Bayesian variable selection for structured variables: applications in genetics

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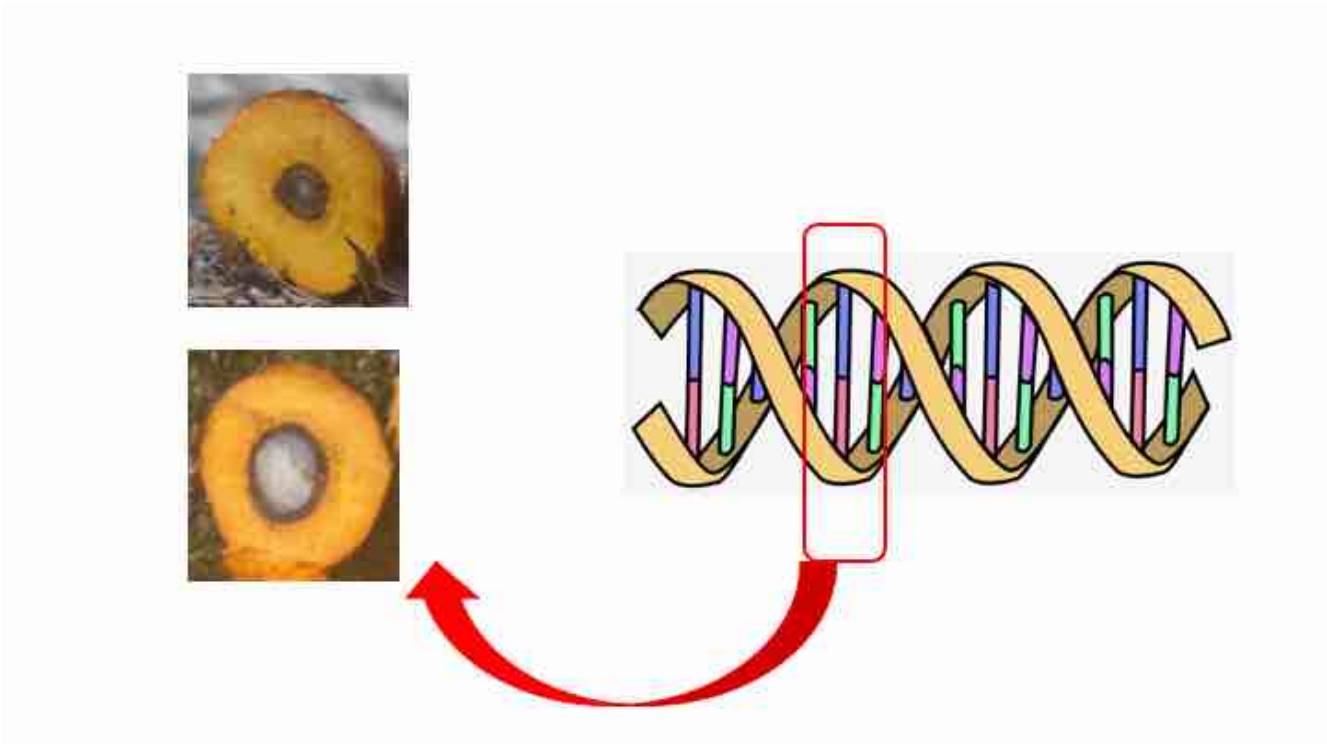
Outline

Biological context

In genetics, one of the most important objective is to identify the genomic regions involved in the variability of a phenotype



Which genomic regions may explain/is related to the differences observed in oil palm fruits?

Biological context

With the advance of high-throughput genotyping and phenotyping technologies:

- ↬ **High-dimensional data**: bring opportunities for gaining insights into complex biological mechanisms involved in processes of interest
- ↬ **High-dimensional data**: bring statistical challenges

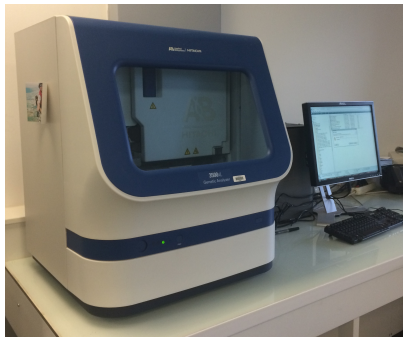


Figure 1: Sequencer Applied 3500 XL (UMR AGAP, Cirad)

Statistical challenges

↬ **A high number** of variables p measured on **a limited number** of individuals n: $p > n$.

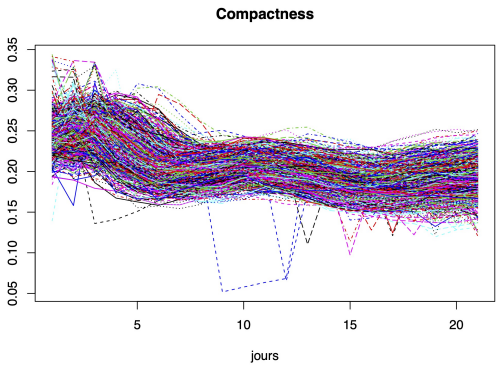
To identify the genomic regions involved in the variability of a phenotype Y

↬ $n = 100$ individuals genotyped with $p = 5,000$ Single Nucleotide Polymorphisms (SNPs) (variables, X)

How to select the most relevant subset of variables out of a large set of variables ?

