FLPCA: A Fused Lasso PCA-based approach to identify influential markers in differentiated populations from dense SNP data

Denis Laloë, Julien Chiquet, Florence Jaffrezic, Mathieu M. Gautier

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The context

Genetic structure of a population

- Natural / Artificial Selection
- Isolation, drift

Markers : SNPs

- Usually biallelic markers
- Throughout the genome
- Mapping SNPs to genes

Geometric Data Analysis

- Duality Diagram: Space of individuals vs Space of markers
- Typological Value
- Modelling through instrumental variables

Subset of influential markers

- Magnitude
- Spatial structure (Linkage Disequilibrium)

SNP Haplotype data

$$\mathbf{X} = [\delta_i^j] = \begin{pmatrix} SNP_1 & SNP_2 & \dots & SNP_k \\ 0 & 1 & \dots & 0 \\ 0 & 0 & \dots & 1 \\ . & . & \dots & . \\ 1 & 0 & \dots & 0 \end{pmatrix}$$

Duality diagram

Dray and Dufour, 2007

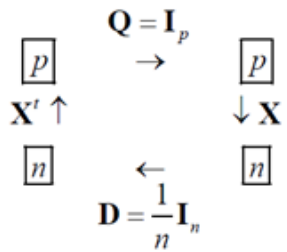
Maximisation of the correlation between variables and components

Variables

V = X'X/*n*

X'XA=AΔ
A'A=I
Principal components

Coordinates of variables
C=X'B



Diagonalisation

X'X **XX'**

same non-null eigenvalues

$\lambda_1 > \lambda_2 > \ldots > \lambda_r > 0$

$\Lambda = \mathrm{diag}(\lambda_1, \ldots, \lambda_r)$

Transition formulae
$XA\Delta^{-0,5} = B$
$X'B\Delta^{-0,5} = A$

Maximisation of the individuals dispersion

Individus

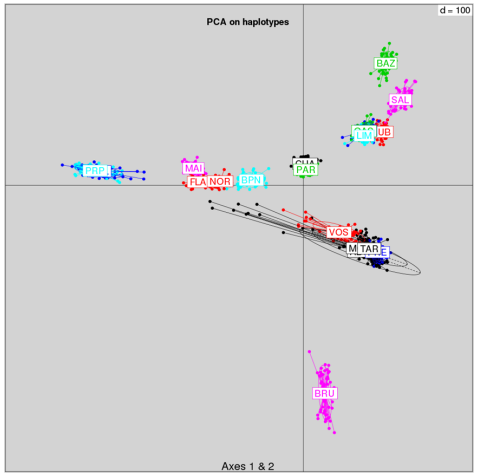
W = XX'/*n*

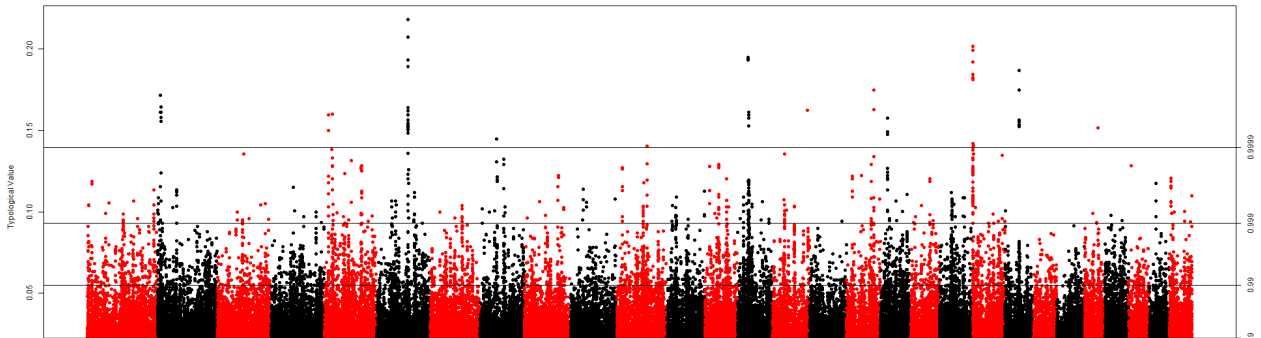
XX'B=BΔ
B'B=I
Principal axes

Coordinates of individuals
L=XA

Typological Values

- **Haplotypes**
  - coordinates of haplotypes along the ith axis $\mathbf{y}^{[i]}$
- **SNPs**
  - coordinates of SNPs along the ith component $\mathbf{c}^{[i]}$
  - $\mathbf{c}_{ij}^2$: Typological value of SNP_j with the ith component
    - R^2 of the model $y^{[i]} = \mu + SNP_j + \epsilon$
    - *Fst* (Laloë and Gautier, 2011)





