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Flow Analysis as Advanced Branch of Flow Chemistry

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Abstract

The effectiveness of the carrying out chemical reactions, especially in terms of syntheses conducted in the laboratory or on a technological scale, is a primary target of the optimization of chemical conditions and physico-chemical parameters of a given process. Since the publication of pioneering works in the beginning of 1970s, it is an increasingly accepted concept that carrying out chemical reactions in continuously flowing streams rather than in batch configuration has numerous advantages, hence flow chemistry can be at present considered as a separate and rapidly increasing area of modern chemistry. Four decades of the development of those methods resulted in thousands of original research works, numerous reported attractive technologies, and also in the presence of numerous specialized instruments on the market.

Keywords: Flow analysis; Analytical determinations; Modern chemistry

Introduction

The vast literature and numerous reported successful applications, demonstrate numerous advantages of flow chemistry in chemical synthesis compared to batch processes. It is first of all a convenient way to ensure precise control of the reaction time, fast carrying out mixing reagents, easy handling solutions containing gases and a simplification of carrying out multi-phase liquid reactions [1,2]. Reactions can be carried out in higher temperature than the solvent's boiling point, and especially convenient is the possibility of arranging systems for multi step reactions, including also application of on-line purification of products. All those aspects are subjects of numerous review papers in recent years, discussing e.g. carrying-out multistep syntheses [3], micro flow reactors [4], or microstructured reactors [5]. An increasing attention in recent years is focused also on the application of microfluidic systems in flow chemistry [6,7], including supercritical microfluidics [8]. The application of flow technologies was reported also for drug discovery [9].

Observed in recent decades is that the increasing need for chemical analyses in all areas of contemporary life is accompanied both by increasing knowledge of the role of chemical analysis in quality control of various materials, clinical diagnostics and environmental protection, and the need for developing instruments for direct use by the end-users of analytical information. These demands are associated also with need for the improvement of quality (accuracy, precision) of analytical determinations. Depending on the area of application, a challenging task in development of new methods can be the shortening time of analysis, minimization of sample amount required for analysis, determining the lowest limit of detection, or simultaneous determination of large number of analytes.

Progress in development of new methods of chemical analysis is taking place on different routes and depends on numerous factors. It depends essentially on developments in fundamentals of natural sciences, material science, electronics and information science, as well as various fields of technology of the production of new materials and instruments for chemical analysis. Human invention both in science and technology is truly unlimited; hence any stage of development should not be considered as definitive. It also obviously concerns the development of analytical chemistry and its methods and instruments for chemical analysis.

Almost two decades prior to the publication of first applications of carrying-out physico-chemical operations in flow conditions for the chemical synthesis, the first instrumental set-ups were developed for analytical determinations. Flow analysis is nowadays a very important area of modern analytical chemistry and can be considered as the important part of flow chemistry. The retrospection on the development of flow methods of chemical analysis and its progress in recent years is the subject of this review.

Beginning –continuous Flow Analysis

Carrying on the chemical analytical procedure in flow conditions at first glance can be considered as a simplification of given procedure by elimination the stage of sampling of analyzed material. Such aspect can be seemingly traced back to 1940s in the area of chemical analysis, which is currently considered a process analysis, where in technological streams certain measurements were pioneered, for instance electrolytic conductivity. Then in the following decades together with development of various detection methods and measuring instruments for the same purpose the measurements of redox potential, pH, turbidity or spectrophotometric absorbance of radiation were also introduced. This area of chemical analysis is nowadays a very reach in different process instrumentation, of which quite substantial part can be classified as flow analyzers.

Another field of application of analytical flow measurements is laboratory flow analysis. It has its own conditions of use and design and is employed in essentially different environments than process analysis. In this case, it is a much simpler task to indicate milestones in development of main concepts of such analytical measurements, well documented in scientific literature and registered patents. The main attributes of laboratory flow analysis is carrying sample processing operations in flow conditions as well as carrying detection of given analyte(s) during the flow of sample through the detector. Pioneering invention of laboratory flow measurements and design of original modules for such instrumentation in the middle of 1950's is commonly arrogated to American biochemist Skeggs [10], who by design of such instruments intended to enhance effectiveness of clinical laboratories in large hospitals. The next decades showed that

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it was a very appropriate intuition, and the concept of continuous flow analyzers had been immediately patented and opened a perspective for essential progress in analytical clinical instrumentation [11]. The concept of conducting detection in flowing stream was already known earlier from the column liquid chromatography. The carrying the determination with segmentation of the solution stream allowed the limitation of dispersion of the analyte in flowing stream (hence coined name "*segmented flow analysis*") (Figure 1A). Such designs of analytical instruments allowed unusual mechanization of various unit operations of sample processing, such as two-phase separations and mixing with different reagents or dialysis; this was the most essential breakthrough in laboratory analysis. For next two decades this concept predominated instrumentation in large (and reach) clinical laboratories with development of numerous analytical methods and instrumental modules [12]. Since 1980's a strongly competitive other types of instrumentation like centrifugal analyzers, or discrete analyzers received a larger attention in clinical analysis, but segmented flow analyzers are still widely used in environmental, industrial and food quality laboratories [13]. The example of commercial instrument available on the market is shown in Figure 1B. The concept of segmentation of flowing stream surprisingly found recently several completely new applications such as use in parallel electrophoretic analysis on chip for high-throughput determination of enzyme activities [14], or detection of bacteria and their sensitivity to antibiotics [15].

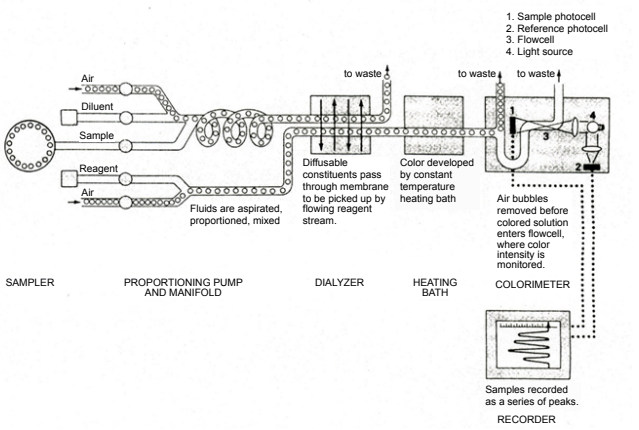

Figure 1a: The schematic diagram of a measuring system with segmented flow for continuous-flow analysis with photometric detection.

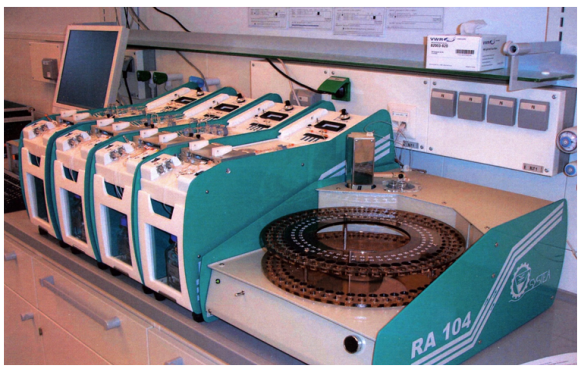

Figure 1b: The example of multichannel commercial instruments FlowSys from Alliance Instruments, Salzburg, Austria for continuous-flow analysis with segmented stream (http://www.alliance-instruments.at).

