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Survival Models built from Gene Expression Data using Gene Groups as Covariates

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Introduction

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Goal **Prediction of survival times from gene expression data with high level of interpretability of estimated models**

Motivation

- Models with good prediction accuracy and parsimony property
- **Problem:** Number of genes by far larger than number of observations (individuals) ($p >> n$)
- Use procedures to select genes that are relevant to patient survival and to build a predictive model for future patients
- Classify future patients into clinically relevant high- and low-risk groups based on the gene expression profile and survival times of previous patients

Introduction

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Prediction of survival from expression data

- Many single genes as covariates in survival models
- Dimension reduction through gene selection
- Evaluation of prediction error with suitable measures

Gene group testing

- Define gene groups through Gene Ontology (GO)
- GO groups: Gene expression values are summarized
  (mean, median, maybe other robust measures)
- Identify significant GO groups:
  Analyze and interpret these groups as well as single genes contained in the groups

Cox Model

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Cox proportional hazards model for hazard of cancer recurrence or death at time *t*

$$\lambda(t) = \lambda_0(t)\exp(\beta_1 X_1 + ... + \beta_p X_p) = \lambda_0(t)\exp(\beta' X)$$

Estimation of the regression coefficients (in classical setting with $n > p$) by maximizing the log partial likelihood

$$l(\beta) = \sum_{i=1}^{n} \delta_i \left[\beta' x_i - \log \left(\sum_{j \in R(t_i)} \exp(\beta' x_j) \right) \right]$$

Methods for Prediction

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Univariate selection

- Fit univariate Cox model for each gene/GO group
- Arrange genes/GO groups according to increasing p-values
- Fit multivariate Cox model using λ top ranked genes/GO groups

Penalized Regression

- Lasso Regression (L1 penalty)
  - Penalized log partial likelihood: $l(\beta) - \lambda \sum_{j=1}^{p} |\beta_j|$
- Ridge Regression (L2 penalty)
  - Penalized log partial likelihood: $l(\beta) - \lambda \sum_{j=1}^{p} \beta_j^2$

For all methods, we choose λ via log partial likelihood cross-validation

Cross-validation

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Choose tuning parameter λ which maximizes the cross-validated log partial likelihood

$$CVPL(\lambda) = \sum_{k=1}^{K} \left[l(\hat{\beta}_{(-k)}(\lambda)) - l_{(-k)}(\hat{\beta}_{(-k)}(\lambda)) \right]$$

$l(\beta)$	log partial likelihood with all subjects
$l_{(-k)}(\beta)$	log partial likelihood when *k*th fold is left out, *k = 1,…,K*
$\hat{\beta}_{(-k)}(\lambda)$	Estimate of β obtained by a given prediction method when the *k*th fold is left out

Optimal value of λ is chosen to maximize the sum of the contributions of each fold to the log partial likelihood

Evaluation Criteria

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Log rank test

- Assign patients to subgroups based on their prognosis, e.g. into one with ‘good’ and one with ‘bad’ prognosis
- Patient *i* in the test set is assigned to the ‘bad’ group if its prognostic index is above the median of the prognostic indices
- Log rank test: use p-value as an evaluation criterion

Prognostic index

- Prognostic index as a single continuous covariate in a Cox model on the test data set
- Likelihood-ratio test: look at p-value to evaluate a method’s performance

Evaluating Procedure

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Algorithm (for a fixed prediction method)

- For each of S random splits into training and test data sets
  - Find the optimal tuning parameter $\hat{\lambda}_{train}$ by *K*-fold cross-validation using the training data set
  - Given $\hat{\lambda}_{train}$, estimate the vector of regression coefficients $\hat{\beta}_{train}$ on the whole training data set
  - Calculate the values of the two performance criteria on the test data set

Comparison of performance with boxplots

Dataset: DLBCL data from Rosenwald et al. (2002)

- 7399 gene expression measurements
- 240 patients with diffuse large-B-cell lymphoma (DLBCL)

`penalized` - Package

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- **penalized: L1 (lasso) and L2 (ridge) penalized estimation in GLMs and in the Cox model**
- A package for fitting possibly high dimensional penalized regression models.
- Penalty structure can be any combination of an L1 penalty (lasso), an L2 penalty (ridge) and a positivity constraint on the regression coefficients.
- Supported regression models are linear, logistic and poisson regression and the **Cox Proportional Hazards model**.
- Cross-validation routines allow optimization of the tuning parameters.
- Version:0.9-21, 2008-04-25, Author: Jelle Goeman

