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Youden Index and the optimal threshold for markers with mass at zero‡

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SUMMARY

The Youden Index is often used as a summary measure of the receiver operating characteristic curve. It measures the effectiveness of a diagnostic marker and permits the selection of an optimal threshold value or cutoff point for the biomarker of interest. Some markers, while basically continuous and positive, have a spike or positive mass of probability at the value zero. We provide a flexible modeling approach for estimating the Youden Index and its associated cutoff point for such spiked data and compare it with the standard empirical approach. We show how this modeling approach can be adjusted to take covariate information into account. This approach is applied to data on the Coronary Calcium Score, a marker for atherosclerosis. Published in 2007 by John Wiley & Sons, Ltd.

Keywords

Box–Cox power transformations; Coronary Calcium Score; diagnostic markers; mixture model; ROC curve; sensitivity; specificity

1. INTRODUCTION

In recent years, the evaluation of the ability of a new diagnostic or screening marker (test) to distinguish a diseased from a non-diseased patient has been widely discussed in the literature [1,2]. A person is assessed as diseased or healthy depending on whether the corresponding marker value is greater than or less than or equal to a given threshold value. Associated with any threshold value (t) is the probability of a true positive (sensitivity = $q(t)$) and the probability of a true negative (specificity = $1 - p(t)$).

A frequently used summary index of marker accuracy is the Youden Index [2-7], which is defined as

$$\begin{aligned} J &= \max_t \{\text{sensitivity}(t) + \text{specificity}(t) - 1\} \\ &= \max_t \{q(t) - p(t)\} \end{aligned} \tag{1}$$

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over all threshold values t. The critical threshold value t^*, which achieves this maximum, will be referred to as the 'optimal' threshold. The optimal threshold is used as a criterion for classifying subjects as healthy (diseased) if their observed marker value is less than or equal to (greater than) t^*. Greiner *et al.* [8] provide a recent discussion of this and other criteria for obtaining the critical threshold value. J and t^* are often seen in the applied biomedical literature [9-12].

The Youden Index gives equal weight to sensitivity and specificity. If a researcher thinks that different weights are appropriate (based perhaps on the cost of different types of error), a generalized Youden Index can be used. The generalized J can be motivated from a decision theoretic perspective. The expected loss function in classifying a subject can be written as $(1 - \kappa)\, p(t) + a\kappa(1 - q(t))$ [5,8,13], where 'a' denotes the relative loss (cost) of a false negative when compared with a false positive and κ is the proportion of diseased individuals in the population of interest (prevalence). It is easy to see that minimizing this expected loss over all possible threshold values is the same as maximizing $r(1 - p(t)) + q(t)$, where $r = (1 - \kappa)/a\kappa$. For $r = 1$, this is equivalent to obtaining J. The relative cost and disease prevalence are often difficult to assess (Greiner *et al.* [8] and the references cited therein). We have, for simplicity, remained with the commonly assumed $r = 1$ [8], both in the theoretical development and in the example of this paper.

In clinical practice, finding the location of the critical threshold value for discriminating cases and controls with minimal misclassification is of central interest. A recent paper by Fluss *et al.* [6] discusses the case when marker measurements are continuous and compares several methods of estimation for both the Youden Index and the critical threshold value. In this paper, we extend the presentation to continuous data with mass at zero. Such zero-spiked data were presented by Schisterman *et al.* [5] in the context of receiver operating characteristic (ROC) curve analysis. The ROC curve is a useful tool for displaying the discriminatory ability of a marker measured through a diagnostic test in distinguishing between diseased and healthy individuals. The ROC curve is a plot of $q(t)$ *versus* $p(t)$ for all possible threshold values. The accuracy of a diagnostic test is often summarized by the area under the ROC curve (AUC) [1].

As an example of zero-spiked data, consider the Coronary Calcium Score (CCS). Calcium in the coronary arteries indicates the presence of atherosclerotic plaque, and the amount of coronary artery calcification correlates with the amount of atherosclerosis (hard and soft plaque) at autopsy. Electron beam tomography (EBT) is a sensitive, non-invasive modality for the detection of subclinical atherosclerosis by coronary calcium measurement. CCS determined by EBT has been shown to be directly associated with the extent of angiographic coronary artery disease and to be predictive of coronary events [14]. A zero CCS value is interpreted as the tested individual having no calcium in the coronary arteries. Any positive amount of coronary calcium can be quantified continuously by EBT. Furthermore, the discriminatory accuracy of a continuous marker may be influenced by covariate factors such as age, general health status, sex, etc. [15,16]. Schisterman *et al.* [16] have shown that the AUC attained from the CCS is a function of age and gender. Based on their findings, it is reasonable to consider that both J and t^* should be functions of these covariates. This paper aims at developing a readily applicable methodology for estimating J and t^* for zero-spiked data.

To evaluate the critical threshold value and the Youden Index of CCS, we examined a prospective cohort study of 10 377 asymptomatic individuals [14] who were referred by their primary care physicians between 1996 and 2000 for coronary calcium screening with EBT. Patients with a history of coronary disease (i.e. a history that included admission to the hospital for chest pain, acute coronary syndrome, or myocardial infarction (MI), as well as prior coronary angiography and revascularization) were excluded. Patients in our cohort who had

an MI within two years from the EBT test were classified as being in the diseased group and otherwise were considered to be in the healthy group.

Schisterman *et al.* [16] showed that this marker has poor discriminatory ability for females. Consequently, in this paper we consider only the 4122 males. Figure 1 provides a histogram for the frequency distribution of CCS by disease status for our sample of males. Note that the CCS has a spike (mass) at zero and the positive CCS marker values have a skewed distribution. The percentages of zeros for the diseased and healthy samples are 18 and 61 per cent, respectively.

Estimation of J and t^* follows the estimation of the sensitivity and specificity functions in (1). Both parametric and non-parametric approaches have been suggested for estimating sensitivity and specificity [1]. These procedures differ by using various methods for estimating the cumulative distribution functions (cdfs) of the marker values, based on samples taken from both the healthy and diseased groups. Using these estimated cdfs, the estimation of $p(t)$ and $q(t)$ and consequently J and t^* follows. The most common non-parametric method, which we will refer to as the empirical method (EMP), estimates the cdf of the marker with the empirical cdf of the sample. Parametric approaches are based on making distributional assumptions, such as normality on the marker values, and can be quite sensitive to the form of the assumed distributions. A more robust approach (TN) assumes that a monotone transformation exists such that the transformed marker values follow the normal distribution. After estimating the transformation using the Box–Cox power transformation procedure, it is applied to the data and estimation based on normal assumptions is used. This approach has been found useful when dealing with ROC curves [17-20]. Recently, for continuous markers, Fluss *et al.* [6] compared a number of procedures for estimating J and t^* and found that in many cases the TN approach performed well. Schisterman *et al.* [16] showed how the TN approach could be generalized to estimate the AUC for spiked data. In Section 2, we discuss the TN and EMP approaches for estimating J and t^* for spiked data. In Section 3, an extensive simulation study comparing these two approaches is presented. Section 4 shows how the TN approach can be adjusted to account for covariate information. Applications to the CCS data are given in Section 5, while Section 6 provides a concluding discussion.

2. ESTIMATION OF J AND t^* FOR SPIKED DATA

2.1. Notation

Following Schisterman *et al.* [16], let Z and W represent the random variables for the diagnostic test markers on the diseased and healthy populations, respectively. Furthermore, let F_Z and G_W denote their respective cdfs. Consequently, $q(t) = 1 - F_Z(t)$ and $p(t) = 1 - G_W(t)$. Suppose the diagnostic test results $Z_1,..., Z_M$ and $W_1,..., W_N$ are available with $M = m_0+m$ and $N = n_0 + n$, where m_0 and n_0 represent the number of observations taking the value zero for the diseased and healthy samples, respectively. Let $x_1,..., x_m$ and $y_1,..., y_n$ represent the non-zero values in these samples.