Injection Methods of Flow Analysis

A particular impetus to further development of laboratory flow analysis was given in early 1970's by pioneering the concept of flow-injection measurements without segmentation of flowing stream with air bubbles, and injection of a small segment of analyzed sample (20-100 μL) to the continuously flowing carrier solution instead of aspiration usually 0.2 to 2 mL solution in segmented flow systems [16,17]. The steady-state equilibrium signal which is recorded in segmented flow systems, in flow-injection analysis (FIA) is replaced mainly by transient signal in the shape of peak, and it can be utilized with satisfactory precision in determinations with different detections. Such measurements can be carried out with special dedicated, often laboratory-made instrumentation, but can be also performed using commercial instrumentation for liquid chromatography [18]. In comparison to conventional liquid chromatography of which the main attribute is multicomponent determination is eliminated, the selectivity of FIA determination of a particular analyte (or analytes) can be obtained by ensuring specific sample processing or selective detection. Since late 1970's, one can observe almost exponential increase of interest in this methodology of analytical measurements by rapid increase of research publications [19]. This methodology has been a subject of about 15 books and two recent ones [20,21]. Several manufacturers supply dedicated instrumentation to the market; however, more often research studies are carried out with the use of laboratory-made set-ups constructed from commercially available basic instruments and modules. FIA methods have been also widely introduced to international standard methods of analysis [22].

In development of various methodologies of FIA measurements several elements are especially important for their successful routine applications. A significant advantages, which has not been sufficiently utilized in development of flow-injection methods is the possibility of getting some effects of kinetic discrimination in recording of a fast transient signal. This was reported in FIA measurements with potentiometric detection with membrane ion-selective electrodes [23]. Such effect can be also utilized for the elimination of interferences of transition metal ions in FIA determinations with hydride generation-AAS measurements [24]. Application of FIA manifolds can also facilitate calibration procedures [25]. In order to widen the potential applications of FIA measurements some attention is also focused on development systems for simultaneous determination of several analytes without typical column chromatographic or electromigration-based separation steps. This is mostly made by a design of branched FIA systems with a single detector, or multi-detector systems, and also systems functioning in multicomponent detection modes. In the last case, they can be voltammetric detectors with fast scan-rate, the diode-array detectors with simultaneous measurements at different wavelengths, or atomic emission ICP-AES detectors. In these systems, the flow-injection configuration is used for a convenient sample introduction step, and eventual on-line sample processing on the way to the detector.

The on-line sample processing can be considered the most attractive feature of all concepts of carrying analytical determinations in flow systems, because in the majority of analytical procedures the sample processing is the most time consuming and difficult step. The most commonly performed on-line operations include preconcentration or separation of analyte from the matrix in flow-through reactors with solid sorbents, in open-tubular reactors or in membrane modules [24]. This is widely employed in hyphenation of FIA systems with atomic spectroscopy instruments [26], gas [27] and liquid [28] chromatography, or capillary electrophoresis [29]. Large attention is focused on development of FIA systems with flow-through reactors

with immobilized enzymes, antibodies, and various nanoparticles [30], but also with flow-through packed-reactors allowing the carrying on other heterogeneous reactions on-line without pumping continuously solutions. The generating of reagents in FIA systems can be also made using electrodialysis [31]. Another concept of limitation of the large consumption of reagents is design of closed-loop FIA systems with circulation and eventual regeneration of liquid reagents [32,33].

Flow-injection methods are being widely developed for speciation analysis [34,35]. The FIA set-up can be employed as additional accessory in complex hyphenated instruments or instruments with single detector allowing simultaneous determination of different forms of elements (HPLC, CE), mostly for improvement of different sample pretreatment operations. The especially challenging attempt, however, is to design a measuring system with a single detector in configuration that allow for determinating the different forms of the target element. In original scientific literature one can find numerous smart concepts and design of such measuring flow injection systems with electrochemical [36] or spectroscopic [37] detections. They allow performing both speciation analysis of different oxidation states and determining free elements in ionic forms employing potentiometric detection and determining different compounds in which target element is bound. The example FIA system developed for determination of free fluoride and fluoride bound in complexes with metal ions is shown schematically in Figure 2, while for simultaneous determination of nitrogen containing species in waters in Figure 3.

As some application of flow-injection methodology can be treated developed FIA systems for carrying different types of titrations with spectrophotometric titrations. They can be based on the producing of series of standard solutions for single primary solution and injection into titrant stream, or injection of standard and sample to titrant stream for injection loop of different volume [38,39].

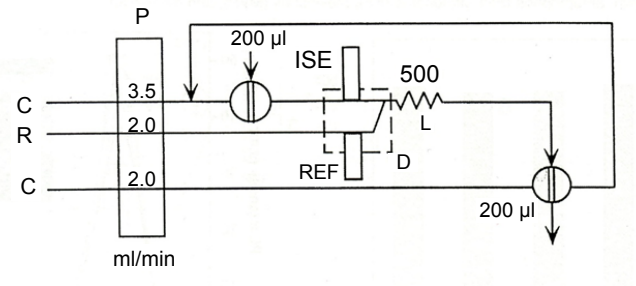

Figure 2: Manifold of FIA system with resampling developed for potentiometric speciation of fluoride [36]: P – peristaltic pump. D – potentiometric flow-through detector with ion-selective electrode, L – mixing coil, W – waste, C – carrier solution, R – reagent solution.

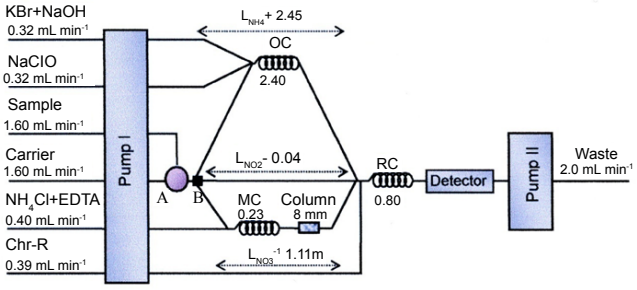

Figure 3: Manifold of FIA system developed for simultaneous determination of nitrite, nitrate, and ammonium [37]. A – injection valve, B – Hoffman key, OC – oxidation coil, RC – reaction coil, MC – mixing coil, Chr-R – chromogenic reagent.

It was reported by several authors that in some cases the hyphenation of FIA and segmented flow systems may essentially expand the application possibilities of FIA technique, for instance for those demanding a long reaction time [40].

Besides numerous advantages of continuous flow systems with segmented streams or FIA systems compared to batch analysis, a troublesome feature of continuous flow systems is a large consumption of reagent solutions, which are continuously pumped during the measurements. Some of reagent solutions can be in certain cases replaced by flow-through reactors with immobilized reagents, but this is not a case for the carrier solutions in both types of systems. Therefore, as significant milestone in the progress of flow analysis, one can consider the development of the concept of sequential injection analysis (SIA) systems [41,42], of which the main attributes were simplification of measuring systems, and essential reduction of the reagent consumption. The SIA systems were a subjects of almost one thousand original papers, some chapters in books [20,21,43], and also reviews on applications with electrochemical [44] and vibrational spectroscopic [45] detections, as well as on some particular applications in chemical speciation analysis [46], water analysis [47], and in process analytical chemistry [48].

