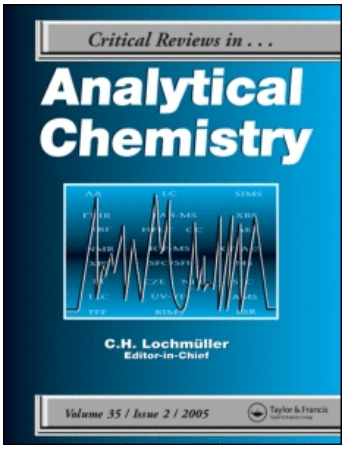

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A REVIEW OF SIMPLEX OPTIMIZATION IN ANALYTICAL CHEMISTRY

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I. INTRODUCTION

The purpose of this review is to summarize in a critical way some of the specific analytical chemical applications of sequential simplex methods of optimization. Although the sequential simplex is a powerful tool for carrying out both linear and nonlinear least-squares fits of models to data, these and other numerical applications will not be considered in this review. Instead, the review will be limited to those applications in which the response being optimized must be determined by actual experiment.

This review is divided into two sections. The first section briefly discusses the history and theory of sequential simplex methods. The second section describes analytical chemical systems to which these optimization techniques have been applied.

This review is somewhat unique because it presents very few specific conditions for carrying out analytical methods; for example, it will not be stated that, "The authors recommended 27°C and pH 7.3 as optimum conditions for the analysis." This absence of analytical detail is purposely done for two reasons. First, the primary subject matter of this review is a method of optimization; the usefulness of the simplex is not just that it can find a specific set of conditions to give improved analyses, but rather that it can do so in a simple,

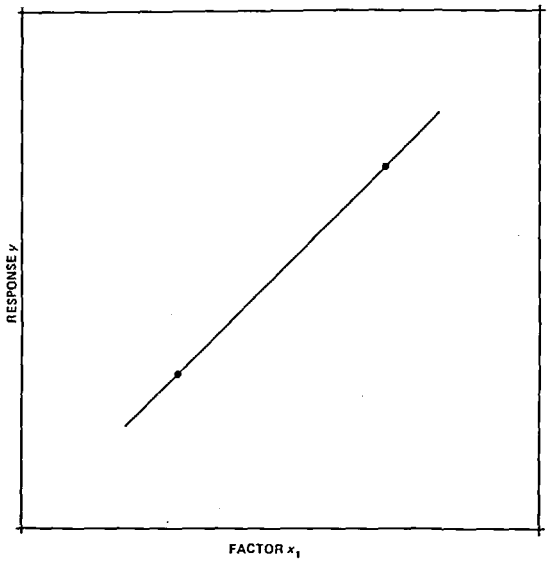

FIGURE 1. Experimental data for two points in a single-factor system.

straightforward, and efficient manner, handling several variables at a time. Second, the reason for not including detailed procedural recommendations is that interlaboratory variations in the implementation of analytical methods are such that one laboratory's optimum might not produce optimum results in another laboratory; for example, optimum burner height on one model of atomic absorption spectrometer might not be optimum on another model. Interlaboratory agreement on optimum conditions becomes achievable only if the analytical procedure can be written in such a comprehensive way that all significant factors can be controlled at the specified level in each laboratory.[1,2] This latter reason need not be of major concern, however, for whatever the optimum set of conditions are within a laboratory, sequential simplex methods offer an approach for achieving them.

II. HISTORY AND THEORY

It is a well-known fact that two nonidentical points uniquely define a straight line. If the coordinates (x_{11}, y_1) and (x_{12}, y_2) represent the data associated with two experiments, then

$$\beta_0 + \beta_1 x_{11} = y_1$$

$$\beta_0 + \beta_1 x_{12} = y_2 \qquad (1)$$

can be solved by linear algebra for β_0 (the y-intercept) and β_1 (the slope with respect to the single factor x_1). Similarly, a plane is uniquely defined by three noncolinear points. Given the data set (x_{11}, x_{21}, y_1), (x_{12}, x_{22}, y_2), and (x_{13}, x_{23}, y_3), it is possible to solve the set of simultaneous linear equations:

$$\beta_0 + \beta_1 x_{11} + \beta_2 x_{21} = y_1$$

$$\beta_0 + \beta_1 x_{12} + \beta_2 x_{22} = y_2$$

$$\beta_0 + \beta_1 x_{13} + \beta_2 x_{23} = y_3 \qquad (2)$$

where β_0 is again the y-intercept, and β_1 and β_2 are the slopes of the plane with respect to the factors x_1 and x_2, respectively. Graphical interpretations are given in Figures 1 and 2.

In general, a set of $k + 1$ linearly independent points in k-dimensional factor space is necessary and sufficient to uniquely fit a hyperplane of dimension k:

$$\beta_0 + \beta_1 x_{11} + \ldots + \beta_k x_{k_1} = y_1$$

$$\beta_0 + \beta_1 x_{12} + \ldots + \beta_k x_{k_2} = y_2$$

$$\beta_0 + \beta_1 x_{1(k+1)} + \ldots + \beta_k x_{k(k+1)} = y_{k+1} \qquad (3)$$

where, again, β_0 is the y-intercept and β_1 through β_k are the partial derivatives of the response with respect to each of the factors x_1 through x_k (i.e., the slopes of the hyperplane with respect to the various contributing factors).

Such a set of points in k-dimensional factor space defines a simplex and has long been known to be a highly efficient experimental design for estimating the parameters of first-order linear models such as Equations 1 to 3.[3] Each point in the design represents a vertex of the simplex; hence, the definition: a simplex is a geometric figure defined by a number of vertexes equal to one more than the number of dimensions of the factor space. In one-dimensional factor space, a simplex is a line segment consisting of two points (vertexes). In two-dimensional factor space, the simplex is a triangle. In three-dimensional factor space, the simplex is a tetrahedron. In higher dimensional factor spaces, the simplexes cannot be readily visualized, but are the "hypertetrahedral" analogs of the three-dimensional tetrahedron. Figure 3 shows several simplexes in factor space.

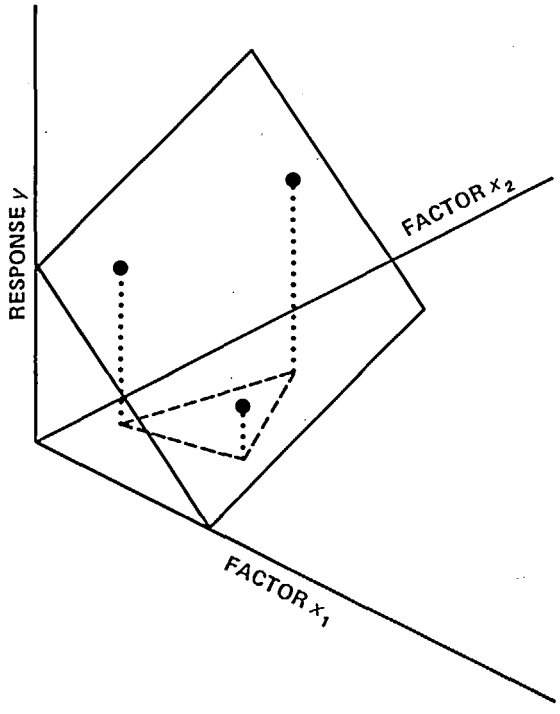

FIGURE 2. Experimental data for three points in a two-factor system.

