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The science of chemical analysis and the technique of mass spectrometry

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Abstract

The subject of chemical analysis is traditionally organized by the techniques employed. This method of classification fragments the subject and provides little basis for learning how to approach the development of new methods. A concept underlying all chemical analyses is the selection and implementation of the quality of the analyte that distinguishes it from the rest of the sample components. The analytical process is the selection of the differentiating characteristic (DC), the development of a probe to test the sample for the DC, the anticipation and measurement of the response of the sample to the probe, the interpretation of the data, and the evaluation and improvement of the method. The range of options available at each step illustrates the latitude for creativity exercised by former analysts and available for methods yet to be developed. In mass spectrometry, the differentiating characteristics are seen to be ionizability, mass-to-charge ratio, and fragmentation pattern. The selectivity of the combination of differentiating characteristics employed greatly affects the detection limit in trace analysis. The methods of probing, measurement, and data analysis are related to the analytical goals (quantitation, detection, or identification). Measurements are based on conversion devices and counting techniques. When counting statistics are considered, the impact of peak overlap in chromatography/mass spectrometry is seen to be a loss of dynamic range in the concentration of the analytes. (Int J Mass Spectrom 212 (2001) 1–11) © 2001 Elsevier Science B.V.

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1. Introduction

The subject of chemical analysis has been organized according to the technique employed for several decades. It is my view that this classification of the topics is no longer suitable, nor does it do justice to the subject or its practitioners. The principal problem, despite several attempts to provide one [1,2], is the lack of a unifying theme with which to bind the various techniques. This lack invites fragmentation of the subject and isolates the practitioners of various techniques into separate categories. The result is isolation and competition within the college curriculum and within the analytical community.

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Dedicated to R. Graham Cooks on the occasion of his sixtieth birthday.

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In teaching chemical analysis, there is little to connect the various techniques presented into a common theme of chemical analysis. The fact that the techniques could be presented in virtually any order attests to the lack of unifying principles and conceptual development. The emphasis on technique fosters the notion that the important goal of learning chemical analysis is to learn how to employ specific techniques. This "trade school" perception of the teaching goal encourages the concept that nothing is lost when the teaching of analytical techniques is relegated to the labs of nonanalytical courses. As a result, the introductory course in analytical chemistry is no longer a requirement for chemistry majors in more than 50% of the bachelor's degree curricula in the USA. In 1963, Hume [3] wrote a stirring article calling for a wider recognition of the differences in the problems solved and approaches taken by analytical chemists and chemists working in other areas. In 1979, Laitinen [4] said, "Analysis can now be more accurately described as being applied to a problem, rather than a sample." In other words, we need to teach and perceive analytical chemistry as a system of approaches to chemical characterization, not a collection of techniques used on different types of samples.

The lack of unifying principles also serves to isolate scientists within the analytical community. Researchers in separations, mass spectrometry, and chemometrics have relatively little interaction even though such interaction could be highly synergistic. Equally significant, the failure of analytical chemists to develop a unifying theme and intellectual framework for the science of chemical analysis has led to a devaluation of analytical chemistry as a serious science among status-conscious colleagues. The irony of these losses of curriculum and status is that they come at a time when the advances in chemical analysis are most profound [5] and most critically needed.

When identified, the science of chemical analysis will surely include the principles of measurement and a systematic approach to the development of analytical methods. The recent trend toward problem-based learning in analytical courses attests to the desire for such an approach. Stimulated to address this need by a conversation with Graham Cooks over seven years ago, I have developed an intellectual framework for chemical analysis that I hope will help relieve some of the problems and reverse some of the trends outlined previously. It is my pleasure to present it here in this issue honoring Cooks. Given this venue, examples familiar to mass spectrometrists will be used.

2. The key role of the differentiating characteristic

A key to the development of a general approach to chemical analysis is the differentiating characteristic used to distinguish the analyte(s) from the rest of the material in the sample matrix. Whether the goal of the analysis is quantitation, detection, identification, or separation, some property of the analyte that is not shared by the rest of the sample components must be discovered. The differentiating characteristic might be the ability to undergo a specific type of chemical reaction, such as an acid-base reaction or an antibody-antigen reaction. When mass spectrometry is used, the differentiating characteristics employed are the ability of the molecule to be ionized and its mass-to-charge ratio (m/z). Additional differentiation may be obtained by characteristic ion fragmentation or adduct formation. The list of potential differentiating characteristics is virtually endless and growing. Advances in chemical analysis revolve around the implementation of new differentiating characteristics (as in fluorescence lifetime) or new ways to exploit familiar techniques (as in cavity ring-down spectrometry).

