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

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CONTEXT

The Fisher Information Matrix (FIM) can be used to design longitudinal studies for nonlinear mixed effect models (NLMEM) [1]. A Monte-Carlo Hamiltonian Monte-Carlo (MC/HMC) method has been developed to evaluate the FIM [2], then the D-optimality can be used to optimize designs. This approach however requires a priori knowledge on models and parameters, leading to design that are only locally optimal.

OBJECTIVES

- To extend the MC/HMC-based method to evaluate the FIM in NLMEM accounting for uncertainty in parameters and/or in models
- To illustrate this approach in robust design optimization for repeated count data

METHODS

Notations

M = population Fisher information matrix

M_R = robust population Fisher information matrix

Ξ ={N,ξ} = population design , N = number of individuals

ξ = elementary design (identical in all individuals)

=> To be optimized

ψ_m = population parameter values for model m

P_m = number of population parameters of model m

$p_m(\psi_m)$ = *a priori* population parameter distribution for model m

b = vector of random effects

y = vector of observations for one individual

α_m = weight quantifying balance between M models ($\sum \alpha_m = 1$)

1) Optimal design for given parameter values ψ_m* of a given model *m*

- Evaluation of **FIM** by **MC/HMC** [2]

$$M(\psi_m, \Xi) = N \, x M(\psi_m, \xi)$$

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

with the likelihood $L(y, \psi_m) = \int \underbrace{p(y|b,\psi_m)}_{\text{pdf of observations } y \text{ given random effects } b} \underbrace{p(b|\psi_m)}_{\text{pdf of } b} db$

=>2 integrals to compute: w.r.t y (MC) and w.r.t b (HMC)

- Use of **D-optimality criterion**

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

2) Robust design accounting for parameter uncertainty for a given model *m*

- Evaluation of **robust FIM** by **MC/HMC**

$$M_R(\Xi) = E_{\psi_m}(M(\psi_m, \Xi))$$

- two integrals **w.r.t. *y*** and **w.r.t. *b*** for evaluation of $M(\psi_m, \Xi)$
- one supplementary integral **w.r.t. ψ_m** for evaluation $M_R(\Xi)$

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

- Use of **DE-optimality criterion**

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

3) Robust design accounting for model uncertainty for given parameter values

- Proposition of a set of M candidate models
- Evaluation of **FIM** by **MC/HMC** for each model *m*
- Evaluation of **D-optimality criterion** on each model *m*
- Use of the **Compound D-optimality** criterion [3,4]

$$\Phi_{CD}(\Xi) = \prod_{m=1}^{M} \Phi_{D,m}(\Xi)^{\alpha_m} = \prod_{m=1}^{M} (det(M(\psi_m^*, \Xi)))^{\alpha_m/P_m}$$

4) Robust design accounting for parameter and model uncertainties

- Proposition of a set of M candidate models (m=1,...,M)
- Evaluation of **robust FIM** by **MC/HMC** for each model *m*
- Evaluation of **DE-optimality criterion** on each model *m*
- Use of the **Compound DE-optimality criterion**:

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

5) Implementation

- Extension of R package MIXFIM [5] using Stan to draw HMC samples and to calculate partial derivatives of the log-likelihood [6]
- *Robust_fisher_evaluation()* function to evaluate $M_R(\Xi)$
- *Combin_optimization()* function to perform combinatorial optimization of design elements in ξ
- *Compound_optimality()* function to evaluate the CD and CDE-optimality criteria

APPLICATION TO DESIGN OPTIMIZATION FOR COUNT DATA

Count data example

- Daily count of events that we want to prevent
- Poisson model for repeated count response [2]: $P(y = k|b) = \frac{\lambda^k e^{-\lambda}}{k!}$

λ: mean number of events / day

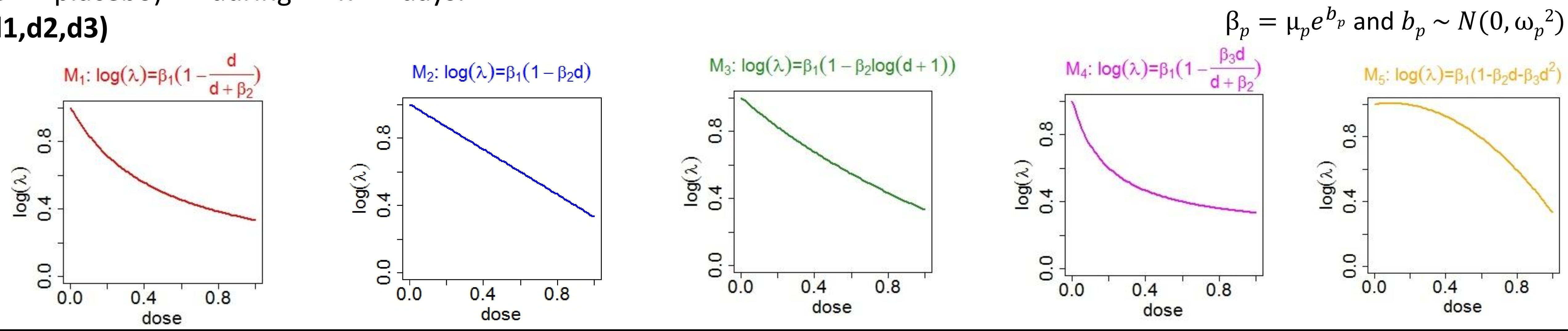
- Each patient observed at 3 dose levels (one placebo) during x days: **ξ=(d1,d2,d3)**

Candidate models

- $M_1: \log(\lambda) = \beta_1(1 - \frac{d}{d+\beta_2})$,
- $M_2: \log(\lambda) = \beta_1(1 - \beta_2 d)$,
- $M_3: \log(\lambda) = \beta_1(1 - \beta_2 \log(d+1))$,
- $M_4: \log(\lambda) = \beta_1\left(1 - \frac{\beta_3 d}{d+\beta_2}\right)$,
- $M_5: \log(\lambda) = \beta_1(-\beta_2 d^2 + \beta_3 d + 1)$.