In many experimental systems, there is value in possessing estimates of the parameters of first-order linear equations (such as Equations 1 to 3); these estimates offer an indication of the direction to be pursued if it is desired to increase (or decrease) the response (y) of the system. As a simple example, the data points shown in Figure 1 might represent the molar absorptivity (y) of a chemical species with respect to wavelength (x_1); it is clear that β_1 of Equation 1 would be positive for this data and that the molar absorptivity could be increased by going to longer wavelengths. As a more complex example, the data points shown in Figure 2 might represent the rate (y) of an enzyme-catalyzed reaction with respect to both pH of the solution (x_1) and temperature of the system (x_2); clearly, in this example, β_1 would be negative and β_2 would be positive. Thus, the rate of the reaction could be increased by decreasing pH (factor x_1) and increasing temperature (factor x_2). In systems where more than two factors are investigated, the simple graphical interpretation of Figures 1 and 2 is less obvious, and more reliance must be placed on the signs and magnitudes of the βs in the mathematical model (see Equation 3).

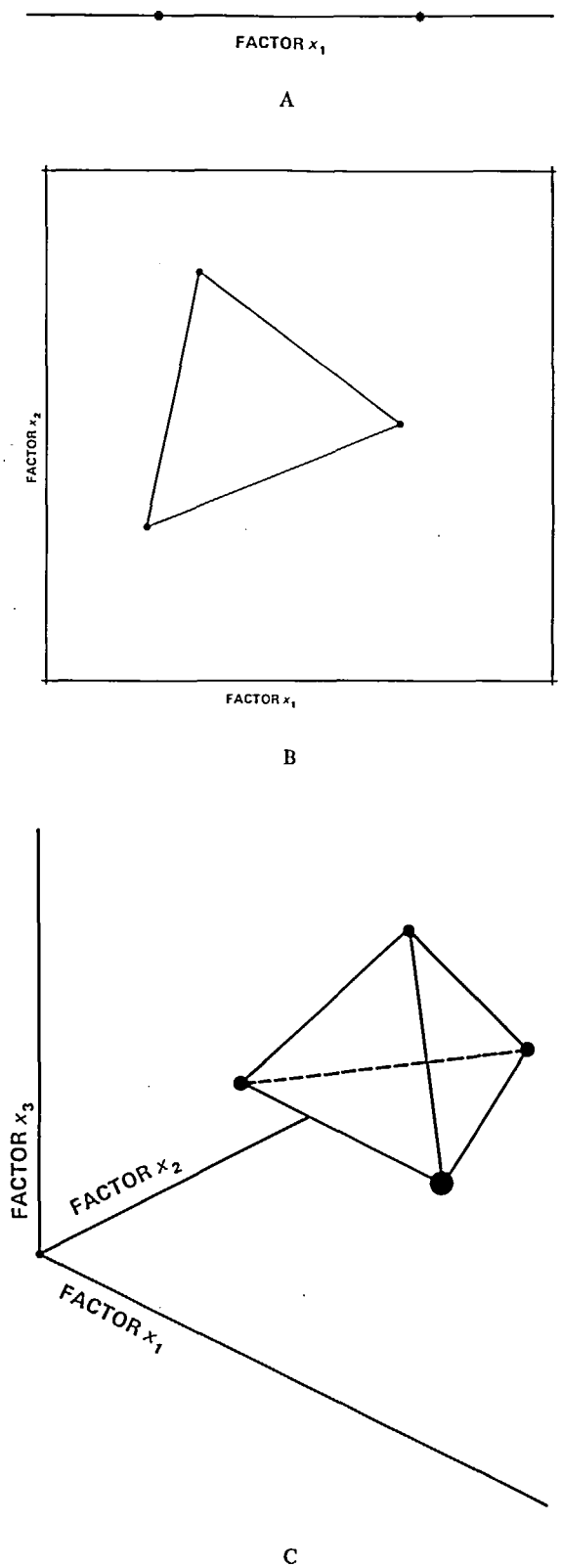

FIGURE 3. Simplexes in factor space.

It is to be noted that in each of these cases, the response can be improved by moving away from the vertex of worst response (see, for example, Figures 1 and 2).

First-order linear equations can be used as tools in determining the direction to move to increase (or decrease) response, but they offer no answer to the question of how far to move in that direction. Other classic experimental designs such as three-level factorial designs[4] or central-composite designs[3] can be used to detect curvature in the response surface and thus estimate the position of the optimum. However, these designs usually contain far more points than the $k + 1$ points of the simplex design.

Spendley and co-workers[5] provided an answer as to how far to move. They suggested that the geometric simplex figure could be made to move in factor space towards the optimum if a single "new" vertex were placed on the "opposite side" of the simplex from the "worst" vertex. The question of how far to move is answered by making the distances equal, that is, the new vertex is as far from the remaining side of the simplex as the old vertex was from that side. This is shown graphically in Figure 4 for the case of a simplex in two-dimensional factor space. For purposes of illustration, two-dimensional simplexes will be used. The method is general and can be applied to any number of factors. Optimization will be taken to mean maximization of response, but it could apply equally well to the process of finding a minimum.

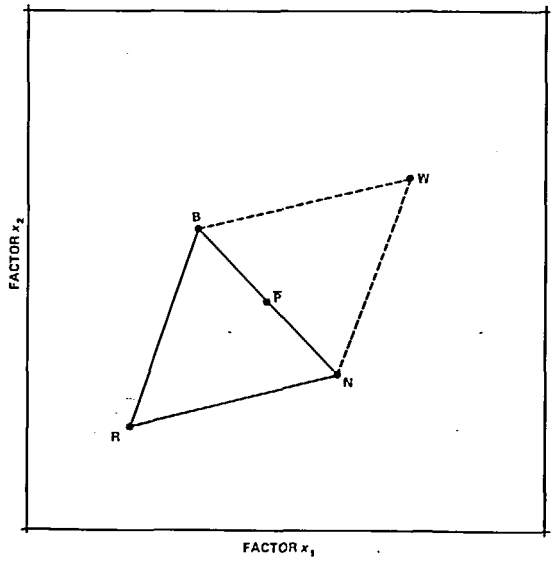

FIGURE 4. Two-dimensional simplex reflection.

The points W, N and B in Figure 4 represent those factor combinations that produced the worst, next-to-worst, and best responses. An example might involve the separation of several components by gas-liquid chromatography. Here, x_1 could represent column temperature, and x_2 could represent carrier gas flow rate. High temperature and high flow rate (e.g., point W in Figure 4) might give a very poor separation of a particular mixture. Slightly lower temperature and much lower flow rate (e.g., point N) might give improved separation. A still lower temperature and an intermediate flow rate (point B) might give the best separation of the three.

The symbols W, N, and B are vector notation for the factor combinations shown in Figure 4:

$$\begin{aligned} B &= (x_{1b} \quad x_{2b}) \\ N &= (x_{1n} \quad x_{2n}) \\ W &= (x_{1w} \quad x_{2w}) \end{aligned} \tag{4}$$

The point $\bar{P}$ in Figure 4 is called the "centroid of the hyperface" remaining after the worst vertex (W) has been eliminated from the simplex. It is simply the average coordinates of the remaining points. For two-factors, this is

$$\bar{P} = \frac{1}{2}(N + B) = \left[\frac{x_{1n} + x_{1b}}{2} \quad \frac{x_{2n} + x_{2b}}{2}\right] \tag{5}$$

The vector $(\bar{P} - W)$ is added to $\bar{P}$ to give the coordinates of a new vertex, the reflection vertex, R (see Figure 4). When vertex W is eliminated and vertex R is produced, a new, adjacent simplex, BNR, is formed. This new simplex can again be ranked; the vertexes then assume the new identities BNW.

Using this basic mechanism, the sequential simplex method causes the simplex to move to the region of optimum response. The decisions required to accomplish this constitute the "rules" of the simplex method.[5]

Rule 1 – A move is made after each observation of response. Once the responses at all vertexes have been evaluated, a decision can be made as to which vertex to reject. As has been seen, a new simplex can be completed by carrying out only one additional measurement (R). Except in the initial simplex, a move can be made after each measurement of response.

