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Putting the Chemistry Back into Analytical Chemistry

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Aspects of the current status of and research in analytical chemistry are briefly discussed and the need for cost effective analytical procedures is emphasized. The present and future of a number of aspects of flow-injection analysis are considered. These include the basic theory, the kinetic features, the control features, time-based methodology, and the coupling of sample pretreatment with instrumentation. Several aspects of this latter topic are considered with particular reference to the flow-injection atomic spectrometry combination. Problems of kinetic mismatch between chemistry, manifold residence, and instrument operation are discussed and some possible solutions proposed including the use of closed loop manifolds.

ANALYTICAL CHEMISTRY

There are many aspects of science and technology whose existence and progress are underpinned by the provision of reliable information about chemical composition. Regardless of the field of activity, a common basis for the practice of analytical chemistry can be discerned. At one end of this general scheme is the material about which information is required and at the other is the decision process. Analytical chemistry provides the information, together with an assessment of the quality of the information, so that a decision may be taken. The detail of how the information is to be obtained and evaluated is a matter for the analytical chemist to decide and calls for the exercise of considerable professional skills and judgment. A number of factors need to be taken into account including the context of the problem. In general, the scheme shown in Fig. 1 will form the basis for the method developed.

It is clear from this view of analytical chemistry that chemistry still occupies a central position and thus the prophesy of H. A. Liebhafsky, ". . . the chemistry is going out of analytical chemistry" (*1*) has proved to be largely unfulfilled. Chemistry embraces the interaction of matter with electrons and photons and, as well as measuring the extent of this interaction as the basis of quantitative measurement, the use of "chemical shifts" as the basis of interpretation of experiments of this type is an important role for chemistry. The chemistry may well be taking place at locations other than reaction vessels on the laboratory bench and thus for those sample materials for which no preparation is required, chemistry still plays an important role in the overall procedure to obtain information about the material. For those samples for which some preparation or pretreatment is required, there is no doubt about the role of reaction chemistry.

ANALYTICAL CHEMISTRY RESEARCH AND DEVELOPMENT

One of the major driving forces in research and development (R and D) in

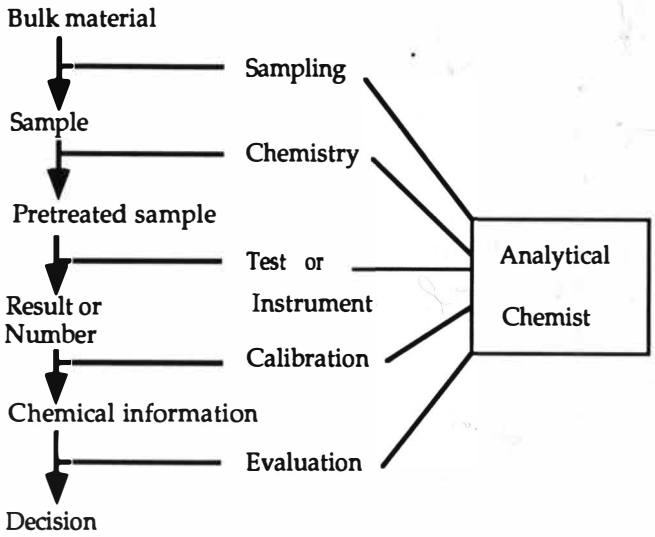

FIG. 1. The major stages in the overall analytical method, which is designed to provide information about the chemical composition of a bulk material and an assessment of the quality of the information so that a decision within the context of the problem may be taken.

analytical chemistry is the need to make analyses more cost effective. In the United States alone, the chemical industry sells something in excess of $80 billion worth of its various products, earning something just under $8 billion. When other activities requiring chemical measurements are taken into account, it has been estimated that 250 million chemical measurements are made each day in the United States (*2*) at total annual cost of some $50 billion. Even if only the existing methodologies were considered, there is clearly a role for the development of greater automation of chemical analyses. As the automation of procedures tends to bring other benefits such as reduced errors of the gross blunder type there is scope for even further savings in costs, as it has been estimated that about 10% of the chemical measurements made must be repeated because of some unsatisfactory feature of the analysis (*2*).

There are, of course, additional driving forces for analytical chemistry R and D, such as (a) the requirement to measure reliably at lower concentrations, (b) the requirement to measure more components in complex mixtures, and (c) the requirement to analyze materials at locations other than the laboratory bench. In this latter regard, although interplanetary exploration may sound more glamorous, the needs of chemical and biotechnological processes for on-line real time monitoring are much more pressing, and there is a growth of interest in the development of analytical technologies in support of such processes (*3*). A fundamental feature of process analytical procedures is that they are automated.

Thus in both the laboratory and the chemical plant, there is considerable interest in the development of automated chemical analysis procedures. In the United States, activities at the National Institute of Standards and Technology (*4*) and at the Center for Process Analysis at the University of Washington, Seattle (*5*),

indicate that with regard to the availability of suitable instrumentation to implement such automated procedures, demand is running ahead of what can be supplied.

At least two approaches to the automation of chemical procedures can be discerned (*6*). In the first of these, samples are handled as discrete entities and are moved in containers from one work station to another at which an appropriate chemical or physical manipulation is made, such as reagent addition, shaking, etc. The mechanism by which this type of automated analytical chemistry was performed was originally of the conveyor belt type but, more recently, a variety of devices have been used, such as spinning disks or robots. The second approach to the automation of chemical analysis has involved the use of fluid flow in closed conduits. Initially this approach was based on the use of glass tubing with air bubbles to (a) divide sample zones into a number of segments and (b) to prevent carryover from one sample to the next. The system was designed to achieve complete mixing in each liquid segment so that when the reaction product was measured, the detector displayed a steady state signal with time. This type of system was highly successful and has become widely used in a great variety of analytical laboratories including those concerned with the analysis of clinical and water samples.

A more recent variant of the continuous analysis principle exploits the reproducible hydrodynamics of fluid flow in nonwettable tubing of diameters around 0.5 mm to achieve mixing between samples and reagents by a variety of processes originating from the predominantly laminar flow characteristics which develop. As the majority of procedures exploiting this type of mixing also use the injection of a discrete volume into the system as a means of sample introduction, the technique has become known as flow-injection analysis (FIA).

FLOW-INJECTION ANALYSIS

The first papers describing experiments which are now recognized as the beginning of that group of analytical methodologies embraced by the term "flow-injection analysis" appeared in the mid-1970s. Essentially two research groups, one in Denmark whose first paper was coauthored by Ruzicka and Hansen (*7*) and the other in the United States, whose first paper was coauthored by Stewart, Beecher, and Hare (*8*), were conducting experiments along similar conceptual lines. The enthusiasm of the former authors for the possibilities of the technique and their continued research innovation in the field has clearly identified Ruzicka (now at the University of Washington, Seattle) and Hansen as leading workers in the area of flow-injection analysis.

The development of FI may be traced through the pages of at least three books of a general nature (*9–11*) and one text dealing particularly with atomic spectrometry applications (*12*). It is clear from the contents of these books that flow injection has proved to be an extraordinarily versatile concept which has gone far beyond the original ideas of mixing by fluid flow as a means of automating analytical procedures in which a spectrophotometric measurement of the reaction product was made. It is also clear that, as in many areas of analytical chemistry

which have direct utility to the practice of the discipline, the development of a theory lags somewhat behind the development of applications.

AN INTRODUCTION TO THE THEORY OF FLOW-INJECTION ANALYSIS

The Present

Fluid hydrodynamics is a large subject and exact mathematical descriptions of flow, under even the relatively limited regimes in a typical flow-injection system, are complicated to say the least and it is unlikely that a complete mathematical expression for the mixing produced by a real system which has useful predictive power will ever be formulated.

