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STATISTICAL METHODS OF FINDING OPTIMUM CONDITIONS FOR A CHEMICAL PROCESS

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I. INTRODUCTION

Problems involving the determination of optimum conditions are frequently encountered in laboratory, pilot-plant, and full-scale studies. Many variables have to be tested in order to find the conditions giving the greatest yield, least cost, highest purity, etc. There is no point in setting out to test all possible combinations of the various factors in such a case, because the number of experiments required would be vast; even if that number were performed, the results from the first ones would not be comparable with those from the last on account of uncontrollable changes in the apparatus and in the reactants. Moreover, the results would be of little practical value, because we do not need to know the effects of the various factors in the yield for conditions far from the best.

In 1951 Box and Wilson [1] proposed a method of finding the best conditions by an application of mathematical statistics to the design of experiments and to the analysis of results. A few tests are made; the shortest route to the optimum region is deduced after each series even though the relation of the yield to the adjustable factors is not known in functional form. As the optimum region is approached, a larger series of tests is planned, and more elaborate methods of analysis are applied in order to deduce the best conditions. The conditions are interpreted by means of models in many-dimensional "factor" space. This method differs from ordinary ones in that the experiments are designed; the number of tests, and the places corresponding to those tests in factor space, are determined from certain mathematical rules. All factors are varied together; the approach is thus different from classical methods, in which only one factor is changed in each test. The differential

approach is also extremely important, because it enables one to perform only a few tests in the early stages in order to determine the direction that subsequent tests should take. The result is that many fewer tests are needed. Moreover, the information relates not merely to the main effects, but also to the effects of interactions (the latter effects are not deducible from the classical treatment). The final step is to formulate the results as an equation that serves to define the optimum conditions, which change in response to a number of factors, e.g. variation in the properties of the reactants. This method should find application to automatic chemical and metallurgical processes, although we know of no work that has yet been done on this topic.

In this review the method is illustrated by means of examples carried through to numerical calculations, and is presented in a form such that mathematical knowledge of undergraduate standard suffices to comprehend it. Familiarity with analysis of variance and regression analysis, and with matrix algebra, is required in order to make practical use of the method. Davies[2] gives a concise and convenient presentation of these subject in an appendix. Collaboration between a chemist and a mathematician is desirable; it is then sufficient for the chemist to be familiar with the basic ideas of the method, so that he speaks the same language as the mathematician. An ordinary calculating machine such as may be found in most laboratories will do for such calculations as are needed, though special machines can be used.

The Box-Wilson method is still under development, and methods of designing experiments are still being refined. There is as yet no practical handbook that covers the whole subject. Sufficient material is given here to illustrate the principles, although the examples do not incorporate the very latest suggestions. At the end a brief review is given of the uses of the method, together with a bibliography designed to fill any gaps.

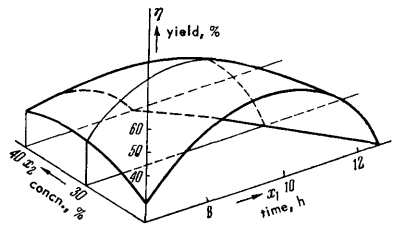


Fig. 1. The yield surface.

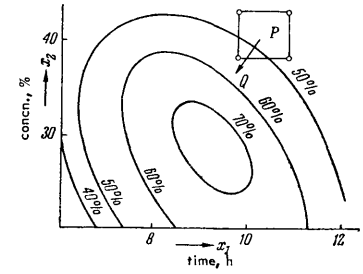


Fig. 2. Contour lines for the yield surface of Fig. 1 for a factorial experiment involving 2^2 tests.

II. DESCRIPTION OF THE METHOD †

Let us suppose that the yield η (or some other "response") depends on k quantitative factors x_1 to x_k. We call the function

$$\eta = \varphi(x_1, x_2, \ldots x_k)$$

the response function. If there are two independent variables, the function can be taken as the equation of a surface in three-dimensional space (Fig. 1). The surface can be represented on a plane as contours of equal yield, as in Fig. 2. Our problem is to pass from some point P to a point Q on a contour of higher yield. [We can use contour surfaces (Fig. 3) to represent the situation if there are three independent variables].

We can represent the response function for two independent variables by means of a terminated Taylor series (polynomial of degree n),

$$\eta = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{11} x_1^2 + \beta_{12} x_1 x_2 + \beta_{111} x_1^3 + \ldots, \qquad (1)$$

in which β_0 is the zero-order coefficient, β_1 and β_2 are the first-order coefficients, β_{ij} $(i, j = 1, 2)$ are the second-order coefficients, and so on. Now

$$\beta_1 = \frac{\partial \varphi}{\partial x_1}, \quad \beta_2 = \frac{\partial \varphi}{\partial x_2}, \quad \beta_{11} = \frac{1}{2}\frac{\partial^2 \varphi}{\partial x_1^2}, \quad \beta_{22} = \frac{1}{2}\frac{\partial^2 \varphi}{\partial x_2^2}, \text{ and } \beta_{12} = \frac{\partial^2 \varphi}{\partial x_1 \partial x_2}$$

The β are also called regression coefficients; here β_1 and β_2 are measures of the linear effects, β_{11} and β_{22} are measures of the quadratic effects, and β_{12} is a measure of the linear-linear interaction.

If we neglect the terms of second and higher orders in (1), we are left with the equation of a plane,

$$\eta = \beta_0 + \beta_1 x_1 + \beta_2 x_2,$$

in which β_1 represents the slope of the plane in the direction of the first variable, and β_2 does the same for the second variable. The surface may be approximated by means of a plane only in some bounded region far from a turning point.

The general principles used to find the maximum value of η may be illustrated as follows for the case of one independent variable, if we need take only terms up to the third order in (1). The least-squares method is used to find the parameters of the cubic giving the best fit, namely

$$Y = b_0 + b_1 x_1 + b_{11} x_1^2 + b_{111} x_1^3, \qquad (2)$$

in which Y is calculated from (2) and differs both from the true value and from the experimentally observed y_i. We

† A shortened and revised version of chapter 11 of Davies's[2] book.

equate the first derivative to zero:

$$\frac{dY}{dx_1} = b_1 + 2b_{11}x_1 + 3b_{111}x_1^2 = 0. \qquad (3)$$

This equation gives us the x_1 corresponding to the peak. The process is readily extended to k independent variables.

In practice this implies a large number of tests; for example, if we wish to examine five factors each at four levels, we must perform $4^5 = 1024$ tests. Sequential analysis [26] enables us to reduce that number greatly; let us consider the case of two independent variables. We assume that the initial conditions correspond to a point P (Fig. 2) far from the peak. The surface near P can be represented as a plane specified by the coefficients b_1 and b_2, which are found (by means of the least-squares method) from a few tests made for conditions in the region of P. Then b_1 and b_2 indicate the conditions to be used in order to reach point Q, which corresponds to a higher yield. Fresh values of b_1 and b_2 are found for Q, and so on. The process becomes more and more troublesome as the peak is approached; a plane becomes an unsatisfactory approximation to the surface, because the second-order constants become more important. The method cannot locate the peak; all it can do is to bring us to the almost-stationary region, in which the b become comparable with the errors of the measurements. The position of the peak (if one exists) can be found from a few tests once that region has been reached. A special method (see below) is used for this purpose.

The above method is based on constructing tangent planes to the surface, not on delineating the surface itself; the results can be wrong if the surface has more than one peak, because the peak reached is determined by the position of the initial point. It is usually safe to suppose that the surface has only one peak; a second peak can arise only if the reaction mechanism alters fundamentally.

The almost-stationary region can take any of the four forms shown in Fig. 4. In a we have a maximum; in b moderate changes in x_1 and x_2 result in almost unchanged yields; in c the best yield is to be reached by decreasing x_1 and increasing x_2; in d we have a saddle point.

