Chapter 7

DESIGNS FOR THE *k*-REGRESSOR NO INTERACTION EXPONENTIAL MODEL

§7.1 Introduction

While some impaired reproduction studies involve only one toxic substance, many of them are based on more complex models which contain two or more toxicants. The environmentalist may be curious about the effect of several chemicals on a specific animal population. The medical researcher may be interested in determining how a "cocktail" of drugs works to impair the reproduction of the AIDS virus. Ultimately, these researchers want to know whether these substances interact and, if they do, how that interaction should be characterized. However, before these issues can be addressed, designs for simpler, no interaction models must be formulated. Thus, the focus of this chapter will be optimal designs for the *k*-regressor no interaction exponential model.

The simplest of these multiple toxicant no interaction models is the two regressor model. The D-optimal design for this model serves as a logical starting point. In the logistic

case, some work has been done in the development of optimal designs for the two regressor model (Atkinson and Haines, 1996; Jia, 1996; Sitter and Torsney, 1995). In the Poisson case, this model takes on the following form

$$y_{ij} = e^{x_i'\beta} + \varepsilon_{ij} = e^{\beta_0+\beta_1 x_{1i}+\beta_2 x_{2i}} + \varepsilon_{ij} \qquad (7.1.1)$$

where i=1,…,3, j=1,…,n_i , and $E(y_{ij}) = \lambda_i = e^{\beta_0+\beta_1 x_{1i}+\beta_2 x_{2i}} = q_i\lambda_c$. Note that the notation here has the same meaning as in the single regressor case; q_i represents the EC and $\lambda_c = e^{\beta_0}$ represents the expected value at the control. The fundamental difference in the multiple regressor model as opposed to the single regressor model is the definition of an effective concentration. An EC now represents the individual amounts of a group of toxicants that work in combination to elicit a particular amount of impairment. Thus, an EC is now defined by a contour rather than a point. This more complex definition of an EC brings about the need for some new notation and definitions.

First, re-express the expected value of (7.1.1) as

$$\lambda_i = e^{\beta_0+\beta_1 x_{1i}+\beta_2 x_{2i}} = q_i\lambda_c = q_{1i}q_{2i}\lambda_c \qquad (7.1.2)$$

where $q_{1i} = e^{\beta_1 x_{1i}}$, $q_{2i} = e^{\beta_2 x_{2i}}$, and $q_i = q_{1i}q_{2i}$. The values of x_{1i} and x_{2i} can be considered as individual effective concentrations (IECs) associated with the proportion of q_1 and q_2 for each regressor. The IECs are viewed in the same way as an EC in the single regressor model: the amount of a single toxicant which produces a particular amount of impairment. Another important quantity in multiple regressor models is the model effective concentration or MEC. Whereas the IEC refers to the concentration of an individual regressor, the value of q_i in the MEC represents the amount of impairment brought about by a combination of levels of all the regressors in the model. Note that the product of q_{1i} and q_{2i} from the IECs yield the value of q_i for the MEC. With the definitions and notation associated with this model detailed, the focus shifts to developing the actual designs.

§7.2 The Pure Component D-Optimal Three Point Design

The first design detailed for the two regressor model is the D-optimal design. Recall that this design is the one which minimizes the generalized variance of the estimates of the coefficients. Since the optimal design for the single regressor model was a saturated two point design, a three point design is the first optimal design to be explored. The search for the D-optimal design begins with the information matrix for the coefficients for this model given in (7.2.1).

$$\mathbf{I}(\mathbf{X},\boldsymbol{\beta}) = \begin{bmatrix} \sum \lambda_i & \sum \lambda_i x_{1i} & \sum \lambda_i x_{2i} \\ \sum \lambda_i x_{1i} & \sum \lambda_i x_{1i}^2 & \sum \lambda_i x_{1i} x_{2i} \\ \sum \lambda_i x_{2i} & \sum \lambda_i x_{1i} x_{2i} & \sum \lambda_i x_{2i}^2 \end{bmatrix} \tag{7.2.1}$$

Recall that the D-optimal design is the one that maximizes the determinant of the information matrix. The determinant is given by

$$\left|\mathbf{I}(\mathbf{X},\boldsymbol{\beta})\right| = n_1 n_2 n_3 \lambda_1 \lambda_2 \lambda_3 \left(x_{11}x_{22} - x_{13}x_{22} - x_{11}x_{23} + x_{12}x_{23} - x_{12}x_{21} + x_{13}x_{21}\right)^2 \tag{7.2.2}$$

The quantities in the determinant can be written as:

$$\begin{aligned} n_i &= p_i N, \\ \lambda_i &= e^{\beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i}} = q_{1i} q_{2i} \lambda_c, \\ x_{1i} &= \frac{1}{\beta_1} \ln\left(e^{\beta_1 x_{1i}}\right) = \frac{1}{\beta_1} \ln\left(q_{1i}\right), \text{ and} \\ x_{2i} &= \frac{1}{\beta_2} \ln\left(e^{\beta_2 x_{2i}}\right) = \frac{1}{\beta_2} \ln\left(q_{2i}\right). \end{aligned} \tag{7.2.3}$$

By substituting the expressions in (7.2.3) into (7.2.2) and employing the Nelder-Mead algorithm, the optimal design can be found in terms of IECs and the percentage of experimental units to allocate to each design point. The design is listed in Table 7.2.1. An interesting feature of this design is that the IECs for each variable in the table are the levels for the optimal two level design. Recall that the non-control point for the single regressor model was the $EC_{13.53}$. In the two regressor model, the non-control levels for each toxicant are the $IEC_{13.53}$. This design is a member of a

special class of designs that can be termed “pure component designs”. This type of design is often used in practice to build multi-factor models and can be likened to simplex design for mixture experiments.

Table 7.2.1 Pure Component D-Optimal Design.

i	p_i	x_{1i}	x_{2i}	***Contour***
1	$0.\overline{3}$	IEC_{100}	IEC_{100}	MEC_{100}
2	$0.\overline{3}$	$IEC_{13.53}$	IEC_{100}	$MEC_{13.53}$
3	$0.\overline{3}$	IEC_{100}	$IEC_{13.53}$	$MEC_{13.53}$

The geometry of the design shown in Figure 7.2.1 gives more insight about it. The control point, point 1, in the upper right corner is located along the MEC_{100}. At this design point 100% of maximum reproduction occurs where neither of the two toxicants is administered. The curve represents the contour of constant $EC_{13.53}$ or the $MEC_{13.53}$. Notice that points 2 and 3 are located at the extremes of this contour. Furthermore, q_{21}=1, or the IEC_{100}, for regressor 2 implies that x_{21}=0 so point 3 only contains substance 1. Similarly q_{13}=1, or IEC_{100}, implies that x_{13}=0 so point 2 only contains substance 2. Since points 2 and 3 contain only one toxicant, the design is called a pure component design.

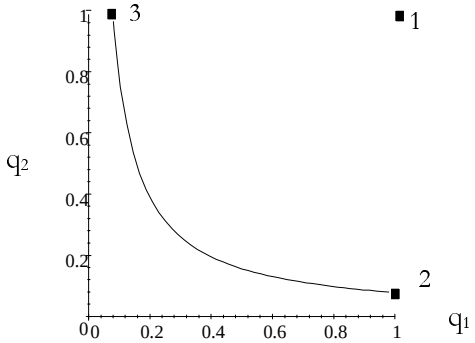

Figure 7.2.1 Geometry Of A Pure Component Design.

§7.3 Equivalence Theory for the Pure Component Design

Since numeric optimization rather than analytic techniques was used to find this design, its optimality is somewhat questionable. In fact, the number of parameters required to define this design render analytic techniques impractical. Thus, this situation lends itself to equivalence theory.

By applying traditional equivalence theory techniques to the pure component design, the optimality of the design can be verified. Recall Theorem 1 of Chapter 5.

> ***Theorem 1:*** If $\boldsymbol{\beta}$ is fixed and if ϕ is increasing and concave on $\mathcal{M}$ and differentiable at $\mathbf{M}(\boldsymbol{\eta}^*,\boldsymbol{\beta})$, then η^* is ϕ-optimal if and only if $F_{\phi}\left[\mathbf{M}(\boldsymbol{\eta}^*,\boldsymbol{\beta}),\mathbf{J}(\mathbf{x},\boldsymbol{\beta})\right] \le 0$ for all $\mathbf{x} \in \mathcal{X}$.

