Evaluation of the bayesian individual information matrix in nonlinear mixed effect models using Monte Carlo integration

Florence Loingeville, Thu Thuy Nguyen, Marie-Karelle Riviere and France Mentré

Monday, 20th June, 2016, PODE, Uppsala

INSERM, IAME, UMR 1137, F-75018 Paris, France ;

Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France

Contents

Contents

Introduction

- Parameter estimation in nonlinear mixed effect models (NLMEM) :
  - Population parameters : by Maximum Likelihood approach
  - Individual parameters : by Bayesian approach
- Design evaluation and optimisation
  - Individual Fisher information matrix (IFIM) : for individual regression
  - Population Fisher information matrix (PFIM) [1] : for analysis with NLMEM, implemented in several design software [2] based on first-order linearization (FO)
  - Individual bayesian information matrix (iBIM) [3] : for bayesian individual estimation, based on FO [4,5]

---

1. Mentré et al. (1997). Biometrika.
2. Nyberg et al. (2014). Br J Clin Pharmacol.
3. Merlé et al. (1995). J Pharmacokinet Biopharm.
4. Combes et al. (2013). Pharm Res.
5. PFIM 4.0. www.pfim.biostat.fr.

Introduction

Limitations of FO :

- High nonlinearity
- High variability + sparse design
- Discrete data

Alternatives proposed :

- For PFIM :
  - Laplace & MC [6],
  - Adaptive Gaussian Quadrature [7], [8]
  - MCMC-based approach [9] implemented in R package MIXFIM [10] using Stan [11]

- **For iBIM : MC-based approach**

6. Nyberg et al. (2009). PAGE meeting.
7. Nguyen et al. (2014). Computational Statistics & Data Analysis.
8. Ueckert et al. (2016). Computational Statistics & Data Analysis.
9. Riviere et al. (2016). Biostatistics.
10. https ://cran.r-project.org/web/packages/MIXFIM/
11. Stan Development Team. http ://mc-stan.org

Objectives

- To evaluate an approach based on Monte-Carlo (MC) to compute the iBIM :
  - on a pharmacokinetic (PK) model
  - on a model for count data

Contents

NLMEM : Notations

For continuous data :   For discrete data :

$$y_i = f(g(\mu, b_i), \xi_i) + \epsilon_i \qquad p(y_i|b_i) = \prod_{j=1}^{n_i} h(y_{ij}, g(\mu, b_i), \xi_i)$$

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

$\theta_i = g(\mu, b_i)$ 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

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

Expression of the iBIM

The individual bayesian information matrix can be expressed as :

$$iBIM(\xi_i) = E_{b_i} \left(E_{y_i|b_i} \left(\frac{\partial \log(p(b_i|y_i))}{\partial b_i} \frac{\partial \log(p(b_i|y_i))^T}{\partial b_i} \right) \right)$$

$$= E_{b_i} \left(E_{y_i|b_i} \left(\frac{\partial \log(p(y_i|b_i))}{\partial b_i} \frac{\partial \log(p(y_i|b_i))^T}{\partial b_i} \right) \right) + E_{b_i} \left(\frac{\partial \log(p(b_i))}{\partial b_i} \frac{\partial \log(p(b_i))^T}{\partial b_i} \right)$$

$$= \underbrace{E_{b_i} \left(M_{IF}(g(\mu, b_i), \xi_i) \right)}_{\substack{\text{Individual} \\ \text{information}}} + \underbrace{E_{b_i} \left(\frac{\partial \log(p(b_i))}{\partial b_i} \frac{\partial \log(p(b_i))^T}{\partial b_i} \right)}_{\text{Prior information}}$$

Expression of the bayesian individual information matrix

$$iBIM(\xi_i) = \underbrace{E_{b_i}\left(M_{IF}(g(\mu, b_i), \xi_i)\right)}_{\substack{\text{Individual} \\ \text{information}}} + \underbrace{E_{b_i}\left(\frac{\partial \log(p(b_i))}{\partial b_i}\frac{\partial \log(p(b_i))^T}{\partial b_i}\right)}_{\text{Prior information}}$$

The first expectation :

Expression of the bayesian individual information matrix

$$iBIM(\xi_i) = \underbrace{E_{b_i}\left(M_{IF}(g(\mu, b_i), \xi_i)\right)}_{\substack{\text{Individual} \\ \text{information}}} + \underbrace{E_{b_i}\left(\frac{\partial \log(p(b_i))}{\partial b_i}\frac{\partial \log(p(b_i))^T}{\partial b_i}\right)}_{\text{Prior information}}$$