On reaching an almost-stationary region our next task is to determine whether that region lies near a real peak (case a) or whether the case is b or c In case c we have to determine the direction of greatest slope, while in case d we have to find the direction corresponding to the maximum upward curvature This problem is solved by performing a second set of tests sufficient to define a quadratic representing the response surface.

The point in the almost-stationary region reached as a result of the first set is determined largely by the initial point, which may have to be taken at random. The point reached may be technically extremely inconvenient (the pressure or temperature may be too high, for example); then the second set of tests has as object to find a technically convenient point providing the optimum yield.

1. Determination of the Almost-Stationary Region

Let us suppose that we have a point O such that the surface near that point can be represented as a plane. We have to find the direction of the motion required to bring us to a point P such that the yield is as large as possible. It can be shown [1] that the direction is to be found by changing the independent variables in proportion to β_1, $\beta_2 \ldots \beta_k$; the direction is that of steepest ascent and lies at right angles

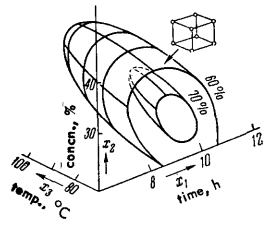


Fig. 3. Contour surfaces in three dimensional factor space for a 2^3 factorial experiment.

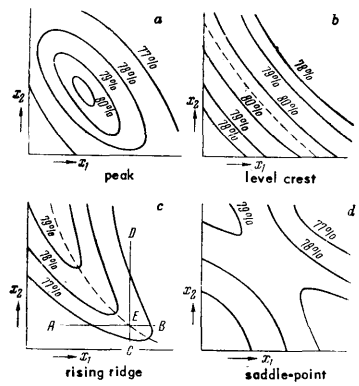


Fig. 4. Types of surface found in the almost-stationary region.

to the contour lines (surfaces).

In planning any such experiment, we must choose the amounts by which the factors are to be varied; this choice is made intuitively on the basis of previous experience. It is desirable to have the function as symmetrical as possible with respect to the factors. The number of tests is reduced very greatly if the levels are chosen properly.

Thus the first step is to determine the coefficients in

$$\eta = \beta_0 x_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_k x_k, \qquad (4)$$

(The modified form for the constant term will be found to be convenient in what follows). Consider the case of three variables; each is used at two levels, which are denoted by +1 and -1; these symbols denote that the levels are centred on O, as shown in Fig. 5. Here there are $2^3 = 8$ tests to be made. Table 1 gives the levels to be used.

It is assumed that interactions are absent, so the number of tests can be halved; for example, we can take the

TABLE 1.

Tests	Levels		
	x_1	x_2	x_3
1	−1	−1	−1
*2**	1	−1	−1
*3**	−1	1	−1
4	1	1	1
*5**	−1	−1	1
6	1	−1	1
7	−1	1	1
*8**	1	1	1

TABLE 2.

Independent variables				Yield
x_0	x_1	x_2	x_3	
1	1	−1	−1	y_2
1	−1	1	−1	y_3
1	−1	−1	1	y_5
1	1	1	1	y_8

tests marked with an asterisk in Table 1 (solid circles in Fig. 5). Since Table 1 is orthogonal †, each coefficient b can be calculated separately; any one b is determined by summing the products of the y by the corresponding independent variable, and dividing this sum by the sum of squares for that variable. Let σ_y be the standard experimental error of y; then the variance of b, $\sigma^2\{b\}$, is found by dividing σ_y^2 by the sum of the squares of the corresponding independent variable

$$b = \Sigma yx/\Sigma x^2, \qquad \sigma^2\{b\} = \sigma_y^2/\Sigma x^2 \simeq s_y^2/\Sigma x^2, \tag{5}$$

in which s_y^2 is an estimate (see below) of σ_y^2. In particular, we can compile Table 2 for this example.

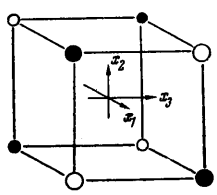


Fig. 5. Division of a complete 2^3 factorial experiment into two parts.

From the above formulae

$$\left.\begin{aligned} b_0 &= (1y_2 + 1y_3 + 1y_5 + 1y_8)/4 = \bar{y} \\ b_1 &= (1y_2 - 1y_3 - 1y_5 + 1y_8)/4 \\ &\cdots\cdots\cdots\cdots\cdots\cdots \\ &\cdots\cdots\cdots\cdots\cdots\cdots \\ \sigma^2\{b_0\} &= \sigma^2\{b_1\} = \sigma^2(b_2) = \sigma^2\{b_3\} = \frac{\sigma_y^2}{4} \end{aligned}\right\} \tag{6}$$

in which the b are estimates † of the β.

We now suppose that (4) is inadequate, being a linear approximation, and that we must include all second-order terms:

$$\eta = \beta_0 x_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{11} x_1^2 + \beta_{22} x_2^2 + \beta_{33} x_3^2 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3. \tag{7}$$

Table 3 shows how we may arrange the values for the independent variables in this equation.

We have only four tests, so we can find only four coefficients; but the second set of five columns merely repeats the first set, so we can put $b_0 \rightarrow \beta_0 + \beta_{11} + \beta_{22} + \beta_{33}$, in which the arrow denotes that the quantity on the left is an estimate of those on the right. Similarly, we have

$$b_1 \rightarrow \beta_1 + \beta_{23};\ b_2 \rightarrow \beta_2 + \beta_{13};\ b_3 \rightarrow \beta_3 + \beta_{12}.$$

The first expression may be interpreted as follows. If the surface is a plane, then b_0 (which equals $\bar{y}$) is an unbiassed estimate of the β_0, which corresponds to the centre of the area covered by the tests; but the estimate is biassed if the surface has a curvature. Again, β_{12}, β_{13}, and β_{23} are not zero if interactions occur, so b_1, b_2, and b_3 are biassed estimates of β_1, β_2, and β_3.

TABLE 3.

Independent variables										Yield
x_0	x_1	x_2	x_3	x_1^2	x_2^2	x_3^2	x_1x_2	x_1x_3	x_2x_3	
1	1	−1	−1	1	1	1	−1	−1	1	y_2
1	−1	1	−1	1	1	1	−1	1	−1	y_3
1	−1	−1	−1	1	1	1	1	−1	−1	y_5
1	1	1	1	1	1	1	1	1	1	y_8

TABLE 4.

Factor	Levels	
	−1	+1
x_1 (amount of solvent E, cm³)	200	250
x_2 (amount of C, mole/mole A)	4.0	4.5
x_3 (concentration of C, %)	90	93
x_4 (reaction time, h)	1	2
x_5 (amount of B, mole/mole A)	3.0	3.5

† Two linear functions

$$a_1x_1 + a_2x_2 \ldots + a_nx_n,$$
$$b_1x_1 + b_2x_2 \ldots + b_nx_n,$$

are said to be orthogonal if

$$a_1b_1 + a_2b_2 + \ldots a_nb_n = 0,$$

which is the condition for the absence of a linear dependence of the one function on the other. An orthogonal design is one in which the various effects are determined directly and separately. The sums of squares for all effects are then independent and additive.

† Few measurements are commonly made in any one research, and these may be treated as a random selection from some hypothetical population, which consists of all meaningful observations that might be made under those particular conditions. The statistical parameters calculated from the selections are treated as estimates of those parameters for the population. The estimates are traditionally denoted by Latin letters; the true parameters of the population by Greek letters. The estimate is termed unbiassed if it is free from systematic error.

TABLE 5.

Test	Levels					Yield y, %
	x_1	x_2	x_3	x_4	x_5	
1	−1	−1	−1	−1	−1	34.4
2	−1	−1	1	1	1	51.6
3	−1	1	−1	1	1	31.2
4	−1	1	1	−1	−1	45.4
5	1	−1	−1	1	−1	54.1
6	1	−1	1	−1	1	62.4
7	1	1	−1	−1	1	50.2
8	1	1	1	1	−1	58.6

These second-order effects must always be considered; the question will be discussed in detail in one of the examples given below.

