Combination of protein biomarkers

UseR! 2009

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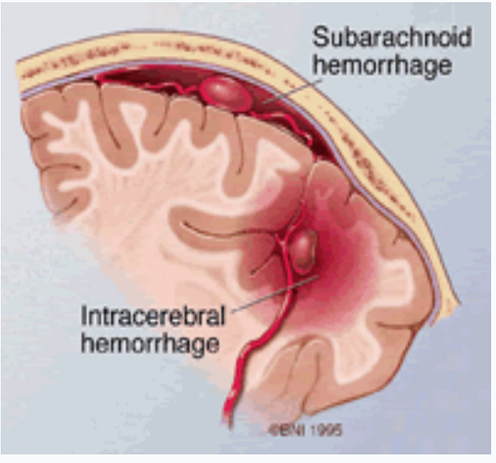
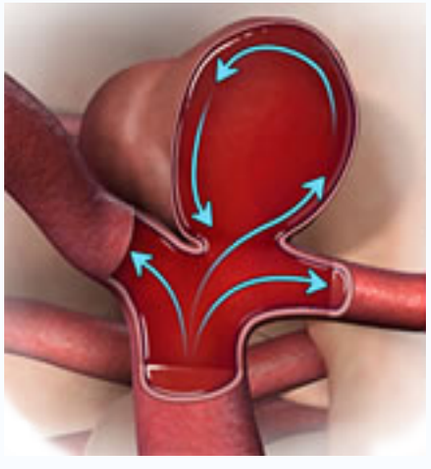
Outline

- Introduction
  - clinical problem
  - biomarkers
- Combining biomarkers
- ROC Curves
  - Comparison
  - Comparing panels with single biomarkers
- Conclusion
- Acknowledgements

Aneurysmal Subarachnoid hemorrhage (aSAH)





- SAH: rupture of a blood vessel just outside the brain
- Main cause (80%): aneurysm (dilation of a blood vessel) : aSAH
- 1/10 000 people each year
- “Young patients” (mean: 55)
- Many patients are chronically disabled
- Needs: prognosis tools to aid physician for the management of patient and family.

Biomarkers

- Biomarkers are “characteristics objectively measured” whose concentration are different in two groups of patients.
  - Diagnosis, prognosis, therapeutic monitoring, …
- At the BPRG we are interested in several brain damage markers
  - discovered by comparing *ante*- and *post*- mortem cerebrospinal fluid
- When several proteins are considered in a single classifier (potentially with clinical information) one calls this a panel
  - New overfitting and reproducibility problems

Biomarkers

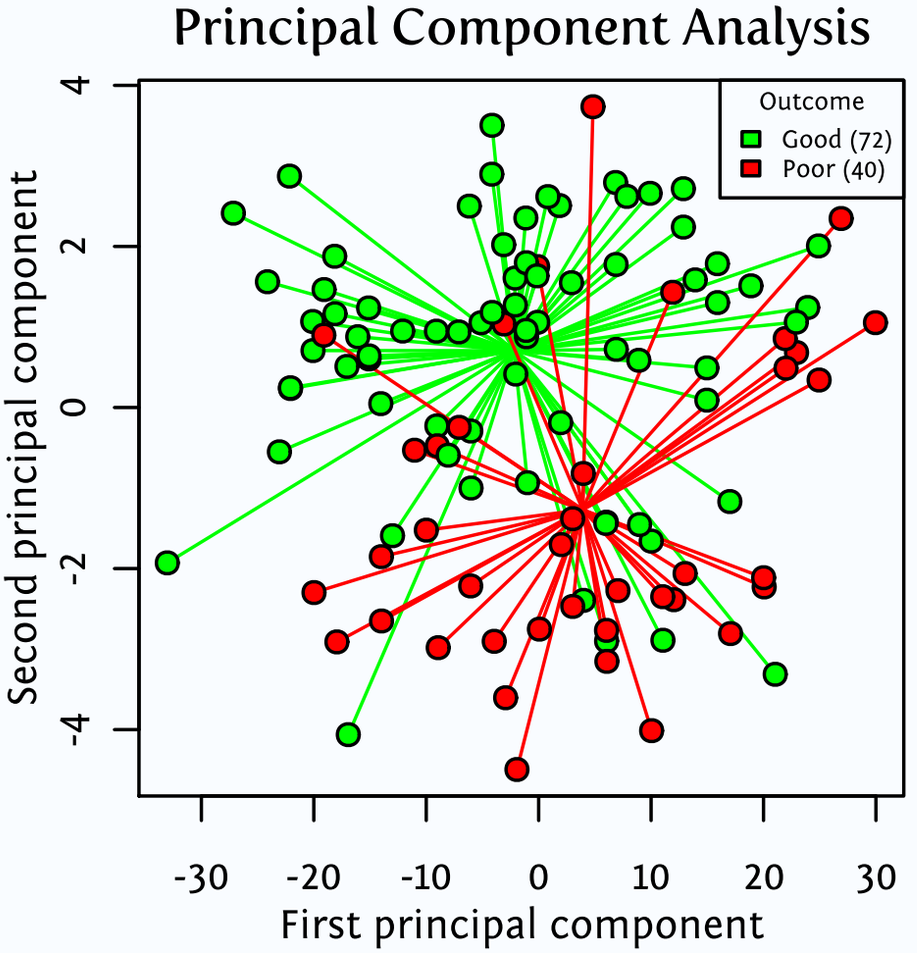
	Name	Biological Role	Marker for
H-FABP	Fatty acid-binding protein	Lipid Binding	Cardiac, brain damage
NDKA	Nucleoside diphosphate kinase A	regulation of apoptosis	Brain damage
UFD1	Ubiquitin fusion degradation protein 1	protein degradation	Brain damage
DJ1	Protein DJ-1	protein binding	Brain damage, Parkinson
S100B	Protein S100-B	protein binding	Brain damage
Troponin-I	Troponin I, cardiac muscle	protein binding	Cardiac (but also brain)

