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# EMPIRICAL LIKELIHOOD-BASED NONPARAMETRIC INFERENCE FOR THE DIFFERENCE BETWEEN TWO PARTIAL AUCS

by

Yan Yuan

Under the direction of Gengsheng Qin

## ABSTRACT

Compare the accuracy of two continuous-scale tests is increasing important when a new test is developed. The traditional approach that compares the entire areas under two Receiver Operating Characteristic (ROC) curves is not sensitive when two ROC curves cross each other. A better approach to compare the accuracy of two diagnostic tests is to compare the areas under two ROC curves (AUCs) in the interested specificity interval. In this thesis, we have proposed bootstrap and empirical likelihood (EL) approach for inference of the difference between two partial AUCs. The empirical likelihood ratio for the difference between two partial AUCs is defined and its limiting distribution is shown to be a scaled chi-square distribution. The EL based confidence intervals for the difference between two partial AUCs are obtained. Additionally we have conducted simulation studies to compare four proposed EL and bootstrap based intervals.

INDEX WORDS: ROC curve, AUC, PAUC, Partial AUC, Empirical Likelihood, Bootstrap, Confidence Interval.

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# LIST OF ABBREVIATION

AUC:              Area under the ROC Curve

BS:               Bootstrap Method

EL:               Empirical Likelihood Method

FPR:              False Positive Rate

PAUC:             Partial Area under the ROC Curve

ROC:              Receiver Operating Characteristic

TPR:              True Positive Rate

$\Delta_{p_0 p_1}$ :          The difference between two partial AUCs

$\delta_{p_0 p_1}$ :          PAUC over the interval $(p_0, p_1)$

# CHAPTER I

# INTRODUCTION

The accuracy of a binary diagnostic test can be measured by its specificity and sensitivity. The sensitivity or true positive rate (TPR) of the test is the proportion of diseased patients who test positive. The specificity or true negative rate (TNR) of the test is the proportion of non-diseased patients who test negative.

When the outcome of a diagnostic test is continuous, a cut-off point for the positive of disease needs to be chosen to compute specificity and sensitivity of the test. Let $Y$ and $X$ be the results of a continuous-scale test for a diseased and a non-diseased subject with cumulative distribution function $G$ and $F$, respectively. For a given cut-off point $c$, the sensitivity and specificity of the test are defined as

$$Se = P(Y \geq c) = 1 - G(c) ; \qquad Sp = P(X \leq c) = F(c)$$

respectively. When specificity is 1-$p$, the corresponding sensitivity of the test is $R(p) = 1 - G(F^{-1}(1 - p))$ , where $F^{-1}$ is the inverse function of $F$ .

The receiver operating characteristic (ROC) curve, denoted by $R$ *(p)*, is the plot of sensitivity against the false positive rate (FPR or 1- specificity ) as the cut-off point runs through the whole range of possible test values. In fact, the non-diseased population is unknown, and the optimal cut-off point is unknown too. For a continuous-scale diagnostic test, the area under the ROC curve (AUC), defined as $\delta = \int_0^1 R(p)dp$ , is commonly used to summarize the accuracy of the diagnostic test across all the possible

cut-off points. The larger is the AUC, the better the diagnostic test will be. Now, the AUC is a very popular tool in diagnostic medicine.

However, the AUC has several limitations that may make it less useful for continuous diagnostic tests (Hilden, 1991). When two ROC curves cross, the two diagnostic tests can have similar AUC even though one test has higher sensitivity for certain specificities while the other test has better sensitivity for other specificities. On the other hand, in diagnostic testing, it is critical to maintain a high sensitivity in order not to miss detecting subjects with "disease" and the interest would be in the region of ROC curve corresponding only to acceptable high sensitivities. For cancer screening, only the lower tail of the ROC curve is of interest because the FPR must be very small to be acceptable (Lilienfeld, 1974). For these reasons, the partial AUC (pAUC) has been proposed as an alternative measure to the full AUC. When using the pAUC, one considers only those regions of the ROC space where data have been observed, or which correspond to clinical relevant values of sensitivity or specificity. The pAUC over the interval $(p_0, p_1)$ of false positive rates, denoted by $\delta_{p_0 p_1}$, is

$$\delta_{p_0 p_1} = \int_{p_0}^{p_1} R(p) dp \qquad \text{for } 0 \leq p_0 < p_1 \leq 1.$$

It can be described as the cumulative value of sensitivity for all possible values of the false positive rates in the interval $(p_0, p_1)$.

Let $X_1, X_2, \ldots, X_m$ be the test results from a random sample of non-diseased population with distribution function $F$; let $Y_1, Y_2, \ldots, Y_n$ be the test results from a random sample of diseased population with distribution function $G$. Dodd and Pepe

(2003) proposed the following nonparametric estimator for the pAUC. When the

quantiles $q_i = F^{-1}(1 - p_i)$ (i=0, 1) are known, the pAUC can be estimated by

$$\tilde{\delta}_{p_0 p_1} = \frac{1}{mn} \sum_{i=1}^{m} \sum_{j=1}^{n} I(Y_j \geq X_i) I(X_i \in (q_1, q_0)).$$

When the quantile $q_i$'s are unknown, the pAUC can be estimated by

$$\hat{\delta}_{p_0 p_1} = \frac{1}{mn} \sum_{i=1}^{m} \sum_{j=1}^{n} I(Y_j \geq X_i) I(X_i \in (\hat{q}_1, \hat{q}_0))$$

where $\hat{q}_i = \hat{F}^{-1}(1 - p_i)$ (i=0,1) and $\hat{F}$ is the empirical distribution of $F$.

Many approaches have been proposed for constructing a confidence interval for

the full or partial AUC. McClish (1989), Thompson and Zucchini (1989), and Jiang,

Metz, and Nishikawa (1996) proposed parametric methods for the interval estimation of

the pAUC using the bi-normal model. But Walsh (1997) found that the inferences for the

pAUC are sensitive to the parametric model assumption. Wieand et al (1989) proposed a

generalized nonparametric method for the inference of both the full and the partial AUC.

However, their method is involved in density and distribution function estimations and

mathematically too complicated to be well applied in practice. Qin and Zhou (2006)

proposed an Empirical Likelihood (EL) based approach for the inference on the full AUC

and recommended the use of an EL-based approach when the underlying distributions for

diseased and non-diseased populations are unknown. Qin, Jin and Zhou (2006) developed

bootstrap and EL-based inference for pAUC and did extensive simulation studies to

compare three nonparametric confidence intervals (Normal Approximation, Bootstrap,

and Empirical Likelihood) for the pAUC. They also recommended the use of EL-based

approach for pAUC when the underlying distributions for diseased and non-diseased populations are unknown.

Comparing two continuous-scale diagnostic tests is increasingly important when a new test is developed and marketed (Delong 1988). How can we know which diagnostic test is better? Investigators often compare the validity of two tests based on the estimated areas under the respective ROC curves. However, the traditional way of comparing entire areas under two ROC curves is not sensitive when two ROC curves cross each other (Zhang et al., 2002). In this thesis, we propose methods to compare the partial area under the curve within a specific range of specificity for two ROC curves, non-parametric methods based on EL and bootstrap have been developed.

This thesis is organized as follows: In Chapter II, we propose two bootstrap confidence intervals for the difference between two partial AUCs. In Chapter III, we propose the EL-based intervals for the difference between two partial AUCs. In Chapter IV, we conduct simulation study to evaluate the performances of these intervals. In Chapter V, we analyze Dermatoscope Example to illustrate the proposed intervals. Finally, the conclusions are discussed in Chapter VI.

# CHAPTER II

## Bootstrap Confidence Interval for the Difference between Two partial AUCS

Consider two diagnostic tests $T_k$ (k=1, 2). Both tests yield continuous measurements and are performed on the same *m* non-diseased and *n* diseased cases. Let $X_{k1}, X_{k2} \ldots X_{km}$ be i.i.d bivariate test results from a non-diseased population with joint distribution function $F(x_1, x_2)$, and let $Y_{k1}, Y_{k2} \ldots., Y_{kn}$ i.i.d bivariate test results from a diseased population with joint distribution function $G(y_1, y_2)$. Denote the marginal distribution functions of $X_{ki}$ and $Y_{kj}$ by $F_k$ and $G_k$, respectively. The pAUC of test $T_k$ (k=1, 2) over the interval $(p_0, p_1)$ of false positive rates, denoted by $\delta_{p_0 p_1}^{(k)}$, is

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

where $R_k(p) = 1 - G_k(F_k^{-1}(1-p))$ is the ROC curve of test $T_k$ (k=1, 2) . The difference between two pAUCS is $\Delta_{p_0 p_1} = \delta_{p_0 p_1}^{(2)} - \delta_{p_0 p_1}^{(1)}$. Our goal is to construct confidence interval for $\Delta_{p_0 p_1}$ based on test results $X_{ki}$'s and $Y_{kj}$'s.

