Bayesian variable selection approach in varying coefficient model: application in functional mapping

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Outline

Objectives

Objectives during this presentation are:

1. to introduce Bayesian variable selection methods,
2. to present a Bayesian variable selection method for selecting variables with effects evolving over time,
3. to apply Bayesian variable selection methods in the genetic context.

Outline

Why use variable selection approaches ?

In various domains **high-dimensional data**:

- Genetic/Genomic: high-throughput sequencing,
- Ecophysiology/Ecology: high-throughput phenotyping,
- Economic: more and more variables,
- ....

resulting in **a high number** of variables p measured on **a limited number** of individuals $n \Rightarrow$ p> n

For example in genetic:

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

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

How to select the relevant SNPs? How to select the best subset of variables?

Variable selection in linear model

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

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

$$\Leftrightarrow Y = \mu + X\beta + \varepsilon, \ \ \varepsilon \sim \mathcal{N}_n(0, \sigma^2 Id_n)$$

$$\Leftrightarrow Y \sim \mathcal{N}_n(\mu + X\beta, \sigma^2 Id_n)$$

with n the number of observations and p the number of variables.

Which variables are relevant ? $\Leftrightarrow$ *Which* $\beta_j \neq 0$ *?*

For example in genetic:

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

Which SNP is relevant $\Leftrightarrow$ *Which* $\beta_j \neq 0$ *?* $\Leftrightarrow$ *Does the position* j *affect the variability of phenotype* Y

Added compared to the initial presentation: Classical regression technique

Ordinary Least Square (OLS) regression

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

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

But

- In presence of structures between predictors (as collinearity): $(X'X)^{-1}$ close to singularity and so, $\hat{\beta}^{OLS}$ not accurate
- 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

↬ Need to use **regularization methods**

Variable selection in linear model

Classical approaches:

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

Problems: approaches not optimal or not feasible when $p > n$: need to use statistical methods allowing to **regularize** models

- ↬ Frequentist context: penalized likelihood approaches (Lasso, Ridge, Elastic-Net,...) (Hoerl and Kennard, 1970; Tibshirani, 1996)
- ↬ Bayesian context: shrinkage priors (spike-and-slab prior, Bayesian Lasso prior,...)

In the following we will focus on Bayesian approaches

Introduction to 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

In the Bayesian context regularization is done by specifying shrinkage priors on the regression coefficients β.

Two classes of shrinkage priors:

- **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)

$\looparrowright$ To shrink towards zero small effects while allowing large signals to escape from the overall shrinkage

Spike-and-slab prior

- Introduction of γ:

$$\gamma_j = \begin{cases} 1 \text{ if variable } j \text{ is selected} \\ 0 \quad \text{otherwise} \end{cases}$$

$$\beta_j | (\gamma_j = 1) \sim p_{Slab}(\beta_j) \,, \qquad \beta_j | (\gamma_j = 0) \sim p_{Spike}(\beta_j)$$

- Bayesian hierarchical model:

$$Y | \mu, \beta, \sigma^2 \sim \mathcal{N}_n(\mu + X_1\beta_1 + \cdots + X_p\beta_p, \sigma^2 I_n)$$

$$\beta_j | \gamma \sim \gamma_j \mathcal{N}(0, \sigma_\beta^2) + (1 - \gamma_j)\delta_0, \quad j = 1, \ldots, p$$

- The estimation of $\mathbb{P}(\gamma_j = 1 | Y)$ gives access to the a posteriori probability of variable selection

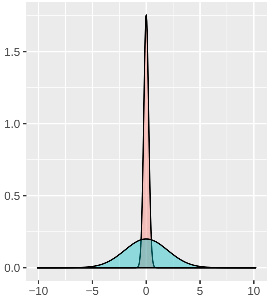


Figure 1: Spike-and-Slab prior distribution. Slab part in blue and spike part in red

Continuous shrinkage prior

- Penalized likelihood approaches:

$$\hat{\beta} = \text{argmin}_\beta \{\| Y - X\beta \|^2 + \nu \sum_{j=1}^{p} \phi(\beta_j^2)\}$$

with ν the penalty parameter and ϕ the penalization function.

