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Invited Review Article

Reflections on the origin and evolution of flow injection analysis

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Abstract

Flow analysis methodologies began in the 1950s. Flow injection methodologies originated in the 1970s. This review focuses on FIA related developments.

Early injection analysis reports included the Nagy, Feher, and Pungor system in which they injected an electroactive sample into an electrolyte stream, and used a magnetic stirrer to ensure complete mixing. White and Fitzgerald injected a sample over a 20 sec. period into a carrier reagent stream. Sarbeck, St. John, and Winefordner injected a microsample into a carrier stream for introduction into atomic spectrometers. Bergmeyer and Hagen injected samples into a circulating enzymatic reagent stream, obtaining step signals. Stewart, Beecher, and Hare injected discrete samples into a carrier stream, using a long mixing coil to ensure complete chemical reaction. Ruzicka and Hansen injected samples into a rapidly flowing carrier stream, without the need for steady-state reaction/reading, being characterized by controlled dispersion and reproducible timing. They termed this Flow Injection Analysis. New generations include sequential injection analysis and lab-on-valve.

Japanese researchers were early adopters of FIA technology, and formed the Japanese Association for Flow Injection Analysis (JAFIA) and the Journal of Flow Injection Analysis (JFIA).

Two conferences are devoted to flow analysis methodologies: the International Conference on Flow Analysis (FA) and the International Conference on Flow Injection Analysis (ICFIA).

These developments are reviewed in detail.

Keywords: flow analysis, flow injection analysis, Japanese contributions, flow analysis conferences

1. Introduction

Flow analysis techniques and methodologies were developed over several decades. They have evolved into useful routine methods, with different techniques. The technique of flow injection analysis (FIA) and related techniques originated in the 1970s and have had a major impact on analytical science. This review will focus on its evolution.

A number of comprehensive reviews and perspectives of FIA have been published over the years, and the reader is referred to them for more details and additional historical records.

Kent Stewart. in 1981, offered his perspective of the development of FIA in "Flow-injection analysis: A review of its early history (Stewart, 1981). The review traces the development of flow-injection analysis, and seeks to establish the various lines of research which led to the present form of the technique.

Elo Hansen, in 1995, traced how the technique matured over twenty years in "Flow-injection analysis: leaving its teen-years and maturing. A personal reminiscence of its conception and early development" (Hansen, 1995). The conception and early development of FIA is recounted, and FIA is placed into context with contemporary procedures for automatic analysis. Possible (and impossible) explanations for the ready acceptance of FIA as an analytical tool for executing chemical assays are discussed. He writes that "without fully appreciating the real significance of our experiments, we nevertheless wrote our first FIA patent application in 1974 and followed our first scientific publication in 1975".

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Elo provided a more recent review of progress in "Flow-injection analysis: Its origin and progress" (Hansen, 2008).

Grudpan, *et al.* solicited reflections on FIA development from two dozen prominent researchers in "How did flow injection analysis, and its related techniques, develop in various parts of the globe?" Reflections of prominent FIA practitioners (Grudpan, Christian, & McKelvie, 2011).

2. Early Flow Analysis Developments

The classic example of a commercially successful flow analysis instrument is the segmented flow analyzer developed by Skeggs in 1957, reported in "An automatic method for colorimetric analysis" (Skeggs, 1957). It allowed multichannel measurements of several analytes, and became widely used for automated clinical chemistry laboratory analyses.

Pioneers such as Walter Blaedel from the University of Wisconsin in the 1960s merged flowing streams of sample and reagent to produce a product that could be detected downstream, in "Automated application of the continuous measurement of reaction rate (Blaedel & Hicks, 1962). The apparatus is illustrated in Figure 1.

Horatio Matolla provided an analysis of continuous flow methods in "Continuous flow analysis revisited" (Matolla, 1981).

