Optimal Designs for a Bivariate Logistic Regression Model

by

Mark A. Heise

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APPROVED:

Raymond H. Myers, Chair

Jeffrey B. Birch

Walter H. Carter, Jr.

Klaus H. Hinkelmann

Marvin M. Lentner

Marion R. Reynolds, Jr.

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Blacksburg, Virginia

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Abstract

In drug-testing experiments the primary responses of interest are efficacy and toxicity. These can be modeled as a bivariate quantal response using the Gumbel model for bivariate logistic regression. D-optimal and Q-optimal experimental designs are developed for this model. The Q-optimal design minimizes the average asymptotic prediction variance of p(1,0;d), the probability of efficacy without toxicity at dose d, over a desired range of doses. In addition, a new optimality criterion, T-optimality, is developed which minimizes the asymptotic variance of the estimate of the therapeutic index.

Most experimenters will be less familiar with the Gumbel bivariate logistic regression model than with the univariate logistic regression models which comprise its marginals. Therefore, the optimal designs based on the Gumbel model are evaluated based on univariate logistic regression D-efficiencies; conversely, designs derived from the univariate logistic regression model are evaluated with respect to the Gumbel optimality criteria.

Further practical considerations motivate an exploration of designs providing a maximin compromise between the three Gumbel-based criteria D, Q and T. Finally, 5-point designs which can be generated by fitted equations are proposed as a practical option for experimental use.

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Introduction and Literature Review

§1.1 Introduction

Experimental design, the primary focus of this paper, has its roots in the agricultural experiments of Fisher and has since flourished as an integral part of statistical research and practice. In the 1950's the concept of an optimal experimental design began to receive considerable attention. Since that time the idea of an optimal design has been expanded, with numerous optimality criteria and their application to various models introduced by statistical researchers (Atkinson 1982).

Much of the design work has focused on the linear model due to its simplicity and practicality. However, as the amount of statistical analysis using non-linear models increased in fields such as the chemical, biological and clinical sciences, the motivation for optimal designs for these models was provided. In particular, optimal designs for fitting binary data to a logistic regression have been the subject of numerous papers in the past fifteen years. This paper seeks to expand this work to include optimal designs for fitting bivariate binary data to a bivariate logistic model. This is a natural model for use in dose-ranging experiments in which the researcher would like to use logistic regressions to model drug efficacy and toxicity (Murtaugh and Fisher 1990).

It is important to note that the bivariate logistic model allows for correlation between efficacy and toxicity. It is preferable to include this correlation rather than to analyze efficacy and toxicity independently: it might be expected that the same biological mechanisms would affect each, resulting in positive correlation between the two. For example, Rowland and Tozer (1980) discuss how cigarette smoking simultaneously reduces the efficacy and toxicity of several therapeutic agents.

This dissertation develops traditional D-optimal designs for the bivariate logistic regression model. In addition, two other design optimality criteria are introduced which are uniquely applicable to the drug-testing situation. Q-optimality addresses prediction of the probability of drug efficacy without toxicity, while T-optimality addresses estimation of the therapeutic index of a drug.

§1.2 The Linear Model and Design Optimality

The early focus of mathematical statistics was upon analysis, with the questions of experimental design left largely up to the intuition of the researcher. As experimental situations became more complex, and thus more expensive, this approach was found to be unsatisfactory. Statistical researchers began actively seeking ways to maximize the information gained from a finite-sized experiment.

As previously mentioned, the vast majority of design optimality work has focused on the situation in which the standard linear model

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\epsilon}$$

is used. In this model

$$\mathbf{y} = \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix}, \quad \mathbf{X} = \begin{bmatrix} 1 & x_{11} & \dots & x_{1k} \\ 1 & x_{21} & \dots & x_{2k} \\ \vdots & \vdots & \ddots & \vdots \\ 1 & x_{n1} & \dots & x_{nk} \end{bmatrix}, \quad \boldsymbol{\beta} = \begin{bmatrix} \beta_0 \\ \beta_1 \\ \vdots \\ \beta_k \end{bmatrix}, \quad \boldsymbol{\epsilon} = \begin{bmatrix} \epsilon_1 \\ \epsilon_2 \\ \vdots \\ \epsilon_n \end{bmatrix},$$

where n equals the number of experimental runs and $k+1$ equals the number of parameters in the model. A common assumption is that of independent error terms with common variance σ^2. Under this assumption the ordinary least squares estimator of $\boldsymbol{\beta}$, $\hat{\boldsymbol{\beta}} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{y}$, has $\mathrm{Var}(\hat{\boldsymbol{\beta}}) = \sigma^2(\mathbf{X}'\mathbf{X})^{-1}$. The prediction variance is $\mathrm{Var}(\hat{y}_0) = \sigma^2\boldsymbol{x}_0'(\mathbf{X}'\mathbf{X})^{-1}\boldsymbol{x}_0$, where $\boldsymbol{x}_0' = (1, x_{01}, \dots, x_{0k})$ represents a particular location in the model space. These two variance quantities play key roles in the optimality criteria which are discussed below. Note that though both these quantities are model- and design-dependent, neither depends on the unknown parameters.

Kiefer and Wolfowitz (1959) laid a foundation upon which subsequent design optimality research has been built. Representing the design by a probability measure on the design space, they developed several design optimality criteria, including D-optimality, which is described below. In addition, persuasive arguments were presented showing the advantages of using optimal designs rather than designs which were in common use at the time.

The most well-known and commonly used of the design optimality criteria is D-optimality. The D-optimal design is defined as the one which maximizes $|\mathbf{X}'\mathbf{X}|$. In addition to its convenience as a norm for the variance-covariance matrix of $\hat{\boldsymbol{\beta}}$, the determinant of $(\mathbf{X}'\mathbf{X})$ is also inversely proportional to the

square of the volume of the confidence ellipsoid of $\boldsymbol{\beta}$. Thus, maximizing $|\mathbf{X}'\mathbf{X}|$ provides the smallest possible confidence region for $\boldsymbol{\beta}$, which the experimenter wishes to estimate.

A second common criterion is A-optimality. This criterion achieves reduction of the variance-covariance matrix of $\hat{\boldsymbol{\beta}}$ by summing the diagonal elements of $(\mathbf{X}'\mathbf{X})^{-1}$, i.e. the A-optimal design is the one in which trace$(\mathbf{X}'\mathbf{X})^{-1}$ is minimized. This gives the design in which the sum of the variances of the $\hat{\beta}_j$, $j = 0, 1, 2, ..., k$, is as small as possible. The A-optimality criterion does not use as much information as does D-optimality since it ignores the values of the covariance elements, which are the off-diagonal elements of $(\mathbf{X}'\mathbf{X})^{-1}$.

E-optimal designs are those which minimize the maximum eigenvalue of $(\mathbf{X}'\mathbf{X})^{-1}$. This is desirable since large prediction variances are associated with large eigenvalues of $(\mathbf{X}'\mathbf{X})^{-1}$. It can be shown that this criterion is equivalent to minimizing the maximum prediction variance on all spheres in the model space, i.e.

$$\min_{\mathrm{D}} \left[\max_{\|\boldsymbol{x}_0\| = r} \sigma^2 \boldsymbol{x}_0'(\mathbf{X}'\mathbf{X})^{-1}\boldsymbol{x}_0 \right],$$

where D is the design space, $\boldsymbol{x}_0'$ is any point in the model space and $r \geq 0$.

The criterion known as Q-optimality also directly addresses prediction variance. A Q-optimal design is defined to be one which minimizes the prediction variance integrated over the design region. Symbolically this is written as

$$\min_{\mathrm{D}} \left[\frac{n}{\mathrm{K}\sigma^2} \int_{\mathrm{R}} \mathrm{Var}[\hat{y}(\boldsymbol{x})] \, \mathrm{d}\boldsymbol{x} \right],$$

where D again is the design region, n is the total sample size and $\mathrm{K} = \int_{\mathrm{R}} \mathrm{d}\boldsymbol{x} =$

the volume of the region in which the researcher wishes to predict well. Q-optimal designs tend to give prediction variances which are fairly uniform throughout the design region.

G-optimality results in a choice of design which minimizes the maximum prediction variance over a given region, and is thus a minimax criterion. In the standard linear model it can be shown that the smallest possible value for $\max_{D}[n\mathrm{Var}(\hat{y})/\sigma^2]$ is $p = k+1$, the number of parameters in the model. This provides a ready benchmark for comparing any design to the G-optimal design.

A final class of optimality criteria are known as partial optimality criteria. These are used when a particular subset, or function of this subset, of the parameters is of particular interest. These criteria are also sometimes called singular optimality criteria since their application may result in singular designs. An example of this type of criterion is the partial D-optimality criterion where the optimal design is the one which minimizes the determinant of the appropriate submatrix of $(\mathbf{X}'\mathbf{X})^{-1}$. The submatrix of interest includes only those elements corresponding to the parameters of interest (Pázman 1986).

A small amount of work has been done regarding design optimality in the situation where linear models are used for each of several responses. This situation is more complicated than the single response case due to multiple unknown variance and covariance parameters to consider. Fedorov (1972) presented an algorithm for the construction of D-optimal designs for the multiple response situation, but his methodology requires that the variance-covariance matrix of the responses be known. Cooray-Wijesinha and Khuri (1987) expanded Fedorov's work to develop a sequential procedure for the construction of designs when the variance-covariance structure of the responses is unknown.

§1.3 Nonlinear Models and Design Optimality

Nonlinear models have a much more general form than do linear models and can be written as

$$\boldsymbol{y} = \boldsymbol{f}(\boldsymbol{x};\boldsymbol{\theta}) + \boldsymbol{\epsilon} \ ,$$

where $\boldsymbol{y}$ and $\boldsymbol{\epsilon}$ are n-dimensional vectors and $\boldsymbol{\theta}$ is a p-dimensional vector of parameters. If the maximum likelihood estimates of $\boldsymbol{\theta}$ are used, the variance-covariance matrix of these estimates $\widehat{\boldsymbol{\theta}}$ is asymptotically the inverse of the Fisher Information Matrix. The elements of the information matrix can be calculated as

$$I_{ij}(\boldsymbol{\theta}) = \mathrm{E}\left[\frac{\partial}{\partial\theta_i} lnL(\boldsymbol{\theta}) \cdot \frac{\partial}{\partial\theta_j} lnL(\boldsymbol{\theta})\right] = -\mathrm{E}\left[\frac{\partial^2}{\partial\theta_i\partial\theta_j} lnL(\boldsymbol{\theta})\right], \qquad (1.3.1)$$

where $L(\boldsymbol{\theta})$ is the likelihood function, assuming that all partial derivatives exist (Lehmann 1983). In the case of the linear model as previously considered, this is equal to $\sigma^2(\mathbf{X}'\mathbf{X})^{-1}$: a function of the design and the constant unknown parameter σ^2 only. Since σ^2 is a single constant, it can be factored out when constructing optimal designs. However, in the nonlinear case, the information matrix is also a function of the parameters $\boldsymbol{\theta}$ which one wishes to estimate. Thus the task of finding an optimal design is complicated by the fact that variances of parameter estimates and other functions of interest are dependent upon the unknown parameters.

One of the early articles dealing with optimal design in a nonlinear setting is by Box and Lucas (1959). In this paper they derive a D-optimal design and

show that the values of the derivatives in the information matrix depend on the parameter values themselves. Therefore one must assume that something is known about the parameters in advance of the experiment. They suggested that this knowledge might be achieved through experimentation in stages.

In a trio of articles, Draper and Hunter (1966, 1967a, 1967b) built on the foundation laid by Box and Lucas and address the question of design for multi-response situations in which the models are nonlinear. They addressed the need for knowledge about the parameters by incorporating both the idea of prior experimentation and the idea of Bayesian priors on the distribution.

§1.4 Logistic Regression and Design Optimality

One of the more popular nonlinear regression models is the logistic regression model for situations in which the response is dichotomous. Examples of cases in which this model may be appropriate include drug-testing, in which the response is either a cure or lack thereof; a test of an insecticide, where the response may be death or survival of the insect; and a test of the breaking point of a cable, in which the cable either breaks or does not. The logistic regression is commonly used in the fields of engineering and the biological and health sciences.

In its most general form, the probability p_i of a "success" at vector $\boldsymbol{x}_i$ of the independent variables is modeled as

$$p_i = \frac{1}{1+\exp(-\boldsymbol{x}_i'\boldsymbol{\beta})}. \tag{1.4.1}$$

Due to the complexity of the design issue in this situation, however, the research to this point has dealt almost exclusively with the simplest situation in which

$x_i' = (\ 1 \quad x_i\ )$ and $\beta' = (\ \beta_0 \quad \beta_1\ )$. This simple model is commonly used in bioassay, where it leads to the concept of tolerance. Each subject is assumed to have a given tolerance level below which there is no response to the treatment and above which there is a response. The tolerance distribution has the properties of a cumulative distribution function (cdf) and is modeled by the cdf. For the logistic probability density function this results in the probabilities given by (1.4.1). The logistic function corresponding to the logistic probability density function for the simple model above is written as

$$f(x) = \frac{\exp(-\beta_0 - \beta_1 x\ )}{(1 + \exp(-\beta_0 - \beta_1 x\ ))^2}\ .$$

Using this model, the observed information matrix is given by

$$I(\beta) = \begin{bmatrix} \sum_{i=1}^{m} n_i p_i(1-p_i) & \sum_{i=1}^{m} n_i p_i(1-p_i)x_i \\ \sum_{i=1}^{m} n_i p_i(1-p_i)x_i & \sum_{i=1}^{m} n_i p_i(1-p_i)x_i^2 \end{bmatrix},$$

where n_i = number of subjects at the i^{th} treatment level, p_i = the probability of a success at the i^{th} treatment level and m = the total number of treatment levels. Clearly in this case the information matrix is a function not only of the design through the treatment levels, but is also a function of the parameters β through the probabilities p_i.

Finney (1978), in his well-known volume on bioassay, presented a discussion of experimental design for the logistic regression in the context of estimating the relative potency of two preparations. Tables giving values of key quantities in the fiducial interval for relative potency were presented. Since these tables assume prior knowledge of the logistic regression curves, Finney also

discussed the effect of missed parameter estimates and how one might choose designs which are more robust to missed parameters.

One of the early works on optimal design for the 2-parameter logistic regression was by Kalish and Rosenberger (1978), who derived two point symmetric D-optimal and G-optimal designs. These designs are designated in terms of the LD_{100p} = (logit(p) - β_0) / β_1, where logit(p) = $ln\left(\frac{p}{1+p}\right)$ is a useful transformation of p. LD_{100p} stands for "lethal dose" at which proportion p of subjects given this dose will die, where death is the response being modeled. It is easily obtained by solving for the dose x_i in equation (1.4.1). It is sometimes known as ED_{100p} for "effective dose", and in this paper the notation will be ED_{100p} and TD_{100p} for "effective dose" and "toxic dose", respectively.

Abdelbasit and Plackett (1983) further pursued D-optimal designs with a discussion of robustness to parameter misspecification for 3-point versus 2-point designs. Sequential methods involving a small number of stages were also covered.

A more efficient 2-stage procedure was proposed by Minkin (1987), who allowed for unequal allocation of subjects among the treatment levels in the second stage to maximize the total log-likelihood. Kalish (1990) derived a method for finding compromise designs which estimate well the LD_{50} without placing design points too close to the center and thus sacrificing overall curve estimation.

Bayesian analogs to D-optimal and A-optimal designs were given by Chaloner and Larntz (1989). The experimenter may indicate the level of uncertainty through the specification of the prior distribution. It was shown that using this approach, the number of design points in the most efficient design may

be quite large when there is a high level of uncertainty in the location of the logistic curve.

Myers (1991) derived Q-optimal and G-optimal designs where the quantity of interest is Var(logit(p)). He also examined cross-efficiencies (e.g. D-efficiency of Q-optimal designs) of D-, G-, and Q-optimal designs and their robustness to parameter misspecification. He proposed a 2-stage "D-Q" design, where the first stage is a 3-point D-optimal design and the second is a 2-point conditionally Q-optimal design in which both the levels and the allocation may be asymmetric. For additional information regarding optimal designs and useful compromise designs see Myers *et al.* (1994).

Chapter 2
Bivariate Logistic Model

§2.1 Gumbel Model

In a drug-testing situation, two natural responses are efficacy and toxicity. If binary responses are used, the efficacy response is 1 if the drug has the desired effect; the toxicity response is 1 if the drug causes undesirable side-effects such as nausea or headaches. These responses are often modeled separately (Perucca and Pisani 1989) with the assumption that they are uncorrelated. However, since the two responses each come from the same subject it seems prudent to allow for correlation in the responses, i.e. model them as a bivariate response. Murtaugh and Fisher (1990) present the (second) "Gumbel model" for this purpose, based on the bivariate logistic cdf given by Gumbel (1961).

The Gumbel model is an attractive choice for several reasons. First, it includes a correlation parameter, α; when $\alpha = 0$ the model is equivalent to two independent logistic models. Second, the marginal densities of both toxicity and efficacy are logistic. This gives a natural link to previous optimal design work cited in §1.4.

There are other bivariate response models based on the logistic regression. Qu *et al.* (1987) present a generalized model of logistic regression which can accommodate multiple responses. However, it makes the restrictive requirement in the bivariate situation that the responses are symmetric. In the drug-testing

application this would imply that the probability of efficacy without toxicity equals the probability of toxicity without efficacy, a restriction which does not fit the application. Bonney (1987) presents a logistic regression model for dependent binary observations. This model is unattractive in the drug-testing application because the conditional probabilities, rather than the marginal probabilities, are logistic.

Lee *et al.* (1993) give a general form for a bivariate model in which the marginal responses follow a logistic regression model. The Gumbel model is a special case of this more general model in which the parameterization lends itself to easy interpretation in the context of drug-testing.

It was noted in §1.4 that in the univariate case the probability of a response at a given dose is expressed as the logistic cdf at that dose. A natural extension in the bivariate case is to express each of the four cell probabilities ((Y=0, Z=0), (Y=1, Z=0), (Y=0, Z=1) and (Y=1, Z=1); Y=1 $\Leftrightarrow$ drug efficacy; Z=1 $\Leftrightarrow$ drug toxicity) as the integral over the corresponding region of the bivariate logistic density. The proper regions are indicated in (2.1.2) below.

The standard Gumbel cdf is given by

$$F_{U,V}(u,v) = \frac{1}{1+e^{-u}} \cdot \frac{1}{1+e^{-v}} \cdot \left[1 + \frac{\alpha e^{-u-v}}{(1+e^{-u})(1+e^{-v})} \right], \quad -1<\alpha<1, \ -\infty<u,v<\infty. \tag{2.1.1}$$

Thus, if the dose d is transformed by the location parameter μ ($\mu_1 = \mathrm{ED}_{50}$, $\mu_2 = \mathrm{TD}_{50}$) and scale parameter σ to the "standard doses" $d_1 = \frac{d-\mu_1}{\sigma_1}$ for efficacy (Y) and $d_2 = \frac{d-\mu_2}{\sigma_2}$ for toxicity (Z), the following relationships can be used to find the individual cell probabilities:

$$p(1,1;d) = P(Y=1, Z=1 \mid D=d) = F(d_1, d_2)$$

$$= \frac{1}{1+e^{-d_1}} \cdot \frac{1}{1+e^{-d_2}} + \frac{\alpha e^{-d_1-d_2}}{\left(1+e^{-d_1}\right)^2 \left(1+e^{-d_2}\right)^2};$$

$$p(1,0;d) = P(Y=1, Z=0 \mid D=d) = F(d_1, \infty) - F(d_1, d_2)$$

$$= \frac{1}{1+e^{-d_1}} - \frac{1}{1+e^{-d_1}} \cdot \frac{1}{1+e^{-d_2}} - \frac{\alpha e^{-d_1-d_2}}{\left(1+e^{-d_1}\right)^2 \left(1+e^{-d_2}\right)^2};$$

$$p(0,1;d) = P(Y=0, Z=1 \mid D=d) = F(\infty, d_2) - F(d_1, d_2)$$

$$= \frac{1}{1+e^{-d_2}} - \frac{1}{1+e^{-d_1}} \cdot \frac{1}{1+e^{-d_2}} - \frac{\alpha e^{-d_1-d_2}}{\left(1+e^{-d_1}\right)^2 \left(1+e^{-d_2}\right)^2};$$

$$p(0,0;d) = P(Y=0, Z=0 \mid D=d) = 1 - F(d_1, \infty) - F(\infty, d_2) + F(d_1, d_2)$$

$$= 1 - \frac{1}{1+e^{-d_1}} - \frac{1}{1+e^{-d_2}} + \frac{1}{1+e^{-d_1}} \cdot \frac{1}{1+e^{-d_2}}$$

$$+ \frac{\alpha e^{-d_1-d_2}}{\left(1+e^{-d_1}\right)^2 \left(1+e^{-d_2}\right)^2}. \qquad (2.1.2)$$

When the Gumbel model is used as a cdf, α must satisfy $-1<\alpha<1$. However, for modeling bivariate binary data this requirement can be relaxed to permit any value α for which cell probabilities are in the interval [0,1] for all doses d. Using this criterion the minimum value for α is always -1 as derived in Appendix A.

The upper bound for α, though, is dependent on the parameters μ_1, σ_1, μ_2 and σ_2 and ranges from 1 to 4. Table 2.1 displays upper limits for α for different

combinations of μ_2 and σ_2, given $\mu_1 = 0$ and $\sigma_1 = 1$. (In §3.1 a transformation is given which transforms any parameterization to a standard parameterization where $\mu_1 = 0$ and $\sigma_1 = 1$ without affecting relative cell probabilities.) This table was derived by starting with cell probabilities as in Appendix A and finding the dose which minimizes the bound on α through the Nelder-Mead iterative search algorithm (Nelder and Mead 1965).

A quick look at the cell probabilities in (2.1.2) reveals that $\alpha < 0$ corresponds to negative correlation between efficacy and toxicity, $\alpha = 0$ to independence and $\alpha > 0$ to positive correlation. Murtaugh and Fisher (1990) give the correlation at dose d as

$$\text{Corr}(Y,Z \mid D=d) = \frac{\alpha}{\left(e^{d_1/2} + e^{-d_1/2}\right)\left(e^{d_2/2} + e^{-d_2/2}\right)}.$$

Cell probabilities are affected most by $\alpha \neq 0$ when $\mu_1 \approx \mu_2$. Figure 2.1 shows the individual logistic probability curves for a specific parameter combination.

Figures 2.2 and 2.3 illustrate the effect of setting $\alpha = -1$ and $\alpha =$ maximum allowable value for the specific parameter combination given in Figure 2.1. Figure 2.2 shows $p(1,0;d)$, the probability of efficacy without toxicity, as a function of dose. Note that the general shape is what one would expect. At low doses the drug is ineffective, resulting in low values for $p(1,0;d)$. As the dose increases, so does the efficacy, and with it the value of $p(1,0;d)$. When the dose reaches high levels, the probability of toxicity becomes high, causing the probability of efficacy without toxicity to decrease. Figures 2.2 and 2.3 both illustrate that different values of α affect the cell probabilities most for the central doses.

§2.2 Information Structure of the Gumbel Model

The importance of the information matrix in the design optimality problem was demonstrated in §1.4. The introduction of the correlation parameter in the Gumbel model creates a considerably more complex information matrix than in the univariate logistic model. Begin by writing the likelihood as

$$L(\boldsymbol{\theta}) = \prod_{m=1}^{k} \prod_{l=1}^{n_m} p(1,1;d_m)^{yz}\, p(1,0;d_m)^{y(1-z)}\, p(0,1;d_m)^{(1-y)z}\, p(0,0;d_m)^{(1-y)(1-z)},$$

where k = number of dosage levels, n_m = number of subjects at the m^{th} dose, $d_m = m^{th}$ dose and $y, z \in \{0,1\}$. The log-likelihood is then

$$ln\ L(\boldsymbol{\theta}) = \sum_{m=1}^{k} \sum_{l=1}^{n_m} \Big\{ yz \cdot ln\ p(1,1;d_m) + y(1-z) \cdot ln\ p(1,0;d_m) + (1-y)z \cdot ln\ p(0,1;d_m) + (1-y)(1-z) \cdot ln\ p(0,0;d_m) \Big\}.$$

If the parameter vector is represented by $\boldsymbol{\theta}' = (\mu_1 \quad \sigma_1 \quad \mu_2 \quad \sigma_2 \quad \alpha)$, the elements of the information matrix can be written as

$$I_{ij}(\boldsymbol{\theta}) = -E_{\boldsymbol{\theta}}\left[\frac{\partial^2\, ln\, L(\boldsymbol{\theta})}{\partial\theta_i \partial\theta_j}\right] = \sum_{m=1}^{k} I_{ij}(\boldsymbol{\theta}\,;\, d_m) \cdot n_m\,,$$

where n_m = the number of subjects at the m^{th} dose. Thus

$$I_{ij}(\boldsymbol{\theta}) = \sum_{m=1}^{k} n_m \left\{ \left(-\frac{\partial^2\, ln\ p(1,1;d_m)}{\partial\theta_i \partial\theta_j} \right) \cdot p(1,1;d_m) +$$

$$\left(-\frac{\partial^2 \, ln \; \mathrm{p}(1,0;d_m)}{\partial\theta_i \partial\theta_j}\right) \cdot \mathrm{p}(1,0;d_m) +$$

$$\left(-\frac{\partial^2 \, ln \; \mathrm{p}(0,1;d_m)}{\partial\theta_i \partial\theta_j}\right) \cdot \mathrm{p}(0,1;d_m) +$$

$$\left(-\frac{\partial^2 \, ln \; \mathrm{p}(0,0;d_m)}{\partial\theta_i \partial\theta_j}\right) \cdot \mathrm{p}(0,0;d_m)\Bigg\}, \qquad (2.2.1)$$

since E[yz] = p(1,1;d_m), E[y(1-z)] = p(1,0;d_m), E[(1-y)z] = p(0,1;d_m) and E[(1-y)(1-z)] = p(0,0;d_m). The task of finding the elements of the information matrix is simplified by noting that

$$\frac{\partial ln \; \mathrm{p}_{ab}}{\partial\theta_i} = \frac{1}{\mathrm{p}_{ab}} \cdot \frac{\partial \mathrm{p}_{ab}}{\partial\theta_i}, \qquad a,b = 0,1 \qquad (2.2.2)$$

and that

$$\frac{\partial^2 \, ln \; \mathrm{p}_{ab}}{\partial\theta_i \partial\theta_j} = -\left(\frac{1}{\mathrm{p}_{ab}}\right)^2 \left(\frac{\partial \mathrm{p}_{ab}}{\partial\theta_i}\right)\left(\frac{\partial \mathrm{p}_{ab}}{\partial\theta_j}\right) + \frac{1}{\mathrm{p}_{ab}} \cdot \frac{\partial^2 \mathrm{p}_{ab}}{\partial\theta_i \, \partial\theta_j}$$

$$= \frac{\mathrm{p}_{ab} \cdot \dfrac{\partial^2 \mathrm{p}_{ab}}{\partial\theta_i \partial\theta_j} - \left(\dfrac{\partial \mathrm{p}_{ab}}{\partial\theta_i}\right)\left(\dfrac{\partial \mathrm{p}_{ab}}{\partial\theta_j}\right)}{\mathrm{p}_{ab}^2}, \qquad a,b = 0,1 \qquad (2.2.3)$$

where $\mathrm{p}_{ab} = \mathrm{p}(a,b;d_m)$ is used for brevity. Further note that all the p_{ab} = p(a,b;d_m) can be expressed as sums of the following:

$$\mathbb{E}_1 = \frac{1}{1+e^{-d_1}},$$

$$\mathbb{E}_2 = \frac{1}{1+e^{-d_2}},$$

$$\mathbb{E}_1\mathbb{E}_2 = \frac{1}{1+e^{-d_1}} \cdot \frac{1}{1+e^{-d_2}} \ ,$$

$$\mathbb{A} = \frac{\alpha e^{-d_1-d_2}}{\left(1+e^{-d_1}\right)^2\left(1+e^{-d_2}\right)^2} \ .$$

Thus by finding the first and second partial derivatives of $\mathbb{E}_1$, $\mathbb{E}_2$, $\mathbb{E}_1\mathbb{E}_2$ and $\mathbb{A}$ with respect to $\theta_1 = \mu_1$, $\theta_2 = \sigma_1$, $\theta_3 = \mu_2$, $\theta_4 = \sigma_2$ and $\theta_5 = \alpha$ one can express the elements of the information matrix as

$$I_{ij}(\boldsymbol{\theta}) = \sum_{m=1}^{k} n_m \left\{ \frac{p_{11}\left(\frac{\partial^2 \mathbb{E}_1\mathbb{E}_2}{\partial\theta_i\partial\theta_j} + \frac{\partial^2 \mathbb{A}}{\partial\theta_i\partial\theta_j}\right) - \left(\frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial\theta_i} + \frac{\partial \mathbb{A}}{\partial\theta_i}\right)\left(\frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial\theta_j} + \frac{\partial \mathbb{A}}{\partial\theta_j}\right)}{p_{11}^2} p_{11} + \right.$$

$$\frac{p_{10}\left(\frac{\partial^2 \mathbb{E}_1}{\partial\theta_i\partial\theta_j} - \frac{\partial^2 \mathbb{E}_1\mathbb{E}_2}{\partial\theta_i\partial\theta_j} - \frac{\partial^2 \mathbb{A}}{\partial\theta_i\partial\theta_j}\right) - \left(\frac{\partial \mathbb{E}_1}{\partial\theta_i} - \frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial\theta_i} - \frac{\partial \mathbb{A}}{\partial\theta_i}\right)\left(\frac{\partial \mathbb{E}_1}{\partial\theta_j} - \frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial\theta_j} - \frac{\partial \mathbb{A}}{\partial\theta_j}\right)}{p_{10}^2} p_{10} +$$

$$\frac{p_{01}\left(\frac{\partial^2 \mathbb{E}_2}{\partial\theta_i\partial\theta_j} - \frac{\partial^2 \mathbb{E}_1\mathbb{E}_2}{\partial\theta_i\partial\theta_j} - \frac{\partial^2 \mathbb{A}}{\partial\theta_i\partial\theta_j}\right) - \left(\frac{\partial \mathbb{E}_2}{\partial\theta_i} - \frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial\theta_i} - \frac{\partial \mathbb{A}}{\partial\theta_i}\right)\left(\frac{\partial \mathbb{E}_2}{\partial\theta_j} - \frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial\theta_j} - \frac{\partial \mathbb{A}}{\partial\theta_j}\right)}{p_{01}^2} p_{01} +$$

$$\left(\frac{p_{00}\left(-\frac{\partial^2 \mathbb{E}_1}{\partial\theta_i\partial\theta_j} - \frac{\partial^2 \mathbb{E}_2}{\partial\theta_i\partial\theta_j} + \frac{\partial^2 \mathbb{E}_1\mathbb{E}_2}{\partial\theta_i\partial\theta_j} + \frac{\partial^2 \mathbb{A}}{\partial\theta_i\partial\theta_j}\right)}{p_{00}^2} \right.$$

$$\left. \left. - \frac{\left(-\frac{\partial \mathbb{E}_1}{\partial\theta_i} - \frac{\partial \mathbb{E}_2}{\partial\theta_i} + \frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial\theta_i} + \frac{\partial \mathbb{A}}{\partial\theta_i}\right)\left(-\frac{\partial \mathbb{E}_1}{\partial\theta_j} - \frac{\partial \mathbb{E}_2}{\partial\theta_j} + \frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial\theta_j} + \frac{\partial \mathbb{A}}{\partial\theta_j}\right)}{p_{00}^2} \right) \times p_{00} \right\} . \qquad (2.2.4)$$

The required partial derivatives of $\mathbb{E}_1$, $\mathbb{E}_2$, $\mathbb{E}_1\mathbb{E}_2$ and $\mathbb{A}$ are derived in Appendix B. Calculation of the information matrix has been accomplished with a computer program written in SAS PROC IML. The computer code is shown in Appendix E.