Rule 2 — A move is made into that adjacent simplex which is obtained by discarding the vertex of the current simplex corresponding to the least desirable response (W) and replacing it with its image (R) across the centroid ($\bar{P}$) of the hyperface of the remaining points. This operation has been discussed above. Figure 5 shows several moves of a simplex. If the new vertex has the worst response in the new simplex, Rule 2 would reflect the current simplex back to the previous simplex. The simplex would then oscillate and become stranded. This situation is shown in Figure 6. An exception to Rule 2 is necessary.

Rule 3 — If the reflected vertex has the least desirable response in the new simplex, do not reapply Rule 2, but instead reject the second lowest response in the simplex and continue. Figure 7 shows how Rule 3 prevents the simplex from becoming stranded.

When dealing with experimentally measured responses, statistical fluctuations are to be expected. To lessen the uncertainty associated with the responses in a simplex, replicate measurements could be made at each vertex, and the mean of these replicates could be used to assign a significance to the differences in response at the vertexes of a simplex. This is, however, not always necessary since a single evaluation of response at each vertex is usually sufficient. This abandonment of traditional statistical procedures can be justified for two reasons: First, if the differences in the responses are large compared to the size of the indeterminate errors, the simplex will move in the proper direction. Repetition of measurement would be wasteful. Second, if the differences in the responses are small enough to be affected by indeterminate errors, the simplex might move in the wrong direction; however, a move in a wrong direction will probably (in a truly statistical sense) yield a lower response that would be quickly

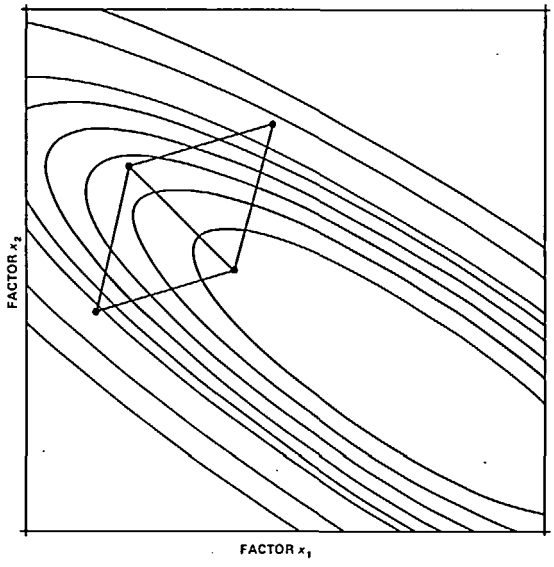

FIGURE 6. Possibility of oscillation.

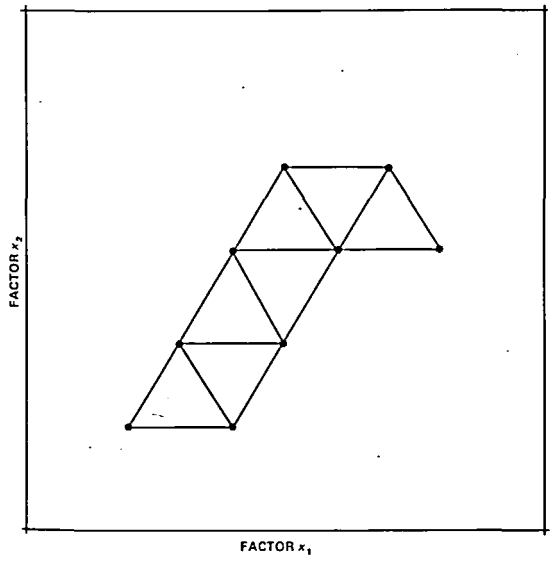

FIGURE 5. Several simplex moves.

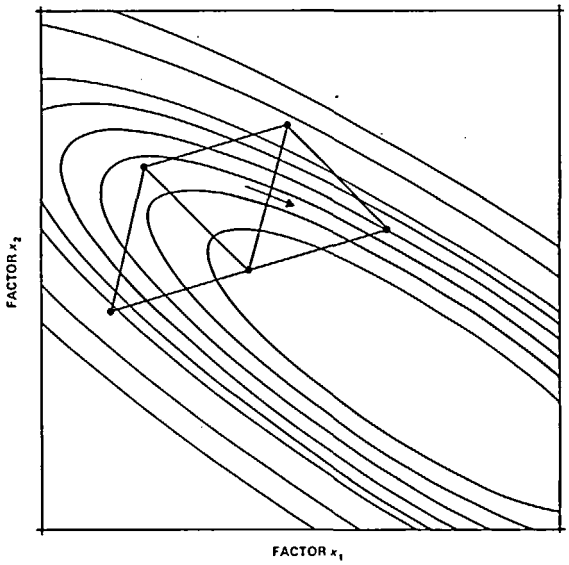

FIGURE 7. Avoidance of oscillation.

corrected by Rules 2 and 3. The simplex, although momentarily thrown off course, would proceed again towards the optimum.

A special case that might cause a problem is that of a large positive error. As the simplex moves, the less desirable responses are naturally discarded. The high responses, however, are retained. Thus, it is possible that the simplex will become fastened to a false high result and mistake it for the true optimum. To help distinguish between an anomalously good response and a valid optimum, the following exception to Rule 1 is used.

Rule 4 – If a vertex has been retained in $k + 1$ simplexes and is not then discarded, before applying Rule 2 re-evaluate the response at the persistent vertex. If the vertex is truly near the optimum, it is probable that the repeated evaluation will be consistently high and the maximum will be retained. If the response at the vertex was high because of an error in measurement, it is improbable that the repeat measurement will also be high, and the vertex will eventually be eliminated. Occasionally, the simplex might try to move beyond boundaries that have been placed on the factors.

Rule 5 – If a new vertex lies outside the boundaries of the independent variables, do not make an experimental observation; instead, assign to it a very undesirable response. Application of Rules 2 and 3 will then force the vertex back inside its boundaries, and it will continue to seek the optimum response.

Further discussions of the fixed-size simplex method may be found in the literature (see, for example, Spendley et al.,[5] Long,[6] and Deming and Morgan.[7])

The fixed-size simplex method of Spendley et al. suffers three limitations when it is used to locate a stationary optimum. In two dimensions, there is no difficulty in determining when the optimum has been located. The simplexes will become superimposed because of the ability of triangles to close pack. Tetrahedra and higher dimensional simplexes will not close pack. Thus, the first limitation is that it is not always clear when an optimum has been reached. Second, the original simplex technique has no provision for acceleration. This is usually overcome by the technique of running several phases, the first using a large simplex to roughly define the region of optimum response, the others to more precisely

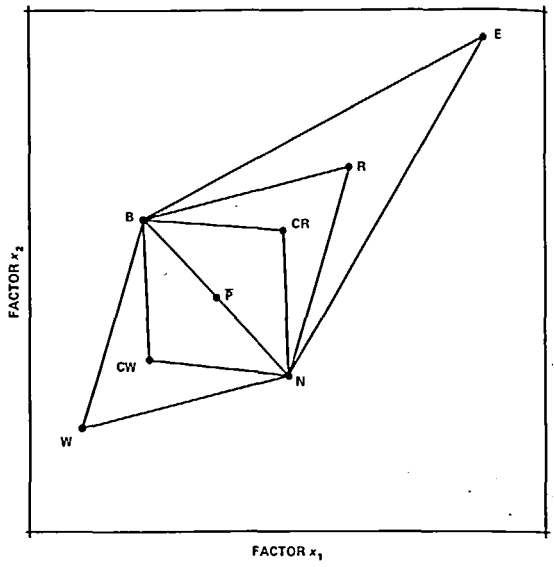

FIGURE 8. Variable-size simplex moves.

