Logistic Kernel: A Sensitive Biomarker for Kidney Cancer by ROC Curve

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Abstract: The receiver operating characteristic (ROC) curve is a well-known graphical method to describe the accuracy of a diagnostic test. In this paper, Logistic kernel is proposed with its optimal bandwidth and mean squared error. To observe the performance of our proposed kernel estimator, the comparison is made with a Gaussian kernel by using different bandwidths and ROC curve and the area under the curve (AUC) are calculated. For illustration, Kidney cancer data is used and the logistic kernel is found more pragmatic and sensitive biomarker to detect Kidney cancer. The outstanding performance of logistic kernel is also observed in simulation studies and we recommend using nonparametric ROC curve using logistic kernel.

Key-Words: nonparametric ROC curve, AUC, symmetrical kernel, Logistic Kernel, Hemoglobin Level, Fibrinogen Concentration

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1 Introduction

In diagnostic medicine, it is important to assess the accuracy of a diagnostic test in discriminating diseased patients from healthy ones. For this purpose, the receiver operating characteristic (ROC) curve is commonly used to describe the performance of a diagnostic test. ROC analysis was first introduced by [1], although the ROC curve only gained its popularity in the 1970s [2,3].

When the response of the test is binary, the accuracy of the test is usually measured by its sensitivity and specificity. When the response of the test is continuous (i.e. blood pressure provides continuous measurements), its accuracy is best measured by the receiver operating characteristic (ROC) curve, which is a plot of sensitivity versus 1- specificity [4]. However, applications of ROC curve are recently extended to many other fields like economics and data mining. More comprehensive review of the literature about the ROC curves and their possible applications can be found, in [4–7]. Suppose that the independent real random variables X and Y denote the test score from healthy (= 0) and diseased (= 1) patients, (defined using a gold standard) respectively. Without loss of generality, and for an appropriate cut-off point $c \in R$, the test result is positive if it is greater than c and negative otherwise. Let F and G be completely unknown distribution functions of the random variables X and Y, respectively. The sensitivity of the test is defined as the SE(t) = 1 − G(t), which is the probability that a truly diseased individual has a positive test result. Similarly, the specificity of the test is given by SP(t) = F(t) and describes the probability that a truly non diseased individual has a negative test result. The receiver operating characteristic (ROC) curve is defined as a plot of SE(t) versus 1−SP(t) for $-\infty \leq c \leq \infty$, or equivalently as a plot of

$$R(t) = 1 - G\left(F^{-1}(1-t)\right), t \in [0,1] \qquad (1)$$

Existing Methods

To estimate ROC curve, mostly methods based on parametric or semi-parametric models [8–12]. Although the empirical ROC curve is very simple and popular, but estimator has some drawbacks; its obvious weakness is being a step function. These methods are sensitive to the assumptions and can only provide a limited range of distributional forms. Moreover, such methods may suffer from large variability, particularly for small sample sizes [13–15]. To overcome these problems nonparametric methods are proposed [13]. The commonly used nonparametric estimator is the empirical ROC curve of the form

$$R(t) = 1 - G_n\left(F_m^{-1}(1-t)\right), t \in [0,1] \qquad (2)$$

where F_m^{-1} and G_n respectively denote the empirical quantile function and the empirical cumulative distribution function of the samples respectively [16,17]. Asymptotic properties of this estimator were studied by [16], they showed that, under some basic assumptions for distribution functions, F and G, converges to the true ROC curve uniformly on [0, 1] with probability one. But it is also not continuous and not very accurate for small sample sizes. Other methods are needed to obtain a smooth estimator of the ROC curve. One of the ways, to obtain a continuous estimator of R(t) is to use the kernel smoothing method proposed by [18]. [13], using kernel estimates directly for F and G, obtained a smooth ROC curve estimator given by

$$R(t) = 1 - \tilde{G}_n\left(\tilde{F}_m^{-1}(1-t)\right), t \in [0,1] \quad (3)$$

[15] extended the idea of [19] and constructed a continuous and easily invertible estimator of the distribution function by using order statistics. They claimed that this idea leads to obtain a continuous and strictly increasing nonparametric estimator of the ROC curve, which is in fact the smoothed version of the empirical ROC curve. To gain invariant under non-decreasing data transformations, [20] proposed the following ROC curve estimator

$$\hat{R}_{m,n}(t) = \frac{1}{n}\sum_{i=1}^{n} K\left(\frac{t-1+F_m(Y_i)}{h}\right), \qquad t \in [0,1] \quad (4)$$

where h > 0 is a bandwidth parameter and F_m denotes the empirical distribution function of the sample X_m. [21] adopted Bernstein polynomials to construct the ROC curve estimator and studied the consistency rate of this estimator. They proposed the following Bernstein estimator of order m > 0 for the ROC curve:

$$ROC_m(t) = \sum_{k=0}^{m} ROC_n\left(\frac{k}{m}\right) P_{k,m}(t) \quad t \in [0,1] \quad (5)$$

In literature, further work has been done to examine the effect of smoothing parameter, with symmetric kernels (usually Bi-weight [18] and Epanechnikov kernel [4,20]. In this paper, we will examine the performance of asymmetrical kernel (Logistic kernel) against symmetrical kernel (Gaussian kernel), with different bandwidths.

The rest of this paper is organized as following. In Section 2, theoretical results are shown. Section 3, discusses different methods of bandwidth. In Section 4 we report the results of simulation studies and compare the efficiency of the nonparametric ROC estimator using symmetric kernel with nonparametric ROC estimator using asymmetrical kernel. In Section 5 the performance is compared on basis of a real data set and section 6 concludes.

