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ESTIMATION OF YOUDEN INDEX AND ITS ASSOCIATED OPTIMAL CUT-POINT WHEN THE PARAMETERS OF GAMMA BIOMARKERS ARE ESTIMATED BY THE METHOD OF MOMENTS

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The ROC (Receiver Operating Characteristics) curves are frequently used to measure the effectiveness of diagnostic biomarkers. A global measure of the ROC curve is the Youden index, the maximum difference between sensitivity and 1-specificity. The cut-point is the value for which the maximum is attained. In this paper we obtain the asymptotic distribution of the optimal cut-point under the assumption that both the healthy and diseased populations are gamma distributed with a common shape parameter and when the gamma parameters are estimated by the method of moments. Based on the asymptotic distribution we construct confidence intervals for the cut-point. We also consider a nonparametric estimator of the Youden index and a measure of its precision based on the kernel estimator of a distribution function. We construct confidence intervals based on this methodology which we compare with those based on the delta method.

Key words: ROC curve, Youden index, Optimal cut-point, Method of moments.

1. INTRODUCTION

The ROC curve is frequently used in assessing the effectiveness of continuous diagnostic markers between diseased and healthy individuals. Without loss of generality we will suppose a person is assessed as diseased or healthy if the corresponding marker value is larger than or less than or equal to a given threshold value. Associated with each marker value is the sensitivity (the probability that a diseased person be detected as such by the test) and the specificity (the probability that a healthy person be detected as such by the test). The ROC curve is defined as the plot of sensitivity versus 1-specificity.

ROC curves are estimated on the basis of two samples of marker values taken in the populations of diseased (X_1) and healthy subjects (X_0). Both parametric and nonparametric methods have been used for estimating the ROC curves (Pepe, 2003; Krzanowski and Hand, 2009).

The most commonly used measure of accuracy of the ROC curve is the area under the curve (AUC) which was showed to equal $AUC = P(X_1 > X_0)$. The probability $P(X_1 > X_0)$ appears also in situations not dealing with the evaluation of biomarkers like stress-strength problems. When one tests the quality of an item or a product X_1 is the strength that varies from item to item and X_0 represents the random value of a stress that the item will be subjected to. $P(X_1 > X_0)$ will be the probability that a randomly selected item functions successfully. The inference on $P(X_1 > X_0)$ in the reliability of stress-strength systems was considered under various assumptions (Reiser and Gutmann, 1986; Constantine and Karson, 1986; McCool, 1991; Surles and Padgett, 1998).

Another frequently used summary index of marker accuracy is the Youden index defined as the largest difference between the sensitivity and 1-specificity taken over all points on the ROC curve or equivalently over all possible threshold values. We will use the notation $J(c) = \mathrm{Se}(c) - (1 - \mathrm{Sp}(c))$, where $\mathrm{Se}(c)$ and $\mathrm{Sp}(c)$ are the sensitivity and the specificity corresponding to threshold c. The Youden index is the maximum of $J(c)$ taken over all possible values of c. The Youden index has an attractive feature not present in AUC. It

provides a criterion for choosing the optimal threshold value which is the value c_{opt} for which the maximum is attained ($\mathrm{YI} = J(c_{opt})$). Based on c_{opt} one will be able to establish weather a person is healthy (if its marker value is less than c_{opt}) or diseased (if its marker value is larger than c_{opt}).

Fluss, Faraggi and Reiser (2005) deal with the estimation of Youden index and its associated cutoff point. They present four different methods (parametric and nonparametric) for estimating YI and c_{opt}, then they compare these methods through an extensive simulation study. The first method supposes that both X_0 and X_1 have independent normal distributions with different means and variances. The second method suppose that there exists some monotonic transformation $t(\cdot)$ such that $t(X_0)$ and $t(X_1)$ are normally distributed. The last two methods are nonparametric and consist of estimating the cumulative distribution functions of X_0 and X_1. The first uses the empirical estimate of cdf of X_0 and X_1 while the second nonparametric method uses a kernel method for cdf estimate of X_0 and X_1. In the nonparametric case numerical methods are needed to find both $\hat{c}_{opt}$ and the Youden index associated with $\hat{c}_{opt}$. The simulations they undertake cover a wide variety of different distributional shapes for X_0 and X_1: symmetric, skewed and bimodal situations often seen in real data.

