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The Design and Analysis of Drug Combination Experiments

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THE DESIGN AND ANALYSIS OF DRUG COMBINATION EXPERIMENTS

by

Thomas J. Vidmar

A Dissertation
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
Degree of Doctor of Philosophy
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THE DESIGN AND ANALYSIS OF DRUG COMBINATION EXPERIMENTS

Thomas J. Vidmar, Ph.D.
Western Michigan University, 1986

Past literature concerning drug combination studies is reviewed. This literature has both biological and statistical origins. The justification of the logit transformation for dichotomous responses in a linear models framework is made by observing its similarities to models proposed by others. Using the logistic linear model, optimal experimental designs are derived. Methods for obtaining parameter estimates are discussed as are diagnostic techniques for logistic regression. Two new robust techniques for logistic regression are proposed and compared to a robust technique suggested in the literature via Monte Carlo simulation. Finally, estimation of the median effective dose (ED50) and the resulting confidence intervals are presented. Two new techniques for ED50 estimation that are resistant to outlying observations are presented.
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Thomas J. Vidmar
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CHAPTER I

EARLY METHODS APPLIED TO DRUG COMBINATION STUDIES

Introduction

In today's society the use of chemicals such as insecticides for insect control, drugs to treat illness and fertilizer for crop control is widespread. With so many chemical entities in our environment a point of mutual concern to everyone involves the interaction of these chemicals. That is, we are interested in understanding the effects due to using these chemicals in combination. The effects could be both positive and negative. An example of a positive effect would be when two insecticides are used in combination to produce better insect control than when either ingredient was used singly. A negative effect would result if a physician administered two drugs to patients and the toxic effect of the combination was greater than when either drug is used by itself. In that same view, it could also be that when two drugs are used in combination the effectiveness of the combination is either less than or greater than the effectiveness of either drug used singly.

We will direct our work towards the area of chemical toxicity. The dependent variable or the response of interest is usually dichotomous when examining toxicity. Hence, most of our work will be directed toward the design of experiments, statistical model specification and
assessing, data analysis and interpretation where the dependent variable is dichotomous.

**Literature Review**

The amount of literature addressing the chemical interaction or combination problem is enormous. A literature review by Carpenter, Marshman, and Gibbins (1975) cites well over 200 references and most of those deal with the interaction of alcohol with other compounds. It appears as though the bulk of the contributions to the literature have come from two scientific disciplines; the statisticians and the pharmacologists.

The earliest contributions from the statistical field appear in the late 1930s. C. I. Bliss (1939) was one of the forerunners in the area of insecticide combination analysis. He proposed three types of actions that chemicals follow when used in combination where the dependent variable is dichotomous. The first he termed independent joint action. When chemicals are used in combination and follow this action, they are said to have different modes of toxic action and act independently of one another. This form of action may be stated in terms of the proportion of test insects that die in an experiment:

$$P_C = P_A + P_B - P_A \cdot P_B$$  \hspace{1cm} (1)

where

$P_C$ represents the proportion dying when the chemicals are used
in combination.

$P_A$ represents the proportion dying when Chemical A is used singly.

$P_B$ represents the proportion dying when Chemical B is used singly.

The second type of action he termed similar joint action. Chemical combinations are said to express similar joint action if in a mixture one ingredient can be substituted at a constant ratio for any proportion of the other without altering the toxicity of the mixture. It is said that in this case the chemicals produce similar but independent effects. Bliss utilized the probit transformation to linearize the usually sigmoid dose response curve for each ingredient. Define

$x = \text{dose of A}$

$x^* = \log_{10}(x)$

$y = \text{dose of B}$

$y^* = \log_{10}(y)$

$P_x = \text{proportion that fails to survive at (x)}$

$P_{xy} = \text{proportion that fails to survive at combination (x,y)}$

The probit transformation (Bliss, 1934) is defined as

$$t = \text{probit}(p) = \Phi^{-1}(p) + 5 \tag{2}$$

where

$$\Phi(t) = \int_{-\infty}^{t} \exp \left(-\frac{1}{2} u^2 \right) du \tag{3}$$

Written in terms of the log dose of the poison, $x^*$, the function becomes
probit \( (P) = (x^* - \mu) / \sigma \) \hspace{1cm} (4)

or

\[
P = \int_{-\infty}^{(x^* - \mu)/\sigma - 5} \frac{1}{\sqrt{2\pi}} \exp \left( -\frac{1}{2} \mu^2 \right) \, du \hspace{1cm} (5)
\]

The parameters \( \mu \) and \( \sigma \) are the usual mean and standard deviation of the normal distribution. They are introduced because of the assumption in this methodology that the frequency distribution of tolerances with respect to the log dose \( x^* \) is the integrated normal. The tolerance dose is that dose level for which a particular subject will respond. If a dose is administered to this particular subject below this tolerance, the subject fails to respond. Conversely, give this subject a dose greater than or equal to this tolerance and the subject will respond. Note that the tolerance varies from subject to subject in the population studied.

We may write

\[ t = \left( \frac{x^* - \mu}{\sigma} \right) + 5 \hspace{1cm} (6) \]

which is commonly written as

\[ t = \alpha + \beta x^* = \text{probit} \ (P) \hspace{1cm} (7) \]

Therefore we shall denote

\[ P_x = \text{probit}^{-1} \left( \alpha + \beta x^* \right) \hspace{1cm} (8) \]

Since the ingredients produce similar effects, the dose response lines should be parallel using the probit transformation and log dose. The ratio of equally effective doses or relative potency, \( P \), can then be expressed as:
\[
\log P = \left( \frac{a_B - a_A}{a_A} \right) / \beta \tag{9}
\]

where the first ingredient can be described by the regression equation

\[
P_x = \text{probit}^{-1} \left[ a_A + \beta x^* \right] \tag{10}
\]

and the second ingredient can be described by the equation

\[
P_y = \text{probit}^{-1} \left[ a_B + \beta y^* \right] \tag{11}
\]

The similar joint action hypothesis infers that we may express the response of a chemical combination as

\[
P_{xy} = \text{probit}^{-1} \left[ a_A + \beta \log_{10} (x + py) \right] \tag{12}
\]

Finally, the third type of joint action was called synergistic action by Bliss (1939). This represents the situation where the toxicity of the combination is greater than that predicted from experiments with each ingredient separately. The term antagonism was defined as being the opposite of synergism.

D. J. Finney continued the work began by Bliss. In Finney's (1971) book, Probit Analysis, he summarizes much of the work in this area by himself, Bliss, and others. Finney suggests a model to describe synergistic action. Let

\[
\pi_2 = \text{the proportion of chemical B in the combination} = \frac{x}{x+y}
\]

\[
\pi_1 = \text{the proportion of chemical A in the combination} = \frac{y}{x+y}
\]

The model to describe synergistic action becomes
\[ P_{xy} = \text{probit}^{-1} \left[ \alpha_A + \beta \log_{10} \left( \frac{p n_1 + n_2 + K n_1 n_2}{p n_1 n_2} \right) \right] + \beta \log (x+y) \] (13)

where

\[ K = \begin{cases} < 0 & \text{synergism} \\ 0 & \text{simple similar action} \\ > 0 & \text{antagonism} \end{cases} \]

This model may be preferred over Bliss's model since interpretation of the joint action is based on one parameter, K. Finney provides examples to illustrate the work of Bliss and others.

Plackett and Hewlett (1952) tried to combine the concepts of similar and independent action into one hypothesis. They also provide models where the probit regression lines no longer need be parallel. In the development of their models Plackett and Hewlett distinguish between the dose administered and the amount of the chemical that reaches the site of action. These differences may be due to metabolism, storage in tissues, or excretion of the chemicals.

They suppose that a dose of chemical, \( x \), is administered and an amount, \( W \), reaches the site of action. Let

\[ w = j w^n, \quad j > 0, n > 0, w \leq x \] (14)

and \( n \) is constant. Note that \( j \) may vary from subject to subject and is related to the amount of drug that fails to reach the site of action.

Further suppose that if a dose \( x' \) is administered to a subject, a response is seen. The value \( x \) is called the tolerance dose for that subject. Define the tolerance of the amount of chemical that reaches the site of action, \( w' \), as
\[ w' = j(x') \quad (15) \]

and let the ratio of the amount of chemical to reach the site of action to the tolerance dose at that site be

\[ u = w / w' = \left( \frac{x}{x'} \right)^n \quad (16) \]

Clearly, a subject responds if and only if \( w > w' \) or \( u > 1 \). That is, if the amount of chemical administered is greater than the tolerance dose.

If two chemicals conform to this model, then the probability that a subject does not respond to a dose \( x \) of the first ingredient is

\[ Q_1 = \Pr \left[ u_1 \leq 1 \right] \quad (17) \]

and the probability that a subject does not respond to a dose \( y \) of the second ingredient is

\[ Q_2 = \Pr \left[ u_2 \leq 1 \right] \quad (18) \]

Assuming that the responses are produced independently, the probability that a subject does not respond to a combination containing \( x \) and \( y \) is

\[ Q = \Pr \left[ u_1 \leq 1, u_2 \leq 1 \right] \quad (19) \]

That is, we see a response if \( u_1 > 1 \) or \( u_2 > 1 \). We say that it is independent action because we fail to see a response unless the dose of chemical one is greater than its tolerance dose or the dose of chemical two is greater than its tolerance dose. Even when both chemicals are administered at doses just below their respective tolerance doses, we fail to see a response.
Assuming that the chemicals produce their effects on the same site (similar action hypothesis), then the probability that a subject does not respond becomes

\[ Q = Pr \left[ u_1 + u_2 \leq 1 \right]. \tag{20} \]

Hewlett and Plackett combine these ideas into one equation

\[ Q = Pr \left[ u_1^{1/\lambda} + u_2^{1/\lambda} \leq 1 \right], \quad 0 < \lambda \leq 1. \tag{21} \]

When \( \lambda = 1 \), then (21) reduces to (20) and when \( \lambda \to 0 \) then (21) approaches (19) as a limit. Hewlett and Plackett provide computing details and examples to illustrate these ideas.

Other contributors to the chemical combination literature from the statistical discipline include Ashford and Cobby (1979). They present a series of mathematical models to describe the joint action of drugs. Their models are based upon the concepts of “sites of dosage” and “sites of action” of drugs. They state that the action of a drug at any particular site is assumed to take place as a result of the occupation of receptors and this occupation is governed by the law of mass action. The occupation of receptors is dependent upon the concentration of the drugs at the site of action. When examining drug combinations, it is noted that if the drugs share a common site of action, they compete for the same receptors and fit into Bliss’s (1939) simple similar action hypothesis. Also, if the drugs do not compete for the same receptors and have no common sites of action, then the combination expresses behavior described by Bliss’s independent action hypothesis. Ashford and Cobby provide mathematical models to
describe these situations. It appears that these models, unlike the ones previously mentioned, are not dependent upon a monotonically increasing dose response curve for each of the two drugs when examined separately.

A major paper from the pharmacologists appeared in 1953. Loewe (1953) described a graphical technique to classify the actions of combined drugs. As displayed in Figure 1, the "tense sail" represents a lack of interaction or additivity between two equipotent drugs. When used singly the drugs have similar effects described by the sigmoid dose response curve. Figure 2 describes the situation where again we have drugs A and B but their combined effect is no longer additive but is described by the "sagging sail". In this situation, it takes more of each drug in the combination to achieve the same response if the two drugs were additive. This type of action in the drug combination is termed synergism by Loewe. Figure 3 describes the opposite situation. Here the effect of the combination of drugs A and B is described by the inflated sail. It takes less of each drug in the combination to display a similar effect if the drugs were additive. This kind of response was classified by Loewe as antagonism. Note that if we examine the intersection of either of the surfaces displayed in Figures 1, 2 or 3 with the plane parallel to the dose of A - dose of B plane at a particular percent of effect, we obtain a straight line, a curve that is concave-down or a curve that is concave-up. Figure 4 illustrates this concept. It is true that everywhere along these intersections the level of response is the same. The term isobole has been
Figure 2. The Sagging Sail.
Figure 4. Levels of Constant Response or Isobols.
assigned to these intersections and a plot like the one shown in Figure 4 is called an isobologram. It is interesting that the analysis of chemical combinations using isobols originated with work published by T. R. Fraser (1870, 1872).

Loewe tries to describe additivity in terms of the dose of chemical A to reach a certain effect, denoted $E_M$, and the dose of chemical B to reach an effect, denoted $E_N$, where $E_N > E_M$ with the following:

$$DoseE_M A + (DoseE_N B - DoseE_M B) = DoseE_N C$$  \hspace{1cm} (22)

where $C$ refers to the combination of $A$ and $B$. This same equation makes more sense when expressed in terms of lethal dose to bring about a percentage $p$ or $q$, $p > q$, of response:

$$LD_q A + (LD_p B - LD_q B) = LD_p C$$  \hspace{1cm} (23)

Equation (23) is similar to Bliss’s (1939) simple similar action hypothesis since the hypothesis underlying equation (23) states that when one half of $D_{E_N} A$ is combined with one half of $D_{E_N} B$, a dose equieffective to $D_{E_N} A$, we see the same intensity of effect as $D_{E_N} A$ or $D_{E_N} B$.

Loewe also offers an equation similar in nature to the independent action hypothesis of Bliss:

$$D_{E_N} A + D_{(E_N - E_M)} B = D_{E_N} C$$  \hspace{1cm} (24)

In equation (24) each component brings its own effect into the combination, independent of the other component.
Gessner and Cabana (1970) use the isobol concept of Loewe to analyze the interaction of chloral hydrate and ethanol in male mice. Using their interpretation of Loewe’s ideas, one assumes that the lethal dose which kills fifty percent (LD$_{50}$) of the subjects is known for each ingredient used singly. One then administers combinations of the drugs in one of two ways: (1) the combinations are such that they are along rays of constant proportion (see Figure 5) or (2) the combinations are such that the dose of one is fixed while the dose of the other varies and vice versa (see Figure 6). LD$_{50}$’s are then computed for either the rays of constant proportion or for each fixed dose, depending on the experimental design. A diagram such as the one found in Figure 7 is prepared with the diagonal line connecting the LD$_{50}$’s of each of the two drugs when administered singly. One then plots the LD$_{50}$’s of the combinations on this diagram. If they fall on this line, within experimental error, then it is concluded that the two drugs follow simple similar action. If the LD$_{50}$’s of the combination fall below the line, the combination is said to have a potentiating effect. The effect is said to be antagonizing when the calculated LD$_{50}$’s of the combination fall above this diagonal line. It is interesting to point out the similarity of Figure 7 with that of Figure 4. The response of effect that Gessner and Cabana choose to study was the 50% response which is typical in toxicological studies.

We have presented a purely graphically demonstration of the ideas by Gessner and Cabana. They accomplish their analysis using a Fortran computer program based on probit analysis (Finney$^4$).
Figure 5. Typical Ray Design.
Figure 6. Typical Factorial Design.
Figure 7. Line Connecting LD50's for the Drugs Used Singly.
More recently, Carter, Wampler, and Stablein (1983) introduced a text which examines survival data in cancer chemotherapy studies. Unlike the material already presented, where the response surfaces are messy functions utilizing the inverse of the probit, Carter et al. employ a much simpler surface, the inverse of the logistic distribution. They also reduce the complexity of the problem by using a polynomial model involving the doses of the two chemicals.

Their goals are somewhat different from ours. Not only are they examining interaction between drugs to treat cancer, they are looking for the combination of doses that provides maximum benefit to the subject.

Carter et al. present methods to analyze dichotomous and continuous data. The logistic model is chosen to describe the dichotomous data situation. When modeling a single cancer treating agent, they suppose that the probability of a favorable response is given by

\[ P_x = \left[ 1 + \exp \left( - \left( \beta_0 + \beta_1 x + \beta_2 x^2 \right) \right) \right]^{-1} \]  (25)

where \( \beta_0, \beta_1, \) and \( \beta_2 \) are unknown consultants and \( x \) represents the dosage. They include the quadratic term since most chemotherapy agents reach a level of toxicity with increasing dosage resulting in a reduction in the favorable response. Hence the model they use to describe the response in a two-drug combination is

\[ P_{xy} = \left[ 1 + \exp \left( - \left( \beta_0 + \beta_1 x + \beta_2 x^2 + \beta_3 y + \beta_4 y^2 + \beta_5 xy \right) \right) \right]^{-1} \]  (26)
where the $\beta$'s are unknown constants and $x$ represents the dosage of the first drug and $y$ represents the dosage of the second drug.

In the case where the data are continuous, usually represented by time to response, both the proportional hazards model and nonproportional hazards model are used to describe the data. Cox (1970) first proposed the proportional hazard model. The model is described by

$$\lambda(t) = \lambda_0(t) \exp \left( \left( \beta_0 + \beta_1 x + \beta_2 x^2 + \beta_3 y + \beta_4 y^2 + \beta_5 x y \right) \right)$$

(27)

where $\lambda(t)$ is the hazard function, $t$ represents time, $\lambda_0(t)$ represents an underlying hazard function, the $\beta$'s are unknown constants, and $x$ and $y$ are dosages as noted above. Note that the relative hazard, denoted by

$$\frac{\lambda(t)}{\lambda_0(t)}$$

(28)

is free from any time effect. If this assumption is not viable, then the nonproportional hazards model is an alternative. The hazard function in this case becomes

$$\lambda(t) = \lambda_0(t) \exp \left[ \beta_0 + \beta_1 x + \beta_2 x^2 + \beta_3 y + \beta_4 y^2 + \beta_5 x y + \gamma_1 xt + \gamma_2 yt + \gamma_3 x^2 + \gamma_4 y^2 \right]$$

(29)

where the parameters $\gamma_1$, $\gamma_2$, $\gamma_3$, and $\gamma_4$ are unknown constants and $t$ represents time.

Carter et al. (1983), discuss estimation procedures for their models. Further, they employ response surface methods to locate the drug combination that provides maximum benefit to the subject.
CHAPTER II

OPTIMAL EXPERIMENTAL DESIGNS - NEW PLANS FOR DRUG COMBINATION STUDIES

Introduction

Over the years a myriad of terms with conflicting definitions have arisen in the area of drug combination experimentation. Therefore, our first task will be to arrive at a set of terms and definitions that will define our problem:

(1) addition - the term we will use to describe the effects when we examine two drugs in combination and the response is what we expect under our null hypothesis of no drug interaction.

(2) potentiation - the term that will be used to describe one alternative hypothesis. That is, when the two drugs are used in combination it takes less of each drug to see the same effect if the drugs were additive.

(3) antagonism - the term that will be used to describe the other alternative hypothesis. This occurs when it takes more of each drug used in the combination to see the same effect if the drugs were additive.

There have also been a number of mathematical models proposed to describe drug combinations. We will present our model and show how the models described by others relate to ours.
Typically, toxicology experiments are run for 14 days. The response of interest after this period of time is dichotomous. We are interested in the number of experimental animals that are alive or dead. For the case where the drugs are used singly we denote the probability of death at the \( i \)th dose of drug by \( P_i \).

Statistical Models

Typically, when the relationship between the dose of drug and the probability of responding at that dose are plotted the result is the sigmoid curve as displayed in Figure 8.

An old and common device for describing the relationship between \( P \) and the dose of drug is to linearize the relationship. The most common transformations used to accomplish this linearization are the probit and logit transformations. These transformations are popular when analyzing data that come from biological assay. The probit transformation, as defined in Chapter I, allows us to write probit \( (P) = \alpha_p + \beta_p x \) where \( \alpha_p \) and \( \beta_p \) are parameters and \( x \) is the dose of drug. Correspondingly, the logit transformation may be defined as

\[
\text{logit}(P) = \log\left(\frac{P}{1-P}\right) = \alpha_1 + \beta_1 x
\]

(30)

where again \( \alpha_1 \) and \( \beta_1 \) are parameters and \( x \) is the dose of drug. These two transformations are known to agree closely except in the tails. Work by Chambers and Cox (1967) has shown that it takes extremely large samples in order to discriminate between the two. Therefore, we choose to
Figure 8. Typical Dose Response Relationship.
consider the simpler of the two transformations, the logistic. Chapter V describes in detail the estimation of the parameters in this model.

In the case for two-drug combination studies we will assume that when both drugs are used singly the probability of response, or death, may be described by Equation (30). We denote by $P_{ij}$ the probability of response at dose $i$ of drug one and dose $j$ of drug two. We further propose the following simple model to study two drug combination studies:

$$\ln \left( \frac{P_{ij}}{1 - P_{ij}} \right) = a_0 + a_1x_i + a_2y_j + a_3x_iy_j$$

(31)

or written in the notation of Chapter I

$$P_{xy} = \frac{1 - \exp \left[ - \left( a_0 + a_1x_i + a_2y_j + a_3x_iy_j \right) \right]}{1 + \exp \left[ - \left( a_0 + a_1x_i + a_2y_j + a_3x_iy_j \right) \right]}^{-1}$$

(32)

Note the similarity between Equation (32) and the model proposed by Finney (1971) described in Chapter I.

Finney's model is similar to ours but he chooses the probit transformation. His model may be expressed as

$$P_{xy} = \text{Probit}^{-1} \left[ a + B \log_{10} \left[ x + p \gamma + K(pxy)^{1/2} \right] \right]$$

(33)

In Finney's model the estimated value of the parameter $K$ is used to interpret the joint action of the drugs as described in Chapter I. The major differences between our proposed model and Finney's are his use of the probit transformation to relate the dose to the $P_{xy}$. Hence in the case of a drug studied singly, Finney would use the following representation to
describe the relationship between $P_x$ and $x_i$:

$$P_{x_i} = \text{Probit}^{-1}\left[ a_0 + a_1 \log_{10}(x_i) \right]$$

(34)

The relationship between his model and ours is obvious if one simply removes the logarithm transformation.

The following relationships may be written:

$$P_{x_i} = \frac{e^{a_0 + a_1 x_i}}{1 + e^{a_0 + a_1 x_i}} = F\left( a_0 + a_1 x_i \right)$$

(35)

where $F$ is the logistic distribution and

$$P_{x_i} = \Phi\left( a_0 + a_1 \log_{10}x_i \right)$$

(36)

where $\Phi$ is the standard normal distribution.

In order to see how our model ties in with the models proposed by Hewlett and Plackett and the models proposed by the pharmacologists we appeal to a paper by Hewlett and Plackett (1959). In that paper Equation (32) states that the relationship

$$\frac{x_i}{LD_p(x)} + \frac{y_j}{LD_p(y)} = 1$$

(37)

must hold for a dose $x_i$ of drug one and $y_j$ of drug two if the drug combination under study expresses additivity. The notation $LD_p(\cdot)$, $0<P<100$ is the dose of drug required to produce a response in $P$ percent of the population under investigation. Hewlett and Plackett call this relationship similar joint action with complete positive correlation of tolerances while the pharmacologists use the term drug addition. In terms of our model the $LD_p(x)$ may be expressed as
for a fixed value of $P_x = P_x^0$. Similarly, the $LD_p(Y)$ may be expressed as

$$LD_{p}(y) = \ln \left( \frac{p_y^0}{1 - p_y^0} \right) - a_0$$

where $p_y^0 = p_x^0 = p^0$.

We may write Equation (37) as

$$\frac{a_1 x_i}{\ln \left( \frac{p_x^0}{1 - p_x^0} \right) - a_0} + \frac{a_2 y_j}{\ln \left( \frac{p_y^0}{1 - p_y^0} \right) - a_0} = 1$$

which implies

$$\ln \left( \frac{p_x^0}{1 - p_x^0} \right) = a_0 + a_1 x_i + a_2 y_j$$

which is our null hypothesis regarding additivity of the two drugs under study. We note that we have allowed a common intercept $a_0$ for both drugs. This only makes sense since $a_0$ is a function of the probability of death when no drug is being administered. Namely

$$P_{x=0, y=0} = \frac{e^{a_0}}{1 + e^{a_0}}$$

In practical situations within toxicology studies we wish to have this value very near zero and experience has shown this to be the case.
When we examine the surface generated by our model in Equation (32), either under the null hypothesis or an alternative hypothesis, we are able to make comparisons between this model and those proposed by the pharmacologists.

In the simple model of Equation (32) the null hypothesis or the hypothesis of drug addition becomes $H_0: \alpha_3 = 0$. If there is evidence, based on the experimental data, to conclude that $\alpha_3 = 0$ we say that the drugs act in a additive manner when used in combination. When the data lead us to conclude that $\alpha_3 < 0$ we say that the drug combination expresses a potentiating effect and when $\alpha_3 > 0$ we say that the combination expresses an antagonistic effect. Chapter V discusses in greater detail the estimation and testing of this parameter. It should also be noted that $H_0: \alpha_3 = 0$ is related to the multiplicative theory of interaction in contingency tables.

We first introduce the concept of “no second-order interaction” in $(2 \times 2 \times t)$ contingency tables where we have two levels of response and two factors. This definition leads to consideration of odds ratios and full factorial logistic modeling. For those who think in terms of probits for LD$_{50}$ data analysis we hasten to point out that the logit is known to have similar fit properties (Finney 1971).

The multiplicative theory of interaction in contingency tables was introduced by Roy and Kastenbaum (1956) when they generalized M.S. Barlett’s definition for the $2 \times 2 \times 2$ table. Discussions in the literature of $r \times s \times t$ contingency tables have each dimension correspond to responses or
response-factors. Bhapkar and Koch (1968) discuss the differences between response models and response-factor models.

Let $P_{hij}$ denote the probability of the $h^{th}$ level response within the $ij$ factor combination, where we consider only two possible response levels. The $P_{hij}$ satisfy (st) constraints of the forms.

$$
\sum_{h=1}^{2} P_{hij} = 1 \quad i=1,2,\ldots,s \quad j=1,2,\ldots,t
$$

(43)

Suppose the relative probabilities (odds) $O_{ij} = P_{1ij}/P_{2ij}$ for $i=1,2,\ldots,s$ and $j=1,2,\ldots,t$ are of interest.

Define

$$
\Delta_{ij} = O_{ij} / O_{sj} = \left( \frac{P_{1ij}}{P_{2ij}} \right) / \left( \frac{P_{1sj}}{P_{2sj}} \right) \quad i=1,2,\ldots,s-1 \quad j=1,2,\ldots,t-1.
$$

(44)

Let

$$
\lambda_{ij} = \frac{\Delta_{ij}}{\Delta_{st}} = \left( \frac{P_{1ij}}{P_{2ij}} \right) / \left( \frac{P_{1st}}{P_{2st}} \right) \quad i=1,2,\ldots,s-1 \quad j=1,2,\ldots,t-1.
$$

(45)

Then "no second order interaction" is defined among the factors if

$$
H_0: \lambda_{ij} = 1 \quad is \quad true.
$$

The null hypothesis states that

$$
O_{ij} / O_{sj} = O_{it} / O_{st} \quad i=1,2,\ldots,s-1 \quad j=1,2,\ldots,t-1
$$

(46)

The expression within Equation (46) may also be re-written as

$$
O_{st} / O_{sj} = O_{it} / O_{ij} \quad i=1,2,\ldots,s-1 \quad j=1,2,\ldots,t-1
$$

(47)
Consider next a full factorial model (sxt) relating some factor A with levels $a_i$, $i = 1, 2, ..., s$ and another factor B with levels $b_j$, $j = 1, 2, ..., t$ to the logit response $\log(O_{ij})$.

Then

$$\log O_{ij} = \mu + a_i + b_j + a\beta_{ij}$$ \hspace{1cm} (48)

This leads to

$$P_{ij} = \frac{\exp(\mu + a_i + b_j + a\beta_{ij})}{1 + \exp(\mu + a_i + b_j + a\beta_{ij})}$$ \hspace{1cm} (49)

for all $i$ and $j$ where the hypothesis of no interaction is

$$H_0: a\beta_{ij} = 0$$ \hspace{1cm} (50)

for all $ij$. This (Gart 1972) is equivalent to the assumption of "no second-order interaction" given by Equation (46) above.

When we examine in greater detail the surface described by Equation (32) at the null hypothesis ($\alpha_3 = 0$) and each of the alternative hypotheses, $\alpha_3 < 0$ and $\alpha_3 > 0$, we obtain surfaces like those depicted in Figures 1, 2, and 3, of Chapter I, respectively. We wish to point out the similarities between these surfaces and those presented by Loewe (1953) in Chapter I. The case when $\alpha_3 = 0$ corresponds to the "tense sail", $\alpha_3 < 0$ corresponds to the "inflated sail" and $\alpha_3 > 0$ corresponds to the "sagging sail".

It is also of interest to compare the similarity between the diagram (Figure 7) described in Chapter I of Gessner and Cabana (1970) and the
display of Equation (31) written in terms of the doses $x_i$ and $y_i$ under the null hypothesis ($\alpha_3 = 0$) and a fixed value for $P_{ij}$ say $P_{ij}^0$. If we let

$$ C = \ln \left( \frac{P_{ij}^0}{1 - P_{ij}^0} \right) \tag{51} $$

Equation (31) may be written as

$$ y_j = \frac{(C - a_0)}{a_2} - \frac{a_1}{a_2} x_i \tag{52} $$

which is clearly a linear relationship between the dose of drug one, $x_i$, and the dose of drug two, $y_j$.

There may be situations in which the model in Equation (32) does not adequately describe the data. A possible solution to that problem would be to expand the simple model by adding more terms, as in a Taylor's Series, if the amount of data allows. Obviously we can't have more parameters than data.

**Experimental Designs**

**2x2 Factorial Design**

Now that we have defined our model and null hypothesis of interest we wish to explore various experimental designs that may be used to perform the experiment needed to study the effects of drugs used in combination. Our goal is to use some optimality criteria that will allow the experimenter to use doses of each drug in such a fashion that maximum information is gleaned from the experiment.
The first design we wish to consider is a complete 2x2 design where there are four mixtures of two drugs being administered to four groups of experimental animals. We choose this design because the four experimental groups allow the use of the model described by Equation (31) to obtain optimality results concerning the estimation of the parameter $\alpha_3$.

Recall that a statistically significant value of $|\alpha_3|$ is an indication of interaction between the two drugs.

Again we denote the dose of drug one by $x_i$ and the dose of drug two by $y_j$ ($i = 1,2; j = 1,2$). We let $P_{ij}$ denote the probability of responding (death) in the $(i,j)$ experimental group. Similarly, we let $n_{ij}$ be the number of experimental animals in the $(i,j)$ group and $d_{ij}$ be the number of deaths recorded.

Using the data collected when the drugs are used singly we may estimate the parameter $\alpha_1$ for the first drug, the parameter $\alpha_2$ for the second drug and a common intercept parameter $\alpha_0$. Ultimately we wish to test $H_0: \alpha_3 = 0$. Simple dose addition is equivalent to the case $\alpha_3 = 0$ in the linear logistic model. We note that when $\alpha_3 = 0$ the isobol described by Equation (31) is linear, the isobol is a curve lying in the antagonistic region (See Figure 7 of Chapter I) when $\alpha_3 > 0$, and the isobol is a curve lying in the potentiating region when $\alpha_3 < 0$.

Our strategy in obtaining the four optimal design points will be to utilize the probability of response, denoted by $P_{ij}$, at each design point. We denote the proportion of the total sample to be allocated to a particular design point by $a_{ij} = n_{ij} / N$. The design points, $x_i$ and $y_j$ are related to their respective probability of response, $P_{ij}$, through the logistic
equation

\[ \ln \left( \frac{P_{ij}}{1 - P_{ij}} \right) = a_0 + a_1 x_i + a_2 y_j. \]  

(53)

Use of the above equation with a symmetry assumption that \( P_{12} = P_{21} \), leads to Equations (18) through (23) in Appendix A which illustrate how we may write the design points as functions of the response probabilities, \( P_{ij} \), and the values of the parameters \( a_0, a_1, \) and \( a_2 \). The two well known design criteria described in the next section are then written in terms of the \( P_{ij}, a_{ij}, \) and \( a_0, a_1, \) and \( a_2 \) using Equations (18) through (23) of Appendix A rather than their usual form containing the \( x_i \) and \( y_j \). The values of \( P_{ij} \) and \( a_{ij} \) that minimize the design criteria are then obtained. Note that these solutions are free of \( x_i \) and \( y_j \) and hence, provide a general solution. In order to find a particular solution for a problem at hand specific values of \( a_0, a_1, \) and \( a_2 \) are substituted into Equations (71) and (72) with the resulting \( x_i \) and \( y_j \) being optimal.

**Design Optimization**

To estimate \( a_0, a_1, \) and \( a_2 \) and \( a_3 \) in Equation (31), we can set up likelihood equations or for the \( n_{ij} \) relatively large we may find weighted least squares estimates which are as efficient as the M.L.E.'s (Berkson 1955).

We will assume that the probability of death in the \( i \) \( j \) experimental group is constant and equal to \( P_{ij} \). Therefore the number of deaths in that group, \( d_{ij} \), is binomially distributed with
Define \( \frac{d_{ij}}{n_{ij}} = P_{ij} \). The logistic transform specifies that

\[
Z_{ij} = \log \left( \frac{P_{ij}}{1 - P_{ij}} \right)
\]

has expected value \( a_0 + a_1 x_i + a_2 y_j + a_3 x_i y_j \) and variance \( \left[ n_{ij} P_{ij} (1 - P_{ij}) \right]^{-1} \), for \( n_{ij} \) large using the delta method on the asymptotic normality of \( \frac{d_{ij}}{n_{ij}} \).

Asymptotically, we may write

\[
Z_{ij} = a_0 + a_1 x_i + a_2 y_j + a_3 x_i y_j + \epsilon_{ij},
\]

where the \( \epsilon_{ij} \)'s are independent, but not indentically distributed asymptotic normal. We may write this in matrix notation as

\[
\begin{bmatrix}
Z_{11} \\
Z_{12} \\
Z_{21} \\
Z_{22}
\end{bmatrix}
= \begin{bmatrix}
1 & x_1 & y_1 & x_1 y_1 \\
1 & x_1 & y_2 & x_1 x_2 \\
1 & x_2 & y_1 & x_2 y_1 \\
1 & x_2 & y_2 & x_2 y_2
\end{bmatrix}
\begin{bmatrix}
a_0 \\
a_1 \\
a_2 \\
a_3
\end{bmatrix}
+ \begin{bmatrix}
e_{11} \\
e_{21} \\
e_{21} \\
e_{22}
\end{bmatrix}
\]

(57)

The weighted least squares estimate of \( A \) is given by

\[
A = (X_1'V^{-1}X_1)^{-1}(X_1'V^{-1}Z)
\]

with the \( \text{Cov}(A) = (X_1'V^{-1}X_1)^{-1} \) where

We choose two design criteria: minimization of \( \text{Var}(a_3) \) and maximization of \( |X_1'V^{-1}X_1| \), so called D-optimality (Federov 1972). Clearly, the maximization of \( |X_1'V^{-1}X_1| \) is equivalent to the minimization of \( |\text{Cov}(A)| \).

The 2X2 factorial design points are considered under the hypothesis of no interaction among the two drugs, that is, \( H_0: a_3 = 0 \). This is due to
the fact that the only prior knowledge about these drugs comes from experiments where the drugs are used singly, not in combination. This may be illustrated as shown in Figure 9. In "Chapter III an investigation is made to study how these designs perform when \( a_3 \neq 0 \).

We let

\[
a_{ij} = \frac{n_{ij}}{N}
\]

be the proportion of the total sample size \( N \) to be allocated to \((x_i, y_j)\) and the \( P_{ij} \) are the probabilities of response (under \( H_0 \)) with \( P_{12} = P_{21} \) (see Appendix A).

