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

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Journée AppliBUGS

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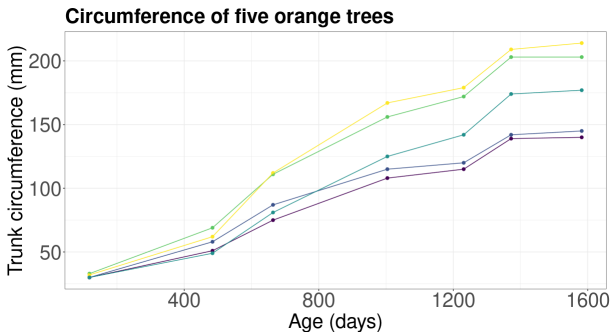
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Framework: repeated measurement data

- ❖ **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 $i \in \{1, \dots, n\}$, $j \in \{1, \dots, J\}$,

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

- $y_{ij} \in \mathbb{R}$: 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**:

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

- $\mu \in \mathbb{R}$: 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**:

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

- $\beta_\ell = 0 \iff$ 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 :

$$S_\beta = \left\{ \ell \in \{1, \dots, p\} \mid \beta_\ell \neq 0 \right\}.$$

High-dimensional covariate selection in NLMEM

- ❖ **Goal:** identify the non-zero components of β .
- ❖ **Specificity of the problem:** $p \gg n$
- ❖ **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

$$\begin{aligned}
 p(y; \theta) &= \int p(y|\varphi; \theta)p(\varphi; \theta)d\varphi = \prod_{i=1}^n \int p(y_i|\varphi_i; \theta)p(\varphi_i; \theta)d\varphi_i \\
 &= C_{\sigma^2, \Gamma^2} \prod_{i=1}^n \int \exp\left(-\sum_{j=1}^J \frac{(y_{ij} - g(\varphi_i, \psi, t_{ij}))^2}{2\sigma^2} - \frac{(\varphi_i - \mu - {}^t\beta V_i)^2}{2\Gamma^2}\right) d\varphi_i
 \end{aligned}$$

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)**: $y_i = \alpha + \beta^t X_i + \epsilon_i$
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.

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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):

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

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

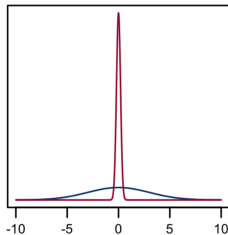
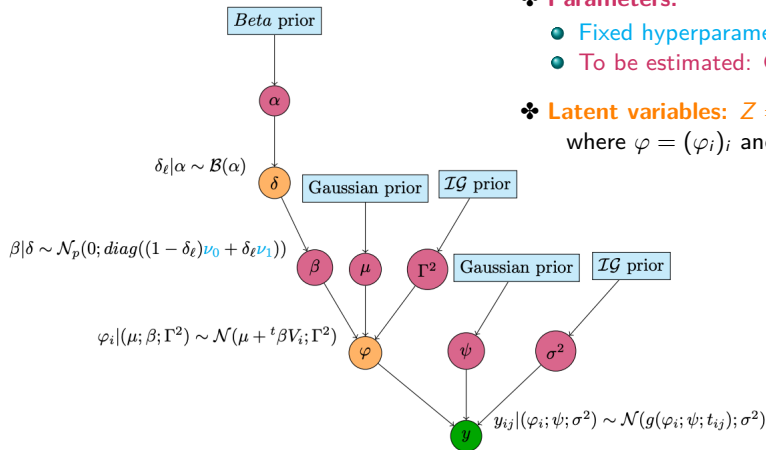


Figure: Spike-and-slab prior. Source: Deshpande et al. (2019)

Bayesian hierarchical model



- ❖ **Observations:** $y = (y_{ij})_{i,j}$
- ❖ **Parameters:**
 - **Fixed hyperparameters:** ν_0, ν_1, \dots
 - **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 .

- Creation of a model collection:** for each $\nu_0 \in \Delta$,
 - ▶ Compute $\hat{\Theta}$ by a MCMC-SAEM algorithm (Kuhn and Lavielle, 2004):

$$\hat{\Theta}_{\nu_0}^{MAP} = \underset{\Theta \in \Lambda}{\operatorname{argmax}} \pi(\Theta|y)$$

- ▶ Estimate $\hat{\delta}$ (Ročková and George, 2014):

$$\hat{\delta} = \underset{\delta}{\operatorname{argmax}} P(\delta | \hat{\Theta}_{\nu_0}^{MAP}) \text{ such as } \hat{\delta}_\ell = 1 \iff \mathbb{P}(\delta_\ell = 1 | \hat{\Theta}_{\nu_0}^{MAP}) \geq 0.5$$

$$\iff \text{Define } \hat{S}_{\nu_0} = \left\{ \ell \in \{1, \dots, p\} \mid |(\hat{\beta}_{\nu_0}^{MAP})_\ell| \geq s_\beta(\nu_0, \nu_1, \hat{\alpha}_{\nu_0}^{MAP}) \right\}$$

