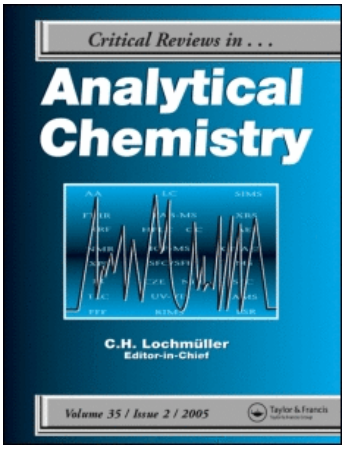

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Multicomponent Kinetic Methods

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ABSTRACT: Methods in use for the resolution of multiple species reacting on the same time scale are reviewed. The different approaches can be divided into two categories. The first is for the resolution of mixtures when large rate constant differences are involved, while the second is for mixtures of species with small rate constant differences. This latter approach is the more involved, and is the focus of this review. Popular historical approaches to this problem are discussed, and the principles behind modern methods are described. Applications utilizing the various approaches are given, followed by some conclusions regarding the current status of multicomponent kinetic methods.

KEY WORDS: multicomponent analysis, kinetic methods, differential kinetics, computer methods

I. INTRODUCTION

Kinetic methods of analysis have become increasingly popular in recent years. This increase in popularity can be seen in the number of international conferences devoted to kinetics in analytical chemistry,[1] and in recent books on the subject.[2,3] Several review articles also have dealt with kinetic methods in analytical chemistry.[4-8]

Kinetic-based determinations offer several advantages over equilibrium methods: simplicity, speed, and precision.[9] Crouch[10] asserts that one of the major reasons for the increased interest in kinetic methods is the increased use of automation in kinetics-based procedures. The use of automation in kinetic methods can be traced to 1960, with the introduction of an automated, variable time method for glucose.[11] The history of developments from this point until 1988 is summarized in Reference 2. Of course, kinetic methods have some disadvantages when compared to equilibrium-based methods. Because the analytical results rest on the measurement of a time-dependent quantity, which is influenced by a rate constant, any factor that affects the value of the rate constant can potentially affect the accuracy and precision of a kinetic technique. Rate constants, and therefore most kinetic methods, are dependent on factors such as pH, ionic strength, and temperature. Therefore, in order to obtain good results with kinetic-based methods, one must control experimental conditions more than is usual in an equilibrium-based method.

Kinetic methods take the time dependence of a chemical reaction or an instrumental response into account in order to obtain analytical information. Although historically analytical chemists have given little or no recognition to kinetic methods, many popular techniques are, in fact, kinetic in nature. Pardue[4] defines a kinetic method as any analytical procedure in which the measurement step is influenced by a transient process and proposes that a majority rather than a minority of modern analytical methods are kinetic in nature. By this definition, many chromatographic, atomic, or mass spectrometric techniques, as well as a number of

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other analytical techniques are kinetic in nature, and may be properly classified as kinetic methods.

Multicomponent kinetic methods, sometimes referred to as differential kinetic methods, are one of the more interesting facets of kinetic determinations. In an historical context, the term "multicomponent" is somewhat of a misnomer because most of the techniques developed to date consist of the resolution of two or at most three components. These techniques might be better called dual-component kinetic methods.

The general goal of multicomponent kinetic methods is to determine the kinetic parameters or the analytical concentrations of the reactants in a system. A general mixture amenable to multicomponent kinetic methods can be described as follows:

$$C_1 + R \xrightarrow{k_1} P_1$$
$$C_2 + R \xrightarrow{k_2} P_2 \qquad (1)$$

where C_1 and C_2 are two different species that react with a common reagent, denoted by R, with two different rate constants, k_1 and k_2, to form similar but not identical products, P_1 and P_2. Reagent concentrations are usually maintained such that pseudo-first order kinetics apply. In such a case Eq. (1 reduces to:

$$C_1 \xrightarrow{k_1'} P_1$$
$$C_2 \xrightarrow{k_2'} P_2 \qquad (2)$$

where $k_1' = k_1[R]_t$ and $k_2' = k_2[R]_t$. By assuring that pseudo-first order kinetics are followed, previous researchers were able to obtain analytical information using the model given in Eq. (2) by a variety of methods. The biggest problem that occurs in all of the previous techniques, however, is that as the ratio of the two rate constants, k_1'/k_2', becomes closer to unity, the errors in the estimated concentrations of the components in the mixture become larger. The most common methods for the kinetic resolution of mixtures are described below, followed by a discussion of several recent techniques that offer the possibility of improved determinations of several components, as well as increased applicability to more complicated systems.

II. PRINCIPLES OF MULTICOMPONENT KINETIC METHODS

Historical approaches to resolving mixtures of reacting species by kinetic methods have been centered on adjusting or taking advantage of differences in the reaction rates of the components.[12] These approaches are subdivided into two categories: methods for mixtures whose reactions have large rate differences and methods for mixtures whose reactions have small rate differences. Because methods for mixtures with small rate differences comprise the majority of the work in this field, each of the most popular techniques are discussed in turn.

A. Methods for Large Rate Differences

If a mixture which is to be determined has large differences in reaction rates, the analysis is quite simple because each species can be treated separately. It is assumed that during any time interval, only a single species is reacting, and that the other species have already completely reacted or are reacting so slowly that they do not interfere with the reaction of interest. The time dependence of the concentrations of C_1 and C_2 in Eq. (2) can be given as:

$$\ln([C_1]_t/[C_1]_0) = k_1't$$
$$\ln([C_2]_t/[C_2]_0) = k_2't \qquad (3)$$

If both C_1 and C_2 react during a given time period, a time-independent expression for the two concentrations can be obtained by dividing the two equations in Eq. (3) to yield:

$$\ln([C_1]_0/[C_1]_t)/\ln([C_2]_0/[C_2]_t) = k_1'/k_2' \qquad (4)$$

With this equation, Mark et al.[12] were able to determine the ratio of rate constants necessary to obtain a given error in the concentration of $[C_1]_0$. They found that if an error

of $< 1\%$ was desired, it was necessary to have a rate constant ratio of > 500. If larger errors were tolerable, smaller rate constant ratios could be used; however, the errors always increased greatly as k'_1/k'_2 became smaller. In general, rate constant ratios of < 50 yield errors of $> 5\%$ by neglecting the slower reaction. The reported errors assume that the measured parameters (e.g., absorbance, diffusion current) are equally sensitive for C_1 and C_2.