Let

\[
x_i = \frac{x_i - \bar{x}}{\Delta x}, \quad y_j = \frac{y_j - \bar{y}}{\Delta y}
\]

(\( X_i \) and \( Y_j \) take on the values \(-1, 1\)) and reformulate our basic model (Equation (31)).

\[
\zeta_{ij} = \beta_0 + \beta_1 x_i + \beta_2 y_j + \beta_3 x_i y_j + \epsilon_{ij}.
\]

To obtain our original parameters, the transformation \( A = C'B \) is applicable, where
Figure 9. 2x2 Factorial Design.
We may find Cov(A) by $C'(X_2'V^{-1}X_2)^{-1}C$ where $X_2$ is the design matrix of the indicator variables:

$$X_2 = \begin{bmatrix} 1 & -1 & -1 & 1 \\ 1 & -1 & 1 & -1 \\ 1 & 1 & -1 & -1 \\ 1 & 1 & 1 & 1 \end{bmatrix}.$$  

(63)

Within Appendix A we derive both $\text{Var}(a_3)$ and $\text{Cov}(A)$ under the assumption $H_0: a_3 = 0$, of no interaction when placing our design on a line of equal response (i.e., $P_{12} = P_{21}$).

For both functions there are four independent parameters: $P_{11}, P_{12}, a_{11},$ and $a_{12}$. We may derive the other parameters as $P_{21} = P_{12}, a_{21} = a_{12}, a_{22} = 1 - a_{11} - 2a_{12}$ and $P_{22} = f(P_{11}, P_{21})$ given by Equation (9) Appendix A.

We minimized (using LaGrange multipliers) both

$$G_1 = \text{Var}(a_3) - \lambda(1 - a_{11} - 2a_{21} - a_{22}) \quad \text{and} \quad (64)$$
\[ G_2 = |\text{Cov}(A)| \cdot \lambda (1 - a_{11} - 2a_{21} - a_{22}) \] with (65)

respect to the four parameters. The resulting equation set was then solved by use of IMSL (1982) computer subroutine ZSPNOW.

**Results of Optimization**

Minimizing \( G_1 \) and \( G_2 \) in the Design Optimization Section gives the optimal solutions for the \( P_{ij} \) and the \( a_{ij} \), which when using the equations given in the next section, provide the optimal design points \( x_{ij} \) and \( y_{ij} \). The \( a_{ij} \) provide the optimal allocation proportion in each \( ij \) experimental group.

For the D-optimality solution we found
\[
\begin{align*}
P_{11} &= .015818 \\
P_{12} &= P_{21} = .500000 \\
P_{22} &= .984182 \\
\text{and} & \quad a_{11} = a_{12} = a_{21} = a_{22} = .25
\end{align*}
\]

For the min. \( \text{Var}(\alpha_3) \) solution we found
\[
\begin{align*}
P_{11} &= .008173 \\
P_{12} &= P_{21} = .500000 \\
P_{22} &= .991827 \\
\text{and} & \quad a_{11} = a_{22} = .423764 \\
a_{21} &= a_{12} = .076296
\end{align*}
\]

Note that the D-optimal solution suggests that the same number of animals be allocated to each design point while the min. \( \text{Var}(\alpha_3) \) solution suggests placing a higher proportion of animals off the line of equal response.

To ascertain which solution is "best", we used the \( \text{Var}(\alpha_3) \) as derived in Appendix A (Equation (27)) and \( |\text{Cov}(A)| \) as derived in Appendix A.
(Equation (31)). Both equations are functions of the $P_{ij}$'s and the $a_{ij}$'s. The associated solutions to the $P_{ij}$'s and the $a_{ij}$'s for the two criteria as displayed above were used to form efficiency indices:

$$\text{Eff}_1 = 100 \left( \frac{\text{Var}(a_3) \text{ using minimization of } \text{Var}(a_3)}{\text{Var}(a_3) \text{ using minimization of } |\text{Cov}(A)|} \right)$$  \hspace{1cm} (66)$$

and

$$\text{Eff}_2 = 100 \left( \frac{|\text{Cov}(A)| \text{ using minimization of } |\text{Cov}(A)|}{|\text{Cov}(A)| \text{ using minimization of } \text{Var}(a_3)} \right)$$  \hspace{1cm} (67)$$

The results are:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Min. Var.(a₃)</th>
<th>Min.</th>
<th>Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Var(a₃)</td>
<td>1.2959</td>
<td>1.8751</td>
<td>69.1% Eff₁</td>
</tr>
</tbody>
</table>

We see that the minimization of the $|\text{Cov}(A)|$ criteria is 69% as efficient as the minimization of the $\text{Var}(a₃)$ criteria when judged on the basis of $\text{Var}(a₃)$. The minimization of the $\text{Var}(a₃)$ criteria is only 24% as efficient as the minimization of the $|\text{Cov}(A)|$ criteria when judged on the basis of $|\text{Cov}(A)|$. In this light one would prefer the minimization of the $|\text{Cov}(A)|$ results as they offer 100% experiment-wise efficiency while at the same time offering 69% efficiency in estimation of $a₃$. It is interesting to note that both criteria suggest the placing of two design points along the $LD_{50}$ isobol. The above solutions may be used with data sets from prior
LD50 studies in the same species (environment, dose, method, etc.) to estimate the doses to be employed as described in the next section.

**Estimation of Drug Doses**

Given our optimal probabilities $P_{11}$ and $P_{21} = P_{12}$ and parameter estimates $a_0$, $a_1$ and $a_2$, we wish to estimate the doses of the first drug ($x_1, x_2$) and the second drug ($y_1, y_2$) to use in the new experiment. The relationships relating the $P_{ij}$ to the $x_i$ and $y_j$ are given in Appendix A (Equations (5)-(8)). The equation given by (9) of Appendix A implies

$$\ln\left(\frac{P_{22}}{1-P_{22}}\right) = 2\ln\left(\frac{P_{21}}{1-P_{21}}\right) - \ln\left(\frac{P_{11}}{1-P_{11}}\right).$$

Due to this dependency, no unique solutions exist. To circumvent this problem, we place a restriction on Equation (5) of Appendix A. Namely,

$$\left[\ln\left(\frac{P_{11}}{1-P_{11}}\right) - a_o\right] = \gamma \left[\ln\left(\frac{P_{11}}{1-P_{11}}\right) - a_o\right] + (1-\gamma) \left[\ln\left(\frac{P_{11}}{1-P_{11}}\right) - a_o\right] = a_1 x_1 + a_2 y_1.$$  

$$0 \leq \gamma \leq 1$$

We further equate

$$a_1 x_1 = \gamma \left[\ln\left(\frac{P_{11}}{1-P_{11}}\right) - a_o\right] \text{ and } a_2 y_1 = (1-\gamma) \left[\ln\left(\frac{P_{11}}{1-P_{11}}\right) - a_o\right].$$

Substituting our parameter estimates we have

$$x_1 = \frac{\gamma}{a_1} \left[\ln\left(\frac{P_{11}}{1-P_{11}}\right) - a_o\right], \quad y_1 = \frac{(1-\gamma)}{a_2} \left[\ln\left(\frac{P_{11}}{1-P_{11}}\right) - a_o\right].$$

Substituting $y_1$, into Equation (6) and $x_1$, into Equation (7) of Appendix A (with our parameter estimates substituted), we may solve for $x_2$ and $y_2$: 

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\[ x_2 = \left( \frac{1}{a_1} \right) \left[ \ln \left( \frac{P_{21}}{1-P_{21}} \right) - a_2 y_1 \right], \quad y_2 = \left( \frac{1}{a_2} \right) \left[ \ln \left( \frac{P_{12}}{1-P_{12}} \right) - a_0 - a_1 x_1 \right] \] (72)

Those estimates are not unique and may be varied through a parameter \( \gamma \) to accommodate the investigator. By varying \( \gamma \) we are effectively moving the box that inscribes our 2x2 design region along the equal response line of \( P_{21} = P_{12} \) (see Figure 10). This gives the experimenter a wide latitude of dosage level choices while still permitting an optimal design. Unless practical constraints dictate otherwise, we recommend using \( \gamma = .5 \). This places the design in the center of the region.

**Case for Sub-Optimal Design**

If there does not exist positive valued solutions to \((x_1, y_1)\), then the optimal \( P_{11} \) needed for the design is lower than that which can be obtained. For the case of fixed \( P_{11} \) which is greater than the optimal \( P_{11} \), we should choose an optimal \( P_{12} = P_{21} \). This results in a conditionally optimal solution.

Table 1 contains optimal \( P_{12} = P_{21} \) for varying values of \( P_{11} \) for use by the experimenter for the D-optimal criterion and the optimal \( a_0, P_{11}, P_{12}, a_{11}, a_{12}, \) and \( a_{22} \) required for the minimization of the \( \text{Var}(a_3) \) criterion.

**2-Ray Designs**

An experimental design advocated by Mantel (1958) and others to study two drugs used in combination is a design which we shall term the “ray” design. The design receives its name from the fact that the design points fall on rays emanating from the origin as can be observed in Figure
Figure 10. Latitude of Dosage Level Choices in a 2x2 Factorial Design.
### Table 1

**Suboptimal Values for 2x2 Design**

Minimization Of The Var(αi)  

<table>
<thead>
<tr>
<th>a0</th>
<th>P11</th>
<th>P12 = P21</th>
<th>a11</th>
<th>a12 = a21</th>
<th>a22</th>
</tr>
</thead>
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<tr>
<td>-4.79871</td>
<td>0.008173</td>
<td>.500000</td>
<td>.423764</td>
<td>.076296</td>
<td>.423764</td>
</tr>
<tr>
<td>-4.7</td>
<td>0.009013</td>
<td>.509062</td>
<td>.414188</td>
<td>.078302</td>
<td>.429207</td>
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<tr>
<td>-4.6</td>
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<tr>
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<td>.446117</td>
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<tr>
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<td>.547473</td>
<td>.375028</td>
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<td>.451789</td>
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<td>.557405</td>
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<td>.088695</td>
<td>.457465</td>
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<tr>
<td>-4.13066</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>-4.1</td>
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<td>.48896</td>
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<td>-3.7</td>
<td>0.024270</td>
<td>.609279</td>
<td>.315824</td>
<td>.099324</td>
<td>.485528</td>
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<td>-3.6</td>
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<td>0.029312</td>
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<td>.103600</td>
<td>.496379</td>
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<td>.501670</td>
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<td>.652161</td>
<td>.277397</td>
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<td>.506853</td>
</tr>
<tr>
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<td>0.039166</td>
<td>.662929</td>
<td>.268068</td>
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<td>.511911</td>
</tr>
<tr>
<td>-3.1</td>
<td>0.043107</td>
<td>.673680</td>
<td>.258886</td>
<td>.112141</td>
<td>.516831</td>
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<tr>
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<td>.684392</td>
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<td>.521595</td>
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</tbody>
</table>

**D-Optimal**  

<table>
<thead>
<tr>
<th>P11</th>
<th>P12 = P21</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0158180</td>
<td>.500000</td>
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<tr>
<td>0.0163025</td>
<td>.502564</td>
</tr>
<tr>
<td>0.0178662</td>
<td>.511034</td>
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<td>0.0198403</td>
<td>.519672</td>
</tr>
<tr>
<td>0.0218813</td>
<td>.528478</td>
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<tr>
<td>0.0241271</td>
<td>.537452</td>
</tr>
<tr>
<td>0.0265970</td>
<td>.546591</td>
</tr>
<tr>
<td>0.0293123</td>
<td>.555893</td>
</tr>
<tr>
<td>0.0322955</td>
<td>.565355</td>
</tr>
<tr>
<td>0.0355713</td>
<td>.574975</td>
</tr>
<tr>
<td>0.0391658</td>
<td>.584748</td>
</tr>
<tr>
<td>0.0431073</td>
<td>.594669</td>
</tr>
<tr>
<td>0.0474260</td>
<td>.604732</td>
</tr>
</tbody>
</table>
5 of Chapter I. An interesting property of this design is the fact that along any given ray the proportion of the two drugs used in the combination remains the same.

In a fashion similar to the 2x2 factorial design we will derive an optimal ray design which uses four design points. Prior to construction of the 2-ray design both the \( x_i \) and \( y_j \) were scaled by dividing them by the estimated doses of \( x_i \) and \( y_j \) which produce a 50% death rate (LD\(_{50}\)) when used alone. These estimates are \( x_{5.5} = (-a_0/a_1) \) and \( y_{5.5} = (-a_0/a_2) \), resulting in the scaled values of \( x_i' = x_i (-a_1/a_0) \) and \( y_j' = y_j (-a_2/a_0) \). The scaled values are equally effective with rate \(-a_0\) when considering the model under the null hypothesis that \( \alpha_3 = 0 \). That is,

\[
Z_{ij} = \alpha_0 + \alpha_1 x_i' + \alpha_2 y_j'
\]

\[
= \alpha_0 + \alpha_1 \left( -\frac{a_0}{a_1} \right) x_i + \alpha_2 \left( -\frac{a_0}{a_2} \right) y_j
\]

\[
= \alpha_0 - \frac{\alpha_0}{a_0} x_i' - \frac{\alpha_0}{a_0} y_j'
\]

(73)

We shall assume that two of the design points lie on one ray with slope \( B_1 \). We label the points as \((x_1', y_1')\) and \((x_2', y_2')\). Figure 5 of Chapter I helps to visualize this design. Similarly we say that the other two design points, labeled \((x_3', y_3')\) and \((x_4', y_4')\), lie on another ray with slope \( B_2 \). Initially we let

\[
B_2 = \frac{1}{B_1}
\]

(74)
which, placed the two rays symmetrically within the $x'$, $y'$ plane. Unfortunately in the 2-ray case this leads to dependencies within the design matrix $X$ so that $\det(x) = 0$ and subsequently the determinant of the variance-covariance matrix of the model parameters becoming indeterminate. As an alternative we chose $B_1 = T^*K (K = \alpha_1/\alpha_2)$ and

$$B_2 = \frac{1}{B_1}$$

(75)

which places the two rays symmetrically within the $x$, $y$ plane. In the $x'$, $y'$ plane the slopes of the two rays are

$$TA^2 \text{ and } \frac{1}{TK^2}.$$  

(76)

This latter approach resolved the problem of indeterminacy of the determinant of the variance-covariance matrix of the parameters and allowed us to proceed to an "optimal" design.

Once again we employ the logistic framework and say that the probability of response at design point $K$, $K = 1,2,3,4$ is $P_k$ where drug one is at dose $x_i$ and drug two is at dose $y_i$, $i = 1,2,3,4$. We express the relationship between the probability of response and dose as

$$\ln \left[ \frac{P_k}{1-P_k} \right] = a_0 + a_1 x_i + a_2 y_i + a_3 x_i y_i + e_k$$

(77)

where the $e_k$'s are independent. As before, the parameter of interest in determining the existence of drug interaction is $\alpha_3$. One further assumption is that the probability of response at the points $(x_1, y_1)$ and $(x_3, y_3)$ is the same and equal to $P_1$. Similarly, the probability of response at $(x_2, y_2)$ and $(x_4, y_4)$ is the same and equal to $P_2$. Figure 5 of Chapter I is
helpful in visualizing this. These assumptions are reasonable when we consider our null hypothesis of no drug interaction \( (\alpha_3 = 0) \) and recalling that the resulting surface is one where its isobols are straight lines (see Figure 4 of Chapter I).

**Design Optimization**

We define

\[
z_1 = \ln \left( \frac{P_1}{1-P_1} \right) = a_0 + a_1 x_1 + a_2 y_1 + a_3 x_1 y_1 . \tag{78}
\]

Using the assumption that the probability of response at \((x_1, y_1)\) is equal to the probability of response at \((x_3, y_3)\) then

\[
z_1 = a_0 + a_1 x_3 + a_2 y_3 + a_3 x_3 y_3 . \tag{79}
\]

Similarly,

\[
z_2 = \ln \left( \frac{P_2}{1-P_2} \right) = a_0 + a_1 x_2 + a_2 y_2 + a_3 x_2 y_2 . \tag{80}
\]

Again using the assumption that the probability of response is equal at \((x_2, y_2)\) and \((x_4, y_4)\) we write

\[
z_2 = a_0 + a_1 x_4 + a_2 y_4 + a_3 x_4 y_4 \tag{81}
\]

These relationships may be expressed in matrix notation as

\[
\begin{bmatrix}
z_1 \\
z_2 \\
z_1 \\
z_2
\end{bmatrix}
= \begin{bmatrix}
1 & x_1 & y_1 & x_1 & y_1 \\
1 & x_2 & y_2 & x_2 & y_2 \\
1 & x_3 & y_3 & x_3 & y_3 \\
1 & x_4 & y_4 & x_4 & y_4
\end{bmatrix}
\begin{bmatrix}
a_0 \\
a_1 \\
a_2 \\
a_3
\end{bmatrix} +
\begin{bmatrix}
e_1 \\
e_2 \\
e_3 \\
e_4
\end{bmatrix} \tag{82}
\]
The weighted least squares solution for $A$ is given by

$$A = (X'V^{-1}X)^{-1} (X'V^{-1}Z)$$

(83)

where $V$ equals

$$
\begin{bmatrix}
(n_1 P_1(1-P_1))^{-1} & 0 & 0 & 0 \\
0 & (n_2 P_2(1-P_2))^{-1} & 0 & 0 \\
0 & 0 & (n_3 P_1(1-P_1))^{-1} & 0 \\
0 & 0 & 0 & (n_4 P_2(1-P_2))^{-1}
\end{bmatrix}
$$

(84)

and the $\text{Cov}(A) = (X'V^{-1}X)^{-1}$.

The D-optimality criterion, which tries to minimize $|\text{Cov}(A)|$, will be employed in obtaining the optimal specification of the design points. Hence, we will try to minimize $|(X'V^{-1}X)^{-1}|$ which may be simplified to $|X^{-1}| |V||X^{-1}|$ and further simplified to

$$\frac{|V|}{|X|^2}.$$ 

(85)

We now use the null hypothesis which states that $\alpha_3 = 0$ and the linear relationships between $x_i$ and the $y_j$ to write

$$x_1 = (x_1 - a_0) / (a_1 + a_2^2/Ta_1)$$

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with

\[ x_2 = (x_2 - a_0)/(a_1 + a_2 T a_1) \]

\[ x_3 = (x_3 - a_0)/(a_1 + a_1 T) \]

\[ x_4 = (x_4 - a_0)/(a_1 + a_1 T) \]

(86)

\[ y_1 = \left( \frac{a_2}{T a_1} \right) x_1 \]

\[ y_2 = \left( \frac{a_2}{T a_1} \right) x_2 \]

\[ y_3 = \left( \frac{T a_1}{a_2} \right) x_3 \]

\[ y_4 = \left( \frac{T a_1}{a_2} \right) x_4 \]

and \( y_4 = \left( \frac{T a_1}{a_2} \right) x_4 \)

(87)

Substituting these values into the Cov (A) and calculating the determinant we obtain \(|\text{Cov}(A)| = N/D\), where

\[ N = 4(1 + K^2 T)^6(1 + T)^6 K^4 a_2^8, \]

\[ D = \left[ (z_1 - z_2)^4(z_1 - a_0)^3(z_2 - a_0)^2(1 + KT)^4(KT - 1)^4 \right] \]
\[ (1 + K)^2 (K - 1)^2 (1 - P_1) (1 - P_2) (2 \omega - 1)^2 T^2 P_1^2 P_2^2 \alpha_1^2, \]  \hspace{1cm} (88)

\[ K = \alpha_1 / \alpha_2, \text{ and, } \frac{n_1}{N} = \omega \text{ with } N \text{ being the total number of animals in the experiment.} \]

**Results of Optimization**

Note that the series of Equations (86) and (87) yield values of \( x_i, y_j \) in terms of \( P_k, T, \) and the parameters \( \alpha_0, \alpha_1, \) and \( \alpha_2 \) which are assumed to be well estimated by data where the two drugs were used singly. Hence, Equation (88) must be minimized with respect to these parameters using a computer subroutine such as ZSPW (IMSL, 1982).

Appendix B contains:

\[ \frac{\delta}{\delta P_i} |\text{Cov}(A)|, \frac{\delta}{\delta \alpha_i} |\text{Cov}(A)|, \text{ and } \frac{\delta}{\delta T} |\text{Cov}(A)|. \]

It was determined that the allocation proportion \( \omega_1 = .25 \) holds for all values of \( \alpha_0, \alpha_1, \) and \( \alpha_2 \). The optimal proportions \( P_1 \) and \( P_2 \) vary only with \( \alpha_0 \) as shown in Table 2. The optimal values of \( T \) are a function of \( K = (\alpha_1 / \alpha_2) \) and appear within Table 3. These tables may be used for interpolation of \( P_1 \) and \( P_2 \) for a given \( \alpha_0 \) value and interpolation of \( T \) for a given \( K = (\alpha_1 / \alpha_2) \) value.
## Table 2
Optimal \( p_1 \) and \( p_2 \) for the 2-Ray Design

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<th>( a_0 )</th>
<th>( p_1 )</th>
<th>( p_2 )</th>
<th>( a_0 )</th>
<th>( p_1 )</th>
<th>( p_2 )</th>
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<th>( p_1 )</th>
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<th>( p_1 )</th>
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Optimal Values of T as a Function of K

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3x3 Factorial Design

The 2x2 factorial design which optimally allocates four design points will be extended to a 3x3 factorial design which optimally allocates nine design points. The notation will be a direct extension of the 2x2 case. Figure 6 of Chapter I illustrates this design. The $P_{ij}$'s in that figure represent the probabilities of response, or death, at a dose of $x_i$ of drug one and drug two at a dose of $y_j$. It is assumed that the logistic transform

$$z_{ij} = \ln \left( \frac{P_{ij}}{1 - P_{ij}} \right) = a_0 + a_1 x_i + a_2 y_j + a_3 x_i y_j + a_4 x_i^2 + a_5 y_j^2$$

$$+ a_6 x_i y_j^2 + a_7 x_i^2 y_j + a_8 x_i^2 y_j^2$$

(89)

adequately models the probability of response.

The assumption of no drug interaction may be written in terms of the logistic model as

$$z_{ij} = a_0 + a_1 x_i + a_2 y_j$$

(90)

Therefore, the test for the lack of drug interaction becomes a test of the hypothesis that

$$\begin{bmatrix}
a_3 \\
a_4 \\
a_5 \\
a_6 \\
a_7 \\
a_8
\end{bmatrix} \begin{bmatrix}0 \\
0 \\
0 \\
0 \\
0 \\
0
\end{bmatrix}$$

(91)
The strategy to be employed to find the optimal design points will be to use the D-optimality criterion, which minimizes the determinant of the covariance of the parameter estimates, to obtain the optimal values of the $P_{ij}$'s. We are able to obtain the optimal $P_{ij}$'s because we are able to express the covariance of the parameter estimates as a function of the $P_{ij}$'s. Estimates of $a_0$, $a_1$, and $a_2$ obtained from using the drugs singly are then used to obtain the nine $(x_i, y_j)$ points.

**Design Optimization Model**

We consider the full rank linear model,

$$z_{ij} = \ln \left( \frac{P_{ij}}{1 - P_{ij}} \right) = a_0 + a_1 x_i + a_2 y_j + a_3 x_i y_j + a_4 x_i^2 + a_5 y_j^2 + a_6 x_i y_j + a_7 y_j^2 = a_0 + a_1 x_i + a_2 y_j + a_3 x_i y_j + a_4 x_i^2 + a_5 y_j^2 + a_6 x_i y_j + a_7 y_j^2 + e_{ij}$$

$$i = 1, 2, 3, \quad j = 1, 2, 3 \quad (92)$$

We will assume that the probability of death in the $ij$ experimental group is constant and equal to $P_{ij}$. Therefore the number of deaths in that group, $d_{ij}$, is

$$E \left( \frac{d_{ij}}{n_{ij}} \right) = P_{ij}, \quad \text{VAR} \left( \frac{d_{ij}}{n_{ij}} \right) = P_{ij} \left( 1 - P_{ij} \right) \frac{n_{ij}}{n_{ij}}, \quad n_{ij}, \quad \text{the total observations in group } ij. \quad (93)$$

The logistic transform specifies that

$$z_{ij} = \log \left( \frac{P_{ij}}{1 - P_{ij}} \right) \quad (94)$$

has expected value
\[ a_0 + a_1 x_i + a_2 y_j + a_3 x_i y_j + a_4 x_i^2 + a_5 y_j^2 + a_6 x_i y_j + a_7 x_i^2 y_j + a_8 x_i^2 y_j^2 \]  

(95)

and variance \( \left[ n_{ij} P_{ij} (1 - P_{ij}) \right]^{-1} \), for \( n_{ij} \) large  

(96)

We may write Equation 92 in matrix notation as

\[
\begin{bmatrix}
z_{11} \\
z_{12} \\
z_{13} \\
z_{21} \\
z_{22} \\
z_{23} \\
z_{31} \\
z_{32} \\
z_{33} \\
\end{bmatrix} = \begin{bmatrix}
1 & x_1 & y_1 & x_1^2 & y_1^2 & x_1 y_1 & x_1^2 y_1 \\
1 & x_2 & y_2 & x_2^2 & y_2^2 & x_2 y_2 & x_2^2 y_2 \\
1 & x_3 & y_3 & x_3^2 & y_3^2 & x_3 y_3 & x_3^2 y_3 \\
1 & x_1 & y_2 & x_1^2 & y_1 y_2 & x_1^2 y_1 & x_3 y_2 \\
1 & x_2 & y_3 & x_2^2 & y_3^2 & x_2 y_3 & x_3 y_2 \\
1 & x_3 & y_1 & x_3^2 & y_1 y_3 & x_3^2 y_3 & x_3 y_1 \\
1 & x_1 & y_3 & x_1^2 & y_3 y_1 & x_1^2 y_3 & x_1 y_3 \\
1 & x_2 & y_1 & x_2^2 & y_2 y_1 & x_2^2 y_2 & x_2 y_1 \\
1 & x_3 & y_2 & x_3^2 & y_2 y_3 & x_3^2 y_3 & x_3 y_2 \\
\end{bmatrix} \begin{bmatrix}
a_0 \\
a_1 \\
a_2 \\
a_3 \\
a_4 \\
a_5 \\
a_6 \\
a_7 \\
a_8 \\
\end{bmatrix} + \begin{bmatrix}
e_{11} \\
e_{12} \\
e_{13} \\
e_{21} \\
e_{22} \\
e_{23} \\
e_{31} \\
e_{32} \\
e_{33} \\
\end{bmatrix}
\]  

(97)

The solution to Equation 97 is given by

\[ A = \left( X_1^1 V^{-1} X_1 \right)^{-1} \left( X_1^1 V^{-1} Z \right) \text{ with } COV(A) = \left( X_1^1 V^{-1} X_1 \right)^{-1} \] and
Design

The 3x3 factorial design points are considered and illustrated in Figure 11.

Let

\[ a_{ij} = \frac{n_{ij}}{N} \]  

be the proportion of the total sample size N to be allocated to \((x_i, y_j)\), the \(P_{ij}\) are the probabilities of response, and

\[ X_i = \frac{x_i - x_2}{\Delta x}, \quad Y_j = \frac{y_j - y_2}{\Delta y}. \]

\(X_i\) and \(Y_j\) take on the values \((-1,0,1)\). Reformulate the basic model Equation (89) as:

\[ z_{ij} = \beta_0 + \beta_1 x_i + \beta_2 y_j + \beta_3 x_i y_j + \beta_4 x_i^2 + \beta_5 y_j^2 + \beta_6 x_i y_i^2 + \beta_7 x_i^2 y_j + \beta_8 x_i^2 y_i^2 + e_{ij}. \]
Figure 11. 3x3 Factorial Design.
To obtain our original parameters, the transformation $A = C'B$ is applicable, where

$$
A = \begin{bmatrix}
1 & -\frac{x}{\Delta x} & -\frac{y}{\Delta y} & \frac{x y}{\Delta x \Delta y} & -\frac{x^2}{\Delta x^2} & \frac{y^2}{\Delta y^2} & \frac{x^2 - y^2}{\Delta x^2 \Delta y^2} & \frac{x^2 y}{\Delta x^2 \Delta y} & \frac{y^2}{\Delta y^2} & \frac{x^2 y}{\Delta x^2 \Delta y^2} \\
\frac{1}{\Delta x} & 0 & -\frac{y}{\Delta y} & -\frac{2 x}{\Delta x \Delta y} & 0 & -\frac{2 x}{\Delta x^2} & \frac{2 x y}{\Delta x^2 \Delta y} & -\frac{2 x y}{\Delta x^2 \Delta y^2} & \frac{2 x y}{\Delta x^2 \Delta y} & \frac{2 x y}{\Delta x^2 \Delta y^2} \\
0 & 0 & 1 & -\frac{x}{\Delta y} & 0 & -\frac{x}{\Delta x \Delta y} & -\frac{2 x y}{\Delta x^2 \Delta y} & -\frac{2 x y}{\Delta x^2 \Delta y^2} & \frac{2 x y}{\Delta x^2 \Delta y} & \frac{2 x y}{\Delta x^2 \Delta y^2} \\
0 & 0 & 0 & 1 & 0 & \frac{1}{\Delta x^2} & 0 & \frac{1}{\Delta x^2 \Delta y^2} & \frac{1}{\Delta x^2 \Delta y} & \frac{1}{\Delta x^2 \Delta y^2} \\
0 & 0 & 0 & 0 & \frac{1}{\Delta y^2} & 0 & \frac{1}{\Delta y^2} & \frac{1}{\Delta x \Delta y^2} & \frac{1}{\Delta x \Delta y} & \frac{1}{\Delta x \Delta y^2} \\
0 & 0 & 0 & 0 & 0 & \frac{1}{\Delta x \Delta y^2} & 0 & \frac{1}{\Delta x \Delta y^2} & \frac{1}{\Delta x \Delta y} & \frac{1}{\Delta x \Delta y^2} \\
0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{\Delta x \Delta y^2} & \frac{1}{\Delta x \Delta y^2} & \frac{1}{\Delta x \Delta y} & \frac{1}{\Delta x \Delta y^2} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & \frac{1}{\Delta x \Delta y^2} & \frac{1}{\Delta x \Delta y^2} \\
\end{bmatrix}
$$

Using (102) we may find Cov($A$) by $C'(X_2^1 V^{-1} X_2)C$ where $X_2$ is the design matrix of the indicator variables:
Within Appendix C we derive Cov(A) under the full rank linear model. The assumption of a simple linear logistic dose response without multiplicative interaction leads to the null hypothesis

\[ H_0: \begin{bmatrix} a_3 \\ a_4 \\ a_5 \\ a_6 \\ a_7 \\ a_8 \end{bmatrix} = 0, \]

i.e.,

\[ z_{ij} = \ln \left( \frac{P_{ij}}{1 - P_{ij}} \right) = a_0 + a_1 x_i + a_2 y_j. \]

Under H_0 it is shown (Appendix C) that any \( z_{ij} \) may be represented as a linear function of \( z_{12} \) and \( z_{22} \). Consequently all \( P_{ij} \) and \( v_{ij} \) are functions of \( P_{12} \) and \( P_{22} \).

From Section 2, of Appendix C we logically made the following
allocations of \( a_{ij} = \frac{n_{ij}}{N} \):

\[
\begin{align*}
a_{12} &= a_{21} \\
a_{23} &= a_{32} \\
a_{22} &= a_{13} = a_{31}.
\end{align*}
\]

We next assumed two further symmetries:

\( a_{11} = a_{33} \) and \( a_{23} = a_{12} \), with \( \Sigma a_{ij} = 1 \).

Solving for \( a_{11} \) using \( \Sigma a_{ij} = 1 \) we have \( a_{11} = (1-4a_{12}-3a_{22})/2 \), with every \( a_{ij} \) a linear function of \( a_{12} \) and \( a_{22} \).

Thus, under the null hypothesis and the allocation symmetry there are four independent parameters: \( P_{12}, P_{22}, a_{12} \), and \( a_{22} \) (see Appendix C-Section 4).

We minimized \( \text{Cov}(A) \) with respect to the four parameters. The resulting equation set was solved by use of IMSL (1982) computer subroutine ZSPOW.

**Results of Optimization**

Minimizing \( \text{Cov}(A) \) as given in Appendix C gives optimal solutions for the \( P_{ij} \) which when using the equations given in Section 4, provide the optimal design points \( x_i \) and \( y_j \). The \( a_{ij} \) provide the optimal allocation proportion in each \( ij \) experimental group.

The D-Optimal Solution is

\[
\begin{align*}
a_{ij} &= .11111 \text{ for all } i \text{ and } j \\
P_{11} &= .00011206, P_{33} = 1-P_{11} = .9998879 \\
P_{12} &= P_{21} = .0104758, P_{23} = P_{32} = (1-P_{12}) = .9895242 \\
P_{13} &= P_{22} = P_{31} = .50
\end{align*}
\]
**Estimation of Drug Doses**

Given our optimal probabilities above and model parameter estimates \(a_0, a_1, \text{ and } a_2\), we wish to estimate the doses of the first drug \((x_1, x_2, x_3)\) and the second drug \((y_1, y_2, y_3)\) to use in the new experiment. The relationships associating the \(P_{ij}\) to the \(x_i\) and \(x_j\) are given by Equations (8-16) in Appendix C-Section 2.

Using Equation (12) of Appendix 3 we have:

\[
\begin{align*}
[22 - a_0] &= a_1 x_2 + a_2 y_2 = y \left[ z_{22} - a_0 \right] + (1 - y) \left[ z_{22} - a_0 \right], \quad 0 \leq y \leq 1. \\
\end{align*}
\]

(106)

We further equate

\[
\begin{align*}
a_1 x_2 &= y \left[ z_{22} - a_0 \right] \quad \text{and} \quad a_2 y_2 = (1 - y) \left[ z_{22} - a_0 \right],
\end{align*}
\]

(107)

substituting our parameter estimates we have

\[
\begin{align*}
x_2 &= \frac{y(z_{22} - a_0)}{a_1}, \quad y_2 = \frac{(1 - y)(z_{22} - a_0)}{a_2}.
\end{align*}
\]

(108)

Using the estimates of \(\Delta x\) and \(\Delta y\) given by Equations (42) and (44) of Appendix C we have \((x_1, x_3) = x_2 \pm \Delta x, (y_1, y_3) = y_2 \pm \Delta y\).

These estimates are not unique and may be varied through the parameter \(y\) to accommodate the investigator. Unless practical constraints dictate otherwise, we recommend using \(y = .5\). This places the design in the center of the region.
Case for Sub-Optimal Design

If there does not exist positive valued solutions to \((x_i, y_i)\), then the optimal \(P_{11}\) need for the design is lower than that which can be obtained. A solution is to place the design at \((0,0)\) with

\[
P_{11} = \frac{e^{\alpha_0}}{1 + e^{\alpha_0}}. \tag{109}
\]

If we keep our symmetry (i.e., \(z_{12} = z_{21}\)) and let \(z_{11} = \alpha_0\) we find from Equation (26) of Appendix C that \(z_{12} = 0.5z_{11} + 0.5z_{22}\). Thus, minimization of the

\[
\text{COV}(A)
\]

with respect to \(\alpha_2\) and \(P_{22}\) results in our restricted case solution.