3. The analytical process

For every analytical process, there is a sequence of seven steps by which an analytical method can be developed. The steps are: (1) The differentiating characteristic must be chosen, (2) A probe for the differentiating characteristic must be devised and applied, (3) The various responses of the sample to the probe should be anticipated, (4) One or more of

the responses to the probe must be measured, (5) The measurement data must be interpreted to obtain the desired analytical information, (6) The method must be evaluated if the goal is methods development or characterization, and (7) If the evaluation reveals that the method does not meet the goals, the limiting steps can be identified and alternatives sought.

This sequence can be very useful as a framework for the study, development, and application of chemical analysis. In the subsections below, the elements of this sequence are considered in detail. It is also within this context that we see that there are actually many options available at each of these steps. This enables comparisons of the options and an appreciation of the ingenuity and creativity of previous analysts in the development of various approaches. It can also provide stimulation for future developments as the range of possibilities for each step is expanded by new science and technology.

3.1. Choosing the differentiating characteristic

The differentiating characteristic upon which an analytical method is based must be a distinctive quality of the analyte. Further, there must exist some method to interrogate the sample for evidence of this characteristic. Differentiating characteristics can be physical properties such as optical absorbance, molecular mass, diffusivity, magnetic moment, and polarity. Chemical properties such as complex formation, precipitation reactivity, and enzymatic reactivity are also used as differentiating characteristics. The distinction between the application of chemical differentiating characteristics and physical differentiating characteristics is not the same as the traditional distinction between “wet” and “instrumental” methods of analysis. For example, the application of immunoassay techniques is based on antibody-antigen reactivity (wet chemistry), but also involves spectrometry or radioactivity counting (instrumental methods) in its implementation.

Clearly, the practical options for the differentiating characteristic in any given analysis will depend greatly on the nature of the analyte as well as that of the sample matrix. When a proposed differentiating characteristic is not unique to the analyte within the sample matrix, some combination of differentiating characteristics must be employed to eliminate interferences. Many techniques inherently use several differentiating characteristics. For example, the technique of liquid chromatography/mass spectrometry involves interphase partition, response to the ionization method applied, and ionic mass-to-charge ratio. Indeed, it is the high selectivity that results from the application of three greatly different differentiating characteristics that gives this approach its great power in trace analysis.

3.2. Devising and applying the probe

The probe for the differentiating characteristic is always a method to stimulate the property or characteristic of the analyte being used for the analysis. Thus, if the differentiating characteristic chosen is the acidic property of the analyte, the probe is to react it with a base. If the differentiating characteristic is its ability to fluoresce, the probe is to stimulate the fluorescence. For the differentiating characteristic of mass, one probe is to ionize the analyte so that a mass analyzer can determine the mass-to-charge ratio of the resulting ion. A second probe is the mass dispersion, which probes the differentiating characteristic of ionic m/z.

Several options may be available in the application of the probe. For example, the base could be added gradually as in a titration or in a batch. The fluorescence may be stimulated by photon, thermal, or chemical excitation. Probes based on mass that are not ionization/mass analyzers have also been devised, though many of these are actually probes of density or diffusivity that may be related to mass. In optical spectrometry, the application of pulsed laser probes rather than continuous light sources has led to several new and powerful techniques including cavity ring down spectrometry, a clever and effective variation on classical absorbance determinations.

In mass spectrometry, there are many ways in which the probes of ionization and m/z discrimination have been accomplished. We realize that many of the species in the sample are likely to be ionized, not just

the analyte. Thus, in mass spectrometry, the selectivity comes from both the ionization and mass dispersion probes. The selectivity of a technique also depends on the nature of the sample and the analytical goals. For example, if the goal is to determine the amino acid constituents of a sample, mass spectrometry can be used. However, it is necessary to distinguish between leucine and isoleucine, or between the D and L forms of the amino acids, ionic *m/z* is not sufficiently differentiating. The addition of chiral chromatography can provide the additional differentiation required.