Criteria are also discussed[12] whereby one can neglect the reactions of faster reacting components. If the reaction rate of C_1 is very large compared to that of C_2, over long periods C_1 can be considered to be completely reacted (i.e., $[C_1]_t = 0$), at which time the change in the signal will be directly proportional to C_2. There are two limitations to this method. The first is the time necessary for the determination, and the second is that a reasonable amount of C_2 must remain when C_1 has completely reacted. This limits the ratio of rate constants under which precise results can be obtained. The actual ratio depends upon conditions, but is generally $> 10{:}1$.

Other methods for simultaneous determination of mixtures of components have been discussed.[12] For example, assume that a binary mixture of C_1 and C_2 is to be determined and that C_1 reacts essentially completely in 20 min. If $k'_1/k'_2 = 500$, C_1 can be easily determined, but a great deal of time must elapse before one can accurately estimate C_2. Methods are also discussed[12] for estimating concentrations under such conditions as changing the reaction temperature after C_1 has reacted to completion, changing the concentration of the common reagent, R, after the first reaction is over, or adding a catalyst after the first reaction. Because these methods are self-explanatory, they are not discussed further.

B. Traditional Methods for Small Rate Differences

If the ratio of the two rate constants is small, the techniques described above are not applicable because the assumptions necessary to neglect one of the reactions are no longer valid. For this case, special techniques have been developed in order to analyze mixtures.

The approaches to solving this problem may be divided into three general categories: masking methods, methods involving changes in the kinetics of a system, and methods for systems having unchangeable rate constant differences.[12] Each of these traditional techniques is described below, and more specific approaches are discussed. Modern computer-based methods are discussed later.

1. Masking Methods

Masking methods generally involve shifting the equilibrium of an interfering species so that it no longer reacts in the presence of the species of interest.[12] The most common example of the masking technique is the conversion of all interfering species into complexes of extremely high stability such that they no longer react with the reagent.[12] A common example of this process is the titration of metal ions with ethylenediaminetetraacetic acid (EDTA). In this case, it is relatively easy to adjust the reaction conditions so that only one metal ion forms a stable complex with EDTA, or to add another complexing agent that selectively complexes an interfering metal ion so that it does not interfere with the ion of interest.

2. Methods Involving Changing the Kinetics of a System

The second method for determinations of mixtures with small differences in the rate constant occurs when it is possible to alter the type of reagent used in order to obtain suitable rate differences.[12] In other cases, the rates of reaction are shifted into a more suitable region. This could be because the rates of reaction are too rapid to determine the species under normal conditions. An example of this method is again the reaction of metal ions with EDTA. In many cases, the reactions of free metal ions with EDTA are

too rapid for common kinetic techniques. If, however, a complexing agent is added to the mixture before the addition of EDTA, the reactions can be slowed. The rates of displacement of the preliminary complexing agent may be different for the ions being studied, in which case the rate constant ratios may be more suitable and analysis more practical.

3. Systems with Unchangeable Rate Constant Differences

The third method is actually a class of techniques that have been developed in order to obtain analytical information regarding systems with small differences in the rate constants. This is an important area of multicomponent kinetics because the rate constants often cannot be separated to a sufficient degree by either of the methods described above. Many of the previous approaches to this problem are well covered in the literature, and are not described in detail here.

The most popular approaches to multicomponent kinetic determinations historically have been graphical extrapolation methods and the method of proportional equations.[2,12] Several methods have been developed recently. These computer-based methods are described in Section II.C.

a. Graphical Extrapolation Methods

The most common graphical method has been the logarithmic extrapolation method.[12] Linear extrapolation methods also have been used, however, they have not found as wide an application as logarithmic extrapolation methods.

The concentration of the products in Eq. (2) can be given by the following if the two products are identical and the initial concentration of the product is zero:

$$[P]_t = ([C_1]_0 - [C_1]_t) + ([C_2]_0 - [C_2]_t) \quad (5)$$

The concentrations of the two reactants at any time follow simple first order kinetics as follows:

$$[C_1]_t = [C_1]_0 \exp(-k_1' t)$$
$$[C_2]_t = [C_2]_0 \exp(-k_2' t) \quad (6)$$

By substituting Eq. (6) into Eq. (5) we obtain the concentration of the product at any time in terms of only the initial reactant concentrations and their respective rate constants. Thus,

$$[P]_t = ([C_1]_0 - [C_1]_0 \exp(-k_1' t)) + ([C_2]_0 - [C_2]_0 \exp(-k_2' t)) \quad (7)$$

The logarithmic extrapolation method assumes that when the faster reacting component, C_1, has reacted to completion, the term $[C_1]_0 \exp(-k_1' t)$ in Eq. (7) becomes negligible. Using Eq. (6) and (7), we can now obtain the following relationship between the concentrations of the reactants and products:

$$([C_1]_t + [C_2]_t) = ([P]_\infty - [P]_t) = [C_2]_0 \exp(-k_2' t) \quad (8)$$

By taking the logarithm of both sides of Eq. (8) and plotting $\ln([C_1]_t + [C_2]_t) = \ln([P]_\infty - [P]_t)$ vs. time, one obtains a straight line with a slope of $-k_2'$ and an extrapolated intercept of $\ln[C_2]_0$. It is then possible to obtain the value of $[C_1]_0$ by subtracting $[C_2]_0$ from the total initial concentration of reactants. The range of rate constant ratios in which this method is applicable depends on a variety of factors, such as concentration ratio and what error is acceptable to the user. A complete error analysis is given by Mark and co-workers;[12] however, they found that under certain conditions, rate constant ratios of as low as 5 could be tolerated with this method.

