Chapter 2

Generalized Lehmann Family for Meta-Analysis Based upon Summary Receiver Operating Characteristic Curves

2.1 Introduction

Meta-analysis is a statistical methodology that combines or integrates the results of several independent clinical trials that are considered to be combinable by an analyst. It is a quantitative, formal, epidemiological study design used to systematically assess previous research studies to derive conclusions. The examination of variability or heterogeneity is also important in meta-analysis. However, different studies may not be comparable due to different cut-off values for the continuous and ordered categorical diagnostic tests. To cope up with this problem, the Summary Receiver Operating Characteristic curve (SROC) is considered which summarizes the performance of a diagnostic test. This curve indicates the relationship between the true positive rate (TPR) and the false positive rate (FPR) of the test at various thresholds to differentiate between diseased cases from non-diseased cases. More recently, the Summary Receiver Operating Characteristic curve (SROC) and the area under the curve (AUC) have been proposed to assess diagnostic accuracy in the context of meta-analysis (Krzanowski and Hand (2009)).

Meta analysis has many applications in the fields of medicine, education, social sciences, business, environmental and agriculture sciences. For example, in the field of medicine, different study results related to risk of a particular disease from various regions may be combined. In education, meta analysis is useful for combining studies about coaching effectiveness to improve Scholastic Aptitude Test (SAT) scores. In social sciences, one may combine several studies of gender differences in separate categories of quantitative, verbal and visual spatial ability. For

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more applications of meta-analysis, one may refer to Cooper and Hedges (1994), Hasselblad and Hedges (1995), Irwig et al. (1995), Sutton et al. (2000), Schulze et al. (2003), Egger et al. (2008), Krzanowski and Hand (2009), Hedges and Olkin (2014) and Swets (2014).

If \( D = 0(1) \) means absence (presence) of a disease and \( T = 0(1) \) negative (positive) test result, then the specificity and sensitivity are defined as

\[
\text{Specificity} = (1 - u) = P(T = 0|D = 0)
\]

and

\[
\text{Sensitivity} = p = P(T = 1|D = 1).
\]

Here the false positive rate is denoted by \( u \).

Suppose there are \( N \) studies under consideration. For \( i = 1, 2, \ldots, N \), let

\( x_i \): the number of false positives out of \( n_i \) healthy individuals,

\( y_i \): the number of true positives out of \( m_i \) diseased individuals.

For \( i^{th} \) study, the estimators of \( u_i \) and \( p_i \) are given by

\[
\hat{u}_i = \frac{x_i}{n_i} \quad \text{and} \quad \hat{p}_i = \frac{y_i}{m_i}.
\]

Summary Receiver Operating Characteristic (SROC) curves are used to cope with different cut off values and comparability problem for sensitivity and specificity in case of independent samples and different diagnostic studies. SROC curve has been recommended to represent the performance of a diagnostic test and is preferred to Youden index (Youden (1950)) or the diagnostic odds ratio (Glas et al. (2003)). It is intended to represent the relationship between TPR and FPR across studies, recognizing the fact that they may have used different thresholds.

For the continuous test \( T \) with potential value \( t \), SROC curves are plotted by using the pair \((u(t), p(t))\) where

\[
u(t) = P(T \geq t|D = 0)
\]

and

\[
p(t) = P(T \geq t|D = 1).
\]
For $N$ possible unknown cut-off values $t_1, ..., t_N$, the pairs $(u(t_i), p(t_i))$ can be estimated by

$$(\hat{u}_i, \hat{p}_i) = \left( \frac{x_i}{n_i}, \frac{y_i}{m_i} \right) \text{ for } i = 1, ..., N,$$

where we write $u_i = u(t_i)$ and $p_i = p(t_i)$.

Holling et al. (2012) proposed Lehmann model for analysis of SROC curves. They studied the elimination of the nuisance parameters through profile likelihood which led to a proper Gaussian likelihood after adjustment. We generalize this model by introducing an additional parameter and explore estimation of parameters through adjusted profile likelihood (APL).

In Section 2.2, we propose the Generalized Lehmann model for the analysis of SROC curves. In this model, the nuisance parameter FPR or (1-specificity) is eliminated by means of profile likelihood (PL) which is discussed in Section 2.3. In Section 2.4, the adjusted profile likelihood is derived. Section 2.5 discusses the problem of heterogeneity. Simulations have been carried out for estimation of unknown parameters in Section 2.6. A real life data set is analysed in Section 2.7. This section also consists of forest, crosshair and ROC ellipse plots for checking heterogeneity in the data. Conclusions of the chapter follow in Section 2.8.

### 2.2 The Generalized Lehmann Model

We propose a Generalized Lehmann family which relates the sensitivity and false positive rate as

$$p(t) = |u(t)|^{\theta \alpha}, \quad \theta > 0 \quad \text{and} \quad \alpha > 0. \quad (2.2.1)$$

If $u(t) \in [0, 1]$, then $p(t) \in [0, 1]$ for $\theta, \alpha > 0$.

The introduction of factor $\alpha$ leads to more flexibility to Lehmann model since higher order relationships can also be established. The parameters $\theta$ and $\alpha$ represent the diagnostic accuracy of the model. For (2.2.1),

$$\frac{\log p(t)}{\log u(t)} = \theta \alpha \quad \text{(a constant)},$$

a property satisfied by proportional hazard model (PHM) (Breslow (1975)). The ROC curves for this model for different values of $\theta$ and $\alpha$ are shown in Figure 2.1.
From Figure 2.1, one can easily see that

- for fixed value of $\theta$ and varying $\alpha$, the diagnostic accuracy is quite good,

- the diagnostic accuracy is not good when $\alpha$ is fixed but $\theta$ varies. This is evident as the ROC curves are below the diagonal line.

It may be noted that the two diagnostic tests represented by different values of $\theta$ and $\alpha$ can be easily compared. The area under the curve (AUC) for this model is given by

\[
AUC = \int_0^1 u^{\theta\alpha} \, du = \frac{1}{1 + \theta^\alpha} \quad \text{for } \theta, \alpha > 0.
\]

### 2.3 Profile Likelihood

In the following discussion, we consider the profile likelihood (PL) which helps in estimation in the presence of a nuisance parameter. This method reduces the infinite dimensional estimation problem to a finite dimensional one. It is a widely used method to eliminate a nuisance parameter
and also possesses invariance property.

