AD-A064 487 WASHINGTON UNIV SEATTLE LAB FOR CHEMOMETRICS F/G 7/4
THE GENERALIZED STANDARD ADDITION METHOD.(U)
SEP 78 B E SAXBERG, B R KOWALSKI N00014-75-C-0536
UNCLASSIFIED NL

1 OF 1
AD
A0 64487

END
DATE
FILMED
4 -- 79
DDC

OFFICE OF NAVAL RESEARCH

Contract N00014-75-C-0536

Task No. NR 051-565

The Generalized Standard Addition Method

Prepared for Publication

in

Analytical Chemistry

by

Bo E.H. Saxberg
and
Bruce R. Kowalski
Laboratory for Chemometrics
Department of Chemistry, BG-10
University of Washington
Seattle, Washington 98195

September 1978

Reproduction in whole or in part is permitted for any purpose of the United States Government

Approved for Public Release; Distribution Unlimited

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER 13	2. GOVT ACCESSION NO. --	3. RECIPIENT'S CATALOG NUMBER (9) --
4. TITLE (and Subtitle) (6) The Generalized Standard Addition Method		5. TYPE OF REPORT & PERIOD COVERED Technical ~~Interim~~ rept. no. 13, 8/78 - 9/78 Aug-Sep 78,
		6. PERFORMING ORG. ~~REPORT NUMBER~~ --
7. AUTHOR(s) (10) Bo E. H. Saxberg Bruce R. Kowalski		8. CONTRACT OR GRANT NUMBER(s) (15) N00014-75-C-0536
9. PERFORMING ORGANIZATION NAME AND ADDRESS Laboratory for Chemometrics, Department of Chemistry, University of Washington, Seattle, WA 98195		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS NR 051-565
11. CONTROLLING OFFICE NAME AND ADDRESS Materials Sciences Division Office of Naval Research Arlington, Virginia 22217		12. REPORT DATE (11) September 1978
		13. NUMBER OF PAGES 38 (12) 41p.
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office) --		15. SECURITY CLASS. (of this report) UNCLASSIFIED
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

--

18. SUPPLEMENTARY NOTES

Prepared for publication in Analytical Chemistry

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

GSAM
analyte
simultaneous determination

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The normal standard addition methods assumes that, for any one analyte in a sample there is an analytical sensor which responds to that analyte and no other unknown in the sample. When the analytical sensor is not completely selective, so-called interference effects results which can be a major source of error. The generalized standard addition method provides a means of accounting for the interference effects, to actually quantify the magnitude of the interferences, and simultaneously to determine the analyte concentrations.

408 726

79 02 09 052

ABSTRACT

The normal standard addition method assumes that, for any one analyte in a sample there is an analytical sensor which responds to that analyte and no other unknown in the sample. When the analytical sensor is not completely selective, so-called interference effects result which can be a major source of error. The generalized standard addition method provides a means of accounting for the interference effects, to actually quantify the magnitude of the interferences, and simultaneously to determine the analyte concentrations. The GSAM as presented here uses multiple linear regression to analyze multi-component samples where the response-analyte concentration relationship is of some arbitrary polynomial form; for a non-linear polynomial relationship, an iterative solution is required.

The standard addition method (SAM) is well known to all analytical chemists. A description of the method can be found in almost every text book on any aspect of quantitative chemical analysis including the most basic texts used in introductory courses. By its use a number of sample- and method-associated interferences can be overcome; it is particularly suited for residual matrix effects and is most often the method of choice for trace analysis.

Assuming a linear change in response for an increased concentration of an analyte, the response is measured before and after several successive additions of the analyte to a sample of unknown analyte concentration. Plotting response (ordinate) by the amount of standard added (abscissa) the analyte concentration is found by fitting a line to the data and finding the intercept on the abscissa.

Certain concepts which occur throughout this paper will now be defined. The "analytical sensor" is that which provides a measurement of one analytically valuable property. The analytical sensor is the source of the "analytical signal" which may undergo a mathematical transformation to form the signal which provides useful information for sample analysis. An example of a single-instrument, single-sensor analytical method is the measurement of the voltage between two electrodes in a sample solution (the pair constitutes a single sensor). An example of a single-instrument, multiple-sensor analytical method is the measurement of u.v. absorbance spectra with a u.v. spectrophotometer, which can provide absorbance values at different wavelengths. The instrument is a sensor when measuring the absorbance at any one wavelength, hence the u.v. spectrophotometer is a multiple sensor instrument as it can take readings at different wavelengths and each wavelength can correspond to a single analyte. The standard addition method assumes that for each analyte in a sample there is an associated analytical signal which, ideally, is a function only of that analyte and no other unknown sample component.

By defining the transformed analytical signal obtained from a sensor by some analytical method for the ℓth analyte of a sample of unknown composition as a "response", R_ℓ, to the concentration, c, of the analyte ("concentration" is used here, though in some applications it may not bear any meaning in relation to the amount of an analyte in a sample), the model implied by the standard addition method is:

$$R_\ell = c \cdot k_\ell = (\Delta c + {}_oc)k_\ell = \Delta c \cdot k_\ell + {}_oc \cdot k_\ell \qquad (1)$$

where Δc is the known change in concentration, ${}_oc$ is the unknown initial concentration of the analyte and k_ℓ is the constant coefficient in the linear relation between property ℓ and the concentration of the analyte. This equation reveals several drawbacks to the traditional standard addition method: 1) the requirement that the function relating response to concentration be linear, 2) the requirement that the response be zeroed, i.e., zero concentration of the analyte should evoke a zero response, and 3) as a result of 2), if the measured property of R_ℓ is affected by other components than the one of interest, then the effect of these components must somehow be eliminated from the samples.

Given a multi-component mixture with several analytes of interest, in order to use the standard addition method the analyst must either A) use analytical methods which, in Kaiser's terms (1), are "fully selective" so that each response will only be affected by one analyte, allowing eq. 1 to be used, or B) be able to remove all of the interfering components for a given response and a given analyte to allow the use of eq. 1. In a large number of cases, the requirement of full selectivity is not obtainable in practice, and the isolation of each analyte from all other interfering components can present formidable problems. In fact, much of the bulk of the current analytical literature amounts to studies of matrix effects. There are several important specialty areas of analytical chemistry (e.g., electroanalytical chemistry, atomic emission spectroscopy, etc.) where the relation between the measured properties and the relative amounts of various components can be transformed into a linear equation analogous to eq. 1, but extended to include contributions from several components for each response (the so-called "interference" effects) as:

$$R_\ell = \sum_{s=1}^{r} c_s \cdot k_{s\ell} = \sum_{s=1}^{r} (\Delta c_s + {}_oc_s) k_{s\ell} = \sum_{s=1}^{r} \Delta c_s \cdot k_{s\ell} + \sum_{s=1}^{r} {}_oc_s \cdot k_{s\ell} \qquad (2)$$

where there are r analytes of interest.

In this paper, we present the "Generalized Standard Addition Method" for the simultaneous determination of any number of analytes using analytical sensors that have responses defined by equation 2. The only assumptions are that each response can be "zeroed" and that the number of analytical sensors is greater than or equal to the number of analytes. The analyst no longer needs to be concerned with the selectivity or interferences of analytical methods.

