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博士論文

多變量迴歸模型之最適校準設計

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摘　要

本篇論文主要研究多反應變數迴歸模型在校準問題上的最適設計。眾所周知的校準問題是由一已知的反應值(或稱目標值)推論與此反應值相對應的未知控制變數的控制量，我們稱此控制量為校準點。一常見的作法是利用控制變數與反應變數的迴歸函數反求校準點。以此種方法求得的校準點的估計量稱為古典估計量。文獻上，已有許多討論校準問題的論文，但是與最適設計相關的論文卻相對較少，且都僅止於討論單反應變數的最適校準設計。在這篇論文裡，我們主要考慮的模型為一具有一個控制變數，但同時有多個具相關性的反應變數的線性迴歸模型。我們的主要目的是對一組給定的反應變數的目標值反求控制量的預測值時，可得到較佳估計校準點的最適校準設計。由於要達到各目標值的校準點可能互異，因此我們考慮的最適校準點為滿足最小化反應期望值與目標值差異的加權平方和的校準點。為了得到一個能準確的預測此控制量校準點的有效設計，我們選取最適校準設計的準則為能最小化校準點與它的估計量的差異的均方平均值的設計。在這個準則下，我們提出具有雙反應變數的簡單線性迴歸模型及二次迴歸模型的最適校準設計。

Optimal Designs for Calibrations in Multivariate Regression Models

by

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Optimal Designs for Calibrations in Multivariate Regression Models

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Abstract

In this dissertation we first consider a parallel linear model with correlated dual responses on a symmetric compact design region and construct locally optimal designs for estimating the location-shift parameter. These locally optimal designs are variant under linear transformation of the design space and depend on the correlation between the dual responses in an interesting and sensitive way.

Subsequently, minimax and maximin efficient designs for estimating the location-shift parameter are derived. A comparison of the behavior of efficiencies between the minimax and maximin efficient designs relative to locally optimal designs is also provided. Both minimax or maximin efficient designs have advantage in terms of estimating efficiencies in different situations.

Thirdly, we consider a linear regression model with a one-dimensional control variable x and an m-dimensional response variable $\mathbf{y} = (y_1, \cdots, y_m)$. The components of $\mathbf{y}$ are correlated with a known covariance matrix. The calibration problem discussed here is based on the assumed regression model. It is of interest to obtain a suitable estimation of the corresponding x for a given target $\mathbf{T} = (T_1, \cdots, T_m)$ on the expected responses. Due to the fact that there is more than one target value to be achieved in the multiresponse case, the m expected responses may meet their target values at different respective control values. Consideration includes the deviation of the expected response $E(y_i)$ from its corresponding target value T_i for each component and the optimal value of calibration point x, say x_0, is considered to be the one which minimizes the weighted sum of squares of such deviations within the range of

x. The objective of this study is to find a locally optimal design for estimating x_0, which minimizes the mean square error of the difference between x_0 and its estimator. It shows the optimality criterion is approximately equivalent to a c-criterion under certain conditions and explicit solutions with dual responses under linear and quadratic polynomial regressions are obtained.

Key words and phrases: Approximate design; Bioassay; C-criterion; Classical estimator; Efficiency; Equivalence theorem; Locally optimal design; Location-shift parameter; Maximin efficient design; Minimax design; Multivariate calibration; Prediction; Relative potency; Scalar optimal design.

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1

Introduction

In this dissertation optimal designs for calibrations in multiresponse regression models are our primary goal of investigation. The calibration problem has a long history receiving significant attention in statistics and other scientific disciplines. Both the design and analysis aspects of the calibration problem are of interest to experimenters and statisticians. The well-known problem of calibration is making inference about an unknown control value from a single observed response. A natural estimate of the control value is given by solving the regression function, which is called the classical estimate. In the past numerous literatures have focused on calibration problems, but not much have been investigated concerning optimality of designs. In this work, we consider a linear regression model with a one-dimensional control variable and a multi-dimensional response variable. The responses are considered to be correlated with a known covariance matrix. We are interested in making inverse prediction of the model for a given target on the expected responses. In order to find an efficient design for making accurate prediction, the optimality criterion has been chosen to minimize the mean square error of the difference between the control value and its estimator in this work.

At first we consider a bioassay experiment that measures a response from different doses of the standard and test preparations. There are many literatures in bioassays, see for example, Govindrajulu [19] and Kshirsagar and Yuan [25]. Design papers for general bioassays are relatively scarce and they include Buonaccorsi [7], Finney [17], Kshirsagar and Yuan [25], and Smith and Ridout [33]. As is often the case in bioassay experiments, the expected responses for the standard and test preparations are assumed to be simple linear parallel models relative to the logarithm of the dosage, see Finney [17] for example. Chai et al [8] and Kshirsagar and Yuan [25] were one of the few who addressed specific design issues for parallel line bioassays. Their interest, however, was on incomplete block designs, which is not the focus here.

The interest here is in estimating the potency of the test preparation relative to the standard, which by definition is the amount of the standard equivalent in effect to one unit of the test. This parameter is important because it is widely used to measure the location-shift between the standard and test preparations in parallel line assays. We follow Kiefer and Wolfowitz's [22] approach and focus on continuous designs. A continuous design is a probability measure with finite number of support points on a given compact design space. A main advantage of continuous designs is that they can be readily verified if they are optimum among all designs defined on the design space using equivalence theorems. Details of the continuous design framework and equivalence theorems are discussed in design monographs, see Fedorov [15] or Pukelsheim [30], for example.

We proposes optimal designs for the parallel line bioassay experiment when the responses from the standard and test preparations may be correlated. Such assumptions are realistic if observations come from each litter or observations are made from the same subjects under two experimental conditions. We provide closed form formulae of optimal designs for estimating the relative potency. Since some type of prior information concerning the relative potency is needed for the experiment designs, the optimal designs are called locally optimal designs.

To put the robustness of the designs into consideration to overcome the problem that the locally optimal designs depend on the unknown relative potency which may be quite sensitive if the prior knowledge departure from the true value is to consider other types of design criterion such as the minimax and maximin efficient criteria. The maximin efficient criterion has been introduced by Müller [27]. There have been some research related to minimax and maximin efficient designs, see for example, Dette and Sahm [14], Dette and Biedermann [12] and Dette and Melas [13], where their interests were mainly in nonlinear regression models with single response.

In this dissertation, closed form formulae for minimax and maximin efficient designs are provided for estimating the relative potency. A necessary and sufficient condition for the minimax design has been presented by Fedorov [16] with only an indication of the proof. A modified general equivalence theorem using a directional derivative approach can be found in Müller and Pázman [28]. The candidate designs are verified to be optimal through the corresponding equivalence theorem. A comparison of the efficiencies between minimax and maximin efficient designs is also provided.

Moreover, in drug-testing experiments a suitable design for dose-finding when both efficacy and toxicity responses are available is also arresting. We thus consider the calibration problem of a linear regression model with one control variable and multi-response variables. The responses are considered to be correlated with a known covariance matrix. It is of interest to obtain a suitable estimation of the corresponding control value for a given target on the expected responses.

Concerning the single response calibration problem, Ott and Myers [29], along with providing corresponding design problems, have discussed the estimation of the independent variable in a regression situation for a measured value of the dependent variable. Buonaccorsi [6] has examined the effects of the choice of designs on calibration in a simple linear regression model. Barlow, Mensing and Smiriga [2] have computed the optimal Bayes design for a calibration model. Bai and Huang [1] have discussed a consistent estimator for locating the maximizer of a non-parametric regression function.

Beside the single response calibration problem, the multiresponse calibration problem also arises in many applications. In Brown [5] the problem of calibration making inferences about an unknown explanatory variable from a single random observed response vector has been discussed. An example for determining the viscosity of the paint samples by using two measurements on certain optical properties of the samples have been described. In Chang et al.

[9] a real example concerning production of the shadow mask which affects the quality of screen image in a monitor or TV set is described, where one of the criteria to determine the fitness of a produced mask depends on whether two response variables, the size of the hole and the depth of the hole, meet the target values. It is of interest to find the optimal setting of the line speed, the input variable x. We therefore investigate in general the calibration design problems for multiresponse-univariate polynomial regression models in this dissertation.

In the following, Chapter 2 centers around the locally optimal designs for estimating the location-shift parameter of parallel models with dual responses. Minimax and maximin efficient designs for estimating the location-shift parameter in the previous chapter are studied in Chapter 3. In Chapter 4, results are presented for designing experiments in the estimation of control values for given target responses. An example discussed in Brown [5] is used to illustrate the procedure to exhibit the optimal calibration design.

2

Optimal Designs for Estimating the Location-shift Parameter of Parallel Models with Correlated Responses

This chapter considers a parallel linear model with correlated dual responses on a symmetric compact design region and construct locally optimal designs for estimating the location-shift parameter. The D-optimal designs for the additive model are invariant under linear transformation of the design space but locally optimal designs for estimating the location shift do not share this property. The latter optimal designs depend on the correlation between the dual responses in an interesting and sensitive way.

Key words and phrases: Approximate design; Bioassay; Locally optimal design; Location-shift parameter; potency.

2.1 Introduction

Consider a bioassay experiment that measures a response from different doses of the standard and test preparations. The interest is in estimating the potency of the test preparation relative to the standard, which by definition is the amount of the standard equivalent in effect to one unit of the test. Specifically, suppose that the dose interval of interest is $[a, b]$ and a dose from this interval is administered to an experimental unit. The response y at this dose level, d, is measured and its expectation under the standard preparation is $E(y_1|d) = F_1(d), \forall d \in [a, b]$, where F_1 is some known functional with unknown parameters. Suppose, as is often the case in bioassay experiments, the expected response for the test preparation is $E(y_2|d) = F_2(d) = F_1(\tau\, d),\ \forall d \in [a, b]$, and τ is an unknown constant representing the relative potency between the standard and test preparations.

It is common practice to assume the regression function $F_1(d)$ is linearly related to $x = \log(d)$, see Finney [17] for example. This implies

$$\begin{aligned} E(y_1|d) &= F(d) = \theta_0 + \theta_1 \log(d) = \theta_0 + \theta_1 x \\ E(y_2|d) &= F(\tau d) = \theta_0 + \theta_1(\log(d) + \log(\tau)) = \theta_0 + \theta_1(x - \mu), \end{aligned}$$

where $\mu = -\log(\tau)$. Therefore, these two simple linear models are parallel with common slope θ_1. The covariance matrix between the two responses from the standard and test preparations is

$$Cov(y_1, y_2) = \Sigma = \sigma^2((1-\rho)I_2 + \rho J_2),$$

where I_2 is the 2×2 identity matrix and J_2 is a 2×2 matrix of one's, and there is no loss in generality to assume that σ^2=1. We also assume throughout that all models in the paper satisfy the parallelism assumption. Some test procedures for testing the hypothesis of parallelism are given in Smith and Choi [34].

There is much research in bioassays, see for example, Govindrajulu [19] and Kshirsagar and Yuan [25]. Design papers for general bioassays are relatively scarce and they include Buonaccorsi [7], Finney [17], Kshirsagar and Yuan [25], and Smith and Ridout [33]. Chai et al [8] and Kshirsagar and Yuan [25] were one of the few who addressed specific design issues for parallel line bioassays. Their interest, however, was on incomplete block designs, which is not the focus here.

This paper proposes optimal designs for a parallel line bioassay experiment when the responses from the standard and test preparations may be correlated. Such assumptions are realistic if observations come from each litter or observations are made from the same subjects under two experimental conditions. We provide closed form formulae for optimal designs for estimating the relative potency.

We follow Kiefer and Wolfowitz's [22] approach and focus on continuous designs. A continuous design ξ is a probability measure with finite number of support points on a given compact design space. If the design has all its mass at the point $\mathbf{x}$, we denote the design by $\delta_{\mathbf{x}}$. A generic design on m

points is denoted by $\xi = w_1\delta_{\mathbf{x_1}} + w_2\delta_{\mathbf{x_2}} + \cdots + w_m\delta_{\mathbf{x_m}}$, where each $\mathbf{x_i}$ in the design space is weighted $w_i > 0$, and $\sum_{i=1}^{m} w_i = 1$. A main advantage of continuous designs is that they can be readily verified if they are optimum within all designs on the design space $\mathcal{X}$ using equivalence theorems. Details of the continuous design framework and equivalence theorems are discussed in design monographs, see Fedorov [15] or Pukelsheim [30], for example.

In the next section we discuss optimal designs for estimating the logarithm of the relative potency. This parameter is important because it is widely used to measure the location-shift between the standard and test preparations in parallel line assays. Section 2.3 provides an application and a discussion.

2.2 Location-shift parameter

Throughout we focus on the parallel model with dose as the control variable and the dose level x_1 for the standard preparation and the dose level x_2 for the test preparation may be different,

$$\begin{cases} E(y_1|x_1) = \theta_{01} + \theta_1 x_1 \\ E(y_2|x_2) = \theta_{02} + \theta_1 x_2 = \theta_{01} + \theta_1(x_2 - \mu). \end{cases} \tag{2.1}$$

We assume that after appropriate scaling, $x_i \in \mathcal{X}_i = [-1, 1]$, $i = 1, 2$. When $\rho = 0$, the two responses are uncorrelated and they do not have to be observed in pairs. We may thus relax our designs to include different number of observations, say n_1, n_2 for the two responses respectively. In this case, different designs, ξ_1 and ξ_2, can be assigned to each response. Designs ξ for such a setup can be expressed as

$$\xi = p_1\xi_1 + p_2\xi_2, \tag{2.2}$$

where $p_1 = n_1/n, p_2 = n_2/n, n = n_1 + n_2$, and $\xi_i, i = 1, 2$, represents the design for the ith response on $[-1, 1]$.

If the dual responses from different preparations are observed in paired for different doses. The dual responses are assumed to be correlated, that is $\rho \neq 0$. We have for design point $\mathbf{x} = (x_1, x_2) \in \mathcal{X} = \mathcal{X}_1 \times \mathcal{X}_2 = [-1, 1]^2$. A design in this case is denoted by

$$\xi = \sum_{i=1}^{m} w_i \delta_{\mathbf{x}_i}, \tag{2.3}$$

where $\mathbf{x}_i \in \mathcal{X}$.

In this section, we consider optimal designs for estimating the location-shift parameter μ in model (2.1). The location-shift parameter μ can be expressed as

$$\mu = \frac{\theta_{01} - \theta_{02}}{\theta_1} = \frac{l_1'\theta}{l_2'\theta} = \frac{\beta_1}{\beta_2},$$

where $\theta = (\theta_{01} \quad \theta_{02} \quad \theta_1)'$, $l_1 = (1 \quad -1 \quad 0)'$, $l_2 = (0 \quad 0 \quad 1)'$, $\beta_1 = l_1'\theta$ and $\beta_2 = l_2'\theta$.

Let $f_1(x_1) = (1 \quad 0 \quad x_1)'$ and $f_2(x_2) = (0 \quad 1 \quad x_2)'$, the information matrix for design ξ_i is

$$M(\xi_i) = \int_{\mathcal{X}_i} f_i(x_i) f_i(x_i)' d\xi_i(x_i),$$

$i = 1, 2$. When $\rho = 0$, we measure the worth of a design ξ as defined in (2.2) by its information matrix

$$M(\xi) \;\; = \;\; p_1 M_1(\xi_1) + p_2 M_2(\xi_2)$$

$$= \begin{pmatrix} p_1 & 0 & p_1c_1 \\ 0 & p_2 & p_2d_1 \\ p_1c_1 & p_2d_1 & p_1c_2 + p_2d_2 \end{pmatrix}, \tag{2.4}$$

where $c_i = \int_{\mathcal{X}_1} {x_1}^i d\xi_1$, $d_i = \int_{\mathcal{X}_2} {x_2}^i d\xi_2$, $i = 1, 2$.

When $\rho \neq 0$, the regression function $F(\mathbf{x})$ of θ is $F(\mathbf{x}) = (\, I_2 \quad X \,)'$, where matrix $X = (\, x_1 \quad x_2 \,)'$. The information matrix of a design as defined in (2.3) is

$$M(\xi) = \int_{\mathcal{X}} F(\mathbf{x})\Sigma^{-1}F(\mathbf{x})'d\xi(\mathbf{x}), \tag{2.5}$$

where Σ is the covariance matrix for the dual responses. It is straightforward to verify that

$$M(\xi) = \frac{1}{1-\rho^2}\begin{pmatrix} 1 & -\rho & c_1 - \rho d_1 \\ -\rho & 1 & d_1 - \rho c_1 \\ c_1 - \rho d_1 & d_1 - \rho c_1 & c_2 + d_2 - 2\rho\gamma \end{pmatrix}, \tag{2.6}$$

where $c_i = \int_{\mathcal{X}} x_1^i d\xi$, $d_i = \int_{\mathcal{X}} x_2^i d\xi, i = 1, 2$, and $\gamma = \int_{\mathcal{X}} x_1 x_2 d\xi$.

Letting $\beta = (\, \beta_1 \quad \beta_2 \,)'$ and $L' = (\, l_1 \quad l_2 \,)$, we have the covariance matrix of the estimator of β as follows

$$\text{Cov}(\hat{\beta}) \approx \begin{pmatrix} l_1' M(\xi)^{-1} l_1 & l_1' M(\xi)^{-1} l_2 \\ l_2' M(\xi)^{-1} l_1 & l_2' M(\xi)^{-1} l_2 \end{pmatrix} = LM(\xi)^{-1}L',$$

By McDonald and Studden [26], the approximate variance of the ratio of the two estimated parameters is

$$\text{Var}(\hat{\beta}_1/\hat{\beta}_2) \approx (\, h_1 \quad h_2 \,)\, LM(\xi)^{-1}L'\, (\, h_1 \quad h_2 \,)',$$

where $h_i = \partial h/\partial \beta_i, i = 1, 2$, with $h(\beta_1, \beta_2) = \beta_1/\beta_2$. In our case, we have

$$\begin{aligned} \text{Var}(\hat{\beta}_1/\hat{\beta}_2) &\approx \frac{1}{\beta_2^2}(\, 1 \quad -\beta_1/\beta_2 \,)\, LM(\xi)^{-1}L'\, (\, 1 \quad -\beta_1/\beta_2 \,)' \\ &= \frac{1}{\beta_2^2} c' M(\xi)^{-1} c, \end{aligned}$$

with $c = (\, 1 \quad -1 \quad -\mu\,)'$. This means that the best design for estimating μ is a locally c-optimal design. Here and throughout the rest of the paper, we construct locally c-optimal designs on the design space $\mathcal{X}$. This means that the dosage levels for both preparations have to be on the logarithmic scale and appropriately standardized. Optimal designs for estimating μ on other design spaces will have to be reconstructed because, unlike D-optimal designs, these designs are not invariant under linear transformation on the design space.

