Bootstrap and Empirical Likelihood-based Semi-parametric Inference for the Difference between Two Partial AUCs

Xin Huang
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by

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Under the Direction of Dr. Gengsheng Qin

ABSTRACT

With new tests being developed and marketed, the comparison of the diagnostic accuracy of two continuous-scale diagnostic tests are of great importance. Comparing the partial areas under the receiver operating characteristic curves (pAUC) is an effective method to evaluate the accuracy of two diagnostic tests. In this thesis, we study the semi-parametric inference for the difference between two pAUCs. A normal approximation for the distribution of the difference between two pAUCs has been derived. The empirical likelihood ratio for the difference between two pAUCs is defined and its asymptotic distribution is shown to be a scaled chi-square distribution. Bootstrap and empirical likelihood based inferential methods for the difference are proposed. We construct five confidence intervals for the difference between two pAUCs. Simulation studies are conducted to compare the finite sample performance of these intervals. We also use a real example as an application of our recommended intervals.

INDEX WORDS: ROC, AUC, Partial AUC, Semi-parametric, Bootstrap, Empirical likelihood, Confidence interval
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This thesis is dedicated to Gengsheng Qin,
    My parents,
    and all my best friends.
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Chapter 1

INTRODUCTION

The laboratory diagnostic test is a vital component of modern medical practice in discriminating diseased subjects from healthy individuals. As far as a continuous-scale test is concerned, a person is assessed as diseased (positive) if the test value is greater than a given threshold, otherwise the subject is diagnosed as healthy (negative). The accuracy of the test can be measured by the true positive rate (sensitivity) and the true negative rate (specificity). Let $X$ and $Y$ be the results of a continuous-scale test for a non-diseased and a diseased subject, respectively. The sensitivity and specificity of the test for a given threshold $c$ are defined as follows:

$$Se = P(Y \geq c) = 1 - G(c); \quad Sp = P(X \leq c) = F(c),$$  \hspace{1cm} (1.1)

respectively, where $F$ and $G$ are the distribution functions of $X$ and $Y$, respectively. From (1.1), there is a trade-off between sensitivity and specificity as the threshold varies, which affects the accuracy of the test.

The receiver operating characteristic (ROC) curve, which is a plot of the sensitivity against 1-specificity over all possible thresholds, is a useful graphical tool for assessing the discriminatory accuracy of a diagnostic test. The ROC curve can mathematically be represented by $R(p) = 1 - G(F^{-1}(1 - p))$, where $F^{-1}(\cdot)$ is the inverse function of $F(\cdot)$. The area under the ROC curve (AUC), defined as $\delta = \int_{0}^{1} R(p)dp$,
is the most popular one-number summary index of the discriminatory accuracy. The larger the AUC is, the better the diagnostic test will be. Under some circumstance, such as a particular range of specificity or sensitivity values is relevant, Shapiro (1999) recommended a more appropriate index, partial AUC (pAUC), as an alternative measurement for the diagnostic accuracy. The pAUC over the interval \((p_0, p_1)\) of FPR is defined as

\[
\delta_{p_0, p_1} = \int_{p_0}^{p_1} R(p) dp, \text{ for } 0 \leq p_0 \leq p_1 \leq 1.
\] (1.2)

With new tests being developed and marketed, the comparison of diagnostic tests are of greatly importance (Delong et al, 1988). A common method for such comparison is based on the full or partial AUC. Metz et al. (1984) proposed a parametric approach to compare two full AUCs under a binormal model assumption. McClish (1989), Thompson et al. (1989), and Jiang et al. (1996) provided parametric normal-theory methods for comparing diagnostic tests with respect to partial AUC. However, the parametric methods, which assume parametric models for both \(X\) and \(Y\), may be sensitive to departures from the distributional assumptions and can only provided a limited range of distributional forms for the diseased and non-diseased populations.

Delong et al. (1988) suggested a non-parametric method for testing the equality of two full AUCs by using the theory on generalized U-statistic. Wieand et al. (1989) gave a class of nonparametric statistics for comparing two partial AUCs based on weighted average of sensitivities, with the asymptotic variance for the difference involved in estimation of distribution and quantile functions. Wieand et al.’s method is mathematically complicated and thus hard to apply in practice. Mossman (1995) suggested using resampling methods such as the bootstrap and jackknife to make inference about the difference of two partial AUCs. Qin et al. (2008) recently proposed
nonparametric inferential methods for the difference of two pAUCs based on bootstrap and empirical likelihood. Although the nonparametric methods are distribution-free, i.e., assuming no parametric forms for the distributions of $X$ and $Y$, they may be less efficient than its parametric counterpart in making inference for the full or partial AUC.

Semi-parametric models are statistical models between pure parametric and nonparametric models. Semi-parametric methods may inherit the good properties of both parametric and nonparametric methods. They have been used for making inference of ROC curves. For instance, Li et al. (1999) proposed a non-parametric approach to estimate the distribution of test results in non-diseased subjects, whereas assuming a parametric model for the distribution of test results in diseased subjects. Dodd and Pepe (2003) proposed a semi-parametric regression model for evaluating covariate effects on ROC curves. Qin and Zhang (2003) developed a semi-parametric approach by assuming a density ratio model for disease and disease-free densities. In diagnostic testing, it may not be reasonable to adopt two parametric models for the test results from the diseased and non-diseased subjects. A semi-parametric model assumption for the test results $X$ and $Y$ seems to be more desirable than a parametric one and the semi-parametric approach may be more efficient than the fully nonparametric one. In this thesis, we will develop new semi-parametric methods for the difference between two partial AUCs. The normal approximation, bootstrap and empirical likelihood will be used for making inference about the difference between two partial AUCs.

The thesis is organized as follows. In Chapter 2, we establish the normal approximation theory and construct normal approximation and bootstrap based confidence intervals for the difference between two partial AUCs under a semi-parametric model for the test results. In Chapter 3, we propose hybrid bootstrap and empirical likelihood based confidence intervals for the difference between two partial AUCs. In
Chapter 4, we conduct a series of simulation studies to evaluate the performance of the proposed intervals. In Chapter 5, we use a pancreatic cancer serum biomarkers example to illustrate the recommended intervals. At last, we discuss the conclusions in Chapter 6.
Chapter 2

NORMAL APPROXIMATION AND
BOOTSTRAP BASED CONFIDENCE
INTERVALS

Consider two diagnostic tests $T_1$ and $T_2$ that yield continuous measurements. Assume that both tests are performed on the same $m$ controls (non-diseased) and $n$ cases (diseased). Let $(X_{1i}, X_{2i}), i = 1, 2, \ldots, m$, be i.i.d. bivariate outcomes from the population $(X_1, X_2)$ that have an unknown joint distribution $F(x_1, x_2)$, and $(Y_{1j}, Y_{2j}), j = 1, 2, \ldots, n$, be i.i.d. bivariate outcomes from the population $(Y_1, Y_2)$ that have a joint parametric distribution $G(y_1, y_2; \theta)$, where the parameter $\theta$ is unknown and belongs to some set $\Theta \subset \mathbb{R}^r$, $r \geq 1$. Assume also $(X_{1i}, X_{2i})$’s and $(Y_{1j}, Y_{2j})$’s are mutually independent. Denote the marginal distribution functions of $F(x_1, x_2)$ and $G(y_1, y_2; \theta)$ by $F_k(x_k)$ and $G_k(y_k; \theta)$, respectively, $k = 1, 2$. The partial AUC of test $T_k$ ($k = 1, 2$) over the interval $(p_0, p_1)$, denoted by $\delta_{p_0, p_1}^{(k)}$, is

$$\delta_{p_0, p_1}^{(k)} = \int_{p_0}^{p_1} R_k(p)dp, \quad 0 \leq p_0 < p_1 \leq 1,$$

where $R_k(p) = 1 - G_k(F_k^{-1}(1 - p); \theta)$ is the ROC curve of test $T_k$ ($k=1, 2$). The difference between two partial AUCs is $\Delta_{p_0, p_1} = \delta_{p_0, p_1}^{(2)} - \delta_{p_0, p_1}^{(1)}$. We wish to make inference about $\Delta_{p_0, p_1}$ based on test results $(X_{1i}, X_{2i})$’s and $(Y_{1j}, Y_{2j})$’s.
2.1 Normal Approximation Based Confidence Interval

One of the most popular methods to construct a confidence interval for an unknown parameter is normal approximation. To construct a normal approximation based confidence interval for $\Delta_{p_0p_1}$, first, we need to obtain an appropriate estimator for $\Delta_{p_0p_1}$; and then, we have to derive the asymptotic normal distribution of this estimator.

