Bayesian high-dimensional variable selection in non-linear mixed-effects models using the SAEM algorithm

Marion Naveau, Guillaume Kon Kam King, Laure Sansonnet, Maud Delattre

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Marion Naveau[1,2]
M. Delattre[2], G. Kon Kam King[2], L. Sansonnet[1]

[1]Université Paris-Saclay, AgroParisTech, INRAE, UMR MIA Paris-Saclay

[2]Université Paris-Saclay, INRAE, MaIAGE

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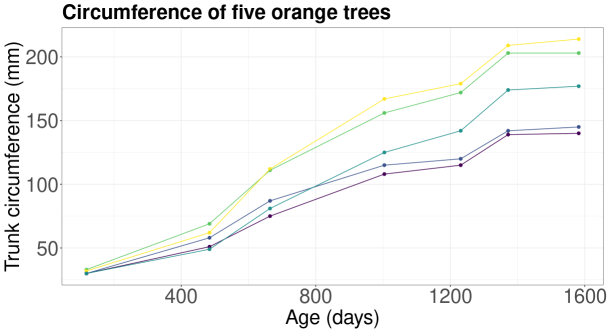
Framework: repeated measurement data

✤ **Mixed-effects models:** analyse observations collected repeatedly on several individuals.



✤ Same overall behaviour but with individual variations.

✤ Non-linear growth.

✤ Are these variations due to known characteristics?

- E.g.: growing conditions, genetic markers, ...

Non-linear mixed-effects model (NLMEM)

1) Description of intra-individual variability:
For all $i \in \{1, \dots, n\}$, $j \in \{1, \dots, J\}$,

$$y_{ij} = g(\varphi_i, \psi, t_{ij}) + \varepsilon_{ij}, \ \varepsilon_{ij} \overset{\text{i.i.d.}}{\sim} \mathcal{N}(0, \sigma^2)$$

- $y_{ij} \in \mathbb{R}$: response of individual i at time t_{ij} (observation).
- $\varphi_i \in \mathbb{R}$: individual parameter, **not observed**.
- $\psi \in \mathbb{R}^q$: fixed effects, **unknown**.
- g: non-linear function with respect to φ_i (known).

2) Description of inter-individual variability:

$$\varphi_i = \mu + {}^t\beta V_i + \xi_i, \ \xi_i \overset{\text{i.i.d.}}{\sim} \mathcal{N}(0, \Gamma^2)$$

- $\mu \in \mathbb{R}$: intercept, **unknown**.
- $V_i \in \mathbb{R}^p$: covariates for individual i (known).
- $\beta = {}^t(\beta_1, \dots, \beta_p) \in \mathbb{R}^p$ covariate fixed effects vector, **unknown**.

Population parameters: $\theta = (\mu, \beta, \psi, \sigma^2, \Gamma^2)$

Variable selection

✤ Aim: identify the most relevant covariates to characterise inter-individual variability.

✤ Active/Non-active covariates: covariates that are actually influential/non-influential for the characteristic under consideration.

✤ Description of inter-individual variability:

$$\varphi_i = \mu + {}^t\beta V_i + \xi_i, \ \xi_i \overset{\text{i.i.d.}}{\sim} \mathcal{N}(0, \Gamma^2)$$

- $\beta_\ell = 0 \iff$ covariate ℓ has no effect on parameter φ_i
- $\beta_\ell \neq 0 \iff$ covariate ℓ gives some information on parameter φ_i

✤ Model selection: variable selection $\iff$ model selection among all the possible supports of β:

$$S_\beta = \left\{ \ell \in \{1, \ldots, p\} \middle| \beta_\ell \neq 0 \right\}.$$

High-dimensional covariate selection in NLMEM

- Goal: identify the non-zero components of β.

