Bayesian Model Comparison for Dose Response Studies

A thesis submitted to the
Manipal Academy of Higher Education
For the degree of
Master of Science in Biostatistics (M.Sc.)

By,
Kodipaka Chathurya Goud
(202402004)

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CERTIFICATE

This is to certify that **Kodipaka Chathurya Goud (202402004)**, a student of M.Sc. Biostatistics from the Department of Data Science, MAHE, Manipal has completed her fourth semester project under my guidance from January to May 2022. The project work entitled **" Bayesian Model Comparison for Dose Response Studies"** embodies the novel work done by her.

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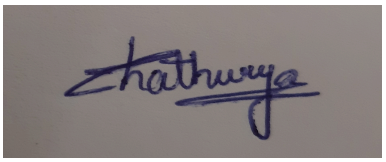
DECLARATION

I hereby declare that the project work entitled **"Bayesian Model Selection and comparison for Dose Response Studies"** submitted to the Department of Data Science, PSPH, MAHE, Manipal, is a record of the work done by me under the guidance of Arunangshu Biswas. This thesis is submitted in partial fulfillment of the requirements for the award of degree of Master of Science in Biostatistics.

The results embodied in this thesis have not been submitted to any other institute or University for the award of any degree/certificate.



Date: 06-June-2022

Place: Bangalore

(Kodipaka Chathurya Goud)

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Kodipaka Chathurya Goud (202402004)

Contents

Abstract

One of the important aspects of a successful drug development is finding one or more appropriate doses in early phase of the development cycle. It is well known in literature [12] that historically drugs were initially marketed at higher doses. Further [5], 20% of approved doses required a post-approval change. Clearly this has a lot of impact on the financial resources of the company.

Traditionally dose response studies were done using pairwise comparisons, between two or more doses, which suffered from serious drawbacks. In the modern paradigm of dose design, statistician propose a (parametric) model based approach, where the problem is to select the best fitting model (according to a pre-specified criteria) among a class of competing models. This analysis has two components - Multiple Comparisons (between doses) and Model building. In a pioneering study by Bretz, Pinheiro and Branson (2005) [1], the two components were merged and the method was called the MCP-Mod procedure. This method is very popular in pharmaceutical research and has obtained the qualification as an efficient statistical methodology by the FDA [14]. Note however that this is a frequentist method where no prior weights are associated to the competing models. In this thesis we first disseminate the existing literature [6] on Bayesian version of MCPMod and propose tools on how this method can be tuned for some specific studies.

Key words: Dose response studies, contrast test, MCPMod, Multiple testing, Bayesian borrowing.

Chapter 1

Introduction

1.1 Preamble

Historically, often the drug initially marketed was subsequently recognized as an excessive dose, at times with unfavorable consequences. The circumstances have been enhanced by the attempts to determine the "minimum dose" with a perceptible effect or a "maximum dose" beyond which no more benefits are seen. Phase II studies are divided into two main categories 2a and 2b: Proof of concept studies and Dose Finding Studies.

The primary purpose of Phase II is to assess efficacy and safety in a greater group of people. Determining the right dose for future clinical trials is one of the most vital components of drug development. Deciding on an over-dose can result in unacceptable toxicity, while too low can increase the probability that the compound affords insufficient proof of effectiveness.

In dose-response studies, choosing the dose-response model and design parameters such as cohort size, frequency of dosing, dosage range, number of doses to be tested, dose allocation and dose spacing is vital.

1.2 Objective

The objective of this project is to study the theory of Multiple Comparison procedure and Modeling (MCP-Mod) along with the Bayesian extension to it, called the Bayesian MCP-Mod. We perform the analyses in `R` on a simulated data.

1.3 Research Methodology

We consider a scenario in which there are K active dose groups and a placebo group, for a total K+1 dose groups. The dose groups are $d_0, d_1, d_2...d_k$, placebo denotes d_0. The response variable Y is normally distributed, for each dose group i, n_i patients are observed. Mixture priors up to four components are considered for the placebo dose group and active groups non-informative/vaguely informative priors are taken. For cohort size n_i, we generate the sample using the prior mean.

In the above setting we obtain the optimal allocation from which we obtain the optimal contrast, both, satisfying some objective criterion.

The Bayesian extension is performed by assuming a mixture prior on the placebo dose response and non-informative prior on the active doses. In the same spirit as above, we obtain the modified optimal allocation from which the optimal contrast is thereby obtained. Finally, a test of significance is performed using the posterior distribution of the dose response and the optimal contrast.

1.4 Chapter Outline

In chapter 2 we discuss the details of a drug development cycle of a study drug. We start with the pre-clinical phase and highlight the significant steps involved in the successful completion of each phase. Although the focus of the thesis is on Dose Response studies, which is primarily done in the phase 2b of a clinical trial, proper understanding of the other phases will enable a better appreciation of the methods used in this thesis. We also discuss the important terminologies used in our context for example dose, regimen and response.

In chapter 3 we discuss the problem of choosing, first, the appropriate dose response model; and second, the appropriate dose for phase 3. We also define other factors that informs on this choice of the dose, for example, the MED (Minimum Effective Dose), MTD(Maximum Tolerated Dose) and the therapeutic window. We discuss the tool, named MCP-Mod (Multiple Comparison Procedure and Modeling), proposed by Bretz, Pinheiro and Branson [1] that enables the comparison of competing dose response models in a class of dose response models. Given other design parameters (that includes the MED) the method also proposes the future dose to be studied extensively in Phase 3 (although we do not discuss it as much). We derive the mathematical details underlying this procedure which involves, among others, the choice of the optimal contrast both in the case of a balanced and the unbalanced dose design. We also discuss the theory of D-optimal designs since D-optimality if the criterion for optimal allocation for a given

dose design.

In chapter 4 we discuss the BMCP-Mod (Bayesian MCP-Mod) procedure which is the Bayesian extension to the MCP-Mod procedure when prior information is available. Here we incorporate prior distribution of the placebo dose response and active doses to obtain the posterior dose response at one or more specified dose levels. We derive the mathematical expression for the posterior mean response at the specified dose and the decision criteria based on this posterior distribution. We also discuss the mathematical details underlying the significance test of the BMCP-Mod procedure.

Chapter 5 we provide some simulations along with some conclusion and directions for future research.

Chapter 2

Drug Development

The process of bringing a new drug to market is referred to as drug development. Initially the compound is identified in the lab and it undergoes various stages of a clinical study. After completing all phases and receiving regulatory permission from medical organizations such as the Food and Medicine Administration (FDA) in the United States, the study drug can be made available to patients. Clinical trials are conducted by government health agencies, independent researchers, researchers affiliated with a hospital or pharmaceutical companies like GlaxoSmithKline (GSK).

A Clinical trial is a well planned scientific study conducted on human to evaluate the safety and efficacy of a drug. These trials adhere to strict scientific guidelines to protect participants lives and to deliver trustworthy clinical trial outcomes.

Clinical trials are one of the last stages in the long process of therapeutic research and development. This process begins in the laboratory, where scientists develop and test new compounds, and concludes with the marketing of a treatment that saves countless lives.

2.1 Phases of Clinical Trial

2.1.1 Pre-Clinical

Investigators perform a pre-clinical trial utilising human cells or animals before conducting a clinical trial. These trials include both in vitro (test tube or laboratory) and animal population trials (in Vivo). Preclinical research is typically small. These studies, however, include specific information about dose and toxicity levels. The primary goal of a pre-clinical trial is to select a safe starting dose for a first-time-in-human (FTiH) trial and to analyze a compound's safety profile.

To acquire preliminary safety, Absorption, Distribution, Metabolism, and Excretion (ADME) profile, toxicity, pharmacokinetic (PK), and pharmacodynamic (PD) parameters of the drug PD, different doses of the study drug were given to different animal populations. Later, this information will be used by the pharmaceuticals to decide if it is safe to go ahead with trials in humans.

2.1.2 Phase I

Phase I studies are the "First-Time-in-Human" trials. These studies are conducted to determine the maximum dose of a drug that may be safely

administered without producing adverse affects. Although the drug has been studied in lab and animal research, it is impossible to predict the adverse effects in humans. These studies also aid in determining the optimal method for providing the new treatment. These studies take place for several months and are done on small numbers possibly 20-100 subjects of healthy volunteers. Pharmacokinetics (drug movement in the body) and Pharmacodynamics (how the body responds) studies are also part of the phase I study. Phase I study is divided into various parts:

1. **Single Ascending Dose [SAD]:** Single ascending dose studies involve a small number of participants who are given a single dose of the drug and then observed for a fixed period of time. If there are no serious side effects and the pharmacokinetic data are broadly in line with anticipated safe values, the dose is increased, either in a new group (same group) of healthy volunteers or in a group of healthy volunteers who got a higher (or lower if the effects are adverse) dose. This is done until the drug achieves its maximum tolerated dosage (MTD). Testing after MTD is not recommended.

