Semiparametric Inferential Procedures for Comparing Multivariate ROC Curves with Interaction Terms

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Supplementary Material

S1. Multivariate normality of ϵ

Define a functional composition map $\phi(\bar{F}, \bar{G}^{-1}) = \bar{F}(\bar{G}^{-1})$. Since the inverse map $\bar{G}^{-1}$ is Hadamard-differentiable (Lema 3.9.20, Van der Vaart and Wellner, 1996), the composition map ϕ of $\bar{F}$ and $\bar{G}^{-1}$ is also Hadamard-differentiable at $(\bar{F}, \bar{G}^{-1})$ (Lemma 3.9.25, Van der Vaart and Wellner, 1996). As a consequence of the derivative Lemma 3.9.27 in Van der Vaart and Wellner (1996), if $m/n \to \lambda$, we get the following expansion:

$$\sqrt{m}\left\{\hat{\bar{F}}(\hat{\bar{G}}^{-1}(u)) - \bar{F}(\bar{G}^{-1}(u))\right\} \quad \text{converges weakly to} \quad \phi'_{\bar{F},\bar{G}^{-1}}(\mathbb{U}_{\bar{F}}, \sqrt{\lambda}\mathbb{U}_{\bar{G}^{-1}})(u),$$

which is the sum of two independent Brownian bridge processes,

$$\mathbb{U}_1(\bar{F}(\bar{G}^{-1}(u))) + \sqrt{\lambda}(\bar{F}(\bar{G}^{-1}(u)))'\mathbb{U}_2(u),$$

where $\mathbb{U}_1$ and $\mathbb{U}_2$ are $Q-$ and standard Brownian bridge processes, respectively.

The Taylor expansion of the transformed ℓth empirical ROC curve implies that $g^{-1}(\widetilde{Q}_\ell(u))$ converges to $g^{-1}(Q_\ell)(u) + 1/\sqrt{m}\mathbb{U}_{\ell 1}(Q_\ell(u))/g'[g^{-1}\{Q_\ell(u)\}] + 1/\sqrt{n}\tilde{\theta}_\ell h'(u)\mathbb{U}_{\ell 2}(u)$, uniformly in u. Denote

$$\epsilon_\ell = \frac{1}{\sqrt{m}}\frac{\mathbb{U}_{\ell 1}(Q_\ell(u_\ell))}{g'[g^{-1}\{Q_\ell(u_\ell)\}]} + \frac{1}{\sqrt{n}}\tilde{\theta}_k h'(u_\ell)\mathbb{U}_{\ell 2}(u_\ell).$$

Then the random vector $\epsilon = (\epsilon_1, ...\epsilon_K)^T$ has an asymptotically multivariate normal distribution.

S2. Proof of Theorem 1

It follows from the multivariate normality of ϵ in S1 that the finite-sample version of the ℓth empirical ROC estimator can be written as

$$\begin{aligned}\widehat{Q}_\ell(u) - Q_\ell(u) &\approx [\hat{\bar{F}}_\ell\{\bar{G}_\ell^{-1}(u)\} - Q_\ell(u))] + Q'_\ell(u)[\hat{\bar{G}}_\ell\{\bar{G}_\ell^{-1}(u) - u\}] \\ &= \frac{1}{m}\sum_r Z^X_{\ell r}(u) + \frac{1}{n}Q'_\ell(u)\sum_v Z^Y_{\ell v}(u)\end{aligned}$$

with

$$Z^X_{\ell r}(u) = I(X_{\ell r} \geq \bar{G}^{-1}_{\ell}(u)) - Q_{\ell}(u),$$

and

$$Z^Y_{\tilde{\ell} v}(u) = I(Y_{\tilde{\ell} v} \geq \bar{G}^{-1}_{\tilde{\ell}}(u)) - u.$$