An example of the logarithmic extrapolation method is shown in Figure 1 for a mixture of two components with a rate constant ratio of 10. By extrapolating the linear portion of the curve over long periods of time, the concentration of the slower reacting species can be determined. This is demon-

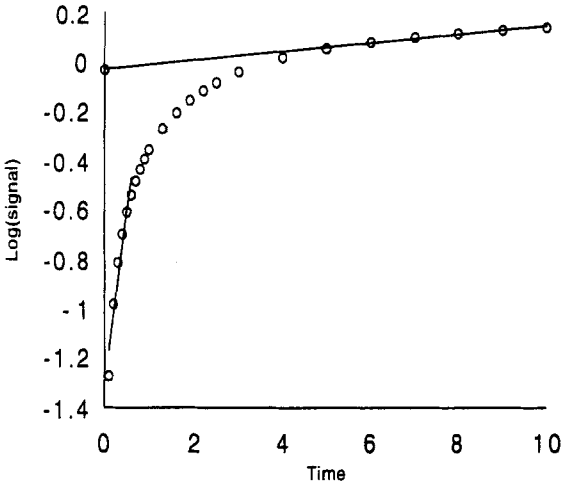

FIGURE 1. Example of logarithmic extrapolation method $k'_1 / k'_2 = 10$ and $[C_1]_= [C_2]_0$.

strated in the figure by extrapolating the linear portion back to zero time, at which the initial concentration of the slower reacting species can be determined.

The linear extrapolation method requires that the total concentration of the two species be known.[13] For two reactions following second order kinetics as described in Eq. (1), and if $[R] = [C_1]_0 + [C_2]_0$, the rate of reaction can be expressed by:

$$\frac{-d[R]}{dt} = \frac{dx}{dt} = k_1[R]_t[C_1]_t + k_2[R]_t[C_2]_t \tag{9}$$

where x is the amount of R consumed at any time, t.

If C_1 reacts faster than C_2, then when the C_1 complex has reacted essentially to completion, Eq. (9) gives, after integration:

$$x = k_1[C_2]_t([R]_0 - x)t + [C_1]_0 \tag{10}$$

The value of $[C_1]_0$ is then determined from the extrapolated intercept at $t = 0$ of a plot of x vs. $([R]_0 - x)t$.

b. Method of Proportional Equations

The method of proportional equations is based on the principle of constant fractional life, which applies to first order reactions and to systems that can be reduced to pseudo-first order kinetics.[14] A species is said to have a constant fractional life if at any given time a constant fraction has reacted irrespective of the initial concentration. This is a well-known property for first order reactions, where half-lives are often used as a measure of the reaction rate. It can be shown that the concentration of the product at any time is directly proportional to the initial concentration of the reactant. For example, in a one-component system following irreversible first or pseudo-first order kinetics, given by:

$$C_1 \xrightarrow{k_1} P \tag{11}$$

the concentration of the product P_1 at any time, t, is given by:

$$[P]_t = [C_1]_0(1 - \exp(-k'_1 t)) \tag{12}$$

or

$$[P]_t = X_1[C_1]_0 \tag{13}$$

where

$$X_1 = (1 - \exp(-k'_1 t)) \tag{14}$$

Therefore, the concentration of P at any time, t, is directly proportional to the initial concentration of C_1.

This treatment can be easily extended to the case of two reactants in a mixture. If C_2 reacts under first order conditions to form P, the concentration of P at any time, t, will be proportional to the initial concentration of C_2 by:

$$[P]_t = X_2[C_2]_0 \tag{15}$$

If the two reactions are independent, the concentration of P at time t for a mixture of C_1 and C_2 can be given by:

$$[P]_t = X_1[C_1]_0 + X_2[C_2]_0 \tag{16}$$

and the concentration of P at some later

time, t', can be given by:

$$[P]_{t'} = X_1'[C_1]_0 + X_2'[C_2]_0 \qquad (17)$$

In order to use the relationships in Eq. (16) and (17) in a real determination, it is first necessary to determine the values of X_1 and X_2 at times t and t'. These values can be determined experimentally from Eq. (13) by measuring the amount of P produced by known concentrations of C_1 only and C_2 only during the two time intervals. These values also could be calculated by substituting the known reaction rate constants into Eq. (14).

The analysis of a two-component mixture is achieved by measuring the concentration of P at times t and t'. The resulting data are then substituted into Eq. (16) and (17), which are solved simultaneously in order to determine the concentrations of C_1 and C_2.

This method can be extended to the case of a larger number of reacting species.[12] However, the errors involved in determining the values of P and of the various X values at different times limits the number of species that can be determined to three or at the most four. The accuracy that can be obtained using this method is dependent on a number of variables. A complete error analysis is found elsewhere;[12] however, this method is generally not applicable to mixtures with rate constant ratios below 5:1.

A variation of the method of proportional equations has also been developed for use with flow injection analysis (FIA).[15] This two-point kinetic method is quite similar to the method of proportional equations, except that it includes a term for the dispersion in the FIA system at each of the two points measured.

Ultimately, however, these increasingly less popular approaches are limited by erroneous assumptions regarding the system model. (This has been overcome in recent years.) The graphical extrapolation technique works under the assumption that one reaction is complete while the other reaction is only in its initial stages. As the ratio of the rate constants approaches unity, this assumption becomes less valid. For this reason, the method of graphical extrapolation becomes limited as the rate constant decreases. The method of proportional equations finds its principal limitation in a different source. Because only two data points are used to determine concentrations in a two-component mixture, the precision of this method is not very good. In a kinetic method, usually a fairly large number of data points is obtained, often on the order of 50 to 1000. However, because the method of proportional equations only uses a small fraction of the available data, the precision of this method is limited. More than two simultaneous equations can be set up, which will improve the precision. This improvement has been utilized using computer data analysis and is discussed in Section II.C. Kopanica and Stará[7] have summarized the conditions in reaction systems under which each of the above techniques is applicable.

c. Single Point Method

The single point method can be applied to systems such as those described in Eq. (2). This method requires knowledge of the total concentration of the mixture and the extent of reaction at a single selected time during the course of the reaction.[16] The method is based on a plot of $([C_1]_t + [C_2]_t)/([C_1]_0 + [C_2]_0)$ or $([C]_\infty - [C]_t)/[C]_\infty$ at any time, t, vs. the initial mole fraction of C_1 in the mixture. This plot yields a straight line which has a slope of $(\exp(-k_1't) - \exp(-k_2't))$ and intercepts of $\exp(-k_2't)$ and $\exp(-k_1't)$ at a mole fraction C_1 equal to zero and unity, respectively. The plot is used as a calibration curve, and is easily constructed by measuring the extent of reaction of pure C_1 and C_2 at the chosen value of t, and then drawing a straight line through the points.

As with the method of proportional equations, the single point method suffers from a lack of precision. Using only a single data point, when many more are readily available, severely limits the precision that can be obtained with this method. It is likely that this lack of precision is one of the main

reasons that the single point method has not found wider applicability.