- Bayesian version of penalized likelihood approaches:

$$\beta_j | \tau^2, \omega_j^2 \sim \mathcal{N}(0, \tau^2 \omega_j^2) \;\; j = 1, \dots, p$$

$$\tau^2, \omega_j^2 \sim \mathcal{F}(\tau^2; \omega_j^2)$$

where

- $\mathcal{F}$ is a distribution to specify,
- τ^2 controls the global shrinkage and ω_j^2 controls the individual shrinkage

$\looparrowright$ Horseshoe prior, Bayesian Lasso prior (Laplace prior), ...

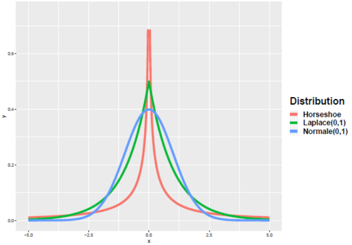


Figure 2: Continuous shrinkage prior distributions

R packages for implementing Bayesian variable selection

Spike-and-slab prior

- `BGLR` (Pérez and de Los Campos, 2014)
- `BoomSpikeSlab` (Scott et al., 2021)

Continuous shrinkage priors

- `bayesreg` (Makalic and Schmidt, 2016)
- `BGLR` (Pérez and de Los Campos, 2014)
- `horseshoe` (van der Pas et al., 2016)
- `fastHorseshoe` (Hahn et al., 2016)
- `dlbayes` (Zhang and Li, 2018)

Monte Carlo Markov Chain (MCMC) algorithms are used to infer parameters

Application in genetic

Objective: to select the genetic markers involved in the variation of the compactness of *Arabidopsis thaliana* (data publicly available at phenotypes (Loudet, 2018) and genotypes)

- Individuals: $n = 357$ under well-watered environmental condition
- Markers: SNP, $q = 532$
- Phenotypic trait: compactness (Ratio between the projected rosette area and the convex hull area)
- Measurement frequency: daily for $T = 21$

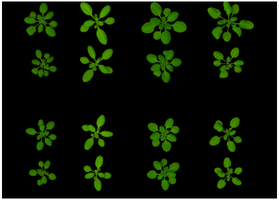
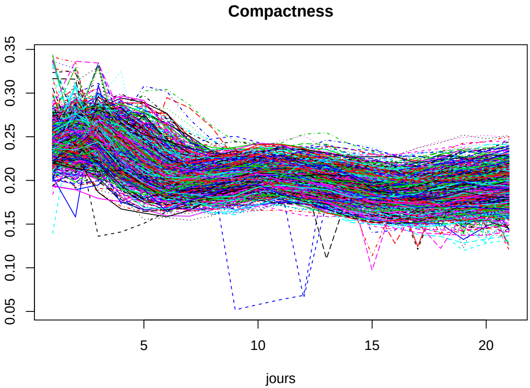


Figure 3: Arabidopsis thaliana (Marchadier et al., 2018)

Application in genetic

Evolution of the compactness over time for each individual:



In this first part the objective is to identify markers involved in the variability of the compactness at **T=21**.

Bayesian variable selection with R

Two R packages for implementing Bayesian variable selection with the spike-and-slab prior and the horseshoe prior:

- `bayesreg` allows to fit Bayesian regression models with continuous shrinkage priors (ridge, lasso, horsehoe, horsehoe+) for normal and non-normal distribution (Poisson, geometric, logistic, binomial, Laplace, Student)
- `BoomSpikeSlab` allows to fit Bayesian regression models with a spike-and-slab prior.