Theorems 2.2.1 and 2.2.2 below present locally optimal designs for estimating μ when the two responses are uncorrelated. Recall that $c_i = \int_{\mathcal{X}_1} x^i d\xi_1$ and $d_i = \int_{\mathcal{X}_2} x^i d\xi_2$. Many of the optimal designs found in the following are by first restricting attention to a subclass of designs and among these designs, find the smallest non-trivial lower bound for the determinant of the inverse of the information matrix, or the variance of the estimate of interest. The optimal design is then found by constructing a design that attains the lower bound.

Theorem 2.2.1 *Suppose model (2.1) holds, $\rho = 0$, $|\mu| \leq 2$ and ξ_1^* and ξ_2^* are two designs supported on $\{-1, 1\}$. The design $\xi^* = \frac{1}{2}\xi_1^* + \frac{1}{2}\xi_2^*$ is a locally optimal design for estimating μ provided $d_1 - c_1 = \mu$.*

Proof. When $\rho = 0$, a direct calculation shows

$$M(\xi) = \begin{pmatrix} p_1 & 0 & p_1 c_1 \\ 0 & p_2 & p_2 d_1 \\ p_1 c_1 & p_2 d_1 & p_1 c_2 + p_2 d_2 \end{pmatrix}.$$

Recalling that $c = (1, -1, -\mu)'$, we have

$$c'M(\xi)^{-1}c = \frac{1}{p_1} + \frac{1}{p_2} + \frac{(\mu - (d_1 - c_1))^2}{p_1c_2 + p_2d_2 - p_1c_1^2 - p_2d_1^2}. \tag{2.7}$$

For any two designs ξ_1^* and ξ_2^* on $[-1, 1]$, we have $|d_1 - c_1| \leq 2$ and $\frac{1}{p_1} + \frac{1}{p_2} \geq 4$. This means that from (2.7), we can find a design ξ^* such that $p_1 = p_2 = \frac{1}{2}$ and $\mu = d_1 - c_1$.

Theorem 2.2.2 *Suppose model (2.1) holds, $\rho = 0$ and $|\mu| > 2$. If designs ξ_1^* and ξ_2^* are supported on $\{-1, 1\}$ and if $\xi^* = p_1\xi_1^* + p_2\xi_2^*$ satisfies: (i) $\frac{1}{|\mu|} < p_1 < 1 - \frac{1}{|\mu|}$, and (ii) $-\mu c_1 p_1 = \mu d_1 p_2 = 1$, where $p_2 = 1 - p_1$, then ξ^* is a locally optimal design for estimating μ. Moreover, $c^T M(\xi^*)^{-1}c = \mu^2$.*

Proof. It is straightforward to verify from (2.7) that

$$c'M(\xi)^{-1}c \geq \frac{1}{p_1} + \frac{1}{p_2} + \frac{(\mu - (d_1 - c_1))^2}{1 - p_1c_1^2 - p_2d_1^2},$$

with equality if the design ξ is supported on $\{-1, 1\}$. In particular, equality is attained for the optimal designs ξ_1^* and ξ_2^*. For $\frac{1}{|\mu|} < p_1 < 1 - \frac{1}{|\mu|}$, define

$$h(p_1, c_1, d_1) = \frac{1}{p_1} + \frac{1}{p_2} + \frac{(\mu - (d_1 - c_1))^2}{1 - p_1c_1^2 - p_2d_1^2}.$$

If we take partial derivatives of the function h with respect to c_1 and d_1 and set them equal to 0, we have

$$\mu = [d_1(p_1c_1 + p_2d_1) - 1]/(p_1c_1) = [1 - c_1(p_1c_1 + p_2d_1)]/(p_2d_1).$$

It follows that $p_1c_1 + p_2d_1 = (p_1c_1 + p_2d_1)(p_1c_1^2 + p_2d_1^2)$ and because $p_1c_1^2 + p_2d_1^2 \neq 1$, we must have $p_1c_1 + p_2d_1 = 0$. By assumption, it follows that

$-\mu p_1 c_1 = 1 = \mu p_2 d_1$ and the optimal design ξ^* satisfies $c' M(\xi^*)^{-1} c = h(p_1, \frac{-1}{\mu p_1}, \frac{1}{\mu p_2}) = \mu^2$.

Example 2. Suppose model (2.1) holds, $\rho = 0$ and $\mu = 3$. If we take an equal number of observations from the test and standard preparations, i.e. $p_1 = p_2 = \frac{1}{2}$, and use designs $\xi_1^* = \frac{5}{6}\delta_{-1} + \frac{1}{6}\delta_1$ for the standard preparation, $\xi_2^* = \frac{1}{6}\delta_{-1} + \frac{5}{6}\delta_1$ for the test preparation, we have $\frac{1}{3} < p_1 < \frac{2}{3}$, $c_1 = -\frac{2}{3}$,$d_1 = \frac{2}{3}$, and condition (ii) of the theorem holds. It follows that the average of these two designs, i.e. the design equally supported at ± 1 is locally optimal for estimating μ.

Table 2.1 and Table 2.2 display selected optimal designs constructed from Theorems 2.2.1 and 2.2.2. For example, in Table 2.1, the third row shows that when $\mu = -0.5$, the designs for the two preparations are $\xi_1^* = \delta_1$ and $\xi_2^* = 0.25\delta_{-1} + 0.75\delta_1$. In addition, they have the property that $d_1 - c_1 = 0.5 - 1 = -0.5 = \mu$ and consequently, the design $\xi^* = \frac{1}{2}\xi_1^* + \frac{1}{2}\xi_2^*$ is locally optimal for estimating μ. Alternatively, if we take $\xi_1^* = 0.75\delta_{-1} + 0.25\delta_1$ and $\xi_2^* = \delta_{-1}$ as shown in the fourth row, the design $\xi^* = \frac{1}{2}\xi_1^* + \frac{1}{2}\xi_2^*$ also satisfies $d_1 - c_1 = -1 - (-0.5) = -0.5 = \mu$ and hence is also locally optimal for estimating μ.

The next three results concern correlated responses from the test and standard preparations with $\rho \neq 0$ and $|\rho| < 1$.

Table 2.1: The optimal design ξ^* for model (2.1) with $\Sigma = I_2$ and a given μ, $|\mu| \leq 2$.

	Design points of ξ_1^*		Design points of ξ_2^*	
μ	-1	1	-1	1
-0.5	0.000	0.500	0.125	0.375
	0.375	0.125	0.500	0.000
0.0	0.500	0.000	0.500	0.000
	0.000	0.500	0.000	0.500
0.5	0.500	0.000	0.375	0.125
	0.125	0.375	0.000	0.500
1.0	0.500	0.000	0.250	0.250
	0.250	0.250	0.000	0.500
1.5	0.500	0.000	0.125	0.375
	0.375	0.125	0.000	0.500
2.0	0.500	0.000	0.000	0.500
	0.500	0.000	0.000	0.500

Theorem 2.2.3 *Suppose model (2.1) holds, $0 < |\rho| < 1$ and $|\mu| \leq 2$. If a design ξ^* satisfies $d_1 - c_1 = \mu$, ξ^* is a locally optimal design for estimating μ.*

Proof. From (2.6), it is straightforward to calculate that

$$c' M(\xi)^{-1} c = 2(1-\rho) + \frac{(1-\rho^2)(\mu - (d_1 - c_1))^2}{c_2 + d_2 - 2\rho\gamma - c_1^2 - d_1^2 + 2c_1 d_1 \rho}. \tag{2.8}$$

Table 2.2: The optimal design ξ^* for model (2.1) with $\Sigma = I_2$ and a given μ, $|\mu| > 2$.

	Design points of ξ_1^*		Design points of ξ_2^*	
μ	-1	1	-1	1
2.5	0.500	0.100	0.000	0.400
	0.400	0.000	0.100	0.500
3.0	0.500	0.167	0.000	0.333
	0.333	0.000	0.167	0.500
4.0	0.500	0.250	0.000	0.250
	0.250	0.000	0.250	0.500
5.0	0.500	0.300	0.000	0.200
	0.200	0.000	0.300	0.500

If $|\mu| \leq 2$, we observe that

$$\begin{aligned} & (c_2 + d_2 - 2\gamma\rho) - (c_1^2 + d_1^2 - 2c_1 d_1 \rho) \\ = & \int (\, x_1 \quad x_2 \,)\, \Sigma^{-1} (\, x_1 \quad x_2 \,)' \, d\xi - (\, c_1 \quad d_1 \,)\, \Sigma^{-1} (\, c_1 \quad d_1 \,)' \\ = & \int (\, \tilde{x}_1 \quad \tilde{x}_2 \,)\, \Sigma^{-1} (\, \tilde{x}_1 \quad \tilde{x}_2 \,)' \, d\xi > 0, \end{aligned}$$

where $\tilde{x}_i = x_i - \int x_i d\xi, i = 1, 2$. It follows that $c' M(\xi)^{-1} c \geq 2(1 - \rho)$, and equality holds if $d_1 - c_1 = \mu$. The desired result follows.

Theorem 2.2.4 *Suppose model (2.1) holds,* $0 < \rho < 1$ *and* $|\mu| > 2$. *The design* $\xi^* = (\frac{1}{2} + \frac{1}{\mu})\delta_{(1,-1)} + (\frac{1}{2} - \frac{1}{\mu})\delta_{(-1,1)}$ *is a locally optimal design for estimating* μ.

Proof. From the general expression of $c'M(\xi)^{-1}c$ in (2.8), we have

$$\begin{aligned} c'M(\xi)^{-1}c &\geq 2(1-\rho) + (1-\rho^2)\frac{(\mu-(d_1-c_1))^2}{2-2\rho\gamma-c_1^2-d_1^2+2c_1d_1\rho} \\ &= 2(1-\rho)+(1-\rho^2)g(c_1,d_1,\gamma), \end{aligned}$$

with equality if ξ is supported on $(-1,-1)$, $(-1,1)$, $(1,-1)$, and $(1,1)$. Now we want to find designs with c_1, d_1 that minimize $g(c_1,d_1,\gamma)$. For fixed γ and ρ, we first take partial derivatives of $g(c_1,d_1,\gamma)$ with respect to c_1, d_1, and set them to 0. A straightforward argument shows the optimal design must have $c_1 = -d_1$. Under this constraint, let

$$h(d_1,\gamma) = g(-d_1,d_1,\gamma) = \frac{(\mu-2d_1)^2}{2-2\rho\gamma-(2d_1^2+2\rho d_1^2)} \tag{2.9}$$

and one may directly verify that $d_1^* = \frac{2(1-\rho\gamma)}{\mu(1+\rho)}$ minimizes the function $h(d_1,\gamma)$ because $\frac{\partial^2 h}{\partial d_1^2} = \frac{(1+\rho)^2\mu^4}{(1-\rho\gamma)^2(-4+4\rho\gamma+\mu^2+\rho\mu^2)} > 0$ when $\gamma \geq -1 > \frac{4-\mu^2(1+\rho)}{4\rho}$. Hence with the additional condition that $\gamma = -1$, $h(d_1^*,\gamma)$ attains its minimum value. Consequently, the locally optimal design for estimating μ is $\xi^* = (1/2+1/\mu)\delta_{(1,-1)} + (1/2-1/\mu)\delta_{(-1,1)}$ because it has the property that $c_1 = -d_1 = -2/\mu$ and $\gamma = -1$.

The next result allows us to construct locally optimal design when $|\mu| > 2$ and $-1 < \rho < 0$. The proof is more complicated and is deferred to the Appendix.

Theorem 2.2.5 *Suppose model (2.1) holds, $-1 < \rho < 0$ and $|\mu| > 2$. Consider a design of the form $\xi = w_1\delta_{(-1,-1)} + w_2\delta_{(-1,1)} + w_3\delta_{(1,-1)} + w_4\delta_{(1,1)}$.*

The design ξ^* is a locally optimal design for estimating μ if

(i) $w_1 = w_4 = \frac{\mu-2}{2(\mu+\mu\rho-2\rho)}$, $w_2 = 1-2w_1$ *and* $w_3 = 0$ *provided* $2 < \mu \leq 2-2/\rho$,

(ii) $w_1 = w_4 = \frac{\mu+2}{2(\mu+\mu\rho+2\rho)}$, $w_2 = 0$ *and* $w_3 = 1 - 2w_1$ *provided* $-2+2/\rho \leq \mu < -2$,

(iii) $w_1 = w_4 = 1/2$ *and* $w_2 = w_3 = 0$ *provided* $|\mu| > 2 - 2/\rho$.

Note that the optimal design has at most three design points in each case.

2.3 An application and discussions

Darby [11] analyzed a data set on the assay of the antibiotic tobramycin where the same levels of dose were used in both the standard and test preparations. The range of the variable x (logdose) in the study was between -1.8 and -3, which is not symmetric about 0. However, the c-optimal design on the interval $[-3, -1.8]$ for estimating μ can still be found by applying results in Section 2.2. In Theorem 2.2.1, we have shown that if the first moments c_1 and d_1 of the design satisfy $d_1 - c_1 = \mu$, then the design is optimal for estimating μ. In this assay, one may verify that c_1 and d_1 are both inside the range $[-3, -1.8]$; in fact, $-1.2 \leq d_1 - c_1 \leq 1.2$. If it is known from prior experience that the location-shift parameter μ is approximately zero, we would be interested in designs such that the design points on the test and standard preparations are the same and that $d_1 - c_1 = 0$ approximately. Such designs are optimal or nearly optimal for estimating μ by Theorem 2.2.1. Moreover, as long as μ is inside the interval $[-1.2, 1.2]$, any design that satisfies $d_1 - c_1 = \mu$ is c-optimal. If $\rho \neq 0$ and μ exceeds the maximum possible values of $d_1 - c_1$, the design problem will have to be specifically worked out. This is a drawback of designs that lack invariance property under a linear change of the design space. D-optimal designs have the invariance property and so they can be constructed on any interval once the optimal design is worked out on the interval $[-1, 1]$.

We note that the information matrices for the optimal designs in Theorem 2.2.3 are actually non-singular even though they have only two support points. This is because under the given bivariate structure, both responses were observed at two levels -1 and 1 of the dose variables x_1 and x_2 and the common slope parameter for the parallel model can be estimated with information from both responses. The nonsingularity of the other information matrices of the optimal designs could be similarly explained.

There are other design issues for the parallel line model not yet addressed here. First, we focused only on symmetrical design spaces; occasionally a non-symmetrical design space is used, see Kent-Jones and Meiklejohn [21] for example. Second, we have assumed the variances of the responses from both preparations are equal. If these variances are unequal, the locally optimal designs found here may not apply. Moreover if the assumption of parallelism of the two regression functions needs to be examined beforehand, the T-optimal design criterion for discriminating between two rival multiresponse models used in Ucinski and Bogacka [35] may also be considered. Although under our model, the results are relatively simple and therefore are not discussed further here. Third, if the researcher is primarily interested to estimate μ but would also like to have information for the remaining parameters, or concerned with both discrimination of models and estimation at the same time, multiple objective designs may be considered, see Cook and Wong [10] and the many references in Wong [37] for more details. Finally, optimal designs for estimating the relative potencies with more than two responses will be discussed in the future.

2.4 Appendix

2.4.1 Proof of Theorem 2.2.5

The following Lemmas are needed for the proof of Theorem 2.2.5, which deals with the case when the dual responses are negatively correlated and μ is large in magnitude. It is helpful to recall from Theorem 2.2.4 that an optimal design for estimating μ on $\mathcal{X}$ must satisfy $c_1 = -d_1$. Accordingly, we focus on designs of the form, $\xi = w_1\delta_{(-1,-1)} + w_2\delta_{(-1,1)} + w_3\delta_{(1,-1)} + w_1\delta_{(1,1)}$.

Lemma 2.4.1. Suppose model (2.1) holds, $-1 < \rho < 0$ and $\mu > 2$. If the design $\xi = w_1\delta_{(-1,-1)} + w_2\delta_{(-1,1)} + w_3\delta_{(1,-1)} + w_1\delta_{(1,1)}$ satisfies $w_2 + w_3 = \alpha$, where α is a fixed constant, and $0 \le \alpha < \frac{2-2\rho}{\mu+\mu\rho-4\rho}$, the design $\xi^* = w_1\delta_{(-1,-1)} + \alpha\delta_{(-1,1)} + w_1\delta_{(1,1)}$ with $w_1 = (1-\alpha)/2$ minimizes $c^T M(\xi)^{-1} c$.

Proof. Since α is fixed, we have $d_1 = \alpha - 2w_3$ and $\gamma = 1 - 2\alpha$. The function

$h(d_1, \gamma)$ in (2.9) can be rewritten as

$$\begin{aligned} h_1(w_3;\alpha) &= h(\alpha - 2w_3, 1-2\alpha) \\ &= \frac{(\mu - 2\alpha + 4w_3)^2}{2 - 2\rho(1-2\alpha) - 2(1+\rho)(\alpha - 2w_3)^2}. \end{aligned} \tag{2.10}$$

It is easy to verify that the derivative of $h_1(w_3;\alpha)$ is

$$\begin{aligned} & \dot{h}_1(w_3;\alpha) \\ = \; & \frac{2(\mu + 4w_3 - 2\alpha)(2 - \alpha\mu + 2\mu w_3 - 2\rho + 4\alpha\rho - \alpha\mu\rho + 2\mu w_3\rho)}{(-1 + \alpha^2 - 4\alpha w_3 + 4w_3^2 + \rho - 2\alpha\rho + \alpha^2\rho - 4\alpha w_3\rho + 4w_3^2\rho)^2} \\ \geq \; & \frac{2(\mu - 2\alpha)(2 - \alpha\mu - 2\rho + 4\alpha\rho - \alpha\mu\rho)}{(-1 + \alpha^2 - 4\alpha w_3 + 4w_3^2 + \rho - 2\alpha\rho + \alpha^2\rho - 4\alpha w_3\rho + 4w_3^2\rho)^2} \\ > \; & 0 \end{aligned} \tag{2.11}$$

for $0 \leq w_3 \leq \alpha$ and $0 \leq \alpha < \frac{2-2\rho}{\mu+\mu\rho-4\rho}$. Thus $h_1(w_3;\alpha)$ is increasing in $[0, \alpha]$ and the minimum of $h_1(w_3;\alpha)$ occurs when $w_3 = 0$.

