Generalized t-statistic and AUC for binary classification

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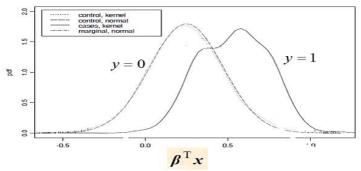
Contents

- Generalized t-statistic (Komori, O., Eguchi, S. and Copas, J., 2015)
 - t-statistics based on a generator function U
 - Optimal-*U* in terms of prediction and classification accuracy
- Generalized AUC (Komori, O., Hung, H., Chen, P. Huang, S. and Eguchi, S.)
- 3 Discussion

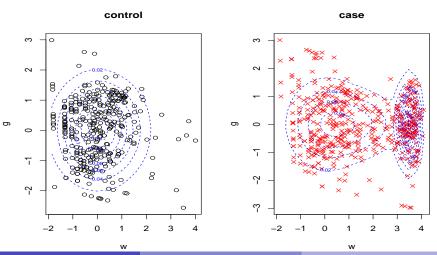
How to deal with the heterogeneity of sample of disease group?

y = 0 (control); y = 1 (diabetes) x =(glucouse level, BMI, diabetes measure)

Distribution of the LDF: controls (y=0, n=500), cases (y=1,n=268)



Gene expression data of asthmatic markers (Dottorini *et al.*, 2011)



Problem setting

- We focus on a linear discriminant function: $F(x) = \beta^{T}x$, where $x \in \mathbb{R}^{p}$
- We assume that the sample of controls (y = 0) are normally distributed:

$$x_0 \sim N(\mu_0, \Sigma_0),$$

where we apply log transformation if necessary.

- We summarize the information of the sample into the sample mean \bar{x}_0 , and sample variance S_0 .
- However, we recognize the distribution of the cases sample (y = 1) is far from normality.
 - We take it into consideration more flexibly.
- ullet We propose the generalized t statistic based on U function.

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Generalization of t-statistic

For two samples $\{x_{0i}: i=1,\ldots,n_0\}$ and $\{x_{1j}: j=1,\ldots,n_1\}$, we consider the following statistic based on $F(x)=\beta^T x$.

Generalized t-statistic (Komori et al., 2015)

$$L_U(\beta) = \frac{1}{n_1} \sum_{j=1}^{n_1} U \left\{ \frac{\beta^{\mathrm{T}}(x_{1j} - \bar{x}_0)}{(\beta^{\mathrm{T}} S_0 \beta)^{1/2}} \right\},\,$$

where U is an arbitrary function: $\mathbb{R} \to \mathbb{R}$; \bar{x}_y , S_y are conditional sample mean and sample variance given y.

$$\mathbb{L}_{U}(\beta) = E_{1} \left[U \left\{ \frac{\beta^{T}(x - \mu_{0})}{\beta^{T} \Sigma_{0} \beta} \right\} \right],$$

where E_{v} , μ_{v} , Σ_{v} are conditional mean and variance given y.

t-statistic, AUC, Fisher, K-L divergence

• t statistic: if U(w) = w, then

$$L_{\rm I}(\beta) = \frac{\beta^{\rm T}(\bar{x}_1 - \bar{x}_0)}{(\beta^{\rm T} S_0 \beta)^{1/2}}.$$

AUC: If $U(w) = \Phi(w)$ (Su and Liu, 1993), then

$$L_{\Phi}(\beta) = \frac{1}{n_1} \sum_{j=1}^{n_1} \Phi \left\{ \frac{\beta^{\text{T}}(x_{1j} - \bar{x}_0)}{(\beta^{\text{T}} S_0 \beta)^{1/2}} \right\} \to \text{AUC}(\beta),$$

- 3 Fisher: If $\hat{U}(w) = -(w \hat{c}_0)^2$, then $\underset{\alpha \in \mathbb{D}^n}{\operatorname{argmax}} \ L_{\hat{U}}(\beta) \propto (\hat{\pi}_0 S_0 + \hat{\pi}_1 S_1)^{-1} (\bar{x}_1 \bar{x}_0).$
- **4** K-L divergence: If $U(w) = U_{opt}(w)$, then

$$\mathbb{L}_{U_{\text{opt}}}(\beta) = \int f_1(w) \log \frac{f_1(w)}{\phi(w, \mu_w, \sigma_w^2)} dw.$$

