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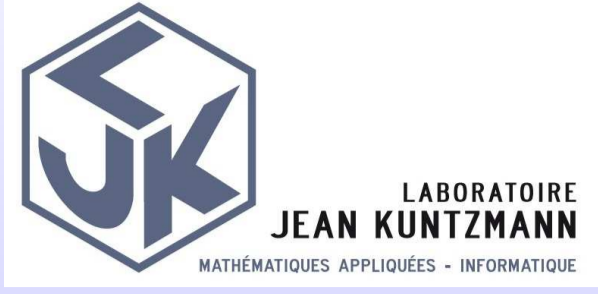
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EXTENSION OF THE EM-ALGORITHM USING PLS TO FIT LINEAR MIXED EFFECTS MODELS FOR HIGH DIMENSIONAL REPEATED DATA



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I. Introduction

To deal with repeated data

- Linear mixed effects models are highly recommended.
- A classical parameter estimation method: Expectation- Maximization (EM) algorithm.

To deal with high-dimensional data

- Reduction dimension methods can be used to summarize the numerous predictors in form of a small number of new components.
- Classical approach : Principal Component Regression (PCR)
 - Does not consider the link between the outcome and the independent variables.
- Alternative method: Partial Least Squares (PLS)
 - Takes the link between the outcome and the independent variables into account.

To solve the high dimensional issue in the repeated data context

→ Introduction of a PLS step into the EM-algorithm for linear mixed models to reduce the high-dimensional data.

- **Idea:** At each iteration, the outcome data is substituted in the input of PLS by a pseudo-variable response whose expected value has a linear relationship with the covariates.

III. Extension of the EM-algorithm for high dimensional repeated data

Extension of the EM-algorithm using PLS (EM-PLS)

At iteration $[t + 1]$:

- E-step: Compute the expectation of the complete data log-likelihood given the observed data and a current value of the parameters $\theta^{[t]}$
- M-step:
 - Define the pseudo-response variable $z^{[t+1]} = X\beta^{[t]} + \sigma^{2[t]} \Gamma^{[t]-1} (y - X\beta^{[t]})$
 - Perform PLS regression of the pseudo-response variable $z^{[t+1]}$ onto X :

$$\beta^{[t+1]} \leftarrow PLS(z^{[t+1]}, X, \kappa)$$

where κ is the PLS component number obtained by cross-validation.

- Calculate new parameter values $\tau^{2[t+1]}$ and $\sigma^{2[t+1]}$ from Equations (2) and (3).

Extension of the EM-algorithm using PCR (EM-PCR)

Similarly, a PCR step is introduced into the EM-algorithm to reduce the high-dimensional data to low-dimensional features.

II. The linear mixed effects model

Definition of the linear mixed effects model

- $Y = (Y_1', \dots, Y_I')'$ with $Y_i = (Y_{i1}, \dots, Y_{in_i})'$ the vector of all measurements for the i th individual, $i = 1, \dots, I$.
- The linear mixed model for the response Y is defined as

$$Y = X\beta + U\xi + \varepsilon$$

with X the $n \times p$ design matrix associated to the p -vector fixed effects β , U the $n \times I$ design vector associated to the random effects $\xi = (\xi_1, \dots, \xi_I)'$, $\xi \sim \mathcal{N}(0_I, \tau^2 I_I)$ and $\varepsilon \sim \mathcal{N}(0_n, \sigma^2 I_n)$.

- The marginal distribution of the response Y is given by

$$Y \sim \mathcal{N}(X\beta, \Gamma) \quad \text{with} \quad \Gamma = \tau^2 U U' + \sigma^2 I_n$$

The ML estimation approach using the EM-algorithm

- The log-likelihood associated with the complete data (y, ξ) is given by

$$L(\theta|y, \xi) = -\frac{1}{2} \left\{ (n+I) \ln 2\pi + I \ln \tau^2 + n \ln \sigma^2 + \frac{(y - X\beta - U\xi)'(y - X\beta - U\xi)}{\tau^2} + \frac{\xi^2}{\sigma^2} \right\}$$

