A Bayesian model to estimate the cutoff and the clinical utility of a biomarker assay

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Outline

- Background and Motivation
- Bayesian model
- Application
- Simulation Results
- Conclusion

Background & Motivation

Cutoff estimation so far..

- Especially in oncology, increasing interest/need to identify potential (treatment) responders
- Using selected (sets of) biomarkers for patient selection requires determination of appropriate cutoff value
- Need to use utility functions that take specific requirements (costs, specificity, sensitivity,…) into account
  - Commonly used measures: Youden index, Predictive values, Diagnostic Likelihood Ratios

Commonly used measures

- Classification probabilities: $Sens = P(T^+|Y = 1)$ and $Spec = P(T^-|Y = 0)$
  - Youden index: $J = max_c\{sens(c) + spec(c) - 1\}$
    - *To what degree does the test reflect the true disease status?*

- Predictive Values: $\mathrm{PPV} = P(Y = 1|T^+)$ and $1 - \mathrm{NPV} = P(Y = 1|T^-)$
  - $PSI = max_c\{PPV(c) + NPV(c) - 1\}$
    - *How likely is disease given test result?*

- Diagnostic likelihood ratios (DLR+, DLR-)
  - *By how much does the test change knowledge of disease status?*

Motivation

How likely is disease given test result?

- Estimate a reliable cutoff (denoted by ***cp***) on a potentially predictive biomarker that can be used for patient selection/classification given their test results
- Estimate the uncertainty around the cutoff
- Take prior information into account

Bayesian Approach

Model

- Binary response $Y \in \{0,1\}$
- Biomarker assay: (Continuous or ordinal) biomarker X
  - Higher values of X are associated with increased probability of response
- A step function is used to model the probability of response
  - The cutoff and predictive values are parameters of the model
- *Model*
  - $Y|X \sim Bernoulli(p)$
  - $$p = P(Y = 1|X) = \begin{cases} P(Y = 1|X \leq cp) = p_1 \\ P(Y = 1|X > cp) = p_2 \end{cases}$$
  - Require $p_2 > p_1$

Priors

- $p_1 \sim Uniform(0,1)$ and $p_2 \sim Uniform(p_1,1)$

- We considered different prior specifications for cp
  - Uniform prior (UP)
  - Informative prior precise (IPP)

(high probability on the true cutpoint)

  - Informative prior imprecise (IPN)

(the true cutpoint is at the tail of the distribution)

  - Mixture prior (UP+IPP)
    - $cp = \mathrm{w} * f_{UP} + (1-w) * f_{IPP}$
    - $w \sim Uniform(0,1)$

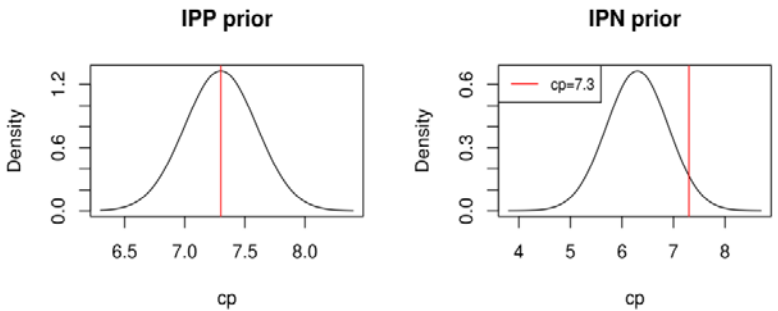

Figure: Density plots for the priors IPP and IPN. For the IPP prior, the true cutoff *cp*, lies in a high probability region, while for the IPN prior the true cutoff value lies on the tail of the distribution.

Application

Application

Prostate Cancer Data

- Total Prostate Specific Antigen (PSA) was measured (on the log scale) on 683 subjects (study by Etzioni et al.,1999 as described in Pepe, 2003)

- Total PSA is found to be a marker with fairly good accuracy

- Estimate a cutoff on the PSA that takes into account the clinical benefit of the marker

Posterior summaries for the PSA cutoff

- For the Bayesian method, we use MCMC Metropolis-Hastings
  - the posterior mean of the cutoff is 1.30 with 95% credible interval (1.27-1.38)

