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THE OPTIMISATION OF DETECTOR SYSTEMS INCORPORATING ION-SELECTIVE ELECTRODES

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ABSTRACT

An outline of factors affecting the throughput of analytical systems based on ion-selective electrodes (ISEs) is presented. The manner in which samples are presented to the electrode sensing element and the adoption of on-line data-handling systems are shown to be of particular importance in optimising throughput. Attention is drawn to the striking similarities between the present considerations and those being faced (and solved) by workers in the field of high performance liquid chromatography. Some guidelines are offered for future improvements in continuous flow analytical systems, particularly those based on unsegmented flowing streams.

INTRODUCTION

Since the many advantages inherent in the adoption of electro-analytical methods in the Life Sciences have been well documented both by other authors in this volume and elsewhere /1-4/, the present contribution will be confined to an elaboration of some theoretical, practical and technical considerations of how these advantages may be most fully realised. My particular purpose will be to survey the fundamental principles involved in the most propitious incorporation of ion-selective electrodes (ISEs) into analytical systems with a view to offering guidelines for the ways in which optimisation (maximisation) of throughput may be achieved. Although identical principles apply to the use of polarographic methods of detection, I shall in general concentrate on potentiometric systems, analysing discrete samples.

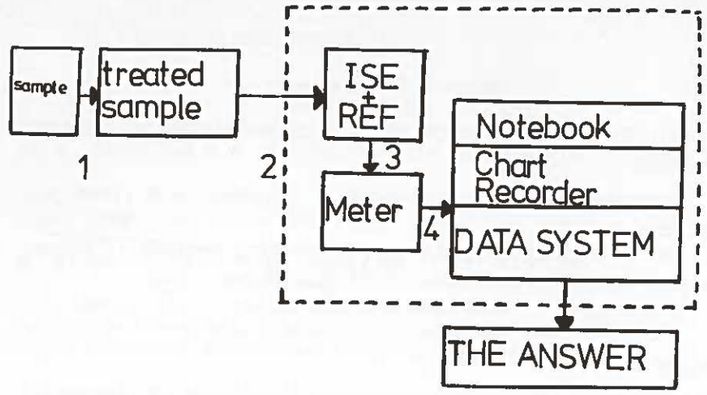


Fig. 1. Block diagram of analytical systems incorporating ISEs. As described in the text, four areas for discussion are identified, corresponding to the numbers above, viz. 1: Sample preparation, 2: Sample presentation, 3: Signal transduction, and 4: Signal recording and data handling. The dotted line signifies that part of the system defined as the 'Detector'.

In Fig. 1, I have diagrammed in block form the principal parts of an analytical system employing ISEs, by which a sample, through being brought into contact with a detector system (Fig. 1), may be coerced into yielding data on various analyte concentrations (activities) which it contains. Four areas for discussion may be distinguished; they constitute the interfaces between the separate parts of the system as defined in Fig. 1. I have given them the soubriquets (1) sample pretreatment, (2) sample presentation, (3) signal transduction and (4) signal recording and data handling. It is assumed that the reader has a working understanding of the principles underlying potentiometric methods of analysis /1 - 7/, and is thus chiefly interested in the suitability of applying such methodologies to his own analyses.

Of the four areas identified for discussion in Fig. 1, two have only a tangential relevance to the question of optimisation of throughput, namely sample pretreatment and signal transduction. Owing to the lack of necessity for optical clarity of samples when using ISEs, sample pretreatment usually involves only the addition

of a Total Ionic Strength Adjusting Buffer ("TISAB") solution to minimise the effects of interfering substances and to ensure a constant ionic strength. The appropriate TISAB reagent for different analytes are well documented both in the literature and in manufacturer's leaflets, and will not be discussed here. Similarly, the signal transduction system (3) is determined by the equipment available (that is to say by the properties of the meters supplied by manufacturers) and thus will also be omitted from consideration, except where suitable suggestions for its desirable properties may be given. Thus, the following is devoted to a consideration of sample presentation, signal recording and data handling, for I believe, and shall endeavour to show, that it is in these areas that the optimisation of detector systems incorporating ISEs may be most fruitfully carried out.