Another work dealing with the Youden index is Schisterman and Perkins (2007). They propose the delta method for estimating the variance of $\hat{c}_{opt}$ and $J(\hat{c}_{opt})$ in two cases: first they assume that X_0 and X_1 are independent normal variables with different means and variances. Then they assume that X_0 and X_1 are independently distributed following gamma distributions with different shape and scale parameters. In the general gamma case with different shape and scale parameters $\hat{c}_{opt}$ and $J(\hat{c}_{opt})$ cannot be determined explicitly, numerical methods being necessary in order to compute them. They undertake a simulation study where confidence intervals for $\hat{c}_{opt}$ and $J(\hat{c}_{opt})$ based on the delta method are compared in terms of coverage probability and length to confidence intervals based on three bootstrapping methods.

In the general gamma case where the shape and scale parameters are different there are no closed expressions for $\hat{c}_{opt}$ and $J(\hat{c}_{opt})$ therefore they have to be determined numerically. The delta method proposed by Schisterman and Perkins (2007) for estimating the variance of $\hat{c}_{opt}$ and $J(\hat{c}_{opt})$ adds to the amount of computation by the fact that one has to deal with the derivatives of *c* and *J* with respect to the parameters of gamma distributions which themselves have to be found numerically.

In this paper we consider the much more tractable case where X_0 and X_1 are independently gamma with common shape but different scale parameters. Instead of estimating the gamma parameters by the maximum likelihood estimator (ML) we chose the method of moments (MM). In section 2 we obtain the asymptotic distribution of $\hat{c}_{opt}$ in a different way then by applying the delta method. Thus we show how a considerable simplified formula for $V(\hat{c}_{opt})$ can be obtained. We undertake a simulation study following the general lines of Schisterman and Perkins (2007). We examine how the properties of the confidence intervals for the optimal cut-point based on its asymptotic distribution are influenced by different sample sizes and parametric situations. Section 3 deals with the Youden index for which we consider a non parametric estimator as well as a nonparametric estimator of its precision. We then compare confidence intervals of the Youden index based on the non parametric estimator with confidence intervals based on the delta method proposed by Schisterman and Perkins (2007).

2. INFERENCE FOR THE OPTIMAL CUT POINT

The special case of X_0 and X_1 being independently gamma distributed with common shape and different scale parameters is briefly considered in (Schisterman et. al., 2005). Faraggi and Reiser (2002) also consider it in the wide variety of distributions they use in their simulation study aimed at comparing several

methods of estimation of the area under the ROC curve. Thus for the population of controls and cases we assume two independent gamma distributions:

$$X_0 \sim \text{Gamma}(\alpha, \beta_0) \text{ and } X_1 \sim \text{Gamma}(\alpha, \beta_1),$$

where $\beta_0 < \beta_1$ (otherwise one may simply switch the cases with controls in the following analysis). $\text{Gamma}(\alpha, \beta)$ is the gamma distribution with density:

$$f_{\alpha,\beta}(x) = \frac{x^{\alpha-1}\exp(-x/\beta)}{\beta^{\alpha}\Gamma(\alpha)}.$$

Let F_0 (F_1) and f_0 (f_1) be the cdf and respectively the density functions of X_0 (X_1). Let $\{x_{10},...,x_{n_0 0}\}$ and $\{x_{11},...,x_{n_1 1}\}$ be the samples of controls and cases with means $\bar{x}_0$ and $\bar{x}_1$ and variances s_0^2 and s_1^2 respectively. $J(c)$ will be given by:

$$J(c) = F_0(c) - F_1(c).$$

A consequence of assuming common shapes is the existence of an explicit formula for c_{opt}. It can be shown (Schisterman et. al., 2005) that the optimal cut point maximizing $J(c)$ is given by:

$$c_{opt} = \frac{\alpha(\log(\beta_1) - \log(\beta_0))}{(\frac{1}{\beta_0} - \frac{1}{\beta_1})}$$

and the associated Youden index by $\text{YI} = J(c_{opt})$.