- Specificity of the problem: $p >> n$

- Main difficulties:
  - High-dimensional variable selection:
    - parsimonious estimation of β
  - Non-explicit likelihood
    - The φ_i's are not observed (latent variables model)
    - g is non-linear

$$p(y;\theta) = \int p(y|\varphi;\theta)p(\varphi;\theta)d\varphi = \prod_{i=1}^{n} \int p(y_i|\varphi_i;\theta)p(\varphi_i;\theta)d\varphi_i$$

$$= C_{\sigma^2,\Gamma^2} \prod_{i=1}^{n} \int \exp\left(-\sum_{j=1}^{J} \frac{(y_{ij} - g(\varphi_i,\psi,t_{ij}))^2}{2\sigma^2} - \frac{(\varphi_i - \mu - {}^{t}\beta V_i)^2}{2\Gamma^2}\right) d\varphi_i$$

State of the art for high-dimensional variable selection in mixed-effects models

- Frequentist framework:
  - LMEM: both theoretical results and algorithmic developments for regularised methods (Schelldorfer et al., 2011; Fan and Li, 2012).
  - NLMEM: algorithmic contribution (Ollier, 2021).
- Bayesian framework:
  - Linear regression (without random effects): $y_i = \alpha + {}^t\beta X_i + \epsilon_i$ theoretical and algorithmic developments using various **sparsity-inducing priors** (cf book Tadesse and Vannucci (2021)).
  - NLMEM: (Lee, 2022) advocated the Bayesian approach for this model but this is only a review, without implementation, does not focus on the high-dimension.

Proposed approach

Association of a Bayesian ***spike-and-slab*** prior for variable selection with a stochastic version of the EM algorithm, called **MCMC-SAEM**, for inference.

Spike-and-slab prior for the coefficients of β

✤ Introduction of latent variables δ_ℓ, $1 \leq \ell \leq p$:

$$\delta_\ell = \begin{cases} 1 & \text{if covariate } \ell \text{ is to be included in the model,} \\ 0 & \text{otherwise.} \end{cases}$$

✤ **Spike-and-slab prior** on β (George and McCulloch, 1997):

$$\pi(\beta|\delta) = \mathcal{N}_p(0, \text{diag}((1-\delta_\ell)\nu_0 + \delta_\ell \nu_1)),\ 0 \leq \nu_0 < \nu_1 \text{ fixed,}$$

i.e. β_ℓ are independent and:

- $\beta_\ell | (\delta_\ell = 0) \sim \mathcal{N}(0, \nu_0)$: "spike" distribution, ν_0 small
- $\beta_\ell | (\delta_\ell = 1) \sim \mathcal{N}(0, \nu_1)$: "slab" distribution, ν_1 large

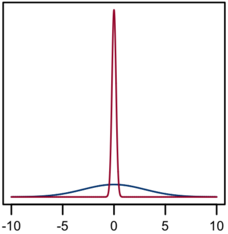
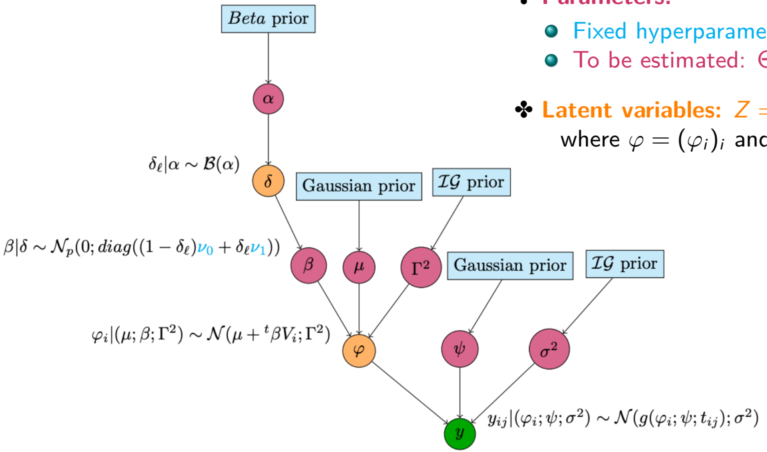


Figure: Spike-and-slab prior. Source: Deshpande et al. (2019)

Bayesian hierarchical model



- **Observations:** $y = (y_{ij})_{i,j}$
- **Parameters:**
  - Fixed hyperparameters: ν_0, ν_1, ...
  - To be estimated: $\Theta = (\theta, \alpha)$
- **Latent variables:** $Z = (\varphi, \delta)$
  where $\varphi = (\varphi_i)_i$ and $\delta = (\delta_\ell)_\ell$

