Some contributions on variable selection in nonlinear mixed-effects models.

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1. Introduction and model formulation

2. Covariate selection
   - On the use of BIC in NLMEM
   - High-dimensional variable selection in NLMEM

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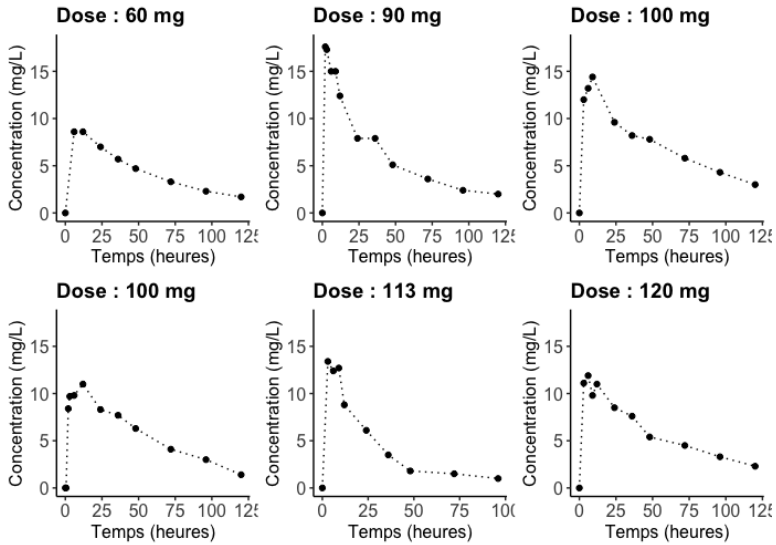
Motivating example : pharmacokinetic (PK) studies

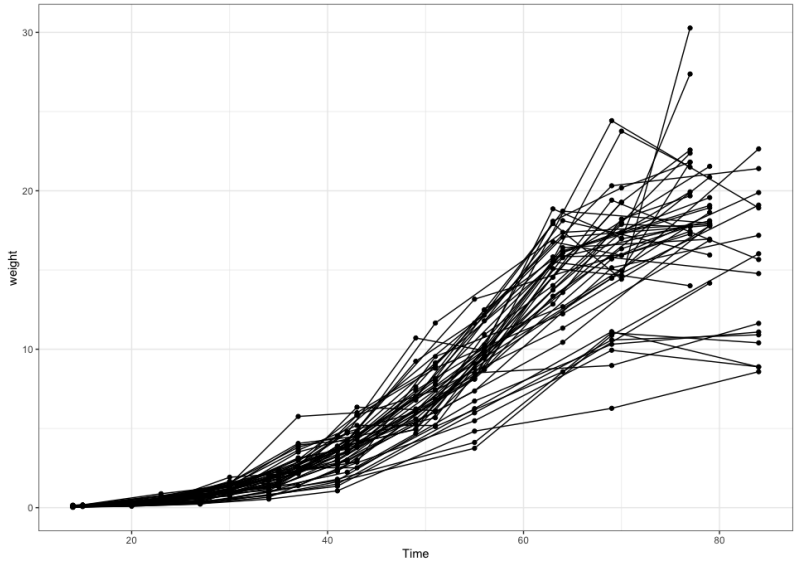


Clinical issues : define the optimal modalities of drug administration

Statistical issues :

- describe the time course of drug absorption, distribution, metabolism, and excretion in the body
- estimate key PK parameters (such as absorption or elimination rates)
- evaluate the influence of covariates (such as age or weight)

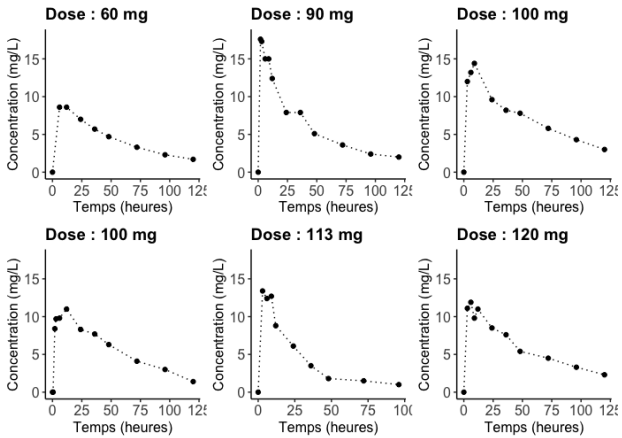
Other example : growth of soybean plants (`nlme`)

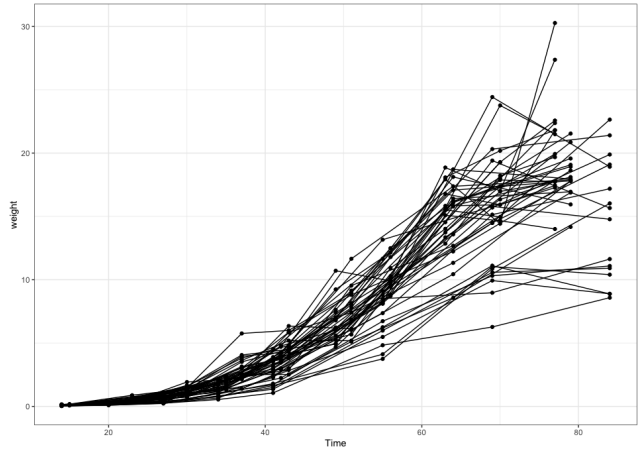


Biological issues : optimize crops

Statistical issues :

- describe the growth curves and estimate meaningful quantities (growth rate, growth plateau, etc.)
- characterize the part due to the genotype and the part due to the year of culture in the observed differences
- be able to make predictions