Statistical challenges

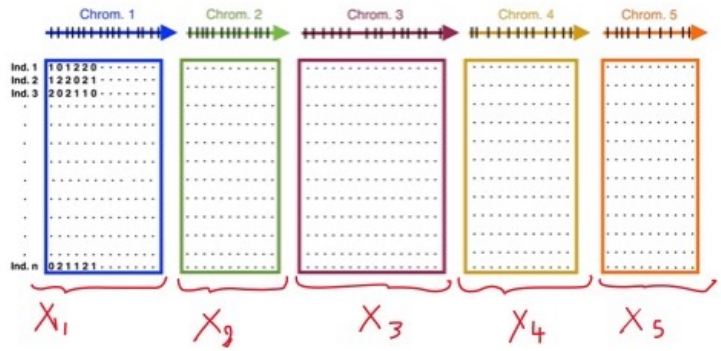
↬ Dependence structure between observations in **the response variable** (longitudinal data)



Y: Compactness over time for each plant in *Arabidopsis thaliana*

Biological context

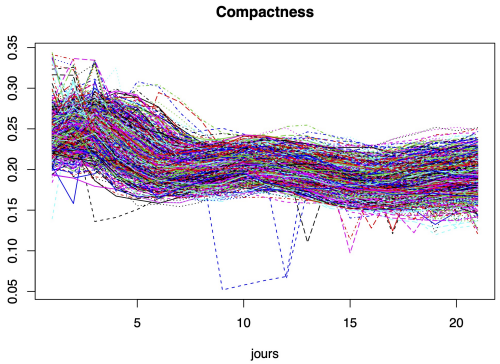
↬ Dependence structure between observations in the response variable (longitudinal data) or between **explanatory variables** that may be induced by various factors

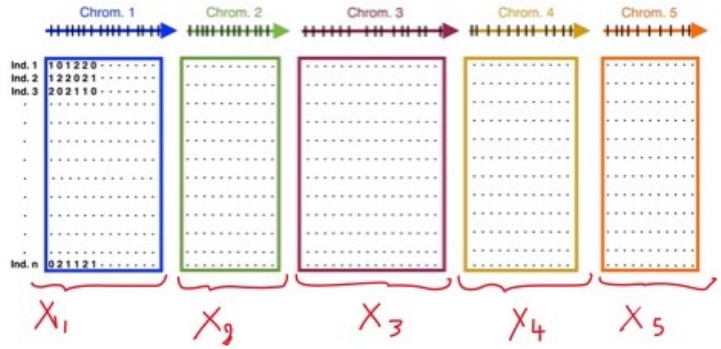


X: Genotype matrix with $X_i \perp X_j$ $(i, j = 1, \ldots, 5)$ and structure within chromosomes $X_{(i-1)1} \not\perp X_{i1}$

Biological context

↬ Dependence structure between observations in **the response variable** or between **explanatory variables** that may be induced by various factors





Y: Compactness over time for each plant in *Arabidopsis thaliana*

X: Genotype matrix with $X_i \perp X_j$ $(i, j = 1, \ldots, 5)$ and structure within chromosomes $X_{i1} \not\perp X_{(i-1)1}$ $(i = 1, \ldots, 5)$

How to analyze all time points simultaneously ? How to integrate dependence structure into variable selection approaches?

Statistical challenges

↬ Need to use appropriate statistical methods dealing with **a high number** of covariates p while considering **dependence structure** between variables

Objectives

To present two developed Bayesian variable selection approaches:

1. for identifying genomic regions related to an outcome measured over time (functional mapping analysis): Bayesian Varying Coefficient model using Group Spike-and-Slab prior (Heuclin et al., 2021)
2. for identifying genomic regions related to an outcome while considering dependence structure between SNPs (QTL mapping analysis): Graph-structured Bayesian variable selection (Denis et al., 2023 (under revision))

Next slides

- Why the "classical" approaches are not appropriate ?
- Why use the Bayesian framework ?

Linear model context

A linear model is a statistical model assuming that the response variable Y may be written as a linear combination of variables X:

$$Y = \mu + X_1\beta_1 + \cdots + X_p\beta_p + \varepsilon = \mu + X\beta + \varepsilon, \quad \varepsilon \sim \mathcal{N}_n(0, \sigma^2 Id_n)$$

with

- $Y = (y_1, \ldots, y_n)'$ the n-vector of outcomes,
- X the $n \times p$ matrix of predictors which may be structured and/or of high dimension,
- $\beta = (\beta_1, \ldots, \beta_p)'$ the p-vector of coefficients, $\varepsilon = (\varepsilon_1, \ldots, \varepsilon_n)'$ the n-vector of residuals, σ^2 the residual variance.

↬ To estimate parameters β and σ^2

In genetics:

$$Y = \mu + SNP_1\beta_1 + \cdots + SNP_p\beta_p + \varepsilon$$

with β marker effects

Classical approaches

By analyzing one SNP by one SNP or a subset of SNPs:

- Student test with multiple testing and adjustment for multiplicity,
- Backward stepwise selection, Forward stepwise selection,
- Comparison of all models by using criteria (R^2, AIC, BIC, cross-validation, Fisher test).

But

- Approaches not optimal (consider that genetic information is carried by one genetic variant)
- Approaches not feasible when $p > n$

Classical approaches

By analyzing all SNPs simultaneously

Ordinary Least Square (OLS) regression

To minimize the loss function $L^{OLS}(\beta) = \| Y - X\beta \|^2$:

$$\hat{\beta}^{OLS} = (X'X)^{-1}(X'Y)$$

But

- When the **number of predictors** is high: $\hat{\beta}^{OLS}$ does not perform well in unseen datasets (overfitting), does not provide parsimonious models (Hadamard, 1902) and in very high dimension $(X'X)^{-1}$ not invertible
- In presence of **structures** between predictors (as collinearity): $(X'X)^{-1}$ close to singularity and so, $\hat{\beta}^{OLS}$ not accurate

$\rightsquigarrow$ Need to use **regularization methods**

Regularization methods

Consist in introducing additional information into the problem:

- By imposing constraints as in ANOVA,
- By adding a penalty term to the minimization of the loss function as in **penalized regressions** (Ridge (Hoerl and Kennard, 1970), Lasso (Tibshirani, 1996),..),
- By specifying a dependence structure for effects of variables,
- ...