C. Modern Computer-Based Methods

The introduction of digital computers in the chemical laboratory has brought an increase in the power of kinetic methods of analysis. Because kinetic systems most often follow nonlinear relationships that can be readily modeled with the aid of computers, many new applications have been discovered. Computers provide several advantages for chemists: speed of computation, ability to perform nonlinear regression rapidly, automation of data acquisition and processing, and graphical applications. Several different approaches involving the use of computers for multicomponent kinetic determinations have been utilized. Some of the more popular methods are discussed in this section.

1. General Methods

Because kinetic systems are nonlinear in nature (except for zero order systems), methods developed before computers were readily available generally tried to transform the data to fit a linear function. Nonlinear regression methods, however, are able to fit functions without the need for linearization. Hence, the nontransformed model is in common usage.

Pausch and Margerum[17] early on applied digital computers to kinetic methods of analysis. They used an IBM mainframe computer to determine mixtures of magnesium, calcium, strontium, and barium by the method of proportional equations. In their work, 30 to 60 data points were used instead of just two, as had been used previously. The larger amount of data leads to greater precision. This method is described by extending Eq. (16) and (17) to develop 30 to 60 simultaneous equations of the form

$$[P]_{t_i} = X_{1_i}[C_1]_0 + X_{2_i}[C_2]_0 \qquad (18)$$

As long as all values of X_j are known, this becomes a system of 30 to 60 simultaneous equations with two unknowns.

A simplified linear least squares method was developed for the analysis of two- and three-component mixtures.[18] The two-component system is described by Eq. (2). If $P_1 = P_2$, the concentration of the product, P, at any time can be expressed by:

$$[P]_t = [C_1]_0(1 - \exp(-k_1't)) + [C_2]_0(1 - \exp(k_2't)) + X \qquad (19)$$

where X is the background signal. At each time, t, the value of P_j can be expressed by:

$$[P]_t = [C_1]_0 a_t + [C_2]_0 b_t + X \qquad (20)$$

where $a_t = (1 - \exp(-k_1't))$ and $b_t = (1 - \exp(-k_2't))$.

The shape of the response time curve (related to $[P]_t$ vs. time) is determined by the values of $[C_1]_0$ and $[C_2]_0$ and not by X. The goal of this method is to find the values of these initial concentrations that best fit the response time curve. It is possible to measure $[P]_t$ at hundreds of times, and therefore to have hundreds of simultaneous equations of the form given by Eq. (20).

The error between the measured value of $[P]_t$ and the predicted value is denoted by μ_t and is given by:

$$\mu_t = a_t[C_1]_0 + b_t[C_2]_0 + X - [P]_t \qquad (21)$$

In order to obtain the least squares error, the sum of the squares of the errors for each data point from $t = 1$ to n is obtained as given by:

$$\Sigma_{t=1}^{n}(\mu_t)^2 = \Sigma_{t=1}^{n} w_t(a_t[C_1]_0 + b_t[C_2]_0 + X - [P]_t)^2 \qquad (22)$$

where w_t is a weighting factor associated with each $[P]_t$ value. The $\Sigma(\mu_t)^2$ values are minimized with respect to each coefficient ($[IC_1]_0$, $[C_2]_0$, and X) by partial differentia-

tion, which leads to three equations:

$$\Sigma\left(a_t^2[C_1]_0 + a_t b_t[C_2]_0 + a_t X\right) = \Sigma\, a_t[P]_t$$

$$\Sigma\left(a_t b_t[C_1]_0 + b_t^2[C_2]_0 + b_t X\right) = \Sigma\, b_t[P]_t$$

$$\Sigma\left(a_t[C_1]_0 + b_t[C_2]_0 + X\right) = \Sigma\,[P]_t \quad (23)$$

The linear combination coefficients are resolved by solution of the matrix equation

$$\begin{vmatrix} \Sigma w_t a_t^2 & \Sigma w_t a_t b_t & \Sigma w_t a_t \\ \Sigma w_t a_t b_t & \Sigma w_t b_t^2 & \Sigma w_t b_t \\ \Sigma w_t a_t & \Sigma w_t b_t & \Sigma w_t \end{vmatrix} \begin{vmatrix} [C_1]_0 \\ [C_2]_0 \\ X \end{vmatrix} = \begin{vmatrix} \Sigma w_t a_t [P]_t \\ \Sigma w_t b_t [P]_t \\ \Sigma w_t [P]_t \end{vmatrix} \quad (24)$$

where the summations for all times, t, are taken. The weighting factor is

$$w_t = \frac{\exp(-k_1' t) + \exp(-k_2' t)}{[P]_t} \quad (25)$$

to account for differences in weight of the measured data in terms of both time and magnitude. The exponential terms in the numerator deemphasize data taken near the end of each reaction. The product concentration term in the denominator is included to prevent the data from slower reacting components from being too heavily weighted.

Nonlinear regression also has been applied to the treatment of simultaneous multicomponent kinetic data.[19] Assuming that a two-component system (see Eq. (2)) undergoes first or pseudo-first order kinetics, and that the products are identical, the concentration of P at any time is given by Eq. (19). This system represents a nonlinear model. Data from such a system can be analyzed by any of a number of common nonlinear regression methods.[19] All of the nonlinear regression methods have the same goal, which is to minimize the differences between the measured value for each point and the estimated value. Good initial estimates of the regression parameters are necessary in order to achieve accurate results.

The Kalman filter has also been applied for the kinetic determination of mixtures.[20] The Kalman filter is a recursive filter and offers the advantages of linear least squares, but is simpler and more efficient. This filter is able to extract parameters from noisy data and to model complex systems.[21] There are several versions of the Kalman filter algorithm in common use, but all versions use a model of the system, which is constructed of a series of state variables, along with a sequence of weighted measurements made on the system.[21] The original form of the Kalman filter, also known as the linear Kalman filter, provides estimates of the state variables, which are optimal according to the mean-square error criterion. Although optimizing by this method is not the same as optimizing by least squares, the two methods provide identical results under certain conditions. The linear Kalman filter requires a model that, as its name implies, is linear with respect to the state variables. If this condition is not met, then the nonlinear form of the Kalman filter may be used. This variant is known as the extended Kalman filter. The actual algorithms for the various forms of the Kalman filter have been well covered in the literature (i.e., Reference 21), and therefore are not included here.