Another result from equivalence theory requires that

$$F_{\phi}\left[\mathbf{M}(\boldsymbol{\eta}^*,\boldsymbol{\beta}),\mathbf{J}(\mathbf{x}_i,\boldsymbol{\beta})\right] = 0 \qquad (7.3.1)$$

for i=1,…,m where m is the number of design points. Silvey shows for $\phi = \log\left|\mathbf{M}(\boldsymbol{\eta},\boldsymbol{\beta})\right|$ that $F_{\phi}\left[\mathbf{M}(\boldsymbol{\eta}^*,\boldsymbol{\beta}),\mathbf{J}(\mathbf{x},\boldsymbol{\beta})\right] = \text{trace}\left[\mathbf{J}(\mathbf{x},\boldsymbol{\beta})\mathbf{M}^{-1}(\boldsymbol{\eta}^*,\boldsymbol{\beta})\right] - p$ where p is the number of parameters which implies $\text{trace}\left[\mathbf{J}(\mathbf{x},\boldsymbol{\beta})\mathbf{M}^{-1}(\boldsymbol{\eta}^*,\boldsymbol{\beta})\right] \le p$ throughout the design space (Silvey, pg 40) and $\text{trace}\left[\mathbf{J}(\mathbf{x}_i,\boldsymbol{\beta})\mathbf{M}^{-1}(\boldsymbol{\eta}^*,\boldsymbol{\beta})\right] = p$ at design points i=1,…,m (Silvey, pg. 23). In this case, $\mathbf{M}(\boldsymbol{\eta},\boldsymbol{\beta}) = \begin{bmatrix} \sum\lambda_i & \sum\lambda_i x_{1i} & \sum\lambda_i x_{2i} \\ \sum\lambda_i x_{1i} & \sum\lambda_i x_{1i}^2 & \sum\lambda_i x_{1i}x_{2i} \\ \sum\lambda_i x_{2i} & \sum\lambda_i x_{1i}x_{2i} & \sum\lambda_i x_{2i}^2 \end{bmatrix}$ and $\mathbf{J}(\mathbf{X},\boldsymbol{\beta}) = \begin{bmatrix} \lambda_j & \lambda_j x_1^2 & \lambda_j x_2 \\ \lambda_j x_1 & \lambda_j x_1^2 & \lambda_j x_1 x_2 \\ \lambda_j x_2 & \lambda_j x_1 x_2 & \lambda_j x_2^2 \end{bmatrix}$. The expression for $f = \text{trace}\left[\mathbf{J}(\mathbf{x},\boldsymbol{\beta})\mathbf{M}^{-1}(\boldsymbol{\eta}^*,\boldsymbol{\beta})\right]$ was calculated and plotted in Figure 7.3.1 for the design in Table 7.2.1.

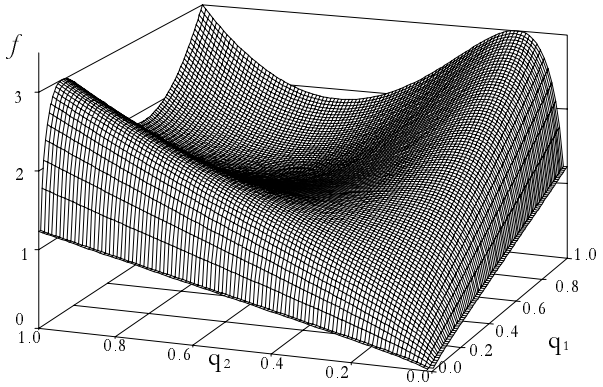

Figure 7.3.1 Graph of f for the Pure Component Design.

Notice that the function mimics the shape of the equivalence theory functions seen in Chapter 5 along the x_1 and x_2 axes. This function satisfies Theorem 1 and the result in (7.3.1) since $f \leq 3$ in the design region and $f = 3$ at the three design points. This demonstrates that the design is indeed optimal.

§7.4 The Three Point D-Optimal Binary Blend Design

While the pure component design is a nice three point design, it may not be useful in many cases. Pure component blends are often not feasible or practical. Consider the case where x_{1i} and x_{2i} represent ingredients in an industrial substance. In this case, the substance may no longer be functional if a pure component blend is used. Also, in a drug combination therapy study, researchers are already aware of how drugs function singly. They are more interested in how combinations of drugs function together. Fortunately, restrictions such as these can be used in conjunction with the D-optimality criterion to formulate an optimal design based on binary blends which fit the needs of the experimenter.

The design is determined by MECs rather than IECs because the MEC's define the contours of constant effective concentration along which the design points must be located. So, any values of x_{1i} and x_{2i} which satisfy the system of equations below are the levels of an optimal design.

$$\begin{aligned} e^{\beta_1 x_{11} + \beta_2 x_{21}} &= 1 \\ e^{\beta_1 x_{12} + \beta_2 x_{22}} &= 0.1353 \\ e^{\beta_1 x_{13} + \beta_2 x_{23}} &= 0.1353 \end{aligned} \qquad (7.4.1)$$

A general design for the binary blends is shown below.

Table 7.4.1 General Form of a Binary Blend D-Optimal Design.

i	p_i	x_{1i}	x_{2i}	***Contour***
1	$0.\overline{3}$	IEC_{100}	IEC_{100}	MEC_{100}
2	$0.\overline{3}$	$IEC_{100q_{12}}$	$IEC_{100q_{22}}$	$MEC_{13.53}$
3	$0.\overline{3}$	$IEC_{100q_{13}}$	$IEC_{100q_{23}}$	$MEC_{13.53}$

where $q_{22} = \frac{0.1353}{q_{12}}$, $q_{13} = \frac{0.1353}{q_{23}}$, and $0.1353 \le q_{12}, q_{23} \le 1$. The individual points of this design cannot be plotted in general since values of q_{12} and q_{23} must be chosen in order to determine the design. While the control is always a design point, the fact that these designs are not unique allows the biologist the potential to select some points of interest within the confines of the constraints.

§7.5 Equivalence Theory for the Binary Blend Design

Figure 7.5.1 demonstrates the optimality of an arbitrary binary blend design by plotting the equivalence theory function, $f = \text{trace}\left[\mathbf{J}(\mathbf{x},\boldsymbol{\beta})\mathbf{M}^{-1}(\boldsymbol{\eta}^*,\boldsymbol{\beta})\right]$, for this design. Again, it is less than three in the entire region and achieves that value at the design points.

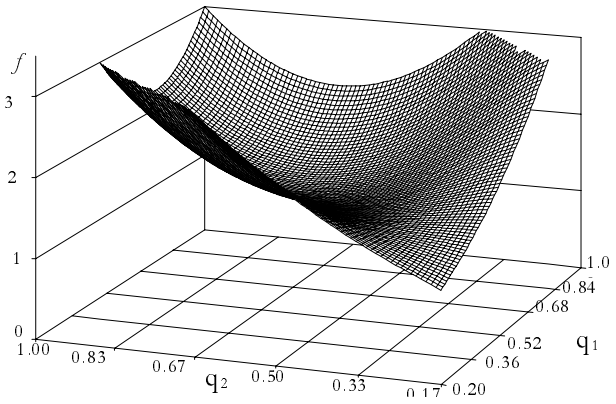

Figure 7.5.1 Graph of f for a Binary Blend D-Optimal Design Example.

§7.6 Optimality of the Binary Blend Design

Of course, an example does not serve as a proof of the optimality of the binary blend design. However, it can be shown using equivalence theory. First, the binary blend design must be expressed in terms of IECs.