For \(i^{th}\) study, let \(X_i\) and \(Y_i\) be Binomial random variables with parameters \((n_i, u_i)\) and \((m_i, p_i)\) respectively. For the sake of simplicity, the index \(i\) is suppressed in the sequel and the product-binomial likelihood can be written as

\[
\binom{n}{x} u^x (1 - u)^{n-x} \binom{m}{y} p^y (1 - p)^{m-y}
\]

where \(x = 0, 1, ...., n\) and \(y = 0, 1, ...., m\), \(0 < p < 1\) and \(0 < u < 1\).

Using Delta Method (Casella and Berger (2002)), it follows that for large \(n\) and \(m\), \(logX\) and \(logY\) follow Normal distribution with

\[
E[logX] = lognu, \\
V[logX] = nu(1 - u) \left[ \frac{d}{d(nu) log(nu)} \right]^2 = \frac{1 - u}{nu},
\]

and

\[
E[logY] = logmp, \\
V[logY] = mp(1 - p) \left[ \frac{d}{d(mp) log(mp)} \right]^2 = \frac{1 - p}{mp}.
\]

Using estimators of \(u\) as \(\frac{x}{n}\) and \(p\) as \(\frac{y}{m}\), we can write for large \(n\) and \(m\)

\[
\hat{V}[logX] = \frac{1}{x} - \frac{1}{n}
\]

and

\[
\hat{V}[logY] = \frac{1}{y} - \frac{1}{m}.
\]

Hence, writing \(\hat{V}[logX]\) as \(t^2\) and \(\hat{V}[logY]\) as \(s^2\), the joint distribution of \(logX_i\) and \(logY_i\) can be written as

\[
\frac{1}{\sqrt{2\pi t^2}} \exp \left[ -\frac{1}{2t^2} [logx - log(nu)]^2 \right] \left( \frac{1}{\sqrt{2\pi s^2}} \exp \left[ -\frac{1}{2s^2} [logy - log(mp)]^2 \right] \right). \quad (2.3.1)
\]

If \(x_i\) and \(y_i\) are assumed to be positive, the estimated variances for the log-proportions, that is,
2.3 Profile Likelihood

\[ \log \left( \frac{x_i}{n_i} \right) \] \text{ and } \log \left( \frac{y_i}{m_i} \right) \text{ are given by}

\[ \hat{\text{Var}}(\log \hat{u}_i) = t_i^2 = \frac{1}{x_i} - \frac{1}{n_i} \text{ and } \hat{\text{Var}}(\log \hat{y}_i) = s_i^2 = \frac{1}{y_i} - \frac{1}{m_i}, \quad i = 1, 2, ..., N. \]

Let \( w_i = \log(x_i) - \log(n_i) \): log-true positive rate,

\( z_i = \log(y_i) - \log(m_i) \): log-false positive rate.

Since in diagnostic studies, the number of observations in each study is not small, hence the normal approximation is valid.

Using (2.3.1), the relevant part of the log-likelihood is

\[ \frac{-1}{2t^2}(\log x - \log n - \log u)^2 - \frac{1}{2s^2}(\log y - \log m - \log p)^2. \tag{2.3.2} \]

If \( u' = \log u \), then (2.3.2) can be written as

\[ l(\theta, \alpha, u') = \frac{-1}{2t^2}(w - u')^2 - \frac{1}{2s^2}(z - \theta^\alpha u')^2. \tag{2.3.3} \]

For fixed \( \theta \) and \( \alpha \), differentiating \( l(\theta, \alpha, u') \) w.r.t. \( u' \) and equating to zero leads to

\[ \frac{1}{t^2}(w - u') + \frac{1}{s^2}(z - \theta^\alpha u')(\theta^\alpha) = 0 \]

\[ \Rightarrow \hat{u}' = \frac{zt^2\theta^\alpha + ws^2}{t^2\theta^\alpha + s^2}. \]

Substituting \( \hat{u}' \) in (2.3.3), the profile log-likelihood becomes

\[ l(\theta, \alpha) = -\frac{1}{2t^2} \left[ w - \left( \frac{zt^2\theta^\alpha + ws^2}{t^2\theta^\alpha + s^2} \right) \right]^2 - \frac{1}{2s^2} \left[ z - \theta^\alpha \left( \frac{zt^2\theta^\alpha + ws^2}{t^2\theta^\alpha + s^2} \right) \right]^2. \]

Simplification leads to

\[ l(\theta, \alpha) = \frac{-(z - \theta^\alpha w)^2}{2(t^2\theta^\alpha + s^2)}. \]

In the next subsection, the properties of Profile log-likelihood have been studied.
2.3.1 Properties of Profile Log-Likelihood

1) Invariance Property

Generalized Lehmann model can be written as

\[ \log p = \theta \alpha \log u \text{ or} \]
\[ \log u = \frac{1}{\theta \alpha} \log p. \]

In the first form, log-sensitivity can be regressed on the log-false positive rate, whereas in the latter, the log-false positive rate is regressed on the log-sensitivity. Both these regression problems are known to have different solutions. Now the profile maximum likelihood is invariant with respect to the choice of nuisance parameter. For example, if \( u \) or \( p \) is chosen to be nuisance parameter, then

\[ l(\theta, \alpha, \widehat{u}) = l(\theta, \alpha, \widehat{p}). \]

Since the labelling of axis is arbitrary in the ROC diagram, hence, irrespective of the choice of model for analysis, the profile log-likelihood is suitable for the inference. This happens because the choice of nuisance parameter (sensitivity or false positive rate) will ultimately not affect the inference about the parameter of interest which gives the invariance property of log-likelihood.

2) Approximation to Gaussian Log-Likelihood

Now we show that \( l(\theta, \alpha) \) is almost a Gaussian log-likelihood.

