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RESPONSE SURFACE METHODOLOGY: 1966-1986

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This paper provides a thorough review of response surface methodology since 1966. The review covers topics pertaining to the design and analysis of response surfaces. Multirespone techniques associated with optimization and lack of fit testing are also covered.

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I. INTRODUCTION

In the November, 1966, issue of *Technometrics*, a paper "A Review of Response Surface Methodology: A Literature Survey" by Hill and Hunter appeared. That particular review emphasized practical applications in the chemical and processing fields and featured an excellent bibliography. In the December, 1975, issue of *Biometrics*, "A Review of Response Surface Methodology from a Biometric Viewpoint" by Mead and Pike appeared. Emphasis was put on biological applications, and a much broader definition of RSM was made than that of the Hill and Hunter paper.

In the Hill and Hunter review, the authors state that RSM began with the work by Box and Wilson (1951). In the Mead and Pike paper, they move back the origin of RSM to include use of "response curves" dating back into the 1930's. Such items as probit analysis, the use of Mitcherlich response equations, and the early work in factorial arrays by Yates (1935) are mentioned as probable motivators of the work by Box and co-workers. In reality there are diverse notions as to what is the proper list of topics to be included under the response surface umbrella. This is not surprising. The term *response surface analysis* could be taken as any analysis dealing with a fitted function, thus accommodating a large collection of techniques. Others view the term as implying a much smaller collection of tools. This confusion is due in part to the very general, perhaps even unfortunate, name *response surface*. The name implies something which is broad and all consuming. Yet it is interesting that all too many subject matter scientists, many of which are experienced in the use of statistical tools, are not aware of the term *response surface analysis* or of the problems it addresses.

There is no question that the motivation for the work by Box et al. was the general and perhaps ancient problem of planning and analyzing experiments in a search for desirable conditions on a set of controllable, or design, variables, *desirable* often being defined more strictly as those conditions which give rise to optimum response. We often refer to this problem in a more general setting as one of *exploring* an experimental region, or exploring a response surface. This gives rise to the inevitable applications in the chemical and process fields and the historical attraction to the subject by *Technometrics* readers. We wish to make it clear to the present *Technometrics* audience that it is not our intention to travel the broad base of experimental design or to review the many

aspects of model building. For example, we wish to minimize any overlap with the recent *Technometrics* reviews by Steinberg and Hunter (1984) in experimental design and Hocking (1983) in regression analysis, though some overlap with both will be necessary. ~~Our intent~~ is to provide a review of important developments in response surface methodology, with the definition being confined to that of a collection of tools in design or data analysis that enhance the exploration of a region of design variables in one or more responses. ~~We will~~ emphasize developments in the statistics literature that have appeared since 1966 but will make reference to some pre-1966 work where historical perspective is necessary.

In terms of subject matter applications, ~~we~~ will not at all confine ourselves to applications in the chemical and processing fields. ~~We~~ feel that one of the more important items to report is the breadth of application of RSM that has evolved in the last 20 years. Applications have expanded to areas such as operations research, nuclear energy, defense systems research, cancer chemotherapy, and many others. ~~We shall~~ review the spectrum from theoretical developments to practical notions of current software availability in both the design and analysis aspects of RSM. Design and analysis will be treated separately though the user must treat the two together in his total analysis. The original intent by Box and company was to highlight a strategy--both experimental and analytic. Yet precious little research employs a simultaneous consideration of both of these aspects. Finally, ~~we attempt to offer~~ suggestions regarding the important areas for future research and future impact of RSM.

The experimental strategy and analysis in RSM revolves around the assumption that a response η is a function of a set of design variables $x_1, x_2, \ldots, x_k$ and that the function can be approximated in some region of the x's by a polynomial model. Prominent among the models considered are the first order model

$$\eta = \beta_0 + \beta_1 x_1 + \cdots + \beta_k x_k \tag{1.1}$$

or the second order model

$$\eta = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \sum_{i=1}^{k} \beta_{ii} x_i^2 + \sum_{i<j}^{k} \sum_{j=1}^{k} \beta_{ij} x_i x_j \qquad (1.2)$$

Also in certain instances in the sequel we will deal specifically with nonlinear models. In what follows, response surface design is treated, with some historical perspective given, followed by many specialized areas such as mixture designs, design robustness, alphabetic optimal design theory, designs for nonlinear models, and many others. This is followed by a treatment of response surface analysis featuring multiple responses, sampling properties of optima, and analysis for models other than polynomials. The paper then features subject matter applications, with emphasis on industrial usage. Finally, software availability is reviewed and potential areas for future directions and research are discussed.

II. RESPONSE SURFACE DESIGN

In this section we deal with several aspects of response surface designs, beginning with the "where we were" status of response surface design in the mid 60's. We consider three very general areas:

i) design classes

ii) optimality criteria and choice of specific designs that achieve certain important properties

iii) designs which accomplish special design goals or have special design features.

Item (i) may be viewed as design *families*, e.g., composite designs, classes of three-level designs, etc. Item (ii) reviews criteria from which choices of *design parameters* in (i) can be made; for example, the choice of a composite design that is rotatable, or the choice of a three-level design that is D-optimal. In item (iii) we consider less general topics such as designs for nonlinear models, robust designs, designs for mixture problems, designs for estimating slope, etc. One may historically view the development of RSM designs as taking on these three general areas of concentration. The user has relied heavily on the application of properties and criteria in (ii) and special features in (iii) to

design families in (i) that can be used in practice. In these areas much progress has been made since the mid 60's.

2.1 Status of Response Surface Design in Mid 1960's

Among the many important works that preceded the Hill and Hunter review, three are noteworthy here. The first was the benchmark paper by Box and Wilson (1951) in which the notion of composite designs was introduced. The introduction of the "axial portion" to augment a two-level factorial array was done to allow for efficient estimation of quadratic terms in the second order model of equation (1.2). This class of designs allows flexibility in the choice of the axial parameter and number of center runs. This would later prove very beneficial as more sophisticated properties and criteria evolved. More details regarding the composite designs are given in section 2.2. Sharing the sphere of influence with Box-Wilson is the Box-Hunter paper (1957) in which the notion of rotatability was introduced. The property of rotatability requires that the variance of a predicted value remain constant at points that are equidistant from the design center. Rotatability was and remains an important design property. The reader can gain insight into its importance by observing that in much of the RSM design research that appeared in the late 60's and 70's, investigators began with the presumption of rotatability. No one doubts the elegance of the work that led to the rotatability property. Most prudent consultants in RSM do not recommend designs that have considerable deviation from rotatability. The influence of the Box-Hunter work was enhanced greatly by the fact that the conditions for rotatability are so easily attained in the case of first and second order designs.

A third very influential piece of work of the 50's and 60's appeared in Box and Draper (1959, 1963). It was an introduction of the notion of robustness of an RSM design to model misspecification, though the word "robustness" was not used in this regard until later. A mean squared error type of design criterion was introduced which accounts for bias introduced when the fitted RSM model is a polynomial of lower degree than the "true" model. Convincing arguments are made that not only can bias not be ignored but that if there is even a modest amount of misspecification, the

approach of choosing the design that "protects" against bias does not deviate substantially from that of minimization of mean squared error.

The fundamental philosophy of the Box-Draper work centered around the consideration of the average mean squared error

$$J = \frac{NK}{\sigma^2} \int_R E[\hat{y}(x) - g(x)]^2 dx$$

where $\hat{y}(x)$ is the fitted polynomial of order d_1 and $g(x)$ is a model of order $d_2 > d_1$ containing unknown parameters and is regarded as the "true" mean response or at least it can be viewed as the model that one chooses to protect against. Here, R is the region of interest in the design variables, K is the reciprocal of the volume of R, N is the total number of observations, and σ^2 is the error variance. The expression J divides into the sum of the variance and squared bias averaged over the region R. The notion of a *minimum bias* design was introduced. In the formulation presented here, the minimum J design cannot be achieved and evidence was put forth that a strategy of design choice that minimizes the bias portion of J is an effective approach across a broad range of model misspecification. The importance of the Box-Draper work lies in the fact that much of the more specialized RSM design work that followed into the late 60's and 70's was flavored by the now established need to consider model underspecification in any serious attempt in developing optimal designs.

While much of the foundation of very fundamental work was established by that cited in the foregoing, the appetite of the practical user of RSM had been satisfied by the establishment of families of useful experimental designs for first order and second order models. In the first order case, the need for orthogonal designs was motivated in the Box-Wilson paper, Box (1951), and an excellent text *Design and Analysis of Industrial Experiments* by Davies (1954). Specific design classes, two-level factorial and fractional factorial designs had been discussed at length in Box and Hunter (1961a, 1961b). Simplex designs and Plackett-Burman (1946) designs were available as economical first order orthogonal designs. For second order models, many subject matter scientists and engineers have a working knowledge of the family of central composite designs and a class of special three-level designs by Box and Behnken (1960). Another important pre-1966 contribution

came from Hartley (1959), in which an effort was made to reduce the number of runs in the composite design from those that had earlier been suggested. It also allowed for more flexibility in choosing two-level fractions for the cube portion of the composite design.

The majority of response surface real-life applications involve the use of a first or second order model. Where a second order model is inappropriate, a nonlinear model is generally used. However, there are instances in which a third order model is successful, and thus there is a need for third order designs. By the mid 1960's, a majority of the work dealing in third order designs essentially involved searching for designs that possess the property of rotatability. Included are papers by Draper (1960, 1961, 1962), Gardiner et al. (1959), and Herzberg (1964).

In the following sections we provide reviews of what we feel are important RSM design topics, with the chronology, for the most part, beginning in the mid 1960's. We begin with specific families of second order designs, with some emphasis put on alternatives to the central composite designs, though the latter remains the most flexible and thus most popular family of second order designs used in practice.

2.2 The Central Composite Design and Alternate Design Plans

The central composite design (c.c.d.) is a special case of the class of composite designs in which the construction consists of three portions:

i) The 2^k vertices of a cube (or a fraction of these vertices)

ii) The $2k$ vertices of a cross-polytope or "star", or axial *portion* with parameter α

iii) A chosen number, n_0, of center runs.

The points in (i) form a two-level factorial or fractional factorial array. The points in (ii) essentially form an augmentation which represents a one-factor-at-a-time portion designed to provide estimation of the β_{ii}, the *pure quadratic* terms in equation (1.2). Center runs in portion (iii) obviously provide an internal estimate of pure error variance. The choice of the number of center runs is very important to the practitioner. Figure 1 provides an illustration of the c.c.d. for k = 3 design variables.

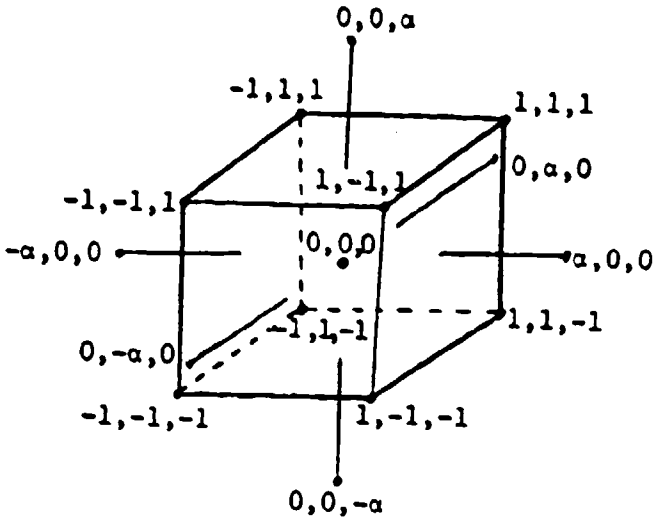

Figure 1. A Central Composite Design for $k = 3$ Design Variables

The design levels are centered and scaled to design units with ± 1 being the levels in the factorial portion and the parameter α being the axial distance as indicated in Figure 1. In large part, the appeal of the c.c.d. is derived from its flexibility and due to the fact that it is a natural design plan for sequential experimentation, since the factorial portion and center runs served as a preliminary phase from which one may fit a first order model and yet gain evidence regarding the importance of pure quadratic contribution. If pure quadratic terms are found to be significant on the basis of the preliminary analysis, the design may be augmented with axial runs for the completion of the second order fit. For a fundamental look at the central composite design, the reader is referred to Davies (1954), Myers (1976), Box et al. (1978), and Cochran and Cox (1957).

Much of the flexibility of the central composite design is derived from the user's choice of α and n_0. There are many criteria used for the choice of these parameters.

Choice of α

For $\alpha > k^{1/2}$, the axial points are further from the design center than the factorial points. A value $\alpha = (F)^{1/4}$, where F is the number of factorial points, guarantees rotatability. Rotatability in the c.c.d. was prominent in the early response surface design research in the late 50's and 60's. However, other criteria such as robustness to model misspecification, quality estimation of the

slope, robustness to errors in design levels, robustness to outliers, generalized variance of model coefficients, and orthogonal blocking are among the important considerations for choice of α considered by researchers. All of these are discussed in later sections where these topics or criteria are introduced. In many cases, of course, the property chosen by the experimenter cannot be satisfied with the rotatable value $\alpha = (F)^{1/4}$. It is generally considered that while exact rotatability is not necessary in practice, a substantial deviation is not wise.

Choice of n_0

The choice of the number of center runs is a vital ingredient in the successful use of the central composite design for the construction of a second order response surface. Center runs have long been considered important as a source of *replication error* in the analysis. From Box and Hunter (1957), it becomes apparent that the early research into the proper choice of n_0 presumed the design in question is indeed rotatable. The recommendation was to choose n_0 for which *uniform information*, or *uniform precision* is achieved; this property provides approximately a uniform value of $Var\ \hat{y}(x)$ inside a sphere of a specific radius. The purpose of this, of course, is to produce a stability in the prediction variance in the region of interest of the design variables or, rather, to control the prediction variance in such a way that equal precision in prediction is achieved everywhere in some portion of the design region. It is a natural extension to the rotatability property, the former requiring $Var\ \hat{y}(x)$ to be constant on a sphere. However, there has long been confusion among users about what constitutes this subregion. See Draper (1982). The original Box-Hunter definition of uniform precision requires n_0 to be chosen such that $Var\ \hat{y}(x)$ is approximately constant inside a sphere of radius 1.0, with the metric of design units requiring scaling so that the second moment of the design variables is unity. In the metric of the standard ± 1 scaling for the factorial portion of the c.c.d., this is equivalent to a radius $\rho = \sqrt{\frac{F + 2F^{1/2}}{F + 2k + n_0}}$. As an example, if a uniform precision rotatable design for k = 2 is constructed, the axial parameter $\alpha = \sqrt{2}$ and $n_0 = 5$. (See Myers (1976)). The implication is that the prediction variance is roughly constant inside a sphere of radius $\rho = \sqrt{\frac{8}{13}} = 0.83$. This does not seem particularly pleasing in light of the fact that, in this case, all design points are at a distance $\rho = \sqrt{2}$ from the design center, and no control is exerted on $Var\ \hat{y}(x)$ at a distance which approaches the perimeter of the design region. Thus the

property of uniform precision does not guarantee stability in $Var\ \hat{y}(x)$ everywhere in the design region, and yet this fact is either overlooked by or unknown to subject matter users.

