The Annals of Mathematical Statistics
1968, Vol. 39, No. 5, 1517–1539

DESIGN AND ANALYSIS OF EXPERIMENTS WITH MIXTURES[1]

By J. S. Murty[2] and M. N. Das

Institute of Agricultural Research Statistics, New Delhi

1. Introduction. A new direction to the study of response surfaces is the investigation of multi-component systems as a function of their composition when the fundamental mechanism of the system is constrained. The first attempt in this direction was made by Claringbold [1] in his study on the joint action of hormones. Important contributions have, however, come from Scheffé [7], [8] and Draper and Lawrence [2], [3] in their studies on experiments with mixtures.

1.1. *A resume.* In an experiment with mixtures the property studied, namely the response, depends on the proportions of the components present but not on the amount of the mixture. Under this criterion the fractions of the components making up any mixture must add to unity. Therefore in an n component mixture if $x_i (x_i \geqq 0)$ be the proportion of the ith component $(i = 1, 2, \cdots, n)$ then

$$x_1 + x_2 + \cdots + x_n = 1. \tag{1.1.1}$$

By virtue of the above restriction, the totality of the unrestricted factor space of n dimensions has been reduced to an $(n - 1)$ dimensional simplex. The n components of this system are called 'mixture variables.' If in addition to the mixture variables certain other variables which are not bounded by the restriction (1.1.1) are present in the system, they are called 'process variables' [8].

Examples of experiments with mixtures can be found in various fields. In agriculture, the mixed crop trials may come under this case because the total yield in a unit area depends on the proportions of the different crop-seeds applied at least in cases where the total amount of seed of the different crops together is same per unit area. Again, the fertilizer trials can be studied as mixture experiments under the assumption that the cost of the total amount of fertilizer mixture applied is constant. Then the proportional costs of the different fertilizers in a combination will be mixture variables so that the effects of the fertilizers are studied by relating their costs with response. In animal husbandry, we have the feeding trials to study the response on milk yield. The total amount of feed an animal takes or its cost might be kept constant but the components of feed or feed cost may differ. In industrial and engineering experiments numerous examples can be found in [4] and [7].

Scheffé [7], [8] evolved the simplex-lattice and the simplex-centroid designs to explore the 'factor-response' relationship within the simplex.

A simplex-lattice (n, m) design for n components consists of the $\binom{m+n-1}{m}$ points

Received 26 June 1967; revised 10 April 1968.

[1] This work was first presented at the 17th Annual Conference of the Indian Society of Agricultural Statistics held at Trivandrum in January 1965. It was later included in [5].

[2] Now at Osmania University Hyderabad.

of the simplex representing all possible mixtures in which the proportion of each component has the $m + 1$ equally spaced values $x_i = 0, 1/m, 2/m, \cdots, 1$.

A simplex-centroid design with $2^n - 1$ points involves observations on mixtures consisting of all those subsets (combinations) of the components where the proportion of each component present is equal.

Assuming that the response can be adequately represented by a real valued function, Scheffé [7], [8] associated certain unique polynomial regression functions which have exactly the same number of parameters as the number of design points.

The general polynomial

$$(1.1.2) \quad \eta = \beta_0 + \sum_{1 \leqq i \leqq n} \beta_i x_i + \sum_{1 \leqq i \leqq j \leqq n} \beta_{ij} x_i x_j + \cdots + \sum_{1 \leqq i_1 \leqq i_2 \leqq \cdots \leqq i_m \leqq n} \beta_{i_1 i_2, \cdots, i_m} x_{i_1} x_{i_2} x_{i_3} \cdots x_{i_m},$$

with $\binom{m+n}{m}$ coefficients can be associated to a simplex-lattice (n, m) design by the substitution

$$(1.1.3) \qquad x_n = 1 - \sum_{1 \leqq i \leqq n-1} x_i$$

by virtue of (1.1.1). But since the resulting form with the absence of x_n will not be appealing, alternate substitutions were suggested through which unique canonical forms of the model could be obtained.

For example, using the substitutions

$$(1.1.4) \qquad \beta_0 = \beta_0 \sum_{1 \leqq i \leqq n} x_i, \qquad x_i^2 = x_i - \sum_{1 \leqq j \leqq n, j \neq i} x_i x_j$$

in the polynomial (1.1.2) for $m = 2$, we have the model associated with the simplex-lattice $(n, 2)$ design given by

$$(1.1.5) \qquad \eta = \sum_{1 \leqq i \leqq n} \beta_i x_i + \sum_{1 \leqq i < j \leqq n} \beta_{ij} x_i x_j .$$

The model for the simplex-lattice $(n, 3)$ is obtained [7] as

$$(1.1.6) \quad \eta = \sum_{1 \leqq i \leqq n} \beta_i x_i + \sum_{1 \leqq i < j \leqq n} \beta_{ij} x_i x_j + \sum_{1 \leqq i < j < k \leqq n} \beta_{ijk} x_i x_j x_k + \sum_{1 \leqq i < j \leqq n} \gamma_{ij} x_i x_j (x_i - x_j).$$

For the model for the simplex-lattice $(n, 4)$ see [4].

For the simplex-centroid design the associated model is obtained [8] as

$$(1.1.7) \quad \eta = \sum_{1 \leqq i \leqq n} \beta_i x_i + \sum_{1 \leqq i < j \leqq n} \beta_{ij} x_i x_j + \cdots + \beta_{12 \cdots n} x_1 x_2 \cdots x_n$$

Utilising the fact that the number of parameters in the associated models is exactly the same as the number of points in the designs Scheffé obtained unique solutions for the parameters. For instance, for a simplex-centroid design

$$(1.1.8) \qquad \beta_{s_r} = r \sum (-1)^{r-t} t^{r-1} Y_r(s_r)$$

where s_r denotes any subset $\{i_1 i_2 \cdots i_r\}$ of r elements of $\{1, 2, \cdots, n\}$ and $Y_r(s_r)$ denotes the sum of the responses of all $\binom{r}{t}$ of t-ary mixtures with equal proportions formed from the r components in s_r. These coefficients β's are called synergisms by him.

1.2. *A discussion.* The main considerations connected with the exploration of a response surface are (i) the choice of a proper model that could approximate the response in the region of interest, (ii) the testing of the adequacy of the model in representing the response surface in that region and (iii) a suitable design for collecting observations, for fitting the model and testing the adequacy of fit. Scheffé's approach in this regard is "to consider an intuitively appealing design and ask what form of regression function would be convenient with this." Accordingly, he considered two designs and associated them with polynomials which are unique in that there is a one-to-one correspondence between the parameters and the points of the design such that the design fixes the model. A more or less obvious limitation with these designs is that they do not explore the interior of the simplex but restrict themselves to the outer surface. This is clear from Plackett's remarks in [8]; also see [3]. It can, therefore, be inferred that the designs and hence the models proposed by Scheffé may not explore the region adequately. In fact, Scheffé [7] himself doubts the 'fit' these models are capable of, as brought out by Quenoulle's remarks in [8]. One can, however, see that the unsatisfactory state of affairs in regard to judging the adequacy of the fit is a consequence of the absence of any degrees of freedom for the 'lack of fit' of the model.

Moreover, if a certain number of points from the interior of the simplex, i.e. points in which all the components are present are included in the design then not only the model loses much of its significance connected as it is with the design but the estimation is no longer simple and one has to fit such high ordered polynomials by least squares only, which, indeed, would be difficult.

Thus, one realises the need to have designs which allow a uniform exploration of the whole simplex and some models suitable for all types of designs. Evidently, the designs should have 'total mixtures' (mixtures with all the components) as points and must provide a sufficient number of observations so that the model fitted to approximate the response can be tested for adequacy by obtaining a component of sum of squares due to lack of fit of the model.

An experimenter, normally, would not like to go in for a very high ordered polynomial to approximate the response surface and thereby go through the difficulties of estimation. He would rather be satisfied with a lower order polynomial in view of its simpler method of estimation. A quadratic model in the variables may thus serve his purpose in approximating the response in the region of interest. In fact, in most of the practical situations this is true. If, however, the quadratic regression function turns out to be inadequate, a cubic model can be utilised with suitable designs so as to arrive at a satisfactory representation of the response surface. The method of fitting in such cases will be by least squares so that the well known test producers may be applied for testing the adequacy of fit.

The attempt of Draper and Lawrence [3], [4] realises some of these objectives in as much as adopting the study of quadratic response surface and obtaining designs which explore the interior of the simplex also. But their study is limited in scope as it provides designs for only three and four component mixture experiments.

Assuming the adequacy of a quadratic surface in representing the response in the region of interest, this work deals with simple methods of estimating the parameters by least squares and obtaining general designs covering a wide range of possibilities of representing the simplex. The case of the presence of process variables is also considered. The studies have been illustrated by an example involving a real set of data

When the quadratic surface turns out to be inadequate to represent the response a cubic model should be employed for the purpose. Results regarding the methods of fitting such models will be reported in a separate paper. The methods of fractionation of the designs for mixture experiments and suitable analysis will also be presented subsequently.