Lemma 2.4.2. Suppose model (2.1) holds, $-1 < \rho < 0$ and $\mu > 2$. Suppose $\xi = w_1\delta_{(-1,-1)} + w_2\delta_{(-1,1)} + w_1\delta_{(1,1)}$ satisfies $0 \leq w_2 \leq \frac{2-2\rho}{\mu+\mu\rho-4\rho}$ and $w_1 = (1-w_2)/2$.

(i) If $2 < \mu \leq 2-2/\rho$, the design ξ^* with $w_1 = \frac{\mu-2}{2(\mu+\mu\rho-2\rho)}$ and $w_2 = \frac{\mu\rho-2\rho+2}{\mu+\mu\rho-2\rho}$ minimizes $c'M(\xi)^{-1}c$.

(ii) If $\mu > 2-2/\rho$, the design ξ^* with $w_1 = 1/2$ and $w_2 = 0$ minimizes $c'M(\xi)^{-1}c$.

Proof. Consider the design $\xi = w_1\delta_{(-1,-1)} + w_2\delta_{(-1,1)} + w_1\delta_{(1,1)}$ with $d_1 = w_2$ and $\gamma = 1 - 2w_2$. The function $h(d_1, \gamma)$ in (2.9) becomes

$$\begin{aligned} h_2(w_2) &= h(w_2, 1-2w_2) \\ &= \frac{(\mu - 2w_2)^2}{2 - 2\rho(1-2w_2) - 2(1+\rho)w_2^2} \end{aligned} \tag{2.12}$$

and it is straightforward to verify that $w_2^* = \frac{\mu\rho-2\rho+2}{\mu+\mu\rho-2\rho}$ is a critical number of $h_2(w_2)$ in interval $[0, \frac{2-2\rho}{\mu+\mu\rho-4\rho}]$ such that the second derivative $\ddot{h}_2(w_2^*) = \frac{(\mu-2\rho+\mu\rho)^4}{(\mu-2)(2+\mu-2\rho+\mu\rho)}$ is positive. The first part of the theorem is proved. The second part of the theorem follows because when $\mu > 2-2/\rho$, the derivative of $h_2(w_2)$ is positive for all $w_2 \in [0, \frac{2-2\rho}{\mu+\mu\rho-4\rho}]$. Therefore, $w_2^* = 0$ minimizes $h_2(w_2)$.

Lemma 2.4.3. Suppose model (2.1) holds, $-1 < \rho < 0$ and $\mu > 2$. Suppose the design $\xi = w_1\delta_{(-1,-1)} + w_2\delta_{(-1,1)} + w_3\delta_{(1,-1)} + w_1\delta_{(1,1)}$ satisfies $w_2+w_3 = \alpha$, α is a fixed constant and $\frac{2-2\rho}{\mu+\mu\rho-4\rho} \leq \alpha \leq 1$. Then the design $\xi^* = w_1\delta_{(-1,-1)} + (\alpha - w_3^*)\delta_{(-1,1)} + w_3^*\delta_{(1,-1)} + w_1\delta_{(1,1)}$ with $w_3^* = \frac{\mu(1+\rho)\alpha-4\rho\alpha-2+2\rho}{2\mu(1+\rho)}$ and $w_1 = (1-\alpha)/2$ minimizes $c'M(\xi)^{-1}c$.

Proof. Direct calculus shows that the restriction $\alpha > \frac{2-2\rho}{\mu+\mu\rho-4\rho}$ on the derivative of $h_1(w_3;\alpha)$ in (2.11) implies that

$$w_3^* = \frac{\mu(1+\rho)\alpha - 4\rho\alpha - 2 + 2\rho}{2\mu(1+\rho)}$$

and satisfies $\dot{h}_1(w_3^*;\alpha) = 0$ and

$$\ddot{h}_1(w_3^*;\alpha) = \frac{4\mu^4(1+\rho)^2}{(1-\rho+2\alpha\rho)^2(\mu^2+4\rho-8\alpha\rho+\mu^2\rho-4)} > 0.$$

The lemma is proved.

Proof of Theorem 2.2.5 Consider $\mu > 2$. By Lemmas 2.4.1 to 2.4.3, we only need to show that $h_1(w_3^*;\alpha)$ in (2.10) and $h_2(w_2^*)$ in (2.12) satisfy $h_1(w_3^*;\alpha) > h_2(w_2^*)$ for all α in the range $\frac{2-2\rho}{\mu+\mu\rho-4\rho} \leq \alpha \leq 1$. Additional calculation shows that if $2 < \mu \leq 2 - 2/\rho$,

$$\begin{aligned}
& h_1(w_3^*;\alpha) - h_2(w_2^*) \\
= \;& \frac{-4+\mu^2+4\rho-8\alpha\rho+\mu^2\rho}{2(1+\rho)(1-\rho+2\alpha\rho)} - \frac{1}{2}(\mu-2)(2+\mu-2\rho+\mu\rho) \\
> \;& (\mu-2)\rho^2(2+\mu-2\rho+\mu\rho)/(2(1-\rho^2)) > 0,
\end{aligned}$$

and if $\mu > 2 - 2/\rho$, we have

$$\begin{aligned}
& h_1(w_3^*;\alpha) - h_2(w_2^*) \\
= \;& \frac{-4+\mu^2+4\rho-8\alpha\rho+\mu^2\rho}{2(1+\rho)(1-\rho+2\alpha\rho)} - \frac{\mu^2}{2-2\rho} \\
> \;& \frac{2(-\mu\rho+\rho-1)}{(1-\rho)(1+\rho)} > 0.
\end{aligned}$$

Hence inequality $h_1(w_3^*;\alpha) > h_2(w_2^*)$ holds for $\mu > 2$. Thus parts (i) and (ii) of the theorem are proved. The remaining parts of the theorem can be proved analogously by considering the case when μ is less than -2.

3

Minimax and Maximin Efficient Designs for Estimating the Location-shift Parameter of Parallel Models with Dual Response

In this chapter minimax designs and maximin efficient designs for estimating the location-shift parameter of a parallel linear model with correlated dual responses over a symmetric compact design region are derived. A comparison of the behavior of efficiencies between the minimax and maximin efficient designs relative to locally optimal designs is also provided. Both minimax or maximin efficient designs have advantage in terms of estimating efficiencies in different situations.

Key words and phrases: Bioassay; Efficiency; Equivalence theorem; Locally optimal design; Location-shift parameter; Maximin efficient design; Minimax design; Relative potency.

3.1 Introduction

Consider a bioassay experiment designed to estimate the relative potency of a test preparation relative to a standard. By definition, the relative potency is the amount of the standard equivalent of one effective unit. In a bioassay experiment, suppose that a dose of a standard preparation is chosen and administered to an experimental unit and the response y_1 at this dose level, d, is measured. In the bioassay, a commonly used function to describe the relation between the dose and the expected response is $E(Y_1|d) = \theta_0 + \theta_1 \log(d)$. The expected response for the test preparation is $E(Y_2|d) = \theta_0 + \theta_1 \log(\tau d)$, where τ, which represents the relative potency is unknown. Finney [17] and Brown [4] have provided a more detailed description.

Let $x_i = \log(d_i) \in \mathcal{X}_i \subset \mathbb{R}$, $i = 1, 2$, be the dosage levels for the standard and the test preparations on logarithmic scale respectively, the expected responses can be expressed as

$$\begin{aligned} E(Y_1|d_1) &= \theta_{01} + \theta_1 x_1; \\ E(Y_2|d_2) &= \theta_{02} + \theta_1 x_2 = \theta_{01} + \theta_1(x_2 - \mu), \end{aligned} \tag{3.1}$$

where $\mu = -\log(\tau) \in B \subset \mathbb{R}$ denotes the location-shift parameter. In such a design, if all the responses are uncorrelated, we may assign a p_1 proportion of responses to the standard preparation and a p_2 proportion to the test, in which case, a design point is denoted by $x,\ x \in \mathcal{X}_1 \cup \mathcal{X}_2$. On the other hand, if dual responses are observed from two preparations with different doses d_1 and d_2, a design point is denoted by $\mathbf{x} = (x_1, x_2)$, $\mathbf{x} \in \mathcal{X}_1 \times \mathcal{X}_2$. If the dual responses are correlated, then the covariance matrix between the dual responses is denoted by $\Sigma = \mathrm{Cov}(Y_1, Y_2) = \sigma^2((1-\rho)I_2 + \rho J_2)$, where I_2 is the 2×2 identity matrix and J_2 is a 2×2 matrix of one's, and without loss of generality, assume that σ^2=1. Throughout, we assume that $\mathcal{X}_i = [-1, 1]$, $i = 1, 2$ and the unknown parameter vector $\tilde{\theta} = (\theta_{01}, \theta_{02}, \theta_1)$.

The form of the dose-response relationship assumed above has been discussed by Finney [17] and Gaines Das [18] with further discussions of the statistical issues concerning the design and analysis of parallel line assays. Huang et al. [20] discussed the situation where the design aspects under the assumptions that the dual responses may be correlated, and provided locally optimal designs for estimating the location-shift parameter μ. An optimal design is called "locally optimal", when some type of prior information concerning the parameter values is needed for the design of an experiment. Other types of design criterion such as the maximin efficient criterion has been introduced by Müller [27], which put the robustness of the designs into consideration to overcome the μ-dependence of the locally optimal design. There has been some research related to minimax and maximin efficient designs, see for example, Dette and Sahm [14], Dette and Biedermann [12] and Dette and Melas [13], where their interest was mainly in nonlinear regression models with single response. In this work, closed form formulae for two types of optimal designs are provided for estimating μ: the minimax design and the maximin efficient design. The interesting point of this work is that both minimax and maximin efficient designs do not depend on the specific value of the correlation coefficient ρ, when ρ is positive, but they are highly dependent on ρ, when ρ is negative. Even more, the maximin efficient designs do not depend on the range of μ when the responses are uncorrelated or the dual responses are positively correlated. The efficiency performances of the two designs relative to the locally optimal design also appear in an attractive manner.

In the next section, we introduce the definitions of the minimax and maximin efficient designs, and the corresponding equivalence theorem. A necessary and sufficient condition for the minimax design has been presented by Fedorov [16] with only an indication of the proof. Wong [36] provided a unified approach for the construction of minimax design. A modified general equivalence theorem using a directional derivative approach can be found in Müller and Pázman [28]. Sections 3.3 and 3.4 give the minimax and maximin efficient designs for various ranges of possible values for the unknown parameter respectively. A comparison of the efficiencies between the two designs is also provided in Section 3.4. Section 3.5 ends with discussion.

3.2 Preliminaries

A design measure ξ with finite support points on a compact design space $\mathcal{T}$ is denoted by $\xi = \sum_{i=1}^{m} w_i \delta_{\mathbf{t}_i}$, where $\delta_{\mathbf{t}_i}$ denotes the one-point measure on $\mathbf{t}_i$, each $\mathbf{t}_i \in \mathcal{T}$ is weighted $w_i > 0$ and $\sum_{i=1}^{m} w_i = 1$. Let Ξ be the set of all possible designs on $\mathcal{T}$. When designs are chosen by the criterion, $\Psi(\gamma, \xi) : \Gamma \times \Xi \longrightarrow R$, which under circumstances depends on some parameter γ, and if $\Psi(\gamma, \xi)$ is a convex criterion for all $\gamma \in \Gamma$, then an optimal design should minimize the maximum with respect to γ. The definition of a minimax design is given below.

Definition 3.2.1 ξ^* *is a minimax design with respect to* $\Psi(\gamma, \xi)$ *in* Ξ *if and only if* $\xi^* \in \arg\min\{\max_{\gamma\in\Gamma} \Psi(\gamma, \xi); \xi \in \Xi\}$.

As shown by Huang et al. [20], an optimal design for minimizing the asymptotic variance of the estimate of the location-shift parameter μ in model (3.1) depends on the unknown parameter μ, and only a locally optimal design can be found. In this particular case, set

$$\Psi(\mu, \xi) = c(\mu)' M(\xi)^{-1} c(\mu) \tag{3.2}$$

to be the asymptotic variance of the estimate of μ with $c(\mu) = (1, -1, -\mu)'$, $\mu \in B$. A minimax design minimizes the maximum of the asymptotic variance.

When the experimental responses are uncorrelated, that is $\rho = 0$, two different designs, ξ_1 and ξ_2, can be assigned to each response. In this case, design ξ can be expressed as $\xi = p_1\xi_1 + p_2\xi_2$, where each $p_i > 0$, and $p_1 + p_2 = 1$. We measure information on $\tilde{\theta}$ contained in ξ by its information matrix

$$\begin{aligned} M(\xi) &= p_1 M_1(\xi_1) + p_2 M_2(\xi_2) \\ &= \begin{pmatrix} p_1 & 0 & p_1 c_1 \\ 0 & p_2 & p_2 d_1 \\ p_1 c_1 & p_2 d_1 & p_1 c_2 + p_2 d_2 \end{pmatrix} \end{aligned} \tag{3.3}$$

where $M_i(\xi_i) = \int_{\mathcal{X}_i} f_i(x_i) f_i(x_i)' d\xi_i$, $i = 1, 2$, $f_1(x_1) = (\,1 \quad 0 \quad x_1\,)'$, $f_2(x_2) = (\,0 \quad 1 \quad x_2\,)'$ and $c_i = \int_{\mathcal{X}_1} {x_1}^i d\xi_1$, $d_i = \int_{\mathcal{X}_2} {x_2}^i d\xi_2$, $i = 1, 2$. The asymptotic variance of the estimate of μ is

$$c(\mu)' M(\xi)^{-1} c(\mu) = \frac{1}{p_1} + \frac{1}{p_2} + \frac{(\mu - (d_1 - c_1))^2}{p_1 c_2 + p_2 d_2 - p_1 {c_1}^2 - p_2 {d_1}^2}. \tag{3.4}$$

The responses from different preparations are observed in pairs for different doses d_1 and d_2. The dual responses are then assumed to be correlated, that is $\rho \neq 0$. A design in this case is denoted by $\xi = \sum_{i=1}^m w_i \delta_{\mathbf{x}_i}$, $\mathbf{x}_i \in \mathcal{X}_1 \times \mathcal{X}_2$. The information matrix of design ξ is $M(\xi) = \int_{\mathcal{X}_1 \times \mathcal{X}_2} F(\mathbf{x}) \Sigma^{-1} F(\mathbf{x})' d\xi$, where $F(\mathbf{x}) = (\,I_2 \quad X\,)'$, matrix $X = (\,x_1 \quad x_2\,)'$. That is

$$M(\xi) = \frac{1}{1-\rho^2} \begin{pmatrix} 1 & -\rho & c_1 - \rho d_1 \\ -\rho & 1 & d_1 - \rho c_1 \\ c_1 - \rho d_1 & d_1 - \rho c_1 & c_2 + d_2 - 2\rho\gamma \end{pmatrix},$$

recall $c_i = \int_{\mathcal{X}_1 \times \mathcal{X}_2} {x_1}^i d\xi$, $d_i = \int_{\mathcal{X}_1 \times \mathcal{X}_2} {x_2}^i d\xi$, $i = 1, 2$, and the variance of μ is

$$\begin{aligned} & c(\mu)' M(\xi)^{-1} c(\mu) \\ = \;& 2(1-\rho) + \frac{(1-\rho^2)(\mu - (d_1 - c_1))^2}{c_2 + d_2 - 2\rho\gamma - {c_1}^2 - {d_1}^2 + 2 c_1 d_1 \rho}. \end{aligned} \tag{3.5}$$

A straightforward extension of the equivalence theorem for minimax designs in Müller and Pázman [28] is described below, when responses are observed in pairs from model (3.1) with correlation coefficient $\rho \neq 0$.

Theorem 3.2.1 *Let $M(\xi^*)$ be regular and*

$$\Lambda = \arg\max_{\mu \in B} c(\mu)' M(\xi^*)^{-1} c(\mu)$$

be a finite set. If $\lambda : \Lambda \longrightarrow [0, 1]$ with $\sum_{\mu \in \Lambda} \lambda(\mu) = 1$, and if

$$\sum_{\mu \in \Lambda} \lambda(\mu) \frac{c(\mu)' M(\xi^*)^{-1} M(\delta_{\mathbf{x}}) M(\xi^*)^{-1} c(\mu)}{c(\mu)' M(\xi^*)^{-1} c(\mu)} \leq 1, \tag{3.6}$$

for all $\mathbf{x} = (x_1, x_2) \in \mathcal{X}_1 \times \mathcal{X}_2$*, then* ξ^* *is a minimax design in* Ξ*. The converse is true if* B *is compact.*

When $\rho = 0$, apply the inequality (3.6) with the asymptotic variance in (3.4) and the information matrix in (3.3) for all $\mathbf{x} = x \in \mathcal{X}_1 \cup \mathcal{X}_2$.

An alternative concept to the minimax design is the maximin efficient design introduced by Müller [27]. This design maximizes the minimum relative efficiency with respect to the locally optimal design.

Definition 3.2.2 *Let* $\xi^*_\mu \in \arg\min\{c(\mu)'M(\xi)^{-1}c(\mu); \xi \in \Xi\}$ *denote the locally optimal design for* $\mu \in B$*. The efficiency of design* ξ *relative to design* ξ^*_μ *is defined as* $\Phi(\mu, \xi) = \frac{c(\mu)'M(\xi^*_\mu)^{-1}c(\mu)}{c(\mu)'M(\xi)^{-1}c(\mu)}$*. Then a design measure* η^* *is called maximin efficient for* μ *in* Ξ *if and only if* $\eta^* \in \arg\max\{\min_{\mu \in B} \Phi(\mu, \xi); \xi \in \Xi\}$.