Proposed method

Idea: explore 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 $\widehat{\Theta}$ by a MCMC-SAEM algorithm (Kuhn and Lavielle, 2004):
   $$\widehat{\Theta}_{\nu_0}^{MAP} = \underset{\Theta \in \Lambda}{\operatorname{argmax}}\ \pi(\Theta|y)$$
   - Estimate $\hat{\delta}$ (Ročková and George, 2014):
   $$\hat{\delta} = \underset{\delta}{\operatorname{argmax}}\ P(\delta|\hat{\Theta}_{\nu_0}^{MAP}) \text{ such as } \hat{\delta}_\ell = 1 \iff \mathbb{P}(\delta_\ell = 1|\hat{\Theta}_{\nu_0}^{MAP}) \geq 0.5$$
   $$\iff \text{Define } \widehat{S}_{\nu_0} = \left\{ \ell \in \{1, \dots, p\} \;\middle|\; |(\widehat{\beta}_{\nu_0}^{MAP})_\ell| \geq s_\beta(\nu_0, \nu_1, \widehat{\alpha}_{\nu_0}^{MAP}) \right\}$$

2. **Select the "best" model** among $(\widehat{S}_{\nu_0})_{\nu_0 \in \Delta}$ by a fast criterion, eBIC (Chen and Chen, 2008):
   $$\hat{\nu}_0 = \underset{\nu_0 \in \Delta}{\operatorname{argmin}} \left\{ -2\log\left(p(y; \hat{\theta}_{\nu_0}^{MLE})\right) + B_{\nu_0} \times \log(n) + 2\log\left(\binom{p}{B_{\nu_0}}\right) \right\}$$
   with B_{ν_0}: number of free parameters in the model $\widehat{S}_{\nu_0}$.

3. **Return** $\widehat{S}_{\hat{\nu}_0}$.

Spike-and-slab regularisation plot

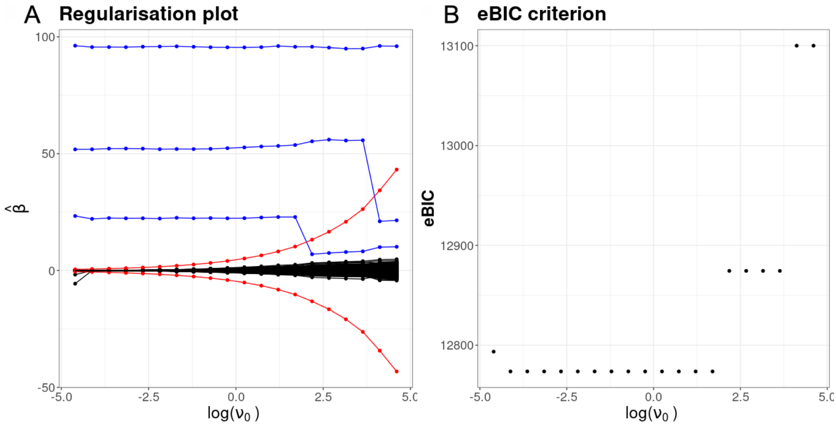


Figure: $n = 200$, $J = 10$, $p = 500$, $\Gamma^2 = 200$, $\sigma^2 = 30$, $\nu_1 = 12000$, $\mu = 1200$, $\beta = {}^t(100, 50, 20, 0, \dots, 0)$

Computing the MAP in a latent variables model

✤ Let's go back to the **first step** of the proposed method:

- Compute the MAP estimator of Θ
- Goal: maximise $\pi(\Theta|y) = \int_{\mathcal{Z}} \pi(\Theta, Z|y)dZ$ with

$$\pi(\Theta, Z|y) = \frac{p(y|\Theta, Z)p(\Theta, Z)}{\int_{\mathcal{Z}} \int_{\Lambda} p(y|\Theta, Z)p(\Theta, Z)d\Theta dZ}$$

- Non-explicit integral

EM algorithm

Reference: Dempster et al. (1977)

1. Initialisation: choose $\Theta^{(0)}$.
2. Iteration $k \geq 0$:
   - **E-step (Expectation):** compute

$$Q(\Theta|\Theta^{(k)}) = \mathbb{E}_{Z|(y,\Theta^{(k)})}\left[\log(\pi(\Theta, Z|y))\middle| y, \Theta^{(k)}\right].$$

   - **M-step (Maximisation):** compute

$$\Theta^{(k+1)} = \underset{\Theta \in \Lambda}{\operatorname{argmax}}\ Q(\Theta|\Theta^{(k)}).$$

3. $\hat{\Theta} = \Theta^{(K)}$, for K large enough.

