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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

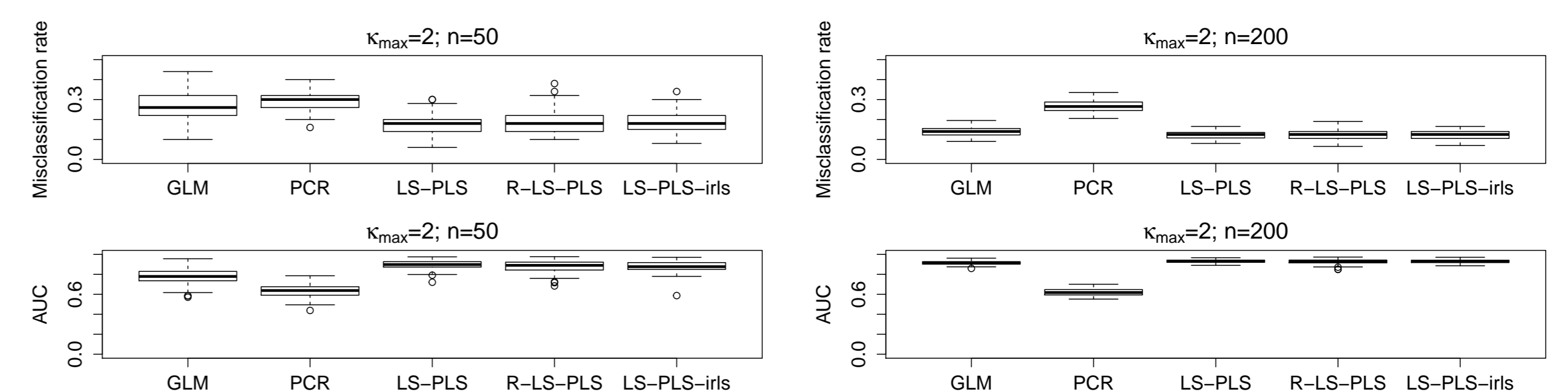
- **Linear Logistic Discrimination**
  - $Y$  : binary response variable  $\{0, 1\}^n$
  - $D$  : matrix of clinical variables of size  $n \times q$
  - $X$  : design matrix for expression levels of the  $p$  genes for the  $n$  microarray samples
    - \*  $X = (x_{ij}), 1 \leq i \leq n, 1 \leq j \leq p$
  - 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  $\gamma$  by maximum likelihood (ML) estimation method
  - Use of Iteratively Reweighted Least Squares (IRLS) algorithm [5]
 
$$z^{(t)} = \tilde{D} \gamma^{(t)} + [W(\gamma^{(t)})^{(t)}]^{-1} (y - \pi^{(t)}), \quad (1)$$

$$\gamma^{(t+1)} \leftarrow \text{weighted regression by } W(\gamma^{(t)})^{(t)} \text{ of } z^{(t)} \text{ on } \tilde{D} \quad (2)$$
- where  $\tilde{D} = [1_n D]$ ,  $1_n = (1, \dots, 1)^T$   
 $W(\gamma^{(t)})$  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  $\beta$  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( $y, D, X, \kappa$ ) where  $\kappa$  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  $\kappa$  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
    - ⇒  $\kappa$  obtained by cross-validation
    - ⇒ Method denoted **LS-PLS**.
  - MARX's APPROACH [9]
    - \* Estimation of the parameter  $\gamma$  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  $\kappa$  components "at convergence" of IRPLS
      - ⇒ Replace PLS by LS-PLS to adopt this approach for LS-PLS
      - ⇒  $\kappa$  obtained by cross-validation
    - ⇒ Method denoted **LS-PLS-irls**.
  - RIDGE PARTIAL LEAST SQUARES APPROACH [4]
    - \* Replace binary by a pseudo-response variable  $z^{\text{inf}} \leftarrow$  linear relationship with the covariates
      - At convergence of IRLS algorithm :  $z^{\text{inf}} = X \hat{\gamma}^R + \varepsilon$
      - $\hat{\gamma}^R$  : the true value of the parameter
      - $\varepsilon$  a centered vector of covariance matrix  $(W^{\text{inf}})^{-1}$ .
    - \* When  $n \ll p \rightarrow$  Regularisation methods as Ridge Penalty with  $\lambda$  the shrinkage parameter [8]
    - \* Extension with LS-PLS
    - ⇒ Method called **R-LS-PLS**
    - ⇒ R-LS-PLS depends on two parameters :  $\lambda$  and  $\kappa$  obtained by cross-validation.
  - BASTIEN's APPROACH [1]
    - \* Not developed at the moment