Common features that require special consideration in the statistical models

- repeated measurements from several subjects
- similarly-shaped individual profiles
- peak/maximum value, rise, decay vary from one individual to another

1) Description of the intra-individual variability

$$y_{ij} \underset{ind.}{\sim} f(t_{ij}, \phi_i) + g(t_{ij}, \phi_i) e_{ij} \ , \ e_{ij} \underset{i.i.d.}{\sim} \mathcal{N}(0,1) \ , \ j = 1 : n_i \ , \ i = 1 : N$$

where

- y_{ij} : jth observation for individual i
- f, g : (nonlinear, often mechanistic) functions governing within-individual behavior/residual variance
- $\phi_i \in \mathbb{R}^d$: parameters for individual i

2) Description of the inter-individual variability

$$\phi_i = \mu + \beta C_i + \eta_i, \ \eta_i \underset{i.i.d.}{\sim} \mathcal{N}(0, \Omega)$$

- $C_i \in \mathbb{R}^q$: vector of covariates for individual i
- $\mu \in \mathbb{R}^d$: intercept vector
- β : $d \times q$ matrix of fixed-effects
- $\theta = (\mu, \beta, \Omega)$

PK example (Data)

1) Observations :

$$y_{ij} = f_{ij} + f_{ij} e_{ij} \ , \ f_{ij} = f(t_{ij}, D_i, \phi_i) \ , \ e_{ij} \underset{i.i.d.}{\sim} \mathcal{N}(0,1)$$

$$f(t, D, k_a, V, Cl) = \frac{D\, k_a}{V\, k_a - Cl} \left(e^{-(Cl/V)\, t} - e^{-k_a\, t} \right)$$

2) Individual parameters :

$$\begin{aligned} \log k_{a,i} &= \mu_{ka} \ , \\ \log V_i &= \mu_V + \beta_V c_i + \eta_{V,i} \ , \ \eta_{V,i} \underset{i.i.d.}{\sim} \mathcal{N}(0, \omega_V^2) \\ \log Cl_i &= \mu_{Cl} + \eta_{Cl,i} \ , \ \eta_{Cl,i} \underset{i.i.d.}{\sim} \mathcal{N}(0, \omega_{Cl}^2) \end{aligned}$$

Typical questions

1) Estimation of the population parameter θ
   - Computation ?
   - Theoretical properties ?
2) Computation of the Fisher information matrix, computation of the likelihood, ...
3) Model building, ...

Difficult questions because of non linearity + latent variable structure of the model

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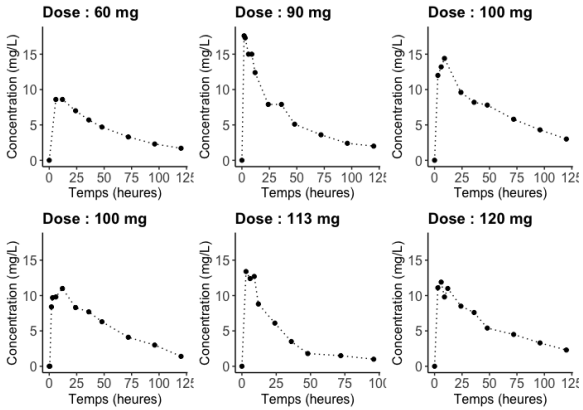
1. Joint work with Marie-Anne Poursat and Marc Lavielle published in *A note on BIC in mixed effects models.*. (2014), Electronic Journal of Statistics 8(1) p. 456-475
2. Joint work with Marie-Anne Poursat published in *An iterative algorithm for joint covariate and random effect selection in mixed effects models.* (2020), The International Journal of Biostatistics 16(2), 20190082

Purpose : Characterizing inter-individual variability



$$y_{ij} \underset{ind.}{\sim} f(t_{ij}, \phi_i) + g(t_{ij}, \phi_i) e_{ij} \ , \ e_{ij} \underset{i.i.d.}{\sim} \mathcal{N}(0,1)$$
$$\phi_i = \mu + \beta C_i + \eta_i, \eta_i \underset{i.i.d.}{\sim} \mathcal{N}(0, \Omega)$$

Questions

- which covariates for which components of ϕ_i ?
  $\hookrightarrow$ support of β (i.e. non nul coefficients in β) ?

$$S_\beta = \{(k, k') \in \{1, \dots, d\} \times \{1, \dots q\} : \beta_{k,k'} \neq 0\}$$

- on which parameters to include random effects, with which covariance structure (i.e. non nul elements in Ω) ?
  $\hookrightarrow$ Related work : tests on variance components in NLMEM, see (Baey et al., 2019)

- State of the art
  - Many methods for linear mixed-effects models
    - LASSO (Bondell H. D. et al., 2010), (Schelldorfer J. et al., 2011)
    - ...

    ...but no contribution in nonlinear models
  - In practice : BIC (Bayesian information criterion) is widely used (Schwarz G., 1978)

$$-2\mathcal{LL} + \dim(\theta) \times \log(\text{sample size})$$

$\rightarrow$ Sample size definition is unclear : $= N$ or $n_{tot} = \sum_{i=1}^{N} n_i$?

no consensus, both definitions are implemented in softwares

- Purpose : propose a good definition of the BIC by revisiting the theoretical foundations of the criterion

Theoretical fundations of the criterion (Schwarz G., 1978)

- Model collection : $\mathfrak{M} = \{\mathcal{M}_1, \ldots, \mathcal{M}_K\}$
- Bayesian model choice :

$$\begin{aligned} \hat{\mathcal{M}} &= \arg\max_{\mathcal{M}\in\mathfrak{M}} p(\mathcal{M}_k|\mathrm{Y}) \\ \text{where } p(\mathcal{M}|\mathrm{Y}) &\propto \pi(\mathcal{M})p(\mathrm{Y}|\mathcal{M}) \\ \text{and } p(\mathrm{Y}|\mathcal{M}) &= \int p(\mathrm{Y}|\theta,\mathcal{M})p(\theta|\mathcal{M})d\theta. \end{aligned}$$