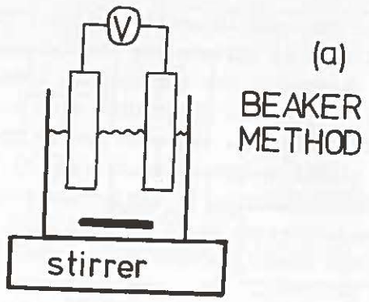
1. SAMPLE PRESENTATION TO ELECTRODES

1.1 Theory

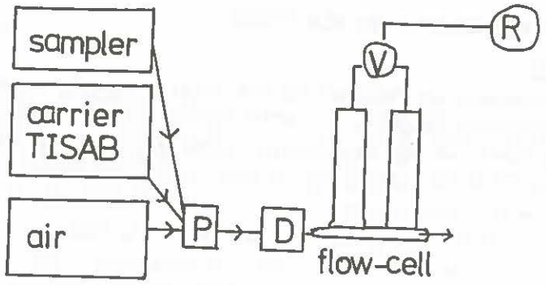
We shall start by considering the relative merits of analysing samples batchwise or using a continuous-flow system. It is well-known from chemical and biochemical engineering theory that in general any form of continuous process has a much faster throughput (and is thereby more economical) than batch processes (e.g. /8 - 10/). The batch process equivalent of analyses using ISEs is the traditional method (Fig. 2) in which the sample is introduced into a beaker equipped with a magentic stirring device and containing the TISAB, the potential developed by the ISE relative to the reference electrode is read from a meter, and this value (in millivolts) is used to determine the analyte concentration from a standard curve constructed in the same way. In contrast, samples may be analysed semi-automatically by the use of systems based on the well-known Autoanalyser concept /11/ (Fig. 2) or using the recently developed 'flow injection' analytical systems /12/ (see Fig. 5). We may characterise the throughput of the analytical system in Fig. 1 by an equation of the form:

$$X = 60Y/(t_a + t_d + t_r + t_e) \qquad (1)$$

where X is the number of samples which may be fully analysed per hour, t_a and t_d are respectively the times (in minutes) for the detector system to respond and for a sample which has just been analysed to be substituted by a new one for analysis. t_r is the time



(a) BEAKER METHOD



(b) AIR-SEGMENTED CFA

Fig. 2. Batch and continuous-flow systems for discrete sample analysis using ISEs

(a) The traditional beaker method for analysing discrete samples, as described in the text;
(b) An autoanalyser-type system for analysing discrete samples loaded into a sample carousel, with air-segmentation of the flowing carrier stream.

Note that the flow-cell is enlarged to show its interaction with the electrode's sensing elements. Abbreviations: V, millivoltmeter; P, pump; R, recorder; D, debubbler; CFA, continuous flow analysis.

(in minutes per sample) for the samples themselves and the reagents used in the analysis to be prepared, whilst t_e is the time (in minutes per sample) for the evaluation of the output of the meter in terms of the analyte concentration and its presentation in a form

suitable for permanent numerical recording. Y is the proportion of actual samples (i.e. number of unknown samples/(number of unknown samples + number of necessary accompanying standards, pools and drifts). It should be noted that equation (1) is a rather general equation and includes the entire analytical system from the production of an array of samples for analysis to obtaining the final results in a meaningful form. I would contend that in evaluating the operation of any proposed analytical system it is necessary to maintain a global perspective of the entire system, for modifications which save time (but involve capital expenditure) in one part of the system may otherwise be associated with no benefit in time (and hence cost) saved in another part of the system.

Now equation (1) is slightly cumbersome, and it would be convenient, for the present purposes, to lump some of the terms together, or even to omit them from consideration. However, the only term for which this may be regarded as legitimate is the term t_r, the time necessary to prepare the reagents to which the sample is added prior to its presentation to the electrodes. This enables us to confine our attention to the question of the optimisation of sample throughput by the manipulation of sample presentation and data handling systems alone. We therefore have:

$$X = 60Y/(t_a + t_d + t_e) \qquad (2)$$

Inspection of the form of this equation yields some useful insights into the manner in which throughput may be maximised. Let us assume that the ratio of unknowns to standards is constant for all methodologies. (This is tantamount to saying that accuracy and precision are independent of throughput.) In Fig. 3. are plotted the number of samples which may be analysed per hour at various values of t_a, t_d and t_e, using a value for Y of 0.8. If we let t_a, t_d and t_e to be equal a rectangular hyperbola, curve (a), is obtained (Fig. 3). Setting t_d and t_e equal to twice t_a causes a marked downward shift of the curve (to curve (b)), whilst causing the evaluation time t_e to be zero returns the curve (c) to the same locus as that given by curve (a). In other words, the provision of on-line data-handling capacity to an analytical system obviates much of the disadvantages of long response- and sample-changing-times. Setting t_d equal to t_a and retaining on-line data-handling gives curve (d). It may be concluded from the curves in Fig. 3, then, that the two most significant areas in which attempts to maximise throughput may be

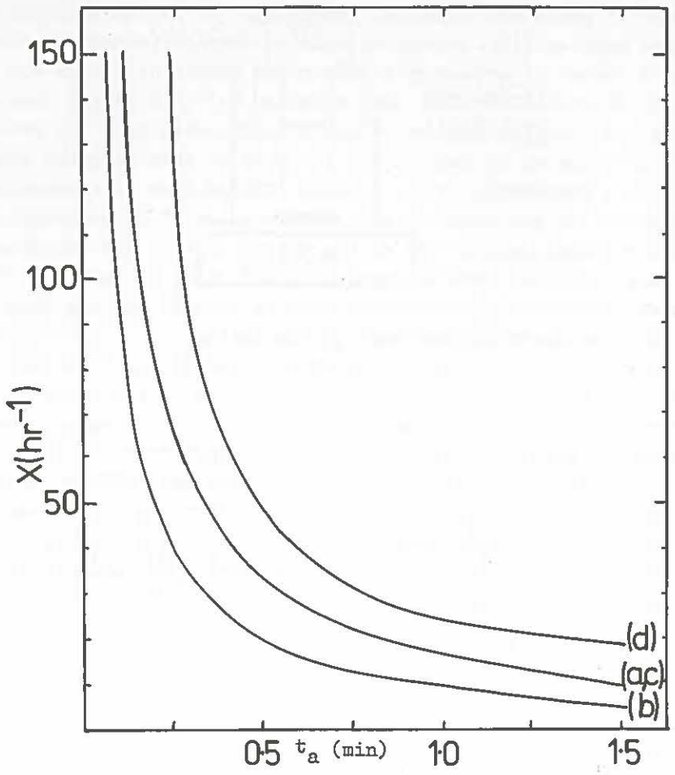


Fig. 3. Effect of detector response time on sample throughput. The ordinate represents the number of samples which may be analysed per hour, whilst the abscissa represents the detector response time, according to equation (2).
(a): $t_a = t_d = t_e$; (b): $t_d = t_e = 2t_a$; (c): $t_d = 2t_a$, $t_e = 0$;
(d): $t_d = t_a$, $t_e = 0$.
For further discussion, see text.

usefully directed and those of reducing response- and changeover-times and in the application of on-line data-handling systems to analyses involving ISEs. I shall cite examples in which academic improvements in throughput by the use or one of these approaches, whilst suggesting that the future application of both of these strategies may be required to bring about the massive increases in throughput that are possible (Fig. 3) using current technologies.

1.2 Data-handling systems with manual sample presentation

To the author's knowledge the only non-dedicated, microprocessor-controlled analytical system employing on-line data analysis of the output from ion-selective electrodes that is currently commercially available is the Orion 901 Ionalyser (see e.g. ref 13). This incorporates a hard-wired program (read-only memory) that calculates analyte concentrations from potential difference readings based on a pair of calibrating standards. This elegant system, however, is only really applicable to manual 'beaker' systems (Fig. 2), such that t_a is equal to the equilibrium response time of the electrodes, since the microprocessor's program is based on the (equilibrium) Nernst equation. Although the model 901 does incorporate a BCD (binary-coded decimal) output, so that, in principle, more elaborate data-handling systems may be directly interfaced to it, such interfaces (with the exception of a printer) are not as yet available. However, the system does have the advantage, noted above, of letting t_e equal zero, and thus if the response time of the electrode is relatively small, the throughput will be governed by the sample changeover time, which is approximately 0.5 to 1 minute. We may set an upper limit, then, on the throughput of this type of system of 30-50 samples (i.e. unknowns) per hour. This is of the same order of that which may be achieved using Autoanalyser methods lacking on-line data-handling facilities. Other, more 'dedicated' microprocessor-based systems (e.g. Orion's Space Stats and the Nova 1 and 2) are available for rapid measurement of serum Na^+, K^+ and Ca^{++} using manual sample injection, but they are intended for small numbers of samples (notably 'emergencies') and will not be discussed further. It should be noted that the use of such systems with manual sample presentation requires the attendance of the analyst throughout the run for the purposes of sample changeover.