In formulating the generalized standard addition method (hereafter referred to as the GSAM), this paper will present the mathematics for a simultaneous multidimensional analysis by multiple regression using multiple standard additions and analytical sensors for the linear model of eq. 2, and for the extension to the quadratic, cubic and higher order models (i.e., allowing $k_{s\ell}$ to depend on the concentrations of the sample components in a linear, quadratic or higher-order manner). We include the method of the determination of the initial concentrations, and we also show how to recover the coefficients of the model (e.g. the selectivity coefficients if the $k_{s\ell}$'s are constants) from the regression coefficients. The equation to be iteratively solved for the initial concentrations for any non-linear model is generalized to a model of arbitrary degree. Some discussion is included of the construction of decision functions to help avoid areas of local divergence of the iteration (if any exist), and the practical considerations of applying the GSAM are discussed.

DEVELOPMENT OF THE METHOD

The simple linear model (eq. 2, with the $k_{s\ell}$'s as constants) is developed first, in traditional vector-matrix notation, to illustrate the motivation for the approach used. The extension to the quadratic model, again in traditional vector-matrix notation, will then be made. For the cubic model, new notation is introduced which allows the extension to a model of arbitrary degree to be readily grasped intuitively. However, certain key expressions are written out in detail using standard summation notation to clarify the meaning of the more abstract notation.

First some background notation is established. Define

$$\vec{R}_m \equiv (R_{m1}, R_{m2}, \ldots, R_{mp}) \tag{3}$$

$$\vec{C}_m \equiv (C_{m1}, C_{m2}, \ldots, C_{mr}) \tag{4}$$

where $\vec{R}_m$ is the vector of responses 1 through p (i.e., there are p different analytical sensors) from a sample after m standard additions containing analytes 1 through r in concentrations listed in vector $\vec{C}_m$ have been made. From eq. 2,

$$R_{m\ell} = \sum_{s=1}^{r} c_{ms}\cdot k_{s\ell} \qquad \ell = 1,\ldots,p \tag{5}$$

Writing this in matrix form,

$$\vec{R}_m = (R_{m1}, R_{m2},\ldots, R_{mp}) = (C_{m1}, C_{m2},\ldots, C_{mr}) \begin{bmatrix} k_{11} & k_{12} & \cdots & k_{1p} \\ k_{21} & k_{22} & & \vdots \\ \vdots & & & \vdots \\ k_{r1} & \cdots & & k_{rp} \end{bmatrix} \tag{6}$$

$$\therefore \vec{R}_m = \vec{C}_m\cdot[K] \tag{7}$$

Now define

$$[R] = \begin{bmatrix} \vec{R}_1 \\ \vec{R}_2 \\ \vdots \\ \vec{R}_n \end{bmatrix} \quad \text{and} \quad [C] = \begin{bmatrix} \vec{C}_1 \\ \vec{C}_2 \\ \vdots \\ \vec{C}_n \end{bmatrix} \tag{8}$$

i.e., [R] and [C] are the matrices of responses and concentrations for the n successive standard additions. This gives the simple formulation:

$$[R] = [C][K] \tag{9}$$

The matrix [R] is known, as it is the matrix of measured responses. The matrix [C] is unknown, as the concentrations of the analytes in the sample during the process of making standard additions are unknown. The matrix of coefficients, [K], is also unknown.

It should be noted that additions can be made for several analytes at the same time in the process of making a single "standard addition" subject to certain restrictions detailed later. The additions will therefore be called "multiple standard additions", or MSA's, to indicate the possibility of changing the concentrations of several components at the same time.

Some way of expressing the relationship in eq. 9 in terms of the known changes in concentration is now desirable. It is assumed that volume corrections, etc., can be made so that any error from not knowing the original concentration in calculating the net change in concentration in the sample will be negligible. Actually this is rarely a problem as minute volumes of high concentration standards can be added so that volume changes are negligible.

A separation of terms leads to,

$$[C] = [\Delta C] + [C_o] \tag{10}$$

where $[C_o]$ is a matrix in which all rows are identically $\overrightarrow{C_c}$, the unknown analyte concentrations, and $[\Delta C]$ is the matrix of the net changes in concentration made through the MSA's (i.e., $\Delta\overrightarrow{C_m}$ is the total change in concentrations made by the end of the mth MSA, and it is the mth row of $[\Delta C]$). Note that in $[C_o]$, each row is the same as every other row because the GSAM begins with a single sample, to which successive MSA's are made to generate each row of $[R]$ and $[\Delta C]$.

The ability to separate terms in c into terms in Δc and ${}_oc$ is crucial to what follows. This places a limit on the possible functional relationships between concentration and response that the GSAM can accomodate. However, as long as one can find a way to transform the relationship so that the aforementioned criterion is satisfied, the GSAM will be applicable to the problem. This will become clearer in the derivations that follow.

Linear Model

The simplest model is given by assuming that the elements of the matrix [K] are constants over the range of the experiment; i.e., that [K] is a constant matrix. Then

$$[R] = [\Delta C][K] + [C_o][K] = [\Delta R] + [R_o]; \; [R_o] = \begin{bmatrix} R_{o1} & R_{o2} \cdots R_{op} \\ R_{o1} & R_{o2} \cdots R_{op} \\ \vdots & \\ R_{o1} & R_{o2} \cdots R_{op} \end{bmatrix}, \tag{11}$$

$$[\Delta R] = [\Delta C][K], \tag{12}$$

$$[R] - [\Delta C][K] = [C_o][K], \tag{13}$$

and

$$[R][K]^{-1} - [\Delta C] = [C_o]. \tag{14}$$

This latter step assumes that $[K]^{-1}$ exists, which requires that the number of analytical signals, p, be the same as the number of analytes, r, as [K] is an r x p matrix. If the number of MSA's is also restricted to the number of analytes, then assuming $[\Delta R]^{-1}$ and $[\Delta C]^{-1}$ exist, the solution for $[C_o]$ is well defined, as seen in

$$([R][\Delta R]^{-1} - I)[\Delta C] = [C_o] \tag{15}$$

$$[K] = [\Delta C]^{-1}[\Delta R] \tag{16}$$

Though the problem is well defined when the number of MSA's is equal to the number of analytes, it is always desirable to use more data to characterize experimental error, i.e., a least squares approach:

$$[\Delta C]^t[\Delta R] = [\Delta C]^t[\Delta C][K] \tag{17}$$

and assuming $([\Delta C]^t[\Delta C])^{-1}$ exists,

$$([\Delta C]^t[\Delta C])^{-1}[\Delta C]^t[\Delta R] = [K] \tag{18}$$

Recalling (14), and remembering r equals p is necessary for [K] to be invertible, $[C_o]$ is found by:

$$([R]([\Delta C]^t[\Delta R])^{-1}[\Delta C]^t - I)[\Delta C] = [C_o]. \tag{19}$$

By checking the results for each row of $[C_o]$, the "goodness of fit" can be determined, as the rows should be identical. Note that the matrix [K] can easily be computed once $[\Delta C]^t[\Delta C]$ has been inverted. Hence both the initial concentrations and the model coefficients are obtained essentially for the price of the inversion of two matrices. Note that the [ΔR] matrix must have rank p which means that none of the analytical signals can be a linear combination of the others.

The preceding derivation has been produced here for two reasons: 1) as an introduction to what follows, and more importantly 2) as a way for the analyst to have access to the fundamental GSAM if, for some reason, a multiple regression routine on a computer system is not available. The above requires only the inversion of two small matrices which can be done with a programmable calculator.

