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Estimation of Parameters for Logistic Regression Model in Dose Response Study with A Single Compound or Mixture of Compounds

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Dedicated to my late Mother. She would have been so happy to see me receiving a Ph.D.

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ABSTRACT OF THE DISSERTATION

Estimation of Parameters for Logistic Regression Model in Dose Response Study with A Single Compound or Mixture of Compounds

by

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Dr. Subir Ghosh, Chairperson

We investigate the estimation issues for count data in dose response model. In this thesis, we are considering logistic dose response model for a mixture experiment with two drugs. We propose two new methods of estimation of parameters for this model by forming the observation pairs. The standard maximum likelihood estimation method uses the numerical methods for solving the estimating equations. This method requires an initial set of values for the parameters in the model. The standard procedure normally uses the initial values as zero or some convenient numbers without any justification. We present two very systematic methods of finding the initial values of parameters of the maximum likelihood estimating equations (MLEE). Our methods are based on two criterion functions, the log-likelihood and the other function Δ. We then use the initial values and the corresponding criterion function to obtain the final solution of MLEE. We demonstrate that when we consider only two doses from the data, we do have an exact analytic expression for the solution of estimating equations. We use that fact to obtain the initial values of parameters in these models. Then we have used the search algorithm for performing the optimization to find the final estimates. The proposed methods are transparent in the selection of the initial values of parameters. The proposed methods are computer intensive like bootstrap and jackknife methods popular among statisticians. We have also compared our estimates with the estimates obtained by SAS and R. The proposed methods compare favorably with SAS and R in terms numerical values of the estimates and the performance time of the estimates. We illustrate our meth-

ods with a data set (Giltinan, 1998). We present also some simulated data to illustrate our methods.

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Chapter 1

Introduction

There was an incident reported in the Winter of 1961 regarding the use of the drug Thalidomide. The incident reported that the thousands of babies born with deformities from the mothers who have taken this drug during their pregnancy. The drug could be a toxic substance. According to Beedie and Davies (1981), it had not been tested on animals for teratogenicity. This fiasco illustrated the adverse effect of the toxic substance on human being. This is a motivating example to study toxicity of a drug or a medication. A dose response model determines the toxic effect of a chemical substance. Dose-Response is a relationship that describes the changes brought in an organism when it is exposed to different levels (doses) of a chemical compound. In this study, the main interest is to study the relationship between exposure levels of drugs (doses) and the responses obtained from the experiment. Dose-response relationship is always based on two simple assumptions:

- There is always a minimum dose to have an observed effect.
- There is always a maximum dose.

We can apply dose response analysis for single drug experiment, for the mixture of two drugs experiments and for the mixture of multiple drugs experiments. In this thesis we consider the dose-response relationship of the mixture of two drugs experiment and a single drug experiment.

There are many statistical models available in literature (Finney, 1971) to analyze dose-response relationship of chemical compounds. In this thesis, we use the Logistic Regression Model (Bliss, 1935) for its computational simplicity. With our fitted model, we analyze the data and the parameter estimates of the assumed model.

1.1 Literature Review

Dose-Response assessment is a two step procedure. The first step analyze the data that are available or gathered from the experiments. And the second step is to estimate the risk or the adverse effect beyond the observe data. First step of the assessment deals with the modeling of the data and the estimation of potency of a chemical substance. The potency is a measure of a drug amount that is required to produce an effect of given intensity. Some of the commonly used potency estimators are, ED_{50}, LD_{50} etc. There are many statistical models exist in the literature to address the dose response assessment of chemical substances. We have considered logistic regression model in our thesis for the assessment. We can use probit, complementary log-log models for the assessment (Finney, 1971). Among other numerous existing models, we found the model proposed by Chen (2007) is relevant to our work. In Pharmaceutical experiments, animals responses are recorded over different time points under different dose levels. Logit and probit models are not appropriate in this situation because it neglects the dependency on time. Chen (2007) proposed a multinomial generalized linear model. We can extend this model with the higher order dose-time interaction terms. With the fitted model, we are generally interested in estimating the potency of the drug or relative potency if we have drug interactions. We have discussed the estimation of most commonly used potency estimator, ED_{50} in our thesis. Since we also consider the drug interactions in our thesis, we discuss about the estimation of relative potency for drug interactions. There are numerous literature exist on the estimation of relative potency. One of the most commonly used method of estimation is Isobologram. This is a graphical method which was

introduced many years ago (Loewe, 1927). This graph is generally constructed on a coordinate system composed of the individual drug doses. It is commonly contains a straight line of additivity that help use to distinguish between different type of drug interactions. However, we have discussed the numerical estimation procedure for relative potency in our thesis.

As we mentioned earlier that dose-response assessment also deals with the risk characterization of chemical substances exposed to the human population. This is the attempt to estimate the chance of obtaining an adverse effect of exposure to an agent (Glowa 1996). The earliest practice used to predict safe level was the acceptable daily intake (ADI) which attempted to predict a dose that could be tolerated over the life time without producing harm. However, arguments in support of the fact that it was impossible to determine the entirely safe dose which led to a revised term called reference dose (RfD) approach. This approach first finds a dose level with no effect (i.e. no observable adverse effect level or NOAEL) or a minimal effect (i.e. lowest observable adverse effect level or LOAEL). NOAEL is the highest experimental dose at which there is no statistically significant increase in the adverse toxicological end point. This NOAEL approach is based on the assumption that if the critical toxic effect is prevented, then all toxic effects are prevented (Barnes and Dourson , 1988). There are several ways of determining NOAEL dose.Besides finding NOAEL we can find "virtually safe" doses (VSDs). A virtually safe dose of a drug is one which produces a very low incidence of response. Several ways of estimating VSDs exist.

1.2 Thesis contribution

In this thesis we discuss the statistical models for the drug interactions between two drugs. We consider logistic regression model for describing dose-response relationship between two drugs. We are interested to determine the mathematical approach to estimate the relative potency of drug interaction. We also consider the potency estimation of ED_{50} for a single

drug experiment. The potency estimation depends on the estimation of parameters in the proposed models. The standard maximum likelihood estimation method uses the numerical methods for solving the estimating equations. These methods requires an initial set of values for the parameters in the model. The standard procedure normally uses the initial values as zero or some convenient numbers without any justification. We propose two new methods of estimation of the parameters for these models by forming the observation pairs. We present two very systematic methods for finding the initial values of parameters of maximum likelihood estimating equations (MLEE). Our methods are based on two criterion functions, the log-likelihood and the other function Δ. We then use the initial values and the corresponding criterion function to obtain the final solution of MLEE. We demonstrate that when we consider only two doses from the data, we do have an exact analytic expression for the solution of estimating equations. We use that fact to obtain the initial values of parameters in these models. Then we use the search algorithm for performing the optimization to find the final estimates. The proposed methods are transparent in the selection of the initial values of parameters. Our methods are highly computer intensive and comparable with the standard methods of estimation used by the software R and SAS.

1.3 Thesis description

In Chapter 2, we present the models that are used to describe the dose response relationship for mixture of experiments. We have considered a data set given by Giltinan (1998) for the computational purpose. In this chapter we present the standard and popular estimation procedures for estimating the unknown parameters in the defined models. In Chapter 3, we present a special case of one of our proposed model from Chapter 2. In this chapter, we present a systematic way to find the initial values of the parameters which can be used for the iteration of the new estimation method . We also present our new estimation method to estimate the unknown parameters in the model that uses our initial values. Our proposed

methods are illustrated on a data set given by Bliss (1935). In Chapter 4, we present a direct performance comparison of our new estimation method with the couple of the standard estimation methods. We also present the comparison with respect to the performance times for our proposed methods and the standard methods. In Chapter 5, we present a systematic way to find the initial values of the parameters in the model which defines the mixture of experiments. We also propose new methods of estimation of the unknown parameters using our proposed initial values. In Chapter 6, we present a comparison study between our methods and the standard methods used for estimating the unknown parameters. Chapter 7 presents the conclusion of this dissertation.

Chapter 2

Model and Estimation

2.1 Summary

In this chapter, we present the statistical models for the dose-response data of mixture of two drugs experiment. Discussions on statistical models can be found at (Finney,1978; Chen, Gaylor, and Laborde,1998; Piegorsch and Bailer, 1997). Generally we have count data for analyzing the dose response relationship between doses and response. The statistical models for describing the count data in drug interactions are developed within the framework of generalized linear models. A detailed expositions on generalized linear models can be found in (McCullag, Nelder, 1989). There are many literature on Maximum Likelihood Estimation (MLE) for estimating the unknown parameters in these models. Some of the studies can be found in (Agresti, 2001). We present MLE of the unknown parameters in these models using Newton-Raphson and Fisher Scoring iteration methods. Besides that we present the results on maximum likelihood estimates of the unknown parameters for a data set from (Giltinan, 1998) using the above two standard iterative procedures.

2.2 Statistical Modeling of Dose response data

As we discussed earlier, dose-response study examines the relationship between dose level of toxic substance and animal mortality. We want to model the probability of mortality (p) as a function of dosages (x).

We define a random variable z for an animal who is exposed to a particular dose. The variable z takes the value 1 when the animal gets killed by the dosages and $z = 0$ when the animal does not get killed by the dosage. A reasonable model assumes that the animal has a certain tolerance T to the toxic substance, with mortality occurring if the dosage is above the tolerance. Then the probability that an animal dies when dosage x is given is,

$$P(z = 1) = P(T \leq x) = \int_{-\infty}^{x} f(t)dt. \tag{2.1}$$

where $f(t)$ is the density function associated with the tolerance. The logistic, probit, complementary log-log link function are the possibly describe the tolerance density models. We use the logistic link function for our analysis.

2.3 Genralized linear model

2.3.1 Binary data

We consider the case where the response Y is binary, assuming only two values, that for convenience coded as one or zero. Suppose y_i is a realization of the random variable Y_i, $i = 1, \ldots, N$, that can take the values one and zero with probabilities π_i and $1 - \pi_i$, respectively. The distribution of Y_i is called a Bernoulli distribution with parameter π_i, can be written in the compact form as,

$$Pr\{Y_i = y_i\} = \pi_i^{y_i}(1 - \pi_i)^{(1-\pi_i)}. \tag{2.2}$$

The expectation and variance of Y_i can be expressed as,

$$\begin{aligned} E(Y_i) &= \pi_i, \\ \text{var}(Y_i) &= \pi_i(1 - \pi_i). \end{aligned} \tag{2.3}$$

2.3.2 Count data

When the response variable is binary (e.g. death or survival), then the probability distribution of the number of deaths in a sample of a particular size is usually assumed to be

binomial. Let n_i denote the number of observations in group i, and let y_i denote the number of units who have the same attribute of interest (e.g. no. of death or survival) in group i. y_i can take the values $0, 1, \ldots, n_i$. If the n_i observations in each group are independent, and if they all have the same probability π_i of having the attribute of interest, then the distribution of Y_i is binomial with parameters n_i and π_i, we write,

$$Y_i \sim B(n_i, \pi_i), \tag{2.4}$$

The probability distribution function of Y_i is given by,

$$Pr\{Y_i = y_i\} = \binom{n_i}{y_i} \pi_i^{y_i} (1 - \pi_i)^{(1-\pi_i)}, \tag{2.5}$$

The expectation and variance of Y_i can be expressed as,

$$\begin{aligned} E(Y_i) &= \mu_i = n_i \pi_i, \\ \text{var}(Y_i) &= n_i \pi_i (1 - \pi_i). \end{aligned} \tag{2.6}$$

For a generalized linear model there is a transformation of μ_i such that

$$g(\mu_i) = \theta_i = x_i^{'} \beta, \tag{2.7}$$

In the above equation g is a monotone and differentiable function which is called the link function; x_i is the p x 1 vector of explanatory variables, β is the p x 1 vector of parameters and we use a canonical link function involving the natural parameter θ_i

A wide choices of link functions are available in the literature. The most commonly used functions are logit, probit and complimentary log-log. We consider logit link function where the monotonic function g is defined as,

$$g(\mu_i) = \log \frac{\pi_i}{1 - \pi_i}, \tag{2.8}$$

In logistic regression model, π_i can be defined as,

$$\pi_i = \frac{\exp(\theta_i)}{1 + \exp(\theta_i)}. \tag{2.9}$$

2.3.3 Likelihood function for the count data

We consider the general case of N independent random variables $Y_1, \ldots, Y_N$ corresponding to the numbers of successes in N different subgroup. We assume that the mortality probability for a subject in the i^{th} group is π_i and the mortalities for subjects are independent. Given that Y_i follows from binomial distribution with parameters (n_i, π_i), the complete likelihood function can be written as,

$$L(\pi_i, \ldots, \pi_N; y_i, \ldots, y_N) = \prod_{i=1}^{N} \binom{n_i}{y_i} \pi_i^{y_i} (1 - \pi_i)^{n_i - y_i}, \tag{2.10}$$

The log-likelihood function is,

$$l(\pi_i, \ldots, \pi_N; y_i, \ldots, y_N) = \sum_{i=1}^{N} y_i \log(\frac{\pi_i}{1 - \pi_i}) + n_i \log(1 - \pi_i) + \log \binom{n_i}{y_i},$$

Substituting π_i in (2.9) in the above equation, we get,

$$\log(L(\theta)) = l(\theta) = \sum_{i=1}^{N} y_i x_i^{'} \theta - \sum_{i=1}^{N} n_i \log(1 + \exp(x_i^{'}\theta)) + \sum_{i=1}^{N} \log \binom{n_i}{y_i}. \tag{2.11}$$

The likelihood in (2.9) are based on the assumption that the count response variable y_i 's for a given subject are independent over the period of the time of study. Under the above structure of likelihood, one can define several classes of models.

2.4 Mixture of Drugs

We, the humans are usually exposed to several toxic substances or chemicals such as environmental pollutants in food, water, air and therapeutic agents etc everyday. Some of the examples are - (i) hospital patients on the average receives 4 drugs daily, (ii) home influenza treatment consists of more than one of the medicine like aspirin, antihistamines, antibiotics,

and cough syrup taken simultaneously, (iii) drinking water and food may contain small amounts of organic and inorganic chemicals, (iv) air often contains mixtures of hundreds of chemicals such as urban and industrial combustion products, (v) cigarette smoke etc., (vi) gasoline vapors include several hydrocarbons and additives etc. (Khan, 2007) There could be an effect of toxicity of these chemicals simultaneously in our body. however, toxicity testing of mixtures is usually difficult because it is impossible to predict the possible combinations of chemicals that will be present in multiple-chemical exposures. Sometimes chemicals which administered simultaneously may act independently of each other. However, in many cases, the presence of one chemical may drastically affect the response to another chemical. The effectiveness or toxicity of a mixture of chemicals may be less or more than would be predicted from the known effects of each individual chemical. The effect that one chemical has on the toxic effect of another chemical is known as an interaction between two chemicals. We have considered drug interactions between two drugs in our thesis. There are three basic types of drug interactions. Before we discuss about the drug interactions, we discuss about the Relative potency of two drugs. Assume two drugs namely, A and B are separately active. We assume that the ratio of equally effective doses of two compounds is constant for all levels of response and is referred as relative potency, ρ, of the drugs. If the potency of B is ρ then z units of B have the same effect as ρz units of A. If a mixture containing x_i units of A and z_i , $i = 1, \ldots, N$ units of B results in a response (i) equivalent to, (ii) greater than or (iii) less than that for $x_i + \rho z_i$ units of A, we shall say that the two drugs exhibit (i)additive behavior (simple similar action), (ii) synergism behavior or (iii) antagonism behavior. these three are the basic type of drug interaction for the mixture of drugs (Giltinan, 1998). Synergism and Antagonism represent deviations from Similar Action in the positive and negative directions respectively. We consider simple similar action interaction between two drugs as our interest. The models and the estimation procedure for estimating the unknown parameters are discussed in the coming chapters.

2.4.1 Models

Model 1 (MM_1)

We propose two different models for describing simple similar action of two drug compounds. Model 1 describes the simple similar action of two drugs when the relative potency is unknown. As we have discussed earlier that we will use logistic regression model to define our models, so that we have considered the mortality probability π_i as

$$\pi_i = \text{logit}^{-1}(\theta_i) = \frac{\exp(\theta_i)}{1+\exp(\theta_i)}, \tag{2.12}$$

Here

$$\theta_i = \beta_1 + \beta_2 \log(x_i + \rho z_i), \tag{2.13}$$

Hence π_i becomes,

$$\pi_i = \frac{\exp(\beta_1 + \beta_2 \log(x_i + \rho z_i))}{1+\exp(\beta_1 + \beta_2 \log(x_i + \rho z_i))}, \tag{2.14}$$

where β_1 , β_2 and ρ are the unknown parameters. x_i and z_i are the covariates used as the measurements of drug amount of drug A and drug B , respectively.

