Clustering with variable selection for longitudinal data.

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Outline

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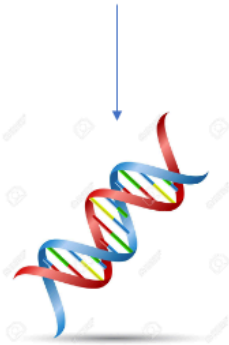
Biological context

In genetic, the main objective is to understand the molecular mechanisms underlying important biological processes

- to identify the best phenotypes in genetic improvement programs,
- to identify markers associated with phenotypes/diseases,
- to improve diagnostics/interventions,
- ...

Differences



$\Rightarrow$ Identification of **genetic variants** involved in the variability of phenotypic traits using **variable selection approaches**

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Biological context

In many fields, longitudinal studies are conducted to obtain a better understanding of the dynamic of biological processes

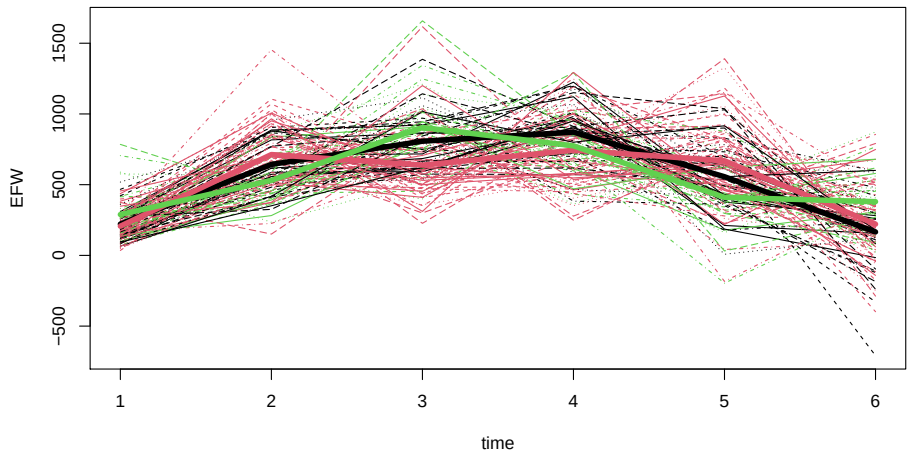

Figure 1: Fetal weights over pregnancy period.

⇒ Identification of **genetic variants** involved in the dynamic of responses and estimation of their effects over time using **variable selection for longitudinal data**

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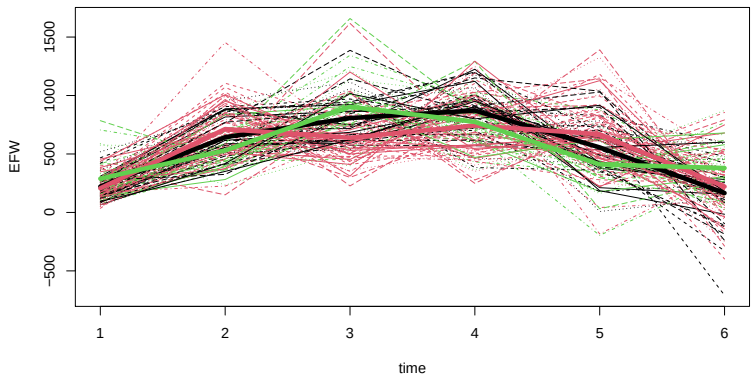
Biological context

Limitations: selection of the **same** subset of genetic variants and estimation of the **same** dynamic effects for all individuals.



↬ Different subsets of genetic variants with different time varying effects may be associated to different groups of individuals

Identifying genetic markers associated with each group for

↬ a finer understanding of molecular mechanisms underlying dynamic processes,

↬ helping design improved medical and phytosanitary treatments

Need to develop a clustering approach with variable selection for longitudinal data

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Clustering approaches

To uncover groups of observations characterized by several variables

Two broad classes of approaches:

1. Based on similarity or dissimilarity distances (hierarchical methods, k-means, ...)
2. Model-based approaches which use mixture models for clustering

In the following we will focus on **model-based approaches** (Banfield and Raftery, 1993; Richardson and Green, 1997; Neal, 2000; Fraley and Raftery, 2002)

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Model-based approaches

Model-based methods without or with variable selection

↬ **Why integrate variable selection ?** Clustering information is contained into a **subset** of covariates (Friedman and Meulman, 2004; Tadesse et al., 2005; Maugis et al., 2009): including all covariates may hide group structures

⚠ Especially for high-dimensional data or data with a higher number of covariates than observations

	no outcome	non-longitudinal outcome	longitudinal outcome
Clustering without variable selection	✓	✓	✓
Clustering with variable selection	✓	✓	✗

Table 1: Existing approaches wrt the type of outcome

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Coming back to our context

Objective:

To **cluster** similar response profiles and to **select** genetic variants that help discriminate them

	no outcome	non-longitudinal outcome	**longitudinal outcome**
Clustering without variable selection	✓	✓	✓
Clustering with variable selection	✓	✓	✗

The proposed approach:

A stochastic partitioning method, based on the work of Monni and Tadesse (2009), which combines ideas of mixture models, mixed effects models, and variables selection.