↬ Selection of 8 markers involved in the variability of the compactness at T=21

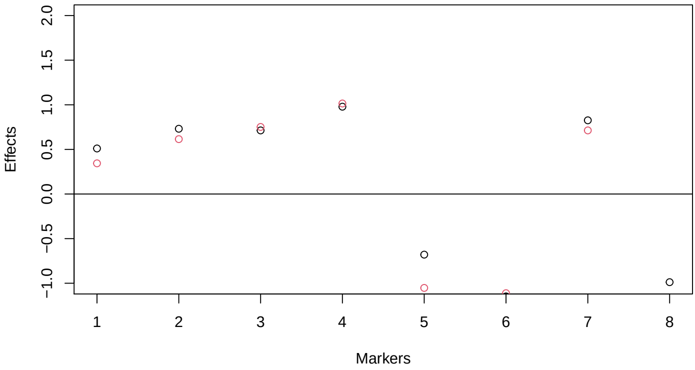
BoomSpikeSlab

To run the main function lm.spike

```
> library(BoomSpikeSlab)
> # to specify the prior inclusion probabilities equal to 0.1
> prior <- SpikeSlabPrior(X.50, y.21, prior.inclusion.probabilities = rep(0.1,ncol(X.50)))
> res.ss <- lm.spike(y.21 ~ X.50-1, niter = niter, prior = prior)
> # posterior inclusion probabilities
> pp <- apply(res.ss$beta, 2, function(c){sum(c != 0) })/niter
> #selected markers
> which(pp > 0.5)
X.50c1_loc26.AA X.50c2_loc28.AA X.50c2_loc47.AA X.50c2_loc63.AA  X.50c3_loc9.AA
              4              17              19              21              23
X.50c3_loc75.AA X.50c5_17844.AA X.50c5_26671.AA
             31              46              50
> beta.ss <- colMeans(res.ss$beta)
```

To plot the estimated effects

```
> plot(rowMeans(res.hs$beta[pp> 0.5,]), ylab = "Effects", xlab = "Markers", ylim = c(-1,2))
> points(beta.ss[pp> 0.5], col =2)
```



How does the genetic architecture evolve over time?

We have identified the genetic markers involved in the variability of the compactness measured at $T = 21$

- Which are the genetic markers involved in the variability of the compactness measured at different time points ? Are they the same over time ?
- How are their effects? Are they the same over time ?

Need to analyze all the measures simultaneously, to select the relevant markers and to estimate their effects over time

$\Rightarrow$ Varying coefficient model

Outline

From linear model to 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:

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

From linear model to 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:

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

From linear model to varying coefficient model

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

Linear model:

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

- Simple analysis at each time point does not take into account the correlations over the time

  $\hookrightarrow$ Can lead to false positive detection and loss of statistical power

Varying coefficient model

Varying coefficient model (Hastie and Tibshirani, 1993)

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

Varying coefficient model

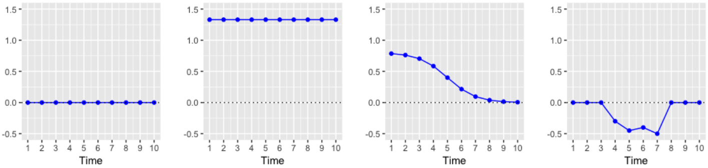
Varying coefficient model (Hastie and Tibshirani, 1993)

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

Varying coefficient model

Varying coefficient model (Hastie and Tibshirani, 1993)

