Evaluation of Biomarker using
Two Parameter Bi-exponential ROC Curve

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Abstract
Receiver Operating Characteristic (ROC) Curve is used for assessing the ability of a biomarker/screening test to discriminate between non-diseased and diseased subject. In this paper, the parametric ROC curve is studied by assuming two-parameter exponential distribution to the biomarker values. The ROC model developed under this assumption is called bi-exponential ROC (EROC) model. Here, the research interest is to know how far the biomarker will make a distinction between diseased and non-diseased subjects when the gold standard is available using parametric EROC curve and its Area Under the EROC Curve (AUC). Here, the standard error is used as an estimate of the precision of the accuracy measure AUC. The properties of EROC curve that explains the behavior of the EROC curve are also discussed. The AUC along with its asymptotic variance and confidence interval are derived.

Keywords: Two parameter bi-exponential ROC model, AUC and variance of AUC, Monte Carlo simulation.

1. Introduction

1.1 Diagnostic Accuracy

In a medical diagnosis, a subject is categorized into either non-diseased or diseased group (a binary classification) by using some clinical measurement based on the selected cut-off value. If the clinical measurement is ‘greater than or equal to’ t, then the subject is labeled as diseased and if the measurement is ‘less than’ t, then the subject is labeled as non-diseased. The clinical measurements are often called as test results or test scores or Biomarker. The accuracy of a biomarker is defined as “its ability to distinguish the diseased group from non-diseased group”. The purpose of evaluating the potentiality of a biomarker in diagnosing a disease is to filter out the patients as those belonging to ‘high risk’ and ‘no risk’ for disease during the initial stage of medical diagnosis/screening process, because it is not necessary for all the in-patient to undergo a gold standard test (e.g. endoscopy) as it proves to be a costly, time consuming process and invasive.

1.2 ROC curve and Diagnostic Accuracy

The accuracy of a binary classification can be visualized as well as quantified by a renowned statistical technique called Receiver Operating Characteristic (ROC) curve. It is a plot of two probabilities namely Sensitivity versus 1-Specificity for various threshold t where the sensitivity can be defined as likelihood of classifying a diseased subject correctly and the specificity can be defined as likelihood of classifying a non-diseased subject correctly. The measure of accuracy explained by the plotted ROC curve is...
quantified by *Area Under the ROC curve* (AUC). Hence, the ROC plot reports the accuracy visually and the AUC reports the accuracy numerically.

### 1.3 Nomenclature

Let the biomarker values of diseased subject by the random variable $Y$ with Probability Density Function (PDF), $g_Y(y)$ and Cumulative Distribution Function (CDF), $G_Y(y)$. Similarly, let the biomarker values of non-diseased subject by the random variable $X$ with PDF, $f_X(x)$ and CDF, $F_X(x)$. Assume that $X$ and $Y$ are independent, continuous and $Y > X$ this is due to the fact that higher values of the biomarker indicates a condition of disease in an individual which in turn implies mean of $Y$ is greater than mean of $X$ for a better discrimination of subjects.

**Sensitivity** of the biomarker can be evaluated using, $\bar{G}_Y(t) = P(Y > t)$, which is the probability of correctly categorizing a diseased subject when a cut-off $t$ for the classification is given. It is also known as “True Positive Rate” (TPR). Similarly, the **Specificity** of the biomarker can be evaluated using, $\bar{F}_X(t) = P(X \leq t)$, which is the probability of correctly categorizing a non-diseased subject for a given $t$ and it is also known as False Negative Rate (FNR). 1- Specificity is called as “False Positive Rate” (FPR).

Then ROC curve is defined as a plot of TPR, $\bar{G}_Y(t)$ on the vertical axis versus the FPR, $\bar{F}_X(t)$ on the horizontal axis for different values of $t$, where $-\infty < t < \infty$. In other words, the mathematical model representing the ROC curve takes the form

$$\text{ROC}(p) = \bar{G}_Y \circ \bar{F}_X^{-1}(p); 0 \leq p \leq 1$$

(1.1)

For an appropriate diagnostic test, the ROC curve should lie very close to upper left corner of the unit square.

### 1.4 Properties

Once the ROC curve is plotted, it is important to study the properties of it, in order to highlight some key understanding from the plot. It is known that a typical parametric ROC curve must satisfy the basic three properties viz. monotonicity, invariance to monotone increasing transformation and the slope defined at a particular threshold $t$ (Krzanowski and Hand, 2002). Recently, Hughes and Bhattacharya (2013) have given a quite interesting property known as asymmetry property of the ROC curve for few ROC models viz. Bi-Exponential, Bi-Normal and Bi-Gamma. In this section, we have more generally discussed the properties satisfied by a parametric ROC curve.