Example. We have a reaction

$$A + B + C \rightarrow D + \text{other products},$$

which occurs in the presence of a solvent E; our object is to find the maximum yield of D for a given amount of A, which is the most expensive of the reactants and whose amount must remain fixed. Conditions are known that give 45% of the theoretical yield; the error of a single measurement is known to be 1% or less. Five factors are varied in Table 4; in planning the experiments, it is assumed that second-order effects are unimportant, so only $1/4$ of the total number of tests need be performed. On the other hand, theoretical considerations indicate that x_1 may interact with x_3, and this interaction was therefore isolated in the experimental design. Table 5 shows the plan of the tests; here we have the defining relations

$$x_4 = x_1x_2x_3 \text{ and } x_5 = -x_2x_3,$$

and further

$$1 = x_1^2 = x_2^2 = x_3^2 = x_4^2 = x_5^2 = x_1x_2x_3x_4 = -x_2x_3x_6 = -x_1x_4x_5.$$

Using (6) we get the estimates

$b_0 \rightarrow +\beta_0(+\beta_{11}^* + \beta_{22} + \beta_{33}^* + \beta_{11} + \beta_{55})$	48.5
$b_1 \rightarrow +\beta_1(-\beta_{15})$	7.9
$b_2 \rightarrow +\beta_2(-\beta_{25})$	−2.2
$b_3 \rightarrow +\beta_3(-\beta_{25})$	6.0
$b_{123} \rightarrow +\beta_4(-\beta_{15})$	0.4
$b_{23} \rightarrow +\beta_5(-\beta_{14} + \beta_{23})$	−0.4
$b_{13} \rightarrow 0(+\beta_{13}^* + \beta_{24})$	−1.8
$b_{12} \rightarrow 0(+\beta_{12} + \beta_{34})$	0.2

Assuming $\sigma = 1$, the standard error of the estimates is about 0.4. The asterisked quantities are ones corresponding to effects that might be expected on chemical grounds, and it is clear that b_{13} corresponds to a real effect (to a finite β_{13}). However, this is small relative to the first-order effects, so the linear approximation is adopted. Table 6 gives the derivation of the direction in which the greatest effect should be found.

The first line in Table 6 gives results for the base level; the second, those for unit change; the third, the coefficients b; the fourth, the product of unit change by the corresponding slope; the fifth, the changes in level corresponding to a change of 10 cm³ in x_1 for x_2 to x_5; the sixth, calculations for possible tests. Theoretical considerations indicate that a large increase in yield is to be expected, so test *9* is actually performed and gives a yield of 80%; test *10* gives 79.4%. It is difficult to attach much weight to this result, so a fresh series is planned with test *10* as the base point.

Before turning to the next stage, it should be pointed out that a failure to find any significant increase in yield in the first set of tests might be caused either by the effects that have been neglected or by experimental errors much larger than those anticipated. In either case the number of tests must be increased. It will be shown below how the first- and second-order effects may be determined simultaneously.

The unit changes may be adjusted as desired when the second set of tests is being designed. Two aspects have to be considered here.

1. Some effects appear small relative to others either because the base levels for those factors are close to the levels giving the maximum yield (certain other factors remaining unchanged), or because the unit changes are too small, or because the result is not dependent on those factors.

This situation can be clarified by means of increased unit changes; the yield is affected if the first two explanations apply, but there is no change if the last applies. In the experiment described above the result is not dependent on x_4 and x_5, so the unit changes for those factors are increased.

2. The unit changes for the factors x_1 to x_3 are chosen with due allowance for the facts that second-order effects become more important as the maximum is approached and that simultaneously the slopes become small and comparable with the experimental error. Any increase in the unit changes will tend to accentuate the first difficulty and to reduce the second. The effects of x_1 to x_3 are large in this case, and β_{13} is clearly finite, so it is decided to decrease the unit changes for those factors.

TABLE 6.

	x_1, cm³	x_2, mole	x_3, %	x_4, h	x_5, mole
Base level	225	4.25	91.5	1.5	3.25
Unit change	25	0.25	1.5	0.5	0.25
Coefficient b	7.9	−2.2	6.0	0.4	0.4
Unit change × b	197.5	−0.55	9.0	0.2	0.1
Change in level per 10 cm³ change in x_1	10	−0.028	0.456	0.010	0.005
	225	4.25	91.5	1.5	3.25
	235	4.22	92.0	1.5	3.25
	245	4.19	92.4	1.5	3.26
	255	4.17	92.9	1.5	3.26
Test 9	265	4.14	93.3	1.5	3.27
	275	4.11	93.8	1.6	3.27
Test 10	285	4.08	94.2	1.6	3.28
	295	4.06	94.7	1.6	3.28
	305	4.03	95.1	1.6	3.29

TABLE 7.

Factor	Levels	
	−1	+1
x_1 (amount of solvent E, cm³)	280	310
x_2 (amount of C, mole/mole A)	3.85	4.15
x_3 (concentration of C, %)	94	96
x_4 (reaction time, h)	2	4
x_5 (amount of B, mole/mole A)	3.5	5.5

TABLE 8.

Test	Levels					Yield y, %
	x_1	x_2	x_3	x_4	x_5	
11	−1	−1	−1	−1	1	77.1
12	−1	−1	1	1	1	69.0
13	−1	1	−1	1	−1	75.5
14	−1	1	1	−1	−1	72.6
15	1	−1	−1	1	−1	67.9
16	1	−1	1	−1	−1	68.4
17	1	1	−1	−1	1	71.5
18	1	1	1	1	1	63.4

Table 7 gives the levels used in the second set and Table 8 gives the design. Here we have

$$x_4 = x_1x_2x_3 \text{ and } x_5 = x_1x_2$$

and further

$$1 = x_1^2 = x_2^2 = x_3^2 = x_4^2 = x_5^2 = x_1x_2x_3x_4 = x_1x_2x_5 = x_3x_4x_5.$$

Some changes have been made in the design; here b_{12} has been used as an estimate of β_5, because the first set showed that the effects corresponding to β_{12} and β_{34} are absent. The calculated results are

$b_0 \rightarrow \beta_0 (+ \beta_{11} + \beta_{22} + \beta_{33} + \beta_{44} + \beta_{55})$	70.7
$b_1 \rightarrow \beta_1 (+ \beta_{25})$	−2.9
$b_2 \rightarrow \beta_2 (+ \beta_{15})$	0.1
$b_3 \rightarrow \beta_3 (+ \beta_{15})$	−2.3
$b_{123} \rightarrow \beta_4 (+ \beta_{35})$	−1.7
$b_{12} \rightarrow \beta_5 (+ \beta_{12} + \beta_{34})$	−0.4
$b_{13} \rightarrow 0 (+ \beta_{13} + \beta_{24})$	0.4
$b_{23} \rightarrow 0 (+ \beta_{23} + \beta_{14})$	−0.4

Assuming $\sigma = 1$, the standard error of the estimates is 0.4.

Here b_0 is larger than in the first set but less than in test *10*, so the surface must be curved. Coefficients β_{11}, β_{22}, etc. are negative near the peak, so b_0 underestimates β_0. Further, b_1 to b_3 have changed in sign, so the best point has been passed. The range of variation in x_4 is very different from that used in test *10*; the large negative value now found for β_4 indicates that the small value found previously was caused by the closeness to a conditional maximum, not by the absence of any effect. The sign indicates that we must return towards the earlier conditions. β_5 is still small, so it is clear that x_5 is not important.

Table 9 gives values calculated for further tests. The yields from tests *19* to *21* are 80.8, 84.0, and 81.5% respectively; the conditions of test *20* correspond to the almost-stationary region, and it was decided at this point to transfer the trials from the laboratory to a pilot plant.

TABLE 9.