Schecter[22] developed a new error-compensating algorithm for kinetic determinations of dual-component mixtures without prior knowledge of reaction orders and rate constants. If a system described by Eq. (1) follows kinetics of unknown order, the rates of change of the two components are

$$\frac{d[C_1]}{dt} = -k_1[C_1]^{n_1}$$

$$\frac{d[C_2]}{dt} = -k_2[C_2]^{n_2} \quad (26)$$

where n_1 and n_2 are the (unknown) reaction orders. The concentrations of C_1 and C_2 at

time, t, are given by:

$$[C_1]_t = \left[k_1(n_1 - 1)t + [C_1]_0^{(1-n_1)}\right]^{1/(1-n_1)}$$

$$[C_2]_t = \left[k_2(n_2 - 1)t + [C_2]_0^{(1-n_2)}\right]^{1/(1-n_2)} \quad (27)$$

If α_x is the detector sensitivity for compound x, and the signal is linearly dependent on the concentrations, then the observed signal at time, t is

$$\begin{aligned} S_t &= \alpha_{C_1}[C_1]_t + \alpha_{C_2}[C_2]_t \\ &\quad + \alpha_{P_1}[P_1]_t + \alpha_{P_2}[P_2]_t + X \\ &= [\alpha_{C_1} - q_1\alpha_{P_1}][C_1]_t \\ &\quad + [\alpha_{C_2} - q_2\alpha_{P_2}][C_2]_t + X \\ &= \beta_1[C_1]_t + \beta_2[C_2]_t + X \end{aligned} \quad (28)$$

where β_i is a constant proportionality factor, q_i accounts for the reaction stoichiometries, and X is the constant background. Equation (28) is then fit to the experimental data by using a modified Levenberg-Marquardt algorithm in order to solve the nonlinear least squares problem. The method was tested with simulated data, and was found to be applicable for the determination of concentrations, rate constants, and reaction orders over a wide range. Some severe limitations and restrictions exist, for example, the applicable range of rate constants, and the initial estimates of each of the parameters must be fairly accurate to ensure accurate final estimates.

Schechter and Schröder[23] have developed an algorithm based on the Levenberg-Marquardt method for nonlinear least squares, which can be used for kinetic determinations in systems of mixed first and second order reactions. The development of the model for use in the algorithm is similar to that described earlier for systems of unknown order. The system can be described as follows:

$$\begin{aligned} C_1 &\xrightarrow{k_1} P \\ C_1 + R &\xrightarrow{k_2} P \end{aligned} \quad (29)$$

The algorithm was tested by simulated data, and the influence of the noise level, the range of the rate constants, and other parameters were studied. It was found to be suitable for a wide range of parameters; only rather poor estimates were needed for the algorithm to converge.

A method applicable to kinetic methods has been developed that estimates component amplitudes in multiexponential data.[24] This technique obtains quantitative information about individual component contributions to multiexponential data by a reiterative regression algorithm that employs a linear least squares determination of component amplitudes within a nonlinear least squares search for exponential decay times. This is a unique application of a combination of the linear and nonlinear least squares methods described above.

2. Multiwavelength Methods

As multiwavelength detectors such as photodiode arrays and charge-coupled devices (CCD) have become more popular, interest has grown in applying them to kinetic methods of analysis. As more of these devices are incorporated into analytical laboratories, it is expected that many new applications will be developed to take advantage of their simultaneous, multiwavelength capabilities.

Multiwavelength methods were first developed in the 1970s using Vidicon-based spectrometers.[25] The use of multiple wavelengths in kinetics experiments allows a greater diversity of systems to be successfully analyzed. Systems that have rate constants that are too close to analyze using normal means may be determined if there are spectral differences present.

Factor analysis also has been applied to the resolution of simultaneous kinetic processes.[26-30] This method has the advantage of requiring neither standards of the components to be determined nor assumptions on the shape of their spectra. The data to be factor analyzed are required to be arranged in a matrix, D, the dimensions of which are $NT \times NW$, where NT is the number of spectra acquired at different times, and NW is the number of wavelengths acquired for each spectrum. Each row of D corresponds to the spectrum of the mixture at a given point in time, and each column matches the kinetic curve at a given wavelength. The algorithm for factor analysis is not included here, as it is well covered in the literature.[30,31]

A procedure, known as the kinetic wavelength-pair method, was reported recently.[32] This method involves measuring the difference in the rate of change of absorbance with respect to time at two preset wavelength pairs. Because the rate of change of absorbance at any wavelength is dependent on the wavelength used, the rate of change of absorbance at two wavelength pairs can be used to determine the concentrations of two species in a mixture. For a mixture of two components (see Eq. (1)), application of the method involves measuring the rate of change of absorbance at two wavelength pairs, (λ_1, λ_2) and (λ_3, λ_4), which are chosen so that the difference between the rates of change of the absorbance for the first wavelength pair, (λ_1, λ_2), is as large as possible for one of the components (e.g., C_1) and as small as possible for the other. The reverse should be true for the second wavelength pair. Data were collected with a diode-array spectrophotometer.

The nonlinear or extended Kalman filter also has been utilized for multicomponent kinetic determinations using absorbance data from several wavelengths.[33,34] This method does not make the assumption that the rate constants are invariant from run to run, which is assumed in all other multicomponent kinetic methods. This allows greater flexibility in that controlling reaction conditions is not as important as for other methods. Resolution of the components of the mixture is based on both the spectral and the kinetic differences. Simulations showed that mixtures could be successfully determined even if the rate constants of the two reactants are identical,[33] as long as spectral differences exist.

3. Miscellaneous Methods

In addition to the approaches described earlier, several other methods have been developed which are not easily placed in the categories already discussed. These so-called miscellaneous methods are described here.

An H-point standard additions method (HPSAM) has been developed for the ultraviolate-visible spectroscopic kinetic analysis of two-component systems.[35] The method is described for two cases: the analysis of two species, of which only one evolves with time, and the analysis of two species with overlapped time evolutions.

The determination of the concentration of C_1 by the HPSAM at equilibrium entails selecting two wavelengths, λ_1 and λ_2, lying on each side of the absorption maximum of C_2, so that the absorbance of the latter component is the same at both wavelengths. Then, known amounts of C_1 are successively added to the mixture and the resulting absorbances are measured at the two wavelengths. The two straight lines thus obtained intersect at the so-called H-point $(-C_H, A_H)$, where $-C_H = (-C_{C1})$ is the unknown concentration of C_1 and $A_H = (A_{C2})$ is the analytical signal of C_2. When one of the species evolves with time, the variables to be fixed are two times, t_1 and t_2. Species C_2, which should not evolve with time over this range, should have constant absorbance. This contrasts with the equilibrium HPSAM, where two wavelengths are chosen. A plot is then prepared of added $[C_1]$ on the ordinate, and ΔA for the two times on the abscissa. The point where $\Delta A = 0$ is equal to $-[C_1]$.