- At iteration $[t + 1]$, the E-step consists of computing the expectation of the complete data log-likelihood given the observed data and a current value of the parameters $\theta^{[t]} = (\beta^{[t]}, \tau^{2[t]}, \sigma^{2[t]})$:

$$Q(\theta|\theta^{[t]}) = E[L(\theta|y, \xi)|y, \theta^{[t]}]$$

- The M-step consists of maximizing $Q(\theta|\theta^{[t]})$. It leads to the following explicit expressions:

$$\beta^{[t+1]} = (X'X)^{-1} X' \left\{ X\beta^{[t]} + \sigma^{2[t]} \Gamma^{[t]-1} (y - X\beta^{[t]}) \right\} \quad (1)$$

$$\tau^{2[t+1]} = \frac{1}{I} \left\{ \tau^{4[t]} (y - X\beta^{[t]})' \Gamma^{[t]-1} U U' \Gamma^{[t]-1} (y - X\beta^{[t]}) + \tau^{2[t]} - \tau^{4[t]} \text{tr}(\Gamma^{[t]-1} U U') \right\} \quad (2)$$

$$\sigma^{2[t+1]} = \frac{1}{n} \left\{ \sigma^{4[t]} (y - X\beta^{[t]})' \Gamma^{[t]-1} \Gamma^{[t]-1} (y - X\beta^{[t]}) + n \sigma^{2[t]} - \tau^{4[t]} \text{tr}(\Gamma^{[t]-1}) \right\} \quad (3)$$