§2.3 Properties of the Information Matrix

Several properties of the information matrix are of interest in the examination of design optimality for this model. First it would be helpful to show that by parameterizing using μ and σ rather than β_0 and β_1 as presented in Chapter 1 optimal designs are not changed. Lehmann (1983) presented the relationship between information matrices under reparameterization as

$$\boldsymbol{I}^*(\boldsymbol{\beta}) = \boldsymbol{J}\boldsymbol{I}(\boldsymbol{\theta})\boldsymbol{J}', \qquad J_{ij} = \frac{\partial \theta_j}{\partial \beta_i},$$

where $\boldsymbol{\theta}$ and $\boldsymbol{\beta}$ represent the original parameterization and the reparameterization, respectively, of the model. In this case $\boldsymbol{\theta}' = (\mu_1 \quad \sigma_1 \quad \mu_2 \quad \sigma_2 \quad \alpha)$ and $\boldsymbol{\beta}' = (\beta_{10} \quad \beta_{11} \quad \beta_{20} \quad \beta_{21} \quad \alpha)$.

For D-optimal designs the determinant $|\boldsymbol{I}^*(\boldsymbol{\beta})| = |\boldsymbol{J}\boldsymbol{I}(\boldsymbol{\theta})\boldsymbol{J}'|$ is of interest. Note that $|\boldsymbol{J}\boldsymbol{I}(\boldsymbol{\theta})\boldsymbol{J}'| = |\boldsymbol{J}| \times |\boldsymbol{I}(\boldsymbol{\theta})| \times |\boldsymbol{J}'|$. Thus the determinants differ by a constant factor, implying that minimizing $|\boldsymbol{I}(\boldsymbol{\theta})|$ will also minimize $|\boldsymbol{I}^*(\boldsymbol{\beta})|$.

For the other optimality criteria under consideration in Chapter 3, the quantity $\boldsymbol{v}'\boldsymbol{I}^{-1}(\boldsymbol{\theta})\boldsymbol{v}$, where $\boldsymbol{v}$ is a vector of partial derivatives, is important. This is the expression which will be used to approximate the variance of estimated functions of the parameters. So it is desired that $\boldsymbol{v}^{*\prime}\boldsymbol{I}^{*-1}(\boldsymbol{\beta})\boldsymbol{v}^* = \boldsymbol{v}'\boldsymbol{I}^{-1}(\boldsymbol{\theta})\boldsymbol{v}$, where

$\boldsymbol{v}^*$ is the vector of partial derivatives under the reparameterization. This equality is proven in Appendix C.

If $\alpha = 0$, that is if the models for efficacy and toxicity are independent, the structure of the information matrix is simplified. Appendix D proves that the information matrix in this case has the following block diagonal form:

$$I(\boldsymbol{\theta}) = \begin{bmatrix} I_{11} & I_{12} & 0 & 0 & 0 \\ I_{21} & I_{22} & 0 & 0 & 0 \\ 0 & 0 & I_{33} & I_{34} & 0 \\ 0 & 0 & I_{43} & I_{44} & 0 \\ 0 & 0 & 0 & 0 & I_{55} \end{bmatrix}.$$

It is easily seen that under location shifts the information matrix remains invariant. This can be seen by noting that location shifts do not affect σ_1, σ_2 or α and that μ_1, μ_2 and the doses enter only through the adjusted doses d_1 and d_2 (see Appendix B).

One final property of the information matrix which shall be of interest is how it changes under a scale change, e.g. if different units are used. If items marked with $*$ have been rescaled by some factor r, then $d_1^* = \frac{d^* - \mu_1^*}{\sigma_1^*} = \frac{rd - r\mu_1}{r\sigma_1}$ $= \frac{d - \mu_1}{\sigma_1} = d_1$ and likewise $d_2^* = d_2$. It has already been noted that the doses and the location parameters μ enter the information matrix only through the adjusted doses d_1 and d_2.

By examination of the individual partial derivatives of $\mathbb{E}_1$, $\mathbb{E}_2$, $\mathbb{E}_1\mathbb{E}_2$ and $\mathbb{A}$ in Appendix B note that all first partial derivatives with respect to θ_i, $i = 1,2,3,4$, have a single σ in the denominator; first partial derivatives with respect to $\theta_5 = \alpha$ are functions of σ_1 and σ_2 only through d_1 and d_2. Likewise, second partial

derivatives with respect to θ_i and θ_j, $i,j = 1,2,3,4$, have two σ parameters in the denominator; second partial derivatives with respect to θ_i and $\theta_5 = \alpha$, $i = 1,2,3,4$ have a single σ parameter in the denominator; and second partial derivatives with respect to $\theta_5 = \alpha$ have no σ parameters. In all these cases the σ parameters enter otherwise only through d_1 and d_2. Thus by replacement in (2.2.4), $I^*(\theta^*)$, the information matrix under rescaling, can be written as

$$I^*(\theta^*) = \begin{bmatrix} r^{-2}I_{11} & r^{-2}I_{12} & r^{-2}I_{13} & r^{-2}I_{14} & r^{-1}I_{15} \\ r^{-2}I_{21} & r^{-2}I_{22} & r^{-2}I_{23} & r^{-2}I_{24} & r^{-1}I_{25} \\ r^{-2}I_{31} & r^{-2}I_{32} & r^{-2}I_{33} & r^{-2}I_{34} & r^{-1}I_{35} \\ r^{-2}I_{41} & r^{-2}I_{42} & r^{-2}I_{43} & r^{-2}I_{44} & r^{-1}I_{45} \\ r^{-1}I_{51} & r^{-1}I_{52} & r^{-1}I_{53} & r^{-1}I_{54} & I_{55} \end{bmatrix}, \qquad (2.3.1)$$

where r is the rescaling factor. This makes intuitive sense: since α is a correlation parameter, it is thus scale-free and should not be affected by a change in scale.

Table 2.1 Maximum Allowable Values for α

$(\mu_1^* = 0, \sigma_1^* = 1)$

	μ_2^*				
σ_2^*	0.0	0.5	1.0	1.5	2.0
0.5	3.61	2.73	2.17	1.80	1.55
1.0	4.00	3.21	2.58	2.20	1.87
1.5	3.85	3.20	2.72	2.35	2.06
2.0	3.61	3.12	2.73	2.42	2.17

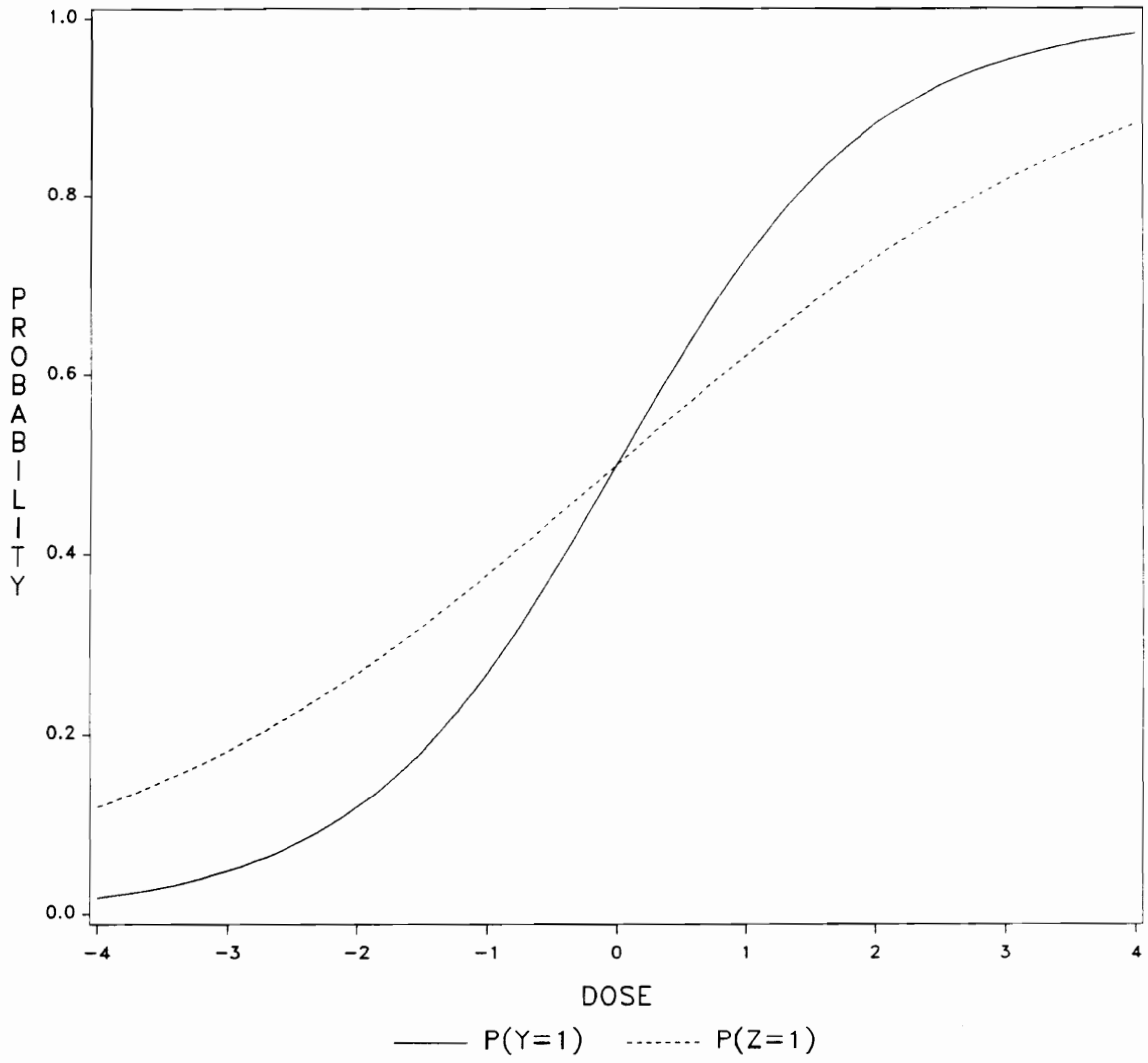

Figure 2.1 Individual Logistic Probability Curves ($\mu_1 = 0,\ \sigma_1 = 1;\ \mu_2 = 0,\ \sigma_2 = 2$)

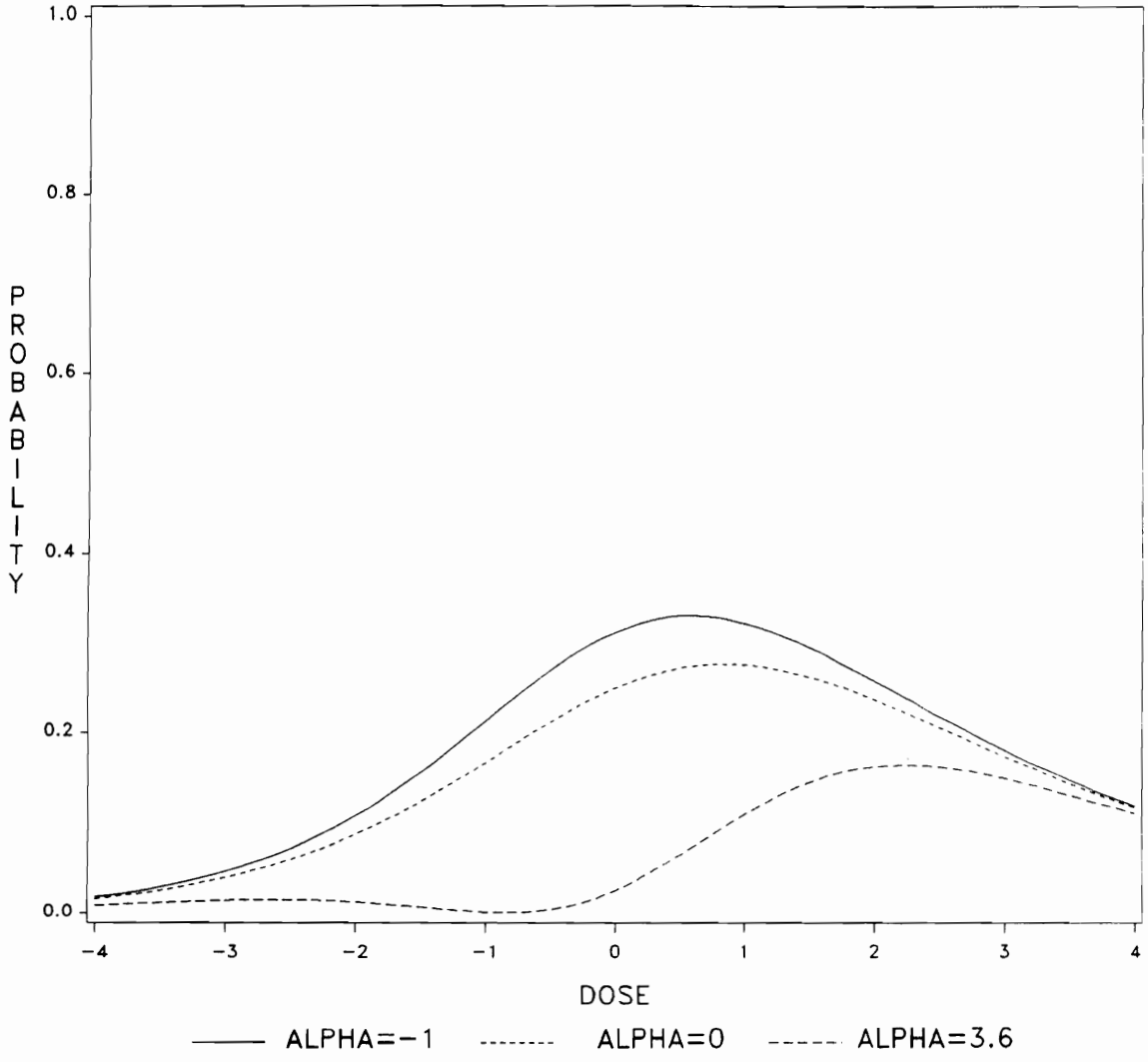

Figure 2.2 P(Y=1,Z=0) when $\mu_1 = 0,\ \sigma_1 = 1,\ \mu_2 = 0,\ \sigma_2 = 2$

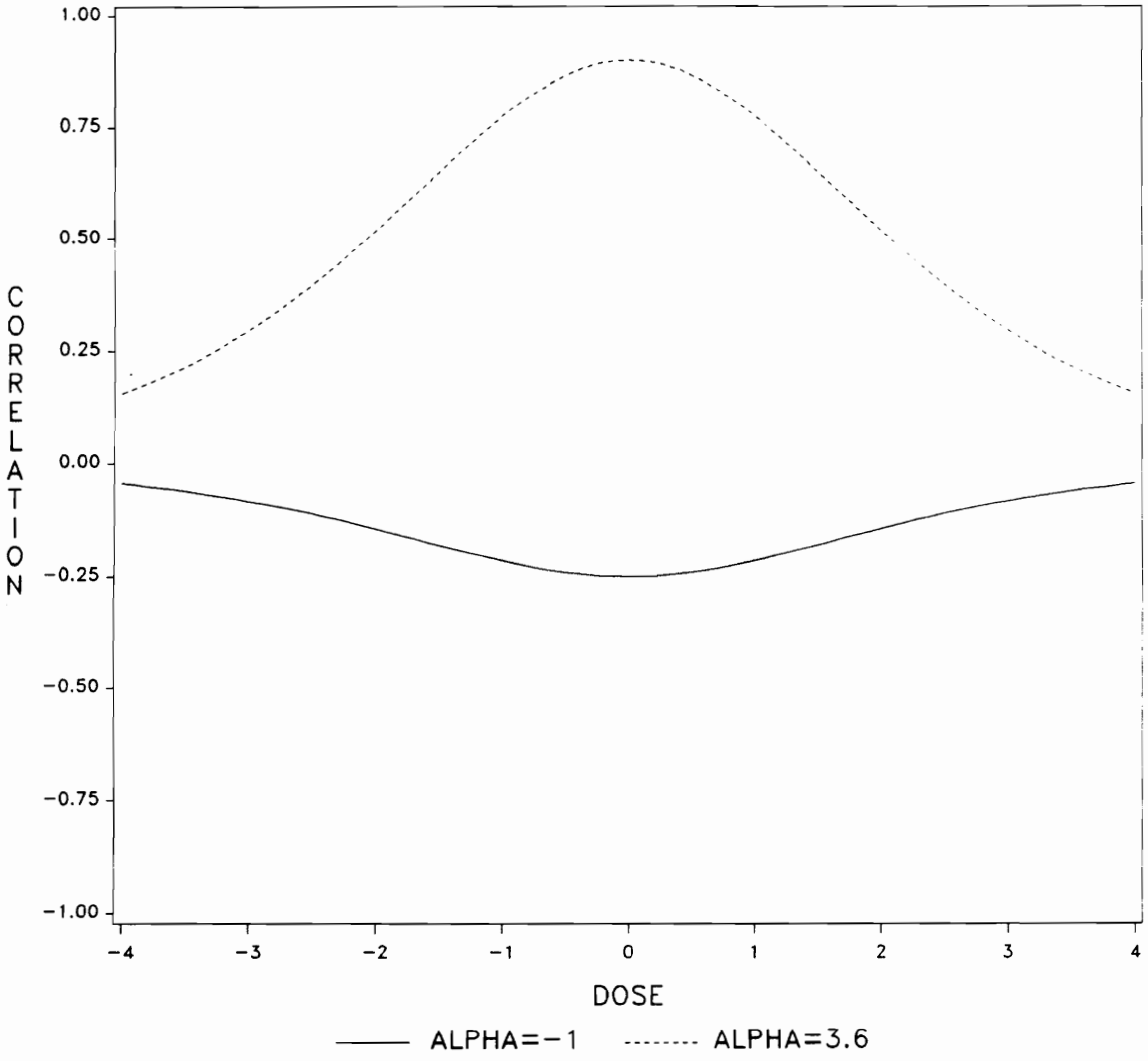

Figure 2.3 Correlation of Y and Z when $\mu_1 = 0,\ \sigma_1 = 1,\ \mu_2 = 0,\ \sigma_2 = 2$

Chapter 3
Optimal Designs for the Gumbel Model

§3.1 Design Considerations

Even in the case of symmetric 2-point designs for the simplest univariate models, as in Kalish and Rosenberger (1978), iterative methods were required to solve for the optimal design points. Thus it is clear that in the bivariate case, with its complex form for the information matrix, an iterative method will be necessary. The Nelder-Mead algorithm (Nelder and Mead 1965) as implemented using SAS PROC IML in Myers (1991) has been used. The Nelder-Mead algorithm requires that the number of points in the design be specified. Any restrictions on allocation of subjects to points in the design must also be specified.

Several types of designs are considered for the Gumbel model with varying numbers of design points and restrictions. It is desirable to be able to make numerical comparisons between different types of designs for any given design optimality criterion. This is accomplished by means of relative efficiency definitions which are given for each criterion.

There are a number of differences between the bivariate and univariate cases which shall become clear as they are discussed. Typically, the designs in the univariate case are symmetric about the ED_{50} and are expressed in terms of $ED_{50 \pm t}$. In the bivariate case there is a clear central dose only in the cases

where $\mu_1 = \mu_2$ or $\sigma_1 = \sigma_2$. In addition, since there are two responses it is no longer as helpful to express designs in terms of the ED_{100p}.

Due to these differences there will be no requirement for designs to be symmetric in any sense. Some sort of standard parameterization is desired so that tabulation of designs does not require five dimensions (one for each parameter). This can be achieved by transforming the doses and parameters as shown below:

$$
\begin{aligned}
d^* &= (d - \mu_1)/\sigma_1, \\
\mu_1^* &= (\mu_1 - \mu_1)/\sigma_1 = 0, \\
\sigma_1^* &= \sigma_1/\sigma_1 = 1, \\
\mu_2^* &= (\mu_2 - \mu_1)/\sigma_1, \\
\sigma_2^* &= \sigma_2/\sigma_1, \\
\alpha^* &= \alpha. \qquad (3.1.1)
\end{aligned}
$$

In earlier work for the univariate case 2- and 3-point designs with equal weighting for all design points were considered. Because of this and their simplicity, these designs were the first ones explored for the bivariate case in this research. The 2- and 3-point designs are discussed more fully and are tabled in the 1992 technical report which represents the early stages of this research (Heise and Myers 1992). Since equal sample sizes are required at each design point, the actual dosages completely specify the design. Thus these designs require the iterative search algorithm to search in 2 or 3 dimensions, respectively.

The next general type of design considered was a 3-point design with complete freedom in the proportion of subjects allocated to each design point.

This design is a generalization of the 2- and 3-point designs with equal weighting described in the previous paragraph since allocation of 0.0% of the subjects to one of the three dosages gives a two point design. These designs require the Nelder-Mead algorithm to search in five dimensions: one for each of the three design points and one for two of the three weightings. (The three weightings must sum to unity, so the third weighting is determined by the first two.) These designs are generally the best calculable given the constraints of the Nelder-Mead algorithm. For this reason, efficiencies for the various design optimality criteria will be calculated with respect to this class of designs.

A fourth type of design considered is a 5-point design with restrictions of equal weighting among the design points and equal spacing between the design points. These 5-point designs have been considered since most practitioners are unwilling to consider a 2- or 3-point design. By restricting the 5-point designs to those with equal weighting and equal spacing, a search in only two dimensions is permitted: if the value of any one of the five ordered doses and the spacing between the five doses are known then the design is completely specified.

Due to the restriction of equal spacing, this design is more stable than the others. In other words, 5-point designs can be expressed very closely as a simple function of the Gumbel parameters. This gives the advantage to the user that close approximations to these designs can be found without the use of the Nelder-Mead algorithm. In addition, the 5-point designs generally have high efficiencies. They will be discussed further in Chapter 4.

§3.2 D-optimal Designs

Previous work in which D-optimal designs were obtained for the univariate logistic model was described in §1.4. Recall that the D-optimal design is the one in which the determinant of the information matrix is maximized. It was observed in §2.3 that the information matrix is invariant to location shifts and (2.3.1) shows how its elements are affected by a change of scale.

It can be shown that the determinant under rescaling as in (3.1.1) is proportional to the determinant under original scaling; as a result dimensionality of the optimal design table can be reduced to three. Recall the definition of a determinant

$$|\mathbf{M}_{n\times n}| = \sum_{S} \pm m_{1j_1} m_{2j_2} \cdots m_{nj_n} ,$$

where $(j_1, j_2, \ldots, j_n)$ is a permutation of the set $\{1, 2, \ldots, n\}$ and S = set of all $n!$ permutations of $\{1, 2, \ldots, n\}$. If this is applied to (2.3.1) it is seen that, since in this case $r = \sigma_1^{-1}$ = rescaling factor,

$$|I^*(\theta^*)| = \sigma_1^8 |I(\theta)|,$$

where $I^*(\theta^*)$ is the information matrix using the rescaled doses and parameters.

Further reduction of the size of the table can be achieved by noting that with respect to D-optimality, the roles of the efficacy and toxicity parameters are interchangeable. Thus designs can be tabulated for only $\mu_2^* \geq 0$ if, by convention, transformation is by the parameter set which has the smaller value of μ. The optimal design tables contain D-optimal designs for all possible combinations of the following sets. The set $\alpha \in \{-1, 0, 1, 2\}$ begins at the lowest possible value of

α and goes up to a value for which correlation is quite high. The set $\sigma_2^* \in \{0.5, 1, 1.5, 2\}$ was used since it allows for a factor 2 ratio between the two scale parameters. Finally, the set $\mu_2^* \in \{0, 0.5, 1, 1.5, 2\}$ was chosen since it allows for a wide range of separation between the location parameters μ.

D-optimal designs with three points (unequal weighting) and five points (equal weighting, equal spacing) are displayed in Tables 3.1 and 3.2. Relative D-efficiencies of the 5-point designs with respect to the 3-point designs are given in Table 3.3. Relative D-efficiency is defined as

$$\text{D-efficiency(B|A)} = \left(\frac{|\boldsymbol{I}_B(\boldsymbol{\theta})|}{|\boldsymbol{I}_A(\boldsymbol{\theta})|}\right)^{1/5},$$

where $\boldsymbol{I}_B(\boldsymbol{\theta})$ is the information matrix of some design B and $\boldsymbol{I}_A(\boldsymbol{\theta})$ is the information matrix of design A (see Minkin 1987). D-efficiency defined in this way satisfies the practical description given in Kiefer and Wolfowitz (1959) that if D-efficiency(B|A) $= q$, then design A requires q times the number of subjects that design B does to achieve the same value for $|\boldsymbol{I}(\boldsymbol{\theta})|$. Note that the 5-point designs do quite well, with only a few D-efficiencies falling below 0.90.

To use these tables one needs to have initial guesses of the parameter values. In practice, the experimenter would probably feel more comfortable giving initial estimates of quantiles of the individual logistic curves than estimating the parameters, which is permissible since any two quantiles uniquely determine each marginal curve. As an example of how these tables might be used, the experimenter may be able to give initial estimates as follows: $\text{ED}_{20} = 3.2$, $\text{ED}_{50} = 6.0$, $\text{TD}_{20} = 5.2$ and $\text{TD}_{50} = 8.0$. Here, $\text{ED}_{50} = \mu_1 = 6.0$ and from (1.4.1), using $d_1 = \frac{d - \mu_1}{\sigma_1}$ instead of $\boldsymbol{x}'\boldsymbol{\beta}$, one can solve to obtain

$\sigma_1 = -\frac{ED_{20} - ED_{50}}{ln\,(.2^{-1} - 1)} = 2.02 \approx 2.0$. (In (1.4.1) with the specified replacement, $p_i = 0.20$, $d = ED_{20} = 3.2$ and $\mu_1 = ED_{50} = 6.0$.) Likewise, $TD_{50} = \mu_2 = 8.0$ and $\sigma_2 = 2.02 \approx 2.0$. Using (3.1.1) gives the standard parameterization $\mu_2^* = (\mu_2 - \mu_1)/\sigma_1 = 1.0$ and $\sigma_2^* = \sigma_2/\sigma_1 = 1.0$. Perhaps it is felt that moderate positive correlation is present between efficacy and toxicity, so that one guesses that $\alpha = 1$. Then from Table 3.2 the standardized 5-point D-optimal design is (-1.367, -0.433, 0.501, 1.435, 2.369). (The first of the five design points is -1.367 and the spacing is 0.934, giving each of the successive design points.) The inverse transformation $d = d^*\sigma_1 + \mu_1$ gives the desired D-optimal design as (3.266, 5.134, 7.002, 8.870, 10.738).

Note that all the tabled designs where $\sigma_1^* = \sigma_2^* = 1.0$ are symmetric about $(\mu_1^* + \mu_2^*)/2$ as one might expect. In addition, all the tabled designs except two where $\mu_2^* = 0$ are symmetric about $\mu_1^* = \mu_2^* = 0$. There are two 3-point unequal weighting designs where $\mu_2^* = 0$ which are anomalous: the designs for which $\sigma_2^* = 0.5$, $\alpha = 2$ and $\sigma_2^* = 2.0$, $\alpha = 2$. A natural question is whether there are symmetric designs which nearly match the performance of these optimal designs. With the restriction of symmetry the design (-1.018, 0, 1.018) with weighting (0.325, 0.350, 0.325) has D-efficiency of .9997 in the former case and the design (-2.035, 0, 2.035) with weighting (0.325, 0.350, 0.325) has D-efficiency of .9997 in the latter. These examples illustrate one way in which the inclusion of the correlation parameter α in the model leads to optimal designs which might not be otherwise expected.

The researcher may be interested in how the D-optimal design for the Gumbel model compares to the D-optimal design for the univariate logistic model when $\mu_1 = \mu_2 = 0$, $\sigma_1 = \sigma_2 = 1$ and $\alpha = 0$. Here it is consistent to

express the design in terms of the ED_{100p} since the parameters for the efficacy and toxicity models are identical. The 2-point D-optimal design for the Gumbel model is ($ED_{22.7}$, $ED_{77.3}$) = (-1.223, 1.223) while the comparable design for the univariate model is ($ED_{17.6}$, $ED_{82.4}$) = (-1.543, 1.543). If optimization is carried out for the Gumbel model utilizing only the determinant of the 4×4 submatrix of the information matrix excluding the α row and column, the univariate D-optimal design is achieved. The need to estimate α efficiently has drawn the design points toward the center.

Although direct comparison with univariate designs makes sense only when $\mu_1 = \mu_2$, $\sigma_1 = \sigma_2$ and $\alpha = 0$, one can compare designs obtained by using the 4×4 submatrix as mentioned above to those obtained using the full 5×5 information matrix when $\alpha = 0$. The relationship between the two methods for 2-point equally weighted designs, based on a small number of trials, appears to be that the spread of the two points in the $D_{5 \times 5}$-optimal design is approximately .8 times the spread of the points in the $D_{4 \times 4}$-optimal design. This is consistent with the example given in the previous paragraph. Intuitively one feels from looking at Figures 2.2 and 2.3 that since the presence of non-zero α has the greatest effect in the "center" of the range of doses, the design points need to move toward the center to efficiently estimate this parameter.

In the univariate case, the 2-point D-optimal design with equal sample sizes at each design point has the highest D-efficiency of all possible designs. The D-efficiency of the 3-point symmetric design ($ED_{13.6}$, ED_{50}, $ED_{86.4}$) with respect to the 2-point design is .930 (Abdelbasit and Plackett 1983, using D-efficiency definition from Minkin 1987). In Table 3.1 it can be seen that some of the optimal 3-point designs with unequal weighting simplify to 2-point designs

since the weighting for one of the points is 0.000; in other cases the optimal designs truly do have 3 points. Thus the number of points in the D-optimal design depends on the values of the Gumbel parameters.

