Robust design in model-based analysis of longitudinal clinical data

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Optimal design in Nonlinear Mixed Effects Models (NLMEM)

- Choosing a good design for a planned study is essential
  - Number of subjects
  - Number of sampling times for each subject
  - Sampling times (allocation in time)
- Optimal design depends on prior information (model and parameters)
  - Adaptive design
  - Robust design (robustness on parameters)

Atkinson, Optimum Experimental Designs. 1995
Dodds, Hooker and Vicini, J Pharmacokinet Pharmacodyn. 2005
Foo L-K, Duffull S. J Biopharm Stat. 2010

Objectives

- To compare various robust design criteria in NLMEM for two examples:
  - Pharmacokinetic/Pharmacodynamic (PKPD) model with continuous data
  - Longitudinal binary model using a new method for the evaluation of the Fisher information matrix (FIM) for NLMEM with discrete data

Basic mixed effect model

- Individual model (one continuous response)

$y_i = f(\phi_i, \xi_i) + \varepsilon_i$ vector of n_i observations

  - ξ_i : individual sampling times t_{ij} $j=1, \dots n_i$
  - ϕ_i : individual parameters (size p)
  - f: nonlinear function defining the structural model
  - ε_i : gaussian zero mean random error
  - $\mathrm{var}(\varepsilon_i) = \mathrm{diag}\left((\sigma_{inter} + \sigma_{slope} f(\phi_i, \xi_i))^2\right)$ combined error model

- Random-effects model

  - $\phi_i = \mu \times \exp(b_i)$ or $\mu + b_i$
  - $b_i \sim N(0, \Omega)$ here Ω diagonal: $\omega_k^2 = \mathrm{Var}(b_{ik})$

- Population parameters: Ψ (size P)

  - μ (fixed effects)
  - unknowns in Ω (variance of random effects)
  - σ_{inter} and/or σ_{slope} (error model parameters)

Basic population design

- Assumption
  - N individuals i
  - same elementary design ξ in all N subjects ($\xi_i = \xi$)

    with $t_1, \dots, t_\mathrm{n}$ sampling times
  - $\mathrm{n_{tot}} = \mathrm{N} \times \mathrm{n}$
- Population design
  - $\Xi = \{\xi, \mathrm{N}\}$

Fisher Information Matrix (FIM) in NLMEM

- Elementary FIM: $M_F(\Psi, \xi) = E\left(\frac{-\partial^2 L(y;\Psi)}{\partial\Psi\partial\Psi^T}\right)$
- No analytical expression for FIM
  - Continuous data → FO approximation
    - M_F is implemented in the R function « PFIM »[1]
  - Discrete data → New method: Adaptive Gaussian Quadrature (AGQ) and Quasi Random Monte Carlo[2,3] (QRMC)
    - M_F is implemented in an R program.
- Population FIM for one group design

$$M_F(\Psi, \Xi) = N \times M_F(\Psi, \xi)$$

- Standard D- criterion: $|M_F(\Psi, \Xi)|^{1/P}$ where $\Psi = \Psi^*$ (fixed values)

[1] www.pfim.biostat.fr

[2] Ueckert S, Mentré F. Computational and Methodological Statistics (CMStatistics). 2015

[3] Ueckert S, Mentré F. Population Optimum Design of Experiments (PODE). 2015

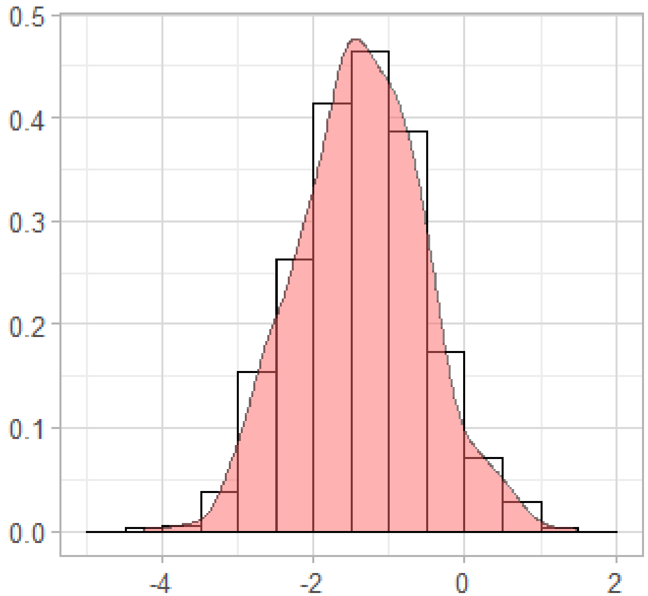
Criteria for optimal robust designs

- For robust design, a distribution for Ψ, $p(\Psi)$, is assumed

Optimal robust designs		Criteria
ξ_{DE}		$\left\|E_{\Psi}\left(M_F(\Psi,\xi)\right)\right\|$
ξ_{ED}		$E_{\Psi}\|M_F(\Psi,\xi)\|$
ξ_{EID}	$= \underset{\xi}{argmax}$	$(E_{\Psi}\|M_F(\Psi,\xi)\|^{-1})^{-1}$
ξ_{ELD}		$E_{\Psi}[log\|M_F(\Psi,\xi)\|]$
ξ_{MM}		$min_{\Psi}\|M_F(\Psi,\xi)\|$

Criteria for robust optimal designs

- Criteria are computed by Monte Carlo simulations (MC)
- K= Total number of MC samples



$\Psi_1 \rightarrow M_F(\Psi_1, \xi)$

.....

$\Psi_k \rightarrow M_F(\Psi_k, \xi)$

.....