2.2. The non-parametric EMP approach

Standard methods [1] provide non-parametric estimations of $p(t)$ and $q(t)$ based on the empirical cdfs for F_Z and G_W, which are denoted by $\hat{F}_Z(t)$ and $\hat{G}_W(t)$, respectively. Thus, from (1),

$$\begin{aligned} \widehat{J} &= \max_t \left\{ \widehat{K}(t) \right\} \\ \widehat{K}(t) &= \widehat{G}_W(t) - \widehat{F}_Z(t) \end{aligned} \tag{2}$$

where t ranges over the observed values of Z and W.

Following Fluss *et al.* [6], we examine two approaches for estimating t^*: (a) the observed marker value where the maximum in (2) was found; (b) merge the sampled maker values for both the diseased and healthy groups and sort them in ascending order, denoting the resulting values by $d_1,..., d_{m+n}$. Suppose that J is obtained at d_j. Since the value of $\hat{K}(t)$ is constant for the interval $[d_j, d_{j+1})$, any value in this range is a reasonable estimate of t^* and we take $(d_j + d_{j+1})/2$. In our simulation, we found a slight difference between these two methods with a small preference to approach (b). For brevity, we report only on the second approach.

2.3. The TN approach

For completeness, we review the discussion in Schisterman *et al.* [16] on sensitivity and specificity for zero-spiked data. Consider the random variable $Z \geq 0$ to be a mixture having a positive probability π_Z at the point $Z = 0$ and otherwise (with probability $1 - \pi_Z$) having a continuous distribution with cdf F_C defined over the positive real line. Thus,

$$F_Z(z) = \begin{cases} \pi_Z, & z=0 \\ \pi_Z + (1-\pi_Z) F_C(z), & z>0 \end{cases}$$

Conditional on the marker values being non-zero, $x_1,..., x_m$ can be considered to be a random sample from F_C. We denote the corresponding (non-zero) random variable by X. In parallel, for the healthy population

$$G_W(w) = \begin{cases} \pi_W, & w=0 \\ \pi_W + (1-\pi_W) G_C(w), & w>0 \end{cases}$$

with $y_1,..., y_n$ being a random sample on the variable Y having a cdf G_C. For any fixed threshold value t, the sensitivity becomes

$$q(t) = P(Z>t) = \begin{cases} 1, & t<0 \\ 1-\pi_Z, & t=0 \\ (1-\pi_Z)(1-F_C(t)), & t>0 \end{cases} \quad (3)$$

while 1−specificity is

$$p(t) = P(W>t) = \begin{cases} 1, & t<0 \\ 1-\pi_W, & t=0 \\ (1-\pi_W)(1-G_C(t)), & t>0 \end{cases} \quad (4)$$

Schisterman *et al.* [16] used this spike model to estimate the area under the ROC curve. In the following, we focus on estimating the Youden Index along with the corresponding critical threshold.

Using the above notation, let

$$K(t) = q(t) - p(t) = \begin{cases} 0, & t<0 \\ \pi_W - \pi_Z, & t=0 \\ (1-\pi_Z)(1-F_C(t)) - (1-\pi_W)(1-G_C(t)), & t>0 \end{cases} \quad (5)$$

while

$$J=\max_t \quad K(t) \tag{6}$$

Following Schisterman *et al.* [16], we assume that the 'continuous' part of the marker distribution can be modeled using the Box–Cox power transformation family. More specifically, we define

$$X^{(\lambda)}=\begin{cases} \frac{X^\lambda-1}{\lambda}, & \lambda \neq 0 \\ \log(X), & \lambda=0 \end{cases} \tag{7}$$

and further assume that $X^{(\lambda)}\mathrm{N}\left(\mu_{\mathrm{D}},\sigma_{\mathrm{D}}^2\right)$. $Y^{(\lambda)}$ is similarly defined with $Y^{(\lambda)}\mathrm{N}\left(\mu_{\mathrm{H}},\sigma_{\mathrm{H}}^2\right)$. Note that this transformation is applied only to the non-zero marker values.

Since these transformations are monotonically increasing

$$F_C(t)=P(X<t)=P\left(X^{(\lambda)}<t^{(\lambda)}\right)=\Phi\left(\frac{t^{(\lambda)}-\mu_{\mathrm{D}}}{\sigma_{\mathrm{D}}}\right) \tag{8}$$

where

$$t^{(\lambda)}=\begin{cases} \frac{t^\lambda-1}{\lambda}, & \lambda \neq 0 \\ \log(t), & \lambda=0 \end{cases}$$

Φ denotes the standard normal cdf and

$$G_C(t)=P(Y<t)=\Phi\left(\frac{t^{(\lambda)}-\mu_{\mathrm{H}}}{\sigma_{\mathrm{H}}}\right) \tag{9}$$

Now, $K(t)$ can be written as

$$K(t)=\begin{cases} 0, & t<0 \\ \pi_W-\pi_Z, & t=0 \\ h(k), & t>0 \end{cases} \tag{10}$$

where

$$h(k)=(1-\pi_Z)\,\Phi\left(\frac{\mu_{\mathrm{D}}-k}{\sigma_{\mathrm{D}}}\right)-(1-\pi_W)\,\Phi\left(\frac{\mu_{\mathrm{H}}-k}{\sigma_{\mathrm{H}}}\right) \tag{11}$$

and

$$k=t^{(\lambda)} \tag{12}$$

We follow the convention that larger marker values are more associated with disease and would thus generally expect that $\mu_D > \mu_H$ and $\pi_W > \pi_Z$.

In order to carry out (6), under the assumption that $\mu_D - \mu_H > 0$ and $\pi_W - \pi_Z > 0$, we first compute $h'(k)$, the first derivative of $h(k)$, set it to zero and solve the resulting quadratic equation. If there is no real solution, then J, the maximum of $K(t)$, is obtained as $J = \pi_W - \pi_Z$, with $t^* = 0$, where a real solution exists, the root

$$k^* = \frac{\mu_D\sigma_H^2 - \mu_H\sigma_D^2 - \sigma_H\sigma_D\sqrt{(\mu_D - \mu_H)^2 + 2\left(\sigma_H^2 - \sigma_D^2\right)\log\left[\frac{(1-\pi_Z)}{(1-\pi_W)}\frac{\sigma_D}{\sigma_H}\right]}}{\sigma_H^2 - \sigma_D^2} \tag{13}$$

can be shown to maximize $h(k)$. The corresponding t^* will be obtained for any given λ by substituting k^* into (12) and solving for t. For the special case of $\pi_Z = \pi_W = 0$, this reduces to the standard solution for continuous normal data [6]. The maximum of $K(t)$ will then be obtained as either $h(k^*)$ or $\pi_W - \pi_Z$ depending on which is greater and t^* will be chosen correspondingly.

For the estimation of J and t^*, we replace the unknown parameters π_W, π_Z, λ, μ_D, μ_H, σ_D, and σ_H with estimates based on sample data from the healthy and diseased populations and carry out the optimization procedure described above.

The probability mass at zero can be estimated immediately from the data as $\widehat{\pi}_Z = m_0/M$ and $\widehat{\pi}_W = n_0/N$.

Based on the non-zero sampled observations on the diseased and healthy subjects, the appropriate likelihood function can be constructed [21] and maximized, resulting in $\widehat{\lambda}$, the maximum likelihood estimator of λ. The sample means and standard deviations calculated from the data transformed according to (7) using $\widehat{\lambda}$ give $\widehat{\mu}_D$, $\widehat{\mu}_H$, $\widehat{\sigma}_D$, and $\widehat{\sigma}_H$.

2.4. Estimation for the CCS marker

The distribution of the non-zero marker values (see Figure 1) shows considerable skewness for both the healthy and diseased male subjects. This is confirmed by Q–Q plots. The Box–Cox procedure results in $\widehat{\lambda} = 0.0113$, which is quite close to 0, suggesting a log transformation. It needs to be emphasized that this transformation is applied only to the non-zero marker values. Applying it to the zero values would only result in the spike being moved from zero to another value. Since the percentage of zeros is substantial for our data (18 per cent for the diseased and 61 per cent for the healthy), including the zeros in the transformation will necessarily result in strongly non-normal and non-symmetrical distributions. Histograms for the positive marker value after the log transformation are given in Figure 2. These indicate an improvement in symmetry and the data appear more normal like. This is confirmed by Q–Q plots, which are omitted for brevity. As pointed out by a referee, the histogram for the diseased group after transformation is still not symmetric or normal like, although it has certainly improved on the pre-transformed data. Figure 3 shows that the ROC curves estimated by both the EMP and TN approaches are quite similar, indicating some robustness for the TN procedure. In various ROC contexts, using the TN procedure for data generated from distributions that are not in the power family has been found to be effective [6,19,22].Hanley [23,24] has also emphasized the robustness of the binormal model to the normality assumption.