3.3. Anticipating the response to the probe

The way in which the sample responds to the probe reveals the methods that can be used for measurement and provides the basis for the interpretation of the measurement data. There are often many responses to the probe, which means that more than one method of measurement may be possible. For instance, in the application of base to an a solution containing an acidic analyte, the pH of the solution increases, the amount of protonated analyte decreases, the amount of analyte in its basic form increases, the amount of the added base increases, the temperature of the solution increases, and the ionic conductivity changes. Any of these changes could be used to determine the extent of the reaction and thus the amount of the analyte present. Each of these can be combined with the various options for the addition of the base probe to reveal a substantial number of ways to carry out this classical analysis.

For the differentiating characteristic of fluorescence, the response of the sample to the application of a photon excitation probe is, of course, the fluorescence of the analyte. However, the response also includes the absorbance of the probe illumination and the absorbance of the emitted radiation. These anticipated responses reveal the effects of primary and secondary absorbance in fluorescence analysis and rationalize the nonlinearity in the working curve that occurs at higher concentrations of analyte. In general, the anticipated response can be correlated with the amount of analyte through a working curve even if the response function does not have a fundamentally predicted form.

In mass spectrometry, the response to the probe for many of the sample species is to become ionized and for the ions to then be dispersed according to their *m/z* values. The dispersion of presently used devices is in space, time, or frequency of oscillation and is based on velocity, momentum, energy, or mass-to-charge ratio. Still other forms of dispersion are possible. For example, ions could be given a constant acceleration and sorted according to the force with which they hit the detector.

3.4. Measuring the responses to the probe

Ideally, the measurement of the responses of the sample to the probe can be interpreted to provide the analytical information we seek. From a consideration of all the responses, the ones we choose to measure will be those that are most useful or most accessible. In a titration, we need to know the amount of titrant used to reach the equivalence point of the titration. This requires a determination of the concentration of one or more of the sample constituents as a function of the amount of titrant added. An indicator provides a single point indication of a sample concentration for which the delivered titrant volume can be determined. A spectrometer or specific ion electrode can continuously monitor a variety of the sample concentrations as titrant is added. Buret reading, digital buret readout, the weight of the titrant container, or counting drops can determine the amount of added titrant. If the response is recorded over the entire titration curve, a series of response:volume data pairs must be acquired.

In mass spectrometry, we record the ion intensity at one or more specific *m/z* values. If we choose a single *m/z* value (selected-ion monitoring), we can obtain abundance information for a specific analyte. If we record the ion intensity for additional *m/z* values, we obtain a larger part of the complete mass spectrum of the sample. From this, we see that we need a way to determine the *m/z* value being sampled by the mass analyzer as well as the intensity of the ion current at each *m/z* value. These data are recorded implicitly or

explicitly as intensity:*m/z* data pairs. Additional dimensions of data can be added. For example, in imaging mass spectrometry, the x-y coordinates of the sample surface being probed are recorded along with the intensity:*m/z* data pairs. In a complete tandem mass spectrometry acquisition, the intensity:*m/z* data pairs for the product spectra are recorded for each precursor *m/z* value sampled.

Note that the measurement step does not include the interpretation of the data. Since the type of data acquired is informed by the nature of the interpretation anticipated, it is helpful to intellectually separate the acquisition of data from their interpretation. Each of these steps involves its own procedures, limitations, and sources of error.

3.5. Interpreting the data

The interpretation of the data depends, first of all, on the goals of the analysis. If the goal is detection of a specific compound, the data interpretation consists of evaluating the measurement data to determine the certainty to which the compound can be said to be present or absent. If the goal is quantitation, the data interpretation (which will often include standardization data) is in the relationship of the response or relative response to the quantity of analyte present. If the goal is identification, the interpretation is in relating spectral data to the pattern of data that would be presented by known compounds. This interpretation can be by empirical matching, heuristics, or both.

The data interpretation process is one of the least emphasized in current analytical courses. There are several possible reasons for this. One is that we have tended to focus on instruments and the methods and devices they use to generate the measurement data. Another is that the field of chemometrics has tended to remain a specialized sub field of analytical chemistry, like electronics. A third reason is that much of the data processing that occurs in instrument computers is inaccessible for study and uses algorithms guarded as trade secrets by the manufacturers. This is indeed unfortunate, as it tends to promote the black box perception of modern instruments and undermines the motivation to learn more of the principles of their operation.