§3.2.1 Robustness to Parameter Misspecification

The issue of robustness of designs to parameter misspecification is complex for the Gumbel model. For the univariate case a 2-dimensional plot or table of design efficiencies under parameter misspecification is obtained relatively easily. For the Gumbel model a 5-dimensional table is necessary for each parameter combination among the 3-dimensional space of standard designs. Generation of such a table is computationally intensive since it requires finding an optimal design at each misspecification of interest so that the specified design may be compared to it.

Due to the unwieldy nature of these robustness tables and because of the impossibility of completeness, none are included here. However, an attempt will be made to generalize some observations made from both 5-dimensional and 2-dimensional robustness tables which were generated for several assumed parameter combinations. This robustness work was done only with 2- and 3-point equally weighted designs due to computing limitations.

The D-optimal designs seem to be fairly robust to mild misspecification of parameters, that is $\frac{(\mu_1 - \mu_{10})}{\sigma_1} \in$ [-0.5, 0.5], $\frac{\sigma_1}{\sigma_{10}} \in$ [0.80, 1.25], $\frac{(\mu_2 - \mu_{20})}{\sigma_2} \in$ [-0.5, 0.5], $\frac{\sigma_2}{\sigma_{20}} \in$ [0.80, 1.25] and α ranging over the tabled values, where a subscript of 0 indicates the initial guess at the parameter value. In most cases the D-efficiencies are greater than .90.

There is definite "interaction" when certain parameters are misspecified simultaneously, and this makes it difficult to generalize results to five dimensions. An example will illustrate what is meant by "interaction". If one of the σ parameters is underestimated, the design used will have its points too close together and its efficiency will be less than unity. But if both σ parameters are simultaneously underestimated initially, the resulting efficiency will be less than what would be obtained by multiplying the efficiencies of misspecifying the σ parameters singly. Similarly, if one σ parameter is overestimated and the other underestimated, it is possible to have compensation and thus achieve efficiency of near unity. One may note from Tables 3.1 and 3.2 in Heise and Myers (1992) that in general the designs for larger values of α have design points which are pulled closer together. Thus there is also interaction if α and σ_1 or σ_2 are misspecified together. Simultaneous misspecification of the location parameters μ bring about interaction in an obvious way.

A final point worth noting in regard to robustness is that 3-point designs in general are more robust to serious departures from the initial parameter estimates than are 2-point designs. This is consistent with robustness in the univariate case as noted by Abdelbasit and Plackett (1983).

§3.3 Q-optimal Designs

Myers (1991) developed Q-optimal designs for the univariate logistic model. The objective was to minimize the integrated variance of the estimate of the logit $\left(ln\left(\frac{p}{1-p}\right)\right)$, where the range of integration is over the doses of interest. In the bivariate case the logit is no longer of primary interest. Rather, a

quantity is sought involving both efficacy and toxicity which the researcher may wish to estimate with minimum variance over some range of interest. One such quantity is p(1,0;d), the probability of a subject responding in the desired manner to the drug without the presence of toxic side effects.

Since p(1,0;d) is a nonlinear function of parameters in a nonlinear model it is clear that asymptotic methods need to be used to approximate the variance of its estimate. Using the delta method for asymptotic variance of a function of multiple parameters gives

$$\text{Var}\left(\hat{\text{p}}(1,0;d)\right) \approx \left(\frac{\partial}{\partial \boldsymbol{\theta}} \text{p}(1,0;d)\right)' \boldsymbol{I}^{-1}(\boldsymbol{\theta}) \left(\frac{\partial}{\partial \boldsymbol{\theta}} \text{p}(1,0;d)\right), \tag{3.3.1}$$

where $\frac{\partial}{\partial \boldsymbol{\theta}} \text{p}(1,0;d)$ is the 5×1 vector of partial derivatives evaluated at the true value of $\boldsymbol{\theta}$. The appropriate partial derivatives of $\text{p}(1,0;d) = \mathbb{E}_1 - \mathbb{E}_1\mathbb{E}_2 - \mathbb{A}$ may be obtained from Appendix B.

Now for Q-optimality the objective is to minimize, through proper design selection, this variance averaged over the region of interest. This is equivalent to minimizing the following integrated prediction variance:

$$\begin{aligned}
\text{IPV} &= \int_{d_l}^{d_h} \left(\frac{\partial}{\partial \boldsymbol{\theta}} \text{p}(1,0;x)\right)' \boldsymbol{I}^{-1}(\boldsymbol{\theta}) \left(\frac{\partial}{\partial \boldsymbol{\theta}} \text{p}(1,0;x)\right) dx \\
&= \int_{d_l}^{d_h} \text{trace}\left[\left(\frac{\partial}{\partial \boldsymbol{\theta}} \text{p}(1,0;x)\right)' \boldsymbol{I}^{-1}(\boldsymbol{\theta}) \left(\frac{\partial}{\partial \boldsymbol{\theta}} \text{p}(1,0;x)\right)\right] dx \\
&= \int_{d_l}^{d_h} \text{trace}\left[\left(\frac{\partial}{\partial \boldsymbol{\theta}} \text{p}(1,0;x)\right)\left(\frac{\partial}{\partial \boldsymbol{\theta}} \text{p}(1,0;x)\right)' \boldsymbol{I}^{-1}(\boldsymbol{\theta})\right] dx \\
&= \text{trace}\left[\int_{d_l}^{d_h} \left(\frac{\partial}{\partial \boldsymbol{\theta}} \text{p}(1,0;x)\right)\left(\frac{\partial}{\partial \boldsymbol{\theta}} \text{p}(1,0;x)\right)' dx \; \boldsymbol{I}^{-1}(\boldsymbol{\theta})\right],
\end{aligned} \tag{3.3.2}$$

where d_l and d_h are the extreme doses in the range of interest. The optimal design must be found iteratively; however, by rearranging the order of matrix multiplication the integration needs to be performed only once since the integrated terms are a function of the parameters only. The design enters only through the information matrix.

To minimize this integrated variance requires evaluation of the integral and an iterative method for finding the Q-optimal design. The integral is evaluated numerically using 24-point Gaussian quadrature. Gaussian quadrature appears to be quite adequate here, giving accuracy to five significant digits as compared to evaluation using a fine grid. The optimal design is found by means of the Nelder-Mead algorithm.

One issue in tabulating designs is how the region of interest should be chosen. In an actual experiment the researcher would simply indicate the dosage region of interest. For the tables of Q-optimal designs which were generated the endpoints were defined to be the lower and upper values at which $p(1,0;d) = 0.01$. The designs appear to change very little with the choice of end-points as long as the range is not drawn in too tightly.

For Q-optimal designs the same standard parameterization can be used as for D-optimal designs. The one difference is that the roles of the efficacy and toxicity parameters are distinct with respect to the Q-optimality criterion; therefore the value for μ_2^* must be extended below zero. The lower value chosen for the tables in this work is -1 since it is not thought that a drug which has TD_{50} much lower than the ED_{50} would be of interest to a researcher.

It is easy to show that the asymptotic variance is invariant to transformation to the standard parameterization. If $\boldsymbol{v}$ is used to denote the vector of

partial derivatives in the raw parameterization and $\boldsymbol{v}^*$ the vector of partial derivatives under the standard parameterization, then

$$\boldsymbol{v}^{*\prime} = [\sigma_1 v_1 \quad \sigma_1 v_2 \quad \sigma_1 v_3 \quad \sigma_1 v_4 \quad v_5] \, .$$

Also, from (2.3.1), since the rescaling factor $r = \sigma_1^{-1}$,

$$\boldsymbol{v}^{*\prime}\boldsymbol{I}^{*-1}(\boldsymbol{\theta}^*)\boldsymbol{v}^* = \begin{bmatrix} \sigma_1 v_1 \\ \sigma_1 v_2 \\ \sigma_1 v_3 \\ \sigma_1 v_4 \\ v_5 \end{bmatrix}' \begin{bmatrix} \sigma_1^{-2} I^{11} & \sigma_1^{-2} I^{12} & \sigma_1^{-2} I^{13} & \sigma_1^{-2} I^{14} & \sigma_1^{-1} I^{15} \\ \sigma_1^{-2} I^{21} & \sigma_1^{-2} I^{22} & \sigma_1^{-2} I^{23} & \sigma_1^{-2} I^{24} & \sigma_1^{-1} I^{25} \\ \sigma_1^{-2} I^{31} & \sigma_1^{-2} I^{32} & \sigma_1^{-2} I^{33} & \sigma_1^{-2} I^{34} & \sigma_1^{-1} I^{35} \\ \sigma_1^{-2} I^{41} & \sigma_1^{-2} I^{42} & \sigma_1^{-2} I^{43} & \sigma_1^{-2} I^{44} & \sigma_1^{-1} I^{45} \\ \sigma_1^{-1} I^{51} & \sigma_1^{-1} I^{52} & \sigma_1^{-1} I^{53} & \sigma_1^{-1} I^{54} & I^{55} \end{bmatrix} \begin{bmatrix} \sigma_1 v_1 \\ \sigma_1 v_2 \\ \sigma_1 v_3 \\ \sigma_1 v_4 \\ v_5 \end{bmatrix}$$

$$= \boldsymbol{v}'\boldsymbol{I}^{-1}(\boldsymbol{\theta})\boldsymbol{v} \, ,$$

where I^{ij} represents the ij-element of $\boldsymbol{I}^{-1}(\boldsymbol{\theta})$.

Tables 3.4 and 3.5 display 3-point unequal weighting and 5-point equal weighting, equal spacing Q-optimal designs. Note that unlike the D-optimal designs, if $\sigma_2^* \neq 1$, the designs for $\mu_2^* = 0$ are not symmetric. This is because of the asymmetry of p(1,0;d) when $\sigma_1 \neq \sigma_2$ (see Figure 2.2). The Q-optimal designs are symmetric when $\sigma_1 = \sigma_2$ ($\sigma_2^* = 1$): both the designs and the probability curve p(1,0;d) are symmetric about $(\mu_1^* + \mu_2^*)/2$. As in the D-optimal designs, in some cases the optimal designs as shown in Table 3.4 are 2-point designs and in other cases they are 3-point designs.

Relative Q-efficiencies are calculated as

$$\text{Q-efficiency(B|A)} = \frac{\text{IPV(A)}}{\text{IPV(B)}},$$

where Q-efficiency(B|A) is the efficiency of design B with respect to design A. Table 3.6 displays the relative Q-efficiencies of 5-point designs with respect to 3-point designs. Most of the 5-point design Q-efficiencies are greater than 0.90.

§3.3.1 Robustness to Parameter Misspecification

Q-optimal designs, like D-optimal designs, seem to be fairly robust to mild misspecification of parameters. However there are some significant differences in behavior under parameter misspecification which deserve discussion.

First, the "interaction" when multiple parameters are simultaneously misspecified, though certainly an issue with Q-optimal designs, is not as uniform as it is with D-optimal designs. So, for example, although the interaction of α and σ is similar for Q-optimal and D-optimal designs, the results are less consistent in Q-optimality.

Second, for σ_1 and σ_2 both overspecified there is negative interaction, as for the D-optimal designs. However, for Q-optimal designs with σ_1 and σ_2 both underspecified, there is no longer negative interaction. In the latter case there are still design points near the peak of p(1,0;d) where there is more variability; thus these designs do not do as poorly as one might expect.

Third, overspecification of μ_1 gives significantly worse results than underspecification of μ_1. Similarly, underspecification of μ_2 gives significantly

worse results than overspecification of μ_2. Even if μ_1 is underspecified and μ_2 is overspecified simultaneously the Q-efficiencies are quite good, provided only these two parameters are misspecified. When other parameters are misspecified as well, the situation is no longer as consistent.

§3.4 T-optimal Designs

A common way to characterize a drug is by its therapeutic index, which is defined as the ratio of the dose at which a specified level of toxicity is reached to the dose at which a specified level of efficacy is attained (Pessina *et al.* 1992). Large values for the therapeutic index are desirable since they indicate that toxicity is reached at far higher doses than is efficacy. Using the notation of this paper, the therapeutic index is written as $\mathrm{T} = \frac{\mathrm{TD}_{100p_2}}{\mathrm{ED}_{100p_1}}$, where p_2 is the specified quantile of toxicity and p_1 is the specified quantile of efficacy.

The researcher would thus like to estimate T with minimum variance. The design criterion which achieves this is called the T-optimality criterion. An alternate approach is to minimize the width of the fiducial interval for T as obtained using the method presented by Fieller (1944). The design criterion achieving this shall be referred to as the T_F-optimality criterion.

An important decision about the tabulated designs is what values of p_2 and p_1 to use in $\mathrm{T} = \frac{\mathrm{TD}_{100p_2}}{\mathrm{ED}_{100p_1}}$. A quick perusal of the bioassay literature reveals that the ED_{50} and TD_{50} receive the predominance of attention. Thus it was decided to use $p_2 = p_1 = .50$; in the subsequent discussion it is assumed that $\mathrm{T} = \frac{\mathrm{TD}_{50}}{\mathrm{ED}_{50}}$.

§3.4.1 Asymptotic Variance and Fiducial Interval Approaches

Both T-optimality and T_F-optimality are partial optimality criteria since T is a function of only the two parameters μ_1 and μ_2 (more generally, the four parameters μ_1, σ_1, μ_2 and σ_2). The asymptotic variance of $\hat{T}$, like the asymptotic variance of $\hat{p}(1,0;d)$, is calculated using the delta method. The therapeutic index is written as

$$T = \frac{TD_{50}}{ED_{50}} = \frac{\mu_2}{\mu_1}\,. \tag{3.4.1.1}$$

The vector of partial derivatives, $\boldsymbol{v}$, has elements as follows:

$$v_1 = \frac{\partial T}{\partial \mu_1} = \frac{-\mu_2}{{\mu_1}^2}\,,$$

$$v_2 = \frac{\partial T}{\partial \sigma_1} = 0,$$

$$v_3 = \frac{\partial T}{\partial \mu_2} = \frac{1}{\mu_1}\,,$$

$$v_4 = \frac{\partial T}{\partial \sigma_2} = 0,$$

$$v_5 = \frac{\partial T}{\partial \alpha} = 0. \tag{3.4.1.2}$$

The Nelder-Mead algorithm was used to find T-optimal designs based on minimization of the asymptotic variance function of $\hat{T}$,

$$VT = \boldsymbol{v}'\boldsymbol{I}^{-1}(\boldsymbol{\theta})\boldsymbol{v}. \tag{3.4.1.3}$$

Alternatively, one can base the optimality criterion on the fiducial interval for T (T_F-optimality). Following Fieller's method as presented in Finney (1978) the interval can be derived in the following fashion.

The estimator for T is $\hat{T} = \frac{\hat{\mu}_2}{\hat{\mu}_1}$ where $\hat{\mu}_1$ and $\hat{\mu}_2$ are the maximum likelihood estimates of μ_1 and μ_2. Consider the quantity $\hat{\mu}_2 - \hat{\mu}_1 T$. Since $\hat{\mu}_1$ and $\hat{\mu}_2$ are m.l.e.'s, asymptotically

$$E(\hat{\mu}_2 - \hat{\mu}_1 T) = 0.$$

In addition,

$$Var(\hat{\mu}_2 - \hat{\mu}_1 T) = Var(\hat{\mu}_2) - 2TCov(\hat{\mu}_1,\hat{\mu}_2) + T^2 Var(\hat{\mu}_1).$$

Exploiting the asymptotic normality of $\hat{\mu}_1$ and $\hat{\mu}_2$ and letting $V_{11}=Var(\hat{\mu}_1)$, $V_{12}=Cov(\hat{\mu}_1,\hat{\mu}_2)$ and $V_{22}=Var(\hat{\mu}_2)$ it is possible to write

$$Pr[z_{\phi/2}(V_{22}\text{-}2TV_{12}+T^2V_{11})^{.5} \leq \hat{\mu}_2 \text{ - } \hat{\mu}_1 T \leq z_{\phi/2}(V_{22}\text{-}2TV_{12} + T^2V_{11})^{.5}]$$

$$= 1 \text{ - } \phi,$$

where $z_{\phi/2}$ is the upper $\phi/2$ percent point of the standard normal distribution. (The notation ϕ is used here rather than the usual α to avoid confusion with the Gumbel parameter α.) Equivalently,

$$Pr[(\hat{\mu}_2 \text{ - } \hat{\mu}_1 T)^2 \leq z^2_{\phi/2}(V_{22}\text{-}2TV_{12} + T^2V_{11})] = 1 \text{ - } \phi.$$

Solving the expression within the probability operator for T will give $(1-\phi)\times 100\%$ fiducial bounds on T:

$$\hat{\mu}_2^2 - 2\mathrm{T}\hat{\mu}_1\hat{\mu}_2 + \hat{\mu}_1^2\mathrm{T}^2 = z_{\phi/2}^2\mathrm{V}_{22} - 2z_{\phi/2}^2\mathrm{T}\mathrm{V}_{12} + z_{\phi/2}^2\mathrm{T}^2\mathrm{V}_{11}$$

$$\Rightarrow \quad 0 = (z_{\phi/2}^2\mathrm{V}_{11} - \hat{\mu}_1^2)\mathrm{T}^2 + 2(\hat{\mu}_1\hat{\mu}_2 - z_{\phi/2}^2\mathrm{V}_{12})\mathrm{T} + (z_{\phi/2}^2\mathrm{V}_{22} - \hat{\mu}_2^2)$$

$$\Rightarrow \quad \mathrm{T} = \frac{-2(\hat{\mu}_1\hat{\mu}_2 - z_{\phi/2}^2\mathrm{V}_{12}) \pm \sqrt{4(\hat{\mu}_1\hat{\mu}_2 - z_{\phi/2}^2\mathrm{V}_{12})^2 - 4(z_{\phi/2}^2\mathrm{V}_{11} - \hat{\mu}_1^2)(z_{\phi/2}^2\mathrm{V}_{22} - \hat{\mu}_2^2)}}{2(z_{\phi/2}^2\mathrm{V}_{11} - \hat{\mu}_1^2)}$$

$$\Rightarrow \quad \mathrm{T} = \frac{-(\hat{\mu}_1\hat{\mu}_2 - z_{\phi/2}^2\mathrm{V}_{12}) \pm \sqrt{(\hat{\mu}_1\hat{\mu}_2 - z_{\phi/2}^2\mathrm{V}_{12})^2 - (z_{\phi/2}^2\mathrm{V}_{11} - \hat{\mu}_1^2)(z_{\phi/2}^2\mathrm{V}_{22} - \hat{\mu}_2^2)}}{-\hat{\mu}_1^2(1-g)},$$

$$\Rightarrow \quad \mathrm{T} = \frac{\hat{\mathrm{T}} - \frac{g\mathrm{V}_{12}}{\mathrm{V}_{11}} \pm \frac{z_{\phi/2}}{\hat{\mu}_1}\sqrt{\mathrm{V}_{22} - 2\hat{\mathrm{T}}\mathrm{V}_{12} + \hat{\mathrm{T}}^2\mathrm{V}_{11} - g(\mathrm{V}_{22} - \frac{\mathrm{V}_{12}^2}{\mathrm{V}_{11}})}}{(1-g)},$$

where $g = \dfrac{z_{\phi/2}^2\mathrm{V}_{11}}{\hat{\mu}_1^2}$. For T_F-optimality it is desired to minimize the width of this interval. However, in the design stage of the experiment, $\hat{\mu}_1$, $\hat{\mu}_2$ and $\hat{\mathrm{T}}$ are of course not available. Thus, for this criterion, the design is specified to minimize the expression

$$\frac{z_{\phi/2}}{(1-g)\mu_1}\sqrt{\mathrm{V}_{22} - 2\mathrm{T}\mathrm{V}_{12} + \mathrm{T}^2\mathrm{V}_{11} - g(\mathrm{V}_{22} - \frac{\mathrm{V}_{12}^2}{\mathrm{V}_{11}})}, \qquad (3.4.1.4)$$

where g has also been redefined as $g = \dfrac{z_{\phi/2}^2\mathrm{V}_{11}}{\mu_1^2}$ and the V_{ij} are the appropriate asymptotic variance quantities. Note that since g includes $z_{\phi/2}^2$ and V_{11}=Var($\hat{\mu}_1$), the placement of g in the minimized expression implies that the

T_F-optimal designs depend upon ϕ and the sample size n as well as the parameter values.

It is straightforward to show the asymptotic equivalence of the T-optimality and T_F-optimality criteria. Begin with the expansion of (3.4.1.3):

$$VT = \boldsymbol{v}'\boldsymbol{I}^{-1}(\boldsymbol{\theta})\boldsymbol{v} = v_1^2 I^{11} - 2v_1 v_3 I^{13} + v_3^2 I^{33},$$

where I^{ij} = the ij^{th} element of $\boldsymbol{I}^{-1}(\boldsymbol{\theta})$. Thus, $I^{11} = V_{11}$, $I^{13} = V_{12}$ and $I^{33} = V_{22}$. Therefore,

$$\begin{aligned} VT &= \left(\frac{\mu_2^2}{\mu_1^4}\right) V_{11} - 2\left(\frac{\mu_2}{\mu_1^3}\right) V_{12} + \left(\frac{1}{\mu_1^2}\right) V_{22} \\ &= \frac{1}{\mu_1^2}\left(T^2 V_{11} - 2TV_{12} + V_{22}\right). \end{aligned} \tag{3.4.1.5}$$

Now, T_F-optimal designs can be found by minimizing (3.4.1.4) squared, i.e.

$$\frac{z_{\phi/2}^2}{(1-g)^2\mu_1^2}\left(V_{22} - 2TV_{12} + T^2V_{11} - g(V_{22} - \frac{V_{12}^2}{V_{11}})\right). \tag{3.4.1.6}$$

But $\lim_{n\to\infty} V_{11} = 0 \Rightarrow \lim_{n\to\infty} g = 0$. Thus, asymptotically, minimizing (3.4.1.6) is equivalent to minimizing

$$\frac{z_{\phi/2}^2}{\mu_1^2}\left(V_{22} - 2TV_{12} + T^2V_{11}\right),$$

which is equivalent to minimizing (3.4.1.5).

One could also give an interpretation which parallels the usual bioassay interpretation: (3.4.1.5) is approximately equal to (3.4.1.6) if $g \approx 0$. Here g is an "index of the significance of the difference of the denominator from 0." The resulting interpretation is that the methods are approximately equivalent if the denominator of $\hat{T}$ ($\hat{\mu}_1 = \hat{ED}_{50}$) is enough larger than 0.

In addition to the asymptotic result derived above, exploratory work has indicated that there are no significant differences between T-optimal and T_F-optimal designs except in cases where there is high probability of either an effective response or a toxic response at dose $d = 0$ ($P(Y{=}1|d = 0) \geq .20$ or $P(Z{=}1|d = 0) \geq .20$). This situation seems unlikely unless there is an unusually large placebo effect.

To compare the two criteria it is necessary to define T-efficiency and T_F-efficiency. Relative T-efficiency is defined as

$$\text{T-efficiency(B|A)} = \frac{\text{VT(A)}}{\text{VT(B)}},$$

where T-efficiency(B|A) is the efficiency of design B with respect to design A. Relative T_F-efficiency is defined as

$$T_F\text{-efficiency(B|A)} = \frac{\text{WFI}^2\text{(A)}}{\text{WFI}^2\text{(B)}},$$

where WFI^2(A) is the squared width of the fiducial interval based on design A.

Take as an illustration the parameter estimates given in the Murtaugh and Fisher (1990) example: $\hat{\mu}_1 = 1.08$, $\hat{\sigma}_1 = 1.45$, implying $\hat{P}(Y{=}1|d = 0) = .32$; $\hat{\mu}_2 = 2.31$, $\hat{\sigma}_2 = 0.81$, implying $\hat{P}(Z{=}1|d = 0) = .05$. This seems to be a fairly extreme case (the model implies that the probability of drug effectiveness at dose $d = 0$ is .32), yet the T-efficiency of the T_F-optimal design and the T_F-efficiency of the T-optimal design both exceeded .970.

Due to the similarity of the T-optimal and T_F-optimal designs, it would seem redundant to table both. Therefore, due to the relative simplicity of the T-optimality concept and since the T_F-optimal designs are not invariant to ϕ

and sample size n, the remainder of this research considers only T-optimal designs.

Unlike the D- and Q-optimality criteria, the T-optimality criterion is not invariant to location shifts, as can be seen by looking at (3.4.1.2). This presents no problem, however, since in a drug-testing experiment the zero dose is absolute and there should be no need for a location shift. The criterion is invariant to changes in scale, though, which is important since one would not want the optimal design to change just because different measurement units are being used. The proof of invariance to changes in scale is identical to the one offered in §3.3 for Q-optimality.

Since T-optimality is not invariant to location shifts, a choice needed to be made regarding the location parameters for tabled optimal designs. It was decided to use a standard of $\mu_1^* = 6$ since for larger values the optimal designs are essentially equivalent after adjustment for the location shift. The same values for the scale parameters σ^* as in the other tables were used, as well as the standardized differences between μ_2 and μ_1. Here the doses and parameters are scaled slightly differently than in (3.1.1):

$$d^* = d/\sigma_1,$$

$$\mu_1^* = \mu_1/\sigma_1 \ (= 6),$$

$$\sigma_1^* = \sigma_1/\sigma_1 = 1,$$

$$\mu_2^* = \mu_2/\sigma_1,$$

$$\sigma_2^* = \sigma_2/\sigma_1,$$

$$\alpha^* = \alpha.$$

This allows for comparison of designs obtained using the different optimality criteria (see §3.5).

When using the delta method for approximate variance of a ratio, the denominator must be several sigma units away from zero. A program was written and run to check what sample size is required for the denominator to be three standard deviations away from zero for the tabled parameter combinations ($\mu_1 = 6$) and the D-optimal, Q-optimal and T-optimal designs. Most of the cases only required sample size of 2 or 3 and the maximum required was 8. This is a far smaller sample than would be used in an experiment of this nature; thus this approximation appears to be adequate.

Tables 3.7 and 3.8 display 3-point unequal weighting and 5-point equal weighting, equal spacing T-optimal designs. Note that designs for $\mu_1 = \mu_2 = 6$ are essentially 1-point designs at dose $d = 6$. Here a strict 1-point design is not generated because it would lead to singularity of the information matrix. The relative T-efficiencies of the 5-point designs with respect to the 3-point designs are displayed in Table 3.9.

In the initial work on the T-optimal designs, the criterion was defined in terms of $ln\ (\hat{T})$ instead of $\hat{T}$. It is interesting to note that the optimal designs produced under the two criteria were identical, as were the relative efficiencies of the 3- and 2-point T-optimal designs.

§3.4.2 Robustness to Parameter Misspecification

Exploratory work has shown that T-optimal designs appear to be less robust to parameter misspecification than are D- or Q-optimal designs. This is

not surprising when one considers the 1-point nature of the T-optimal designs when $\mu_1 = \mu_2 = 6$.

One interesting feature of the robustness properties of T-optimal designs is that the designs are more robust if σ_1 and/or σ_2 are underestimated than if they are overestimated. In terms of the design, it is better to have the design points pulled in too closely than to have them spread too far apart.

A second feature of the T-optimal designs is that they are more robust to misspecification of the scale parameters σ_1 and σ_2 than to the location parameters μ_1 and μ_2. This might be expected since the therapeutic index has been defined in terms of μ_1 and μ_2 only.

§3.5 Comparisons of Optimal Designs Under Various Criteria

Given the three optimality criteria presented here, D-, Q- and T-optimality, one naturally wonders how efficient each type of optimal design is with respect to the other criteria. Tables 3.10 - 3.12 attempt to address that question by presenting cross-efficiencies of the optimal 2- and 3-point designs.

The D-efficiencies of the Q-optimal designs are in general quite high, with many above .90. All the 3-point unequally weighted Q-optimal designs have D-efficiencies greater than 0.79. The Q-efficiencies of the corresponding D-optimal designs are fairly good as well, but in general are not as high. These Q-efficiencies are above .80 for all tabled cases where $\sigma_2^* = 1$ or $\sigma_2^* = 1.5$. However, when σ_1 and σ_2 differ by a factor of 2.0 ($\sigma_2^* = 0.5$ or $\sigma_2^* = 2.0$), the Q-efficiencies of the tabled 3-point unequally weighted designs are frequently between 0.70 and 0.80.

In general, the D-optimal and Q-optimal designs are much more similar to one another than they are to the T-optimal designs. The cross-efficiencies of both D- and Q-optimal designs with T-optimal designs are generally lower than the cross-efficiencies of the Q-optimal designs with the D-optimal designs. Note the near-zero D- and Q-efficiencies of the T-optimal designs when $\mu_1 = \mu_2 = 6$. This is due, of course, to the near-singularity of these T-optimal designs. Though this is the extreme case, cross-efficiencies displayed in these tables are not infrequently quite low, particularly for the comparison of T- and Q-optimal designs.