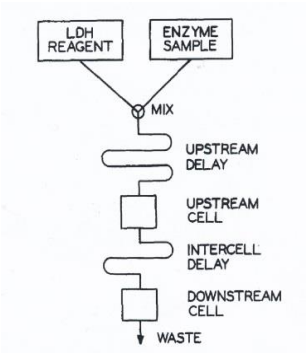

Figure 1. Outline of continuous method for LDH. (From Blaedel, 1962)

3. Beginnings and Early Evolution of FIA

Perhaps the first example of an injection analysis system for rapid serial analysis of electroactive substances was reported in 1970 by Nagy, Feher, and Pungor in "Application of silicone rubber measurements. Part II. Voltammetric study of active substances injected into electrolyte streams" (Nagy, Feher, & Pungor, 1970). Their apparatus is illustrated in Figure 2. They injected 0.1 ml of an electroactive sample into a stream of flowing supporting electrolyte with a Hamilton syringe through rubber tubing. A magnetic stirrer was used to ensure reproducibility of the measurement, which resulted in a drawn out peak. There was no chemical reaction

White and Fitzgerald provided a means to introduce a sample into a carrier stream of reagent in "Continuous determination of ascorbic acid by photobleaching of methylene blue, submitted in 1971 and published in 1972

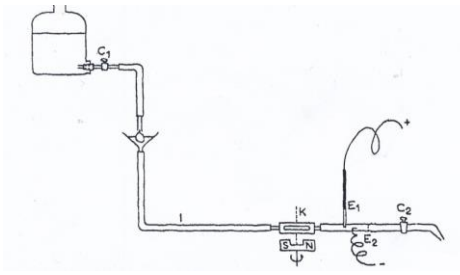

Figure 2. Experimental apparatus of Nagy *et al.* (From Nagy, 1970).

(White & Fitzgerald, 1972). They injected a 1 ml. volume of sample over 20 sec. into the carrier stream of reagent. Their apparatus is shown in Figure 3.

Perhaps the first example of injection of a discrete microsample into a carrier stream was reported by Sarbeck, St. John, and Winefordner in "Measurement of microsamples in atomic emission and atomic fluorescence flame spectrometry" (Sarbeck, St. John, & Winefordner, 1972). It was submitted in 1971 and published in 1972. Their apparatus is illustrated in Figure 4. A microsample was injected with a microsyringe into a rubber septum into a carrier stream that carried it to an atomic spectrometry detector. Again, there was no chemical reaction.

Bergmeyer and Hagen published "Ein neues prinzip enzymatischer analyse" in 1972 (Bergmeyer & Hagen, 1972). A buffer solution containing an enzyme was pumped continuously and the samples were fed into the circuit, accurately dosed by a novel applicator, see Figure 5. Glucose was measured at a rate of 60 samples/hr, using an oxygen sensor in the loop. Step signals were obtained.

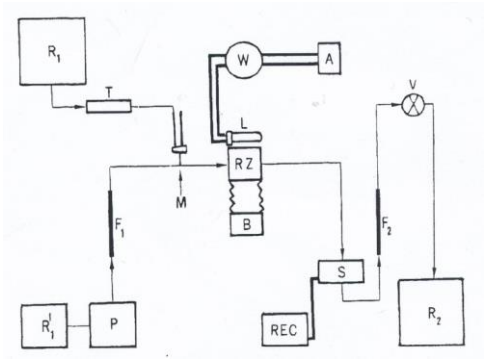

Figure 3. Diagram of apparatus of White and Fitzgerald. R = reservoirs, P = pump, RZ = reaction zone, S = spectrometer. (From White, 1972).

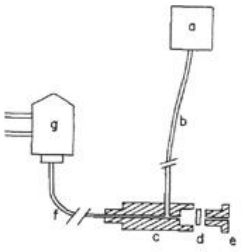

Figure 4. Discrete microsampling apparatus of Sarbeck, *et al.* a =liquid carrier reservoir, e = injection port septum. (From Sarbeck, 1972).