As we have described here, many of the recommendations regarding the number of center runs for a c.c.d. have been confined to the rotatable c.c.d. Lucas (1977) offers alternative ideas on number of center runs for both the family of composite designs and other designs. An excellent general discussion of center runs in response surface designs appears in Draper (1982).

2.3 Orthogonal Blocking

The central composite design is the second order family that is rich in candidate designs that *block orthogonally*. The latter describes a condition in which regression coefficients are orthogonal to block effects and thus the analysis can be conducted with minimal effort free from blocks. Box and Hunter (1957, 1961a, 1961b) developed the general conditions that give rise to orthogonal blocking in the second order case. The Box-Behnken design also gives rise to orthogonal blocking in some situations.

2.4 Other Second Order Designs

Though the central composite remains the second order design family that is most often used, there are other design classes that are attractive in various circumstances. We earlier made reference to the class of Box-Behnken designs. The Box-Behnken designs can be very useful in cases when it is important that three levels be used. In what follows, we review other second order designs that appeared in the literature after the 1960's.

Hoke Design

Hoke (1974) developed a class of economical second order designs based on irregular fractions of the 3^n factorial plan. These fractions are based on sets of partially balanced arrays and are compared to Box-Behnken and other competing designs.

Hybrid Design

Roquemore (1976) developed a family of second order designs for $k = 3, 4, 6$, and 7 that are either saturated or near saturated and have some similarities to the central composite design. The design for k variables is constructed by augmenting a $(k - 1)$ dimensional central composite design with an additional column in the design matrix. The values for the additional column are chosen to achieve design moment characteristics that allow a degree of orthogonality that is similar to that of the c.c.d. It is of interest to show an example. For $k = 3$, we have the following design matrix

$$D = \begin{array}{c} \begin{matrix} x_1 & x_2 & x_3 \end{matrix} \\ \begin{bmatrix} -1 & -1 & 0.6386 \\ -1 & 1 & 0.6386 \\ 1 & -1 & 0.6386 \\ 1 & 1 & 0.6386 \\ 1.1736 & 0 & -0.9273 \\ -1.1736 & 0 & -0.9273 \\ 0 & -1.1736 & -0.9273 \\ 0 & 1.1736 & -0.9273 \\ 0 & 0 & 1.2906 \\ 0 & 0 & -0.1360 \end{bmatrix} \end{array}$$

Note the central composite type structure in x_1 and x_2 while constant levels in x_3 reside at the factorial portion and the axial portion of x_1 and x_2. In addition, two points enter along the axis of x_3. Center runs are also suggested. The constants in the design are determined so that all pure second moments are equal and all odd moments are zero.

Other Second Order Economical Designs

The work by Hartley (1959) cited earlier and additional work by Westlake (1965) and Draper (1985) produced a class of designs called *small composite designs*. These are central composite designs but they are worthy of special note because, like the class of hybrid designs, they find considerable use when experimentation is costly. The designs allow considerable reduction of cost below what is required by the original and perhaps standard concept of the c.c.d., the latter requiring the design to contain a full 2^k or a fraction of resolution V or more, combined with the axial portion. The purpose of this restriction, of course, is to allow orthogonality among the linear coefficients and two factor interactions in the second order model. The notion of "small" composite results from the fact that additional information on linear coefficients is obtained from the axial

portion of the design though the interaction coefficients are estimated only from the factorial portion. One may take advantage of this by using as the factorial portion a fraction in which linear coefficients are aliased with two factor interactions. An example of a small composite design for three design variables is given by

$$D = \begin{array}{c} \begin{matrix} x_1 & x_2 & x_3 \end{matrix} \\ \begin{bmatrix} -1 & -1 & -1 \\ 1 & 1 & -1 \\ 1 & -1 & 1 \\ -1 & 1 & 1 \\ -\alpha & 0 & 0 \\ \alpha & 0 & 0 \\ 0 & -\alpha & 0 \\ 0 & \alpha & 0 \\ 0 & 0 & -\alpha \\ 0 & 0 & \alpha \end{bmatrix} \end{array}$$

The above defines a saturated second order design in which all coefficients in the standard second order model are estimable. Draper (1985) demonstrated that in some cases, Plackett-Burman designs can be used in the factorial portion.

The classes of small composite designs and hybrid designs are by no means the only choices that are available when one seeks a saturated or near saturated second order design. For example, Notz (1982) suggested a method of constructing designs that are very efficient in terms of generalized variance, i.e., D-efficiency. (For more complete details on the use of D-efficiency and D-optimality, see Section 2.5.) His designs are saturated and constructed from the 3^k lattice. For saturation, we have $N = \frac{1}{2}(k + 1)(k + 2) = p$, the number of parameters in a second order model, and the design matrix is given by

$$D = \begin{bmatrix} D_1 \\ \cdots \\ D_2 \end{bmatrix}$$

where D_1 is a $(p - k) \times k$ matrix chosen as a specific irregular fraction of a 2^k, whereas D_2 is a $k \times k$ taken from $(0,1)^k$ with at least one coordinate being zero. For example, the $k = 3$ design matrix is given by

$$D = \begin{array}{c} \begin{matrix} x_1 & x_2 & x_3 \end{matrix} \\ \begin{bmatrix} 1 & 1 & 1 \\ 1 & 1 & -1 \\ 1 & -1 & 1 \\ -1 & 1 & 1 \\ 1 & -1 & -1 \\ -1 & 1 & -1 \\ -1 & -1 & 1 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \end{array}$$

The designs are shown to compare favorably (in the sense of D-efficiency) with other economical second order designs.

Box and Draper (1971, 1974) produce practical designs that are saturated, efficient from a generalized variance standpoint, and contain four levels for each variable. An example for $k = 3$ is as follows:

$$D = \begin{array}{c} \begin{matrix} x_1 & x_2 & x_3 \end{matrix} \\ \begin{bmatrix} -1 & -1 & -1 \\ 1 & -1 & -1 \\ -1 & 1 & -1 \\ -1 & -1 & 1 \\ \lambda & \lambda & -1 \\ \lambda & -1 & \lambda \\ -1 & \lambda & \lambda \\ \mu & 1 & 1 \\ 1 & \mu & 1 \\ 1 & 1 & \mu \end{bmatrix} \end{array}$$

where $\lambda = 0.1925$ and $\mu = -0.2912$. The λ and μ are chosen to minimize the generalized variance of the regression coefficients in the second order model.

During the 70's and early 80's, much of the work that resulted in the development of new second order designs revolved around the concept of D-optimality and D-efficiency. Some of this work produced designs that are very practical and, from the foregoing, one can see that many useful saturated or near saturated designs came from that search. The consideration of D-efficiency and D-optimality also produced other interesting results that allowed for a better understanding of the comparison of competing designs. In a very interesting and timely paper by Lucas (1974), he emphasizes that in terms of generalized variance, if there is an experimental region fixed by practical

considerations (say a cube or hypersphere), the optimum central composite design is one in which the experimental points are moved to the edge of the experimental region. If the permissible experimental region is a hypercube, the factorial points should be at the vertices of the hypercube ($\pm$ 1) and the axial parameter $\alpha = 1.0$. If the region is a hypersphere with radius $\sqrt{k}$, then the optimum $\alpha = \sqrt{k}$.

2.5 Application of Criteria Dealing with Optimal Design Theory

The important development of optimal design theory in the field of experimental design emerged following World War II. It was motivated by various authors including Elfving (1952, 1955, 1959), Chernoff (1953), Kiefer (1958, 1959, 1960, 1961, 1962a, 1962b) and Kiefer and Wolfowitz (1959, 1960). Kiefer, in particular, was instrumental in providing the mathematical groundwork for optimal design theory. Actually, the origin of this theory can be traced back to a paper by Smith (1918). Some early work in this area was done by Wald (1943) and Mood (1946).

Optimal design theory has clearly become an important component in the general development of experimental design for the case of regression models. It also had an impact on how researchers viewed and proposed response surface design criteria in the 1970's and early 1980's. Methods were proposed for choosing RSM design parameters and developing second order economical designs through the use of this theory. Though no one can reasonably deny contribution and impact of optimal design theory, there are many who feel as if its use in RSM design work should be done with extreme caution. In fact, the contrast in the views concerning this issue has resulted in what some refer to as the "Kiefer approach" and others refer to as the "Box approach". In Kiefer's approach a design is a probability measure, s, defined on a closed and bounded subset χ of a Euclidean space of dimension equal to the number of design variables in the fitted model. Hence, this measure must satisfy the conditions

$$s(\underline{x}) \geq 0 \qquad \text{for all } \underline{x} \in \chi$$

$$\int_{\chi} ds(\underline{x}) = 1 \quad .$$

In particular, a collection of N points in χ, not necessarily distinct, form a design measure. In this case

$$s(x_i) = \begin{cases} n_i/N & \text{if } x_i \text{ is a design point } (i = 1, 2, \ldots, m) \\ 0 & \text{otherwise} , \end{cases} \tag{2.1}$$

where n_i denotes the number of replications at the i th design point, and m is the number of distinct design points. Such a design measure is said to be discrete and is denoted by D_N. Discrete design measures are the traditional designs considered in Box's approach. Design measures other than discrete are said to be continuous. These include design measures of the form

$$s(x_i) = \begin{cases} \lambda_i & \text{if } x_i \text{ is a design point } (i = 1, 2, \ldots, \ell) \\ 0 & \text{otherwise} , \end{cases} \tag{2.2}$$

where $\lambda_i \geq 0$ and $\sum_{i=1}^{\ell} \lambda_i = 1$, and at least one λ_i is an irrational number, that is, it is not expressible as a fraction. A continuous design measure is sometimes referred to as an approximate design measure since it is not realizable in practice, but can be approximated fairly closely by a discrete design of the form given in (2.1). The latter design is, therefore, referred to as an exact design measure.

Suppose that the fitted model is of the form

$$y = f'(x)\beta + \varepsilon, \tag{2.3}$$

where y is the measured response at a point $x \in \chi$, $f(x)$ is a vector of known functions of x, β is an unknown vector of p parameters, and ε is a random error. If the design measure is discrete, then model (2.3) can be written in vector form as

$$\underline{y} = X\underline{\beta} + \underline{\varepsilon}, \tag{2.4}$$

where X is an $N \times p$ matrix whose ith row consists of the elements of $f'(x_i)$ $(i = 1, 2, \ldots, N)$. In general, for any design measure s on χ, the information matrix of s, denoted by $M(s)$, is defined as the $p \times p$ matrix $[m_{ij}(s)]$, where

$$m_{ij}(s) = \int_{\chi} f_i(\underline{x}) f_j(\underline{x}) ds(\underline{x}) \ , \quad i,j = 1, 2, \ldots, p \ , \tag{2.5}$$

where $f_i(\underline{x})$ is the ith element of $f(\underline{x})$ $(i = 1, 2, \ldots, p)$. In particular, if s is a discrete design measure, D_N, then $M(D_N) = X'X/N$, where X is the matrix in (2.4). In this case if we assume that $E(\underline{\varepsilon}) = \underline{0}$ and $\mathrm{Var}(\underline{\varepsilon}) = \sigma^2 I_N$, then the variance of the predicted response at a point $\underline{x}$ is

$$\mathrm{Var}\ \hat{y}(\underline{x}) = \sigma^2 f'(\underline{x})(X'X)^{-1} f(\underline{x}) \ . \tag{2.6}$$

Let $v(\underline{x}, D_N)$ denote the standardized prediction variance $(N/\sigma^2)\ \mathrm{Var}\ \hat{y}(\underline{x})$, then

$$v(\underline{x}, D_N) = N f'(\underline{x})(X'X)^{-1} f(\underline{x}) \ . \tag{2.7}$$

If $\underline{\varepsilon}$ in (2.4) is normally distributed, then a confidence region for $\underline{\beta}$ of a given confidence coefficient has the form

$$\{\underline{\beta}: (\underline{\beta} - \hat{\underline{\beta}})' X'X (\underline{\beta} - \hat{\underline{\beta}}) \leq \text{constant}\} \ ,$$

which is an ellipsoid centered at $\hat{\underline{\beta}}$, the least squares estimator of $\underline{\beta}$. The volume of this ellipsoid is proportional to $|X'X|^{-1/2}$, where $|X'X|$ denotes the determinant of $X'X$. This volume can, therefore, be minimized if the discrete design D_N is chosen such that $|X'X|$ is maximum over the class of N-point discrete designs. A design having this property is said to be a discrete D-optimal design.

In general, for any design measure s defined on χ, the standardized prediction variance described in (2.7) will have the form

$$v(\underline{x}, s) = f'(\underline{x}) M^{-1}(s) f(\underline{x}) \tag{2.8}$$

provided that the information matrix $M(s)$ is nonsingular. If H denotes the class of all design measures on χ, then a design measure s^* is D-optimal if it maximizes $|M(s)|$ over H, that is,

$$|M(s^*)| = \sup_{s \in H} |M(s)| \ . \tag{2.9}$$

This is an extension of the concept of D-optimality in the discrete case.

The D-optimality criterion has received a great deal of attention as evidenced by the numerous articles written about it. The review articles by St. John and Draper (1975), Ash and Hedayat (1978), and more recently Atkinson (1982) contain many references on D-optimality and other optimal design criteria.

The objective function in the D-optimality criterion, namely $|M(s)|$, can be expressed in terms of the eigenvalues $\lambda_i(s)$ of the matrix $M(s)$ since $|M(s)| = \prod_{i=1}^{p} \lambda_i(s)$, where p is the number of parameters in the model. Other functions of these eigenvalues were considered in the development of mainly continuous design measures. These include $\mathrm{tr}[M(s)] = \sum_{i=1}^{p} \lambda_i(s)$ and $\lambda_{(1)}(s)$, where $\lambda_{(1)}(s)$ is the smallest eigenvalue of $M(s)$. The design criteria based on these functions are called A-optimality and E-optimality, respectively. More specifically,

i) a design measure s^* is A-optimal if it maximizes $\sum_{i=1}^{p} \lambda_i(s)$ over H, the class of all design measures on χ.

ii) a design measure s^* is E-optimal if it maximizes $\lambda_{(1)}(s)$ over H.

Another design criterion which is closely related to D-optimality is the G-optimality criterion. A design measure s^* is G-optimal if it minimizes over H the maximum variance function given in (2.8), where the latter maximization is carried out over the experimental region χ, that is,

$$\sup_{x \in \chi} v(x, s^*) = \inf_{s \in H} \left\{ \sup_{x \in \chi} v(x, s) \right\}, \tag{2.10}$$

Kiefer and Wolfowitz (1960) proved that the D-optimality and the G-optimality, as defined in (2.9) and (2.10), respectively, are equivalent. Furthermore, they showed that these two extremum problems are equivalent to yet another extremum problem, namely

$$\sup_{x \in \chi} v(x, s^*) = p \ . \tag{2.11}$$

It is to be noted that, in general,

$$\sup_{x \in \chi} v(x, s^*) \geq p \tag{2.12}$$

(see Fedorov 1972, p. 69). Hence, the maximum standardized variance of the predicted response achieves its minimum value of p whenever the design measure s^* is D- or G-optimal.