$\Psi_K \rightarrow M_F(\Psi_K, \xi)$

Compute Robust Criteria

Outline

Part I

Comparison of robust design criteria in NLMEM with continuous data

Designs were evaluated using

(i) D-criterion and predicted Relative Standard Errors (RSE)

(ii) Relative Root Mean Squared Errors (RRMSE) derived from Clinical Trial Simulations (CTS)

Part 2

Comparison of robust design criteria in NLMEM with discrete data (NEW way to compute FIM)

Designs were evaluated using

(i) D-criterion and predicted Relative Standard Errors (RSE)

Objectives

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Part I - Example: PKPD model with continuous data

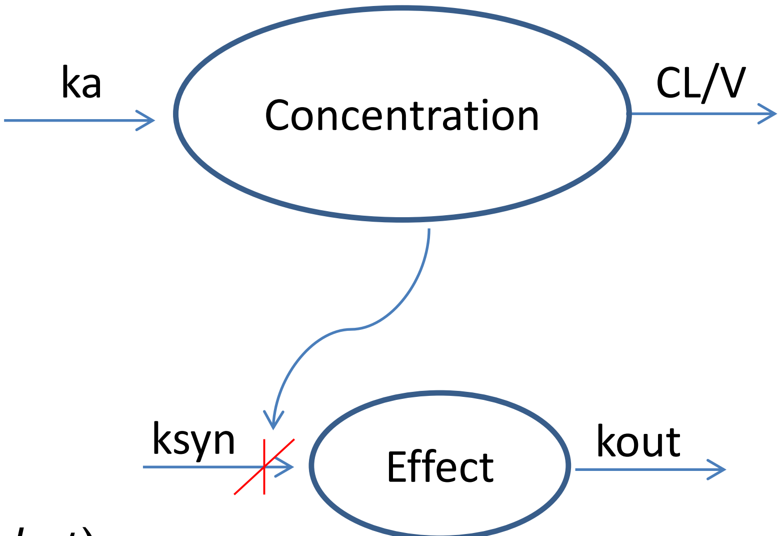
- 2 responses model, for a biomarker in oncology $(\mathrm{TGF}-\beta)$

PK: concentration

$$f_{PK}(\phi, t) = \frac{DOSE}{V}\frac{k_a}{k_a - k}\left(e^{-kt} - e^{-k_a t}\right),$$

$$k = \frac{CL}{V}$$

Parameters: k_a, V, CL



PD: relative inhibition of TGF-β

$$\frac{df_{PD}(\phi, t)}{dt} = k_{out}\frac{I_{max}\cdot f_{PK}(\phi, t)}{f_{PK}(\phi, t) + IC_{50}} - k_{out}\cdot f_{PD}(\phi, t),$$

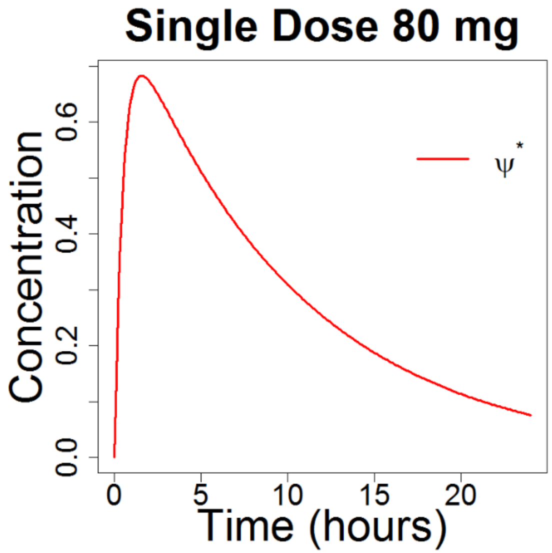
$$I_{max} = 1$$

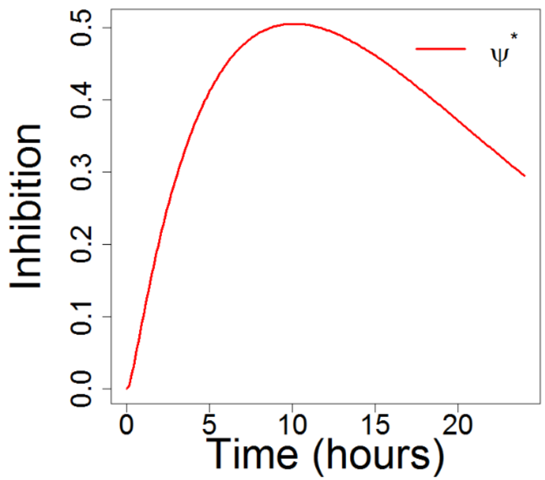
Parameters: k_{out}, IC_{50}

$\Longrightarrow$ The model is implemented in the DDMoRe model repository

Gueorguieva et al., Comput Methods Programs Biomed. 2007
Gueorguieva et al., Br J Clin Pharmacol. 2014
Bueno et al., Eur J Cancer. 2008
Lestini et al., Pharm Res. 2015

Part I - Example: PKPD model with continuous data





PK Parameters	Ψ*	$p(\Psi)$
$\mu_{k_a}(h^{-1})$	2	2
μ_V (L)	100	100
$\mu_{CL}(Lh^{-1})$	10	10
ω_V^2	0.49	0.49
ω_{CL}^2	0.49	0.49
$\sigma_{slope,PK}$	0.2	0.2