Results

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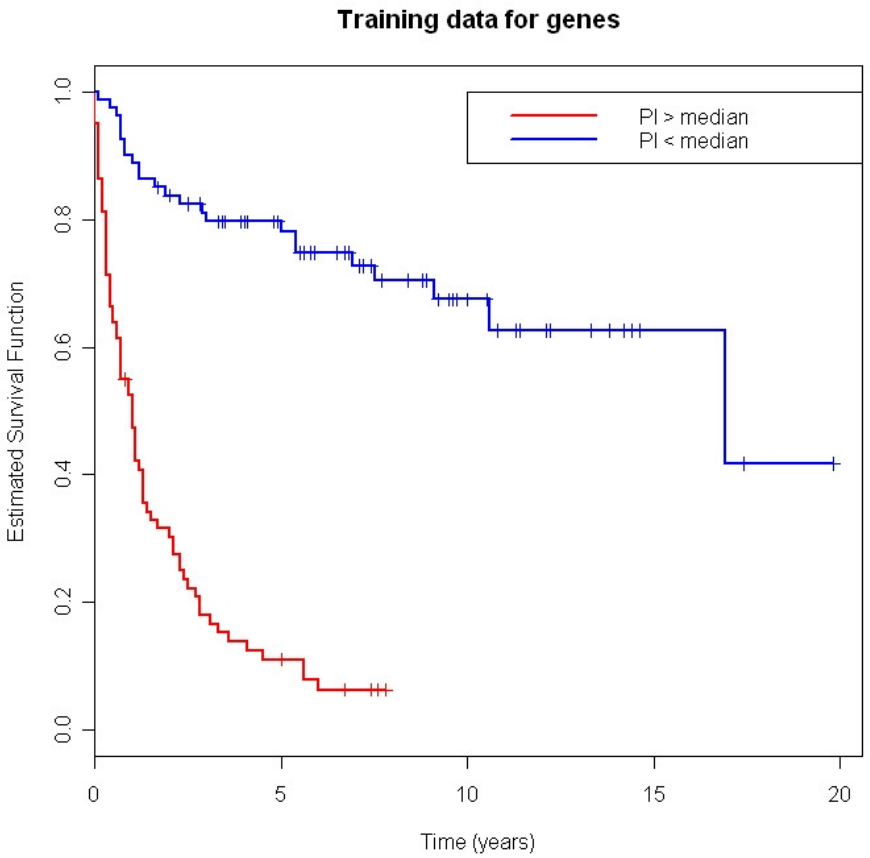
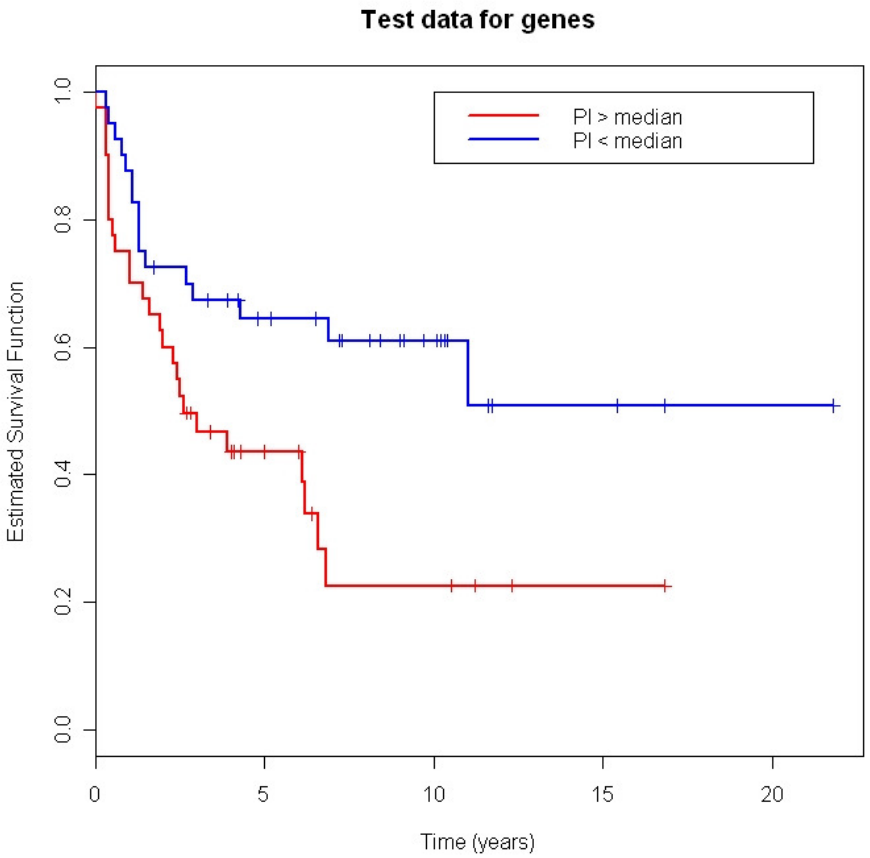
Lasso Regression - one split - median cutoff





