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EMPIRICAL LIKELIHOOD CONFIDENCE INTERVALS FOR THE SENSITIVITY OF A CONTINUOUS-SCALE DIAGNOSTIC TEST

by

ANGELA E. DAVIS

Under the Direction of Gengsheng Qin

ABSTRACT

Diagnostic testing is essential to distinguish non-diseased individuals from diseased individuals. More accurate tests lead to improved treatment and thus reduce medical mistakes. The sensitivity and specificity are two important measurements for the diagnostic accuracy of a diagnostic test. When the test results are continuous, it is of interest to construct a confidence interval for the sensitivity at a fixed level of specificity for the test. In this thesis, we propose three empirical likelihood intervals for the sensitivity. Simulation studies are conducted to compare the empirical likelihood based confidence intervals with the existing normal approximation based confidence interval. Our studies show that the new intervals had better coverage probability than the normal approximation based interval in most simulation settings.

INDEX WORDS: Empirical Likelihood, Confidence Intervals, Diagnostic Test, Sensitivity, Specificity

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ANGELA E. DAVIS

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2007

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"To whom much is given, much more is also required."

To those who stood in the gap, this is dedicated to you.

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Chapter I

INTRODUCTION

Diagnostic testing, an integral facet of medical testing, aids in classifying the presence or absence of a disease or condition. There are two types of diagnostic tests: qualitative and quantitative. A qualitative test classifies patients as diseased or non-diseased based on clinical signs or symptoms. A quantitative test classifies patients according to *c*, a predetermined cutoff point. Disease or non-disease status is dependent upon whether or not the test result falls above or below the cutoff point. A more accurate diagnostic test leads to more effective treatment and thus reduces medical malpractice and mortality. The results of a diagnostic test help to answer two questions: If the test is positive, what is the probability that the person actually has the disease, and if the test is negative, what is the probability that the person actually doesn't have the disease? These questions can simply be answered in terms of the test's sensitivity and specificity respectively. A model test would have high sensitivity and high specificity.

The Receiver Operating Characteristic (ROC) curve, developed in World War II, was initially used in signal detection theory. It has since become widely used in diagnostic medicine as an efficient way to graphically display the tradeoff between sensitivity and specificity. When the specificity is high, the sensitivity is low and vice versa. More specifically, a ROC curve is a plot of 1 - specificity against sensitivity. In order to classify the results of a diagnostic test as positive or negative, a cutoff point *c*

must be defined when the response is continuous. When a level of specificity is chosen (commonly 80 %, 90% or 95%), it is of interest to construct confidence intervals for the sensitivity at the selected level of specificity.

Empirical likelihood (EL), introduced by Owen (1988, 1990), is a powerful non-parametric method. The EL method has many advantages over normal approximation based methods. For example, it has better small sample performance than approaches based on normal approximation; EL-based confidence regions are range preserving and transformation respecting; the regularity conditions for EL-based methods are weak and natural etc. The use of EL methods has becoming increasingly common in recent years and is attractive in many applied area (Wu and Rao, 2006). Claeskens et al. (2003), one of few studies on the EL method for ROC analysis, developed an empirical likelihood confidence interval for a ROC curve. Their EL confidence interval had better coverage probability than the normal approximation based interval. However, their method still needs kernel distribution estimation and the selection of smoothing parameters are problematic. It thus has not been well applied in practice.

In this thesis, we propose new empirical likelihood based confidence intervals and compare them with the existing normal approximation based interval. The thesis is organized in the following manner: Chapter I is an introduction, Chapter II lists concepts and terminology used throughout the thesis, existing confidence intervals for sensitivity at a fixed level of specificity for a continuous-scale test are presented in Chapter III, Chapter IV introduces three new empirical likelihood intervals for sensitivity at a fixed level of specificity, in Chapter V we conduct simulations studies to evaluate the

performance of new confidence intervals and in Chapter VI we apply the proposed methods to a real dataset. Lastly, there is a discussion of our findings in Chapter VII.

Chapter II

CONCEPTS AND TERMINOLOGY

2.1 Sensitivity and Specificity of a Binary Diagnostic Test

Sensitivity – probability that a diseased patient will have a positive test result.
P(positive test | patient has the disease)

Specificity – probability that a non-diseased patient will have a negative test result.
P(negative test | patient doesn't have the disease)

Classification of individuals according to diagnostic test results are shown in the following table:

Test Result	**Disease/Condition**	
	Present	**Absent**
Positive	True Positive (TP)	False Positive (FP)
Negative	False Negative (FN)	True Negative (TN)

Figure 1. 2x2 classification table of diagnostic test results

The following formulas are used to estimate the sensitivity and specificity:

$$Sensitivity = \frac{TP}{TP + FN}$$

$$Specificity = \frac{TN}{FP + TN}$$

2.2 Sensitivity and Specificity of a Continuous-Scale Diagnostic Test

For a continuous-scale diagnostic test, let X be the test result from a non-diseased patient, and let Y be the test result from a diseased patient. At a given cutoff point c, the sensitivity and specificity are defined as

$$S_e = P(Y \geq c), \quad S_p = P(X \leq c),$$

respectively. If F is the distribution function of X and G is the distribution function of Y, the sensitivity and specificity can then be written as

$$S_e = 1\text{-}G(c), \quad S_p = F(c).$$

At a fixed level p of specificity, the corresponding sensitivity of the test is

$$R(p) = 1 - G(F^{-1}(p)),$$

where F^{-1} is the inverse function of F.

One problem that arises is how to construct a (1-α)100% confidence interval for $R(p)$ based on, $X_1,\ldots,X_m$, the results from the non-diseased group, and $Y_1,\ldots,Y_n$, the results from the diseased group.