Table 7.6.1 General Form for Binary Blend D-Optimal Design.

i	p_i	q_{1i}	q_{2i}	***Contour***
1	$0.\overline{3}$	1	1	MEC_{100}
2	$0.\overline{3}$	q_{12}	$\frac{0.1353}{q_{12}}$	$MEC_{13.53}$
3	$0.\overline{3}$	$\frac{0.1353}{q_{23}}$	q_{23}	$MEC_{13.53}$

where $0.1353 \le q_{12} \le 1,\ 0.1353 \le q_{23} \le 1,$ and $q_{12} \ne \frac{0.1353}{q_{23}}$. Since the equations associated with this proof are quite lengthy, they will not be shown. However, its basic logic is provided in the following paragraphs. This optimality is demonstrated using equivalence theory so it must be shown that the equivalence theory function $f = \text{trace}\left[\mathbf{J}(\mathbf{x}_i, \boldsymbol{\beta})\mathbf{M}^{-1}(\boldsymbol{\eta}^*, \boldsymbol{\beta})\right] = 3$ for i=1,2,3 and that $f \le 3$ for all points in the design space. It can be verified by substitution that $f(1,1) = 3$, $f\left(q_{12}, \frac{0.1353}{q_{12}}\right) = 3$, and $f\left(q_{23}, \frac{0.1353}{q_{23}}\right) = 3$ for all $0.1353 \le q_{12}, q_{23} \le 1$ where $q_{12} \ne \frac{0.1353}{q_{23}}$. Also, f' equaled zero at the three design points indicating that the equivalence theory function reaches its maximum of 3 at those three points. (Note that f'' was also evaluated at the design points in order to verify that the inflection points were indeed maxima.) Since the function achieves a maximum value of 3 at the three design points, *Theorem 1* and (7.3.1) are satisfied indicating that the design is indeed optimal.

§7.7 Examples of the Three Point Design

An example of the pure component design in Table 7.7.1 is detailed below. Since the value of the parameters must be known in order to determine the design points, the model for this example is shown below with the true value of $\boldsymbol{\beta}$.

$$y_{ij} = e^{5.8 - 1.5x_{1i} - 0.5x_{2i}} + \boldsymbol{\varepsilon}_{ij} \qquad (7.7.1)$$

The values of the design points in natural variables as well as their IEC counterparts are listed in Table 7.3. Recall that the expression for an IEC is the same as that for an EC in the single regressor model so $q_{1i} = e^{\boldsymbol{\beta}_1 x_{1i}}$ and $q_{2i} = e^{\boldsymbol{\beta}_2 x_{2i}}$. The design point x_{13}, in natural units is then expressed by $x_{13} = \frac{\ln 0.1353}{-1.5} = 1.\overline{3}$. The other design points can be found in natural units in a similar way.

Table 7.7.1 Example of a Pure Component Design.

	x_{1i}		x_{2i}		
i	***IEC***	***Natural Units***	***IEC***	***Natural Units***	***Contour***
1	$IEC1_{100}$	0	$IEC2_{100}$	0	MEC_{100}
2	$IEC1_{100}$	0	$IEC2_{13.53}$	4	$MEC_{13.53}$
3	$IEC1_{13.53}$	$1.\overline{3}$	$IEC2_{100}$	0	$MEC_{13.53}$

Of course, one third of the available experimental units are placed at each design point. This design can be view geometrically in natural units in Figure 7.7.1. Note that the transformation of ECs to natural units produces a corresponding change in the contour of constant EC. It is now a contour of constant ln(EC) so it is a line rather than a curve.

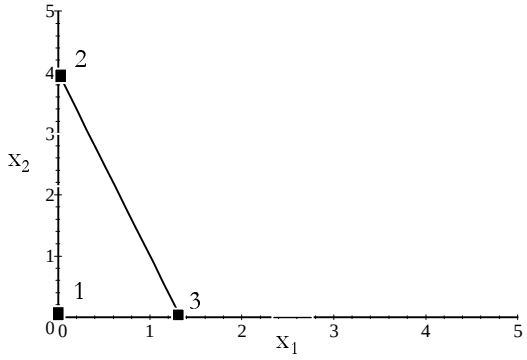

Figure 7.7.1. Geometry of a Pure Component Design in Natural Units.

In the Table 7.7.2, an example for a binary blend design is detailed. Notice the difference in the values of the individual ECs from Table 7.7.1 of the pure component design. Since this design is defined by the general form in Table 7.4.1, many different values could have been chosen for design points 2 and 3 located on the contours of the $EC_{13.53}$.

Table 7.7.2 Example of a General D-Optimal Design.

	x_{1i}		x_{2i}		
i	x_{1i}	***Natural Units***	x_{2i}	***Natural Units***	***Contour***
1	IEC_{100}	0	IEC_{100}	0	MEC_{100}
2	$IEC_{22.31}$	1	$IEC_{60.65}$	1	$MEC_{13.53}$
3	$IEC_{36.79}$	$\frac{2}{3}$	$IEC_{36.79}$	2	$MEC_{13.53}$

An example of binary blend design is also provided. This design is also shown geometrically in Figure 7.7.2. Notice that the points fall on the same contour of ln(EC) as the pure component design in Figure 7.7.1. However, these points are not at the extremes of this contour. They represent blends of the two toxicants rather than a pure component mixture.

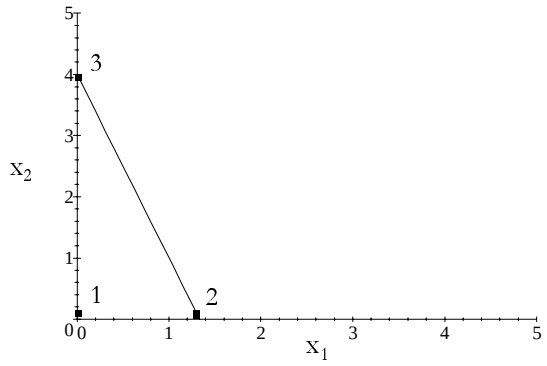

Figure 7.7.2 Geometry of a General D-Optimal Design in Natural Units.

§7.8 The Non-existence of D-Optimal Designs with Four or More Points

The three point design in the two regressor case has the same disadvantage as the two level design in the single regressor case: it does not provide for lack of fit testing. Of course, this prompts the search for an optimal design with four or more points for the two regressor model. However, it is shown in the following proof that these designs do not exist because the information matrix based on a four or more point design will always degenerate to a three point design. This proof will be shown for the four point case first and then extended to the *d*-point case, $d = 4, 5, 6, \ldots$.

Consider the determinant for a three level design in the following form:

$$\left|I_3\right| = n_1 n_2 n_3 \lambda_1 \lambda_2 \lambda_3 \left(x_{11}x_{22} - x_{13}x_{22} - x_{11}x_{23} + x_{12}x_{23} - x_{12}x_{21} + x_{13}x_{21}\right)^2 . \qquad (7.8.1)$$

The determinant for a four level design is

$$
\begin{aligned}
\left|I_4\right| = {} & n_1 n_2 n_3 \lambda_1 \lambda_2 \lambda_3 \left(x_{11}x_{22} - x_{13}x_{22} - x_{11}x_{23} + x_{12}x_{23} - x_{12}x_{21} + x_{13}x_{21}\right)^2 \\
& + n_1 n_2 n_4 \lambda_1 \lambda_2 \lambda_4 \left(x_{11}x_{22} - x_{14}x_{22} - x_{11}x_{24} + x_{12}x_{24} - x_{12}x_{21} + x_{14}x_{21}\right)^2 \\
& + n_1 n_3 n_4 \lambda_1 \lambda_3 \lambda_4 \left(x_{11}x_{23} - x_{14}x_{23} - x_{11}x_{24} + x_{13}x_{24} - x_{13}x_{21} + x_{14}x_{21}\right)^2 \\
& + n_2 n_3 n_4 \lambda_2 \lambda_3 \lambda_4 \left(x_{12}x_{23} - x_{14}x_{23} - x_{12}x_{24} + x_{13}x_{24} - x_{13}x_{22} + x_{14}x_{22}\right)^2
\end{aligned}
\tag{7.8.2}
$$

In order to show that a D-optimal four point design exists, it must be shown that there exists choices of n_i, λ_i, x_{1i}, and x_{2i}, i = 1, …, 4, such that $\left|I_4\right| \geq \left|I_3\right|$ at its maximum. Maximizing $\left|I_4\right|$ requires that each of the terms that compose its sum must be maximized. The factors that maximized each one of these terms must in turn be maximized. Consider the factor, f_{123}, from the first term expressed as where

$$
f_{123} = n_1 n_2 n_3 \lambda_1 \lambda_2 \lambda_3 \left(x_{11}x_{22} - x_{13}x_{22} - x_{11}x_{23} + x_{12}x_{23} - x_{12}x_{21} + x_{13}x_{21}\right)^2 . \tag{7.8.3}
$$

The values which maximize f_{123} are those from the three point design in Table 7.2.1. Now, consider f_{124},

$$
f_{124} = n_1 n_2 n_4 \lambda_1 \lambda_2 \lambda_4 \left(x_{11}x_{22} - x_{14}x_{22} - x_{11}x_{24} + x_{12}x_{24} - x_{12}x_{21} + x_{14}x_{21}\right)^2 . \tag{7.8.4}
$$

From f_{123}, the values of $n_1, n_2, \lambda_1, \lambda_2$, and their associated x_{1i}s and x_{2i}s have been determined. This implies that $\lambda_4 = \lambda_3, x_{14} = x_{13}$, and $x_{24} = x_{23}$ in order to maximize f_{124}. Thus, the design is composed of only three points. Since the optimal three point design places one third of the available experimental units at those three points, it can be concluded that the criterion for the four point design selects the optimal three point design derived in Section 7.2. One may also wish to note that this proof can easily be altered to accommodate restricted experimental regions where design points are pushed to the extremes of the contour of $EC_{13.53}$ within the given region.