Test	x_1, cm³	x_2, mole	x_3, %	x_4, h	x_5, mole
19	295	4.0	95.0	3.0	4.5
	285	4.0	94.5	2.6	4.4
20	275	4.0	93.9	2.2	4.3
	265	4.0	93.4	1.8	4.2
21	255	4.0	92.8	1.4	4.1

2. Tests on the Almost-Stationary Region

The reaction is

$$A + B + C \rightarrow D + E + \text{other products.}$$

The objects here are to increase the yield of D and to decrease the yield of E (the product is useless if the proportion of E exceeds a certain level). The levels of variation are taken as the same for both factors. The initial yields are 64% for D and 15% for E; two sets of tests give 92% for D and less than 0.5% for E. Subsequently, a second series of tests was performed in order to maximise the yield of E; three sets raise it to 70%. The techniques used are those described above.

TABLE 10.

Test	Levels		Yield y, %
	x_1	x_2	
1	−1	−1	71.7
2	0	−1	79.2
3	1	−1	80.1
4	−1	0	75.2
5	0	0	81.5
6	1	0	79.1
7	−1	1	76.3
8	0	1	80.2
9	1	1	75.8

TABLE 11.

Test	Independent variables						Yield y, %
	x_0	x_1	x_2	$x_1^2 - \frac{2}{3}$	$x_2^2 - \frac{2}{3}$	x_1x_2	
1	1	−1	−1	1/3	1/3	1	71.7
2	1	0	−1	−2/3	1/3	0	79.2
3	1	1	−1	1/3	1/3	−1	80.1
4	1	−1	0	1/3	−2/3	0	75.2
5	1	0	0	−2/3	−2/3	0	81.5
6	1	1	0	1/3	−2/3	0	79.1
7	1	−1	1	1/3	1/3	−1	76.3
8	1	0	1	−2/3	1/3	0	80.2
9	1	1	1	1/3	1/3	1	75.8

The nature of the surface must be established once the almost-stationary region has been reached. Let us suppose that there are two independent variables; the first- and second-order effects can be determined by means of 3^2 tests. The levels used are -1, 0, and +1; Table 10 gives the matrix used in designing the series. It is supposed that the surface can be represented adequately by the second-degree equation

$$\eta = \beta_0x_0 + \beta_1x_1 + \beta_2x_2 + \beta_{11}x_1^2 + \beta_{22}x_2^2 + \beta_{12}x_1x_2 \ldots \quad (8)$$

It is more convenient to use (8) in a slightly different form. The design of Table 10 has the following properties:

$$\sum x_1/n = \sum x_2/n = \sum x_1x_2/n = 0 ,$$

$$\sum x_1^2/n = \sum x_2^2/n = {}^2/_3 .$$

From (8) we find that the mean η, denoted by η_0, is given by

$$\eta_0 = \beta_0 + {}^2/_3\beta_{11} + {}^2/_3\beta_{22}.$$

We subtract this from (8) to get

$$\eta = \eta_0 x_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{11}(x_1^2 - {}^2/_3) + \beta_{22}(x_2^2 - {}^2/_3) + \beta_{12} x_1 x_2 \ldots \quad (9)$$

The estimates are as before, except that b_0 (for β_0) is replaced by $\overline{y}$ (for η_0). We can find b_0 from

$$b_0 = \overline{y} - {}^2/_3 b_{11} - {}^2/_3 b_{22}. \quad (10)$$

Table 11 gives the values of the independent variables and the corresponding η. Now (9) implies that the sum of the products is zero for any two columns of independent variables. The orthogonality then gives us the simple expressions

$$\left.\begin{aligned} b &= \Sigma yx/\Sigma x^2 \\ \sigma^2\{b\} &= \sigma^2/\Sigma x^2 \end{aligned}\right\}, \quad (11)$$

and the sum of the squares (for the analysis of variance for the b) as

$$(\Sigma yx)^2/\Sigma x^2. \quad (12)$$

Table 12 gives the results; at the bottom we have the total sum of squares of the deviations, which is used in estimating the scatter of the observed quantities about the values predicted by the regression equation. There are three degrees of freedom, so the variance is $0.38/3 \simeq 0.13$. Here σ^2 is estimated as about 0.6 (from previous experience); this is larger than 0.13 (the residual variance), so we may assume that the experimental points fit adequately a second-degree equation †.

Now b_0 is

$$b_0 = 77.68 + (3.93 \times 0.67) + (1.38 \times 0.67) = 81.22.$$

The quantities are uncorrelated, so we have

$$\sigma^2\{b_0\} = \sigma^2\{y\} + \left(\frac{2}{3}\right)^2 \sigma^2\{b_{11}\} + \left(\frac{2}{3}\right)^2 \sigma^2\{b_{22}\} = 0.5555\sigma^2,$$

TABLE 12.

Constant	Σx^2	Σyx	$\Sigma yx/\Sigma x^2$	Degrees of freedom	$(\Sigma yx)^2/\Sigma x^2$	
η_0	9	699.1	77.68	1	54304.53	
β_1	6	11.8	1.97	1	23.21	
β_2	6	1.3	0.22	1	0.28	
β_{11}	2	— 7.87	— 3.93	1	30.97	78.10
β_{22}	2	— 2.77	— 1.38	1	3.84	
β_{12}	4	— 8.9	— 2.22	1	19.80	
Deviation from the regression line*					0.38	
Sum					54383.01	

* The regression equation is the equation relating one variable to the other variables under conditions in which random errors cause a spread in one or more of the variables.

† This statistical analysis may be illustrated by a simpler example. Let us suppose that we wish to construct a linear calibration graph from n quantities y_1 to x_n, which correspond to values x_1 to x_n. We find b_0 and b_1 by means of the least-squares method; it is usual to test for linearity at this stage by means of the F test (a test for the statistical significance of the variance ratio), which is used to compare the variance representing the scatter of the points about the line with the variance arising from experimental error. The assumption as to the linearity is justified if the ratio is statistically without significance. This means that the scatter is controlled solely by the errors of experiment, so a first regression equation represents the results adequately.

the final results being

$$b_0 = 82.22 \pm 0.58 \quad b_{11} = -3.93 \pm 0.55,$$
$$b_1 = 1.97 \pm 0.32 \quad b_{22} = -1.38 \pm 0.55,$$
$$b_2 = 0.22 \pm 0.32 \quad b_{12} = -2.22 \pm 0.39,$$
$$\sigma^2 = 0.6 \text{ (from previous experience).}$$

In particular b_2 does not differ significantly from zero, but we have no sufficient theoretical reason for putting β_2 equal to zero, so we adopt 0.22 as the best estimate of β_2.

Thus a quadratic equation gives an adequate description of the response function in the range covered by the tests:

$$Y = 81.22 + 1.97x_1 - 0.22x_2 - 3.93x_1^2 - 1.38x_2^2 - 2.22x_1x_2.$$

The figure corresponding to this equation is an ellipse; Fig. 6 shows the contours for $Y = 80\%$ and $Y = 75\%$. For any given x_1 we may find the x_2 corresponding to a particular yield, and so on.

A three-dimensional model may be used to interpret the behaviour of a system having three independent variables. No model can represent more complex cases; analysis of the equation (in canonical form) must suffice. When there are two variables, the canonical form is

$$Y - Y_S = B_{11}X_1^2 + B_{22}X_2^2. \quad (13)$$

This corresponds to placing the origin at S and to replacing the x_1 and x_2 axes by axes X_1 and X_2. Here Y_S is the yield at S (the peak). The case considered above gives us the canonical equation

$$Y - 81.49 = -4.35X_1^2 - 0.96X_2^2$$

whose centre lies at (0.30, 0.16) (see Fig. 6).