The distinction of the measurement process from the data interpretation process can help reverse this trend. Data processing can be introduced with the simplest of experiments. For example, the advantages of using multiple points in a titration curve rather than just an end point can be discussed and demonstrated. Improvements in precision resulting from curve fitting can be readily demonstrated with this classic technique. Similarly, the advantages of principal component analysis for the resolution of whole spectra compared to the usual two-wavelength, two-component example can be shown. In mass spectrometry, the spectral matching method can be compared with heuristic approaches for the identification of unknown compounds.

3.6. Evaluation and improvement of the method

A critical review of how well the analytical method is achieving its goals in the given analysis is part of good laboratory practice and serves to illuminate the limiting factors in any analysis. The criteria of precision or certainty, accuracy, detection limit, dynamic range, and the nature of interferences can all be studied in the light of the four steps outlined previously. Interferences can result from an insufficiently selective differentiating characteristic, given the nature of the sample. They can also result from the anticipation of the response of all the sample constituents to the application of the probe (matrix effects). Of course, the lower the detection limit we are trying to achieve, the more selective the differentiating characteristic must be. When a single differentiating characteristic is not sufficiently discriminating, more than one can be applied. As mentioned earlier, the differentiating characteristics used in mass spectrometry are response to particular modes of ion formation, resulting ion *m/z* value, and pattern of ion fragment *m/z* values. When even these are insufficient, the differentiating characteristic of interphase partition can be added in the form of extraction or chromatography. The application of antibody-antigen reactivity as a differentiating characteristic, in con-

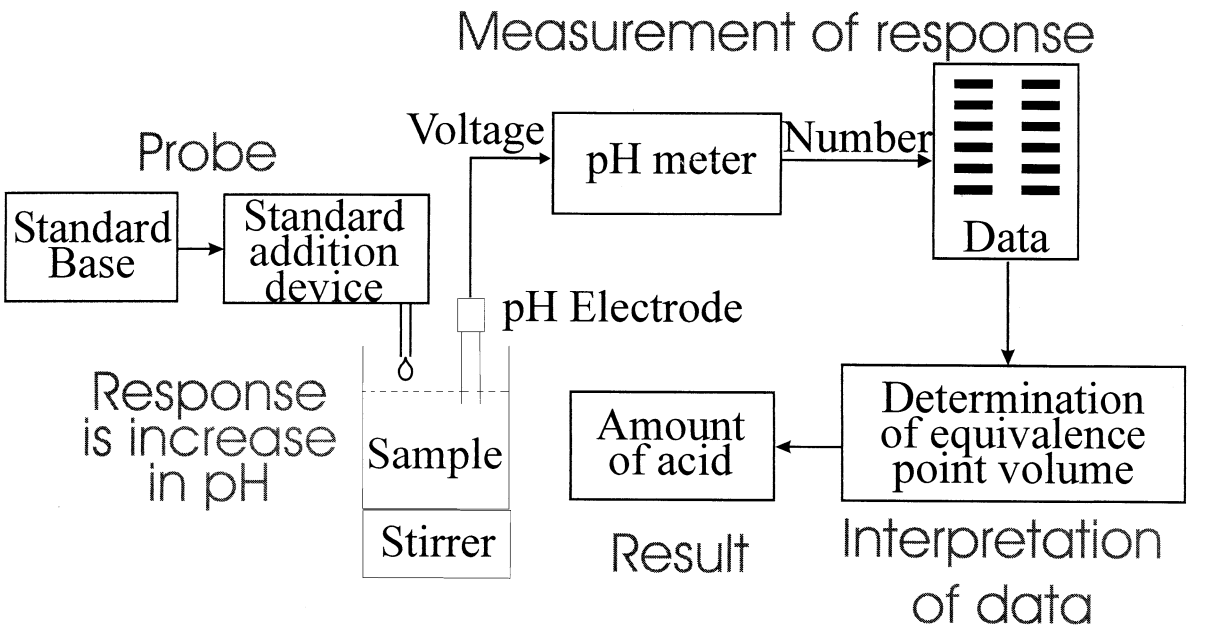

Fig. 1. Diagram of the titration of an acid with a base. The standard base and addition device is the probe, the increase in pH is one response to the probe; the pH meter is one way to measure this response. The response versus amount of base added data are interpreted to discover the equivalence point volume, which, in turn, is used with other data to calculate the amount of acid in the original sample.

junction with ionization and *m/z*, results in one of the most exquisitely selective techniques available.