Parameters α, β_0 and β_1 have to be estimated. Instead of using the ML estimators we will propose methods of moments estimators $\hat{\alpha}, \hat{\beta}_0$ and $\hat{\beta}_1$. Even if the method of moments estimators have not the optimality properties of the ML estimators they don't need numeric methods to be computed as in this case is needed for the ML estimators.

$$E(s_0^2) = \alpha_0\beta_0^2 = \sigma_0^2 \text{ and } E(s_1^2) = \alpha_1\beta_1^2 = \sigma_1^2.$$

On the other hand:

$$E(\bar{x}) = \frac{(n_0\alpha\beta_0 + n_1\alpha\beta_1)}{(n_0 + n_1)} = \frac{(n_0\mu_0 + n_1\mu_1)}{(n_0 + n_1)},$$

where $\bar{x}$ is the mean of the sample of cases and controls put together. From these one can derive method of moments estimators by equaling s_0^2, s_1^2 and $\bar{x}$ to their respective means. Solving the equations one obtains:

$$\hat{\alpha} = \frac{(n_0 + n_1)^2\bar{x}^2}{(n_0 s_0 + n_1 s_1)^2},\ \hat{\beta}_0 = \frac{s_0(n_0 s_0 + n_1 s_1)}{(n_0 + n_1)\bar{x}} \text{ and } \hat{\beta}_1 = \frac{s_1(n_0 s_0 + n_1 s_1)}{(n_0 + n_1)\bar{x}}.$$

We will plug $\hat{\alpha}, \hat{\beta}_0$ and $\hat{\beta}_1$ into the formula of c_{opt} to get an estimator of the optimal cut point and of the Youden index:

$$\hat{c}_{opt} = \frac{\hat{\alpha}(\log(\hat{\beta}_1) - \log(\hat{\beta}_0))}{(\frac{1}{\hat{\beta}_0} - \frac{1}{\hat{\beta}_1})} \text{ and } \widehat{\text{YI}} = J(\hat{c}_{opt}).$$

We proved the following theoretical result for the asymptotic distribution of $\hat{c}_{opt}$ (proofs are available from the authors):

Result 1: With the notations and under the conditions introduced so far the asymptotic distribution of $\hat{c}_{opt}$ is given by:

$$\sqrt{n_0 + n_1}(\hat{c}_{opt} - c_{opt}) \to_d N(0, \sigma^2)$$

with σ^2 given by:

$$\sigma^2 = c_{opt}^2(1+k)\left[\left(\frac{\sigma_0}{\mu_0 + k\mu_1}, L_0\right)\boldsymbol{\Sigma}\begin{pmatrix}\frac{\sigma_0}{\mu_0 + k\mu_1}\\ L_0\end{pmatrix} + \frac{1}{k}\left(\frac{k\sigma_1}{\mu_0 + k\mu_1}, L_1\right)\boldsymbol{\Sigma}\begin{pmatrix}\frac{k\sigma_1}{\mu_0 + k\mu_1}\\ L_1\end{pmatrix}\right],$$

where $k = \frac{n_1}{n_0}$, $L_0 = \frac{2\sigma_0 + \sigma_1}{2(\sigma_0 + \sigma_1)} - \frac{1}{\ln\sigma_1^2 - \ln\sigma_0^2} - \frac{\sigma_0}{2(\sigma_0 + k\sigma_1)} + \frac{\sigma_0^2}{(\sigma_1^2 - \sigma_0^2)}$,

$L_1 = \frac{2\sigma_1 + \sigma_0}{2(\sigma_0 + \sigma_1)} + \frac{1}{\ln\sigma_1^2 - \ln\sigma_0^2} - \frac{k\sigma_1}{2(\sigma_0 + k\sigma_1)} - \frac{\sigma_1^2}{(\sigma_1^2 - \sigma_0^2)}$ and $\boldsymbol{\Sigma} = \begin{pmatrix} 1 & \frac{2}{\sqrt{\alpha}} \\ \frac{2}{\sqrt{\alpha}} & \frac{2(\alpha+3)}{\alpha} \end{pmatrix}$.

