Estimation of Optimally-Combined-Biomarker Accuracy in the Absence of a Gold-Standard Reference Test

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Outline

Problem setting
- Accuracy definition
- Optimal combination of biomarkers
- Absence of gold-standard reference

Bayesian latent-class mixture model
- ”Naive” prior definition
- Controlled prior definition

Simulation study
- Data
- Results

Conclusions

Outline

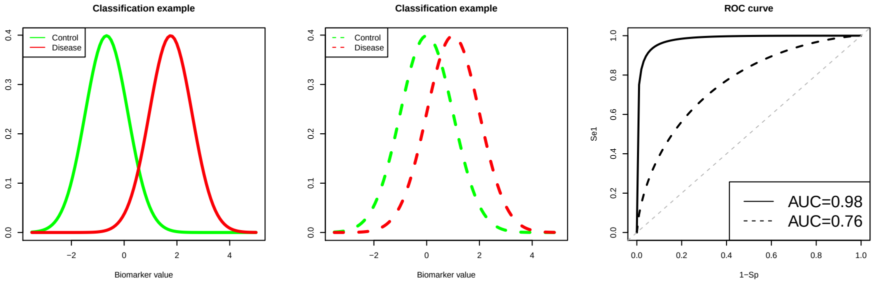
Problem setting

Establish accuracy of a combination of biomarkers in the absence of a gold-standard reference test

- Area under the Receiver Operating Characteristics (ROC) curve (AUC) as measure of accuracy
- Choose combination of biomarkers that maximizes AUC
- Imperfect reference test leads to biased estimates of accuracy

=> To this end a Bayesian latent-class mixture model will be proposed

Area under the Receiver Operating Characteristics curve



Data assumptions and notation

Underlying true biomarker distribution

- Mixture of two K-variate normal distributions by true disease status (D)
  - $\mathbf{Y}|_{D=0} \sim N_K(\boldsymbol{\mu}_0, \boldsymbol{\Sigma}_0)$
  - $\mathbf{Y}|_{D=1} \sim N_K(\boldsymbol{\mu}_1, \boldsymbol{\Sigma}_1)$
- Se: Unknown sensitivity of the reference test (T)
- Sp: Unknown specificity of the reference test (T)
- θ: Unknown true prevalence of disease in the data set
- Reference test is imperfect
  - Conditionally on true disease status, misclassification independent of biomarker value
  - Ignoring will UNDERESTIMATE performance of biomarker

ROC parameters optimal combination of biomarkers

According to Siu and Liu (1993) the linear combination maximizing AUC is of the form:

$$\mathbf{a'Y}|_{D=0} \sim N(\mathbf{a'}\boldsymbol{\mu_0}, \mathbf{a'}\boldsymbol{\Sigma_0}\mathbf{a})$$
$$\mathbf{a'Y}|_{D=1} \sim N(\mathbf{a'}\boldsymbol{\mu_1}, \mathbf{a'}\boldsymbol{\Sigma_1}\mathbf{a})$$

For which:

$$\mathbf{a'} \propto (\boldsymbol{\Sigma}_0 + \boldsymbol{\Sigma}_1)^{-1}(\boldsymbol{\mu}_1 - \boldsymbol{\mu}_0)$$

Area Under the ROC Curve:

$$AUC_{OptComb} = \Phi\left\{((\boldsymbol{\mu_1} - \boldsymbol{\mu}_0)'(\boldsymbol{\Sigma}_0 + \boldsymbol{\Sigma}_1)^{-1}(\boldsymbol{\mu_1} - \boldsymbol{\mu}_0))^{\frac{1}{2}}\right\}$$

This is all under the assumption of a gold standard reference test. We propose to extend this to the imperfect reference test case.