There are a number of reasons for this. First, most FI practitioners are not primarily interested in the dispersion processes suffered by the injected solutes (as might be of concern to a chromatographer), but are concerned about the magnitude of the analytical signal (or some closely related function such as the signal to noise ratio). The relationship between the dispersion of the injected solute and the analytical signal involves (a) the kinetic and thermodynamic characteristics of the reaction chemistry involved and (b) characteristics of the detector such as the geometry of the flow cell and the transducer response function.

Second, a real FI system has features which influence the dispersion but which cannot be quantified, such as the nonuniformity of the tube internal diameter, the extent to which the tube is kinked, the number of connectors which are imperfect, the pulsations of the pump, the geometry of the confluence points, and the surging which occurs when the injection valve is switched.

Third, mathematical descriptions of fluid flow systems produce equations which describe the variation of concentration with parameters such as distance and time. Such concentrations will be at points or infinitely thin slices across the tube. These mathematical concentrations have no meaning in reality as concentration is only defined for a finite volume. To obtain useful information from equations of this sort it is necessary to be able to integrate over the volume of fluid which the detector will interrogate. It is often difficult in practice to obtain accurate information about the dimensions of this volume for the particular detector used.

Fourth, the dimensions of the tubing and values of flow rates used in typical flow-injection experiments fall into a region of the factor space for which it is not possible to provide a solution to the basic laminar flow equations governing convection and diffusion except by the application of numerical techniques.

For flow manifolds which consist predominantly of open tubular reactors, laminar flow is the dominant hydrodynamic regime. This flow is characterized by flow in which molecules of fluid tend to move in stream lines parallel to the tube walls and the development of a parabolic velocity gradient between the center stream line and the tube wall. The center stream line moves at twice the average linear velocity.

As the tubes typically used for FI analyses are of the order of 0.5 mm internal diameter (i.d.), it is difficult to draw to scale an accurate representation of the effects of such a flow pattern on an injected sample bolus. Illustrations which

accompany introductory articles on FI are often misleading. Some simple calculations are instructive in this respect.

Two useful equations concerned with the theory of FI are (a) distance equals speed times time ($l = st$) and (b) the volume of a cylinder is the product of π, the square of the radius, and the length ($V = \pi r^2 l$). Thus a sample volume of 100 μl in tubing of internal diameter 0.5 mm occupies a length of 509 mm and the difficulties of scale drawing become immediately apparent. At a flow rate of 2 ml min^{-1}, the average linear velocity is 170 mm s-1 and thus the center stream line is moving at 340 mm s-1 or just over 1.2 km h^{-1}. At this rate, the rear of the center stream line takes 1.5 s to reach the position originally occupied by the front boundary. The situation typically shown in basic illustrations of a rounded, hollow bullet-type of shape represents only the first few milliseconds of flow (*13, 14*).

For a manifold length of 100 cm and a detector (such as a conductivity detector or simple photometer) which sensed a narrow slice across the tube, it would be expected, on the basis of the flow pattern just described, that the center stream line from the leading boundary would appear after 2.94 s and from the trailing boundary would appear at 4.44 s. It would be expected that the peak maximum would be observed within this time interval.

Two further equations may be used for calculations which give an approximate indication of the relative magnitude of some of the relevant processes. When semi-infinite linear diffusion in a liquid is interrogated by absorption spectrometry normal to the boundary (*15*) it appears as though the bulk concentration is moving such that after time t, the distance moved is $2(D_m t/\pi)^{0.5}$, where D_m is the diffusion coefficient. Although it is often stated that diffusion in liquids is slow, an approximate calculation based on semi-infinite linear diffusion shows that a residence time of 4 s would produce a movement of 0.07 mm, in an initially sharp boundary, for a diffusion coefficient of 10^{-5} cm^2 s^{-1}. As the laminar flow pattern is symmetrical about the tube center line, a distance of 0.07 mm represents 28% of the maximum radial distance.

Under conditions of laminar flow, the ratio of the velocity of any stream line, u, to the maximum velocity (that of the center stream line), u_{max}, is given by $1 - 4(r/d)^2$, where r is the distance from the tube center and d is the tube internal diameter. A molecule which moved from the center stream line by 0.07 mm would thus suffer a reduction in velocity from 340 to 313 mm s^{-1} (for the conditions outlined above), but a molecule which moved from the wall by this distance would experience an increase in velocity from 0 to 164 mm s^{-1}. The effect of diffusion, even in this short time, is to slow down the leading edge slightly and increase the speed of the trailing edge considerably.

The Future

Flow injection thus shares a characteristic common to many analytical methodologies which find use in providing solutions to real analytical problems, in that the practice runs well ahead of the theory. However, if the best possible performance is to be obtained from any analytical methodology it is necessary that the fundamental underlying theory be fully developed. This not only allows the tech-

nique to be exploited to its full potential but also allows ways in which the technique could be used for improved performance to be predicted. If Koltoff's maxim of "Let theory guide, experiment decide" is to be implemented, a better and more widespread understanding of the nature of flow processes in flow-injection manifolds is needed.

The production of equations which relate various FI peak parameters such as height, basewidth, precision, etc., to fundamental manifold properties such as tube length, internal diameter, nature of coiling, extent of packing of solid phases, and so on presents a considerable challenge. And, for the reasons outlined above, may be impossible to achieve. Several approaches to obtaining improved quantitative relationships may be discerned. Empirical equations may be obtained by fitting coefficients and exponents to terms in an equation by the use of an appropriate regression procedure (16).

The role of individual components may be studied by deconvolution of peak shapes obtained with manifolds incorporating and without the selected component (*17*). Flow processes may be modeled. Several models based on various combinations of well-stirred tanks have been proposed (*18*) as well as on random walk processes (*19*), axially dispersed plug flow (*20*), and mass transfer based on laminar flow and diffusion (*21, 22*). Although these research efforts represent only a small fraction of the total research effort in FI, they are to be encouraged.

KINETIC FEATURES

The Present

Many of the unique features of FI arise from the control over the kinetic features of the processes occuring within the manifold. At the most basic level, the precise injection and pumping processes mean that the resulting controlled hydrodynamics give rise to reproducible concentration profiles which in turn give rise to reproducible analytical signals. These signals may be produced by monitoring the concentration time profile of an injected component, a component of the carrier stream, or a reaction product. Reactions monitored under such conditions do not need to exhibit the stability of reactions which form the basis for determinations based on the production of a time-invariant reaction product. Most spectrophotometric determinations in common use have been selected for this feature and the associated conditions (pH, ionic strength, concentrations, temperature, etc.) have been optimized to produce a reaction product whose absorbance (or luminescence) does not change during the time needed to perform the analysis. All of these conditions can be relaxed when the FI mode is used.

Kinetic discrimination or masking is also possible with FI systems. The most widely exploited are reactions in which biological catalysts (enzymes) are used to speed up the desired reaction with the target species (*23*). A further feature of FI systems may be exploited here, namely the good contact which may be obtained between an immobilized reagent and an analyte species in solution in a reactor of typical FI dimensions (*24*). Thus an expensive reagent may be conserved by the use of a solid-phase reactor.

The kinetic control features may also be exploited in the combination of FI with certain instrumental measurement techniques. In particular the techniques of chemiluminescence (*25*), potentiometry (*26*), and voltammetry (*27*) have benefitted from the kinetic control of a FI sample presentation system. The analytical utility of chemiluminescence depends on the reproducible mixing of sample and reagent as the resulting emission of photons is controlled by the kinetics of the processes by which analyte and reagent molecules are brought together in solution.

