



Research Article

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Interval Estimation and Inferential Procedures for the Measures of Hybrid ROC (HROC) Curve



Balaswamy S¹ and Vishnu Vardhan R^{2*}

¹Department of Statistics, Indira Gandhi National Tribal University, India

²Department of Statistics, Podicherry University, India

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*Corresponding author: Vishnu Vardhan R, Department of Statistics, Podicherry University, India, Email: rvcrr@gmail.com

Abstract

Receiver Operating Characteristic (ROC) Curve is used to classify the individuals into one of the two populations, which underlie a particular distribution. In real life scenario, we come across situations where two populations will follow different distributions. Taking this into consideration, the ROC Curve was proposed using Half Normal and Exponential distributions for normal and abnormal populations respectively; hence named as Hybrid ROC (HROC) Curve. In this paper, the measures of HROC Curve and their corresponding confidence intervals are derived and evaluated. The accuracy of a test can be explained by the measures of ROC Curve and a better test procedure can be identified through inferential procedures. In order to explain the behaviour of HROC Curve and to identify the better test, simulation studies are conducted at various sample sizes with different combinations of scale parameters of both populations. To demonstrate the utility of HROC methodology in practice, APACHE IV score is used for early detection of mortality rate and the prognosis of the disease.

Keywords: Optimal Threshold; Youden's Index; AUC; HROC Curve

Introduction

The Receiver Operating Characteristic (ROC) Curve originated during Second World War to analyse radar signals by observing the relationship between signal and noise [1]. The framework of ROC Curve has a wide spread of interdisciplinary applications such as human perception, decision making [2], industrial quality control [3], military monitoring [4] etc. In later years, the applications of ROC Curve branched to many other fields such as experimental psychology, engineering, machine learning, biosciences etcetera [5]. Leo Lusted [6] introduced the concept of ROC Curve analysis into medicine for analysing radiographic images. Smoothed ROC Curves were fitted when the populations have certain probability distribution, such as Binormal and Bi-Logistic models [2]. Further, Maximum Likelihood Estimation of ROC Curve from categorical confidence rating data was first used by Dorfman & Alf [7] based on the conventional Binormal model. In particular, the conventional Binormal ROC Curve and its extension to continuously distributed data have been applied successfully to a wide variety of problems in Radiology [8,9]. The Binormal model assumes independent Normal distributions with different population means and variances, other models considered in the literature include Bi-Logistic [10], Bi-Exponential model [11]. Campbell & Ratnaparkhi [12] derived an ROC model by considering that the rating data follows Lomax

Distribution. Further, Dorfman et. al. [13] proposed a model which assumes Gamma Distributions.

In most of the situations, the distribution of abnormal population tends to follow some distribution other than normal due to high variability in data. In the context of classification, the variability exists in both the populations but larger variability is usually observed to a maximum extent in abnormal population. Apart from this, data so collected always do not explain the nature of normal distribution but tend to have some skewed nature that leads to skewed distributions such as Exponential, Rayleigh, Weibull and many more. Therefore, proposed ROC Curve is based upon the skewed distributions Half Normal and Exponential distributions and hence it is named as Hybrid ROC (HROC) Curve [14]. In the present work, it is assumed that the test scores of normal and abnormal populations follow Half Normal and Exponential distributions. The motivation for considering Exponential is its mathematical approximations, where it can easily be derived from all other distributions and also has a mathematical ease over other distributions. Moreover, the concept of ROC evolved by analyzing radar signals (Signal Detection Theory) and an important application of Exponential distribution is to analyze and assess the signals received. Hence, Exponential distribution is an appropriate distribution to explain

the spread in the abnormal population and helps in identifying the exact status of the objects/individuals. Further, another type of HROC Curve along with its confidence intervals is developed by considering Half Normal and Rayleigh distributions [15].

If the test scores of normal and abnormal populations follow different distributions, then the bi-distributional ROC forms will not produce reliable outputs. For instance, consider that a marker, namely, APACHE (Acute Physiology and Chronic Health Evaluation) II, is used to predict the mortality status of patients who are admitted into ICU. The pattern of APACHE scores for live and dead patients' does not possess normality and explains skewed nature of the data. In this dataset, the normal and abnormal populations follow Half Normal and Rayleigh distributions respectively. From this discussion about the practical tractability of data, the conventional binormal ROC model will fail or overestimate the accuracy (AUC) and intrinsic measures (sensitivity and specificity) and threshold. Hence, the main concentration of this paper lies in handling the situations when distributions of two populations are different (In particular Half Normal and Exponential distributions of normal and abnormal populations). For example, this paper adopts a real dataset which is about the ICU scoring system of mortality rate and this scoring system evaluates the critical conditions of a patient who admits in ICU, namely, APACHE IV, since the normal and abnormal populations follow Half Normal and Exponential distributions respectively. The remaining details have been given about this dataset and goodness of fit of the data is detailed in the results section.

The ROC Curve is a classification technique used to assess the performance of a test or a procedure. An individual will be classified into one of the two groups by means of a threshold. A threshold is said to be an optimal, if it provides maximum accuracy with more number of abnormal (sensitive) cases. In order to identify the optimal threshold, the most familiar and widely accepted measures are Area under the Curve (AUC) and Youden's Index. Further, the ROC Curve is defined as a graphical representation of $1-Sp$ (False Positive Rate, FPR) as a function of Sn (True Positive Rate, TPR) across all possible thresholds, where Sn is the probability that a truly abnormal individual has a positive test result, and Sp is the probability that a truly normal individual has a negative test result. The Youden's Index (J), is a measure of overall diagnostic effectiveness, first introduced to the medical literature by Youden [16]. The Youden's Index provides a pair of Sensitivity and Specificity at each point of threshold and these intrinsic measures are inversely related to each other. More importantly, J occurs at the threshold that optimizes the biomarkers differentiating ability when equal weight is given to sensitivity and Specificity [16-19]. Conventionally, J is found by evaluating sensitivity and specificity for all possible thresholds, with the optimal threshold corresponding to Youden's Index.