Problem formulation : the Fused Lasso Signal Approximator (FLSA)

(Tibshirani *et al*,2005; Hoefling, 2010)

- $\mathbf{y} = (y_1, ...y_n)$ an ordered vector of data
- identification of consecutive points with high and constant values.
- FLSA solution

$$\hat{\boldsymbol{\beta}}(\lambda_1, \lambda_2) = \arg\min_{\boldsymbol{\beta}} \left\{ \frac{1}{2} \|\mathbf{y} - \boldsymbol{\beta}\|_2^2 + \lambda_1 \sum_{i=1}^{n} |\beta_i| + \lambda_2 \sum_{i=1}^{n-1} |\beta_{i+1} - \beta_i|. \right\}$$

  - λ_1 controls the level of sparsity
  - λ_2 controls the level of smoothness

Adaptive FLSA

A two step procedure (Rinaldi, 2009).

1. Fusion step
   1.1 Fit the FLSA model with $\lambda_1 = 0$, i.e., $\hat{\boldsymbol{\beta}}(0, \lambda_2)$.
   1.2 For the partition $\mathcal{B} = \{B_1, \ldots, B_J\}$ of J blocks (or segments) associated to $\hat{\boldsymbol{\beta}}(0, \lambda_2)$, compute:

$$\tilde{\boldsymbol{\beta}} = \sum_{j=1}^{J} \bar{y}_j \mathbf{1}_{B_j}, \quad \bar{y}_j = \text{card}(B_j)^{-1} \sum_{j=1}^{J} y_j,$$

2. Adaptive step
   Fit the following weighted lasso problem:

$$\hat{\boldsymbol{\beta}}^{\text{AFL}} = \arg\min_{\boldsymbol{\beta}} \left\{ \frac{1}{2} \left\| \boldsymbol{\beta} - \tilde{\boldsymbol{\beta}} \right\|_2^2 + \lambda_1 \sum_{i=1}^{n} w_i |\beta_i| \right\}, \quad w_i = \sum_{j=1}^{J} \frac{\mathbf{1}_{B_j}}{\sqrt{\text{card}(B_j)}}$$

Hard thresholding : $\text{hard}(x; \lambda) = x \cdot \mathbf{1}_{\{|x| > \lambda\}}$

Model selection

- Cross Validation : Construction of fold not obvious in the case of ordered data
- Penalized Criterion

Penalized Criteria

- IC penalized criterion of the form

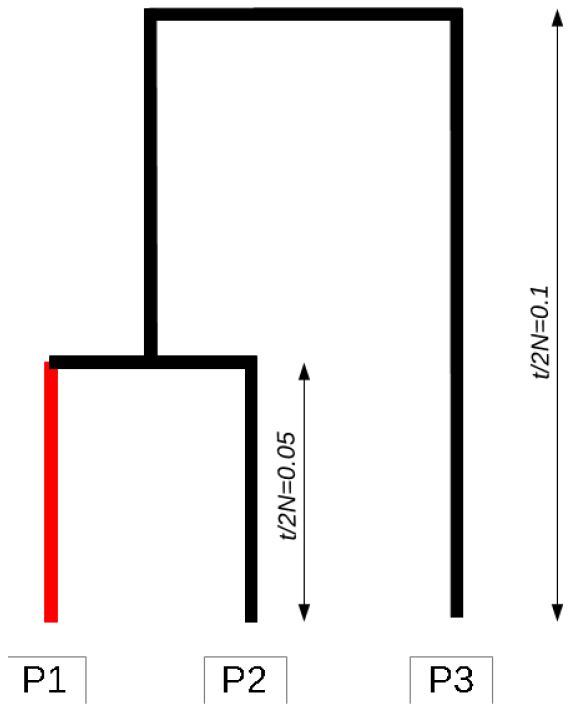
$$\mathrm{IC}(\hat{\boldsymbol{\beta}}(\lambda_1, \lambda_2)) = \frac{1}{2n} \left\| \mathbf{y} - \hat{\boldsymbol{\beta}} \right\|_2^2 + \frac{\sigma^2}{n} \mathrm{pen}(\mathrm{df}),$$