Bayesian approach: a natural framework

Bayesian approaches

In Bayesian framework additional information integrating into models via prior distributions

$\rightsquigarrow$ Regularization is done by specifying **specific priors**

Selection

- To shrink towards zero small coefficients while leaving large signals large: **Shrinkage** priors

$\rightsquigarrow$ SNPs with small/medium/large effects

Structure

- Priors with a **variance-covariance matrix** related to structure information between variables

$\rightsquigarrow$ SNPs structured by genes/chromosomes

Bayesian linear model

In the Bayesian context **prior** distributions are placed on the parameters (here: μ, β, σ^2)

Bayesian linear model

$$
\begin{aligned}
Y|\mu, \beta, \sigma^2 &\sim \mathcal{N}_n(\mu + X\beta, \sigma^2 I_n) \\
\beta_j &\sim p_\beta(\beta_j), \quad j = 1, \ldots, p \\
\mu &\sim p_\mu(\mu) \\
\sigma^2 &\sim p_{\sigma^2}(\sigma^2)
\end{aligned}
$$

Usual prior distributions:

- σ^2: Inverse Gamma distribution
- β: Normal distribution (no selection)
- μ: Uniform distribution

Bayesian variable selection

Two classes of shrinkage priors $p_\beta(.)$:

- **Spike-and-slab priors**: Discrete mixture of two distributions (Mitchell and Beauchamp, 1988; George and McCulloch, 1997)
- **Continuous shrinkage priors**: Unimodal continuous distributions (Bayesian Lasso prior, Horseshoe prior, Elastic-Net prior, ...) (Kyung et al., 2010; Carvalho et al., 2008)

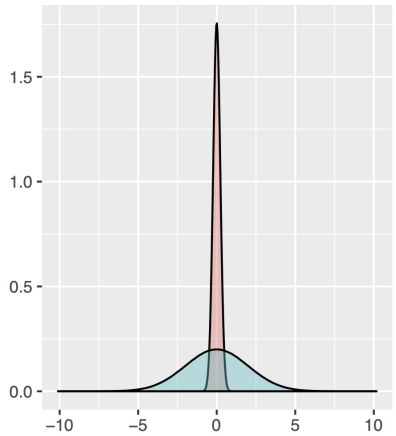


Figure 2: Spike-and-Slab prior distribution. Slab part in blue and spike part in red

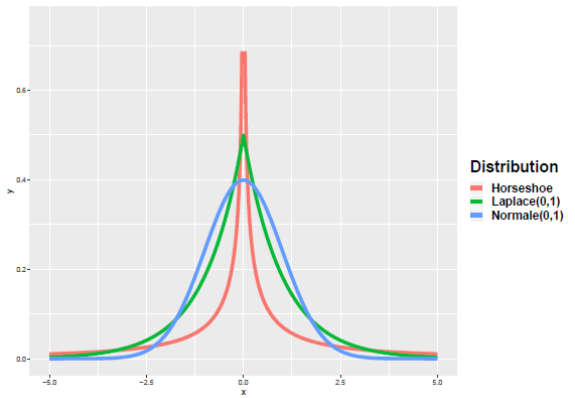


Figure 3: Continuous shrinkage prior distributions

↬ SNPs with small/medium/large effects

Integration of the dependence structure into Bayesian models

$$Y = X_1\beta_1 + \cdots + X_p\beta_p + \varepsilon,\ \varepsilon \sim \mathcal{N}_n(0, \sigma^2)$$

- X the $n \times p$ matrix of predictors which may be structured and/or of high dimension,

$\rightsquigarrow$ $\beta = (\beta_1, \ldots, \beta_p)' \sim \mathcal{N}_p(0, \Sigma)$ with $\mathbf{\Sigma}$ related to structure between variables

$\rightsquigarrow$ **Context dependent**

Examples

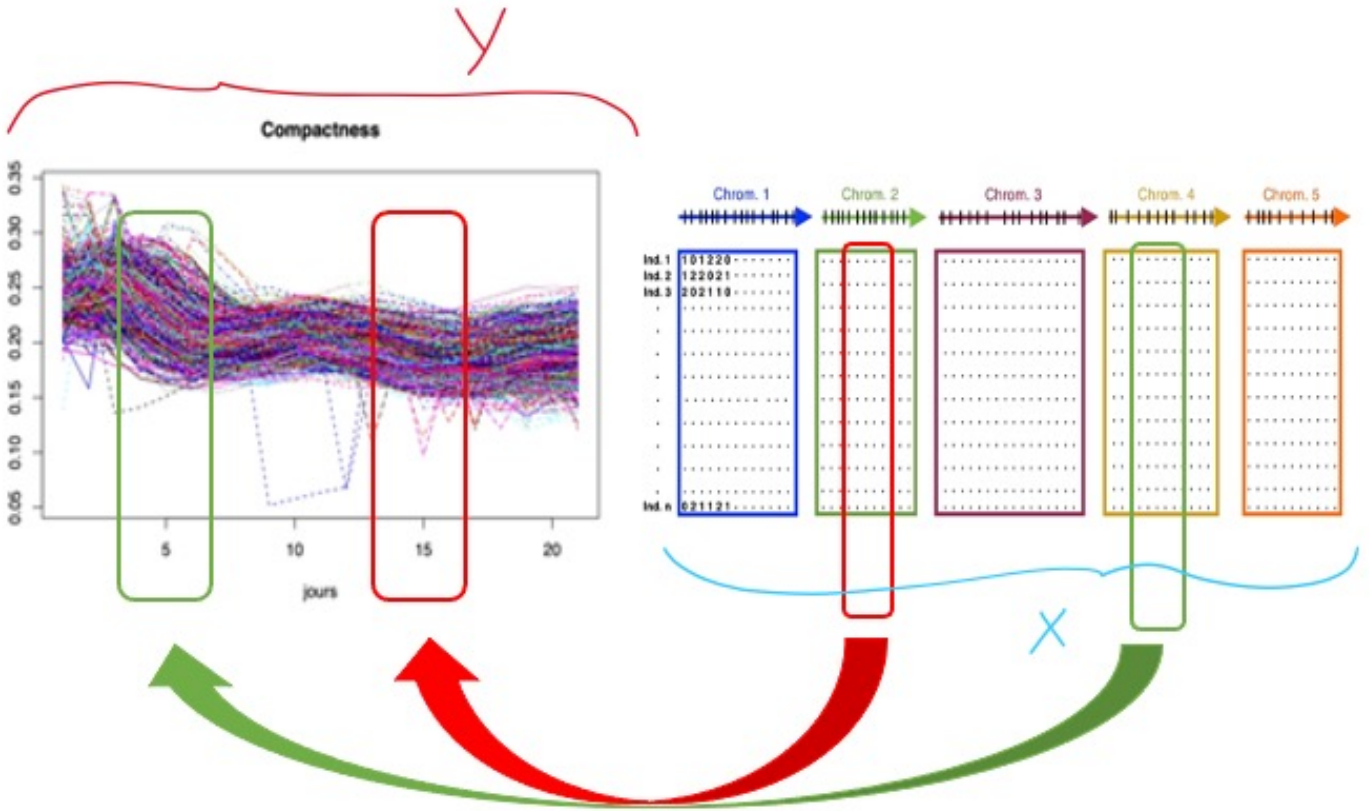
- $X_{t-1} \not\perp\!\!\!\perp X_t$: $\Sigma = AR(\rho)$ with ρ autoregressive parameter
- X_i's belong to a same group (pathways in genomic, genes in genetic, ...)