1.3 Automatic sample presentation without data handling

It was of course due to the limits on throughput set by the necessity for manually presenting analytical systems with samples that continuous-flow analyses were introduced. Although in rare instances systems have been devised that include on-line data-handling as well as automatic sample presentation, such systems do not in general include those based on potentiometric detection (a notable exception are the most recent Technicon SMAC systems), and we shall confine

our attention in this section to the question of optimising the presentation of samples to ISEs so as to maximise the throughput. Two related but mutually antagonistic factors operate. The first is the necessity of having the sample in contact with the electrode for a sufficient time to allow a characteristic potential to develop, whilst the second is the need to move the sample on sufficiently rapidly to allow the next sample to contact the working electrode's sensing element, without allowing cross-sample carryover. To preface a proper analysis of the lassitude in sampling rates permitted by these contradictory considerations, then, we will next present a brief review of the magnitudes of, and factors affecting, the response times of ion-selective electrodes.

1.3.1. Factors affecting the response time of ISEs

Three main factors affect the response time of a given ISE to a step change in analyte activity: the magnitude, absolute value and direction of sample activity at the electrode surface. The response time characteristics of an ion-exchange-type ISE are given by an exponential equation of the form /14, 15/:

$$E_t = E_\infty + S \log \left[1 - \left(1 - \frac{a_i^\bullet}{a_i} \right) \exp t/\tau \right] \qquad (3)$$

where τ, the apparent time constant, is given by $\tau = \delta^2/2D'$. D' is a single-ion diffusion coefficient and δ is the thickness of the unstirred layer adjacent to the electrode. In contrast, the response-time characteristics of neutral carrier-based electrodes (e.g. those selective for K^+ and based on the ionophore valinomycin) are described /15/ by a square root function:

$$E_t = E_\infty + S \log \left[1 - \left(1 - \frac{a_i^\bullet}{a_i} \right) \frac{1}{\sqrt{\frac{t}{\tau}} + 1} \right] \qquad (4)$$

where the symbols are as before, except that $\tau = DK^2\delta^2/D'^2$, D is the mean diffusion coefficient in the membrane phase and K the partition coefficient between the aqueous and the membrane phases. For the present purposes we may confine our consideration to electrodes based on ion-exchange phenomena, where the approach to equilibrium is describable by an exponential relationship. In general τ values are most rapid for the following types of system: increase in analyte activity, solid-state membrane, large concentration of analyte. Under these conditions the time necessary

for 95% of the equilibrium change in potential (t_{95}) to be reached may be measured in seconds. In contrast, when electrodes are sensing low activities of ions, the step change in concentration is negative, and the electrodes are of the liquid ion-exchanger or gas-sensing types, t_{95} may be several minutes. Under these latter conditions it is clear that methodologies based on waiting for equilibrium to occur are unacceptably slow, although we note that acceptable precision may be obtained /3, 16/ by taking the reading of emf at a fixed time after immersion of the electrodes in the sample-containing solution. An obvious way round this difficulty (apart from developing electrodes of lower impedance), implicit in the use of continuous-flow systems /12, 17-20/, is to assume a constant response-time function for differing samples, and assay for the height of a peak using a constant sampling rate.