It is, however, with the use of multiple regression complete with its associated statistics that the GSAM fully comes into its own as an analytical technique. Equations 7 and 11 are combined to obtain,

$$\vec{R}_m = \Delta\vec{C}_m \cdot [K] + \vec{C}_o \cdot [K] \qquad m = 1,\ldots,n \tag{20}$$

which can be solved for [K] and $\vec{C}_o$ using a little algebra and a standard multiple linear regression program found on most computers. Technically it is a linear multiple linear regression, the first "linear" referring to the linear relationship of the model, and the second "linear" referring to the assumption by the regression that the independent variables (whether they are linear, square, cross terms, etc., in some primary variable such as change in concentration here) are related to the dependent variable by a multi-linear relationship as in

$$Y = b + a_1X_1 + a_2X_2 + a_3X_3 + \cdots + a_rX_r. \tag{21}$$

Using $\Delta c_1, \Delta c_2, \ldots, \Delta c_r$ as the independent variables for the linear multiple regression, the coefficients for each independent variable for each response will be found. The matrix [K] will be just the matrix of these regression coefficients for the r independent Δc_i variables and the p dependent response variables, and the intercepts from the linear regression will be the entries of the vector $\vec{C}_o[K]$. If r equals p, $[K]^{-1}$ can be found, and since

$(\vec{C}_o[K])[K]^{-1} = \vec{C}_o$, $\vec{C}_o$ can be recovered from the intercepts of the regression.

As seen from eq. 16 and eq. 18 or 19, the analyst should make certain that the $[\Delta C]$ matrix encompasses a minimum of r equals p independent vectors; this is necessary because of the inversion of $([\Delta C]^t[\Delta C])$ (essentially the same argument holds for the multiple linear regression) which can be shown to be invertible if and only if the n x r matrix $[\Delta C]$ contains r independent vectors ($n \geqslant r+1$, because there are r+1 unknowns: the r coefficients and the intercept, for each response). This requires the analyst to choose with some consideration the changes in concentrations he introduces: the more orthogonal the $\Delta\vec{C}_m$ vectors are to each other, the more information one effectively obtains. However, in making up standards for the MSA's one can make up standards containing several components of interest. By adding a known amount of one of these multicomponent standards, one effectively moves along a non-axial line in the concentration domain (the basis vectors for the concentration domain being exactly as implied by the notation used above). In practice, all the analyst must take care to do is to span the concentration domain through the additions made. Taking the argument to extreme, a single standard, consisting of a mixture of all components is insufficient by itself as it spans only a single dimension.

It should be noted that the matrix [K] is found in the regression, so that the analyst automatically can see the nature and magnitude of the interferences, and can obtain a measure of the selectivity of his experimental design.

It should be evident to the reader at this point that there is no longer any particular advantage associated with a "fully selective" set of analytical sensors; in fact, it may actually be better to have a non-selective set in some cases, as this will allow the use of information from several sources at the same time for one analyte, thereby obtaining more information than one might obtain from a single information source that is "fully selective".

Quadratic Model

The assumption that the response coefficients, $k_{s\ell}$, are constant over the working range of the analytical sensor may not be warranted. In that case, the linear analysis of the previous section is insufficient. The obvious next extension is to quadratic terms by including linear terms in the concentrations of the components in the response coefficients:

$$k_{s\ell} = \sum_{i=s}^{r} a_i(s\ell)\cdot c_i + \gamma_{s\ell};\ \gamma_{s\ell} \text{ is a constant} \qquad (22)$$

where $k_{s\ell}$ is the response coefficient-function of the sth component for the ℓth response. This model generates the following equation for the response ℓ (hereafter the subscript m is left off, as the reader should understand that the equations apply at every step of the GSAM, so there is no need to distinguish the different MSA's at this point):

$$R_\ell = \sum_{s=1}^{r} c_s\left(\sum_{i=s}^{r} a_i(s\ell)\cdot c_i + \gamma_{s\ell}\right) = \sum_{s=1}^{r}\sum_{i=s}^{r} c_s\cdot a_{is}(\ell)\cdot c_i + \sum_{s=1}^{r} c_s\cdot\gamma_{s\ell} \qquad (23)$$

where in the last form a subscript is moved to a more convenient location for what follows. The reason that i ranges only from s to r in eq. 22 is to remove redundancy in eq. 23 with regard to cross terms.

Again c_i should be rewritten as $\Delta c_i + {}_oc_i$ to express the function in terms of the changes in concentration, but because of the concentration cross terms and square terms in eq. 23, a separation of all cross terms, square terms, and linear terms in the Δc_i's, changes the coefficients. This can be seen in a more general sense from

$$[R] = [C][K] = [\Delta C + C_o][\Delta K + K_o] = [\Delta C][\Delta K] + [C_o][\Delta K] + [\Delta C][K_o] + [C_o][K_o] \qquad (24)$$

where $[\Delta K]$ is the change in $[K]$ due to change in $[C]$. In the simple, linear model, $[\Delta K] = [0]$, so the equation reduced to the form in eq. 11. Now, however, $[\Delta K] \neq [0]$ and the linear terms in Δc_i arise from both $[C_o][\Delta K]$ and $[\Delta C][K_o]$.

Writing eqs. 22 and 23 to correspond to the form of eq. 24 gives,

$$k_{s\ell} = \Delta k_{s\ell} + {}_ok_{s\ell} = \sum_{i=s}^{r} a_i(s\ell)\cdot\Delta c_i + \sum_{i=s}^{r} a_i(s\ell)\cdot{}_oc_i + \gamma_{s\ell} \qquad (25)$$

$$R_\ell = \sum_{s=1}^{r}(\Delta c_s + {}_oc_s)(\Delta k_{s\ell} + {}_ok_{s\ell}) = \sum_{s=1}^{r}\Delta c_s\cdot\Delta k_{s\ell} + \sum_{s=1}^{r}{}_oc_s\cdot\Delta k_{s\ell} + \sum_{s=1}^{r}\Delta c_s\cdot{}_ok_{s\ell} + \sum_{s=1}^{r}{}_oc_s\cdot{}_ok_{s\ell} \qquad (26)$$

$$= \sum_{s=1}^{r}\sum_{i=s}^{r}\Delta c_i\cdot a_{is}(\ell)\cdot\Delta c_s + \sum_{s=1}^{r}\sum_{i=s}^{r}\Delta c_i\cdot a_{is}(\ell)\cdot{}_oc_s + \sum_{s=1}^{r}\Delta c_s\cdot{}_ok_{s\ell} + \sum_{s=1}^{r}{}_oc_s\cdot{}_ok_{s\ell}$$

(${}_ok_{s\ell}$ will not be decomposed into its constituent terms for the moment). Keeping in mind the following relation:

$$\sum_{s=1}^{r}\sum_{i=s}^{r}\Delta c_i\cdot a_{is}(\ell)\cdot{}_oc_s = \sum_{i=1}^{r}\sum_{s=1}^{i}\Delta c_i\cdot a_{is}(\ell)\cdot{}_oc_s, \qquad (27)$$

the coefficients of the linear terms in eq. 26 can be collected as:

$$\sum_{i=1}^{r} \Delta c_i \left(\sum_{s=1}^{i} a_{is}(\ell) \cdot {}_oc_s + {}_ok_{i\ell} \right), \tag{28}$$

Equation 26 now condenses to,

$$R_\ell = \sum_{i=1}^{r} \sum_{s=1}^{i} \Delta c_i \cdot a_{is}(\ell) \cdot \Delta c_s + \sum_{i=1}^{r} \Delta c_i \left(\sum_{s=1}^{i} a_{is}(\ell) \cdot {}_oc_s + {}_ok_{i\ell} \right) + \sum_{s=1}^{r} {}_oc_s \cdot {}_ok_{s\ell} \tag{29}$$

where the last summation term is the constant ${}_oR_\ell$, the initial value of response ℓ, before any MSA's have been performed.