The covariances of $Z^X_{\ell,r}(v)$ and $Z^Y_{\tilde{\ell},r}(t)$, with ℓth and $\tilde{\ell}$th biomarkers, are given by

$$\begin{aligned} cov(Z^X_{\ell,r}(s), Z^X_{\tilde{\ell},r}(t)) &= \iint [I(X_{\ell,r} \geq \bar{G}^{-1}_{\ell}(s)) - Q_{\ell}(s)][I(X_{\tilde{\ell},r} \geq \bar{G}^{-1}_{\tilde{\ell}}(t)) - Q_{\tilde{\ell}}(t)] \\ &\quad f(X_{\ell,r}, X_{\tilde{\ell},r}) dX_{\ell,r} dX_{\tilde{\ell},r} \\ &= \bar{F}_{\ell,\tilde{\ell}}(\bar{G}^{-1}_{\ell}(s), \bar{G}^{-1}_{\tilde{\ell}}(t)) - Q_{\ell}(s) Q_{\tilde{\ell}}(t), \end{aligned}$$

and similarly,

$$cov(Z^Y_{\ell,r}(s), Z^Y_{\tilde{\ell},r}(t)) = \bar{G}_{\ell,\tilde{\ell}}(\bar{G}^{-1}_{\ell}(s), \bar{G}^{-1}_{\tilde{\ell}}(t)) - st,$$

Thus, the result in Theorem 1 follows.

S3. Proof of Theorem 2

We give a brief proof of Theorem 2. Denote

$$J_P = \frac{m}{b-a}(M^T M)^{-1} \begin{pmatrix} I_2 & I_2 & \cdots & I_2 \\ O & I_2 & \cdots & O \\ & & \ddots & \\ O & O & \cdots & I_2 \end{pmatrix}.$$

Further calculation gives that

$$J_P = \left(\frac{b-a}{m} \begin{pmatrix} \sum_{\ell} M_{\ell}^T M_{\ell} & M_2^T M_2^* & \cdots & M_K^T M_K^* \\ M_2^{*T} M_2 & M_2^{*T} M_2^* & \cdots & O \\ \vdots & \vdots & \ddots & \vdots \\ M_K^{*T} M_K & O & \cdots & M_K^{*T} M_K^* \end{pmatrix} \right)^{-1} \begin{pmatrix} I_2 & I_2 & \cdots & I_2 \\ O & I_2 & \cdots & O \\ & & \ddots & \\ O & O & \cdots & I_2 \end{pmatrix}.$$

As $P_{\ell} \to \infty$, it is obvious that $J_P \to J$ in probablity. We let

$$\widetilde{Y} = \frac{b-a}{m} \left(\begin{pmatrix} \sum_{p=1}^{P_1} \widetilde{Y}_{1,p} \\ \sum_{p=1}^{P_1} h(u_{1,p}) \widetilde{Y}_{1,p} \end{pmatrix}^T, \cdots, \begin{pmatrix} \sum_{p=1}^{P_K} \widetilde{Y}_{K,p} \\ \sum_{p=1}^{P_K} h(u_{K,p}) \widetilde{Y}_{K,p} \end{pmatrix}^T \right)^T,$$

the LS estimator $\hat{\theta}^{LS}$ can be written as $\hat{\theta}^{LS} = J_P \widetilde{Y}$. The covariance matrix of $\widetilde{Y}$ is a $2K \times 2K$ symmetric matrix $\widetilde{\Sigma}^y = (\widetilde{\Sigma}^y_{\ell,\tilde{\ell}})$, where $\widetilde{\Sigma}^y_{\ell,\tilde{\ell}}$ is a 2×2 sub-matrix of $\widetilde{\Sigma}^y$:

$$\widetilde{\Sigma}^y_{\ell,\tilde{\ell}} = (\frac{b-a}{m})^2 cov \left(\begin{pmatrix} \sum_{p=1}^{P_{\ell}} \widetilde{Y}_{\ell,p} \\ \sum_{p=1}^{P_{\ell}} h(u_{\ell,p}) \widetilde{Y}_{\ell,p} \end{pmatrix}, \begin{pmatrix} \sum_{p=1}^{P_{\tilde{\ell}}} \widetilde{Y}_{\tilde{\ell},p} \\ \sum_{p=1}^{P_{\tilde{\ell}}} h(u_{\tilde{\ell},p}) \widetilde{Y}_{\tilde{\ell},p} \end{pmatrix} \right),$$

for $\ell, \tilde{\ell} = 1, 2, ..., K$. We let

$$
\begin{aligned}
Z_\ell(s,t) &= \frac{Q_\ell(s \wedge t) - Q_\ell(s)Q_\ell(t)}{g'[g^{-1}\{Q_\ell(s)\}]g'[g^{-1}\{Q_\ell(t)\}]}, \\
W_\ell(s,t) &= \tilde{\theta}_{\ell 1}^2 h'(s)h'(t)(s \wedge t - st),
\end{aligned}
$$

where $\ell = 1, ..., K$, and

$$
\begin{aligned}
\widetilde{Z}_{\ell,\tilde{\ell}}(s,t) &= \frac{\bar{F}_{\ell,\tilde{\ell}}(\bar{G}_\ell^{-1}(s), \bar{G}_{\tilde{\ell}}^{-1}(t)) - Q_\ell(s)Q_{\tilde{\ell}}(t)}{g'[g^{-1}\{Q_\ell(s)\}]g'[g^{-1}\{Q_{\tilde{\ell}}(t)\}]}, \\
\widetilde{W}_{\ell,\tilde{\ell}}(s,t) &= \tilde{\theta}_{\ell 1}\tilde{\theta}_{\tilde{\ell}1} h'(s)h'(t)\{\bar{G}_{\ell,\tilde{\ell}}(\bar{G}_\ell^{-1}(s), \bar{G}_{\tilde{\ell}}^{-1}(t)) - st\},
\end{aligned}
$$

for $\ell, \tilde{\ell} = 1, 2, ..., K$, and $\ell \neq \tilde{\ell}$. Here, it follows that when $\ell = \tilde{\ell}$ and $m, n \to \infty$, the elements in $m^{\frac{5}{2}}\widetilde{\Sigma}_{\ell,\ell}^y$ converge in probability to the follows:

$$
\begin{aligned}
\sigma_{\ell\ell}^{(1,1)} &= (b-a)^2 \sum_p \sum_q \{Z_\ell(u_{\ell,p}, u_{\ell,q}) + \lambda W_\ell(u_{\ell,p}, u_{\ell,q})\}, \\
\sigma_{\ell\ell}^{(1,2)} &= (b-a)^2 \sum_p \sum_q h(u_{\ell,q}) \{Z_\ell(u_{\ell,p}, u_{\ell,q}) + \lambda W_\ell(u_{\ell,p}, u_{\ell,q})\}, \\
\sigma_{\ell\ell}^{(2,2)} &= (b-a)^2 \sum_p \sum_q h(u_{\ell,p})h(u_{\ell,q}) \{Z_\ell(u_{\ell,p}, u_{\ell,q}) + \lambda W_\ell(u_{\ell,p}, u_{\ell,q})\}.
\end{aligned}
$$

When $\ell \neq \tilde{\ell}$, $\widetilde{\Sigma}_{\ell\tilde{\ell}}^y$ is calculated differently. Theorem 1 gives that the elements in $m^{5/2}\widetilde{\Sigma}_{\ell,\tilde{\ell}}^y$ converge in probability to