Three assumptions

- normality assumption of data for y = 0: $x_0 \sim N(\mu_0, \Sigma_0)$.
- consistency

(A)
$$E_1(g \mid w = a) = 0$$
 for all $a \in \mathbb{R}$,

asymptotic variance

(B)
$$\operatorname{var}_1(g \mid w = a) = Q_0 \text{ for all } a \in \mathbb{R},$$

where $w=\beta_0^{\rm T}(x-\mu_0), \ g=Q_0(x-\mu_0), \ Q_0=I_p-\beta_0\beta_0^{\rm T}.$ The target parameter is defined as.

$$\beta_0 = \frac{\Sigma_0^{-1}(\mu_1 - \mu_0)}{\{(\mu_1 - \mu_0)^T \Sigma_0^{-1}(\mu_1 - \mu_0)\}^{1/2}} \approx \beta_F,$$

where $\beta_F = (\Sigma_0 + \Sigma_1)^{-1} (\mu_1 - \mu_0) / \{(\mu_1 - \mu_0)^T (\Sigma_0 + \Sigma_1)^{-1} (\mu_1 - \mu_0)\}^{1/2}$ and we can assume $\Sigma_0 = I_p$ and $\mu_0 = 0$ in general.

Consistency

We consider the estimator that maximizes the generalized t-statistic:

$$\widehat{\beta}_U = \underset{\beta \in \mathbb{R}^p}{\operatorname{argmax}} \ L_U(\beta).$$

Theorem 1

Under Assumption (A) $\widehat{\beta}_U$ is consistent to β_0 for any U.

Proof.

Using $w = \beta_0^{\mathrm{T}}(x - \mu_0)$ and $g = Q_0(x - \mu_0)$, we have

$$\frac{\partial}{\partial\beta}\mathbb{L}(\beta)=E_1[U'(w)g],$$

which is 0 if $\beta = \beta_0$ on account of the assumption (A). Hence from the strong law of large numbers,

 $\widehat{\beta}_U$ is asymptotically consistent with β_0 .

What is assumption (A)?

Proposition 1

If it holds that

$$p_1(x) = p_1((I - Q_0)(x - \mu_0) + \mu_0),$$

then (A) is satisfied where $p_1(x)$ is the probability density function of x given y = 1.

This means that $p_1(x)$ is symmetrical with respect to $\mu_0 + a\beta_0$ ($a \in \mathbb{R}$). That is, it covers a wide range of distributions such as the elliptical distributions including the multivariate t-distribution with mean μ_1 and the precision matrix I_p .

Gaussian mixture model

$$p_1(x) = \sum_{k=1}^{\infty} \epsilon_k \phi(x, \nu_k, V_k).$$

Proposition 2

Assumptions (A) and (B) under the infinite mixture model are rewritten as

(A')
$$\sum_{k \in K_{\ell}} \epsilon_k (Q_0 - Q_k) = 0, \quad \sum_{k \in K_{\ell}} \epsilon_k Q_k (\nu_k - \mu_0) = 0 \text{ for any } \ell \in \mathbb{N}$$

(B')
$$\sum_{k \in K_*} \epsilon_k \{ Q_k V_k Q_0 - Q_0 \} = 0 \text{ for any } \ell \in \mathbb{N}$$

 $\text{where } Q_k = I_p - V_k \beta_0 \beta_0^{\mathrm{T}} / (\beta_0^{\mathrm{T}} V_k \beta_0) \text{ and } K_\ell = \{k \mid \beta_0^{\mathrm{T}} \nu_k = \beta_0^{\mathrm{T}} \nu_\ell, \ \beta_0^{\mathrm{T}} V_k \beta_0 = \beta_0^{\mathrm{T}} V_\ell \beta_0 \}.$

