Bayesian variable selection and classification with control of predictive values

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Workshop on Bayesian methods in the development and assessment of new therapies
Goettingen, Germany
December 7, 2018

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567

Outline

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Motivation

Case study example

- Protein (biomarker) measurements $X_1, \ldots, X_{187}$ and $n = 53$ patients

- Q: How can one best select a subset of biomarkers to classify patients?
- A: a) Perform variable selection (e.g. penalization methods) and define a risk score

  b) Patient classification requires determination of appropriate cutoff value on the risk score

  - Youden index: $J = max_c\{sensitivity(c) + specificity(c) - 1\}$
    - *To what degree does the test reflect the true disease status?*
  - $PSI = max_c\{PPV(c) + NPV(c) - 1\}$
    - *How likely is disease given test result?*

PPV : Positive Predictive Value
NPV : Negative Predictive Value

Motivation *cont'd*

Biomarker selection and cutoff estimation

- However, in clincial practice, a target performance is required
- Simultaneously perform variable selection and cutoff estimation
- Build in the selection procedure a minimun (pre-specified) predictive value of the risk score
- Take prior information into account
- Quantify the uncertainty around the cutoff and the predictive values

Model

- Binary response $Y \in \{0,1\}$
- Biomarkers $X_1, X_2, \ldots, X_d$
- A step function is used to model the probability of response
  - The cutoff and predictive values are parameters of the model
- *Model*
  - $Y|X \sim Bernoulli(p)$
  - $p = P(Y = 1|Z = X\beta) = \begin{cases} P(Y = 1|Z \leq cp) = p_1 \\ P(Y = 1|Z > cp) = p_2 \end{cases}$
  - $\beta \sim F$

- $p_1 \sim Uniform(0, p_2)$, $\boldsymbol{p_2 \sim Uniform(l, 1)}$ *i.e.* $l = 0.8$ and $cp \sim Uniform(a, b)$

Thresholding criteria for variable selection

- Laplace (Bayesian Lasso): $\beta_j \sim DE(0, \frac{1}{\lambda})$, $\lambda \sim Gamma(a, b)$
  - Indicator variable $\gamma_j = 1$ if β_j is included in the model and $\gamma_j = 0$ otherwise
  - incorporated in the linear predictor $\eta^* = XD_\gamma\beta$ where $D_\gamma = diag(\gamma_1, \gamma_2, \dots, \gamma_d)$
- Spike and slab prior: $\beta_j \sim (1-\gamma_j)\delta_0 + \gamma_j N(0, \sigma^2)$, $\gamma_j \sim Bernoulli(\pi)$ and $\pi \sim Unif(0,1)$
  - By construction, γ_j indicates if β_j is included in the model
- Horseshoe prior $\beta_j \sim \mathrm{N}(0, {\lambda_j}^2\tau^2)$, with local shrinkage $\lambda_j \sim Cauchy^+(0,1)$ and global shrinkage $\tau \sim Cauchy^+(0, c^2)$ usually with $c^2 = 1$
  - Proposed by Carvalho et al. (2010) $\gamma_j \geq 0.5$ where $\gamma_j := 1 - \frac{1}{1+{\lambda_j}^2\tau^2}$
- Variable selection is *ad hoc*
  - based on the posterior inclusion probabilities $f(\gamma_j = 1|\mathrm{y}) \geq 0.5$ (suggested by Barbieri and Berger, 2004)

Estimation of cutoff *cp*

MCMC Gibbs sampling, „*R2jags*“ library in R

- Fit the model with the step function
  - Estimate (marginal) posterior inclusion probabilities for each variable and select X_j by $f(\gamma_j = 1 | y) \geq 0.5$
  - Calculate the estimated risk score of the selected variables $X\hat{\beta}$, where $\hat{\beta}$ is taken for example as the mean of the posterior density

- Fit the model with the step function but now for fixed $\hat{\beta}$
  - From the posterior $f(cp, p_1, p_2 | X, \hat{\beta}, y)$ marginalize over cp, over p_1, over p_2

Scenario 1 (Null model)

$X \sim MVN(0, \Sigma)$, $m=10$ noisy predictors, $k=0$ informative predictors, $n=200$

- Generating model: logistic function
- Fiting model: step function

	Laplace	SpSl	HS
Average of correct selections of the null model	0.879	0.943	0.849