"home in" on the optimum. Third, one orientation of a simplex will cause it to attain a false optimum.[7] This problem can be overcome if another phase is run in which the new simplex is rotated with respect to the previous simplex.

There are applications in which none of these limitations are serious, applications that are truly "evolutionary operations"[8] in which the simplex method is used to attain and follow an optimum around a response surface that changes with time. Such applications are not rare in analytical chemistry. Keeping instruments in their best operating conditions as various of their components change characteristics with age is one example of such an application.

The modified simplex method of Nelder and Mead[9] is a logical algorithm consisting of reflection, expansion, contraction, and massive contraction rules. These rules can be understood by referring to Figure 8 and the initial simplex BNW.

Reflection is accomplished by extending the line segment $\overline{WP}$ beyond $\bar{P}$ to generate the new vertex R:

$$R = \bar{P} + (\bar{P} - W) \quad (6)$$

Three possibilities exist for the measured response at R:

1. The response at R is more desirable than the response at B. An attempted expansion is indicated, and the new vertex E is generated:

$$E = \bar{P} + 2(\bar{P} - W) \quad (7)$$

If the response at E is better than the response at B, it is retained as the new simplex BNE. If the response at E is not better than at B, the expansion is said to have failed, and BNR is taken as the new simplex. The algorithm is restarted using the new simplex.

2. If the response at R is between that of B and N, neither expansion nor contraction is recommended, and the process is restarted with the new simplex BNR.

3. If the response at R is less desirable than the response at N, a step in the wrong direction has been made, and the simplex should be contracted. One of two possible vertexes must be generated. First, if the response at R is worse than the response at N but not worse than that at W, the new vertex should lie closer to R than to W:

$$C_r = \bar{P} + \frac{1}{2}(\bar{P} - W) \quad (8)$$

The process is restarted with the new simplex BNC_r. Second, if the response at R is worse than the previous worst vertex W, then the new vertex should lie closer to W than to R:

$$C_w = \bar{P} - \frac{1}{2}(\bar{P} - W) \quad (9)$$

The process is restarted with the new simplex BNC_w.

A failed contraction results if the response at C_r is worse than the response at R, or if the response at C_w is worse than the response at W. Nelder and Mead[9] recommend a massive contraction in which the size of the simplex is diminished even further. This is shown graphically in Figure 9.

The massive contraction, although effective, suffers from two distinct disadvantages. First, it requires the evaluation of k new simplex vertexes before the algorithm can continue. Second, the volume of the simplex is contracted by $(\frac{1}{2}^k)$ which might give rise to premature convergence in the presence of error.

Ernst[10] recognized this second difficulty and recommended translation of the entire simplex following a failed contraction (see Figure 10). The simplex does not contract, but the process of translation does require the evaluation of $k + 1$ new vertexes.

King[11] has suggested the reintroduction of Rule 2 of Spendley and co-workers[5]: if the contraction vertex is the worst vertex in the new simplex, do not reject that vertex, but rather reject the next-to-worst vertex N. The procedure is simple, does not cause excessive contraction of the simplex, and does not require the evaluation of additional vertexes. It has been used effectively by Morgan and Deming.[12]

III. APPLICATIONS

One of the earliest applications of the sequential simplex in analytical chemistry was by

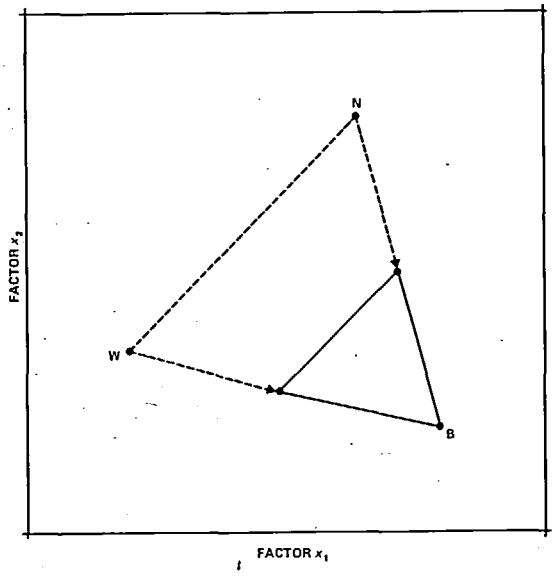

FIGURE 9. Massive contraction of simplex.

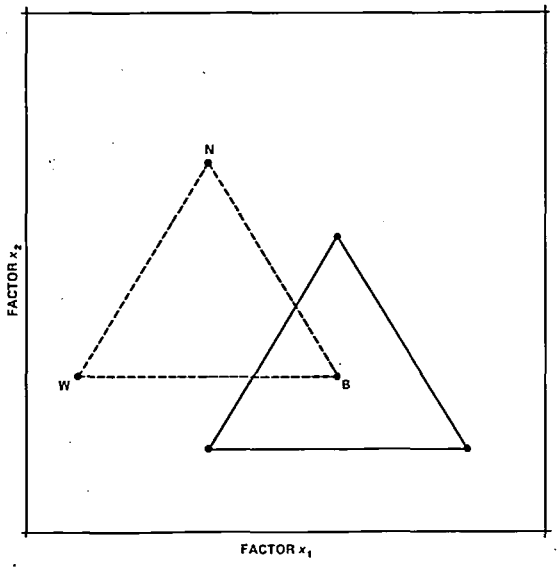

FIGURE 10. Translation of simplex.

Ernst,[10] who used the variable-size algorithm to improve nuclear magnetic resonance (NMR) magnetic field homogeneity; as a result, linear y-gradient and quadratic y-gradient magnetic shim coil currents were controlled (see Figure 11). The experiment was interfaced to a Varian® 620I computer which performed the simplex calculations and varied the currents supplied to the coils by means of stepping motors attached to the NMR's potentiometer controls. In this work, the performance of the simplex method was compared to the performance of the steepest descent (or gradient) method. It was concluded that the simplex converges faster and is the more efficient of the two. The need for repeating measurements on vertexes (the $k + 1$ rule) was re-emphasized.

Long[6] discussed many aspects of simplex optimization as applied to analytical chemistry. Among the points included were selection of factors and response, step sizes, boundaries, starting coordinates, the effect of error, and a shifting optimum. Specific cautions warned not to use the concentration of the substance being determined as a factor and to combine two interdependent factors into a single factor. Long pointed out that too large an initial step size could cause the simplex to miss the optimum; this is a problem only when using the fixed-size simplex. Long also recommended initial screening experiments (e.g., factorial) to determine which factors were important enough to be included in the simplex optimization. Later work[13,14] has shown that this is not necessary and that any potentially important factors can be included (factors of apparently small importance do not adversely affect the simplex). The concept of response surfaces, especially in regard to ridges, was also discussed.

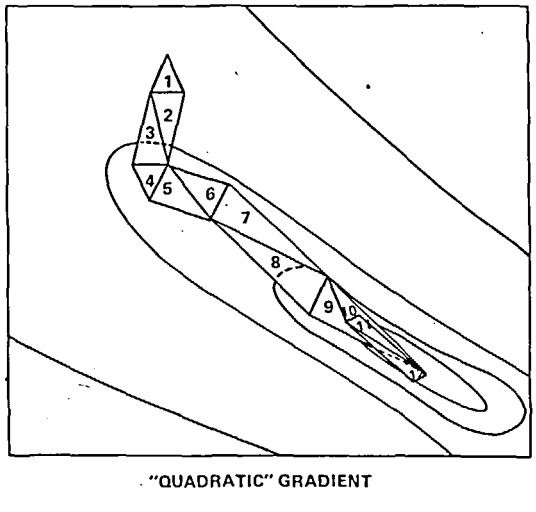

FIGURE 11. Example of performance of the simplex method for peak finding. (From Ernst, R. R., *Rev. Sci. Instrum.*, 39, 998 [1968]. With permission.)

