi_m) = \int p(y|b, \psi_m) p(b|\psi_m) db$ with p : p.d.f
 => 2 integrals to compute: w.r.t y (using MC) and w.r.t b (using HMC)

Optimality criteria Φ

Efficiency of a design, for a criterion X :
 $E_{X,m}(\Xi) = \frac{\Phi_{X,m}(\Xi)}{\Phi_{X,m}(\Xi_{X,m})}$ with $\Xi_{X,m}$ the X -optimal design for model m

Table 1: Optimality criteria

Parameters of interest	Given model m	Averaging over candidate models $m = 1, \dots, M$
ψ_m	D-optimality [3] $\Phi_{D,m}(\Xi) = \text{Det}(\mathcal{M}(\psi_m, \Xi)) \frac{1}{P_m}$	CD-optimality [3,5] $\Phi_{CD}(\Xi) = \prod_{m=1}^M \Phi_{D,m}(\Xi) w_m$
$\psi_{S,m}$	D_S -optimality [3] $\Phi_{D_S,m}(\Xi) = \left(\frac{\text{Det}(\mathcal{M}(\psi_m, \Xi))}{\text{Det}(\mathcal{M}_t(\psi_m, \Xi))} \right)^{\frac{1}{S_m}}$	CD _S -optimality $\Phi_{CD_S}(\Xi) = \prod_{m=1}^M \Phi_{D_S,m}(\Xi) w_m$
Compromise between $\psi_{S,m}$ and $\psi_{t,m}$	DD _S -optimality [3,4] $\Phi_{DD_S,m}(\Xi, \alpha_m) = \left(\text{Det}(\mathcal{M}_t(\psi_m, \Xi)) \right)^{\frac{1-\alpha_m}{P_m-S_m}} \left(\frac{\text{Det}(\mathcal{M}(\psi_m, \Xi))}{\text{Det}(\mathcal{M}_t(\psi_m, \Xi))} \right)^{\frac{\alpha_m}{S_m}}$	CDD _S -optimality $\Phi_{CDD_S}(\Xi) = \prod_{m=1}^M \Phi_{DD_S,m}(\Xi) w_m$

Application to design optimization for binary outcomes

Illustration example

- One year study (inspired of [6]) including 2 balanced treatment groups and repeated binary data
- 4 candidate models describing the response probability over time
- β quantifies the treatment effect on the parameter explaining the evolution of the response probability over time
- Parameter of interest for the computation of D_S - and DD_S -optimality

Table 2: Parameters

	ψ_1	ψ_2	ψ_3	ψ_4
H1	-2	-2	-2	-2
H2	0.09	0.42	0.0075	0.020
H3	-	-	-	0.33
β	5	5	5	5
ω_1	0.7	0.7	0.7	0.7
ω_2	0.17	0.79	0.014	0.038

ψ_m : parameter value of model m
 μ : fixed effect
 β : treatment effect
 ω : standard deviation of random effect