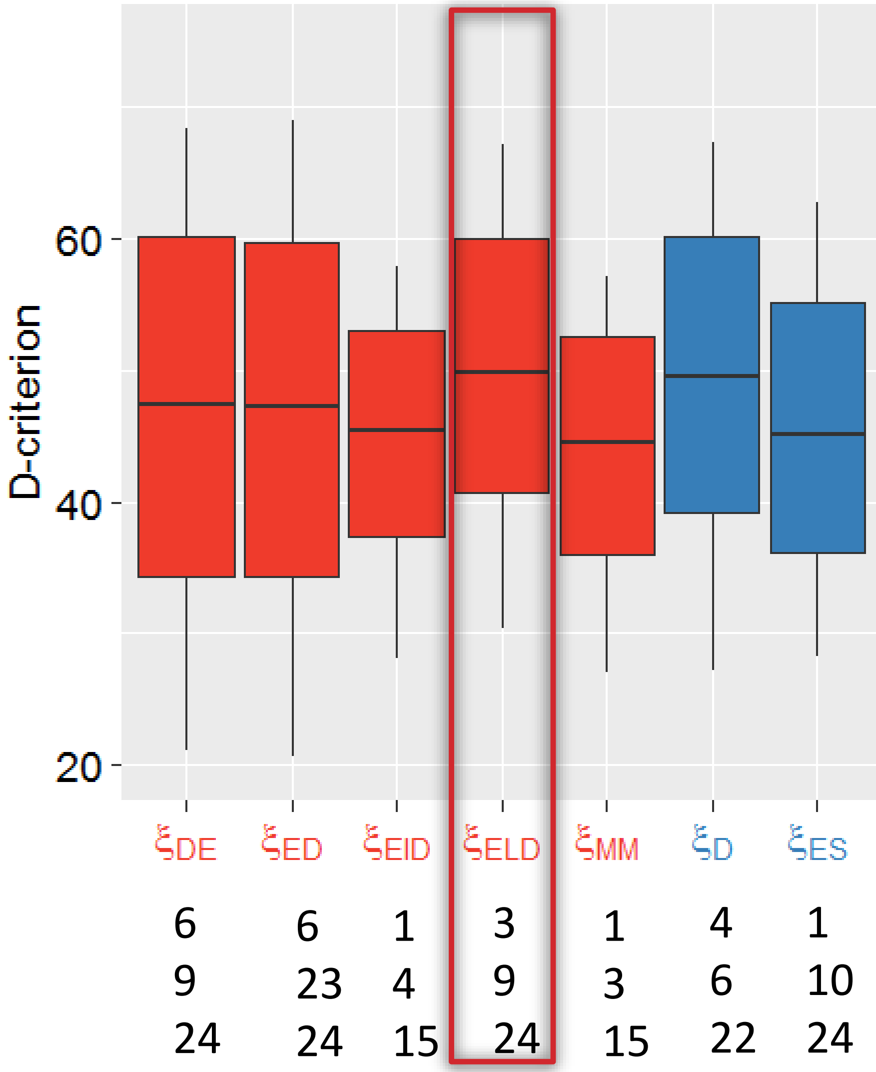
PD Parameters	Ψ*	$p(\Psi)$
$\mu_{k_{out}}(h^{-1})$	0.2	$\log N(\log(0.2)\,, 0.8^2)$
$\mu_{IC_{50}}(mg/L)$	0.3	$\log N(\log(0.3)\,, 0.8^2)$
$\omega_{k_{out}}^2$	0.49	0.49
ω_{IC50}^2	0.49	0.49
$\sigma_{inter,PD}$	0.2	0.2

Design optimization

- Constraints
  - N = 50 patients
  - n = 3 observations per patient
  - For PK, times fixed to $0.1, 4, 12$ h
  - For PD, 3 sampling times among possible times: $1, 2, 3, 4, 6, 9, 10, 15, 22, 23, 24$ h

  $\Rightarrow \binom{11}{3} = 165$ elementary designs
- FIM Computation
  - FIM was computed in PFIM with FO approximation
- Optimization
  - Find the D-optimal design ξ_{D} using D-criterion for Ψ^*
  - Find optimal robust designs $\xi_{\mathrm{DE}}, \xi_{\mathrm{ED}}, \xi_{\mathrm{EID}}, \xi_{\mathrm{ELD}}, \xi_{\mathrm{MM}}$ using MC with K=1000
- Evaluation
  - For each optimal design, and for a fixed equispaced design ξ_{ES} compute D-criterion and predicted RSE(%) for each set simulated parameters $\Psi_k,\ k = 1, .., K$