The reproducibility of the result can be evaluated from repetitive measurements. Improvements to methods are often made out of the range of options sometimes referred to as the "analyst's tool kit." It includes techniques such as synchronous modulation, Fourier transformation, ratioing responses, principal component analysis, and so on. The study of the detection limit reveals the various sources of noise (chemical, shot, quantization, Johnson, etc.) and may suggest methods for improving the signal-to-noise ratio. Similarly, investigation of the dynamic range should result in an understanding of the mechanism of saturation and possible extensions of this parameter. For example, saturation can be the result of a limitation in the amount of probe available (such as a limit to the amount of excess charge available in electrospray ionization) or coming to the limit of a component in the measurement system (such as the analog-to-digital converter).

Lowering the detection limit improves the precision of quantitation at levels near the detection limit and the certainty of detection at any given level. The detection limit is generally lowered by reductions in the variance and decreases in interference. Identification is improved by an increase in the differentiating power of the information gathered about the compound. For example, the value of the molecular mass to the milli-Dalton level is much more discriminating than knowledge of the unit molecular mass. Improvements in separation are achieved by increasing the discriminating power of the partitioning and by implementing the partitioning as a continuous process rather than as a batch process (as in chromatography vs. extraction).

4. Merits and implementation of the scheme

To bring the scheme closer to home, two analytical methods have been diagramed in Figs. 1 and 2. An

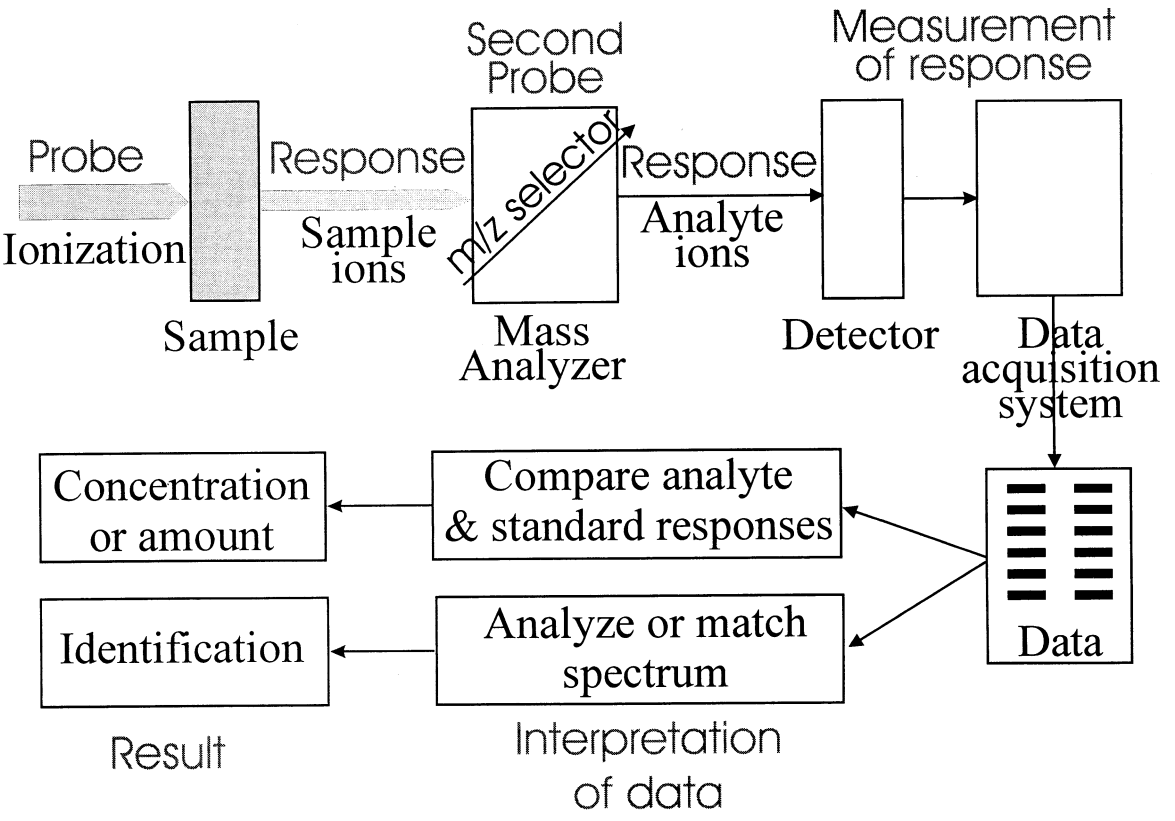

Fig. 2. Diagram of mass spectrometric determination. Shown are the two probes involved in ionization and mass selection, the response of the sample (selected ion flux), the measurement of the response, and the acquisition of intensity:*m/z* pairs of data. These data are then interpreted to provide quantitative or qualitative information.