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Statistical model

Data

n independent samples with a repeated outcome and p covariates:

- $\mathcal{Y} = (Y_1, \ldots, Y_n)'$ with $Y_i = (Y_{i1}, \ldots, Y_{iT})'$ for $i = 1, \ldots, n$,
- $\mathcal{X} = (X_1, \ldots, X_p)$ with $X_j = (X_{j1}, \ldots, X_{jn})'$ for $j = 1, \ldots, p$.

Partitioning approach

- Variables partitioned into sets of pairs (X_J, Y_I) with $J \subset \{1, \ldots, p\}$ and $I \subset \{1, \ldots, n\}$
- Individuals in a pair have similar dependence on the subset of covariates
- A configuration: a partition of data where the components are the pairs

For example, a configuration of length K is defined by:

$$\mathcal{S}_1 \oplus \cdots \oplus \mathcal{S}_K = (X_{J_1}, Y_{I_1}) \oplus \cdots \oplus (X_{J_K}, Y_{I_K}) = (|J_1|, |I_1|) \oplus \cdots \oplus (|J_K|, |I_K|)$$

with $0 \leq |J_k| \leq p$, $1 \leq |I_k| \leq n$ and $\sum_{k=1}^{K} |I_k| = n$ and $\sum_{k=1}^{K} |J_k| \leq Kp$.

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Hierarchical Bayesian model

↬ Mixture of multivariate Gaussian models such that the model associated with individuals $Y_{l_1}, \ldots, Y_{l_{n_k}}$ belonging to the component $\mathcal{S}_k = (|J_k|, |I_k|) = (m_k, n_k)$ is:

$$
\begin{aligned}
Y_i | \boldsymbol{\beta}_k, \sigma_k^2, \rho &\sim \mathcal{N}_T(\boldsymbol{\mu}_{ki}, \sigma_k^2 \Omega), \quad i = l_1, \ldots, l_{n_k}, \\
\boldsymbol{\beta}_{ks_r} | \tau_k^2, \sigma_k^2 &\sim \mathcal{N}_T(0, \sigma_k^2 \tau_k^2 (D'D)^{-1}), \quad r = 1, \ldots, m_k, \\
\tau_k^2 &\sim \mathcal{IG}(a, b), \ \sigma_k^2 \sim \mathcal{IG}(\sigma_0^2, \nu) \\
\rho &\sim \mathcal{U}_{(-1,1)}
\end{aligned}
$$

$$
p((m_1, n_1) \oplus \ldots \oplus ((m_K, n_K)) \propto \prod_{k=1}^{K} \pi^{m_k}
$$

- $\boldsymbol{\mu}_{ki} = \sum_{r=1}^{m_k} x_{is_r} \boldsymbol{\beta}_{ks_r}$ with $\boldsymbol{\beta}_{ks_r} = (\beta_{ks_r}^1, \ldots, \beta_{ks_r}^T)'$ the time varying effects.
- Ω a $T \times T$ auto-regressive correlation matrix of order 1 with unknown parameter ρ.
- τ_k^2, σ_k^2 variance parameters.
- $a, b, \sigma_0^2, \nu, \pi$ fixed hyperparameters.
- D matrix representation of first order finite difference operator.

↬ Parameters $\boldsymbol{\beta_k}$ and σ_k^2 are integrated out

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MCMC implementation

1. Update of configuration via a reversible jump Markov chain Monte Carlo algorithm:
   1. **Type 1**: Add or delete covariate to/from a component
   2. **Type 2**: Reallocate observations by choosing to split/merge components (m, n) (with $n > 0$) or to reassign a single observation.
2. Update of τ_k^2 for $k = 1, \ldots, K$ via a Metropolis-Hasting algorithm,
3. Update of ρ via a Metropolis-Hasting algorithm.