In contrary to widely used multi-channel FIA systems, the SIA measurements are usually carried out in single line systems. As accuracy and precision of determinations essentially depends on accuracy of sampling of analyzed sample and reagent solutions into a holding coil, the SIA system has to be equipped with complex and high-precision multiposition valve, the pump with instant and precise changing of the pumping direction, and whole system should be precisely computer programmed and controlled. Some special types of SIA systems are those employing capillary measuring setups with electro osmotic driven flow [49]. SIA measurements are commonly carried out with continuous flow of carrier solution with segments of sample and reagents through the flow-through detector, and analytical signal is typically obtained as the height of recorded peak. Similarly to conventional FIA, the SIA measurements can be also carried out with flow stopped after sample zone has reached the detector cell, which allows kinetic measurements.

The two-analyte determinations can be carried out in SIA systems equipped with two detectors or by introducing the sample segment between zones of different reagents that reacting specifically with each analyte; this was shown for determination of calcium and magnesium in waters [50]. For similar determination in SIA system with diode array spectrophotometric detector the expert system was reported for appropriate configuration of measuring system [51]. The multi-analyte SIA system was also described, based on extraction of analytes with dithizone into a thin layer of extracting solution onto walls of Teflon tubing and simultaneous diode array detection in wavelength range from 300 to 700 nm [52]. The multi-analyte determinations can be obviously made in measuring systems hyphenating the SIA sample processing with liquid chromatography, which was reported for determination of paracetamol, caffeine and acetylsalicylic acid in pharmaceutical preparations [53], and some other such systems were also reviewed [54].

Flow-injection measurements with the application of moveable beads, BIFA (bead-injection flow analysis), which are also described in the literature by abbreviations BI or BIA, where introduced into the SIA methodology twenty years ago [55]. Direct absorptive

spectrophotometric measurements were earlier employed in conventional batch measurements as "ion-exchange absorptiometry" [56]. They were adapted to flow measurements in the form of a renewable optical detector, where detection is based on the use of a small amounts of solid state adsorbent with adsorbed colour forming reagent, and directly for such a bead the absorptive spectrophotometric measurement is carried out [55]. For a convenient performing of such measurements, a special construction of injection valve was introduced, where in appropriate microchannels a sorbent bead can be retained, and for this a name lab-on-valve (LOV) was coined [57,58]. Its design allows the eluting of adsorbed analytes from the retained bed to the detector, as well as transfer of whole sorbent bed with retained analyte to the detector. Example of commercial instrument for FIA and SIA measurements, which employs the concept of lab-on-valve is shown in Figure 4, while manifold for particular determination with on-line preconcentration is shown in Figure 5.

As further step in a simplification of measuring systems for flow analysis can be considered the concept of tube-less flow measurements, which is also described as batch injection analysis (BIA). In this case, a small volume of an analyzed sample in injected directly onto the sensing surface of detector, and the transient analytical signal is recorded during the flushing the sensing surface with the sample solution. The pioneering work on this concept of flow measurements was reported with amperometric detector of a wall-jet type with sensing surface of conventional working electrode positioned up-side down (Figure 6) [59]. This configuration of measuring system, however, seems to create some limitations of essential advantages in typical flow injection methods (CFA, FIA, SIA, BFIA), which is a possibility of carrying on-line different sample processing operations. Some exception is this case can be, for instance, amperometric measurement with enzymes immobilized on the surface of working electrode, which catalyze the conversion of analytes into products, which are detected. Such systems were reported for determination of glucose with carbon paste enzymatic biosensor [59] or with enzymatic biosensors with oxidases immobilized on membranes covering the surface of a platinum working electrode [60]. As another example of BIA measurements combined with sample processing step can be considered anodic stripping voltammetric measurements [61,62]

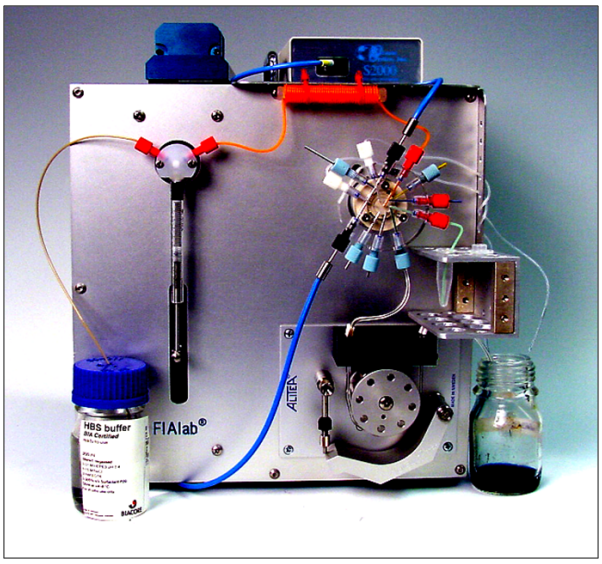

Figure 4: The flow injection commercial analyzer model FIAlb-3500 from FIAlab Instruments, Bellevue, WA, USA equipped with Lab-on-Valve for FIA and SIA determinations (www.floinjection.com).

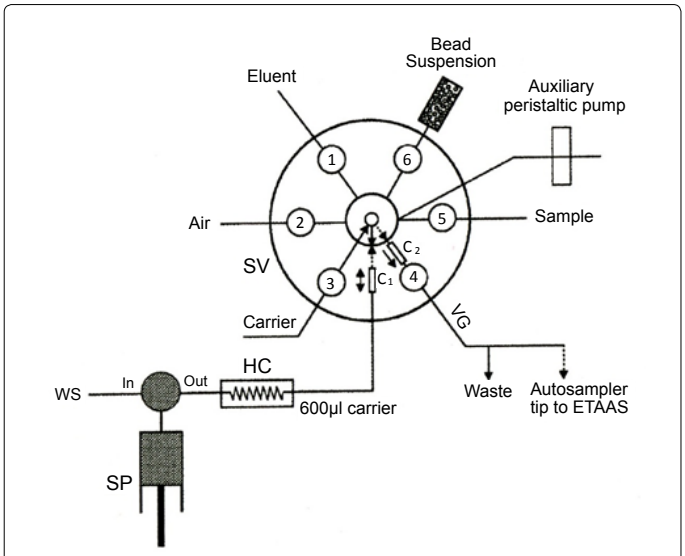

Figure 5: Manifold for sequential bead injection-elution on-line preconcentration developed for measurements with electrothermal atomic absorption spectrometry [58]. SV – six-port selection valve, SP – syringe pump. HC – holding coil, C_1,C_2 – microcolumns.

