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High-speed Computers as a Supplement to Graphical Methods

I. Functional Behavior of the Error Square Sum

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The paper discusses the principles underlying "LETAGROP", a computer program being used for calculating, from experimental data $(y_i, a_{1i}, a_{2i} \ldots)$, $(i = 1 \ldots n)$, a set of unknown constants k_r $(r = 1 \ldots N)$, assuming a functional relationship $y = f(k_r, a_1, a_2 \ldots)$. The "best" values k_r'' searched for, are those that minimize the error square sum U (eqn. 7). The method may be described as a generalized least-squares method, valid also for non-linear and implicit functions, which are hard to treat by the standard treatment for linear functions or by the Gauss' approximation method.

The functional behavior of U $(k_1 \ldots k_N)$ is discussed for the general linear case, and for $N = 1$ and $N = 2$. The "standard deviations" D_r are interpreted geometrically by means of the extreme values $k_r'' \pm D_r$ of each k_r on the "D boundary", defined by $U - U_0 = \sigma^2$ (47).

A high-speed computer can very easily "map" U $(k_1 \ldots k_N)$, even for non-linear and implicit functions. As an approximation it is assumed that U is a second-degree function of the k_r; then $\frac{1}{2}(N + 1) \cdot (N + 2)$ points suffice to calculate the position of the minimum and the D boundary. Starting from a first, approximate set k_r', the "best" values k_r'' are reached by (usually only two or a few) successive approximations. The need for choosing the k_r as independent as possible is pointed out.

The limitations of the whole "least squares" approach are discussed. At present there seems to be still more need for better chemical work than for better statistical treatment.

The following papers will deal with a number of computer programs that have proved very helpful in our present work on complicated equilibria. One of these programs, called "LETAGROP" was designed to adjust a number of equilibrium constants simultaneously, once the formulas of the complexes and the approximate values of the equilibrium constants had been found by means of graphical methods. It can also be applied to other types of problems where several unknown parameters are to be determined.

As distinguished from the usual "least squares" method, "LETAGROP" ("pit-mapping") can be applied also to cases where the measured quantity cannot be expressed as a linear or even as an explicit function of the unknown parameters.

Since this way of treatment has not been described in any source that the author is aware of, and at any rate may prove useful for many chemical problems, it seems appropriate to describe its principles in brief.

GENERAL PROBLEM

We have n measurements y_i of the variable quantity y and assume that we know the functional relationship.

$$y = f(k_1,\ k_2 \ldots k_r \ldots k_N\ ;\ a_1, a_2 \ldots) \tag{1}$$

Here, a_1 a_2, *etc.* are quantities that can be varied but whose values (a_{1i}, a_{2i}, *etc.*) are assumed to be known accurately in each experiment. From the n sets of data (y_i, a_{1i}, a_{2i} ...), $i = 1, 2 \ldots n$, we want to determine the set of N unknown constants k_r, $r = 1, 2 \ldots N$.

Example I a. Mononuclear complexes A_pB, data (A, B, a, b). We have a series of n solutions in each of which one knows the total concentrations A and B, and the concentrations a and b of free A (ligand) and free B (central group). In the expression

$$y = B/b = 1 + \beta_1 a + \beta_2 a^2 + \beta_3 a^3 + \ldots = 1 + \Sigma\beta_p a^p \tag{2}$$

one wants to determine the unknown stability constants $\beta_1 \ldots \beta_N$ from a number of experimental sets (y, a).

Example I b. Mononuclear complexes A_pB, data (A, B, a). From the data we may calculate the ligand number Z (or $\bar{n}$) $= (A - a)/B$. For calculating $\beta_1 \ldots \beta_N$ we may use the relationship

$$Z = \frac{\Sigma p\beta_p a^p}{1 + \Sigma\beta_p a^p} \tag{3}$$

One may rearrange (3) to give, for instance,

$$y = Z + \Sigma(Z - p)\beta_p a^p = 0 \tag{4}$$

Because of experimental errors, the value found is usually not exactly zero. Other rearrangements can also be made. Again, we want to determine the N unkown β_p from n sets (Z, a).

Example II. Polynuclear complexes A_pB_q, data (B, A, a). If there are several polynuclear complexes in a system, the mass balance and the law of mass action give

$$B = b + \Sigma\Sigma q\beta_{pq} a^p b^q \tag{5a}$$

$$BZ = A - a = \Sigma\Sigma p\beta_{pq} a^p b^q \tag{5b}$$

The unknown constants β_{pq} should be determined from n sets (B, Z, a). Nature in general does not seem anxious to provide such sets of (p, q) as would make it easy to eliminate b from (5a) and (5b). So, in general, no explicit expression for Z can be derived.