2 Development of Logistic kernel estimator

Let $X_1, \ldots, X_n$ be a random sample from a distribution with an unknown probability density function f which has support on -∞, ∞. Representation of *pdf* of Logistic (μ, s) is

$$f(t) = \frac{e^{-\left(\frac{t-\mu}{s}\right)}}{s\left(1+e^{-\left(\frac{t-\mu}{s}\right)}\right)^2}, \quad (6)$$

where $t > 0,\ s > 0$. The mean and variance of T are equal to μ and $\frac{s^2\pi^2}{3}$, respectively.

As, $\mu = x$ and $s = h^{\frac{1}{2}}$, the class of Logistic kernels considered is;

$$K_{Logistic\left(x,h^{\frac{1}{2}}\right)}(t) = \frac{e^{-\left(\frac{t-x}{h^{\frac{1}{2}}}\right)}}{h^{\frac{1}{2}}\left(1+e^{-\left(\frac{t-x}{h^{\frac{1}{2}}}\right)}\right)^2}. \quad (7)$$

Where, h is bandwidth satisfying the condition that $h \to 0$ and $nh \to \infty$ as $n \to \infty$. If a random variable X has a pdf, $K_{Logistic\left(x,h^{\frac{1}{2}}\right)}(x)$, then $E(X) = x$ and $var(X) = \frac{h\pi^2}{3}$.

The corresponding estimator of pdf is

$$\hat{f}_{Logistic}(X) = n^{-1}\sum_{i=1}^{n} K_{Logistic\left(x,h^{\frac{1}{2}}\right)}(X_i) \quad (8)$$

Such transformation technique is firstly used by [22] for developing asymmetrical kernels. Some others also follow the Chen's idea. Here, we used such technique to develop a symmetrical kernel.

The bias of proposed Logistic estimator is given by;

$$Bias\{\hat{f}_{Logistic}(x)\} = \frac{1}{2}f''(x)\frac{\pi^2 h}{3} + o(1), \quad (9)$$

and variance of the proposed Logistic estimator is as follows;

$$var\left(\hat{f}_{Logistic}(x)\right) = \frac{1}{2h^{\frac{1}{2}}}xf(x) + o(h^{-2}x^{-2}). \quad (10)$$

Mean squared errors for Logistic kernel estimator is $MSE[\hat{f}_{Logistic}(x)] = Bias^2[\hat{f}_{Logistic}(x)] + var[\hat{f}_{Logistic}(x)]$

$$= \frac{f''^2(x)\pi^4 h^2}{36} + \frac{xf(x)}{2h^{\frac{1}{2}}},$$

and

$$h_{opt(Logistic)} = \left[\frac{81(\int xf(x)dx)^2}{4\pi^8(\int f''^2(x)dx)^2}\right]^{\frac{1}{5}}. \quad (12)$$

The smooth version of $\hat{F}$ and $\hat{G}$, after smoothing the diseased and healthy data by Logistic kernel; will be used for construction of ROC curve in Section 4 and 5.

3 Bandwidth selection

This section deals with selection of the smoothing parameter (*h)*, appearing in (1). Selection of h is a critical issue. Lots of bandwidth selection methods are available in literature but although no selection method performed uniformly best in all cases. Here we consider the following bandwidths and examine the performance with our proposed method.

3.1 Normal scale rule (NSR)

The idea of normal scale rule or rule of thumb first coined by [23] and latter discussed by [24].

$$h = 1.06\sigma(n)^{-\frac{1}{5}} \quad (13)$$

3.2 Generalized cross validation (GCV)

This method was proposed by [25] and defined as

$$h_{GCV} = \frac{\sum\{y_i - \hat{f}_h(X_i)\}^2}{n\{1 - n^{-1}tr(S_h)\}^2}, \quad (14)$$

where S_h is a matrix and $\hat{f}_h = \begin{bmatrix} \hat{f}_h(x_1) \\ \hat{f}_h(x_2) \\ \vdots \\ \hat{f}_h(x_n) \end{bmatrix} = S_h \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix}$,

with

$$S_h = \sum_{i=1}^{n}\{y_i - f(x_i)\}^2 + h\int_a^b \{f''(x)\}^2 dx.$$

3.3 Least square cross validation (LSCV)

[26] introduced the method known as unbiased cross validation which is closely related to the idea of [27] and [25] GCV. Least square cross validation or unbiased cross validation (LSCV) also discussed by [28] and [29].

$$UCV(h;r) = \frac{R(K^{(r)})}{nh^{2r+1}} + \frac{(-1)^r}{n(n-1)h^{2r+1}}\sum_{i=1}^{n}\sum_{j=1;j\neq i}^{n}(K^{(r)} * K^{(r)} - 2K^{(2r)}(\frac{X_j - X_i}{h}) \quad (15)$$

3.4 Altman and Leger plug-in (AL)

[30] elucidated the leave-one-out bandwidth of [31]. They showed that their leave-one-out bandwidth method provided results are asymptotically equivalent to leaving none out. Additionally, simulations showed that unfortunately [31] method do not work in practice, even for sample size of 1000. On other side, this bandwidth performed well even for size 10 and not far from the finite sample bandwidth.

Their proposed bandwidth is;

$$\hat{h}_{opt} = (0.25\hat{V}_2/\hat{B}_3)^{1/3}n^{-1/3} \quad (16)$$

3.5 Direct plug in method (DPI)

The DPI bandwidth selection method is modified form of [32] method. They claimed that their method is superior in sense of theoretical performance, computational advantages and showed best performance in simulation studies. Their DPI bandwidth is given below;

$$\hat{h}_{DPI,2} = \left[\frac{R(K)}{\mu_2(K)^2\widehat{\psi_4}(g_n)n}\right]^{1/5}, \quad (17)$$

where $R(K) = \int_R K(x)^2 dx$.