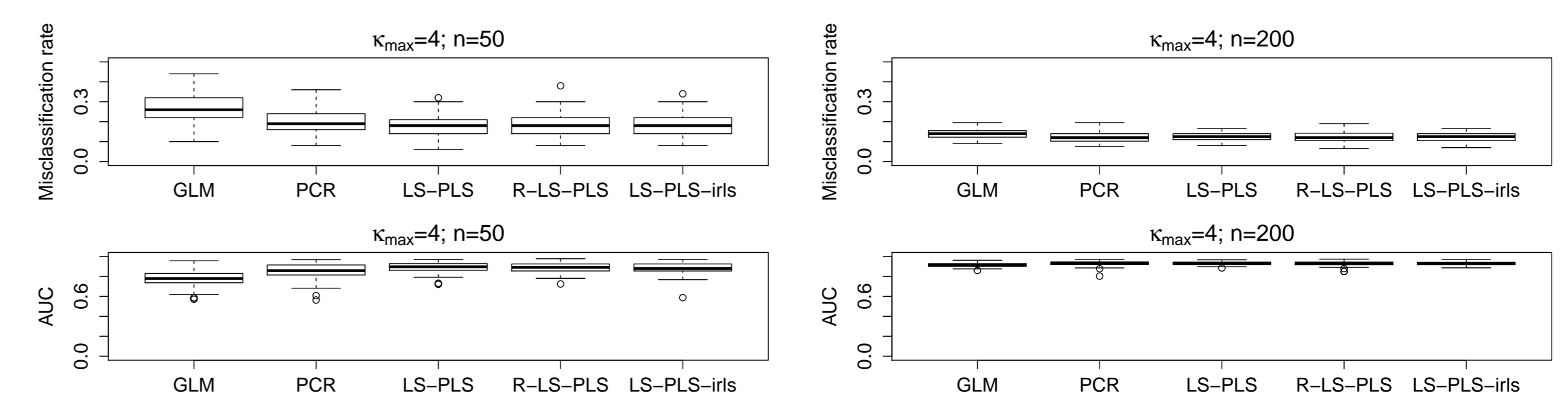
## SIMULATION STUDY - A "STANDARD" EXAMPLE

- **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  $i$  ( $i = 1, \dots, n$ ),  $y_i \sim \mathcal{B}(\pi_i)$
      - $\beta_X = \{\{0\}^8, \{2\}^8\}$  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  $k = 1, \dots, 4$ ,  $i = 1, \dots, 4$ ,  $j = 1, \dots, 4$  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  $i = 1, \dots, q$  and  $j = 1, \dots, q$  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 :
      - $\kappa$  (for all approaches) obtained by cross-validation over a grid 1 to  $\kappa_{\max}$  (for  $\kappa_{\max} = 2, 4, 8$ )
      - $\lambda$  (for R-LS-PLS) obtained by cross-validation
    - \*  $n = 50, 200$
    - \* Criterion of comparison
      - Computation of AUC and Missclassification rate error for each method

## Results



- No optimal conditions for PCR → Poor performance especially when  $n$  increase
- Similar compartment 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  $\kappa$  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

## REFERENCES

- [1] P. Bastien, V. E. Vinzi, and M. Tenenhaus. PLS generalised linear regression. *Computational Statistics & Data Analysis*, 48(1):17–46, January 2005.
- [2] A.-L. Boulesteix and W. Sauerbrei. Added predictive value of high-throughput molecular data to clinical data and its validation. *Briefings in Bioinformatics*, 12(3):215–229, 2011.
- [3] N. S. Bovelstad H.M and B. O. Survival prediction from clinico-genomic models—a comparative study. *BMC Bioinformatics*, 10(413), 2009.
- [4] G. Fort and S. Lambert-Lacroix. Classification using partial least squares with penalized logistic regression. *Bioinformatics*, 21(7):1104–1111, 2005.
- [5] P. J. Green. Iteratively reweighted least squares for maximum likelihood estimation and some robust and resistant alternatives. *Journal of the Royal Statistical Society, B*, 46(2):149–192, 1984.
- [6] I. Helland. On the structure of Partial Least Squares Regression. *Commun. Stat., Simulation Comput.*, 17(2):581–607, 1988.
- [7] K. T. K. Jorgensen, V. Segtnan and T. Naes. A comparison of methods for analysing regression models with both spectral and designed variables. *Journal of Chemometrics*, 18:451–464, 2004.
- [8] S. Le Cessie and J. Van Houwelingen. Ridge estimators in logistic regression. *J. R. Stat. Soc., Ser. C*, 41(1):191–201, 1992.
- [9] B. D. Marx. Iteratively Reweighted Partial Least Squares estimation for Generalized Linear Regression. *Technometrics*, 38(4):374–381, 1996.
- [10] W. F. Massy. Principal components regression in exploratory statistical research. *J. Amer. Stat. Assoc.*, 60:234–246, 1965.
- [11] D. Nguyen and D. Rocke. Tumor classification by Partial Least Squares using microarray gene expression data. *Bioinformatics*, 18(1):39–50, 2002.