2. **Multiple Ascending Dose [MAD)]:** Multiple Ascending dose study come before the Single Ascending dose study. "Multiple" indicates that each participant receives varied doses of a drug, and "Ascending" indicates that the number of medications supplied to each new cohort of subjects increases (the dose level ascends as the study goes on). MAD studies are used to evaluate the pharmacokinetics (PK) and

pharmacodynamics (PD) of several pharmacological doses, as well as to look into dose accumulation, dose proportionality, and determining the Maximum Tolerated Dose (MTD).

3. **Food Effect:** Food effect studies are undertaken to see how the body affects the absorption of a medicine before and after it is taken with a meal. Here, the participant received the same drugs before and after being fed in this study.

2.1.3 Phase II

Clinical trials in Phase II, sometimes known as "therapeutic exploratory" trials, are typically larger than those in Phase I. The purpose of a Phase II study is to assess the safety and therapeutic efficacy of a drug in a smaller group of patients with the diseases that the drug is intended to treat.
Phase II is sub classified as Phase IIa and Phase IIb . Phase IIa trials are pilot studies that look into the clinical efficacy or biological activity of a drug. These are commonly referred to as "proof of concept" studies. Phase IIb trials, also known as dose-response studies, were performed to determine the dose at which the drug showed biological activity with minimum side effects in the Phase III target group. The key focus of this thesis is the Phase IIb stage of the drug development cycle.

2.1.4 Phase III

Phase III studies are sometimes known as "therapeutic confirmatory," "comparative efficacy," or "pivotal trial" since they are based on previous research established

drug safety and efficacy. Phase III studies are used to confirm the drug's qualities that were discovered during Phase II of the drug development process. This phase compares a drug's efficacy to that of existing treatment and "gold standard treatment." The Phase III stage of medication development involves testing a large group of patients, maybe 300 to 3000, to determine effectiveness and to detect and estimate the incidence of common adverse side effects. As a result, some of the adverse effects that were missed during Phase II could be discovered. When deciding whether or not to approve a new drug, regulatory health authorities such as the US Food and Drug Administration (FDA) will consider the findings of clinical trials up to and including Phase III trials.

2.1.5 Phase IV

After a drug has been approved by regulatory health authorities like the FDA, phase IV studies, sometimes known as "post-marketing" trials, begin. "The purpose of this phase is to determine the drug's long-term efficacy and safety." Clinical trials are designed to give patients with the most effective and safe treatments currently available.

2.2 Dose

Any form of chemical exposure is referred to as a "dose". The dose is the amount of medicine we give to achieve or sustain a desired benefit while minimising the risks or level of side effects.

Frequency of Dosing

Dosing frequency is defined as the number of times a "dose" is taken in a certain time interval. e.g. once a week or daily twice.

Range of Doses and Number of Doses

Dose ranges between the start dose(placebo) and the highest dose (MTD) with some intermediate doses. The general recommendation is to have 4 to 7 actives doses with a dose range of 10 fold (is the rule of thumb).

Dose allocation

A placebo control is the starting dose and the highest dose is that which is close to the maximum tolerated dose. Equal Dose spacing from lowest to highest dose was introduced by Wong and Lachenbruch in the year 1996 [4].

2.3 Response

"Response" is a clinical outcome involves changes in how they feel, functions, or survives. Response can be a early reaction/responses, such as biochemical abnormalities to far complex, such as cancer or developmental issues. Common examples of responses are decrease in blood pressure after administration of anti-hypertensives or reduced tumor after administration to cancer treatment. Dose responses fall into one of the categories: (i) Continuous e.g. changes in body weight (ii) Binary e.g to test whether treatment is successful or a failure. (iii) Discrete e.g the count of Adverse Events (iv) Ordinal e.g categorical data in a predetermined order say disease classification as mild,

moderate, severe.

Chapter 3

Multiple Comparison Procedure-Modelling (MCP-Mod)

3.1 Introduction

Multiple Comparison Procedure - Modelling (MCP-Mod) Technique approach was proposed by Bretz, Pinheiro, and Branson (2005) [1]. The MCP-Mod procedure is an efficient statistical method for examining phase 2 dose finding studies under model uncertainty. The main aim of this method is to determine set of candidate models in design stage and to evaluate the significance of contrasts between different doses while keeping the family-wise error rate at pre-fixed level α. Family-Wise error is the probability of making at least one incorrect discovery, when performing multiple testing. This method consists of 5 parts, but is divided into two discrete stages:

1. Trial Design Stage

   (a) Define an appropriate research population to represent the true dose-response shape.

   (b) Selection of the candidate dose-response models based on the available information.

(c) Dose and sample size calculation to achieve the target.

2. Analysis Stage

(a) The first step (MCP-step) involves determining whether a dose-response signal exists using a trend test derived from a set of pre-specified candidate model and selecting a model from a set of significant models.

(b) To determine the "Best" dose for confirmatory trials (phase 3), the second step (Mod-step) uses parametric modeling.

3.2 Dose Response Models

The general structure adopted here is for a given set of parallel groups of patients referring to doses d_1,d_2, d_3,..., d_k where placebo is d_1, for a total of k arms, a response y (possibly an efficacy or PD endpoint variable) is recorded. The fundamental assumption of a model-based dose response analysis is the existence of a deterministic function $f(d, \theta)$ which has arguments in dose d and vector of parameters θ. The function $f(d, \theta)$ is completely known except, possibly the vector θ. The dose-response relationship is;

$$y_{ij} = f(d_i, \theta) + \epsilon_{ij}, \quad \epsilon_{ij} \overset{\text{i.i.d}}{\sim} N(0, \sigma^2) \quad i = 1, ..., k, j = 1, ...n_i$$

where, y_{ij} is the response of the j^{th} patient at dose level i; d_i is the dose at the level i. We assume a homoscedastic model, i.e., σ^2 is constant for all the dose levels; ϵ_{ij}'s the error for the j^{th} patient at the i^{th} dose level which

is assumed to be independent and identically distributed. Combining the above we can write

$$y_{ij} \overset{\text{i.i.d}}{\sim} N(f(d_i, \theta), \sigma^2) \quad i = 1, ..., k, j = 1, ...n_i.$$

The rest of this sections describes the common dose response model used in most clinical trials.

3.2.1 Emax Model

The Emax model is a non-linear model (in its parameters) which is widely used in dose-response studies. $\theta = (E_0, E_{max}, ED_{50})$ is the vector of unknown parameters of the Emax model.

$$f(d, \theta) = E_0 + E_{max}\frac{d}{d + ED_{50}}, \quad d = 1, 2, \ldots, k \quad arms \tag{3.1}$$

Where,

- E_0 denotes the response at dose 0 (i.e placebo response)
- E_{max} denotes change in maximum response from placebo
- ED_{50} is median dose, that is the dose which gives half of the maximum response.

In terms of $f(d, \theta)$ we have $f(0, \theta) = E_0$; $\lim_{d\to\infty} f(d, \theta) = E_0 + E_{max}$ and $f(ED_{50}, \theta) = E_0 + \frac{E_{max}}{2}$. The Emax model is a monotonic response model where the dose response curve is increasing or decreasing according as the value of E_{max} is positive or negative. Therefore it is not appropriate to apply

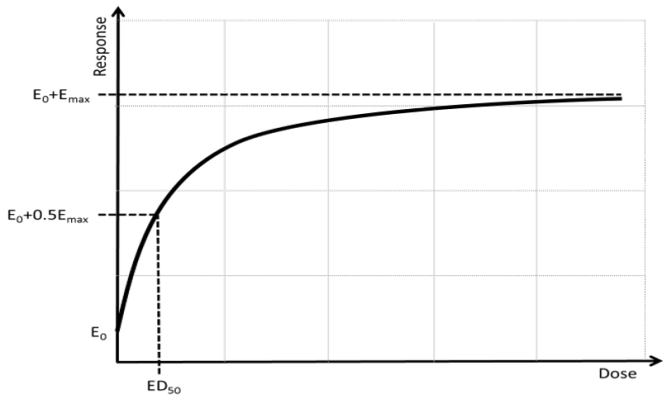

Figure 3.1: Emax model

the Emax model where the dose-response relationship is not monotonic.

