

Computation of uncertainty at finite distance in non linear mixed effects models

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Introduction

Non linear mixed effects models (NLMEM) are a powerful tool to model longitudinal data. In the **frequentist paradigm**:

- The population parameters are considered as **point estimates**
- The uncertainty of the maximum likelihood estimator (MLE) can be computed **asymptotically** through the standard errors (SE) based on the Fisher Information Matrix (FIM) and a gaussian approximation, method hereafter called **Asympt**

When working at **finite distance** (i.e. far from the asymptotic):

- Asympt** underestimates the SE of NLMEM
- It has been proposed to use bootstrap [1] or Sampling Importance Resampling (SIR) [2] methods

Ueckert et. al. [3] proposed to compute uncertainty in a **Bayesian paradigm following the frequentist inference**:

- The population parameters are considered as **random variables**, with priors based on the frequentist estimation
- 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)
- The posterior distributions are used to compute uncertainty, e.g. confidence intervals using quantiles

→ This method has been implemented via Hamiltonian Monte Carlo algorithm in Stan (**Post**) [4]

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 [5]

NLMEM

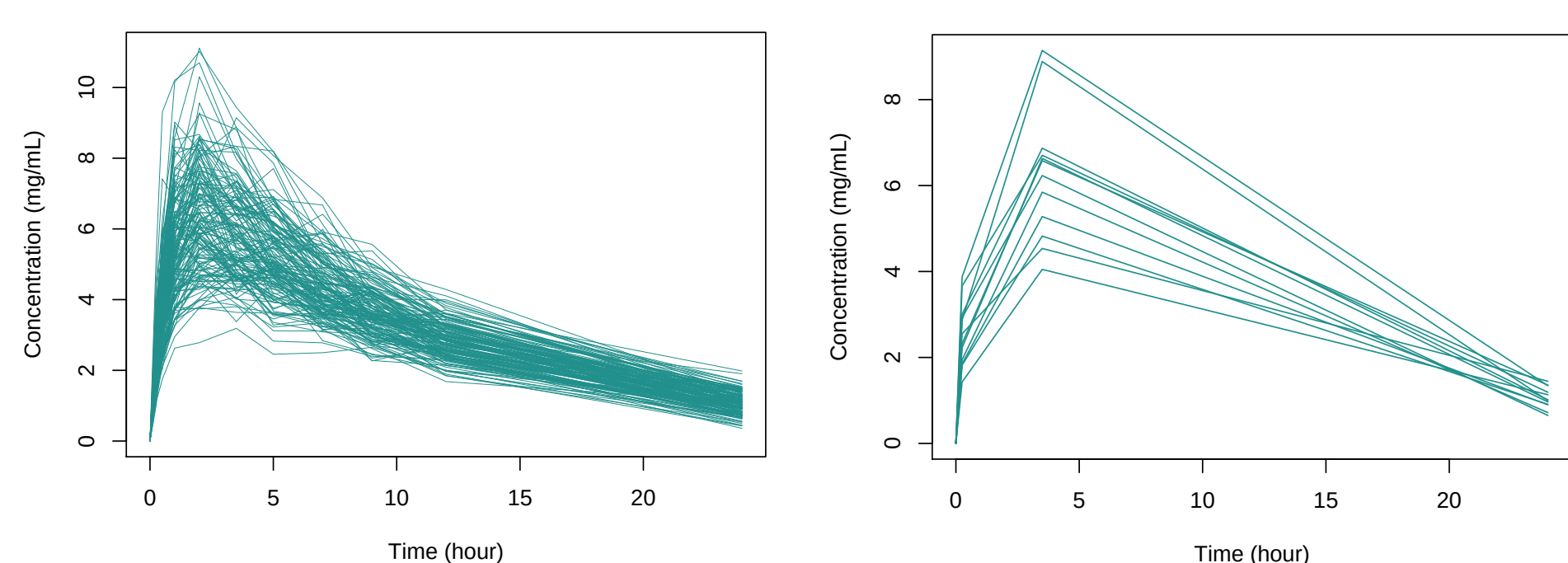
$$y_{ij} = f(t_{ij}, \psi_i) + g(t_{ij}, \psi_i)\epsilon_{ij}$$
$$\psi_i = h(\mu, \beta, \eta_i)$$