Simulation study. In a simulation study we assessed the coverage percentage and the length of confidence intervals for c_{opt} based on the asymptotic distribution derived in A1. For $(n_0, n_1) = (50,50), (100,100)$ and $(200,200)$ we generated gamma samples for controls and cases with $\alpha = 1, \beta_0 = 0.5, 1$ and 2 and β_1 taken such that the Youden index be equal to 0.2, 0.4, 0.6, 0.8 and 0.9. The left part of Table 1 contains for each parameter combination the values of β_1 and c_{opt}.

Table 1

$RB(\hat{c}_{opt}) / RB(\hat{V}(\hat{c}_{opt}))$ and Coverage probability/Average length of CI for c_{opt}

				$RB(\hat{c}_{opt}) / RB(\hat{V}(\hat{c}_{opt}))$			Cov. Prob./Av. length of CI for c_{opt}		
	YI	β_1	c_{opt}	$n_0 = n_1 = 50$	$n_0 = n_1 = 100$	$n_0 = n_1 = 200$	$n_0 = n_1 = 50$	$n_0 = n_1 = 100$	$n_0 = n_1 = 200$
$\alpha = 1, \beta_0 = 0.5$	0.2	0.86	0.65	-1.18/-0.43	-0.58/0.54	-0.35/0.71	93.4/0.266	94.2/0.190	94.7/0.135
	0.4	1.57	0.84	-0.84/3.55	-0.40/3.10	-0.24/1.80	94.3/0.396	94.8/0.284	94.8/0.202
	0.6	3.22	1.10	-0.50/8.03	-0.27/6.71	-0.15/2.75	95.0/0.614	95.0/0.440	95.0/0.313
	0.8	9.20	1.54	0.16/6.90	0.13/4.14	0.08/4.19	95.3/1.013	95.3/0.723	95.5/0.514
	0.9	23.45	1.96	0.60/7.19	0.16/4.91	0.02/3.38	95.2/1.411	95.2/1.006	95.2/0.713
$\alpha = 1, \beta_0 = 1$	0.2	1.73	1.30	-1.04/0.67	-0.55/0.51	-0.20/2.15	93.4/0.533	94.3/0.380	94.9/0.270
	0.4	3.14	1.68	-0.85/3.84	-0.36/2.62	-0.18/2.23	94.4/0.792	94.5/0.568	95.1/0.404
	0.6	6.44	2.20	-0.63/6.53	-0.23/3.46	-0.03/4.67	94.6/1.228	95.0/0.880	95.2/0.627
	0.8	18.41	3.08	0.02/7.48	0.06/7.06	0.15/4.29	95.2/2.025	95.3/1.446	95.3/1.029
	0.9	46.91	3.93	0.46/9.97	0.25/2.88	0.11/1.87	95.4/2.821	95.1/2.012	95.0/1.428
$\alpha = 1, \beta_0 = 2$	0.2	3.46	2.60	-0.98/0.69	-0.60/-0.43	-0.23/1.72	93.7/1.065	94.1/0.760	94.8/0.540
	0.4	6.29	3.36	-0.76/2.70	-0.41/2.99	-0.20/2.09	94.4/1.586	95.1/1.136	95.0/0.809
	0.6	12.88	4.41	-0.53/5.33	-0.23/5.38	-0.15/2.78	94.9/2.457	95.2/1.762	95.1/1.254
	0.8	36.82	6.16	-0.15/7.71	-0.01/3.85	0.14/3.86	95.0/4.041	95.0/2.892	95.3/2.058
	0.9	93.82	7.86	0.35/9.09	0.24/6.02	0.10/2.59	95.2/5.639	95.3/4.021	95.0/2.859