SAEM and MCMC-SAEM algorithms

References: Delyon et al. (1999), Kuhn and Lavielle (2004)

1. Initialisation: choose $\Theta^{(0)}$ and $Q_0(\Theta) = 0$,
2. Iteration $k \geq 0$:
   - **S-step (Simulation):** simulate $Z^{(k)}$ using the result of one iteration of an MCMC procedure with $\pi(Z|y, \Theta^{(k)})$ for target distribution,
   - **SA-step (Stochastic Approximation):** compute an approximation of $Q(\Theta|\Theta^{(k)})$ according to:
   $$Q_{k+1}(\Theta) = Q_k(\Theta) + \gamma_k(\log \pi(\Theta, Z^{(k)}|y) - Q_k(\Theta)),$$
   - **M-step (Maximisation):** compute
   $$\Theta^{(k+1)} = \underset{\Theta \in \Lambda}{\operatorname{argmax}}\ Q_{k+1}(\Theta),$$
3. $\hat{\Theta} = \Theta^{(K)}$, for K large enough,

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

Specifics in Spike-and-Slab-NLMEM

Decomposition of Q:

$$Q(\Theta|\Theta^{(k)}) = \mathbb{E}_{(\varphi,\delta)|(y,\Theta^{(k)})}[\log(\pi(\Theta,\varphi,\delta|y))|y,\Theta^{(k)}]$$

$$= C + \underbrace{\mathbb{E}_{\varphi|y,\Theta^{(k)}}\left[\widetilde{Q}_1(y,\varphi,\theta,\Theta^{(k)})\middle|y,\Theta^{(k)}\right]}_{\text{non-explicit}} + \underbrace{\widetilde{Q}_2(\alpha,\Theta^{(k)})}_{\text{explicit}}$$

M-step:

- θ and α estimated separately.
- $\widehat{\alpha}$ updated as in an EM algorithm with $\widetilde{Q}_2(\alpha,\Theta^{(k)})$.
- $\widehat{\theta}$ updated via stochastic approximation of:

$$\mathbb{E}_{\varphi|y,\Theta^{(k)}}\left[\widetilde{Q}_1(y,\varphi,\theta,\Theta^{(k)})\middle|y,\Theta^{(k)}\right].$$

MCMC-SAEM algorithm in SSNLMEM

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

$$Q_{1,k+1}(\theta) = Q_{1,k}(\theta) + \gamma_k(\widetilde{Q}_1(y, \varphi^{(k)}, \theta, \Theta^{(k)}) - Q_{1,k}(\theta)),$$

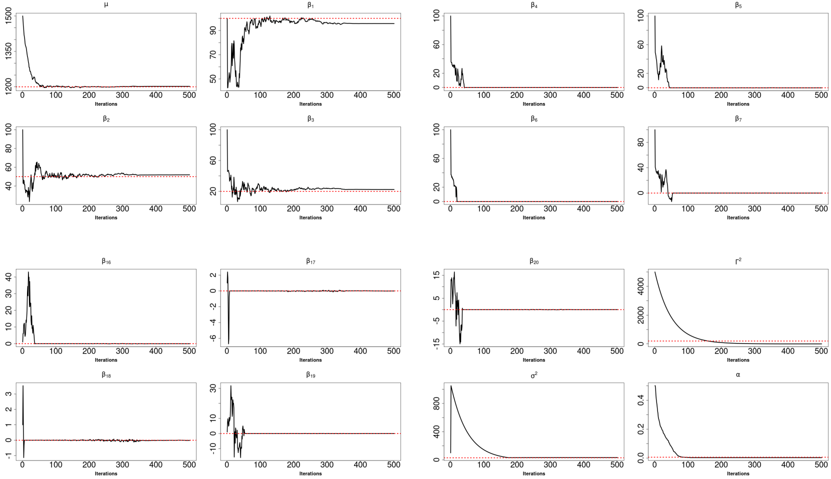
     and $\widetilde{Q}_2(\alpha, \Theta^{(k)})$,
   - **M-step (Maximisation):**