The equation has the following meaning. The change in the yield associated with any deviation from S is given by the right-hand side of the equation; here the two coefficients on that side are negative, so any displacement from S is associated with a fall in the yield (S is in fact the peak). Fig. 7 shows the four cases that are met with in practice, namely a peak, a ridge with a level crest, a rising ridge, and a saddle point. The first is considered above; the two coefficients are negative, and the centre corresponds to the best yield. The ellipse is elongated along X_2 if $|B_{22}| < |B_{11}|$; if both coefficients are positive, the centre is a point of least yield. The saddle-point type occurs when B_{11} is negative and B_{22} is positive; the contours are then hyperbolae, and their elongation depends on the ratio of the B ($|B_{11}| > |B_{22}|$ in Fig. 6). The level-crest

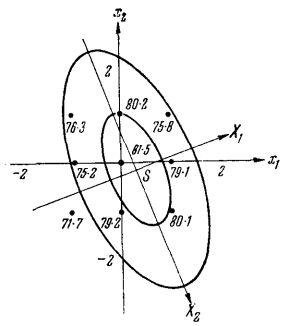


Fig. 6. The 80% and 75% ellipses and the experimentally observed yields.

type occurs if B_{11} is negative and B_{22} is zero; it forms a a common limit to the two previous types (elongation along X_2 indefinitely great). There is no unique point of best yield, but instead there is a line of best yield coincident with the X_2 axis. The equation is

$$Y - Y_S = B_{11}X_{11}^2 \qquad (14)$$

in which Y_S is the yield at any point on the X_2 axis.

The rising-ridge type occurs when the centre lies at infinity on X_2; B_{11} is negative, and any contour line is a parabola. The equation referred to an origin at any suitable point on the X_2 axis is

$$Y - Y_S = B_{11}X_1^2 + B_2X_2.$$

Here B_2 is the rate at which the yield increases, i.e. the slope, along the X_2 axis. This type is also a common limit to the first and last types; the centre is at infinity.

Only the first and last types are at all probable in practice; a case apparently of the second type is almost certainly one in which B_{22} has some small positive or negative value, so the contour lines are really curves greatly elongated along the X_2 axis, although the curvature may not be apparent. Again, it is very unlikely that the centre lies at infinity; an apparent third type is actually one in which the centre lies outside the region covered by the experiments.

The X_1 and X_2 axes will be turned relative to the x_1 and x_2 axes if $b_{12} \neq 0$, so the highest value obtained by varying x_1 will depend on the value assigned to x_2. Due allowance must be made for b_{11} and b_{22} in interpreting interaction effects.

Any equation obtained in this way is an adequate approximation to the response surface only in the neighbourhood of the region covered by the experiments. Analysis may show that the peak lies outside that region, in which case the previous tests have brought us to the area of a rising ridge. It may be impossible to draw any conclusion about the position or existence of a remote peak; attention must be devoted to the local ridge, which must form the subject of further tests.

As a second example we consider the case of a rising ridge. Assume that we have obtained an equation

$$Y - 60.64 = 3.672x_1 + 11.661x_2 - 3.514x_1^2 - 0.924x_2^2 + 2.220x_1x_2.$$

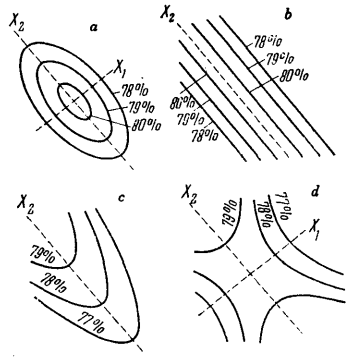


Fig. 7. Systems of contour lines for second-degree equations with two variables.

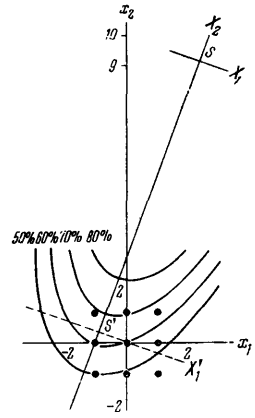


Fig. 8. Canonical representation of the region of a rising ridge (two variables).

The coordinates of S, and the predicted Y_S, are

$$x_{1S} = 2.370; \quad x_{2S} = 9.157; \quad Y_S = 109.68\%,$$

the canonical equation being

$$Y - 109.68 = 3.925X_1^2 - 0.513X_1^2,$$

and the equations relating X_1 and X_2 to x_1 and x_2 being

$$X_1 = 0.938(x_1 - 2.370) - 0.348(x_2 - 9.157),$$
$$X_2 = 0.348(x_1 - 2.370) + 0.938(x_2 - 9.157),$$

The contour lines are ellipses elongated along X_2, the maximum yield being at S; but that point is very far distant from O (the centre of the tests), so no conclusion can be drawn about the surface near S. The predicted Y_S is about 110%, which is clearly impossible. All the same, the equation represents the region near O quite adequately, and that region is the one of interest to us. Let us treat the problem in terms of the coordinates X_1 and X_2; with $x_1 = x_2 = 0$ we have the coordinates of O as

$$X_1 = 0.964; \quad X_2 = -9.414.$$

These are the shortest distances from O to the X_2 and X_1 axes respectively; the X_2 axis passes near O, and B_{22} is small, so the contour lines are drawn out in the direction of that axis. The conclusion is that we are in the neighbourhood of a rising ridge, whose direction lies parallel to the X_2 axis. We refer the canonical equation to a new origin S' whose coordinates are $X_1 = 0$, $X_2 = -9.414$ (this is the point on the ridge closest to O). In the new coordinate system

$$X_1' = X_1; \quad X_2' = X_2 + 9.414.$$

The X_1 and X_2 given by these expressions are inserted in the canonical equation to refer it to the new origin S':

$$Y - 64.22 = -3.925X_1'^2 - 0.513X_2'^2 + 9.659X_2'.$$

Here 9.659 is a measure of the slope of the crest, which is steep, so the next step is to follow the X_2' axis in the direction of increasing yield. Fig. 8 illustrates the situation; no such illustration can be given if the variables are numerous, but the canonical form often serves to elucidate the nature of the case.

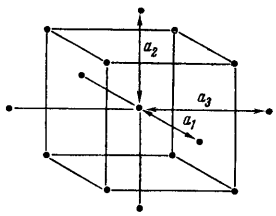


Fig. 9. Three-factor composite design.

TABLE 13.

Test	Levels			Test	Levels		
	x_1	x_2	x_3		x_1	x_2	x_3
1	−1	−1	−1	9	$-\alpha_1$	0	0
2	1	−1	−1	10	α_1	0	0
3	−1	1	−1	11	0	$-\alpha_2$	0
4	1	1	−1	12	0	α_2	0
5	−1	−1	1	13	0	0	$-\alpha_3$
6	1	−1	1	14	0	0	α_3
7	−1	1	1	15	0	0	0
8	1	1	1				

TABLE 14.

	Number of factors, k			
	2	3	4	5
Basic experiment (two levels)	2^2	2^3	2^4	2^{5}_{2} $(x_1x_2x_3x_4x_5=1)$
No. of extra points, $2k+1$	5	7	9	11
Distances of axial points from centre	1.000	1.215	1.414	1.547

3. Several Independent Variables

If the number of factors k is greater than two, the number of tests to be made is n^k (n is the number of levels), which is much larger than the number of independent variables. For example, if $k = 4$ and $n = 3$ we need $3^4 = 81$ tests in the usual factorial design, although first- and second-order effects are determined by only 15 quantities:

	Order	Number
β_0 (yield at the centre)	0	1
β_1 to β_4 (linear effects)	1	4
β_{11} to β_{44} (square-law effects)	2	4
β_{ij} ($i, j = 1$ to 4, $i \neq j$; interactions)	2	6
Total		15

The number of tests can be reduced by means of a composite design †. This design is effected as follows. Firstly, the entire system is tested at two levels in order to determine all first-order and interaction effects; then extra tests are made to establish the square-law effects.

