Using Hamiltonian Monte Carlo to design clinical trials with longitudinal data

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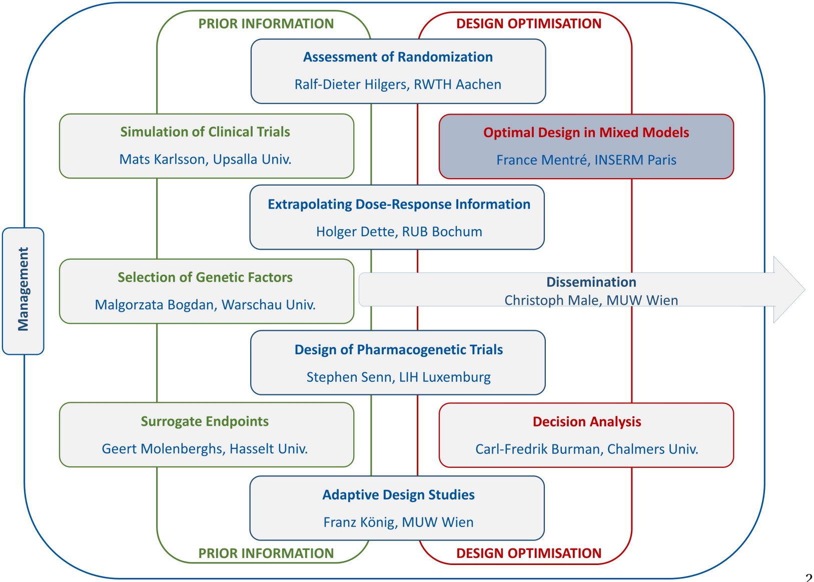
Workpackage structure



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

- **From FIM**
  - Derive predicted Relative Standard Errors (RSE) and/or power
  - Compare and/or optimise designs
- **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
- **New approaches needed for computation of FIM**
  - Without model linearisation
  - For both continuous and discrete data
    ⇒ Monte Carlo - Adaptive Gaussian Quadrature (MC-AGQ)[4, 5]
    ⇒ Monte Carlo - Hamiltonian Monte Carlo (MC-HMC)[6]

[2] PFIM group. www.pfim.biostat.fr.
[3] Nyberg et al. *Br J Clin Pharmacol*, 2014.
[4] Nguyen and Mentré. *Comput Stat Data Anal*, 2014.
[5] Ueckert and Mentré. *Comput Stat Data Anal*, 2016.
[6] 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

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

with the **likelihood**:

$$L(y,\Psi) = \int p(y|b,\Psi)\,p(b|\Psi)\,db$$

where $p(y|b,\Psi)$: pdf of observations y given random effects b
$p(b|\Psi)$: pdf of b

⇒ **Two integrals to compute: w.r.t. y and w.r.t. b**

- Use of **MC** and **AGQ** [5]
- Use of **MC** and **HMC** **(in Stan** [7]**)** [6]

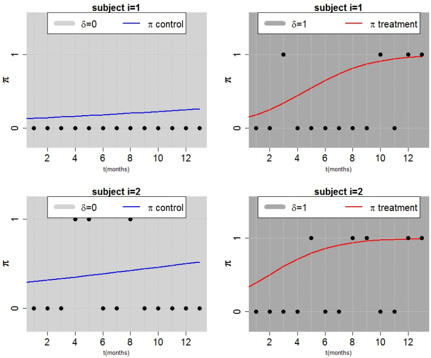
⇒ Both approaches **evaluated by CTS** on several examples (from [8])

[5] Ueckert and Mentré. *Comput Stat Data Anal*, 2016.
[6] Riviere, Ueckert and Mentré. *Biostatistics*, 2016.
[7] Stan Development Team. Stan: A C++ Library for Probability and Sampling.
[8] Ogungbenro et al. *J Pharmacokinet Pharmacodyn*, 2011.

