Sequential ED-Design for Binary Dose–Response Experiments

by

Xiaoli Yu

M.Sc., The University of British Columbia, 2011
B.Sc., The University of Alberta, 2009

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

The Faculty of Graduate and Postdoctoral Studies

(Statistics)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

October 2017

Abstract

Dose–response experiments and subsequent data analyses are often carried out according to optimal designs for the purpose of accurately determining a specific effective dose (ED) level. If the interest is the dose–response relationship over a range of ED levels, many existing optimal designs are not accurate. In this dissertation, we propose a new design procedure, called two-stage sequential ED-design which directly and simultaneously targets several ED levels. We use a small number of trials to provide a tentative estimation of the model parameters. The doses of the subsequent trials are then selected sequentially, based on the latest model information, to maximize the efficiency of the ED estimation over several ED levels.

Although the commonly used logistic and probit models are convenient summaries of the dose–response relationship, they can be too restrictive. We introduce and study a more flexible albeit slightly more complex three-parameter logistic dose-response model. We explore the effectiveness of the sequential ED-design and the D-optimal design under this model, and develop an effective model fitting strategy. We develop a two-step iterative algorithm to compute the maximum likelihood estimate of the model parameters. We prove that the algorithm iteration increases the likelihood value, and therefore will lead to at least a local maximum of the likelihood

function. We also study the numerical solution to the D-optimal design for the three-parameter logistic model. Interestingly, all our numerical solutions to the D-optimal design are three-point-support distributions.

We also discuss the use of the ED-design when experimental subjects become available in groups. We introduce the group sequential ED-design, and demonstrate how to construct this design. The ED-design has a natural extension to more complex models and can satisfy a broad range of the demands that may arise in applications.

Lay Summary

Dose–response experiments are routinely conducted in the early phase of clinical trials. The most common goal of these experiments is to collect information about the relationship between the dosage of an investigational drug and the responses of patients. This goal is often accomplished by accurately determining a specific dose level. In medical research, it is also important to determine the effective and safe dose range so that it is high enough to induce desired beneficial effects, and low enough to avoid potential adverse effects. Motivated by this observation, we propose a new design procedure that simultaneously estimates several dose levels. We demonstrate how to carry out this design. We find that the new design compares favourably with many existing designs that we are aware of.

Preface

This thesis is under the supervision of Drs. Jiahua Chen and Rollin Brant. A paper based on Chapter 3 of the dissertation has been published in Yu et al. (2016). Chapter 4 is based on a manuscript in preparation coauthored with Dr. Jiahua Chen. Dr. Brant raised the research problem and Dr. Chen helped to formulate the idea and suggested specific approaches in these manuscripts. Both had given me valuable constructive criticisms, helped me to organize my ideas. They supported, encouraged and inspired me during the writing of the manuscripts.

Table of Contents

List of Tables

List of Figures

Acknowledgements

First, I would like to express my sincere gratitude to my principal supervisor Dr. Jiahua Chen, who has inspired and guided me throughout my Ph.D. study. Thank you, Dr. Chen, for your invaluable suggestions, guidance, and continuing support. I also would like to express my gratitude to my co–supervisor Dr. Rollin Brant for his suggestions and encouragement during the course of my Ph.D. study.

Secondly, I would like to extend my appreciation to my supervisory committee, Dr. Lang Wu for his suggestions and support throughout my Ph.D. study.

Most importantly, I thank my parents and husband for their whole-hearted love and support. They have dedicated all their time and energy to help me take care of my daughter, whom was born when I started my PhD study. They also have encouraged me and brought me much joy and happiness. Without the help from my supervisor Dr. Chen or the support from my beloved family, the writing of this thesis would never have been possible.

To Yi, Hui, Zhennian, and Mia

Chapter 1

Introduction

1.1 Dose–response experiments and design issues

When a stimulus is administrated to a subject, some changes in the subject might be observed immediately or after a certain exposure time. Studying dose–response relationship and developing dose–response models are of central importance in various applications. Dose–response experiments collect data on the level or dosage of the stimulus applied and the response of the subject. The information collected is used for model development and to determine "safe", "hazardous" and beneficial levels or dosages for investigational drugs, pollutants, foods, and other substances to which humans, other organisms, or non-living systems are exposed. These conclusions are the basis for public policy or safety manuals.

In drug developments, dose–response experiments are involved in both Phases I and II clinical trials. The main goal of clinical trials is to uncover the relationship between the doses of an investigational drug and the probability of toxicity or beneficial responses of patients in the target population. The dose given to a patient is ideally high enough to induce the desired response and low enough to avoid potential adverse effects (Dette et al., 2005; Dragalin et al., 2008a). An easily understandable example is the dosage

an anesthesiologist must decide: it must be low enough to not harm their patients, but high enough to induce the desired anesthetic effect. The accurate dose–response relationship is clearly vital in guiding the selection of the dose levels in such practices (Pace et al., 2007).

Poor understanding of the underlying dose–response relationship in Phase I/II clinical trials may result in selecting the wrong target doses to be used in Phase III large scale confirmatory clinical trials. This may cause serious ethical and financial consequences. Selecting too high a dose may cause a large number of toxic responses in experimental subjects, and choosing too low a dose may fail to establish adequate efficacy. Both can lead to unwarranted failure to obtain the regulatory approval of an investigational drug (Dette et al., 2008; Bretz et al., 2010). We refer to Ting (2006) and Bretz et al. (2008) for additional general discussion on issues and challenges in dose–response experiments in the context of the drug development process.

The dose–response relationship also plays a vital role in other applications. In pyrotechnics applications, we must have a thorough understanding of the sensitivity of a new explosive to the stress of a shock to avoid catastrophic consequences. See Dror and Steinberg (2008) and Wu and Tian (2013) for more vivid descriptions. In pyrotechnics experiments, the stress level may be the drop height of an explosive, or the pressure on a pile of ammunition. The response is either explosion or nonexplosion (Wu and Tian, 2013). For example, in testing the sensitivity of new pyrotechnics to ignition, each sample is assumed to have a threshold stress level. Ignition pulses that are larger than this level will ignite the sample. Ignition pulses that are smaller than this level will not ignite the sample. Repeated testing

on any sample is not possible, because the pulse that is not large enough to cause ignition will damage the sample. To estimate the parameters of the underlying response model, samples are tested at various stress levels and their responses are observed. Researchers then analyze the data to obtain an estimate of the model parameters (Neyer, 1994). See Neyer (1994), Dror and Steinberg (2008) and Wu and Tian (2013) for more vivid descriptions.

The task of accurately characterizing the dose–response relationship may not appear to be challenging. One may simply administer various dose levels to a large number of subjects. The data on the responses of these subjects would likely give a clear picture of the dose–response relationship. This practice is clearly not feasible. In drug developments it will hurt a large number of patients or volunteers. In other applications, the cost can be unacceptably high. We may not be able to find sufficient resources to run the experiment, and it may take a long time to complete.

Fortunately, experience and our intuition indicate that the relationship between the dose level and the probability of response is smooth and monotone. Based on this belief, statistical design theory can be used to maximize the information content of each experimental run/trial. A well-designed experiment reduces the cost and saves time in the drug development process or other applications.

In the general context, an optimal design maximizes the expected information content in the anticipated data given a fixed number of experimental runs. When a parametric model is selected for the relationship between the response variable and design variables (also called explanatory variables, covariates, or dosage in drug development examples), an optimal design often

aims to maximize the Fisher information by running experiments at specific level combinations of the design variables. If the parametric model is linear, the Fisher information does not depend on the true parameter values of the model. Hence, the optimal design is possible without the knowledge of the true parameter values (Montgomery, 2008).

The dose–response relationship is apparently nonlinear. No matter how low or how high a dose level is, the probability of responding to a stimulus takes a value between 0 and 1. For this reason, a nonlinear parametric model is often selected. Suppose a specific dose–response relationship such as logistic is assumed. Under this model, the Fisher information is a function of unknown parameters, as well as the specific design. Without knowledge of the specific parameter values, it is not possible to determine whether a design maximizes the Fisher information. When the parameter values are known, it is at least possible in principle to find the design that gives the most efficient estimation of the model parameters (Wu, 1985b,a; Ford et al., 1985; Sitter and Fainaru, 1997; Sitter and Forbes, 1997).

Clearly, if we knew the parameter values, there would be no point to run experiments to estimate them. To overcome this dilemma, one may first run a pilot study in which the dose levels are selected based on prior knowledge. The resulting data will provide an improved estimate of the model parameters over the prior guess. The optimal design based on the fitted model is then used for selecting the dose levels of further trials. This is called a two-stage design.

Because the precision of the parameter estimation based on a pilot study is necessarily low, the resulting second stage design may markedly differ from

an optimal one. To overcome this shortcoming, a full sequential approach can be used; the parameter estimates are updated after each trial of the experiment, and used to determine appropriate dose levels for the subsequent trials.

Suppose the only model assumption we wish to make is the monotonicity between the response probability and the dose level. The popular up-and-down design works well under such a nonparametric model assumption. It addresses both ethical and safety concerns as well (Anderson et al., 1946; Békésy, 1947; Dixon and Mood, 1948).

The up-and-down design is also of sequential nature: depending on the outcome of the current run/trial, the dose of the next trial will be made one level higher or lower. By the appropriate choice of several criteria, the majority runs will concentrate on the target dose level. An appropriate estimate of the target dose level wii thereby be obtained.

Despite its long history, design theory for binary experiments remains an active research area. For recent developments, see Li and Wiens (2011), Wang et al. (2013), Wang et al. (2015), and Wu and Tian (2013).

Wang et al. (2015) considered a two-stage sequential D-optimal design. They proposed first obtaining a tentative estimate of the model parameters. The D-optimality criterion is then used to select the dose level of every additional subject. Wu and Tian (2013) presented a three-phase sequential design. The first phase aims to ensure a viable fitted model, and the second phase chooses the dose levels to satisfy D-optimality. The third phase clusters the dose levels around the target ED level.

In this dissertation, we wish to contribute to the literature of optimal

designs concerning the dose–response experiment and the estimation of the dose–response relationship. The motivation of the research problem is from the following observations. While many designs are optimal if estimating the median effective dose level is the sole goal of the experiment, they are not the best when a range of ED levels are targeted. In many applications, it is desirable to accurately determine several ED levels. For example, Rosenberger and Grill (1997) studied the dose–response experiment problem where ED50 is the primary target, but ED25 and ED75 or other ED levels are also of interest. This prompted them to propose a new sequential design, and apply this design to a psychophysical experiment where the objective was to observe how patients respond to a range of stimulus levels. From this consideration, we propose a new criterion and the corresponding sequential solution to its implementation. We research the usefulness of the new method in achieving higher precision for estimating the dose–response relationship over a specific range of interest. More specific details are given in the next section.

1.2 Major contributions

The most important contribution of this dissertation is the introduction of a new optimality criterion. Traditionally, when a parametric dose–response model is assumed, we often search for designs which enable us to most accurately estimate the model parameters. In applications, we consider, the ultimate goal of the investigation is to accurately determine the various effective dose levels. These two goals are closely related but not equivalent. Based on this consideration, we propose a new design criterion which we im-

plement it sequentially. Because we directly aim at the accurate estimation of the effective dose levels, we call it sequential ED-design.

We conduct extensive computer simulation to demonstrate that the proposed sequential ED-design indeed improves the efficiency of the experiment by changing the optimality target from model parameters to effective dose levels of interest compared with many existing designs. A paper based on this part of the dissertation has been published in Yu et al. (2016).

The logistic regression model is the most popularly assumed dose–response model in applications. Either the proposed sequential ED-design or other existing sequential designs often require some preliminary estimate of the parameter values based on a pilot experiment with a small number of runs/trials. The maximum likelihood approach is often the choice to give a preliminary estimate of the model parameters based on the pilot data. A technical hurdle is that the maximum likelihood estimate under the logistic regression model may fail to exist when the data have a specific configuration, i.e., the likelihood does not attain its maximum at a infinite parametric value. This is even more likely for pilot data. In this dissertation, we employ the idea of adding pseudo observations. This approach takes advantage of our prior knowledge of the dose–response curve and enables a maximum likelihood like estimate for any data configurations.

Based on these results, we further explore the application of the proposed sequential ED-design to a more flexible three-parameter logistic regression model. We develop a two-step iterative algorithm to compute the maximum likelihood estimate of the model parameters. We prove that the algorithm iteration increases the likelihood value and therefore will lead to at least

a local maximum of the likelihood function. We also study the numerical solution to the D-optimal design for the three-parameter logistic regression model. It is of interest to find that all our numerical solutions to the D-optimal design are three-point-support distributions. Simulation results indicate that the more flexible three–parameter logistic regression model can be easily implemented, and the sequential ED-design remains effective.

In addition to these achievements, we discuss the use of ED-design when experimental subjects become available in groups. For instance, two patients may become available for the next experimental trial at the same time. We may be required to decide their appropriate dose levels simultaneously.

1.3 Outline of the dissertation

The thesis is organized as follows. In the next chapter we introduce some notation and some parametric dose–response models. We give a general review of the corresponding optimal design theory. We derive the analytical and numerical results for locally D-optimal designs under the standard logistic model. We give a comprehensive review of some existing sequential design procedures of dose–response experiments such as the up-and-down and related designs, and discuss their advantages and shortcomings.

In Chapter 3, we introduce our two-stage sequential ED-design. We use a small number of trials to provide a tentative estimation of the model parameters. The dose levels of the subsequent trials are then selected sequentially, based on the latest model information, to maximize the efficiency of the ED estimation over several ED levels. Some details of the ED-design under a

logistic regression model are given. Simulations indicate that the ED-design compares favorably with several existing designs under various scenarios. In addition, we provide some simulation evidence for the limiting ED-design when the sample size n goes to infinity. It appears that as a distribution over the dose range, the design has a limit with two support points.

In Chapter 4, we introduce the three-parameter logistic model. Some details of the ED-design under the three-parameter logistic regression model are given. We investigate the effectiveness of the sequential ED-design, the D-optimal design, and the up-and-down design under this model, and develop an effective model fitting strategy. Simulations show that the combination of the proposed model and the data analysis strategy performs well. When the logistic model is correct, using the more complex model suffers hardly any efficiency loss. When the three-parameter model holds but the logistic model is violated, the new approach can be more efficient. In addition, we apply the new approach to a real dataset.

In Chapter 5, we introduce a group sequential ED-design, and show how to construct it. Simulation studies indicate that our group ED-design compares favorably with several existing group design procedures under various scenarios.

In Chapter 6, the asymptotic properties of the two-stage sequential ED-design are investigated. The method of maximum likelihood is one of the classical methods of estimation. We present some general results on the asymptotic properties of the maximum likelihood estimators following a two-stage sequential design. We provide evidence that the maximum likelihood estimators from the two-stage sequential design exist and have the usual

asymptotic properties (i.e., consistency, asymptotically normality).

Chapter 7 summarizes the dissertation, adds some conclusions and discusses areas of future research.

Chapter 2

Preliminaries

To explain our idea clearly, let us first introduce some specific notation and concepts.

2.1 Dose–response curves and parametric models

We use X or x to denote the dose level of a drug or a stimulus in a dose–response experiment. We use Y for the random outcome of the response. In toxicity studies, we put $Y = 1$ if the subject has toxicity reaction, and $Y = 0$ otherwise. In the study of drug efficacy, we put $Y = 1$ if the desired medical effect is achieved, and $Y = 0$ otherwise. At this moment, we only consider the situation where the response is not a vector. Namely, we do not consider multiple responses.

Suppose a stimulus at dosage $X = x$ is applied to a subject/recipient, and the outcome is Y. The dose–response relationship is defined to be the function

$$\pi(x) = P(Y = 1|X = x).$$

When the dose–response relationship $\pi(x)$ for a stimulus is fully and precisely determined, the user may decide on a suitable level of the stimulus in

applications. She will have full knowledge of the risk of a catastrophic event when a specific dosage is applied. She can also be nearly certain of when a desired effect will occur by applying a high enough level of the stimulus.

We assume that $\pi(x)$ is a monotone increasing function. Conceptually, $\pi(0) = 0$ and $\pi(\infty) = 1$. It is very unlikely to be true in most applications, especially in medical fields. In applications, some dose levels are of particular interest to scientists. For instance, ED50 is a dose level at which 50% of subjects/recipients respond ($Y = 1$). In other words, it is the dosage such that

$$\pi(\text{ED}50) = 0.5.$$

In general, the effective dose level EDγ for some $\gamma \in (0, 100)$ is the x value such that

$$\pi(\text{ED}\gamma) = \gamma/100.$$

We use ED25, ED50, ED75 and so on for dosages at which 25%, 50% and 75% of the subjects respond. See Figure 2.1 for an illustration of the dose–response relationship.

It is feasible to have the dose–response relationship $\pi(x)$ estimated based on binary dose–response experiments nonparametrically. This practice is safe against potential model misspecification. However, nonparametric inference generally has lower efficiency compared with parametric inference. Hence, a parametric model assumption is often imposed if it can provide a good description of the dose–response relationship. There are many commonly used models for this purpose. We limit our review on a few specific ones.

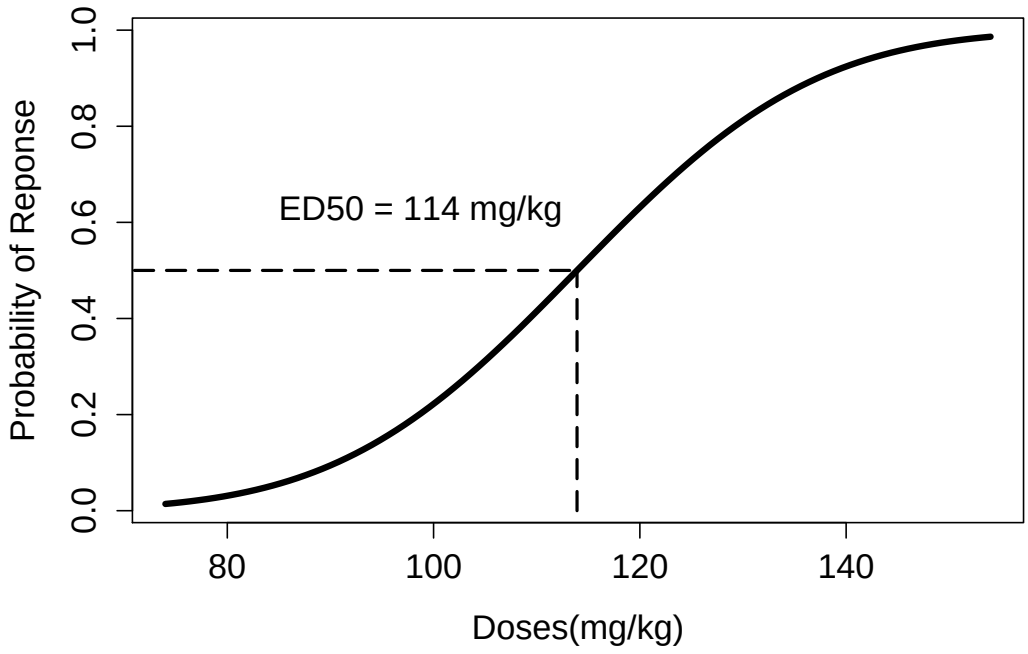


Figure 2.1: A sample dose–response curve.

Logistic regression model. Under the logistic regression model assumption, we postulate the dose–response curve satisfying

$$\text{logit}\{\pi(x)\} = \log\big[\frac{\pi(x)}{1-\pi(x)}\big] = \alpha + \beta x \tag{2.1}$$

for some parameter α and β. It is seen that under this model,

$$\pi(x) = \frac{\exp(\alpha+\beta x)}{1+\exp(\alpha+\beta x)}. \tag{2.2}$$

For any $\gamma \in (0, 100)$, we have

$$\text{ED}\gamma = \frac{\text{logit}(\gamma/100) - \alpha}{\beta} \tag{2.3}$$

In particular, we have $\text{ED}50 = -\alpha/\beta$.

When $x = \infty$, we have $\pi(\infty) = 1$ with $\beta > 0$. We do not generally have $\pi(0) = 0$. This does not seem to be a problem in most applications. We will discuss other properties of the logistic regression model later.

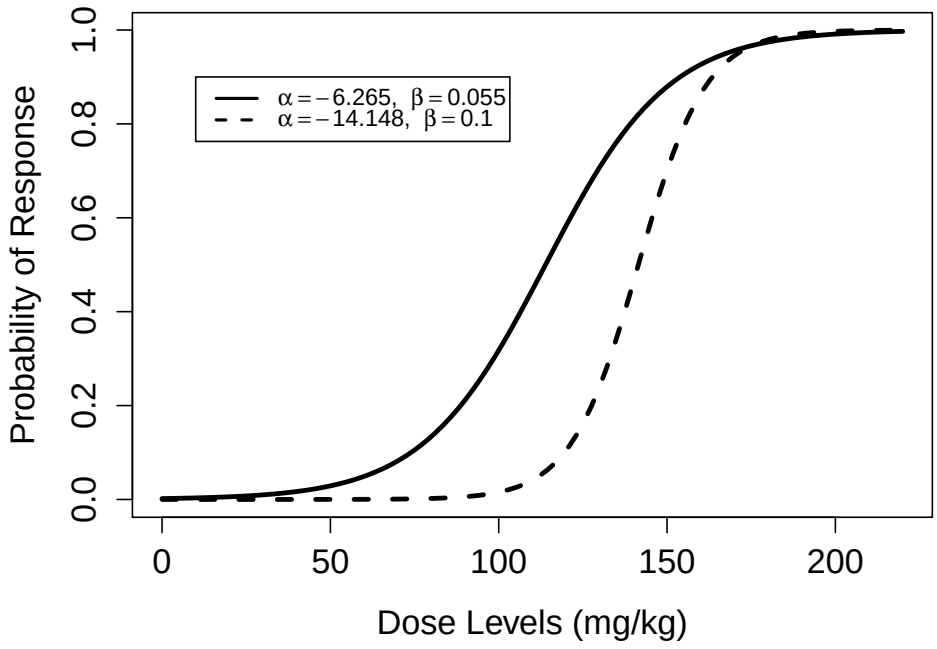


Figure 2.2: Two sample logistic regression curves.

Probit regression model. Under the probit regression model assumption, we postulate the dose–response curve satisfying

$$\pi(x) = \Phi(\alpha + \beta x) \tag{2.4}$$

where $\Phi(\cdot)$ is the cumulative distribution function of the standard normal distribution, and α and β are two model parameters.

The probit regression model can be motivated by the existence of a latent variable. Suppose there exists an auxiliary random variable

$$Z = \alpha + \beta X + \epsilon$$

such that ϵ has the standard normal distribution. Suppose a positive response to the stimulus occurs only when $Z > 0$. In this case, we have

$$\pi(x) = P(Z > 0|X = x) = P(\alpha + \beta X + \epsilon > 0) = \Phi(\alpha + \beta x).$$

In applications, the latent variable may be regarded as some unobserved stress index. The subject will respond to a stimulus only if its level exceeds some threshold value.

Three-parameter logistic regression model. The two-parameter logistic regression model in (2.1) can be easily generalized to allow additional flexibility:

$$\text{logit}\{\pi^{\lambda}(x)\} = \log\big[\frac{\pi^{\lambda}(x)}{1 - \pi^{\lambda}(x)}\big] = \alpha + \beta x \tag{2.5}$$

for a parameter $\lambda > 0$. El-Saidi (1993) proposed the use of this model for the doseresponse relationship. Note that when $\lambda < 0$, we will find $1 - \pi^{\lambda}(x) < 0$. Then the logit function is not defined. Hence, the restriction on λ is a mathematical necessity.

A two-parameter logistic regression model has some build-in symmetry. For instance, it satisfies

$$\text{ED}\gamma + \text{ED}(100 - \gamma) = -\frac{2\alpha}{\beta}$$

assuming $\beta \neq 0$. Such a restriction is hard to justify in applications. Introduction of the parameter λ helps to soften this restriction without overcomplicating the system. Under the proposed model, the effective dose level at γ is given by

$$\text{ED}\gamma = \frac{\text{logit}\big((\gamma/100)^{\lambda}\big) - \alpha}{\beta}. \tag{2.6}$$

An explicit expression of the dose–response relationship is

$$\pi(x) = P\{Y = 1|X = x\} = \Big\{\frac{\exp(\alpha + \beta x)}{1 + \exp(\alpha + \beta x)}\Big\}^{1/\lambda}. \tag{2.7}$$

Clearly, we may also introduce the three–parameter probit model in a similar fashion. For the purpose of this dissertation, we focus on the three–parameter logistic regression model. It will be seen that our idea is generally applicable.

2.2 Optimal designs

An experimental design is a plan for the set of level combinations of explanatory/design variables. Namely, it specifies the number of experimental trials, running at specific level combinations. For example, in a dose–response experiment, a simple plan is to run 20 trials at dose level x_1, and another 10 trials at dose level x_2, with the total number of trials $n = 30$. The dose level is the explanatory/design variable in this example. The explanatory variable can be vector valued, for instance, when a trial is running with two drugs being administered together. The combination of dose levels of drugs A and B is a "level combination". To develop optimal design theory for dose–response experiments, we first review concepts of generic optimal designs.

Consider the situation where the conditional distribution of the response variable Y given the value of the explanatory variable $X = x$ has a parametric form $f(y; x, \theta)$ in the experiment to be carried out. Suppose observations at independently selected X values $x_1, x_2, \ldots, x_n$ are obtained and denoted as $y_1, \ldots, y_n$. In this case, the likelihood function is given by

$$\ell_n(\theta) = \sum_{i=1}^{n} \log f(y_i; x_i, \theta). \tag{2.8}$$

One may then estimate θ by its maximum likelihood estimator $\hat{\theta}$. Under general regularity conditions on the conditional density function and some restrictions on the design, namely the configuration of $\{x_1, x_2, \ldots, x_n\}$, the

maximum likelihood estimator is asymptotically normal. That is, as $n \to \infty$,

$$\mathbb{I}_n^{-1/2}(\hat{\theta} - \theta) \to N(\mathbf{0}, \mathbf{I})$$

where $\mathbb{I}_n$ is the Fisher information matrix defined as

$$\mathbb{I}_n(\theta) = \sum_{i=1}^{n} E\left\{\frac{\partial \log f(y_i; x_i, \theta)}{\partial \theta}\right\}\left\{\frac{\partial \log f(y_i; x_i, \theta)}{\partial \theta}\right\}^{\tau}.$$

We have adopted the convention that θ is regarded as the true parameter value.

The asymptotic result implies that the variance matrix of $\hat{\theta}$ is approximately given by $\mathbb{I}_n^{-1}$. The precision of the estimator $\hat{\theta}$ is higher when $\mathbb{I}_n$ is larger. Because $\mathbb{I}_n$ is a matrix, its magnitude is not well-defined. At the same time, a matrix with a large determinant is deemed large in common sense. Hence, a popular optimality criterion is to search for a design such that

$$\{\det[\mathbb{I}_n(\theta)] : \quad x_1, \ldots, x_n \in \mathcal{X}\}$$

is maximized. Here $\mathcal{X}$ is the space of possible x values. We usually call $\mathcal{X}$ the design space. The outcome of the design is a set of specific level combinations $\{x_1, \ldots, x_n\}$. The resulting design is called D-optimal: D for determinant.

The determinant of a symmetric matrix is the product of its eigenvalues. A positive definite matrix is seen as large if the sum of its eigenvalues is large. Recall that the sum of eigenvalues of a matrix is called its trace. Hence, one may also choose a design so that the trace of the Fisher information is

maximized:

$$\max\{\text{tr}[\mathbb{I}_n(\theta)] : \quad x_1, \ldots, x_n \in \mathcal{X}\}.$$

The corresponding solution is called A-optimal.