This is now a suitable model for multiple linear regression. The variables for the regression are all terms of the form $\Delta c_i \Delta c_j$ $(j \leq i)$ and all linear terms Δc_i. The regression analysis will then provide the coefficients of these variables. From eq. 29 it can be seen that the coefficients of the cross terms and square terms are exactly the model coefficients, $a_{is}(\ell)$. The intercept for each response, ${}_oR_\ell$, is also given by the regression. However, the coefficients of the linear terms are not simply related to the original model linear coefficients.

Now let R_ℓ be redefined by

$$R_\ell\{\overrightarrow{\Delta C}\} = R_\ell \tag{30}$$

where R_ℓ is as expressed in eq. 29 and $\overrightarrow{\Delta C}$ is the vector $(\Delta c_1, \Delta c_2, \ldots, \Delta c_r)$; in this way the functional relationship is more explicit. The equation for the regression analogous to eq. 29 is then written in vector-matrix notation as

$$R_\ell\{\overrightarrow{\Delta C}\} = \overrightarrow{\Delta C} \cdot [A(\ell)] \cdot \overrightarrow{\Delta C} + \overrightarrow{\Delta C}^T \cdot [H(\ell)] + R_\ell\{\overrightarrow{C_o}\} \tag{31}$$

where $[A(\ell)] = [a_{is}(\ell)]$ (note that $[A(\ell)]$ is a lower triangular matrix, the matrix of all regression coefficients for the cross terms and square terms, which are the same as the model coefficients for these terms, for the ℓth response), $[H(\ell)]$ is a column vector of the regression coefficients of the linear terms in changes in concentration, and $R_\ell\{\overrightarrow{C_o}\}$ is the intercept from the regression. The reader should keep in mind that equation 31 is a function of the net changes in concentration, since these are the known independent variables.

There is, however, a special case when one can use total concentration as an argument for the function; this is when $\overrightarrow{\Delta C} = \overrightarrow{-C_o}$:

$$\begin{aligned} R_\ell\{-\overrightarrow{C_o}\} &= (-\overrightarrow{C_o})^T[A(\ell)](-\overrightarrow{C_o}) + (-\overrightarrow{C_o})^T[H(\ell)] + R_\ell\{\overrightarrow{C_o}\} \\ &= (\overrightarrow{C_o})^T[A(\ell)](\overrightarrow{C_o}) - (\overrightarrow{C_o})^T[H(\ell)] + R_\ell\{\overrightarrow{C_o}\} \end{aligned} \tag{32}$$

$R_\ell\{-\overrightarrow{C_o}\}$ corresponds to the response when all of the initial concentrations of the analytes have been subtracted from the sample, and since

$$[R] = [C][K] = [\Delta C+C_o][K] = [-C_o+C_o][K] = [0][K] = 0 \tag{33}$$

equation 31 leads, in this special case, to,

$$\begin{aligned} 0 = F_\ell(\overrightarrow{C_o}) \equiv (\overrightarrow{C_o})^T[A(\ell)](\overrightarrow{C_o}) - (\overrightarrow{C_o})^T[H(\ell)] + R_\ell\{\overrightarrow{C_o}\} \\ \ell = 1, \ldots , p \end{aligned} \tag{34}$$

The interested reader may actually show that this is the equation which results when one attempts to solve for $\overrightarrow{C_o}$ using eqs. 29 and 30 to relate the model and regression coefficients.

The only unknown in eq. 34 is $\overrightarrow{C_o}$; all the rest of the variables are the regression coefficients for the responses. The problem of solving for $\overrightarrow{C_o}$ then reduces to solving this system of p simultaneous equations. The general problem of solving

$$F(\vec{x}) = 0;\ F: \mathbb{R}^r \longrightarrow \mathbb{R}^p, \text{ one component of } F \text{ being } F_\ell: \mathbb{R}^r \longrightarrow \mathbb{R}^1 \qquad (35)$$

is a well known one, and many theorems and techniques exist for approaching it (2). Note that eq. 34 is a quadratic in $\vec{C_o}$, so an iterative technique such as a Newton-Raphson procedure is suggested. The condition of the iteration problem will depend on the regression coefficients. There are computer programs available in computer libraries which can solve eq. 35 even without knowing the analytical form of the Jacobian, which is convenient as the model becomes complex.

Using equation 29 the original model coefficients can be recovered from the regression coefficients. This would be of interest to the analyst concerned not only with knowing $\vec{C_o}$, but also the values of the model coefficients which can provide a measure of the selectivity of the responses to the various components.

For the following, it is assumed that $\vec{C_o}$ is known, either because a known sample was used to begin with or because eq. 34 was solved for $\vec{C_o}$. From equation 29, the $a_{is}(\ell)$'s are the regression coefficients of the square and cross terms. The only coefficients left to recover are the $\gamma_{s\ell}$'s from equation 22. This can easily be done, using eqs. 29 and 31 to give,

$$\sum_{s=1}^{i} a_{is}(\ell)\cdot {}_oc_s + {}_ok_{i\ell} = H_i(\ell) = \sum_{s=1}^{i} a_{is}(\ell)\cdot {}_oc_s + \sum_{j=i}^{r} a_{ji}(\ell)\cdot {}_oc_j + \gamma_{i\ell}$$

$$= ([A(\ell)] + [A(\ell)]^T)_i \cdot \vec{C_o} + \gamma_{i\ell} \qquad i = 1, \ldots, r \qquad (36)$$

making use of eq. 21, the fact that $H_i(\ell)$ is the regression coefficient for Δc_i for response ℓ, and the fact that $[A(\ell)]$ is lower triangular. Therefore,

$$\gamma_{i\ell} = H_i(\ell) - ([A(\ell)] + [A(\ell)]^T)_i \cdot \overrightarrow{C_o} \tag{37}$$

and since $\overrightarrow{C_o}$ is assumed known, either a priori or by solving eq. 34, all the terms on the right hand side are known.

Thus the GSAM can simultaneously find the initial concentrations of all the analytes as well as generate the coefficients of eq. 22 to obtain the functional relation between response and concentration according to the original model.

Cubic Model & Models of Arbitrary Degree

The above results are now extended to the cubic model. Extensions to an arbitrary order to solve for $\overrightarrow{C_o}$ are also formulated; however the expansion and decomposition of the coefficients is only done for the cubic case; sufficient information is presented to allow the interested reader to perform this for higher degree models if necessary. As shall be discussed later, there are some problems associated with extending the models to high degrees if there is no underlying, theoretical reason to do so.

For the cubic case the equation analogous to eq. 22 becomes,

$$k_{s\ell} = \sum_{i=s}^{r} \sum_{j=i}^{r} b_{ji}(s\ell) \cdot c_i \cdot c_j + \sum_{i=s}^{r} a_i(s\ell) \cdot c_i + \gamma_{s\ell} \tag{38}$$

and this generates the following equation for response ℓ:

$$R_\ell = \sum_{s=1}^{r} c_s \cdot k_{s\ell} = \sum_{s=1}^{r} \sum_{i=s}^{r} \sum_{j=i}^{r} b_{ji}(s\ell) \cdot c_s \cdot c_i \cdot c_j + \sum_{s=1}^{r} \sum_{i=s}^{r} a_i(s\ell) \cdot c_s \cdot c_i + \sum_{s=1}^{r} c_s \cdot \gamma_{s\ell} \tag{39}$$

By analogy to earlier results, the regression model for the cubic case is:

$$R_{\ell}\{\overrightarrow{\Delta C}\} = \sum_{s=1}^{r} \sum_{i=s}^{r} \sum_{j=i}^{r} {}^{4}G_{jis\ell}\cdot\Delta c_s\cdot\Delta c_i\cdot\Delta c_j + \sum_{s=1}^{r} \sum_{i=s}^{r} {}^{3}G_{is\ell}\cdot\Delta c_s\cdot\Delta c_i + \sum_{s=1}^{r} {}^{2}G_{s\ell}\cdot\Delta c_s + {}^{1}G_{\ell} \qquad (40)$$

where $[{}^{n}G]$ is the n-dimensional matrix of regression coefficients for the p responses for the terms containing $(n-1)\Delta c$'s. For example, $[{}^{3}G]$ is the three dimensional matrix of coefficients for the square and cross terms in change in concentration. Note also that these coefficient matrices are lower triangular in an (n-1) dimensional sense (observe the limits of the indices in eq. 40 and recall that ℓ runs from 1 through p).

