Web Appendix:
The Length of the ROC Curve and the Two Cutoff Youden Index within a Robust Framework for Discovery, Evaluation, and Cutoff Estimation in Biomarker Studies Involving Improper ROC Curves

Leonidas E. Bantis, John V. Tsimikas, Gregory Chambers, Michela Capello, Samir M. Hanash, and Ziding Feng

Web-Appendix A (Proofs of theoretical results related to Theorem 2 of the main manuscript)

Lemma 1. *Suppose we have a line segment* pq *of length* l*, and a point* x *which has height* h *above the line segment, and which is a horizontal distance of* a *from* p*. The larger* $|\alpha - \frac{l}{2}|$ *is, the larger the sum of the arcs from* p *to* x *and from* q *to* x *is.*

Proof. The sum of the lengths of the two arcs is $L(\alpha) = \sqrt{\alpha^2 + h^2} + \sqrt{(l-\alpha)^2 + h^2}$ (see Figure 1 for a representation). Differentiating yields:

$$\frac{\partial L}{\partial \alpha} = \frac{\alpha}{\sqrt{\alpha^2 + h^2}} - \frac{(l-\alpha)}{\sqrt{(l-\alpha)^2 + h^2}}. \tag{1}$$

Finding the zeros:

$$\begin{aligned}
\frac{\alpha}{\sqrt{\alpha^2 + h^2}} - \frac{(l-\alpha)}{\sqrt{(l-\alpha)^2 + h^2}} &= 0 \\
&\Rightarrow (l-\alpha)^2(\alpha^2 + h^2) = \alpha^2\left((l-\alpha)^2 + h^2\right) \\
&\Rightarrow (l-\alpha)^2 = \alpha^2 \\
&\Rightarrow l^2 = 2l\alpha \\
&\Rightarrow \frac{l}{2} = \alpha.
\end{aligned}$$

By computing the second derivative, we see that this is a local minimum. Combining this with the fact that $L(\alpha) = L(l-\alpha)$, we have that the larger $|\frac{l}{2} - \alpha|$ is, the larger the $L(\alpha)$ is. This completes the proof. ☐

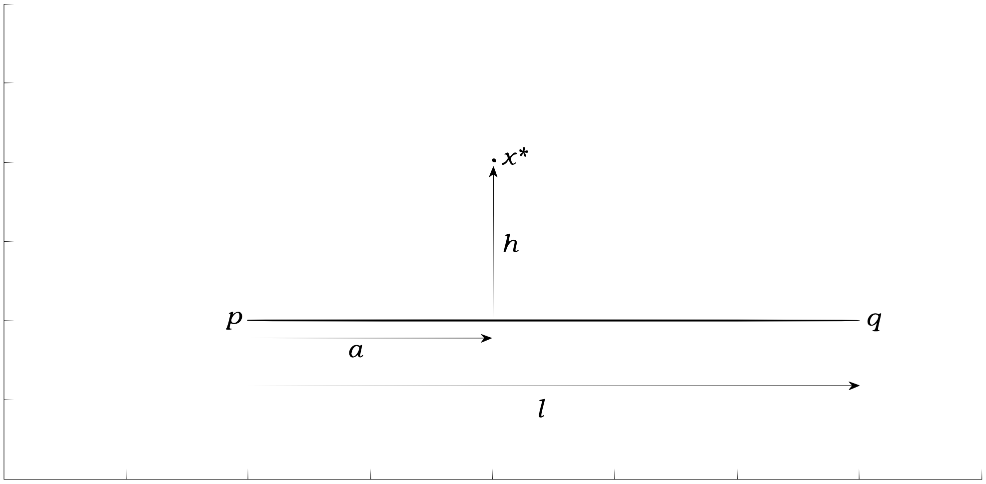

Figure 1: Configuration considered in Lemma 1.