Evaluation by CTS: Example of binary response

Logistic model for repeated binary response at several time points with treatment increasing the slope of the logit of the response with time [5,6,9]

$$\text{logit}(\pi) = \beta_1 + \beta_2(1 + \mu_3\delta)t, \qquad \text{where}$$



- π is the probability of success
- $\beta_p = \mu_p + b_p$; $b_p \sim \mathcal{N}(0, \omega_p^2)$
- t: time among 13 points equally spaced between 0 and 12 months
- 2 treatment groups ($\delta = 0$ & $\delta = 1$)
- $N = 50$ subjects/treatment group

Parameters	Ψ^*
μ_1	-2
μ_2 (month^{-1})	0.09
μ_3	5
ω_1	0.70
ω_2 (month^{-1})	0.17

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

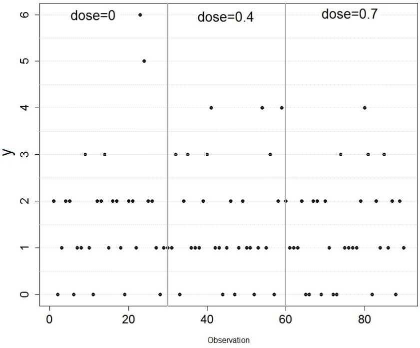
[6] Riviere, Ueckert and Mentré. *Biostatistics*, 2016.

[9] Lestini, Ueckert and Mentré. *PODE*, Uppsala, Sweden, 2016.

Evaluation by CTS: 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 [5,6]

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



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

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

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

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

Evaluation by CTS: Methods

Comparison of several approaches for evaluation of FIM:

- MC-HMC implemented in R package *MIXFIM* available on CRAN [10]
  - 1000 MC / 200 HMC with 500 burn
  - 1000 MC / 1000 HMC with 1000 burn
  - 5000 MC / 200 HMC with 500 burn
  - 5000 MC / 1000 HMC with 1000 burn
- MC-AGQ implemented in R: 5000 MC / 10 AGQ nodes
- Laplace approximation (LA): 5000 MC / 1 AGQ node

with clinical trial simulations (CTS):

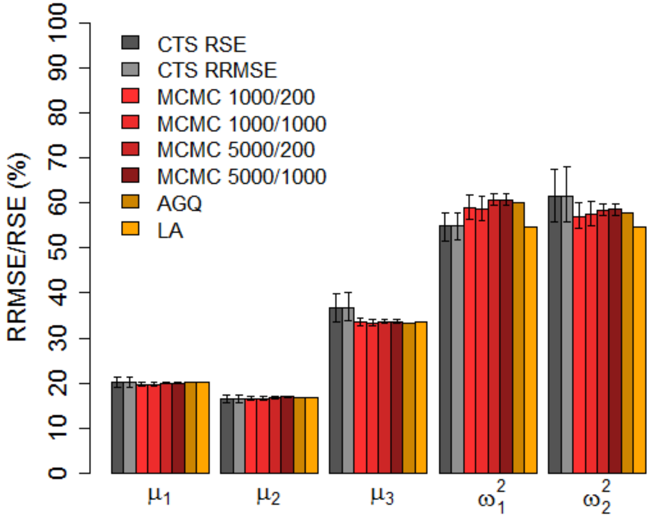
- Simulation of 1000 datasets with $\Psi = \Psi^*$ using R
- For each dataset: estimate $\hat{\Psi}$ using Monolix 4.3

in terms of:

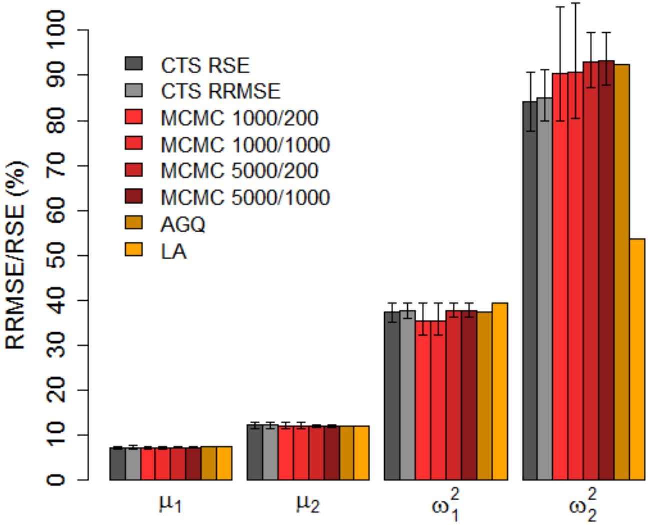
- observed RSE and RRMSE from CTS
- *versus* predicted RSE from expected FIM