The above proof can be extended using induction to show that a design criterion for the two regressor model formulated to select *d* design points, *d* = 4, 5, 6, … , will degenerate to the optimal three point design. In the previous paragraphs, the assumption was proven for the first case where *d*

$= 4$. Now, assume that $\lambda_k = \lambda_3, x_{1m} = x_{13}$, and $x_{2m} = x_{23}$ for some $d = m$. It must be proven that this holds for $d = m + 1$. Consider the expression (7.8.5) for the determinant of the information matrix of the two regressor model with $m + 1$ design points.

$$\begin{aligned} \left|I_{m+1}\right| &= \sum_{i=1}^{m-1} \sum_{j=i+1}^{m} \sum_{k=j+1}^{m+1} n_i n_j n_k f_{ijk} \\ &= n_1 n_2 n_3 f_{123} + n_1 n_2 n_4 f_{124} + \cdots + n_1 n_2 n_d f_{12(m+1)} + \cdots \end{aligned} \tag{7.8.5}$$

Following the same logic as in the case where $d = 3$, it is concluded that $\lambda_{m+1} = \lambda_3, x_{1(m+1)} = x_{13}$, and $x_{2(m+1)} = x_{23}$. Thus, any d -point D-optimal design criterion for the two regressor exponential model will degenerate to the optimal three point design derived in Section 7.2.

§7.9 Efficient Four Point Designs for the No-Interaction Model

While no truly D-optimal four point design exists, it is of interest to find efficient four point designs with favorable lack of fit properties. These designs would be capable of detecting the presence of quadratic terms in the linear predictor. A four point design which is as similar to the optimal three point design as possible will be the most efficient design. Thus, the four point design will consist of the same points from the D-optimal design (one point at the control and two points at the extremes of the contour of constant $EC_{13.53}$) augmented by a fourth point. This format for the design leaves two issues to be resolved: the location of the fourth point and the number of experimental units to be placed at that point.

First, the allocation percentages to the four points will be discussed. Since the goal is to make the four point design as similar to the three point design as possible, the majority of the points must be distributed among these three points. Both the Nelder-Mead algorithm and the grid search method over all design possibilities are not plausible solutions in this case. However, a restricted grid search is a tractable solution to this problem. By forcing equal allocation at the three design points from the D-optimal design, a reasonable grid search can be performed. In addition, many researchers would favor a design with equal allocation at the optimal points. A reasonable range for these restricted percentages is 25% to 32%-- an equal allocation design to nearly a three point

design. However, another restriction was needed before proceeding with the optimization. The placement of a design point within the coordinate system of IECs has an impact on the precision with which the LOF parameter is estimated. Since the researcher is unsure as to whether the LOF is due to the presence of x_1^2 or x_2^2, the design should estimate these with equal precision. In order to accomplish this, the search was restricted to the line where $IEC_1=IEC_2$, i.e. the effective concentrations of the individual substances are equal. Thus, the four point design will consist of points 1, 2, and 3 from the three point design and a point along line *l* as shown in Figure 7.9.1.

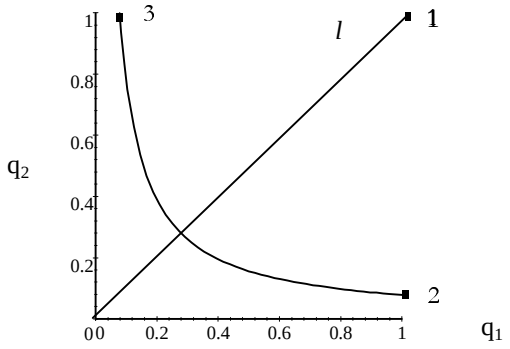

Figure 7.9.1. Basic Geometry for the Four Point Design.

Define p as the proportion of experimental units placed at each of the three D-optimal design points. One must keep in mind that the additional degrees of freedom generated by this point truly allows estimation of a linear combination of x_1^2 and x_2^2. In order to demonstrate how the efficiencies change for each value of p as the point moves along *l*, the efficiencies were graphed vs. the value of $IEC_1=IEC_2$. The graph for p=0.25 is shown below. Graphs for p=0.26 to 0.32 can be found in Appendix E.

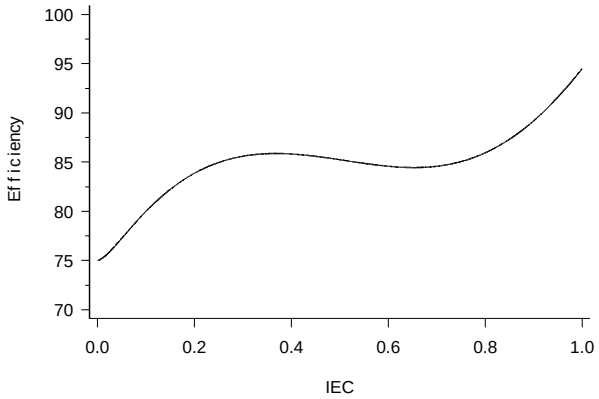

Figure 7.9.2. D-efficiency for the Four Point Design vs. the Three Point Design for p=0.25.

Note that efficiencies increase as the point approaches the control. However, researchers would not be interested in a design which places the fourth point so close to the control. "Reasonable" points include those where $q_1=q_2$ ranges from 0 to 0.8. Three designs of interest include those where the fourth point is located at (0.3678, 0.3678), (0.56765,0.56765), and (0.7071, 0.7071). Respectively, these points are the center of the $MEC_{13.53}$, the centroid of the hypotenuse of the right triangle created by the other three points, and the center of the MEC_{50}. These designs are graphed in Figures 7.9.3-7.9.5. Tables 7.9.1 to 7.9.3 show how the efficiencies change as the percentage of allocation to the three original points changes.

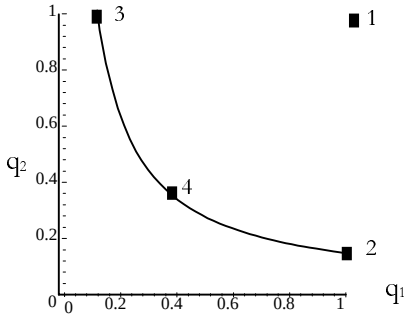

Figure 7.9.3. Geometry for the $MEC_{13.53}$ Design.

Table 7.9.1. Efficiencies for the $MEC_{13.53}$ Design.

p	***Efficiency***
0.25	85.87%
0.26	87.75%
0.27	89.58%
0.28	91.36%
0.29	93.08%
0.30	94.76%
0.31	96.40%
0.32	97.98%

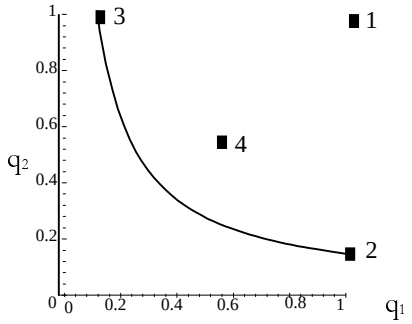

Figure 7.9.4. Geometry for the Centroid Design.

Table 7.9.2. Efficiencies for the Centroid Design.

p	***Efficiency***
0.25	84.75%
0.26	86.74%
0.27	88.67%
0.28	90.57%
0.29	92.42%
0.30	94.24%
0.31	96.01%
0.32	97.76%

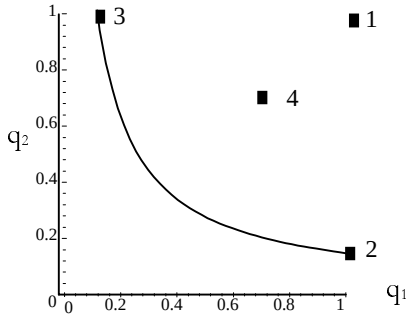

Figure 7.9.5. Geometry for the MEC_{50} Design.