The above results can be formalized in the following theorem, known as the Equivalence Theorem of Kiefer and Wolfowitz:

Theorem: If H is the class of all design measures defined on a subset χ of the k-dimensional Euclidean space (k is the number of design variables in the model), and if p is the number of parameters in the model, then the following assertions are equivalent:

i) s^* is D-optimal

ii) s^* is G-optimal

iii) $\sup_{x \in \chi} v(x, s^*) = p$.

Assertion (iii) of the Equivalence Theorem is very useful. It provides an easy check on whether a design measure is D-optimal by comparing the maximum of $v(x, s)$ over χ with the number of parameters in the corresponding model. Furthermore, it can be effectively used to construct a D-optimal design from a nondegenerate discrete design D_{N_0} (nondegenerate means that the corresponding $X'X$ matrix is nonsingular) by augmenting it sequentially with design points chosen appropriately (see Wynn 1970, Silvey 1980, Chapter 4). The first point, x_1, is chosen such that

$$v(x_1, D_{N_0}) = \sup_{x \in \chi} v(x, D_{N_0}). \tag{2.13}$$

By augmenting D_{N_0} with x_1 we get D_{N_1}, which, in turn, is augmented with the point x_2 which satisfies

$$v(x_2, D_{N_1}) = \sup_{x \in \chi} v(x, D_{N_1}). \tag{2.14}$$

This process continues and results in the sequence of designs $D_{N_0} \subset D_{N_1} \subset D_{N_2} \ldots$, which, according to the Equivalence Theorem, must converge to a D-optimal design measure (see Fedorov 1972, Th. 2.5.3; Wynn 1970, Th. 1). Note that since by (2.12),

$$v(x_i, D_{N_{i-1}}) - p \geq 0 \ , \quad i = 1, 2, \ldots , \tag{2.15}$$

the sequential generation of a D-optimal design can be terminated whenever the difference in (2.15) is less than some value $\delta > 0$ chosen a priori. Thus, it is possible to approximate, with a given precision, a D-optimal design measure with a discrete design. This fact has in effect brought D-optimal designs out of the realm of theory into factual existence. Nalimov et al. (1970), and Box and Draper (1971) pointed out, however, that the number of design points needed to adequately approximate a D-optimal design measure might be too large as compared to the number of parameters in the model. It is for this reason that discrete D-optimal designs, that were mentioned earlier, became attractive. We refer to an N-point D-optimal design as D_N -optimal (see St. John and Draper 1975). It is important here to point out that the Equivalence Theorem mentioned earlier does not apply to D_N -optimal designs.

Several algorithms are available to construct D_N -optimal designs. The DETMAX algorithm by Mitchell (1974) and the one by Fedorov (1972, pp. 160-165) generate a sequence of N-point designs with nondecreasing values of $|X'X|$ for a given N. Mitchell and Bayne (1978) constructed D-optimal fractions of three-level factorial designs for second order models. Welch (1982) presented a catalog of D_N -optimal designs which can also perform well by other design criteria for a small loss in the D-optimality efficiency. A review of algorithms for constructing D_N -optimal designs was given by Cook and Nachtsheim (1980).

The D-optimality criterion can also be used in situations where a subset of q ($< p$) parameters in a model are of interest, whereas the remaining $p - q$ parameters are regarded as nuisance parameters. A design measure, s_q^*, is D_q-optimal if it minimizes the determinant of the submatrix of the inverse of the information matrix $M(s)$ which corresponds to the vector of the q parameters of interest. An equivalence theorem similar to the Kiefer and Wolfowitz Equivalence Theorem holds for D_q-optimality (see Kiefer 1961).

A lesser known optimality criterion is the c-optimality criterion. A design measure s^* is c-optimal if it minimizes the variance of the least-squares estimator of a linear function of the parameter vector β. Thus, if $M(s)$ is the information matrix and c is a given vector of known elements, then s^* is c-optimal if it minimizes $c'M^{-1}(s)c$ over the class of all design measures. Murty and Studden (1972) used this criterion to obtain optimal designs for estimating the slope of a response surface at a given point of the experimental region.

Design Efficiency

Any of the previously discussed optimal designs can be used to evaluate and compare designs on the basis of efficiency. For example, for the D- and G-optimality criteria the corresponding efficiencies, as defined by Atwood (1969), are, respectively,

$$D\text{-efficiency} = \left[|M(s)| / \sup_{s \in H} |M(s)| \right]^{1/p}$$

$$G\text{-efficiency} = p / \sup_{x \in \chi} v(x, s),$$

where s is a given design measure, p is the number of parameters in the model, H is the class of all design measures, and $v(x, s)$ is the standardized prediction variance described in (2.8). Note that by (2.12) the G-efficiency (as well as the D-efficiency) of s is less than or equal to unity and greater than or equal to zero. Lucas (1974, 1976, 1977) used the D- and G-efficiencies to evaluate the performance of some traditional response surface designs for second order models.

Additional Remarks Concerning Optimal Designs

The various optimality criteria described earlier are usually referred to as alphabetic design optimality. This term was originally coined by Box (1982) who expressed certain reservations about "the usefulness of this approach as far as response surface designs are concerned". Researchers in this theory have produced outstanding results based on intricate mathematical formulations, but have neglected to address important practical difficulties that are present in RSM applications. As a result, there has been some confusion on the part of RSM practitioners who attempt to use the alphabetic optimality results.

In the design optimality approach, the design of experiment is set within a rigid framework governed by a set of assumptions, the most prominent of which characterizes the fitted model as the true model over the experimental region. It is rarely the case when an experimenter would be willing to make such an assumption. Furthermore, the experimental conditions can vary in time and may not conform to assumptions made a priori at the outset of the experiment. This has prompted Box et al. (1978, p. 472) to state that "in recent years the study of optimal design has become separated from real experimentation with the predictable consequence that its limitations have not been stressed, or, often, even realized."

In the traditional RSM approach, bias suspected of being present in the fitted model plays a significant role. This is the basis for the Box-Draper criterion discussed in Section 2.1. In fact the concern about model inadequacy in this approach has prompted other researchers to consider designs solely on the basis of bias (see Karson et al. 1969). The bias criterion, however, provides protection against a specific form of model inadequacy according to what we postulate as the true model. Kiefer (1975, pp. 284-286) criticized certain aspects of the preoccupation with bias, pointing out examples in which the variance criterion is compromised for the sake of the bias criterion. Both Kiefer and Box agree that design selection should be guided by more than one criterion, "no single simple prescription can be expected to yield satisfactory designs in all, or even most, applications" (Kiefer 1975, p. 286) (see also Box 1982, Section 7).

The work of Fedorov represents a "middle ground" between Box's and Kiefer's approaches. It provides the mathematical apparatus for the derivation of the theoretical results, as well as the necessary algorithms needed to apply them so that they are accessible to comparatively "broad circles of researchers and technologists" as Fedorov (1972) stated in the preface of his book on optimal experiments.

In addition to Fedorov's book, the book by Silvey (1980) and the review articles by Bandemer (1980) and Atkinson (1982) provide recent surveys of optimal experimental designs.

2.6 Design of Mixture Experiments

Throughout this review we restate our frustration that much of the technology advanced in RSM seems to not have been communicated to subject matter users and thus they are "far behind" recent advances. However, the area of mixture experiments is an exception. From the early pioneering work in the late 50's, techniques in the use of mixture designs became important to users of RSM where the response to a mixture of ingredients depends on the relative proportions of the ingredients. These experiments are characterized as follows: If x_i, $i = 1, 2, \ldots, k$ represents the proportion of the ith component in a k factor combination then for each experimental run $0 \le x_i \le 1$, $i = 1, 2, \ldots, k$ and $\sum_{i=1}^{k} x_i = 1$. The development of designs and the analysis of data collected under these constraints has been the subject of much research. Indeed, the particular area has been the subject of two reviews by Cornell (1973, 1979), mentioned prominently in two additional reviews by Mead and Pike (1975), Steinberg and Hunter (1984), and the subject of a text Cornell (1981).

Some highlights in the development of this area follow. Scheff&eac. (1958) is credited by most with having initially considered the mixture problem although Claringbold (1955) recognized that designs for studying such relationships are on a simplex. Scheff&eac. proposed the simplex lattice design as well as a family of polynomial models to use in approximating the underlying relationship between the response and mixture components. A deficiency of the simplex lattice design is that its use tends to result in mixtures involving only two components regardless of the total number of components under consideration. To remedy this Scheff&eac. (1963) proposed the simplex centroid design which consists of $2^k - 1$ design points which are the centroid of the simplex and the centroid of all lower dimensional simplices contained within the original $(k - 1)$ dimensional simplex.

Thompson and Myers (1968) developed designs that allow the use of the minimum average bias and variance criteria of Box and Draper. They make use of a transformation to $(k - 1)$ dimensional variables so that the standard designs can be used. A transformation is given to the user which produces the design in the natural, mixture variables.

It is not unusual for a mixture experiment to be such that there are bounds on some or all of the components of the combination. McLean and Anderson (1966) proposed the extreme vertices design for such situations. Snee (1981) uses the gasoline blending problem to illustrate some practical problems that occur when considering mixture experiments. Attention is focused on the design of the blending studies and appropriate models for analysis as well as the use to which the fitted model is put. In this paper currently available algorithms are used in the construction of linear and quadratic model designs where there are single and multiple component constraints on the region of feasible blends. Piepel (1983a) discusses several guidelines for developing constraints on the levels of components in mixtures and presents techniques for checking the consistency of the constraints that are developed. Piepel (1983b) notes that the centroid of a constraint region in mixture experiments has been defined as the average of all extreme vertices of the region. Utilizing the definition of the centroid as the center of mass or volume of the region Piepel develops an algorithm to calculate centroids of various dimensional faces of the constraint region as well as the centroid of the $(k - 1)$ dimensional simplex. Whenever constraints, in the form of upper and lower bounds, are placed on the components of a mixture the size and possibly the slope of the experimental region is altered. Crosier (1984) proposes a transformation to pseudo components to reduce the ill-conditioning created by the constraints. Conditions are given which can be used to determine when the use of the transformation is preferable to that of other transformations.

Hare (1979) considers the development of designs for the situation where some of the design variables, called process variables, are not subject to the simplex constraint, $\sum_{i=1}^{k} x_i = 1$. Of concern here is the choice of settings for the mixture variables as well as the process variables. The problem has also been considered by Vuchkov et al. (1981) who proposed the use of a sequential procedure to produce designs that were nearly D-optimal. The traditional Scheffé model in mixture experiments that contain process variables contain cross-product terms between the mixture and process variables as well as indicate that the process by mixture cross-product terms estimate the effects of the process variables on the blending properties of the mixture variables only and do not give an overall measure of the main effects and interactions of the process variables alone. They develop a reparameterized model that permits the experimenter to separate the effects of the process

variables from the mixture variables. From such a model it is demonstrated that reduced model forms can be obtained through the use of a variable selection procedure.

Aitchison and Bacon-Slone (1984) show that the constant sum constraint, i.e. $\sum_{i=1}^{k} x_i = 1$ can be removed by a log ratio transformation, $z_i = \log \frac{x_i}{x_k}$ $i = 1, 2, \ldots, k-1$. When this is done the modeled expected response can be expressed as a polynomial in the z_i. Since the z_i can be varied independently the polynomial can include all terms of appropriate degree. For this paper attention is restricted to linear and complete quadratic models.

Rotatability in mixture experiments has received very little attention by comparison to other more general response surface investigations. In an attempt to obtain constant prediction variance within the simplex factor space, Thompson and Myers (1968) developed rotatable response surface designs on the basis of their transformation of the k mixture variables to $k-1$ mathematically independent variables. These designs were used to fit polynomial models over some ellipsoidal region inside the simplex factor space. Cornell and Khuri (1979) introduced a different configuration of rotatability, one that is suited for ternary mixture problems. In this new configuration, the predicted response has constant variance on each triangle of a set of concentric triangles within the simplex factor space. This is achieved by using a nonlinear transformation which maps concentric circles in a new coordinate system onto concentric equilateral triangles in the mixture space. Standard rotatable response surface designs in the new coordinate system can then be mapped onto designs in the mixture space resulting in the prediction variance being constant on concentric triangles.

2.7 Designs for the Slope

In many applications of RSM, good estimation of the derivatives of the response function may be as important or perhaps more important than estimation of mean response. Certainly, the computation of a stationary point in a second order analysis, or the use of gradient techniques, e.g., steepest ascent or ridge analysis depend heavily on the partial derivatives of the estimated response function with respect to the design variables. Since designs that attain certain properties in $\hat{y}$ (estimated response) do not enjoy the same properties for the *estimated derivatives* (slopes), it is im-

portant for the user to consider experimental designs that are constructed with the derivatives in mind.

Atkinson (1970) considered designs for estimation of the slope at a fixed point with the response function being of order one. The criterion used is the expected mean squared error for a directional derivative, averaged over all possible directions. Ott and Mendenhall (1972) dealt with the special case of a single design variable and a second order model. No model misspecification was considered and the primary focus was on the properties of the variance of the estimated slope. They considered optimum spacing of the levels of the design variables that gave desirable properties of the variance function. Murty and Studden (1972) considered polynomial regression models with the criterion being the variance of an estimated slope at a fixed point and averaged over an interval.

Hader and Park (1978) extended the notion of rotatability to cover the slope for the case of second order models. They developed design parameters for central composite designs that result in "slope rotatability," i.e., the variance of the estimated derivatives is constant for all points equidistant from the design center. Tables are produced of designs for values of $k = 2, 3, ..., 8$. Some of the designs featured have replicated axial points rather than heavy replication in the design center.

Myers and Lahoda (1975) extend the Box and Draper integrated mean squared error criterion under model misspecification to cover sets of parametric functions with the slopes being primary applications. For the second order case they develop designs that are *minimum slope variance*, conditional on achieving minimum integrated slope bias in case of both spherical and cuboidal regions of interest. Their designs are central composite designs with dual axial levels and are tabulated for $k = 2, 3, ..., 7$.

Mukerjee and Heda (1985) develop designs associated with minimum variance of the estimated slope maximized over all points in the factor space for second and third polynomial models over a spherical region.

2.8 Design for Minimum Bias Estimation

Karson et al. (1969) introduced the notion of minimum bias estimation in response surface analysis. The motivation was derived from the work of Box and Draper in which it was made clear that consideration of bias in RSM is at least as important as consideration of variance. As a result, an alternative to least squares was introduced for minimizing average bias at the estimation stage.