Proposition 1. *Among all convex piecewise linear sets in the triangle* ABC *for which* BC *is included in their perimeter, the two configurations shown in panels (b) and (c) of Figure 3 maximize the perimeter of the convex set for a fixed enclosed area* R*.*

Proof. Denote with γ the piecewise linear curve with B and C as endpoints (see Figure 3). Suppose that there are more than 3 segments in γ. Then we can find a sequence of two segments whose endpoints are not B or C. We apply our first lemma to these two segments and three vertices. All positions are valid for x^* (γ is still convex, and the area is still R) as long as x^* does not leave lines k_1 and k_2. The lemma implies that the length of the two arcs is attained when x^* lies on k_1 or when x^* lies on k_2.
Moving x^* to this position, the new γ still bounds an area of R, is still a piecewise linear curve but with one fewer segment. We can repeat this procedure until there are three segments remaining. Applying Lemma 1 to the triangle x^*y^*C (see panel (b) of Figure 2), this either reduces the number of segments to 2, at which point we apply Lemma 1 again to finish the proof, or it produces the configuration given in panel (c) of Figure 2. We apply Lemma 1 to the triangle By^*x^*. Since the angle ABy^* is less than the angle Ay^*B, placing x^* on the edge of CB maximizes $|\frac{l}{2} - \alpha|$, which means that this maximizes the length of Bx^*y^*. Uniqueness follows since each one of these arrangements strictly increases the length. □

Theorem 1. *Among all convex sets in the triangle ABC for which BC is included in their perimeter, the two configurations shown in panels (b) and (c) of Figure 3 maximize the perimeter of the convex set for a fixed enclosed area. Furthermore, these are the only maximizers.*

Proof. Divide BC into n equal segments, and let the endpoints be $x_0^* = B, x_1^*, \ldots, x_n^* = C$. Each x_i^* is the $x-$coordinate of exactly on point on γ (the rope) since the region between BC and the rope γ is convex. Call these points (x_i^*, y_i^*). For every n, we construct a piecewise linear curve γ_n which goes from $B = (x_0^*, y_0^*)$ to (x_1^*, y_1^*) and so on until we reach $C = (x_n^*, y_n^*)$. This piecewise linear curve has n segments.

By Lemma 1, the length of γ_n is no less than the length of the configurations (b) and (c) shown in Figure 3 of the main manuscript, that bound the same area as γ_n bounds. Let the configuration of that type, which shares a segment with BA be called γ_n^*. Then

$$lim_{n\to\infty} length(\gamma_n^*) \geq lim_{n\to\infty} length(\gamma_n) \tag{2}$$

and

$$lim_{n\to\infty} area(\gamma_n^*) = lim_{n\to\infty} length(\gamma_n) = area(\gamma). \tag{3}$$

Thus, $lim_{n\to\infty}\gamma_n^*$, which is of the above configuration, bounds the same area as γ, but has no smaller length.

Regarding uniqueness:

We already know that the two configurations are maximizers. Suppose that γ which bounds area A', and which is not one of those configurations. We can then find two distinct points p and q on γ such that (1): p is not on the first configuration and (2): q is not on the second configuration. Let $p = (p_1, p_2)$ and $q = (q_1, q_2)$. Without loss of generality we assume that $p_1 \leq q_1$. We follow a procedure similar to the one presented before. Divide the interval from B to p_1 into n pieces of the same length, divide the interval from p_1 to q_1 up to into n pieces of the same length, and divide the interval from C up to n pieces of the same length. Let these points, as before, be

$$x_0 = B, x_1, \ldots, x_n = p_1, x_{n+1}, \ldots, x_{2n} = q, x_{2n+1}, \ldots, x_{3n} = C.$$

Each point corresponds to a distinct point (x_i, y_i) on γ, with $(x_n, y_n) = p$ and

$$(x_{2n}, y_{2n}) = q.$$

We construct γ_n as before and repeatedly apply Lemma 1. However, we do not choose any triangle which contains p or q on its interior. By doing this we obtain a piecewise linear curve of length no smaller than that of γ_n, and which has at most 6 segments. Let this curve be γ_n^*. Let β be the piecewise linear curve of at most 6 segments, which contains p and q, and which bounds the same area that γ bounds, and which maximizes the length. Note that β exists and is not unique.