3.2.2 Exponential Model

The exponential model can represent a sub-linear or convex dose-response relationship. $\theta = (E_0, E_1, \delta)$ is the vector of parameters of exponential model. It is defined as

$$f(d, \theta) = E_0 + E_1 \exp(\frac{d}{\delta}) \tag{3.2}$$

$E_0, E_1 > 0, \delta \in \mathbb{R}$, where,

- $E_0 + E_1$ is a placebo response that corresponds to the dose d=0.
- δ is the shape parameter of the curve which is increasing or decreasing according as the value of δ is positive or negative.

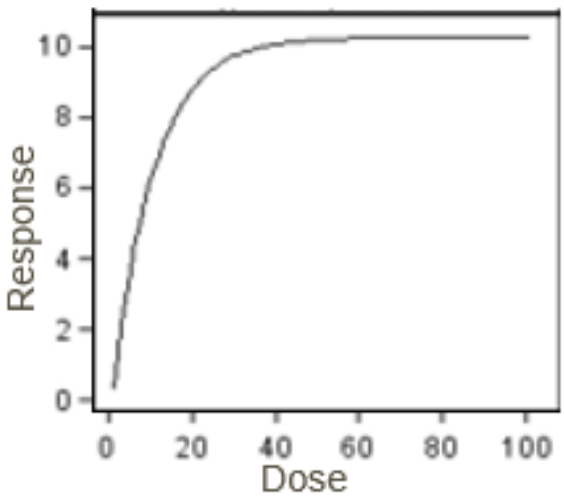

Figure 3.2: Exponential model

3.2.3 Logistic Model

The logistic model is intended to represent general sigmoid, monotone dose-response relationships. Logistic is a four-parameter model, where $\theta = (E_0, E_{max}, ED_{50}, \delta)$, and the model is given by;

$$f(d, \theta) = E_0 + E_{\max} \frac{1}{1 + \exp^{\frac{ED_{50} - d}{\delta}}}. \tag{3.3}$$

Similar to the Emax model we have $f(ED_{50}, \theta) = E_0 + \frac{E_{max}}{2}$; $\lim_{d \to \infty} f(d, \theta) = E_0 + E_{max}$ if $\delta > 0$. If $\delta < 0$ then $\lim_{d \to \infty} f(d, \theta) = E_0$. However $f(0, \theta) = E_0 + \frac{E_{max}}{1 + \exp^{\frac{ED_{50}}{\delta}}}$. Note that $f(0, \theta) < (>) f(ED_{50}, \theta)$ according as $\delta > (<) 0$. That is the logistic curve is increasing or decreasing according as δ positive or negative.

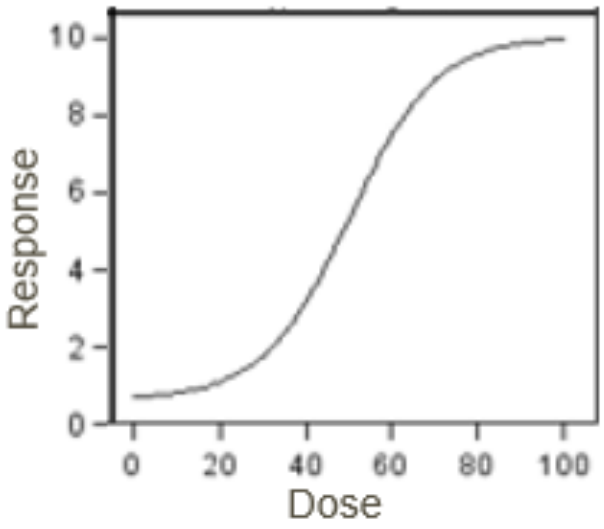

Figure 3.3: Logistic model

3.2.4 Sigmoid Model

Sigmoid model is an extension of Emax model that adds a hill parameter h. Sigmoid is a four parameter model, where $\theta = (E_0, E_{max}, ED_{50}, \delta)$, and the model is given by;

$$f(d, \theta) = E_0 + E_{max} \times \frac{d^{\delta}}{d^{\delta} + ED_{50}^{\delta}} \tag{3.4}$$

where,

- E_0 denotes the response at dose 0 (i.e placebo response)
- E_{max} denotes change in maximum response from placebo
- ED_{50} is median dose, that is the dose which gives half of the maximum response.
- h is the hill parameter which determines the shape of the curve. Note that if $h = 1$ then Sigmoid Emax boils down to the usual Emax.

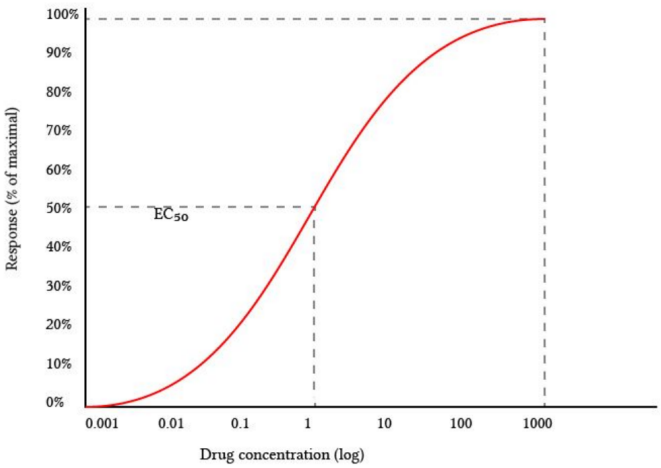

Figure 3.4: Sigmoid model

Similar to Emax model we have $f(0,\theta) = E_0$; $\lim_{d\to\infty} f(d,\theta) = E_0 + E_{max}$ and $f(ED_{50},\theta) = E_0 + \frac{E_{max}}{2}$. If the value of hill parameter is greater than 1, then curve is steeper and it is shallow when the value is less than 1.

3.2.5 Standardized model

Note that for all the dose response model $f(d,\theta)$ defined above can be rewritten in the form

$$f(d,\theta) = E_0 + E_1 f_0(d,\tilde{\theta}),$$

where $E_0, E_1 \in \theta$ and $\tilde{\theta} \subset \theta$. The following table gives a list of standardized form of the above dose response models. The function $f_0(d,\tilde{\theta})$ is called the standard model. As we later see the standard model is sufficient for the purpose of MCP-Mod analysis.

Model	θ	f(d,θ)	$\tilde{\theta}$	$f_0(d,\tilde{\theta})$
Emax	(E_0, E_{max}, ED_{50})	$E_0 + E_{max}\frac{d}{d+ED_{50}}$	ED_{50}	$\frac{d}{d+ED_{50}}$
Logistic	$(E_0, E_{max}, ED_{50}, \delta)$	$E_0 + E_{max}\frac{1}{1+exp(\frac{ED_{50}-d}{\delta})}$	(ED_{50}, δ)	$\frac{1}{1+exp(\frac{ED_{50}-d}{\delta})}$
Exponential	(E_0, E_1, δ)	$E_0 + E_1\ \exp(\frac{d}{\delta})$	δ	$\exp(\frac{d}{\delta})$
Sigmoid	$(E_0, E_{max}, ED_{50}, \delta)$	$E_0 + E_{max}\frac{d^\delta}{d^\delta+ED_{50}^\delta}$	(ED_{50}, δ)	$\frac{d^\delta}{d^\delta+ED_{50}}$

Table 3.1: Table of models used in the analysis

3.3 Optimal allocation

The problem of optimal allocation in design of experiments is to choose design parameters in order to optimize a pre-specified criterion. This criterion can be information or likelihood based. In the context of Phase 2b clinical design where we have more than one cohort of patients corresponding to different dose levels, the problem is to assign the patients to different dose levels, for a fixed sample size N, in order to optimize a certain criterion. Mathematically the experimental design is described by a set of design points $d_1 \cdots d_m$, corresponding to the different dose levels and a set of weights $w_1 \cdots w_m$ assigned to the design points, which in our case correspond to the cohort size. Therefore we define a design ξ as a collection of two vectors

$$\xi = \{(d_1 \cdots d_m), (w_1 \cdots w_m)\}$$

Here weights of all the design points sum up to one $\sum_{i=1}^{m} w_i$=1. The rest of the section illustrates information/optimality criterion that is commonly

used.

3.3.1 D-optimality:

The most significant feature of optimal design is the information matrix M(ξ,θ), which sums up all information in a mathematical form. For a given design ξ the information matrix is given by

$$M(\xi, \theta) = \sum_{i=1}^{m} w_i \frac{\partial f(d,\theta)}{\partial \theta} \frac{\partial f(d,\theta)^\top}{\partial \theta} \tag{3.5}$$

where $\frac{\partial f(d,\theta)}{\partial \theta} = (1, f_0(d,\tilde{\theta}), \theta_1 \frac{\partial f_0(d,\tilde{\theta})}{\partial \theta_2}, \cdots, \theta_1 \frac{\partial f_0(d,\tilde{\theta})}{\partial \theta_p})$ is a gradient of function $f(d,\theta)$ with respect to the parameter θ.