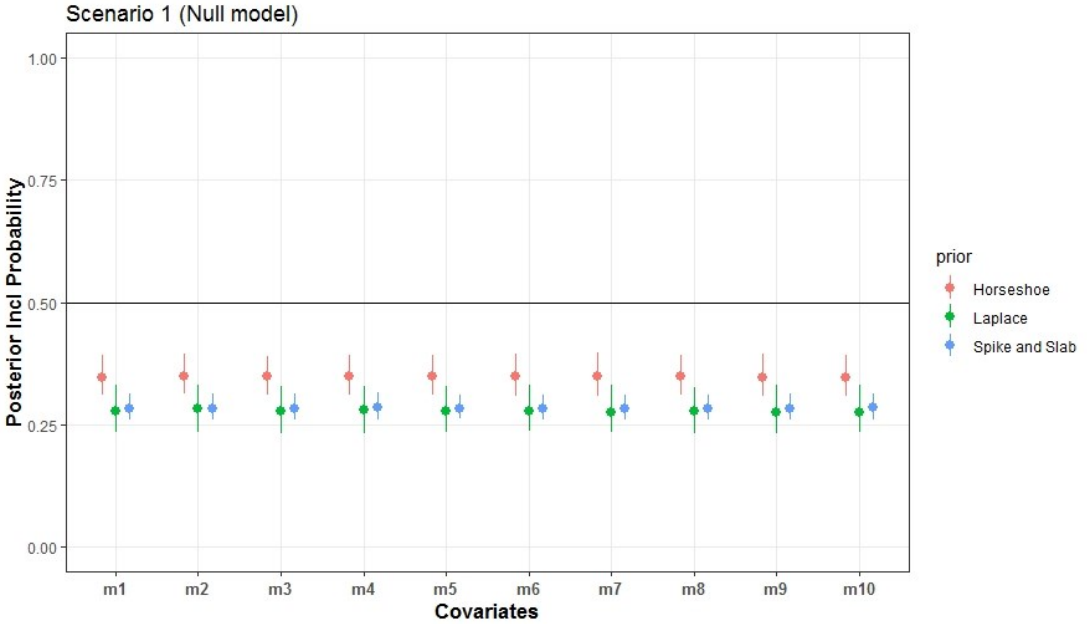


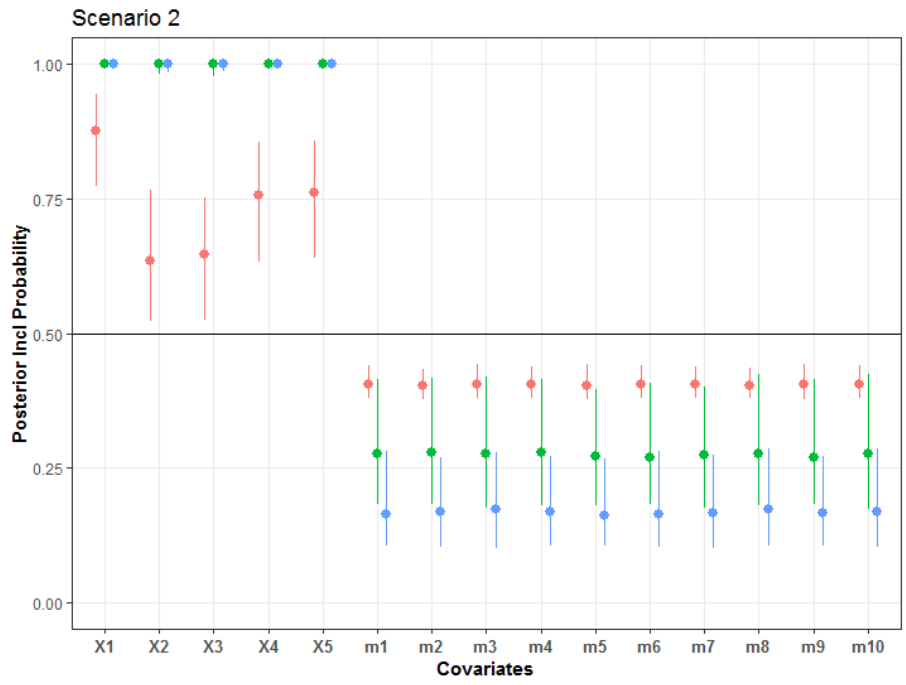
Figure: Plot of the median posterior inclusion probabilities (dots) over 1,000 simulation runs, together with the 1st and 3rd quantile. The horizontal black line corresponds to the value 0.5 that was used as a threshold for variable inclusion.