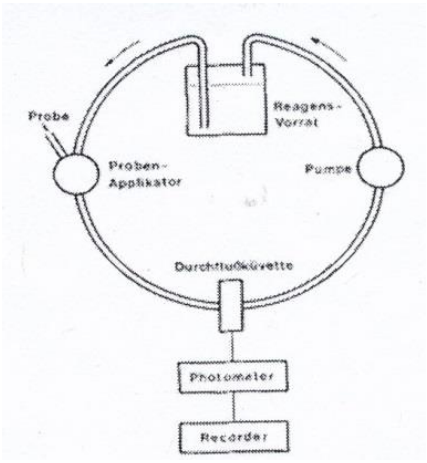

Figure 5. Continuous pumping system of Bergmeyer and Hagan. (From Bermeyer, 1972).

Stewart, Beecher, and Hare published "Rapid analysis of discrete samples: The use of nonsegmented, continuous flow", submitted January 22, 1975 and accepted August 9 (Stewart, Beecher, & Hare, 1976). Their apparatus is shown in Figure 6. The discrete sample was introduced via a stream sampling valve. A long mixing coil (8-10 meters) was used to ensure complete chemical reaction**.** Sampling rates of 120/hr were demonstrated, with peak signals. They applied for a U.S**.** patent, based on automation.

Ruzicka and Hansen published the first of a series of reports of the technique they termed Flow Injection Analysis in "Flow Injection Analyses. Part I. A new concept of fast continuous flow analysis", submitted February 10, 1975 (Ruzicka & Hansen, 1975). It was preceded by Danish Patent Appl. No. 4846/74, Sept. 1974, followed by a U.S. patent. They injected a 0.5 mL volume of sample with a 1 mL syringe through a silicone rubber septum, in a rapidly flowing carrier stream of 18 mL/min, see Figure 7. Their system was characterized by injection, controlled dispersion, and reproducible timing, with no need for steady-state reaction/reading. They demonstrated sampling rates of 120/hr for the determination of phosphate by the molybdenum blue method**.** They provided a theoretical analysis of the development of the FIA peak.

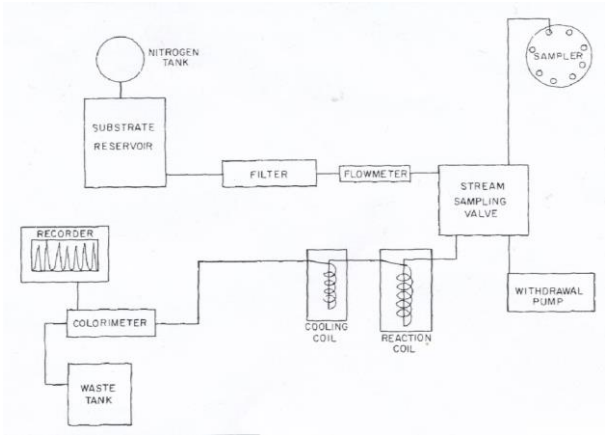

Figure 6. Discrete sample analyzer of Stewart, *et al.* (From Stewart, 1976).

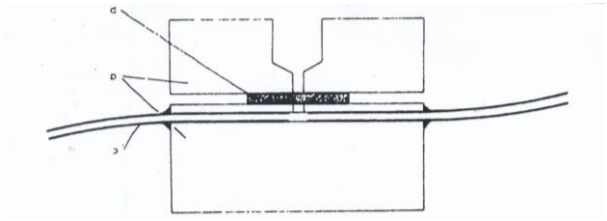

Figure 7. Sampling system of Ruzicka and Hansen. (From Ruzicka, 1975).

A summary of these early developments of FIA related techniques, their characteristics and their time history, is giving in Table 1.

Table 1. Summary of early FIA related techniques, their characteristics and timeline.