1. $\text{ROC}(t)$ is monotonically increasing function i.e. $\frac{d\text{ROC}(t)}{d\bar{F}_X(t)}>0$.
2. $\text{ROC}(t)$ is said to be concave, if $\frac{d^2\text{ROC}(t)}{d\bar{F}_X(t)^2}<0$ and convex, if $\frac{d^2\text{ROC}(t)}{d\bar{F}_X(t)^2}>0$. 
3. The slope of the ROC curve at any operating point is equal to the ratio of PDF of diseased to PDF of non-diseased at cut-off point ‘t’ (Krzanowski and Hand, 2002) is given by
\[
slope = \frac{g(t)}{f(t)}
\] (1.2)

4. If f(x) and g(y) denote the continuous PDF for non-diseased and diseased groups respectively. Let \( KL(f, g) \) denote the Kullback–Leibler (KL) divergence between the distributions of non-diseased and diseased group with f(x) as the comparison distribution and g(y) as the reference distribution (Hughes and Bhattacharya, 2013). Then
\[
KL(f, g) = \int f(x) \ln \left( \frac{f(x)}{g(y)} \right) dx
\] (1.3)
where z is the common range of x and y i.e. \{LL=max[LL(x), LL(y)], UL=[min(UL(x), UL(y)] where LL-Lower Limit, UL – Upper limit. D is based on z, let us represent x and y by z.
\[
KL(f, g) = \int f(z) \ln \left( \frac{f(z)}{g(z)} \right) dz
\] (1.4)

Similarly, \( KL(g, f) \) denote the KL divergence between the distribution of diseased and non-diseased population with g(y) as the comparison distribution and f(x) as the reference distribution, then
\[
KL(g, f) = \int g(y) \ln \left( \frac{g(y)}{f(x)} \right) dy
\] (1.5)
where z is the common range of x and y i.e. \{LL=max[LL(x), LL(y)], UL=[min(UL(x), UL(y)] where LL-Lower Limit, UL – Upper limit. D is based on z, let us represent x and y by z. Hence we have,
\[
KL(g, f) = \int g(z) \ln \left( \frac{g(z)}{f(x)} \right) dz
\] (1.6)

It is to be noted that \( KL(f, g) \) and \( KL(g, f) \) are positive and \( KL(f, g) = KL(g, f) = 0 \), if and only if \( f(x) = g(y) \). These two measures tell us about the asymmetry of ROC curve about the negative diagonal of the ROC plot. If \( KL(f, g) < KL(g, f) \), then the ROC curve is said to be TPR asymmetric and if \( KL(f, g) > KL(g, f) \) then the ROC curve is said to be FPR asymmetric.

5. ROC(t) is invariance with respect to any monotonically increasing transformation.

**Result: 1 (Proper ROC curve):** The concavity property of ROC curve implies Proper. A ROC curve is said to be a proper ROC curve if it never crosses the chance line (the line connecting the co-ordinates [0, 0] and [1, 1]). Otherwise, TPR is a strictly increasing function over the range of all possible FPR.
Proof: Consider any two points ‘x’ and ‘y’ (say) where 0 < x, y < 1 on the FPR.

![Diagram of a proper ROC curve in the interval [x, y]](image)

By the definition of concavity, the line segment connecting the point on the ROC curve parallel to x and y never lies above the curve. If we take the extreme point i.e., x=0 and y=1, it becomes the chance line which never lies above the curve. Hence we have proved that the concavity property of ROC curve implies it is also proper.

Area under the ROC curve is the frequently used measure for quantifying the biomarker or performance of a diagnostic test. It is defined as the probability that in a randomly selected pair of non-diseased and diseased subjects, the biomarker value of diseased subject is higher than the non-diseased subject. The analytical expression for AUC is given by

\[
AUC = P(Y > X) = \int_0^1 G_y(t)d\overline{F}_X(t).
\]  

The evaluation of AUC and its inference are the crucial part of ROC curve analysis.

The classic ‘bi-normal’ ROC model consists in assuming normal distribution to the biomarker values from diseased and non-diseased groups while modeling the ROC curve. Many authors have encountered intensive study on parametric bi-normal ROC curve in a diversified directions such as by using Bayesian approach (O. Malley et al. 2002), regression modeling (Zhang, and Pepe 2012), pooling the biomarkers when drawing sample is expensive (Mumford et al. 2006), limit of detection when the biomarkers are unobserved (Perkins, Schisterman, and Vexler 2006), etc., especially for bi-normal ROC model. A very similar work of analyzing the ROC curves based on other distributional assumptions are bi-lomax ROC curve using Lomax distribution (Campbell and Ratnaparkhi 1993), bi-logistic ROC model using logistic distribution (Oglive, and Creelman 1968) and proper bi-gamma model using gamma distribution (Dorffman et al. 1996) for rating data. The ROC curve modeling for two discrete distributions viz. Uniform, Triangular and two continuous distributions such as Normal and Beta (Marzban
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2004), bi-exponential ROC model using one parameter exponential distribution (Betinec 2008 and Pundir and Amala 2014). Betinec has provided an analysis of ROC curves based on Exponential distribution to compare two classification methods namely Linear discriminant analysis and Support Vector machine. Bi-generalized exponential ROC model (Hussian 2011), bi-lognormal ROC model makes use of lognormal distribution (Amala and Pundir 2012), bi-rayleigh (Pundir and Amala 2012a) and left truncated bi-rayleigh ROC model using Rayleigh distribution (Pundir and Amala 2015). Pundir and Amala 2014d have studied the constant shape bi-weibull ROC curve using Weibull distribution and a review of all parametric ROC curves have been presented by Pundir and Amala 2014a and bi-variate bi-lognormal ROC model (Pundir and Amala 2015).