Example: Consider the situation where the design variable X is one dimensional, and a linear model is appropriate:

$$y = \theta_0 + \theta_1 x + \epsilon$$

where ϵ has the standard normal distribution. Based on n independent observations $\{(x_i, y_i) : i = 1, 2, 3, \ldots, n\}$, the Fisher information matrix is given by

$$\mathbb{I}_n(\theta) = \begin{bmatrix} n & \sum x_i \\ \sum x_i & \sum x_i^2 \end{bmatrix}.$$

One may notice that the Fisher information does not depend on the unknown parameter θ. If $\mathcal{X} = \{-1, +1\}$ and $n = 2k$, then the optimal design is given by

$$\{x_1, \ldots, x_n\} = \{-1, -1, \cdots, -1; +1, +1, \ldots, +1\}.$$

In other words, the D-optimal design for the experiment is to collect data by running k trials at $x = -1$ and other k trials at $x = +1$. It is also convenient to regard this design as a uniform distribution on $\{-1, 1\}$. We may hence denote a design as ξ_n.

When it comes to nonlinear models, the solution to optimal designs is no longer so simple.

Example: Consider the logistic regression model given by (2.1). In this case, we have

$$\log f(y; x, \theta) = y \log\{\pi(x)\} + (1 - y) \log\{1 - \pi(x)\}$$

where we have used new notation $\theta = (\alpha, \beta)^\tau$. The Fisher information matrix based on a single observation at $X = x$ is therefore given by

$$\mathbb{I}(x) = \begin{bmatrix} \pi(x)\{1 - \pi(x)\} & x\pi(x)\{1 - \pi(x)\} \\ x\pi(x)\{1 - \pi(x)\} & x^2\pi(x)\{1 - \pi(x)\} \end{bmatrix}.$$

When n observations are obtained at $x_1, \ldots, x_n$, the Fisher information becomes

$$\mathbb{I}_n(\xi_n) = \sum_{i=1}^{n} \begin{bmatrix} \pi(x_i)\{1 - \pi(x_i)\} & x_i\pi(x_i)\{1 - \pi(x_i)\} \\ x_i\pi(x_i)\{1 - \pi(x_i)\} & x_i^2\pi(x_i)\{1 - \pi(x_i)\} \end{bmatrix}.$$

Here we have introduced ξ_n for the design which subscribes trials at dose levels $x_1, \ldots, x_n$. We pointed out earlier that ξ_n can be regarded as a uniform distribution on $x_1, \ldots, x_n$.

Clearly, the Fisher information is a function of θ because $\pi(x)$ depends on θ. Consequently, the D-optimal design for the dose–response experiment depends on θ. According to Sitter and Wu (1993), given θ, the D-optimal design under the logistic dose–response model is a uniform distribution on ED17.6 and ED82.4. Because ED values depend on the true value of θ, the optimal design cannot be directly used to guide the experiment unless the θ value is known. Yet if the θ value is known, there is no need to conduct the

experiment. Nevertheless, the result of the D-optimal design can be used in other ways. For instance, it reveals the limit of how efficient a design can be based on the D-optimal criterion.

To avoid the dilemma that a good design is possible only if the dose–response relationship is known, sequential approaches are often used. The general idea is simple: run a small pilot experiment based on the prior information of the applicants to obtain a rough idea on the dose–response relationship. Updating our knowledge of the dose–response relationship, and select the "optimal design" for the next stage of experiment. In the most extreme case, a completely sequential design is used.

2.3 D-optimal design under the logistic model

As mentioned in the last section, the D-optimal design under the logistic dose–response model has two optimal dose levels, ED17.6 and ED82.4. The derivation of these two optimal doses has been extensively studied, and is already available in the literature (See Abdelbasit and Plackett (1983); Minkin (1987); Sitter and Wu (1993); Mathew and Sinha (2001), among others). In this section, we shall only give a brief derivation of the D-optimal design under the logistic model.

In order to get the D-optimal design, we need to maximize the determinant of the Fisher information matrix $I(\alpha, \beta)$. Let $a_i = \alpha + \beta x_i$. We write

the Fisher information matrix as

$$\mathbb{I}(\alpha,\beta) = \begin{bmatrix} \sum_{i=1}^{n} \frac{\exp(-a_i)}{(1+\exp(-a_i))^2} & \sum_{i=1}^{n} x_i \frac{\exp(-a_i)}{(1+\exp(-a_i))^2} \\ \sum_{i=1}^{n} x_i \frac{\exp(-a_i)}{(1+\exp(-a_i))^2} & \sum_{i=1}^{n} x_i^2 \frac{\exp(-a_i)}{(1+\exp(-a_i))^2} \end{bmatrix}$$

Minkin (1987) studied the following representation for the determinant of the above Fisher information,

$$\begin{aligned} \beta^2|\mathbb{I}(\alpha,\beta)| &= \Big[\sum_{i=1}^{n} \frac{\exp(-a_i)}{\big(1+\exp(-a_i)\big)^2}\Big]\Big[\sum_{i=1}^{n} a_i^2 \frac{\exp(-a_i)}{\big(1+\exp(-a_i)\big)^2}\Big] \\ &- \Big[\sum_{i=1}^{n} a_i \frac{\exp(-a_i)}{\big(1+\exp(-a_i)\big)^2}\Big]^2. \end{aligned}$$

Let $w_i = \exp(a_i)/\big(1+\exp(a_i)\big)^2$. The above equation is simplified to

$$\beta^2|\mathbb{I}(\alpha,\beta)| = \big(\sum_{i=1}^{n} w_i\big)\big(\sum_{i=1}^{n} w_i a_i^2\big) - \big(\sum_{i=1}^{n} w_i a_i\big)^2. \tag{2.9}$$

Using similar arguments in Abdelbasit and Plackett (1983), Minkin (1987) showed that the first term in equation (2.9) is maximized when a_i satisfies the following equation,

$$a_i = \big(\exp(a_i)+1\big)/\big(\exp(a_i)-1\big),$$

which is solved as $a_i = \pm 1.5434$.

Minkin (1987) claimed that when n is even, it is possible to simultaneously maximize the first term in (2.9) and minimize the second term being subtracted, by assigning $n/2$ subjects to the dose corresponding to $a_j = 1.5434$, and assigning the remaining $n/2$ subjects to the dose corre-

sponding to $a_j = -1.5434$. Therefore, the D-optimal design consists of two doses x_1 and x_2, which satisfy $\alpha + \beta x_1 = 1.5434$, and $\alpha + \beta x_2 = -1.5436$. Hence,

$$x_1 = (1.5434 - \alpha)/\beta,$$

and

$$x_2 = (-1.5434 - \alpha)/\beta.$$

Note that the corresponding probabilities of responses for x_1 and x_2 are $\pi(-1.5434) = 0.176$ and $\pi(1.5434) = 0.824$. Thus, x_1 and x_2 correspond to ED17.6 and ED82.4 doses, i.e., the corresponding optimal doses are ED17.6 and ED82.4. For the probit dose–response model, the corresponding optimal dose levels are ED12.8 and ED87.2.

The direct use of the above D-optimal design is not always plausible. First, the above derivation for the D-optimal design clearly shows that optimal designs rely on the complete knowledge of the model parameters which are always unknown or no experiments are needed. Thus, optimal designs are often considered as benchmarks or reference points for comparing with alternative designs.

2.4 Sequential D-optimal design

The D-optimal design requires complete knowledge of the dose–response relationship. We can overcome this difficulty by implementing the design sequentially. The experiment runs in a trial-by-trial way with the next dose determined by the D-optimal criterion updated based on the most recent

trial results.

Sequential D-optimal designs usually use a pilot study and maximum likelihood to give an initial estimate of the model parameters. However, this procedure can be applied only if the MLE of the model parameters exist. The MLE may not exist under the logistic regression model. According to Silvapulle (1981), the MLE exists if there is an overlapping pattern in the data. Hence, the sequential D-optimal design generally needs to start with an initial stage which ends when the trial results meet the condition for the existence of the MLE (Silvapulle, 1981; Albert and Anderson, 1984; Santner and Duffy, 1986).

Wang et al. (2013) and Wang et al. (2015) are recent examples. Following Neyer (1991, 1994) and Langlie (1963), they proposed a sequential two–stage D–optimality design. Their designs consist of two stages: an initial stage and a D–optimality stage. The first stage is designed to find an overlap between stimuli that generate responses and those that generate nonresponses, and tentatively estimate the model parameters. The overlap guarantees the existence of the MLE of the unknown model parameters (Silvapulle, 1981). The estimates will then be used in the next stage of the experiment. In the second stage, the parameter estimation is updated after each additional trial. The subsequent design points are then selected sequentially to maximize the determinant of the Fisher information matrix of the parameters. The procedure continues until the number of trials reaches the predetermined sample size.

Other relevant literatures on the sequential D-optimal design include Wu (1985a), Wu (1985b), Neyer (1991), Neyer (1994), Dror and Steinberg

(2008), Wu and Tian (2013), among others.

2.5 Three-phase sequential design

The design proposed by Wu and Tian (2013) is another interesting sequential approach. They developed a three-phase sequential procedure to quickly and efficiently estimate a single ED level.

Their design consists of three stages. The first and second stages provide information for an initial estimate of the dose–response model. The goal of the first stage is to quickly identify a reasonable experimental range by generating some responses and nonresponses, and to allocate the design points to find an overlap in the data. In the second stage, subsequent design points are then chosen to optimize the parameter estimation based on the D-optimal criterion. In the third stage, Robbins-Monro-Joseph procedure (Robbins and Monro, 1951; Joseph, 2004) is applied to cluster the design points around the unknown target ED level.

Wu and Tian (2013) descried their procedures as follows. Let X or x denote the dose level of a stimulus. Let Y be the random outcome. In pyrotechnics study, $Y = 1$ if the experimental subject has exploded, and $Y = 0$ otherwise. Wu and Tian considered the location-scale model

$$\pi(x) = P(Y = 1|X = x) = f((x - \mu)/\sigma). \tag{2.10}$$

where μ and σ are unknown parameters, and f is a known distribution function. Under this model, the effective dose level EDγ for some $\gamma \in (0, 100)$

is the x value such that

$$\pi(\text{ED}\gamma) = \gamma/100.$$

Hence,

$$\text{ED}\gamma = \mu + \sigma f^{-1}(\gamma/100).$$

2.5.1 First stage

To implement the three-phase sequential design, a key ingredient is the update of the parameter estimate after each trial. The MLE is a popular choice, however, it may not exist under the logistic regression model (Silvapulle, 1981). To ensure the existence of MLE, the first stage aims to find a reasonable range of the design points by generating some responses and nonresponses, and to find an overlap in the data using a searching scheme. See Wu and Tian (2013) for more vivid descriptions of the first stage design.

2.5.2 Second stage

In the second stage, the subsequent design points are selected based on the D-optimal criterion. The MLEs of the model parameters are updated after each additional trial.

- Compute the MLE $(\hat{\mu}_s, \hat{\sigma}_s)$ of (μ, σ) based on the observed data $(x_1, y_1), \ldots, (x_s, y_s)$.

- Denote $x_m = \min(x_1, \ldots, x_s)$ and $x_M = \text{Max}(x_1, \ldots, x_s)$. To ensure the estimates are in the design region, Wu and Tian suggested to

truncate the estimates $\hat{\mu}_s$ and $\hat{\sigma}_s$ as

$$\tilde{\mu}_s = \text{Max}\{x_m, \min(\hat{\mu}_s, x_M)\}$$

and

$$\tilde{\sigma}_s = \text{Min}\{\hat{\sigma}_s, x_M - x_m\}.$$

Hence, $\tilde{\mu}_s$ is in $[x_m, x_M]$, and $\tilde{\sigma}_s$ dose not exceed $x_M - x_m$.

- Then, select the next design point x_{s+1} such that the determinant of the Fisher information matrix evaluated at $(\tilde{\mu}_s,\ \tilde{\sigma}_s)$ based on the existing s trials and an extra trial at dose level x_{s+1} is maximized.

- Suppose n_1 runs are assigned for the first and second stage of the design. The above process will then be repeated until the number of trials reaches the predetermined size n_1.

2.5.3 Third stage

The goal of the thirst stage is to cluster the design points around the unknown target ED level. Wu and Tian applied the Robbins-Monro-Joseph procedure. See Robbins and Monro (1951), Lai and Robbins (1979), Joseph (2004), and Wu and Tian (2013) for detailed descriptions of the Robbins-Monro-Joseph procedure. The third stage consists of two main steps.

- The first step is to choose an initial value. Wu and Tian applied

$$x_{n_1+1} = \tilde{\mu}_{n_1} + f^{-1}(\gamma/100)\tilde{\sigma}_{n_1}$$

where $\tilde{\mu}_{n_1}$ and $\tilde{\sigma}_{n_1}$ are MLEs of (μ, σ) based on the first n_1 observations $(x_1, y_1), \ldots, (x_{n_1}, y_{n_1})$ obtained from the first and second stage of the experiment. Denote the Fisher information matrix as $\mathbb{I}_{n_1}(\tilde{\mu}_{n_1}, \tilde{\sigma}_{n_1})$. Compute the inverse of Fisher information matrix.

$$V = \mathbb{I}_{n_1}(\tilde{\mu}_{n_1}, \tilde{\sigma}_{n_1})^{-1} = \begin{bmatrix} v_{00} & v_{01} \\ v_{10} & v_{11} \end{bmatrix}$$

Here $v_{00} = \text{var}(\tilde{\mu}_{n_1})$, $v_{11} = \text{var}(\tilde{\sigma}_{n_1})$, and $v_{01} = v_{10} = \text{cov}(\tilde{\mu}_{n_1}, \tilde{\sigma}_{n_1})$ are elements of the variance-covariance matrix of $(\tilde{\mu}_{n_1}, \tilde{\sigma}_{n_1})$. Then let $\tau_1^2 = v_{00} + \{f^{-1}(\gamma/100)\}^2 v_{11}$.

- The second step is to cluster the design points around the target ED level. Denote y_{n_1+1} be the observed response at x_{n_1+1}. Wu and Tian proposed to select the subsequent design points based on the Robbins-Monro-Joseph iterative scheme (Joseph, 2004),

$$x_{n_1+i+1} = x_{n_1+i} - a_i(y_{n_1+i} - b_i), \ i \geq 1.$$

Here x_{n_1+i} and y_{n_1+i} are the ith design point and its corresponding response, and a_i and b_i are some positive constants. See Joseph (2004) and Wu and Tian (2013) for a general discussion on the choice of a_i and b_i.

- Suppose n_2 runs are assigned to the third stage of the experiment. The above procedure is then repeated until the number of trials reaches the predetermined size n_2.

2.6 Up-and-down design

Both the D-optimal design and the sequential D-optimal design are possible only if a parametric model is assumed for the dose–response relationship. Without a parametric model, the up-and-down design proposed by Dixon and Mood (1948) is an effective way of determining the median effective dose level ED50. See Pace et al. (2007), among others.

The following is a quick description of the up-and-down design. Prior to the trial, K ordered discrete dose levels,

$$\Omega = \{x_1 < x_2 < \ldots < x_K\}$$

are specified based on prior information. The experiment starts with the first subject at dose $X(1) = x_1$, or at a level thought to be close to the true target dose such as ED50, or at a level selected randomly from Ω. Suppose that the first trial is completed at $X(1) = x_k$. If the observed response of the first subject is $Y_1 = 1$, the second subject is assigned to a lower dose $X(2) = x_{k-1}$. If the observed response of the first subject is $Y_1 = 0$, the second subject is assigned to a higher dose $X(2) = x_{k+1}$. If $X(1) = x_1$ or $X(1) = x_K$, appropriate adjustments are made.

Research shows that the up-and-down design tends to assign doses $X(i)$ in the long run clustered unimodally around ED50. Because of this, after n trials, one may estimate ED50 using the empirical mean $\hat{\mu} = n^{-1} \sum_{i=1}^{n} X(i)$. Other estimators may also be used. For example, Brownlee et al. (1953) proposed to not include the initial dose $X(1)$ in the calculation of the es-

timate, but include x_{n+1}, the dose that would have been assigned to the $(n+1)$th subject:

$$\hat{\mu} = \frac{1}{n}\sum_{i=2}^{n+1} X(i)$$

Another commonly used nonparametric estimator for ED50 is the turning point estimator (See Wetherill (1963), Choi (1971), Choi (1990), among others). If $x_1, \ldots, x_n$ is a sequence of dose levels, we say that there is a turning point at time j, $1 < j < n$, if $x_{j-1} < x_j$ and $x_j > x_{j+1}$ (peak) or if $x_{j-1} > x_j$ and $x_j < x_{j+1}$(trough), that is, the sequence of dose levels turns from increasing to decreasing, or from decreasing to increasing. Let σ denote the difference between successive dose levels. Let $t_1, t_2, \ldots,$ denote the doses at the turning points (peaks and troughs). Define

$$w_i = \begin{cases} t_i + \sigma/2 & \text{if} \quad t_i \text{ is a trough} \\ t_i - \sigma/2 & \text{if} \quad t_i \text{ is a peak.} \end{cases}$$

The turning point estimator for ED50 based on k turning points is

$$\bar{w} = \sum_{i=1}^{k} w_i/k$$

The turning point estimator is widely used in anesthesia up-and-down studies.

2.7 Biased-coin up-and-down design

The standard up-and-down design is developed specifically for estimating ED50. If a different ED level is of interest, one may use the biased-coin

up-and-down design of Durham and Flournoy (1994). Let the ED level of interest be EDγ for some $\gamma \in (0, 100)$. The generalization aims to cluster the assigned doses around EDγ to enable efficient estimation.

The biased-coin up-and-down design is as follows. Let the dose level of the first subject be X(1).

- Suppose the nth subject is assigned at dose $X(n) = x_k$, and responds with $Y_n = 0$. For $\gamma \leq 0.5$, the $(n+1)$th subject will be assigned at the lower dose $X(n+1) = x_{k-1}$. Otherwise, the $(n+1)$th subject will be randomized with probability $b = \gamma/(100 - \gamma)$ to the next higher dose level, and $1 - b$ to the same dose.

- Suppose the nth subject is assigned at dose $X(n) = x_k$, and responds with $Y_n = 1$. For $\gamma > 50$, the $(n+1)$th subject will be assigned at the lower dose $X(n+1) = x_{k-1}$. Otherwise, the $(n+1)$th subject will be randomized with probability $b = (100 - \gamma)/\gamma$ to the next higher dose level, and $1 - b$ to the same dose.

Appropriate adjustments are made, if $X(n) = x_1$ or $X(n) = x_K$, where x_1 and x_K are the lowest and highest dose levels specified in Ω.

Durham and Flournoy (1994) showed that the assigned doses $X(i)$ cluster unimodally around the target ED level in a biased-coin up-and-down experiment. They suggested to use the mode of the assigned doses as a nonparametric estimator of the target ED level.

2.8 Group up-and-down design

Sometimes, a group of experimental subjects become available at the same time. Hence, it may be desirable to assign the same dose level to all subjects in this group. A group up-and-down design has been developed, and it is another widely used sequential design in clinical trials. The design was first described by Anderson et al. (1946), followed by Wetherill (1963).

Tsutakawa (1967a,b) analyzed the group up-and-down design with the goal to estimate ED50. Gezmu and Flournoy (2006) generalized their method, and constructed the group up-and-down design to target any ED levels.

The group up-and-down design proceeds with groups of s experimental subjects for some s. Let c_{low} and c_{upper} be the integers between 0 and s, such that $0 \leq c_{low} < c_{upper} \leq s$. Constants c_{low} and c_{upper} are usually referred to as the cutoff points. Prior to the trial, K ordered discrete dose levels,

$$\Omega = \{x_1 < x_2 < \ldots < x_K\}$$

are specified, just like the case of the standard up-and-down design.

The experiment starts with the first group at dose $X(1)$, where $X(1)$ may be chosen as the lowest dose level in Ω. The responses of the subjects from the first group are used to determine the dose level assigned to the next group.

- If there are at most c_{low} subjects in the first group with response $Y = 1$ at dose $X(1) = x_k$, the second group are assigned to the next higher dose $X(2) = x_{k+1}$.

- If there are at least c_{upper} subjects in the first group with response $Y = 1$ at dose $X(1) = x_k$, the second group are assigned to the next lower dose $X(2) = x_{k-1}$.
- Otherwise, the second group are assigned to the same dose level.

If $X(n)$ is at the lowest dose x_1 or highest dose x_K, appropriate adjustments are made.

Given the target effective dose level EDγ, Gezmu and Flournoy (2006) studied the choice of the cutoff points c_{low} and c_{upper}, and the group size s so that the assigned doses cluster around EDγ. Similar to the biased-coin up-and-down designs, the mode of the assigned doses are suggested as a nonparametric estimator of the target EDγ under the group up-and-down design.

2.9 Accelerated biased-coin design

The sequential designs discussed above are easy to implement and widely used in dose–response experiments. In these designs, the dose assigned to a subject depends on the response of the preceding subject. Therefore, a new subject cannot enter the trial until the preceding subject has responded. To utilize these sequential designs, a subject's response needs to be observed quickly, otherwise, the above designs may cause long trial duration, which is obvious not desirable in clinical trial practice.

Motivated by this, Stylianou and Follmann (2004) proposed to modify the biased-coin up-and-down design to deal with the situation that a sub-

ject's response to a stimulus is not observed quickly. Their idea is to assign doses to subjects as they enter the trial based on the response of the last subject who has completed the trial. This modification allows researchers to evaluate several subjects simultaneously.

Their design follows the dose assigning paradigm of the biased-coin up-and-down design, and is referred to as the accelerated biased-coin up-and-down design. If a subject enters the trial before the response of the preceding subject has been observed, the new subject will be assigned to a dose based on the last observed response.

Stylianou and Follmann (2004) compared the accelerated design with the biased-coin up-and-down design, and found that the accelerated design greatly reduces the duration of the trial, and does not affect the estimation precision of the target ED level, when estimated by an isotonic regression estimator (Stylianou and Flournoy (2002)).

2.10 Generalized Pólya Urn design

Rosenberger and Grill (1997) proposed a sequential design procedure based on the generalized Pólya urn (GPU) model from Athreya and Ney (2012) to efficiently estimate ED50, while potentially estimate other ED levels such as ED25 and ED50.

The GPU model can be used to design dose–response experiments (Rosenberger, 1996; Rosenberger and Grill, 1997). A number of does levels are prespecified. The procedure starts with a urn containing a population of particles. Each particle is labeled with a dose level. A particle is drawn at

random and its dose level is assigned to the experimental subject. If the experimental subject responds (or does not respond), one particle for each of the next k lower (or higher) doses are added to the urn. The procedure is then repeated until the end of the experiment.

Rosenberger and Grill (1997) suggested $k = 5$ and referred to this scheme as the 5-up/5-down rule. They found the design points are unimodally distributed around ED50. To better estimate other ED levels such as ED25 and ED50, they proposed to alter the design so that the dose levels would spread out further. Based on the simulation result of Rosenberger and Grill (1997), the GPU design is efficient for estimating ED50. However, its performance for estimating other ED levels such as ED25 and ED75 are variable when the number of trials is small, but its performance improves when the number increases.

The sequential designs discussed above are simple to implement in practice. However, they all aim to estimate a single ED level of dose–response curves. If one is interested in knowing the dose–response relationship over a dose range, these designs are not most appropriate.

Chapter 3

Two-stage Sequential ED-Design

3.1 Introduction

In the last two chapters, we have introduced and reviewed many dose–response models and some related design issues. We pointed out that many classical designs such as the up-and-down design and its generalizations in the literature aim to most accurately estimate a specific ED level. The D-optimal and other optimal designs aim to most accurately estimate model parameters. While a more accurate parameter estimation should generally lead to more accurate characterization of the dose–response relationship, these two goals are not equivalent. For this reason, we propose a new approach in designing a binary experiment, and investigate whether it leads to a more efficient model estimation from this angle of interest.

More specifically, we study a situation where the dose–response relationship over a range of ED levels is of interest. We believe such a relationship can be well characterized after several carefully chosen ED levels are accurately estimated simultaneously. Based on these considerations, we propose

a two-stage sequential ED-design.

In the next section, we will give a detailed description of the proposed design.

3.2 New criterion

Assume that the dose–response relationship is given by the conditional probability mass function $f(y; x, \theta)$ where θ is the model parameter. We assume that the total number of trials n will be used to obtain data for the model fitting.

Under the parametric model assumption, each ED level ξ is a smooth function of the unknown parameter θ: $\xi = g(\theta)$. Suppose that following some scheme, i trials have been carried out. Let $\hat{\theta}_i$ be an estimate of θ based on the data obtained from the first i trials. When i is large, the variance-covariance matrix of $\hat{\theta}_i$ is well approximated by the inverse of the Fisher information $\mathbb{I}_i(\theta)$. The variance of $g(\hat{\theta}_i)$ is therefore approximately

$$\{\bigtriangledown g^{\tau}(\theta)\}\{\mathbb{I}_i^{-1}(\theta)\}\{\bigtriangledown g(\theta)\} \tag{3.1}$$

where $\bigtriangledown g(\theta)$ is the gradient of $g(\cdot)$.

When i is small, the approximate variance (3.1) is not accurate. Nevertheless, it remains a good metric of the relative informativeness of the data collected so far. Because of this, we propose to select dose $(i + 1)$ to minimize the total observed variance of several ED levels chosen by the user. Let $\mathbb{I}_i(\theta; +x)$ be the Fisher information based on the first i trials and the

potential $(i+1)$th trial to be run at dose level x. The proposed ED-criterion is to select the next dose level x which minimizes

$$\sum_{j=1}^{K_0}\{\bigtriangledown g_j^{\tau}(\hat{\theta}_i)\}\{\mathbb{I}_i^{-1}(\hat{\theta}_i;+x)\}\{\bigtriangledown g_j(\hat{\theta}_i)\} \tag{3.2}$$

where $g_j(\theta) = \xi_j$ are K_0 selected target ED levels. In this thesis, we use $K_0 = 3$, and our criterion will not be affected if other K_0 values are selected.

Starting from some K initial pilot trials, the sequential ED-criterion is used to select dose levels for the $(K+1)$th, $(K+2)$th trials until the experiment terminates.

Let $\{(X_i, Y_i), i = 1, 2, \ldots, n\}$ be the doses and responses. Under a sequential design such as our proposed one, they are not independent of each other. However, the dependence of Y_i on $(Y_1, X_1), \ldots, (Y_{i-1}, X_{i-1})$ is only through X_i. As a consequence, the likelihood constructed from $(Y_1, X_1), \ldots, (Y_i, X_i)$ retains a product form $\prod_{r=1}^{i} f(Y_r; X_r, \theta)$ despite the dependence structure of the data arising from the sequential design (Chaudhuri and Mykland, 1993, 1995). Hence, the likelihood based on the proposed sequential design is identical to that arising from the independent observations. A general discussion on the validity of this likelihood function will be given in Chapter 6.

The ED-design can be implemented with θ estimated by its MLE sequentially. It is natural to have all target EDγ and the entire dose–response curve estimated based on the likelihood method. We now discuss details under the logistic model.

3.2.1 The pilot experiment

To apply the proposed ED-design, we need a pilot experiment to give us an initial parameter estimation. We propose to identify a dose range covering the anticipated dose levels ED10 to ED90. We then create set Ω with k dose levels from ED10 to ED90. The data collected in the pilot experiment will be used to provide an initial parameter estimation for the implementation of the proposed ED-design sequentially.