When both species evolve with time, $[C_1]$ can be calculated by plotting ΔA for the two times against the added concentration of C_1 at two wavelengths, λ_1 and λ_2, provided the

absorbances of C_2 at these two wavelengths are the same.

The continuous addition of reagent technique is also applicable to multicomponent kinetic determinations.[36] This method is based on the continuous addition of reagent at a constant rate to the species to be determined.[37] The model for this method is developed here for a single component, but can be extended readily to multiple reacting species. Consider the reaction given by Equation 1, where only one analyte is present. If a solution of a reagent, R, with a concentration, $[R]_0$, is added at a constant rate, u, to a volume V_0 of a solution containing the analyte C_1, the overall rate of the process can be given by:

$$\frac{-d[C_1]}{dt} = -\left(\frac{d[C_1]}{dt}\right)_{\text{reaction}} - \left(\frac{d[C_1]}{dt}\right)_{\text{dilution}} \quad (30)$$

if C_1 is the monitored species. The reaction rate can be expressed by:

$$-\left(\frac{d[C_1]}{dt}\right)_{\text{reaction}} = k_1[C_1][R] \quad (31)$$

where k_1 is the pseudo-second order rate constant. The reagent concentration increases with time according to:

$$[R] = \left(\frac{u[R]_0}{V_0 + ut}\right)t \quad (32)$$

The term ut, the volume of reagent added in time t, is also a dilution factor for the reagent. The dilution of the analyte C_1 takes place according to:

$$[C_1] = [C_1]_0\left(\frac{V_0}{V_0 + ut}\right) \quad (33)$$

Taking the derivative of Eq. (33) gives the rate of dilution

$$-\left(\frac{d[C_1]}{dt}\right)_{\text{dilution}} = \left(\frac{u}{V_0 + ut}\right)[C_1] \quad (34)$$

By combining Eq. (31), (32), and (34), the overall rate can be shown to be

$$-\frac{d[C_1]}{dt} = k\left(\frac{u[R]_0}{V_0 + ut}\right)t[C_1] + \left(\frac{u}{V_0 + ut}\right)[C_1] \quad (35)$$

In practice, Eq. (35) forms the basis of the initial rate version of the continuous addition of reagent method. Under short reaction times ($ut \ll V_0$), dilution of the analyte can be neglected and Eq. (35) can be rewritten as:

$$-\frac{d[C_1]}{dt} = k\left(\frac{u[R]_0}{V_0}\right)t[C_1]_0 \quad (36)$$

Equation (36) is used for the construction of a linear calibration graph by plotting the initial slopes of the kinetic curves as a function of $[C_1]_0$ over a fixed time interval in all experiments.

III. APPLICATIONS OF MULTICOMPONENT METHODS

Several different approaches have been applied for the simultaneous kinetic resolution of mixtures in recent years. This section discusses the applications for which multicomponent kinetic methods have been utilized for methods with small rate constant differences.

A. Graphical Extrapolation Methods

The most popular graphical technique used for simultaneous kinetic determinations has been the logarithmic extrapolation method (see Section II). This method has been applied to several problems in analytical chemistry. Table 1 summarizes some re-

TABLE 1
Applications Utilizing Graphical Extrapolation Methods

System	Conc. range	Rate constant ratios	Errors	Ref.
Alkaline earth-DCTA[a] / Cd(II) substitution reaction	10^{-6}–10^{-5} *M*	1:7.3:109 Mg:Ca:Sr	9.5% av.	13
Aniline and derivatives / DMPD[c]	10^{-4}–10^{-3} *M*	[b]	< 14%	38
Fe and Co with pyridoxal thiosemicarbazone	10^{-5} *M*	10.5	⩽ 5%	51
Ni and Cu with pyridoxal thiosemicarbazone	μg / ml	NR	⩽ 6%	52
Displacement of Co, Ni, and Cu pyridoxal thiosemicarbazone complexes with DCTA	μg / ml	∞[d]	⩽ 6%	39
Displacement of In and Ga / PAR[e] complexes with EDTA[f]	μg / ml	NR	< 10%	56

Note: NR = not reported.
[a] DCTA = 1,2,diaminocyclohexane-*N*,*N*,*N'*,*N'*-tetraacetic acid.
[b] Only total concentration determined.
[c] DMPD-*N*,*N*-dimethyl-*p*-phenylenediamine.
[d] Co does not undergo the exchange reaction ($k_{Co} = 0$).
[e] PAR = 4-(2-pyridylazo)resorcinol.
[f] EDTA-ethylenediaminetetraacetic acid.

cent applications that have taken advantage of graphical extrapolation methods.

As can be seen from Table 1, graphical extrapolation methods have performed well as long as sufficient differences in rate constants exist among the species being determined. The smallest ratio yielding accurate results reported in the references in the table was 7.3.[13] Some of the mixtures determined by the reaction of aniline and its derivatives with *N*,*N*-dimethyl-*p*-phenylenediamine (DMPD)[38] had rate constant ratios of < 2. However, in these experiments, the total concentration of the two species in the mixture was successfully determined, not the individual concentrations of each species.

The displacement reaction of the cobalt complex of pyridoxal thiosemicarbazone with 1,2,diaminocyclohexane-*N*,*N*,*N'*,*N'*-tetraacetic acid (DCTA) does not occur, and this allowed the analysis of mixtures of cobalt and nickel and cobalt and copper.[39] Because both nickel and copper complexes undergo the exchange reaction, their binary mixtures with cobalt can be analyzed by graphical methods, as the effective rate constant ratio is infinity. The rate constant ratio for the binary mixture of nickel and copper was 4.40, however, and they could not be successfully determined by this method. In order to determine this mixture, the single-point method was used.