In this paper, the bi-exponential ROC curve is studied by assuming two parameter exponential distribution along with its properties, asymptotic variance and confidence interval for $AUC$. This paper is organized as follows: In Section 2, Bi-exponential ROC model, its properties and Maximum Likelihood Estimation of parameters are discussed. Section 3, provides estimation of $AUC$, asymptotic distribution and confidence interval for $AUC$. In Section 4, the proposed theory is validated by using Monte Carlo Simulation.

2. Two Parameter Bi-Exponential Roc Model

Let $Z$ be a random variable that follows two parameter exponential distribution with scale parameter $\lambda$ and location parameter $\gamma$ which is denoted by $Z \sim \text{exp}(\lambda, \gamma)$. It possess the PDF as

$$f_Z(z, \lambda, \gamma) = \lambda e^{-\lambda(z-\gamma)}, z > \gamma, \lambda > 0.$$ (2.1)

The CDF of $Z$ is given by

$$F_Z(z) = P(Z \leq z) = 1 - e^{-\lambda(z-\gamma)}, \lambda > 0, z > \gamma.$$ (2.2)

Let us assume that $X$ and $Y$ are independent and exponentially distributed with different parametric values ($\lambda_x, \gamma_x$) and ($\lambda_y, \gamma_y$) respectively. Notationally, $X \sim \text{exp}(\lambda_x, \gamma_x)$ and $Y \sim \text{exp}(\lambda_y, \gamma_y)$ with the constraint $\gamma_y > \gamma_x$, $\lambda_x > \lambda_y$. This restrictive condition is because to satisfy the assumption of higher values of biomarker values of the diseased subjects. The ROC model developed under this assumption is represented by “EROC”.

The $FPR$ of $EROC$ curve at the threshold ‘$t$’ is found to be

$$\overline{F}_x(t) = P(X > t) = \int_{t}^{\infty} \lambda_x e^{-\lambda_x(x-\gamma_x)} dx = e^{-\lambda_x(t-\gamma_x)}.$$ (2.3)

The $TPR$ of $EROC$ curve at the threshold ‘$t$’ is found to be

$$\overline{G}_y(t) = P(Y > t) = \int_{t}^{\infty} \lambda_y e^{-\lambda_y(y-\gamma_y)} dy = e^{-\lambda_y(t-\gamma_y)}.$$ (2.4)
where the parameters can be estimated from the sample data by any of the standard estimation procedure. If \( X \) and \( Y \) are two independent random variables of size ‘\( m \)’ and ‘\( n \)’ respectively, with PDF given in (2.1), the MLE of parameters (Johnson, Kotz and Balakrishnan, 2004) are determined as follows:

\[
\hat{\lambda}_x = \frac{m}{\sum_{i=1}^{m} (x_i - x_{(1)})}, \quad \hat{\lambda}_y = \frac{n}{\sum_{j=1}^{n} (y_j - y_{(1)})}, \quad \hat{\gamma}_x = x_{(1)} \quad \text{and} \quad \hat{\gamma}_y = y_{(1)}
\]

(2.5)

where \( x_{(1)} = \min(x_1, x_2, x_3 \ldots x_m) \) and \( y_{(1)} = \min(y_1, y_2, y_3 \ldots y_n) \). By substituting the above estimates in (2.3) and (2.4), one would get the estimates of \( \bar{F}_x(t) \) and \( \bar{G}_y(t) \). By plotting \( \bar{F}_x(t) \) on the horizontal axis and \( \bar{G}_y(t) \) on the vertical axis, one will get the EROC curve.

**Aliter:**

One can also obtain an analytical form of the EROC curve as follows: From (2.3), we get the expression for threshold ‘\( t \)’ as

\[
t = \gamma_x - \frac{\ln \bar{F}_x(t)}{\hat{\lambda}_x}.
\]

(2.6)

Since, ROC model is TPR as a function of FPR. By substituting (2.6) in (2.4), we can get the two parameter Bi-exponential ROC model as

\[
\text{EROC}(t) = \exp\left[-\hat{\lambda}_y \left(\gamma_x - \gamma_y\right) - \frac{\ln \bar{F}_x(t)}{\hat{\lambda}_x}\right]^{\hat{\lambda}_y} = \exp[\lambda_y (\gamma_y - \gamma_x) \bar{F}_X(t)^{\frac{\lambda_y}{\lambda_x}} ; 0 \leq \bar{F}_X(t) \leq 1, \hat{\lambda}_x > \hat{\lambda}_y, \gamma_y > \gamma_x].
\]

(2.7)

Plotting \( \text{EROC}(t) \) along y-axis and \( \bar{F}_x(t) \) along x-axis for different values of \( t \), we get an estimate of EROC curve. Now, we will discuss some of the properties of two parameter exponential ROC curve.