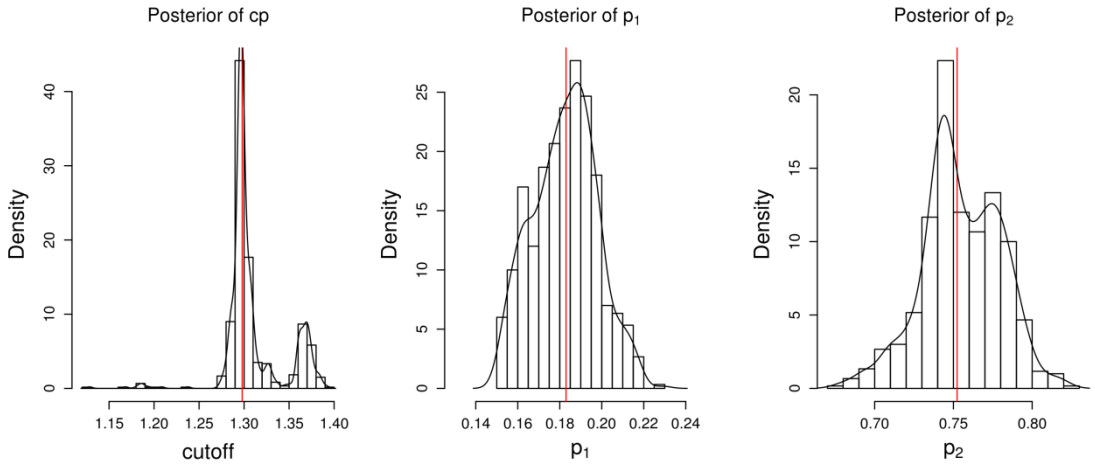

Figure: Plot of the posterior distribution for the parameter cp (left panel), p_1 (middle panel) p_2 (right panel) estimated by the Bayesian model. The red vertical line denotes the median of the distribution.

Posterior mean of p_1 is 0.18 with 95% credible interval (0.15-0.21)

Posterior mean of p_2 is 0.75 with 95% credible interval (0.70-0.79)

Results for PSA cutoff

- Maximum Likelihood Estimator with 95% confidence interval
  - The MLE of the cutoff is 1.29 with 95% CI (1.27-1.31)
  - The MLE for $p_1$is 0.18 with 95% confidence interval (0.15-0.21) and for p_2 is 0.75 with 95% confidence interval (0.68-0.81)

- PSI= max$\{p_2 - p_1\}$ with 95% Bootstrapped confidence interval.
  - Resampling the data B=500 times
  - The cutoff with the PSI method is 3.63 with 95% bootstrapped CI (2.00-3.77)
  - At that cut-off the p_2 and p_1 is equal to 1 and 0.32 respectively.

