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How did flow injection analysis, and its related techniques, develop in various parts of the globe? Reflections of prominent FIA practitioners

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We present here some reflections gathered from responses to questions that were sent to FIA-researchers and practitioners who have devoted themselves to flow injection analysis and its related techniques during the last four decades. These comments were obtained shortly before the commencement of the 16th International Conference on Flow Injection Analysis, including related techniques (April 25–30, 2010, Pattaya, Thailand). These responses were arranged into a Power Point presentation for the opening session (see: http://www.science.cmu.ac.th/icfia2010/. (Follow the links http://www.science.cmu.ac.th/icfia2010/downloads fiabio icfia16.html or http://www.science.cmu.ac.th/icfia2010/icfia16/fiabio part1-4.pdfwww.science.cmu.ac.th/icfia2010/ where more details of each respondent's recollections are provided, along with pioneering pictures.)

The questions were:

1. What initiated your interest in flow injection analysis?
2. When and where did you start working in this area of research? Your present affiliation?
3. What aspects of your work in flow analysis do you find most intriguing or satisfying?
4. In your opinion, what are the likely trends/future directions of flow analysis (which may include aspects such as fields of application, manifold architecture, modes of detection, etc.).
5. Please indicate five key publications that you feel are representative your work.

The information reflects how FIA and kindred techniques were developed in various places, and also emphasizes the usefulness of the techniques.

1. Jarda Růžička, Co-inventor of FIA (Denmark and USA)

". . .In 1965, Technicon Company, who marketed Skegg's AutoAnalyzer, organized a workshop in London which I attended. It was a fascinating experience.

For next ten years this flow technique captured my imagination, and allowed me to develop a new approach to automated radiochemical analysis. The AutoAnalyzer technology dominated clinical and industrial analysis for almost 20 years, since the air segmentation was believed to be the only way, of preserving identity of serially analyzed samples.

In spring 1974 we made, with Elo Hansen, in Copenhagen, an experiment of injecting a well-defined volume of a sample into a continuously flowing non-segmented carrier stream.

To our surprise, the response peaks were well defined and the sampling frequency was far higher than what was achievable by AutoAnalyzer.

We realized that we discovered something important, and we stuck to the idea, named the method flow injection analysis, and published, with Brazilian colleagues first ten papers, before the analytical community paid any attention to it. The story, should you be interested, is, in more details told in Chapter 5 of the Tutorial.

Versatility and applicability of the technique to a wide range of analytical assays for agriculture, environmental research, pharmacology, biochemistry and even biology.

Similar to chromatography, FIA techniques easily accommodate technological advances (such as solid state detectors, fiber optics and computerization), as they become available, making FIA increasingly more powerful, and better suited for real life applications.

There are almost 20,000 papers and 21 monographs dealing with FIA techniques.

And now my question, to you: Since chromatography is "separation technique based on difference in migration velocities of sample components" and flow injection analysis "is a technique based on sample injection into a carrier stream containing regents" and Skegg's AutoAnalyzer "is a technique based on sample aspiration into a continuously moving stream of

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reagents segmented by air", how you would define flow analysis? Does it include chromatography, or only reagent based techniques? Let me know, please. . .. . ."

2. Elo Hansen, Co-inventor of FIA (Denmark)

". . .. . .Back in the 70s Jarda and I were, as dedicated analytical chemists, compelled to effect analytical procedures in the most efficient way to attain optimal sensitivity and selectivity. This guided us, via numerous experiments, to the invention of FIA. . .. . ..
. . .. . .The exploitation of the 3 cornerstones of FIA, that is, sample injection, controllable dispersion and reproducible timing. These aspects have, in my opinion (and as mentioned above), opened up entirely new avenues in analytical chemistry, such as using bio- and chemiluminescence as detection procedures, taking advantage of intermediate/transient constituents of chemically interesting characteristics; and advantageously exploiting kinetic discrimination procedures. . .. . ..
. . .. . .Intelligent utilisation of the foundations of FIA and its extension SIA and LOV. Merely the fantasy and individual imagination sets the limitations. There are applications in legion where the basics of FIA/SIA/LOV can be exploited in order to meet the goals of modern analytical chemistry, that is, obtaining the ultimate sensitivity and selectivity. . .. . ."