Let us suppose that $k = 3$; here 2^3 tests are needed. If effects of order higher than the second are negligible, we can take b_0 as an estimate of $\beta_0 + \Sigma\beta_{ii}$, while the β_i and β_{ij} ($i \neq j$) are estimates of the corresponding β, and b_{123} is an estimate of the errors of experiment. A further seven tests are used to find the β_{ii}; one of these tests lies at the centre and the others lie at points whose coordinates are $\pm\alpha_1$, $\pm\alpha_2$, $\pm\alpha_3$. Table 13 gives the matrix for the design; the first eight points correspond to the 2^3 tests, the next six are those displaced from the centre, and the last is the one at the centre. Fig. 9 shows the arrangement. In general, for k factors we need an extra $2k + 1$ points, of which $2k$ are displaced (lie at $\pm\alpha_1 \ldots \pm\alpha_k$) and one lies at the centre.

This design enables us to use sequential methods. If the first set of tests shows that the first-order effects are large and that the interaction effects are slight, the extra tests are not needed; the method of steepest ascent is applied. On the other hand, the extra points are needed if second-order effects are to be allowed for.

The design may be orthogonal by giving all the α ($\alpha_1 \ldots \alpha_k$) a suitably chosen value, α. Table 14 illustrates orthogonal designs for two, three, and four factors. The second row covers the basic design for two levels, which involves 2^5_2 tests for five factors (here $x_1x_2x_3x_4x_5 = 1$); the design in that case involves a total of 2^4 tests with the extra column $x_5 = x_1x_2x_3x_4$. The fourth line gives the α for the orthogonal design, which corresponds to 3^2 tests for $k = 2$.

Example. Suppose the basic levels are such that -1 and +1 correspond to 65° and 75°; then the test corresponding to the point $(\alpha, 0, 0)$ with $\alpha = -1.215$ will fall at 70° - (5 × 1.215) = 63.9°.

We have to find the coefficients in the equation

$$\eta = \beta_0x_0 + \beta_1x_1 + \beta_2x_2 + \beta_3x_3 + \beta_{11}x_1^2 + \beta_{22}x_2^2 + \beta_{33}x_3^2 + \beta_{12}x_1x_2 + \beta_{13}x_1x_3 + \beta_{23}x_2x_3 \quad (16)$$

which we put in the more convenient form

$$\eta = \eta_0x_0 + \beta_1x_1 + \beta_2x_2 + \beta_3x_3 + \beta_{11}x_{11} + \beta_{22}x_{22} + \beta_{33}x_{33} + \beta_{12}x_1x_2 + \beta_{13}x_1x_3 + \beta_{23}x_2x_3 \quad (17)$$

in which $x_{11} = x_1^2 - \Sigma x_1^2/n$, etc. The estimates so obtained are as before, except that β_0 is found not directly but via the relation

$$b_0 = \overline{y} - b_{11}\Sigma x_1^2/n - b_{22}\Sigma x_2^2/n - b_{33}\Sigma x_3^2/n. \quad (18)$$

The sum of products between any two columns in the table of independent variables is zero if the equation is in this form and if $\alpha = 1.215$. The coefficients are found as before; we take the sum of the products of the responses by the elements of the corresponding independent variable and divide by the sum of squares of the elements of the independent variable.

Three-dimensional contour surfaces are readily derived by generalising from the two-dimensional contour lines; for example, A of Fig. 10 is a surface for which B_{11}, B_{22}, and B_{23} are negative (the figure is an ellipsoid of revolution). Here there is a point of maximum yield. Surface B is an elliptic cylinder, with B_{11} and B_{22} negative (B_{33} is zero).

† A composite design is one in which the number of tests is made not very much larger than the number of quantities to be determined (including in those quantities all second-order terms).

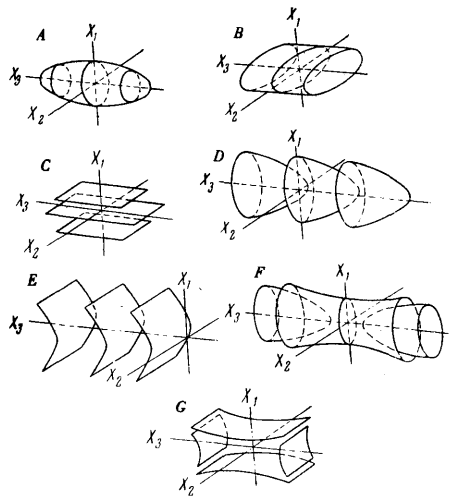


Fig. 10. Some three-dimensional contour surfaces for the almost-stationary region.

TABLE 15.

Factor	Levels −1	Levels +1	Base level	Unit change
T, °C	142	152	147	5
c, concentration of A, %	35	40	37.5	2.5
t, h	7	10	8.5	1.5

TABLE 16.

Test	Levels x_1	Levels x_2	Levels x_3	Yield y, %
1	−1	−1	−1	55.9
2	−1	−1	1	63.3
3	−1	1	−1	67.5
4	−1	1	1	68.8
5	1	−1	−1	70.6
6	1	−1	1	68.0
7	1	1	−1	63.6
8	1	1	1	62.4

TABLE 17.

Factor	Levels −2	Levels 0	Levels 2
T, °C	137	147	157
c, %	32.5	37.5	42.5
t, h	5 5	8.5	11.5

The X_3 axis is the line of maximum yield (a stationary one-dimensional level). Any deviation from that line results in a fall in the yield. Surface C is a plane parallel to the plane containing the X_2 and X_3 axes (a stationary two-dimensional level); here B_{22} and B_{33} are zero, and B_{11} is negative. Surface D is an elliptic paraboloid; the centre lies at infinity and B_{33} is zero. The origin may be displaced to a suitable point on the X_3 axis, whereupon the second-degree equation becomes:

$$Y - Y_S = B_{11}X_1^2 + B_{22}X_2^2 + B_3X_3, \qquad (19)$$

in which B_{11} and B_{22} are negative, B_{33} is zero, and B_3 is a measure of the slope of the crest along the X_3 axis. The system is equivalent to that of B, the only difference being that the crest is rising instead of level.

The reader can analyse the others for himself.

A good idea of the form of the surface may be obtained if one or more of the B are small relative to the others. The crest represents an almost-stationary region if the centre lies close to the region covered by the tests; but if the centre is far away, it is common to find that the ridge lies not far from the region covered by the tests, because the first-order coefficients will have been made small in the preceding sets of tests. In that case we select a new origin in order to determine the nature of the crest. Suppose B_{tt} is small relative to the others, for example; then the X_t axis represents the line of the crest, which passes near the experimental region. The new origin is taken near that region on the X_t axis; then the resulting equation contains a coefficient B_t, which will define the slope at the crest if the centre is far away. Again, B_{tt} and B_{ss} may both be small relative to the other B; then the plane of the X_t and X_s axes defines the plane of the ridge, which is likely to pass near the experimental region. The new origin is taken in that plane near the region; the new equation then contains coefficients B_t and B_s, which, if they are not small, point to a rising crest, whose slope may be determined as that of the line of steepest ascent.