Given that minimum bias estimators are used, Karson (1970) introduced a design criterion to provide protection against certain higher order model terms. This criterion results in conditions on the design moments being met. With a single independent variable, conditions are given for fitting up to a cubic polynomial and protecting against a possible fifth degree polynomial. The author also considers the two factor case for fitting a first order polynomial and protecting against the presence of second and third order terms. A general p factor result for the linear to quadratic case is also given. Karson and Spruill (1975) examine four alternative design criteria given that minimum bias estimation is used in the case of a single independent variable. The alternative design criteria are minimaxes or minimum averages of the squared differences between the expected value of the stationary point found by fitting the approximating polynomial and either a prior guess at the location of the stationary point or the location of the stationary point as determined from the true model. Evans and Manson (1978) utilize the design flexibility associated with the use of minimum bias estimation to construct D-optimal, V-optimal, and A-optimal experimental designs in two dimensions via a simplex search procedure. The designs are obtained for both square and circular regions of interest.

In a related work, Kupper and Meydrech (1973) consider the use of an estimator of the form $K\hat{\beta}$ for the parameter of the fitted polynomial. They give conditions under which it is possible to determine K's providing smaller J than when $K = I$ for any choice of experimental design. The case where the fitted polynomial is of degree one and the true polynomial is of degree two is considered. These same authors (1974) compare their approach to that of Box and Draper (1959) as well as that due to Karson et al. (1969).

2.9 RSM Design Robustness

As we indicated earlier in this paper, the first notion of RSM design robustness appeared in the work by Box and Draper (1959, 1963) dealing in protection against model underspecification. It formalized, in an RSM setting, the notion of proper placing of the design points *in from the boundary* of the region of interest when underspecification is a concern. While specifics in the Box and Draper work dealt with spherical regions, Draper and Lawrence (1965) applied the Box and Draper approach to generate designs robust to model inadequacies in the case of cuboidal regions.

Aside from model misspecification, RSM design robustness includes the following categories

i) Robustness to outliers in the data

ii) Robustness to errors in the design levels

iii) Robustness to nonnormality in the model errors

iv) Designs for extrapolation under conditions of model misspecifications.

We feel committed to extend the notion of RSM to include F-tests that are developed through regression analysis. Papers by Jensen et al. (1975) and Vuchkov and Solakov (1980) demonstrate that experimental design has a substantial impact on the robustness to normality of the F-test in a regression or RSM model. In the former paper, the class of orthogonal designs was found to be robust in the case of a first order response surface model. In the latter case, a similar result was demonstrated. The approach was taken of considering the property of "quadratic balance" in a design. This property is one making the *hat diagonals* equal, where the hat diagonals are the diagonal elements of

$$H = X(X'X)^{-1}X'$$

Khuri and Myers (1981) implement the robustness criterion of Box and Watson (1962) for first order RSM models. Again, the robustness here is a resistance of tests of significance to failure of the distribution of errors to be normal. A method is described for construction of a robust design assuming a fixed number of experimental runs. Here, of course X is an $N \times p$ model matrix given in the general linear model

$$\underline{y} = X\underline{\beta} + \underline{\varepsilon}$$

One very intriguing, albeit predictable, result from the Vuchkov and Solakov work is that the most desirable prescription in terms of this type of robustness is a design with uniformly replicated trials and equal hat diagonals. Example designs are the 2^k factorial arrays and appropriate fractions.

From a point of view of motivation, the paper by Box and Draper (1975) would appear to have been very timely. Since the early 70's considerable attention has been paid to the detection of outliers and the accommodation of outliers in regression analysis. This work by Box and Draper linked the awareness of outliers to notions of RSM experimental designs. Design properties were sought that resulted in "minimal impact" of outliers in the resulting data. The result was the choice of designs for which $\sum_{i=1}^{N} h_{ii}^2$ is minimized where, again, the h_{ii} are diagonals of the hat matrix. Again, in the first order case, the orthogonal designs are optimal.

Herzberg and Andrews (1976) deal with optimal designs under nonoptimal conditions such as missing observations and presence of outliers while dealing mostly in designs that are constrained to be economical. They introduce a measure of robustness which is called a "probability of breakdown", given by

$$Pr(|X'DX| = 0)$$

where D is a diagonal matrix with ith main diagonal element

$$d_{ii} = \begin{cases} 0 & \text{with probability } \alpha(\underline{x}) \\ 1 & \text{with probability } 1 - \alpha(\underline{x}) \end{cases}$$

and $\alpha(\underline{x})$ is the probability of losing a data point. When $|X'DX| = 0$, the coefficients cannot all be estimated. In addition, they consider $E(|X'D^2X|^{1/p})$ as an alternative measure of robustness. In Andrews and Herzberg (1979) they introduce the notion of efficiency by working with the quantity

$$\frac{1}{N} \frac{E|X'D^2X|^{1/p}}{|M|^{1/p}}$$

where M is the Fisher information matrix for the appropriate D optimal design. Examples are given to indicate how notions like this can be used to select robust designs. The numerator of the above expression is compared for central composite designs with varying number of center runs. The probability value $\alpha(\chi)$ is varied in the study and the results indicate clearly that criteria like these can be used to provide a choice between designs when the user fears a loss of information in the form of missing data.

In a paper that considers protection against model misspecification and outliers simultaneously, Draper and Herzberg (1979) deal with n integrated mean squared error criterion much like that of Box and Draper in 1959 and 1963. The purpose, though, seemed to be to determine if the presence of outliers produced any substantial change in the recommendations made earlier, when one only considers model misspecification. Special cases of a single outlier and two or more outliers are considered. As expected, in the case of a first order fitted model with protection against the existence of second order terms, an orthogonal design is recommended. In addition, the recommendation for the second moment is to make it slightly larger than the "minimum bias" value uncovered in 1959. Specifically, a value roughly 10% larger is recommended. Simply put, this implies that if outliers are present, the variance portion of the integrated prediction mean square error becomes somewhat more important. Extensions to the case of the second order fitted model were made with similar recommendations.

A related notion of robustness deals with errors in the factor levels. Vuchkov and Boyadjieva (1983) consider this problem and attempt to determine design families that are robust. The interested reader should first read Box (1963) in which the effect of errors in factor levels is considered in both first and second order models. While no specific design criteria are considered in this work by Box, it is an excellent account of what is the extent of the damage when errors in design variables occur.

In the paper by Vuchkov and Boyadjieva, some of the same concepts covered in Box are restated. They define an estimator that is BLUE under the conditions of errors in factor levels, and which depends upon the moments of the factor levels. Assuming this particular form of estimation (which reduces to least squares if the model errors are unbiased), they define "criteria for robustness"

and make some comparisons among the Box-Behnken designs, rotatable central composite designs, Hartley's small composite design, Lucas' optimal composite designs, and others.

Finally, we deal in a type of design property that some may not generally classify as *robustness*, namely designs that are *resistant to errors in extrapolation*. This is particularly important in RSM work since a response surface is often used by necessity for extrapolation purposes. Draper and Herzberg (1973) discuss designs that are robust in this sense under the setting that the fitted model is first order and one's ability to extrapolate is influenced by the existence of second order terms in the true structure. Their work is confined to consideration of extrapolation in a specified direction with a spherical region of interest.

Draper and Herzberg (1979) considered both the first and second order case in which interest is in extrapolation outside a sphere. The region of extrapolation is a spherical shell. Again, variance and bias due to model misspecification are considered and are integrated over the region. In the first order case, they reduce the problem to one of selecting the pure second moment. All odd moments through order three are assumed zero. They are able to find the second design moment that minimizes what they call a "proportional mean square error." Designs with *maximum spread*, i.e., points placed on the perimeter of the region of interest, are found to be optimal. In the second order case, their work was restricted to second order rotatable designs with all odd moments less than or equal to five being zero. Emphasis is put on the central composite design. The conclusions indicate that the rotatable central composite designs that are most robust to extrapolation require design points that are expanded to the edge of the region of interest.

In this section and in many others in this review, the influence of the Box and Draper *protection against model inadequacy* becomes evident. What we have seen occur in much of the design robustness work is a blending of the problem of model inadequacy with other deviations from ideality.

Though the foregoing might be viewed as representing the bulk of the "robust design" work involved strictly in the use of RSM, there certainly are other important pieces of work that deal in design robustness in regression models. Atkinson (1972) discusses designs that are best for detection of model inadequacy. Atwood (1971, 1975) deals in robust procedures for estimating polynomial

regression and methods for estimating a response surface when the number of parameters are uncertain.

One important note of caution should be made to any user or potential user of RSM. Designs are chosen because they are optimal or near optimal in some sense, or because they are robust or near robust in some sense. But a design may indeed be near optimal in one sense (say D-optimality) but not near optimal with respect to another criterion. Obviously, a desirable robustness property of an RSM design is one in which the design enjoys a near optimal or at least "steady" performance in several criteria that is important to the user. For example, Galil and Kiefer (1977) and Kiefer (1975) show variation in performance of designs as one moves across criteria.

2.10 Designs for Special Goals

Designs for Nonlinear Models

A nonlinear model is a model of the form

$$y = f(\underline{x}, \underline{\theta}) + \varepsilon \quad , \tag{2.16}$$

where $\underline{x} = (x_1, x_2, \ldots, x_k)'$ is a vector of design variables, $\underline{\theta} = (\theta_1, \theta_2, \ldots, \theta_p)'$ is a vector of unknown parameters, ε is a random error, and $f(\underline{x}, \underline{\theta})$ is a known function nonlinear with respect to at least one element of $\underline{\theta}$. Nonlinear models have not received a great deal of attention in RSM, even though they have many applications in several areas, particularly, in biological and chemical sciences.

The main design criterion for nonlinear models is the D-optimality criterion, which actually applies to a linearized form of the model in (2.16) (Box and Lucas 1959). More specifically, if $f(\underline{x}, \underline{\theta})$ is approximately linear in $\underline{\theta}$ in a neighborhood of $\underline{\theta} = \underline{\theta}_0$, then a design D is chosen so that the determinant $|F'(D, \underline{\theta}_0) F(D, \underline{\theta}_0)|$ is maximum, where $F(D, \underline{\theta}_0)$ is an $N \times p$ matrix whose (i, j)th element is

$$f_{ij} = \frac{\partial f(\underline{x}_i, \underline{\theta})}{\partial \theta_j}\Big|_{\underline{\theta} = \underline{\theta}_0} \qquad \begin{matrix} i = 1, 2, \ldots, N; \\ j = 1, 2, \ldots, p. \end{matrix} \tag{2.17}$$

In (2.17), $\frac{\partial f}{\partial \theta_j}$ denotes the partial derivative of f with respect to θ_j, x_i is the value of x in the ith experimental run, and N is the number of experimental runs. An optimal design obtained under this criterion is more appropriately called a locally D-optimal design, a terminology used by Chernoff (1953). A similar design criterion is available if the interest is in only a subset of the parameter vector $\underline{\theta}$ (see Box 1971, Hill and Hunter 1974).

Unlike D-optimal designs for linear models, those for nonlinear models depend upon the unknown values of $\underline{\theta}$. This is an unappealing characteristic of nonlinear models and was most appropriately depicted by Cochran (1973): "You tell me the value of $\underline{\theta}$ and I promise to design the best experiment for estimating $\underline{\theta}$." There are several procedures to remedy, or at least alleviate, the problem of design dependency. One procedure treats $\underline{\theta}_0$ as an initial guess which is used to obtain a p-point design. Observations collected at the points of this design are then used to provide an estimate of $\underline{\theta}$. Thereafter, additional design points are augmented sequentially while updating the estimate of $\underline{\theta}$ (see Box and Hunter 1965). One advantage of this sequential approach is that it helps reduce the dimensionality of the design optimization problem. If the initial value, $\underline{\theta}_0$, of $\underline{\theta}$ is a good "guess", then under certain conditions, Atkinson and Hunter (1968) showed that when the number of design points N is a multiple of p, the number of parameters, the optimal N-point design consists of replications of the optimal p-point design obtained on the basis of $\underline{\theta}_0$.

An alternative strategy for dealing with design dependency is to adopt a Bayesian approach. Zacks (1977) considered maximizing the expected value of the determinant $|F'(D, \underline{\theta}) F(D, \underline{\theta})|$ with respect to some prior distribution of $\underline{\theta}$. Bayes sequential designs can also be obtained. An optimal design for a new stage of experimentation is determined by maximizing the aforementioned expected value with respect to the posterior distribution of $\underline{\theta}$ given the results from the previous stages. Another strategy that is applicable when the number of design variables is equal to one is to approximate the nonlinear function in (2.16) with a Lagrange interpolating polynomial (Khuri 1982). The interpolation points are chosen as the zeros of a Chebyshev polynomial of the first kind. Another approximation using spline functions was considered by Bumrungsup (1984).

The dependency of the optimal nonlinear design on the parameter vector $\underline{\theta}$ is less severe if the model is partially nonlinear. By that we mean that some elements of $\underline{\theta}$ appear linearly in the model

while others appear nonlinearly. Hill (1980) showed that a locally D-optimal design for a partially nonlinear model depends only on the model's nonlinear parameters. This property, however, does not always hold when the design is for estimating a subset of the parameter vector (see Khuri 1984).

The use of the D-optimality criterion for choosing a nonlinear design may not always be appropriate particularly in an RSM setting. One must remember that it is a variance criterion which does not account for any possible bias in the model. Just like in linear models, bias is an important consideration for the choice of design. In fact, in nonlinear models more emphasis should be given to the subject of bias since it is not quite clear how bias should be defined. Unfortunately, little appears to be known about this subject. A brief mention of bias in nonlinear models is given in a paper by Atkinson (1972, Section 5).

Designs for Fitting Spline Functions

Let $[a, b]$ be an interval that is partitioned into $h + 1$ subintervals by the points $a = \tau_0 < \tau_1 < \tau_2 < \cdots < \tau_h < \tau_{h+1} = b$. A spline function in one design variable x is a continuous function $f(x)$ defined on $[a, b]$ such that $f(x)$ restricted to $[\tau_{i-1}, \tau_i]$, $i = 1, 2, \ldots, h + 1$, is a polynomial, and satisfies certain differentiability conditions at the points $\tau_1, \tau_2, \ldots, \tau_h$. The polynomials defined on these subintervals are different, and the partition points, $\tau_1, \tau_2, \ldots,$ and τ_h are called knots. Spline functions are, therefore, segmented, or piecewise polynomials. This definition of spline functions can be extended to more than one dimension.

Spline functions are useful in approximating continuous functions, just like polynomials. In certain situations, however, they are more suitable than polynomials. This is particularly true when the function to be approximated is defined over a wide region where its behavior in one part of the region is unrelated to (or undetermined by) its behavior in another part. Polynomial approximation on the other hand forces some kind of unwarranted semblance on the behavior of the function. This is because the behavior of a polynomial over an entire region can be fully determined by its behavior over only a part of the region.

Even though spline functions have received considerable attention in the mathematical literature, their introduction into the statistical literature is relatively recent. Wold (1974) gave a review

of the use of spline functions in least squares fitting and provided several useful references on the subject. Gallant and Fuller (1973) discussed the estimation of the location of the knots when fitting a spline function to a data set. Very little is known about the choice of design for fitting a spline function. Studden (1971) discussed D-optimal and L-optimal designs for spline functions. Draper et al. (1977) applied the Box-Draper (1959) design criterion for protection against model bias. Park (1978) adopted the D-optimality criterion when fitting a spline function with only one knot. In all of these papers, the knots of the fitted spline function were considered known. More recently, Bumrungsup (1984) used spline functions to approximate the mean response in a nonlinear model. The knots were chosen so that the error of approximation did not exceed some specified value chosen a priori. The approximating spline function was then used to obtain optimal designs for the nonlinear model. These designs have the advantage of being not dependent on the model's parameters.