Using the same argument as in the quadratic model, the zero of the following function must be found

$$F_{\ell}(\vec{x}) = {}^{1}G_{\ell} - \sum_{s=1}^{r} {}^{2}G_{s\ell}\cdot x_s + \sum_{s=1}^{r} \sum_{i=s}^{r} {}^{3}G_{is\ell}\cdot x_s\cdot x_i - \sum_{s=1}^{r} \sum_{i=s}^{r} \sum_{j=i}^{r} {}^{4}G_{jis\ell}\cdot x_s\cdot x_i\cdot x_j \qquad (41)$$

since $F(\vec{x}) = 0$ implies that $\vec{x} = \overrightarrow{C_o}$. This can be extended to a regression model of arbitrary degree n:

$$R_{\ell}\{\overrightarrow{\Delta c}\} = \sum_{i_1=1}^{r} \sum_{i_2=i}^{r} \cdots \sum_{i_n=i_{n-1}}^{r} {}^{n+1}G_{i_n\cdots i_1,\ell}\cdot\Delta c_{i_1}\cdot\Delta c_{i_2}\cdots\Delta c_{i_n} \qquad (42)$$

$$+ \sum_{i_1=1}^{r} \cdots \sum_{i_{n-1}=i_{n-2}}^{r} {}^{n}G_{i_{n-1}\cdots i_1,\ell}\cdot\Delta c_{i_1}\cdots\Delta c_{i_{n-1}} + \cdots + \sum_{i_1=1}^{r} {}^{2}G_{i_1\ell}\cdot\Delta c_{i_1} + {}^{1}G_{\ell}$$

$$F_\ell(\vec{x}) = {}^1G_\ell - \sum_{i_1=1}^{r} {}^2G_{i_1\ell}\cdot x_{i_1} + \sum_{i_1=1}^{r} \sum_{i_2=i_1}^{r} {}^3G_{i_2 i_1 \ell}\cdot x_{i_1}\cdot x_{i_2} + \cdots$$

$$+ (-1)^n \sum_{i_1=1}^{r} \sum_{i_2=i_1}^{r} \cdots \sum_{i_n=i_{n-1}}^{r} {}^{n+1}G_{i_n \cdots i_1 \ell}\cdot x_{i_1}\cdot x_{i_2}\cdots x_{i_n} \qquad (43)$$

and, as before, the solution to $F(\vec{x}) = 0$ must be determined.

The relationship between the regression coefficients and the model coefficients for the cubic model are determined with the introduction of a notational convenience: because $R_\ell = \sum_{s=1}^{r} c_s \cdot k_{s\ell}$, an effective dot product in the index s, an operator symbol "$\langle\ \rangle^*$" is used to represent this operation (the standard products of matrices and vectors can be used with only two indices, as in the quadratic model, but now three indices must be dealt with). In other words, define

$$R_\ell = \sum_{s=1}^{r} c_s \cdot k_{s\ell} \equiv \langle c_s \rangle^* k_{s\ell} \qquad (44)$$

and

$$\langle c_s, c_i \rangle^* x_{si} = \sum_{s=1}^{r} \sum_{i=1}^{r} x_{si} \cdot c_s \cdot c_i \qquad (45)$$

where it is understood that the product is over the index attached to the variable inside the brackets for that variable's operation. Equation 39 can now be written as,

$$R_\ell = \langle c_s \rangle^* k_{s\ell} = \langle c_s, c_i, c_j \rangle^* b_{ij}(s\ell) + \langle c_s, c_i \rangle^* a_i(s\ell) + \langle c_s \rangle^* \gamma_{s\ell} \qquad (46)$$

where several terms have been grouped into the brackets, subject to the following properties:

Commutative: $\langle c_s, c_i \rangle^* x_{si} = \langle c_i, c_s \rangle^* x_{si}$ (47)

$$\text{Associative:}\quad \langle c_s\rangle * (\langle c_i, c_j\rangle * x_{sij}) = \langle c_s, c_i\rangle * (\langle c_j\rangle * x_{sij}) \qquad (48)$$

$$\text{Distributive:}\quad \langle c_s\rangle * (\langle c_i\rangle + \langle c_j\rangle) * x_{sij} = (\langle c_s, c_i\rangle + \langle c_s, c_j\rangle) * x_{sij} \qquad (49)$$

All of the above properties follow from the definition of the operator in eq. 44 and eq. 45, and they can easily be verified by the reader.

Proceeding as before, separating c into $\Delta c + c_o$, the expression for R_ℓ becomes,

$$\begin{aligned} R_\ell = {} & \langle \Delta c_s + {}_o c_s, \Delta c_i + {}_o c_i, \Delta c_j + {}_o c_j\rangle * b_{ij}(s\ell) + \langle \Delta c_s + {}_o c_s, \Delta c_i + {}_o c_i\rangle * a_i(s\ell) \\ & + \langle \Delta c_s + {}_o c_s\rangle * \gamma_{s\ell} \\ = {} & \big(\langle \Delta c_s, \Delta c_i, \Delta c_j\rangle + \langle \Delta c_s, \Delta c_i, {}_o c_j\rangle + \langle \Delta c_s, {}_o c_i, \Delta c_j\rangle + \langle {}_o c_s, \Delta c_i, \Delta c_j\rangle \\ & + \langle \Delta c_s, {}_o c_i, {}_o c_j\rangle + \langle {}_o c_s, \Delta c_i, {}_o c_j\rangle + \langle {}_o c_s, {}_o c_i, \Delta c_j\rangle + \langle {}_o c_s, {}_o c_i, {}_o c_j\rangle\big) * b_{ij}(s\ell) \\ & + \big(\langle \Delta c_s, \Delta c_i\rangle + \langle {}_o c_s, \Delta c_i\rangle + \langle \Delta c_s, {}_o c_i\rangle + \langle {}_o c_s, {}_o c_i\rangle\big) * a_i(s\ell) \\ & + (\langle \Delta c_s + {}_o c_s\rangle) * \gamma_{s\ell} \end{aligned} \qquad (50)$$

By collecting terms of similar power in Δc's, and consequently renaming and reordering subscripts (actually, some order was preserved for clarity, being otherwise unnecessary due to the commutativity of eq. 47), equation 50 becomes,

$$\begin{aligned} R_\ell = {} & \langle \Delta c_{j_1}, \Delta c_{j_2}, \Delta c_{j_3}\rangle * b_{j_2 j_3}(j_1\ell) \\ & + \langle \Delta c_{j_1}, \Delta c_{j_2}\rangle * \big(\langle {}_o c_{j_3}\rangle * (b_{j_2 j_3}(j_1\ell) + b_{j_3 j_2}(j_1\ell) + b_{j_1 j_2}(j_3\ell)) + a_{j_2}(j_1\ell)\big) \\ & + \langle \Delta c_{j_1}\rangle * \big(\langle {}_o c_{j_2}, {}_o c_{j_3}\rangle * (b_{j_2 j_3}(j_1\ell) + b_{j_1 j_2}(j_3\ell) + b_{j_2 j_1}(j_3\ell)) \\ & \qquad + \langle {}_o c_{j_2}\rangle * (a_{j_1}(j_2\ell) + a_{j_2}(j_1\ell)) + \gamma_{j_1\ell}\big) \\ & + \langle {}_o c_{j_1}\rangle * \big(\langle {}_o c_{j_2}, {}_o c_{j_3}\rangle * b_{j_2 j_3}(j_1\ell) + \langle {}_o c_{j_2}\rangle * a_{j_2}(j_1\ell) + \gamma_{j_1\ell}\big) \end{aligned} \qquad (51)$$

The reader will note the essential symmetry underlying the permutations of the subscripts in eq. 51; this is expected from the symmetry in eq. 50.

