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To cite this version:

Caroline Bazzoli, Sophie Lambert-Lacroix. A Comparison of Methods for Analysing Logistic Regression Models with both Clinical and Genomic Variables. ERCIM 2014 - 7th International Conference of the ERCIM Working Group on Computational and Methodological Statistics, Dec 2014, Pise, Italy. hal-01905592

HAL Id: hal-01905592

https://hal.science/hal-01905592v1

Submitted on 25 Oct 2018

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A COMPARISON OF METHODS FOR ANALYSING LOGISTIC REGRESSION MODELS WITH BOTH CLINICAL AND GENOMIC VARIABLES

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INTRODUCTION

- An active field in today medical research : prediction from high-dimensional genomic data
  - → Number of samples relatively small compared to the number of covariates
  - → Collinear measurements

⇒ Use of reduction dimension methods
  - Traditional approach : Principal Component Regression (PCR) [10]
  - Most useful : Partial Least Square (PLS) [6]
- Most of this studies included clinical data in addition to genomic data
  - However most of the proposed prediction methods used only genomic data
  - Recent studies consider situations combining both type of covariates improving predictions
    - → Development of Clinico-genomic models
    - → For survival prediction with Cox model's [3], for classification of patients [2]

  ⇒ Few of them used dimension reduction or applied dimension reduction only to the high-dimensional genomic variables
- Recently, prediction method have been proposed to combine both type of covariates [7]
  - Developed only in regression Gaussian context
    - ∗ Method based on combination of PLS and ordinary least square (OLS)=> LS-PLS

    ⇒ More information from the experiment

    ⇒ Lower variance in the parameter estimates
- Adaptation to logistic regression model
  - Not relevant to combine both type of variables without reduction dimension
  - An alternative → compress the information from genomic data into new few components before modelling
    - ∗ Partial Least Squares (PLS) adapted to logistic regression [11, 9, 4, 1]

OBJECTIVES

- **To adapt LS-PLS to combine clinical and genomic variables for logistic regression model**
- **To perform a comparison by simulation of the performance of these approaches**

LS-PLS FOR LOGISTIC REGRESSION

- **Linear Logistic Discrimination**
  - Y : binary response variable $\{0,1\}^n$
  - D : matrix of clinical variables of size $n \times q$
  - X : design matrix for expression levels of the p genes for the n microarray samples
    - ∗ $X = (x_{ij})$, $1 \le i \le n, 1 \le j \le p$
  - General statistical model
    - ∗ The conditional expectation of y_i given $D_{i\cdot}$, given by $\pi_i = P(y_i = 1|D_{i\cdot} = d_i)$
    - ∗ Related to linear predictor $\eta_i = [1; d_i]\gamma$
      - · with $\gamma \in \mathbb{R}^{q+1}$ and the non-linear relation $\pi_i = h(\eta_i)$
      - · where $h(\eta_i) = 1/(1+\exp(-\eta_i))$
  - Estimation of γ by maximum likelihood (ML) estimation method
  - Use of Iteratively Reweighted Least Squares (IRLS) algorithm [5]

$$z^{(t)} = \tilde{D}\gamma^{(t)} + \left[W(\gamma^{(t)})^{(t)}\right]^{-1}\left(y - \pi^{(t)}\right), \quad (1)$$

$$\gamma^{(t+1)} \Leftarrow \textit{weighted regression by } W(\gamma^{(t)})^{(t)} \textit{ of } z^{(t)} \textit{ on } \tilde{D} \quad (2)$$

where $\tilde{D} = [1_n\ D]$, $1_n = (1, \cdots, 1)^T$
$W(\gamma^{(t)})$ the diagonal $n \times n$ matrix with entries $W_{i,i}(\gamma) = \pi_k(1-\pi_k)$.

- **LS-PLS in Gaussian context [7]**
  - Iterative procedure
    1. Perform ordinary least squares regression of Y on $(\tilde{D})$ and estimate the regression coefficients β and calculate residuals.
    2. Perform PLS regression of the residuals on centred X and combine the design $(\tilde{D})$
    3. Perform OLS regression on the combined matrix design $(\tilde{D})$ and the score T to predict Y.
    4. Calculate the predicted $\hat{y}$ based on $(\tilde{D})$ and calculate new residuals.
    5. Repeat steps 2 to 4 until convergence.

  ⇒ Method denoted LS-PLS(y, D, X, κ) where κ the PLS component number
- **Some extensions for logistic regression**
  - *NGUYEN and ROCKE's APPROACH [11]*
    - ∗ Extension of PLS to logistic regression substituting X by a $n \times \kappa$ matrix T
      - · Columns of which are the first κ PLS-scores given by PLS regression of y on X
      - · Estimation of the parameter with ML with IRLS(y, T).