Table 7.9.3. Efficiencies for the MEC_{50} Design.

p	***Efficiency***
0.25	84.62%
0.26	86.61%
0.27	88.56%
0.28	90.47%
0.29	92.34%
0.30	94.17%
0.31	95.97%
0.32	97.72%

One can see that efficiencies change very little across the three designs. This is pleasing because it allows the experimenter a great deal of freedom in the choice of the fourth point without sacrificing efficiency. This feature allows the experimenter to choose a point that may be of particular interest to him or her. Finally, one may want to note that the dominating factor in the efficiency of the designs is allocation of the design points which is consistent with previous results.

§7.10 Lack-of-Fit Properties of Four Point Designs for the No-Interaction Model

While efficient four point designs are desirable, efficiency is not the primary reason for the development of these designs. The primary reason for the four point design in this model is the need for lack-of-fit (LOF) testing in the model. Hence, the ultimate goal is to find a design which is

both powerful in detecting LOF of the model while attaining a reasonable D-efficiency for estimating the parameters of the model.

In order to understand LOF in the Poisson exponential model, it is helpful to review LOF testing in the traditional linear model setting. Consider the model

$$y_{ij} = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \varepsilon_{ij}. \qquad (7.10.1)$$

The D-optimal design in this situation is a factorial. The factorial design is augmented with center runs if curvature is suspected. In order to detect curvature, either the x_1^2 or the x_2^2 term is fit in the model. This coefficient is then tested to determine if curvature is significant or if the model in (7.10.1) is adequate.

The same method applies to the Poisson exponential model. A four point design is chosen to fit the model

$$y_{ij} = e^{\beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i}} + \varepsilon_{ij}. \qquad (7.10.2)$$

which leaves one degree of freedom for LOF. By adding one of the quadratic terms to the model, the adequacy of (7.10.2) can be tested. Of course, one typically wants the most powerful test in any situation. In this case, the LOF parameter is asymptotically normal as are all estimated coefficents in GLM models. Finding the most powerful test requires that the noncentrality parameter of the normal distribution be maximized which means that the variance of the LOF parameter must be minimized. Since this variance is a function of the design this most powerful test must be found by selecting the design which minimizes the variance of the LOF coefficient.

The first step in determining this process is finding the variance of the LOF coefficient via the information matrix. In this case, the x_1^2 term was fit in order to estimate the LOF parameter. The information matrix is given in (7.10.3).

$$\mathbf{I}(\mathbf{X},\boldsymbol{\beta}) = \begin{bmatrix} \sum\lambda_i & \sum\lambda_i x_{1i} & \sum\lambda_i x_{2i} & \sum\lambda_i x_{1i}^2 \\ \sum\lambda_i x_{1i} & \sum\lambda_i x_{1i}^2 & \sum\lambda_i x_{1i}x_{2i} & \sum\lambda_i x_{1i}^3 \\ \sum\lambda_i x_{2i} & \sum\lambda_i x_{1i}x_{2i} & \sum\lambda_i x_{2i}^2 & \sum\lambda_i x_{1i}^2 x_{2i} \\ \sum\lambda_i x_{1i}^2 & \sum\lambda_i x_{1i}^3 & \sum\lambda_i x_{1i}^2 x_{2i} & \sum\lambda_i x_{2i}^4 \end{bmatrix} \tag{7.10.3}$$

$$= \begin{bmatrix} a & f & g & h \\ f & b & j & k \\ g & j & c & l \\ h & k & l & d \end{bmatrix}$$

The expression for the variance of the LOF parameter is

$$\text{var}(\text{LOF}) = \frac{\text{num}}{\det} \tag{7.10.4}$$

where

$$\text{num} = -abc + aj^2 + f^2c - 2fgj + g^2b$$

and

$$\begin{aligned} \det = {} & -abcd + abl^2 + aj^2d - 2ajkl + ack^2 + f^2dc \\ & - l^2f^2 - 2fjdg + 2fjlh + 2fkgl - 2fchk + bdg^2 \\ & - 2gblh - g^2k^2 + 2gkhj + bch^2 - h^2j^2. \end{aligned}$$

The design which minimizes the expression for var(LOF) and thus provides the most powerful test for LOF is the centroid design from the previous section where the fourth point is placed at (0.56765,0.56765). This holds regardless of the allocation of the points. Of course, the design which places more experimental units at the centroid of the hypotenuse is more powerful at detecting LOF. In the Table 7.10.1 a comparison of the performance of the centroid design to the other two designs detailed in Section 7.9 is shown. These designs are denoted by the contour of constant EC on which the fourth point is located. An efficiency is calculated based on the ratio of the $\text{var}(\text{LOF})$ for each design. These efficiencies were calculated for values of p ranging from 0.25

to 0.32. Since the efficiencies are considerably greater than 100%, this indicates that the centroid design is much more efficient that the other two.

Table 7.10.1. LOF-Efficiency for the Centroid Design vs. the Indicated Four Point Designs for Various Values of p .

p	$MEC_{13.53}$	MEC_{50}
0.25	163.96%	128.76%
0.26	163.26%	128.81%
0.27	162.56%	128.89%
0.28	161.82%	128.97%
0.29	161.17%	129.07%
0.30	160.38%	129.16%
0.31	159.65%	129.27%
0.32	158.89%	129.37%

However, placing more points at the fourth point as shown in Tables 7.9.1-7.9.3 does reduce the D-efficiency. Thus, the experimenter must find a comfortable balance between the two when using the four point design, much like the balance required in the choice of center runs in the linear model analogy cited previously.

To conclude this section, a connection is drawn between response surface designs in the linear model and the Poisson model. The best design for LOF in the Poisson exponential model is analogous to the same design in the traditional linear models setting. Note that the centroid design points from the exponential model parallel the center points in the traditional model as far as their role in determining LOF. The balance between a powerful LOF test and favorable D-efficiency is also an issue when designing for the traditional linear model. In addition, the similarity of the optimal three point design to a simplex design in mixture problems was noted in Section 7.2. For the LOF design, a similarity can be noted to another mixture design, the simplex centroid design, which allows one to test for LOF in mixture models (Myers and Montgomery, 1995).

§7.11 D-Optimal Designs on Restricted Regions for the No-Interaction Model

The designs presented for the no-interaction model thus far are very useful to experimenters. However, in some cases, the experimental region must be restricted by a certain model EC which means that the designs in the previous section could not be carried out. For this reason, designs on

restricted regions will be considered now. The regions selected for this section are the ones bounded below by contours of constant EC_{20}, EC_{25}, and EC_{30}.

As one might imagine, D-optimal designs on these confined regions consist of three points. The first point selected was the control and the other two points are the pure component points at the extremes of the contours which bound the region. Experimental units are split evenly among the three points. In other words, this design mimics the one shown in Figure 7.2.1 except points two and three are located at the extremes of the bounding contour. It is interesting to note the efficiencies of these designs with respect to the unrestricted D-optimal design. These efficiencies are listed in Table 7.11.1.

Table 7.11.1. D-Efficiencies for Designs on Restricted Regions.

Region	***D-Efficiency***
EC_{20}	97.13%
EC_{25}	92.37%
EC_{30}	86.43%

As the contours move towards the control, efficiency drops. However, these designs still do very well in comparison to their unrestricted counterpart.

Of course, the issue of lack of fit is very important in restricted regions as well so four point designs must be addressed. Designs considered for lack of fit testing are the class discussed in Section 7.9 where the design consists of the three points from the D-optimal design and the fourth point is chosen from comprising the line ℓ as shown in Figure 7.9.1. Like the unrestricted designs for LOF, allocation percentages for the three original points, p, ranged from 0.25 to 0.32. Regardless of allocation percentage or region, the design which provided the most powerful test for LOF (i.e. minimized the variance of the LOF parameter) was the one where the fourth point is located at the centroid. Note that this is consistent with the case in the unrestricted region. Of course, the design which allocates 25% of the points to the centroid is the most powerful at

detecting LOF and also the least D-efficient. In Table 7.11.2, the restricted and unrestricted D-efficiency is listed for each of the regions and allocation percentages.

