

Retro-review of flow-injection analysis

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It is indeed unusual for authors to review their own monograph – J. Ruzicka, E.H. Hansen, *Flow Injection Analysis*, 2nd Edition, Wiley, Chichester, West Sussex, UK, 1988. – and even more so if the book was published 20 years ago. Yet such an exercise might yield a perspective on the progress of analytical instrumentation in general and on the development of flow-injection analysis (FIA) techniques in particular. By reviewing what was written and proposed 20 years ago, it is interesting to observe what proved to be of lasting value, what became accepted, and, above all, what we missed and failed to anticipate.

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1. Introduction

The monograph, *Flow Injection Analysis* [1], is unusual for several reasons. It is still in print, and there are not many scientific monographs in print after two decades. According to Braun et al. [2], it was the third most frequently quoted monograph in the area of analytical chemistry in the period 1980–99 (after *Electrochemical Methods: Fundamentals and Applications* by A.J. Bard and L.R. Faulkner, and almost equaling the number of citations of *Introduction to Modern Liquid Chromatography* by L.R. Snyder and J.J. Kirkland). It was also the first of what was to become a series of 19 monographs, published on the same topic in the years to follow (Table 1).

2. Content of the monograph

Seen from today's perspective, the chapters on Principles (Ch. 2) and Theoretical Aspects of FIA (Ch. 3) have survived the passage of time, and, surprisingly, can be applied to techniques the existence of which was not foreseen by us at the time of writing. Indeed, not only "classical FIA" but also its novel forms, sequential injection (SI) and bead injection (BI), are based on

the same principles. The mixing patterns, the importance of gradient formation and their description by the tanks-in-series model (borrowed from chemical-reactor engineering) are valid for all these flow-based techniques. While we can observe this with satisfaction, we also included material that was superfluous, ambiguous, or already obsolete by then.

In all fairness, FIA was born and the book was written at a time when chart recorders were far more common than computers, and when peristaltic pumps and manually-operated two-position valves were the norm. With the first FIA paper published in 1975 [3], and, despite the fact that the ensuing years merely gave birth to some 100 FIA publications, we decided, and were strongly encouraged by the then Editor-in-Chief of *Analytica Chimica Acta*, Alison McDonald, to embark on writing the first edition of our monograph, which was published in 1981. (We deliberately waited to submit the manuscript to the publisher until we had managed to scrape together exactly 100 references).

The purpose of the book was to lay out the principles of FIA and to document, via numerous examples, that it actually worked (to accentuate this, we proudly wrote in the Preface: "All the response curves shown are reproduced photographically from recorder charts."). Indeed, we proved right, because the second edition, the main purpose of which was to demonstrate the versatility of FIA, comprised well over 1400 references, documenting acceptance of the technique by the analytical community. For the very same reason, FIA is nowadays often abbreviated to FI in order to emphasize that it is a conceptual approach in addition to a means of performing analysis.

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Table 1. Monographs published on flow-injection analysis