Methods of evaluating and comparing the performance of diagnostic tests are of increasing importance as new tests are developed and marketed. Therefore, to identify a better

test procedure among several or to test the significance of the estimated accuracy of a test with standard test or a procedure, the statistical significance tests and comparison procedures were developed. Greenhouse & Nathan [20] provided significance test procedures to compare diagnostic tests for independent and dependent samples. Gourevitch & Galanter [21] proposed a statistical significance test for pair wise comparisons of ROC curves based on single parameter estimated from a single operating point. The statistical significance tests were derived and evaluated [22] for measuring differences between obtained and expected Binormal ROC Curve, between two independent Binormal ROC Curves, and among groups of independent Binormal ROC Curves. They have used an approximate Chi-square statistics for each of the three tests which were constructed from maximum likelihood estimates of the two parameters defining the Binormal ROC Curve. '

Further, Hanley & McNeil [23] provided the comparison for assessing the performance of a diagnostic test based on the areas under two ROC Curves derived from same set of patients by taking correlation between paired samples into account. Vardhan & Sarma [24] proposed an approach of estimating the Area under the ROC Curve using confidence interval of means. Further, Vardhan & Balaswamy [25] proposed a new method to estimate the AUC of Binormal ROC model by taking into account of the confidence intervals of mean and corresponding variances. The present paper brings out the mathematical aspects of HROC Curve such as constructing the asymptotic confidence intervals for the indices β , AUC, FPR and TPR; identification of optimal threshold and testing the significance using AUC. The practical importance of the above proposed are demonstrated using a real dataset and simulated datasets too.

Methods

Let x_1 and x_2 be the test scores (S) which are distributed according to Half Normal and Exponential distributions in normal (H) and abnormal (D) populations respectively. The cumulative distribution and probability density functions of Half Normal and Exponential distributions are as follows,

$$F(x_1) = erf\left(\frac{x_1}{\sigma_H\sqrt{2}}\right) \tag{1}$$

$$f(x_1) = \frac{1}{\sigma_H} \sqrt{\frac{2}{\pi}} \exp\left(\frac{-x_1^2}{2\sigma_H^2}\right) \tag{2}$$

Where $erf(x) = 2\Phi(x\sqrt{2}) - 1$ is the error function.

$$G(x_2) = 1 - \exp\left(\frac{-x_2}{\sigma_D}\right) \tag{3}$$

$$g(x_2) = \frac{1}{\sigma_D} \exp\left(\frac{-x_2}{\sigma_D}\right) \tag{4}$$

Where σ_H and σ_D are the scale parameter of H and D populations. Since both x_1 and x_2 are continuous, every data value acts as a possible threshold. As usual let t be threshold so that in the usual notations for sensitivity (TPR) and specificity (1-FPR) are

$$S_n = P(S > t | D) = 1 - P(S \leq t | D) = 1 - G(t)$$

$$S_p = P(S \leq t | H) = F(t)$$

The expression for FPR is defined as

$$x(t) = P(S > t | H) = 2 \left[1 - \Phi \left(\frac{t}{\sigma_H} \right) \right] \quad (5)$$

The expression for t can be obtained as

$$t = \sigma_H \Phi^{-1} \left(1 - \frac{x(t)}{2} \right) \quad (6)$$

Where $\Phi^{-1}(\cdot)$ is the inverse cumulative standard normal distribution function. Similarly TPR is defined as

$$y(t) = P(S > t | D) = \exp \left(\frac{t}{\sigma_D} \right)$$

Now substituting the expression for t in the above expression, we get

$$ROC(t) = \exp \left(-\beta \Phi^{-1} \left(1 - \frac{x(t)}{2} \right) \right) \quad (7)$$

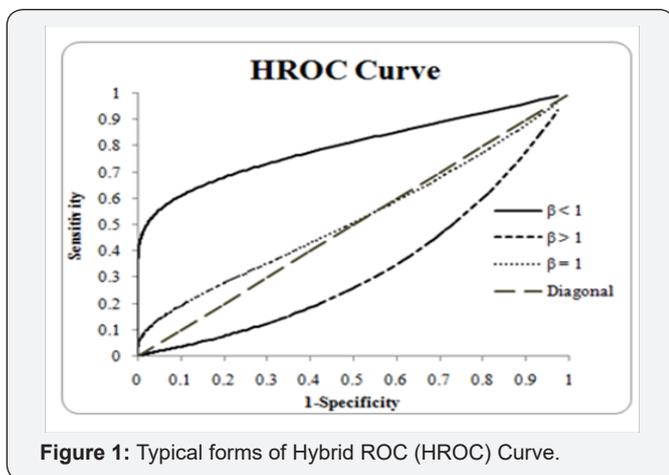


Figure 1: Typical forms of Hybrid ROC (HROC) Curve.

Where $\beta = \frac{\sigma_H}{\sigma_D}$ and $\Phi^{-1}(\cdot)$ is the inverse of standard normal deviate. The expression in (7) is called as the Hybrid ROC (HROC) Curve [14], since it is obtained on using two different skewed distributions. Here, the ratio β can be used to explain the functional behaviour of the HROC Curve. The typical forms of the HROC Curve are shown in Figure 1 by considering three different cases such as $\beta=1$, $\beta < 1$ and $\beta > 1$.

We observe the following pattern

If $\beta=1$ then the HROC Curve roughly coincides with the chance line.

If $\beta > 1$ then HROC Curve explains worst-case scenario. This is unusual in any field as it occurs only when $\sigma_H > \sigma_D$.

If $\beta < 1$ then the HROC Curve lies above chance diagonal. Lower β values lead to better classification.

Area under the Curve (AUC)

The accuracy of a diagnostic test can be explained using the Area under the Curve (AUC) of an ROC curve. AUC describes the ability of the test to discriminate between abnormal and normal. AUC gives information about the general goodness of a test as

well as interpretation of a test result.

$$AUC = \int_0^1 \exp \left(-\beta \Phi^{-1} \left(1 - \frac{x(t)}{2} \right) \right) dx(t)$$

On further simplification, the closed form of AUC is

$$AUC = \exp \left(\frac{\beta^2}{2} \right) \left[1 - \sqrt{\frac{2}{\pi}} \beta \right] \quad (8)$$

Identifying Optimal Threshold (t) & Youden's Index (J)

Once, the HROC Curve and AUC are estimated, another important aspect in classification is to obtain the optimal threshold, which is unique and provides a better percentage of correct classification. This criterion can be met in two ways, first one depends on the condition that the probability density functions of two populations are equal and second way is to make use of the widely accepted measure, namely Youden's Index (J). To obtain the optimal threshold for the HROC Curve, let us assume that both population densities are equal i.e. $f(t) = g(t)$,

$$\frac{1}{\sigma_H} \sqrt{\frac{2}{\pi}} \exp \left(\frac{-t^2}{2\sigma_H^2} \right) = \frac{1}{\sigma_D} \exp \left(\frac{-t}{\sigma_D} \right)$$

on further simplification, the expression for t, which is a quadratic equation given in equation(9)

$$t^2 - 2\beta\sigma_H t + \beta^2\sigma_D^2 \ln \left(\beta^2 \frac{\pi}{2} \right) = 0 \quad (9)$$