Chapter III

EXISTING METHODS

3.1 Normal Approximation Based Confidence Interval

If $R(p) = P(Y \geq F^{-1}(p))$, then the estimator for $R(p)$ is the observed sensitivity at the *p*-th sample quantile from the test results of the non-diseased individuals. If we let $\hat{F}$ be the empirical distribution function based on $X_1,...,X_m$, then the estimator for $R(p)$ becomes

$$\hat{R}(p) = \frac{\sum_{j=1}^{n} I(Y_j \geq \hat{F}^{-1}(p))}{n}. \tag{1}$$

Linnet (1987) presented a formula for the variance of $\hat{R}(p)$ defined as

$$Var(\hat{R}(p)) = \frac{R(p)(1-R(p))}{n} + \frac{p(1-p)}{m} \cdot \frac{g^2(F^{-1}(p))}{f^2(F^{-1}(p))}, \tag{2}$$

where *f* and *g* are the probability density functions of *F* and *G* respectively. It has been shown that when both *m* and *n* are large, $\hat{R}(p)$ has an approximately normal distribution with mean *R(p)* and variance $Var(\hat{R}(p))$, given by (2). By substituting unknown quantities in (2) by their corresponding sample estimates, we can obtain a (1-α)100% normal approximation based confidence interval for $R(p)$. However, this interval may be greatly affected by poor empirical density and quantile estimation. Platt et al. (2000)

studied this issue and found via simulation study that the normal approximation based confidence interval could have poor coverage probability.

3.2 Empirical Likelihood Interval

Let $\theta = R(p) = 1 - G(F^{-1}(1-p))$ then there exists a quantity η such that

$$F^{-1}(1-p) = G^{-1}(1-\theta) = \eta .$$

Using this relationship between sensitivity and specificity, Claeskens, Jing, Peng and Zhou (2003) proposed a smoothed empirical likelihood for $R(p)$ defined as follows:

$$L(\theta) = \sup_{p,q,\eta}\left(\prod_{i=1}^{n} p_i\right)\left(\prod_{j=1}^{m} q_j\right)$$

subject to the following constraints

$$\sum_{i=1}^{n} p_i G_1\left(\frac{\eta - Y_i}{h_1}\right) = 1-\theta, \quad \sum q_j G_2\left(\frac{\eta - X_j}{h_2}\right) = 1-p$$

where **p** and **q** are probability vectors, G_1 and G_2 are known functions and $h_j's$ are unknown smoothing parameters. Claeskens et al (2003), under certain conditions, illustrated that the empirical log-likelihood ratio is a chi-square distribution,

$$\ell(\theta) \to \chi_1^2 ,$$

and by inversing $\ell(\theta)$, they obtained an empirical likelihood confidence interval for $R(p)$ defined as

$$\left\{\theta : \ell(\theta) \le \chi_1^2(1-\alpha)\right\}. \tag{3}$$

Their new confidence interval performed much better than the normal approximation based interval. However, the smoothed empirical likelihood method has two main drawbacks: (1) The method is computationally extensive, three nonlinear equations have to be solved to calculate the value of $\ell(\theta)$; (2) Two smoothing parameters $h_j's$ have to be selected, which is problematic in practice.

Chapter IV

NEW CONFIDENCE INTERVALS

Qin and Zhou (2006) successfully applied the empirical likelihood method to the inference for an area under the ROC curve. We will define the empirical likelihood method in this section for the sensitivity of a diagnostic test. Pepe (2003) defined a placement value for a given test value *Y* from a diseased subject as

$$U = 1 - F(Y).$$

This value is the proportion of the non-diseased population with a test value greater than *Y*, essentially marking the placement of *Y* within the non-diseased distribution. It is evident that

$$E(I(U \le p)) = P(F(Y) \ge p) = P(Y \ge F^{-1}(p)) = R(p).$$

Based on the relationship between $R(p)$ and the placement value U, an empirical likelihood procedure is derived for the sensitivity of a diagnostic test. Let **p** = $(p_1, p_2, ..., p_n)$ be a probability vector, i.e., $\sum_{j=1}^{n} p_j = 1$ and $p_j \ge 0$ for all *j*. The profile empirical likelihood for $R(p)$ can be defined as

$$\widetilde{L}(R(p)) = \sup\left\{\prod_{j=1}^{n} p_j : \sum_{j=1}^{n} p_j = 1, \quad \sum_{j=1}^{n} p_j W_j(p) = 0\right\},$$

where $W_j(p) = I(U_j \le p) - R(p)$ with $U_j = 1 - F(Y_j), \quad j = 1,2,...,n.$ Placement values, U_j's, depend on the unknown distribution function *F* of the non-diseased population.

Therefore, by replacing F by its empirical distribution $\hat{F}$, we get an adjusted empirical likelihood for $R(p)$:

$$L(R(p)) = \sup\left\{\prod_{j=1}^{n} p_j : \sum_{j=1}^{n} p_j = 1, \quad \sum_{j=1}^{n} p_j \hat{W}_j(p) = 0 = 0\right\},$$

where $\hat{W}_j(p) = I(\hat{U}_j \le p) - R(p)$ with $\hat{U}_j = 1 - \hat{F}(Y_j) \quad j = 1,2,...,n.$ Then, by Lagrange multiplier, we get

$$p_j = \frac{1}{n}\left\{1 + \lambda \hat{W}_j(p))\right\}^{-1}, \quad j = 1,2,...n,$$

where λ is the solution of

$$\frac{1}{n}\sum_{j=1}^{n} \frac{\hat{W}_j(p)}{1 + \lambda \hat{W}_j(p)} = 0. \tag{4}$$

Note that $\prod_{j=1}^{n} p_j$, subject to $\sum_{j=1}^{n} p_j = 1$, attains its maximum n^{-n} at $p_j = n^{-1}$. So the empirical likelihood ratio for $R(p)$ is defined as

$$r(R(p)) = \prod_{j=1}^{n} (np_j) = \prod_{j=1}^{n} \left\{1 + \lambda \hat{W}_j(p)\right\}^{-1}.$$

The resulting log-pseudo-empirical likelihood ratio is

$$l(R(p)) = -2\log r(R(p)) = 2\sum_{j=1}^{n} \log\left\{1 + \lambda \hat{W}_j(p)\right\}, \tag{5}$$

where λ is the solution of (4).

Qin (2006) established the following theorem for the asymptotic distribution for the log-pseudo-empirical likelihood ratio.