[10] Riviere and Mentré. R Package *MIXFIM*, 2015.

Evaluation by CTS: Results for binary example



Evaluation by CTS: Results for count example

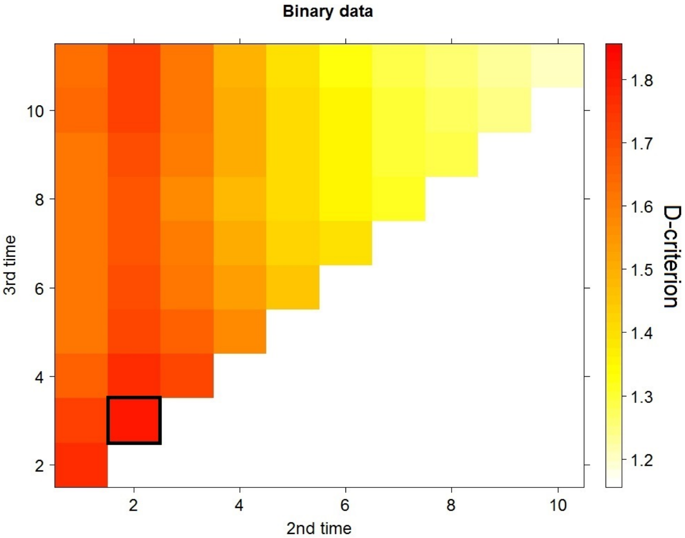


D-optimal designs for discrete data: Methods

		Binary example	Count example
Constraints	N n_{rep} n	100 subjects 1 replication 4 times	60 subjects 10 replications 3 doses
	fixed design variables	$t_1 = 0,\ t_4 = 12$	$d_1 = 0$
	optimised design variables	$t_2,\ t_3$ from 1 to 11 ($step = 1$, no repetition)	$d_2,\ d_3$ from 0.1 to 1 ($step = 0.1$, no repetition)
Optimisation method	Evaluation of FIM for all possible designs	500 Quasi MC [11] 3 AGQ nodes	5000 MC 200 HMC
	D-optimality criterion Φ_D	$\det(\mathscr{M}(\Psi^*,\Xi))^{1/P}$	$\det(\mathscr{M}(\Psi^*,\Xi))^{1/P}$

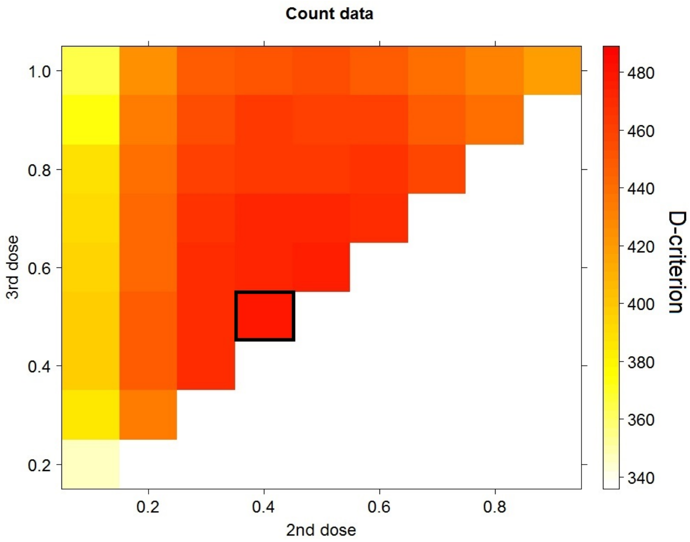
[11] Ueckert and Mentré. *CM Statistics Conference*, London, UK, 2015.