3.6 Polansky and Baker plug-in (PB)

[33] presented a multistage type of optimal bandwidth and also derived its asymptotic properties. They described a b-stage estimator of bandwidth in 3- step procedure in which they presented bandwidth as

$$h_b = \left[\frac{R(K)}{\mu_2(K)^2\widehat{\psi_2}(\hat{g}_2) - n}\right]^{1/3} \quad (18)$$

In the following sections, we are initially going to compare newly proposed kernel with Gaussian kernel to show the outstanding performance of our kernel on basis of AMSE for density estimation. Then we use the Logistic kernel for construction of ROC curve and calculation of AUC by using simulated and kidney cancer data.

4 Simulation

To examine the performance of proposed kernel estimator for density estimation, we conduct a simulation study with 1000 replications. For this purpose, data is generated through $y_i \sim N(0,1)$ and density is estimated through Gaussian and Logistic kernel with 400 gird points. Comparison is made on the basis of average mean square error (AMSE) with different sample sizes and bandwidths; as discussed in Section 3.

Table 1. AMSE by Logistic and Gaussian kernel

	AMSE by Logistic Kernel	AMSE by Gaussian Kernel
n\h	**NSR**	
25	0.0075	0.0205
50	0.0061	0.0134
100	0.0049	0.0091
200	0.0039	0.0060
500	0.0029	0.0035
	GCV	
25	0.0306	0.0562
50	0.0244	0.0447
100	0.0212	0.0375
200	0.0193	0.0322
500	0.0176	0.0276
	LSCV	
25	0.0088	0.0242
50	0.0067	0.0154
100	0.0052	0.0099
200	0.0040	0.0064
500	0.0029	0.0037
	AL	
25	0.0074	0.0202
50	0.0052	0.0119
100	0.0037	0.0070
200	0.0026	0.0041
500	0.0016	0.0020
	DPI	
25	0.0067	0.0191
50	0.0057	0.0129
100	0.0046	0.0086
200	0.0037	0.0058
500	0.0029	0.0035
	PB	
25	0.0072	0.0202
50	0.0053	0.0124
100	0.0039	0.0073
200	0.0029	0.0043
500	0.0018	0.0021

From Table 1, it can be observed that performance of Logistic kernel is better than Gaussian in all cases. Results are consistent with both kernels, as AMSEs are decreased as sample size increased, but performance of logistic kernel is outstanding.

Now, to investigate the performance of our proposed ROC curve estimator a simulation study is performed with 500 replications for the limited sample size ($m=n=20$) to calculate the area under the curve (AUC) [34];

$$Area\ Under\ Curve\ (AUC) = \frac{SE\ (t)+SP\ (t)}{2} \quad (19)$$

Four different combinations of the distribution functions are considered for X and Y. These types of combinations are also considered by [15, 20, 21], in which they used Normal and Logistic distribution to generate data. These combinations are given as;

$X\sim N(0,9), Y\sim LG(2.5,1);$
$X\sim N(0,1), Y\sim N(0,1);$
$X\sim LG(0,2), Y\sim LG(3,2);$

$X \sim LG(0,1), Y \sim N(2.5,9)$.
We also calculate AUC by using symmetrical (Gaussian) kernel for comparison with above mentioned bandwidths. Figure 1 to 4 present ROC curves of Gaussian and logistic kernels.

Table 2. AUC of kernels with different bandwidths

Kernels/Bandwidths	Logistic	Gaussian
Model 1	$X \sim N(0,9), Y \sim LG(2.5,1)$	
NSR	0.5124	0.488
GCV	0.5259	0.5181
UBCV	0.5428	0.5054
AL	**0.7124**	0.5451
DPI	0.5181	0.5156
PB	0.5187	0.498
Model 2	$X \sim N(0,1), Y \sim N(0,1)$	
NSR	0.5278	0.4872
GCV	0.5097	0.4754
UBCV	0.5421	0.5219
AL	**0.5844**	0.5222
DPI	0.5298	0.5179
PB	0.5285	0.5180
Model 3	$X \sim LG(0,2), Y \sim LG(3,2)$	
NSR	0.5138	0.5072
GCV	0.5071	0.4986
UBCV	**0.5389**	0.4939
AL	0.5334	0.4818
DPI	0.5243	0.4977
PB	0.5273	0.5096
Model 4	$X \sim LG(0,1), Y \sim N(2.5,9)$	
NSR	0.5273	0.5056
GCV	0.5181	0.5165
UBCV	**0.5282**	0.5078
AL	0.5054	0.4814
DPI	0.5270	0.4941
PB	0.5160	0.5102