We define $d_i = \log(x_i + \rho z_i), i = 1, \ldots, N$. The equation (2.14) can be written as

$$\pi_i = \frac{\exp(\beta_1 + \beta_2 d_i)}{1+\exp(\beta_1 + \beta_2 d_i)}. \tag{2.15}$$

Model 2 (MM_2)

Model 2 describes the joint action of two drugs when the relative potency (ρ) is known. We denote the known relative potency as ρ_0 in Model 2. We consider logit link function to define our model as in similar fashion as Model 1. The θ_i in (2.12) is defined as

$$\theta_i = \beta_1 + \beta_2 \log(x_i + \rho_0 z_i), \tag{2.16}$$

Hence π_i becomes,

$$\pi_i = \frac{\exp(\beta_1 + \beta_2 \log(x_i + \rho_0 z_i))}{1+\exp(\beta_1 + \beta_2 \log(x_i + \rho_0 z_i))}, \tag{2.17}$$

We consider $d_{0i} = x_i + \rho_0 z_i$. The equation (2.17) can be written as

$$\pi_i = \frac{\exp(\beta_1 + \beta_2 d_{0i})}{1 + \exp(\beta_1 + \beta_2 d_{0i})}. \tag{2.18}$$

In (2.17) , x_i and z_i are the covariates i.e., the measurements of drug amounts and β_1 , β_2 are the unknown parameters.

In this thesis we are developing a new estimation procedure for the unknown parameters in both MM_1 and MM_2 in the subsequent chapters.

2.5 Estimation of unknown parameters for two models

In this section, we discuss about the estimation procedure for the unknown parameters for two models. There are several estimation procedures exist in the literature, however, the most popular estimation procedure is maximum likelihood estimation procedure (MLEE). The idea behind the maximum likelihood parameter estimation is to determine the parameters that maximize the likelihood function given the sample data. The likelihood function and estimating equations for two models are discussed in the subsequent sections.

2.6 Maximum Likelihood estimation: model MM_1

2.6.1 Likelihood function

The maximum likelihood estimates of the parameters β_1 , β_2 and ρ are $\hat{\beta}_1$, $\hat{\beta}_2$ and $\hat{\rho}$ can be evaluated satisfying

$$(\hat{\beta}_1, \hat{\beta}_2, \hat{\rho}) = \arg \max_{\beta_1, \beta_2, \rho} l(\beta_1, \beta_2, \rho), \tag{2.19}$$

where $l(\beta_1, \beta_2, \rho)$ is the log likelihood function of model MM_1 defined in (2.13).
Since, Y_i, the number of responses follows from binomial distribution with parameters (n_i, π_i), the complete likelihood function can be written as

$$L(\pi_1, \ldots, \pi_N; y_1, \ldots, y_N) = \prod_{i=1}^{N} \binom{n_i}{y_i} \pi_i^{y_i} (1 - \pi_i)^{n_i - y_i}, \tag{2.20}$$

In the above equation, n_i subjects are exposed to x_i units of drug A and z_i units of drug B. The log-likelihood of model MM_1 after substituting π_i from (2.15) can be derived as

$$l(\beta_1, \beta_2, \rho) = \sum_{i=1}^{N}(\beta_1 + \beta_2 d_i)y_i - \sum_{i=1}^{N} n_i \log(1 + \exp(\beta_1 + \beta_2 d_i)) + \sum_{i=1}^{N} \log \binom{n_i}{y_i}. \qquad (2.21)$$

2.6.2 Estimating Equations

As we mentioned, the maximum likelihood estimates can be obtained by maximizing the maximum likelihood function. We need the estimating equations for maximizing the log likelihood equation. The estimating equations can be found taking the partial derivative of the log-likelihood equation with respect to unknown parameters. We have three unknown parameters in model MM_1 namely β_1, β_2 and ρ. The maximum likelihood estimating equations are,

$$\begin{aligned}
\frac{\delta l(\beta_1, \beta_2, \rho)}{\delta \beta_1} &= \sum_{i=1}^{N} \left(y_i - \frac{n_i \exp(\beta_1 + \beta_2 \log(x_i + \rho z_i))}{1 + \exp(\beta_1 + \beta_2 \log(x_i + \rho z_i))} \right) = 0, \\
\frac{\delta l(\beta_1, \beta_2, \rho)}{\delta \beta_2} &= \sum_{i=1}^{N} \log(x_i + \rho z_i) \left(y_i - \frac{n_i \exp(\beta_1 + \beta_2 \log(x_i + \rho z_i))}{1 + \exp(\beta_1 + \beta_2 \log(x_i + \rho z_i))} \right) = 0, \\
\frac{\delta l(\beta_1, \beta_2, \rho)}{\delta \rho} &= \sum_{i=1}^{N} \frac{\beta_2 z_i}{(x_i + \rho z_i)} \left(y_i - \frac{n_i \exp(\beta_1 + \beta_2 \log(x_i + \rho z_i))}{1 + \exp(\beta_1 + \beta_2 \log(x_i + \rho z_i))} \right) = 0.
\end{aligned} \qquad (2.22)$$

The solutions $\hat{\beta}_1$, $\hat{\beta}_2$ and $\hat{\rho}$ of (2.22) are called maximum likelihood estimates of β_1 , β_2 and ρ. From (2.15), we get $\hat{\pi}_i$ is

$$\hat{\pi}_i = \frac{\exp(\hat{\beta}_1 + \hat{\beta}_2 \hat{d}_i)}{1 + \exp(\hat{\beta}_1 + \hat{\beta}_2 \hat{d}_i)}, \qquad (2.23)$$

and hence the fitted values of y_i are,

$$\hat{y}_i = n_i \frac{\exp(\hat{\beta}_1 + \hat{\beta}_2 \hat{d}_i)}{1 + \exp(\hat{\beta}_1 + \hat{\beta}_2 \hat{d}_i)}. \qquad (2.24)$$

The estimating equations in (2.22)can be rewritten as

$$\begin{aligned} \sum_{i=1}^{N}(y_i - \hat{y}_i) &= 0, \\ \sum_{i=1}^{N}\log(x_i + \rho z_i)(y_i - \hat{y}_i) &= 0, \\ \sum_{i=1}^{N}\frac{\beta_1 z_i}{(x_i + \rho z_i)}(y_i - \hat{y}_i) &= 0, \end{aligned} \tag{2.25}$$

where $\hat{d}_i = \log(x_i + \hat{\rho} z_i)$.

2.6.3 Iteration methods used for estimating the parameters

The estimating equations are nonlinear in parameters β_1, β_2 and ρ. The exact closed-form expressions of the solutions of (2.22) do not exist. Some popular iterative methods are commonly used in the literature, textbooks and software packages for solving nonlinear equation (2.22). We consider Newton-Raphson and Fisher Scoring iteration methods for estimating the parameters in model MM_1 and Model MM_2 in this chapter.

Newton-Raphson Method

The Newton-Raphson is frequently used iterative method for solving nonlinear equations. This method starts with an initial values for the solution. It improves the initial values through iterations. It improves the solution at the next step by approximating the objective function in a neighborhood of the initial value by a second degree polynomial and then finding the location of that polynomial's maximum value. Then it approximate the function in a neighborhood of the solution at second step by another second degree polynomial and the solution at the third step is the location of its maximum. In this manner, the method generates a sequence of solutions. These converge to the location of its maximum when the function is well behaved and initial value is good choice. Mathematically, the Newton-

Raphson method determines the value of $\hat{\theta} = (\hat{\beta}_1, \hat{\beta}_2, \hat{\rho})$ at which the log likelihood function in (2.19) is maximum. We define

$$u^{'} = (\frac{\delta l(\theta)}{\delta \beta_1}, \frac{\delta l(\theta)}{\delta \beta_2}, \frac{\delta l(\theta)}{\delta \rho}). \tag{2.26}$$

Let H is the Hessian matrix,

$$H = \begin{pmatrix} \frac{\delta^2 l(\theta)}{\delta^2 \beta_1} & \frac{\delta^2 l(\theta)}{\delta \beta_1 \delta \beta_2} & \frac{\delta^2 l(\theta)}{\delta \beta_1 \delta \rho} \\ \frac{\delta^2 l(\theta)}{\delta \beta_1 \delta \beta_2} & \frac{\delta^2 l(\theta)}{\delta^2 \beta_2} & \frac{\delta^2 l(\theta)}{\delta \beta_2 \delta \rho} \\ \frac{\delta^2 l(\theta)}{\delta \beta_1 \delta \rho} & \frac{\delta^2 l(\theta)}{\delta \beta_2 \delta \rho} & \frac{\delta^2 l(\theta)}{\delta^2 \rho} \end{pmatrix}. \tag{2.27}$$

We define $u^{(t)}$ and $H^{(t)}$ are u and H evaluated atθ= $\theta^{(t)}$, where t is the number of iterations. At the t^{th} step of iteration, the solutions are

$$\theta^{(t+1)} = \theta^{(t)} - (H^{(t)})^{-1} u^{(t)}, \tag{2.28}$$

when $H^{(t)}$ is nonsingular. Iteration proceeds until changes in $l(\theta^{(t)})$ between successive cycles are sufficiently small.

Fisher Scoring Method

Fisher-Scoring is an alternative and very popular iterative methods for solving non-linear equations. This method resembles the Newton-Raphson method with the distinction that Fisher scoring method uses the expected value of the Hessian matrix whereas Newton-Raphson uses the matrix itself. We define I, the expected information matrix

$$I = \begin{pmatrix} -E(\frac{\delta^2 l(\theta)}{\delta^2 \beta_1}) & -E(\frac{\delta^2 l(\theta)}{\delta \beta_1 \delta \beta_2}) & -E(\frac{\delta^2 l(\theta)}{\delta \beta_1 \delta \rho}) \\ -E(\frac{\delta^2 l(\theta)}{\delta \beta_1 \delta \beta_2}) & -E(\frac{\delta^2 l(\theta)}{\delta^2 \beta_2}) & -E(\frac{\delta^2 l(\theta)}{\delta \beta_2 \delta \rho}) \\ -E(\frac{\delta^2 l(\theta)}{\delta \beta_1 \delta \rho}) & -E(\frac{\delta^2 l(\theta)}{\delta \beta_2 \delta \rho}) & -E(\frac{\delta^2 l(\theta)}{\delta^2 \rho}) \end{pmatrix}. \tag{2.29}$$

The estimation of parameters θ is given by

$$\theta^{(t+1)} = \theta^{(t)} - (I^{(t)})^{-1} u^{(t)}, \tag{2.30}$$

where t is the number of iteration and $u^{(t)}$ is the same defined in the Newton Raphson Method. Iteration will converge if the differences of two successive values of $l(\theta^{(t)})$ are sufficiently small.

2.7 Maximum Likelihood estimation: Model MM_2

2.7.1 Likelihood

The maximum likelihood estimates of the parameters β_1 and β_2 are $\hat{\beta}_1$ and $\hat{\beta}_2$ can be evaluated satisfying

$$(\hat{\beta}_1, \hat{\beta}_2) = \arg\max_{\beta_1,\beta_2} l(\beta_1, \beta_2), \tag{2.31}$$

where $l(\beta_1, \beta_2)$ is the log likelihood function of model MM_2 defined in (2.16). Model MM_2 describes the joint action of two drugs; when relative potency $\rho = \rho_0$ is known. Combining (2.11) and (2.18), log likelihood function of the MM_2 is written as

$$l(\beta_1, \beta_2) = \sum_{i=1}^{N} (\beta_1 + \beta_2 d_{0i}) y_i - \sum_{i=1}^{N} n_i \log(1 + \exp(\beta_1 + \beta_2 d_{0i})) + \sum_{i=1}^{N} \log \binom{n_i}{y_i}, \tag{2.32}$$

where n_i, y_i and d_{0i} are same as defined in section (2.3.2). We need to find the estimating equations for estimating these unknown parameters taking derivative of the log likelihood function with respect to β_1 and β_2.

2.7.2 Estimating Equations: MM_2

Model MM_2 has only two unknown parameters. The estimating equations are obtained by maximizing the log likelihood $l(\beta_1, \beta_2)$ in (2.33) with respect to β_1 and β_2. The equations are

$$\begin{aligned} \frac{\delta l(\beta_1, \beta_2)}{\delta \beta_1} &= \sum_{i=1}^{N} \left(y_i - n_i \frac{\exp(\beta_1 + \beta_2 d_{0i})}{1 + \exp(\beta_1 + \beta_2 d_{0i})} \right) = 0, \\ \frac{\delta l(\beta_1, \beta_2)}{\delta \beta_2} &= \sum_{i=1}^{N} d_{0i} \left(y_i - n_i \frac{\exp(\beta_1 + \beta_2 d_{0i})}{1 + \exp(\beta_1 + \beta_2 d_{0i})} \right) = 0. \end{aligned} \tag{2.33}$$

The solutions $\hat{\beta}_1$ and $\hat{\beta}_2$ of (2.32) are called maximum likelihood estimates of β_1 and β_2. From (2.17), we get $\hat{\pi}_i$ as

$$\hat{\pi}_i = \frac{\exp(\hat{\beta}_1 + \hat{\beta}_2 \hat{d_{0i}})}{1 + \exp(\hat{\beta}_1 + \hat{\beta}_2 \hat{d_{0i}})}, \tag{2.34}$$

and hence the fitted values of y_i are

$$\hat{y}_i = n_i \frac{\exp(\hat{\beta}_1 + \hat{\beta}_2 \hat{d_{0i}})}{1 + \exp(\hat{\beta}_1 + \hat{\beta}_2 \hat{d_{0i}})}. \tag{2.35}$$

These equations are further written as

$$\begin{aligned} \sum_{i=1}^{N} (y_i - \hat{y}_i) &= 0, \\ \sum_{i=1}^{N} d_{0i}(y_i - \hat{y}_i) &= 0. \end{aligned} \tag{2.36}$$

2.7.3 Iteration methods

The estimating equations in (2.36) are nonlinear in parameters β_1 and β_2. And there is no closed form solution for them. Hence the iteration methods are used to estimate the parameters. We have already discussed some of the standard iterative methods for the Model MM_1 in the earlier chapters. We will use the same iterative methods to estimate the parameters for model MM_2. Since we have only two unknown parameters in model MM_2, the Hessian matrix in Newton-Raphson method and the Information matrix in Fisher Scoring method will be different than (2.29) and (2.30). The new Hessian matrix and Information matrix can be written as

$$H = \begin{pmatrix} \frac{\delta^2 l(\theta)}{\delta^2 \beta_1} & \frac{\delta^2 l(\theta)}{\delta \beta_1 \delta \beta_2} \\ \frac{\delta^2 l(\theta)}{\delta \beta_1 \delta \beta_2} & \frac{\delta^2 l(\theta)}{\delta^2 \beta_2} \end{pmatrix}, \tag{2.37}$$

and

$$I = \begin{pmatrix} -E(\frac{\delta^2 l(\theta)}{\delta^2 \beta_1}) & -E(\frac{\delta^2 l(\theta)}{\delta \beta_1 \delta \beta_2}) \\ -E(\frac{\delta^2 l(\theta)}{\delta \beta_1 \delta \beta_2}) & -E(\frac{\delta^2 l(\theta)}{\delta^2 \beta_2}) \end{pmatrix}, \tag{2.38}$$

where $\theta = (\beta_1, \beta_2)$ in Model MM_2.

2.8 Results obtained from the above methods

For the Giltinan (1998) data presented in Table (5.1) in Chapter 5, we present the standard initial values used by the statistical softwares and numerical values of parameter estimates using Newton-Raphson and Fisher Scoring iterative methods for model MM_1 in Table (2.1) and Table (2.3). The estimation procedures are performed using SAS 9.2.

In Model MM_2, the relative potency ρ is known. We have taken the known $\rho = 0.89$ for

Table 2.1: The Initial values of the parameters of Model MM_1

Model	Iteration method	Initial β_1	Initial β_2	Initial ρ
MM_1	Newton-Raphson	0	0	0.1
MM_1	Fisher Scoring	0	0	0.1

Table 2.2: The parameter estimates of Model MM_1

Model	Iteration method	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\rho}$
MM_1	Newton-Raphson	-4.6348929151	1.7352218691	0.8961564623
MM_1	Fisher Scoring	-4.6348929151	1.7352218691	0.8961564623

Giltinan data and then estimated the parameters (β_1, β_2). The parameter estimates obtain for MM_1 and MM_2 are presented in Table (2.2) and Table (2.4) respectively.

The parameter estimates obtained by Newton-Raphson and Fisher Scoring methods are identical up to 7 decimal places for MM_1. The parameter estimates using Newton-Raphson and Fisher Scoring methods are identical up to two decimal places for MM_2.