Example III. Hydrolysis studies in self-medium. We have the equations (Hietanen and Sillén [1]):

$$B = b + \Sigma\Sigma q\beta_{pq}h^{-p}b^q \tag{6a}$$

$$BZ = h - H - \Delta = \Sigma\Sigma p\beta_{pq}h^{-p}b^q \tag{6b}$$

$$E = E_0 - 59.154 \log h + jh \tag{6c}$$

Here, H is the total (analytical) proton excess, E is the measured emf, E_0 and j are constants, which cannot be determined independently, and Δ is the correction for a possible analytical error in H. The experimental data are (E, H), the unknown constants are the β_{pq}, E_0, j, and Δ, whereas b and h should be eliminated. Even here, it is in general not possible to give an explicit expression $E(H)$.

Of these examples, Ia is easily accessible to the standard "least squares" treatment Refs.[2-6], which can also be applied to I b after some transformation. For finding and refining the constants in examples II and III (and even in I) successive approximations have usually been used.

Error square sum

It is customary to search for that set of constants k_r'': $k_1'' \ldots k_N''$, that will minimize the error-square sum U

$$U = \Sigma w_i[y_i - f(k_1 \ldots k_N ; a_{1i}, a_{2i} \ldots)]^2 \tag{7}$$

where w_i is the "weight" assigned to each measurement y_i. The mathematical condition for our criterion

$$U = \text{minimum} \tag{8}$$

is a set of N "normal equations"

$$(\partial U/\partial k_r) = 0, r = 1 \ldots N \tag{8a}$$

Whether the person using (8) realizes this or not it is a strictly valid criterion for "maximum likelihood" only under the following conditions:

(*a*) The functional relationship (1) is correct; for instance, no important terms have been left out.

(*b*) There are no other errors to be considered than the random experimental error in y. Especially, there are no systematic errors.

(*c*) The random errors in y follow a "normal" (Gaussian) distribution.

(*d*) The weight

$$w_i (y_i, a_{1i}, a_{2i} \ldots) \tag{9}$$

assigned to each measurement is an exact measure of its inherent accuracy as defined by (28).

These conditions call for some comments:

(*a*) The choice of (1) is a matter of judgment. Sometimes, several functions f_{I}, f_{II} *etc.* are compared, and one is in general inclined to prefer the function that gives the lowest value for $U_{\min}$. The judgment comes in especially when one considers the functions that were never tried. With the standard "least squares" treatment one is restricted to functions linear in the k_r.

(*b*) It is usually not difficult to choose the variable y, that should "carry" the experimental error. In the examples above one would probably use Z in

I and II and H or E in III. If there are random errors also in a_1 *etc.* these can usually be accounted for by a corresponding increase in the random error in y. However, if there is a range where the random variation in, say, a would correspond to a variation in y, much greater than any experimental errors, then misleading results will be obtained; this is illustrated in Ref.[3], p. 2031, where the authors have started from eqn. (4) but put the error on the ligand concentration instead of on the ligand number. Thus, some caution is needed.

The most important condition, which is, alas, frequently not fulfilled, is the absence of systematic errors. An especially insidious combination is that of systematic errors and an erroneous function (1) which may sometimes give an agreement between experiment and erroneous theory that seems quite convincing. A wrong conclusion can of course be reached also without the aid of a computer, or statistics.

There is evidently no statistical way of avoiding this risk. One must keep an open mind for the possibilities of systematic errors, apply as many independent experimental approaches as possible, and always strive to prove oneself wrong.

(*c*) There may be shades of opinion among statisticians as to whether a "normal" distribution is a frequent phenomenon or not in this harsh world of reality. At any rate, if the errors in a quantity x are "normally" distributed, then the errors are not "normally" distributed in non-linear functions of x like $\log x$, x^{-1}, or x^2.

If, as is usually the case, nothing is known about the real error distribution, out of all guesses that can be made, the "normal" distribution is the one that gives the simplest calculations.

(*d*) is the second point where judgment (or lack of it) creeps into all calculations founded on (7) and (8).

It is certainly seldom that one can hope that all these assumptions (*a*) — (*d*) are correct. Nevertheless, the "least squares" criterion (8) is often employed because of its simplicity, and this will be done in the present paper also.

