Automated Chemical Instrumentation of the Future

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Analytical instrumentation is in an evolutionary state undergoing rapid change. During the next 4- or 5-year period, many new automated instruments will be developed for the commercial market. Some features of these new instruments will be discussed briefly in this Account. However, I predict that one of the most significant changes in analytical instrumentation will come only in the 1980's, when instrumentation is viewed as an integral part of an overall system. At that time, much of the instrumentation will be interfaced to on-line digital computers and will be integrated into the process-control and manufacturing facilities. There will be more effective utilization of chemical measurements so that the measurements will be more nearly optimal, both quantitatively and qualitatively, with regard to the user's *needs*.

There are many attributes of modern society that will force us, as analytical chemists, to begin taking a *systems* approach to the utilization and implementation of chemical analyses. That is, we shall be compelled to examine critically, as a whole, the combination of chemical procedures, chemical instrumentation, computer automation, and the needs for chemical measurements. Figure 1 suggests that the complexity of problems requiring chemical measurements, together with emerging technology, will gradually force a change in the techniques used for chemical analysis. Thirty years ago the products being produced often utilized more sophisticated technology than the manufacturing and/or process-control methods by which the product was produced or its quality was controlled. For many products this is no longer true. Even for sophisticated products, the manufacturing or process-control operations often are more complex and employ more advanced technology than the products being produced. Likewise, the associated analytical chemistry practices are correspondingly more complex and sophisticated.

Consider clinical chemical quality control (QC) or analytical research and development laboratories where, in the past, there has been a steady increase in the need for analytical services. Accompanying the increased need for services has been an increase in the complexity of analytical instruments and the calculations required for quantitative analyses. These complex forcing functions (Figure 1) have often resulted in the development and growth of rather unwieldy organizations that have not always been effective in coping with the needs of the parent organization. Fortunately, the emerging technology (involving improved instrumentation, inexpensive computers, and cheap bulk digital storage) made available through advanced large-scale integrated circuit (LSI) technology will provide the tools to effect imaginative solutions to many of the problems we now face. The forcing functions (Figure 1) will gradually change the methods used for the implementation of analytical chemical systems, design of chemical instrumentation, and utilization of chemical measurements.

Development of Existing Analytical Laboratories

Existing large complex systems have not necessarily been specified and designed from the outset. Rather, they have grown as a result of many activities that proceeded simultaneously and operated more or less independently. Consider, as an example, a typical QC laboratory whose dominant responsibility is chemical analyses for a process-control or manufacturing facility in the pharmaceutical or petrochemical industry. In the past, such a service-oriented analytical laboratory has often expanded with the growth of the parent company and its development of new products, new chemical processes, or new manufacturing techniques. The QC laboratory was therefore forced to develop new, improved analytical methods and, sometimes, new instrumentation which were then incorporated into the older operational procedures. The result of this combination was gradual, but piecemeal, development of analytical capabilities to meet the organizational needs.

With the advent of digital computers and improved instrumentation we are now attempting to combine automation of the instruments in these laboratories with the record-keeping procedures of the companies. However, automation of the record-keeping procedures associated with chemical measurements has also evolved in a piecemeal fashion and is often in such a state of disorganization that their inclusion into the automation project is often more difficult than the automation of the individual analytical instruments.

When undertaking the complete automation of a large QC facility, many simple but difficult-to-answer questions immediately arise. Should the automation start with the laboratory instruments or with the sample identification and record keeping? Should the automation start now or after better hardware and/or software has been developed? Should one begin with a large computer for record keeping or with small computers for the automation of instruments? Should the *system* consist of individually dedicated computers, a distributive system, or a hierarchical system? Too seldom are the above questions answered as a result of good planning and system specifications. Instead, these and other pertinent questions are often answered one at a time and

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Complexity of
1. Process control for
   Chemical production
   Manufacturing operations
2. Quality control
   Laboratory procedures
3. Problems associated with
   Pollution control
   Clinical analyses

and

Availability of
1. Improved chemical instrumentation
2. Inexpensive computer components
   Large-scale integrated circuits
   Bulk storage
   Input/output devices
3. Experience gained
   In design and implementation of large computer systems

Gradually forcing a change in

1. Design of chemical instrumentation
2. Where and how chemical measurements are made
3. Methods of implementing analytical chemical systems

Figure 1. Factors forcing analytical chemists to take a systems approach to utilization of chemical analyses.