Many potentiometric sensors have slow responses and only reach a steady state response on exposure to a new analyte activity after some minutes. Presentation of samples in a FI format ensures (a) a reproducible contact time, (b) a limited contact time, which can be of benefit if other sample components are potential interferents, and (c) the continuous presence of carrier solution to establish an appropriate baseline. The currents which flow during electrolysis at electrodes depend, among a number of factors, on the characteristics of the mass transfer processes by which electroactive material is presented to the electrode surface. In many ways flow procedures are the ideal way of performing such electrochemical experiments. Two stage procedures, such as stripping voltammetry, may also be readily implemented (*28*).

The Future

As reaction product stability is not a requirement, a FI procedure may be optimized with respect to a more appropriate parameter such as signal to noise ratio (SNR) or a more complex response function involving SNR and sample throughput. There is thus considerable scope for the application of optimization strategies to flow-injection systems, which together with an improved understanding of the fundamental flow processes should result in the production of methods with considerably improved performance characteristics in comparison with those of the conventional procedures, many of which are currently incorporated into standard methods. Freedom from kinetic restrictions means that new chemistries can be considered as candidates for particular determinations. Interest in kinetic methods, especially those based on enzyme-catalyzed reactions will increase.

Interest in the development of chemiluminescent methods and others which exploit the precise flow characteristics (particularly electrochemical techniques) will undoubtedly be sustained. There are a number of instrumental techniques which, as yet, have seen little development in terms of flow analytical applications which could be more widely used. These include mass spectrometry and the magnetic resonance spectrometries. There are also some simple benefits in the presentation of appropriate samples to instruments such as infrared spectrometers for quantitative purposes, as the baseline is unambiguously established (*29*).

It is possible that techniques which are currently little used for quantitative analytical purposes such as those involving the measurement of enthalpy (*30*) or magnetic susceptibility changes (*31*) could be exploited though coupling with FI sample handling and presentation procedures.

TIME-BASED METHODS

The Present

Many kinetic methods of analysis have been proposed (*32*), but few have found their way into routine laboratory use. Most likely this is due to the difficulties associated with obtaining the controlled mixing and timing required over the reagent addition and measurement stages, respectively. As the basic features of FI ensure reproducible mixing and presentation to the detector, FI is an ideal way to perform kinetic methods. To monitor the change in the concentration of reaction product with time it is only required that the flow be stopped at a controlled interval after the injection at which the required portion of the product profile is in the detector (*33*). By varying this interval different reagent to determinand concentration ratios can be selected. The analytical procedure is then based on the change of detector response as a function of time, which in suitable cases can be reduced to measuring the time required for a fixed change to occur. This procedure has the advantage that any background signal is automatically subtracted and thus samples which contain material giving a high and variable blank signals can be analyzed (*34*).

It is also possible to obtain quantitative information from the width of a FI peak. The time interval between two points on the profile represents the time between points of equal dispersion in the system. It has been shown by several research groups that for exponential peak shapes (which are produced by well-stirred tanks) the width of the peak is a logarithmic function of concentration (*35–37*). This has the advantage that (a) the quantitative parameter is no longer dependent on a particular detector response–concentration relationship and thus restrictions, such as adherence to Beer's law, may be relaxed and (b) the working range is considerably increased at the high concentration end. Many spectrophotometric procedures in common use have been designed for trace analytical applications and cannot be used for the determination of minor or major components without considerable prior dilution of the sample. A number of FI dilution procedures have been devised (*38*), but for analyses which do not require the best precision they may not be necessary in view of the characteristics of the peak width measurement. Peak width methods have the disadvantage of poorer precision, as the uncertainty in the measurement parameter is related to uncertainty in the concentration of the analyte species by a loarithmic function.

The Future

With the relaxation of the requirement for Beer's law to be obeyed, spectrophotometric detectors of much simpler construction could be used for methods based on peak width. Devices which made use of photodiodes and light emitting diodes (*39*) or laser diodes would be considerably smaller and more robust than the conventional laboratory spectrophotometer and could be located in much more aggressive environments such as those encountered for the monitoring of chemical plant processes or effluent stream or surface waters.

Analytical techniques with a limited working range for which the best precision was required could use a preliminary peak width measurement as an indication of

the dilution factor necessary to bring the concentration of an off-range sample to that near the minimum in the precision vs concentration curve (*40*).

If the physical dispersion of the flow system are well characterized then it should be possible to interpret the shape of the reaction product profile in terms of the fundamental kinetic (*41*) and thermodynamic (*42*) properties of the reaction being studied. The simplest system is one in which the flow-injection peaks are formed from the overlap of only a single boundary between injected and carrier streams. Two such overlapping zones may be produced by the injection of a sufficiently large volume into a single line of reagent (*43*). If the injection was produced by timed switching of a valve, then two identical dispersion patterns should be obtained on the leading and trailing boundaries. If the more normal slug injection is used in which the trailing boundary traverses the length of the injection loop, then this boundary has both a different dispersion character and a longer residence time.

The recently introduced technique of sequential injection (SI) analysis (*44*), in which the reagent zone and sample zone are aspirated sequentially into an inert carrier stream before transport to the detector by flow reversal, has only one boundary at which reaction product is formed rather than the two of the conventional flow-injection experiment. Once the physical dispersion characteristics of the system have been established, it should be possible to interpret peak shapes in terms of properties of the chemical reactions observed.

One feature of both FI and SI procedures that has yet to be exploited fully is that the time window within which a peak is expected is known. This knowledge should allow the implementation of a number of signal to noise enhancement procedures including the use of gated integrating (*45*), ensemble averaging (*46*), and correlation procedures (*47, 48*).

COUPLING REACTION CHEMISTRY WITH INSTRUMENTATION

The Present

The one characteristic which distinguishes FI from other automated analytical chemistry procedures is that all aspects of the method performed in the flow-injection system are under control. Both the extent of mixing and the residence times are controlled by the nature of the fluid flow. The variables involved, flow rate, tube length, and volume injected, are readily changed and a wide range of possible combinations is available for optimization. Additional features such as the use of stopped flow and/or other reactor types (such as the single-bead string reactors or a three-dimensionally disorientated reactor) are also relatively easy to incorporate.

It is also possible to consider the flow-injection valve as an interface between flow systems, allowing independent optimization of each. This may be illustrated by considering the position of a flow-injection valve in a manifold for the pretreatment of a sample solution by liquid–liquid extraction (LLE) which is connected directly to a flame atomic absorption spectrometer. The basic FI-LLE manifold is shown in Fig. 2. In this the sample is injected into a carrier stream, merged with reagent and extractant and after segmentation, extraction, and phase

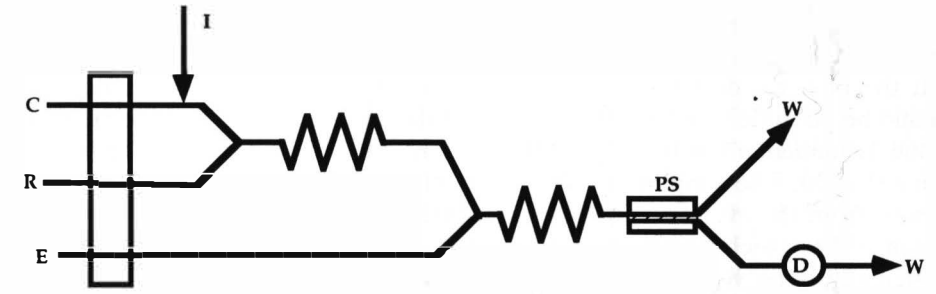

FIG. 2. A flow-injection liquid–liquid extraction manifold. The sample is injected at I into a carrier stream C, merged with reagent R and after reaction with extraction E. Segmentation occurs in the extraction coil and phase separation, PS, is effected with the phase of interest directed to the detector.

separation the extracted components are presented to the detector. If a flame atomic absorption detector is used, the required flow rate is one at which the instrument gives a maximum signal to noise ratio, typically 5 ml min-1. This value is too fast to obtain efficient mass transfer in the LLE manifold and causes problems if the LLE is to be used for preconcentration as the flow rate of the sample phase must be greater than that of the extractant phase if a concentration enhancement is to be obtained. Thus the total flow rate required becomes large and impractical.