Since

$$\lim_{n\to+\infty} area(\gamma_n^*) = area(\gamma)$$

and since

$$\lim_{n\to+\infty} length(\gamma_n^*) \leq \lim_{n\to+\infty} length(\beta)$$

with

$$\lim_{n\to+\infty} length(\gamma_n^*) \geq \lim_{n\to+\infty} length(\gamma_n) = lim_{n\to+\infty} length(\gamma)$$

we have

$$length(\beta) \geq length(\gamma)$$

and both enclose the same area. However, since $p, q, \in \beta$, β is not one of the two original configurations, and so by Lemma 1, the two configurations have larger length than the length of β. This means that γ cannot be a maximizer. This completes the proof. $\square$

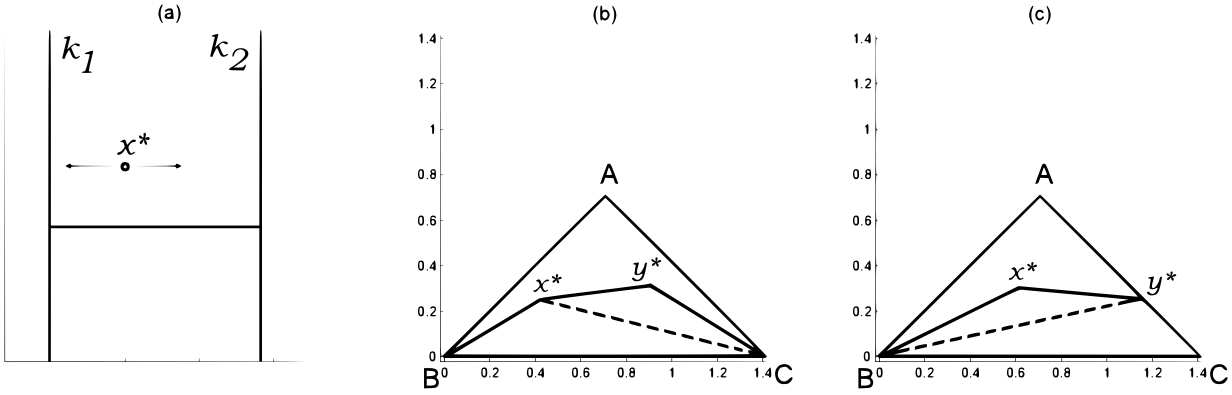

Figure 2: Configurations discussed in Proposition 1.

Web Appendix B (Inference under the Box-Cox)

It is often the case that the normality assumption is too restrictive and not justified by the data at hand. In many cases, a transformation to normality might be sufficient to transform the scores of the healthy and the diseased to be approximately normal. The Box-Cox transformation (Box and Cox (1964)) has been used before under the ROC setting (see Faraggi and Reiser (2002), Bantis, et al. (2014), Fluss, et al. (2005), and Molodianovitch, et al. (2006), among others). The Box-Cox transformation implies that a given random variable X, may be transformed by $X^{(\lambda)} = \frac{X^{(\lambda)}-1}{\lambda}$ when $\lambda \neq 0$, and $X^{(\lambda)} = log(X)$ when $\lambda = 0$ to approximately follow a normal distribution. The Box-Cox transformation is based on the flexibility of the power normal distribution, and it has been shown that it is fairly robust, even for models that are not included in the Box-Cox family such as the gamma distribution (see Bantis, et al. (2014) and Bantis, et al. (2017)). The transformation parameter λ is not known, and in a given application it needs to be estimated by the data at hand. Hence, there is variability induced due to that estimation. Many authors have been ignoring that variability by considering the transformed version of X, $X^{(\lambda)}$, as approximately normally distributed and proceed to inferences as if the value of the estimated λ is fixed and known. This issue was initially discussed under an ROC framework in Bantis et al. 2014 where the underlying profile likelihood for estimating λ is provided. After its maximization, we derive estimates of the means and variances of $X^{(\lambda)}$ and $Y^{(\lambda)}$, denoted as $\mu_0^{(\lambda)}$, $\sigma_0^{(\lambda)}$, $\mu_1^{(\lambda)}$, and $\sigma_1^{(\lambda)}$, by simply taking the maximum likelihood estimates based on normality of $X^{(\lambda)}$ and $Y^{(\lambda)}$.