$$\theta^{(k+1)} = \underset{\theta \in \Lambda_\theta}{\text{argmax}}\ Q_{1,k+1}(\theta) \text{ and } \alpha^{(k+1)} = \underset{\alpha \in [0,1]}{\text{argmax}}\ \widetilde{Q}_2(\alpha, \Theta^{(k)}),$$

3. $\hat{\Theta} = \Theta^{(K)}$, for K large enough,

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

Convergence graphs



Logistic growth model

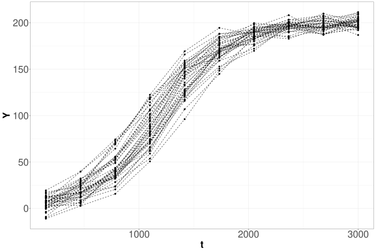


Figure: Simulated data

- Size of plant $i \in \{1, \ldots, n\}$ at time t_{ij}, $j \in \{1, \ldots, 10\}$:
  $y_{ij} = g(\varphi_i, \psi, t_{ij}) + \varepsilon_{ij}, \ \varepsilon_{ij} \overset{\text{iid}}{\sim} \mathcal{N}(0, \sigma^2)$ where:

$$g(\varphi_i, \psi, t_{ij}) = \frac{\psi_1}{1 + \exp\left(-\frac{t_{ij} - \varphi_i}{\psi_2}\right)}$$

  $\psi = (\psi_1, \psi_2)$ fixed effects.

- φ_i: characteristic time
  $\varphi_i = \mu + {}^t\beta V_i + \xi_i, \ \xi_i \overset{\text{iid}}{\sim} \mathcal{N}(0, \Gamma^2)$

$$\theta = (\mu, \beta, \psi, \sigma^2, \Gamma^2)$$

Simulation design

✤ Parameters:

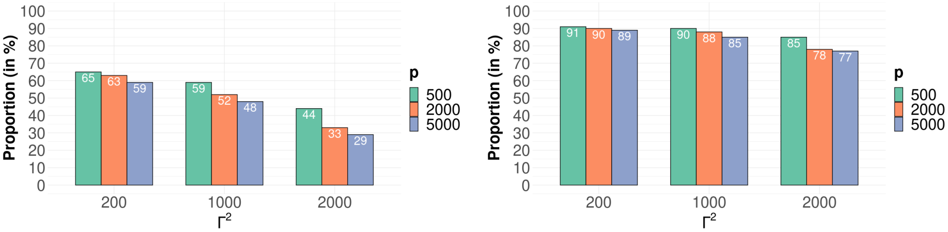
- $n \in \{100, 200\}$ individuals,
- $p \in \{500, 2000, 5000\}$ simulated covariates according to $V_i \sim \mathcal{N}(0, \Sigma)$:
  - ▶ Scenario i.i.d.: $\Sigma = Id$ ▶ Correlated scenarios: $\Sigma \neq Id$
- $\beta = {}^t(100, 50, 20, 0, \ldots, 0)$ covariate fixed effects vector,
- $\Gamma^2 \in \{200, 1000, 2000\}$ inter-individual variance,
- $\mu = 1200$, $\sigma^2 = 30$, $\psi = (\psi_1, \psi_2) = (200, 300)$.

✤ Spike-and-slab hyperparameters:

- $\nu_1 = 12000$ slab variance,
- $\log_{10}(\Delta) = \left\{ -2 + k \times \frac{4}{19}, k \in \{0, \ldots, 19\} \right\}$ grid of ν_0 values.

▶ For each combination of (n, p, Γ^2), the method is applied on 100 different simulated datasets.

Results for independent covariates



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

Figure: Empirical probability of correct model selection.