In Fig. 3, a manifold is shown in which the FI valve is located after the phase separation and serves to inject a discrete volume of extractant into an aqueous carrier stream for direct transport to the instrument. In this manifold, the flow rates for LLE and transport to the instrument may be independently optimized. If the extractant phase has only limited miscibility with water, further dispersion in the carrier stream connected to the spectrometer is avoided. This system was first described by Nord and Karlberg (*49*).

A similar design of manifold may be used for liquid–solid extraction in which the solid phase reagent is located in the loop of a rotary six-port injection valve

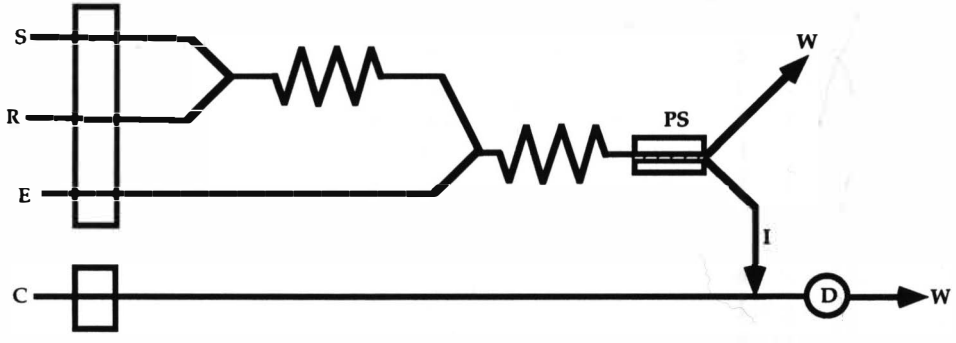

FIG. 3. Relocation of the flow-injection valve in the liquid extraction manifold allows independent optimization of flow rates of extraction and transport to the detector, D. This design imposes a limitation on the volume of sample available, which must be sufficient to produce a steady state concentration flowing through the loop of the injection valve, I.

(*50*). After a controlled volume of sample has been loaded onto the column, the valve is switched to insert the column into an eluent stream. The basic concept is illustrated in Fig. 4 from which it can be seen that the flow rates for loading and elution can be independently optimized. It is also possible to select whether the column is eluted in the original direction of flow or whether it is backflushed.

The Future

It seems unlikely that flow analytical procedures have reached their limit as far the number of processes that can be incorporated into a single flow system for a particular analytical purpose. As it takes only the insertion of a suitable valve at an appropriate point in the system to link one part to the next, it is likely that flow-based processes will be built into an increasing number of automated analytical methodologies for performing an increasing number of stages in the overall analytical method. The area most likely to see the valve interface involved in all the procedures from sampling through pretreatment to measurement is that of process analysis (*51*) where an analytical unit is installed at strategic locations throughout the production plant. There is no reason why flow analytical methodologies have to be restricted to the pressures and temperatures typically encountered in open-vessel laboratory procedures and thus developments in "high performance" (HP) FI are to be expected. Liquid and gas chromatographic equipment is already available for such experiments and the use of on-line heating with thermal ovens (*52, 53*) and microwave ovens (*54*) is already attracting some attention. The potential of ultrasound (*55*) as a means of coupling energy into chemical systems is yet to be fully exploited (this comment also applies to microwave energy) and there are many possibilities in this area. There is clearly some way to go before fire assay may be performed in a flow-injection system.

It has also become clear that the use of flow injection procedures can enhance the performance of an analytical method simply by the exploitation of some basic features such as the contamination-free handling environment, the use of small

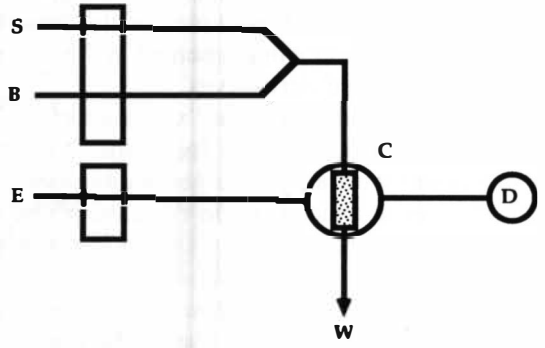

FIG. 4. A flow-injection solid phase extracton manifold with the extractant located in a column, C, in the loop of the injection valve. The sample is merged with buffer, B, and the desired components loaded onto the column. Actuation of the injection valve is equivalent to the rotation of the column into the eluent stream E. The sample, S, is loaded at constant speed for a controlled time. Unretained sample components are delivered to waste, W.

amounts of sample and reagent and the precise nature of the sample delivery. This is particularly true for methods in which atomic spectrometry techniques are used as the quantitative measurement stage (*12*).

FLOW-INJECTION ATOMIC SPECTROMETRY

The Present

Much has been written about the benefits of the combination of FI sample handling and introduction methods for use in combination with the various analytical atomic spectrometries. A summary of the various review articles is provided in Table 1. This combination is clearly one which has resulted in many significant improvements in atomic spectrometry methods. It is also an area in which there are developments in the availability of commercially produced equipment with several manufacturers introducing FI "accessories" for atomic spectrometry.

Much of the current interest in flow-injection atomic spectrometry centers around the development of procedures for the removal of interference effects. As most interference effects arise from the presence of other components in the sample, these FI procedures are typically ones in which separation of analyte and matrix species occurs. The 1990 FIAS literature is briefly summarized in Table 2, from which it can be seen that the majority of recently published papers are concerned with the coupling of sample pretreatment procedures directly with the instrumentation.

As far as FIAS is concerned it appears as though liquid–liquid extraction is not a procedure of choice compared with liquid–solid extraction. Both of these have the potential for preconcentration as well as matrix removal, but the use of a solid phase extractant is considerably easier to implement. There is also considerable interest in the implementation of chemical vapor generation processes in the FI manifold. The first publication in this area (*121*) clearly showed the potential for decreasing the extent of interference effects due to metallic matrix components and this aspect of the procedure has proved attractive to several research groups. Many of the advantages accrue from the controlled kinetic features of the FI procedure and this area provides good examples of the benefits of kinetic discrimination, a strategy which cannot be implemented in the "conventional" batch method of generation of the volatile derivatives.

Recently it has been demonstrated that the "valve interface" design could be used to combine a matrix removal procedure (retention of copper or nickel on a strong cation-exchange resin) with a hydride generation manifold for the determination of selenium (*122*) or arsenic (*123*). In the case of the arsenic there is a further problem in that the use of an oxidative sample dissolution produces arsenic in the +5 oxidation state, which is determined at about 20% of the sensitivity at which As(III) is determined. For some analyses it is necessary to implement an on-line reduction step. The most commonly used reducing agent, potassium iodide, is effective but slow when compared to typical residence times in an flow-injection system. One solution has been to develop a stopped flow method, in which the sample is first passed through the resin to remove the potentially interfering matrix cations and then merged with a stream of potassium iodide solu-