acid-base titration is shown in Fig. 1. The probe is the system for adding standard base to the sample. It must include a method for the determination of the amount of standard base added. We see that the method for measuring the response to the probe is a separate operation. This figure illustrates the use of a pH meter, though other options are possible. From the data, which consists of at least one pH:volume pair, the equivalence point volume is determined and the amount of acid analyte calculated.

An analysis involving mass spectrometry is diagrammed in Fig. 2. The sequence of the ionization and mass selection probes is shown. The flux of analyte ions meeting the ionization and *m/z* probe criteria is measured by the detector and data acquisition system. The recorded data are a set of intensity:*m/z* values. If the goal of the analysis is quantitation, the responses of the analyte and standard materials are compared at one or more *m/z* values, and the concentration or amount of analyte is calculated. For the goal of identification, intensities at many values of *m/z* are acquired and the resulting spectrum is heuristically interpreted or the spectrum is matched against a library of standard spectra.

From these examples, we can see that the study of an analytical technique according to the scheme introduced previously enables a clearer understanding of the methodology used. In addition, it focuses the study on the analytical aspects of the approach rather than just on the physics of the devices or the electronics of the instrumentation. One can see the impact of the analytical goal on the choices made for each of the

steps in this sequence. The measurement and interpretation steps employed are quite different depending on whether one seeks quantitation of a targeted analyte, detection of one or more analytes, or identification of one or more species. This scheme can also stimulate improvements in the technique by clearly showing which aspects of the approach are limiting. When this system is used in the teaching of chemical analysis, it is desirable to organize the course according to the differentiating characteristic employed rather than the technique of probe and measurement. A new text [6] for the introductory course in chemical analysis implements this approach and demonstrates its effectiveness.

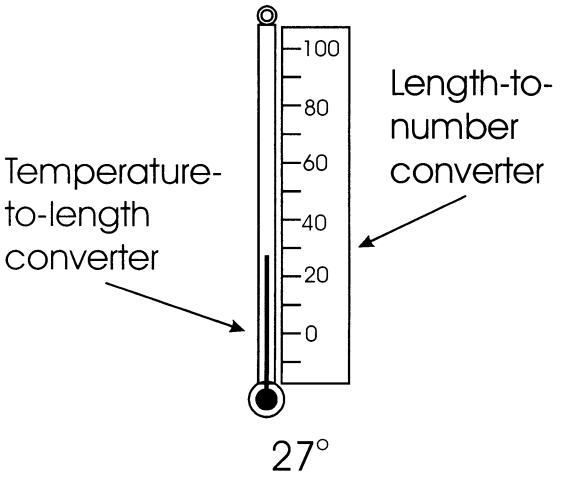

Fig. 3. The bulb and stem thermometer. This device is a combination of two conversion devices. The bulb and stem with liquid converts temperature into the length of the liquid column in the stem. The linear scale converts this length into a number equal to, or related to the temperature.

5. The elements of measurement

In a perfect world, it should not fall to the analytical chemist to teach the fundamentals of measurement. However, since measurement principles have not been taught to most of us since learning to read a clock and a ruler in kindergarten, and since an understanding of measurement principles should be prerequisite for a course in chemical measurements, we must undertake the task. The challenge is further complicated by the fact that measurement basics seemingly have not received a scholarly development. We can learn of the design and operation of various measurement devices and circuits and study advanced mathematical data analysis, but a general approach to the means by which the numerical results we call a measurement are obtained is singularly lacking from the literature. To fill this gap, I have extended some earlier work [7] to provide a general basis for an understanding and analysis of the measurement process. This approach is briefly summarized below with special emphasis on mass spectrometry.

6. Conversion devices

In this study, measurement is defined as the determination of a numerical quantity of unit values of the property inherent in the sample or object. In other words, the result of a measurement is a number of units of the quantity being measured. Numerical measurement results are obtained from only three sources: counting, reading a scale, or reading a numerical display. Among these, only manual counting does not require some device to produce the number (assuming we are mentally keeping track of the count). When scales or numerical displays are used, the measured quantity must be converted into the quantity compatible with the scale or display. For example, if the measurement number is obtained from the position of a recorder pen on the chart paper, the measured quantity must be converted into the position of the pen on the chart paper. The number is then obtained by reading the chart paper scale at the pen position. As it turns out, all measurement systems, however complex, can be considered a series of conversion devices whose functions and characteristics can be studied independently of the physics and/or electronics by which they operate.

