Using Hamiltonian Monte-Carlo to design longitudinal count studies accounting for parameter and model uncertainties

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Integrated DEsign and AnaLysis of small population group trials

Contents

Designs in pharmacometrics

- Last decades: several methods/software for **maximum likelihood estimation** of population parameters from **longitudinal data** using **nonlinear mixed effect models** (NLMEM)
- Problem beforehand: **choice of "population" design**
  - To obtain precise estimates / adequate power
    - number of individuals (N) ?
    - number of sampling times/individual (n)?
    - allocation of sampling times?
    - other design variables (doses, etc.)
  - **Clinical trial simulation (CTS)**: time consuming
  - Asymptotic theory: **expected Fisher Information Matrix** [1] (FIM)

[1] Mentré et al. *Biometrika*, 1997.

Fisher Information Matrix in NLMEM

- **Analytical expression for FIM in NLMEM**
  - Current approach in PFIM [2] and other design software programs [3]: first order linearisation of model around the expectation of random effects (FO)
    - Only for continuous data
    - Performs well but has limitations in case of complex nonlinear models and/or large variability
- **FIM for discrete longitudinal data**:
  - Methods based on approximations [4,5]
  - We propose new approaches for computation of FIM
    - Monte Carlo - Adaptive Gaussian Quadrature (MC-AGQ)[6]
    - Monte Carlo - Hamiltonian Monte Carlo (MC-HMC)[7]

  These approaches:
    - Without model linearisation
    - Evaluated and compared to CTS and Laplace approx. on 4 longitudinal data types: continuous, binary, count, time to event

[2] PFIM group, www.pfim.biostat.fr.

[3] Nyberg et al. *Br J Clin Pharmacol*, 2014.

[4] Waite and Woods. *Biometrika*, 2015.

[5] Ogungbenro and Aarons. *J Pharmacokinet Pharmacodyn*, 2011.

[6] Ueckert and Mentré. *Comput Stat Data Anal*, 2016.

[7] Riviere, Ueckert and Mentré. *Biostatistics*, 2016.

Parameter and model uncertainty in designs

- **Optimal design depends on knowledge on model and parameters**
  - Local planification: given the model m and parameter values Ψ_m^*
  - Widely used criterion: D-optimality
- **Alternative: Robust designs**
  - Taking into account uncertainty on parameters
  - Across a set of candidate models
  - Example in dose-response study proposed [8, 9] and implemented in MCP-MOD [10]

[8] Bretz, Pinheiro and Branson. *Biometrics*, 2005.

[9] Pinheiro et al. *Stat Med*, 2014.

[10] Bornkamp et al, cran.r-project.org/web/packages/MCPMod/index.html

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NLMEM: Notations

For continuous data:
$y_i = f(g(\mu, b_i), \xi_i) + \epsilon_i$

For discrete data:
$p(y_i|b_i) = \prod_{j=1}^{n_i} h(y_{ij}, g(\mu, b_i), \xi_i)$

with

- $y_i = (y_{i1}, \ldots, y_{in_i})^T$ response for individual i ($i = 1, \ldots, N$)
- f, h structural model
- ξ_i elementary design for subject i
- $\beta_i = g(\mu, b_i)$ individual parameters vector
- μ vector of fixed effects
- b_i vector of random effects for individual i, $b_i \sim \mathcal{N}(0, \Omega)$
- ϵ_i vector of residual errors, $\epsilon_i \sim \mathcal{N}(0, \Sigma)$ and Σ diagonal matrix
- Ψ: Population parameters (μ, ω, σ)

$p(y_i|b_i) = \mathcal{N}(f, \Sigma)$

MC-HMC method for computation of FIM in NLMEM

Population FIM for one group design: $\mathcal{M}(\Psi,\Xi) = N \times \mathcal{M}(\Psi,\xi)$
Population design $\Xi = \{\xi, N\}$ with identical elementary design ξ in all N subjects

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

$$\mathcal{M}(\psi,\xi)_{k,l} = E_y\left(\underbrace{\frac{\partial \log(L(y,\psi))}{\partial \psi_k}\frac{\partial \log(L(y,\psi))}{\partial \psi_l}^T}_{D_y}\right)$$

Monte Carlo - MC

After calculation... $D_y \Longleftrightarrow$

$$\int_{b_1} \frac{\partial\left(\log(p(y|b_1,\psi)p(b_1|\psi))\right)}{\partial \psi_k}\frac{p(y|b_1,\psi)p(b_1|\psi)}{\int p(y|b,\psi)p(b|\psi)db}db_1 . \int_{b_2} \frac{\partial\left(\log(p(y|b_2,\psi)p(b_2|\psi))\right)}{\partial \psi_l}\frac{p(y|b_2,\psi)p(b_2|\psi)}{\int p(y|b,\psi)p(b|\psi)db}db_2$$