3.3 Sequential ED-design under the logistic model

Recall that the logistic dose–response model assumes that

$$\text{logit}\{\pi(x)\} = \log\{\pi(x)/(1-\pi(x))\} = \alpha + \beta x. \tag{3.3}$$

Under this model, $\theta = (\alpha, \beta)^\tau$ and the probability mass function

$$P(Y = 1; X = x, \theta) = f(1; x, \theta) = \pi(x)$$

and

$$P(Y = 0; X = x, \theta) = f(0; x, \theta) = 1 - \pi(x)$$

with

$$\pi(x) = [1 + \exp(-(\alpha + \beta x))]^{-1}.$$

To implement our proposed ED-design and other sequential designs, a

key ingredient is the update of the parameter estimate after each trial. The MLE is a popular choice in the literature. However, the MLE may not exist under the logistic regression model. Suppose A_1 is the set of dose levels at which the subjects responded to the stimulus and A_0 is the set of dose levels at which the subjects did not respond. The MLE exists only if the convex hulls of A_1 and A_0 overlap (Silvapulle, 1981; Albert and Anderson, 1984).

Particularly in simulation studies or the early stages of a sequential experiment, the above condition may not be satisfied. Various suggestions have been made in the literature. For instance, one may extend the pilot experiment until the data collected permit a valid MLE. In this dissertation we investigate a novel approach.

In most applications, the user has some idea on a sufficiently low dose level at which the subject will not respond ($Y = 0$), and a high enough dose level at which the subject will respond ($Y = 1$). Our idea is to make use of such prior information in a non-Bayesian way. For this purpose, let s_1 and s_2 be the anticipated ED01 and ED99 values. Based on this, we create four pseudo-outcomes: at dose level s_1, we create two weighted responses of $Y = 0$ and $Y = 1$ with weights 0.99 and 0.01; at dose level s_2, we create two weighted responses of $Y = 0$ and $Y = 1$ with weights 0.01 and 0.99. After K observations obtained from some pilot experiment, they are expanded with these four pseudo-outcomes. It can be seen that the resulting A_1 and A_0 have overlapping convex hulls. Hence, the MLE based on the expanded data set under the logistic regression model always exists. The pseudo-outcomes are clearly based on our prior knowledge, which gives this approach a Bayesian flavour. However, the prior information is not accommodated as a prior

distribution on the parameter value.

Given a dose level x, the Fisher information based on a single trial under the logistic model is given by

$$\begin{bmatrix} \pi(x)\{1-\pi(x)\} & x\pi(x)\{1-\pi(x)\} \\ x\pi(x)\{1-\pi(x)\} & x^2\pi(x)\{1-\pi(x)\} \end{bmatrix}.$$

The Fisher information after n trials with doses $x_1, \ldots, x_n$ is given by

$$\mathbb{I}_n(\alpha, \beta) = \sum_{i=1}^{n} \begin{bmatrix} \pi(x_i)\{1-\pi(x_i)\} & x_i\pi(x_i)\{1-\pi(x_i)\} \\ x_i\pi(x_i)\{1-\pi(x_i)\} & x_i^2\pi(x_i)\{1-\pi(x_i)\} \end{bmatrix}.$$

If an additional trial were carried out at dose level x, the Fisher information would be

$$\mathbb{I}_n(\alpha, \beta; +x) = \mathbb{I}_n(\alpha, \beta) + \begin{bmatrix} \pi(x)\{1-\pi(x)\} & x\pi(x)\{1-\pi(x)\} \\ x\pi(x)\{1-\pi(x)\} & x^2\pi(x)\{1-\pi(x)\} \end{bmatrix}.$$

Note that the ED level is related to the model parameter by

$$\xi_\gamma = \mathrm{ED}\gamma = g_\gamma(\alpha, \beta) = \frac{\mathrm{logit}(\gamma/100) - \alpha}{\beta}.$$

Under the current model, for a generic ED level ξ, (3.2) becomes

$$\frac{v^{00} + 2\xi v^{01} + \xi^2 v^{11}}{\beta^2} \tag{3.4}$$

where v^{ij} are the elements of $\mathbb{I}^{-1}(\alpha, \beta)$.

Recall that we use $\mathbb{I}_i(\alpha, \beta; +x)$ for the Fisher information after i trials,

and another trial at the proposed dose level x. We use

$$\hat{v}_i^{00}(x), \quad \hat{v}_i^{01}(x), \quad \hat{v}_i^{10}(x), \quad \hat{v}_i^{11}(x)$$

for the elements of $\mathbb{I}_i(\hat{\alpha}, \hat{\beta}; +x)$ where $\hat{\alpha}, \hat{\beta}$ are estimated parameter values based on the first i trials and the pseudo-observations.

In the second stage of our sequential ED-design, we choose the $(i+1)$th dose level as

$$x_{i+1} = \arg\min_x \sum_{j=1}^{3} \{\hat{v}_i^{00}(x) + 2\hat{\xi}_j \hat{v}_i^{01}(x) + \hat{\xi}_j^2 \hat{v}_i^{11}(x)\}.$$

Clearly, the sequential ED-design can be used for any number of ED levels. The numerical computation of x_{i+1} is also easy: a simple linear search suffices. Hence, the new design can satisfy a broad range of the demands that may arise in applications.

More specially, let us suppose ED25, ED50 and ED75 are the target ED levels. We now demonstrate how to select the next dose level in the ED-design. Denote ED25, ED50 and ED75 as ξ_j, $j = 1, 2, 3$. Note that

$$\xi_j = \frac{\text{logit}(\pi) - \alpha}{\beta}$$

with π being one of 0.25, 0.50 and 0.75.

The ξ_j value can be written as a function of α and β, i.e., $\xi_j = g(\alpha, \beta)$. Let $\hat{\xi}_j = g(\hat{\alpha}_k, \hat{\beta}_k)$, via the delta-method, one can easily obtained the asymp-

totic variance of $g(\hat{\alpha}_k, \hat{\beta}_k)$ as follows.

$$\text{var}(g(\hat{\alpha}_k, \hat{\beta}_k)) = \bigtriangledown g(\hat{\alpha}_k, \hat{\beta}_k)^T \mathbb{I}_k^{-1}(x; \hat{\alpha}_k, \hat{\beta}_k) \bigtriangledown g(\hat{\alpha}_k, \hat{\beta}_k) \tag{3.5}$$

where $\bigtriangledown g(\hat{\alpha}_k, \hat{\beta}_k)$ is the gradient of $g(\hat{\alpha}_k, \hat{\beta}_k)$, and $\mathbb{I}_k^{-1}(x; \hat{\alpha}_k, \hat{\beta}_k)$ is the inverse of the Fisher information matrix. Then the asymptotic variance of $\hat{\xi_j}$, for $j = 1, 2, 3$, is

$$\text{var}(\hat{\xi_j}) = \frac{v_{00} + 2\hat{\xi_j} v_{01} + (\hat{\xi_j})^2 v_{11}}{\hat{\beta}_k^2} \tag{3.6}$$

Here $v_{00} = \text{var}(\hat{\alpha}_k)$, $v_{11} = \text{var}(\hat{\beta}_k)$, and $v_{01} = v_{10} = \text{cov}(\hat{\alpha}_k, \hat{\beta}_k)$ are elements of the variance-covariance matrix of $(\hat{\alpha}_k, \hat{\beta}_k)$,

$$V = \mathbb{I}_k^{-1}(x; \hat{\alpha}_k, \hat{\beta}_k) = \begin{bmatrix} v_{00} & v_{01} \\ v_{10} & v_{11} \end{bmatrix}$$

Then the $(k+1)$th dose level is determined by minimizing the total variance of $\hat{\xi_j}$, for $j = 1, 2, 3$, i.e.,

$$x_{k+1} = \arg\min_x \sum_{j=1}^{3} \text{var}\big(g_j(\hat{\alpha}_k, \hat{\beta}_k)\big).$$

3.4 Simulation studies

We conduct simulations to investigate the performance of the ED-design. We compare the new design with existing designs including the standard up-and-down design, the D-optimal design, and the two-stage D-optimal design.

3.4.1 Detailed specifications

We investigate the performance of the designs through a hypothetical dose–response experiment with a binary outcome. For any given design, the response values of the experiment are generated at the dose levels prescribed by the design according to the assumed dose–response relationship. The goal of the experiment is to estimate the dose–response curve, namely $f(y; \theta, x)$. The detailed specifications are as follows.

1. Up-and-down design: As discussed in Section 2.6, this design places the doses on a grid of prespecified dose levels:

$$\Omega = \{x_1, \ldots, x_K\}$$

   for some K. In this simulation, we choose $K = 7$ with x_1 and x_K being the anticipated ED01 and ED90. The choice of the first dose level will be decided case by case in the simulation.

2. D-optimal design: According to Sitter and Wu (1993), a D-optimal design for the logistic response curve is a uniform distribution on two dose levels: ED17.6 and ED82.4. Hence, we assign half of the subjects to ED17.6 and half to ED82.4, since the data generating dose–response curves are known in the simulation.

3. Two-stage D-optimal design: We first form a grid of nine doses from the anticipated ED10 to ED90. The first stage is carried out at the middle $k = 7$ dose levels. The subsequent dose x is chosen to maximize $\det\{\mathbb{I}_i(\hat{\theta}_i; +x)\}$.

4. Sequential ED-design: The first seven trials are at the dose levels for the two-stage D-optimal design. The subsequent dose x is chosen to minimize (3.2).

The two-stage D-optimal design of Wang et al. (2015) has a complex scheme for its first stage. We have replaced this with our own more practical first-stage design. In all cases, we obtain the MLE for θ at the conclusion of the n trials. We repeat the simulation N times for all designs. The RMSEs are computed as follows:

$$\text{RMSE}(\hat{\xi}_j) = \sqrt{N^{-1}\sum_{r=1}^{N}(\hat{\xi}_{rj} - \xi_j)^2},$$

where $\hat{\xi}_{rj}$ is the estimate of ξ_j in the rth repetition. The overall RMSE is computed as

$$\text{RMSE} = \sqrt{\sum_{j=1}^{3}\text{RMSE}^2(\hat{\xi}_j)}.$$

In this study, we choose $N = 1000$ and the sample sizes $n = 30, 60$, and 120.

3.4.2 Performance comparison when the response model is correctly specified

In applications, we do not know the true form of the dose–response curve or the corresponding parameter values. Yet all designs must start with a guess of the true response curve. In this section, we consider the situation where the observed response curve agrees well with the true curve. In particular,

we generate data according to the logistic regression model

$$\text{logit}\big[\pi(x)\big] = -6.265 + 0.055x. \tag{3.7}$$

These parameter values are taken from Gezmu and Flournoy (2006). They illustrated their group up-and-down design using the same example from Flournoy (1993). The drug studied in the example is cyclophosphamide, measured in mg/kg. This response model was constructed from expert opinion as described in Flournoy (1993). Under this model, ED25= 94, ED50 = 114, and ED75 = 134.

The details of the four designs to be simulated under this model are as follows:

- For the up-and-down design, the specific dose levels are $x_1 = 34$ and $x_7 = 154$. The dose range is given by

  $$\Omega = \{34, 54, 74, 94, 114, 134, 154\}.$$

  The initial dose level is set to $x_4 = 94$.

- For the D-optimal design, the optimal dose levels are ED17.6 = 86 and ED82.4 = 143.

- For the two-stage D-optimal design and the ED-design, we use the following grid of $K = 7$ doses in the first stage:

  $$\Omega = (84, 94, 104, 114, 124, 134, 144).$$

Table 3.1: Simulated RMSEs under the logistic model targeting range ED25–ED75

n		ED-design	Two-stage D	Up-and-down	D-optimal
30	**Total**	**17.14**	**18.05**	**18.12**	**20.18**
	ED25	10.55	10.88	10.48	12.48
	ED50	8.12	9.03	8.06	9.89
	ED75	10.79	11.21	12.39	12.40
60	**Total**	**12.54**	**12.83**	**12.79**	**12.63**
	ED25	7.80	7.67	7.90	7.70
	ED50	5.89	6.42	5.53	6.15
	ED75	7.85	8.03	8.40	7.90
120	**Total**	**8.74**	**9.01**	**9.16**	**8.87**
	ED25	5.46	5.51	5.89	5.49
	ED50	4.09	4.50	3.88	4.41
	ED75	5.46	5.53	5.85	5.39

In the first simulation, we choose ED25, ED50, and ED75 as the targets. The results are given in Table 3.1.

The results show that our ED-design has the lowest total RMSE when $n = 30$. Its RMSE is generally lower when $n = 60$ and $n = 120$, but the differences are smaller. Our design is noticeably superior to the two-stage D-optimal design. If ED50 is the target, then the up-and-down approach is competitive or superior. However, even in this case, our ED-design is among the best.

It may be surprising that the D-optimal design based on a known dose–

response relationship is not the best. This may be explained by the fact that D-optimal designs aim to maximize the determinant of the Fisher information matrix. However, the performance measure in this simulation is the RMSE. Indeed, the averages of the determinants of the Fisher information of the ED-design divided by n^2 for $n = 30$, 60, and 120 are 15.4, 14.4, and 14.6. The corresponding value for the D-optimal design is 17.08.

In the second simulation, we consider the situation where a lower range of ED levels is of interest. We use ED10, ED25, and ED40 as the targets. The simulation settings remain the same except that the initial dose level for the biased-coin up-and-down design is set to $x_3 = 74$. This approach can select only one target dose level in each simulation. We simulate all three possibilities and Table 3.2 gives the results for each case.

Adjusting the target ED levels of our ED-design has the desired effect. The resulting data enable much more efficient estimation over the target range in terms of the total RMSE. In comparison with both D-optimal designs, it has the lowest RMSE at both ED10 and ED25. The difference is smaller at ED40, but our design has the lowest RMSE levels in two of the three sample sizes simulated. Tuning the biased-coin up-and-down design to specific ED levels improves its results. Particularly when $n = 120$, the up-and-down design achieved the lowest RMSE at the targeted ED level. However, this is at the cost of lower precision at the other ED levels. If the goal is to determine a single ED level, the up-and-down design is the best approach.

We repeat the first and second simulation studies 20 times under the same simulation setting. We note that the resulting total RMSEs and indi-

Table 3.2: Simulated RMSEs under the logistic model targeting range ED10–ED40.

n		ED-design	Two-stage D	Up-and-down			D-optimal
				Target ED10	Target ED25	Target ED40	
30	**Total**	**17.93**	**20.81**	**21.82**	**18.81**	**20.24**	**23.58**
	ED10	12.68	15.13	11.61	13.18	15.59	17.53
	ED25	8.93	10.84	11.15	8.92	9.71	12.15
	ED40	9.01	9.29	14.74	10.02	8.51	10.07
60	**Total**	**13.25**	**15.23**	**17.38**	**13.25**	**15.02**	**15.79**
	ED10	9.48	11.13	8.57	9.69	11.90	11.96
	ED25	6.52	7.89	8.98	6.09	7.11	8.02
	ED40	6.56	6.75	12.17	6.69	5.78	6.46
120	**Total**	**9.35**	**10.76**	**13.38**	**9.36**	**10.57**	**10.87**
	ED10	6.73	7.90	6.14	6.93	8.52	8.02
	ED25	4.55	5.58	6.96	4.24	4.92	5.63
	ED40	4.63	4.70	9.64	4.66	3.88	4.69

vidual RMSEs are quite similar. For example, when ED25, ED50, and ED75 are the targets, the standard error between the resulting total RMSEs is 0.12 for $n = 30$; when ED10, ED25, and ED40 are the targets, the standard error between the resulting total RMSEs is 0.26 for $n = 30$.

3.4.3 Performance comparison when the response model is mis-specified

In applications, the dose–response relationship is unknown. In this section, we consider the case where the observed response curve is mis-specified. Specifically, we consider the case where the observed dose–response relationship is logistic but the true model is probit. Thus, we generate data according to the probit model,

$$\text{probit}(\pi) = \Phi^{-1}(\pi) = -6.265 + 0.055x \tag{3.8}$$

where $\Phi(\cdot)$ is the cumulative distribution function of the standard normal distribution

$$\Phi(z) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{z} \exp\{-\frac{1}{2}x^2\}dx.$$

Note that under model (3.8), we have

$$\text{ED}\gamma = \frac{\Phi^{-1}(\gamma/100) - \alpha}{\beta}.$$

Under this model, ED25 = 102, ED50 = 114, and ED75 = 127. The dose–response curve is assumed to be model (3.7), and the simulation is otherwise identical to that in the last section. The results are presented in Tables 5.3 and 5.4. For ED25–ED75, we set ED50 as the target for the up-and-down design. For ED10–ED40, we target each level separately, as before.

With the same regression coefficients, the probit model has a steeper slope in the range ED25–ED75 compared with the logistic model. The sequential designs seem to have some ability to recover from the mis-specified

Table 3.3: Simulated RMSEs under probit mis-specified as logistic targeting ED range 25–75.

n		ED-design	Two-stage D	Up-and-down	D-optimal
30	**Total**	**10.08**	**10.59**	**11.29**	**18.93**
	ED25	6.25	6.33	6.70	11.45
	ED50	4.86	5.36	5.03	10.20
	ED75	6.23	6.59	7.57	11.09
60	**Total**	**7.16**	**7.46**	**7.63**	**13.98**
	ED25	4.53	4.56	4.71	8.23
	ED50	3.38	3.76	3.46	7.50
	ED75	4.39	4.55	4.90	8.46
120	**Total**	**5.00**	**5.05**	**5.39**	**9.13**
	ED25	3.09	3.09	3.38	5.47
	ED50	2.38	2.54	2.43	4.88
	ED75	3.13	3.09	3.42	5.44

model, and their RMSEs are hence lower than those in the last section. Our ED-design clearly has the best overall performance in both ranges. The up-and-down design again has good performance at the target ED level but poorer performance overall. Targeting ED25 achieves the best trade-off.

Both the logistic and probit models are symmetric in the ED levels: EDγ + ED$(100-\gamma) = 2 \times$ ED50 for any $\gamma \in (0, 100)$.

In the following example, we generate data according to the model

$$\text{logit}\big[\pi(x)\big] = -11.95 + 1.12\sqrt{x}, \tag{3.9}$$

Table 3.4: Simulated RMSEs under probit mis-specified as logistic targeting ED range 10–40.

n		ED-design	Two-stage D	Up-and-down			D-optimal
				Target ED10	Target ED25	Target ED40	
30	**Total**	**11.16**	**12.53**	**14.54**	**11.62**	**11.81**	**20.76**
	ED10	7.80	9.19	6.96	7.55	8.82	13.81
	ED25	5.59	6.46	7.84	5.92	5.87	11.46
	ED40	5.69	5.57	10.07	6.56	5.24	10.44
60	**Total**	**7.62**	**8.65**	**10.73**	**8.03**	**8.45**	**14.93**
	ED10	5.34	6.41	4.84	5.57	6.38	9.88
	ED25	3.78	4.44	5.71	3.99	4.21	8.23
	ED40	3.90	3.74	7.68	4.20	3.59	7.58
120	**Total**	**5.30**	**5.84**	**7.70**	**5.56**	**5.94**	**9.85**
	ED10	3.76	4.32	3.53	3.83	4.41	6.51
	ED25	2.59	3.01	4.14	2.79	3.02	5.47
	ED40	2.69	2.55	5.45	2.91	2.59	4.98

but we again analyze the data under model (3.7). We choose the above parameter values so that the corresponding ED levels (i.e., ED25, ED50, and ED75) roughly match the ED levels derived from model (3.7). Note that under model (3.9),

$$\xi_j = \Big[\frac{\text{logit}(\pi) - \alpha}{\beta}\Big]^2.$$

Under this model, ED25 = 94, ED50 = 114, and ED75= 136. As discussed

in Section 2.6, for the first stage, we use a grid of $K = 7$ doses:

$$\Omega = (84, 94, 104, 114, 124, 134, 144).$$

The subsequent dose x is chosen to minimize (3.2).

In this simulation, we first consider the situation where the lower ED levels are of interest, choosing ED10, ED25, and ED40 as the targets. For the biased-coin up-and-down design, we select ED25 as the target with the initial dose level at $x_2 = 94$. This choice gives the best performance. The simulation is repeated for ED25, ED50, and ED75. The results are given in Tables 3.5 and 3.6.

The results show that our ED-design has a lower total RMSE when the lower ED levels are of interest. It helps to improve efficiency over the whole range of interest and is particularly efficient at ED10. When the middle ED levels are of interest, the ED-design remains competitive, and none of the three designs is a clear winner.

Table 3.5: Simulated RMSEs under the mis-specified logistic model

n		ED-design	Two-stage D	Up-down	D-optimal
30	**Total**	**16.47**	**19.22**	**17.68**	**24.40**
	ED10	11.61	13.94	11.76	18.14
	ED25	8.13	10.00	8.64	12.55
	ED40	8.39	8.68	9.99	10.43
60	**Total**	**12.33**	**14.57**	**12.76**	**16.53**
	ED10	8.82	10.75	8.89	12.52
	ED25	5.88	7.49	6.06	8.34
	ED40	6.28	6.39	6.88	6.87
120	**Total**	**8.87**	**10.29**	**9.29**	**11.57**
	ED10	6.17	7.39	6.44	8.65
	ED25	4.20	5.27	4.46	5.84
	ED40	4.80	4.86	4.99	4.99

3.5 Limiting design as n increases

We have so far focused on the performance of the ED-design. Recall that a design for a binary dose–response experiment is equivalently a probability distribution on the design space or dose range. The D-optimal design is known to be a two-support-point design at ED17.6 and ED82.4 under the logistic regression model. Because of its sequential nature, the ED-design has many more support points. When n goes to infinity, it is possible that the limiting distribution has two support points.

We simulated the ED-design for two scenarios with $n = 5000$, first tar-

Table 3.6: Simulated RMSEs under the mis-specified logistic model

n		ED-design	Two-stage D	Up-down	D-optimal
30	**Total**	**17.53**	**17.56**	**19.12**	**20.29**
	ED25	10.23	10.00	10.70	12.55
	ED50	8.06	8.63	8.54	10.02
	ED75	11.72	11.56	13.35	12.41
60	**Total**	**13.18**	**12.83**	**13.58**	**13.55**
	ED25	7.82	7.49	7.53	8.34
	ED50	5.99	6.28	5.81	6.61
	ED75	8.76	8.32	9.69	8.40
120	**Total**	**9.26**	**9.61**	**9.41**	**9.49**
	ED25	5.36	5.27	5.55	5.84
	ED50	4.36	4.93	4.01	4.83
	ED75	6.16	6.35	6.45	5.70

geting ED25, ED50, ED75 and then ED10, ED25, ED40. In the first scenario the observed and true response curves agree and are logistic. In the second scenario the observed dose–response model is logistic and the true model is probit. The resulting histograms are given in Figures 3.1 and 3.2. There are clear indications that in both scenarios, the limiting distribution is binomial around ED20 and ED80 when the target ED levels are ED25, ED50, and ED75. We hope to prove this in the future.

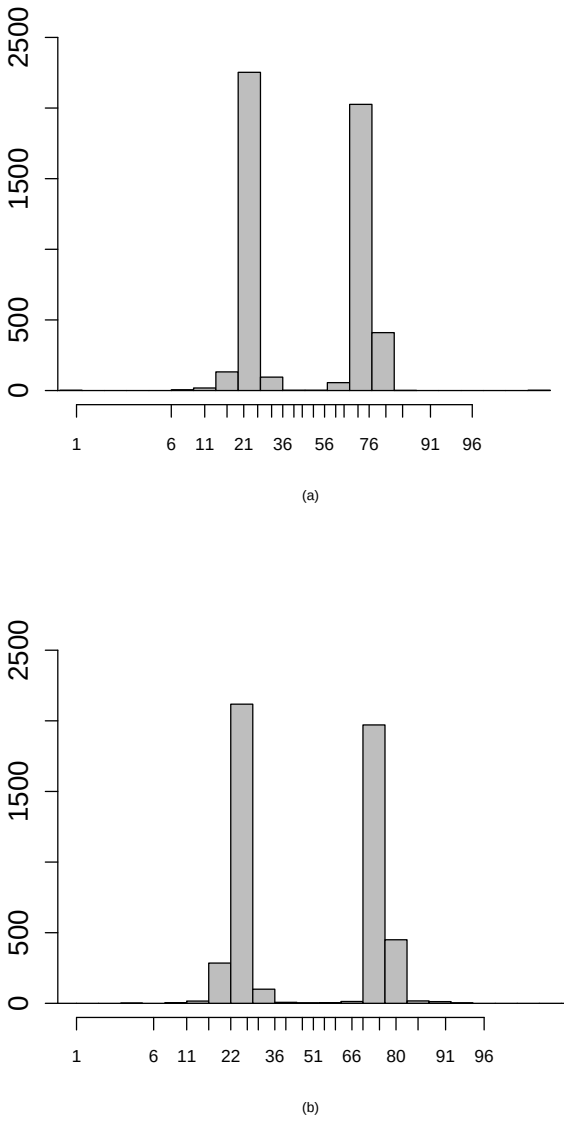
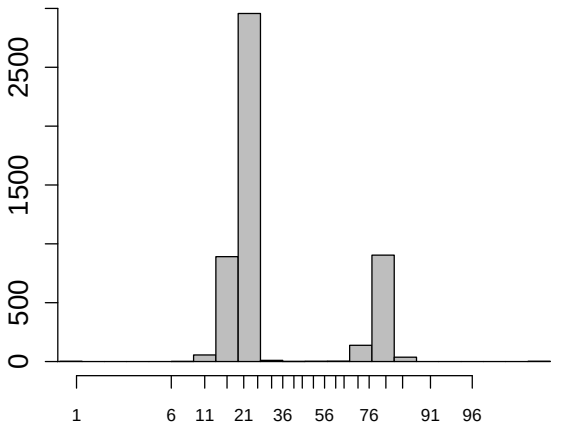


Figure 3.1: Histogram of the ED-design for (a) estimating ED25, ED50, and ED75 when the response curve is correctly specified as logistic; (b) estimating ED25, ED50, and ED75 when the response is mis-specified; The x-axes correspond to the ED levels.



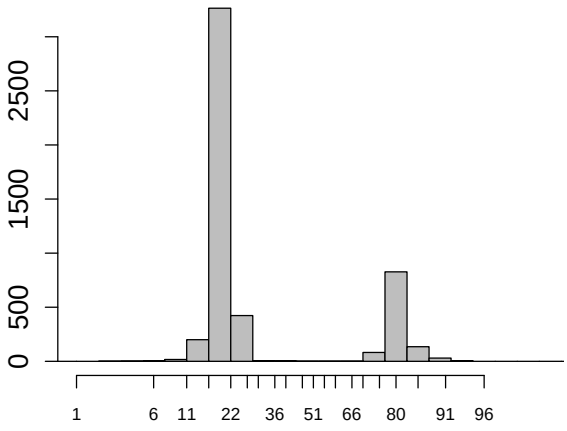


Figure 3.2: Histogram of the ED-design for (c) estimating ED10, ED25, and ED40 when the response curve is correctly specified as logistic, and (d) estimating ED10, ED25, and ED40 when the response is mis-specified. The x-axes correspond to the ED levels.

3.6 Concluding remarks

In dose–response experiments, there may be insufficient or inaccurate knowledge of the dose–response curve for the dose levels to be chosen properly. Dose–response information gathered from such an experiment is often unreliable.

We have therefore proposed a two-stage sequential ED-design for such experiments that unitize a second stage sequential experiment to compensate for the scarcity or inaccuracy of the dose–response information in the first stage experiment.