Log-rank test: $p < 10^{-10}$ $p = 0.01$

Results

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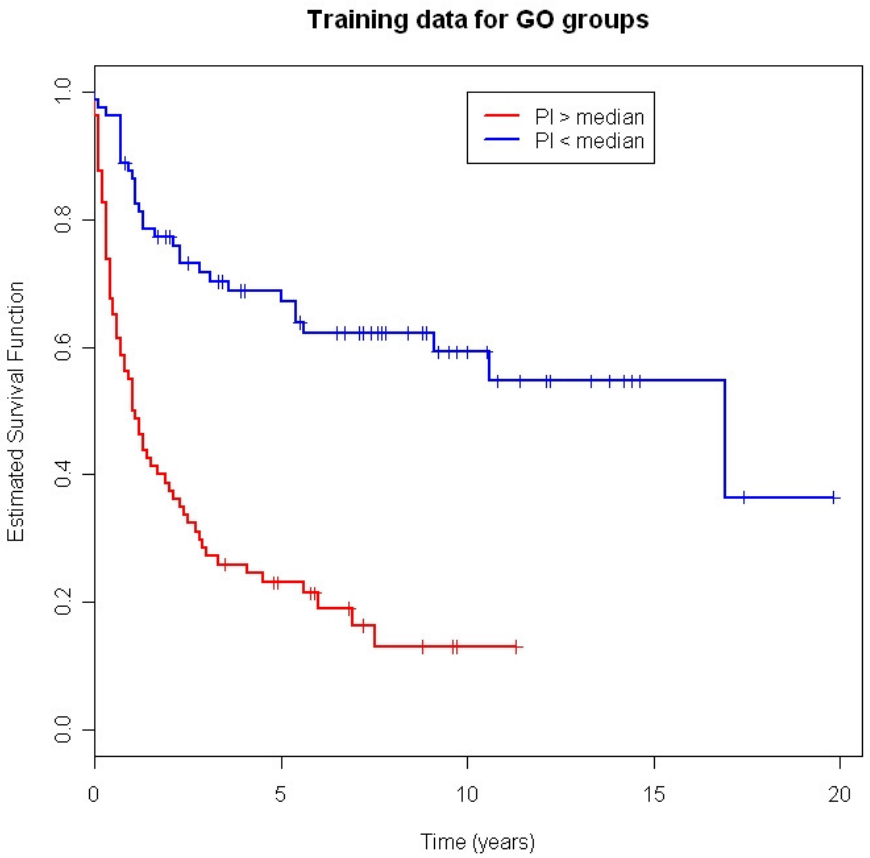
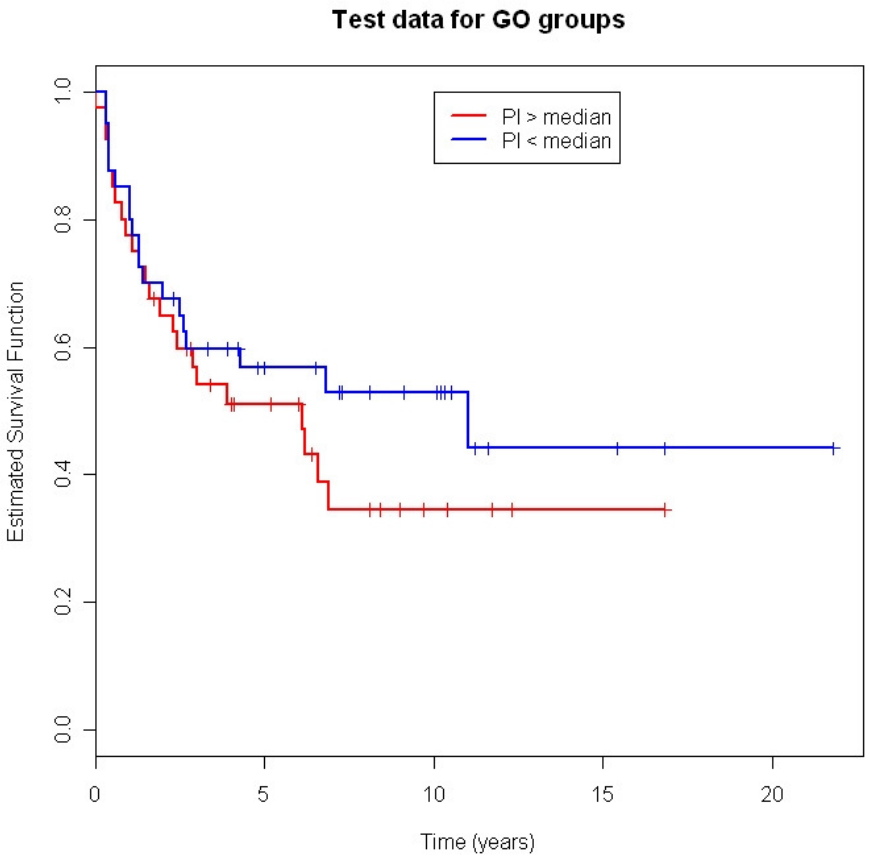
Lasso Regression - one split - median cutoff