- Laplace approximation :

$$\log p(\mathrm{Y}|\mathcal{M}) \approx \log p(\mathrm{Y}|\hat{\theta},\mathcal{M}) - \frac{1}{2}\log\det\left(H_{\hat{\theta}}\right), H_{\hat{\theta}} = -\frac{\partial^2 \log p(\mathrm{Y}|\theta,\mathcal{M})}{\partial\theta\partial\theta'}|_{\theta=\hat{\theta}}$$

- In models based on n independent observations, $H_{\hat{\theta}} \approx n\mathcal{I}_{\hat{\theta}}$ when $n \to \infty$ and

$$\frac{1}{2}\log\det\left(H_{\hat{\theta}}\right) \approx \frac{\dim(\theta)}{2}\log n + \frac{1}{2}\log\det\left(\mathcal{I}_{\hat{\theta}}\right),$$

- Parameter partitioning :

$$\begin{pmatrix} \phi_{F,i} \\ \phi_{R,i} \end{pmatrix} = \begin{pmatrix} \mu_F \\ \mu_R \end{pmatrix} + \begin{pmatrix} \beta_F \\ \beta_R \end{pmatrix} C_i + \begin{pmatrix} 0 \\ \eta_{R,i} \end{pmatrix} \ , \ \eta_{R,i} \underset{i.i.d.}{\sim} \mathcal{N}(0, \Omega_R)$$

- Asymptotic framework : $N \to \infty$, $\min_i n_i \to \infty$ [Nie, 2007]

$$\begin{pmatrix} \sqrt{n_{tot}} & 0 \\ 0 & \sqrt{N} \end{pmatrix} \begin{pmatrix} \widehat{\beta_F} - \beta_F^\star \\ \widehat{\beta_R} - \beta_R^\star \end{pmatrix} \longrightarrow \mathcal{N}\left(\mathbf{0}, \begin{pmatrix} \mathcal{I}_1 & 0 \\ 0 & \mathcal{I}_2 \end{pmatrix} \right)$$

  - $H_{\hat{\theta}} \approx$ block diagonal
  - $\log\det\left(H_{\hat{\theta}}\right) \approx \log\det(n_{\text{tot}}\mathcal{I}_1) + \log\det(N\,\mathcal{I}_2)$

Result

Select model (i.e. covariate structure) minimizing :

$$BIC_h = -2\mathcal{LL} + \dim(\beta_R)\log N + \dim(\beta_F)\log n_{\text{tot}}$$

Now implemented in the `saemix` *R package*

$$BIC_h = -2\mathcal{LL} + \dim(\beta_R)\log N + \dim(\beta_F)\log n_{\text{tot}}$$

Remarks

- Covariate selection depends on Ω.
- Hybrid version of the two simplest (empirical) BIC definitions :
  - If $\dim(\beta_R) = 0$,
$$BIC_{n_{\text{tot}}} = -2\mathcal{LL} + \dim(\beta)\log n_{\text{tot}}.$$
  - If $\dim(\beta_F) = 0$,
$$BIC_N = -2\mathcal{LL} + \dim(\beta)\log N.$$

Numerical experiments

- BIC_h performs better than BIC_N and $BIC_{n_{\text{tot}}}$
- Results evoke theoretical consistency for BIC_h (theoretical study under progress)

Algorithm for joint selection

- Simultaneous selection of covariates and random effects

$$\phi_i = \mu + \beta C_i + \eta_i, \eta_i \underset{i.i.d.}{\sim} \mathcal{N}(0, \Omega)$$

$\rightarrow$ Exhaustive search impossible

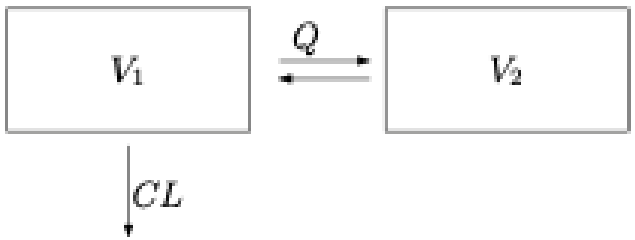
Ex. $q = 6$ covariates, $d = 3$ individual parameters $\Rightarrow \approx 2$ millions possible combinations

$\rightarrow$ Incorrect specification of $\beta \Leftrightarrow$ Incorrect specification of Ω

- Iterative algorithm, iteration t
  1. Selection of the random effect structure (BIC_Ω, $pen = \cdots \log N$)
  2. Selection of the covariate structure (stepwise, BIC_β, $pen = \cdots \log N + \cdots \log n_{tot}$)

- Numerical experiments :
  - Performance equivalent to exhaustive search or competitive methods
  - Substantial reduction of the calculation time

- Biological context : PK of an antibiotic administered by infusion (Burdet C. et al., 2015)
- Model :



$$\frac{dA_1(t,\phi)}{dt} = \frac{Q}{V_2}A_2(t,\phi) - \frac{Q+CL}{V_1}A_1(t,\phi) + \frac{dose}{T_{inf}}\frac{1}{V_1}\mathbb{1}_{0\leq t-t_D\leq T_{inf}}$$

$$\frac{dA_2(\phi)}{dt} = \frac{Q}{V_1}A_1(t,\phi) - \frac{Q}{V_2}A_2(t,\phi)$$

$$Y_{ij} = A_1(t_{ij},\phi_i) + (a + bA_1(t_{ij},\phi_i))\epsilon_{ij} \ , \ \epsilon_{ij} \underset{i.i.d.}{\sim} \mathcal{N}(0,1)$$