Summary of the results

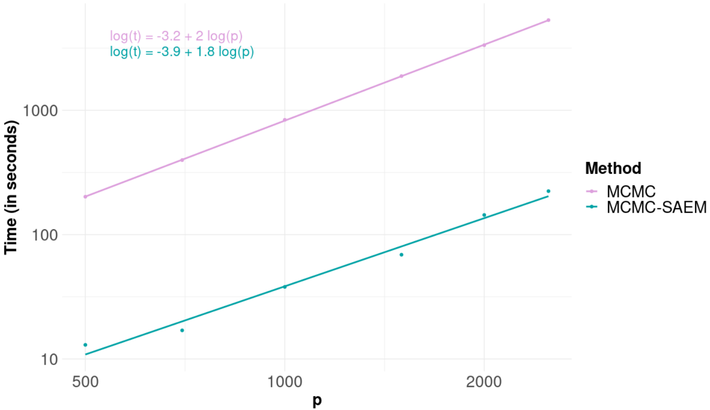
✤ Uncorrelated covariates $V_i \sim \mathcal{N}(0, I_p)$:

- Results improve as n increases.
- Degradation of results when p or Γ^2 increases.
- When the procedure fails, it is most often because it under-selects:
  - "Cautious" approach, few false positives!

✤ Correlated covariates $V_i \sim \mathcal{N}(0, \Sigma)$:

- Fairly similar good performance.
- More false positives and/or false negatives in some correlation scenarios:
  - $+$ false positives: correlations between active and non-active covariates.
  - $+$ false negatives: correlated active covariates.

Comparison with an MCMC implementation



NB: fast C++ adaptive MCMC (Nimble) versus R code

- Both methods have an execution time that grows **polynomially** with p.
- The proposed inference method can browse grid of about **20 values** of ν_0 while adaptive MCMC explores a single value.

1. Introduction

2. Methodology
   - Prior specification
   - Method
   - Computation of the MAP

3. Simulation study

4. Application to a real dataset

5. Conclusion

Presentation of the dataset

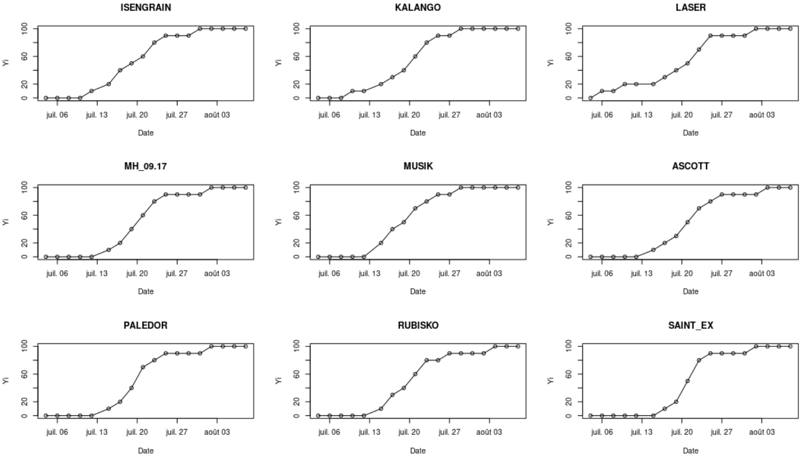
✤ Wheat leaf senescence data.

✤ **Panel:** $n = 216$ soft wheat varieties subjected to nitrogen stress, observed $J = 18$ times.

✤ Varieties respond differently to stress: for example, some of them tolerate stress better and senescence is delayed.

✤ **Aim:** select molecular markers, from among $p = 34838$ markers, which could be associated with this tolerance.