D-optimal designs for discrete data: Results



Optimal times: $\xi_D = (0, 2, 3, 12)$.

D-optimal designs for discrete data: Results



Optimal doses: $\xi_D = (0, 0.4, 0.5)$.

Conclusion (1)

New methods developed for computation of FIM avoiding FO

- MC-AGQ and MC-HMC based methods
  - adapted for continuous and discrete NLMEM
  - high agreement with CTS
  - new tool for designs using MC-HMC: R package *MIXFIM* on CRAN
- Enable first applications to design optimisation for binary and count data

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Methods for Robust designs (1)

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)
- DE-criterion for optimisation of robust design Ξ_{DE}

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

with P, number of population parameters of the model

Methods for Robust designs (2)

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

- D-criterion for optimisation of design $\Xi_{D,m}$ for each model m given population parameter values Ψ^*_m

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

with P_m, number of population parameters of model m

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

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

with α_m, weight quantifying the balance between M models, $\sum_m \alpha_m = 1$

Implementation in R

- Extension of *MIXFIM* for evaluation of robust FIM using MC-HMC
- 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.

Illustration in Robust designs for count data

Application to design optimisation in the previous count example

- **Robust optimal design accounting for uncertainty on parameters**
  - Using robust FIM (5000 MC - 200 HMC) and DE-optimality criterion
  - Comparison between Ξ_D and Ξ_{DE} in terms of
    - Allocation of optimal doses
    - Relative efficiencies of a design Ξ w.r.t. an optimal design

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

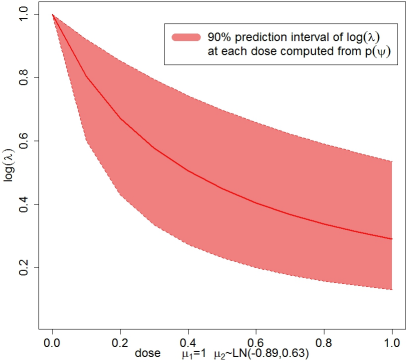
- **Robust optimal design across *M* candidate models**
  - Using FIM by MC-HMC (5000 MC - 200 HMC) and compound D-optimality ($\alpha_m = 1/M$)
  - Comparison between different $\Xi_{D,m}$ and Ξ_{CD} in terms of
    - Allocation of optimal doses
    - Relative efficiencies of a design Ξ w.r.t. an optimal design

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

Robust design for count data: uncertainty on parameters

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

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

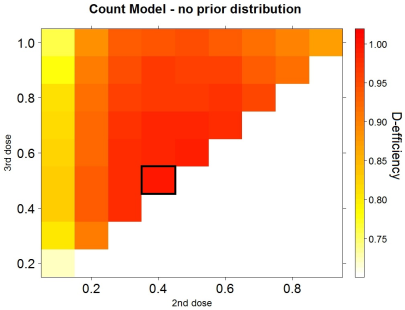


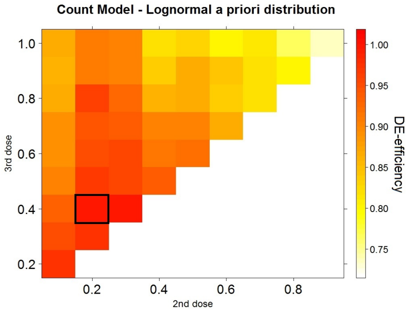
- $\beta_p = \mu_p exp(b_p)$; $b_p \sim \mathcal{N}(0, \omega_p^2)$
- Assuming uncertainty on parameters μ_2 and ω_2

	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	$\mathcal{LN}(-1.50, 0.77)$ $E(\omega_2) = 0.3$; $CV(\omega_2) = 90\%$