The D-optimality criterion is the most commonly used optimality criterion used to estimate the model parameters. A design ξ is D-optimal if it minimizes the determinant of the inverse of the Fisher information matrix defined in Equation 3.5. That is the D-optimal design ξ_{opt} is

$$\xi_{opt} = \text{argmin}_\xi \det[M(\xi,\theta)^{-1}]$$

In most cases the above optimization does not yield a closed form results. Therefore we look for look for sufficient condition that a given design ξ is D-optimal. One such set of sufficient condition is the Generalized Equivalence Theorem [8] due to Kiefer and Wolfowitz (1960), reformulated by Fackle Fornius(2008) [7] for the univariate case and stated by Magnúsdóttir (2014) [9] for the multivariate and it has the following three equivalent conditions:

1. $\xi^* = \text{argmin}_\xi log \det[M(\xi,\theta)^{-1}]$

2. $g(d)^\top M(\xi,\theta)^{-1}g(d) \leq p$ for all $d \in \{d_1, d_2, \cdots, d_m\}$

where p is the number of parameters in the full model $f(d,\theta)$ and $g(d) = \frac{\partial f(d,\theta)}{\partial \theta}$. If any one of the above conditions is satisfied, then the design is D-optimal.

Given the design specifications that is, the number of doses m and doses $d_0, d_1, \cdots, d_{k+1}$ the `optDesign` function in library `DoseFinding` in `R` can give the D-optimal allocation. The following piece of code in R gives the D-optimal allocation for 5 doses (0, 0.033, 0.1, 0.33, 1) using only the Emax model (here $k = 4, m = 5$)

```
#Dose
dose <- c(0,0.033,0.1,0.33,1)
#Considering Emax model
models <- Mods(emax = 0.1, doses = dose)
#Optimal design
allocation <- optDesign(models, probs = 1)
```

Extensions to more than one models is obtained in the same package.

3.4 Optimal Model Contrasts

We consider the problem to determining the optimal contrast for dose response function $f(d,\theta)$, when model is correct. The hypothesis for the dose response model m we test is:

- $H_0 : c_m'\boldsymbol{\mu} = 0$

- $H_0 : c'_m \boldsymbol{\mu} \neq 0$

where $\mu = (\mu_1, \mu_2, \cdots, \mu_m)$ is the mean vector at different dose levels $d_1, d_2, \cdots, d$ corresponding to certain model m in the candidate dose response model set. A contrast $\boldsymbol{c} = (c_1, c_2, , c_m)$ is defined as a vector such that $\sum_{i=1}^{m} c_i = 0$. The problem is to find the optimal contrast $\boldsymbol{c}_m$ corresponding to a model m. The contrast maximizes the chances of rejecting the null hypothesis and is used to identify the best model.

It is derived in [1] that the optimal contrast c_m for the model m is that $\boldsymbol{c}$ that satisfies:

$$c_m = \text{argmin}_c g(c, \mu), \tag{3.6}$$

where

$$g(\boldsymbol{c}, \boldsymbol{\mu}) := \frac{(\boldsymbol{c}'\mu)^2}{\sum_{i=1}^{k} \frac{c_i^2}{n_i}} \tag{3.7}$$

Since $g(c, \mu) = g(\lambda c, \mu)$ so a $\boldsymbol{c}$ that satisfies above equation also satisfies the same with $g(\boldsymbol{c}, \mu)$ replaced by $g(\lambda \boldsymbol{c}, \mu)$. We therefore solve the above equation in the class of $\boldsymbol{c}$ such that $||\boldsymbol{c}|| = 1$.

Further we have the restriction that $\boldsymbol{c}'\mathbf{1} = 0$. Therefore

$$(\boldsymbol{c}'\boldsymbol{\mu})^2 = [\boldsymbol{c}'(\boldsymbol{\mu} - \bar{\boldsymbol{\mu}}1)]^2 \leq \|\boldsymbol{\mu} - \bar{\mu}\mathbf{1}\|^2,$$

where the last inequality follows from Cauchy Schwartz inequality and

$$\bar{\mu} := \boldsymbol{\mu}'\mathbf{1}/m = \frac{1}{m}\sum_{i=1}^{m} \mu_i$$

is the grand mean of the group means. Equality holds i.f.f

$$\boldsymbol{c}_m \propto (\boldsymbol{\mu} - \bar{\mu}\mathbf{1})\,.$$

Therefore the optimum value of c_m under balanced allocation is (using $||c_m|| = 1$) is :

$$\begin{aligned} c_m &= \frac{\boldsymbol{\mu} - \bar{\mu}\mathbf{1}}{||\boldsymbol{\mu} - \bar{\mu}\mathbf{1}||} \\ &= \frac{\boldsymbol{\mu}^0 - \bar{\mu}^0\mathbf{1}}{||\boldsymbol{\mu}^0 - \bar{\mu}^0\mathbf{1}||} \end{aligned}$$

where $\boldsymbol{\mu}^0 = (f_0(d_1,\theta), f_0(d_2,\theta), \ldots, f_0(d_m,\theta))$ is the mean dose response under the standard model $f_0(d,\theta)$ and $\bar{\mu}^0 = \frac{1}{m}\sum_{i=1}^{m} f_0(d_i;\theta)$ is the mean of the dose levels for the same model. Therefore, as pointed earlier, only the standard dose response model $f_0(d,\theta)$ should be completely specified to obtain the optimal contrast $\boldsymbol{c}_m$.

3.4.1 Unbalanced design

In the general case of unbalanced cohort size at different dose levels the computations are a slightly complicated. Here $g(\boldsymbol{c},\mu)$ is defined as

$$g(\boldsymbol{c},\mu) = \frac{\boldsymbol{c}'\mu}{\sqrt{\boldsymbol{c}'S\boldsymbol{c}}},$$

where $S = \text{Diag}(n_1, n_2, \ldots, n_m)$ is the matrix of the inverse of the cohort sizes. We perform the same minimisation problem as in Equation (3.6).

Using some mathematical theory (see [11] for details) the optimal contrast $\boldsymbol{c}_m$ fro a model m is directly proportional to:

$$\boldsymbol{c}_m \propto \boldsymbol{S}^{-1}\left(\boldsymbol{\mu}_m^0 - \frac{\boldsymbol{\mu}_m^{0\,\prime}\boldsymbol{S}^{-1}\mathbf{1}}{\mathbf{1}'\boldsymbol{S}^{-1}\mathbf{1}}\right) \tag{3.8}$$

where $\boldsymbol{\mu_m^0}$ has been defined earlier. For the similar reason explained in the above section we normalise the optimal contrast so that $||\boldsymbol{c}_m|| = 1$.

The optimal contrast $\boldsymbol{c}_m$ can be obtained using the function `optContr()` in the library `DoseFinding` in `R`.

3.5 Contrast Test

We assume that j^{th} patient's response $y_{i,j}$ in the i^{th} cohort follows:

$$y_{ij} = \mu_i + \epsilon_{ij}, \quad \epsilon_{ij} \overset{\text{i.i.d}}{\sim} N(0, \sigma^2) \tag{3.9}$$

where μ_i indicates the mean dose response with $\mu = (\mu_1, \cdots, \mu_m)$. The following are the group means for each dose group:

$$\bar{y}_i = \frac{1}{n_i}\sum_{j=1}^{n_i} y_{ij},$$

and the pooled variance is determined as

$$s^2 = \frac{1}{v}\sum_{i=1}^{k}\sum_{j=1}^{n_i}\left(y_{ij} - \bar{y}_i\right)^2.$$

where $v = n - k$ is also the degrees of freedom and $n = \sum_{i=1}^{k} n_i$ cohort size of k treatment groups. The pre-specified candidate models are represented as m=$1,\cdots, M$. Each of these models are represented by a fixed mean vector as $\mu_m^0 = (\mu_{m,1}^0, \cdots, \mu_{m,k}^0)$, obtained from standardized model $f_0^m =$

$(d, \theta_m) = \mu_0^m$. We use models in Table (3.1) at different dose levels for dose estimation. The main aim is to find the best-fitting model(s) from the candidate set $\{1, 2, \ldots, M\}$. Thus the null hypothesis is as follows:

Null Hypotheses:

$$H_0^m : c_m' \boldsymbol{\mu} = 0$$

for all $m \in \{1, 2, \ldots, M\}$.

