



# Some Accelerations of MLE Algorithm

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# Notations

- **Population approach.** Consider  $N$  individuals.  
 $y_i = (y_{ij}, 1 \leq j \leq n_i)$  vector of  $n_i$  measurements for individual  $i$  and  $c_i$  individual covariates.
- **Incomplete data** Individual parameters  $\psi_i$  are latent.
- **Parametrized hierarchical model.** The distribution of  $y_i$  depends on the latent variable  $\psi_i$

$$\begin{aligned}y_i &\sim p(y_i | \psi_i, \theta) \\ \psi_i &\sim p(\psi_i | c_i, \theta) \\ c_i &\sim p(c_i, \theta)\end{aligned}\tag{1}$$

- **Mixed Effects Model.** The individual parameters are decomposed as follows:

$$\psi_i = g(\beta, c_i, \eta_i)\tag{2}$$

where  $\beta$  is the population parameter (fixed effect) and  $\eta_i$  is the random effect. We assume  $\eta_i \sim \mathcal{N}(0, \Omega)$ .

# Example: Continuous data model

- Continuous, non linear and mixed effects models:

$$y_{ij} = f(t_{ij}; \psi_i) + \epsilon_{ij} \quad (3)$$

Where:

- The structural model  $f(t_{ij}, .)$  is a non linear function of  $\psi_i$
- $\epsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$  and  $\sigma \in \mathbb{R}$
- $\psi_i = \beta + \eta_i \Rightarrow \psi_i \sim \mathcal{N}(\beta, \Omega)$
- Here  $\theta = (\beta, \Omega, \sigma)$
- The goal is to compute the maximum likelihood estimate

$$\theta^{ML} = \arg \max_{\theta \in \Theta} p(y, \theta) \quad (4)$$

# Example: Non Continuous data model

- Here, the model for the observations of individual  $i$  is the conditional distribution of  $y_i$  given the set of individual parameters  $\psi_i$ . There is no analytical relationship between the observations and the individual parameters
- For repeated event models, times when events occur for individual  $i$  are random times  $(T_{ij}, 1 \leq j \leq n_i)$  for which conditional survival functions can be defined:

$$\mathbb{P}(T_{ij} > t | T_{i,j-1} = t_{i,j-1}) = e^{-\int_{t_{i,j-1}}^t h(u, \psi_i) du} \quad (5)$$

- Then, we can show (see [?]) for more details) that the conditional pdf of  $y_i = (y_{ij}, 1 \leq n_i)$  writes

$$p(y_i | \psi_i) = \exp \left\{ - \int_0^{\tau_c} h(u, \psi_i) du \right\} \prod_{j=1}^{n_i-1} h(t_{ij}, \psi_i) \quad (6)$$

# Maximum likelihood: EM

The EM algorithm (Dempster, Laird and Rubin, 1977) is an iterative algorithm that computes MLE. At a given  $\theta^{k-1}$ :

1.  $Q(\theta, \theta^{k-1}) = \mathbb{E}_{p(\psi|y, \theta^{k-1})} [\log p(y, \psi, \theta)]$
2.  $\theta^k = \arg \max_{\theta \in \Theta} Q^k(\theta)$

# SAEM

Given  $\theta^{k-1}$ , SAEM (Delyon, Lavielle, Moulines, 1999)  $k$ -th update consists in:

1.  $\psi_i^k \sim p(\psi_i | y_i, \theta^{k-1})$  (MCMC [?])
2.  $Q^k(\theta) = Q^{k-1}(\theta) + \gamma_k (\sum_{i=1}^N \log p(y_i, \psi_i^k, \theta) - Q^{k-1}(\theta))$
3.  $\theta^k = \arg \max_{\theta \in \Theta} Q^k(\theta)$