For each combination of parameters we generated 10000 gamma samples for cases and controls. Based on these samples we simulated the Monte Carlo values of $E(\hat{c}_{opt})$, $V(\hat{c}_{opt})$ and $E(\hat{V}(\hat{c}_{opt}))$ where $\hat{V}(\hat{c}_{opt}) = \hat{\sigma}^2/(n_0+n_1)$ and $\hat{\sigma}^2$ is σ^2 with α, β_0, β_1 replaced by their respective MM estimators. Then we computed the relative bias of $\hat{c}_{opt}$ and $\hat{V}(\hat{c}_{opt})$. The values of $RB(\hat{c}_{opt})$ and $RB(\hat{V}(\hat{c}_{opt}))$ are in the middle part of Table 1. Values for $RB(\hat{c}_{opt})$ confirm that $\hat{c}_{opt}$ is unbiased for c_{opt} while values for $RB(\hat{V}(\hat{c}_{opt}))$ prove that $\hat{V}(\hat{c}_{opt})$ derived from Result 1 is asymptotically unbiased for $V(\hat{c}_{opt})$ as its bias decreases as n_0 and n_1 increase.

For each sample we computed a 95% confidence interval for c_{opt} based on the formula $\hat{c}_{opt} \pm 1.96\sqrt{\hat{V}(\hat{c}_{opt})}$. The 10000 confidence intervals were used to compute the coverage percentage and the average length which are reported in the right part of Table 1. The coverage probabilities are close to the nominal value for larger values of n_0 and n_1. There is a tendency for them to increase and approach the nominal value when YI takes larger values. A large value of YI is indicative of a biomarker with a good power to discriminate between healthy and diseased patients thus these are the situations which are interesting from a practical point of view. The value of β_0 doesn't seem to have an important impact on the coverage probabilities.

There is a clear tendency for the average length to increase when both YI and β_0 increase which is what one expects as c_{opt} also increases as can be seen from the left part of Table 1. On the other hand the length decreases as (n_0, n_1) increase. However if one compares the average length of the c_{opt} confidence interval to the value of c_{opt} by the ratio between these values it can be noticed that the ratios still increase as functions of YI and β_0 and they decrease as functions of (n_0, n_1).

3. INFERENCE FOR THE YOUDEN INDEX

The Youden index is given by $\mathrm{YI} = F_0(c_{opt}) - F_1(c_{opt})$. If we replace c_{opt} by $\hat{c}_{opt}$ then we obtain the parametric estimator of YI denoted by $\widehat{\mathrm{YI}}$ and equal to $\widehat{\mathrm{YI}} = F_0(\hat{c}_{opt}) - F_1(\hat{c}_{opt})$. Schisterman and Perkins (2007) estimated the variance of $\widehat{\mathrm{YI}}$ using the delta method. In this section we estimate the cdfs F_0 and F_1 by kernel estimators as in (Lloyd, 1998) who used such nonparametric estimators to estimate a ROC curve and the area under it.

Denoting by Φ the cdf of a standard normal distribution, $\hat{F}_0$ and $\hat{F}_1$ will be given by:

$$\hat{F}_0(x) = \frac{1}{n_0}\sum_{i=1}^{n_0}\Phi\left(\frac{x - x_{i0}}{h_0}\right) \quad \text{and} \quad \hat{F}_1(x) = \frac{1}{n_1}\sum_{i=1}^{n_1}\Phi\left(\frac{x - x_{i1}}{h_1}\right).$$

Below we will need nonparametric estimators for the first and the second derivative of F_0 and F_1. These can be obtained by deriving two times $\hat{F}_0(x)$ and $\hat{F}_1(x)$ with respect to x:

$$\hat{F}_0^{'}(x) = \frac{1}{n_0 h_0}\sum_{i=1}^{n_0}\varphi\left(\frac{x - x_{i0}}{h_0}\right) \quad \text{and} \quad \hat{F}_0^{''}(x) = \frac{1}{n_0 h_0^2}\sum_{i=1}^{n_0}\varphi'\left(\frac{x - x_{i0}}{h_0}\right),$$

where $\varphi(x) = \Phi'(x)$ and similar expressions for $\hat{F}_1^{'}(x)$ and $\hat{F}_1^{''}(x)$ hold.