Bamber (1975) showed that the full AUC $\delta^{(k)} = AUC_k(0, 1) = P(Y_k \geq X_k)$, which can be interpreted as the probability that in a randomly selected pair of diseased and non-diseased subjects, the $k-th$ test value of the diseased subject is higher than or equal to that of the non-diseased subject. The partial AUC where $p$ falls in $(p_0, p_1)$ can be expressed as follows:

\[
\delta_{p_0p_1}^{(k)} = AUC_k(p_0, p_1) = \int_{p_0}^{p_1} R_k(p) dp = P(Y_k \geq X_k, X_k \in (q_{k1}, q_{k0}); \theta) = E[P(Y_k \geq X_k; \theta)|X_k \in (q_{k1}, q_{k0})] = E[V_k(X_k; \theta)], \tag{2.1}
\]

where $k = 1, 2$, $q_{kl} = F_k^{-1}(1 - p_l)$, $l = 0, 1$, $F_k^{-1}$ is the inverse function of $F_k$, and

\[
V_k(X_k; \theta) = P(Y_k \geq X_k; \theta|X_k \in (q_{k1}, q_{k0})) = [1 - G_k(X_k; \theta)]I(X_k \in (q_{k1}, q_{k0})). \tag{2.2}
\]

We can use maximum likelihood method to estimate the unknown parameter $\theta$ based on test results $(Y_{1j}, Y_{2j})$'s from the population $G(y_1, y_2; \theta)$, and then obtain estimators
for $\delta_{p_0p_1}^{(k)}$ and $\Delta_{p_0p_1}$:

$$\hat{\delta}_{p_0p_1}^{(k)} = \frac{1}{m} \sum_{i=1}^{m} V_k(X_{ki}; \hat{\theta}),$$

$$\hat{\Delta}_{p_0p_1} = \hat{\delta}_{p_0p_1}^{(2)} - \hat{\delta}_{p_0p_1}^{(1)},$$

(2.3)

where $\hat{\theta}$ is the MLE of $\theta$ based on $(Y_{1j}, Y_{2j})', j = 1, \ldots, n$, $V_k(X_{ki}; \hat{\theta}) = [1 - G_k(X_{ki}; \hat{\theta})] I(X_{ki} \in (q_{k1}, q_{k0}))$, $q_{kl} = \hat{F}_k^{-1}(1 - p_l), l = 0, 1$, and $\hat{F}_k$ is the empirical distributions of $F_k$ ($k = 1, 2$).

Using Central Limit Theorem (CLT) for multivariate variables, we derive the asymptotic distribution of $\hat{\Delta}_{p_0p_1}$ in the following theorem.

**Theorem 2.1.** Assume that $0 < \lim_{m,n \to \infty} m/n \equiv \nu < \infty$ is a constant. Then

$$\sqrt{m}(\Delta_{p_0p_1} - \hat{\Delta}_{p_0p_1}) \longrightarrow N(0, \Sigma^2_{p_0p_1}),$$

where

$$\Sigma^2_{p_0p_1} = \text{Var}\left[\sum_{k=1}^{2} B_k(X_k; \theta, q_{k0}, q_{k1})\right] + \nu \left[\sum_{k=1}^{2} D_k(\theta, q_{k0}, q_{k1})\right]^T \Sigma_\theta \left[\sum_{k=1}^{2} D_k(\theta, q_{k0}, q_{k1})\right],$$

$$B_k(X_k; \theta, q_{k0}, q_{k1}) \equiv \left[1 - G_k(X_k, \theta)\right] I(X_k \in (q_{k1}, q_{k0})) - \delta_{p_0p_1}^{(k)},$$

$$D_k(\theta, q_{k0}, q_{k1}) \equiv E[g_k(X_k; \theta) I(X_k \in (q_{k1}, q_{k0}))],$$

$g_k(X_k; \theta)$ is the derivative of $G_k(X_k, \theta)$ with respect to $\theta \in \Theta \subset \mathbb{R}^r$, and $\Sigma_\theta$ is the asymptotic covariance matrix of $\sqrt{n}(\hat{\theta} - \theta)$. The asymptotic variance $\Sigma^2_{p_0p_1}$ of $\hat{\Delta}_{p_0p_1}$ in Theorem 2.1 is a function of unknown parameter $\theta$ and quantiles $q_{kl}$'s. To construct
a confidence interval for $\Delta_{p_0, p_1}$, we have to estimate $\Sigma^2_{p_0, p_1}$. Replacing $\theta$ and $q_{kl}$'s by the MLE $\hat{\theta}$ and sample quantiles $\hat{q}_{kl}$'s respectively, we obtain the following estimator for $\Sigma^2_{p_0, p_1}$:

$$
\hat{\Sigma}^2_{p_0, p_1} = (m - 1)^{-1} \sum_{i=1}^{m} ((\hat{B}_{1i} + \hat{B}_{2i}) - (\overline{\hat{B}}_1 + \overline{\hat{B}}_2))^2 +
(m/n) \left[ \sum_{k=1}^{2} \hat{D}_k(\hat{\theta}, \hat{q}_{k0}, \hat{q}_{k1}) \right]^2 
\sum_{k=1}^{2} \hat{D}_k(\hat{\theta}, \hat{q}_{k0}, \hat{q}_{k1}),
$$

where

$$
\hat{B}_{ki} = \left[ (1 - G_k(X_{ki}, \hat{\theta})) I(X_{ki} \in (\hat{q}_{k1}, \hat{q}_{k0})) - \hat{j}^{(k)}_{p_0 p_1} \right] -
\sum_{l=0}^{1} \left[ 1 - G_k(\hat{q}_{kl}; \hat{\theta}) \right] I(X_{ki} \leq \hat{q}_{kl}) - (1 - p_l),
$$

$$
\overline{\hat{B}}_k = m^{-1} \sum_{i=1}^{m} \hat{B}_{ki},
$$

$$
\hat{D}_k(\hat{\theta}, \hat{q}_{k0}, \hat{q}_{k1}) = m^{-1} \sum_{i=1}^{m} \hat{g}_k(X_{ki}; \hat{\theta}) I(X_{ki} \in (\hat{q}_{k1}, \hat{q}_{k0})],
$$

and $\hat{\Sigma}_\theta$ is a consistent estimate for $\Sigma_\theta$.

Therefore, a $(1 - \alpha)$-th normal approximation (NA) based confidence interval for $\Delta_{p_0 p_1}$ can be constructed as follows:

$$
\hat{\Delta}_{p_0 p_1} \pm z_{1-\frac{\alpha}{2}} \cdot \frac{\hat{\Sigma}^2_{p_0, p_1}}{\sqrt{m}},
$$

where $z_{1-\frac{\alpha}{2}}$ is the $(1 - \alpha/2)$-th quantile of the standard normal distribution.

The estimate for the asymptotic variance $\Sigma^2_{p_0 p_1}$ is a plug-in estimate by using the MLE $\hat{\theta}$ and sample quantiles. It may be an unstable estimate for the asymptotic variance. In fact, our simulation studies in this thesis indicate that the NA-based intervals have longer interval length and are too conservative than its competitors.
such as the bootstrap and EL-based intervals introduced in the following chapters.

2.2 Bootstrap Based Confidence Interval

When the asymptotic variance of an estimator is unknown and of a complex form, bootstrap method is usually used to estimate the asymptotic variance. In this section, we apply bootstrap method to estimate the asymptotic variance of $\hat{\Delta}_{p_0p_1}$ and then construct confidence intervals for the difference between two pAUCs.

We draw a bootstrap resample $\{X_{k_1}^*, \ldots, X_{km}^*\}$ with replacement from $\{X_{k_1}, \ldots, X_{km}\}$, and another bootstrap resample $\{Y_{k_1}^*, \ldots, Y_{kn}^*\}$ with replacement from $\{Y_{k_1}, \ldots, Y_{kn}\}$. Then calculate a bootstrap copy of $\hat{\delta}(k)_{p_0p_1}$:

$$\hat{\delta}^{(k)*}_{p_0p_1} = \frac{1}{m} \sum_{i=1}^{m} V_k(X_{ki}^*; \theta^*),$$

where

$$V_k(X_{ki}^*; \theta^*) = [1 - G_k(X_{ki}^*; \theta^*)]I(X_{ki}^* \in (q_{k1}^*, q_{k0}^*)),$$

$\theta^*$ is the bootstrap version of $\hat{\theta}$, and $q_{kl} = F_{k}^{-1}(1 - p_l)$ is the $(1 - p_l)$-th sample quantile of $\{X_{k1}^*, \ldots, X_{km}^*\}$, $k = 1, 2$, $l = 0, 1$. Then the bootstrap estimate for the difference between two pAUCs can be calculated as:

$$\Delta^*_{p_0p_1} = \hat{\delta}^{(2)*}_{p_0p_1} - \hat{\delta}^{(1)*}_{p_0p_1}.$$

After $B$ repetitions of above processes, $B$ bootstrap copies of $\hat{\delta}^{(k)}_{p_0p_1}$ and $\hat{\Delta}_{p_0p_1}$ are obtained:

$$\{\hat{\delta}^{(k)*}_{p_0p_1,b} : b = 1, 2, \ldots, B\}, \quad k = 1, 2,$$

$$\{\Delta^*_{p_0p_1,b} = \hat{\delta}^{(2)*}_{p_0p_1,b} - \hat{\delta}^{(1)*}_{p_0p_1,b} : b = 1, 2, \ldots, B\}.$$
The bootstrap estimate for the variance of $\hat{\Delta}_{p_0p_1}$ is:

$$\Sigma_{p_0p_1}^* = \frac{1}{B - 1} \sum_{b=1}^{B} (\Delta_{p_0p_1,b}^* - \bar{\Delta}_{p_0p_1}^*)^2,$$

where $\bar{\Delta}_{p_0p_1}^* = \frac{1}{B} \sum_{b=1}^{B} \Delta_{p_0p_1,b}^*$.