Table 3.1 3-Point D-optimal Designs with Unequal Weighting ($\mu_1^* = 0$, $\sigma_1^* = 1$)

		μ_2^*									
		0.0		0.5		1.0		1.5		2.0	
α	σ_2^*	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.
-1	0.5	---	0.000	---	0.000	---	0.000	-1.294	0.178	-1.268	0.190
		-0.882	0.500	-0.553	0.490	-0.230	0.474	0.744	0.360	1.263	0.378
		0.882	0.500	1.222	0.510	1.593	0.526	2.135	0.462	2.620	0.433
-1	1.0	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		-1.404	0.500	-1.162	0.500	-0.936	0.500	-0.726	0.500	-0.532	0.500
		1.404	0.500	1.662	0.500	1.936	0.500	2.226	0.500	2.531	0.500
-1	1.5	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		-1.648	0.500	-1.474	0.508	-1.303	0.517	-1.206	0.508	-1.058	0.502
		1.648	0.500	1.842	0.492	2.050	0.483	2.213	0.492	2.465	0.498
-1	2.0	---	0.000	---	0.000	---	0.000	---	0.000	-1.269	0.011
		-1.764	0.500	-1.624	0.504	-1.476	0.521	-1.371	0.532	-1.264	0.530
		1.763	0.500	1.939	0.496	2.110	0.479	2.271	0.468	2.463	0.459
0	0.5	---	0.000	---	0.000	-1.363	0.174	-1.388	0.186	-1.340	0.192
		-0.789	0.500	-0.533	0.482	0.381	0.418	0.871	0.456	1.332	0.483
		0.789	0.500	1.078	0.518	1.630	0.408	2.109	0.359	2.593	0.324
0	1.0	---	0.000	---	0.000	---	0.000	-0.832	0.376	-0.997	0.296
		-1.223	0.500	-0.981	0.500	-0.753	0.500	0.750	0.249	1.000	0.410
		1.223	0.500	1.480	0.500	1.753	0.500	2.332	0.376	3.002	0.294
0	1.5	---	0.000	---	0.000	---	0.000	---	0.000	-1.085	0.385
		-1.450	0.500	-1.249	0.502	-1.067	0.504	-0.853	0.513	1.140	0.384
		1.450	0.500	1.677	0.498	1.903	0.496	2.207	0.487	3.581	0.230
0	2.0	---	0.000	---	0.000	---	0.000	-1.292	0.438	-1.260	0.408
		-1.577	0.500	-1.364	0.511	-1.163	0.521	1.269	0.396	1.239	0.418
		1.578	0.500	1.805	0.489	2.057	0.479	4.102	0.166	4.726	0.174

3-Point D-optimal Designs with Unequal Weighting ($\mu_1^* = 0$, $\sigma_1^*=1$) (Continued)

		μ_2^* = 0.0		0.5		1.0		1.5		2.0	
α	σ_2^*	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.
1	0.5	-1.013	0.348	-1.289	0.178	-1.437	0.173	-1.452	0.182	-1.401	0.189
		0.000	0.305	0.061	0.434	0.474	0.478	0.893	0.506	1.297	0.527
		1.013	0.348	1.320	0.388	1.754	0.349	2.211	0.312	2.676	0.284
1	1.0	-1.413	0.384	-1.243	0.361	-1.197	0.319	-1.208	0.282	-1.232	0.256
		0.000	0.233	0.249	0.277	0.500	0.363	0.750	0.437	1.000	0.488
		1.413	0.384	1.743	0.362	2.196	0.319	2.708	0.282	3.232	0.256
1	1.5	-1.744	0.369	-1.558	0.384	-1.465	0.369	-1.411	0.344	-1.376	0.319
		0.000	0.262	0.427	0.308	0.687	0.380	0.859	0.434	1.003	0.472
		1.744	0.369	2.121	0.308	2.668	0.252	3.275	0.222	3.868	0.209
1	2.0	-2.025	0.348	-1.746	0.397	-1.640	0.388	-1.566	0.369	-1.508	0.349
		0.000	0.305	0.676	0.382	0.878	0.434	0.975	0.460	1.052	0.478
		2.025	0.348	2.776	0.221	3.577	0.179	4.272	0.171	4.876	0.173
2	0.5	-1.219	0.245	-1.515	0.144	-1.617	0.147	*	*	*	*
		-0.217	0.367	0.040	0.485	0.384	0.518	*	*	*	*
		0.874	0.389	1.336	0.371	1.770	0.335	*	*	*	*
2	1.0	-1.572	0.319	-1.412	0.303	-1.369	0.275	-1.362	0.253	*	*
		0.000	0.363	0.250	0.394	0.500	0.449	0.750	0.493	*	*
		1.571	0.319	1.912	0.303	2.368	0.276	2.862	0.254	*	*
2	1.5	-1.875	0.320	-1.668	0.360	-1.586	0.347	-1.522	0.326	-1.460	0.307
		0.001	0.361	0.527	0.418	0.749	0.464	0.925	0.494	1.129	0.517
		1.876	0.320	2.408	0.222	2.997	0.190	3.582	0.180	4.161	0.176
2	2.0	-2.439	0.245	-1.710	0.389	-1.671	0.371	-1.612	0.352	-1.541	0.335
		-0.434	0.366	0.781	0.454	0.920	0.485	1.055	0.503	1.232	0.518
		1.747	0.389	3.331	0.158	4.030	0.144	4.653	0.145	5.235	0.147

* α exceeds maximum allowable value at this parameter combination

Table 3.2 5-point D-optimal Designs with Equal Weighting, Equal Spacing

$(\mu_1^* = 0,\ \sigma_1^* = 1)$

			μ_2^*				
α	σ_2^*		0.0	0.5	1.0	1.5	2.0
-1	0.5	PT1	-1.317	-0.997	-0.734	-0.539	-0.424
		SPACE	0.659	0.670	0.704	0.763	0.846
-1	1.0	PT1	-1.991	-1.757	-1.553	-1.384	-1.246
		SPACE	0.995	1.003	1.027	1.067	1.123
-1	1.5	PT1	-2.381	-2.204	-2.051	-1.919	-1.808
		SPACE	1.190	1.198	1.217	1.251	1.297
-1	2.0	PT1	-2.636	-2.491	-2.366	-2.258	-2.166
		SPACE	1.318	1.323	1.340	1.368	1.408
0	0.5	PT1	-1.245	-0.945	-0.690	-0.498	-0.382
		SPACE	0.623	0.632	0.661	0.712	0.788
0	1.0	PT1	-1.847	-1.612	-1.409	-1.238	-1.097
		SPACE	0.923	0.931	0.954	0.994	1.049
0	1.5	PT1	-2.225	-2.028	-1.853	-1.698	-1.565
		SPACE	1.113	1.119	1.137	1.167	1.211
0	2.0	PT1	-2.490	-2.320	-2.165	-2.029	-1.906
		SPACE	1.245	1.251	1.264	1.288	1.322
1	0.5	PT1	-1.219	-0.923	-0.670	-0.472	-0.347
		SPACE	0.610	0.619	0.648	0.698	0.773
1	1.0	PT1	-1.808	-1.573	-1.367	-1.196	-1.055
		SPACE	0.904	0.911	0.934	0.973	1.028
1	1.5	PT1	-2.179	-1.979	-1.803	-1.647	-1.511
		SPACE	1.089	1.095	1.113	1.143	1.186
1	2.0	PT1	-2.440	-2.269	-2.109	-1.972	-1.845
		SPACE	1.220	1.225	1.238	1.262	1.295
2	0.5	PT1	-1.165	-0.860	-0.878	*	*
		SPACE	0.582	0.588	0.663	*	*
2	1.0	PT1	-1.731	-1.492	-1.285	-1.172	*
		SPACE	0.865	0.871	0.892	0.961	*
2	1.5	PT1	-2.083	-1.879	-1.685	-1.475	-1.456
		SPACE	1.042	1.047	1.061	1.097	1.281
2	2.0	PT1	-2.328	-2.151	-1.980	-1.796	-1.548
		SPACE	1.164	1.167	1.176	1.190	1.325

* α exceeds maximum allowable value at this parameter combination

Table 3.3 Relative D-Efficiency of 5-pt. vs. 3-pt. D-optimal Designs

$(\mu_1^* = 0,\ \sigma_1^* = 1)$

		μ_2^*				
α	σ_2^*	0.0	0.5	1.0	1.5	2.0
-1	0.5	0.961	0.964	0.972	0.943	0.910
-1	1.0	0.941	0.944	0.951	0.963	0.981
-1	1.5	0.949	0.950	0.954	0.961	0.971
-1	2.0	0.961	0.962	0.963	0.966	0.971
0	0.5	0.990	0.993	0.976	0.947	0.909
0	1.0	0.976	0.978	0.984	0.993	0.991
0	1.5	0.981	0.983	0.986	0.993	0.987
0	2.0	0.990	0.991	0.993	0.985	0.976
1	0.5	0.998	0.989	0.965	0.926	0.882
1	1.0	0.992	0.993	0.992	0.985	0.970
1	1.5	0.994	0.994	0.992	0.986	0.974
1	2.0	0.998	0.995	0.989	0.979	0.965
2	0.5	1.000	0.971	0.892	*	*
2	1.0	0.993	0.990	0.974	0.924	*
2	1.5	0.996	0.991	0.976	0.946	0.880
2	2.0	1.000	0.989	0.971	0.942	0.892

* α exceeds maximum allowable value at this parameter combination

Table 3.4 3-Point Q-optimal Designs with Unequal Weighting ($\mu_1^* = 0$, $\sigma_1^*=1$)

		μ_2^*													
		-1.0		-0.5		0.0		0.5		1.0		1.5		2.0	
α	σ_2^*	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.
-1	0.5	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	-1.018	0.467	-0.994	0.431
		-2.211	0.565	-1.903	0.553	-1.599	0.548	-1.291	0.550	-0.995	0.557	0.732	0.147	1.207	0.218
		-0.294	0.435	0.115	0.447	0.535	0.452	0.984	0.450	1.420	0.443	1.970	0.387	2.497	0.351
-1	1.0	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		-1.790	0.500	-1.601	0.500	-1.421	0.500	-1.250	0.500	-1.086	0.500	-0.928	0.500	-0.776	0.500
		0.789	0.500	1.100	0.500	1.421	0.500	1.750	0.500	2.086	0.500	2.428	0.500	2.776	0.500
-1	1.5	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		-1.402	0.466	-1.301	0.469	-1.265	0.483	-1.110	0.471	-1.031	0.492	-0.921	0.469	-0.826	0.467
		1.918	0.533	2.136	0.531	2.320	0.517	2.605	0.529	2.928	0.508	3.117	0.531	3.386	0.533
-1	2.0	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		-1.231	0.447	-1.158	0.450	-1.093	0.451	-1.029	0.451	-0.967	0.450	-0.905	0.447	-0.849	0.460
		2.805	0.553	2.999	0.550	3.187	0.549	3.384	0.549	3.583	0.550	3.784	0.553	3.998	0.540
0	0.5	-2.101	0.376	---	0.000	---	0.000	---	0.000	---	0.000	-1.097	0.443	-1.039	0.419
		-0.685	0.497	-2.043	0.530	-1.668	0.538	-1.312	0.547	-0.965	0.548	0.792	0.208	1.231	0.256
		2.010	0.127	-0.081	0.470	0.377	0.462	0.839	0.453	1.350	0.452	1.966	0.349	2.499	0.325
0	1.0	-2.146	0.306	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		-0.500	0.388	-1.443	0.500	-1.264	0.500	-1.097	0.500	-0.945	0.500	-0.803	0.500	-0.671	0.500
		1.145	0.306	0.943	0.500	1.263	0.500	1.598	0.500	1.945	0.500	2.303	0.500	2.671	0.500
0	1.5	-3.242	0.093	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		-0.774	0.459	-0.959	0.491	-0.857	0.500	-0.809	0.484	-0.746	0.479	-0.687	0.475	-0.627	0.470
		1.979	0.449	2.235	0.509	2.475	0.500	2.643	0.516	2.858	0.521	3.089	0.525	3.337	0.530
0	2.0	-4.722	0.068	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		-0.667	0.451	-0.794	0.467	-0.753	0.462	-0.716	0.458	-0.680	0.454	-0.642	0.449	-0.608	0.444
		2.867	0.482	3.208	0.533	3.336	0.538	3.474	0.542	3.624	0.546	3.789	0.551	3.968	0.556

3-Point Q-optimal Designs with Unequal Weighting ($\mu_1^* = 0$, $\sigma_1^* = 1$) (Continued)

		μ_2^* = -1.0		μ_2^* = -0.5		μ_2^* = 0.0		μ_2^* = 0.5		μ_2^* = 1.0		μ_2^* = 1.5		μ_2^* = 2.0	
α	σ_2^*	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.
1	0.5	-2.089	0.382	---	0.000	---	0.000	---	0.000	-1.242	0.467	-1.174	0.428	-1.084	0.412
		-0.736	0.477	-2.087	0.558	-1.688	0.558	-1.308	0.562	0.480	0.215	0.821	0.262	1.227	0.284
		2.104	0.141	-0.161	0.442	0.285	0.442	0.750	0.438	1.476	0.318	2.013	0.310	2.521	0.304
1	1.0	-2.447	0.251	-1.894	0.312	-1.427	0.391	---	0.000	---	0.000	---	0.000	---	0.000
		-0.500	0.498	-0.250	0.377	0.000	0.218	-1.004	0.500	-0.857	0.500	-0.723	0.500	-0.599	0.500
		1.447	0.251	1.394	0.312	1.427	0.391	1.503	0.500	1.857	0.500	2.223	0.500	2.598	0.500
1	1.5	-3.557	0.109	-2.726	0.036	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		-0.565	0.468	-0.649	0.467	-0.660	0.483	-0.577	0.498	-0.570	0.474	-0.535	0.469	-0.497	0.464
		2.094	0.423	2.390	0.497	2.566	0.517	2.758	0.502	2.875	0.526	3.068	0.531	3.291	0.536
1	2.0	-4.949	0.083	-4.123	0.037	---	0.000	---	0.000	---	0.000	-0.855	0.327	-0.952	0.318
		-0.494	0.431	-0.533	0.430	-0.569	0.442	-0.530	0.440	-0.500	0.438	0.765	0.171	1.040	0.215
		2.866	0.486	3.181	0.533	3.376	0.558	3.484	0.560	3.615	0.562	4.054	0.503	4.484	0.467
2	0.5	-1.985	0.619	---	0.000	---	0.000	-1.486	0.496	-1.387	0.434	*	*	*	*
		-0.515	0.243	-2.050	0.633	-1.664	0.601	-0.054	0.173	0.249	0.245	*	*	*	*
		2.259	0.137	-0.149	0.367	0.238	0.399	0.831	0.331	1.362	0.321	*	*	*	*
2	1.0	-2.506	0.270	-2.027	0.290	-1.583	0.333	-1.211	0.389	---	0.000	---	0.000	*	*
		-0.500	0.461	-0.250	0.420	0.000	0.334	0.249	0.221	-0.774	0.500	-0.641	0.500	*	*
		1.507	0.270	1.527	0.290	1.584	0.333	1.711	0.389	1.774	0.500	2.141	0.500	*	*
2	1.5	-3.892	0.116	-3.140	0.065	---	0.000	---	0.000	---	0.000	-0.675	0.380	-0.595	0.387
		-0.579	0.409	-0.506	0.422	-0.516	0.453	-0.472	0.457	-0.447	0.457	1.091	0.157	1.354	0.155
		2.014	0.475	2.333	0.513	2.578	0.547	2.685	0.543	2.810	0.543	3.268	0.463	3.575	0.458
2	2.0	---	0.000	---	0.000	---	0.000	-0.479	0.317	-0.664	0.331	-0.740	0.319	-0.724	0.321
		-0.701	0.368	-0.569	0.387	-0.475	0.399	-0.161	0.091	1.108	0.174	1.295	0.225	1.501	0.245
		3.099	0.632	3.220	0.613	3.330	0.601	3.443	0.591	3.973	0.496	4.383	0.456	4.772	0.434

* α exceeds maximum allowable value at this parameter combination

Table 3.5 5-point Q-optimal Designs with Equal Weighting, Equal Spacing

$(\mu_1^* = 0, \sigma_1^* = 1)$

α	σ_2^*		μ_2^* = -1.0	-0.5	0.0	0.5	1.0	1.5	2.0
-1	0.5	PT1	-2.699	-2.407	-2.164	-1.962	-1.794	-1.662	-1.573
		SPACE	0.740	0.772	0.818	0.875	0.941	1.015	1.097
-1	1.0	PT1	-2.483	-2.305	-2.144	-2.002	-1.875	-1.764	-1.671
		SPACE	0.992	1.028	1.073	1.126	1.187	1.257	1.336
-1	1.5	PT1	-2.377	-2.268	-2.163	-2.064	-1.972	-1.888	-1.808
		SPACE	1.262	1.301	1.348	1.401	1.462	1.528	1.601
-1	2.0	PT1	-2.361	-2.286	-2.214	-2.144	-2.077	-2.008	-1.940
		SPACE	1.544	1.587	1.635	1.690	1.749	1.813	1.882
0	0.5	PT1	-2.652	-2.383	-2.144	-1.939	-1.772	-1.643	-1.557
		SPACE	0.692	0.728	0.777	0.837	0.908	0.989	1.078
0	1.0	PT1	-2.297	-2.136	-1.996	-1.873	-1.769	-1.680	-1.606
		SPACE	0.898	0.943	0.998	1.062	1.134	1.215	1.303
0	1.5	PT1	-2.135	-2.026	-1.934	-1.853	-1.781	-1.719	-1.663
		SPACE	1.166	1.212	1.265	1.326	1.394	1.468	1.550
0	2.0	PT1	-2.059	-1.987	-1.924	-1.869	-1.816	-1.768	-1.720
		SPACE	1.457	1.502	1.553	1.611	1.674	1.742	1.816
1	0.5	PT1	-2.778	-2.470	-2.196	-1.962	-1.779	-1.645	-1.560
		SPACE	0.687	0.714	0.757	0.816	0.890	0.975	1.069
1	1.0	PT1	-2.196	-2.042	-1.908	-1.796	-1.705	-1.629	-1.567
		SPACE	0.848	0.896	0.954	1.023	1.103	1.190	1.284
1	1.5	PT1	-1.923	-1.820	-1.742	-1.682	-1.637	-1.600	-1.569
		SPACE	1.123	1.167	1.220	1.283	1.354	1.434	1.520
1	2.0	PT1	-1.770	-1.710	-1.665	-1.631	-1.604	-1.583	-1.561
		SPACE	1.428	1.466	1.514	1.569	1.633	1.703	1.780
2	0.5	PT1	-3.519	-2.668	-2.275	-1.988	-1.735	*	*
		SPACE	0.766	0.713	0.742	0.794	0.866	*	*
2	1.0	PT1	-2.196	-1.974	-1.821	-1.704	-1.612	-1.531	*
		SPACE	0.848	0.862	0.910	0.977	1.056	1.141	*
2	1.5	PT1	-1.733	-1.597	-1.522	-1.481	-1.461	-1.447	-1.405
		SPACE	1.135	1.145	1.182	1.237	1.307	1.388	1.471
2	2.0	PT1	-1.368	-1.401	-1.389	-1.379	-1.378	-1.395	-1.460
		SPACE	1.426	1.450	1.485	1.531	1.588	1.655	1.733

* α exceeds maximum allowable value at this parameter combination

Table 3.6 Relative Q-Efficiency of 5-pt. vs. 3-pt. Q-optimal Designs

$(\mu_1^* = 0, \sigma_1^* = 1)$

		μ_2^*						
α	σ_2^*	-1.0	-0.5	0.0	0.5	1.0	1.5	2.0
-1	0.5	0.978	0.955	0.934	0.920	0.921	0.930	0.930
-1	1.0	0.990	0.963	0.938	0.916	0.900	0.892	0.893
-1	1.5	0.968	0.950	0.935	0.919	0.910	0.902	0.901
-1	2.0	0.955	0.944	0.934	0.925	0.920	0.918	0.922
0	0.5	0.993	0.970	0.954	0.946	0.954	0.950	0.941
0	1.0	0.996	0.985	0.967	0.951	0.938	0.930	0.931
0	1.5	0.981	0.973	0.960	0.948	0.940	0.935	0.936
0	2.0	0.961	0.961	0.954	0.949	0.946	0.947	0.952
1	0.5	0.873	0.958	0.958	0.964	0.966	0.958	0.945
1	1.0	0.980	0.993	0.988	0.977	0.965	0.958	0.961
1	1.5	0.961	0.971	0.965	0.963	0.959	0.960	0.965
1	2.0	0.941	0.955	0.958	0.960	0.964	0.967	0.966
2	0.5	0.816	0.936	0.957	0.974	0.970	*	*
2	1.0	0.937	0.976	0.990	0.986	0.984	0.982	*
2	1.5	0.917	0.950	0.961	0.967	0.975	0.973	0.972
2	2.0	0.936	0.947	0.957	0.969	0.974	0.973	0.970

* α exceeds maximum allowable value at this parameter combination

Table 3.7 3-point T-optimal Designs with Unequal Weighting ($\mu_1^* = 6$, $\sigma_1^*=1$)

		μ_2^* = 5.0		5.5		6.0		6.5		7.0		7.5		8.0	
α	σ_2^*	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.
-1	0.5	---	0.000	---	0.000	6.000	0.333	---	0.000	---	0.000	---	0.000	---	0.000
		4.924	0.522	5.431	0.615	6.000	0.333	5.569	0.498	5.561	0.550	5.671	0.638	5.752	0.680
		6.552	0.478	6.602	0.385	6.000	0.333	6.640	0.502	7.054	0.450	7.594	0.362	8.075	0.320
-1	1.0	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		4.537	0.517	5.087	0.501	6.000	0.500	5.590	0.501	5.600	0.532	5.567	0.526	5.726	0.578
		6.390	0.483	6.383	0.499	6.000	0.500	6.885	0.499	7.467	0.468	7.815	0.474	8.415	0.422
-1	1.5	---	0.000	---	0.000	5.999	0.333	---	0.000	---	0.000	---	0.000	---	0.000
		4.283	0.499	4.677	0.365	6.000	0.333	5.834	0.681	5.785	0.599	5.668	0.529	5.777	0.538
		6.276	0.501	6.186	0.635	6.001	0.333	7.437	0.319	7.930	0.401	8.315	0.471	8.870	0.462
-1	2.0	---	0.000	---	0.000	5.999	0.333	---	0.000	---	0.000	5.231	0.003	---	0.000
		4.134	0.498	4.399	0.303	6.001	0.333	5.908	0.736	5.868	0.632	5.868	0.582	5.847	0.548
		6.246	0.502	6.106	0.697	6.001	0.333	7.765	0.264	8.265	0.368	8.761	0.416	9.144	0.452
0	0.5	---	0.000	---	0.000	6.000	0.333	---	0.000	---	0.000	---	0.000	---	0.000
		4.942	0.537	5.459	0.645	6.000	0.333	5.322	0.395	5.449	0.545	5.578	0.630	5.680	0.676
		6.710	0.463	6.776	0.355	6.000	0.333	6.547	0.605	7.092	0.455	7.586	0.370	8.076	0.324
0	1.0	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		4.457	0.505	5.069	0.519	5.999	0.500	5.540	0.501	5.568	0.544	5.615	0.563	5.678	0.580
		6.432	0.495	6.460	0.481	6.001	0.500	6.928	0.499	7.534	0.456	8.027	0.437	8.498	0.420
0	1.5	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		4.044	0.460	4.361	0.302	5.999	0.500	5.895	0.733	5.833	0.629	5.703	0.534	5.664	0.511
		6.207	0.540	6.113	0.698	6.001	0.500	7.780	0.267	8.223	0.371	8.583	0.466	8.874	0.489
0	2.0	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		3.970	0.493	4.062	0.256	5.999	0.500	5.956	0.774	5.921	0.661	5.901	0.599	5.894	0.562
		6.242	0.507	6.049	0.744	6.001	0.500	8.149	0.226	8.634	0.339	9.092	0.401	9.536	0.438

3-point T-optimal Designs with Unequal Weighting ($\mu_1^* = 6$, $\sigma_1^* = 1$) (Continued)

		μ_2^*													
		5.0		5.5		6.0		6.5		7.0		7.5		8.0	
α	σ_2^*	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.	Dose	Wgt.
1	0.5	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		4.966	0.540	5.487	0.659	6.000	0.500	5.171	0.375	5.333	0.538	5.480	0.627	5.607	0.676
		6.877	0.460	6.950	0.341	6.000	0.500	6.513	0.625	7.056	0.462	7.564	0.373	8.069	0.324
1	1.0	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		4.516	0.544	4.988	0.500	6.000	0.500	5.490	0.500	5.477	0.520	5.568	0.564	5.639	0.580
		6.553	0.456	6.454	0.500	6.000	0.500	6.957	0.500	7.505	0.480	8.088	0.436	8.568	0.420
1	1.5	---	0.000	---	0.000	6.000	0.333	---	0.000	---	0.000	---	0.000	---	0.000
		3.713	0.419	3.934	0.252	6.000	0.333	5.901	0.715	5.914	0.654	5.871	0.597	5.866	0.567
		6.088	0.581	6.025	0.748	6.000	0.333	7.829	0.285	8.620	0.346	8.989	0.403	9.438	0.433
1	2.0	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	3.346	0.001
		3.480	0.397	3.752	0.233	5.999	0.500	5.906	0.713	5.974	0.672	5.952	0.605	5.934	0.564
		6.024	0.603	6.002	0.767	6.001	0.500	7.953	0.287	9.001	0.328	9.463	0.395	9.868	0.436
2	0.5	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	*	*	*	*
		4.972	0.503	5.507	0.643	6.000	0.500	5.118	0.396	5.225	0.552	*	*	*	*
		6.982	0.497	7.059	0.357	6.000	0.500	6.496	0.604	7.011	0.448	*	*	*	*
2	1.0	4.155	0.424	---	0.000	6.000	0.333	---	0.000	5.161	0.416	---	0.000	*	*
		5.690	0.278	3.959	0.272	6.000	0.333	4.456	0.272	6.659	0.274	5.328	0.526	*	*
		6.777	0.298	6.014	0.728	6.000	0.333	6.514	0.728	7.784	0.310	7.896	0.474	*	*
2	1.5	3.226	0.007	---	0.000	---	0.000	---	0.000	5.979	0.321	---	0.000	---	0.000
		3.396	0.401	3.650	0.249	6.000	0.500	6.019	0.770	6.003	0.331	5.948	0.593	5.869	0.555
		5.984	0.592	5.973	0.751	6.000	0.500	8.616	0.230	9.044	0.347	9.393	0.407	9.501	0.445
2	2.0	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000	---	0.000
		3.439	0.424	3.919	0.280	5.999	0.500	6.002	0.762	6.013	0.656	6.000	0.588	5.982	0.550
		6.005	0.576	6.019	0.720	6.001	0.500	8.512	0.238	9.262	0.344	9.801	0.412	10.261	0.450

* α exceeds maximum allowable value at this parameter combination

Table 3.8 5-point T-optimal Designs with Equal Weighting, Equal Spacing

$(\mu_1^* = 6,\ \sigma_1^* = 1)$

α	σ_2^*		μ_2^* = 5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	PT1	4.545	5.093	5.9990	5.354	5.112	4.927	4.776
		SPACE	0.572	0.386	0.0005	0.380	0.560	0.720	0.871
-1	1.0	PT1	4.108	4.800	5.9992	5.302	5.115	4.990	4.891
		SPACE	0.665	0.467	0.0004	0.466	0.666	0.830	0.977
-1	1.5	PT1	3.853	4.644	5.9987	5.293	5.140	5.048	4.978
		SPACE	0.718	0.505	0.0007	0.512	0.734	0.913	1.070
-1	2.0	PT1	3.709	4.555	5.9991	5.291	5.160	5.088	5.037
		SPACE	0.747	0.527	0.0005	0.538	0.776	0.970	1.142
0	0.5	PT1	4.508	5.064	5.9983	5.277	5.000	4.809	4.672
		SPACE	0.611	0.414	0.0008	0.405	0.594	0.757	0.904
0	1.0	PT1	3.992	4.722	5.9993	5.223	5.001	4.859	4.759
		SPACE	0.717	0.504	0.0004	0.504	0.718	0.888	1.037
0	1.5	PT1	3.704	4.547	5.9992	5.234	5.058	4.949	4.867
		SPACE	0.768	0.542	0.0004	0.551	0.791	0.981	1.145
0	2.0	PT1	3.560	4.461	5.9993	5.245	5.099	5.016	4.955
		SPACE	0.794	0.561	0.0004	0.574	0.832	1.040	1.222
1	0.5	PT1	4.489	5.055	5.9996	5.196	4.881	4.686	4.564
		SPACE	0.649	0.438	0.0002	0.426	0.625	0.790	0.934
1	1.0	PT1	3.872	4.646	5.9996	5.148	4.883	4.722	4.624
		SPACE	0.766	0.538	0.0002	0.538	0.768	0.945	1.094
1	1.5	PT1	3.544	4.447	5.9992	5.193	4.997	4.867	4.773
		SPACE	0.814	0.574	0.0004	0.586	0.845	1.048	1.218
1	2.0	PT1	3.408	4.368	5.9978	5.224	5.074	4.980	4.906
		SPACE	0.832	0.587	0.0011	0.605	0.883	1.107	1.301
2	0.5	PT1	4.483	5.063	5.9995	5.103	4.743	*	*
		SPACE	0.691	0.462	0.0002	0.445	0.657	*	*
2	1.0	PT1	3.727	4.560	5.9991	5.062	4.743	4.570	*
		SPACE	0.820	0.574	0.0004	0.574	0.822	1.006	*
2	1.5	PT1	3.349	4.331	5.9993	5.174	4.957	4.798	4.693
		SPACE	0.858	0.603	0.0003	0.621	0.904	1.123	1.297
2	2.0	PT1	3.239	4.259	5.9984	5.223	5.083	4.975	4.879
		SPACE	0.867	0.613	0.0008	0.635	0.934	1.182	1.391

* α exceeds maximum allowable value at this parameter combination

Table 3.9 Relative T-Efficiency of 5-pt. vs. 3-pt. T-optimal Designs

$(\mu_1^* = 6,\ \sigma_1^* = 1)$

		μ_2^*						
α	σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	0.954	0.981	1.000	0.988	0.967	0.930	0.884
-1	1.0	0.980	0.995	1.000	0.995	0.980	0.958	0.925
-1	1.5	0.987	0.994	1.000	0.992	0.979	0.964	0.941
-1	2.0	0.989	0.993	1.000	0.990	0.979	0.965	0.947
0	0.5	0.943	0.973	1.000	0.981	0.962	0.925	0.878
0	1.0	0.981	0.995	1.000	0.995	0.980	0.954	0.921
0	1.5	0.984	0.990	1.000	0.986	0.973	0.960	0.937
0	2.0	0.987	0.988	1.000	0.983	0.969	0.953	0.934
1	0.5	0.927	0.958	1.000	0.971	0.954	0.918	0.871
1	1.0	0.984	0.998	1.000	0.998	0.985	0.957	0.920
1	1.5	0.977	0.979	1.000	0.975	0.959	0.943	0.920
1	2.0	0.977	0.979	1.000	0.974	0.952	0.935	0.915
2	0.5	0.904	0.938	1.000	0.959	0.941	*	*
2	1.0	0.995	0.989	1.000	0.989	0.995	0.969	*
2	1.5	0.959	0.956	1.000	0.943	0.930	0.920	0.904
2	2.0	0.968	0.973	1.000	0.957	0.928	0.906	0.886

* α exceeds maximum allowable value at this parameter combination

Table 3.10 Cross-efficiencies of 3-pt. D-optimal and Q-optimal Designs

Relative D-Efficiency of 3-pt. Q-optimal Designs ($\mu_1^* = 0$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	-1.0	-0.5	0.0	0.5	1.0	1.5	2.0
-1	0.5	0.909	0.904	0.900	0.899	0.897	0.895	0.900
-1	1.0	0.992	0.999	1.000	0.997	0.993	0.987	0.982
-1	1.5	0.960	0.962	0.969	0.960	0.955	0.954	0.951
-1	2.0	0.904	0.902	0.901	0.900	0.899	0.898	0.902
0	0.5	0.948	0.892	0.906	0.912	0.889	0.896	0.894
0	1.0	0.985	0.999	0.999	0.994	0.984	0.970	0.940
0	1.5	0.959	0.955	0.959	0.960	0.958	0.954	0.934
0	2.0	0.920	0.900	0.906	0.910	0.912	0.901	0.886
1	0.5	0.939	0.874	0.899	0.894	0.897	0.890	0.884
1	1.0	0.991	0.998	1.000	0.990	0.969	0.931	0.878
1	1.5	0.961	0.951	0.954	0.959	0.947	0.926	0.892
1	2.0	0.914	0.902	0.899	0.901	0.894	0.899	0.897
2	0.5	0.803	0.828	0.870	0.870	0.843	*	*
2	1.0	0.998	0.999	0.999	0.987	0.901	0.739	*
2	1.5	0.944	0.940	0.932	0.927	0.893	0.882	0.794
2	2.0	0.828	0.854	0.870	0.861	0.870	0.865	0.843