The formulas for the obtained sensitivity, specificity, extended Youden index, as well as the corresponding cutoffs remain the same as in the previous section. Let $\hat{\Sigma}$ be an estimate of the asymptotic full variance-covariance matrix of the all 5 parameters $(\mu_0^{(\lambda)}, \sigma_0^{(\lambda)}, \mu_1^{(\lambda)}, \sigma_1^{(\lambda)})$. Denote with $\hat{\Sigma}^*$ its 4×4 upper left part. In order to take into account the variability of $\hat{\lambda}$, we use $\hat{\Sigma}^*$. For the full likelihood, as well as the derivation of $\Sigma^{(\lambda)}$ in closed form, see Bantis, et al. (2014). Matrix $\Sigma_0^{(\lambda)}$ and $\Sigma_1^{(\lambda)}$ that refer to the means and variances of $X^{(\lambda)}$ and $Y^{(\lambda)}$ can be readily extracted by the full 5×5 covariance matrix that refers to all 5 parameters, which includes the variance of $\hat{\lambda}$, and thus the variability of latter is taken into account. Inference regarding confidence regions and marginal CIs for the sensitivity and specificity at a given pair of cutoffs, or in the case where the cutoffs are estimated, can then be directly derived, as discussed in the section that discusses the normality assumption in our main manuscript.

Web-Appendix C (Simulations)

Simulations

Acronyms of methods used:

- length-N: The length test using the normality assumption (in an asymptotic fashion)
- length-BC: The length test using the Box-Cox transformation (in an asymptotic fashion)
- length-K-r: The length test using kernels (randomization based test (1000 permutations))
- length-N-r: The length test using the normality assumption (randomization based test (1000 permutations))
- length-BC-r: The length test using the Box-Cox transformation (randomization based test (1000 permutations))
- KS-test: the regular Kolmogorov Smirnov test
- Wilcoxon: the regular Wilcoxon test (rank sum)
- t-test: the well known t-test (unequal variances)

Table 1: Power and size results for normally generated data under proper and improper ROC curve scenarios. In the first two columns we show the sample size as well as the true values of the underlying length and AUC. For the randomization based tests we used 1000 permutations. All simulations results are based on 1000 Monte Carlo iterations.

			Generate from Normals: Proper ROC curves (power results)							
n_A, n_B	*length* healthy	*AUC* diseased	Power of *length* $-(N)$	Power of *length* $-BC$	Power of *length* $-(K)-r$	Power of *length* $-(N)-r$	Power of *length* $-(BC)-r$	Power of KS-test	Power of Wilcoxon	Power of t-test
$50, 50$	1.4160	0.5282	0.046	0.043	0.072	0.074	0.078	0.060	0.081	0.084
	1.4212	0.5562	0.101	0.104	0.122	0.148	0.141	0.120	0.172	0.184
	1.4295	0.5840	0.213	0.203	0.212	0.277	0.267	0.240	0.301	0.312
	1.4408	0.6114	0.337	0.339	0.365	0.434	0.421	0.371	0.489	0.497
	1.4544	0.6380	0.526	0.517	0.543	0.613	0.595	0.539	0.679	0.705
	1.5465	0.7602	0.993	0.963	0.991	0.996	0.967	0.987	0.998	0.999
$100, 100$	1.4160	0.5282	0.069	0.074	0.072	0.089	0.097	0.089	0.093	0.107
	1.4212	0.5562	0.197	0.194	0.198	0.234	0.238	0.244	0.274	0.283
	1.4295	0.5840	0.419	0.418	0.395	0.477	0.474	0.475	0.543	0.566
	1.4408	0.6114	0.695	0.694	0.641	0.731	0.726	0.708	0.797	0.824
	1.4544	0.6380	0.894	0.887	0.857	0.916	0.909	0.883	0.944	0.952
	1.5465	0.7602	1.000	0.987	1.000	1.000	0.987	1.000	1.000	1.000
$200, 200$	1.4160	0.5282	0.125	0.128	0.112	0.140	0.141	0.154	0.176	0.184
	1.4212	0.5562	0.392	0.396	0.348	0.413	0.419	0.423	0.497	0.507
	1.4295	0.5840	0.733	0.733	0.645	0.763	0.770	0.724	0.823	0.837
	1.4408	0.6114	0.951	0.949	0.908	0.956	0.952	0.935	0.978	0.985
	1.4544	0.6380	0.997	0.996	0.994	0.997	0.996	0.993	0.998	0.999
	1.5465	0.7602	1.000	0.999	1.000	1.000	0.999	1.000	1.000	1.000