Table 7.11.2. D-Efficiencies for Four Point Designs on Restricted Regions vs. Restricted and Unrestricted Counterparts.

	Region 1: EC_{20}		***Region 2: EC_{25}***		***Region 3: EC_{30}***	
p	***Restricted***	***Unrestricted***	***Restricted***	***Unrestricted***	***Restricted***	***Unrestricted***
0.25	84.11%	68.84%	83.69%	71.11%	83.79%	72.28%
0.26	86.15%	70.38%	85.95%	72.81%	85.87%	74.10%
0.27	88.15%	71.87%	87.98%	74.47%	87.90%	75.87%
0.28	90.11%	73.29%	89.96%	76.09%	89.89%	77.63%
0.29	92.04%	74.67%	91.91%	77.67%	91.86%	79.35%
0.30	93.93%	76.00%	93.83%	79.22%	93.79%	81.04%
0.31	95.79%	77.28%	95.71%	80.73%	95.69%	82.69%
0.32	97.62%	78.50%	97.57%	82.19%	97.55%	84.32%

§7.12 D-Optimal Designs for an Arbitrary Restricted Region

As mentioned in the previous section, in many multiple regressor models design points along the contour of the $EC_{13.53}$ may not be feasible due to restricted regions of operability. Restrictions may be placed on individual ECs on model ECs in which case appropriate restrictions must be placed on individual ECs. Of course, an optimal design must be found for cases of restricted regions. While this has been addressed in specific cases, a more general solution must be offered. It will be shown that designs maintain their basic geometry within a restricted region. In addition, design levels for individual variables set at the control will also remain the same. However, the points set at the $IEC_{13.53}$ will be brought in to the extremes of the region. This will be shown for the two variable case with and without interaction and then generalized to the k-variable no interaction and the k-variable interaction case.

Consider the D-optimal design for the two variable no interaction case on the unrestricted region shown in Table 7.2.1 and Figure 7.2.1. Now, let the design regions be restricted so that $IEC_1 \in (r_1,1)$ and $IEC_2 \in (r_2,1)$ where $r_1, r_2 \geq 0.1353$. This is denoted by the gray area in Figure 7.12.1.

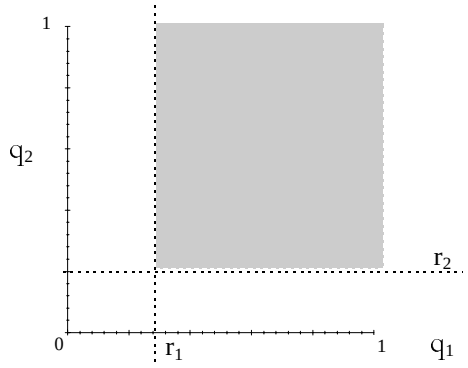

Figure 7.12.1. Example of a Restricted Region.

Thus, the structure of the design is now given in Table 7.12.1.

Table 7.12.1. General Form for a Design on a Restricted Region.

p_i	q_1	q_2
$0.\overline{3}$	1	1
$0.\overline{3}$	$0.1353 + c_1$	1
$0.\overline{3}$	1	$0.1353 + c_2$

where $c_1 \geq r_1 - 0.1353$ and $c_2 \geq r_2 - 0.1353$. Thus, in order to demonstrate that placing the design points at the extremes of the region is optimal, it must be shown that making c_1 and c_2 as small as possible will maximize $|\mathbf{I}|$.

The form of the $|\mathbf{I}|$ for the two variable no interaction case is

$$|\mathbf{I}| = n_1 n_2 n_3 \lambda_1 \lambda_2 \lambda_3 (x_{11}x_{22} - x_{13}x_{22} - x_{11}x_{23} + x_{12}x_{23} - x_{12}x_{21} + x_{13}x_{21})^2 . \qquad (7.12.1)$$

Obviously $n_1 = n_2 = n_3 = \frac{N}{3}$ is the allocation of experimental units that maximize the determinant. Substituting the points in Table 7.12.1 into the determinant apart from λ_c yields the form in expression (7.12.2). (Recall $\lambda_i = q_i \lambda_c$, $q_i = q_{1i} q_{2i}$, and $x_{ki} = \frac{\ln q_{ki}}{\beta_k}$.)

$$|\mathbf{I}| = (0.1353 + c_1)(0.1353 + c_2)(\ln(0.1353 + c_1)\ln(0.1353 + c_2))^2 . \qquad (7.12.2)$$

The determinant can then be partitioned into two quantities, $|\mathbf{I}| = Q_1 Q_2$ where

$$Q_1 = (0.1353 + c_1)\left[\ln(0.1353 + c_1)\right]^2 \qquad (7.12.3)$$

and

$$Q_2 = (0.1353 + c_2)\left[\ln(0.1353 + c_2)\right]^2 .$$

Thus c_1 and c_2 must be chosen so that Q_1 and Q_2 are individually maximized. By taking derivatives of Q_1 and Q_2, it can be shown that Q_1 and Q_2 are decreasing functions in c_1 and c_2 since $\frac{\partial Q_1}{\partial c_1} < 0$ and $\frac{\partial Q_2}{\partial c_2} < 0$ for all c_1 and c_2. Thus, choosing $c_1 = r_1 - 0.1353$ and $c_2 = r_2 - 0.1353$, the extremes of their respective regions, would maximize (7.12.1).

§7.13 The D-Optimal Design for the Three Variable No-Interaction Model

The D-optimal design for the three regressor model with no interaction is simply an extension of the two variable design into three-space. Geometrically, the two variable design formed an isosceles triangle with vertices at the control and the extremes of the model $EC_{13.53}$ (see Figure 7.13.1). Again, note that the non-control level of the three regressor design is the same as the non-control point in the single regressor model as well as the non-control level in the two regressor model.

Experimental units were then equally allocated to each of the three points. The three variable design is simply a tetrahedron with experimental units distributed evenly to its four vertices.

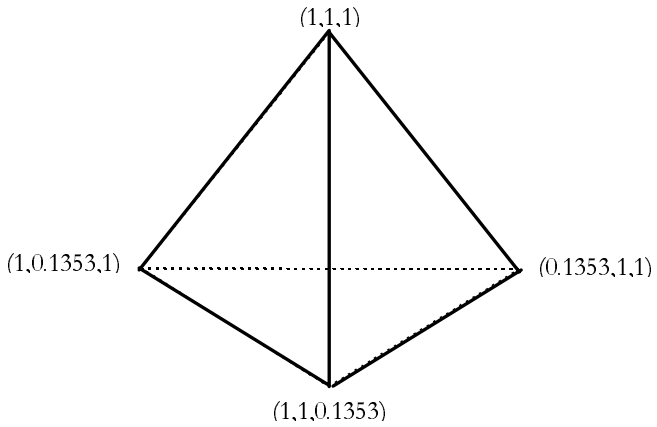

Figure 7.13.1 Geometry of the Three Regressor No Interaction Design

As one might imagine, the vertices are located at the control and at the pure component points on the plane of constant model $EC_{13.53}$ as shown in Table 7.13.1. One should again note the similarity of this design to that of the simplex designs from mixture problems.

Table 7.13.1. Pure Component D-Optimal Design for the Three Regressor No-Interaction Model.

i	p_i	x_{1i}	x_{2i}	x_{3i}	***Plane***
1	0.25	$IEC1_{100}$	$IEC2_{100}$	$IEC2_{100}$	MEC_{100}
2	0.25	$IEC1_{13.53}$	$IEC2_{100}$	$IEC2_{100}$	$MEC_{13.53}$
3	0.25	$IEC1_{100}$	$IEC2_{13.53}$	$IEC2_{100}$	$MEC_{13.53}$
4	0.25	$IEC1_{100}$	$IEC2_{100}$	$IEC2_{13.53}$	$MEC_{13.53}$

The optimality of this design has been verified by evaluating the equivalence theory function over a fine grid of **x** values. The function is less than or equal to 4 at all points in the design space and equal to 4 at the design points. Finally, one should note that this design could easily be augmented with its centroid to provide for lack of fit testing.