## 2.1 Normal Approximation Method

For one diagnostic test, Let $\{ Y_1, Y_2, \ldots, Y_n \}$ and $\{ X_1, X_2, \ldots, X_m \}$ be the results of a continuous-scale test for a diseased and a non-diseased subject with cumulative distribution function *F* and *G*. Dodd and Pepe (2003) defined the restricted placement value of X as $V(X) = (1 - G(x))I(X \in (q_1, q_0))$ when assume the quantiles $q_1$ and $q_0$ are known. Let $\hat{G}(y) = \frac{1}{n} \sum_{j=1}^{n} I(Y_j \leq y)$ be the empirical distribution of *G*, and

$\tilde{V}_i = (1 - \hat{G}(X_i))I(X_i \in (q_1, q_0))$, $i = 1, 2, \ldots, m$. Then, $\tilde{\delta}_{p_0 p_1} = \frac{1}{m}\sum_{i=1}^{m}\tilde{V}_i$ is the mean of $m$

'sample' restricted placement value $\tilde{V}_i$'s. Noticing that $\tilde{\delta}_{p_0 p_1}$ is a two-sample U-statistic,

it follows from the asymptotic normality for U-statistic (Lehmann, 1998) that

$$\frac{1}{m\sigma_{mn}}\sum_{i=1}^{m}(\tilde{V}_i - \delta_{p_0 p_1}) \xrightarrow{L} N(0, 1),$$

Where

$$\sigma_{mn}^2 = \frac{1}{m}\sigma_1^2 + \frac{1}{n}\sigma_0^2, \quad \sigma_1^2 = Var[V(X)], \quad \sigma_0^2 = Var[F(min(Y, q_0))].$$

Since both $q_1$, $q_0$ are unknown, $\tilde{V}_i$ is still unknown. The above normal approximation

cannot be directly used to produce a confidence interval for the pAUC. Therefore Qin, Jin

and Zhou (2007) introduced a bootstrap method to produce a confidence interval for

pAUC.

For two diagnostic tests $T_k$ (k=1, 2), we can use $\hat{\Delta}_{p_0 p_1} = \hat{\delta}^{(2)}_{p_0 p_1} - \hat{\delta}^{(1)}_{p_0 p_1}$ to estimate

$\Delta_{p_0 p_1}$, where $\hat{\delta}^{(k)}_{p_0 p_1} = \frac{1}{mn}\sum_{i=1}^{m}\sum_{j=1}^{n}I(Y_{kj} \geq X_{ki})I(X_{ki} \in (\hat{q}_{k1}, \hat{q}_{k0}))$, $\hat{q}_{kl} = \hat{F}_k^{-1}(1 - p_l)$

$(l = 0, 1)$, and $\hat{F}_k$ is the empirical distribution of $F_k$. It can be proved that

$$\sqrt{m+n}\left(\hat{\Delta}_{p_0 p_1} - \Delta_{p_0 p_1}\right) \xrightarrow{L} N(0, \sigma^2_{p_0 p_1}),$$

where $\sigma^2_{p_0 p_1}$ is the asymptotic variance of $\hat{\Delta}_{p_0 p_1}$. Since $\sigma^2_{p_0 p_1}$ is an unknown function of

$F_k$, $G_k$, $F_k^{-1}$ and $G_k^{-1}$, the estimation of $\sigma^2_{p_0 p_1}$ involves in complex density and quantile

estimation. This normal approximation cannot be directly used to produce a confidence

interval for the $\Delta_{p_0 p_1}$. In next subsection, we will extend the method used in Qin, Jin and

Zhou (2006) to construct confidence intervals for the difference between two partial AUCS.

2.2 Bootstrap Method

Bootstrap method is a popular non-parametric method for constructing confidence intervals of unknown parameter; it can be applied to very complex problems. In this chapter we will propose use bootstrap method to construct confidence interval for the difference between two partial AUCS.

We draw a bootstrap resample { $X_{k1}^{*}$, $X_{k2}^{*}$,..., $X_{km}^{*}$ } of size $m$ with replacement from { $X_{k1}$, $X_{k2}$, ..., $X_{km}$ } and a separate bootstrap resample { $Y_{k1}^{*}$, $Y_{k2}^{*}$, ..., $Y_{kn}^{*}$ } of size $n$ with replacement from { $Y_{k1}$, $Y_{k2}$, ..., $Y_{kn}$ }. The partial AUC can be estimated by

$$\hat{\delta}_{p_0 p_1}^{(k)*} = \frac{1}{mn} \sum_{i=1}^{m} \sum_{j=1}^{n} I(Y_{kj}^{*} \geq X_{ki}^{*}) I\left(X_{ki}^{*} \in (\hat{q}_{k1}^{*}, \hat{q}_{k0}^{*})\right), \quad k=1, 2,$$

where $\hat{q}_{kl}^{*} = \hat{F}_{k}^{-1*}(1 - p_l)$ $(l = 0, 1)$ is the $(1 - p_l)$-th sample quantile based on bootstrap resample { $X_{k1}^{*}$, $X_{k2}^{*}$,..., $X_{km}^{*}$ }. Then the bootstrap estimate for the difference of two partial AUCs can be calculated as

$$\hat{\Delta}_{p_0 p_1}^{*} = \hat{\delta}_{p_0 p_1}^{(2)*} - \hat{\delta}_{p_0 p_1}^{(1)*}.$$

After $B$ repetitions of above process, $B$ bootstrap copies of $\hat{\Delta}_{p_0 p_1}^{*}$ are obtained

$$\{ \hat{\Delta}_{p_0 p_1 (b)}^{*} : b=1, 2, ..., B \}.$$

The bootstrap estimator for the variance of $\hat{\Delta}_{p_0 p_1}$ is given by

$$V^{*} = \frac{1}{B-1} \sum_{b=1}^{B} (\hat{\Delta}_{p_0 p_1 (b)}^{*} - \overline{\Delta}_{p_0 p_1}^{*})^2,$$

where $\overline{\Delta}^*_{p_0 p_1} = \dfrac{1}{B} \sum\limits_{b=1}^{B} \hat{\Delta}^*_{p_0 p_1 (b)}$ .

Two bootstrap $(1-\alpha)100\%$ confidence intervals for $\Delta_{p_0 p_1}$ can be proposed based on the bootstrap variance estimator $V^*$.

First one, called BS interval is defined as follows:

$$( \overline{\Delta}^*_{p_0 p_1} - z_{1-\alpha/2} \sqrt{V^*} , \quad \overline{\Delta}^*_{p_0 p_1} + z_{1-\alpha/2} \sqrt{V^*} ).$$

Second one, called BT interval is given by

$$( \hat{\Delta}_{p_0 p_1} - z_{1-\alpha/2} \sqrt{V^*} , \quad \hat{\Delta}_{p_0 p_1} + z_{1-\alpha/2} \sqrt{V^*} ).$$

# CHAPTER III

## Empirical Likelihood Based Confidence Interval for

## The difference between two partial AUCs

In this chapter, we will use empirical likelihood method to construct the confidence interval for the difference between two partial AUCs.

Empirical likelihood (EL) (Owen, 1990, 2001) also is a popular non-parametric method traditionally used for providing confidence intervals. The EL method has many advantages over other non-parametric methods. For example, it has better small sample performance than approaches based on normal approximation, it studentizes internally, thereby eliminating the need for a pivot. But the applications of EL method to the ROC study are relatively few. The main challenge of developing the EL-based theory for the difference between two partial AUCs is the standard EL method can't be applied directly when the underlying distributions are unknown (Qin and Zhou 2006) and the empirical log-likelihood ratio for the partial AUC is a sum of non-independent random variables (Qin, Jin and Zhou 2006). Hence, the standard EL theory cannot be directly applied in the partial AUC setting.

For test value $X_k$ from a "non-diseased" subject, Dodd and Pepe (2003) defined the restricted placement value of $X_k$ as

$$V_k(X_k) = (1 - G_k(X_k))I(X_k \in (q_{k1}, q_{k2})), \text{ k=1, 2,}$$

where $q_{kl} = F_k^{-1}(1 - p_l)$, $l = 1, 2$.

When the quantiles are unknown, we can use

$$\hat{V}_k(X_k) = (1 - \hat{G}_k(X_k))I(X_k \in (\hat{q}_{k1}, \hat{q}_{k2})), \text{ k=1, 2,}$$

where $\hat{q}_{kl} = \hat{F}_k^{-1}(1 - p_l)$, $l = 1, 2$.

$V_k$ can be interpreted as the restricted placement value of a given "non-diseased" test value $X_k$, in the survival function of the results of "diseased". It is evident that

$$E(V_k(X_k)) = p\{Y_k > X_k, X_k \in (q_{k1}, q_{k2})\} = pAUC_k(p_0, p_1) = \delta_{p_0 p_1}^{(k)}$$

Therefore,

$$\Delta_{p_0 p_1} = \delta_{p_0 p_1}^{(2)} - \delta_{p_0 p_1}^{(1)} = E(V_2(X_2) - V_1(X_1)) .$$

Based on this relationship between the difference between two partial AUCs and the restricted placement values $V_1(X_1)$ and $V_2(X_2)$, the profile empirical likelihood for $\Delta_{p_0 p_1}$ can be defined as

$$L(\Delta_{p_0 p_1}) = \sup\{\prod_{k=1,2} \prod_{i=1}^{m} p_{kj} : \sum_{j=1}^{n} p_{ki} = 1, \ \sum_{i=1}^{m} p_{ki}(\hat{V}_{ki} - \delta_{p_0 p_1}^{(k)}), \ \sum_{i=1}^{m} p_{2i}\hat{V}_{2i} - \sum_{i=1}^{m} p_{1i}\hat{V}_{1i} = \Delta_{p_0 p_1}\} ,$$

where $\hat{V}_{ki} = \hat{V}_k(X_{ki})$, i=1, 2, …, m,  k=1, 2.