B. Proportional Equations-Based Methods

The method of proportional equations described in Section III.B also has been used extensively in analytical chemistry. Table 2 summarizes some recent applications that have utilized the method of proportional equations. Several of these applications[40-48] have taken advantage of the FIA technique to allow large numbers of samples to be

TABLE 2
Applications Utilizing the Method of Proportional Equations

System	Conc. range	Rate constant ratios	Errors	Ref.
Dissociation of Mg and Sr complexes of trans-1,2-diaminocyclohexanetetraacetic acid	10^{-4}–10^{-3} *M*	175	< 10%	40
Dissociation of metal / cryptand complexes	10^{-4}–10^{-3} *M*	Large[a]	< 10%	41–43
Dissociation of citrate complexes of Co and Ni	μm / ml	43.4	< 10	15
Fe(III) and Mn(II) or Ni and Co with 2OH-BAT[b]	ng / ml 10^{-4} *M*	27.7 (Fe,Mn) 24.9 (Ni, Co)	< 4 < 10%	44, 49
2-Component mixtures of ammonia, hydrazine, and hydroxylamine with 2OH-BAA[c]	10^{-4}–10^{-2} *M*	NR	< 6%	57
Formation of molybdate heteropoly acids of silicate and phosphate	ng / ml 10^{-6}–10^{-5} *M*	130	< 5%	58
Furfural and vanillin with p-aminophenol	μg / ml	NR	< 6%	59
Histidine and 1-methylhistidine with *o*-phthaldialdehyde	μg / ml	NR	< 6%	60
Fe(II) and Fe(III) with pyrocatechol violet	μg / ml	Large	< 5%	61
Fe(II) and Fe(III) by differential catalysis	μg / ml	NR	< 10%	46
Co and Ni by ligand exchange with PSAA[d] and nitrilotriacetic acid	μg / ml	> 100	< 5%	47
Fe(II), Fe(III), and Ti(IV) with Tiron[e]	μg / ml	NR	< 5%	48
Mo(VI) and W(VI) with DAP[f] and H_2O_2	10^{-6} *M*	NR	< 5%	50
Ethanol and methanol with alcohol oxidase	10^{-6}–10^{-5}	NR	< 8%	62

[a] The second dissociation did not occur at room temperature. It was necessary to elevate the temperature after the first dissociation.
[b] 2OH-BAT = 2-hydroxybenzaldehyde thiosemicarbazone.
[c] 2OH-BAA = 2-hydroxybenzaldehyde azine.
[d] PSAA = 2-(5-bromo-2-pyridylazo)-5-(*N*-propyl-*N*-sulfopropylamino) aniline.
[e] Tiron = Sodium 1,2-diyhydroxybenzene-3,5-disulfonate.
[f] DAP = 2,4-diaminophenol dihydrochloride.

processed in a short amount of time. Sampling rates of 60/h or more have often been reported when using this configuration.

Several of the systems utilized also required the use of two procedures.[45,46,48-50] Each of the procedures was optimized for the response of one of the components. In this manner, it is possible to determine more closely related species.

Overall, the method of proportional equations can be quite useful. Its biggest drawback occurs when the species being de-

termined are closely related kinetically. Under these conditions, the results obtained from this technique are not favorable, and it would be best to use a different method.

C. Single-Point Method

The single-point method, as described in Section III.B, also has been used for several applications. Table 3 describes some of the recent studies that have utilized the single-point method. As is apparent from the table, this method is applicable to systems with smaller rate constant ratios than either the logarithmic extrapolation method or the method of proportional equations. However, once this ratio falls below approximately 5, the errors start to increase rapidly. Also, as mentioned in Section III.B, this method generally has a lower precision than does the logarithmic extrapolation method.

The single-point method has been compared to the logarithmic extrapolation method; several of the chemical systems are shown in Table 3.[39,51-53] Generally, it was found that the graphical method is preferable to the single-point method, unless the rate constant ratio is small. More modern techniques, such as computer methods, have been shown to be superior to either of these methods.[53]

D. Computer Methods

As mentioned previously, the introduction of computers in the analytical laboratory has allowed a broader range of systems to be studied. Table 4 summarizes some recent applications of computer methods to kinetic methods of analysis. Also included in the table is the specific computer analysis method, described in Section II, used for each application.

Simulation studies are now commonplace for testing new methods (see Table 4). Simulations allow easy control of the "system" being studied. It is quite easy to change conditions on one, some, or all of the parameters of interest. In a real system, it is often difficult to change only one parameter without changing others. In most of the simulation studies listed in Table 4, many factors were varied: rate constant ratios, concentration ratios, amount of noise present, and data acquisition rate. The errors found in the simulated systems varied greatly, often from 0 to > 100%, depending on the conditions chosen for each "experiment".

TABLE 3
Modern Applications Utilizing the Single-Point Method

System	Conc. range	Rate constant ratios	Errors	Ref.
Fe and Co with pyridoxal thiosemicarbazone	10^{-5} *M*	10.5	< 5%	51
Co, Ni, Cu / pyridoxal thiosemicarbazone ligand exchange with DCTA	μg / ml	4.4 (Ni:Cu)	< 5%	39
Ni and Cu / pyridoxal thiosemicarbazone	μg / ml	Large	< 5%	52
Co and Cu and Co and Ni with TrADAT[a]	μg / ml	Large	< 5%	63
Secondary amines with carbon disulfide	10^{-3}–10^{-1} *M*	18–232	< 10%	64
Cortisone and hydrocortisone with blue tetrazolium	μg / ml	1.8	Most < 30%	53

[a] TrADAT = 3-(1′*H*-1′,2′,4′-triazolyl-3′-azo)-2,6-diaminotoluene.