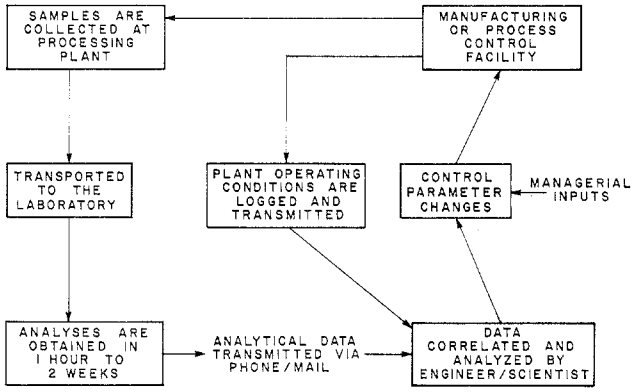

Figure 2. Chemical analyses for quality assurance and process control.

not necessarily in an order that provides a scientist the opportunity to develop an optimally automated system. Hence, there is a definite need for a systematic approach to chemical measurements. At least part of the leadership and direction for the development of such an approach should be provided by analytical chemists.

Digital Computers in Chemical Instrumentation. The advent of minicomputers has made automation economically feasible for many applications. Moreover, this automation will be accelerated in the near future by the availability of LSI computers. One such computer is the National Semiconductor, IMP-16C Integrated MicroProcessor, whose features are listed in Table I.

Although small in size, it is nevertheless a powerful computer that can readily be utilized to automate complex instrumentation. Several other companies are developing similar LSI computers; it can be safely predicted that this class of computers will be available in large quantities for a few hundred dollars each before 1980. With such low-cost capabilities and our present minicomputer experience, the automation of most major laboratory instruments will rapidly become a reality. To automate a system optimally, individually automated instruments will often be interconnected. In some instances, the resulting system will be distributive in design, *i.e.*, all computers are more or less equal in size and command position. Other systems will be hierarchical, *i.e.*, the several computers vary greatly in size and command position.

Some of the features that will set these digitally automated instruments apart from present analog instrumentation are: (a) discrete automatic-control algorithms; (b) complex data-reduction techniques; (c) man–machine interactive capabilities; (d) time-response and data rates; (e) instrument-to-instrument communications. Any attempt to assign these instruments to specific categories is, as yet, full of pitfalls. However, it is instructive to examine a few of the above features as they relate to three general classes of instruments. The trend indicated in Table II is toward very sophisticated instrumentation incorporating multiple computers to facilitate fail-safe procedures, complex high-speed data reduction for control, and improved man–machine interactive capabilities.

Table I
General Features of the IMP-16C MicroProcessor

Word length	16 bits
Instruction set	42 (implemented by CPU-resident microprogram)
Arithmetic	Parallel, binary, fixed point, twos complement
Memory	Expandable to 65,536 16-bit words (1.4- to 1.75-μsec cycle time, contingent on type of memory)
Registers	4 general purpose
Push-down stack	16 16-bit words
Addressing modes	Page size of 256 words; for direct and indirect modes
Typical instruction execution speeds	Register-to-register addition, 4.9 μsec Memory-to-register addition, 7.7 μsec Register input/output, 10 μsec
Operating speed	1.4-μsec cycle time
Input/output and control	16-bit peripheral data input port; 4 general purpose jump condition inputs 16-bit memory data input port; 1 general interrupt input 16-bit data output bus; 1 control panel interrupt input 16-bit address bus; 6 general-purpose flags

Chemical Analyses: a Systematic Approach

In the past, many analytical services have been performed predominantly in central locations. The samples are taken at the process-control site, transferred to a laboratory, and analyzed, and the results are reported back to the chemist, chemical engineer, physiologist, biochemist, or physicist who requested the analysis (Figure 2). These personnel then make decisions regarding the requirements for control of a chemical process *via* secondary measurements such as the pressure, temperature, and flow characteristics of the process. This slow, cumbersome procedure was a necessary stage in our evolution, and the present trend is to automate these existing instruments and operational procedures. Is automation of analytical chemistry going to result in nothing more than computer-aided instrumentation, sample identification, and record keeping, each of which is implemented within our present operational procedures? Must we look forward to automated laboratories and