In Definition 3.2.2, it can be seen that a maximin efficient design η^* is also minimax in terms of the weighted variances, (see Müller and Pázman [28]), since

$$\begin{aligned} \eta^* &\in \arg\max\{\min_{\mu \in B} \Phi(\mu, \xi); \xi \in \Xi\} \\ &= \arg\min\{\max_{\mu \in B} \Phi(\mu, \xi)^{-1}; \xi \in \Xi\} \\ &= \arg\min\{\max_{\mu \in B} \frac{c(\mu)'M(\xi)^{-1}c(\mu)}{c(\mu)'M(\xi^*_\mu)^{-1}c(\mu)}; \xi \in \Xi\}. \end{aligned}$$

Denoting $\Upsilon(\mu, \xi) = \frac{c(\mu)'M(\xi)^{-1}c(\mu)}{c(\mu)'M(\xi^*_\mu)^{-1}c(\mu)}$ and knowing that it is an convex criterion, by the equivalence theorem of minimax design presented by Müller and Pázman [28] we obtain the equivalence theorem for $\rho \neq 0$ described as follows.

Theorem 3.2.2 *Let $M(\eta^*)$ be regular and*

$$\Lambda = \arg\max_{\mu \in B} \frac{c(\mu)' T M(\eta^*)^{-1} c(\mu)}{c(\mu)' M(\xi_\mu^*)^{-1} c(\mu)}$$

be a finite set. If $\lambda : \Lambda \longrightarrow [0,1]$ with $\sum_{\mu \in \Lambda} \lambda(\mu) = 1$, and if

$$\sum_{\mu \in \Lambda} \lambda(\mu) \frac{c(\mu)' M(\eta^*)^{-1} M(\delta_{\mathbf{x}}) M(\eta^*)^{-1} c(\mu)}{c(\mu)' M(\eta^*)^{-1} c(\mu)} \leq 1, \tag{3.7}$$

for all $\mathbf{x} = (x_1, x_2) \in \mathcal{X}_1 \times \mathcal{X}_2$, then η^* is a maximin efficient design in Ξ. The converse is true if B is compact.

When $\rho = 0$, the results may be obtained by applying the inequality (3.7) with the asymptotic variance in (3.4) and the information matrix in (3.3) for all $\mathbf{x} = x \in \mathcal{X}_1 \cup \mathcal{X}_2$.

3.3 Minimax designs

In this section we assume that the location-shift parameter μ is located on interval $[-b, b]$ or $[0, b]$, $b > 0$. If prior experience cannot be used to indicate the sign of μ clearly, then the symmetrical interval $[-b, b]$ can be considered for μ. The minimax designs are presented below for cases for $\mu \in [-b, b]$ or $[0, b]$ respectively.

Theorem 3.3.1 *Suppose model (3.1) holds and $\mu \in [-b, b]$. The design ξ^* is a minimax design for μ if (i) $\xi^* = \frac{1}{2}\xi_1^* + \frac{1}{2}\xi_2^*$, $\xi_1^* = \xi_2^* = \frac{1}{2}\delta_{-1} + \frac{1}{2}\delta_1$ provided $\rho = 0$; (ii) $\xi^* = \frac{1}{2}\delta_{(-1,1)} + \frac{1}{2}\delta_{(1,-1)}$ provided $0 < \rho < 1$; (iii) $\xi^* = \frac{1}{2}\delta_{(-1,-1)} + \frac{1}{2}\delta_{(1,1)}$ provided $-1 < \rho < 0$.*

When $\mu \in [0, b]$, $b > 0$, the minimax designs described below are found by first restricting attention to a subclass of designs and finding the designs that minimize the largest upper bound for the variance of the estimate.

Theorem 3.3.2 *Suppose model (3.1) holds with $\rho = 0$, $\mu \in [0, b]$ and ξ_i^* is a design supported on $\mathcal{X}_i$, $i = 1, 2$. The design $\xi^* = \frac{1}{2}\xi_1^* + \frac{1}{2}\xi_2^*$ is a minimax design for μ if (i) $\xi_1^* = (\frac{1}{2} + \frac{b}{8})\delta_{-1} + (\frac{1}{2} - \frac{b}{8})\delta_1$ and $\xi_2^* = (\frac{1}{2} - \frac{b}{8})\delta_{-1} + (\frac{1}{2} + \frac{b}{8})\delta_1$ provided $0 < b \leq 2\sqrt{2}$; (ii) $\xi_1^* = (\frac{1}{2} + \frac{1}{b})\delta_{-1} + (\frac{1}{2} - \frac{1}{b})\delta_1$ and $\xi_2^* = (\frac{1}{2} - \frac{1}{b})\delta_{-1} + (\frac{1}{2} + \frac{1}{b})\delta_1$ provided $b > 2\sqrt{2}$.*

The next two results concern correlated responses from the standard and test preparations where $\rho \neq 0$ and $|\rho| < 1$.

Theorem 3.3.3 *Suppose model (3.1) holds with $0 < \rho < 1$ and $\mu \in [0, b]$. The design ξ^* is a minimax design for μ if (i) $\xi^* = (\frac{1}{2}+\frac{b}{8})\delta_{(-1,1)}+(\frac{1}{2}-\frac{b}{8})\delta_{(1,-1)}$ provided $0 < b \leq 2\sqrt{2}$; (ii) $\xi^* = (\frac{1}{2}+\frac{1}{b})\delta_{(-1,1)}+(\frac{1}{2}-\frac{1}{b})\delta_{(1,-1)}$ provided $b > 2\sqrt{2}$.*

Theorem 3.3.4 *Suppose model (3.1) holds with $-1 < \rho < 0$ and $\mu \in [0, b]$. The design $\xi^* = w_1\delta_{(-1,-1)} + w_2\delta_{(-1,1)} + w_1\delta_{(1,1)}$ is a minimax design for μ if*
(i) $w_1 = \frac{1}{2} - \frac{b}{8}$, $w_2 = \frac{b}{4}$ provided $0 < b \leq \frac{3\rho+\sqrt{8+\rho^2}}{1+\rho}$;
(ii) $w_1 = \frac{b-2}{2b-4\rho+2b\rho}$, $w_2 = \frac{2-2\rho+b\rho}{b-2\rho+b\rho}$ provided $\frac{3\rho+\sqrt{8+\rho^2}}{1+\rho} < b \leq 2 - \frac{2}{\rho}$;
(iii) $w_1 = \frac{1}{2}$, $w_2 = 0$ provided $b > 2 - \frac{2}{\rho}$.

All the results described above are proved by similar arguments and therefore only the proof of Theorem 3.3.4 is provided and is deferred to the Appendix A.

3.4 Maximin efficient designs

In this section, we investigate the maximin efficient designs and compare the efficiencies with the minimax designs obtained in section 3.3. From Definition 3.2.2, it can easily be seen that a maximin efficient design η^* satisfies

$$\eta^* \in \arg\min\{\max_{\mu \in B} \Phi(\mu, \xi)^{-1}\},$$

therefore it is also minimax in terms of the weighted variances, i.e. the inverse of efficiencies with respect to the locally optimal design. Under various conditions of ρ and b, the maximin efficient designs are derived and presented as follows. For the corresponding locally optimal designs ξ_μ^* under different ρ and μ values, the values of $\Psi(\mu, \xi_\mu^*)$ as defined in (3.2) are listed in Table 3.1.

In the case of $\mu \in [-b, b]$, we obtain that the maximin efficient designs are the same as the minimax designs.

Theorem 3.4.1 *Suppose model (3.1) holds with $\mu \in [-b, b]$. The designs ξ^* in Theorem 3.3.1 are maximin efficient designs for μ.*

When $0 < \mu \leq 2$, $\Psi(\mu, \xi_\mu^*)$ is a constant equals to 4 provided $\rho = 0$ and to $2(1-\rho)$ provided $\rho \neq 0$, therefore, the maximin efficient designs are the same as the minimax design provided $\mu \in [0, b]$ and $0 < b \leq 2$. Those minimax designs can be found in Theorems 3.3.2 to 3.3.4. When $b > 2$, the maximin efficient designs are different from the minimax designs and are presented in the following theorems.

Table 3.1: The values of $\Psi(\mu, \xi^*_\mu) = c(\mu)' M(\xi^*_\mu)^{-1} c(\mu)$ for the corresponding locally optimal designs ξ^*_μ under different ρ values

ρ	μ	$\Psi(\mu, \xi^*_\mu)$
$\rho = 0$	$\|\mu\| \le 2$	4
	$\|\mu\| > 2$	μ^2
$0 < \rho < 1$	$\|\mu\| \le 2$	$2(1-\rho)$
	$\|\mu\| > 2$	$(1-\rho)\mu^2/2$
$-1 < \rho < 0$	$\|\mu\| \le 2$	$2(1-\rho)$
	$2 < \|\mu\| \le 2 - \frac{2}{\rho}$	$(1-\rho)(\|\mu\| + \|\mu\|\rho - 2\rho)^2/2$
	$\|\mu\| > 2 - \frac{2}{\rho}$	$(\mu^2 + \mu^2\rho + 4 - 4\rho)/2$

Theorem 3.4.2 *Suppose model (3.1) holds with $\mu \in [0, b]$, $b > 2$. The design η^* is a maximin efficient design for μ if (i) $\eta^* = \frac{1}{2}\eta_1^* + \frac{1}{2}\eta_2^*$, $\eta_1^* = \frac{3}{4}\delta_{-1} + \frac{1}{4}\delta_1$ and $\eta_2^* = \frac{1}{4}\delta_{-1} + \frac{3}{4}\delta_1$ provided $\rho = 0$; (ii) $\eta^* = \frac{3}{4}\delta_{(-1,1)} + \frac{1}{4}\delta_{(1,-1)}$ provided $0 < \rho < 1$.*

When $\rho \ge 0$ and $b > 2$, the maximin efficient designs are not dependent on ρ and b. This property is invariant when $-1 < \rho < 0$ provided $2 < b \le 2 - \frac{2}{\rho}$.

Theorem 3.4.3 *Suppose model (3.1) holds for $-1 < \rho < 0$ and $\mu \in [0, b]$. The design $\eta^* = w_1\delta_{(-1,-1)} + w_2\delta_{(-1,1)} + w_1\delta_{(1,1)}$ is a maximin efficient design for μ if (i) $w_1 = \frac{1}{4}$, $w_2 = \frac{1}{2}$ provided $2 < b \le 2 - \frac{2}{\rho}$; (ii) $w_1 = \frac{(b-2)^2(1-\rho)}{4(b^2-2b+2b\rho+4-4\rho)}$, $w_2 = 1 - 2w_1$ provided $b > 2 - \frac{2}{\rho}$.*

The proof of Theorem 3.4.1 is provided and is deferred to the Appendix B. The others are proved by similar arguments. Tables 3.2 and 3.3 display the efficiencies of the minimax designs ξ^* and the maximin efficient designs η^* relative to locally optimal designs under various conditions. A comparison of the behavior of the efficiencies between a minimax design ξ^* and a maximin efficient design η^*, where $\rho = 0.2$, and $\mu \in [0, 8]$ is shown, for example, in Fig. 3.1. It is evident that the efficiencies of ξ^* and η^* are quite different. The lower bound of the efficiencies of η^* is higher than ξ^* since the maximin efficient criterion is to maximize the minimum efficiency. Nevertheless, the efficiencies of ξ^* are higher than η^* and approximates to 1 when μ tends to 0 or b. From Tables 3.2 and 3.3 and Fig. 3.1, an experimenter may need to decide which optimal criterion to use.

3.5 Discussions

Under a situation in which observations are made for the same subject with k experimental periods, it is of interest to simultaneously estimate the corresponding relative potency for each period. We may then generalize the parallel model for k responses, $k \geq 3$. In this case, assume that the covariance matrix of k responses is $\Sigma_k = (1-\rho)I_k + \rho J_k$. The expected responses for design points $\mathbf{x}_k = (x_1, \cdots, x_k)^T \in \mathcal{X}_1 \times \cdots \times \mathcal{X}_k$ can be expressed as

$$E(Y_i|x_i) = \theta_{0i} + \theta_1 x_i = \theta_{01} + \theta_1(x_i - \mu_i),\ i = 1, \cdots, k,$$

where $\mu_1 = 0$, $\mu_i \in B$, $i = 2, \cdots, k$ are the location-shift parameters for each period. The information matrix for the unknown parameter vector $\tilde{\theta}_k =$

Table 3.2: Efficiencies of the minimax design ξ^* relative to the locally optimal design for parameter μ provided $\mu \in [0, b]$ under different ρ values

ρ	b	μ	efficiency of ξ^*
$0 \le \rho < 1$	$0 < b \le 2\sqrt{2}$	$0 < \mu \le 2$	$\frac{16-b^2}{4(\mu^2-b\mu+4)}$
		$2 < \mu \le b$	$\frac{\mu^2(16-b^2)}{16(\mu^2-b\mu+4)}$
	$b > 2\sqrt{2}$	$0 < \mu \le 2$	$\frac{4(b^2-4)}{b(b\mu^2-8\mu+4b)}$
		$2 < \mu \le b$	$\frac{\mu^2(b^2-4)}{b(b\mu^2-8\mu+4b)}$
$-1 < \rho < 0$	$0 < b < \frac{3\rho+\sqrt{8+\rho^2}}{1+\rho}$	$0 < \mu \le 2$	$\frac{(4-b)(4+b-4\rho+b\rho)}{4(4-b\mu+\mu^2-4\rho+2b\rho-b\mu\rho+\mu^2\rho)}$
		$2 < \mu \le b$	$\frac{(4-b)(4+b-4\rho+b\rho)(\mu-2\rho+\mu\rho)^2}{16(4-b\mu+\mu^2-4\rho+2b\rho-b\mu\rho+\mu^2\rho)}$
	$\frac{3\rho+\sqrt{8+\rho^2}}{1+\rho} < b \le 2-2/\rho$	$0 < \mu \le 2$	$\frac{16p^*(1-p^*-p^*\rho)}{8p^*(\mu-2\rho+\mu\rho)+(\mu-2)^2(1+\rho)}$ †
		$2 < \mu \le b$	$\frac{4p^*(1-p^*-p^*\rho)(\mu-2\rho+\mu\rho)^2}{8p^*(\mu-2\rho+\mu\rho)+(\mu-2)^2(1+\rho)}$
	$b > 2-2/\rho$	$0 < \mu \le 2$	$\frac{4(1-\rho)}{4+\mu^2-4\rho+\mu^2\rho}$
		$2 < \mu \le 2-2/\rho$	$\frac{(1-\rho)(\mu-2\rho+\mu\rho)^2}{4+\mu^2-4\rho+\mu^2\rho}$
		$2-2/\rho < \mu \le b$	1

† $p^* = \frac{b-2}{2b-4\rho+2b\rho}$

Table 3.3: Efficiencies of the maximin efficienct design η^* relative to the locally optimal design for parameter μ provided $\mu \in [0, b]$ under different ρ values

ρ	b	μ	efficiency of η^*
$0 \le \rho < 1$	$0 < b \le 2$	$0 < \mu \le 2$	$\frac{16-b^2}{4(\mu^2-b\mu+4)}$
	$b > 2$	$0 < \mu \le 2$	$\frac{3}{3+(\mu-1)^2}$
		$2 < \mu \le b$	$\frac{3\mu^2}{12+4(\mu-1)^2}$
$-1 < \rho < 0$	$0 < b < 2$	$0 < \mu \le 2$	$\frac{(4-b)(4+b-4\rho+b\rho)}{4(4-b\mu+\mu^2-4\rho+2b\rho-b\mu\rho+\mu^2\rho)}$
	$2 < b \le 2-2/\rho$	$0 < \mu \le 2$	$\frac{1}{1+(\mu-1)^2(1+\rho)/(3-\rho)}$
		$2 < \mu \le b$	$\frac{(\mu-2\rho+\mu\rho)^2}{4+4(\mu-1)^2(1+\rho)/(3-\rho)}$
	$b > 2-2/\rho$	$0 < \mu \le 2$	$\frac{16w^*(1-w^*-w^*\rho)}{(\mu-2)^2(1+\rho)+8w^*(\mu-2\rho+\mu\rho)}$ ††
		$2 < \mu \le 2-2/\rho$	$\frac{4w^*(1-w^*-w^*\rho)(\mu-2\rho+\mu\rho)^2}{(\mu-2)^2(1+\rho)+8w^*(\mu-2\rho+\mu\rho)}$
		$2-2/\rho < \mu \le b$	$\frac{4w^*(1-w^*-w^*\rho)(4+\mu^2-4\rho+\mu^2\rho)}{(1-\rho)((\mu-2)^2(1+\rho)+8w^*(\mu-2\rho+\mu\rho))}$

†† $w^* = \frac{(b-2)^*(1-\rho)}{4(4-2b+b^2-4\rho+2b\rho)}$

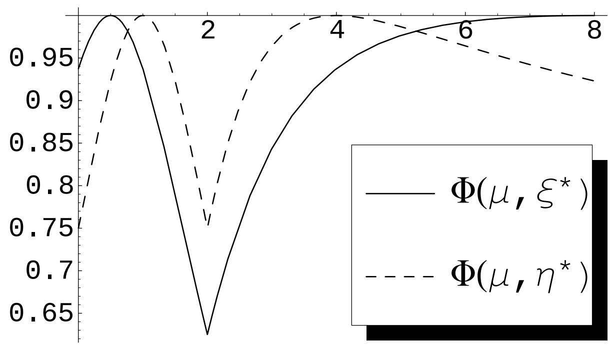

Figure 3.1: Plots of $\Phi(\mu, \xi^*)$ versus $\Phi(\mu, \eta^*)$ for $\rho = 0.2$ and $\mu \in [0, 8]$

$(\theta_{01}, \cdots, \theta_{0k}, \theta_1)$ of design ξ becomes $M_k(\xi) = \int_{\mathcal{X}_1 \times \cdots \times \mathcal{X}_k} F(\mathbf{x}_k)\Sigma_k^{-1} F(\mathbf{x}_k)^T d\xi$. Take the mean dispersion of the estimates of the location-shift parameters as the criterion

$$\Psi(\mathbf{u}, \xi) = \mathrm{tr}\{C(\mathbf{u})' M(\xi)^{-1} C(\mathbf{u})\},$$

where matrix $C(\mathbf{u}) = (\mathbf{1}_{k-1} \ \ -I_{k-1} \ \ -\mathbf{u})^T$, $\mathbf{1}_{k-1}$ is a $(k-1)$-dimensional vector of one's and $\mathbf{u} = (\mu_2 \ \cdots \ \mu_k)^T$ is the location-shift parameter vector. Provided that $\rho = 0$ and $\mu_i \in [-b, b]$, $b > 0$, $i = 2, \cdots, k$, the minimax design ξ^* assigns the same design with the same weights to the test preparation at different periods, that is

$$\xi^* = \frac{\sqrt{k-1} - 1}{k-2} \xi_1^* + \sum_{i=2}^{k} \frac{k - 1 - \sqrt{k-1}}{(k-1)(k-2)} \xi_i^*,$$

where $\xi_i^* = \frac{1}{2}\delta_{-1} + \frac{1}{2}\delta_1$, for each i. In the other cases, closed form formulae for optimal designs are not easy to find. Wong [36] provided an approach for the construction of minimax variance optimal designs. It would be interesting to know how the optimal designs would behave. For example, when $k = 3$,

$\rho = 0$ and $\mu_1,\ \mu_2 \in [0, b]$, after some numerical computations it is found that when $0 < b < 2.714$, the minimax design is $\xi^* = (\sqrt{2}-1)\xi_1^* + \sum_{i=2}^{3}(1-\frac{\sqrt{2}}{2})\xi_i^*$, where $\xi_1^* = (\frac{1}{2}+\frac{b}{8})\delta_{-1} + (\frac{1}{2}-\frac{b}{8})\delta_1$ and $\xi_2^* = \xi_3^* = (\frac{1}{2}-\frac{b}{8})\delta_{-1} + (\frac{1}{2}+\frac{b}{8})\delta_1$. Compared with the minimax design for dual responses, the design for the test preparation is simply replicated at later $k-1$ periods. The number of the periods and the endpoint of the range of μ will affect only the weighting at its support points.