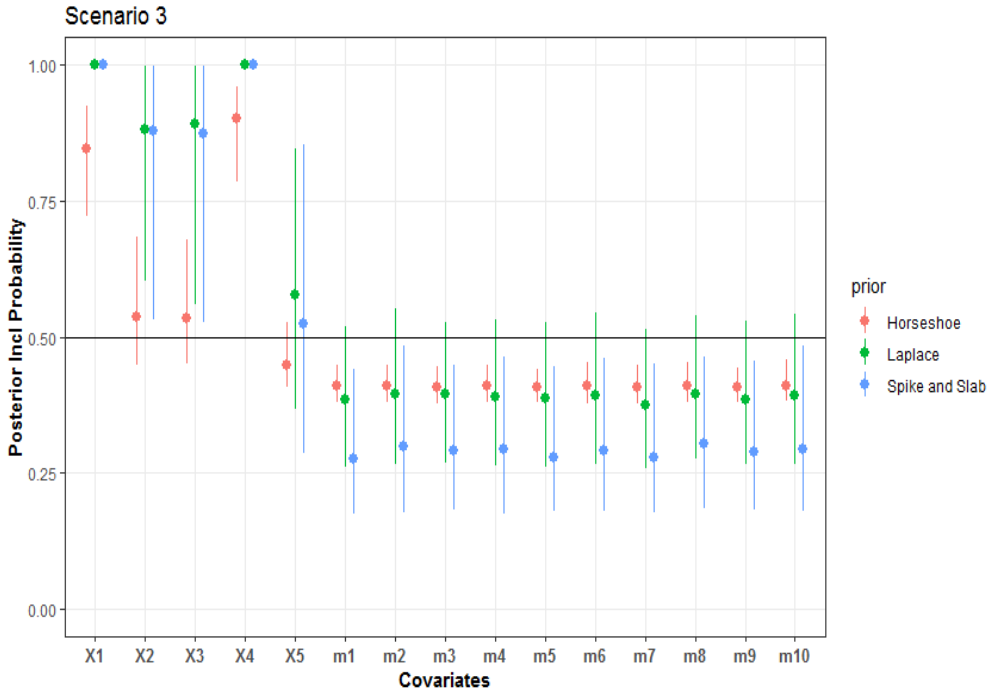
Posterior inclusion probabilities

$X \sim MVN(0, \Sigma)$, $m=10$ noisy predictors , $k=5$ informative predictors, $n=200$

Scenario 2: generate from a step function and fit a step model $\beta = (1.5, \mathbf{0.7}, \mathbf{0.7}, -1, -1)$

Scenario 3: generate from a logistic function and fit a step model $\beta = (1.5, \mathbf{0.7}, \mathbf{0.7}, -2, \mathbf{-0.5})$