Finally, to illustrate these points, Long gave an analytical example: optimizing the absorbance in the p-rosaniline test for SO_2, where the factors were volume of HCl and volume of formaldehyde added. A fixed-size simplex was used, which soon circled the optimum. A smaller simplex was then begun, and the optimum was located more precisely.

Long's cautions were not heeded in a 1970 paper by Houle and co-workers.[15] They were attempting to optimize the sensitivity of the chromotropic acid (CTA) method for the colorimetric determination of formaldehyde. The factors chosen were sample volume, reagent concentration (percent CTA in sulfuric acid), and reagent volume; the response chosen was absorbance. Sensitivity (the quality the authors claimed to optimize) is usually defined as the change in absorbance per unit change in concentration of the analyte. If Houle had not used sample volume as a factor (but had fixed it at some level), sensitivity would have been proportional to absorbance (assuming a linear relationship between absorbance and concentration); if the absorbance had been divided by the sample volume and the result used as the response, sensitivity might have been optimized. However, by using absorbance as the response and sample volume as a factor, the simplex simply moved to higher relative sample volumes which, as would be expected, yielded higher absorbance. If the simplex were allowed to continue until an apparent optimum was found, the sample volume would increase towards whatever was set as its upper limit. This is in conflict with Long's caution[6] not to use the concentration or amount of the substance being determined as a factor. In addition, the other two factors used by Houle, reagent concentration and reagent volume, are interrelated and could be expressed as one factor – the amount of reagent added. Again, Long[6] recommended combining interdependent factors. Finally, the criterion used by Houle for stopping the large simplex and going to a second, smaller simplex was that a reflection gave a lower response. This is highly suspect, as the simplex might have passed over a ridge, not an optimum,

and, if allowed to continue, could have reoriented itself and moved towards a different region.[16]

In a later work,[17] Olansky and Deming re-optimized this wet chemical method for formaldehyde. The sample volume of formaldehyde solution was fixed at 2.00 ml, and the factors varied were volume of CTA and volume of sulfuric acid added (in order to investigate these factors independently). Absorbance was used as the response, and, since the amount of analyte was held constant, the authors were able to optimize sensitivity (again, assuming a linear response function). An important finding was that an optimum exists in the ratio of sulfuric acid volume to total volume (see Figure 12). Later regression analysis used a model which, among other things, accounted for the effect of dilution upon response (increasing the volume of added reagents may produce more of the colored species, but it also increases the total volume, which tends to lower the absorbance).

Two applications of simplex methods have been published by Czech.[18,19] In the first paper, the optimization of the J-acid method for the determination of formaldehyde was described. However, the procedures of Houle et al. were repeated here. The author claimed to optimize sensitivity, yet the response used was absorbance and the sample volume was one of the factors. Also, two interrelated factors, reagent concentration and reagent volume, were used. The second application by Czech[19] was the acetylacetone method for the determination of formaldehyde. The factors and response were again the same as in the J-acid method. Czech also questions the need for replicating any experiments; however, as Spendley et al.[5] pointed out and Long re-emphasized,[6] failure to replicate in accordance with the $k + 1$ rule may lead to the simplex converging to a false optimum on an experimental system with noise.

Furthermore, Czech made the statement that simplex optimization can increase productivity (or, in an analytical method, sensitivity) from six- to eightfold.[19] Such a statement is misleading, as some processes or methods may already be near their optima; also, there is no guarantee that simplex optimization can improve a process by any arbitrarily selected amount.

Deming and Morgan[7] outlined the simplex rules, including the next-worst reflection and $k + 1$, and also discussed handling vertexes which lie outside boundaries. The advantages of the variable-size simplex over the fixed-size simplex were also discussed. Two examples of the use of simplex techniques were given: first, a numerical example in which an exponential model was fit to absorbance vs. time data (nonlinear least squares); second, an experimental example in which the

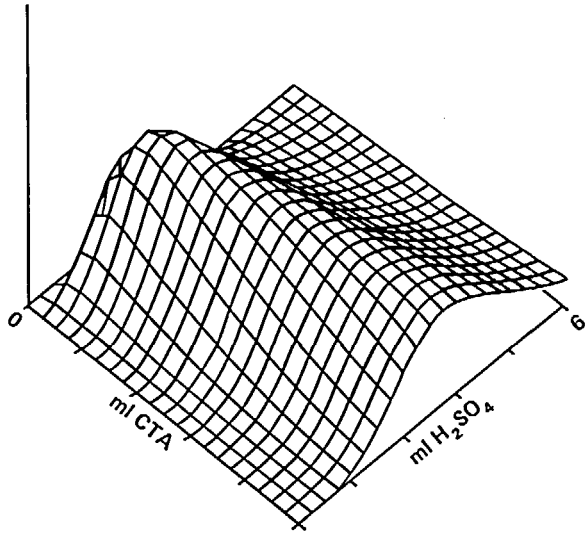

FIGURE 12. Absorbance response surface as a function of chromotropic acid volume and concentrated sulfuric acid volume. (From Olansky, A. S. and Deming, S. N., *Anal. Chim. Acta*, 83, 241 [1976]. With permission.)

absorbance of the Liebermann-Burchard method for cholesterol determination was optimized.

Morgan and Deming[13] further discussed the moves of the simplex and showed, as Box[20] had previously, how traditional, univariate optimization procedures can fail to find the optimum. The cholesterol optimization study briefly mentioned earlier[7] was presented in greater detail. The sample volume was fixed, and four factors (volume percents of solvent [acetic acid], dehydrating reagent [sulfuric acid], color reagent [also sulfuric acid], and color development time) were varied. A preliminary screening factorial experiment, as recommended by Long,[6] indicated that a potential fifth factor, dehydration time, was not important. The response used was a weighted combination of the absorbance and stability of the colored species. The use of derivatives as an indication of when the optimum has been reached (see Figure 13) was discussed. A univariate mapping was performed in the region of the optimum, and the data from the initial screening experiments, simplex optimization, and mapping were used to fit a full second-order polynomial model by regression analysis.

The use of a preliminary two-level factorial design to screen for potentially significant factors is suspect. As the authors stated: "Ideally, the question that should be asked is not, 'What factors are significant at the x level of probability?', but rather, 'What factors are *insignificant* at the x level of probability?' The number of factors retained when using the second criterion will in general be larger than the number retained when using the first; the investigator will, however, be assured that he is probably not omitting from investigation any factors that are important."[13]

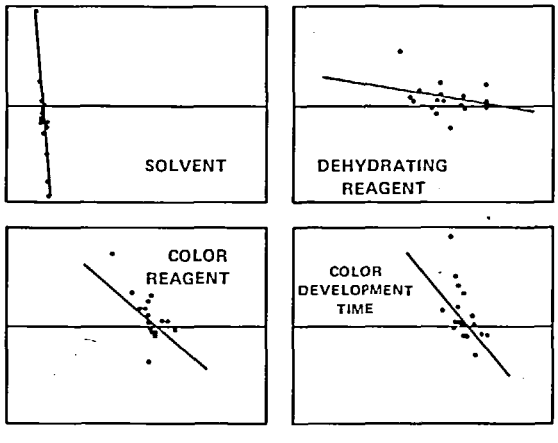

FIGURE 13. Derivative plots. (From Morgan, S. L. and Deming, S. N., *Anal. Chem.*, 46, 1170 [1974]. With permission.)