Theorem 3.1. *If* $R_0(p)$ *is the true value of sensitivity* $R(p)$ *at a fixed level p of specificity, and 0 < R(p) <1 for 0 < p < 1, then the limiting distribution of* $l(R_0(p))$, *defined by (5), is a scaled chi-square distribution with one degree of freedom. That is,*

$$c(p)l(R_0(p)) \longrightarrow \chi_1^2, \tag{6}$$

where the scale constant $c(p)$ *is*

$$c(p) = \frac{\sigma^2(p)}{\sigma_1^2(p)}$$

with

$$\sigma^2(p) = R(p)(1 - R(p)),$$
$$\sigma_1^2(p) = \sigma^2(p) + \frac{n}{m} \cdot p(1-p) \cdot \frac{g^2(F^{-1}(p))}{f^2(F^{-1}(p))}.$$

Here f and g are the density functions of F and G respectively.

In order to construct confidence intervals for $R(p)$ based on Theorem 3.1, we need to estimate $\sigma^2(p)$ and $\sigma_1^2(p)$. Let

$$\hat{\sigma}^2(p) = \hat{R}(p)(1 - \hat{R}(p)),$$
$$\hat{\sigma}_1^2(p) = \hat{\sigma}^2(p) + \frac{n}{m} \cdot p(1-p) \cdot \frac{\hat{g}^2(\hat{F}^{-1}(p))}{\hat{f}^2(\hat{F}^{-1}(p))}.$$

where $\hat{F}^{-1}(p)$ is the *p-th* sample quantile of X_i's, $\hat{f}$ and $\hat{g}$ are the estimates of density functions *f* and *g*. Then, a (1-α)-*th* empirical likelihood based confidence interval, called ELI interval, for $R(p)$, is defined by

$$CI_{2,\alpha}(R(p)) = \{R(p) : \hat{c}(p)\ell R(p)) \le \chi_1^2(1-\alpha)\}, \tag{7}$$

where $\hat{c}(p) = \dfrac{\hat{\sigma}^2(p)}{\hat{\sigma}_1^2(p)}$. By Theorem 3.1, $CI_{1,\alpha}(R(p))$ gives an approximate confidence interval for $R_0(p)$ with asymptotically correct coverage probability 1-α, i.e.,

$$P(R_0(p) \in CI_{2,\alpha}(R(p))) = 1 - \alpha + o(1).$$

The performance of the ELI interval depends on the density estimates $\hat{f}$ and $\hat{g}$, particularly when the sample sizes are small. We now propose a bootstrap method to estimate $\sigma_1^2(p)$. The bootstrap estimate is motivated by the fact that $\sigma_1^2(p)$ is the asymptotic variance of $n^{1/2}(\hat{R}(p) - R(p))$. The procedure for computing the bootstrap variance can be summarized in the following steps:

1. Draw a resample of size n, $Y_i^*'s$, with replacement from the diseased sample $Y_i's$ and a separate resample of size m, $X_i^*'s$, with replacement from the non-diseased sample $X_i's$.
2. Calculate the bootstrap version of $\hat{R}(p)$,

$$\hat{R}^*(p) = \frac{\sum_{i=1}^{n} I\left[Y_i^* \ge \hat{F}^{-1*}(p)\right]}{n},$$

where $\hat{F}^{-1*}(p)$ is the p-th sample quantile based on the bootstrap resample $X_j^*'s$.

3. Repeat the first two steps B times to obtain the set of bootstrap replications $\left\{\hat{R}^{*b}(p): b=1,2,...,B\right\}$. Then, the bootstrap estimate $\sigma_1^{*2}(p)$ for $\sigma_1^2(p)$ is defined by

$$\sigma_1^{*2}(p)=\frac{n}{B-1}\sum_{b=1}^{B}(\hat{R}^{*b}(p)-\overline{R}^{*}(p))^2,$$

where $\overline{R}^{*}(p)=(1/B)\sum_{b=1}^{B}R^{*b}(p)$.

Now we propose two new empirical likelihood based confidence intervals for $R(p)$ by using the bootstrap variance $\sigma_1^{*2}(p)$.

The first one, called ELII interval, is defined by

$$\left\{R(p): c_1^{*}(p)l(R(p))\le \chi_1^2(1-\alpha)\right\}, \tag{8}$$

where $c_1^{*}(p)=\dfrac{\hat{\sigma}^2(p)}{\hat{\sigma}_1^{*2}(p)}$.

The second one, called ELIII interval, is defined by

$$\left\{R(p): c_2^{*}(p)l(R(p))\le \chi_1^2(1-\alpha)\right\}, \tag{9}$$

where $c_2^{*}(p)=\dfrac{\overline{R}^{*}(p)(1-\overline{R}^{*}(p))}{\hat{\sigma}_1^{*2}(p)}$.

Chapter V

SIMULATION STUDIES FOR THE CONFIDENCE INTERVALS

We conducted three simulation studies to compare the coverage accuracy of the newly proposed intervals to that of the normal approximation based interval. In simulation studies, we generate 3,000 random samples of size m from the distribution function F for test responses of non-diseased patients and another independent random sample of size n from the distribution function G for test responses of diseased patients. In these studies, the sample sizes (m,n) were chosen to be (20,50), (50,20), (50,100), (100,50), (50,50) and (100,100), respectively.

In the first simulation study, the distribution function F was chosen to be a standard normal distribution whereas the distribution function G was a normal distribution with mean μ and variance 1. The specificity was fixed at 80% or 90% level for different values of μ (See Table I). The results of the simulation study at the nominal level of 95% are given in Tables IV-IX.

Table I. Parameter settings for the normal distribution at fixed levels of specificity.

Run	μ	Specificity (p)	Sensitivity ($R(p)$)
1	2.9264	0.90	0.95
2	2.5631	0.90	0.90
3	2.1231	0.90	0.80
4	2.4865	0.80	0.95
5	1.6832	0.80	0.80

Our distributions, *F* and *G*, were beta distributions with parameters (a_0,b_0) and (a_1,b_1) respectively in the second simulation study. The specificity was also fixed at 80% or 90% for different values of (a_0,b_0) and (a_1,b_1) to get the corresponding sensitivities (See Table II). The coverage probabilities resulting from the simulation study at the nominal level of 95% are given in Tables X-XV.

Table II. Parameter setting for the Beta Distribution at fixed levels of specificity.