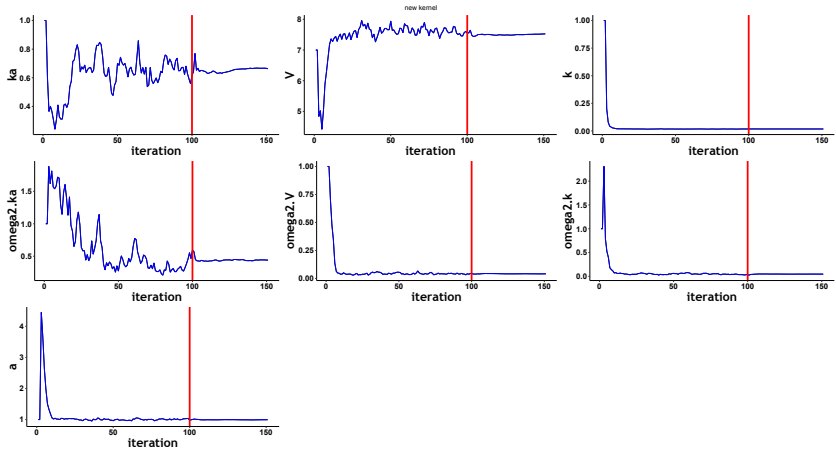
Example (PK model):

$$f(t_{ij}; \psi_i) = \frac{Dka_i}{V_i(ka_i - k_i)} (e^{-k_i t_{ij}} - e^{-ka_i t_{ij}})$$

where  $\psi_i = (ka_i, V_i, k_i)$  and

$$\begin{aligned} \log(ka_i) &\sim \mathcal{N}(\log(ka), \omega_{ka}^2) \\ \log(V_i) &\sim \mathcal{N}(\log(V), \omega_V^2) \\ \log(k_i) &\sim \mathcal{N}(\log(k), \omega_k^2) \end{aligned} \tag{7}$$

# Convergence behaviour: example



**Figure 1:** SAEM convergence ( $K1 = 100$ ,  $K2 = 50$ )

# MCMC Sampling

## Metropolis Hastings:

- Random Walk Metropolis: proposals are centered in the current state with a diagonal variance-covariance matrix, with variance terms which are adaptively adjusted at each iteration in order to reach some optimal acceptance rate [?, ?]
- Attempts: SDE-based (Fox, Ma, 2015) methods using the direction of the gradient of the target distribution (tuning and heavy calculus)
- Metropolis Adjusted Langevin Algorithm (MALA) [?, ?] and its variants [?, ?]
- The Hamiltonian Monte Carlo (HMC) and its extension the "No U-Turns Sampler" [?, ?] that takes advantage of Hamiltonian dynamics to propose candidates.



# Fast MCMC sampling: New proposal

**In the continuous case:** For a given individual  $i$

- Compute the Maximum A Posteriori (MAP):

$$\hat{\psi}_i = \arg \max_{\psi_i} p(\psi_i | y_i, \theta) = \arg \max_{\psi_i} p(y_i | \psi_i, \theta) p(\psi_i, \theta)$$

- Taylor expansion of the structural model  $f$  around this point:

$$f_i(\psi_i) \approx f_i(\hat{\psi}_i) + \nabla f_i(\hat{\psi}_i)(\psi_i - \hat{\psi}_i), \quad (8)$$

## Proposition

*Under this linear model, the conditional distribution of  $\psi_i$  is a Gaussian distribution with mean  $\mu_i$  and variance-covariance  $\Gamma_i$  where*

$$\begin{aligned} \mu_i &= \hat{\psi}_i, \\ \Gamma_i &= \left( \frac{\nabla f_i(\hat{\psi}_i)' \nabla f_i(\hat{\psi}_i)}{\sigma^2} + \Omega^{-1} \right)^{-1}. \end{aligned} \quad (9)$$