IV. A simulation study

Simulation framework

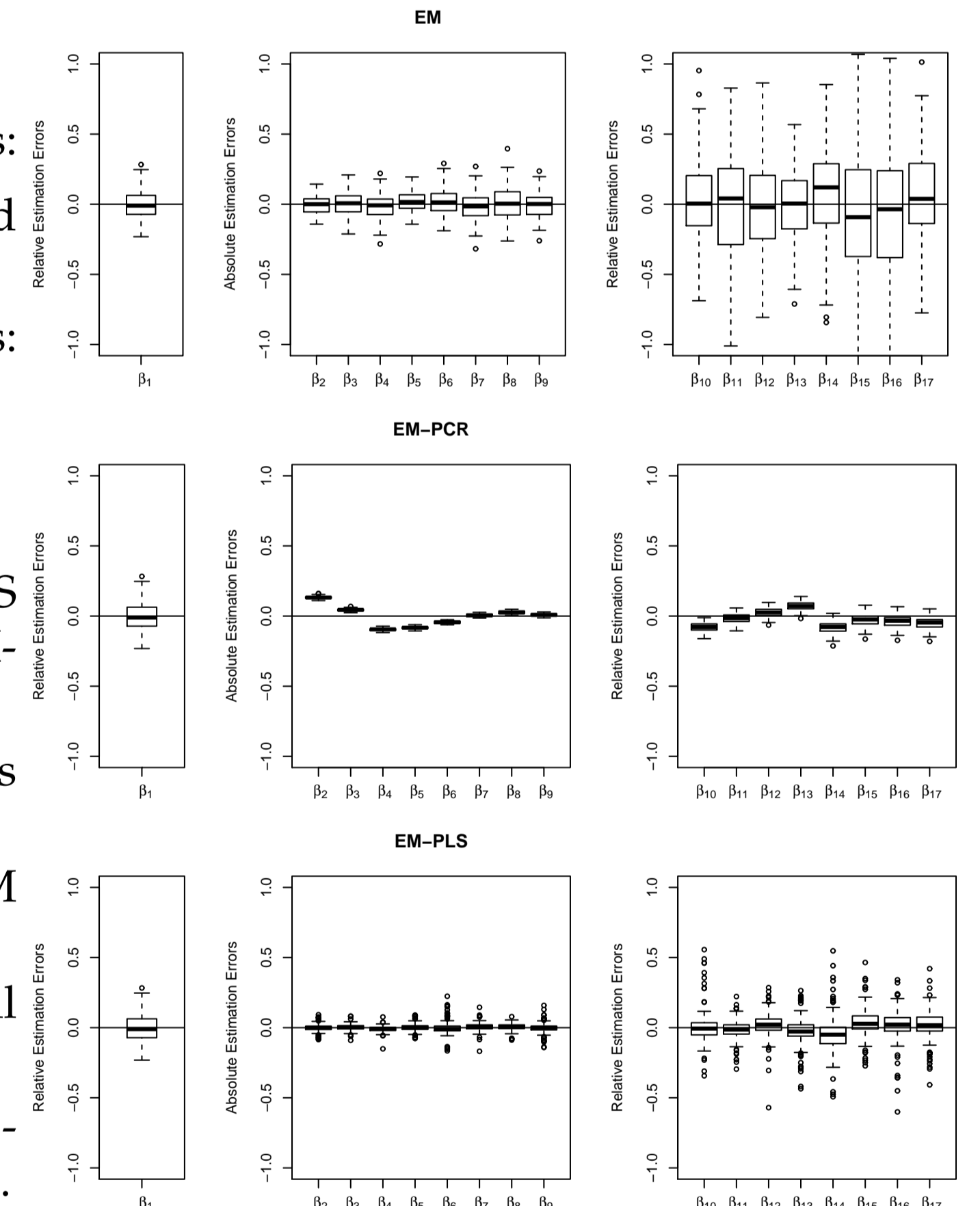
- For each individual i ($i = 1, \dots, 20$), $Y_i = X_i \beta + U_i \xi_i + \varepsilon_i$
- $X_i = (\mathbb{1}_{n_i}, X_i^1, X_i^2, X_i^3, X_i^4)$ where X_i^k is the $n_i \times 4$ fixed centered design matrix, $k = 1, \dots, 4$ and $U_i = \mathbb{1}_{n_i}$ with $n_i = 12 \quad \forall i = 1, \dots, 20$.
- $\beta = \{2.5, \{0\}^4, \{0\}^4, \{0.5\}^4\}$
- $\xi_i \sim \mathcal{N}(0, \tau^2)$ and $\varepsilon_i \sim \mathcal{N}(0_{12}, \sigma^2 I_{12})$ where σ^2 and τ^2 are respectively defined from a given signal-to-noise ratio SNR and a given variances ratio TAU by $\sigma^2 = \frac{1}{SNR^2} \frac{\|X\beta - E(X\beta)\|_2}{n}$ and $\tau^2 = \frac{\sigma^2}{TAU}$.
- $N = 100$ simulated data sets of size $n = 20 \times 12 = 240$ with different SNR and TAU values (learning set= 100 and test set=100).
- Criteria comparison:
 - Relative parameter estimation errors: $\frac{(\hat{\beta}_{jk} - \beta_j)}{\beta_j}$, $k = 1, \dots, 100$, $j = 1$ and $10, \dots, 17$
 - Absolute parameter estimation errors: $\hat{\beta}_{jk} - \beta_j$, $k = 1, \dots, 100$, $j = 2, \dots, 9$

Results for $SNR = 3$ and $TAU = 1$

→ Concerning the β_j 's estimation, EM-PLS method performs better than EM and EM-PCR methods:

- On average, good parameter estimations are obtained with EM-PLS method
- Large variability is obtained with EM method for all β_j different to 0
- EM-PCR method performs poorly for all β_j equal to 0

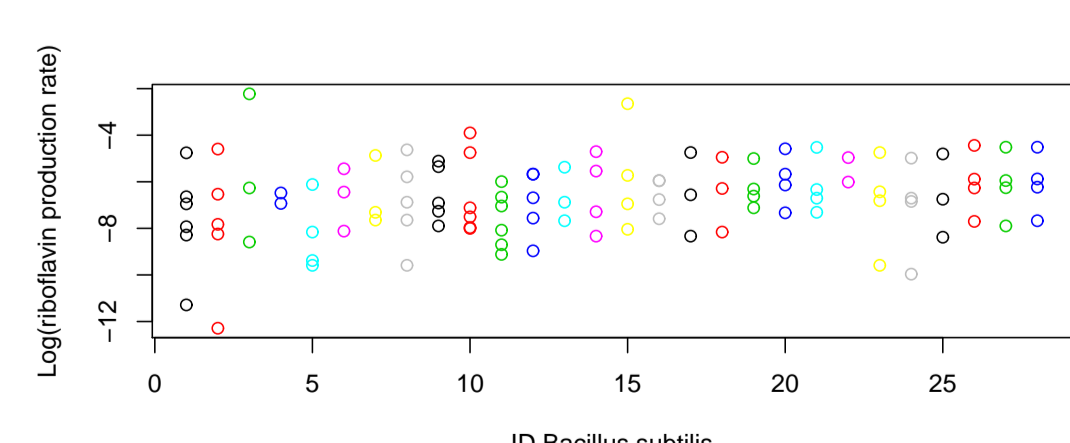
→ Globally, good estimation results are obtained with the three methods for τ^2 and σ^2 .