Table II

Distinguishing Features of Laboratory Automation

Control functions	Data-reduction techniques	Man–machine interaction	CPU-to-CPU communications
	Lowest Level		
Limited on/off Preselected timing sequence	Simple calculations Concentration Integral First derivative Digital filtering	Off-line	Slave only Unidirectional
	Intermediate Level		
Integral, derivative and proportional Continuous optimization of instruments Digital control Boolean algebra Baseline correction	Transforms Auto- and cross-correlations	On-line adjustment of operating parameters On-line CRT, etc.	Request service Data can be utilized to adjust operating parameters
	Highest Level (Multiple Processors)		
Adaptive control For fail-safe operation [*i.e.*, noncatastrophic failure by stepwise degradation without system failure] and complex control capabilities	Pattern recognition and learing systems High throughput computations for control and data reduction	Scientist interaction in real-time To superimpose his intuition and experience	Master or slave For sending or receiving data

processes designed to do business in the same old way? I hope not!

We shall gradually begin to take a more systematic approach to providing analytical services. There are two reasons, other than those discussed above, why we must change the approach to analytical services. First, limited resources, consumerism, and technology assessment will gradually force improved quality control; second, increasing labor costs will force improved systematic automation techniques in order to retain a competitive position in international trade. These two forcing functions will result in a large increase in automated on-line analytical instrumentation. On-line chemical analyses will be used *directly* for digital control processes. A simple example would be use of the new stable mass spectrometers for chemical processing, and possibly, of ESCA for LSI manufacturing where these instruments are on-line and fully automated and supply necessary information for adaptive control.

Consider the implications of fully automated systems where most of the analytical chemistry is performed on-line and the results are used directly for control purposes. How does such an environment affect the analytical chemistry and the analytical instrumentation? What will be the role of the analytical chemist of the future? I suggest that a limited number of analytical chemists assume an expanded role to include that of a system designer with regard to chemical analyses and their use. Such a role and the activities involved might better be discussed in the form of an example of a manufacturing process that is automated *via* analog techniques in which the chemical analyses are performed by taking samples, moving them to the laboratory, and reporting the results at some later date.

With the impending energy crisis, it is becoming necessary to automate the analytical systems that are required as support for the plants engaged in the production of nuclear fuel rods for power reactors. There is a need to account continuously for all fissionable materials in order to prevent diversion of materials to other uses or to the environment. Note that such a manufacturing process and its analytical requirements are not dissimilar from the needs of many manufacturing processes where accountability is of comparable importance for control of the yield and quality of the product.

Traditionally, we have started with an existing plant and have converted it by automating one instrument at a time, testing it in place, reporting the results on terminals, and then, by separate calculational routines, performing required inventory analysis. However, let us assume that all of the automation could be planned at the outset and incorporated into the system. As a hypothetical example, examine Figure 3 which represents part of a nuclear-fuel-rod manufacturing process.[1] In a system such as this, where should one start to implement on-line instrumentation? It is not readily apparent from a simple evaluation of the processing procedure that one knows the answers to typical questions that arise for accounting purposes. For example, where are analyses most needed in the manufacturing process? Second, how often are analyses required per unit time (through-put)? Next, how soon are results needed in order to maintain tight accountability (response time)? Finally, what accuracy and precision are required at each sampling point in order to maintain the limit of error for material that is unaccounted for? Answers to these and other similar questions needed to develop system specifications can often be obtained through the utilization of a simulation model. Many current processing and manufacturing systems are equally complex with regard to meeting inventory-control requirements and systems of the future will be even more complex.

System Simulation. I suggest that analytical chemists are in a unique position to take a systematic approach both to designing the instrumentation and solving the analytical problems associated with the project. First, they should begin by carefully defining the objectives of the analyses to be performed. To do so, they must communicate well with all personnel responsible for the manufacturing process. Next, they must develop a simulation model that will provide answers to questions like those itemized above. Note that, if it were possible to specify the

(1) C. Placek and E. D. North, *Ind. Eng. Chem.*, **52**, 460 (1960).