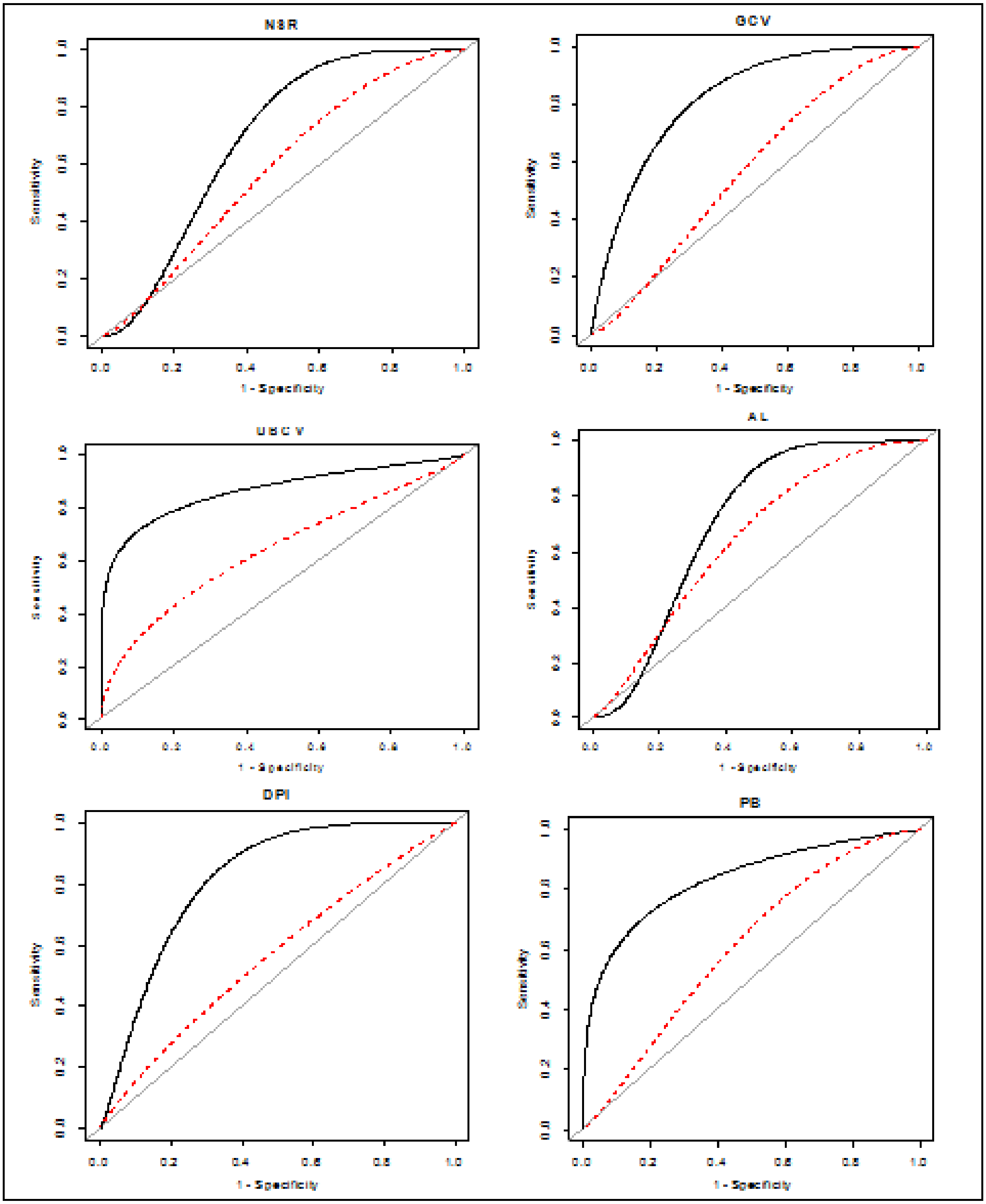

Figure 1. ROC curve by using different bandwidths for Model 1. Black line is estimated by using Logistic kernel and Red line (---) represents the performance of Gaussian kernel.