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

Robust design for count data: uncertainty on parameters



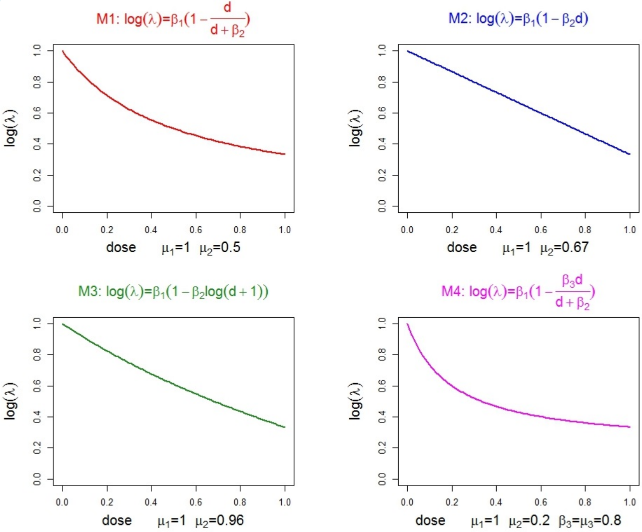


Optimal doses: $\xi_D = (0, 0.4, 0.5)$. **Optimal doses:** $\xi_{DE} = (0, 0.2, 0.4)$.

Efficiencies

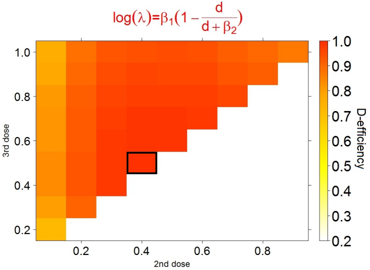
Design Ξ	D-eff(Ξ)	DE-eff(Ξ)
Ξ_D $\{N = 60, \xi = (0, 0.4, 0.5)\}$	100%	94.1%
Ξ_{DE} $\{N = 60, \xi = (0, 0.2, 0.4)\}$	93.3%	100%

Robust design for count data: 4 candidate models

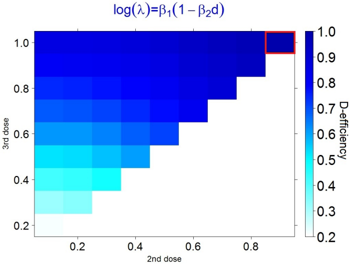


- Fixed effects μ_1, μ_2 for M2, M3, M4 chosen to have similar mean value of $\log(\lambda)$ as for M1 at dose 0 and at dose 1
- Variability $\omega_1 = \omega_2 = 0.3$

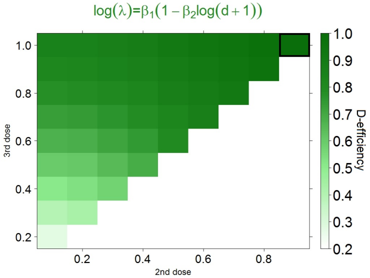
Robust design for count data: 4 candidate models



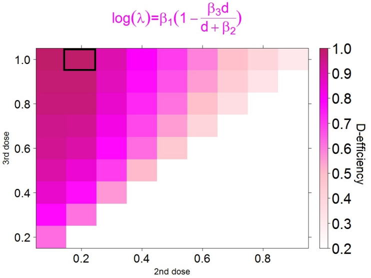
Optimal doses: $\xi_{D,M1} = (0, 0.4, 0.5)$.



Optimal doses: $\xi_{D,M2} = (0, 0.9, 1)$.



Optimal doses: $\xi_{D,M3} = (0, 0.9, 1)$.



Optimal doses: $\xi_{D,M4} = (0, 0.2, 1)$.