MC-HMC method for computation of FIM in NLMEM

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

$$\mathcal{M}(\psi,\xi)_{k,l} = E_y\left(\underbrace{\frac{\partial \log(L(y,\psi))}{\partial\psi_k}\frac{\partial \log(L(y,\psi))}{\partial\psi_l}^T}_{D_y}\right)$$

Monte Carlo - MC

After calculation... $D_y \Longleftrightarrow$

$$\int_{b_1}\frac{\partial\big(\log(p(y|b_1,\psi)p(b_1|\psi))\big)}{\partial\psi_k}\underbrace{\frac{p(y|b_1,\psi)p(b_1|\psi)}{\int p(y|b,\psi)p(b|\psi)db}}_{\substack{\text{conditional density}\\ \text{of } b \text{ given } y}}db_1 . \int_{b_2}\frac{\partial\big(\log(p(y|b_2,\psi)p(b_2|\psi))\big)}{\partial\psi_l}\underbrace{\frac{p(y|b_2,\psi)p(b_2|\psi)}{\int p(y|b,\psi)p(b|\psi)db}}_{\substack{\text{conditional density}\\ \text{of } b \text{ given } y}}db_2$$

MC-HMC method for computation of FIM in NLMEM

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

$$\mathcal{M}(\psi,\xi)_{k,l} = E_y\left(\underbrace{\frac{\partial \log(L(y,\psi))}{\partial \psi_k}\frac{\partial \log(L(y,\psi))}{\partial \psi_l}^T}_{D_y}\right)$$

Monte Carlo - MC

After calculation... $D_y \Longleftrightarrow$

$$\int_{b_1}\frac{\partial\left(\log(p(y|b_1,\psi)p(b_1|\psi))\right)}{\partial\psi_k}\underbrace{\frac{p(y|b_1,\psi)p(b_1|\psi)}{\int p(y|b,\psi)p(b|\psi)db}}_{\text{conditional density of } b \text{ given } y}db_1.\int_{b_2}\frac{\partial\left(\log(p(y|b_2,\psi)p(b_2|\psi))\right)}{\partial\psi_l}\underbrace{\frac{p(y|b_2,\psi)p(b_2|\psi)}{\int p(y|b,\psi)p(b|\psi)db}}_{\text{conditional density of } b \text{ given } y}db_2$$

$$E\left(\frac{\partial(\log(p(y|b,\psi)p(b|\psi)))}{\partial\psi_k}\middle|Y\right).E\left(\frac{\partial(\log(p(y|b,\psi)p(b|\psi)))}{\partial\psi_l}\middle|Y\right)$$

Markov Chains Hamiltonian Monte Carlo - MC-HMC

$\Rightarrow$ **Two integrals to compute: w.r.t. y and w.r.t. b**

The (k,l) term of the FIM estimated as:

$$\tilde{\mathcal{M}}(\psi,\xi)_{k,l} = \frac{1}{R}\sum_{r=1}^{R} A_{k,r}^{(1)}.A_{l,r}^{(2)}$$

with
$$A_{k,r}^{(1)} = \frac{1}{M}\sum_{m=1}^{M} \frac{\partial\left(\log(p(y_r|b_{m,r}^{(1)},\psi)\,p(b_{m,r}^{(1)}))\right)}{\partial\psi_k}$$
$$A_{l,r}^{(2)} = \frac{1}{M}\sum_{m=1}^{M} \frac{\partial\left(\log(p(y_r|b_{m,r}^{(2)},\psi)\,p(b_{m,r}^{(2)}))\right)}{\partial\psi_l}$$

where

- $(y_r)_{r=1,\dots,R}$ is a R-sample of the marginal distribution of y *(MC)*
- $(b_{m,r}^{(1)})_{m=1,\dots,M}$ and $(b_{m,r}^{(2)})_{m=1,\dots,M}$ are $2R$ M-samples of the conditional density of b given y_r *(HMC)*

To be symmetric $\Rightarrow \hat{\mathcal{M}}(\psi,\xi) = \frac{\tilde{\mathcal{M}}(\psi,\xi)+\tilde{\mathcal{M}}(\psi,\xi)^T}{2}$

Use of MC and **Hamiltonian Monte Carlo (HMC) (in Stan** [11]) [7]

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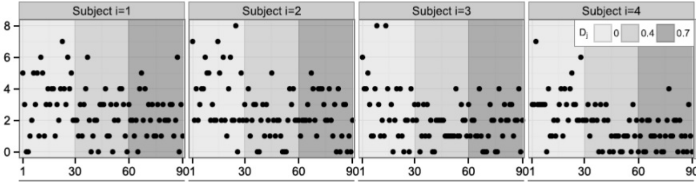
[7] Riviere, Ueckert and Mentré. *Biostatistics*, 2016.

[11] Stan Development Team. Stan: A C++ Library for Probability and Sampling.