In a bulb and stem thermometer, the temperature dependence of the liquid density converts the temper-

ature of the bulb to the position of the liquid meniscus in the stem, and a linear scale provides a numerical value for this position. Two conversion devices are involved: the temperature-to-length converter and the length-to-number converter as shown in Fig. 3. Scales and digital readouts are readout conversion devices since they produce the final measurement number. The conversion device for which the input is the quantity being measured is the initial conversion device, sometimes called the sensor.

Sometimes the output quantity of the sensor is not compatible with the readout conversion device, in which case an intermediate conversion device is required. For example, the electron multiplier detector for ions in a mass spectrometer converts ion flux to a related electrical current. The analog-to-digital converter (ADC) that produces the measurement number does so in response to the voltage level at its input. An intermediate conversion device that converts input current to a related voltage is thus required as shown in Fig. 4. Each conversion device has its own transfer function, which is the relationship between the input quantity and the output quantity. The sensitivity of the conversion device is the slope of the transfer function plot. The response of the overall measurement system, consisting of the several conversion devices employed, is the product of the separate transfer functions. The overall sensitivity is the product of the individual device sensitivities. In another example familiar to mass spectrometrists is the determination of magnetic field strength. One might begin with a Hall effect probe for which an output voltage v_H is related to the magnetic field strength B surrounding the device. The transfer function for this device is $v_H = KB$. A voltage amplifier follows to bring the low voltages from the Hall probe into the range suitable for an ADC readout device. The transfer function for the voltage amplifier is $v_{out} = K'v_H$ and for the ADC is $\# = K''v_{out}$. The overall transfer function is thus $\# = KK'K''B$.

Limits of resolution as well as sources of nonlinearity, noise, drift, and saturation (upper response limit) can be traced to the characteristics of the conversion devices involved.

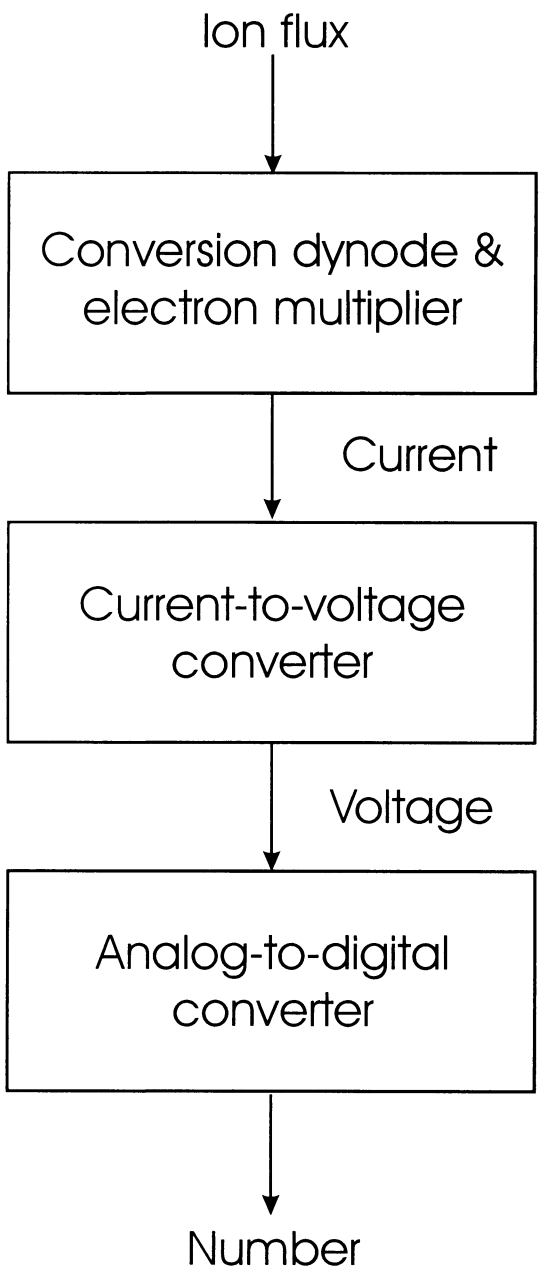

Fig. 4. The three conversion devices involved in the measurement of ion flux in a mass spectrometer. The initial conversion device converts the ion flux into a related current. The intermediate conversion device converts current to a related voltage. The analog-to-digital converter converts the voltage into a related number.