Three variables. The reaction under investigation is of the type

$$A + B \rightarrow C + D;$$

the final product is a mixture of C and D with residual A and B. The problem is to obtain the best yield of C subject to the condition that the proportion of D must not exceed 20%. The factors that may be varied are the temperature (T), the initial concentration of A (c), and the reaction time (t); the initial amount of B is kept constant. A 2^3 factorial experiment is first performed; Table 15 gives the levels, the unit changes being

$$\left.\begin{aligned} x_1 &= (T - 147)/5 \\ x_2 &= (c - 37.5)/2.5 \\ x_3 &= (t - 8.5)/1.5 \end{aligned}\right\}. \qquad (20)$$

Table 16 gives the design and the results. The usual formulae lead to the following estimates:

b_0	$\rightarrow \beta_0 + \beta_{11} + \beta_{22} + \beta_{33}$	65.64 ± 0.4
b_1	$\rightarrow \beta_1$	1.76 ± 0.4
b_2	$\rightarrow \beta_2$	1.19 ± 0.4
b_3	$\rightarrow \beta_3$	-0.01 + 0.4
b_{12}	$\rightarrow \beta_{12}$	-3.09 ± 0.4
b_{13}	$\rightarrow \beta_{13}$	-2.19 ± 0.4
b_{23}	$\rightarrow \beta_{23}$	-1.21 ± 0.4
b_{123}	$\rightarrow 0$	(0.31 ± 0.4)

Previous experience indicates that the standard experimental error is about 1%. It is clear that the three interaction effects are large relative to the first-order effects, so no useful result is to be expected from the steepest-ascent method. Seven extra points with $\alpha = 2$ are added as in Table 17; the results are given in Table 18. The design is not completely orthogonal; α has been taken as two † in

† There is no point in making α greater than three, because the higher-order interactions then tend to become important.

order to reduce the variance of the second-order coefficients. The design is orthogonal for the first-order and interaction effects, so the coefficients for those effects are calculated as above [see (5)]. We find b_0, b_{11}, b_{22} and b_{33} from the equations:

$$\begin{aligned} 15b_0 + 16b_{11} + 16b_{22} + 16b_{33} &= 976.0, \\ 16b_0 + 40b_{11} + 8b_{22} + 8b_{33} &= 1014.3, \\ 16b_0 + 8b_{11} + 40b_{22} + 8b_{33} &= 1055.1, \\ 16b_0 + 8b_{11} + 8b_{22} + 40b_{33} &= 1041.9, \end{aligned}$$

which are best solved by matrix inversion; the usual methods give the reciprocal matrix as

$$\frac{1}{288}\begin{bmatrix} 224 & -64 & -64 & -64 \\ -64 & 26 & 17 & 17 \\ -64 & 17 & 26 & 17 \\ 64 & 17 & 17 & 26 \end{bmatrix}$$

whereupon the coefficients are found in the usual way. For example,

$$b_0 = (1/288)[(976 \times 224) - (64 \times 1014.3) - (64 \times 1055.1) - (64 \times 1041.9)]$$

and

$$\sigma^2\{b_0\} = (224/288)\,\sigma^2$$

Taking $\sigma^2 = 1$, we obtain $\sigma\{b_0\} = 0.9$. The final results are

$$\begin{aligned} b_0 &= 67.711 \pm 0.9 & b_{22} &= -0.264 \pm 0.3 \\ b_1 &= 1.944 \pm 0.3 & b_{33} &= -0.676 \pm 0.3 \\ b_2 &= 0.906 \pm 0.3 & b_{12} &= -3.088 \pm 0.4 \\ b_3 &= 1.096 \pm 0.3 & b_{13} &= -2.188 \pm 0.4 \\ b_{11} &= 1.539 \pm 0.3 & b_{23} &= -1.212 \pm 0.4 \end{aligned}$$

The estimate for the residual mean square is 4.85 (five degrees of freedom); this is larger than the expected value, but is not so large as to make the second-degree approximation inapplicable. If we take 4.85 as our measure of the variance due to experimental error, we must multiply the standard deviations of all the b by $\sqrt{4.85} = 2.20$.

The equation obtained,

$$Y = 67.711 + 1.944x_1 + 0.906x_2 + 1.069x_3 - 1.539x_1^2 - 0.264x_2^2 - 0.676x_3^2 - 3.088x_1x_2 - 2.188x_1x_3 - 1.212x_2x_3,$$

must be put in canonical form. The new origin at S is found by differentiating with respect to x_1, x_2, and x_3, and equating the derivatives to zero:

$$\begin{aligned} 2b_{11} + b_{12}x_2 + b_{13}x_3 &= -b_1, \\ b_{12}x_1 + 2b_{22}x_2 + b_{23}x_3 &= -b_2, \\ b_{12}x_1 + b_{23}x_2 + 2b_{33}x_3 &= -b_3. \end{aligned}$$

In the present case we have:

$$\begin{aligned} 3.078x_1 + 3.088x_2 + 2.188x_3 &= 1.944, \\ 3.088x_1 + 0.528x_2 + 1.212x_3 &= 0.906, \\ 2.188x_1 + 1.212x_2 + 1.352x_3 &= 1.069, \end{aligned}$$

and the solutions are

$$x_{1S} = 0.60; \quad x_{2S} = 0.215; \quad x_{3S} = 0.501.$$

These give $Y_S = 68.14$. Then we use (20) to revert to the ordinary units, whereupon the coordinates of the peak are found as 147.3°, 38.04% and 9.25 h.

The canonical form

$$Y - Y_S = B_{11}X_1^2 + B_{22}X_2^2 + B_{33}X_3^2$$

is derived by finding B_{11} to B_{33} from the characteristic equation

$$f(B) = \begin{vmatrix} b_{11} - B & \frac{1}{2}b_{12} & \frac{1}{2}b_{13} \\ \frac{1}{2}b_{12} & b_{22} - B & \frac{1}{2}b_{23} \\ \frac{1}{2}b_{13} & \frac{1}{2}b_{23} & b_{33} - B \end{vmatrix}$$

TABLE 18.

Test	Levels x_1	x_2	x_3	Yield, y, %
9	0	0	0	66.9
10	2	0	0	65.4
11	−2	0	0	56.9
12	0	2	0	67.5
13	0	−2	0	65.0
14	0	0	2	63.9
15	0	0	−2	60.3

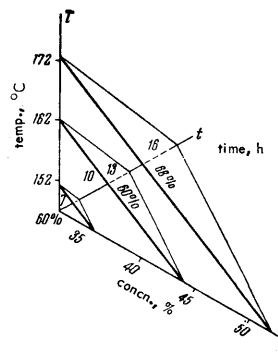


Fig. 11. Plane of almost-stationary yield (about 68%) and the planes for 60% yield.

or

$$f(B) = B^3 + \alpha B^2 + \beta B + \gamma = 0,$$

in which α, β, and γ are calculated from the known values of b_{11}, b_{12}, etc; the three roots are the coefficients in the canonical form. Here we have

$$B_{11} = -3.189, \quad B_{22} = -0.068, \quad B_{33} = 0.781.$$

The usual methods then give us the equations for the new coordinates in terms of the old as

$$\left.\begin{aligned} X_1 &= 0.7511(x_1 - x_{1S}) + 0.4884(x_2 - x_{2S}) + 0.4443(x_3 - x_{3S}) \\ X_2 &= 0.3066(x_1 - x_{1S}) + 0.3383(x_2 - x_{2S}) - 0.8897(x_3 - x_{3S}) \\ X_3 &= 0.5848(x_1 - x_{1S}) - 0.8044(x_2 - x_{2S}) - 0.1044(x_3 - x_{3S}) \end{aligned}\right\} \quad (21)$$

The canonical form is

$$Y - 68.14 = -3.190X_1^2 - 0.069X_2^2 + 0.780X_3^2\,\dagger,$$

in which B_{22} is negligible relative to B_{11} and B_{33}; it is not significantly different from zero. As B_{33} is positive, the yield should increase as we leave S in either direction along the X_3 axis, if the value is correct. Special tests do not confirm this prediction. The additional points are incorporated in further calculations, which show that B_{33} is also negligible relative to B_{11}, whose value is not essentially affected by the new results.

Neglecting B_{22} and B_{33}, we have the canonical form as

$$Y - 68.14 = -3.190X_1^2$$

† The coefficients in this equation are not exactly consistent with those given above. The same point occurs in Davies's book without explanation (Ed. of Translation).