- Select the "best" model** among $(\hat{S}_{\nu_0})_{\nu_0 \in \Delta}$ by a fast criterion, eBIC (Chen and Chen, 2008):

$$\hat{\nu}_0 = \underset{\nu_0 \in \Delta}{\operatorname{argmin}} \left\{ -2 \log(p(y; \hat{\theta}_{\nu_0}^{MLE})) + B_{\nu_0} \times \log(n) + 2 \log \left(\binom{p}{B_{\nu_0}} \right) \right\}$$

with B_{ν_0} : number of free parameters in the model \hat{S}_{ν_0} .

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

Spike-and-slab regularisation plot

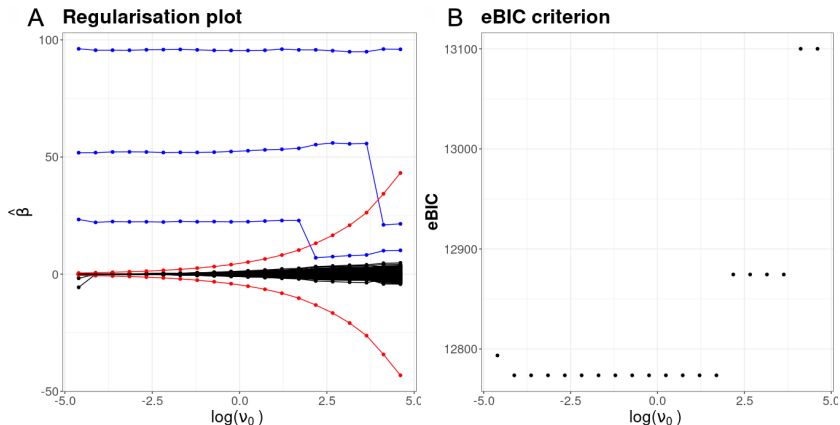


Figure: $n = 200$, $J = 10$, $p = 500$, $\Gamma^2 = 200$, $\sigma^2 = 30$, $\nu_1 = 12000$, $\mu = 1200$, $\beta = {}^t(100, 50, 20, 0, \dots, 0)$

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

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

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

$$\Theta^{(k+1)} = \operatorname{argmax}_{\Theta \in \Lambda} Q_{k+1}(\Theta),$$

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 :

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

❖ M-step:

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

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

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

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

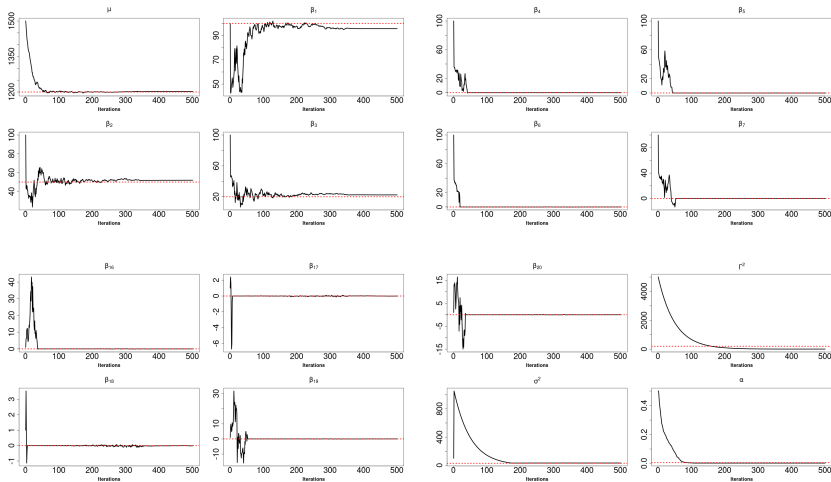
and $\tilde{Q}_2(\alpha, \Theta^{(k)})$,

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

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

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



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Logistic growth model

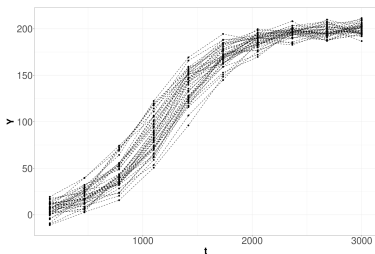


Figure: Simulated data

- Size of plant $i \in \{1, \dots, n\}$ at time t_{ij} , $j \in \{1, \dots, 10\}$:
 $y_{ij} = g(\varphi_i, \psi, t_{ij}) + \varepsilon_{ij}$, $\varepsilon_{ij} \stackrel{\text{iid}}{\sim} \mathcal{N}(0, \sigma^2)$ 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
 $\varphi_i = \mu + \beta V_i + \xi_i$, $\xi_i \stackrel{\text{iid}}{\sim} \mathcal{N}(0, \Gamma^2)$