The set of constants, k_r'' ($r = 1 \ldots N$) that fulfil (8) we shall call the "best" set of constants. It is "objective" in the sense that with the same set of data, the same theoretical function (1), and the same weight function (9), the condition (8) should give the same "best" set of constants in the hands of different workers. This is an example of how some quantities that are defined exactly (under given conditions) in mathematical statistics, have acquired highly suggestive names, which may lead non-statisticians to over-estimate their significance in the world of reality: "normal" distribution, "maximum likelihood", "probable" error, "significant" result, "standard" deviation, "best" values.

Remembering the limitations of the whole approach, we shall not forget the quotation marks around "best". Some other authors leave them out.

The standard "least squares" treatment

If f in (1) is a linear function of the various k_r, say $f = \Sigma k_r a_r$, then (8a) leads to a system of linear equations which can be solved by elimination methods or, for not too large N values, by means of determinants.

Most of the larger high-speed computers have standard "least squares" programs that can be adapted to this type of problem. Of the examples I—III given above, only I a and (with some transformation and difficulty) I b can be treated in this way. The "least squares" treatment has been applied to equilibria of complex formation by several authors, especially by Sullivan, Rydberg and Miller [3-6]. Earlier work in this direction has been summarized by Rydberg [6].

If f in (1) is not a linear function, the general trend has been to reduce it to a linear one, either by transformation (as was done in example I b), or by Gauss' approximation method, in which one starts with an approximative set k_r', expresses the derivatives of U (8a) around k_r' by means of Taylor series for f and uses only the first terms. Programming a computer for Gauss' method is not always simple, and according to Moore and Ziegler [8] its performance is somewhat unpredictable. It seems hard to apply Gauss' method to cases such as II and III above, where no explicit relationship (1) can be given.

"Pit-mapping"

However, one can make oneself free from the condition that (1) should be linear, or even explicit, if one considers directly the functional behavior of the error-square sum

$$U(k_1 \ldots k_N) \tag{10}$$

as a function of the various k_r. By means of a high-speed computer one may rapidly calculate U for various sets of k_r and it is natural to ask whether one could not use a selected set of points of the function (10) for finding the lowest point:

$$U_{\min} = U_0 = U(k_1'', k_2'' \ldots k_N'') \tag{11}$$

If f is linear, (10) is a second-degree surface, as will be seen below. (Eqn. 40, *cf.* eqn. 39). With $N = 1$ it is a parabola, with $N = 2$ an elliptic paraboloid, and for higher N a generalized elliptic paraboloid in $(N + 1)$-dimensional space. For any value of N we shall refer to the lowest point U_0 and its immediate surroundings as the "pit". The procedure to be proposed, which was indicated in a short note by Dyrssen, Ingri and Sillén [9], we shall call "pit-mapping" since in a way it describes the shape of the pit. We shall see how this map can be used also for estimating the statistical "standard deviation" which may be obtained, for the linear case, as a by-product of the standard computer programs.

LINEAR EQUATIONS

As a starting point we shall study the behavior of U in the linear case. The symbolism will, to a large extent, be the same as is used by Cramér [7]. For a stochastic varable , say x, with the distribution function $F(x)$ (probability that it in a particular case is $\leq x$), the average will be written

$$\bar{x} = E\{x\} = \int_{-\infty}^{\infty} x \, \mathrm{d}F(x) \tag{12}$$

and the standard deviation

$$D\{x\} = \sigma_x \tag{13}$$

will be defined by

$$D^2\{x\} = E\{(x - \bar{x})^2\} \tag{14}$$

(Some other textbooks use D for what is here called D^2). These definitions do not presume any special form of $F(x)$.

We shall carry out the mathematical discussion only insofar as this is necessary to explain our method. We shall set down for future use a result, which is easily seen from the usual treatment, although usually not written this way: the minimum value U_0 is a stochastic variable, for which

$$E(U_0) = \sigma^2 (n - N) \tag{15}$$

$$D^2(U_0) = 2\sigma^4 (n - N) \tag{16}$$

$U_0\sigma^{-2}$ follows a χ^2-distribution with $(n - N)$ degrees of freedom. Here, σ is the "standard deviation" for y_i in a point with the weight $w_i = 1$. In the following, we shall take the "best" experimental value of σ from

$$U_0 = \sigma^2(n - N) \tag{17}$$

f linear, $N = 1$

If $N = 1$ there is only one constant, k_1, to be determined. If (1) is linear, we can always transform it to read

$$(y \approx)\, f = k_1$$

We have n measurements, y_i $(i = 1, 2 \ldots n)$, to each of which we ascribe a weight w_i $(i = 1, 2 \ldots n)$. The error square sum is

$$U = \Sigma w_i(y_i - k_1)^2 = \Sigma(w_i y_i^2 - 2\, w_i y_i k_1 + w_i k_1^2) \tag{19}$$