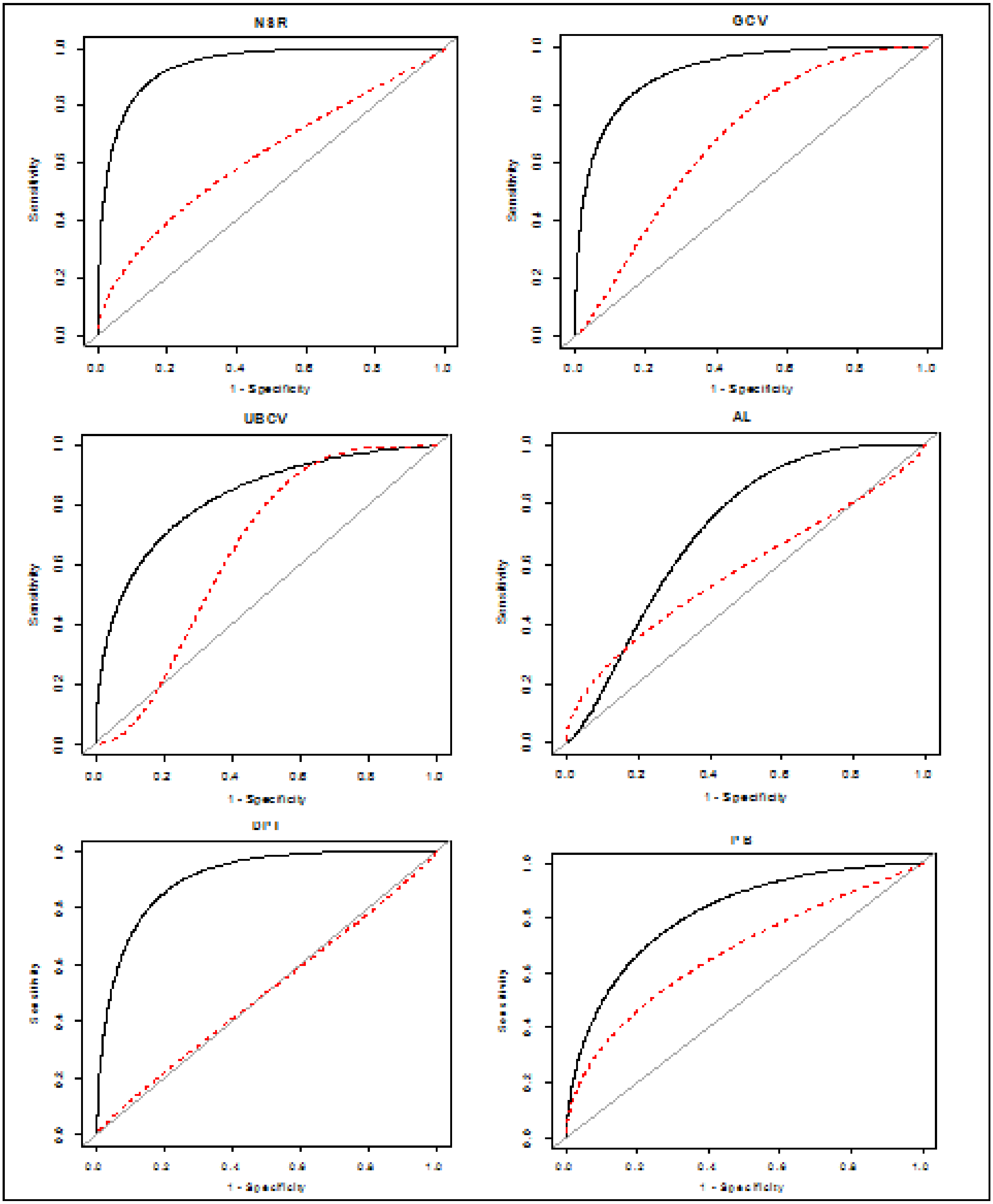

Figure 2. ROC curve by using different bandwidths for Model 2. Black line is estimated by using Logistic kernel and Red line (---) represents the performance of Gaussian kernel.

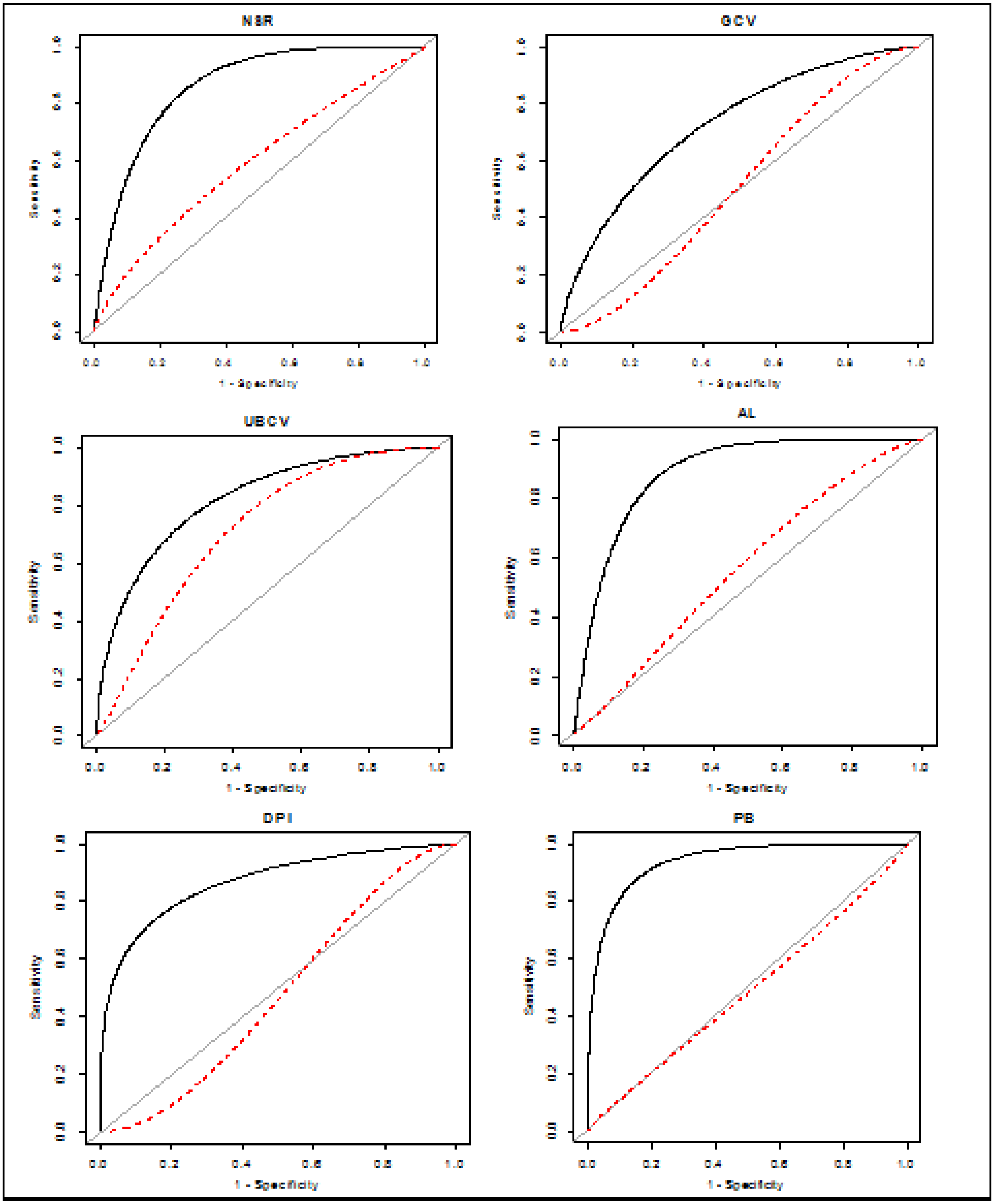

Figure 3. ROC curve by using different bandwidths for Model 3. Black line is estimated by using Logistic kernel and Red line (---) represents the performance of Gaussian kernel.