2. The quadratic model and the estimation of its parameters by least squares.

2.1. *The model and the problem of least squares.* Let η_u represent the true response at an experimental point $(x_{1u}, x_{2u}, \cdots, x_{nu})$ where $x_{1u}, x_{2u}, \cdots, x_{nu}$ are the proportions of the components $1, 2, \cdots, n$ respectively at the point u such that

$$\sum_{1 \leqq i \leqq n} x_{iu} = 1. \tag{2.1.1}$$

If there are N such responses on N points so that $u = 1, 2, \cdots, N$, the array of these N points defines a design matrix of order $N \times n$. Let us assume that a quadratic model

$$\begin{aligned} \eta_u = \beta_0' &+ \beta_1' x_{1u} + \beta_2' x_{2u} + \cdots + \beta_n' x_{nu} \\ &+ \beta_{11}' x_{1u}^2 + \beta_{22}' x_{2u}^2 + \cdots + \beta_{nn}' x_{nu}^2 \\ &+ \beta_{12}' x_{1u} x_{2u} + \beta_{13}' x_{1u} x_{3u} + \cdots + \beta_{n+1n}' x_{n-1u} x_{nu} \end{aligned} \tag{2.1.2}$$

represents the response surface. By virtue of the restriction (2.1.1) the equation of the surface on the simplex can be written as

$$\eta_u = \beta_1 x_{1u} + \beta_2 x_{2u} + \cdots + \beta_n x_{nu} + \beta_{12} x_{1u} x_{2u} + \cdots + \beta_{n-1n} x_{n-1u} x_{nu} \tag{2.1.3}$$

which is evident from the substitutions (1.1.4) in (2.1.2).

Let y_u denote the observed response at the point $(x_{1u}, x_{2u}, \cdots, x_{nu})$. The method of least squares for fitting the regression function (2.1.3) requires that

$$\sum_u \Big(y_u - \sum_{1 \leqq i \leqq n} \beta_i x_{iu} - \sum_{1 \leqq i < j \leqq n} \beta_{ij} x_{iu} x_{ju}\Big)^2 \tag{2.1.4}$$

be minimised with respect to the parameters β's. The normal equations for the estimation of the parameters are then obtained by differentiating (2.1.4) with respect to β's and equating the differentials to zero. It is well known that the estimates of the parameters are given by

$$b = (X'X)^{-1}X'Y \tag{2.1.5}$$

where b' is the $1 \times \{n + \binom{n}{2}\}$ vector of the estimates of the parameters,

$$X = [x_{1u}, x_{2u}, \cdots, x_{nu}, x_{1u}x_{2u}, \cdots, x_{n-1u}x_{nu}], \quad \text{the} \quad N \times \{n + \binom{n}{2}\} \text{ matrix, and}$$

$$Y' = [y_1, y_2, \cdots, y_N], \quad \text{the} \quad 1 \times N \quad \text{vector of the observed responses.}$$

The main problem with the least squares method of estimation is to obtain the inverse of the matrix $(X'X)$. Inversion of such matrices, however, proves very difficult particularly when the number of components is large and proper designing is not adopted. An alternative method of solving the normal equations for certain types of designs instead of inverting the matrix as such was therefore attempted as described below.

2.2. *The method of estimation.* Differentiating (2.1.4) with respect to the parameters, say, β_λ and $\beta_{\lambda\mu}$ and equating the differentials to zero we obtain the following two typical normal equations.

$$\begin{aligned} \textstyle\sum_u x_{\lambda u}y_u = {} & b_1 \textstyle\sum_u x_{1u}x_{\lambda u} + \cdots + b_\lambda \textstyle\sum_u x_{\lambda u}^2 + \cdots + b_n \textstyle\sum_u x_{\lambda u}x_{nu} \\ & + b_{12} \textstyle\sum_u x_{1u}x_{2u}x_{\lambda u} + \cdots + b_{1\lambda} \textstyle\sum_u x_{1u}x_{\lambda u}^2 \\ & + \cdots + b_{n-1n} \textstyle\sum_u x_{\lambda u}x_{u-1u}x_{nu} ; \end{aligned} \tag{2.2.1}$$

$$\begin{aligned} \textstyle\sum_u x_{\lambda u}x_{\mu u}y_u = {} & b_1 \textstyle\sum_u x_{1u}x_{\lambda u}x_{\mu u} + \cdots + b_s \textstyle\sum_u x_{\lambda u}^2x_{\mu u} \\ & + \cdots + b_\mu \textstyle\sum_u x_{\lambda u}x_{\mu u}^2 + \cdots + b_n \textstyle\sum_u x_{\lambda u}x_{\mu u}x_{nu} \\ & + \cdots + b_{12} \textstyle\sum_u x_{1u}x_{2u}x_{\lambda u}x_{\mu u} + \cdots + b_{1\lambda} \textstyle\sum_u x_{1u}x_{\lambda u}^2x_{\mu u} \\ & + \cdots + b_{\lambda\mu} \textstyle\sum_u x_{\lambda u}^2x_{\mu u}^2 \\ & + \cdots + b_{n-1n} \textstyle\sum_u x_{\lambda u}x_{\mu u}x_{n-1u}x_{nu} . \end{aligned} \tag{2.2.2}$$

Let us now suppose that the design matrix satisfies the following symmetry conditions.

$$\begin{aligned} \textstyle\sum_u x_{iu}^2 &= \text{constant} = A, \\ \textstyle\sum_u x_{iu}x_{ju} &= \text{constant} = B, \\ \textstyle\sum_u x_{iu}^2x_{ju} &= \text{constant} = C, \\ \textstyle\sum_u x_{iu}x_{ju}x_{ku} &= \text{constant} = D, \\ \textstyle\sum_u x_{iu}^2x_{ju}^2 &= \text{constant} = E, \\ \textstyle\sum_u x_{iu}^2x_{ju}x_{ku} &= \text{constant} = F, \\ \textstyle\sum_u x_{iu}x_{ju}x_{ku}x_{lu} &= \text{constant} = G, \end{aligned} \tag{2.2.3}$$

for all i, j, k and l $(i \neq j \neq k \neq l)$ ranging over the n columns of the design matrix corresponding to the n components, the summation on u being over all the N design points (or rows).

Using the constants (2.2.3), the two normal equations (2.2.1) and (2.2.2) can be written as

$$(2.2.4)\qquad \sum_u x_{\lambda u} y_u = A b_\lambda + B \sum_{1 \leqq i \leqq n, i \neq \lambda} b_i + C \sum_{1 \leqq i \leqq n, i \neq \lambda} b_{\lambda i} + D \sum_{1 \leqq i < j \leqq n, i, j \neq \lambda} b_{ij};$$

$$(2.2.5)\qquad \sum_u x_{\lambda u} x_{\mu u} y_u = C(b_\lambda + b_\mu) + D \sum_{1 \leqq i \leqq n, i \neq \lambda, \mu} b_i + E b_{\lambda \mu} + F\left(\sum_{i \neq \lambda} b_{\lambda i} + \sum_{i \neq \mu} b_{\mu i}\right) + G \sum_{1 \leqq i < j \leqq n, i, j \neq \lambda, \mu} b_{ij}.$$

Next, summing the normal equations (2.2.4) over all $\lambda = 1, 2, \cdots, n$, we obtain

$$(2.2.6)\qquad \sum_{1 \leqq i \leqq n} \left(\sum_u x_{iu} y_u\right) = (A + (n-1)B) \sum_{1 \leqq i \leqq n} b_i + (2C + (n-2)D) \sum_{1 \leqq i < j \leqq n} b_{ij}.$$

Summing the equations (2.2.5) over all $\lambda, \mu = 1, 2, \cdots, n$, we obtain

$$(2.2.7)\qquad \sum_{1 \leqq i < j \leqq n} \left(\sum_u x_{iu} x_{ju} y_u\right) = \left\{(n-1)C + \binom{n-1}{2} D\right\} \sum_{1 \leqq i \leqq n} b_i + \left\{E + 2(n-2)F + \binom{n-2}{2} G\right\} \sum_{1 \leqq i < j \leqq n} b_{ij}.$$

From the two equations (2.2.6) and (2.2.7) we can determine the two unknowns $\sum b_i$ and $\sum b_{ij}$ which are given by

$$(2.2.8)\qquad \sum b_i = \left\{P_4 \sum_i \left(\sum_u x_{iu} y_u\right) - P_2 \sum_{i<j} \left(\sum_u x_{iu} x_{ju} y_u\right)\right\} / P,$$

$$(2.2.9)\qquad \sum b_{ij} = \left\{P_1 \sum_{i<j} \left(\sum_u x_{iu} x_{ju} y_u\right) - P_3 \sum_i \left(\sum_u x_{iu} y_u\right)\right\} / P,$$

where

$$P_1 = A + (n-1)B, \qquad P_2 = 2C + (n-2)D,$$

$$P_3 = (n-1)C + \binom{n-1}{2} D, \qquad P_4 = E + 2(n-2)F + \binom{n-2}{2} G,$$

$$P = P_1 P_4 - P_2 P_3.$$

Next we rewrite the normal equation (2.2.1) as

$$(2.2.10)\qquad \sum_u x_{\lambda u} y_u = (A - B) b_\lambda + B \sum_i b_i + (C - D) \sum_{i \neq \lambda} b_{\lambda i} + D \sum_{i<j} b_{ij}.$$

Equation (2.2.10) has only two unknowns b_λ and $\sum b_{\lambda i}$ in view of solutions (2.2.8) and (2.2.9). Fixing λ now and summing the equation (2.2.5) over all the $(n-1)$ μ's ($\mu \neq \lambda$) we obtain

$$\sum_{i \neq \lambda} \left(\sum_u x_{\lambda u} x_{iu} y_u\right) = (n-1) C b_\lambda + (C + (n-2)D) \sum_{i \neq \lambda} b_i + (E + (n-2)F) \sum_{i \neq \lambda} b_{\lambda i} + (2F + (n-3)G) \sum_{i < j \neq \lambda} b_{ij}$$

which can be rewritten as

$$(2.2.11)\qquad \sum_{i \neq \lambda} \left(\sum_u x_{\lambda u} x_{iu} y_u\right) = (n-2)(C - D) b_\lambda + (C + (n-2)D) \sum_i b_i + (E + (n-4)F - (n-3)G) \sum_{i \neq \lambda} b_{\lambda i} + (2F + (n-3)G) \sum_{i<j} b_{ij}.$$