Then the nonparametric estimator of the Youden index will be $\widehat{\mathrm{YI}}^{NP} = \hat{F}_0(\hat{c}_{opt}) - \hat{F}_1(\hat{c}_{opt})$. h_0 and h_1 are the bandwidths used for estimating F_0 and F_1 which control for the level of smoothing. In estimating a cdf

the optimal choice for *h* is of order $n^{-1/3}$. Therefore we will take $h_0 = n_0^{-1/3}$ and $h_1 = n_1^{-1/3}$. We proved Result 2 below which gives expressions for the bias and the variance of $\widehat{\mathrm{YI}}^{NP}$ up to terms of order $O(1/n)$ and $O(1/n^2)$ respectively (proofs are available from the authors):

Result 2: With the notations and under the conditions introduced above the bias and variance of $\widehat{\mathrm{YI}}^{NP}$ are given by:

$$Bias(\widehat{\mathrm{YI}}^{NP}) = \frac{1}{2}(F_0^{"}(c_{opt})h_0^2 - F_1^{"}(c_{opt})h_1^2) + O(\frac{1}{n}),$$

$$V(\widehat{\mathrm{YI}}^{NP}) = \frac{1}{n_0}[F_0(c_{opt}) - F_0(c_{opt})^2 - 2h_0\alpha_1 F_0^{'}(c_{opt}) + \frac{1}{2}h_0^2 F_0^{"}(c_{opt})(1-2F_0(c_{opt})] +$$

$$+\frac{1}{n_1}[F_1(c_{opt}) - F_1(c_{opt})^2 - 2h_1\alpha_1 F_1^{'}(c_{opt}) + \frac{1}{2}h_1^2 F_1^{"}(c_{opt})(1-2F_1(c_{opt})] + O(\frac{1}{n^2}).$$

An estimator $\hat{V}(\widehat{\mathrm{YI}}^{NP})$ of $V(\widehat{\mathrm{YI}}^{NP})$ will then be obtained by replacing in the formula above c_{opt} by $\hat{c}_{opt}$ and the cdfs and their derivatives by their respective nonparametric estimators. Confidence intervals for the Youden index can then be computed by $\widehat{\mathrm{YI}}^{NP} \pm 1.96\sqrt{\hat{V}(\widehat{\mathrm{YI}}^{NP})}$. We also followed Schisterman and Perkins (2007) to estimate the YI and its variance. Thus we estimated the Youden index by $\widehat{\mathrm{YI}} = \tilde{F}_0(\hat{c}_{opt}) - \tilde{F}_1(\hat{c}_{opt})$ where $\tilde{F}_0$ and $\tilde{F}_1$ are estimators of F_0 and F_1 obtained by replacing the gamma parameters by their method of moments estimators. Then we obtained an estimator of $V(\widehat{\mathrm{YI}})$ based on the delta method which we denoted by $\hat{V}(\widehat{\mathrm{YI}})^{DM}$. In the following subsection through a simulation study we compared the behavior of both approaches.