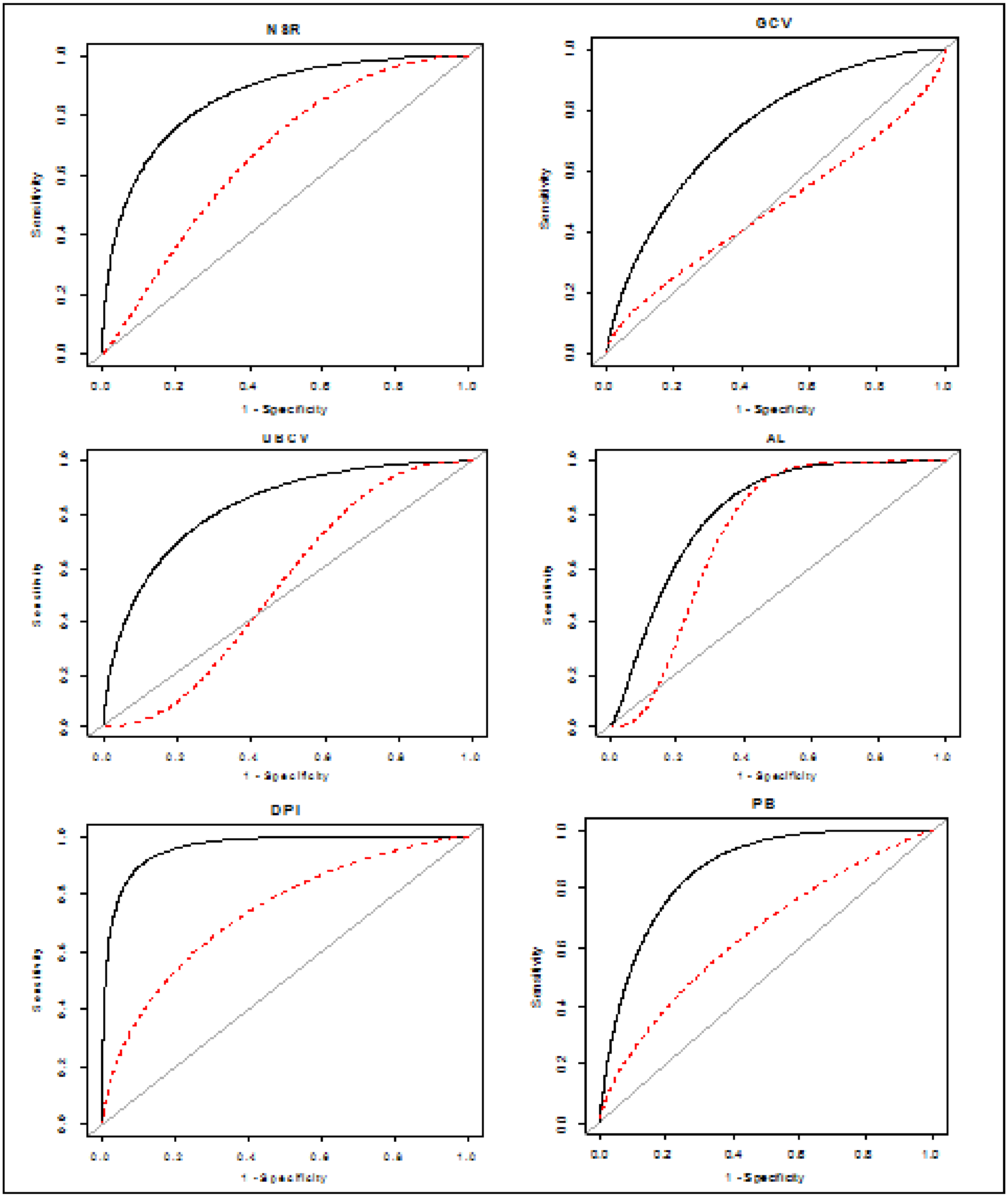

Figure 4. ROC curve by using different bandwidths for Model 4. Black line is estimated by using Logistic kernel and Red line (---) represents the performance of Gaussian kernel.

Figures 1 to 4 display the results of the simulations for the sample sizes $m = n = 20$ for different considered models. Every figure contains six plots corresponding to six different bandwidths as discussed in Section 3 and every single plot compares the considered ROC curve estimators. The results indicate that, for this small sample size, the proposed use of kernel estimator is competitive with another estimator. In the problem of estimation of the ROC curve it performs better than Gaussian kernel.

Here, every model is plotted with each considered bandwidth to examine the influence of bandwidth on distributions. It can be observed from Figure 1 to Figure 4, that no bandwidth is unanimously the best. In some cases, Altman and Leger Plug-in (AL) bandwidth performs the best and rest of models perform good with unbiased cross validation bandwidth (UBCV). This can be inspected from Table 2, which provides the AUC of those models (which are computed by 500 replications).

A study is conducted by using same models, where we examined the performance of each bandwidth at a same time, with 500 replications. Those findings are not included due to same results, where performance of AL and UBCV is better than the other bandwidths.

5 Example: Diagnostic for Kidney Cancer

To illustrate our proposed technique, we apply it on real dataset. The dataset comes from clinical study, by a research team led by Dr. Krzysztof Tupikowski from Department of Urology and Oncological Urology, Wroclaw Medical University, Poland, performed from November 2008 to August 2011. One investigated the efficacy of combined treatment of interferon alpha and metronomic cyclophosphamide in patients with metastatic kidney cancer not eligible for tyrosine kinase inhibitors treatment with various negative prognostic factors for survival. One of the secondary goals of the study was to assess if there are any predictive factors for response to this novel combination treatment. The data set contains presence (1) or absence (0) of clinical response (CR) observed at 24-th week of treatment, hemoglobin level (HL) and serum fibrinogen concentration (FC) of 31 patients treated per protocol. Missing data are denoted by x. Low HL has been previously associated with short survival and poor response to treatment in disseminated disease [35]. High FC is examined as a negative predictor for response to treatment in metastatic kidney cancer patients for the first time.