Example of count response

Poisson model for repeated count response at several dose levels with a full Imax model describing the relationship between $\log(\lambda)$ and dose [7]

$$P(y = k|b) = \frac{\lambda^k exp(-\lambda)}{k!} \qquad \text{with } \log(\lambda) = \beta_1\left(1 - \frac{d}{d+\beta_2}\right)$$



- $\beta_p = \mu_p exp(b_p)$; $b_p \sim \mathcal{N}(0, \omega_p^2)$
- d: dose among 3 levels $\{0, 0.4, 0.7\}$
- $N = 20$ subjects, $n_{rep} = 30$ replications/subject/dose

Parameters	Ψ^*
μ_1	1
μ_2	0.5
ω_1	0.3
ω_2	0.3

[7] Riviere, Ueckert and Mentré. *Biostatistics*, 2016.

Example of count response: FIM evaluation

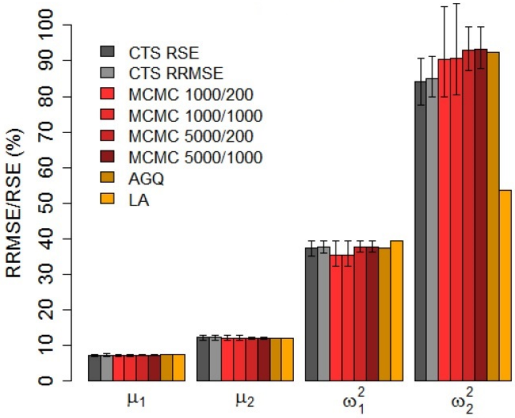
We compared 3 approaches:

- MCMC-based approach (package *MIXFIM*)
  - 1000 MC / 200 MCMC with 500 burn
  - 1000 MC / 1000 MCMC with 1000 burn
  - 5000 MC / 200 MCMC with 500 burn
  - 5000 MC / 1000 MCMC with 1000 burn
- Adaptive Gaussian Quadrature (AGQ) implemented in R
- Laplace approximation (LA) ($\Longleftrightarrow$ AGQ with 1 node)

with clinical trial simulations (CTS):

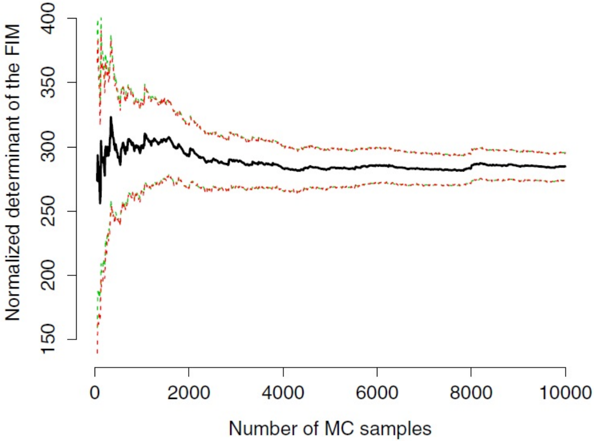
- Simulate 1000 datasets Y with $\Psi = \Psi_T$ using R
- For each Y: estimate $\hat{\Psi}$ using Monolix 4.3

Example of count response: RSE/RRMSE [7]



[7] Riviere, Ueckert and Mentré. *Biostatistics*, 2016.

Example of count response: convergence of the normalized determinant of the FIM

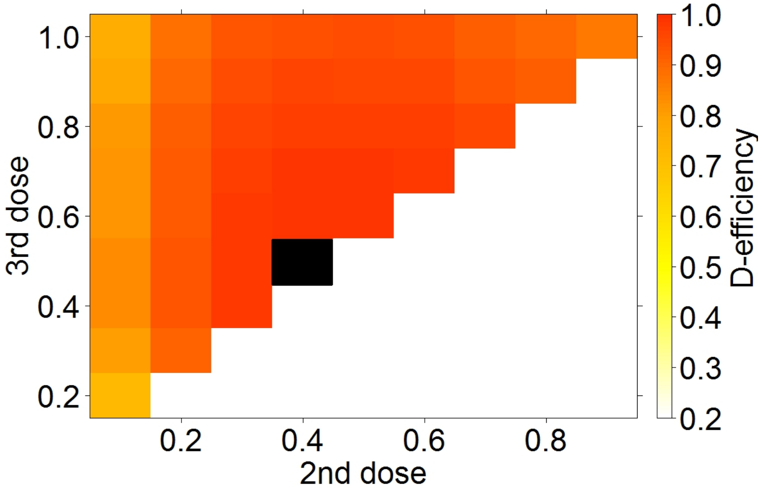


The number of MCMC samples M is fixed at 200 with 500 burn-in.

Example of count response: design optimization

		Count example
Constraints	N n_{rep} n	60 subjects 10 replications 3 doses
	choice of doses	$d_1 = 0$ (placebo) d_2, d_3 from 0.1 to 1 ($step = 0.1$, no repetition)
Combinatorial optimization	Evaluation of FIM for all possible designs	5000 MC 200 HMC
	D-efficiency	$\text{D-eff}(\Xi) = \frac{\Phi_D(\Xi)}{\Phi_D(\Xi_D)}$

D-optimal design for count data: Results



Optimal doses: $\xi_D = \{0, 0.4, 0.5\}$.