TABLE 4
Applications of Computer Methods to Multicomponent Kinetic Determinations

System	Conc. range	Rate constant ratios	Errors	Method	Ref
Alkaline earths with CyDTA	10^{-5}–10^{-4} *M*	6.5–1660	< 10% (2) < 20% (3)	MPE, LLS	17, 18
Al(III) and Al-citrate with calcein blue	10^{-5} *M*	> 100,000	< 5%	NLR	19
Metal–zincon[a] dissociation	10^{-6}–10^{-5} *M*	12–183	< 8%	LLS	65
Epinephrine, norepinephrine, and *L*-Dopa with ascorbic acid	10^{-5}–10^{-4} *M*	2.4–20.3	< 15% (> 15% for $k = 2.4$)	LLS	65
Hg(II) and Zn(II) with zincon	10^{-5} *M*	1.6	NR	WLS	25
Amino acids with trinitrobenzenesulfonic acid	10^{-5} *M*	2.5	< 14%	KF	20
Alkaline phosphatase isozymes / guanidinium hydrochloride	10^{-6}–10^{-5} *M*	4.6	15%	KF	66
Cortisone and hydrocortisone with blue tetrazolium	μg / ml	1.8	< 8%	KF	53
Co-EGTA and Ni-EGTA complex displacement with PAR	μg / ml	20	NR	FA	30
La, Pr, and Nd complexation with PAR	10^{-6}–10^{-5} *M*	1.1–1.9	< 15%	EKF	34
Co-EGTA and Ni-EGTA complex displacement with PAR	μg / ml	20	< 10%	NLR	67
Alcohols with alcohol dehydrogenase nicotinamide adenine dinucleotide	10^{-8}–10^{-6} *M*	2.2–2.3	< 10%	KF	68
Simulation studies	Varied	Varied	Varied	NLR LLS, KF, EKF, and FA	20, 22–24 30, 33 34, 69, 70

Abbreviations:
MPE = modified proportional equations.
LLS = linear least squares.
NLR = nonlinear regression.
KF = Kalman filter.
EKF = extended Kalman filter.
WLS = weighted least squares.
FA = factor analysis.
[a] Zincon = 2-carboxy-2′-hydroxy-5′-sulfoformazylbenzene.

Some of the computer methods also utilized detection at multiple wavelengths.[25,30,33,34] This allows a broader range of systems to be studied. Because using data at multiple wavelengths allows resolution of signals due to both spectral and kinetic differences, these methods are applicable to even more systems. It is expected that more work in this area will appear shortly.

E. Multiwavelength Methods

Rapid-scanning spectrometers were the first devices used to perform multiwavelength studies for multicomponent kinetic analysis. Since then, diode array spectrometers have become popular tools for multiwavelength kinetic determinations. Table 5 summarizes the progress in multiwavelength methods. Quencer and Crouch[33] used simulations of multicomponent kinetic reactions at multiple wavelengths in order to test the applicability of the extended Kalman filter to these systems. By a combination of spectral and kinetic differences, concentrations were successfully determined even if the rate constant ratio of the two components was 1.0. This method was then used to determine mixtures of lanthanum, praseodymium, and neodymium based on their complex formation with 4-(2-pyridylazo) resorcinol.[34] Errors of < 10% were reported for two-component mixtures, while three-component samples had errors of < 18%.

F. Miscellaneous Methods

In addition to the methods for multicomponent kinetic determinations categorized above, several applications have not used one of the common techniques. These methods are discussed in Section III.B, and the applications that utilize them are summarized in Table 6.

Although the two methods listed have had few applications to date, they seem quite promising. It is entirely possible that either or both of these techniques will be applied widely to multicomponent kinetic determinations.

IV. CONCLUSIONS

The introduction of computers in the analytical laboratory has had a great impact on

TABLE 5
Applications Utilizing Multiwavelength Detection

System	Conc. range	Rate constant ratios	Errors	Ref.
Hg(II) and Zn(II) with zincon	10^{-5} *M*	1.64	NR	25
Hemoglobin and methemoglobin with cyanide and hexacyanoferrate(III)	10^{-3} *M*	NR	< 7%	71
Formaldehyde and acrolein with MBTH[a]	μg / ml	2.9	< 10%	32
Co and Ni-EGTA complex displacement with PAR	μg / ml	20	NR	30
Co and Ni-EGTA complex displacement with PAR	μg / ml	20	< 10%	67
La, Pr, and Nd complexation with PAR	10^{-6}–10^{-5} *M*	1.1–1.9	< 15%	34
Simulation studies	Varied	1.0–5.0	Varied	33, 34

[a] MBTH = 3-methylbenzothiazolin-2-one hydrazone.

kinetic methods. This advance has allowed kinetic methods to become more highly automated, and has led to the changes in data analysis methods previously discussed. Kinetic methods are well suited to intelligent automation[10] because these techniques require precise timing and careful control over such reaction conditions as temperature, pH, ionic strength, and reagent concentrations.

Computer technology has led to new data processing methods such as the Kalman filter and nonlinear regression methods. These techniques generally lead to more accurate and faster results than those used before the advent of computers.

Similarly, the recent increase in the popularity of array-type detectors has begun to have an impact on multicomponent kinetic methods. Although relatively few applications have incorporated these new detectors, it is expected that a large increase in the applications using them will occur in the next few years. The CCD detector, in particular, should become more widely used because it allows for spatial imaging studies on time-dependent systems.

The future should see many advances in multicomponent kinetic methods. By incorporating new data analysis techniques and taking advantage of the greater amounts of information available from array-type detectors, it is expected that the speed and accuracy of these methods will improve substantially over the next decade. Methods that compensate for changes in rate constants from run to run are among those that should continue to improve. Rate constants are often functions of such variables as temperature, pH, and ionic strength. Several methods have been developed for single-component kinetics that compensate for the changes in the rate constant between runs. For example, Wentzell and Crouch[54] developed the two-rate method, which involves measuring the rate of change of the reaction at two different times, and then taking the ratio of the two rates. This ratio is not dependent on the value of the rate constant. Another approach to the same problem is the predictive kinetic approach of Mieling and Pardue.[9] This method uses a model of the chemical reaction under study to predict the position of equilibrium. This offers the advantages of equilibrium methods without having to wait for equilibrium to take place. Corcoran and Rutan[55] used the extended Kalman filter to correct for changes in the rate constant within a run.

Multicomponent kinetic methods have been shown to be a powerful tool for the analytical chemist. These techniques offer selectivity and throughput advantages over equilibrium-based methods. However, equilibrium methods are generally more sensitive than kinetic methods. It is expected that kinetic methods will improve in both precision

TABLE 6
Miscellaneous Applications

System	Conc. range	Rate constant ratios	Errors	Method	Ref.
Zineb and maneb with zincon	μg / ml	5.4	< 5%	CAR[a]	72
Cu and Fe with pyridoxal thiosemicarbazone	μg / ml	4.67	< 5%	CAR	73
Mn and V with pyrogallol red	μg / ml	Large	< 20%	HPSAM[b]	35
Creatinine and albumin by the Jaffé method	μg / ml	Large	< 8%	HPSAM	35

[a] CAR = continuous addition of reagent technique.
[b] HPSAM = H-point standard additions method.

and accuracy, and will have even greater reliability and throughput than they do today.

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