	ψ_m*					$p_m(\psi_m)$				
	μ_1*	μ_2*	μ_3*	ω_1*	ω_2*	μ_1	μ_2 (CV(μ_2)=70%)	μ_3	ω_1	ω_2 (CV(ω_2)=90%)
M_1	1	0.5		0.3	0.3	1	*LN*(-0.89,0.63)		0.3	*LN*(-1.50,0.77)
M_2	1	0.67		0.3	0.3	1	*LN*(-0.60,0.63)		0.3	*LN*(-1.50,0.77)
M_3	1	0.96		0.3	0.3	1	*LN*(-0.24,0.63)		0.3	*LN*(-1.50,0.77)
M_4	1	0.2	0.8	0.3	0.3	1	*LN*(-1.81,0.63)	0.8	0.3	*LN*(-1.50,0.77)
M_5	1	0.8	0.13	0.3	0.3	1	*LN*(-0.60,0.63)	0.13	0.3	*LN*(-1.50,0.77)

$\beta_p = \mu_p e^{b_p}$ and $b_p \sim N(0, {\omega_p}^2)$

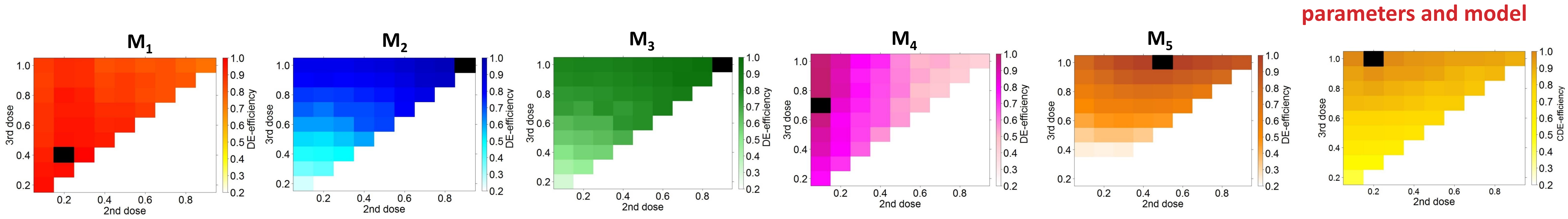


- N=60 subjects, nrep=10 rep/subject/dose
- Combinatorial optimization of 2 dose levels between 0 and 1 with step=0.1, without repetition, with d_1=0 (placebo)
- For computation of M_R: 5000 MC, 200 HMC
- **Robust design optimization w.r.t. parameters and model**

RESULTS

Robust design with respect to parameters for each model

Robust design with respect to parameters and model



$\xi_{DE,1}$=(0,0.2,0.4) $\xi_{DE,2}$=(0,0.9,1) $\xi_{DE,3}$=(0,0.9,1) $\xi_{DE,4}$=(0,0.1,0.7) $\xi_{DE,5}$=(0,0.5,1) ξ_{CDE}=(0,0.2,1)

$$E_{X,m}(\Xi) = \frac{\Phi_{X,m}(\Xi)}{\Phi_{X,m}(\Xi_{X,m})} \quad \text{for X=DE,CDE}$$

	$E_{DE,1}(\Xi)$	$E_{DE,2}(\Xi)$	$E_{DE,3}(\Xi)$	$E_{DE,4}(\Xi)$	$E_{DE,5}(\Xi)$
$\xi_{DE,1}$=(0, 0.2, 0.4)	100%	46.9%	56.7%	77.5%	23.6%
$\xi_{DE,2}$=(0, 0.9, 1)	73.3%	100%	100%	43.5%	87.1%
$\xi_{DE,3}$=(0, 0.9, 1)	73.3%	100%	100%	43.5%	87.1%
$\xi_{DE,4}$=(0, 0.1, 0.7)	89.1%	68.1%	73.9%	100%	51.4%
$\xi_{DE,5}$=(0, 0.5, 1)	83.1%	87.8%	89.6%	58.5%	100%
ξ_{CDE}=(0, 0.2, 1)	90.9%	83.8%	83.9%	84.6%	82.8%

CONCLUSIONS

- Proposition of a new MC/HMC-based method for computation of the FIM avoiding linearization, introducing robustness w.r.t. parameters and/or models
- First applications to design optimization for count data
- Accounting or not for uncertainty in parameters may lead to different allocations of optimal doses but has little impact on efficiencies
- Misspecification of models can lead to low efficiencies
- The CD/CDE-optimal designs provided a good compromise for different candidate models

PERSPECTIVES

- Replacement of MC in MC/HMC by more efficient approach: quasi-random sampling [7]
- Implementation of a more efficient optimization algorithm
- Combination of these methods with adaptive designs [8]

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Integrated DEsign and AnaLysis of small population group trials

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