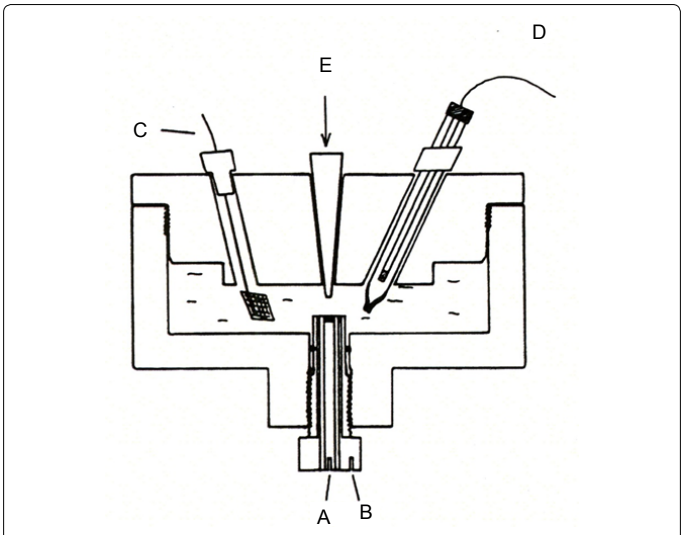

Figure 6: Schematic diagram of cell made of Perspex, and used for batch-injection analysis measurements with amperometric detection [63]. A – disk electrode, B – ring electrode, C – auxiliary electrode, D – reference electrode, E – micropipette tip.

or absorptive stripping voltammetry [63], where two separate steps of whole procedure are involved, namely the accumulation of trace analyte on the working electrode surface and a phase of stripping of analyte with signal recording. The application of an additional ion-exchange Nafion membrane for covering the surface of a mercury film working electrode allows reducing some interferences occurring in measurements with complex matrices [64]. For similar purposes in anodic voltammetric stripping measurements in BIA system, an additional sample clean-up step using small bed a solid sorbent in the pipette tip can be employed [65]. As a similarity of a BIA methodology to other flow injection methods, one can indicate the application of reproducible transport of the segment of injected sample to the sensing surface of a detector. Especially convenient for this is the application of mechanical pipette with adjusted injection volume and controlled speed of the injection. Tube-less BIA systems were designed also with other than amperometric or voltammetric detections.

For instance, the potentiometry with ion-selective electrodes seems to be a very convenient detection to use, due to sufficient selectivity of many indicating membrane electrodes; some examples include measurements of pH with glass electrode with flat membrane [66], determination of chloride [59], fluoride [66], and also sodium and potassium [67]. Such determinations can be also carried out with spectrophotometric detection with appropriate design of a flow-through cuvette [68]. Detection with the use of thermistor with immobilized catalase and glucose oxidase was employed for determination of glucose [69].

Microsystems in Flow Analysis

The pioneering step in the miniaturization of flow analysis was a design of integrated microconduits with miniature detectors and a large hydraulic part for transport of solutions [70,71]. Other attempts included the replacement of typical peristaltic pumps with small syringes or piezoelectric pumping devices [72] and the incorporation of various parts of typical flow systems (flow-through reactors, detectors [73]) into a rotary valve for sample injection in Lab-on-Valve [74]. Each miniaturized FIA systems has dimensions in centimeters and diameters of channels being fraction of millimeters.

An important next significant step in miniaturization of instrumentation for flow analysis was the development of first flow microsystems in beginning of 1990's, which are commonly described as microfluidics (Figure 7) [75,76]. In those devices, the diameters of channels were decreased down to tens of micrometers, and the same systems were very successfully employed in capillary electrophoresis. Some examples include that they can be used in determination of amino acids in meteorite samples with fluorescence detection [77] or for the measuring activity of enzymes for clinical and pharmaceutical needs [78]. Such microfluidics are most commonly produced in the format of a thin piece of glass or polymeric plate of width and length to a few centimeters, with pattern of microchannels, and the possibility of performing various different unit operations in microscale format. For flow-injection measurements they were already developed with various methods of detection including. amperometric detection for immunochemical assays [79], ion-selective potentiometric electrodes for determination of copper [80], fluorimetric detection for the determination of pH [81], employing chemiluminescence detection for enzymatic glucose determination [82], and spectroelectrochemical detection employing with thermal lens spectroscopy for determination Co (II) [75], where different microunit operations can be combined in a dedicated microsystem.

Numerous commercial microfluidic devices are already on the market; however, so far, they are available for only particular applications. Generally, they have to be interfaced to electronic controlling system, equipped with a reagent supply, and detectors. They are usually constructed to perform only a limited set of operations such as the transport of liquids, simple separation processes, or sensing. Further developments of microfluidics towards a Micro Total Analytical Systems (described as μTAS) require the definition of architectural and performance concepts for assembling microfluidics devices into networks [83]. A very intensive progress in this area is reported in the literature. As the example of such a monolithic integrated flow injection systems, it can be shown that one employing Berthelot's reaction for the determination of ammonia [84]. It consists of four piezoelectrically driven micropumps, the reaction chamber, fluidic channels and optical detection cell, which are integrated on a 10-cm diameter silicon plate.

Another approach in this field is the concept of digital microfluidics, which arose in the late 1990's and involved the manipulation of discrete volumes of liquids on a surface [85]. The manipulation of droplets

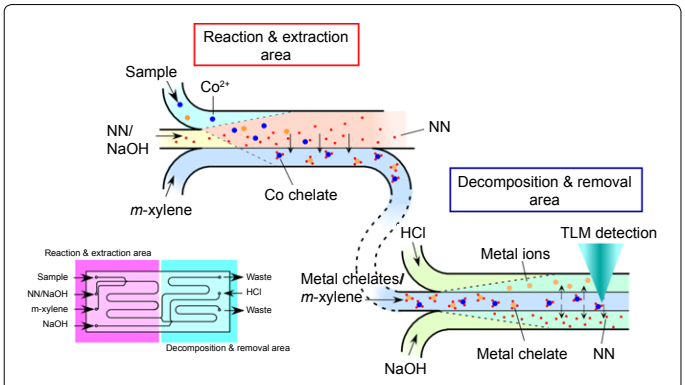

Figure 7: Schematic illustration of microfluidic system and concept of on-line sample processing which was developed for Co(II) determination with thermal lens microscopy detection [75].

on the surface can occur through electrowetting, dielectrophoresis, thermocapillary transport, or surface acoustic transport. In contrary to continuous-flow microfluidics discussed above, the architecture of digital microfluidics is under software-driven electronic control, which eliminates the need of the use of mechanical tubes, pumps, or valves.

Nanofluidics for Flow Analysis

The flow analysis carried out in microfluidic systems is already very advanced, but increasing research activity is being focused on the design of nano-flow systems or nanofluidics [86]. Nanometer dimension concerns the inner diameters of channels transporting solution and numerous studies are devoted to theoretical prediction and description of phenomena and interactions, which take place on this scale. In the movement of analyte molecules in the nanometer dimensions, there are essential changes of physical and chemical interactions compared to micrometer scale. Many interactions, which are marginal in microfluidics, play an essential role in nanofluidics. Especially strong interactions, which should be considered in nanoscale is the capillary force, which originates from the adhesion between the liquid and the solid surface molecules. In some cases a considerable contribution can be dielectrophoretic forces, which are generated in rapidly changing high electrical filed gradients and results from differences in dielectric properties between analyte molecules and medium. The forces acting in nanochannels may influence ionic equilibria and kinetic properties [87]. In capillaries of nanometer dimensions with charged wall surfaces, the extension of the electrical double layer, which affects the permselectivity of such structures, results in the electrostatic exclusion of co-ions and enrichment in counter-ions? As a result, the electric double layer may also induce certain selectivity of transport. In model calculations, it was shown that streaming potential in nanochannels can decrease the effective diffusion coefficient of the analyte [88].