1.3.2 Non-equilibrium potentiometric assays

The approach mooted above, of assaying samples before equilibrium between ionic activity in the solution and the working electrode's final potential is attained, has been explicitly applied to potentiometric detection using an Autoanalyser-type system by Cowell /20, 21/. Cowell's studies have concentrated on the use of the fluoride electrode in urine and serum samples, and on a careful consideration of the importance of factors affecting the accuracy, precision and throughput of the system. By careful optimisation of the manifold used and the bubble-injection frequency, excellent accuracy, essentially identical to that of the manual potentiometric method previously employed, was obtained /20/, aided, in some instances, by the use of curve regeneration techniques. Since the equilibrium response-time of the fluoride electrode used was approximately 15 minutes at the low levels generally sensed (10^{-6} - 10^{-5} M F^-), and the dynamic response time of comparable relative length (see above), Cowell concluded /20/: "The practical consequences of the kinetics of continuous flow analysis, when incorporating ion-selective electrodes, appear to be governed by the response of the electrode itself. This is in complete contrast to colorimetric systems where the colorimeter plays little or no part in the kinetics of continuous flow analysis." Whilst noting that this is likely to be much less true for faster-responding electrodes, these studies /20, 21/ do stress the importance of electrode response-time in determining throughput.

Since the rate of rise and fall of sample peaks in continuous flow analysis /17, 18, 22/, the equilibrium electrode potential in the Nernstian region /1 - 7/ and the rate of electrode response (see above) are all exponential functions, a linear relationship between peak height and analyte concentration should be obtainable, at least over a decade of concentration. Thus, as well as considering the rate of electrode response, we must also consider the fact that, as a result of dispersion effects in the manifold, the actual changes in sample concentration noted by an ion-selective electrode in a continuous-flow system will also depend on the rate of change of actual sample concentration. To obtain the highest throughput, therefore, it is necessary to arrange conditions such that the narrowest peaks and the minimum flowcell volume are attained. The former objective may be achieved by keeping the length of manifold between the sample aspirator and the ion-selective electrode as short as possible (50 mm is often regarded as the minimum practical length attainable), whilst the latter is a matter of careful design of the flowcell, a topic to which we now turn.

1.4 The design of flowcells for ion-selective electrodes

Since the reference electrode of a potentiometric system exhibits a potential that is in principle independent of the activity of analyte, it is only necessary that electrical contact be maintained between it and the working electrode. For this reason, most investigators who have addressed themselves to the problem of the optimisation of flowcells for ion-selective electrodes have been content to keep the reference electrode in an effluent reservoir, a practice that seems entirely suitable for all but the most critical work. Consequently, attention has been focussed on flowcells for the ion-sensitive electrode. For a given sample volume an increase in flow rate might be expected to have two beneficial effects; the number of concentration changes presented to the electrode per sample will be increased (and thus peaks sharpened and carryover minimised) and the thickness of the unstirred layer adjacent to the electrode (and thus electrode response time per se) also minimised. Naturally, however, there is a limit to the size of the sample, particularly in clinical work (!), and it is therefore desirable to minimise the 'dead volume' in the flowcell itself. This is particularly true in the light of the adverse effects on dispersion (and hence peak height) of increasing flow rate noted below.

The ideal flowcell, then, will have the following characteristics: (a) perfect plug flow, with no mixing of sample stream within the flowcell and (b) an exceedingly small volume, which, for a given electrode sensing area means a minimal stream thickness. Three typical examples of attempts to achieve these objectives in real systems are presented in Fig. 4. The first (Fig. 4a), typified for instance by the early Orion designs and that of Spencer /22/, seeks to minimise both the depth of the cell and the area of contact with the electro-active material in the electrode. Whilst relatively fast response times may be obtained with this type of system some degree of mixing within the cell takes place /20/, and no way of obviating unstirred layers is available. The elegant design (Fig. 4b) of Thompson and Rechnitz /22a/ uses the full sensing area of the electrode and by having one inlet and four perimeter outlets ensures (i) that a negligible degree of mixing takes place, and (ii) tube wall effects /23/ are minimised. An entirely different approach to the design of flowcells for ISEs was used by Hansen et al /24, 25/. They dispensed with an enclosed system and allowed the flowing, sample-containing stream to squirt at the surface of the working electrode, whence it ran under the influence of gravity into the reservoir containing the reference electrode (Fig. 4c). Differential pumping rates ensured that the height of the liquid in the reservoir was constant. This elegant method, although successful in the laboratory of its originators, requires careful positioning of the inlet tube, which (in this author's experience!) has a distressing tendency to elute almost everywhere except along the electrode sensing surface, regardless of the surface tension of the inflowing stream. However, one should point out that exceedingly small dead volumes have been obtained using this method, such that the throughput is apparently limited by the peak sharpness attainable per se rather than by the characteristics of the flowcell.