The first expectation :

- Can be approximated by FO as $M_{IF}(g(\mu, 0), \xi_i)$

Expression of the bayesian individual information matrix

$$iBIM(\xi_i) = \underbrace{E_{b_i}\left(M_{IF}(g(\mu, b_i), \xi_i)\right)}_{\substack{\text{Individual} \\ \text{information}}} + \underbrace{E_{b_i}\left(\frac{\partial \log(p(b_i))}{\partial b_i}\frac{\partial \log(p(b_i))^T}{\partial b_i}\right)}_{\text{Prior information}}$$

The first expectation :

- Can be approximated by FO as $M_{IF}(g(\mu, 0), \xi_i)$
- Can be evaluated by MC :

$$E_{b_i}\left(M_{IF}(g(\mu, b_i), \xi_i)\right) = E_{b_i, y_i}\left(\frac{\partial\left(\log(p(y_i|b_i))\right)}{\partial b_{i,k}} . \frac{\partial\left(\log(p(y_i|b_i))\right)}{\partial b_{i,l}}\right)$$

$$\approx \frac{1}{R}\sum_{r=1}^{R}\frac{\partial\left(\log(p(y_{i,r}|b_{i,r}))\right)}{\partial b_{i,k}} . \frac{\partial\left(\log(p(y_{i,r}|b_{i,r}))\right)}{\partial b_{i,l}}$$

where $(b_{i,r}, y_{i,r})_{r=1,...,R}$ is a R-sample of the joint distribution of (b_i, y_i).

Expression of the bayesian individual information matrix

$$iBIM(\xi_i) = \underbrace{E_{b_i}\left(M_{IF}(g(\mu, b_i), \xi_i)\right)}_{\substack{\text{Individual} \\ \text{information}}} + \underbrace{E_{b_i}\left(\frac{\partial \log(p(b_i))}{\partial b_i}\frac{\partial \log p(b_i))^T}{\partial b_i}\right)}_{\text{Prior information}}$$

Second expectation :

MC-based evaluation

$$E_{b_i}\left(\frac{\partial \log(p(b_i))}{\partial b_i}\frac{\partial \log p(b_i))^T}{\partial b_i}\right) = \frac{1}{R}\sum_{r=1}^{R}\frac{\partial \log(p(b_{i,r}))}{\partial b_{i,k}}\frac{\partial \log(p(b_{i,r}))}{\partial b_{i,l}}$$

where $(b_{i,r})_{r=1,\dots,R}$ is a R-sample of the marginal prior distribution of b_i.

Expression of the bayesian individual information matrix

$$iBIM(\xi_i) = \underbrace{E_{b_i}\left(M_{IF}(g(\mu, b_i), \xi_i)\right)}_{\substack{\text{Individual} \\ \text{information}}} + \underbrace{E_{b_i}\left(\frac{\partial \log(p(b_i))}{\partial b_i}\frac{\partial \log p(b_i))^T}{\partial b_i}\right)}_{\text{Prior information}}$$

Second expectation :

MC-based evaluation

$$E_{b_i}\left(\frac{\partial \log(p(b_i))}{\partial b_i}\frac{\partial \log p(b_i))^T}{\partial b_i}\right) = \frac{1}{R}\sum_{r=1}^{R}\frac{\partial \log(p(b_{i,r}))}{\partial b_{i,k}}\frac{\partial \log(p(b_{i,r}))}{\partial b_{i,l}}$$

where $(b_{i,r})_{r=1,\ldots,R}$ is a R-sample of the marginal prior distribution of b_i.

Normal random effects

$$E_{b_i}\left(\frac{\partial \log(p(b_i))}{\partial b_i}\frac{\partial \log p(b_i))^T}{\partial b_i}\right) = \Omega^{-1}$$

Implementation in R

MC-based approach : implemented in R based on functions of rstan package :

- Monte Carlo (MC) sampler to sample in posterior distributions
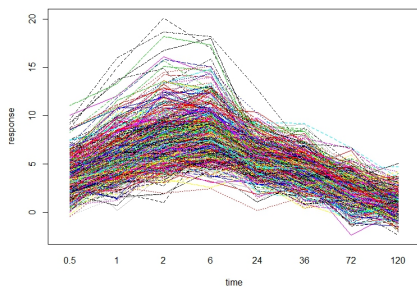- Calculation of the gradient of the log probability function