V. An application: the Riboflavin data set

- Data about riboflavin (vitamin B2) production in *Bacillus subtilis*.
 - Response variable : logarithm of the riboflavin production rate
 - Design matrix : the logarithm of the expressions levels of 4088 genes (normalized)
- 28 *Bacillus subtilis* with a total number of samples equal to 111
 - Observations at different times in the same conditions
 - From 2 to 6 measurements by *Bacillus subtilis*

Logarithm of the riboflavin production rate (vitamin B2) produced in 28 *Bacillus subtilis*. Different colors are used for the different *Bacillus subtilis*.

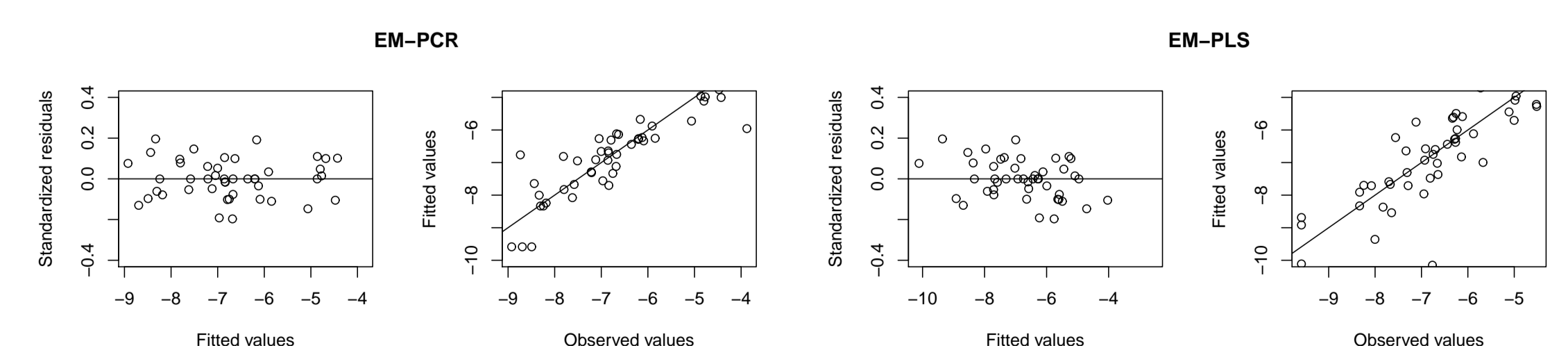


Method

- Subdivision of the data set into a learning set and a test set (ratio: 70 % - 30 %)
- Application of EM, EM-PCR and EM-PLS methods
- Computation of the mean absolute prediction error: $MAE = \frac{1}{n} \sum_{i=1}^n |\hat{y}_i - y_i|$
- Diagnostics plots: Normalized residuals vs fitted values and fitted values vs observed values plots.

Results

| | EM-PCR | EM-PLS |
|------------------------------|--------|--------|
| Number of optimal components | 8 | 8 |
| MAE | 0.43 | 0.63 |
| $\hat{\sigma}^2$ | 0.62 | 0.02 |
| $\hat{\tau}^2$ | 44.53 | 47.83 |



- No results with EM method because of numerical problems.
- Similar results are obtained with EM-PLS and EM-PCR methods.
- Possible improvement: a pre-selection step such as a Sure Independence Screening (SIS) procedure could be applied.

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