Table 4 contains optimal \(P_{12} = P_{21}\) for varying values of \(\alpha_0\) for use by the experimenter. For all \(\alpha_0\) the optimal \(a_{ij} = 0.111111\) for all \(i\) and \(j\).

3-Ray Design

In a manner similar to the extension of the 2x2 factorial optimal design to the 3x3 factorial design we extend the 4-point ray design to the 9-point ray design. For the 9-point ray design there are three rays emanating from the origin with three design points on each ray. Figure 12 illustrates the construction of this design. The assumption is made that the probability that an animal succumbs to drug one at a dose of \(x_i\) and drug two at a dose of \(y_i, i = 1, \ldots, 9\) is modeled by the saturated logistic.
Table 4
Suboptimal Values for 3x3 Design

<table>
<thead>
<tr>
<th>$a_0$</th>
<th>$P_{12} = P_{21}$</th>
<th>$P_{22}$</th>
<th>$a_0$</th>
<th>$P_{12} = P_{21}$</th>
<th>$P_{22}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>-9.0</td>
<td>0.1111807</td>
<td>0.508839</td>
<td>-6.0</td>
<td>0.0906119</td>
<td>0.800218</td>
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<tr>
<td>-8.9</td>
<td>0.119642</td>
<td>0.518090</td>
<td>-5.9</td>
<td>0.0973314</td>
<td>0.809310</td>
</tr>
<tr>
<td>-8.8</td>
<td>0.128040</td>
<td>0.527415</td>
<td>-5.8</td>
<td>0.104546</td>
<td>0.818259</td>
</tr>
<tr>
<td>-8.7</td>
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<td>0.536871</td>
<td>-5.7</td>
<td>0.112289</td>
<td>0.827048</td>
</tr>
<tr>
<td>-8.6</td>
<td>0.146699</td>
<td>0.546276</td>
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<td>0.825666</td>
</tr>
<tr>
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<td>0.555806</td>
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<td>0.129490</td>
<td>0.844099</td>
</tr>
<tr>
<td>-8.4</td>
<td>0.168163</td>
<td>0.565399</td>
<td>-5.4</td>
<td>0.139018</td>
<td>0.852337</td>
</tr>
<tr>
<td>-8.3</td>
<td>0.180082</td>
<td>0.575051</td>
<td>-5.3</td>
<td>0.149208</td>
<td>0.868181</td>
</tr>
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<td>-8.2</td>
<td>0.192873</td>
<td>0.584753</td>
<td>-5.2</td>
<td>0.160096</td>
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</tr>
<tr>
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<td>0.206603</td>
<td>0.594516</td>
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<td>0.883115</td>
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<tr>
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<td>0.604321</td>
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<td>0.890218</td>
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</tr>
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</tr>
<tr>
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<td>0.653877</td>
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<td>0.703747</td>
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<td>0.353432</td>
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<td>-6.9</td>
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<td>0.713676</td>
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<td>0.946677</td>
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<tr>
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<td>0.723570</td>
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<td>0.950851</td>
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<td>-6.3</td>
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<td>0.973402</td>
</tr>
</tbody>
</table>

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Slope $= 1/\beta_1$

$Slopes$ $1 > (X_5, Y_5)$

$Prob$ $of$ $response = P_j$

$Dose$ $of$ $Drug$ $One$ $(X)$

$Slope = \beta_1$

Figure 12. 3-Ray Design.
model

\[ z_i = \ln \left( \frac{P_i}{1 - P_i} \right) = a_0 + a_1 x_i + a_2 y_i + a_3 x_i y_i + a_4 x_i^2 + a_5 y_i^2 + a_6 x_i y_i + a_7 y_i^2 + a_8 x_i^2 y_i + a_9 y_i^2 \]  

(111)

Similar to the procedure for the 2-ray design we again divide the \( x_i \)
by \( x_5 \) and \( y_i \) by \( y_5 \). This results in \( x_{i}' = (-a_1/a_0) x_i \) and \( y_{i}' = (-a_2/a_0) y_i \).

A further assumption is made regarding the probabilities of response. These are stated below:

1. \( P_{11} = P_{44} = P_{77} \)
2. \( P_{22} = P_{55} = P_{88} \)
3. \( P_{33} = P_{66} = P_{99} \)  

(112)

These assumptions imply that the probability of response is the same at design points \((x_{1}', y_{1}')\), \((x_{4}', y_{4}')\) and \((x_{8}', y_{8}')\) and the resulting isobol is linear. Similar conditions exist for the design point triplets \([x_{2}', y_{2}']\), \([x_{5}', y_{5}']\), \([x_{8}', y_{8}']\) and \([x_{3}', y_{3}'], [x_{6}', y_{6}'], [x_{9}', y_{9}']\).

**Design Optimization**

Recall the property of the ray design which states that along any particular ray the proportion of dose one to dose two is a constant. We make the assumption that slope of the first ray is \( B_1 \), the slope of the second ray is 1, and the slope of the third ray is \( 1/B_1 \). The ray design property taken together with the slope assumptions just stated allow us to express Equation (111) in matrix notation as follows (where all \( b_i = -a_0 \)).
The weighted least squares solution to Equation (113) is given by

$$ \beta = (X' (W^{-1} X')^{-1} (X' (W^{-1} Z))$$

where

$$ V = \begin{bmatrix} v_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & v_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & v_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & v_4 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & v_5 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & v_6 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & v_7 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & v_8 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & v_9 \end{bmatrix} $$

and

$$ v_i = [n_i P_i(1-P_i)]^{-1} \quad (115) $$

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Employing the D-optimality criterion requires that we minimize the determinant of the Cov(B) which may be expressed as

\[
\begin{vmatrix}
(\mathbf{X}' \mathbf{V}^{-1} \mathbf{X})^{-1}
\end{vmatrix}
\]

which, due to the structure of \( \mathbf{X}' \) and \( \mathbf{V} \), may be simplified to

\[
\begin{vmatrix}
\mathbf{V} \\
\mathbf{X}'
\end{vmatrix}^2
\]

Here \( \det(\mathbf{X}') \neq 0 \) and we may proceed. It should be noted that in terms of the original (non-scaled) \( x \)'s that there exists a matrix \( \mathbf{Q} \) such that \( \mathbf{X}'\mathbf{Q} = \mathbf{X} \). Then

\[
|\text{Cov}(A)| = \frac{|\mathbf{V}|}{|\mathbf{X}'|^2} = \frac{|\mathbf{V}|}{|\mathbf{X}'|^2} = |\text{Cov}(\beta)|. \tag{118}
\]

Then minimization of \( |\text{Cov}(B)| \) minimizes \( |\text{Cov}(A)| \). The hypothesis of no drug interaction may be written as

\[
\begin{bmatrix}
b_1 \\
b_2 \\
b_3 \\
b_4 \\
b_5 \\
b_6 \\
b_7 \\
b_8
\end{bmatrix} = 0. \tag{119}
\]

When written in terms of the response probabilities becomes

\[
z_i = \ln \left( \frac{\bar{P}_i}{1 - \bar{P}_i} \right) = a_0 + b_1 x_i + b_2 y_i = a_0 + a_0 \cdot x_i - a_0 y_i \quad \tag{120}
\]

Using this assumption we may express \( x' \) through \( x'9 \) as
\[ x_1 = (x_1 - a_0) / -a_0(1 + \beta_1) \]

\[ x_2 = (x_2 - a_0) / -a_0(1 + \beta_1) \]

\[ x_3 = (x_3 - a_0) / -a_0(1 + \beta_1) \]

\[ x_4 = (x_1 - a_0) / -a_0(2) \]

\[ x_5 = (x_2 - a_0) / -a_0(2) \]

\[ x_6 = (x_3 - a_0) / -a_0(2) \]

\[ x_7 = (x_1 - a_0) / -a_0(2) \]

\[ x_8 = (x_2 - a_0) / -a_0(2) \]

\[ x_9 = (x_3 - a_0) / -a_0(2) \] (121)

These values of \( x_1 \) through \( x_9 \) are then substituted into Equation (117). Since we have made the assumption that \( P_1 = P_4 = P_7, \ P_2 = P_5 = P_8, \) and \( P_3 = P_6 = P_9, \) we make a similar statement about the number of test animals at each design point. That is, \( n_1 = n_4 = n_7, \ n_2 = n_5 = n_8, \) and \( n_3 = n_6 = n_9. \) This allows us to write

\[ \frac{3n_1 + 3n_2 + 3n_3}{N} = 1 \] (122)

where \( N \) is the total sample to be used in the experiment. Solving for \( n_3 \)
we have

\[ n_3 = \frac{N}{3} - n_1 - n_2 \]  
\[ \text{(123)} \]

We define the sample allocated to a design point as

\[ \omega_i = \frac{n_i}{N} \]  
\[ \text{(124)} \]

Making this substitution into Equation (123) allows us to write

\[ \omega_3 = \frac{1}{3} - \omega_1 - \omega_2 \]  
\[ \text{(125)} \]

The values of \( \omega_1, \omega_2 \) and \( \omega_3 = 1/3 - \omega_1 - \omega_2 \) are also substituted into Equation (117). A solution to Equation (117) expressed in terms of \( P_1, P_2, P_3, \omega_1, \) and \( \omega_2 \) may now be derived.

\[ \text{Cov}(A) = 27 \cdot (a_2 \cdot \beta_1 + a_1)^{18} \cdot (a_2 + a_1 \cdot \beta_1)^{18} \cdot (a_2 + a_1)^{18} / ((P_1 - 1)^3 \cdot (P_2 - 1)^3 \cdot (x_3 - x_2)^6 \]

\[ \cdot (z_2 - a_0)^6 \cdot (z_2 - z_1)^6 \cdot (z_2 - a_0)^6 \cdot (a_2^6 \cdot \beta_1^2 - 3a_2^4 \cdot a_1^2 \cdot \beta_1) \]

\[ -3 \cdot a_2^4 \cdot a_1^2 \cdot \beta_1^2 - 3a_2^4 \cdot a_1^2 \cdot \beta_1 - a_2^3 \cdot a_1^3 \cdot \beta_1^4 - 2a_2^3 \cdot a_1^3 \cdot \beta_1^4 - 10 \cdot a_2^3 \cdot \]

\[ a_1^2 \cdot \beta_1^2 - 2a_2^2 \cdot a_1^2 \cdot \beta_1 - a_2^3 \cdot a_1^3 \cdot \beta_1^2 - a_2^4 \cdot \beta_1^2 - 3a_2^2 \cdot \beta_1^2 - 3a_2^2 \cdot \]

\[ a_1^4 \cdot \beta_1 + a_1^4 \cdot \beta_1^2 \cdot (a_2^2 - a_2 \cdot a_1 + a_1^2)^2 \cdot (a_0 - Z_1)^6 \cdot (\beta_1 + 1)^6 \]

\[ (\beta_1 - 1)^{18} \cdot \beta_1^2 \cdot (P_3 - 1)^3 \cdot (3w_2 + 3w_1 - 1)^3 \cdot P_1^3 \cdot P_2^3 \cdot P_3^3 \cdot w_2^3 \cdot w_1^3 \]  
\[ \text{(126)} \]

where

\[ z_i = \log (\bar{P}_i / 1 - \bar{P}_i), \quad i = 1, 2, 3 \]  
\[ \text{(127)} \]
Equation (126) is then minimized with respect to $\beta_1, P_1, P_2, P_3, w_1,$ and $w_2$.

Note that the solutions change when the values of $a_0$ vary. Hence, for each different experiment, where the values of $a_0$ change, a new solution must be determined. Appendix D contains:

$$\frac{\delta}{\delta p_i} Cov(A), \frac{\delta}{\delta \beta_1} Cov(A), \text{ and } \frac{\delta}{\delta w_i} Cov(A).$$

In Appendix D we show that the optimal solution to the $\alpha_i$ is independent of $a_0$ and is equal to $1/9$.

**Results of Optimization**

Once the optimal solution for $\beta_1, P_1, P_2, P_3, w_1$ and $w_2$ for a given $a_0$ have been obtained then the values of $x_1'$ through $x_9'$ are obtained by substitution into the series of equations displayed in Equation (121). Consequently, the values of $y_1'$ through $y_9'$ are obtained using the optimal solution of $\beta_1$ and the slope relationships:

$$y_1' = \beta_1 x_1'$$
$$y_2' = \beta_1 x_2'$$
$$y_3' = \beta_1 x_3'$$
$$y_4' = x_4'$$
$$y_5' = x_5'$$
$$y_6' = x_6'$$
$$y_7' = x_7'/\beta_1$$
$$y_8' = x_8'/\beta_1$$
$$y_9' = x_9'/\beta_1.$$  \hspace{1cm} (128)

To transform from $x_i', y_i'$ to $x_i, y_i$ we use the relationships $x_i = (-a_0/a_1)x_i'$ and $y_i = (-a_0/a_2)y_i'$, resulting in the design points:

$$x_1 = (z_1-a_0)/(a_1 + a_1\beta_1)$$
$$y_1 = (z_1-a_0)/(a_2 + a_2/\beta_1)$$
\[
\begin{align*}
  x_2 &= \frac{z_2 - a_0}{a_1 + a_1 \beta_1} \\
  x_3 &= \frac{z_3 - a_0}{a_1 + a_1 \beta_1} \\
  x_4 &= \frac{z_1 - a_0}{2a_1} \\
  x_5 &= \frac{z_2 - a_0}{2a_1} \\
  x_6 &= \frac{z_3 - a_0}{2a_1} \\
  x_7 &= \frac{z_1 - a_0}{a_1 + a_1 \beta_1} \\
  x_8 &= \frac{z_2 - a_0}{a_1 + a_1 \beta_1} \\
  x_9 &= \frac{z_3 - a_0}{a_1 + a_1 \beta_1} \\
  y_2 &= \frac{z_2 - a_0}{a_2 + a_2 \beta_1} \\
  y_3 &= \frac{z_3 - a_0}{a_2 + a_2 \beta_1} \\
  y_4 &= \frac{z_1 - a_0}{2a_2} \\
  y_5 &= \frac{z_2 - a_0}{2a_2} \\
  y_6 &= \frac{z_3 - a_0}{2a_2} \\
  y_7 &= \frac{z_1 - a_0}{a_2 + a_2 \beta_1} \\
  y_8 &= \frac{z_2 - a_0}{a_2 + a_2 \beta_1} \\
  y_9 &= \frac{z_3 - a_0}{a_2 + a_2 \beta_1}
\end{align*}
\]

We found that the slope for the 3-ray design $\beta_1 = 0.01641995$ and the sample allocations $a_1...a_9 = 0.111111$ for all values of $a_0$, $a_1$, and $a_2$. The optimal probabilities $P_1$, $P_2$, and $P_3$ vary only with the intercept parameter $a_0$. These relationships are given in Table 5 and may be used for interpolation given a particular value for $a_0$. 

\(129\)
<table>
<thead>
<tr>
<th></th>
<th>a₀</th>
<th>P₁</th>
<th>P₂</th>
<th>P₃</th>
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<th>P₂</th>
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### Table 5

Optimal Values for the 3-way Design - cont'd.

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<th>$a_0$</th>
<th>$P_1$</th>
<th>$P_2$</th>
<th>$P_3$</th>
<th>$a_0$</th>
<th>$P_1$</th>
<th>$P_2$</th>
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CHAPTER III
EXPERIMENTAL DESIGN EXAMPLES AND EFFICIENCIES

Introduction

We will use a data set taken from the literature to illustrate the techniques in obtaining the 2x2, 2-ray, 3x3, and 3-ray optimal design points. The data are from an experiment (Finney (1971)) that examined the toxicity to frogs of digitalis and quinidine. Table 11 below displays the data and the parameter estimates resulting from fitting the model

\[
\ln \left( \frac{P_{ij}}{I - P_{ij}} \right) = \alpha_0 + \alpha_1 x_i + \alpha_2 y_j
\]

where \( x_i \) denotes the logarithm of the ith dose of digitalis and \( y_j \) denotes the logarithm of the jth dose of quindine. Note that the logarithm of each dose of drug was used since the model using untransformed doses resulted in a significant lack of fit (\( x^2 (7) = 21.36, p = .003 \)).

For the data set a point by point description of the procedures used to obtain the design points for each of the four design types will be given. Included will be all of the necessary equations with the required algebra.
Table 11

Digitalis and Quinidine Toxicity Data

<table>
<thead>
<tr>
<th>Dose (10^-3ml/q Body Wt.)</th>
<th>Dead/ Total</th>
<th>Dose (10^-2mg/q Body Wt.)</th>
<th>Dead/ Total</th>
<th>Parameter Estimates</th>
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<tr>
<td>8.0</td>
<td>1/17</td>
<td>10.0</td>
<td>0/26</td>
<td>α₁ = -12.878 (1.670)</td>
</tr>
<tr>
<td>9.4</td>
<td>1/19</td>
<td>15.0</td>
<td>2/24</td>
<td>α₂ = 4.998 (.656)</td>
</tr>
<tr>
<td>12.5</td>
<td>7/17</td>
<td>22.5</td>
<td>9/23</td>
<td>α₃ = 3.831 (.500)</td>
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<tr>
<td>15.6</td>
<td>13/17</td>
<td>33.7</td>
<td>17/24</td>
<td></td>
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<tr>
<td>19.5</td>
<td>16/17</td>
<td>50.5</td>
<td>20/26</td>
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</table>

Note: From "Probit Analysis" by D.J. Finney, 1971, pg. 251. Goodness of fit, x²(7) = 9.38, p = .23.

2x2 Factorial Design

Within Chapter II we noted that the derived D-optimal solution occurs at P₁₁ = .015818 and P₁₂ = .50, with equal allocation at all four points.

The estimating equations, equations (71) and (72) of Chapter II, for the design and the resulting estimates are:
\[ \log(x_1) = \frac{5}{a_1} \left[ \log\left( \frac{P_{11}}{1-P_{11}} \right) - a_0 \right] = \frac{5}{4.99835} \left[ \log\left( \frac{0.015818}{0.984182} \right) + 12.8782 \right] = 0.87504 \]

\[ \log(y_1) = \frac{5}{a_2} \left[ \log\left( \frac{P_{11}}{1-P_{11}} \right) - a_0 \right] = \frac{5}{3.83111} \left[ \log\left( \frac{0.015818}{0.984182} \right) + 12.8782 \right] = 1.1416 \]

\[ \log(x_2) = \left( \frac{1}{a_1} \right) \left[ \left( \log\left( \frac{P_{12}}{1-P_{12}} \right) - a_0 \right) - a_2 y_1 \right] = \]

\[ \frac{1}{4.99835} \left[ 12.8782 - 2.398(1.1416) \right] = 1.7015 \]

\[ \log(y_2) = \left( \frac{1}{a_2} \right) \left[ \left( \log\left( \frac{P_{12}}{1-P_{12}} \right) - a_0 \right) - a_1 x_1 \right] = \]

\[ \frac{1}{3.83111} \left[ 12.8782 - 4.99835(0.87504) \right] = 2.2198 \]

Taking antilogarithms results in:

\[ x_1 = 2.398 \quad y_1 = 5.4822 \]
\[ x_2 = 3.1318 \quad y_2 = 9.20 \]

2-Ray Design

Usually \( P_1, \ P_2, \) and \( T(K_1) \) will be estimated from Tables 2 and 3 of Chapter II. The resulting values in conjunction with \( B_1 = K_1 \cdot T(K_1) \) and \( B_2 = 1/B_1 \) will lead to a near D-optimal solution. How close this is to the D-optimal solution will be shown using the "exact" derived D-optimal solution values of \( P_1 = .218403 \) and \( P_2 = .858741, \) and \( T(K_1) = .129062. \) It should be noted that these latter three values were solved for by differentiating \( |\text{Cov}(A)| \) with respect to \( P_1, \) \( P_2, \) and \( T(K_1) \) and solving the resulting three equations by use of the
subroutine ZSPOW mentioned within Chapter II. The 2-ray design allocation is equal at all four points.

The result of interpolation from Table 2 is:

<table>
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<th>α₀</th>
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<th>P₂</th>
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<td>-12.75</td>
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<tr>
<td>-12.8782</td>
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<tr>
<td>-13.00</td>
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\[
P₁ = \frac{.218860}{.25} (\frac{1281}{.25}) (\frac{.218860 - .217977}{.218860 - .217977}) = .218407
\]

\[
P₂ = \frac{.859050}{.25} (\frac{1282}{.25}) (\frac{.859050 - .858454}{.859050 - .858454}) = .858744
\]

The result of interpolation from Table 3 is:

\[
K₂ = \frac{α₂}{α₁} \quad T(K₂) \quad K₁ = \frac{α₁}{α₂} \quad T(K₁) = K₂^2 \cdot T(K₂)
\]

<table>
<thead>
<tr>
<th>K₂</th>
<th>T(K₂)</th>
<th>K₁</th>
<th>T(K₁)</th>
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<td>.22128800</td>
<td>.76</td>
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<td>.7647493</td>
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<td>1.3046741</td>
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</tr>
<tr>
<td>.77</td>
<td>.21882100</td>
<td>.77</td>
<td>.21969063</td>
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</table>

\[
T(K₂) = .221288 - \left( \frac{.00647493}{.01} \right) (\frac{.221288 - .218821}{.221288 - .218821}) = .21969063
\]

\[
T(K₁) = (.7647493)^2 (.21969063) = .1290647
\]

\[\text{then, } B₁ = T(K₁)K₁ = .168384 \text{ and } B₂ = \frac{1}{B₁} = 5.93381\]

will be the slopes for the rays employed.

These values are accurate to five places and their use should not place our design points far from the "exact" D-optimal points.
We will next explore the practical effects of estimating $P_1$ and $P_2$ through $a_0$ and $B_1 = T(K_1)$ where $K_1 = (a_1/a_2)$. The first calculations use rearrangements of equations (86) and (87) of Chapter II with our "exact" values of $P_1, P_2,$ and $T(K_1)$.

\[
\log(x_1) = (z_1 - a_0)/(a_1 + a_2 B_1) \\
= \left[ \log\left(\frac{.218403}{.781597}\right) + 12.8782 \right] / (4.99833 + 3.83111 \times 1.68384) \\
= 2.0560
\]

\[
\log(x_2) = (z_2 - a_0)/(a_1 + a_2 B_1) \\
= \left[ \log\left(\frac{.858741}{.141259}\right) + 12.8782 \right] / (4.99833 + 3.83111 \times 1.68384) \\
= 2.6018
\]

\[
\log(x_3) = (z_3 - a_0)/(a_1 + a_2 B_1) \\
= \left[ \log\left(\frac{.218403}{.781597}\right) + 12.8782 \right] / (4.99833 + 3.83111 \times 1.68384) \\
= .41812
\]

\[
\log(x_4) = (z_4 - a_0)/(a_1 + a_2 B_1) \\
= \left[ \log\left(\frac{.858741}{.141259}\right) + 12.8782 \right] / (4.99833 + 3.83111 \times 1.68384) \\
= .52911
\]

\[
\log(y_1) = B_1(z_1 - a_0)/(a_1 + a_2 B_1) \\
= .168384 \left[ \log\left(\frac{.218403}{.781597}\right) + 12.8782 \right] / (4.99833 + 3.83111 \times 1.68384) \\
= .34620
\]
\[
\log(y_2) = B_1(z_2 - a_0)/(a_1 + a_2 B_1) \\
= .168384 \left[ \frac{0.858741}{1.41259} + 12.8782 \right] / (4.99833 + 3.83111x.168384) \\
= .43810 \\
\log(y_3) = (z_1 - a_0)/(a_2 + a_1 B_1) \\
= \left[ \log\left( \frac{0.218403}{0.781597} \right) + 12.8782 \right] / (3.83111 + 4.99833x.168384) \\
= 2.4832 \\
\log(y_4) = (z_2 - a_0)/(a_2 + a_1 B_1) \\
= \left[ \log\left( \frac{0.858741}{1.41259} \right) + 12.8782 \right] / (3.83111 + 4.99835x.168384) \\
= 3.1423 \\
\]

Taking antilogarithms we have the design points:

<table>
<thead>
<tr>
<th>( x_1 )</th>
<th>( y_1 )</th>
<th>( x_2 )</th>
<th>( y_2 )</th>
<th>( x_3 )</th>
<th>( y_3 )</th>
<th>( x_4 )</th>
<th>( y_4 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.8150</td>
<td>1.4137</td>
<td>13.488</td>
<td>1.5497</td>
<td>1.5191</td>
<td>11.979</td>
<td>1.6974</td>
<td>23.157</td>
</tr>
</tbody>
</table>

If we were to repeat the above exercise using the \( a_0 \) interpolated values of \( P_1 = .218407 \), \( P_2 = .858741 \), and \( T(K_1) = .1290647 \) our solutions would result in the following design points:

<table>
<thead>
<tr>
<th>( \log(x_1) )</th>
<th>( \log(y_1) )</th>
<th>( \log(x_2) )</th>
<th>( \log(y_2) )</th>
<th>( \log(x_3) )</th>
<th>( \log(y_3) )</th>
<th>( \log(x_4) )</th>
<th>( \log(y_4) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0560</td>
<td>.34625</td>
<td>2.6018</td>
<td>.43811</td>
<td>.41813</td>
<td>2.4831</td>
<td>.52912</td>
<td>3.1423</td>
</tr>
</tbody>
</table>
the nearly identical values as when using the "exact" values for $P_1$, $P_2$, and $T(K_1)$. Subsequently we have the same design points after taking antilogarithms.

**3x3 Factorial Design**

Within Chapter II the derived D-optimal solution was shown to occur at $P_{12} = .0104758$ and $P_{22} = .50$ with equal allocation to all nine points. The $P_{ij}$ values were solved for by differentiating $|\text{Cov}(A)|$ with respect to $P_{12}$ and $P_{22}$ and solving these two equations by use of the subroutine ZSPOW mentioned earlier.

Our estimating equations for this design are reiterated:

$$\log(x_2) = \frac{.5}{a_1} \left[ \ln \left( \frac{p_{22}}{1-p_{22}} \right) - a_0 \right] = \frac{.5}{4.99835} \left[ 12.8782 \right] = 1.2882$$

$$\log(y_2) = \frac{.5}{a_2} \left[ \ln \left( \frac{p_{22}}{1-p_{22}} \right) - a_9 \right] = \frac{.5}{3.83111} \left[ 12.8782 \right] = 1.6807$$

$$\Delta x = \left[ \ln \left( \frac{p_{22}}{1-p_{22}} \right) - \ln \left( \frac{p_{12}}{1-p_{12}} \right) \right] / a_1 = \left[ -\ln \left( \frac{.0104758}{.9895242} \right) \right] / 4.99835 = .90993$$

$$\Delta y = \left[ \ln \left( \frac{p_{22}}{1-p_{22}} \right) - \ln \left( \frac{p_{12}}{1-p_{12}} \right) \right] / a_2 = \left[ -\ln \left( \frac{.0104758}{.9895242} \right) \right] / 3.83111 = 1.1872$$

$$\log(x_1) = \log(x_2) - \Delta x = .37827$$

$$\log(x_3) = \log(x_2) + \Delta x = 2.1981$$

$$\log(y_1) = \log(y_2) - \Delta y = .49350$$

$$\log(y_3) = \log(y_2) + \Delta y = 2.8679, $$

taking antilogarithms we get:

$$x_1 = 1.4597 \quad y_1 = 1.6380$$

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We will estimate $P_1$, $P_2$, and $P_3$ using $a_0$ and Table 5 of Chapter II. The resulting values with $B_1 = .057765$ will be used to develop the near D-optimal solution. How close these points are to the true D-optimal solution will be investigated using the "exact" derived values of $P_1 = .093548$, $P_2 = .647284$, and $P_3 = .985973$. These values were derived in the usual manner by differentiating |Cov(A)| with respect to $P_1$, $P_2$, and $P_3$ and solving the resulting equations by use of the subroutine ZSPOW. Again this design must have equal allocation among the nine points to achieve optimality.

Our first points are computed using the "exact" D-optimal values of $P_1$, $P_2$, and $P_3$:

$$\log(x_1) = \left( \log \left( \frac{P_1}{1-P_1} \right) - a_0 \right) / (a_1 + a_1 B_1)$$

$$= \left( \log \left( \frac{.093548}{.906452} \right) + 12.8782 \right) / (4.99835(1.057765))$$

$$= 2.0062$$

$$\log(x_2) = \left( \log \left( \frac{P_2}{1-P_2} \right) - a_0 \right) / (a_1 + a_1 B_1)$$

$$= \left( \log \left( \frac{.647284}{.352716} \right) + 12.8782 \right) / (4.99835(1.057765))$$
\[ log(x_3) = \left( \log\left( \frac{P_3}{1-P_3} \right) - a_0 \right)/(a_1 + a_1 B_1) \]

\[ = \left( \log\left( \frac{.985973}{.014027} \right) + 12.8782 \right)/(4.99835(1.057765)) \]

\[ = 2.5506 \]

\[ log(x_4) = \left( \log\left( \frac{P_4}{1-P_4} \right) - a_0 \right)/(2a_1) \]

\[ = \left( \log\left( \frac{.093548}{.906452} \right) + 12.8782 \right)/(2(4.99835)) \]

\[ = 3.2401 \]

\[ log(x_5) = \left( \log\left( \frac{P_5}{1-P_5} \right) - a_0 \right)/(2a_1) \]

\[ = \left( \log\left( \frac{.547284}{.352716} \right) + 12.8782 \right)/(2(4.99835)) \]

\[ = 1.0611 \]

\[ log(x_6) = \left( \log\left( \frac{P_6}{1-P_6} \right) - a_0 \right)/(2a_1) \]

\[ = \left( \log\left( \frac{.985973}{.014027} \right) + 12.8782 \right)/(2(4.99835)) \]

\[ = 1.3490 \]
\[ = 1.7136 \]

\[ \log(x_1) = \left( \log \left( \frac{P_1}{1-P_1} \right) - a_0 \right) / (a_1 + a_1/B_1) \]

\[ = \left( \log \left( \frac{.093548}{.906452} \right) + 12.8782 \right) / (4.99835(1 + \frac{1}{.057765})) \]

\[ = .11589 \]

\[ \log(x_2) = \left( \log \left( \frac{P_2}{1-P_2} \right) - a_0 \right) / (a_2 + a_2/B_2) \]

\[ = \left( \log \left( \frac{.647284}{.352716} \right) + 12.8782 \right) / (4.99835(1 + \frac{1}{.057765})) \]

\[ = .14734 \]

\[ \log(x_3) = \left( \log \left( \frac{P_3}{1-P_3} \right) - a_0 \right) / (a_3 + a_3/B_3) \]

\[ = \left( \log \left( \frac{.985973}{.014027} \right) + 12.8782 \right) / (4.99835(1 + \frac{1}{.057765})) \]

\[ = .187171 \]

\[ \log(y_1) = \left( \log \left( \frac{P_1}{1-P_1} \right) - a_0 \right) / (a_2 + a_2/B_2) \]

\[ = \left( \log \left( \frac{.093548}{.906452} \right) + 12.8782 \right) / (3.83111(1 + \frac{1}{.057765})) \]
\[
\log(y_2) = \left( \log\left( \frac{P_2}{1-P_2} \right) - a_0 \right) / (a_2 + a_2/B_1) \\
= \left( \log\left( \frac{.647284}{.352716} \right) + 12.8782 \right) \left( 3.83111 \left( 1 + \frac{1}{.057765} \right) \right) \\
= .15120
\]

\[
\log(y_3) = \left( \log\left( \frac{P_3}{1-P_3} \right) - a_0 \right) / (a_2 + a_2/B_1) \\
= \left( \log\left( \frac{.985973}{.014027} \right) + 12.8782 \right) \left( 3.83111 \left( 1 + \frac{1}{.057765} \right) \right) \\
= .19223
\]

\[
\log(y_4) = \left( \log\left( \frac{P_1}{1-P_1} \right) - a_0 \right) / (2a_2) \\
= \left( \log\left( \frac{.093548}{.906452} \right) + 12.8782 \right) / (2 \times 3.83111) \\
= 1.3843
\]

\[
\log(y_5) = \left( \log\left( \frac{P_2}{1-P_2} \right) - a_0 \right) / (2a_2)
\]
\[
log(y_6) = (\log\left(\frac{P_3}{1-P_3}\right) - a_0)/(2a_2)
\]

\[
= (\log\left(\frac{.985973}{.014027}\right) + 12.8782)/(2 \times 3.83111)
\]

\[
= 2.2357
\]

\[
log(y_7) = (\log\left(\frac{P_1}{1-P_1}\right) - a_0)/(a_2 + a_2B_1)
\]

\[
= (\log\left(\frac{.903548}{.906452}\right) + 12.8782)/(3.83111(1.057765))
\]

\[
= 2.6175
\]

\[
log(y_8) = (\log\left(\frac{P_2}{1-P_2}\right) - a_0)/(a_2 + a_2B_1)
\]

\[
= (\log\left(\frac{.647284}{.352716}\right) + 12.8782)/(3.83111(1.057765))
\]

\[
= 3.3277
\]

\[
log(y_9) = (\log\left(\frac{P_3}{1-P_3}\right) - a_0)/(a_2 + a_2B_1)
\]
\[
= \left( \log \left( \frac{0.985973}{0.614027} \right) + 12.8782 \right) / (3.83111(1.057765))
\]

= 4.2273

Taking antilogarithms we have:

\[x_1 = 7.4350 \quad y_1 = 1.1632\]
\[x_2 = 12.815 \quad y_2 = 1.2119\]
\[x_3 = 25.536 \quad y_3 = 1.2766\]
\[x_4 = 2.8895 \quad y_4 = 3.9920\]
\[x_5 = 3.8536 \quad y_5 = 5.8124\]
\[x_6 = 5.5489 \quad y_6 = 9.3530\]
\[x_7 = 1.1229 \quad y_7 = 13.701\]
\[x_8 = 1.1587 \quad y_8 = 27.874\]
\[x_9 = 1.2058 \quad y_9 = 68.532\]

Normally \(P_1\), \(P_2\), and \(P_3\) will be obtained by interpolation from Tables 5 of Chapter II using \(a_0 = -12.8782\).