Alternative Hypotheses:

$$H_1^m : \boldsymbol{c}_m' \boldsymbol{\mu} \neq 0$$

for at least one $m \in \{1, 2, \ldots, M\}$.

We know that

$$y_{i,j} \sim N(\mu_i, \sigma^2)$$

which implies $\bar{y} \sim N(\mu_i, \sigma^2/n_i)$. Therefore

$$\boldsymbol{c}_m' \bar{y} \sim N(\boldsymbol{c}_m' \boldsymbol{\mu}, \sigma^2 \sum_{i=i}^{k} c_{mi}^2/n_i).$$

Note that under H_0, $\boldsymbol{c}_m' \bar{\boldsymbol{y}} / \sqrt{\sigma^2 \sum_{i=1}^{k} \frac{c_{mi}^2}{n_i}} \sim N(0, 1)$ and

$$\sqrt{\frac{S^2}{\sigma^2}} \sim \sqrt{\chi_{n-k}^2/(n-k)}.$$

Therefore for a single contrast test the test statistic

$$T_m := \frac{\boldsymbol{c}_m' \overline{\boldsymbol{Y}}}{\sqrt{S^2 \sum_{i=1}^{k} c_{mi}^2/n_i}}, \quad m = 1, \ldots, M$$

follows t-distribution with n-k degrees of freedom under H_0. If H_1 is true for

any model m then T_m follows non-central t-distribution with non-centrality parameter given by the quantity $g(\boldsymbol{c}, \boldsymbol{\mu})$ as defined in Equation (3.7). Therefore we obtain a significance test for the above hypotheses using the statistic

$$T_{\max} = \max_{m \in \{1,2,\ldots,M\}} T_m.$$

We reject the multiple hypotheses if $T_{\max} > q$ for some suitably chosen cut-off value q that controls the family wise error rate at α. We select those model(s) with a non-zero trend for which $T_m > T_{\max}$. Alternatively, we can find the p-value p_m for each hypothesis and reject those models for which the p-value is smaller than that multiplicity adjusted p-value p^*. The values of q and p^* can be obtained in the function `MCTtest()` in package `DoseFinding` in `R`.

Chapter 4

Bayesian MCP-Mod

4.1 Introduction

Multiple Comparison Procedure and Modelling (MCPMod) has been proved to be an effective statistical method for enhancing the design and analysis of dose finding studies in the presence of model uncertainty. However, due to its frequentist nature, it is not possible to incorporate historical information into model. Fleischer et al.(2022) [6] recently developed a Bayesian version of MCPMod (BMCP-Mod) to address this issue, which is specially adapted to the circumstance where there is some knowledge about the placebo dose group and active dose group, which may often be accessible from prior trials, either within the same development program or from other trials in this area. BMCP-Mod performs the same operation as MCPMod except that now we incorporate priors (possibly non-informative) on the mean dose response of the active and placebo arms. This allows borrowing of historical data which in turn leads to better efficacy. In this thesis we discuss the BMCP-Mod approach that is based on MCPMod and Bayesian borrowing.

We consider a total of k+1 dose levels $\mathcal{D} = \{d_0, d_1 \cdots, d_k\}$ where d_0 indicates the placebo dose. Given the mean dose response μ_i at dose level d_i the conditional distribution of the response variable Y_{ij} for the j^{th} patient in the i^{th} dose level follows a normal distribution with mean μ_i and variance σ^2, that is

$$Y_{ij}|\mu_i \sim \mathcal{N}\left(\mu_i, \sigma^2\right), i = 0, \ldots, k; j = 1, \ldots, n_i \tag{4.1}$$

where n_i represents the cohort size of the i^{th} dose group d_i for $i \in \{0, \ldots, K\}$ In the Bayesian paradigm we assume that μ_i is random with equal variance throughout all the dose levels. Further the response is independent within and between the dose level.

4.2 Choice of the prior for placebo

The correct choice of the prior is an important step for any Bayesian analysis. Typically in clinical trials historical information is available for the placebo and for the active groups. Presently there are lot of activities that try to bring together placebo information for different drugs in different pharmaceutical companies. Consequently available information on placebo for different drugs (and/or companies) can be modelled as a mixture distribution, where the information obtained from each source constitutes individual component of the mixture distribution. Comparatively information on the active dose can be sometimes limited. This can happen with drugs with a new mechanism of action or drugs that has not been studied earlier. A common choice is

to use a non-informative prior (a prior with a large variance, also called a diffused prior) for the active arm. In comparison, the prior for the placebo arm can be quite informative. This is the approach that has been followed in Fleischer et al.(2022) [6] and the present thesis.

4.2.1 BMCP-Mod methodology

A multivariate normal distribution or mixture of multivariate normal distribution is considered as the prior for $\boldsymbol{\mu} = (\mu_0, \cdots, \mu_k)$ where the components of boldsymbolμ are assumed to be independent $N(\theta_i, \sigma^2_{0,i})$. To simplify computation we write $\sigma^2_{0,i} = \sigma^2/n_{0,i}$ for a prior effective sample size $n_{0,i}$ (ESS) for known variance σ^2 of Y. In this section, we are only considering a single-component priors. That is we assume

$$\boldsymbol{\mu} \sim \mathcal{N}_{K+1}\left(\boldsymbol{\theta}_0, \frac{\sigma^2}{\boldsymbol{n}_0} I\right) \tag{4.2}$$

where $\boldsymbol{n}_0 = (n_{0,0}, n_{0,1}, \cdots, n_{0,k})$ is the vector of prior effective sample size. The posterior distribution of $\boldsymbol{\mu}$ given the data $\mathcal{Y}$ is a straightforward derivation;

$$\mu_i|\mathcal{Y} \sim \mathcal{N}\left(\frac{\frac{\theta_{0,}}{\sigma^2/n_{0,i}} + \frac{\bar{Y}_i}{\sigma^2/n_i}}{\frac{n_{0,}}{\sigma^2} + \frac{n_i}{\sigma^2}}, \frac{1}{\frac{n_{0,}}{\sigma^2} + \frac{n_i}{\sigma^2}}\right) = \mathcal{N}\left(\frac{n_{0,i}\theta_{0,i} + n_i\bar{y}_i}{n_{0,i} + n_i}, \frac{\sigma^2}{n_{0,i} + n_i}\right) \tag{4.3}$$

In vector notations we have:

$$\boldsymbol{\mu} \mid \mathcal{Y} \sim \mathcal{N}_{K+1}\left(\underbrace{\frac{\boldsymbol{n_0\theta_0} + \boldsymbol{n}\bar{Y}}{\boldsymbol{n_0} + \boldsymbol{n}}}_{=\theta_y}, \frac{\sigma^2}{\boldsymbol{n_0} + \boldsymbol{n}} I\right) \tag{4.4}$$

using the independence assumption between the dose levels. Here $\bar{\boldsymbol{Y}} = (\bar{Y}_0, \bar{Y}_1, \cdots, \bar{Y}_k)$ is the mean response of the i^{th} cohort. Here $\boldsymbol{ab}$ and $\boldsymbol{a} + \boldsymbol{b}$ is the component wise multiplication and addition of the vectors $\boldsymbol{a}$ and $\boldsymbol{b}$.

4.3 Mixture priors

In this section we will look into mixture prior. Mixture prior is a combination or a mixture of information borrowed from the previous trials. One such borrowing is called Dynamic borrowing. In Dynamic borrowing the amount of information borrowed from historical trials is dynamically controlled. When historical information is incorporated in the analysis of new trial, it reduces the cohort size, cost and trial duration. However in the case of prior-data conflict, a too optimistic use of historical data might be inappropriate. In such situation the Bayesian meta-analytic-predictive (MAP) prior is used which is then merged with new data. Although technically there is no limit on the number of mixture components, in practice three components are more than enough to adequately approximate a MAP prior. Further to ensure robustness the fourth component of the mixture prior may be introduced, usually as a vaguely informative component. We therefore use a mixture prior with four components only. We restrict information to only placebo group, therefore we define mixture conjugate prior to placebo dose group with $L(\leq 4)$ components. We assume that the i^{th} component of the

mixture prior of the placebo group follows

$$N(\theta_{0,0,i}, \frac{\sigma^2)}{n_{0,0,i}}$$

where $n_{0,0,i}$ is the ESS for the i^{th} component. Therefore the mixture normal distribution of the placebo prior takes the form

$$\mu_0 \sim w_1.N(\theta_{0,0,1}, \frac{\sigma^2}{n_{0,0,1}}) + \cdots + w_4.N(\theta_{0,0,4}, \frac{\sigma^2}{n_{0,0,4}}) \tag{4.5}$$