Then the corresponding empirical log-likelihood ratio (ELR) for $\Delta_{p_0 p_1}$ is

$$l(\Delta_{p_0 p_1}) = 2[\ \sum_{i=1}^{m} \log(1 - 2\lambda(\hat{V}_{1i} - \delta_{p_0 p_1}^{(1)})) + \sum_{i=1}^{m} \log(1 + 2\lambda(\hat{V}_{2i} - \delta_{p_0 p_1}^{(2)}))] ,$$

where $\lambda$ and $\delta_{p_0 p_1}^{(k)}$ (k=1, 2) are the solutions of the following equations:

$$\frac{1}{m} \sum_{i=1}^{m} \frac{\hat{V}_{1i} - \delta_{p_0 p_1}^{(1)}}{1 - 2\lambda(\hat{V}_{1i} - \delta_{p_0 p_1}^{(1)})} = 0 \qquad\qquad (1)$$

$$\frac{1}{m} \sum_{i=1}^{m} \frac{\hat{V}_{2i} - \delta_{p_0 p_1}^{(2)}}{1 + 2\lambda(\hat{V}_{2i} - \delta_{p_0 p_1}^{(2)})} = 0 \qquad\qquad (2)$$

$$\frac{1}{m} \sum_{i=1}^{m} \frac{\hat{V}_{2i}}{1 + 2\lambda(\hat{V}_{2i} - \delta_{p_0 p_1}^{(2)})} - \frac{1}{m} \sum_{i=1}^{m} \frac{\hat{V}_{1i}}{1 - 2\lambda(\hat{V}_{1i} - \delta_{p_0 p_1}^{(1)})} = \Delta_{p_0 p_1} \qquad\qquad (3)$$

**Theorem 3.1:** If $\Delta_{p_0 p_1}$ is the true value of the difference between two partial AUCs, and

$\lim_{m,n \to \infty} \dfrac{m}{n} = \rho$ is a constant, then the limiting distribution of $l(\Delta_{p_0 p_1})$ is a scaled chi-square distribution with one degree of freedom.

$$C(\Delta_{p_0 p_1}) \, l(\Delta_{p_0 p_1}) \ \xrightarrow{L} \chi_1^2 \,,$$

where $C(\Delta_{p_0 p_1}) = \dfrac{(\sigma_{p_0 p_1}^{(1)\ 2} + \sigma_{p_0 p_1}^{(2)\ 2})/m}{\sigma_{p_0 p_1}^2 /(m+n)}$ , $\sigma_{p_0 p_1}^{(k)\ 2} = Var[V_k(X_k)]$, $k = 1, 2.$

Using Theorem 3.1, two empirical and bootstrap based intervals for the difference between two partial AUCs can be constructed as follows:

*The first hybrid empirical and bootstrap interval* (**EL**) is defined as

$$R_\alpha(\Delta_{p_0 p_1}) = \{ \Delta_{p_0 p_1} : \ \hat{C}(\Delta_{p_0 p_1}) \, l(\Delta_{p_0 p_1}) \le \chi_1^2(1-\alpha) \} ,$$

where $\chi_1^2(1-\alpha)$ is the $(1-\alpha)$-th quantile of the chi-square distribution $\chi_1^2$, $\hat{C}(\Delta_{p_0 p_1})$ is an estimate for $C(\Delta_{p_0 p_1})$:

$$\hat{C}(\Delta_{p_0 p_1}) = \dfrac{(\hat{\sigma}_{p_0 p_1}^{(1)\ 2} + \hat{\sigma}_{p_0 p_1}^{(2)\ 2})/m}{V^*} , \qquad \hat{\sigma}_{p_0 p_1}^{(k)\ 2} = \dfrac{1}{m-1} \sum_{i=1}^{m} (\hat{V}_{ki} - \dfrac{1}{m} \sum_{i=1}^{m} \hat{V}_{ki})^2 , \text{ k=1, 2,}$$

and $V^*$ is the bootstrap variance estimate defined in chapter II.

$R_\alpha(\Delta_{p_0 p_1})$ is an approximate confidence intervals for the difference between two partial AUCs with asymptotically correct coverage probability $1-\alpha$, i.e.,

$$P(\Delta_{p_0 p_1} \in R_\alpha(\Delta_{p_0 p_1})) = 1-\alpha + o(1) .$$

We can solve the following equations to get the lower and upper bounds of the confidence interval for the difference between the two partial AUCs:

$$\frac{1}{m}\sum_{i=1}^{m}\frac{\hat{V}_{1i}-\delta_{p_0p_1}^{(1)}}{1-2\lambda(\hat{V}_{1i}-\delta_{p_0p_1}^{(1)})}=0 \tag{1}$$

$$\frac{1}{m}\sum_{i=1}^{m}\frac{\hat{V}_{2i}-\delta_{p_0p_1}^{(2)}}{1+2\lambda(\hat{V}_{2i}-\delta_{p_0p_1}^{(2)})}=0 \tag{2}$$

$$\frac{1}{m}\sum_{i=1}^{m}\frac{\hat{V}_{2i}}{1+2\lambda(\hat{V}_{2i}-\delta_{p_0p_1}^{(2)})}-\frac{1}{m}\sum_{i=1}^{m}\frac{\hat{V}_{1i}}{1-2\lambda(\hat{V}_{1i}-\delta_{p_0p_1}^{(1)})}=\Delta_{p_0p_1} \tag{3}$$

$$\hat{C}(\Delta_{p_0p_1})\,l(\Delta_{p_0p_1})\ =\chi_1^2(1-\alpha) \tag{4}$$

In these four equations, $\lambda$ and $\delta_{p_0p_1}^{(k)}$ (k=1, 2) and $\Delta_{p_0p_1}$ are unknown and can be solved.

The $\Delta_{p_0p_1}$ will have two solutions. The smaller one is the lower bound of the **EL** interval and larger one is the upper bound of the **EL** interval.

*The second hybrid empirical and bootstrap interval* (**HBEL**) is given by

$$R_\alpha^*(\Delta_{p_0p_1})=\{\Delta_{p_0p_1}:\quad \hat{C}^*(\Delta_{p_0p_1})\,l(\Delta_{p_0p_1})\le\chi_1^2(1-\alpha)\},$$

where $\hat{C}^*(\Delta_{p_0p_1})=\dfrac{(\bar{\hat{\sigma}}_{p_0p_1}^{*(1)\ 2}+\bar{\hat{\sigma}}_{p_0p_1}^{*(2)\ 2})/m}{V^*}$, $\bar{\hat{\sigma}}_{p_0p_1}^{*(k)\ 2}$ is the mean of $B$ bootstrap copies of

$\hat{\sigma}_{p_0p_1}^{(k)\ 2}$ ( k=1,2), and $V^*$ is the bootstrap variance estimate defined in chapter II.

Similarly, $R_\alpha^*(\Delta_{p_0p_1})$ is an approximate confidence intervals for the difference between two partial AUCs with asymptotically correct coverage probability $1-\alpha$, i.e.,

$$P(\Delta_{p_0p_1}\in R_\alpha^*(\Delta_{p_0p_1}))=1-\alpha+o(1).$$

The lower and upper bound of **HBEL** interval can be obtained by solving the following equations:

$$\frac{1}{m}\sum_{i=1}^{m}\frac{\hat{V}_{1i}-\delta_{p_0p_1}^{(1)}}{1-2\lambda(\hat{V}_{1i}-\delta_{p_0p_1}^{(1)})}=0 \tag{5}$$

$$\frac{1}{m}\sum_{i=1}^{m}\frac{\hat{V}_{2i}-\delta_{p_0p_1}^{(2)}}{1+2\lambda(\hat{V}_{2i}-\delta_{p_0p_1}^{(2)})}=0 \tag{6}$$

$$\frac{1}{m}\sum_{i=1}^{m}\frac{\hat{V}_{2i}}{1+2\lambda(\hat{V}_{2i}-\delta_{p_0p_1}^{(2)})}-\frac{1}{m}\sum_{i=1}^{m}\frac{\hat{V}_{1i}}{1-2\lambda(\hat{V}_{1i}-\delta_{p_0p_1}^{(1)})}=\Delta_{p_0p_1} \tag{7}$$

$$\hat{C}^{*}(\Delta_{p_0p_1})\,l(\Delta_{p_0p_1})\ =\chi_1^2(1-\alpha) \tag{8}$$

# CHAPTER IV

## Simulation Study

In this chapter, we conduct a simulation study to evaluate coverage accuracy and interval length of the newly proposed four intervals for the difference $\Delta_{p_0 p_1}$ of two pAUCs. In the study, the difference $\Delta_{p_0 p_1}$ between two pAUCs is taken to be 0 and 0.2. We generate 1000 random samples of size $n$ from $G(y_1, y_2)$ for test responses of diseased patients, and another set of independent random samples of size $m$ from $F(x_1, x_2)$ for test responses of non-diseased patients.

The distribution $F(x_1, x_2)$ is chosen to be a bivariate normal distribution having means $E(X_1) = 0$, $E(X_2) = 0$ with a common standard deviation 1 and correlation $\rho$. The distribution $G(y_1, y_2)$ is chosen to be a bivariate normal distribution having means $E(Y_1) = \mu_1$, $E(Y_2) = \mu_2$ with a common standard deviation 2 and correlation $\rho$. $\mu_1$ and $\mu_2$ are calculated by solving the following equations

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

When $\Delta_{p_0 p_1} = 0$, we choose three groups of $(\hat{\delta}_{p_0 p_1}^{(1)}, \hat{\delta}_{p_0 p_1}^{(2)})$ to calculate three groups of $(\mu_1, \mu_2)$ and generate random samples from the $G(y_1, y_2)$:

(i) $\delta_{(0,0.4)}^{(2)} = \delta_{(0,0.4)}^{(1)} = 0.2$ with $(p_0, p_1) = (0, 0.4)$,

(ii) $\delta_{(0,0.7)}^{(2)} = \delta_{(0,0.7)}^{(1)} = 0.45$ with $(p_0, p_1) = (0, 0.7)$,

(iii) $\delta_{(0.05,0.50)}^{(2)} = \delta_{(0.05,0.50)}^{(1)} = 0.26$ with $(p_0, p_1) = (0.05, 0.50)$.