Parker et al.[14] applied simplex optimization to a five-factor atomic absorption system. Here, no initial screening experiments were performed. Four factors thought to be important were included in the study: air flow rate, fuel flow rate, hollow cathode lamp current, and burner height. Because this strategy can lead to the inclusion of insignificant factors, it was also desired in this work to investigate what effect such a factor would have upon the simplex. Therefore, a fifth, insignificant factor, the volume of water in a graduated cylinder far removed from the instrument, was included. The response used was the absorbance for a fixed concentration of calcium.

The authors reached three major conclusions:

1. The inclusion of an insignificant factor did not appear to affect the progress of a simplex toward an optimum in the other factors, although this was not confirmed since a second optimization omitting the fifth factor was not conducted. However, a one third-fractional 3^5 factorial experiment did indicate that the simplex had achieved an optimum in the three factors found to be significant (air flow rate, fuel flow rate, and burner height).
2. Convergence of a factor (variable-size simplex) does not necessarily mean that the factor is at an optimum; as the simplex contracts, it shrinks in all factors simultaneously; therefore, additional experiments (mapping, factorial) are needed in the region of the optimum to verify whether each factor is at an optimum.
3. The system studied had a major ridge (air-fuel ratio) over which the simplex moved extremely well; replotting the simplex data for air and fuel as the air-fuel ratio showed tight convergence (see Figure 14).

Johnson and co-workers[21] also applied simplex optimization to atomic absorption using pulsed hollow cathode lamps. They conducted several studies optimizing peak intensity and integrated intensity of the output from various lamps. Factors varied included pulse height (peak current), DC level (background current between pulses), pulse width, average current, and duty factor. Rippetoe et al.[22] used simplex optimization to tune a spectrophotometer before undertaking a

study of a DC plasma arc. Variables used were arc current, slit width, slit height, and the arc optical path; the response used was the signal-to-noise ratio of the emission intensity for calcium. The optimum found was then used for all the elements in the study. This practice should be used with caution since response surfaces often change when a certain discrete factor (such as element being determined) is changed.

Michel and co-workers[23] have used simplex optimization in the construction of electrodeless discharge lamps for atomic fluorescence using ten factors. A large initial simplex, as recommended by Yarbro and Deming,[24] was used, resulting in 9 of the 11 initial vertexes giving no response. They adjusted the coordinates of the vertexes to obtain responses from all 11 lamps. This must be done carefully, however, as arbitrary changes to the initial simplex may result in two or more vertexes lying in the same hyperplane, thus removing a degree of freedom of movement from the simplex.

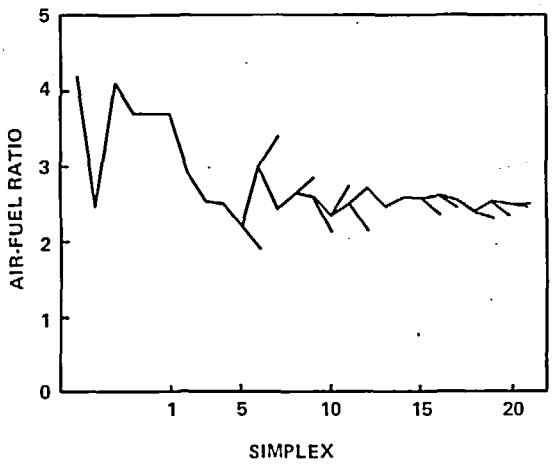

FIGURE 14. Air-fuel ratio vs. simplex number. (From Parker, L. R., Morgan, S. L., and Deming, S. N., *Appl. Spectrosc.*, 29, 429 [1975]. With permission.)

Smits et al.[25] applied simplex methods to the optimization of information in cation exchange chromatography. The concentrations of two compounds (HCl and dimethylsulfoxide) in the eluting agent were the factors; the response was a summation of the amount of overlap of each peak with the two adjoining peaks (see Figure 15). The response was divided by the time of elution in an attempt to maximize the information content per unit time. However, the simplex simply moved towards shorter time (see Figure 16). As the time (denominator in the response function) decreased, the response increased. This, therefore, points to an additional caution: dividing the response by a factor (such as absorbance divided by concentration for sensitivity) or by a secondary response (such as division by time) may lead to the simplex decreasing that factor or secondary response; the response function will be at a maximum when the denominator is zero. They repeated the optimization, but with an upper boundary on the amount

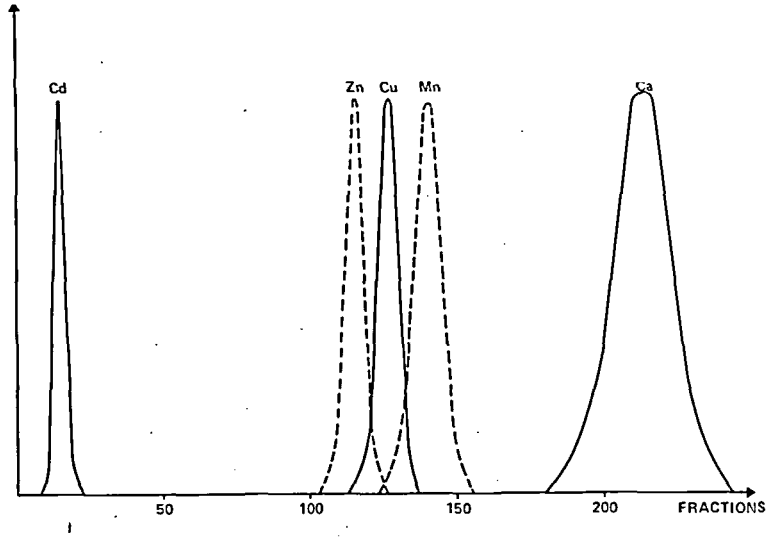

FIGURE 15. Initial separation. (From Smits, R., Vanroelen, C., and Massert, D. L., *Z. Anal. Chem.*, 273, 1 [1975]. With permission.)

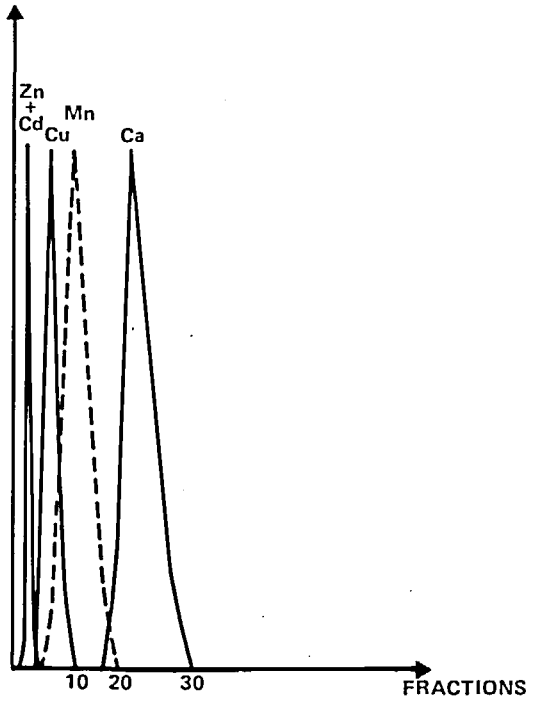

FIGURE 16. Optimal separation when no boundary is applied. (From Smits, R., Vanroelen, C., and Massert, D. L., *Z. Anal. Chem.*, 273, 1 [1975]. With permission.)