For the CCS data, both the EMP and the TN procedures result in the same estimates of the Youden Index and the optimal threshold, namely $\hat{J} = 0.431$ and $\hat{t}^* = 0$. The estimated specificity

and sensitivity at this point are 0.61 and 0.82, respectively. Thes results do not take into account a possible age effect, which will be considered in Section 5. Figure 4 provides a plot of $K(t)$ as estimated by the TN method for various levels of the threshold t. This clearly indicates the peak obtained at $t = 0$ and the falloff of the curve for larger t values.

3. SIMULATION STUDY

We carried out a simulation study to compare the EMP and TN estimators in terms of bias and root mean-square error (RMSE) for both J and t^* *via* an extensive simulation study. Our simulation considers a variety of distributional shapes and probabilities for observing zero, each for several choices of J and with $M = N = 100, 200, 2000$. A sampling of these distributions is presented in Figure 5. For a given N, M, π_W, and π_Z, the number of zero values n_0 and m_0 was generated from the appropriate binomial distributions. Then, samples of size $N - n_0$ and $M - m_0$ were generated, respectively, for the continuous part of the distribution. In order to obtain various shapes for this continuous part, the Box–Cox model (7) was used to generate data using $\lambda = -2, -1, -0.5, 0, 0.5, 1, and 2$. The values of μ_D, μ_H, σ_D, and σ_H were chosen to provide the specified choice of J. The distributions in Figure 5 are standardized to give $J = 0.8$, $\pi_W = 0.4$ and $\pi_Z = 0.15$. The rectangles representing the spikes at zero have been constructed to have areas 0.4, and 0.15. For comparing bias and RMSE, 1000 simulations were carried out for each scenario.

Tables I and II summarize the results for J, whereas Tables III and IV provide those for t^*. As expected, both bias and RMSE decrease with larger sample sizes. For both J and t^* estimation, the TN procedure usually has lower bias and RMSE. For estimating the Youden Index, EMP can have an RMSE as much as 25 per cent larger than that of TN. For the optimal threshold estimation, the RMSE of EMP can be more than double that of TN. Note that for threshold estimation the EMP procedure can exhibit a bias substantially higher than TN even for large sample size. The overall superiority of TN in estimating both J and t^* is clear.

4. ADJUSTING FOR COVARIATES

For the CCS data, information on the age for each subject is available. Such explanatory factors (covariates) may influence the ROC curve, the Youden Index, and the optimal threshold value of the marker of interest. Faraggi [15] and Smith and Thompson [25] considered adjustments for continuous covariates, while Tosteson and Begg [26] considered ordinal test results. Schisterman *et al.* [16] discussed how the TN approach for estimating the ROC curve and its AUC for spiked data could be adjusted for covariates using standard linear and logistic regression methods.

We briefly review their methodology and apply it to adjusting $\hat{J}$ and $\hat{t}^*$ for covariates. Generally, they assume that the the (possibly transformed) non-zero marker values X and Y depend linearly on $p_1 - 1$ and $p_2 - 1$ explanatory variables, respectively. Set

$$\begin{aligned} \tilde{X} &= \tilde{Z}_D \beta_D + \varepsilon_D \\ \tilde{Y} &= \tilde{Z}_H \beta_H + \varepsilon_H \end{aligned} \tag{14}$$

where $\tilde{X} = (x_1, x_2, ..., x_m)'$, $\tilde{Y} = (y_1, y_2, ..., y_n)'$, and β_D and β_H are column vectors of unknown parameters of sizes p_1 and p_2, respectively. Let Z_D be an $m \times p_1$ matrix where the elements of the first column are all 1's and the other elements are the values of the explanatory variables for the diseased sample. Z_H is similarly defined for the healthy sample. ε_D and ε_H are column vectors of size m and n, respectively, which are assumed to be composed of independently distributed normal variables with expectation 0 and variances σ_D^2 and σ_H^2, respectively. The

covariates for the diseased sample are not necessarily identical to those of the healthy sample. Standard regression modeling techniques need to be used in order to decide on which covariates to include. The adequacy of the model should be examined using residual analysis.

These linear regression models apply only to the non-zero part of the mixture distribution of the marker. The probability that the marker is zero (for the diseased or healthy subjects) can also be affected by covariates. A logistic model can be used to model these probabilities. For the diseased and healthy groups, respectively, we set

$$\begin{aligned} \log\left(\frac{\pi_Z}{1-\pi_Z}\right) &= \gamma_{\mathrm{D}}' V_{\mathrm{D}} \\ \log\left(\frac{\pi_W}{1-\pi_W}\right) &= \gamma_{\mathrm{H}}' V_{\mathrm{H}} \end{aligned} \tag{15}$$

where γ_{D} and γ_{H} are p_3 and p_4 dimensional column vectors of unknown parameters, whereas V_{D} and V_{H} are column vectors of sizes p_3 and p_4, respectively, having 1 as the first element. V_{D} and V_{H} represent the covariates on which the probability of a zero marker value is dependent. These are not necessarily the same as the covariates used in (14).

The formulae in Section 2.3 for sensitivity, specificity, J, and t^* remain the same, but now π_Z, π_W, μ_{D}, and μ_{H} are to be interpreted as functions of given covariate values. Confidence intervals for J and t^* can be readily obtained using the bootstrap [27].

5. AGE ADJUSTMENT FOR THE CCS DATA

For the CCS marker data, information on each subject's age is available. The linear regression models (14) after a log transformation, using age as a possible explanatory variable, were examined. For both the healthy and diseased groups, age was found to be statistically significant ($p = 0.0001$, 0.001 for the healthy and diseased, respectively). Residual analysis showed no reason to reject the normal assumption for the log-transformed marker data. We examined the addition of a quadratic term in age to the linear models and it was found not to be significant. The logistic models (15) were also applied and age was found to be necessary for the healthy group and not significant ($p = 0.131$) for the diseased group. These models were then used to estimate J and t^* as a function of age. The results are presented in Figure 6. The point-wise confidence intervals are computed using the percentile bootstrap method. The estimated Youden Index falls with increasing age. At age 30, $\hat{J} = 0.76$ (specificity = 0.94, sensitivity = 0.82), at age 56, $\hat{J} = 0.43$ (specificity = 0.61, sensitivity = 0.82), while at age 70, $\hat{J} = 0.14$ (specificity = 0.58, sensitivity = 0.57). The $\hat{J} = 0.431$ obtained when ignoring age (see Section 2) corresponds to an age of 56 and gives a wrong impression of the effectiveness of the marker.

Figure 6(a) demonstrates how ignoring age gives an incorrect picture of the marker effectiveness. Clearly, the marker is better for younger men and is less effective with increasing age. Figure 6(b) indicates that the estimated optimal threshold remains at zero for most of the age range and is greater than zero for higher ages for which the marker is not very useful. This seems to suggest that the detection of the presence or absence of calcium captures most of the information in this marker.

6. DISCUSSION

This paper deals with the estimation of the Youden Index and its associate threshold or cutoff value for marker data that has a mass at zero but can be considered continuous on the positive real line. We combine a parametric mixture approach along with the use of a Box–Cox transformation. The estimates of the Youden Index and its associated threshold value obtained

through this TN approach were shown by simulation to perform better than the commonly used non-parametric empirical procedure. In addition, the TN approach is shown to be readily generalizable to permit adjustment of the estimates for explanatory variables. A referee has pointed out that a mass at another point (with the remaining values greater than that point) could be handled similarly simply by a translation of the marker values. A mass at some other point in the midst of the data would require more complicated procedures since formulae (3) and (4) for sensitivity and specificity would no longer hold.