Since \( p = u^\alpha \Rightarrow \log p = \theta \alpha \log u \Rightarrow \log \frac{y}{m} = \theta \alpha \log \frac{x}{n}, \) hence

\[ z = \theta \alpha \log \frac{x}{n} \text{ and} \]
\[ E(z) = \theta \alpha [E(\log x) - E(\log n)] = \theta \alpha [\log(nu) - \log(n)] = \theta \alpha \log(u) = \theta \alpha w. \]

We also have

\[ V(z) = V \left( \log \left( \frac{y}{m} \right) \right) = V(\log y) = s^2 \text{ and} \]
\[ V(\theta \alpha w) = \theta^{2 \alpha} V \left( \log \left( \frac{x}{n} \right) \right) = \theta^{2 \alpha} V(\log x) = \theta^{2 \alpha} t^2 \text{ so that} \]
\[ V(z - \theta \alpha w) = s^2 + \theta^{2 \alpha} t^2 = \sigma^2(\theta, \alpha)(\text{say}). \]

This implies that \( (z - \theta \alpha w) \sim N[0, \sigma^2(\theta, \alpha)] \) which shows \( l(\theta, \alpha) \) is almost a Gaussian
log-likelihood and
\[
 l(\theta, \alpha) = \frac{-(z - \theta^* w)^2}{2(s^2 + \theta^2 \alpha t^2)} = \frac{-(z - \theta^* w)^2}{2(\sigma^2(\theta, \alpha))}.
\]

(2.3.4)

If \( L(\theta, \alpha) \) denotes the proper log-likelihood, then
\[
 L(\theta, \alpha) = \frac{-log\sigma^2(\theta, \alpha)}{2} - \frac{(z - \theta^* w)^2}{2(\sigma^2(\theta, \alpha))}.
\]

(2.3.5)

The profile log-likelihood \( l(\theta, \alpha) \) differs from \( L(\theta, \alpha) \) only by \(-\frac{log\sigma^2(\theta, \alpha)}{2}\) which shows that \( l(\theta, \alpha) \) is not a proper log-likelihood.

In particular, first and second-order properties don’t hold necessarily and the curvature of the profile likelihood does not provide an estimate of the variance. Since the profile likelihood considers the estimated nuisance parameter as a true parameter value, it can underestimate the variance of the parameter of interest (Barndorff-Nielsen (1983), Cox and Reid (1987) and Lee et al. (2006)). In addition, the profile log-likelihood \( l(\theta, \alpha) \) fails in case of heterogeneity if further variance components are incorporated. Because of these shortcomings, we use the concept of adjusted profile likelihood, which is discussed in next section.

### 2.4 The Adjusted Profile Likelihood

For fixed \( \theta \) and \( \alpha \), the observed Fisher information \( \hat{I}(\hat{u}) \) evaluated at \( \hat{u} \) is the modified or adjusted profile likelihood and is given by
\[
 \hat{I}(\hat{u}) = -\frac{\partial^2 l(\theta, \alpha, u')}{\partial u'^2} = \frac{\partial^2}{\partial u'^2} \left[ \frac{1}{2t^2}(w - u')^2 + \frac{1}{2s^2}(z - \theta^* u')^2 \right]
\]
\[
 = \frac{\theta^2 \alpha t^2 + s^2}{s^2 t^2} = \frac{\sigma^2(\theta, \alpha)}{s^2 t^2}.
\]

Hence using (2.3.5),
\[
 L(\theta, \alpha) = -\frac{1}{2} log(\hat{I}(\hat{u})) + l(\theta, \alpha) + constant
\]
\[
 = -\frac{-log\sigma^2(\theta, \alpha)}{2} + \frac{log(s^2 t^2)}{2} + l(\theta, \alpha) + constant \quad (2.4.1)
\]
where constant is independent of $\theta$ and $\alpha$. $L(\theta, \alpha)$ becomes a proper log-likelihood if the constant term is chosen to be \( -\frac{\log(s^2 t^2)}{2} \) which is independent of $\theta$ and $\alpha$.

For $N$ studies, using (2.3.4) and (2.4.1), the full-sample adjusted profile log-likelihood can be written as

\[
L(\theta, \alpha) = -\sum_{i=1}^{N} \frac{\log \sigma_i^2(\theta, \alpha)}{2} - \frac{1}{2} \sum_{i=1}^{N} \frac{(z_i - \theta^\alpha w_i)^2}{\sigma_i^2(\theta, \alpha)}
\]

where $\sigma_i^2(\theta, \alpha) = \theta^{2\alpha} t_i^2 + s_i^2$.

This form implies that $Z_i \sim N(\theta^\alpha w_i, \sigma_i^2(\theta, \alpha))$.

For formulation of the model and adjusted for $w_i$, we may write

\[
\frac{Z_i}{w_i} = \theta^\alpha + \epsilon_i,
\]

where $\epsilon_i$ are the error terms following $N\left(0, \frac{\sigma_i^2(\theta, \alpha)}{w_i^2}\right)$.

Since $E\left(\frac{Z_i}{w_i}\right) = \theta^\alpha$ and $V\left(\frac{Z_i}{w_i}\right) = \frac{\sigma_i^2(\theta, \alpha)}{w_i^2}$, hence the associated log-likelihood takes the form

\[
L(\theta, \alpha) = -\frac{1}{2} \left[ \sum_{i=1}^{N} \log \left(\frac{\sigma_i^2(\theta, \alpha)}{w_i^2}\right) + \sum_{i=1}^{N} \frac{(z_i/w_i - \theta^\alpha)^2}{\sigma_i^2(\theta, \alpha)/w_i^2} \right].
\]

This gives

\[
\frac{\partial L(\theta, \alpha)}{\partial \theta} = -\sum_{i=1}^{N} \frac{(2\alpha t_i^2 \theta^{2\alpha-1})}{2(\sigma_i^2(\theta, \alpha))} + \sum_{i=1}^{N} \frac{\alpha(z_i - \theta^\alpha w_i)w_i \theta^{\alpha-1}}{\sigma_i^2(\theta, \alpha)}
\]

\[+ \frac{1}{2} \sum_{i=1}^{N} \frac{(z_i - \theta^\alpha w_i)^2(2\alpha t_i^2 \theta^{2\alpha-1})}{(\sigma_i^2(\theta, \alpha))^2}.\]
Putting \( v_i = \frac{1}{\sigma_i^2(\theta, \alpha)} \), we get

\[
\frac{\partial L(\theta, \alpha)}{\partial \theta} = \alpha \theta^{a-1} \left[ - \sum_{i=1}^{N} t_i^2 \theta^a v_i + \sum_{i=1}^{N} w_i v_i (z_i - \theta^a w_i) + \sum_{i=1}^{N} (z_i - \theta^a w_i)^2 t_i^2 \theta^a v_i^2 \right]
\]

\[
= \alpha \theta^{a-1} \left[ \theta^a \sum_{i=1}^{N} v_i t_i^2 [(z_i - \theta^a w_i)^2 v_i - 1] + \sum_{i=1}^{N} w_i v_i (z_i - \theta^a w_i) \right]. \tag{2.4.2}
\]