More research is needed in this area. Optimal designs chosen on the basis of spline approximation depend on the number and location of the knots. Even if the number of knots is determined so that a certain degree of approximation is achieved, the positioning of the knots is an important consideration which should be addressed. Extensions to more than one dimension are also needed.

Design Augmentation

Design augmentation is an increasingly important component in the progression of RSM research. It is consistent with the "sequential spirit" of RSM. In a large percentage of RSM applications more than one stage of experimentation and analysis is required. The notion of moving from one experimental region to another and planning an experiment in sequence often becomes necessary in real RSM situations. Quite often additional experimental runs are taken after an experiment has been carried out. This may be necessary in the following situations:

i) When the initial experiment is poorly planned and, consequently, results in observations that are not as informative about the fitted model as is desired.

ii) When the prescribed design settings are not attained by the actual values of the design variables used in the initial experiment. This might be caused, for example, by technical limitation or by equipment malfunction.

iii) When there is a need to fit a model that is more complex than the original model, which may be inadequate, and the initial design does not accommodate such an action.

iv) When the experimenter decides to change, or modify, the region of interest in the original experiment. This usually occurs in sequential experimentation where information obtained in one stage is used to plan the next stage. Also, there might be a need to gain more information about the response in certain parts of the region that are not adequately covered by the initial design.

In any of the above situations, the additional runs are chosen in a manner that remedies, or *repairs*, the initial design. Situation (i) was considered by several authors. Dykstra (1966) and Gaylor and Merrill (1968) augmented a nonorthogonal design for fitting a first order model with additional runs in order to reduce multicollinearity effects among the design variables. Dykstra (1966) suggested several other criteria for augmenting a nonorthogonal first order design. Covey-Crump and Silvey (1970) and Mayer and Hendrickson (1973) adopted the maximization of $|X'X|$ criterion for the selection of the additional experimental runs, where X is the matrix of design variables associated with the linear model for both the initial design and the augmented runs. In Covey-Crump and Silvey (1970) the augmented design points were selected from a spherical region, whereas in Mayer and Hendrickson (1973), the augmented design points were constrained by cost considerations. Dykstra (1971) described a method for augmenting the initial design with additional points taken one at a time. Each point is chosen from a list of candidates, the selection criterion being the choice of the location for which prediction variance is maximized. This is equivalent to the maximization of $|X'X|$ with each added point. Hebble and Mitchell (1972) followed a similar procedure, except that the entire region of interest, instead of a set of candidate points, is searched for the next design point. Wynn (1970) showed that this process leads in the limit to a D-optimal design. Hebble and Mitchell's (1972) procedure can also be useful in situations (iii) and (iv). Evans (1979) used the simplex search technique to add several points simultaneously under the maximum

of $|X'X|$ criterion. Suich and Derringer (1977), in their discussion of the adequacy of the regression model, considered data augmentation as a means to satisfy their criterion of adequacy. They did not, however, provide a systematic procedure for the choice of the added points.

The main criterion used in design augmentation has been the maximization of $|X'X|$. Recently, Khuri (1985a) introduced a measure of rotatability which can be used to quantitatively assess departure from rotatability of a nonrotatable design. Using rotatability as a criterion, this measure can be utilized to repair a nonrotatable design by design augmentation. Hebble and Mitchell (1972) have indirectly restored rotatability through their maximization of $|X'X|$ over a spherical region. The measure of rotatability is particularly useful in situation (ii) where a design, originally planned to be rotatable, becomes nonrotatable due to failure to attain the prescribed design settings for a rotatable design. It can also be used in situation (iv) where a rotatable design is intentionally modified by design augmentation in order to gain more information in certain areas of interest (see Littell and Mott 1974). Such a modification usually results in loss of rotatability.

Designs to Increase the Power of the Lack of Fit Test

Checking the adequacy of a fitted model is an important consideration in RSM. Draper and Herzberg (1971) provided some insight into the nature of hypotheses that can be tested by the lack of fit test when replicate observations are available at one or more design points. Equally important is the ability to detect lack of fit in a model at an early stage of the experimental process. This necessitates the use of a design which can induce a certain degree of sensitivity in the lack of fit test. To accomplish this the design should be selected so as to maximize the power of the associated lack of fit test.

Suppose that at some stage of the experiment the following model is fitted:

$$\eta(x) = X_1\beta_1 \ , \tag{2.18}$$

where $\eta(x)$ denotes the mean response vector. The random errors associated with the observed response values are assumed to be independently and identically normally distributed with zero mean and constant variance. The true model is assumed to have the form

$$\eta(x) = X_1\beta_1 + X_2\beta_2. \tag{2.19}$$

The noncentrality parameter associated with the lack of fit test for model (2.18) is proportional to the quadratic form

$$\theta = \beta'_2 L \beta_2 \ , \tag{2.20}$$

where

$$L = X'_2X_2 - X'_2X_1(X'_1X_1)^{-1}X'_1X_2 \ .$$

In order to maximize the power of the lack of fit test, the design should, therefore, be chosen to make θ as large as possible.

Unfortunately, designs chosen under the above criterion depend on β_2 , which is unknown. Several approaches were considered to overcome this problem. Atkinson (1972) proposed the maximization of the determinant $|L|$. This is the same as the D_s-optimality criterion discussed in Section 2.5 for the precise estimation of a subset of the parameters consisting of the elements of β_2. Designs chosen in this manner, however, may provide poor estimates of β_1 if the fitted model is adequate. Atkinson (1972) suggested the maximization of $|L|$ subject to maintaining a lower bound on the efficiency of the lack of fit design for estimating β_1 . Atkinson and Fedorov's (1975) T-optimality criterion is essentially the same as the one we have mentioned. They suggested three possible solutions to deal with the problem of dependency on β_2 ; these are (i) a sequential procedure to construct a T-optimal design whereby observations obtained at a given stage are used to estimate β_2 and then select the next design point, (ii) a Bayesian solution which requires specification of a prior distribution on β_2 , (iii) a maximin procedure in which the minimum value of θ over a convex region φ in the β_2-space is maximized by a proper choice of design. A special case of the maximin procedure was adopted by Jones and Mitchell (1978) using a particular convex region φ determined by the moment matrices of the experimental region. They called a design obtained under the maximin criterion a A_1-optimal design. They also considered another variant of the maximin procedure, namely, the maximization of the average of θ over the boundary of the region

φ. A design obtained under this criterion is called a Λ_2-optimal design. The latter criterion is preferred over the Λ_1-optimality criterion which cannot be used in situations where the minimum value of θ over φ is equal to zero.

The Λ_2-optimality criterion was also applied by Morris and Mitchell (1983) to obtain designs to detect the presence of two-factor interactions among several two-level factors when fitting a first order model in these factors. An extension of the Λ_1-optimality criterion as well as the Λ_2-optimality criterion to a multiresponse situation was recently developed by Wijesinha and Khuri (1987).

The traditional lack of fit test mentioned earlier requires the availability of replicate observations. This allows the partitioning of the residual sum of squares from the analysis of the fitted model into a sum of squares due to lack of fit and a sum of squares due to pure error. When such a partitioning is not feasible (this occurs when the number of terms in the fitted model is equal to the number of distinct design points), the method of check points (see Scheffé 1958, Snee 1977) can be used instead. Check points are points in the experimental region where data are collected and compared to the predicted response values (at these points) as obtained under the fitted model. Shelton et al. (1983) introduced a method for selecting the check points so as to maximize the power of Scheffé's (1958) lack of fit test statistic, which makes use of the residuals at the check points.

III. RESPONSE SURFACE ANALYSIS

In the Hill and Hunter review of 1966, four steps were outlined as part of standard procedure in a response surface analysis. We think they are worth repeating here. They are (i) perform a statistically designed experiment, (ii) estimate the coefficients in the response surface equation, (iii) check on the adequacy of the equation (via a lack of fit test), and (iv) study the response surface in the region of interest. It is (iv) that we plan to consider in this section. We consider subsections on multiple responses, sampling properties of optima, and models that are alternatives to the standard polynomial models. However, underlying all of these topics is the question "What do we mean by a response surface exploration?"

The purpose of an RSM analysis is to answer certain general questions regarding the nature of the response function in the region of the experimental design Determining whether the system contains a maximum or minimum, or is a saddle system may be very important to the experimenter. On the other hand, the existence of a ridge system may indicate the need for further experimentation in another region. In some situations, response surface analysis serves as more than merely an empirical device. It can lead to what Hill and Hunter call an "elucidation of an underlying mechanism", and thus uncover theoretical information.

A distinction should be made between analyses whose goals are to explore the response surface as indicated above and that in which the major goal is *quality estimation of optimum conditions*. The method of steepest ascent remains a viable technique for sequentially moving toward the optimum response. The reader is referred to Davies (1954) and Myers (1976) for details and examples. Brooks and Mickey (1961) and Myers and Khuri (1979) discuss strategy in steepest ascent.

It is interesting to note that in the Mead and Pike review, they note that there were relatively few applications of response surface *optimization* with the use of procedures other than steepest ascent. At this point, 11 years later, we might echo a similar observation but add that there have been applications with the use of the Nelder Mead (1965) simplex procedure. What still surprisingly appears to be lacking are many examples of formal RSM optimization in which a response model other than first order is used. One of Mead and Pike's conjectures may still be valid, namely there is a general conservative nature in many research workers. Of course, the theory associated with most numerical optimization methods is developed in the literature under an assumed *deterministic model*. There are overriding reasons why the optimization phase of RSM is not formally applied in practical situations. There is a general unawareness among RSM users that optimization techniques are available. And certainly the commercially available software that data analysts use for other phases of analysis generally does not contain the optimization phase. Numerical analysis has advanced to the extent that optimization of second order or certain nonlinear response functions with or without constraints presents no serious difficulty. And yet how many software packages put together a RSM package complete with canonical analysis *and* optimization

procedures? Indeed, we have experienced a real need for such packages in industry. We attempt to shed more light on this subject in subsequent sections.

One useful procedure in a second order response surface analysis is *ridge analysis*, introduced by Hoerl (1959) and formalized by Draper (1963). The method is discussed with examples in Myers (1976). Hoerl (1985) gives a historical, almost anecdotal account of his father's development of ridge analysis. Reasons are given for what has appeared to be a relative obscurity of this procedure, which essentially is a steepest ascent procedure for second order models. It serves as a practical optimization procedure in which maximum (or minimum) values of $\hat{y}$ are determined on radii varying from zero to the perimeter of the design region. The resulting locus of points not only produces an alternative to canonical analysis for exploring the response surface but it also can offer a recommended set of operating conditions often sought by the analyst when the canonical analysis does not indicate an optimum at a stationary point within the design region. With the entire locus of points produced by the maximum ridge and a knowledge of the properties of the experimental design at or near the design perimeter, the user becomes armed with information that allows a reasonable recommendation.

It has been our observation that, in practical RSM problems, occasions in which the stationary point produces a satisfactory result are rare. More often than not, ridge conditions or saddle systems are experienced. As a result, ridge analysis, the notion of finding best conditions subject to 'anchoring' the results inside the experimental region, or some other type of constrained optimization, is often indicated. The advantage in ridge analysis as an exploratory tool has intuitive appeal. Most users, e.g., engineers, biologists, etc., understand it and would certainly prefer it to drawing conclusions from response contour plots for cases where $k \geq 3$. Hoerl (1985) laments the lack of attention to ridge analysis in the statistics literature. He walks the reader through a nice practical application. Smith (1976) relates situations in which ridge analysis is misleading. Khuri and Myers (1979) offer modifications to ridge analysis in cases where the design is not near rotatable. They suggest that the constraint applied should be on the prediction variance and point out that if the design is not rotatable, the modification provides more desirable results for the user.

In the subsections that follow, response surface analysis in the case of multiple responses is reviewed. Both exploration of the response and estimation of coefficients are considered. This is followed by the vitally important topic of sampling properties of estimated optimum conditions. Mead and Pike, in the 1975 review, indicated that statistical research into experimental design (say RSM design) has outstripped research in the area of analysis. To a great extent, this remains true. A quick count of the volume of our bibliography in design as opposed to papers in analysis (in statistical journals) will underscore the point.

3.1 Multiresponse Analysis

In many experimental situations a number of responses can be measured at a time for each setting of a group of design variables. Examples of multiresponse situations are numerous. In chemical engineering kinetics, several reactants might be involved in a chemical reaction which give rise to a number of responses that can be measured simultaneously. These responses are usually represented by nonlinear mechanistic models, or by linear empirical models whenever the reaction mechanism is too complex such as in an industrial reaction. Ziegel and Gorman (1980) gave an interesting exposé of the use of multiresponse data for studying kinetic models in the petroleum industry. The area of foods and other consumer product research also represents a challenge because of the need to almost always study many responses. Typical studies require panel-type responses or 'scores' on many features of the product. The review by Hill and Hunter (1966) listed several examples of multiresponse experiments and is perhaps the first paper in the statistical literature to direct attention to their important applications.

Subsequent papers on this subject have stressed the utility of analyzing multiresponse data by means of multivariate techniques which take into account interrelations among the responses. A univariate analysis in which responses are analyzed individually does not recognize such interrelations and will undoubtedly fail to adequately describe the true mechanism underlying the multiresponse system. Unfortunately, of the very few techniques that are currently available in the statistical literature for the analysis of multiresponse data, even fewer are actually used by practitioners. Our search for practical RSM applications reveal that users are far from up-to-date in the

use of multiresponse techniques. (See Section IV.) It is, therefore, imperative that existing as well as future multiresponse techniques be made accessible to data analysts. It is also equally important to demonstrate the utility of using the multiresponse approach when several responses are analyzed.