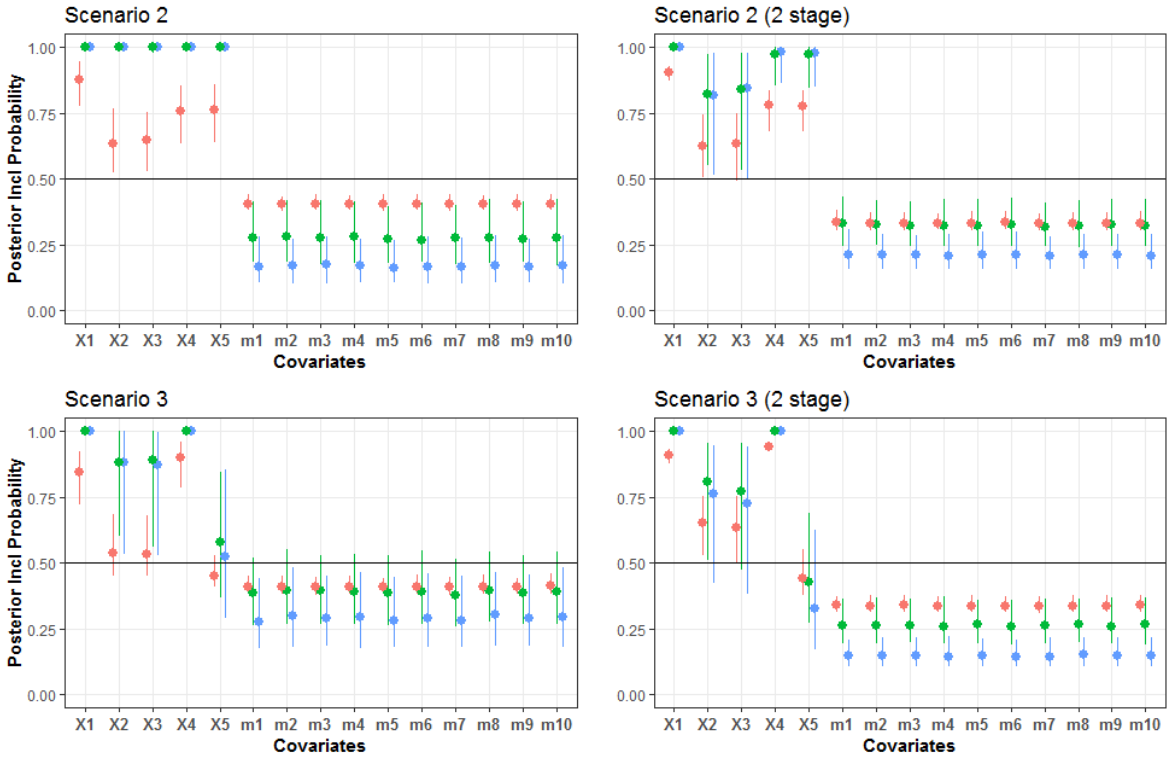




Posterior inclusion probabilities

Scenario 2: generate from a step function and fit the 2 stage approach
Scenario 3: genarate from a logistic function and fit the 2 stage approach

- 2 stage approach:
- at the 1st stage fit a *logistic* model for variable selection and
- at the 2nd stage fit a *step* model for cutoff estimation



Classification error

Brier score on a validation dataset

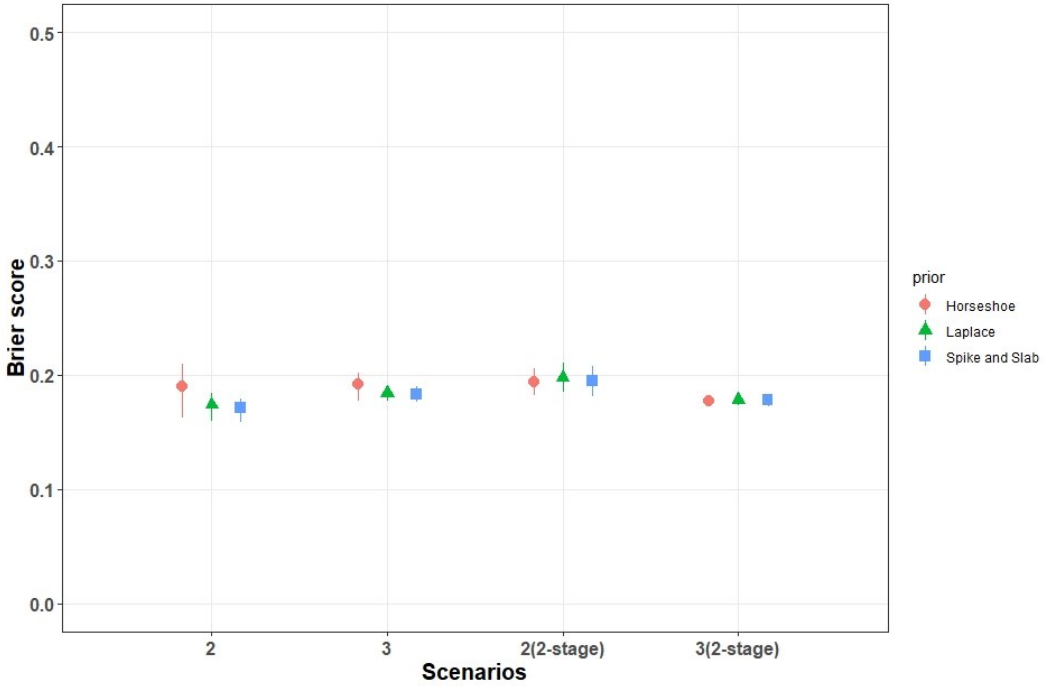


Figure: Mean, 1st and 3rd quantile over 1,000 simulation runs for the Brier score, calculated on a validating dataset.