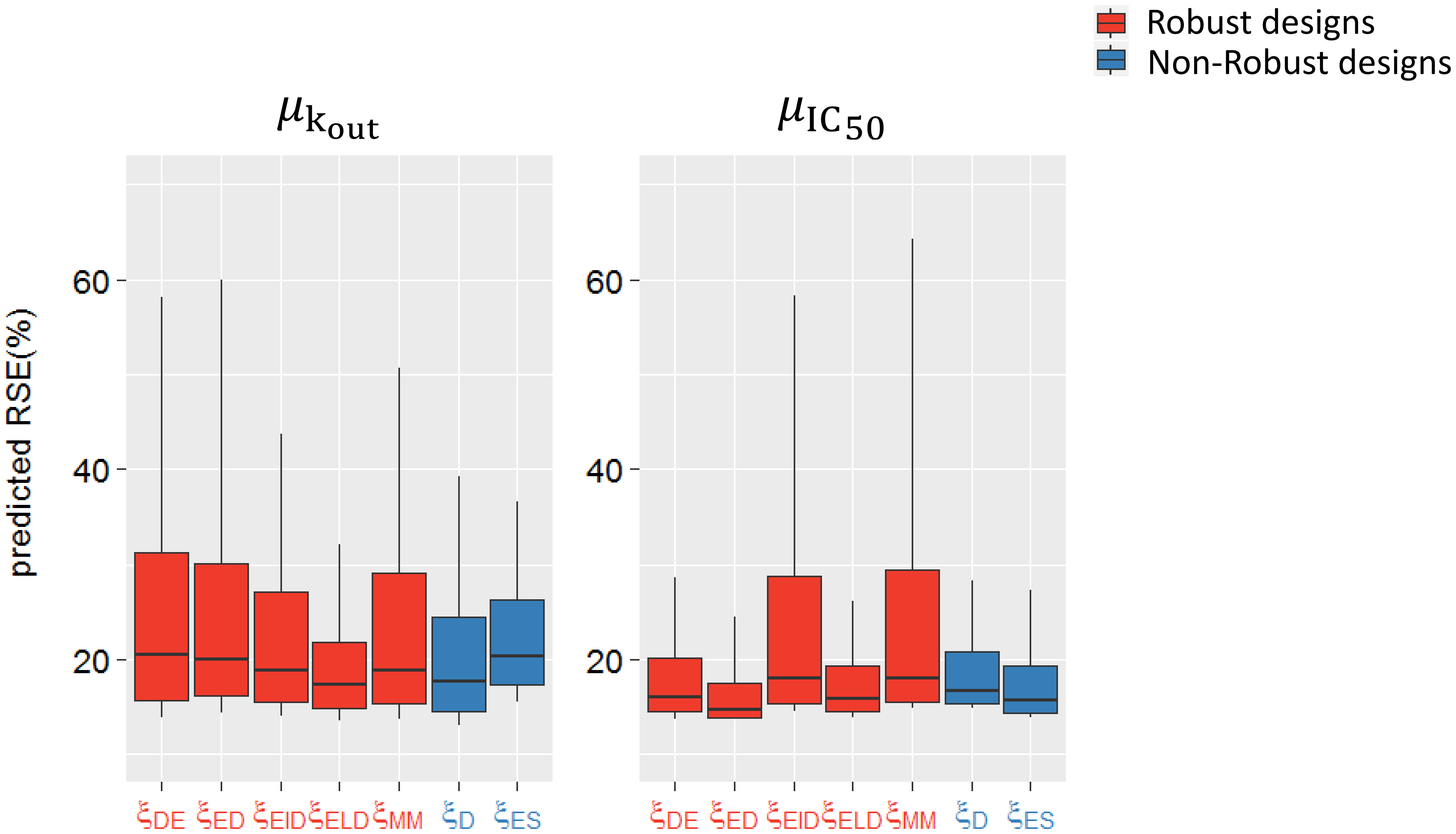
D-criterion for optimal designs



Best design with highest median: ξ_{ELD}

Whiskers of boxplot: 10th and 90th percentiles

Predicted Relative Standard Errors (RSE)



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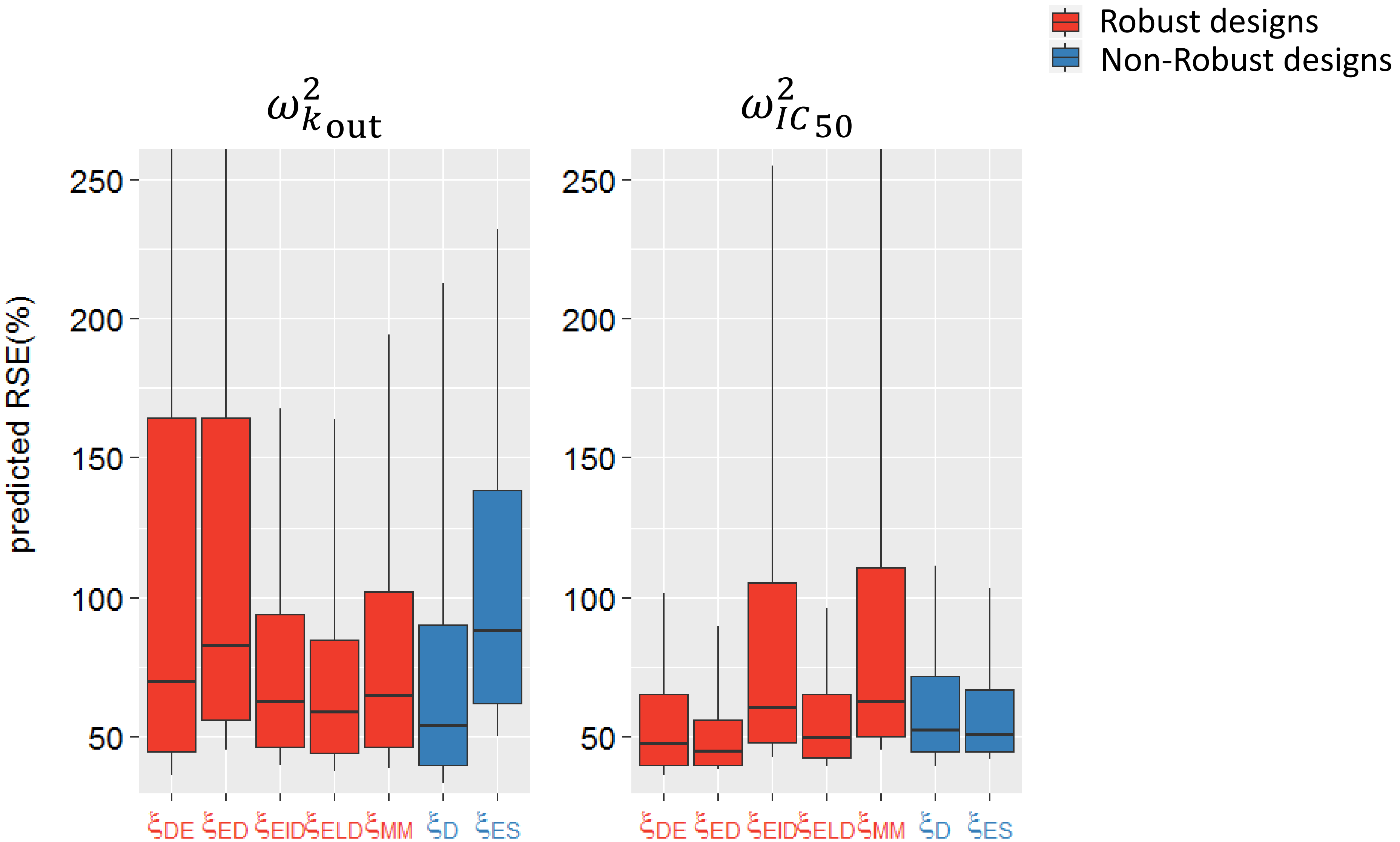


Whiskers of boxplot: 10th and 90th percentiles

Simulation Study

- For each design ξ

$\Psi_1 \rightarrow$

.....