	Timeline	Characteristics
Nagy, Feher, and Pungor	April 20, 1970	Stirrer
White and Fitzgerald	April 14, 1971	1 mL injection over 20 seconds
Sarbeck, St. John, and Winefordner	May 13, 1971	Microliter injection, atomic spectroscopy. No reagent.
Bergmeyer and Hagen	June 10, 1972	Emphasized immobilized enzyme. Step signal increase.
Stewart, Beecher, and Hare	January 22, 1975	Long reaction coil, complete reaction U.S. patent applied for, mainly based on automation
Ruzicka and Hansen	February 10, 1975	Controlled dispersion, reproducible timing Dan. Patent Appl. No. 4846/74, Sept. 1974 Subsequent U.S. Patent No. 4,022.525

4. Establishing the FIA Technique

Following the first report of FIA, Ruzicka and coworkers published a series of ten papers over the period 1975-1978 on different applications and theory. They were all published in Analytica Chimica Acta as Parts 1-X, with the assistance of ACA Editor-in-Chief, Alison McDonald. The list of their papers is given in Table 2.

Much of the pioneering work on development of FIA as a routine method was done in Brazil when Ruzicka and Hansen spent over a year there. Papers 3, 4, and 7 were coauthored with Brazilian pioneers H. Bergamin-Filho and E. A. G. Zagatto. Hansen and Ruzicka reflected on this in "FIA is already a routine tool in Brazil (Hansen & Ruzicka, 1983).

In subsequent years, there have been over 24,000 publications on FIA related techniques, providing variants on instrument design and numerous applications. Elo Hansen maintains a complete list of FIA related publications in his website: http://www.flowinjectiontutorial.com/Database.html. It can be downloaded from Jarda Ruzicka's tutorial: http://www.flowinjectiontutorial.com/. The tutorial has a wealth of information, from the FIA story to theory, and methods.

Table 2. Ruzicka and coworkers sequence of FIA papers establishing the technique.

No.	Papers
1	J. Ruzicka, & E. H. Hansen. (1975). Flow injection analyses. Part I. A new concept of fast continuous flow analyses. *Analytica Chimica Acta, 78,* 145.
2	J. Ruzicka, & J. W. B. Stewart. (1975). Flow injection analysis. Part II. Ultrafast determination of phosphorus in plant material by continuous flow spectrophotometry. *Analytica Chimica Acta, 79*, 79.
3	J. W. B. Stewart, J. Ruzicka, H. Bergamin-Filho, & E. A. G. Zagatto. (1976). Flow injection analysis. Part III. Comparison of continuous flow spectrophotometry and potentiomety for the rapid determination of total nitrogen content in plant digests. *Analytica Chimica Acta, 81,* 371.
4	J. Ruzicka, J. W. B. Stewart, & E.A.G. Zagatto. (1976). Flow injection analysis. Part IV. Stream sample splitting and its application to the continuous spectrophotometric determination of chloride in brackish waters. *Analytica Chimica Acta, 81,* 387.
5	J. W. B. Stewart, & J. Ruzicka. (1976). Flow injection analysis. Part V. Simultaneous determination of nitrogen and phosphorus in acid digests of plant material with a single spectrophotometer. *Analytica Chimica Acta, 82,* 137.
6	J. Ruzicka, & E. H. Hansen. (1976). Flow injection analysis. Part VI. The determination of phosphate and chloride in blood serum by dialysis and sample dilution. *Analytica Chimica Acta, 87,* 353.
7	J. Ruzicka, E. H. Hansen, & E. A. G. Zagatto. (1977). Flow injection analysis. Part VII. Use of ion-selective electrodes for rapid analysis of soil extracts and blood serum. Determination of potassium, sodium and nitrate. *Analytica Chimica Acta, 88,* 1.
8	E. H. Hansen, J. Ruzicka, & B. Rietz. (1977). Flow injection analysis. Part VIII. Determination of glucose in blood serum with glucose dehydrogenase, *Analytica Chimica Acta, 89,* 241.
9	J. Ruzicka, E. H. Hansen, & H. Mosbaek. (1977). Flow injection analysis. Part IX. A new approach to continuous flow titrations. *Analytica Chimica Acta, 92,* 235.
10	J. Ruzicka, & E. H. Hansen. (1978). Flow injection analysis. Part X. Theory, techniques and trends. *Analytica Chimica Acta, 99,* 37.