Robust design for count data: 4 candidate models

D-efficiencies

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

Design Ξ	D-eff$_{M1}$ (Ξ)	D-eff$_{M2}$ (Ξ)	D-eff$_{M3}$ (Ξ)	D-eff$_{M4}$ (Ξ)
$\boldsymbol{\Xi_{D,M1}}$ $\{N=60, \xi=(0,0.4,0.5)\}$	100%	60.8%	68.9%	50.3%
$\boldsymbol{\Xi_{D,M2}}$ $\{N=60, \xi=(0,0.9,1)\}$	87.0%	100%	100%	30.8%
$\boldsymbol{\Xi_{D,M3}}$ $\{N=60, \xi=(0,0.9,1)\}$	87.0%	100%	100%	30.8%
$\boldsymbol{\Xi_{D,M4}}$ $\{N=60, \xi=(0,0.2,1)\}$	88.4%	85.7%	85.4%	100%

Robust design for count data: 4 candidate models

D-efficiencies

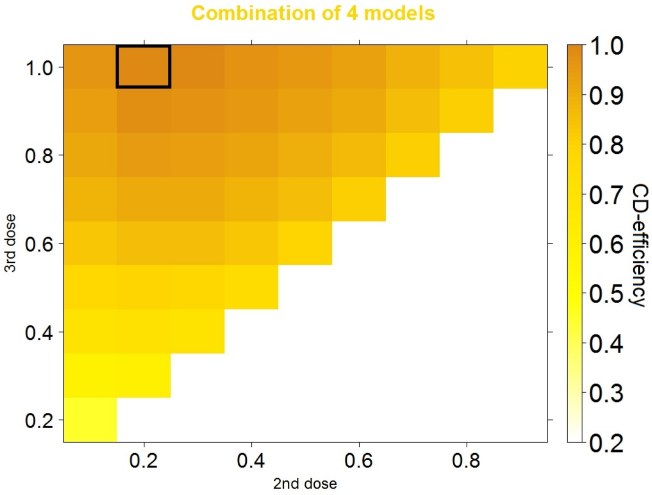
$$\text{D-eff}_m(\Xi) = \frac{\Phi_{D,m}(\Xi)}{\Phi_{D,m}(\Xi_{D,m})}$$

Design Ξ	D-eff$_{M1}(\Xi)$	D-eff$_{M2}(\Xi)$	D-eff$_{M3}(\Xi)$	D-eff$_{M4}(\Xi)$
$\boldsymbol{\Xi_{D,M1}}$ $\{N=60, \xi=(0,0.4,0.5)\}$	100%	60.8%	68.9%	50.3%
$\boldsymbol{\Xi_{D,M2}}$ $\{N=60, \xi=(0,0.9,1)\}$	87.0%	100%	100%	30.8%
$\boldsymbol{\Xi_{D,M3}}$ $\{N=60, \xi=(0,0.9,1)\}$	87.0%	100%	100%	30.8%
$\boldsymbol{\Xi_{D,M4}}$ $\{N=60, \xi=(0,0.2,1)\}$	88.4%	85.7%	85.4%	100%

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

Robust design for count data: 4 candidate models

Compound D-optimal design: $\xi_{CD} = (0, 0.2, 1)$.



Robust design for count data: 4 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	$\text{D-eff}_{M1}(\Xi)$	$\text{D-eff}_{M2}(\Xi)$	$\text{D-eff}_{M3}(\Xi)$	$\text{D-eff}_{M4}(\Xi)$	$\text{CD-eff}(\Xi)$
$\Xi_{D,M1}$ $\{N=60, \xi=(0,0.4,0.5)\}$	100%	60.8%	68.9%	50.3%	75.5%
$\Xi_{D,M2}$ $\{N=60, \xi=(0,0.9,1)\}$	87.0%	100%	100%	30.8%	80.2%
$\Xi_{D,M3}$ $\{N=60, \xi=(0,0.9,1)\}$	87.0%	100%	100%	30.8%	80.2%
$\Xi_{D,M4}$ $\{N=60, \xi=(0,0.2,1)\}$	88.4%	85.7%	85.4%	100%	100%
Ξ_{CD} $\{N=60, \xi=(0,0.2,1)\}$	88.4%	85.7%	85.4%	100%	100%