Relative Q-Efficiency of 3-pt. D-optimal Designs ($\mu_1^* = 0$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	-1.0	-0.5	0.0	0.5	1.0	1.5	2.0
-1	0.5	0.904	0.878	0.846	0.799	0.738	0.778	0.785
-1	1.0	0.988	0.998	1.000	0.995	0.986	0.974	0.960
-1	1.5	0.963	0.959	0.950	0.933	0.916	0.888	0.874
-1	2.0	0.890	0.867	0.845	0.827	0.794	0.762	0.736
0	0.5	0.926	0.838	0.798	0.774	0.791	0.789	0.790
0	1.0	0.982	0.999	0.999	0.988	0.969	0.929	0.889
0	1.5	0.942	0.940	0.928	0.913	0.895	0.887	0.855
0	2.0	0.832	0.819	0.798	0.781	0.770	0.786	0.790
1	0.5	0.906	0.880	0.802	0.786	0.787	0.788	0.787
1	1.0	0.982	0.996	0.999	0.985	0.953	0.917	0.889
1	1.5	0.944	0.934	0.916	0.901	0.883	0.868	0.857
1	2.0	0.864	0.833	0.802	0.788	0.786	0.787	0.788
2	0.5	0.719	0.830	0.761	0.762	0.764	*	*
2	1.0	0.998	0.999	0.998	0.977	0.943	0.902	*
2	1.5	0.913	0.915	0.899	0.878	0.865	0.844	0.823
2	2.0	0.830	0.800	0.765	0.758	0.762	0.763	0.764

* α exceeds maximum allowable value at this parameter combination

Table 3.11 Cross-efficiencies of 3-pt. D-optimal and T-optimal Designs

Relative D-Efficiency of 3-pt. T-optimal Designs ($\mu_1^* = 6$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	0.906	0.828	0.003	0.832	0.879	0.828	0.737
-1	1.0	0.895	0.746	0.003	0.746	0.897	0.953	0.978
-1	1.5	0.842	0.706	0.004	0.709	0.850	0.932	0.949
-1	2.0	0.823	0.690	0.004	0.694	0.828	0.882	0.908
0	0.5	0.931	0.896	0.002	0.892	0.919	0.836	0.733
0	1.0	0.964	0.840	0.003	0.839	0.961	0.989	0.970
0	1.5	0.915	0.788	0.003	0.791	0.922	0.980	0.975
0	2.0	0.895	0.761	0.004	0.765	0.895	0.931	0.930
1	0.5	0.903	0.904	0.003	0.901	0.894	0.784	0.660
1	1.0	0.970	0.886	0.003	0.886	0.971	0.958	0.902
1	1.5	0.932	0.823	0.002	0.832	0.936	0.954	0.927
1	2.0	0.896	0.789	0.003	0.812	0.902	0.920	0.902
2	0.5	0.724	0.881	0.003	0.882	0.723	*	*
2	1.0	0.968	0.899	0.003	0.899	0.970	0.766	*
2	1.5	0.914	0.845	0.001	0.843	0.910	0.856	0.640
2	2.0	0.878	0.814	0.003	0.818	0.878	0.838	0.723

Relative T-Efficiency of 3-pt. D-optimal Designs ($\mu_1^* = 6$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	0.809	0.837	0.767	0.844	0.783	0.642	0.550
-1	1.0	0.867	0.788	0.683	0.788	0.868	0.927	0.960
-1	1.5	0.838	0.792	0.715	0.783	0.832	0.864	0.883
-1	2.0	0.831	0.820	0.767	0.807	0.821	0.810	0.786
0	0.5	0.817	0.870	0.779	0.872	0.776	0.660	0.563
0	1.0	0.945	0.852	0.703	0.852	0.945	0.957	0.896
0	1.5	0.891	0.835	0.732	0.828	0.893	0.937	0.901
0	2.0	0.869	0.847	0.779	0.836	0.866	0.848	0.827
1	0.5	0.790	0.832	0.750	0.829	0.748	0.640	0.554
1	1.0	0.943	0.860	0.663	0.860	0.945	0.930	0.858
1	1.5	0.867	0.819	0.696	0.816	0.880	0.892	0.867
1	2.0	0.826	0.821	0.750	0.814	0.832	0.824	0.801
2	0.5	0.748	0.802	0.743	0.800	0.716	*	*
2	1.0	0.976	0.884	0.617	0.884	0.978	0.930	*
2	1.5	0.840	0.802	0.665	0.798	0.864	0.864	0.828
2	2.0	0.796	0.808	0.743	0.796	0.803	0.784	0.754

* α exceeds maximum allowable value at this parameter combination

Table 3.12 Cross-efficiencies of 3-pt. Q-optimal and T-optimal Designs

Relative Q-Efficiency of 3-pt. T-optimal Designs ($\mu_1^* = 6$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	0.756	0.546	0.000	0.509	0.711	0.815	0.813
-1	1.0	0.903	0.618	0.000	0.499	0.711	0.792	0.853
-1	1.5	0.684	0.451	0.000	0.413	0.624	0.772	0.837
-1	2.0	0.490	0.314	0.000	0.324	0.536	0.674	0.761
0	0.5	0.759	0.614	0.000	0.608	0.840	0.877	0.839
0	1.0	0.970	0.733	0.000	0.605	0.809	0.888	0.923
0	1.5	0.763	0.527	0.000	0.495	0.724	0.880	0.920
0	2.0	0.536	0.361	0.000	0.388	0.629	0.771	0.856
1	0.5	0.742	0.635	0.000	0.678	0.890	0.899	0.832
1	1.0	0.950	0.814	0.000	0.699	0.880	0.945	0.960
1	1.5	0.783	0.567	0.000	0.552	0.790	0.890	0.932
1	2.0	0.556	0.381	0.000	0.423	0.697	0.831	0.887
2	0.5	0.579	0.600	0.000	0.727	0.904	*	*
2	1.0	0.928	0.785	0.000	0.693	0.942	0.978	*
2	1.5	0.743	0.568	0.000	0.595	0.820	0.884	0.910
2	2.0	0.517	0.362	0.000	0.476	0.745	0.848	0.859

Relative T-Efficiency of 3-pt. Q-optimal Designs ($\mu_1^* = 6$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	0.468	0.581	0.606	0.746	0.832	0.844	0.812
-1	1.0	0.922	0.812	0.677	0.752	0.805	0.844	0.870
-1	1.5	0.711	0.706	0.658	0.717	0.761	0.807	0.836
-1	2.0	0.574	0.610	0.606	0.673	0.726	0.767	0.803
0	0.5	0.616	0.533	0.584	0.774	0.875	0.869	0.822
0	1.0	0.941	0.867	0.687	0.801	0.869	0.909	0.930
0	1.5	0.713	0.695	0.647	0.744	0.819	0.874	0.907
0	2.0	0.582	0.573	0.584	0.682	0.761	0.821	0.862
1	0.5	0.595	0.470	0.538	0.784	0.884	0.872	0.823
1	1.0	0.942	0.869	0.652	0.828	0.913	0.951	0.965
1	1.5	0.685	0.655	0.600	0.761	0.846	0.908	0.941
1	2.0	0.543	0.542	0.538	0.669	0.775	0.840	0.870
2	0.5	0.466	0.391	0.476	0.792	0.904	*	*
2	1.0	0.965	0.876	0.596	0.829	0.950	0.985	*
2	1.5	0.624	0.604	0.543	0.735	0.865	0.909	0.935
2	2.0	0.364	0.433	0.476	0.639	0.780	0.850	0.880

* α exceeds maximum allowable value at this parameter combination

Chapter 4
Practical Designs for the Gumbel Model

§4.1 Designs Based on Univariate Optimality

Since the Gumbel model has been proposed only recently as a model for drug efficacy and toxicity, researchers may wish to consider the univariate logistic regression models for efficacy and toxicity as well. This section will address some of the design considerations raised by this approach.

Table 4.1 shows the univariate D-efficiencies (indicated by D_{U1}-efficiency for the D-efficiency based on the univariate marginal logistic regression model for efficacy and D_{U2}-efficiency for the D-efficiency based on the univariate marginal toxicity model) of the Gumbel D-optimal designs (D_G-optimal). Note that the D_{U1}-efficiency and D_{U2}-efficiency vary depending on the particular parameter combination. In situations where the two marginal curves are very close to one another, the efficiencies tend to be fairly good. This is not surprising, since if a design has a good D_{U1}-efficiency it should also have a good D_{U2}-efficiency if the two marginal curves are similar. However, when the locations are spread or the scale parameters have a sizable difference, the efficiencies suffer. These results are also expected since when the marginal curves differ, the D_G-optimal design serves as a compromise between the D_{U1}-optimal and the D_{U2}-optimal designs. Thus neither the D_{U1}-efficiency nor the D_{U2}-efficiency is as high as one would achieve with a design specifically for estimation of just one marginal curve.

Q_G-optimal designs and their resulting Q_{U1}- and Q_{U2}-efficiencies were also considered. However, these efficiencies tended to be quite low. This is an expected result, since the goals of the Q_G-optimal and Q_U-optimal design criteria are completely different. The Q_G-optimal designs focus on p(1,0;d) while the Q_U-optimal designs focus on logit(p).

Someone wishing to utilize the two univariate models may want to incorporate the univariate D-optimal designs. An obvious way to accomplish this would be to essentially construct two separate designs: the first would be the D-optimal design based on the parameters for the efficacy model, the second would be the D-optimal design based on the parameters for the toxicity model. Of course, both designs would be used to obtain data on both efficacy and toxicity. Thus, if one uses 2-point D-optimal designs (giving a 2×2-point D_U-optimal design), the resulting design would have 4 doses. One could also use 3-point D-optimal designs giving a 2×3-point D_U-optimal design with 6 doses.

These two approaches are shown in Tables 4.2 and 4.3. For the 2×2-point D_U-optimal design and the 2×3-point D_U-optimal design, the D_{U1}-, D_{U2}-, D_G-, Q_G-, and T-efficiencies are given. Note that for the D_U-efficiencies, the value of the correlation parameter α does not need to be specified since neither the designs nor the models include consideration of α. The 2×2-point designs tend to do better with respect to D_U-efficiencies than do the 2×3-point designs; however, the opposite is true with respect to D_G-, Q_G-, and T-efficiencies. Thus, a person who had greater interest in using the univariate marginal models might opt for the 2×2-point design, while one who had greater interest in using the Gumbel model might wish to use the 2×3-point design.

Notice that even though these designs are directly based upon the univariate D-optimality criterion, the D_U-efficiencies exhibit the same general pattern as do the D_U-efficiencies of the D_G-optimal designs. Comparing the D_U-efficiencies in Table 4.1 with those in Tables 4.2 and 4.3, one cannot say that either the D_U-based designs or the D_G-optimal designs present a clear advantage with respect to D_U-efficiencies. The univariate based designs do have the advantage, though, that they are easily found without the use of the iterative search routine required for the Gumbel based designs.

Based on the above discussion, the 2×2-point and 2×3-point D_U-optimal designs appear to be reasonable approaches to the design problem for the Gumbel model, with or without specific consideration of the univariate models. If the researcher wishes to have at least 5 points in the experimental design, however, one needs to note that the 2×3-point design may have fewer than 6 actual doses. For example, if $\mu_1 = \mu_2$ and $\sigma_1 = \sigma_2$, then the D_{U1}-optimal and D_{U2}-optimal designs will be identical, resulting in an overall design with only three doses. If the number of points in the design is a concern, the researcher may want to consider a 5-point design as discussed in Chapter 3, a 5-point compromise design to be presented in §4.2 or a 5-point fitted design to be presented in §4.3.

§4.2 Compromise Designs

The discussion of the three Gumbel optimality criteria (D, Q and T) in Chapter 3 assumes that the researcher is primarily interested in either parameter estimation, estimation of $p(1,0;d)$ or estimation of the therapeutic index. More

commonly, however, there may be interest in estimation of all three of the above quantities. In this case the experimental design should present a reasonable compromise and allow for good estimation of all the quantities of interest.

One approach to this problem is to use a maximin criterion. Using this compromise criterion, the design chosen would be the one which maximizes the minimum efficiency across the three criteria of interest.

An example, along with contour plots of design efficiencies in Figures 4.1-4.3, will help to illustrate the merits of such an approach. Consider the situation where $\mu_1 = 6.0$, $\sigma_1 = 1.0$, $\mu_2 = 7.5$, $\sigma_2 = 0.5$ and $\alpha = 1$. Recall that 5-point designs with equal weighting and equal spacing can be characterized by the value of any of the five design points along with the spacing between those points. Thus, in Figures 4.1-4.3, the efficiencies of designs can be displayed as functions of the midpoint of the design and the spacing between design points. In these figures, all efficiencies are with respect to the "optimal" 3-point designs with unequal weighting. The "D" on each figure indicates the location of the best 5-point design based on the D-optimality criterion. The D-efficiency of this design is .926. Similarly, the "Q" indicates the location of the design based on the Q-optimality criterion with Q-efficiency = .958, and the "T" indicates the location of the design based on the T-optimality criterion with T-efficiency = .918. Note that if the D-optimal design were used in this situation, the resulting Q-efficiency would be .735 and the resulting T-efficiency would be .677. However, using the maximin compromise design indicated on the plots by a "C" yields D-efficiency = T-efficiency = 0.896 and Q-efficiency = 0.909. Thus, the compromise gives up a little in each of the three criteria, yet still does well in each. An overall good design results.

Five-point equally weighted, equally spaced compromise designs are presented in Table 4.4. The 5-point designs were chosen because they are more appealing to many users than are 2- or 3-point designs. In addition, the resulting efficiencies are quite good. Table 4.5 displays the efficiencies corresponding to the compromise designs of Table 4.4. The minimum efficiencies are mainly in the upper .80's. The exception is when $\mu_1^* = \mu_2^* = 6$: in these cases, the efficiencies are lower due to the 1-point nature of the T-optimal designs. One could also include the D_U-efficiencies in the maximin criterion. Doing this reduces the minimum efficiencies so that they lie primarily between 0.80 and 0.90.

In using these compromise designs one needs to be aware that they are based on T-efficiencies evaluated for $\mu_1^* = 6.0$. One could shift them to accommodate other values of μ_1^*, but this requires the assumption that the designs are relatively insensitive to the location. Observation indicates that in many cases this is a reasonable assumption. One needs to be most careful in situations where μ_1^* is close to 0 ($\mu_1^* < 2$, or equivalently $\mu_1 < 2\sigma_1$).

§4.3 Five-Point Fitted Designs

Some advantages of 5-point designs were mentioned in §3.1. One attractive feature of these designs is that they change fairly consistently as the Gumbel parameters change. If one compares the 5-point design tables with the 2- or 3-point design tables, particularly those with unequal weighting, one easily notices that the 5-point designs are much more regular than the others. This regularity suggests that it may be possible to approximate these designs using

functions of the Gumbel parameters. This was done by fitting a quadratic regression model (including second order interaction terms) to the designs in Tables 3.2, 3.5 and 4.4. (T-optimal designs were not fit in this way since it would not be advisable to design an experiment based solely on the T-optimality criterion, particularly when $\mu_1 = \mu_2$.) The two dependent variables which are modeled are 1) the smallest of the five design points and 2) the spacing between the design points. The independent variables are the Gumbel parameters as standardized using (3.1.1).

Table 4.6 gives the coefficients of the fitted equations for the D-optimal, Q-optimal and Compromise based designs. The efficiencies of the fitted designs come within 0.01 of the tabled D-optimal and Q-optimal 5-point designs. The one exception to this is for $\mu_2^* = -1$, $\sigma_2^* = .5$, $\alpha = 2$, where the Q-efficiency of the fitted design is 0.049 less than the optimized 5-point design.

The compromise designs are not approximated as closely by the fitted designs. This might be expected, since the fitted compromise designs are trying to capture the characteristics of all three efficiency contours. With two exceptions, all the minimum efficiencies of the fitted compromise designs are within .05 of the minimum of the compromise designs as shown in Table 4.5. Both the exceptions occur when $\mu_1 = \mu_2 = 6$ and are driven by the behavior of the T-efficiency contour. It is worth noting, however, that although the T-efficiency of the fitted design drops, the D-efficiency and Q-efficiency are both higher than for the best compromise design. Although it is not always true, due to the nature of the compromise designs if the efficiency in one criterion decreases, the efficiency of another usually will increase. For an example of this, look at

Figures 4.1-4.3. If the compromise design is moved in any direction on the plot but straight down, at least one efficiency will decrease while another increases.

Two words of warning are in order. First, the fitted designs have not been tested outside the region represented by the optimal design tables ($\alpha \in$ [-1, 2], $\sigma_2^* \in$ [0.5, 2], $\mu_2^* \in$ [-1, 2] for D- and Q-based designs; $\alpha \in$ [-1, 2], $\sigma_2^* \in$ [0.5, 2], $\mu_2^* \in$ [5, 8] for compromise designs). Extreme caution should be taken if one desires to use these designs for parameter combinations outside the range of this table. Second, the compromise designs are based on T-efficiencies evaluated for $\mu_1^* = 6.0$ and the comments at the end of §4.2 apply.

§4.3.1 Robustness Case Study

One important consideration regarding the 5-point designs in general and the 5-point fitted designs in particular is how robust they are to parameter misspecification in comparison to the "optimal" 3-point designs with unequal weighting. As discussed in §3.2.1, the robustness question is difficult to address exhaustively. In order to attempt to gain some insight, however, a brief case study was performed.

Consider the situation where the initial parameter guesses are given as $\mu_{10} = 0$, $\sigma_{10} = 1$, $\mu_{20} = 1$, $\sigma_{20} = 1.5$ and $\alpha_0 = 1$. In this case study, two degrees of misspecification were considered: mild misspecification, where $\frac{(\mu_1 - \mu_{10})}{\sigma_1} = \pm 0.5$, $\frac{\sigma_1}{\sigma_{10}} = 0.80,\ 1.25$, $\frac{(\mu_2 - \mu_{20})}{\sigma_2} = \pm 0.5$, $\frac{\sigma_2}{\sigma_{20}} = 0.80,\ 1.25$ and $\alpha = \alpha_0 \pm 1$; and severe misspecification, where $\frac{(\mu_1 - \mu_{10})}{\sigma_1} = \pm 1.0$, $\frac{\sigma_1}{\sigma_{10}} = 0.50,\ 2.00$, $\frac{(\mu_2 - \mu_{20})}{\sigma_2} = \pm 1.0$, $\frac{\sigma_2}{\sigma_{20}} = 0.50,\ 2.00$ and $\alpha = \alpha_0 \pm 1$. Table 4.7a gives the D-optimal based designs which are compared. Table 4.7b shows the D-efficiency

of this design for selected situations in which different combinations of the parameters are misspecified simultaneously to a mild degree. The first line represents a perfect guess, i.e. no parameters misspecified. Thus, the D-efficiency of the 3-point design is 1.00. The second block of five lines are situations where one of the five parameters are misspecified. Similarly, there are blocks where two, three and four parameters are missed, and the final line is when all five parameters were misspecified.

For this particular set of mild misspecifications, the D-efficiencies of the 3-point and both 5-point designs are quite good--all greater than 0.90. In addition, although the 3-point design has higher D-efficiency than the 5-point designs in most of the cases, there is not a large discrepancy in any.

Table 4.7c presents parameter misspecifications of the same combinations and directions as Table 4.7b, but the misses are of a larger magnitude. Again, many of the D-efficiencies are fairly good; however, in several instances they are between 0.60 and 0.80. As with the mild misspecification, none of the designs presents itself as a clear winner. Each of the three designs appears to perform reasonably well with respect to the others.

The comparable cases for the Q-optimality criterion are examined in Tables 4.8a-c. Note that the 3-point unequal weighting design is actually a 2-point design in this case since the weighting for the first design point is 0.00. For mild misspecifications the Q-efficiencies are all reasonably good, and there are no major differences between the three designs. For severe misspecifications some of the Q-efficiencies do quite poorly. Perhaps the most striking characteristic of Table 4.8c, though, is that while there are no cases where the 3-point design performs much better than the 5-point designs, there are some

situations where the 5-point designs have much higher Q-efficiencies than does the 3-point design. For example, when $\mu_1 = 0$, $\sigma_1 = 0.5$, $\mu_2 = 1$, $\sigma_2 = 1.5$ and $\alpha = 1$ (the third line from the top), the Q-efficiency of the 3-point design is only 0.691, compared to Q-efficiencies of 0.905 and 0.911 for the best 5-point design and the fitted 5-point design, respectively.

Thus, although these results are not conclusive by any means, there is some evidence that 5-point designs may offer better protection against parameter misspecification. Intuitively, one might suspect that designs with more design points might withstand incorrect parameter guesses better because the design points are more spread out and are thus more likely to obtain information at critical (but unknown prior to the experiment) locations in the design space. It is not clear from this limited case study whether the differences in results between D- and Q-optimal designs are due to differences in the criteria, due to the particular parameter combination examined, due to the Q-optimal design having only two design points in this particular case, or due to some combination of the above reasons.

Table 4.1 D_U-Efficiencies of 3-pt. D_G-optimal Designs

D_{U1}-Efficiency of 3-pt. D_G-optimal Designs ($\mu_1^* = 0$, $\sigma_1^* = 1$)

		μ_2^*				
α	σ_2^*	0.0	0.5	1.0	1.5	2.0
-1	0.5	0.816	0.800	0.757	0.797	0.777
-1	1.0	0.993	0.984	0.958	0.917	0.863
-1	1.5	0.996	0.991	0.975	0.958	0.925
-1	2.0	0.984	0.979	0.967	0.950	0.925
0	0.5	0.757	0.756	0.794	0.798	0.786
0	1.0	0.960	0.951	0.926	0.882	0.840
0	1.5	0.997	0.991	0.973	0.934	0.866
0	2.0	1.000	0.992	0.970	0.895	0.860
1	0.5	0.768	0.778	0.790	0.793	0.784
1	1.0	0.928	0.917	0.890	0.857	0.826
1	1.5	0.950	0.939	0.913	0.879	0.848
1	2.0	0.931	0.918	0.893	0.866	0.843
2	0.5	0.746	0.764	0.772	*	*
2	1.0	0.901	0.891	0.868	0.841	*
2	1.5	0.920	0.914	0.895	0.872	0.852
2	2.0	0.919	0.901	0.883	0.868	0.856

D_{U2}-Efficiency of 3-pt. D_G-optimal Designs ($\mu_1^* = 0$, $\sigma_1^* = 1$)

		μ_2^*				
α	σ_2^*	0.0	0.5	1.0	1.5	2.0
-1	0.5	0.984	0.969	0.927	0.844	0.817
-1	1.0	0.993	0.984	0.958	0.917	0.863
-1	1.5	0.920	0.915	0.897	0.862	0.827
-1	2.0	0.816	0.816	0.804	0.785	0.762
0	0.5	1.000	0.969	0.860	0.813	0.785
0	1.0	0.960	0.951	0.926	0.882	0.840
0	1.5	0.862	0.860	0.848	0.837	0.829
0	2.0	0.757	0.756	0.755	0.786	0.794
1	0.5	0.931	0.893	0.843	0.806	0.781
1	1.0	0.928	0.917	0.890	0.857	0.826
1	1.5	0.848	0.845	0.838	0.829	0.818
1	2.0	0.768	0.771	0.778	0.784	0.790
2	0.5	0.919	0.883	0.856	*	*
2	1.0	0.901	0.891	0.868	0.841	*
2	1.5	0.832	0.827	0.818	0.809	0.797
2	2.0	0.746	0.757	0.764	0.769	0.772

* α exceeds maximum allowable value at this parameter combination

Table 4.2 Efficiencies of 2×2-point D_U-optimal Designs

D_{U1}-Efficiency ($\mu_1^* = 6$, $\sigma_1^* = 1$)

	μ_2^*						
σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
0.5	0.898	0.917	0.924	0.917	0.898	0.876	0.853
1.0	0.937	0.982	1.000	0.982	0.937	0.882	0.835
1.5	0.902	0.932	0.942	0.932	0.902	0.857	0.808
2.0	0.823	0.830	0.832	0.830	0.823	0.807	0.781

D_{U2}-Efficiency ($\mu_1^* = 6$, $\sigma_1^* = 1$)

	μ_2^*						
σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
0.5	0.781	0.823	0.832	0.823	0.781	0.724	0.715
1.0	0.937	0.982	1.000	0.982	0.937	0.882	0.835
1.5	0.942	0.959	0.965	0.959	0.942	0.918	0.893
2.0	0.917	0.922	0.924	0.922	0.917	0.908	0.898

Relative D_G-Efficiency ($\mu_1^* = 6$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	0.982	0.953	0.936	0.953	0.982	0.965	0.959
-1	1.0	0.971	0.987	0.993	0.987	0.971	0.957	0.960
-1	1.5	0.969	0.971	0.972	0.971	0.969	0.966	0.966
-1	2.0	0.952	0.940	0.936	0.940	0.952	0.967	0.981
0	0.5	0.954	0.932	0.913	0.932	0.954	0.970	0.981
0	1.0	0.964	0.959	0.957	0.959	0.964	0.971	0.977
0	1.5	0.952	0.942	0.939	0.942	0.952	0.965	0.970
0	2.0	0.932	0.918	0.913	0.918	0.932	0.942	0.954
1	0.5	0.927	0.907	0.897	0.907	0.927	0.948	0.980
1	1.0	0.946	0.935	0.930	0.935	0.946	0.957	0.969
1	1.5	0.929	0.920	0.916	0.920	0.929	0.940	0.950
1	2.0	0.907	0.899	0.897	0.899	0.907	0.917	0.927
2	0.5	0.872	0.867	0.868	0.867	0.872	*	*
2	1.0	0.874	0.879	0.878	0.879	0.874	0.826	*
2	1.5	0.874	0.873	0.873	0.873	0.874	0.867	0.805
2	2.0	0.867	0.865	0.868	0.865	0.867	0.872	0.872

* α exceeds maximum allowable value at this parameter combination

Efficiencies of 2×2-point D_U-optimal Designs (continued)

Relative Q_G-Efficiency ($\mu_1^* = 6$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	0.933	0.898	0.885	0.884	0.881	0.863	0.840
-1	1.0	0.967	0.977	0.992	0.990	0.957	0.900	0.846
-1	1.5	0.935	0.938	0.945	0.943	0.935	0.910	0.879
-1	2.0	0.898	0.889	0.885	0.884	0.884	0.883	0.882
0	0.5	0.872	0.873	0.854	0.867	0.891	0.882	0.862
0	1.0	0.907	0.918	0.943	0.971	0.972	0.937	0.892
0	1.5	0.893	0.893	0.901	0.915	0.926	0.924	0.909
0	2.0	0.864	0.858	0.854	0.858	0.867	0.878	0.889
1	0.5	0.831	0.824	0.812	0.846	0.879	0.883	0.870
1	1.0	0.817	0.830	0.875	0.938	0.975	0.963	0.927
1	1.5	0.815	0.819	0.838	0.874	0.908	0.928	0.929
1	2.0	0.809	0.808	0.812	0.826	0.846	0.866	0.879
2	0.5	0.841	0.789	0.768	0.821	0.859	*	*
2	1.0	0.668	0.691	0.770	0.880	0.966	0.983	*
2	1.5	0.717	0.722	0.759	0.821	0.885	0.918	0.925
2	2.0	0.789	0.764	0.768	0.793	0.821	0.844	0.859

Relative T-Efficiency ($\mu_1^* = 6$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	0.767	0.719	0.645	0.731	0.752	0.714	0.634
-1	1.0	0.816	0.735	0.634	0.735	0.817	0.859	0.830
-1	1.5	0.765	0.711	0.636	0.700	0.757	0.809	0.841
-1	2.0	0.734	0.700	0.645	0.683	0.714	0.741	0.768
0	0.5	0.768	0.704	0.609	0.717	0.751	0.713	0.632
0	1.0	0.825	0.716	0.580	0.716	0.825	0.876	0.844
0	1.5	0.759	0.685	0.589	0.672	0.749	0.819	0.859
0	2.0	0.724	0.676	0.609	0.656	0.698	0.735	0.769
1	0.5	0.761	0.679	0.565	0.695	0.742	0.704	0.625
1	1.0	0.832	0.688	0.509	0.688	0.834	0.898	0.858
1	1.5	0.742	0.646	0.528	0.632	0.731	0.816	0.865
1	2.0	0.702	0.645	0.565	0.622	0.672	0.720	0.763
2	0.5	0.752	0.645	0.514	0.666	0.734	*	*
2	1.0	0.843	0.635	0.409	0.636	0.844	0.930	*
2	1.5	0.710	0.584	0.447	0.563	0.695	0.810	0.871
2	2.0	0.676	0.604	0.514	0.571	0.634	0.697	0.752

* α exceeds maximum allowable value at this parameter combination

Table 4.3 Efficiencies of 2×3-point D_U-optimal Designs

D_{U1}-Efficiency ($\mu_1^* = 6$, $\sigma_1^* = 1$)

	μ_2^*						
σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
0.5	0.845	0.851	0.853	0.851	0.845	0.837	0.825
1.0	0.898	0.922	0.929	0.922	0.898	0.860	0.819
1.5	0.883	0.883	0.881	0.883	0.883	0.867	0.832
2.0	0.820	0.801	0.792	0.801	0.820	0.833	0.828

D_{U2}-Efficiency ($\mu_1^* = 6$, $\sigma_1^* = 1$)

	μ_2^*						
σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
0.5	0.828	0.820	0.792	0.820	0.828	0.757	0.677
1.0	0.898	0.922	0.929	0.922	0.898	0.860	0.819
1.5	0.882	0.892	0.896	0.892	0.882	0.868	0.852
2.0	0.851	0.853	0.853	0.853	0.851	0.848	0.845

Relative D_G-Efficiency ($\mu_1^* = 6$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	0.978	0.938	0.914	0.938	0.978	0.957	0.923
-1	1.0	0.944	0.944	0.943	0.944	0.944	0.944	0.950
-1	1.5	0.944	0.935	0.930	0.935	0.944	0.954	0.962
-1	2.0	0.938	0.921	0.914	0.921	0.938	0.958	0.977
0	0.5	0.969	0.967	0.951	0.967	0.969	0.952	0.932
0	1.0	0.970	0.969	0.969	0.969	0.970	0.969	0.962
0	1.5	0.970	0.963	0.961	0.963	0.970	0.977	0.970
0	2.0	0.967	0.956	0.951	0.956	0.967	0.969	0.969
1	0.5	0.953	0.967	0.964	0.967	0.953	0.918	0.897
1	1.0	0.974	0.984	0.986	0.984	0.974	0.955	0.936
1	1.5	0.975	0.977	0.976	0.977	0.975	0.966	0.949
1	2.0	0.967	0.965	0.964	0.965	0.967	0.964	0.953
2	0.5	0.862	0.952	0.964	0.952	0.862	*	*
2	1.0	0.945	0.979	0.985	0.979	0.945	0.822	*
2	1.5	0.958	0.972	0.975	0.972	0.958	0.909	0.733
2	2.0	0.952	0.959	0.964	0.959	0.952	0.929	0.862