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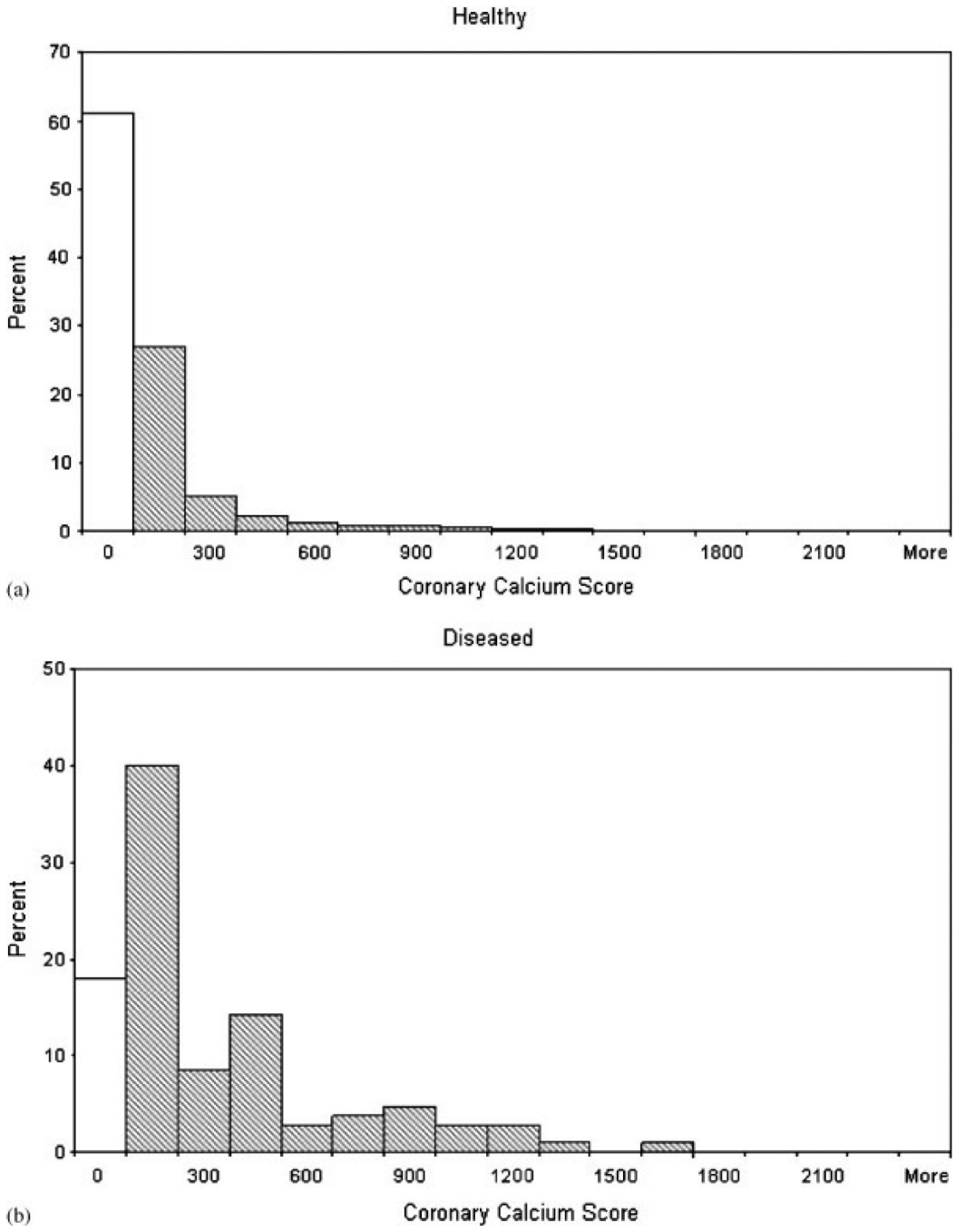

Figure 1.
Histograms of CCS data. The first cell in the histograms represents the frequency of just the value zero, while the other cells represent intervals.

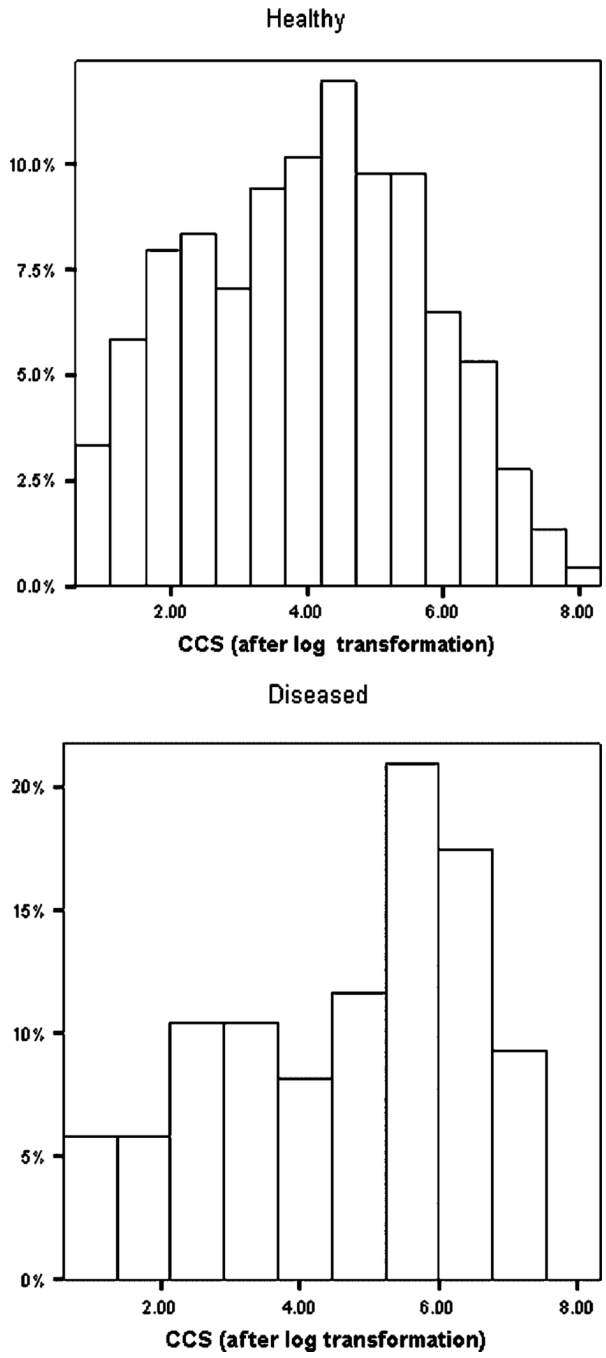

Figure 2.
Histograms of log(CCS) for positive marker values.