# Fast MCMC sampling: New proposal

## In the non continuous case

- Use Laplace Approximation of the incomplete likelihood

$$p(y_i) = \int e^{\log(p(y_i, \psi_i))} d\psi_i$$

- After TD of the complete log likelihood around the MAP ( $\nabla \log p(y_i, \hat{\psi}_i) = 0$ ) we obtain:

$$\log(p(\hat{\psi}_i|y_i)) \approx -\frac{p}{2} \log 2\pi - \frac{1}{2} \log \left( \left| -\nabla^2 \log p(y_i, \hat{\psi}_i) \right| \right),$$

## Proposition

*Let  $(y_i, \psi_i)$  be a pair of random variables where  $\psi_i$  is normally distributed with variance-covariance matrix  $\Omega$ . Then, the conditional distribution of  $\psi_i$  can be approximated by a Gaussian distribution with mean  $\hat{\psi}_i$  and variance-covariance*

$$\Gamma_i = -\nabla^2 \log(p(y_i, \hat{\psi}_i))^{-1} = \left( -\nabla^2 \log(p(y_i|\hat{\psi}_i)) + \Omega^{-1} \right)^{-1}.$$

# Fast MCMC sampling: State-of-the-art

- The MALA consists in proposing a new state  $\psi_i^c$  using the gradient of the target measure at the current state  $\psi_i^{(k)}$ :

$$\psi_i^c \sim \mathcal{N}(\psi_i^{(k)} - \gamma_k \nabla \log \pi(\psi_i^{(k)}), 2\gamma_k), \quad (10)$$

where  $(\gamma_k)_{k>0}$  is a sequence of positive integers. It is a particular case of the RWM with a drift term [?] and a covariance matrix that is diagonal and isotropic (uniform in all directions).

- In [?], the authors proposed a novel MCMC algorithm for conditional sampling, extending the existing Hamiltonian Monte Carlo sampler. The performance of the HMC algorithm suffers from the various parameters to tune such as the step size and the number of steps to run in order to produce the candidate sample using the Hamiltonian dynamics. The NUTS uses a recursive algorithm to build a set of candidate samples that spans a broad range of the target distribution without requiring the user to choose how many steps it wants to execute. We use the implementation of NUTS in rstan (R Package [?])

# Fast ML Estimation: Algorithm

Assume that our new proposal is used at iteration  $k$ , then the simulation step of SAEM decomposes as follows:

1. compute the MAP under the current model parameter estimate  $\theta_{k-1}$  for all individuals  $i$ :

$$\hat{\psi}_i^{(k)} = \arg \max_{\psi_i} p(\psi_i | y_i, \theta_{k-1}). \quad (11)$$

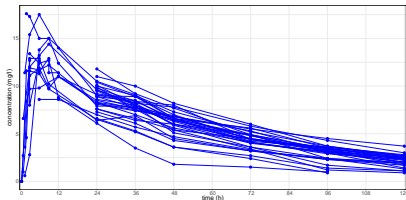
2. Compute the covariance matrix  $\Gamma_i^{(k)}$  such as:

$$\Gamma_i^{(k)} = \begin{cases} \left( \frac{\nabla f_i(\hat{\psi}_i^{(k)}) \nabla f_i(\hat{\psi}_i^{(k)})'}{\sigma^2} + \Omega^{-1} \right)^{-1} & \text{if the data model is continuous,} \\ \left( \nabla l(\hat{\psi}_i^{(k)}) \nabla l(\hat{\psi}_i^{(k)})' + \Omega^{-1} \right)^{-1} & \text{otherwise.} \end{cases} \quad (12)$$

3. Run a small number of iterations of the MH algorithm with the proposal  $\mathcal{N}(\hat{\psi}_i^{(k)}, \Gamma_i^{(k)})$ .

# Numerical Experiment: Warfarin Data

- 32 healthy volunteers received a 1.5 mg/kg single oral dose of warfarin, an anticoagulant normally used in the prevention of thrombosis [?].