Cohorts and Goal of the study

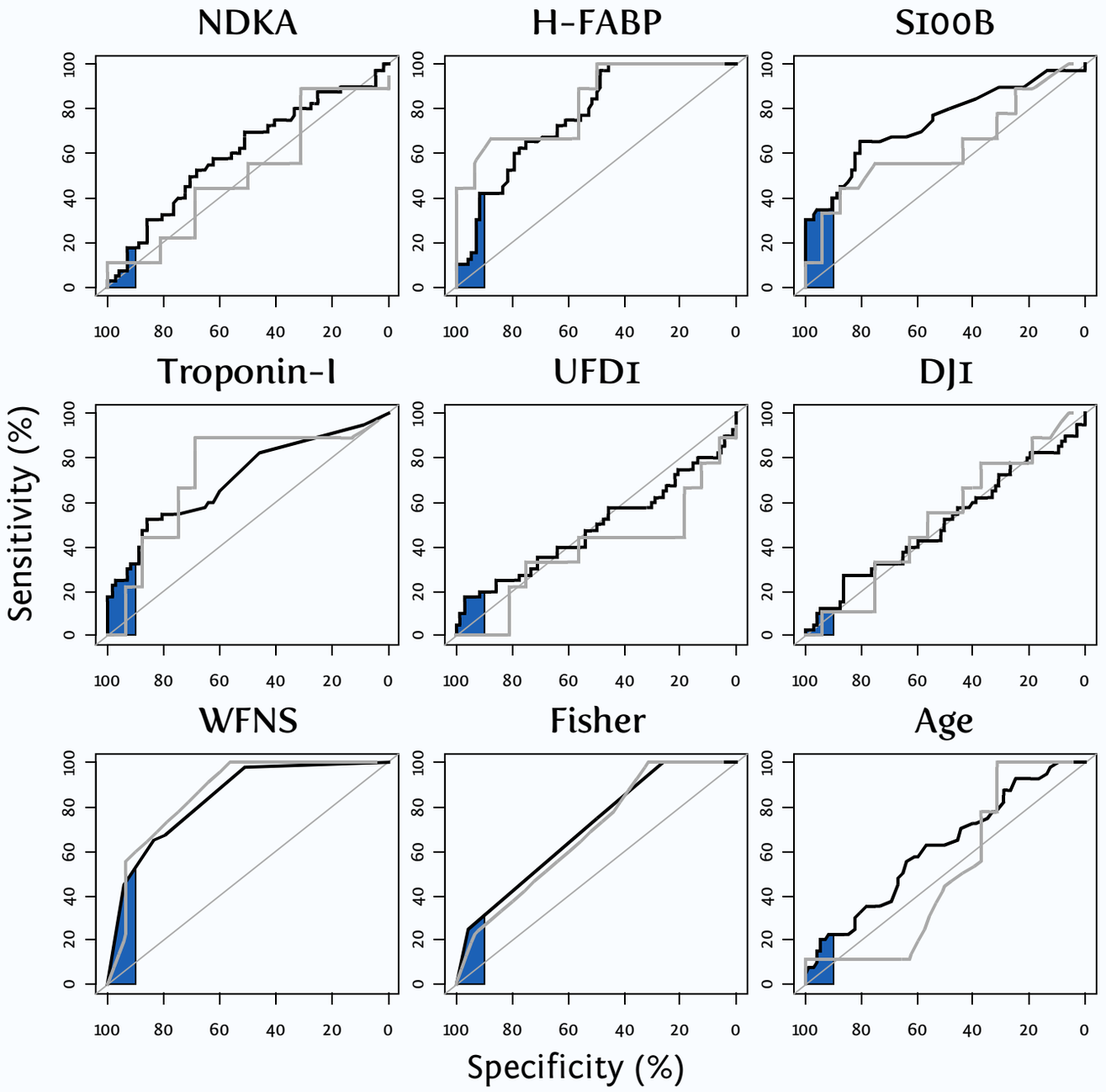
- Cohort:
  - 113 patients
  - validation: 25 patients from the same hospital collected later
- Goal:
  - Predict outcome after 6 months
    - Focus attention on patients at risk of poor outcome
  - Want a high specificity to avoid false positives (good outcome patients classified as poor outcome) and give them the best management.
    - Use partial area under the ROC curve
  - With biomarkers or a combination of them