5. Modifications of FIA

There have been numerous second and third generations of variants of flow injection analysis, dealing with instrument variations, sample handling, miniaturization, and so forth. A few that have been fairly widely adopted are described here.

Ruzicka and Marshall developed a new system for more efficient use of reagents in "Sequential injection: A new concept for chemical sensors, process analysis and laboratory assays (Ruzicka & Marshall, 1990). The concept is illustrated in Figure 8. A multiposition valve is used to sequentially aspirate sample and reagent into a holding coil. Then the flow is reversed to propel the two zones to a detector while they overlap and react. This avoids the monotonous continuous flow in conventional FIA, minimizing reagent consumption and waste. This has become a widely adopted methodology.

Ruzicka developed a precise monolithic structure mounted atop a multiposition valve to perform all the FIA operations in "Lab-on-valve: universal microflow analyzer based on sequential and bead injection (Ruzicka, 2000). The lab-on-valve is shown in Figure 9. The system downsizes reagent based assays to micro- and submicroliter levels. It is demonstrated that sample handling in the sequential injection mode can be programmed to accommodate a wide variety of assays in the same microfluidic device. Solution metering, mixing, dilution, incubation, and monitoring can be executed in any desired sequence in a system of channels, integrated with a multiposition flow cell.

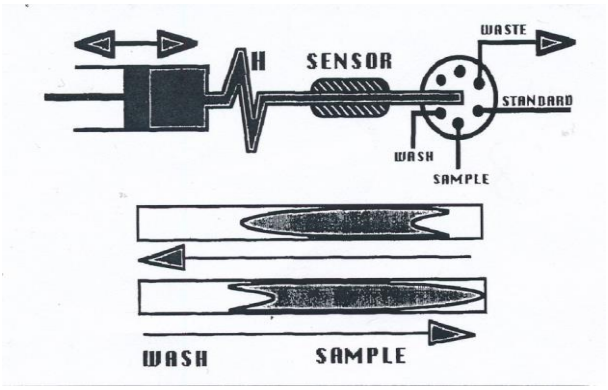

Figure 8. Concept of sequential injection analysis of Ruzicka and Marshall. (From Ruzicka, 1990).

Jakmunee, *et al.* developed a related lab-at-valve system in "Sequential injection with lab-at-valve (LAV) approach for potentiometric determination of chloride" (Jakmunee, Patimapornlert, Suteerapataranon, Lenghor, & Grudpan, 2005). In the apparatus shown in Figure 10, sample processing and detection units are attached or plugged into ports of a multiposition selection valve.

6. The Japanese Connection

Japanese researchers became early adopters of FIA and published some of the first papers. Professor Nobohiko Ishibashi from Kyushu University was a driving force and published the first paper in 1978, "Ultramicro solvent extraction and fluorimetry based on the flow injection method" (Kina, Shiraishi, & Ishibashi, 1978).

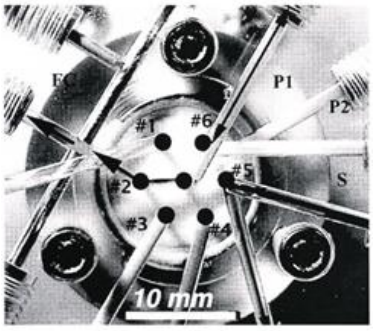

Figure 9. Lab-on-valve of Ruzicka. (From Ruzicka, 2000).

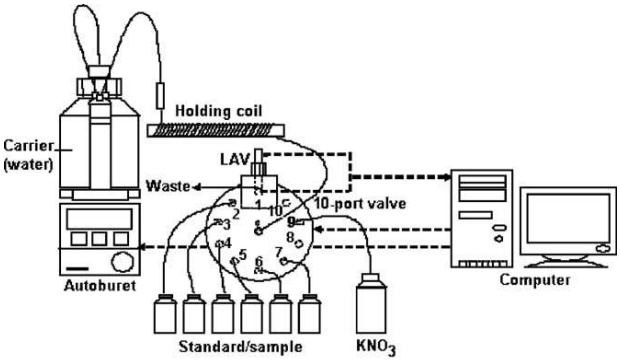

Figure 10. Lab-at-valve system of Jakmunee *et al.* (From Jakmunee, 2005).