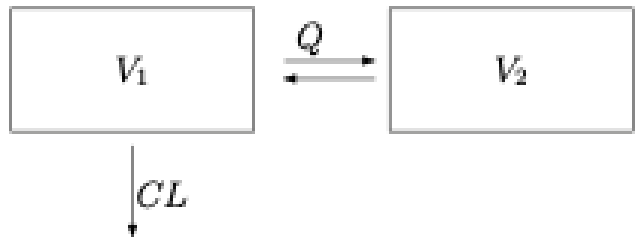
$$\phi_i = (\log CL_i, \log V_{1,i}, \log Q_i, \log V_{2,i})^\top = \mu + \beta C_i + \eta_i \ , \ \eta_i \underset{i.i.d.}{\sim} \mathcal{N}(0,\Omega)$$

- Observations (y_{ij}) : blood concentration of the antibiotic
  - $N = 53$ patients, $n_{tot} = 247$
  - $q = 12$ covariates

Pharmacokinetics example

- Model for the individual parameters :

$$\phi_i = (\log CL_i, \log V_{1,i}, \log Q_i, \log V_{2,i})^\top$$
$$= \mu + \beta C_i + \eta_i \ , \ \eta_i \underset{i.i.d.}{\sim} \mathcal{N}(0, \Omega)$$



- Result :

covariates — random effects

ϕ	$CICr$	age	$weight$	sex	P/F	η
CL	$\star\bullet$	$\star$				$\star\bullet$
V_1			$\star\bullet$		$\star\bullet$	$\star\bullet$
Q				$\star$		$\bullet$
V_2	$\star$					$\star\bullet$

	BIC_N
$\star$	1492.624
$\bullet$	1643.676

($\star$) our method

($\bullet$) (Burdet C. et al., 2015)

$\rightarrow$ best compromise between covariates and random effects

$\rightarrow$ best choice of dose according to the sex and age of the patients ?

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First part of M. Naveau's PhD

Preprint available at `https://hal.inrae.fr/hal-03685060`

M. Naveau et al. (2022) *Bayesian high-dimensional covariate selection in non-linear mixed-effects models using the SAEM algorithm.*

Model

1) Description of the intra-individual variability

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2) Description of the inter-individual variability

$$\phi_i = \mu + \beta C_i + \eta_i, \ \eta_i \underset{i.i.d.}{\sim} \mathcal{N}(0, \Omega)$$

Issue : covariate selection in large dimension framework, *ie* $q >> N$
$\hookrightarrow$ BIC can not be used anymore

Consider $d = \dim(\phi_i) = 1$ (but extension to $d > 1$ should be straightforward)

Frequentist framework :

- Linear mixed-effects models : theoretical consistency results on Lasso-type methods (Schelldorfer J. et al., 2011).
- Nonlinear mixed-effects models : computational aspects only (Bertrand J. and Balding D. J., 2013), (Ollier, 2022).

Bayesian framework :

- Linear (fixed-effects) models : use of sparsity priors with both computational and theoretical contributions (see Tadesse and Vannucci (2021)).
- Nonlinear mixed-effects models : implementation of MCMC methods (Lee, 2022).

Our approach : Combining *spike-and-slab* priors for variable selection and the *MCMC-SAEM* algorithm.

Spike-and-slab prior (George and McCulloch, 1997)