Run	(a_1,b_1)	(a_0,b_0)	Specificity (p)	Sensitivity ($R(p)$)
1	(4,1)	(1,3.5)	0.90	0.95
2	(3,1)	(1,3)	0.80	0.93
3	(3,1)	(1,3)	0.90	0.85
4	(4,2)	(2,4)	0.80	0.82
5	(3,2)	(2,3)	0.80	0.55

In the third simulation study, we chose the distributions *F* and *G* to be the standard exponential distribution (with rate = 1) and an exponential distribution with rate = $1/\delta - 1$, where δ represents the area under the receiver operating characteristic curve (AUC). Here, δ was taken to be 0.95. Specificity was set at 0.60, 0.70, 0.80, 0.90 and 0.95 along with the corresponding sensitivities (See Table III). The coverage probabilities resulting from the simulation study at the nominal level of 95% are given in Tables XVI-XXI.

Table III. Parameter settings for the exponential distribution

Run	δ	Specificity (p)	Sensitivity ($R(p)$)
1	0.95	0.60	0.95
2	0.95	0.70	0.94
3	0.95	0.80	0.92
4	0.95	0.90	0.89
5	0.95	0.95	0.85

The simulation studies illustrate that the newly proposed intervals generally performed better than the normal approximation based interval at the 95% nominal level in most settings.

Chapter VI

REAL APPLICATION

In this chapter, we apply the newly proposed intervals to a real life data example. The data is from 403 subjects out of a group of 1046 who were selected to gain more understanding regarding the prevalence of diabetes, obesity, etc. among African Americans in central Virginia. The risk factors that were chosen from the study were the waist and hip measurements, as they have been known to be a predictor of diabetes.

6.1 Detection of Diabetes

Diabetes is a disease resulting from the way our bodies use blood glucose. The glucose (sugar) is your body's energy source. Insulin, produced by the pancreas, helps the body produce sugar, which is used for energy. Too little insulin or the body using it improperly causes diabetes. It is the 5th leading cause of death in America and more prevalent among African Americans. Left untreated, diabetes leads to amputations, organ failure and even death in some cases.

Our study used the waist and hip measurements (in inches) of 388 female and male subjects to determine the waist/hip ratio (WHR). The waist/hip ratio is just one way of detecting diabetes in patients. Excess abdominal fat has been associated with higher levels of insulin, which can raise blood sugar and pressure among other things. A WHR greater than 0.8 in women and 0.9 in men is said to increase the risk of diabetes in

patients. Snijder et al. (2004) found that waist and hip measurements are important factors in predicting diabetes and other diseases.

The new empirical likelihood confidence intervals were applied to the data to determine the accuracy of the WHR in predicting diabetes. There were 305 non-diseased patients and 83 diseased patients. The results of the computation are found in Table XXII. The interval lengths were shorter when specificity was fixed at 90% and 95%.

Chapter VII

DISCUSSION

Diagnostic testing is essential in distinguishing diseased patients from non-diseased patients. When the result of a test is more accurate, there is less misconduct and better treatment options can be implemented. The ROC curve provides a summary of the performance of a diagnostic test (Claeskens et. al, 2003). For a quantitative test, the cutoff point c is imperative because it determines which patients will be classified as diseased and non-diseased. When the response of a test is continuous, it is of interest to construct confidence intervals for the sensitivity of the test at this point. Calculating the sensitivity and specificity of a test at various cutoff points is effective in determining the best point at which to classify the test. The normal approximation confidence intervals are inadequate when the distribution is skewed or the parameter range is restricted (Wu and Rao, 2006). We proposed three new empirical likelihood confidence intervals for the sensitivity of a continuous scale diagnostic test at a fixed level of specificity. The newly proposed intervals were shown to generally perform better than the normal approximation based interval at the 95% nominal level in most simulation settings.

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APPENDIX I: SIMULATION TABLES

A. Normal Distribution Tables

Table IV. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the normal distribution with m=20 and n=50.

Run	Method	Coverage Probability 95%
1	Normal	0.9957
	ELI	0.9810
	ELII	0.9793
	ELIII	0.9836
2	Normal	0.9280
	ELI	0.9746
	ELII	0.9628
	ELIII	0.9678
3	Normal	0.8500
	ELI	0.9557
	ELII	0.9412
	ELIII	0.9335
4	Normal	0.9987
	ELI	0.9895
	ELII	0.9717
	ELIII	0.9745
5	Normal	0.9277
	ELI	0.9790
	ELII	0.9619
	ELIII	0.9519

Table V. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the normal distribution with m=50 and n=20.

Run	Method	Coverage Probability
		95%
1	Normal	0.9983
	ELI	0.9576
	ELII	0.9731
	ELIII	0.9759
2	Normal	0.9910
	ELI	0.9736
	ELII	0.9821
	ELIII	0.9842
3	Normal	0.8510
	ELI	0.9708
	ELII	0.9785
	ELIII	0.9795
4	Normal	0.9983
	ELI	0.9668
	ELII	0.9706
	ELIII	0.9745
5	Normal	0.8953
	ELI	0.9780
	ELII	0.9791
	ELIII	0.9832

Table VI. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the normal distribution with m=50 and n=100.

Run	Method	Coverage Probability
		95%
1	Normal	0.9793
	ELI	0.9820
	ELII	0.9716
	ELIII	0.9737
2	Normal	0.9220
	ELI	0.9670
	ELII	0.9616
	ELIII	0.9543
3	Normal	0.8873
	ELI	0.9267
	ELII	0.9583
	ELIII	0.9543
4	Normal	0.9940
	ELI	0.9884
	ELII	0.9700
	ELIII	0.9714
5	Normal	0.9367
	ELI	0.9730
	ELII	0.9600
	ELIII	0.9533

Table VII. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the normal distribution with m=100 and n=50.

Run	Method	Coverage Probability
		95%
1	Normal	0.9907
	ELI	0.9802
	ELII	0.9833
	ELIII	0.9832
2	Normal	0.9333
	ELI	0.9729
	ELII	0.9736
	ELIII	0.9730
3	Normal	0.9067
	ELI	0.9433
	ELII	0.9703
	ELIII	0.9673
4	Normal	0.9977
	ELI	0.9835
	ELII	0.9816
	ELIII	0.9835
5	Normal	0.9383
	ELI	0.9620
	ELII	0.9690
	ELIII	0.9627

Table VIII. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the normal distribution with m=n=50.