The results of interpolation are:

\[
\begin{align*}
\alpha_0 & \quad P_1 & \quad P_2 & \quad P_3 \\
-12.75 & \quad .094827 & \quad .648585 & \quad .986100 \\
-12.8782 & \quad .093821 & \quad .647294 & \quad .985973 \\
-13.00 & \quad .092866 & \quad .646068 & \quad .985853
\end{align*}
\]

\[P_1 = .094827 - \left( \frac{.1282}{.25} \right)(.094827 - .092866) = .093821\]

\[P_2 = .648585 - \left( \frac{.1282}{.25} \right)(.648585 - .646068) = .647294\]

\[P_3 = .986100 - \left( \frac{.1282}{.25} \right)(.986100 - .985853) = .985973\]

We note that these values are to within three or more places of the "exact" D-optimal values of \(P_1\), \(P_2\), and \(P_3\).
If we were to use our interpolated values for $P_1$, $P_2$, and $P_3$ our solutions would result in the following design points:

\[
\begin{align*}
\log(x_1) &= 2.0068 & \log(y_1) &= .15129 \\
\log(x_2) &= 2.5506 & \log(y_2) &= .19223 \\
\log(x_3) &= 3.2401 & \log(y_3) &= .24419 \\
\log(x_4) &= 1.0614 & \log(y_4) &= 1.3848 \\
\log(x_5) &= 1.3490 & \log(y_5) &= 1.7600 \\
\log(x_6) &= 1.7136 & \log(y_6) &= 2.2357 \\
\log(x_7) &= .11592 & \log(y_7) &= 2.6183 \\
\log(x_8) &= .14734 & \log(y_8) &= 3.3277 \\
\log(x_9) &= .18717 & \log(y_9) &= 4.2273
\end{align*}
\]

With the exception of $\log(y_7)$ which is accurate to three places these values are accurate to four or more places. Taking antilogarithms results in:

\[
\begin{align*}
x_1 &= 7.4395 & y_1 &= 1.1633 \\
x_2 &= 12.815 & y_2 &= 1.2119 \\
x_3 &= 25.536 & y_3 &= 1.2766 \\
x_4 &= 2.8904 & y_4 &= 3.9940 \\
x_5 &= 3.8536 & y_5 &= 5.8124 \\
x_6 &= 5.5489 & y_6 &= 9.3530 \\
x_7 &= 1.1229 & y_7 &= 13.712 \\
x_8 &= 1.1587 & y_8 &= 27.874 \\
x_9 &= 1.2058 & y_9 &= 68.532
\end{align*}
\]

Notice that as compared to the x’s and y’s using the "exact" solution these values are to at least three places accuracy and from a practical view are similar. The points of the 2x2, 3x3, 2-ray, and 3-ray designs are presented in Figures 13-16.
Figure 13. The Estimated Design Points for the 2x2 Design.
Figure 14. The Estimated Design Points for the 3x3 Design.
Figure 15. The Estimated Design Points for the 2-Ray Design.
Figure 16. The Estimated Design Points for the 3-Ray Design.
Interaction Quantification

The designs presented within Chapter II provide an investigator with the initial points to begin a study of drug interaction. Since the only available information is for each drug used singly the designs were necessarily constructed under the single requirement of no interaction.

We would like to investigate how these designs fare when in fact the drug combination study does produce an interaction (antagonism or potentiation). In order to investigate these non-null efficiencies, an analytical quantification of interaction is necessary.

Four Point Designs

The full rank linear model used in constructing our designs is given as

$$z(x_i, y_j) = \ln \left( \frac{P(x_i, y_j)}{1 - P(x_i, y_j)} \right) = a_0 + a_1 x_i + a_2 y_j + a_3 x_i y_j \quad (i=1, 2; j=1, 2) \quad (130)$$

where $x_i$ is the dose of Drug 1, $y_j$ is the dose of Drug 2 and $P(x_i, y_j)$ denotes the probability of responding in the $(i,j)$ experimental group.

Under the null hypothesis assumption $H_0: \alpha_3 = 0$ we have designed experiments with the determinant of the parameter variance-covariance matrix given by

$$\left| \text{Cov}(A)_{H_0} \right| = \frac{|V_{H_0}|}{|X_{H_0}|^2} \text{ a minimum.} \quad (131)$$

In the case of interaction the alternative hypothesis $H_a: \alpha_3 \neq 0$ pertains and the determinant of the parameter variance-covariance matrix is given by...
\[
\left| \text{Cov}(A)_{\text{Ha}} \right| = \frac{|V_{\text{Ha}}|}{|X_{\text{Ha}}|^2}.
\]

The efficiency, \( E \), of the proposed designs, given in percent, when the alternative hypothesis holds is

\[
100 \left( \frac{|\text{Cov}(A)_{\text{Ha}}|}{|\text{Cov}(A)_{\text{Ho}}|} \right) = 100 \left( \frac{|V_{\text{Ho}}|}{|X_{\text{Ho}}|} \frac{|X_{\text{Ha}}|^2}{|V_{\text{Ha}}|} \right).
\]

Since our evaluations will be made at \( X_{\text{Ha}} = X_{\text{Ho}} \) (i.e. The same design points are used in both \( \text{Ho} \) and \( \text{Ha} \)) we have

\[
E = 100 \left( \frac{|V_{\text{Ho}}|}{|V_{\text{Ha}}|} \right).
\]

What is needed is a vehicle for quantifying \( \alpha_3 \) when the alternative hypothesis holds. Then, \( |V_{\text{Ha}}| \) may be obtained for use in the efficiency evaluations.

Let \((X,5)/2 \) and \((Y,5)/2 \) denote one-half the \( \text{LD}_{50} \) dose of Drug 1 and Drug 2, respectively. These values are given by \((-a_0/2a_1)\) and \((-a_0/2a_2)\), respectively. If the null hypothesis \( \alpha_3 = 0 \) pertains we have

\[
z((x,5)/2, (y,5)/2) = a_0 + a_1 (-a_0/2a_1) + a_2 (-a_0/2a_2)
\]

\[
= a_0 - a_0/2 - a_0/2 = 0,
\]
implying that the probability of responding to doses \((x, y)/2\) of Drug 1 and 
\((x, y)/2\) of Drug 2 which is expressed as 
\[ P((x, y)/2, (y, y)/2) = 0.5 \]
If the alternative hypothesis \(a_3 \neq 0\) pertains we have

\[
z((x, y)/2, (y, y)/2) = a_0 + a_1(-a_y/2a_1) + a_2(-a_y/2a_2) + a_3(-a_y/2a_1)(-a_y/2a_2)
\]

\[
= a_0 - a_y/2 - a_y/2 + \frac{a_3a_0^2}{4a_1a_2}
\]

\[
= a_3a_0^2/4a_1a_2
\]

implying that 
\[ P((x, y)/2, (y, y)/2) \neq 0.5 \]
Allowing 
\[ P((x, y)/2, (y, y)/2) \]
to vary, say 
\[ .05, .95(.05) \] results in 
\[
\frac{4a_1a_2z((x, y)/2, (y, y)/2)}{a_0^2}
\]

derived from equation (136).

For each \(a_3\) we can construct the probability of responding at the design points for use in obtaining the \(|V_{Ha}|\) used in calculating the efficiencies under the alternative hypothesis.

**Nine Point Designs**

The full rank linear model used in our designs is given as

\[
z(x, y) = \ln\left( \frac{P(x, y)}{1 - P(x, y)} \right) = a_0 + a_1x_i + a_2y_j + a_3x_iy_j + a_4x_i^2 + a_5y_j^2
\]

\[
+ a_6x_iy_j^2 + a_7x_i^2y_j + a_8x_iy_j^2 (i=1,2,3; j=1,2,3)
\]

(138)
The $x_i, y_j$ and $P(x_i, y_j)$ are as defined for the four point designs.

Under the hypothesis $H_0$:

$$\begin{bmatrix}
\alpha_3 \\
\alpha_4 \\
\alpha_5 \\
\alpha_6 \\
\alpha_7 \\
\alpha_8
\end{bmatrix} = 0,$$

we have designed experiments with the determinant of the parameter variance-covariance matrix, given by

$$|\text{Cov}(A)|_{H_0} = \frac{|V_{H_0}|}{|X_{H_0}|^2}, \text{ a minimum.} \tag{139}$$

In considering the case of interaction we will assume that the simple model given by

$$z(x_i, y_j) = \ln\left(\frac{P(x_i, y_j)}{1 - P(x_i, y_j)}\right) = a_0 + a_1 x_i + a_2 y_j + a_3 x_i y_j \quad (i=1,2,3; j=1,2,3) \tag{140}$$

describes the data. In this way we may calculate our alternative hypothesis efficiencies,

$$E = 100\left(\frac{|V_{H_0}|}{|V_{H_1}|}\right), \tag{141}$$

for the nine point designs in a manner similar to that used for the four point designs.
Four Point Design Efficiencies Under The Alternative Hypothesis

The designs have 100% efficiency when $P((x,s)/2, (y.s)/2) = .5$ (i.e.: $\alpha_3 = 0$). For values of $P_{Ha} = P((x.s)/2, (y.s)/2) \neq .5$ the design efficiencies will vary. That is, when the dose levels $(x.s)/2$ and $(y.s)/2$ produce probabilities of response that differ from .5 we have interaction ($\alpha_3 \neq 0$).

Table 12 contains the 2x2 and 2-ray design efficiencies for the data set introduced in Table 11. It appears that the 2x2 design is excellent (greater than or equal to 100% efficiency for cases where we expect antagonism ($P_{Ha}$: from .20 to .50). If we have small amounts of potentiation ($P_{Ha}$: from .50 to .55) we have approximately a 30% efficiency or greater. The 2-ray design also has efficiencies greater than or equal to 100% when antagonism exists ($P_{Ha}$: from .20 to .50), although not as great as for the 2x2 design. The 2-ray design also appears to have greater efficiencies than the 2x2 design when moderate potentiation exists. In the range of $P_{Ha}$: from .50 to .60 the 2-ray design has approximately a 30% or greater efficiency.

To investigate further the efficiencies of the 2x2 design we varied $\alpha_0$ over a wide range (-4.25, -10.375, -15, -20.0 and -25.000) and computed the efficiencies for $P_{Ha}$: of .05 to .95 as found in Table 13. Similarly, we varied $\alpha_0$ over the same range for the 2-ray design with the additional parameter $K_1 = \alpha_1/\alpha_2$ varying as .015 (66.67), .15 (6.67), 1.0, 1.5 (.67), and 15 (.067) in Tables 14 to 18. Note that the 2-ray design described in Chapter II uses the parameter $K_1 = \alpha_1/\alpha_2$ to specify the location of the rays.

In general for $\alpha_0 \geq -20.00$ the 2x2 design has greater efficiencies with antagonism ($P_{Ha}$: from .15 to .50) than does the 2-ray design. At low $\alpha_0$
<table>
<thead>
<tr>
<th>PHa:</th>
<th>α3</th>
<th>2x2 Efficiency (%)</th>
<th>2-ray Efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>.05</td>
<td>-1.3599</td>
<td>20.4</td>
<td>70.5</td>
</tr>
<tr>
<td>.10</td>
<td>-1.0148</td>
<td>107.2</td>
<td>111.5</td>
</tr>
<tr>
<td>.15</td>
<td>- .80112</td>
<td>181.7</td>
<td>129.6</td>
</tr>
<tr>
<td>.20</td>
<td>- .64026</td>
<td>215.0</td>
<td>135.9</td>
</tr>
<tr>
<td>.25</td>
<td>- .50739</td>
<td>218.0</td>
<td>135.7</td>
</tr>
<tr>
<td>.30</td>
<td>- .39132</td>
<td>203.6</td>
<td>131.8</td>
</tr>
<tr>
<td>.35</td>
<td>- .28590</td>
<td>180.3</td>
<td>125.5</td>
</tr>
<tr>
<td>.40</td>
<td>- .18726</td>
<td>153.3</td>
<td>117.9</td>
</tr>
<tr>
<td>.45</td>
<td>- .092679</td>
<td>126.0</td>
<td>109.2</td>
</tr>
<tr>
<td>.50</td>
<td>0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>.55</td>
<td>.092679</td>
<td>76.5</td>
<td>90.3</td>
</tr>
<tr>
<td>.60</td>
<td>.18726</td>
<td>56.2</td>
<td>80.4</td>
</tr>
<tr>
<td>.65</td>
<td>.28590</td>
<td>39.2</td>
<td>70.3</td>
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<td>25.7</td>
<td>60.0</td>
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<tr>
<td>.75</td>
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<td>49.6</td>
</tr>
<tr>
<td>.80</td>
<td>.64026</td>
<td>8.2</td>
<td>39.1</td>
</tr>
<tr>
<td>.85</td>
<td>.80112</td>
<td>3.5</td>
<td>28.5</td>
</tr>
<tr>
<td>.90</td>
<td>1.0148</td>
<td>1.1</td>
<td>17.9</td>
</tr>
</tbody>
</table>
Table 13

2x2 Efficiencies (%)

<table>
<thead>
<tr>
<th>$P_{Ha}$</th>
<th>$a_0 = -4.25$</th>
<th>$a_0 = -15.00$</th>
<th>$a_0 = -10.375$</th>
<th>$a_0 = -20.00$</th>
<th>$a_0 = -25.00$</th>
</tr>
</thead>
<tbody>
<tr>
<td>.05</td>
<td>4.2</td>
<td>16.9</td>
<td>25.3</td>
<td>26.0</td>
<td>8.8</td>
</tr>
<tr>
<td>.10</td>
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Table 15

2-Ray Efficiencies (%)

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Table 17

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Table 18

2-Ray Efficiencies (%)

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\[ K_1 = \alpha_1/\alpha_2 \]

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When potentiation exists ($P_{Ha}: > .5$) the 2-ray design has larger efficiencies than the $2x2$ design for all levels of $\alpha_0$. In fact, the 2-ray efficiencies with potentiation are quite invariant to the $K_1 = \alpha_1/\alpha_2$ levels. These results are depicted within Figures 17 to 26.

**Nine Point Design Efficiencies Under The Alternative Hypothesis**

These designs have 100% efficiency under $H_0$: (i.e. $P(x,.5/2, y,.5/2) = .5$ with $\alpha_3 = 0$). For values of $P(x,.5/2, y,.5/2) \neq .5$ the design efficiencies will vary as in the case of the four point designs discussed in the previous section. Table 19 contains the $3x3$ and 3-ray design efficiencies for the data set given in Table 11. The $3x3$ design is exceedingly efficient (much greater than 100% efficiency) for cases where we expect antagonism ($P_{Ha}:$ from .30 to .50). We note that these increased efficiencies may drop off abruptly for antagonisms related to $P_{Ha}: < .30$, particularly when the intercept $\alpha_0$, is $\geq -4.5$. The 3-ray design efficiencies are also much greater than 100% for antagonisms related to $P_{Ha}:$ values in the range of .20 to .50. The drop in efficiency for antagonisms associated with $P_{Ha}: < .20$ is not as severe as that seen with the $3x3$ design. When potentiation exists ($P_{Ha}: > .50$) the $3x3$ design has little if any efficiency when the intercept $\alpha_0$, is $\geq -4.5$. For values of $\alpha_0 < -4.5$ and moderate potentiation ($P_{Ha}: = .55$) the $3x3$ design efficiency is still very low, but greater than zero. The 3-ray design efficiency is much better than the $3x3$ design efficiency when potentiation exists. For values of the intercept $\alpha_0 < -4.5$ we have
Figure 17. The Efficiency of the 2x2 Factorial Design in the Presence of Potentiation.
Figure 18. The Efficiency of the Presence of Antagonism.

Efficiency of Design

-25.000  -10.375  -4.250

Alternate P Less Than .5

Intercept

-35.000

-10.375

-4.250

-25.000

-40.250

-35.000

-30.000

-25.000

-20.000

-15.000

-10.000

-5.000

0.0

0.1

0.2

0.3

0.4

0.5

100  200  300  400  500  600  700  800  900  1000  1100  1200  1300  1400  1500  1600
Figure 19. 2-Ray Efficiencies for K1 = .015 (66.67) in the Presence of Potentiation.
Figure 20. 2-Ray Efficiencies for $K_1 = .15 \ (6.67)$ in the Presence of Potentiation.
Figure 21. 2-Ray Efficiencies for K1 = 1.5 (.67) in the Presence of Potentiation.
Figure 22. 2-Ray Efficiencies for K1 = 15 (.067) in the Presence of Potentiation.
Figure 23. 2-Ray Efficiencies for $K_1 = .015 (66.67)$ in the Presence of Antagonism.
Figure 24. 2-Ray Efficiencies for K1 = .15 (6.67) in the Presence of Antagonism.
Figure 25. 2-Ray Efficiencies for $K_1 = 1.5 (.67)$ in the Presence of Antagonism.
Figure 26. 2-Ray Efficiencies for K1 = 15 (.067) in the Presence of Antagonism.
Table 19
Nine Point Design Efficiency

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<th>3-ray Efficiency (%)</th>
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acceptable efficiencies (10%-52%) for levels of potentiation associated with $p_{Ha}$ values of .55 to .60.

To investigate further the efficiencies of both the 3x3 and 3-ray designs we varied the intercept parameter $a_0$ over a wide range (-4.25, -10.375, -15.0, -20.0, and -25.0) and computed the efficiencies for $p_{Ha}$ from .05 to .95 found in Table 20. In general for all $a_0$ the 3x3 design has greater efficiencies with antagonism ($p_{Ha}$ from .15 to .50) than does the 3-ray design. When potentiation exists ($p_{Ha} > .5$) the 3-ray design has larger efficiencies than the 3x3 design for all levels of $a_0$. These results are depicted in Figures 27 to 30.

Summary

Typically within an animal toxicology study the response of interest is the probability of death, while in human cancer trials the response of interest is usually the probability of living. In both arenas the drug interaction study is designed to test whether the combination of agents acts to potentiate or increase the probabilities of interest, above that which is expected if the drugs behaved in an additive and non-interactive manner. This then, causes us to be particularly interested in the behavior of the experimental design plans when $p_{Ha} > .5$ (potentiation).

For the four point designs (2x2 Factorial and 2-ray) we have seen that for all of the intercept levels investigated ($a_0 = -4.25, -10.375, -15.00, -20.00, and -25.00$), that the ray designs have greater efficiencies than the factorial designs under the alternative hypothesis of potentiation. This finding also holds for the nine point designs (3x3 Factorial and 3-ray) over the same levels of the intercept $a_0$. 

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Table 20
3x3 and 3-RAY DESIGN EFFICIENCIES

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<th>3-ray (%)</th>
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<th>3-ray (%)</th>
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Figure 27. The Efficiency of the 3x3 Factorial Design in the Presence of Potentiation.
Figure 28. The Efficiency of the 3x3 Factorial Design in the Presence of Antagonism.
Figure 29. The Efficiency of the 3-Ray Design in the Presence of Potentiation.
Figure 30. The Efficiency of the 3-Ray Design in the Presence of Antagonism.
An additional benefit of the 2-ray and 3-ray designs is that the "optimal" slopes of the rays are independent of the optimal values of P to be used. Then, if the optimal values of P render dosages (x_i, y_j) which are in some way not acceptable, the experiment may still be run using the optimal slopes, but changing the values of P away from the optimal. This would result in a quasi-optimal design, but most likely one that is better than a design with no optimality considerations at all.
CHAPTER IV

TESTS OF HYPOTHESES IN LOGISTIC REGRESSION

Introduction

Once we have designed an experiment to test for potentiation or antagonism of two chemicals and collected the data, we will perform a statistical analysis. There are several methods available for analyzing such data and we will describe several of these.

For this chapter we will assume that each drug is administered at two different levels so there are four different ways of combining the drugs in a two-drug combination. The response variable in this experiment will be dichotomous; the animal is alive or dead after a specified amount of time. As stated in an earlier chapter, modeling the dependence of the binary response probabilities on the explanatory variables using the logistic transform and then testing for interaction between these explanatory variables will provide a test of potentiation or synergism between the chemicals.

We will denote the binary dependent variable by $s_{kc}$ and the explanatory variables by $x_i$ and $y_j$ where $i = 1, 2; j = 1, 2; k_c = 1, 2, \ldots, n_c$. The number of animals in each $i,j$ combination is denoted $n_c$; $c = 1, 2, 3, 4$ and $n = n_1 + n_2 + n_3 + n_4$. The explanatory variables are the dose of chemical one, $x_i$, and the dose of chemical two, $y_j$, used in the chemical combination. Denote the Pr ($S_{kc} = 1$) by $P_{kc}$. We will model the $P_{kc}$ as
Suppose that in the $c$th group the probability of success is constant and equal to $P_c$. Let $r_c$ denote the number of deaths in that group containing $n_c$ animals. Recall that $P_c = r_c/n_c$. We call

$$Z_c = \log \left[ \frac{P_c}{1-P_c} \right]$$

(143)

the logistic transform of $P_c$. Again, we wish to make inferences about the parameter $\beta_3$.

We will focus on three methods that are available that will allow us to make inferences concerning $\beta_3$: ordinary least squares, weighed least squares or minimum $\chi^2$, maximum likelihood, and an exact analysis.

**Least Squares Estimation**

One simple method to analyze data of this sort is to assume that

$$z_c = \beta_0 + \beta_1 x_i + \beta_2 y_j + \beta_3 x_i y_j$$

(144)

where $(x_i, y_j)$ are known constants and $\beta_0$, $\beta_1$, $\beta_2$, and $\beta_3$ are unknown constants. This can be written in matrix notation as

$$Z = X\beta$$

(145)

If we treat the dichotomous observations as if they were quantitative observations, we may then apply the method of least squares.
in the usual way. That is, the least squares estimates \( \beta \) of \( \beta \) satisfy

\[
(X'X)\beta = X'Z
\]  

(146)

However, this method has some serious limitations. As shown earlier, for large \( n \)

\[
\text{var}(z_c) = \frac{1}{n_c (P_c P_c) (1-P_c)}.
\]  

(147)

Therefore, the condition of constant variance required for the theory of least squares does not apply. However, Cox (1970) observes that for \( .2 < P_c < .8 \), the function \( P_c (1-P_c) \) changes relatively little and so there is unlikely to be a serious loss of efficacy when using this analysis.

When the \( P_c (1-P_c) \) vary appreciably, the use of least squares may result in a serious loss of information. An alternative analysis may be to use a weighted least squares analysis using \( [n_c P_c (1-P_c)] \) as weights. Berkson (1955) termed this the minimum \( \chi^2 \) statistic which minimizes

\[
\sum_c W_c (z_c - z_c)^2
\]  

(148)

Recall \( z_c \) is the linear transform in terms of \( \beta_0, \beta_1, \beta_2, \) and \( \beta_3 \) and \( 1/W_c \) is any consistent estimate of the variance of \( z_c \).

For example

\[
W_c = n_c P_c (1-P_c)
\]  

(149)

\[
z_c = \ell n \left( \frac{P_c}{1-P_c} \right)
\]  

(150)
In most cases, especially with the nonlinear term $\beta_3 x_i y_j$, an iterative procedure is required to provide estimates in the minimization of Equation (148). The minimum $x^2$ method is motivated by a Taylor series expansion of $z_c$ around $P_c$. That is,

$$z_c = X'_c \beta + u_c$$

(152)

where

$$u_c = (P_c - P_e)/(P_c(1 - P_c))$$

These methods are related to maximum likelihood estimation and we will discuss these relationships following the presentation of the maximum likelihood estimation.

**Maximum Likelihood Estimation**

We have assumed that we may model the dependence of the $P_{kc}$ on the dose of chemicals using the logistic model. Hence

$$P_{kc} = \frac{X_{kc}^\beta}{1 + e^{-X_{kc}^\beta}}$$

(153)

$$1 - P_{kc} = \frac{1}{1 + e^{-X_{kc}^\beta}}$$

(154)

Here $X_{kc}$ represents the $k_c$ row of the design matrix $X$. Let $s_{kc}$ denote the
observed value of the dichotomous random variable \( S_kc \). The likelihood function will contain a term like Equation (153) when \( s_kc = 1 \) and a term like Equation (154) when \( s_kc = 0 \). This allows us to write the likelihood as

\[
\prod_{c=1}^{4} \frac{X_kc \cdot \beta \cdot s_kc}{1 + e^{X_kc \cdot \beta}} = \exp\left( \sum_{c=1}^{4} \beta_c \cdot t_c \right)
\]

where \( t_c = \sum X_{kc} \cdot s_kc \). We observe that \( t_c \) is the sum of the cth column of the matrix \( X \) corresponding to successes, \( s_kc = 1 \).

The log likelihood becomes

\[
L(\beta) = \sum_{c=1}^{4} \beta_c \cdot t_c - \sum \log\left( 1 + e^{X_kc \cdot \beta} \right)
\]

The maximum likelihood estimates, \( \beta \), satisfies the equation

\[
\left[ \frac{\delta L(\beta)}{\delta \beta} \right] = 0
\]

An iterative procedure such as the Newton-Raphson is required in order to solve these equations. A procedure in the Statistical Analysis System (Harrell, 1983) provides such estimates and their standard errors.

In order to compare the maximum likelihood procedure to the procedure suggested by Berkson, we will once again make use of the fact that the probability of death in the cth drug combination is constant and equal to \( P_c \). We may then write the likelihood function as

\[
\prod_{c=1}^{4} \left( \frac{n_c}{r_c} \right) P_c^{r_c} \left( 1 - P_c \right)^{n_c - r_c}
\]
where \( r_c \) is the number of deaths in the \( c \)th experimental group. The log likelihood function is then

\[
L(\beta) = \text{constant} + \sum_c r_c \log P_c + n_c - r_c \log \left(1 - P_c\right)
\]  

(159)

To find the estimates for \( \beta \), we examine

\[
\frac{\delta L(\beta)}{\delta \beta} = \sum_c \left[ \frac{r_c}{P_c} - \left(\frac{n_c - r_c}{1 - P_c}\right) \right] \frac{\delta P_c}{\delta \beta}
\]  

(160)

If we denote

\[
P_c = \frac{r_c}{n_c},
\]

we may write equation (160) as

\[
\frac{\delta L(\beta)}{\delta (\beta)} = \sum_c \left[ \frac{n_c}{P_c(1 - P_c)} \cdot (P_c - P_c) \left(\frac{\delta P}{\delta \beta}\right) \right]
\]

\[
= \sum_c \left[ w_c^* \cdot (P_c - P_c) \left(\frac{\delta P}{\delta \beta}\right) \right]
\]  

(161)

It is interesting to note the similarity between Equation (161) and the equation for the parameter estimates using weighted least squares.

**Exact Analysis for the Estimation of a Single Parameter**

Since each chemical is administered at two doses, we may code the explanatory variables so that the Low dose = 0 and the High dose = 1. Therefore \( x_i = 0 \) or 1 for \( i = 1,2 \) and \( y_j = 0 \) or 1 for \( j = 1,2 \). Now our logistic transformed variables may be modeled as
where

\[
E(S) = P = \frac{e^{a\beta}}{1 + e^{a\beta}} \quad \text{(162)}
\]

We call \( S = x\beta \) a linear logistic model.

Using the technique discussed by Cox (1970), we may derive an exact analysis for the single parameter \( \beta_3 \) when the other parameters, \( \beta_0, \beta_1, \) and \( \beta_2 \), are regarded as nuisance parameters. By exact methods we mean that, assuming the logistic linear model, the methods have exactly known probabilistic properties.
With the assumption of the logistic linear model, the likelihood of an observed binary sequence $s_1, s_2, ..., s_n$ where $n_1 + n_2 + n_3 + n_4 = n$ is

$$L = \prod_{k=1}^{n} \frac{e^{x_k \beta s_i}}{\prod_{k=1}^{n} \left(1 + e^{x_k \beta}\right)}$$

(163)

Note that $x_k$ represents the $k$th row of $x$.

The expression given in Equation (163) may be written as

$$\frac{\exp\left(\sum_{k=1}^{4} \beta c - t_c\right)}{\prod_{k=1}^{n} \left(1 + e^{x_k \beta}\right)}$$

(164)

where $t_c$ equals

$$\sum_{k} x_k \cdot s_k$$

(165)

and $T_c$ equals

$$\sum_{k} x_k \cdot S_k$$

(166)

where $S_k$ is the binary random variable and $s$ is the observed value.

Therefore, we have four simple sufficient statistics: $T_1, T_2, T_3,$ and $T_4$.

The distribution of the random variables $T_1, T_2, T_3,$ and $T_4$ is constructed by summing over all binary sequences that generate the observed values $t_1, t_2, t_3,$ and $t_4$. Result (4.4) from Cox yields
\[ Pr[T_1 = t_1, T_2 = t_2, T_3 = t_3, T_4 = t_4] = \frac{c(t_1, t_2, t_3, t_4) \exp \left[ \sum_{k=1}^{4} \beta_k t_k \right]}{\prod_{k=1}^{n} \left[ 1 + e^{\beta_k} \right]} \]  

(167)

where \( c(t_1, t_2, t_3, t_4) \) is the number of distinct binary sequences that yield \( t_1, t_2, t_3, t_4 \). Cox also provides a generating function for \( c(t_1, t_2, t_3, t_4) \).

\[
C(\zeta_1, \zeta_2, \zeta_3, \zeta_4) = \sum (t_1, t_2, t_3, t_4) \zeta_1^{t_1} \zeta_2^{t_2} \zeta_3^{t_3} \zeta_4^{t_4} = \prod_{k=1}^{n} \left( 1 + \zeta_1^{k_1} \zeta_2^{k_2} \zeta_3^{k_3} \zeta_4^{k_4} \right).
\]

(168)

Note that \( x_{ij} \) represents the \( i,j \) element in \( X \). In the case at hand we have

\[
C(\zeta_1, \zeta_2, \zeta_3, \zeta_4) = (1 + \zeta_1)^{n_1} (1 + \zeta_1 \zeta_2)^{n_2} (1 + \zeta_1 \zeta_3)^{n_3} (1 + \zeta_1 \zeta_2 \zeta_3 \zeta_4)^{n_4}
\]

(169)

Use of the binomial theorem yields

\[
(1 + \zeta_1)^{n_1} = \sum_{k_1=0}^{n_1} \binom{n_1}{k_1} (\zeta_1)^{k_1}
\]

(170)

\[
(1 + \zeta_1 \zeta_2)^{n_2} = \sum_{k_2=0}^{n_2} \binom{n_2}{k_2} (\zeta_1 \zeta_2)^{k_2}
\]

(171)

\[
(1 + \zeta_1 \zeta_3)^{n_3} = \sum_{k_3=0}^{n_3} \binom{n_3}{k_3} (\zeta_1 \zeta_3)^{k_3}
\]

(172)

\[
(1 + \zeta_1 \zeta_2 \zeta_3 \zeta_4)^{n_4} = \sum_{k_4=0}^{n_4} \binom{n_4}{k_4} (\zeta_1 \zeta_2 \zeta_3 \zeta_4)^{k_4}
\]

(173)
Therefore

\[
\sum_{k_1=0}^{n_1} \sum_{k_3=0}^{n_3} \sum_{k_2=0}^{n_2} \sum_{k_4=0}^{n_4} \binom{n_1}{k_1} \binom{n_3}{k_3} \binom{n_2}{k_2} \binom{n_4}{k_4} \left( \sum_{i} \zeta_i^{k_1} \zeta_3^{k_3} \right)^{k_2} \left( \zeta_2^{k_2} \zeta_4^{k_4} \right)^{k_4}
\]

\[= \sum_{k_1} \sum_{k_3} \sum_{k_2} \sum_{k_4} \binom{n_1}{k_1} \binom{n_3}{k_3} \binom{n_2}{k_2} \binom{n_4}{k_4} \zeta_1^{k_1+k_2+k_3+k_4} \zeta_2^{k_2+k_4} \zeta_3^{k_2+k_4} \zeta_4^{k_4} \] (174)

Since we are searching for the coefficient of \( \zeta_1, \zeta_2, \zeta_3, \zeta_4 \), we have

\[
k_1 = t_1 - t_3 - t_2 + t_4
\]

\[
k_2 = t_3 - t_4
\]

\[
k_3 = t_2 - t_4
\]

\[
k_4 = t_4
\]

Thus,

\[
c(t_1, t_2, t_3, t_4) = \binom{n_1}{t_1-t_3-t_2+t_4} \binom{n_2}{t_2-t_4} \binom{n_3}{t_3-t_4} \binom{n_4}{t_4}. \] (175)

Recall that we are interested in the regression parameter \( \beta_3 \) and we may regard the parameters \( \beta_0, \beta_1, \) and \( \beta_2, \) as nuisance parameters. In order to use the data to make judgments about \( \beta_3, \) we consider the conditional distribution of \( T_4 \) given the observed values of \( T_1, T_2, \) and \( T_3. \)

As discussed in Lehmann (1959), this approach allows a way to obtain independence of the nuisance parameters. In deriving the distribution of \( T_4 \) given \( T_1 = t_1, T_2 = t_2, T_3 = t_3, \) we have
where the numerator of Equation (176) is given by Equation (167) and the denominator is derived by summing over all possible values of \( k \).

Therefore, we may form the ratio below from (176).

\[
Pr(T_4 = t_4 \mid T_1 = t_1, T_2 = t_2, T_3 = t_3) = \frac{Pr(T_1 = t_1, T_2 = t_2, T_3 = t_3, T_4 = t_4)}{Pr(T_1 = t_1, T_2 = t_2, T_3 = t_3)}
\]  

(176)

The special case of testing \( \beta_4 = 0 \) leads to

\[
PT_4(t_4 \mid 0) = \frac{c(t_1, t_2, t_3, t_4)}{\sum_{\mu} c(t_1, t_2, t_3, \mu)}
\]

(178)

When we consider the problem of testing the null hypothesis \( \beta_4 = \beta^* \) vs. \( \beta_4 = \beta' \) with \( \beta' > \beta^* \) application of the Neyman-Pearson lemma to Equation (177) allows us to form a most powerful test. That is,
where $k'$ is independent of $t_4$, i.e., form a critical region from the sample points having large values of the likelihood ratio. The critical region consists of the upper tail of the value of $t_4$.

For an observed value of $t_4$, the one-sided significance level, $P_{T_4}$, versus the alternative $\beta_4 > \beta^*$ is

$$\sum_{\mu \geq t} P_{T_4}(\mu; \beta^*)$$

In particular, when the null hypothesis is $\beta_4 = 0$ versus an alternative $\beta_4 = \beta'$ where $\beta' > 0$, we have
\[ P_+(t_{4^*} 0) = \sum_{\mu \geq t_4} \frac{c(t_1, t_2, k_3, \mu)}{\sum_{\mu} c(t_1, t_2, t_3, \mu)} \] (181)

and against the alternative \( \beta' < 0 \)

\[ P_-(t_{4^*} 0) = \sum_{\mu \leq t_4} \frac{c(t_1, t_2, k_3, \mu)}{\sum_{\mu} c(t_1, t_2, t_3, \mu)} \] (182)

The 2-sided alternatives then become

\[ P(t_{4^*} 0) = 2 \min \{ P_+(t_{4^*} 0), P_-(t_{4^*} 0) \} \] (183)

The particular null hypothesis \( \beta_4 = 0 \) is important in this experiment situation since rejection of this hypothesis leads us to believe that there is potentiation or antagonism of the two drugs.

**Recommendations**

The method of maximum likelihood was compared to the minimum chi square method via simulation by Smith, Savin, and Robertson (1984). Their results confirm results previously reported in the literature regarding point estimation. That is, the minimum chi square method is preferred over the maximum likelihood method for point estimation. The minimum chi square method provided the smallest mean squared error. However, the maximum likelihood technique is superior with regard to inference. The minimum chi square method showed larger biases for the test statistic.
With regard to exact logistic regression, Tritchler (1984), has developed an algorithm and the associated computer program to implement the calculations. Currently the algorithm has been developed to make inferences about $\beta_1$ using exact methods in the simple model

$$\ln \left( \frac{p}{1-p} \right) = \beta_0 + \beta_1 x.$$ 

Further work to expand the algorithm to make inferences about the $\beta$'s in a more complicated model would be needed.
CHAPTER V

DIAGNOSTICS FOR LOGISTIC REGRESSION

Introduction

Regression diagnostic tools, mostly graphical, have been used for some time to help assess the fit of a standard linear model. Cook and Weisberg (1982) address this topic in depth. The basic “tools” that have been used as diagnostics are the residuals, denoted by $r_i$, and the projection matrix, denoted by $V$. In order to define these quantities, we first express the standard linear model as

$$y_i = x_i \beta + \epsilon_i, \quad i=1,\ldots,N$$  \hspace{1cm} (184)

where $X'\beta = x_i \beta_1 + \ldots + x_p \beta_p$ and $\epsilon_i \sim N(0, \sigma^2)$. Let $X$ be the design matrix whose rows are $x_i$. Using least squares, the parameter estimates, $\beta$, are obtained by solving the normal equations

$$(X'X)\beta = X'y$$ \hspace{1cm} (185)

yielding the solution, $\beta = (X'X)^{-1}X'y$. It is known that the solution is sensitive to non-normal error distributions. In particular, a few outlying observations can spoil the least squares fit. A measure of the discrepancy between the data, $y_i$, and the predicted value, $y_i$, is the residual $r_i$ defined as

$$r_i = y_i - x_i \beta = y_i - y_i.$$ \hspace{1cm} (186)

When the model we have fit is an incorrect one, the distribution of the $\epsilon_i$ which from Equation (184) may be written as
\[ e_i = y_i - x_i \beta \]  

(187)

will change. This change will be reflected to some extent by examination of the \( r_i \) due to their similarity. Hence, the goal is to use the \( r_i \) to observe incorrect assumptions about the \( \epsilon_i \).