where prior weights are denoted as $w_1, \cdots, w_4$ in such that $\sum_{l=1}^{4} w_l = 1$. Active dose groups are assumed to have a one-component vaguely informative prior. Note that a one-component prior for active groups can be written as a mixture prior with 4 components where the weights for only one of the components is one. Using this the prior distribution $\boldsymbol{\mu}$ is

$$\begin{aligned} \boldsymbol{\mu} \sim w_1 \cdot \mathcal{N} \left(\begin{pmatrix} \theta_{0,0,1} \\ \theta_{0,1} \\ \vdots \\ \theta_{0,k} \end{pmatrix}, \begin{pmatrix} \frac{\sigma^2}{n_{0,0,1}} & \frac{\sigma^2}{n_{0,1}} & \cdots & \frac{\sigma^2}{n_{0,k}} \end{pmatrix} I \right) + \ldots + \\ w_4 \cdot \mathcal{N} \left(\begin{pmatrix} \theta_{0,0,4} \\ \theta_{0,1} \\ \vdots \\ \theta_{0,k} \end{pmatrix}, \begin{pmatrix} \frac{\sigma^2}{n_{0,0,4}} & \frac{\sigma^2}{n_{0,1}} & \cdots & \frac{\sigma^2}{n_{0,k}} \end{pmatrix} I \right) \end{aligned} \tag{4.6}$$

Posterior distribution for $\boldsymbol{\mu}$ is derived as

$$\mu \mid \mathcal{Y} \sim w_1^*.\mathcal{N}\left(\underbrace{\begin{pmatrix} \frac{n_{0,0,1}\theta_{0,0,1}+n_0\bar{Y}_0}{n_{0,0,1}+n_0} \\ \frac{n_{0,1}\theta_{0,1}+n_1}{n_{0,1}+n_1} \\ \vdots \\ \frac{n_{0,K}\theta_{0,K}+n_K\bar{Y}_K}{n_{0,K}+n_K} \end{pmatrix}}_{\theta_{\mathcal{Y}}^1}, \underbrace{\begin{pmatrix} \frac{\sigma^2}{n_{0,0,1}+n_0} \cdots \frac{\sigma^2}{n_{0,K}+n_K} \end{pmatrix} I}_{\tau_1}\right) +$$

$$\ldots + w_4^*.\mathcal{N}\left(\underbrace{\begin{pmatrix} \frac{n_{0,0,4}\theta_{0,0,4}+n_0\bar{Y}_0}{n_{0,0,4}+n_0} \\ \frac{n_{0,1}\theta_{0,1}+n_1}{n_{0,1}+n_1} \\ \vdots \\ \frac{n_{0,K}\theta_{0,K}+n_K\bar{Y}_K}{n_{0,K}+n_K} \end{pmatrix}}_{=\theta_{\mathcal{Y}}^4}, \underbrace{\begin{pmatrix} \frac{\sigma^2}{n_{0,0,4}+n_0} \cdots \frac{\sigma^2}{n_{0,K}+n_K} \end{pmatrix} I}_{=\tau_4}\right) \tag{4.7}$$

where $w_1^*, \cdots, w_4^*$ are updated posterior weights such that $\sum_{l=1}^4 w_l^* = 1$. Let $f(x; l, \theta)$ be the density of the data x under component l and θ then using Bayes theorem it turns that the posterior weights are

$$w_l^* = w_l f(x|l,\theta) / \sum_{l=1}^4 w_l f(x|l,\theta).$$

The posterior distribution of $\boldsymbol{c'\mu}$ given the data is thereby

$$\boldsymbol{c}_m^T\boldsymbol{\mu} \mid \mathcal{Y} \sim \underbrace{w_1^*\mathcal{N}\left(\boldsymbol{c}_m^T\boldsymbol{\theta}_{\mathcal{Y}}^1, \sum_{i=0}^K c_{m,i}^2\tau_1[i,i]\right)}_{\sim Z_1} + \cdots + \underbrace{w_4^*\mathcal{N}\left(\boldsymbol{c}_m^T\boldsymbol{\theta}_{\mathcal{Y}}^4, \sum_{i=0}^K c_{m,i}^2\tau_4[i,i]\right)}_{\sim Z_4}$$

where $\tau_l[i,i]$ is the i^{th} diagonal matrix of the posterior dispersion matrix

of $\boldsymbol{\mu}$. The posterior distribution comes with a probability weights assigned to each of the component distribution which is the same as the posterior weights w_l^*. The test of significance can be based on the posterior probabilities:

$P\left(\boldsymbol{c}_m^T\boldsymbol{\mu} > 0 \mid \mathcal{Y}\right) = \sum_{l=1}^{4} w_l^* \cdot P\left(Z_l > 0\right)$

where the equality follows from the law of total proability. Now for any model m

$$
\begin{aligned}
P\left(\mathbf{c}_m^T\mu > 0 \mid \mathcal{Y} = y\right) &= 1 - P\left(\mathbf{c}_m^T\mu \leq 0 \mid \mathcal{Y} = y\right) \\
&= 1 - P\left(\mathbf{c}_m^T\mu - \mathbf{c}_m^T\boldsymbol{\theta}_y \leq 0 - \mathbf{c}_m^T\boldsymbol{\theta}_{\mathcal{Y}} \mid \mathcal{Y} = y\right) \\
&= 1 - P\left(\frac{\mathbf{c}_m^T\mu - \mathbf{c}_m^T\theta_y}{\sqrt{\sum_{i=0}^{k} c_{m,i}^2 \frac{\sigma^2}{n_{p,i}+n_i}}} \leq \frac{-\mathbf{c}_m^T\theta_{\mathcal{Y}}}{\sqrt{\sum_{i=0}^{k} c_{m,i}^2 \bar{\sigma}_{p,i} + n_i}} \mid \mathcal{Y} = y\right) \\
&= 1 - \Phi\left(\frac{-\mathbf{c}_m^T\boldsymbol{\theta}_y}{\sqrt{\sum_{i=0}^{k} c_{m,i}^2 \frac{\sigma^2}{p_{p,i}+n_i}}}\right) \\
&= \Phi\left(\frac{\mathbf{c}_m^T\boldsymbol{\theta}_{\mathcal{Y}}}{\sqrt{\sum_{i=0}^{k} c_{m,i}^2 \frac{\sigma^2}{n_{p,i}+n_i}}}\right)
\end{aligned}
$$

Therefore the probability can be explicitly obtained as:

$$
P\left(\boldsymbol{c}_m^T\boldsymbol{\mu} > 0 \mid \mathcal{Y}\right) = \sum_{l=1}^{4} w_l^* \Phi\left(\frac{\boldsymbol{c}_m^T\boldsymbol{\theta}_y^l}{\sqrt{\sum_{i=0}^{K} c_{m,i}^2 \tau_l^2[i,i]}}\right) = p_m^{\mathcal{Y}}. \tag{4.8}
$$

A significance test for the multiple hypotheses H_0^m: $c_m'\boldsymbol{\mu} = 0$ against H_1^m: $c_m'\boldsymbol{\mu} > 0$ can be performed using the quantity

$$
\max_{m \in \{1,..,m\}} p_m^{\mathcal{Y}} > 1 - \alpha^*
$$

where α^* is the adjusted critical value of the probability such that it ensures that the family wise error is controlled at α. That is $1 - \alpha^* = \Phi(q)$ where q is the minimum threshold value for comparing the T_{max} statistics [1]. Computation of q is built in the `DoseFinding` package.

4.4 Contrast vector and allocation ratio

In the above section 3.3 we have discussed optimal allocation ratio for MCP-Mod. For BMCPMod, we use a simpler approach by subtracting the Effective sample size (ESS) of placebo from the cohort size on placebo group (obtained from the MCPMod). For the active groups the allocation is kept same as it was in MCPMod. Later the ratio of the MCPMod and BMCPMod will be multiplied with the respective number of subject in dose group this is done to make the allocation balanced throughout. Thus we obtain the BMCPMod allocation ratio.

Contrast vectors can be obtained by two approaches: First is to use contrasts obtained by MCPMod, ignoring the prior information. Second, the allocation ratio is calculated using the posterior effective sample size, adding actual sample size and the prior effective sample size and the contrasts calculated by regular MCPMod method.