Log-rank test: $p < 10^{-10}$ $p = 0.329$

Results

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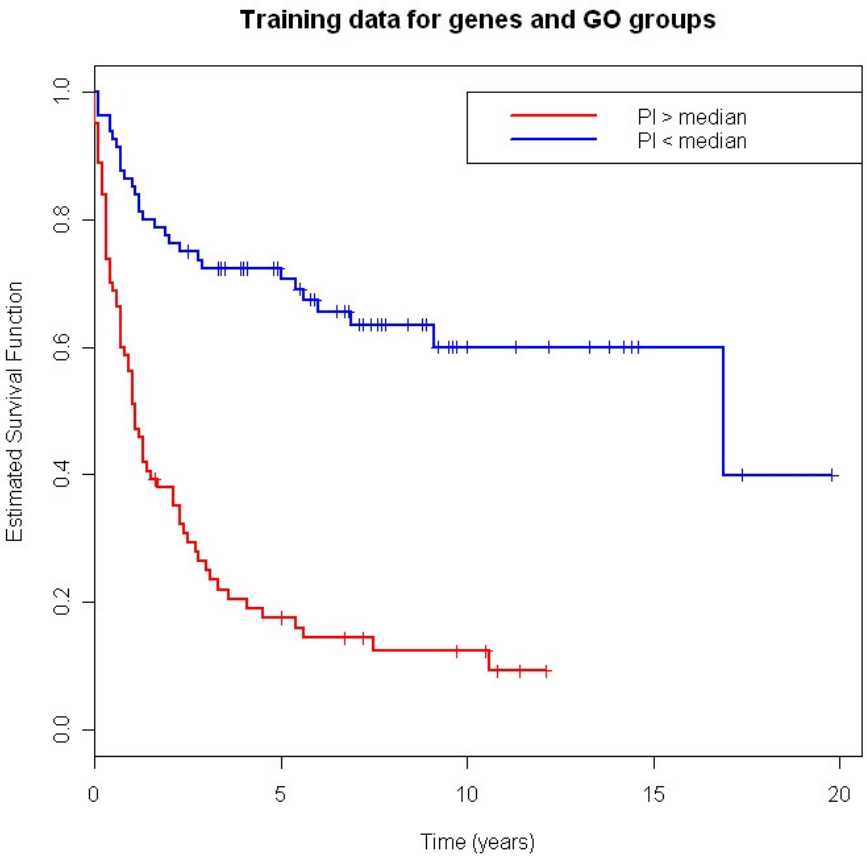
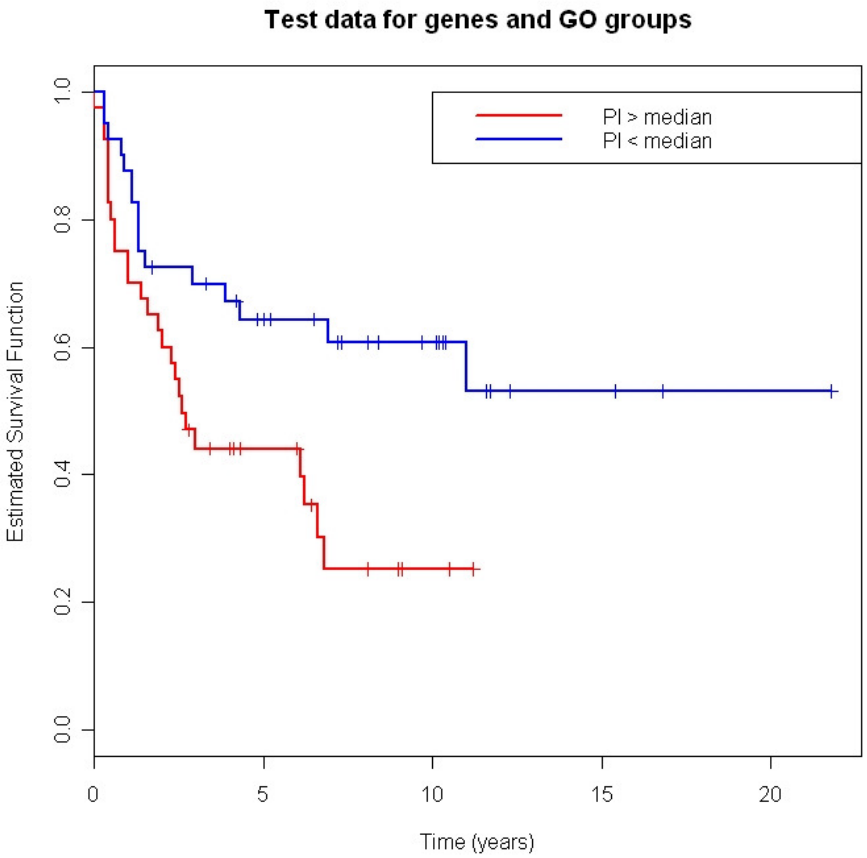
Lasso Regression - one split - median cutoff