A historical account of early Japanese contributions and activities is given in Table 3. As the FIA technique gained popularity, Professors Ishibashi and Norimasa Yoza in 1983 translated Ruzicka and Hansen's 1981 book "Flow Injection Analysis" into Japanese to further promote the technique in Japan.

The widespread adoption of FIA in Japan led to the establishment of the Japanese Association for Flow Injection Analysis (JAFIA) in 1984, with some 200 Japanese FIA researchers. The Journal of Flow Injection Analysis (JFIA) was started at the same time. Professor Ishibashi was the inaugural President of JAFIA, and the first editor of JFIA. Then in 1987, Rokuro Kuroda, Koichi Oguma, and Hiroshi Nakamura published a Japanese monograph on FIA, フローインジェクション分析法 ("Flow injection analysis method").

Table 3. Historical Japanese contributions.

Year	Contributions
1978	Dr. Kina, Shiraishi and Prof. Ishibashi reported "Ultramicro solvent extraction and fluorimetry based on the flow injection method" in Talanta, Vol.26, 295.
1983	Prof. Ishibashi and Dr. Yoza translated "Flow Injection Analysis" by Profs. Ruzicka and Hansen into Japanese.
1987	Prof. Kuroda, Drs. Nakamura, Oguma, published a Japanese monograph on FIA.
1984	JAFIA was founded and JFIA, Vol.1, No.1 was published.
1991	Flow Analysis V was held in Kumamoto.
1995	JAFIA semi-annual meeting joined to ICFIA (August, Seattle, Washington)

Several Japanese leaders of FIA have served as President of JAFIA:

1984-1991	Prof. Nokuhiko Ishibashi (Kyushu University)
1991-1993	Prof. Yosuke Ohkura (Kyushu University)
1994 -2004	Prof. Shoji Motomizu (Okayama University)
2005-2011	Prof. Tadao Sakai (Aichi Institute of Technology)
2012-2017	Prof. Toshihiko Imato (Kyushu University)
2018-	Prof. Norio Teshima (Aichi Institute of Technology)

The editors of JFIA include:

1984-1991	Prof. Nokuhiko Ishibashi (Kyushu University)
1992-1995	Prof. Hiroko Wada (Nagoya Institute of Technology)
1996-1997	Prof. Takuji Kawashima (Tsukuba University)
1998-2004	Prof. Tadao Sakai (Aichi Institute of Technology)
2005-2011	Prof. Toshihiko Imato (Kyushu University)
2012-2016	Prof. Tsutomu Nagaoka (Osaka Prefecture University)
2017-	Prof. Hideji Tanaka (Tokushima University)

7. The Thai Connection

Thailand early on embraced flow injection analysis. Professor Kate Grudpan from Chiang Mai University has been key in training numerous researchers in the field, and many are practicing in several universities. Example centers are Mahidol University (Assoc. Prof. Dr. Duangjai Nacapricha), Chulalongkorn University (Prof. Dr. Orawon Chailapakul), Prince of Songkla Universtiy (Assoc. Prof. Dr. Proespichaya Kanatharana), and Khon Kaen University (Assoc. Prof. Rodjana Burakham). Professor Jaroon Jakmunee, a former Grudpan student, is a leader at Chiang Mai University.

8. History of Flow Analysis Conferences

Two main conferences devoted to flow analysis techniques are the International Conference on Flow Analysis (FA), and the International Conference on Flow Injection Analysis (ICFIA). A historical account of these two conferences up to 2009 is chronicled in the report by Christian (Christian, 2009). A summary of the FA conferences, their topics, and their hosts is given in Table 4. The first FA conference was held in Amsterdam in September 1979, with the theme FIA theory and sample dispersion. Papers from the conference are traditionally submitted for a special issue of Analytica Chimica Acta.