Table 3. AUC of kernels with different bandwidths for real data

	Logistic	**Gaussian**
	UBCV	
HL	**0.9969**	0.6534
FC	**0.8736**	0.5602
	AL	
HL	**0.9115**	0.6534
FC	**0.7631**	0.5602

This dataset is already used by [4,15,20] and [21]. Table 3 represents the AUC by using proposed and symmetric kernel. The estimators of the ROC curves for HL (left) and FC (right) as the predictive factors (positive and negative, respectively) are plotted in Figure 5, with AL and UBCV bandwidth due to better performance in simulation study.

In the ROC curve analysis of HL and FC mean of their kernel estimated values are used as cut-off points for both Logistic and Gaussian kernel for predicting kidney cancer. It can be examined that for this data Gaussian kernel is immune of bandwidth impact but use of Logistic kernel provides different AUC with different bandwidth. Furthermore, there are significant differences in the area under the curve between Gaussian and Logistic kernel which may indicate that the diagnostic validity of the Logistic is increased as compared to Gaussian kernel for both HL and FC.

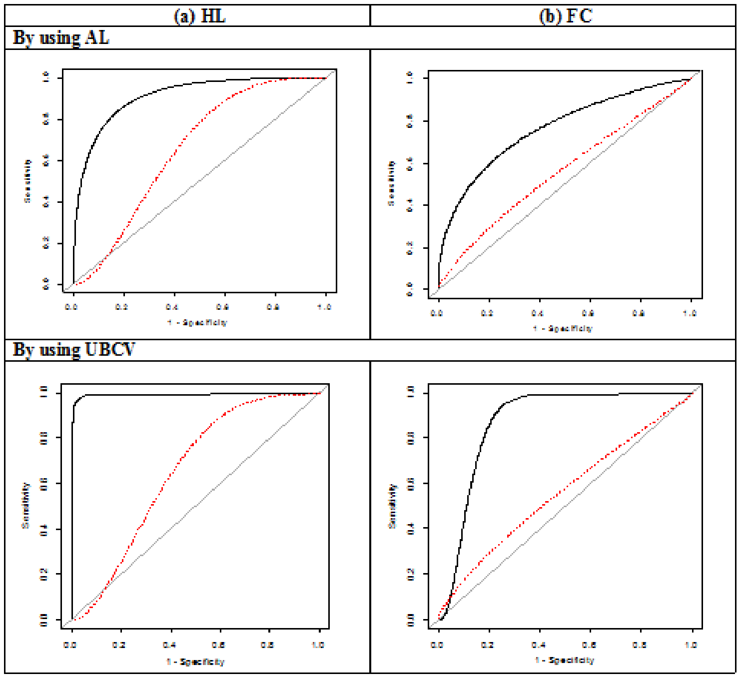

Figure 5. ROC curve by using different bandwidths for Kidney Cancer data.

6 Conclusion

In this study, we have developed a logistic kernel estimator with its MSE and optimal bandwidth. Then we show that our proposed kernel performs better than Gaussian kernel. Further, we have provided an important application of the new proposed kernel. We used Logistic kernel in generating ROC curve and calculating AUC. For this purpose, we considered a hemoglobin levels (HL) and serum fibrinogen concentration (FC), data as an indicator of kidney cancer. As we mentioned, in literature different researchers utilizes this data by using nonparametric ROC curve estimation method with symmetric (Gaussian) kernel. We showed that newly proposed kernel not only performed well for density estimation but also exhibit more rigid actions for indicating Kidney cancer.

This work can be extended for further fields of life. Because not only density estimation, ROC curve has also a wide application. For example; in environmental science density estimation is used to track animals where they spend time and ROC curve can be applied for qualitative prediction. Similarly, both have wide application in engineering, agriculture, hydrology and others.

References:

[1] Lusted LB, Logical Analysis in Roentgen Diagnosis: Memorial Fund Lecture, *Radiology*, Vol.74, No.2, 1960, pp. 178–193.

[2] Zangiacomi E, Louzada-Neto F, Braganca B, A Curva ROC Para Testes Diagn´osticos, *Cadernos Sa´ude Coletiva, Rio de Janeiro*, Vol.11, No.1, 2003, pp. 7–31.

[3] Zhou XH, McClish DK, Obuchowski NA, *Statistical Methods in Diagnostic Medicine*, John Wiley & Sons, 2011.

[4] Zhou XH, Harezlak J, Comparison of Bandwidth Selection Methods for Kernel Smoothing of ROC Curves, *Statistics in Medicine*, Vol.21, No.14, 2002, pp. 2045–2055.

[5] Swets JA, Form of Empirical ROCs in Discrimination and Diagnostic Tasks: Implications for Theory and Measurement of Performance, *Psychological Bulletin*, Vol.99, No.2, 1986, pp. 181.

[6] Pepe MS, *The Statistical Evaluation of Medical Tests for Classification and Prediction*, Oxford university press, 2003.

[7] Krzanowski WJ, Hand DJ, *ROC Curves for Continuous Data*, Crc Press, 2009.

[8] Zweig MH, Campbell G, Receiver-Operating Characteristic (ROC) Plots: A Fundamental Evaluation Tool in Clinical Medicine, Clinical Chemistry, Vol.39, No.4, 1993, pp. 561–577.