3. Gary D. Christian (USA)

". . .. . .It goes back to my sabbatical in Europe in 1978/1979. I had been following the early literature in FIA, and while at the University of Geneva in 1979, I spent a lot of time in the library searching the literature in the field (before the availability of electronic databases!), in preparation for submission of a proposal to NSF. I uncovered some early references not known before and included them in the NSF proposal. While the proposal was not funded (a fate of early work in the field), ..."
My first FIA work was with my student, Tim Kelly, and our first publication was "Fluorometer for Flow Injection Analysis with Application to Oxidase Enzyme Dependent Reactions", T.A. Kelly and G.D. Christian, *Anal. Chem.*, **53**, 2110 (1981).
I was lucky to arrange for visits of Jarda Ruzicka to the University of Washington, and as a result, in 1987 we were fortunate to have him join our department as professor, moving from the Technical University of Denmark.
We enjoyed a fruitful research collaboration for many years, and our first publication together was "Stopped-Flow Determination of Reaction Rate Parameters", J. H. Hungerford, G.D. Christian, J. Ruzicka and J. C. Giddings, *FIA Newslett.*, **1(2)**, June, 1984, followed with "Reaction Rate Measurement by Flow Injection Analysis Using the Gradient Stopped-Flow Method", J.H. Hungerford, G.D. Christian, J. Ruzicka and J.C. Giddings, *Anal. Chem.*, **57**, 1794–1798 (1985). We have over 100 joint publications. . .. . .."

4. Alan Townshend (UK)

". . .. . .FIA was introduced into our research program whilst I was a lecturer at Birmingham University. It was first taken up by Dr. Alison Macdonald in ca. 1976, and we were both very impressed by a visit to Lyngby soon after to the laboratories of Ruzicka and Hansen.
I moved to the University of Hull in 1980, where I remain, and my FIA research group expanded rapidly.
I was joined in 1984 by Paul Worsfold.
In particular FIA proved ideal for monitoring chemiluminescent reactions, which required isolation from ambient light, and also for the use of solid phase reagents, especially immobilized enzymes. Systems could readily be devised for a wide variety of analyses, the responses were fast and reproducible, and expense was modest."

5. Bo Karlberg (Sweden)

". . .. . .FIA, yes this technique has governed and changed my entire life. It started as early as 1975 which means that I became aware of this technique just slightly after its conception. My research at that time was devoted to ion selective electrodes, so I knew both Ruzicka and Hansen since they were active in the same research field just before they invented FIA. We had met at several conferences and also visited each other at our respective universities. . .. . ..
. . .. . .I heard about FIA very early and went to Copenhagen and purchased one of the LEGO-based FIA systems from Růžička and Hansen and started to develop quality control methods at Astra Pharmaceuticals based on FIA. Shortly thereafter we developed a new liquid–liquid extraction method for the determination of acetylsalicylic acid. We could run several thousand of samples in a feasibility study for the manufacturing site at the company. After having gained experience with both air-segmented flow analysis and non-segmented flow analysis we were struck and impressed by the simplicity and swift behavior of FIA. Thus, we realized its tremendous potential at an early stage. . .. . ..
. . .. . .I started to work for Bifok/Tecator in September 1979. It was at the very start a small company so the tasks were very shifting, patent portfolio management, product development, application development, marketing, service, and education. Since then I have more or less worked with FIA in one way or another. In 1993 I became professor at Stockholm University and I retired in 2008. . .. . ..
. . .. . .The coupling of FIA to CE, no doubt. This approach is indeed challenging and promising. . .. . .".

6. Tadao Sakai (Japan)

". . .. . .In 1983, at Gifu College of Dentistry, interests with FIA spectrophotometry for determination of metals with new reagents such as nitroso-ESAP, Nitroso-PAPS, 5-Br-PSAA. . .. . .
. . .. . .Coupling of instrumentations for sensitive and/or multicompound detection. . .. Highly sensitive detection systems, Simultaneous detection systems, application to clinical, pharmaceutical, environmental analysis, FIA/SIA with SPE. . .."

7. Shoji Motomizu (Japan)

".... the first Journal of Flow Injection Analysis, Vol. 1, No. 1 was published in June, 1984. In 1991, Flow Analysis V was held in August 21–24, 1991 in Kumamoto. . .. . ."
". . .. . .. In my case, I started FIA research around 1980. I was interested in numbers of special characteristics and advantages of FIA in chemical analysis, such as possibility of the improvement of sensitivity, selectivity and reproducibility of measurement, simplicity and rapidity of sample throughput, automation of chemical procedures, and lowering of contamination from experimental circumstances. . .. . .."

8. Jacobus (Koos) Frederick van Staden (Romania)

". . ..There are a number of issues that initiated my interest in flow based systems that eventually culminated into flow injection analysis.