The relation between the regression coefficients of eq. 40 and the model coefficients of eq. 39 can now be seen. Once a solution for $\overrightarrow{c_o}$ has been found, then beginning by identifying the matrix [B] (with elements $b_{ji}(s\ell)$) with the matrix $[{}^4G]$, the matrix [A] (with elements $a_i(s\ell)$) can be obtained using the coefficients of $[{}^3G]$, and then the matrix $[\gamma]$ (with elements $\gamma_{s\ell}$) is found using the coefficients of $[{}^2G]$. It is noteworthy that the original model coefficients can be recovered with only the simple operations of vector and matrix multiplication, addition and subtraction; there is no matrix inversion involved.

Using the notation introduced above, it should be apparent to the reader how to express the regression coefficients in terms of the model coefficients for a model of any degree. As an aid to understanding, the reader can go back and solve the equations for the quadratic case using this new notation, checking the results with the ones obtained above.

Rewriting eq. 43 for clarity gives

$$
\begin{aligned}
F_\ell(\vec{x}) = {}^1G_\ell - \langle x_{i_1} \rangle * {}^2G_{i_1\ell} + \langle x_{i_1}, x_{i_2} \rangle * {}^3G_{i_2 i_1 \ell} - \cdots \\
+ (-1)^n \langle x_{i_1}, \ldots, x_{i_n} \rangle * {}^{n+1}G_{i_n, \ldots i_1, \ell}
\end{aligned}
\qquad (52)
$$

as the general function to solve for $F(\vec{x}) = [0]$ to find $\overrightarrow{c_o}$. However, as is usually the case for higher order models, as the degree of the model increases, the number of coefficients in the model increases at a greater rate, despite the fact that the matrices of coefficients are "lower triangular" in an n-1 dimensional sense. In order for regression analysis to succeed, at least one measurement must be made for each coefficient to be determined. Hence, as the degree of the model rises, the number of measurements that must be made increases rapidly. The GSAM also becomes more demanding the greater the number of analytes under study as shown in Table I. In addition, in a multiple linear regression analysis the covariance of various variables must also be considered. If some variables have high intercorrelation, then the regression problem becomes ill-conditioned, and it may not be possible to obtain a solution. Because the above model takes into account all possible terms, such a problem might arise if the degree of the model is too large for a given set of measurements. But it should be noted that not all of the terms in eq. 42 need be included in the regression; it may prove more fruitful for the analyst to drop certain terms from the model by not including the corresponding variable in the list of variables for the regression. This effectively forces the coefficients of that particular variable to be zero in the model of eq. 42. For example, suppose it was decided to include only the cross terms and not the square terms of the quadratic model. Then the variables used for the multiple linear regression would be the Δc_i's and the $\Delta c_i \cdot \Delta c_j$'s for $j<i$. The analyst should remember, however, that there is an important difference between forcing a regression coefficient to zero by not including the corresponding variable, and calculating a zero coefficient from the regression when the variable is included.

Several excellent methods can be used to select a specified number of variables from among a larger list of variables in order to obtain a good fit to the measurements. Stepwise regression is one example of a forward selecting method. In fact, a number of these methods are available in computer program libraries. This means that by specifying the maximum size of the set the analyst will allow, the number of regression coefficients the model will have at any one time can be controlled, and the possibility of two variables of high correlation being used in the model at the same time is reduced. This in turn allows models of high degree to be considered, without requiring an excessive number of data points.

TABLE I

Model	Formula	Minimum No. of Data Points*				
	p=r=	2	3	4	5	10
Linear	$p + p \cdot r$	6	12	20	30	110
Quadratic	$p + p \cdot r + \frac{p \cdot r(r+1)}{2}$	12	30	60	105	660
Cubic	$p + p \cdot r + \frac{p \cdot r(r+1)}{2} + \frac{p \cdot r(r+1)(2r+1)}{6}$	22	72	180	380	4510

*(assuming model includes all possible terms for each degree)

The GSAM can be generalized even further than has been done. The restriction is that terms in c be separable into terms in Δc and c_o. The word "separation" is deliberately vague, for the nature of this separation will depend on several factors. If

$$R\{\vec{c}\} = R\{\Delta\vec{c} + \vec{c}_o\} = \Phi\{\Delta\vec{c}\} \qquad (53)$$

where the terms in c_o are now mixed in with other coefficients, using the same argument as before, in general,

$$\Phi\{-(\vec{x})\} = 0 \qquad (54)$$

must be solved as the solution is $\vec{x} = \vec{C}_o$. In principle it is possible to develop routines for multiple regression on functions other than linear sums of independent variables. If, in a particular problem, the theoretical relation can be transformed to one which is suitable for a multiple regression, and if the terms in $\vec{C}_o$ will combine with other coefficients to make up the regression coefficients when the relation is expressed as a function of the changes in concentrations, then the fitted regression curve can be used to solve for $\vec{C}_o$ in eq. 54 (perhaps iteratively, perhaps by some other means, depending on the nature of the function in the regression), and possibly recover the original model coefficients. The severity of the required separation between terms in Δc and c_o thus depends on the type of function used for a model of the relationship between response and concentration and on the type of function used for multiple regression. As an example, if the only available technique is multiple linear regression, then the relation $y = \ln(ac) = \ln(a\Delta c + ac_o)$ does not have a sufficient separation between terms in Δc and c_0, i.e., the normal equations using $\ln(\Delta c)$ as the independent variable will be nonlinear. Transforming the relation by exponentiation solves this problem, and the separation is then sufficient for a multiple linear regression.

In this paper attention has been restricted to polynomial forms, which allow multiple linear regression to be used. However, the basic concepts behind the GSAM can still be put to work for quantitative chemical analysis and the understanding of systems of analytical sensors with models having other than simple polynomial forms.

CONSIDERATIONS IN THE APPLICATION OF THE GSAM

Error Analysis

1) Random Error: Along with each coefficient, multiple linear regression analysis also provides an estimate of the variance in that coefficient which can be propagated to the model coefficients or initial concentrations (see Larson et. al. for this in the standard addition method (3)). In many cases, particularly for the iterative solution required for the quadratic and higher order models, this can become very tedious. Another estimate of the error can be made based on the fact that with each regression coefficient upper and lower confidence bounds can be obtained. Given confidence bounds of, say, 90% or 95%, a measure of the error in a regression coefficient can be taken as the following:

$$\mathrm{err}(x) = \frac{|\mathrm{U.C.B.}(x) - \mathrm{L.C.B.}(x)|}{2} \qquad (55)$$

$$\text{or} \quad \mathrm{err}(x) = \max\{\mathrm{U.C.B.}(x)-x,\ x-\mathrm{L.C.B.}(x)\}$$

where "U.C.B." and "L.C.B." are the upper and lower confidence bounds. An error estimate for the solution of eq. 52 for $\vec{C_o}$ would appear most readily obtainable by perturbing the regression coefficients within the confidence bounds and performing the iteration again to solve for a new $\vec{C_o}$. The error in the initial concentration can then be estimated by,

$$\mathrm{err}({}_oC_i) = \max_{k=1,\ldots,t} \{|{}_o\vec{C}_i - {}^{k}_{o}\vec{C}_i|\} \qquad (56)$$

where ${}^{k}_{o}\vec{C}_i$ corresponds to the kth perturbed iterative solution for the initial concentration of component i. If t, the total number of perturbations carried through, is large enough (which may not be practical if the solution does not converge quickly), a better estimate might be

$$\mathrm{err}({}_{o}C_{i}) = \sqrt{\sum_{k=1}^{t} \frac{({}_{o}\overrightarrow{C_{i}} - {}^{k}_{o}\overrightarrow{C_{i}})^{2}}{t-1}} \tag{57}$$

Using 95% confidence bounds can be expected to provide a conservative estimate of the precision of the solution.