The preparation of structures with nanochannels was reported from different materials [89,90]. Three-dimensional structures can be formed as multimembrane structures of nanocapillary membranes, where each membrane plays a different role in the system. Such systems have been already applied with the fluorimetric detection for determination; an example is calcium binding to calcium-labeled dextrans with the presence of complexone EGTA [91]. The determination of lead (II) was based on lead-specific DNAzyme in nanocapillary interconnected microfluidic device [92]. Nanofluidics with so-called entropic traps was employed for separation in flow conditions, as alternative to chromatographic or capillary electrophoretic separations [93]. The immobilization of an antibody-based molecular recognition element onto the nanopore surface was demonstrated for selective capture and release of human insulin [94].

Amore advanced approach includes a design of nanofluidics employing molecular nanomechanics, where motors are made from nanoscale building blocks that derive on-board or off-board power from *in-situ* chemical reactions [95]. Molecular nanomachines can convert energy inputs into controlled motion on a surface and transport of nano-cargo (material or information) from one place to another on the surface [96].

Conclusions and Perspectives

Several hundred research papers published every year on flow analysis and its applications in different fields indicate that it is a very important and vital area of flow chemistry. Besides the optimization of sample processing methods and devices, a very significant trend of research involves improving the detection methods. In this case an increasing importance is observed for current achievements of nanotechnology [97].

As especially pronounced developing trends in flow analysis one can indicate the improvement of sample processing methods, their application in hyphenated methods, and quickly progressing miniaturization of flow analysis systems [98]. Numerous improvements in on-line sample processing reported frequently in literature for analytical purposes results mostly from progress in material science and dedicated composites and from the adoption of different chemical interactions and new design of dedicated instrumental modules. The necessity of hyphenation of miniaturized instrumentation with processes occurring in micro- or even nano-dimensions resulted in suggesting a new description of such systems as *mesofluidic systems* [99], although it concerns types of flow systems, which were being developed for many years in the past. An example of the progress in this area can be a development of systems for handling a suspension of non-uniformly sized bead materials [100] or developing mesofluidic systems for synthetic purposes which allows the formation of micro- and millimeter droplets [101].

A very efficient way of practical analytical utilization of the on-line sample processing is hyphenation of flow systems with large spectroscopic of chromatographic instrumental set-ups, which leads to convenient mechanization of whole analytical procedures and to the improvement of functional parameters of multicomponent determinations [102]. Particular attention in recent years is focused on hyphenation of flow analytical systems with mass spectrometry. ICP-MS spectrometers allow the sensitive elemental determinations (Figure 8) [103] or labeled molecules in cellular samples [104]. MS systems with ionization of organic compounds can be applied for very sensitive determinations of chemical residues [105], profiling of different groups of compounds [106], or replacing immunoassays in determination of different stimulants and their metabolites [107].

The third mentioned development trend of flow analysis involves the miniaturization of measuring devices. Microfluidics already has wide applications in medical diagnostics [108] and environmental analysis [109]. New instrumental constructions are focused on the design of paper-based devices (Figure 9) [110,111], which are simple items for mass-production and inexpensive ones, which can find numerous

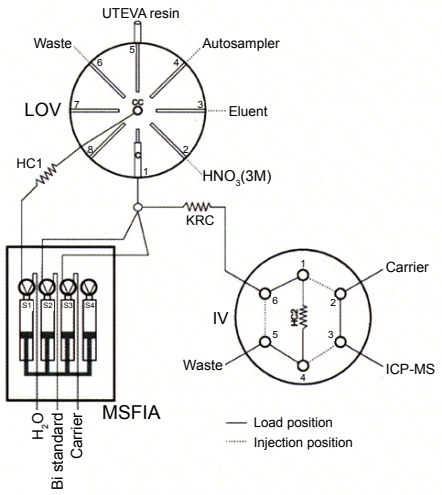

Figure 8: Manifold of miniaturized Lab-on-Valve system with multisyringe flow injection developed for thorium and uranium isolation, preconcentration and ICP-MS detection [103]. S – syringe, LOV – lab-on-valve, HC – holding coil, C – column, CC – central conduit.

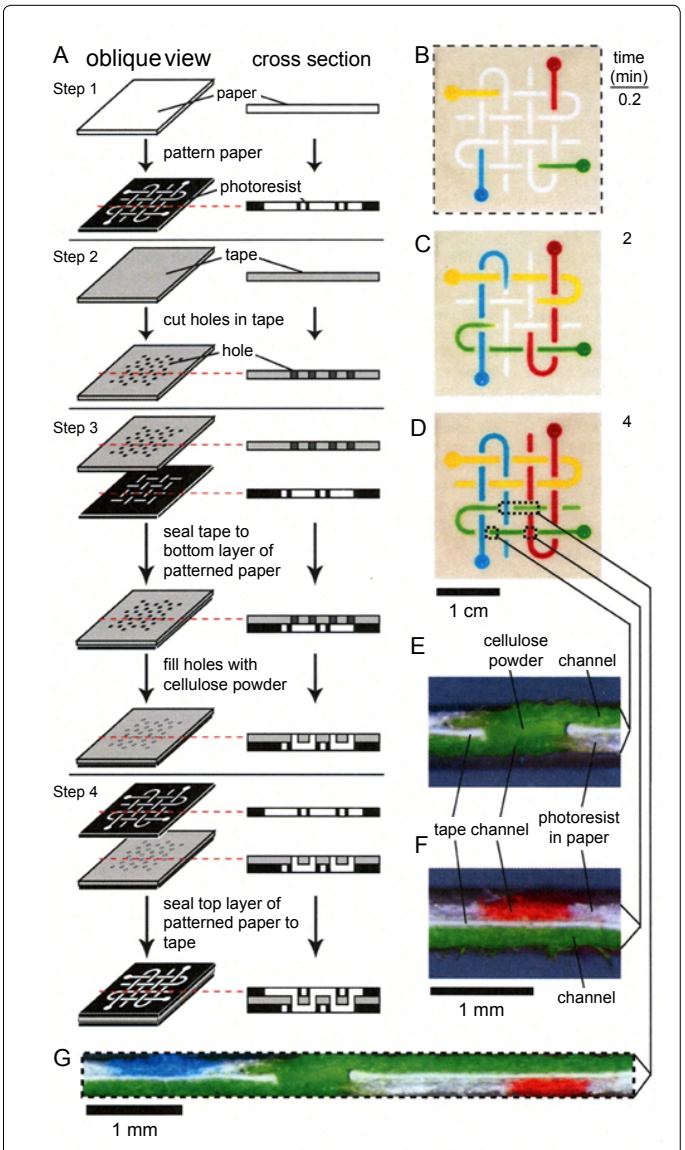

Figure 9: Schematic illustration of preparation and functioning of three-dimensional microfluidic devices fabricated in layered paper and tape, which are potentially suitable for inexpensive personal health diagnostics and environmental monitoring [110]. A – steps of fabrication, B-D – photograph of basket-weave system after adding solutions of dyes, E-G – cross sections of the device showing distribution of fluids in different parts of microfluidics.

