High-dimensional variable selection in non-linear mixed effects models using a stochastic EM spike-and-slab

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1 - Introduction

Mixed-effects models:

- Analyse observations collected repeatedly on several individuals.
- Individuals with the same overall behaviour but with individual variations.
- Different sources of variability: intra-individual, inter-individual, residual.

Fields of application: pharmacokinetics, biological growth, ...

Variable selection:

- Inter-individual variability may be explained by some among a very large number of covariates (*e.g.* genomic data).
- High-dimensional context: focus on the few most relevant covariates through a variable selection procedure.

2 - Non-linear mixed-effects model (NLMEM)

For $i \in \{1, \dots, n\}$ and $j \in \{1, \dots, J\}$, denoting y_{ij} the response of individual i at time t_{ij} and V_i the p covariates measured on individual i, with $p >> n$:

$$\begin{cases} y_{ij} = g(\varphi_i, \psi, t_{ij}) + \varepsilon_{ij} & , \varepsilon_{ij} \overset{\text{i.i.d.}}{\sim} \mathcal{N}(0, \sigma^2), \quad (1a) \\ \varphi_i = \mu + {}^t\beta V_i + \xi_i & , \xi_i \overset{\text{i.i.d.}}{\sim} \mathcal{N}(0, \Gamma^2), \quad (1b) \end{cases}$$

where

- $\varphi_i \in \mathbb{R}$: individual parameter, not observed
- g: **non-linear** function with respect to φ_i
- $\psi \in \mathbb{R}^q$: fixed effects, unknown
- $\mu \in \mathbb{R}$: intercept, unknown
- $\beta = {}^t(\beta_1, \dots, \beta_p) \in \mathbb{R}^p$: covariate fixed effects vector, unknown

Population parameter to be estimated: $\theta = (\mu, \beta, \psi, \sigma^2, \Gamma^2)$

3 - Aim and contribution

- **Aim:** Identify the most relevant covariates to characterise inter-individual variability, *i.e.* identify the non-zero components of β.
- **Main difficulties:** non-explicit likelihood and high-dimensional problem.
- **Proposed approach:** Association of a Bayesian **spike-and-slab prior** for variable selection with **MCMC-SAEM** algorithm (stochastic version of EM) for inference [4].

4 - Bayesian hierarchical model

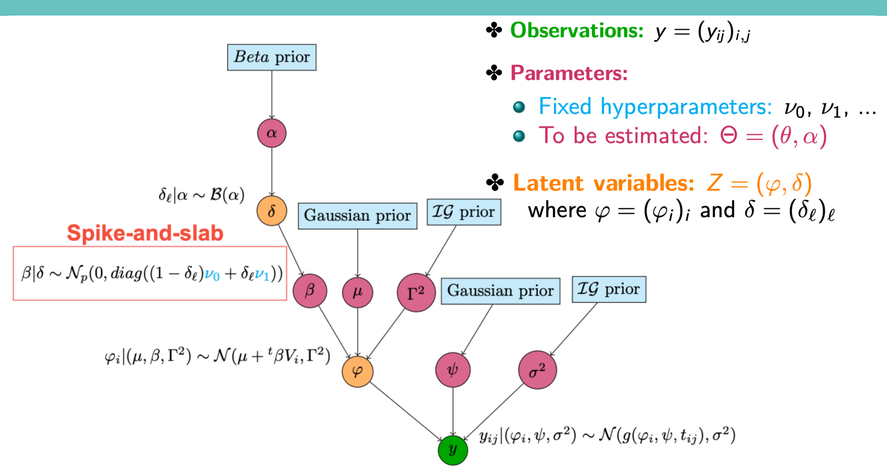


Fig. 1: Bayesian hierarchical model

5 - Method

Idea: we could choose ν_0 small, deduced from a practitioner chosen threshold for "negligible" covariate effect. However, we may be interested in exploring different levels of sparsity in β by varying the value of ν_0 in a grid Δ.