From equations (2.2.10) and (2.2.11) substituting (2.2.8) and (2.2.9) we obtain b_λ and $\sum b_{\lambda i}$ as

$$b_\lambda = \{PQ_4 \textstyle\sum_u x_{\lambda u} y_u - PQ_2 \sum_i (\sum_u x_{\lambda u} x_{iu} y_u) - \Delta_1 \sum_i (\sum_u x_{iu} y_u) + \Delta_2 \sum_{i<j} (\sum_u x_{iu} x_{ju} y_u)\}/PQ, \tag{2.2.12}$$

$$\textstyle\sum_i b_{\lambda i} = \{PQ_1 \sum_i (\sum_u x_{\lambda u} x_{iu} y_u) - PQ_3 (\sum_u x_{\lambda u} y_u) + \Delta_3 \sum_i (\sum_u x_{iu} y_u) - \Delta_4 \sum_{i<j} (\sum_u x_{iu} x_{ju} y_u)\}/PQ, \tag{2.2.13}$$

where

$$Q_1 = A - B, \qquad Q_2 = C - D, \qquad Q_3 = (n-2)(C-D),$$

$$Q_4 = E + (n-4)F - (n-3)G, \qquad Q = Q_1Q_4 - Q_2Q_3;$$

$$\Delta_1 = P_4\{BQ_4 - Q_2(C + (n-2)D)\} - P_3\{DQ_4 - (2F + (n-3)G)Q_2\},$$

$$\Delta_2 = P_2\{BQ_4 - Q_2(C + (n-2)D)\} - P_1\{DQ_4 - (2F + (n-3)G)Q_2\},$$

$$\Delta_3 = P_4\{BQ_3 - Q_1(C + (n-2)D)\} - P_3\{DQ_3 - (2F + (n-3)G)Q_1\},$$

$$\Delta_4 = P_2\{BQ_3 - Q_1(C + (n-2)D)\} - P_1\{DQ_3 - (2F + (n-3)G)Q_1\}.$$

By symmetry of the designs, the solutions for any b_λ and $\sum b_{\lambda i}$ can be written down from (2.2.12) and (2.2.13).

Finally, the normal equation (2.2.5) can be rewritten as

$$\begin{aligned}\textstyle\sum_u x_{\lambda u} x_{\mu u} y_u = {} & (C - D)(b_\lambda + b_\mu) + D \textstyle\sum_{1 \leqq i \leqq n} b_i \\ & + (E - 2F + G) b_{\lambda\mu} \\ & + (F - G)(\textstyle\sum_{i \neq \lambda} b_{\lambda i} + \sum_{i \neq \mu} b_{\mu i}) + G \sum_{1 \leqq i < j \leqq n} b_{ij}.\end{aligned} \tag{2.2.14}$$

Substituting the values of b_λ, b_μ, $\sum b_{\lambda i}$, $\sum b_{\mu i}$, $\sum b_i$ and $\sum b_{ij}$ obtained from (2.2.8), (2.2.9), (2.2.12) and (2.2.13), we get the solution for $b_{\lambda\mu}$ as

$$\begin{aligned} PQ(E - 2F + G) b_{\lambda\mu} = {} & PQ \textstyle\sum_u x_{\lambda u} x_{\mu u} y_u - P\{Q_4(C - D) \\ & - Q_3(F - G)\}(\textstyle\sum_u x_{\lambda u} y_u + \sum_u x_{\mu u} y_u) \\ & + P\{Q_2(C - D) - Q_1(F - G)\}\{\textstyle\sum_i (\sum_u x_{\lambda u} x_{iu} y_u) \\ & + \textstyle\sum_i (\sum_u x_{\mu u} x_{iu} y_u)\} \\ & - \{(DP_4 - GP_3)Q - 2(C - D)\Delta_1 + 2(F - G)\Delta_3\} \textstyle\sum_i (\sum_u x_{iu} y_u) \\ & + \{(DP_2 - GP_1)Q - 2(C - D)\Delta_2 + 2(F - G)\Delta_4\} \textstyle\sum_{i<j} (\sum_u x_{iu} x_{ju} y_u). \end{aligned} \tag{2.2.15}$$

The solution for any $b_{\lambda\mu}$ can be written directly from (2.2.15) due to symmetry of the design.

Thus, it has been possible to obtain the estimates of the parameters of a quadratic model fitted through these designs with symmetry conditions (2.2.3) by a simple procedure of first solving a set of two equations, then another set of two equations and finally a single equation.

2.3. *Variances and covariances of the estimated parameters.* The variance-covariance matrix of the estimates is equal to

$$E[(b - \beta)(b - \beta)'] = (X'X)^{-1}\sigma^2 \tag{2.3.1}$$

where it is supposed that the responses are distributed independently with equal variance σ^2. A comparison of (2.3.1) with (2.1.5) shows that

$$V(b_i) = (\text{coefficient of } \textstyle\sum_u x_{iu}y_u \text{ in the estimate } b_i)\sigma^2,$$
$$V(b_{ij}) = (\text{coefficient of } \textstyle\sum_u x_{iu}x_{ju}y_u \text{ in the estimate } b_{ij})\sigma^2,$$

and similar coefficients for the covariances. Therefore, by collecting the appropriate coefficients from the estimates b's obtained above, we have the following variances and covariances.

$$V(b_i) = (PQ)^{-1}[P_4Q_4(A + (n-2)B) - P_3Q_4(2C + (n-3)D) + P_4Q_2(C + (n-2)D) + P_3Q_2(2F + (n-3)G)]\sigma^2, \tag{2.3.2}$$

$$V(b_{ij}) = (PQ(E - 2F + G))^{-1}[PQ - 2P\{Q_1(F - G) - Q_2(C - D)\} + Q(DP_2 - GP_1) - 2(C - D)\Delta_2 + 2(F - G)\Delta_4]\sigma^2; \tag{2.3.3}$$

$$\text{Cov}\,(b_ib_j) = (-\Delta_1/PQ)\sigma^2,$$
$$\text{Cov}\,(b_ib_{ij}) = (-PQ_2 + \Delta_2)\sigma^2/PQ,$$
$$\text{Cov}\,(b_ib_{jk}) = (\Delta_2/PQ)\sigma^2,$$
$$\text{Cov}\,(b_{ij}b_{ik}) = (PQ(E - 2F + G))^{-1}[-P\{Q_1(F - G) - Q_2(C - D)\} + Q(DP_2 - GP_1) - 2(C - D)\Delta_2 + 2(F - G)\Delta_4]\sigma^2,$$
$$\text{Cov}\,(b_{ij}b_{kl}) = (PQ(E - 2F + G))^{-1}[(DP_2 - GP_1)Q - 2(C - D)\Delta_2 + 2(F - G)\Delta_4]\sigma^2.$$

Then the variance of the estimated response $\hat{y}_0$ at the point $(x_{10}, x_{20}, \cdots, x_{n0})$ comes out as

$$\begin{aligned} V(\hat{y}_0)\sigma^{-2} = {} & V(b_i)\textstyle\sum_i x_{i0}^2 + V(b_{ij})\sum_i x_{i0}^2x_{j0}^2 + 2\,\text{Cov}\,(b_ib_j)\sum_{i<j} x_{i0}x_{j0} \\ & + 2\,\text{Cov}\,(b_ib_{ij})\textstyle\sum_{i<j} x_{i0}^2x_{j0} + 2\,\text{Cov}\,(b_ib_{jk})\sum_{i<j<k} x_{i0}x_{j0}x_{k0} \\ & + 2\,\text{Cov}\,(b_{ij}b_{kl})\textstyle\sum_{i<j<k<l} x_{i0}x_{j0}x_{k0}x_{l0}. \end{aligned} \tag{2.3.4}$$

2.4. *Interpretation of the parameters.* A question that arises after fitting by least squares a quadratic or a suitable general model to the observations on mixtures is what interpretation one could give to the estimates of the parameters. It is obvious that Scheffé's terminology of 'response to pure components' or 'synergism' is not applicable since the estimate, say, b_i of our model is not just based on the response to the ith component, nor does the term $b_{ij}x_ix_j$ give the excess of response over linear blending of the components i and j. Moreover, the customary terminology of the factorial designs, namely, 'main effects' and 'interactions' does not apply because the estimates of β's are not actually given by the same contrasts as for the usual main effects or interactions. Further, the 'general mean' is confounded with the estimates b_i due to the restriction $\sum x_i = 1$.

It may, therefore, be advisable to understand the parameters as the usual 'regression coefficients'. One might, however, call b_i as the effect of the ith component and b_{ij} as the joint effect of the components i and j without attaching much specific significance to the terminology. The interpretation of the results on testing the regression coefficients might then be given accordingly, such as, the effect of the ith component is significant, the joint effect of the components i and j is significant and so on. The main utility of the fit will, however, lie in its prediction.

2.5. *Analysis of variance.* Let the experiment with a design of N points be replicated r times with a view to increasing the accuracy of the estimates. If the quadratic model (2.1.3) in n components is fitted by least squares through the observations, the sum of squares (s.s.) due to fitted regression with $n + \binom{n}{2} - 1$ degrees of freedom is given by

$$(2.4.1)\quad S_R = b_1 \sum x_{1u}y_u + \cdots + b_n \sum x_{nu}y_u + b_{12} \sum x_{1u}x_{2u}y_u + \cdots + b_{n-1n} \sum x_{n-1u}x_{nu}y_u - \text{C.F.}$$

Since the general mean is confounded with the estimates b_i's and each individual b_i is not a contrast but the contrasts among the b_i's are contrasts free from b_0, the s.s. due to the general mean (C.F.) with one degree of freedom has to be separated to get an independent estimate of the s.s. due to the regressions.