The expression in equation(9) can be simplified to achieve the optimal threshold as follows

$$t = \beta\sigma_D \left[\beta \pm \sqrt{\beta^2 - \ln \left(\beta^2 \frac{\pi}{2} \right)} \right]$$

In choosing positive or negative sign to obtain the optimal cut-off, positive sign must be considered because the expression $\sqrt{\beta^2 - \ln \left(\beta^2 \frac{\pi}{2} \right)}$ is always positive whether $\beta > 1$ or $\beta < 1$. Therefore, the expression for optimal threshold is given by,

$$\hat{t} = \beta\sigma_D \left[\beta + \sqrt{\beta^2 - \ln \left(\beta^2 \frac{\pi}{2} \right)} \right] \quad (10)$$

If $\sigma_H = \sigma_D = \sigma$ or $\beta = 1$ then equation(10) reduces to

$$\hat{t} = \sigma \left[1 + \sqrt{1 - \ln \left(\frac{\pi}{2} \right)} \right] \quad (11)$$

Here, description on the use of Youden's Index in validating the obtained optimal threshold is given. In ROC context, the Youden's Index is defined as

$$J = \text{maximum} \{ \text{Sensitivity}(t) + \text{Specificity}(t) - 1 \} \quad (12)$$

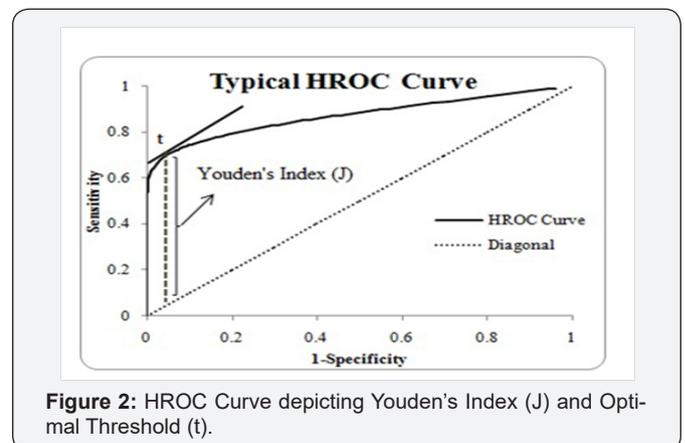


Figure 2: HROC Curve depicting Youden's Index (J) and Optimal Threshold (t).

over all cut points $t, -\infty < t < \infty$ The index (J) ranges between 0 and 1 with a value of 1 indicating perfect diagnostic effectiveness and 0 indicating an ineffective test. With respect to the ROC curve, J is the maximum vertical distance between the curve and the diagonal (chance line) and acts as a global measure of the optimum diagnostic ability (Figure 2). Evaluating sensitivity and specificity at t and then substituting in (12), we have

$$j = \exp\left(-\frac{t}{\sigma_D}\right) - 2 + 2\Phi\left(\frac{t}{\sigma_H}\right) \quad (13)$$

Where Φ denotes the standard normal cumulative distribution function. When distributional parameters are unknown, estimators \hat{t} and \hat{j} are found by substituting the estimated variances $\hat{\sigma}_H^2$ and $\hat{\sigma}_D^2$ for σ_H^2 and σ_D^2 respectively in equations (10) and (13) or equations (11) and (13) for equal variance case.

In the next subsections, the $100(1-\alpha)\%$ asymptotic confidence intervals are derived for the measures of HROC Curve such as beta, AUC, ... , AUC, FPR and TPR. For parametric and semi-parametric methods, maximum likelihood theory will provide asymptotic expressions for variances and covariances of the parameters and delta method can be used to obtain the required variance to construct asymptotic confidence intervals.

Asymptotic Confidence Intervals for \widehat{AUC}

In order to obtain asymptotic confidence intervals for true AUC, one needs to have an estimate of $\text{var}(\widehat{AUC})$. The $100(1-\alpha)\%$ asymptotic confidence interval for AUC is given by $\widehat{AUC} \pm Z_{1-\frac{\alpha}{2}} \sqrt{\text{var}(\widehat{AUC})}$, where $\text{var}(\widehat{AUC})$ is the variance of \widehat{AUC} and $Z_{1-\frac{\alpha}{2}}$ the $1-\frac{\alpha}{2}$ standard normal percentile. While the exact variance of \widehat{AUC} is unknown, we find a reasonable approximation through the delta method, $\text{var}(\widehat{AUC})$ Therefore, the resulting asymptotic confidence intervals is $\widehat{AUC} \pm Z_{1-\frac{\alpha}{2}} \sqrt{\text{var}(\widehat{AUC})}$, where $\text{var}(\widehat{AUC})$ is the estimated variance of \widehat{AUC} . Using Delta method [22] the approximate estimated variance of \widehat{AUC} , noting the independence of σ_H^2 and σ_D^2 is given in equation (14)

$$\widehat{\text{var}}(\widehat{AUC}) = \left(\frac{\partial AUC}{\partial \sigma_H}\right)^2 \text{var}(\widehat{\sigma}_H) + \left(\frac{\partial AUC}{\partial \sigma_D}\right)^2 \text{var}(\widehat{\sigma}_D) \quad (14)$$

The delta method is used (Appendix 1) to estimate and is given below,

$$\text{var}(\widehat{\sigma}_H) \approx \left(\frac{\partial(\sigma_H^2)^{1/2}}{\partial \sigma_H^2}\right)^2 \text{var}(\widehat{\sigma}_H^2) \quad (15)$$

Further, the variance of σ_D is estimated (Appendix 1) using its asymptotic distribution property and given by

$$\text{var}(\widehat{\sigma}_D) = \frac{\sigma_D^2}{n_D} \quad (16)$$

The partial derivatives of AUC with respect to the parameters are

$$\frac{\partial AUC}{\partial \sigma_H} = \frac{\partial}{\partial \sigma_H} \left\{ \exp\left(\frac{\beta^2}{2}\right) \left[1 - \sqrt{\frac{2}{\pi}} \beta \right] \right\}$$

$$\frac{\partial AUC}{\partial \sigma_H} = \frac{1}{\sigma_D} \exp\left(\frac{\beta^2}{2}\right) \left[\beta - \sqrt{\frac{2}{\pi}} (\beta^2 + 1) \right] \quad (17)$$

$$\frac{\partial AUC}{\partial \sigma_D} = \frac{\partial}{\partial \sigma_D} \left\{ \exp\left(\frac{\beta^2}{2}\right) \left[1 - \sqrt{\frac{2}{\pi}} \beta \right] \right\}$$

$$\frac{\partial AUC}{\partial \sigma_D} = \frac{1}{\sigma_D} \exp\left(\frac{\beta^2}{2}\right) \left[\sqrt{\frac{2}{\pi}} (\beta^2 + 1) \beta - \beta^2 \right]$$