Application: *Back to the motivating example*

$n=53$, $d=187$ protein measurements, binary response , $p_2 \sim Unif(0.8,1)$

	Laplace	SpSl	HS	HS (2stage)
#selected variables	11	78	63	72

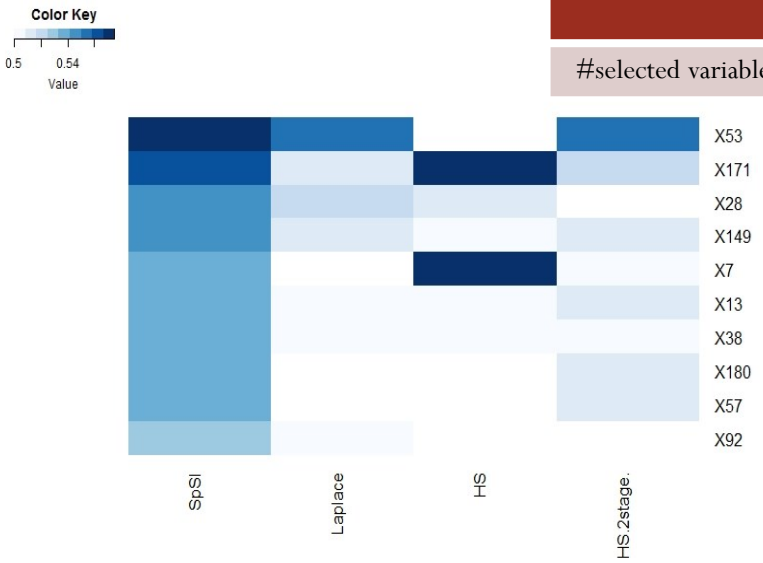


Figure: Heatmap of inclusion probabilities of the top 10 variables selected by the SpSl prior. Matched with the variables selected by the Laplace, HS and HS (2-stage).
The SpSl (2 stage) and Laplace (2stage) selected the null model, i.e the posterior inclusion probabilities were below 0.5

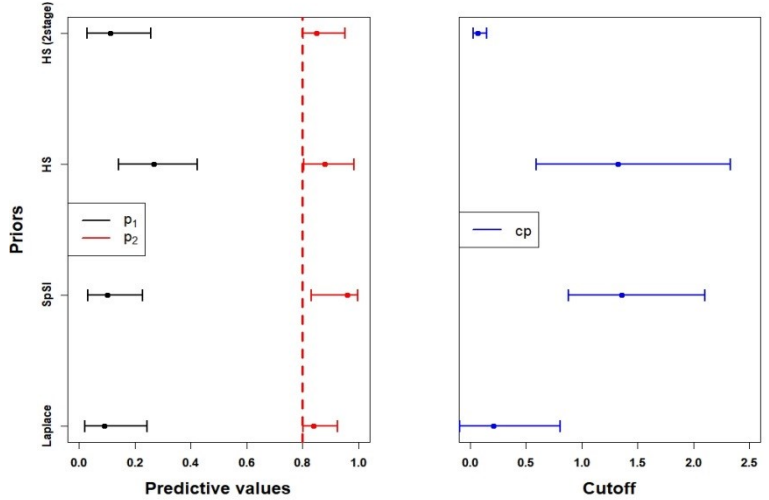


Figure: Posterior median of cp, p_1, p_2 together with the 95% credible intervals for the different priors. The vertical red dshed line is the lower bound for p_2

Conclusion

- We proposed a Bayesian method for biomarker selection and classification
  - Built-in pre-specified predictive value of the risk score (of the selected variables)

- Simulation results showed that the proposed method
  a. performs well in terms of selecting the important variables
  b. classification error was found on average below 20%
  c. performs as well and occasionaly better that the classical 2-stage approach

- For the proposed approach, the SpSl prior was found to perform overall better than the Laplace and the HS priors in terms of including the important variables and good classification performance

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Thank you for your attention!

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567