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

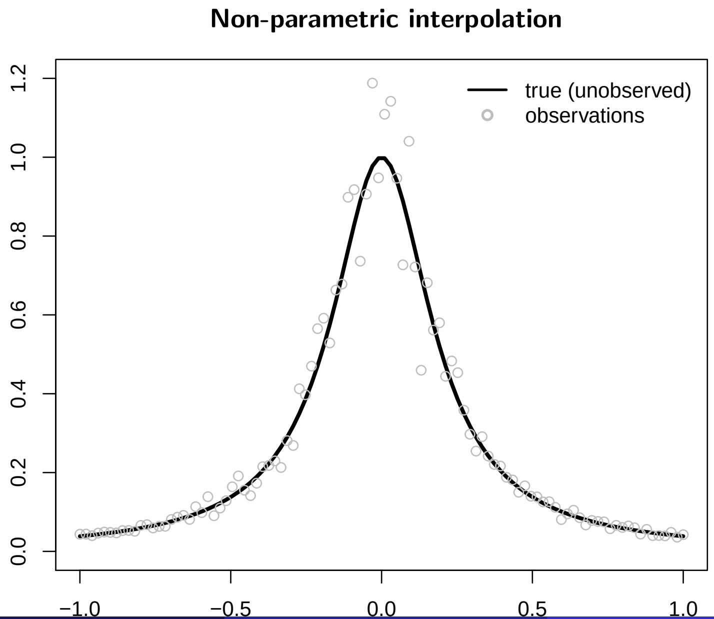


$(\beta_j^{t_1}, \dots, \beta_j^{t_T})'$ are assumed to be a realization of a function $\beta_j(t)$

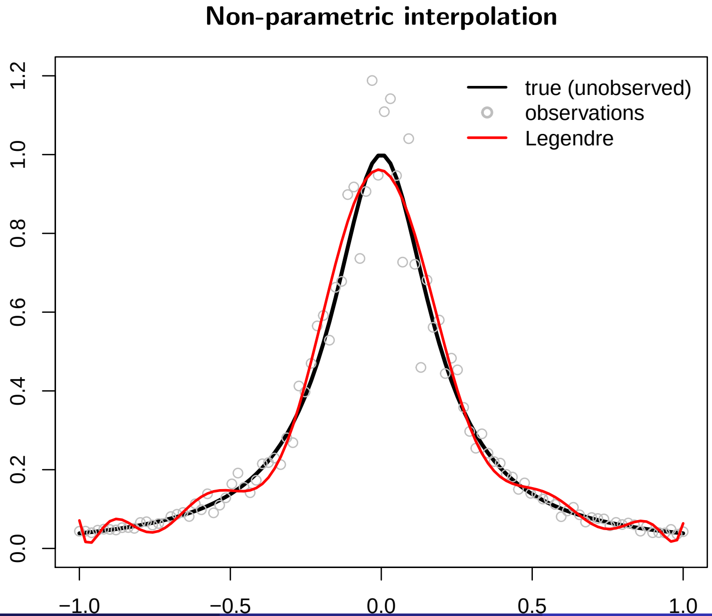
- $\hookrightarrow$ Estimation of $\beta_j(t)$ with functional or non functional methods
- $\hookrightarrow$ Selection of significant variables X_j such that $(\beta_j^{t_1}, \dots, \beta_j^{t_T})' = (0, \dots, 0)'$ with a spike-and-slab prior