Illustration of typical examples

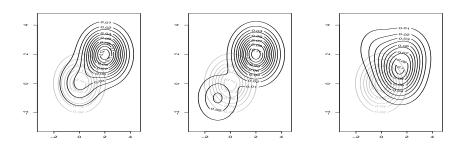


Figure 1: Contour plots of probability densities of y=0 in gray and y=1 in black, which satisfy Assumptions (A) and (B). For all three panels, $\mu_0=(0,0)^T$, $\Sigma_k=\Sigma_0=\mathrm{diag}(1,1)$ for all k. $\nu_1=(0,0)^T$, $\nu_2=(2,2)^T$, $\epsilon_1=0\cdot 2$ and $\epsilon_2=0\cdot 8$ in the left panel; $\nu_1=(-1,-1)^T$, $\nu_2=(2,2)^T$, $\epsilon_1=0\cdot 2$ and $\epsilon_2=0\cdot 8$ in the middle panel; $\nu_1=(1,1)^T$, $\nu_2=(1\cdot 5,0\cdot 5)^T$, $\nu_3=(0\cdot 5,1\cdot 5)^T$, $\nu_4=(-0\cdot 5,2\cdot 5)$, $\nu_5=(2,2)^T$, $\epsilon_1=\epsilon_3=\epsilon_4=0\cdot 1$, $\epsilon_2=0\cdot 4$ and $\epsilon_5=0\cdot 3$ in the right panel

Semiparametric model

Theorem 2

Under the assumption $x_0 \sim N(\mu_0, \Sigma_0)$, if it holds that

$$p_1(x) = \psi(c + \beta^\top x) p_0(x),$$

then

- **1** β is proportional to the target parameter β_0
- assumptions (A) and (B) hold.

If we consider $\psi(z) = \exp(z)$, it corresponds to logistic linear model. ψ is an arbitrary non-parametric function.

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Asymptotic variance

Let $f_1(w)$ be a probability density function of $w = \beta_0^T(x - \mu_0)$ given y = 1.

Theorem 3

Under assumptions (A) and (B), $n_1^{1/2}(\widehat{\beta}_U - \beta_0)$ is asymptotically distributed as $N(0, \Sigma_U)$, where

$$\begin{split} \Sigma_U &= c_U Q_0^-, \\ c_U &= \frac{E_1 \{ U'(w)^2 \} + \pi_1 / \pi_0 \big[E_1 \{ U'(w) w \} \big]^2 + \pi_1 / \pi_0 \big[E_1 \{ U'(w) \} \big]^2}{\big[E_1 \{ U'(w) S(w) \} + E_1 \{ U'(w) w \} \big]^2}, \end{split}$$

where Q_0^- is the generalized inverse of Q_0 , $S(w) = \partial \log f_1(w)/\partial w$ and U' is the first derivative of U.

Optimal U function

Theorem 4

The optimal U that minimizes the asymptotic variance of $\widehat{\beta}_U$ is given as

$$U_{\text{opt}}(w) = \log \frac{f_1(w)}{\phi(w, \mu_w, \sigma_w^2)},$$

where $\mu_w = E(w)$, $\sigma_w^2 = \text{var}(w)$. Moreover, we have

$$\min_{U} c_{U} = \frac{\sigma_{w}^{2}}{\mu_{1,S^{2}} - 1 + (\pi_{0}\mu_{1,w}^{2} + \sigma_{1,w}^{2} - 1)(\pi_{0} + \pi_{1}\mu_{1,S^{2}})},$$

where $\mu_{1,w} = E_1(w)$, $\sigma_{1,w}^2 = E_1\{(w - \mu_{1,w})^2\}$, $\mu_{1,S^2} = E_1\{S(w)^2\}$.