Data representation: percentage of desiccated leaves



⟹ Logistic growth

Modelling

$$
\begin{cases}
y_{ij} = g(\phi_i, t_{ij}) + \varepsilon_{ij} & , \varepsilon_{ij} \overset{\text{i.i.d.}}{\sim} \mathcal{N}(0, \sigma^2), \text{with } \phi_i = (\varphi_i, \psi_i) \in \mathbb{R}^2 \\
\varphi_i = \mu + {}^t\lambda v_i + {}^t\beta V_i + \xi_i & , \xi_i \overset{\text{i.i.d.}}{\sim} \mathcal{N}(0, \Gamma^2) \\
\psi_i = \eta + \omega_i & , \omega_i \overset{\text{i.i.d.}}{\sim} \mathcal{N}(0, \Omega^2)
\end{cases}
$$

where:

- $g(\phi_i, t_{ij}) = \dfrac{100}{1 + \exp\left(-\dfrac{t_{ij} - \varphi_i}{\psi_i}\right)}$,
- v_i: covariates not subject to selection, allows the inclusion of sub-populations in the model,
- V_i: molecular markers, subject to selection, which contains QTLs identified by biologists and markers associated with heading date which is highly correlated with φ_i.

$$\theta = (\mu, \lambda, \beta, \eta, \sigma^2, \Gamma^2, \Omega^2)$$

Data processing

✤ $p >> n$: ultra-high dimensional problem.

✤ Molecular markers $\Longrightarrow$ strong correlations/collinearity between covariates.

✤ Covariates have few modalities:

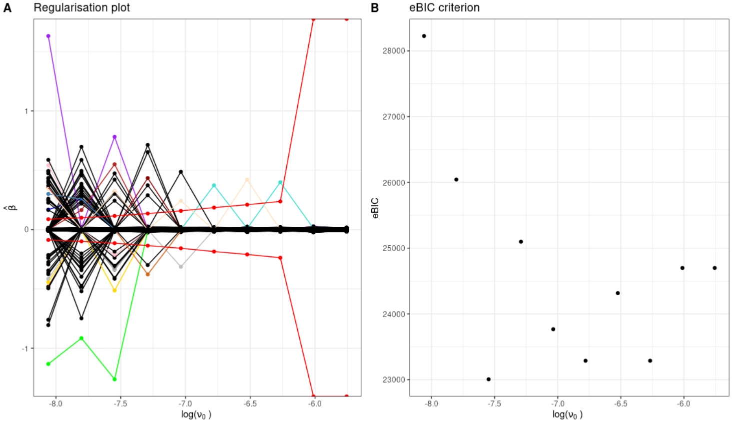
```
> table(nb_mod_cov)
nb_mod_cov
    1     2     3     4
   45  9237 19712  5844
```

✤ With "too many" 0's or "too many" 1's for some covariates, we remove:

- markers filled in the same way for all individuals,
- markers entered as the exact opposite of another marker (marker1=1-marker2).
- markers whose minimum and maximum modalities are not represented at least 10 times.
- markers that have a correlation > 0.7.

$$p = 6164$$

Results



- Selected support size: 20
- Number of covariates selected at least once along the grid: 90
- "Peak" structure could be explained by correlations between the covariates.

Conclusion and perspectives

✤ Summary:

- Development of an original method that combines SAEM and Bayesian variable selection.
- Very encouraging numerical results on simulated data.
- Faster method than a full MCMC implementation.

⇒ **Preprint:** Naveau and al. (2022). Bayesian high-dimensional covariate selection in non-linear mixed-effects models using the SAEM algorithm. arXiv:2206.01012.

✤ Perspectives:

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

Thanks for your attention!

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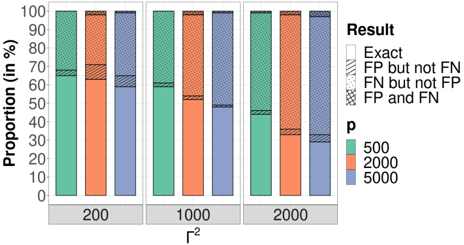
Specifics in Spike-and-Slab-NLMEM