  where
  - $\mathrm{pen}(\cdot)$ is a function that penalized the number of parameters of the model, df (number of segments different from zero).
  - σ^2 estimated by the plug-in estimator of P Hall (Lebarbier, 2005)
- Criteria
  - AIC: $\mathrm{pen}(\mathrm{df}) = 2 \cdot \mathrm{df}$
  - BIC: $\mathrm{pen}(\mathrm{df}) = \log(n) \cdot \mathrm{df}$
  - BML (*for Birgé, Massart, Lebarbier*; Lebarbier, 2005) : $\mathrm{pen}(\mathrm{df}) = \mathrm{df} * (2 * log(n/\mathrm{df}) + 5)$

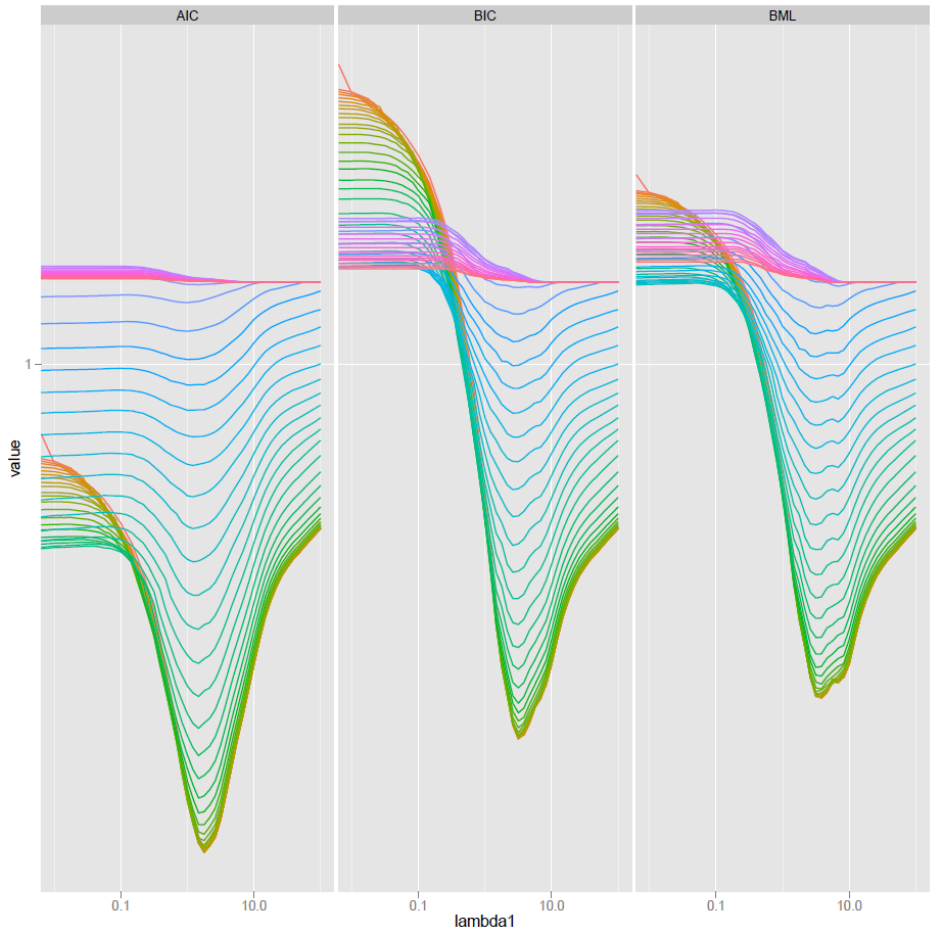
Simulations

- Three populations
- Five 5 Mb-chromosomes
- 1000 SNPs per chromosome
- 1 causal variant at position 2.5 Mb of chromosome1

  driven to fixation via selection in population P1
- Program msms coalescent simulator *Ewing and Hermison, 2010*
- 100 simulations
- First PC : Highest node P1-P2 *vs* P3