Optimality in terms of AUC

The expected generalized t-statistic asymptotically satisfies

$$E\{\mathbb{L}_{U}(\hat{\beta}_{1})\} - E\{\mathbb{L}_{U}(\hat{\beta}_{2})\} = \frac{1}{2n_{1}} tr[H_{U}(\beta_{0})\{var_{A}(\hat{\beta}_{1}) - var_{A}(\hat{\beta}_{2})\}] \ge 0$$

optimality of $\hat{eta}_{U_{ ext{opt}}}$

$$\mathrm{E}\{\mathbb{L}_{U}(\hat{\beta}_{U_{\mathrm{opt}}})\} \geq \mathrm{E}\{\mathbb{L}_{U}(\hat{\beta})\}.$$

For example, if we take $\Phi(w)$ as U(w), then we have

$$H_{\Phi}(\beta_0) = -2 \int \phi(w) w f_1(w) dw Q_0.$$

Here we have $\int w f_1(w) dw = E_1(w) = (\mu_1^{\rm T} \mu_1)^{1/2} > 0$. This implies that $\int \phi(w) w f_1(w) dw > 0$ because of the symmetry of $\phi(w)$ with respect to the original point. Hence, the estimator $\hat{\beta}_{U_{\rm out}}$ asymptotically has a maximum value of AUC.

Algorithm for estimation of β_0

- **1** Initialize as $\beta^{(1)} = S_0^{-1}(\bar{x}_1 \bar{x}_0)$.
- - Estimate $f_1(w)$ based on kernel method to produce $\hat{U}_{\mathrm{opt}}(w)$.
 - Update $\beta^{(t-1)}$ to $\beta^{(t)}$ as

$$\beta^{(t)} = \underset{\beta \in \mathbb{R}^p}{\operatorname{argmax}} \frac{1}{n_1} \sum_{j=1}^{n_1} \hat{U}_{\text{opt}} \left\{ \frac{\beta^{\text{T}}(x_{1j} - \bar{x}_0)}{(\beta^{\text{T}} S_0 \beta)^{1/2}} \right\}$$

Output $\widehat{\beta}_U = \beta^{(T)}$.

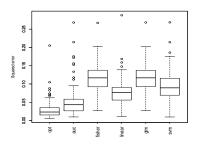
Note that the initial value $\beta^{(1)}$ in step 1 above could be replaced by any other value, so avoiding the need to calculate the inverse of S_0 .

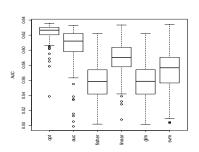
Simulation

Setting

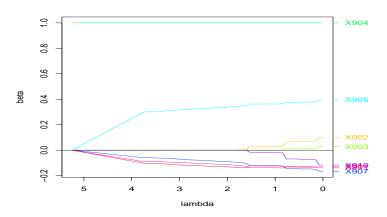
$$x_0 \sim N(\mathbf{0}, \mathbf{I}_p), \ x_1 \sim (1 - \epsilon_1 - \epsilon_2)N(\mathbf{v}_0, \mathbf{V}_0) + \epsilon_1 N(\mathbf{v}_1, \mathbf{V}_1) + \epsilon_2 N(\mathbf{v}_2, \mathbf{V}_2),$$

where
$$\epsilon_1 = \epsilon_2 = 0.1$$
, $\boldsymbol{v}_0 = (-1, -0.1, \dots, -0.1)^{\top} \in \mathbb{R}^p$, $\boldsymbol{v}_1 = (1, 0.1, \dots, 0.1)^{\top}$
 $\boldsymbol{v}_2 = (3, 0.3, \dots, 0.3)^{\top} \in \mathbb{R}^p$, $\boldsymbol{V}_0 = \boldsymbol{V}_1 = \boldsymbol{V}_2 = \boldsymbol{I}_p$ and $\boldsymbol{\pi}_0 = \boldsymbol{\pi}_1$, $p = 10$ and $n = 200$.