In this work, it is noteworthy that one of the characteristics of these optimal designs is that with a positive ρ, the optimal designs are supported on points $(-1, 1)$ and $(1, -1)$ and with a negative ρ, the design points are $(-1, -1)$ and $(1, 1)$ and $(-1, 1)$. It seems when the two responses are positively correlated, the optimal designs choose end points with opposite signs, and vice versa for responses with a negative correlation.

Lastly, it is observed that the minimax and maximin efficient designs are invariant with scale changes on the design regions $\mathcal{X}_i$, $i = 1, 2$ and the range of μ simultaneously, that is, if $\mathcal{X}_i$, $i = 1, 2$ is extended to $[-a, a]$ and the range of μ is $[-ab, ab]$ or $[0, ab]$, then the optimal designs are invariant, except the design points are changed to the corresponding new vertices.

3.6 Appendix

3.6.1 Proof of Theorem 3.3.4

To recall from Huang et al. [20] that when $-1 < \rho < 0$, an optimal design for estimating μ must satisfy $c_1 = -d_1$. Accordingly, we focus on designs of the form, $\xi = w_1\delta_{(-1,-1)} + w_2\delta_{(-1,1)} + w_3\delta_{(1,-1)} + w_1\delta_{(1,1)}$. The asymptotic variance in (3.5) becomes $\Psi(\mu,\xi) = 2(1-\rho) + \frac{(1-\rho^2)(\mu-2d_1)^2}{2-2\rho\gamma-2d_1^2(1+\rho)}$, where $\gamma = \int_{\mathcal{X}_1\times\mathcal{X}_2} x_1x_2 d\xi$. To find the minimax design, the process is divided into two parts.

Part (I) Consider $B = [0,b]$, $0 < b \leq 4$.

(1) Let $\xi \in \Xi_1 = \{\xi | \ \frac{b}{4} \leq d_1 \leq 1\}$, we have

$$\arg\max_{\mu\in B} \Psi(\mu,\xi) = \{0\}.$$

The design $\xi_1^* = (\frac{1}{2}-\frac{b}{8})\delta_{(-1,-1)} + \frac{b}{4}\delta_{(-1,1)} + (\frac{1}{2}-\frac{b}{8})\delta_{(1,1)}$ is a minimax design in Ξ_1 with $\Psi(\mu,\xi_1^*) = \frac{16(1-\rho)(2-2\rho+b\rho)}{(4-b)(4+b-4\rho+b\rho)}$.

(2) Let $\xi \in \Xi_2 = \{\xi | \ -1 < d_1 \leq \frac{b}{4}\}$, we have

$$\arg\max_{\mu\in B} \Psi(\mu,\xi) = \{b\}.$$

(i) if $0 < b \leq \frac{3\rho+\sqrt{8+\rho^2}}{1+\rho}$, the design

$$\xi_2^* = (\frac{1}{2}-\frac{b}{8})\delta_{(-1,-1)} + \frac{ii}{4}\delta_{(-1,1)} + (\frac{1}{2}-\frac{b}{8})\delta_{(1,1)}$$

is a minimax design in Ξ_2 with

$$\Psi(\mu,\xi_2^*) = \frac{16(1-\rho)(2-2\rho+b\rho)}{(4-b)(4+b-4\rho+b\rho)};$$

(b) if $\frac{3\rho+\sqrt{8+\rho^2}}{1+\rho} < b \leq 4$, the design

$$\begin{aligned}\xi_3^* &= \frac{b-2}{2b-4\rho+2b\rho}\delta_{(-1,-1)} + \frac{2-2\rho+b\rho}{b-2\rho+b\rho}\delta_{(-1,1)} \\ &+ \frac{b-2}{2b-4\rho+2b\rho}\delta_{(1,1)}\end{aligned}$$

is a minimax design in Ξ_2 with $\Psi(\mu,\xi_3^*) = \frac{1}{2}(1-\rho)(b-2\rho+b\rho)^2$.

We observe from the above that when $\frac{3\rho+\sqrt{8+\rho^2}}{1+\rho} < b \leq 4$, $\Psi(\mu, \xi_3^*)$ is less than $\Psi(\mu, \xi_1^*)$. It follows that ξ_1^* is a minimax design in Ξ provided $0 < b \leq \frac{3\rho+\sqrt{8+\rho^2}}{1+\rho}$ and ξ_3^* is a minimax design in Ξ provided $\frac{3\rho+\sqrt{8+\rho^2}}{1+\rho} <$ $b \leq 4$.

Part (II) Consider $B = [0, b]$, $b > 4$. The minimax designs can be found by using the similar technic as in part (I). We have $\arg\max_{\mu\in B} \Psi(\mu, \xi) =$ $\{b\}$.

(1) if $4 < b \leq 2 - \frac{2}{\rho}$, the design $\xi_3^* = \frac{b-2}{2b-4\rho+2b\rho}\delta_{(-1,-1)} + \frac{2-2\rho+b\rho}{b-2\rho+b\rho}\delta_{(-1,1)} +$ $\frac{b-2}{2b-4\rho+2b\rho}\delta_{(1,1)}$ is a minimax design in Ξ;

(2) if $b > 2 - \frac{2}{\rho}$, the design $\xi_4^* = \frac{1}{2}\delta_{(-1,-1)} + \frac{1}{2}\delta_{(1,1)}$ is a minimax design in Ξ with $\Psi(\mu, \xi_4^*) = \frac{1}{2}(4 + b^2 - 4\rho + b^2\rho)$.

Combining the results in Part (I) and (II), we obtain the minimax designs described in theorem 3.3.4. This candidate design can be verified to be the minimax design through equivalence theorem 4.1, as shown in the following. If $0 < b \leq \frac{3\rho+\sqrt{8+\rho^2}}{1+\rho}$, we have $\Lambda = \{0, b\}$. Take $\lambda(b) = \frac{2(4-4\rho+b\rho)}{(4-b)(4+b-4\rho+b\rho)}$ and $\lambda(0) = 1 - \lambda(b)$,

$$\begin{aligned}
&\sum_{\mu\in\Lambda} \lambda(\mu) \frac{c(\mu)' M(\xi^*)^{-1} M(e_{(x_1,x_2)}) M(\xi^*)^{-1} c(\mu)}{\Psi(\mu, \xi^*)} \\
= \quad & \frac{1}{((4-b)(4+b-4\rho+b\rho)(2-2\rho+b\rho))} \cdot \\
& (32 - 4b^2 + b^2x_1^2 + b^2x_2^2 - 64\rho + 32b\rho - b^3\rho + 2b^2x_1\rho \\
& + b^2x_1^2\rho - 2b^2x_2\rho - 2b^2x_1x_2\rho + b^2x_2^2\rho + 32\rho^2 - 32b\rho^2 \\
& + 12b^2\rho^2 - b^3\rho^2 + 2b^2x_1\rho^2 - 2b^2x_2\rho^2 - 2b^2x_1x_2\rho^2)
\end{aligned}$$

$$\leq \frac{32 - 2b^2 - 64\rho + 32b\rho - b^3\rho + 32\rho^2 - 32b\rho^2 + 10b^2\rho - b^3\rho^2}{(4-b)(4+b-4\rho+b\rho)(2-2\rho+b\rho)}$$
$$= 1,$$

$\forall\,(x_1, x_2) \in \mathcal{X}_1 \times \mathcal{X}_2$. The others results are proved by similar arguments and are omitted here.

3.6.2 Proof of Theorem 3.4.1

Throughout, we denote that $I_A(\mu) = 1$, if $\mu \in A$ and $I_A(\mu) = 0$, if $\mu \notin A$, and verify the candidate designs to be maximin efficient through inequality (3.7).

(1) Consider $\rho = 0$,

i) if $b < 2$, then $\Psi(\mu, \xi^*_\mu) = 4$ is a constant and

$$\begin{aligned} \eta^* &\in \arg\min\{\max_{\mu \in B} \Upsilon(\mu, \xi); \xi \in \Xi\} \\ &= \arg\min\{\max_{\mu \in B} \frac{\Psi(\mu, \xi)}{4}; \xi \in \Xi\} \\ &= \arg\min\{\max_{\mu \in B} \Psi(\mu, \xi); \xi \in \Xi\} \end{aligned}$$

which implies a minimax design is a maximin efficient design for $\mu \in [-b, b]$, $b < 2$.

ii) if $b > 2$, the minimax design is $\xi^* = \frac{1}{2}\xi^*_1 + \frac{1}{2}\xi^*_2$, with $\xi^*_1 = \xi^*_2 = \frac{1}{2}\delta_{-1} + \frac{1}{2}\delta_1$, we obtain that $\Psi(\mu, \xi^*) = \mu^2 + 4$, then

$$\Upsilon(\mu, \xi^*) = (\mu^2 + 4)(\frac{1}{4} I_{\{|\mu| \leq 2\}}(\mu) + \frac{1}{\mu^2} I_{\{|\mu| > 2\}}(\mu)),$$

and $\Lambda = \{-2, 2\}$.

Consider the one-point measures δ_{x_1} with $x_1 \in \mathcal{X}_1$ on the first regression of the parallel model, it yields that

$$\begin{aligned} & c(\mu)' M(\xi^*)^{-1} M(\delta_{x_1}) M(\xi^*)^{-1} c(\mu) \\ = & ((1,-1,-\mu) M(\xi^*)^{-1} (1,0,x_1)^T)^2 \\ = & (\mu x_1 - 2)^2. \end{aligned}$$

Take $\lambda(-2) = \lambda(2) = \frac{1}{2}$, then

$$\begin{aligned} & \sum_{\mu \in \Lambda} \lambda(\mu) \frac{c(\mu)' M(\xi^*)^{-1} M(\delta_{x_1}) M(\xi^*)^{-1} c(\mu)}{c(\mu)^T M(\xi^*)^{-1} c(\mu)} \\ = & \frac{1}{2} \frac{(2x_1+2)^2 + (2x_1-2)^2}{(2^2+4)} \leq 1, \end{aligned}$$

$\forall x_1 \in \mathcal{X}_1$. Similar result can be obtained when the one-point measures δ_{x_2} with $x_2 \in \mathcal{X}_2$ on the second regression of the parallel model is taken. The desired result follows.

(2) Consider $0 < \rho < 1$,

i) if $b \leq 2$, then $\Psi(\mu, \xi^*_\mu) = 2(1-\rho)$ is a constant which implies a minimax design is a maximin efficient design for $\mu \in [-b, b]$, $b < 2$, as in (1)(i) of the proof of Theorem 3.4.1.

ii) if $b > 2$, the minimax design is $\xi^* = \frac{1}{2}\delta_{(-1,1)} + \frac{1}{2}\delta_{(1,-1)}$, we obtain that $\Psi(\mu, \xi^*) = (1-\rho)(2 + \mu^2/2)$, and

$$\begin{aligned} \Upsilon(\mu, \xi^*) &= (1-\rho)(2+\mu^2/2)\{\frac{1}{2(1-\rho)} I_{\{|\mu| \leq 2\}}(\mu) \\ &+ \frac{1}{(1-\rho)\mu^2/2} I_{\{|\mu|>2\}}(\mu)\}, \end{aligned}$$

and $\Lambda = \{-2, 2\}$. Take $\lambda(-2) = \lambda(2) = \frac{1}{2}$, then

$$\begin{aligned} & \sum_{\mu\in\Lambda} \lambda(\mu) \frac{c(\mu)' M(\xi^*)^{-1} M(\delta_{(x_1,x_2)}) M(\xi^*)^{-1} c(\mu)}{c(\mu)^T M(\xi^*)^{-1} c(\mu)} \\ = & \frac{(1-\rho)(x_1^2 + x_2^2 - 2\rho x_1 x_2 + 2\rho + 2)/(1+\rho)}{(1-\rho)(2 + 2^2/2)} \leq 1, \end{aligned}$$

$\forall (x_1, x_2) \in \mathcal{X}_1 \times \mathcal{X}_2$. Hence, ξ^* is maximin efficient.

(3) Consider $-1 < \rho < 0$, the minimax design is $\xi^* = \frac{1}{2}\delta_{(-1,-1)} + \frac{1}{2}\delta_{(1,1)}$, we obtain that $\Psi(\mu, \xi^*) = 2(1-\rho) + (1+\rho)\mu^2/2$, and

$$\begin{aligned} \Upsilon(\mu, \xi^*) &= [2(1-\rho) + (1+\rho)\mu^2/2]\{\frac{1}{2(1-\rho)} I_{\{|\mu|\leq 2\}}(\mu) \\ &+ \frac{1}{(1-\rho)(|\mu| - 2\rho + |\mu|\rho)^2/2} I_{\{2<|\mu|\leq 2-2/\rho\}}(\mu) \\ &+ \frac{1}{2(1-\rho) + (1+\rho)\mu^2/2} I_{|\mu|>2-2/\rho}(\mu)\}. \end{aligned}$$

(i) If $b \leq 2$, ξ^* is maximin efficient.

(ii) If $b > 2$, then $\Lambda = \{-2, 2\}$. Taking $\lambda(-2) = \lambda(2) = \frac{1}{2}$, we obtain that

$$\begin{aligned} & \sum_{\mu\in\Lambda} \lambda(\mu) \frac{c(\mu)' M(\xi^*)^{-1} M(\delta_{(x_1,x_2)}) M(\xi^*)^{-1} c(\mu)}{c(\mu)^T M(\xi^*)^{-1} c(\mu)} \\ = & \frac{2 + x_1^2 + x_2^2 - 4\rho + x_1^2\rho - 2x_1x_2\rho + x_2^2\rho + 2\rho^2 - 2x_1x_2\rho^2}{4(1-\rho)} \\ \leq & 1. \end{aligned}$$

Inequality (3.7) holds $\forall (x_1, x_2) \in \mathcal{X}_1 \times \mathcal{X}_2$. Hence, ξ^* is maximin efficient.

4

Optimal Designs for Calibrations in Multiresponse-univariate Regression Models

This chapter considers a linear regression model with a one-dimensional control variable x and an m-dimensional response variable $\mathbf{y} = (y_1, \cdots, y_m)$. The components of $\mathbf{y}$ are correlated with a known covariance matrix. The calibration problem discussed here is based on the assumed regression model. This is of interest to obtain a suitable estimation of the corresponding x for a given target $\mathbf{T} = (T_1, \cdots, T_m)$ on the expected responses. Due to the fact that there is more than one target value to be achieved in the multiresponse case, the m expected responses may meet their target values at different re-

spective control values. Consideration includes the deviation of the expected response $E(y_i)$ from its corresponding target value T_i for each component and defines the optimal value of calibration point x, say x_0, to be the one which minimizes the weighted sum of squares of such deviations within the range of x. The objective of this study is to find a locally optimal design for estimating x_0, which minimizes the mean square error of the difference between x_0 and its estimator. It shows the optimality criterion is equivalent to a c-criterion under certain conditions and explicit solutions with dual responses under linear and quadratic polynomial regressions are obtained.

Key words and phrases: c-criterion, classical estimator, equivalence theorem, locally optimal design, multivariate calibration, prediction, scalar optimal design.

4.1 Introduction

In this work, optimal designs for calibration in multiresponse models are investigated. The calibration problem has a long history receiving significant attention in statistics and other scientific disciplines (particularly in analytical chemistry). Both the design and analysis aspects of the calibration problem are of interest to experimenters and statisticians. But before stating our objectives toward finding optimal designs for calibration in multiresponse models, we first review the design problem for calibration in a single response experiment with simple linear regression model.

Consider an experiment with simple linear regression model,

$$E(Y) = \beta_0 + \beta_1 x,$$

if n pairs of observations (x_i, y_i), $i = 1, 2, \cdots, n$, are obtained, the objective of calibration is to estimate the corresponding control value x_0 to achieve a given target value T. There are two estimators for estimating x_0, the classical estimator X_c and the inverse estimator X_I defined respectively as

$$X_c = (T - b_0)/b_1,$$

where b_0 and b_1 are the least square estimators of β_0 and β_1 respectively, and

$$X_I = c + dT,$$

where $d = [\sum_{i=1}^{n}(x_i - \bar{x})(y_i - \bar{y})]/[\sum_{i=1}^{n}(y_i - \bar{y})^2]$ and $c = \bar{x} - d\bar{y}$.