Two bootstrap based normal approximation confidence intervals are defined as follows:

1. BI interval:

$$\hat{\Delta}_{p_0p_1} \pm z_{1 - \frac{\alpha}{2}} \cdot \Sigma_{p_0p_1}^*,$$

2. BII interval:

$$\bar{\Delta}_{p_0p_1}^* \pm z_{1 - \frac{\alpha}{2}} \cdot \Sigma_{p_0p_1}^*.$$
Chapter 3

EMPIRICAL LIKELIHOOD BASED
CONFIDENCE INTERVALS

Another popular nonparametric method to obtain confidence intervals for the mean is the empirical likelihood (EL) method introduced by Owen (1990). The EL method has several advantages over the other nonparametric methods (Owen, 2001). For example, it has better small performance than normal approximation based approaches; there is no need for a pivot due to its internal studentization. Qin et al (2006) developed an EL approach for the inference on the full AUC. In this chapter, we extend the EL approach to the semi-parametric models for the inference about the difference between two partial AUCs.

From (2.2) and (2.3), we can have:

$$\Delta_{p_0p_1} = \delta_{p_0p_1}^{(2)} - \delta_{p_0p_1}^{(1)} = E[V_2(X_2;\theta) - V_1(X_1;\theta)],$$

where $V_k(X_k;\theta) = [1 - G_k(X_k;\theta)]I(X_k \in (q_{kl}, q_{k0}))$, $k = 1, 2$, and $q_{kl} = F_k^{-1}(1 - p_l)$, $l = 0, 1$.

Based on the relationship of the difference between two pAUCs and the restricted placement values $V_2(X_2;\theta)$ and $V_1(X_1;\theta)$, we can define the profile EL for $\Delta_{p_0p_1}$ as
follows:

\[ L(\Delta_{p0p1}) = \sup \left\{ \prod_{k=1,2} \prod_{i=1}^{m} P_{ki} : \sum_{i=1}^{m} P_{ki} = 1, P_{ki} \geq 0, i = 1, \cdots, m, \right\} \]

\[ \sum_{i=1}^{m} P_{ki}(V_k(X_{ki}; \hat{\theta}) - \delta_{p0p1}^{(k)}) = 0, \quad k = 1, 2, \]

\[ \sum_{i=1}^{m} P_{2i}V_2(X_{2i}; \hat{\theta}) - \sum_{i=1}^{m} P_{1i}V_1(X_{1i}; \hat{\theta}) = \Delta_{p0p1}. \]

Then, by the Lagrange multiplier, we obtain the following empirical log-likelihood ratio (ELR) for \( \Delta_{p0p1} \):

\[ l(\Delta_{p0p1}) = 2\left[ \sum_{i=1}^{m} \log\left(1 - 2\lambda(V_1(X_{1i}; \hat{\theta}) - \delta_{p0p1}^{(1)})\right) \right. + \]

\[ \left. \sum_{i=1}^{m} \log\left(1 + 2\lambda(V_2(X_{2i}; \hat{\theta}) - \delta_{p0p1}^{(2)})\right) \right], \quad (3.1) \]

where \( \lambda, \delta_{p0p1}^{(k)} \) satisfy the following equations:

\[ \frac{1}{m} \sum_{i=1}^{m} \frac{V_1(X_{1i}; \hat{\theta}) - \delta_{p0p1}^{(1)}}{1 - 2\lambda(V_1(X_{1i}; \hat{\theta}) - \delta_{p0p1}^{(1)})} = 0, \quad (3.2) \]

\[ \frac{1}{m} \sum_{i=1}^{m} \frac{V_2(X_{2i}; \hat{\theta}) - \delta_{p0p1}^{(2)}}{1 + 2\lambda(V_2(X_{2i}; \hat{\theta}) - \delta_{p0p1}^{(2)})} = 0, \quad (3.3) \]

\[ \frac{1}{m} \sum_{i=1}^{m} \frac{V_2(X_{2i}; \hat{\theta})}{1 + 2\lambda(V_2(X_{2i}; \hat{\theta}) - \delta_{p0p1}^{(2)})} = \Delta_{p0p1}. \quad (3.4) \]

The empirical log-likelihood ratio \( l(\Delta_{p0p1}) \) for the difference between two pAUCs is a sum of dependent variables. Hence, we can not directly apply the standard EL theory to derive its asymptotic distribution. However, in the following theorem, we show that \( l(\Delta_{p0p1}) \) follows a scaled \( \chi^2 \) distribution.
**Theorem 3.1.** If $\Delta_{p0p1}$ is the true value of the difference between two partial AUC’s, $\lim \frac{m}{n} = \nu > 0$, then

$$r(\Delta_{p0p1})l(\Delta_{p0p1}) \longrightarrow \chi^2_1,$$

where

$$r(\Delta_{p0p1}) = \frac{(S_{p0p1}^{(1)} + S_{p0p1}^{(2)})}{\sum_{p0p1}^2},$$

$$S_{p0p1}^{(k)2} = Var[(1 - G_k(X_k; \theta))I(X_k \in (q_{k1}, q_{k0})], \ k = 1, 2.$$

Notice that the scale constant $r(\Delta_{p0p1})$ is a function of unknown parameter $\theta$ and quantiles $q_{kl}$’s. In order to obtain a good estimate for $r(\Delta_{p0p1})$ and avoid possibly poor empirical variance estimate, we can consider using the bootstrap method defined in Chapter 2 to estimate the variances. We propose two hybrid bootstrap and empirical likelihood (HBEL) confidence intervals for the difference between two pAUCs as follows:

1. The first $(1 - \alpha)$ level semi-parametric HBEL (HBELI) confidence interval for $\Delta_{p0p1}$ is defined by

$$\{\Delta : \hat{r}(\Delta_{p0p1})l(\Delta) \leq \chi^2_1(1 - \alpha)\},$$

where

$$\hat{r}(\Delta_{p0p1}) = \frac{\hat{S}_{p0p1}^{(1)} + \hat{S}_{p0p1}^{(2)}}{\sum_{p0p1}^2},$$

$$\hat{S}_{p0p1}^{(k)2} = \frac{1}{m} \sum_{i=1}^m [V_k(X_{ki}; \hat{\theta}) - \hat{\delta}_{p0p1}^{(k)}]^2, \ k = 1, 2,$$

and $\chi^2_1(1 - \alpha)$ is the $(1 - \alpha)$-quantile of $\chi^2_1$. 


This interval can be found by solving equations (3.2), (3.3), (3.4) and

\[ \hat{r}(\Delta_{p_{0p1}})l(\Delta) - \chi^2_1(1 - \alpha) = 0 \quad (3.5) \]

for the unknown \( \lambda, \delta^{(k)}_{p_{0p1}} (k=1,2) \) and \( \Delta_{p_{0p1}} \). There will be two solutions for \( \Delta_{p_{0p1}} \): the smaller one is lower bound of the HBELI interval while the bigger one is upper bound of the interval.

2. The second \((1 - \alpha)\) level semi-parametric HBEL (HBELII) confidence interval for \( \Delta_{p_{0p1}} \) is given by

\[ \{ \Delta : r^*(\Delta_{p_{0p1}})l(\Delta) \leq \chi^2_1(1 - \alpha) \} \]

where

\[ r^*(\Delta_{p_{0p1}}) = \frac{\bar{S}^{(1)}_{p_{0p1}} + \bar{S}^{(2)}_{p_{0p1}}}{\sum_{p_{0p1}}^{*2}}, \]

\[ \bar{S}^{(k)}_{p_{0p1}} = \frac{1}{B} \sum_{i=1}^{B} S^{(k)2}_{p_{0p1},b}, \quad k = 1, 2, \]

\[ S^{(k)2}_{p_{0p1},b} = \frac{1}{m} \sum_{i=1}^{m} [V_k(X_{ki,b}; \hat{\theta}_b) - \delta^{(k)}_{p_{0p1},b}]^2, \quad b = 1, \ldots, B, \]

\( \theta^*_b \) is the \( \hat{\theta} \) and \( \delta^{(k)}_{p_{0p1},b} \) is the \( \hat{\delta}^{(k)}_{p_{0p1}} \) based on the b-th bootstrap resample from \( \{X_1, \ldots, X_m\} \).