When $\Delta_{p_0 p_1} = 0.2$, we also choose three groups of $(\hat{\delta}^{(1)}_{p_0 p_1}, \hat{\delta}^{(2)}_{p_0 p_1})$ to calculate three groups

of $(\mu_1, \mu_2)$ and generate random samples from the $G(y_1, y_2)$:

(i) $\delta^{(2)}_{(0,0.4)} = 0.37, \delta^{(1)}_{(0,0.4)} = 0.17$ with $(p_0, p_1) = (0, 0.4)$,

(ii) $\delta^{(2)}_{(0,0.7)} = 0.61, \delta^{(1)}_{(0,0.7)} = 0.41$ with $(p_0, p_1) = (0, 0.7)$,

(iii) $\delta^{(2)}_{(0.05,0.50)} = 0.39, \delta^{(1)}_{(0.05,0.50)} = 0.19$ with $(p_0, p_1) = (0.05, 0.50)$.

In the bootstrap step, we draw B = 150 bootstrap re-samples from the original samples. We construct both 90% and 95% confidence intervals for $\Delta_{p_0 p_1}$. The results of the simulation study are shown in Table I to Table VIII. From these tables, the following observations were made.

(1) When the correlation $\rho = 0$ and $\Delta_{p_0 p_1} = 0$, the four proposed intervals have similar coverage probabilities but the hybrid empirical likelihood and bootstrap intervals (EL and HBEL) have slightly shorter interval length.

(2) When $\Delta_{p_0 p_1} > 0$, all the intervals over-cover the true difference between two pAUCs when sample sizes are small. As the sample sizes increase, the coverage probabilities of all the intervals approach to the nominal level. Although in most time all the interval have similar coverage probabilities, the EL and HBEL intervals have much shorter interval length than bootstrap (BS and BT) intervals.

(3) When the correlation is positive ($\rho = 0.3$), bigger sample sizes ($m, n \geq 150$) are needed to get better coverage accuracy for all the intervals.

In summary, the simulation study indicates that the hybrid empirical likelihood and bootstrap based intervals perform better than the bootstrap intervals when two partial AUCs are different. When there is no difference between two partial AUCs, the four

proposed intervals have similar performance. Therefore, we recommend the use of hybrid empirical likelihood and bootstrap method for construction of confidence interval of difference between two pAUCs when the underlying distributions for diseased and non-diseased populations are unknown.

# CHAPTER V

## Dermatoscope Example

Malignant melanoma (MM) is one of the most deadly kinds of skin disease. Melanomas of less than 1mm are not likely to have spread to the lymph nodes or to other parts of the body, called early stage; they have a very good chance of cure. The thinner the melanoma, the better chance of a complete cure. Early diagnosis of malignant melanoma is essential for cure.

Dermatoscopy is a hand- held instrument for skin surface microscopy at 10 times magnification and is a noninvasive diagnostic technique for the early diagnosis of melanoma and the evaluation of other pigmented and non-pigmented lesions on the skin that are not as well seen with the unaided eye [www.medterms.com]. Stolz et al (1994) studied the accuracy of clinical evaluations with or without the aid of Dermatoscopy in detecting MM by using the ABCD rule (Asymmetry, irregular border, different colors, and Diameter larger than 6mm). In this study, two tests were applied for detecting MM; the first test is the clinical assessment without the aid of dermatoscopy, and the second test is the clinical assessment with the aid of dermatoscopy. The data set we used here includes 21 patients with MM and 51 patients with benign melanocytic lesions; all patients have both tests results. The objective of this study is to find out whether the aid of dermatoscopy can improve for detecting MM. We estimate the difference of two pAUCs of the two tests and construct confidence intervals for the difference by using the proposed methods. The 90% and 95% confidence intervals for the difference between two pAUCs over three intervals of FPR are shown in Table IX and Table X.

The estimates of the differences between two pAUCs over the three intervals (0, 0.4), (0, 0.7) and (0.05, 0.50) of FPR for the two tests are all close to 0. Also, all the confidence intervals for the differences contain zero. Therefore, we conclude that there is no significant advantage in adopting the clinical assessment with the aid of dermatoscopy in detecting MM. The same conclusion has been obtained in Qin, Hsu and Zhou (2006) where they compared those two tests by using the sensitivities at a fixed level of specificity.

# CHAPTER VI

## Discussion and Conclusion

Comparing the accuracy of two continuous-scale tests is increasingly important when a new test is developed and marketed. There are many ways to do such a comparison. For example, we can compare the sensitivities at a fixed common specificity or we can compare the areas under the ROC curves. But traditional ways of comparing entire areas under two ROC curves are not sensitive when two ROC curves cross each other. Comparing the areas under two ROC curves on the interested FPR interval is a more appropriate way to compare the accuracy of two diagnostic tests. In this thesis, we have proposed two bootstrap based confidence intervals (BS and BT) and two hybrid empirical likelihood and bootstrap confidence intervals (EL and HBEL). The simulation study indicates that two hybrid empirical likelihood and bootstrap intervals performed better than the bootstrap intervals in most cases, especially when there is a difference between two pAUCs. The proposed hybrid empirical likelihood and bootstrap based method combines the power of both bootstrap and empirical likelihood methods. The unknown scale constant in the empirical likelihood theorem can be conveniently and accurately estimated by using bootstrap method. The confidence intervals can be constructed by using the empirical likelihood theorem. Based on this study, we recommend the use of the proposed hybrid empirical likelihood and bootstrap confidence intervals for the difference between two partial AUCs when the underlying distributions for diseased and non-diseased populations are unknown.

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**APPENDIX**


**APPENDIX A: Simulation Tables**

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

| True $\Delta_{p_0 p_1}$ | Sample size (m,n) | Method | $(p_0, p_1)$=(0-0.4) | | $(p_0, p_1)$=(0-0.7) | | $(p_0, p_1)$=(0.05-0.5) | |
|---|---|---|---|---|---|---|---|---|
| | | | Coverage probability | Length | Coverage probability | Length | Coverage probability | Length |
| 0 | (20, 20) | HBEL | 0.965 | 0.2810 | 0.963 | 0.4118 | 0.964 | 0.3203 |
| | | EL | 0.977 | 0.2959 | 0.975 | 0.4099 | 0.970 | 0.3297 |
| | | BT | 0.981 | 0.2996 | 0.971 | 0.4343 | 0.974 | 0.3372 |
| | | BS | 0.976 | 0.2996 | 0.963 | 0.4343 | 0.965 | 0.3372 |
| | (50, 50) | HBEL | 0.954 | 0.1651 | 0.951 | 0.2551 | 0.962 | 0.1843 |
| | | EL | 0.959 | 0.1693 | 0.953 | 0.2586 | 0.964 | 0.1869 |
| | | BT | 0.963 | 0.1699 | 0.950 | 0.2647 | 0.968 | 0.1879 |
| | | BS | 0.958 | 0.1699 | 0.946 | 0.2647 | 0.959 | 0.1879 |
| | (80, 80) | HBEL | 0.944 | 0.1274 | 0.942 | 0.1970 | 0.950 | 0.1448 |
| | | EL | 0.948 | 0.1294 | 0.943 | 0.1975 | 0.951 | 0.1461 |
| | | BT | 0.950 | 0.1297 | 0.940 | 0.1981 | 0.954 | 0.1466 |
| | | BS | 0.950 | 0.1297 | 0.939 | 0.1981 | 0.942 | 0.1466 |
| | (50, 20) | HBEL | 0.922 | 0.2280 | 0.947 | 0.3486 | 0.948 | 0.2575 |
| | | EL | 0.929 | 0.2370 | 0.951 | 0.3529 | 0.952 | 0.2642 |
| | | BT | 0.942 | 0.2390 | 0.945 | 0.3658 | 0.955 | 0.2673 |
| | | BS | 0.938 | 0.2390 | 0.943 | 0.3658 | 0.950 | 0.2673 |
| | (80, 50) | HBEL | 0.936 | 0.1510 | 0.945 | 0.2364 | 0.957 | 0.1725 |
| | | EL | 0.943 | 0.1540 | 0.947 | 0.2376 | 0.961 | 0.1744 |
| | | BT | 0.947 | 0.1545 | 0.945 | 0.2389 | 0.963 | 0.1752 |
| | | BS | 0.937 | 0.1545 | 0.947 | 0.2389 | 0.963 | 0.1752 |

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

| True $\Delta_{p_0 p_1}$ | Sample size (m,n) | Method | ($p_0$, $p_1$)=(0-0.4) | | ($p_0$, $p_1$)=(0-0.7) | | ($p_0$, $p_1$)=(0.05-0.5) | |
|---|---|---|---|---|---|---|---|---|
| | | | Coverage probability | Length | Coverage probability | Length | Coverage probability | Length |
| 0.2 | (20, 20) | HBEL | 0.987 | 0.1277 | 0.984 | 0.2342 | 0.985 | 0.1528 |
| | | EL | 0.987 | 0.1308 | 0.976 | 0.2089 | 0.988 | 0.1555 |
| | | BT | 0.988 | 0.2693 | 0.974 | 0.3906 | 0.990 | 0.3084 |
| | | BS | 0.981 | 0.2693 | 0.973 | 0.3906 | 0.976 | 0.3084 |
| | (50, 50) | HBEL | 0.968 | 0.0728 | 0.959 | 0.1165 | 0.963 | 0.0917 |
| | | EL | 0.972 | 0.0736 | 0.959 | 0.1162 | 0.964 | 0.0925 |
| | | BT | 0.971 | 0.1424 | 0.958 | 0.2214 | 0.964 | 0.1682 |
| | | BS | 0.960 | 0.1424 | 0.956 | 0.2214 | 0.959 | 0.1682 |
| | (80, 80) | HBEL | 0.955 | 0.0513 | 0.956 | 0.0822 | 0.965 | 0.0602 |
| | | EL | 0.956 | 0.0517 | 0.956 | 0.0821 | 0.967 | 0.0605 |
| | | BT | 0.957 | 0.1062 | 0.955 | 0.1708 | 0.969 | 0.1281 |
| | | BS | 0.957 | 0.1062 | 0.959 | 0.1708 | 0.963 | 0.1281 |
| | (50, 20) | HBEL | 0.951 | 0.0942 | 0.944 | 0.1603 | 0.958 | 0.1243 |
| | | EL | 0.953 | 0.0957 | 0.945 | 0.1613 | 0.959 | 0.1262 |
| | | BT | 0.957 | 0.1936 | 0.941 | 0.3209 | 0.961 | 0.2332 |
| | | BS | 0.953 | 0.1936 | 0.945 | 0.3209 | 0.951 | 0.2332 |
| | (80, 50) | HBEL | 0.949 | 0.0595 | 0.947 | 0.1022 | 0.953 | 0.0740 |
| | | EL | 0.950 | 0.0600 | 0.948 | 0.1025 | 0.954 | 0.0745 |
| | | BT | 0.953 | 0.1252 | 0.945 | 0.2042 | 0.956 | 0.1528 |
| | | BS | 0.948 | 0.1253 | 0.944 | 0.2042 | 0.953 | 0.1528 |