**2.1 Properties and Characteristics**

1. **EROC curve is monotonically increasing in nature for \( \hat{\lambda}_y > \hat{\lambda}_x \).**

**Proof:** Since, the first derivative of EROC curve with respect to \( \bar{F}_X(t) \) is positive i.e.

\[
\frac{d}{d\bar{F}_X(t)}\text{EROC}(t) = \exp[\lambda_y (\gamma_y - \gamma_x)] \frac{\hat{\lambda}_y}{\hat{\lambda}_x} \left[\bar{F}_X(t)^{\frac{\lambda_y}{\hat{\lambda}_x}}\right]^\left(\frac{\lambda_y}{\hat{\lambda}_x} - 1\right) > 0.
\]

(2.8)

EROC curve is monotonically increasing in nature.
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Aliter:
Consider two FPR values $\bar{F}_X(t_1)$ and $\bar{F}_X(t_2)$ such that $\bar{F}_X(t_1) < \bar{F}_X(t_2)$. Now raising the power $\frac{\lambda_y}{\lambda_x}$ and multiplying the constant $\exp[\lambda_y (y_x - y_x)]$, the inequality remains the same and hence

$$\exp[\lambda_y (y_x - y_x)]\left(\frac{\lambda_y}{\lambda_x}\right)^{\lambda_x} < \exp[\lambda_y (y_x - y_x)]\left(\frac{\lambda_y}{\lambda_x}\right)^{\lambda_x}$$

$$EROC(t_1) < EROC(t_2). \tag{2.9}$$

Hence, the EROC curve is monotonically increasing.

2. EROC curve is concave when $\lambda_y > \lambda_x$ and proper as long as it is concave.

Proof: The second derivative of $EROC(t)$ is given by

$$\frac{d^2}{d\bar{F}_X(t)^2} EROC(t) = \frac{\lambda_y}{\bar{F}_X(t)}\left(\frac{\lambda_y}{\lambda_x} - 1\right) \exp[\lambda_y (y_x - y_x)]\left[\frac{\lambda_x}{\lambda_x^2}\right] < 0. \tag{2.10}$$

The ratio $\frac{\lambda_y}{\lambda_x}$ will always be less than one since we assumed that $\lambda_y > \lambda_x$ and hence the term $\left(\frac{\lambda_y}{\lambda_x} - 1\right) < 0$, $\exp[\lambda_y (y_x - y_x)] > 0$ and $\left[\frac{\lambda_x}{\lambda_x^2}\right] > 0$ since $0 \leq \bar{F}_X(t) \leq 1$. On the whole, we will get $\frac{d^2}{d\bar{F}_X(t)^2} EROC(t) < 0$ for $\lambda_y > \lambda_x$. Hence, EROC curve is concave in nature and by using result 1, it is also proper.

Though normal distribution is thought to fit many real world datasets (Hanley, 1988), it is not concave in nature in [0,1] i.e. the Bi-Normal ROC curve may lies below the chance line which in turn reduces the AUC. Therefore, we prefer a model that estimates ROC curve for biomarker which is concave in nature.

3. The slope of the EROC curve at the threshold ‘t’ is found as

$$slope(t) = \frac{\lambda_y}{\lambda_x} \exp[t(\lambda_x - \lambda_y) + (y_x \lambda_x - y_y \lambda_y)]. \tag{2.11}$$

4. EROC curve is TNR asymmetric.

Proof: The KL divergence between the distribution of diseased and non-diseased group with $f(x)$ as the comparison distribution and $g(x)$ as the reference distribution has been derived as

$$KL(f,g) = \exp[\lambda_y (y_x - y_x)]\left[\frac{\lambda_x}{\lambda_x} - 1 + \lambda_y (y_x - y_x) + \ln\left(\frac{\lambda_x}{\lambda_y}\right)\right]. \tag{2.12}$$
Similarly, the KL divergence between the distribution of non-diseased and diseased group with \( g(x) \) as the comparison distribution and \( f(x) \) as the reference distribution has been given as

\[
KL(g, f) = \frac{\lambda_x}{\lambda_y} - 1 + \lambda_x (\gamma_x - \gamma_y) + \ln \left( \frac{\lambda_x}{\lambda_y} \right). \tag{2.13}
\]

It is found that \( KL(f, g) > KL(g, f) \). A numerical check for this condition is also presented in simulation studies. These two divergence measures would be zero, if the non-diseased and diseased groups are identical. Hence, we have proved that, the EROC curve is TNR asymmetric.

5. EROC curve is invariance with respect to monotonically increasing transformation.

3. AUC of EROC Curve and Its Asymptotic Confidence Interval

Let \( X \) and \( Y \) be two independent and continuous random variables representing non-diseased and diseased group respectively, following two parameter exponential distribution individually with respective parameters \((\lambda_x, \gamma_x)\) and \((\lambda_y, \gamma_y)\). According to the relationship between \( \gamma_x \) and \( \gamma_y \), AUC of EROC takes two different forms which are given as follows.