Outline

Biological motivation: functional mapping

Objectives:

To select the genetic markers involved in the variation of the compactness of *Arabidopsis thaliana* over time and to estimate their functional effects



Statistical motivations

- To select the relevant variables and to estimate their effects over time by analyzing simultaneously all time points and considering temporal dependence between successive measures

↬ Bayesian Varying Coefficient model using Group Spike-and-Slab prior (Heuclin et al., 2021)

Varying coefficient model

We assume that the response variables is followed over T times such that for the individual i we have: $y_i = (y_i^{t_1}, \ldots, y_i^{t^T})'$.

Linear model:

$$y_i^{t_1} = \mu^{t_1} + (\beta_1^{t_1}, \ldots, \beta_q^{t_1}) \begin{pmatrix} X_{i,1} \\ \vdots \\ X_{i,q} \end{pmatrix} + \varepsilon_i^{t_1}, \quad \varepsilon_i^{t_1} \sim N(0, \sigma^2)$$

Varying coefficient model

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Linear model:

$$\begin{array}{lllllllll} y_i^{t_1} & = & \mu^{t_1} & + & (\beta_1^{t_1}, & \ldots, & \beta_q^{t_1}) & + & \varepsilon_i^{t_1}, \quad \varepsilon_i^{t_1} \sim N(0, \sigma^2) \\ y_i^{t_2} & = & \mu^{t_2} & + & (\beta_1^{t_2}, & \ldots, & \beta_q^{t_2}) \begin{pmatrix} X_{i,1} \\ \vdots \\ X_{i,q} \end{pmatrix} & + & \varepsilon_i^{t_2}, \quad \varepsilon_i^{t_2} \sim N(0, \sigma^2) \end{array}$$

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\vdots & & \vdots & & \vdots & & \vdots & \vdots & \\
y_i^{t_T} & = & \mu^{t_T} & + & (\beta_1^{t_T}, & \ldots, & \beta_q^{t_T}) & + \varepsilon_i^{t_T}, & \varepsilon_i^{t_T} \sim N(0, \sigma^2)
\end{array} \begin{pmatrix} X_{i,1} \\ \vdots \\ X_{i,q} \end{pmatrix}$$

- Simple analysis at each time point does not take into account the correlations over time
  - ↪ Can lead to false positive detection and loss of statistical power

Varying coefficient model

Varying coefficient model(Hastie and Tibshirani, 1993)

$$\begin{pmatrix} y_i^{t_1} \\ \vdots \\ y_i^{t_T} \end{pmatrix} = \begin{pmatrix} \mu^{t_1} \\ \vdots \\ \mu^{t_T} \end{pmatrix} + \begin{pmatrix} \beta_1^{t_1} & \dots & \beta_q^{t_1} \\ \vdots & & \vdots \\ \beta_1^{t_T} & \dots & \beta_q^{t_T} \end{pmatrix} \begin{pmatrix} X_{i,1} \\ \vdots \\ X_{i,q} \end{pmatrix} + \begin{pmatrix} \varepsilon_i^{t_1} \\ \vdots \\ \varepsilon_i^{t_T} \end{pmatrix}, \quad \begin{array}{l} \varepsilon_i \sim N_T(0, \sigma^2 \Gamma) \\ \Gamma_{i,j} = \rho^{|i-j|} \\ -1 < \rho < 1 \end{array}$$

Varying coefficient model

Varying coefficient model (Hastie and Tibshirani, 1993)

$$\begin{pmatrix} y_i^{t_1} \\ \vdots \\ y_i^{t_T} \end{pmatrix} = \begin{pmatrix} \mu^{t_1} \\ \vdots \\ \mu^{t_T} \end{pmatrix} \begin{pmatrix} \beta_1^{t_1} & \dots & \beta_q^{t_1} \\ \vdots & & \vdots \\ \beta_1^{t_T} & \dots & \beta_q^{t_T} \end{pmatrix} \begin{pmatrix} X_{i,1} \\ \vdots \\ X_{i,q} \end{pmatrix} + \begin{pmatrix} \varepsilon_i^{t_1} \\ \vdots \\ \varepsilon_i^{t_T} \end{pmatrix}, \quad \begin{array}{l} \varepsilon_i \sim N_T(0, \sigma^2 \Gamma) \\ \Gamma_{i,j} = \rho^{|i-j|} \\ -1 < \rho < 1 \end{array}$$