Multiresponse Estimation

The general multiresponse model is

$$y_{ul} = f_l(\underline{x}_u, \underline{\beta}) + \varepsilon_{ul}, \qquad \begin{matrix} u = 1, 2, \ldots, N; \\ l = 1, 2, \ldots, r \end{matrix} \tag{3.1}$$

where $\underline{x}_u$ is the vector of settings of k design variables at the uth experimental run, $\underline{\beta}$ is a vector of unknown parameters, f_l is a function of known form for the lth responses, and ε_{ul} is a random error associated with the lth response for the experimental run u. It is assumed that the ε_{ul}'s are normally distributed such that $E(\varepsilon_{ul}) = 0$, $E(\varepsilon_{ul}\varepsilon_{vj}) = 0$ for all $l, j, u \neq v$; $\mathrm{Var}(\varepsilon_{ul}) = \sigma_{ll}$, $l = 1, 2, \ldots, r$; $E(\varepsilon_{ul}\varepsilon_{vj}) = \sigma_{lj}$ for all u, $l \neq j$. If the σ_{lj}'s are known, then an estimate of $\underline{\beta}$ can be obtained by using weighted least squares. Most often, however, the σ_{lj}'s are unknown. In this case, Box and Draper (1965) using the Bayesian approach and assuming noninformative prior distributions for $\underline{\beta}$ and the σ_{lj}'s were able to show that an estimate of $\underline{\beta}$ can be obtained by minimizing the determinant $|S(\underline{\beta})|$ with respect to $\underline{\beta}$, where

$$S(\underline{\beta}) = (Y - F)'(Y - F) \ . \tag{3.2}$$

In (3.2), $Y = [\underline{y}_1 : \underline{y}_2 : \ldots : \underline{y}_r]$ is the data matrix with $\underline{y}_l$ being the vector of lth response values ($l = 1, 2, \ldots, r$), and F is an $N \times r$ matrix whose (u, l)th element is $f_l(\underline{x}_u, \underline{\beta})$. The method of estimation, which is basically equivalent to the maximization of the marginal posterior density of $\underline{\beta}$ (under the assumed noninformative priors), is referred to as the Box-Draper estimation criterion. This is a general criterion and applies to models whose functional forms can be either linear or nonlinear in the parameters.

Box et al. (1973) cautioned that the Box-Draper estimation criterion can lead to meaningless results when exact linear relationships exist among the responses. They called such relationships stoichiometric. They also pointed out that small rounding errors in the responses can cause

$|S(\beta)|$ to be different from zero and to change as the elements of β are changed, even under stoichiometric relationships. To resolve this confusing situation, they introduced an eigenvalue analysis which checks for the possibility of $S(\beta)$ having a zero eigenvalue after accounting for round-off errors. They were able to accomplish this by devising a detection procedure which involves the examination of the eigenvalues of the matrix DD', where D is the $r \times N$ matrix

$$D = Y'[I - \mathbf{1}\mathbf{1}'/N] \ . \tag{3.3}$$

In (3.3), I is the identity matrix of order $N \times N$ and $\mathbf{1}$ is the vector of ones of order $N \times 1$. Box et al. (1973) demonstrated that m linearly independent relationships exist among the responses if and only if the matrix DD' has a zero eigenvalue of multiplicity m. The orthonormal eigenvectors of DD' which correspond to a zero eigenvalue of DD' are used to identify linear relationships among the responses. These relationships can then be used to drop m responses (if m linear relationships exist among the responses) so that the remaining $r - m$ responses are not linearly related. It is not always easy to determine which m responses to drop. In many cases, the structure of the problem may well dictate a natural way for dropping responses. Having selected a subset of $r - m$ linearly independent responses, the estimation process can then proceed by applying the Box-Draper criterion to these responses.

Further problems associated with the use of the Box-Draper estimation criterion were considered by McLean et al. (1979). Box et al. (1970) and Stewart and Sorensen (1981) discussed applications of the criterion when some of the observations are missing. More recently, Bates and Watts (1985) proposed a new computing method for the determination of the parameter estimates using this criterion. The method is based on a generalized Gauss-Newton algorithm for the minimization of $|S(\beta)|$. The partial derivatives of the expected responses (with respect to the elements of β), which are required in this algorithm, are generated automatically whenever the response models are determined by dynamic models defined by a system of differential equations. An approximate confidence region on the parameter vector β was also described and developed by Bates and Watts (1985) using a quadratic approximation of $|S(\beta)|$.

This is an important aspect of multiresponse analysis, yet it is probably the least developed. We would be understating by indicating that the development of multiresponse designs has been lagging. Yet, as we reveal in subsequent sections on practical applications, nearly all RSM applications are multiresponse in nature. In a multiresponse situation, the choice of design should be based on a criterion which involves all the responses.

Draper and Hunter (1966, 1967) obtained design criteria for parameter estimation for models of the form described in (3.1). These criteria, however, require knowledge of Σ, the variance-covariance matrix for the r responses. Fedorov (1972) introduced an algorithm for the construction of a D-optimal design for a linear multiresponse model using a procedure whereby design points are chosen sequentially. Fedorov's algorithm also requires knowledge of Σ . Recently, Wijesinha and Khuri (1986) introduced a modification of Fedorov's algorithm which can be used when Σ is not known.

Another criterion for the choice of a multiresponse design for a linear multiresponse model is based on the multivariate lack of fit test developed by Khuri (1985b). The design is chosen so as to increase the power of this test. Details concerning the construction of such a design are given in Wijesinha and Khuri (1987).

A Test for Lack of Fit of a Linear Multiresponse Model

When fitting a multiresponse model, provision should be made to test the adequacy of the model to represent the behavior of the multiresponse system. Since, in general, the responses can be correlated, one should avoid applying the usual single-response lack of fit test to each response model individually. Lack of fit in one response model may influence the fit of the other responses. Therefore, multivariate techniques are required to assess the overall adequacy of the response models under consideration. Khuri (1985b) presented such a test for linear multiresponse models.

Multiresponse Optimization

When several responses are considered simultaneously, the problem of determining "the optimum" is undefined until some multivariate optimization criterion has been chosen. In a multiresponse situation, no unique way exists for ordering values of a multiresponse function. Furthermore, conditions which are optimal for one response may be far from optimal or even physically impractical for the other responses. It is interesting that many (perhaps most) users require multiresponse optimization and the primary medium for doing the analysis is simply overlapping response contour maps. Evidence of this will be revealed in the treatment of subject matter applications in IV.

Graphical methods were used early in the history of RSM development. By superimposing response contours and visually searching for a common region where the responses achieve near optimal values (if such a region exists), a practitioner might be able to somehow arrive at a location (or locations) of a "compromised" optimum. Lind et al. (1960) used this procedure to obtain operating conditions for maximizing the yield and minimizing the cost of a certain antibiotic. Obviously, this procedure is difficult, if not impossible, to apply when the number of design variables exceeds three. Myers and Carter (1973) introduced an algorithm for determining conditions on the design variables which maximize a "primary response" function subject to the condition that a "secondary response" function not exceeds a certain value. The development of this algorithm is somewhat similar to that of ridge analysis used with a single-response model. Biles (1975) extended this concept of constrained optimization by placing bounds on the values of several "secondary response" functions. Biles' procedure employs a modification of the method of steepest ascent.

A different optimization approach based on the concept of utility or desirability was followed by Harrington (1965) and Derringer and Suich (1980). In this approach, each response function undergoes a certain transformation into a desirability function, φ, such that $0 \leq \varphi \leq 1$. The choice of the transformation depends on a subjective judgment concerning the importance (or desirability) of the corresponding response values. A measure of the overall desirability of the responses is obtained by combining the individual desirability functions using the geometric mean $(\varphi_1 \times \varphi_2 \times \cdots \times \varphi_r)^{1/r}$, where φ_i is the desirability function for the ith response. The simultaneous

optimization of the r response functions is then achieved by maximizing the overall desirability function over the experimental region.

More recently, Khuri and Conlon (1981) introduced a procedure for the simultaneous optimization of responses that are represented by linear models of the form

$$E(\underline{y}_i) = \tilde{X}\underline{\beta}_i \quad , \quad i = 1, 2, \ldots, r,$$

where $\tilde{X}$ is an $N \times p$ matrix of full-column rank and $\underline{\beta}_i$ is a vector of p unknown parameters ($i = 1, 2, \ldots, r$). The rows of $Y = [\underline{y}_1 : \underline{y}_2 : \ldots : \underline{y}_r]$ are statistically independent with each having a zero mean and a variance-covariance matrix Σ. A distance function is chosen which measures the overall closeness of the response functions to achieving their respective optimal values at the same set of operating conditions. This is referred to as an "ideal optimum". Optimum operating conditions are then derived by maximizing this distance function over the experimental region. The distance function approach permits the user to take into consideration the variance-covariance structure for the r responses.

3.2 Sampling Properties of Optima

In the typical analysis of a second degree response surface one is interested in

i) The location of the stationary point

ii) The response at the stationary point

iii) The characterization of the stationary point, i.e. as a point of maximum or minimum response or a saddle point

iv) The contours of constant response

By writing the *true* response equation as

$$\eta = \beta_0 + \underline{x}'\underline{\beta} + \underline{x}'B\underline{x} \qquad (3.4)$$

where $\underline{x} = (x_1, x_2, \ldots, x_k)'$, $\underline{\beta} = (\beta_1, \beta_2, \ldots, \beta_k)'$ and

$$B = \begin{bmatrix} \beta_{11} & \frac{\beta_{12}}{2} & \cdots & \frac{\beta_{1k}}{2} \\ & \beta_{22} & \cdots & \frac{\beta_{2k}}{2} \\ \text{sym.} & & & \beta_{kk} \end{bmatrix}$$

the location of the stationary point can be shown to be

$$x_0 = -B^{-1}\frac{\beta}{2}$$

The response at the stationary point is given by

$$\eta_0 = \beta_0 - \frac{1}{4}\beta' B^{-1}\beta \tag{3.5}$$

The nature of the stationary point can be ascertained by considering the matrix B. If B is a positive (negative) definite matrix then the stationary point is a point of minimum (maximum) response. If B is an indefinite matrix the stationary point is a saddle point. From this it follows that the eigenvalues of B are important to the proper description of the stationary point.

The contours of constant response are obtained by finding all values of x for which (3.4) takes on specified values. These contours are useful in graphically representing a response surface since they permit the presentation of a k dimensional surface in $k - 1$ dimensions.

Since the model parameters are unknown, they must be estimated. Point estimates of the location of the stationary point, the response there, the eigenvalues of B, and contours of constant response can be obtained by replacing the model parameters by their respective point estimates obtained, for example, by the methods of least squares or maximum likelihood. Far too many users of RSM allow conclusions to be drawn concerning the nature of a response surface and the location of optimum response without taking into account the distributional properties of the *estimated* attributes of the underlying response surface. While the distribution of these quantities has not been considered directly, efforts have been made to develop interval estimates for them.

Box and Hunter (1954) consider the development of the $100(1-\alpha)\%$ confidence region for the location of the stationary point. Letting $\underline{\xi}$ denote the coordinates of the true stationary point and assuming the adequacy of (3.4) it follows that

$$\frac{\partial \eta}{\partial \underline{x}}\Big|_{\underline{\xi}} = \underline{0} \tag{3.6}$$

If $\underline{\delta}$ represents the estimator of the left-hand side of (3.6) formed by replacing the parameters in (3.5) with normally distributed, unbiased estimates, it follows that

$$\underline{\delta}'(\sigma^2 V)^{-1}\underline{\delta} \sim \chi^2_k$$

where the elements of V are functions of the elements of $(X'X)^{-1}$ and X is associated with (3.4) when expressed in general linear model notation. After accounting for the estimate of σ^2 it can be shown that

$$\frac{\underline{\delta}' V^{-1}\underline{\delta}}{(N-p)s^2} \leq F_{\alpha, k, N-p}$$

constitute a $100(1-\alpha)\%$ confidence region for the location of the stationary point. Here s^2 is the usual error mean square. It should be noted that this technique is applicable to any surface represented by a linear model and not just for the quadratic model considered.

The construction of a confidence interval about the response at the stationary point of the true surface has only recently been a subject of interest in the statistical literature. Khuri and Conlon (1981) give an expression for the bounds of such an interval conditional on the estimated location of the stationary point. For the general linear model

$$\underline{y} = X\underline{\beta} + \underline{\varepsilon}\ ,\ \underline{\varepsilon} \sim N(\underline{0}, \sigma^2 I)$$

Spjøtvoll (1972) and Rao (1973) indicate that for any particular continuous function $g(\underline{\beta})$

$$\Pr(\min_{\underline{\beta} \in C} g(\underline{\beta}) \leq g(\underline{\beta}) \leq \max_{\underline{\beta} \in C} g(\underline{\beta})) \geq 1-\alpha$$

where $C = \{\underline{\beta}: (\hat{\underline{\beta}} - \underline{\beta})'X'X(\hat{\underline{\beta}} - \underline{\beta})/ps^2 \leq F_{\alpha,p,N-p}\}$ is the $100(1-\alpha)\%$ confidence region for $\underline{\beta}$, $\hat{\underline{\beta}} = (X'X)^{-1}X'\underline{y}$ is the least squares estimator of $\underline{\beta}$, and s^2 is as defined previously. Thus $\left[\min_{\underline{\beta} \in C} g(\underline{\beta}), \max_{\underline{\beta} \in C} g(\underline{\beta})\right]$ is a confidence interval for $g(\underline{\beta})$ with a confidence coefficient of at least $(1-\alpha)$. Carter et al. (1984) make use of this result to obtain a conservative confidence interval on the response at the stationary point in RSM. They also discuss the computational aspects of methodology.

The user of RSM techniques gains considerable insight into the nature of the stationary point and the nature of the response system from estimates of the eigenvalues of B. As a result, some indication of the quality of estimation of the eigenvalues of B should become an essential part of a RSM analysis. Since the eigenvalues of the B matrix can be expressed as particular functions of the model parameters, the approach described above can be used to obtain a conservative $100(1-\alpha)\%$ confidence interval about each eigenvalue of B. Carter et al. (1986) illustrate this methodology for constructing such intervals for the eigenvalues of B. In addition, they consider the implications of having such an interval contain zero on the sampling properties of the estimated response at the stationary point. They conclude in this case that a change in the strategy of analysis is required and they suggest and illustrate one such change.

It is sometimes the case that the stationary point is outside the region of interest or that the stationary point is unsatisfactory due to associated secondary responses. When either is the case, constraints must be placed on the optimization. The estimation of the location of the stationary point subject to constraints is considered elsewhere in this review. Stablein et al. (1983) extend the methodology developed by Box and Hunter (1954) to obtain a confidence region about the location of the stationary point in the presence of constraints. In their , · Carter et al. (1986) discuss the construction of a conservative confidence interval about the response at a constrained stationary point. It is shown that when there is evidence that there is a ridge condition as opposed to a true optimum point, i.e., the confidence interval about the largest or smallest eigenvalue of B contains zero, the sampling properties of the response at an unconstrained optimum may be undesirable. In such cases, it is shown that use of a region constraint as in a ridge analysis will provide a tighter confidence interval about the response at the stationary point.

3.3 Use of Alternate Models

There are many typical RSM situations in which the user can make use of known information concerning the distribution of the observed response. Examples of such response variates are survival time, proportion of experimental units assigned to a given treatment group responding in a predetermined way, and the number of events occurring per treatment group, i.e. count data. To the extent that a continuous symmetric distribution can be made to adequately approximate the distribution of such data, the classical application of RSM has provided satisfactory results. Once a proper distributional form has been determined the usual approach is to express the mean of the distribution as a function of the experimental conditions. Most often a second order polynomial is used. However, in their review article Mead and Pike (1975) give an excellent discussion regarding the choice of the response function to graduate the relationship between the dependent and independent variables. They provide the algebraic form of a number of different response functions that have been used and discuss the usefulness of each. The choice of the form of the underlying response function is based on the assumed shape of the underlying relationship. While an important topic, it is limited only by the ability of the investigator to formulate the mathematical relationship with the desired properties. The distributional form of the underlying data has an impact on the estimation of the model parameters and on the inferences drawn from a RSM analysis. Thus, for the remainder of this section some developments in the choice of a distributional form will be reviewed.