4.5 Expected local-information-ratio

In case of mixture priors we consider Expected local-information ratio effective sample size (ESS_{elir}) according to reference [10]. It is given as

$$ESS_{elir} = E_{\mu}(i(p(\mu)/i_F(\mu)) \tag{4.9}$$

where, $i_F(\mu)$ is the Fisher information of the sampling model $i_F(\mu) = E_{Y_1|\mu}\left\{i_F\left(Y_1\mu\right)\right\} = -E_{Y_1|\mu}\left\{\frac{d^2 \log f(Y_1|\mu)}{d\mu^2}\right\}$ and $i(p(\mu)) = -\frac{d^2 \log p(\mu)}{d\mu^2}$ is the prior distribution of μ. If the prior is a k components mixture distribution, $p(\mu) = \sum_{j=1}^{K} w_j p_j(\mu)$, its information $i(p(\mu)$ is

$$\begin{aligned} i(p(\mu)) =& - d_{\mu}^2 \log p(\mu) \\ =& \frac{1}{p^2(\mu)} \left[\sum_{j=1}^{K} w_j p_j(\mu) d_{\mu} \log p_j(\mu)\right]^2 \\ & - \frac{1}{p(\mu)} \sum_{j=1}^{K} w_j p_j(\theta) \left[\left\{d_{\mu} \log p_j(\mu)\right\}^2 + d_{\mu}^2 \log p_j(\mu)\right] \end{aligned}$$

Here, d_{μ} and d_{μ}^2 denote the first and second derivative, respectively. The ESS_{elir} gives a measure for the ESS of the mixture that meets the predictive consistency condition, with the expected posterior ESS equaling the sum of the prior ESS and the sample size.

For a mixture normal prior with 3 components. weights are 0.5, 0.25, 0.25. prior means (0, 0.25, -0.25) and standard deviation(SD) (0.20,0.78,0.78). Note SD is obtained by diving σ by prior ESS. We use `mixnorm` and `ess` functions from library `RBest` in R to get ESS_{elir}

```
#mixture normal distribution

library(RBesT)

mixture <- mixnorm(norm1 = c(0.5,0,0.20), norm2 = c(0.25,0.25,0.78),

norm3 = c(0.25,-0.25,0.78), sigma =1.1)

ess(mixture, "elir")
```

Chapter 5

Simulation Study

In this thesis we will use simulated data. We consider $k = 4$ active arms and a placebo group. These treatment groups represent different dose levels of $d_0 = 0, d_1 = 0.033, d_2 = 0.1, d_3 = 0.33$, and $d_4 = 1$. The standard deviation of the data is $\sigma = 1.1$. We investigate $M = 6$ different models as illustrated in 5.1: exponential, linear, logistic and three Emax models. For the six models considered the optimal allocation and the cohort size for a total sample size of $n = 300$ was obtained using `optDesign` function in the `DoseFinding` package. The table of optimal allocation is given in 5.1. Optimal contrasts following the MCPMod procedure (as defined in Chapter 3) for the optimal allocation as define in Table 5.1 are also obtained using the same package. The values of the optimal contrast for all the models are displayed in the Table 5.2.

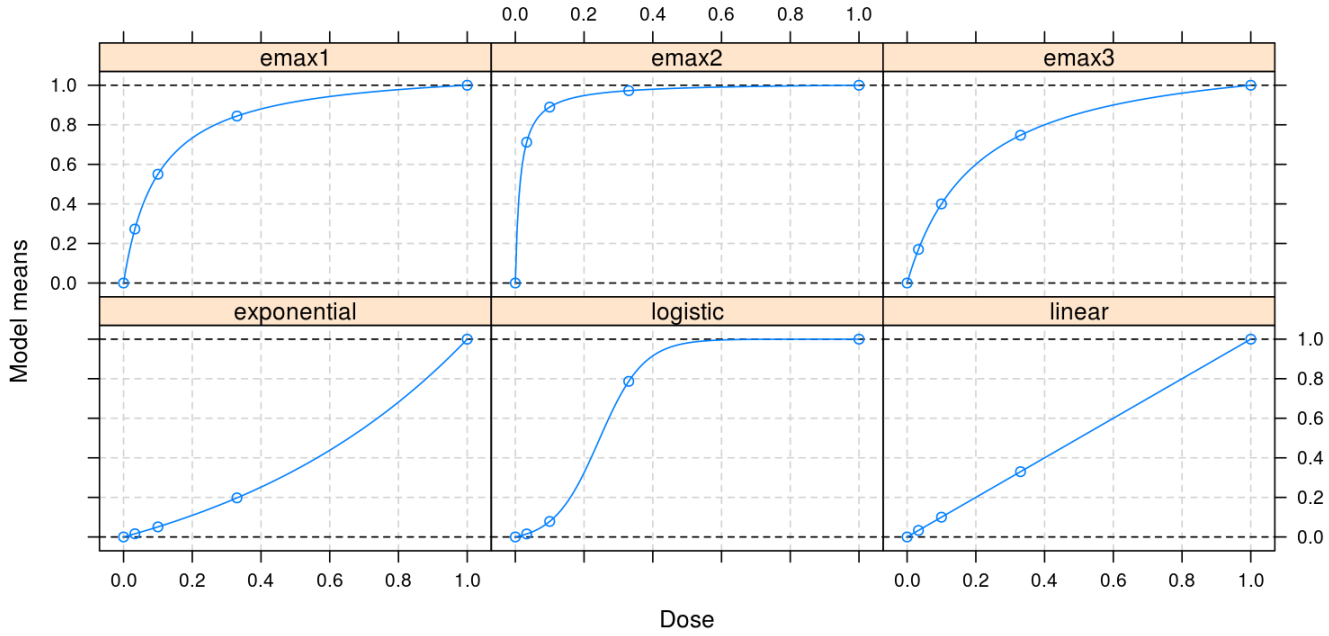

Figure 5.1: Dose Response curve for the different models

80	33	44	48	95

Table 5.1: MCPMod optimal allocation

	Emax1	Emax2	Emax3	Exponential	Logistic	Linear
0	-0.705	-0.841	-0.639	-0.408	-0.529	-0.454
0.03	-0.159	0.006	-0.183	-0.161	-0.212	-0.173
0.1	-0.007	0.144	-0.077	-0.192	-0.241	-0.185
0.33	0.214	0.219	0.176	-0.109	0.231	-0.040
1	0.657	0.473	0.722	0.871	0.751	0.853

Table 5.2: Optimal Contrast

5.1 Illustration of the BMCP-Mod

We consider a case where the prior to the placebo group is informative and other dose groups are vaguely informative. All priors are built on components that are normally distributed. For the placebo group, a mixture

prior has 3 different components: one informative and two non-informative components. The prior mean of informative component is $\theta_{0,0,1} = 0$. One of the non-informative (weakly) informative prior has a mean of $\theta_{0,0,2} = 0.25$ while the other has a value of $\theta_{0,0,3} = -0.25$. ESS of the informative prior component is two with a weight of 0.5. The non-informative prior components have weight of 0.25 each with an ESS of 2. For mixture priors, we calculate the Expected local-informative-ratio Effective Sample Size (ESS_{elir}) as defined in 4.5. As described in 4.4 we calculate the optimal allocation ratio of BMCPMod using the same package as MCPMod optimal allocation. The optimal allocation for BMCPMod is given in Table 5.3. Optimal contrasts for the BMCP-Mod procedure are obtained using the optimal allocation as defined in Table 5.3 using the `optContr` function from `DoseFinding` library in R. Table 5.5, Table 5.6 and Table 5.7 describes the posterior means, variance and weights for the respective mixture component i.

73	34	46	50	98

Table 5.3: BMCP-Mod optimal allocation

	Emax1	Emax2	Emax3	exponential	logistic	linear
0	-0.685	-0.837	-0.613	-0.379	-0.499	-0.425
0.03	-0.182	-0.006	-0.204	-0.172	-0.229	-0.186
0.1	-0.021	0.142	-0.094	-0.206	-0.262	-0.201
0.33	0.215	0.221	0.174	-0.120	0.231	-0.050
1	0.672	0.480	0.737	0.877	0.759	0.861

Table 5.4: BMCP-Mod Optimal Contrast

dose levels	Components: 1,2,3		
0	0.11974736	0.66469304	-0.33530696
0.03	0.20525087	0.20525087	0.20525087
0.1	0.18281357	0.18281357	0.18281357
0.33	0.13942832	0.13942832	0.13942832
1	0.02760001	0.02760001	0.02760001

Table 5.5: Posterior means for different dose levels

dose levels	Components: 1,2,3		
0	0.01179343	0.01621994	0.01621994
0.03	0.03424989	0.03424989	0.03424989
0.1	0.02583178	0.02583178	0.02583178
0.33	0.02392278	0.02392278	0.02392278
1	0.01226546	0.01226546	0.01226546

Table 5.6: Posterior variance for different dose levels

Posterior weights	0.24718320	0.21560190	0.52255809	0.01465681

Table 5.7: Posterior weights

It should be noted that the posterior distribution might be derived from any of the three distributions, with weight of w_i^* given in Table 5.7. We fix contrast vector $\boldsymbol{c}$ obtained in Table 5.4 to the posterior means and variance in Table 5.5 and 5.6 as defined in 4.3 to obtain $\boldsymbol{c_m'\mu}$. For a given data we are interested in the posterior probability that our linear contrast for a certain model is greater than zero. The posterior probabilities for $M = 6$ models mentioned above are given in Table 5.8.