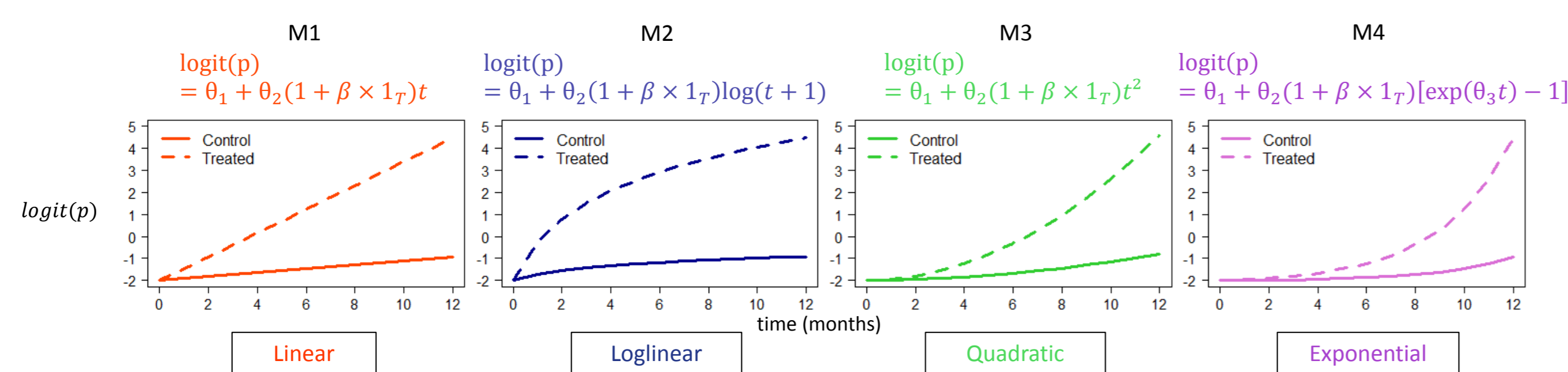


Figure 1: Candidate models

Aim

- To propose a design with 4 among 13 possible sampling times from 0 to 12 months:
- accounting for model uncertainty
- allowing the detection of the treatment effect β and provide decent precision of other parameters

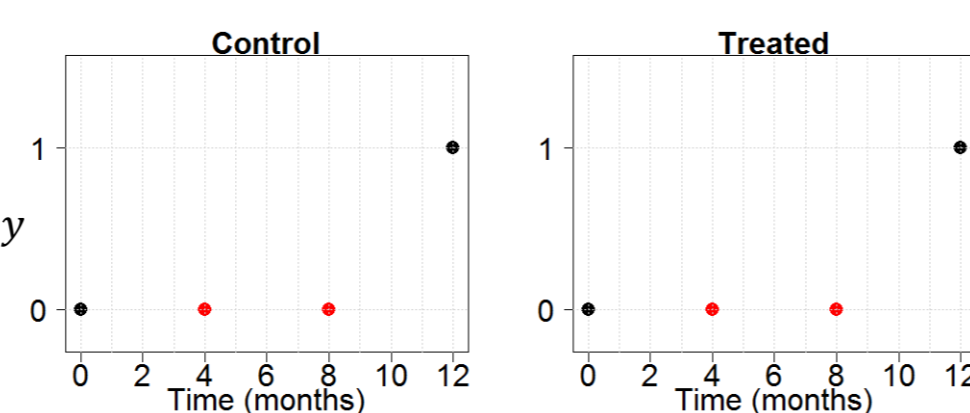


Figure 2: The equispaced design $\xi_{ES} = \{0, 4, 8, 12\}$

Design optimization procedure

- Combinatorial optimisation of t_2 and t_3 among 11 possible times ($\xi = \{0, t_2, t_3, 12\}$)
- FIM evaluation using *MIXFIM* with 5000 MC and 200 HMC samples
- For each model, maximisation of Φ_{DD_S} (with α_m chosen as: $E_{D,m} > 0.8$, $E_{D_S,m} > 0.8$ and maximal $E_{D,m} \times E_{D_S,m}$)
- Averaging over 4 models, maximisation of Φ_{CDD_S} (with $w_1 = w_2 = w_3 = w_4 = 1/4$)

Predictions from FIM

- Power π_m to detect the treatment effect β using a model m
- Average power: $\pi_{average} = \sum_{m=1}^M w_m \times \pi_m$
- Number of subjects needed to reach a $\pi_{average}$ of 0.9 (NSN_{average}) for a type I error of 5%

Results

- Loss of efficiency if misspecified
- The robust design ξ_{CDD_S} provides better average power than $\xi_{DD_S,1}$ and ξ_{ES}

Table 3: D-efficiencies of main designs

Design	Model	M1 Linear	M2 Loglinear	M3 Quadratic	M4 Exponential
$\xi_{CD} = \{0, 5, 11, 12\}$		0.860	0.805	0.994	0.958
$\xi_{CD} = \xi_{CDD_S} = \{0, 4, 11, 12\}$		0.910	0.828	0.977	0.882
$\xi_{DD_S,1} = \{0, 2, 11, 12\}$		1	0.898	0.812	0.706
$\xi_{DD_S,2} = \{0, 1, 11, 12\}$		0.932	0.998	0.796	0.685
$\xi_{DD_S,3} = \{0, 5, 11, 12\}$		0.860	0.805	0.994	0.958
$\xi_{DD_S,4} = \{0, 9, 11, 12\}$		0.771	0.777	0.813	0.864
$\xi_{ES} = \{0, 4, 8, 12\}$		0.908	0.826	0.975	0.869