Log-rank test: $p < 10^{-10}$ $p = 0.001$

Results

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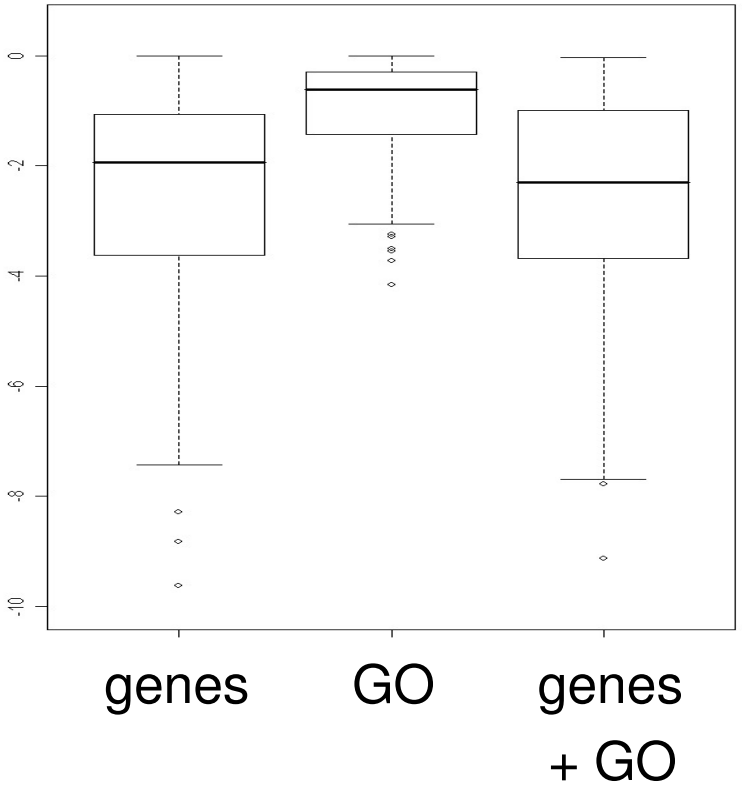
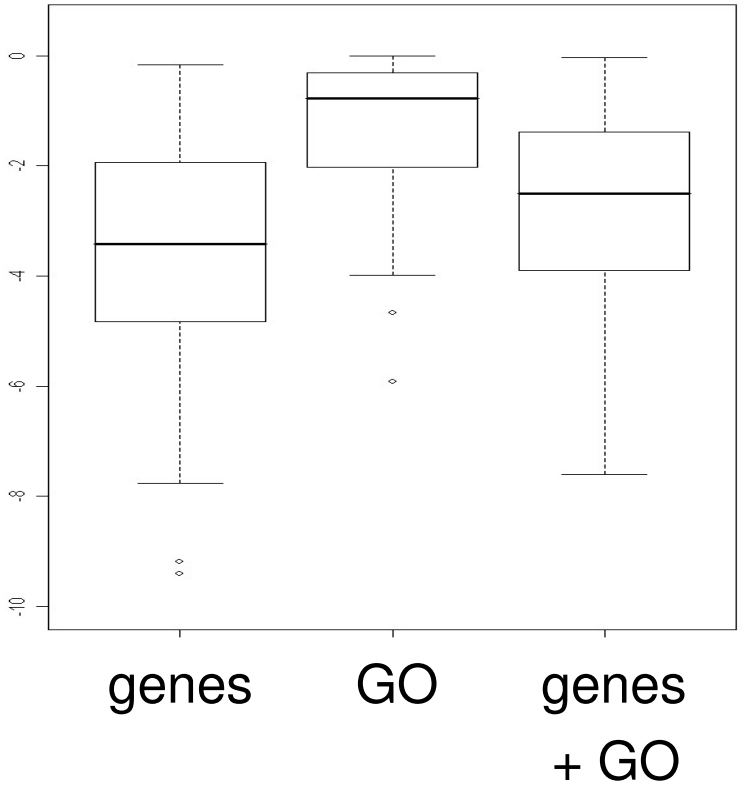
Log-rank test - 100 random splits into training and test data