[9] Pepe MS, An Interpretation for The ROC Curve and Inference Using GLM Procedures, *Biometrics*, Vol.56, No.2, 2000, pp. 352–359.

[10] Zou KH, Hall W, Two Transformation Models for Estimating An ROC Curve Derived from Continuous Data, *Journal of Applied Statistics*, Vol.27, No.5, 2000, pp. 621–631.

[11] Qin J, Zhang B, Using Logistic Regression Procedures for Estimating Receiver Operating Characteristic Curves, *Biometrika*, Vol.90, No.3, 2003, pp. 585–596.

[12] Davidov O, Nov Y, Improving An Estimator of Hsieh and Turnbull for The Binormal ROC Curve, *Journal of Statistical Planning and Inference*, Vol.142, No.4, 2012, pp. 872–877.

[13] Lloyd CJ, Using Smoothed Receiver Operating Characteristic Curves to Summarize and Compare Diagnostic Systems, *Journal of the American Statistical Association*, Vol.93, No.444, 1998, pp. 1356–1364.

[14] Lloyd CJ, Yong Z, Kernel Estimators of The ROC Curve Are Better Than Empirical, *Statistics & Probability Letters*, Vol.44, No.3, 1999, pp. 221–228.

[15] Jokiel-Rokita A, Pulit M, Nonparametric Estimation of The ROC Curve Based on Smoothed Empirical Distribution Functions, *Statistics and Computing*, Vol.23, No.6, 2013, pp. 703–712.

[16] Hsieh F, Turnbull BW, Nonparametric and Semiparametric Estimation of The Receiver Operating Characteristic Curve, *The Annals of Statistics*, Vol.24, No.1, 1996, pp. 25–40.

[17] Bowyer K, Kranenburg C, Dougherty S, Edge Detector Evaluation Using Empirical ROC Curves, *Computer Vision and Image Understanding*, Vol.84, No.1, 2001, pp. 77–103.

[18] Zou KH, Hall WJ, Shapiro DE, Smooth Non-Parametric Receiver Operating Characteristic (ROC) Curves for Continuous Diagnostic Tests, *Statistics in Medicine*, Vol.16, No.19, 1997, pp. 2143–2156.

[19] Zielinski R, Kernel Estimators and The Dvoretzky-Kiefer-Wolfowitz Inequality, *Applicationes Mathematicae*, Vol.34, No.4, 2007, pp. 401.

[20] Pulit M, A New Method of Kernel-Smoothing Estimation of The ROC Curve, *Metrika*, Vol.79, No.5, 2016, pp. 603–634.

[21] Wang X, Song L, Sun L, et al, Nonparametric Estimation of The ROC Curve Based on The Bernstein Polynomial, *Journal of Statistical Planning and Inference*, Vol.203, 2019, pp. 39–56.

[22] Chen SX, Beta Kernel Smoothers for Regression Curves, *Statistica Sinica*, Vol.10, 2000, pp. 73–91.

[23] Deheuvels, P, Estimation Nonparametrique De La Densite Par Histogrammes Qeneralises, *Revue de statistique appliquée*, Vol.25, No.3, 1977, pp. 5-42.

[24] Silverman B, *Density Estimation*, Chapman Hall, London, 1986.

[25] Craven P, Wahba G, Smoothing Noisy Data with Spline Functions, *Numerische mathematik*, Vol.31, No.4, 1978, pp. 377–403.

[26] Scott DW, Terrell GR, Biased and Unbiased Cross-Validation in Density Estimation, *Journal of The American Statistical Association*, Vol.82, No.400, 1987, pp. 1131–1146.

[27] Scott DW, Factor LE, Monte Carlo Study of three Data Based Nonparametric Probability Density Estimators, *Journal of American statistical association*, Vol.76, 1981, pp. 9-15.

[28] Bowman AW, An Alternative Method of Cross-Validation for The Smoothing of Density Estimates, *Biometrika*, Vol.71, pp. 353-360.

[29] Rudemo M, 1982, Empirical Choice of Histogram and Kernel Density Estimators, *Scandinavian Journal of Statistics*, Vol.9, 1984, pp. 65-78.

[30] Altman N, Leger C, Bandwidth Selection for Kernel Distribution Function Estimation, *Journal of Statistical Planning and Inference*, Vol.46, No.2, 1995, pp. 195–214.

[31] Sarda P, Smoothing Parameter Selection for Smooth Distribution Functions, *Journal of statistical planning and inference*, Vol.35, 1993, pp. 65-75.

[32] Park BU, Marron JS, Comparison of Data-Driven Bandwidth Selectors, *Journal of the American Statistical Association*, Vol.85, No.409, 1990, pp. 66–72.

[33] Polansky AM, Baker ER, Multistage Plug-In Bandwidth Selection for Kernel Distribution Function Estimates, *Journal of Statistical Computation and Simulation*, Vol.65, No.1-4, 2000, pp. 63–80.

[34] DeLong ER, DeLong DM, Clarke-Pearson DL, Comparing The Areas Under Two or More Correlated Receiver Operating Characteristic Curves: A Nonparametric Approach, *Biometrics*, 1988, pp. 837–845.

[35] Tonini G, Fratto ME, Imperatori M, et al., Predictive Factors of Response to Treatment in Patients with Metastatic Renal Cell Carcinoma: New Evidence, *Expert Review of Anticancer Therapy*, Vol.11, No.6, 2011, pp. 921–930.

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Javaria Ahmad Khan: conceived the idea, developed the kernel, programming, graph making, writing, performed the computations and final approval of the version to be published. Atif Akbar: editing, proof reading and final approval for publication.

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