Simulation Study

Scenario 1

$X \sim Normal(7,1)$ ***n=200*** *generating model: step function*

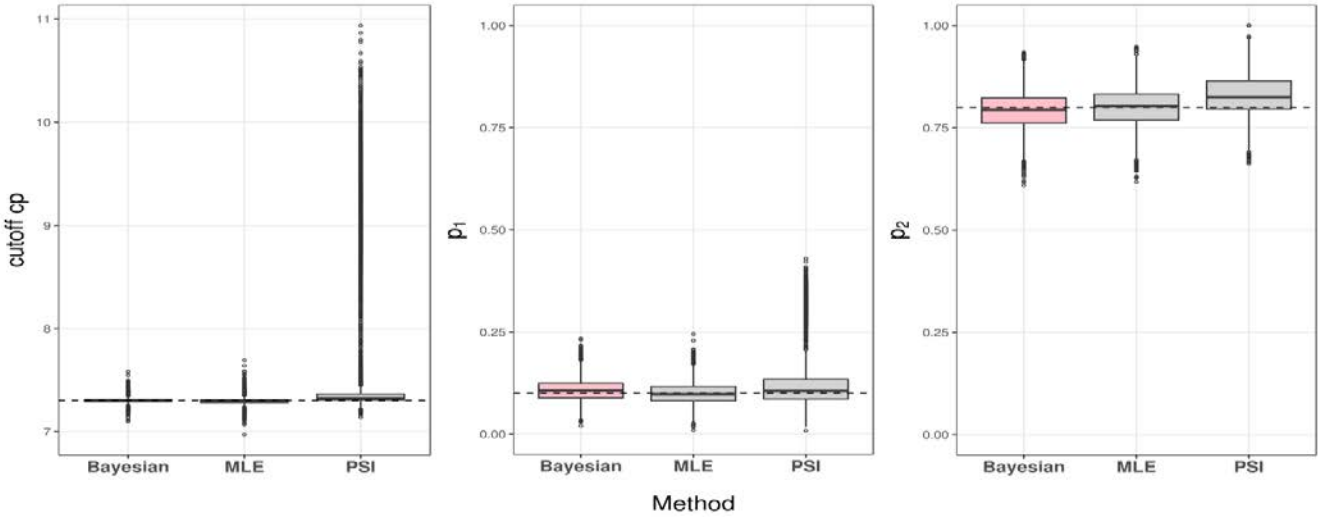

Figure: Bayesian posterior means (left boxplots), MLE (middle boxplots) and PSI (right boxplots) estimators for the parameters cp, p_1, p_2 over 10 000 simulation runs for n=200. The black horizontals dashed lines are the true parameter values

Scenario 1

$X \sim Normal(7,1)$ ***n=50*** *generating model: step function*

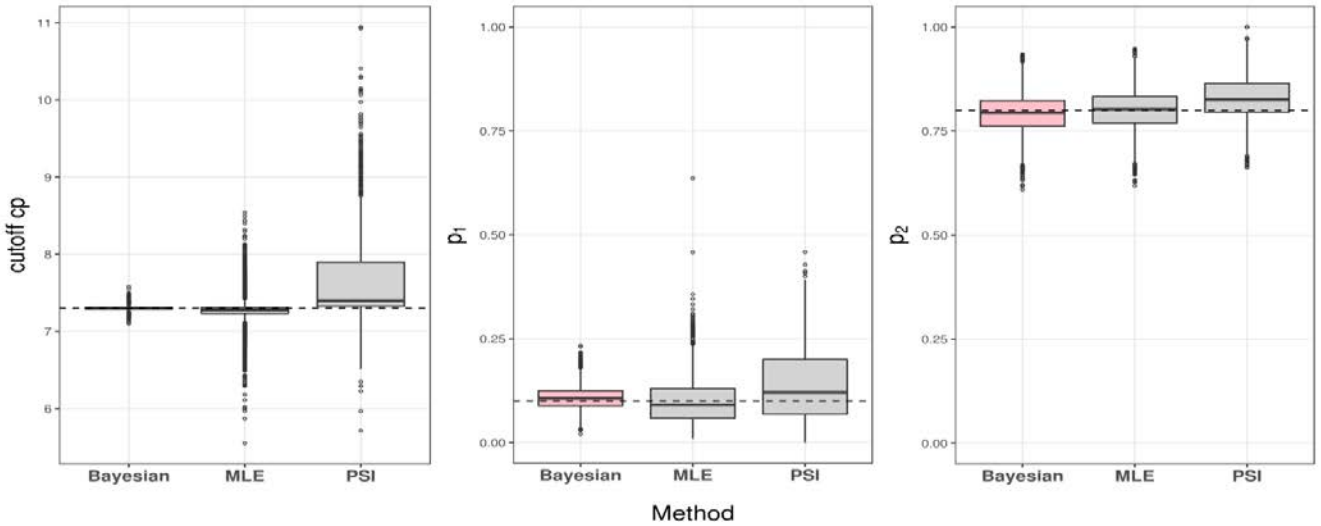

Figure: Bayesian posterior means (left boxplots), MLE (middle boxplots) and PSI (right boxplots) estimators for the parameters cp, p_1, p_2 over 10 000 simulation runs for n=50. The black horizontals dashed lines are the true parameter values