Using the model defined in Equation (184), it is easy to establish the following distribution properties associated with \( z = (r_1, ..., r_n)^T \).

\[
\begin{align*}
E(r_i) &= 0 \\
\text{Var}(r) &= \sigma^2 (I - X (X'X)^{-1} X') \\
&= \sigma^2 (I - V) \\
&= \sigma^2 (M)
\end{align*}
\]

(188)

where \( V \) and \( M \) denote the projection matrices onto the range of \( X \) and its orthogonal complement, respectively. It is apparent that the residuals have a distribution that is scale dependent. The usual solution is to construct a scale-free statistic \( r_i^* \) as

\[
r_i^* = \frac{r_i}{\sigma \sqrt{1 - v_{ii}}} 
\]

(189)

where \( \sigma^2 = \Sigma r_i^2 / (n-p) \) and \( v_{ii} \) is the \( i,i \) element of the matrix \( V \) defined in Equation (188). The \( r_i^* \) are often referred to as studentized residuals. Whenever the \( v_{ii} \) show large variation, then the studentized residual should be used in place of the ordinary residuals.

An important tool that may help achieve our goal of using the residuals to observe incorrect assumptions about the \( \epsilon_i \) is the Q-Q plot, a technique named by Wilk and Gnanadesikan (1968). Basically, the Q-Q plot, or quantile-quantile plot, compares the cdf's of two random variables which
we will call $x$ and $y$, respectively. Suppose that $y$ is a linear function of $x$, namely $y = ax + b$ with $a > 0$. Denote the $p$-th quantile of $y$ by $q_y(p)$. Then
\[
Pr[y \leq q_y(p)] = Pr[ax + b \leq q_y(p)] = Pr[x \leq (q_y(p) - b)/a]
\]
Hence
\[
q_x(p) = (q_y(p) - b)/a \quad \text{or} \quad q_y(p) = a \cdot q_x(p) + b \quad (190)
\]

As a check for normality in the model defined in Equation (184), the ordered residuals are estimates of the quantiles of the true errors. Hence we may use a Q-Q plot of the ordered residuals versus the quantiles of the standard normal distribution to determine the appropriateness of the hypothesized normal distribution. An approximation for these standard normal quantities was suggested by Blom (1958) to be $\Phi^{-1} \left( \frac{(i-3/8)}{(n+1/4)} \right)$. Work by Looney and Gulledge (1985) support the use of this approximation.

If this plot appears to be a straight line, then we would retain the model. If nonlinearity is detected, then further investigation of the data and model is warranted.

Unfortunately, examination of the residuals is not sufficient for assessing the fit of the model. Simultaneously, the elements of the matrix $V$ or $M = I - V$ must be considered. As mentioned in Hoaglin and Welsch (1978), $V$ is the projection matrix onto the column space of $X$. J. W. Tukey (1977) has termed $V$ the "hat" matrix since it maps the vector of observations, $Y$, into the vector of predicted values $\hat{Y}$.

This is easy to see when $Y$ is written as
\[ Y = X(X^TX)^{-1}X^Ty = VY \]  

(192)

Earlier, the similarity between the \( \varepsilon_i \) and \( r_i \) was pointed out. The exact relationship between those two quantities will now be examined in detail.

The definition of the residual can be manipulated as follows:

\[
\begin{align*}
    r &= Y - Y \\
    &= Y - VY \\
    &= (I - V)Y \\
    &= (I - V)(X\beta + \varepsilon) \\
    &= (I - V)\varepsilon
\end{align*}
\]

or for \( i = 1, 2, \ldots, N \)

\[
    r_i = \varepsilon_i - \sum_{j=1}^{N} v_{ij} \varepsilon_j
\]

(194)

Hence if the \( v_{ij} \) are large, then the residuals do not closely resemble the \( \varepsilon_i \). Therefore, for a complete understanding of the model fit, the behavior of \( V \) or \( M = I - V \) must be examined.

Note that the matrix \( V \) is idempotent and symmetric, hence

\[
v_{ii} = \sum_{j=1}^{N} v_{ij}^2
\]

(195)

Therefore, \( v_{ii} \geq 0 \).

Also from Equation (188)

\[
    \text{Var}(r) = \sigma^2(I - V)
\]

(196)

Therefore \( 0 \leq v_{ii} \leq 1 \) and \( v_{ii}^2 \geq v_{ij}^2 \) for all \( j \). The same boundaries hold for the \( m_{ii} = 1 - v_{ii} \). That is, \( m_{ii}^2 \geq m_{ij}^2 \) for all \( j \). But

\[
    y_i = \sum_{j} v_{ij} y_j
\]

(197)
Thus, the prediction of $y_i$ is influenced the most by the largest values in the matrix $V$, namely the $v_{ii}$. Thus, as Cook and Weisberg (1982) note, it is the diagonal entries of $V$ (or $M$) that play an important role in diagnostics. To visualize the relationship between the design matrix and the $v_{ii}$, it is useful to define $x_i^* = x_i - \bar{x_i}$, where $x_i$ is the $i$th row of the design matrix $X$.

Also assume that the intercept is included in the model and denote the eigenvalues of $X^TX^*$ by $\mu_1 \geq \mu_2 \geq \mu_3 \geq \ldots \geq \mu_p$ and the corresponding eigenvectors by $p_1, \ldots, p_p$. Then, by the spectral decomposition of $X^TX^*$ (Cook and Weisberg (1982))

$$v_{ii} = \frac{1}{n} + \sum_{k=1}^{p} \left( \frac{p_k^T x_i}{\sqrt{\mu_k}} \right)^2 \tag{198}$$

By letting $\theta_{ki}$ denote the angle between $p_k$ and $x_i$, we may write

$$\cos(\theta_{ki}) = p_k^T x_i / (x_i^* x_i)^{1/2} \tag{199}$$

and

$$v_{ii} = \frac{1}{n} + x_i^* x_i \sum_{k=1}^{p} \frac{\cos^2(\theta_{ki})}{\mu_k} \tag{200}$$

By examining Equation (200) we notice that $v_{ii}$ is large when $x_i^* x_i^*$ is large. This implies that $x_i^*$ is removed from the other $x_i^*$'s. Also $v_{ii}$ could be large when $x_i^*$ is in a direction of an eigenvector which corresponds to a small eigenvalue of $X^TX^*$. Therefore, large values of $v_{ii}$ are indicative of points of high leverage in the experimental design.

Examination of either the residuals or the $v_{ii}$ without examination of the other provides an incomplete understanding of the model fit. For
example, large $v_\parallel$ may correspond to small residuals so examination of the residuals alone will not distinguish points of high leverage.

As discussed in Chapter II, one of the models we will employ for the interaction between two chemicals utilizes the logistic distribution and logistic regression. In order to provide a more complete understanding of the relationship between the data and the model, we wish to consider analogues of the residuals and the $v_\parallel$ in the logistic regression setting.

**Pearson Residuals**

As mentioned in McCullagh and Nelder (1983), a useful and simple definition of a residual when describing binary data is the Pearson residual. This residual is defined as

$$r_{ij} = \frac{y_{ij} - n_{ij}P_{ij}}{\sqrt{n_{ij}P_{ij}(1-P_{ij})}}$$

(201)

where $y_{ij}$ in our context, is the number of deaths in experimental group $i,j$ which contains $n_{ij}$ animals and $P_{ij}$ is the estimate of $P_{ij}$, the probability of death in that group. Pregibon (1981) refers to these quantities as the individual components of $\chi^2$ (Chi-square) since the $\chi^2$ goodness of fit statistic is equal to

$$\chi^2 = \sum_{j=1}^{N} (r_{ij})^2$$

(202)

where $N$ represents the number of experimental groups. Since the distribution of the $r_{ij}$ is, asymptotically normal (McCullagh & Nelder, pg. 87), the Q-Q plot described earlier is a helpful graphical tool in determining the appropriateness of the hypothesized distribution.
To illustrate this concept, we use some actual data from an experiment that was designed to study the effects when two chemicals, MOC and DFDT were combined (Plackett and Hewett, 1963). The endpoint of interest was dichotomous; the animals either lived or they died after a certain time period. The actual doses of the drugs and proportion of animals that died are presented in Table 21. The model for simple additive action

\[ \log \left( \frac{P_{ij}}{1-P_{ij}} \right) = \beta_0 + \beta_1 \cdot (\text{dose of MOC}) + \beta_2 \cdot (\text{dose of DFDT}) \]  

(203)

Figure 31 displays a Q-Q plot of the resulting Pearson residuals. We see from our Q-Q plot two suspicious points, namely those at .05 MOC and .14 DFDT and .025 MOC and .10 DFDT. It is interesting to note that more animals died than we would have expected under the simple additive model as depicted in Table 21. Due to Pregibon (1981), many of the diagnostics used in the linear model setting may be generalized and used to assess the fit when using logistic regression.

Consider the logistic transformation

\[ z_{ij} = \log \left( \frac{P_{ij}}{1-P_{ij}} \right) \]

(204)

where \( x_{ij} \) represents the dose of the chemical combination at level i of the first drug and level j of the second drug. The \( P_{ij} \) represent the probability of death at the combination \( i,j \) and \( y_{ij} \) is the observed number of deaths at that combination. The \( y_{ij} \) are binomially distributed with parameters \( B(n_{ij}, P_{ij}) \). More complete details on parameter estimation, that is, estimates of \( \beta \), were provided in Chapter IV. For the present discussion we
Table 21
Example Data

<table>
<thead>
<tr>
<th>Observation No.</th>
<th>Dose of MOC</th>
<th>Dose of DFDT</th>
<th>Fraction That Died</th>
<th>Predicted No. of Deaths (Simple Additive Model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.14</td>
<td>0</td>
<td>46/48</td>
<td>46.84</td>
</tr>
<tr>
<td>2</td>
<td>0.10</td>
<td>0</td>
<td>42/48</td>
<td>40.10</td>
</tr>
<tr>
<td>3</td>
<td>0.07</td>
<td>0</td>
<td>22/48</td>
<td>24.81</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>0</td>
<td>9/48</td>
<td>13.19</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0.56</td>
<td>28/48</td>
<td>29.51</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0.40</td>
<td>18/48</td>
<td>16.09</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0.28</td>
<td>7/49</td>
<td>8.59</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0.20</td>
<td>5/48</td>
<td>5.12</td>
</tr>
<tr>
<td>9</td>
<td>0.07</td>
<td>0.20</td>
<td>37/48</td>
<td>39.30</td>
</tr>
<tr>
<td>10</td>
<td>0.05</td>
<td>0.14</td>
<td>32/48</td>
<td>24.45</td>
</tr>
<tr>
<td>11</td>
<td>0.035</td>
<td>0.10</td>
<td>13/48</td>
<td>12.64</td>
</tr>
<tr>
<td>12</td>
<td>0.025</td>
<td>0.07</td>
<td>5/48</td>
<td>7.024</td>
</tr>
<tr>
<td>13</td>
<td>0.05</td>
<td>0.20</td>
<td>27/48</td>
<td>29.53</td>
</tr>
<tr>
<td>14</td>
<td>0.035</td>
<td>0.14</td>
<td>16/48</td>
<td>15.50</td>
</tr>
<tr>
<td>15</td>
<td>0.025</td>
<td>0.10</td>
<td>14/48</td>
<td>8.420</td>
</tr>
<tr>
<td>16</td>
<td>0.0175</td>
<td>0.07</td>
<td>4/47</td>
<td>4.891</td>
</tr>
</tbody>
</table>

Figure 31. The Q-Q Plot of the Ordered Chi-Squared Components Versus the Standard Normal Quantiles.
will assume that we have estimated $P_{ij}$ using the logistic framework and now we are interested in assessing the fit of the model.

We will begin with a discussion of the definition of residuals in this framework.

**Components of Deviance**

Another method for defining residuals for the logistic regression is to construct the components of deviance defined as

$$d_{ij} = \pm \sqrt{2 \left[ \ell(z_{ij}; y_{ij}) - \ell(x_{ij}\beta; y_{ij}) \right]^2}$$  \hspace{1cm} (205)

where plus or minus is used as $Z_{ij} > x_{ij}\beta$ or $Z_{ij} < x_{ij}\beta$, respectively. The function $\ell(\cdot)$ represents the loglikelihood function and

$$z_{ij} = \ln \left[ \frac{y_{ij}/n_{ij}}{1 - y_{ij}/n_{ij}} \right].$$  \hspace{1cm} (206)

Hence, $\ell(z_{ij}, y_{ij})$ represents the loglikelihood evaluated at the observed $z_{ij}$ and $\ell(x_{ij}\beta, y_{ij})$ represents the loglikelihood evaluated at the fitted $x_{ij}\beta$. The components of deviance can be thought of as measuring the disagreement between the maxima of the observed and fitted loglikelihood functions. Asymptotic arguments suggest that the deviance has a limiting $X^2$ distribution. We note that $z_{ij}$ is not defined when $y_{ij} = 0$ or when $y_{ij} = n_{ij}$. It is interesting to note that $d_{ij}$ is defined for all values of $y_{ij}$ even when $z_{ij}$ is not defined as shown below.
**Case 1.** \((y_{ij} = 0)\)

\[
d_{ij}^2 = 2 \left[ \ell(z_{ij}; y_{ij}) - \ell(x_{ij}; y_{ij}) \right]
\]

\[
= 2 \left[ y_{ij} \left( z_{ij} - x_{ij} \beta \right) + n_{ij} \log \left( 1 + e^{x_{ij} \beta} \right) + n_{ij} \log \left( 1 - y_{ij}/n_{ij} \right) \right]
\]

Let

\[
\ell n \left( \frac{p_{ij}}{1-p_{ij}} \right) = x_{ij} \beta
\]

\[
d_{ij}^2 = 2 \left[ y_{ij} \left( z_{ij} - x_{ij} \beta \right) - n_{ij} \log \left( 1 - p_{ij} \right) + n_{ij} \log \left( 1 - y_{ij}/n_{ij} \right) \right]
\]

Let

\[
y_{ij} = 0
\]

\[
d_{ij}^2 = 2 \left[ -n_{ij} \log \left( 1 - p_{ij} \right) \right] = -2n_{ij} \log \left( 1 - p_{ij} \right)
\]

**Case 2.** \((y_{ij} = n_{ij})\)

\[
d_{ij}^2 = 2 \left[ n_{ij} \log \left( y_{ij}/n_{ij} \right) - n_{ij} \log \left( 1 - \frac{y_{ij}}{n_{ij}} \right) - n_{ij} x_{ij} \beta - n_{ij} \log \left( 1 - p_{ij} \right) + n_{ij} \log \left( 1 - \frac{y_{ij}}{n_{ij}} \right) \right]
\]

\[
= 2 \left[ n_{ij} \log \left( y_{ij}/n_{ij} \right) - n_{ij} x_{ij} \beta - n_{ij} \log \left( 1 - p_{ij} \right) \right]
\]

Let

\[
y_{ij} = n_{ij}
\]

\[
d_{ij}^2 = 2 n_{ij} \left[ x_{ij} \beta + \log \left( 1 - p_{ij} \right) \right]
\]
But

\[ x_{ij}^\beta = \log \left( \frac{P_{ij}}{1 - P_{ij}} \right) \]

therefore

\[ d_{ij}^2 = -2n_{ij} \left[ \log \left( \frac{P_{ij}}{1 - P_{ij}} \right) + \log \left( 1 - P_{ij} \right) \right] = -2n_{ij} \log (P_{ij}) . \]

Note that in the linear model, residuals are uniquely defined; but in the case for the logistic regression we have already defined residuals on two different scales.

As in the case for the Pearson residual, graphical displays are helpful in calling attention to outlying points. We construct a Q-Q plot using the components of deviance calculated from the data displayed in Table 21. This plot may be found in Figure 32. We again spot the same two points as being suspect as we did in the Q-Q plot of the Pearson residuals, those being observations numbered 10 and 15.

**Adjusted Components of Deviance**

McCullagh and Nelder (1983) suggest an adjustment to the deviance residual that is helpful for small \( n_{ij} \) or for \( P_{ij} \) near 0 or 1. It is defined by

\[ d_{ij(adj)} = d_{ij} + \frac{(2P_{ij} - 1)}{\left[ 6 \left( n_{ij}P_{ij}(1 - P_{ij}) \right) \right]^\dagger} \quad (207) \]

This adjustment is made in order to make the deviance, assuming binomial variation, closer to the reference chi-squared distribution (Lawley (1956)). Hence, the adjusted deviance residuals are more nearly normally distributed than the Pearson residual defined earlier. Figure 33 displays
Figure 32. The Q-Q Plot of the Ordered Deviance Components Versus the Standard Normal Quantiles.
graphically the Q-Q plot for the adjusted deviance components. As expected, observations 10 and 15 stand out.

Influence Points

As discussed in the introduction, the matrix defined as $M$ is helpful in diagnosing influential points in the design space. The construction of an analog for the logistic model is discussed by Pregibon (1981). To gain intuition for the development of this analog, it is helpful to examine the iterative calculations necessary to compute the maximum likelihood estimates of the parameters $\beta$. Most often the Newton-Ralphson method is employed leading to the iterative scheme

$$\beta^{t+1} = \beta^t + \left( X^T V X \right)^{-1} X^T (y - y^t)$$  \hspace{1cm} (208)

where $V_{px} = \text{diagonal}(n_i p_i q_i)$ and $y_i^t = n_i p_i^t$ are evaluated at $\beta^t$. When convergence is achieved ($t = c$), then $\beta = \beta^c$ and $y_i = n_i p_i$

We may write Equation (208) as

$$\beta^{t+1} = \left( X^T V X \right)^{-1} \left( X^T V X \right) \beta^t + \left( X^T V X \right)^{-1} X^T V V^{-1} (y - y^t)$$

$$= \left( X^T V X \right)^{-1} X^T V \left[ X \beta^t + V^{-1} (y - y^t) \right]$$

$$= \left( X^T V X \right)^{-1} X^T V Z^t$$  \hspace{1cm} (209)

$Z^t$ is referred to as the pseudo observation vector. At convergence

$$Z = X \beta + V^{-1} (\hat{y} - y)$$  \hspace{1cm} (210)

and
Figure 33. The Q-Q Plot of the Ordered Adjusted Deviance Components Versus the Standard Normal Quantiles.
\[ \beta = \left( X^T V X \right)^{-1} X^T V Z \]  

(211)

A closer look at \( Z \), noting that the logit transformation is defined as 
\[ \ln(p/(1-p)) = X\beta \] reveals why it is named the pseudo observation vector. \( Z \) can be thought of as \( X\beta \) + residual.

The vector of pseudo residuals may now be defined as

\[ Z - X\beta = Z - X \left[ X^T V X \right]^{-1} X^T V Z \]

\[ = \left[ I - X \left( X^T V X \right)^{-1} X^T V \right] Z \]

\[ = \left[ V^{-1} \left[ I - V^+ X \left( X^T V X \right)^{-1} X^T V \right] V^{-1} \right] \cdot Z \]

\[ = V^{-1} M V^+ Z \]  

(212)

The matrix \( M \) defined above is the analogue to the linear model case. \( M \) is seen to be symmetric and idempotent. \( M \) also has the property that it spans the residual space where the standardized residual is defined as \( V^{-1} (\hat{y} - y) \). This may be seen by substituting \( Z = X\beta + V^{-1} (\hat{y} - y) \) into Equation (212). That is,

\[ Z - X\beta = V^{-1} M V^+ Z \]

\[ X\beta + V^{-1} (\hat{y} - y) - X\beta = V^{-1} M V^+ \left( X\beta + V^{-1} (\hat{y} - y) \right) \]

\[ V^{-1} (\hat{y} - y) = V^{-1} M V^+ X\beta + V^{-1} M V^+ (\hat{y} - y) \]
But

\[ v^{-1}Mv^T x_\beta = v^{-1}
\{I - v^T x (x^T v x)^{-1} x^T v^T \} v^T x (x^T v x)^{-1} x^T v z \]

\[ = x (x^T v x)^{-1} x^T v z - x (x^T v x)^{-1} (x^T v x) (x^T v x)^{-1} x^T v z \]

\[ = 0. \]

Therefore

\[ v^{-1}(\hat{y} - y) = v^{-1}Mv^{-1}(\hat{y} - y) . \]

Premultiplication by \( v^T \) yields

\[ v^{-1} (\hat{y} - y) = M v^{-1} (\hat{y} - y) \]

(213)

As in the linear model case, the diagonal values of \( M \) should be important in logistic regression diagnostics. Pregibon’s (1981) experience indicates that this is the case.

Again, a graphical representation is helpful in detecting small values of \( m_{ij} \). Figure 34 provides a display of \( m_{ij} \) vs. \( i \) for the data in Table 21. It points out that observation number 5 at a dose of MOC equal to 0.0 and a dose of DFDT equal to .56 is an influential point with \( M_{5,5} = .397 \). Hoaglin and Welsch (1978) suggest that when \( 1 - m_{ij} > 2 \) (no. of parameter)/(no. of drug combinations) those points indicate influential observations.

When observation number 5 is removed and the model fit again, there is no dramatic improvement in the fit. The deviance with all the data is 15.15 with 13 degrees of freedom. When observation 5 is removed, the deviance becomes 14.65 with 12 degrees of freedom. However, when the two observations flagged by the residual analysis are removed,
Figure 34. The plot of the $\text{M}(i,i)$ versus the observation number.
numbers 10 and 15, the deviance becomes 4.55 with 11 degrees of freedom.

Computer Program - GLIM

The computer package GLIM (NAG, 1978) provides an excellent tool to extract the needed components of the diagnostic tools we have discussed. Found in Appendix E are a listing of the program statements and program output needed to compute the diagnostics for the data presented in Table 21.

Summary

Just as residual analysis and other diagnostics should be examined for normal-theory linear regression problems, their importance for logistic regression problems should not be overlooked. This is especially true when fitting logistic regression models using maximum likelihood which is extremely sensitive to "bad" data.

Unlike the normal-theory regression problem where the residual is uniquely defined, for logistic regression problems this is not the case. We have defined two residuals, the Pearson residual and the deviance residual. When the data are such that the $n_{ij}$ are small or the $P_{ij}$ are near 0 or 1, the Pearson residual becomes unstable and the deviance residual becomes the residual of choice.

Finally, the GLIM software package allows easy extraction of the diagnostics needed to assess the fit in logistic regression problems.
CHAPTER VI

A GUIDE TO THE APPLICATION OF LOGISTIC REGRESSION IN DRUG COMBINATION STUDIES

Introduction

The purpose of this chapter is to illustrate in detail the analysis and interpretation of data generated in drug combination experiments. The data sets were chosen to illustrate different problems that may arise when using the logistic model to analyze and interpret the interaction of two drugs used in a combination experiment. Data Set One comes from the literature and represents the simplest case, no interaction between the two drugs where the data conform well to this simple model. The second data set was chosen since it is well described by the logistic model with a simple expression for interaction. This data set also comes from the literature. It is interesting to note the difference between the response surface described by the model for Data Set One illustrated in Figure 41 and the surface described by the model for Data Set Two found in Figure 46. These figures illustrate the isobol terminology defined in Chapter I.

Finally, the third data set comes from an experiment performed in the pharmaceutical industry using two drugs that could potentially be used in combination by humans. This data set illustrates the use of a model more complicated than the one used to describe drug interaction in
the second data set. Of particular interest is the interpretation of results from this more complicated model.

It is hoped that this chapter will illustrate many of the tools necessary to analyze and interpret such data and point to some of the problems encountered in their implementation.

Data Set One

The data for this example come from Martin (1948). This experiment was designed to test the synergistic effects of two insecticides, Rotenone and Deguelin concentrate, using the chrysanthemum aphid as the test insect. The data are presented in Table 22. The response of interest is dichotomous as we are interested in the number of insects that lived or died after being exposed to the differing drug combinations.

For the initial model we used

\[
\log \left( \frac{P_{ij}}{1 - P_{ij}} \right) = \\
\alpha_0 + \alpha_1 (\text{dose of Rotenone}) + \alpha_2 (\text{dose of Deguelin}) + \alpha_3 (\text{dose of Rotenone} \times \text{dose of Deguelin})
\]

where

\[
P_{ij} = \frac{\text{No. of deaths at dose } i \text{ of Rotenone and dose } j \text{ of Deguelin}}{\text{No. of insects used at dose } i \text{ of Rotenone and dose } j \text{ of Deguelin}}
\]
Table 22
Rotenone and Deguelin Combination Data

<table>
<thead>
<tr>
<th>Rotenone (mg/l)</th>
<th>Deguelin (mg/l)</th>
<th>No. of Insects</th>
<th>No. of Deaths (% Mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.2</td>
<td>0.0</td>
<td>50</td>
<td>44 (88.0)</td>
</tr>
<tr>
<td>7.7</td>
<td>0.0</td>
<td>49</td>
<td>42 (85.7)</td>
</tr>
<tr>
<td>5.1</td>
<td>0.0</td>
<td>46</td>
<td>24 (52.2)</td>
</tr>
<tr>
<td>3.8</td>
<td>0.0</td>
<td>48</td>
<td>16 (33.3)</td>
</tr>
<tr>
<td>2.6</td>
<td>0.0</td>
<td>50</td>
<td>6 (12.0)</td>
</tr>
<tr>
<td>0.0</td>
<td>50.5</td>
<td>48</td>
<td>48 (100.0)</td>
</tr>
<tr>
<td>0.0</td>
<td>40.4</td>
<td>50</td>
<td>47 (94.0)</td>
</tr>
<tr>
<td>0.0</td>
<td>30.3</td>
<td>49</td>
<td>47 (95.9)</td>
</tr>
<tr>
<td>0.0</td>
<td>20.2</td>
<td>48</td>
<td>34 (70.8)</td>
</tr>
<tr>
<td>0.0</td>
<td>10.1</td>
<td>48</td>
<td>18 (37.5)</td>
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<tr>
<td>0.0</td>
<td>5.1</td>
<td>49</td>
<td>16 (32.6)</td>
</tr>
<tr>
<td>5.1</td>
<td>20.3</td>
<td>50</td>
<td>48 (96.0)</td>
</tr>
<tr>
<td>4.0</td>
<td>16.3</td>
<td>46</td>
<td>43 (93.5)</td>
</tr>
<tr>
<td>3.0</td>
<td>12.2</td>
<td>48</td>
<td>38 (79.2)</td>
</tr>
<tr>
<td>2.0</td>
<td>8.1</td>
<td>46</td>
<td>27 (58.7)</td>
</tr>
<tr>
<td>1.0</td>
<td>4.1</td>
<td>46</td>
<td>22 (47.8)</td>
</tr>
<tr>
<td>0.5</td>
<td>2.0</td>
<td>47</td>
<td>7 (14.9)</td>
</tr>
</tbody>
</table>


The model was fit and the parameters were estimated using the maximum likelihood algorithm contained in the GLIM software system (NAG, 1978). The parameter estimates and their corresponding standard errors are displayed below.

| Parameter | Estimate | Standard Error | $|t||
|-----------|----------|----------------|------|
| $\alpha_0$ | -1.859 | .185 | 10.05 |
| $\alpha_1$ | .3897 | .03957 | 9.85 |
| $\alpha_2$ | .1430 | .01361 | 10.51 |
| $\alpha_3$ | .00735 | .006018 | 1.22 |
The estimate of the interaction parameter, $\alpha_3$, is not significantly different from zero. The reduced model yielded the maximum likelihood estimates:

| Parameter | Estimate | Standard Error | $|t|_1$ |
|-----------|----------|----------------|--------|
| $\alpha_0$ | -1.902   | .1836          | 10.36  |
| $\alpha_1$ | .406     | .038           | 10.68  |
| $\alpha_2$ | .151     | .013           | 11.61  |

We conclude that all of the parameters in our new model are significantly different from zero. However, the deviance for this model is calculated to be 29.56 with 14 degrees of freedom with the probability of observing a larger value being less than .01. As was mentioned in Chapter V, the deviance function is a measure of the goodness of fit and asymptotically follows a chi-square distribution.

Figures 35, 36, and 37 contain the Q-Q plot of the individual deviance components, the individual deviance components versus the observation number and the $m_{ii}$ components versus the observation number, all for the reduced model, respectively. These plots are useful for detecting the lack of conformity of the data to the model and are described in detail in Chapter V. We observe in Figure 36 that observation number five, which is a dose of Rotenone used alone at 2.6 mg/l, has the largest absolute deviance component, therefore is a point not well fit by the model. Since this observation is not one of the combination doses, we chose to remove it and refit the model. Doing so reduces the deviance to 18.9 with 13
Figure 35. Q-Q Plot of the Ordered Deviance Components Versus the Standard Normal Quantiles for Data Set One.
Figure 36. Individual Deviance Components Versus Observation Number for Data Set One.

DEVIANCE (D)

OBSERVATION NUMBER
Figure 37. Indicators of High Leverage Points Versus Observation Number for Data Set One.
degrees of freedom and we would accept the fit of this model to the data with the following parameter estimates.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_0$</td>
<td>-1.696</td>
<td>.1902</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>.3899</td>
<td>.0382</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>.1397</td>
<td>.0126</td>
</tr>
</tbody>
</table>

The diagnostic plots for this model may be found in Figures 38-40.

It is interesting to note that when Finney (1971) analyzed the same data he removed observations numbered 11, 16, and 17 in order to fit his model. Observation numbers 16 and 17 are both drug combination doses and removal of those two observations represents a removal of 33.3% of the drug combination data. However, his conclusions match ours. That is, there exists simple similar action between Rotenone and Deguelin.

The next step in the analysis is to provide an estimate of the dose that causes a response in 50% of the animals. This number is known as the LD$_{50}$. Figure 41 illustrates the entire fitted response surface with the LD$_{50}$ line. The 95% confidence bands about that line were obtained with the methods by Carter et al. (1983) described in detail in Chapter VIII. Note that the fitted response surface in Figure 41 is a plane with linear isobols as we would expect when the two drugs express simple similar action. Figure 42 provides a two-dimensional representation of Figure 41 that allows for easier interpretation. Since the simple similar action model adequately describes this data, we would conclude that the drugs act in an
Figure 38. Q-Q Plot of the Ordered Deviance Components Versus the Standard Normal Quantiles for Data Set One With One Observation Removed.
Figure 39. Individual Deviance Components Versus Observation Number for Data Set One With One Observation Removed.
Figure 40. Indicators of High Leverage Points Versus Observation Number for Data Set One With One Observation Removed.
Figure 41. 3-Dimensional Representation of the Fitted Surface for Data Set One With LD50 Line and Confidence Bounds.
Figure 42. 2-Dimensional Representation of the LD50 Line and 95% Confidence Bounds for Data Set One.
additive fashion. Isobols generated for this model should be linear (see Chapter I) and, as can be seen in Figures 41 and 42, they indeed are.

**Data Set Two**

The data for this example come from Goldin, Venditti, Humphreys, and Dennis (1955) who were investigating the interactive effects of amethopterin and 6-mercaptopurine in mice for the treatment of leukemia. One goal in their experiment was to investigate the possibility of increased toxicity when the drugs were used in combination as opposed to being used singly. Again, the data are dichotomous and represent a count of the dead animals treated by various drug combinations. The data are displayed in Table 23.
Table 23
Amethopterin and 6-Mercaptopurine Combination Data

<table>
<thead>
<tr>
<th>Amethopterin (mg/kg)</th>
<th>6-Mercaptopurine (mg/kg)</th>
<th>No. of Mice</th>
<th>No. of Deaths (% Mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>0</td>
<td>8</td>
<td>0 (0)</td>
</tr>
<tr>
<td>50</td>
<td>0</td>
<td>8</td>
<td>0 (0)</td>
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<tr>
<td>67</td>
<td>0</td>
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<td>1 (12.5)</td>
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<tr>
<td>90</td>
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<td>0 (0)</td>
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<tr>
<td>120</td>
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<td>8</td>
<td>1 (12.5)</td>
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<tr>
<td>160</td>
<td>0</td>
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<td>1 (12.5)</td>
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<td>213</td>
<td>0</td>
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<td>6 (75)</td>
</tr>
<tr>
<td>284</td>
<td>0</td>
<td>8</td>
<td>5 (62.5)</td>
</tr>
<tr>
<td>379</td>
<td>0</td>
<td>8</td>
<td>7 (87.5)</td>
</tr>
<tr>
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</tr>
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</tr>
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<td>67</td>
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<td>120</td>
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<td>8</td>
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<td>160</td>
<td>21.8</td>
<td>8</td>
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</tr>
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</tr>
<tr>
<td>284</td>
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<td>8</td>
<td>6 (75)</td>
</tr>
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<td>50.8</td>
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</tr>
<tr>
<td>506</td>
<td>67.8</td>
<td>8</td>
<td>8 (100)</td>
</tr>
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</table>
Table 23 (Cont.)