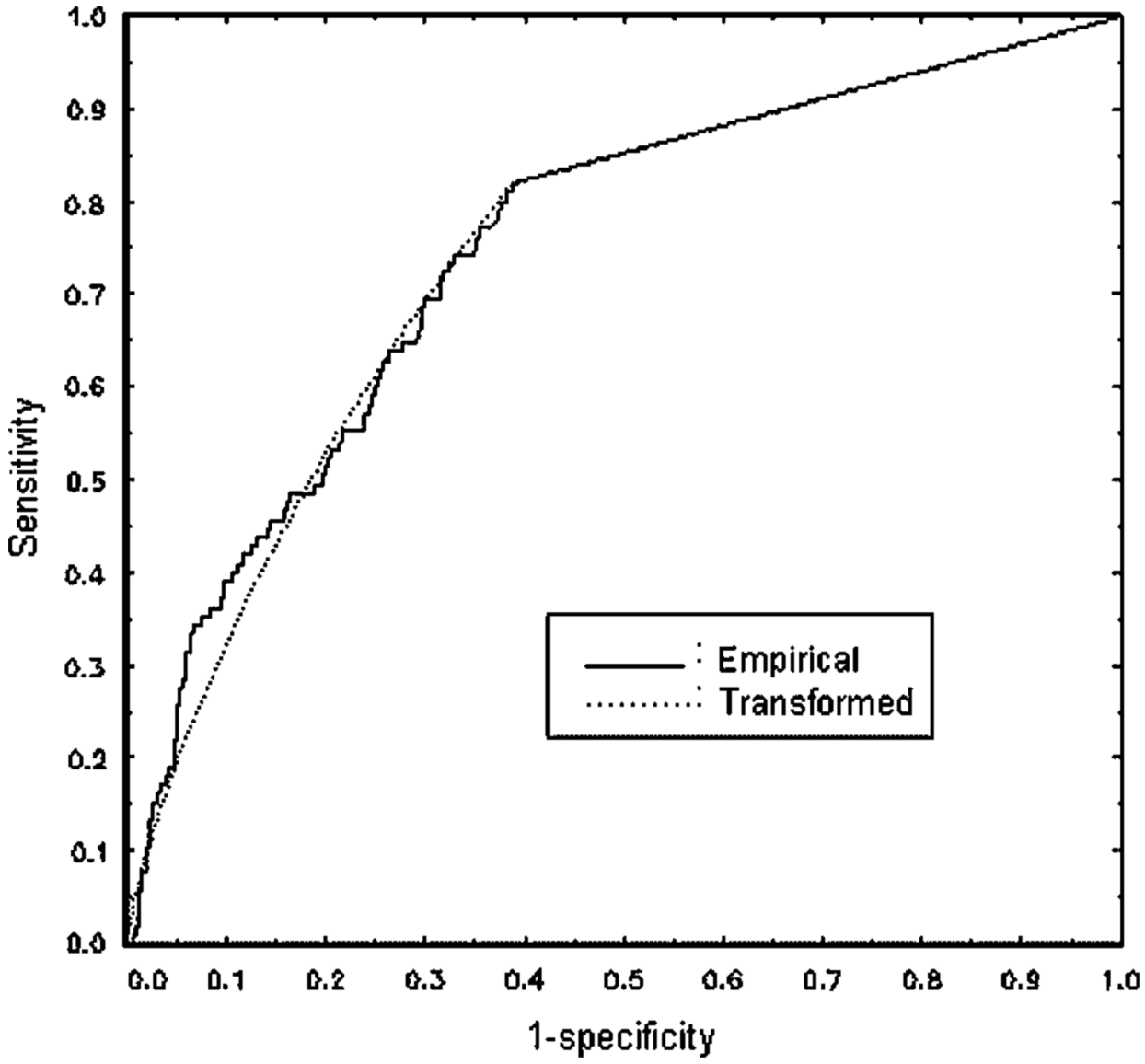

Figure 3.
Empirical and TN ROC curves for CCS data.

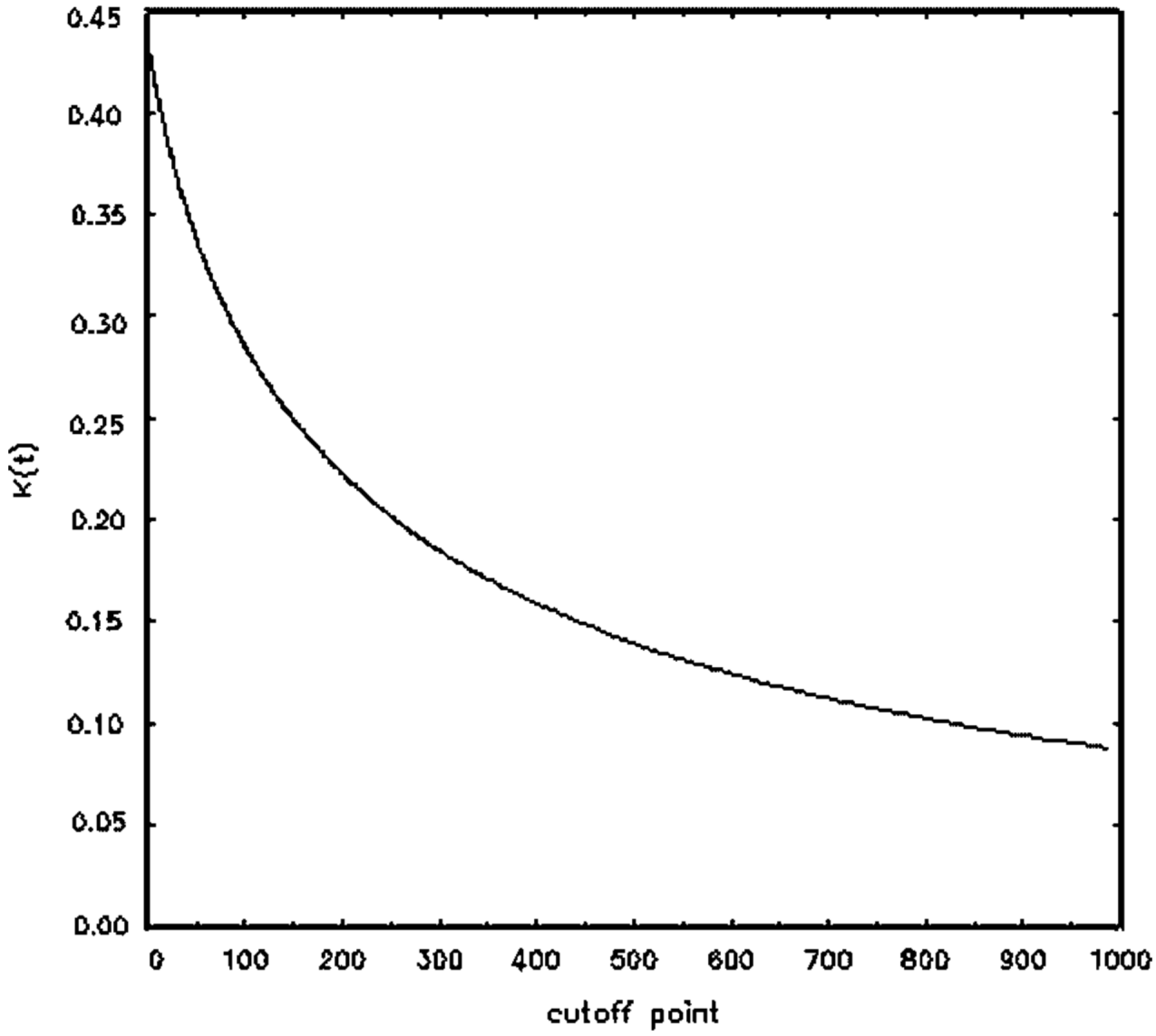

Figure 4.
The *K* function estimated by the TN method.