(i) If \( \gamma_x > \gamma_y \), then the AUC is obtained as

\[
P(Y > X) = \int_{\gamma_x}^{\gamma_y} \int_{\gamma_x}^{\infty} \lambda_x \exp[-\lambda_x (x-\gamma_x)] \lambda_y \exp[-\lambda_y (y-\gamma_y)] dx dy
\]

\[
= 1 - \frac{\lambda_x}{\lambda_x + \lambda_y} \exp \left[ \lambda_x (\gamma_x - \gamma_y) \right]. \tag{3.1}
\]

(ii) If \( \gamma_x < \gamma_y \), then the AUC is obtained as

\[
P(Y > X) = \int_{\gamma_x}^{\infty} \int_{\gamma_x}^{\gamma_y} \lambda_x \exp[-\lambda_x (x-\gamma_x)] \lambda_y \exp[-\lambda_y (y-\gamma_y)] dx dy
\]

\[
= \frac{\lambda_x}{\lambda_x + \lambda_y} \exp \left[ \lambda_y (\gamma_y - \gamma_x) \right]. \tag{3.2}
\]

Hence, the AUC takes the following form

\[
AUC = \begin{cases} 
\frac{\lambda_x}{\lambda_x + \lambda_y} \exp \left[ \lambda_x (\gamma_x - \gamma_y) \right] & \text{for } \gamma_x > \gamma_y \\
1 - \frac{\lambda_y}{\lambda_x + \lambda_y} \exp \left[ \lambda_y (\gamma_y - \gamma_x) \right] & \text{for } \gamma_y > \gamma_x.
\end{cases} \tag{3.3}
\]

The MLE of AUC can be numerically be obtained by substituting the estimates from the sample data by using (2.5) with the help of invariant property of MLE (Casella and Berger, 2002).
Theorem 1: If \( m \to \infty, n \to \infty \) then \( \sqrt{m+n}(\hat{AUC} - AUC) \) tends to be normally distributed with mean zero and variance,

\[
\tau = \exp \left\{ 2\lambda_x (\gamma_x - \gamma_y) \right\} \left( \frac{\lambda_x^2 + \lambda_y^2}{m^2 + n^2} + \frac{\lambda_x^2 \lambda_y^2}{m(\lambda_x + \lambda_y)} \right) \left[ -1 + (\gamma_x - \gamma_y)(\lambda_x + \lambda_y) \right] + \frac{2\lambda_x^2 \lambda_y^2}{n(\lambda_x + \lambda_y)}
\]

Proof: Let \( L(\theta \mid x, y); \theta = (\gamma_x, \gamma_y, \lambda_x, \lambda_y) \) be the likelihood function of the sample observations from \( X \) and \( Y \) which is given by

\[
\ln L = m \ln \lambda_x - \lambda_x \sum_{i=1}^{m} (x_i - \gamma_x) + n \ln \lambda_y - \lambda_y \sum_{j=1}^{n} (y_j - \gamma_y).
\]

Asymptotic normality of MLE, states that a consistent solution of the likelihood equation is asymptotically normally distributed about the true value \( \theta \) i.e. \( \hat{\theta} \sim N(\theta, I^{-1}(\theta)) \).

\[
\Rightarrow \sqrt{N}(\hat{\theta} - \theta) \to N(0, I^{-1}(\theta)).
\]

The \( I(\theta) \) is the Fisher Information matrix is given by

\[
I(\theta) = - \begin{bmatrix}
E \left( \frac{\partial^2 \ln L}{\partial \gamma_x^2} \right) & E \left( \frac{\partial^2 \ln L}{\partial \gamma_x \partial \gamma_y} \right) & E \left( \frac{\partial^2 \ln L}{\partial \gamma_y \partial \lambda_x} \right) & E \left( \frac{\partial^2 \ln L}{\partial \gamma_y \partial \lambda_y} \right) \\
E \left( \frac{\partial^2 \ln L}{\partial \gamma_x \partial \gamma_y} \right) & E \left( \frac{\partial^2 \ln L}{\partial \gamma_y^2} \right) & E \left( \frac{\partial^2 \ln L}{\partial \gamma_y \partial \lambda_x} \right) & E \left( \frac{\partial^2 \ln L}{\partial \gamma_y \partial \lambda_y} \right) \\
E \left( \frac{\partial^2 \ln L}{\partial \lambda_x \partial \gamma_y} \right) & E \left( \frac{\partial^2 \ln L}{\partial \lambda_x \partial \gamma_y} \right) & E \left( \frac{\partial^2 \ln L}{\partial \lambda_x^2} \right) & E \left( \frac{\partial^2 \ln L}{\partial \lambda_x \partial \lambda_y} \right) \\
E \left( \frac{\partial^2 \ln L}{\partial \lambda_x \partial \gamma_y} \right) & E \left( \frac{\partial^2 \ln L}{\partial \lambda_x \partial \gamma_y} \right) & E \left( \frac{\partial^2 \ln L}{\partial \lambda_x \partial \lambda_y} \right) & E \left( \frac{\partial^2 \ln L}{\partial \lambda_x^2} \right)
\end{bmatrix}
\]