Table 2.3: The Initial values of the parameters of Model MM_2

Model	Iteration method	Initial β_1	Initial β_2
MM_2	Newton-Raphson	0	0
MM_2	Fisher Scoring	0	0

Table 2.4: The parameter estimates of Model MM_2

Model	Iteration method	Initial β_1	Initial β_2
MM_2	Newton-Raphson	-4.6348883598	1.7352202923
MM_2	Fisher Scoring	-4.628610787	1.735021315

Chapter 3

Estimation when relative Potency is known: Initial values and New Methods

3.1 Summary

In this chapter, we consider the dose-response assessment of a single drug experiment. We proposed two methods of finding the initial values of parameters of the maximum likelihood estimating equations (MLEE) for a logistic regression model using two criterion functions. Our proposed approach starts with all possible pairs of doses from the doses considered in the experiment. It then chooses the pair giving the optimum value of a criterion function and the corresponding exact solutions for the parameters based on two observations in the pair as the initial values of parameters for solving MLEE for all observations. We then use the initial values and the corresponding criterion functions to obtain the final solutions of MLEE. We use our estimates to determine a lethal dose like ED_{50}. We illustrate our two methods of finding the initial values with an observed beetle mortality data (Dobson, 2002, page 119; originally from Bliss,1935). We also present a simulation study to illustrate our proposed methods.

3.2 Model for single drug experiment

We consider a single drug is applied to the subjects. Mathematically, our new model can be seen as a special case of the model MM_2, since the model MM_2 describes the dose-response model when the relative potency ρ is known and $\rho = 0$. We call this model MM_3 which is derived from the model MM_2, substituting $\rho = 0$. The MM_3 can be expressed as

$$MM_3 : \theta_i = \beta_1 + \beta_2 x_i, \tag{3.1}$$

where β_1 and β_2 are unknown parameters and x_i is the drug amount given to the subjects. We consider a dose-mortality trial where the i^{th} group of n_i subjects are exposed to a drug amount x_i for a specified period of time, $i = 1, \ldots, N$. The mortality count for the i^{th} group at the end of the period is $y(x_i)$. We assume that the mortality probability for a subject in the i^{th} group is $\pi(x_i)$, the dependence of $\pi(x_i)$ on x_i can be described by

$$\pi(x_i) = \frac{e^{\beta_1+\beta_2 x_i}}{1 + e^{\beta_1+\beta_2 x_i}}. \tag{3.2}$$

3.2.1 Likelihood Equation

The likelihood of the collected observations can be described as

$$L = \prod_{i=1}^{N} \binom{n_i}{y(x_i)} [\pi(x_i)]^{y(x_i)} [1 - \pi(x_i)]^{n_i - y(x_i)}. \tag{3.3}$$

The log-likelihood function is

$$l(\beta_1, \beta_2) = log_e L, \tag{3.4}$$

Combining (3.2) and (3.3), the log-likelihood becomes

$$l(\beta_1, \beta_2) = \sum_{i=1}^{N} y_i(\beta_1 + \beta_2 x_i) - n_i \log(1 + \exp(\beta_1 + \beta_2 x_i)) + \log \binom{n_i}{y(x_i)}. \tag{3.5}$$

3.2.2 Estimation

We want to estimate the dose which achieves 50% subject mortality, is known as ED_{50} and is equal to

$$ED_{50} = -\frac{\beta_1}{\beta_2}. \tag{3.6}$$

The estimation of the unknown parameters (β_1 and β_2) is usually done by the maximum likelihood estimation procedure. The maximum likelihood estimates of $\hat{\beta}_1$ and $\hat{\beta}_2$ satisfy

$$\left(\hat{\beta}_1, \hat{\beta}_2\right) = \arg\max_{\beta_1,\beta_2} \quad l(\beta_1, \beta_2). \tag{3.7}$$

We obtain the following score functions after taking the derivative of the log-likelihood in (3.5) with respect to β_1, β_2 and setting them equal to 0.

$$\frac{\delta l(\beta_1, \beta_2)}{\delta \beta_1} = \sum_{i=1}^{N} \left(y_i - \frac{n_i \exp(\beta_1 + \beta_2 x_i)}{1 + \exp(\beta_1 + \beta_2 x_i)} \right) = 0,$$

$$\frac{\delta l(\beta_1, \beta_2)}{\delta \beta_2} = \sum_{i=1}^{N} \left(y_i x_i - \frac{n_i x_i \exp(\beta_1 + \beta_2 x_i)}{1 + \exp(\beta_1 + \beta_2 x_i)} \right) = 0. \tag{3.8}$$

The estimating equations can be rewritten as

$$\sum_{i=1}^{N} (y(x_i) - \hat{y}(x_i)) = 0,$$

$$\sum_{i=1}^{N} x_i \left(y(x_i) - \hat{y}(x_i)\right) = 0, \tag{3.9}$$

where

$$\hat{y}(x_i) = n_i \hat{\pi}(x_i) = n_i \frac{e^{\hat{\beta}_1 + \hat{\beta}_2 x_i}}{1 + e^{\hat{\beta}_1 + \hat{\beta}_2 x_i}}. \tag{3.10}$$

The $\hat{\beta}_1$ and $\hat{\beta}_2$ are solutions of the equations in (3.8). The exact solution of (3.8) do not exist since the equations are non-linear in variables. The numerical methods like Newton-Raphson and Fisher scoring are commonly used in the literature, textbooks, and software packages [Morgan(1992), Dobson (2002), Givens and Hoeting (2005)]. The iterative procedure for finding the maximum likelihood estimates $\hat{\beta}_1$ and $\hat{\beta}_2$ from (3.8) require the use of initial

values. Standard softwares usually assume $\log(\frac{p}{1-p})$ as the initial value for β_1 and 0 for β_2, where $p = \frac{\sum_{i=1}^{N} y(x_i)}{\sum_{i=1}^{N} n_i}$. An alternative choice is 0 for both β_1 and β_2. We do not have sufficient justifications for such choices of the initial values in the iterative process and whether one choice is better over other. We feel strongly about the need for such justifications on any choice of the initial values, particularly in view of solving the estimating equations. An advantage of this new choice is that the initial values chosen are always close to the values for the final solution of the estimating equations right from the beginning of our iterative process. Moreover, the new choice has a solid logical basis. In the next section, we describe the new methodology to find the initial values of β_1 and β_2 using a very logical and systematic way.

3.3 Initial values

The new method starts with the special situation $N = 2$, i.e., we consider only two doses applied to the subjects. The score functions for $N = 2$ can be written as,

$$\frac{n_1 \exp(\beta_1 + \beta_2 x_1)}{1 + \exp(\beta_1 + \beta_2 x_1)} + \frac{n_2 \exp(\beta_1 + \beta_2 x_2)}{1 + \exp(\beta_1 + \beta_2 x_2)} = y_1 + y_2,$$

$$\frac{n_1 x_1 \exp(\beta_1 + \beta_2 x_1)}{1 + \exp(\beta_1 + \beta_2 x_1)} + \frac{n_2 x_2 \exp(\beta_1 + \beta_2 x_2)}{1 + \exp(\beta_1 + \beta_2 x_2)} = y_1 x_1 + y_2 x_2. \tag{3.11}$$

We now substitute $\exp(-\beta_1) = a$ and $\exp(-\beta_2) = b$ and the score functions reduce to,

$$\frac{n_1}{1 + ab^{x_1}} + \frac{n_2}{1 + ab^{x_1}} = y_1 + y_2,$$

$$\frac{n_1 x_1}{1 + ab^{x_1}} + \frac{n_2 x_2}{1 + ab^{x_1}} = y_1 x_1 + y_2 x_2. \tag{3.12}$$

We can obtain exact analytic solution of a and b from (3.12). Hence exact analytic solution exist for $\hat{\beta}_1$ and $\hat{\beta}_2$.

It follows from equation (3.12)

$$\frac{n_1}{y(x_1)} - 1 = e^{-\hat{a} - \hat{b} x_1},$$

$$\frac{n_2}{y(x_2)} - 1 = e^{-\hat{a}_1 - \hat{b}x_2}. \tag{3.13}$$

The solution of $\hat{a}$ and $\hat{b}$ is given as,

$$\hat{b}^{x_1 - x_2} = e^{-\hat{\beta}_2(x_1 - x_2)} = \frac{\frac{n_1}{y(x_1)} - 1}{\frac{n_2}{y(x_2)} - 1},$$

$$\hat{a}^{x_1 - x_2} = e^{-\hat{\beta}_1(x_1 - x_2)} = \frac{\left(\frac{n_2}{y(x_2)} - 1\right)^{x_1}}{\left(\frac{n_1}{y(x_1)} - 1\right)^{x_2}}. \tag{3.14}$$

The exact analytic expression of $\hat{\beta}_1$ and $\hat{\beta}_2$ can be derived easily from (3.14). The estimates are written as,

$$-\hat{\beta}_1(x_1 - x_2) = \left[x_2 \log_e \frac{y(x_1)}{n_1 - y(x_1)} - x_1 \log_e \frac{y(x_2)}{n_2 - y(x_2)}\right],$$

$$\hat{\beta}_2(x_1 - x_2) = \left[\log_e \frac{y(x_1)}{n_1 - y(x_1)} - \log_e \frac{y(x_2)}{n_2 - y(x_2)}\right]. \tag{3.15}$$

Hence an estimator of ED_{50} is

$$\frac{-\hat{\beta}_1}{\hat{\beta}_2} = \frac{x_2 \log_e \frac{y(x_1)}{n_1 - y(x_1)} - x_1 \log_e \frac{y(x_2)}{n_2 - y(x_2)}}{log_e \frac{y(x_1)}{n_1 - y(x_1)} - \log_e \frac{y(x_2)}{n_2 - y(x_2)}}. \tag{3.16}$$

The exact closed-form expression of $\hat{\beta}_1$ and $\hat{\beta}_2$ do not exist for for $N \geq 3$. We use the above observation from $N = 2$ for the estimation of the parameters when $N \geq 3$.

We consider for general N, all S $\left(\leq \binom{N}{2}\right)$ subsets of two groups with $0 < y(x_1) < n_1$ and $0 < y(x_2) < n_2$. For the group pair u, $u = 1, \ldots, S$ we calculate $\hat{\beta}_1$ and $\hat{\beta}_2$ from (3.14). We denote them $\hat{\beta}_{1u}$ and $\hat{\beta}_{2u}$. If the pair u consists of group i_1 and group i_2, we obtain from (3.14)

$$-\hat{\beta}_{1u}(x_{i_1} - x_{i_2}) = \left[x_{i_2} \log_e \frac{y(x_{i_1})}{n_{i_1} - y(x_{i_1})} - x_{i_1} \log_e \frac{y(x_{i_2})}{n_{i_2} - y(x_{i_2})}\right],$$

$$\hat{\beta}_{2u}(x_{i_1} - x_{i_2}) = \left[\log_e \frac{y(x_{i_1})}{n_{i_1} - y(x_{i_1})} - \log_e \frac{y(x_{i_2})}{n_{i_2} - y(x_{i_2})}\right]. \tag{3.17}$$

We obtain from (3.2) $\hat{\pi}_u(x_i)$ by substituting $\hat{\beta}_{1u}$ for β_1 and $\hat{\beta}_{2u}$ for β_2. Finally, we get $\hat{y}_u(x_i)$ from(3.10) by substituting $\hat{\pi}_u(x_i)$ for $\hat{\pi}(x_i)$. We write

$$L^{(1)} = \sum_{i=1}^{N} \hat{y}(x_i), \quad L^{(2)} = \sum_{i=1}^{N} x_i \hat{y}(x_i),$$

$$R^{(1)} = \sum_{i=1}^{N} y(x_i), \quad R^{(2)} = \sum_{i=1}^{N} x_i y(x_i). \tag{3.18}$$

We define two criterion functions for finding the initial values of $\hat{\beta}_1$ and $\hat{\beta}_2$ based on the above idea. The criterion functions are defined below

$$\triangle = |L_u^{(1)} - R^{(1)}| + |L_u^{(2)} - R^{(2)}|, \tag{3.19}$$

$$l = \sum_{i=1}^{N} y_i(\beta_1 + \beta_2 x_i) - n_i \log(1 + \exp(\beta_1 + \beta_2 x_i)) + \binom{n_i}{y_i}. \tag{3.20}$$

The criterion function $\triangle$ is proposed in (3.19) for finding the accurate final solution of MLEE in (3.8). We obtain the most accurate final solution of MLEE when the numerical value of $\triangle$ is equal to zero. So the smaller numerical value to $\triangle$ means the better accuracy on the final solutions of MLEE in (3.8).

The criterion function l is proposed in (3.20) because we obtain the most accurate fitted observations in (3.10) when the numerical value of l is maximum, or equivalently the numerical value of $(-l)$ is minimum.

For $u = 1, \ldots, S$, we find from (3.18) , $L^{(1)}$, $L^{(2)}$, $R^{(1)}$, $R^{(2)}$. Similarly we find for $u = 1, \ldots S$, $\triangle_u$ and l_u from (3.19) and (3.20).

We calculate for $u = 1, \ldots, S$ to calculate

$$u_1 = \arg\min_u \triangle_u,$$

$$u_2 = \arg\max_u l_u = \arg\min_u(-l_u). \tag{3.21}$$

to obtain two possible sets of initial values $\hat{\beta}_{1u}$ and $\hat{\beta}_{2u}$ of β_1 and β_2, respectively, one set of initial value from $u = u_1$ using $\triangle$ criterion function and another set of initial value from

Table 3.1: The Observed Beetle Mortality Data

Group (i)	Dose (x_i)	Number of beetles (n_i)	Number of Beetle Mortality ($y(x_i)$)
1	1.6907	59	6
2	1.7242	60	13
3	1.7552	62	18
4	1.7842	56	28
5	1.8113	63	52
6	1.8369	59	53
7	1.8610	62	61
8	1.8839	60	60

$u = u_2$ using l criterion function. In the next section, we take one data set to illustrate our described method.

3.3.1 An observed beetle mortality data

We present the beetle mortality data (Dobson (2002), page 119; originally from Bliss (1935)) in Table 3.1. The numbers of beetle mortality were observed (y values) when the groups of beetles were exposed to gaseous carbon disulphide at various doses measured in the log scale (x values). The numbers of beetles in the groups considered are the n values.

We have $N = 8$ groups of doses. For the group 8, we have $y(x_8) = n_8$. Therefore, we will not take the group in forming the group pairs. Consequently, we have $S = \binom{8}{2} - 7 = \binom{7}{2} = 21$. We have from Table 3.1, $R^{(1)} = 291$ and $R^{(2)} = 532.2083$. In Table 3.2, we present the numerical values of β_{1u}, β_{2u} , $\triangle_u$ and l_u for $u = 1, \ldots 21$.

From Table 3.2, we observe that $\triangle_u$ is minimum at $u_1 = 15$ which is 3^{rd} and 7^{th} dose from the Beetle data, similarly l is maximum at the pair $u_2 = 10$ which is 2^{nd} and 6^{th} dose from the data. We remember that we got u_1 from the criterion function $\triangle$ and u_2 from another criterion function l. Table 3.3 presents the four initial values, labeled by I_1, I_2, I_3 and I_4 of β_1 and β_2 as well as the numerical values of $\triangle$, l. In this table we present the numerical value of ED_{50} for I_1 and I_2. The initial values labeled by I_1 and I_2 represent the groups

Table 3.2: The numerical value of $\beta_{1u}, \beta_{2u}, \triangle_u$ and l_u

u	Pair	β_{1u}	β_{2u}	$\triangle_u$	l_u
1	(1,2)	-47.26390952	26.66669254	15.887702808	-22.867605143
2	(1,3)	-35.85398858	19.91805532	168.342338336	-55.066025005
3	(1,4)	-41.57152500	23.29981224	84.452813350	-33.094452175
4	(1,5)	-54.49603676	30.94428599	52.660997436	-22.343838473
5	(1,6)	-52.56491827	29.80208542	36.136253396	-21.353149001
6	(1,7)	-64.61834011	36.93133475	122.635812612	-37.678204257
7	(2,3)	-23.05352182	12.62517317	261.410614322	-102.349265395
8	(2,4)	-38.21751179	21.41997074	87.787626111	-36.964042009
9	(2,5)	-57.47603869	32.58951424	41.983011552	-20.808719716
10	(2,6)	-54.27689703	30.73407887	26.044500842	-20.223575463
11	(2,7)	-69.29621820	39.44497155	87.916809572	-30.028626959
12	(3,4)	-54.99137429	30.82130607	74.101113252	-24.846009639
13	(3,5)	-77.45828005	43.62150306	14.488150434	-23.398215771
14	(3,6)	-66.89858265	37.60526708	37.642859856	-21.042366568
15	(3,7)	-83.92061317	47.30332458	3.332652221	-26.713599605
16	(4,5)	-102.26879325	57.31913084	58.703389201	-46.487813019
17	(4,6)	-73.75593145	41.33837655	65.346208667	-26.884243201
18	(4,7)	-95.50287954	53.52700344	59.838270704	-40.660238789
19	(5,6)	-42.68086158	24.42124994	101.569072648	-35.263354320
20	(5,7)	-91.65481635	51.45926395	42.372869149	-34.726327307
21	(6,7)	-145.10437022	80.18014190	211.481591055	-188.439733656

Table 3.3: The initial values of β_1 and β_2 with the values of $\triangle$, l and ED_{50}

Label	Group	Initial β_1	Initial β_2	$\triangle$	l	ED_{50}
I_1	u_1	-83.920613	47.303325	3.332651	-26.713600	1.774095
I_2	u_2	-54.276897	30.734079	26.044501	-20.223575	1.766017
$I3$		0	0	151.285350	-165.883525	-
$I4$		0.426299	0	10.195562	-155.200244	-

u_1 and u_2 respectively, defined in (3.21). The initial values $(0, 0)$ and $(\log \frac{p}{1-p}, 0)$, where $\log \frac{p}{1-p} = 0.426299$, are labeled by I_3 and I_4, respectively.

