Support of temporal structure in the statistical analysis of high-throughput proteomic data

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Support of temporal structure in the statistical analysis of high-throughput proteomic data

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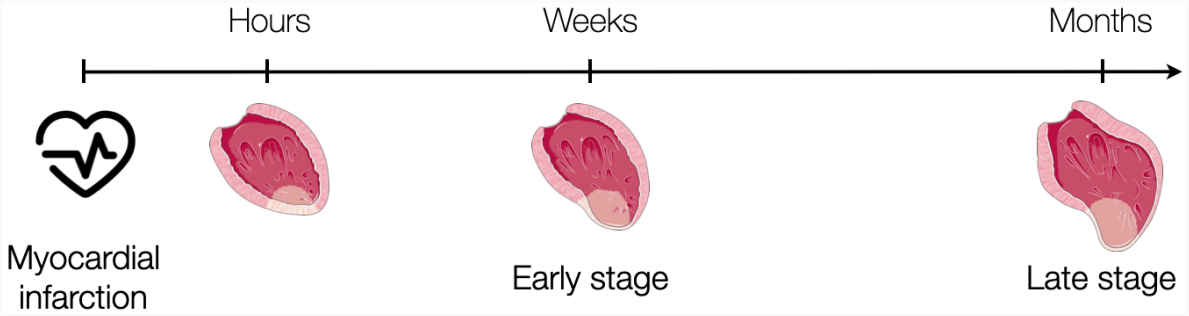
Plan

Scientific context

Heart failure (HF) : multi-factor disease resulting in the incapacity of the heart to pump enough blood to supply all organs.

→ In France, **70 000** persons die from heart failure each year.



Left Ventricular Remodeling (LVR) : Progressive dilatation of the LV leading to a growth of the LV that occurs in response to myocardial infarction (MI).

LVR quantification is given by :

$$\text{LVR} = \frac{\text{LV volume 1 year after MI} - \text{LV volume after MI}}{\text{LV volume after MI}}$$

→ LVR is an indicator of a high risk of HF or death after MI. (St John Sutton et al., 1994)

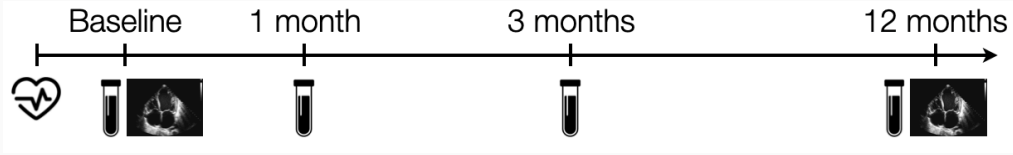
REVE-1 and REVE-2 cohorts

In order to study LVR and longterm survival, two cohorts were designed by Pr. Bauters where included patients were :

- Affected by a **first myocardial infarction**
- Monitored with blood samples (1 to 4 samples)
- **Followed for up to 13 years** for heart failure or death for cardiovascular reasons

REVE-1 : (2002-2004)
255 patients
77 events observed

REVE-2 : (2006-2008)
238 patients
41 events observed



→ **Over 5000 plasma proteins were measured** out of each plasma sample collected during the two studies

Questions

1. Can we predict longterm survival using baseline measurements of both cohorts ?

2. Can we build a selection method that support the temporal structure and the high dimension of the data in order to select proteins we could use for prediction based on REVE-2 measurements ?

Plan

Scientific Context

Survival predictive models

Taking into account temporal structure

- k-means
- Mixture model

Problematic

Objective : Selecting proteins in order to predict a clinical outcome using baseline measurements of the two cohorts.

Statistical framework

- Construction of a predictive model for a variable Y with a set of variables $X_1, \ldots, X_p$ measured over n individuals.