Our design simultaneously targets several ED levels of the underlying dose–response curve. We propose that the dose–response relationship can be well described by accurately estimating several ED levels simultaneously.

Simulations are conducted to investigate the performance of the proposed design under various scenarios. They are designed to mimic a real dose–response experiment with the goal to estimate the unknown dose–response curve over a wide dose range. Simulations show that in general our design is more robust and compares favourably with existing designs.

Although the commonly used logistic and probit models are convenient summaries of the dose–response relationship, they can be too restrictive. Our ED-design has a natural extension to more complex models. This will be seen in the next chapter.

3.7 R-code for the ED-design and simulation

```
# define function
q.logit <- function (x) {
  p = (logit(x)  - alpha ) / beta
  return (p)
}
q.probit <- function (x) {
  p = (qnorm(x)  - alpha ) / beta
  return (p)
}


logit <-function(p) log(p/(1-p))
g <- function(x, alpha, beta) alpha + beta*x
l <- function(g) exp(g)/(1+exp(g))
p <- function(x, alpha, beta) l(g(x, alpha, beta))


# Function f.fisher() computes the fisher information matrix
f.fisher <- function(x) {
  a <- alpha_hat + beta_hat * x
  fisher <- matrix(c(sum(exp(a)/(1+exp(a))^2),
                     sum(x*exp(a)/(1+exp(a))^2),
                     sum(x*exp(a)/(1+exp(a))^2),
                     sum(x^2*exp(a)/(1+exp(a))^2)), 2, 2)
  return(fisher)
```

```
}

# function f.dose() selects the next dose at the second stage

f.dose <- function (x)
{
  a.sel <- alpha_hat + beta_hat * x
  fisher.sel <- fisher + matrix(c(exp(a.sel)/(1+exp(a.sel))^2,
                                  x*exp(a.sel)/(1+exp(a.sel))^2,
                                  x*exp(a.sel)/(1+exp(a.sel))^2,
                                  x^2*exp(a.sel)/(1+exp(a.sel))^2), 2, 2)
  cov.sel <- solve(fisher.sel)
  v00.sel <- cov.sel[1,1]
  v01.sel <- cov.sel[1,2]
  v11.sel <- cov.sel[2,2]
  # variane
  var1.sel <- (v00.sel + 2*v01.sel*mu_hat1 + v11.sel*mu_hat1^2) / beta_hat ^ 2
  var2.sel <- (v00.sel + 2*v01.sel*mu_hat2 + v11.sel*mu_hat2^2) / beta_hat ^ 2
  var3.sel <- (v00.sel + 2*v01.sel*mu_hat3 + v11.sel*mu_hat3^2) / beta_hat ^ 2
  sum.se   <- var1.sel + var2.sel + var3.sel
  return(sum.se)
}

# initial design
n1 <- 7
```

```
delta <- (max-min)/(n1+1)
c    <-  seq (from = 1, to = n1, by = 1)
x1 <- min + delta * c[1]
x2 <- min + delta * c[2]
x3 <- min + delta * c[3]
x4 <- min + delta * c[4]
x5 <- min + delta * c[5]
x6 <- min + delta * c[6]
x7 <- min + delta * c[7]
dose.initial <- c(x1, x2, x3, x4, x5, x6, x7)

# proposed.R Function
# add two pseudo points on each boundary point
# ensure the existence of MLE
y_pes1 = 1
y_pes2 = 0
x_pes1 =  (logit (0.01) - alpha) / beta
x_pes2 =  (logit (0.99) - alpha) / beta

y_pes3 = 0
y_pes4 = 1
x_pes3 = (logit (0.01) - alpha) / beta
x_pes4 = (logit (0.99) - alpha) / beta

for (k in 1:m)
```

```
{
  # change with different response models
    yhat <- rbinom(length(dose.initial), 1, p(dose.initial, alpha, beta))
    data <- data.frame(rbind(cbind (y_pes1, x_pes1), cbind (y_pes2, x_pes2),
                             cbind (y_pes3, x_pes3), cbind (y_pes4, x_pes4),
                             cbind (yhat, dose.initial)))
    names(data)[1] <- paste("y")
    names(data)[2] <- paste("x")

  # weight for the initial experiment
  weight <- c(0.01, 0.01, 0.99, 0.99, rep (1, 7))
  fit <- glm(y ~ x, weights = weight, data = data, family = binomial)
  alpha_hat <- fit$coef[[1]]
  beta_hat  <- fit$coef[[2]]
  r <- dose.p (fit, p = ed)
  mu_hat1 <- r[[1]]
  mu_hat2 <- r[[2]]
  mu_hat3 <- r[[3]]

  # Second stage
  # Select the next dose level
  for (j in 1:(n-7))
  {
    w <- c(0.01, 0.01, 0.99, 0.99, rep (1, 7+j-1))  # weight
    # calculate fisher information
```

```
x <- data $ x
a <- alpha_hat + beta_hat * x
fisher <- matrix(c(sum(w*exp(a)   / (1+exp(a))^2),
                   sum(w*x*exp(a)  / (1+exp(a))^2),
                   sum(w*x*exp(a)  / (1+exp(a))^2),
                   sum(w*x^2*exp(a)/ (1+exp(a))^2)), 2, 2)



# choose the next dosage
for (i in 1:length(t))
{
  sum[i] <- f.dose(t[i])
}
opt <- t[which(sum == min (sum))]

# change with different response models
 prob <- p(opt, alpha, beta)
 y    <- rbinom (1, 1, prob)
 data <- rbind (data, data.frame (y, x = opt))
 weight_opt <- c(0.01, 0.01, 0.99, 0.99, rep (1, 7 + j))
 fit        <- glm(y ~ x, data, weights = weight_opt, family = binomial)
 alpha_hat  <- fit$coef[[1]]
 beta_hat   <- fit$coef[[2]]
mu_hat1 <- r[[1]]
mu_hat2 <- r[[2]]
```

```
    mu_hat3 <- r[[3]]
  }

  weight_final <- c(0.01, 0.01, 0.99, 0.99, rep (1, n))
  fit <- glm(as.factor(y) ~ x, data = data,
                 weights = weight_final, family = binomial)
  r <- dose.p (fit, p = ed)
  mu_temp1[k] <- r[[1]]
  mu_temp2[k] <- r[[2]]
  mu_temp3[k] <- r[[3]]
  mu_temp [k, ] <- c(mu_temp1[k], mu_temp2[k], mu_temp3[k])
  diff1[k] <- (mu_temp1[k] - mu1) ^ 2
  diff2[k] <- (mu_temp2[k] - mu2) ^ 2
  diff3[k] <- (mu_temp3[k] - mu3) ^ 2
  diff[k]   <- diff1[k] + diff2[k] + diff3[k]
  datatotal[, 2*k -1] <- c(data[, 1])
  datatotal[, 2*k]    <- c(data[, 2])
  print(k)
}

# General settings
rm(list=ls())
graphics.off()
library(stats)
library(MASS)
```

```
library(logistf)

n <- 30

m <- 1000

alpha <- -6.2647

min <- 74

max <- 154

ed <- c(0.25, 0.50, 0.75)

a1 <- (logit(0.01)-alpha)/beta

a2 <- (logit(0.99)-alpha)/beta

t <- seq(from = a1, to = a2, by = 5)

mu1 <- (logit (ed[1])  - alpha) / beta

mu2 <- (logit (ed[2])  - alpha) / beta

mu3 <- (logit (ed[3])  - alpha) / beta

mu  <- c(mu1, mu2, mu3)


# define objects

diff1 <- rep (0, m)

diff2 <- rep (0, m)

diff3 <- rep (0, m)

diff  <- rep (0, m)

mu_temp1 <- rep (0, m)

mu_temp2 <- rep (0, m)

mu_temp3 <- rep (0, m)

mu_hat1  <- rep (0, m)

mu_hat2  <- rep (0, m)
```

```
mu_hat3  <- rep (0, m)
sum   <- rep(0, length(t))


# main part
# proposed two-stage
 source("initialDesign.R")
 source("proposed.R")
# outputs
mse1 <- mean(diff1)
mse2 <- mean(diff2)
mse3 <- mean(diff3)
mse  <- mean(diff)  #average mse
sqrt(c(mse1, mse2, mse3, mse))
```

Chapter 4

ED-design under the Three-parameter Logistic Model

In the last chapter, we have explored the two-stage sequential ED-design under the logistic and probit models. Simulation studies show the ED-design is more robust and compares favourably with existing designs. Although the commonly used logistic and probit models are convenient summaries of the dose–response relationship, they can be too restrictive in applications. Our ED-design has a natural extension to more complex models, and we will explore this in this chapter.

4.1 Problem description

Naturally, if the model is mis-specified in an application, the optimal design is then misguided, and the resulting data analyses may cause an unreliable estimation of the ED levels. One way to lower this risk is to design the experiment that targets an accurate estimation of a range of ED levels, instead

of a single median dose level or model parameters as we discussed in the last chapter.

Another apparent approach to lower the risk of model misspecification is to apply a more flexible and hence more complex dose–response model. The choice of such a model invariably reflects a trade-off between the model flexibility and inference efficiency. A nonparametric model has ultimate flexibility, and therefore is free from the risk of model misspecification. However, it likely needs more trials to achieve the same estimation precision compared with the analyses under approximately valid parametric model assumptions. Commonly used logistic or probit models are simple and have good mathematical and statistical properties. They are satisfactory in many applications. Nevertheless, their model assumptions do impose some severe restrictions on the dose–response relationship. Hence, a mildly more complex model can be useful to lower the risk of model misspecification if it does not complicate the issues related to optimal designs and data analyses, as well as maintaining good efficiency in estimating the ED levels.

In this chapter, we show that the three-parameter logistic regression model goes some distance in this direction. We investigate the effectiveness of the sequential ED-design, the D-optimal design, and the up-and-down design under this model, and develop an effective model fitting strategy. We develop an easy way to implement an iterative numerical algorithm with guaranteed convergence for computing the maximum likelihood estimation of the model parameters. The sequential ED-design can be implemented after some laborious but simple mathematical derivations. Although we have yet to generate any theory on its D-optimal designs, a numerical procedure

via the well-developed vertex direction method (VDM) works well.

Simulation studies show that the combination of the proposed model and the data analysis strategy performs well. When the logistic model is correct, applying the more complex model suffers hardly any efficiency loss. When the three-parameter model holds but the logistic model is violated, the new approach is more efficient. Our research is a useful addition to the toolbox of the dose–response experiment.

4.2 Three-parameter logistic model

Statisticians and scientists are keenly aware that both the logistic and probit models can be poor approximations of the true dose–response relationship in an application. A more flexible model can be advantageous if it does not cause complex issues. The three-parameter logistic dose–response model introduced in Chapter 2 ideally meets this demand. El-Saidi (1993) have already proposed the use of this model for the dose–response relationship. The three-parameter logistic regression model assumes that

$$\text{logit}(\pi^{\lambda}(x)) = \ln\big\{\frac{\pi^{\lambda}(x)}{1-\pi^{\lambda}(x)}\big\} = \alpha + \beta x. \tag{4.1}$$

We require $\lambda > 0$ to ensure $\pi^{\lambda}(x)$ is between 0 and 1, and do not place restrictions on α and β.

We note that when $\lambda = 1$, the three-parameter model becomes the commonly used logistic model. In this case, for any $\gamma \in (0, 100)$, the model

satisfies

$$\text{ED}\gamma + \text{ED}(100-\gamma) = -\frac{2\alpha}{\beta}$$

assuming $\beta \neq 0$. Such a restriction is hard to justify in applications. Introduction of parameter λ helps to soften this restriction without over-complicating the system. Under this model, the effective dose level at γ is given by

$$\text{ED}\gamma = \frac{\text{logit}\big((\gamma/100)^{\lambda}\big) - \alpha}{\beta}. \tag{4.2}$$

An explicit expression of dose–response relationship is

$$\pi(x) = P\{Y=1|X=x\} = \Big\{\frac{\exp(\alpha+\beta x)}{1+\exp(\alpha+\beta x)}\Big\}^{1/\lambda}. \tag{4.3}$$

As discussed in previous chapters, many sequential designs, including the ED-design, contain a step to update the estimation of the model parameters. The maximum likelihood estimate is a common choice. For this reason, we investigate the problem of parameter estimation via maximum likelihood in the next Section.

4.3 Maximum likelihood estimation

Let $(x_i, y_i) : i = 1, \ldots, n$ be observations from a dose–response experiment, and assume model (4.1). Under commonly used designs, the log-likelihood based on this data set is given by

$$\ell_n(\theta) = \sum_{i=1}^{n} \Big\{ y_i \ln\big(\pi(x_i)\big) + (1-y_i)\ln\big(1-\pi(x_i)\big)\Big\}$$

where $\theta = (\alpha, \beta, \lambda)^\tau$.

When $\lambda = 1$ is fixed, the model becomes the usual logistic model, and $\ell_n(\theta)$ is known to be concave in α and β. The concavity permits a simple numerical solution to the maximum likelihood estimate of α and β. We remark that when x_i's corresponding to $y = 1$ is completely separated from those corresponding to $y = 0$, the maximum point $\hat{\beta} = \pm\infty$. The problem can be easily addressed by adding some informative pseudo observations as suggested in Chapter 3. This technique will also be used for the procedure being developed.

After some investigation, we find that given any value of λ, the log likelihood remains concave in α and β. Given any α and β, the log-likelihood is concave in λ. Because of these properties, the following two-loop iterative numerical algorithm works nicely. We propose to start the algorithm with the initial value $\lambda^{(0)} = 1$, and set $k = 0$. Let ϵ be a small positive value such as 10^{-5}.

1. Let
$$\ell_n^{(k)}(\alpha, \beta) = \ell_n(\alpha, \beta, \lambda^{(k)}).$$
Use an iterative algorithm to solve
$$(\alpha^{(k+1)}, \beta^{(k+1)}) = \arg\max_{\alpha,\beta} \ell_n^{(k)}(\alpha, \beta).$$

2. Define
$$a_i = \frac{\exp(\alpha^{(k+1)} + \beta^{(k+1)} x_i)}{1 + \exp(\alpha^{(k+1)} + \beta^{(k+1)} x_i)}$$

and

$$\ell_n^{(k)}(\lambda) = \sum_{i=1}^{n} \{(1-y_i)\ln(1-a_i^{\lambda}) + \lambda y_i \ln(a_i)\}.$$

Use an iterative algorithm to solve

$$\lambda^{(k+1)} = \arg\max_{\lambda} \ell_n^{(k)}(\lambda).$$

If $\ell_n(\theta^{(k+1)}) - \ell_n(\theta^{(k)}) \leq \epsilon$, stop and report $\theta^{(k+1)}$ and $\ell_n(\theta^{(k+1)})$. Otherwise, set $k = k+1$ and go back to Step 1.

In the above presentation, we have used $\ell_n^{(k)}(\alpha, \beta)$ and $\ell_n^{(k)}(\lambda)$ as two different functions. We pointed out that the objective functions in both loops are concave that guarantee the convergence of any sensible iterative procedures that we may use in these two steps, and hence of the entire algorithm. We state the concave conclusions in two lemmas, and start with the simpler one.

Lemma: Function $\ell_n^{(k)}(\lambda)$ in Step 2 is concave in λ given any data set (x_i, y_i) for $i = 1, 2, \ldots, n$ with $n \geq 1$.

Proof: To prove the concavity, it suffices to show that the second derivative of this function is always non-negative. Some straightforward algebra shows that

$$\frac{\partial \ell_n^{(k)}(\lambda)}{\partial \lambda} = \sum_{i=1}^{n} \frac{(y_i - a_i^{\lambda})(\ln a_i)}{1 - a_i^{\lambda}}$$

and subsequently,

$$\frac{\partial^2 \ell_n^{(k)}(\lambda)}{\partial \lambda^2} = \sum_{i=1}^{n} \frac{a_i^{\lambda}(y_i - 1)(\ln a_i)^2}{(1 - a_i^{\lambda})^2} \leq 0$$

since $y_i \leq 1$ for all i. Therefore, the function is concave as claimed. □

Lemma: Given any data set (x_i, y_i) for $i = 1, 2, \ldots, n$ with $n \geq 1$, the objective function $\ell_n^{(k)}(\alpha, \beta)$ in Step 1 is concave in α, β, under the assumption $\lambda > 0$.

Proof: For notational simplicity, we will drop the superscript (k) and subscript n from $\ell_n^{(k)}(\alpha, \beta)$, and denote it simply as $\ell(\alpha, \beta)$ in this proof. We start working on the case where $n = 1$ so that we further drop summation and subindex i.

To prove this result, it suffices to show that the Hessian matrix

$$H = - \begin{bmatrix} \frac{\partial^2 \ell}{\partial \alpha^2} & \frac{\partial^2 \ell}{\partial \alpha \partial \beta} \\ \\ \frac{\partial^2 \ell}{\partial \alpha \partial \beta} & \frac{\partial^2 \ell}{\partial \beta^2} \end{bmatrix}$$

is positive definite. For this purpose, we note that

$$\frac{\partial \ell}{\partial \alpha} = \{ \frac{y}{\pi(x)} - \frac{(1-y)}{1-\pi(x)} \} \frac{\pi(x)}{\partial \alpha} = \frac{(y - \pi(x))(1 - \pi^\lambda)}{\lambda(1 - \pi(x))}.$$

and

$$\begin{aligned} \frac{\partial^2 \ell}{\partial \alpha^2} &= \{ \frac{(y-1)(1-\pi^\lambda(x))}{\lambda(1-\pi(x))^2} - \frac{\lambda \pi^{\lambda-1}(y - \pi(x))}{1 - \pi(x)} \} \frac{\pi(x)}{\partial \alpha} \\ &= \frac{1}{\lambda^2} \pi(x)(1 - \pi^\lambda(x)) \{ \frac{(y-1)(1-\pi^\lambda(x))}{(1-\pi(x))^2} - \frac{\lambda \pi^{\lambda-1}(y - \pi(x))}{1 - \pi(x)} \}. \end{aligned}$$

We first show that the above second derivative is less than or equal to 0. Note that the first factor in $\partial^2 \ell / \partial \alpha^2$ is nonnegative. So we only need to

determine the sign of the second factor. We consider the cases of $y = 1$ and $y = 0$ separately.

(a) When $y = 1$, the first term in the second factor vanishes, and the second term is clearly less than or equal to 0.

(b) When $y = 0$, the second factor becomes

$$\frac{\lambda\pi^{\lambda}(1-\pi(x)) - (1-\pi^{\lambda}(x))}{(1-\pi^{\lambda}(x))^2}.$$

Denote its numerator as $f(\lambda)$ whose derivative is given by

$$\begin{aligned} f'(\lambda) &= \pi^{\lambda}(1-\pi(x)) + \lambda\pi^{\lambda}(1-\pi(x))\ln\pi(x) + \pi^{\lambda}(x)\ln\pi(x) \\ &= \pi^{\lambda}(x)\{1-\pi(x) + (1+\lambda-\lambda\pi(x))\ln\pi(x)\} \\ &\leq \pi^{\lambda}(x)\{\ln\pi(x) + (1+\lambda-\lambda\pi(x))\ln\pi(x)\} \\ &= \lambda\pi^{\lambda}(x)(1-\pi(x))\ln\pi(x) \leq 0 \end{aligned}$$

where we have made use of the inequality $1 - \pi(x) \leq -\ln\pi(x)$. Combined with the fact that $f(0) = 0$, we find $f(\lambda) \leq 0$ for all $\lambda \geq 0$. This further implies $\partial^2\ell/\partial\alpha^2 \leq 0$ when $y = 0$.

Combining (a) and (b), noticing that y is either 0 or 1, we formally state that for all $\lambda > 0$,

$$\frac{\partial^2\ell}{\partial\alpha^2} \leq 0.$$

To finish the proof, we note that

$$\frac{\partial^2\ell}{\partial\alpha\partial\beta} = x\frac{\partial^2\ell}{\partial\alpha^2}; \quad \frac{\partial^2\ell}{\partial\beta^2} = x^2\frac{\partial^2\ell}{\partial\alpha^2}.$$

Therefore, in the sense of being nonnegative definiteness, we find

$$H = -\begin{bmatrix} \frac{\partial^2 \ell}{\partial \alpha^2} & \frac{\partial^2 \ell}{\partial \alpha \partial \beta} \\ \frac{\partial^2 \ell}{\partial \alpha \partial \beta} & \frac{\partial^2 \ell}{\partial \beta^2} \end{bmatrix} = -\frac{\partial^2 \ell}{\partial \alpha^2} \begin{bmatrix} 1 & x \\ x & x^2 \end{bmatrix} \geq 0.$$

When the design contains n dose levels, the Hessian matrix is the sum of n nonnegative definite matrices. Hence it remains nonnegative definite. This completes the proof. □

By these two lemmas, $\ell_n(\theta^{(k)})$ is an increasing sequence in k with an upper bound 0. Hence, $\ell_n(\theta^{(k)})$ has a finite limit as $k \to \infty$. The corresponding $\theta^{(k)}$ is almost guaranteed to converge to at least a local maximum point. Rigorous discussion on global maximum can be tedious and distractive. We do not pursue the issue in this dissertation.

4.4 Potential designs for the three-parameter logistic model

The choice of a new model does not lead to new design issues, but some additional technical work. All optimality criteria introduced previously remain effective under the three-parameter logistic model (4.1). We merely work on existing procedures under the new model. In the following, we selectively discuss some particulars.

4.4.1 Up-and-down design

The up-and-down design and its variations do not require a parametric model on the dose–response relationship $\pi(x)$. The design is used for the purpose of accurately estimating a specific effective dose level EDγ, and commonly the target is $\gamma = 50$. The design requires a user to choose before hand a grid of dose levels

$$\Omega = \{x_1, \ldots, x_K\} \tag{4.4}$$

for some K based on prior information on $\pi(x)$ so that $x_1 < \text{ED}\gamma < x_K$.

The experiment starts with assigning a stimulus at level x_j in Ω to the subject. If the subject responds, the level is moved down to x_{j-1}, and otherwise up to x_{j+1}. Special rules are needed if x_j is on the boundary of Ω. Variations are needed such as staying at x_j with a specific positive probability related to the target EDγ. A nonparametric estimate of EDγ may be used. Our experience shows that such estimators are not efficient. For more informative comparison, we obtain the maximum likelihood estimate (MLE) under the assumed model, and estimate EDγ in the simulation, even if the data are obtained under the up-and-down design in this chapter. Clearly, introducing the three-parameter model leads to no new issues.

4.4.2 D-optimal design

As pointed out in previous chapters, the variance-covariance matrix of the MLE of the parameter θ is well approximated by $\mathbb{I}_n^{-1}(\theta)$ when the number of runs n is large, where $\mathbb{I}_n(\theta)$ is the Fisher information. A D-optimal design is a design which maximizes the determinant of $\mathbb{I}_n(\theta)$. As far as we are

aware, there have been no direct results on the D-optimal design for the three-parameter logistic model. In this section, we do not aim to give a theoretical solution to the D-optimal design for the three-parameter logistic model. Rather, we provide a numerical approach to get approximate D-optimal designs. Solutions to the D-optimal designs will be used in our simulation studies.

Sitter and Wu (1993) showed that under the (two-parameter) logistic response model, Ψ^* is a uniform distribution on ED17.6 and ED82.4; and under the probit model, Ψ^* is a uniform distribution on ED12.8 and ED87.2.

We do not have a comparable theory for the D-optimal design under the new model but point out that a vertex direction method (VDM) remains effective for numerical solutions. This method will be illustrated in the next section.

We implemented VDM as an R function for the three-parameter logistic model (4.1). The resulting D-optimal design for $\alpha = -6.265$, $\beta = 0.055$ and $\lambda = 0.5$ is a uniform distribution on ED2, ED35 and ED91. The resulting D-optimal design for $\alpha = -14.148$, $\beta = 0.1$ and $\lambda = 2$ is a uniform distribution on ED6, ED55, and ED95. These two designs are used in simulations for the purpose of comparison. We also implemented VDM for the three-parameter probit model. Under the three-parameter logistic and probit models, design points and design weights change with different λ values. A number of λ values are given in Tables 4.1 and 4.2. For more discussions of VDM, we refer to Fedorov (1972), Wynn (1972), and Wu (1978).

Table 4.1: D-optimal design under three-parameter Logistic model.

Model	Three-parameter Logistic Model	
	$\alpha = -6.265, \beta = 0.055$	$\alpha = -14.148, \beta = 0.1$
$\lambda = 0.5$	ED2 ED35 ED91 0.33 0.33 0.33	ED2 ED35 ED91 0.33 0.33 0.33
$\lambda = 0.75$	ED3 ED39 ED92 0.33 0.33 0.33	ED3 ED39 ED92 0.33 0.33 0.33
$\lambda = 1$	ED3 ED43 ED93 0.33 0.33 0.33	ED3 ED43 ED93 0.33 0.33 0.33
$\lambda = 1.25$	ED4 ED46 ED94 0.33 0.33 0.33	ED4 ED46 ED94 0.33 0.33 0.33
$\lambda = 1.5$	ED5 ED49 ED94 0.33 0.33 0.33	ED5 ED49 ED94 0.33 0.33 0.33
$\lambda = 1.75$	ED5 ED52 ED95 0.33 0.33 0.33	ED5 ED52 ED95 0.33 0.33 0.33
$\lambda = 2$	ED6 ED55 ED95 0.33 0.33 0.33	ED6 ED55 ED95 0.33 0.33 0.33

4.4.3 Vertex Direction Method(VDM)

A number of algorithms have been proposed for numerical computation of the D-optimal design. In this dissertation, we apply a well-known iterative strategy, vertex direction method (see Fedorov (1972), Wynn (1972), and Wu (1978)) to numerically compute the D-optimal design under the three-parameter logistic regression model. Let's consider a finite design space $\mathcal{X}$ of permissible dose levels, $x_1, \ldots, x_k$. A design is a set of dose levels $x_1, \ldots, x_k$ together with how often they are applied: $m_1, \ldots, m_k$, ignoring

Table 4.2: D-optimal design under the three-parameter probit model.

Model	three-parameter probit Model	
	$\alpha = -6.265, \beta = 0.055$	$\alpha = -14.148, \beta = 0.1$
$\lambda = 0.5$	ED4 ED53 ED97 0.33 0.33 0.33	ED4 ED53 ED97 0.33 0.33 0.33
$\lambda = 0.75$	ED4 ED55 ED98 0.33 0.33 0.33	ED4 ED55 ED98 0.33 0.33 0.33
$\lambda = 1$	ED4 ED57 ED98 0.33 0.33 0.33	ED4 ED57 ED98 0.33 0.33 0.33
$\lambda = 1.25$	ED5 ED59 ED98 0.33 0.33 0.33	ED5 ED59 ED98 0.33 0.33 0.33
$\lambda = 1.5$	ED5 ED60 ED98 0.33 0.33 0.33	ED5 ED60 ED98 0.33 0.33 0.33
$\lambda = 1.75$	ED5 ED61 ED98 0.33 0.33 0.33	ED5 ED61 ED98 0.33 0.33 0.33
$\lambda = 2$	ED5 ED62 ED98 0.33 0.33 0.33	ED5 ED62 ED98 0.33 0.33 0.33

the order of the runs. This design is characterize by a distribution Ψ on $\mathcal{X}$ whose probability mass function is given by $\psi(x_j) = m_j/n$. To reflect the dependence on Ψ, we denote the Fisher information as $\mathbb{I}(\Psi)$ here. A Ψ degenerates at x is denoted as δ_x, and we use $\mathbb{I}(x)$ for $\mathbb{I}(\delta_x)$. It is seen that

$$\mathbb{I}(\Psi) = \int_{\mathcal{X}} \mathbb{I}(x) d\Psi(x).$$

The popular D-optimal design is defined to be

$$\Psi^* = \arg\max\{\ln[\det(\mathbb{I}(\Psi))]\}.$$

Define the directional derivative

$$D(\Psi; x) = \lim_{\epsilon \to 0+} \frac{\ln[\det(\mathbb{I}((1-\epsilon)\Psi) + \epsilon\delta_x)] - \ln[\det(\mathbb{I}(\Psi))]}{\epsilon}.$$

It is known that Ψ^* is the D-optimal design if and only if $D(\Psi^*; x) \leq 0$ for any x. Starting from an initial design $\Psi = \Psi^{(0)}$, VDM searches for $x^* = \arg\max D(\Psi; x)$ and

$$\epsilon^* = \arg\max \ln[\det(\mathbb{I}((1-\epsilon)\Psi + \epsilon\delta_{x^*})\}.$$

Iterate to obtain $\Psi^{(k)}$, $k = 1, 2, \ldots$ until the determinant stops increasing.