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

Simulation design

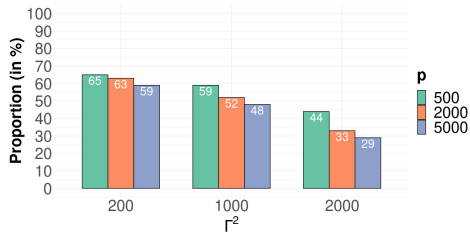
❖ Parameters:

- $n \in \{100, 200\}$ 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: $\Sigma \neq Id$
- $\beta = {}^t(100, 50, 20, 0, \dots, 0)$ covariate fixed effects vector,
- $\Gamma^2 \in \{200, 1000, 2000\}$ inter-individual variance,
- $\mu = 1200, \sigma^2 = 30, \psi = (\psi_1, \psi_2) = (200, 300)$.

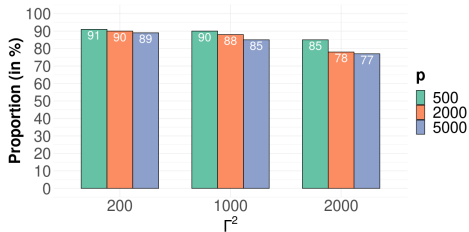
❖ Spike-and-slab hyperparameters:

- $\nu_1 = 12000$ slab variance,
 - $\log_{10}(\Delta) = \left\{ -2 + k \times \frac{4}{19}, k \in \{0, \dots, 19\} \right\}$ 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

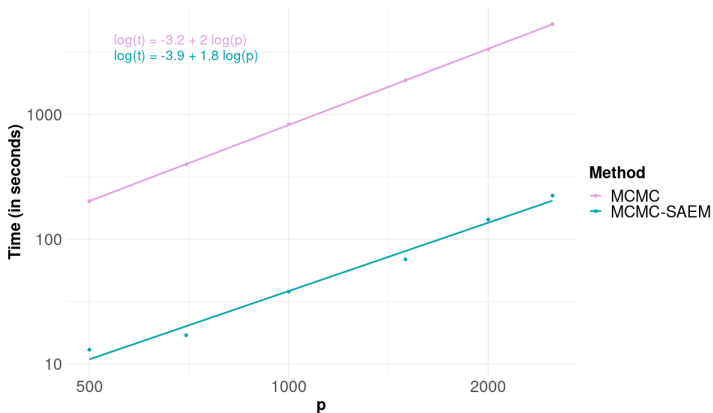
❖ Uncorrelated covariates $V_i \sim \mathcal{N}(0, I_p)$:

- 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.

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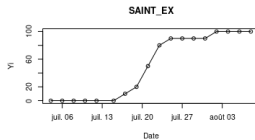
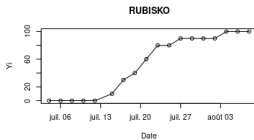
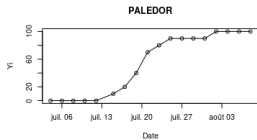
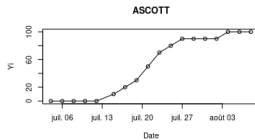
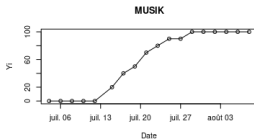
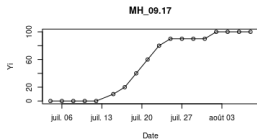
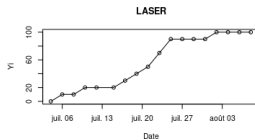
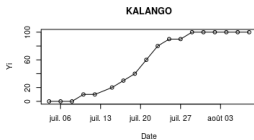
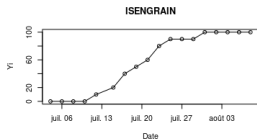
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Presentation of the dataset

- ❖ 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

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

where:

- $g(\phi_i, t_{ij}) = \frac{100}{1 + \exp\left(-\frac{t_{ij} - \varphi_i}{\psi_i}\right)}$,
- 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

- ❖ $p \gg n$: **ultra-high dimensional** problem.
- ❖ Molecular markers \implies **strong correlations/collinearity** between covariates.