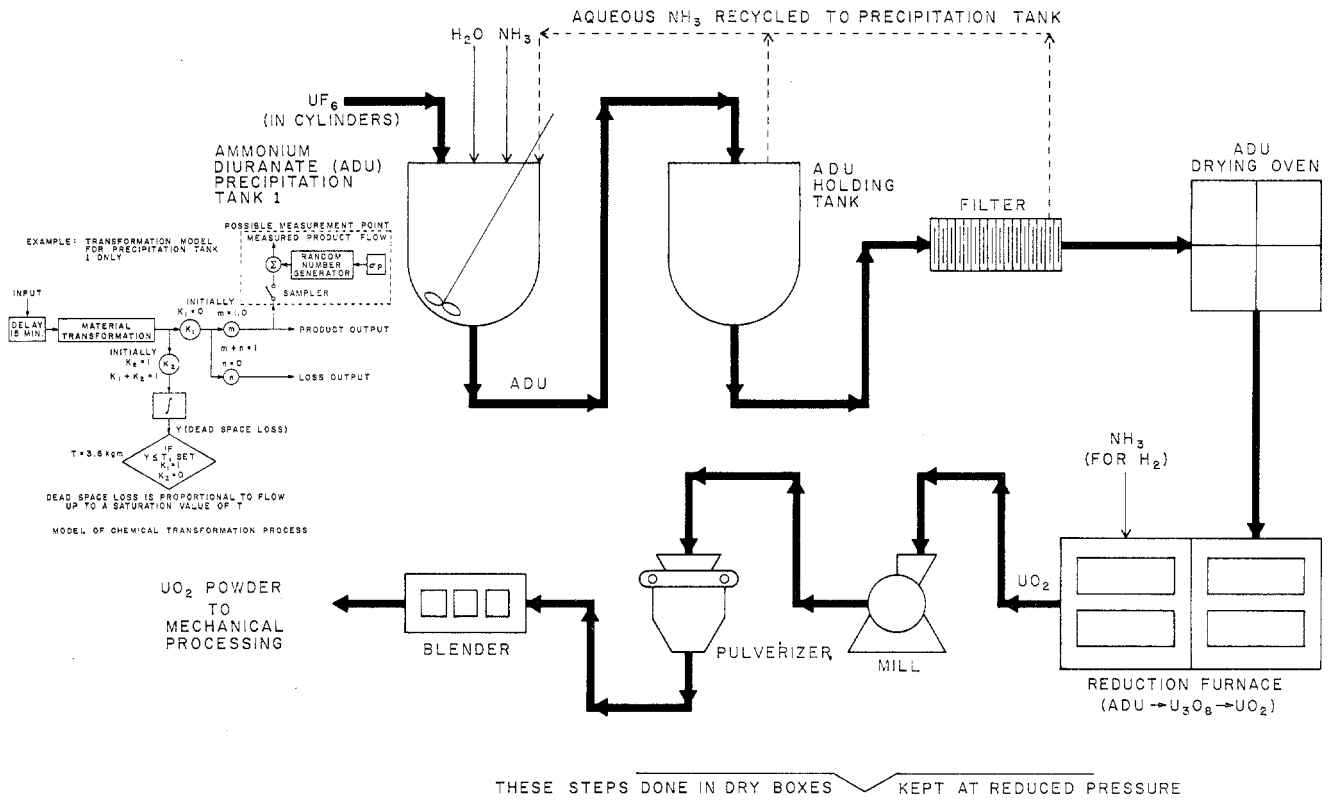

Figure 3. Flowsheet for the manufacture of uranium dioxide nuclear fuel, Mallinckrodt Nuclear Corp., Hematit, Mo.

system fully, there would be no unanswered questions and no need for simulating the system. *However, since all of the questions related to system specifications cannot be answered because of the many interdependencies of the various system parameters, simulation will be advantageous.* To develop the model, one must first obtain as many specifications as possible for the plant operation. Those specifications will provide the inputs needed to obtain a mathematical description of each phase of the operation. This mathematical description will be, in practice, the set of transformations of the manufacturing processing steps and will constitute the basis for the model. The model then provides guidance with regard to instrumentation requirements, *e.g.*, accuracy, precision, sampling rates, time-response characteristics, and choices of locations of instruments.

Developing a Functional Design. After specifications of the overall system have been completed, it will be desirable to develop a functional design to meet the specifications obtained either directly or from the simulation model. For the nuclear fuel plant, the design will show the locations of required instruments, data-reporting stations of various types, information paths with associated data rates, automatic control requirements, and the time-response characteristics needed to maintain careful inventory control of the fissionable materials. Remember that, in the particular application of Figure 3, emphasis is placed not on controlling the manufacturing process but on the prevention of material losses, *i.e.*, a dynamic inventory of all materials within the system. From the functional design, one can readily determine the computer requirements as to total number and their capacities needed for automation of the required analytical instrumentation. The analytical methods and chemical instrumentation can then be developed to meet the functional needs of the system.