then \( I^{-1}(\theta) \) is calculated as

\[
I^{-1}(\theta) = \begin{bmatrix}
V(\hat{\gamma}_x) & Cov(\hat{\gamma}_x, \hat{\gamma}_y) & Cov(\hat{\gamma}_x, \hat{\lambda}_x) & Cov(\hat{\gamma}_x, \hat{\lambda}_y) \\
Cov(\hat{\gamma}_y, \hat{\gamma}_x) & V(\hat{\gamma}_y) & Cov(\hat{\gamma}_y, \hat{\lambda}_x) & Cov(\hat{\gamma}_y, \hat{\lambda}_y) \\
Cov(\hat{\lambda}_x, \hat{\gamma}_x) & Cov(\hat{\lambda}_x, \hat{\gamma}_y) & V(\hat{\lambda}_x) & Cov(\hat{\lambda}_x, \hat{\lambda}_y) \\
Cov(\hat{\lambda}_y, \hat{\gamma}_x) & Cov(\hat{\lambda}_y, \hat{\gamma}_y) & Cov(\hat{\lambda}_y, \hat{\lambda}_x) & V(\hat{\lambda}_y)
\end{bmatrix}
\]

\[
= \begin{bmatrix}
a_{11} & a_{12} & a_{13} & a_{14} \\
a_{21} & a_{22} & a_{23} & a_{24} \\
a_{31} & a_{32} & a_{33} & a_{34} \\
a_{41} & a_{42} & a_{43} & a_{44}
\end{bmatrix}
\]
where
\[
\begin{align*}
    a_{11} &= \frac{1}{m^2\lambda_x^2}; \quad a_{12} = a_{21} = a_{41} = a_{44} = 0, \quad a_{13} = a_{31} = \frac{-1}{m}, \quad a_{23} = a_{32} = 0, \quad a_{22} = \frac{1}{n^2\lambda_x^2}, \\
    a_{24} &= a_{42} = -\frac{1}{n}, \quad a_{44} = \frac{\lambda_y^2}{n}, \quad a_{34} = a_{43} = 0 \quad \text{and} \quad a_{33} = \frac{\lambda_y^2}{m}.
\end{align*}
\]

Since area under the EROC curve is a function of parameters \( \theta = (\gamma_x, \gamma_y, \lambda_x, \lambda_y) \), we will adopt the delta method for finding the approximate variance. \( V(\hat{AUC}) \) is obtained as follows:

\[
V(\hat{AUC}) = \begin{pmatrix}
\frac{1}{m^2\lambda_x^2} & 0 & -\frac{1}{m} & 0 \\
0 & \frac{1}{n^2\lambda_x^2} & 0 & -\frac{1}{n} \\
-\frac{1}{m} & 0 & \frac{\lambda_y^2}{m} & 0 \\
0 & -\frac{1}{n} & 0 & \frac{\lambda_y^2}{n}
\end{pmatrix}
\]

\[
= \exp\left\{\frac{2\lambda_x(\gamma_x, -\gamma_y)}{(\lambda_x + \lambda_y)^2}\right\}\left\{\frac{\lambda_x^2}{m^2} + \frac{\lambda_y^2}{n^2} + \frac{\lambda_x^2 \lambda_y^2}{m(\lambda_x + \lambda_y)^2}[-1 + (\gamma_x - \gamma_y)(\lambda_x + \lambda_y)]^2
\right.
\]

\[
+ \frac{\lambda_x^2 \lambda_y^2}{n(\lambda_x + \lambda_y)^2} - \frac{2\lambda_x^2 \lambda_y^2}{m(\lambda_x + \lambda_y)} + \frac{2\lambda_x^2 \lambda_y^2}{n(\lambda_x + \lambda_y)}\right\}.
\]

The estimate of variance is obtained by substituting the estimates of the parameters \( \lambda_x, \gamma_x \) and \( \lambda_y, \gamma_y \). Hence,

\[
\sqrt{N}(\hat{AUC} - AUC) \rightarrow N(0,1).
\]

(3.9)

where \( AUC \) is the true area under the ROC curve. Thus, it is proved that \( \hat{AUC} \sim N(AUC, \sigma) \). Numerically, this result can be visualized from a numerical example presented in the simulation studies.

The standard error of \( \hat{AUC} \) can be obtained by taking square root of \( V(\hat{AUC}) \) in (3.8). The 100(1-\( \alpha \))% confidence interval is obtained by

\[
[AUC \pm Se(AUC)Z_{\alpha/2}]
\]

(3.10)

where \( \alpha \) is the level of significance and \( Z_{\alpha/2} \) is the critical value.
4. Numerical Example

(i) Simulation studies
In this Section, we observed the behavior of asymptotic variance of $AUC$ by using Monte Carlo simulation. We have considered four different samples of size $(m, n) = (30, 30)$ with different parametric values for $\lambda_x$ and $\lambda_y$. The MLE of $\lambda_x$, $\gamma_x$, $\lambda_y$, and $\gamma_y$ can be obtained by using (2.5). The assumed parametric values, $A\hat{U}C$, $Se(A\hat{U}C)$ and 95% confidence interval for $A\hat{U}C$ of EROC curve using asymptotic MLE and Monte Carlo methods are presented in Table 1.