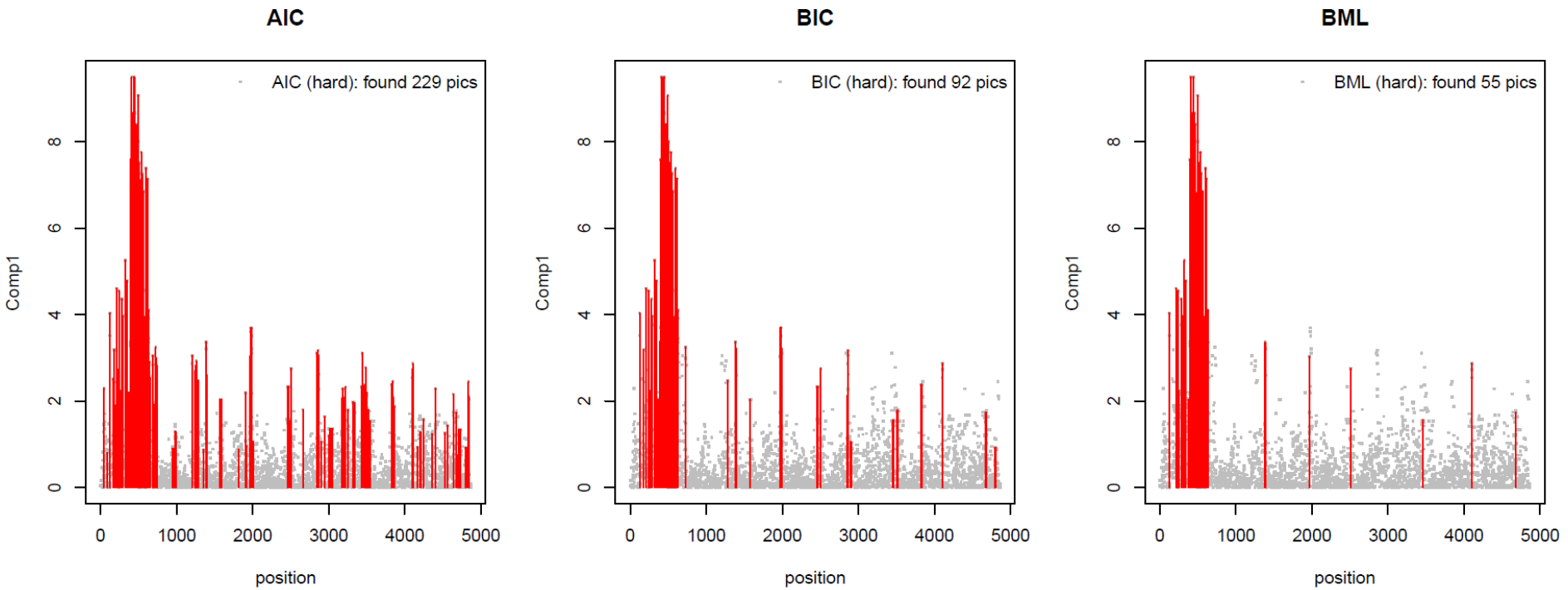


A simulation example. Parameter optimization



Choice of λ_1 and λ_2 according to the penalization criterion

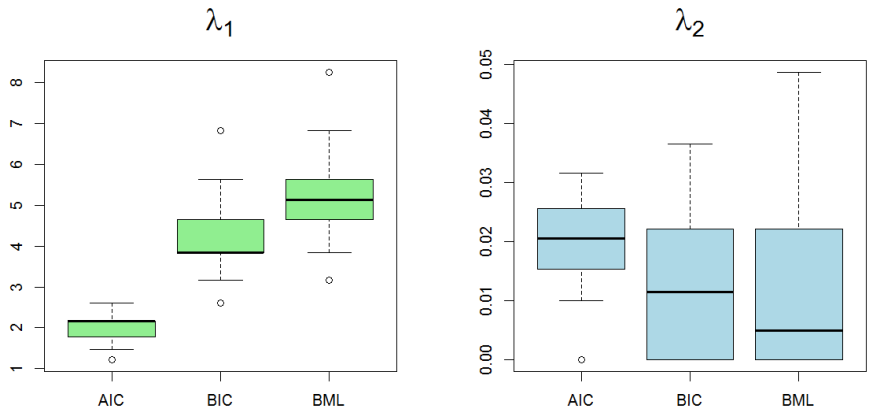
A simulation example. Selected regions



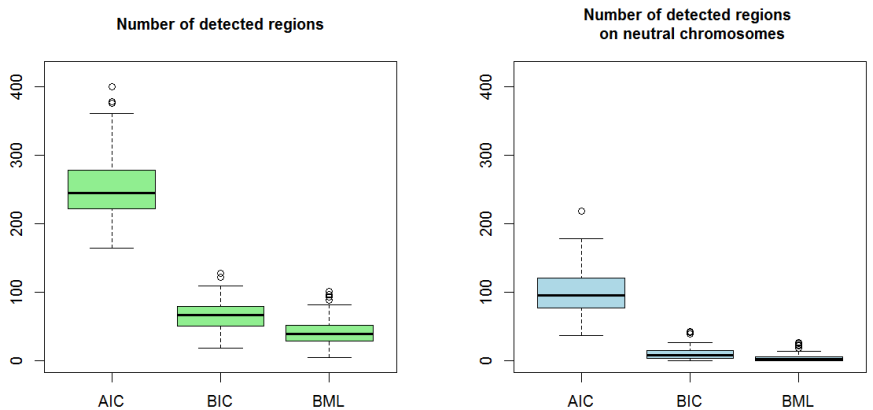
Selected SNPs according to the penalization criterion