Posterior probabilities
0.3107429
0.4103961
0.2813772
0.2122869
0.2528265
0.2225135

Table 5.8: Caption

From the above Table 5.8 we observed that second Emax model has the maximum posterior probability out of all the other models that is $P^* = 0.4103$. Fixing α at 0.05, adjusted critical value $1-\alpha^*$ is obtained taking the distributive function of multivariate t distribution of q (the critical value of MCPMod). We obtained a critical value of 0.14823 using `MCTtest` function in `DoseFinding` package in R. Therefore as p^* is greater than $1 - \alpha^*$ that is $0.41035 > 0.14823$ we say that a significant test is established (trend is observed). The best description of the trend is explained by the second Emax model.

5.1.1 Summary and Future Research

In this expository project we discuss the well accepted procedure of MCP-Mod that enables us to make model comparison correcting for multiplicity. We discuss the mathematical details involved in the computations. We also discuss the Bayesian version of the MCP-Mod and also provide some simulations where we use existing and improvised codes in `R` to illustrate how the above theory can be executed in practice. We believe that the theory of BMCP-Mod needs to be explored further. For example, we discussed the special cases

where the active doses were single component non-informative priors. Clearly this assumption can be expanded. Also the extension of the above theory for time to event, binary and ordinal data has not been explored. We also believe that in this present era of drug development where we are focusing much on 'dynamic borrowing', that is, borrowing more information from historical studies, the present theory has a lot of scope. The 'dynamic' aspect of BMCP-Mod where the prior weights are not fixed apriori, but updated based on the consistency between the present and the historical data, has not been explored too much. We hope to study these topics in a future research.

Chapter 6

Appendix

6.1 Appendix

R code

```
#library

rm(list=ls())

library(DoseFinding)

library(tidyverse)

library(RBesT)

set.seed(12345)


#dose levels

dose <- c(0,0.03,0.1,0.33,1)

N <- 300 #Fixed sample size

sigma <- 1.1

k=length(dose) #treatment arms

#candidate models

models <- Mods(emax=c(0.1,0.014,0.2),exponential= 0.748,

logistic = c(0.2431,0.0651), linear=NULL, doses = dose)
```

```
M=6 #models
plot(models)
n_iter <- 1e3 #length of posterior sample
elements <- c(1,2,3) #components
m=length(elements)

mu00 <- c(0,0.25,-0.25) #Placebo prior mean
mu0 <- c(0,0,0,0) #Active prior mean
n00 <- c(30,2,2) #Placebo prior ESS
n0 <- c(1,1,1,1) #Active prior ESS
weights <- c(0.5,0.25,0.25) #prior weights

#ESS_elir for mixture prior
mixture_prior <- mixnorm(norm1 = c(0.5,0,0.20),
norm2 = c(0.25,0.25,0.78), norm3 = c(0.25,-0.25,0.78), sigma = 1.1)
ess <- ess(mixture_prior, "elir")

#optimal allocation for MCPMod
mcp_allocationratio <- optDesign(models, probs = rep(1/6,6))
mcp_allocation <- N*mcp_allocationratio$design

#optimal allocation for BMCP-Mod
bmcp_allocation <- c(mcp_allocation[1]-ess,mcp_allocation[2:k])
ratio <- sum(mcp_allocation)/sum(bmcp_allocation)
```

```
sample_ss <- bmcp_allocation*ratio


#optimal contrast for BMCP-Mod
BMCP_contrast<- optContr(models, doses=dose, S = diag(1/sample_ss))


sample <- matrix(NA, ncol = max(sample_ss), nrow = k)
post_mean <- matrix(NA, nrow = k, ncol = m)
post_sigma_sq <- post_mean
phi <- rep(0,m)
post_sample <- matrix(NA, nrow = n_iter, ncol = k)
Mean <- matrix(NA, ncol = m, nrow = M)
Sigma2 <- Mean


#sample generation
for(i in 1: k){
  if (i == 1)
  {
    ind <- sample(elements, replace = TRUE, size = sample_ss[i],
    prob = weights)
    for(j in 1: sample_ss[i]){
      z <- rnorm(n = 1, mean = mu00[ind[j]],
      sd = sqrt(sigma^2/n00[ind[j]]))
      sample[i,j] <- rnorm(n = 1, mean = z, sd = sigma)
    }
```

```
  }
  else{
    z <- rnorm(n = sample_ss[i], mean = mu0[i-1],
    sd = sqrt(sigma^2/n0[i-1]) )
    sample[i,1:sample_ss[i]] <- rnorm(n = sample_ss[i], mean = z,
    sd = sigma)
  }
}
sample
View(t(sample))
sample_mean <- rowMeans(sample, na.rm = TRUE)

#reshaping the data
sample <- data.frame(t(sample))
response <- c(sample$X1, sample$X2,sample$X3,sample$X4,sample$X5)
dose <- rep()
for(i in 1:k){
  dose <- append(dose, rep(i,length(sample$X1)))
}
dose = ifelse(dose==1,0,ifelse(dose==2,0.03,ifelse(dose==3,0.1,
ifelse(dose==4,0.33,1))))
sample_dataset <- data.frame(dose,response)
sample_data <- na.omit(sample_dataset)
```

```
#posterior mean and variance
for(i in 1:k){
  for(j in 1:m){
    if(i == 1){
      post_mean[i,j] <-  n00[j]*mu00[j] +
      sample_ss[i]*sample_mean[i]/ (n00[j] + sample_ss[i])
      post_sigma_sq[i,j] <- sigma^2/ (n00[j] + sample_ss[i])
    }
    else{
      post_mean[i,j] <- n0[i-1]*mu0[i-1] +
      sample_ss[i]*sample_mean[i]/ (n0[i-1] + sample_ss[i])
      post_sigma_sq[i,j] <- sigma^2/ (n0[i-1] + sample_ss[i])
    }
  }
}
post_mean
post_sigma_sq

#posterior weights
for(i in 1:m){
  z <- c(mu00[i],mu0)
  Sigma <- matrix(0, nrow=k, ncol = k)
  for(j in 1:k){
```

```
    if(j ==1)
      Sigma[j,j] <- sigma ^2/sample_ss[j] + sigma ^2/n00[i]
    else
      Sigma[j,j] <- sigma ^2/sample_ss[j] + sigma ^2/n0[j-1]
  }
  phi[i] <- dmvnorm(sample_mean, mean = z , sigma = Sigma)
}
post_weights <- weights*phi/sum(weights*phi); post_weights
sum(post_weights)

#posterior generation
p_ind <- sample(elements, replace = TRUE,
size = n_iter, prob = post_weights)
for(i in 1:n_iter){
  post_sample[i,] <- rmvnorm(1, mean = post_mean[,p_ind[i]],
  sigma = diag(post_sigma_sq[,p_ind[i]]))
}

#specifying the contrast
for(i in 1:M){
  for(j in 1:m){
  Mean[i,j] <- t(BMCP_contrast$contMat[,i])%*%post_mean[,j]
  Sigma2[i,j] <- sum(BMCP_contrast$contMat[,i]^2%*%
  diag(post_sigma_sq[,j]))
```

```
 }
}
Mean
Sigma2

#posterior probabilities
post_prob <- matrix(NA,nrow=M)
for(j in 1:M){
  post_prob[j,] <- post_weights[1]*(pnorm(0,mean =Mean[j,1],
  sd=sqrt(Sigma2[j,1]),lower.tail = FALSE))+post_weights[2]*
   (pnorm(0,mean =Mean[j,2], sd=sqrt(Sigma2[j,2]),
   lower.tail = FALSE))+post_weights[3]*(pnorm(0,mean =Mean[j,3],
   sd=sqrt(Sigma2[j,3]),lower.tail = FALSE))
}
pstar <- max(post_prob)

#critical Value
q <- MCTtest(dose, response, sample_data, models=models,
critV = TRUE, pVal = FALSE, alpha = 0.05)
critv <- pmvt(q$critVal[1])

#Proof of Concept
pstar > critv[1]
```

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