1. **Creation of a model collection:** for each $\nu_0 \in \Delta$,
   - ▶ compute the maximum *a posteriori* estimator with a MCMC-SAEM algorithm [1]:
   $$\widehat{\Theta}_{\nu_0}^{MAP} = \underset{\Theta \in \Lambda}{\text{argmax}}\ \pi(\Theta|y)$$
   - ▶ estimate $\hat{\delta}$ to find good models with high posterior probability [2]:
   $$\hat{\delta} = \underset{\delta}{\text{argmax}}\ P(\delta|\hat{\Theta}_{\nu_0}^{MAP}) \text{ such as } \hat{\delta}_\ell = 1 \iff \mathbb{P}(\delta_\ell = 1|\hat{\Theta}_{\nu_0}^{MAP}) \geq 0.5$$
   $$\iff \text{Define } \widehat{S}_{\nu_0} = \left\{ \ell \in \{1, \dots, p\} \;\middle|\; |(\widehat{\beta}_{\nu_0}^{MAP})_\ell| \geq s_\beta(\nu_0, \nu_1, \widehat{\alpha}_{\nu_0}^{MAP}) \right\}$$
2. **Select the "best" model** among $(\widehat{S}_{\nu_0})_{\nu_0 \in \Delta}$ by a fast criterion, *e.g.* eBIC [3]:
   $$\hat{\nu}_0 = \underset{\nu_0 \in \Delta}{\text{argmin}} \left\{ -2\log\left(p(y; \hat{\theta}_{\nu_0}^{MLE})\right) + B_{\nu_0} \times \log(n) + 2\log\left(\binom{p}{B_{\nu_0}}\right) \right\}$$
   with B_{ν_0} the number of free parameters in the sub-model $\widehat{S}_{\nu_0}$.
3. **Return** $\widehat{S}_{\hat{\nu}_0}$.

[1] Kuhn, E. and Lavielle, M. (2004). Coupling a stochastic approximation version of EM with an MCMC procedure. ESAIM: Probability and Statistics.
[2] Rocková, V. and George, E. I. (2014). EMVS: The EM approach to Bayesian variable selection. Journal of the American Statistical Association.
[3] Chen, J. and Chen, Z. (2008). Extended Bayesian information criteria for model selection with large model spaces. Biometrika.
[4] Naveau, M. et al. (2022). Bayesian high-dimensional covariate selection in non-linear mixed-effects models using the SAEM algorithm. arXiv:2206.01012.

6 - Regularisation plot and eBIC criterion

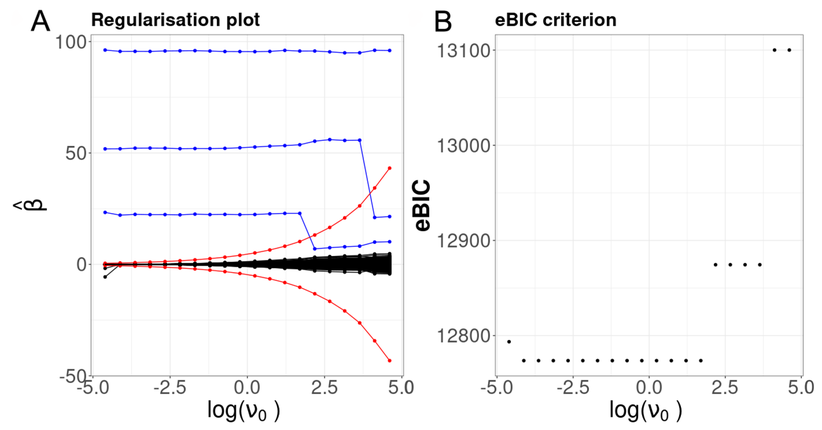


Fig. 2: Example of a regularisation plot (A) with eBIC criterion graph (B) for model selection. On (A), the red lines correspond to the selection threshold of the covariates.