For each $1 \leq \ell \leq q$: inclusion variable

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

and distribution

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

i.e. the β_ℓ's 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

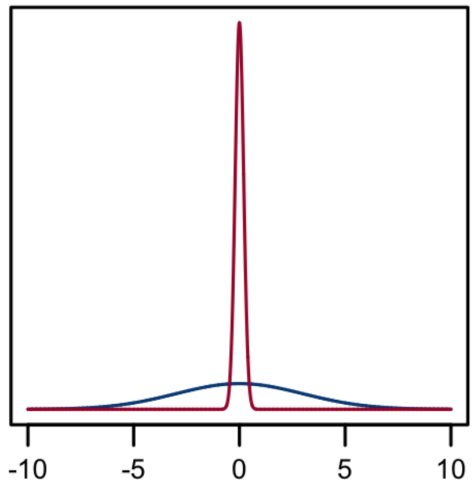
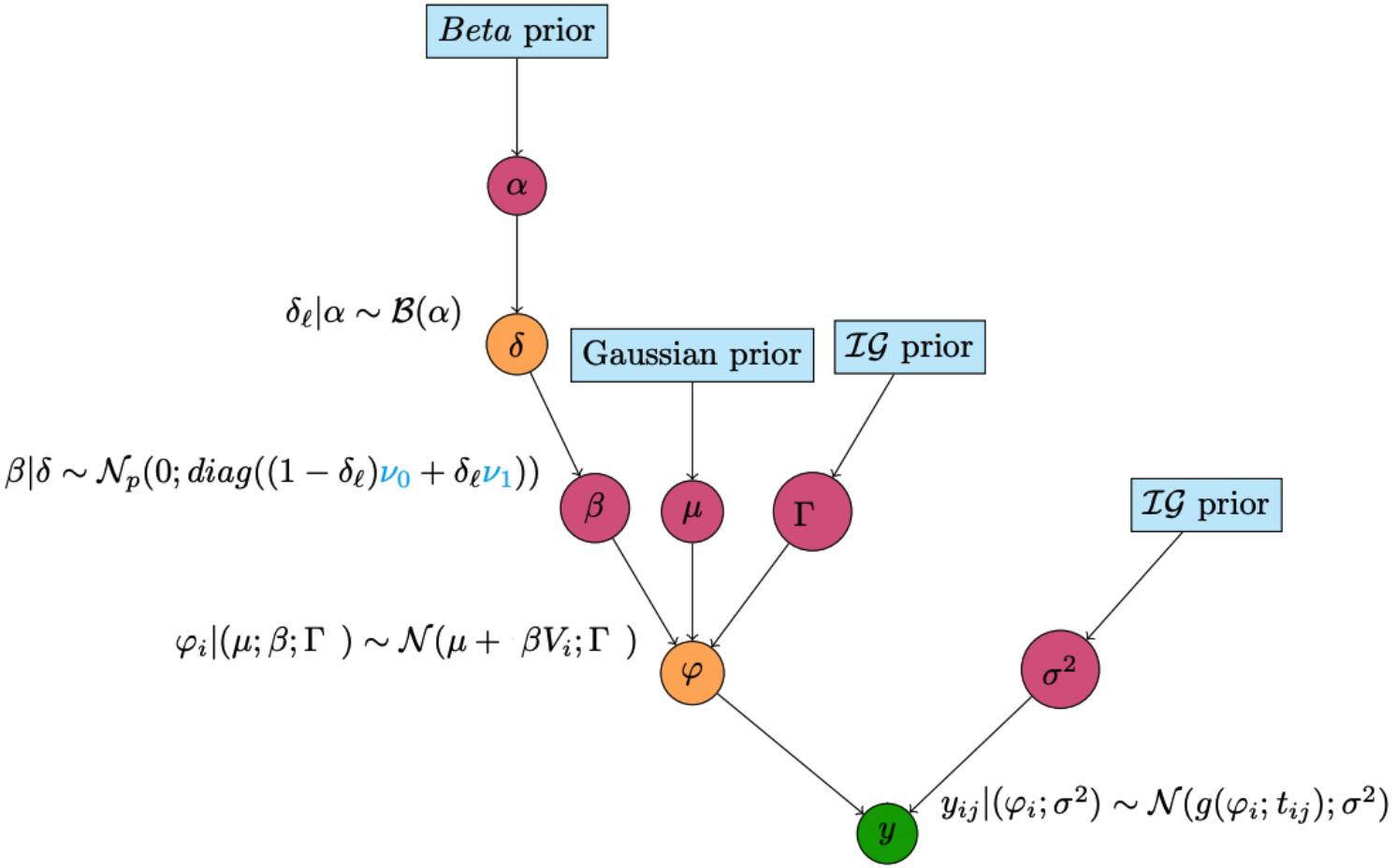


Figure – Prior spike-and-slab. Source : Deshpande et al. (2019)

Hierarchical bayesian model



Proposed method : explore different levels of sparsity for β by trying different values for ν_0

1. For $\nu_0 \in \Delta$,
   - Compute the maximum *a posteriori* estimator of Θ with an MCMC-SAEM algorithm :

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

   - Select covariates (Ročková and George, 2014) :

$$\widehat{S}_{\nu_0} = \left\{ \ell \in \{1, \ldots, p\} \;\middle|\; |(\widehat{\beta}_{\nu_0}^{MAP})_\ell| \geq s_\beta(\nu_0, \nu_1, \widehat{\alpha}_{\nu_0}^{MAP}) \right\}$$

2. Select the "best" model among $(\widehat{S}_{\nu_0})_{\nu_0 \in \Delta}$ with eBIC (Chen and Chen, 2008) :

$$\hat{\nu}_0 = \underset{\nu_0 \in \Delta}{\text{argmin}} \left\{ eBIC(\widehat{S}_{\nu_0}) \right\}$$

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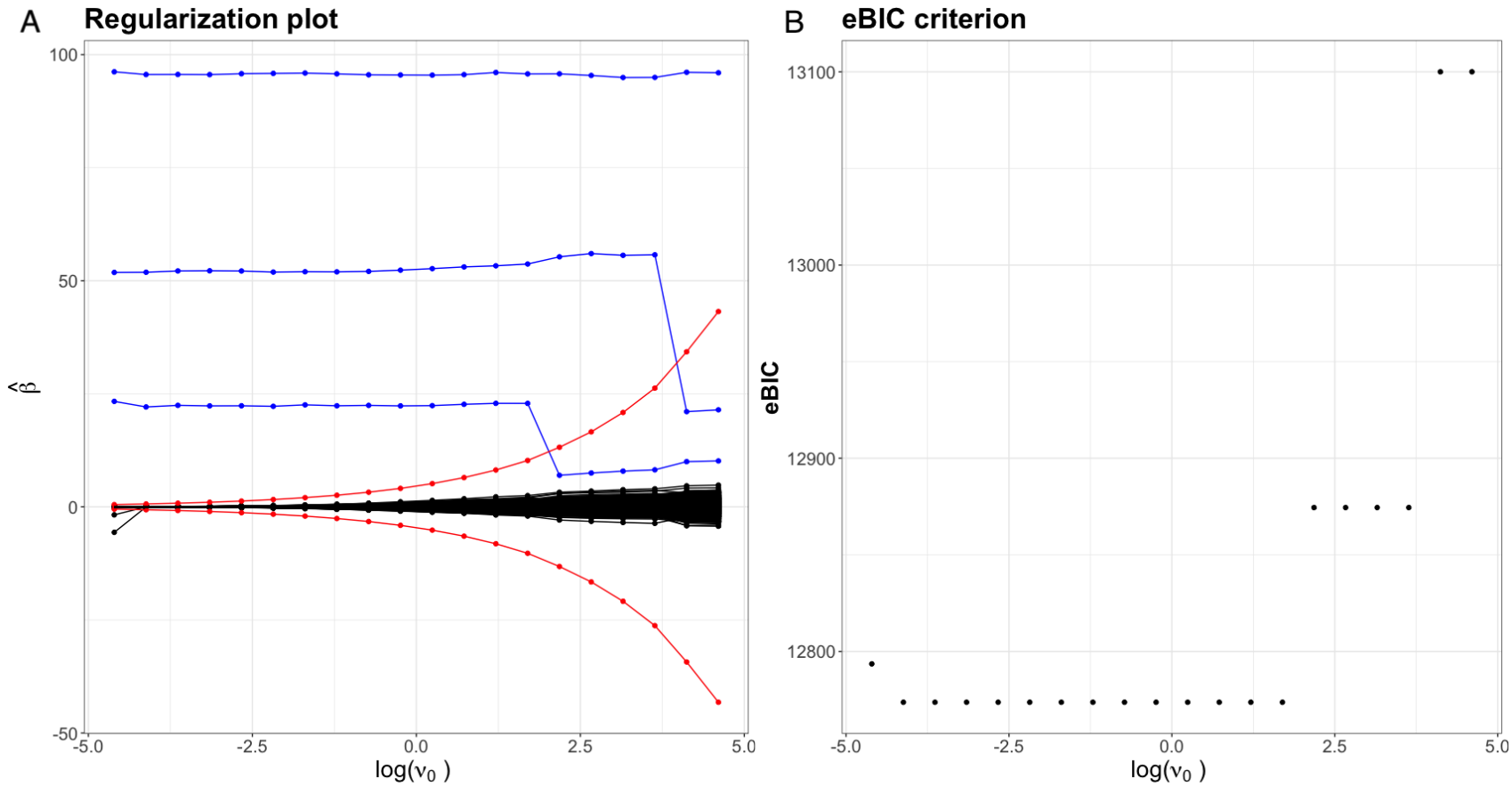
   Threshold ? Estimate the *a posteriori* inclusion probabilities of each covariate :