Run	Method	Coverage Probability
		95%
1	Normal	0.9947
	ELI	0.9782
	ELII	0.9798
	ELIII	0.9844
2	Normal	0.9133
	ELI	0.9771
	ELII	0.9750
	ELIII	0.9757
3	Normal	0.8853
	ELI	0.9343
	ELII	0.9637
	ELIII	0.9567
4	Normal	0.9983
	ELI	0.9859
	ELII	0.9821
	ELIII	0.9840
5	Normal	0.9313
	ELI	0.9663
	ELII	0.9646
	ELIII	0.9600

Table IX. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the normal distribution with m=n=100.

Run	Method	Coverage Probability
		95%
1	Normal	0.9610
	ELI	0.9837
	ELII	0.9745
	ELIII	0.9748
2	Normal	0.9253
	ELI	0.9730
	ELII	0.9673
	ELIII	0.9620
3	Normal	0.9017
	ELI	0.9320
	ELII	0.9537
	ELIII	0.9527
4	Normal	0.9787
	ELI	0.9854
	ELII	0.9661
	ELIII	0.9678
5	Normal	0.9353
	ELI	0.9563
	ELII	0.9540
	ELIII	0.9533

B. Beta Distribution Tables

Table X. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the beta distribution with m=20 and n=50.

Run	Method	Coverage Probability
		95%
1	Normal	0.9883
	ELI	0.9757
	ELII	0.9753
	ELIII	0.9817
2	Normal	0.9900
	ELI	0.9848
	ELII	0.9770
	ELIII	0.9803
3	Normal	0.8497
	ELI	0.9645
	ELII	0.9522
	ELIII	0.9436
4	Normal	0.9297
	ELI	0.9802
	ELII	0.9758
	ELIII	0.9670
5	Normal	0.8853
	ELI	0.9283
	ELII	0.9413
	ELIII	0.9330

Table XI. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the beta distribution with m=50 and n=20.

Run	Method	Coverage Probability
		95%
1	Normal	0.9957
	ELI	0.9567
	ELII	0.9671
	ELIII	0.9726
2	Normal	0.9953
	ELI	0.9702
	ELII	0.9757
	ELIII	0.9785
3	Normal	0.9457
	ELI	0.9726
	ELII	0.9823
	ELIII	0.9827
4	Normal	0.9240
	ELI	0.9724
	ELII	0.9794
	ELIII	0.9801
5	Normal	0.9023
	ELI	0.9330
	ELII	0.9603
	ELIII	0.9483

Table XII. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the beta distribution with m=50 and n=100.

Run	Method	Coverage Probability
		95%
1	Normal	0.9490
	ELI	0.9760
	ELII	0.9739
	ELIII	0.9732
2	Normal	0.9697
	ELI	0.9876
	ELII	0.9705
	ELIII	0.9685
3	Normal	0.8830
	ELI	0.9363
	ELII	0.9517
	ELIII	0.9477
4	Normal	0.9380
	ELI	0.9703
	ELII	0.9527
	ELIII	0.9470
5	Normal	0.9090
	ELI	0.9220
	ELII	0.9503
	ELIII	0.9473

Table XIII. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the beta distribution with m=100 and n=50.

Run	Method	Coverage Probability
		95%
1	Normal	0.9877
	ELI	0.9752
	ELII	0.9770
	ELIII	0.9804
2	Normal	0.9657
	ELI	0.9792
	ELII	0.9751
	ELIII	0.9764
3	Normal	0.8960
	ELI	0.9503
	ELII	0.9646
	ELIII	0.9586
4	Normal	0.9360
	ELI	0.9687
	ELII	0.9650
	ELIII	0.9573
5	Normal	0.9230
	ELI	0.9330
	ELII	0.9560
	ELIII	0.9533

Table XIV. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the beta distribution with m=n=50.

Run	Method	Coverage Probability
		95%
1	Normal	0.9817
	ELI	0.9702
	ELII	0.9744
	ELIII	0.9767
2	Normal	0.9800
	ELI	0.9841
	ELII	0.9789
	ELIII	0.9813
3	Normal	0.8847
	ELI	0.9558
	ELII	0.9648
	ELIII	0.9615
4	Normal	0.9260
	ELI	0.9696
	ELII	0.9616
	ELIII	0.9566
5	Normal	0.9070
	ELI	0.9290
	ELII	0.9547
	ELIII	0.9503

Table XV. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the beta distribution with m=n=100.

Run	Method	Coverage Probability
		95%
1	Normal	0.9370
	ELI	0.9762
	ELII	0.9708
	ELIII	0.9684
2	Normal	0.9573
	ELI	0.9853
	ELII	0.9675
	ELIII	0.9651
3	Normal	0.8960
	ELI	0.9370
	ELII	0.9587
	ELIII	0.9530
4	Normal	0.9520
	ELI	0.9667
	ELII	0.9623
	ELIII	0.9590
5	Normal	0.9227
	ELI	0.9320
	ELII	0.9507
	ELIII	0.9483

C. Exponential Distribution Tables

Table XVI. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the exponential distribution with m=20 and n=50.

Run	Method	Coverage Probability 95%
1	Normal	0.9993
	ELI	0.9837
	ELII	0.9783
	ELIII	0.9791
2	Normal	0.9940
	ELI	0.9875
	ELII	0.9811
	ELIII	0.9840
3	Normal	0.9423
	ELI	0.9860
	ELII	0.9818
	ELIII	0.9846
4	Normal	0.8893
	ELI	0.9815
	ELII	0.9737
	ELIII	0.9690
5	Normal	0.8357
	ELI	0.9369
	ELII	0.9452
	ELIII	0.9459

Table XVII. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the exponential distribution with m=50 and n=20.

Run	Method	Coverage Probability
		95%
1	Normal	0.9983
	ELI	0.9771
	ELII	0.9766
	ELIII	0.9776
2	Normal	0.9977
	ELI	0.9493
	ELII	0.9620
	ELIII	0.9638
3	Normal	0.9950
	ELI	0.9723
	ELII	0.9733
	ELIII	0.9729
4	Normal	0.9677
	ELI	0.9770
	ELII	0.9788
	ELIII	0.9800
5	Normal	0.9733
	ELI	0.9694
	ELII	0.9729
	ELIII	0.9765

Table XVIII. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the exponential distribution with m=50 and n=100.