Table 1: Estimated parameters, $A\hat{U}C$, $Se(A\hat{U}C)$, and 95% confidence interval for $A\hat{U}C$ of EROC curve using asymptotic MLE and Monte Carlo methods

| Description | Asymptotic MLE method | Monte Carlo method | $\bar{Y} - \bar{X}$ |
|-------------|-----------------------|--------------------|-------------------|
| $\gamma_x=0.15$ | 0.1577 (0.0061) | 0.1573 (0.0074) | 1.7192 |
| $\gamma_y=0.99$ | 0.9975 (0.0354) | 1.0301 (0.0394) | |
| $\lambda_x=4.50$ | 5.4691 (0.9985) | 4.8354 (0.9375) | |
| $\lambda_y=0.82$ | 0.8086 (0.1719) | 0.8799 (0.1692) | |
| $A\hat{U}C(Se(A\hat{U}C))$ | 0.9985 (0.0020) | 0.9966 (0.0029) | |
| CI (95%) | [0.9947, 1.0000] | [0.9909, 1.0000] | |
| $\gamma_x=0.15$ | 0.1846 (0.0119) | 0.1734 (0.0133) | 0.9211 |
| $\gamma_y=0.44$ | 0.4674 (0.0186) | 0.4458 (0.0255) | |
| $\lambda_x=2.00$ | 2.8006 (0.5113) | 2.6760 (0.5088) | |
| $\lambda_y=1.00$ | 1.7937 (0.3275) | 1.3954 (0.2683) | |
| $A\hat{U}C(Se(A\hat{U}C))$ | 0.8232 (0.0864) | 0.8289 (0.0854) | |
| CI (95%) | [0.6539, 0.9935] | [0.6625, 0.9973] | |
| $\gamma_x=0.16$ | 0.1788 (0.0612) | 0.1784 (0.0184) | 0.3963 |
| $\gamma_y=0.42$ | 0.4509 (0.0459) | 0.4458 (0.0255) | |
| $\lambda_x=1.80$ | 1.8325 (0.3346) | 1.9299 (0.3728) | |
| $\lambda_y=1.30$ | 1.3761 (0.2512) | 1.3890 (0.2642) | |
| $A\hat{U}C(Se(A\hat{U}C))$ | 0.7395 (0.1081) | 0.7450 (0.1083) | |
| CI (95%) | [0.5265, 0.9526] | [0.5327, 0.9573] | |
| $\gamma_x=0.18$ | 0.1826 (0.0126) | 0.1933 (0.0132) | 0.23428 |
| $\gamma_y=0.32$ | 0.3288 (0.0155) | 0.3367 (0.0165) | |
| $\lambda_x=2.5$ | 2.6462 (0.4831) | 2.6804 (0.5108) | |
| $\lambda_y=2.0$ | 2.1457 (0.3918) | 2.1459 (0.4101) | |
| $A\hat{U}C(Se(A\hat{U}C))$ | 0.6958 (0.1179) | 0.6932 (0.1045) | |
| CI (95%) | [0.4647, 0.9270] | [0.4884, 0.8980] | |

*CI : Confidence Interval
In Table 1, first column represents the assumed parametric values, second column represents the MLE of parameters with their standard errors given within the parenthesis along with the 95% asymptotic confidence interval for $\hat{AUC}$, the third column provides the Monte Carlo estimates of parameters with their standard errors given within parenthesis along with the 95% confidence interval for $\hat{AUC}$ and the final column represents the difference between the mean of diseased ($\bar{Y}$) and the mean of non-diseased ($\bar{X}$) samples i.e. ($\bar{Y} - \bar{X}$) As far as the discrimination is concerned, the measure ($\bar{Y} - \bar{X}$) indirectly tells us the degree of separation between the two groups.

We also observe that, as the measure ($\bar{Y} - \bar{X}$) or the deviation between the estimated parameters of non-diseased and diseased group increases, the $AUC$ tends to increase which in turn decreases the standard error of $AUC$. We also notice that there is no major difference in the estimates of parameters and $\hat{AUC}$, obtained by asymptotic and Monte Carlo methods from Table 1. The $EROC$ curves for different parametric values are plotted in Figure 1.

![EROC curve for different values of AUC](image1)

**Fig. 1** $EROC$ curve for different values of $AUC$

![Histogram of the AUC statistic](image2)

**Fig. 2** Histogram of the AUC statistic

In support of the theorem, we have plotted the values of the statistic, $AUC$ in the following Figure.
Table 2: \( \hat{AUC}, \) \( Se(\hat{AUC}), 95\% \) asymptotic confidence interval for \( \hat{AUC} \) of EROC curve for different values of parameters