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Robustness w.r.t. parameters: method

Robustness w.r.t. parameters of a given model

- Robust FIM, assuming a distribution $p(\Psi)$ on the parameters

$$\mathcal{M}_R(\Xi) = E_\Psi(\mathcal{M}(\Psi, \Xi))$$

  - two integrals **w.r.t.** $\boldsymbol{y}$ and **w.r.t.** $\boldsymbol{b}$ for evaluation of $\mathcal{M}(\Psi, \Xi)$
  - one supplementary integral **w.r.t.** $\boldsymbol{\Psi}$ for evaluation of $\mathcal{M}_R(\Xi)$

- Evaluation by **MC-HMC** using Stan (drawing jointly Ψ and y by MC)

Robustness w.r.t. parameters: method (2)

Robustness w.r.t. parameters of a given model

- Using robust FIM (5000 MC - 200 HMC)
- Using DE-criterion for robust design Ξ_{DE}

$$\Phi_{DE}(\Xi) = \det(\mathscr{M}_R(\Xi))^{1/P}$$

with P, number of population parameters of the model

Implementation

- in R using Stan : extension of MIXFIM

Application to count data example

- Comparison between Ξ_D vs Ξ_{DE} in terms of
  - Allocation of optimal doses
  - Relative efficiencies

$$\text{D-eff}(\Xi) = \frac{\Phi_D(\Xi)}{\Phi_D(\Xi_D)} \quad \text{and} \quad \text{DE-eff}(\Xi_D) = \frac{\Phi_{DE}(\Xi)}{\Phi_{DE}(\Xi_{DE})}$$

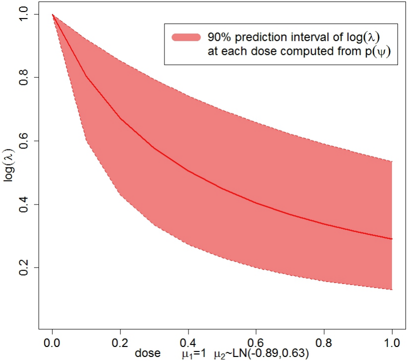
where

$$\phi_D(\Xi) = \det(\mathscr{M}(\psi^*, \Xi))^{1/P} \quad \text{and} \quad \phi_{DE}(\Xi) = \det(\mathscr{M}(p(\psi), \Xi))^{1/P}$$

Robustness w.r.t. parameters: count data example

Poisson model for repeated count outcome at several dose levels with a full Imax model describing the relationship between $\log(\lambda)$ and dose

$$P(y=k|b) = \frac{\lambda^k exp(-\lambda)}{k!} \qquad \text{with } \log(\lambda) = \beta_1\left(1 - \frac{d}{d+\beta_2}\right)$$



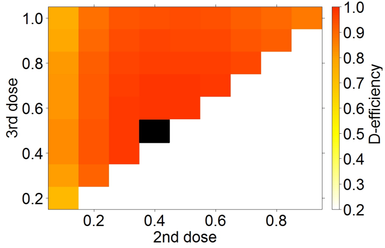
- $\beta_p = \mu_p exp(b_p)$; $b_p \sim \mathcal{N}(0,\omega_p^2)$
- Assuming uncertainty on parameters μ_2 and ω_2

	Ψ^*	$p(\Psi)$
μ_1	1	1
μ_2	0.5	$\mathcal{LN}(-0.89, 0.63)$ $E(\mu_2) = 0.5$; $CV(\mu_2) = 70\%$
ω_1	0.3	0.3
ω_2	0.3	$\mathcal{LN}(-1.50, 0.77)$ $E(\omega_2) = 0.3$; $CV(\omega_2) = 90\%$

- Optimization of 3 doses with $N = 60$, $n_{rep} = 10$
  - fixing $d_1 = 0$
  - choosing d_2 and d_3 from 0 to 1

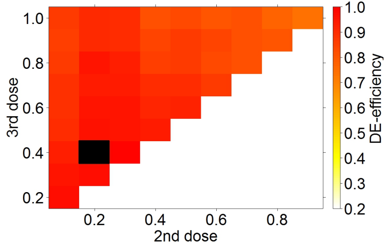
Robustness w.r.t. parameters: count data example

$$\text{D-eff}(\Xi) = \frac{\Phi_D(\Xi)}{\Phi_D(\Xi_D)}$$



Optimal doses: $\xi_D = \{0, 0.4, 0.5\}$.

$$\text{DE-eff}(\Xi_D) = \frac{\Phi_{DE}(\Xi)}{\Phi_{DE}(\Xi_{DE})}$$



Optimal doses: $\xi_{DE} = \{0, 0.2, 0.4\}$.

