New Bayesian approach for uncertainty computation at finite distance in nonlinear mixed effects models: simulation study and application

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Introduction

Non linear mixed effects models (NLMEM): powerful tool to model longitudinal data

$\theta = c(\mu, \beta, \Omega, a, b)$: vector of population parameters to estimate (μ: fixed effects , β: covariate effects, Ω: variance matrix of random effects, a,b: error parameters)

Frequentist paradigm:

- Uncertainty of the maximum likelihood estimator (MLE) can be computed **asymptotically** through the standard errors (SE) based on the Fisher Information Matrix (FIM), and confidence intervals are built under a gaussian hypothesis (Asympt)
- When working at **finite distance**, Asympt underestimates the SE of NLMEM [1,2]
- Bootstrap or Sampling Importance Resampling (SIR) [3] methods have been proposed
- Sampling methods computationally heavy

Ueckert et. al. [4] proposed to compute uncertainty in a **Bayesian paradigm following the frequentist inference**:

- Under some regularity conditions on the prior, the limit distributions of the MLE and the maximum a posteriori (MAP) estimator are equivalent (Bernstein-von Mises theorem)
- Posterior distributions are used to compute uncertainty, e.g. confidence intervals using quantiles

→ Method implemented via Hamiltonian Monte Carlo algorithm in Stan (Post) [5,6]

Objective: To borrow from the **Bayesian paradigm** to estimate uncertainty through posterior distributions in NLMEM at finite distance, **in parallel of the frequentist estimation** in SAEM

Methods

In the `saemix` R package [7], integration of a Bayesian step based on the Metropolis Hastings (MH) algorithm (SAEM_MH) [8]

At each iteration k of SAEM at convergence phase, after simulation step/stochastic approximation/maximisation step

Bayesian step:

Set a prior distribution $p(.)$ on θ

$\theta_{0_k}^{MH} = \theta_k$ the current frequentist estimation of SAEM

For $m_k = 1, ..., M_k$:

- Draw θ_{m_k} in a kernel distribution $q(.)$
- θ_{m_k} is accepted with probability α:

$$\alpha = \min\left(1, \frac{ll(\theta_{m_k}, \bar{\psi}_{m_k}) p(\theta_{m_k}) q(\theta_{m_k-1}^{MH})}{ll(\theta_{m_k-1}^{MH}, \bar{\psi}_{m_k-1}^{MH}) p(\theta_{m_k-1}^{MH}) q(\theta_{m_k})}\right)$$

with $\bar{\psi}_{m_k}$ the mean of $z = 50$ samples drawn from the conditional distribution $\mathbb{P}(\psi_{m_k}|y, \theta_{m_k})$

Keep the last iteration $\theta_{M_k}^{MH}$ of each MH chain to get a chain of K2 samples

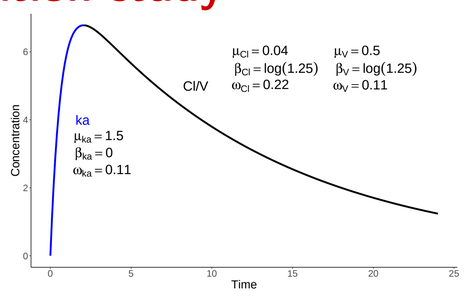
Parameters to be calibrated:

- M_k, here $M_k = 100$
- Prior distribution, here $p = \mathcal{N}(\theta_p, sd_p)$ with θ_p the simulated values of θ and a coefficient of variation sd_p/θ_p=30% for μ and 50% for β, Ω, a and b
- Kernel distribution, here $q = \mathcal{N}(\theta_q, sd_q)$, $\theta_q = \theta_k$ and $sd_q = \text{inf}_q \times FIM_k^{-1}$, with $\text{inf}_q = 1, 1.5, 2$

PK simulation study

- Inspired by theophylline data
- Proportional error model (b)
- Treatment groups of equal size

$$C(t) = \frac{dose}{V} \frac{k_a}{k_a - \frac{Cl}{V}} e^{(\frac{Cl}{V}t - k_a t)}$$