Contents

Continuous example[7] : PK Warfarin

One compartment model with first order absorption and elimination :

$$f((K_a, V, CL), t) = \frac{70}{V} \frac{K_a}{K_a - \frac{CL}{V}} \left(e^{-\frac{CL}{V}t} - e^{-K_a t} \right)$$
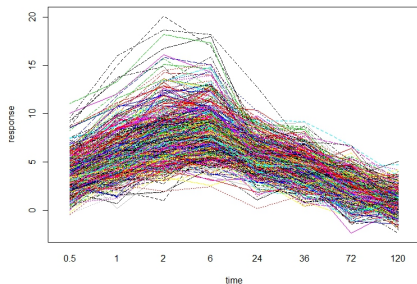

- Fixed effects :
  $(\mu_{Ka}, \mu_V, \mu_{CL}) = (1.00, 8.00, 0.15)$
- Exponential random effects with :
  $(\omega_{Ka}, \omega_V, \omega_{CL}) = (0.3, 0.3, 0.3)$
- Residual error : $\Sigma(g(\mu, b_i), \xi) = diag((\sigma_{inter} + \sigma_{slope} f(\theta, \xi))^2)$

12. Nyberg et al. (2014). British Journal of Clinical Pharmacology.

Continuous example [7] : PK Warfarin

One compartment model with first order absorption and elimination :

$$f((K_a, V, CL), t) = \frac{70}{V} \frac{K_a}{K_a - \frac{CL}{V}} \left(e^{-\frac{CL}{V}t} - e^{-K_a t} \right)$$
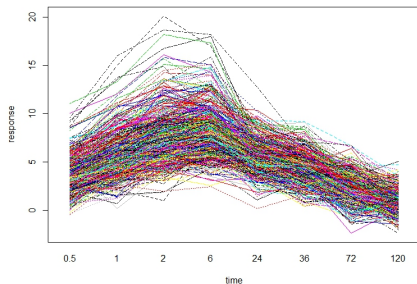

2 error models :

- Proportional residual error :
  $\sigma_{inter} = 0$ and $\sigma_{slope} = 0.1$
- Additive residual error : $\sigma_{inter} = 1$
  and $\sigma_{slope} = 0$

Continuous example [7] : PK Warfarin

One compartment model with first order absorption and elimination :

$$f((K_a, V, CL), t) = \frac{70}{V} \frac{K_a}{K_a - \frac{CL}{V}} \left(e^{-\frac{CL}{V}t} - e^{-K_a t} \right)$$

2 error models :

- Proportional residual error : $\sigma_{inter} = 0$ and $\sigma_{slope} = 0.1$
- Additive residual error : $\sigma_{inter} = 1$ and $\sigma_{slope} = 0$

  with 2 designs :

- Rich : $\xi = (0.5, 1, 2, 6, 24, 36, 72, 120)$
- Sparse (optimal design for proportional error, obtained with FO) : $\xi = (0.5, 120)$

Discrete example [7] : Poisson model

The observations are repeated counts for each patient at different dose levels. The probability of each count was modeled using a Poisson distribution :

$$P(y = k|b) = \frac{\lambda exp(\lambda)}{k!} \qquad \text{with} \ \ \log(\lambda) = \theta_1 \left(1 - \frac{d}{d + \theta_2}\right)$$

where

- 3-dose-levels design : $\xi = (0, 0.4, 0.7)$ with 30 observations per subject per dose
- Fixed effects : $(\mu_1, \mu_2) = (1, 0.5)$
- Exponential random effects with : $(\omega_1, \omega_2) = (0.3, 0.3)$

---

7. Riviere et al. (2016). Biostatistics.

Methods

Comparison of standard errors for estimation of random effects b_i :

- FO : predicted standard error pSE_{FO}
- MC : predicted standard error pSE_{MC}
- with clinical trial simulation (CTS) :
  - Simulation of one dataset with 500 subjects using R
  - Estimation of b as the mean of the a posteriori distribution $b|y$ using Stan (with 200 iterations and 500 burns)
  - Computation of SE_{CTS} as the standard deviation of the a posteriori distribution $b|y$
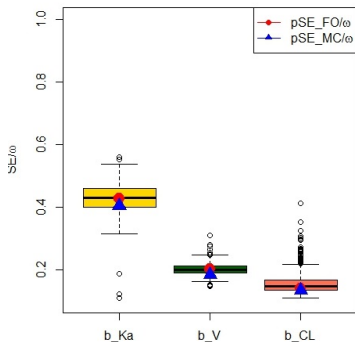
Results : PK Warfarin model with proportional error