We introduce the weight sum W, and the weighted average $\bar{y}$, defined by

$$W = \Sigma w_i \,;\; \bar{y}\, W = \Sigma w_i y_i \tag{20}$$

Inserting (20) into (19) gives

$$U = \Sigma w_i y_i^2 - 2\, k_1 \bar{y}\, W + k_1^2 W \tag{21}$$

By differentiation with respect to k_1 we find the condition for a minimum in U:

$$\partial U/\partial k_1 = 2W(k_1 - \bar{y}) = 0 \tag{22}$$

At the minimum point we have, from (22) and (21)

$$k_1'' = \bar{y} \tag{23}$$

$$U_0 = \Sigma w_i y_i^2 - W\, k_1''^2 \tag{24}$$

According to (23) the "best" value is the weighted average. We shall study the behavior of $U(k_1)$ around this point, for simplicity replacing k_1 by its deviation d_1 from the "best" value:

$$k_1 = k_1'' + d_1 \tag{25}$$

Inserting (24) and (25) into (21) gives

$$U = U_0 + Wd_1^2 \tag{26}$$

Hence, the "pit" $U(d_1)$ is a parabola. The squared standard deviation of k_1'' will be, using (23) and (20):

$$D_1^2 = D^2\{k_1''\} = D^2\{\Sigma w_i y_i/W\} = \Sigma(w_i/W)^2 D^2\{y_i\} \tag{27}$$

Up to now, we have made no assumption about the error distribution or weights. Let us assume, however, that we have managed to choose, for each y_i, its weight so that

$$D^2\{y_i\} = \sigma^2/w_i\ ;\ \sigma = \text{constant} \tag{28}$$

Inserting (28) into (27) we find

$$D_1^2 = \sigma^2\ \Sigma w_i/W^2 = \sigma^2/W \tag{29}$$

If we may assume that we have a "normal" distribution, we can apply (17) $U_0 = \sigma^2(n - N)$.

One may ask what value U has for $d_1 = D_1 = D\{k_1''\}$. Inserting this value into (26) and applying (29) we find

$$U(D_1) = U_0 + \sigma^2 \tag{30}$$

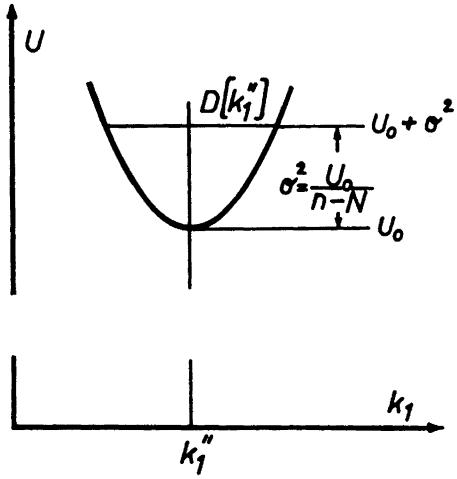

Fig. 1. Direct method for calculating the "best" value k_1'' and its "standard deviation" D_1 provided the functional relationship between the error square sum U and k_1 is known. The "best" value, k_1'', is the one that gives the minimum value, U_0, for U. The points where $U - U_0 = U_0/(n - N)$ are $k_1'' \pm D_1$.

or using (17)

$$U - U_0 = \frac{U_0}{n-N} \text{ for } d_1 = D\{k_1''\} \tag{30a}$$

Thus, if the shape of the "pit" is known, (30a) gives a direct method for finding the "best" value for $D\{k_1''\}$ (Fig. 1).

General linear case

Let us assume that the theoretical function has the general linear form

$$y_i \approx f_i = \sum_r k_r a_r \tag{31}$$

and that we have n measurements y_i ($i = 1, 2 \ldots n$), each of weight w_i, to determine the N unknown constants k_r ($r = 1, 2 \ldots N$) searched for. In the following, r, s and t will be used indiscriminately for the index of k, and sums over them imply "from 1 to N"; sums over i are " from 1 to n".