Scenario 2

$X \sim Normal(7,2)$ *n=200* *generating model:* ***logistic function***

$\beta_0 = -3, \beta_1 = 0.5$

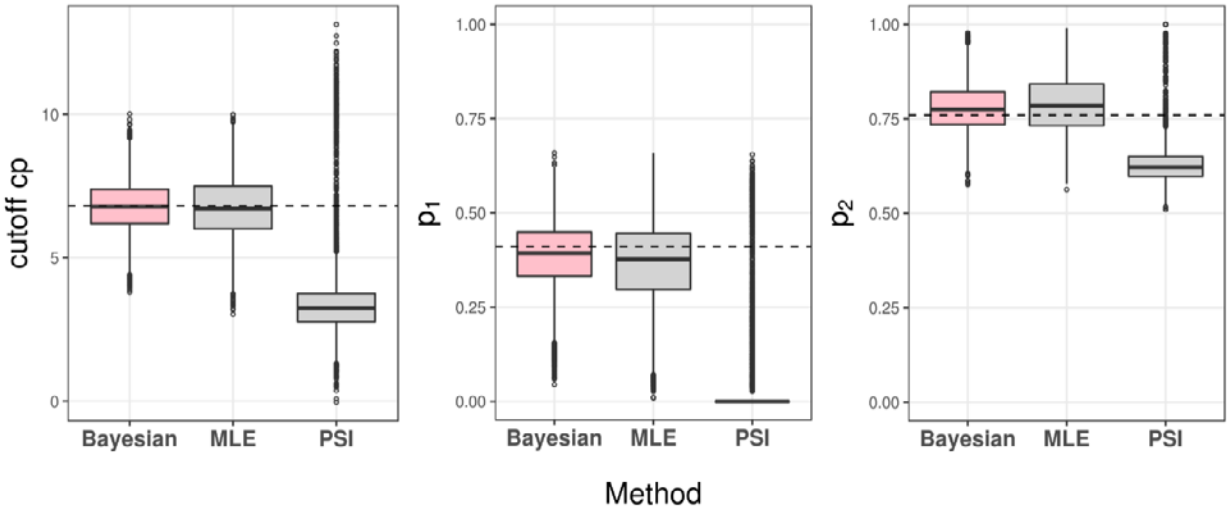

Figure: Bayesian posterior means (left boxplots), MLE (middle boxplots) and PSI (right boxplots) estimators for the parameters cp, p_1, p_2 over 10 000 simulation runs. The black horizontals lines are the population parameters as calculated by minimizing the Kullback-Liebler divergence.

Scenario 3

$X \sim Normal(5,1) + Normal(9,1)$ *n=200* *generating model: step function with 2 steps*

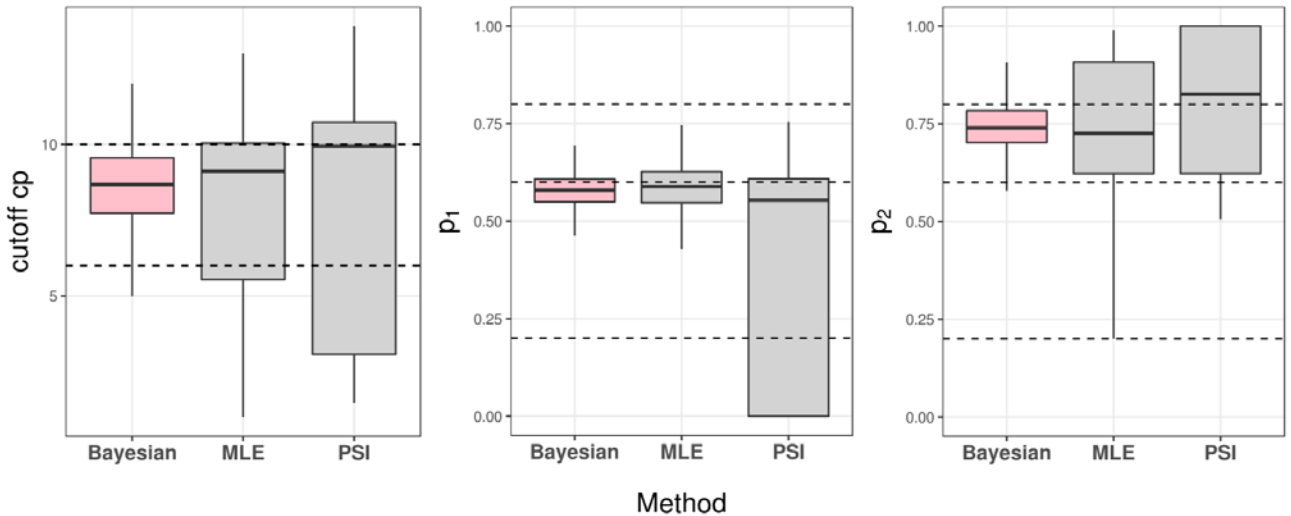

Figure: Boxplots of the Bayesian posterior mean (left boxplots), MLE (middle boxplots) and PSI (right boxplots) estimators for cp, p_1, p_2 over 10 000 simulation runs. The black lines correspond to the true values of $cp_1, cp_2, p_1, p_2, p_3$.