Now, the r observations due to replication of a point give rise to a sum of squares with $(r - 1)$ degrees of freedom and the total of these sums of squares from the N points belongs to the component of error in the analysis of variance with $N(r - 1)$ degrees of freedom. The error mean square obtained therefrom will be an estimate of the experimental variance. The sum of squares due to lack of fit is then obtained by subtraction in the analysis of variance table and the mean square due to lack of fit tested against the error mean squares gives an idea of the representational adequacy of the model.

The analysis of variance table can be written as follows.

Source of Variation	d.f.	s.s.	m.s.
Due to Regression	$n + \binom{n}{2} - 1$	S_R	
Due to lack of fit	$N - n - \binom{n}{2}$	By subtraction	
Error	$N(r - 1)$	S_E	
Total	$Nr - 1$		

3. Designs for the exploration of a quadratic response surface. A simple method of estimation of the parameters of a quadratic model has been obtained in Section 2 assuming the symmetry conditions (2.2.3). We now proceed to obtain designs which satisfy these conditions.

3.1. *Symmetric simplex design.* Let the point $(x_{1u}, x_{2u}, \cdots, x_{nu})$ of a design for a mixture experiment in n components where d of the x_{iu}'s are non-zero elements (fractions) be called a dth ordered mixture and be denoted by S_d. Further, let d_1 of the x_{iu}'s of S_d be each equal to q_1, d_2 of the x_{iu}'s equal to q_2, so on and d_h of the x_{iu}'s equal to q_h so that $d_1 + d_2 + \cdots + d_h = d$ and $d_1q_1 + d_2q_h + \cdots + d_hq_h = 1$. Let all the dth ordered mixtures S_d that are obtainable by permutation of the different fractions in the mixture over the n components be written in the form of a group called the group G_d, each mixture S_d forming a row of G_d and the ith component being represented by the ith column of G_d. Then it is easy to see that the number of rows in the group G_d is given by

$$W_d = \binom{n}{d_1}\binom{n-d_1}{d_2}\binom{n-(d_1+d_2)}{d_3}\cdots\binom{n-(d_1+d_2+\cdots+d_{h-1})}{d_h}. \tag{3.1.1}$$

Further, it can be easily shown that the rows of G_d considered as design points satisfy all the conditions in (2.2.3) since the fractions occur in different columns symmetrically. Thus we define a symmetric simplex design for experiments with mixtures through which the quadratic model (2.1.3) can be fitted by the methods of Section 2.2 as follows:

DEFINITION. A symmetric simplex design for experiments with mixtures consists of some or all the groups G_d, $d = 1, 2, \cdots, n$, where every group G_d is obtained by permuting the different fractions over the n components in a dth ordered mixture with d_1 components taking a proportion q_1, d_2 of them taking a proportion q_2, so on, d_h of them taking a proportion q_h such that $d_1 + d_2 + \cdots + d_h = d$ and $d_1q_1 + d_2q_2 + \cdots + d_hq_h = 1$.

It can be seen that given a point P of a group G_d, all such points on the simplex which are symmetrically placed as P with respect to every one of the n vertices are included in the group G_d and hence in the design.

3.2. *Particular cases.* The simplex-lattice design and the simplex-centroid design are obviously particular cases of the symmetric simplex design. The simplex-lattice (n, m) design has a different number of groups G_d for every $d = 1, 2, \cdots, m$. For example, there are three groups G_2 in a $(n, 6)$ simplex-lattice design with points of the type $(\frac{1}{6}\ \frac{5}{6}\ 0\ 0 \cdots 0)$, $(\frac{1}{3}\ \frac{2}{3}\ 0\ 0 \cdots 0)$ and $(\frac{1}{2}\ \frac{1}{2}\ 0 \cdots 0)$. The simplex-centroid has all the n groups G_d, each of the non-zero fractions being equal to $1/d$ in every mixture S_d.

The radial-lattice and the radial-centroid designs proposed by Plackett in [8] are also particular cases of the symmetric simplex design.

The symmetric simplex design offers much flexibility in the choice of the different proportions q_i's and hence in the choice of the design points so that the representation on the simplex is uniform. All such choices of the points for the design such as the centroid alone or simplex-lattice alone or one of these designs along with certain total mixtures are entertained by this flexibility of the design. For instance, one might consider a symmetric simplex design in which a simplex-lattice or simplex-centroid is augmented with a radial-lattice so that a uniformly spaced distribution of points over the simplex is achieved. Any other choice of the design points as demanded by the occasion is open to the experimenters. In other words, only a few of the groups G_d, $d = 1, 2, \cdots, n$, may be considered for the design, the number of total mixtures and incomplete mixtures being decided according to the situation. In this connection, it may be noted that the number of points in a group G_d increases with increasing d and h. They will be maximum if $d_1 = d_2 = \cdots = d_h$ and $q_1 \neq q_2 \neq \cdots \neq q_h$. Therefore the number of points in a group will be less if d and h are small and may be further reduced if in every mixture the number of components taking different distinct proportions is less. That is, $d_1, d_2, \cdots, d_h$ must take low integral values. It is, however, obvious that the number will be minimum if each q_i of G_d is equal to $1/d$.

Another point that may be noted is about the values of the constants (2.2.3) for a symmetric simplex design. Since the evaluation of them for a design with groups G_d of all orders $d = 1, 2, \cdots, n$ is difficult, the evaluation of the constants for a single group G_d which may contain any proportions q_i's has been made in [6]. We however, give here only two examples which may be helpful to experimenters.

EXAMPLE 1. Consider the symmetric simplex design in n components with the three groups G_d; $d = 1, 2, 3$ where the components in each group G_d take the proportion $1/d$. The design thus consists of the n points of the type $(100 \cdots 0)$, the $\binom{n}{2}$ points of the type $(\frac{1}{2}, \frac{1}{2}, \cdots 0)$ and the $\binom{n}{3}$ points of the type $(\frac{1}{3}\ \frac{1}{3}\ \frac{1}{3}\ 0 \cdots 0)$.

When a quadratic model (2.1.3) is fitted through the above design to represent the response surface, the values of the constants (2.2.3) are given as below:

$$\begin{aligned} &A = (2n^2 + 3n + 31)/36, && D = 1/27, \\ &B = (4n + 1)/9, && E = (16n + 49)/1296, \\ &C = (8n + 11)/216, && F = 1/81, \\ & && G = 0. \end{aligned} \tag{3.2.1}$$

By substituting these values in (2.2.12) and (2.2.15) we get the estimates as

$$\begin{aligned} b_\lambda = {} & [2(32n - 15) \textstyle\sum_u x_{\lambda u} y_u + 12(8n + 3) \sum_i (\sum_u x_{\lambda u} x_{iu} y_u)] \\ & \cdot (n^2 + 59n - 24)^{-1} \\ & - [4(n - 2)(8n + 3) \textstyle\sum_i (\sum_u x_{iu} y_u) + 48(2n^2 - n + 30) \\ & \cdot \textstyle\sum_{i<j} (\sum_u x_{iu} x_{ju} y_u][(n^2 + 29n - 8)(n^2 + 59n - 24)]^{-1} \end{aligned} \tag{3.2.2}$$

$$\begin{aligned} (16n + 17)(1296)^{-1} b_{\lambda\mu} \\ = \textstyle\sum_u x_{\lambda u} x_{\mu u} y_u - [(16n + 17)(8n + 3)(\sum_u x_{\lambda u} y_u + \sum_u x_{\mu u} y_u)] \\ \cdot [108(n^2 + 59n - 24)]^{-1} \\ + (32n^2 + 64n - 471)[18(n^2 + 59n - 24)]^{-1} \end{aligned}$$

$$(3.2.3)\qquad \cdot\{\textstyle\sum_i(\sum_u x_{\lambda u}x_{iu}y_u) + \sum_i(\sum_u x_{\mu u}x_{iu}y_u)\}$$
$$+ (16n + 17)(2n^2 - n + 30)$$
$$\cdot[27(n^2 + 29n - 8)(n^2 + 59n - 24)]^{-1}\textstyle\sum_i(\sum_u x_{iu}y_u)$$
$$+ (32n^3 + 48n^2 + 508n - 8664)$$
$$\cdot[9(n^2 + 29n - 8)(n^2 + 59n - 24)]^{-1}\textstyle\sum_{i<j}(\sum_u x_{iu}x_{ju}y_u).$$

Also, we have the following variances:

$$V(b_i) = [64n^3 + 1794n^2 - 1330n + 264]\sigma^2[(n^2 + 29n - 8)(n^2 + 59n - 24)]^{-1},$$
$$V(b_{ij}) = 144(41n^4 + 1752n^3 + 16192n^2 - 25191n + 14160)$$
$$\cdot((16n + 17)(n^2 + 29n - 8)(n^2 + 59n - 24))^{-1}\sigma^2.$$

The other covariances can be easily gotten from (3.2.2) and (3.2.3) so that the variance of the estimated response can be obtained from (2.3.4). The $V(b_i)$ and $V(b_{ij})$ above, as also the other covariances are descreasing functions of n. It may, however, be interesting to note the order of decrease in the functions as n increases. It must be noted that the variance of b_i's and b_{ij} given by Scheffé [8] for the simplex-centroid design are invariant whatever be the number of components. The variances in his case are $V(b_i) = \sigma^2$, $V(b_{ij}) = 24\sigma^2$. We tabulate below the variances of the estimates upto the case when $n = 10$.

n	$V(b_i)/\sigma^2$	$V(b_{ij})/\sigma^2$
2	1.0000	24.0000
3	.9924	20.9697
4	.9813	18.5557
5	.9689	16.6444
6	.9562	15.1225
7	.9432	13.8982
8	.9305	12.8898
9	.9179	12.0468
10	.9055	11.3312

Considerable decrease in the variance of b_{ij} can be noted.