**Table III: Level of 95 per cent confidence interval for $\Delta_{p_0 p_1}$. Bivariate normal distribution with $\rho = 0.3$.**

| True $\Delta_{p_0 p_1}$ | Sample size (m,n) | Method | ($p_0$, $p_1$)=(0-0.4) | | ($p_0$, $p_1$)=(0-0.7) | | ($p_0$, $p_1$)=(0.05-0.5) | |
|---|---|---|---|---|---|---|---|---|
| | | | Coverage probability | Length | Coverage probability | Length | Coverage probability | Length |
| 0 | (50, 50) | HBEL | 0.976 | 0.1650 | 0.981 | 0.2533 | 0.982 | 0.1846 |
| | | EL | 0.978 | 0.1693 | 0.981 | 0.2543 | 0.982 | 0.1872 |
| | | BT | 0.981 | 0.1699 | 0.979 | 0.2558 | 0.987 | 0.1882 |
| | | BS | 0.982 | 0.1699 | 0.977 | 0.2558 | 0.979 | 0.1882 |
| | (80, 80) | HBEL | 0.974 | 0.1278 | 0.972 | 0.1974 | 0.974 | 0.1447 |
| | | EL | 0.976 | 0.1299 | 0.972 | 0.1979 | 0.975 | 0.1460 |
| | | BT | 0.978 | 0.1302 | 0.972 | 0.1985 | 0.975 | 0.1465 |
| | | BS | 0.977 | 0.1302 | 0.969 | 0.1985 | 0.972 | 0.1465 |
| | (150, 150) | HBEL | 0.971 | 0.0917 | 0.980 | 0.1416 | 0.977 | 0.1025 |
| | | EL | 0.973 | 0.0925 | 0.979 | 0.1418 | 0.978 | 0.1030 |
| | | BT | 0.974 | 0.0926 | 0.979 | 0.1420 | 0.978 | 0.1032 |
| | | BS | 0.973 | 0.0926 | 0.974 | 0.1420 | 0.977 | 0.1032 |
| | (80, 50) | HBEL | 0.970 | 0.1516 | 0.975 | 0.2355 | 0.965 | 0.1730 |
| | | EL | 0.974 | 0.1546 | 0.975 | 0.2368 | 0.969 | 0.1750 |
| | | BT | 0.974 | 0.1551 | 0.975 | 0.2378 | 0.972 | 0.1757 |
| | | BS | 0.979 | 0.1551 | 0.975 | 0.2378 | 0.967 | 0.1757 |
| | (150, 80) | HBEL | 0.974 | 0.1171 | 0.976 | 0.1829 | 0.965 | 0.1320 |
| | | EL | 0.977 | 0.1185 | 0.976 | 0.1836 | 0.964 | 0.1330 |
| | | BT | 0.979 | 0.1188 | 0.975 | 0.1840 | 0.965 | 0.1333 |
| | | BS | 0.978 | 0.1188 | 0.972 | 0.1840 | 0.963 | 0.1333 |

**Table IV: Level of 95 per cent confidence interval for $\Delta_{p_0 p_1}$. Bivariate normal distribution with $\rho = 0.3$.**

| True $\Delta_{p_0 p_1}$ | Sample size (m,n) | Method | $(p_0, p_1)$=(0-0.4) | | $(p_0, p_1)$=(0-0.7) | | $(p_0, p_1)$=(0.05-0.5) | |
|---|---|---|---|---|---|---|---|---|
| | | | Coverage probability | Length | Coverage probability | Length | Coverage probability | Length |
| 0.2 | (50, 50) | HBEL | 0.982 | 0.0747 | 0.981 | 0.1158 | 0.983 | 0.0899 |
| | | EL | 0.982 | 0.0754 | 0.981 | 0.1157 | 0.983 | 0.0906 |
| | | BT | 0.983 | 0.1425 | 0.981 | 0.2261 | 0.984 | 0.1683 |
| | | BS | 0.983 | 0.1425 | 0.977 | 0.2261 | 0.981 | 0.1683 |
| | (80, 80) | HBEL | 0.983 | 0.0521 | 0.970 | 0.0878 | 0.976 | 0.0644 |
| | | EL | 0.984 | 0.0525 | 0.970 | 0.0880 | 0.977 | 0.0648 |
| | | BT | 0.984 | 0.1062 | 0.970 | 0.1741 | 0.978 | 0.1285 |
| | | BS | 0.982 | 0.1062 | 0.967 | 0.1741 | 0.971 | 0.1285 |
| | (150, 150) | HBEL | 0.963 | 0.0348 | 0.972 | 0.0632 | 0.968 | 0.0469 |
| | | EL | 0.963 | 0.0349 | 0.972 | 0.0632 | 0.968 | 0.0471 |
| | | BT | 0.965 | 0.0745 | 0.969 | 0.1241 | 0.968 | 0.0894 |
| | | BS | 0.961 | 0.0745 | 0.967 | 0.1241 | 0.967 | 0.0894 |
| | (80, 50) | HBEL | 0.971 | 0.0595 | 0.972 | 0.1088 | 0.971 | 0.0742 |
| | | EL | 0.972 | 0.0601 | 0.973 | 0.1092 | 0.973 | 0.0747 |
| | | BT | 0.971 | 0.1250 | 0.968 | 0.2186 | 0.974 | 0.1520 |
| | | BS | 0.970 | 0.1250 | 0.969 | 0.2186 | 0.972 | 0.1520 |
| | (150, 80) | HBEL | 0.958 | 0.0475 | 0.964 | 0.0828 | 0.962 | 0.0590 |
| | | EL | 0.961 | 0.0478 | 0.965 | 0.0829 | 0.963 | 0.0592 |
| | | BT | 0.961 | 0.0941 | 0.960 | 0.1616 | 0.966 | 0.1143 |
| | | BS | 0.957 | 0.0941 | 0.961 | 0.1616 | 0.963 | 0.1143 |

**Table V: Level of 90 per cent confidence interval for $\Delta_{p_0 p_1}$. Bivariate normal distribution with $\rho = 0$.**

| True $\Delta_{p_0 p_1}$ | Sample size (m,n) | Method | ($p_0$, $p_1$)=(0-0.4) | | ($p_0$, $p_1$)=(0-0.7) | | ($p_0$, $p_1$)=(0.05-0.5) | |
|---|---|---|---|---|---|---|---|---|
| | | | Coverage probability | Length | Coverage probability | Length | Coverage probability | Length |
| 0 | (20, 20) | HBEL | 0.919 | 0.2374 | 0.939 | 0.3522 | 0.935 | 0.2704 |
| | | EL | 0.930 | 0.2506 | 0.939 | 0.3529 | 0.942 | 0.2792 |
| | | BT | 0.942 | 0.2522 | 0.932 | 0.3656 | 0.944 | 0.2832 |
| | | BS | 0.934 | 0.2522 | 0.925 | 0.3656 | 0.933 | 0.2832 |
| | (50, 50) | HBEL | 0.922 | 0.1390 | 0.912 | 0.2130 | 0.925 | 0.1556 |
| | | EL | 0.927 | 0.1424 | 0.915 | 0.2137 | 0.927 | 0.1578 |
| | | BT | 0.927 | 0.1428 | 0.908 | 0.2148 | 0.929 | 0.1582 |
| | | BS | 0.925 | 0.1428 | 0.902 | 0.2148 | 0.919 | 0.1582 |
| | (80, 80) | HBEL | 0.896 | 0.1078 | 0.922 | 0.1659 | 0.900 | 0.1214 |
| | | EL | 0.902 | 0.1095 | 0.922 | 0.1663 | 0.906 | 0.1225 |
| | | BT | 0.906 | 0.1097 | 0.922 | 0.1667 | 0.907 | 0.1228 |
| | | BS | 0.902 | 0.1097 | 0.919 | 0.1667 | 0.896 | 0.1228 |
| | (50, 20) | HBEL | 0.880 | 0.1921 | 0.910 | 0.2959 | 0.907 | 0.2168 |
| | | EL | 0.891 | 0.1997 | 0.915 | 0.3002 | 0.912 | 0.2223 |
| | | BT | 0.902 | 0.2010 | 0.906 | 0.3077 | 0.915 | 0.2240 |
| | | BS | 0.894 | 0.2010 | 0.905 | 0.3077 | 0.908 | 0.2240 |
| | (80, 50) | HBEL | 0.889 | 0.1276 | 0.889 | 0.1987 | 0.900 | 0.1445 |
| | | EL | 0.894 | 0.1302 | 0.889 | 0.1998 | 0.903 | 0.1463 |
| | | BT | 0.898 | 0.1304 | 0.887 | 0.2006 | 0.908 | 0.1468 |
| | | BS | 0.891 | 0.1304 | 0.885 | 0.2006 | 0.902 | 0.1468 |