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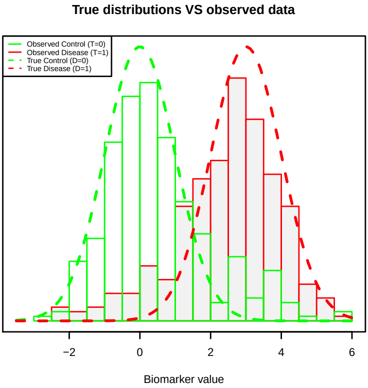
Underlying versus observed data

Ignoring misclassification in imperfect reference test will lead to bias of estimated accuracy:



- In example: conditionally independent misclassification
- Misclassification in reference test causes skewed observed distributions
- Goal: retrieve accuracy of true underlying biomarker by observed data

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Full data likelihood

$$
\begin{aligned}
&L(\boldsymbol{\mu}_0, \boldsymbol{\mu}_1, \boldsymbol{\Sigma}_0, \boldsymbol{\Sigma}_1, \theta, Se, Sp | \mathbf{Y}, \mathbf{T}, \mathbf{D}) \\
&= \prod_{i=1}^{N} \left(\theta Se^{t_i} (1 - Se)^{(1-t_i)} \frac{1}{\sqrt{2\pi |\boldsymbol{\Sigma}_1|}} \times EXP \left\{ -\frac{1}{2} (\mathbf{Y}_i - \boldsymbol{\mu}_1)' \boldsymbol{\Sigma}_1^{-1} (\mathbf{Y}_i - \boldsymbol{\mu}_1) \right\} \right)^{d_i} \\
&\times \left((1-\theta)(1 - Sp)^{t_i} Sp^{(1-t_i)} \frac{1}{\sqrt{2\pi |\boldsymbol{\Sigma}_0|}} \times EXP \left\{ -\frac{1}{2} (\mathbf{Y}_i - \boldsymbol{\mu}_0)' \boldsymbol{\Sigma}_0^{-1} (\mathbf{Y}_i - \boldsymbol{\mu}_0) \right\} \right)^{(1-d_i)}
\end{aligned}
$$

"Naive" prior definition

Hyperprior

$\theta \sim$ Uniform(0.1,0.9)

Priors

$D_i \sim$ Bernoulli(θ) (Observation i: 1,. . . ,N)

$\mu_{kj} \sim$ N(0,10^6) (Disease indicator j: 0, 1; Biomarker k: 1,. . .,K)

$\boldsymbol{\Sigma}_j^{-1} \sim$ Wish($\boldsymbol{S}$,K) (Disease indicator j: 0, 1)

with **S** = VarCov-matrix of observed control group

Se = Sp $\sim$ Beta(1,1)T(0.51,∞) [Non-informative]

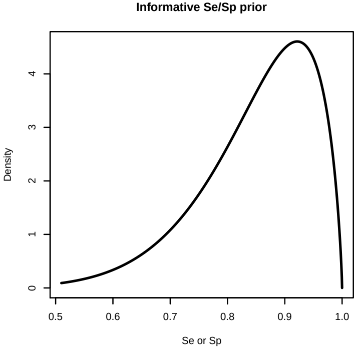
OR Se = Sp $\sim$ Beta(10,1.764706)T(0.51,∞) [Informative]