Simulation study. In a similar manner as in the preceding simulation study for different parameters values we generated 10000 samples of cases an controls aimed at estimating the relative bias of both the Youden index estimator and its variance estimator. We first used the delta method and then the nonparametric approach in order to compare them. The left part of Table 2 contains the relative biases of $\widehat{\mathrm{YI}}$ and $\widehat{\mathrm{YI}}^{NP}$ as the right part of Table 2 contains the relative biases of $\hat{V}(\widehat{\mathrm{YI}})^{DM}$ and $\hat{V}(\widehat{\mathrm{YI}}^{NP})$.The bias of $\widehat{\mathrm{YI}}$ is small for most values of (n_0, n_1). On the other hand the bias of $\widehat{\mathrm{YI}}^{NP}$ can be as large as –9.54% for $(n_0, n_1) = (50,50)$ and YI=0.2 but is asymptotical unbiased with a negligible bias as (n_0, n_1) increase. The value of YI affects both the biases of $\widehat{\mathrm{YI}}$ and $\widehat{\mathrm{YI}}^{NP}$. Larger values of YI means smaller relative biases with negligible biases even for $(n_0, n_1) = (50,50)$. It is important to notice this fact given that in practice one will deal with biomarker having YI larger that 0.6. For $\beta_0 = 0.5$ the relative bias of $\widehat{\mathrm{YI}}$ is smaller than that of $\widehat{\mathrm{YI}}^{NP}$. For $\beta_0 = 1$ or $\beta_0 = 2$ and if $\mathrm{YI} > 0.6$ the relative bias of $\widehat{\mathrm{YI}}^{NP}$ is smaller than the relative bias of $\widehat{\mathrm{YI}}$ showing that in these cases the nonparametric approach is superiror to the delta method.The right part of Table 2 shows that the relative bias of $\hat{V}(\widehat{\mathrm{YI}})^{DM}$ as an estimator of $V(\widehat{\mathrm{YI}})$ can be large especially for small values of (n_0, n_1) and large value of YI. $\hat{V}(\widehat{\mathrm{YI}}^{NP})$ performs better with relative biases less than 5% in absolute value. However both $\hat{V}(\widehat{\mathrm{YI}})^{DM}$ and $\hat{V}(\widehat{\mathrm{YI}}^{NP})$ are asymptotically unbiased but almost everywhere $\hat{V}(\widehat{\mathrm{YI}}^{NP})$ is superior to $\hat{V}(\widehat{\mathrm{YI}})^{DM}$ in terms of bias. In the left part of Table 3 there are the coverage probabilities and the average length of the confidence interval for YI using $\widehat{\mathrm{YI}}^{NP}$ and $\hat{V}(\widehat{\mathrm{YI}}^{NP})$. Larger values of YI seem to diminish the coverage probability to values as small as 88.2% if $(n_0, n_1) = (50,50)$ and

YI=0.9. However the coverage probability increases as (n_0, n_1) increase. β_0 also influences the coverage probability by diminishing it as β_0 increases.

Table 2

Values of $RB(\widehat{\mathrm{YI}}) / RB(\widehat{\mathrm{YI}}^{NP})$ and $RB(\hat{V}(\widehat{\mathrm{YI}})^{DM}) / RB(\hat{V}(\widehat{\mathrm{YI}}^{NP}))$ (%)

		$RB(\widehat{\mathrm{YI}}) / RB(\widehat{\mathrm{YI}}^{NP})$			$RB(\hat{V}(\widehat{\mathrm{YI}})^{DM}) / RB(\hat{V}(\widehat{\mathrm{YI}}^{NP}))$		
	YI	$n_0 = n_1 = 50$	$n_0 = n_1 = 100$	$n_0 = n_1 = 200$	$n_0 = n_1 = 50$	$n_0 = n_1 = 100$	$n_0 = n_1 = 200$
$\alpha = 1, \beta_0 = 0.5$	0.2	1.70/-9.54	0.74/-6.44	0.12/-3.77	6.34/2.40	1.79/3.02	0.47/4.54
	0.4	1.47/-5.58	0.51/-3.23	0.42/-1.95	5.40/4.96	4.02/0.51	4.92/2.60
	0.6	1.43/-2.81	0.72/-1.59	0.34/-1.06	7.38/0.54	3.88/2.15	2.02/2.31
	0.8	1.03/-1.06	0.49/-0.60	0.26/-0.43	14.67/0.002	8.04/1.57	4.20/0.45
	0.9	0.46/-0.24	0.22/-0.20	0.04/-0.16	19.01/1.21	10.25/-0.28	7.99/0.55
$\alpha = 1, \beta_0 = 1$	0.2	1.31/-2.56	0.74/-0.91	-0.13/-0.96	4.28/-0.64	3.18/-1.09	1.16/-0.68
	0.4	1.27/-1.65	0.77/-0.95	0.27/-0.50	4.09/-0.64	2.33/2.05	3.78/0.77
	0.6	1.62/-0.87	1.01/-0.35	0.43/-0.40	4.98/-0.89	5.07/2.77	0.96/-0.99
	0.8	1.01/-0.25	0.61/-0.11	0.20/-0.07	13.54/-4.42	7.87/-1.98	4.54/-0.96
	0.9	0.40/0.08	0.25/0.04	0.15/-0.02	20.56/-3.40	10.54/-0.57	4.76/2.18
$\alpha = 1, \beta_0 = 2$	0.2	1.80/-0.41	0.92/-0.81	0.04/-0.57	8.11/-2.04	3.07/-1.26	3.60/-0.04
	0.4	1.20/-0.90	0.85/-0.39	0.49/-0.11	3.24/-0.05	2.37/-1.30	0.56/0.60
	0.6	1.46/-0.12	0.68/-0.26	0.37/0.02	5.40/-0.32	2.41/1.38	0.50/-0.22
	0.8	0.95/-0.06	0.49/-0.003	0.21/-0.12	15.52/-2.73	6.36/0.03	1.73/-2.85
	0.9	0.52/0.16	0.22/0.04	0.15/0.002	22.97/-5.52	11.62/-0.18	5.09/-1.87