TABLE 1
Review Articles Concerned with Flow-Injection Atomic Spectrometry

Date	Title	Comments	Ref.
1985	Flow injection analysis techniques for atomic absorption spectrometry	First comprehensive review. Section on ICP-ES included.	(*56*)
1985	Flow injection techniques for flame atomic absorption spectrophotometry	Brief survey.	(*57*)
1986	Flow injection analysis—A survey of its potential for spectroscopy	Survey of both AAS and ICP.	(*58*)
1986	Combination of flow injection techniques with atomic spectrometry in agricultural and environmental analysis	Covers FAAS, chemical vapor generation and ICP.	(*59*)
1986	Sample preparation and presentation in inductively coupled plasma spectrometry	Discussion of limitations of ICP techniques and advantages of FI.	(*60*)
1987	Flow injection analysis: A novel tool for plasma spectroscopy	Basic principles and all aspects of sample pretreatment.	(*61*)
1987	Flow injection techniques in inductively coupled plasma spectrometry	All aspects of sample introduction ICP-MS as well as ICP-OES.	(*62*)
1988	Flow injection calibration techniques	Examples taken mainly from atomic spectrometry.	(*38*)
1988	Atomic spectrometry and flow-injection analysis: A synergic combination	Survey with emphasis on reduced uptake rate, air compensation, peak area measurement.	(*63*)
1989	Flow injection atomic spectrometry	Book with chapters contributed by leading workers including Stewart, van der Linden, van Staden, Fang, Valcarcel and Gallego, Zagatto, Krug, Bergamin and Jorgensen, Sherwood and Rocks, J. Burguera, M. Burguera, and Pacey.	(*12*)
1990	Flow injection analysis and chromatography: Twins or siblings?	General survey with some examples of sample pretreatment for AAS.	(*64*)
1990	Atomic spectrometric detectors for flow injection analysis	Survey of all atomic spectrometry techniques.	(*65*)
1990	Flow injection analysis	Chapter in book; emphasis on coupled continuous separation methods.	(*66*)
1991	Flow injection on-line column preconcentration in atomic spectrometry	Discussion of quantitative performance parameters and practical aspects.	(*67*)
1991	Inductively coupled plasma mass spectrometry in hyphenation: A multielemental analysis technique with almost unlimited potential	Survey includes both flow injection and chromatography.	(*68*)
1991	Flow injection atomic spectrometry	Comprehensive review of all aspects, including real sample analyses.	(*69*)

tion (*124*). After a suitable short time to allow for mixing, the flow is stopped for about 20 s with the sample solution located in the loop of the valve. Activating the valve after the desired stop time injects the now reduced arsenic into the hydride generation manifold.

TABLE 2
A Survey of the 1990 Flow-Injection Atomic Spectrometry Literature

Title of publication	Ref.
Solid phase extraction	
Flow injection on-line sorbent extraction pre-concentration for graphite furnace AAS	(*70*)
Characterisation and optimization of HPIC for on-line preconcentration of trace metals with detection by ICP-MS	(*71*)
On-line preconcentration of trace copper for flame AAS using spherical cellulose sorbent with chemically bound quinolin-8-ol	(*72*)
Use of masking agents in the determination of lead in tap water by flame AAS with FI preconcentration	(*73*)
On-line preconcentration of silver on activated alumina and determination in borehole water by FI-AAS	(*74*)
Prekoncentrace na chelatacnich sorbentech v prutokove injekcni analyze detekci plamenovou atomovou absorpcni spektrometrii	(*75*)
Determination of chromium by on-line preconcentration on a poly(hydroxamic acid) resin in FI-AAS	(*76*)
FI-ICP-MS for the determination of platinum in airborne particulate matter	(*77*)
On-line aluminium preconcentration and its application to the determination of the metal in dialysis concentrates by atomic spectrometric methods	(*78*)
Determination of trace amounts of cadmium, lead, copper and zinc in natural waters by ICP-AES with thermospray nebulization after enrichment on Chelex-100	(*79*)
Preconcentration of refractory elements for ICP atomic fluorescence spectrometry	(*80*)
On-line preconcentration of refractory elements for atomiser, source, inductively coupled plasmas in atomic fluorescence spectrometry (ASIA)	(*81*)
Minimization of interferences in ICP-MS using on-line preconcentration	(*82*)
Chemical vapor generation	
Atomic absorption spectroscopy instrumentation FIAS-200 (Perkin–Elmer)	(*83*)
Determination of the hydride forming elements with the FIAS-200 flow injection-mercury/hydride system	(*84*)
Design and optimisation of a FI hydride generator and its use for automated standard additions	(*85*)
Use of FI for in-line elimination of interferences in hydride generation AAS	(*86*)
Bismuth(III) hydride generation, its separation and the determination of bismuth(III) by AAS using FI	(*87*)
Determination of selenium in blood plasma by FI hydride generation AAS	(*88*)
Trace determination of nickel by microwave-induced plasma atomic emission spectrometry after preconcentration of nickel tetracarbonyl on chromosorb	(*89*)
Use of FI techniques for the analysis of hydride-forming elements with the Perkin–Elmer Sciex ELAN 500 ICP-mass spectrometer	(*90*)
Sample introduction	
A computer-assisted metal analyser using FI coupled with direct current plasma optical emission spectrometry	(*91*)
FI-ICP-AES with a multielement photodiode-array spectrometer	(*92*)
Determination of potassium in gasoline and lubricating oil by a FI technique with flame atomic emission spectrometric detection	(*93*)
Determination of magnesium by flame AAS detection with FI analysis	(*94*)
Determination of gold at femtomolar levels in natural waters by FI-ICP quadrupole MS	(*95*)
On-line microwave oven digestion flame atomic absorption analysis of solid samples	(*96*)
Slurries introduction in FI atomic absorption spectroscopic analysis of sewage sludges	(*97*)
Rapid determination of zinc and iron in foods by FI analysis with flame AAS and slurry nebulization	(*98*)

TABLE 2—*Continued*

Title of publication	Ref.
Calibration	
Determination of magnesium by FIA-FAAS using single standard solution continuous dilution calibration technique	(*99*)
On-line isotope dilution and sample dilution by FI and ICP-MS	(*100*)
Intelligent FI-ICP system for matrix matching	(*101*)
On-line dilution, steady-state concentrations by tandem injection and merging stream. Applications to ICP-AES sequential multi-element soil analysis	(*102*)
Speciation	
Speciation of tetraalkyl lead compounds by FI-AAS	(*103*)
Rapid differential FI of phosphorus compounds in wastewater by sequential spectrophotometry and ICP-AES using a vacuum ultraviolet emission line	(*104*)
Thermospray enhanced ICP-AES detection for liquid chromatography	(*105*)
Simultaneous determination of total and free calcium in milk by FI	(*106*)
Three component FIA with on-line dialysis. Simultaneous determination of free calcium, total calcium and total chloride in milk by FIA and on-line dialysis	(*107*)
Indirect methods	
Determination of chlordiazepoxide by zinc or cadmium reduction in a continuous system followed by AA spectrometric detection	(*108*)
Indirect FI determination of methadone by AAS	(*109*)
Determination of chloramphenicol by coupling a continuous reduction system to an AA spectrometer	(*110*)
Indirect determination of chloride and carbonate by reversed FIA coupled with AAS and in-line preconcentration by precipitation	(*111*)
Indirect AA spectrometric determination of ammonia, thiosulfate and cyanide in an unsegmented flow system	(*112*)
Indirect ICP-AES determination of fluoride in water samples by FI solvent extraction	(*113*)
Indirect determination of diethyldithiocarbamate by AAS with continuous extraction: application to the determination of the fungicide ziram	(*114*)
Matrix removal	
Design of a continuous flow two-step extraction sample work-up system for graphite furnace AAS	(*115*)
Prutokova injekcni extrakce (FIE) v plamenove atomove absorpcni spektrometrii	(*116*)
Tandem on-line continuous separation and determination of arsenic by ICP-AES	(*117*)
FI manifolds with membrane filters for preconcentration and interference removal by precipitation FI FAAS	(*118*)
Electrolytic microcell for on-line preconcentration of trace metals in flow systems	(*119*)
Minimisation of sample matrix effects and signal enhancement for trace analytes using anodic stripping voltammetry with detection by ICP-AS and ICP-MS	(*120*)

The Future

There are a number of FIAS themes that will be studied further. There are several sample pretreatment procedures whose kinetics are too slow for the direct coupling of a continuous flow manifold directly with the spectrometer detector, which would be desirable to implement in an automated FI or continuous flow mode. The reduction of one oxidation state of a hydride forming element to a lower more sensitive state has already been discussed as an illustration of one method in which the kinetic mismatch may be accommodated, namely by the use of stopped flow. This procedure has also been used in a high pressure digestion

system in which the sample as a slurry is merged with a nitric acid stream and the flow stopped with the sample zone inside a resistively heated oven. Pressures of up to several hundred psi may be produced by the evolving gases which are released in a two-stage depressurization system before the digest is subsampled by a second flow-injection valve and transported to the spectrometer (*53*). Other on-line digestion systems are currently under development (*125, 126*) and this is an area where there is likely to be considerable developments in the near future. This may be regarded as sample pretreatment involving matrix removal by the conversion of the matrix to suitable volatile derivatives followed by gas–liquid separation.