- with i the individual ($i=1, \dots, N$), n_i the number of observations, and y_{ij} the observation at time t_{ij} ($j=1, \dots, n_i$)
- f the structural PK model, g the error model, and h the transformation model (e.g. identity, exponential, logit, probit) applied to Gaussian individual parameters
- $\epsilon_{ij} \sim \mathcal{N}(0, 1)$ the residual error
- ψ_i the vector of parameters for individual i
- μ the fixed effects, β the covariates effects, $\eta_i \sim \mathcal{N}(0, \Omega)$ the random effects

We call θ the vector of all population parameters to estimate, composed of μ , β , Ω and the parameters of the error model g .

PK simulation settings

- One-compartment structural model with linear absorption and elimination
- Parameter values inspired by theophylline data
- Proportional error model $g(t, \psi) = b f(t, \psi)$
- Two treatment groups of equal size
- Treatment effect on Cl and V at $\log(1.25)$
- Two designs with 1000 datasets simulated in each:
Rich: $N=150$, $n=10$ Sparse: $N=12$, $n=3$



Ten population parameters to estimate: a fixed effect μ , treatment effect β and inter-individual random effect variance ω for each parameter ka , Cl and V , and one error parameter b

Note: β_{ka} is simulated at 0 and estimated

Methods

We integrate in the saemix R package [5] a Bayesian step based on the Metropolis Hastings (MH) algorithm, hereafter called **SAEM_MH**:

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

Bayesian step:

Set a prior distribution $p(\cdot)$ on θ and create a chain of M samples of θ with MH

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

For $m_k = 1, \dots, M$:

- Draw θ_{m_k} in a kernel distribution $q(\cdot)$
- Draw ψ_{m_k} from the conditional distribution $\mathbb{P}(\psi_{m_k} | y, \theta_{m_k})$
- Compute the loglikelihood $ll(\theta_{m_k}, \psi_{m_k})$
- Compute the acceptance rate α using loglikelihood, prior p and kernel q densities of θ_{m_k} and $\theta_{m_{k-1}}^{MH}$:

$$\alpha = \min \left(1, \frac{ll(\theta_{m_k}, \psi_{m_k}) p(\theta_{m_k}) q(\theta_{m_{k-1}}^{MH})}{ll(\theta_{m_{k-1}}^{MH}, \psi_{m_{k-1}}^{MH}) p(\theta_{m_{k-1}}^{MH}) q(\theta_{m_k})} \right)$$

- $\theta_{m_k}^{MH} = \theta_{m_k}$ with probability α , else $\theta_{m_k}^{MH} = \theta_{m_{k-1}}^{MH}$