EXAMPLE 2. Consider the symmetric simplex design with the n groups G_d, $d = 1, 2, \cdots, n$, such that any particular group G_d has design points with each of the non-zero fractions equal to $1/d$. Let the group G_d be replicated r_d times so as to get sufficient degrees of freedom for the estimation of experimental variance. Then the constants (2.2.3) take the values shown below:

$$A = r_1 + (n - 1)r_2/2^2 + \tbinom{n-1}{2}r_3/3^2 + \cdots + r_n/n^2,$$
$$B = r_2/2^2 + (n - 2)r_3/3^2 + \tbinom{n-2}{2}r_4/4^2 + \cdots + r_n/n^2,$$
$$C = r_2/2^3 + (n - 2)r_3/3^3 + \tbinom{n-2}{2}r_4/4^3 + \cdots + r_n/n^3,$$

$$D = r_3/3^3 + (n - 3)r_4/4^3 + \binom{n-3}{2}r_5/5^3 + \cdots + r_n/n^3,$$

$$E = r_2/2^4 + (n - 2)r_3/3^4 + \binom{n-2}{2}r_4/4^4 + \cdots + r_n/n^4,$$

$$F = r_3/3^4 + (n - 3)r_4/4^4 + \binom{n-3}{2}r_5/5^4 + \cdots + r_n/n^4,$$

$$G = r_4/4^4 + (n - 4)r_5/5^4 + \binom{n-4}{2}r_6/6^4 + \cdots + r_n/n^4.$$

When these values are known, further analysis and interpretation of the results follow along familiar lines. (The corresponding values for the simplex-centroid design can be obtained by putting each $r_d = 1$. It should be noted that when the simplex-centroid is replicated, the observed responses at a particular design point enter only as an average in the estimates of Scheffé's model while this is not so in the present case.)

4. Experiments with mixtures with the presence of process variables.

4.1. *Some examples of the presence of process variables.* Suppose in an experiment with crop mixtures we want to study the response (which may be the total yield in money value) due to application of certain fertilizers to the crop mixtures in addition to the study of proportions of the crops. We are thus extending the crop mixture experiment by trying it at different levels of some fertilizer or combinations of two or more fertilizers. The new factors which do not form any component of the mixtures, in the present case the fertilizers, are called the 'process variables' of the experiment and the crops, as usual, are called the 'mixture variables.' Other examples of mixture experiments with the presence of process variables might be (i) the feeding trials in which factors like age, breed, lactation, etc., can be varied in addition to the proportions of different feeds, (ii) the gasoline blends in which if the response is road octane number of a blend the make and the speed of the car can be varied as well as the proportions of the blend [8].

4.2. *The complete simplex-centroid* $\times$ *factorial experiment.* Scheffé [8], while introducing the process variables, defined a complete simplex-centroid $\times$ Factorial experiment as one in which at each of the $2^n - 1$ points of the simplex-centroid design a complete s^p factorial experiment is made with the p process variables each at s levels. Then he proposed a method of analysis which can be briefly described as follows:

Without loss of generaility, let us suppose that there are three process variables A, B, C at I, J, K levels respectively. For a fixed combination (ijk) of the process variables, we shall have $2^n - 1$ points from the simplex-centroid design. The model (1.1.7) can be fitted to the $2^n - 1$ observations at each combination of the process variables as was indicated. The previous coefficients denoted by β_{s_r} in the model (1.1.7) may now be written as β_{s_r} ; ijk. The estimates of these β's are then given by (1.1.8). Now fixing s_r and varying i, j, k, we resolve the β_{s_r} ; ijk into main effects and interactions as in a general factorial model to get

$$(4.2.1) \quad \beta_{s_r;ijk} = \beta^0_{s_r} + \beta^{A,i}_{s_r} + \beta^{B,j}_{s_r} + \beta^{C,k}_{s_r} + \beta^{AB,ij}_{s_r} + \beta^{AC,ik}_{s_r} + \beta^{BC,jk}_{s_r} + \beta^{ABC,ijk}_{s_r}.$$

On replacing the β_{s_r} in (1.1.8) by (4.2.1) we get a regression equation with coefficients $\beta_{s_r}^0, \beta_{s_r}^{A,i}, \cdots, \beta_{s_r}^{ABC,ijk}$; the equation will represent an arbitrary set of responses at the points of the simplex-centroid $\times$ IJK design, and these coefficients will be uniquely determined by those responses.

As regards the ability of the model (4.2.1) and the simplex-centroid design to explore the surface with respect to the mixture variables, whatever is said in the discussion (1.2) or subsequently holds good. But, coming to the process variables, it is not clear how the full model with $\beta_{s_r}^0, \beta_{s_r}^{A,i}, \cdots, \beta_{s_r}^{ABC,ijk}$ can be used as a prediction equation. No doubt the model can be used for prediction at the points of the design, but, as with any general factorial model using main effects and interactions, it cannot be used for prediction at points other than the design points though they are within the range of the variables. That is, the model cannot be used for interpolation purposes which is expected of any prediction equation.

In order to overcome this limitation of representation and prediction we first suggest below an alternative design and then propose a general quadratic model in both the mixture and process variables.

4.3. *The symmetric simplex $\times$ factorial design.* Consider a symmetric simplex design in n components with N points and a complete s^p factorial design in p factors and s levels. Associate these two designs such that at each combination of one design all the combinations of the other design occur. The resulting design in $n + p$ factors and $N \times s^p$ points is called the symmetric simplex $\times$ factorial design.

4.4. *The quadratic regression function and its fitting. Let* $[x_{1u}, x_{2u}, \cdots, x_{nu}, z_{1u}, z_{2u}, \cdots, z_{pu}]$ denote the uth point of a symmetric simplex $\times$ factorial design where x_{iu}, $i = 1, 2, \cdots, n$, denote the proportions of the n mixture variables such that $\sum_i x_{iu} = 1$ and z_{ju}, $j = 1, 2, \cdots, p$, denote the levels of the p process variables in the uth point.

A quadratic polynomial in the $n + p$ variables is of the form

$$f(x, z) = \beta_0' + \textstyle\sum_i \beta_i' x_i + \sum_j \beta_j' z_j + \sum_i \beta_{ii}' x_i^2 + \sum_j \beta_{jj}' z_j^2 + \sum_{i<i'} \beta_{ii'}' x_i x_{i'} + \sum_{j<j'} \beta_{jj'}' z_j z_{j'} + \sum_{i,j} \beta_{ij}' x_i z_j. \tag{4.4.1}$$

Now, supposing that the response η_u at the uth point can be represented by a quadratic polynomial in the $n + p$ variables, it reduces to the form,

$$\eta_u = \textstyle\sum_{1 \le i \le n} \beta_i x_{iu} + \sum_{1 \le j \le p} \beta_{jj} z_{ju}^2 + \sum_{1 \le i < i' \le n} \beta_{ii'} x_{iu} x_{i'u} + \sum_{1 \le j < j' \le p} z_{ju} z_{j'u} + \sum_{1 \le i \le n, 1 \le j \le p} x_{iu} z_{ju} \tag{4.4.2}$$

because of the following substitutions, $\sum_i x_{iu}$ being equal to unity.

(i) $\beta_0' = \beta_0' \sum x_{iu}$
(ii) $\beta_j' z_{ju} = \beta_j' z_{ju} \sum x_{iu} = \beta_j' \sum x_{iu} z_{ju}$
(iii) $\beta_{ii}' x_{iu}^2 = \beta_{ii}' - (x_{iu} \to \sum_{i' \ne i} x_{iu} x_{i'u})$

so that

$$\beta_i = \beta_0' + \beta_i' + \beta_{ii}', \qquad \beta_{ii'} = \beta_{ii'}' - \beta_{ii}', \quad \beta_{ij} = \beta_{ij}' + \beta_j'. \tag{4.4.3}$$

(For convenience we shall denote the mixture variables using the subscripts i, i' etc., and the process variables using the subscripts j, j' etc.)

The estimates of the parameters β's of the model (4.4.1) are given by minimising

$$\sum_u (y_u - \sum \beta_i x_{iu} - \sum \beta_{jj} z_j^2 - \sum \beta_{ii'} x_{iu} x_{i'u} - \sum \beta_{jj'} z_{ju} z_{j'u} - \sum \beta_{ij} x_{iu} z_{ju})^2 \tag{4.4.4}$$

with respect to β's, where y_u is the observed response at the uth point.

To facilitate writing the normal equations, we shall use the following constants which are satisfied by the symmetric simplex $\times$ factorial design due to its symmetry.

$$\begin{aligned}
&\sum x_{iu}^2 = A, && \sum x_{iu} z_{ju} = O,\\
&\sum x_{iu} x_{i'u} = B, && \sum x_{iu}^2 z_{ju} = P_1,\\
&\sum x_{iu}^2 x_{i'u} = C, && \sum x_{iu} x_{i'u} z_{ju} = P_2\\
&\sum x_{iu} x_{i'u} x_{i''u} = D, && \sum x_{iu} z_{ju}^2 = Q_1,\\
&\sum x_{iu}^2 x_{i'u}^2 = E, && \sum x_{iu} z_{ju} z_{j'u} = Q_2,\\
&\sum x_{iu}^2 x_{i'u} x_{i''u} = F, && \sum x_{iu}^2 z_{ju}^2 = R_1,\\
&\sum x_{iu} x_{i'u} x_{i'u'} x_{i'''u} = G, && \sum x_{iu}^2 z_{ju} z_{j'u} = R_2,\\
&\sum z_{ju}^2 = H, && \sum x_{iu} x_{i'u} z_{ju}^2 = R_3,\\
&\sum z_{ju} z_{j'u} = I, && \sum x_{iu} x_{i'u} z_{ju} z_{j'u} = R_4,\\
&\sum z_{ju}^4 = J, && \sum x_{iu}^2 x_{i'u} z_{ju} = S_1,\\
&\sum z_{ju}^3 z_{j'u} = K, && \sum x_{iu} x_{i'u} x_{i''u} z_{ju} = S_2,\\
&\sum z_{ju}^2 z_{j'u}^2 = L, && \sum x_{iu} z_{ju}^3 = T_1,\\
&\sum z_{ju}^2 z_{j'u} z_{j''u} = M, && \sum x_{iu} z_{ju} z_{j'u}^2 = T_2,\\
&\sum z_{ju} z_{j'u} z_{j''u} z_{j'''u} = N, && \sum x_{iu} z_{ju} z_{j'u} z_{j''u} = T_3,
\end{aligned} \tag{4.4.5}$$

for all $i \neq i' \neq i'' \neq i'''$ and $j \neq j' \neq j''$, the i's ranging over mixture variables and the j's over process variables, where the summations range over $u = 1, 2, \cdots, N$, the design points.