Efficiencies

Design Ξ	D-eff(Ξ)	DE-eff(Ξ)
$\boldsymbol{\Xi_D}$ $\{N = 60, \xi = (0, 0.4, 0.5)\}$	100%	94.1%
$\boldsymbol{\Xi_{DE}}$ $\{N = 60, \xi = (0, 0.2, 0.4)\}$	93.3%	100%

Robustness w.r.t. a set of M candidate models: method

- Using FIM (5000 MC - 200 HMC)
- Using D-criterion for of optimal design $\Xi_{D,m}$ for each model m

$$\Phi_{D,m}(\Xi) = \det(\mathcal{M}(\Psi^*_m, \Xi))^{1/P_m}$$

- Compound D-criterion [12], [13] for of common design Ξ_{CD}

$$\Phi_{CD}(\Xi) = \prod_{m=1}^{M} \Phi_{D,m}(\Xi)^{\alpha_m} = \prod_{m=1}^{M} \left(\det(\mathcal{M}(\Psi^*_m, \Xi))\right)^{\alpha_m/P_m}, \text{ with}$$

  - P_m, number of population parameters of model m
  - α_m, weight quantifying the balance between M models, $\sum_m \alpha_m = 1$

Implementation in R

- Use of compound optimality criterion to combine several models

[12] Atkinson et al. *J Stat Plan Inference*, 2008.

[13] Nguyen et al. *Pharm Stat*, 2016.

Robustness w.r.t. a set of M candidate models: method

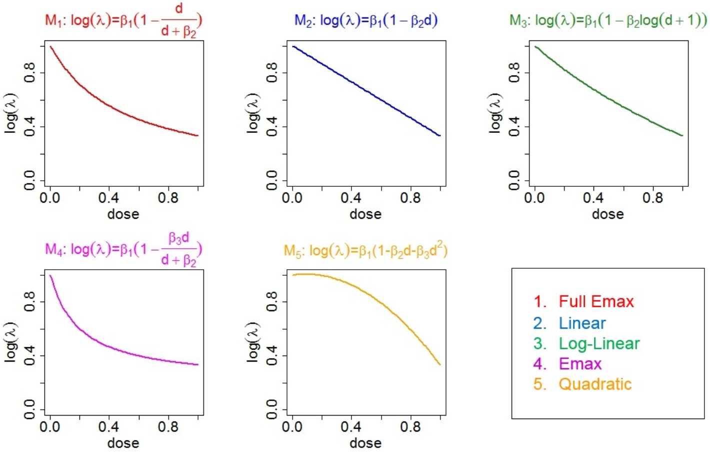
Application to design in a count example

Robust optimal design across M candidate models

- Using FIM by MC-HMC and compound D-optimality ($\alpha_m = 1/M$)
- Comparison between $\Xi_{D,m}$ vs Ξ_{CD} in terms of
  - Allocation of optimal doses
  - Relative efficiencies

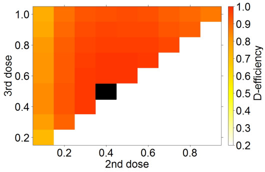
$$\text{D-eff}_m(\Xi) = \frac{\Phi_{D,m}(\Xi)}{\Phi_{D,m}(\Xi_{D,m})} \qquad \text{and} \qquad \text{CD-eff}(\Xi) = \frac{\Phi_{CD}(\Xi)}{\Phi_{CD}(\Xi_{CD})}$$

Robust design for count data: 5 candidate models

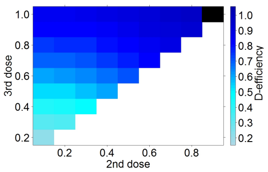


- Fixed effects μ_1, μ_2 for M2, M3, M4 chosen to have similar mean value of $\log(\lambda)$ as for M1 at dose 0 and at dose 1
- Variability $\omega_1 = \omega_2 = 0.3$ and $\omega_3 = 0$

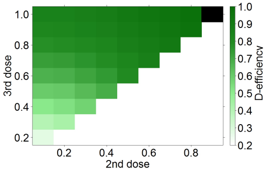
Robust design w.r.t model: application on count data



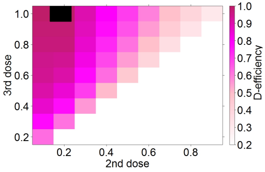
Optimal doses: $\xi_{D,1} = \{0, 0.4, 0.5\}$.



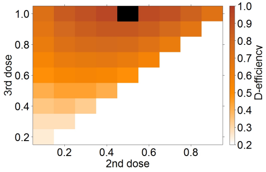
Optimal doses: $\xi_{D,2} = \{0, 0.9, 1\}$.



Optimal doses: $\xi_{D,3} = \{0, 0.9, 1\}$.



Optimal doses: $\xi_{D,4} = \{0, 0.2, 1\}$.



Optimal doses: $\xi_{D,5} = \{0, 0.5, 1\}$.