§7.14 D_s-Optimality: Addressing EC Estimation

The estimation of a particular EC is, perhaps, the most important goal of impaired reproduction studies. In fact, this goal often takes precedence over minimization of the generalized variance of

the coefficients. In the multi-regressor case precise estimation of an EC is often imperative. Examples include the estimation of the dosage of several chemotherapy drugs which in combination impair reproduction of 95% of cancer cells or the amount of several toxicants which impair reproduction of ceriodaphnia in an ecosystem. In the single regressor case, effective estimation of an EC is addressed by F-optimality which minimizes the width of the Fieller interval or equivalently the var(b_1). However, in the k-regressor case, finding a design which estimates an EC as precisely as possible becomes slightly more complicated. No longer does the interest lie in estimating the concentration of a single toxicant that elicits a particular response but in estimating the amounts of several individual substances which, in combination, produce an overall amount of impairment. In order to address this goal in the multiple regressor case, the model must be examined more closely. The model is given by

$$y_{ij} = e^{\mathbf{x}_i'\boldsymbol{\beta}} + \boldsymbol{\varepsilon}_{ij}. \tag{7.14.1}$$

Taking the expected value yields

$$\boldsymbol{\lambda}_i = e^{\mathbf{x}_i'\boldsymbol{\beta}} \tag{7.14.2}$$

which can be written as

$$q_i\boldsymbol{\lambda}_c = e^{\boldsymbol{\beta}_0 + \mathbf{x}_i^{(s)'}\boldsymbol{\beta}^{(s)}}. \tag{7.14.3}$$

Note that $\boldsymbol{\beta} = \left[\boldsymbol{\beta}_0 \mid \boldsymbol{\beta}^{(s)}\right]$ so that $\boldsymbol{\beta}^{(s)}$ represents the model parameters excluding the intercept, and $\mathbf{x}^{(s)}$ is a row of the model matrix with the exception of the 1 associated with the intercept. Recall that $\boldsymbol{\lambda}_c = e^{\boldsymbol{\beta}_0}$ so

$$q_i = e^{\mathbf{x}_i^{(s)}\boldsymbol{\beta}^{(s)}}. \tag{7.14.4}$$

Thus, the EC is expressed in terms of the model parameters with the exception of the intercept. Now the generalized variance of $\boldsymbol{\beta}^{(s)}$ must be minimized in order to estimate an EC as well as

possible. This task lends itself to a different type of optimality known as D_s-optimality. D_s-Optimality minimizes the generalized variance of a subset of size s of the p parameters in the model. D_s-Optimality for the estimation of a MEC requires the variance-covariance matrix of $\mathbf{b}^{(s)}$. In order to accomplish this the information matrix must be partitioned as in (7.14.5). (Recall $N \cdot \mathbf{M}(\boldsymbol{\eta},\boldsymbol{\beta}) = \mathbf{I}(\mathbf{X},\boldsymbol{\beta})$. Note that $\mathbf{M}(\boldsymbol{\eta},\boldsymbol{\beta})$ will replace $\mathbf{I}(\mathbf{X},\boldsymbol{\beta})$ in the following paragraphs to be consistent with the notation of Silvey for the equivalence theory applied in the following section. The quantity N is dropped since it is a constant with respect to the design.)

$$\mathbf{M}(\boldsymbol{\eta},\boldsymbol{\beta}) = \begin{bmatrix} \mathbf{M}_{11} & \mathbf{M}_{12} \\ \mathbf{M}'_{12} & \mathbf{M}_{22} \end{bmatrix} \tag{7.14.5}$$

where $\mathbf{M}_{11}$ is a scalar associated with the $\text{var}(b_0)$, $\mathbf{M}_{12}$ is a row vector associated with the covariance of $\mathbf{b}_0$ with the parameters that compose $\mathbf{b}^{(s)}$, and finally $\mathbf{M}_{22}$ is an $(s \times s)$ matrix that represents the elements associated with the information of the parameters comprising $\mathbf{b}^{(s)}$. In order to minimize the generalized variance of the coefficients in $\mathbf{b}^{(s)}$, $\mathbf{M}^{-1}(\boldsymbol{\eta},\boldsymbol{\beta})$ must be found in terms of its partitioned form. This is given by

$$M^{-1}(\boldsymbol{\eta},\boldsymbol{\beta}) = \begin{bmatrix} \mathbf{C}_{11}^{-1} & \mathbf{M}_{11}^{-1}\mathbf{M}_{12}\mathbf{C}_{22} \\ \mathbf{C}_{22}\mathbf{M}'_{12}\mathbf{M}_{11}^{-1} & \mathbf{C}_{22}^{-1} \end{bmatrix} \tag{7.14.6}$$

where $\mathbf{C}_{11}^{-1} = \left(\mathbf{M}_{11} - \mathbf{M}_{12}\mathbf{M}_{22}^{-1}\mathbf{M}_{12}^{/}\right)^{-1}$ and $\mathbf{C}_{22}^{-1} = \left(\mathbf{M}_{22} - \mathbf{M}_{12}^{/}\mathbf{M}_{11}^{-1}\mathbf{M}_{12}\right)^{-1}$. Thus the design which minimizes the generalized variance of $\boldsymbol{\beta}^{(s)}$ is the one which minimizes the determinant of $\left(\mathbf{M}_{22} - \mathbf{M}_{12}^{/}\mathbf{M}_{11}^{-1}\mathbf{M}_{12}\right)^{-1}$ or equivalently maximizes the determinant of $\left(\mathbf{M}_{22} - \mathbf{M}_{12}^{/}\mathbf{M}_{11}^{-1}\mathbf{M}_{12}\right)$.

§7.15 D_s-Optimal Design Example for the Two Regressor Model with No Interaction

In order to understand this process more thoroughly, an example is in order. The technique of finding a D_s-optimal design for the two regressor model with no interaction will be demonstrated. For this model, the expected value at a point i is given by

$$\lambda_i = q_i \lambda_c = e^{\beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i}} \tag{7.15.1}$$

which implies

$$q_i = e^{\beta_1 x_{1i} + \beta_2 x_{2i}} \tag{7.15.2}$$

where q_i represents the EC in the EC_{100qi}. Thus for the two regressor model the interest is in estimating the subset of coefficients $\boldsymbol{\beta}^{(s)} = \left[\beta_1 \;\; \beta_2\right]$ as well as possible in order to best estimate the EC. Now, the information matrix, $\mathbf{M}$, in terms of its partitions, $\mathbf{M}_{11}, \mathbf{M}_{12}$, and $\mathbf{M}_{22}$, must be defined. So $\mathbf{M}_{11} = \left[\sum \lambda_i\right]$, $\mathbf{M}_{12} = \left[\sum \lambda_i x_{1i} \;\; \sum \lambda_i x_{2i}\right]$, and $\mathbf{M}_{22} = \begin{bmatrix} \sum \lambda_i x_{1i}^2 & \sum \lambda_i x_{1i} x_{2i} \\ \sum \lambda_i x_{1i} x_{2i} & \sum \lambda_i x_{2i}^2 \end{bmatrix}$. In Section 7.14 it was shown that the design which maximizes

$$\left|\mathbf{M}_{22} - \mathbf{M}_{12}^{\mathrm{T}} \mathbf{M}_{11}^{-1} \mathbf{M}_{12}\right| \tag{7.15.3}$$

is the D_s-optimal design. In this case,

$$\begin{aligned} \left(\mathbf{M}_{22} - \mathbf{M}_{12}^{\mathrm{T}} \mathbf{M}_{11}^{-1} \mathbf{M}_{12}\right) &= \begin{bmatrix} \sum \lambda_i x_{1i}^2 & \sum \lambda_i x_{1i} x_{2i} \\ \sum \lambda_i x_{1i} x_{2i} & \sum \lambda_i x_{2i}^2 \end{bmatrix} - \frac{1}{\sum \lambda_i} \begin{bmatrix} \sum \lambda_i x_{1i} \\ \sum \lambda_i x_{2i} \end{bmatrix} \left[\sum \lambda_i x_{1i} \;\; \sum \lambda_i x_{2i}\right] \\ &= \frac{1}{\sum \lambda_i} \begin{bmatrix} \sum \lambda_i \sum \lambda_i x_{1i}^2 - \left(\sum \lambda_i x_{1i}\right)^2 & \sum \lambda_i \sum \lambda_i x_{1i} x_{2i} - \sum \lambda_i x_{1i} \sum \lambda_i x_{2i} \\ \sum \lambda_i \sum \lambda_i x_{1i} x_{2i} - \sum \lambda_i x_{1i} \sum \lambda_i x_{2i} & \sum \lambda_i \sum \lambda_i x_{2i}^2 - \left(\sum \lambda_i x_{2i}\right)^2 \end{bmatrix} \end{aligned} \tag{7.15.3}$$

and

$$\begin{aligned} \det\left(\mathbf{M}_{22} - \mathbf{M}_{12}^{\mathrm{T}} \mathbf{M}_{11}^{-1} \mathbf{M}_{12}\right) = &\frac{\left(\sum \lambda_i \sum \lambda_i x_{1i}^2 - \left(\sum \lambda_i x_{1i}\right)^2\right)\left(\sum \lambda_i \sum \lambda_i x_{2i}^2 - \left(\sum \lambda_i x_{2i}\right)^2\right)}{\sum \lambda_i} \\ &- \frac{\left(\sum \lambda_i \sum \lambda_i x_{1i} x_{2i} - \sum \lambda_i x_{1i} \sum \lambda_i x_{2i}\right)^2}{\sum \lambda_i} \end{aligned} \tag{7.15.4}$$

The design which maximizes (7.15.4) is shown in Table 7.15.1.