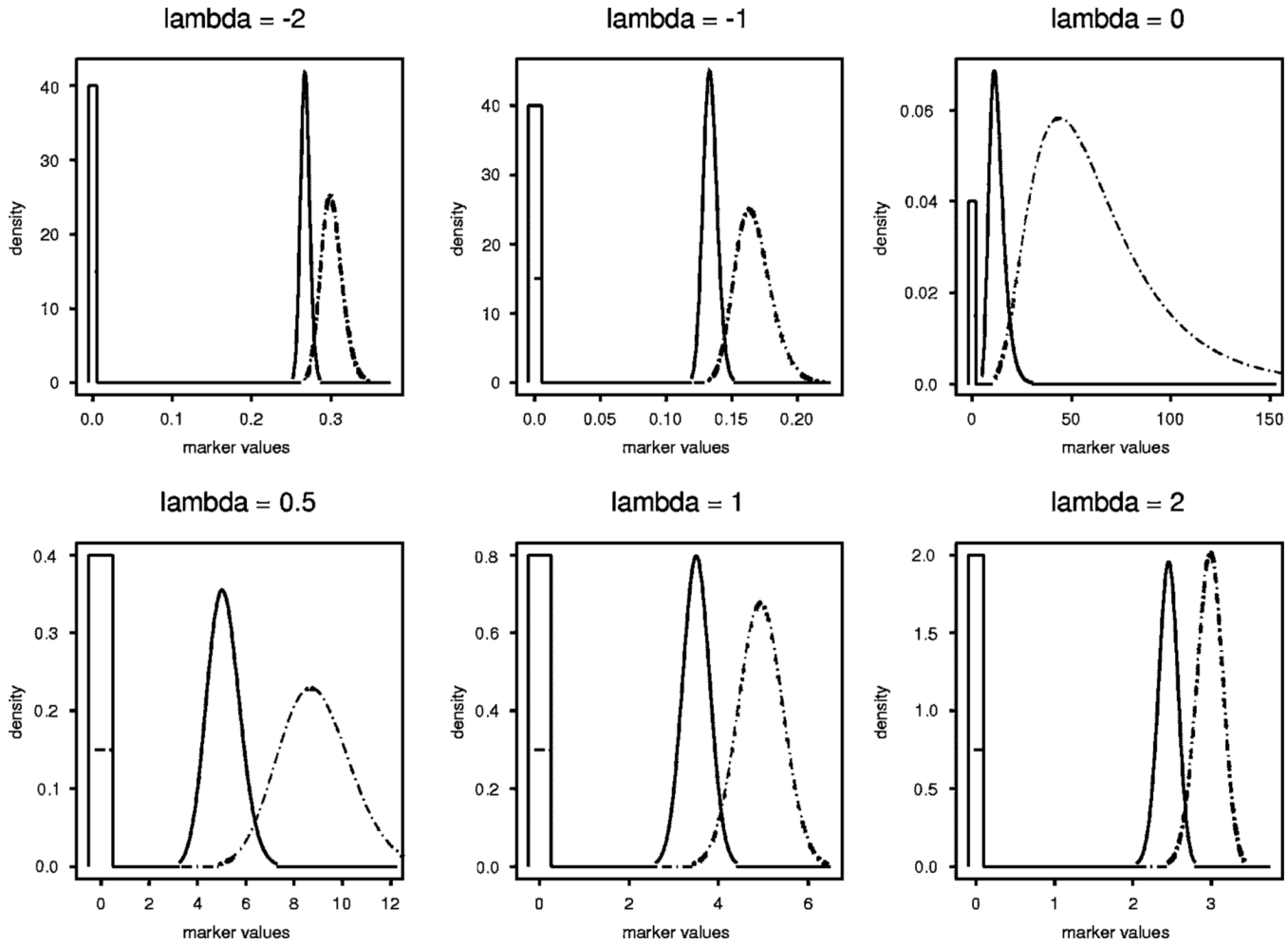

Figure 5.
Distributions used in the simulation study.

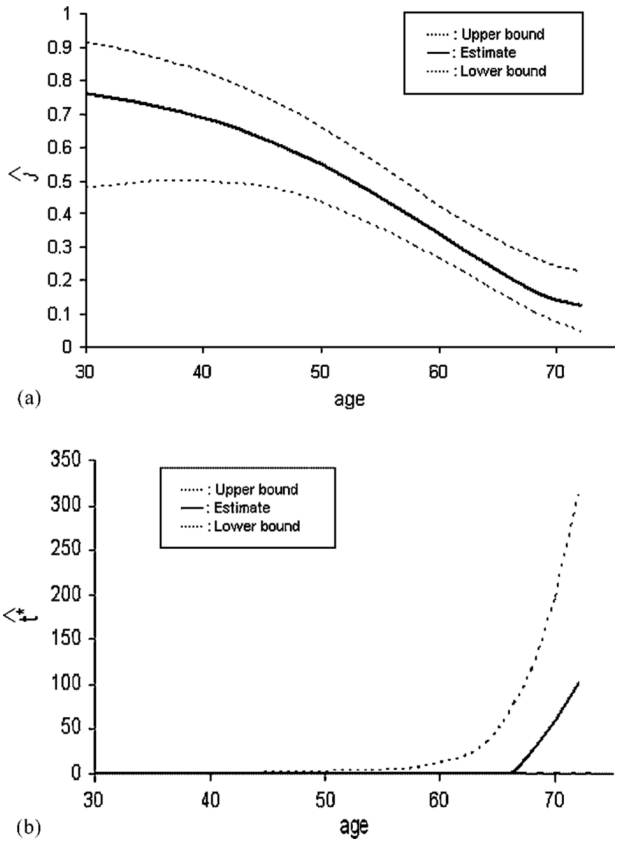

Figure 6.
(a) Youden Index and (b) optimal threshold with 95 per cent confidence intervals for the CCS marker.

Table I

Simulated bias for the Youden Index estimator.

				$\lambda = -2$		$\lambda = -1$		$\lambda = -0.5$		$\lambda = 0$		$\lambda = 0.5$		$\lambda = 1$		$\lambda = 2$	
J	π_W	π_Z	$M = N$	EMP	TN	EMP	TN	EMP	TN	EMP	TN	EMP	TN	EMP	TN	EMP	TN
0.4	0.2	0.1	100	0.0350	0.0026	0.0368	0.0053	0.0377	0.0061	0.0372	0.0048	0.0353	0.0024	0.0369	0.0041	0.0368	0.0037
			200	0.0247	0.0029	0.0240	0.0024	0.0219	0.0012	0.0237	0.0018	0.0245	0.0024	0.0233	0.0010	0.0241	0.0016
			2000	0.0053	−0.0002	0.0058	0.0006	0.0053	0.0001	0.0052	−0.0003	0.0062	0.0005	0.0053	−0.0004	0.0064	0.0007
	0.3	0.2	100	0.0315	0.0032	0.0334	0.0055	0.0340	0.0058	0.0318	0.0033	0.0332	0.0032	0.0346	0.0051	0.0332	0.0037
			200	0.0225	0.0032	0.0220	0.0025	0.0200	0.0012	0.0208	0.0016	0.0222	0.0025	0.0213	0.0013	0.0224	0.0025
			2000	0.0049	−0.0001	0.0057	0.0010	0.0049	0.0003	0.0052	0.0005	0.0057	0.0006	0.0047	−0.0003	0.0056	0.0005
	0.4	0.15	100	0.0355	0.0038	0.0375	0.0059	0.0380	0.0068	0.0381	0.0054	0.0365	0.0034	0.0386	0.0060	0.0377	0.0050
			200	0.0254	0.0041	0.0241	0.0026	0.0220	0.0013	0.0242	0.0021	0.0249	0.0029	0.0241	0.0020	0.0247	0.0026
			2000	0.0056	0.0000	0.0062	0.0008	0.0054	0.0001	0.0055	0.0001	0.0064	0.0008	0.0054	−0.0003	0.0065	0.0008
0.6	0.2	0.1	100	0.0270	0.0024	0.0286	0.0046	0.0289	0.0054	0.0288	0.0039	0.0275	0.0026	0.0293	0.0043	0.0282	0.0036
			200	0.0195	0.0028	0.0185	0.0021	0.0175	0.0007	0.0177	0.0019	0.0188	0.0023	0.0182	0.0010	0.0185	0.0016
			2000	0.0039	−0.0001	0.0046	0.0005	0.0041	0.0000	0.0042	0.0002	0.0047	0.0005	0.0037	−0.0004	0.0047	0.0006
	0.3	0.2	100	0.0231	0.0023	0.0240	0.0038	0.0246	0.0042	0.0222	0.0016	0.0234	0.0028	0.0250	0.0045	0.0233	0.0031
			200	0.0164	0.0026	0.0159	0.0020	0.0146	0.0003	0.0157	0.0019	0.0158	0.0020	0.0150	0.0009	0.0160	0.0022
			2000	0.0034	0.0000	0.0045	0.0010	0.0037	0.0002	0.0038	0.0000	0.0042	0.0007	0.0029	−0.0004	0.0038	0.0004
	0.4	0.15	100	0.0258	0.0026	0.0269	0.0043	0.0281	0.0053	0.0260	0.0025	0.0266	0.0032	0.0280	0.0050	0.0268	0.0042
			200	0.0193	0.0033	0.0173	0.0021	0.0162	0.0004	0.0176	0.0018	0.0182	0.0022	0.0176	0.0014	0.0176	0.0022
			2000	0.0039	0.0000	0.0048	0.0008	0.0039	0.0000	0.0034	−0.0004	0.0048	0.0008	0.0035	−0.0004	0.0046	0.0006
0.8	0.2	0.1	100	0.0167	0.0004	0.0175	0.0018	0.0179	0.0022	0.0168	0.0009	0.0169	0.0010	0.0174	0.0022	0.0173	0.0036
			200	0.0119	0.0012	0.0119	0.0006	0.0100	−0.0010	0.0113	0.0005	0.0118	0.0009	0.0108	0.0001	0.0110	0.0016
			2000	0.0025	−0.0001	0.0030	0.0003	0.0027	−0.0000	0.0028	0.0000	0.0030	0.0004	0.0022	−0.0004	0.0027	0.0006
	0.4	0.15	100	0.0124	−0.0002	0.0126	0.0003	0.0138	0.0010	0.0122	−0.0002	0.0124	0.0006	0.0130	0.0013	0.0127	0.0006
			200	0.0093	0.0009	0.0089	0.0000	0.0072	−0.0010	0.0082	0.0000	0.0087	0.0003	0.0079	−0.000	0.0083	0.0001
			2000	0.0022	0.0000	0.0026	0.0005	0.0021	−0.0000	0.0024	0.0002	0.0027	0.0006	0.0017	−0.0004	0.0021	0.0001

Table II

Simulated RMSE for the Youden Index estimator.