$$\hat{\delta} = \underset{\delta}{\text{argmax}}\ P(\delta|\hat{\Theta}^{MAP}_{\nu_0}) \text{ s.t. } \hat{\delta}_\ell = 1 \Longleftrightarrow \mathbb{P}(\delta_\ell = 1|\hat{\Theta}^{MAP}_{\nu_0}) \geq 0.5$$

2. Select the "best" model among $(\widehat{S}_{\nu_0})_{\nu_0 \in \Delta}$ with eBIC (Chen and Chen, 2008) :

$$\hat{\nu}_0 = \underset{\nu_0 \in \Delta}{\text{argmin}} \left\{ eBIC(\widehat{S}_{\nu_0}) \right\}$$

Regularization plot



Numerical experiments

Model

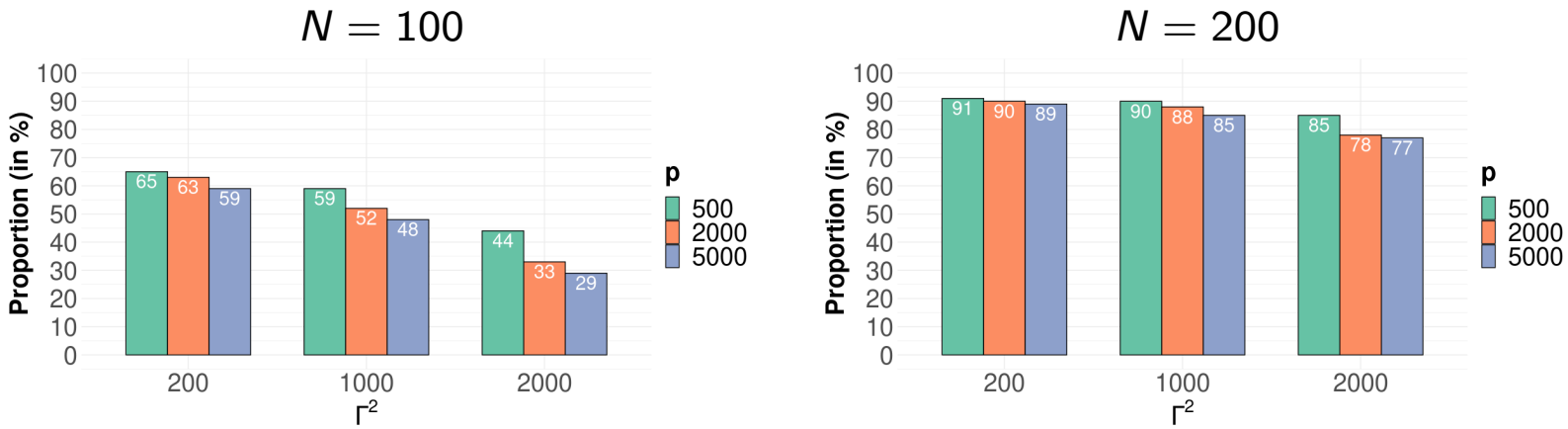
- $y_{ij} = f(\varphi_i, \psi, t_{ij}) + \varepsilon_{ij},\ \varepsilon_{ij} \overset{\text{iid}}{\sim} \mathcal{N}(0, \sigma^2)$ where