Se/Sp Beta(10,1.764706) Prior

Mean = 0.85

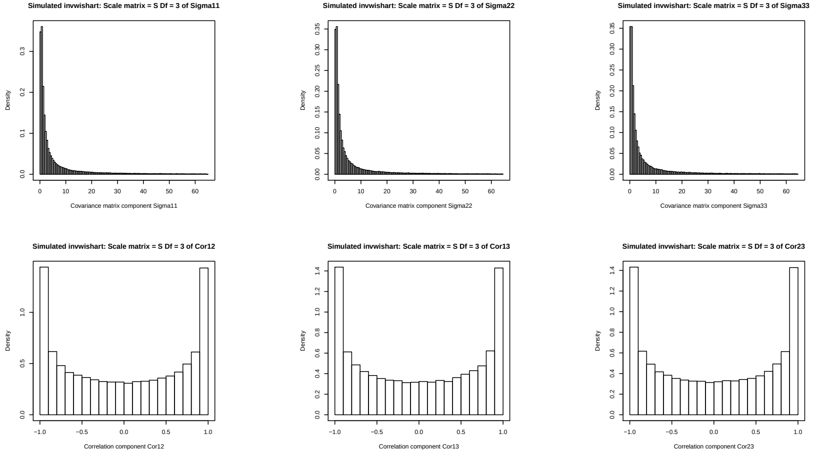
Var = 0.009988479

Equal-tail 95%-probability interval: 0.6078 - 0.9834



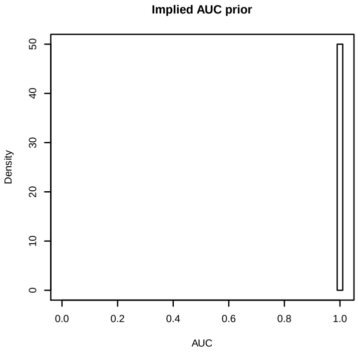
Implied priors

Variances and correlations



Implied priors

AUC



- Prior specification is used commonly (e.g. O'Malley and Zou (2006))
- Uninformative mixture component priors lead to prior point mass distribution centred at 1 for AUC
- Extremely informative prior for component of interest!

Controlled prior definition ($\boldsymbol{\Sigma}$)

Set $\boldsymbol{\Sigma}_j = \mathbf{V}_j \mathbf{R}_j \mathbf{V}_j$*

For: $\mathbf{V}_j = \sigma_{k,j} I_K$ and $\mathbf{R}_j$ is a correlation matrix. [j:0,1; k:1,. . .,K]

Then: $\mathbf{C}_j$ = Cholesky factor of $\mathbf{R}_j$.

$\sigma_{k,j} \sim$ Uniform(0,1000)

Say K=3 then:

$$C_{j,12} = \rho_{j,12} \sim \text{Uniform(-1,1)}$$
$$C_{j,13} = \rho_{j,13} \sim \text{Uniform(-1,1)}$$
$$C_{j,23} \sim \text{Uniform}\left(-\sqrt{1-\rho_{j,13}^2}, \sqrt{1-\rho_{j,13}^2}\right)$$
$$\rho_{j,23} = \rho_{j,12}\rho_{j,13} + C_{j,22}C_{j,23}$$

* Wei, Y and Higgins, J.P.T (2013)

Controlled prior definition (AUC)

Set $\mathbf{\Delta} = \mathbf{L}(\boldsymbol{\mu}_\mathbf{1} - \boldsymbol{\mu}_\mathbf{0})$

For $\mathbf{L}$ = the Cholesky factor of $(\mathbf{\Sigma}_0 + \mathbf{\Sigma}_1)^{-1}$

$$\mathbf{\Delta} \sim N_K(\boldsymbol{\kappa}, \Psi)$$
$$\mu_{0k} \sim N(0, 10^6) \ \ \text{(k: 1,...,K)}$$
$$\boldsymbol{\mu}_1 = \mathbf{\Delta} L^{-1} + \boldsymbol{\mu}_\mathbf{0}$$