Amethopterin and 6-Mercaptopurine Combination Data

<table>
<thead>
<tr>
<th>Amethopterin (mg/kg)</th>
<th>6-Mercaptopurine (mg/kg)</th>
<th>No. of Mice</th>
<th>No. of Deaths (% Mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>675</td>
<td>90</td>
<td>8</td>
<td>8 (100)</td>
</tr>
<tr>
<td>900</td>
<td>120</td>
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<td>8 (12.5)</td>
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<td>8</td>
<td>1 (12.5)</td>
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<td>38</td>
<td>38</td>
<td>8</td>
<td>1 (12.5)</td>
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<td>2 (25)</td>
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<td>0 (0)</td>
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<td>4 (50)</td>
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<tr>
<td>284</td>
<td>284</td>
<td>8</td>
<td>8 (100)</td>
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<tr>
<td>379</td>
<td>379</td>
<td>8</td>
<td>8 (100)</td>
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<td>506</td>
<td>8</td>
<td>8 (100)</td>
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<tr>
<td>12</td>
<td>90</td>
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<td>0 (0)</td>
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<td>16</td>
<td>120</td>
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<td>0 (0)</td>
</tr>
<tr>
<td>21</td>
<td>160</td>
<td>8</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>28</td>
<td>213</td>
<td>8</td>
<td>4 (50)</td>
</tr>
<tr>
<td>38</td>
<td>284</td>
<td>8</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>50</td>
<td>379</td>
<td>8</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>67</td>
<td>506</td>
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<td>8 (100)</td>
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<td>90</td>
<td>675</td>
<td>8</td>
<td>8 (100)</td>
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<tr>
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<td>900</td>
<td>8</td>
<td>8 (100)</td>
</tr>
<tr>
<td>160</td>
<td>1200</td>
<td>8</td>
<td>8 (100)</td>
</tr>
</tbody>
</table>


We fit the same initial model as in Data Set One:

\[
\log \left[ \frac{\bar{P}_{ij}}{1 - \bar{P}_{ij}} \right] =
\]
\[
\alpha_0 + \alpha_1 \text{ (dose of Amethopterin)} + \alpha_2 \text{ (dose of 6-Mercaptopurine)} \\
+ \alpha_3 \text{ (dose of Amethopterin \times dose of 6-Mercaptopurine)}.
\]

Our goodness of fit statistic, the deviance, was calculated to be 57.71 with 54 degrees of freedom with the probability of observing a more extreme value being .34. Examination of the diagnostic plots in Figures 43, 44, and 45 fail to reveal any gross deviations from the model. We will assume that this model provides an acceptable fit and observe the following maximum likelihood estimates:

| Parameter | Estimate | Standard Error | \( |t| \) |
|-----------|----------|----------------|-------|
| \( \alpha_0 \) | -3.541 | .327 | 10.83 |
| \( \alpha_1 \) | .0145 | .0018 | 8.05 |
| \( \alpha_2 \) | .0056 | .00076 | 7.37 |
| \( \alpha_3 \) | .000063 | .000019 | 3.32 |

We observe that the interaction parameter is positive with a value significantly different from zero. The interpretation of this result is that the two drugs do not act in an additive fashion but rather in a potentiating fashion. This means that less of each drug is required to elicit the same response than would be required if the drugs were additive. This phenomenon is illustrated in Figure 46 where the three-dimensional surface is drawn. Note that the isobol is no longer a straight line, but rather a curve. The 95% confidence bounds in Figure 46 were again calculated using the methodology provided by Carter et al. Figure 47 illustrates this same isobol in two dimensions. The analysis of this data by Goldin et al. leads to the same conclusion.
Figure 43. Q-Q Plot of the Ordered Deviance Components Versus the Standard Normal Quantiles for Data Set Two.
Figure 44. Individual Deviance Components Versus Observation Number for Data Set Two.
Figure 45. Indicators of High Leverage Points Versus Observation Number for Data Set Two.
Figure 46. 3-Dimensional Representation of the Fitted Surface for Data Set Two With LD50 Line and Confidence Bounds.
Figure 47. 2-Dimensional Representation of the LD50 Line and 95% Confidence Bounds for Data Set Two.
Data Set Three

The third and final set of data comes from The Upjohn Company. Two drugs, which have the potential of being used by humans in combination, were tested in mice for possible interactive effects. For the sake of confidentiality, we shall refer to the two drugs as A and B, respectively. Table 24 lists the doses employed and the responses observed.

Table 24
The Upjohn Company Combination Data

<table>
<thead>
<tr>
<th>Drug A (mg/kg)</th>
<th>Drug B (mg/kg)</th>
<th>No. of Mice</th>
<th>No. of Deaths (% Mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0</td>
<td>5</td>
<td>0 (0)</td>
</tr>
<tr>
<td>20.0</td>
<td>0</td>
<td>5</td>
<td>0 (0)</td>
</tr>
<tr>
<td>40.0</td>
<td>0</td>
<td>5</td>
<td>1 (20)</td>
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<tr>
<td>80.0</td>
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<td>3 (60)</td>
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<tr>
<td>160.0</td>
<td>0</td>
<td>5</td>
<td>3 (60)</td>
</tr>
<tr>
<td>320.0</td>
<td>0</td>
<td>5</td>
<td>5 (100)</td>
</tr>
<tr>
<td>0.0</td>
<td>600</td>
<td>5</td>
<td>1 (20)</td>
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<td>.625</td>
<td>600</td>
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<td>600</td>
<td>10</td>
<td>2 (20)</td>
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<td>5.0</td>
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<td>6 (60)</td>
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<tr>
<td>10.0</td>
<td>600</td>
<td>10</td>
<td>5 (50)</td>
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<tr>
<td>20.0</td>
<td>600</td>
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<td>8 (80)</td>
</tr>
<tr>
<td>2.5</td>
<td>200</td>
<td>10</td>
<td>0 (10)</td>
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<tr>
<td>5.0</td>
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<td>10</td>
<td>(1) (10)</td>
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<tr>
<td>(10.0)</td>
<td>200</td>
<td>10</td>
<td>(4) (40)</td>
</tr>
<tr>
<td>(20.0)</td>
<td>200</td>
<td>10</td>
<td>(6) (60)</td>
</tr>
<tr>
<td>2.5</td>
<td>60</td>
<td>10</td>
<td>0 (0)</td>
</tr>
<tr>
<td>5.0</td>
<td>60</td>
<td>10</td>
<td>0 (0)</td>
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<td>3 (30)</td>
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<tr>
<td>20.0</td>
<td>60</td>
<td>10</td>
<td>4 (40)</td>
</tr>
</tbody>
</table>
Again we started with the simple interaction model:

\[
\ln \left( \frac{\bar{P}_{ij}}{1-\bar{P}_{ij}} \right) = a_0 + a_1 \text{ (dose of Drug A)} + a_2 \text{ (dose of Drug B)} + a_3 \text{ (dose of Drug A } \times \text{ dose of Drug B)}.
\]  

This model provided the following maximum likelihood parameter estimates:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a_0)</td>
<td>-2.064</td>
<td>.3718</td>
</tr>
<tr>
<td>(a_1)</td>
<td>.021</td>
<td>.0062</td>
</tr>
<tr>
<td>(a_2)</td>
<td>-0.000145</td>
<td>.001</td>
</tr>
<tr>
<td>(a_3)</td>
<td>.00036</td>
<td>.0000946</td>
</tr>
</tbody>
</table>

The coefficient associated with Drug B, namely \(a_2\), is not significantly different from zero. We choose to remove \(a_2\) from the model and perform the analysis again with the reduced model

\[
\ln \left( \frac{\bar{P}_{ij}}{1-\bar{P}_{ij}} \right) = a_0 + a_1 \text{ (dose of Drug A)} + a_3 \text{ (dose of Drug A } \times \text{ dose of Drug B)}
\]

Many schools of thought suggest that \(a_3\) should not be in the model unless \(a_1\) and \(a_2\) are both included. For example, purposes \(a_2\) is removed and the analysis continued. Fitting this new model results in a deviance of 30.8 with 18 degrees of freedom and the probability of observing a larger value equal to .03. Figures 48, 49 and 50 contain the diagnostic plots for this model. Examining these plots fails to reveal particular points that are
Figure 48. Q-Q Plot of the Ordered Deviance Components Versus the Standard Normal Quantiles for Data Set Three.
Figure 49. Individual Deviance Components Versus Observation Number for Data Set Three.
Figure 50. Indicators of High Leverage Points Versus Observation Number for Data Set Three.
not well fit by the model. Note that the chi-square goodness of fit statistic was 25.24 with 18 degrees of freedom and the probability of observing a larger value being .12. Considering both goodness of fit measures, we would consider the fit of the data to the model as marginally acceptable and continue to the next stage of the analysis procedure, the LD$_{50}$ estimation.

The parameter estimates are listed below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_0$</td>
<td>-2.098</td>
<td>.2885</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>.021</td>
<td>.00585</td>
</tr>
<tr>
<td>$\alpha_3$</td>
<td>.000355</td>
<td>.00008139</td>
</tr>
</tbody>
</table>

All the parameter estimates are significantly different from zero. The positive value of the interaction parameter, $\alpha_3$, indicates a potentiating response. That is, when used in combination, these drugs express a response which is greater than would be expected based on the simple additive model. Note that again the isobol is no longer linear but a curve bending the same direction as the isobol for Data Set Two. Figure 51 illustrates the surface described by this model with the corresponding LD$_{50}$ curve and 95% confidence limits. Figure 52 displays the two-dimensional LD$_{50}$ curve with 95% confidence levels for this model.

An attempt was made to fit a more complicated model to this data set in order to provide a more satisfactory fit. The model which performed the best was
Figure 52. 2-Dimensional Representation of the LD50 Line and 95% Confidence Bounds for Data Set Three.
\[
\ln \left( \frac{\bar{p}_{ij}}{1 - \bar{p}_{ij}} \right) = \alpha_0 + \alpha_1 (\text{dose of Drug A}) + \alpha_3 (\text{Drug A} \times \text{Drug B}) + \alpha_4 ((\text{Drug A})^2 \times \text{Drug B}) + \alpha_5 (\text{Drug A} \times (\text{Drug B})^2)
\]  

This model had a deviance of 22.9 with 16 degrees of freedom where the probability of observing a larger value is .12. Using the likelihood ratio to test \( H_0: \alpha_4 = 0 \) and \( \alpha_5 = 0 \), we obtain a \( \chi^2 = 7.9 \) with 2 degrees of freedom. The probability of obtaining a larger value is .02. Figure 53 displays the shape of this surface. Since it is hard to interpret such a surface and the improvement in the fit is minimal, we would choose the earlier model to describe this data. However, there are certainly occasions when a more complicated model would be useful, but we point out that there are problems in terms of interpretation of such a model. We can no longer state that our interaction is potentiating or antagonistic but rather the additive model is not appropriate and some sort of synergism does exist.
Figure 53. 3-Dimensional Representation of the Fitted Surface for Data Set Three Using a More Complicated Model.
CHAPTER VII

ROBUST LOGISTIC REGRESSION

Introduction

As described in Chapter IV, the estimation and testing of parameters defined by logistic regression models can be carried out using maximum likelihood techniques. Recall from that Chapter the development of maximum likelihood estimates. That is, for the simple case where the drug is administered at dosages $x_i$, $i = 1, \ldots, d$ with $n_i$ animals at each dose we model the probability of response, $p_i$, as

$$z_i = \log \left( \frac{p_i}{1 - p_i} \right) = a_0 + a_i x_i \quad (219)$$

We record the number of responses, $r_i$, at each dose level and define $p_i = r_i/n_i$. We also assume that the $r_i \sim \text{Binomial} \ (n_i, p_i)$ leading to the log likelihood function:

$$l(X; r) = \sum_{i=1}^{d} r_i x_i a - n \log (1 + e^{x_i a}) + k \quad (220)$$

where $k = \log \left( \frac{n_i}{r_i} \right)$.

$x_i$ is the $i$th row of the design matrix $X$, and $a$ is a vector of parameters. In this special case
\[ X = \begin{bmatrix} 1 & x_1 \\ 1 & x_p \end{bmatrix}, \quad a = \begin{bmatrix} a_0 \\ a_1 \end{bmatrix} \]

Hence the maximum likelihood solution maximizes Equation (220) and is a solution to \( \delta \delta_a \ell (Xa; r) = 0 \). It is possible to write \( \delta \delta_a \ell (Xa; r) \) as

\[
\delta \delta_a \ell (Xa; r) = \delta \delta_a \left[ \sum_{i=1}^{d_1} r_i a - n_i \log \left( l + e^{x_i a} \right) + k \right]
\]

\[
= \sum_{i=1}^{d} x_{ij} r_i - n_i x_{ij} \left[ \frac{x_i a}{e^{x_i a}} \right]
\]

\[
= \sum_{i=1}^{d} x_{ij} \left[ r_i - n_i P_i \right]
\]

(221)

Therefore the maximum likelihood estimates satisfy the system of equations

\[
\sum_{i=1}^{d} x_{ij} \left[ r_i - n_i P_i \right] = 0.
\]

(222)

Interestingly, the maximum likelihood solution can be obtained using a nonlinear least squares approach. Starting with the weighted nonlinear least squares formulation which minimizes with respect to \( a \)
where

\[ P_i = \left( \frac{x_i^a}{1 + e^{x_i^a}} \right), \quad w_i = \frac{1}{n_i P_i (1 - P_i)} \]

and taking derivatives with respect to \( a \), where \( w_i \) is considered a constant, yields the following system of equations:

\[
\sum_{i=1}^{d_i} w_i (r_i - n_i P_i)(n_i P_i (1 - P_i)) x_{ij} = 0
\]

or,

\[
\sum_{i=1}^{d_i} (r_i - n_i P_i) \frac{n_i P_i (1 - P_i)}{n_i P_i (1 - P_i)} x_{ij} = 0
\] (224)

Equation (224) is identical to Equation (222) verifying the equivalence between the two formulations. Therefore, maximum likelihood estimates may be computed using many of the nonlinear estimation computer programs. As outlined in a paper by Jennrich and Moore (1975), the standard errors provided by the nonlinear estimation routines are the appropriate standard errors for the maximum likelihood estimates.

Unfortunately, as illustrated in the following example, maximum likelihood estimation is sensitive to and influenced by observations poorly described by the model.
Table 25
Simulated Data

<table>
<thead>
<tr>
<th>Original Data</th>
<th>Modifying Observation No 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>( x_i )</td>
<td>( r_i )</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
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<td>5</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
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</tr>
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<td>7</td>
<td>6</td>
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<tr>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

\( \alpha_0 = -5.758 \ (1.134) \quad \alpha_0 = -3.259 \ (1.6776) \)

\( \alpha_1 = 1.01 \ (0.1913) \quad \alpha_1 = .6299 \ (0.1188) \)

\( \text{Dev} = 9.558 \text{ d.f.} = 8 \quad \text{Dev} = 22.93 \text{ d.f.} = 8 \)

\( p = .30 \quad p = .003 \)

Presented in Table 25 are data that have been simulated for the purpose of illustration. The data are generated from the model

\[
z_i = \ln \left( \frac{p_i}{1 - p_i} \right) = -5 + .83 x_i
\]  
(225)
where \( x = (1, 2, \ldots, 10) \), \( r_i \sim \text{binomial}(10, p_i) \). These data were then analyzed using maximum likelihood techniques and the results reported in Table 25.

For purposes of illustration the value of \( r_2 \) was inflated from 0 to 5 and the maximum likelihood estimates recalculated. As can be observed in Table 1, the influence of one observation can have pronounced effects.

The resulting estimate of the slope, \( a_1 \), changes from 1.01 using the original data to .6299 using the modified data, a decrease of 38%. The intercept estimate, \( a_0 \), is -5.758 based on the original data and -3.259 using the modified data resulting in a percent change of 43%. Even more importantly one assessment of the fit of the model, the deviance, shifts from 9.558 with 8 degrees of freedom \( (p = .30) \) to 22.93 with 8 degrees of freedom \( (p < .003) \), rejecting adequacy of fit. The inferences about this modified data set using standard techniques would then be questionable.

Pregibon's Method

Pregibon (1982) proposed a maximum likelihood estimate that is resistant to observations poorly fit by the logistic model. Recalling the definition from Chapter IV of the deviance function, \( d(P, r) = -2(l(x_a, r) - l_{\text{max}}(x_a, r)) \), it was shown that maximizing the loglikelihood function was equivalent to minimizing

\[
\sum_{i=1}^{d} d(P_i, r_i).
\]

Pregibon proposed the estimate \( a_P \) which is a solution to
\[ \min \| \sum_{i=1}^{d} \lambda (d(P_i, r_i)) \|, \quad (227) \]

where \( \lambda (d) \) is based on Huber's (1972) loss function:

\[ \lambda (d) = \begin{cases} 
  d, & d \leq H \\
  2(dH)^{1/2} - H, & \text{otherwise} 
\end{cases} \quad (228) \]

where \( H = (1.345)^2 \).

Use of Pregibon's technique to re-analyze the data from Example 1 leads to the estimates presented in Table 26.

Table 26
Pregibon's Resistant Fit

<table>
<thead>
<tr>
<th>Original Data</th>
<th>Modifying Observation No. 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a_0 = -5.79 ) ( (1.14) )</td>
<td>( a_0 = -4.26 ) ( (.913) )</td>
</tr>
<tr>
<td>( a_1 = 1.01 ) ( (.19) )</td>
<td>( a_1 = .78 ) ( (.15) )</td>
</tr>
</tbody>
</table>

Notice that the use of Pregibon's method results in a change in the slope estimates of 23%, from 1.01 to .78 while the intercept changes 26%, from -5.77 to -4.26. Clearly, the use of this method tapers the influence of \( r_2 \) and the resulting estimates are not as adversely effected as are standard maximum likelihood techniques.
Alternative Robust Procedures

Note that Equation (223) can be written as

\[ \sum_{i=1}^{d_i} \left( \left( y_i - n_i p_i \right) \psi(w_i) \right)^2 \]  \hspace{1cm} (229)

In order to minimize the effect of outlying observations, Huber (1972) in the linear models problem proposed replacing the quadratic function by

\[ p(x) = \begin{cases} \frac{1}{2}x^2, & |x| \leq H \\ H|x| - H^2 / 2, & |x| > H \end{cases} \] (230)

Applying this to our problem leads us to estimate \( \alpha \) by minimizing

\[ \sum_{i=1}^{d_i} P \left( \left( y_i - n_i p_i \right) \psi(w_i) \right)^2 \] (231)

Differentiation of this equation with respect to \( \alpha \) leads to

\[ \sum_{i=1}^{d_i} \psi \left( \frac{r_i - n_i p_i}{\sqrt{n_i p_i (1 - p_i)}} \right) \cdot \frac{n_i p_i (1 - p_i)}{\sqrt{n_i p_i (1 - p_i)}} \cdot \psi'(r_{sd}) = 0 \] (232)

The function \( \psi(r_{sd}) \) is defined as

\[ \psi(r_{sd}) = \begin{cases} r_{sd}, & |r_{sd}| \leq H \\ sgn(r_{sd}) \cdot H, & |r_{sd}| > H \end{cases} \] (233)

The weights \( w_{H}(r_{sd}) \) are then

\[ w_{H}(r_{sd}) = \begin{cases} 1, & |r_{sd}| \leq H \\ H/|r_{sd}|, & |r_{sd}| > H \end{cases} \] (234)

Note that this robustification is more natural than Pregibon’s and the standarized residual that we choose to robustify,
is the Pearson residual described in Chapter VI. Again we let \( H = 1.345 \).
This leads to estimates with approximately 95% asymptotic relative efficiency in the linear models problem.

Table 27 summarizes the results when the data from Example 1 are analyzed using the proposed method. As can be observed in Table 27, the influence of \( r_2 \) is minimal changing the intercept estimate from -5.79 to -4.82 (16.7%) and the estimate of slope from 1.015 to .866 (14.68%).

**Table 27**

**Alternative Weighting Using \( W_H \)**

<table>
<thead>
<tr>
<th>Original Data</th>
<th>Modifying Observation No. 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a_0 = -5.79 \quad (1.14) )</td>
<td>( a_0 = -4.82 \quad (1.01) )</td>
</tr>
<tr>
<td>( a_1 = 1.015 \quad (.19) )</td>
<td>( a_1 = .866 \quad (.17) )</td>
</tr>
</tbody>
</table>

A third weighting scheme is also based on Huber's estimate. Let ...
Where $a = 1.48(\text{med}_i(\text{abs}(r_i - n_i P_0) - \text{med}_i(r_i - n_i P_0))))$, $P_0$ is the maximum likelihood estimate of $P$, and $H = 1.345$. Table 28 summarizes the estimates using this proposed weighting scheme on the data from Example 1.

**Table 28**

<table>
<thead>
<tr>
<th>Alternative Weighting Using $W_M$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Data</td>
</tr>
<tr>
<td>$a_0 = -6.437$ (1.37)</td>
</tr>
<tr>
<td>$a_1 = 1.067$ (0.214)</td>
</tr>
<tr>
<td>Modifying Observation No. 2</td>
</tr>
<tr>
<td>$a_0 = -3.89$ (0.81)</td>
</tr>
<tr>
<td>$a_1 = 0.72$ (0.14)</td>
</tr>
</tbody>
</table>

Note that the use of this weighting scheme on the original data leads to estimates that are slightly different than the usual maximum likelihood estimates. We see that for this set of data that modifying observation No. 2 changes the intercept estimate from -6.437 to -3.89 (39%) and the slope estimate from 1.067 to .72 (32%). The influence of the change in observation No. 2 is not as great as least squares but greater than Pregibon’s method or the method based on $W_H(rsd)$. 

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Analysis of Drug Combination Data Using Robust Methods

Recall the data presented in Chapter VI, Table 31. The use of maximum likelihood methods to fit a logistic model to this data resulted in a significant lack of fit as indicated by the deviance calculated to be 29.56 with 14 degrees of freedom (p < .01). We noted in Chapter VI that our diagnostics revealed that observation number five, which is a dose of rotenone used alone at 2.6 mg/l to be a point that is not fit by the model. The individual deviance component for this observation was approximately -3.0, an indication that this point is indeed an outlier.

That same data set will be analyzed using the three robust methods described earlier. A comparison of the resulting estimators may be found in Table 29.

**Table 29**

Comparison Of Methods

<table>
<thead>
<tr>
<th></th>
<th>Maximum Likelihood</th>
<th>Pregibon's w_i</th>
<th>W_H</th>
<th>W_M</th>
</tr>
</thead>
<tbody>
<tr>
<td>a_0 (s.e.)</td>
<td>-1.902(.184)</td>
<td>-1.918(.1995)</td>
<td>-1.974(.2040)</td>
<td>-1.893(.197)</td>
</tr>
<tr>
<td>a_1 (s.e.)</td>
<td>.406(.0381)</td>
<td>.413(.0396)</td>
<td>.420(.0401)</td>
<td>.411(.0393)</td>
</tr>
<tr>
<td>a_2 (s.e.)</td>
<td>.151(.0127)</td>
<td>.153(.0135)</td>
<td>.157(.0140)</td>
<td>.149(.0130)</td>
</tr>
</tbody>
</table>
It may be observed from Table 29 that in every case the estimate of $\alpha_1$ has been increased by all three robust methods. This is not surprising in view of the fact that $\alpha_1$ is a measure of the slope of the rotenone response curve and the outlying observation number 5 seems to deflate this estimate in the maximum likelihood analysis.

**Computer Software to Perform Robust Regression Analysis**

Pregibon (1982) indicates that the GLIM (1978) system can be adapted to calculate these robust analyses. In fact, most nonlinear estimation computer programs may also be adapted to perform the necessary calculation. In the Appendix F we illustrate the use of SAS procedure NLIN (1985) to perform the three robust estimates described above.

**Simulation Description**

Eight Monte Carlo experiments were conducted to investigate the performance of the maximum likelihood procedure and the three robust techniques. For all the experiments a factorial type design was used with the model

$$\ln\left(\frac{P}{1-P}\right) = \alpha_0 + \alpha_1 x + \alpha_2 y + \alpha_3 xy,$$

for $x = 0,2,4,6$ and $y = 0,2,4,6$. All experiments had twenty observations in a cell and were replicated 1500 times. For every experiment the true values of the parameters were $\alpha_0 = -5.00$, $\alpha_1 = .83$, $\alpha_2 = .83$, and $\alpha_3 = .00$ or $\alpha_3 = .10$. The true probabilities of response, $P$, are found in Table 30 for $\alpha_3 = .00$ and Table 31 for $\alpha_3 = .10$. 
Table 30
True Value Of P for $\alpha_3 = 0.0$

<table>
<thead>
<tr>
<th>Y</th>
<th>0.495</th>
<th>0.837</th>
<th>0.964</th>
<th>0.993</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0.157</td>
<td>0.495</td>
<td>0.837</td>
<td>0.964</td>
</tr>
<tr>
<td>4</td>
<td>0.034</td>
<td>0.157</td>
<td>0.495</td>
<td>0.837</td>
</tr>
<tr>
<td>2</td>
<td>0.007</td>
<td>0.034</td>
<td>0.157</td>
<td>0.495</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0 2 4 6

Table 31
True Value Of P for $\alpha_3 = 0.1$

<table>
<thead>
<tr>
<th>Y</th>
<th>0.495</th>
<th>0.945</th>
<th>0.997</th>
<th>1.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0.157</td>
<td>0.686</td>
<td>0.962</td>
<td>0.997</td>
</tr>
<tr>
<td>4</td>
<td>0.034</td>
<td>0.217</td>
<td>0.686</td>
<td>0.945</td>
</tr>
<tr>
<td>2</td>
<td>0.007</td>
<td>0.034</td>
<td>0.157</td>
<td>0.495</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0 2 4 6

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Notice that in Table 30 the design is symmetric about the linear 50 percent response isobol while in Table 31 the 50 percent response isobol is a curve going through the lower region of the grid.

The usual assumption regarding data in drug combination experiments is that they are binomially distributed, designated as \( B(n,P) \). Using the logistic model, the relationship between \( P \) and the dose levels \( x \) and \( y \) is

\[
P = \frac{e^{a_0 + a_1 x + a_2 y + a_3 xy}}{1 + e^{a_0 + a_1 x + a_2 y + a_3 xy}}
\]

The expected value of a random variable from a \( B(n,p) \) distribution is \( np \) with variance \( np(1-P) \). In order to study the robust estimators, the data were contaminated in various ways using the Poisson distribution, designated as \( P(\lambda) \), with expected value \( \lambda \) and variance \( \lambda \). Consider \( \lambda \) equal to \( n \cdot p \). Since \( 0 \leq p \leq 1 \), the variance of data from this distribution have the same mean but a variance that is larger than the \( B(n,p) \) distribution except for values of \( p = 1.0 \) where the variance is the same.

When generating data from a \( P(\lambda) \) distribution, data may be observed with values larger than \( n \). To overcome this problem, we censored the data with values greater than \( n \) to have values equal to \( n \). The Poisson parameter \( \lambda \) is then adjusted so that the distribution still has mean \( \lambda^* = np \). For example, with \( n = 20 \) and \( p = .837 \) the usual value of \( \lambda \) would be set equal to 16.74, but to account for the censored values, \( \lambda^* = 17.51579 \). The binomial random variables were generated with the IMSL (1982) subroutine GGBN and the Poisson random variables
generated with the IMSL (1982) subroutine GGPOS. Table 32 describes the methods of contamination for the eight experiments.

Table 32
Methods Of Contamination

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Designation</th>
<th>$\alpha_3$</th>
<th>Contamination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FN</td>
<td>0</td>
<td>No contamination</td>
</tr>
<tr>
<td>2</td>
<td>FNC15</td>
<td>0</td>
<td>Each cell had a 15% prob. of contamination</td>
</tr>
<tr>
<td>3</td>
<td>FNC25</td>
<td>0</td>
<td>Each cell had a 25% prob. of contamination</td>
</tr>
<tr>
<td>4</td>
<td>FNC-(2,4)</td>
<td>0</td>
<td>Cells with $(x,y) = (2,2)$ and $(4,4)$ contaminated</td>
</tr>
<tr>
<td>5</td>
<td>FNC-ALL</td>
<td>0</td>
<td>All cells contaminated</td>
</tr>
<tr>
<td>6</td>
<td>FI</td>
<td>.1</td>
<td>No contamination</td>
</tr>
<tr>
<td>7</td>
<td>FI05</td>
<td>.1</td>
<td>Each cell had a 5% prob. of contamination</td>
</tr>
<tr>
<td>8</td>
<td>FI15</td>
<td>.1</td>
<td>Each cell had a 15% prob. of contamination</td>
</tr>
</tbody>
</table>

The computer programs in Appendix F were used to compute the necessary estimates.
Simulation Results

The Monte Carlo estimates of the mean square errors, bias, and variance of the sampling distributions of the estimated regression coefficients are presented in Table 33. The results for experiments FN and Fl, which are noncontaminated, for the maximum likelihood estimator (mle) are similar in magnitude to results obtained by Smith, Savin, and Robertson (1984) in a simulation that compared maximum likelihood estimation to the minimum chi-square estimator for logistic regression. Also, the robust-estimators perform in a manner similar to the mle for those two experiments. Examination of the contaminated experiments show fairly similar results for all the estimators except in experiment FNC-(2,4). In that experiment the mle estimator had the largest mean square error, bias and variance as compared to the three robust estimators. Among the robust procedures, the mean absolute deviance (MAD) estimator and Pregibon’s estimator appear to perform the best in that experiment.
## Monte Carlo Results For Estimators Of Regression Coefficients

<table>
<thead>
<tr>
<th>Design</th>
<th>Estimator</th>
<th>MSE Bias Variance  ( a_2 )</th>
<th>MSE Bias Variance  ( a_1 )</th>
<th>MSE Bias Variance  ( a_2 )</th>
<th>MSE Bias Variance  ( a_1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>FN</td>
<td>Huber</td>
<td>1.2789 - 4.079 1.1132</td>
<td>0.0871 0.0706 0.3438</td>
<td>0.4692 0.0882 0.422</td>
<td>0.023 - 0.018 0.022</td>
</tr>
<tr>
<td></td>
<td>Mad</td>
<td>1.099 - 2.064 1.0391</td>
<td>0.0441 0.0451 0.0424</td>
<td>0.4363 0.0445 0.0417</td>
<td>0.023 - 0.003 0.023</td>
</tr>
<tr>
<td></td>
<td>Mle</td>
<td>0.956 - 1.581 0.9312</td>
<td>0.0388 0.0284 0.0381</td>
<td>0.0382 0.0271 0.0375</td>
<td>0.022 - 0.010 0.022</td>
</tr>
<tr>
<td></td>
<td>Pregibon</td>
<td>0.980 - 2.173 0.9334</td>
<td>0.0396 0.0387 0.0383</td>
<td>0.0387 0.0369 0.0374</td>
<td>0.021 - 0.014 0.021</td>
</tr>
<tr>
<td>FNC1S</td>
<td>Huber</td>
<td>1.3150 - 3.582 1.1876</td>
<td>0.0527 0.0605 0.0491</td>
<td>0.0496 0.0586 0.0462</td>
<td>0.027 - 0.001 0.027</td>
</tr>
<tr>
<td></td>
<td>Mad</td>
<td>1.0646 - 2.000 1.0253</td>
<td>0.0436 0.0347 0.0424</td>
<td>0.0417 0.0315 0.0407</td>
<td>0.024 - 0.003 0.024</td>
</tr>
<tr>
<td></td>
<td>Mle</td>
<td>1.0979 - 2.697 1.0258</td>
<td>0.0445 0.0457 0.0424</td>
<td>0.0424 0.0429 0.0406</td>
<td>0.023 - 0.005 0.023</td>
</tr>
<tr>
<td></td>
<td>Pregibon</td>
<td>1.4154 - 4.087 1.2492</td>
<td>0.0524 0.0674 0.0479</td>
<td>0.0516 0.0677 0.0471</td>
<td>0.027 - 0.007 0.027</td>
</tr>
<tr>
<td>FNC2S</td>
<td>Huber</td>
<td>1.2381 - 3.110 1.1422</td>
<td>0.0478 0.0508 0.0452</td>
<td>0.0470 0.0552 0.0443</td>
<td>0.028 - 0.000 0.028</td>
</tr>
<tr>
<td></td>
<td>Mad</td>
<td>4.0650 - 5.027 3.8148</td>
<td>0.1277 0.0827 0.1210</td>
<td>0.1282 0.0827 0.1214</td>
<td>0.042 - 0.019 0.042</td>
</tr>
<tr>
<td></td>
<td>Mle</td>
<td>0.8126 - 0.101 0.8134</td>
<td>0.0345 0.0019 0.0345</td>
<td>0.0321 - 0.004 0.0321</td>
<td>0.022 - 0.002 0.022</td>
</tr>
<tr>
<td></td>
<td>Pregibon</td>
<td>9.9871 - 6.6845 7.1546</td>
<td>0.3133 0.2462 0.2315</td>
<td>0.3171 - 0.2832 0.2370</td>
<td>0.008 - 0.009 0.0067</td>
</tr>
<tr>
<td>FNC-</td>
<td>Huber</td>
<td>5.3986 - 6.624 4.0045</td>
<td>0.1833 - 0.1503 0.1608</td>
<td>0.0097 - 0.0004 0.0059</td>
<td>0.009 - 0.0004 0.0059</td>
</tr>
<tr>
<td>(2,4)</td>
<td>Mad</td>
<td>4.1872 - 4.123 4.0185</td>
<td>0.1474 - 0.0752 0.1418</td>
<td>0.0465 - 0.0717 0.1443</td>
<td>0.001 - 0.0000 0.0051</td>
</tr>
<tr>
<td></td>
<td>Mle</td>
<td>4.5456 - 3.420 4.1526</td>
<td>0.1644 - 0.1427 0.1441</td>
<td>0.1669 - 0.1407 0.1472</td>
<td>0.054 - 0.012 0.0054</td>
</tr>
<tr>
<td></td>
<td>Pregibon</td>
<td>9.133 - 3.297 0.8051</td>
<td>0.0362 - 0.0533 0.0334</td>
<td>0.0355 - 0.0568 0.0323</td>
<td>0.026 - 0.059 0.026</td>
</tr>
<tr>
<td>Fi</td>
<td>Huber</td>
<td>9.739 - 2.937 0.8883</td>
<td>0.0384 - 0.0468 0.0363</td>
<td>0.0379 - 0.0489 0.0355</td>
<td>0.029 - 0.006 0.029</td>
</tr>
<tr>
<td></td>
<td>Mad</td>
<td>0.7028 - 1.165 0.6779</td>
<td>0.0300 - 0.0259 0.0293</td>
<td>0.0291 - 0.0292 0.0283</td>
<td>0.024 - 0.002 0.024</td>
</tr>
<tr>
<td></td>
<td>Mle</td>
<td>0.7459 - 2.006 0.7098</td>
<td>0.0314 - 0.0316 0.0304</td>
<td>0.0306 - 0.0352 0.0294</td>
<td>0.025 - 0.005 0.025</td>
</tr>
<tr>
<td></td>
<td>Pregibon</td>
<td>1.5100 - 4.836 1.2769</td>
<td>0.0566 - 0.0814 0.0499</td>
<td>0.0544 - 0.0789 0.0482</td>
<td>0.025 - 0.002 0.025</td>
</tr>
<tr>
<td>Fi5</td>
<td>Huber</td>
<td>1.3150 - 3.582 1.1876</td>
<td>0.0527 - 0.0605 0.0491</td>
<td>0.0496 - 0.0586 0.0462</td>
<td>0.026 - 0.001 0.026</td>
</tr>
<tr>
<td></td>
<td>Mad</td>
<td>1.0646 - 2.000 1.0253</td>
<td>0.0436 - 0.0347 0.0424</td>
<td>0.0417 - 0.0315 0.0407</td>
<td>0.024 - 0.002 0.024</td>
</tr>
<tr>
<td></td>
<td>Mle</td>
<td>1.0979 - 2.697 1.0258</td>
<td>0.0445 - 0.0457 0.0423</td>
<td>0.0424 - 0.0429 0.0406</td>
<td>0.023 - 0.005 0.023</td>
</tr>
<tr>
<td></td>
<td>Pregibon</td>
<td>17.3621 - 2.1678 12.6723</td>
<td>0.5694 - 3.7552 0.4290</td>
<td>0.5111 - 3.6644 0.3771</td>
<td>0.057 - 0.028 0.0149</td>
</tr>
<tr>
<td>Fi5</td>
<td>Huber</td>
<td>8.0706 - 1.264 6.4769</td>
<td>0.2546 - 0.2172 0.2076</td>
<td>0.2581 - 0.2160 0.2116</td>
<td>0.0108 - 0.0162 0.0105</td>
</tr>
<tr>
<td></td>
<td>Mad</td>
<td>5.3870 - 5.216 5.1184</td>
<td>0.1771 - 0.0952 0.1682</td>
<td>0.1761 - 0.0914 0.1678</td>
<td>0.0071 - 0.0037 0.0007</td>
</tr>
<tr>
<td></td>
<td>Mle</td>
<td>5.5568 - 1.019 4.5210</td>
<td>0.1835 - 0.1812 0.1508</td>
<td>0.1815 - 0.1767 0.1504</td>
<td>0.0085 - 0.0119 0.0008</td>
</tr>
</tbody>
</table>
The most commonly used test statistic for the hypothesis that $\beta_i = \beta^*$, $i = 0, 1, 2$ is

$$Z_i = \frac{(\hat{\beta}_i - \beta^*)}{(\text{standard error of } \beta_i)}.$$

Table 34 presents the Monte Carlo estimates of the mean, variance, skewness, and the number of times that $|Z_i| \geq 1.96$. Results from Table 34 for the noncontaminated experiments FN and FI show close agreement between the three robust estimators and the mle. For the contaminated experiments, the variance of the test statistic using mle has a universally larger variance than the robust estimators with the MAD estimator tending to have a variance closer to the reference value of 1.0 than Pregibon's estimate or the Huber estimate. As with estimation, the experiment that shows the largest differentiation between the robust estimators and the mle is FNC-(2,4). For that design the test statistic using mle has universally larger bias, as reflected by its mean value being farthest from 0.0, larger variance and tail probabilities much larger than the expected .05. Among the robust estimators, the MAD and Pregibon estimators appear to perform the best followed by the Huber estimate. Over all the contaminated experiments, especially with reference to $Z_3$, the test statistic using the MAD estimate appears to perform similarly or slightly better than the Pregibon estimate and those two followed by the Huber estimate. Note that for experiment FI15 with 15% contamination the model is no longer logistic but closer to the Poisson. This is reflected by the no. of rejections/1500 which is far from the reference .05 value for all the estimates.
<table>
<thead>
<tr>
<th>Design</th>
<th>Estimator</th>
<th>Mean Variance</th>
<th>Skewness Rejections $z_1$</th>
<th>Mean Variance</th>
<th>Skewness Rejections $z_2$</th>
<th>Mean Variance</th>
<th>Skewness Rejections $z_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>FN</td>
<td>Huber</td>
<td>.1920</td>
<td>1.1034</td>
<td>.2279 .0589</td>
<td>.1927 .1034</td>
<td>-2175 .0555</td>
<td>.0140 .0398</td>
</tr>
<tr>
<td></td>
<td>Mad</td>
<td>.1343</td>
<td>1.0744</td>
<td>-2756 .0519</td>
<td>.1322 .1017</td>
<td>.3070 .0583</td>
<td>.0109 .0152</td>
</tr>
<tr>
<td></td>
<td>Mle</td>
<td>.0664</td>
<td>1.0812</td>
<td>-2638 .0513</td>
<td>.0651 .1019</td>
<td>-2744 .0500</td>
<td>.0099 .0007</td>
</tr>
<tr>
<td></td>
<td>Pregibon</td>
<td>.0915</td>
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<td>1.3229</td>
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<td>-1524 .0742</td>
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<td>1.4170</td>
<td>-2307 .1094</td>
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<td>1.2619</td>
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<td>-5108 .3478</td>
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<td>-4277 .2837</td>
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<td>-4422 .2801</td>
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<tr>
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<td>-2208 .0791</td>
<td>.0011 1.3113</td>
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<td>.0134 1.2680</td>
</tr>
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<td>Huber</td>
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<td>.9499 .22518</td>
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<td>-.5874 .2567</td>
<td>.2528 .2432</td>
<td>-.5474 .2522</td>
<td>.0926 2.3868</td>
</tr>
</tbody>
</table>

Table 34

Monte Carlo Results For The Test Statistics Of The Regression Coefficient Estimators

* reject $H_0$ if $|z| \geq 1.96/1500$
Summary

Occasionally the maximum likelihood fit can be spoiled by one or two observations that are not well fit by the logistic model. We have presented three robust methods that reduce the influence of these outlying observations by assigning these observations a weight smaller than they would normally receive. Additionally, the robust analyses can be carried out using existing statistical software.
CHAPTER VIII

ESTIMATION OF THE ED50 IN DRUG COMBINATION EXPERIMENTS

Introduction

A parameter that scientists and pathologists rely on to aid interpretation of drug combination experiments is the ED50 which is defined as the dosages required of each drug in the combination to produce a fifty percent response. It may be recalled from Chapter I that the ED50 is an isobol corresponding to a probability of response equal to 0.5. Figure 54 illustrates the estimation of the ED50 from three logistic models. The first model

\[ \ln\left(\frac{P}{1-P}\right) = a_0 + a_1 x_1 + a_2 x_2 \]

where \( x_1 \) represents the dose of drug A and \( x_2 \) represents the dose of drug B, is the model where there is no interaction between the two drugs. The second and third models are

\[ \ln\left(\frac{P}{1-P}\right) = a_0 + a_1 x_1 + a_2 x_2 + a_3 x_1 x_2 \]

and

\[ \ln\left(\frac{P}{1-P}\right) = a_0 + a_1 x_1 + a_2 x_2 - a_3 x_1 x_2 \]

respectively. Note the second model has a positive interaction coefficient denoting antagonism and the third model is representative of a model illustrating potentiation. In all three cases the estimation of the ED50 is accomplished by setting \( P = 0.5 \). Notice that the ED50 estimates form a straight line using the no interaction model and the curves above and
Figure 54. Estimation of the ED50 From Three Logistic Models.
below this line are the ED$_{50}$ estimates from the antagonism and potentiation models, respectively.