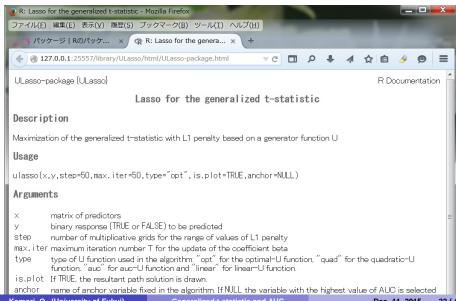
U-lasso



Solution paths by $U_{
m opt}$ -lasso for variables in X group

$$L_U^{\lambda}(\beta) = L_U(\beta) - \lambda \sum_{k=1}^p |\beta_k|,$$

R package of U-lasso



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Generalization of Area under the ROC curve (AUC)

Fro two samples $\{x_{0i}: i=1,\ldots,n_0\}$ and $\{x_{1j}: j=1,\ldots,n_1\}$, we consider a linear predictor $F(x)=\beta^T x$ and propose

Generalized AUC

$$L_U(\beta) = \frac{1}{n_0 n_1} \sum_{i=1}^{n_0} \sum_{j=1}^{n_1} U \left\{ \frac{\beta^{\mathrm{T}}(x_{1j} - x_{0i})}{(\beta^{\mathrm{T}} S \beta)^{1/2}} \right\},\,$$

where U is a generator function: $\mathbb{R} \to \mathbb{R}$; \bar{x}_y is a conditional sample mean of x given y; $S = S_0 + S_1$.

$$\widehat{\beta}_U = \underset{\beta \in \mathbb{R}^p}{\operatorname{argmax}} \ L_U(\beta)$$

Two assumptions

consistency

(A)
$$E_y(g_y \mid w_y = a) = 0$$
 for all $a \in \mathbb{R}$, for $y = 0, 1$

asymptotic variance

(B)
$$\operatorname{var}_y(g_y \mid w_y = a) = \Sigma_y^* \text{ for all } a \in \mathbb{R}, \text{ for } y = 0, 1$$

where $w_y = \beta_F^T x_y$, $g_y = Q x_y$, $Q = I - \beta_F \beta_F^T$, $\Sigma_y^* = Q \Sigma_y Q^T$. And we define a target parameter of β as

$$\beta_{\rm F} = \frac{\Sigma^{-1}(\mu_1 - \mu_0)}{\{(\mu_1 - \mu_0)^{\rm T} \Sigma^{-1}(\mu_1 - \mu_0)\}^{1/2}},$$

where we assume $\Sigma = \Sigma_0 + \Sigma_1 = I_p$ and $\mu_0 + \mu_1 = 0$ without loss of generality

The target parameter is the coefficient of Fisher linear predictor. No normality assumption of x_0 .

Gaussian mixture

We consider Gaussian mixture such that

$$p_{y}(x) = \sum_{k=1}^{\infty} \epsilon_{yk} \phi(x, \nu_{yk}, V_{yk}) \text{ for } y = 0, 1.$$

Proposition 3

Then assumption (A) and (B) are rewritten

$$(\mathrm{A}') \qquad \sum_{k \in K_{y\ell}} \epsilon_k (Q - Q_{yk}) = 0, \ \sum_{k \in K_{y\ell}} \epsilon_{yk} Q_{yk} \nu_{yk} = 0, \text{ for } ^\forall \ell \in \mathbb{N}, \ y = 0, 1$$

(B')
$$\sum_{k \in K_{y\ell}} \epsilon_{yk} \left\{ Q_{yk} V_{yk} Q - Q \Sigma_{y} Q \right\} = 0, \text{ for } \forall \ell \in \mathbb{N}, y = 0, 1$$

where $Q_{yk} = I_p - V_{yk}\beta_F\beta_F^\top/(\beta_F^\top V_{yk}\beta_F)$, $K_{y\ell} = \{k \mid \beta_F^\top v_{yk} = \beta_F^\top v_{y\ell}, \beta_F^\top V_{yk}\beta_F = \beta_F^\top V_{y\ell}\beta_F\}$.