method: univariate



method: Lasso



Results

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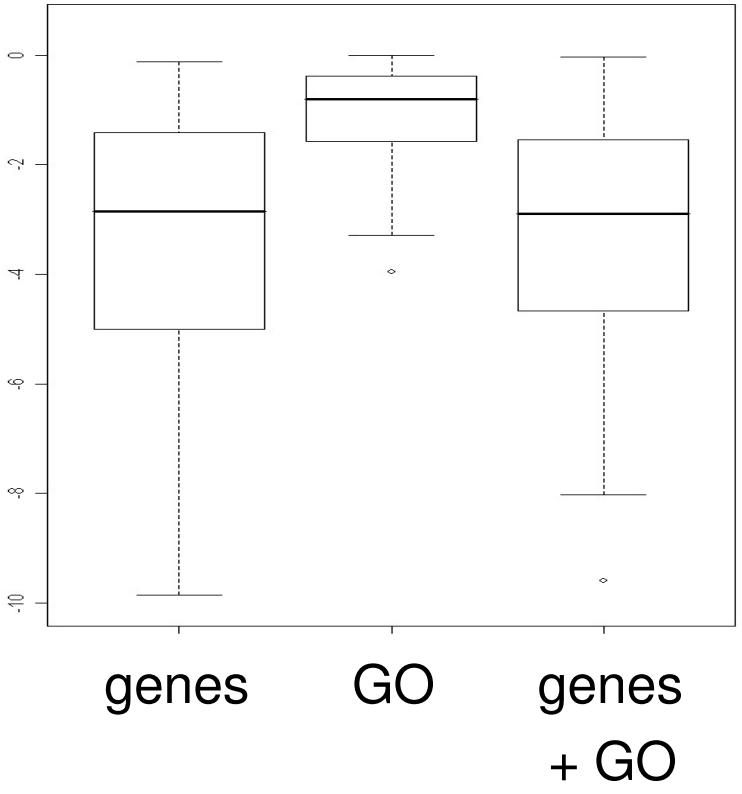
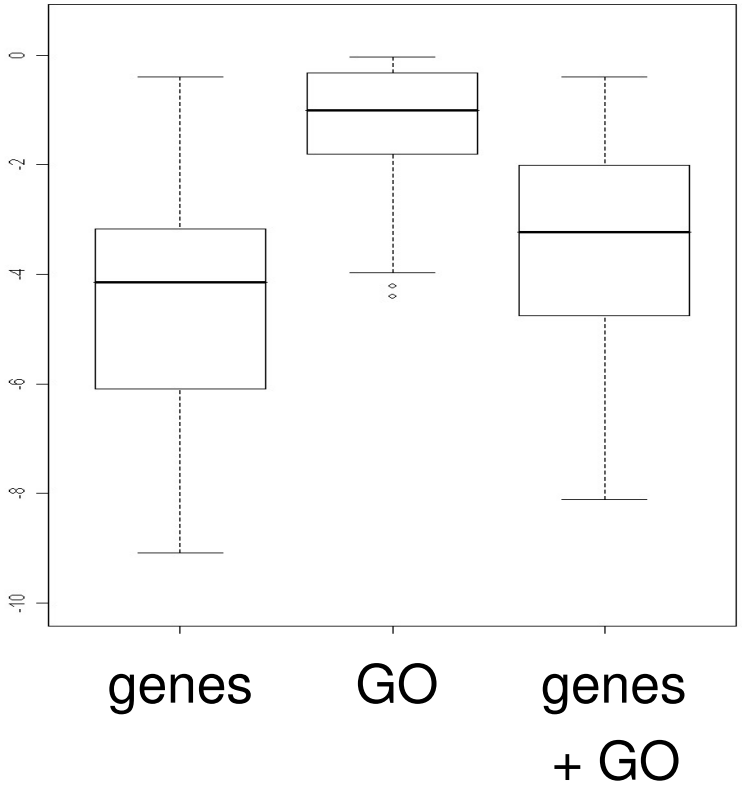
Prognostic Index - 100 random splits into training and test data