In particular, for the three-parameter logistic regression model (4.1),

$$D(\Psi; x) = \mathrm{tr}(\mathbb{I}^{-1}(\Psi)\mathbb{I}(x)) - 3$$

where the constant 3 is the dimension of $\mathbb{I}$. Additional details for the explicit expression of $\mathbb{I}$ will be given at the end of this section.

We implemented VDM as an R function for the three-parameter logistic model (4.1). The steps of VDM applied in our simulations are as follows. In the experiment, suppose m_i patients are assigned to doses x_i, $i = 1, \ldots, k$, and $\sum_{i=1}^{k} m_i = n$. Here k is the number of distinct dose levels. The corre-

sponding experimental design is

$$\xi = \begin{pmatrix} x_1 & x_2 & \cdots & x_k \\ \\ m_1 & m_2 & \cdots & m_k \end{pmatrix}$$

Denote $w_j = m_j/n$ as the design weight for x_j, $j = 1, \ldots, k$. Let

$$w = (w_1, \ldots, w_k) \in \Omega = \{w : \sum_{i=1}^{k} w_i = 1,\ w_i \geq 1\}$$

be the vector of design weights. Give a parametric model, the goal of the D-optimal design is to find an allocation of weights, $w_1, \ldots, w_k$, to the design points, $x_1, \ldots, x_k$, such that the determinant of the Fisher information matrix of the model parameters is maximized.

1. Choose an initial design

$$\xi = \begin{pmatrix} x_1 & x_2 & \cdots & x_k \\ \\ w_1^{(1)} & w_2^{(1)} & \cdots & w_k^{(1)} \end{pmatrix}$$

In the simulation, we choose to have equal weights at all n design points. Let $n = 200$. The dose level x_i is chosen based on the assumed dose–response model used in the simulation. Then the initial design we choose is

$$\xi = \begin{pmatrix} 1 & 2 & \cdots & 200 \\ \\ 1/200 & 1/200 & \cdots & 1/200 \end{pmatrix}$$

2. For the current design, $w_1^{(t)}, w_2^{(t)}, \ldots, w_k^{(t)},\ t = 1, 2, \ldots$, find the index i_{max} with the maximum directional derivative, that is,

$$D(i_{max}, w^{(t)}) = \max_{1 \le i \le n} D(i, w^{(t)}).$$

Then set the new design weight at the $(t+1)$th iteration as

$$w_i^{(t+1)} = \begin{cases} (1 - \delta^{(t)}) w_i & i \neq i_{max} \\ (1 - \delta^{(t)}) w_i + \delta^{(t)} & i = i_{max} \end{cases}$$

where

$$\delta^{(t)} = \frac{D(i_{max}, w^{(t)})/m - 1}{D(i_{max}, w^{(t)}) - 1}.$$

Here m = 3 for the three-parameter logistic regression model.

3. Repeat step 2 until

$$D(i, w^{(t)}) - m \le \epsilon.$$

Here ϵ is a small positive constant.

Each iteration of the vertex directional derivative method moves the weight w in the direction of a design point at which the directional derivative is the largest.

4.5 Two-stage sequential ED-design

The D-optimal design as well as many other optimal designs focus on the precision of the parameter estimation under the assumed model. The form of

the parameter in consideration is generally chosen as the one permitting the most convenient analytical presentation of the dose–response model. Under the three-parameter logistic regression model, for instance, one naturally takes $\theta = (\alpha, \beta, \lambda)$ as the target parameter. In some applications, we are more interested in the precise estimation of ED levels. Hence, the proposed ED-design can be easily applied here.

Let $\xi = g(\theta)$, for some smooth function g with gradient function $\bigtriangledown g(\theta)$. The variance of its MLE is approximately

$$\{\bigtriangledown g^{\tau}(\theta)\}\{\mathbb{I}^{-1}(\theta)\}\{\bigtriangledown g(\theta)\} \tag{4.5}$$

where $\bigtriangledown g(\theta)$ is the gradient of $g(\cdot)$. The sequential ED-design aims to minimize

$$\sum_{j=1}^{m}\{\bigtriangledown g_j^{\tau}(\theta)\}\{\mathbb{I}^{-1}(\theta)\}\{\bigtriangledown g_j(\theta)\} \tag{4.6}$$

with $\xi_j = g_j(\theta)$ being m selected ED levels. Clearly, this solution depends on the value of the unknown parameter θ. Hence, a sequential version is needed.

Suppose the experiment has been carried out at dose levels $x_1, \ldots, x_i$ with response values $y_1, \ldots, y_i$. Let $\hat{\theta}_i$ be the intermediate MLE of θ based on the data obtained from the first i trials. Let $\mathbb{I}_i(\hat{\theta}_i; +x)$ be the Fisher information based on the first i trials and the potential $(i+1)$th trial to be run at dose level x. We choose the next dose level x that minimizes

$$\mathrm{V}(i; x) = \sum_{j=1}^{m}\{\bigtriangledown g_j^{\tau}(\hat{\theta}_i)\}\{\mathbb{I}_i^{-1}(\hat{\theta}_i; +x)\}\{\bigtriangledown g_j(\hat{\theta}_i)\}. \tag{4.7}$$

Repeat this rule until $i = n$.

The sequential ED-design needs an initial set of trials and the corresponding $\hat{\theta}$. We recommend and use a uniform initial design on a set of dosage $\Omega = \{x_1, \ldots, x_K\}$ for $K = 7$ with x_1 and x_K being equally spaced grids between the perceived ED01 and ED99.

Some algebra for implementation of the ED-design. The numerical value of $\mathrm{V}(i; x)$ can be computed based on the following simple mathematical results. Denote the single observation log-likelihood as

$$\ell(\theta) = y \ln \pi(x) + (1 - y) \ln \big(1 - \pi(x)\big).$$

We have

$$\frac{\partial \ell(x)}{\partial \theta} = \frac{(y - \pi(x))}{\pi(x)(1 - \pi(x))} \frac{\partial \pi(x)}{\partial \theta}.$$

The contribution of a single trial at dose level x to the Fisher information matrix is therefore given by

$$\begin{aligned} \mathbb{I}(\theta; x) &= E\big[\frac{(y - \pi(x))}{\pi(x)(1 - \pi(x))}\big]^2 \{\frac{\partial \pi(x)}{\partial \theta}\}\{\frac{\partial \pi(x)}{\partial \theta}\}^\tau \\ &= \frac{1}{\pi(x)(1 - \pi(x))} \{\frac{\partial \pi(x)}{\partial \theta}\}\{\frac{\partial \pi(x)}{\partial \theta}\}^\tau \end{aligned}$$

and $\partial \pi(x)/\partial \theta$ have three entries given by

$$\begin{aligned} \frac{\partial \pi(x)}{\partial \alpha} &= \lambda^{-1} \pi(x)(1 - \pi^\lambda(x)) \\ \frac{\partial \pi(x)}{\partial \beta} &= \lambda^{-1} x \pi(x)(1 - \pi^\lambda(x)) = x \frac{\partial \pi(x)}{\partial \alpha} \\ \frac{\partial \pi(x)}{\partial \lambda} &= -\lambda^{-1} \pi(x) \ln \pi(x). \end{aligned}$$

Finally, for $\xi_\gamma = \text{ED}\gamma$, we have

$$\begin{aligned} g(\theta;\gamma) &= \frac{\text{logit}\big((\gamma/100)^\lambda\big) - \alpha}{\beta} \\ \nabla g(\theta;\gamma) &= -\frac{1}{\beta}\big(1, \xi, -\frac{\ln(\gamma/100)}{1-(\gamma/100)^\lambda}\big)^\tau. \end{aligned}$$

These calculations lead to a simple way to evaluate $\text{V}(i;x)$ and the numerical solution to its minimization.

4.6 Simulation studies

We conduct simulation studies to demonstrate several issues related to the use of the extended three-parameter logistic regression model (4.1) for the dose–response experiment. We repeat the simulation $N = 1000$ times for all model/design combinations. The sample sizes are chosen to be $n = 30, 60,$ and 120. We choose three effective dose levels each time as the targets for estimation and obtain their MLEs. Under each model/design setting, we compute the RMSE of a single ED level as

$$\text{RMSE}(\hat{\xi}_j) = \sqrt{N^{-1}\sum_{r=1}^{N}(\hat{\xi}_{rj} - \xi_j)^2},$$

where $\hat{\xi}_{rj}$ is the estimate of ξ_j in the rth repetition. The total RMSE is computed as

$$\text{RMSE} = \sqrt{\sum_{j=1}^{3}\text{RMSE}^2(\hat{\xi}_j)}.$$

Three designs are included in the simulation. One is the up-and-down design whose implementation does not depend on the model, but a specific target ED level will be indicated in the summary of the simulation result. We choose a set of doses $\Omega = \{x_1, \ldots, x_7\}$ with x_1 and x_7 being equally spaced grids between the anticipated ED01 and ED99. We simulate on the D-optimal design and the sequential ED-design, assuming the relevant knowledge of the dose–response model as discussed in the last section. For the sequential ED-design, we use a uniform initial design on Ω as specified for the up-and-down design.

We wish to use simulations to answer several questions related to the combination of the ED-design and the three-parameter model under the dose–response experiment.

The first question is how the ED-design fairs. Does it have any advantage compared with other potential designs under a three-parameter model? As you will see, the ED-design works very well in this respect.

The second question is whether the use of the three-parameter model necessary? Based on our simulation, if one focuses on the precision of the estimation of ED levels over a local region as we did in the last chapter, we can observe the advantage of employing the correct three-parameter logistic model.

Finally, if the true dose–response relationship is a two-parameter logistic model, how much efficiency do we lose by using a more complex three-parameter logistic? Our simulation shows the loss is very limited or can hardly be noticed.

We now present our simulation results in three subsequent sections.

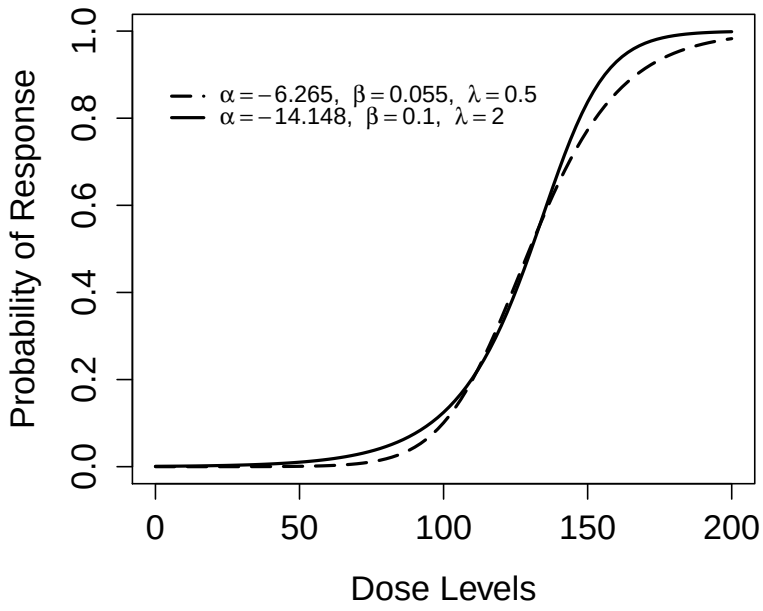
4.6.1 The three-parameter model is both the assumed and the truth for the dose–response experiment

We generate data according to the three-parameter logistic regression model (4.1) with $\alpha = -6.265$, $\beta = 0.055$, $\lambda = 0.5$, and $\alpha = -14.148$, $\beta = 0.1$, $\lambda = 2$ in two separate simulations. The corresponding dose–response curves are depicted in Figure 4.1.

The simulations are done for each of the three sets of the targeting dose levels: (a) ED25, ED50, ED75; (b) ED10, ED25, ED40; and (c) ED60, ED75, ED90.

The use of the up-and-down design requires us to identify a target ED level. In our simulation, we always take the middle one as its target. The ED01 and ED99 values under $\lambda = 0.5$ is (74, 211); The ED01 and ED99 values under $\lambda = 2$ is (49, 180). These values are used in determining the first stage design Ω. The simulation results are reported in Tables 4.3 and 4.4.

We take note that the RMSEs under each design decrease when n increases. Their sizes are not dramatically different, but those of the D-optimal design are higher. The sequential ED-design has the best overall performance. The up-and-down design gives the lowest RMSEs for some single ED level. These are expected as the D-optimality aims at the precise estimation of θ, not ED levels, and the up-and-down design is never intended for the current purpose: estimating ED levels under a parametric model. Nevertheless, it is nice to find that the sequential ED-design works well.



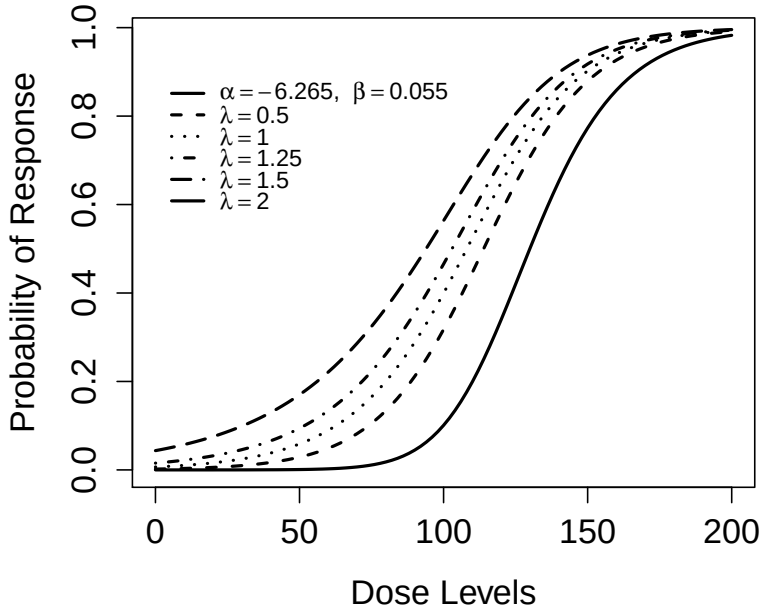


Figure 4.1: Dose–response curves in the simulation

Table 4.3: Simulated RMSEs under the three-parameter model ($\alpha = -6.265$, $\beta = 0.055$, $\lambda = 0.5$)

Size	n = 30			n = 60			n = 120		
Design	ED	Up-down	D-opt	ED	UP-down	D-opt	ED	Up-down	D-opt
Total	**13.32**	**16.20**	**16.82**	**9.87**	**10.33**	**11.96**	**6.93**	**7.42**	**8.44**
ED10	8.62	9.39	11.33	6.66	6.79	8.16	4.71	4.97	5.82
ED25	6.78	8.09	9.03	4.78	5.05	6.34	3.23	3.61	4.45
ED40	7.55	10.43	8.54	5.50	5.92	6.02	3.93	4.15	4.19
Total	**14.02**	**15.68**	**16.97**	**10.49**	**10.85**	**11.95**	**7.47**	**7.69**	**8.46**
ED25	8.20	8.00	9.03	6.15	5.83	6.33	4.46	4.38	4.45
ED50	6.72	7.68	8.72	4.83	5.06	6.16	3.48	3.51	4.29
ED75	9.17	11.09	11.42	7.00	7.62	8.05	4.88	5.25	5.77
Total	**17.36**	**21.59**	**22.27**	**12.63**	**13.49**	**16.01**	**8.89**	**9.26**	**11.61**
ED60	9.00	9.08	8.94	6.29	6.01	6.45	4.39	4.24	4.60
ED75	8.69	10.64	11.23	5.92	6.45	8.09	4.07	4.34	5.82
ED90	12.04	16.44	17.03	9.22	10.21	12.21	6.57	7.00	8.93

Table 4.4: Simulated RMSEs under the three-parameter model ($\alpha = -14.148$, $\beta = 0.1$, $\lambda = 2$)

Size	n = 30			n = 60			n = 120		
Design	ED	Up-down	D-optimal	ED	Up-down	D-optimal	ED	Up-down	D-optimal
Total	**16.76**	**18.61**	**21.35**	**12.26**	**12.98**	**15.84**	**8.92**	**9.09**	**11.05**
ED10	12.01	12.16	15.58	9.03	9.00	11.63	6.61	6.66	8.22
ED25	8.34	9.44	11.23	5.79	6.38	8.24	4.12	4.45	5.66
ED40	8.21	10.46	9.32	5.93	6.85	6.91	4.35	4.30	4.75
Total	**13.05**	**14.65**	**16.23**	**9.36**	**10.01**	**11.78**	**6.76**	**6.92**	**8.06**
ED25	8.76	8.67	11.23	6.37	6.52	8.24	4.69	4.65	5.66
ED50	6.37	6.32	8.48	4.42	4.42	6.28	3.12	3.25	4.28
ED75	7.28	9.97	8.10	5.25	6.18	5.61	3.74	3.96	3.82
Total	**12.32**	**15.42**	**16.30**	**8.67**	**9.98**	**11.54**	**6.23**	**6.66**	**8.30**
ED60	6.84	7.22	7.93	4.81	4.99	5.77	3.46	3.52	3.89
ED75	6.24	7.63	8.10	4.14	4.96	5.61	2.83	3.27	3.82
ED90	8.12	11.28	11.72	5.90	7.08	8.28	4.35	4.61	6.26

4.6.2 Effects of fitting a three-parameter model when a two–parameter logistic model suffices

When the logistic model is appropriate, but a three-parameter model is assumed in the design and analysis, the results are likely suboptimal. In this section, we use simulations to examine the degree of the efficiency loss. We simulate dose–response data from the logistic regression model with two sets of designs, and analyze the data: one set is under the two-parameter logistic regression model, and the other set is under the three-parameter logistic regression model. We only include the D-optimal design and the sequential ED-design in this simulation. The up-and-down design is not included, because it does not depend on the model assumption, although the data analysis could be performed under a model assumption.

In this simulation, we generate data from the two-parameter model:

$$\text{logit}(\pi(x)) = -6.265 + 0.055x.$$

The results are presented in Tables 4.5 and 4.6. Table 4.5 is obtained under the correct two-parameter logistic regression model assumption. The D-optimal design in this case is a uniform distribution on ED17.6 and ED82.4 which are known to us though not known in applications. Table 4.6 is obtained under the also correct three-parameter logistic regression model assumption, though it is more complex than needed.

According to these results, we notice that the use of the ED-design has advantages compared with the D-optimal design. The simulated RMSEs under the ED-design are always lower than those under the D-optimal design.

The efficiency gain can be as much as 40%.

In addition, the use of the more complex and necessary three-parameter model does not hurt the efficiency significantly. In the case of targeting ED10, ED25, and ED40, the total RMSE increases from 17.93 to 18.36 when the sample size $n = 30$. This loss is below 2.4%. The worst case is when $n = 120$, the total RMSE increases from 9.35 to 9.88. The loss is below 5.7%.

In comparison, the efficiency of the D-optimal design can be affected more markedly. In the case when ED60, ED75 and ED90 are targeted with $n = 120$, the loss is as high as 18%. When $n = 30$, the use of the more complex three-parameter logistic regression model makes the D-optimal design more efficient. This might be due to the fact that the initial design takes up a large proportion of the number of trials.

Overall speaking, if the ED-design is used, the use of a more than necessary three-parameter logistic regression model does not hurt much of the efficiency in estimating ED levels.

Table 4.5: Simulated RMSEs when fitting a simple logistic model when a two–parameter model suffices.

	Fit a Simple Logistic Regression Model					
Design	ED-design			D-optimal design		
Size	30	60	120	30	60	120
Total	**17.93**	**13.25**	**9.35**	**23.58**	**15.79**	**10.87**
ED10	12.68	9.48	6.73	17.53	11.96	8.02
ED25	8.93	6.52	4.55	12.15	8.02	5.63
ED40	9.01	6.56	4.63	10.07	6.46	4.69
Total	**17.14**	**12.54**	**8.74**	**20.18**	**12.63**	**8.87**
ED25	10.55	7.80	5.46	12.48	7.70	5.49
ED50	8.12	5.89	4.09	9.89	6.15	4.41
ED75	10.79	7.85	5.46	12.40	7.90	5.39
Total	**18.91**	**13.42**	**9.40**	**26.03**	**15.76**	**10.58**
ED60	9.49	6.64	4.86	9.09	6.45	4.62
ED75	9.39	6.51	4.57	12.87	8.01	5.47
ED90	13.40	9.67	6.63	20.72	11.94	7.79

Table 4.6: Simulated RMSEs when fitting a three-parameter model when a two–parameter model suffices.

	Fit the three-parameter Logistic Model					
Design	ED-design			D-optimal		
Size	30	60	120	30	60	120
Total	**18.36**	**13.63**	**9.88**	**23.56**	**17.50**	**12.41**
ED10	12.30	9.60	7.03	17.29	13.04	9.32
ED25	9.55	6.57	4.68	12.03	8.76	6.18
ED40	9.74	7.10	5.13	10.56	7.72	5.37
Total	**17.52**	**12.33**	**8.86**	**19.99**	**14.52**	**10.22**
ED25	10.64	7.80	5.66	12.03	8.76	6.18
ED50	8.45	5.48	4.04	10.33	7.56	5.23
ED75	11.06	7.81	5.48	12.17	8.77	6.23
Total	**19.00**	**13.48**	**9.92**	**23.77**	**17.25**	**12.49**
ED60	9.77	6.97	5.08	10.57	7.70	5.33
ED75	9.43	6.36	4.51	12.17	8.77	6.23
ED90	13.30	9.64	7.22	17.47	12.70	9.42

4.6.3 Effects under model misspecification

In this section, we investigate the effect of two kinds of model misspecification. One is when the dose–response relationship satisfies the three-parameter logistic regression model with $\lambda \neq 1$. The other is when the dose–response relationship is not even a three-parameter logistic model.

In both situations, we compute two sets of RMSEs of ED estimates. One set is when the design and analysis are done under the three-parameter logistic regression model assumption; the other set is done under the usual two-parameter logistic regression model assumption. We wish to demonstrate that the design and analysis based on the three-parameter logistic regression model leads to a more accurate estimation of the target ED levels.

For the first kind of model misspecification, we generate data from two three-parameter models:

$$\text{logit}(\pi^{\lambda}(x)) = -6.265 + 0.055x \tag{4.8}$$

with $\lambda = 0.5$, and

$$\text{logit}(\pi^{\lambda}(x)) = -14.148 + 0.1x \tag{4.9}$$

with $\lambda = 2$. Under model (4.8), ED25 = 114, ED50 = 130, and ED75 = 148 when $\lambda = 0.5$; and under model (4.9), ED25 = 114, ED50 = 130, and ED75 = 144 when $\lambda = 2$. The results are presented in Tables 4.7 and 4.8, and Tables 4.9 and 4.10 . Tables 4.7 and 4.9 are obtained under the two-parameter logistic regression model assumption. The D-optimal design in this case is a uniform distribution on ED17.6 and ED82.4. Tables 4.8 and 4.10

are obtained under the correct three-parameter logistic regression model assumption.

According to these results, we notice that the use of the ED-design is noticeably superior to the D-optimal design in both situations. The simulated RMSEs under the ED-design are always lower than those under the D-optimal design. The efficiency gain can be as much as 30%.

In addition, the use of the more complex three-parameter model when data are generated under the three-parameter logistic model gains the efficiency significantly. In the case of $\lambda = 2$, targeting ED25, ED50, and ED75, the total RMSE decreases from 15.57 to 14.02 when the sample size $n = 30$. This gain is as much as 11%. Overall speaking, the use of the more complex three-parameter logistic regression model makes the ED-design more efficient in estimating ED levels.

For the second kind of model misspecification, we generate data from the three-parameter probit model:

$$\pi(x) = \Phi^{1/\lambda}(-6.265 + 0.055x)$$

with $\lambda = 0.5$, and

$$\pi(x) = \Phi^{1/\lambda}(-14.148 + 0.1x)$$

$\lambda = 2$. Under this model, ED25 = 114, ED50 = 124, and ED75 = 134 when $\lambda = 0.5$; and ED25 = 86, ED50 = 102, and ED75 = 117 when $\lambda = 2$. The simulation results are presented in Tables 4.11 and 4.12, and Tables 4.13 and 4.14. Tables 4.11 and 4.13 are obtained under the two-parameter logistic regression model assumption. The D-optimal design in this case is

Table 4.7: Simulated RMSEs under the three parameter model ($\alpha = -6.265, \beta = 0.055, \lambda = 0.5$).

	Fit a Simple Logistic Regression Model					
Design	ED-design			D-optimal Design		
Size	30	60	120	30	60	120
Total	**13.87**	**9.96**	**7.16**	**16.62**	**13.38**	**11.04**
ED10	10.14	7.08	4.99	11.75	9.50	7.77
ED25	6.53	4.74	3.43	8.63	7.15	6.09
ED40	6.86	5.17	3.82	7.97	6.14	4.94
Total	**15.57**	**11.14**	**7.65**	**15.72**	**11.46**	**8.69**
ED25	9.45	6.63	4.30	8.63	7.15	6.09
ED50	6.64	5.06	3.57	8.12	5.82	4.30
ED75	10.44	7.39	5.22	10.34	6.81	4.47
Total	**18.98**	**12.89**	**8.98**	**19.80**	**13.86**	**10.23**
ED60	8.16	5.78	4.23	8.65	5.82	3.90
ED75	8.74	5.90	4.21	10.34	6.81	4.47
ED90	14.73	9.89	6.71	14.50	10.57	8.34

Table 4.8: Simulated RMSEs under the three-parameter model ($\alpha = -6.265, \beta = 0.055, \lambda = 0.5$).

	Fit the three-parameter Logistic Regression Model					
Design	ED-design			D-optimal Design		
Size	30	60	120	30	60	120
Total	**13.32**	**9.87**	**6.93**	**16.82**	**11.96**	**8.44**
ED10	8.62	6.66	4.71	11.33	8.16	5.82
ED25	6.78	4.78	3.23	9.03	6.34	4.45
ED40	7.55	5.50	3.93	8.54	6.02	4.19
Total	**14.02**	**10.49**	**7.47**	**16.97**	**11.95**	**8.46**
ED25	8.20	6.15	4.46	9.03	6.34	4.45
ED50	6.72	4.83	3.48	8.72	6.16	4.29
ED75	9.17	7.00	4.88	11.42	8.05	5.77
Total	**17.36**	**12.63**	**8.89**	**22.40**	**15.83**	**11.48**
ED60	9.00	6.29	4.39	9.33	6.58	4.63
ED75	8.69	5.92	4.07	11.42	8.05	5.77
ED90	12.04	9.22	6.57	16.86	11.94	8.78

Table 4.9: Simulated RMSEs under the three-parameter model ($\alpha = -14.148, \beta = 0.1, \lambda = 2$).