The initial values labeled I_1 are better over the other initial values in Table 2 with respect to the criterion function $\triangle$. On the other hand, the initial value labeled I_2 are better over the other initial values in Table 3.3 with respect to the criterion function l. Hence the initial values labeled I_1 are better over the other initial values in Table 3.3 for achieving more accurate final solutions of Maximum likelihood estimating equations (MLEE) in (3.8) and the initial values labeled I_2 are better over the other initial values in Table 3.3 for achieving more accurate fitted observations in (3.9). The numerical values of ED_{50} are also fairly close for u_1 and u_2.

3.4 Final solutions

We want to investigate the effect of the initial values and the criterion functions for determining the initial values to the final solutions of MLEE as well as the values of ED_{50}. For this purpose, we present two methods for obtaining the final solutions as well as ED_{50}. First method uses $\triangle$ as the criterion function to perform search algorithm while second method uses l as the criterion function to perform search algorithm using our initial values.

3.4.1 Method 1 (M1)

Method 1 uses $\triangle$ as the criterion function for performing the search algorithm to achieve the final answer of MLEE using the initial values I_1 and I_2. We use MATLAB to perform

Table 3.4: Final Solutions of β_1 and β_2 using Method 1 with the values $\triangle$, l^* and ED_{50}

Method	Initial Value	Final β_1	Final β_2	$\triangle$ x 10^6	l^*	Final ED_{50}
M1	I_1	-60.717474	34.270337	0.769880	-186.235403	1.771721
M1	I_2	-60.717454	34.270325	0.929338	-186.235403	1.771721
M1	I_3	-60.717455	34.270326	0.021737	-186.235403	1.771721
M1	I_4	-60.717455	34.270326	0.022106	-186.235403	1.771721

the search algorithm. We start with the initial values labeled either I_1 or I_2.Then use the optimset function in MATLAB with $\triangle$ criterion function in TolFun option and the parameters β_1 and β_2 in TolX option, the chosen initial values in fminsearch function to perform the iterative process with the stopping rule requiring that the iteration stops when two consecutive $\triangle$ values as well as two consecutive values of each β_1 and β_2 simultaneously become less than or equal to a specific small value. We have chosen this value to be 10^{-6} in our calculations. If

$$|\beta_{1_v} - \beta_{1_{v-1}}| \leq 10^{-6}, \quad |\beta_{2_v} - \beta_{2_{v-1}}| \leq 10^{-6}, \tag{3.22}$$

and

$$|\triangle_v - \triangle_{v-1}| \leq 10^{-6}, \tag{3.23}$$

are true simultaneously then we will get the final estimate of MLEE, where $\triangle_v$ and $\triangle_{v-1}$ are the values of criterion function $\triangle$ in (3.18) at the v and $(v-1)$ stages of iteration respectively. Similarly, β_{1_v} and $\beta_{1_{v-1}}$ are the values of β_1 at v and $(v-1)$ stages of iteration respectively and β_{2_v} and $\beta_{2_{v-1}}$ are the values of β_2 at v and $(v-1)$ stages of iteration respectively. Table 3 presents the final solutions of β_1 and β_2 obtained from M1 with the initial values I_1, I_2, I_3 and I_4. Table 3.4 also presents the numerical values of $\triangle$, l^* and ED_{50} for M1 using four initial values. The numerical values of the final solutions of both β_1 and β_2 are identical up to at least four decimal places and their ED_{50} values are identical up to sixth decimal places.

Table 3.5: Final Solutions of β_1 and β_2 using Method 2 with the values $\triangle$, l^* and ED_{50}

Method	Initial Value	Final β_1	Final β_2	$\triangle$ x 10^6	l^*	Final ED_{50}
M2	$I1$	-60.717471	34.270335	2.706614	-186.235403	1.771721
M2	$I2$	-60.717454	34.270325	1.165784	-186.235403	1.771721
M2	$I3$	-60.717456	34.270326	2.313600	-186.235403	1.771721
M2	$I4$	-60.717455	34.270326	2.461417	-186.235403	1.771721

3.4.2 Method 2 (M2)

Method 2 uses l as the criterion function for performing the search algorithm to achieve the final answer of MLEE using the initial values I_1 and I_2.We start with the initial values either I_1 or I_2. Then we use the optimset function in MATLAB with the l criterion function in TolFun option and the parameters β_1 and β_2 in TolX option, the chosen initial values in fminsearch function to perform the iterative process with the stopping rule requiring that the iteration stops when two consecutive l values as well as two consecutive values of each of β_1 and β_2 simultaneously become less than or equal to a specified small value as in Method 1. In the computation of l at the stages of iteration, it is unnecessary to keep the terms $\binom{n_i}{y(x_i)}$ because they do not depend on β_1 and β_2. We therefore exclude this term from l in (3.5) and perform the iteration. The new term is now denoted by l^*. If

$$|\beta_{1_v} - \beta_{1_{v-1}}| \leq 10^{-6}, \quad |\beta_{2_v} - \beta_{2_{v-1}}| \leq 10^{-6}, \tag{3.24}$$

and

$$|l_v^* - l_{v-1}^*| \leq 10^{-6}, \tag{3.25}$$

are true simultaneously then we will get the final estimate of MLEE, where l_v^* and l_{v-1}^* are the values of criterion function l^* at the v and $(v-1)$ stages of iteration respectively. Table 3.5 presents the final solutions of β_1 and β_2 obtained from M2 with the initial values I_1, I_2, I_3 and I_4. Table 3.5 also presents the numerical values of $\triangle$, l^* and ED_{50} for M2 using four initial values. The numerical values of the final solutions of both β_1 and β_2 are identical

up to at least four decimal places and their ED_{50} values are identical up to sixth decimal places. Our method is comparable with other methods. We have done some comparison with some standard softwares in the next chapter. Now we want to discuss some properties of the fitted values.

3.5 Goodness of fit test

In this section, we discuss the goodness of fit to our data. After fitting the logistic regression model, we want to evaluate the goodness of fit of this model (Dobson, 2001). The null and alternative hypotheses for this test are

H_0 : The logistic regression model is a good fit to the data.

H_a : The logistic regression model is not a good fit to the data.

The numerical values of standard Deviance statistic and Chi-square statistics are

$$D = 2\sum_{i=1}^{N}\left[y_i \log\left(\frac{y_i}{\hat{y}_i}\right) + (n_i - y_i)\log\left(\frac{n_i - y_i}{n_i - \hat{y}_i}\right)\right] = 11.23,$$

$$\chi^2 = \sum_{i=1}^{N}\frac{(y_i - \hat{y}_i)^2}{\hat{y}_i} = 4.946178,$$

where $\hat{y}_i$ is defined in (3.10)

The test statistics follow χ^2 distributions with df = (8-2) = 6 under H_0. The p-value for Deviance test is 0.081523 and the p-value for Chi-Square test is 0.550745. We do not reject the null hypothesis for both of cases since our p-values are greater than $\alpha = 0.05$. Therefore, we conclude that there is significance evidence the logistic regression in (3.1) is a good fit to the data.

3.6 Properties of the fitted values

The group pairs of mortality observations formed out of all groups play a central role in finding the initial values discussed in Section (3.3). We now present some properties of the

fitted values in (3.10) obtained from the group pairs of observations.For two group pairs u and $u^{'}$, the exact estimates of the parameters $\hat{\beta}_1$ and $\hat{\beta}_2$ obtained from (3.17) are denoted by ($\hat{\beta}_{1u}$ and $\hat{\beta}_{2u}$)and ($\hat{\beta}_{1u'}$ and $\hat{\beta}_{2u'}$). We have from (3.10)

$$\hat{y}^{(u)}(x_i) = n_i \frac{\exp(\hat{\beta}_{1u} + \hat{\beta}_{2u} x_i)}{1 + \exp(\hat{\beta}_{1u} + \hat{\beta}_{2u} x_i)}, \tag{3.26}$$

$$\hat{y}^{(u^{'})}(x_i) = n_i \frac{\exp(\hat{\beta}_{1u'} + \hat{\beta}_{2u'} x_i)}{1 + \exp(\hat{\beta}_{1u'} + \hat{\beta}_{2u'} x_i)}. \tag{3.27}$$

It follows from (3.26) and (3.27) that

$$\begin{aligned}
\hat{y}^{(u)}(x_i) &= \hat{y}^{(u^{'})}(x_i) \quad \text{if and only if} \quad \hat{\beta}_{1u} + \hat{\beta}_{2u} x_i = \hat{\beta}_{1u'} + \hat{\beta}_{2u'} x_i, \\
\hat{y}^{(u)}(x_i) &> \hat{y}^{(u^{'})}(x_i) \quad \text{if and only if} \quad \hat{\beta}_{1u} + \hat{\beta}_{2u} x_i > \hat{\beta}_{1u'} + \hat{\beta}_{2u'} x_i, \\
\hat{y}^{(u)}(x_i) &< \hat{y}^{(u^{'})}(x_i) \quad \text{if and only if} \quad \hat{\beta}_{1u} + \hat{\beta}_{2u} x_i < \hat{\beta}_{1u'} + \hat{\beta}_{2u'} x_i.
\end{aligned} \tag{3.28}$$

Suppose that a group pair u consists of groups i_1 and i_2 with the mortality observations y_{i_1} and y_{i_2}. We have from (3.10)

$$\hat{y}^{(u)}(x_{i_1}) = y_{i_1}, \quad \hat{y}^{(u)}(x_{i_2}) = y_{i_2}. \tag{3.29}$$

For the final solutions $\hat{\beta}_1$ and $\hat{\beta}_2$ of (3.6), we get $\hat{y}(x_i)$ as given in (3.10) for $i = 1, \ldots, N$. It follows from (3.29) that

$$\begin{aligned}
\frac{\sum_{u=1}^{\binom{N}{2}} \left[\hat{y}^{(u)}(x_{i_1}) + \hat{y}^{(u)}(x_{i_2})\right]}{(N-1)} &= \sum_{i=1}^{N} y_i = \sum_{i=1}^{N} \hat{y}(x_i), \\
\frac{\sum_{u=1}^{\binom{N}{2}} \left[x_{i_1}\hat{y}^{(u)}(x_{i_1}) + x_{i_2}\hat{y}^{(u)}(x_{i_2})\right]}{(N-1)} &= \sum_{i=1}^{N} x_i y_i = \sum_{i=1}^{N} x_i \hat{y}(x_i).
\end{aligned} \tag{3.30}$$

Table 3.6: The Simulated Beetle Mortality Data

Group (i)	Dose (x_i)	Number of beetles (n_i)	Number of Beetle Mortality ($y(x_i)$)
1	1.6907	59	14
2	1.7242	60	26
3	1.7552	62	34
4	1.7842	56	40
5	1.8113	63	47
6	1.8369	59	48
7	1.8610	62	57
8	1.8839	60	55

We denote the set of all $(N-1)$ group pairs u containing the group i_1 by S_{i_1}. From (3.28), we get

$$\left(\sum_{S_{i_1}}\left[\hat{y}^{(u)}(x_{i_1})+\hat{y}^{(u)}(x_{i_2})\right]\right)-(N-2)y_{i_1}=\sum_{i=1}^{N}y_i=\sum_{i=1}^{N}\hat{y}(x_i),$$

$$\left(\sum_{S_{i_1}}\left[x_{i_1}\hat{y}^{(u)}(x_{i_1})+x_{i_2}\hat{y}^{(u)}(x_{i_2})\right]\right)-(N-2)x_{i_1}y_{i_1}=\sum_{i=1}^{N}x_iy_i=\sum_{i=1}^{N}x_i\hat{y}(x_i). \tag{3.31}$$

3.7 A simulated Beetle Mortality data

We generate a data from (3.2) and (3.3) so that $\beta_1=-35, \beta_2=20$, and (n_i, x_i), $i=1,\ldots,8$ are the same as Table 3.1. The data $y(x_i)$'s are given in Table 3.6. We have $N=8$ groups of doses as well. So our $S=\binom{8}{2}=28$. We have $R^{(1)}=321$ and $R^{(2)}=582.5376$. We estimate β_{1u}, β_{2u}, Δ_u and l_u for all $u=1,\ldots,28$ combinations. We find that Δ_u is minimum at $u_1=18$ from this simulated data. Similarly, l_u is maximum at $u_2=18$ combination for this data. We again remember that we got u_1 from criterion function Δ and we got u_2 from criterion function l. The initial values from $(0,0)$ and $(\log\frac{p}{1-p},0)$, where $\log\frac{p}{1-p}=0.696267$ are leveled by I_3 and I_4 respectively. Table 3.7 presents the initial values labeled as I_1, I_2 , I_3 and I_4 of β_1 and β_2 as well as the numerical values of Δ, l and ED_{50}. We use Method 1 and Method 2 to get the final estimates of β_1 , β_2 and ED_{50} and the results are presented in

Table 3.7: The initial values of β_1 and β_2 with the values of $\triangle$, l and ED_{50}

Label	Group	Initial β_1	Initial β_2	$\triangle$	l	ED_{50}
I_1	u_1	-29.860258	17.123071	3.62035404	-17.6672618	1.743861
I_2	u_2	-29.860258	17.123071	3.62035404	-17.6672618	1.743861
I_3		0	0		-101.5552	
I_4		0.696267	0		-74.08311	

Table 3.8: Final Solutions of β_1 and β_2 using Method 1 with the values $\triangle$, l^* and ED_{50} for simulated data

Method	Initial Value	Final β_1	Final β_2	$\triangle$	l^*	Final ED_{50}
M1	I_1	-31.982569	18.32682	4.42993837e-08	-249.313185	1.7451237
M1	I_2	-31.982569	18.32682	4.42993837e-08	-249.313185	1.7451237
M1	I_3	-31.982568	18.32682	1.7181536e-05	-249.313185	1.7451237
M1	I_4	-31.982568	18.326826	3.72867276-06	-249.313185	1.7451231

Table 3.8 and Table 3.9. The numerical values of the final solutions of both β_1 and β_2 are identical up to at least four decimal places and their ED_{50} values are identical up to sixth decimal places. So our method is showing favorable results for simulated data also.

Table 3.9: Final Solutions of β_1 and β_2 using Method 2 with the values $\triangle$, l^* and ED_{50} for simulated data

Method	Initial Value	Final β_1	Final β_2	$\triangle$	l^*	Final ED_{50}
M2	I_1	-31.982569	18.32682698	4.429938e-08	-249.31318	1.745123
M2	I_2	-31.982569	18.32682698	4.429938e-08	-249.31318	1.745123
M2	I_3	-31.982568	18.32682	1.7181536e-05	-249.31318	1.745123
M2	I_4	-31.982568	18.326826	3.72867276-06	-249.31318	1.745123

Chapter 4

Performance comparisons with standard softwares

4.1 Summary

In this chapter, we present the performance comparisons between our proposed methods (M_1, M_2) and the methods using two standard softwares, SAS and R. We present the comparison of numerical values of ED_{50} obtained by our method as well as the numerical values ED_{50} obtained from SAS and R. We also present the performance times of M_1 and M_2 as well as SAS and R. The numerical values of ED_{50} and performance times are also presented for the simulation study. The numerical values of ED_{50} obtained by our approach are almost the same as the numerical values of ED_{50} obtained from SAS and R. This closeness of the estimated ED_{50} values from the comparisons make our proposed methods very special. In addition, the proposed methods M_1 and M_2 stand favorably with SAS and R in terms of the CPU time values.