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

Robust design w.r.t model: application on count data

D-efficiencies

$$\text{D-eff}_m(\Xi) = \frac{\Phi_{D,m}(\Xi)}{\Phi_{D,m}(\Xi_{D,m})}$$

Design Ξ	$\text{D-eff}_1(\Xi)$	$\text{D-eff}_2(\Xi)$	$\text{D-eff}_3(\Xi)$	$\text{D-eff}_4(\Xi)$	$\text{D-eff}_5(\Xi)$
$\Xi_{\boldsymbol{D,1}}$ $\{N=60, \xi=(0,0.4,0.5)\}$	100%	60.8%	68.9%	50.3%	27.7%
$\Xi_{\boldsymbol{D,2}}$ $\{N=60, \xi=(0,0.9,1)\}$	87.0%	100%	100%	30.8%	67.2%
$\Xi_{\boldsymbol{D,3}}$ $\{N=60, \xi=(0,0.9,1)\}$	87.0%	100%	100%	30.8%	67.2%
$\Xi_{\boldsymbol{D,4}}$ $\{N=60, \xi=(0,0.2,1)\}$	88.4%	85.7%	85.4%	100%	85.6%
$\Xi_{\boldsymbol{D,5}}$ $\{N=60, \xi=(0,0.5,1)\}$	94.6%	89.9%	91.7%	69.9%	100%

Robust design w.r.t model: application on count data

D-efficiencies

$$\text{D-eff}_m(\Xi) = \frac{\Phi_{D,m}(\Xi)}{\Phi_{D,m}(\Xi_{D,m})}$$

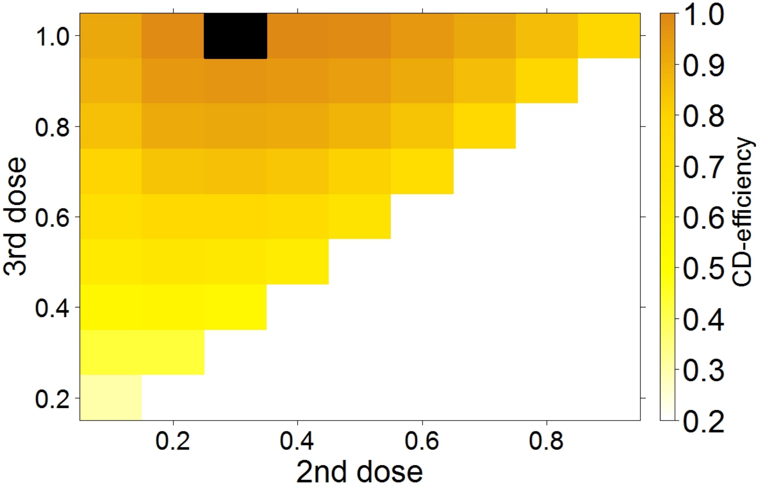
Design Ξ	D-eff$_1$ (Ξ)	D-eff$_2$ (Ξ)	D-eff$_3$ (Ξ)	D-eff$_4$ (Ξ)	D-eff$_5$ (Ξ)
$\Xi_{D,1}$ $\{N=60, \xi=(0, 0.4, 0.5)\}$	100%	60.8%	68.9%	50.3%	27.7%
$\Xi_{D,2}$ $\{N=60, \xi=(0, 0.9, 1)\}$	87.0%	100%	100%	30.8%	67.2%
$\Xi_{D,3}$ $\{N=60, \xi=(0, 0.9, 1)\}$	87.0%	100%	100%	30.8%	67.2%
$\Xi_{D,4}$ $\{N=60, \xi=(0, 0.2, 1)\}$	88.4%	85.7%	85.4%	100%	85.6%
$\Xi_{D,5}$ $\{N=60, \xi=(0, 0.5, 1)\}$	94.6%	89.9%	91.7%	69.9%	100%

- Important loss of efficiency in some scenarios where the model is not correctly pre-specified

Robust design w.r.t model: application on count data

Compound D-optimal design: $\xi_{CD} = (0, 0.3, 1)$.

$$\text{CD-eff}(\Xi) = \frac{\Phi_{CD}(\Xi)}{\Phi_{CD}(\Xi_{CD})}$$



Robust design for count data: 5 candidate models

D-efficiencies

$$\text{D-eff}_m(\Xi) = \frac{\Phi_{D,m}(\Xi)}{\Phi_{D,m}(\Xi_{D,m})}$$

CD-efficiencies

$$\text{CD-eff}(\Xi) = \frac{\Phi_{CD}(\Xi)}{\Phi_{CD}(\Xi_{CD})}$$

Design Ξ	D-eff$_1$ (Ξ)	D-eff$_2$ (Ξ)	D-eff$_3$ (Ξ)	D-eff$_4$ (Ξ)	D-eff$_5$ (Ξ)	CD-eff (Ξ)
$\Xi_{D,1}$ $\{N=60, \xi=(0,0.4,0.5)\}$	100%	60.8%	68.9%	50.3%	27.7%	65.1%
$\Xi_{D,2}$ $\{N=60, \xi=(0,0.9,1)\}$	87.0%	100%	100%	30.8%	67.2%	82.3%
$\Xi_{D,3}$ $\{N=60, \xi=(0,0.9,1)\}$	87.0%	100%	100%	30.8%	67.2%	82.3%
$\Xi_{D,4}$ $\{N=60, \xi=(0,0.2,1)\}$	88.4%	85.7%	85.4%	100%	85.6%	98.0%
$\Xi_{D,5}$ $\{N=60, \xi=(0,0.5,1)\}$	94.6%	89.9%	91.7%	69.9%	100%	98.5%
Ξ_{CD} $\{N=60, \xi=(0,0.3,1)\}$	94.1%	88.1%	88.5%	79.7%	93.1%	100.0%