Clinical framework

- Y : Time before the occurrence of a event (survival analysis).
- $X_1, \ldots, X_p$: Clinical variables (~ 10) + Proteomic variables (~ 5000)

Statistical difficulties : High dimension of the data ($n \ll p$)

- Considered solution : variable selection and individual clustering $\rightarrow$ identification of patients subtypes

Cox Model

Used model : Cox proportional hazards regression model

$$\underbrace{h(t,X)}_{\text{Risk function}} = \underbrace{h_0(t)}_{\text{Baseline risk}} \underbrace{\exp(\beta^T X)}_{\text{Variables effect}}$$

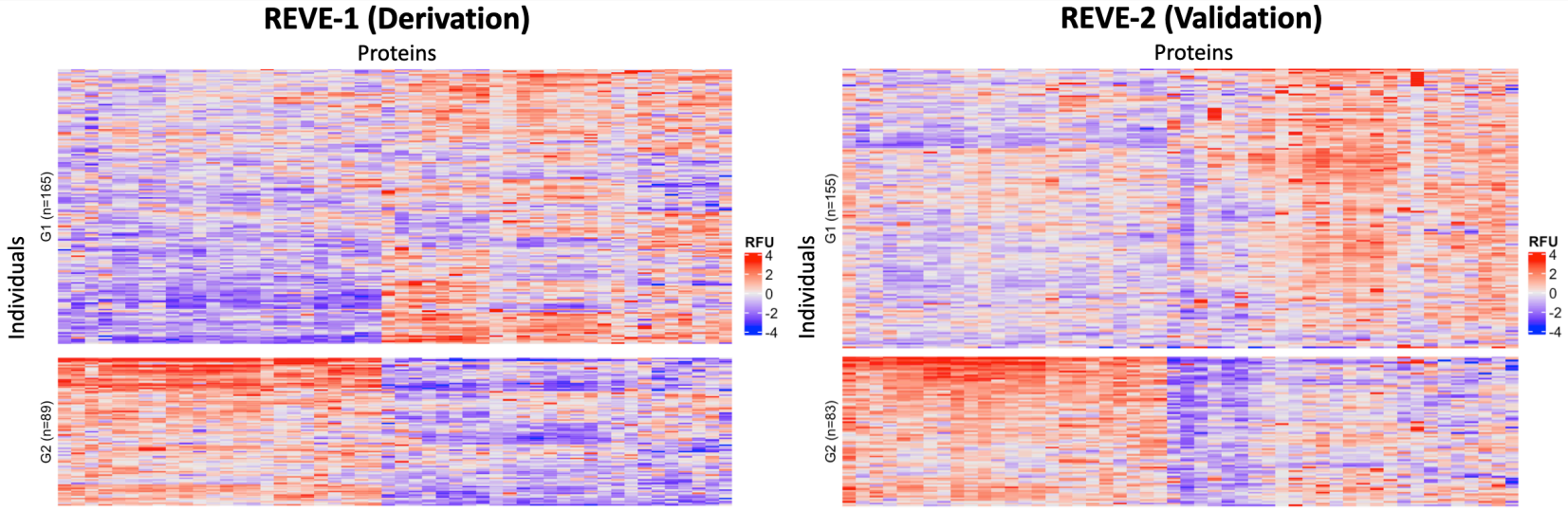
Variable Selection : Univariate analysis

Univariate Cox models were fitted for each protein and the **50 proteins** significantly associated to longterm survival were selected.

Clustering of patients : k-means clustering was used in order to identify groups of patients based on protein expression related to longterm survival.