Using the foregoing approach, instrumentation will not be developed in a piecemeal manner. As more complex instrumentation and more thoroughly automated instrument systems are required, it will become increasingly advantageous to take a more systematic approach to their design and implementation. This systematic approach to automation will in many ways resemble the professional procedures of older disciplines such as civil and architectural engineering.

Future Instrumental Practices

System specification and design are of prime importance to the implementation of automated instrumentation. However, the overall requirements of a system often cannot be sufficiently well specified to allow the designer to develop *all* of the desired control or decision algorithms. This is especially true in experimental research projects, but it also applies often to chemical processing where the composition of the feedstock changes periodically and unpredictably and where the yield of various products must be altered to meet demands. In such cases there is a need for "value judgment" of the type that can, at present, be provided only by a person. Some scientists are approaching these types of problems by attempting to develop "artificial intelligence" or by the utilization of direct digital control techniques. Direct digital control works well when the operation can be fully specified. The "artificial intelligence" approach will be feasible *when* we can specify how a man thinks.

I believe that the complex control problems can more readily be solved by the construction of "inter-

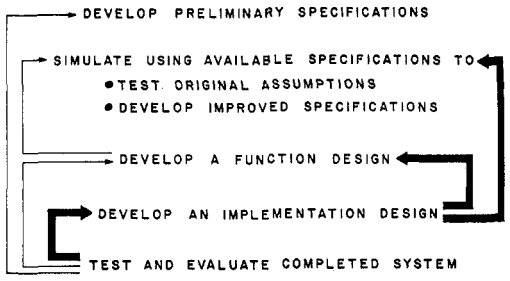

Figure 4. Procedures for development of complex chemical measurements systems requiring multiple instruments.

active (learning) systems." That is, a system should consist of one or more computers performing all the tasks that have been well defined, plus a capability for the scientist to superimpose on the control algorithms his imagination, creative thinking, and observation of unusual events as they relate to the process or experiment being controlled. Crucial variables will be displayed in real-time on CRT's together with selected functions related to variable deviations. These analog waveforms will be the medium through which the scientist will communicate rapidly with the system. Ultimately, interactive instrumentation (or systems) will contain a distributed computer network to provide the required data processing throughput (bandwidth) and time-response characteristics. Such interactive instrumentation will, in the next decade, revolutionize our capabilities to solve difficult problems.

Figure 4 represents the interrelationships of the different steps in one possible design procedure. Note that this procedure involves many iterations (single-shaft arrows) for the feedback of information necessary for the development of system specification and overall design. The *development procedure* of complex automated systems has many of the aspects of feed-forward and feedback control in automation. In Figure 4, the double-shafted arrows indicate some of these control-function pathways.

The trend toward putting analytical instrumentation on-line to the process or the research it is supporting will accelerate. Furthermore, the chemical measurements will often be used directly for control purposes. In the more complex process-control systems, where the feedstock composition varies with time and where the product composition must change with demand, but in a different way, closed-loop control may be very difficult.

It appears that, where automation is required for these very complex processes, the control functions will sometimes be broken down into two classes. The first class will include those control boundary conditions that can be fully specified and are never violated. This portion of the control can then be allocated to direct digital control (computer(s) A, Figure 5). Where the exact control requirements cannot be fully specified, a second computer system (B, Figure 5) will be interfaced and implemented for on-line interactive "tuning" of the control algorithm. The engineer/scientist will be able to utilize his knowledge rapidly in assessing effects of environmental changes and in acting upon unusual observations so as to optimize production. To assist him will be the interactive computer system which will display correlation and error functions, provide easy mechanisms for

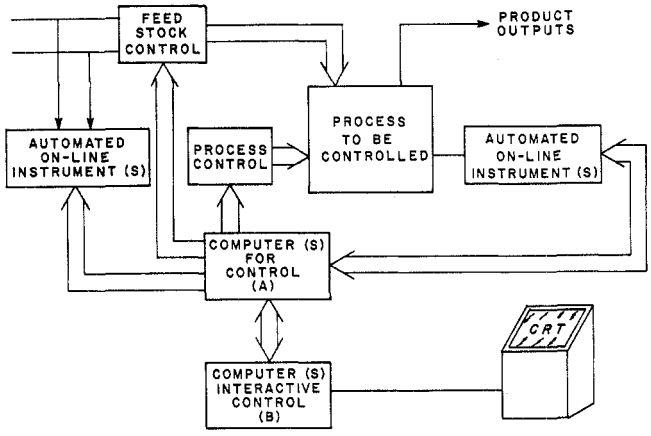

Figure 5. Interactive control and experimentation.

changing the weighting functions in the control algorithm, and for measuring, calculating, and presenting the results of such changes.