| Parametric values | Sample size |
|-------------------|-------------|
|                  | (5, 5)      | (10, 10)    | (30, 30)    | (50, 50)    | (80, 80)    | (100, 100) |
| \( \gamma_x=0.15; \) \( \gamma_y=0.99; \) \( \lambda_x=4.5; \) \( \lambda_y=0.82 \) | 0.9985      | 0.9985      | 0.9985      | 0.9985      | 0.9985      | 0.9985      |
|                  | 0.0046      | 0.0031      | 0.0018      | 0.0014      | 0.0011      | 0.0010      |
|                  | [0.9896, 1.0000] | [0.9952, 1.0000] | [0.9960, 1.0000] | [0.9966, 1.0000] | [0.9968, 1.0000] |
| \( \gamma_x=0.16; \) \( \gamma_y=0.42; \) \( \lambda_x=2.5; \) \( \lambda_y=1.3 \) | 0.8232      | 0.8232      | 0.8232      | 0.8232      | 0.8232      | 0.8232      |
|                  | 0.2199      | 0.1520      | 0.0864      | 0.0667      | 0.0526      | 0.0470      |
|                  | [0.3922, 0.5253] | [0.6539, 0.7200] | [0.6925, 0.7309] | [0.9263, 0.9154] |
| \( \gamma_x=0.16; \) \( \gamma_y=0.42; \) \( \lambda_x=1.80; \) \( \lambda_y=1.30 \) | 0.7395      | 0.7395      | 0.7395      | 0.7395      | 0.7395      | 0.7395      |
|                  | 0.2778      | 0.1916      | 0.1087      | 0.0839      | 0.0662      | 0.0592      |
|                  | [0.1951, 0.3640] | [0.5265, 0.5751] | [0.6925, 0.7309] | [0.6098, 0.6236] |
| \( \gamma_x=0.18; \) \( \gamma_y=0.32; \) \( \lambda_x=2.50; \) \( \lambda_y=2.00 \) | 0.6958      | 0.6958      | 0.6958      | 0.6958      | 0.6958      | 0.6958      |
|                  | 0.3020      | 0.2080      | 0.1179      | 0.0910      | 0.0718      | 0.0640      |
|                  | [0.1039, 0.2881] | [0.4647, 0.5175] | [0.5552, 0.5701] |

In Table 2, the data has been generated by assuming different parametric values for various sample sizes namely \{(5, 5), (10, 10), (30, 30), (50, 50), (80, 80), (100, 100)\}. The first element in each row represents the accuracy; second element is the standard error of \( \hat{AUC} \), the third and fourth value being the lower and upper confidence limits. It is obvious that the asymptotic estimate of standard error holds good for large sample size. As we go through the columns, the standard error tends to decrease and the confidence intervals get narrow as the sample size increase.

(ii) Real life example

The proposed method is applied to Prostate cancer markers(PSA). PSA is a biomarker which is significant in detecting the prostate cancer. The data consisted of 50 randomly chosen individuals who were affected by prostate cancer and 50 non-diseased individuals who were participated in a lung cancer prevention trial (Etzioni, 1999). The two correlated prostate cancer biomarkers were considered namely total serum PSA (tPSA) and the ratio of (percent) free to total PSA (fPSA). Among these biomarkers tPSA has higher \( AUC \) than fPSA and hence it is preferred to assess the accuracy of diagnosis for prostate cancer.

The tPSA has been evaluated for the Goodness of Fit for two parameter exponential distribution using Kolmogrov-Smirnov, Anderson-Darling and Chi-Square test. The results are reported for significance level \((\alpha) 20, 10, 5, 2 \) and \(1\%\) in Table 3 from the software ‘Easy Fit’. The EROC curve is plotted for tPSA and it is presented in Figure 2.
Table 3: Goodness of Fit test for tPSA biomarker

| Group | Test | Statistic | p-value | Rank | α % |
|-------|------|-----------|---------|------|-----|
| H     | K-S  | 0.121     | 0.426   | 18   | 20, 10, 5, 2, 1 |
|       | $\chi^2$ | 0.6441   | 0.958   | 3    | 20, 10, 5, 2, 1 |
|       | A-D  | 1.219     | -       | 23   | 20, 10, 5, 2, 1 |
| D     | K-S  | 0.128     | 0.357   | 29   | 20, 10, 5, 2, 1 |
|       | $\chi^2$ | 4.004   | 0.5488  | 24   | 20, 10, 5, 2, 1 |
|       | A-D  | 1.747     | -       | 31   | 10, 5, 2, 1 |

Fig. 2 EROC curve for tPSA biomarker

The EROC model showed that the marker ‘tPSA’ is able to identify the prostate cancer individual with an accuracy of 93% with the estimated Standard error, 0.055 with a confidence interval [0.8079, 1.000]. The sensitivity and specificity of tPSA by using EROC are 83% and 76% respectively at the threshold 2.865 ng/ml.

From sensitivity and specificity, we could infer that an individual who is having the “tPSA” marker value greater than 2.865 ng/ml is 83% likely to be detected with the prostate cancer. Similarly, an individual having the marker value less than 2.865 ng/ml is 76% likely to be not detected with the prostate cancer.

5. Conclusion

In this paper, we have also extended the one parameter Bi-Exponential ROC curve analysis to two parameter exponential ROC curve analysis. The properties of the two parameter bi-exponential ROC curve have been studied. It is found that, EROC is monotonically increasing, concavity an important property for a ROC to be proper, TNR asymmetric which is justified theoretically as well as graphically. The 95% asymptotic confidence interval for $\hat{AUC}$ have been derived. For the prostate cancer data, the EROC
model showed that the biomarker ‘tPSA’ is able to identify the prostate cancer individual with an accuracy of 91% with the estimated standard error, 0.055 with a confidence interval [0.8079, 1.000]. The sensitivity and specificity are 83% and 76% respectively at the threshold 2.865 ng/ml. The proposed EROC curve analysis can be adopted for assessing the accuracy of classification made by a particular biomarker provided the goodness of fit test is evaluated.

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