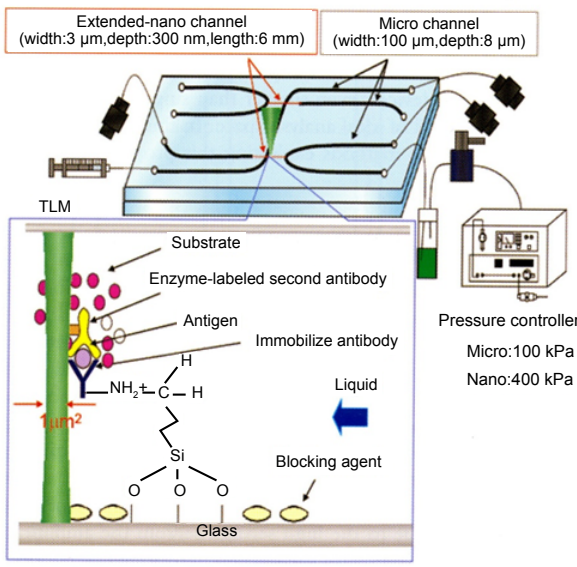

Figure 10: Scheme of a design and functioning principle of a microfluidic immunoassay system inside an extended nanospace channel which was fabricated on a glass substrate [113].

potential applications. Especially promising seems to be fast progress in design of nanofluidics, (Figure 10) which are the most advanced devices for slow analysis, and also for flow synthetic chemistry [112,113].

References

1. Carroll D (1971) Continuous-flow salt gradient dialysis for the preparation of polynucleotide-polypeptide complexes. Anal Biochem 44: 496-502.
2. Albeck M, Rav-Acha C (1970) An apparatus for investigation of heterogeneous reactions in a flow system. Experientia 26: 1043-1045.
3. Wegner J, Ceylan S, Kirschning A (2012) Flow chemistry – A key enabling technology for (multistep) organic synthesis. Advanced Synthesis & Catalysis 354: 17-57.
4. Watts P, Wiles C (2012) Micro reactors, flow reactors and continuous flow synthesis. Journal of Chemical Research 36: 181-193.
5. Illg T, Löb P, Hessel V (2010) Flow chemistry using milli- and microstructured reactors-From conventional to novel process windows. Bioorg Med Chem 18: 3707-3719.
6. Tanaka K, Fukase K (2009) Acid-mediated reactions under microfluidic conditions: a new strategy for practical synthesis of biofunctional natural products. Beilstein J Org Chem.
7. Badilescu S, Packirisamy M (2012) Microfluidics-nano-integration for synthesis and sensing. Polymers 4: 1278-1310.
8. Marre S, Roig Y, Aymonier C (2012) Supercritical microfluidics: Opportunities in flow-through chemistry and materials science. J Supercrit Fluids 66: 251-264.
9. Sadler S, Moeller AR, Jones GB (2012) Microwave and continuous flow technologies in drug discovery. Expert Opin Drug Discov 7: 1107-1128.
10. Skeggs LT Jr. (1957) An automatic method for colorimetric analysis. Am J Clin Pathol 28: 311-322.
11. Skeggs LT Jr. (2000) Persistence….and prayer: from the artificial kidney to the Autoanalyzer. Clin Chem 46: 1425-1436.
12. Furman WB (1976) Continuous flow analysis. Theory and practice. Marcel Dekker, New York, USA.
13. Hollaarm K, Neele B (2008) Industrial and environmental applications of continuous flow analysis. Chapter in M. Trojanowicz (Ed.). Advances in Flow Analysis. Wiley-VCH.
14. Pei J, Nie J, Kennedy RT (2010) Parallel electrophoretic analysis of segmented samples on chip for high-throughput determination of enzyme activities. Anal Chem 82: 9261-9267.
15. Boedicker JQ, Li L, Kilne TR, Ismagilov RF (2008) Detecting bacteria and determining their susceptibility to antibiotics by stochastic confinement in nanoliter droplets using plug-based microfluidics. Lab Chip 8: 1265-1272.
16. Nagy G, Fegher Z, Pungor E (1970) Application of silicone rubber-based graphite electrodes for continuous flow measurements: Part II. Voltammetric study of active substances injected into electrolyte streams. Analytica Chimicca Acta 52: 47-54.
17. Ruzicka J, Hansen EH (1975) Flow injection analyses: Part I. A new concept of fast continuous analysis. Analytica Chimica Acta 78: 145-157.
18. Stewart KK, Beecher GR, Hare PE (1976) Rapid analysis of discrete samples: the use of nonsegmented, continuous flow. Anal Biochem 70: 167-173.
19. Hansen EH (2004) The impact of flow injection on modern chemical analysis: has it fulfilled our expectations? And where are we going? Talanta 64: 1076-1083
20. M. Trojanowicz M (Ed.) (2008) Advances in Flow Analysis. Wiley-VCH.
21. Kolev S, McKelvie I (Eds.) (2008) Advances in Flow Injection Analysis and Related Techniques.
22. Chalk SJ (2008) Flow analysis and the Internet – databases, instrumentation, and resources. Chapter in M. Trojanowicz (Ed.) Advances in Flow Analysis. Wiley-VCH.
23. Krawczynski vel Krawczyk T, Trojanowicz M, El-Murr N (2000) Enhancement of selectivity of electrochemical detectors by kinetic discrimination in flow-injection systems. Laboratory Robotics and Automation 12: 205-215.
24. Fang ZL (1993) Flow-Injection Separation and Preconcentration. VCH, Weinheim.
25. Kościelniak P, Wieczorek M, Kozak J, Herman M (2007) Versatile flow injection manifold for analytical calibration. Anal Chim Acta 600: 6-13.
26. Trojanowicz M, Olbrych-Śleszyńska E (1992) Flow-injection sample processing in atomic absorption spectrometry. Chem Anal (Warsaw) 37: 111-138.
27. Szpunar-Łobińska J, Ceulemans M, Łobiński R, Adams FC (1993) Flow-injection sample preparation for organotin speciation analysis of water by capillary gas chromatography-microwave-induced plasma atomic emission spectrometry. Anal Chim Acta 278: 99-113.
28. Poboży E, Halko R, Krasowski M, Wierzbicki T, Trojanowicz M (2003) Flow-injection sample preconcentration for ion-pair chromatography of trace metals in waters. Water Res 37: 2019-2026.
29. Lu WJ, Chen YL, Zhu JH, Chen XG (2009) The combination of flow injection with electrophoresis using capillaries and chips. Electrophoresis 30: 83-91.
30. Cruz-Vera M, Lucena R, Cardenas S, Valcarcel M (2010) Highly selective and non-conventional sorbents for the determination of biomarkers in urine by liquid chromatography. Anal Bioanal Chem 397: 1029-1038.
31. Mishra SK, Dasgupta PK (2010) Electrodialytic reagent introduction in flow systems. Anal Chem 82: 3981-3984.
32. Wolff CM, Mottola HA (1978) Enzymic substrate determination in closed flow-through systems by sample injection and amperometric monitoring of dissolved oxygen levels. Anal Chem 50: 94-98.
33. Zenki M, Tanishita A, Yokoyama T (2004) Repetitive determination of ascorbic acid using iron(III)-1,10-phenanthroline-peroxodisulfate system in a circulatory flow injection method. Talanta 64: 1273-1277.
34. Luque de Castro MD (1992) The role of flow injection analysis in speciation studies. Microchimica Acta 109: 165-168.
35. Campanella L, Pyrzyńska K, Trojanowicz M (1996) Chemical speciation by flow-injection analysis. A review. Talanta 43: 825-838.
36. Trojanowicz M, Alexander PW, Hibbert DB (1998) Flow-injection analysis with potentiometric detection for the speciation of fluoride and calcium. Analytica Chimica Acta 366: 23-33.
37. Lopez Pasquali CE, Fernandez Hernando P, Durand Alegria JS (2007) Spectrophotometric simultaneous determination of nitrite, nitrate and ammonium in soils by flow injection analysis. Anal Chim Acta 600: 177-182.
38. Wójtowicz M, Kozak J, Kościelniak P (2007) Novel approach to analysis by flow injection gradient titration. Anal Chim Acta 600: 78-83.