The error square sum is then

$$U = \sum_i w_i(y_i - \sum_r k_r a_{ri})^2 = \sum_i w_i y_i^2 - 2 \sum_i \sum_r w_i y_i k_r a_{ri} + \sum_i \sum_r \sum_s w_i k_r k_s a_{ri} a_{si} \tag{32}$$

We replace the sums over i by the sets of quantities b_{rs} and c_r defined by

$$W b_{rs} = \sum_i w_i a_{ri} a_{si} \tag{33}$$

$$W c_r = \sum_i w_i y_i a_{ri} \tag{34}$$

As before, $W = \sum_i w_i$. (eqn. 20) Then, (32) takes the form

$$U = \sum_i w_i y_i^2 - 2W \sum_r c_r k_r + W \sum_r \sum_s k_r k_s b_{rs} \tag{35}$$

Differentiation with respect to the k_r gives a set of conditions (the normal equations, 8a) for U to have a minimum:

$$\sum_s k_s'' b_{rs} = c_r \tag{36}$$

The solution of (36) is

$$k_r'' = B^{-1} \sum_s c_s B_{rs} \tag{37}$$

were B is the determinant of the symmetrical matrix $\| b_{rs} \|$ and B_{rs} is the subdeterminant corresponding to b_{rs}. Combining (35) and (36) we find at the minimum point

$$U_0 = \sum_i w_i y_i^2 - W \sum_r k_r'' c_r \tag{38}$$

We replace k_r by the difference d_r from the "best" value

$$k_r = k_r'' + d_r \tag{39}$$

After some arithmetic, (35) can be transformed, using (39), (38), and (36):

$$U - U_0 = W \sum_r \sum_s d_r d_s b_{rs} \tag{40}$$

So, $U - U_0$ is a homogeneous function of second degree in the d_r.

The standard deviations of the "best" values k_r'' are deduced as follows. Using (37) and (34) we have,

$$D_r^2 = D^2\{k_r''\} = D^2\{B^{-1}W^{-1} \sum_i \sum_r w_i a_{si} B_{rs} y_i\} = B^{-2}W^{-2} \sum_i w_i^2 (\sum_s a_{si} B_{rs})^2 D^2\{y_i\}$$

If we assume that the weights have been chosen so that (28) holds, we find, using (33)

$$D_r^2 = \sigma^2 B^{-2} W^{-2} \sum_i \sum_s \sum_t w_i a_{si} a_{ti} B_{rs} B_{rt} = \sigma^2 B^{-2} W^{-1} \sum_s \sum_t b_{st} B_{rs} B_{rt}$$

It follows from the properties of determinants that the double sum equals BB_{rr} so that

$$D_r^2 = D^2\{k_r''\} = \sigma^2 B_{rr}/BW \tag{41}$$

Calculation of k_r'' and D_r from a map of U

Suppose that we start from a set of approximate constants $k_1' \ldots k_N'$ and that we have calculated values of U for a sufficient number of sets in the neighborhood, to determine the coefficients in

$$U = c_0 + 2 \sum_r c_{0r} x_r + \sum_r \sum_s c_{rs} x_r x_s \tag{42}$$

$$x_r = k_r - k_r' \tag{42a}$$

The minimum point is then found from the equation system (differentiating U):

$$\sum_s x_s'' c_{rs} + c_{0r} = 0, \; (r = 1,2 \ldots N) \tag{43}$$

which gives the "best values"

$$x_r'' = -\sum_s c_{0s} C_{rs} C^{-1}; \; k_r'' = k_r' + x_r'' \tag{43a}$$

Here, C is the determinant of the matrix $\| c_{rs} \|$, and C_{rs} the subdeterminant of c_{rs}.

Inserting (43) into (42) gives

$$U_0 = U_{\min} = c_0 + 2 \sum_r c_{0r} x_r'' - \sum_r c_{0r} x_r'' = c_0 + \sum_r c_{0r} x_r'' \tag{44}$$

We may compare (35) or (40) and (42). Since the second-degree terms must be independent of parallel shifts of the coordinates, we have

$$c_{rs} = b_{rs} W; \; C_{rs} = B_{rs} W^{N-1}; \; C = BW^N \tag{45}$$

We may derive an expression for the standard deviations, starting from (41), taking $\sigma^2 = U_0/(n - N)$ from (17), and inserting (45):

$$D_r^2 = D^2\{k_r''\} = U_0 C_{rr}/C(n - N) \tag{46}$$

The procedure would then be as follows. In order to find the constants c_0, c_{0r} and c_{rs} in (42), one determines at least as many, thus $1 + N + \frac{1}{2} N (N + 1) = \frac{1}{2}(N + 1)(N + 2)$ values for U: 3 values for $N = 1$, 6 values

for $N = 2$, 10 for $N = 3$, *etc.* From these one calculates the constants in (42), then the "best" values k_r'' from (43a), U_0 from (44), the "standard deviation" in y, σ, from (17) and the "standard deviations" of the k_r'' from (46). For both (43a) and (46) one should calculate the reciprocal matrix of c_{rs}, with elements $C_{rs}C^{-1}$.