It is sometimes desired to weight certain measurements more highly than others (perhaps due to experimental design, errors are smaller in a certain range of concentrations), in which case a weighted multiple linear regression could be envisaged. The introduction of weights, however, greatly complicates the statistics of the regression.

2) Systematic Error: In reality, the response function may not be zeroed when the concentrations are zero. In this case the response function is better represented by

$$[R] = [C][K] + [\delta R] = [\Delta C][K] + [{}_{o}C][K] + [\delta R] \tag{58}$$

The effective change is that

$$[{}^{1}G] = [{}_{o}C][K] + [\delta R] \tag{59}$$

is the regression intercept. Comparison with eq. 51 shows that

$$F(\vec{x}) = -[\delta R] \tag{60}$$

is actually the equation that must be solved. The problem of iteratively solving a perturbed system instead of the ideal system, and the effect the perturbation has on the solution, is a well known one, though not so well understood. The specific effects of the perturbation will depend on the application and the nature of the function $F(\vec{x})$ that is produced.

If δR is small compared to values of R, and the problem is reasonably insensitive to perturbations (for example, a problem with large gradients that converges quickly), then one can expect the effect on the final solution to be small. By using a "blank" to obtain a $[\rho_o]$ (effectively the background signal), and using

$$[R'] = [R] - [\rho_o] \tag{61}$$

as the reponse function, [R'] will usually be expected to follow eq. 58 with $[\delta R]$ being small (an exception to this is considered below). The problem of zeroing the response function is simply the multidimensional generalization of the same problem with the standard addition method.

Notes on the Iterative Solution of Equation 35

Most methods for solving eq. 35 by iteration require an initial approximation, a "guess", as to the final solution in order to start the iteration. The speed of convergence will often depend on the accuracy of the estimate; if several zeroes exist, convergence to the "correct" zero (the zero corresponding to the initial analyte concentrations) will also depend on the initial approximation. It would be possible, for example, for the iteration to converge to a solution with large negative concentration values in some problem--obviously a solution that should be rejected, but nevertheless a potential solution which could be found by the iteration.

The natures of local and global convergence have been studied for iterative solutions to eq. 35 and some elegant theorems exist, which are beyond the scope of this paper. The analyst using the GSAM for a non-linear model should be aquainted with the theorems and their conditions, in order to recognize if the nature of his function in eq. 51 is such that certain theorems (Ortega and Rheinboldt (2)) concerning convergence and divergence (local and global) apply.

An estimate of an interval in which to start the iteration can be obtained as follows. To obtain the best values for $\overrightarrow{C_o}$, the analyst should attempt to collect most of the data (obtained by the MSA's) near the starting response values $R_\ell(0)$, $\ell=1,..,p$, as this will make the regression model fit the "true" function nearest the point of interest, namely $\overrightarrow{C_o}$. This means that, for a sample of components of completely unknown concentrations, the analyst must begin with low concentration MSA's which will result in small changes in concentration of each analyte in the sample until a change in the response from one sensor is achieved. At this point, the unknown initial concentration must be within a few orders of magnitude of the known added concentration, depending on the size of the response change that can be detected. (In this method for establishing a starting interval, it is assumed that the concentration of only one component at a time is being changed as shall be made clear in the following discussion.) This motivates the definition

$$\underline{\Delta c_i} = \min\left\{\Delta c_i \,\middle|\, \alpha \leqslant \max_{\ell=1,..,p} \frac{|R_\ell\{\overrightarrow{\Delta c}\} - R_\ell\{0\}|}{|R_\ell\{0\}|}\right\} \tag{63}$$

$$\overline{\Delta c_i} = \max\left\{\Delta c_i \,\middle|\, \max_{\ell=1,..,p} \frac{|R_\ell\{\overrightarrow{\Delta c}\} - R_\ell\{0\}|}{|R_\ell\{0\}|} \leqslant \beta\right\} \tag{64}$$

$\Delta\underline{c}_i$ is then the smallest added concentration of analyte i which produces a relative response change in at least one analytical sensor greater than or equal to $(\alpha\text{x}100)\%$. $\Delta\bar{c}_i$ is the largest added concentration of analyte i which produced a relative response change no greater than $(\beta\text{x}100)\%$ for any sensor. The interval in which to start the iteration is then $[\Delta\underline{c}_i, \Delta\bar{c}_i]$. α and β are the parameters which define the width of the interval. For example, if $\alpha=0.5$ and $\beta=10$ then $\Delta\underline{c}_i$ is the added concentration which gives at least a 50% response change, in at least one analytical sensor and $\Delta\bar{c}_i$ is the added concentration which gives a 1000% response change on no more than one sensor. In both cases, one looks at the response most sensitive to changes in concentration for analyte i (most sensitive in the sense of largest relative gradient).

When $\alpha=\beta=1$, the change in analyte i required to double the response in the most sensitive sensor for analyte i is found. If a linear model is assumed, then $\Delta\underline{c}_i=\Delta\bar{c}_i$ would be the same size as ${}_oc_i$, provided that the most sensitive sensor for component i in this concentration range is not affected by the presence of other components than i nearly as much as it is by i. A "fully selective" set of sensors would have this property no matter what the concentrations of the components. This can be seen in eq. 66 given the condition of eq. 65.

$$R_\ell\{c\} = k_\ell \cdot c_\ell = k_\ell \cdot \Delta c_\ell + k_\ell \cdot {}_oc_\ell = k_\ell \cdot \Delta c_\ell + R_\ell\{0\} \quad \ell=1,..,p=r \qquad (65)$$

$$R_\ell\{\Delta c\} = 2R_\ell\{0\} \Rightarrow k_\ell \cdot \Delta c_\ell = R_\ell\{0\} \Rightarrow \Delta c_\ell = {}_oc_\ell \quad \ell=1,..,p=r \qquad (66)$$

In any case, for most reasonable models, $\alpha=0.1$ and $\beta=10$ provide a broad enough interval so that, of several starting points in the interval, at least one should be close enough to $\vec{C}_o$ to allow convergence. The parameters α and β allow moderate interference effects to be taken into account. Under extenuating conditions (e.g., large interference effects on all responses for analyte i), the parameters α and β would have to be adjusted by the analyst, unless the regression coefficients provide good convergence qualities to the iteration (i.e., if global, or a very large region of rapid convergence exists, then the analyst can take any reasonable starting guess).

It should be noted that the above technique has assumed that large relative changes in the concentrations of interfering components in the sample has not occurred, as these could interfere with the responses to changes in analyte i's concentration. Instead of using eqs. 65 and 66, which require using a fresh amount of the unknown sample for each component to determine the starting point for the iteration, the following, slightly less accurate method is suggested:

1) To a given amount of the unknown sample make successive changes in the concentration of analyte 1 only until the criterion for $\Delta\bar{c}_1$ has been surpassed.