Scenario 3

$X \sim Normal(5,1) + Normal(9,1)$ *n=200* *generating model: step function with 2 steps*

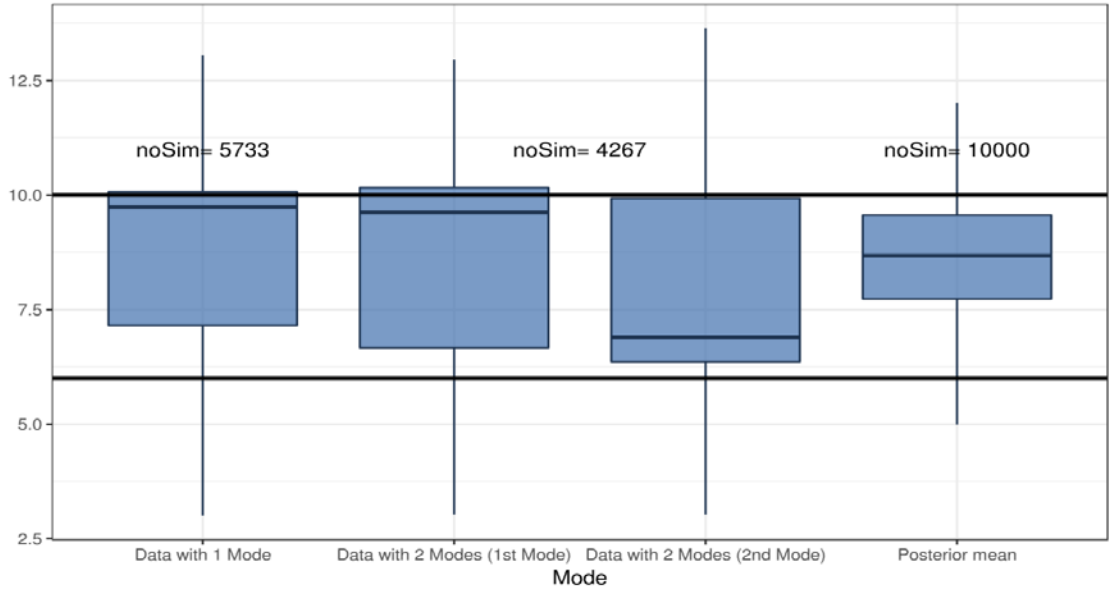

Figure: Distribution of the modes of the posterior distribution for the $\widehat{cp}$, over 10,000 simulation runs estimated by the Bayesian model. If the posterior density is unimodal, then the only mode of the distribution is plotted (noSim=5,733) (left boxplot). In case the posterior distribution is bimodal (noSim=4,267), then the two modes are plotted (middle boxplots). The black lines correspond to the true values of $cp_1 = 6,\ cp_2 = 10$.

Conclusion

- A Bayesian model to estimate the cutoff of a biomarker assay and the uncertainty around this estimate
  - Derive probabilistic statements about the predictive values
- Even though a step function is a strong assumption, the estimates of the assumed step model are consistent for the parameter values for which the KL divergence from the true model is minimized
- The estimates (posterior mean) are shown to be nearly unbiasted
- Good coverage (95%) and small interval width (precision)
- Highly informative prior -> gain in precision and accuracy
  - Mixture prior to deal with a possible data-prior conflict

Future work

- Estimate the cutoff associated with a target utility value, i.e. PPV=0.9
  - (!) Whether this cutoff exists would depend on the relationship between the biomarker and response

- Extensions
  - Time-to-event data
  - Multiple cutoffs
  - Multiple biomarkers

References

- Youden WJ. Index for rating diagnostic tests. Cancer. 1950 Jan 1;3(1):32-5
- Linn S, Grunau PD. New patient-oriented summary measure of net total gain in certainty for dichotomous diagnostic tests. Epidemiologic Perspectives & Innovations. 2006 Dec;3(1):11
- Bunke O, Milhaud X. Asymptotic behavior of Bayes estimates under possibly incorrect models. *The Annals of Statistics*. 1998;26(2):617-44.
- Kullback S, Leibler RA. On information and sufficiency. *The annals of mathematical statistics*. 1951 Mar 1;22(1):79-86.
- Pepe, M.S., 2003. *The statistical evaluation of medical tests for classification and prediction*. Medicine.
- Etzioni R, Pepe M, Longton G, Hu C, Goodman G. Incorporating the time dimension in receiver operating characteristic curves: a case study of prostate cancer. *Medical Decision Making*. 1999 Aug;19(3):242-51.

Thank you!

Bye-Bye

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