Ott and Myers [29], along with providing corresponding design problems, have discussed the estimation of the independent variable in a regression situation for a measured value of the dependent variable. Krutchkoff [24] and Shukla [31] have compared the efficiencies of the classical and inverse estimators based on the mean square errors (MSE). Berkson [3] has given an expression for MSE when n is very large and showed that in some situations the asymptotic MSE of the classical estimator is smaller than the inverse estimator. Buonaccorsi [6] has examined the effects of the choice of designs on calibration in a simple linear regression model again. Barlow, Mensing and Smiriga [2] have computed the optimal Bayes design for a calibration model. Bai and Huang [1] have discussed a consistent estimator for locating the maximizer of a non-parametric regression function.

Beside the single response calibration problem, the multiresponse calibration problem also arises in many applications. In Brown [5] the problem of calibration making inferences about an unknown explanatory variable from a single random observed response vector has been discussed. An example for determining the viscosity of the paint samples by using two measurements on certain optical properties of the samples have been described. In Chang et al. [9] a real example concerning production of the shadow mask which affects the quality of screen image in a monitor or TV set is described, where one of the criteria to determine the fitness of a produced mask depends on whether two response variables, the size of the hole and the depth of the hole, meet the target values. It is of interest to find the optimal setting of the line speed, the input variable x. We therefore investigate in general the calibration design problems for multiresponse-univariate polynomial regression models in this work.

In the next section, we introduce scalar optimal design for multiresponse linear regression model. In Section 4.3, by using the classical estimator, the optimal designs for calibrations in various models with dual responses and with uncorrelated or correlated responses are presented respectively. An example has been given in Section 4.4 for illustration of how to obtain the optimal designs by the related theorems. Section 4.5 concludes with discussions.

4.2 Scalar optimal design for multiresponse linear regression model

4.2.1 Preliminaries

Consider a linear regression model with a one-dimensional control variable x and an m-dimensional response variable $\mathbf{Y}(x) = (Y_1(x), \cdots, Y_m(x))$. With $\mathcal{X} = [a, b]$ being the design space, we consider the following setting:

$$E[Y_i(x)] = \sum_{j=0}^{d} \beta_{ij}\, x^j, \qquad 1 \le i \le m, \tag{4.1}$$

where β_{ij}, $i = 1, 2, \cdots, m$, $j = 0, 1, \cdots, d$, are unknown parameters. Let Σ be the covariance matrix of $\mathbf{Y}(x)$, β be the parameter vector,

$$\beta = (\beta_1', \beta_2', \ldots, \beta_m')' \quad \text{with} \quad \beta_i' = (\beta_{i0}, \beta_{i1}, \ldots, \beta_{id}),$$

and $\mathbf{b}$ be the Gauss-Markov estimator of β. Let $\mathbf{c} = (\mathbf{c}_1', \mathbf{c}_2', \cdots, \mathbf{c}_m')'$ denote a coefficient vector with $\mathbf{c}_i' = (c_{i0}, \cdots, , c_{id}), i = 1, 2, \cdots, m$. A design problem for an arbitrary linear function of the regression coefficients, $\mathbf{c}'\beta$, is to find a design on $\mathcal{X}$ which minimizes the variance of $\mathbf{c}'\mathbf{b}$, the design is called a **scalar optimal design** or **c-optimal design**.

Let $\xi = \sum_{k=1}^{n} p_k \delta_{t_k}$ be a design that the measurements are taken at point $t_k \in \mathcal{X}$ with weight $p_k > 0$, $k = 1, 2, \cdots, n$ and $\sum_{k=1}^{n} p_k = 1$. Some notations for model (4.1) under design ξ are established in the following:

Let I_m be the m-dimensional identity matrix and

$$X = I_m \otimes \mathbf{f}(x) \quad \text{with} \quad \mathbf{f}(x) = (\,1, x, \cdots, x^d\,)', \tag{4.2}$$

where $I_m \otimes \mathbf{f}(x)$ denotes the right direct product of I_m with $\mathbf{f}(x)$. The information matrix of $\mathbf{b}$ under design ξ is expressed as

$$M(\xi) = \int_{\mathcal{X}} X \Sigma^{-1} X' d\xi. \tag{4.3}$$

Let $A(x)$ be the information matrix of a one-point measure δ_x. From the equivalence theorem for scalar optimality in Pukelsheim ([30], p.52), it is known that a design ξ^* is $\mathbf{c}$-optimal if and only if

$$\Psi(x) = \frac{\mathbf{c}' M(\xi^*)^{-1} A(x) M(\xi^*)^{-1} \mathbf{c}}{\mathbf{c}' M(\xi^*)^{-1} \mathbf{c}} \leq 1, \qquad \forall x \in \mathcal{X},$$

and $\Psi(x)$ attains the maximum value 1 at each support point of ξ^*. For any dth-degree polynomial regression model, the corresponding $\Psi(x)$ is a polynomial of order $2d$. Therefore, for a $\mathbf{c}$-optimal design, there may be at most $d+1$ points which may achieve the maximum value of $\Psi(x)$ including the two endpoints on design space $\mathcal{X}$ (See e.g. Figure 4.1). Hence from now on we will consider designs with exactly $d+1$ support points and denote the support vector as $\mathbf{t} = (t_1, t_2, \cdots, t_{d+1})$, where $-1 = t_1 < t_2 < \cdots < t_{d+1} = 1$.

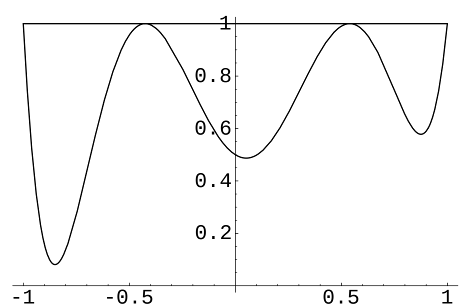

Figure 4.1: Dependence of $\Psi(x)$ on x for a $\mathbf{c}$-optimal design of a polynomial regression model of degree 3.

The following technique for finding a c-optimal design is due to Fedorov [15], p.146. Let $F(\mathbf{t})$ be a square matrix of order $d+1$,

$$F(\mathbf{t}) = (\, \mathbf{f}(t_1) \quad \mathbf{f}(t_2) \quad \cdots \quad \mathbf{f}(t_{d+1}) \,), \tag{4.4}$$

and $F_k(x)$ be a square matrix obtained from $F(\mathbf{t})$ by deleting the kth column $\mathbf{f}(t_k)$ and replacing it by $\mathbf{f}(x)$. Then define the kth Lagrange interpolation polynomial $l_k(x)$ with respect to nodes $t_1, t_2, \cdots, t_{d+1}$ by

$$l_k(x) = \frac{|F_k(x)|}{|F(\mathbf{t})|} = \prod_{\substack{i=1 \\ i \neq k}}^{d+1} \frac{x - t_i}{t_k - t_i}, \qquad k = 1, 2, \cdots, d+1.$$

It follows that the power basis $1, x, \cdots, x^d$ is related to the basis $l_1(x), l_2(x), \cdots,$ $l_{d+1}(x)$ and satisfies $\mathbf{f}(x) = F(\mathbf{t})l(x)$, where $l(x) = (l_1(x), l_2(x), \cdots, l_{d+1}(x))'$. Then matrix X in (4.2) can be expressed as

$$\begin{aligned} X &= I_m \otimes (F(\mathbf{t})l(x)) \\ &= (I_m \otimes F(\mathbf{t}))(I_m \otimes l(x)) = F_I(\mathbf{t})(I_m \otimes l(x)), \end{aligned}$$

where $F_I(\mathbf{t}) = I_m \otimes F(\mathbf{t})$.

4.2.2 Scalar optimal design

(1) Scalar optimal design with uncorrelated responses

If the m responses are uncorrelated with equal variance, assuming that $\Sigma =$ I_m, then the information matrix in (4.3) turns to

$$\begin{aligned} M(\xi) = \int_{\mathcal{X}} XX'd\xi &= F_I(\mathbf{t})[\int_{\mathcal{X}} (I_m \otimes l(x))(I_m \otimes l(x)')d\xi]F_I(\mathbf{t})' \\ &= F_I(\mathbf{t})(I_m \otimes P(\xi))F_I(\mathbf{t})', \end{aligned} \tag{4.5}$$

where $P(\xi) = \int_{\mathcal{X}} l(x)l(x)'d\xi = \text{diag}(p_1, p_2, \cdots, p_{d+1})$, is a diagonal matrix with diagonal entries $p_k, k = 1, 2, \cdots, d+1$.

The variance of $\mathbf{c}'\mathbf{b}$ under design ξ can be easily computed by using (4.5),

$$\begin{aligned} \text{Var}(\mathbf{c}'\mathbf{b}) = \mathbf{c}'M(\xi)^{-1}\mathbf{c} &= \text{tr}(M(\xi)^{-1}\mathbf{c}\mathbf{c}') \\ &= \text{tr}([I_m \otimes P(\xi)^{-1}][F_I(\mathbf{t})^{-1}\mathbf{c}\mathbf{c}'(F_I(\mathbf{t})')^{-1}]) \end{aligned}$$

where tr denotes the trace of the matrix. Since the m responses are uncorrelated, we may divide the variance into m subvariances, so the variance takes the following form

$$\begin{aligned} \text{Var}(\mathbf{c}'\mathbf{b}) &= \sum_{i=1}^{m} \text{tr}(P(\xi)^{-1}F(\mathbf{t})^{-1}\mathbf{c}_i\mathbf{c}_i'(F(\mathbf{t})')^{-1})) \\ &= \sum_{i=1}^{m}\sum_{k=1}^{d+1} \frac{(F_{[k]}^{-1}(\mathbf{t})\mathbf{c}_i)^2}{p_k} = \sum_{k=1}^{d+1} \frac{h_k(\mathbf{t})}{p_k}, \end{aligned}$$

where $F_{[k]}^{-1}(\mathbf{t})$ is the kth row of $F(\mathbf{t})^{-1}$ and $h_k(\mathbf{t}) = \sum_{i=1}^{m}(F_{[k]}^{-1}(\mathbf{t})\mathbf{c}_i)^2$.

The variance is minimized when $p_k = \lambda\sqrt{h_k(\mathbf{t})}$, λ is a constant such that $\sum_{k=1}^{d+1} p_k = 1$. Then, a design ξ^* is $\mathbf{c}$-optimal if its support vector $\mathbf{t}^*$ satisfies

$$\mathbf{t}^* \in \arg\min_{\mathbf{t}\in\mathcal{X}^{d+1}} \sum_{k=1}^{d+1} \sqrt{h_k(\mathbf{t})} \tag{4.6}$$

and the corresponding weights are

$$p_k^* = \frac{\sqrt{h_k(\mathbf{t}^*)}}{\sum_{k=1}^{d+1}\sqrt{h_k(\mathbf{t}^*)}}, \quad k = 1, 2, \cdots, d+1.$$

This nicely exhibits that the weights depend on the support $\mathbf{t}^*$, then the optimal design problem is reduced to that of finding the optimal support vector $\mathbf{t}^*$.

(2) Scalar optimal design with correlated responses

If the m responses are correlated with covariance matrix Σ which is symmetric positive definite, then there exists a symmetric positive definite matrix V of rank m such that $V^2 = \Sigma$ or denotes as $V = \Sigma^{\frac{1}{2}}$. Let $\tilde{X} = XV^{-1}$, then we may rewrite $X\Sigma^{-1}X'$ to the form $\tilde{X}\tilde{X}'$ and obtain that

$$\begin{aligned} \tilde{X} &= (I_m \otimes F(\mathbf{t}))(I_m \otimes l(x))(V^{-1} \otimes 1) \\ &= (V^{-1} \otimes F(\mathbf{t}))(I_m \otimes l(x)) \\ &= F_\Sigma(\mathbf{t})(I_m \otimes l(x)) \end{aligned}$$

where $F_\Sigma(\mathbf{t}) = V^{-1} \otimes F(\mathbf{t})$. A similar procedure as in subsection 4.2.2 (1) yields

$$\begin{aligned} \mathrm{Var}(\mathbf{c}'\mathbf{b}) &= \mathrm{tr}((I_m \otimes P(\xi)^{-1})(F_\Sigma(\mathbf{t})^{-1}\mathbf{c}\mathbf{c}'(F_\Sigma(\mathbf{t})')^{-1})) \\ &= \sum_{i=1}^{m}\sum_{k=1}^{d+1} \frac{e_{ik}(\mathbf{t})}{p_k} = \sum_{k=1}^{d+1} \frac{\tilde{h}_k(\mathbf{t})}{p_k} \end{aligned} \tag{4.7}$$

where $e_{ik}(\mathbf{t})$ is the $[(d+1)(i-1)+k]$th diagonal element of $F_\Sigma(\mathbf{t})^{-1}\mathbf{c}\mathbf{c}'(F_\Sigma(\mathbf{t})')^{-1}$ and $\tilde{h}_k(\mathbf{t}) = \sum_{i=1}^{m} e_{ik}(\mathbf{t})$. The scalar optimal design is reduced in a similar way as in the uncorrelated case.

4.3 Optimal designs for calibrations

The calibration problem discussed here is based on the assumed regression model (4.1). It is of interest to find a suitable estimation of the corresponding control value x for a given target $\mathbf{T} = (T_1, \cdots, T_m)$ on the expected responses. Due to the fact that there is more than one target value to be achieved in the multiresponse case, and each response may meet its target value at different control values, we therefore consider the deviation of the expected response $E(Y_i(x))$ from its corresponding target value T_i for each component and define the optimal value of calibration point, say x_0, to be the one which minimizes the weighted sum of squares of such deviations within the range of x. More explicitly, with $w_i > 0$ and $\sum_{i=1}^{m} w_i = 1$, let

$$\psi(x) = \sum_{i=1}^{m} w_i [E(Y_i(x)) - T_i]^2,$$

then

$$x_0 \in \arg\min_{x \in \mathcal{X}} \psi(x).$$

The weights w_i's are chosen in a manner to reflect the impact of the deviation, the technique, the price, or other considerations about the experiments.

The objective of this study is to find an optimal calibration design ξ^*, which minimizes the MSE on the difference between x_0 and its estimator $\hat{x}_0$. That is, if Ξ is the set of all feasible designs on $\mathcal{X}$ then

$$\xi^* \in \arg\min_{\xi \in \Xi} E(\hat{x}_0 - x_0)^2.$$

In the following, we will focus on dual responses regression models. We assume that each target value is in the range of the corresponding regression function. If this is not the case, the outerpolation is used to find the corresponding control value. If the optimal control value x_0 is outside of the design region then the closest endpoint to x_0 is considered as the estimator of x_0.

4.3.1 Simple linear regression model

(1) The optimal control value x_0

Consider an experiment performed at an $x \in \mathcal{X}$, assumed that the two response variables are both with simple linear regression model,

$$\begin{cases} E(Y_1(x)) = \beta_{10} + \beta_{11}x; \\ E(Y_2(x)) = \beta_{20} + \beta_{21}x. \end{cases} \tag{4.8}$$

Let $s_i \in \mathcal{X}$ denote the value such that

$$E(Y_i(s_i)) = T_i = \beta_{i0} + \beta_{i1}s_i, \quad i = 1, 2, \tag{4.9}$$

then

$$\begin{aligned} \psi(x) &= \sum_{i=1}^{2} w_i[\beta_{i1}(x - s_i)]^2 = \sum_{i=1}^{2} w_i\beta_{i1}^2(x - s_i)^2 \\ &= (w_1\beta_{11}^2 + w_2\beta_{21}^2)[r(x - s_1)^2 + (1 - r)(x - s_2)^2], \end{aligned} \tag{4.10}$$

where $r = w_1\beta_{11}^2/(w_1\beta_{11}^2 + w_2\beta_{21}^2)$. It is clear that x_0 is the vertex of the parabola in (4.10), that is

$$x_0 = \phi(\beta) = rs_1 + (1 - r)s_2.$$

(2) The coefficient vector $\mathbf{c}_{\beta,\mathbf{T}}$

To estimate x_0, we use the Gauss-Markov estimator $\hat{x}_0 = \phi(\mathbf{b})$. Using the Taylor theorem and letting $\dot{\phi}_\beta = \frac{\partial}{\partial\beta}\phi(\beta)$, the approximation of the corresponding MSE under design ξ can be expressed as

$$E(\hat{x}_0 - x_0)^2 \approx \dot{\phi}_\beta' M(\xi)^{-1}\dot{\phi}_\beta = \mathbf{c}_{\beta,\mathbf{T}}' M(\xi)^{-1}\mathbf{c}_{\beta,\mathbf{T}},$$

where $\mathbf{c}_{\beta,\mathbf{T}} = \dot{\phi}_\beta = (\,\mathbf{c}'_{\beta_1,\mathbf{T}}, \mathbf{c}'_{\beta_2,\mathbf{T}}\,)'$ with

$$\mathbf{c}'_{\beta_1,\mathbf{T}} = \dot{\phi}'_{\beta_1} = (\,-\tfrac{r}{\beta_{11}} \quad -\tfrac{r}{\beta_{11}}[(2r-1)s_1 + (2-2r)s_2]\,)\,, \tag{4.11}$$

$$\mathbf{c}'_{\beta_2,\mathbf{T}} = \dot{\phi}'_{\beta_2} = (\,-\tfrac{1-r}{\beta_{21}} \quad -\tfrac{1-r}{\beta_{21}}[2rs_1 + (1-2r)s_2]\,)\,. \tag{4.12}$$

See e.g. Silvey [32], p.57.

Note that s_1, s_2 depend on T_1, T_2 according to the formula (4.9). Since vector $\mathbf{c}_{\beta,\mathbf{T}}$ contains the unknown parameter vector β, therefore, the optimal design obtained in the following is also called a **locally c-optimal design**. The problem of choosing a design minimizing the MSE has now turned to find a scalar optimal design.