39. Wójtowicz M, Kozak J, Danielewska K, Kościelniak P (2009) Flow injection titration basing on the merging-zone technique. Talanta 79: 1006-1010.

40. Zhi ZL (1998) Segmental flow injection analysis, a hybrid technique of segmented continuous flow analysis and flow injection analysis. Trends in Analytical Chemistry 17: 411-417.

41. Ruzicka J, Marshal GD (1990) Sequential injection: a new concept for chemical sensors, process analysis and laboratory assays. Analytica Chimica Acta 237: 329-343.

42. Ruzicka J (2009) Flow injection analysis. CD-ROM Tutorial, 3rd Ed. FIALab Instruments Inc., Bellevue, WA, USA.

43. Trojanowicz M (2000) Flow Injection Analysis. Instrumentation and Applications. World Scientific. Singapore.

44. Perez-Olmos R, Soto JC, Zarate N, Araujo AN, Montenegro MCBSM (2005) Sequential injection analysis using electrochemical detection: A review. Analytica Chimica Acta 554: 1-16.

45. Armenta S, Garrigues S, de la Guardia M (2007) Recent developments in flow-analysis vibrational spectroscopy. Trends in Analytical Chemistry 26: 775-787.

46. Van Staden JF, Stefan RI (2004) Chemical speciation by sequential injection analysis: an overview. Talanta 64: 1109-1113.

47. Mesquita RB, Rangel AO (2009) A review on sequential injection methods for water analysis. Anal Chim Acta 648: 7-22.

48. Barnett NW, Lenehan CE, Lewis SW (1999) Sequential injection analysis: an alternative approach to process analytical chemistry. Trends in Analytical Chemistry 18: 346-353.

49. Liu S, Dasgupta PK (1994) Sequential injection analysis in capillary format with an electroosmotic pump. Talanta 41: 1903-1910.

50. Gomez E, Tomas C, Cladera A, Estela JM, Cerda V (1995) Multicomponent techniques in sequential injection analysis. Analyst 120: 1181-1184.

51. Rius A, Callao MP, Rius FX (1995) Self-configuration of sequential injection analytical systems. Analytica Chimica Acta 316: 27-37.

52. Van Staden JF, Taljaard RE (2004) Determination of lead(II), copper (II), zinc (II), cobalt (II), cadmium (II), iron (III) and mercury (II) using sequential injection extractions. Talanta 64: 1203-1212.

53. Satinsky D, Neto I, Solich P, Sklenarova H, Montenegro MCBSM, et al. (2004) Sequential injection chromatographic determination of paracetamol, caffeine, and acetylsalicylic acid in pharmaceutical tablets. J Sep Sci 27: 529-536.

54. Chocholous P, Solich P, Satinsky D (2007) An overview of sequential injection chromatography. Anal Chim Acta 600: 129-135.

55. Ruzicka J, Pollema CH, Scudder KM (1993) Jet ring cell: a tool for flow injection spectroscopy and microscopy on a renewable solid support. Anal Chem 65: 3566-3570.

56. Yoshimura K, Waki H (1985) Ion-exchange phase absorptiometry for trace analysis. Talanta 32: 345-352.

57. Wang J, Hansen EH (2000) Coupling on-line preconcentration by ion-exchange with ETAAS: A novel flow injection approach based on the use of a renewable microcolumn as demonstrated for the determination of nickel in environmental and biological samples Analytica Chimica Acta 424: 223-232.

58. Wang J, Hansen EH (2001) Coupling sequential injection on-line preconcentration by means of a renewable microcolumn with ion-exchange beads with detection by electrothermal atomic absorption spectrometry. Analytica Chimica Acta 435: 331-342.

59. Wang J, Taha Z (1991) Batch injection analysis. Anal Chem 63: 1053-1056.

60. Amine A, Kaufmann JM, Palleschi G (1993) Investigation of the batch injection analysis technique with amperometric biocatalytic electrodes using a modified small-volume cell. Analytica Chimica Acta 273: 213 –218.

61. Wang J, Lu J, Chen L (1992) Batch injection stripping voltammetry of trace metals. Analytica Chimica Acta 259: 123-128.

62. Brett CMA, Brett AMO, Tugalea L (1996) Anodic stripping voltammetry of trace metals by batch injection analysis. Analytica Chimica Acta 322: 151-157.

63. Brett CMA, Brett AMO, Tugulea L (1996) Batch injection analysis with adsorptive stripping voltammetry for the determination of traces of nickel cobalt. Electroanalysis 8: 639-642.

64. Brett CM, Brett AMO, Matysik FM, Matysik S, Kumbhat S (1996) Nafion-coated mercury thin film electrodes for batch-injection analysis with anodic stripping voltammetry. Talanta 43: 2015-2022.

65. Trojanowicz M, Koźmiński P, Dias H, Brett CM (2005) Batch injection stripping voltammetry (tube-less flow injection analysis) of trace metals with on-line sample pretreatament. Talanta 68: 394-400.

66. Wang J, Taha Z (1991) Batch injection with potentiometric detection. Analytica Chimica Acta 252: 215-221.

67. Lu J, Chen Q, Diamond D, Wang J (1993) Inverted poly(vinyl chloride)-liquid membrane ion-selective electrodes for high-speed batch injection potentiometric analysis. Analyst 118: 1131-1135.

68. Wang J, Agnes L (1993) Bach injection spectrometry. Anal Lett 26: 2329-2339.

69. Wang J, Taha Z (1991) Batch Injection Analysis with Thermistor Sensing Devices. Analytical Letters 24: 1389-1400.

70. Ruzicka J, Hansen EH (1984) Integrated microconduits for flow injection analysis. Analytica Chimica Acta 161: 1-25.

71. Ruzicka J, Christian GD (1990) Reversible optosensing in packed flow-through detectors: flow injection or chromatography? Analytica Chimica Acta 234: 31-40.

72. Van der Schoot BH, Jeanneret S, Van den Berg A, de Rooij NF (1993) Microsystems for Flow Injection Analysis. Analytical Methods and Instrumentation 1: 38-42.

73. Wang J, Li RL (1990) On-valve electrochemical detector for high-speed flow injection analysis. Anal Chem 62: 2414-2416.

74. Ruzicka J (2000) Lab-on-valve: universal microflow analyzer based on sequential and bead injection. Analyst 125: 1053-1060.

75. Kikutani Y, Tokeshi M, Sato K, Kitamori T (2002) Integrated chemical systems on microchips for analysis and assay. Potential future, mobile high-performance detection system for chemical weapons. Pure Appl Chem 74: 2299-2309.

76. Lichtenberg J, de Rooij NF, Verpoorte E (2002) Sample pretreatment on microfabricated devices. Talanta 56: 233-266.

77. Hutt LD, Glavin DP, Bada JL, Mathies RA (1999) Microfabricated capillary electrophoresis amino acid chirality analyzer for extraterrestial exploration. Anal Chem 71: 4000-4006.