Similarly,

\[
\frac{\partial L(\theta, \alpha)}{\partial \alpha} = -\sum_{i=1}^{N} \frac{(t_i^2 \theta^{2a} \log \theta)}{2(\sigma_i^2(\theta, \alpha))} - \sum_{i=1}^{N} \frac{(z_i - \theta^a w_i)(-w_i \theta^a \log \theta)}{\sigma_i^2(\theta, \alpha)}
\]

\[
+ \sum_{i=1}^{N} \frac{(z_i - \theta^a w_i)^2 (t_i^2 \theta^{2a} \log \theta)}{2(\sigma_i^2(\theta, \alpha))^2}
\]

\[
= \frac{\theta^a \log \theta}{2} \left[ - \sum_{i=1}^{N} v_i t_i^2 \theta^a + 2 \sum_{i=1}^{N} w_i v_i (z_i - \theta^a w_i) + \sum_{i=1}^{N} t_i^2 v_i (z_i - \theta^a w_i)^2 \theta^a v_i \right]
\]

\[
= \frac{\theta^a \log \theta}{2} \left[ \theta^a \sum_{i=1}^{N} v_i t_i^2 [(z_i - \theta^a w_i)^2 v_i - 1] + 2 \sum_{i=1}^{N} w_i v_i (z_i - \theta^a w_i) \right]. \tag{2.4.3}
\]

Using \( E[z_i - \theta^a w_i] = 0 \) and \( E[(z_i - \theta^a w_i)^2] = \sigma_i^2(\theta, \alpha) \),

we get \( E \left[ \frac{\partial L(\theta, \alpha)}{\partial \theta} \right] = 0 \) and \( E \left[ \frac{\partial L(\theta, \alpha)}{\partial \alpha} \right] = 0 \).

Hence, the expected values of the scores of the adjusted profile log-likelihood satisfy the conventional first-order property.

It also follows that

\[
\frac{z_i - \theta^a w_i}{\sigma_i(\theta, \alpha)} = \frac{z_i / w_i - \theta^a}{\sigma_i(\theta, \alpha) / w_i} \text{ is approximately a standard normal variate and }
\]

\[
\chi^2_{N-2} = \sum_{i=1}^{N} \frac{(\hat{\theta}^a - \hat{\theta}^a)^2}{\sigma_i^2(\hat{\theta}, \hat{\alpha}) / w_i^2}
\]

has an approximate \( \chi^2 \) distribution with \( (N - 2) \) degrees of freedom (df).

This chi-square statistic is used for testing goodness of fit of the model.
For finding maximum likelihood estimates (MLEs) of \( \theta \) and \( \alpha \), we equate (2.4.2) and (2.4.3) to zero and solve them. Since this results into two non linear equations, hence numerical approximation is used for estimating \( \theta \) and \( \alpha \). For this, we use OPTIM function in R software. This provides the maximum likelihood estimates using the adjusted profile likelihood known as adjusted profile maximum likelihood estimates (APMLEs).

### 2.5 Heterogeneity

Different studies have different false positive rates but identical proportionality parameters \( \theta \) and \( \alpha \). However, \( \theta \) and \( \alpha \) may also vary from study to study. For the diagnostic accuracy of test in case of heterogeneity, \( \frac{\sigma_i^2(\theta, \alpha)}{w_i^2} \) is replaced by \( \left( \frac{\sigma_i^2(\theta, \alpha)}{w_i^2} + \tau^2 \right) \) in \( L(\theta, \alpha) \), where \( \tau^2 \) is the appropriate random effect variance component parameter. This is accomplished by extending the fixed effect model using a further random effect \( \delta_i \) which helps us in writing

\[
\frac{Z_i}{w_i} = \theta^\alpha + \delta_i + \epsilon_i \sim N\left( \theta^\alpha, \left( \frac{\sigma_i^2(\theta, \alpha)}{w_i^2} + \tau^2 \right) \right)
\]

where \( \delta_i \) is the random effect independent of \( \epsilon_i \) with \( E(\delta_i) = 0, Var(\delta_i) = \tau^2 \) and \( \epsilon_i \) are error terms following \( N\left( 0, \left( \frac{\sigma_i^2(\theta, \alpha)}{w_i^2} + \tau^2 \right) \right) \).

The full-sample adjusted profile log-likelihood with random effect is written as

\[
L(\theta, \alpha, \tau^2) = -\sum_{i=1}^{N} \log\left( \frac{\sigma_i^2(\theta, \alpha)}{w_i^2} + \tau^2 \right) - \sum_{i=1}^{N} \frac{(\hat{\theta}_i^\alpha - \theta^\alpha)^2}{2(\frac{\sigma_i^2(\theta, \alpha)}{w_i^2} + \tau^2)}.
\]

(2.5.1)

The score vector \( U = (\partial L/\partial \theta, \partial L/\partial \alpha, \partial L/\partial \tau^2) \), where using \( r_i = \frac{1}{\left( \frac{\sigma_i^2(\theta, \alpha)}{w_i^2} + \tau^2 \right)} \),

\[
\frac{\partial L}{\partial \theta} = \sum_{i=1}^{N} (\hat{\theta}_i^\alpha - \theta^\alpha) r_i w_i (\alpha \theta^\alpha - 1) + \sum_{i=1}^{N} (\hat{\theta}_i^\alpha - \theta^\alpha)^2 \left( \alpha t_i^2 \theta^{2\alpha-1} r_i \right) - \sum_{i=1}^{N} \alpha t_i^2 \theta^{2\alpha-1} r_i.
\]

(2.5.2)
\[
\frac{\partial L}{\partial \alpha} = - \sum_{i=1}^{N} \frac{r_i l_i^2 \theta^{2\alpha} \log \theta}{2 w_i^2} + \sum_{i=1}^{N} \frac{(\hat{\theta}_i^\alpha - \theta^\alpha)^2 r_i l_i^2 \theta^{2\alpha} \log \theta}{2 w_i^2} + \sum_{i=1}^{N} r_i w_i (\hat{\theta}_i^\alpha - \theta^\alpha)(\theta^\alpha \log \theta) ;
\]

(2.5.3)

and

\[
\frac{\partial L}{\partial \tau^2} = - \sum_{i=1}^{N} \frac{1}{2(\frac{\tau^2}{w_i^2} + \tau^2)} + \sum_{i=1}^{N} \frac{(\hat{\theta}_i^\alpha - \theta^\alpha)^2}{2(\frac{\tau^2}{w_i^2} + \tau^2)^2}
\]

\[
= \sum_{i=1}^{N} \frac{(\hat{\theta}_i^\alpha - \theta^\alpha)^2 r_i^2}{2} - \sum_{i=1}^{N} \frac{r_i}{2}.
\]