Both HBELI and HBELII are approximate confidence intervals for the difference between two pAUCs with coverage probability \( 1 - \alpha \).
In this chapter, we report series of simulation results for evaluating coverage accuracy and interval length of the NA, BI, BII, HBELI, HBELII intervals proposed in chapter 2 and chapter 3. For each study, we generate 1000 random samples of size $m$ from $F$ for test responses of non-diseased subjects and another 1000 independent random samples of size $n$ from $G$ for test responses of diseased subjects. In these studies, three interested intervals of FPR under the ROC curves are chosen: $(p_0, p_1) = (0, 0.4), (0, 0.7), (0.05, 0.5)$; meanwhile the difference between two pAUCs, $\Delta_{p_0p_1}$, is chosen to be 0 and 0.2, respectively. For computational simplicity, we randomly pre-selected specific pAUC for the corresponding ROC curve. Under this simulation setting, the parameters in $F$ and $G$ can be obtained by solving the following equations:

$$
\delta_{p_0, p_1}^{(k)} = \int_{p_0}^{p_1} R_k(p) \, dp \quad \text{with} \quad R_k(p) = 1 - G_k(F_k^{-1}(1 - p); \theta), \quad k = 1, 2. \tag{4.1}
$$

In the first simulation study, $F$ is chosen to be a two-dimensional normal distribution with mean $\begin{bmatrix} 0 \\ 0 \end{bmatrix}$, and covariance $\begin{bmatrix} 1 & r \\ r & 1 \end{bmatrix}$, where $r$ is a pre-selected correlation coefficient. $G$ is chosen to be another two-dimensional normal distribution with mean $\begin{bmatrix} \mu_1 \\ \mu_2 \end{bmatrix}$, and covariance $\begin{bmatrix} 2^2 & r \\ r & 2^2 \end{bmatrix}$, where $\mu_1$ and $\mu_2$ are the solutions to (4.1).

When constructing the normal approximation confidence interval for $\Delta_{p_0p_1}$, ac-
According to Theorem 2.1, we have to derive the asymptotic covariance matrix of \( \sqrt{n}(\hat{\theta} - \theta) \). Shao (2003) showed that, for normal distribution,

\[
\sqrt{n}(\hat{\theta} - \theta) \overset{d}{\sim} N_4(0, \Sigma_\theta^2),
\]

where \( \Sigma_\theta^2 \) can be derived from the Fisher information matrix.

In the second simulation study, the distributions \( F(x_1, x_2) \) and \( G(y_1, y_2; \theta) \) are chosen to be different bivariate exponential distributions that have exponential distributions as their marginal distributions. Marshall et al. (1967) proposed a method to generate bivariate exponential distributions. Depending on the possible correlation between the test results from two diagnostic tests, we use two different procedures to generate the random samples of test responses. First, we choose the correlation as zero. We generate two independent samples from standard exponential distributions, i.e., \( X_1 \sim exp(1) \), \( X_2 \sim exp(1) \); and two independent samples from exponential distributions with rates \( \lambda_1 \) and \( \lambda_2 \) for \( G(y_1, y_2; \theta) \) with \( \theta = (\lambda_1, \lambda_2) \), i.e., \( Y_1 \sim exp(\lambda_1) \), \( Y_2 \sim exp(\lambda_2) \), where the rates \( \lambda_1 \) and \( \lambda_2 \) are solutions to equation (4.1). Second, to generate bivariate exponential random samples with positive correlation, we first generate random samples \( U_{ti} \sim exp(0.5), i = 1, \ldots, m, \) for \( t = 1, 2, 3 \), \( W_{kj} \sim exp(l_k), j = 1, \ldots, n, k = 1, 2, \) where the rates \( l_k = \lambda_k - 0.02 \), and \( \lambda_k \)’s are solutions to (4.1); and \( W_{3j} \sim exp(0.02), j = 1, \ldots, n \). Thus the simulated test responses for the non-diseased subjects are \( X_{ki} = \min(U_{ki}, U_{3i}), k = 1, 2, i = 1, 2, \ldots, m \), which are random samples from two standard exponential distributions with positive correlation; and those for diseased subjects are \( Y_{kj} = \min(W_{kj}, W_{3j}), k = 1, 2, j = 1, 2, \ldots, n \), which are random samples from two exponential distributions with positive correlation and rates \( l_k + 0.02 = \lambda_k \), respectively.

In the bootstrap step of these simulation studies, we draw \( B = 150 \) bootstrap
resamples with replacement from our generated samples. Various 95% confidence intervals for $\Delta_{p_0,p_1}$ are constructed for different combinations of sample size $(m,n)$. The coverage probability and average length of these confidence intervals for $\Delta_{p_0,p_1}$ are shown in Tables 1-8.

From Tables 1-8, we can observe that the most of NA-based intervals are the most conservative intervals and have the longest interval length. The HBELI, HBELII, BI and BII intervals have similar coverage probabilities, but the HBELI and HBELII have slightly shorter interval length. When the sample size is small, all intervals overcover $\Delta_{p_0,p_1}$, but the HBELI and HBELII intervals perform slightly better than the others.
Chapter 5

PANCREATIC CANCER SERUM BIOMARKERS EXAMPLE

There are two continuous positive scale serum biomarkers used to diagnose a patient who has pancreatic cancer (Wieand et al., 1989): CA-125, a cancer antigen, and CA-19-9, a carbohydrate antigen. The dataset comes from a case-control study at Mayo Clinic which include 90 patients with pancreatic cancer and 51 subjects with pancreatitis. This dataset have been used by various statisticians for the purpose of diagnostic tests. It has been first used by Wieand et al. (1989) to illustrate the non-parametric method for comparing the accuracy of two diagnostic tests. Molodimanovitch et al. (2006) examined the normality of this data set. They pointed out that for diseased and non-diseased subjects, both biomarkers are not normally distributed. They suggested to apply a Box-Cox type power transformation to the data to reduce the skewness. They shown that, applying the Box-Cox transformation, the CA-125 values be taken to the power -0.424 while CA-19-9 values to the power -0.015, the data is more normal like.

After the Box-Cox transformation, we apply our bootstrap and empirical likelihood-based semi-parametric inference method to test the difference between the pAUCs for biomarkers CA-125 and CA-19-9. Wieand et al. (1989) plotted the sensitivity against specificity, and demonstrated that when the specificity falls in (0.8,
1), the difference of the curves is obvious. Since the false positive rate (FPR) equals 1-specificity, we choose to compare the partial areas under the ROC curves over the interval (0, 0.2) of FPR.

Table 9 shows the 95% confidence intervals for the difference between pAUCs on (0, 0.2) for biomarkers CA-125 and CA-19-9. All the four confidence intervals, BI, BII, HBELI and HBELII, demonstrate that CA-19-9 have larger pAUC than CA-125 over (0, 0.2). If we want the specificity of the biomarkers to be at least 80%, CA-19-9 will have better diagnostic accuracy than CA-125 in detecting pancreatic cancer. Wieand et al. (1989) also reached the same conclusion based on their non-parametric method.
Chapter 6

DISCUSSION

With new tests being developed and marketed, comparing the accuracy of two continuous-scale diagnostic tests are of great importance. Comparing the partial areas under the ROC curves is an effective way to evaluate the accuracy of two diagnostic tests. In medical diagnostic studies, it may not be reasonable to adopt two parametric models for the test results from the diseased and non-diseased subjects. The semi-parametric models may be an useful alternative. In this thesis, we have studied the semi-parametric inferences for the difference between two partial AUCs. We have derived a normal approximation (NA) based confidence interval, two bootstrap (BI and BII) based confidence intervals and two hybrid bootstrap and empirical likelihood (HBELI and HBELII) based confidence intervals. The simulation studies shows that the bootstrap and empirical likelihood based intervals are superior to the NA-based intervals. The Pancreatic Cancer Serum Biomarkers example also suggests that the hybrid bootstrap and empirical likelihood based confidence intervals have better interval estimates.
REFERENCES


**APPENDIX A: SIMULATION TABLES**

Table I: Level of 95 per cent confidence interval for $\Delta_{p_0 p_1} = 0$. Bivariate normal distribution with $\rho = 0$.

<table>
<thead>
<tr>
<th>True $\Delta_{p_0 p_1}$</th>
<th>Sample size $(m,n)$</th>
<th>Method</th>
<th>$(p_0, p_1) = (0.0-0.4)$</th>
<th>$(p_0, p_1) = (0.0-0.7)$</th>
<th>$(p_0, p_1) = (0.05-0.5)$</th>
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<td></td>
<td></td>
<td>Coverage probability</td>
<td>Length</td>
<td>Coverage probability</td>
</tr>
<tr>
<td>0 (20, 20)</td>
<td>HBELI</td>
<td>0.956</td>
<td>0.260</td>
<td>0.973</td>
<td>0.387</td>
</tr>
<tr>
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<td>0.973</td>
<td>0.387</td>
</tr>
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</tr>
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<td>0.958</td>
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Table 2: Level of 95 per cent confidence interval for $\Delta_{p_0p_1} = 0.2$. Bivariate normal distribution with $\rho = 0$.