78. Perrin D, Fremaux C, Scheer A (2006) Assay development and screening of a serine/ threonine kinase in an on-chip mode using caliper nanofluidics technology. J Biomol Screen 11: 359-368.

79. Choi JW, Oh KW, Thomas JH, Heineman WR, Halsall HB, et al. (2002) An integrated microfluidic biochemical detection system for protein analysis with magnetic bead-based sampling capabilities. Lab Chip 2: 27-30.

80. Hűller J, Pham MT, Howitz S (2003) Thin layer copper ISE for fluidic microsystem, Sensors and Actuators B: Chemical 91: 17-20.

81. Mela P, Onclin S, Goedbloed MH, Levi S, Garcia-Parajo MF, et al. (2005) Monolayer-functionalized microflu-idics devices for optical sensing of acidity. Lab Chip 5: 163-170.

82. Lv Y, Zhang Z, Chen F (2003) Chemiluminescence microfluidic system sensor on a chip for determination of glucose in human serum with immobilized reagents. Talanta 59: 571-576.

83. Zhang T, Chakrabarty K, Fair RB (2002) Microfluidic systems modeling and simulation. CRC Press.

84. Gardeniers H, van den Berg A (2004) Micro- and nanofluidic devices for environmental and biomedical applications. International Journal of Environmental Analytical Chemistry 84: 809-819.

85. Fair RB (2007) Digital microfluidics: is a true lab-on-a-chip possible? Microfluid Nanofluid 3: 245-281.

86. Eijkel JCT, van den Berg A (2005) Nanofluidics: what is it and what can we expect from it? Microfluid Nanofluid. 1: 249-267.

87. Plecis A, Schoch RB, Renaud P (2005) Ionic transport phenomena in nanofluidics: experimental and theoretical study of the exclusion-enrichment effect on a chip. Nano Lett. 5: 1147-1155.

88. Xuan X, Sinton D (2007) Hydrodynamic dispersion of neutral solutes in nanochannels: the effect of streaming potential. Microfluidics and Nanofluidics 3: 723-728.

89. Abgrall P, Low LN, Ngyuen NT (2007) Fabrication of planar nanofluidic channels in a thermoplastic by hot-embossing and thermal bonding. Lab Chip 7: 520-522.

90. Tamaki E, Hibara A, Kim HB, Tokeshi M, Ooi T, et al. (2006) Liquid filling method for nanofluidic channels utilizing the high solubility of CO_2. Anal Sci 22: 529-532.

91. Kuo TC, Kim HK, Cannon DM, Shannon MA, Sweedler JV, et al. (2004) Nanocapillary Arrays Effect Mixing and Reaction in Multilayer Fluidic Structures. Angewandte Chemie 116: 1898-1901.

92. Chang IH, Tulock JJ, Liu J, Kim WS, Cannon DM Jr, et al. (2005) Miniaturized lead sensor based on lead-specific DNAzyme in a nanocapillary interconnected microfuidic device. Environ Sci Technol 39: 3756-3761.

93. Han J, Craighead HG (2000) Separation of Long DNA Molecules in a Microfabricated Entropic Trap Array. Science 288: 1026-1029.

94. Kim BY, Swearingen CB, Ho JA, Romanova EV, Bohn PW, et al. (2007) Direct immobilization of Fab' in nanocapillaries for manipulating mass-limited samples. J Am Chem Soc 129: 7620-7626.

95. Ozin GA, Manners I, Fournier-Bidoz S, Arsenault A (2005) Dream nanomachines. Advanced Materials 17: 3011-3018.

96. Shirai Y, Morin JF, Sasaki T, Guerrero JM, Tour JM (2006) Recent progress on nano-vehicles. Chemical Society Reviews 35: 1043-1055.

97. Valcarcel M, Simonet BM, Cardenas S (2008) Analytical nanoscience and nanotechnology today and tomorrow. Anal Bioanal Chem 391: 1881-1887.

98. Miro M, Hansen EH (2012) Recent advances and future prospects of mesofluidic lab-on-a-valve platforms in analytical sciences – a critical review. Anal Chim Acta 750: 3-15.

99. Wang J (2005) Lab-on-valve mesofluidic analytical system and its perspectives as a "world-to-chip" front-end. Anal Bioanal Chem 381: 809-811.

100. Oliveira HM, Miro M, Segundo MA, Lima JL (2011) Universal approach for mesofluidic handling of bead suspensions in lab-on-valve format. Talanta 84: 846-852.

101. Steinbacher JL, Lui Y, Mason BP, Olbricht WL, McQuade DT (2012) Simplified Mesofluidic Systems for the Formation of Micron to Millimeter Droplets and the Synthesis of Materials. J Flow Chem 2: 56-62.

102. Pinto PCAG, Lucia M, Saraiva MFS, Lima JLFC (2011) Sequntial Injection Analysis Hyphenated with Other Flow Techniques: A review. Analytical Letters 44: 374-397.

103. Avivar J, Ferrer L, Casas M, Cerda V (2012) Fully automated lab-on-valve-multisyringe flow injection analysis-ICP-MS system: an effective tool for fast, sensitive and selective determination of thorium and uranium at environmental levels exploiting solid phase extraction. J Anal At Spectrom 27: 327-334.

104. Kretschy D, Groger M, Zinki D, Petzelbauer P, Koellensperger G, et al. (2011) High-throughput flow injection analysis of labeled peptides in cellular samples-ICP-MS analysis versus fluorescence based detection. Int J Mass Spectrom 307: 105-111.

105. Nanita SC (2011) High-throughput chemical residue analysis by fast extraction and dilution flow injection mass spectrometry. Analyst 136: 285-287.

106. Regazzoni L, Arlandini E, Garzon D, Santagati NA, Beretta G, et al. (2013) A rapid profiling of gallotannins and flavonoids of the aqueous extract of *Rhus coriaria L.* by flow injection analysis with high-resolution mass spectrometry with database searching. J Pharm Biomed Anal 72: 202-207.

107. Lua IA, Lin SL, Lin HR, Lua AC (2012) Replacing immunoassays for mephedrone, ketamines and six amphetamine-type stimulants with flow injection analysis tandem mass spectrometry. J Anal Toxicol 36: 575-581.

108. Weigl BH, Bardell RL (2004) Microfluidics for clinical diagnostics – Promise and current reality. Lab Medicine 35: 233-237.

109. Gardeniers H, Van Den Berg A (2004) Micro- and nanofluidic devices for environmental and biomedical applications. International Journal of Environmental Analytical Chemistry 84: 809-819.

110. Martinez AW, Phillips ST, Whitesides GM (2008) Three-dimensional microfluidic devices fabricated in layered paper and tape. Proc Natl Acad Sci USA 105: 19606-19611.

111. Klasner SA, Price AK, Hoeman KW, Wilson RS, Bell KJ, et al. (2010) Paper-based microfluidic devices for analysis of clinically relevant analytes present in urine and saliva. Anal Bioanal Chem 397: 1821-1829.

112. Piruska A, Gong M, Sweedler JV, Bohn PW (2010) Nanofluidics in chemical analysis. Chem Soc Rev 39: 1060-1072.

113. Mawatari LK, Tsukahara T, Kazoe Y, Dextras P, Kitamori T, et al. (2012) Extended-nano fluidic systems for chemistry and biotechnology. Imperial College Press, London, UK.