(2.5.4)

The score vector \( U = \left( \frac{\partial L}{\partial \theta} \frac{\partial L}{\partial \alpha} \frac{\partial L}{\partial \tau^2} \right) \) satisfies the first-order property \( E(U) = 0 \) because for \( \hat{\theta}_i^\alpha \sim N(\theta^\alpha, \frac{1}{r_i}) \),

\[
E\left( \frac{\partial L}{\partial \theta} \right) = \sum_{i=1}^{N} \alpha (E(\hat{\theta}_i^\alpha - \theta^\alpha)) r_i w_i \theta^{\alpha-1} + \sum_{i=1}^{N} \frac{(E(\hat{\theta}_i^\alpha - \theta^\alpha))^2}{\frac{\alpha l_i^2 \theta^{2\alpha-1} r_i^2}{w_i^2}} - \sum_{i=1}^{N} \frac{(\alpha l_i^2 \theta^{2\alpha-1} r_i)}{w_i^2} \]

\[
= \sum_{i=1}^{N} (\alpha \times 0 \times r_i \times w_i \times \theta^{\alpha-1}) + \sum_{i=1}^{N} \frac{1}{r_i} \frac{(\alpha l_i^2 \theta^{2\alpha-1} r_i^2)}{w_i^2} - \sum_{i=1}^{N} \frac{\alpha l_i^2 \theta^{2\alpha-1} r_i}{w_i^2} = 0 ;
\]

(2.5.5)

\[
E\left( \frac{\partial L}{\partial \alpha} \right) = \frac{r_i l_i^2 \theta^{2\alpha} \log \theta}{2 w_i^2} + \sum_{i=1}^{N} \frac{(E(\hat{\theta}_i^\alpha - \theta^\alpha))^2}{\frac{\alpha l_i^2 \theta^{2\alpha-1} r_i^2}{w_i^2}} + \sum_{i=1}^{N} r_i w_i (E(\hat{\theta}_i^\alpha - \theta^\alpha)) \theta^\alpha \log \theta
\]

\[
= - \sum_{i=1}^{N} r_i l_i^2 \theta^{2\alpha} \log \theta + \sum_{i=1}^{N} \frac{r_i l_i^2 \theta^{2\alpha} \log \theta}{2 w_i^2} + \sum_{i=1}^{N} (r_i \times w_i \times \theta^\alpha \times \log \theta) = 0 ;
\]

(2.5.6)

and

\[
E\left( \frac{\partial L}{\partial \tau^2} \right) = \sum_{i=1}^{N} \frac{(E(\hat{\theta}_i^\alpha - \theta^\alpha))^2}{2} - \sum_{i=1}^{N} \frac{r_i}{2} = 0.
\]

(2.5.7)

The adjusted \( \chi^2 \) for testing goodness of fit in case of heterogeneity is

\[
\chi^2_{het} = \sum_{i=1}^{N} \frac{(\hat{\theta}_i^\alpha - \theta^\alpha)^2}{\sigma_i^2(\hat{\theta}_i^\alpha, \hat{\alpha})/w_i^2 + \tau^2}
\]

which follows chi-square distribution with \( (N - 3) \) degrees of freedom.
2.6 Simulations

In this section, we carry out simulations to find estimates of \( \theta \), \( \alpha \) and also the heterogeneity parameter \( \tau^2 \) by using numerical approximation and the non-linear equations given in Sections 2.4 and 2.5.

A simulation study to find the adjusted profile maximum likelihood estimates (APMLE) of parameters for different number of studies have been obtained by taking \( N = 5, 10, 15, 20 \) and \( 50 \). The \( n \) and \( m \) are generated from Poisson distributions with means 25 and 50 respectively. False positive rates \( u_i \)'s are sampled from a Uniform distribution on (0,1). Sensitivities \( p_i \)'s are calculated according to the Generalised Lehmann model given by (2.2.1). Finally, \( x_i \)'s are sampled from a Binomial distribution with parameters \( n_i \) and \( u_i \) whereas \( y_i \)'s are sampled from a Binomial distribution with parameters \( m_i \) and \( p_i \) for \( i = 1, 2, ..., N \). The number of repetitions is taken to be 10000. The used numerical method is L-BFGS-B in optim function in R. Method "L-BFGS-B" allows box constraints, that is each variable can be given a lower and/or upper bound. The initial value must satisfy the constraints.

2.6.1 Estimation in case of No Heterogeneity

Tables 2.1-2.3 give the estimates and corresponding Root Mean Square Errors (RMSEs) of \( \theta \) and \( \alpha \) for \( N \) studies. We consider the following cases

1. Both \( \theta \) and \( \alpha \) are unknown (Table 2.1);

2. \( \theta \) is unknown and \( \alpha \) is known (Table 2.2);

3. \( \theta \) is known and \( \alpha \) is unknown (Table 2.3).
In Table 2.1, the initial values of $\theta$ and $\alpha$ are assumed to be 0.1 and 0.4 respectively.

**Table 2.1: Estimates of $\theta$ and $\alpha$ and corresponding RMSEs**

<table>
<thead>
<tr>
<th>$N$</th>
<th>$\hat{\theta}$</th>
<th>$\hat{\alpha}$</th>
<th>RMSE($\hat{\theta}$)</th>
<th>RMSE($\hat{\alpha}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.11079</td>
<td>0.45122</td>
<td>0.04165</td>
<td>0.09994</td>
</tr>
<tr>
<td>10</td>
<td>0.10624</td>
<td>0.44575</td>
<td>0.02880</td>
<td>0.08176</td>
</tr>
<tr>
<td>15</td>
<td>0.10489</td>
<td>0.44196</td>
<td>0.02244</td>
<td>0.07020</td>
</tr>
<tr>
<td>20</td>
<td>0.10384</td>
<td>0.44105</td>
<td>0.01991</td>
<td>0.06503</td>
</tr>
<tr>
<td>50</td>
<td>0.10134</td>
<td>0.43648</td>
<td>0.00179</td>
<td>0.04614</td>
</tr>
</tbody>
</table>

In Table 2.2, $\alpha = 0.4$ is assumed to be known and initial value of $\theta$ is taken to be 0.1.