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Simulation study

Objectives

- Evaluate sensitivity to hyperparameter π
- Evaluate performance under different simulation settings:
  - varying residual variance, σ_k^2
  - varying number of covariates, p
  - varying number of relevant predictors per cluster
- Compare to a two-step approach:
  1. Clustering step: model-based clustering for longitudinal data (McNicholas and Subedi, 2012) implemented in the R package `longclust`
  2. Selection step: Bayesian varying coefficient model with selection using group spike-and-slab prior (Heuclin et al., 2021) in each identifying cluster

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Simulation parameters

- Number of individuals $n = 75$, number of time steps $T = 10$, number of clusters/groups $K = 3$
- Number of covariates $p = 150$ or $1,000$ with a varying number of relevant predictors per cluster with different varying time effects for each cluster
- Residual variance equal to 0.1 or 1
- X elements randomly sampled from the set $\{0, 1, 2\}$ to mimic SNP data

Figure 2: Simulated dynamic effects.

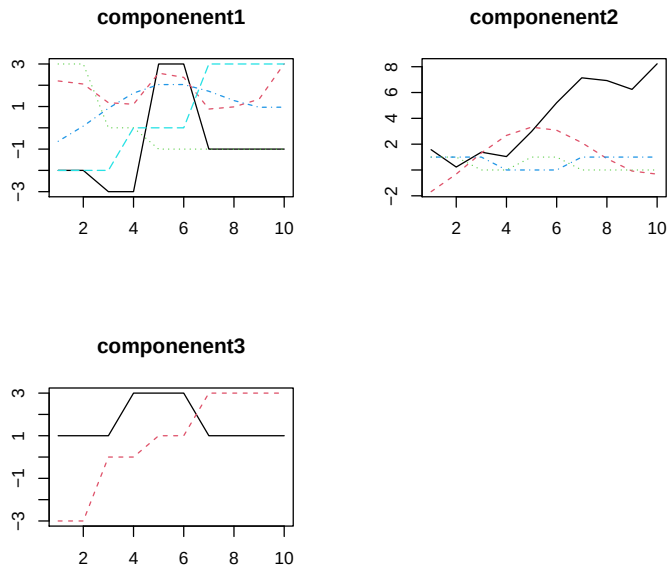
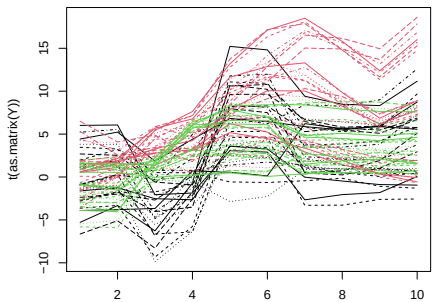


Figure 3: Simulated response profiles over time.



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Criterion for evaluating model performance

- Convergence evaluation:
  - Acceptance rates over iterations for type 1 and type 2 moves
  - Ratio of acceptance rate of type 1 over type 2 moves (RAR)
- Prediction evaluation:
  - Confusion matrix of cluster allocation
- Selection evaluation:
  - False positives (FP), false negatives (FN), true positives (TP), true negatives (TN) for each cluster

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Sensitivity to hyperparameter π

(n=75, p=150, $\sigma_k^2 = 0.1$, 1 to 5 relevant covariates per cluster)