The ICFIA conference started out as the Winter Conference on Flow Injection Analysis (WCFIA), organized by Jarda Ruzicka, Gil Pacey, and Gary Christian, first held in Orlando, Florida in 1989. The two conferences are complimentary and generally held every two to three years to avoid overlap. As WCFIA matured, it attracted numerous international participants, particularly from JAFIA members. There are regular participants from other countries such as Thailand, Spain, and Portugal. In 1995, JAFIA joined with WCFIA for their semi-annual meeting, and it became the International Conference on Flow Injection Analysis.

A history of the ICFIA conferences is given in Table 5. Sue and Gary Christian hosted it for several years in the U.S., then beginning in 1999 volunteers from around the world arranged and hosted the conference, now a truly international conference. Special issues of Talanta published submissions from the conference beginning with ICFIA VII in 1995. Reports of the conference have been published beginning with ICFIA IV in 1992, some early ones in TrAC,

Table 4. Historical summary of International Conference on Flow Analysis (FA).

No.	International conference
1	September 11–13, 1979 Amsterdam Gerrit den Boef, Willem van der Linden. B. Griepink FIA Theory of sample dispersion
2	June 18–21, 1982 Lund Folke Ingman, Gillis Johannson FIA applications
3	September 5–8, 1985 Birmingham James Miller, Allison McDonald Segmented flow analysis
4	April 17–20, 1988 Las Vegas Gilbert Pacey Alison McDonald elected "Flow Injection Queen"
5	August 21–24, 1991 Kumamoto Nobuhiko Ishibashi Ishibashi died during conference Helicopter rides
6	June 8–11, 1994 Toledo Miguel Valcarcel, M. D. (Lola) Luque de Castro Innovative techniques & applications, nomenclature, History FIA Elo Hansen
7	August 25–28, 1997 Piracicaba Henrique Bergamin Filho, Elias A.G. Zagatto Dedicated to Bergamin who died December, 1996 FA in education roundtable
8	June 25–29, 2000 Warsaw Marek Trojanowicz Inclusive of flow varieties: sequential and flow injection analysis, segmented flow
9	February 17–21, 2003 Geelong Ian McKelvie. Daryl Tucker, Neil Barnett 14 Plenary & invited lectures on a variety of techniques, applications, & fundamental studies
10	September 3–8, 2006 Porto José Luis F.C. Lima Two sessions dedicated to pioneers Nobuhiko Ishibashi & Henrique Bergamin Filho
11	September 14–18, 2009 Mallorca Victor Cerdà
12	September, 2012, Thessalonia Aristidis Anthemides
13	July 5-10, 2015, Prague Petr Solich
14	December 2-7, 2018, Bangkok, Duangai Nacapricha

but most in JFIA. A detailed list of special issues and reports through 2014 is given in reference 20 (Christian, 2014).

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Table 5. History of ICFIA conferences

ICFIA	City	Year	Oral	Posters	Total	Attender	Exhibitors
1	Orlando	1989	21	3	24	-	3
2	Orlando	1990	22	0	22	-	-
3	Scottsdale	1991	28	0	28	46	-
4	Scottsdale	1992	23	14	37	49	4
5	Banana Bay	1993	37	6	43	60	5
6	San Diego	1994	21	3	24	52	6
7	Seattle	1995	40	27	67	77	7
8	Orlando	1997	32	21	53	64	5
9	Seattle	1998	38	25	73	69	5
10	Prague	1999	37	70	107	110	3
11	Chiang Mai	2001	36	72	108	124	-
12	Merida	2003	43	64	107	123	-
13	Las Vegas	2005	54	76	130	117	2
14	Berlin	2007	43	108	151	116	5
15	Nagoya	2008	44	121	165	188	6
16	Pattaya	2011	46	142	188	189	6
17	Krakow	2013	54	74	128	140	7
18	Porto	2014	45	115	160	140	4
19	Fukuoka	2015	69	108	177	198	22
20	Mallorca	2016	71	87	158	143	5
21	St. Petersburg	2017	61	59	120	116	4
22	Marseille	2020	-	-	-	-	-

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