Addelman et al. (1966) devised an experimental scheme for estimating the optimal combination of two drugs in preclinical cancer research. The procedure is such that at most three experiments must be performed. The first experiment uses three doses from within the effective range of each of the individual drugs and nine combinations arrived at by considering three different ratios between the levels of the two drugs. The data from this experiment are analyzed by fitting the quadratic function

$$y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{12} X_1 X_2$$

where

y = survival time of the experimental subject

$X_i = \log\left[\frac{X_{iL}}{100} + \text{dose level of compound } i\right], \quad i = 1, 2$

X_{iL} = lower extreme of effective range of compound i

After the model parameters have been estimated by the method of least squares, the underlying response surface is explored and the optimal combination is estimated. From this a second, and sometimes third, experiment is performed and depending upon the realization of given conditions data from the initial experiments are included in the final analysis. Unfortunately, the authors illustrated their work with hypothetical data. Consequently, it was not possible to determine the applicability of it.

Due to the nature of survival data, the assumptions required for the appropriate use of the method of least squares may not be satisfied. Cox (1972) proposed the proportional hazards model as a means of relating survival time to a set of independent variables. Instead of working directly with survival times this model relates the hazard, or instantaneous risk of failure, $\lambda(t)$, at time t to the concomitant variables $\underline{x}$ as

$$\lambda(t) = \lambda_0(t)\exp(\underline{x}'\underline{\beta}) \tag{3.7}$$

where $\lambda_0(t)$ is the hazard function, the form of which does not need to be specified, of the appropriately scaled reference group and $\underline{\beta}$ is the vector of unknown regression coefficients which can be estimated by the method of maximum partial likelihood. This model has been used by Carter et al. (1979) in preclinical cancer therapy to relate the risk of failure to dosage levels of cytotoxic agents given in combination. Since it is reasonable to assume that the risk of failure decreases with increasing treatment levels until a minimum is reached and then increases due to toxicity with increasing treatment levels beyond the minimum point, a complete second order polynomial was used to approximate $\underline{x}'\underline{\beta}$ in equation (3.7) for the obvious RSM application. An exploration of the fitted surface followed.

When it is desired to relate the number of events that have occurred to a set of concomitant variables, a Poisson regression analysis is often appropriate. However, in many experimental situations counting variables exhibit extra-Poisson variability in the sense that there is more variability

in the data set than can be explained by the Poisson distribution. A generalization of the Poisson is the negative binomial distribution. The particular form of the negative binomial was discussed by Collings and Margolin (1985). Rao's efficient score principle (1973) can be applied to test the adequacy of the Poisson model. Solana et al. (in press) make use of these results to model the mean number of sister chromatid exchanges induced per cell as a polynomial function of the concentrations of ethylnitrosourea and cis-diaminedichloroplatinum. The function used was a complete quadratic with three additional higher order interaction terms. Such an analysis yielded a more complete description of the interaction occurring between these two compounds than had been obtained previously.

In some applications binary (e.g. response/no response) responses are encountered. In such situations it is often desired to relate the proportion, p, of responses to a set of concomitant variables. Assuming a constant probability of response within treatment groups, this has been accomplished through use of the logit transformation of the binomial parameter, i.e.,

$$\ln \frac{p}{1-p} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k$$

The estimation of the model parameters and other aspects of the analysis of such data are given by Cox (1977).

Such an approach has been used to relate the probability of a favorable treatment outcome to the dosage levels of two anticancer drugs given in combination (Carter et al. 1977). The use of a complete second order model was justified. The fit of the model was shown to be adequate and the fitted dose response surface was explored and the estimated optimal treatment was obtained.

It sometimes is the case that there is more variability in the data than can be explained by the binomial distribution. In such situations, the beta-binomial distribution, a generalization of the binomial, has been useful.

The form of the beta binomial distribution was discussed by Segreti and Munson (1981). As in the use of the negative binomial distribution to account for extra-Poisson variability Rao's efficient score principle (1973) can be applied to test the adequacy of a binomial model. Chinchilli

and Chinnici (1986) have used this approach to model the proportion of *Drosophila melanogaster* eggs that hatch as a function of exposure to caffeine and aflatoxin B1 given in combination. They used a full second order polynomial to approximate the dose-response relationship and found extra-binomial variability in their data.

IV. SUBJECT MATTER APPLICATIONS

In the two previous RSM reviews, much attention was given to subject matter applications. In the Hill and Hunter review, chemical and processing applications were illustrated, with real life examples demonstrating canonical analysis and use of multiple responses. An example where a canonical analysis provided some insight ("elucidation") into the mechanism in question was also given. The Mead-Pike review produced examples in the biological area. From our search, it is clear that standard use of RSM has accelerated. In this section we separate applications that were reported in subject matter journals from applications that are finding use in industry. As expected, many imaginative applications were found in the chemical and processing areas. But we were somewhat surprised to find that uses have spread rather dramatically into other areas. We choose to highlight a number of applications here. In this survey of the subject matter literature, several interesting facts become apparent:

i) The central composite is used more than any other family of RSM designs.

ii) While the methods of exploring the response surface have become somewhat more sophisticated, users nevertheless are not close to making maximal use of the enormous wealth of analytic tools that are available. This is due, in large part, to the "lag time" that naturally exists between the time at which a publication appears in the statistics literature and the point at which it is adopted by subject matter users. However, as in the case of many areas of statistics, our communication with the user remains woefully inadequate. Perhaps the quickest medium of communication is through effective computer software. But in the area of RSM, there has been little planning and leadership in this area of development, though there have been some recent rays of hope.

iii) Nearly all practical RSM problems are truly *multiple* response in nature. Many users handle multiple responses with some creativity but little sophistication.

In what follows, examples of subject matter applications are given in areas of science and engineering, biology and biomedicine, and applications in management science, operations research, and food science.

4.1 Applications in Physical and Engineering Sciences

In the late 70's scientists dealing in the important area of gas chromotography began using RSM methods. Scott (1970), Swingle and Rogers (1972), Kambara et al. (1968), and Turina et al. (1974) use variations of RSM to determine optimum conditions for gas chromotography. Morgan and Jacques (1978) study relationships between flow rate, temperature, stationary phase loading, and the responses, level of separation and analysis time. They indicate how helpful an understanding of the system comes from elucidating the nature of the response surface. Cross sectional plots in this, a natural three variable system, were used to estimate the conditions where desirable separation and analysis time were achieved. A modified simplex algorithm was used to demonstrate the minimization of analysis time *at fixed* threshold values of peak separation.

Person (1978) used RSM notions to analyze containment leakage from a sodium fire. "Sensitivity studies" were conducted in which a study was made of the influence of sodium mass, containment volume, radiation heat transfer coefficient, and sodium oxide fraction on fraction leakage. Prato and Morris (1984) studied the effect of detergent concentration, agitation time, and washing time on the amount of soil removed from fabric. In order to underscore the natural application of RSM and second order composite designs in human factors engineering type experiments, Simon (1970) illustrates with a study involving three display panel-type variables and their effect on target recognition for airline pilots.

Olivi (1980) discusses the need for use of RSM in exploring and identifying certain features of systems. He uses as a "typical" application a study involving five design variables with an

orthogonal central composite design. The application involves factors that influence ballooning time, an important variable in nuclear safety.

Bodden and Edwards (1982) use a Box-Behnken design in an RSM study in the investigation of the mechanism involved in the assay of cretinine. Claycomb and Sullivan (1976) use a three factor central composite design and a ridge analysis of the data to illustrate the methodology for selecting a cutting tool for maximization of profit.

Contour plots of constant response without an analytic method for finding optimum conditions are often the source of conclusions drawn by RSM analysts. Such was the case in the work by Bretaudiere et al. (1980) in a study of the Analine Aminotransferase Kinetic Assay. Fujiwara et al. (1975) study the atomization mechanism in air-acetylene flames using response contours. Burtis et al. (1981) used data from a central composite design to produce useful contours of constant response and a canonical analysis that allowed for optimization of a kinetic method that applies to the enzymatic measurement of ethanol. Response contours are also the subject of information obtained from a response surface analysis in which interest centers on formulation and optimization of vitreous bonds in a paper by Chait and Fotlz (1981). The field of nuclear engineering has not been without studies involving RSM, particularly where simulation is involved. Heller et al. (1977) use data from a central composite design to study the mechanism involved in thermal-hydraulic margin analysis. Vaurio and Mueller (1978) use response surfaces generated from reactor simulations to obtain probability distributions of selected consequences of a liquid-metal fast breeder reactor core accident.

4.2 Applications in Food Science

The food industry has been a prime user of RSM since the early 1970's. This is reflected in study of content of journal articles and industrial usage as well. We cannot begin to cite all of the work in this area. Johnson and Zabik (1981) use a mixture design to build a response surface to study interactions among proteins in angel food cake. Lah et al. (1980) use a 2^{7-3} factorial with an impressive application of steepest ascent to optim... whipping properties of an ultrafiltered soy product. R.G. Henika began using RSM at Foremost Foods in the early 1970's. His leadership

resulted in usage by others even though many of the applications in this field involve rather precarious or tricky panel data from sensory evaluations. The papers by Henika and Palmer (1976) and Henika (1982) are certainly important contributions. In the latter, particular attention is paid to applications with sensory data.

Second order models were used to find the nature of the system relating gelling properties of a *meat loaf* analog to pH, salt content, cooking time, soil isolate, and egg white level. While formal optimization procedures were not used, the response surface allowed Jao et al. (1982) to better understand the mechanism. Desirable gelling properties can be obtained with reduced egg white usage with proper manipulation of salt content and cooking time.

The extrusion of starch has important applications in food and industrial applications. El-Dash et al. (1983) used response surface methods to find ideal operating conditions in this area of technology. They discovered that, depending on the application, one can control levels of extrusion temperature, screw speed, and moisture content to produce the proper level of gelatination.

Daley et al. (1978) used RSM to determine the optimal combination of soy, sodium tripolyphosphate, and water to produce the most acceptable sausage-type product from minced mullet. A central composite design was used to study the effects of calcium chloride and cysteine on heat induced whey protein gelatin by Schmidt et al. (1979). After the parameters of a second order polynomial were estimated, plots of the fitted surface were generated. Sefa-Dedeh and Stanley (1979) made use of a central composite design to fit the percent of nitrogen extracted from a type of meal as a complete quadratic in time of extraction, temperature of extraction and meal to solvent ratio. The fitted polynomial was explored to estimate the levels of the independent variables associated with optimal extraction of protein nitrogen. Mixture response surface methodology was used by Huor et al. (1980) in conjunction with laboratory sensory evaluation and small scale consumer tests to optimize the proportions of watermelon, pineapple, and orange juice in a fruit punch. Min and Thomas (1980) utilized RSM analytic techniques to determine the relationship between ingredients and physical characteristics of dairy whipped topping and optimize the ingredient concentration by the simultaneous analysis of fat, corn syrup solids, and stabilizer to produce a dairy whipped topping which could be frozen for storage and distribution without adverse affects. Lee

and Hosency (1982) used response surface methodology to optimize the formulation of single-stage cake mixes for white layer cakes. RSM techniques were used by Tseo et al. (1983) to determine the optimum combination of levels of washing temperature, washing ratio of water volume to sample weight and washing time on the quality of minced mullet flesh. Tong et al. (1984) used a central composite design to study the effects of safflower oil concentration, emulsifier concentration and freezing temperature on maximum overrun and fat destabilization of ice cream. McLellan et al. (1984) used a rotatable experimental design to generate data for a sensory analysis of carbonated apple juice as a function of levels of carbonation and soluble solids. The fitted surface for acceptability was described as having a ridge of high acceptability running through the range of typical soluble solids and carbonation levels.

4.3 Applications in Social Sciences

Much use has been made of RSM in certain areas in social sciences. Economics, operations research, and system simulation are but a few fields that have benefitted. Shechter and Heady (1970) use response surface techniques to design and analyze experiments from a simulation model dealing with the feed grain program. Four responses, net farm revenue, net farm revenue participants, stock accumulation, and government costs were considered. Multiple response analysis is discussed. In this case, the analysis allows for an optimum decision rule regarding trade-offs between increasing farm income and reducing government costs. Montgomery and Bettencourt (1977) produced an excellent account in which the advantages of RSM methods in simulation studies were reviewed. Heavy emphasis is put on use in multiple response studies. An interesting illustration was given in which a simulation of a military tank duel is analyzed to ascertain the values of two design variables (mean time to fire first round and mean time between rounds) that give desirable values of four responses. They use a nonlinear programming technique to analyze data taken from a rotatable central composite design.

Montgomery and Evans (1975) discuss the use of various classes of second order response surface designs in simulation work. Two variable equiradial designs, uniform precision rotatable ccd's and other designs are discussed. An illustration is given in which a simulation of a six inter-

section street network system was used. Data was taken using a rotatable c.c.d. with two design variables. Canonical analysis revealed a maximum at the stationary point. The results produced optimum conditions on the selection of traffic signal settings. Hunter and Naylor (1970) point out that a simulation system is, indeed, the source of an *experiment* similar to a biological or chemical system and thus experimental design and RSM methods do apply. Factorial and fractional factorial arrays are discussed in the context of an inventory problem.

Smith (1975) made an empirical study of various optimum seeking procedures that are frequently used in computer simulation situations. The methods studied were random search, one factor at a time movement, RSM *Version I* and RSM *Version II*. Version I involves use of two-level first order designs and the method of steepest ascent, while Version II involved steepest ascent with the use of the simplex design. In addition, acceleration versions of steepest ascent were studied. RSM Version I appeared to give best results. Any attempt to accelerate the steepest ascent procedure was fruitless. Biles (1981) describes a two phase procedure in which a complex search procedure is employed followed by a second order analysis of the resulting data. An illustration of the method is given from an inventory system.

4.4 Applications in the Biological Sciences

The techniques that comprise a response surface analysis are being used more and more often in the biological sciences. This is evidenced by the large number of citations in the bibliography of this report. In this section some of the more novel applications will be highlighted.

RSM techniques have been found useful in the study of the relationship between the chemical structure of a compound and its biological activity. Mager (1982a, 1983) studied the structure-neurotoxicity relationship of organophosphorous pesticides in this manner and used a canonical analysis of the fitted equation to elucidate properties of the response surface. Mager (1982b) also studied the activity of rifamycin derivatives against a rifamycin-MS-resistant mutant of Staphylococcus aureus.

Several references in the microbiologic literature, Maddox and Richert (1977), Cinto et al. (1977) and Farrand et al. (1983), indicate the useful application of RSM techniques, including the

use of rotatable central composite designs, to optimize microbiological media for the growth of various microorganisms. Cheynier et al. (1983) were able to demonstrate that a yeast isolated from the digestive tube of the larva of a parasite of eucalyptus trees was capable of bioconverting citronellal to citronellol. RSM procedures were used to achieve the optimization of the experimental conditions for that bioconversion process.