In some cases, the approach toward the development of the *first* decision algorithm to be tested *could* follow a completely different procedure. Instead of developing partial specifications based on known parameters utilized by the scientist, one could take the more arbitrary approach used by Perone, *et al.*[2] A method was needed for the detection of doublet peaks in stationary electrode polarography. In their approach as many peak parameters as possible are listed. Then pattern recognition techniques are applied using a large selection of waveforms of known classifications as training sets to identify the most important features and to obtain a weighting vector. The information thus obtained could be used to develop a decision algorithm for peak deconvolution.

Laboratory Example

The preceding discussion has dealt with the overall considerations involved in designing a very complex system. However, an actual working example that represents a much lower level of complexity will be used to illustrate a basic approach to interactive data-reduction systems. Consider a computer-controlled apparatus consisting of a small 12-bit computer, 8 × 11 in. CRT, "light" pen, function box for easy operator interaction, teletypewriter, x-y plotter, digital buret, and cell containing an ion-selective electrode and reference electrode. The computer controls the digital buret and acquires data from the ion-selective electrode.[3] The data are displayed on the CRT as a standard titration curve (Figure 6a) and as the anti-log plot (Figure 6b) utilizing the Gran function[4,5]

$$\text{Gran function} = (V + V_0)e^{\pm(nE/0.08616T)}$$

where V is initial volume of sample, V_0 is the volume of added titrant, E is the potential of the electrode in millivolts, n is the ionic charge, and T is the temperature in degrees Kelvin. These waveforms are presented simultaneously to the scientist to allow him interactively to extract useful information. This pro-

(2) L. B. Sybrandt and S. P. Perone, *Anal. Chem.*, 44, 2331 (1972).
(3) J. W. Frazer, W. Selig, A. M. Kray, and R. Lim, *J. Elecchem. Soc.*, submitted for publication.
(4) G. Gran, *Analyst*, 77, 661 (1952).
(5) K. Srinivasan and G. A. Rechnitz, *Anal. Chem.*, 42, 1172 (1970).

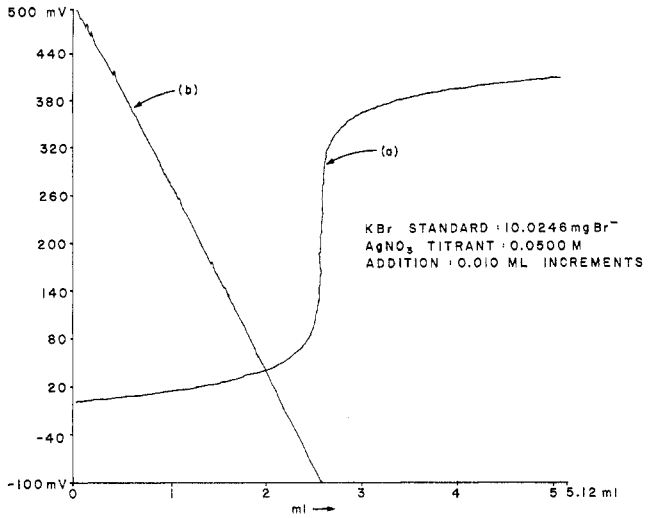

Figure 6. CRT display of the titration of a KBr standard with $AgNO_3$ titrant.

cedure obviates the necessity for developing calibration curves.