On substituting equations (17) and (18) along with its variances in equation(14), the expression for $\widehat{\text{var}}(\widehat{AUC})$ is obtained as

$$\widehat{\text{var}}(\widehat{AUC}) = \left\{ \frac{1}{\sigma_D} \exp\left(\frac{\beta^2}{2}\right) \left[\beta - \sqrt{\frac{2}{\pi}} (\beta^2 + 1) \right] \right\}^2 \left[\frac{\sigma_H^2}{2(n_H - 1)} \right] + \left\{ \frac{1}{\sigma_D} \exp\left(\frac{\beta^2}{2}\right) \left[\sqrt{\frac{2}{\pi}} (\beta^2 + 1) \beta - \beta^2 \right] \right\}^2 \left[\frac{\sigma_D^2}{n_D} \right] \quad (19)$$

Asymptotic Confidence Intervals for HROC Curve

The confidence interval estimation for the HROC Curve represents the range of the curve at each point of FPR and its corresponding TPR. Therefore, the $100(1-\alpha)\%$ asymptotic confidence intervals for FPR and TPR are as follows,

$$\widehat{FPR} \pm Z_{1-\frac{\alpha}{2}} \sqrt{\widehat{\text{var}}(\widehat{FPR})}; \quad \widehat{TPR} \pm Z_{1-\frac{\alpha}{2}} \sqrt{\widehat{\text{var}}(\widehat{TPR})}$$

where

$$\widehat{\text{var}}(\widehat{FPR}) = \left(\frac{\partial FPR}{\partial \sigma_H}\right)^2 \text{var}(\widehat{\sigma}_H) + \left(\frac{\partial FPR}{\partial \sigma_D}\right)^2 \text{var}(\widehat{\sigma}_D) \quad (20 a)$$

$$\widehat{\text{var}}(\widehat{TPR}) = \left(\frac{\partial TPR}{\partial \sigma_H}\right)^2 \text{var}(\widehat{\sigma}_H) + \left(\frac{\partial TPR}{\partial \sigma_D}\right)^2 \text{var}(\widehat{\sigma}_D) \quad (20 b)$$

Now, by substituting the partial derivatives (Appendix 2) along with its variances of both parameters in equations (20a) and (20b), the variances of FPR and TPR are as follows

$$\widehat{\text{var}}(\widehat{FPR}) = \left[\frac{2}{\sigma_H} \phi\left(\frac{t}{\sigma_H}\right) \left[2\beta + \sqrt{\beta^2 - 2 \ln\left(\beta \sqrt{\frac{\pi}{2}}\right)} + \frac{\beta^2 - 1}{\sqrt{\beta^2 - 2 \ln\left(\beta \sqrt{\frac{\pi}{2}}\right)}} \right] \frac{2t}{\sigma_H} \phi\left(\frac{t}{\sigma_H}\right) \right]^2 \left[\frac{\sigma_H^2}{2(n_H - 1)} \right] +$$

$$\left[\frac{2}{\sigma_H} \phi\left(\frac{t}{\sigma_H}\right) \left[-\beta^2 + \frac{(\beta - \beta^3)}{\sqrt{\beta^2 - 2 \ln\left(\beta \sqrt{\frac{\pi}{2}}\right)}} \right] \right]^2 \left[\frac{\sigma_D^2}{n_D} \right]$$

$$\widehat{\text{var}}(\widehat{TPR}) = \left[\frac{\exp\left(-\frac{t}{\sigma_D}\right)}{\sigma_D} \left[2\beta + \sqrt{\beta^2 - 2 \ln\left(\beta \sqrt{\frac{\pi}{2}}\right)} + \frac{\beta^2 - 1}{\sqrt{\beta^2 - 2 \ln\left(\beta \sqrt{\frac{\pi}{2}}\right)}} \right] \right]^2 \left[\frac{\sigma_H^2}{2(n_H - 1)} \right] +$$

$$\left[\frac{t \exp\left(-\frac{t}{\sigma_D}\right)}{\sigma_D} \frac{\exp\left(-\frac{t}{\sigma_D}\right)}{\sigma_D} \left[-\beta^2 + \frac{(\beta - \beta^3)}{\sqrt{\beta^2 - 2 \ln\left(\beta \sqrt{\frac{\pi}{2}}\right)}} \right] \right]^2 \left[\frac{\sigma_D^2}{n_D} \right]$$

Asymptotic Confidence Intervals for $\hat{\beta}$

The behaviour of HROC Curve depends upon scale parameters of both populations σ_H and σ_D . Therefore, their ratio β is very important in construction of HROC Curve. As β varies, shape of the HROC Curve will vary between convex and concave forms. The interest is to estimate a $100(1-\alpha)\%$ asymptotic confidence interval for β and is as $\hat{\beta} \pm Z_{1-\frac{\alpha}{2}} \sqrt{\widehat{\text{var}}(\hat{\beta})}$,

The variance of $\hat{\beta}$ can be obtained through delta method and is given below,

$$\widehat{\text{var}}(\hat{\beta}) = \left(\frac{\partial \beta}{\partial \sigma_H}\right)^2 \text{var}(\widehat{\sigma}_H) + \left(\frac{\partial \beta}{\partial \sigma_D}\right)^2 \text{var}(\widehat{\sigma}_D) \quad (21)$$

On further simplification, the expression for $\widehat{\text{var}}(\hat{\beta})$ is ,

$$\widehat{\text{var}}(\hat{\beta}) = \beta^2 \left[\frac{n_D + 2(n_H - 1)}{2n_D(n_H - 1)} \right] \quad (22)$$

Testing of Hypothesis based on AUC

So far, the concentration is in estimating the summary characteristics of HROC Curve such as AUC, β , FPR and TPR. Then the asymptotic confidence intervals for AUC, FPR and TPR are constructed to know the variability of these estimates. Now,

the inferential matter of HROC Curve is considered for testing the significance of the curve. The main aim of the HROC Curve is to classify the subjects into one of the two populations. So, to measure the extent of classification between the population scores, one needs to measure the difference between HROC Curve and its chance diagonal. The most common one to test the classification is the difference between the AUC and chance line. So, the way of testing whether the classifier under study has any ability to discriminate between two populations is to test whether its AUC is significantly greater than the area under the chance line, i.e., 0.5. The hypothesis is defined, as the classifier will only be useful if its HROC Curve lies uniformly above the chance diagonal.

The null and alternative hypothesis are $H_0: AUC=0.5$ versus $H_1: AUC > 0.5$ and a natural test statistic is,

$$Z = \frac{\widehat{AUC} - 0.5}{\sqrt{\widehat{var}(\widehat{AUC})}}$$

Where $\widehat{var}(\widehat{AUC})$ is the estimated variance of \widehat{AUC} . On employing asymptotic arguments [26], the distribution of Z under the null hypothesis can be approximated by an asymptotic standard normal distribution.