Outline

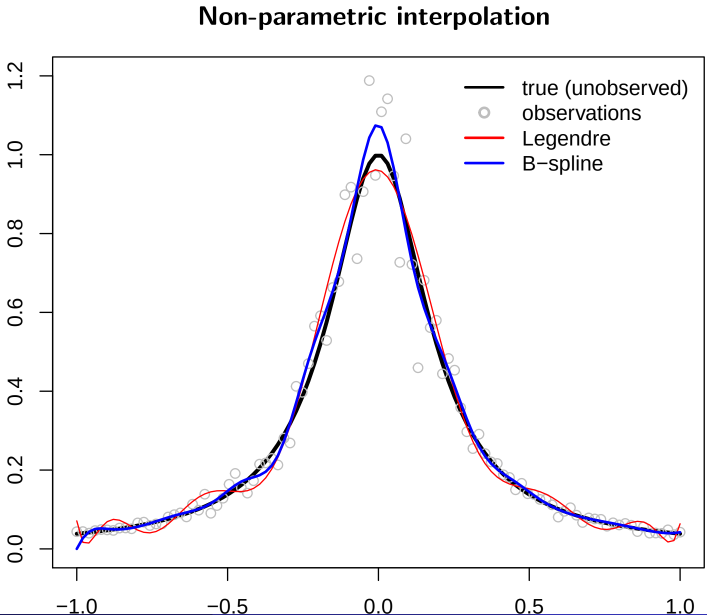
Functional method



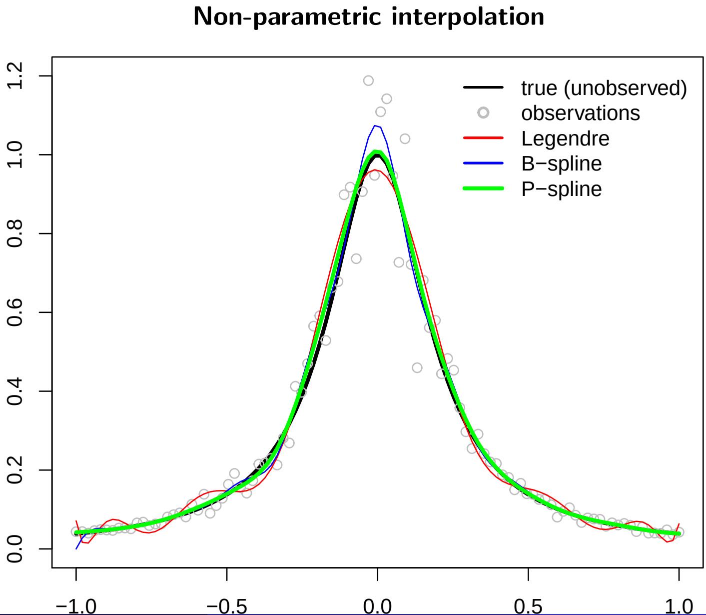
Functional method



Functional method



Functional method



Functional method

What is P-spline ?

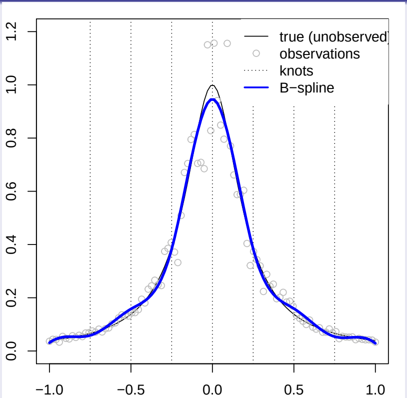
P-spline = B-spline + Penalisation

Functional method

B-spline (Eubank, 1999)

- Approximates a real function as a linear combination of B-spline basis functions defined on K knots (K-1 intervals):

$$\beta_j(t) = \sum_{k=1}^{v} B_k b_{k,j} = B\ b_j,$$



Functional method: P-spline (Eilers and Marx, 1996)

B-spline approach strongly depends on the number of knots and the choice of their positions

$\hookrightarrow$ A misspecification may lead to over- or under-fitting.

$\hookrightarrow$ Penalized B-splines (P-splines) induce smoothness,

$\hookrightarrow$ Penalize the first- or second-order finite differences in adjacent spline regression coefficients

Functional method

Bayesian P-splines (Lang and Brezger, 2004):

Replace the penalties by their stochastic analogues

$\hookrightarrow$ first-order random walk such that $b_{k,j} \sim N(b_{k-1,j}, \lambda_j^{-1})$

$\Leftrightarrow$ $b_j|\lambda_j \sim N_v(0, (\lambda_j K)^{-1})$, K the known appropriate penalty matrix defined by

$$K = \begin{pmatrix} 1 & -1 & & & \\ -1 & 2 & -1 & & \\ & \ddots & \ddots & \ddots & \\ & & -1 & 2 & -1 \\ & & & -1 & 1 \end{pmatrix}.$$

Functional versus non functional methods

Functional method: P-spline interpolation (Eilers and Marx, 1996)

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

$+$ penalization on $(b_{k,j} - b_{k-1,j})$ of order 1 or 2
$\hookrightarrow$ PS_1 and PS_2

Non functional method: direct estimation of time coefficient functions) Li and Sillanpää (2013)

$$\begin{pmatrix} \beta_j^{t_1} \\ \vdots \\ \beta_j^{t_T} \end{pmatrix} = b_j$$

$+$ penalization on $(b_{t_T,j} - b_{t_{T-1},j})$ of order 1 or 2
$\hookrightarrow$ RW_1 and RW_2

In both methods we assume that:

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

with K a structured matrix.