(3) The optimal calibration design

From the property of a scalar optimal design, it holds that for the linear regression model (4.8) the support vector of an optimal design is $\mathbf{t}^* = (-1, 1)$. As defined in (4.4), we obtain

$$F(\mathbf{t}^*) = \begin{pmatrix} 1 & 1 \\ -1 & 1 \end{pmatrix} \quad \text{and} \quad F(\mathbf{t}^*)^{-1} = \begin{pmatrix} \frac{1}{2} & -\frac{1}{2} \\ \frac{1}{2} & \frac{1}{2} \end{pmatrix}. \tag{4.13}$$

Following from subsection 4.2.2 (1), we have the following Theorem.

Theorem 4.3.1 *Consider the linear regression model (4.8) with $\Sigma = I_2$, for the given target expected response value $\mathbf{T} = (T_1, T_2)$, the optimal calibration design is $\xi^* = p_1^*\delta_{-1} + p_2^*\delta_1$, with $p_k^* = \sqrt{h_k(\mathbf{t}^*)}/(\sum_{k=1}^2 \sqrt{h_k(\mathbf{t}^*)})$, where $h_k(\mathbf{t}^*) = \sum_{i=1}^2 (F_{[k]}^{-1}(\mathbf{t}^*)\mathbf{c}_{\beta_i,\mathbf{T}})^2$, $\mathbf{c}_{\beta_i,\mathbf{T}}$ is as in (4.11) and (4.12), and $F_{[k]}^{-1}(\mathbf{t}^*)$ is the kth row of $F(\mathbf{t}^*)^{-1}$ in (4.13) with $t^* = (-1, 1)$, $i, k = 1, 2$.*

If the responses are correlated, let $\Lambda = \text{diag}(\lambda_1, \lambda_2)$, where λ_i, $i = 1, 2$, are the eigenvalues of Σ, and let Q be the orthogonal matrix consisting of the corresponding eigenvectors such that $\Sigma = Q\Lambda Q'$, then take matrix

$$V = [v_{ij}]_{2\times 2} = \Sigma^{\frac{1}{2}} = Q\Lambda^{\frac{1}{2}}Q'. \tag{4.14}$$

Recalling formula (4.7) of Section 4.2.2(2), we have

$$\begin{aligned} F_\Sigma(\mathbf{t})^{-1}\mathbf{c}_{\boldsymbol{\beta},\mathbf{T}} &= (V \otimes F(\mathbf{t})^{-1}) \begin{pmatrix} \mathbf{c}_{\boldsymbol{\beta}_1,\mathbf{T}} \\ \mathbf{c}_{\boldsymbol{\beta}_2,\mathbf{T}} \end{pmatrix} \\ &= (\begin{pmatrix} v_{11} & v_{12} \\ v_{21} & v_{22} \end{pmatrix} \otimes \begin{pmatrix} \frac{1}{2} & \frac{1}{2} \\ -\frac{1}{2} & \frac{1}{2} \end{pmatrix}) \begin{pmatrix} \mathbf{c}_{\boldsymbol{\beta}_1,\mathbf{T}} \\ \mathbf{c}_{\boldsymbol{\beta}_2,\mathbf{T}} \end{pmatrix}, \end{aligned}$$

and obtain that $\tilde{h}_k(\mathbf{t}) = \sum_{i=1}^{2}(F_{[k]}^{-1}(\mathbf{t})\mathbf{u}_i)^2$ with $\mathbf{u}_i = v_{i1}\mathbf{c}_{\boldsymbol{\beta}_1,\mathbf{T}} + v_{i2}\mathbf{c}_{\boldsymbol{\beta}_2,\mathbf{T}}$. Then the optimal calibration design with correlated responses is obtained by replacing $h_k(\mathbf{t})$ in Theorem 4.3.1 with $\tilde{h}_k(\mathbf{t})$.

4.3.2 Quadratic regression model

In this subsection we consider the calibration problem of quadratic regression model,

$$\begin{cases} E(Y_1(x)) = \beta_{10} + \beta_{11}x + \beta_{12}x^2; \\ E(Y_2(x)) = \beta_{20} + \beta_{21}x + \beta_{22}x^2. \end{cases} \tag{4.15}$$

Through this section, for convenience, we assume that $\beta_{i2} > 0$, $i = 1, 2$. That is geometrically, the two parabolas are concave up with corresponding minimum point $q_i = -\beta_{i1}/(2\beta_{i2})$, $i = 1, 2$, respectively. The other cases are dealt in a same manner.

(1) The optimal control value x_0

For the quadratic model (4.15), it is possible that within $\mathcal{X}$ there may be more than one control value which may attain the same target value in each response. We therefore divide the discussions into three cases to find out the location of x_0 in order to decide the coefficient vector **c**.

Case 1: $q_1, q_2 \notin \mathcal{X}$.

If this is the case, then both of the regression functions are one-to-one over the entire design interval $\mathcal{X}$. Each function will assign the target value T_i to the unique control value s_i in $\mathcal{X}$ which satisfies

$$E(Y_i(s_i)) = T_i = \beta_{i0} + \beta_{i1}s_i + \beta_{i2}s_i^2, \quad i = 1, 2.$$

The optimal control value x_0 becomes

$$x_0 \in \arg\min_{x\in\mathcal{X}} \psi(x) = \arg\min_{x\in\mathcal{X}} \{\sum_{i=1}^{2} w_i[\beta_{i1}(x - s_i) + \beta_{i2}(x^2 - s_i^2)]^2\}.$$

Since ψ is a polynomial in x, the minimum point x_0 must be either a critical point of ψ or an endpoint of $\mathcal{X}$. If x_0 is a critical point, then there exists a number $r \in (0, 1)$ which can be expressed as a function of β such that

$$x_0 = rs_1 + (1 - r)s_2,$$

which is illustrated in a more detail in Appendix A.

Case 2: $q_1 \notin \mathcal{X}$ and $q_2 \in \mathcal{X}$.

In this case, the first quadratic function is one-to-one over $\mathcal{X}$ and will assign the target value T_1 to the unique control value s_1. As for the second function, assume that $q_2 \in (0, 1)$, we have the following two situations.

(i) If $E(Y_2(q_2)) < T_2 \leq E(Y_2(1))$, then the function may assign T_2 to two different control values s_2 and $\tilde{s}_2$ which satisfy $E(Y_2(s)) = T_2$, $s = s_2, \tilde{s}_2$ (see e.g. Figure 4.2). Setting $\Phi = \{1, -1, s_1, s_2, \tilde{s}_2, q_2\}$, if the minimum point x_0 is a critical point of ψ, then x_0 will be located between two points $\tilde{x}_1$, $\tilde{x}_2$ in Φ, which is illustrated in more details in Appendix B. Similarly as in Case 1, we can find a number $r \in (0, 1)$ expressed as a function of $\boldsymbol{\beta}$ such that

$$x_0 = r\tilde{x}_1 + (1 - r)\tilde{x}_2, \quad \tilde{x}_1, \tilde{x}_2 \in \Phi.$$

(ii) If $E(Y_2(1)) < T_2 \leq E(Y_2(-1))$ or $T_2 = E(Y_2(q_2))$ then the function will assign T_2 to one control value s_2 (see e.g. Figure 4.3). In a similar manner as in **(i)**, we have $x_0 = r\tilde{x}_1 + (1 - r)\tilde{x}_2$, $\tilde{x}_1, \tilde{x}_2 \in \Phi = \{1, -1, s_1, s_2, q_2\}$.

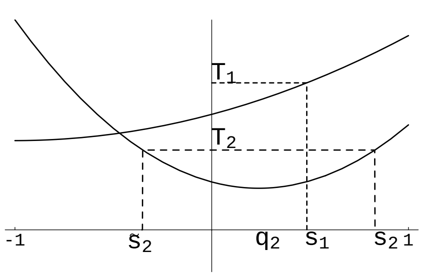

Figure 4.2: The quadratic function assigns T_2 to s_2 and $\tilde{s}_2$.

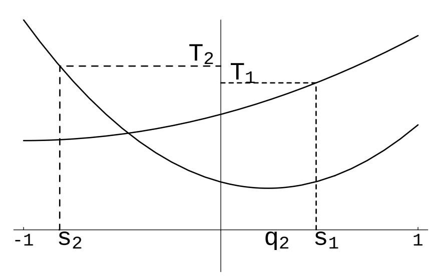

Figure 4.3: The quadratic function assigns T_2 to s_2.

Case 3: $q_1, q_2 \in \mathcal{X}$.

Similarly, the ith regression function may assign T_i to one or two control values s_i and $\tilde{s}_i$, $i = 1, 2$. Then $x_0 = r\tilde{x}_1 + (1-r)\tilde{x}_2$, $\tilde{x}_1, \tilde{x}_2 \in \Phi = \{1, -1, s_1, \tilde{s}_1, s_2, \tilde{s}_2, q_1, q_2\}$.

(2) The coefficient vector $\mathbf{c}_{\boldsymbol{\beta},\mathbf{T}}$

By the results obtained in subsection 4.3.2(1), let

$$\phi(\beta) = x_0 = r\tilde{x}_1 + (1-r)\tilde{x}_2, \quad \tilde{x}_1, \tilde{x}_2 \in \Phi,$$

and $\phi(\mathbf{b})$ is used to estimate x_0. Then the corresponding $\mathbf{c}$ vector for estimating x_0 can be expressed as $\mathbf{c}_{\beta,\mathbf{T}} = (\mathbf{c}'_{\beta_1,\mathbf{T}}, \mathbf{c}'_{\beta_2,\mathbf{T}})'$, with $\mathbf{c}_{\beta_i,\mathbf{T}} = \dot{\phi}_{\beta_i}$, $i = 1, 2$. Though the explicit formula for x_0 is not easy to find, but when x_0 is a critical point then $\dot{\psi}(x_0) = \dot{\psi}(x)|_{x=x_0} = 0$ defines x_0 implicitly as a function of β. Using implicit differentiation,

$$\dot{\phi}_{\beta_i} = \frac{\partial x_0}{\partial \beta_i} = -\frac{\partial \dot{\psi}(x_0)}{\partial \beta_i} \Big/ \frac{\partial \dot{\psi}(x_0)}{\partial x_0}, \tag{4.16}$$

$\mathbf{c}_{\beta,\mathbf{T}}$ can be obtained and is provided in Appendix C.

(3) The optimal calibration design

For a quadratic regression model, an optimal calibration design is with support vector $\mathbf{t}^* = (-1, t_2^*, 1)$. Now we have to determine the point t_2^*.

It follows from (4.4),

$$F(\mathbf{t}) = \begin{pmatrix} 1 & 1 & 1 \\ -1 & t_2 & 1 \\ 1 & t_2^2 & 1 \end{pmatrix}$$

and

$$F(\mathbf{t})^{-1} = \frac{1}{2(1-t_2^2)} \begin{pmatrix} t_2 - t_2^2 & t_2^2 - 1 & 1 - t_2 \\ 2 & 0 & -2 \\ -t_2^2 - t_2 & 1 - t_2^2 & 1 + t_2 \end{pmatrix}, \tag{4.17}$$

we obtain the following result from subsection 4.2.2(1).

Theorem 4.3.2 *Consider the quadratic regression model (4.15) with* $\Sigma = I_2$*, for the given target expected response value* $\mathbf{T} = (T_1, T_2)$*, the optimal calibration design is* $\xi^* = p_1^*\delta_{-1} + p_2^*\delta_{t_2^*} + p_3^*\delta_1$*, where*

$$t_2^* \in \arg\min_{t_2 \in (-1,1)} \sum_{k=1}^{3} \sqrt{h_k(\mathbf{t})},$$

with $h_k(\mathbf{t}) = \sum_{i=1}^2 (F_{[k]}^{-1}(\mathbf{t})\mathbf{c}_{\boldsymbol{\beta}_i,\mathbf{T}})^2$*,* $\mathbf{c}_{\boldsymbol{\beta}_i,\mathbf{T}}, i = 1,2$*, is defined as in (4.16) and* $F_{[k]}^{-1}(\mathbf{t})$ *is the kth row of* $F(\mathbf{t})^{-1}$ *in (4.17), and* $p_k^* = \sqrt{h_k(\mathbf{t}^*)}/(\sum_{k=1}^3 \sqrt{h_k(\mathbf{t}^*)})$*,* $k = 1,2,3$.

If the responses are correlated, the optimal calibration design is obtained by replacing $h_k(\mathbf{t}^*)$ in Theorem 4.3.2 with $\tilde{h}_k(\mathbf{t}^*) = \sum_{i=1}^2 (F_{[k]}^{-1}(\mathbf{t}^*)\mathbf{u}_i)^2$, where $\mathbf{u}_i = v_{i1}\mathbf{c}_{\boldsymbol{\beta}_1,\mathbf{T}} + v_{i2}\mathbf{c}_{\boldsymbol{\beta}_2,\mathbf{T}}$, and v_{ij}, $i,j = 1,2$, are defined as in (4.14).

A special case of Theorem 4.3.2 is when the targets T_1 and T_2 are the extreme values of the corresponding regression models, the points of extremum are $s_i = -\beta_{i1}/(2\beta_{i2})$, $i = 1,2$. We obtain $x_0 = rs_1 + (1-r)s_2$ with $r = (1 + \sqrt[3]{\frac{w_2\beta_{22}^2}{w_1\beta_{12}^2}})^{-1}$, w_1 is the corresponding weight for achieving the first target value. A similar procedure will lead to the optimal design.

Corollary 1 *Consider the dual responses quadratic regression model (4.15). Let the target expected response value* $T_i = \beta_{i0} - \beta_{i1}^2/(4\beta_{i2})$*,* $i = 1,2$*, be the* *extreme values of the two regression function respectively, then the optimal calibration design is* $\mathbf{c}$*-optimal with scalar vector* $\mathbf{c}_{\boldsymbol{\beta},\mathbf{T}} = (\, \mathbf{c}'_{\boldsymbol{\beta}_1,\mathbf{T}} \quad \mathbf{c}'_{\boldsymbol{\beta}_2,\mathbf{T}} \,)'$*, where*

$$\begin{aligned} \mathbf{c}'_{\boldsymbol{\beta}_1,\mathbf{T}} &= (\, 0 \quad \tfrac{r}{2\beta_{12}} \quad \tfrac{r}{\beta_{12}}(\tfrac{2}{3}(1-r)(s_2-s_1)+s_1)\,)\,, \\ \mathbf{c}'_{\boldsymbol{\beta}_2,\mathbf{T}} &= (\, 0 \quad \tfrac{1-r}{2\beta_{22}} \quad \tfrac{1-r}{\beta_{22}}(\tfrac{2}{3}r(s_1-s_2)+s_2)\,)\,, \end{aligned}$$

and $s_i = -\beta_{i1}/(2\beta_{i2})$*,* $i = 1, 2$*.*

4.4 An example

In this section an example discussed in Brown [5] is used to illustrate the procedure to exhibit the optimal calibration design of the multiresponse-univariate regression model. In this example, x is a scalar representing the viscosity of the paint samples, $x \in \mathcal{X} = [-1, 1]$. The response $\mathbf{y} = (y_1, y_2)$ is a bivariate observation vector consisting of two measurements on certain optical properties of the samples: y_1 is the spectrometer measurements of incident light and y_2 is the peak-height on a recording goniophotometer. We apply data from Brown [5] to be our prior information for choosing optimal calibration design in investigation. The sample covariance matrix for the dual responses is

$$S = \begin{pmatrix} 0.01 & -0.02 \\ -0.02 & 1.51 \end{pmatrix} \quad \text{and} \quad V = S^{\frac{1}{2}} = \begin{pmatrix} 0.10 & -0.02 \\ -0.02 & 1.23 \end{pmatrix}.$$

The correlation coefficient of the dual responses is $\rho = -0.16$. To standardize the variation of the two responses, we choose $w_1 = \frac{1}{\sigma_{11}}/(\frac{1}{\sigma_{11}} + \frac{1}{\sigma_{22}}) = 0.99$ and $w_2 = 1 - w_1 = 0.01$.

(1) Simple linear regression model

Following the procedure as in Brown [5], a linear regression model is fitted first. Then for a given target $\mathbf{T} = (1.74, 39.31)$, it can be seen that following the procedure discussed in subsection 4.3.1, we have

(i) $x_0 = \phi(\beta) = rs_1 + (1-r)s_2$,

where $r = \frac{0.99\beta_{11}^2}{0.99\beta_{11}^2+0.01\beta_{21}^2}$, $s_1 = \frac{1.74-\beta_{10}}{\beta_{11}}$ and $s_2 = \frac{39.31-\beta_{20}}{\beta_{21}}$.

(ii) Applying the prior data $\beta = (1.75, -0.13, 37.94, -1.69)'$ to formula (4.11) and (4.12), we obtain that

$$\mathbf{c}_{\beta,\mathbf{T}} = (2.84, -2.96, 0.37, -0.06)'.$$

(iii) By formulas extended from Theorem 4.3.2 for correlated responses,

$$\begin{aligned}
\mathbf{u}_1 &= 0.10\begin{pmatrix} 2.84 \\ -2.96 \end{pmatrix} - 0.02\begin{pmatrix} 0.37 \\ -0.06 \end{pmatrix} = \begin{pmatrix} 0.28 \\ -0.29 \end{pmatrix}, \\
\mathbf{u}_2 &= \begin{pmatrix} 0.40 \\ -0.01 \end{pmatrix}; \\
\tilde{h}_1(\mathbf{t}) &= \sum_{i=1}^{2}(F_{[1]}^{-1}(\mathbf{t})\mathbf{u}_i)^2 = \sum_{i=1}^{2}((\,\tfrac{1}{2} \quad -\tfrac{1}{2}\,)\,\mathbf{u}_i)^2 = 0.12, \\
\tilde{h}_2(\mathbf{t}) &= 0.04
\end{aligned}$$

This yields $p_1^* = \sqrt{0.12}/(\sqrt{0.12} + \sqrt{0.04}) = 0.63$. Thus, the optimal calibration design for target $\mathbf{T} = (1.74, 39.31)$ is $\xi^* = 0.63\delta_{-1} + 0.37\delta_1$.