I started my research work on flow injection analysis in January 1977 at the University of Pretoria on the determination of calcium in animal feeds. The continuous flow equipment was supplied by Cenco, Breda, The Netherlands. We used a transfer sampler, a peristaltic pump, a colorimeter fitted with a first-generation 15-mm tubular flow cell without de-bubbler, a two-pen Model 1200 W & W potentiometric recorder and a Carle micro-volume valve. We designed a timer to actuate and drive the sampler and valve.
I was honoured, after Graham Marshall completed his MSc-degree with myself as supervisor, to share with Jarda Ruzicka, on the venture of sequential injection analysis (for) which Graham was awarded a PhD-degree at the University of Pretoria. There are a number of publications Graham and I shared on SIA, but the first two will always lie near to my heart. . .."

9. Elias A.G. Zagatto (Brazil)

". . .. . ..it should be recalled that flow injection analysis was originally applied to large scale analyses in CENA, University of S. Paulo, Piracicaba, Brazil, and I was nearby. The enthusiasm of pioneers such as, *e.g.*, H. Bergamin-Filho, J. Růžička, J.W.B. Stewart and CENA staff was the driving force towards my engagement in flow injection analysis.
Regarding developments, early contributions such as, *e.g.*, confluent stream addition, merging zones, zone sampling, use of solid reagents, liquid–liquid extraction, ion-exchange, isothermal distillation, and commutation as well as the implementation of turbidimetry, ICP-OES and gravimetry in flow injection systems, were given by the research group at CENA. Since the earlier 1990s, scientific collaboration with Portuguese colleagues has resulted in important innovations such as, *e.g.*, multisite detection, multi-commutation, fluidized beads, multipumping flow analysis and single interface flow analysis. Other recent aspects refer to Schlieren compensation, differential kinetic analysis relying on PLS application, exploitation of sugar alkaline degradation, turbulent mixing, etc. . . ."

10. Boaventura F. Reis (Brazil)

"I started the work with FIA process at 1976 as an MS student, under the supervision of the Prof. Henrique Bergamin, São Paulo University (Brazil). Today, I'm a full Professor, Center of Nuclear Energy in Agriculture (São Paulo University).
My favorite aspect of FIA is the versatility to handle chemical solutions, a feature that has been exploited to develop analytical procedures comprising a wide range of sample matrices, which has been implemented using all detection techniques usually employed in analytical chemistry."

11. Paul Worsfold (UK)

". . .The early papers by Jarda Růžička and Elo Hansen which encouraged me to successfully apply for a postdoctoral position with them.
The application to challenging issues in environmental science, particularly biogeochemical processes in aquatic systems.
Long term remote deployments to acquire unique, high temporal and spatial resolution environmental data.
The technique of flow injection (FI) analysis provides an integrating theme for my research activities, with particular emphasis on the design, construction and deployment of automated FI instrumentation *in situ*, i.e. outside of the laboratory. . ."

12. Sandy Dasgupta (USA)

". . ..With the first papers on flow injection published in 1975 (at the time I was a graduate student trying to measure sulfuric acid aerosol in air), flow injection was a mature technique by the time I became an independent investigator. What struck me as wonderful about flow injection analysis is the ease of automation without involving air segmentation and perhaps more importantly, the aspect of controlled reproducible dispersion.
In 1984 I had obtained a grant from the United States EPA to measure atmospheric peroxides. Even before I ever did any experiments I proposed that I will build a continuous instrument based on the continuous unsegmented flow analysis concept.
I find the reproducibly controlled dispersion in unsegmented continuous flow the most intriguing. Paradoxically, this has been the least practically exploited use of FIA."

13. Lola Luque de Castro (Spain)

". . .. . .we started with the design of two-channel manifolds such as that for the catalytic-fluorimetric determination of copper. . .. . ..
. . .. . .for on-line development of filtration and preconcentration steps after leaching a complex sample and prior to injection of the analytical sample into GC–MS/MS equipment. . .
. . .. . . mainly focused on metabolomics/proteomics and on exploitation of by-products from the agrofood industry. Both fields require the help of more or less complicated FI manifolds, which are designed by *consensus* of several members of the team. . .
. . .I dare to say the present trends in FI are mainly focused on easy automation of the bridge between sample and either a more or less complex detector or high-resolution separation equipment. . .. . ."