Semiparametric model

Theorem 5

Let ψ_{v} be a function: $\mathbb{R} \to \mathbb{R}_{+}$ such that

$$p_y(x) = \psi_y(c + \beta^T x)\phi(x, 0, \Sigma_y), \text{ for } y = 0, 1,$$

and

$$\Sigma_{y}\beta = \lambda_{y}\beta$$
, for $y = 0, 1$.

where $\lambda_y(\neq 0)$. Then

- \bigcirc β is proportional to $\beta_{\rm F}$
- assumption (A) and (B) are satisfied,

where $\phi(x, \mu, \Sigma)$ is a normal distribution of mean μ and variance Σ . ψ_{ν} is an arbitrary non-parametric function.

Asymptotic variance

Let f(w) be a density function of $w = w_1 - w_0 = \beta_F^T(x_1 - x_0)$.

Theorem 6

Under assumptions (A) and (B) with $\Sigma_0^*/\pi_0 = \Sigma_1^*/\pi_1$, $n^{1/2}(\widehat{\beta}_U - \beta_F)$ is asymptotically distributed as $N(0, \Sigma_U)$

$$\begin{split} \Sigma_U &= c_U Q^-, \\ c_U &= \frac{E_0 \Big[E_1 \{ U'(w) \} \Big]^2 + E_1 \Big[E_0 \{ U'(w) \} \Big]^2 + 2 \rho E \{ U'(w) \} E \{ U'(w) w \} - \Big[E \{ U'(w) w \} \Big]^2}{\Big[E \{ U'(w) S(w) + U'(w) w \} \Big]^2}. \end{split}$$

where Q^- is the generalized inverse of Q; $\Sigma_y^* = Q\Sigma_yQ^T$; $S(w) = \partial \log f(w)/\partial w$; U' is the first derivative of U and $\rho = E(w)$.

Optimal U function

By variational method, the optimal-U minimizing the asymptotic variance should satisfy

$$E_0[U'(w)] + E_1[U'(w)] = \lambda S(w) + aw + b,$$

where $w = w_1 - w_0$; $S(w) = \partial \log f_1(w)/\partial w$; λ, a, b are some constants.

Remark 1

Note that there does not exist U(w) if S(w) is a non-linear function.

- \Rightarrow \[\text{No optimal-} U \text{ for generalized AUC in general} \]
- β_0 is easy to estimate efficiently (generalized t-statistic)
- β_F is difficult to estimate efficiently (generalized AUC)

upper-U

The scalar term c_U in asymptotic variance is upper-bounded by

$$c_{U} \leq \frac{2E\{U'(w)^{2}\} + 2\rho E\{U'(w)\}E\{U'(w)w\} - \left[E\{U'(w)w\}\right]^{2}}{\left[E\{U'(w)S(w) + U'(w)w\}\right]^{2}},$$

where the equality holds when U(w) = aw + b.

Proposition 4

The upper-bound is minimized by

$$U_{\text{upper}}(w) = \log f(w) + \frac{1}{2}w^2 - \frac{\rho^3}{2 + \rho^2}w.$$

Based on $U_{\mathrm{upper}}(w)$ we construct optimal-U by polynomial approximation

$$U_{\text{opt}}(w) = U_{\text{upper}}(w) + a_1 w + a_2 w^2 + \dots + a_m w^m,$$

Optimal order of polynomial approximation

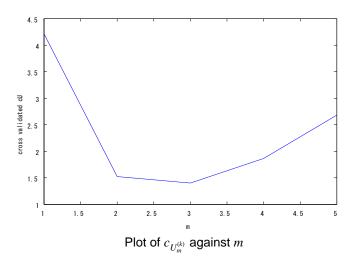
$$c_{U_{m}^{(k)}} = \frac{\overline{E}_{0}^{(k)} {\left[\overline{E}_{1}^{(k)} U_{m}^{(k)'}(w)\right]^{2}} + \overline{E}_{1}^{(k)} {\left[\overline{E}_{0}^{(k)} U_{m}^{(k)'}(w)\right]^{2}} + 2\hat{\rho} \overline{E}^{(k)} \{U_{m}^{(k)'}(w)\} \overline{E}^{(k)} \{U_{m}^{(k)'}(w)w\} - {\left[\overline{E}\{U_{m}^{(k)'}(w)w\}\right]^{2}} }{\left[\overline{E}^{(k)} \{U_{m}^{(k)'}(w)S(w) + U_{m}^{(k)'}(w)(w)\}\right]^{2}}$$