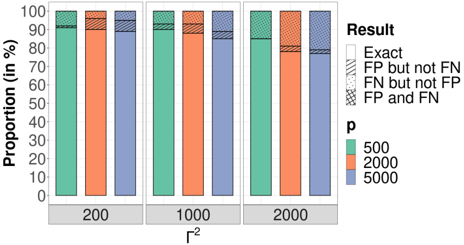
✤ Decomposition of Q:

$$
\begin{aligned}
Q(\Theta|\Theta^{(k)}) &= \mathbb{E}_{(\varphi,\delta)|(y,\Theta^{(k)})}[\log(\pi(\Theta,\varphi,\delta|y))|y,\Theta^{(k)}] \\
&= \mathbb{E}_{\varphi|(y,\Theta^{(k)})}\left[\mathbb{E}_{\delta|(\varphi,y,\Theta^{(k)})}\left[\log(\pi(\Theta,\varphi,\delta|y))|\varphi,y,\Theta^{(k)}\right]\middle| y,\Theta^{(k)}\right] \\
&= \mathbb{E}_{\varphi|(y,\Theta^{(k)})}\left[\widetilde{Q}(y,\varphi,\Theta,\Theta^{(k)})\middle| y,\Theta^{(k)}\right] \\
&= C + \underbrace{\mathbb{E}_{\varphi|y,\Theta^{(k)}}\left[\widetilde{Q}_1(y,\varphi,\theta,\Theta^{(k)})\middle| y,\Theta^{(k)}\right]}_{\text{non-explicit}} + \underbrace{\widetilde{Q}_2(\alpha,\Theta^{(k)})}_{\text{explicit}}
\end{aligned}
$$

Results for uncorrelated covariates



(a) For $n = 100$

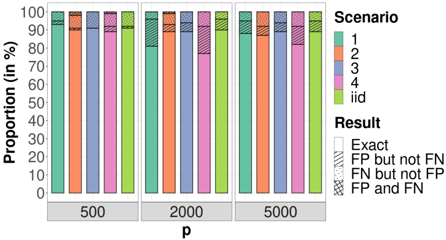


(b) For $n = 200$

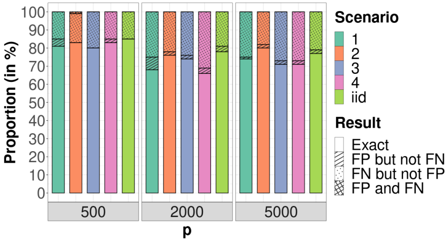
Correlated covariates $V_i \sim \mathcal{N}(0, \Sigma)$

Scenario	Σ
iid	I_p
1	$\begin{pmatrix} I_3 & 0_{3,p-3} \\ 0_{p-3,3} & (\rho_\Sigma^{\vert i-j \vert})_{i,j\in\{4,\dots,p\}} \end{pmatrix}$
2	$\begin{pmatrix} I_3 & A \\ {}^tA & I_{p-3} \end{pmatrix}$, with $A = \begin{pmatrix} 0 & 0 & \dots & 0 \\ 0 & 0 & \dots & 0 \\ & (\rho_\Sigma^{\vert 3-j \vert})_{j\in\{4,\dots,p\}} & & \end{pmatrix}$
3	$\begin{pmatrix} (\rho_\Sigma^{\vert i-j \vert})_{i,j\in\{1,\dots,3\}} & 0_{3,p-3} \\ 0_{p-3,3} & I_{p-3} \end{pmatrix}$
4	$(\rho_\Sigma^{\vert i-j \vert})_{i,j\in\{1,\dots,p\}}$

Results for $\rho_\Sigma = 0.3$

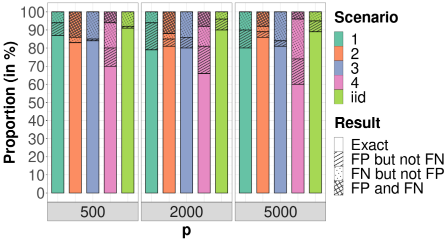


(c) For $\Gamma^2 = 200$

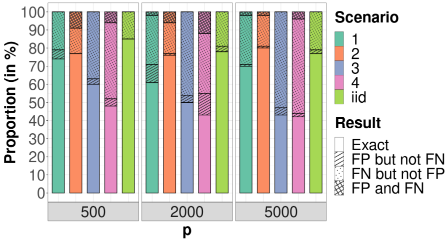


(d) For $\Gamma^2 = 2000$

Results for $\rho_\Sigma = 0.6$



(e) For $\Gamma^2 = 200$



(f) For $\Gamma^2 = 2000$