			Generate from Normals: Improper ROC curves (power results)							
n_A, n_B	*length* (true)	*AUC* (true)	Power of *length* $-(N)$	Power of *length* $-BC$	Power of *length* $-(K)-r$	Power of *length* $-(N)-r$	Power of *length* $-(BC)-r$	Power of KS-test	Power of Wilcoxon	Power of t-test
50,50	1.4173	0.500	0.051	0.050	0.073	0.081	0.084	0.041	0.058	0.054
	1.4249	0.500	0.136	0.133	0.144	0.168	0.166	0.055	0.056	0.056
	1.4349	0.500	0.238	0.240	0.268	0.313	0.298	0.065	0.058	0.058
	1.4462	0.500	0.394	0.380	0.406	0.480	0.456	0.088	0.059	0.056
	1.4580	0.500	0.594	0.572	0.578	0.667	0.621	0.117	0.058	0.056
	1.4700	0.500	0.755	0.733	0.705	0.805	0.776	0.147	0.057	0.054
100,100	1.4173	0.500	0.088	0.092	0.092	0.113	0.107	0.055	0.043	0.046
	1.4249	0.500	0.280	0.285	0.269	0.325	0.312	0.080	0.046	0.044
	1.4349	0.500	0.563	0.546	0.511	0.589	0.576	0.143	0.046	0.044
	1.4462	0.500	0.787	0.778	0.731	0.815	0.801	0.220	0.045	0.047
	1.4580	0.500	0.924	0.919	0.878	0.935	0.929	0.310	0.046	0.047
	1.4700	0.500	0.982	0.981	0.958	0.986	0.983	0.421	0.045	0.047
200,200	1.4173	0.500	0.171	0.169	0.155	0.177	0.178	0.062	0.050	0.048
	1.4249	0.500	0.583	0.571	0.500	0.608	0.595	0.137	0.052	0.050
	1.4349	0.500	0.913	0.906	0.837	0.916	0.914	0.257	0.055	0.051
	1.4462	0.500	0.997	0.997	0.984	0.997	0.996	0.456	0.053	0.050
	1.4580	0.500	1.000	1.000	1.000	1.000	1.000	0.676	0.052	0.047
	1.4700	0.500	1.000	1.000	1.000	1.000	1.000	0.842	0.056	0.049

			Generate from identical Normals: (size results)							
n_A, n_B	*length* (true)	*AUC* (true)	Size of *length* $-(N)$	Size of *length* $-BC$	Size of *length* $-(K)-r$	Size of *length* $-(N)-r$	Size of *length* $-(BC)-r$	Size of KS-test	Size of Wilcoxon	Size of t-test
$50, 50$	$\sqrt{2}$	0.500	0.033	0.031	0.045	0.047	0.047	0.039	0.059	0.057
$100, 100$	$\sqrt{2}$	0.500	0.034	0.036	0.037	0.047	0.049	0.047	0.041	0.043
$200, 200$	$\sqrt{2}$	0.500	0.039	0.035	0.048	0.045	0.042	0.048	0.050	0.049

Table 2: Power and size results for gamma generated data under proper and improper ROC curve scenarios. In the first two columns we show the sample size as well as the true values of the underlying length and AUC. For the randomization based tests we used 1000 permutations. All simulations results are based on 1000 Monte Carlo iterations.