Summing over the n normal equations obtained by differentiating (4.4.4) wrt β_i, $1 \leqq i \leqq n$, we get the equation

$$\begin{aligned}
&\textstyle\sum_{1 \leqq i \leqq n} (\sum_u x_{iu} y_u)\\
&= (A + (n-1)B) \textstyle\sum_{1 \leqq i \leqq n} b_i + nQ_1 \sum_{1 \leqq j \leqq p} b_{jj}\\
&\quad + (2C + (n-2)D) \textstyle\sum_{1 \leqq i < i' \leqq n} b_{ii'} + nQ_2 \sum_{1 \leqq j < j' \leqq p} b_{jj'}\\
&\quad + (P_1 + (n-1)P_2) \textstyle\sum_{1 \leqq i \leqq n, 1 \leqq j \leqq p} b_{ij}
\end{aligned} \tag{4.4.6}$$

where the b's are the estimates of the parameters β's.

Summing over the p normal equations obtained by differentiating (4.4.4) wrt β_{jj}, $1 \leqq j \leqq p$, we get the equation

$$\sum_{1 \leqq j \leqq p} \left(\sum_u z_{ju}^2 y_u\right)$$

$$= pQ_1 \sum b_i + (J + (p-1)L) \sum b_{jj} + pR_3 \sum b_{ii''} + (2K + (p-2)M) \sum b_{jj'} + (T_1 + (p-1)T_2) \sum b_{ij}. \tag{4.4.7}$$

Summing over the $\binom{n}{2}$ normal equations obtained by differentiating (4.4.4) wrt $\beta_{ii'}$, $1 \leqq i < i' \leqq n$, we get the equation

$$\sum_{1 \leqq i < i' \leqq n} \left(\sum_u x_{iu} x_{i'u} y_u\right)$$

$$= \{(n-1)C + \tbinom{n-1}{2} D\} \sum b_i + \tbinom{n}{2} R_3 \sum b_{jj} + \{E + 2(n-2)F + \tbinom{n-2}{2} G\} \sum b_{ii'} + \tbinom{n}{2} R_4 \sum b_{jj'} + \{(n-1)S_1 + \tbinom{n-1}{2} S_2\} \sum b_{ij}. \tag{4.4.8}$$

Summing over the $\binom{p}{2}$ normal equations obtained by differentiating (4.4.4) wrt $\beta_{jj'}$, $1 \leqq j < j' \leqq p$, we get

$$\sum_{1 \leqq j < j' \leqq p} \left(\sum_u z_{ju} z_{j'u} y_u\right)$$

$$= \tbinom{p}{2} Q_2 \sum b_i + \{(p-1)K + \tbinom{p-1}{2} M\} \sum b_{jj} + \tbinom{p}{2} R_4 \sum b_{ii'} + \{L + 2(p-2)M + \tbinom{p-2}{2} N\} \sum b_{jj'} + \{(p-1)T_2 + \tbinom{p-1}{2} T_3\} \sum b_{ij}. \tag{4.4.9}$$

And lastly, summing over the np normal equations obtained by differentiating (4.4.4) wrt β_{ij}, $1 \leqq i \leqq n$, $1 \leqq j \leqq p$, we get

$$\sum_{i,j} \left(\sum_u x_{iu} z_{ju} y_u\right)$$

$$= \{pP_1 + (n-1)pP_2\} \sum b_i + \{nT_1 + (p-1)nT_2\} \sum b_{jj} + \{2pS_1 + (n-2)pS_2\} \sum b_{ii'} + \{2nT_2 + (p-2)nT_3\} \sum b_{jj'} + \{R_1 + (p-1)R_2 + (n-1)R_3 + (p-1)(n-1)R_4\} \sum b_{ij}. \tag{4.4.10}$$

These five equations on solving give us the solutions of $\sum b_i$, $\sum b_{jj}$, $\sum b_{ii'}$, $\sum b_{jj'}$, and $\sum b_{ij}$.

Let us consider the normal equation obtained by differentiating (4.4.4) wrt β_λ, $1 \leqq \lambda \leqq n$, which can be written as

$$\sum_u x_{\lambda u} y_u = (A - B) b_\lambda + B \sum_{1 \leqq i \leqq n} b_i + Q_1 \sum_{1 \leqq j \leqq p} b_{jj} + (C - D) \sum_{1 \leqq i \leqq n, i \neq \lambda} b_{\lambda i} + D \sum_{1 \leqq i < i' \leqq n} b_{ii'} + Q_2 \sum_{1 \leqq j < j' \leqq p} b_{jj'} + (P_1 - P_2) \sum_{1 \leqq j \leqq p} b_{\lambda j} + P_2 \sum_{1 \leqq i \leqq n, 1 \leqq j \leqq p} b_{ij}. \tag{4.4.11}$$

This equation has only three unknowns, namely, b_λ, $\sum_{i \neq \lambda} b_{\lambda i}$ and $\sum_{1 \leqq j \leqq p} b_{\lambda j}$ since $\sum b_i$, $\sum b_{jj'}$, $\sum b_{ii'}$, $\sum b_{jj'}$ and $\sum b_{ij}$ are already known from the preceding steps.

Now, summing over the $(n-1)$ normal equations obtained by differentiating (4.4.4) wrt $\beta_{\lambda i}$, $i = 1, 2, \cdots, \lambda-1, \lambda+1, \cdots, n$, we get the equation,

$$\begin{aligned} &\textstyle\sum_{1 \leqq i \leqq n, i \neq \lambda} (\sum_u x_{\lambda u} x_{iu} y_u) \\ &\quad = (n-2)(C-D)b_\lambda + (C+(n-2)D)\sum b_i + (n-1)R_3 \sum b_{jj} \\ &\quad + (E+(n-4)F-(n-3)G)\sum b_{\lambda i} + (2F+(n-3)G)\sum b_{ii'} \\ &\quad + (n-1)R_4 \sum b_{jj'} + (n-2)(S_1-S_2)\sum b_{\lambda j} \\ &\quad + (S_1+(n-2)S_2)\sum b_{ij}. \end{aligned} \tag{4.4.12}$$

Again, summing over the p normal equations obtained by differentiating (4.4.4) wrt all $\beta_{\lambda j}$, $j = 1, 2, \cdots, p$, we get

$$\begin{aligned} &\textstyle\sum_{1 \leqq j \leqq p} (\sum_u x_{\lambda u} z_{ju} y_u) \\ &\quad = p(P_1-P_2)b_\lambda + pP_2 \sum b_i + (T_1+(p-1)T_2)\sum b_{jj} \\ &\quad + p(S_1-S_2)\sum b_{\lambda i} + pS_2 \sum b_{ii'} + (2T_2+(p-2)T_3)\sum b_{jj'} \\ &\quad + \{R_1-R_3+(p-1)(R_2-R_4)\}\sum b_{\lambda j} \\ &\quad + (R_3+(p-1)R_4)\sum b_{ij}. \end{aligned} \tag{4.4.13}$$

The equations (4.4.11), (4.4.12) and (4.4.13) therefore give us the solutions of b_λ, $\sum b_{\lambda i}$ and $\sum b_{\lambda j}$. And, by symmetry of the design we can immediately write down the solutions for any λ.