In the sections which follow we will illustrate the estimation of the ED$_{50}$ with asymptotic confidence regions using the method of Carter et al. (1986) which assumes that the logistic model adequately describes the data. We also describe a bootstrap adaptation of the Carter et al. (1986) method.

**Estimation of the ED$_{50}$ and the Asymptotic Confidence Regions Assuming a Logistic Model**

We shall make the assumption that the drug combination trials consist of two drugs. Extensions to more drugs are straightforward but computationally and graphically more difficult to illustrate. The interested reader is referred to Carter et al. (1986).

Recall the logistic model,

$$\ln\left(\frac{P}{1-P}\right) = a_0 + a_1 x_1 + a_2 x_2 + a_3 x_1 x_2$$

where for each different combination of $x_1$ and $x_2$, the number of responses $r_i$ is binomial $(n_i, P_i)$ for $i = 1, \ldots, n$. We shall let $N$ denote the number of different combinations of $x_1$ and $x_2$ and let

$$\mathbf{z} = \begin{bmatrix} 1, x_1, x_2, x_1 x_2 \end{bmatrix}$$

and

$$\mathbf{a} = \begin{bmatrix} a_0, a_1, a_2, a_3 \end{bmatrix}.$$

Recall that Equation (236) may conveniently be written as
With the model described by Equation (236) the maximum likelihood estimate \( \hat{a} \) of \( a \) has an asymptotic normal distribution,

\[
N(\hat{a}, \frac{1}{N} \Sigma)
\]

where \( \Sigma \) is the covariance matrix of the multivariate normal distribution.

Assuming that \( N \) is large enough for the asymptotic result mentioned above to be a good approximation, we may write:

\[
N(\hat{a} - a) \Sigma^{-1}(\hat{a} - a) \xrightarrow{d} \chi^2
\]

(238)

Note that the large sample covariance matrix for \( a \), \( \Sigma/N \), is consistently estimated from the inverse of the sample information matrix. To be explicit

\[
\hat{\Sigma}/N = J^{-1}
\]

(239)

where

\[
J_{ij} = -\frac{\partial^2}{\partial a_i \partial a_j} l(a, x)
\]

and \( l(a, x) \) is the log likelihood. Replacing \( \Sigma/N \) in Equation (238) by the estimator just mentioned, we have

\[
(\hat{a} - a)' J(\hat{a} - a) \approx \chi^2
\]

(240)

from which it may be written

\[
Pr\left((\hat{a} - a)' J(\hat{a} - a) \leq \chi^2\right) \approx 1 - a
\]

(241)
which is 1-\(\alpha\) confidence ellipsoid for \(\mathbf{a}\). By the extended Cauchy-Schwartz inequality

\[
(\hat{\mathbf{a}} - \mathbf{a})' J (\hat{\mathbf{a}} - \mathbf{a}) \geq \left[ (\hat{\mathbf{a}} - \mathbf{a})' \mathbf{x} \right]^2 / \left[ \mathbf{x}' J^{-1} \mathbf{x} \right]
\]

(242)

for any \(\mathbf{x}\).

Combining Equations (241) and (242), we have

\[
\Pr \left[ \left( \frac{(\hat{\mathbf{a}} - \mathbf{a})' \mathbf{x}}{\sqrt{\mathbf{x}' J^{-1} \mathbf{x}}} \right)^2 \leq \chi^2_{\alpha \mathbf{1}, 1} \right. \text{ for all } \mathbf{x} = 1 - \alpha
\]

which may be written as

\[
\Pr \left[ \frac{(\hat{\mathbf{a}} - \mathbf{a})^2 / \mathbf{x}' J^{-1} \mathbf{x}}{\chi^2_{\mathbf{x}'; \mathbf{a} \mathbf{1}, \alpha}} \leq \chi^2_{\mathbf{x}'; \mathbf{a} \mathbf{1}, \alpha} + \left((\hat{\mathbf{a}} - \mathbf{a})^2 / \chi^2_{\mathbf{x}'; \mathbf{a} \mathbf{1}, \alpha}\right)^{1/2}, \text{ for all } \mathbf{x} \right] = 1 - \alpha
\]

(243)

Recalling that we are interested in the inverse of the logistic function, Equation (243) may be written as

\[
\Pr \left[ g^{-1}(\hat{\mathbf{a}} - \mathbf{a}) / (\chi^2_{\mathbf{x}'; \mathbf{a} \mathbf{1}, \alpha})^{1/2} \leq g^{-1}(\mathbf{x}' J^{-1} \mathbf{x}) / (\chi^2_{\mathbf{x}'; \mathbf{a} \mathbf{1}, \alpha})^{1/2}, \text{ for all } \mathbf{x} \right] = 1 - \alpha
\]

(244)

where \(g^{-1}(t) = \frac{e^t}{1 + e^t} = [1 + e^{-t}]^{-1}\)

For a particular value of \(\mathbf{x}\) define

\[
P_L(\mathbf{x}) = [1 + \exp \{-\hat{\mathbf{a}}' + (\mathbf{x}' J^{-1} \mathbf{x})^{1/2}\}]^{-1}
\]

(245)

and

\[
P_u(\mathbf{x}) = [1 + \exp \{-\hat{\mathbf{a}}' - (\mathbf{x}' J^{-1} \mathbf{x})^{1/2}\}]^{-1}
\]

(246)

Define the ED50 set, \(S_{50}(\mathbf{a})\), as the set of all \(\mathbf{x}\) belonging to \(\mathbf{R}^2\) such that
The set $S_{50}(a)$ estimates $S_{50}(g)$. Note that we are interested in a subset of $\mathbf{x}$. In particular we are interested in $\mathbf{x}^* = \{x_1, x_2\}' \in \mathbf{X} = \{1, x_1, x_2, x_1x_2\}'$. We may now write

\[
0.5 = \left( \frac{e^{x' \alpha}}{1 + e^{x' \alpha}} \right).
\]

A conservative confidence region for the ED$_{50}$ set, $S_{50}(a)$, with approximate confidence greater or equal to $1-\alpha$ is then given by

\[
\{ \mathbf{y} \in \mathbb{R}^2 | \mathbb{P}_{L}(\mathbf{y}) \leq \left[ \frac{e^{y' \gamma}}{1 + e^{y' \gamma}} \right] \leq \mathbb{P}_{U}(\mathbf{y}) \text{ for all } \mathbf{x}^* \in S_{50}(a) \} \quad (247)
\]

It must be noted that this confidence band procedure is conservative in the sense that the $1-\alpha$ probability statements like Equation (243) applies to all $\mathbf{x}$ so confidence bands for a particular subset of $\mathbf{x}$ will have confidence level greater than or equal to $1-\alpha$. However, this methodology is a practical solution to an applied problem.

To illustrate this technique, the data found in Table 35 below were simulated from the logistic model,

\[
ln \left( \frac{P}{1-P} \right) = -5.0 + .83 x_1 + .83 x_2 + .3 x_1x_2
\]

assuming there were twenty animals observed at each drug combination using the IMSL (1982) routine GGBN to generate binomial random observations.
Table 35
Simulated Logistic Data

<table>
<thead>
<tr>
<th>Dose of Drug 1 ($x_1$)</th>
<th>Dose of Drug 1 ($x_2$)</th>
<th>No. of Observations</th>
<th>No. of Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>0.0</td>
<td>2.0</td>
<td>20</td>
<td>1</td>
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<tr>
<td>0.0</td>
<td>4.0</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>0.0</td>
<td>6.0</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>2.0</td>
<td>0.0</td>
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<td>0</td>
</tr>
<tr>
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<td>2.0</td>
<td>20</td>
<td>7</td>
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<td>4.0</td>
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<td>18</td>
</tr>
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<td>2.0</td>
<td>6.0</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>4.0</td>
<td>0.0</td>
<td>20</td>
<td>2</td>
</tr>
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<td>4.0</td>
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<tr>
<td>6.0</td>
<td>6.0</td>
<td>20</td>
<td>20</td>
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</table>
Using the GLIM (1978) software package, the maximum likelihood estimates were computed and are displayed in Table 36.

Table 36
Maximum Likelihood Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>Deviance</th>
<th>Degrees of Freedom</th>
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<td>12</td>
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<td>.185</td>
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<td>$a_2$</td>
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<td>.187</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$a_3$</td>
<td>.315</td>
<td>.069</td>
<td></td>
<td></td>
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</table>

As expected, the deviance $= 2.29$ with 12 degrees of freedom indicates a good fit of this model to the data. The $ED_{50}$ set is then determined as the set of all $(x_1,x_2)$ such that .5 = $(1 + \exp(5.803-.899 x_1-.990 x_2-.315 x_1 x_2))^{-1}$. The approximate 95% confidence region is determined using Equations (241), (242), and (243). Figure 55 depicts the $ED_{50}$ set and the corresponding 95% confidence region. As can be observed in Figure 55, the $ED_{50}$ set describes a curve in the potentiation region which corresponds to the significant value of $a_3 = .315$. Other examples illustrating the application of this technique may be found in Chapter VI.
Figure 55. Estimation of the ED50 and Corresponding Confidence Bound.

Legend
- ED 50
- 95% UP BD
- 95% LOW BD
Bootstrap Methods

The method for obtaining ED$_{50}$ confidence bands proposed by Carter et al. (1986) appears to be adequate when the size of the sample is sufficient to allow the asymptotic results to apply and when the data are well fit by the logistic model. When this second assumption is not met, the estimate of the covariance of the logistic parameters, $\alpha$, may be in considerable error. Efron (1979) suggests that bootstrap methods may be useful in obtaining a more representative estimate of this covariance when there is little or no information regarding the distribution of the underlying errors.

We would like to propose that when a significant lack of fit to the logistic model is detected that the bootstrap estimate of the covariance of the estimated parameters, which are estimated using one of the robust techniques suggested in Chapter VII be substituted into the Carter et al. (1986) formulation. This recommendation includes the use of the parameters estimated using the robust procedures in the ED$_{50}$ estimate. It is felt that since the logistic model, using maximum likelihood estimation, does not adequately fit the data that both the resulting parameter estimates and covariance estimates may be in error, while the parameter estimates from one of the robust procedures with the corresponding bootstrap estimate will more accurately reflect the underlying model. Further, when the logistic model provides an adequate fit to the data, the robust estimates with the bootstrap covariance will lead to an estimate of
the ED\textsubscript{50} and confidence intervals that are not substantially different from the results obtained using maximum likelihood methods.

The Bootstrap Technique

It is assumed that the relationship between the probability of response \( P_j \) at a given combination of drug 1 and drug 2, denoted \( x_1 \) and \( x_2 \), respectively and \( x_1 \) and \( x_2 \) is of the form

\[
P_i = g^{-1}(\alpha x)
\]

where \( g^{-1}(t) = \left[ \frac{e^{\alpha x}}{1 + e^{\alpha x}} \right] \).

The estimate \( \alpha \) minimizes

\[
\Sigma_p \left( \frac{r_i - n_i P_i}{\sqrt{\omega_i}} \right)
\]

where \( p(x) \) is the function proposed by Huber\textsuperscript{5} and discussed in Chapter VII. We will view \( T_i = (x_{1i}, x_{2i}, r_i, n_i); i = 1, \ldots, N \) as independent random quantities from an unknown distribution \( F \). To estimate the covariance of \( \alpha \), the Monte Carlo algorithm described by Efron will be implemented:

1. Fit the nonparametric MLE of \( F \),

\[
F = \text{mass} \frac{1}{N} \text{at } T_i = (x_{1i}, x_{2i}, r_i, n_i); i = 1, \ldots, N
\]

2. Draw a bootstrap sample from \( F \),

\[
T_1^*, T_2^*, \ldots, T_N^* \text{ iid } F
\]
and calculate $a^*$ using the bootstrap sample and one of the robust maximum likelihood methods.

3. Independently repeat Step 2 a large number ($B$) of times obtaining $a_1^*,...,a_B^*$, and calculate

$$\text{Cov}(a^*) = \left\{ \frac{1}{B-1} \sum_{i=1}^{B} (a_{i}^* - a^*)^2 \right\}^{1/2}, \text{ where } a_i^* = \frac{\sum_{i=1}^{B} a_i^*}{B}.$$

As in all bootstrap applications, the accuracy of the method depends on the quality of our estimate $F$.

**Applications of the Bootstrap Estimate**

The data found earlier in Chapter VI, Table 23 will be used for illustration. Recall that the data found in that table come from Goldin et al. (1955) who were investigating the interactive effects of amethopterin and 6-mercaptopurine in mice. It was concluded that the logistic model

$$\ln\left( \frac{P}{1-P} \right) = -3.541 + .0145 x_1 + .0056 x_2 + .000063 x_1 x_2$$

adequately fit the data. The robust technique using Huber’s weights was applied to the same data resulting in the model:

$$\ln\left( \frac{P}{1-P} \right) = -3.802 + .0155 x_1 + .0058 x_2 + .000055 x_1 x_2.$$

As expected the two model estimates are close. Found in Table 37 is a comparison between the estimates of covariance using the maximum likelihood techniques and the bootstrap estimates.
Table 37
A Comparison Of The Estimates Of Covariance From Maximum Likelihood And The Bootstrap

<table>
<thead>
<tr>
<th></th>
<th>(a_0)</th>
<th>(a_1)</th>
<th>(a_2)</th>
<th>(a_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a_0)</td>
<td>.1069 (max likelihood)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>.271 (bootstrap)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a_1)</td>
<td>-4.6E-04</td>
<td>3.40E-06</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-14.0E-04</td>
<td>9.40E-06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a_2)</td>
<td>-1.75E-04</td>
<td>7.84E-07</td>
<td>5.78E-07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-7.28E-04</td>
<td>3.45E-06</td>
<td>5.36E-06</td>
<td></td>
</tr>
<tr>
<td>(a_3)</td>
<td>-7.79E-07</td>
<td>-6.59E-09</td>
<td>-2.40E-09</td>
<td>3.60E-10</td>
</tr>
<tr>
<td></td>
<td>3.8E-06</td>
<td>-3.07E-08</td>
<td>-3.04E-08</td>
<td>5.49E-10</td>
</tr>
</tbody>
</table>

The estimates found in Table 37 were then used to calculate the \(ED_{50}\) curve and its confidence found using the method of Carter et al. (1986) described earlier. Figure 56 illustrates the \(ED_{50}\) curve and the resulting 95% confidence bound using the maximum likelihood technique to obtain the parameter estimates. Compare Figure 56 with Figure 57 which contains the \(ED_{50}\) and 95% confidence bound using Huber’s method to estimate the parameters and the bootstrap with \(B = 100\) repetitions to estimate the variance-covariance of the parameters. The results do not differ greatly, but the bootstrap method does provide slightly larger confidence intervals.

For a second example, the data from Chapter VI - Table 22 testing the synergistic effects of two insecticides using the insect chrysanthemum aphis will be used. Recall from Chapter VI that the logistic model
Figure 56. Estimation of the ED50 and Corresponding Confidence Bound Using MLE Technique.
Figure 57. Estimation of the ED50 and Corresponding Confidence Bound Using Huber's Technique and the Data in Table 23.
\[ \ln \left( \frac{P}{1-P} \right) = a_0 + a_1 x_1 + a_2 x_2 \]

was the model which best fit the data, but this fit was not adequate resulting in a deviance of 29.56 with 14 degrees of freedom. Table 38 compares the covariance estimates when using maximum likelihood and the bootstrap estimates when using Huber’s robust method.

### Table 38

**A Comparison Of The Estimates Of Covariance From Maximum Likelihood And The Bootstrap**

<table>
<thead>
<tr>
<th></th>
<th>(a_0)</th>
<th>(a_1)</th>
<th>(a_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a_0)</td>
<td>.034 (max likelihood)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a_0)</td>
<td>.150 (bootstrap)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a_1)</td>
<td>-5.37E-03</td>
<td>1.45E-03</td>
<td></td>
</tr>
<tr>
<td>(a_1)</td>
<td>-19.00E-03</td>
<td>3.83E-03</td>
<td></td>
</tr>
<tr>
<td>(a_2)</td>
<td>-1.67E-03</td>
<td>2.21E-04</td>
<td>1.61E-04</td>
</tr>
<tr>
<td>(a_2)</td>
<td>-7.65E-03</td>
<td>8.52E-04</td>
<td>5.25E-04</td>
</tr>
</tbody>
</table>

As Table 38 illustrates, the maximum likelihood estimates of covariance are always much less than that of the bootstrap estimates and, perhaps even more importantly, the parameter estimates themselves differ slightly as displayed in Table 39.
Table 39
Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter Estimate</th>
<th>Max. Likelihood</th>
<th>Max. Likelihood With 2 Outliers Removed</th>
<th>Hubers Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>a₀</td>
<td>-1.902</td>
<td>-1.902</td>
<td>-1.974</td>
</tr>
<tr>
<td>a₁</td>
<td>.406</td>
<td>.417</td>
<td>.420</td>
</tr>
<tr>
<td>a₂</td>
<td>.151</td>
<td>.148</td>
<td>.157</td>
</tr>
</tbody>
</table>

Referring to Figure 36 of Chapter VI one notices that there are 2 outliers, observation number 5 which has an actual value less than that predicted by the model and observation number 16 which has an actual value greater than that predicted by the model. As a result of these two observations, the fit using maximum likelihood method is poor but the parameter estimates do not differ greatly from the robust estimates. This is due in part to the fact that the two outliers are in opposite directions with respect to the fitted model. Figure 58 illustrates the ED₅₀ and its 95% confidence bound using the maximum likelihood method. Comparing this result with Figure 59, which depicts the ED₅₀ and the 95% confidence bound using Huber’s method to estimate the parameters and the bootstrap to estimate the covariance of the parameters, we see that the bootstrap method provides a much broader confidence bound. In light of the fact that the logistic model does not adequately describe the data, one would prefer the ED₅₀ estimate with the 95% confidence bounds computed using the bootstrap procedure. Appendix G contains the
Figure 58. Estimation of the ED50 and Corresponding Confidence Bound Using MLE Technique and the Data in Table 22.
Figure 59. Estimation of the ED50 and Corresponding Confidence Bound Using Hubers Technique and the Data in Table 22.
program statements used to compute these estimates using this data set and the popular statistical software package, SAS (1985).

**Determining the ED\textsubscript{50} with a Nonparametric Kernal Estimate**

Although the logistic model may be used in many cases to fit the data from a drug combination experiment, there are occasions when the fit of this model is not adequate. We would like to propose a nonparametric procedure to estimate the ED\textsubscript{50} which is an extension of the work by Kappenman (submitted for publication). Kappenman developed a nonparametric estimate for the ED\textsubscript{50} based on a kernal estimate of the underlying distribution when a single drug is under consideration. Simulation studies performed by Kappenman indicate that his proposed estimate performed well against the 10\% trimmed Spearman-Karber (SKIO) estimator which is the estimate recommended by the simulation results of Hamilton (1979) and Miller and Halpern (1980). At a sample size of n = 20 per dose level the Kappenman estimator was comparable to the SKIO, but at n = 30 per dose the Kappenman estimate was superior in terms of empirical mean-squared error over all the contaminated logistic distributions studied. In light of these results, we chose to extend Kappenman's estimate to the two drug combination setting.

Let \((x_1, y_1, r_1), \ldots, (x_N, y_N, r_N)\) denote triplets of the dose of drug one, x the dose of drug two, y, and the binary random variable, r. If x and y were discrete and the number of observations at each combination of x and y are large enough to create meaningful proportions, a natural estimate of
the probability of response at combination $(x, y)$ may be written as

$$Pr[\mathbf{r} = 1 | (x_i, y_j)] = \frac{\text{number of success at } (x_i, y_j)}{\text{number of observations at } (x_i, y_j)}$$

However, $x$ and $y$ are not discrete but continuous so an averaging over neighboring values of $(x_i, y_j)$ is needed. One such method to accomplish this averaging would be to use a kernel function. An example is presented below.

$$Pr[\mathbf{r} = 1 | (x_i, y_j)] = F(x, y) = \frac{\sum_{i=1}^{N} r_i e^{-h(x-x_i)^2(y-y_i)^2}}{N \sum_{i=1}^{e} e^{-h(x-x_i)^2(y-y_i)^2}} \quad (248)$$

where $h$ is a smoothing parameter. Copas (1983) used the univariate form of this estimate to plot $F(x)$ against $x$. Unfortunately, Copas did not derive a procedure to estimating $h$, rather, he considered it as a constant to be chosen subjectively.

Once an estimate for $h$ is selected, the ED50 is then obtained by equating Equation (248) to $.5$ and solving the resulting equation, in an iterative fashion, for $x$ and $y$. The procedure adopted by Kappenman for estimating $h$ will be extended to the two drug combination experiment.

Basically, if $P_j = Pr[r_j = 1 | (x_j, y_j)]$ for $j = 1, ..., N$, then the density function of $r_j$ is

$$g_j(r_j) = P_j^r_j (1 - P_j)^{1-r_j}, \quad r_j = 0, 1 \ldots (249)$$

The expected value of $g_j(r_j)$ is
The proposed estimate for h is

\[ P_j^2 + (1 - P_j)^2. \]  

(250)

where

\[ \sum_{j=1}^{N} g_j (r_j) = \sum_{j=1}^{N} \left[ P_j(h) \right]^{r_j} \left[ 1 - P_j(h) \right]^{1-r_j} \]  

(251)

which is referred to as a sample reuse estimate. Work by Kappenman in the case of a single drug has shown that estimating h in this fashion was superior to others that have been suggested. A few of the other suggested methods are described in his article. To calculate the estimate of h, the Regula False method works well. In the examples that follow, the IMSL (1982) routine ZXMWD was used to obtain h. As stated earlier, once an estimate for h is obtained, the ED50 is estimated by equating (248) to .5 and obtaining \( \chi \) and y. The IMSL (1982) subroutine ZXMWD was also used to obtain these estimates.

In the first example the data in Table 40 were generated from a logistic distribution of the following form:

\[ \log \left( \frac{P}{1-P} \right) = -5 + .83x + .83y + .30xy \]

When the data were fit using maximum likelihood techniques, the fit was...
good \text{ (deviance} = 2.289, 12 \text{ degrees of freedom}) \text{ as would be expected.}

The parameter estimates are detailed at the bottom of Table 40.

Table 40

\textbf{Simulated Logistic Data}

\[
\log \left( \frac{p}{1-p} \right) = -5.0 + .83x + .83y + .30xy
\]

<table>
<thead>
<tr>
<th>Dose of Drug 1 (x)</th>
<th>Dose of Drug 2 (y)</th>
<th>Number of Observations</th>
<th>Number of Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>4</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Maximum likelihood estimates

\begin{align*}
\alpha_0 &= -5.803 (.9365) \\
\alpha_1 &= .899 (.1854) \\
\alpha_2 &= .9898 (.1872) \\
\alpha_3 &= .3150 (.06953)
\end{align*}

Deviance = 2.289, 12 \text{ degrees of freedom}

The estimate of h obtained using the methods just described was equal to 1.95415. Using this value of h, Equation (248) was equating to .5 and solved for various values of y and x. Figure 60 summarizes the results for both the logistic solution and the proposed nonparametric solution of
the ED$_{50}$ for the data in Table 40. Since the data were generated from a logistic model, the two solutions are in close agreement.

As a second example, data was generated with the same expected value at each $x,y$ combination but with the variance contaminated with a Poisson random variable as described in Chapter VI. Table 41 summarizes the data and the maximum likelihood solution.

**TABLE 41**

Simulated Logistic Contaminated With A Poisson

$\log(p/1-p) = -5.0 + .83x + .83y + .30xy$

<table>
<thead>
<tr>
<th>Dose of Drug 4 $(x)$</th>
<th>Dose of Drug 2 $(y)$</th>
<th>Number of Observations</th>
<th>Number of Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>4</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Maximum likelihood estimates

$\alpha_0 = -5.711 (.8436)$  \hspace{1cm}  Deviance = 32.84, 12 degrees of freedom  
$\alpha_1 = 1.070 (.1769)$  
$\alpha_2 = .9864 (.1720)$  
$\alpha_3 = .10261 (.05301)$

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The data are not well fit by the logistic model as indicated by the deviance = 32.84 with 12 degrees of freedom and so inference from this model would be questionable. On the other hand, the estimation of $h$ for this data was 1.95415 (same as before). The resulting $ED_{50}$ estimates are plotted in Figure 61. If one compares Figures 60 and 61, the logistic estimates change the most between the two figures while the nonparametric estimate remains more stable.
Figure 60. Comparing Estimates of the ED50 Using MLE Technique and Kernel Technique.
Figure 61. Comparing Estimates of the E50 Using MLE Technique and Kernel Technique Where the Data are Contaminated.

Legend
- MLE
- Kernel
CONCLUSIONS AND FUTURE WORK

A Summary of the Research

Experimentation on the effects of drugs or chemicals used in combination is increasing. This is in part due to the fact that the discovery of new and unique entities that are safe and effective is decreasing. Researchers have turned to the use of known substances to be used in combination in the hope that the resulting combination is safe and more effective than when the substances are used singly. We have attempted to present results that are beneficial to the researcher and statistician when designing, analyzing and conveying the results obtained from drug combination experiments.

Many of the statistical models proposed by others were cumbersome and difficult to implement. The logistic model used with dichotomous data has been proposed as an alternative. Terms may be added and subtracted from the model and used to approximate some of these more complicated models in much the same manner that a polynomial equation is used to approximate a more complicated equation. The logistic model is relatively easy to fit and leads to the development of diagnostic and robust techniques.

The experimental designs that have been presented assume that there is no knowledge about the substances used in the combination, but
information is available when the substances are used singly. Future work would include an investigation using knowledge about the interaction to obtain optimal designs given this additional information.

Diagnostics are important in accessing the fit of the data to the model. They often reveal individual data points not well fit by the model that spoil the fit to the remaining data. Future work in this area would include investigations into new and unique diagnostic techniques that provide additional insight into the relationship between the data collected and the proposed model. In particular, it seems advantageous to develop a goodness of fit test for the robust regression techniques presented for the logistic model.

The techniques available for fitting the data generated from combination experiments to the logistic model were explored. When the diagnostics reveal data points not well fit by the model, robust techniques were developed that minimize the influence of these outlying observations and provide a model that more accurately reflects the data. In the future, work will continue on fine tuning the robust techniques presented and the development of new techniques.

Finally, transmission of the results of a combination experiment are incomplete without an estimation of the ED₅₀. These results convey important summary information to the investigator. However, as in the model fitting stage of the analysis, current methods of estimating the ED₅₀ in combination experiments are influenced by data not well fit by the model. In this case the current methods assume that the estimate of the probability of response is a good one even when that is not the case.
and tend to underestimate the variability associated with the ED$_{50}$ estimate. We have presented methods, using the bootstrap technique, that provide a more accurate description of the variability. Also, estimation of the logistic model parameters used in calculating the ED$_{50}$ may be in error. We have presented a nonparametric estimate of the ED$_{50}$ to overcome this problem. In the future, work needs to be done in expanding this nonparametric technique to include an estimate of the variability associated with it.
Appendix A

2x2 Factorial Design

1. Solution of \((X_2'V^{-1}X_2)^{-1}\).

Clearly, \((X_2'V^{-1}X_2)^{-1} = X_2^{-1}V(X_2')^{-1}\),

\[
\begin{align*}
X_2^{-1} & = \frac{1}{4} \cdot X_2', \\
V & \text{ is a diagonal matrix, hence we may write}
\end{align*}
\]

\[
X_2^{-1}V(X_2')^{-1} = \frac{1}{16} X_2'VX_2.
\]

Letting \(n_{11}P_{11}(1-P_{11}) = V_1, n_{12}P_{12}(1-P_{12}) = n_{21}P_{21}(1-P_{21}) = V_2\)

and \(n_{22}P_{22}(1-P_{22}) = V_3\), we have

\[
(X_2'V^{-1}X_2)^{-1} = \frac{1}{16}
\begin{bmatrix}
\left(\frac{1}{V_1} + \frac{2}{V_2} + \frac{1}{V_3}\right) & \left(\frac{1}{V_1} - \frac{1}{V_3}\right) & \left(-\frac{1}{V_1} + \frac{1}{V_3}\right) & \left(\frac{1}{V_1} - \frac{2}{V_2} + \frac{1}{V_3}\right) \\
\left(-\frac{1}{V_1} + \frac{1}{V_3}\right) & \left(\frac{1}{V_1} - \frac{2}{V_2} + \frac{1}{V_3}\right) & \left(\frac{1}{V_1} + \frac{2}{V_2} + \frac{1}{V_3}\right) & \left(\frac{1}{V_1} - \frac{1}{V_3}\right) \\
\left(\frac{1}{V_1} - \frac{1}{V_3}\right) & \left(\frac{1}{V_1} - \frac{2}{V_2} + \frac{1}{V_3}\right) & \left(\frac{1}{V_1} + \frac{2}{V_2} + \frac{1}{V_3}\right) & \left(\frac{1}{V_1} + \frac{1}{V_3}\right) \\
\left(\frac{1}{V_1} - \frac{2}{V_2} + \frac{1}{V_3}\right) & \left(\frac{1}{V_1} + \frac{1}{V_3}\right) & \left(\frac{1}{V_1} - \frac{1}{V_3}\right) & \left(\frac{1}{V_1} + \frac{2}{V_2} + \frac{1}{V_3}\right)
\end{bmatrix}
\]

2. \(P_{22}\) as a Function of \(P_{11}\) and \(P_{21}\)

Under the null hypothesis we have the following four identities
\[ \ln \left( \frac{P_{11}}{1-P_{11}} \right) = a_0 + a_1X_1 + a_2Y_1 \]  

(5)

\[ \ln \left( \frac{P_{21}}{1-P_{21}} \right) = a_0 + a_1X_2 + a_2Y_1 \]  

(6)

\[ \ln \left( \frac{P_{12}}{1-P_{12}} \right) = a_0 + a_1X_1 - a_2Y_2 \left( P_{12} = P_{21} \right) \]  

(7)

\[ \ln \left( \frac{P_{22}}{1-P_{22}} \right) = a_0 + a_1X_2 + a_2Y_2 \]  

(8)

Adding (6) and (7) and rearranging terms of the R.H.S., we have

\[
2 \ln \left( \frac{P_{21}}{1-P_{21}} \right) = \ln \left( \frac{P_{11}}{1-P_{11}} \right) + \ln \left( \frac{P_{22}}{1-P_{22}} \right) \text{ with}
\]

\[
\left( \frac{P_{21}}{1-P_{21}} \right)^2 = \left( \frac{P_{11}}{1-P_{11}} \right) \left( \frac{P_{22}}{1-P_{22}} \right), \text{ which when solved for } P_{22}
\]

leads to

\[
P_{22} = \frac{P_{21}^2 (1-P_{11})}{P_{11} (1-P_{21})^2 + P_{21}^2 (1-P_{11})}
\]  

(9)

To see how the assumption of \( P_{12} = P_{21} \) comes about, consider the situation where both drugs have identical scales. That is, a unit change in the dose of drug 1, denoted \( x \), has the same effect as a unit change in the dose of drug 2, denoted \( y \). In a practical situation one can achieve similar scales by forming
Then,

\[ x_i^* = \frac{x_i}{(LD_{50} \text{ of } x)}, \quad y_j^* = \frac{y_j}{(LD_{50} \text{ of } y)} \]  

(10)

Likewise,

\[ \ln\left( \frac{P_{11}}{1 - P_{11}} \right) = \beta_0 + \beta_1 x_1^* + \beta_2 y_1^* \]

(11)

\[ = \beta_0 + \beta_1 x_1^* (LD_{50} \text{ of } x) + \beta_2 y_1^* (LD_{50} \text{ of } y) \]

\[ = \beta_0 + \beta_1 x_1^* \left( \frac{-\beta_0}{\beta_1} \right) + \beta_2 y_1^* \left( \frac{-\beta_0}{\beta_2} \right) \]

\[ = \beta_0 - \beta_0 x_1^* - \beta_0 y_1^* \]

Likewise,

\[ \ln\left( \frac{P_{12}}{1 - P_{12}} \right) = \beta_0 - \beta_0 x_1^* - \beta_0 y_2^* \]  

(12)

\[ \ln\left( \frac{P_{21}}{1 - P_{21}} \right) = \beta_0 - \beta_0 x_2^* - \beta_0 y_1^* \]  

(13)

The logical 2 by 2 factorial design where both \( x^* \) and \( y^* \) have the same scale and effect would be a square in the \( x^*y^* \) plane. This implies

\[ x_2^* - x_1^* = y_2^* - y_1^* \]  

(14)

or

\[ x_2 - x_1 = y_2 - y_1 \]
\[ \beta_0(x^*_2 - x^*_1) = \beta_0(y^*_2 - y^*_1) \]  \hspace{1cm} (15)

or

\[ \beta_0 - \beta_0 x^*_1 - \beta_0 y^*_2 = \beta_0 - \beta_0 y^*_1 - \beta_0 x^*_2 \]  \hspace{1cm} (16)

which implies

\[ \ln \left( \frac{P_{12}}{1 - P_{12}} \right) = \ln \left( \frac{P_{21}}{1 - P_{21}} \right) \]  \hspace{1cm} (17)

or

\[ P_{12} = P_{21}. \]

We could then naturally allocate

\[ a_{12} = \frac{n_{12}}{N} = a_{21} = \frac{n_{21}}{N}. \]

3. \( \Delta x \) and \( \Delta y \) as Functions \( P_{11} \) and \( P_{21} \).