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<th>$(p_0, p_1) = (0.0-0.7)$</th>
<th>$(p_0, p_1) = (0.05-0.5)$</th>
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<td>Length</td>
<td>Coverage probability</td>
<td>Length</td>
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<tr>
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<tr>
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<tr>
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<td>0.969</td>
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<tr>
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<tr>
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<td>0.134</td>
<td>0.954</td>
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<td>0.180</td>
<td>0.950</td>
</tr>
<tr>
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<tr>
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Table 3: Level of 95 per cent confidence interval for $\Delta_{p_0p_1} = 0$. Bivariate normal distribution with $\rho = 0.3$.

<table>
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<th>$(p_0, p_1) = (0.0, 0.7)$</th>
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<td>Length</td>
<td>Coverage probability</td>
</tr>
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Table 4: Level of 95 per cent confidence interval for $\Delta_{p_0 p_1} = 0.2$. Bivariate normal distribution with $\rho = 0.3$.

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<th>$(p_0, p_1) =$ (0-0.7)</th>
<th>$(p_0, p_1) =$ (0.05-0.5)</th>
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Table 5: Level of 95 per cent confidence interval for $\Delta_{p_0p_1} = 0$. Bivariate exponential distribution with $\rho = 0$.

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Table 6: Level of 95 per cent confidence interval for $\Delta_{p_0p_1} = 0.2$. Bivariate exponential distribution with $\rho = 0$.

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<th>True $\Delta_{p_0p_1}$</th>
<th>Sample size (m,n)</th>
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<th>$(P_0, P_1)=(0.0-0.7)$</th>
<th>$(P_0, P_1)=(0.05-0.5)$</th>
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28
Table 7: Level of 95 per cent confidence interval for $\Delta_{p_0 p_1} = 0$. Bivariate exponential distribution with $\rho > 0$.

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<th>$\left( p_0, p_1 \right) = (0.05 - 0.5)$</th>
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<td></td>
<td>HBELII</td>
<td>0.944</td>
<td>0.094</td>
<td>0.944</td>
<td>0.111</td>
</tr>
<tr>
<td></td>
<td>BI</td>
<td>0.946</td>
<td>0.095</td>
<td>0.944</td>
<td>0.111</td>
</tr>
<tr>
<td></td>
<td>BII</td>
<td>0.941</td>
<td>0.095</td>
<td>0.943</td>
<td>0.112</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>0.988</td>
<td>0.12</td>
<td>1</td>
<td>0.283</td>
</tr>
</tbody>
</table>
Table 8: Level of 95 per cent confidence interval for $\Delta_{p_0p_1} = 0.2$. Bivariate exponential distribution with $\rho > 0$.

<table>
<thead>
<tr>
<th>True $\Delta_{p_0p_1}$</th>
<th>Sample size (m,n)</th>
<th>Method</th>
<th>( $P_0$, $P_1$)=(0-0.4)</th>
<th>( $P_0$, $P_1$)=(0-0.7)</th>
<th>( $P_0$, $P_1$)=(0.05-0.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Coverage probability</td>
<td>Length</td>
<td>Coverage probability</td>
</tr>
<tr>
<td>0.2</td>
<td>(50, 50)</td>
<td>HBELI</td>
<td>0.964</td>
<td>0.124</td>
<td>0.937</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBELII</td>
<td>0.964</td>
<td>0.125</td>
<td>0.937</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BI</td>
<td>0.964</td>
<td>0.125</td>
<td>0.959</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BII</td>
<td>0.974</td>
<td>0.125</td>
<td>0.961</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>1</td>
<td>0.249</td>
<td>1</td>
</tr>
<tr>
<td>(80, 80)</td>
<td></td>
<td>HBELI</td>
<td>0.970</td>
<td>0.093</td>
<td>0.951</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBELII</td>
<td>0.971</td>
<td>0.094</td>
<td>0.949</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BI</td>
<td>0.970</td>
<td>0.094</td>
<td>0.964</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BII</td>
<td>0.975</td>
<td>0.094</td>
<td>0.967</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>1</td>
<td>0.191</td>
<td>1</td>
</tr>
<tr>
<td>(150, 150)</td>
<td></td>
<td>HBELI</td>
<td>0.945</td>
<td>0.065</td>
<td>0.939</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBELII</td>
<td>0.946</td>
<td>0.065</td>
<td>0.939</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BI</td>
<td>0.944</td>
<td>0.065</td>
<td>0.946</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BII</td>
<td>0.948</td>
<td>0.065</td>
<td>0.945</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>1</td>
<td>0.136</td>
<td>1</td>
</tr>
<tr>
<td>(80, 50)</td>
<td></td>
<td>HBELI</td>
<td>0.965</td>
<td>0.103</td>
<td>0.934</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBELII</td>
<td>0.965</td>
<td>0.103</td>
<td>0.933</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BI</td>
<td>0.965</td>
<td>0.103</td>
<td>0.952</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BII</td>
<td>0.969</td>
<td>0.103</td>
<td>0.955</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>1</td>
<td>0.237</td>
<td>1</td>
</tr>
<tr>
<td>(150, 80)</td>
<td></td>
<td>HBELI</td>
<td>0.953</td>
<td>0.076</td>
<td>0.968</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBELII</td>
<td>0.953</td>
<td>0.076</td>
<td>0.968</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BI</td>
<td>0.953</td>
<td>0.076</td>
<td>0.967</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BII</td>
<td>0.957</td>
<td>0.076</td>
<td>0.965</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>1</td>
<td>0.183</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 9: Pancreatic Cancer Serum Biomarkers Example
Level of 95 percent confidence interval for $\Delta_{(0,0.2)}$

<table>
<thead>
<tr>
<th>Method</th>
<th>Lower-Limit</th>
<th>Upper-Limit</th>
<th>Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBELI</td>
<td>-0.079</td>
<td>-0.004</td>
<td>0.075</td>
</tr>
<tr>
<td>HBELII</td>
<td>-0.080</td>
<td>-0.003</td>
<td>0.077</td>
</tr>
<tr>
<td>BI</td>
<td>-0.079</td>
<td>-0.002</td>
<td>0.077</td>
</tr>
<tr>
<td>BII</td>
<td>-0.084</td>
<td>-0.008</td>
<td>0.076</td>
</tr>
</tbody>
</table>
### Code for normal simulation studies ###

#### part 1: Functions

- **Function R(p)**
  
  ```r
  Rp<-function(p, muy, stdd) 1-pnorm(qnorm(1-p),muy, stdd)
  ```

- **solveNonlinear**
  
  ```r
  solveNonlinear <- function(f, y0, x, ...){
    # solve f(x) = y0
    # x is vector of initial guesses, same length as y0
    # ... are additional arguments to nlmin (not to f)
    g <- function(x, y0, f) sum((f(x) - y0)^2)
    g$s0 <- y0  # set g's default value for y0
    g$sf <- f   # set g's default value for f
    nlmin(g, x, max.fcal = 10000, max.iter = 10000, ...)
  }
  ```

- **calculate x[1]=y1.mean x[2]=y2.mean**
  
  ```r
  mu <- function(x){
    c( integrate(Rp, muy=x[1], stdd=y1.sd, lower=p0, upper = p1)$integral,
        integrate(Rp, muy=x[2], stdd=y2.sd, lower=p0, upper = p1)$integral)
  }
  ```

- **Function for S_{p_0p_1}^2**
  
  ```r
  my.mean <- function(vv) mean((vv-mean(vv))^2)
  g2 <- function(x) c(
    mean((V.hat[,1]-x[1])/(1-2*x[3]*(V.hat[,1]-x[1]))),
    mean((V.hat[,2]/(1+2*x[3]*(V.hat[,2]-x[2]))) - mean(V.hat[,1]/(1-2*x[3]*(V.hat[,1]-x[1]))) - x[4],
    mean((V.hat[,2]/(1+2*x[3]*(V.hat[,2]-x[2]))) - mean(V.hat[,1]/(1-2*x[3]*(V.hat[,1]-x[1]))) - x[4],
    # why we need the absolute value for the LOG function??
    r.deltap0p1.hat*(2*(sum( log(abs(1-2*x[3]*(V.hat[,1]-x[1]))) + sum( log(abs(1+2*x[3]*(V.hat[,2]-x[2]))) ) ) ) ) - CritVal)
  ```