Efficiencies under 0.8 are in bold and italic font
 $\alpha_m = 0.5$ for all the models

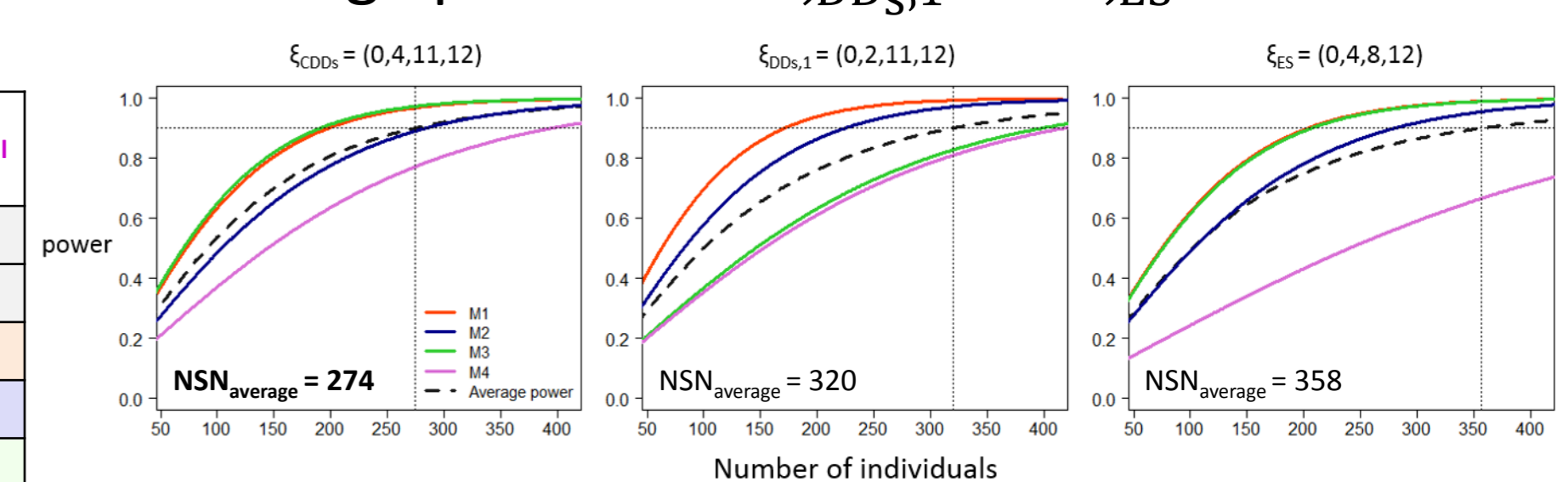


Figure 3: Predicted power vs. the number of individuals N for each candidate model and in average. The vertical dotted line shows the NSN_{average} to reach an average power of 0.9 to detect the treatment effect

Evaluation by simulation

Settings

- 500 datasets
- simulated under each model (under H_0 with $\beta = 0$ and under H_1 with $\beta = 5$)
- with $N = 274$
- with 3 designs: the robust design ξ_{CDD_S} , the optimal design for linear model $\xi_{DD_S,1}$ and the non-optimized equispaced design ξ_{ES}
- Analysis by nonlinear mixed effect models with SAEM algorithm [7] in *MONOLIX 2016R1*

Comparisons between 3 designs

- Better performances of ξ_{CDD_S} than $\xi_{DD_S,1}$ and ξ_{ES} overall, especially for M4