4.2 Comparison of estimates with SAS

We will compare our methods with two standard numerical methods using two standard softwares. We have considered SAS and R two softwares for the comparison. SAS uses Proc Logistic or Proc Genmod for estimating the maximum likelihood estimates of β_1 and β_2.

Table 4.1: Final Solutions of β_1 and β_2 using SAS PROC LOGIT with the values $\triangle$, l^* and ED_{50}

Method	Initial Value	Final β_1	Final β_2	$\triangle$ x 10^6	l^*	Final ED_{50}
SAS	I1	-60.717455	34.270326	0.000009	-186.235403	1.771721
SAS	I2	-60.717455	34.270326	0.000021	-186.235403	1.771721
SAS	I3	-60.717455	34.270326	0.000008	-186.235403	1.771721
SAS	I4	-60.717454	34.270325	0.888890	-186.235403	1.771721

Table 4.2: Final Solutions of β_1 and β_2 using R with the values $\triangle$, l^* and ED_{50}

Method	Initial Value	Final β_1	Final β_2	$\triangle$ x 10^6	l^*	Final ED_{50}
R	I1	-60.717455	34.270326	0.000011	-186.235403	1.771721
R	I2	-60.717453	34.270325	1.108823	-186.235403	1.771721
R	I3	-60.717455	34.270326	0.000001	-186.235403	1.771721
R	I4	-60.717454	34.270325	0.888862	-186.235403	1.771721

We have used Proc Logistic to obtain the final estimates of $(\hat{\beta}_1, \hat{\beta}_2)$ defined in (3.6). Table 4.1 presents the values of $\hat{\beta}_1, \hat{\beta}_2, \triangle, l$ and ED_{50} values for each initial values I_1, I_2, I_3 and I_4. SAS PROC Logistic use the Newton Raphson iterative method for obtaining the final estimates.

The software R uses GLM procedure for estimating the parameters in a logistic regression model. We use R to obtain the final estimates $(\hat{\beta}_1, \hat{\beta}_2)$ defined in (3.8). R uses the Fisher Scoring iterative method for obtaining the final estimates. Table 4.2 presents the values of $\hat{\beta}_1, \hat{\beta}_2, \triangle, l$ and ED_{50} values for each initial values I_1, I_2, I_3 and I_4 using R software.

4.2.1 Effects on the final solutions and ED_{50} compared with SAS and R

The numerical values of the final solutions of both β_1 and β_2 of our methods are identical up to at least four decimal places and their ED_{50} values are identical up to the sixth decimal places compared with SAS and R results. So our methods are performing favorably compared with all standard methods. We want to compare the performance time of Method 1 and

Method 2 with SAS and R.

4.3 Performance time

We now present the performance times of $M1$ and $M2$ as well as SAS and R. We want to evaluate whether the performance times of $M1$ and $M2$ are comparable to the performance times of SAS and R. In all four programs the stopping rules are different. Furthermore, different runs with the same program give different CPU time values. These issues are major obstacles in our comparisons among the methods with their CPU time values. However, the overall comparisons on closeness of the CPU time values for different programs are meaningful.

In SAS, we have chosen ABSFCONV stopping rule option which is

$$|l_v - l_{v-1}| < \epsilon_1, \tag{4.1}$$

where l_v and l_{v-1} are the values of l in (3.5) at the v and $(v-1)$ stages of iteration, respectively. The ϵ_1 is specified as 10^{-6}. In R, the stopping rule depends on the deviance

$$D = 2\sum_{i=1}^{N}\left[y(x_i)\, log\left(\frac{y(x_i)}{\hat{y}(x_i)}\right) + (n_i - y(x_i))\, log\left(\frac{n_i - y(x_i)}{(n_i - \hat{y}(x_i))}\right)\right], \tag{4.2}$$

and the stopping rule is

$$\frac{|D_v - D_{v-1}|}{|D_v| + 0.1} < \epsilon_2, \tag{4.3}$$

where D_v and D_{v-1} are the values of D in (4.2) at the v and $(v-1)$ stages of iteration, respectively. The ϵ_2 is also specified as 10^{-6} at the beginning. In M1 and M2 using MATLAB, the stopping rule depends on TolX and TolFun in Optimset. The TolX value represents the common values of ϵ_3 and ϵ_4 in the conditions for stopping rules

$$|\beta_1^v - \beta_1^{v-1}| < \epsilon_3,\ |\beta_2^v - \beta_2^{v-1}| < \epsilon_4, \tag{4.4}$$

where (β_1^v, β_2^v) and $(\beta_1^{v-1}, \beta_2^{v-1})$ are the values of (β_1, β_2) at the v and $(v-1)$ stages of iteration, respectively. The ϵ_3 and ϵ_4 are equal and their common value is specified as 10^{-6}. In M1, TolFun generally represents the value of ϵ_5 in the condition for the stopping rules

$$|\Delta^v - \Delta^{v-1}| < \epsilon_5, \tag{4.5}$$

where Δ^v and Δ^{v-1} are the values of Δ at the v and $(v-1)$ stages of iteration, respectively. In M2, TolFun generally represents the value of ϵ_6 in the condition for the stopping rules

$$|l^{*(v)} - l^{*(v-1)}| < \epsilon_6, \tag{4.6}$$

where $l^{*(v)}$ and $l^{*(v-1)}$ are the values of l^* at the v and $(v-1)$ stages of iteration, respectively. We note that

$$l^{*(v)} - l^{*(v-1)} = l_v - l_{v-1}, \tag{4.7}$$

which implies that the rules (4.1) and (4.7) are identical. The combinations of optimset and fminsearch with the objective functions Δ in M1 and l^* in M2 are performed in our proposed methods M1 and M2. In order to make our CPU time values as meaningful as possible in terms of their comparative merits for the four methods M1, M2, SAS, and R, we choose the ϵ values starting with 10^{-6} so that in M1, the numerical values of Δ become less than or equal to 1.588192276358313 x 10^{-6}; in M2, the numerical values of l become greater than or equal to -18.71513465725594 or equivalently the numerical values of l^* become greater than or equal to -186.23540327176846; in SAS and R, the numerical values of Δ become less than or equal to 1.588192276358313 x 10^{-6} as well as the numerical values of l become greater than or equal to -18.71513465725594 or equivalently the numerical values of l^* become greater than or equal to -186.23540327176846 in addition to satisfying the stopping rule conditions for these methods.

Repeated runs of the same program give different CPU time values. We repeat each program 10 times and present the mean, standard deviation (SD), minimum (Min), first

Table 4.3: The Distributions of CPU Time Values for M1

	Mean	SD	Min	Q1	Median	Q3	Max
I_1	0.0663	0.0019	0.0640	0.0650	0.0660	0.0678	0.0690
I_2	0.0548	0.0040	0.0510	0.0520	0.0530	0.0575	0.0610
I_3	0.0544	0.0141	0.0440	0.0453	0.0480	0.0595	0.0900
I_4	0.0436	0.0052	0.0370	0.0390	0.0430	0.0478	0.0510

Table 4.4: The Distributions of CPU Time Values for M2

	Mean	SD	Min	Q1	Median	Q3	Max
I_1	0.0518	0.0079	0.0450	0.0460	0.0470	0.0560	0.0670
I_2	0.0457	0.0030	0.0430	0.0433	0.0450	0.0470	0.0520
I_3	0.0598	0.0152	0.0210	0.0600	0.0615	0.0683	0.0760
I_4	0.0580	0.0069	0.0520	0.0530	0.0540	0.0628	0.0710

quartile (Q_1), median, third quartile (Q_3), and maximum (Max) of CPU time values from our ten repetitions of the programs. The CPU time values for Method 1 is presented in Table 4.3. The CPU time values for Method 2 is presented in Table 4.4. The CPU time values from SAS and R are presented in Table 4.5 and in Table 4.6.

4.3.1 Effects of CPU time values compared with SAS and R

The CPU time values in Tables 4.3-4.6 demonstrate that the mean CPU values lie between 0.0400 and 0.0676 in all four methods with the initial values I_1, I_2, I_3, and I_4. The proposed methods M1 and M2 stands favorably with the established popular methods in SAS and R

Table 4.5: The Distributions of CPU Time Values for SAS

	Mean	SD	Min	Q1	Median	Q3	Max
I_1	0.0450	0.0158	0.0300	0.0325	0.0400	0.0500	0.0800
I_2	0.0470	0.0142	0.0200	0.0400	0.0450	0.0575	0.0700
I_3	0.0530	0.0133	0.0300	0.0425	0.0550	0.0600	0.0700
I_4	0.0400	0.0170	0.0200	0.0225	0.0400	0.0575	0.0600

Table 4.6: The Distributions of CPU Time Values for R

	Mean	SD	Min	Q1	Median	Q3	Max
I_1	0.0648	0.0196	0.0290	0.0600	0.0650	0.0775	0.0900
I_2	0.0676	0.0225	0.0290	0.0623	0.0700	0.0865	0.0900
I_3	0.0675	0.0122	0.0500	0.0593	0.0645	0.0768	0.0900
I_4	0.0624	0.0174	0.0300	0.0590	0.0.0640	0.0698	0.0890

Table 4.7: The Distributions of CPU Time Values for M1(Simulated Data)

	Mean	SD	Min	Q1	Median	Q3	Max
I_1	0.0597	0.018	0.021	0.05825	0.06050	0.07400	0.08000
I_2	0.0597	0.018	0.021	0.05825	0.06050	0.07400	0.08000
I_3	0.0508	0.013	0.04000	0.04225	0.04550	0.05475	0.08600
I_4	0.0458	0.012	0.0250	0.0425	0.0475	0.0535	0.0650

with a special feature that the initial values in the proposed methods give the values of ED_{50} that are almost identical with its common final value from all the four methods.

4.4 Performance time for simulated data

We now present the performance time comparison of our method with SAS and R for the simulated data. The simulated data were presented in the previous chapter. The stopping rules are kept same as the Beetle mortality data computation. Here we present the CPU time values for Method $M1$, $M2$, SAS and R in the Tables 4.7 ,4.8, 4.9 and 4.10.

The CPU times are varying from 0.01 to 0.09 in all methods. The proposed methods M1

Table 4.8: The Distributions of CPU Time Values for M2 (Simulated Data)

	Mean	SD	Min	Q1	Median	Q3	Max
I_1	0.0567	0.0090	0.0410	0.0535	0.0580	0.0640	0.0670
I_2	0.0567	0.0090	0.0410	0.0535	0.0580	0.0640	0.0670
I_3	0.0598	0.0152	0.0210	0.0600	0.0615	0.0683	0.0760
I_4	0.0580	0.0069	0.0520	0.0530	0.0540	0.0628	0.0710

Table 4.9: The Distributions of CPU Time Values for SAS (Simulated Data)

	Mean	SD	Min	Q1	Median	Q3	Max
I_1	0.045	0.017	0.0100	0.0425	0.0500	0.0500	0.0700
I_2	0.045	0.017	0.0100	0.0425	0.0500	0.0500	0.0700
I_3	0.0646	0.016	0.022	0.064	0.065	0.070	0.0830
I_4	0.0655	0.009	0.0530	0.0570	0.0665	0.07075	0.0840

Table 4.10: The Distributions of CPU Time Values for R (Simulated data)

	Mean	SD	Min	Q1	Median	Q3	Max
I_1	0.071	0.017	0.0400	0.0600	0.0750	0.0875	0.0900
I_2	0.071	0.017	0.0400	0.0600	0.0750	0.0875	0.0900
I_3	0.061	0.014	0.0400	0.0525	0.0600	0.0700	0.0800
I_4	0.066	0.017	0.030	0.060	0.070	0.0775	0.0900

and M2 stands favorably with the established popular methods in SAS and R with respect to CPU time values for simulated data also. Hence, We can conclude that our methods are performing favorably in comparison to the other standard and popular methods.

4.5 Conclusion

We can conclude that our proposed method is equally competent as the other methods in terms of performance time and numerical time. However, our proposed methods are very transparent in selecting the initial values of the parameters and these initial values are generally very close to the final solution. So our proposed methods which performs favorably well compared to other methods, have an unique merit.

Chapter 5

Estimation when relative potency is unknown: Initial values and New methods

5.1 Summary

In this chapter, we consider the model in Chapter 2 for the mixture experiments with unknown relative potency. We propose two methods of finding the initial values of the maximum likelihood estimating equations (MLEE) using two criterion functions. Our proposed methods start with a fixed value of relative potency (ρ) and then we obtain all possible pairs of doses in the experiment. It then chooses the fixed value ρ giving the optimum value of a criterion function with the corresponding exact solutions for the parameters (β_1, β_2) based on two observations in the pair as the initial values of parameters. We then use the initial values and the corresponding criterion functions to obtain the final solutions of MLEE. We illustrate our proposed methods of finding the initial values and the final estimates with an observed mortality data (Giltinan, 1998) and also with a simulated data.

5.2 Model when ρ is unknown

In this chapter we consider a mixture of two drugs applied to the subjects with relative potency is assumed to be unknown. In the earlier chapter, we have discussed the dose-response

model when ρ is unknown in (2.13) with where β_1, β_2 and ρ as the unknown parameters. The mortality probability π_i is given in (2.14) and the log-likelihood function $l(\beta_1, \beta_2, \rho)$ for MM_1 is given in (2.19). The Maximum likelihood estimates of β_1 , β_2 and ρ satisfy

$$(\hat{\beta}_1, \hat{\beta}_2, \hat{\rho}) = \arg \max_{\beta_1, \beta_2, \rho} l(\beta_1, \beta_2, \rho). \tag{5.1}$$

We want to estimate the unknown parameters in (5.1). In the earlier chapter, we have defined the estimating equations of model MM_1 in (2.22). We do not have a closed-form solution for β_1, β_2 and ρ and, therefore, we use the iterative procedure for estimating them. We have discussed two of the standard iteration methods - Newton Raphson and Fisher Scoring in Chapter 2. In all these iterative methods we have to define initial values of β_1, β_2 and ρ. We do not have any systematic way of defining the initial values of these parameters. In the earlier Chapters, we have proposed new methods for finding the initial values of β_1 and β_2 for a single drug experiment with only x. We want to use the same idea in here to determine the initial values of the parameters. When ρ is known, we can use the same method for finding the initial values of β_1 and β_2 as in Chapter 3. So we define a range of known ρ's and for different fixed values of ρ, we perform the same procedure to find the initial values of β_1, β_2 and ρ.

5.3 Initial values

The new method starts with the special situation $N = 2$, i.e., we consider only two mixture of doses applied to the subjects. The estimating equations in (2.22) for $N = 2$ can be written as

$$n_1 \frac{\exp(\beta_1 + \beta_2 d_1)}{1 + \exp(\beta_1 + \beta_2 d_1)} + n_2 \frac{\exp(\beta_1 + \beta_2 d_2)}{1 + \exp(\beta_1 + \beta_2 d_2)} = y_1 + y_2,$$

$$n_1 d_1 \frac{\exp(\beta_1 + \beta_2 d_1)}{1 + \exp(\beta_1 + \beta_2 d_1)} + n_2 d_2 \frac{\exp(\beta_1 + \beta_2 d_2)}{1 + \exp(\beta_1 + \beta_2 d_2)} = y_1 d_1 + y_2 d_2,$$

$$n_1 \frac{\beta_2 z_1}{(x_1+\rho z_1)} \frac{\exp(\beta_1+\beta_2 d_1)}{1+\exp(\beta_1+\beta_2 d_1)} + n_2 \frac{\beta_2 z_2}{(x_2+\rho z_2)} \frac{\exp(\beta_1+\beta_2 d_2)}{1+\exp(\beta_1+\beta_2 d_2)}$$

$$= y_1 \frac{\beta_2 z_1}{(x_1+\rho z_1)} + y_2 \frac{\beta_2 z_2}{(x_2+\rho z_2)}, \tag{5.2}$$

where $d_i = \log(x_i + \rho z_i)$, $i = 1, 2$. We cannot obtain the exact analytic solution of β_1, β_2 and ρ from (5.2). However, if ρ is known, we can obtain the exact analytic solution for β_1 and β_2 from (5.2). If ρ is known then we have two estimating equations in two unknown parameters β_1 and β_2. For a fixed value of ρ_0 of ρ, the estimating equations in (5.2) become

$$n_1 \frac{\exp(\beta_1+\beta_2 d_{01})}{1+\exp(\beta_1+\beta_2 d_{01})} + n_2 \frac{\exp(\beta_1+\beta_2 d_{02})}{1+\exp(\beta_1+\beta_2 d_{02})} = y_1 + y_2,$$

$$n_1 d_{01} \frac{\exp(\beta_1+\beta_2 d_{01})}{1+\exp(\beta_1+\beta_2 d_{01})} + n_2 d_{02} \frac{\exp(\beta_1+\beta_2 d_{02})}{1+\exp(\beta_1+\beta_2 d_{02})} = y_1 d_{01} + y_2 d_{02}, \tag{5.3}$$

where $d_{0i} = \log(x_i + \rho_0 z_i)$, $i = 1, 2$. The exact analytic solutions of β_1 and β_2 for the estimating equations in (5.3) are

$$\exp\left(-\hat{\beta}_2(d_1 - d_2)\right) = \frac{\frac{n_1}{y_1} - 1}{\frac{n_2}{y_2} - 1},$$

$$\exp\left(-\hat{\beta}_1(d_1 - d_2)\right) = \frac{\left(\frac{n_2}{y_2} - 1\right)^{d_1}}{\left(\frac{n_1}{y_1} - 1\right)^{d_2}}. \tag{5.4}$$

We have observed in the earlier chapter that the exact solutions of β_1 and β_2 do not exist for $N \geq 3$. We use the above observation from $N = 2$ for the estimation of the parameters when $N \geq 3$. We consider, for a general N, all $S(\leq \binom{N}{2})$ subsets of two groups with $0 < y_1 < n_1$ and $0 < y_2 < n_2$. For the group pair u, $u = 1, \ldots, S$, we calculate $\hat{\beta}_1$ and $\hat{\beta}_2$ from (5.4). We denote them $\hat{\beta}_{1u}$ and $\hat{\beta}_{2u}$. If the pair u consists of group i_1 and group i_2, we obtain from (5.4)

$$-\hat{\beta}_{1u}(d_{i_1} - d_{i_2}) = \left[d_{i_2} \log_e \frac{y_{i_1}}{n_{i_1} - y_{i_1}} - d_{i_1} \log_e \frac{y_{i_2}}{n_{i_2} - y_{i_2}} \right],$$

$$\hat{\beta}_{2u}(d_{i_1} - d_{i_2}) = \left[\log_e \frac{y_{i_1}}{n_{i_1} - y_{i_1}} - \log_e \frac{y_{i_2}}{n_{i_2} - y_{i_2}}\right]. \tag{5.5}$$

We obtain from (2.14) $\hat{\pi}_{ui}$ by substituting $\hat{\beta}_{1u}$ for β_1 and $\hat{\beta}_{2u}$ for β_2. Finally we get $\hat{y}_{ui}$ from (2.22) by substituting $\hat{\pi}_{ui}$ for $\hat{\pi}_i$.