$\Psi_k \rightarrow$ K=1000 Simulations N=50 subjects

.....

$\Psi_K \rightarrow$

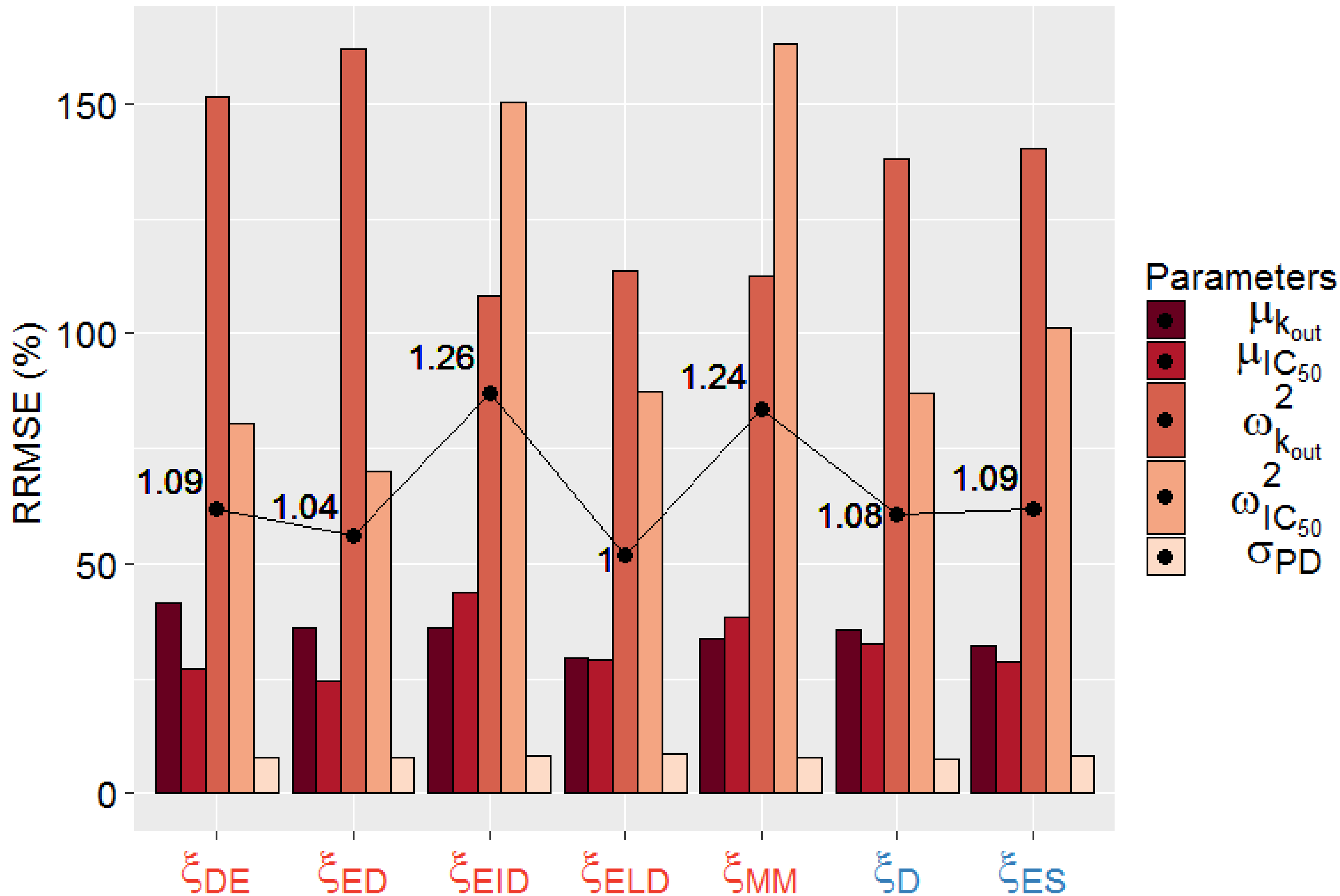
Y_1	$\hat{\Psi}_1$
.....	.....
Y_k	$\hat{\Psi}_k$
.....	.....
Y_K	$\hat{\Psi}_K$

Compute Relative Root Mean Squared Error (RRMSE)

$$\xi = \xi_{DE}, \xi_{ED}, \xi_{EID}, \xi_{ELD}, \xi_{MM}, \xi_{D}, \xi_{ES}$$

- Parameter estimation: SAEM algorithm in MONOLIX 4.3
  - 5 chains, initial estimates: Ψ^*

Relative Root Mean Squared Errors (RRMSE)



• = Means across parameters of RRMSEs standardized to ξ_{ELD} RRMSEs

Conclusion (Part 1)

- All criteria led to various designs rather different
- ξ_{ELD} performed globally the best in terms of median of D-criteria across the 1000 MC simulations
- RRMSE obtained from the CTS study confirm the results, showing ξ_{ELD} being globally the more robust design of the 1000 simulations