**Table VI: Level of 90 per cent confidence interval for $\Delta_{p_0 p_1}$. Bivariate normal distribution with $\rho = 0$.**

| True $\Delta_{p_0 p_1}$ | Sample size (m,n) | Method | $(p_0, p_1)=(0\text{-}0.4)$ | | $(p_0, p_1)=(0\text{-}0.7)$ | | $(p_0, p_1)=(0.05\text{-}0.5)$ | |
|---|---|---|---|---|---|---|---|---|
| | | | Coverage probability | Length | Coverage probability | Length | Coverage probability | Length |
| 0.2 | (20, 20) | HBEL | 0.965 | 0.1197 | 0.953 | 0.1871 | 0.953 | 0.1261 |
| | | EL | 0.966 | 0.1228 | 0.953 | 0.1851 | 0.957 | 0.1283 |
| | | BT | 0.969 | 0.2250 | 0.946 | 0.3305 | 0.960 | 0.2577 |
| | | BS | 0.962 | 0.2250 | 0.944 | 0.3305 | 0.936 | 0.2577 |
| | (50, 50) | HBEL | 0.938 | 0.0638 | 0.927 | 0.0985 | 0.942 | 0.0744 |
| | | EL | 0.939 | 0.0645 | 0.926 | 0.0986 | 0.943 | 0.0750 |
| | | BT | 0.940 | 0.1201 | 0.920 | 0.1892 | 0.944 | 0.1408 |
| | | BS | 0.938 | 0.1201 | 0.920 | 0.1892 | 0.932 | 0.1408 |
| | (80, 80) | HBEL | 0.923 | 0.0446 | 0.915 | 0.0715 | 0.927 | 0.0521 |
| | | EL | 0.924 | 0.0449 | 0.915 | 0.0715 | 0.928 | 0.0523 |
| | | BT | 0.924 | 0.0893 | 0.911 | 0.1463 | 0.928 | 0.1079 |
| | | BS | 0.923 | 0.0893 | 0.909 | 0.1463 | 0.915 | 0.1079 |
| | (50, 20) | HBEL | 0.912 | 0.0869 | 0.911 | 0.1363 | 0.893 | 0.1045 |
| | | EL | 0.916 | 0.0882 | 0.912 | 0.1370 | 0.896 | 0.1061 |
| | | BT | 0.919 | 0.1630 | 0.907 | 0.2700 | 0.901 | 0.1963 |
| | | BS | 0.913 | 0.1630 | 0.909 | 0.2700 | 0.879 | 0.1963 |
| | (80, 50) | HBEL | 0.921 | 0.0539 | 0.892 | 0.0879 | 0.915 | 0.0665 |
| | | EL | 0.922 | 0.0544 | 0.892 | 0.0880 | 0.916 | 0.0670 |
| | | BT | 0.929 | 0.1054 | 0.891 | 0.1749 | 0.916 | 0.1276 |
| | | BS | 0.919 | 0.1054 | 0.887 | 0.1749 | 0.900 | 0.1276 |

**Table VII: Level of 90 per cent confidence interval for $\Delta_{p_0 p_1}$. Bivariate normal distribution with $\rho = 0.3$.**

| True $\Delta_{p_0 p_1}$ | Sample size (m,n) | Method | ($p_0$, $p_1$)=(0-0.4) | | ($p_0$, $p_1$)=(0-0.7) | | ($p_0$, $p_1$)=(0.05-0.5) | |
|---|---|---|---|---|---|---|---|---|
| | | | Coverage probability | Length | Coverage probability | Length | Coverage probability | Length |
| 0 | (50, 50) | HBEL | 0.954 | 0.1387 | 0.966 | 0.2138 | 0.954 | 0.1550 |
| | | EL | 0.961 | 0.1422 | 0.966 | 0.2146 | 0.956 | 0.1572 |
| | | BT | 0.965 | 0.1426 | 0.964 | 0.2154 | 0.957 | 0.1578 |
| | | BS | 0.959 | 0.1426 | 0.962 | 0.2154 | 0.953 | 0.1578 |
| | (80, 80) | HBEL | 0.935 | 0.1072 | 0.950 | 0.1654 | 0.949 | 0.1219 |
| | | EL | 0.939 | 0.1090 | 0.950 | 0.1659 | 0.951 | 0.1230 |
| | | BT | 0.939 | 0.1091 | 0.948 | 0.1662 | 0.952 | 0.1233 |
| | | BS | 0.936 | 0.1091 | 0.945 | 0.1662 | 0.949 | 0.1233 |
| | (150,150) | HBEL | 0.952 | 0.0772 | 0.953 | 0.1193 | 0.944 | 0.0861 |
| | | EL | 0.953 | 0.0779 | 0.954 | 0.1195 | 0.945 | 0.0866 |
| | | BT | 0.955 | 0.0780 | 0.951 | 0.1197 | 0.947 | 0.0867 |
| | | BS | 0.950 | 0.0780 | 0.947 | 0.1197 | 0.946 | 0.0867 |
| | (80, 50) | HBEL | 0.935 | 0.1279 | 0.941 | 0.1994 | 0.946 | 0.1450 |
| | | EL | 0.939 | 0.1305 | 0.941 | 0.2004 | 0.949 | 0.1467 |
| | | BT | 0.941 | 0.1308 | 0.941 | 0.2007 | 0.951 | 0.1472 |
| | | BS | 0.934 | 0.1308 | 0.936 | 0.2007 | 0.945 | 0.1472 |
| | (150, 80) | HBEL | 0.940 | 0.0984 | 0.940 | 0.1541 | 0.935 | 0.1109 |
| | | EL | 0.942 | 0.0995 | 0.941 | 0.1547 | 0.936 | 0.1117 |
| | | BT | 0.947 | 0.0997 | 0.939 | 0.1549 | 0.938 | 0.1119 |
| | | BS | 0.938 | 0.0997 | 0.938 | 0.1549 | 0.934 | 0.1119 |

**Table VIII: Level of 90 per cent confidence interval for $\Delta_{p_0 p_1}$. Bivariate normal distribution with $\rho = 0.3$.**

| True $\Delta_{p_0 p_1}$ | Sample size (m,n) | Method | $(p_0, p_1)$=(0-0.4) | | $(p_0, p_1)$=(0-0.7) | | $(p_0, p_1)$=(0.05-0.5) | |
|---|---|---|---|---|---|---|---|---|
| | | | Coverage probability | Length | Coverage probability | Length | Coverage probability | Length |
| 0.2 | (50, 50) | HBEL | 0.956 | 0.0602 | 0.946 | 0.0914 | 0.965 | 0.0775 |
| | | EL | 0.958 | 0.0608 | 0.946 | 0.0912 | 0.965 | 0.0781 |
| | | BT | 0.958 | 0.1197 | 0.948 | 0.1902 | 0.965 | 0.1411 |
| | | BS | 0.954 | 0.1197 | 0.946 | 0.1902 | 0.963 | 0.1411 |
| | (80, 80) | HBEL | 0.940 | 0.0438 | 0.935 | 0.0766 | 0.948 | 0.0531 |
| | | EL | 0.941 | 0.0441 | 0.935 | 0.0765 | 0.948 | 0.0534 |
| | | BT | 0.942 | 0.0889 | 0.935 | 0.1457 | 0.949 | 0.1075 |
| | | BS | 0.938 | 0.0889 | 0.934 | 0.1457 | 0.935 | 0.1075 |
| | (150, 150) | HBEL | 0.925 | 0.0310 | 0.944 | 0.0510 | 0.954 | 0.0380 |
| | | EL | 0.925 | 0.0312 | 0.945 | 0.0510 | 0.955 | 0.0381 |
| | | BT | 0.925 | 0.0622 | 0.941 | 0.1040 | 0.954 | 0.0748 |
| | | BS | 0.925 | 0.0622 | 0.938 | 0.1040 | 0.944 | 0.0748 |
| | (80, 50) | HBEL | 0.931 | 0.0542 | 0.946 | 0.0868 | 0.931 | 0.0648 |
| | | EL | 0.934 | 0.0546 | 0.947 | 0.0871 | 0.936 | 0.0653 |
| | | BT | 0.933 | 0.1053 | 0.942 | 0.1752 | 0.936 | 0.1279 |
| | | BS | 0.929 | 0.1053 | 0.940 | 0.1752 | 0.930 | 0.1279 |
| | (150, 80) | HBEL | 0.909 | 0.0413 | 0.936 | 0.0651 | 0.931 | 0.0492 |
| | | EL | 0.913 | 0.0415 | 0.936 | 0.0652 | 0.933 | 0.0494 |
| | | BT | 0.912 | 0.0792 | 0.935 | 0.1350 | 0.933 | 0.0957 |
| | | BS | 0.909 | 0.0792 | 0.932 | 0.1350 | 0.925 | 0.0957 |

**APPENDIX B: Real Data Analysis Tables**

**Table IX: Dermatoscope Example**
**Level of 95 per cent confidence interval for $\Delta_{p_0 p_1}$**

| Method | CI & Length | $(p_0, p_1)=$ (0-0.4) | $(p_0, p_1)=$ (0-0.7) | $(p_0, p_1)=$ (0.05-0.5) |
|---|---|---|---|---|
| HBEL | Lower-Limit | -0.10722 | -0.11170 | -0.09468 |
| | Upper-Limit | 0.10722 | 0.11170 | 0.09468 |
| | CI_Length | 0.21444 | 0.22340 | 0.18936 |
| EL | Lower-Limit | -0.10913 | -0.11129 | -0.09512 |
| | Upper-Limit | 0.10913 | 0.11129 | 0.09512 |
| | CI_Length | 0.21826 | 0.22258 | 0.19024 |
| BT | Lower-Limit | -0.10931 | -0.11155 | -0.09533 |
| | Upper-Limit | 0.10931 | 0.11155 | 0.09533 |
| | CI_Length | 0.21862 | 0.22310 | 0.19066 |
| BS | Lower-Limit | -0.10945 | -0.11714 | -0.10025 |
| | Upper-Limit | 0.10917 | 0.10596 | 0.09041 |
| | CI_Length | 0.21862 | 0.22310 | 0.19066 |
| Estimate of $\Delta_{p_0 p_1}$ | | -0.00014 | -0.00559 | -0.00492 |