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

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

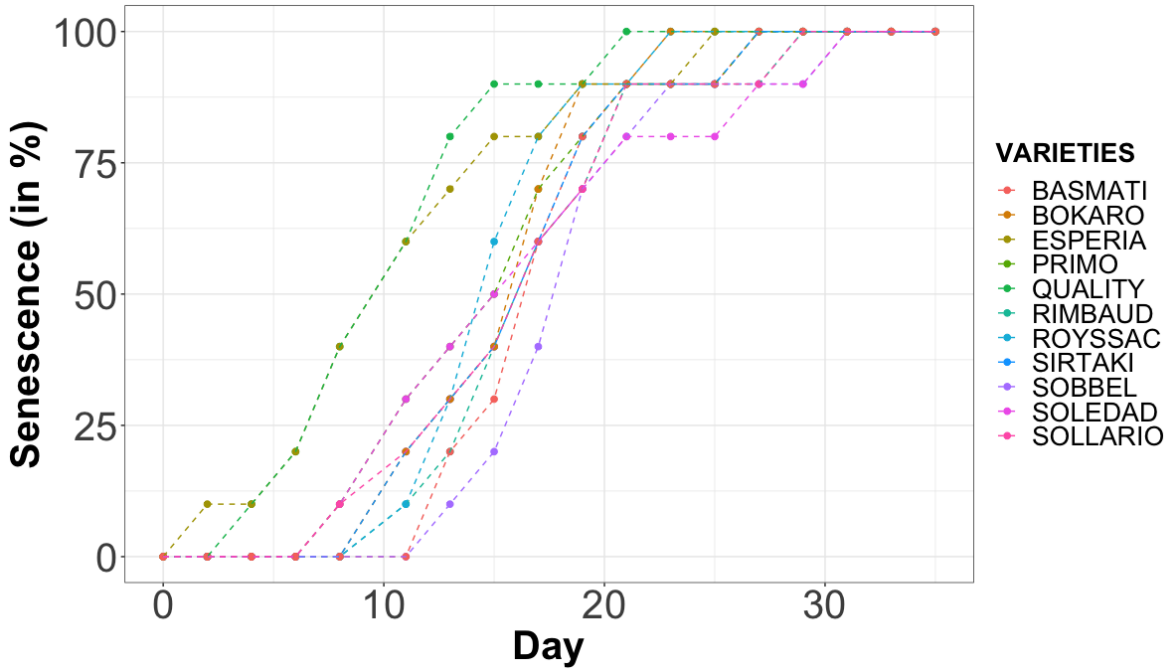
- $\varphi_i = \mu + {}^t\beta V_i + \xi_i,\ \xi_i \overset{\text{iid}}{\sim} \mathcal{N}(0, \Gamma^2)$

Results



Application : plant senescence genetic marker identification

- Observations : proportion of senesced surface of the canopy (y_{ij}) for $N = 220$ wheat varieties at $n = 18$ time points



- Goal : identify genetic markers associated to senescence
  - 26 189 SNPs in total
  - chromosome by chromosome analysis $\Rightarrow q \equiv 2000 >> N$ for each chromosome