**Table 2.2: Estimates of $\theta$ and corresponding RMSEs for known $\alpha$**

<table>
<thead>
<tr>
<th>$N$</th>
<th>$\hat{\theta}$</th>
<th>RMSE($\hat{\theta}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.08899</td>
<td>0.04820</td>
</tr>
<tr>
<td>10</td>
<td>0.08571</td>
<td>0.03235</td>
</tr>
<tr>
<td>15</td>
<td>0.08462</td>
<td>0.02849</td>
</tr>
<tr>
<td>20</td>
<td>0.08392</td>
<td>0.02601</td>
</tr>
<tr>
<td>50</td>
<td>0.08263</td>
<td>0.02143</td>
</tr>
</tbody>
</table>

In the following table, $\theta = 0.1$ is known and initial value of $\alpha = 0.4$.

**Table 2.3: Estimates of $\alpha$ and corresponding RMSEs for known $\theta$**

<table>
<thead>
<tr>
<th>$N$</th>
<th>$\hat{\alpha}$</th>
<th>RMSE($\hat{\alpha}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.43803</td>
<td>0.09483</td>
</tr>
<tr>
<td>10</td>
<td>0.43458</td>
<td>0.06990</td>
</tr>
<tr>
<td>15</td>
<td>0.43529</td>
<td>0.06084</td>
</tr>
<tr>
<td>20</td>
<td>0.43378</td>
<td>0.05441</td>
</tr>
<tr>
<td>50</td>
<td>0.43468</td>
<td>0.04414</td>
</tr>
</tbody>
</table>

From the Tables 2.1-2.3, it can be concluded that as the number of studies increases, the RMSE of the estimates gets lower.
2.6.2 Estimation in case of Heterogeneity

It is assumed that there is heterogeneity present in the data set and the corresponding parameter is $\tau^2$. Tables 2.4–2.6 provide estimates of $\theta$, $\alpha$ and $\tau^2$ under different setups.

Table 2.4 contains the values of maximum likelihood estimates of $\theta$, $\alpha$ and $\tau^2$ and the corresponding Root Mean Square Errors (RMSEs) by using profile likelihood (PL) and adjusted profile likelihood (APL) for purpose of comparison. The initial values are taken to be $\theta = 0.1$, $\alpha = 0.4$ and $\tau^2 = 0.01$. Profile maximum likelihood (PMLE) gives the maximum likelihood estimate (MLE) using Profile likelihood function. Similarly, APMLE is the MLE using adjusted profile likelihood function.

<table>
<thead>
<tr>
<th></th>
<th>$N$</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>APMLE ($\hat{\theta}$)</td>
<td>0.10784</td>
<td>0.11063</td>
<td>0.11533</td>
<td>0.11423</td>
<td>0.10927</td>
<td></td>
</tr>
<tr>
<td>RMSE ($\hat{\theta}$)</td>
<td>0.06278</td>
<td>0.05684</td>
<td>0.06326</td>
<td>0.04880</td>
<td>0.01783</td>
<td></td>
</tr>
<tr>
<td>PMLE ($\hat{\theta}$)</td>
<td>0.56306</td>
<td>0.78348</td>
<td>0.50063</td>
<td>0.62242</td>
<td>0.94809</td>
<td></td>
</tr>
<tr>
<td>RMSE ($\hat{\theta}$)</td>
<td>0.65128</td>
<td>0.74343</td>
<td>0.63812</td>
<td>0.66355</td>
<td>0.85227</td>
<td></td>
</tr>
<tr>
<td>APMLE ($\hat{\alpha}$)</td>
<td>0.43230</td>
<td>0.42192</td>
<td>0.42144</td>
<td>0.42133</td>
<td>0.40932</td>
<td></td>
</tr>
<tr>
<td>RMSE ($\hat{\alpha}$)</td>
<td>0.14490</td>
<td>0.09247</td>
<td>0.08084</td>
<td>0.07231</td>
<td>0.02063</td>
<td></td>
</tr>
<tr>
<td>PMLE ($\hat{\alpha}$)</td>
<td>77.4904</td>
<td>84.5658</td>
<td>210.3141</td>
<td>173.0123</td>
<td>242.4411</td>
<td></td>
</tr>
<tr>
<td>RMSE ($\hat{\alpha}$)</td>
<td>121.3141</td>
<td>108.5433</td>
<td>297.0212</td>
<td>270.6695</td>
<td>278.8208</td>
<td></td>
</tr>
<tr>
<td>APMLE ($\hat{\tau^2}$)</td>
<td>0.00678</td>
<td>0.00858</td>
<td>0.00958</td>
<td>0.00982</td>
<td>0.00809</td>
<td></td>
</tr>
<tr>
<td>RMSE ($\hat{\tau^2}$)</td>
<td>0.01675</td>
<td>0.01475</td>
<td>0.01463</td>
<td>0.01173</td>
<td>0.00466</td>
<td></td>
</tr>
<tr>
<td>PMLE ($\hat{\tau^2}$)</td>
<td>432254.0</td>
<td>414663.6</td>
<td>153350.1</td>
<td>125864.0</td>
<td>446019.0</td>
<td></td>
</tr>
<tr>
<td>RMSE ($\hat{\tau^2}$)</td>
<td>782146.6</td>
<td>652924.7</td>
<td>202888.1</td>
<td>234503.0</td>
<td>873458.4</td>
<td></td>
</tr>
</tbody>
</table>

It is evident from Table 2.4 that the RMSEs are lower when APL function is used. This supports the using of APL in place of PL function for finding MLEs. This is true for other setups as well and hence the tables that follow, show only MLEs obtained through APL function.
Table 2.5 gives the ML estimates and corresponding RMSEs when one of the three parameters is known. Table 2.6 gives the ML estimates and corresponding RMSEs when two of the three parameters are unknown.