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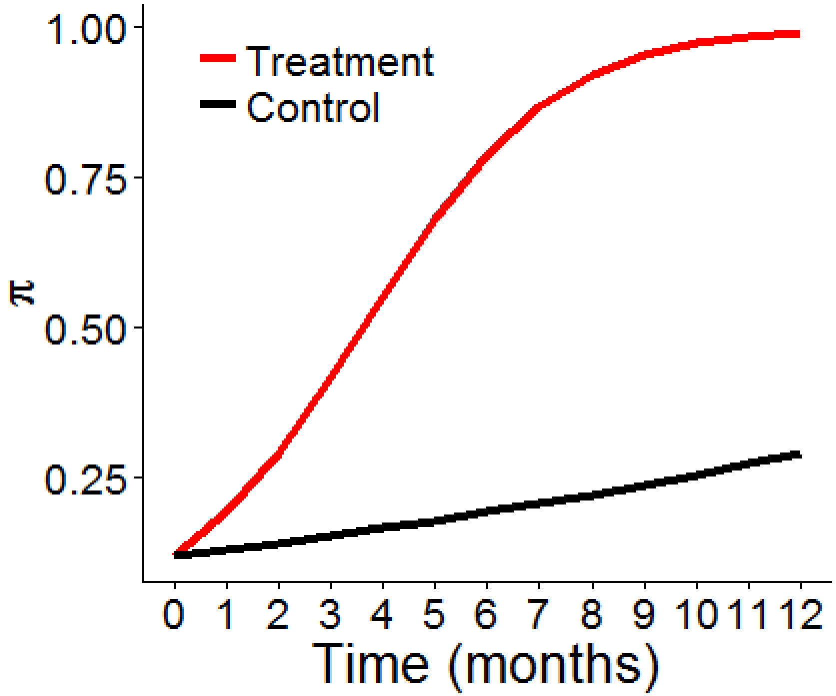
Method

Part 2 - Example: NLMEM with binary data

- Logistic model for repeated binary response with treatment increasing the slope of the logit of the response with time
- $\text{logit}(\pi) = \beta_1 + \beta_2(1 + \mu_3\delta)t$ where $\beta = g(\mu, b) = \mu + b;$



π is the probability of success

2 treatment groups $(\delta = 0 \,\&\, \delta = 1)$

Parameters	Ψ^*	$p(\Psi)$
μ_1	-2	-2
μ_2 (months)	0.09	$N(0.09, 0.2^2)$
μ_3	5	$N(5, 2^2)$
ω_1^2	0.49	0.49
ω_2^2 (months)	0.3	0.3

Ogungbenro K, Aarons L.. J Pharmacokinet Pharmacodyn. 2011

Ueckert S, Mentré F. Computational and Methodological Statistics (CMStatistics). 2015

Design optimization

Constraints

- $N = N_T$ (treatment) + N_C (control) = 100 patients
- n = 4 observations per patient including 0 and 12 months
- Possible intermediate times: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 months

$\Rightarrow \binom{11}{2} = 55$ elementary designs (first and last times are fixed)

FIM Computation

- FIM was computed with the new method by Ueckert and Mentré, 2015, based on AGQ and QRMC, with 3 nodes and 500 integrations samples

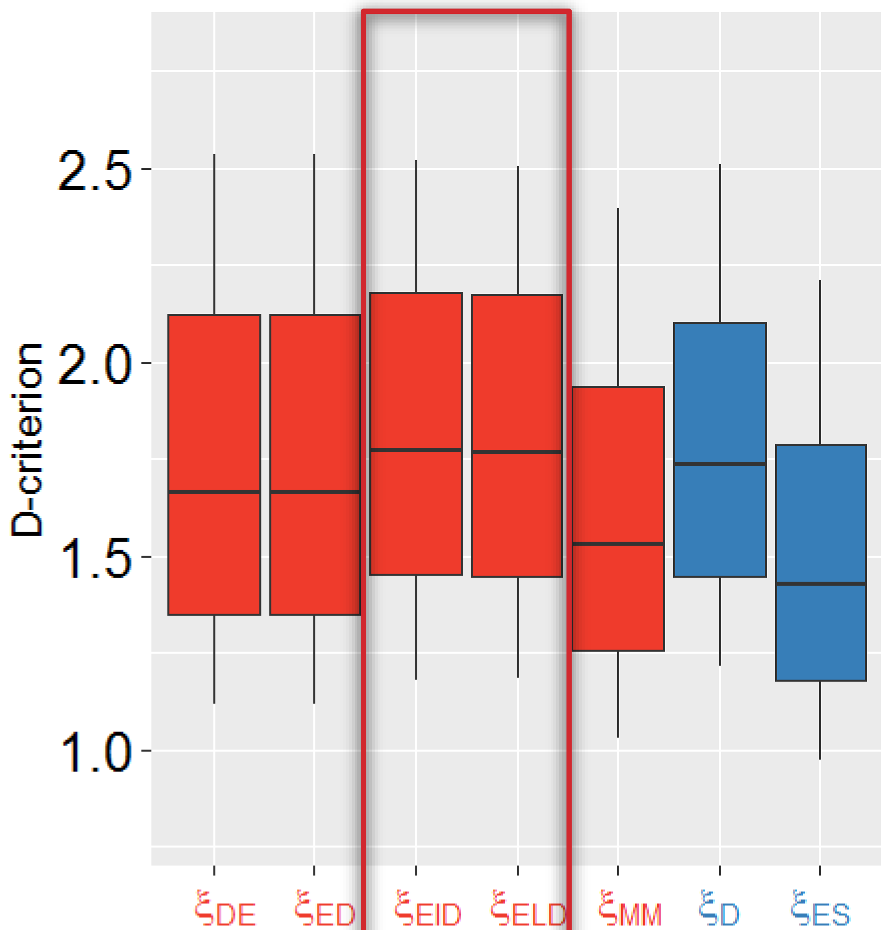
Optimization

- Find the D-optimal design ξ_D using D-criterion for Ψ^*
- Find optimal robust designs $\xi_{DE}, \xi_{ED}, \xi_{EID}, \xi_{ELD}, \xi_{MM}$ using MC with K=1000