Geometrical interpretation; the D boundary

We may imagine the function $U(k_1 \ldots k_N)$ as an N-dimensional surface in $(N + 1)$-dimensional space. We shall introduce, as a generalization of the result (30), the D *boundary*, characterized by

$$U = U_0 + \sigma^2 \tag{47}$$

From (47) and (40), on the D boundary

$$\sum_r \sum_s d_r d_s b_{rs} = \sigma^2/W \tag{48}$$

If $N = 2$, the U surface (the pit) is an elliptic paraboloid and the D boundary an ellipse; if $N = 3$, the D boundary is an ellipsoid *etc;* in general, the U surface is a generalized elliptic paraboloid and the D boundary a generalized ellipsoid.

Now we propose that for each k_r the standard deviation D_r is equal to the maximum value that d_r can attain on the D boundary. Differentiating (48) gives

$$\sum_r \mathrm{d}d_r \sum_s d_s b_{rs} = 0$$

For d_r to be extreme we must then have

$$\sum_s d_s b_{ts} = 0,\ t \neq r\ ;\ \sum_s d_s b_{rs} = c \neq 0 \tag{49}$$

where c is a constant to be eliminated. The solution of (49) is

$$(d_r)_{\max} = c\, B_{rr}B^{-1}\ ;\ d_s = c\, B_{rs}B^{-1} = (d_r)_{\max} B_{rs}B_{rr}^{-1} \tag{49a}$$

Inserting into (48) first (49), then (49a), we find

$$\sigma^2/W = (d_r)_{\max} \sum_s d_s b_{rs} = (d_r)^2_{\max} \sum_s B_{rs}b_{rs}B_{rr}^{-1} = (d_r)^2_{\max} B B_{rr}^{-1} \tag{50}$$

Comparison of (50) and (41) confirms our proposition:

$$(d_r)_{\max} = D_r = D\{k_r''\} \tag{51}$$

Example, $N = 2$. Let us, for illustration, assume that we measure

$$y \approx f = k_1 + k_2 a \tag{52}$$

Hence in (31), $a_{1i} = 1$, $a_{2i} = a_i$ and, from (33) and (34)
$Wb_{11} = \Sigma w_i = W$; $Wb_{12} = \Sigma w_i a_i = W\bar{a}$ etc., or in brief
$b_{11} = 1$; $b_{12} = \bar{a}$; $b_{22} = \overline{aa}$; $c_1 = \bar{y}$; $c_2 = \overline{ay}$; $B = \overline{aa} - \bar{a}^2$;

The bar stands for average: $\overline{aa}$ is the average of a^2, *etc.* From (37) we find:

$$k_1'' = (\bar{y}\,\overline{aa} - \overline{ay}\,\bar{a})\, B^{-1}\ ;\ k_2'' = (\overline{ay} - \bar{a}\,\bar{y})\, B^{-1} \tag{53}$$

The D boundary (48) is an ellipse:

$$d_1^2 + 2\bar{a}\, d_1 d_2 + \overline{aa}\, d_2^2 = \sigma^2/W \tag{54}$$

The "standard deviations" (41) of the "best" values are:

$$D_1 = \sigma\sqrt{\overline{aa}}\,/\sqrt{BW}\,;\; D_2 = \sigma\,/\sqrt{BW} \tag{55}$$

By a shift of origin we may replace k_1 by k_1^*, and a by a^*, defined by

$$k_1^* = k_1 + k_2\bar{a}\,;\; a^* = a - \bar{a}\,;\; y = k_1^* + k_2 a^* \tag{52a}$$

We then find

$$b_{11}^* = 1, b_{12}^* = 0\,;\; b_{22}^* = \overline{aa} - \bar{a}^2 = B^* = B\,;\; c_1^* = \bar{y}\,;\; c_2^* = \overline{ay} - \bar{a}\,\bar{y}\,;\; k_1^{*\prime\prime} = k_1^{\prime\prime} + k_2^{\prime\prime}\,\bar{a} \tag{53a}$$