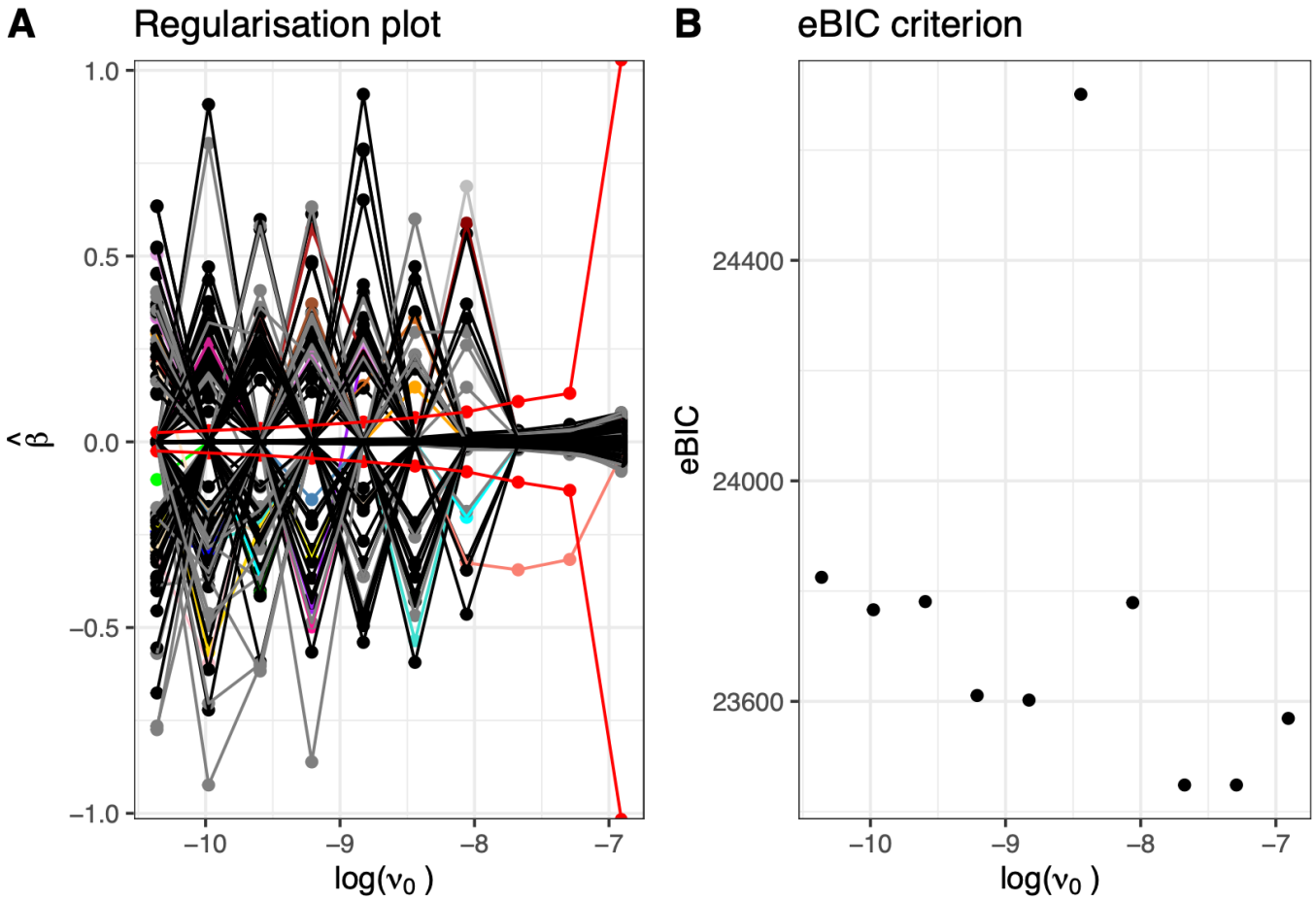
Model

$$\begin{cases} y_{ij} = \dfrac{100}{1 + \exp\left(-\dfrac{t_{ij} - \varphi_i}{\psi_i}\right)} + \varepsilon_{ij}, & \varepsilon_{ij} \overset{\text{i.i.d.}}{\sim} \mathcal{N}(0, \sigma^2), \\ \varphi_i = \mu + \lambda v_i + \beta C_i + \xi_i, & \xi_i \overset{\text{i.i.d.}}{\sim} \mathcal{N}(0, \Gamma^2), \\ \psi_i = \eta + \omega_i, & \omega_i \overset{\text{i.i.d.}}{\sim} \mathcal{N}(0, \Omega^2), \end{cases}$$

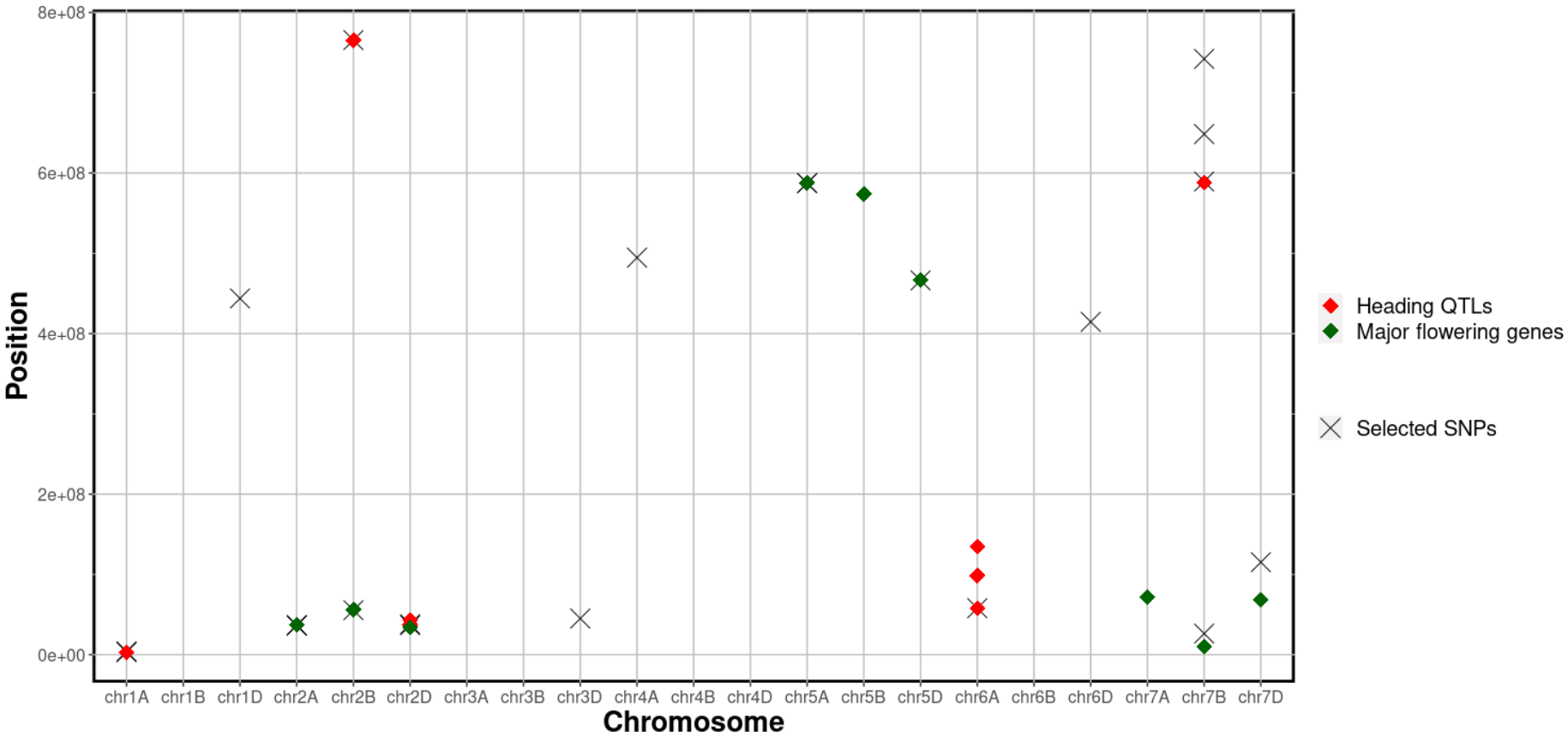
where

- C_i : q-vector of genetic markers for variety i, $1 \leq i \leq N$
- v_i : sub-populations covariates, not subject to selection

Regularization plot for Chromosome 6A



Results


8e+08
6e+08
4e+08
2e+08
0e+00
Position
chr1A chr1B chr1D chr2A chr2B chr2D chr3A chr3B chr3D chr4A chr4B chr4D chr5A chr5B chr5D chr6A chr6B chr6D chr7A chr7B chr7D
Chromosome
Heading QTLs
Major flowering genes
Selected SNPs

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