**Table 2.5 : ML Estimates and RMSEs in case of one unknown parameter**

<table>
<thead>
<tr>
<th></th>
<th>( \theta, \alpha ) known and ( \tau^2 ) unknown</th>
<th>( \theta, \tau^2 ) known and ( \alpha ) unknown</th>
<th>( \alpha, \tau^2 ) known and ( \theta ) unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial value of ( \tau^2 = 0.01 )</td>
<td>Initial value of ( \alpha = 0.4 )</td>
<td>Initial value of ( \theta = 0.1 )</td>
</tr>
<tr>
<td>( N )</td>
<td>( \hat{\tau}^2 )</td>
<td>( \hat{\alpha} )</td>
<td>( \hat{\tau} )</td>
</tr>
<tr>
<td>5</td>
<td>0.01578</td>
<td>0.43362</td>
<td>0.10489</td>
</tr>
<tr>
<td>10</td>
<td>0.01349</td>
<td>0.42183</td>
<td>0.10645</td>
</tr>
<tr>
<td>15</td>
<td>0.01275</td>
<td>0.41718</td>
<td>0.10737</td>
</tr>
<tr>
<td>20</td>
<td>0.01188</td>
<td>0.41425</td>
<td>0.10660</td>
</tr>
<tr>
<td>50</td>
<td>0.01083</td>
<td>0.40919</td>
<td>0.10355</td>
</tr>
</tbody>
</table>

**Table 2.6: ML Estimates and RMSEs in case of two unknown parameters**

<table>
<thead>
<tr>
<th></th>
<th>( \theta ) known, ( \alpha ) and ( \tau^2 ) unknown</th>
<th>( \theta ) known, ( \alpha ) and ( \tau^2 ) unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial value of ( \alpha = 0.1 ) and ( \tau^2 = 0.01 )</td>
<td>(Initial value of ( \alpha = 0.1 ) and ( \tau^2 = 0.01 ))</td>
</tr>
<tr>
<td>( N )</td>
<td>( \hat{\alpha} )</td>
<td>( \text{RMSE} (\hat{\alpha}) )</td>
</tr>
<tr>
<td>5</td>
<td>0.43265</td>
<td>0.11537</td>
</tr>
<tr>
<td>10</td>
<td>0.41957</td>
<td>0.07476</td>
</tr>
<tr>
<td>15</td>
<td>0.41247</td>
<td>0.06041</td>
</tr>
<tr>
<td>20</td>
<td>0.40934</td>
<td>0.05172</td>
</tr>
<tr>
<td>50</td>
<td>0.40330</td>
<td>0.02851</td>
</tr>
<tr>
<td>( \hat{\tau} )</td>
<td>0.00740</td>
<td>0.01797</td>
</tr>
<tr>
<td>5</td>
<td>0.00740</td>
<td>0.01797</td>
</tr>
<tr>
<td>10</td>
<td>0.01063</td>
<td>0.01698</td>
</tr>
<tr>
<td>15</td>
<td>0.01028</td>
<td>0.01418</td>
</tr>
<tr>
<td>20</td>
<td>0.01047</td>
<td>0.00916</td>
</tr>
<tr>
<td>50</td>
<td>0.01047</td>
<td>0.00916</td>
</tr>
<tr>
<td>( \text{RMSE} (\hat{\tau}^2) )</td>
<td>0.01771</td>
<td>0.01698</td>
</tr>
<tr>
<td>5</td>
<td>0.01771</td>
<td>0.01698</td>
</tr>
<tr>
<td>10</td>
<td>0.01797</td>
<td>0.01698</td>
</tr>
<tr>
<td>15</td>
<td>0.01418</td>
<td>0.00916</td>
</tr>
<tr>
<td>20</td>
<td>0.01418</td>
<td>0.00916</td>
</tr>
<tr>
<td>50</td>
<td>0.01418</td>
<td>0.00916</td>
</tr>
<tr>
<td>( \hat{\theta} )</td>
<td>0.09931</td>
<td>0.06213</td>
</tr>
<tr>
<td>5</td>
<td>0.09931</td>
<td>0.06213</td>
</tr>
<tr>
<td>10</td>
<td>0.10102</td>
<td>0.04755</td>
</tr>
<tr>
<td>15</td>
<td>0.10259</td>
<td>0.04102</td>
</tr>
<tr>
<td>20</td>
<td>0.10400</td>
<td>0.03473</td>
</tr>
<tr>
<td>50</td>
<td>0.10474</td>
<td>0.02087</td>
</tr>
<tr>
<td>( \text{RMSE} (\hat{\tau}^2) )</td>
<td>0.00766</td>
<td>0.00954</td>
</tr>
<tr>
<td>5</td>
<td>0.00766</td>
<td>0.00954</td>
</tr>
<tr>
<td>10</td>
<td>0.00999</td>
<td>0.00999</td>
</tr>
<tr>
<td>15</td>
<td>0.01023</td>
<td>0.01023</td>
</tr>
<tr>
<td>20</td>
<td>0.01052</td>
<td>0.01052</td>
</tr>
<tr>
<td>50</td>
<td>0.01052</td>
<td>0.01052</td>
</tr>
<tr>
<td>( \text{RMSE} (\hat{\theta}) )</td>
<td>0.01965</td>
<td>0.01755</td>
</tr>
<tr>
<td>5</td>
<td>0.01965</td>
<td>0.01755</td>
</tr>
<tr>
<td>10</td>
<td>0.01755</td>
<td>0.01509</td>
</tr>
<tr>
<td>15</td>
<td>0.01382</td>
<td>0.00922</td>
</tr>
<tr>
<td>20</td>
<td>0.01382</td>
<td>0.00922</td>
</tr>
<tr>
<td>50</td>
<td>0.01382</td>
<td>0.00922</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>( \tau^2 ) known, ( \theta ) and ( \alpha ) unknown</th>
<th>( \tau^2 ) known, ( \theta ) and ( \alpha ) unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial value of ( \theta = 0.4 ) and ( \alpha = 0.1 )</td>
<td>(Initial value of ( \theta = 0.4 ) and ( \alpha = 0.1 ))</td>
</tr>
<tr>
<td>( N )</td>
<td>( \hat{\tau} )</td>
<td>( \text{RMSE} (\hat{\tau}) )</td>
</tr>
<tr>
<td>5</td>
<td>0.14409</td>
<td>0.36472</td>
</tr>
<tr>
<td>10</td>
<td>0.14942</td>
<td>0.34314</td>
</tr>
<tr>
<td>15</td>
<td>0.13505</td>
<td>0.31863</td>
</tr>
<tr>
<td>20</td>
<td>0.12969</td>
<td>0.29260</td>
</tr>
<tr>
<td>50</td>
<td>0.11436</td>
<td>0.03565</td>
</tr>
<tr>
<td>( \hat{\alpha} )</td>
<td>0.45689</td>
<td>0.36472</td>
</tr>
<tr>
<td>5</td>
<td>0.45689</td>
<td>0.34314</td>
</tr>
<tr>
<td>10</td>
<td>0.45001</td>
<td>0.31863</td>
</tr>
<tr>
<td>15</td>
<td>0.43853</td>
<td>0.29260</td>
</tr>
<tr>
<td>20</td>
<td>0.43007</td>
<td>0.03565</td>
</tr>
<tr>
<td>50</td>
<td>0.42170</td>
<td>0.42170</td>
</tr>
<tr>
<td>( \text{RMSE} (\hat{\tau}) )</td>
<td>0.17965</td>
<td>0.16151</td>
</tr>
<tr>
<td>5</td>
<td>0.17965</td>
<td>0.16151</td>
</tr>
<tr>
<td>10</td>
<td>0.16151</td>
<td>0.11802</td>
</tr>
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<td>0.09132</td>
<td>0.09132</td>
</tr>
<tr>
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<td>0.05433</td>
<td>0.05433</td>
</tr>
<tr>
<td>50</td>
<td>0.05433</td>
<td>0.05433</td>
</tr>
</tbody>
</table>
On the basis of values of RMSEs of the estimates given in Tables 2.5 and 2.6, it can be concluded that the estimates perform better when more and more studies are included in the analysis.