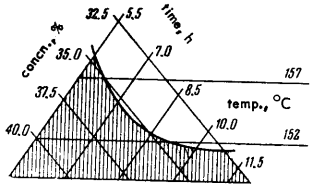


Fig. 12. Plane of greatest yield (about 68%) for product C. The yield of D is greater than 20% in the hatched region.

or

$$X_1 = \pm \sqrt{\frac{Y = 68.14}{-3.190}}.$$

This is the equation for a pair of planes; for $Y_S = 68.14$ we obtain the plane $X_1 = 0$, on which the yield is maximal at 68%. The first equation of (21) gives us the equation of this plane referred to the x coordinate system:

$$0.7511(x_1 - x_{1S}) + 0.4884(x_2 - x_{2S}) + 0.4443(x_3 - x_{3S}) = 0,$$

or in T, c, t, units,

$$0.1502\,T + 0.1954\,c + 0.2962\,t = 32.30.$$

This equation defines the various sets of conditions giving the same yield; Fig. 11 shows the plane of maximum yield and also the planes for $Y = 60$. We have here an illustration of the behaviour when the effects of a change in one variable are balanced out by changes in other variables. Fig. 11 gives a visual representation of the alternative conditions that lead to the same yield.

The next step is to find the conditions that make the yield (Z) of D less than 20%; we have to locate the region in the plane of maximum yield that has $Z < 20\%$. The second-degree equation obtained is

$$Z = 18.379 + 5.150x_1 + 2.362x_2 + 2.188x_3 + 0.728x_1^2 + 0.103x_2^2 + 1.303x_3^2 + 2.175x_1x_2 + 2.075x_1x_3 + 1.300x_2x_3.$$

This is transformed to the X coordinates; the values $X_1 = 0$ and $Z = 20$ are inserted, with the result

$$-0.855 = -0.319X_2 + 0.972X_3 + 0.380X_2^2 - 0.712X_3^2 + 0.079X_2X_3.$$

This equation defines the boundary for Z, (20% or more) on the surface of maximum yield, as shown in Fig. 12.

III. REVIEW OF APPLICATIONS OF THE BOX-WILSON METHOD

There are many examples of the use of this method in Great Britain and the USA; it is stated[3] that the American Cyanamid Company uses it to solve about half the chemical problems arising in its extensive research programme. The method has not yet been widely adopted, partly because the traditional training of chemists, metallurgists, or even physicists tends to neglect mathematical statistics.

The method has been expounded and illustrated in many books and papers[2,4,5]; three three-day seminars were devoted to the topic in the USA in 1956 and 1957[6]. Examples carried through to numerical calculations are presented in the mathematical literature in the abstract form illustrated above. Several such examples may be considered. Box and Youle[7] have examined a system that can be described in terms of two successive competing reactions

$$\left.\begin{aligned} 2a + bNb &\rightarrow aNb + ab \\ 2a + aNb &\rightarrow aNa + ab \end{aligned}\right\}, \qquad (22)$$

in which the initial compound bNb contains a large nucleus N bearing two groups b. The object is to maximise the yield of aNb by adjusting the temperature, reaction time, and concentrations. Baun and Schneider[3] have examined three problems, namely (1) a three-factor problem related to spray drying, (2) a problem of maximising the yield of the organic intermediate product in the reaction $A + B + C \rightarrow$ $\rightarrow$ product + intermediate product (here A/C and B/C are used as the independent variables), and (3) a reaction occurring in several reaction vessels arranged in series (here there were five factors, namely the concentrations of the reactants, a quality factor at two levels, and the effect caused by the use of reactors in series). Problems in chemical technology may be solved with reference to their economic aspects; for example, Box[8] has considered the technique of producing a compound C by fusing the reactants A and B; the factors were the temperature, the time of fusion, and the molar ratio of A to B, the effect being that on the cost of C, which is controlled by the yield of C and by the cost of performing the process. The cost of C is treated as a directly measurable dependent variable.

Problems have been considered in applied detail in certain journal articles; Morris and Bozalek[9] have used a response surface in studies of the accuracy of assays of sulphate in superphosphate, while Hackler et al.[10] have studied the uptake of water by fired whiteware compositions as a function of the composition (three factors) and of the firing temperature. Linear regression analysis has been applied[11] to the precipitation of $CaHPO_4$; four factors were used, namely the temperature, the concentrations of the reagents [$(NH_4)_2HPO_4$ and $CaCl_2$], and the rate at which the first reagent is added to the second. Li[12] has proposed a special table for representing the results of all steepest-ascent calculations in a standard form. One example of the use of this table is that of the choice of a composition for a complex-alloy steel in order to ensure the greatest resistance to fracture at high temperatures.

Applications have been made in organic chemistry, e.g. to the vapour-phase oxidation of naphthalene[13], to the emulsion polymerisation of vinyl chloride[14], and to the conditions for the best yield of 3-aminopropionitrile[15]. The Box-Wilson method has been combined with linear programming in order to optimise a catalytic cracking process[16]. The sealing strength of a wax-polyethylene blend used as a wrapping material has been examined[17].

Interesting applications have been found in biochemistry. The best values have been sought for the sodium citrate and glycerol concentrations and for the equilibration time in relation to the survival of bovine spermatozoa frozen at -79°[18]. A study has been made of the relationships between Cu, Fe, and Mo in the growth and nutrition of lettuce; the form of the nitrogen and the initial valence state of the iron were examined for their effects on the copper-dependent effects of the interaction and on the critical level of the copper[19,20]. The concentrations of Cu, Mo, and Fe giving the most rapid growth were determined.

It has not been possible to obtain some of the reports and conference proceedings listed below, and the contents can be judged only from the titles. For example, a study has been made of the flooding capacity of a pulsed column[21]; it has been pointed out[7] that here the experimental results have to be represented by a third-degree equation.

Whidden[22] deals with experimental design in metal processing; Shewell[23] deals with catalytic cracking, and so on.

Box and Wilson first presented the theoretical basis of their method in 1951[1]; subsequent developments[24] introduce the concept of the variance function, and in particular spherical variance functions. Since the location of the point of greatest yield (or other such point) is not known at the start, the experiment should be planned to make the variance of the predicted yield the same for all points at the same distance from the centre of the group of tests. Such designs are called "rotatable", because the orthogonal axes may take any orientation without effect on the confidence limits of the predicted yield. For these factors a central composite design is rotatable if the points lie at the corners of a cube and of an octahedron inscribed in the cube (Fig. 9), the coordinates of the corners of the octahedron being (±1.68, 0, 0), (0, ±1.68, 0), and (0, 0, ±1.68). Several examples of such designs have been given[4,5,19,20].

Box and Hunter[24] have considered rotatable experimental designs with satisfactory variance functions for their first- and second-degree polynomials and with independent variables numbering from two to infinity. Box and Draper[25] emphasize that a polynomial represents the real response surface only approximately; systematic errors accompany the random errors, and certain additional conditions are imposed on the design.

This new approach is complementary to the theoretical considerations commonly adopted by chemists. The general features of an experiment are established by selecting those factors that should be varied and the levels at which they are to be taken on the basis of general principles. However, those principles usually cannot predict precisely the conditions that will give the best yield, least cost, etc. The experimental work forms a link between the theory and the process; it has been called "creeping empiricism", because no general basis has yet been proposed for peak-seeking experiments. For example, the open-hearth process has been used in making steel for about a hundred years; much attention has been given to the theory of the process, but it is not possible to use theoretical considerations alone in designing a detailed programme suitable (say) for controlling the process by means of a computer. Between the theory and the finished steel there comes the steel worker, who uses his experience to interpret the information he receives during the melting and to find a means of performing the process in the best way. He has no formalised rules for interpreting the information and for reaching his conclusions, and their reliability cannot be assessed. The peak-seeking problem is solved intuitively; the theory of the open-hearth process indicates its general direction, but it cannot describe it fully. The same is true of any other complicated chemical process. The Box-Wilson method enables us to pass from intuitive methods to rigorously defined and mathematically sound ones.

The method may also be of use in solving certain theoretical problems in chemistry. Box and Youle[7] have examined the system described by (22) and have made an interesting comparison between the empirical response surface and the theoretical one. The first is obtained by fitting a polynomial to the experimental results; the second, by representing those results by means of a function derived from the general principles of reaction kinetics. Comparisons of this kind permit a more exact understanding of the mechanism of the process.

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