Table 7.15.1. D_s-Optimal Design for the Two Regressor No-Interaction Model.

i	p_i	x_{1i}	x_{2i}	***Contour***
1	0.162	$IEC1_{100}$	$IEC2_{100}$	MEC_{100}
2	0.419	$IEC1_{100}$	$IEC2_{9.2}$	$MEC_{9.2}$
3	0.419	$IEC1_{9.2}$	$IEC2_{100}$	$MEC_{9.2}$

A geometric view is shown in Figure 7.15.1.

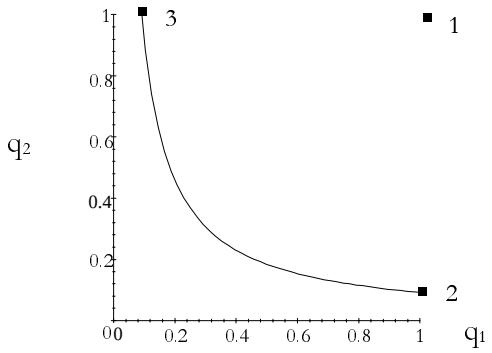

Figure 7.15.1. Geometry of the D_s-Optimal Design for the Two Regressor No-Interaction Model.

Although the design points are pushed to the extremes of a different contour, note that this design takes on the same basic shape as the D-optimal design presented in Section 7.2. It too can be likened to a simplex design from mixture problems since it is comprised of pure component points. The most notable difference between this design and the D-design is the way the experimental units are allocated to each of the design points. Only 16.2% of the observations are placed at the control. This reflects the fact that we are no longer interested in estimating β_0 as well as possible. In addition, 41.9% of the experimental units are placed at each of the pure component points. This shows that the majority of the experimental units are used for the estimation of β_1 and β_2. Note that point 2 only estimates β_2 and point 3 only estimates β_1. The equal allocation of experimental units to points 2 and 3 indicates that equal emphasis is placed on estimating each of the two parameters that define the model EC.

§7.16 Equivalence Theory for D_s-Optimal Designs

The design shown above was, of course, found by a computer algorithm rather than analytically. Thus, equivalence theory must be employed to verify its optimality. Silvey (pg. 45) states that a design measure with nonsingular information matrix $\mathbf{M}$ is D_s-optimal if and only if

$$h = \left(x^{(s)} - \mathbf{M}_{12}'\mathbf{M}_{11}^{-1}\mathbf{M}_{12}x^{(1)}\right)' \left(\mathbf{M}_{22} - \mathbf{M}_{12}'\mathbf{M}_{11}^{-1}\mathbf{M}_{12}\right)\left(x^{(s)} - \mathbf{M}_{12}'\mathbf{M}_{11}^{-1}\mathbf{M}_{12}x^{(1)}\right) \le s \qquad (7.16.1)$$

for all $x \in \mathcal{X}$ and $h = s$ at the design points. The quantity s is the number of parameters in the subset $\boldsymbol{\beta}^{(s)}$ of all parameters $\boldsymbol{\beta}$, $x^{(s)}$ is a vector corresponding to a single row of the model terms included in the subset of size s, and $x^{(1)}$ is a vector corresponding to a single row of the model matrix of the terms not included in the subset. Note that $x^{(s)}$ and $x^{(1)}$ play the role of $\mathbf{J}(\mathbf{x},\boldsymbol{\beta})$, the information matrix for a single observation.

Figure 7.16.1 shows that the equivalence theory relationship holds for the design in Table 7.15.1. The quantity *h* in (7.16.1) takes on the value s=2 at the design points and is less than or equal to 2 for all points in design space.

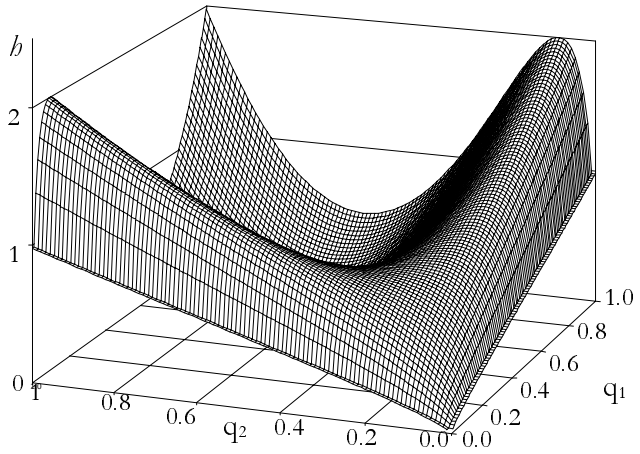

Figure 7.16.1 Equivalence Theory Function for the D_s-Optimal Design.

§7.17 The D_s-Optimal Design for the Three Variable No Interaction Model

The motivation for the D_s-optimal design remains the same as in the two variable model: precise estimation of an EC. This model EC is defined by three parameters: β_1, β_2, and β_3. The design which results from minimizing the determinant of the partition of the inverse of information matrix associated with these three parameters has similar characteristics to that of the D-optimal design. It, too, has a tetrahedron shape. However, it is based on a different plane of constant model EC and has different allocation percentages. The design points are tabled below.

Table 7.17.1. D_s-Optimal Design for the Three Variable No Interaction Model

i	p_i	x_{1i}	x_{2i}	x_{3i}	***Plane***
1	0.133	$IEC1_{100}$	$IEC2_{100}$	$IEC2_{100}$	MEC_{100}
2	0.289	$IEC1_{10.00}$	$IEC2_{100}$	$IEC2_{100}$	$MEC_{10.00}$
3	0.289	$IEC1_{100}$	$IEC2_{10.00}$	$IEC2_{100}$	$MEC_{10.00}$
4	0.289	$IEC1_{100}$	$IEC2_{100}$	$IEC2_{10.00}$	$MEC_{10.00}$

The reduced allocation of experimental units to the control point reflects the fact that β_0 does not play a role in the estimation of an EC. Also note that the other three points are represented in equal proportion which indicates equal emphasis on estimation of all three parameters which define the model EC. In conclusion, one should be aware that the optimality of this design was verified via equivalence theory. The equivalence theory function was indeed equal to three at the design points and less than three everywhere else in the design space.

§7.18 Conclusion

In this chapter, many exciting designs and design concepts have been detailed for the D and D_s-optimal criteria. Of course, one must consider how these techniques extend to the k-regressor model. In the D-optimal case for the k-regressor models, it has been verified through 5 regressors that the D-optimal design is composed of a control point and k pure component points based on the $EC_{13.53}$. In addition, the D-optimal design is always an equal allocation design. Given the general pattern that emerges for the form of the determinant for the *k*-regressor model, one can be assured that for k>5, the D-optimal design follows this same template. In contrast, D_s-optimal designs do not

appear to have a general form which can be cataloged in terms of specific ECs and allocation percentages. The most general comment which can be made about these designs is that they are composed of pure component points based on a model dependent EC, have equal allocation at the k-main effect points, and fewer design points at the control. As a final comment, research strongly indicates that designs on restricted regions as well as designs which provide a degree of freedom for LOF will continue to display the same characteristics as the ones detailed in this chapter.