## Table X: Dermatoscope Example
### Level of 90 per cent confidence interval for $\Delta_{p_0 p_1}$

| Method | CI & Length | $(p_0, p_1)=$ (0-0.4) | $(p_0, p_1)=$ (0-0.7) | $(p_0, p_1)=$ (0.05-0.5) |
|---|---|---|---|---|
| HBEL | Lower-Limit | -0.08697 | -0.08704 | -0.08132 |
|  | Upper-Limit | 0.08697 | 0.08704 | 0.08132 |
|  | CI_Length | 0.17394 | 0.17408 | 0.16263 |
| EL | Lower-Limit | -0.08837 | -0.08674 | -0.08163 |
|  | Upper-Limit | 0.08837 | 0.08674 | 0.08163 |
|  | CI_Length | 0.17674 | 0.17349 | 0.16326 |
| BT | Lower-Limit | -0.08846 | -0.08687 | -0.08176 |
|  | Upper-Limit | 0.08846 | 0.08687 | 0.08176 |
|  | CI_Length | 0.17693 | 0.17374 | 0.16353 |
| BS | Lower-Limit | -0.08675 | -0.08216 | -0.08214 |
|  | Upper-Limit | 0.09018 | 0.09158 | 0.08139 |
|  | CI_Length | 0.17693 | 0.17374 | 0.16353 |
| Estimate of $\Delta_{p_0 p_1}$ | | 0.00171 | 0.00471 | -0.00037 |

# APPENDIX C:  The Splus code for simulation studies

```
#####################part 1: Functions#####################

## Function R(p)##
  Rp<-function(p, muy, stdd) 1-pnorm(qnorm(1-p),muy, stdd)


## solveNonlinear##
##nlmin can be used to solve a system of nonlinear equations:
  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$y0 <- y0    # set g's default value for y0
  g$f <- 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##
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 sigma##
my.mean <- function(vv) mean((vv-mean(vv))^2) ;


##solve  x[1]: p0p1.1  x[2]: p0p1.2  x[3]: lamda
f <- function(x) c( mean((V.hat[,1]-x[1])/(1-2*x[3]*(V.hat[,1]-x[1]))),
                    mean((V.hat[,2]-x[2])/(1+2*x[3]*(V.hat[,2]-x[2]))),
  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[1]: p0p1.1  x[2]: p0p1.2  x[3]: lamda x[4]: delta using C.deltap0p1.hat
g2 <- function(x) c( mean((V.hat[,1]-x[1])/(1-2*x[3]*(V.hat[,1]-x[1]))),
                    mean((V.hat[,2]-x[2])/(1+2*x[3]*(V.hat[,2]-x[2]))),
     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],
     C.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)


##x[1]: p0p1.1  x[2]: p0p1.2  x[3]: lamda x[4]: delta using C.deltap0p1
g1 <- function(x) c( mean((V.hat[,1]-x[1])/(1-2*x[3]*(V.hat[,1]-x[1]))),
                    mean((V.hat[,2]-x[2])/(1+2*x[3]*(V.hat[,2]-x[2]))),
     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],
     C.deltap0p1*(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 deltapAUC.hat##
deltapAUC <- function(X1X2, Y1Y2, p0, p1, m){

  # 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-p1);
   q1.2.hat<-quantile(X1X2[,2],1-p1);

    # Caculate V(ki).hat & C(deltap0p1).hat
    V.hat<-matrix(, m, 2)

   for (i in 1 : m){
      V.hat[i,1]<-(1-mean(Y1Y2[,1]<= X1X2[i,1]))*(q1.1.hat <=
    X1X2[i,1])*(X1X2[i,1]<=q0.1.hat)
      V.hat[i,2]<-(1-mean(Y1Y2[,2]<= X1X2[i,2]))*(q1.2.hat <=
    X1X2[i,2])*(X1X2[i,2]<=q0.2.hat)
      }
   delta.pAUC.hat<-mean(V.hat[,2])-mean(V.hat[,1])
   C.deltap0p1.hat<-(my.mean(V.hat[,1])+my.mean(V.hat[,2]))/(m*Vstar)

   list(delta.pAUC.hat, C.deltap0p1.hat, V.hat)
 }


##bootstrap function##
booth.trap <- function(B, X1X2, Y1Y2, m, n, p0, p1){
   delta.pAUC<-0;
  sigma <- matrix(,B, 2)
  for (b in 1:B) {
        X1B <- sample(X1X2[,1], m, replace = T)
        X2B <- sample(X1X2[,2], m, replace = T)
        Y1B <- sample(Y1Y2[,1], n, replace = T)
        Y2B <- sample(Y1Y2[,2], n, replace = T)

        q0B.1.hat<-quantile(X1B, c(1-p0)) # hatq0, hatq1: sample quantiles of F
        q0B.2.hat<-quantile(X2B, c(1-p0)) # hatq0, hatq1: sample quantiles of F
        q1B.1.hat<-quantile(X1B, c(1-p1))
        q1B.2.hat<-quantile(X2B, c(1-p1))

        VB     <- matrix(,m, 2)

for (i in 1:m)
    {
VB[i,1]<- (1-mean(Y1B <= X1B[i])) *(q1B.1.hat <= X1B[i])*(X1B[i] <= q0B.1.hat)
VB[i,2]<- (1-mean(Y2B <= X2B[i])) *(q1B.2.hat <= X2B[i])*(X2B[i] <= q0B.2.hat)
    }

        sigma[b,1]<-my.mean(VB[,1])
        sigma[b,2]<-my.mean(VB[,2])

        delta.pAUC[b]<-mean(VB[,2])-mean(VB[,1])
        }
  list(delta.pAUC, sigma)
  }

########################### End function part ####################

########################### Part2: initial value#################
iter<-1000
B=150
rho=0
#rho=0.3
m<-50; n<-20;
y1.sd<-2; y2.sd<-2;

levelc<-0.95
#levelc<-0.90
```

```
CritVal<-qchisq(levelc,1)
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<-c(0,0,0,0)
CIL<-c(0,0,0)
#LP<-c(0,0,0,0)
#UP<-c(0,0,0,0)


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))

  ##### 1. bootstrap ######
  boot.list<- booth.trap(B, X1X2, Y1Y2, m, n, p0, p1)

  delta.pAUC <- boot.list[[1]]
  sigma <- boot.list[[2]]

  delta.pAUCbar.B<-mean(delta.pAUC); delta.pAUCbar.B  # Estimate mean
   difference of two pAUCs by bootstrap

  Vstar<-var(delta.pAUC);         #Variance of delta.pAUC by bootstrap

  C.deltap0p1<-(mean(sigma[,1])+mean(sigma[,2]))/(m*Vstar);

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


  ###### 2. Caculate delta.pAUC.hat######

  delta.pAUC.hat.list <- deltapAUC(X1X2, Y1Y2, p0, p1, m)

  delta.pAUC.hat <- delta.pAUC.hat.list[[1]]
  C.deltap0p1.hat <- delta.pAUC.hat.list[[2]]
  V.hat <- delta.pAUC.hat.list[[3]]

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

```
###### 3. caculate L.deltap0p1######
# EL Method #

#x[1]: p0p1.1  x[2]: p0p1.2  x[3]: lamda

x<-solveNonlinear(f, c( 0,0, deltapAUC.true), c(0.1, 0.2, 0))

p0p1.1<-x$x[1];
p0p1.2<-x$x[2];
lamda<-x$x[3];

l.delta.p0p1<-2*(sum( log(1-2*lamda*(V.hat[,1]-p0p1.1)))+sum(
  log(1+2*lamda*(V.hat[,2]-p0p1.2))))


Vel<-C.deltap0p1*l.delta.p0p1;
Vel.hat<-C.deltap0p1.hat*l.delta.p0p1;
####END OF 3. ######

###### 4. Caculate C.I and coverage######

## compute the HBEL interval(Vel from bootstrap)##
     if (Vel <= CritVal)
     CovCount[1]<-CovCount[1]+1

    #x[1]: p0p1.1  x[2]: p0p1.2  x[3]: lamda x[4]: delta

     bd<-solveNonlinear(g1, c( 0,0,0,0), c(0.3, 0.1, 0.001, -0.9))
     #low.HBEL<-bd$x[4]  # lower limit of the CI

     b<-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

    #low and up band HBEL
    #LP[1]<- LP[1]+bd$x[4]
     #UP[1]<- UP[1]+ b$x[4]

     # The length of HBEL CI
     CIL[1]<- CIL[1]+(b$x[4]- bd$x[4])


## compute the EL interval(Vel.hat)##
     if (Vel.hat <= CritVal)
     CovCount[2]<-CovCount[2]+1

     #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, -0.999))
    #low.EL<-lw$x[4]       # lower limit of the CI

    upb<-solveNonlinear(g2, c( 0,0,0,0), c(0.1, 0.3, 0.001, 0.999))
    #up.EL<-upb$x[4]        # upper limit of the CI

    #low and up band of El
     #LP[2]<- LP[2]+lw$x[4]
     #UP[2]<- UP[2]+ upb$x[4]

    # The length of EL CI
     CIL[2]<- CIL[2]+(upb$x[4]- lw$x[4])


## compute the BTI interval.
   hwidth<-Z*sqrt(Vstar)
```

```
     # tlow<- delta.pAUC.hat-hwidth              # lower limit of the CI
      #tup<- delta.pAUC.hat+hwidth               # upper limit of the CI

     if (((delta.pAUC.hat-hwidth)<= deltapAUC.true) & ((delta.pAUC.hat+hwidth)
   >= deltapAUC.true)) CovCount[3]<-CovCount[3]+1