Run	Method	Coverage Probability
		95%
1	Normal	0.9616
	ELI	0.9899
	ELII	0.9689
	ELIII	0.9448
2	Normal	0.9520
	ELI	0.9873
	ELII	0.9669
	ELIII	0.9599
3	Normal	0.9467
	ELI	0.9850
	ELII	0.9643
	ELIII	0.9567
4	Normal	0.9363
	ELI	0.9653
	ELII	0.9647
	ELIII	0.9597
5	Normal	0.9130
	ELI	0.9337
	ELII	0.9457
	ELIII	0.9477

Table XIX. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the exponential distribution with m=100 and n=50.

Run	Method	Coverage Probability
		95%
1	Normal	0.9773
	ELI	0.9709
	ELII	0.9764
	ELIII	0.9768
2	Normal	0.9806
	ELI	0.9867
	ELII	0.9765
	ELIII	0.9779
3	Normal	0.9063
	ELI	0.9763
	ELII	0.9736
	ELIII	0.9763
4	Normal	0.9087
	ELI	0.9625
	ELII	0.9678
	ELIII	0.9655
5	Normal	0.9127
	ELI	0.9489
	ELII	0.9619
	ELIII	0.9606

Table XX. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the exponential distribution with m=n=50.

Run	Method	Coverage Probability
		95%
1	Normal	0.9907
	ELI	0.9870
	ELII	0.9759
	ELIII	0.9773
2	Normal	0.9850
	ELI	0.9838
	ELII	0.9764
	ELIII	0.9792
3	Normal	0.9147
	ELI	0.9793
	ELII	0.9793
	ELIII	0.9806
4	Normal	0.9097
	ELI	0.9695
	ELII	0.9709
	ELIII	0.9702
5	Normal	0.9020
	ELI	0.9375
	ELII	0.9469
	ELIII	0.9496

Table XXI. Coverage probabilities of intervals at the nominal level of 95 percent when the data are generated from the exponential distribution with m=n=100.

Run	Method	Coverage Probability
		95%
1	Normal	0.9397
	ELI	0.9807
	ELII	0.9582
	ELIII	0.9548
2	Normal	0.9323
	ELI	0.9799
	ELII	0.9655
	ELIII	0.9592
3	Normal	0.9523
	ELI	0.9687
	ELII	0.9563
	ELIII	0.9543
4	Normal	0.9207
	ELI	0.9550
	ELII	0.9577
	ELIII	0.9540
5	Normal	0.9247
	ELI	0.9463
	ELII	0.9580
	ELIII	0.9580

APPENDIX II: REAL APPLICATION TABLE

Table XXII. Confidence Intervals for R(p) for the real data application at the 95% nominal level.

Specificity *(p)*	Method	Sensitivity *R(p)*	Confidence Intervals	Length
0.95	ELI	0.1446	(0.0714, 0.2473)	.1759
	ELII	0.1446	(0.0591, 0.2741)	.2150
	ELIII	0.1446	(0.0590, 0.2742)	.2152
0.90	ELI	0.2410	(0.1457, 0.3576)	.2119
	ELII	0.2410	(0.1521, 0.3480)	.1959
	ELIII	0.2410	(0.1505, 0.3503)	.1998
0.85	ELI	0.3133	(0.2055, 0.4366)	.2311
	ELII	0.3133	(0.1989, 0.4454)	.2465
	ELIII	0.3133	(0.1983, 0.4462)	.2479
0.80	ELI	0.4096	(0.2920, 0.5347)	.2427
	ELII	0.4096	(0.2864, 0.5410)	.2546
	ELIII	0.4096	(0.2857, 0.5419)	.2562
0.70	ELI	0.5181	(0.3941, 0.6406)	.2465
	ELII	0.5181	(0.4094, 0.6256)	.2162
	ELIII	0.5181	(0.4094, 0.5419)	.1325