Survival

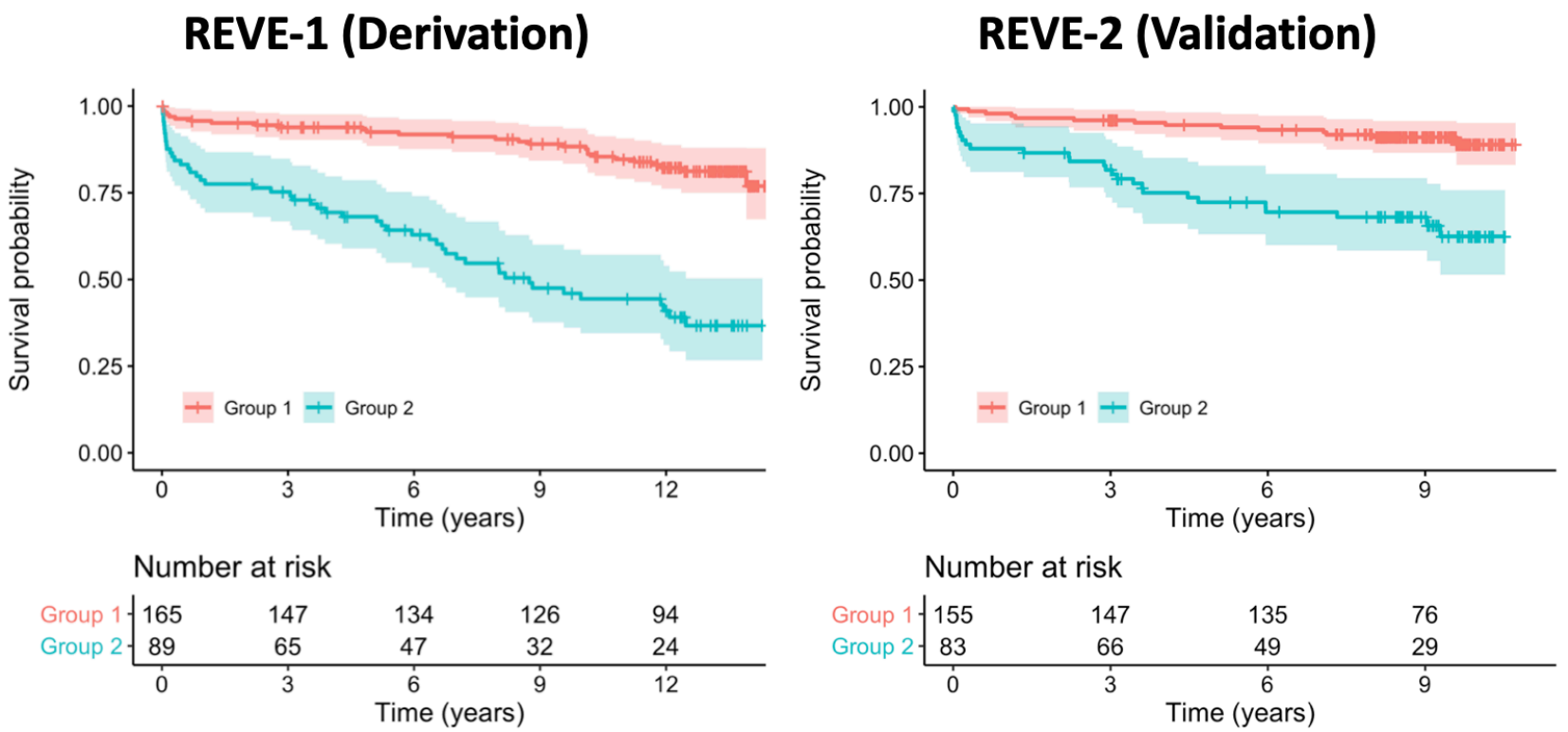
2 clusters of patients were identified on REVE-1 using k-means and were applied to REVE-2 showing **opposite proteomic expression profiles** and **distinct clinical profiles**.



→ Significant differences on Age, Diabetes, Hypertension and WMSI (Wall Motion Systolic Index) between patients of the 2 clusters for both cohorts.

Survival

Clusters were used as a new variable to predict longterm survival :



→ Cluster effect was significant on both cohorts even when adjusted on clinical variables with significant **hazard ratio of 2.6** for both cohorts after adjusment on clinical variables.

Plan

Scientific Context

Survival predictive models

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Problematic

Classic goal :

Prediction of Y with baseline measurement

Particularity of the data

Proteomic measures are available at baseline (for both cohorts) and at 3 other times for REVE-2.

