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SUPPORT OF TEMPORAL STRUCTURE IN THE STATISTICAL ANALYSIS OF HIGH-THROUGHPUT PROTEOMIC DATA

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Scientific Context

Survival predictive models

Taking into account temporal structure

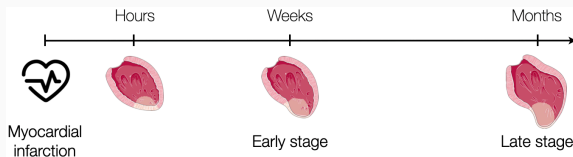
k-means

Mixture model

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)

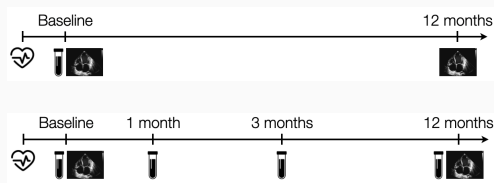
255 patients

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 ?

Scientific Context

Survival predictive models

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k-means

Mixture model

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, \dots, X_p measured over n individuals.

Clinical framework

- Y : Time before the occurrence of a event (survival analysis).
- X_1, \dots, 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

Used model : Cox proportional hazards regression model

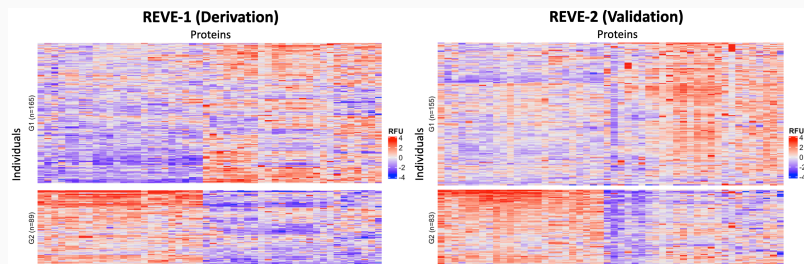
$$\underbrace{h(t, X)}_{\text{Risk function}} = \underbrace{h_0(t)}_{\text{Baseline risk}} \underbrace{\exp(\beta^T X)}_{\text{Variables effect}}$$

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.

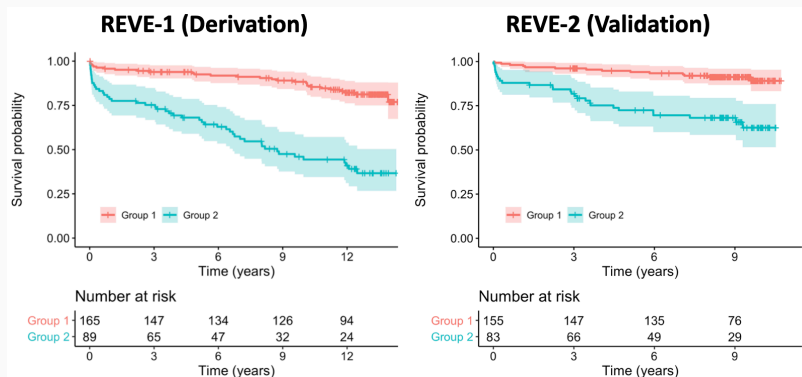
2 clusters of patients were identified on REVE-1 using k-means and were applied to REVE-2 showing **opposite proteomic expression profiles** and **distinct clinical profiles**.



→ 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 adjustment on clinical variables.

Scientific Context

Survival predictive models

Taking into account temporal structure

- k -means

- Mixture model

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 → more meaningful groups

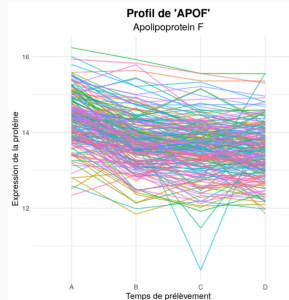
Usefulness for the prediction of Y :

- 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

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

Idea : Create groups of proteins varying together

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

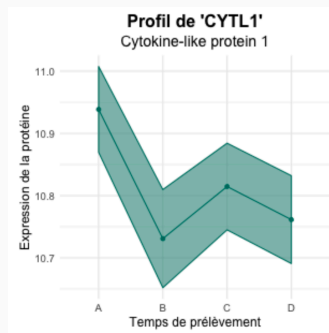
$$d_{jl} = \frac{\bar{x}_{jt_{l+1}} - \bar{x}_{jt_l}}{\sqrt{\frac{\sigma_{jt_l}^2}{n} + \frac{\sigma_{jt_{l+1}}^2}{n}}},$$

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

k-means criteria :

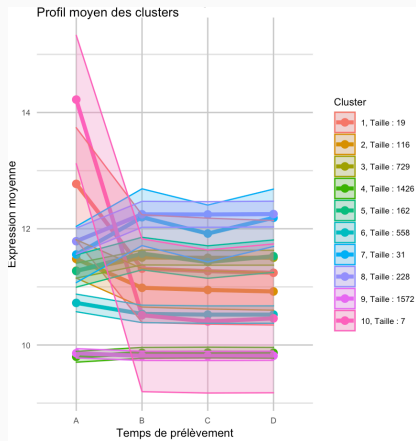
$$\arg \min_{\mu_1, \dots, \mu_G} \sum_{k=1}^G \sum_{\mathbf{d}_j \in S_k} \|\mathbf{d}_j - \mu_k\|^2$$

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



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 for G groups :

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

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 :

- $\mathbf{z}_j = (z_{j1}, \dots, z_{jG}) \sim \mathcal{M}(\pi_1, \dots, \pi_G)$ 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 :

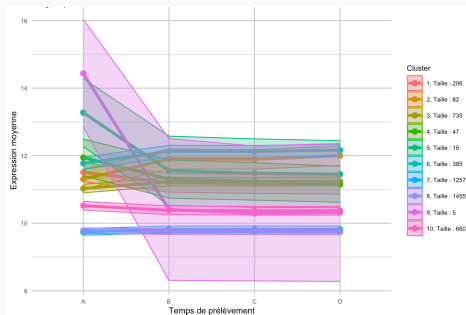
- μ_k the fixed effect of protein of class k
- $b_{ij} \sim \mathcal{N}(0, \sigma_{1,k}^2)$ random effect of individual i for proteins of class k
- β_{kt} the fixed effect of time t for proteins of class k
- $\varepsilon_{ijt} \sim \mathcal{N}(0, \sigma_{2,k}^2)$ the error term for proteins of class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

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 !