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

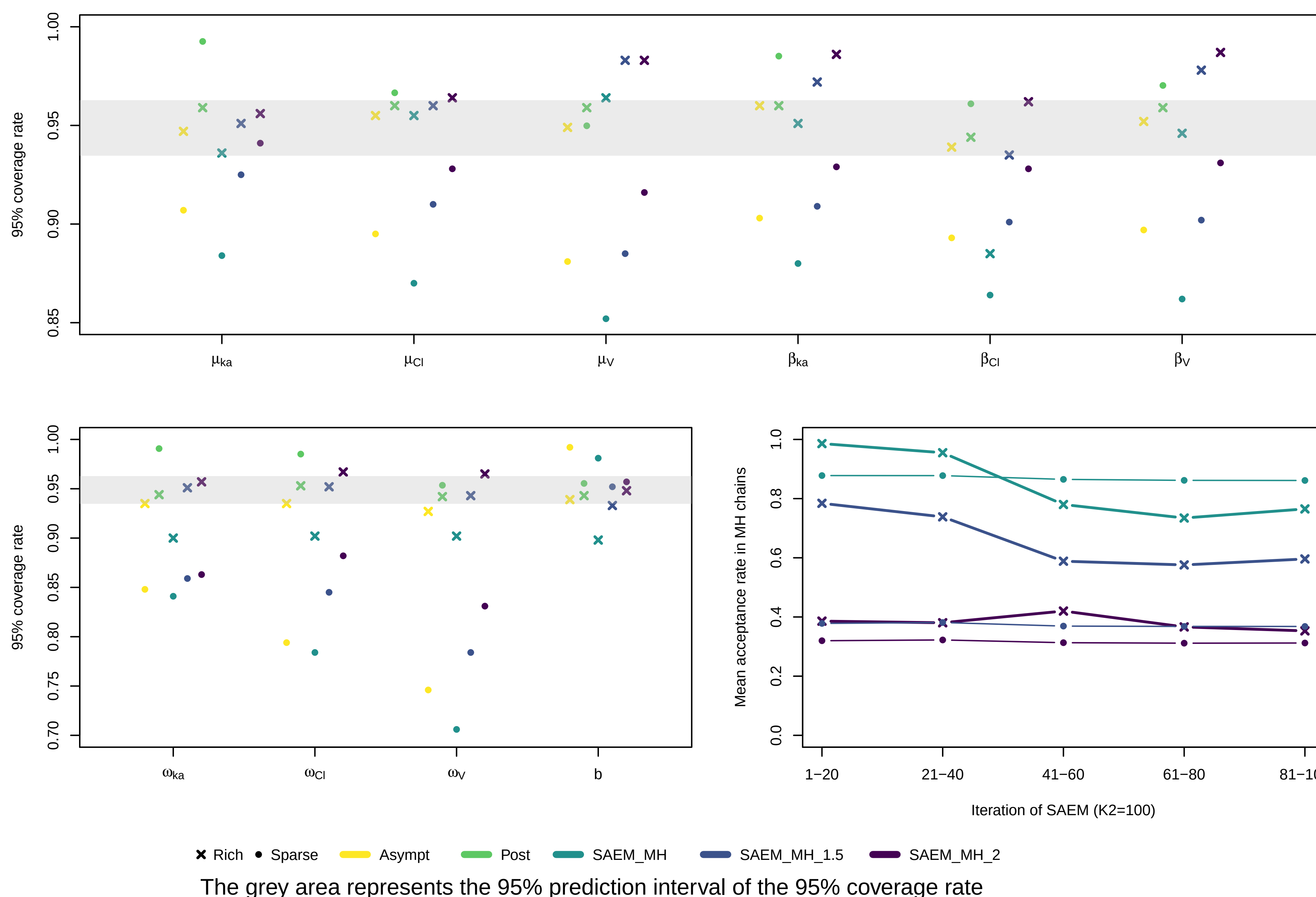
Parameters to be calibrated:

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

→ We obtain a frequentist and a Bayesian estimation of the uncertainty, respectively obtained from the FIM and the distribution of the samples

Evaluation:

- 95% coverage rates (CR) and comparison with its 95% prediction interval for 1000 simulations
- Acceptance rates
- Comparison with **Asympt** (FIM) and **Post** (HMC)



Results

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

- Asympt** and **Post** methods provide CR within the target range (95% prediction interval)
- With **SAEM_MH**, the acceptance rate is about 80% and CR for the variance parameters are under the target
- SAEM_MH_1.5**, with inflated kernel variance by a factor 1.5, gives lower acceptance rates, about 60%, and better results on ω and b
- Computation times : 3 minutes for **Post**, 30 minutes for **SAEM_MH**, **SAEM_MH_1.5** and **SAEM_MH_2**

On $N=12$ and $n=3$ (•):

- With **Asympt**, CR are systematically below the prediction interval
- Post** gives CR above the target
- With **SAEM_MH**, the acceptance rate is about 90% and CR are below the target
- SAEM_MH_2**, with inflated kernel variance by a factor 2, gives lower acceptance rate, about 35%, and the CR return to the prediction interval except for the ω
- Computation times : 15/20 seconds for **Post**, 3/4 minutes for **SAEM_MH**, **SAEM_MH_1.5** and **SAEM_MH_2** (but no optimisation of the code yet)

Conclusion

- As expected, **Asympt**, the FIM-based method of computation of uncertainty, is degraded at finite distance
- Post** gives CR above the target on the sparse design and needs further work to investigate suitable priors
- SAEM_MH** seems promising but needs further investigation for the calibration of the prior and kernel distributions
 - the acceptance rate may be used as a guide for the level of inflation
 - we could inflate the variance for each parameter separately, notably fixed effects and random effects variances
- Future work: compare **SAEM_MH** to SIR

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