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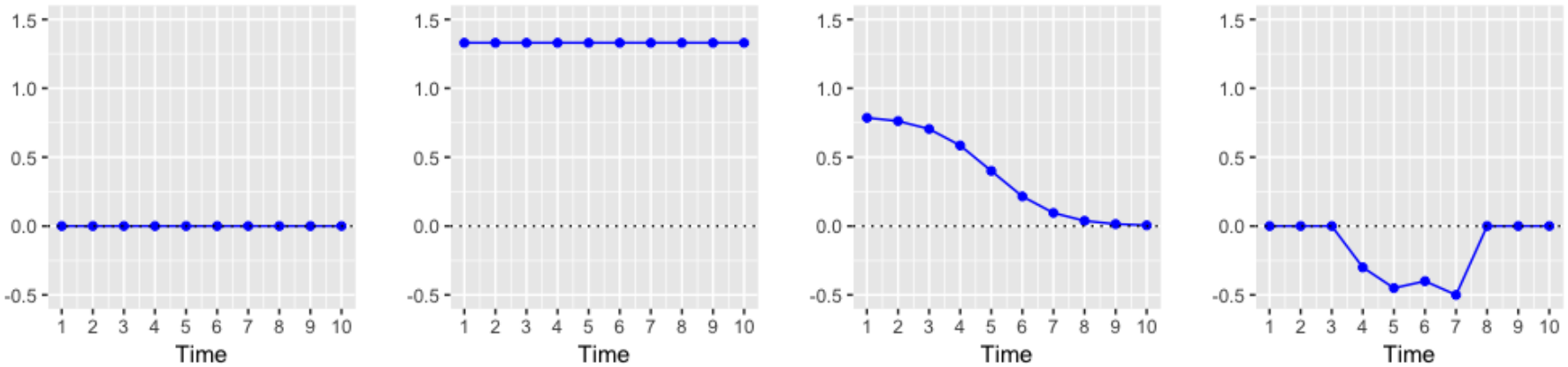


$(\beta_j^{t_1}, \dots, \beta_j^{t_T})'$ are assumed to be a realization of a function $\beta_j(t)$

↪ Estimation of $\beta_j(t)$ with functional or non functional methods

↪ Selection of significant variables X_j such that $(\beta_j^{t_1}, \dots, \beta_j^{t_T})' = (0, \dots, 0)'$ with a spike-and-slab prior

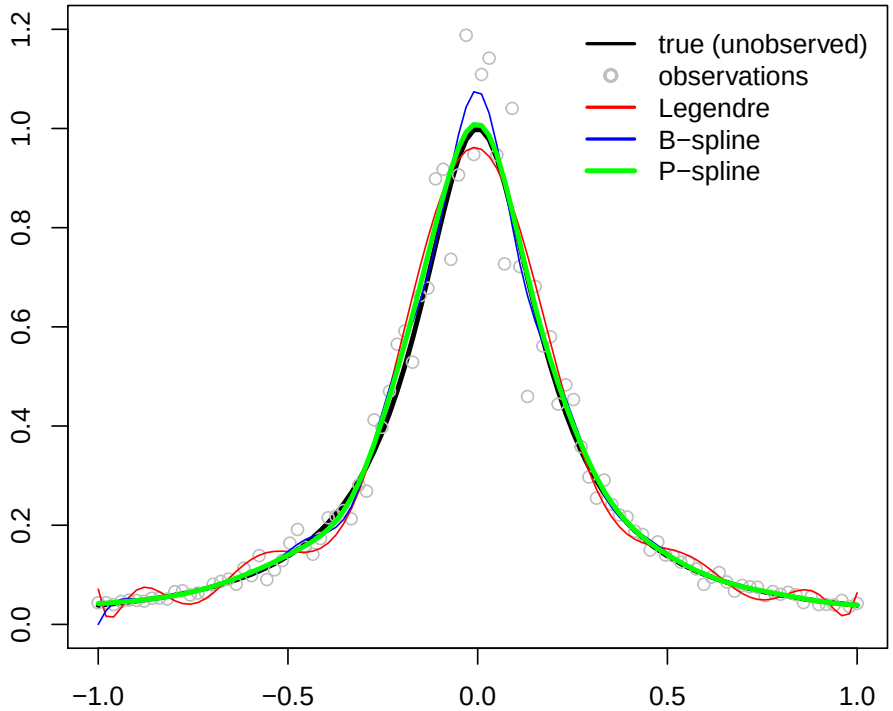
Functional method: Non-parametric interpolation

- Bayesian P-spline interpolation (Eilers and Marx, 1996; Lang and Brezger, 2004) for inducing smoothness

$$\begin{pmatrix} \beta_j^{t_1} \\ \vdots \\ \beta_j^{t_T} \end{pmatrix} = \sum_{k=1}^{v} B_k b_{k,j} = B\ b_j,$$

$$b_j \sim \mathcal{N}(0, (\lambda_j K)^{-1})$$

with K a structured matrix.



Selection in varying coefficient model

Selection of relevant variables X_j, $j = 1, \ldots, p$:

$$(b_{1,j}, \ldots, b_{v,j})' = (0, \ldots, 0)'?$$

↬ Group spike-and-slab prior on b_j (Yang and Narisetty, 2020):

$$b_j|\gamma_j, \lambda_j \sim \gamma_j N_v(0, (\lambda_j K)^{-1}) + (1 - \gamma_j)\delta_v(0)$$
$$\lambda_j \sim Gamma(s, r),$$
$$\gamma_j \sim Ber(\pi),$$

Bayesian Varying Coefficient model using Group Spike-and-Slab prior (Heuclin et al., 2021)

Bayesian hierarchical model

$$Y_i|m, b, \rho, \sigma^2 \sim N_T(Bm + BbX_i, \sigma^2\Gamma)$$

$$m|\lambda_0 \sim N_v(0, (\lambda_0 K)^{-1})$$

$$b_j|\gamma_j, \lambda_j \sim \gamma_j N_v(0, (\lambda_j^2 K)^{-1}) + (1-\gamma_j)\delta_v(0), \quad j = 1, \ldots, q$$

$$\lambda_j \sim Gamma(s, r), \quad j = 0, \ldots, q$$

$$\gamma_j \sim Ber(\pi), \quad j = 1, \ldots, q$$

$$\rho \sim U_{[-1,1]}$$

$$\sigma^2 \sim I - Gamma(s_{\sigma^2}, r_{\sigma^2})$$

To infer the distribution of $m, b_j, \lambda_j, \gamma_j, \rho, \sigma^2|Y$**:**

↪ Gibbs algorithm (Markov Chain Monte Carlo algorithm)

VCGSS package

VCGSS: an R package for implementing the sparse Bayesian **V**arying **C**oefficient model using **G**roup **S**pike-and-**S**lab prior

↬ Available on https://github.com/Heuclin/VCGSS

We will explore the two main functions:

`VCM_fct()`

To run the Bayesian Varying Coefficient model using Group Spike-and-Slab prior.