Figure 4.4 is a plot of the posterior optimal weight p_1^* of design point -1 as a function of T_1 and T_2. Note that the design concentrates mass at high viscosity while the target values are both achieved at high viscosity, the converse is true, too. Figure 4.5 presents the efficiencies of the uniform design ξ_u with the least design points, $\xi_u = \frac{1}{2}\delta_{-1} + \frac{1}{2}\delta_1$, relative to the optimal calibration design, where the efficiency is defined as

$$\textit{efficiency of design } \xi_\mu = \frac{c_{\beta,\mathbf{T}}^T M(\xi^*)^{-1} c_{\beta,\mathbf{T}}}{c_{\beta,\mathbf{T}}^T M(\xi_u)^{-1} c_{\beta,\mathbf{T}}}.$$

Note that the efficiency approaches to 1 while the viscosities of the two targets are contrary, since in this situation an optimal calibration design would distribute the supports approximately as an uniform design. Meanwhile, the closer to the endpoint -1 or 1 of the two viscosities are, the less efficient the uniform design is.

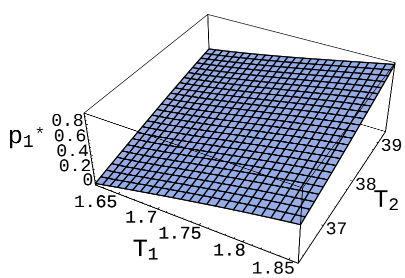

Figure 4.4: Plot of weight p_1^* with respect to T_1 and T_2.

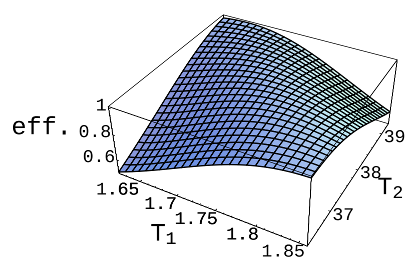

Figure 4.5: Plot of efficiency of design $\xi_u = \frac{1}{2}\delta_{-1} + \frac{1}{2}\delta_1$ relative to the optimal calibration design.

(2) Quadratic regression model

The quadratic regression model is considered secondly as in Brown [5], the optimal design for the same target $\mathbf{T} = (1.74, 39.31)$ is obtained as follows.

(i) From the prior data $\beta = (1.78, -0.13, -0.05, 38.61, -1.69, -1.01)'$, we obtain the following prior information on the two curves

$$\begin{pmatrix} q_1 & q_2 & s_1 & s_2 & \tilde{s}_2 \\ -1.30 & -0.83 & 0.28 & -0.75 & -0.92 \end{pmatrix}.$$

The optimal control value is $x_0 = -0.07$, which is located between s_1 and s_2, hence we may express it as $x_0 = 0.86s_1 + 0.14s_2$.

(ii) Applying the prior data β to formulas derived in subsection 3.2.2, we obtain the coefficient vector

$$\mathbf{c}_{\beta,\mathbf{T}} = (4.41, -1.35, 0.15, 1.82, -1.07, 0.87)'.$$

(iii) Substituting $\mathbf{c}_{\beta,\mathbf{T}}$ into formulas $\tilde{h}_k(\mathbf{t})$ for quadratic model and setting $\mathbf{t} = (-1, t_2, 1)$, we get $t_2^* = -0.02$. After evaluating the corresponding weight of design points by formulas extended from Theorem 4.3.2 for correlated responses, we obtain the optimal calibration design $\xi^* = 0.18\delta_{-1} + 0.68\delta_{-0.02} + 0.14\delta_1$ for the given $\mathbf{T}$.

Figures 4.6 to 4.9 are plots of the optimal design point t_2^* and optimal weights p_1^*, p_2^* and p_3^* as functions of target values T_1 and T_2 respectively. In view of the geometric shape of those plots, the ridge and the valley occur while the viscosities of the two targets are close, in that case, the optimal designs concentrate the mass near the similar viscosity targets. Figure 4.10 gives efficiencies of the uniform design $\xi_u = \frac{1}{3}\delta_{-1} + \frac{1}{3}\delta_0 + \frac{1}{3}\delta_1$ relative to the optimal calibration design, the uniform design is less efficient than the optimal calibration design especially when the target optical values are at closer viscosities.

Other than presenting results for quadratic model with two parabolas with both apexes up, the case that the quadratic model with one with an apex up and one with an apex down is also studied. The plots of the corresponding results are presented in Figure 4.11 to 4.15, which are similar to Figure 4.6 to 4.10, but the ridge rotates about 90 degrees.

(3) Linear-quadratic regression model

In Brown [5], a null hypothesis for testing $\beta_{12} = 0$ was accepted, which means there is no quadratic association between y_1 and x. This has generated a situation with linear and quadratic regressions for the dual responses. The model is presented as follows:

$$\begin{cases} E(Y_1(x)) = \beta_{10} + \beta_{11}x; \\ E(Y_2(x)) = \beta_{20} + \beta_{21}x + \beta_{22}x^2. \end{cases} \tag{4.18}$$

When the two regression functions are of different orders which makes it difficult to separate the support points and their weights as in (4.7). The method introduced above does not apply in this case, as we would need to solve three unknown values t_2^*, p_1^* and p_2^* simultaneously. At the moment, following the procedure provided in previous section, we use computation algorithm in Mathematica to find the optimal calibration design, which is somewhat complicated. The optimal design for target $\mathbf{T} = (1.74, 39.31)$ is $\xi^* = 0.31\delta_{-1} + 0.68\delta_{0.06} + 0.01\delta_1$. The efficiency of the optimal design for

Quadratic model: $\beta_{12} < 0$, $\beta_{22} < 0$, $\rho = -0.16$

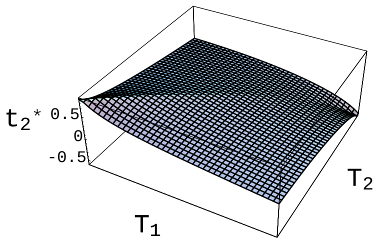

Figure 4.6: Plot of design point t_2^* corresponding to T_1 and T_2.

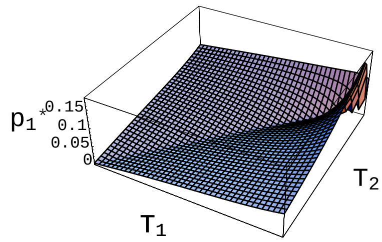

Figure 4.7: Plot of weight p_1^* corresponding to T_1 and T_2.

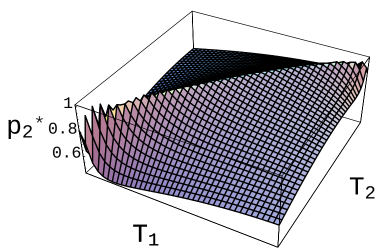

Figure 4.8: Plot of weight p_2^* corresponding to T_1 and T_2.

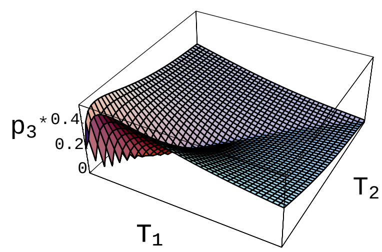

Figure 4.9: Plot of weight p_3^* corresponding to T_1 and T_2.

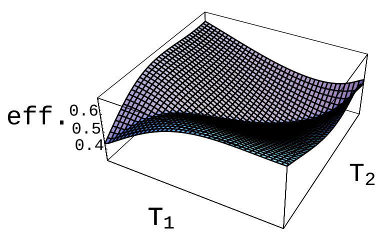

Figure 4.10: Plots of efficiency of design $\xi_u = \frac{1}{3}\delta_{-1} + \frac{1}{3}\delta_0 + \frac{1}{3}\delta_1$ relative to the optimal calibration design.

Quadratic model: $\beta_{12} < 0$, $\beta_{22} > 0$, $\rho = -0.16$

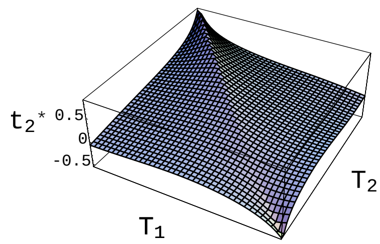

Figure 4.11: Plot of design point t_2^* corresponding to T_1 and T_2.

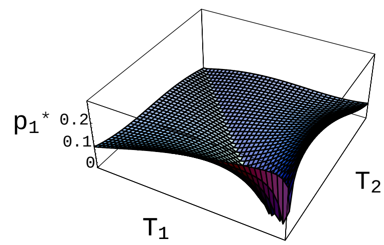

Figure 4.12: Plot of weight p_1^* corresponding to T_1 and T_2.

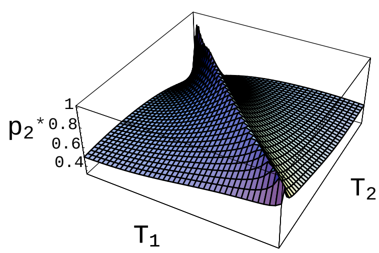

Figure 4.13: Plot of weight p_2^* corresponding to T_1 and T_2.

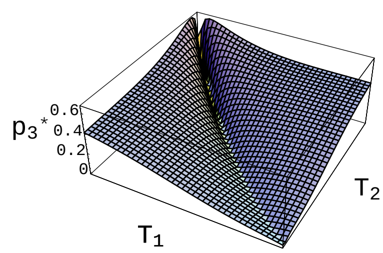

Figure 4.14: Plot of weight p_3^* corresponding to T_1 and T_2.

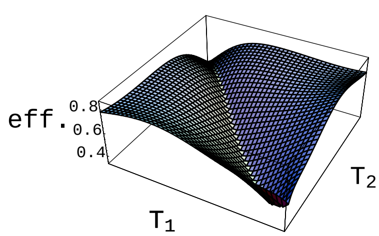

Figure 4.15: Plots of efficiency of design $\xi_u = \frac{1}{3}\delta_{-1} + \frac{1}{3}\delta_0 + \frac{1}{3}\delta_1$ relative to the optimal calibration design.

quadratic model in (4.15) relative to the optimal design for linear-quadratic model in (4.18) is 0.86.

4.5 Discussions

In this work, it is noteworthy that when the target control values s_1 and s_2 are nearby, these optimal calibration designs are suggesting the experimenters to take a higher proportion of the observations under the experimental conditions that are near the target control values. The prior information used for finding the optimal calibration designs is very helpful for increasing the efficiency of the design while comparing to a uniform design. Krafft and Schaefer [23] has shown that under rather mild assumptions the D-optimal designs for a multiresponse-univariate linear regression model do not depend on the covariance matrix of response variables. In this work, it is observed that the level of the correlation of the dual responses does make some differences on the corresponding optimal calibration design. In Table 4.1, it shows that the optimal designs concentrate more mass on design point t_2^* when the two responses are positively correlated. Meanwhile, the efficiencies of the uniform design ξ_μ and the optimal calibration design ξ_0^* with uncorrelated responses relative to the optimal calibration design ξ_ρ^* with correlation coefficient ρ under quadratic model for target $\mathbf{T} = (1.74, 39.31)$ are presented. In the last column of Table 4.1, it shows that the correlation of the dual responses can not be neglected when the two responses are highly correlated; but if the dual responses are more uncorrelated, then the optimal design for uncorrelated responses can be considered. To simplify the expressions we

Table 4.1: The efficiencies of designs ξ_μ and ξ_0^* relate to the corresponding optimal calibration designs $\xi_\rho^* = p_1^*\delta_{-1} + p_2^*\delta_{t_2^*} + p_3^*\delta_1$ under quadratic models with correlation coefficient ρ for target $\mathbf{T} = (1.74, 39.31)$.

ρ	p_1^*	p_2^*	p_3^*	t_2^*	Efficiencies of the uniform design ξ_u	Efficiencies of design ξ_0^*
-0.90	0.35	0.39	0.26	0.09	0.97	0.63
-0.60	0.25	0.56	0.19	0.01	0.80	0.89
-0.30	0.20	0.65	0.15	-0.01	0.68	0.97
0.00	0.16	0.72	0.12	-0.03	0.60	1
0.30	0.13	0.77	0.10	-0.04	0.53	0.98
0.60	0.09	0.84	0.07	-0.05	0.47	0.93
0.90	0.05	0.91	0.04	-0.06	0.40	0.83

have discussed the case with design interval $\mathcal{X} = [-1, 1]$. It is observed that the optimal designs are not invariant with scale changes on the design interval, but the theoretical result remains invariant except changing support $\mathbf{t}$ for a new scale.

There are other design issues for the polynomial regression models not yet addressed here. First, we have found the optimal design for calibrations on models with response functions up to the same order; occasionally a multiresponse polynomial model with unequal orders is used, see Chang [9] for example. The advantage of the procedure in finding the scalar optimal design in Section 2 is that the optimal weights may be obtained once the support points are determined which simplifies the problem significantly. If the orders of the model are unequal, the information matrix $M(\xi)$ fails to factor into two parts, matrix of design points and matrix of weights separately. The computation of finding optimal calibration designs becomes an ill specified problem. We therefore need an efficient algorithm to find the numerical solution.

Second, the optimal calibration designs presented here are only locally optimal, since the prior information concerning the model and the corresponding parameter values are needed for the design of an experiment and different targets deduce different optimal designs. If we have to calibrate more than one target simultaneously, some kind of robust design may be helpful to overcome the target-dependence of the calibration optimal design.

Third, we focus only on models with one-dimensional control variable; sometimes a multiresponse-multivariate design is used, see Brown [5] for example. Moreover if the regression function is nonlinear, computational methods for constructing optimal designs would be needed. All these design issues for calibrations will be discussed in the future.

4.6 Appendix

4.6.1 The optimal control value for $q_1, q_2 \notin \mathcal{X}$

Let $m_i(x) = \beta_{i1} + 2\beta_{i2}x$, be the derivative of the ith quadratic function in (4.15) with respect to x, $i = 1, 2$. Note that

$$\psi(x) = \sum_{i=1}^{2} w_i(x - s_i)^2[\beta_{i1} + \beta_{i2}(x + s_i)]^2$$

$$= \sum_{i=1}^{2} \frac{1}{4} w_i (x - s_i)^2 (m_i(x) + m_i(s_i))^2,$$

then the derivative of $\psi(x)$ with respect to x is

$$\begin{aligned} \dot{\psi}(x) &= \sum_{i=1}^{2} \frac{1}{2} w_i \{(x - s_i)(m_i(x) + m_i(s_i))^2 \quad (4.19) \\ &+ 2\beta_{i2}(x - s_i)^2 (m_i(x) + m_i(s_i))\} \\ &= \sum_{i=1}^{2} w_i (x - s_i)(m_i(x) + m_i(s_i)) m_i(x). \quad (4.20) \end{aligned}$$

Since the two regression functions are assumed to be monotonic on $\mathcal{X}$, hence $(m_i(x) + m_i(s_1))m_i(x) > 0, \forall x \in \mathcal{X}, i = 1, 2$. Thus $\dot{\psi}(x) = 0$ holds only when x is between s_1 and s_2. If x_0 is a critical point, then we can find a number $r \in (0, 1)$ expressed as a function of β such that $x_0 = rs_1 + (1-r)s_2$.

4.6.2 The optimal control value for $q_1 \notin \mathcal{X}$ and $q_2 \in \mathcal{X}$

Since $q_1 \notin \mathcal{X}$, it follows $[m_1(x) + m_1(s_1)]m_1(x) > 0, \ \forall x \in \mathcal{X}$. Recalling from (4.20) and letting $\dot{\psi}_2(x) = (x - s_2)(m_2(x) + m_2(s_2))m_2(x)$, the equation $\dot{\psi}(x) = 0$ holds only when $x - s_1$ and $\dot{\psi}_2(x)$ have opposite signs.

Setting $s_2 > \tilde{s}_2$, we obtain the sign analysis of $\dot{\psi}_2(x)$ in Table 4.2. It yields $\dot{\psi}_2(x) < 0$ if $-1 < x < \tilde{s}_2$ or $q_2 < x < s_2$, and on the contrary $\dot{\psi}_2(x) > 0$ if $\tilde{s}_2 < x < q_2$ or $s_2 < x < 1$. Thus, the critical points x_0 will be either in the set

$$[s_1, 1] \cap ([-1, \tilde{s}_2] \cup [q_2, s_2])$$

or

$$[-1, s_1] \cap ([\tilde{s}_2, q_2] \cup [s_2, 1]).$$

Table 4.2: The sign analysis of $\dot{\psi}_2(x)$

Interval	$(x - s_2)[m_2(x) + m_2(s_2)]m_2(x)$	$\dot{\psi}_2(x)$
$-1 < x < \tilde{s}_2$	$(-)(-)(-)$	$-$
$\tilde{s}_2 < x < q_2$	$(-)(+)(-)$	$+$
$q_2 < x < s_2$	$(-)(+)(+)$	$-$
$s_2 < x < 1$	$(+)(+)(+)$	$+$

We conclude that $x_0 \in (\tilde{x}_1, \tilde{x}_2), \tilde{x}_1, \tilde{x}_2 \in \Phi$, $(\tilde{x}_1, \tilde{x}_2)$ is the smallest interval contains x_0.

4.6.3 The coefficient vector

The derivative $\dot{\phi}_{\beta_i} = \frac{\partial x_0}{\partial \beta_i} = -\frac{\partial \dot{\psi}(x_0)}{\partial \beta_i} / \frac{\partial \dot{\psi}(x_0)}{\partial x_0}$, $i = 1, 2$, in (4.16) can be obtained after computation of the following derivatives.

$$\begin{aligned}
\frac{\partial \dot{\psi}(x_0)}{\partial \beta_{i0}} &= 2w_i m_i(x_0), \\
\frac{\partial \dot{\psi}(x_0)}{\partial \beta_{i1}} &= 2w_i(x_0 m_i(x_0) + E(Y_i(x_0)) - T_i), \\
\frac{\partial \dot{\psi}(x_0)}{\partial \beta_{i2}} &= 2w_i(x_0^2 m_i(x_0) + 2x_0(E(Y_i(x_0)) - T_i)), \\
\frac{\partial \dot{\psi}(x_0)}{\partial x_0} &= \sum_{i=1}^{2} 2w_i(m_i^2(x_0) + 2\beta_{i2}(E(Y_i(x_0)) - T_i)).
\end{aligned}$$

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