Results and Discussion

The proposed methodology is demonstrated using simulation studies as well as a real data (APACHE IV).

Simulation Studies

Random samples of different sizes are generated with various combinations of scale parameters of considered distributions using Inverse Cumulative Method. The algorithms which are used to generate random samples of different sizes for Half Normal and Exponential distributions are as follows.

Generating Random Samples from Half Normal Distribution

- I. Generate random samples from $u_1 \sim U(0,1)$.

- II. Using the expression, $x = \sigma_H \sqrt{2} \operatorname{erf}^{-1}(u_1)$ to obtain random samples of Half Normal distribution.

- III. Repeat steps (1) and (2) for generating random samples of different sizes.

Generating Random Samples from Exponential Distribution

- I. Generate random samples from $u_2 \sim U(0,1)$.

- II. Using the expression, $y = -\sigma_D \ln(1-u_2)$ to obtain random samples of Exponential distribution.

- III. Repeat steps (1) and (2) for generating random samples of different sizes.

Table 1: Estimated Intrinsic Measures of HROC Curve.

Experiment	σ_H	σ_D	β	t	j	AUC
Experiment 1	0.6	0.9	0.66	1.1624	0.2221	0.5845
	0.6	1.5	0.40	1.3420	0.3834	0.7375
	0.6	2	0.30	1.4463	0.4692	0.7956
Experiment 2	1.5	1.5	1	2.6108	0.0936	0.3332
Experiment 3	1	1.5	0.66	1.9373	0.2221	0.5845
	0.8	1.5	0.53	1.6523	0.2934	0.6622

In order to illustrate the proposed methodology and on using the above two algorithms, random samples are generated at different sample sizes i.e., $n = n_H = n_D = \{25, 50, 100, 200, 500\}$ with various combinations of scale parameters. From Table 1, it is clear that as β tends to have a smaller value ($\beta < 1$), the accuracy of a test increases indicating higher value of J. The worst case of HROC Curve can also be observed when $\sigma_H = \sigma_D$.

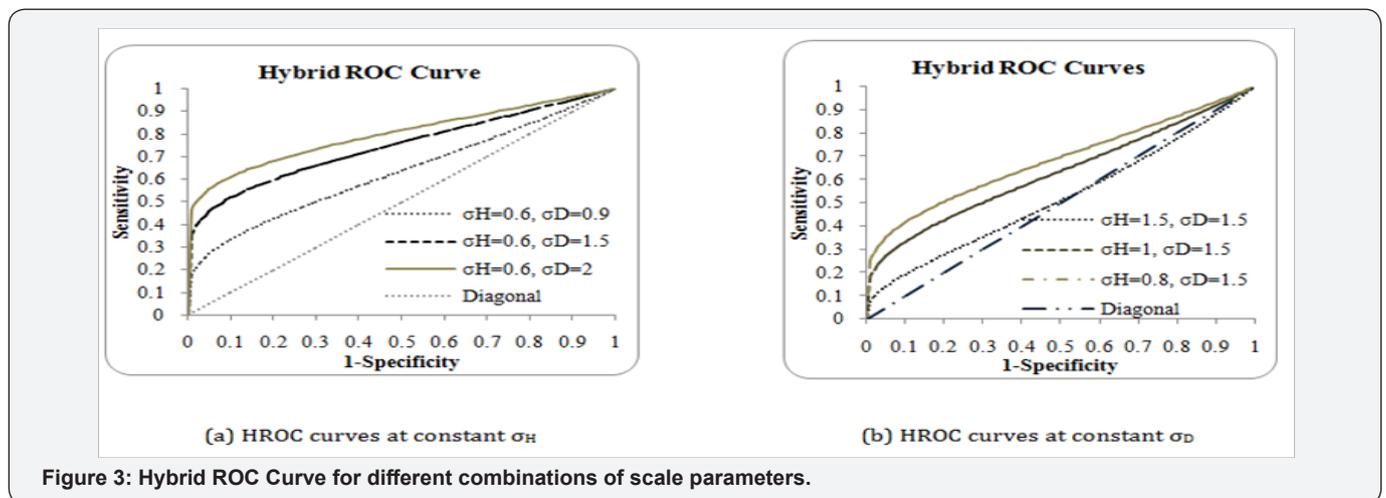


Figure 3: Hybrid ROC Curve for different combinations of scale parameters.

Figure 3a & 3b depict the proposed HROC Curves at various combinations of scale parameters. These curves will deviate from chance line as the variability between the scale values of both D

and H populations becomes larger, otherwise. On observing the different forms of the Hybrid ROC Curves in Figure 3a & 3b, it is clear that the curve is monotonically increasing.

Table 2: Estimates and Confidence Intervals for β and AUC at various combinations of scale parameters and sample sizes.