- Good performance of the compound D-optimal design

Robustness w.r.t. model and parameters: method

- Using robust FIM (5000 MC - 200 HMC)
- Using DE-criterion for robust design for each model M_m, $\Xi_{DE,m}$

$$\Phi_{DE,m}(\Xi) = \det(\mathcal{M}_R(\Xi))^{1/P_m}$$

with P_m, number of population parameters of the model M_m

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

$$\Phi_{CDE}(\Xi) = \prod_{m=1}^{M} \Phi_{DE,m}(\Xi)^{\alpha_m} = \prod_{m=1}^{M} (\det(\mathcal{M}_R(\Xi))^{\alpha_m/P_m}$$

Implementation

- in R using Stan : extension of MIXFIM

Application to count data example

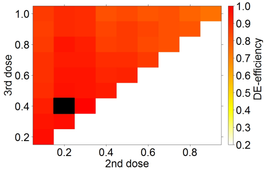
- Comparison between Ξ_{CD} and Ξ_{CDE} and between $\Xi_{DE,m}$ and Ξ_{CDE} in terms of

  - Allocation of optimal doses

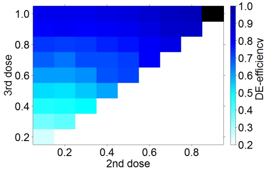
  - Relative efficiencies

$$\text{CDE-eff}(\Xi) = \frac{\Phi_{CDE}(\Xi)}{\Phi_{CDE}(\Xi_{CDE})}$$

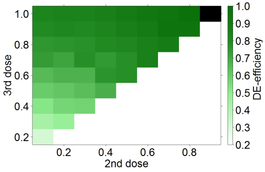
Robust design w.r.t model and parameters: application on count data



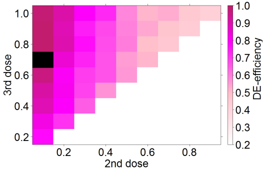
Optimal doses: $\xi_{DE,1} = \{0, 0.2, 0.4\}$.



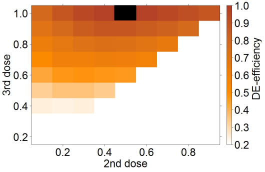
Optimal doses: $\xi_{DE,2} = \{0, 0.9, 1\}$.



Optimal doses: $\xi_{DE,3} = \{0, 0.9, 1\}$.



Optimal doses: $\xi_{DE,4} = \{0, 0.1, 0.7\}$.



Optimal doses: $\xi_{DE,5} = \{0, 0.5, 1\}$.

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

Robust design w.r.t model and parameters: application on count data

DE-efficiencies

$$\text{DE-eff}_m(\Xi) = \frac{\Phi_{DE,m}(\Xi)}{\Phi_{DE,m}(\Xi_{DE,m})}$$

Design Ξ	DE-eff$_1$ (Ξ)	DE-eff$_2$ (Ξ)	DE-eff$_3$ (Ξ)	DE-eff$_4$ (Ξ)	DE-eff$_5$ (Ξ)
$\Xi_{DE,1}$ $\{N = 60, \xi = (0, 0.2, 0.4)\}$	100%	49.9%	56.7%	77.5%	23.6%
$\Xi_{DE,2}$ $\{N = 60, \xi = (0, 0.9, 1)\}$	73.3%	100%	100%	43.5%	87.1%
$\Xi_{DE,3}$ $\{N = 60, \xi = (0, 0.9, 1)\}$	73.3%	100%	100%	43.5%	87.1%
$\Xi_{DE,4}$ $\{N = 60, \xi = (0, 0.1, 0.7)\}$	89.1%	68.1%	73.9%	100%	51.4%
$\Xi_{DE,5}$ $\{N = 60, \xi = (0, 0.5, 1)\}$	83.1%	87.8%	89.6%	58.5%	100%