To illustrate the procedure, let us examine the titration with F^- of an unknown Al^{3+} sample using a fluoride-selective electrode for detection.[6] The titration is automatically carried out and the results are presented as shown in Figure 7. The chemist then interrogates the Gran plot using the light pen and function box to place four cursors on selected positions of the waveform. Cursors 1 and 2 bound a segment of the curve (window) to be examined. (The actual window width is chosen to meet operator needs.) The distance between cursors 2 and 3 defines the step length the window is to be advanced and cursor 4 acts as a "stop" for the advancing window. Next the function box key labeled "linear least squares" is depressed. The system takes all of the data points between cursors 1 and 2, calculates a linear least-squares fit to the data, determines the intersection of the extrapolated line with the titrant volume axis, calculates the difference between the present intersection and the previously determined intersection, and plots that difference as part of the error function (curve C). The "window" (X-axis length) bounded by cursors 1 and 2 is then advanced toward cursor 4 an amount determined by the distance between cursors 2 and 3. The least-squares fit is again calculated and the process repeated until cursor 1 passes the X-axis position occupied by cursor 4.

If the titration were ideal, the Gran plot would be linear and all of the extrapolated line segment intersections would be superimposed. However, the example is far from ideal, as shown by the error-function curves. Utilization of a three-step interrogation of the titration curve allowed the chemist to identify rapidly the equivalence point (Figure 7c) and obtain a quantitative result. No calibration curve was required. In addition, the interactive experimentation enabled us to rapidly obtain *specifications* for a mathematical algorithm that could be implemented to perform the above functions on future titrations without further aid from a chemist. Hence, with the aid of an interactive system, we effectively utilized our knowledge, experience, and intuition to develop

(6) K. Srinivasan and G. A. Rechnitz, *Anal. Chem.*, 40, 1818 (1968).

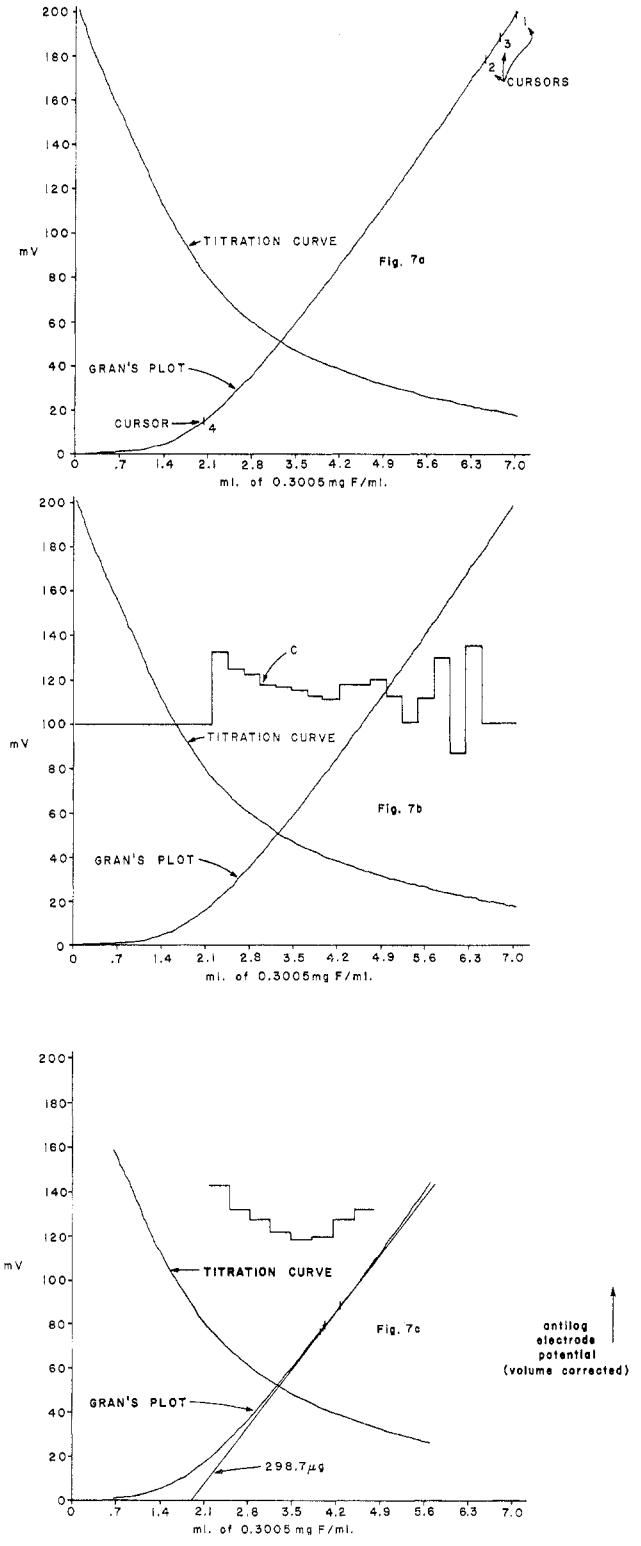

Figure 7. Run, 300 μg of Al, as an unknown titration with 0.3005 mg of F^-/ml of solution using a fluoride electrode.

the new techniques and specifications required for closed-loop control.