- Good performance of the compound D-optimal design

Conclusion (2)

- **Proposed methods for Robust designs**
  - Extension of R package *MIXFIM* to compute the DE-optimality criterion from robust FIM
  - Use of compound optimality criterion to combine several candidate models
- **MC-HMC, relevant approach allowing for the first time robust design optimisation for repeated count data**
  - Robustness w.r.t. parameters: different optimal designs with *versus* without uncertainty on parameters
  - Robustness w.r.t. models: compound D-optimal design providing a good compromise for different candidate models
- **Ongoing work**
  - Robustness w.r.t. parameters AND models: use of robust FIM in the compound optimality criterion

Contents

Discussion

Summary

- New methods developed for computation of FIM avoiding FO
  - MC-AGQ and MC-HMC: relevant methods for designs
  - New tool for designs using MC-HMC: R package *MIXFIM* on CRAN
  - Computationally challenging, much slower than FO approach
- Extension of these methods to propose robust optimal designs accounting for uncertainty w.r.t. parameters and/or models

Perspectives

- Replacement of MC in MC-HMC by more efficient approach: quasi-random sampling [11]
- Evaluation of two-stage designs
  - Approaches already proposed and evaluated on continuous data [14, 15]
  - To be evaluated in models for discrete data, accounting for uncertainty w.r.t. parameters and/or models
- Individual and Population Bayesian information matrix

[11] Ueckert and Mentré. *CM Statistics Conference*, London, UK, 2015.

[14] Dumont, Chenel, Mentré. *Commun Stat Simul C*, 2016.

[15] Lestini, Dumont, Mentré. *Pharm Res*, 2015.

Back-up

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)

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

Fisher Information Matrix (FIM)

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

with the likelihood:
$$L(y, \psi) = \int p(y|b, \psi)\, p(b|\psi)\, db$$

where $p(y|b, \psi)$: pdf of y given the random effects b

$p(b|\psi)$: pdf of b

MC-HMC method for FIM evaluation

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

MC-HMC method for FIM evaluation

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

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

Monte Carlo - MC

MC-HMC method for FIM evaluation

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

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

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 FIM evaluation

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

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

Monte Carlo - MC

After calculation... $D_y \Longleftrightarrow$

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

MC-HMC method for FIM evaluation

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

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

Monte Carlo - MC

After calculation... $D_y \Longleftrightarrow$

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

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

Markov Chains Monte Carlo - MCMC

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

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

with

$$A^{(1)}_{k,r} = \frac{1}{M}\sum_{m=1}^{M} \frac{\partial\left(\log(p(y_r|b^{(1)}_{m,r},\psi)\,p(b^{(1)}_{m,r}))\right)}{\partial\psi_k}$$

$$A^{(2)}_{l,r} = \frac{1}{M}\sum_{m=1}^{M} \frac{\partial\left(\log(p(y_r|b^{(2)}_{m,r},\psi)\,p(b^{(2)}_{m,r}))\right)}{\partial\psi_l}$$

where

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

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

MC-HMC method for Robust FIM evaluation

Robust FIM: $\mathcal{M}_R(\xi) = E_\Psi(\mathcal{M}(\Psi, \xi))$

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

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

Monte Carlo - MC - joint sampling of ψ and y

MC-HMC method for Robust FIM evaluation

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

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

Monte Carlo - MC - joint sampling of ψ and y

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

Markov Chains Monte Carlo - MCMC

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

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

with

$$B^{(1)}_{k,r} = \frac{1}{M}\sum_{m=1}^{M} \frac{\partial\left(\log(p(y_r|b^{(1)}_{m,r},\psi_r)p(b^{(1)}_{m,r},\psi_r)\right)}{\partial\psi_k}$$

$$B^{(2)}_{l,r} = \frac{1}{M}\sum_{m=1}^{M} \frac{\partial\left(\log(p(y_r|b^{(2)}_{m,r},\psi_r)p(b^{(2)}_{m,r},\psi_r)\right)}{\partial\psi_l}$$

where

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

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