- allows to implement functional and non functional methods with penalty of order 1 or 2,
- calls an MCMC sampler implementation in C++,
- allows to run many repetitions in parallel,
- applies convergence diagnostics

`plot_functional_effects()`:

To visualize the dynamic effects

Application on *Arabidopsis thaliana*: functional mapping

Objective:

To select the genetic markers involved in the variation of the compactness of *Arabidopsis thaliana* (data publicly available)

- Individuals: $n = 357$ under well-watered environmental condition
- Markers: SNPs, $p = 532$ to reduce the collinearity between adjacents markers all markers with correlations higher than 0.95 removed $\Rightarrow$ 125 markers
- Phenotypic trait: compactness (Ratio between the projected rosette area and the convex hull area)
- Measurement frequency: daily for $T = 21$

Application on *Arabidopsis thaliana*

Marginal posterior inclusion probabilities

- 14 markers with posterior probability greater than 0.5
- Switch between some markers:

↬ identification of new genomic regions compared Marchadier et al. (2018) (with a single time point analysis) with potentially small effects

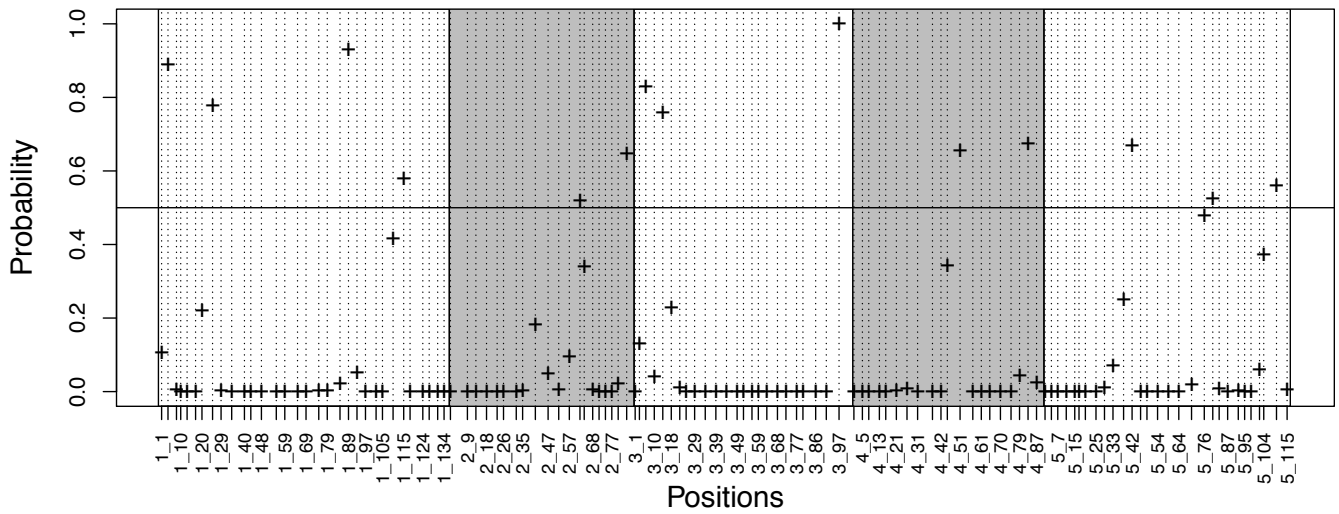
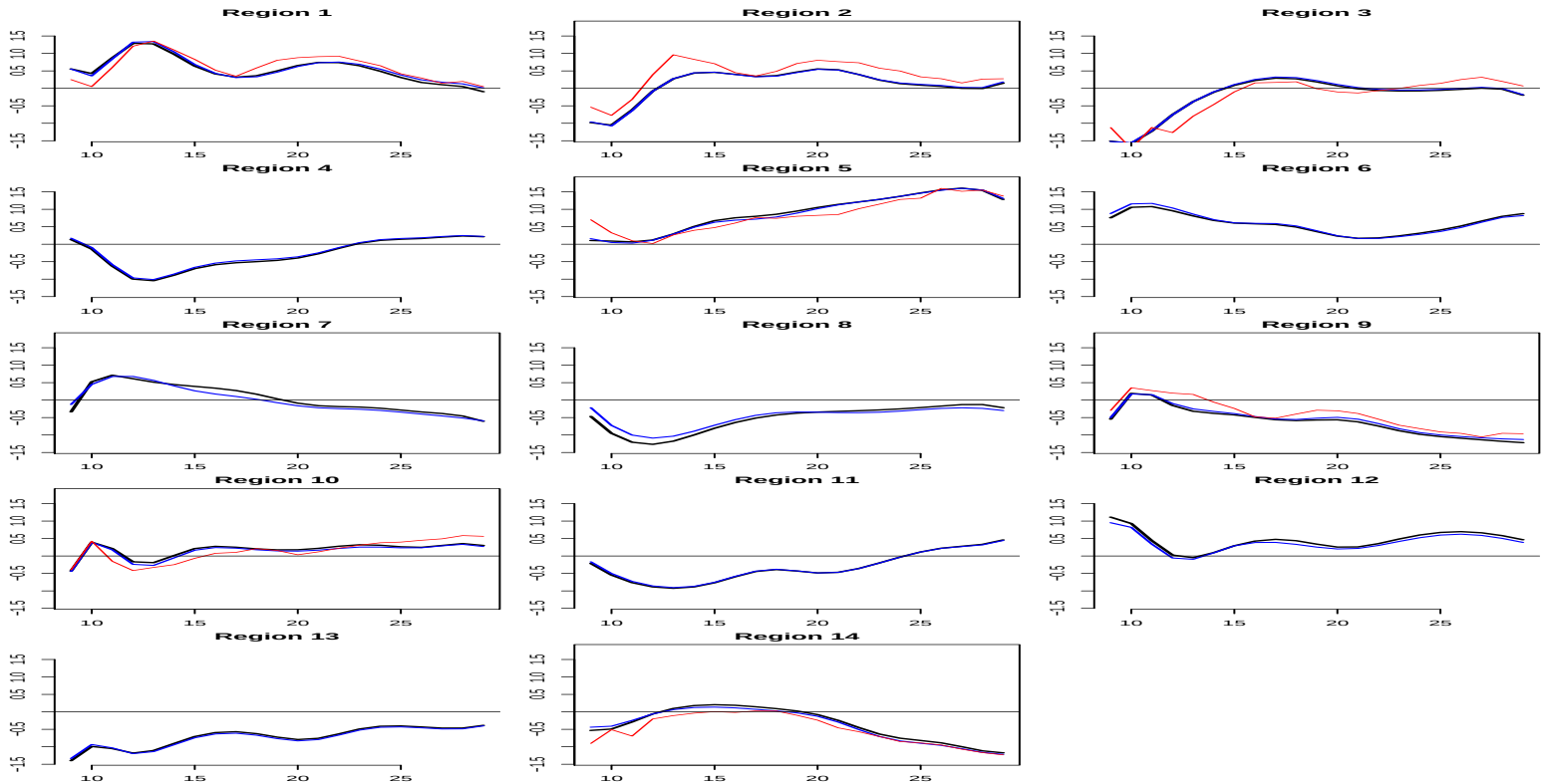