- **Function for deltamp0p1**
  
  ```r
  deltamp0p1 <- function(X1X2, Y1Y2, p0, p1, m){
    # Calculate X Quantile of 1-pi (i=0,1) for p.hat
    q0.1.hat<-quantile(X1X2[,1],1-p0);
    q0.2.hat<-quantile(X1X2[,2],1-p0);
    q1.1.hat<-quantile(X1X2[,1],p1);
    q1.2.hat<-quantile(X1X2[,2],p1);
    # Calculate V(kj).hat & deltamp0p1
    V.hat<-matrix(n, m, 2)
    Y1mean <- mean(Y1Y2[,1])
    Y1sd <- stdev(Y1Y2[,1])
    Y2mean <- mean(Y1Y2[,2])
    Y2sd <- stdev(Y1Y2[,2])
    for (i in 1 : m){
      V.hat[,1]<-(1-pnorm(X1X2[,1], mean=Y1mean, sd=Y1sd))*(q1.1.hat <= X1X2[,1])*(X1X2[,1]<=q0.1.hat)
    }
  }
  ```

- **Function for deltAUC**
  
  ```r
  deltAUC <- function(X1X2, Y1Y2, p0, p1, m){
    # Calculate X Quantile of 1-pi (i=0,1) for q.hat
    q0.1.hat<-quantile(X1X2[,1],1-p0);
    q0.2.hat<-quantile(X1X2[,2],1-p0);
    q1.1.hat<-quantile(X1X2[,1],p1);
    q1.2.hat<-quantile(X1X2[,2],p1);
    # Calculate V(kj).hat & delta.pAUC.hat
    V.hat<-matrix(n, m, 2)
    Y1mean <- mean(Y1Y2[,1])
    Y1sd <- stdev(Y1Y2[,1])
    Y2mean <- mean(Y1Y2[,2])
    Y2sd <- stdev(Y1Y2[,2])
    ```
\[ V.hat[i,2] <= \{1-\text{pnorm}(X1X2[i,2], \text{mean}=Y2mean, sd=Y2sd)\} \times (q1.2.hat <= X1X2[i,2]) \times (X1X2[i,2] <= q0.2.hat) \]

\[
delta.pAUC.hat <= \text{mean}(V.hat[,2]) - \text{mean}(V.hat[,1])
\]

\[
r.deltap0p1.hat <= (\text{my.mean}(V.hat[,1]) + \text{my.mean}(V.hat[,2]))/(m \times Vstar)
\]

\[
\text{list}(\delta.pAUC.hat, r.deltap0p1.hat, V.hat)
\]

### bootstrap function ###

\[
\text{booth.trap} \leftarrow \text{function}(B, X1X2, Y1Y2, m, n, p0, p1)\{
\]

\[
delta.pAUC < 0;
\]

\[
sigma \leftarrow \text{matrix}(B, 2)
\]

\[
\text{for } (b \text{ in } 1:B) \{ \\
\]

\[
\text{sampleX.index} \leftarrow \text{sample}(\text{size} = m, \text{replace} = T, \text{prob} = \text{NULL}, n = m) \\
X1B \leftarrow X1X2[\text{sampleX.index},1] \\
X2B \leftarrow X1X2[\text{sampleX.index},2]
\]

\[
\text{sampleY.index} \leftarrow \text{sample}(\text{size} = n, \text{replace} = T, \text{prob} = \text{NULL}, n = n) \\
Y1B \leftarrow Y1Y2[\text{sampleY.index},1] \\
Y2B \leftarrow Y1Y2[\text{sampleY.index},2]
\]

\[
\text{Y1Bmean} \leftarrow \text{mean}(Y1B) \\
\text{Y1Bsd} \leftarrow \text{stdev}(Y1B) \\
\text{Y2Bmean} \leftarrow \text{mean}(Y2B) \\
\text{Y2Bsd} \leftarrow \text{stdev}(Y2B)
\]

\[
q0B.1.hat \leftarrow \text{quantile}(X1B, \{1-p0\}) \# \text{hat}q0; \text{hat}q1: \text{sample quantiles of } F \\
q0B.2.hat \leftarrow \text{quantile}(X2B, \{1-p0\}) \# \text{hat}q0; \text{hat}q1: \text{sample quantiles of } F \\
q1B.1.hat \leftarrow \text{quantile}(X1B, \{1-p1\}) \\
q1B.2.hat \leftarrow \text{quantile}(X2B, \{1-p1\}) \\
VB \leftarrow \text{matrix}(m, 2)
\]

\[
\text{for } (i \text{ in } 1:m) \{ \\
VB[i,1] \leftarrow (1-\text{pnorm}(X1B[i], \text{mean}=Y1Bmean, sd=Y1Bsd)) \times (q1B.1.hat <= X1B[i]) \times (X1B[i] <= q0B.1.hat) \\
VB[i,2] \leftarrow (1-\text{pnorm}(X2B[i], \text{mean}=Y2Bmean, sd=Y2Bsd)) \times (q1B.2.hat <= X2B[i]) \times (X2B[i] <= q0B.2.hat) \\
\}
\]

\[
sigma[b,1] \leftarrow \text{my.mean}(VB[,1]) \\
sigma[b,2] \leftarrow \text{my.mean}(VB[,2]) \\
\text{delta.pAUC}[b] \leftarrow \text{mean}(VB[,2]) - \text{mean}(VB[,1])
\]

\[
\text{list}(\delta.pAUC, sigma)
\}
\]

### Part2: initial value ###

\[
\text{iter} <= 100 \\
B <= 150 \\
rho <= 0 \\
# rho <= 0.3 \\
m <= 50; n <= 20; \\
y1.sd <= 2; y2.sd <= 2; \\
i12 <= 1; \\
levelc <= 0.95 \\
# levelc <= 0.90 \\
\text{CritVal} <= \text{qchisq}(\text{levelc}, 1) \\
Z <= \text{qnorm}(1-(1-\text{levelc})/2) \\
y1.mean <= y2.mean <= 0 \\
p0 <= 0; pl <= 0.4 \\
pAUC1 <= 0.17 \\
pAUC2 <= 0.37
deltapAUC.true <- pAUC2 - pAUC1
S <- solveNonlinear(mu, c(pAUC1, pAUC2), c(0.1, 0.1))
y1.mean <- S$x[1]
y2.mean <- S$x[2]

############################ End part2 ##################################

############################ Part3: Loop ################################
CovCount <- c(0, 0, 0, 0)
CIL <- c(0, 0, 0)

while (i12 <= iter) {
    # generate non-diseased population F(X1, X2)
    # the sample from 2-dimensinal multinormal distribution with mean 0 and std=1
    X1X2 <- rmvnorm(m, mean = c(0, 0), cov = matrix(c(1, rho, rho, 1), 2))

    # generate diseased population G(Y1, Y2)
    # the sample from 2-dimensinal multinormal distribution with mean
    # (y1.mean, y2.mean) and std=(y1.sd, y2.sd)
    Y1Y2 <- rmvnorm(n, mean = c(y1.mean, y2.mean),
                   cov = matrix(c(y1.sd^2, rho*y1.sd*y2.sd, rho*y1.sd*y2.sd, y2.sd^2), 2))

    ##### 1. bootstrap ######
    boot.list <- booth.trap(B, X1X2, Y1Y2, m, n, p0, p1)
    delta.pAUC <- boot.list[[1]]
    sigma <- boot.list[[2]]
    delta.pAUC.B <- mean(delta.pAUC); delta.pAUC.B # Estimate mean
    difference of two pAUCs by bootstrap
    Vstar <- var(delta.pAUC); # Variance of delta.pAUC by bootstrap
    r.deltap0p1 <- (mean(sigma[, 1]) + mean(sigma[, 2])) / (m * Vstar);

    ##### END OF BOOTSTRAP######

    ##### 2. Calculate delta.pAUC.hat######
    delta.pAUC.hat.list <- deltapAUC(X1X2, Y1Y2, p0, p1, m)
    delta.pAUC.hat <- delta.pAUC.hat.list[[1]]
    r.deltap0p1.hat <- delta.pAUC.hat.list[[2]]
    V.hat <- delta.pAUC.hat.list[[3]]

    ##### END OF 2.  ######

    ##### 3. Calculate C.I and coverage######
    # compute the HBEL interval (Vel from bootstrap)##
    #x[1]: p0p1.1  x[2]: p0p1.2  x[3]: lamda  x[4]: delta
    bdc <- solveNonlinear(g1, c(0, 0, 0, 0), c(0.3, 0.1, 0.001, 0.08))
    bd <- solveNonlinear(g1, c(0, 0, 0, 0), c(0.1, 0.3, 0.001, 0.28))
    if (bd$x[4] < b$x[4]) {low.HBEL <- bd$x[4]; up.HBEL <- b$x[4]} else {low.HBEL <-
    b$x[4]; up.HBEL <- bd$x[4]};
    if (abs(up.HBEL - low.HBEL) < 0.01) next;
    # compute the EL interval (Vel.hat)##
    #x[1]: p0p1.1  x[2]: p0p1.2  x[3]: lamda  x[4]: delta
    lw <- solveNonlinear(g2, c(0, 0, 0, 0), c(0.3, 0.1, 0.001, 0.08))
    upb <- solveNonlinear(g2, c(0, 0, 0, 0), c(0.1, 0.3, 0.001, 0.28))
    if (lw$x[4] < upb$x[4]) {low.EL <- lw$x[4]; up.EL <- upb$x[4]} else {low.EL <-
    upb$x[4]; up.EL <- lw$x[4]};
    if (abs(up.EL - low.EL) < 0.01) next;

    ###compute the CI and coverage for HBEL and EL###