APPENDIX III: S-PLUS CODE FOR SIMULATION

```
# Computing the pseudo empirical likelihood ratio confidence intervals for ROC
   curve
#
# December 3, 2005
#
##############################################################################

   m<-20
   n<-50

   #sp<-0.7  # 0.90, 0.80, 0.70
   iter<-3000
   levelc1<-0.90
   levelc2<-0.95


##############################################################################
#normal distribution.

   #muy<-1   # the mean of diseased population
   #sens<-1-pnorm(qnorm(sp),muy,1)

   #sp = 0.9; muy = 2.9264
   #sp = 0.9; muy = 2.5631
   #sp = 0.9; muy = 2.1231
   #sp = 0.8; muy = 2.4865
   #sp = 0.8; muy = 1.6832
   #sens<-1-pnorm(qnorm(sp),muy,1)
##############################################################################
#Exponential distribution.

   #sp<- 0.95         #  specificity = 0.6, 0.7, 0.8, 0.9, 0.95
   #delta<- 0.95      #   AUC = 0.95
   #sens<- 1-pexp(qexp(sp), rate= (1/delta -1))
##############################################################################

##############################################################################
#Beta(a,b) distribution.

#Table 2:

#Run 1: specificity=1-tt=0.9, sensitivity=0.95
#sp<-0.9; a0<-1; b0<-3.5; a1<-4; b1<-1;# sensitivity=0.946002
    # Delete the "#" before "tt"  when you run "Run 1" for Beta(a,b)
   distribution.

#Run 2: specificity=1-tt=0.8, sensitivity=0.93
#sp<-0.8; a0<-1; b0<-3; a1<-3; b1<-1; # sensitivity=0.9284251
    # Delete the "#" before "tt"  when you run "Run 2" for Beta(a,b)
   distribution.

#Run 3: specificity=1-tt=0.9, sensitivity=0.85
```

```
#sp<-0.9; a0<-1; b0<-3; a1<-3; b1<-1; # sensitivity=0.8461462
    # Delete the "#" before "tt"  when you run "Run 3" for Beta(a,b)
   distribution.

#Run 4: specificity=1-tt=0.8, sensitivity=0.82
#sp<-0.8; a0<-2; b0<-4; a1<-4; b1<-2; # sensitivity=0.8245191
    # Delete the "#" before "tt"  when you run "Run 4" for Beta(a,b)
   distribution.

#Run 5: specificity=1-tt=0.8, sensitivity=0.55
#sp<-0.8; a0<-2; b0<-3; a1<-3; b1<-2; # sensitivity=0.5548815
    # Delete the "#" before "tt"  when you run "Run 5" for Beta(a,b)
   distribution.

#sens<- 1-pbeta(qbeta(sp,a0,b0),a1,b1)  #sensitivity
    # Delete the "#" before "Rtt"  when you run the S code for Beta(a,b)
   distribution.

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


   p<-1-sp

   coverage1<-0
   coverage2<-0

   coverageb11<-0      # First bootstrap
   coverageb12<-0

   coverageb21<-0      # Second bootstrap
   coverageb22<-0

   coveraget1<-0
   coveraget2<-0

   CILT1<-c(rep(0,iter))
   CILT2<-c(rep(0,iter))


# Loop

Rp<-0

for ( i in c(1:iter))
{
   #normal distribution:
   #x<-rnorm(m,0,1)           # obs from non-diseased population
   #y<-rnorm(n,muy,1)         # obs from diseased population

   #Exponential distribution: rexp(n, rate=1, scale)
   #x<-rexp(m, rate= 1)             # obs from non-diseased population
   #y<-rexp(n, rate= (1/delta -1))  # obs from diseased population

   #Beta(a,b) distribution:
   #x<-rbeta(m,a0,b0) #nondesease:
                      # Delete the "#" before "x"  when you run the S code for
                        Beta(a,b) distribution.
   #y<-rbeta(n,a1,b1) #desease
```

```
                    # Delete the "#" before "y"  when you run the S code for
                      Beta(a,b) distribution.


u<-rep(100,n)              # hat U =1- hat F
for (j in 1:n)
{
   u[j]<-1-mean((x<=y[j]))
}

indU<-(u <= p)*1           # indicator function of U: I(U_j <=p)

Rp[i]<-mean(indU)

#  compute the scale constant c(p).
   if ((Rp[i]!=1) & (Rp[i]!=0))
      {
         sigma<-Rp[i]*(1-Rp[i])
            # estimate for sigma^2

         hg<-bandwidth.sj(y, nb=1000, method="dpi")
            # Uses the method of Sheather & Jones (1991)
            # to select the bandwidth of a Gaussian kernel density
              estimator for g
         hf<-bandwidth.sj(x, nb=1000, method="dpi")
            # Uses the method of Sheather & Jones (1991)
            # to select the bandwidth of a Gaussian kernel density
              estimator for f

         quantileF<-quantile(x,1-p)
         densityg<-density(y,n=1,window="g",width=hg, from=quantileF)$y
            #density(.): density estimate at (1-p)-th quantile of F.
         densityf<-density(x,n=1,window="g",width=hf, from=quantileF)$y
            #density(.): density estimate at tt-th quantile of F.
         hatsigma1<-sigma + n*p*(1-p)*densityg/(m*densityf)
            # estimate for sigma_1^2
         #sigma1<-sigma + n*p*(1-p)*dnorm(qnorm(1-p), muy,
                   1)/(m*dnorm(qnorm(1-p),0,1))
            # True value  of sigma_1^2

         #bootstrap estimates for R(p). Bootstap variance estimate of R(p)
         test<-sensb(y,x,1-p,300,0)
         Rpboot<-mean(test)
         Rpvar<-var(test)

         cp<-sigma/hatsigma1
         cpstar1<- sigma/(n*Rpvar)
         cpstar2<- Rpboot*(1-Rpboot)/(n*Rpvar)


         #  cat("the scale constant cp=",cp, "\n")
         wjhat<-indU-sens

         funclambda<-function(lam)mean(wjhat/(1+lam*wjhat))
         lambda<-solveNonlinear(funclambda, c(0), c(0.01))$x
         #lambda<-sum(wjhat)/sum(wjhat^2)

         lroc<-2*sum( log(abs(1+lambda*wjhat)) )
```

```
            coverage1[i]<-(cp*lroc <= qchisq(levelc1,1))*1
            coverage2[i]<-(cp*lroc <= qchisq(levelc2,1))*1

            coverageb11[i]<-(cpstar1*lroc <= qchisq(levelc1,1))*1    # First
   bootstrap
            coverageb12[i]<-(cpstar1*lroc <= qchisq(levelc2,1))*1

            coverageb21[i]<-(cpstar2*lroc <= qchisq(levelc1,1))*1    # second
   bootstrap
            coverageb22[i]<-(cpstar2*lroc <= qchisq(levelc2,1))*1

         }else{
              coverage1[i]<-NA; coverage2[i]<-NA
              coverageb11[i]<-NA; coverageb12[i]<-NA
              coverageb21[i]<-NA; coverageb22[i]<-NA
              }


   #  compute the normal approximation based interval.

      hwidth1<-qnorm(1-(1-levelc1)/2)*(hatsigma1/n)^(1/2)
      tlow1<-Rp[i]-hwidth1          # lower limit of the CI
      tup1<- Rp[i]+hwidth1          # upper limit of the CI
      if ((tlow1 <= sens) & (tup1 >= sens))coverageт1<-coverageт1+1
      CILT1[i]<-2*hwidth1           # The length of CI

      hwidth2<-qnorm(1-(1-levelc2)/2)*(hatsigma1/n)^(1/2)
      tlow2<-Rp[i]-hwidth2          # lower limit of the CI
      tup2<- Rp[i]+hwidth2          # upper limit of the CI
      if ((tlow2 <= sens) & (tup2 >= sens))coverageт2<-coverageт2+1
      CILT2[i]<-2*hwidth2           # The length of CI

}

sink("pseudoelroc1bootres")

#Normal distribution: # Delete the "#"'s before "cat" when you run the S code
   for normal distribution.
#cat("Normal distribution: m=", m, "n=", n, "specificity=", sp, "sensitivity=",
   sens, "mu=", muy, "iter=", iter, "\n")

#Exponential distribution: # Delete the "#"'s before "cat" when you run the S
   code for Exponential distribution.
#cat("Exponential dist: m=", m, "n=", n, "sp=", sp, "sens=", sens, "AUC=",
   delta, "iter=", iter, "\n")

# Beta distribution: # Delete the "#"'s before "cat"  when you run the S code
   for Beta distribution.
#cat("Beta distribution:  m=", m, "n=", n, "iter=", iter, "\n")
#cat("specifity=",sp, "sens=", sens, "a0=",a0,"a1=",a1,"b0=",b0,"b1=",b1, "\n")


cat("CI for sensitivity at level=", levelc1, "\n")
cat("Coverage of the ELRCI :", mean(sort(coverage1)), "\n")
cat("First bootstrap method. Coverage of the ELRCI :", mean(sort(coverageb11)),
   "\n")
```

```
cat("second bootstrap method. Coverage of the ELRCI :",
   mean(sort(coverageb21)), "\n")
cat("Coverage of the Normal CI :", coveraget1/iter, "\n")
#cat("Average length of ELRCI:  ", mean(CIL), " STD=", (var(CIL))^(1/2), "\n")
cat("Average length of Normal CI:  ", mean(CILT1),  "  STD=",
   (var(CILT1))^(1/2), "\n")
#cat("Midpoint:", mean(Mid),  "   STD=", (var(Mid))^(1/2), "\n")
cat("-----------------------------------------------------------------","\n")

cat("CI for sensitivity at level=", levelc2, "\n")

cat("Coverage of the ELRCI :", mean(sort(coverage2)), "\n")
cat("First bootstrap method. Coverage of the ELRCI :", mean(sort(coverageb12)),
   "\n")
cat("second bootstrap method. Coverage of the ELRCI :",
   mean(sort(coverageb22)), "\n")
cat("Coverage of the Normal CI :", coveraget2/iter, "\n")
#cat("Average length of ELRCI:  ", mean(CIL), " STD=", (var(CIL))^(1/2), "\n")
cat("Average length of Normal CI:  ", mean(CILT2),  "  STD=",
   (var(CILT2))^(1/2), "\n")
#cat("Midpoint:", mean(Mid),  "   STD=", (var(Mid))^(1/2), "\n")
cat("Mean estimate for sensitivity:", mean(Rp),  "  STD=", (var(Rp))^(1/2),
   "\n")
cat("=================================================================","\n")
sink()
```