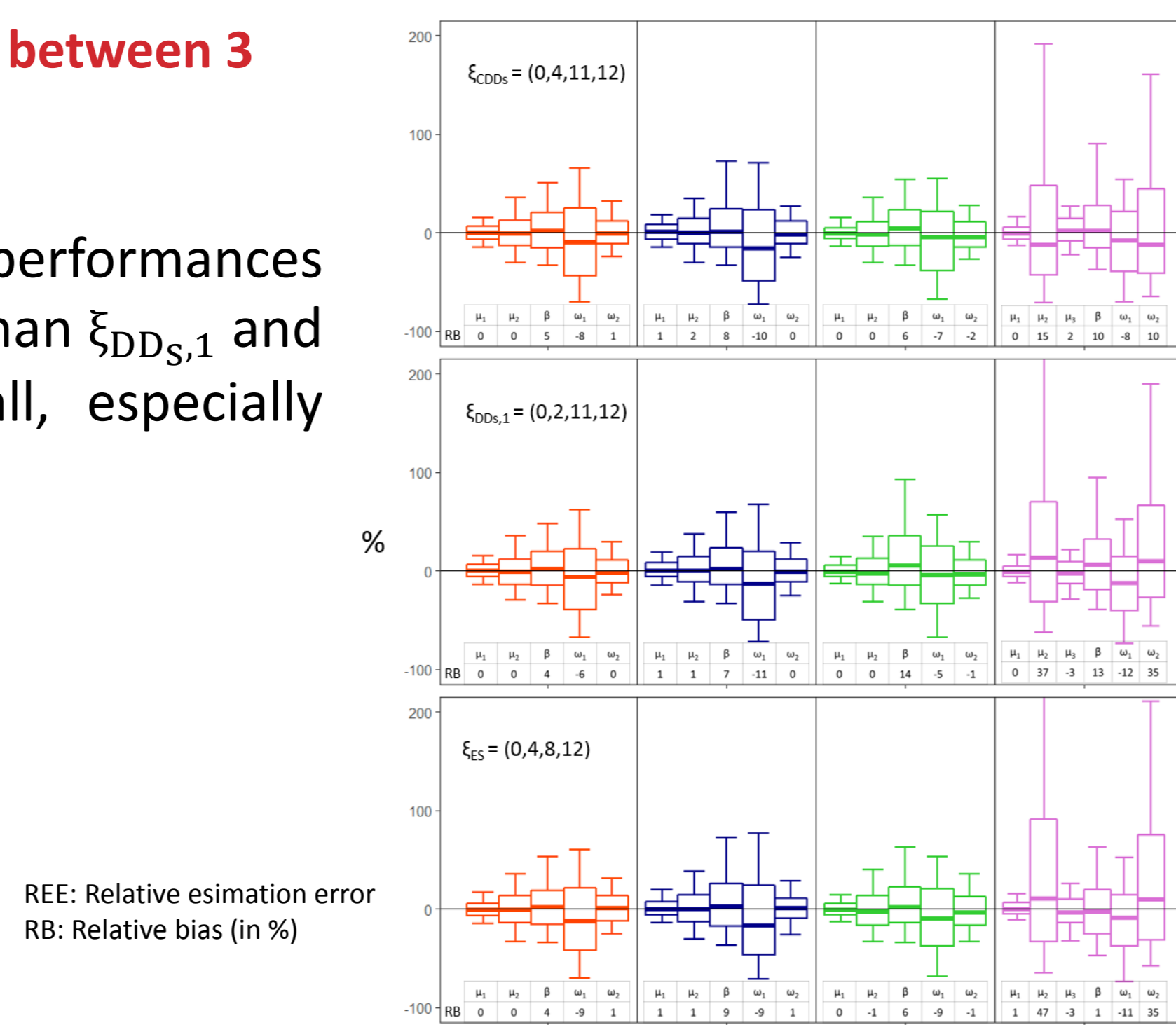


Figure 4: REE distribution and relative bias of parameters

Adequation between FIM predictions and CTS with the robust design ξ_{CDD_S}

- Empirical RSE in the same range as Predicted RSE

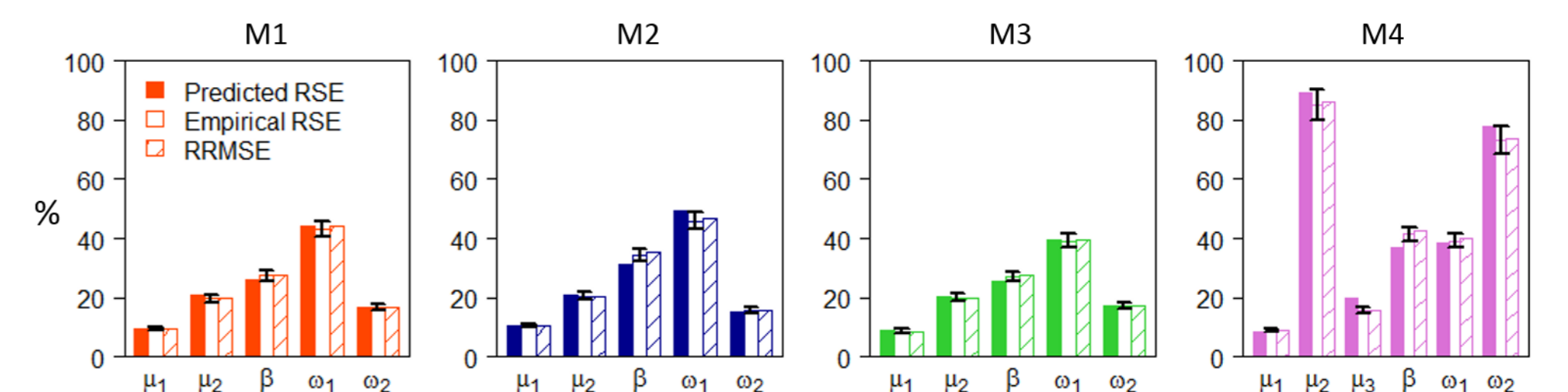


Figure 5: Predicted Relative Standard Error (RSE, full bars) vs. Empirical RSE (empty bars, with IC₉₅) and Relative Root Mean Square Error (RRMSE, hatched bars)

- Controlled type I error
- Slight underprediction of power linked to bias in estimated β (cf. Figure 4)

Table 4: Power of the Wald test to detect treatment effect

	Under H_0		Under H_1	
	Nominal type I error [IP ₉₅]	Observed type I error	FIM predicted power [IP ₉₅]	Observed power
M1	0.05 [0.033, 0.073]	0.048	0.967 [0.949, 0.982]	0.988
M2		0.060	0.889 [0.859, 0.916]	0.988
M3		0.068	0.973 [0.956, 0.986]	0.996
M4		0.036	0.769 [0.731, 0.806]	0.860

Conclusion

- The proposed design strategy, based on MC/HMC and compound optimality theory, is a relevant approach which can be used to efficiently design longitudinal studies
- The robust design provided decent efficiencies across all the candidate models and an optimised average power to detect a treatment effect, confirmed by CTS
- The Compound DD_S-criterion may be applicable with other methods for evaluating the FIM (e.g. AGQ), and with other type of data (continuous, time to event etc.)
- Perspectives: to implement a more efficient optimisation algorithm and to extend these methods to adaptive designs

References

- [1] Riviere M-K, Ueckert S, Mentré F. An MCMC method for the evaluation of the Fisher information matrix for non-linear mixed effect models. *Biostat. Oxf. Engl.* 2016;17:737-50. ; [2] Riviere M-K, Mentré F. R package MIXFIM, version 1.0 <http://mc-stan.org/>. 2015. ; [3] Atkinson A, Donev A, Tobias R. *Optimum Experimental Designs*, with SAS. Oxford, New York: Oxford University Press; 2007
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- [6] Lestini G, Ueckert S, Mentré F. Model-based optimal robust design in pharmacometrics. *PODE*, Uppsala, Sweden; 2016. ; [7] Kuhn E, Lavielle M. Maximum Likelihood Estimation in Nonlinear Mixed Effects Models. *Comput Stat Data Anal.* 2005;49:1020-1038.