There are sample pretreatment requirements which involve digestion and not dissolution. For example the determination of total mercury in a sample of biological or environmental origin requires that any organic forms of mercury be oxidized to mercury(II), prior to the generation of the mercury "cold vapor" by the addition of a suitable reducing agent. It is possible that such digestions could be carried out in FI manifolds (*127*).

The concept of the generation of a volatile derivative as the basis for analyte and matrix separation is attractive as it has the additional benefit of bypassing the nebulizer-spray chamber of the conventional solution introduction system with consequent increases in the atomization efficiency. It should be possible to extend this general concept of chemical vapor generation to other volatile metal derivatives (*89, 128*). The most likely candidates (carbonyls and chelates such as the trifluoroacetylacetonates) differ from hydrides and mercury vapor in one important respect, namely that they are less volatile than the solvent in which they are generated. This presents a challenge for the separation and delivery of such derivatives to the spectrometer. One possible approach is to transfer the derivatives to a carrier of supercritical carbon dioxide and use the thermospray generated at a heated restrictor as the interface between the sample delivery system and the spectrometer (*129*). High atomization efficiencies should be obtained.

So far there have been few reports of the interfacing of FI sample handling directly with electrothermal atomization atomic absorption spectrometry (ETAAS). One of the difficulties is again kinetic in nature. Spectrometers for ETAAS are intermittent in operation, typically requiring only 50 μl of sample every 2 min or so. Manifolds which contain two-stage matrix removal and/or preconcentration procedures, such as liquid–solid extraction (*130, 131*), are better able to interface with the intermittent operation of ETAAS spectrometers than are manifolds which deliver carrier solution continuously.

The technique of ETAAS, despite the substantial improvements in the performance of commercially available instrumentation in recent years, still presents a severe challenge to the analyst wishing to devise a method for the determination of analyte species present at ppb concentrations in samples in the presence of intractable matrix components present in vast concentration excesses. The strategy of recent years has been to devise matrix modification procedures for implementation in the graphite furnace and to couple these with accurate background correction and greater temporal and spatial isothermality of the furnace during the atomization stage with delayed atomization of the analyte.

An alternative approach is to perform the matrix isolation chemistry outside the furnace (in a FI manifold) and present the sample in some simple matrix, such as dilute nitric acid, to the instrument. Problems of contamination from air-borne particulate material are nontrivial for this technique and FI may have some advantages in terms of providing a contamination-free handling system. It is, however, unlikely that the requirement for clean laboratory facilities for this technique will be completely avoided.

One way in which the requirement for accurate synchronization of the spectrometer sampling system and the operation of the flow manifold may be avoided is to use a closed loop as part of the interface (*132*). Closed loops also allow procedures which are typically slower than the operation of the spectrometer and slower than the typical reagent residence time in a conventional manifold to be implemented. Such procedures include leaching of analyte species from a solid sample (*132*) and filtration of a large amount of precipitated matrix (*132*). The general principle is illustrated in Fig. 5. The loop may be opened and closed by four-way valves and solutions can be inserted and removed by incorporating the loops of injection valves as part of the circulating loop. Such a loop system has some potential as a means of diluting off-range samples and the preparation of a series of calibration standards by serial dilution from a single concentrated standard (*132*).

CONCLUSIONS

There would seem to be no end to the ways in which sample preparation and pretreatment procedures can be implemented in flow systems. The performance of a number of instrumental analytical techniques has been significantly enhanced by the coupling with FI pretreatment procedures. Foremost among such techniques have been the atomic spectrometries, for which a considerable amount of commercial hardware is available. As some of this hardware uses procedures which require high pressure pumps and fittings and as some of the procedures involve separation by the relative affinities for sample components for a solid stationary phase material, the differences between flow injection and liquid chro-

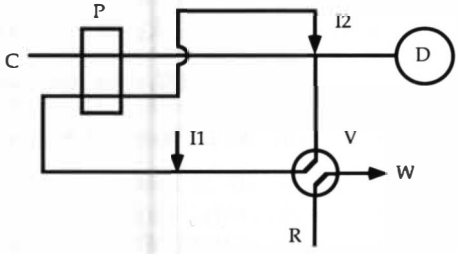

FIG. 5. A recirculating closed loop manifold. By switching the four-way valve, V the loop can be filled with reagent R. Switching back closes the loop. Sample may be injected into the loop at I1 and allowed to circulate until the desired processes have reached an appropriate state. A subsample of the loop contents may be injected into a carrier C for transport to the detector, D, by the valve I2. When this valve is returned to the initial position, carrier is introduced into the loop. This may be exploited for the sequential dilution of a concentration standard for calibration purposes or of an off-range sample.

matography are difficult to discern in some circumstances. It is to be hoped that the problems of analytical chemistry taxonomy do not get in the way of further developments of what is surely a most versatile concept: analytical chemistry in flowing streams.

With the benefit of hindsight, it may be argued that it is doubtful whether the chemistry was ever really "going out of analytical chemistry" (*2*), it was just on the move.