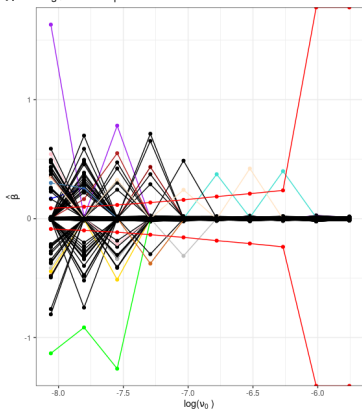
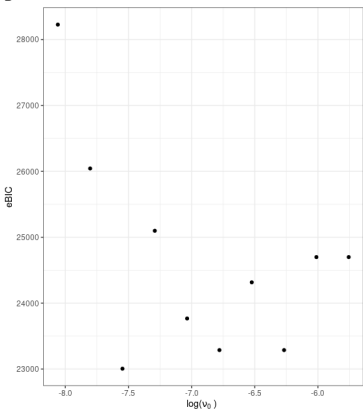
- ❖ Covariates have **few modalities**:

```
> 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

A Regularisation plot**B** eBIC criterion

- 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.

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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](https://arxiv.org/abs/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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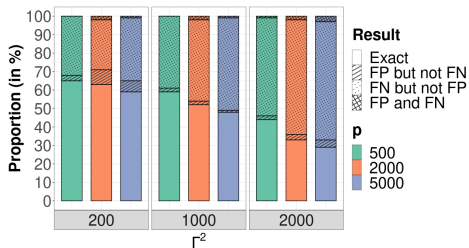
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Specifics in Spike-and-Slab-NLMEM

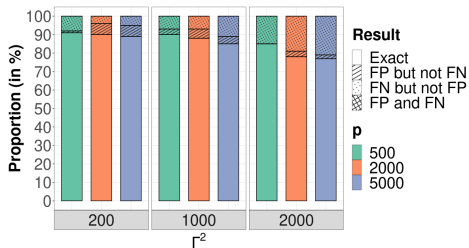
❖ Decomposition of Q :

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

Results for uncorrelated covariates



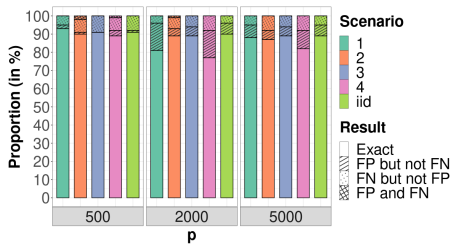
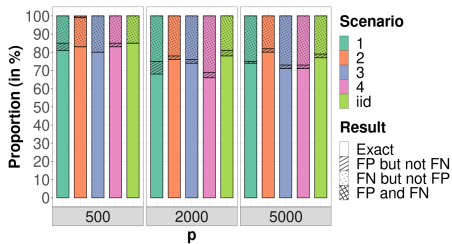
(a) For $n = 100$



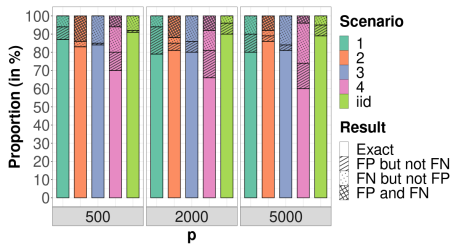
(b) For $n = 200$

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

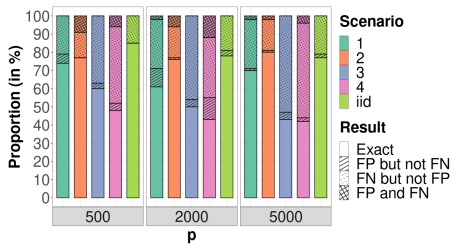
Scenario	Σ
iid	I_p
1	$\left(\begin{array}{c c} I_3 & 0_{3,p-3} \\ \hline 0_{p-3,3} & (\rho_\Sigma^{ i-j })_{i,j \in \{4, \dots, p\}} \end{array} \right)$
2	$\left(\begin{array}{c c} I_3 & A \\ \hline {}^t A & I_{p-3} \end{array} \right), \text{ with } A = \begin{pmatrix} 0 & 0 & \dots & 0 \\ 0 & 0 & \dots & 0 \\ & & (\rho_\Sigma^{ 3-j })_{j \in \{4, \dots, p\}} & \end{pmatrix}$
3	$\left(\begin{array}{c c} (\rho_\Sigma^{ i-j })_{i,j \in \{1, \dots, 3\}} & 0_{3,p-3} \\ \hline 0_{p-3,3} & I_{p-3} \end{array} \right)$
4	$(\rho_\Sigma^{ i-j })_{i,j \in \{1, \dots, p\}}$

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 $\Gamma^2 = 2000$