APPENDIX IV: S-PLUS CODE FOR REAL APPLICATION

```
# Computing the pseudo empirical likelihood ratio confidence intervals for ROC
   curve
#
# Jan. 3, 2006

   #Diabetes example
   xx<-NON[,1]            # obs from non-diseased population
   yy<-DIS[,1]            # obs from diseased population

   x<-sort(xx)
   y<-sort(yy)

   m<-length(x)
   n<-length(y)

   levelc<-0.95

   crit<-qchisq(levelc,1)

   sp<- 0.95           # specificity
   p<-1-sp          # p<-1-sp   # False Positive Rate

   ELlow<-0         # EL interval
   ELup<-0

   BELlow1<-0          # First bootstrap EL-based CI
   BELup1<-0

   BELlow2<-0          # Second bootstrap EL-based CI
   BELup2<-0

   u<-rep(100,n)              # hat U =1- hat F
   for (j in 1:n)
   {
      u[j]<-1-mean((x<=y[j]))
   }

   hg<-bandwidth.sj(y, nb=1000, method="dpi")
      # Uses the method of Sheather & Jones (1991)
      # to select the bandwidth of a Gaussian kernel density estimator for g
   hf<-bandwidth.sj(x, nb=1000, method="dpi")
      # Uses the method of Sheather & Jones (1991)
      # to select the bandwidth of a Gaussian kernel density estimator for f

   indU<-(u <= p)*1           # indicator function of U: I(U_j <=p)

   Rp<-mean(indU)             # estimate for R(p). Sensitivity

#  compute the scale constant c(p).

   sigma<-Rp*(1-Rp)       # estimate for sigma^2

   quantileF<-quantile(x,1-p)
```

```
   densityg<-density(y,n=1,window="g",width=hg, from=quantileF)$y
      #density(.): density estimate at (1-p)-th quantile of F.
   densityf<-density(x,n=1,window="g",width=hf, from=quantileF)$y
      #density(.): density estimate at tt-th quantile of F.
   hatsigma1<-sigma + n*p*(1-p)*densityg^2/(m*densityf^2)
      # estimate for sigma_1^2

#bootstrap estimates for R(p). Bootstap variance estimate of R(p)

   test<-sensb(y,x,1-p,1000,0)
   Rpboot<-mean(test)
   Rpvar<-var(test)

   cp<-sigma/hatsigma1
   cpstar1<- sigma/(n*Rpvar)
   cpstar2<- Rpboot*(1-Rpboot)/(n*Rpvar)

   #  cat("the scale constant cp=",cp, "\n")

      critcp_crit/cp            # EL interval

      critcps1_crit/cpstar1     # First bootstrap EL-based CI

      critcps2_crit/cpstar2     # second bootstrap EL-based CI


   # EL confidence intervals

      y<-elciroc(n,indU,critcp)        # calling "elciroc" to compute the EL
   interval.
      ELlow<-y[4]                  # lower limit of the EL CI
      ELup<-y[5]                   # upper limit of the EL CI


   # first bootstrap EL based CI:

      y<-elciroc(n,indU,critcps1)   # calling "elciroc" to compute the EL
   interval.
      BELlow1<-y[4]                # lower limit of the bootstrap EL CI
      BELup1<- y[5]                # upper limit of the bootstrap EL CI


   # Second bootstrap EL based CI:

      y<-elciroc(n,indU,critcps2)   # calling "elciroc" to compute the EL
   interval.
      BELlow2<-y[4]                # lower limit of the bootstrap EL CI
      BELup2<- y[5]                # upper limit of the bootstrap EL CI



sink("realexampleres")

cat("CI for sens at level=", levelc, "m=", m, "n=", n, "\n")
cat("specificity =", sp, "\n")
cat("R(p)=", Rp, "\n")

cat("lower limit of the EL CI :", ELlow, "\n")
```

```
cat("upper limit of the EL CI :", ELup, "\n")

cat("lower limit of the First bootstrap EL CI :", BELlow1, "\n")
cat("upper limit of the First bootstrap EL CI :", BELup1, "\n")

cat("lower limit of the second bootstrap EL CI :", BELlow2, "\n")
cat("upper limit of the second bootstrap EL CI :", BELup2, "\n")

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

sink()
```