σ_H	σ_D	n	β (LCL, UCL)	AUC (LCL, UCL)	Z - tatictic
0.6	0.9	25	0.6999 (0.3615, 1.0382)	0.5640 (0.3527, 0.7754)	0.5944
		50	0.6913 (0.4558, 0.9268)	0.5694 (0.4235, 0.7153)	0.9326
		100	0.6432 (0.4886, 0.7979)	0.5986 (0.5063, 0.6908)	2.0959
		200	0.5773 (0.4792, 0.6753)	0.6371 (0.5808, 0.6935)	4.7703
		500	0.6307 (0.5630, 0.6985)	0.6060 (0.5659, 0.6460)	5.1896
0.6	1.5	25	0.4113 (0.2124, 0.6101)	0.7311 (0.6182, 0.8439)	4.0138
		50	0.3998 (0.2636, 0.5360)	0.7376 (0.6601, 0.8151)	6.0072
		100	0.3251 (0.2470, 0.4033)	0.7807 (0.7348, 0.8266)	11.9816
		200	0.3835 (0.3183, 0.4486)	0.7469 (0.7096, 0.7842)	12.9800
		500	0.3948 (0.3524, 0.4372)	0.7404 (0.7163, 0.7646)	19.4945
0.6	2	25	0.3479 (0.1797, 0.5161)	0.7674 (0.6697, 0.8651)	5.3665
		50	0.3288 (0.2168, 0.4408)	0.7785 (0.7129, 0.8442)	8.3162
		100	0.3058 (0.2323, 0.3794)	0.7921 (0.7484, 0.8358)	13.1113
		200	0.3678 (0.3053, 0.4303)	0.7559 (0.7199, 0.7919)	13.9458
		500	0.3466 (0.3094, 0.3839)	0.7681 (0.7465, 0.7898)	24.3028
1.5	1.5	25	0.8872 (0.4583, 1.3160)	0.4329 (0.0905, 0.7754)	-0.3835
		50	0.9550 (0.6297, 1.2803)	0.3754 (0.0825, 0.6683)	-0.8331
		100	0.9909 (0.7526, 1.2291)	0.3420 (0.1122, 0.5719)	-1.3466
		200	1.0816 (0.8978, 1.2653)	0.2458 (0.0316, 0.4601)	-2.3242
		500	1.0286 (0.9182, 1.1391)	0.3042 (0.1891, 0.4192)	-3.3355
1	1.5	25	0.6314 (0.3262, 0.9367)	0.6056 (0.4250, 0.7861)	1.1465
		50	0.6403 (0.4222, 0.8584)	0.6003 (0.4705, 0.7301)	1.5157
		100	0.6784 (0.5152, 0.8415)	0.5774 (0.4774, 0.6773)	1.5280
		200	0.6064 (0.5034, 0.7095)	0.6202 (0.5602, 0.6803)	3.9265
		500	0.6518 (0.5818, 0.7218)	0.5934 (0.5514, 0.6354)	4.3636
0.8	1.5	25	0.5417 (0.2798, 0.8036)	0.6574 (0.5087, 0.8061)	2.0757
		50	0.5201 (0.3429, 0.6973)	0.6696 (0.5695, 0.7698)	3.3215
		100	0.5169 (0.3926, 0.6412)	0.6715 (0.6013, 0.7417)	4.7883
		200	0.5574 (0.4627, 0.6521)	0.6485 (0.5945, 0.7025)	5.3897
		500	0.5437 (0.4853, 0.6021)	0.6563 (0.6231, 0.6895)	9.2384

Table 2 depicts the Confidence intervals for AUC and β at different sample sizes with various combinations of scale parameters. As variance expression of the measures of HROC Curve involves sample size n, it reflects in the width of the confidence interval. It is also observed that whenever the difference between scale parameters is zero (i.e., $\sigma_H - \sigma_D = 0$) the lower bound will be equal to zero and upper bound will attain a value one, which means that the C.I's are not able to produce any information about the true accuracy, since it is a case of random classification. Also, it is clear that whenever

the accuracy of a test is high (i.e., at $\sigma_H = 0.6$ and $\sigma_D = 2$), this situation leads to provide a very short confidence intervals with true AUC at all sample sizes and these intervals are precise when compared to other combinations.

The statistical significance tests are evaluated to validate the accuracy of a test at $\alpha/2$ percentile (Table 2). From the results, it is observed that the hypothesis will be accepted with $Z_{AUC} < 1.96$ in the case of worst classification (i.e., $\sigma_H = \sigma_D = 1.5$) over all sample sizes, whereas at other combinations, the hypothesis is rejected when the difference between scale parameters is high,

giving rise to a better phenomenon (i.e., at $\sigma_H = \{0.8, 0.6, 0.3\}$ and $\sigma_D = \{1.5, 2\}$). From Figure 4, it is observed that as the difference between scale parameters increases, width of the confidence interval moves nearer to X-axis, indicating a better classification. In the case of worst classification, i.e., whenever the difference between scale parameters is equal to zero, width of confidence interval line will be above all other combinations of HROC Curve. This is due to the density curves of both populations, since the confidence intervals depends on variance of measures and these measures are estimated through the overlapping area of density curves. The confidence intervals for the HROC Curve at various combinations are drawn to show the variability of the curve at each point on the ROC Curve (Figure 5). Further, the optimal threshold along with the pair of FPR and TPR is highlighted in each combination, which can be used to classify the individuals into one of the two groups.

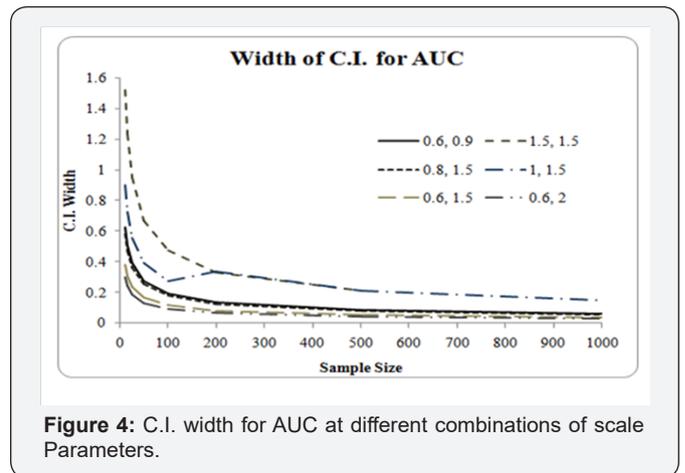


Figure 4: C.I. width for AUC at different combinations of scale Parameters.