2) Then make successive changes in the concentration of analyte 2 only, until the criterion for $\Delta\bar{c}_2$ has been surpassed, using not $R_{\ell_2}\{0\}$ but ${}^1R_{\ell_2}\{0\}$, the final value of response ℓ_2 after the additions of step 1 (ℓ_2 is that response which is most sensitive to analyte 2), in order to subtract out the response due to the presence of components before the additions of analyte 2.

3) Repeat for analyte 3, using ${}^2R_{\ell_3}\{0\}$, defined similarily to ${}^1R_{\ell_2}\{0\}$, in the criterion for $\Delta\bar{c}_3$ and continue with the rest of the analytes.

The eqs. 65 and 66 would be altered to appear as

$$\underline{\Delta c_i} = \min\left\{\Delta c_i \,\middle|\, \alpha_i \leq \max_{\ell=1,..,p} \frac{|R_\ell\{\overrightarrow{\Delta c}\} - {}^{(i-1)}R_\ell\{0\}|}{|R_\ell\{0\}|}\right\} \tag{67}$$

$$\overline{\Delta c_i} = \max\left\{\Delta c_i \,\middle|\, \max_{\ell=1,..,p} \frac{|R_\ell\{\overrightarrow{\Delta c}\} - {}^{(i-1)}R_\ell\{0\}|}{|R_\ell\{0\}|} \leq \beta_i\right\} \tag{68}$$

(the subscript on α and β denotes the fact that different parameters may be needed for different components). Performing the above operation should give the analyst some idea of where $\overrightarrow{C_o}$ lies, and he can then use another sample of the unknown to collect more data with simultaneous additions of several components, thus allowing a more detailed exploration of the functional surface for the regression, if it is needed. Adjustment of the parameters will require some examination of the interference coefficients, so the analyst may wish to run a rough preliminary GSAM to obtain some idea of the magnitudes of the interferences.

The reader should keep in mind that if he is fortunate enough to have a problem which requires only the linear model, he need not concern himself with the iterative process or with finding some interval to start the iteration. Also, the problem of finding the initial starting point for the GSAM is the same problem facing the analyst applying the simple standard addition method.

Dimensionality

Up until now little attention has been paid to the dimensions or ranks of the various matrices. Yet, as the reader may already suspect, this is of great importance. As was stated earlier in the linear model, it is required that the [ΔC] matrix span an r dimensional space, where r is the number of analytes. That this is also a requirement for all higher degree models can be intuitively grasped through the realization that r independent $\Delta\vec{C}_m$'s are needed to allow multiple linear regression to recover all of the coefficients for each analyte; with less than r, at least one of the analyte concentrations could then be expressed as a linear function of the others', and the regression for r analytes would no longer be meaningful. Also stated in the linear model was that p, the number of linearly independent analytical signals, had to equal r. This extends to the model of arbitrary degree. If p is less than r, then sufficient information cannot be obtained to determine the initial concentrations of all analytes, i.e., $F(\vec{x})=[0]$ is p equations in r unknowns, and so would have an infinite number of solutions. If p is greater than r, then the simultaneous equations cannot be solved for all p sensors (4).

Of course, one can select r of the p sensors and solve the equation, then select a new set of r and solve again and so on, finally comparing the results for each iteration, which should be identical. This may be useful if the analytical sensors are very non-linear leading to several possible solutions for a given iteration. In most cases, restricting solutions to have nonnegative or, if negative, close to zero concentrations should be sufficient to eliminate all solutions except one. If not, then by comparing the sets of solutions obtained from each set of r out of p information sources, the analyst may find only one solution that is consistent in all sets, which hopefully is $\vec{C}_o$. This is, however, a worst case scenario, as the majority of problems will not behave this badly; p=r sensors should be sufficient to provide the solution $\vec{C}_o$.

An important consequence of the above discussion surfaces when there is a component in the sample that is not an analyte but affects one or more of the responses, and if that component's concentration is unknown so that it cannot be subtracted out as background with the blank in eq. 61. Then, another sensor must be included to make $p=r+1$ because the model must take into account the interference of the component even though it is not of interest. The advantage of the GSAM is that the response of this sensor need only be a function of the concentrations of any of the components in the sample that affect the other responses without regard for the number or combination of components involved. With this freedom, the problem should be easily resolved in most cases. The above condition can be expressed using a "binary dependence" matrix, D, which is $r' \times p$ and whose elements are defined by

$$d_{ij} = \begin{cases} 1 \text{ if component } i \text{ affects response } j \\ 0 \text{ otherwise} \end{cases} \qquad (69)$$

where it is understood that none of the p analytical signals are linearly dependent on the others. The GSAM requires only that the rank of D be r', where r' is the total number of sample components which affect the p responses. Naturally, if an analyst is interested in only two analytes in a mixture of, say, ten, then by using two sensors that are affected only by the two analytes there is no need to worry about more sensors. The case corresponds to a 2 x 2 diagonal submatrix of the matrix D required for analysis of all ten components; note that D is <u>required</u> <u>only</u> to be square, but as stated before, one can have $p>r$.

The number of MSA's the analyst must make to just have enough information to determine the regression coefficients depends on the degree of the model and the number of components under study. Table I gives the formulas and some selected values for the linear, quadratic, and cubic models; from the general derivation of the models (keeping in mind the (n-1) dimensional triangularity of the n dimensional [^nG] coefficient matrix), the reader should see in principle how to perform this calculation for any degree model. Good practice in a regression analysis would require that the number of data points taken exceed by a significant amount the minimum required to just determine the system. As a rule of thumb, try to collect at least twice as many data points as the minimum required.

CONCLUSION

The method described in this paper is exactly what it purports to be: the generalized standard addition method. It shares some of the disadvantages of the traditional standard addition method in that response must be zeroed and some additional effort to transform the measured property values into suitable form relating response to concentrations may be required. This transformation may introduce so-called "constants", which are constant in theory, but are often determined in practice by calibrating a given analytical sensor (e.g., the term RT/nF in ion-selective electrodes). If these constants must be used in the transformation, then applying the GSAM requires a calibration of the measuring instrument, which is not the usual case in the traditional standard addition method.

The advantage of being able to simultaneously analyze for different components in a mixture, while accounting for interferences, certainly outweighs the relatively minor disadvantages. The ability to use non-linear models allows the analyst to better fit the data for solving for the initial concentrations of the components than may be possible with a simple linear model; it also allows the GSAM as presented here to be used whenever a transformation can bring the data into a polynomial relationship of some degree from a known theoretical relationship. The GSAM even permits theoretical studies to be done on the relationship between underlying independent and dependent variables.

There are a great many areas where the GSAM will be applicable, especially where interferences have been of concern in the past. Indeed, our laboratory is currently applying this method to multiple ion selective electrodes where this is the case. We expect the GSAM will become a standard analytical method in the near future.

ACKNOWLEDGMENT

The authors acknowledge helpful suggestions from Bob Gerlach and Maynarhs da Koven.

CREDIT

This work was partially supported by the Office of Naval Research.

REFERENCES

1. Kaiser, H., "Guiding Concepts Relating to Trace Analysis", Pure Appl. Chem., 34, 35-61 (1973).

2. Ortega, J. M., and Rheinboldt, W. C., Iterative Solution of Nonlinear Equations in Several Variables, Academic Press: New York (1970).

3. Larsen, I. L., N. A. Hartmann, and J. J. Wagner, "Estimating Precision for the Method of Standard Additions", Anal. Chem., 45, 1511-13 (1973).

4. pp. 129-131 in (2).