CIL[2]<- CIL[2] + (up.EL - low.EL);
if ((low.HBEL<= deltapAUC.true) & (up.HBEL >= deltapAUC.true)) CovCount[1]<-CovCount[1]+1;
record[i12,1]<-low.HBEL;
record[i12,2]<-up.HBEL;
if ((low.EL <= deltapAUC.true) & (up.EL >= deltapAUC.true)) CovCount[2]<-CovCount[2]+1;
## compute the BTI interval.
height<-2*sqrt(Vstar)
#tlow<- delta.pAUC.hat-height    # lower limit of the CI
#tup<- delta.pAUC.hat+height    # upper limit of the CI
#low and up band
## compute the bootstrap(BS) interval
#bslow<- delta.pAUCbar.B-height    # lower limit of the CI
#bsup<- delta.pAUCbar.B+height   # upper limit of the CI
#low and up band
i12 <- i12+1;
}
#End of LOOP##

cov<-CovCount/iter; cov
wid<-CIL/iter; wid
#Result Output
sink("C:\Temp\semipAUC.txt",append = T)
cat("iter", iter,"At level=", levelc, "m=", m, "n=",
n,"rho=".rho,"Delta=".deltapAUC.true, "p0=".p0, "pl=".pl, "\n")
cat("mean1","y1.mean","mean2="., y2.mean,"y1std="., y1.sd, "y2std="., y2.sd, "B="., B, "\n")
cat("Coverage of the (HBEL, EL, BT, BS) CI's for delta ":, cov, "\n")
cat("Average length of (HBEL,EL,BT&BS) ", wid, "\n")
cat("-----------------------------------------------------------------------------------","\n")
sink();
##### Code for Normal approximation CI for Normal simulation ######
##### One more function is added to calculate the NA variance: #######
#function for normal approximation variance 

normalApr <- function(X1X2, Y1Y2, p0, pl, m, n, V.hat, rho) {
  # Caculate X Quantile of 1-pi (i=0,1) for q.hat 
  q0.1.hat<-quantile(X1X2[,1],1-p0); 
  q0.2.hat<-quantile(X1X2[,2],1-p0); 
  q1.1.hat<-quantile(X1X2[,1],1-pl); 
  q1.2.hat<-quantile(X1X2[,2],1-pl); 
  # Caculate V(ki).hat & delta.pAUC.hat 
  Bv1.hat<-matrix(,m,1) 
  Bv2.hat<-matrix(,m,1) 
  Dv.hat<-matrix(,m,4) 
  Y1mean <- mean(Y1Y2[,1]) 
  Y1sd <- stdev(Y1Y2[,1]) 
  Y2mean <- mean(Y1Y2[,2]) 
  Y2sd <- stdev(Y1Y2[,2]) 
  meanV1.hat <- mean(V.hat[,1]) 
  meanV2.hat <- mean(V.hat[,2]) 
  for (i in 1:m) {
    Bv1.hat[i] <- (1-pnorm(X1X2[i,1], mean=Y1mean, sd=Y1sd))*(q1.1.hat <= X1X2[i,1])*(X1X2[i,1]<=q0.1.hat) - meanV1.hat - (1-pnorm(q0.1.hat, mean=Y1mean, sd=Y1sd))*(q1.1.hat <= q0.1.hat) - (1-pnorm(q1.1.hat - (1-p1)) 
    Bv2.hat[i] <- (1-pnorm(X1X2[i,2], mean=Y2mean, sd=Y2sd))*(q1.2.hat <= X1X2[i,2])*(X1X2[i,2]<=q0.2.hat) - meanV2.hat - (1-pnorm(q0.2.hat, mean=Y2mean, sd=Y2sd))*(q1.2.hat <= q0.2.hat) - (1-pnorm(q1.2.hat - (1-p1)) 
    Dv.hat[i,1] <- -dnorm(X1X2[i,1], mean=Y1mean, sd=Y1sd)*(q1.1.hat <= X1X2[i,1])*(X1X2[i,1]<=q0.1.hat) 
    Dv.hat[i,2] <- ((X1X2[i,1]-Y1mean)/Y1sd)*Dv.hat[i,1] 
    Dv.hat[i,3] <- -dnorm(X1X2[i,2], mean=Y2mean, sd=Y2sd)*(q1.2.hat <= X1X2[i,2])*(X1X2[i,2]<=q0.2.hat) 
    Dv.hat[i,4] <- ((X1X2[i,2]-Y2mean)/Y2sd)*Dv.hat[i,2] 
  } 
  B.hat <- Bv1.hat + Bv2.hat 
  VarB <- var(B.hat) 
  D.hat <- matrix(c(mean(Dv.hat[,1]),mean(Dv.hat[,2]),mean(Dv.hat[,3]),mean(Dv.hat[,4])
),1) 
  sigmaY1=matrix(c(Y1sd,0,0,sqrt(2)*Y1sd^2),2) 
  sigmaY2=matrix(c(Y2sd,0,0,sqrt(2)*Y2sd^2),2) 
  i1 <- matrix(c(1,0,0,0),2) 
  i2 <- matrix(c(0,1,1,0),2) 
  i3 <- matrix(c(0,0,0,1),2) 
  l1 <- kronecker(i1, sigmaY1^2) 
  l2 <- kronecker(i2, rho*sigmaY1^%sigmaY2) 
  l3 <- kronecker(i3, sigmaY2^2) 
  sigma.theta <- l1+l2+l3 
  sigma.p0p1 <- VarB + m/n*D.hat%^%sigma.theta%^%t(D.hat) 
  list(sigma.p0p1) 
}

################################## Part2: initial value###################################
iter<-100 
B=150 
rho=0 
#rho=0.3 
m<-50; n<-20;
y1.sd<-2; y2.sd<-2;

levelc<-0.95
#levelc<-0.90
Z<-qnorm(1-(1-levelc)/2)
y1.mean<-y2.mean<-0
p0<-0; p1<-0.4
pAUC1 <- 0.2
pAUC2 <- 0.2
deltapAUC.true<- pAUC2-pAUC1
S<-solveNonlinear(mu, c( pAUC1, pAUC2), c(0.1, 0.1))
y1.mean<-S$x[1]
y2.mean<-S$x[2]

#################### End part2  ###########################

########################################################

Part3:  Loop  ##################################################################

CovCount<-0
CIL<-0
for ( i12 in c(1:iter)){
  # generate non-diseased population F(X1, X2)
  # the sample from 2-dimensinal multinormal distribution with mean 0 and std=1
  X1X2<-rmvnorm(m, mean=c(0,0), cov=matrix(c(1,rho,rho,1),2))

  # generate diseased population G(Y1,Y2)
  # the sample from 2-dimensinal multinormal distribution with mean
  # (y1.mean,y2.mean) and std=(y1.sd,y2.sd)
  Y1Y2<-rmvnorm(n, mean=c(y1.mean,y2.mean),
                cov=matrix(c(y1.sd^2,rho*y1.sd*y2.sd, rho*y1.sd*y2.sd, y2.sd^2),2))

  2.  Calculate delta.pAUC.hat

  delta.pAUC.hat.list <- deltapAUC(X1X2, Y1Y2, p0, p1, m)
  delta.pAUC.hat <- delta.pAUC.hat.list[[1]]
  V.hat <- delta.pAUC.hat.list[[2]]

  END OF 2.  

  2.5 calculate sigma for delta.pAUC.hat

  sqrt.rho.y1y2 <- sqrt(rho*y1.sd*y2.sd)
  Ycov <- matrix(c(y1.sd,sqrt.rho.y1y2, sqrt.rho.y1y2, y2.sd),2)
  sigma.delta.pAUC.hat.list <- normalApr(X1X2, Y1Y2, p0, p1, m, n, V.hat, rho)
  sigma.normalApr <- sigma.delta.pAUC.hat.list[[1]]

  END OF 2.5  

  4.  Calculate C.I and coverage

  aprwidth <- Z*sqrt(sigma.normalApr)/sqrt(m)
  if (((delta.pAUC.hat-aprwidth) <= deltapAUC.true) &&
      ((delta.pAUC.hat+aprwidth) >= deltapAUC.true)) CovCount<-CovCount+1
}

#End of LOOP##
cov<-CovCount/iter
wid<-CIL/iter

Result Output

sink("C:\Temp\semipAUC.txt",append = T)
cat("iter=", iter,"At level=", levelc, "m=", m, "n=",
n,"rho="", rho,"Delta="",deltapAUC.true, "p0="", p0, "p1="", p1, "\n")
cat("mean1=",y1.mean,"mean2="", y2.mean,"y1std="", y1.sd, "y2std="", y2.sd, "B=",
B, "\n")
cat("Coverage of the normal approximation CI’s for delta :", cov, "\n")
cat("Average length of normal approximation:", wid, "\n")
cat("---------------------------------------------------------------------
---------------------------------------------------------------------","\n")
sink();
#### Code for exponential simulation study ####

The function part is the same as normal case, except all the normal related function have been changed into exponential distribution.

The generating part for no covariance case is the same as normal case, except change normal function into exponential function.

Here just show how to generate the bivariate exponential function with covariance > 0.