	Fit a Simple Logistic Regression Model					
Design	ED-design			D-optimal Design		
Size	30	60	120	30	60	120
Total	**17.43**	**12.39**	**8.99**	**24.82**	**15.78**	**12.04**
ED10	14.00	9.78	6.98	19.42	12.80	10.33
ED25	7.50	5.40	3.95	12.51	7.47	5.11
ED40	7.19	5.35	4.06	9.07	5.42	3.50
Total	**13.80**	**9.57**	**6.95**	**16.25**	**10.09**	**6.93**
ED25	9.43	6.64	4.76	12.51	7.47	5.11
ED50	5.95	4.25	3.47	7.52	4.69	3.13
ED75	8.14	5.43	3.70	7.13	4.90	3.49
Total	**13.06**	**8.75**	**6.35**	**15.63**	**10.30**	**7.10**
ED60	6.27	4.57	3.49	6.59	4.37	3.06
ED75	6.22	4.08	2.96	7.13	4.90	3.49
ED90	9.63	6.25	4.40	12.25	7.93	5.37

Table 4.10: Simulated RMSEs under the three-parameter model ($\alpha = -14.148, \beta = 0.1, \lambda = 2$).

	Fit the three-parameter Logistic Regression Model					
Design	ED-design			D-optimal Design		
Size	30	60	120	30	60	120
Total	**16.76**	**12.26**	**8.92**	**21.35**	**15.84**	**11.05**
ED10	12.01	9.03	6.61	15.58	11.63	8.22
ED25	8.34	5.79	4.12	11.23	8.24	5.66
ED40	8.21	5.93	4.35	9.32	6.91	4.75
Total	**13.05**	**9.36**	**6.76**	**16.23**	**11.78**	**8.06**
ED25	8.76	6.37	4.69	11.23	8.24	5.66
ED50	6.37	4.42	3.12	8.48	6.28	4.28
ED75	7.28	5.25	3.74	8.10	5.61	3.82
Total	**12.32**	**8.67**	**6.23**	**16.30**	**11.54**	**8.30**
ED60	6.84	4.81	3.46	7.93	5.77	3.89
ED75	6.24	4.14	2.83	8.10	5.61	3.82
ED90	8.12	5.90	4.35	11.72	8.28	6.26

a uniform distribution on ED12.8 and ED87.2. Tables 4.12 and 4.14 are obtained under the three-parameter logistic regression model assumption. Both model assumptions are incorrect. However, we wish to demonstrate the use of the three-parameter logistic model makes the ED-design more efficient in estimating ED levels.

According to the simulation result, we notice that the use of the ED-design is noticeably superior to the D-optimal design in both situations. The simulated RMSEs under the ED-design are always lower than those under the D-optimal design. In the case of $\lambda = 2$, targeting ED10, ED25, and ED40, the total RMSE increases from 8.39 to 12.89 when the sample size $n = 30$. The efficiency gain is as much as 54%.

In addition, the use of the more complex model when data are generated under the three-parameter probit model gains the efficiency noticeably. In the case of $\lambda = 2$, targeting ED60, ED75, and ED90, the total RMSE decreases from 8.29 to 7.12 when the sample size $n = 30$. This efficiency gain is as much as 16%. Overall speaking, the use of the more complex model makes the ED-design more efficient in estimating ED levels, when the model is mis-specified.

Table 4.11: Simulated RMSEs under probit mis-specified as logistic ($\alpha = -6.265, \beta = 0.055, \lambda = 0.5$).

	Fit a Simple Logistic Regression Model					
Design	ED-design			D-optimal Design		
Size	30	60	120	30	60	120
Total	**9.27**	**6.29**	**4.31**	**9.02**	**6.81**	**7.48**
ED10	6.68	4.49	3.01	5.44	3.98	4.69
ED25	4.36	3.08	2.11	4.85	3.86	4.37
ED40	4.72	3.16	2.24	5.31	3.95	3.85
Total	**9.73**	**6.22**	**4.38**	**10.29**	**7.28**	**6.40**
ED25	6.22	3.91	2.72	4.85	3.86	4.37
ED50	4.18	2.71	2.00	5.72	4.06	3.52
ED75	6.21	4.01	2.80	7.05	4.65	3.07
Total	**10.17**	**6.71**	**4.45**	**12.75**	**8.38**	**5.64**
ED60	5.05	3.29	2.21	6.19	4.23	3.25
ED75	4.78	3.17	2.14	7.05	4.65	3.07
ED90	7.41	4.90	3.21	8.63	5.55	3.44

Table 4.12: Simulated RMSEs under probit mis-specified as logistic ($\alpha = -6.265, \beta = 0.055, \lambda = 0.5$).

	Fit the three-parameter Logistic Regression Model					
Design	ED-design			D-optimal Design		
Size	30	60	120	30	60	120
Total	**8.58**	**5.75**	**4.25**	**12.36**	**7.65**	**4.95**
ED10	5.76	3.94	2.94	7.24	4.40	3.14
ED25	4.42	2.85	2.06	7.11	4.41	2.77
ED40	4.57	3.08	2.27	7.06	4.43	2.64
Total	**8.57**	**6.00**	**4.25**	**12.09**	**7.56**	**4.83**
ED25	5.17	3.70	2.68	7.11	4.41	2.77
ED50	4.27	2.85	2.00	6.99	4.41	2.65
ED75	5.34	3.77	2.61	6.84	4.28	2.94
Total	**9.14**	**6.52**	**4.58**	**12.55**	**7.71**	**5.26**
ED60	4.77	3.45	2.47	6.89	4.36	2.72
ED75	4.49	3.07	2.12	6.84	4.28	2.94
ED90	6.37	4.60	3.22	7.94	4.70	3.42

Table 4.13: Simulated RMSEs under probit mis-specified as logistic ($\alpha = -14.148, \beta = 0.1, \lambda = 2$).

	Fit a Simple Logistic Regression Model					
Design	ED-design			D-optimal Design		
Size	30	60	120	30	60	120
Total	**8.52**	**5.65**	**3.70**	**8.75**	**5.95**	**4.31**
ED10	6.33	4.13	2.67	6.24	4.19	3.05
ED25	3.97	2.69	1.79	4.63	3.10	2.16
ED40	4.09	2.75	1.83	4.04	2.87	2.14
Total	**8.25**	**5.39**	**3.52**	**7.51**	**5.80**	**4.77**
ED25	5.42	3.50	2.28	4.63	3.10	2.16
ED50	3.40	2.36	1.57	3.93	3.00	2.41
ED75	5.20	3.36	2.17	4.43	3.89	3.50
Total	**8.29**	**5.30**	**3.55**	**8.29**	**7.05**	**6.24**
ED60	3.97	2.66	1.79	3.99	3.27	2.80
ED75	3.87	2.51	1.71	4.43	3.89	3.50
ED90	6.17	3.84	2.55	5.76	4.88	4.33

Table 4.14: Simulated RMSEs under probit mis-specified as logistic ($\alpha = -14.148, \beta = 0.1, \lambda = 2$).

	Fit the three-parameter Logistic Regression Model					
Design	ED-design			D-optimal Design		
Size	30	60	120	30	60	120
Total	**8.39**	**5.43**	**3.13**	**12.89**	**7.62**	**4.33**
ED10	5.81	3.80	2.13	9.13	5.16	2.80
ED25	4.24	2.67	1.57	6.67	4.02	2.39
ED40	4.32	2.82	1.68	6.19	3.91	2.28
Total	**7.33**	**5.21**	**3.66**	**10.47**	**6.59**	**4.21**
ED25	4.59	3.21	2.31	6.67	4.02	2.39
ED50	3.67	2.57	1.78	5.98	3.82	2.24
ED75	4.37	3.19	2.21	5.42	3.57	2.66
Total	**7.12**	**5.06**	**3.65**	**9.63**	**6.39**	**4.99**
ED60	3.97	2.77	2.05	5.76	3.70	2.29
ED75	3.76	2.51	1.71	5.42	3.57	2.66
ED90	4.56	3.41	2.48	5.48	3.79	3.54

4.7 Numerical example

To illustrate the ideas described in this chapter, we consider a real clinical study. Brown (1982) assumed a logistic response curve to model the relationship between the wheezing symptom and the age of British coal miners. The number of subjects being examined and the number of subjects showing the symptom are copied in Table 4.15.

We first fit the observed data using model (4.1). The MLE of the model parameters are $\hat{\alpha} = -1.798$, $\hat{\beta} = 0.044$, and $\hat{\lambda} = 0.400$. We then fit the observed data using a simple logistic model. The MLE of the model parameters are $\hat{\alpha} = -4.225$ and $\hat{\beta} = 0.065$. For comparison, we draw the observed data and the two fitted curves in Figure 4.2. The result of Figure 4.2 shows that the three-parameter logistic model (4.1) is a better fit than the simple logistic model.

Table 4.15: Number of subjects examined and showing the wheezing symptom for British coal miners.

Group	Age	Number Examined	Number showing symptom	proportion showing symptom
1	22	1952	104	0.053
2	27	1791	128	0.072
3	32	2113	231	0.109
4	37	2783	378	0.136
5	42	2274	442	0.194
6	47	2393	593	0.248
7	52	2090	649	0.311
8	57	1750	631	0.361
9	62	1136	504	0.447

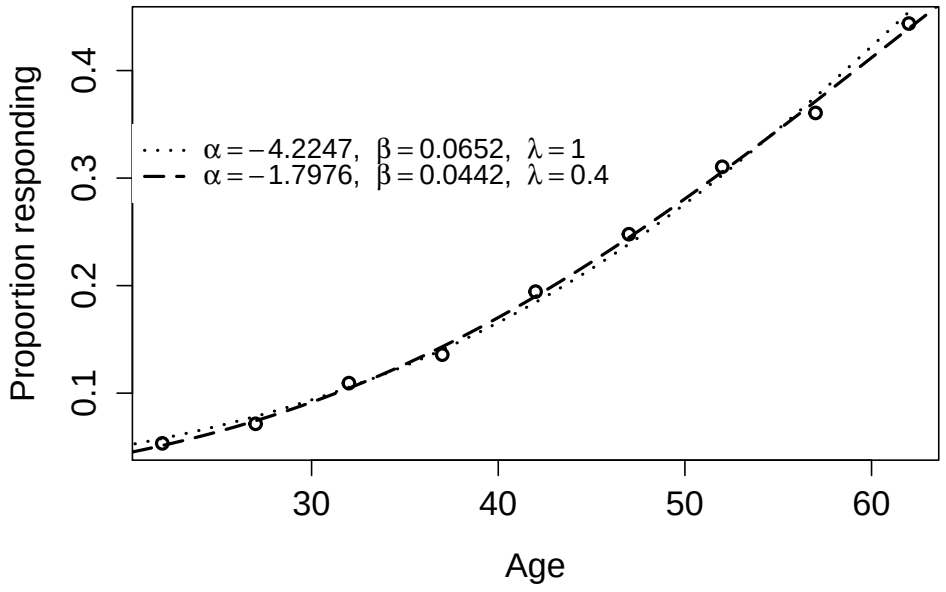


Figure 4.2: Observed Data and the fitted curve for British Coal Miners

4.8 Limiting design as n increases

We have so far focused on implementing the ED-design under the three-parameter logistic regression model. Recall that a design for a binary dose–response experiment is a probability distribution on the design space or dose range. From Section 4.4.2, the D-optimal design is roughly a three-support-point design under the three-parameter logistic regression model. Because of its sequential nature, the ED-design likely has many more support points. When n goes to infinity, it is possible that the limiting distribution has three support points. We simulated the ED-design for two scenarios with $n = 1000$, first targeting ED25, ED50, ED75, and then targeting ED10, ED25, ED40, and targeting ED60, ED75, ED90. In the first scenario, we consider the case where the data are generated under the three-parameter logistic model with $\alpha = -6.265$, $\beta = 0.055$ and $\lambda = 0.5$. In the second scenario, we set $\alpha = -14.148$, $\beta = 0.1$ and $\lambda = 2$. The resulting histograms are given in Figures 4.3 and 4.4. There are clear indications that in both scenarios, the limiting distribution has three support points around ED6, ED32 and ED86 when the target ED levels are ED25, ED50, and ED75, or ED10, ED25, and ED40. We hope to prove this in the future.

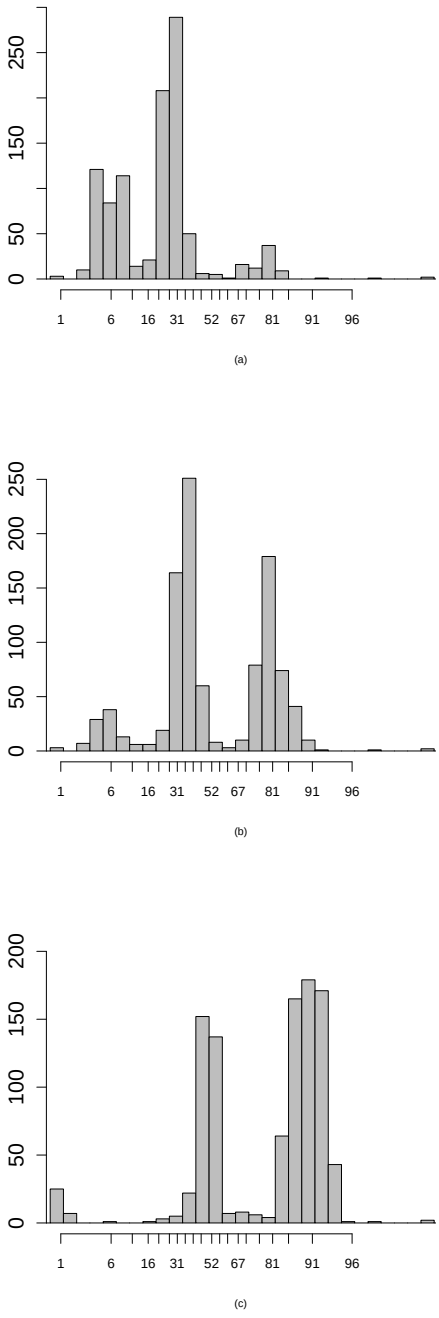


Figure 4.3: Histogram of the ED-design with respect to ED levels ($\alpha_1 = -6.265, \beta = 0.055, \lambda = 0.5$) for (a) estimating ED10, ED25, and ED40; (b) estimating ED25, ED50, and ED75, and (c) estimating ED60, ED75, and ED90.

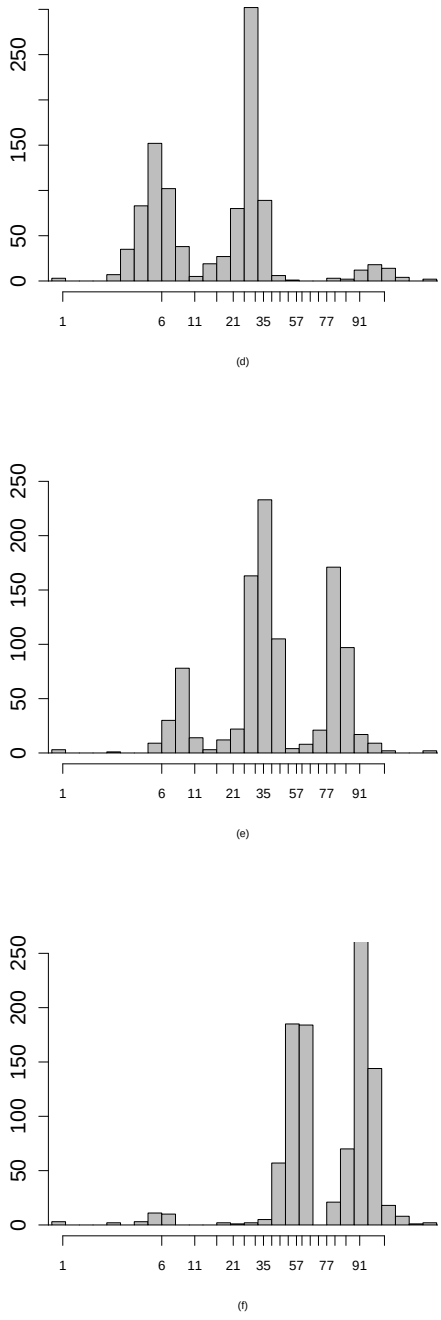


Figure 4.4: Histogram of the ED-design with respect to ED levels (α = −14.148, $\beta = 0.1$ and $\lambda = 2$) for (a) estimating ED10, ED25, and ED40; (b) estimating ED25, ED50, and ED75, and (c) estimating ED60, ED75, and ED90.

4.9 Concluding remarks

We explore the use of the three-parameter logistic regression model for dose–response experiments. We show that the sequential ED-design can be easily carried out under this model assumption, and the resulting data analysis is very effective.

Simulation results show that the three-parameter logistic regression model is an effective extension of the commonly used logistic regression model without leading to more complex data analysis issues.

Simulation studies also show that the combination of the proposed model and data the analysis strategy works well. When the logistic model is correct, applying the more complex model suffers hardly any efficiency loss. When the three-parameter model holds but the logistic model is violated, the new approach gains substantial ground. Our finding leads to a useful addition to the toolbox of the dose–response experiment.

4.10 R-code for simulations

```
rm(list=ls())

library(MASS)

# define objects

m = 1000

n = 30

diff1 <- rep (0, m)

diff2 <- rep (0, m)

diff3 <- rep (0, m)

diff  <- rep (0, m)

mu_temp1 <- rep (0, m)

mu_temp2 <- rep (0, m)

mu_temp3 <- rep (0, m)

mu_temp  <- matrix(0, m, 3)

t        <- seq(from = 40, to = 200, by = 1)

sum      <- rep(0, length(t))

alpha    <- -6.2647

beta     <- 0.05478

lambda <- 0.5

maxit  <- 50

ed     <- c(0.25, 0.50, 0.75)

dose.initial <- seq(from=(logit(0.01^lambda)-alpha)/beta,

                            to=(logit(0.99^lambda)-alpha)/beta, by=20)

mu1 <- (logit (ed[1]^lambda) - alpha) / beta
```

```
mu2 <- (logit (ed[2]^lambda) - alpha) / beta
mu3 <- (logit (ed[3]^lambda) - alpha) / beta

# Define functions

# Function f.lr.p() computes the probability vector
# under the logistic model
f.lr.p <- function (x, alpha, beta, lambda) {
  prob = (exp(alpha + beta * x)/(1+exp(alpha + beta *x)))^(1/lambda)
  return (prob)
}

f.lr.l <- function(x, y, theta, lambda) {
  alpha <- theta[1]
  beta <- theta[2]
  ai <- (exp(x * beta +  alpha) / (1+ exp(x * beta +  alpha)))
  w <- c(0.1, 0.1, 0.9, 0.9, rep (1, length(x)-4))
  l <- sum(w * (-y * log(ai^(1/lambda)) - (1 - y) * log(1 - ai^(1/lambda))))
  return(l)
}

# function for the parameter estimation
f.est <- function(x, y, theta)
{
  lambda.start = 1
```

```
  theta.start <- theta
  mle = optim(theta.start, f.lr.l, x = x, y = y, lambda = lambda.start)
  alpha_hat <- mle$par[[1]]
  beta_hat  <- mle$par[[2]]
  theta.hat = c(alpha_hat, beta_hat)
   mle = optimize(f.lr.l, c(0.01,100), x = x, y = y, theta = theta.hat)
  lambda_hat <- mle$minimum
  like.1 <- mle$objective
  i <- 0 # initial iteration index
  diff.like <- 1
  while (i <= maxit & diff.like > 1e-6)
  {
    i <- i + 1
     mle = optim(theta.hat, f.lr.l, x = x, y = y, lambda = lambda_hat)
    alpha_hat <- mle$par[[1]]
    beta_hat  <- mle$par[[2]]
    theta.hat = c(alpha_hat, beta_hat)
     mle = optimize(f.lr.l, c(0.01,100), x = x, y = y, theta = theta.hat)
    lambda_hat <- mle$minimum
    like.2 <- mle$objective
    diff.like <- like.1 - like.2
    like.1 <- like.2
  }
  para=c(alpha_hat, beta_hat, lambda_hat, like.2)
}
```

```
fisher <- function (x,theta,lambda)
{
  w <- c(0.01, 0.01, 0.99, 0.99, rep (1, length(x)-4))
  alpha <- theta[1]
  beta <- theta[2]
  pi <-  f.lr.p(x, alpha, beta, lambda)
  v00 <- sum(w*lambda^(-2) * pi * (pi-1)^(-1)* (1-pi^lambda)^2)
  v11 <- sum(w*x^2 * lambda^(-2) * pi * (pi-1)^(-1) * (1-pi^lambda)^2)
  v22 <- sum(w*log(pi)^2 * lambda^(-2) * pi * (pi-1)^(-1))
  v01 <- sum(w*x * lambda^(-2) * pi * (pi-1)^(-1) * (1-pi^lambda)^2)
  v02 <- sum(w*log(pi) * lambda^(-2) * pi * (1-pi)^(-1) * (1-pi^lambda))
  v12 <- sum(w*x * log(pi) * lambda^(-2) * pi * (1-pi)^(-1) * (1-pi^lambda))
  fisher.infor <- - matrix(c(v00, v01, v02, v01, v11,
                                      v12, v02, v12, v22), 3,3)
  return(fisher.infor)
}

# dose selection function
f.dose.box <- function (x, theta, lambda, fisher.infor, ed)
{
  alpha <- theta[1]
  beta  <- theta[2]
  pi <-  f.lr.p(x, alpha, beta, lambda)
  v00 <- sum(lambda^(-2) * pi * (pi-1)^(-1)* (1-pi^lambda)^2)
```

```
v11 <- sum(x^2 * lambda^(-2) * pi * (pi-1)^(-1) * (1-pi^lambda)^2)
v22 <- sum(log(pi)^2 * lambda^(-2) * pi * (pi-1)^(-1))
v01 <- sum(x * lambda^(-2) * pi * (pi-1)^(-1) * (1-pi^lambda)^2)
v02 <- sum(log(pi) * lambda^(-2) * pi * (1-pi)^(-1) * (1-pi^lambda))
v12 <- sum(x * log(pi) * lambda^(-2) * pi * (1-pi)^(-1) * (1-pi^lambda))
fisher.sel <- fisher.infor - matrix(c(v00, v01, v02, v01,
                                      v11, v12, v02, v12, v22), 3,3)
cov.sel <- solve(fisher.sel)
v00.sel <- cov.sel[1,1]
v11.sel <- cov.sel[2,2]
v22.sel <- cov.sel[3,3]
v01.sel <- cov.sel[1,2]
v02.sel <- cov.sel[1,3]
v12.sel <- cov.sel[2,3]

# variane
mu_hat1 <- (logit (ed[1]^lambda)  - alpha) / beta
mu_hat2 <- (logit (ed[2]^lambda)  - alpha) / beta
mu_hat3 <- (logit (ed[3]^lambda)  - alpha) / beta

var1.sel <- (v00.sel + v11.sel*mu_hat1^2
             + (log(ed[1])/(1-ed[1]^lambda))^2*v22.sel
             + 2*v01.sel*mu_hat1 - 2*v02.sel*log(ed[1])/(1-ed[1]^lambda)
             - 2*v12.sel*mu_hat1*log(ed[1])/(1-ed[1]^lambda)) / beta ^ 2
```

```
  var2.sel <- (v00.sel + v11.sel*mu_hat2^2
                + (log(ed[2])/(1-ed[2]^lambda))^2*v22.sel
                + 2*v01.sel*mu_hat2-2*v02.sel*log(ed[2])/(1-ed[2]^lambda)
                - 2*v12.sel*mu_hat2*log(ed[2])/(1-ed[2]^lambda)) / beta ^ 2


  var3.sel <- (v00.sel + v11.sel*mu_hat3^2
               + (log(ed[3])/(1-ed[3]^lambda))^2*v22.sel
               + 2*v01.sel*mu_hat3-2*v02.sel*log(ed[3])/(1-ed[3]^lambda)
               - 2*v12.sel*mu_hat3*log(ed[3])/(1-ed[3]^lambda)) / beta ^ 2
   sum.se   <- var1.sel + var2.sel + var3.sel
  return(sum.se)
}


# main part


y_pes1 = 1
y_pes2 = 0
x_pes1 =  (logit (0.01^lambda) - alpha) / beta
x_pes2 =  (logit (0.99^lambda) - alpha) / beta


y_pes3 = 0
y_pes4 = 1
x_pes3 = (logit (0.01^lambda) - alpha) / beta
x_pes4 = (logit (0.99^lambda) - alpha) / beta
```

```
for (k in 1:m)
{
  # initial design
  # generate data
  yhat <- rbinom(length(dose.initial), 1,
                 f.lr.p(dose.initial, alpha, beta, lambda))
  data <- data.frame(rbind(cbind (y_pes1, x_pes1), cbind (y_pes2, x_pes2),
                           cbind (y_pes3, x_pes3), cbind (y_pes4, x_pes4),
                           cbind (yhat, dose.initial)))
  names(data)[1] <- paste("y")
  names(data)[2] <- paste("x")

  theta <- c(alpha, beta)
  out <- f.est (data$x, data$y, theta)
  alpha_hat  <- out[1]
  beta_hat   <- out[2]
  lambda_hat <- out[3]

  # Second stage
  # Select the next dose level
  for (j in 1:(n-length(dose.initial)))
  {
    # calculate fisher information
    theta <- c(alpha_hat, beta_hat)
    fisher.info <- fisher(data$x, theta, lambda_hat)
```

```
  for (i in 1:length(t))
  {
    sum[i] <- f.dose.box(t[i], theta, lambda_hat,fisher.info, ed)
  }
  opt <- t[which(sum == min (sum))]
  prob <-  f.lr.p(opt, alpha, beta, lambda)
  y    <- rbinom (1, 1, prob)
  data <- rbind (data, data.frame (y, x = opt))

  # new function
  theta <- c(alpha_hat, beta_hat)
  out <- f.est (data$x, data$y, theta)
  alpha_hat  <- out[1]
  beta_hat   <- out[2]
  lambda_hat <- out[3]
}

theta <- c(alpha_hat, beta_hat)
out <- f.est (data$x, data$y, theta)
alpha_hat  <- out[1]
beta_hat   <- out[2]
lambda_hat <- out[3]

mu_temp1[k] <- (logit (ed[1]^lambda_hat)  - alpha_hat) / beta_hat
```

```
  mu_temp2[k] <- (logit (ed[2]^lambda_hat)  - alpha_hat) / beta_hat
  mu_temp3[k] <- (logit (ed[3]^lambda_hat)  - alpha_hat) / beta_hat
  mu_temp [k, ] <- c(mu_temp1[k], mu_temp2[k], mu_temp3[k])


  diff1[k] <- (mu_temp1[k] - mu1) ^ 2
  diff2[k] <- (mu_temp2[k] - mu2) ^ 2
  diff3[k] <- (mu_temp3[k] - mu3) ^ 2
  diff[k]   <- diff1[k] + diff2[k] + diff3[k]
  print(k)
}


sqrt(mean(diff1))
sqrt(mean(diff2))
sqrt(mean (diff3))
sqrt(mean(diff))
```

Chapter 5

Group Sequential ED-Design

5.1 Introduction

The standard up-and-down design of Dixon and Mood (1948) has been introduced in Chapter 2. Under this design, the dose of the next trial is one level higher or lower than that of the current trial depending on the outcome of the current subject. Much of the discussion of the up-and-down design (Dixon and Mood, 1948; Derman, 1957; Durham and Flournoy, 1994, 1995; Durham et al., 1997; Stylianou and Flournoy, 2002) focused on the situation where there is only one subject at each trial: only one subject is admitted, and its response is used to choose the next dose level.