Figure 4: Marginal posterior inclusion probabilities for the 125 markers

Application on *Arabidopsis thaliana*

Estimations of varying effects

Estimation of the effects for markers with the highest marginal posterior probabilities (PS_1: blue, PS_2: black, RW_2: red)



Application on *Arabidopsis thaliana*

Results

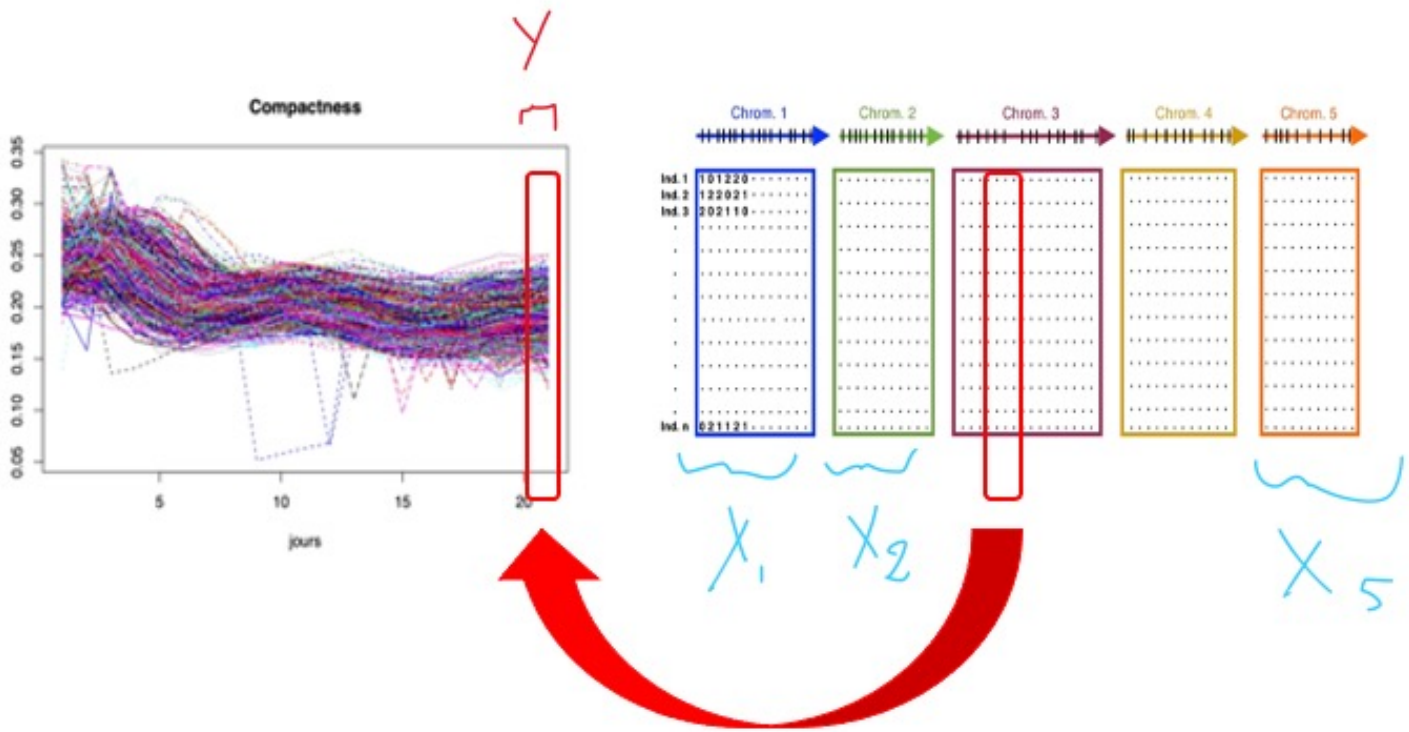
- Approach considering all SNPs and all time points: identification of new regions with potentially small effects and related to known genes,
- Dynamic effects: better biological interpretation for the identification of markers "active/inactive" at different stages of the process,
- Based on simulations: better selection and prediction accuracy.