1. J. Ruzicka, E.H. Hansen, *Flow Injection Analysis*, Wiley & Sons Inc., New York, USA, 1981.
2. J. Ruzicka, E.H. Hansen, *Flow Injection Analysis (Japanese)*, Kagakudonin, Kyoto, Japan, 1983.
3. K. Ueno, K. Kina, *Introduction to Flow Injection Analysis. Experiments and Applications (Japanese)*, Kodansha Scientific, Tokyo, Japan, 1983.
4. M. Valcarcel Cases, M.D. Luque de Castro, *Flow-Injection Analysis (Spanish)*, Imprenta San Pablo, Cordoba, Spain, 1984.
5. E.H. Hansen, *Flow Injection Analysis*, Polyteknisk Forlag, Copenhagen, Denmark, 1986.
6. J. Ruzicka, E.H. Hansen, *Flow Injection Analysis (Chinese)*, Science Press, Beijing, China, 1986.
7. M. Valcarcel, M.D. Luque de Castro, *Flow-Injection Analysis. Principles and Applications*, Ellis Horwood Ltd., Chichester, West Sussex, UK, 1987.
8. J. Ruzicka, E.H. Hansen, *Flow Injection Analysis*, 2nd Edition, Wiley & Sons Inc., New York, USA, 1988.
9. J.L. Burguera (Editor), *Flow Injection Atomic Spectroscopy*, Marcel Dekker, New York, USA, 1989.
10. B. Karlberg, G.E. Pacey, *Flow Injection Analysis. A Practical Guide*, Elsevier, Amsterdam, The Netherlands, 1989.
11. J. Ruzicka, E.H. Hansen, *Flow Injection Analysis*, 2nd Edition (Chinese), Beijing University Press, Beijing, China, 1991.
12. Z.-L. Fang, *Flow-Injection Separation and Preconcentration*, VCH Verlags GmbH, Weinheim, Germany, 1993.
13. W. Frenzel, *Flow Injection Analysis. Principles, Techniques and Applications*, Technical University Berlin, Berlin, Germany, 1993.
14. M. Valcarcel, M.D. Luque de Castro, *Flow-Through (Bio)Chemical Sensors*, Elsevier, Amsterdam, The Netherlands, 1994.
15. Z.-L. Fang, *Flow Injection Atomic Spectrometry*, Wiley, Chichester, West Sussex, UK, 1995.
16. J.M. Calatayud (Editor), *Flow Injection Analysis of Pharmaceuticals: Automation in the Laboratory*, Taylor & Francis, London, UK, 1997.
17. A. Sanz-Medel (Editor), *Flow Analysis with Atomic Spectrometric Detectors*, Elsevier, Amsterdam, The Netherlands, 1999.
18. Z. Fang (Editor), *Flow Injection Analysis (Chinese)*, Science Press, Beijing, China, 1999.
19. M. Trojanowicz, *Flow Injection Analysis. Instrumentation and Applications*, World Scientific. Ltd., Singapore, 2000.

While the chapters discussing gradient techniques, kinetic discrimination schemes and the adaptability of FIA to spectroscopic and electrochemical detectors documented valuable features of the method, we also included, in our enthusiasm, some impractical ideas. Thus, Parallel FIA ([1], Section 4.4.) and some rather complex valving systems ([1], pp. 262–267) were already obsolete by the time of writing. We also emphasized flow-based titrations that, although feasible, never found wide practical application.

2.1. Real-life assays

The use of FIA for real-life assays, as reviewed in the monograph, became in the following years spectacularly successful in many areas, with two notable exceptions, namely in the clinical field and for industrial process control.

Clinical analysis was at that time already dominated by assays performed automatically in the discrete format using prepackaged reagents, so introduction of a new technique, that had yet to be verified, was neither warranted nor feasible.

Application of FIA for process control, while very desirable and proved to be feasible, met another obstacle. The apparatus designed for the laboratory environment, where continuous supervision of its function was the norm, was not sufficiently reliable for application in industrial settings [4]. It took two decades to resurrect the idea (i.e. by replacing the peristaltic pumps with a single syringe pump, the injection valve with a multi-position valve, continuous flow with reagent saving programmable flow, and human supervision with computer control). Autonomous SI systems are now deployed in industry as well as in remote locations to

provide 24/7 (24 hours/7 days a week) monitoring of variety of analytes ranging from spectrophotometric determinations of dyes to fluorescence/enzymatic assays of bacteria [5].

2.2. Miniaturization

As to miniaturization, we discussed two different approaches. Superminiaturized FIA systems ([1], pp. 103,104) to be fashioned by a straightforward down-scaling of system dimensions (going from a channel I.D. of 0.5 mm to 125 μm , channel lengths down to 3 cm, and flow rates of the order of 1 nL/s), with the aim of letting diffusion do the job of mixing. While we were rather critical of this approach ([1], p. 105), we do in retrospect wish that we had never floated the idea – since it, except for very simple chemistries, leads to a blind alley when applied to reagent-based assays (see below). Thus, hopefully the idea of the micro-total analytical system (μTAS) was not – although it might have been – inspired by our thoughts on this subject.

The second approach to miniaturization was to minimize the volume of the flow path between the injector and the detector. By embossing short, relatively-wide channels (0.8 mm I.D.) into rigid PVC plates, wherein electrochemical and/or fiber-optical flow cells were micro-fabricated in situ, it was possible to design well-working prototypes of FIA analyzers the size of a credit card ([1], Section 4.12). However, it was 10 years before the advent of green chemistry, and precious few were then concerned about reagent consumption and waste disposal. Also, pre-fabricated microfluidic systems were not practical, since different assay protocols required the imprinting of different flow patterns. By contrast, conventional FIA systems could be reconfigured manually

and conveniently by adding coils and other components as needed.