The idea of the up-and-down design can also be used so that multiple subjects are admitted to the experiment at each trial. Anderson et al. (1946); Wetherill (1963); Tsutakawa (1967b); Gezmu and Flournoy (2006) among others, proposed a group version of the up-and-down design. They considered the problem that a group of m subjects are admitted to a single dose level at each trial. They proposed to determine the dose level for the next trial based on the number of positive responses at the current trial. If the number of positive responses in the group is less than or equal to a threshold s, the dose level of the next trial will be moved one level higher.

If the number of positive responses is greater than or equal to a threshold t, the dose of the next trial will be moved one level lower. Otherwise, the dose level for the next trial stays the same. With appropriate values of the group size m, and thresholds s and t, Gezmu and Flournoy (2006) showed that the group up-and-down design allocates a large number of dose levels around the prespecified target dose.

Clinical trials involving developing new drugs include all drug development experiments that are conducted on human beings. They can last for many years with high financial and human costs. "Phase II/III Study Trends and Market Outlook (2016-2020)" reported that large drug development Sponsors (R&D $500M+) spent $465,725,000 in Phase II/III trials in 2015 on average. Despite the high financial costs of clinical trials, there are greater human costs. New drugs studied in clinical trials can be unsafe and inferior. It is unethical to make any decision lightly. Thus, it is desirable to design the experiments to speed up the clinical trial, and prevent waste of valuable resources. In practice, clinical trials are carried out over a certain period of time, and individuals often enter the trial sequentially in groups. Thus, for ethical, scientific and economic reasons, it is often more practical and natural to treat individuals sequentially in groups.

The sequential ED-design proposed in Chapter 3 has been developed to have one subject admitted at each trial. It appears that the same idea works when a group of subjects admits at each trial. In this chapter, we propose a group scheme and call it two-stage group sequential ED-design. The first stage will be a fix-point design. A group of subjects will be assigned to some pre-selected dose levels. The responses of these subjects will be used

to obtain a rough parameter estimation. At the second stage, we use a group sequential procedure. We look for the most informative dose combination for the next group of subjects with respect to some criterion. This procedure is then repeated until the experimental subjects are exhausted.

A simulation study is conducted to investigate the performance of the proposed two-stage group sequential ED-design under various scenarios. We mimic real dose–response experiments with the goal of accurately estimating the unknown dose–response curve over a wide dose range.

5.2 Two-stage group sequential ED-design under the logistic regression model

We only consider the case where each group is made of two subjects and two different dose levels are permitted. The idea can be used to groups with different sizes and more dose levels. We investigate three possible ways to select two doses at each trial.

Suppose ξ_j, $j = 1, 2, 3$ are the target ED levels. Each ED level is a function of the model parameters α and β under the logistic regression model: $\xi_j = g_j(\alpha, \beta)$ for some smooth function g_j. Let $\hat{\alpha}_k, \hat{\beta}_k$ be the maximum likelihood estimators of the model parameters based on the outcomes of the first k trials. As it has been pointed out before, the variance of $\hat{\xi} = g(\hat{\alpha}_k, \hat{\beta}_k)$ is conceptually approximated by

$$\text{var}(\hat{\xi}) = \bigtriangledown g(\hat{\alpha}_k, \hat{\beta}_k)^T \mathbb{I}_k^{-1}(x; \hat{\alpha}_k, \hat{\beta}_k) \bigtriangledown g(\hat{\alpha}_k, \hat{\beta}_k)$$

where $\bigtriangledown g(\hat{\alpha}_k, \hat{\beta}_k)$ is the gradient of $g(\hat{\alpha}_k, \hat{\beta}_k)$ and $\mathbb{I}_k(x; \hat{\alpha}_k, \hat{\beta}_k)$ is the Fisher information matrix based on the existing k trials and an extra trial at dose level x, at the model parameter value $\hat{\alpha}_k, \hat{\beta}_k$. Each of the next three proposed dose selection methods aims to minimize some criterion.

1. Let $\hat{\xi}_2$ be the maximum likelihood estimate of ξ_2 based on the outcomes of the first k trials. We compute

$$\begin{aligned} x_1 &= \arg\min_{x \le \hat{\xi}_2} \Big\{ \sum_{j=1}^{3} \bigtriangledown g(\hat{\alpha}_k, \hat{\beta}_k)^T \mathbb{I}_k^{-1}(x; \hat{\alpha}_k, \hat{\beta}_k) \bigtriangledown g(\hat{\alpha}_k, \hat{\beta}_k) \Big\} \\ x_2 &= \arg\min_{x \ge \hat{\xi}_2} \Big\{ \sum_{j=1}^{3} \bigtriangledown g(\hat{\alpha}_k, \hat{\beta}_k)^T \mathbb{I}_k^{-1}(x; \hat{\alpha}_k, \hat{\beta}_k) \bigtriangledown g(\hat{\alpha}_k, \hat{\beta}_k) \Big\} \end{aligned} \quad (5.1)$$

   A simple linear search can be used to find solutions easily.

2. We select two doses to minimize the total anticipated asymptotic variance of the target ED levels in the second stage of our group sequential ED-design:

$$(x_1, x_2) = \arg\min_{x_1, x_2} \Big\{ \sum_{j=1}^{3} \bigtriangledown g(\hat{\alpha}_k, \hat{\beta}_k)^T \mathbb{I}_k^{-1}(x_1, x_2; \hat{\alpha}_k, \hat{\beta}_k) \bigtriangledown g(\hat{\alpha}_k, \hat{\beta}_k) \Big\}. \quad (5.2)$$

   where $\mathbb{I}_k(x_1, x_2; \hat{\alpha}_k, \hat{\beta}_k)$ is the Fisher information matrix based on the existing k trials and two extra trials at dose levels x_1 and x_2, at the model parameter value $\hat{\alpha}_k, \hat{\beta}_k$.

3. Remember that

$$\sum_{j=1}^{3} \bigtriangledown g(\hat{\alpha}_k, \hat{\beta}_k)^T \mathbb{I}_k^{-1}(x; \hat{\alpha}_k, \hat{\beta}_k) \bigtriangledown g(\hat{\alpha}_k, \hat{\beta}_k)$$

represents the potential total asymptotic variance of $\hat{\xi}_j$, $j = 1, 2, 3$ after the first k trials and one single additional trial at x. Our experience indicates that, as a function of x, it can have two local minima. We propose to choose two dose levels for the next group of two subjects at these two local minima. We again use a simple linear search for this purpose.

5.3 Simulation

We conduct simulations to investigate the performance of the group sequential ED-design. We compare the new design with several existing designs, and repeat the simulation $N = 1000$ times for all model/design combinations. The simulation sample sizes are chosen to be $n = 30, 60$, and 120. We choose three effective dose levels each time as the targets and obtain their MLEs. Under each model/design setting, we compute the RMSE of a single ED level as

$$\text{RMSE}(\hat{\xi}_j) = \sqrt{N^{-1} \sum_{r=1}^{N} (\hat{\xi}_{rj} - \xi_j)^2},$$

where $\hat{\xi}_{rj}$ is the estimate of ξ_j in the rth repetition. The total RMSE is computed as

$$\text{RMSE} = \sqrt{\sum_{j=1}^{3} \text{RMSE}^2(\hat{\xi}_j)}.$$

5.3.1 Detailed specifications

The detailed simulation specifications are as follows. Four designs are included in the simulation: the up-and-down design, the group up-and-down design, the sequential ED-design, and the group ED-design. Similar to the setting of Chapter 3.4, for the up-and-down design, we choose $K = 7$ equal spaced grids for Ω between the anticipated ED01 and ED90. For the group ED-design and the sequential ED-design, the initial design is uniform on Ω. The group up-and-down design uses the same Ω as its grids. The choice of the first dose level, thresholds s and t, and the group size s will be specified later in the simulation.

5.3.2 Performance comparison when the response model is correctly specified

In this section, we consider the situation where the assumed response curve agrees with the true curve. We generate data according to the following logistic regression model

$$\text{logit}\big[\pi(x)\big] = -6.265 + 0.055x.$$

Under this model, ED25 = 94, ED50 = 114, and ED75 = 134.

The details of the four designs under this model are as follows:

- For the up-and-down design, the specific dose levels are $x_1 = 34$ and $x_7 = 154$. The dose range is given by

$$\Omega = \{34, 54, 74, 94, 114, 134, 154\}.$$

The initial dose level is set to $x_4 = 94$.

- For the ED-design, we use the following grid of $K = 7$ doses in the first stage:

$$\Omega = (84, 94, 104, 114, 124, 134, 144).$$

- For the group up-and-down design, the dose range is given by

$$\Omega = \{34, 54, 74, 94, 114, 134, 154\}.$$

The initial dose level is set at $x_4 = 94$. We choose thresholds $s = 0$, $t = 2$, and group size $s = 2$.

- For the group ED-design, we use the following grid of $K = 8$ doses in the first stage:

$$\Omega = (74, 84, 94, 104, 114, 124, 134, 144).$$

The subsequent doses are chosen according to each of the three proposed dose selection methods.

In the first simulation, we set ED25, ED50, and ED75 as the target dose levels. The simulation results are given in Table 5.1. The results show that the group sequential ED-design is noticeably superior to the group up-and-down design with lower total RMSEs when $n = 30$, $n = 60$ and $n = 120$. The differences are getting smaller as n increases.

Its individual RMSEs is generally lower except targeting ED50 when $n = 60$ and $n = 120$. The group ED-design based on the third selection

method has lower RMSEs than the group ED-design with the first and second selection methods. If ED25 is the target, the group ED-design (method 3) is superior than the ED-design with lower RMSE. Comparing with the up-and-design, group ED-design (method 3) is generally superior with lower total RMSEs.

Table 5.1: Simulated RMSEs under the logistic model targeting range ED25–ED75

n		ED	Group ED-design			Group UD	Up-and-down
			M 1	M 2	M 3		
30	**Total**	**17.14**	**18.60**	**18.04**	**17.80**	**22.81**	**18.12**
	ED25	10.55	10.79	11.36	10.20	11.75	10.48
	ED50	8.12	7.86	8.94	8.66	9.24	8.06
	ED75	10.79	12.95	10.80	11.75	17.23	12.39
60	**Total**	**12.54**	**13.16**	**12.93**	**12.73**	**14.67**	**12.79**
	ED25	7.80	7.79	8.41	7.42	8.67	7.90
	ED50	5.89	5.89	6.31	6.05	5.69	5.53
	ED75	7.85	8.81	7.52	8.40	10.37	8.40
120	**Total**	**8.74**	**9.02**	**9.00**	**8.84**	**9.92**	**9.16**
	ED25	5.46	5.49	5.73	5.22	6.25	5.89
	ED50	4.09	4.30	4.35	4.23	3.80	3.88
	ED75	5.46	5.72	5.40	5.74	6.69	5.85

In the second simulation, we consider the situation where a lower range of ED levels is of interest. We take ED10, ED25, and ED40 as the target

dose levels. The simulation settings remain the same except that the initial dose level for the up-and-down design is set at $x_3 = 74$. This approach can select only one target dose level in each simulation. We simulated all three possibilities, and the simulation results are given in Table 5.2.

The results show that the group ED-design is noticeably superior to the group up-and-down design with lower total RMSEs. In comparison with the up-and-down design, the group ED-design is generally superior with lower RMSEs. Tuning the biased-coin up-and-down design to specific ED levels improves its results. Particularly when targeting ED25, the up-and-down design achieved lower RMSEs. If ED25 is the target, the group ED-design (method 1) is superior to the ED-design with lower RMSEs in all three sample sizes simulated.

5.3.3 Performance comparison when the response model is mis-specified

In applications, the dose–response relationship is unknown. In this section, we consider the case where the observed response curve is mis-specified. We investigate the performance of the group ED-design. Specifically, we consider the case where the observed dose–response relationship is logistic but the true model is probit. Thus, we generate data according to the probit model (3.8). Recall that under model (3.8), we have

$$\text{ED}\gamma = \frac{\Phi^{-1}(\gamma/100) - \alpha}{\beta},$$

Table 5.2: Simulated RMSEs under the logistic model targeting range ED10–ED40.

n		ED	Group-ED design			Up-and-down			Group UD
			M 1	M 2	M 3	Target ED10	Target ED25	Target ED40	
30	**Total**	**17.93**	**19.58**	**20.16**	**19.07**	**21.82**	**18.81**	**20.24**	**24.11**
	ED10	12.68	15.13	15.19	13.62	11.61	13.18	15.59	19.00
	ED25	8.93	8.92	10.02	9.50	11.15	8.92	9.71	11.24
	ED40	9.01	8.66	8.67	9.37	14.74	10.02	8.51	9.70
60	**Total**	**13.25**	**14.39**	**14.44**	**13.38**	**17.38**	**13.25**	**15.02**	**17.69**
	ED10	9.48	10.94	10.87	9.72	8.57	9.69	11.90	14.38
	ED25	6.52	6.33	7.15	6.49	8.98	6.09	7.11	8.34
	ED40	6.56	6.88	6.28	6.51	12.17	6.69	5.78	6.05
120	**Total**	**9.35**	**9.36**	**10.06**	**9.13**	**13.38**	**9.36**	**10.57**	**12.60**
	ED10	6.73	6.65	7.68	6.57	6.14	6.93	8.52	10.28
	ED25	4.55	4.42	4.92	4.36	6.96	4.24	4.92	5.99
	ED40	4.63	4.88	4.25	4.61	9.64	4.66	3.88	4.15

and ED25 = 102, ED50 = 114, and ED75 = 127. The dose–response curve is given by Model (3.7), and the simulation is otherwise identical to that in the last section. The results are presented in Tables 5.3 and 5.4. For ED25–ED75, we set ED50 as the target for the up-and-down design. For ED10–ED40, we target each level separately, as before.

In the next simulation, we repeat the simulation with the target dose levels changed to ED10, ED25, and ED40. In comparison with the group up-and-down design, the group ED-design clearly has the best overall performance in both ranges. The up-and-down design again has good perfor-

Table 5.3: Simulated RMSEs under probit mis-specified as logistic targeting ED range 25–75.

n		ED	Group ED-design			Group UD	Up-and-down
			M 1	M 2	M 3		
30	**Total**	**10.08**	**11.29**	**11.03**	**11.29**	**13.45**	**11.29**
	ED25	6.25	6.77	6.82	6.68	7.14	6.70
	ED50	4.86	5.15	5.64	5.66	5.74	5.03
	ED75	6.23	7.42	6.58	7.12	9.84	7.57
60	**Total**	**7.16**	**7.58**	**7.85**	**7.78**	**8.53**	**7.63**
	ED25	4.53	4.69	5.05	4.67	4.94	4.71
	ED50	3.38	3.48	3.97	3.83	3.53	3.46
	ED75	4.39	4.83	4.01	4.91	6.00	4.90
120	**Total**	**5.00**	**5.32**	**5.57**	**5.46**	**5.73**	**5.39**
	ED25	3.09	3.22	3.53	3.18	3.55	3.38
	ED50	2.38	2.53	2.78	2.69	2.34	2.43
	ED75	3.13	3.40	3.29	3.53	3.84	3.42

mance at the target ED level, but poorer performance overall. Targeting ED25 achieves the best trade-off.

The group ED-design based on the third selection method has lower total RMSEs than the other two methods. The sequential ED-design has the best performance, except when targeting ED40 with $n = 120$.

Table 5.4: Simulated RMSEs under probit mis-specified as logistic targeting ED range 10–40.

n		ED	Group-ED design			Up-and-down			Group UD
			M 1	M 2	M 3	Target ED10	Target ED25	Target ED40	
30	**Total**	**11.16**	**11.74**	**12.13**	**11.49**	**14.54**	**11.62**	**11.81**	**14.65**
	ED10	7.80	8.39	8.84	7.99	6.96	7.55	8.82	11.08
	ED25	5.59	5.78	6.11	5.62	7.84	5.92	5.87	7.24
	ED40	5.69	5.83	5.63	6.05	10.07	6.56	5.24	6.27
60	**Total**	**7.62**	**8.20**	**8.53**	**7.75**	**10.73**	**8.03**	**8.45**	**10.08**
	ED10	5.34	5.92	6.25	5.40	4.84	5.57	6.38	7.98
	ED25	3.78	3.84	4.25	3.80	5.71	3.99	4.21	4.89
	ED40	3.90	4.18	3.94	4.05	7.68	4.20	3.59	3.74
120	**Total**	**5.30**	**5.32**	**5.86**	**5.46**	**7.70**	**5.56**	**5.94**	**7.21**
	ED10	3.76	3.74	4.40	3.78	3.53	3.83	4.41	5.75
	ED25	2.59	2.67	2.89	2.69	4.14	2.79	3.02	3.53
	ED40	2.69	2.68	2.57	2.88	5.45	2.91	2.59	2.55

5.4 Concluding remarks

Clinical trials are planned experiments on human beings with high financial and human costs. It is desirable to design the experiments to speed up the trial and prevent waste of valuable resources. In practice, individuals often enter the trial sequentially in groups. Hence, it is often more practical to treat individuals by groups. Motivated by this observation, in this chapter, we propose a group sequential ED-design.

Our group ED-design has a natural extension to more complex models.

Moreover, the group ED-design can also be used for any ED levels, and meet a broad range of the demands that may arise in applications. Simulations show that in general our design is more robust, and compares favourably with existing designs.

Chapter 6

Asymptotic Properties

In dose–response experiments with sequential designs, doses administrated to experimental subjects are selected depending on previous doses and responses. Data generated from such experiments are not independent. Despite the dependence structure arising from such designs, the likelihood is identical to the one derived from independent observations. For discussions in this respect, see Chaudhuri and Mykland (1993, 1995); Stylianou and Flournoy (2002); Hu and Rosenberger (2006); Fedorov and Leonov (2013); Rosenberger and Lachin (2015).

In this chapter, we first investigate the likelihood function derived from the dependent observations generated from dose–response experiments with sequential designs. We present the derivation of the likelihood function for the up-and-down experiment.

Next we study the asymptotic properties of the maximum likelihood estimators from designs with certain properties. When independent and identically distributed observations are available, it is well known that under some regularity conditions, maximum likelihood estimators are the solutions to their score functions. They are consistent and asymptotically normal. We present some general results on the asymptotic properties of the maximum

likelihood estimators following a two-stage sequential design. We provide evidence that the maximum likelihood estimators from the two-stage sequential design exist, and have the usual asymptotic properties.

6.1 Data structure

Following Hu and Rosenberger (2006), we begin with a useful data structure which facilitates the derivation of the likelihood. Consider an experiment with n experimental subjects. Each subject is assigned to a stimulus at one of K dose levels. Suppose that subjects are assigned sequentially and respond immediately. Let $T = (T_1, \ldots, T_n)^T$ be a matrix of randomization sequence, where $T_i = (T_{i1}, \ldots, T_{iK})$ is a vector of zeroes with a 1 in the jth entry, if jth dose level is assigned to the ith subject.

Let $Y = (Y_1, \ldots, Y_n)^T$ be a matrix of responses, where $Y_i = (Y_{i1}, \ldots, Y_{iK})$ is a sequence of responses which would be observed, if every dose level is assigned to the ith subject independently. Note that only one element of Y_i is observable.

Let $t_i = (t_{i1}, \ldots, t_{iK})$ and $y_i = (y_{i1}, \ldots, y_{iK})$ be the realized dose assignments and responses from the ith subject, $i = 1, 2, \ldots, n$. The observed data for the ith subject is $z_i = \{t_i, \ \sum_{j=1}^{K} t_{ij} y_{ij}\}$. Note that Y_{ij} is observed only if $T_{ij} = 1$.

6.1.1 The likelihood

Based on the above data structure, $Y_{1j}, Y_{2j}, \ldots, Y_{nj}$, are independent and identically distributed. Denote their density function as

$$Y_{1j} \sim f(\cdot; \theta_j) \tag{6.1}$$

where θ_j is the unknown parameter of interest. For $s = 1, \ldots, n$, Y_s is independent of $Y_1, Y_2, \ldots, Y_{s-1}, T_1, \ldots, T_s$. However, T_s is dependent on $Y_1, Y_2, \ldots, Y_{s-1}, T_1, \ldots, T_{s-1}$.

Now we consider a sequentially designed dose–response experiment, in which doses assigned to subjects are selected sequentially based on previous responses and doses. Let us first consider the situation where $K = 2$ and $n = 1$. The observed data in this case are $z_1 = \{t_1,\ t_{11}y_{11} + t_{12}y_{12}\}$. We have

$$P(Z_1 = z_1) = \begin{cases} P(Z_1 = y_{11}) = f(y_{11}; \theta_1) & \text{if} \quad t_{12} = 0 \\ \\ P(Z_1 = y_{12}) = f(y_{12}; \theta_2) & \text{if} \quad t_{12} = 1 \end{cases}$$

The likelihood function is

$$L(\theta_1, \theta_2) = f(y_{11}; \theta_1)^{t_{11}} f(y_{12}; \theta_2)^{t_{12}}.$$

Next we consider the situation where $K = 2$ and $n = 2$. The observed data for these two subjects are $z_1 = \{t_1, t_{11}y_{11} + t_{12}y_{12}\}$, and $z_2 = \{t_2, t_{21}y_{21} + t_{22}y_{22}\}$. Since the dose assignment of the second subject is completely determined by the dose assignment and response of the first subject,

$P(T_2 = t_2|Z_{=}z_1) = 1$. Hence, the likelihood function is given by

$$\begin{aligned}
L(\theta_1, \theta_2) &= P(Z_1 = z_1, Z_2 = z_2) \\
&= P(Z_2 = z_2|Z_1 = z_1)P(Z_1 = z_1) \\
&= P(Z_2 = z_2|Z_1 = z_1, T_2 = t_2)P(T_2 = t_2|Z_{=}z_1)P(Z_1 = z_1) \\
&= P(Z_2 = z_2|T_2 = t_2)P(T_2 = t_2|Z_{=}z_1)P(Z_1 = z_1) \\
&= P(Z_2 = z_2|T_2 = t_2)P(Z_1 = z_1) \\
&= f(y_{21}; \theta_1)^{t_{21}} f(y_{22}; \theta_2)^{t_{22}} f(y_{11}; \theta_1)^{t_{11}} f(y_{12}; \theta_2)^{t_{12}}.
\end{aligned}$$

Following the same principle, the likelihood derived from the sequential experiment with K doses and n observations is as follows:

$$\begin{aligned}
L(\theta_1, \ldots, \theta_K) = f(y_{11}; \theta_1)^{t_{11}} &\times f(y_{12}; \theta_2)^{t_{12}} \times \ldots \times f(y_{1K}; \theta_K)^{t_{1K}} \\
&\times f(y_{21}; \theta_1)^{t_{21}} \times f(y_{22}; \theta_2)^{t_{22}} \times \ldots \times f(y_{2K}; \theta_K)^{t_{2K}} \\
&\times f(y_{31}; \theta_1)^{t_{31}} \times f(y_{32}, \theta_2)^{t_{32}} \times \ldots \times f(y_{3K}; \theta_K)^{t_{3K}} \\
&\vdots \\
&\times f(y_{n1}; \theta_1)^{t_{n1}} \times f(y_{n2}; \theta_2)^{t_{n2}} \times \ldots \times f(y_{nK}; \theta_K)^{t_{nK}} \\
&= \prod_{i=1}^{n} \prod_{j=1}^{K} \{f(y_{ij}; \theta_j)\}^{t_{ij}}.
\end{aligned}$$

Note that this likelihood is identical to the one based on independent observations.

In the up-and-down experiment, Y_{ij} is a Bernoulli random variable. It equals to 1 if the ith subject responds at the jth dose level, and 0 otherwise, $j = 1, \ldots, K$. Thus, $f(\cdot; \theta_j)$ is the probability function of the Bernoulli dis-

tribution, with the probability of success p_j being the probability of response at jth dose level. The likelihood function is therefore given by

$$\begin{aligned} L(\cdot) &= \prod_{i=1}^{n}\prod_{j=1}^{K}[p_j^{y_{ij}}(1-p_j)^{1-y_{ij}}]^{t_{ij}} \\ &= \prod_{i=1}^{n}\prod_{j=1}^{K}p_j^{t_{ij}y_{ij}}(1-p_j)^{t_{ij}(1-y_{ij})} \\ &= \prod_{j=1}^{K}p_j^{\sum_{i=1}^{n}t_{ij}y_{ij}}(1-p_j)^{\sum_{i=1}^{n}t_{ij}(1-y_{ij})}. \end{aligned}$$

Let $N_j = \sum_{i=1}^{n} T_{ij}$ be the number of subjects assigned to dose level j, and let $S_j = \sum_{i=1}^{n} Y_{ij}T_{ij}$ be the number of subjects respond at dose level j. Let n_j and s_j be the observed values of N_j and S_j. The likelihood function is therefore written as

$$L(\cdot) = \prod_{j=1}^{K} p_j^{s_j}(1-p_j)^{n_j-s_j} \tag{6.2}$$

The above likelihood function is generally applicable.

6.2 Maximum likelihood estimation

As discussed above, data generated from the sequential design are dependent. Chaudhuri and Mykland (1993) showed that despite the dependence structure in the data, the resulting likelihood function is the same to the one derived from the independent observations. Following Chaudhuri and Mykland (1993), we investigate the likelihood function from the sequential ED-design.

6.2.1 Data structure and assumptions

Following Chaudhuri and Mykland (1993), we consider a dose–response experiment with the response variable Y and explanatory variable X whose values are chosen from a finite experiment space Ω. Let the response space, the set of all possible outcomes of the experiment, be $\mathcal{R}$. Denote the conditional distribution of Y given $X = x$ as $f(y|\theta, x)$. Let Θ be the parameter space. Here $\theta \in \Theta$ is the unknown parameter, and f is a known distribution function. In addition, we assume $f(y|\theta, x)$ is smooth and regular so that $\log f(y|\theta, x)$ is differentiable in θ, and the Fisher information matrix, denoted as $\mathbb{I}(\theta; x)$, exists finitely. The Fisher information matrix $\mathbb{I}(\theta; x)$ is

$$\int_{\mathcal{R}} [\nabla \log\{f(y|\theta, x)\}][\nabla \log\{f(y|\theta, x)\}]^T \, \mu(dy),$$

where ∇ is the gradient operator, and μ is the usual counting measure.