Comparison of penalization criteria

1. Choice of parameters



2. Selected regions

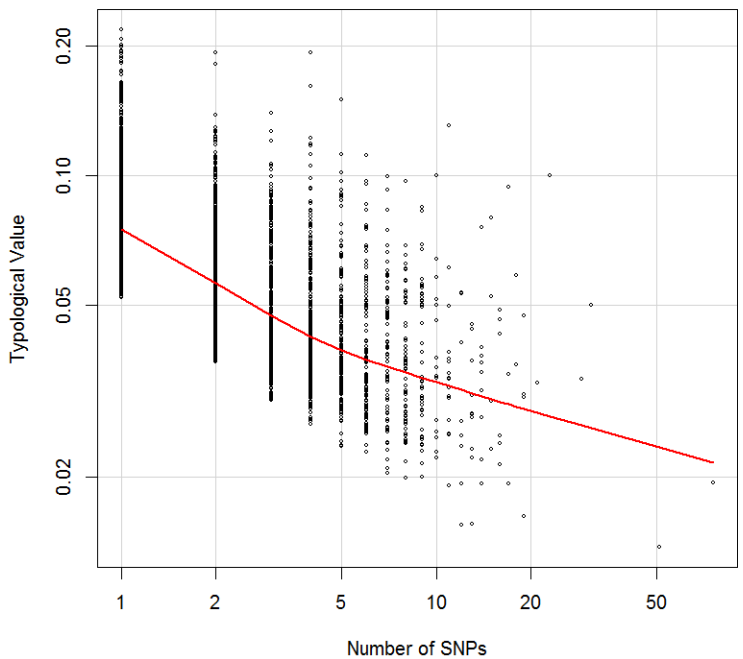


French bovine data

- 600 animals from 20 French dairy and beef cattle breeds
- HD 770k SNP array
- PCA on haplotypes
- a between **beef** vs **dairy** analysis