Robust design w.r.t model and parameters: application on count data

DE-efficiencies

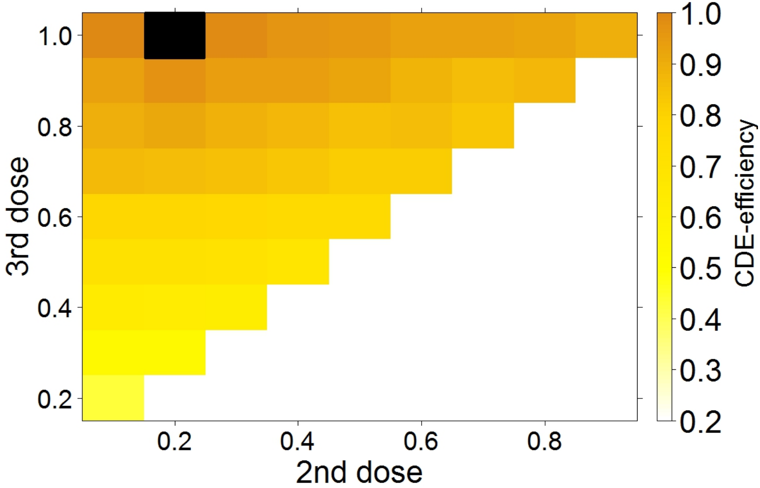
$$\text{DE-eff}_m\,(\Xi) = \frac{\Phi_{DE,m}(\Xi)}{\Phi_{DE,m}(\Xi_{DE,m})}$$

Design Ξ	DE-eff$_1$ (Ξ)	DE-eff$_2$ (Ξ)	DE-eff$_3$ (Ξ)	DE-eff$_4$ (Ξ)	DE-eff$_5$ (Ξ)
$\Xi_{DE,1}$ $\{N=60, \xi=(0,0.2,0.4)\}$	100%	49.9%	56.7%	77.5%	23.6%
$\Xi_{DE,2}$ $\{N=60, \xi=(0,0.9,1)\}$	73.3%	100%	100%	43.5%	87.1%
$\Xi_{DE,3}$ $\{N=60, \xi=(0,0.9,1)\}$	73.3%	100%	100%	43.5%	87.1%
$\Xi_{DE,4}$ $\{N=60, \xi=(0,0.1,0.7)\}$	89.1%	68.1%	73.9%	100%	51.4%
$\Xi_{DE,5}$ $\{N=60, \xi=(0,0.5,1)\}$	83.1%	87.8%	89.6%	58.5%	100%

- Important loss of efficiency in some scenarios where the model is not correctly pre-specified

Robust design w.r.t model and parameters: application on count data

$\text{CDE-eff}(\Xi) = \frac{\Phi_{CDE}(\Xi)}{\Phi_{CDE}(\Xi_{CDE})}$ **Compound DE-optimal design:** $\xi_{CDE} = (0, 0.2, 1)$.



Robust design w.r.t model and parameters: application on count data

Design Ξ	DE-eff$_1$ (Ξ)	DE-eff$_2$ (Ξ)	DE-eff$_3$ (Ξ)	DE-eff$_4$ (Ξ)	DE-eff$_5$ (Ξ)	CDE-eff (Ξ)
$\Xi_{DE,1}$ $\{N = 60, \xi = (0, 0.2, 0.4)\}$	100%	46.9%	56.7%	77.5%	23.6%	63.5%
$\Xi_{DE,2}$ $\{N = 60, \xi = (0, 0.9, 1)\}$	73.3%	100%	100%	43.5%	87.1%	89.9%
$\Xi_{DE,3}$ $\{N = 60, \xi = (0, 0.9, 1)\}$	73.3%	100%	100%	43.5%	87.1%	89.9%
$\Xi_{DE,4}$ $\{N = 60, \xi = (0, 0.1, 0.7)\}$	89.1%	68.1%	73.9%	100%	51.4%	86.6%
$\Xi_{DE,5}$ $\{N = 60, \xi = (0, 0.5, 1)\}$	83.1%	87.8%	89.6%	58.5%	100%	95.8%
Ξ_{CDE} $\{N = 60, \xi = (0, 0.2, 1)\}$	90.9%	83.8%	83.9%	84.6%	82.8%	100.0%
Ξ_{CD} $\{N = 60, \xi = (0, 0.3, 1)\}$	90.0%	83.6%	83.8%	75.9%	94.1%	99.0%

- CDE-optimal design: robust w.r.t model and parameters

Contents

Discussion

Summary

- MC-HMC method for computation of FIM [7] enables applications to design optimization for discrete data
- Extension of this method to propose robust optimal designs accounting for uncertainty w.r.t. parameters and/or models
- Computationally challenging, much slower than FO approach

Perspectives

- Replacement of MC by more efficient approach: quasi-random sampling [14]
- Application to continuous data, and to other type of discrete data (binary, time to event)
- Use in model-based adaptive design, for instance two-stage designs [15], [16]
- Implementation of an optimization algorithm

[7] Riviere, Ueckert and Mentré. *Biostatistics*, 2016.
[14] Ueckert and Mentré. *CM Statistics Conference*, London, UK, 2015.
[15] Dumont, Chenel and Mentré. *Commun Stat Simul Comput*, 2016.
[16] Sinha and Xu. *J Stat Plan Inference*, 2011.

Thank you for your attention