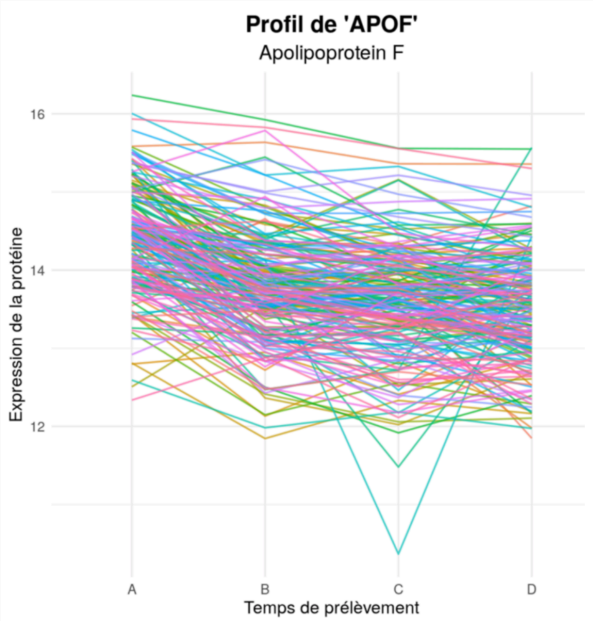
Offered outlook :

- Study of the temporal evolution of the protein measurements
- Proteins clustering with measures at all times $\rightarrow$ more meaningful groups

Usefulness for the prediction of Y :

- Construction of a penalty taking in charge the temporal structure with the previously created groups
- Selected proteins potentially more relevant

Proteins clustering



Notation

- x_{ijt} : measurement of protein j for patient i at time t
- $\mathbf{x}_j = (x_{ijt})_{i,t}$: all measurements of protein j stored as a $n(= 238) \times T(= 4)$ matrix.

Considered clustering approaches

- *k-means* algorithm
  - on all the data $\mathbf{x}_j$ which could be vectorized as a $n \times T$ vector.
  - on a summary of $\mathbf{x}_j$ (mean slope for example)
- Use of a mixture model based approach

$$g(x) = \sum_{k=1}^{G} \pi_k f_k(x)$$

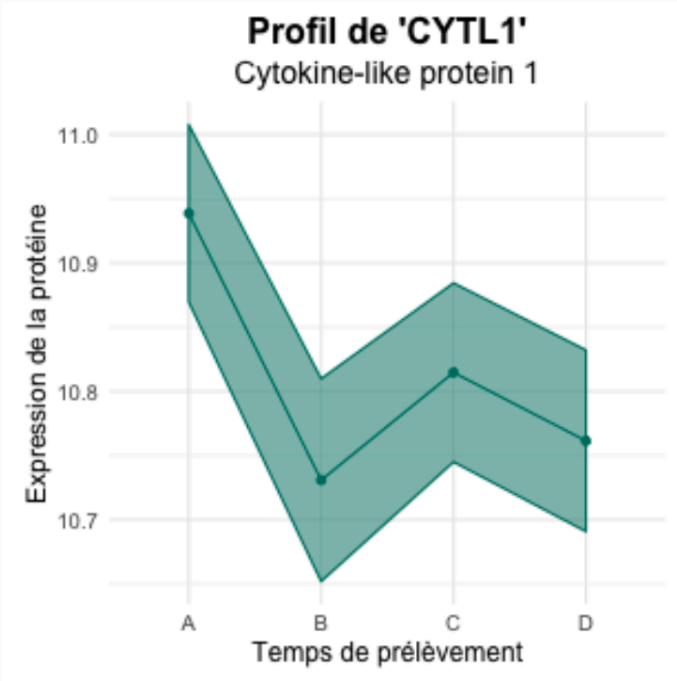
k-MEANS

Idea : Create groups of proteins varying together

$\rightarrow$ Slope formula to sum-up $\mathbf{x}_j$ to a vector of size $T-1$:

$$d_{jl} = \frac{\bar{\mathbf{x}}_{jt_{l+1}} - \bar{\mathbf{x}}_{jt_l}}{\sqrt{\frac{\sigma^2_{jt_l}}{n} + \frac{\sigma^2_{jt_{l+1}}}{n}}},$$

where $\bar{\mathbf{x}}_{jt_l} = \frac{1}{n}\sum_{i=1}^{n} x_{ijt_l}$ and $\sigma^2_{jt_l} = \frac{1}{n}\sum_{i=1}^{n}(x_{ijt_l} - \bar{\mathbf{x}}_{jt_l})$.



k-means criteria :

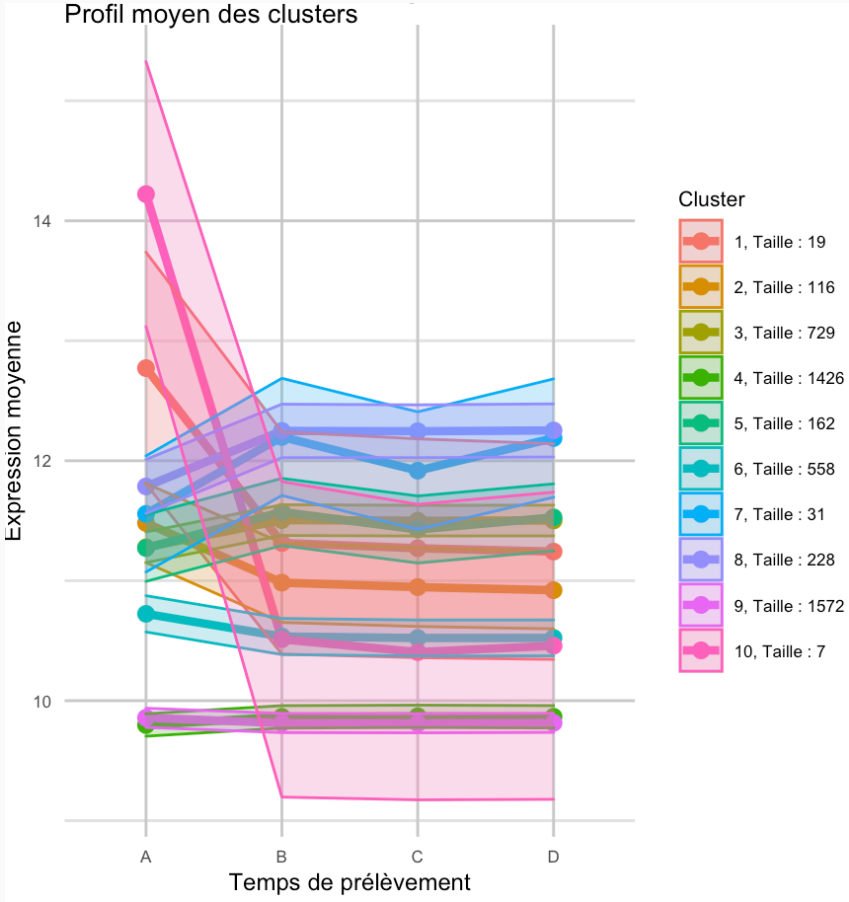
$$\underset{\mu_1,\ldots,\mu_G}{\arg\min} \sum_{k=1}^{G} \sum_{\mathbf{d_j} \in \mathbf{S_k}} \|\mathbf{d_j} - \mu_\mathbf{k}\|^2$$

where $\mathbf{d}_j = (d_{jt_1}, \ldots, d_{jt_{T-1}})$.

k-MEANS

Number of groups : inertia criteria.

Groups obtained with *k*-means algorithm are stable (specially for groups with distinctive profiles).



Huge **sensitivity to data pre-treatment (slope modelization) and difficulties to interpret groups.**

Mixture model

Mixture model for G groups :

$$g(x) = \sum_{k=1}^{G} \pi_k f_k(x)$$

where g is the law of a model to model proteins.