2.7 Data Analysis

2.7.1 Brain Natriuretic Peptides Data for Heart Failure

We consider the data set used by Doust et al. (2004) for the diagnostic accuracy of Brain Natriuretic Peptides (BNP) for Heart Failure. It is found that \( \hat{\theta} = 0.3153677 \) and \( \hat{\alpha} = 2.1678286 \). This corresponds to an AUC of 0.92, which indicates good diagnostic accuracy. Holling et al. (2012) found the AUC of Lehmann model as 0.83. So, our model performs better in case of diagnostic accuracy of BNP than the Lehmann model considered by Holling et al. (2012).

2.7.2 Alcohol Use Disorder Identification Data

Alcohol Use Disorder Identification Test (AUDIT) is a recommended instrument for screening all forms of unhealthy alcohol use (risky drinking, alcohol abuse, alcohol dependence). The full AUDIT consists of 10 items and has been extensively investigated in several settings and countries (Reinert and Allen (2002)). We consider a meta-analysis study in measuring the diagnostic accuracy of the AUDIT data provided by Kriston et al. (2008) and given in Table 2.7.
<table>
<thead>
<tr>
<th>Study i</th>
<th>Alcohol disorder</th>
<th>No disorder</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>y_i (TP)</td>
<td>m_i - y_i (FN)</td>
<td>n_i - x_i (TN)</td>
</tr>
<tr>
<td>1</td>
<td>48</td>
<td>7</td>
<td>738</td>
</tr>
<tr>
<td>2</td>
<td>138</td>
<td>39</td>
<td>1506</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>5</td>
<td>173</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>2</td>
<td>227</td>
</tr>
<tr>
<td>5</td>
<td>137</td>
<td>12</td>
<td>936</td>
</tr>
<tr>
<td>6</td>
<td>73</td>
<td>13</td>
<td>127</td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>14</td>
<td>508</td>
</tr>
<tr>
<td>8</td>
<td>571</td>
<td>180</td>
<td>5707</td>
</tr>
<tr>
<td>9</td>
<td>54</td>
<td>10</td>
<td>172</td>
</tr>
<tr>
<td>10</td>
<td>148</td>
<td>44</td>
<td>2687</td>
</tr>
<tr>
<td>11</td>
<td>143</td>
<td>18</td>
<td>334</td>
</tr>
<tr>
<td>12</td>
<td>47</td>
<td>13</td>
<td>464</td>
</tr>
<tr>
<td>13</td>
<td>34</td>
<td>1</td>
<td>65</td>
</tr>
<tr>
<td>14</td>
<td>154</td>
<td>49</td>
<td>261</td>
</tr>
</tbody>
</table>

In the above table, m_i and n_i denote the number of persons with and without alcohol disorder for i-th study. x_i and y_i denote the number of false positives and true positives.

The meta-analysis on AUDIT and alcohol disorder provides adjusted profile maximum likelihood estimates (APMLEs) as \( \hat{\theta} = 0.3952426 \) and \( \hat{\alpha} = 1.7096843 \). The estimate of area under the ROC, that is, AUROC is 0.83 which indicates good diagnostic accuracy. It is observed that value of \( \chi^2 \) statistic is 25.26 (df = 12) which provides strong evidence of heterogeneity in the data set. In case of heterogeneity, \( \hat{\theta} = 0.0496030 \), \( \hat{\alpha} = 0.5278279 \) and \( \tau^2 = 0.0010000 \) for the given data.

For the AUDIT data, Forest plots, Crosshair and ROCellipse plots have been presented. Forest plots used for diagnostic test accuracy report the estimated sensitivity and specificity along with their confidence intervals. The plots are also known as coupled forest plots as they contain two graphical sections: one depicting sensitivity and the other specificity. The Forest plots for estimated sensitivity and specificity are given in Figures 2.2 and 2.3.

The middle part shows the confidence intervals for estimated sensitivities and specificities for different studies.
Two high level plots viz Crosshair plot (Phillips et al. (2010)) and ROCellipse plot can be obtained using mada function in R. The R-package mada is a tool for the meta-analysis of diagnostic accuracy. The open source package mada written in R provides some established and some current approaches to diagnostic meta-analysis, as well as functions to produce
descriptive statistics and graphics. It is hopefully complete enough to be the only tool needed for a diagnostic meta-analysis. Crosshair plot displays the individual studies in ROC space with paired confidence intervals representing sensitivity and specificity and allow for the results of meta-analysis to be overlaid on the plot. It can be used for comparison of the heterogeneity of two variables in the same plot.

Figure 2.4 displays the Crosshair plot for the AUDIT data.

![Crosshair Plot](image)

**Figure 2.4: Crosshair Plot**
Figure 2.5: ROCellipse Plot

Figure 2.5 displays the ROCellipse plot for the AUDIT data.

ROCellipse plot gives individual confidence regions (in the form of ellipses) for estimate from each of the studies. These regions show the uncertainty of the pair of sensitivity and false positive rate. These regions are ellipses on logit ROC space and by back-transforming them to regular ROC space the (sometimes oddly shaped) regions are produced.

2.8 Conclusions

In this chapter, we consider the modelling of Summary Receiver Operating Characteristic (SROC) curve used in meta-analysis of diagnostic studies. This is done through Generalized Lehmann model which relates the log-sensitivity and the log false positive rate across various studies. The nuisance parameters (study specific false positive rates) are eliminated through the use of profile likelihood. The estimation for the parameters of the Generalized Lehmann family has been carried out using adjusted profile likelihood. This model is extended further to accommodate unobserved heterogeneity by allowing the constant of proportionality to vary
across studies. Simulations have been carried out for estimation of unknown parameters. Forest, crosshair and ROC ellipse plots for checking heterogeneity in the data are also derived.