We define two criterion functions for finding the initial values of $\hat{\beta}_1$ and $\hat{\beta}_2$ in the similar way as in Chapter 3. The criterion functions are

$$\Delta|(\rho = \rho_0) =\mid L_u^{(1)} - R^{(1)} \mid + \mid L_u^{(2)} - R^{(2)} \mid + \mid L_u^{(3)} - R^{(3)} \mid, \tag{5.6}$$

$$l|(\rho = \rho_0) = \sum_{i=1}^{N} y_i(\beta_1 + \beta_2 d_i) - n_i \log\left(1 + \exp(\beta_1 + \beta_2 d_i)\right) + \sum_{i=1}^{N} \binom{n_i}{y_i}, \tag{5.7}$$

where

$$L_u^{(1)} = \sum_{i=1}^{N} \hat{y}_i, \quad L_u^{(2)} = \sum_{i=1}^{N} d_i \hat{y}_i,$$

$$L_u^{(3)} = \sum_{i=1}^{N} \frac{\hat{\beta}_2 z_i}{x_i + \rho_0 z_i} \hat{y}_i, \tag{5.8}$$

$$R^{(1)} = \sum_{i=1}^{N} y_i, \quad R^{(2)} = \sum_{i=1}^{N} d_i y_i,$$

$$R^{(3)} = \sum_{i=1}^{N} \frac{\hat{\beta}_2 z_i}{x_i + \rho_0 z_i} y_i. \tag{5.9}$$

We obtain the most accurate solution of β_1 and β_2 when the numerical value of $\Delta|(\rho = \rho_0)$ is equal to zero. So the smaller numerical value of $\Delta|(\rho = \rho_0)$ means the better accuracy on the solutions of β_1 and β_2.

The criterion function $l|(\rho = \rho_0)$ is proposed in (5.7) because we obtain the most accurate fitted observations when the numerical value of $l|(\rho = \rho_0)$ is maximum, or equivalently the numerical value of $(-l|\rho = \rho_0)$ is minimum.

We calculate for $u = 1, \ldots, N$,

$$u_1 = \arg\min_u \Delta_u|(\rho = \rho_0),$$

$$u_2 = \arg\max_u l_u | (\rho = \rho_0). \tag{5.10}$$

to obtain two possible sets of values $\hat{\beta}_{1u}$ and $\hat{\beta}_{2u}$ of β_1 and β_2 for $\rho = \rho_0$.

We define a set ω with 99 ρ values as $\omega = (\rho | \rho = 0.1, 0.11, \ldots, 0.99)$. For each value p in ω , $p = 1, \ldots, 99$, we obtain β_1 and β_2 using the above methods. We denote them by β_{1_p} and β_{2_p}.

We now use the same criterion functions to obtain the initial values of β_1, β_2 and ρ simultaneously. The criterion functions are calculated using p_1 and p_2. The criterion functions are

$$\Delta_p = \mid L_p^{(1)} - R^{(1)} \mid + \mid L_p^{(2)} - R^{(2)} \mid + \mid L_p^{(3)} - R^{(3)} \mid, \tag{5.11}$$

$$l_p = \sum_{i=1}^{N} y_i(\beta_1 + \beta_2 d_i) - n_i \log\left(1 + \exp(\beta_1 + \beta_2 d_i)\right), \tag{5.12}$$

where

$$L_p^{(1)} = \sum_{i=1}^{N} \hat{y}_i, \quad L_p^{(2)} = \sum_{i=1}^{N} d_i \hat{y}_i,$$

$$L_p^{(3)} = \sum_{i=1}^{N} \frac{\hat{\beta}_2 z_i}{x_i + \rho z_i} \hat{y}_i, \tag{5.13}$$

$$R^{(1)} = \sum_{i=1}^{N} y_i, \quad R^{(2)} = \sum_{i=1}^{N} d_i y_i,$$

$$R^{(3)} = \sum_{i=1}^{N} \frac{\hat{\beta}_2 z_i}{x_i + \rho z_i} y_i, \tag{5.14}$$

and $d_i = \log(x_i + \rho z_i)$.

The criterion function Δ is proposed in (5.11) for finding the accurate final solution of MLEE in (5.1). We obtain the most accurate final solution of MLEE when the numerical value of Δ is equal to zero. So the smaller numerical value to Δ means the better accuracy on the final solutions of MLEE in (5.1).

The criterion function l is proposed in (5.12) because we obtain the most accurate fitted observations when the numerical value of l is maximum, or equivalently the numerical value of $(-l)$ is minimum.

Two possible sets of initial values k_1 and k_2 of β_1, β_2, and ρ are

$$k_1 = \arg\min_p \Delta_p,$$

$$k_2 = \arg\max_p l_p = \arg\min_p(-l_p). \tag{5.15}$$

One set of initial value from k_1 using Δ criterion function and other set of initial value from k_2 using l criterion function. We illustrate our method with the data set (Giltinan, 1998) in the following section.

5.4 An observed mortality data

We present a data set that would help us to illustrate our proposed methodology for the joint action of two drugs. The data are collected from an experiment to investigate the joint activity of two insecticides (Giltinan et al. 1988). Two insecticides are denoted here by A and B. The mixtures are chosen in the ratios 0 : 100, 25 : 75, 50 : 50, 75 : 25 and 100 : 0. 30 insects were tested at each of 4 dose levels of each mixture, by direct application of one microlitre of the treatment to the body of each insect. The insects were exposed for 96 hours to these insecticides and the morality count were recorded after that. The number of dead insects and total number of insects exposed are presented in Table 5.1.

5.4.1 Results

We have $N = 20$ groups of mixtures of doses. Therefore, we have $S = \binom{20}{2} = 190$ groups of pairs for each $\rho = \rho_0$. We have 99 observations in the set of ω, i.e., we have 99 numerical values of β_{1p} and β_{2p} . For presentation purpose, we present the numerical values of β_{1p}, β_{2p} and the value of ρ. Also, we present some of the selective numerical values of ρ and β_{1p} and β_{2p}. In Table 5.2, we present the numerical values of ρ, u , β_{1p} and β_{2p} with the corresponding value of Δ. In Table 5.3, we present the numerical values of ρ, u , β_{1p} and β_{2p}

Table 5.1: Mortality in response to mixtures of insecticides

Mixture	Amount of A (ppm)	Amount of B (ppm)	Number of dead insects	Number of insects tested
B	0	30.00	26	30
B	0	15.00	19	30
B	0	7.50	7	30
B	0	3.75	5	30
A25: B75	6.50	19.50	23	30
A25: B75	3.25	9.75	11	30
A25: B75	1.625	4.875	3	30
A25: B75	0.813	2.438	0	30
A50: B50	13.00	13.00	15	30
A50: B50	6.50	6.50	5	30
A50: B50	3.25	3.25	4	29
A50: B50	1.625	1.625	0	29
A75: B25	19.50	6.50	20	30
A75: B25	9.75	3.25	13	30
A75: B25	4.875	1.625	6	29
A75: B25	2.438	0.813	0	30
A	30.00	0	23	30
A	15.00	0	21	30
A	7.50	0	13	30
A	3.75	0	5	30

with the value of l

From Table 5.2, we observe that Δ is minimum when ρ is 0.98. The corresponding β_1 and β_2 estimates are $\beta_1 = -4.7044625372$ and $\beta_2 = 1.73293283002$ which are obtained by using the above method. The estimates of β_1 and β_2 are the estimates of $u_1 = 172$ which is 14^{th} and 17^{th} dose from the data. So the initial values of (β_1, β_2, ρ) = (-4.7044625372 ,1.73293283002, 0.98).

Similarly, we see from Table 5.3 that l is maximum when $\rho = 0.93$. The corresponding estimates of β_1 and β_2 are $\beta_1 = -4.61719869164$ and $\beta_2 = 1.70727602868$. So our initial values of $(\beta_1, \beta_2, \rho) = (-4.61719869164, 1.70727602868, 0.93)$. Table 5.4 presents the two sets of initial values labeled as I_1 and I_2 of β_1, β_2 and ρ as well as the numerical values of Δ

Table 5.2: The numerical values of ρ, β_1 , β_2 and Δ

ρ	u	β_1	β_2	Δ
0.1	174	-0.268263986595	0	91.116525947
0.2	134	-1.00631643473	0.366296759999	71.8120148098
0.3	69	-1.69270493697	0.706952610549	53.2306419025
0.4	47	-2.22535152068	0.94279616612	47.1937536401
0.5	47	-2.56993584004	1.04433188900	28.6250652997
0.6	187	-3.38858080885	1.34604504296	25.6971953265
0.7	54	-3.25873973264	1.24781126008	23.1474089789
0.8	169	-3.22396245321	1.22149983525	15.6626777853
0.9	177	-4.35247883799	1.62944465815	6.79584718731
0.91	177	-4.36162241965	1.63213300012	10.2225169961
0.92	172	-4.59992465773	1.70219721908	11.0330405567
0.93	172	-4.61719869164	1.70727602868	8.47603052529
0.94	172	-4.63453182132	1.71237221327	7.29878528712
0.95	172	-4.65192440681	1.71748587870	6.81552712194
0.96	172	-4.66937681071	1.72261713159	5.96347791733
0.97	172	-4.68688939823	1.72776607932	5.09776049247
0.98	172	-4.7044625372	1.73293283002	4.72019349302
0.99	172	-4.72209659812	1.73811749264	7.26913573479

and l . The initial values labeled by I_1 and I_2 represent the groups k_1 and k_2 respectively, defined in (5.15).

The initial values labeled I_1 are better over the initial value I_2 because the Δ value in I_1 is smaller than the Δ value in I_2. On the other hand, the initial value labeled I_2 are better over the I_1 in Table 5.4 because the l value in I_2 is bigger than the l value in I_1. Hence the initial values labeled I_1 are better over the other initial values in Table 5.4 for achieving more accurate final solutions of Maximum likelihood estimating equations (MLEE) in Table 5.4 and the initial values labeled I_2 are better over the other initial values in Table 5.4 for achieving more accurate fitted observations.

Table 5.3: The numerical values of ρ, β_1 , β_2 and l

ρ	u	β_1	β_2	l
0.1	92	-1.69008202863	0.793562135751	-110.893171583
0.2	186	-2.38716638482	1.05161507855	-91.0439796538
0.3	98	-3.15264441912	1.43152320639	-79.1192136321
0.4	99	-3.78635344322	1.64698763942	-70.0706016248
0.5	99	-3.42643868486	1.37468715285	-64.1569041528
0.6	94	-4.53089427336	1.80428235847	-59.7941247807
0.7	177	-4.17096662348	1.57607750707	-57.8833730451
0.8	177	-4.26140600504	1.60266796079	-56.1906618275
0.9	172	-4.56555244979	1.69209130517	-55.555965864
0.91	172	-4.5827093621	1.69713567936	-55.5385110583
0.92	172	-4.59992465773	1.70219721908	-55.5297096254
0.93	172	-4.61719869164	1.70727602868	-55.5294115007
0.94	172	-4.63453182132	1.71237221327	-55.5374726852
0.95	172	-4.65192440681	1.71748587870	-55.5537549815
0.96	172	-4.66937681071	1.72261713159	-55.5781257442
0.97	172	-4.68688939823	1.72776607932	-55.6104576434
0.98	172	-4.7044625372	1.73293283002	-55.6506284407
0.99	172	-4.72209659812	1.73811749264	-55.698520777

5.5 Final Solutions

We want to investigate the effect of the initial values and the criterion functions for determining the initial values to the final solutions of MLEE for the mixture of drugs. For this purpose, we present two methods for obtaining the final solutions of the parameters.

5.6 Methods

5.6.1 Method 1 (M_1)

Method 1 uses Δ as the criterion function for performing the search algorithm to achieve the final answer of MLEE using the our proposed initial values, I_1 and I_2. We use MATLAB to perform the search algorithm. We start with the initial values labeled either I_1 or I_2. Then use the optimset function in MATLAB with Δ criterion function in TolFun option

Table 5.4: The initial values of ρ, β_1 , β_2 with the values of Δ and l

Label	Group	Initial β_1	Initial β_2	ρ	Δ	l
I_1	k_1	-4.7044625372	1.73293283002	0.98	4.7201934	-55.65063
I_2	k_2	-4.61719869164	1.70727602868	0.93	8.4760305	-55.52941

and the parameters β_1 , β_2 and ρ in TolX option, the chosen initial values in fminsearch function to perform the iterative process with the stopping rule requiring that the iteration stops when two consecutive Δ values as well as two consecutive values of each β_1, β_2 and ρ simultaneously become less than or equal to a specific small value. We have chosen this value to be 10^{-6} in our calculations. If

$$|\beta_{1_v} - \beta_{1_{v-1}}| \leq 10^{-6}, \quad |\beta_{2_v} - \beta_{2_{v-1}}| \leq 10^{-6},$$

$$|\rho_v - \rho_{v-1}| \leq 10^{-6} \quad \text{and} \quad |\Delta_v - \Delta_{v-1}| \leq 10^{-6}, \tag{5.16}$$

are simultaneously true then we shall get the final estimate of MLEE. In (5.16), Δ_v and Δ_{v-1} are the values of criterion function Δ at the v and $(v-1)$ stages of iteration respectively. Similarly, β_{1_v} and $\beta_{1_{v-1}}$ are the values of β_1 at v and $(v-1)$ stages of iteration respectively , β_{2_v} and $\beta_{2_{v-1}}$ are the values of β_2 at v and $(v-1)$ stages of iteration respectively and ρ_v and ρ_{v-1} are the values of ρ at v and $(v-1)$ stages of iteration respectively. Table 5.5 presents the final solutions of β_1 , β_2 and ρ obtained from M_1 with the initial values I_1 and I_2.
The numerical values of the final solutions of β_1, β_2 and ρ are identical up to at least two

Table 5.5: The final solutions of ρ, β_1 , β_2 with the values of Δ and l

Method	Initial value	Final β_1	Final β_2	ρ	Δ	l
M_1	I_1	-4.634889	1.735221	0.8961529	2.13143 x 10^{-4}	-55.5308840
M_1	I_2	-4.636015	1.735486	0.8966553	4.039207 x 10^{-2}	-55.5308840

decimal places. However, the initial value I_1 is giving the more accurate solutions of the parameters since the value of criterion function Δ is smaller compared to the Δ value for

the initial values I_2. On the other hand, the numerical value of another criterion function l is identical up to six decimal places.