Using linear mixed models (Celeux, 2005) we could :

- Use objective statistical criteria to compare models (and groups)
- Control more accurately the temporal structure
- Adapt the model to the data by adding multiple effects

Mixture model of linear mixed models

Using a mixture model, for each protein $\mathbf{x}_j$ we have :

- $\mathbf{z}_j = (z_{j1}, ..., z_{jG}) \sim \mathcal{M}(\pi_1, ..., \pi_G)$ the class of the variable $\mathbf{x}_j$
- Knowing $\mathbf{x}_j | z_{jk} = 1 \sim MM(\theta_k)$, the protein $\mathbf{x}_j$ will be modeled by :

$$x_{ijt} = \mu_k + b_{ij} + \beta_{kt} + \varepsilon_{ijt}$$

Where :

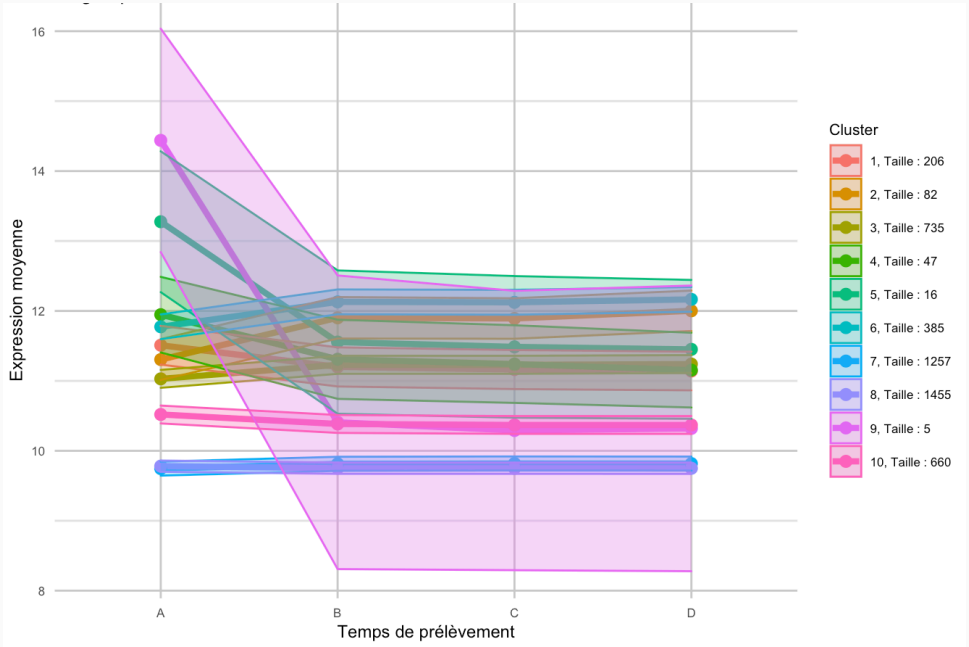
- μ_k the fixed effect of protein of class k
- $b_{ij} \sim \mathcal{N}(0, \sigma^2_{1,k})$ random effect of individual i for proteins of class k
- β_{kt} the fixed effect of time t for proteins of class k
- $\varepsilon_{ijt} \sim \mathcal{N}(0, \sigma^2_{2,k})$ the error term for proteins of class k

Mixture model of linear mixed models

Using this model we obtain classification like this one :

Number of group was decided a priory

High specificity of the groups depending on the effects of the linear mixed model.



Unlike *k*-means clusters, groups can be interpreted by interpreting the parameters of their linear mixed model.

Conclusion

Prediction of longterm survival

- Selection of proteins
- Meaningful clusters of individuals
- Prediction of longterm survival

Temporal Structure

- Mixture model of mixed model
- Very flexible modelisation of temporal structure
- Use the created groups for the prediction of the outcome

Thank you for your attention !