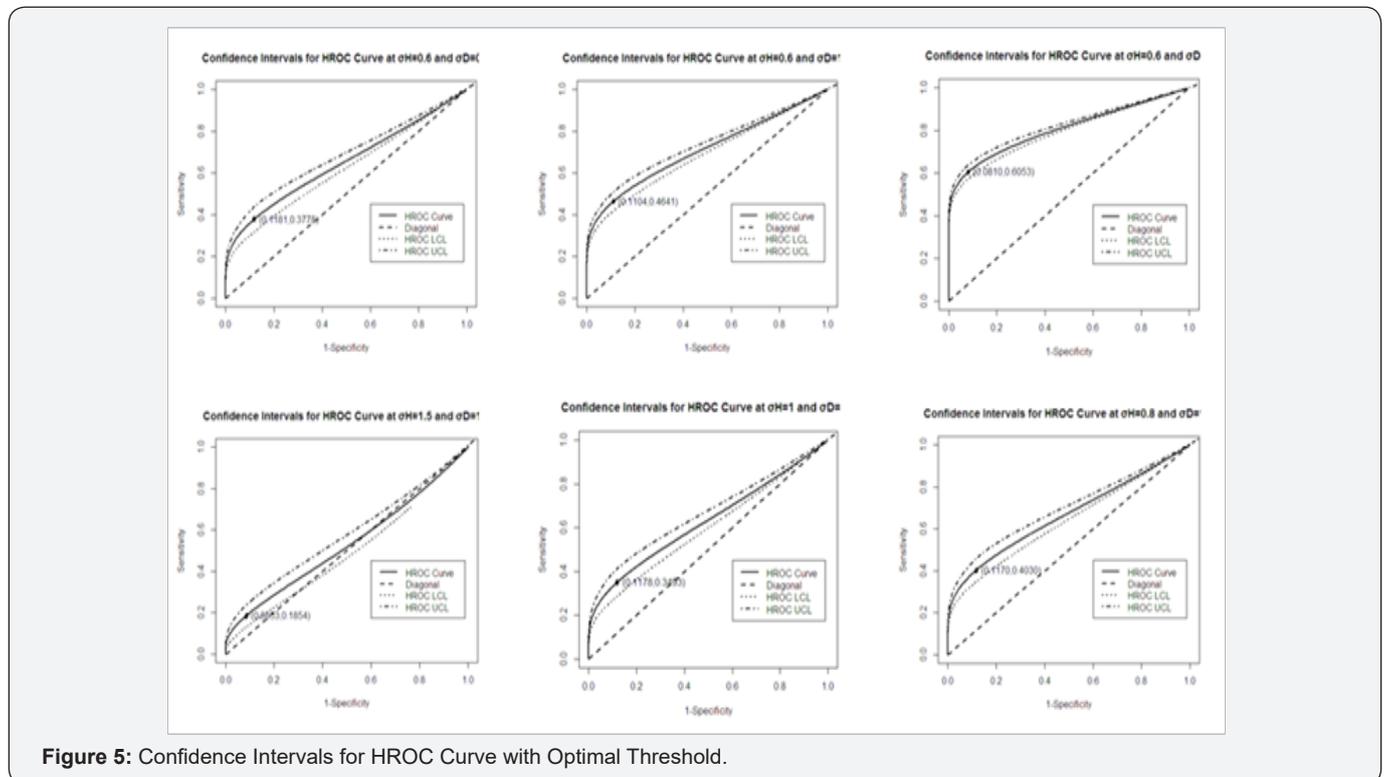


Figure 5: Confidence Intervals for HROC Curve with Optimal Threshold.

Real Dataset

Table 3: Results for APACHE IV using HROC Curve Methodology.

σ_H	σ_D	β	t	J	AUC (LCL, UCL)	Z - Value
10.1499	16.4584	0.6167 (0.5968,0.6365)	15.8643	0.2634	0.6143 (0.6027,0.6259)	19.2670

The real dataset is about the ICU scoring system, APACHE IV, which is used to predict the status of the patients (Dead or Alive) that takes into consideration various parameters like physiological variables, vital signs, urine output, neurological score along with age related parameters and co-morbid

conditions. This data consist of 111respondents, of which 66 (59.46%) are alive and 45 (40.54%) dead. From this dataset, it is observed that the APACHE IV scores for dead patients follow Exponential distribution (one sample K-S Statistic = 0.0794; p-value= 0.9175 at alpha = 0.05) and for those patients who

are alive follow Half Normal distribution (one sample K-S Statistic = 0.1091; p-value = 0.3835 at alpha = 0.05). The results are reported in Table 3 and it is observed that the accuracy of APACHE IV test is 61.43% with the ratio equals to 0.6.

This means that the APACHE IV score can predict survivors from non survivors with an accuracy of 61.43% with an optimal threshold of 15.86. This means that when an individual's APACHE IV score exceeds 15.86, then the patient will have a higher chance of attaining the critical event, death. The confidence intervals explain the variability in the estimated measures of HROC Curve. Further, the test statistic reveals that the HROC Curve for APACHE IV is significant enough to explain the mortality rate ($Z > 1.96$) and uniformly lies above the chance line. Figure 6 depicts the lower and upper confidence intervals for HROC Curve along with optimal threshold.

Conclusion

In real life situations, the researcher or practitioner anticipates some advanced statistical tools which can handle his/her data pattern easily. Often, a practitioner wishes to identify a subject's status using a diagnostic test or procedure. Under every diagnostic test or procedure, there exists a biomarker, by which the classification of subjects will be done and usually these biomarkers are continuous in nature. In reality many situations arise where the biomarker tends to have skewed type of distribution and also the biomarkers of normal and abnormal populations tend to have different distributions. In such situations, the conventional Binormal and Bi-distributional ROC models are not appropriate and mislead (overestimate or underestimate) the results (accuracy and threshold). Moreover, in most of the situations the abnormal population will be more skewed than normal population. Therefore, this paper addresses all these issues in the context of skewed distributions in classification. This paper focuses on the HROC Curve based upon two different distributions such as Half Normal and Exponential. The AUC and related measures of ROC curve are derived for this proposed model. The HROC Curve completely relies on its scale parameters; further the ratio of normal to abnormal scale parameters plays a prominent role in shaping the HROC Curve. In the context of classification, the abnormal test scores will always be higher than the normal, therefore, the HROC Curve gets the shape of concavity, which reflects to produce a better accuracy when $\beta < 1$. The other case is to have a convexity, when $\beta > 1$ and such situations lead to a worst classification.

Here, an attempt made is to observe the impact of sample size resulted positively in the construction of confidence intervals for the measures considered. Further, inferential procedures are provided to validate the significance of a test compared to random one. An observation made in the simulation study is that a proper discrepancy will not be possible at smaller sample sizes when it is tested against random classification (AUC=0.5). Further, the real dataset for detection of mortality rate using APACHEIV explains an accuracy of 61.43% along with the ratio

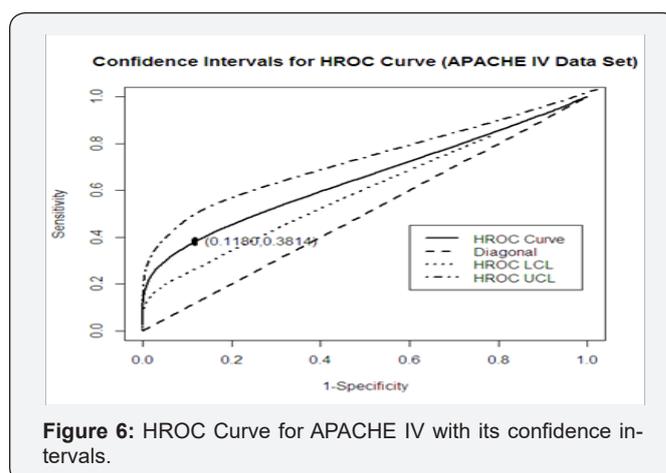


Figure 6: HROC Curve for APACHE IV with its confidence intervals.

$\beta = 0.6$. This means that the APACHE IV score is able to identify the status of patients with 61.43% of correct classification at an optimal threshold equals to 15.86 meaning to that an individual's APACHE IV score exceeds this value then that individual's life is at risk.