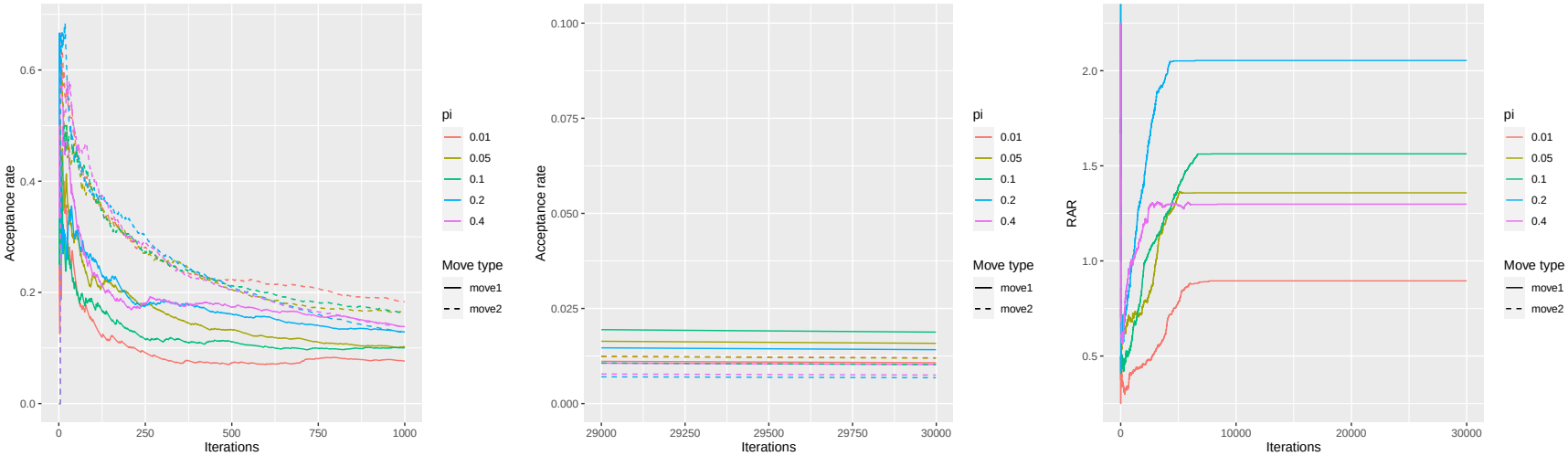

Figure 4: Acceptance rates over the first 1,000 iterations (on left), over the last 1,000 iterations (in middle), and RARs over 30,000 iterations (on right).

- Clustering: successful recovery of groups for all values of π
- Selection: successful identification of cluster-specific predictors for all values of π

↬ Weak sensitivity to hyperparameter π

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Impact of the residual variances (n=75, p=150, 1 to 5 significant covariates per cluster)

- Convergence diagnostic based on RAR:

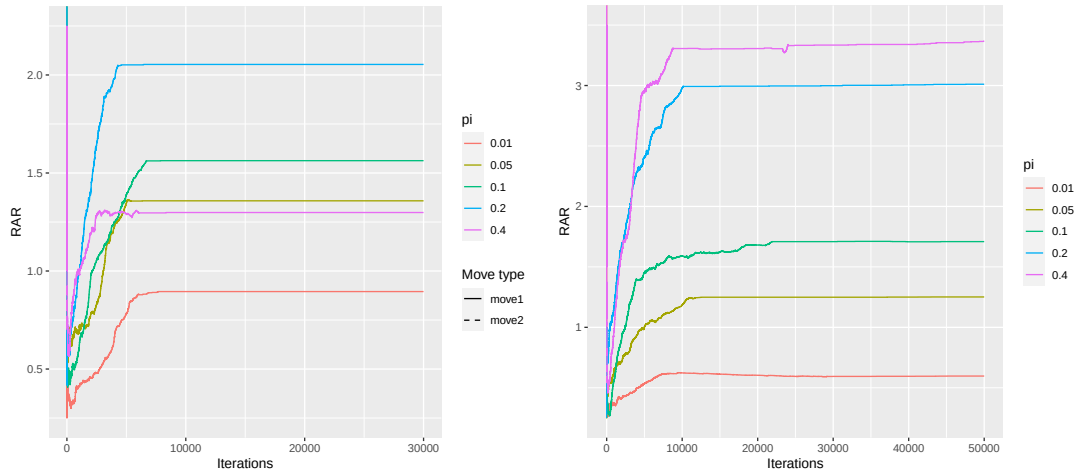

Figure 5: RARs over iterations for simulation with $\sigma_k^2 = 0.1$ (right) and $\sigma_k^2 = 1$ (left).

↬ Slower convergence for higher residual variances

- After convergence, successful inference for clustering and selection

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Impact of the number of relevant covariates per cluster

(n=75, p=150, $\sigma_k^2 = 1$)

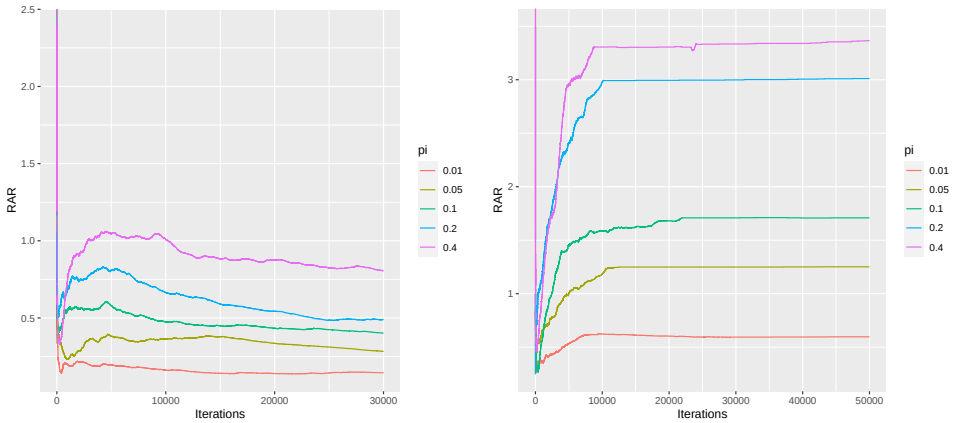

Figure 6: RARs over iterations for simulation with one relevant covariate per cluster (on right) and with 1 to 5 relevant covariates per cluster (on left).