The D boundary (48) is now another ellipse:

$$d_1^{*2} + Bd_2^2 = \sigma^2/W \tag{54a}$$

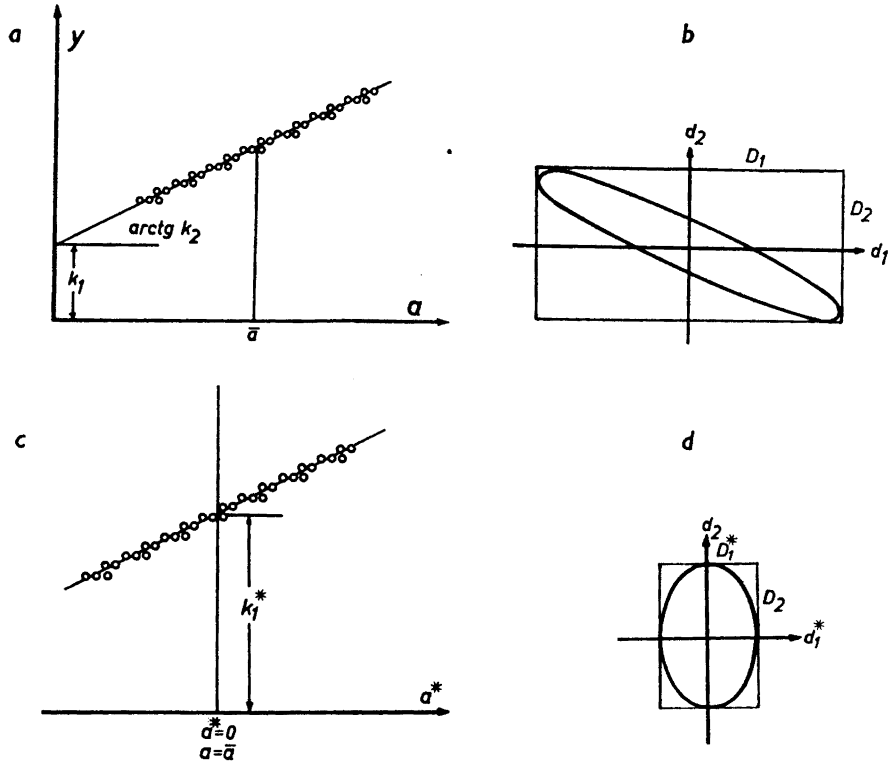

Fig. 2. (Schematic) a) experimental points $y(a)$ and "best" line, $y = k_1 + k_2 a$. b) "D boundary", in this case a skew ellipse. c) = Fig. 2 a, with origin shifted to the average value $\bar{a}$. d) D boundary corresponding to 2 c: now the axes of the ellipse coincide with the coordinate axes. Explanations, see text.

The standard deviations (41) are

$$D_1^* = \sigma / \sqrt{W} \; ; D_2 = \sigma / \sqrt{BW} \tag{55a}$$

The schematic Figs. 2a and 2c indicate the experimental points and "best" line, with the two different choices of origin; Figs. 2b and 2d give the corresponding D boundaries, which indicate the shape of the "pit". The scale of d_1 and d_1^* is magnified in comparison with k_1 and k_1^*. The scale for d_2 is arbitrary.

For a given set of points, the "best" line is independent of the transformation (52a), and so is the standard deviation D_2 of the slope. However, the standard deviation of the constant k_1 is larger than the value D_1^* obtained if the origin is taken at the average $\bar{a}$.

In Figs. 2a—2b the pit is skew: if k_1 is fixed at another value than the "best", say at a higher value, then the minimum for U is obtained at a slope k_2 which is smaller than the "best" one. In Figs. 2c—2d, however, the two unknown constants are independent: the same value for the slope k_2 is obtained whatever value is assumed for k_1^*.

The general non-linear case

Now let us assume that we have a non-linear relationship — perhaps not even explicit — between $y \approx f$ in (1) and the various k_r. Such a case is hard to attack by the standard straight-forward "least squares" method. We shall, however, still adopt as a criterion for the "best" values k_r that they should give a minimum in U (8a).

By means of a high-speed computer it is relatively easy to calculate U for a number of sets of the k_r. In principle one might start with some approximate set of k_r — calculated, estimated or guessed — by trial and error find one's way to regions with lower and lower U values, and finally come as close as desired to the minimum point U_0. With one unknown ($N = 1$) this is easy enough, but some experience has shown us that even with $N = 2$ this may be a lengthy procedure, especially if the "pit" is skew (*cf.* Fig. 2b). A more systematic method of search is therefore needed.