Generate from Gammas: Proper ROC curves (power results)

n_A, n_B	*length* (true)	*AUC* (true)	Power of *length* $-(N)$	Power of *length* $-BC$	Power of *length* $-(K)-r$	Power of *length* $-(N)-r$	Power of *length* $-(BC)-r$	Power of KS-test	Power of Wilcoxon	Power of t-test
$50, 50$	1.4236	0.5586	0.001	0.131	0.114	0.081	0.175	0.129	0.171	0.135
	1.4535	0.6259	0.021	0.553	0.434	0.303	0.638	0.493	0.611	0.468
	1.4890	0.6803	0.085	0.907	0.826	0.635	0.937	0.846	0.905	0.801
	1.5248	0.7248	0.252	0.982	0.960	0.868	0.988	0.963	0.976	0.947
$100, 100$	1.4236	0.5586	0.000	0.274	0.199	0.110	0.323	0.256	0.290	0.201
	1.4535	0.6259	0.006	0.896	0.782	0.499	0.919	0.848	0.897	0.764
	1.4890	0.6803	0.073	1.000	0.992	0.921	1.000	0.996	0.999	0.980
	1.5248	0.7248	0.307	1.000	1.000	0.998	1.000	1.000	1.000	0.999
$200, 200$	1.4236	0.5586	0.000	0.523	0.391	0.161	0.569	0.485	0.536	0.39
	1.4535	0.6259	0.003	0.998	0.981	0.808	1.000	0.984	0.995	0.966
	1.4890	0.6803	0.047	1.000	1.000	0.996	1.000	1.000	1.000	1.000
	1.5248	0.7248	0.348	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Generate from Gammas: Improper ROC curves (power results)

n_A, n_B	*length* (true)	*AUC* (true)	Power of *length* $-(N)$	Power of *length* $-BC$	Power of *length* $-(K)-r$	Power of *length* $-(N)-r$	Power of *length* $-(BC)-r$	Power of KS-test	Power of Wilcoxon	Power of t-test
$50, 50$	1.4205	0.5000	0.000	0.069	0.092	0.109	0.103	0.047	0.055	0.057
	1.4408	0.5000	0.001	0.346	0.297	0.327	0.423	0.090	0.055	0.120
	1.4758	0.5000	0.152	0.792	0.715	0.714	0.825	0.174	0.058	0.109
	1.5125	0.5000	0.500	0.984	0.944	0.939	0.987	0.356	0.062	0.146
$100, 100$	1.4205	0.5000	0.000	0.152	0.129	0.159	0.197	0.054	0.043	0.068
	1.4408	0.5000	0.000	0.714	0.590	0.595	0.764	0.203	0.041	0.181
	1.4758	0.5000	0.227	0.994	0.973	0.959	0.994	0.486	0.045	0.212
	1.5125	0.5000	0.767	1.000	1.000	0.998	1.000	0.844	0.052	0.305
$200, 200$	1.4205	0.5000	0.000	0.313	0.250	0.253	0.351	0.099	0.049	0.095
	1.4408	0.5000	0.000	0.987	0.915	0.907	0.993	0.439	0.042	0.354
	1.4758	0.5000	0.265	1.000	1.000	0.998	1.000	0.910	0.051	0.426
	1.5125	0.5000	0.947	1.000	1.000	1.000	1.000	0.998	0.055	0.565

Generate from identical Gammas: (size results)

n_A, n_B	*length* (true)	*AUC* (true)	Size of *length* $-(N)$	Size of *length* $-BC$	Size of *length* $-(K)-r$	Size of *length* $-(N)-r$	Size of *length* $-(BC)-r$	Size of KS-test	Size of Wilcoxon	Size of t-test
$50, 50$	$\sqrt{2}$	0.500	0.000	0.032	0.055	0.046	0.049	0.042	0.054	0.048
$200, 200$	$\sqrt{2}$	0.500	0.000	0.030	0.035	0.052	0.049	0.044	0.041	0.039
$200, 200$	$\sqrt{2}$	0.500	0.000	0.034	0.055	0.045	0.051	0.058	0.045	0.050

Table 3: Coverage and areas of joint confidence regions for underlying (specificity,sensitivity) pair associated with the estimated cutoffs: egg shaped vs rectangular regions. The targeted coverage is 95%. 1000 Monte Carlo iterations are used for each result.