↬ Higher number of significant covariates per cluster helps uncover groups and improves convergence

		Truth		
		1	2	3
Predicted	1	24	0	0
	2	1	25	3
	3	0	0	22

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Impact of total number of covariates (n=75, $\sigma_k^2 = 1$)

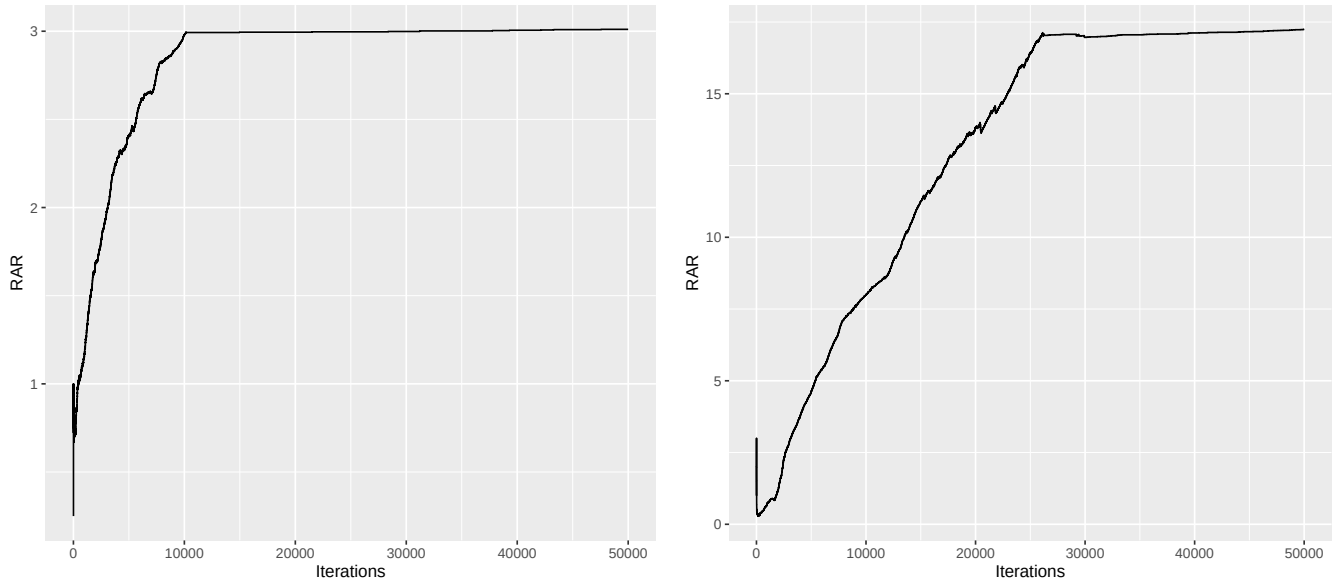

Figure 7: RARs over iterations for simulation with 150 covariates (on right) and with 1,000 (on left) using $\pi = 0.1$.

↬ Slower convergence for a higher number of covariates

- After convergence, successful recovery of groups
- Selection for $p = 1,000$: all TP identified, 2FP and 1 FN

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Comparison with two-step approach

(n=75, p=150, 1 to 5 relevant covariates per cluster)

- Step 1: Clustering with the `longclust` package:

		Truth		
		1	2	3
Predicted	1	24	0	7
	2	1	25	18

Table 2: For simulation with $\sigma_k^2 = 0.1$.

		Truth		
		1	2	3
Predicted	1	14	11	4
	2	0	0	12
	3	0	5	0
	4	9	0	0
	5	2	0	9
	6	0	9	0

Table 3: For simulation with $\sigma_k^2 = 1$.

↬ Difficulty separating some clusters

- Step 2: Variable selection in each identified cluster using Heuclin et al. (2021) fails to select the relevant covariates

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Conclusion

We proposed an innovative approach for clustering longitudinal data with variable selection

- Promising results
  - Robust to signal-to-noise ratio
  - Higher number of relevant predictors markers per cluster helps their successful recovery
  - Clustering of observations based on their profiles as well as their dependence on subsets of variables
- Perspectives
  - Need to improve computational speed
  - P-spline modeling for longitudinal effects for large number of repeated measures or high resolution outcome data
  - Extension to time varying covariates

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Thanks for your attention!

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