Various industrial pollution studies have employed response surface methodology. Huck et al. (1977) determined the polymer properties and mixing conditions required to produce optimal flocculation for mine waters of specified strengths containing iron, zinc, and copper either singly or in combination. Wallis (1978) reports on the use of RSM in studies related directly to power station cooling systems.

Dincer and Ozdurmus (1977) used the method of steepest descent to determine the most suitable combination of four independent formulation and process variables for the disintegration time of coated tablets in simulated intestinal fluid. Shek et al. (1980) evaluated the potential of the Nelder-Mead simplex search procedure for optimizing a capsule formulation. At the completion of the search, these investigators fitted a polynomial model to the data and plotted the estimated response surface. In a similar study Chowhan et al. (1982) studied the effects of moisture and crushing strength on tablet friability and *in vitro* dissolution. They used a complete second order model in the independent variables to graduate the response surface. The fitted model was explored by plotting contours of constant response and estimating the location of the stationary point. Fast et al. (1983) used a central composite design with five independent variables in an assay for creatine kinase. A simplex maximization algorithm was used to determine areas of maximum sensitivity. Belloto et al. (1985) used RSM to study the solubility of pharmaceutical formulations. They also discussed the optimization of one response in the presence of constraints due to the consideration of other response variables.

There are numerous reports in the clinical chemistry literature on the use of response surface methods. Rautela et al. (1979) describe the theory and application of the response surface approach to simultaneous optimization of multiple interdependent variables. They point out that such an approach permits the determination of accurate optima which is required for the formulation of

analytically reliable clinical methods. Thompson et al. (1981) report on the use of simultaneous RSM optimization techniques to optimize an assay for alkaline phosphatase. London et al. (1982) use RSM to optimize the assay of gamma-glutamyltransferase. The authors note that while such techniques do not yield a mechanistic understanding of an enzyme assay they do produce an operational understanding of how an assay functions. In a similar paper, Coleman et al. (1983) use RSM to optimize assays for antithrombin III and plasminogen.

Roush et al. (1979) discuss the usefulness of a RSM approach in poultry nutrition research. Body weight and feed conversion response for Japanese quail were optimized as functions of protein and energy levels. Heady et al. (1980) express egg production as a quadratic function of the amounts of corn and soybean meal with time as an independent variable. Contours of constant response were generated to help determine the least cost feed mix. Roush (1983) utilizes a central composite experimental design with male broilers to examine quantitatively the protein levels in starter and finisher rations and the time of ration change to optimize body weight, carcass weight, feed conversion, and net profit. The optimization was done for each response variate independently of the other responses.

Response surface methods have been used to elucidate the actions and interactions of cytotoxic drugs in combination and to estimate the optimal levels of each drug for the treatment of cancer with and without side effect constraints. Carter et al. (1983) discuss the use of logistic and proportional hazards regression models to this end. These authors give software for the estimation of the stationary point and confidence regions about its location obtained from the use of these models. The history of the use of RSM in cancer research has been reviewed by Carter and Wampler (1986). While the examples used involve data from animal studies there is interest in applying these techniques to clinical studies. The biggest change required to accomplish this will be in the design of the studies. The classical clinical trial in cancer research results in a number of patients being randomized to two or more treatment groups and followed until an event occurs. The number of patients assigned is determined so that there is a reasonable chance of detecting a difference of a predetermined size among the treatment groups. While such an approach provides considerable information about a few treatment groups, it does not offer much about the underlying

dose response relationship. Box (1958) in a discussion of a paper by Mantel (1958) was early to suggest the usefulness of RSM in this area. Currently the Mid Atlantic Oncology Program is running a clinical trial in the study of breast cancer that is designed as a factorial experiment and will be analyzed using response surface techniques.

4.5 Industrial Use of RSM

The 1980's brought a new urgency in industry in the U.S., an urgency that underscores the need for *quality*. There is a new motivation in American industry brought about by the success enjoyed in Japan in the use of Quality Control and efficient statistical methods. The areas of experimental design and, specifically, response surface methods are receiving considerably more attention than ever before. This *new* and *renewed* interest are "fallout" from this search for quality and precision.

In our communication with industrial statisticians and research workers, we found use of RSM among a wide variety of types of industrial companies. In most cases they sought and, of course, were promised anonymity. As expected, we found response surface analysis and design in the chemical industry, and we were able to uncover a growing number of applications in the areas of foods, tobaccos, military research, pharmaceuticals, petroleum, electronics, and many other fields. Our search did reveal some interesting but not unexpected information:

i) Aside from the central composite and Box-Behnken designs, fractions of 2-level factorials and Plackett-Burman designs are used to a large extent, with the simplex design used in conjunction with the Nelder-Mead Simplex Search Algorithm. There is also a growing usage of computer generated RSM designs.

ii) In regard to RSM analysis, some analysts carry the computations through to an optimization phase, while others do not. Ridge analysis is used for finding candidates for optimum operating conditions though usage is not as extensive as one might expect. Some users merely use graphical methods with overlaid contour plots.

There is no universal software tool for doing RSM analysis. In particular, some users use IMSL (International Mathematical and Statistical Libraries) subroutines, while some resort to in-house software versions for finding optimum conditions. Some users in industry appear frustrated by the lack of software for finding optimum conditions and resort to two dimensional contours for analysis.

In what follows, a sample of RSM scenarios is given that apply to actual RSM users in industry. We have attempted here to give samples across many fields of application.

A tobacco company uses RSM as a primary tool for elucidation of fundamental relationships and searching for optimum conditions in the case of nearly every new product considered in a research effort. They use no software for design construction but use in-house software developed from numerical analysis algorithms for analysis. The latter allows for optimization under various types of constraints on the design variables. The designs used vary considerably. For problems where cost is important, Plackett-Burman screening designs are used and hybrid and small composite designs are used in the second order case. Central composite and Box-Behnken designs are used extensively. Problems are almost always multiple response in nature, though the responses are too many in number to often do formal multiple response optimization. Some of the responses are discrete "scores" from sensory analysis but many responses are naturally continuous in nature.

A large oil company uses RSM to a moderate extent. Applications vary from polymer optimization to the exploration of a detergent system. In some applications the design variables are of the *mixture* type. Mixture variables and process variables often occur in the same setting. The computer program, ACED (see Welch 1985), is often used to generate the design in the mixture situation. Basic 2-level factorials and central composite designs are also used. In some cases, determination of optimum conditions is important. The algorithms in GRG2 (see Cornell 1981) and XSTAT (1984) are generally used to find optimum conditions. This company also envisions considering RSM in the future for plant scale problems dealing in perhaps more than 1000 variables, i.e., allow the technique to play a role in control theory.

A chemical company finds that RSM design and analysis can be used to solve two types of problems. The first is a region seeking procedure in which one is seeking the general vicinity of

"best" operating conditions. The method of EVOP described by Box (1957) is used with slight modification. Steepest ascent has been used at times with little success. Some success has been experienced with the Spendley et al. (1962) simplex algorithm. A computer program has been developed which makes use of various types of designs, allows input of experimental results, and calculation of the next experimental run. It has been found that the most difficult aspect of this procedure is obtaining from the experimenter a commitment on combining response values from the multiple dependent variables so that the simplex will move. In the second problem encountered by the chemical company, they are near the optimum and wish to locate or confirm its exact location. Central composite designs are used almost exclusively. Small composite designs are often used with no concern for either orthogonality or rotatability. An in-house program is used to construct central composite designs for researchers. The model fitting aspect of the analysis is done by the all possible subset procedure in BMDP. Optimization is "accomplished" with two dimensional contour plots.

A large food company uses RSM in several cases. It is used in product development in developing new products and in cost reducing old products. The responses are either continuous variables or consumer acceptability ratings. RSM is also used in process control and in the evaluation of new equipment. Generally, for first order models, 2-level factorial or Plackett-Burman designs are used. In the case of second order models, Box-Behnken designs and central composite designs are used. At times, the c.c.d. is resisted by the experimenter because five levels become inconvenient because it is difficult to adjust equipment accordingly. Errors in controlling factor levels occur quite often.

Another large and well diversified chemical company makes use of RSM on a research level. This company has a large group of professional statisticians and an in-depth program to teach basic experimental design to engineers and scientists. They make use of an in-house computer program that assists non-statisticians in designing and analyzing experiments. The program involves contour plots and optimization routines. There is great potential for use of RSM in this company, and most problems are multiresponse in nature. Mixture problems are the rule, and an algorithm has been programmed in-house to generate mixture designs described in Thompson and Myers (1968).

Extreme vertices designs are used as well. In addition, considerable use is made of the ACED (Welch, 1985) algorithm for design construction.

A large research and development organization makes use of RSM in several topical areas, including chemical and fermentation optimization and development of consumer food products. In addition, it is also used for optimization of settings associated with processes in the refining and hydrogenation of vegetable oils. In almost all cases, "optimization" requires arriving at the most agreeable compromise among various conflicting responses. In the case of two design variables, the choice of best conditions is found by use of graphical overlay contour plots. For more than two variables, a utility function is constructed and a Nelder-Mead simplex optimization routine is used to identify an acceptable region in the design space. In some instances ridge analysis is used to either find optimum conditions in a single response situation or to find regions for subsequent experimentation. The class of central composite designs is relied upon heavily. Blocking is often required and c.c.d.'s are used which block orthogonally. At times rather involved constraints are induced on the "optimum" conditions. In this case they use "brute force" grid search routines that are supplemented with confirmatory trials.

A consulting firm used the results of an RSM study to develop a generic method for evaluating submarine tracking algorithms. Simulation experiments were conducted under common sets of scenarios and then algorithm performance was evaluated according to the behavior of the response surfaces generated. RSM is also under consideration for several sonar operator studies to determine the effects on performance of various processing schemes. Their analyses are performed using IMSL subroutines.

V. FUTURE DIRECTIONS OF RSM

To comment about future directions of RSM, one must ponder the present status with regard to utilization and importance. It is rather unfortunate that the expanse of knowledge gained over the past 25 years in RSM has not blossomed into a full-scale deployment of the techniques developed in this area. As we indicated earlier, RSM is being used in industry more and more, but the use does not reflect recent advances as much as one might wish. This is true more in analysis than

design. The "fallout" of the recent, almost passionate, "push" for quality and experimental design in industry is bringing RSM to the attention of many potential users. However, usage lags far behind its potential. Several factors may have contributed to this, the most prominent of which we believe are explained in the following paragraphs.

There is a severe lack of communication between academic statisticians in this country and those in industry. There are some attempts at communication and few successes. This is true in many areas, not merely RSM. One testament to this is the fact that Japanese statisticians give lectures and short courses to industrial companies in this country on effective use of experimental designs that are based, in large part, on basic concepts developed in the U.S. years ago. There is no question that the historical underpinnings of RSM were produced *with particular applications in mind* When we move away from research that does not have particular problem solving as motivation, we lose our line of communication. Statisticians in academia bear much but not the entire burden. They have little access to what is actually going on in industry as far as the deployment (or lack of it) of RSM is concerned. This can be partly attributed to the fact that "sometimes, those in industry are dissuaded from publishing for fear of revealing proprietary information", as Gerald Hahn (1984) explains. As a result, some of the research that has been undertaken in RSM was not geared to solving a particular practical problem. Even a search of the literature, statistical or otherwise, in an effort to find a real data set to use in an example, can sometimes be unwieldy.

There is a severe software problem. It is unfortunate but true that data analysts are attracted to statistical techniques for which software has been written. There are many historical illustrations of this in our field. Good efficient, well documented software is a swift and sure form of communication. As we indicated in a previous section, there is no commercial up-to-date RSM package for doing analysis. Of course, there are many new available packages for constructing experimental designs, and RSM designs are the subjects of some of these packages. But as it was expressed in the Steinberg and Hunter experimental design review, the "expert system" for design generation is not near, particularly in RSM situations.

There is apathy on the part of some practitioners who either believe that RSM is of little use to them, or simply ignore new developments in favor of antiquated, and often ad hoc, methods. There is also insufficient training in RSM. In academia, very few statistics departments offer a course in RSM. In industry, little exposure, if any, to RSM is provided in the form of short courses.

The review paper by Steinberg and Hunter (1984) along with the several discussion papers that followed it have expressed concern about the above-mentioned communication problems and offered several remedies. We believe that greater emphasis should be placed on the teaching of RSM. A better cooperation and more formal lines of communication between academia and industry is needed. Statisticians, scientists, and engineers can learn and benefit from one another. This fact is certainly not specific to RSM but applies more broadly in our profession. Far too many academicians conduct and are rewarded (i.e., tenure and promotion) for research in which mathematical elegance is far more prominent than application to real problems. More academic researchers need to let their work be motivated by real problems, much like the case of Box in the early 50's and Scheffé with the development of mixture designs in the mid 50's. New developments in RSM should be made accessible to practitioners and research workers with the proper software. In return, engineers and applied statisticians working in industry should make a genuine effort to share their experience with those in academia.

There is no doubt that many scientists and engineers can benefit from tools of RSM but do not know that they exist. We do not presume that this is a problem solely with RSM. Our earlier comments may very well be relevant in regard to all areas of applied statistics. However, the enormity of the problem becomes evident when one "reaches out" and essentially contacts and interviews many scientists in industry as we have done. In what follows, we indicate what, in our opinion, are proper directions for future research. But let us emphasize that users are sufficiently "far behind" in use of RSM tools that the need for proper communication is far more pressing.

Future Research Directions

Multiple responses, sequential designs and analyses, and designs for the less orthodox RSM applications are many areas where one may benefit from immediate research. Both design and analysis involving multiple responses have received precious little attention in spite of the acute need for it. Biologists as well as engineers are finding applications of RSM in which the model is nonlinear, e.g., logistic and other standard growth models. A fruitful area of research deals in the study of designs or certain specific nonlinear functional forms.

Much has been written, of course, about computer generated design. The comments on the Steinberg-Hunter review reflect the general opinion that computer generated designs present a very promising area for the future. This is certainly true in regard to the field of RSM designs. The "danger" that is projected by concerned academicians is even more acute in the RSM area. Many (though not all) methods of generating experimental designs employ special criteria that do not address robustness notions such as model misspecification, anticipation of outliers, errors in control, extrapolation, etc. Model misspecification is the most crucial of these since one often presumes from the outset that the model is empirical and is, indeed, an approximation. All of this suggests that preparing for the nonideal and very detailed interactive properties are high priorities in a computer generated RSM design. We would like to underscore the opinion that construction of the "expert system" in computer driven design must be a product of considerable deliberation and patience.

There appears to be some need for the development of nonparametric techniques in RSM. Most of our analytic procedures depend on a model. The use of model-free techniques would avoid the assumption of model adequacy or low order polynomial approximations and, in particular, the imposed symmetry associated with a second degree polynomial. The use of nonparametric kernel estimation shows some promise.

Analytic methods need to be developed for the case of repeated measures and other situations where correlated observations are encountered. This is a frequent occurrence in biological applications.

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