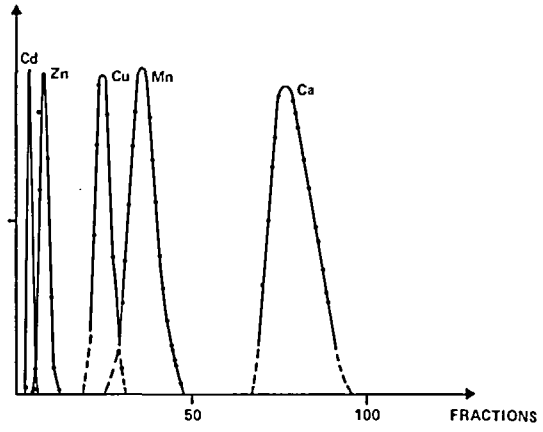

FIGURE 17. Optimal separation when a boundary is applied. (From Smits, R., Vanroelen, C., and Massert, D. L., *Z. Anal. Chem.*, 273, 1 [1975]. With permission.)

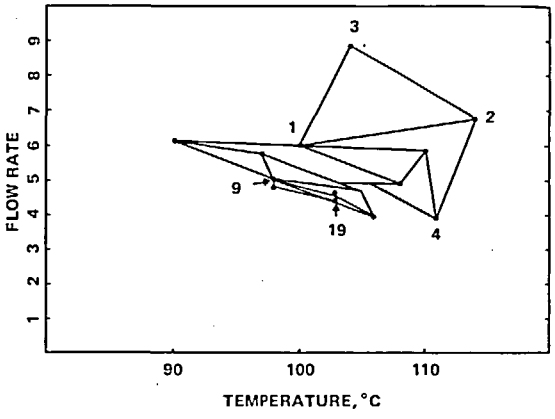

FIGURE 18. Simplex progress for five-component system, 30-min time constraint. (From Morgan, S. L. and Deming, S. N., *J. Chromatogr.*, 112, 267 [1975]. With permission.)

of overlap (see Figure 17); this resulted in an optimum in informing power within the given constraint.

Morgan and Deming[12] also applied simplex optimization to separation, using gas chromatography. Here, two instrumental parameters (column temperature and carrier gas flow rate) were the factors varied; the response was a measure of the separation between pairs of adjacent peaks. Two modifications to the variable-size simplex were used here. First, after a failed contraction, a massive contraction[9] was not performed; instead, a next-worst reflection[5] was performed. Second, a limit was set on the minimum simplex size; if a contraction attempted to shrink the simplex below the limit, the contraction was disallowed (this was to prevent the simplex from becoming too small to be able to move on a response surface with error). Two-, three-, and five-component mixtures were run (see Figure 18), each followed by a factorial experiment (see Figure 19) and a regression analysis (see Figure 20). Morgan and Deming set an upper limit on elution time, a means of controlling an undesirable second response (long elution time with an accompanying loss of sensitivity), while keeping the actual response function simple. They[26] have also discussed optimization in chromatography in a more general sense.

Vanroelen and co-workers[27] carried out a factorial design with replication on the optimization of the absorbance in an extraction procedure for the determination of phosphate (using as factors concentration of $HClO_4$, concentration of ammonium molybdate, and isobutanol-to-benzene ratio in the extracting agent). Although the factorial study was well designed, the authors concluded that additional factorials (each consisting of 81 experiments) would be needed to more closely define the optimum. A simplex optimization was then undertaken and proved far more efficient, as it converged to an apparent optimum

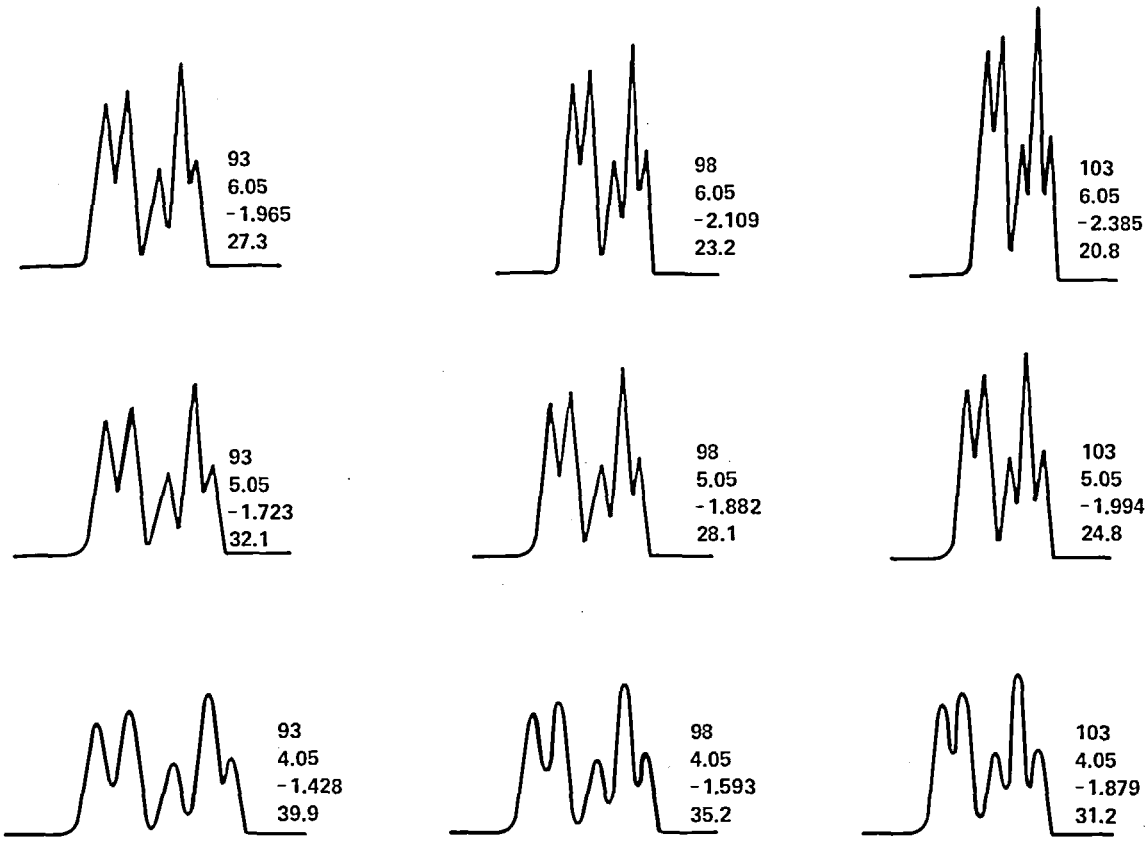

FIGURE 19. Chromatograms from factorial design on five-component system. (From Morgan, S. L. and Deming, S. N., *J. Chromatogr.*, 112, 267 [1975]. With permission.)

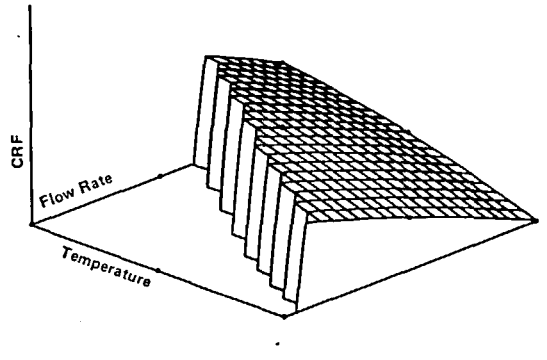

FIGURE 20. Time-contrained CRF regression surface for five-component system. Dots correspond to factorial experiments in Figure 19. (From Morgan, S. L. and Deming, S. N., *J. Chromatogr.*, 112, 267 [1975]. With permission.)

in only 19 experiments. This apparent optimum agreed well with the optimum predicted by the factorial study.

King and Deming[28] gave the name UNIPLEX® to the special case of simplex optimization where only one factor is varied. The system reported on was the maximization of absorbance of dichromate; the factor varied was the amount of chromate which reacted with a fixed amount of acid to produce the dichromate (see Figure 21). The system described was automated, with computer interfacing and stepper motors driving pumps for the chromate and acid. A later work by Cantor and Jonas[29] also used UNIPLEX, the goal being to optimize first the phase and then the length of pulses in pulsed NMR spectrometry.