			Generate from Gamma: Improper ROC curves							
			Smooth Bootstrap				Regular Bootstrap			
n_0, n_1	*Dist.of* healthy	*Dist.of* diseased	*Coverage of egg*	*Area of egg*	*Coverage of rect*	*Area of rect*	*Coverage of egg*	*Area of egg*	*Coverage of rect*	*Area of rect*
$50, 50$	$G(20, 1.2)$	$G(4, 7)$	0.9440	0.0525	0.9590	0.0626	0.944	0.0559	0.9530	0.0701
$100, 100$	$G(20, 1.2)$	$G(4, 7)$	0.9490	0.0299	0.9540	0.0360	0.9440	0.0315	0.9530	0.0402
$200, 200$	$G(20, 1.2)$	$G(4, 7)$	0.9540	0.0170	0.9530	0.0208	0.9520	0.0176	0.9580	0.0227

			Generate from Mixtures: Improper ROC curves							
			Smooth Bootstrap				Regular Bootstrap			
n_0, n_1	*Dist.of* healthy	*Dist.of* diseased	*Coverage of egg*	*Area of egg*	*Coverage of rect*	*Area of rect*	*Coverage of egg*	*Area of egg*	*Coverage of rect*	*Area of rect*
$50, 50$	$N(10, 1)$	$0.5N(8, 3^2) + 0.5N(14, 3^2)$	0.9230	0.0184	0.934	0.0200	0.8830	0.0197	0.909	0.2180
$100, 100$	$N(10, 1)$	$0.5N(8, 3^2) + 0.5N(14, 3^2)$	0.9370	0.0105	0.9430	0.0114	0.9310	0.0111	0.9450	0.0122
$200, 200$	$N(10, 1)$	$0.5N(8, 3^2) + 0.5N(14, 3^2)$	0.9370	0.0066	0.9440	0.0061	0.9370	0.0064	0.9410	0.0070

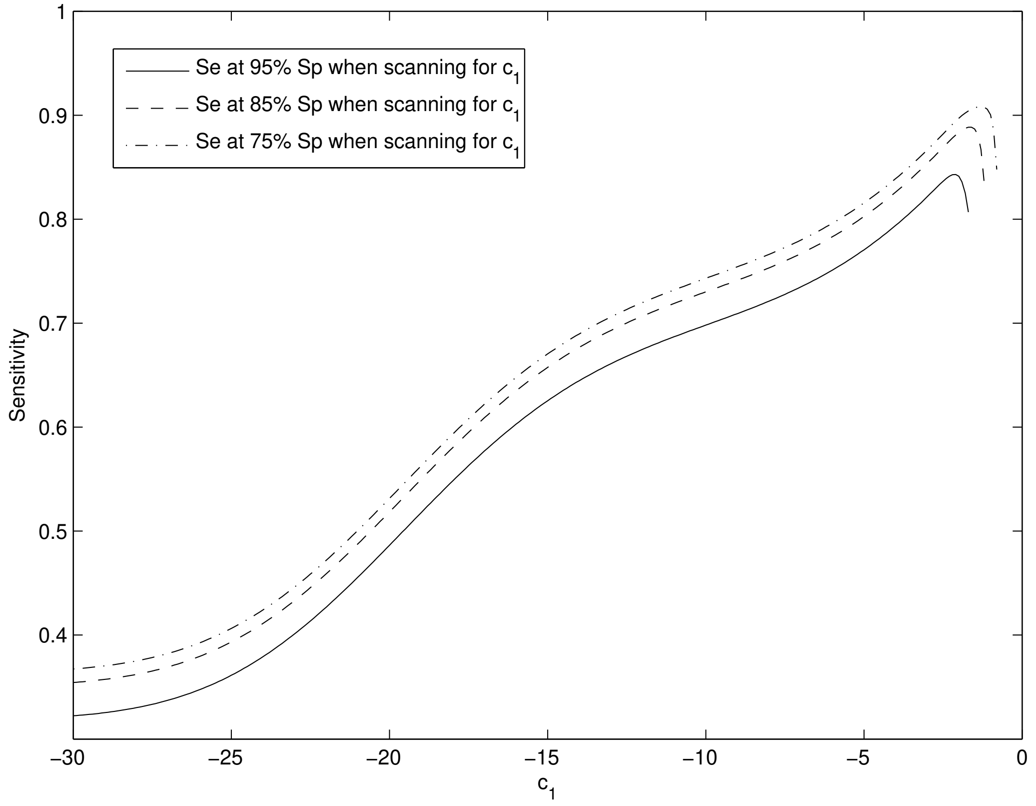

Figure 3: Sensitivity at different levels of specificity: 95%, 85% and 75%.