5.6.2 Method 2 (M_2)

Method 2 uses l as the criterion function for performing the search algorithm to achieve the final answer of MLEE using the initial values I_1 and I_2.We start with the initial values either I_1 or I_2. Then we use the optimset function in MATLAB with the l criterion function in TolFun option and the parameters β_1, β_2 and ρ in TolX option, the chosen initial values in fminsearch function to perform the iterative process with the stopping rule requiring that the iteration stops when two consecutive l values as well as two consecutive values of each of β_1 , β_2 and ρ simultaneously become less than or equal to a specified small value as in Method 1. In the computation of l at the stages of iteration, it is unnecessary to keep the terms $\binom{n_i}{y_i}$ because they do not depend on β_1, β_2 and ρ. We therefore exclude this term from l in (2.21) and perform the iteration. The new term is now denoted by l^*. If

$$|\beta_{1_v} - \beta_{1_{v-1}}| \leq 10^{-6}, \quad |\beta_{2_v} - \beta_{2_{v-1}}| \leq 10^{-6},$$

$$|\rho_v - \rho_{v-1}| \leq 10^{-6} \quad \text{and} \quad |l_v^* - l_{v-1}^*| \leq 10^{-6}, \tag{5.17}$$

are simultaneously true then we will get the final estimate of MLEE. In (5.17), l_v^* and l_{v-1}^* are the values of criterion function l^* at the v and $(v-1)$ stages of iteration respectively. Table 5.6 presents the final solutions of β_1, β_2 and ρ obtained from M_2 with the initial values I_1 and I_2. Table 5.6 also presents the numerical values of Δ and l^* for M_2 using two sets of initial values of the parameters.

The numerical values of β_1, β_2 and ρ are identical up to five decimal points for both of the initial values I_1 and I_2. The numerical value of criterion function l are also identical up to six decimal places.

Table 5.6: The final solutions of ρ, β_1 , β_2 with the values of Δ and l

Method	Initial value	Final β_1	Final β_2	ρ	Δ	l
M_2	I_1	-4.634892	1.735221	0.8961562	1.287059 x 10^{-5}	-55.5308840
M_2	I_2	-4.634892	1.735221	0.8961564	7.663848 x 10^{-5}	-55.5308840

5.6.3 Conclusion

We observe that the β_1, β_2 and ρ values are identical up to at least two decimal places obtained from both of the methods. If we compare the Δ values then M_2 is providing more accurate estimates than M_1, since the Δ value is smallest in M_2 for the initial value I_1. However, if we compare the l values, we get the same values of l from any method or from any initial values. We cannot compare these methods in terms of the criterion function l. Both of the methods are performing equally well.

5.7 Goodness of fit test

In this section, we discuss the goodness of fit. After fitting the logistic regression model, we want to evaluate the goodness of fit of this model. The null and alternative hypotheses are

H_0 : The logistic regression model is a good fit to the data.

H_a : The logistic regression model is not a good fit to the data.

The numerical values of standard Deviance Statistics and Chi-Square statistics are

$$D = 2\sum_{i=1}^{N}\left[y_i \log\left(\frac{y_i}{\hat{y}_i}\right) + (n_i - y_i)\log\left(\frac{n_i - y_i}{n_i - \hat{y}_i}\right)\right] = 19.711,$$

$$\chi^2 = \sum_{i=1}^{N}\frac{(y_i - \hat{y}_i)^2}{\hat{y}_i} = 26.146,$$

where $\hat{y}_i$ is defined in (3.10). The test statistics follow χ^2 distribution with df = (20-3) = 17. The p-value for Deviance test is 0.289277 and the p-value for Chi-Square test is 0.071841. We do not reject the null hypothesis for both of cases since our p-values are greater than

$\alpha = 0.05$. We conclude that there is significance evidence the logistic regression in (2.13) is a good fit to the data.

5.8 One interesting phenomenon of our data set

We plot in Figure 5.1 the log-likelihood function l in (5.12) against the values of the parameter ρ in $\omega = \{\rho|\rho = 0.01, \ldots, 0.99\}$ for the fixed values of $\beta_1 = -4.634892$ and $\beta_2 = 1.735221$. The plot indicates that the log-likelihood is a monotonically increasing function of ρ up to $\rho = 0.90$ and then it is a decreasing function in ρ for the values $\rho > 0.90$. We also present this plot in Figure 5.2 in a small region around $\rho = 0.90$, $\omega = \rho|0.80, 0.81, \ldots, 0.99$. This plot demonstrates the symmetric nature of l in the defined region. The log-likelihood value

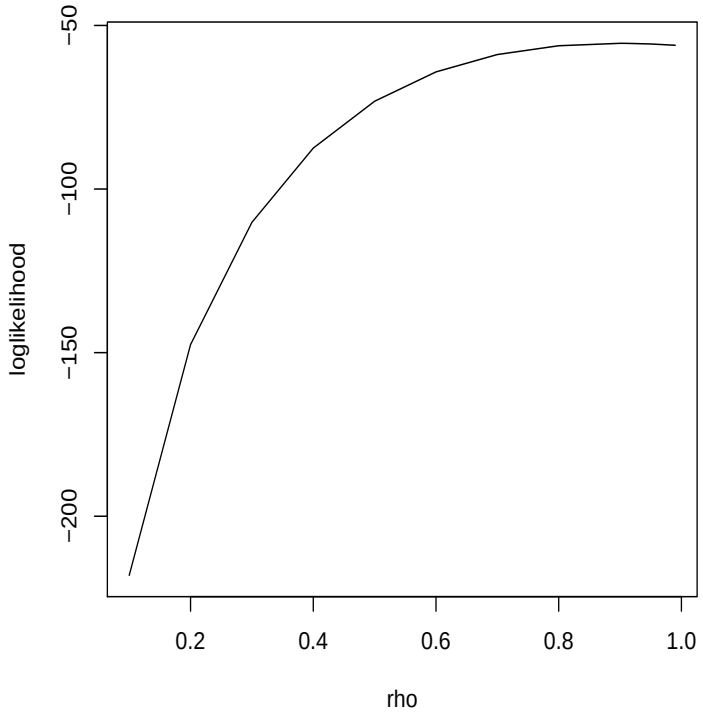

Figure 5.1: Plot of log likelihood function with ρ

at $\rho = 0.88$ is -55.47736 whereas the log-likelihood value at $\rho = 0.90$ is -55.45889, which are

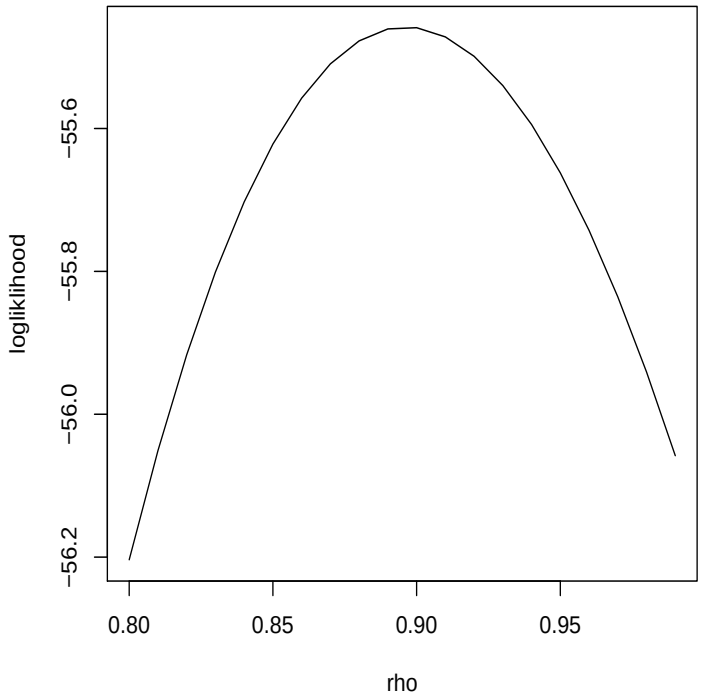

Figure 5.2: Plot of log likelihood function with ρ in ω

very close.

5.9 A simulated mortality data

We present a simulated mortality data to illustrate our methods. We generate a data from (2.2) and (2.3) so that $\beta_1 = -4$, $\beta_2 = 1.5$ and $\rho = 0.70$, and (n_i, x_i, z_i) $i = 1, \ldots, 20$ are same as Table 5.1. The response variable y_i 's are given in Table 5.7. We have $N = 20$

Table 5.7: Mortality in response to mixtures of insecticides (Simulated data)

Mixture	Amount of A (ppm)	Amount of B (ppm)	Number of dead insects	Number of insects tested
B	0	30.00	16	30
B	0	15.00	10	30
B	0	7.50	5	30
B	0	3.75	3	30
A25: B75	6.50	19.50	13	30
A25: B75	3.25	9.75	8	30
A25: B75	1.625	4.875	5	30
A25: B75	0.813	2.438	2	30
A50: B50	13.00	13.00	18	30
A50: B50	6.50	6.50	13	30
A50: B50	3.25	3.25	10	29
A50: B50	1.625	1.625	1	29
A75: B25	19.50	6.50	20	30
A75: B25	9.75	3.25	12	30
A75: B25	4.875	1.625	5	29
A75: B25	2.438	0.813	0	30
A	30.00	0	22	30
A	15.00	0	10	30
A	7.50	0	12	30
A	3.75	0	3	30

groups of mixture of doses. Therefore, we have $S = \binom{20}{2} = 190$ groups of pair observations for each $\rho = \rho_0$. We have $p = 1, \ldots, 99$ ρ's and corresponding estimates of β_{1p} and β_{2p} obtained by our proposed method. Table 5.8 presents the numerical values of some ρ with the corresponding estimates of β_1, β_2 and the criterion function Δ. Table 5.9 presents the numerical values of ρ with the corresponding estimates of β_1 , β_2 and the criterion function l values.

We observe that the criterion function Δ is minimum at $\rho = 0.60$ out of these 99 observations

Table 5.8: The numerical values of ρ, β_1 , β_2 and Δ

ρ	u	β_1	β_2	Δ
0.1	153	-1.048300	0.3190400	45.95888
0.2	39	-1.890277	0.6926332	36.4165
0.3	38	-2.297104	0.8479969	23.02925
0.4	121	-3.391471	1.294565	27.58201
0.5	64	-2.821980	0.9938708	15.44174
0.6	6	-3.529693	1.267389	2.457157
0.7	35	-4.136608	1.467278	6.109941
0.8	43	-4.262108	1.480483	11.06764
0.9	119	-4.220017	1.435919	12.34224
0.95	113	-4.299177	1.455293	14.86023
0.99	113	-4.352344	1.462553	15.11327

Table 5.9: The numerical values of ρ, β_1 , β_2 and l

ρ	u	β_1	β_2	l
0.1	86	-2.254475	0.8624965	-62.99082
0.2	72	-2.53385	0.9674525	-52.85814
0.3	121	-3.173921	1.230602	-47.81689
0.4	121	-3.391471	1.294565	-44.7891
0.5	118	-3.55851	1.296793	-43.41708
0.6	118	-3.760905	1.364228	-42.93855
0.7	101	-3.812716	1.362648	-43.22282
0.8	101	-3.995411	1.395891	-43.88622
0.9	135	-4.022176	1.380703	-44.82772
0.95	135	-3.997371	1.361935	-45.3875
0.99	135	-3.978445	1.347616	-45.87734

from Table 5.8. In our proposed method 1 we define the initial value of (β_1, β_2, ρ) = (-3.760905, 1.364228, 0.60). Let us call this initial values as I_1. We use this initial values in our proposed method and obtain the final estimates of these parameters. The results are presented in Table 5.10 Similarly, we see that the other criterion function l is maximum at $\rho = 0.60$ in ω. So our second set of initial values are, (β_1, β_2, ρ) = (-3.760905, 1.364228,

Table 5.10: The final solutions of ρ, β_1 , β_2 with the values of Δ and l

Method	Initial value	Final β_1	Final β_2	ρ	Δ	l
M_1	I_1	-3.683533	1.325378	0.60850857	4.6733504 x 10^{-3}	-42.89265
M_1	I_2	-3.683533	1.325378	0.60850857	4.6733504 x 10^{-3}	-42.89265

0.60). We call them as I_2. We use the initial values I_1 and I_2 in Method 2 to obtain the final solution. Table 5.11 presents the final estimates of β_1, β_2 and ρ.

From Table 5.10 and Table 5.11, we observe that the final estimated $\rho = 0.60850857$ using

Table 5.11: The final solutions of ρ, β_1 , β_2 with the values of Δ and l

Method	Initial value	Final β_1	Final β_2	ρ	Δ	l
M_1	I_1	-3.682873	1.325152	0.608408508	1.02153747 x 10^{-5}	-42.89264
M_1	I_2	-3.682873	1.325152	0.608408508	1.02153747 x 10^{-5}	-42.89264

Method 1 and $\rho = 0.608408508$ using Method 2. Both of the methods are performing favorably well for simulated data.

Chapter 6

Other methods using the standard softwares

6.1 Summary

In this chapter, we present performance comparisons between our proposed methods (M_1, M_2) with five other methods using the standard software SAS and R $(M_3 - M_7)$. We present the the parameter estimates obtained from all these seven methods. The numerical values of β_1, β_2 and ρ from our methods are almost same as the numerical values the parameters obtained from the other methods using SAS and R and they are identical up to at least two decimal places. This closeness of the estimated parameter values from our methods compared to other methods make our proposed methods very special.

6.2 Method 3 using R software (M_3)

We present four additional methods of estimation of β_1, β_2 and ρ from the estimating equations in (2.19) using the R software. There is no in built program for estimating such parameters using the R software. We propose two methods using the criterion functions Δ and l defined in (5.11) and (5.12).

This method starts with a fixed value ρ_0 of ρ and finds estimate of β_1 and β_2 using GLM procedure in the R. For each of 99 known values of ρ in $\omega = \{0.1, 0.11, \ldots, 0.99\}$, we es-

timate the 99 pairs of $\hat{\beta}_1$ and $\hat{\beta}_2$ values. We then calculate the corresponding estimated log-likelihood function l given in (2.19). We choose the ρ that maximizes the log-likelihood function l. We choose the starting values for ρ and β_1 , β_2 in the search algorithm as the chosen value of ρ and the corresponding values of $\hat{\beta}_1$ and $\hat{\beta}_2$.

We assume that l is maximum at $\rho = \rho_1$ for a ρ_1 in ω. We start our search algorithm for finding the global maximum value of log-likelihood in a region $\omega_1 = (\rho_1 - h_1 \ , \ \rho_1 + h_1)$. Our program calculates the value of l in this region and also find which ρ is giving the maximum value of l in that region. We assume

$$\rho_2 = \arg\max_{\rho} l. \tag{6.1}$$

We begin the search again in the region $\omega_2 = (\rho_2 - h_2, \rho_2 + h_2)$ and continue this until we find the estimate of ρ by maximizing l. We find this estimate of ρ correct to five decimal places. We have taken $h_1 = 0.1$ and

$$h_i = h_1^{\frac{1}{i}}, \tag{6.2}$$

$i = 2, .., k$ where k is the number of searches needed to get the desired estimate of ρ.

6.2.1 Results

We present some of the steps using Method 3 for the data in Table 5.1. For chosen value of ρ with the corresponding values of $\hat{\beta}_1$, $\hat{\beta}_2$ and the estimated l in Table 6.1. We also present the steps for the search algorithm Table 6.2 - Table 6.5. We observe that l is maximum at $\rho = 0.90$ with corresponding $\beta_1 = -4.638748$ and $\beta_2 = 1.735325$. We start our search with $\rho_1 = 0.90$. The region for first search is (0.8, 0.99). We see that l is maximum again at $\rho = 0.90$ from Table 6.4. The region for second search is $(0.85, 0.95)$. We find that log-likelihood is maximum at $\rho = 0.90$. For third search our region is given as $(0.875, 0.925)$. We again observe that the l is still maximum at $\rho = 0.90$ in Table 6.4, so we continue our search. The l is maximum at $\rho = 0.89375$ from Table 6.5. Since we mentioned that we stop

Table 6.1: The numerical values of β_1, β_2, ρ with values of l

ρ	β_1	β_2	l
0.1	-1.639916	0.711427	-110.053469
0.2	-2.383855	1.054164	-91.040056
0.3	-2.989408	1.296764	-77.999668
0.4	-3.473802	1.467098	-69.028115
0.5	-3.851436	1.582525	-63.019352
0.6	-4.140398	1.657334	-59.173602
0.7	-4.358400	1.702651	-56.899941
0.8	-4.520502	1.726678	-55.766216
0.9	-4.638748	1.735325	-55.458243
0.91	-4.648543	1.735519	-55.463462
0.92	-4.658003	1.735606	-55.474413
0.93	-4.667137	1.735590	-55.490911
0.94	-4.675951	1.735473	-55.512778
0.95	-4.684455	1.735259	-55.539842
0.96	-4.692654	1.734952	-55.571935
0.97	-4.700556	1.734553	-55.608895
0.98	-4.708169	1.734067	-55.650564

the search when we have a five decimal value of ρ, so we stop after the fourth search and our estimated $\rho = 0.89375$.