Table 3

Coverage probability/Average length of CI for YI

		Non parametrical approach			Delta Method approach		
	YI	$n_0 = n_1 = 50$	$n_0 = n_1 = 100$	$n_0 = n_1 = 200$	$n_0 = n_1 = 50$	$n_0 = n_1 = 100$	$n_0 = n_1 = 200$
$\alpha = 1, \beta_0 = 0.5$	0.2	94.7/0.301	95.0/0.224	95.2/0.164	95.1/0.387	94.6/0.273	94.5/0.193
	0.4	94.7/0.302	94.6/0.220	94.6/0.159	95.2/0.338	95.4/0.238	95.5/0.168
	0.6	94.5/0.278	95.0/0.200	95.0/0.143	94.3/0.285	94.7/0.202	94.9/0.143
	0.8	94.1/0.216	94.9/0.155	94.9/0.110	92.8/0.230	93.7/0.166	94.3/0.118
	0.9	92.0/0.157	93.5/0.113	94.5/0.081	90.0/0.172	92.7/0.125	94.0/0.090
$\alpha = 1, \beta_0 = 1$	0.2	94.6/0.336	94.7/0.243	94.8/0.174	94.9/0.386	95.0/0.273	94.8/0.193
	0.4	94.7/0.323	95.2/0.232	95.1/0.166	94.9/0.338	94.8/0.238	95.3/0.168
	0.6	94.7/0.288	94.8/0.206	94.7/0.147	93.8/0.285	94.7/0.202	94.6/0.143
	0.8	92.8/0.220	93.9/0.157	94.3/0.112	92.6/0.230	93.6/0.165	94.6/0.118
	0.9	89.8/0.158	92.6/0.114	94.7/0.082	90.1/0.173	92.4/0.125	93.5/0.089
$\alpha = 1, \beta_0 = 2$	0.2	94.4/0.352	94.7/0.252	94.8/0.179	95.2/0.386	94.7/0.273	95.4/0.193
	0.4	94.2/0.334	94.6/0.238	94.8/0.169	94.8/0.338	94.8/0.238	94.8/0.168
	0.6	94.2/0.295	95.2/0.210	94.7/0.149	94.3/0.285	94.6/0.202	94.7/0.143
	0.8	92.7/0.223	93.9/0.159	94.2/0.114	92.8/0.231	93.9/0.166	94.2/0.118
	0.9	88.2/0.159	92.9/0.116	93.7/0.083	90.1/0.172	92.6/0.125	93.9/0.089

We also computed the coverage probabilities and their average length of CI using $\widehat{\mathrm{YI}}$ and $\hat{V}(\widehat{\mathrm{YI}})^{DM}$. The right part of Table 3 contains the results. By comparing the left and right parts of Table 3 we can notice similar values for coverage percentage especially for $(n_0, n_1) = (100,100)$ and $(n_0, n_1) = (200,200)$, as for $(n_0, n_1) = (50,50)$ the delta method provided coverage probability a bit higher than the nonparametric approach. As for the average length the nonparametric approach outperforms the delta method by providing confidence intervals shorter than those using the delta method for all the parameters values considered by the simulation study.

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