REFERENCES

1. Hertz, H. S. *Anal. Chem.*, 1988; **60**, 75A–80A.
2. Liebhavsky, H. A. *Anal. Chem.*, 1962, **34**(7), 23A–33A.
3. Reibe, M. T.; Eustace, D. J. *Anal. Chem.*, 1990, **62**, 65A–71A.
4. Kingston, H. M. *Anal. Chem.*, 1989, **61**, 1381A–1384A.
5. Illman, D. L. *Trends Anal. Chem.*, 1986, **5**, 164.
6. Foreman, J. K.; Stockwell, P. B. *Automatic Chemical Analysis*, Ellis Horwood, Chichester, 1975.
7. Ruzicka, J.; Hansen, E. H. *Anal. Chim. Acta*, 1975, **78**, 145.
8. Stewart, K. K.; Beecher, G. R.; Hare, P. E. *Anal. Biochem*, 1976, **70**, 167.
9. Ruzicka, J.; Hansen, E. H. *Flow Injection Analysis*, 2nd ed., Wiley, New York, 1988.
10. Valcarcel, M.; Luque de Castro, M. D. *Flow Injection Analysis Principles and Applications*, Ellis Horwood, Chichester, 1987.
11. Karlberg, B.; Pacey, G. E. *Flow Injection Analysis a Practical Guide*, Elsevier Amsterdam, 1989.
12. Burguera, J. L. (Ed.) *Flow Injection Atomic Spectrometry*, Dekker, New York, 1989.
13. Tyson, J. F. *Fresenius' Z. Anal. Chem.*, 1987, **329**, 675–677.
14. Tyson, J. F. *Anal. Proc.*, 1988, **25**, 111–114.
15. Tyson, J. F. *Talanta*, 1986, **33**, 51.
16. Gomez-Nieto, M. A.; Luque de Castro, M. D.; Martin, A.; Valcarcel, M. *Talanta*, 1985, **319**, 319.
17. van Nugteren-Osinga, I. C.; Bos, M.; van der Linden, W. E. *Anal. Chim. Acta*, 1988, **214**, 77.
18. Stone, D. C.; Tyson, J. F. *Analyst*, 1989, **114**, 1453.
19. Crow, C. D.; Levin, H. W.; Betteridge, D.; Wade, A. P. *Anal. Chim. Acta*, 1985, **194**, 32.
20. Kolev, K. D.; Pungor, E. *Anal. Chim. Acta*, 1988, **208**, 133.
21. Atwood, J. G.; Golay, M. J. E. *J. Chromatogr.*, 1981, **218**, 97.
22. Bysouth, S. R.; Tyson, J. F. *Anal. Chim. Acta*, in press.
23. Schmid, R. D. (Ed.) *Flow Injection Analysis Based on Enzymes or Antibodies*. VCH, Weinheim, 1991.
24. Ho, M. H. In *Methods in Enzymology* (Mosbach, K., Ed.), Vol. 137, pp. 271–287, Academic Press, San Diego, 1988.
25. Alwarthan, A. A.; Townshend, A. *Anal. Chim. Acta*, 1988, **205**, 261–265.
26. Frenzel, W. *Analyst*, 1988, **113**, 1039–1046.
27. Canete, F.; Rios, A.; Luque de Castro, M. D.; Valcarcel, M. *Anal. Chim. Acta*, 1988, **211**, 287–292.
28. Wang, J. *Anal. Chem.*, 1984, **56**, 156.
29. Collier, W. G.; Curran, D. C. *Anal. Chim. Acta*, 1985, **177**, 259–262.
30. van der Linden, W. E.; Box, M.; Heskamp, H. H.; Wilms, H. *Fresenius' Z. Anal. Chem.*, 1987, **329**, 440–443.
31. Tyson, J. F.; LaRue, R. L.; Bogdanski, S. *Anal. Chim. Acta*, in press.
32. Mottola, H. A. *CRC Crit. Rev. Anal. Chem.*, 1975, **4**, 75.
33. Hungerford, J. M.; Christian, G. D.; Ruzicka, J.; Giddings, J. C. *Anal. Chem.*, 1985, **57**, 1794–1798.
34. Rujicka, J.; Hansen, E. H. *Anal. Chim. Acta*, 1980, **114**, 3.
35. Rujicka, J.; Hansen, E. H.; Mosbaek, H. *Anal. Chim. Acta*, 1977, **92**, 325–249.

36. Pardue, H. L.; Fields, B. *Anal. Chim. Acta,* 1981, **124,** 39–63.
37. Tyson, J. F. *Anal. Chim. Acta,* 1986, **179,** 131–148.
38. Tyson, J. F. *Fresenius' Z. Anal. Chem.,* 1988, **329,** 663–667.
39. Trojanowicz, M.; Worsfold, P. A.; Clinch, J. R. *Trends Anal. Chem.,* 1988, **7,** 301–305.
40. Bysouth, S. R.; Tyson, J. F. *Anal. Chim. Acta,* 1986, **179,** 481–486.
41. Vanderslice, J. T.; Beecher, G. R.; Rosenfeld, A. G. *Anal. Chem.,* 1984, **56,** 268.
42. Tyson, J. F. *Analyst,* 1987, **112,** 527–529.
43. Tyson, J. F. *Analyst,* 1987, **112,** 523–526.
44. Gubeli, T.; Christian, G. D.; Ruzicka, J. *Anal. Chem.,* 1991, **63,** 2407–2413.
45. Voigtman, E. *Appl. Spectrosc.,* 1991, **45,** 237–241.
46. Bekjarov, G.; Kmetov, V.; Futekov, L. *Fresenius' Z. Anal. Chem.,* 1989, **335,** 971–974.
47. Johnson, M. E.; Voigtman, E. *Anal. Chim. Acta,* 1991, **248,** 195–205.
48. Curran, D. C.; McKean, R. E. *Electroanalysis,* in press.
49. Nord, L.; Karlberg, B. *Anal. Chim. Acta,* 1983, **145,** 151.
50. Bysouth, S. R.; Tyson, J. F.; Stockwell, P. B. *Anal. Chim. Acta,* 1988, **214,** 329.
51. van der Linden, W. E. *Anal. Chim. Acta,* 1986, **179,** 91–101.
52. Appleton, J. M. H.; Tyson, J. F.; Mounce, R. P. *Anal. Chim. Acta,* 1986, **179,** 269–278.
53. Gluodenis, T. J., Jr.; Tyson, J. F. *J. Anal. At. Spectrom.,* in press.
54. Carbonell, V.; de la Guardia, M.; Salvador, A. *Anal. Chim. Acta,* 1990, **238,** 417–421.
55. Lazaro, F.; Luque de Castro, M. D.; Valcarcel, M. *Anal. Chim. Acta,* 1991, **242,** 283.
56. Tyson, J. F. *Analyst,* 1985, **110,** 419–429.
57. Tyson, J. F. *Trends Anal. Chem.,* 1985, **4,** 124–128.
58. Ruzicka, J. *Fresenius' Z. Anal. Chem.,* 1986, **324,** 745–749.
59. Fang, Z.; Xu, S.; Wang, X.; Zhang, S. *Anal. Chim. Acta,* 1986, **169,** 325–340.
60. Barnes, R. M. *Spectroscopy,* 1986, **1,** 24–30.
61. Christian, G. D.; Ruzicka, J. *Spectrochim. Acta,* 1987, **42B,** 157–167.
62. McLeod, C. W. *J. Anal. At. Spectrom.,* 1987, **2,** 549–552.
63. Tyson, J. F. *Anal. Chim. Acta,* 1988, **214,** 57–75.
64. Ruzicka, J.; Christian, G. D. *Analyst,* 1990, **115,** 475–485.
65. Tyson, J. F. *Anal. Chim. Acta,* 1990, **234,** 3–12.
66. Valcarcel, M. Flow injection analysis. In *Sample Introduction in Atomic Spectroscopy* (J. Sneddon, Ed.), pp. 289–328. Elsevier, Amsterdam, 1990.
67. Fang, Z. *Spectrochim. Acta Rev.,* 1991, **14,** 235–259.
68. Beauchemin, D. *Trends Anal. Chem.,* 1991, **10,** 71–76.
69. Tyson, J. F. *Spectrochim. Acta Rev.,* 1991, **14,** 169–234.
70. Fang, Z.; Sperling, M.; Welz, B. *J. Anal. At. Spectrom.* 1990, **5,** 639.
71. Boomer, D. W.; Powell, M. J.; Hipfner, J. *Talanta,* 1990, **47,** 127–134.
72. Beinrohr, E.; Cakrt, M.; Garaj, J.; Rapta, M. *Anal. Chim. Acta,* 1990, **231,** 163–170.
73. Bysouth, S. R.; Tyson, J. F.; Stockwell, P. B. *Analyst,* 1990, **115,** 571.
74. Coetzee, P. P.; Talijaard, I.; de Beer, J. *Fresenius' J. Anal. Chem.,* 1990, **336,** 201–204.
75. Komárek, J.; Kubán, V.; Zdráhal, Z. *Chemické listy,* 1990, **84.**
76. Shah, A.; Devi, S. *Anal. Chim. Acta,* 1990, **236,** 469–473.
77. Mukai, H.; Ambe, Y.; Morita, M. *J. Anal. At. Spectrom.* 1990, **5,** 75.
78. Pereiro Garcia, M. R.; Lopez Garcia, A.; Diaz Garca, M. E.; Sanz-Medel, A. *J. Anal. At. Spectrom.,* 1990, **5,** 15.
79. Vermeiren, K.; Vandecasteele, C.; Dams, R. *Analyst,* 1990, **115,** 17.
80. Kaya, S.; Durrani, T. M.; Greenfield, S.; Tyson, J. F. Preconcentration of refractory elements for inductively coupled plasma atomic fluorescence spectrometry. In *Metal Speciation of the Environment* (J. A. C. Broekaert, S. Guget, and F. Adams, Eds.), Vol. G23, pp. 241–252. Springer-Verlag, Heidelberg, 1990.
81. Greenfield, S.; Durrani, T. M.; Kaya, S.; Tyson, J. F. *Analyst,* 1990, **115,** 531.
82. Heithmar, E. M.; Hinners, T. A.; Rowan, J. T.; Riviello, J. M. *Anal. Chem.,* 1990, **62,** 857–864.
83. Broekaert, J. A. C. *Spectrochim. Acta Part B,* 1990, **45,** 845–856.
84. Guo, T.; Erler, W.; Schulze, H.; McIntosh, S. *At. Spectrosc.,* 1990, **11,** 24–28.
85. Marshall, G. D.; van Staden, J. F. *J. Anal. At. Spectrom.* 1990, **5,** 675.