2.3. Flow programming

What we failed to foresee was the power and versatility of flow programming. Indeed continuous flow was the only *modus operandi* that we considered at that time, and, while we proposed stopping the flow for reaction rate measurements, we did not consider manipulating the flow in more sophisticated ways. Perhaps our imagination was limited by the then existing technology.

While we had already predicted more widespread use of personal computers in the first edition, we did not practise it. The peristaltic pump was the only fluid drive that we viewed as practical. However, at that time, our main concern was to document that FIA presented itself as a viable, practical alternative to traditional ways of solution handling in the analytical laboratory. The read-outs of chemical assays had, for centuries, been based on homogenous mixing of sample with reagent solutions, preferably while reaching chemical equilibrium. Read-out based on peak height, as obtained by a sample zone dispersing in a stream of reagent, forming a concentration gradient, was an unproved novelty. More than additionally 16,000 papers on the FIA techniques had yet to be published during the next 20 years [6].

2.4. Sequential injection and 'lab-on-valve'

Sequential injection (SI) is now widely accepted and miniaturized in the "lab-on-valve" (LOV) format, where a microconduit monolith is mounted atop a selection valve and designed to contain all facilities for conducting chemical manipulations and even detection.

However, in the late 1990s, it was not obvious that there might be something more versatile than the continuous flow concept. Designing SI, which is based on flow programming and synchronized merging of sample and reagent zones [7], met with skepticism and technical obstacles, such as lack of reliable syringe pumps and suitable software. Now, 12 years later, SI has been accepted, and in the SI-LOV format used for variety of assays [8–10].

It is interesting to note that the LOV concept is based on two principles:

- optimizing the volume of the flow path between the injector and the detector; and,
- flow programming that comprises stopped-flow, flow reversals and accelerated flow.

Relatively wide (0.8 mm I.D.), yet short, channels allow μL volumes of samples, reagents and even solid beads to be mixed efficiently within seconds, and stopped, as needed, within the detector for reaction-rate measurement, or transported for monitoring in externally attached detection devices (e.g., atomic absorption spectrometry (AAS), inductively coupled plasma atomic emission spectrometry (ICP-AES) or ICP

mass spectrometry (ICP-MS). Thus, and most importantly and in contrast to the μTAS systems of fixed architecture, the SI-LOV systems allow us to exploit the interplay between thermodynamics and kinetics, which not only graces us with an additional degree of freedom, but is also imperative if more than just single-step and very fast chemistries are to be used. As any analytical chemist knows by experience, this is, in many instances, not the case, hence requiring careful sequencing of the ongoing chemical reactions. A detailed discussion and comparison of the LOV approach and the lab-on-a-chip (LOC) devices has recently been published [10].

3. And since the monograph?

By the beginning of 2008, more than 17,500 FIA publications had appeared in the international scientific periodicals [6], to which should be added hundreds of Ph.D. theses. Published in numerous languages, they comprise the application of virtually any detection principle available, ranging from optical and electrochemical over atomic to radiochemical devices, and usage in areas as diverse as environmental chemistry, process control, and bioscience. It is therefore virtually impossible to compile into a single table a generalized overview of the current situation regarding the classification of the many FIA publications. However, it is apparent that there are trends towards proper hyphenations, which are based on usage of intelligent chemistries, and taking advantage of the fact that the systems operate under dynamic conditions (i.e. permitting exploitation of the interplay between thermodynamics and kinetics). These will facilitate not only obtaining suitable or sufficient selectivity and sensitivity for a given analyte, but also speciation of it.

It would be tempting to start predicting where this novel technology may lead, but because we failed in the past, it is better not to proceed in that direction. Since FI techniques have surpassed not only our imagination, but also our ability to recall all their variants as they are being developed worldwide, we do not consider ourselves in a position to make further generalizations. Only a few years ago we were surprised by the novel concept of sequential injection chromatography [11]. Indeed, FI techniques and applications have expanded to the point that it would be very difficult for an individual to cover the entire field. Fortunately, there are currently two teams of authors toiling towards this goal [12,13].

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