Method	Random factor	ω=0.3			
		pSE_MC 5000 iter	pSE_MC 10000 iter	pSE_MC 20000 iter	pSE_MC 100000 iter
Rich design (n=8)	Ka	0.12	0.12	0.12	0.12
	V	0.05	0.06	0.05	0.05
	CL	0.04	0.04	0.04	0.04
Sparse Design (n=2)	Ka	0.19	0.19	0.20	0.20
	V	0.14	0.14	0.14	0.14
	CL	0.10	0.10	0.10	0.10

Results : PK Warfarin model with proportional error

Method	Random factor	ω=0.3			
		pSE_MC 5000 iter	pSE_MC 10000 iter	pSE_MC 20000 iter	pSE_MC 100000 iter
Rich design (n=8)	Ka	0.12	0.12	0.12	0.12
	V	0.05	0.06	0.05	0.05
	CL	0.04	0.04	0.04	0.04
Sparse Design (n=2)	Ka	0.19	0.19	0.20	0.20
	V	0.14	0.14	0.14	0.14
	CL	0.10	0.10	0.10	0.10

Rich design   Sparse design
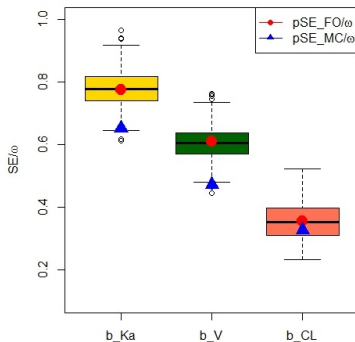
Results : PK Warfarin model with additive error
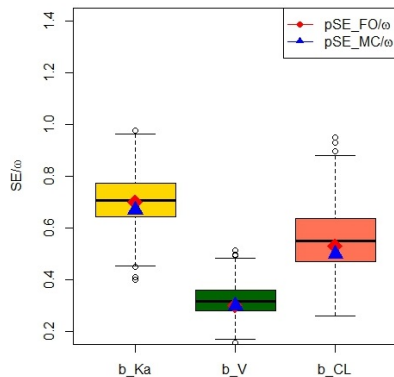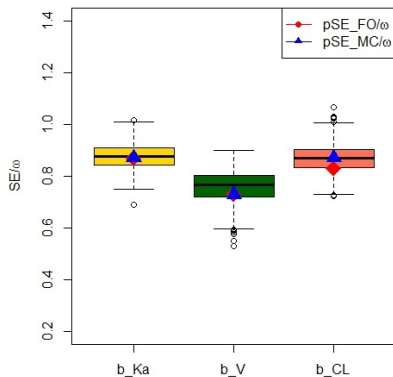
Results : Poisson model

ω=0.3			
pSE_MC (5000 iter)	pSE_MC (10000 iter)	pSE_MC (20000 iter)	pSE_MC (100000 iter)
b1	0.07	0.07	0.07	0.08
b2	0.26	0.24	0.24	0.24
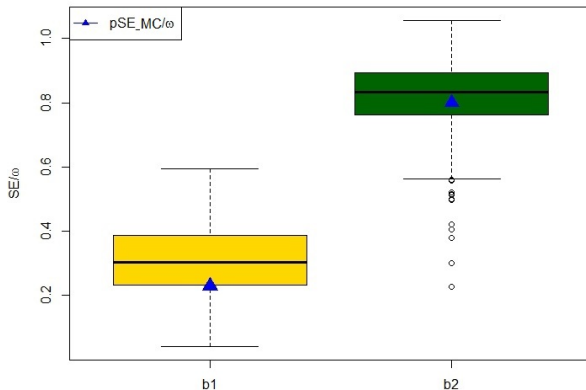
Contents

Discussion

- Alternative to FO, based on MC, to compute the iBIM
  - Adapted for continuous and discrete models
  - No model linearization
  - Agreement with clinical trial simulation results
- Work in progress
  - Evaluation with higher inter-individual variability
  - Evaluation of the uncertainty on the estimation of the iBIM
  - R package on CRAN

Thank you for your attention !

Questions ?