				$\lambda = -2$		$\lambda = -1$		$\lambda = -0.5$		$\lambda = 0$		$\lambda = 0.5$		$\lambda = 1$		$\lambda = 2$	
J	π_W	π_Z	$M = N$	EMP	TN	EMP	TN	EMP	TN	EMP	TN	EMP	TN	EMP	TN	EMP	TN
0.4	0.2	0.1	100	0.0665	0.0521	0.0675	0.0524	0.0670	0.0519	0.0695	0.0552	0.0678	0.0532	0.0671	0.0517	0.0659	0.0513
			200	0.0475	0.0369	0.0463	0.0365	0.0450	0.0360	0.0472	0.0365	0.0467	0.0364	0.0468	0.0368	0.0469	0.0367
			2000	0.0146	0.0118	0.0146	0.0116	0.0140	0.0112	0.0146	0.0118	0.0147	0.0116	0.0141	0.0113	0.0150	0.0119
	0.3	0.2	100	0.0638	0.0514	0.0644	0.0511	0.0650	0.0523	0.0635	0.0514	0.0666	0.0540	0.0649	0.0519	0.0629	0.0511
			200	0.0457	0.0365	0.0450	0.0364	0.0433	0.0357	0.0438	0.0360	0.0450	0.0365	0.0448	0.0369	0.0457	0.0367
			2000	0.0140	0.0116	0.0143	0.0116	0.0137	0.0115	0.0140	0.0116	0.0141	0.0113	0.0136	0.0112	0.0144	0.0119
	0.4	0.15	100	0.0663	0.0522	0.0670	0.0520	0.0671	0.0524	0.0685	0.0538	0.0678	0.0538	0.0682	0.0532	0.0665	0.0520
			200	0.0482	0.0374	0.0471	0.0375	0.0445	0.0364	0.0478	0.0372	0.0471	0.0372	0.0471	0.0374	0.0478	0.0379
			2000	0.0146	0.0118	0.0150	0.0119	0.0141	0.0115	0.0145	0.0117	0.0148	0.0116	0.0141	0.0114	0.0150	0.0120
0.6	0.2	0.1	100	0.0579	0.0471	0.0585	0.0472	0.0584	0.0470	0.0575	0.0458	0.0580	0.0475	0.0575	0.0468	0.0578	0.0465
			200	0.0412	0.0331	0.0403	0.0330	0.0405	0.0326	0.0400	0.0327	0.0406	0.0328	0.0405	0.0329	0.0409	0.0335
			2000	0.0129	0.0107	0.0130	0.0105	0.0122	0.0101	0.0126	0.0105	0.0126	0.0104	0.0123	0.0102	0.0130	0.0107
	0.3	0.2	100	0.0565	0.0474	0.0549	0.0464	0.0563	0.0475	0.0550	0.0466	0.0561	0.0488	0.0563	0.0479	0.0552	0.0468
			200	0.0389	0.0333	0.0386	0.0330	0.0393	0.0330	0.0388	0.0333	0.0391	0.0336	0.0387	0.0335	0.0394	0.0334
			2000	0.0122	0.0106	0.0127	0.0106	0.0124	0.0107	0.0120	0.0103	0.0120	0.0103	0.0120	0.0104	0.0125	0.0108
	0.4	0.15	100	0.0576	0.0476	0.0567	0.0469	0.0576	0.0474	0.0570	0.0489	0.0577	0.0480	0.0578	0.0479	0.0571	0.0474
			200	0.0409	0.0339	0.0402	0.0340	0.0400	0.0332	0.0412	0.0343	0.0405	0.0339	0.0404	0.0334	0.0410	0.0343
			2000	0.0127	0.0107	0.0130	0.0107	0.0124	0.0105	0.0125	0.0109	0.0126	0.0104	0.0123	0.0104	0.0129	0.0108
0.8	0.2	0.1	100	0.0432	0.0363	0.0428	0.0361	0.0425	0.0357	0.0417	0.0348	0.0416	0.0352	0.0432	0.0362	0.0424	0.0465
			200	0.0299	0.0253	0.0305	0.0255	0.0302	0.0256	0.0295	0.0249	0.0299	0.0251	0.0296	0.0250	0.0301	0.0335
			2000	0.0094	0.0082	0.0096	0.0081	0.0093	0.0079	0.0093	0.0080	0.0095	0.0080	0.0093	0.0079	0.0095	0.0107
	0.4	0.15	100	0.0415	0.0382	0.0406	0.0369	0.0413	0.0376	0.0410	0.0378	0.0409	0.0370	0.0422	0.0381	0.0414	0.0377
			200	0.0297	0.0269	0.0292	0.0267	0.0293	0.0269	0.0289	0.0261	0.0297	0.0270	0.0289	0.0264	0.0292	0.0267
			2000	0.0093	0.0085	0.0093	0.0085	0.0093	0.0085	0.0092	0.0083	0.0094	0.0083	0.0091	0.0084	0.0091	0.0085

Table III

Simulated bias for the optimal threshold estimator.