method: univariate



method: Lasso



Outlook

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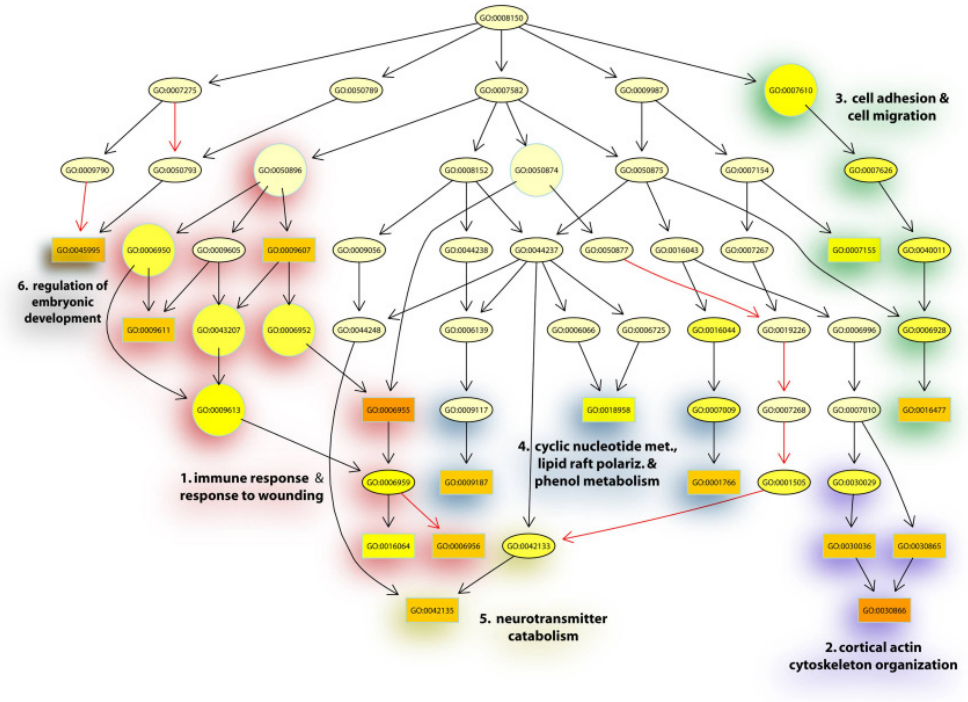
- Additional methods for prediction/evaluation
- Robust measures to summarize gene expression values for one GO group
- Coping with high correlations in GO groups
- Integrate GO graph structure
  - Remove correlations between neighboring GO groups and construct survival models using only significant GO groups
  - Analyze single genes obtained from these GO groups



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Results

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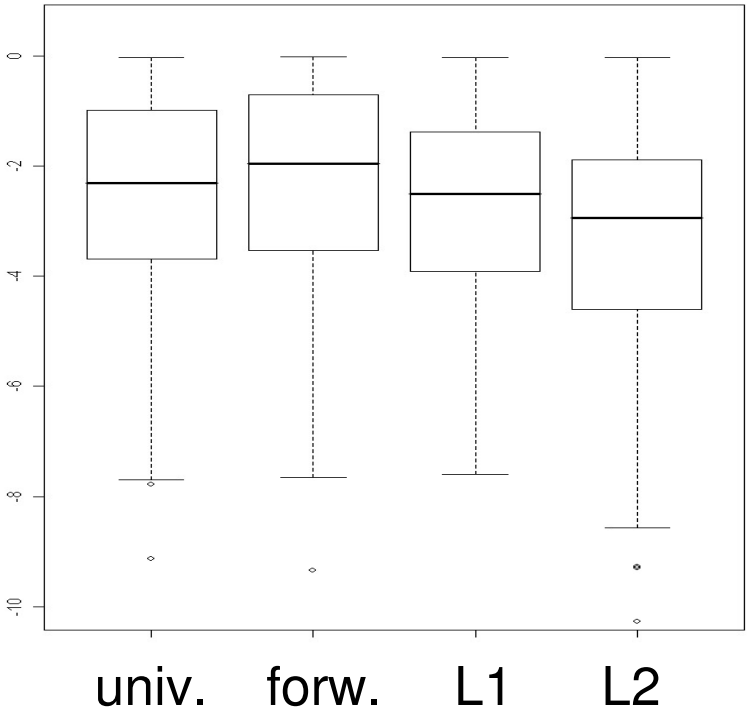
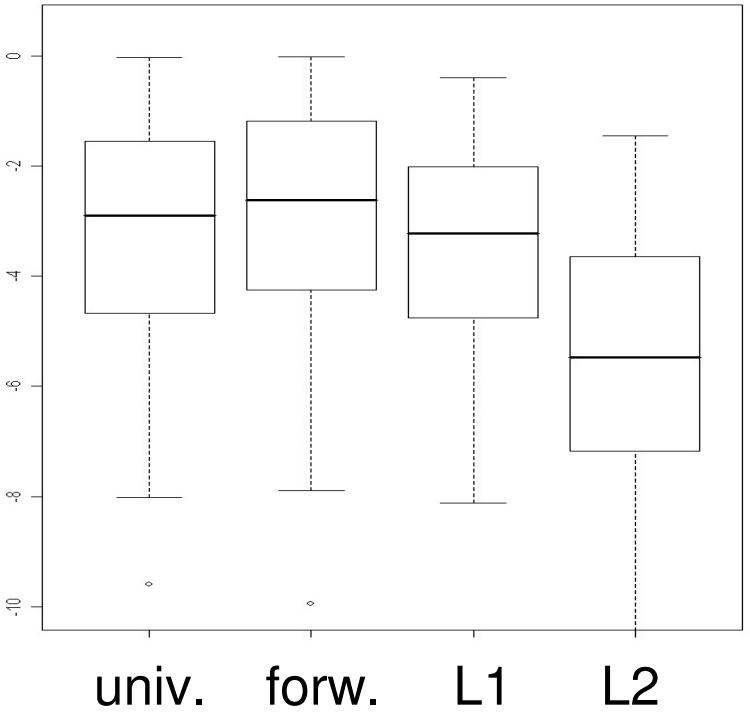
All methods - 100 random splits into training and test data