* α exceeds maximum allowable value at this parameter combination

Efficiencies of 2×3-point D_U-optimal Designs (continued)

Relative Q_G-Efficiency ($\mu_1^* = 6$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	0.961	0.915	0.853	0.822	0.830	0.845	0.840
-1	1.0	0.978	0.965	0.945	0.921	0.893	0.860	0.831
-1	1.5	0.951	0.928	0.905	0.883	0.869	0.855	0.845
-1	2.0	0.915	0.883	0.853	0.831	0.822	0.822	0.831
0	0.5	0.891	0.925	0.876	0.847	0.857	0.862	0.855
0	1.0	0.962	0.972	0.968	0.955	0.934	0.904	0.875
0	1.5	0.952	0.945	0.928	0.911	0.898	0.888	0.880
0	2.0	0.916	0.901	0.876	0.857	0.847	0.847	0.855
1	0.5	0.844	0.905	0.873	0.858	0.860	0.863	0.857
1	1.0	0.926	0.972	0.986	0.979	0.961	0.934	0.908
1	1.5	0.925	0.938	0.930	0.921	0.913	0.908	0.905
1	2.0	0.889	0.887	0.873	0.862	0.858	0.858	0.860
2	0.5	0.744	0.870	0.859	0.858	0.859	*	*
2	1.0	0.873	0.960	0.985	0.982	0.978	0.965	*
2	1.5	0.884	0.918	0.920	0.918	0.921	0.917	0.911
2	2.0	0.870	0.865	0.859	0.858	0.858	0.858	0.859

Relative T-Efficiency ($\mu_1^* = 6$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	0.796	0.786	0.719	0.790	0.779	0.730	0.670
-1	1.0	0.849	0.784	0.684	0.784	0.849	0.876	0.854
-1	1.5	0.810	0.769	0.696	0.764	0.810	0.840	0.853
-1	2.0	0.789	0.769	0.719	0.761	0.784	0.794	0.799
0	0.5	0.796	0.782	0.697	0.786	0.776	0.724	0.662
0	1.0	0.865	0.783	0.647	0.783	0.865	0.890	0.861
0	1.5	0.813	0.760	0.665	0.754	0.814	0.853	0.867
0	2.0	0.787	0.759	0.697	0.750	0.780	0.793	0.799
1	0.5	0.787	0.772	0.673	0.776	0.765	0.711	0.650
1	1.0	0.884	0.784	0.600	0.784	0.886	0.908	0.867
1	1.5	0.810	0.745	0.628	0.740	0.813	0.853	0.866
1	2.0	0.777	0.747	0.673	0.737	0.769	0.784	0.791
2	0.5	0.772	0.756	0.652	0.761	0.753	*	*
2	1.0	0.915	0.784	0.538	0.785	0.917	0.934	*
2	1.5	0.797	0.722	0.583	0.714	0.803	0.849	0.862
2	2.0	0.762	0.732	0.652	0.717	0.752	0.766	0.772

* α exceeds maximum allowable value at this parameter combination

Table 4.4 5-point Compromise Designs with Equal Weighting, Equal Spacing

$(\mu_1^* = 6, \sigma_1^* = 1)$

α	σ_2^*		μ_2^* = 5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	PT1	4.040	4.367	4.709	4.596	4.564	4.718	4.857
		SPACE	0.717	0.660	0.594	0.697	0.798	0.855	0.912
-1	1.0	PT1	3.701	4.162	4.554	4.467	4.417	4.422	4.524
		SPACE	0.881	0.788	0.723	0.887	1.032	1.150	1.211
-1	1.5	PT1	3.362	3.794	4.230	4.320	4.375	4.405	4.475
		SPACE	1.071	1.012	0.937	1.071	1.199	1.322	1.406
-1	2.0	PT1	2.888	3.361	3.833	4.069	4.234	4.351	4.459
		SPACE	1.347	1.269	1.187	1.275	1.374	1.472	1.551
0	0.5	PT1	4.093	4.413	4.780	4.644	4.615	4.793	4.800
		SPACE	0.711	0.646	0.560	0.661	0.757	0.817	0.908
0	1.0	PT1	3.820	4.256	4.699	4.578	4.509	4.522	4.613
		SPACE	0.811	0.739	0.650	0.830	0.981	1.091	1.142
0	1.5	PT1	3.390	3.878	4.375	4.477	4.522	4.545	4.608
		SPACE	1.043	0.958	0.861	1.002	1.138	1.262	1.340
0	2.0	PT1	2.901	3.423	3.962	4.239	4.421	4.541	4.642
		SPACE	1.334	1.226	1.120	1.205	1.304	1.399	1.471
1	0.5	PT1	3.815	4.385	4.803	4.656	4.689	4.882	4.830
		SPACE	0.755	0.659	0.544	0.636	0.740	0.791	0.916
1	1.0	PT1	3.800	4.285	4.813	4.640	4.543	4.562	4.623
		SPACE	0.823	0.722	0.593	0.797	0.959	1.056	1.094
1	1.5	PT1	3.375	3.899	4.475	4.605	4.651	4.682	4.748
		SPACE	1.064	0.943	0.815	0.958	1.093	1.196	1.240
1	2.0	PT1	2.862	3.422	4.041	4.378	4.589	4.705	4.786
		SPACE	1.367	1.229	1.088	1.166	1.253	1.342	1.411
2	0.5	PT1	3.424	4.324	4.801	4.643	4.950	*	*
		SPACE	1.030	0.692	0.536	0.616	0.697	*	*
2	1.0	PT1	3.804	4.266	4.921	4.691	4.614	4.827	*
		SPACE	0.848	0.727	0.539	0.767	0.943	0.962	*
2	1.5	PT1	3.321	3.886	4.575	4.766	4.816	4.798	4.543
		SPACE	1.121	0.946	0.773	0.904	1.023	1.123	1.281
2	2.0	PT1	2.709	3.386	4.111	4.545	4.777	4.883	4.671
		SPACE	1.425	1.250	1.072	1.123	1.205	1.278	1.374

* α exceeds maximum allowable value at this parameter combination

Table 4.5 Relative Efficiencies of 5-pt. Compromise Designs

Minimum of D-, Q- and T-Efficiency ($\mu_1^* = 6$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	0.887	0.864	0.807	0.870	0.896	0.900	0.866
-1	1.0	0.939	0.913	0.828	0.873	0.884	0.885	0.883
-1	1.5	0.910	0.877	0.819	0.858	0.876	0.883	0.885
-1	2.0	0.864	0.843	0.807	0.841	0.863	0.877	0.886
0	0.5	0.893	0.866	0.801	0.888	0.923	0.911	0.869
0	1.0	0.971	0.939	0.830	0.902	0.919	0.919	0.911
0	1.5	0.923	0.889	0.817	0.875	0.902	0.914	0.914
0	2.0	0.863	0.843	0.801	0.848	0.880	0.898	0.907
1	0.5	0.809	0.844	0.781	0.896	0.929	0.896	0.850
1	1.0	0.979	0.956	0.819	0.925	0.947	0.944	0.920
1	1.5	0.907	0.881	0.799	0.880	0.916	0.927	0.920
1	2.0	0.838	0.824	0.781	0.845	0.886	0.907	0.909
2	0.5	0.731	0.809	0.760	0.901	0.886	*	*
2	1.0	0.937	0.955	0.792	0.939	0.973	0.924	*
2	1.5	0.865	0.853	0.771	0.873	0.918	0.920	0.880
2	2.0	0.813	0.799	0.760	0.837	0.886	0.901	0.878

Relative D-Efficiency ($\mu_1^* = 6$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	0.968	0.963	0.954	0.941	0.929	0.900	0.866
-1	1.0	0.939	0.917	0.895	0.936	0.951	0.960	0.978
-1	1.5	0.945	0.937	0.922	0.938	0.944	0.948	0.956
-1	2.0	0.963	0.961	0.954	0.950	0.942	0.937	0.937
0	0.5	0.971	0.993	0.983	0.968	0.934	0.911	0.869
0	1.0	0.971	0.954	0.922	0.972	0.984	0.988	0.986
0	1.5	0.982	0.971	0.951	0.970	0.976	0.980	0.974
0	2.0	0.991	0.990	0.983	0.978	0.971	0.956	0.945
1	0.5	0.954	0.988	0.989	0.959	0.929	0.896	0.850
1	1.0	0.984	0.968	0.919	0.984	0.991	0.982	0.965
1	1.5	0.991	0.984	0.957	0.977	0.979	0.974	0.965
1	2.0	0.985	0.995	0.989	0.978	0.962	0.947	0.933
2	0.5	0.826	0.961	0.993	0.932	0.886	*	*
2	1.0	0.973	0.977	0.908	0.983	0.973	0.924	*
2	1.5	0.975	0.987	0.959	0.970	0.961	0.936	0.880
2	2.0	0.957	0.987	0.993	0.967	0.936	0.906	0.878

* α exceeds maximum allowable value at this parameter combination

Relative Efficiencies of 5-pt. Compromise Designs (continued)

Relative Q-Efficiency ($\mu_1^* = 6$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	0.887	0.864	0.807	0.870	0.896	0.900	0.888
-1	1.0	0.980	0.913	0.828	0.873	0.884	0.885	0.883
-1	1.5	0.910	0.877	0.819	0.858	0.876	0.883	0.885
-1	2.0	0.864	0.843	0.807	0.841	0.863	0.877	0.886
0	0.5	0.893	0.866	0.801	0.888	0.923	0.911	0.902
0	1.0	0.988	0.939	0.830	0.902	0.919	0.919	0.911
0	1.5	0.923	0.889	0.817	0.875	0.902	0.914	0.914
0	2.0	0.863	0.843	0.801	0.848	0.880	0.898	0.907
1	0.5	0.809	0.844	0.781	0.896	0.929	0.909	0.916
1	1.0	0.979	0.956	0.819	0.925	0.947	0.944	0.927
1	1.5	0.907	0.881	0.799	0.880	0.916	0.927	0.920
1	2.0	0.838	0.824	0.781	0.845	0.886	0.907	0.909
2	0.5	0.731	0.809	0.760	0.901	0.886	*	*
2	1.0	0.937	0.955	0.792	0.939	0.973	0.956	*
2	1.5	0.865	0.853	0.771	0.873	0.918	0.926	0.934
2	2.0	0.813	0.799	0.760	0.837	0.886	0.901	0.893

Relative T-Efficiency ($\mu_1^* = 6$, $\sigma_1^* = 1$)

		μ_2^*						
α	σ_2^*	5.0	5.5	6.0	6.5	7.0	7.5	8.0
-1	0.5	0.887	0.864	0.807	0.870	0.896	0.900	0.866
-1	1.0	0.939	0.913	0.828	0.873	0.884	0.885	0.883
-1	1.5	0.910	0.877	0.819	0.858	0.876	0.883	0.885
-1	2.0	0.864	0.843	0.807	0.841	0.863	0.877	0.886
0	0.5	0.893	0.866	0.801	0.888	0.923	0.911	0.869
0	1.0	0.971	0.939	0.830	0.902	0.919	0.919	0.911
0	1.5	0.923	0.889	0.817	0.875	0.902	0.914	0.914
0	2.0	0.863	0.843	0.801	0.848	0.880	0.898	0.907
1	0.5	0.809	0.844	0.781	0.896	0.929	0.896	0.850
1	1.0	0.979	0.956	0.819	0.925	0.947	0.944	0.920
1	1.5	0.907	0.881	0.799	0.880	0.916	0.927	0.920
1	2.0	0.838	0.824	0.781	0.845	0.886	0.907	0.909
2	0.5	0.751	0.809	0.760	0.901	0.886	*	*
2	1.0	0.988	0.955	0.792	0.939	0.976	0.959	*
2	1.5	0.865	0.853	0.771	0.873	0.918	0.920	0.899
2	2.0	0.813	0.799	0.760	0.837	0.886	0.901	0.878

* α exceeds maximum allowable value at this parameter combination

Table 4.6 Fitted 5-point Designs (in Standardized Metric)

	Coefficients for Calculating Lowest (Standardized) Dose		
Regressor	D-optimality Criterion	Q-optimality Criterion	Compromise Criterion
Intercept	-0.375	-2.486	-1.224
μ_2^*	0.570	0.565	0.269
σ_2^*	-1.857	0.649	-0.182
α	0.000	-0.119	-0.021
μ_2^{*2}	-0.053	-0.052	-0.223
σ_2^{*2}	0.392	-0.171	-0.124
α^2	-0.017	-0.018	-0.019
$\mu_2^*\sigma_2^*$	-0.090	-0.231	0.238
$\mu_2^*\alpha$	0.012	-0.009	0.037
$\sigma_2^*\alpha$	0.073	0.205	0.064

	Coefficients for Calculating Spacing Between Doses		
Regressor	D-optimality Criterion	Q-optimality Criterion	Compromise Criterion
Intercept	0.246	0.599	0.477
μ_2^*	0.017	0.109	0.017
σ_2^*	0.843	0.328	0.222
α	-0.036	-0.025	0.001
μ_2^{*2}	0.040	0.021	0.097
σ_2^{*2}	-0.169	0.076	0.066
α^2	0.011	0.009	0.011
$\mu_2^*\sigma_2^*$	-0.026	-0.006	-0.012
$\mu_2^*\alpha$	0.008	0.000	-0.021
$\sigma_2^*\alpha$	-0.016	-0.019	-0.024

Note: $\mu_2^* = (\mu_2 - \mu_1)/\sigma_1$ and $\sigma_2^* = \sigma_2/\sigma_1$.

Transform design to original metric by using $d = d^*\sigma_1 + \mu_1$, where d^* is a dose in the transformed metric.

Table 4.7a D-optimality Robustness Case Study

Guessed Parameter Values				
μ_1	σ_1	μ_2	σ_2	α
0	1	1	1.5	1

D-optimal Based Designs			
3-pt Uneq. Wt.		5-pt.	5-pt fitted
Dose	Weight	Dose	Dose
-1.465	0.369	-1.803	-1.792
0.687	0.379	-0.690	-0.685
2.668	0.252	0.423	0.422
		1.536	1.529
		2.649	2.636

Table 4.7b D-optimality Robustness Case Study--Mild Misspecification

Parms Missed	Actual Parameters					D-efficiencies		
	μ_1	σ_1	μ_2	σ_2	α	3-pt	5-pt	5-pt fitted
0	0.00	1.00	1.00	1.50	1	1.000	0.992	0.992
1	-0.50	1.00	1.00	1.50	1	0.989	0.979	0.979
1	0.00	0.80	1.00	1.50	1	0.990	0.979	0.980
1	0.00	1.00	0.25	1.50	1	0.990	0.987	0.987
1	0.00	1.00	1.00	1.20	1	0.995	0.988	0.988
1	0.00	1.00	1.00	1.50	0	0.991	0.986	0.986
2	0.63	1.25	1.00	1.50	1	0.982	0.978	0.978
2	0.00	1.00	0.40	1.20	1	0.983	0.982	0.983
2	0.50	1.00	1.75	1.50	1	0.967	0.964	0.964
2	0.00	1.25	1.00	1.88	1	0.981	0.973	0.972
2	0.00	1.25	1.00	1.50	2	0.994	0.982	0.981
3	-0.40	0.80	1.00	1.50	0	0.986	0.976	0.976
3	0.50	1.00	1.75	1.50	2	0.936	0.940	0.940
3	-0.50	1.00	0.25	1.50	2	0.962	0.960	0.960
3	0.00	0.80	1.00	1.20	0	0.973	0.971	0.972
3	0.40	0.80	1.75	1.50	1	0.958	0.953	0.953
4	0.00	1.25	0.06	1.88	0	0.957	0.949	0.948
4	-0.40	0.80	1.94	1.88	1	0.941	0.919	0.919
4	0.63	1.25	1.00	1.20	0	0.964	0.966	0.966
4	0.40	0.80	1.75	1.50	0	0.961	0.962	0.962
4	0.40	0.80	0.06	1.88	1	0.987	0.991	0.992
5	-0.63	1.25	1.94	1.88	0	0.956	0.943	0.942

Table 4.7c D-optimality Robustness Case Study--Severe Misspecification

Parms Missed	Actual Parameters					D-efficiencies		
	μ_1	σ_1	μ_2	σ_2	α	3-pt	5-pt	5-pt fitted
0	0.00	1.00	1.00	1.50	1	1.000	0.992	0.992
1	-1.00	1.00	1.00	1.50	1	0.953	0.947	0.947
1	0.00	0.50	1.00	1.50	1	0.871	0.869	0.871
1	0.00	1.00	-0.50	1.50	1	0.965	0.967	0.967
1	0.00	1.00	1.00	0.75	1	0.950	0.942	0.944
1	0.00	1.00	1.00	1.50	0	0.991	0.986	0.986
2	2.00	2.00	1.00	1.50	1	0.900	0.892	0.891
2	0.00	1.00	0.25	0.75	1	0.922	0.932	0.934
2	1.00	1.00	2.50	1.50	1	0.880	0.888	0.887
2	0.00	2.00	1.00	3.00	1	0.840	0.828	0.826
2	0.00	2.00	1.00	1.50	2	0.958	0.951	0.950
3	-0.50	0.50	1.00	1.50	0	0.834	0.857	0.858
3	1.00	1.00	2.50	1.50	2	0.820	0.857	0.857
3	-1.00	1.00	-0.50	1.50	2	0.899	0.895	0.894
3	0.00	0.50	1.00	0.75	0	0.811	0.819	0.822
3	0.50	0.50	2.50	1.50	1	0.766	0.768	0.769
4	0.00	2.00	-2.00	3.00	0	0.776	0.766	0.763
4	-0.50	0.50	4.00	3.00	1	0.645	0.638	0.638
4	2.00	2.00	1.00	0.75	0	0.909	0.922	0.922
4	0.50	0.50	2.50	1.50	0	0.780	0.786	0.787
4	0.50	0.50	-2.00	3.00	1	0.675	0.708	0.708
5	-2.00	2.00	4.00	3.00	0	0.716	0.704	0.702

Table 4.8a Q-optimality Robustness Case Study

Guessed Parameter Values				
μ_1	σ_1	μ_2	σ_2	α
0	1	1	1.5	1

Q-optimal Based Designs			
3-pt Uneq. Wt.		5-pt.	5-pt fitted
Dose	Weight	Dose	Dose
——	0.000	-1.637	-1.539
-0.570	0.474	-0.283	-0.231
2.875	0.526	1.072	1.108
		2.426	2.447
		3.781	3.786

Table 4.8b Q-optimality Robustness Case Study--Mild Misspecification

Parms Missed	Actual Parameters					Q-efficiencies		
	μ_1	σ_1	μ_2	σ_2	α	3-pt	5-pt	5-pt fitted
0	0.00	1.00	1.00	1.50	1	1.000	0.959	0.959
1	-0.50	1.00	1.00	1.50	1	0.946	0.945	0.940
1	0.00	0.80	1.00	1.50	1	0.983	0.956	0.958
1	0.00	1.00	0.25	1.50	1	0.996	0.953	0.953
1	0.00	1.00	1.00	1.20	1	0.970	0.942	0.941
1	0.00	1.00	1.00	1.50	0	0.992	0.939	0.937
2	0.63	1.25	1.00	1.50	1	0.993	0.974	0.974
2	0.00	1.00	0.40	1.20	1	0.953	0.919	0.918
2	0.50	1.00	1.75	1.50	1	0.957	0.927	0.929
2	0.00	1.25	1.00	1.88	1	0.952	0.928	0.925
2	0.00	1.25	1.00	1.50	2	0.993	0.974	0.971
3	-0.40	0.80	1.00	1.50	0	0.957	0.943	0.941
3	0.50	1.00	1.75	1.50	2	0.943	0.942	0.945
3	-0.50	1.00	0.25	1.50	2	0.947	0.948	0.945
3	0.00	0.80	1.00	1.20	0	0.965	0.913	0.915
3	0.40	0.80	1.75	1.50	1	0.915	0.916	0.920
4	0.00	1.25	0.06	1.88	0	0.943	0.931	0.925
4	-0.40	0.80	1.94	1.88	1	0.871	0.881	0.880
4	0.63	1.25	1.00	1.20	0	0.974	0.946	0.945
4	0.40	0.80	1.75	1.50	0	0.944	0.903	0.906
4	0.40	0.80	0.06	1.88	1	0.924	0.923	0.926
5	-0.63	1.25	1.94	1.88	0	0.803	0.822	0.814

Table 4.8c Q-optimality Robustness Case Study--Severe Misspecification

Parms Missed	Actual Parameters					Q-efficiencies		
	μ_1	σ_1	μ_2	σ_2	α	3-pt	5-pt	5-pt fitted
0	0.00	1.00	1.00	1.50	1	1.000	0.959	0.959
1	-1.00	1.00	1.00	1.50	1	0.764	0.891	0.878
1	0.00	0.50	1.00	1.50	1	0.691	0.905	0.911
1	0.00	1.00	-0.50	1.50	1	0.986	0.939	0.938
1	0.00	1.00	1.00	0.75	1	0.762	0.835	0.834
1	0.00	1.00	1.00	1.50	0	0.992	0.939	0.937
2	2.00	2.00	1.00	1.50	1	0.936	0.962	0.959
2	0.00	1.00	0.25	0.75	1	0.743	0.766	0.765
2	1.00	1.00	2.50	1.50	1	0.851	0.829	0.833
2	0.00	2.00	1.00	3.00	1	0.704	0.737	0.731
2	0.00	2.00	1.00	1.50	2	0.828	0.869	0.858
3	-0.50	0.50	1.00	1.50	0	0.660	0.926	0.928
3	1.00	1.00	2.50	1.50	2	0.844	0.840	0.844
3	-1.00	1.00	-0.50	1.50	2	0.733	0.869	0.859
3	0.00	0.50	1.00	0.75	0	0.533	0.727	0.733
3	0.50	0.50	2.50	1.50	1	0.569	0.765	0.770
4	0.00	2.00	-2.00	3.00	0	0.735	0.792	0.782
4	-0.50	0.50	4.00	3.00	1	0.340	0.439	0.438
4	2.00	2.00	1.00	0.75	0	0.762	0.875	0.869
4	0.50	0.50	2.50	1.50	0	0.619	0.768	0.773
4	0.50	0.50	-2.00	3.00	1	0.640	0.729	0.730
5	-2.00	2.00	4.00	3.00	0	0.390	0.457	0.449

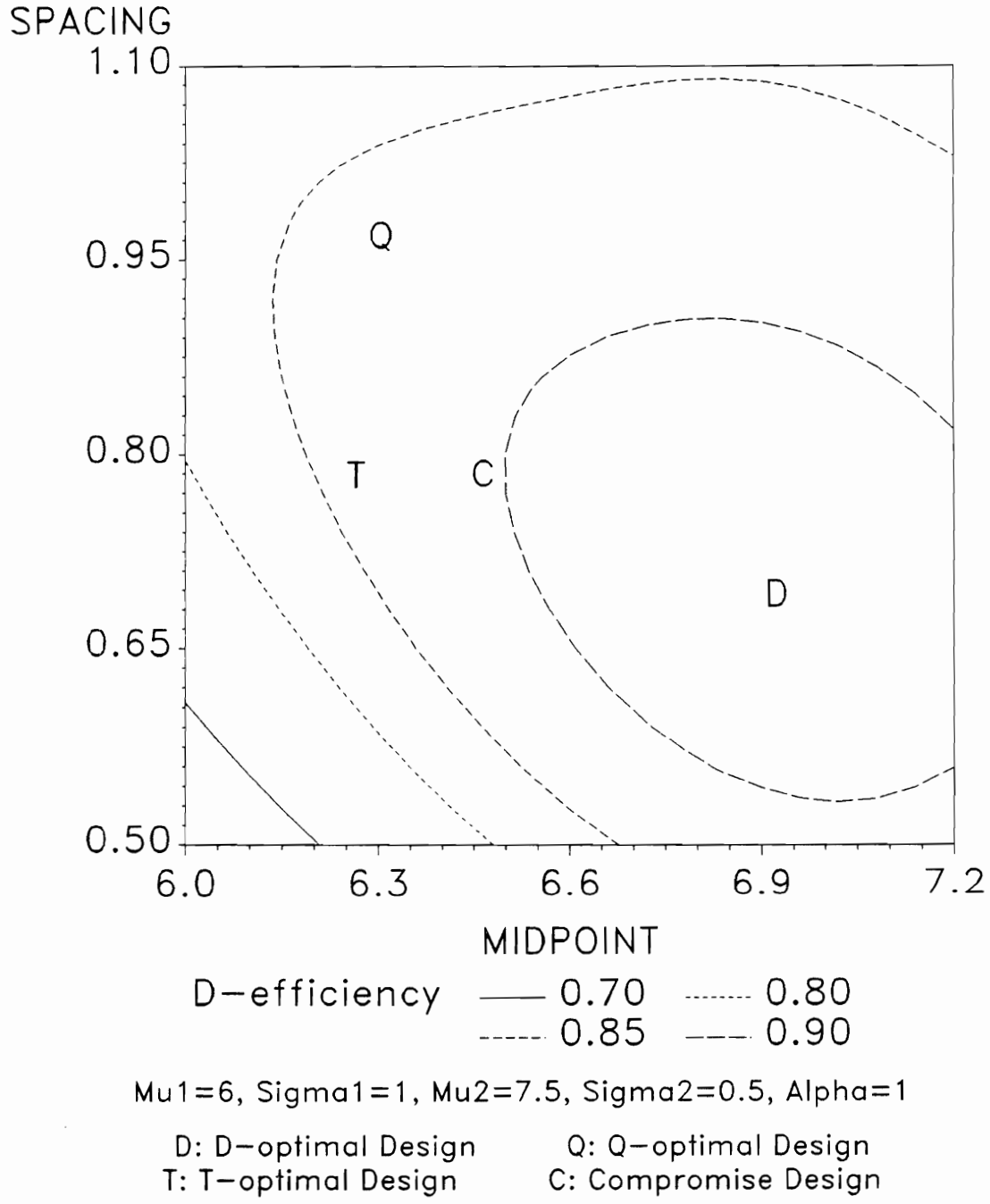

Figure 4.1 Contour Plot of 5-point Design D-efficiencies

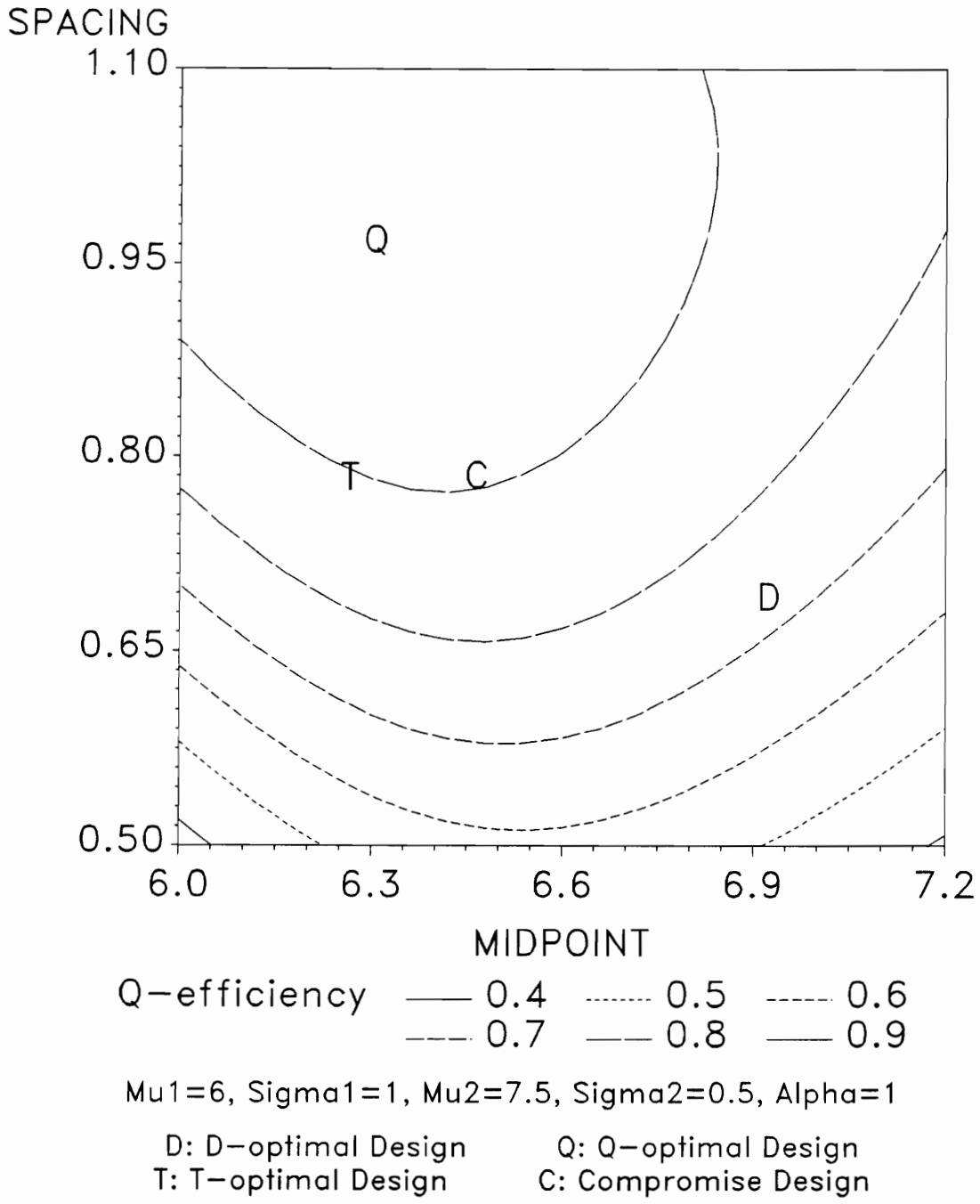

Figure 4.2 Contour Plot of 5-point Design Q-efficiencies

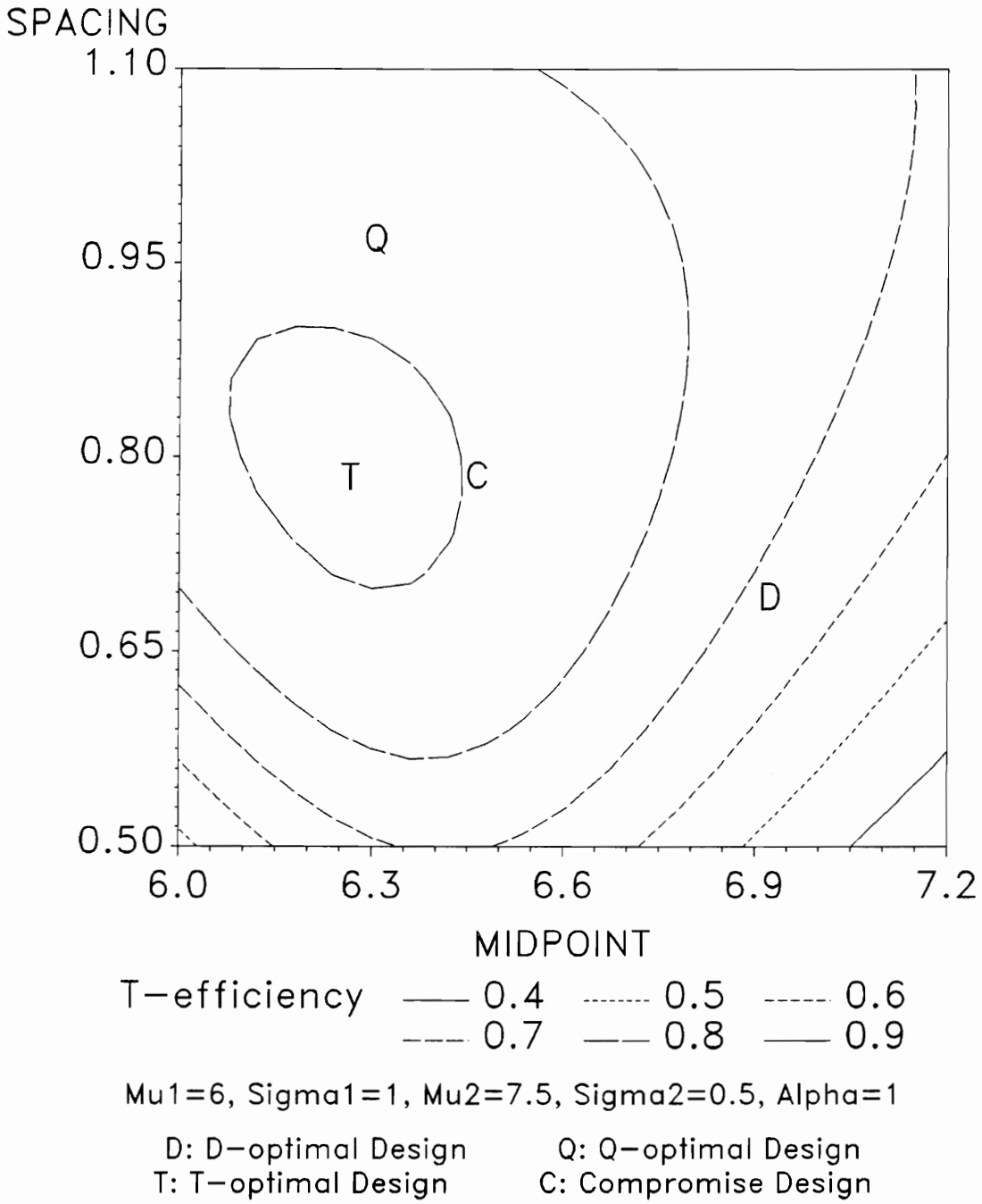

Figure 4.3 Contour Plot of 5-point Design T-efficiencies

Chapter 5
Summary and Future Work

§5.1 Summary and Future Work

In this dissertation we seek to examine some of the design considerations associated with the use of the Gumbel bivariate logistic regression model in a drug-testing setting. Design optimality criteria were developed for each of three different experimental goals and associated optimal design tables were produced. Emphasis has been placed on finding designs which would be suitable for practical use.