It is germane to point out here that the minimisation of dead volume in detectors in flowing streams has also been a key objective of workers in the field of high performance liquid chromatography (HPLC) and gas chromatography (GC), in which electrochemical detectors are also being rapidly introduced /26-32/. In this type of system, in contrast to that based on the Autoanalyser concept, no air bubbles are injected into the flowing stream, and the idea of analysing discrete samples in a non-segmented flowing stream has recently attracted much attention; particularly through the

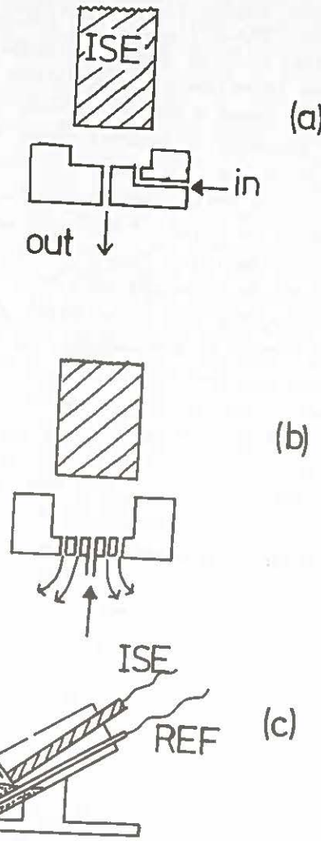


Fig. 4. Various micro-flowcells for ISEs.
3 typical types of flowcell are shown. The early Orion designs (a) caused the flow of liquid to pass in a plane parallel to the sensing surface of the ISE, allowing unstirred layers to form. An alternative design, (b) in which the flowing stream is directed perpendicular to the electrode surface, obviates these difficulties. A design that dispenses with the lower half of the flowcell is shown in (c). Literature references to these designs are given in the text.

extensive work of Růžička, Hansen and their collaborators (reviewed in refs. 12, 23) the concept has become known as flow injection analysis. Whilst only one flow injection analytical system (the BISFOK FIA 06 distributed by EDT Research) is currently commercially

available, (April 1979), it is the author's belief that the principles and practice of flow injection analysis will have a dramatic influence on the performance of future continuous-flow analytical systems, especially those incorporating ISEs. As pointed out by Betteridge /23/, the rediscovery /33/ of the utility of non-segmented streams has resulted in dramatic decreases in sample flow rates, sample volume and reagent consumption, with attendant massive increases in potential throughput, whilst the excellent accuracy and precision attainable with the method have been established for numerous analytes. Thus one may cite studies from serum ionised calcium levels /25/ to fertiliser nitrate levels /24/. With these advances has come the realisation, stressed earlier in the present paper, that throughput becomes limited by the need to analyse peaks in terms of analyte concentrations at a rapid rate (cf. Fig. 3), and the literature testifies /12, 23/ that a number of groups are nearing completion of the development of on-line data-handling systems for incorporation into, and indeed the control of, flow injection analytical systems. With t_a values of the order of a few seconds under suitable conditions, one may realistically expect that sample throughput may exceed 200-300 unknowns per hour. This is a truly remarkable throughput, and to justify the author's confidence in this prediction a brief discussion of the current status of this fertile marriage between chromatographic theory and continuous-flow potentiometry is warranted /12, 23, 34, 35/.

1.5 Flow injection analysis

In the flow injection system (Fig. 5) a sample is introduced into an unsegmented carrier stream, which will in general contain a TISAB and/or a titrant, either by direct injection or by the use of a chromatography-type sample loop. The sample passes down the tubing to a detector system, where a peak is generated. This simple conception has now been sufficiently studied that a number of principles for minimising the sample dispersion have been formulated /12/; one can do no better than paraphrase these principles, which are in several cases far from self-evident, and even contrary to what what one might a priori have expected:

1. A decrease of the flow rate in narrow tubes will lead to a decrease in the peak width.
2. Symmetrical peak profiles will be obtained in a long, narrow, perfectly cylindrical tube.