The equation of the "pit" (10) in the general case may be very complicated. However, we may use Taylor's series to develop U as a power series of the coordinates d_r measured from the minimum point k_r''. The constant term is then U_0, and all terms of first degree in the d_r are zero, since U_0 is a minimum value. So, near the bottom of the pit we would have

$$U - U_0 = \sum_r \sum_s c_{rs} d_r d_s \; (+ \sum_r \sum_s \sum_t c_{rst} d_r d_s d_t + \ldots) \tag{56}$$

In the computer program "LETAGROP" to be described in a following paper (Ingri and Sillén [10]) all terms of higher degree than second are neglected in (56). This approximation should be better, the closer one is to the bottom of the pit.

Starting from an approximate set k_r' of the unknown constants, one calculates, by a systematic approach, the appropriate number of U values, $\frac{1}{2}(N + 1)(N + 2)$, and from them the constants in (42). Using the procedure

for the linear case, one then calculates with (43a) the parameters k_r'' of the minimum point.

If f is linear, one would get the correct coordinates of the minimum point, however bad the guessed k_r'. In the general case, because of the presence of terms of higher degree, the minimum point must be found by a series of successive approximations. In our experience hitherto with "LETAGROP" it seems that the procedure is reasonably rapidly convergent: 2—3 approximations suffice, dependent on how good the original guess is. However, there is certainly still much to be learnt about the complications that may arise in special cases.

Again, we shall define the D boundary by the equation

$$U - U_0 = \sigma^2 \tag{47}$$

As a measure of the standard deviations of the various k_r'' we shall use the maximum values D_r of the various d_r on the D boundary.

Once one knows the c_{rs} and hence the approximate shape of the pit, D_r can be calculated using (46). The influence of the terms of higher degree in (56) is minimized, and hence the approximation of D_r and k_r'' is better, if in the final approximation step the estimate k_r' is close to the minimum point, and the other points used are close to the D boundary.

A few additional points may be made in connection with Fig. 2. It is advisable to choose the constants to be determined, in such a way that their influence on the data is independent, thus so that the "pit" is as little skew as possible. For instance, if B/b is studied with mononuclear complexes (Example Ia), $\beta_1 \ldots \beta_N$ may be the best choice, whereas for data $Z(a)$, the step-wise constants K_1, $K_2 \ldots K_N$ are more independent: there are often ranges, where the Z value is only influenced by one or two of the K_r values.

A systematic error may often be thought of as an additional unknown constant (for instance an analytical error, Example III) which one should have included in the calculations, and which gives a skew pit (see Fig. 2b); if it did not, it would do little harm.

The expressions for the standard deviations $D\{k_r''\}$ in (41) contain the standard deviation in the y measurements, σ, and in addition only factors that depend on the arrangement of the experiments (the various a_{si}, see eqn. 33). It might thus be said (provided the general assumptions (*a*) — (*d*), page 161 are valid) that the standard deviation of each constant is determined as soon as the series of experiments has been designed. If the standard deviation for a specific constant is found to be relatively large, this may be because the constant is relatively small, or because the experiments were not particularly well designed for determining this constant.

Methods founded on the principle described may be used, as will be shown in subsequent papers, for a fairly rapid refining of the unknown constants in a number of problems, which have been inaccessible to the standard "least squares" treatment, and may thus save much time. However, ultimately they depend on graphical methods: especially the choice of the function f, and the choice of the first set of constants is preferably made by graphical methods, and the last step will be a graph, to check for systematic deviations.

In a development of the program one might check that the distribution of the deviations $(y_i - f_i)$ is "normal" or at least symmetrical, for instance by studying the various moments $\Sigma w_i(y_i - f_i)^m$, $m = 1, 3, 4...$ and the relation to the sum with $m = 2$ (which is U_0). One might even apply a chi-square test. It may be noted in passing that what Rydberg and Sullivan [4] denote as a χ^2 test (chi-square test) is not what is usually meant by the expression (Ref. [7], chapter 30) but rather a test that the σ^2 calculated from U_0 using (17) agrees reasonably well with the estimated experimental inaccuracy of y.

It would be deplorable if the use of LETAGROP or other, less powerful computer methods should lead to an over-estimate of the significance of "best" values. The main purpose of computer methods is to save time, for with good data the differences in results obtained by graphical and computer refining should not be large enough to be interesting. Most of the errors in chemical literature, unfortunately, would not be reduced by statistical treatment. Sometimes what is wanted is some theoretical understanding, or some imagination concerning the various possible reactions that may take place in a solution. Often, results can be improved, not by mathematical analysis but only bu purifying the reagents, repeating the experiments, varying the factors that may influence the results (range of concentrations *etc.*), and checking with independent experimental methods.

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