A practical suggestion would be to use the 5-point design corresponding to the goals of the experiment. If parameter estimation is of primary interest, the D-optimal design should be used. Similarly, if the researcher is most interested in prediction of p(1,0;d), the probability of efficacy without toxicity, the Q-optimal design is most appropriate. If estimation of the therapeutic index is the most important goal, one should use the T-optimal design, provided this design has more than one design point. Finally, if all three of these goals are of interest to the researcher, the 5-point compromise design is the recommended design.

Several major areas for future research based upon this work present themselves. A major assumption throughout this dissertation is that the researcher can offer reasonable parameter guesses *a priori*. Either of two

alternate approaches would probably be more effective. One approach would be to use Bayesian priors on the parameters, thus including in the design considerations some measure of the uncertainty associated with the parameter guesses (see Chaloner and Larntz 1989). Another approach would be to develop 2-stage designs following the work of Myers (1991). In the 2-stage experiment, the initial stage would be a 3-point design based on one of the optimality criteria presented in Chapter 3. Based on this initial experiment estimates of the parameters would be obtained. Two additional design points could then be chosen in such a way as to maximize any given criterion based on the total log-likelihood, which equals the sum of the log-likelihood of the first stage and the log-likelihood of the second stage given the first. This approach has the appeal to the practitioner of giving a 5-point design in which poor initial parameter estimates may be compensated for in the second stage.

A related area of research concerns the robustness of these designs. Some robustness properties were examined through case studies, but a more thorough examination of this problem might reveal with more certainty a particular type of experimental design which has good robustness properties for the Gumbel model.

Finally, since there are bivariate logistic regression models other than the Gumbel model, one might explore the robustness of these designs to the particular model which is chosen. Similarly, if one is not restricted to logistic regression, it would be of interest to find how well these designs perform if one uses a bivariate probit or other bivariate model.

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Appendices

Appendix A Proof of Minimum Value for α

It can be seen by examining p(0,0;d) that the minimum value for α is always -1. It is required that p(0,0;d) ≥ 0 $\forall d$. This implies that

$$1 - \frac{1}{1+e^{-d_1}} - \frac{1}{1+e^{-d_2}} + \frac{1}{1+e^{-d_1}} \cdot \frac{1}{1+e^{-d_2}} \geq \frac{-\alpha e^{-d_1-d_2}}{\left(1+e^{-d_1}\right)^2\left(1+e^{-d_2}\right)^2}$$

$$\Leftrightarrow (1+e^{-d_1})(1+e^{-d_2}) - (1+e^{-d_1}) - (1+e^{-d_2}) + 1 \geq \frac{-\alpha e^{-d_1-d_2}}{\left(1+e^{-d_1}\right)\left(1+e^{-d_2}\right)}$$

$$\Leftrightarrow -\alpha \leq (1+e^{-d_1})(1+e^{-d_2}) .$$

However,

$$\lim_{d\to\infty} \left(1+e^{-d_1}\right)\left(1+e^{-d_2}\right) = 1 ,$$

implying that $\alpha \geq -1$.

Appendix B Partial Derivatives of $\mathbb{E}_1$, $\mathbb{E}_2$, $\mathbb{E}_1\mathbb{E}_2$ and $\mathbb{A}$

It is necessary to find first and second partial derivatives of $\mathbb{E}_1$, $\mathbb{E}_2$, $\mathbb{E}_1\mathbb{E}_2$ and $\mathbb{A}$ with respect to $\theta_1 = \mu_1$, $\theta_2 = \sigma_1$, $\theta_3 = \mu_2$, $\theta_4 = \sigma_2$ and $\theta_5 = \alpha$, where

$$\mathbb{E}_1 = \frac{1}{1+e^{-d_1}} \ ,$$

$$\mathbb{E}_2 = \frac{1}{1+e^{-d_2}} \ ,$$

$$\mathbb{A} = \frac{\alpha e^{-d_1-d_2}}{\left(1+e^{-d_1}\right)^2\left(1+e^{-d_2}\right)^2} = \alpha\left(\frac{e^{-d_1}}{\left(1+e^{-d_1}\right)^2}\right)\left(\frac{e^{-d_2}}{\left(1+e^{-d_2}\right)^2}\right) \ .$$

Begin by noting that many of the partial derivatives in question evaluate to zero:

$$\frac{\partial \mathbb{E}_1}{\partial \theta_i} = \frac{\partial^2 \mathbb{E}_1}{\partial \theta_i \partial \theta_j} = 0 \ , \qquad \theta_i = \mu_2, \sigma_2, \alpha,$$

$$\frac{\partial \mathbb{E}_2}{\partial \theta_i} = \frac{\partial^2 \mathbb{E}_2}{\partial \theta_i \partial \theta_j} = 0 \ , \qquad \theta_i = \mu_1, \sigma_1, \alpha,$$

$$\frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial \alpha} = \frac{\partial^2 \mathbb{E}_1\mathbb{E}_2}{\partial \theta_i \partial \alpha} = \frac{\partial^2 \mathbb{A}}{\partial \alpha^2} = 0.$$

Also note that

$$\frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial \theta_i} = \mathbb{E}_2 \frac{\partial \mathbb{E}_1}{\partial \theta_i} \ , \qquad \theta_i = \mu_1, \sigma_1,$$

$$\frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial \theta_i} = \mathbb{E}_1 \frac{\partial \mathbb{E}_2}{\partial \theta_i} \ , \qquad \theta_i = \mu_2, \sigma_2,$$

$$\frac{\partial^2 \mathbb{E}_1\mathbb{E}_2}{\partial \theta_i \partial \theta_j} = \frac{\partial \mathbb{E}_1}{\partial \theta_i} \cdot \frac{\partial \mathbb{E}_1}{\partial \theta_j} \ , \qquad \theta_i = \mu_1, \sigma_1 \ ; \qquad \theta_j = \mu_2, \sigma_2,$$

$$\frac{\partial^2 \mathbb{E}_1 \mathbb{E}_2}{\partial \theta_i^2} = \mathbb{E}_2 \frac{\partial^2 \mathbb{E}_1}{\partial \theta_i^2}, \qquad \theta_i = \mu_1, \sigma_1,$$

$$\frac{\partial^2 \mathbb{E}_1 \mathbb{E}_2}{\partial \theta_i^2} = \mathbb{E}_1 \frac{\partial^2 \mathbb{E}_2}{\partial \theta_i^2}, \qquad \theta_i = \mu_2, \sigma_2.$$

Finally, observe that a number of the partial derivatives may be obtained from others simply by reversing the roles of the efficacy and toxicity quantities. With these facts in mind, those partial derivatives necessary to calculate the entire information matrix are now found.

$$\frac{\partial \mathbb{E}_1}{\partial \mu_1} = \frac{-e^{-d_1}}{\left(1+e^{-d_1}\right)^2 \sigma_1},$$

$$\frac{\partial \mathbb{E}_1}{\partial \sigma_1} = \frac{-e^{-d_1} d_1}{\left(1+e^{-d_1}\right)^2 \sigma_1},$$

$$\frac{\partial \mathbb{A}}{\partial \mu_1} = \frac{\alpha e^{-d_2}}{\left(1+e^{-d_2}\right)^2} \cdot \frac{(e^{-d_1})(\sigma_1^{-1})\left(1+e^{-d_1}\right)^2 - (e^{-d_1})(2)\left(1+e^{-d_1}\right)(e^{-d_1})\sigma_1^{-1}}{\left(1+e^{-d_1}\right)^4}$$

$$= \frac{\alpha e^{-d_2}}{\left(1+e^{-d_2}\right)^2} \cdot \frac{e^{-d_1}(1+e^{-d_1}-2e^{-d_1})}{\left(1+e^{-d_1}\right)^3 \sigma_1} = \frac{\alpha e^{-d_2}}{\left(1+e^{-d_2}\right)^2} \cdot \frac{e^{-d_1}(1-e^{-d_1})}{\left(1+e^{-d_1}\right)^3 \sigma_1},$$

$$\frac{\partial \mathbf{A}}{\partial \sigma_1} = \frac{\alpha e^{-d_2}}{\left(1+e^{-d_2}\right)^2} \cdot \frac{(e^{-d_1})(d_1\sigma_1^{-1})\left(1+e^{-d_1}\right)^2 - (e^{-d_1})(2)\left(1+e^{-d_1}\right)(e^{-d_1})(d_1\sigma_1^{-1})}{\left(1+e^{-d_1}\right)^4}$$

$$= \frac{\alpha e^{-d_2}}{\left(1+e^{-d_2}\right)^2} \cdot \frac{d_1 e^{-d_1}(1-e^{-d_1})}{\left(1+e^{-d_1}\right)^3 \sigma_1},$$

$$\frac{\partial \mathbf{A}}{\partial \alpha} = \left(\frac{e^{-d_1}}{\left(1+e^{-d_1}\right)^2}\right)\left(\frac{e^{-d_2}}{\left(1+e^{-d_2}\right)^2}\right),$$

$$\frac{\partial^2 \mathbf{E}_1}{\partial \mu_1^2} = \frac{(-e^{-d_1})(\sigma_1^{-1})\left(1+e^{-d_1}\right)^2 \sigma_1 - (-e^{-d_1})(\sigma_1)(2)\left(1+e^{-d_1}\right)(e^{-d_1})\sigma_1^{-1}}{\left(1+e^{-d_1}\right)^4 \sigma_1^2}$$

$$= \frac{-e^{-d_1}(1+e^{-d_1}-2e^{-d_1})}{\left(1+e^{-d_1}\right)^3 \sigma_1^2} = \frac{-e^{-d_1}(1-e^{-d_1})}{\left(1+e^{-d_1}\right)^3 \sigma_1^2},$$

$$\frac{\partial^2 \mathbf{E}_1}{\partial \mu_1 \partial \sigma_1} = \frac{(-e^{-d_1})(d_1\sigma_1^{-1})\left(1+e^{-d_1}\right)^2 \sigma_1}{\left(1+e^{-d_1}\right)^4 \sigma_1^2}$$

$$- \frac{(-e^{-d_1})\left[(2)\left(1+e^{-d_1}\right)(e^{-d_1})(d_1\sigma_1^{-1})\sigma_1 + \left(1+e^{-d_1}\right)^2\right]}{\left(1+e^{-d_1}\right)^4 \sigma_1^2}$$

$$= \frac{-e^{-d_1}(d_1 - d_1 e^{-d_1} - 1 - e^{-d_1})}{\left(1+e^{-d_1}\right)^3 \sigma_1^2},$$

$$\frac{\partial^2 \mathbf{E}_1}{\partial \sigma_1^2} = \frac{\left[(-e^{-d_1})(d_1\sigma_1^{-1})(d_1) + (-e^{-d_1})(-d_1\sigma_1^{-1})\right]\left(1+e^{-d_1}\right)^2\sigma_1}{\left(1+e^{-d_1}\right)^4\sigma_1^2}$$

$$- \frac{(-e^{-d_1})(d_1)\left[(2)\left(1+e^{-d_1}\right)(e^{-d_1})(d_1\sigma_1^{-1})\sigma_1 + \left(1+e^{-d_1}\right)^2\right]}{\left(1+e^{-d_1}\right)^4\sigma_1^2}$$

$$= \frac{(-e^{-d_1})(d_1)(d_1 + d_1e^{-d_1} - 1 - e^{-d_1} - 2d_1e^{-d_1} - 1 - e^{-d_1})}{\left(1+e^{-d_1}\right)^3\sigma_1^2}$$

$$= \frac{-d_1e^{-d_1}(d_1 - d_1e^{-d_1} - 2 - 2e^{-d_1})}{\left(1+e^{-d_1}\right)^3\sigma_1^2},$$

$$\frac{\partial^2 \mathbf{A}}{\partial \mu_1^2} = \frac{\alpha e^{-d_2}}{\left(1+e^{-d_2}\right)^2}\left\{\frac{\left[(e^{-d_1})(\sigma_1^{-1})(1-e^{-d_1}) + (e^{-d_1})(-e^{-d_1})\sigma_1^{-1}\right]\left(1+e^{-d_1}\right)^3\sigma_1}{\left(1+e^{-d_1}\right)^6\sigma_1^2}\right.$$

$$\left. - \frac{(e^{-d_1})(1-e^{-d_1})(\sigma_1)(3)\left(1+e^{-d_1}\right)^2(e^{-d_1})\sigma_1^{-1}}{\left(1+e^{-d_1}\right)^6\sigma_1^2}\right\}$$

$$= \frac{\alpha e^{-d_2}}{\left(1+e^{-d_2}\right)^2} \cdot \frac{e^{-d_1}(1 - e^{-2d_1} - e^{-d_1} - e^{-2d_1} - 3e^{-d_1} + 3e^{-2d_1})}{\left(1+e^{-d_1}\right)^4\sigma_1^2}$$

$$= \frac{\alpha e^{-d_2}}{\left(1+e^{-d_2}\right)^2} \cdot \frac{e^{-d_1}(1 - 4e^{-d_1} + e^{-2d_1})}{\left(1+e^{-d_1}\right)^4\sigma_1^2},$$

$$\frac{\partial^2 \mathbb{A}}{\partial \mu_1 \partial \sigma_1} = \frac{\alpha e^{-d_2}}{\left(1+e^{-d_2}\right)^2} \left\{ \frac{\left[(e^{-d_1})(d_1\sigma_1^{-1})(1-e^{-d_1}) + (e^{-d_1})(-e^{-d_1})(d_1\sigma_1^{-1})\right]\left(1+e^{-d_1}\right)^3 \sigma_1}{\left(1+e^{-d_1}\right)^6 \sigma_1^2} \right.$$

$$\left. - \frac{(e^{-d_1})(1-e^{-d_1})\left[(3)\left(1+e^{-d_1}\right)^2 (e^{-d_1})(d_1\sigma_1^{-1})\sigma_1 + \left(1+e^{-d_1}\right)^3\right]}{\left(1+e^{-d_1}\right)^6 \sigma_1^2} \right\}$$

$$= \frac{\alpha e^{-d_2}}{\left(1+e^{-d_2}\right)^2} \cdot \frac{e^{-d_1}(d_1 - d_1 e^{-2d_1} - d_1 e^{-d_1} - d_1 e^{-2d_1} - 3d_1 e^{-d_1} + 3d_1 e^{-2d_1} - 1 + e^{-2d_1})}{\left(1+e^{-d_1}\right)^4 \sigma_1^2}$$

$$= \frac{\alpha e^{-d_2}}{\left(1+e^{-d_2}\right)^2} \cdot \frac{e^{-d_1}(-1 + d_1 - 4d_1 e^{-d_1} + e^{-2d_1} + d_1 e^{-2d_1})}{\left(1+e^{-d_1}\right)^4 \sigma_1^2},$$

$$\frac{\partial^2 \mathbb{A}}{\partial \sigma_1^2} = \frac{\alpha e^{-d_2}}{\left(1+e^{-d_2}\right)^2} \times$$

$$\left\{ \frac{\left[(-d_1\sigma_1^{-1})(e^{-d_1})(1-e^{-d_1}) + d_1(e^{-d_1})(d_1\sigma_1^{-1})(1-e^{-d_1}) + d_1 e^{-d_1}(-e^{-d_1})d_1\sigma_1^{-1}\right]\left(1+e^{-d_1}\right)^3 \sigma_1}{\left(1+e^{-d_1}\right)^6 \sigma_1^2} \right.$$

$$\left. - \frac{(d_1 e^{-d_1})(1-e^{-d_1})\left[(3)\left(1+e^{-d_1}\right)^2 (e^{-d_1})(d_1\sigma_1^{-1})\sigma_1 + \left(1+e^{-d_1}\right)^3\right]}{\left(1+e^{-d_1}\right)^6 \sigma_1^2} \right\}$$

$$= \frac{\alpha e^{-d_2}}{\left(1+e^{-d_2}\right)^2}$$

$$\times \frac{d_1 e^{-d_1}(-1 + e^{-2d_1} + d_1 - d_1 e^{-2d_1} - d_1 e^{-d_1} - d_1 e^{-2d_1} - 3d_1 e^{-d_1} + 3d_1 e^{-2d_1} - 1 + e^{-2d_1})}{\left(1+e^{-d_1}\right)^4 \sigma_1^2}$$

$$= \frac{\alpha e^{-d_2}}{\left(1+e^{-d_2}\right)^2} \cdot \frac{d_1 e^{-d_1}\left(-2+d_1+2e^{-2d_1}-4d_1 e^{-d_1}+d_1 e^{-2d_1}\right)}{\left(1+e^{-d_1}\right)^4 \sigma_1^2},$$

$$\frac{\partial^2 \mathbf{A}}{\partial \mu_1 \partial \mu_2} = \alpha \cdot \frac{e^{-d_1}(1-e^{-d_1})}{\left(1+e^{-d_1}\right)^3 \sigma_1} \cdot \frac{e^{-d_2}(1-e^{-d_2})}{\left(1+e^{-d_2}\right)^3 \sigma_2},$$

$$\frac{\partial^2 \mathbf{A}}{\partial \mu_1 \partial \sigma_2} = \alpha \cdot \frac{e^{-d_1}(1-e^{-d_1})}{\left(1+e^{-d_1}\right)^3 \sigma_1} \cdot \frac{d_2 e^{-d_2}(1-e^{-d_2})}{\left(1+e^{-d_2}\right)^3 \sigma_2},$$

$$\frac{\partial^2 \mathbf{A}}{\partial \sigma_1 \partial \sigma_2} = \alpha \cdot \frac{d_1 e^{-d_1}(1-e^{-d_1})}{\left(1+e^{-d_1}\right)^3 \sigma_1} \cdot \frac{d_2 e^{-d_2}(1-e^{-d_2})}{\left(1+e^{-d_2}\right)^3 \sigma_2},$$

$$\frac{\partial^2 \mathbf{A}}{\partial \mu_1 \partial \alpha} = \frac{e^{-d_2}}{\left(1+e^{-d_2}\right)^2} \cdot \frac{e^{-d_1}(1-e^{-d_1})}{\left(1+e^{-d_1}\right)^3 \sigma_1},$$

$$\frac{\partial^2 \mathbf{A}}{\partial \sigma_1 \partial \alpha} = \frac{e^{-d_2}}{\left(1+e^{-d_2}\right)^2} \cdot \frac{d_1 e^{-d_1}(1-e^{-d_1})}{\left(1+e^{-d_1}\right)^3 \sigma_1}.$$

Appendix C Proof of Equality of Asymptotic Variances under Reparameterization

Let $\boldsymbol{\theta}$ and $\boldsymbol{\beta}$ represent the original parameterization and the reparameterization, respectively, of the model. In this case $\boldsymbol{\theta}' = (\mu_1 \quad \sigma_1 \quad \mu_2 \quad \sigma_2 \quad \alpha)$ and $\boldsymbol{\beta}' = (\beta_{10} \quad \beta_{11} \quad \beta_{20} \quad \beta_{21} \quad \alpha)$. In this Appendix it is proven that $\boldsymbol{v}^{*\prime}\boldsymbol{I}^{*-1}(\boldsymbol{\beta})\boldsymbol{v}^{*} = \boldsymbol{v}'\boldsymbol{I}^{-1}(\boldsymbol{\theta})\boldsymbol{v}$, where $\boldsymbol{v}$ and $\boldsymbol{v}^{*}$ are the vectors of partial derivatives under the original parameterization and the reparameterization, respectively. The vector $\boldsymbol{v}$ is expressed as

$$\boldsymbol{v}' = \left[\frac{\partial f}{\partial \theta_1} \quad \frac{\partial f}{\partial \theta_2} \quad \frac{\partial f}{\partial \theta_3} \quad \frac{\partial f}{\partial \theta_4} \quad \frac{\partial f}{\partial \theta_5}\right],$$

where f is the function of the parameters which the researcher desires to estimate with minimum variance. Now by the chain rule for derivatives of a function of several variables,

$$\boldsymbol{v}^{*} = \begin{bmatrix} \partial f / \partial \beta_1 \\ \partial f / \partial \beta_2 \\ \partial f / \partial \beta_3 \\ \partial f / \partial \beta_4 \\ \partial f / \partial \beta_5 \end{bmatrix} = \begin{bmatrix} \sum_{j=1}^{5} \partial f / \partial \theta_j \cdot \partial \theta_j / \partial \beta_1 \\ \sum_{j=1}^{5} \partial f / \partial \theta_j \cdot \partial \theta_j / \partial \beta_2 \\ \sum_{j=1}^{5} \partial f / \partial \theta_j \cdot \partial \theta_j / \partial \beta_3 \\ \sum_{j=1}^{5} \partial f / \partial \theta_j \cdot \partial \theta_j / \partial \beta_4 \\ \sum_{j=1}^{5} \partial f / \partial \theta_j \cdot \partial \theta_j / \partial \beta_5 \end{bmatrix} = \boldsymbol{J}\boldsymbol{v} .$$

Therefore,

$$\boldsymbol{v}^{*\prime}\boldsymbol{I}^{*-1}(\boldsymbol{\beta})\boldsymbol{v}^{*} = \boldsymbol{v}^{*\prime}(\boldsymbol{J}\boldsymbol{I}(\boldsymbol{\theta})\boldsymbol{J}')^{-1}\boldsymbol{v}^{*} = \boldsymbol{v}'\boldsymbol{J}'(\boldsymbol{J}'^{-1}\boldsymbol{I}^{-1}(\boldsymbol{\theta})\boldsymbol{J}^{-1})\boldsymbol{J}\boldsymbol{v} = \boldsymbol{v}'\boldsymbol{I}^{-1}(\boldsymbol{\theta})\boldsymbol{v},$$

which is the desired result.

Appendix D Proof of Information Matrix Structure when $\alpha = 0$

This Appendix proves that the information matrix assumes a special block diagonal structure when $\alpha = 0$. First examine the block containing elements $I_{13} = I_{31}$, $I_{14} = I_{41}$, $I_{23} = I_{32}$ and $I_{24} = I_{42}$. Referring to (2.2.4) and Appendix B it can be seen that $\alpha = 0$ implies that $\mathbb{A}$ and all its pertinent derivatives disappear. Also note that if $i = 1,2$ and $j = 3,4$ then

$$\frac{\partial \mathbb{E}_1 \mathbb{E}_2}{\partial \theta_i} = \mathbb{E}_2 \frac{\partial \mathbb{E}_1}{\partial \theta_i} ,$$

$$\frac{\partial \mathbb{E}_1 \mathbb{E}_2}{\partial \theta_j} = \mathbb{E}_1 \frac{\partial \mathbb{E}_2}{\partial \theta_j} ,$$

$$\frac{\partial^2 \mathbb{E}_1 \mathbb{E}_2}{\partial \theta_i \partial \theta_j} = \frac{\partial \mathbb{E}_1}{\partial \theta_i} \cdot \frac{\partial \mathbb{E}_2}{\partial \theta_j} ,$$

$$\frac{\partial \mathbb{E}_1}{\partial \theta_j} = \frac{\partial \mathbb{E}_2}{\partial \theta_i} = \frac{\partial^2 \mathbb{E}_1}{\partial \theta_i \partial \theta_j} = \frac{\partial^2 \mathbb{E}_2}{\partial \theta_i \partial \theta_j} = 0 .$$

Therefore the numerators in (2.2.4) reduce to zero as follows:

$$p_{11}\left(\frac{\partial \mathbb{E}_1}{\partial \theta_i} \cdot \frac{\partial \mathbb{E}_2}{\partial \theta_j}\right) - \left(\mathbb{E}_2 \frac{\partial \mathbb{E}_1}{\partial \theta_i}\right)\left(\mathbb{E}_1 \frac{\partial \mathbb{E}_2}{\partial \theta_j}\right)$$

$$= \mathbb{E}_1 \mathbb{E}_2 \left(\frac{\partial \mathbb{E}_1}{\partial \theta_i}\right)\left(\frac{\partial \mathbb{E}_2}{\partial \theta_j}\right) - \mathbb{E}_1 \mathbb{E}_2 \left(\frac{\partial \mathbb{E}_1}{\partial \theta_i}\right)\left(\frac{\partial \mathbb{E}_2}{\partial \theta_j}\right) = 0 ,$$

$$p_{10}\left(-\frac{\partial \mathbb{E}_1}{\partial \theta_i} \cdot \frac{\partial \mathbb{E}_2}{\partial \theta_j}\right) - \left(\frac{\partial \mathbb{E}_1}{\partial \theta_i} - \mathbb{E}_2 \frac{\partial \mathbb{E}_1}{\partial \theta_i}\right)\left(-\mathbb{E}_1 \frac{\partial \mathbb{E}_2}{\partial \theta_j}\right)$$

$$= -(\mathbb{E}_1 - \mathbb{E}_1\mathbb{E}_2)\left(\frac{\partial \mathbb{E}_1}{\partial \theta_i}\right)\left(\frac{\partial \mathbb{E}_2}{\partial \theta_j}\right) + \mathbb{E}_1(1-\mathbb{E}_2)\left(\frac{\partial \mathbb{E}_1}{\partial \theta_i}\right)\left(\frac{\partial \mathbb{E}_2}{\partial \theta_j}\right) = 0 ,$$

$$p_{01}\left(-\frac{\partial \mathbb{E}_1}{\partial \theta_i}\cdot\frac{\partial \mathbb{E}_2}{\partial \theta_j}\right) - \left(-\mathbb{E}_2\frac{\partial \mathbb{E}_1}{\partial \theta_i}\right)\left(\frac{\partial \mathbb{E}_2}{\partial \theta_j} - \mathbb{E}_1\frac{\partial \mathbb{E}_2}{\partial \theta_j}\right)$$

$$= -(\mathbb{E}_2 - \mathbb{E}_1\mathbb{E}_2)\left(\frac{\partial \mathbb{E}_1}{\partial \theta_i}\right)\left(\frac{\partial \mathbb{E}_2}{\partial \theta_j}\right) + \mathbb{E}_2(1-\mathbb{E}_1)\left(\frac{\partial \mathbb{E}_1}{\partial \theta_i}\right)\left(\frac{\partial \mathbb{E}_2}{\partial \theta_j}\right) = 0 ,$$

$$p_{00}\left(\frac{\partial \mathbb{E}_1}{\partial \theta_i}\cdot\frac{\partial \mathbb{E}_2}{\partial \theta_j}\right) - \left(-\frac{\partial \mathbb{E}_1}{\partial \theta_i} + \mathbb{E}_2\frac{\partial \mathbb{E}_1}{\partial \theta_i}\right)\left(-\frac{\partial \mathbb{E}_2}{\partial \theta_j} + \mathbb{E}_1\frac{\partial \mathbb{E}_2}{\partial \theta_j}\right)$$

$$= (1 - \mathbb{E}_1 - \mathbb{E}_2 + \mathbb{E}_1\mathbb{E}_2)\left(\frac{\partial \mathbb{E}_1}{\partial \theta_i}\right)\left(\frac{\partial \mathbb{E}_2}{\partial \theta_j}\right) - (-1 + \mathbb{E}_2)(-1 + \mathbb{E}_1)\left(\frac{\partial \mathbb{E}_1}{\partial \theta_i}\right)\left(\frac{\partial \mathbb{E}_2}{\partial \theta_j}\right) = 0 .$$

Thus this block evaluates to a null matrix when $\alpha = 0$.