Data Description

- Quantitative measure of protein (continuous) and clinical (discrete) data
- Box-cox transformation (Yeo and Johnson, 2000)



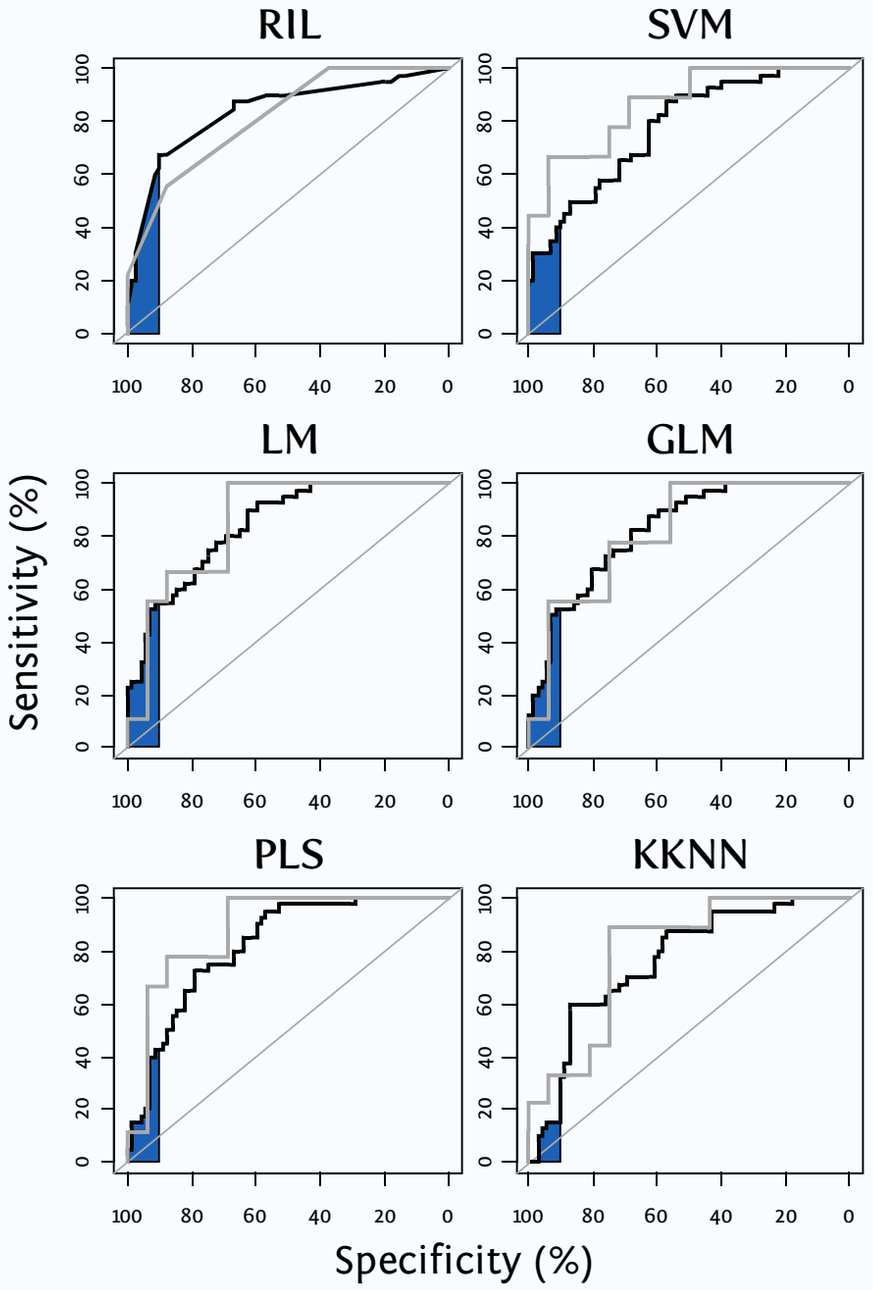
Biomarkers & Clinical parameters



- S100B is the best protein biomarker
- WFNS is the best clinical marker
- Their accuracies are low (3.4% of the total area)

— 113-set
— 25-set
◆ pAUC

Combining biomarkers



- RIL : simple threshold-based method
- Packages used:
  - kernlab (svm)
  - stats (lm & glm)
  - pls
  - kknn

— 113-set
— 25-set
◆ pAUC

Combining biomarkers