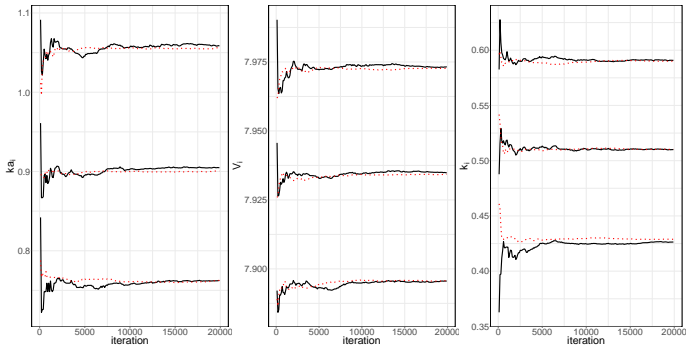
**Figure 2:** Warfarin concentration (mg/l) over time (h) for 32 subjects

- One-compartment pharmacokinetics (PK) model for oral administration, assuming first-order absorption and linear elimination processes:

$$f(t, ka, V, k) = \frac{D ka}{V(ka - k)}(e^{-ka t} - e^{-k t}), \quad (13)$$

# MCMC convergence: RWM

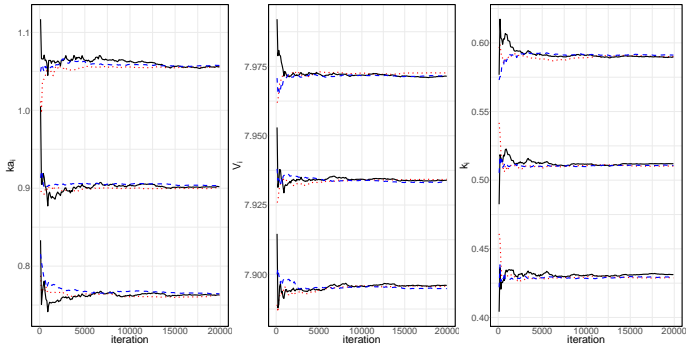
- Nonlinear continuous model: We use Proposition 1



**Figure 3:** Modelling of the warfarin PK data: convergence of the empirical quantiles of order 0.1, 0.5 and 0.9 of  $p(\psi_i | y_i; \theta)$  for a single individual. The reference MH algorithm is in black and solid and the new version is in red and dotted.

# MCMC convergence: MALA and NUTS

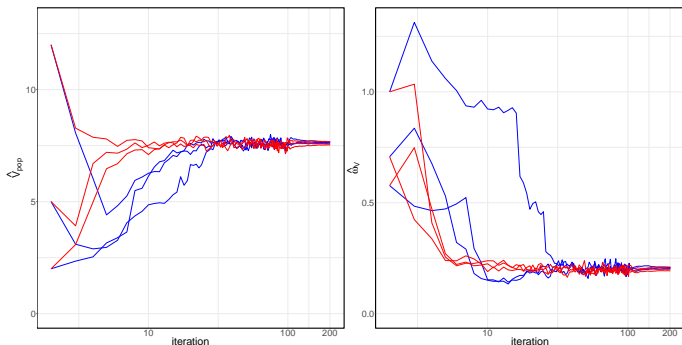
- MALA and NUTS



**Figure 4:** Modelling of the warfarin PK data: convergence of the empirical quantiles of order 0.1, 0.5 and 0.9 of  $p(\psi_i | y_i; \theta)$  for a single individual. The new version is in red, the MALA is in black and the NUTS is in blue.

# ML Estimation

- With our new proposal (red) versus reference RWM (blue)



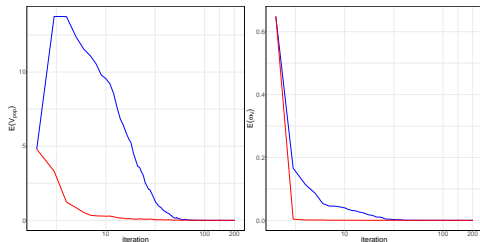
**Figure 5:** Estimation of the population PK parameters for the warfarin data: convergence of the sequences of estimates ( $\hat{V}_{pop,k}, 1 \leq k \leq 200$ ) and ( $\hat{\omega}_{V,k}, 1 \leq k \leq 200$ ) obtained with SAEM and three different initial values using the reference MH algorithm (blue) and the new proposal during the first 10 iterations (red).