We shall now consider the estimation of any β_{jj}, say, $\beta_{\mu\mu}$. The corresponding normal equation can be written as

$$\begin{aligned} \textstyle\sum_u z_{\mu u}^2 y_u &= Q_1 \sum b_i + (J-L)b_{\mu\mu} + L\sum b_{jj} + R_3 \sum b_{ii'} \\ &\quad + (K-M)\textstyle\sum_{j \neq \mu} b_{\mu j} + (T_1-T_2)\sum_{1 \leqq i \leqq n} b_{i\mu} + T_2 \sum b_{ij}. \end{aligned} \tag{4.4.14}$$

It can be seen that (4.4.14) has only three unknowns $b_{\mu\mu}$, $\sum_{j \neq \mu} b_{\mu j}$ and $\sum_{1 \leqq i \leqq n} b_{i\mu}$. Summing the $(p-1)$ normal equations obtained by differentiating (4.4.4) wrt all $\beta_{\mu j}$, $j = 1, 2, \cdots, \mu-1, \mu+1, \cdots, p$, we have

$$\begin{aligned} &\textstyle\sum_{1 \leqq j \leqq p, j \neq \mu} (\sum_u z_{\mu u} z_{ju} y_u) \\ &\quad = (p-1)Q_2 \sum b_i + (p-2)(K-M)b_{\mu\mu} + (K+(p-2)M)\sum b_{jj} \\ &\quad + (p-1)R_4 \sum b_{ii'} + \{L+(p-4)M-(p-3)N\}\sum b_{\mu j} \\ &\quad + (2M+(p-3)N)\sum b_{jj'} + (T_2-T_3)\sum b_{i\mu} \\ &\quad + (T_2+(p-2)T_3)\sum b_{ij}. \end{aligned} \tag{4.4.15}$$

Again, summing the n normal equations obtained by differentiating (4.4.4) wrt all $\beta_{i\mu}$, $i = 1, 2, \cdots, n$, we get

$$\begin{aligned} &\textstyle\sum_{1 \leqq i \leqq n} (\sum_u x_{iu} z_{\mu u} y_u) \\ &\quad = (P_1+(n-1)P_2)\sum b_i + n(T_1-T_2)b_{\mu\mu} + nT_2 \sum b_{jj} \\ &\quad + (2S_1+(n-2)S_2)\sum b_{ii'} + n(T_2-T_3)\sum b_{\mu j} + nT_3 \sum b_{jj'} \\ &\quad + \{R_1-R_2+(n-1)(R_3-R_4)\}\sum b_{i\mu} \\ &\quad + (R_2+(n-1)R_4)\sum b_{ij}. \end{aligned} \tag{4.4.16}$$

The three equations (4.4.14), (4.4.15) and (4.4.16) give us the solutions of $b_{\mu\mu}$, $\sum b_{\mu j}$ and $\sum b_{i\mu}$.

Let us consider the normal equation obtained by differentiating (4.4.4) wrt any $\beta_{\lambda\lambda'}$, $1 \leqq \lambda < \lambda' \leqq n$, which can be written as

$$\begin{aligned}
&\textstyle\sum_u x_{\lambda u} x_{\lambda' u} y_u \\
&= (C - D)(b_\lambda + b_{\lambda'}) + D \sum b_i + R_3 \sum b_{jj} + (E - 2F + G) b_{\lambda\lambda'} \\
&\quad + (F - G)(\textstyle\sum b_{\lambda i} + \sum b_{\lambda' i}) + G \sum b_{ij} + R_4 \sum b_{jj'} \\
&\quad + (S_1 - S_2)(\textstyle\sum b_{\lambda j} + \sum b_{\lambda' j}) + S_2 \sum b_{ij}.
\end{aligned} \tag{4.4.17}$$

It can be observed that (4.4.17) contains only one unknown $b_{\lambda\lambda'}$ since all others are known from the preceding steps, so that it can be solved easily.

Similarly the normal equation for $b_{\mu\mu'}$, $1 \leqq \mu < \mu' \leqq p$, is given by

$$\begin{aligned}
&\textstyle\sum_u z_{\mu u} z_{\mu' u} y_u \\
&= Q_2 \textstyle\sum b_i + (K - M)(b_{\mu\mu} + b_{\mu'\mu'}) + M \sum b_{jj} + T_3 \sum b_{ii'} \\
&\quad + (L - 2M + N) b_{\mu\mu'} + (M - N)(\textstyle\sum b_{\mu j} + \sum b_{\mu' j}) + N \sum b_{jj'} \\
&\quad + (T_2 - T_3)(\textstyle\sum b_{i\mu} + \sum b_{i\mu'}) + T_3 \sum b_{ij}.
\end{aligned} \tag{4.4.18}$$

Finally, the normal equation for $b_{\lambda\mu}$, $1 \leqq \lambda \leqq n$, $1 \leqq \mu \leqq p$, is given by

$$\begin{aligned}
&\textstyle\sum_u x_{\lambda u} z_{\mu u} y_u \\
&= (P_1 - P_2) b_\lambda + P_2 \textstyle\sum b_i + (T_1 - T_2) b_{\mu\mu} + T_2 \sum b_{jj} \\
&\quad + (S_1 - S_2) \textstyle\sum b_{\lambda i} + S_2 \sum b_{ii'} + (T_2 - T_3) \sum b_{\mu j} + T_3 \sum b_{jj'} \\
&\quad + (R_1 - R_2 - R_3 + R_4) b_{\lambda\mu} + (R_2 - R_4) \textstyle\sum b_{\lambda j} + (R_3 - R_4) \sum b_{i\mu} \\
&\quad + R_4 \textstyle\sum b_{ij}.
\end{aligned} \tag{4.4.19}$$

Equation (4.4.19) gives us the estimates $b_{\lambda\mu}$ so that by symmetry the solution for any λ and μ can be written down.

Thus it has been possible to estimate all the parameters of the model (4.4.2) by first solving five equations, then two independent sets of three equations each and finally three equations each with only one unknown.

After the parameters of the model are estimated the other procedures of analysis including the finding of the variances and covariances of the estimates follow as usual.

5. An illustrative example. We now illustrate the above methods by analysing the data reported by Claringbold [1] relating to an experiment to study the joint action of oestrogens on the vagina of the overiectomized mouse in which the quantal response is cornification of the vaginal epithelium.

Three oestrogens, namely, oestrone (x_1), oestradiol (x_2) and oestriol (x_3) are administered either independently or as mixtures where x_1, x_2, x_3 are the

TABLE 1

Percentage response of groups of 12 ovariectomized mice to joint intravaginal administration of oestrone, oestradiol and oestriol

Oestrogen mixtures			Response at the three levels of the process variable		
x_1	x_2	x_3	z_{-1}	z_0	z_1
1	0	0	17	42	83
$\frac{2}{3}$	$\frac{1}{3}$	0	0	33	75
$\frac{1}{3}$	$\frac{2}{3}$	0	33	33	75
0	1	0	58	58	100
0	$\frac{2}{3}$	$\frac{1}{3}$	17	33	67
0	$\frac{1}{3}$	$\frac{2}{3}$	33	33	58
0	0	1	25	50	42
$\frac{1}{3}$	0	$\frac{2}{3}$	25	42	42
$\frac{2}{3}$	0	$\frac{1}{3}$	0	25	75
$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	17	25	58
1	0	0	42	50	75
$\frac{1}{2}$	$\frac{1}{2}$	0	17	33	83
0	1	0	75	67	83
0	$\frac{1}{2}$	$\frac{1}{2}$	33	42	67
0	0	1	50	42	67
$\frac{1}{2}$	0	$\frac{1}{2}$	17	42	58
$\frac{2}{3}$	$\frac{1}{6}$	$\frac{1}{6}$	33	33	58
$\frac{1}{6}$	$\frac{2}{3}$	$\frac{1}{6}$	50	50	58
$\frac{1}{6}$	$\frac{1}{6}$	$\frac{2}{3}$	33	33	50
$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	17	42	42

mixture variables denoting the proportions of the oestrogens in each mixture so that the factor space is a 2-dimensional simplex. Further, the following three doses of each mixture were tried $z_{-1} = 0.75 \times 10^{-4}\ \mu g$, $z_0 = 1.50 \times 10^{-4}\ \mu g$ and $z_1 = 3.00 \times 10^{-4}\ \mu g$. Thus there is a single process variable (z) at three levels conveniently denoted by -1, 0 and 1. The design and the data as reported by Claringbold [1] are presented in Table 1.

5.1. *The analysis.* The design is obviously a symmetric simplex $\times$ factorial design with three groups having points of the types $(1\,0\,0)$, $(\frac{1}{2}\,\frac{1}{2}\,0)$, $(\frac{1}{3}\,\frac{2}{3}\,0)$, $(\frac{1}{6}\,\frac{1}{6}\,\frac{2}{3})$ and $(\frac{1}{3}\,\frac{1}{3}\,\frac{1}{3})$. Since the observations are percentages, an angular transformation of the data is made, the variable y now denoting the observed response on the transformed scale.

For illustration we shall consider the fitting of the following two types of models:

CASE (i). Fitting quadratic models at each level of the process variable.

At the level z_{-1} we have the following values of the constants in (2.2.3) from the 20 points:

$$A = 4.3333, \quad C = 0.5185, \quad E = 0.2114, \quad G = 0.$$
$$B = 1.1667, \quad D = 0.1296, \quad F = 0.0432,$$

Further

$$\sum x_1y = 163.7471, \qquad \sum x_1x_2y = 29.1448,$$
$$\sum x_2y = 248.4985, \qquad \sum x_1x_3y = 27.1965,$$
$$\sum x_3y = 209.1600, \qquad \sum x_2x_3y = 32.2463.$$

Substituting these values in (2.2.12) and (2.2.15) we get the estimates of the parameters and finally the response surface:

$$(5.1.1) \quad y = 27.12\, x_1 + 59.36\, x_2 + 43.99\, x_3 - 72.68\, x_1x_2 - 48.73\, x_1x_3 - 93.25\, x_2x_3 .$$

The sum of squares due to regression is 2635.25. The error sum of squares obtained from observations on the four repeated points (1 0 0), (0 1 0), (0 0 1), ($\frac{1}{3}$ $\frac{1}{3}$ $\frac{1}{3}$) works out to 274.66. The s.s. due to lack of fit is then obtained by subtraction of these from the total s.s. 3938.97.

Similar analyses were made on data at levels z_0 and z_1 also. The response surfaces together with Analysis of Variance Table are shown.
Response surfaces:

$$(5.1.2) \quad \text{At} \quad z_0 : y = 41.45\, x_1 + 52.01\, x_2 + 42.8\, x_3 - 41.60\, x_1x_2 - 19.91\, x_1x_3 - 39.78\, x_2x_3 - 49.$$

$$(5.1.3) \quad \text{At} \quad z_1 : y = 64.66\, x_1 + 76.63\, x_2 + 47.85\, x_3 - 49.99\, x_1x_2 - 35.45\, x_1x_3 - 49.74\, x_2x_3 .$$

ANALYSIS OF VARIANCE TABLE

Source	d.f.	*M.S.* at z_{-1}	*F*	*M.S.* at z_0	*F*	*M.S* at z_1	*F*
Regression	5	527.07	7.67*	119.28	5.33	323.17	2.80
Lack of fit	10	102.91		6.83		47.14	
Error	4	68.66		22.39		115.38	

* Significant at 5% level.