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Appendix 1

Estimation of Parameters

Here, X and Y are independent random variables from Half Normal and Exponential distributions with scale parameters σ_H and σ_D respectively. Then the likelihood function for the Half Normal distribution is

$$L(x, \sigma_H) = \prod_{i=1}^n \frac{1}{\sigma_H} \sqrt{\frac{2}{\pi}} \exp\left(-\frac{x_i^2}{2\sigma_H^2}\right)$$

on further simplification, we get

$$L(x, \sigma_H) = \left(\frac{2}{\pi}\right)^{n/2} \left(\frac{1}{\sigma_H}\right)^n \exp\left(-\sum \frac{x_i^2}{2\sigma_H^2}\right)$$

The likelihood function is

$$\frac{\partial}{\partial \sigma_H} \ln L(x, \sigma_H) = \frac{n_H}{\sigma_H} - \frac{1}{\sigma_H^3} \sum x_i^2$$

On partially differentiating the above expression with respect to the parameter σ_H and the associated gradient is as follows

$$\frac{\partial}{\partial \sigma_H} \ln L(x, \sigma_H) = \frac{n_H}{\sigma_H} - \frac{1}{\sigma_H^3} \sum x_i^2$$

$$\hat{\sigma}_H^2 = \frac{1}{n_H} \sum x_i^2$$

It is known that the Half Normal distribution follows $N(0, \sigma_H^2)$, therefore $\frac{x_i}{\sigma_H} \sim N(0,1)$. Further, it is nown that

$$(n_H - 1) \frac{\sum x_i^2}{\sigma_H^2} \sim \chi_{(n_H-1)}^2$$

$$(n_H - 1) \frac{S_H^2}{\sigma_H^2} \sim \chi_{(n_H-1)}^2$$

Therefore, variance of S_H^2 can be obtained from the Chi-square distribution with $(n_H - 1)$ degrees of freedom.

$$Var(S_H^2) = \frac{2(\sigma_H^2)^2}{(n_H - 1)}$$

Similarly, the likelihood function for the Exponential distribution is

$$L(y, \sigma_D) = \prod_{i=1}^n \frac{1}{\sigma_D} \exp\left(-\frac{y_i}{\sigma_D}\right)$$

on further simplification, we get

$$L(y, \sigma_D) = \left(\frac{1}{\sigma_D}\right)^n \exp\left(-\sum \frac{y_i}{\sigma_D}\right)$$

log likelihood function is

$$\ln L(x, \sigma_H) = \frac{n_H}{2} \ln\left(\frac{2}{\pi}\right) + n_H \ln\left(\frac{1}{\sigma_H}\right) - \sum \frac{x_i^2}{2\sigma_H^2}$$

On partially differentiating the above expression with respect to the parameter σ_D and the associated gradient is as follows

$$\frac{\partial}{\partial \sigma_H} \ln L(x, \sigma_H) = \frac{n_H}{\sigma_H} - \frac{1}{\sigma_H^3} \sum x_i^2$$

$$\hat{\sigma}_H^2 = \frac{1}{n_H} \sum x_i^2$$

here, y_i follows Exponential distribution with parameter σ_D , which implies that $\sum y_i \sim G\left(\frac{1}{\sigma_D}, n_D\right)$

$$\text{i.e., } \tau \sim G\left(\frac{1}{\sigma_D}, n_D\right)$$

where $\tau = \sum y_i$. Using the relation between Gamma and Chi-square distribution, it is easy to show that

$$\tau \sim \frac{\sigma_D}{2} \chi_{2n_D}^2$$

$$\text{i.e., } n_D \bar{\tau} \sim \frac{\sigma_D}{2} \chi_{2n_D}^2$$

where $\bar{\tau} = \frac{1}{n_D} \sum y_i = \sigma_D$. Therefore, variance of $\bar{\tau}$ can be obtained from Chi-square distribution with $2n_D$ degrees of freedom.

$$Var(\bar{\tau}) = \frac{\sigma_D^2}{n_D}$$

Appendix 2

Further, the partial differentiations of FPR and TPR with respect to their parameters are as follows,

$$\frac{\partial FPR}{\partial \sigma_H} = \frac{\partial}{\partial \sigma_H} \left\{ 2 \left[1 - \Phi \left(\frac{t}{\sigma_H} \right) \right] \right\}$$

$$\frac{\partial FPR}{\partial \sigma_H} = \frac{2}{\sigma_H} \phi \left(\frac{t}{\sigma_H} \right) \left[2\beta + \sqrt{\beta^2 - 2 \ln \left(\beta \sqrt{\frac{\pi}{2}} \right)} + \frac{\beta^2 - 1}{\sqrt{\beta^2 - 2 \ln \left(\beta \sqrt{\frac{\pi}{2}} \right)}} \right] - \frac{2t}{\sigma_H^2} \phi \left(\frac{t}{\sigma_H} \right)$$

$$\frac{\partial FPR}{\partial \sigma_D} = \frac{\partial}{\partial \sigma_D} \left\{ 2 \left[1 - \Phi \left(\frac{t}{\sigma_H} \right) \right] \right\}$$

$$\frac{\partial FPR}{\partial \sigma_D} = \frac{2}{\sigma_H} \phi \left(\frac{t}{\sigma_H} \right) \left[-\beta^2 + \frac{(\beta - \beta^3)}{\sqrt{\beta^2 - 2 \ln \left(\beta \sqrt{\frac{\pi}{2}} \right)}} \right]$$

$$\frac{\partial TPR}{\partial \sigma_H} = \frac{\partial}{\partial \sigma_H} \left\{ \exp \left(\frac{-\sigma_H}{\sigma_D} \Phi^{-1} \left(1 - \frac{x(t)}{2} \right) \right) \right\}$$

$$\frac{\partial TPR}{\partial \sigma_H} = \frac{\exp \left(-\frac{t}{\sigma_D} \right)}{\sigma_D} \left[2\beta + \sqrt{\beta^2 - 2 \ln \left(\beta \sqrt{\frac{\pi}{2}} \right)} + \frac{\beta^2 - 1}{\sqrt{\beta^2 - 2 \ln \left(\beta \sqrt{\frac{\pi}{2}} \right)}} \right]$$

$$\frac{\partial TPR}{\partial \sigma_D} = \frac{\partial}{\partial \sigma_D} \left\{ \exp \left(\frac{-\sigma_H}{\sigma_D} \Phi^{-1} \left(1 - \frac{x(t)}{2} \right) \right) \right\}$$

$$\frac{\partial TPR}{\partial \sigma_D} = \frac{t \exp \left(-\frac{t}{\sigma_D} \right)}{\sigma_D^2} - \frac{\exp \left(-\frac{t}{\sigma_D} \right)}{\sigma_D} \left[-\beta^2 + \frac{(\beta - \beta^3)}{\sqrt{\beta^2 - 2 \ln \left(\beta \sqrt{\frac{\pi}{2}} \right)}} \right]$$



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