14. Victor Cerdà (Spain)

". . ..Some times more than 20 h were needed for potentiometric titrations to obtain high precision results. My conclusion was that this was not a task to be done by a person, but by a machine. When I moved in 1982 to the University of the Balearic Islands we decide to develop some kinds of flow systems to make the potentiometric and spectrophotometric measurements. . .. . .
. . .. . .Finally after a night of insomnia we had the idea to integrate in a flow system the advantages of the previous ones and removing their drawbacks: the MSFIA was born.
. . .. . .This new technique allowed to dispense liquids in parallel (like FIA), do not use peristaltic tubes (robustness of SIA), the use of the solenoid valves placed in the head of the syringes allow to dispense sample and reagents when the measure is needed (like MCFIA). Do not think (how) to apply a specific flow technique; *think about the solution (to) your problem* and on the possible advantages in combining different flow systems (both) separative and non-separative."

15. José Martínez Catalayud (Spain)

"In those times, the possibility of analytical automation by not using a "black box" was fascinating. It was possible to "see" through the tubing how the solutions were advancing or merging. In addition the required instrument was available (*e.g.*, spectrophotometer, fluorimeter, etc.) in lab; only flow cells, a peristaltic pump and tubing were required. All this led to a clear conclusion: "It was possible to continue the research on

analytical chemistry under modern methods" with the probability of experiencing . . .major breakthroughs. At present, we can conclude those predictions were not wrong."

16. Manuel Miró (Spain)

"My interest for FIA and related techniques started as undergraduate student when listening to Victor (Cerdà's) lectures on FIA and SIA and realising that most of the limitations of batch assays could be overcome exploiting flow-based approaches. In fact, my MS thesis at the University of the Balearic Islands involved the development of a sequential injection liquid-phase micro-extraction procedure based on wetting film extraction for determination of nitrophenol derivatives. This was my very first publication in 2000 in Analytica Chimica Acta. My PhD thesis defended in 2002 in Spain compiled research work on SIA and Multisyringe flow analysis for on-line SPE and LLE sample treatment.
My two mentors, Wolfgang Frenzel and Elo Hansen, with whom I conducted post-doctorate research stays, acted as catalysts for pursuing further research work in the flow analysis field.
In my opinion the future of flow-based approaches is the miniaturization (*e.g.*, via the LOV platform) and automation of sample pretreatment which are still not fully exploited in combination with atomic spectrometry for determination of inorganic species and chromatographic/electrophoretic separation for organic compounds."

17. José Luis F. Costa Lima (Portugal)

". . . . . .Flow analysis became a passion in the beginning of the 80s when I found out the immense potential of combining flow injection with potentiometric detection. The previous years have been spent developing several ion-selective electrodes (ISE) without internal reference solution and we came to conclude that coupling these devices with flow analysis would improve the electrodes performance as a consequence of the continuous renewal of the membrane/solution interface and the reproducible timing of all measurements. . .
. . . . . .Multi-commutation (MCFIA) and the binary sampling concept appeared in mid 90s as a consequence of the cooperative work with the Analytical Chemistry group of CENA (Piracicaba, Brazil). The multicommutated flow networks thereafter developed have demonstrated the analytical potential of the concept. Later on and aiming at achieving even a more simplified configuration, control and operation, multipumping flow systems (MPFS) were developed putting an emphasis on flow manifolds with a single active component and bringing to light the mixing capability of pulsed flowing streams. More recently, the implementation of reaction schemes based on a single interface (SIFA) that do not require the insertion of pre-set sample of reagents volumes has been one of our main research interests.
Flow-based techniques are in a transition stage: technological developments in recent years have been scarce and a significant part of the research efforts have been focused on the application field with a particular relevance on the utilisation of heterogeneous systems combining a liquid and a solid phase, either as reagent support or for pre-concentration purposes, interference suppression, etc. We believe that this trend will evolve eventually throughout the utilisation of fluidized bed or membrane-based solid reactors. Nanotechnology is also reaching flow analysis with an increasing utilisation of nanomaterials."

18. José Luis Burguera (Venezuela)

". . ..the research topic of my PhD Thesis was about chemiluminescence (CL) in aqueous media. My supervisor was Professor Alan Townshend. As Marcela (my wife) also finished her PhD at almost the same time, she hurried up to return to Venezuela to meet our twin sons.
I did not want to turn back to Venezuela without having both titles, and therefore I remained from April to July waiting for the date of the University congregation. So, as meanwhile I had nothing to do, Alan (I call him like this as a close friendship developed between us) asked me to do a work related to the coupling of CL with a "new technique" called "flow injection analysis" (FIA).
In my opinion, the likely trends and future directions of flow analysis would be miniaturization of FIA systems for the determination of different species (metallic and non-metallic) in micro-samples with rather complex composition. Speciation analysis using surfactant-based organized assemblies would eventually be the field of greatest contributions to the knowledge of biological, environmental and other different kinds of complex samples. All these aspects would be a challenge."