Evaluation

- For each optimal design, and for a fixed equispaced design ξ_{ES} compute D-criterion and predicted RSE(%) for each set simulated parameters $\Psi_k,\ k = 1, .., K$

D-criterion distribution for selected designs



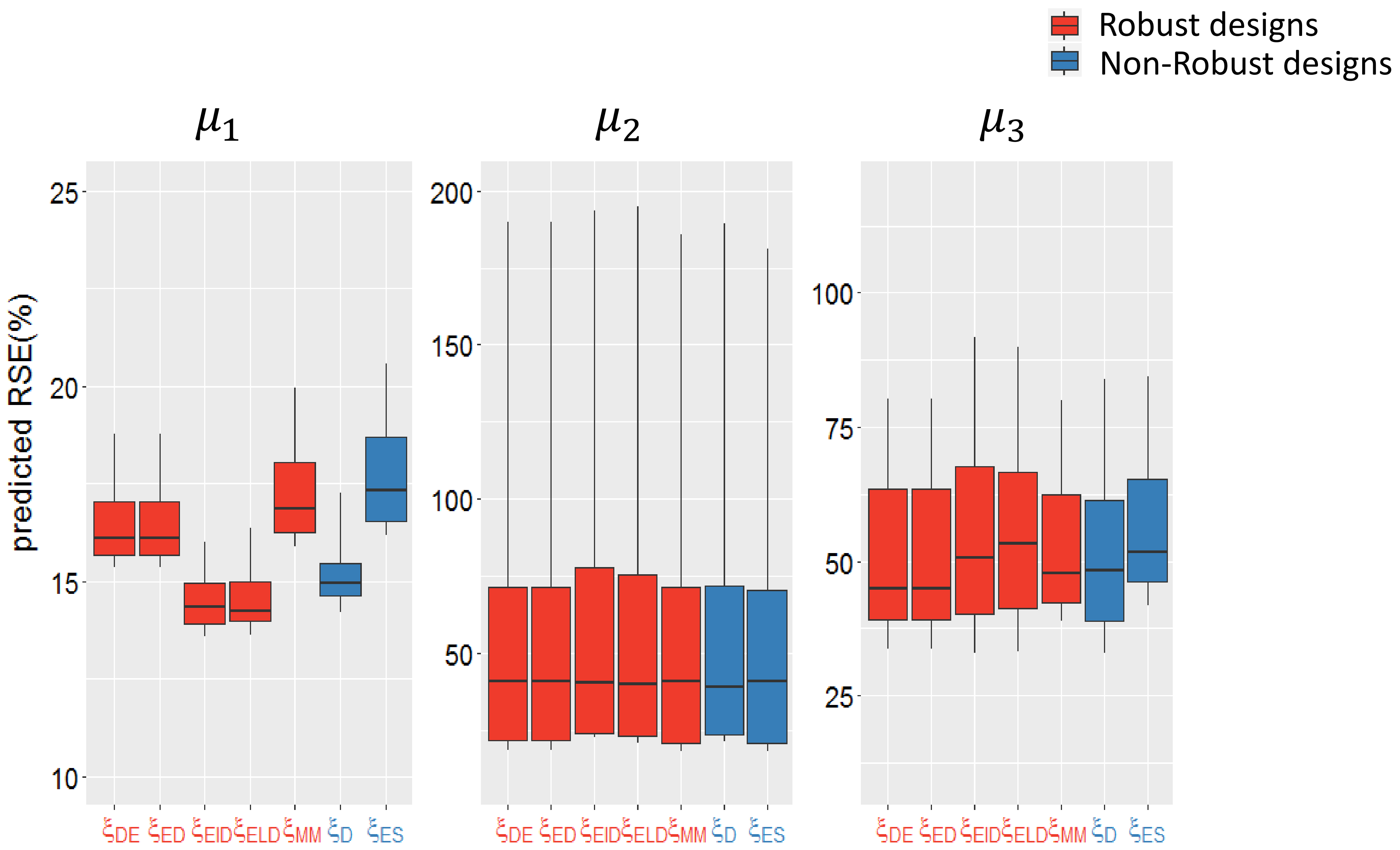
ξ_{DE}	ξ_{ED}	ξ_{EID}	ξ_{ELD}	ξ_{MM}	ξ_{D}	ξ_{ES}
0	0	0	0	0	0	0
2	**2**	**1**	**1**	**3**	**2**	4
7	**7**	**2**	**3**	**8**	**3**	8
12	12	12	12	12	12	12