Table 4: Simulations for comparing the Silverman's plug in bandwidth and kernels via duffusion for estimating the length of the ROC. We considered 1000 Monte Carlo iterations for all gama scenarios and the bimodal mixture scenario.

		Silverman			Diffusion		
Sample size	true length	Bias	SE	MSE	Bias	SE	MSE
(30,30)	1.4205	0.1298	0.0351	0.0181	0.0838	0.0442	0.0090
	1.4408	0.1188	0.0400	0.0157	0.0680	0.0457	0.0067
	1.4758	0.0723	0.0391	0.0068	0.0436	0.0501	0.0044
	1.5125	0.0571	0.0439	0.0052	0.0335	0.0564	0.0043
(50,50)	1.4205	0.0905	0.0242	0.0088	0.0365	0.0192	0.0017
	1.4408	0.0855	0.0277	0.0081	0.0251	0.0228	0.0012
	1.4758	0.0517	0.0305	0.0036	0.0115	0.0308	0.0011
	1.5125	0.0339	0.0347	0.0023	0.0048	0.0353	0.0013
(100,100)	1.4205	0.0541	0.0141	0.0031	0.0168	0.0104	0.0004
	1.4408	0.0483	0.0183	0.0027	0.0085	0.0151	0.0003
	1.4758	0.0263	0.0222	0.0012	0.0004	0.0201	0.0004
	1.5125	0.0164	0.0255	0.0009	-0.0041	0.0236	0.0006
(200,200)	1.4205	0.0315	0.0091	0.0011	0.0110	0.0070	0.0002
	1.4408	0.0265	0.0124	0.0009	0.0039	0.0107	0.0001
	1.4758	0.0118	0.0145	0.0003	-0.0025	0.0133	0.0002
	1.5125	0.0062	0.0171	0.0003	-0.0058	0.0158	0.0003
Bimodal Mixture:							
Sample size	true length	Bias	SE	MSE	Bias	SE	MSE
(30,30)	1.7103	-0.0069	0.0231	0.0006	-0.0028	0.0180	0.0003
(50,50)	1.7103	0.0077	0.0456	0.0021	0.0466	0.0550	0.0052
(100,100)	1.7103	-0.0009	0.0317	0.0010	0.0075	0.0276	0.0008
(200,200)	1.7103	0.0075	0.0583	0.0035	0.1089	0.0968	0.0212

References

Bantis, L.E., Nakas, C.T., and Reiser, B. (2014). Construction of confidence regions in the ROC space after the estimation of the optimal Youden index-based cut-off point. *Biometrics* **70**, 212–223.

Bantis, L.E., Nakas, C.T., Reiser, B., Daniel M., Dalrymple-Alford JC. (2017). Construction of joint confidence regions for the optimal true class fractions of Receiver Operating Characteristic (ROC) surfaces and manifolds. *SMMR* **26(3)**, 1429–1442.

Box, G.E.P., and Cox, D.R. (1964). An analysis of transformations. *Journal of the Royal Statistical Society, Series B* **26**, 211–252.

Faraggi, D., and Reiser, B. (2002). Estimation of the area under the ROC curve. *Statistics in Medicine* **21**, 3093–3106.

Fluss, R., Faraggi, D., and Reiser, B. (2005). Estimation of the Youden index and its associated cutoff point. *Biometrical Journal* **47**, 458–472.

Molodianovitch, K., Faraggi, D., and Reiser B. (2006). Comparing the areas under two correlated ROC curves: parametric and nonparametric approaches. *Biometrical Journal* **48**, 45–757.