Implied priors

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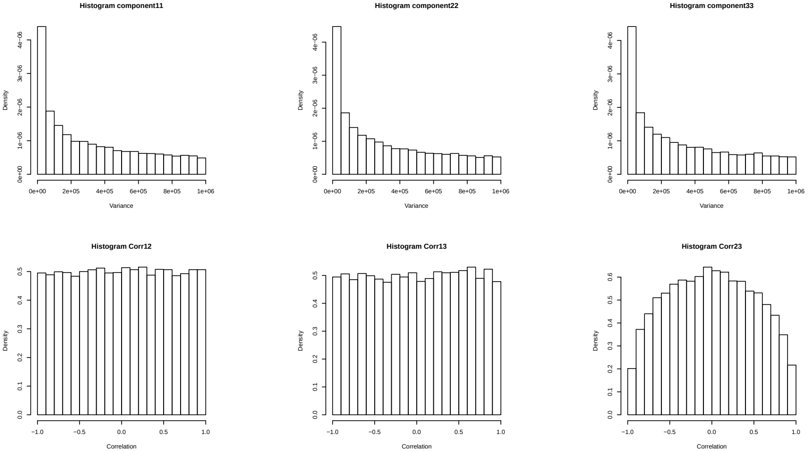
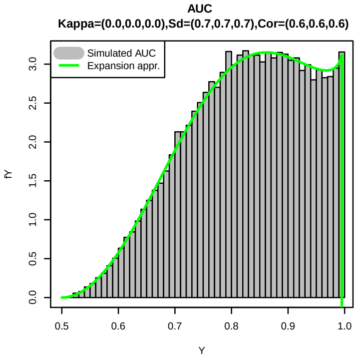


Implied priors

AUC

For $\boldsymbol{\kappa} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}$, $\sigma_i = 0.7$ and $\rho_{ij} = 0.6$ [i,j: 1,. . .,K]



- Less informative prior distribution for AUC
- Prior on $\boldsymbol{\Delta}$ gives control over informativeness AUC prior

Outline

400 datasets for 3 independent biomarkers

N = 100, 400 or 600
$\theta = 0.5$
Se = Sp = 0.85

Mixture component parameters set such that:

AUC of biomarker 1 = 0.75
AUC of biomarker 2 = 0.75
AUC of biomarker 3 = 0.75

$AUC_{OptimalCombination} = 0.88$

AUC Results (Average of median posterior AUC)

True AUC = 0.8786

Prior Formulation	Se/Sp Prior	Sample Size		
		N=100	N=400	N=600
GS	/	0.7710 (0.0361)	0.7661 (0.0210)	0.7614 (0.0157)

- Gold Standard model fit leads to severe underestimation
- Naive AUC prior specification causes slight overestimation
  - Increased sample size reduces overestimation and decreases standard errors
  - Informative Se/Sp prior also reduces this bias, but seems to increase standard errors
- Controlled AUC prior reduces overestimation compared to Naive-prior case
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Naive	**Non-Inf**	0.9241 (0.0279)	0.8890 (0.0279)	0.8836 (0.0262)
Naive	**Inf**	0.9068 (0.0344)	0.8827 (0.0286)	0.8785 (0.0263)

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Naive	**Inf**	0.9068 (0.0344)	0.8827 (0.0286)	0.8785 (0.0263)
Controlled	**Non-Inf**	0.8907 (0.0347)	0.8803 (0.0290)	0.8773 (0.0271)
Controlled	**Inf**	0.8728 (0.0388)	0.8741 (0.0292)	0.8722 (0.0269)

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Conclusions

- Bayesian latent-class mixture model:
  - Takes unknown true disease status into account
  - Incorporates information from reference test while acknowledges imperfectness
    - Provides estimates of accuracy of the reference test
- Simulation study
  - Model is able to retrieve true AUC
- Careful prior specification
  - Complex function of uninformative prior distributions => informative prior => biased estimates
  - Controlled prior specification is proposed

Further considerations

- Sensitivity to misspecified Se/Sp prior distribution
- Extend to incorporate non-normally distributed biomarkers
- Evaluate impact of conditional independence assumption

References

- O'Malley, A.J., Zou, K.H.: Bayesian multivariate hierarchical transformation models for ROC analysis. Statistical Medicine. **25**, 459–479 (2006)
- Su, J.Q., Liu, J.S.: Linear combinations of multiple diagnostic markers. Journal of the American Statistical Association. **88**, 1350–1355 (1993)
- Wei, Y, Higgins, P.T.: Bayesian multivariate meta-analysis with multiple outcomes. Statistics in Medicine (2013) doi: 10.1002/sim.5745

Thank you for your attention !