Robust designs
Non-Robust designs

Best designs with highest median:
ξ_{EID} and ξ_{ELD}

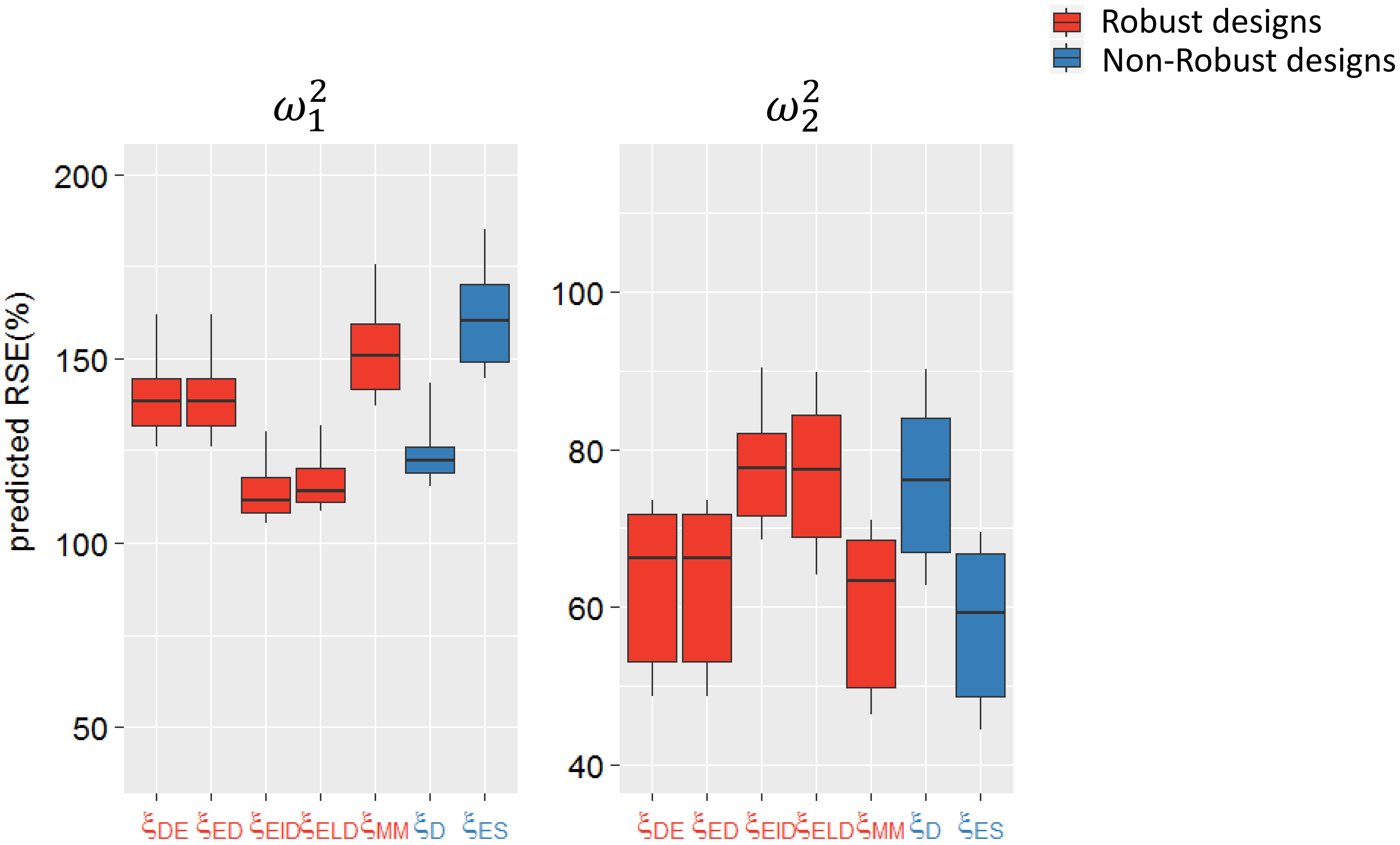
Whiskers of boxplot: 10th and 90th percentiles

Predicted Relative Standard Errors (RSE)



Whiskers of boxplot: 10th and 90th percentiles

Predicted Relative Standard Errors (RSE)



Whiskers of boxplot: 10th and 90th percentiles

Conclusion (Part 2)

- The evaluation of FIM with the new approach is rather fast, allowing for the first time robust design optimization for discrete longitudinal models
- From median of 1000 simulated D-criteria, ξ_{ELD} and ξ_{EID} performed globally the best
- ξ_{ES} has efficiency of 0.82 compare to ξ_{D}. When prior uncertainty is assumed, the efficiency is 0.66 compared to ξ_{ELD}

General conclusions

- All these robust criteria were never systematically compared in NLMEM
- Different criteria led to various optimal designs, with different impact on predicted RSE
- From median of 1000 simulated D-criteria
  - For PKPD model: ELD led to the best designs
  - For longitudinal binary model: ELD and EID led to the best designs (which are very close)

Perspectives

- Perform CTS for binary data example (Part 2)
- Perform robust and adaptive design
- Perform model averaging

Thank You !

Thank you for your attention !

Drug Disease Model Resources

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Back-up

Criteria for robust optimal designs

- For robust design, a distribution for Ψ, $p(\Psi)$, is assumed

Optimal designs		Criteria	Compute Criteria
ξ_{DE}		$\left\|E_{\Psi}\left(M_F(\Psi,\xi)\right)\right\|$	$\left\|\frac{1}{K}\sum_{k=1}^{K}\left(M_F(\Psi_k,\xi)\right)\right\|$
ξ_{ED}		$E_{\Psi}\|M_F(\Psi,\xi)\|$	$\frac{1}{K}\sum_{k=1}^{K}\|M_F(\Psi_k,\xi)\|$
ξ_{EID}	$= \underset{\xi}{argmax}$	$(E_{\Psi}\|M_F(\Psi,\xi)\|^{-1})^{-1}$	$\left(\frac{1}{K}\sum_{k=1}^{K}\|M_F(\Psi_k,\xi)\|^{-1}\right)^{-1}$
ξ_{ELD}		$E_{\Psi}[log\|M_F(\Psi,\xi)\|]$	$\frac{1}{K}\sum_{k=1}^{K}log\|M_F(\Psi_k,\xi)\|$
ξ_{MM}		$min_{\Psi}\|M_F(\Psi,\xi)\|$	$min_{k(k=1,\ldots K)}\|M_F(\Psi_k,\xi)\|$