The final estimates of β_1, β_2 and ρ with the corresponding Δ and l values is presented in Table 6.6.

Table 6.2: The numerical values of β_1, β_2, ρ with values of l for the first search

ρ	β_1	β_2	l
0.80	-4.520502	1.726678	-55.766216
0.85	-4.584463	1.732626	-55.524985
0.90	-4.638748	1.735325	-55.458243
0.95	-4.684455	1.735259	-55.539842
0.99	-4.715499	1.733496	-55.69679

Table 6.3: The numerical values of β_1, β_2, ρ with values of l for the second search

ρ	β_1	β_2	l
0.85	-4.584463	1.732626	-55.524985
0.875	-4.612743	1.734350	-55.471534
0.90	-4.638748	1.735325	-55.458243
0.925	-4.662611	1.735611	-55.48198
0.95	-4.684455	1.735259	-55.539842

Table 6.4: The numerical values of β_1, β_2, ρ with values of l for the third search

ρ	β_1	β_2	l
0.875	-4.612743	1.734350	-55.471534
0.8875	-4.626022	1.734928	-55.46007
0.90	-4.638748	1.735325	-55.458243
0.9125	-4.650939	1.735551	-55.46567
0.925	-4.662611	1.735611	-55.48198

Table 6.5: The numerical values of β_1, β_2, ρ with values of l for the fourth search

ρ	β_1	β_2	l
0.8875	-4.626021	1.734927	-55.460070
0.89375	-4.632453	1.735148	-55.457977
0.90	-4.638748	1.735325	-55.458243
0.90625	-4.64491	1.735459	-55.46082
0.9125	-4.650939	1.735551	-55.46567

Table 6.6: Final solution of β_1, β_2, ρ with Δ and l from Method 1 Using R

Final β_1	Final β_2	Final ρ	Δ	l
-4.632453	1.735148	0.89375	1.454624 x 10^{-1}	-55.45798

6.3 Method 4 using R software (M_4)

We present a method similar to M_3 using the R software and the criterion function Δ defined in (5.11). This method starts with a fixed value of ρ say ρ_0 and finds estimate of β_1 and β_2 using GLM procedure in the R software. For each of 99 known values of ρ in $\omega = \{0.1, 0.11, \ldots, 0.99\}$, we estimate the 99 pairs of $\hat{\beta}_1$ and $\hat{\beta}_2$ values. We then calculate the corresponding estimated Δ. We choose the ρ that minimizes the Δ, we choose the starting values for ρ and β_1 , β_2 in the search algorithm as the chosen value of ρ and the corresponding values of $\hat{\beta}_1$ and $\hat{\beta}_2$.

We assume that Δ is minimum at $\rho = \rho_1$ for a ρ_1 in ω. We start our search to find the global minimum value of Δ in a region involving $\omega_1 = (\rho_1 - h_1, \rho_1 + h_2)$. Our program calculates the value of Δ in the this region and finds out for which ρ is giving minimum value of Δ in that region. We assume

$$\rho_2 = \arg\min \Delta. \tag{6.3}$$

We begin the search again in the region $\omega_2 = (\rho_2 - h_2; \rho_2 + h_2)$ and continue this until we find the estimate of ρ by minimizing Δ. We find this estimate of ρ correct to five decimal places. We have taken $h_1 = 0.1$ and

$$h_i = h_1^{\frac{1}{i}}, \tag{6.4}$$

where $i = 2, \ldots k$ and k is the number of searches needed to get the desired estimate of ρ.

6.3.1 Results

We present some of the steps using Method 4 for the data in Table 5.1. For the chosen value of ρ with the corresponding values of $\hat{\beta}_1$, $\hat{\beta}_2$ and the estimated Δ in Table 6.7. We also present the steps for the search algorithm Table 6.8 - Table 6.11. We observe from Table 6.7 that Δ is minimum at $\rho = 0.90$ with corresponding $\hat{\beta}_1 = -4.638748$ and $\hat{\beta}_2 = 1.735325$. We start our search in $(0.8, 0.99)$ region. From Table 6.8, we see that Δ is smallest again at $\rho = 0.90$. The new search region is $(0.85, 0.95)$. The next search region is $(0.875, 0.925)$ from Table

Table 6.7: The numerical values of β_1, β_2, ρ with Δ values

ρ	β_1	β_2	Δ
0.1	-1.639916	0.711427	232.537107
0.2	-2.383855	1.054164	155.778318
0.3	-2.989408	1.296764	107.861899638
0.4	-3.473802	1.467098	73.363843
0.5	-3.851436	1.582525	48.132462
0.6	-4.140398	1.657334	29.759394
0.7	-4.358400	1.702651	16.427245
0.8	-4.520502	1.726678	6.765492
0.9	-4.638748	1.735325	0.229006
0.91	-4.648543	1.735519	0.811568
0.92	-4.658003	1.735606	1.375444
0.93	-4.667137	1.735590	1.921208
0.94	-4.675951	1.735473	2.449417
0.95	-4.684455	1.735259	2.960608
0.96	-4.692654	1.734952	3.455301
0.97	-4.700556	1.734553	3.933999
0.98	-4.708169	1.734067	4.397190

6.9. We observe from Table 6.11, our desired value of $\rho = 0.89375$ since the Δ is smallest in the defined region. We obtain the final estimate of $\rho = 0.89375$ with $\hat{\beta}_1 = -4.632453$ and $\hat{\beta}_2 = 1.735148$ by minimizing Δ. The final estimates are given in Table 6.12

Table 6.8: The numerical values of β_1, β_2, ρ with Δ values for the first search

ρ	β_1	β_2	Δ
0.80	-4.520502	1.726678	6.765492
0.85	-4.584463	1.732626	2.985595
0.90	-4.638748	1.735325	0.229006
0.95	-4.684455	1.735260	2.960609
0.99	-4.715499	1.733496	4.845344

Table 6.9: The numerical values of β_1, β_2, ρ with Δ values for the second search

ρ	β_1	β_2	Δ
0.85	-4.584463	1.732626	2.985595
0.875	-4.612743	1.734350	1.313096
0.90	-4.638748	1.735325	0.229006
0.925	-4.662611	1.735611	1.650555
0.95	-4.684455	1.735260	2.960609

Table 6.10: The numerical values of β_1, β_2, ρ with Δ values for the third search

ρ	β_1	β_2	Δ
0.875	-4.612743	1.734350	1.313096
0.8875	-4.626021	1.734927	0.526380
0.90	-4.638748	1.735325	0.229006
0.9125	-4.650939	1.735551	0.954266
0.925	-4.662611	1.735611	1.650555

Table 6.11: The numerical values of β_1, β_2, ρ with Δ values for fourth search

ρ	β_1	β_2	Δ
0.8875	-4.626021	1.734927	0.526380
0.89375	-4.632453	1.735148	0.144847
0.90	-4.638748	1.735325	0.229006
0.90625	-4.64491	1.735459	0.5953285

Table 6.12: Final solution of β_1, β_2, ρ with Δ and l from Method 2 Using R

Final β_1	Final β_2	Final ρ	Δ	l
-4.632453	1.735148	0.89375	1.454624 x 10^{-1}	-55.45798

6.4 Methods 5 using SAS software (M_5)

In this method, we use SAS software to estimate the unknown parameters defined in (2.13). There are several Procedures (Proc' s) are available in SAS to estimate β_1, β_2 and ρ for the joint action of two drugs such as, Proc NLIN, Proc NLMIXED etc. We have used Proc NLMIXED for estimating the maximum likelihood estimates of (β_1, β_2, ρ) defined in (2.19).

6.4.1 Method

The NLMIXED procedure generally fits nonlinear mixed models, that is, models in which both fixed and random effects enter nonlinearly. This is a very powerful procedure in SAS to estimate the parameters for nonlinear models. Proc NLMIXED enables us to analyze data that are normal, binomial, or Poisson. This finds the maximum likelihood estimates by maximizing the log-likelihood function of the given model. A variety of optimization techniques are available to carry out the maximization. We can choose a particular optimizer with the TECH=name option in the PROC NLMIXED statement.

The factors that go into choosing a particular optimization technique for a particular

Table 6.13: The optimization techniques in Proc NLMIXED

Algorithm	Tech=
trust region Method	TRUREG
Newton-Raphson method with line search	NEWRAP
Newton-Raphson method with ridging	NRRIDG
quasi-Newton methods (DBFGS, DDFP, BFGS, DFP)	QUANEW
double-dogleg method (DBFGS, DDFP)	DBLDOG
conjugate gradient methods (PB, FR, PR, CD)	CONGRA
Nelder-Mead simplex method	NMSIMP

problem are complex and may involve trial and error. We have used NRRIDG optimization technique to estimate the maximum likelihood estimates in (5.4).

In NLMIXED procedure we have to define the initial values of the parameter in PARMS statement. A common choice of initial values for the parameters (β_1, β_2) are $(0, 0)$. However, there is no common choices of initial values of ρ exist in literature. For the comparison purpose, we have chosen the initial values of $(\beta_1, \beta_2, \rho) = (0, 0, 0.1)$. We call these initial values as I_3. Table 6.14 presents $\hat{\beta}_1, \hat{\beta}_2, \hat{\rho}$, Δ, l values for I_3 initial value.

Table 6.14: Final solution of β_1, β_2, ρ with Δ and l

Initial value	Final β_1	Final β_2	Final ρ	Δ	l
I_3	-4.634892	1.735221	0.896156	7.956599 x 10^{-4}	-55.45780

6.5 Methods using our proposed initial values in SAS software

In this section, we discuss about more methods using Proc NLMIXED in SAS. We use the initial values of the parameters obtained by our proposed method in Chapter 5. In Chapter 5 as the initial values in Proc NLMIXED. We proposed two sets of initial values, one set of initial values we obtained from the criterion function Δ and another set of initial values obtained from the another criterion function l in Chapter 5.

6.5.1 Method 6 with the initial values obtained from Δ criterion function (M_6)

In the PARMS option in Proc NLMIXED syntax we have defined, $\beta_1 = -4.7044625372$, $\beta_2 = 1.73293283002$ and $\rho = 0.98$ as the initial values for the execution of Proc NLMIXED. The results are presented in Table 6.15.

From Table 6.15, we can see that the final estimates of (β_1, β_2, ρ) are identical up to 3 decimal places compared to our proposed method in Chapter 5. We can conclude that the initial values obtained by our method is working favorably compared to any standard methods for solving non linear equations.

Table 6.15: Final solution of β_1, β_2, ρ with Δ and l

Final β_1	Final β_2	Final ρ	Δ	l
-4.6348929169	1.7352218697	0.8961564624	1.9615072 x 10^{-8}	-55.45780

6.5.2 Method 7 with the initial values from l criterion function (M_7)

We use the initial values of β_1, β_2 and ρ obtained from our proposed method in Chapter 5 by minimizing the criterion function l which is defined as I_2 in Chapter 5. In the PARMS option in Proc NLMIXED syntax we have defined, $\beta_1 = -4.61719869164$, $\beta_2 = 1.70727602868$ and $\rho = 0.93$ as the initial values for the execution of Proc NLMIXED. The results are presented in Table 6.16. We observe from Table 6.16 that the final estimates of (β_1, β_2, ρ) are identical

Table 6.16: Final solution of β_1, β_2, ρ with Δ and l

Final β_1	Final β_2	Final ρ	Δ	l
-4.6348929169	1.7352218697	0.8961564624	1.9615072 x 10^{-8}	-55.45780

up to 3 decimal places compared to our proposed method in Chapter 5. We can conclude that the initial values obtained by our method is working favorably compared to any standard methods for solving non linear equations.

6.6 Performance comparisons of $M_1 - M_7$

We compare our proposed methods M_1, M_2, defined in Chapter 5 with the methods M_3, M_4, M_5, M_6 and M_7 , defined in Chapter 6. For comparison purpose, we need to define same stopping rule for all the methods.

6.6.1 Stopping rule for Methods $M_5, M_6,$ and M_7

For Method M_5, M_6 and M_7 we have used Proc NLMIXED in SAS for estimating the parameters. In Proc NLMIXED, we have chosen ABSFCONV as stopping rule option which is

$$|l_v - l_{v-1}| < \epsilon_1, \tag{6.5}$$

where l_v and l_{v-1} are the values of l in (2.5) at the v and $(v-1)$ stages of iteration, respectively. The ε_1 is specified as 10^{-6}.

6.6.2 Stopping rule for Method M_3 and M_4

Method M_3 and M_4 use the same stopping rule which depends on the deviance statistics defined in (4.2). The stopping rule is

$$\frac{|D_v - D_{v-1}|}{|D_v| + 0.1} < \epsilon_2, \tag{6.6}$$

where D_v and D_{v-1} are the values of D in (2.19) at the v and $(v-1)$ stages of iteration, respectively. The ε_2 is also specified as 10^{-6} at the beginning.

6.6.3 Stopping rule for Method M_1 and M_2

In our proposed Methods (M_1 and M_2) from Chapter 5 we have used fminsearch option in MATLAB to estimate the parameters. The stopping rule in fminsearch depends on TolX and TolFun in Optimset option. The TolX value represents the common values of ϵ_3 , ϵ_4 and ϵ_5 in the conditions for stopping rules

$$|\beta_{1_v} - \beta_{1_{v-1}}| < \epsilon_3, \quad |\beta_{2_v} - \beta_{2_{v-1}}| < \epsilon_4,$$

$$|\rho_v - \rho_{v-1}| < \varepsilon_5, \tag{6.7}$$

where $(\beta_{1_v}, \beta_{2_v}, \rho_v)$ and $(\beta_{1_{v-1}}, \beta_{2_{v-1}}, \rho_{v-1})$ are the values of (β_1, β_2, ρ) at the v and $(v-1)$ stages of iterations, respectively. The ε_3, ε_4 and ε_5 are equal and their common value is

specified as 10^{-6}. Table 6.17 presents the parameter estimates of β_1, β_2 and ρ with the corresponding value of the criterion functions Δ and l obtained from all of these different methods.

Table 6.17: Comparison of the parameter estimates of different methods

Method	Final β_1	Final β_2	Final ρ	Δ	l
M_1	-4.634892	1.735221	0.8961562	1.287059 x 10^{-5}	-55.5308840
M_2	-4.634892	1.735221	0.8961564	7.663848 x 10^{-5}	-55.5308840
M_3	-4.632453	1.735148	0.89375	1.454624 x 10^{-1}	-55.45798
M_4	-4.632453	1.735148	0.89375	1.454624 x 10^{-1}	-55.45798
M_5	-4.634892	1.735221	0.896156	7.956599 x 10^{-4}	-55.45780
M_6	-4.634892	1.735221	0.896156	7.956599 x 10^{-4}	-55.45780
M_7	-4.634892	1.735221	0.896156	7.956599 x 10^{-4}	-55.45780

6.6.4 Conclusion

We observe from Table 6.17 that the numerical values of the final solutions of β_1, β_2 and ρ obtained from our methods (M_1 and M_2) are identical up to at least two decimal places obtained from other methods (M_3, M_4 , M_5 , M_6 and M_7) using SAS and R. So our methods are performing favorably compared with all standard methods. If we compare the value of the criterion function Δ, our methods are performing better than the rest of the methods. Similarly, we compare the values of other criterion function l, the other methods are performing slightly better than our proposed methods. So we can conclude that our methods are providing more accurate solutions of the parameters β_1, β_2 and ρ while the other methods using SAS and R are proving better fitted values of the response compared to our methods.

Chapter 7

Conclusions

In this dissertation, we propose new methods of estimation for estimating the unknown parameters in the logistic regression models which are used to assess the dose-response relationship between two drugs or for a single drug. Our methods find the initial values of the parameters of the logistic regression model in a very systematic way. In our proposed methods of finding the initial values of parameters, we make use of the pairs of observations. Our methods are based on two different criterion functions. The first criterion function Δ which is used for obtaining the most accurate final solutions of MLEE and the second criterion function l or equivalently (-l) is used for obtaining the most accurate fitted observations. We use our initial values and the corresponding criterion functions to obtain the final solutions of the parameters in the models. We also estimated the relative potency and ED_{50} for our data. Our methods are computer intensive like the popular bootstrap and jackknife methods in statistics (Efron and Tibshirani, 1993). We compare our proposed methods with the standard and popular methods of estimation. The performances of our methods are almost the same as the performances of the standard methods. The parameter estimate values are almost identical for all these methods. This closeness of the numerical values of the estimates obtained from our methods compared to the estimates obtained from the standard methods make our proposed methods very special.

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