Next examine the block of the information matrix which contains elements $I_{15} = I_{51}$ and $I_{25} = I_{52}$. Note that since neither $\mathbb{E}_1$ nor $\mathbb{E}_2$ contain α, for $i = 1,2$

$$\frac{\partial \mathbb{E}_1}{\partial \theta_5} = \frac{\partial \mathbb{E}_2}{\partial \theta_5} = \frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial \theta_5} = \frac{\partial^2 \mathbb{E}_1}{\partial \theta_i \partial \theta_5} = \frac{\partial^2 \mathbb{E}_2}{\partial \theta_i \partial \theta_5} = \frac{\partial^2 \mathbb{E}_1\mathbb{E}_2}{\partial \theta_i \partial \theta_5} = \frac{\partial \mathbb{A}}{\partial \theta_i} = \mathbb{A} = 0.$$

Also note the following relationships from Appendix B:

$$\frac{\partial^2 \mathbb{A}}{\partial \theta_i \partial \theta_5} = -\mathbb{E}_1\mathbb{E}_2^2\frac{\partial \mathbb{E}_1}{\partial \theta_i}\left(e^{-d_2} - e^{-d_1-d_2}\right),$$

$$\frac{\partial \mathbb{A}}{\partial \theta_5} = \mathbb{E}_1^2\mathbb{E}_2^2\left(e^{-d_1-d_2}\right),$$

$$\frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial \theta_i} = \mathbb{E}_2\frac{\partial \mathbb{E}_1}{\partial \theta_i} .$$

Using these relationships in (2.4.4) it is seen by the following that the terms associated with p_{11} and p_{10} negate each other as do the terms associated with p_{01} and p_{00}.

$$\mathbf{p_{11}}: \quad \frac{\partial^2 \mathbb{A}}{\partial\theta_i \partial\theta_5} - p_{11}^{-1}\left(\frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial\theta_i}\right)\left(\frac{\partial \mathbb{A}}{\partial\theta_5}\right)$$

$$= -\mathbb{E}_1\mathbb{E}_2^2 \frac{\partial \mathbb{E}_1}{\partial\theta_i}\left(e^{-d_2} - e^{-d_1-d_2}\right) - (\mathbb{E}_1\mathbb{E}_2)^{-1}\left(\mathbb{E}_2 \frac{\partial \mathbb{E}_1}{\partial\theta_i}\right)\left(\mathbb{E}_1^2\mathbb{E}_2^2\, e^{-d_1-d_2}\right)$$

$$= -\mathbb{E}_1\mathbb{E}_2^2 \frac{\partial \mathbb{E}_1}{\partial\theta_i}\, e^{-d_2}$$

$$\mathbf{p_{10}}: \quad -\frac{\partial^2 \mathbb{A}}{\partial\theta_i \partial\theta_5} - p_{10}^{-1}\left(\frac{\partial \mathbb{E}_1}{\partial\theta_i} - \frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial\theta_i}\right)\left(-\frac{\partial \mathbb{A}}{\partial\theta_5}\right)$$

$$= \mathbb{E}_1\mathbb{E}_2^2 \frac{\partial \mathbb{E}_1}{\partial\theta_i}\left(e^{-d_2} - e^{-d_1-d_2}\right) + (\mathbb{E}_1 - \mathbb{E}_1\mathbb{E}_2)^{-1}\left(\frac{\partial \mathbb{E}_1}{\partial\theta_i}(1-\mathbb{E}_2)\right)\left(\mathbb{E}_1^2\mathbb{E}_2^2\, e^{-d_1-d_2}\right)$$

$$= \mathbb{E}_1\mathbb{E}_2^2 \frac{\partial \mathbb{E}_1}{\partial\theta_i}\, e^{-d_2}$$

$$\mathbf{p_{01}}: \quad -\frac{\partial^2 \mathbb{A}}{\partial\theta_i \partial\theta_5} - p_{01}^{-1}\left(-\frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial\theta_i}\right)\left(-\frac{\partial \mathbb{A}}{\partial\theta_5}\right)$$

$$= \mathbb{E}_1\mathbb{E}_2^2 \frac{\partial \mathbb{E}_1}{\partial\theta_i}\left(e^{-d_2} - e^{-d_1-d_2}\right) - (\mathbb{E}_2 - \mathbb{E}_1\mathbb{E}_2)^{-1}\left(\mathbb{E}_2 \frac{\partial \mathbb{E}_1}{\partial\theta_i}\right)\left(\mathbb{E}_1^2\mathbb{E}_2^2\, e^{-d_1-d_2}\right)$$

$$= (1-\mathbb{E}_1)^{-1}\mathbb{E}_1\mathbb{E}_2^2 \frac{\partial \mathbb{E}_1}{\partial\theta_i}\left[\left(e^{-d_2} - e^{-d_1-d_2}\right) - \mathbb{E}_1\left(e^{-d_2} - e^{-d_1-d_2}\right) - \mathbb{E}_1\, e^{-d_1-d_2}\right]$$

$$= (1-\mathbb{E}_1)^{-1}\mathbb{E}_1\mathbb{E}_2^2 \frac{\partial \mathbb{E}_1}{\partial\theta_i}\left[e^{-d_2} - e^{-d_1-d_2} - \mathbb{E}_1 e^{-d_2}\right]$$

$\mathbf{p_{00}}$: $\frac{\partial^2 \mathbb{A}}{\partial\theta_i \partial\theta_5} - p_{00}^{-1}\left(-\frac{\partial \mathbb{E}_1}{\partial\theta_i} + \frac{\partial \mathbb{E}_1\mathbb{E}_2}{\partial\theta_i}\right)\left(\frac{\partial \mathbb{A}}{\partial\theta_5}\right)$

$$= -\mathbb{E}_1\mathbb{E}_2^2 \frac{\partial \mathbb{E}_1}{\partial\theta_i}\left(e^{-d_2} - e^{-d_1-d_2}\right) + (1-\mathbb{E}_1-\mathbb{E}_2+\mathbb{E}_1\mathbb{E}_2)^{-1}\left(\frac{\partial \mathbb{E}_1}{\partial\theta_i}(1-\mathbb{E}_2)\right)\left(\mathbb{E}_1^2\mathbb{E}_2^2\, e^{-d_1-d_2}\right)$$

$$= (1-\mathbb{E}_1)^{-1}\mathbb{E}_1\mathbb{E}_2^2 \frac{\partial \mathbb{E}_1}{\partial\theta_i}\left[\left(-e^{-d_2} + e^{-d_1-d_2}\right) + \mathbb{E}_1\left(e^{-d_2} - e^{-d_1-d_2}\right) + \mathbb{E}_1 e^{-d_1-d_2}\right]$$

$$= -(1-\mathbb{E}_1)^{-1}\mathbb{E}_1\mathbb{E}_2^2 \frac{\partial \mathbb{E}_1}{\partial\theta_i}\left[e^{-d_2} - e^{-d_1-d_2} - \mathbb{E}_1 e^{-d_2}\right].$$

Likewise, the elements $I_{35} = I_{53}$ and $I_{45} = I_{54}$ can be seen to reduce to zero by reversing the roles of $\mathbb{E}_1$ and $\mathbb{E}_2$ and the roles of d_1 and d_2. The term associated with p_{11} negates the p_{01} term and the p_{10} term negates the p_{00} term. Thus, when $\alpha = 0$, the information matrix takes on the following block diagonal structure:

$$I(\boldsymbol{\theta}) = \begin{bmatrix} I_{11} & I_{12} & 0 & 0 & 0 \\ I_{21} & I_{22} & 0 & 0 & 0 \\ 0 & 0 & I_{33} & I_{34} & 0 \\ 0 & 0 & I_{43} & I_{44} & 0 \\ 0 & 0 & 0 & 0 & I_{55} \end{bmatrix}.$$

```
*********************************************************************
* PROGRAM NAME:  INFMAT                                             *
*                                                                   *
* PURPOSE:  CALCULATES THE INFORMATION MATRIX FOR THE GUMBEL MODEL  *
*                                                                   *
* THIS PROGRAM IS WRITTEN IN SAS PROC IML AND IS DESIGNED TO BE     *
* CALLED FROM ANOTHER SAS PROC IML PROGRAM.                         *
*                                                                   *
* INPUT VARIABLES:                                                  *
*     K=NUMBER OF DOSES IN THE DESIGN                               *
*     MU1, SIG1, MU2, SIG2, ALPHA=GUMBEL PARAMETERS                 *
*     DOSE=1 BY K DIMENSIONAL VECTOR CONTAINING THE DOSES IN DESIGN *
*     SUBJ=1 BY K DIMENSIONAL VECTOR CONTAINING ALLOCATION OF       *
*            SUBJECTS IN THE DESIGN                                 *
*                                                                   *
* OUTPUT VARIABLES:                                                 *
*     INF=5 BY 5 INFORMATION MATRIX CORRESPONDING TO INPUT VARIABLES*
*********************************************************************;

PROC IML;

START INFMAT;

* INITIALIZE MATRICES TO ZERO (MANY ARRAY ELEMENTS REMAIN ZERO);

D1E1=J(1,5,0);   D2E1=J(5,5,0);  D1E1E2=J(1,5,0);  D2E1E2=J(5,5,0);
D1E2=J(1,5,0);   D2E2=J(5,5,0);  D1A12=J(1,5,0);   D2A12=J(5,5,0);
INF=J(5,5,0);  * INFORMATION MATRIX ;

* LOOP THROUGH ONCE FOR EACH DESIGN POINT;

DO D=1 TO K;
  D1 = (DOSE[D]-MU1)/SIG1; * DOSE STANDARDIZED BY 1ST LOGISTIC MODEL;
  D2 = (DOSE[D] - MU2)/SIG2; * DOSE STANDARDIZED BY SECOND LOGISTIC;
  E1 = 1/(1+EXP(-D1));
  E2 = 1/(1+EXP(-D2));
  P11 = E1*E2 + ALPHA*EXP(-D1-D2)*(E1*E2)**2;
  P10 = E1 - E1*E2 - ALPHA*EXP(-D1-D2)*(E1*E2)**2;
  P01 = E2 - E1*E2 - ALPHA*EXP(-D1-D2)*(E1*E2)**2;
  P00 = 1 - P11 - P10 - P01;

  * DEFINE VALUES FOR THE FOLLOWING, WHICH ARE PARTIAL DERIVATIVES
  * AS INDICATED.  SUBSCRIPTS REPRESENT DERIVATIVES WITH RESPECT TO
  * 1: MU1   2: SIG2   3: MU2   4: SIG2   5: ALPHA.
  * D1E1[I]:  FIRST PARTIALS OF E1 W.R.T. I
  * D1E2[I]:  FIRST PARTIALS OF E2 W.R.T. I
  * D2E1[I,J]:  SECOND PARTIALS OF E1 W.R.T. I,J
```

```
* D2E2[I,J]:  SECOND PARTIALS OF E2 W.R.T. I,J
* D1E1E2[I]:  FIRST PARTIALS OF E1*E2 W.R.T. I
* D2E1E2[I,J]:  SECOND PARTIALS OF E1*E2 W.R.T. I,J
* D1A12[I]:  FIRST PARTIALS OF A12 = ALPHA*EXP(-D1-D2)*(E1*E2)**2
* D2A12[I,J]:  SECOND PARTIALS OF A12 W.R.T. I,J ;

D1E1[1] = -EXP(-D1)*E1**2/SIG1;      D1E1[2]=D1*D1E1[1];
D1E2[3] = -EXP(-D2)*E2**2/SIG2;      D1E2[4]=D2*D1E2[3];
D1E1E2[1] = E2*D1E1[1];              D1E1E2[2]=E2*D1E1[2];
D1E1E2[3] = E1*D1E2[3];              D1E1E2[4]=E1*D1E2[4];
D1A12[1] = ALPHA*EXP(-D2-D1)*E2**2*E1**3*(1-EXP(-D1))/SIG1;
D1A12[3] = ALPHA*EXP(-D1-D2)*E1**2*E2**3*(1-EXP(-D2))/SIG2;
D1A12[2] = D1*D1A12[1];              D1A12[4] = D2*D1A12[3];
D1A12[5] = EXP(-D1-D2)*(E1*E2)**2;
D2E1[1,1] = -EXP(-D1)*E1**3*(1-EXP(-D1))/(SIG1**2);
D2E2[3,3] = -EXP(-D2)*E2**3*(1-EXP(-D2))/(SIG2**2);
D2E1[1,2] = -EXP(-D1)*E1**3*(D1-D1*EXP(-D1)-1-EXP(-D1))/(SIG1**2);
D2E2[3,4] = -EXP(-D2)*E2**3*(D2-D2*EXP(-D2)-1-EXP(-D2))/(SIG2**2);
D2E1[2,2] = -D1*EXP(-D1)*E1**3*(D1-D1*EXP(-D1)-2-2*EXP(-D1))
             /(SIG1**2);
D2E2[4,4] = -D2*EXP(-D2)*E2**3*(D2-D2*EXP(-D2)-2-2*EXP(-D2))
             /(SIG2**2);
D2E1E2[1,1] = E2*D2E1[1,1];          D2E1E2[1,2]=E2*D2E1[1,2];
D2E1E2[2,2] = E2*D2E1[2,2];
D2E1E2[3,3] = E1*D2E2[3,3];          D2E1E2[3,4] = E1*D2E2[3,4];
D2E1E2[4,4] = E1*D2E2[4,4];
D2E1E2[1,3] = D1E1[1]*D1E2[3];       D2E1E2[1,4] = D1E1[1]*D1E2[4];
D2E1E2[2,3] = D1E1[2]*D1E2[3];       D2E1E2[2,4] = D1E1[2]*D1E2[4];
D2A12[1,1] = ALPHA*EXP(-D2-D1)*E2**2*E1**4*(1-4*EXP(-D1)
                                      +EXP(-2*D1))/(SIG1**2);
D2A12[3,3] = ALPHA*EXP(-D1-D2)*E1**2*E2**4*(1-4*EXP(-D2)
                                      +EXP(-2*D2))/(SIG2**2);
D2A12[1,2] = ALPHA*EXP(-D2-D1)*E2**2*E1**4*(-1+D1-4*D1*EXP(-D1)
              +EXP(-2*D1)+D1*EXP(-2*D1))/(SIG1**2);
D2A12[3,4] = ALPHA*EXP(-D1-D2)*E1**2*E2**4*(-1+D2-4*D2*EXP(-D2)
              +EXP(-2*D2)+D2*EXP(-2*D2))/(SIG2**2);
D2A12[2,2] = ALPHA*EXP(-D2-D1)*E2**2*E1**4*D1*(-2+D1+2*EXP(-2*D1)
             -4*D1*EXP(-D1)+D1*EXP(-2*D1))/(SIG1**2);
D2A12[4,4] = ALPHA*EXP(-D1-D2)*E1**2*E2**4*D2*(-2+D2+2*EXP(-2*D2)
             -4*D2*EXP(-D2)+D2*EXP(-2*D2))/(SIG2**2);
D2A12[1,3] = ALPHA*EXP(-D1-D2)*E1**3*E2**3*(1-EXP(-D1))
              *(1-EXP(-D2))/(SIG1*SIG2);
D2A12[1,4] = ALPHA*EXP(-D1-D2)*E1**3*E2**3*D1*(1-EXP(-D1))
              *(1-EXP(-D2))/(SIG1*SIG2);
D2A12[2,3] = ALPHA*EXP(-D1-D2)*E1**3*E2**3*D2*(1-EXP(-D1))
              *(1-EXP(-D2))/(SIG1*SIG2);
D2A12[2,4] = ALPHA*EXP(-D1-D2)*E1**3*E2**3*D1*D2*(1-EXP(-D1))
              *(1-EXP(-D2))/(SIG1*SIG2);
D2A12[1,5] = EXP(-D2-D1)*(1-EXP(-D1))*E2**2*E1**3/SIG1;
D2A12[3,5] = EXP(-D1-D2)*(1-EXP(-D2))*E1**2*E2**3/SIG2;
```

```
  D2A12[2,5] = D1*D2A12[1,5];
  D2A12[4,5] = D2*D2A12[3,5];

  DO I=1 TO 5;
    DO J=I TO 5;
      INF[I,J]=INF[I,J]-SUBJ[D]*(P11*(D2E1E2[I,J]+D2A12[I,J])
        -(D1E1E2[I]+D1A12[I])*(D1E1E2[J]+D1A12[J]))/P11;
      INF[I,J]=INF[I,J]-
          SUBJ[D]*(P10*(D2E1[I,J]-D2E1E2[I,J]-D2A12[I,J])
          -(D1E1[I]-D1E1E2[I]-D1A12[I])
          *(D1E1[J]-D1E1E2[J]-D1A12[J]))/P10;
      INF[I,J]=INF[I,J]-SUBJ[D]*(P01*(D2E2[I,J]-D2E1E2[I,J]
          -D2A12[I,J])-(D1E2[I]-D1E1E2[I]-D1A12[I])
          *(D1E2[J]-D1E1E2[J]-D1A12[J]))/P01;
     INF[I,J]=INF[I,J]-SUBJ[D]*(P00*(-D2E1[I,J]-D2E2[I,J]+D2E1E2[I,J]
          +D2A12[I,J]) - (-D1E1[I]-D1E2[I]+D1E1E2[I]+D1A12[I])
          *(-D1E1[J]-D1E2[J]+D1E1E2[J]+D1A12[J]))/P00;
    END;
  END;
END;
DO I=2 TO 5;
  DO J=1 TO I-1;
    INF[I,J]=INF[J,I];
  END;
END;

FINISH;
RESET STORAGE=KEEP.IT;
STORE;
```

```
*************************************************************************
* PROGRAM NAME:  NUMINT                                                 *
*                                                                       *
* PURPOSE:  CALCULATES INTEGRAL BY MEANS OF GAUSSIAN QUADRATURE         *
*                                                                       *
* THIS PROGRAM IS WRITTEN IN SAS PROC IML AND IS DESIGNED TO BE         *
* CALLED FROM ANOTHER SAS PROC IML PROGRAM.                             *
*                                                                       *
* INPUT VARIABLES:                                                      *
*     MU1, SIG1, MU2, SIG2, ALPHA=GUMBEL PARAMETERS                    *
*     LO_D=LOW DOSE IN RANGE OF INTEGRATION                             *
*     HI_D=HIGH DOSE IN RANGE OF INTEGRATION                            *
*                                                                       *
* OUTPUT VARIABLES:                                                     *
*     INTDXDP=5 BY 5 MATRIX CONTAINING INTEGRAL OF                      *
*             (DP(1,0)/DTHETA X DP(1,0)/DTHETA') FROM EQN. (3.3.2)      *
*************************************************************************;

PROC IML;

START NUMINT;
   * HGR=GAUSSIAN QUADRATURE POINTS;
   HGR = {      -0.9951872199970214  ,-0.9747285559713095  ,
                -0.9382745520027328  ,-0.8864155270044010  ,
                -0.8200019859739029  ,-0.7401241915785544  ,
                -0.6480936519369756  ,-0.5454214713888395  ,
                -0.4337935076260451  ,-0.3150426796961634  ,
                -0.1911188674736163  ,-0.0640568928626056  };
   * HGW=GAUSSIAN WEIGHTS;
   HGW = {       0.0123412297999872  , 0.0285313886289337  ,
                 0.0442774388174198  , 0.0592985849154368  ,
                 0.0733464814440803  , 0.0861901615319533  ,
                 0.0976186521041139  , 0.1074442701159655  ,
                 0.1155056680537256  , 0.1216704729278034  ,
                 0.1258374563468283  , 0.1279381953467522  } ;

GR = J(24,1,0);  GW = J(24,1,0);  INTDXDP = J(5,5,0);

  DO _F_ = 1 TO 12;
    _G_ = 25-_F_;
    GR[_F_] = (HGR[_F_]+1)*(HI_D - LO_D)/2 + LO_D;
    GR[_G_] = (-HGR[_F_]+1)*(HI_D - LO_D)/2 + LO_D;
    GW[_F_] = HGW[_F_]*(HI_D - LO_D)/2;
    GW[_G_] = HGW[_F_]*(HI_D - LO_D)/2;
  END;

  D1E1 = J(1,5,0);  D1E2 = J(1,5,0);  D1A12 = J(1,5,0);
  DP10 = J(1,5,0);  D1E1E2 = J(1,5,0);

  DO _F_ = 1 TO 24;
```

```
    _DOSE_ = GR[_F_];
    D1 = (_DOSE_ - MU1)/SIG1; * DOSE STANDARDIZED BY 1ST LOG. MODEL;
    D2 = (_DOSE_ - MU2)/SIG2; * DOSE STANDARDIZED BY SECOND LOGISTIC;
    E1 = 1/(1+EXP(-D1));
    E2 = 1/(1+EXP(-D2));

    D1E1[1] = -EXP(-D1)*E1**2/SIG1;      D1E1[2]=D1*D1E1[1];
    D1E2[3] = -EXP(-D2)*E2**2/SIG2;      D1E2[4]=D2*D1E2[3];
    D1E1E2[1] = E2*D1E1[1];              D1E1E2[2]=E2*D1E1[2];
    D1E1E2[3] = E1*D1E2[3];              D1E1E2[4]=E1*D1E2[4];
    D1A12[1] = ALPHA*EXP(-D2-D1)*E2**2*E1**3*(1-EXP(-D1))/SIG1;
    D1A12[3] = ALPHA*EXP(-D1-D2)*E1**2*E2**3*(1-EXP(-D2))/SIG2;
    D1A12[2] = D1*D1A12[1];              D1A12[4] = D2*D1A12[3];
    D1A12[5] = EXP(-D1-D2)*(E1*E2)**2;

  DO _G_ =1 TO 5;
    DP10[_G_] = D1E1[_G_] - D1E1E2[_G_] - D1A12[_G_];
  END;

  DO _G_ =1 TO 5;
    DO _H_ = _G_ TO 5;
   INTDXDP[_G_,_H_] = INTDXDP[_G_,_H_] + GW[_F_]*DP10[_G_]*DP10[_H_];
    END;
  END;
  END;

  DO _F_ = 2 TO 5;
    DO _G_ = 1 TO _F_-1;
      INTDXDP[_F_,_G_] = INTDXDP[_G_,_F_];
    END;
  END;
FINISH;
RESET STORAGE=KEEP.IT;
STORE;
```

```
*********************************************************************
* PROGRAM NAME:  DOPT                                               *
*                                                                   *
* PURPOSE:  CALCULATES 2 OR 3 POINT EQUALLY WTD D-OPTIMAL DESIGN    *
*                                                                   *
* THIS PROGRAM IS WRITTEN IN SAS PROC IML AND IS DESIGNED TO BE     *
* CALLED FROM ANOTHER SAS PROC IML PROGRAM.                         *
*                                                                   *
* INPUT VARIABLES:                                                  *
*     MU1, SIG1, MU2, SIG2, ALPHA=GUMBEL PARAMETERS                *
*     K=NUMBER OF DOSES IN DESIGN                                   *
*     SUBJ=1 BY K DIMENSIONAL VECTOR CONTAINING ALLOCATION OF       *
*            SUBJECTS IN THE DESIGN                                 *
*                                                                   *
* OUTPUT VARIABLES:                                                 *
*     DPT=1 BY K VECTOR CONTAINING DOSES IN D-OPTIMAL DESIGN        *
*     FN_VALUE=-DET(INFORMATION MATRIX) (SIMPLEX IS A MINIMIZATION  *
*                                        ALGORITHM)                 *
*********************************************************************;

PROC IML;

START DOPT;

 START DFUNC;
  INDIC8 = 0;
  DO I = 1 TO K-1;
     IF (PARMS[I]>PARMS[I+1]) THEN INDIC8=1; * RESTRICTS DESIGNS TO
                                             THOSE WITH ORDERED DOSES;
  END;
  IF (INDIC8=1) THEN FN_VALUE = 100000;
  ELSE DO;
    DOSE = PARMS`;   * DOSAGE LEVELS;

    CALL INFMAT;

    FN_VALUE = -DET(INF);

  END;
  PARMSP = PARMS`;
 FINISH DFUNC;
   _P_ = J(K,K+1,0); * _P_ IS AN INPUT TO STRTSIMP;
   CALL STRTSIMP;  * STRTSIMP GENERATES THE STARTING SIMPLEX FOR
                     THE NELDER-MEAD ALGORITHM BASED ON FUNCTION
                     EVALUATIONS ON A GRID;
   RUN SIMPLEX2;    * NELDER-MEAD ALGORITHM;
   DPT = PARMS`;       * PARMS IS 1 BY K VECTOR IN SIMPLEX2 WHICH
                         GIVES THE OPTIMAL DESIGN;
FINISH DOPT; RESET STORAGE=KEEP.IT;
STORE;
```

```
*************************************************************************
* PROGRAM NAME:  QOPT                                                   *
*                                                                       *
* PURPOSE:  CALCULATES 2 OR 3 POINT EQUALLY WTD Q-OPTIMAL DESIGN        *
*                                                                       *
* THIS PROGRAM IS WRITTEN IN SAS PROC IML AND IS DESIGNED TO BE         *
* CALLED FROM ANOTHER SAS PROC IML PROGRAM.                             *
*                                                                       *
* INPUT VARIABLES:                                                      *
*     MU1, SIG1, MU2, SIG2, ALPHA=GUMBEL PARAMETERS                    *
*     K=NUMBER OF DOSES IN DESIGN                                       *
*     LO_D=LOW DOSE IN RANGE OF INTEGRATION (PASSED TO NUMINT)          *
*     HI_D=HIGH DOSE IN RANGE OF INTEGRATION (PASSED TO NUMINT)         *
*     SUBJ=1 BY K DIMENSIONAL VECTOR CONTAINING ALLOCATION OF           *
*            SUBJECTS IN THE DESIGN                                     *
*                                                                       *
* OUTPUT VARIABLES:                                                     *
*     QPT=1 BY K VECTOR CONTAINING DOSES IN T-OPTIMAL DESIGN            *
*     FN_VALUE=INTEGRATED VARIANCE OF ESTIMATE OF P(1,0) FOR            *
*                Q-OPTIMAL DESIGN                                       *
*************************************************************************;

PROC IML;

START QOPT;

 START QFUNC;
  INDIC8 = 0;
  DO I = 1 TO K-1;
     IF (PARMS[I]>PARMS[I+1]) THEN INDIC8=1; * RESTRICTS TO DESIGNS
                                               WITH ORDERED DOSES;
  END;
  IF (INDIC8=1) THEN FN_VALUE = 100000;
  ELSE DO;
    DOSE = PARMS`;    * DOSAGE LEVELS;
    CALL INFMAT;
    IF (DET(INF)=0) THEN FN_VALUE=1000000;  * ELIMINATES SINGULAR
                                              DESIGNS;
    ELSE FN_VALUE = TRACE(INTDXDP*INV(INF));
  END;
  PARMSP = PARMS`;
 FINISH QFUNC;
 CALL NUMINT; *NUM. INTEGRATION TO GET INTDXDP =
                          INT(DP(1,0)*DP(1,0)`);
       _P_ = J(K,K+1,0);
       CALL STRTSIMP;
       RUN SIMPLEX2;
   QPT = PARMS`;
FINISH QOPT; RESET STORAGE=KEEP.IT;
STORE;
```

```
*********************************************************************
* PROGRAM NAME:  TOPT                                               *
*                                                                   *
* PURPOSE:  CALCULATES 2 OR 3 POINT EQUALLY WTD Q-OPTIMAL DESIGN    *
*                                                                   *
* THIS PROGRAM IS WRITTEN IN SAS PROC IML AND IS DESIGNED TO BE     *
* CALLED FROM ANOTHER SAS PROC IML PROGRAM.                         *
*                                                                   *
* INPUT VARIABLES:                                                  *
*     MU1, SIG1, MU2, SIG2, ALPHA=GUMBEL PARAMETERS                *
*     K=NUMBER OF DOSES IN DESIGN                                   *
*     PX=QUANTILE OF ED=.5 FOR TABLED DESIGNS                       *
*     PY=QUANTILE OF TD=.5 FOR TABLED DESIGNS                       *
*     SUBJ=1 BY K DIMENSIONAL VECTOR CONTAINING ALLOCATION OF       *
*            SUBJECTS IN THE DESIGN                                 *
*                                                                   *
* OUTPUT VARIABLES:                                                 *
*     TPT=1 BY K VECTOR CONTAINING DOSES IN T-OPTIMAL DESIGN        *
*     FN_VALUE=ASYMPTOTIC VARIANCE OF THERAPEUTIC INDEX             *
*                FOR T-OPTIMAL DESIGN                               *
*********************************************************************;

PROC IML;

START TOPT;

 START TFUNC;
  INDIC8 = 0;
  DO I = 1 TO K-1;
   IF (PARMS[I]>PARMS[I+1]) THEN INDIC8=1; *ORDERED DOSES IN DESIGN;
  END;
  IF (PARMS[1]<0) THEN INDIC8=1;
  IF (INDIC8=1) THEN FN_VALUE = 10000000;
  ELSE DO;
    DOSE = PARMS`;   * DOSAGE LEVELS;

    CALL INFMAT;

     IF (DET(INF)=0) THEN FN_VALUE=1000000; * CHECKS FOR
                                              SINGULAR DESIGN;
     ELSE FN_VALUE = DLOGT`*INV(INF)*DLOGT;

  END;
  PARMSP = PARMS`;

 FINISH TFUNC;

  DLOGT = J(5,1,0); * VECTOR OF PARTIAL DERIVATIVES
                      OF THERAPEUTIC INDEX;
  DLOGT[1] = -(MU2-SIG2*LOG(1/PY-1))/(MU1-SIG1*LOG(1/PX-1))##2;
```

```
   DLOGT[2] = -LOG(1/PX-1)*DLOGT[1];
   DLOGT[3] = 1/(MU1-SIG1*LOG(1/PX-1));
   DLOGT[4] = -LOG(1/PY-1)*DLOGT[3];

        _P_ = J(K,K+1,0);
        CALL STRTSIMP;
        RUN SIMPLEX2;

    TPT = PARMS';

FINISH TOPT;
RESET STORAGE=KEEP.IT;
STORE;
```

Vita

The author was born on May 23, 1964 in Greenville, Ohio. He graduated from Tri-Village High School, New Madison, Ohio. Upon completion of three years at Messiah College, he married Melissa Rorabaugh and began full-time employment in the Actuarial Department of Pennsylvania National Mutual Casualty Insurance Company. One year later, in May, 1986, he received his Bachelor of Arts in Mathematics from Messiah College, Grantham, Pennsylvania.

After four years of employment in the insurance industry, the author left to pursue graduate studies in Statistics at Virginia Polytechnic Institute and State University in August, 1989. Upon completion of the Doctor of Philosophy degree in Statistics, he will work in the Biometrics and Statistical Sciences Department of Procter & Gamble's Regulatory and Clinical Development Organization in Cincinnati, Ohio.