	Mean of k*n pAUCs	pAUC of means of n predictions	Validation
RIL	5.6	4.0	3.6
SVM	3.1	3.1	5.3
PLS	4.2	2.3	3.2
LM	5.1	3.7	2.8
GLM	4.6	3.1	2.8
KNN	2.9	1.0	2.6

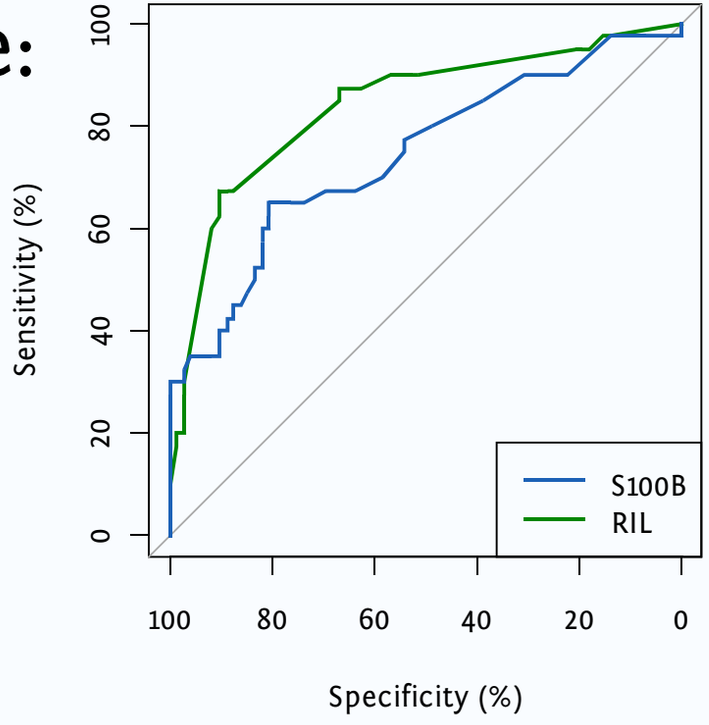
- RIL: best on cross-validation
- SVM: best on validation cohort

- Different methods to compute pAUC give different results
- Validation cohort is small (25 patients)

Comparing ROC Curves

- Several methods are available:
  - Bootstrapping
  - DeLong, 1988
- We will compare:
  - The best individual predictor (S100B)
  - The best combination method (RIL)