```r
define non-diseased population \( F(X_1, X_2) \)
define the sample from bivariate exponential distribution with rate=1
  \( u_1 \leftarrow \text{rexp}(m, \text{rate}=explambda) \)
  \( u_2 \leftarrow \text{rexp}(m, \text{rate}=explambda) \)
  \( u_3 \leftarrow \text{rexp}(m, \text{rate}=explambda) \)
  for (k in 1:m) {
    \( X1X2[k,1] \leftarrow \min(u1[k], u3[k]) \)  #Exp(1): the sample from the first non-disease pop.
    \( X1X2[k,2] \leftarrow \min(u2[k], u3[k]) \)  #Exp(1): the sample from the second non-disease pop.
  }
define diseased population \( G(Y_1, Y_2) \)
define the sample from bivariate exponential distribution with rate \((y1.mean, y2.mean)\)
  \( v1 \leftarrow \text{rexp}(n, \text{rate}=y1.mean) \)
  \( v2 \leftarrow \text{rexp}(n, \text{rate}=y2.mean) \)
  \( v3 \leftarrow \text{rexp}(n, \text{rate}=expcov) \)
```
### The normal approximation function for exponential case ###

```r
normalApr <- function(X1X2, Y1Y2, p0, pl, m, n, V.hat, rho) {

  # Calculate X Quantile of 1-pi (i=0,1) for q.hat
  q0.1.hat <- quantile(X1X2[,1], 1-p0);
  q0.2.hat <- quantile(X1X2[,2], 1-p0);
  q1.1.hat <- quantile(X1X2[,1], 1-pl);
  q1.2.hat <- quantile(X1X2[,2], 1-pl);

  # Calculate V(ki).hat & delta.pAUC.hat
  Bv1.hat <- matrix(, m, 1)
  Bv2.hat <- matrix(, m, 1)
  Dv.hat <- matrix(, m, 2)
  sigma.theta <- matrix(, 2, 2)
  Y1mean <- 1/mean(Y1Y2[,1])
  Y2mean <- 1/mean(Y1Y2[,2])
  meanV1.hat <- mean(V.hat[,1])
  meanV2.hat <- mean(V.hat[,2])
  for (i in 1:m) {
    Bv1.hat[i] <- (1-pexp(X1X2[i,1], rate=Y1mean))*(q1.1.hat <= X1X2[i,1] <= q0.1.hat) - meanV1.hat - (1-pexp(q0.1.hat, rate=Y1mean))*(q1.1.hat <= q0.1.hat) - (1-pexp(q1.1.hat, rate=Y1mean))*(X1X2[i,1] <= q1.1.hat)
    Bv2.hat[i] <- (1-pexp(X1X2[i,2], rate=Y2mean))*(q1.2.hat <= X1X2[i,2] <= q0.2.hat) - meanV2.hat - (1-pexp(q0.2.hat, rate=Y2mean))*(q1.2.hat <= q0.2.hat) - (1-pexp(q1.2.hat, rate=Y2mean))*(X1X2[i,2] <= q1.2.hat)
    Dv.hat[i,1] <- dexp(X1X2[i,1], rate=Y1mean)*(q1.1.hat <= X1X2[i,1] <= q0.1.hat)
    Dv.hat[i,2] <- dexp(X1X2[i,2], rate=Y2mean)*(q1.2.hat <= X1X2[i,2] <= q0.2.hat)
  }

  B.hat <- Bv1.hat + Bv2.hat
  VarB <- var(B.hat)
  D.hat <- matrix(c(mean(Dv.hat[,1]), mean(Dv.hat[,2])), 1)
  sigma.theta[1,1] <- (1/Y1mean)^2
  sigma.theta[2,2] <- (1/Y2mean)^2
  sigma.theta[1,2] <- sigma.theta[2,1] <- rho*(1/Y1mean)*(1/Y2mean)
  sigma.p0p1 <- VarB + m/n*D.hat%*%sigma.theta%*%t(D.hat)
  list(sigma.p0p1)
}
```
The Splus code for real data analysis

```
# Part2: data input
coln<-c("T1", "T2","D")
realdata<-read.table("C:\Temp\wiedat2b.txt", sep=',', col.names=coln, header=T)
realdata
m=51;
n=90;
X1X2 <- matrix(nrow=51, ncol=2);
Y1Y2 <- matrix(nrow=90, ncol=2);

# Box-Cox transformation

X1X2[,1]<-(realdata$T1[realdata$D==0]^(-0.015)-1)/-0.015;
X1X2[,2]<-(realdata$T2[realdata$D==0]^(-0.424)-1)/-0.424;
Y1Y2[,1]<-(realdata$T1[realdata$D==1]^(-0.015)-1)/-0.015;
Y1Y2[,2]<-(realdata$T2[realdata$D==1]^(-0.424)-1)/-0.424;

B=500
levelc<-0.9;
CritVal<-qchisq(levelc,1)
Z<-qnorm(1-(1-levelc)/2)
p0<-0 ; p1<-0.2

# End part2

# Part3: real example

### 1. bootstrap ###

boot.list<- booth.trap(B, X1X2, Y1Y2, m, n, p0, p1)
delta.pAUCbar <- boot.list[[1]]
sigma <- boot.list[[2]]
delta.pAUCbar.B <- mean(delta.pAUCbar) # Estimate mean difference of two pAUCs by bootstrap
Vstar<-(mean(sigma[,1])+mean(sigma[,2]))/(m*Vstar);

### 2. Calculate delta.pAUC.hat ###

delta.pAUC.hat <- deltapAUC(X1X2, Y1Y2, p0, p1, m)
delta.pAUC.hat <- delta.pAUC.hat.list[[1]]
r.deltap0p1.hat <- mean(sigma[,1])+mean(sigma[,2])/(m*Vstar);

### 3. Calculate C.I and coverage ###

 BD<-solveNonlinear(g1, c(0,0,0,0), c(0.3, 0.1, 0.001, -0.999))
 low.HBEL<-BD$x[4] # lower limit of the CI
 bd<-solveNonlinear(g1, c(0,0,0,0), c(0.1, 0.3, 0.001, 0.999))
 up.HBEL<-b$x[4] # upper limit of the CI
```
## compute the EL interval (Vel.hat)##

### x[1]: P0P1.1 x[2]: P0P1.2 x[3]: lamda x[4]: delta

\[ lw<-\text{solveNonlinear}(g2, c(0,0,0,0), c(0.3, 0.1, 0.001, -0.999)) \]

\[ \text{low.EL<-} lw$x[4] \]  

\[ \text{upb<-solveNonlinear}(g2, c(0,0,0,0), c(0.1, 0.3, 0.001, 0.999)) \]

\[ \text{up.EL<-} upb$x[4] \]

## compute the BTI interval.##

\[ hwidth<-Z*sqrt(Vstar) \]

\[ tlow<- \text{delta.pAUC.hat-hwidth} \]  

\[ \text{tup<- delta.pAUC.hat+hwidth} \]

## compute the bootstrap (BS) interval ##

\[ bslow<- \text{delta.pAUCbar.B-hwidth} \]  

\[ \text{bsup<- delta.pAUCbar.B+hwidth} \]

# Result Output

\[ \text{sink("C:\\Temp\\real.txt", append = T)} \]

\[ \text{cat("B=", B,"At level="},m, m,"n=", n, "p0=", p0, "p1=", p1, "\n")} \]

\[ \text{cat("The difference between two pAUCs are:", delta.pAUC.hat,"\n")} \]

\[ \text{cat("Confidence Interval of the HBEL for delta is :"}, low.HBEL,","funcname="up.HBEL, "\n")} \]

\[ \text{cat("Confidence Interval of the EL for delta is :"}, low.EL, "to", up.EL, "\n")} \]

\[ \text{cat("Confidence Interval of the BTI for delta is :"}, tlow, "to", tup, "\n")} \]

\[ \text{cat("Confidence Interval of the BS for delta is :"}, bslow, "to", bsup, "\n")} \]

\[ \text{sink();} \]