$$
\begin{aligned}
\sigma_{\ell,\tilde{\ell}}^{(1,1)} &= (b-a)^2 \sum_p \sum_q \left\{\widetilde{Z}_{\ell,\tilde{\ell}}(u_{\ell,p}, u_{\tilde{\ell},q}) + \lambda \widetilde{W}_{\ell,\tilde{\ell}}(u_{\ell,p}, u_{\tilde{\ell},q})\right\}, \\
\sigma_{\ell,\tilde{\ell}}^{(2,1)} &= (b-a)^2 \sum_p \sum_q h(u_{\ell,p}) \left\{\widetilde{Z}_{\ell,\tilde{\ell}}(u_{\ell,p}, u_{\tilde{\ell},q}) + \lambda \widetilde{W}_{\ell,\tilde{\ell}}(u_{\ell,p}, u_{\tilde{\ell},q})\right\}, \\
\sigma_{\ell,\tilde{\ell}}^{(1,2)} &= (b-a)^2 \sum_p \sum_q h(u_{\ell,q}) \left\{\widetilde{Z}_{\ell,\tilde{\ell}}(u_{\ell,p}, u_{\tilde{\ell},q}) + \lambda \widetilde{W}_{\ell,\tilde{\ell}}(u_{\ell,p}, u_{\tilde{\ell},q})\right\}, \\
\sigma_{\ell,\tilde{\ell}}^{(2,2)} &= (b-a)^2 \sum_p \sum_q h(u_{\ell,p})h(u_{\tilde{\ell},q}) \left\{\widetilde{Z}_{\ell,\tilde{\ell}}(u_{\ell,p}, u_{\tilde{\ell},q}) + \lambda \widetilde{W}_{\ell,\tilde{\ell}}(u_{\ell,p}, u_{\tilde{\ell},q})\right\},
\end{aligned}
$$

respectively. Thus, as $m/n \to \lambda$ when $m, n, P_\ell \to \infty$, the multivariate normal theory gives the result in Theorem 2.

S4. Proof of Theorem 3

Denote

$$
\Sigma_k = \begin{pmatrix} \Sigma_{11} & \Sigma_{1k} \\ \Sigma_{k1} & \Sigma_{kk} \end{pmatrix}.
$$

The Cauchy-Schwartz inequality (Rao, 2002, p 54) gives

$$(\hat{\theta}_1 - \theta_1)^T \Sigma_1^{-1} (\hat{\theta}_1 - \theta_1) \geq \frac{\{\widetilde{H}(\hat{\theta}_1 - \theta_1)\}^2}{\widetilde{H}\Sigma_1 \widetilde{H}^T}, \quad \text{and}$$

$$\{(\hat{\theta}_1^T, \hat{\theta}_k^T) - (\theta_1^T, \theta_k^T)\}\Sigma_k^{-1}\{(\hat{\theta}_1^T, \hat{\theta}_k^T) - (\theta_1^T, \theta_k^T)\}^T \geq \frac{[\widetilde{H}\{(\hat{\theta}_1^T, \hat{\theta}_k^T) - (\theta_1^T, \theta_k^T)\}^T]^2}{\widetilde{H}\Sigma_k \widetilde{H}^T}.$$

Therefore, we can obtain the following $(1-\alpha)100\%$ confidence band for $\widetilde{H}(\hat{\theta}_1 - \theta_1)$:

$$Pr\left\{\sup_{0<a\leq u\leq b<1} \frac{\{\widetilde{H}(\hat{\theta}_1 - \theta_k)^T\}^2}{\widetilde{H}\Sigma_1 \widetilde{H}^T} \leq \chi^2_{2,\alpha}\right\} \approx 1 - \alpha,$$

and for $\widetilde{H}\{(\hat{\theta}_1^T, \hat{\theta}_k^T) - (\theta_1^T, \theta_k^T)\}^T$, $k \geq 2$, we can obtain the following result:

$$Pr\left\{\sup_{0<a\leq u\leq b<1} \frac{[\widetilde{H}\{(\hat{\theta}_1^T, \hat{\theta}_k^T) - (\theta_1^T, \theta_k^T)\}^T]^2}{\widetilde{H}\Sigma_k \widetilde{H}^T} \leq \chi^2_{4,\alpha}\right\} \approx 1 - \alpha.$$

Then the result follows.