Outline

Biological motivation: QTL mapping

Objectives:

To select the genetic markers involved in the variation of the compactness of *Arabidopsis thaliana* at one time point while considering the structure along the genome.



Statistical motivations

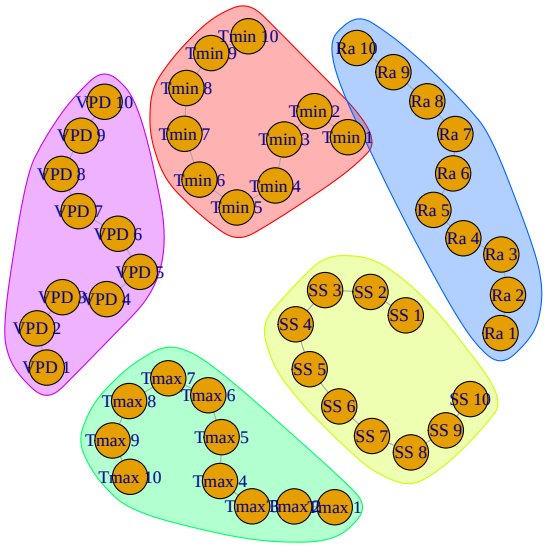
- To select the relevant variables (X_j, $j = 1, \ldots, p$) while considering the dependence structure between them,

↬ Graph-structured Bayesian variable selection (Denis et al., 2023 (under revision))

Graph-structured Bayesian variable selection

Combination of

1. a **continuous shrinkage prior** (horseshoe prior (HS)) for the selection with
2. a **Gaussian Markov random field** (GMRF) for the integration of a dependence structure between explanatory variables characterized by a graph



Bayesian hierarchical model

We assume that $\mathcal{G} = \bigcup_{i=1}^{I} \mathcal{G}_i = \bigcup_{i=1}^{I} (V_i, E_i)$ a disjoint union of I subgraphs and $\mathcal{S}$ the set of indices associated to one representative of each of the I subgraphs.

HS-GMRF model

$$
\begin{aligned}
\boldsymbol{y}|\boldsymbol{\beta}, \sigma^2 &\sim \mathcal{N}_n(\boldsymbol{X}\boldsymbol{\beta}, \sigma^2 \mathsf{I}_n) \\
\beta|\tau^2, \lambda^2 &\sim \mathcal{N}_p(0, \lambda^2 \mathsf{Q}^{-1}), \\
\tau_{jj'} &\sim \mathcal{C}^+(0,1) \text{ for } (j,j') \in \bigcup_{i=1}^{I} E_i; \tau_j \sim \mathcal{C}^+(0,1) \text{ for } j \in \mathcal{S} \\
\lambda|\sigma &\sim \mathcal{C}^+(0,\sigma);\ \sigma^2 \sim \mathcal{IG}(a_0, b_0)
\end{aligned}
$$

- $s_{jj'} = \text{sign}\{\text{cor}(X_j, X_{j'})\}$: to encourage regression coefficients of negatively correlated variables to take opposite signs,
- Q: the precision matrix integrating the graph information

$$
Q_{jj} = \begin{cases} \frac{1}{\tau_j^2} + \sum_{j' \in \mathcal{N}(j)} s_{jj'} \frac{1}{\tau_{jj'}^2} & \text{if } \ j \in \mathcal{S} \\ \sum_{j' \in \mathcal{N}(j)} s_{jj'} \frac{1}{\tau_{jj'}^2} & \text{otherwise} \end{cases}
$$

Application on *Arabidopsis thaliana*: QTL mapping

Objective:

To select SNPs involved in the variation of the compactness at $T = 21$

- Methods picks contiguous markers: selection of genomic regions
- Overlapping with markers/regions found in Marchadier et al. (2018) and Heuclin et al. (2021) and new ones that are related to genes involved in compactness

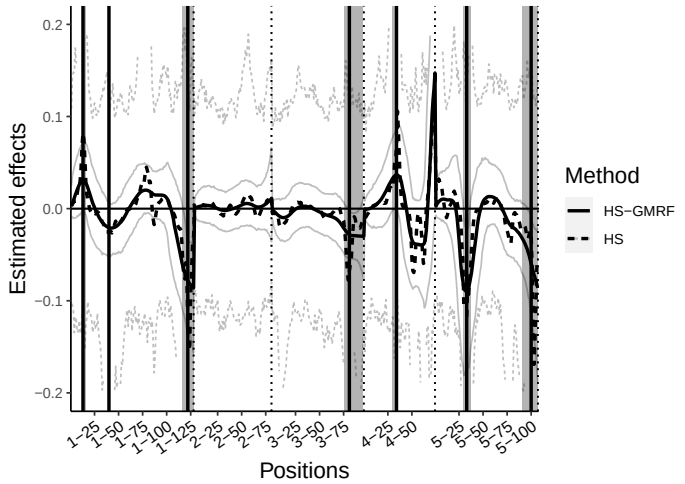


Figure 5: Estimated coefficients along the genome.

Outline

Conclusions/perspectives

↬ Variable selection approaches considering dependence structure between variables give better results and improve biological understanding.

Simulation study (results not shown)

- Increase power to detect associations: encourages the identification of groups of dependent variables acting jointly on the response, especially those with subtle individual effects,
- Improves the predictive power,
- Helps the model building process by reducing the complexity of models and by circumventing the problem of high collinearity through identifiability.

Conclusions/perspectives

Biological interpretation

- Identification of regions versus single molecular marker make more sense for identifying QTLs,
- Identification of markers/regions with small effects (rare allele),
- Better understanding of the dynamic genetic architecture via estimations of marker effects over time.

Perspectives

- More complex structures between variables may be considered (as spectrum, gene networks, ...),
- To combine both approaches for analyzing outcomes measured over time as well as structured covariates.

Thanks for your attention !

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Outline

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