86. Marshall, G. D.; van Staden, J. F. *J. Anal. At. Spectrom.*, 1990, **5**, 681.
87. Chan, W.-F.; Hon, P.-K. *Analyst*, 1990, **115**, 567.
88. McLaughlin, K.; Dadgar, D.; Smyth, M. R.; Mc Master,D. *Analyst*, 1990, **115**, 275.
89. Drews, W.; Weber, G.; Tölg, G. *Anal. Chim. Acta*, 1990, **231**, 265–271.
90. Völlkopf, U.; Günsel, A.; Janssen, A. *At. Spectrosc.*, 1990, **11**, 135–137.
91. Brennan, M. C.; Simons, R. A.; Svehla, G.; Stockwell, P. B. *J. Auto. Chem.*,1990, **12**, 183–188.
92. Brushwyler, K. R.; Carter, L. D.; Hieftje, G. M. *Appl. Spectrosc.* 1990, **44**, 1438.
93. Roscoe, G. E.; Miles, R.; Taylor, C. G.; *Anal. Chim. Acta*, 1990, **234**, 439–444.
94. Kuban, V.; Komarek, J.; Cajkova, D.; Zdrahal, Z. *Chem. Papers*, 1990, **44**, 339–346.
95. Falkner, K. K.; Edmond, J. M. *Anal. Chem.*, 1990, **62**, 1477–1481.
96. Carbonell, V.; de la Guardia, M.; Salvador, A.; Burguera, J. L.; Burguera, M. *Anal. Chim. Acta*, 1990, **238**, 417–421.
97. Martiniz-Avila, R.; Carbonell, V.; de la Guardia, M.; Salvador, A. *J. Assoc. Off. Anal. Chem.*, 1990, 73(3), 389.
98. Carlos de Andrade, J.; Strong, F. C., III; Martin, N. J. *Talanta*, 1990, 37(7), 711–718.
99. Hou, X.; Xu, P.; Sun, Z. Guangpuxue Yu Guangpu Fenxi, 1990, **10**, 38–41.
100. Viczián, M.; Lásztity, A.; Wang, X.; Barnes, R. M. *J. Anal. At. Spectrom.* 1990, **5**, 125.
101. Giné, M. F.; Bergamin, H., F°; Reis, B. F.; Tuon, R. L. *Anal. Chim. Acta*, 1990, **234**, 207–212.
102. Israel, Y.; Barnes, R. M. *Analyst*, 1990, **115**, 1411.
103. Borja, R.; de la Guardia, M.; Salvador, A.; Burguera, J. L.; Burguera, M. *Fresenius' J. Anal. Chem.*, 1990, **338**, 9–15.
104. Manzoori, J. L.; Miyazaki, A.; Tao, H. *Analyst*, 1990, **115**, 1055.
105. Roychowdhury, S. B.; Koropchak, J. A. *Anal. Chem.*, 1990, **62**, 484–489.
106. van Staden, J. F.; van Rensburg, A. *Analyst*, 1990, **115**, 605.
107. van Staden, J. F.; van Rensburg, A. *Fresenius' J. Anal. Chem.*, 1990, **337**, 393–397.
108. Montero, R.; Gallego, M.; Valcarcel, M. *Analyst*, 1990, **115**, 943.
109. Montero, R.; Gallego, M.; Valcarcel, M. *Anal. Chim. Acta*, 1990, **234**, 433–437.
110. Montero, R.; Gallego, M.; Valcarcel, M. *Talanta*, 1990, 37(12), 1129–1132.
111. Esmadi, F. T.; Kharoaf, M. A.; Attiyat, A. S. *Talanta*, 1990, 37(12), 1123–1128.
112. Esmadi, F. T.; Kharoaf, M.; Attiyat, A. S. *Anal. Lett.* 1990, **23**(6), 1069–1086.
113. Manzoori, J. L.; Miyazaki, A. *Anal. Chem.*, 1990, **62**, 2457–2460.
114. Jimenez de Blas, O.; Pereda de Paz, J. L.; Hernandez Mendez, J. *J. Anal. At. Spectrom.*, 1990, **5**, 693.
115. Bäckström, K.; Danielsson, L.-G. *Anal. Chim. Acta*, 1990, **232**, 301–315.
116. Kuban, V.; Komarek, J.; Cajkova, D. *Chemické listy*, 1990, **84**, 376.
117. Menendez Garcia, A.; Sanchez Uria, E.; Sanz-Medel, A. *Anal. Chim. Acta*, 1990, **234**, 133–139.
118. Debrah, E.; Adeeyinwo, C. E.; Bysouth, S. R.; Tyson, J. F. *Analyst*, 1990, **115**, 1543.
119. Beinrohr, E. *Fresenius' J. Anal. Chem.*, 1990, **338**, 735–737.
120. Pretty, J. R.; Evans, E. H.; Blubaugh, E. A.; Shen, W.-L.; Caruso, J. A.; Davidson, T. M. *J. Anal. At. Spectrom.*, 1990, **5**, 437.
121. Astrom, O. *Anal. Chem.*, 1982, **54**. 190.
122. Offley, S. G.; Seare, N. J.; Tyson, J. F.; Kibble, H. A. B. *J. Anal. At. Spectrom.*, 1991, **6**, 133–138.
123. Riby, P. G.; Haswell, S. J.; Grzeskowiak, R. *J. Anal. At. Spectrom.*, 1989, **4**, 181–184.
124. Tyson, J. F.; Offley, S. G.; Seare, N. J., Kibble, H. A. B.; Fellows, C. *J. Anal. At. Spectrom.*, in press.
125. Karanassios, V.; Li, F. H.; Liu, B.; Salin, E. D. *J. Anal. At. Spectrom.*, 1991, **6**, 457–463.
126. Haswell, S. J.; Barclay, D. A. Presented at *The Eighteenth Annual Meeting of FACSS, Anaheim, CA, 6th–11th October 1991*, paper 14.
127. Tyson, J. F.; Hanna, C. P.; Haigh, P.; McIntosh, S. Work in progress.
128. Tyson, J. F.; Adeeyinwo, C. E.; Bysouth, S. R. *J. Anal. At. Spectrom.*, 1989, **4**, 191–194.
129. Tyson, J. F.; Bysouth, S. R. *Anal. Chim. Acta*, in press.
130. Sperling, M.; Yin, X.; Welz, B. *J. Anal. At. Spectrom.*, 1991, **6**, 295–300.
131. Porta, V.; Abollino, O.; Mentasti, E.; Sarzanini, C. *J. Anal. At. Spectrom.*, 1991, **6**, 119–122.
132. Tyson, J. F.; Bysouth, S. R.; Grzeszczyk, E. A.; Debrah, E. *Anal. Chim. Acta*, in press.