$n = 200$, $J = 10$, $p = 500$, $\Gamma^2 = 200$, $\sigma^2 = 30$, $\nu_1 = 12000$, $\mu = 1200$, $\beta = {}^t(100, 50, 20, 0, \dots, 0)$

7 - MCMC-SAEM algorithm for computing the MAP

At each step k of this iterative algorithm, the idea is to maximise:

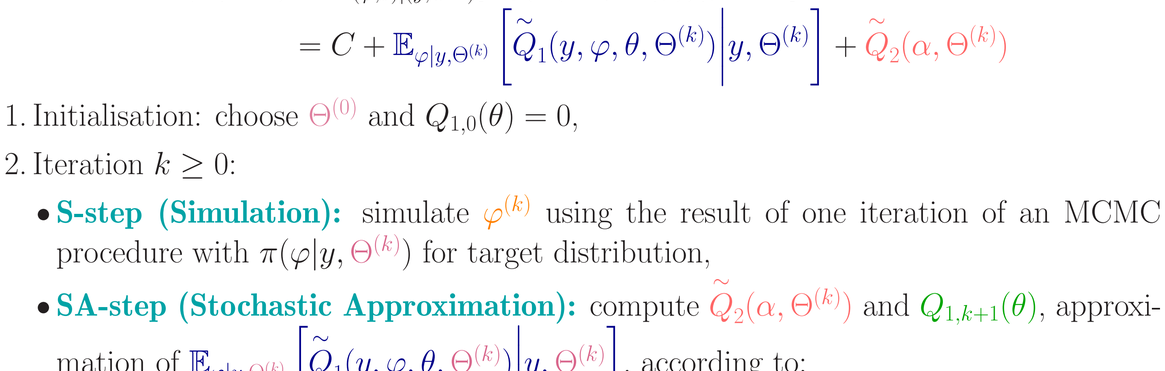
$$Q(\Theta|\Theta^{(k)}) = \mathbb{E}_{(\varphi,\delta)|(y,\Theta^{(k)})}[\log(\pi(\Theta, \varphi, \delta|y))|y, \Theta^{(k)}]$$
$$= C + \mathbb{E}_{\varphi|y,\Theta^{(k)}}\left[\widetilde{Q}_1(y, \varphi, \theta, \Theta^{(k)})\middle|y, \Theta^{(k)}\right] + \widetilde{Q}_2(\alpha, \Theta^{(k)})$$

1. Initialisation: choose $\Theta^{(0)}$ and $Q_{1,0}(\theta) = 0$,
2. Iteration $k \geq 0$:
   - **S-step (Simulation):** simulate $\varphi^{(k)}$ using the result of one iteration of an MCMC procedure with $\pi(\varphi|y, \Theta^{(k)})$ for target distribution,
   - **SA-step (Stochastic Approximation):** compute $\widetilde{Q}_2(\alpha, \Theta^{(k)})$ and $Q_{1,k+1}(\theta)$, approximation of $\mathbb{E}_{\varphi|y,\Theta^{(k)}}\left[\widetilde{Q}_1(y, \varphi, \theta, \Theta^{(k)})\middle|y, \Theta^{(k)}\right]$, according to:
   $$Q_{1,k+1}(\theta) = Q_{1,k}(\theta) + \gamma_k(\widetilde{Q}_1(y, \varphi^{(k)}, \theta, \Theta^{(k)}) - Q_{1,k}(\theta)),$$
   - **M-step (Maximisation):** compute
   $$\theta^{(k+1)} = \underset{\theta \in \Lambda_\theta}{\text{argmax}}\ Q_{1,k+1}(\theta) \text{ and } \alpha^{(k+1)} = \underset{\alpha \in [0,1]}{\text{argmax}}\ \widetilde{Q}_2(\alpha, \Theta^{(k)}),$$
3. $\hat{\Theta} = \Theta^{(K)}$, for K large enough,

where $(\gamma_k)_k$ is a step sizes sequence decreasing towards 0 such that $\forall k$, $\gamma_k \in [0, 1]$, $\sum_k \gamma_k = \infty$ and $\sum_k \gamma_k^2 < \infty$ [1].

8 - Simulation results in a logistic growth model

- **Uncorrelated covariates:**



(a) $n = 100$ (b) $n = 200$

Fig. 3: Proportion of data-sets on which the proposed method selects the correct model ("Exact"), a model that contains false positives (FP) but not false negatives (FN), FN but not FP, or FP and FN.

- **Correlated covariates:** Fairly similar performance but with more false positives and/or false negatives in some correlation scenarios.
- The proposed method is about 20 times faster than a full MCMC implementation.

9 - Perspectives

- Apply our method to a **real dataset** (in progress).
- Consider a **multidimensional** individual parameter.
- Provide theoretical guarantees: **selection consistency**.