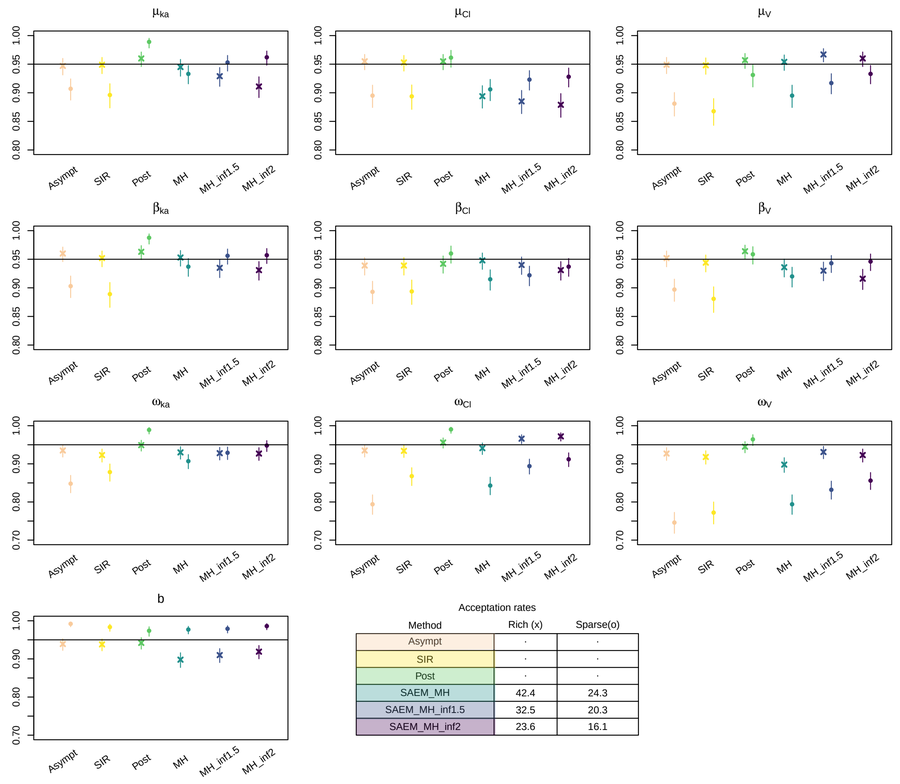


Two designs of 1000 simulated datasets:

Rich	N=150 patients	n=10 points
Sparse	N=12	n=3

Evaluation:

- 10 population parameters (β_{ka} estimated)
- 95% coverage rates (CR) and their confidence intervals
- Acceptation rates (AR)
- Comparison with Asympt, SIR and Post



Acceptation rates

Method	Rich (x)	Sparse(o)
Asympt	.	.
SIR	.	.
Post	.	.
SAEM_MH	42.4	24.3
SAEM_MH_inf1.5	32.5	20.3
SAEM_MH_inf2	23.6	16.1

On N=150 and n=10 (x):

- All methods provide CR within the target range

On N=12 and n=3 (•):

- With Asympt, SIR and SAEM_MH, CR systematically below the target
- Post gives CR below or above the target
- SAEM_MH_2, with inflated kernel variance by a factor 2, gives more controlled CR

In both cases, AR of MH between 15% and 40%: seems reasonable given the number of dimensions

Problem : when simulating additional data with increased variability and/or strong correlations, AR dropped

SAEM_MH seems promising but needs further investigation on more challenging settings to higher the AR

Alternatives to the current MH algorithm currently investigated:

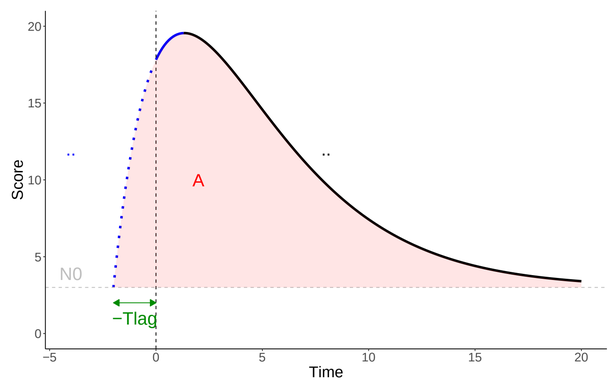
- Use AR as a guide for adaptive inf_q on sd_q
- Adaptive kernel variance from litterature [9]
- Block sampling of fixed effects and variance parameters separately
- Conditional univariate sampling (Gibbs sampling) with or without variance inflation for each parameter separately
- Random walks

NEWS-2 modelling

- Discovery trial [10] (promoted by Inserm, PI: Pr Florence Ader): European clinical trial aiming to evaluate antiviral drugs for the treatment of Covid19
- Patients hospitalised for Covid19 followed for 29 days (patients recovering left the hospital but were followed up at day 15 and day 29)
- NEWS-2 [11]: composite score ranging from 0 (best) to 20 (worst), used in emergency medicine to assess the clinical status of patients
- Our objective: model the evolution of NEWS-2 and test for a treatment effect between:
  - the standard of care (SoC, N=408 patients) arm
  - the SoC + remdesivir (N=402 patients) arm