    ⇒ Replace PLS by LS-PLS

    ⇒ κ obtained by cross-validation

  ⇒ Method denoted **LS-PLS**.
  - *MARX's APPROACH [9]*
    - ∗ Estimation of the parameter γ with ML using IRLS(y, T) algorithm
    - ∗ Where T defined by IRPLS, an algorithm that extends PLS to generalized linear models
    - ∗ Matrix T collects the first κ components "at convergence" of IRPLS

    ⇒ Replace PLS by LS-PLS to adopt this approach for LS-PLS

    ⇒ κ obtained by cross-validation

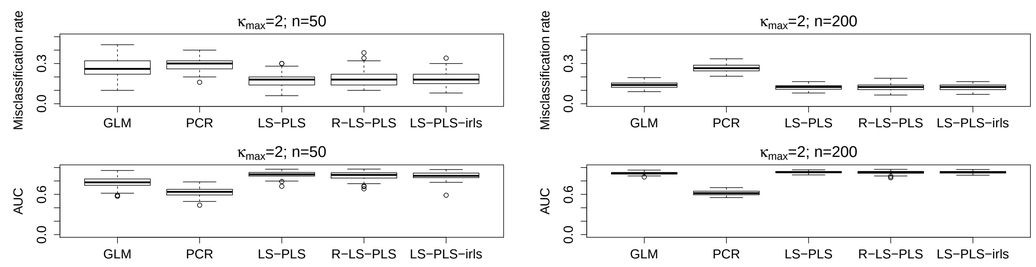
  ⇒ Method denoted **LS-PLS-irls**.
  - *RIDGE PARTIAL LEAST SQUARES APPROACH [4]*
    - ∗ Replace binary by a pseudo-response variable $z^{\inf}$ ⟵ linear relationship with the covariates
      - · At convergence of IRLS algorithm : $z^{\inf} = X\hat{\gamma}^R + \varepsilon$
      - · $\hat{\gamma}^R$: the true value of the parameter
      - · ε a centered vector of covariance matrix $(W^{\inf})^{-1}$.
    - ∗ When $n << p$ → Regularisation methods as Ridge Penalty withλ the shrinkage parameter [8]
    - ∗ Extension with LS-PLS

  ⇒ Method called **R-LS-PLS**

  ⇒ R-LS-PLS depends on two parameters : λ and κ obtained by cross-validation.
  - *BASTIEN's APPROACH [1]*
    - ∗ Not developed at the moment

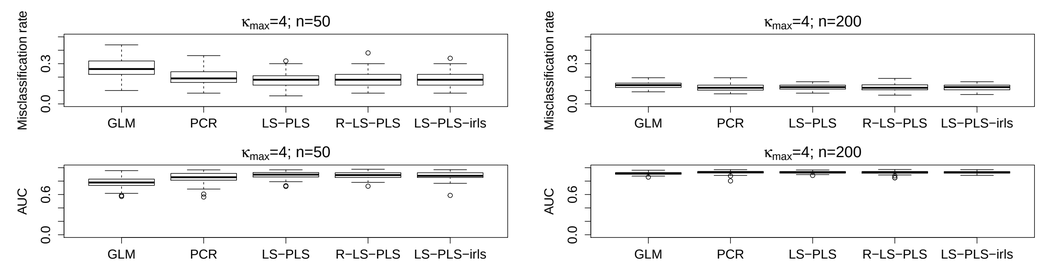
SIMULATION STUDY - A "STANDARD" EXAMPLE

- **Methods**
  - Simulation framework (R software)
    - ∗ Simulation of 100 data sets of size n (learning set=100 and test set = 100)
    - ∗ Statistical model
      - · For an individual i $(i = 1, ..., n)$, $y_i \sim \mathcal{B}(\pi_i)$
      - · $\beta_X = \{\{0\}^8, \{2\}^8\}$ and $\beta_D = \{0.5\}^4$ ($p = 16$ and $q = 4$)
      - · X such as $X = (X^1, X^2, X^3, X^4)$ where $X^k \sim N(0_4, \Sigma_X^k)$ with $\Sigma_{i,j}^k = c^k\rho^{|i-j|}$ with $k = 1, ...4$, $i = 1, ..., 4$, $j = 1, ..., 4$ where $c^1 = 8$, $c^2 = 4$, $c^3 = 2$, $c^4 = 1$ and $\rho = 0.9999$
      - · $D \sim N(0_q, \Sigma_D)$ with $\Sigma_D = \rho^{\{|i-j|}$ with $i = 1, ..., q$ and $j = 1, ..., q$ and $\rho = 0.5$
  - Comparison of the different prediction methods to analyse both X and D matrices :
    - ∗ **1) GLM 2) PCR on X then GLM on $[DX_{PCR}]$ 3) LS-PLS 4) LS-PLS-irls 5) R-LS-PLS**
    - ∗ Choice for hyperparameters :
      - · κ (for all approaches) obtained by cross-validation over a grid 1 to κ_{max} (for κ_{max} =2,4, 8)
      - · λ (for R-LS-PLS) obtained by cross-validation
    - ∗ $n = 50, 200$
    - ∗ Criterion of comparison
      - · Computation of AUC and Missclassification rate errror for each method
- **Results**



  - No optimal conditions for PCR → Poor performance especially when n increase
  - Similar comportment for GLM only when n=50

  ⇒ Relevance of method using reduction
  - Closed distribution of Missclassification rate and AUC for new approaches and GLM when $n = 200$



  - Slightly poor performance of GLM when $n = 50$
  - ⇒ Correct and closed distribution of missclassification rate and AUC when n and κ increase

  ⇒ Relevance of all the approaches as well as PCR

CONCLUSION

- Comparison by simulation of prediction methods developed for logistic regression model to analyse both clinical and genomic data based on LS-PLS approach
  - Poor performance of GLM compared to other approaches especially n small
  - Similar relevance for proposed extensions of LS-PLS and PCR with ideal number of components

  ⇒ Interest of reduction even if reasonable case of "high dimensional" case

  ⇒ Need of extensive simulations to explore high-dimensional situations
- Some applications of these approaches to real data without relevant results

  ⇒ Need further exploration
- Extension of LS-PLS approach to survival prediction model Cox'models

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