Deming and King[30] used the same automated system as described above[28] in a simplex optimization of the acetylacetone method for the determination of formaldehyde; factors varied were acetylacetone and ammonium ion. These reagents were pumped from fixed concentrations; a make-up reagent (water) was added via a third pump to keep the total flow constant, thus achieving

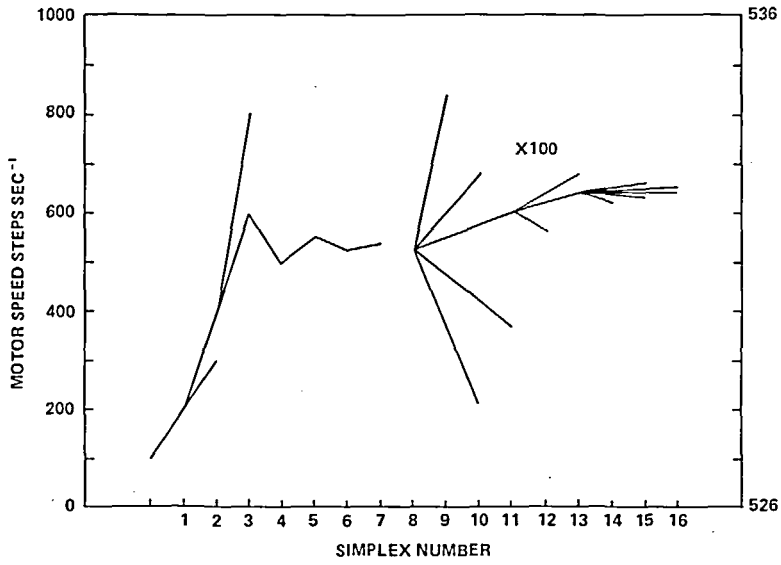

FIGURE 21. Factor level vs. simplex progress. Scale expanded after simplex 7. (From King, P. G. and Deming, S. N., *Anal. Chem.*, 46, 1476 [1974]. With permission.)

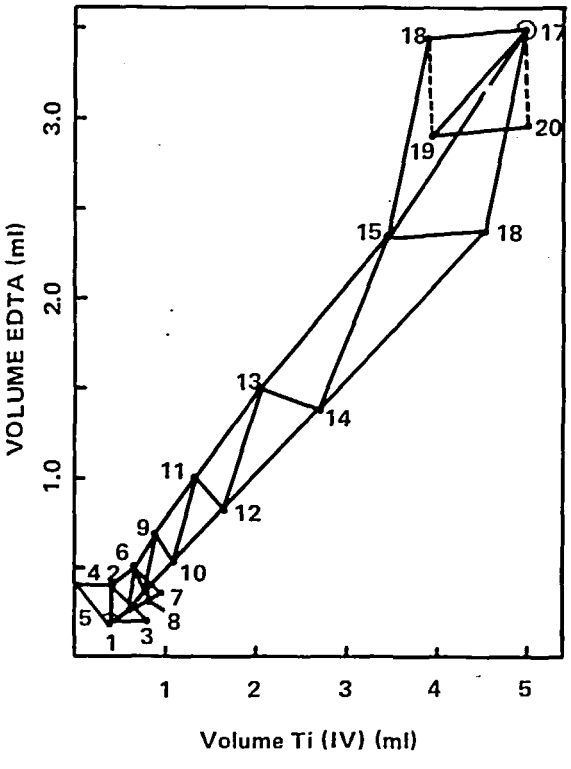

FIGURE 22. Two-factor simplex experiment performed automatically on the Ti(IV)-EDTA-H_2O_2 reaction. (From Mieling, G. E., Taylor, R. W., Hargis, L. G., English, J., and Pardue, H. L., *Anal. Chem.*, 48, 1688 [1976]. With permission.)

independent variation of the two factors. The response was the absorbance for a fixed concentration of formaldehyde (from a fourth pump).

Mieling and co-workers[31] also used an automated system in a simplex optimization (see Figure 22). The study was performed on the reaction of H_2O_2 with Ti(IV) in the presence of EDTA. They optimized a response function containing both the absorbance and stability of the complex; the factors chosen were the concentrations of the Ti(IV) and EDTA. The optimal levels of these two factors agreed well with earlier studies by the same authors.

Krause and Lott[32] used a commercially available automated instrument, the Technicon Auto-Analyzer,® for simplex optimization studies. Two studies were undertaken: (1) The interaction between samples in the system for the determination of copper was minimized by varying the sample-to-wash ratio and the flowcell pull-through rate (see Figure 23). The authors noted that these factors were not truly continuously variable due to the physical limitations of the system (for example, changing flowcell pull-through required changing the size of tubing, a discrete factor). (2) The interaction between samples in the determination of glucose was minimized by varying the percent sample (determined by the sample-to-wash ratio), percent pull-through, and percent air in the sample stream.

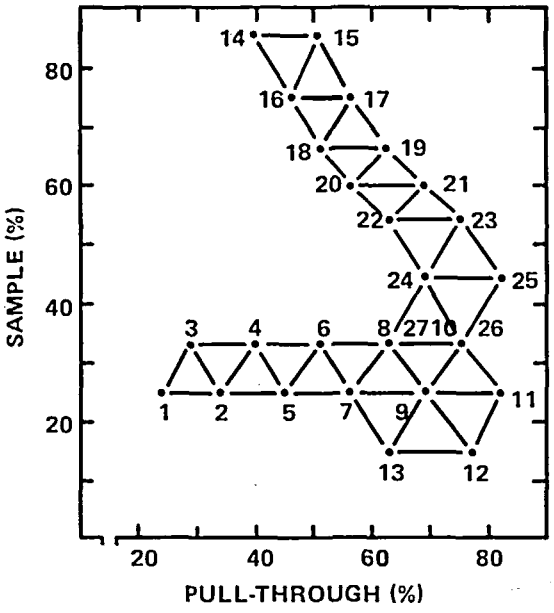

FIGURE 23. Progress of simplex in optimization of simplified ($CuSO_4$) continuous-flow system. (From Krause, R. D. and Lott, J. A., *Clin. Chem.* (Winston-Salem), 20, 775 [1974]. With permission.)

Krause and Lott then performed two additional simplex optimization studies in the area of clinical chemistry: (1) In a kinetic method (the LD-catalyzed pyruvate-to-lactate reaction), four factors (pH and concentrations of Tris buffer, pyruvate, and NADH) were varied to find the optimal rate of conversion. (2) Using the GEM-SAEC centrifugal analyzer, the optimal conditions found for the pyruvate-to-lactate reaction were set, and the times between readings and the number of readings were varied; the response was the coefficient of variation (CV). The simplex optimization reduced the CV from 3.1 at the manufacturer's recommended settings to 1.6 at the optimum.

When Lott and Turner[33] applied simplex optimization to an automated continuous-flow method, the object was to maximize the absorbance in the glucose-oxidase method for determining glucose in serum. The factors chosen were glucose oxidase and peroxidase activities and concentrations of two reagents (4-aminoantipyrine and phenol). The simplex was terminated upon reaching an adequate level of response.

Basson and co-workers[34] have also worked with the simplex technique on a Technicon Auto-Analyzer. The goal was to optimize the absorbance in the method for the determination of boron. Because the indicator, azomethine H, deteriorated rapidly, they decided to synthesize it *in situ* from H-acid and salicylaldehyde. The factors chosen, therefore, were concentrations of salicylaldehyde and H-acid and pH. No details of the method or the optimization were given.

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