Recall from Chapter 3, the sequential ED-design consists of two stages. Assume that the total number of trials n is predetermined prior to the experiment. Suppose that n_1 trials are carried out in the first stage. The remaining $(n - n_1)$ trials are carried out in the second stage. Compute the maximum likelihood estimator $\hat{\theta}_{n_1}$ of the model parameter θ based on the observed data $(y_1, x_1), \ldots, (y_{n_1}, x_{n_1})$ from the first n_1 trials. In the second stage, suppose ξ_j, $j = 1, 2, 3$, are the target ED levels. Each ED level is a function of the model parameter θ, i.e., $\xi_j = g(\theta)$. Let $\hat{\theta}_{i-1}$ be the maximum likelihood estimator of θ based on $(y_1, x_1), \ldots, (y_{i-1}, x_{i-1})$, $n_1 + 1 \leq i \leq n$. Let $\hat{\xi}_j = g(\hat{\theta}_{i-1})$, via delta-method, the asymptotic variance of $\hat{\xi}_j$ can be

approximated by

$$\bigtriangledown g(\hat{\theta}_{i-1})^T \mathbb{I}_{i-1}^{-1}(\hat{\theta}_{i-1}; x) \bigtriangledown g(\hat{\theta}_{i-1})$$

where $\bigtriangledown g(\hat{\theta}_{i-1})$ is the gradient of $g(\hat{\theta}_{i-1})$ and $\mathbb{I}_{i-1}^{-1}(\hat{\theta}_{i-1}; x)$ is the inverse of the Fisher information matrix after $(i-1)$ trials and the potential ith trial to be run at dose level x. Hence, for each i, $n_1 + 1 \leq i \leq n$, the ith design point is determined by

$$x_i = \arg\min_x \sum_{j=1}^{3} \text{var}(\hat{\xi}_j),\ j = 1, 2, 3.$$

From the sequential scheme discussed above, the ith design point X_i is determined based on the past observations $(Y_1, X_1), \ldots, (Y_{i-1}, X_{i-1})$. Thus, the observations generated from this sequential design are no longer independent. The standard asymptotic properties of the maximum likelihood estimates may not be applicable. However, the dependence of Y_i on $(Y_1, X_1), \ldots, (Y_{i-1}, X_{i-1})$ is only through X_i. As a consequent, the likelihood constructed from $(Y_1, X_1), \ldots, (Y_i, X_i)$ remains in the product form $\prod_{r=1}^{i} f(Y_r|\theta, X_r)$, despite the dependence structure of the data arising from the sequential design (See Chaudhuri and Mykland (1993)). Hence, the likelihood conducted from the sequential ED-design is identical to the one arising from the independent and identically distributed observations. As a result, the resulting MLE of θ can be computed as usual. We denote the

MLE of θ based on $(Y_1, X_1), \ldots, (Y_n, X_n)$ as

$$\hat{\theta}_n = \arg\max_{\theta\in\Theta} \prod_{r=1}^{n} f(Y_r|\theta, X_r)$$

In the next section, we investigate the asymptotic properties (i.e., consistency and asymptotically normality) of $\hat{\theta}_n$ derived from the sequential ED-design. Following Chaudhuri and Mykland (1995), we identify some regularity conditions which will guarantee the desirable asymptotic behaviours of the maximum likelihood estimates.

6.3 Asymptotic properties of the maximum likelihood estimate

In this section, we investigate the asymptotic properties of $\hat{\theta}_n$ from the sequential ED-design. Following Chaudhuri and Mykland (1993, 1995), we summarize the following general conditions on the response model $f(y;\theta,x)$.

- Condition 1: The response space $\mathcal{R}$ does not depend on θ and x. For every $y \in \mathcal{R}$ and $x \in \Omega$, $\log f(y;\theta,x)$ is thrice continuously differentiable in θ at any $\theta \in \Theta$.

- Condition 2: Let $\nabla \log f(y;\theta,x) = G(y;\theta,x)$ be the gradient vector of $\log f(y|\theta,x)$ with respective to θ. Then $G(y;\theta,x)$ should satisfy

$$\int_{\mathcal{R}} G(y;\theta,x) f(y;\theta,x)\, \mu(dy) = 0,$$

and

$$\sup_{x\in\Omega}\int_{\mathcal{R}} |G(y;\theta,x)|^{2+t} f(y;\theta,x)\,\mu(dy) < \infty$$

for some $t > 0$. Here $|\cdot|$ is the usual Euclidean norm.

- Condition 3: Let $H(y;\theta,x)$ be the Hessian matrix of $\log f(y;\theta,x)$ as the second order partial derivatives of $\log f(y;\theta,x)$ with respective to θ. Then

$$\begin{aligned} & \int_{\mathcal{R}} H(y;\theta,x) f(y;\theta,x)\,\mu(dy) \\ = & -\int_{\mathcal{R}} \big(G(y;\theta,x)\big)\big(G(y;\theta,x)\big)^T f(y;\theta,x)\,\mu(dy) \\ = & -\mathbb{I}(\theta;x), \end{aligned}$$

and

$$\sup_{x\in\Omega}\int_{\mathcal{R}} |H(y;\theta,x))|^2 f(y;\theta,x)\,\mu(dy) < \infty.$$

- Condition 4: For every $\theta \in \Theta$, there is an open neighbourhood $N(\theta) \subset \Theta$, and a nonnegative random variable $K(y;\theta,x)$ which satisfies

$$\sup_{x\in\Omega}\int_{\mathcal{R}} K(y;\theta,x) f(y;\theta,x)\,\mu(dy) < \infty.$$

  Each of the third order partial derivatives of $\log f(y;\theta',x)$ with respective to θ' is dominated by $K(y;\theta,x)$ for all $\theta' \in N(\theta)$.

In addition, Chaudhuri and Mykland (1995), presented the following asymptotic results for the maximum likelihood estimate in a general adaptive sequential design setting. We summarize their findings in the following.

Theorem 1: Assume that Condition 1 through Condition 4 hold, and $(Y_1, X_1), \ldots, (Y_n, X_n)$ are observations generated from an adaptive sequential design. Denote λ_n as the smallest eigenvalue of

$$\frac{1}{n}\sum_{r=1}^{n} \mathbb{I}(\theta; X_r).$$

Suppose the design is that for some positive constant $\alpha < 1/4$, $n^{\alpha}\lambda_n$ remains bounded away from zero in probability as $n \to \infty$ for any $\theta \in \Theta$. Then the maximum likelihood estimator $\hat{\theta}_n$ of θ exists and is weakly consistent for θ.

Theorem 2: Assume that Condition 1 through Condition 4 hold, and $(Y_1, X_1), \ldots, (Y_n, X_n)$ are observations generated from an adaptive sequential design. Suppose

$$\frac{1}{n}\sum_{r=1}^{n} \mathbb{I}(\theta; X_r) \xrightarrow{p} A \text{ as } n \to \infty,$$

where A is a nonrandom positive definite matrix. Then there exists a maximum likelihood estimator $\hat{\theta}_n$ of θ such that the distribution of $\sqrt{n}(\hat{\theta}_n - \theta)$ converges weakly to a multivariate normal distribution with mean zero and variance-covariance matrix A^{-1} as $n \to \infty$.

The proofs of Theorems 1 and 2 were given in Chaudhuri and Mykland (1993, 1995). Their proofs utilize some standard martingale techniques introduced in Lai and Wei (1982) for an adaptive sequential design. We present and summarize their proofs as follows.

Proof of Theorem 1. Let $\{\mathcal{F}_{ni},\ 1 \le i \le n\}$ be an increasing sequence of σ-fields generated by $Y_1, \ldots, Y_i$, that is, $\mathcal{F}_{ni} = \sigma(Y_1, \ldots, Y_i)$. It follows from Condition 2 that

$$\Big\{ \sum_{r=1}^{i} G(Y_r; \theta, X_r); \mathcal{F}_{ni},\ 1 \le i \le n \Big\}$$

is a square integrable martingale. Then,

$$E\big| \sum_{r=1}^{n} G(Y_r; \theta, X_r)\big|^2 = E\Big(\sum_{r=1}^{n} \big|G(Y_r; \theta, X_r)\big|^2 \Big) = O_p(n)$$

as $n \to \infty$. Hence,

$$\sum_{r=1}^{n} G(Y_r; \theta, X_r) = O_p(n^{1/2}). \tag{6.3}$$

Next, consider the sequence

$$\Big\{ \sum_{r=1}^{i} \big[H(Y_r; \theta, X_r) + \mathbb{I}(\theta; X_r)\big]; \mathcal{F}_{ni},\ 1 \le i \le n \Big\}.$$

Condition 3 implies that it is also a square integrable martingale. By a similar argument,

$$\sum_{r=1}^{n} \big[H(Y_r; \theta, X_r) + \mathbb{I}(\theta; X_r)\big] = O_p(n^{1/2}). \tag{6.4}$$

For any $\delta > 0$, let $N_\delta(\theta)$ be the neighbourhood centred at θ with radius δ. Let $\delta_n = n^{-\beta}$ for some $\alpha < \beta < (1/2) - \alpha$. Then, the smallest eigenvalue of

the Hessian matrix of

$$n^{\alpha-1}\sum_{r=1}^{n}\log f(Y_r|\theta', X_r)$$

is negative and bounded away from zero in probability as $n \to \infty$ for all $\theta' \in N_\delta(\theta)$. This implies that

$$\lim_{n\to\infty} P\Big(\sum_{r=1}^{n}\log\{f(Y_r;\theta', X_r)\} \text{ is concave for } \theta' \in N_\delta(\theta)\Big) = 1. \tag{6.5}$$

Next consider the third order Taylor expansion of the log-likelihood around θ,

$$\begin{aligned}\sum_{r=1}^{n}\log f(Y_r;\theta', X_r) = \sum_{r=1}^{n}\log\{f(Y_r;\theta, X_r)\} + (\theta'-\theta)^T\Big[\sum_{r=1}^{n}G(Y_r;\theta, X_r)\Big] \\ + (\theta'-\theta)^T\Big[\sum_{r=1}^{n}H(Y_r;\theta, X_r)\Big](\theta'-\theta) + R_n(\theta', \theta).\end{aligned}$$

Under Condition 4, the remainder term in the above equation satisfies

$$\sup_{\theta':|\theta'-\theta|\le\delta_n}|R_n(\theta', \theta)| = O_p(n\delta_n^3). \tag{6.6}$$

Now (6.5) and (6.6) imply that the probability of the event that the likelihood equation has a root within the neighbourhood $N_\delta(\theta)$ will tend to 1 as $n \to \infty$. Because the size of the neighbourhood can be made arbitrarily small, this further implies the consistency of the maximum likelihood estimator. □

Proof of Theorem 2. Using the result in Theorem 1, let $\hat{\theta}_n$ be a weakly consistent estimator for θ. Consider a first order Taylor expansion around θ,

$$\begin{aligned} n^{-1}\sum_{r=1}^{n} G(Y_r;\hat{\theta}_n,X_r) &= n^{-1}\sum_{r=1}^{n} G(Y_r;\theta,X_r) \\ &\quad + \Big[n^{-1}\sum_{r=1}^{n} H(Y_r;\theta,X_r) + \Delta_n(\theta)\Big]^T(\hat{\theta}-\theta) \end{aligned}$$

where $\Delta_n(\theta)$ is a random matrix of size $o_p(1)$ under Condition 4 and weak consistency of $\hat{\theta}_n$. Following Conditions 2 and 3, and the design condition in Theorem 2, by the martingale central limit theorem (Hall and Heyde, 2014),

$$n^{-1/2}\sum_{r=1}^{n} G(Y_r,\theta,X_r)$$

converges weakly to a multivariate normal distribution with mean zero and variance-covariance matrix A. □

Note that Conditions 1 through 4 are standard Cramer-type conditions that hold for a large class of models. The response models, $f(y;\theta,x)$, (e.g. standard logistic regression model) considered in this thesis for dose–response experiments are smooth and regular. These Cramer-type conditions 1 through 4 are satisfied. In addition, under the sequential ED-design, the design points are sequentially selected in the same fashion as in Chaudhuri and Mykland (1995). Hence, the sequence of design points satisfy the conditions assumed in Theorem 1. Other than the eigenvalue condition, all other conditions are satisfied. As a result, we have nearly proved that the maximum likelihood estimator derived from our sequential ED-design is

consistent and asymptotically normal.

6.4 Concluding remarks

Following Chaudhuri and Mykland (1995), we went through the derivation of the likelihood function based on the dependent observations generated from the proposed design. We show that it is identical to the one with independent observations. We identify some regularity conditions under which the resulting maximum likelihood estimators are consistent and asymptotically normal.

Chapter 7

Contributions and Future Research

Dose–response experiments are routinely conducted in Phases I and II clinical trials to study the relationship between the doses of a stimulus and the responses of experimental subjects. Estimating the underlying dose–response relationship is the primary goal of dose–response experiments (Dette et al., 2005; Dragalin et al., 2008a,b).

Accurately charactering the dose–response relationship is a key step in the clinical development process of pharmaceutical drugs. Poor understanding of the underlying dose–response relationship may lead to select wrong target doses to be used in large scale confirmatory clinical trials, which may cause serious ethical and financial consequences. Selecting too high a dose may cause potential toxicity to experimental subjects, and choosing too low a dose may fail to establish adequate efficacy, and fail to obtain the regulatory approval of the drug. See Bretz et al. (2008), Bretz et al. (2010), and Dette et al. (2008).

Statistical design theory is therefore developed to most effectively collect the needed information while minimizing potential side effects. Despite its

long history, design theory for binary dose–response experiments remains an active research area.

7.1 Contributions

The first contribution of this dissertation is the introduction of a new optimality criterion. Traditionally, when a parametric dose–response model is assumed, we often search for designs which enable us to most accurately estimate the model parameters. In applications as we observed, the ultimate goal of the investigation is to accurately determine various ED levels. In this dissertation, we take a new approach in designing a binary dose–response experiment. We consider a situation where the dose–response relationship over a range of ED levels is of interest.

We proposed a new design criterion which directly and simultaneously targets several ED levels. We believe such a relationship can be well characterized after several tactically chosen ED levels are accurately estimated. Based on these considerations, we propose a two-stage sequential design. The proposed sequential design is easy to implement in general and leads to more efficient estimation of ED levels. Because our design is sequential and aims to efficiently estimate several chosen ED levels, we call it two-stage sequential ED-design or simply ED-design.

We conducted extensive computer simulations to demonstrate that the proposed sequential ED-design indeed improves the efficiency of the experiment by changing the optimality target from estimating model parameters to ED levels of interest compared with many existing designs. First, we

confirm that our ED-design is indeed more efficient for estimating several targeted ED levels based on the total root mean square error (RMSE) or the individual RMSEs. The D-optimal design and its sequential version do not have this flexibility, and the up-and-down design cannot target more than one ED level. These results provide strong support for the proposed design. Second, because in practice the true dose–response relation never fully conforms to the model, optimal designs do not perform at their peak levels in general. We therefore use simulation studies to evaluate the effect of model misspecification. The ED–design still has the best performance in terms of the RMSE. We also provide some simulation evidence for the limiting ED-design when the sample size n goes to infinity. It appears that as a distribution over the dose range, the design has a limit with two support points.

Another apparent approach to reduce the risk of model misspecification is to apply a more flexible and hence more complex dose-response model. The choice of such a model reflects a trade-off between the model flexibility and inference efficiency. Commonly used logistic or probit models are simple and have good mathematical and statistical properties. They are satisfactory in many applications. Nevertheless, their model assumptions impose some severe restriction on the dose-response relationship. Hence, a mildly more complex model can be useful to lower the risk of model misspecification if it does not complicate the issues related to optimal designs and data analyses as well as maintaining good efficiency in estimating the ED levels.

In this dissertation, we introduced the three–parameter logistic model. Some details of the ED-design under the three–parameter logistic regres-

sion model are given. We investigate the effectiveness of the sequential ED-design, the D-optimal design, and the up-and-down design under this model, and develop an effective model fitting strategy. We develop an easy way to implement an iterative numerical algorithm with guaranteed convergence for computing the maximum likelihood estimation of the model parameters. The sequential ED-design can be implemented after some laborious but simple mathematical derivations. Although we have yet to generate any theory on its D-optimal design, a numerical procedure via the well-developed vertex direction method (VDM) works well. Simulations show that the combination of the proposed model and the data analysis strategy performs well. When the logistic model is correct, using the more complex model suffers hardly any efficiency loss. When the three-parameter model holds but the logistic model is violated, the new approach can be more efficient.

In addition to these achievements, we discuss the use of the ED-design when experimental subjects become available in groups. We introduce the group sequential ED–design, and show how to construct this design.

7.2 Future Research

In this dissertation, the property of the ED-design is studied numerically and analytically. The theoretical aspect of the proposed design has not been fully explored. We will focus on the theoretical aspect such as the asymptotic properties of the ED-design in future research. For example, simulation studies show that for sample size $n = 1000$, the doses generated from the ED-design cluster around two ED levels of the underlying dose–

response curve. In the future, we will investigate if doses generated from the ED-design converge to these two specific ED levels as n tends to infinity.

In this dissertation, we apply the vertex direction method (VDM) to numerically compute the D-optimal designs under the three-parameter logistic and probit models. The resulting D-optimal designs are uniform distributions on three support points. Under these two models, design points and design weights change with different λ values. We do not have a comparable theory for the D-optimal design under new models but point out that a vertex direction method remains effective for numerical solutions. In future research, we plan to generate a theory on the D-optimal design under more complicated models.

The proposed two-stage ED-design is very easy to implement in medical research. To utilize this design, the responses of experimental subjects need to be observed quickly, such as in anesthesia research, a subject's response to anesthetic drugs, i.e., being anesthetized or not, is observed immediately. However, in most clinical practice, especially in cancer trials, a subject's response is not immediately obtained. The ED-design may delay the assignment of the subsequent subjects and lead to long trial duration. Thus, it is interesting to modify our design to incorporate delayed responses.

We may also generalize our proposed design in many ways. In this dissertation, we mainly focus on studying the ED-design under the logistic response model. As a starting point, we have investigated the performance of our proposed design under the three–parameter logistic model. We believe that the same results can be generalized to other popular response models, such as the double exponential model.

We also believe that the proposed design can be extended to estimate other sets of ED levels, including sets of two or more ED levels of the underlying dose-response curve, for example, estimating ED25 and ED75 simultaneously. More simulations will be carried out to confirm the above claims.

More studies will be conducted to modify and extend our proposed design in the future. Our group ED-design has a natural extension to more complex models and can also be used for any ED levels, and satisfy a broad range of demands that may arise in applications. We feel that our proposed design reveals some interesting directions and provides great potential for further research.

Bibliography

Abdelbasit, K. M. and Plackett, R. (1983). Experimental design for binary data. *Journal of the American Statistical Association*, 78(381):90–98.

Albert, A. and Anderson, J. (1984). On the existence of maximum likelihood estimates in logistic regression models. *Biometrika*, 71(1):1–10.

Anderson, T. W., McCarthy, P. J., and Tukey, J. W. (1946). Staircase methods of sensitivity testing. Technical report, DTIC Document.

Athreya, K. B. and Ney, P. E. (2012). *Branching processes*, volume 196. Springer Science & Business Media.

Békésy, G. V. (1947). A new audiometer. *Acta Oto-Laryngologica*, 35(5-6):411–422.

Bretz, F., Dette, H., and Pinheiro, J. C. (2010). Practical considerations for optimal designs in clinical dose finding studies. *Statistics in medicine*, 29(7-8):731–742.

Bretz, F., Hsu, J., Pinheiro, J., and Liu, Y. (2008). Dose finding–a challenge in statistics. *Biometrical Journal*, 50(4):480–504.

Brown, C. C. (1982). On a goodness of fit test for the logistic model based

on score statistics. *Communications in Statistics-Theory and Methods*, 11(10):1087–1105.

Brownlee, K., Hodges Jr, J., and Rosenblatt, M. (1953). The up-and-down method with small samples. *Journal of the American Statistical Association*, 48(262):262–277.

Burkholder, D. L. (1973). Distribution function inequalities for martingales. *The Annals of Probability*, pages 19–42.

Chaudhuri, P. and Mykland, P. A. (1993). Nonlinear experiments: Optimal design and inference based on likelihood. *Journal of the American Statistical Association*, 88(422):538–546.

Chaudhuri, P. and Mykland, P. A. (1995). On efficient designing of nonlinear experiments. *Statistica Sinica*, pages 421–440.

Choi, S. (1971). An investigation of Wetherill's method of estimation for the up-and-down experiment. *Biometrics*, pages 961–970.

Choi, S. C. (1990). Interval estimation of the LD50 based on an up-and-down experiment. *Biometrics*, pages 485–492.

Derman, C. (1957). Non-parametric up-and-down experimentation. *The Annals of Mathematical Statistics*, 28(3):795–798.

Dette, H., Bretz, F., Pepelyshev, A., and Pinheiro, J. (2008). Optimal designs for dose-finding studies. *Journal of the American Statistical Association*, 103(483):1225–1237.

Dette, H., Neumeyer, N., and Pilz, K. F. (2005). A note on nonparametric estimation of the effective dose in quantal bioassay. *Journal of the American Statistical Association*, 100(470):503–510.

Dixon, W. J. and Mood, A. M. (1948). A method for obtaining and analyzing sensitivity data. *Journal of the American Statistical Association*, 43(241):109–126.

Dragalin, V., Fedorov, V., and Wu, Y. (2008a). Adaptive designs for selecting drug combinations based on efficacy–toxicity response. *Journal of Statistical Planning and Inference*, 138(2):352–373.

Dragalin, V., Fedorov, V. V., and Wu, Y. (2008b). Two-stage design for dose-finding that accounts for both efficacy and safety. *Statistics in medicine*, 27(25):5156–5176.

Dror, H. A. and Steinberg, D. M. (2008). Sequential experimental designs for generalized linear models. *Journal of the American Statistical Association*, 103(481):288–298.

Durham, S. D. and Flournoy, N. (1994). Random walks for quantile estimation. In *Statistical decision theory and related topics V*, pages 467–476. Springer.

Durham, S. D. and Flournoy, N. (1995). Up-and-down designs I: Stationary treatment distributions. *Lecture Notes-Monograph Series*, pages 139–157.

Durham, S. D., Flournoy, N., and Rosenberger, W. F. (1997). A random walk rule for phase I clinical trials. *Biometrics*, pages 745–760.

El-Saidi, M. A. (1993). A power transformation for generalized logistic response function with application to quantal bioassay. *Biometrical journal*, 35(6):715–726.

Fedorov, V. V. (1972). *Theory of optimal experiments*. Elsevier.

Fedorov, V. V. and Leonov, S. L. (2013). *Optimal design for nonlinear response models*. CRC Press.

Flournoy, N. (1993). A clinical experiment in bone marrow transplantation: Estimating a percentage point of a quantal response curve. In *case studies in Bayesian Statistics*, pages 324–336. Springer.

Ford, I., Titterington, D., and Wu, C. (1985). Inference and sequential design. *Biometrika*, 72(3):545–551.

Gezmu, M. and Flournoy, N. (2006). Group up-and-down designs for dose-finding. *Journal of statistical planning and inference*, 136(6):1749–1764.

Hall, P. and Heyde, C. C. (2014). *Martingale limit theory and its application*. Academic press.

Hu, F. and Rosenberger, W. F. (2006). *The theory of response-adaptive randomization in clinical trials*, volume 525. John Wiley & Sons.

Joseph, V. R. (2004). Efficient Robbins-Monro procedure for binary data. *Biometrika*, pages 461–470.

Lai, T. L. and Robbins, H. (1979). Adaptive design and stochastic approximation. *The annals of Statistics*, pages 1196–1221.

Lai, T. L. and Wei, C. Z. (1982). Least squares estimates in stochastic regression models with applications to identification and control of dynamic systems. *The Annals of Statistics*, pages 154–166.

Langlie, H. (1963). A reliability test method for "one-shot" items. Technical report, DTIC Document.

Li, P. and Wiens, D. P. (2011). Robustness of design in dose–response studies. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 73(2):215–238.

Mathew, T. and Sinha, B. K. (2001). Optimal designs for binary data under logistic regression. *Journal of Statistical Planning and Inference*, 93(1):295–307.

Minkin, S. (1987). Optimal designs for binary data. *Journal of the American Statistical Association*, 82(400):1098–1103.

Montgomery, D. C. (2008). *Design and analysis of experiments*. John Wiley & Sons.

Neyer, B. T. (1991). Sensitivity testing and analysis. In *16th International Pyrotechnics Seminar*.

Neyer, B. T. (1994). A D-optimality-based sensitivity test. *Technometrics*, 36(1):61–70.

Pace, N. L., Stylianou, M. P., and Warltier, D. C. (2007). Advances in and limitations of up-and-down methodology: A précis of clinical use, study

design, and dose estimation in anesthesia research. *The Journal of the American Society of Anesthesiologists*, 107(1):144–152.

Robbins, H. and Monro, S. (1951). A stochastic approximation method. *The annals of mathematical statistics*, pages 400–407.

Rosenberger, W. F. (1996). New directions in adaptive designs. *Statistical Science*, pages 137–149.

Rosenberger, W. F. and Grill, S. E. (1997). A sequential design for psychophysical experiments: an application to estimating timing of sensory events. *Statistics in Medicine*, 16(19):2245–2260.

Rosenberger, W. F. and Lachin, J. M. (2015). *Randomization in clinical trials: theory and practice*. John Wiley & Sons.

Santner, T. J. and Duffy, D. E. (1986). A note on A. Albert and JA Anderson's conditions for the existence of maximum likelihood estimates in logistic regression models. *Biometrika*, pages 755–758.

Silvapulle, M. J. (1981). On the existence of maximum likelihood estimators for the binomial response models. *Journal of the Royal Statistical Society. Series B (Methodological)*, pages 310–313.

Sitter, R. and Wu, C. (1993). Optimal designs for binary response experiments: Fieller, D, and A criteria. *Scandinavian Journal of Statistics*, pages 329–341.

Sitter, R. R. and Fainaru, I. (1997). Optimal designs for the logit and probit models for binary data. *Canadian Journal of Statistics*, 25(2):175–190.

Sitter, R. R. and Forbes, B. (1997). Optimal two-stage designs for binary response experiments. *Statistica Sinica*, pages 941–955.

Stylianou, M. and Flournoy, N. (2002). Dose finding using the biased coin Up-and-Down design and isotonic regression. *Biometrics*, 58(1):171–177.

Stylianou, M. and Follmann, D. A. (2004). The accelerated biased coin up-and-down design in phase I trials. *Journal of biopharmaceutical statistics*, 14(1):249–260.

Ting, N. (2006). *Dose finding in drug development.* Springer Science & Business Media.

Tsutakawa, R. (1967a). Asymptotic properties of the block up-and-down method in bio-assay. *The Annals of Mathematical Statistics*, 38(6):1822–1828.

Tsutakawa, R. (1967b). Random walk design in bio-assay. *Journal of the American Statistical Association*, 62(319):842–856.

Wang, L., Liu, Y., Wu, W., and Pu, X. (2013). Sequential LND sensitivity test for binary response data. *Journal of Applied Statistics*, 40(11):2372–2384.

Wang, L., Pu, X., Li, Y., and Liu, Y. (2015). Sequential two-stage D-optimality sensitivity test for binary response data. *Communications in Statistics-Simulation and Computation*, 44(7):1833–1849.

Wetherill, G. (1963). Sequential estimation of quantal response curves. *Journal of the Royal Statistical Society. Series B (Methodological)*, pages 1–48.

Wu, C. (1978). Some algorithmic aspects of the theory of optimal designs. *The Annals of Statistics*, pages 1286–1301.

Wu, C. (1985a). Asymptotic inference from sequential design in a nonlinear situation. *Biometrika*, pages 553–558.

Wu, C. (1985b). Efficient sequential designs with binary data. *Journal of the American Statistical Association*, 80(392):974–984.

Wu, C. and Tian, Y. (2013). Three-phase sequential design for sensitivity experiments. In *Proc. Spring Res. Conf., Enabling Inter. Statist. Eng.*

Wynn, H. P. (1972). Results in the theory and construction of D-optimum experimental designs. *Journal of the Royal Statistical Society. Series B (Methodological)*, pages 133–147.

Yu, X., Chen, J., and Brant, R. (2016). Sequential design for binary dose–response experiments. *Journal of Statistical Planning and Inference*, 177:64–73.