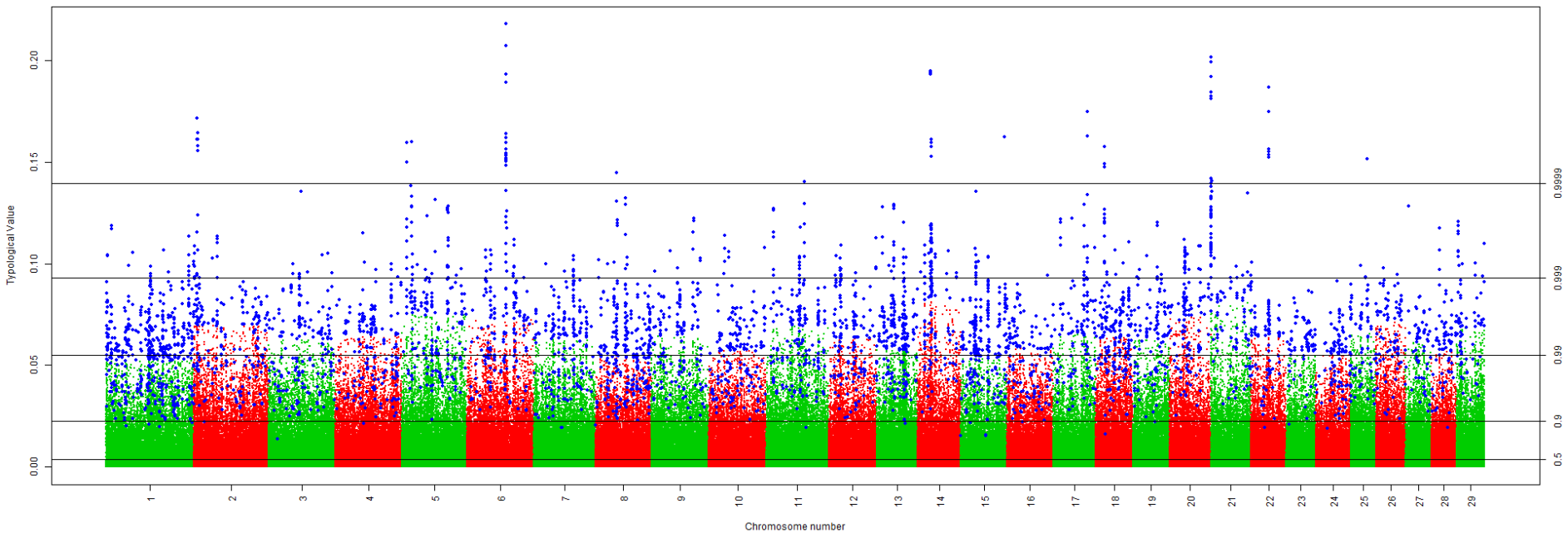
Results

- 10675 selected markers (out of 656152): 1.6%
- Accounts for spatial structure, selected regions containing from 1 to 76 SNPs ($\mu = 2.5$)



Magnitude of selected SNPs according to the block length

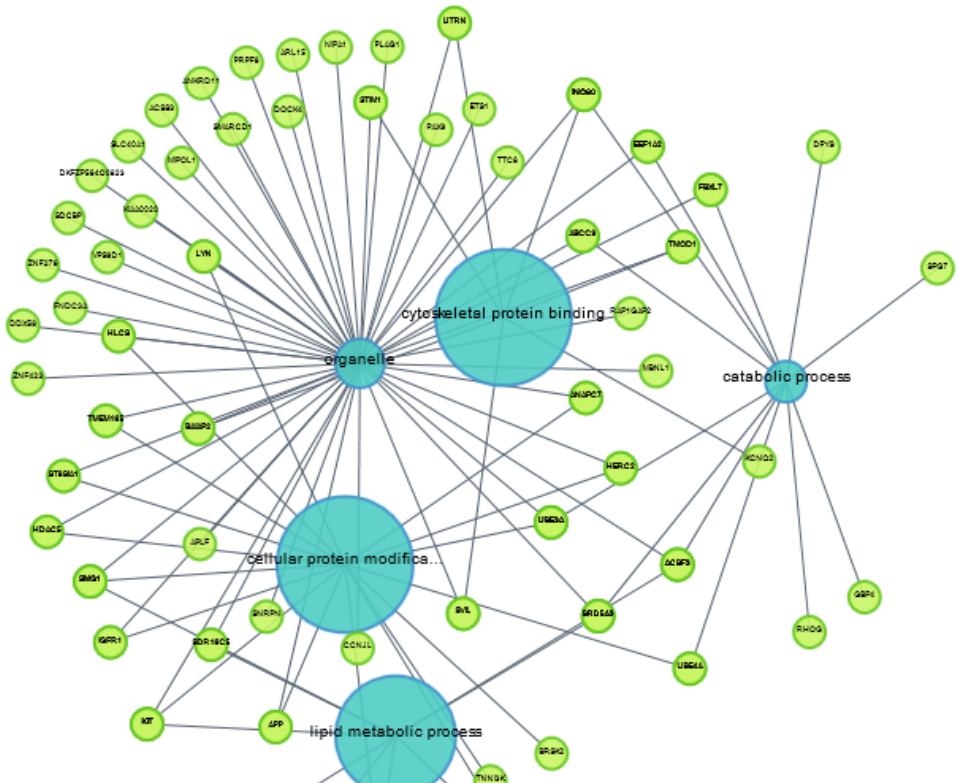
Results



Manhattan plot of typological values. Selected SNPs

Results

- 1067 genes containing selected markers
- Enrichment analysis on the first 100 genes
  - Cytoskeletal protein binding (Muscle)
  - Lipid metabolism process (Milk/Muscle)



Conclusions and Future Work

- Selection of 1.6 % markers
- Accounts for spatial structure, selected regions containing from 1 to 76 SNPs ($\mu = 2.5$)
- Sensitivity to penalization criterion
- Sensitivity to parameter tuning

- Stability selection strategy (Meinshausen and Bühlmann, 2010 ; Yang et al, 2011)
  - Reducing false positives
  - Reducing the effect of parameter tuning

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