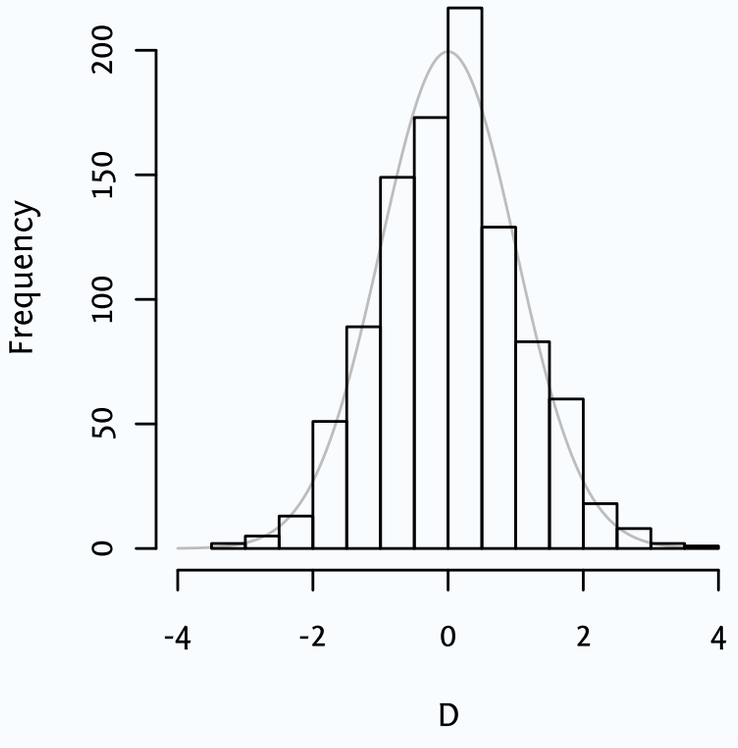
and see how comparison methods perform



Comparing ROC curves: Bootstrap

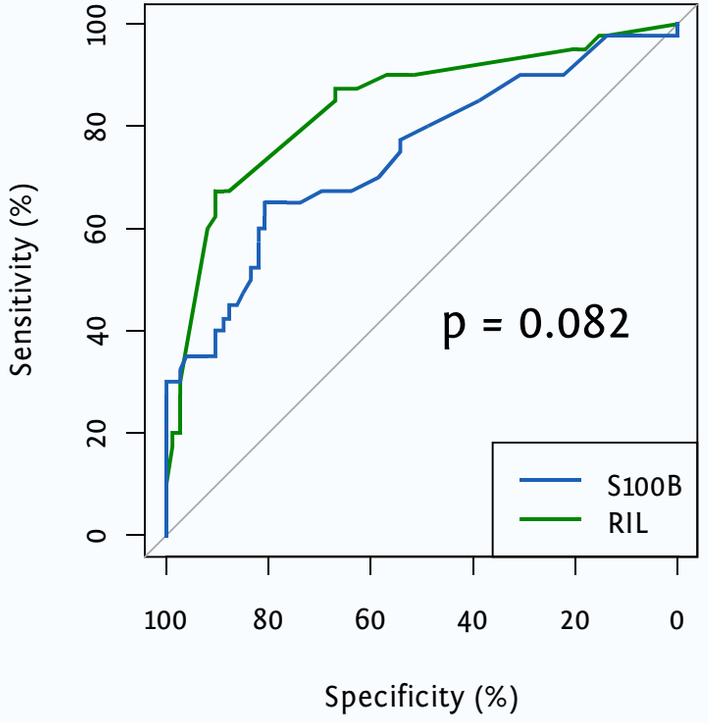
$$D = \frac{AUC1 - AUC2}{\sigma}$$

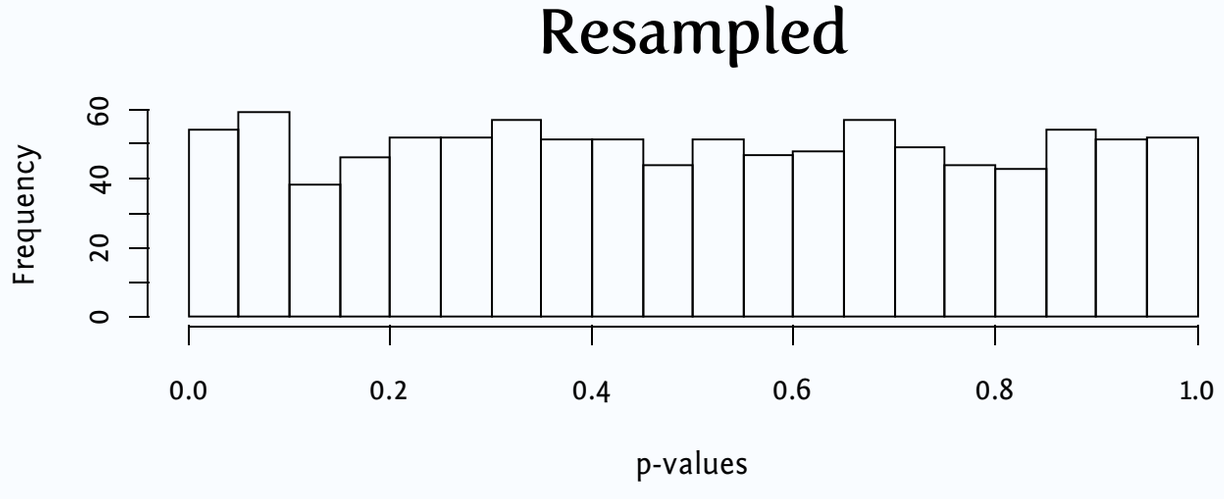
- Sigma computed by bootstrapping
- D ~ N(0, 1)
  (see Hanley & McNeil,
  Radiology, 1983)



Comparing ROC curves: Bootstrap

- Advantage:
  - Flexible
  - Applicable to pAUCs