Outline

Selection in varying coefficient model

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

$$(b_{t_1,j}, \dots, b_{t_T,j})' = (0, \dots, 0)'?$$

↬ Group spike-and-slab prior on b_j (Ghosh and Ghattas, 2015; 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

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

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

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

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

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

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

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

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

$\hookrightarrow$ Gibbs algorithm (Markov Chain Monte Carlo algorithm)

Outline

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

To run the model

To run the model with a P-spline interpolation using a second order difference penalty

```
> library(VCGSS)
> fit <- VCM_fct(Y, X, ENV = NULL, selection = TRUE,
+                interpolation = "P-spline",
+                order_diff = 2,
+                save = FALSE, core = -1,
+                rep = 2, niter = 1000, burnin = 500)
```

Arguments:

- `selection`: TRUE/FALSE
- `interpolation`: functional method = "P-spline", "B-spline", "Legendre", non-functional method = "RW",
- `order_diff`: order of the difference penalty,
- `niter`, `burnin`, `thin`: MCMC parameters,
- ...

Outline

Application in 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

To reduce the collinearity between adjacents markers

↬ We remove all markers with correlations higher than 0.95: 125 markers

Application on *Arabidopsis thaliana*

Marginal posterior probabilities

Results

- 14 markers with posterior probability greater than 0.5
- Switch between some markers: Identification of genomic regions

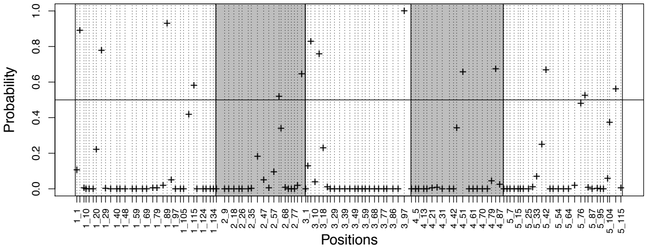
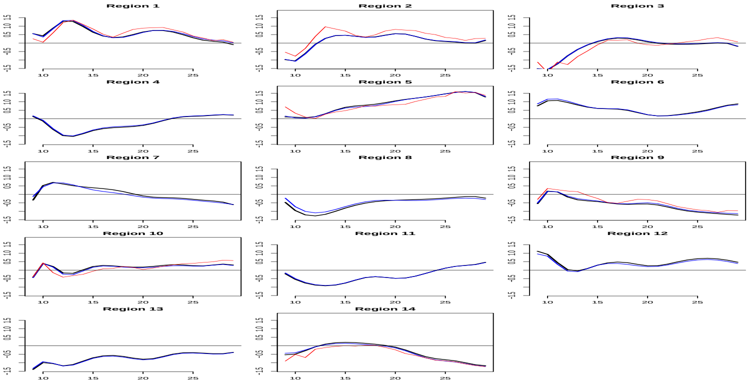


Figure 4: Marginal posterior inclusion probabilities for the 125 markers

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)



Conclusions

Conclusions

- Estimation:
  - Functional approach allows reduction of the number of parameters
  - Non-parametric interpolation does not restrict the form of the effect curves
  - P-spline allows fitting smooth or rather complicated curve
- Selection:
  - Spike-and-slab does not give biased estimations
  - Spike-and-slab has a good selection performance
- Various applications: Arabidopsis, Eucalyptus, Human, ...

Perspectives

Group spike-and-slab can have poor mixing when T increases
$\hookrightarrow$ extend continuous shrinkage prior: group horseshoe prior.

Thanks for your attention !

Outline

1. Introduction
2. Bayesian variable selection
3. Varying coefficient model
   - Estimation of $\beta_j(t)$
   - Selection of relevant variables X_j
   - VCGSS package
   - Results
4. Bibliography

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Why classical regression techniques do not work?

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

↬ Need to use **regularization methods**