From our initial diagram (Figure 9 of Chapter II) we observe \( x_1 = x - \Delta x \), \( x_2 = x + \Delta x \), \( y_1 = y - \Delta y \) and \( y_2 = y + \Delta y \). Substitution into equations (5)-(8) above results in

\[ \ln \left( \frac{P_{11}}{1 - P_{11}} \right) = \mu - a_1 \Delta x - a_2 \Delta y \]  \hspace{1cm} (18)

\[ \ln \left( \frac{P_{12}}{1 - P_{12}} \right) = \mu - a_1 \Delta x + a_2 \Delta y \]  \hspace{1cm} (19)

\[ \ln \left( \frac{P_{21}}{1 - P_{21}} \right) = \mu + a_1 \Delta x - a_2 \Delta y \]  \hspace{1cm} (20)
\[
\ln\left(\frac{P_{22}}{1-P_{22}}\right) = \mu + a_1 \Delta x + a_2 \Delta y, \quad \mu = \left(a_0 + a_1 \bar{x} + a_2 \bar{y}\right). \tag{21}
\]

Subtraction of (18) from (20) and solving for \(\Delta x\) results in
\[
\Delta x = \left[\ln\left(\frac{P_{21}}{1-P_{21}}\right) - \ln\left(\frac{P_{11}}{1-P_{11}}\right)\right]/2a_1. \tag{22}
\]

Similarly subtracting (20) from (21), substituting for \(P_{22}\) by Equation (9), and solving for \(\Delta y\) results in
\[
\Delta y = \left[\ln\left(\frac{P_{21}}{1-P_{21}}\right) - \ln\left(\frac{P_{11}}{1-P_{11}}\right)\right]/2a_2. \tag{23}
\]

4. Variance of \(a_3\)

The \(\text{var} (a_3)\) is found by pre-multiplying and post-multiplying matrix (4) by the vector
\[
\left(0, 0, 0, \frac{1}{\Delta x \Delta y}\right) \tag{24}
\]
and its transpose resulting in
\[
\text{Var}(a_3) = \frac{\left(\frac{1}{v_3} + \frac{2}{v_2} + \frac{1}{v_1}\right)}{16(\Delta x)^2(\Delta y)^2}. \tag{25}
\]

By substituting the appropriate \(n_{ij}P_{ij}(1-P_{ij})\) for each of

the \(v\)'s, replacing \(P_{22}\) by equation (9), and using expressions (22) and (23) for \(\Delta x\) and \(\Delta y\) and using
\[
a_{ij} = \frac{n_{ij}}{N}, \tag{26}
\]

we have
\[ \text{Var}(a_3) = \frac{a_1^2 a_2^2}{N \left[ \ln \left( \frac{P_{21}}{1 - P_{21}} \right) - \ln \left( \frac{P_{11}}{1 - P_{11}} \right) \right]^4} \left[ \frac{1}{a_{11} P_{11} (1 - P_{11})} + \frac{2}{a_{21} P_{21} (1 - P_{21})} \right] \]

\[ + \left( \frac{P_{11} (1 - P_{21})^2 + P_{21} (1 - P_{11})^2}{a_{22} P_{21}^2 (1 - P_{11}) P_{11} (1 - P_{21})^2} \right) \]

(27)

5. Determinant of \( \text{Cov}(A) \)

\[ \left| \text{Cov}(A) \right| = \left| C'(X_2 V^{-1} X_2)^{-1} C \right| = \left| C' \right|^2 \left( X_2 V^{-1} X_2 \right)^{-1} = \frac{\left| C \right|^2}{\left| X_2 V^{-1} X_2 \right|} \]

(28)

Noting that

\[ \left| X_2 V^{-1} X_2 \right| = \left| X_2 \right|^2 \left| V^{-1} \right| = 16 V_1 V_2 V_3 \]

(29)

and

\[ \left| C' \right| = \left( \frac{1}{\Delta x \Delta y} \right)^2 \]

(30)

We may substitute for \( \Delta x, \Delta y, V_1, V_2, V_3, P_{22} \) and the \( n_{ij} \) as above and write

\[ \left| \text{Cov}(A) \right| = \frac{a_1^4 a_2^4}{N^4 \left[ \ln \left( \frac{P_{21}}{1 - P_{21}} \right) - \ln \left( \frac{P_{11}}{1 - P_{11}} \right) \right]^8} \left( \frac{P_{11} (1 - P_{21})^2 + P_{21} (1 - P_{11})^2}{a_{11} a_{12} a_{22} P_{11}^2 (1 - P_{11})^2 P_{21}^4 (1 - P_{21})^4} \right) \]

(31)
Appendix B

2-Ray Design

8 | Cov (A) 8T

\[ 8T = \left( 8.\times (K^{54}T^{54} - 2.\times K^{54}T^{32} - K^{50}T^{30} - 10.\times K^{52}T^{28} \right) \]

8 | Cov (A) 8p

\[ 8p = \left( 8.\times ((P1-1) + P1) \times (LOG((-P1)/(P1-1)) - A0) - 1. \times (LOG(( -P1)/(P1-1)) - LOG((-P2)/(P2-1))) + 2.\times (LOG((-P2)/(P2-1)) - A0) \right) \]

8 | Cov (A) 8p2

\[ 8p2 = \left( 8.\times ((P2-1) + P2) \times (LOG((-P2)/(P2-1)) - A0) - 1. \times (LOG(( -P1)/(P1-1)) - LOG((-P2)/(P2-1))) + 2.\times (LOG((-P2)/(P2-1)) - A0) \right) \]

8 | Cov (A) 8ω1

\[ 8ω1 = \left( 8.\times (K^{52}T^{32} + 1.) \times 6.\times (T^{1.}) \times 6.\times (4.\times W1 - 1.) \times K^{54} \right) \]

(1)

(2)

(3)

(4)
where \(A_0 = a_0, A_1 = a_1, A_2 = a_2, P_1 = p_1, P_2 = p_2, \) and \(W = w\)

\[
\text{Setting } \frac{\delta \text{Cov}(A)}{\delta w_1} = 0 \text{ implies } \quad (5)
\]

\[4w_1 - 1 = 0
\]
\[w_1 = 1/4
\]

Since \(a_2 = a_1 = 1/4\) and \(a_3 = a_4\) we have

\[1 - 1/2 - a_3 - a_4 = 0
\]
\[a_3 + a_4 = 1/2
\]
\[a_3 = a_4 = 1/4 \quad (6)
\]
Appendix C

3x3 Factorial Design

1. Solution of Cov(A) = (X'V^{-1}X')^{-1}  

From Section 2 we have (X'V^{-1}X')^{-1} = C'(X_2V^{-1}X_2)^{-1}C .  

C and X_2 are both square nonsingular matrices. Using the properties of the inverse and determinants of such matrices we have

\[ \det (C'(X_2V^{-1}X_2)^{-1}C) = \det (C'X_2^{-1}V(X_2')^{-1}C) \]

\[ = \left| C' \right| \left| X_2^{-1} \right| \left| V \right| \left| (X_2')^{-1} \right| \left| C \right| \]

\[ = \left| C' \right|^2 \left| V \right| \left| X_2^{-1} \right|^2 = \frac{\left| C' \right|^2 \left| V \right|}{\left| X_2 \right|^2} . \]

It may be shown

\[ \det (X_2) = -64, \quad \det (V) = \prod_{i=1}^{3} \prod_{j=1}^{3} v_{ij} \text{ and } C' = \Delta x^{-9} \Delta y^{-9}, \text{ leading to } \det (Cov(A)) \]

\[ = \prod_{i=1}^{3} \prod_{j=1}^{3} n_{ij} P_{ij} (1 - P_{ij})^{-1} \]

\[ = \frac{\prod_{i=1}^{3} \prod_{j=1}^{3} n_{ij} P_{ij} (1 - P_{ij})^{-1}}{(64)^2 \Delta x^{18} \Delta y^{18}} = \frac{\prod_{i=1}^{3} \prod_{j=1}^{3} n_{ij} P_{ij} (1 - P_{ij})^{-1}}{(64)^2 \Delta x^{18} \Delta y^{18}} . \]
Factorial Design (Appendix 1) we may show that:

2. \( P_{ij}'s \) as a function of \( P_{11}, P_{12} \) and \( P_{21} \)

Using arguments of scale similar to those used for the 2x2

\[
P_{12} = P_{21}
\]

\[
P_{32} = P_{23}
\]

\[
P_{31} = P_{13} = P_{22}.
\] (7)

We would naturally make allocations \( a_{12} = a_{21}, a_{32} = a_{23}, \) and \( a_{31} = a_{13} = a_{22} \) where \( a_{ij} = n_{ij}/N. \) Further simplifications may be made by considering that under our hypothesis of a simple linear \( x, y \) - logistic response with no multiplicative interaction we have the following nine identities:

\[
Z_{11} = a_0 + a_1x_1 + a_2y_1
\] (8)

\[
Z_{12} = a_0 + a_1x_1 + a_2y_2
\] (9)

\[
Z_{13} = a_0 + a_1x_1 + a_2y_3
\] (10)

\[
Z_{21} = a_0 + a_1x_2 + a_2y_1
\] (11)

\[
Z_{22} = a_0 + a_1x_2 + a_2y_2
\] (12)

\[
Z_{23} = a_0 + a_1x_2 + a_2y_3
\] (13)

\[
Z_{31} = a_0 + a_1x_3 + a_2y_1
\] (14)
\[ Z_{32} = a_0 + a_1x_3 + a_2y_2 \quad (15) \]
\[ Z_{33} = a_0 + a_1x_3 + a_2y_3 \quad (16) \]

From our initial diagram we observe

\[ x_1 = \bar{x} - \Delta x, \quad x_2 = \bar{x}, \quad x_3 = \bar{x} + \Delta x, \quad y_1 = \bar{y} + \Delta y, \quad y_2 = \bar{y} \quad \text{and} \quad y_3 = \bar{y} + \Delta y. \]

Substitution into Equations (8)-(16) results in

\[ (Z_{11} - Z_{22}) = -a_1\Delta x - a_2\Delta y \quad (17) \]
\[ (Z_{12} - Z_{22}) = -a_1\Delta x \quad (18) \]
\[ (Z_{13} - Z_{22}) = -a_1\Delta x + a_2\Delta y \quad (19) \]
\[ (Z_{21} - Z_{22}) = -a_2\Delta y \quad (20) \]
\[ Z_{22} = \mu \quad (21) \]
\[ (Z_{23} - Z_{22}) = a_2\Delta y \quad (22) \]
\[ (Z_{31} - Z_{22}) = a_1\Delta x - a_2\Delta y \quad (23) \]
\[ (Z_{32} - Z_{22}) = a_1\Delta x \quad (24) \]
\[ (Z_{33} - Z_{22}) = a_1\Delta x + a_2\Delta y \quad (25) \]

with \( \mu = (a_0 + a_1x + a_2y) \)

Equating (18) + (20) = (17), and solving for \( Z_{11} \)
Results in \( Z_{11} = (Z_{12} + Z_{21} - Z_{22}) = (2Z_{12} - Z_{22}) \) \( (26) \)

Equating (18)-(20) = (19), and solving for \( Z_{13} \)
Results in \( Z_{13} = (Z_{12} - Z_{21} + Z_{22}) = (Z_{22}) \) \( (27) \)

Equating (20) = (22), and solving for \( Z_{23} \)
Results in \( Z_{23} = (2Z_{22} - Z_{21}) = (2Z_{22} - Z_{12}) \) \( (28) \)
Equating \((Z_{31} = Z_{13})\)

Results in \(Z_{31} = (Z_{22})\) \quad (29)

Equating \((Z_{32} = Z_{23})\)

Results in \(Z_{32} = (2Z_{22} - Z_{12})\) \quad (30)

Lastly, equating \((17) = -(25)\), solving for \(Z_{33}\) and substituting

Results in \(Z_{33} = (2Z_{22} - Z_{11}) = (3Z_{22} - 2Z_{12})\). \quad (31)

We recognize that all the \(Z_{ij}\) are a linear function of \(Z_{22}\) and \(Z_{12}\).

Consequently, all \(P_{ij}\) are functions of \(P_{22}\) and \(P_{12}\).

By a little algebra we find

\[
v_{11} = \left[ n_{11} P_{11} (1 - P_{11}) \right]^{-1} = \frac{[P_{12}^2 (1 - P_{22}) + P_{22} (1 - P_{12})^2]^2}{N a_{11} P_{12} (1 - P_{22}) P_{22} (1 - P_{12})^2}
\]

\[
v_{12} = \left[ n_{12} P_{12} (1 - P_{12}) \right]^{-1} = \frac{1}{N a_{12} P_{12} (1 - P_{12})}
\]

\[
v_{13} = \left[ n_{13} P_{13} (1 - P_{13}) \right]^{-1} = \frac{1}{N a_{13} P_{22} (1 - P_{22})}
\]

\[
v_{21} = \left[ n_{21} P_{21} (1 - P_{21}) \right]^{-1} = \frac{1}{N a_{21} P_{12} (1 - P_{12})}
\]

\[
v_{22} = \left[ n_{22} P_{22} (1 - P_{22}) \right]^{-1} = \frac{1}{N a_{22} P_{22} (1 - P_{22})}
\]
\[
\nu_{23} = \left[ n_{23}P_{23}(1-P_{23}) \right]^{-1} = \frac{[P_{12}(1-P_{22})^2 + P_{22}(1-P_{12})^2]}{Na_{23}P_{12}(1-P_{12})P_{22}(1-P_{22})^2} 
\]

(37)

\[
\nu_{31} = \left[ n_{31}P_{31}(1-P_{31}) \right]^{-1} = \frac{1}{Na_{31}P_{22}(1-P_{22})} 
\]

(38)

\[
\nu_{32} = \left[ n_{32}P_{32}(1-P_{32}) \right]^{-1} = \frac{[(1-P_{12})P_{22}^2 + P_{12}(1-P_{22})^2]^2}{Na_{32}P_{12}(1-P_{12})P_{22}(1-P_{22})} 
\]

(39)

\[
\nu_{33} = \left[ n_{33}P_{33}(1-P_{33}) \right]^{-1} = \frac{[P_{12}^2(1-P_{22})^3 + P_{22}(1-P_{12})^3]^2}{Na_{33}P_{12}^2(1-P_{12})^2P_{22}(1-P_{22})^3} 
\]

(40)

3. \textbf{X and Y as functions of } P_{22}, \text{ and } P_{21}

From Equations (8-16) in Appendix 2 we note that

\[
\frac{[((14)+(15)+(16))-(18)+(19)+(10))]}{6\alpha_1} = \Delta x. 
\]

(41)

Substitution of the \(Z_{ij}\) as linear function of \(Z_{22}, Z_{21}\) and \(Z_{12}\) given in 2. results in

\[
\Delta x = \left[ \ln \left( \frac{P_{22}}{1-P_{22}} \right) - \ln \left( \frac{P_{12}}{1-P_{12}} \right) \right] \alpha_1 
\]

(42)

Similarly, we recognize

\[
\frac{[((16)+(10)+(13))-(18)+(19)+(11)]}{6\alpha_2} = \Delta y 
\]

(43)

Substitution of the \(Z_{ij}\) as linear functions of \(Z_{22}, Z_{21}\) and \(Z_{12}\)

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given in II results in

$$\Delta y = \left[ \ln \left( \frac{P_{22}}{1 - P_{22}} \right) - \ln \left( \frac{P_{21}}{1 - P_{21}} \right) \right]/a_2$$

(44)

4. Cov(A) under Ho:

From 1. we have

$$\text{Cov}(A) = \frac{3}{(64)^2 \Delta x^{18} \Delta y^{18}} \left[ \prod_{i=1}^{3} \prod_{j=1}^{3} \left[ n_{ij} P_{ij} (1 - P_{ij}) \right]^{-1} \right] = \frac{3}{N(64)^2 \Delta x^{18} \Delta y^{18}} \left[ \prod_{i=1}^{3} \prod_{j=1}^{3} \left[ a_{ij} P_{ij} (1 - P_{ij}) \right]^{-1} \right]$$

$$a_{ij} = n_{ij}/N.$$  

Substitution of Equations (32-40) from 2. with the $n_{ij}$'s replaced by the $a_{ij}$'s and Equations ((41 and (43)) from 3. results

$$\text{Cov}(A) = \frac{a_{1}^{18} a_{2}^{18}}{N(64)^2 \left[ \ln \left( \frac{P_{22}}{1 - P_{22}} \right) - \ln \left( \frac{P_{12}}{1 - P_{12}} \right) \right]^{36}}$$

$$\left( \prod_{i=1}^{3} \prod_{j=1}^{3} a_{ij} \right) = \frac{1}{p_{12}^8 (1 - P_{12})^8 p_{12}^{11} (1 - P_{12})^{11}}$$

$$\left[ P_{12}^8 (1 - P_{22}) + P_{22} (1 - P_{12}) \right]^2$$

$$\left[ P_{12}^4 (1 - P_{22}) + P_{22}^2 (1 - P_{12}) \right]^4$$

$$\left[ P_{12}^2 (1 - P_{22})^3 + P_{22}^3 (1 - P_{12})^2 \right]^2$$

where
\[
\prod_{i=1}^{3} \prod_{j=1}^{3} a_{ij} = \frac{(1 - 4a_{12} - 3a_{22})^2 a_{12}^4 a_{22}^3}{2}.
\]
Appendix D
3-Ray Design

\[ \delta \text{Cov} (A) = \frac{\text{Var}(A)}{\sigma^2} \]

(1)

\[ \delta p = \frac{1}{\text{Cov}(A)} \]

(2)

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\[
\delta p_i = (-(B1 \times A1 + A2) \times 16 \times (B1 \times A2 + A1) \times 16 \times (A1 + A2) \times 16) / ((B1 \times A2 \times 2 - 3) \times A1 \times 2) \times B1 \times 2 + 4 \times (B1 + 1) \times 3 \times (W1 + 3) \times (W2 - 1) \times 3 \times (A1 \times 2 - A1 \times 2 + 2) \times 2 \times (P3 - 1) \times 3 \times (P1 \times 3 \times P2 \times 4 \times B1 \times 2 \times W1 \times 3 \times W2 \times 3 \times P3 \times 3).
\]

\[
\delta p_i = (-(B1 \times A1 + A2) \times 16 \times (B1 \times A2 + A1) \times 16 \times (A1 + A2) \times 16) / ((B1 \times A2 \times 2 - 3) \times A1 \times 2) \times B1 \times 2 + 4 \times (B1 + 1) \times 3 \times (W1 + 3) \times (W2 - 1) \times 3 \times (A1 \times 2 - A1 \times 2 + 2) \times 2 \times (P3 - 1) \times 3 \times (P1 \times 3 \times P2 \times 4 \times B1 \times 2 \times W1 \times 3 \times W2 \times 3 \times P3 \times 3).
\]

\[
\delta a_i = (-B1 \times A1 + A2) \times 16 \times (B1 \times A2 + A1) \times 16 \times (A1 + A2) \times 16 / ((B1 \times A2 \times 2 - 3) \times A1 \times 2) \times B1 \times 2 + 4 \times (B1 + 1) \times 3 \times (W1 + 3) \times (W2 - 1) \times 3 \times (A1 \times 2 - A1 \times 2 + 2) \times 2 \times (P3 - 1) \times 3 \times (P2 \times 4 \times B1 \times 2 \times W1 \times 3 \times W2 \times 3 \times P3 \times 4).
\]
where $A_0 = a_0, A_1 = a_1, A_2 = a_2, P_1 = p_1, P_2 = p_2, P_3 = p_3, B_1 = \beta_1$.

W1 = $\omega_1$, and W2 = $\omega_2$.  

\begin{equation}
\delta \text{Cov} (A)  \frac{\delta \omega}{\delta \omega_1} = 0 \text{ implies}
6\omega_1 + 3\omega_2 - 1 = 0 \text{ or } \omega_1 = 1/6 \left( 1 - 3 \omega_2 \right) 
\end{equation}
\[ 3\omega_1 + 6\omega_2 - 1 = 0 \text{ or } \omega_2 = \frac{1}{6} \left( 1 - 3\omega_1 \right) \]

Solving (7) and (8) for \( \omega_1 \) and \( \omega_2 \)

we find \( \omega_1 = \omega_2 = \frac{1}{9} \) and \( \omega_3 = \frac{1}{3} - \omega_1 - \omega_2 = \frac{1}{9} \).
APPENDIX E.

COMPUTER PROGRAM TO COMPUTE DIAGNOSTICS

$C$ HEWLETT-PLACKET DATA PAGE 521
$C$ UNITS 16
$C$ DATA MOC DFDT RES N
$C$ READ
.14 0 47 48
.10 0 42 48
.07 0 22 48
.05 0 9 48
0 .56 28 48
0 .40 18 48
0 .28 7 49
0 .20 5 48
.07 .20 37 48
.05 .14 32 48
.035 .10 13 48
.025 .07 5 48
.05 .20 27 48
.035 .14 16 48
.025 .10 14 48
.0175 .07 4 4.7
$C$ TAKING NO TRANSFORM
$C$ CAL X1= (MOC); X2= (DFDT)$
$C$ BINOMIAL ERROR TERM
$C$ YVAR RES $ERROR B N$
$C$ FIT X1+X2$
$C$ VARIANCE COVARIANCE MATRIX
$C$ EXTRACT %VC
$C$ PARAMETER ESTIMATES
$C$ EXTRACT %PE
$C$ PRINT %PE$
$C$ CALCULATING XB
$C$ CAL XB=(%PE(1)+%PE(2)*X1+%PE(3)*X2)
$C$ PRINT XB$
$C$ CALCULATED P-HATS
$C$ CAL PHAT=%FV/N
$C$ PRI PHAT
$C$ DEVIANCE SQUARED
$C$ CAL DT =(-2)*N*%LOG(1-PHAT)*%EQ(RES, 0)
+(-2)*N*%LOG(PHAT)*%EQ(RES, N)+
(LT(RES,N)%%GT(RES, 0))%*
2*(RES*%LOG((RES/N)/(1-RES/N)))-XB)
+N*%LOG((1-RES/N)/(1-PHAT)))$
$C$ DEVIANCE COMPONENTS
$C$ CAL DEV=1*%SQRT(DT)%EQ(RES, 0)
+(-1)*%SQRT(DT)%EQ(RES, N)+

255

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(%LT(RES,N)*%GT(RES,0))
*%IF(%GT(%LOG((RES/N)/(1-RES/N)),XB),1,-1)
*%SQRT(DT) $ 
$C SUM OF THE DEVIANCE SQUARED COMPONENTS 
$CAL %U=%CU(DT)
$PRI %U%LOO DT$
$C DEV(I)
$LOO DEV$
$DIS E VC$
$C FITTED VALUES OBSERVED VALUES 
$LOO %FV %YV
$C PEARSON RESIDUALS 
$CAL CHI=N*PHAT*(1-PHAT)
$CAL CH2=(%YV-N*PHAT)/(%SQRT(N*PHAT*(1-PHAT)))
$LOO CH2
$C CH(I)
$CAL CH3=CH2*CH2:%T=%CU(CH3)
$C TOTAL CHI SQUARE
$PRINT %T
$CAL ON=%GL(20,1)
$C PLOT OF CHI(I) VS I 
$PLOT CH2 ON*$
$C CALCULATING THE MII 
$EXT %VL$CAL M=1-%WT%VL$
$LOO M
$C PLOT OF M(I,I) VS I 
$PLOT M ON*$
$C PLOT OF D(I) VS I 
$PLOT DEV ON*$
$STOP$FINISH$
APPENDIX F.

COMPUTER PROGRAM TO COMPUTE ROBUST ESTIMATES

* SAS CALCULATION OF PREGIBONS ESTIMATES FOR ROBUST LOGISTIC;
DATA MARTIN; INPUT
X1 X2 Y N;
CARDS;
10.2 0 44 50
7.7 0 42 49
5.1 0 24 46
3.8 0 16 48
2.6 0 6 50
0 50.5 48 48
0 40.4 47 50
0 30.3 47 49
0 20.2 34 48
0 10.1 18 48
0 5.1 16 49
5.1 2 0.3 48 50
4.0 16.3 43 46
3.0 12.2 38 48
2.0 8.1 27 46
1.0 4.1 22 46
0.5 2.0 7 47
PROC NLIN
TITLE PREGIBONS ESTIMATES USING MARTIN DATA;
** MLE STARTING VALUES;
PARMS B0=-1.902 B1=.406 B2=.151;
E = (B0+B1*X1+B2*X2);
P = 1/(1 + EXP(-E));
MODEL Y=N*P;
** TUNING CONSTANT;
HP=1.345*1.345;
RESID=Y-MODEL.Y;
DER=N*P*(1-P);
DER.B0=DER;
DER.B1=DER*X1;
DER.B2=DER*X2;
W=(N*P*(1-P));
** PREGIBONS METHOD - DEFINING WEIGHTS;
PHAT=Y/N;
IF Y =0 THEN DEV=-2*N*LOG(1-P);
ELSE IF Y =N THEN DEV=-2*N*LOG(P);
ELSE DEV=2*(Y*LOG(PHAT/P)+((N-Y)*LOG((1-PHAT)/(1-P))));
IF DEV<=HP THEN _WEIGHT_=1/W;
ELSE _WEIGHT_=SQRT(HP/DEV)/W;
**

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*SAS CALCULATION OF ROBUST REGRESSION USING HUBERS METHOD;
DATA MARTIN; INPUT
  X1  X2  Y  N;
CARDS;
  10.2 0  44 50
  7.7 0  42 49
  5.1 0  24 46
  3.8 0  16 48
  2.6 0  6  50
  0 50.5 48 48
  0 40.4 47 50
  0 30.3 47 49
  0 20.2 34 48
  0 10.1 18 48
  0  5.1 16 49
  5.1 20.3 48 50
  4.0 16.3 43 46
  3.0 12.2 38 48
  2.0  8.1 27 46
  1.0 4.1  22 46
  0.5  2.0  7  47
PROC NLIN NOHALVE SIGSQ=1;
TITLE HUBER USING MATIN DATA;
** MLE STARTING VALUES;
PARMS B0=-1.902 B1=.406 B2=.151;
E = (B0 +B1*X1+B2*X2);
P=1/(1+EXP(-E));
MODEL Y=N*P;
** PARTIAL DERIVATIVES;
DER=N*P*(1-P);
DER.B0=DER;
DER.B1=DER*X1;
DER.B2=DER*X2;
**;
** TUNING CONSTANT;
HP=1.345;
** RESIDUAL;
RESID=Y-MODEL.Y;
** VARIANCE CALCULATION;
W=(N*P*(1-P));
** HUBERIZATION - DEFINING WEIGHTS;
PEARSON=ABS(RESID/SQRT(W));
IF PEARSON<=HP THEN DO; _WEIGHT_=1/W;
RHO=RHO+(PEARSON)**2; END;
ELSE DO; _WEIGHT_=HP/((PEARSON)**W);
ELSE DO; _WEIGHT_=HP/((RESID)**W);
RHO=RHO+((HP*PEARSON)-(HP*HP/2)); END;
** ;
*SAS Calculation of Robust Logistic Regression Using MAD;
DATA A; INPUT
   X1 X2 Y N ;
CARDS;
  10.2  0  44  50
  7.7  0  42  49
  5.1  0  24  46
  3.8  0  16  48
  2.6  0  6   50
  0  50.5 48  48
  0  40.4 47  50
  0  30.3 47  49
  0  20.2 34  48
  0  10.1 18  48
  0  5.1  16  49
  5.1  2  0.3  48  50
  4.0  16.3 43  46
  3.0  12.2 38  48
  2.0  8.1  27  46
  1.0  4.1  22  46
  0.5  2.0  7   47
PROC NLIN NOHALVE SIGSQ=1;
TITLE MAD USING MARTIN DATA ;
** WLS STARTING VALUES;
PARMS B0=-1.902 B1=.406 B2=.151 ;
MAD= 1.48x2.155157 ;
E = (B0+B1*X1+B2*X2);
P=1/(1+EXP(-E));
MODEL Y=N*P;
** PARTIAL DERIVATIVES;
DER=N*P*(1-P) ;
DER.B0=DER;
DER.B1=DER*X1 ;
DER.B2=DER*X2 ;
**
** TUNING CONSTANT ;
HP=1.345 ;
** RESIDUAL ;
RESID=Y-MODEL.Y;
** VARIANCE CALCULATION ;
W=(N*P*(1-P));
** HUBERIZATION - DEFINING WEIGHTS ;
MADEST=ABS(RESID/MAD);
IF MADEST <=HP THEN DO; _WEIGHT_=1/W;
PROP=PROP+((RESID*RESID)) ;
PROP=PROP+(2); RHO=RHO+((RESID*RESID)/2); END;
ELSE DO; _WEIGHT_=HP/(MADEST*W);PROP=PROP+(HP*HP);
RHO=RHO+((HP*ABS(RESID))-HP*HP/2)) ; END;
APPENDIX G.

COMPUTER PROGRAM TO COMPUTE ED50 USING ROBUST ESTIMATES AND A BOOTSTRAP ESTIMATE OF THE VARIANCE

*PARAMETER DATA SET;

DATA PARMS; INPUT B0 B1 B2 ;
CARDS;
*OBSERVED DATA;

DATA A; INPUT X1 X2 Y N ; INDEX=_N_; X3=X1*X2;
CARDS;
10.2 0 44 50
7.7 0 42 49
5.1 0 24 46
3.8 0 16 48
2.6 0 6 50
0 50.5 48 48
0 40.4 47 50
0 30.3 47 49
0 20.2 34 48
0 10.1 18 48
0 5.1 16 49
5.1 20.3 48 50
4.0 16.3 43 46
3.0 12.2 38 48
2.0 8.1 27 46
1.0 4.1 22 46
0.5 2.0 7 47
PROC SORT; BY INDEX;
%MACRO GOFQRIT;
* RANDOM SELECTION OF DATA WITH REPLACEMENT ;
CMS FI FT20F001 DISK RAN DATA A (LRECL 80);
%DO I=1 %TO 100;
PROC PRINTTO NEW UNIT=20;
PROC PLAN ;
FACTORS BLOCK=17 ORDERED A=1 OF 17;
PROC PRINTTO;

CMS FI IN DISK RAN DATA A(LRECL 80);
DATA B; INFILE IN; IF _N_ = 1 THEN
INPUT ; ; ; ; ; ; ; ; DUM2 INDEX ;
ELSE INPUT DUM1 $ 1-4 @; IF DUM1=' ' THEN INPUT DUM2 INDEX ;
KEEP INDEX;
PROC SORT; BY INDEX;
DATA C; MERGE A (IN=A) B (IN=B) ; BY INDEX; IF B;

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CMS FT19F001 DISK NLIN DATA A (LRECL 132;
PROC PRINTTO NEW UNIT=19;

PROC NLIN OUTEST=P NOHALVE SIGSQ=1;
TITLE HUBER ESTIMATE USING MARTIN DATA ;
PARMS B0=0 B1=0 B2=0 ;
E = (B0+B1*X1+B2*X2 ) ;
P=1/(1+EXP(-E)) ;
MODEL Y=N*P ;
DER=N*P*(1-P) ;
DER.B0=DER ;
DER.B1=DER*X1 ;
DER.B2=DER*X2 ;
** TUNING CONSTANT ;
HP=1.345 ;
** RESIDUAL ;
RESID=Y-MODEL.Y ;
** VARIANCE CALCULATION ;
W=(N*P*(1-P));
** HUBERIZATION - DEFINING WEIGHTS ;
PEARSON=ABS(RESID/SQRT(W)) ;
IF PEARSON<=HP THEN DO; _WEIGHT_=1/W ;
RHO=RHO+(PEARSON)**2; END;
ELSE DO;_WEIGHT_=HP/((PEARSON)**W); 
RHO=RHO+((HP*PEARSON)-(HP*HP/2)); END ;
** ;
PROC PRINTTO ;
DATA P ;SET P; IF _TYPE_ = 'FINAL' ;
DATA PARMS ; SET PARMS P ;
%END ;
%MEND GOFORIT ;
%GOFORIT
PROC PRINT DATA=PARMS ;
DATA VAR ; SET PARMS ; KEEP B0 B1 B2 ;
PROC MATRIX PRINT ;
FETCH X DATA=VAR ;
N=NROW(X) ;
MEAN=X(+,)/N ;
SUM=X(+,);
XPX=X'*X-SUM'*SUM/N ;
COV=XPX#/((N-1));
BIBLIOGRAPHY


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