where $\overline{E}^{(k)}U'(w) = 1/(n_0^{(k)}n_1^{(k)})\sum_{i\in I_k}\sum_{j\in J_k}U'(w_{1j}-w_{0i}),$ $\overline{E}_0^{(k)}U'(w) = 1/n_0^{(k)}\sum_{i\in I_k}U'(w_{1j}-w_{0i}),$ $\overline{E}_1^{(k)}U'(w) = 1/n_1^{(k)}\sum_{j\in J_k}U'(w_{1j}-w_{0i}).$ And $n_0^{(k)}$ are numbers of elements of I_k and J_k , respectively, where

$$I_k \cap I_{k'} = \emptyset (k \neq k'), \bigcup_{k=1}^K I_k = \{1, \dots, n_0\}$$

$$J_k \cap J_{k'} = \emptyset (k \neq k'), \bigcup_{k=1}^K J_k = \{1, \dots, n_1\}.$$

Cross validation



Summary

- We propose generalized t-statistic and derive an optimal-U minimizing asymptotic variance. The lasso-type method is also considered to allow for high dimensional data analysis.
- ② In order to allow for heterogeneity for both populations, we consider generalized AUC and its approximated optimal U.
- We have confirmed that our proposed methods work well in simulation studies as well as real data analysis (not shown in details).

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Discussion 1

Fisher linear discriminant analysis

$$F(x) = \widehat{\beta}_{\mathrm{F}}^{\mathsf{T}} x + c,$$

where $\widehat{\beta}_F = (S_0 + S_1)^{-1}(\bar{x}_1 - \bar{x}_0)$ and c is a constant.

- 1 It is proposed by Ronald A. Fisher (Fisher, 1936).
- It is derived by maximizing the ratio of the variance between the two classes to the variance within the classes.
- It is still valid and useful in real data analysis (Dudoit et al., 2002; Hess et al., 2006)
- Regularized LDA (Guo et al., 2007; Witten and Tibshirani, 2011), LDA in the reproducing kernel Hilbert space (Mika et al., 1999) and LDA with Lasso (Trendafilov and Jolliffe, 2007)

Discussion 2: Breast cancer data analysis

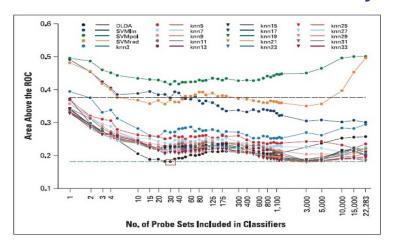


Figure 2: Mean area above the ROC curves plotted against the number of top genes included in the classifiers (Hess *et al.*, 2006)

Discussion 3: Consistency of $\widehat{\beta}_U$ to β_F

The important assumption is the one about consistency

(A)
$$E_{y}(g_{y} \mid w_{y} = a) = 0$$
 for all $a \in \mathbb{R}$, for $y = 0, 1$

For practical purpose, we can omit assumption (B)

(B)
$$\operatorname{var}_{y}(g_{y} \mid w_{y} = a) = \Sigma_{y}^{*} \text{ for all } a \in \mathbb{R}, \text{ for } y = 0, 1$$

In that case we need the optimization regarding the asymptotic variance (matrix)

$$U_{\text{opt}} = \underset{U}{\operatorname{argmin}} |\Sigma_{U}|,$$

where U can be modeled using natural cubic spline or sigmoid function with some scale parameter.

Discussion 4: open problems

- 1 How far can Fisher linear discriminant analysis be extended by $F(x) = \widehat{\beta}_{II}^{T} x$? Especially in high dimensional data analysis?
- What are conditions of probability density function $p_0(x)$ and $p_1(x)$ such that $\widehat{\beta}_U$ has consistency to β_F ?
- ullet How do we derive the optimal-U to estimate $eta_{
 m F}$?

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