- Disadvantage:
  - Slow
  - Same observations





Comparing ROC curves: DeLong

- Based on U statistics:

$$AUC = \frac{1}{mn} \sum_{j=1}^{n} \sum_{j=1}^{m} \psi(X_i, Y_j)$$

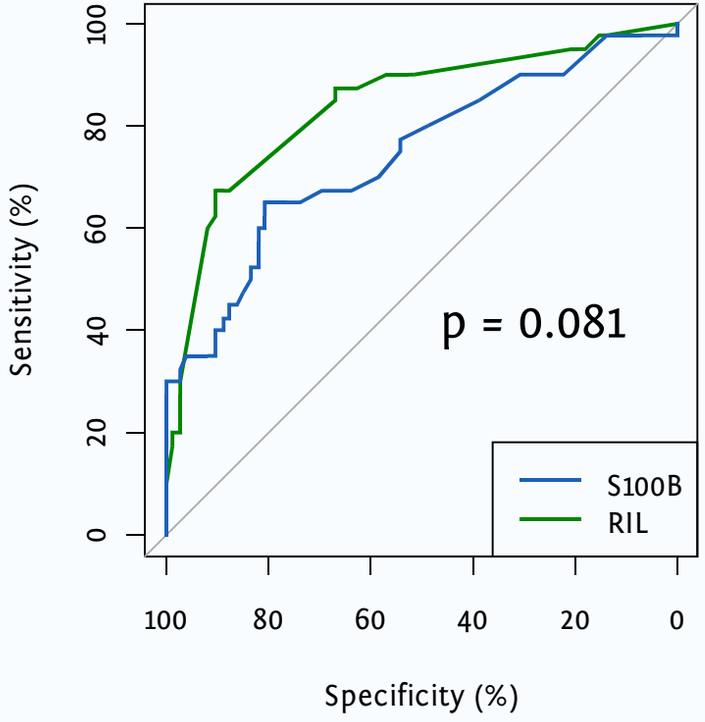
$$\psi(X, Y) = \begin{cases} 1 & Y < X \\ ½ & Y = X \\ 0 & Y > X \end{cases}$$

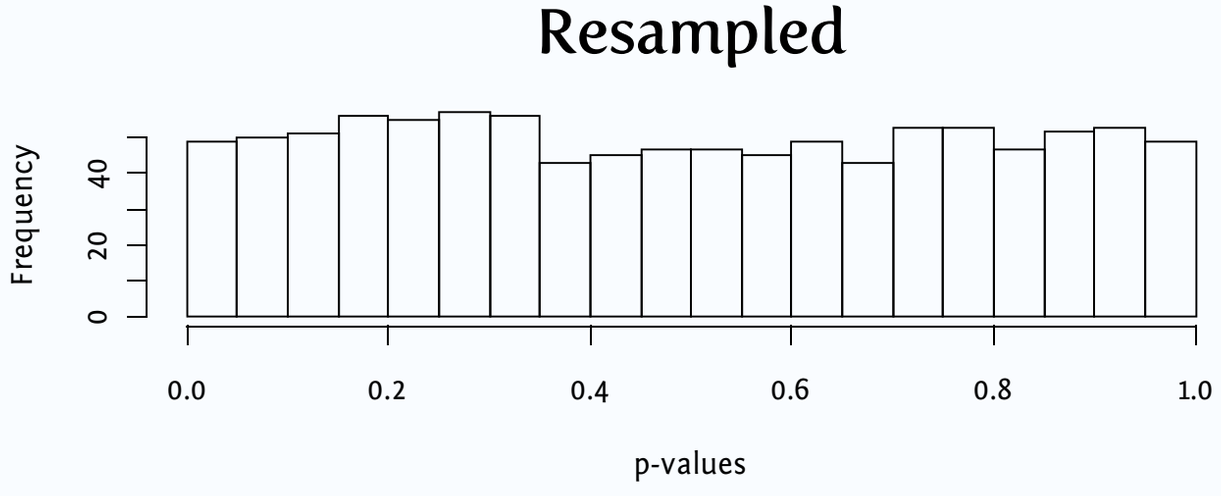
- Variance computed according to Hoeffding's theory