				$\lambda = -2$		$\lambda = -1$		$\lambda = -0.5$		$\lambda = 0$		$\lambda = 0.5$		$\lambda = 1$		$\lambda = 2$	
J	π_W	π_Z	$M = N$	EMP	TN	EMP	TN	EMP	TN	EMP	TN	EMP	TN	EMP	TN	EMP	TN
0.4	0.2	0.1	100	−0.0005	−0.0001	−0.0005	−0.0001	−0.0003	0.0000	−0.3105	0.1132	−0.0616	−0.0085	−0.0283	−0.0071	−0.0107	−0.0020
			200	−0.0003	−0.0001	−0.0003	0.0000	−0.0002	0.0000	−0.2061	0.0527	−0.0357	−0.0048	−0.0185	−0.0025	−0.0052	−0.0009
			2000	−0.0001	0.0000	−0.0001	0.0000	0.0000	0.0000	−0.0463	0.0016	−0.0061	−0.0007	−0.0033	0.0003	−0.0015	−0.0001
	0.3	0.2	100	−0.0004	−0.0001	−0.0004	−0.0001	−0.0003	0.0000	−0.2847	0.1170	−0.0560	−0.0078	−0.0221	−0.0073	−0.0101	−0.0023
			200	−0.0002	0.0000	−0.0002	0.0000	−0.0001	0.0000	−0.0998	0.0488	−0.0159	−0.0062	−0.0099	−0.0028	−0.0030	−0.0013
			2000	−0.0001	0.0000	−0.0001	0.0000	0.0000	0.0000	−0.0543	0.0030	−0.0065	−0.0008	−0.0030	0.0002	−0.0020	−0.0001
	0.4	0.15	100	−0.0006	−0.0008	−0.0008	−0.0008	−0.0004	−0.0002	−0.3971	0.1095	−0.0775	−0.0242	−0.0356	−0.0227	−0.0181	−0.0159
			200	−0.0003	−0.0001	−0.0003	0.0000	−0.0002	0.0000	−0.1562	0.0343	−0.0312	−0.0098	−0.0191	−0.0061	−0.0065	−0.0029
			2000	−0.0001	0.0000	−0.0001	0.0000	−0.0001	0.0000	−0.0716	0.0084	−0.0093	−0.0019	−0.0029	0.0000	−0.0022	−0.0002
0.6	0.2	0.1	100	−0.0004	0.0000	−0.0004	0.0000	−0.0003	0.0000	−0.2481	0.1160	−0.0460	−0.0044	−0.0232	−0.0049	−0.0088	−0.0012
			200	−0.0003	0.0000	−0.0003	0.0000	−0.0002	0.0000	−0.2297	0.0509	−0.0342	−0.0025	−0.0153	−0.0021	−0.0057	−0.0004
			2000	−0.0001	0.0000	−0.0001	0.0000	0.0000	0.0000	−0.0305	0.0038	−0.0088	0.0001	−0.0019	0.0002	−0.0012	0.0000
	0.3	0.2	100	−0.0004	0.0000	−0.0004	0.0000	−0.0003	0.0000	−0.2374	0.1075	−0.0500	−0.0023	−0.0189	−0.0040	−0.0094	−0.0011
			200	−0.0004	0.0000	−0.0003	0.0000	−0.0002	0.0000	−0.1830	0.0706	−0.0385	−0.0030	−0.0143	−0.0020	−0.0065	−0.0006
			2000	−0.0001	0.0000	−0.0001	0.0000	0.0000	0.0000	−0.0684	0.0025	−0.0066	0.0003	−0.0025	0.0002	−0.0015	−0.0001
	0.4	0.15	100	−0.0005	0.0000	−0.0004	0.0000	−0.0003	0.0000	−0.3128	0.1172	−0.0538	−0.0037	−0.0222	−0.0048	−0.0098	−0.0014
			200	−0.0003	0.0000	−0.0003	0.0000	−0.0002	0.0000	−0.2035	0.0567	−0.0360	−0.0024	−0.0150	−0.0026	−0.0065	−0.0006
			2000	−0.0001	0.0000	−0.0001	0.0000	0.0000	0.0000	−0.0513	0.0005	−0.0098	−0.0004	−0.0038	0.0001	−0.0018	−0.0001
0.8	0.2	0.1	100	−0.0004	0.0000	−0.0004	0.0000	−0.0003	0.0000	−0.3558	0.0993	−0.0376	0.0017	−0.0211	−0.0018	−0.0075	−0.0002
			200	−0.0003	0.0000	−0.0003	0.0000	−0.0003	0.0000	−0.2469	0.0455	−0.0350	−0.0005	−0.0144	−0.0013	−0.0064	0.0001
			2000	−0.0001	0.0000	−0.0001	0.0000	0.0000	0.0000	−0.0662	0.0002	−0.0094	0.0011	−0.0038	0.0002	−0.0020	0.0000
	0.4	0.15	100	−0.0006	0.0000	−0.0006	0.0000	−0.0004	0.0000	−0.4483	0.1102	−0.0576	0.0062	−0.0274	−0.0004	−0.0087	0.0001
			200	−0.0003	0.0000	−0.0003	0.0000	−0.0002	0.0000	−0.2639	0.0688	−0.0362	0.0004	−0.0193	−0.0012	−0.0066	0.0002
			2000	−0.0001	0.0000	−0.0001	0.0000	−0.0001	0.0000	−0.1253	0.0074	−0.0173	0.0015	−0.0057	0.0000	−0.0017	−0.0001

Table IV

Simulated RMSE for the optimal threshold estimator.

				$\lambda = -2$		$\lambda = -1$		$\lambda = -0.5$		$\lambda = 0$		$\lambda = 0.5$		$\lambda = 1$		$\lambda = 2$	
J	π_W	π_Z	$M = N$	EMP	TN	EMP	TN	EMP	TN	EMP	TN	EMP	TN	EMP	TN	EMP	TN
0.4	0.2	0.1	100	0.0021	0.0009	0.0020	0.0009	0.0014	0.0006	1.5855	0.6834	0.2417	0.1070	0.1040	0.0459	0.0411	0.0173
			200	0.0017	0.0007	0.0016	0.0006	0.0011	0.0004	1.2958	0.4576	0.1926	0.0750	0.0844	0.0316	0.0317	0.0120
			2000	0.0008	0.0002	0.0008	0.0002	0.0006	0.0001	0.5992	0.1366	0.0912	0.0238	0.0388	0.0096	0.0147	0.0038
	0.3	0.2	100	0.0021	0.0010	0.0020	0.0009	0.0015	0.0007	1.6744	0.7421	0.2491	0.1123	0.1036	0.0486	0.0410	0.0186
			200	0.0017	0.0007	0.0016	0.0006	0.0012	0.0005	1.3018	0.4708	0.1966	0.0822	0.0838	0.0343	0.0322	0.0131
			2000	0.0008	0.0002	0.0007	0.0002	0.0006	0.0002	0.6234	0.1500	0.0929	0.0256	0.0380	0.0103	0.0148	0.0040
	0.4	0.15	100	0.0026	0.0136	0.0042	0.0098	0.0020	0.0033	1.8280	0.7217	0.3029	0.2854	0.1307	0.2280	0.0809	0.1807
			200	0.0020	0.0009	0.0018	0.0008	0.0014	0.0006	1.4163	0.4512	0.2318	0.1592	0.1011	0.0936	0.0400	0.0590
			2000	0.0009	0.0003	0.0008	0.0003	0.0006	0.0002	0.6640	0.1366	0.1078	0.0312	0.0436	0.0128	0.0179	0.0051
0.6	0.2	0.1	100	0.0019	0.0008	0.0017	0.0007	0.0013	0.0005	1.4508	0.7340	0.2113	0.0904	0.0863	0.0383	0.0346	0.0142
			200	0.0015	0.0006	0.0013	0.0005	0.0010	0.0004	1.1808	0.4908	0.1650	0.0649	0.0703	0.0270	0.0270	0.0100
			2000	0.0007	0.0002	0.0006	0.0002	0.0005	0.0001	0.5429	0.1458	0.0789	0.0209	0.0324	0.0083	0.0125	0.0032
	0.3	0.2	100	0.0018	0.0008	0.0017	0.0008	0.0013	0.0006	1.5546	0.7771	0.2178	0.0937	0.0872	0.0393	0.0347	0.0150
			200	0.0015	0.0006	0.0013	0.0005	0.0010	0.0004	1.2705	0.5229	0.1712	0.0695	0.0700	0.0284	0.0270	0.0106
			2000	0.0007	0.0002	0.0006	0.0002	0.0005	0.0001	0.5834	0.1505	0.0775	0.0220	0.0317	0.0087	0.0126	0.0033
	0.4	0.15	100	0.0019	0.0009	0.0018	0.0008	0.0013	0.0006	1.5057	0.7608	0.2199	0.1030	0.0920	0.0441	0.0375	0.0168
			200	0.0016	0.0006	0.0015	0.0006	0.0010	0.0004	1.2393	0.4976	0.1810	0.0757	0.0744	0.0318	0.0292	0.0121
			2000	0.0007	0.0002	0.0007	0.0002	0.0005	0.0001	0.5749	0.1489	0.0845	0.0236	0.0347	0.0095	0.0135	0.0037
0.8	0.2	0.1	100	0.0018	0.0008	0.0018	0.0007	0.0013	0.0006	1.6429	0.7715	0.2082	0.0899	0.0870	0.0365	0.0324	0.0136
			200	0.0015	0.0006	0.0014	0.0005	0.0011	0.0004	1.3347	0.5104	0.1683	0.0654	0.0683	0.0257	0.0253	0.0094
			2000	0.0006	0.0002	0.0007	0.0002	0.0005	0.0001	0.6427	0.1557	0.0780	0.0206	0.0313	0.0082	0.0120	0.0031
	0.4	0.15	100	0.0021	0.0010	0.0021	0.0009	0.0015	0.0007	1.9928	0.8118	0.2458	0.1133	0.0972	0.0451	0.0357	0.0168
			200	0.0017	0.0007	0.0015	0.0006	0.0012	0.0005	1.6514	0.5513	0.1955	0.0809	0.0779	0.0321	0.0291	0.0116
			2000	0.0007	0.0002	0.0007	0.0002	0.0005	0.0002	0.7475	0.1643	0.0887	0.0247	0.0352	0.0099	0.0130	0.0037