The regression is significant only at z_{-1} while it is barely significant (at 10% level) at z_0.

However, an overall empirical conclusion that can be drawn from the three surfaces (5.1.1), (5.1.2) and (5.1.3) is that while the percentage cornification generally reduces at mixtures near the centroid because of the negative joint effects, the response surely increases as the dose of the mixture of the oestergens increases.

Case (ii). Fitting of a quadratic model including the process variable.

The model corresponding to (4.4.2) is

$$(5.1.4) \quad y = \beta_1x_1 + \beta_2x_2 + \beta_3x_3 + \beta_{11}z_1^2 + \beta_{12}x_1x_2 + \beta_{13}x_1x_3 + \beta_{23}x_2x_3 + \beta_1'x_1z + \beta_2'x_2z + \beta_3'x_3z.$$

The symmetric simplex × factorial design has in this case 60 points. The values of the constants in (4.4.5) are

$$A = 13, \quad B = 7/2, \quad C = 14/9, \quad D = 7/18, \quad E = 137/216,$$

$$F = 7/54, \quad H = 40, \quad J = 40, \quad Q_1 = 40/3, \quad R_1 = 26/3, \quad R_3 = 7/3.$$

All other constants are zero. Substituting these values in equations (4.4.6), (4.4.7), (4.4.8) and (4.4.10) we get,

$$\text{(5.1.5)} \qquad \sum_{1 \leqq i \leqq 3} \left(\sum x_i y\right) = 20 \sum b_i + 40\, b_{11} + 3.5 \sum b_{ii'}\,,$$

$$\text{(5.1.6)} \qquad \sum z^2 y = 13.33 \sum b_i + 40\, b_{11} + 2.33 \sum b_{ii'}\,,$$

$$\text{(5.1.7)} \qquad \sum_{1 \leqq i < i' \leqq 3} \left(\sum x_i x_{i'} x_\lambda\right) = 3.5 \sum b_i + 7\, b_{11} + 0.894 \sum b_{ii'}$$

$$\text{(5.1.8)} \qquad \sum_{1 \leqq i \leqq 3} \left(\sum x_i z y\right) = 13.33 \sum b_i'.$$

After obtaining as usual the values of $\sum x_1 y$, $\sum x_1 x_2 y$ etc., from the transformed observations and using them in the above equations, we get

$$\sum b_i = 144.89, \qquad b_{11} = 3.82,$$

$$\sum b_{ii'} = -152.60, \qquad \sum b_i' = 36.34.$$

From equations (4.4.11) and (4.4.12) we have

$$\text{(5.1.9)} \qquad \sum x_\lambda y = 9.500\, b_\lambda + 3.500 \sum b_i + 13.333\, b_{11} + 1.667 \sum b_{\lambda i} + 0.389 \sum b_{ii'}\,,$$

$$\text{(5.1.10)} \qquad \sum \left(\sum x_\lambda x_i y\right) = 1.167\, b_\lambda + 1.944 \sum b_i + 4.667\, b_{11} + 0.50 \sum b_i + 0.259 \sum b_{ii'}\,.$$

Substituting the values of $\sum b_i$, b_{11}, $\sum b_{ii'}$ and $\sum b_i'$ in these equations, we get

$$b_1 = 41.99, \qquad \sum b_{1i} = -91.22,$$

$$b_2 = 60.32, \qquad \sum b_{2i} = -118.05,$$

$$b_3 = 42.54, \qquad \sum b_{3i} = -97.00.$$

Again, from the equation (4.4.17) we get

$$\text{(5.1.11)} \qquad \sum x_\lambda x_{\lambda'} y = 1.167\, (b_\lambda + b_\lambda') + 0.389 \sum b_i + 2.333\, b_{11} + 0.375\, b_{\lambda\lambda'} + 0.129 \left(\sum b_{\lambda i} + \sum b_{\lambda' i}\right)$$

from which we get

$$b_{12} = -55.93, \qquad b_{13} = -34.90, \qquad b_{23} = -61.74$$

Again, from equation (4.4.19)

$$\text{(5.1.12)} \qquad \sum x_\lambda z y = 6.33\, b_\lambda' + 2.33 \sum b_i'.$$

Therefore

$$b_1' = 20.06, \qquad b_2' = 11.78, \qquad b_3' = 4.50$$

Thus we have the response surface,

$$(5.1.13)\quad \begin{aligned} y = {} & 41.99\, x_1 + 60.32\, x_2 + 42.54\, x_3 + 3.82\, z^2 - 55.93\, x_1x_2 - 34.90\, x_1x_3 \\ & - 61.74\, x_2x_3 + 20.06\, x_1z + 11.78\, x_2z + 4.50\, x_3z. \end{aligned}$$

The analysis of variance is thus obtained as:

Source	d.f.	*M.S.*	*F*
Regression	9	1183.41	17.20**
Lack of fit	38	48.15	
Error	12	68.81	

** Significant at 1% level.

The regression in this case can be seen to be highly significant and the fit of the quadratic model is also quite adequate.

Regarding the effects of oestrogens, while the earlier remarks hold, it can be observed from (5.1.13) that the dose has an increasing effect on response.

Variances and Covariances of the estimates. From equations (5.1.5), (5.1.6) and (5.1.7) we can obtain the solution of b_{11} as

$$(5.1.14)\qquad b_{11} = 0.07 \sum z^2y - 0.05 \sum (\sum x_iy).$$

Similarly from (5.1.9) and (5.1.10)

$$(5.1.15)\quad \begin{aligned} b_\lambda = {} & 0.15 \sum x_\lambda y - 0.34 \sum (\sum x_\lambda x_i y) + 0.04 \sum (\sum x_i y) \\ & - 0.05 \sum z^2 y - 0.02 \sum (\sum x_i x_{i'} y). \end{aligned}$$

Again from (5.1.11)

$$(5.1.16)\quad \begin{aligned} b_{\lambda\lambda'} = {} & 2.67 \sum x_{\lambda\lambda'} y - 0.34 (\sum x_\lambda y + \sum x_{\lambda'} y) \\ & + 0.10 \{\sum (\sum x_\lambda x_i y) + \sum (\sum x_{\lambda'} x_i y)\} \\ & - 0.02 \sum (\sum x_i y) + 1.64 \sum (\sum x_i x_{i'} y). \end{aligned}$$

And from (5.1.12)

$$(5.1.17)\qquad b_\lambda' = 0.16 \sum x_\lambda z y - 0.03 \sum (\sum x_i z y).$$

Therefore from (5.1.14), (5.1.15), (5.1.16) and (5.1.17) we get the following variances and covariances of the estimates by collecting the appropriate coefficients:

$$\begin{aligned} V(b_{11}) &= 0.07\hat{\sigma}^2, & \text{Cov}\,(b_{ii'}b_j') &= -0.02\hat{\sigma}^2, \\ V(b_i) &= 0.19\hat{\sigma}^2, & \text{Cov}\,(b_{ij}b_{ij'}) &= 1.74\hat{\sigma}^2, \\ V(b_{ij}) &= 4.51\hat{\sigma}^2, & \text{Cov}\,(b_{ij}b_{i'j'}) &= 1.64\hat{\sigma}^2, \\ V(b_i') &= 0.13\hat{\sigma}^2, & \text{Cov}\,(b_{11}b_i) &= -0.05\hat{\sigma}^2, \\ \text{Cov}\,(b_ib_j) &= 0.04\hat{\sigma}^2, & \text{Cov}\,(b_i'b_j') &= -0.03\hat{\sigma}^2, \\ \text{Cov}\,(b_ib_{ij}) &= -0.36\hat{\sigma}^2, \end{aligned}$$

where $\hat{\sigma}^2 = 68.81$ (from the analysis of variance table).

The variance of the estimated response $\hat{y}_0$ at a point $(x_{10}x_{20}x_{30}z_0)$ from the surface (5.1.13) is then obtained as in (2.3.4).

6. Acknowledgments. The authors are grateful to the referee for several suggestions to improve the quality of the paper.

One of the authors (JSM) is thankful to the Indian Council of Agricultural Research, New Delhi for the award of a Senior Research Fellowship.

REFERENCES

[1] CLARINGBOLD, P. J. (1955). Use of the simplex design in the study of joint action of related hormones. *Biometrics* **11** 174–185.

[2] DRAPER, N. R. and LAWRANCE, W. (1965). Mixture designs for three factors. *J. Roy. Statist. Soc. Ser. B* **26** 450–465.

[3] DRAPER, N. R. and LAWRENCE, W. (1965). Mixture designs for four factors. *J. Roy. Statist. Soc. Ser. B* **26** 473–478.

[4] GORMAN, J. W. and HINMAN, J. E. (1962). Simplex-lattice designs for multi-component systems. *Technometrics* **4** 463–488.

[5] MURTY, J. S. (1965). Design and analysis of experiments with mixtures (Abstract). *J. Indian Soc. Agr. Statist.* **17**.

[6] MURTY, J. S. (1966). Problems of construction and analysis of designs of experiments. Unpublished thesis submitted to the Delhi University for the award of Ph.D. degree.

[7] SCHEFFÉ, H. (1958). Experiments with mixtures. *J. Roy. Statist. Soc. Ser B* **20** 344–360.

[8] SCHEFFÉ, H. (1963). Simplex-Centroid designs for experiments with mixtures, *J. Roy. Statist. Soc. Ser. B* **25** 235–263.