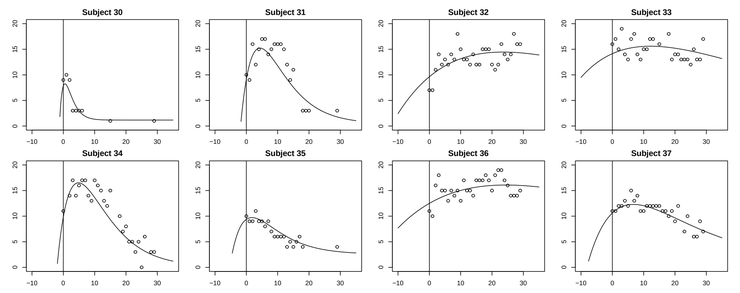
Bateman function to model the typical evolution of the score considered as continuous:

$$\text{NEWS2(t)} = N_0 + A\ \lambda^2\ (t + T_{lag}) e^{-\lambda(t + T_{lag})}$$



- T_{lag}, λ and A follow a log-normal distribution
- N_0 follows a logit-normal distribution between 0 and 3
- log-transformation of the data and model as log(1+NEWS2) to account for the score being bounded by 0, with a constant error (a) model

		RSE (%)			
Parameter	Estimate	Asympt	SIR	Post	MH
$\mu_{T_{lag}}$ (days)	2.85	10	9	7	13
$\beta_{age}(T_{lag})$	0.50	23	23	24	13
$\beta_{remde}(T_{lag})$	0.13	81	79	71	21
μ_A (days)	106.60	9	7	1	7
$\beta_{age}(A)$	0.56	18	18	16	6
$\beta_{remde}(A)$	-0.02	566	441	2084	12
μ_{N_0}	0.18	19	19	16	29
$\beta_{cardiac}(N_0)$	0.21	174	175	196	57
$\beta_{diabetes}(N_0)$	1.01	38	40	52	42
μ_λ (days^{-1})	0.20	7	6	2	6
$\beta_{age}(\lambda)$	-0.53	16	16	15	5
$\beta_{remde}(\lambda)$	-0.03	245	151	233	12
$\omega_{T_{lag}}$	1.11	5	5	6	4
ω_A	1.28	3	3	3	3
ω_{N_0}	2.86	6	6	8	5
ω_λ	1.05	3	3	4	3
$r_{Tlag,\lambda}$	0.83	10	10	2	14
$r_{Tlag,A}$	-0.90	10	11	3	15
$r_{A,\lambda}$	-0.97	8	8	0	9
a	0.25	1	1	1	2



→ With SAEM_MH method:

- AR were critically low due to the challenging setting
- Calibration is needed to use SAEM_MH on this data

Conclusion

- As expected, Asympt is degraded at finite distance
- SIR does not improve the results
- Post gives CR above the target on sparse design and needs further work to investigate suitable priors
- SAEM_MH also needs further investigation for the calibration of the prior and kernel distributions on challenging settings

[1] Bertrand J, Comets E, Lafont CM, Chenel M, Mentré F, Pharmacogenetics and population pharmacokinetics: impact of the design on three tests using the SAEM algorithm, Biometrics 2011.
[2] Dubois A, Lavielle M, Gsteiger S, Pigeolet E, Mentré F, Model-based analyses of bioequivalence crossover trialsusing the stochastic approximation expectationmaximisation algorithm, Stat in Med 2012.
[3] Dosne AG, Bergstrand M, Harling K, Karlsson MO, Improving the estimation of parameter uncertainty distributions in nonlinear mixed effects models using sampling importance resampling, J Pharmacokinet Pharmacodyn 2016.
[4] Ueckert S, Rivière MK, Mentré F, Alternative to Resampling Methods in Maximum Likelihood Estimation for NLMEMs by Borrowing from Bayesian Methodology, Abstr 3632, PAGE 24 2015.
[5] Loingeville F, Bertrand J, Nguyen T, Sharan S, Feng K et al., New model-based bioequivalence statistical approaches for pharmacokinetic studies with sparse sampling, AAPS J 2020.
[6] Guhl M, Mercier F, Hofmann C, Sharan S, Donnelly M et.al, Impact of model misspecification on model-based tests in PK studies with parallel design: real case and simulation studies, J Pharmacokinet Pharmacodyn 2022.
[7] Comets E, Lavenu A and Lavielle M, Parameter estimation in nonlinear mixed effect models using saemix, an R implementation of the SAEM algorithm, J Stat Soft 2017.
[8] Guhl M, Bertrand J, Comets E, Computation of standard errors at finite distance in non linear mixed effects models, Abstr 9719, PAGE 29 2021.
[9] Garthwaite PH, Fan Y, Sisson SA, Adaptive optimal scaling of Metropolis–Hastings algorithms using the Robbins–Monro process, Commun Stat - Theory Methods 2016.
[10] Ader F, Bouscambert-Duchamp M, Hites M, Peiffer-Smadja N, Poissy J et al., Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial, Lancet Infect Dis 2022.
[11] Smith GB, Prytherch DR, Meredith P, Schmidt PE and Featherstone PI, The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death, Resuscitation 2013.