DeLong et al., Biometrics, 1988

Comparing ROC curves: DeLong

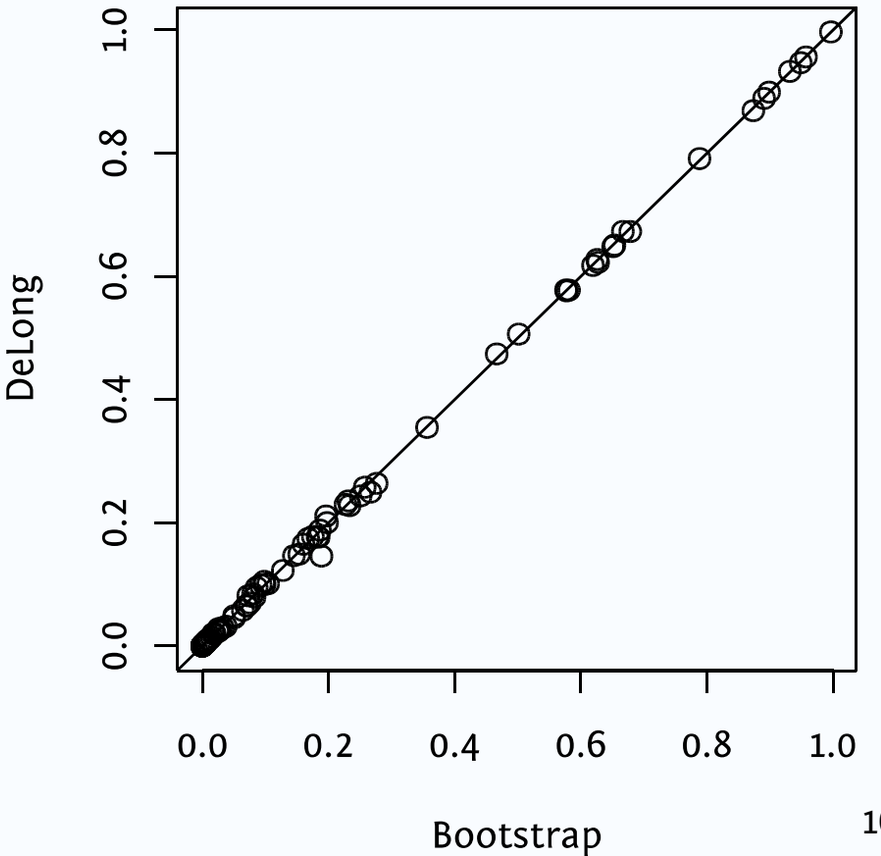
- Advantages:
  - Fast and easy
  - Based on robust statistics
  - Non parametric





Comparing ROC curves

- Bootstrap is flexible and displays good results
- DeLong's method works equally well
- pAUC computations should be straightforward
- Combinations does not appear significantly better than individual biomarkers



Comparing panels with single biomarkers

- We want to be sure that the chosen panel performs better than the biomarkers taken individually
- Panel performances are cross-validated; individual biomarkers are not
- How can we compare them fairly?
  - Do we absolutely need a “validation” cohort?

Conclusion

- The use of protein biomarkers is already widely spread
- We are not sure if using combination of several protein or clinical parameters can significantly increase accuracy
  - we don't know the influence of no cross-validation for single molecules
- Acceptance by the medical community
  - Model must be simple and clear, understandable to non-experts

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