19. Petr Solich (Czech Republic)

"The main interesting aspects I found in flow methods are: easy automation with any expensive instrumentation, reproducibility of the flow system, flexibility of all modes of flow analysis, generally "easy to see-easy to use" instrumentation.

The future trends could include:

1. Development of flexible manifolds for sample preparation.
2. Development of manifolds using various separation techniques (including membrane and column technologies).
3. Flow-manipulation techniques (as SIA, MSFIA) will be more attractive due to their flexibility.
4. To increase the attractiveness for practical application, the (flow) methods have to be as simple as possible for the operator.

The main interesting aspects I found in flow methods are: easy automation with any expensive instrumentation, reproducibility of the flow system, flexibility of all modes of flow analysis, generally "easy to see-easy to use" instrumentation."

20. Miroslav Polášek (Czech Republic)

"My interest in FIA was initiated in the early years of my professional career at the Faculty of Pharmacy, Charles University (which is still my alma mater and employer) in Hradec Kralove in the beginning of 1980s after reading the early FIA works of Jarda Ruzicka and and Elo Hansen
Surely the development of FIA and SIA led to the introduction of chemiluminescence methods in analytical practice. In my opinion, the future of automated FIA/SIA is in their application in on-line process control, on-site monitoring of pollutants in environmental analysis and analytical screening in, *e.g.*, pharmaceutical and biomedical research."

21. Spas D. Kolev (Australia)

". . . . . ..my supervisor, Prof. Ernö Pungor, asked me to suggest an analytical project I'd like to work on. . . . . ..
FIA was still an emerging technique, and I was fascinated by the possibilities it opened to chemical analysis and by its strong

similarities to chemical reactor systems I was already familiar with.

I expect exciting future developments in the areas of:

- Low cost miniaturized (*e.g.*, lab-on-chip) and disposable (*e.g.*, paper-based micro fluidic systems) flow analyzers for environmental and clinical applications.
- Flow systems utilizing both chromatographic and non-chromatographic separation coupled with sophisticated detection techniques (*e.g.*, mass spectrometry).
- Applications of flow analysis in scientific research."

22. Marek Trojanowicz (Poland)

". . ..In 1980 in my school at University of Warsaw, after study visit to Ruzicka and Hansen's lab in Copenhagen. . ..
Fabrication of various modules in lab, and also playing with transient signals.

Definitely two directions in the coming future:

- miniaturization to microfluidic formats of the same dimensions as common capillary electrophoretic chips, to employ this as truly portable devices,
- designing flow systems as accessories hooked up to large instrumentation to provide a well mechanized sample processing."

23. Ian D McKelvie (Australia)

". . .. . .My interest in FIA was triggered by a Talanta paper by Shoji Motomizu in 1983 on phosphate analysis using the Malachite Green method. My colleagues and I were studying phosphorus cycling in mountain streams, and we needed a sensitive phosphate method that was cheaper, faster and more portable than the IC techniques that we were using at the time. So we tried FIA. . .

. . .. . .What still endears FIA to me, is the ability to do fast, sensitive and precise environmental analyses, *e.g.*, at sea, using relatively simple, low cost instruments. . ..
. . .We have only scratched the surface in our application of FIA to autonomous environmental monitoring, and in my view, it is here that flow techniques still show greatest promise."

24. Kate Grudpan (Thailand)

". . .No experience until nearly the end of PhD study under Dr Colin Taylor in Liverpool, by support of the British Council for a visit (1980) to Prof Betteridge's FIA lab in Swansea. Various ideas in cost effective FIA set-ups were created. This line of research is very useful where budget is limited. In 1986, I had the chance to start collaboration with Ian McKelvie, still in the line of cost effective approach. In 1990, during Alexander von Humboldt Foundation Fellowship at (Nuclear) Karlsruhe Research Center in Germany, FIA for radioactivity was investigated. In 1996, a visit to the University of Washington, under support from the International Atomic Energy Agency (IAEA), was the first opportunity to meet Gary Christian and Jarda Růžička. Researches in flow-based analysis in Thailand have been increasing since, with the direct and indirect support of Gary Christian. Close collaboration has been established with Japanese Association for Flow Injection Analysis (especially with Shoji Motomizu and Tadao Sakai). All of the abovementioned concern "cost effective" approaches.
Recently, the THAI Association for Flow-based Analysis has been established.
The development of cost effective analysis flow techniques for telehealth, clinical and environmental analysis is a major future challenge, and as part of this, utilisation of natural reagents should be further explored."