7. Counting

Measurements performed by counting have many characteristics quite different from those performed by conversion devices. First of all, there is no aspect of the counting process itself that should invoke error. Therefore, we might expect that counting measurements would always be perfectly accurate. However, this is not so. Errors and variance in counting measurements occur in three areas. One is in the definition of the objects or events to be counted. These are often fuzzy and involve some subjective or arbitrary judgment on the part of the counter or the device that discriminates between the events to be counted and other phenomena. The second is in the boundary over which the events or objects are to be counted. There is always the possibility of an event or object occurring too close to the event boundary to determine whether it is in or out. The third is in the reproducibility of the counts of randomly occurring events. Here, two aspects are important. One is the variance due to the basic count uncertainty, which is one part in the inverse root of the number of counts. The other is an error due to the possibility of two or more events occurring at times too close to resolve. This latter error involves Poisson statistics, which apply in many analytical situations.

Ion counting has increasing application in mass spectrometry and we even use the unit of counts to express the values of measured ion intensities. For the ultimate sensitivity, we would like each detected ion to advance the analog-to-digital converter by at least one integer. Assuming we have set the multiplier voltage so that this is the case, we can predict the random uncertainty due to the count statistics. For an uncertainty of 1%, we would need to detect at least 10 000 ions. Actual ion counting is used in some quadrupole instruments and in many time-of-flight instruments. For these instruments, ion overlap can cause a significant deviation from linear response at higher count rates. Dual mode detectors [8] and calculated compensation can alleviate this problem to a large extent.

Another aspect of event overlap occurs in chromatography and was elucidated by Davis and Giddings [9]. They demonstrate that in the typical relatively crowded chromatogram, most of the compounds will be overlapped beyond the power of a single universal detector to resolve. The resolution, in this case, is limited by the time width of the chromatographic peak. Users of chromatography have largely ignored this finding of Giddings because the frequency of mixed spectra in chromatographic peaks appears to be much lower than Giddings predicts. The basis for this discrepancy is that in event overlap theory, all events are considered roughly equivalent. However, the components eluting from a chromatographic column can have greatly varying concentrations. Therefore, the reason for the apparent lack of component overlap is because the minor components are being ignored! The consequence of the Poisson overlap in chromatography is then a loss in dynamic range. The more crowded the chromatogram, the smaller the dynamic range of the analysis. For array detection mass spectrometry (time-of-flight, ion trap, Fourier transform mass spectrometry, sector with diode array), this becomes an opportunity. By providing frequent, full spectra with a wide dynamic range, the minor components can be discovered and quantitated through the analysis of the individual ion chromatograms [10,11]. The solution to this problem, and the challenge to mass spectrometry instrumentalists, is to provide 20 or more high-quality, full mass spectra per chromatographic peak width, with wide dynamic range ion detection. This capability is most likely to be achieved with time-of-flight mass spectrometry [12]. The challenge is to obtain the ionization and transfer efficiencies required to produce frequent, full spectra with precise amplitudes for ultra-trace components.

8. Conclusions

Establishing a framework or conceptual scheme for the process of chemical analysis is an important aid in solving problems in chemical analysis, developing new methods of analysis, and improving previously developed techniques. The breakdown of a method into its component elements clarifies the function of each so the options for alternative ap-

proaches become more obvious. It becomes possible to determine whether the limitations of a technique are fundamental or whether it simply lacks a device not yet implemented. A fundamental limitation for an acid-base titration in water is that the analyte acid concentration must be greater than 1×10^{-7} M. Similarly, the mass scan rate for a mass analyzer cannot be faster than the mass resolution times the ion velocity over the length of the ion trajectory through the mass analyzer. Distinguishing fundamental limitations from operational ones opens the door to the development and implementations of improved or novel approaches. This is exemplified by the resurgence of time-of-flight mass spectrometry through the availability of rapid data collection and the development of electrospray ionization through the use of an old principle in a novel application. Realization of the crucial role of the differentiating characteristic allows us to explore each newly discovered phenomenon, property or reaction with regard to its potential as the basis for a new method of analysis.

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