log-rank test



prognostic index



Results

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10 most significant GO groups (univariate selection, one split)

GO Group	P-value	P-value adjusted	#Genes	Function
01562	0.00049	0.47	3	Response to protozoan
40012	0.00053	0.47	2	Regulation of locomotion
40029	0.00142	0.54	4	Regulation of gene expression, epigenetic
30149	0.00149	0.54	3	Sphingolipid catabolic process
51310	0.00151	0.54	5	Metaphase plate congression
01816	0.00312	0.63	19	Cytokine production
50764	0.00359	0.63	6	Regulation of phagocytosis
21700	0.00363	0.63	11	Development maturation
30282	0.00366	0.63	1	Bone mineralization
02268	0.00370	0.63	7	Fillicular dendritic cell differentiation

Results

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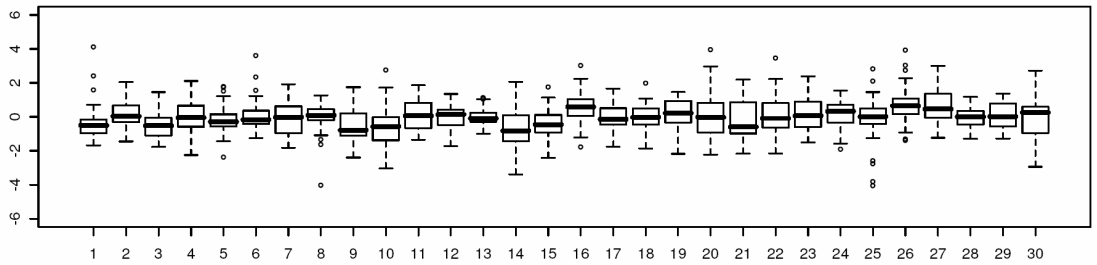
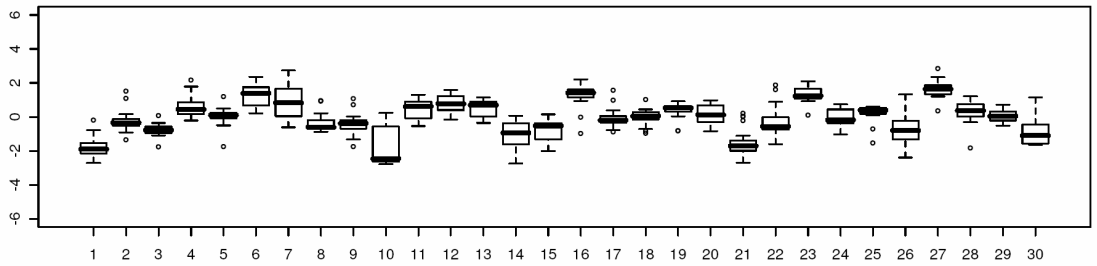
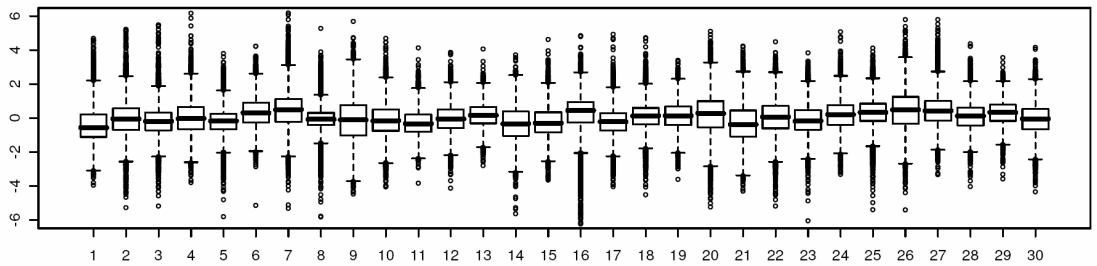


Non-significant GO group



Significant GO group



All genes