# Monte Carlo Study

- For a given sequence of estimates, we can then define, at each iteration  $k$  and for each component  $\ell$  of the parameter, the mean square distance over the replicates

$$E_k(\ell) = \frac{1}{M} \sum_{m=1}^M \left( \theta_k^{(m)}(\ell) - \theta_K^{(m)}(\ell) \right)^2. \quad (14)$$



**Figure 6:** Mean square distances for  $V_{\text{pop}}$  and  $\omega_V$  obtained with SAEM on  $M = 50$  synthetic datasets using the reference MH algorithm (blue) and the new proposal during the first 10 iterations (red).

# Numerical Experiment: Time-To-Event

- Weibull model for time-to-event data [?, ?]. The hazard function of this model for individual  $i$  is:

$$h(t, \psi_i) = \frac{\beta_i}{\lambda_i} \left( \frac{t}{\lambda_i} \right)^{\beta_i - 1}. \quad (15)$$

- The vector of individual parameters is  $\psi_i = (\lambda_i, \beta_i)$  assumed to be independent and lognormally distributed:

$$\begin{aligned} \log(\lambda_i) &\sim \mathcal{N}(\log(\lambda_{\text{pop}}), \omega_\lambda^2), \\ \log(\beta_i) &\sim \mathcal{N}(\log(\beta_{\text{pop}}), \omega_\beta^2). \end{aligned} \quad (16)$$

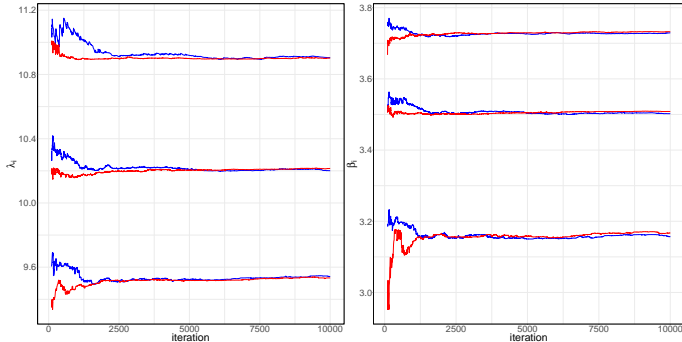
Then, the vector of population parameters is

$$\theta = (\lambda_{\text{pop}}, \beta_{\text{pop}}, \omega_\lambda^2, \omega_\beta^2).$$

- Individual parameters for  $N = 100$  individuals were generated using model (16) with  $\lambda_{\text{pop}} = 10$ ,  $\omega_\lambda = 0.3$ ,  $\beta_{\text{pop}} = 3$  and  $\omega_\beta = 0.3$ . Then, repeated events were generated for each individual using the Weibull model (15) and assuming a right censoring time  $\tau_c = 20$ .

# MCMC convergence: RWM

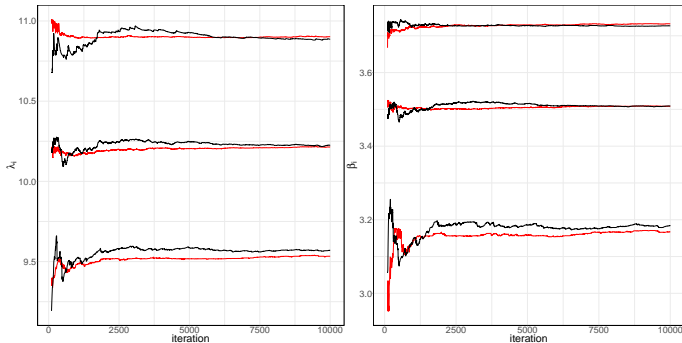
- Noncontinuous model: We use Proposition 2



**Figure 7:** Convergence of the empirical quantiles of order 0.1, 0.5 and 0.9 of  $p(\psi_i|y_i; \theta)$  for a single individual. The reference MH algorithm is in blue and the new version is in red.