       #low and up band
        #LP[3]<-LP[3]+(delta.pAUC.hat-hwidth)
       #UP[3]<-UP[3]+(delta.pAUC.hat+hwidth)
        CIL[3]<- CIL[3]+2*hwidth                 # The length of BT and BS CI




## compute the bootstrap(BS) interval
      #bslow<- delta.pAUCbar.B-hwidth            # lower limit of the CI
      #bsup<- delta.pAUCbar.B+hwidth              # upper limit of the CI

      if (((delta.pAUCbar.B-hwidth) <= deltapAUC.true) &
   ((delta.pAUCbar.B+hwidth)>= deltapAUC.true)) CovCount[4]<-CovCount[4]+1
      #low and up band
      #LP[4]<-LP[4]+(delta.pAUCbar.B-hwidth)
      #UP[4]<-UP[4]+(delta.pAUCbar.B+hwidth)


}

 cov<-CovCount/iter; cov
  #bound.L<-LP/iter
  #bound.U<-UP/iter
  wid<-CIL/iter;wid

#Result Output
sink("C:\\Temp\\new5020.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 (HBEL, EL, BT, BS) CI's for delta :", cov, "\n")
cat("Average length of (HBEL,EL,BTI&BS):", wid, "\n")

cat("-------------------------------------------------------------------------
   ------------------------------","\n")


sink();
```

**APPENDIX D:  The Splus code for real data analysis**

```
coln<-c("ID", "MTH1", "MTH2","GP")
realdata<-read.table("C:\\TEMP\\Thesis\\exam3.dat",col.names=coln, header=F)
realdata
X1<-realdata$MTH1[realdata$GP==0]; X1
X2<-realdata$MTH2[realdata$GP==0]; X2
Y1<-realdata$MTH1[realdata$GP==1]; Y1
Y2<-realdata$MTH2[realdata$GP==1]; Y2
m=length(X1)
n=length(Y1)

levelc<-0.90;
CritVal<-qchisq(levelc,1)
#Z<-qnorm(levelc);
Z<-qnorm(1-(1-levelc)/2)
p0<-0.05;  p1<-0.5;


###### part 1: Bootstrap  ######
  #### Bootstrap start ####
   B=500;
   sigma=pAUC=matrix(,B, 2)


   for (b in 1:B)
    {
    X1B <- sample(X1, m, replace = T)
    X2B <- sample(X2, m, replace = T)
    Y1B <- sample(Y1, n, replace = T)
    Y2B <- sample(Y2, n, replace = T)

    q0B.1.hat<-quantile(X1B, c(1-p0)) # hatq0, hatq1: sample quantiles of F
    q0B.2.hat<-quantile(X2B, c(1-p0)) # hatq0, hatq1: sample quantiles of F
    q1B.1.hat<-quantile(X1B, c(1-p1))
    q1B.2.hat<-quantile(X2B, c(1-p1))


    VB <- matrix(,m,2)
    for (i in 1:m)
       {
        VB[i,1]<- (1-mean(Y1B <= X1B[i])) *(q1B.1.hat <= X1B[i])*(X1B[i] <=
   q0B.1.hat)
        VB[i,2]<- (1-mean(Y2B <= X2B[i]))*(q1B.2.hat <= X2B[i])*(X2B[i] <=
   q0B.2.hat)
       }

       sigma[b,1]<-mean((VB[,1]-mean(VB[,1]))^2)    ##my.mean(VB[,1]) if using
   function
       sigma[b,2]<-mean((VB[,2]-mean(VB[,2]))^2)


       pAUC[b,1]<-mean(VB[,1])
       pAUC[b,2]<-mean(VB[,2])

   }

  delta.pAUCbar.B<-mean(pAUC[,2]-pAUC[,1])      # Estimate mean difference of
   two pAUCs by bootstrap

   ##Variance of delta.pAUC by bootstrap
```

```
   #Vstar1<-var(pAUC[,1])+var(pAUC[,2]); #Vstar1

#  V12<- sum((pAUC[,1]-mean(pAUC[,1]))*(pAUC[,2]-mean(pAUC[,2])))/(B-1)
 # Vstar2<-var(pAUC[,1])+var(pAUC[,2])-2*V12;    #Vstar2

   Vstar <- var(pAUC[,2]-pAUC[,1]);  Vstar

   C.deltap0p1<-(mean(sigma[,1])+mean(sigma[,2]))/(m*Vstar); C.deltap0p1;
    #bootstrap C.deltap0p1 to caculate HBEL




   ######################Bootstrap end #################


   ######Part 2:  Caculate delta.pAUC.hat######

 ## Caculate X Quantile of 1-pi (i=0,1) for q.hat
  q0.1.hat<-quantile(X1,1-p0);q0.1.hat
  q0.2.hat<-quantile(X2,1-p0);q0.2.hat
  q1.1.hat<-quantile(X1,1-p1); q1.1.hat
  q1.2.hat<-quantile(X2,1-p1); q1.2.hat

  ## Caculate V(ki).hat & C(deltap0p1).hat
  V1.hat<-V2.hat<-0
  for (i in 1 : m){
     V1.hat[i]<-(1-mean(Y1<= X1[i]))*(q1.1.hat <= X1[i])*(X1[i]<=q0.1.hat)
     V2.hat[i]<-(1-mean(Y2<= X2[i]))*(q1.2.hat <= X2[i])*(X2[i]<=q0.2.hat)
     }

  V1.hat
  V2.hat
  delta.pAUC.hat<-mean(V2.hat)-mean(V1.hat); delta.pAUC.hat

  #V1.hat; #V2.hat
  sigmap0p1.1.hat<-mean((V1.hat-mean(V1.hat))^2)
  sigmap0p1.2.hat<-mean((V2.hat-mean(V2.hat))^2)
  C.deltap0p1.hat<-(sigmap0p1.1.hat+sigmap0p1.2.hat)/(m*Vstar);
   C.deltap0p1.hat




   ######Part 3: Caculate C.I and coverage######

   ## compute the HBEL1 interval(Vel from bootstrap)##

     #x[1]: p0p1.1  x[2]: p0p1.2  x[3]: lamda x[4]: delta

     g1 <- function(x) c( mean((V1.hat-x[1])/(1-2*x[3]*(V1.hat-x[1]))),
                   mean((V2.hat-x[2])/(1+2*x[3]*(V2.hat-x[2]))),
     mean(V2.hat/(1+2*x[3]*(V2.hat-x[2])))-mean(V1.hat/(1-2*x[3]*(V1.hat-
  x[1])))-x[4],
     C.deltap0p1*(2*(sum( log(abs(1-2*x[3]*(V1.hat-x[1]))))+sum(
  log(abs(1+2*x[3]*(V2.hat-x[2])))))))-CritVal)

     bd<-solveNonlinear(g1, c( 0,0,0,0), c(0.3, 0.1, 0.001, -0.9))
     low.HBEL<-bd$x[4]  # lower limit of the CI

     b<-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
```

```
        # The length of HBEL CI
        CIL.HBEL=up.HBEL- low.HBEL


     ## compute the EL interval(Vel.hat)##

        #x[1]: p0p1.1  x[2]: p0p1.2  x[3]: lamda x[4]: delta
        g2 <- function(x) c( mean((V1.hat-x[1])/(1-2*x[3]*(V1.hat-x[1]))),
                    mean((V2.hat-x[2])/(1+2*x[3]*(V2.hat-x[2]))),
         mean(V2.hat/(1+2*x[3]*(V2.hat-x[2])))-mean(V1.hat/(1-2*x[3]*(V1.hat-
    x[1])))-x[4],
        C.deltap0p1.hat*(2*(sum( log(abs(1-2*x[3]*(V1.hat-x[1]))))+sum(
    log(abs(1+2*x[3]*(V2.hat-x[2])))))-CritVal)

      lw<-solveNonlinear(g2, c( 0,0,0,0), c(0.3, 0.1, 0.001, -0.999))
      low.EL<-lw$x[4];       # lower limit of the CI

      up<-solveNonlinear(g2, c( 0,0,0,0), c(0.1, 0.3, 0.001, 0.999))
      up.EL<-up$x[4];         # upper limit of the CI

       # The length of EL CI
        CIL.EL=up.EL- low.EL




     ## compute the BT interval.

      hwidth<-Z*sqrt(Vstar); hwidth
       tlow<- delta.pAUC.hat-hwidth            # lower limit of the CI
       tup<- delta.pAUC.hat+hwidth           # upper limit of the CI

        CIL.BT<-2*hwidth              # The length of BT and BS CI


     ## compute the bootstrap(BS) interval.
       bslow<- delta.pAUCbar.B-hwidth        # lower limit of the CI
       bsup<- delta.pAUCbar.B+hwidth            # upper limit of the CI


 up=c(up.HBEL, up.EL, tup, bsup);up
 low=c(low.HBEL, low.EL, tlow, bslow);low
 wid=c(CIL.HBEL, CIL.EL, CIL.BT, CIL.BT);wid


#Result Output;

sink("C:\\temp\\real.txt", append = T)

cat("Real data At level=", levelc, "p0=", p0, "P1=", p1,
 "m=", m, "n=", n, "B=",  B, "\n")
cat("delta.pAUCbar.B=", delta.pAUCbar.B, "delta.pAUC.hat=", delta.pAUC.hat,
   "\n" )
cat("upbound of the (HBEL, EL, BT, BS) CI's for real data are:",
 up , "\n")
cat("lowbound of the (HBEL, EL, BT, BS) CI's for real data are:",
low , "\n")
cat("length of (HBEL,EL,BTI&BS):",
wid, "\n")

cat("----------------------------------------------------------------","\n")


sink();
```