Without the aid of a computer we never would have completed this work on ion-selective electrodes. The use of a computer greatly accelerated the development of the analytical method, especially the specifications needed to construct inexpensive hardware to perform the task routinely. The same can be said of process-control automation. Hence, the use of computers greatly improves our effectiveness in ex-

perimentation, in routine analyses, and in the control of processes. Furthermore, when computer systems are properly specified and implemented their utilization results in improved measurement accuracy and control.

Conclusions

Analytical chemistry, as a service-oriented discipline, is entering a transition period when many of our instruments will be automated and placed on-line. The design of these chemical measuring systems of the future will follow improved development procedures. Many of these new measuring systems will have advanced interactive capabilities.

To summarize, there are three ways of handling difficult automation projects. First is the conventional method where the system is specified, designed, implemented, tested, and modified until operative. This is usually a long and complex procedure. A second procedure will be similar to the first but will encompass the use of such techniques as pattern recognition to help in the generation of system control and measurement specifications. However, the variables to be controlled are generally well known. It is the control algorithm that is difficult to optimize.

Therefore, a third approach to automation will utilize the capabilities of interactive experimentation and control. These systems will permit fine tuning of the control algorithms as well as rapid interrogation of data and waveforms for significant features (information) to be used together with our knowledge and intuition to reach new conclusions.

Analytical chemists already have at their command significant technology and expertise so that they can contribute to the design and implementation of automated chemical measuring systems. A partial list of that technology includes: understanding the instrumentation to be automated; designing a new instrument; writing the detailed specifications for the chemical methods; understanding the use of modeling techniques; and writing the detailed specifications for the data-reduction techniques required for processing the instrument signals, *i.e.*, spectral analysis and digital signal-processing techniques.

Analytical chemists have an exceptionally bright future, but it will require change in their skills and a significant change in the definition of their role in society.

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Allylic Sulfoxides: Useful Intermediates in Organic Synthesis

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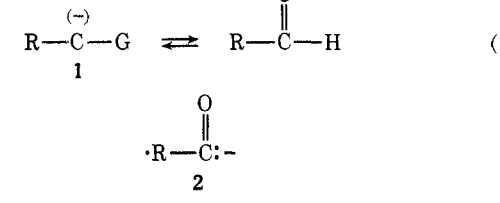
As a consequence of the central role that polar or Lewis acid–base reactions play in the synthesis of organic molecules, organic chemists have endeavored to develop new, general ways in which such reactions can be employed in synthesis.

During the last decade a great deal of effort has been focused on synthetic transformations which *invert* the inherent chemical reactivity that functional groups confer upon organic molecules. Such operations enable the chemist to reverse the Lewis acid–base properties of a given functionally activated carbon, adding new dimensions of flexibility to the design of complex molecules.

Equation 1 illustrates one such transformation. Normally, the carbonyl carbon serves as the electrophilic partner in a polar condensation process. Synthetic operations that reversibly interconvert the carbonyl function with those classes of functions, G,



(1)

which are capable of adjacent anion stabilization as indicated in **1**, enable a synthetic equivalency to be established between **1** and the inherently unstable "carbonyl anion" **2**.[2] In the literature, representations such as **1** have been referred to as either "masked" acyl anions,[3] or more recently as carbonyl anion equivalents.[4]

In the ensuing discussion, transformations which *invert* the Lewis acid–base properties of a given carbon atom *via* the interchange of activating functions (*cf.* eq 1) will be referred to as "charge affinity inver-

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(1) After July 1, 1974: California Institute of Technology, Pasadena, Calif. 91109.

(2) L. S. Trzupek, T. L. Newirth, E. G. Kelly, N. E. Sbarbati, and G. M. Whitesides, *J. Amer. Chem. Soc.*, **95**, 8118 (1973), and references cited therein.

(3) D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969).

(4) J. E. McMurry, and J. Melton, *J. Amer. Chem. Soc.*, **93**, 5309 (1971).