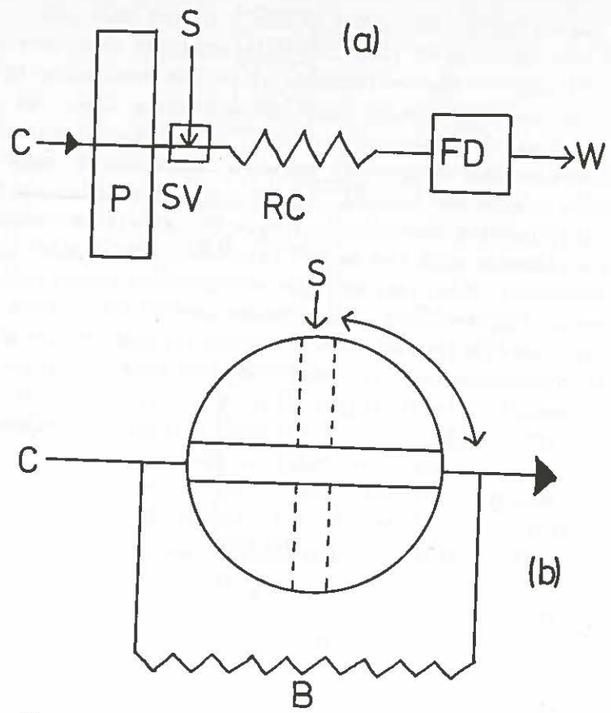


Fig. 5. Unsegmented continuous flow analysis
(a) The principle of flow injection analysis. The sample S is injected into the carrier stream of TISAB (C) by means of a sample injection valve (SV). The carrier stream is pumped by means of the pump (P) through a reaction coil (RC) which allows the desired degree of dispersion to take place, and the analyte concentration is determined at the flow-through detector, before flowing to waste (W).

(b) Chromatographic sample injection valve for introducing samples into a carrier stream without allowing air bubbles to enter the system. The bypass (B) offers a higher hydrodynamic resistance to flow than the sample valve when carrier is flowing through the sample valve, but allows the carrier to pass through it during loading of the sample into the sample loop. (After reference 12.)

3. Maximum peak sharpness is obtained by injecting a sample volume corresponding to a minimum of one $S_{\frac{1}{2}}$ into a carrier stream pumped at the minimum practical flow rate, and by having the shortest possible length of 0.4 mm i.d. tubing between the injection port and the detector, where $S_{\frac{1}{2}}$ is the volume of sample solution giving a peak height of 50% of that obtained by continuous aspiration of sample.

4. The peak sharpness of a sample decreases with increased pumping rate but only as the square root of the travelled distance or of the residence time.

In essence, then, the major difference between the more traditional air-segmented Autoanalyser type of system (Fig. 2) and the flow injection-type of analytical system (Fig. 5) lies in the abandonment in the latter of the use of air-bubbles to prevent sample dispersion and carryover, and its substitution by an optimisation of the geometrical and rheological characteristics of carrier streams flowing in narrow tubing. The advantages of this are a more rapid throughput, simpler manifolds and a greater degree of flexibility in the types of analysis which may be performed /12, 23/, although some controversy remains /36, 37/ concerning the question of the relative reagent consumption of the 2 types of systems. It is useful to point out that the precision of a flow injection system will depend very critically on the stability (freedom from pulsing) of the pumping system used to convey the carrier stream to the detector; in this regard, the low flow-rates used (as little as 1 ml per minute) are similar to those employed in HPLC, so that the new pump designs for the latter systems will be most suitable for flow-injection, another example of the cross-fertilisation between chromatography and continuous-flow analysis that is producing, and will doubtless continue to produce, a new generation of notable analytical progeny.

CONCLUDING REMARKS

Two main points have emerged from the present treatment of the question of optimising detector systems employing ISEs. The first was that on-line data-handling systems offer an appropriate (and cheaper) alternative to enhancing throughput than the adoption of continuous-flow analyses, up to fairly high rates of throughput. The second was that consideration should be given to the emerging technique of non-segmented continuous-flow analysis, and in particular, to the questions of flow cell geometry, stable pumping systems and the incorporation of on-line data- (and sample-) handling systems. Adoption of these principles may be expected to bring about a genuine revolution in the throughput attainable

by analytical systems incorporating ISEs.

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