# MCMC convergence: MALA

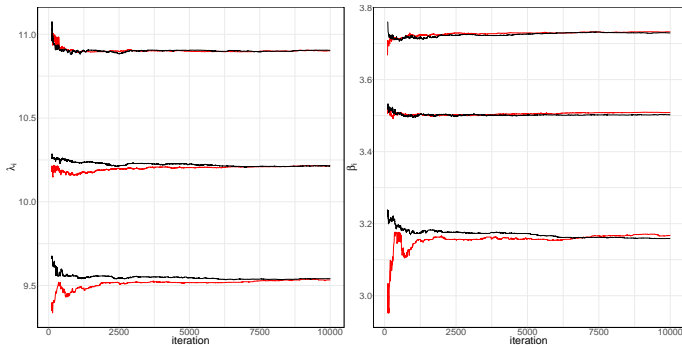
- MALA



**Figure 8:** Convergence of the empirical quantiles of order 0.1, 0.5 and 0.9 of  $p(\psi_i|y_i; \theta)$  for a single individual. The new version is in red, the MALA is in black.

# MCMC convergence: NUTS

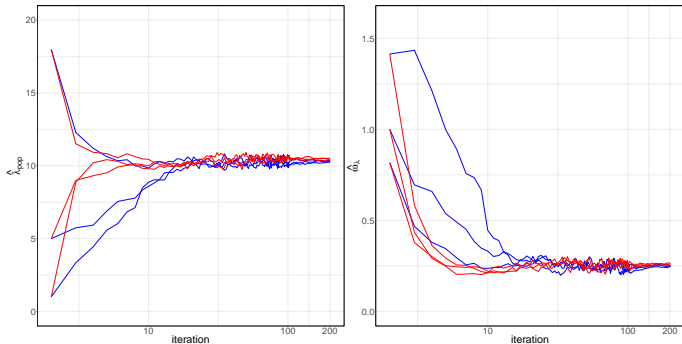
- NUTS



**Figure 9:** Convergence of the empirical quantiles of order 0.1, 0.5 and 0.9 of  $p(\psi_i|y_i; \theta)$  for a single individual. The new version is in red, the NUTS is in black.

# ML Estimation

- With our new proposal (red) versus reference RWM (blue)

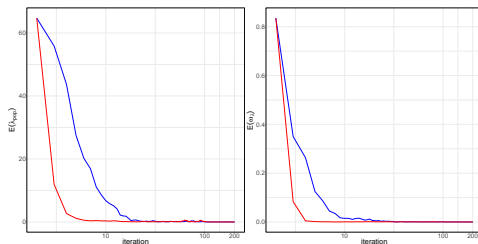


**Figure 10:** Convergence of the sequences of estimates  $(\hat{\lambda}_{pop,k}, 1 \leq k \leq 200)$  and  $(\hat{\omega}_{\lambda,k}, 1 \leq k \leq 200)$  obtained with SAEM and three different initial values using the reference MH algorithm (blue) and the new proposal during the first 5 iterations (red).

# Monte Carlo Study

- Plot of the mean square distance over the replicates

$$E_k(\ell) = \frac{1}{M} \sum_{m=1}^M \left( \theta_k^{(m)}(\ell) - \theta_K^{(m)}(\ell) \right)^2. \quad (17)$$



**Figure 11:** Convergence of the sequences of mean square distances for  $\lambda_{pop}$  and  $\omega_\lambda$  obtained with SAEM on  $M = 50$  synthetic datasets using the reference MH algorithm (blue) and the new proposal during the first 5 iterations (red).

*Thank you!*



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