TRENDS

Where are modern flow techniques heading to?

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Abstract

This article aims to provide an overview on the transition from earlier laboratory automation using analytical flow approaches toward today's applications of flow methodologies, recent developments, and future trends. The article is directed to flow practitioners while serving as a valuable reference to newcomers in the field in providing insight into flow techniques and conceptual differences in operation across the distinct flow generations. In the focus are the recently developed and complementary techniques Lab-On-Valve and Lab-In-Syringe. In the following, a brief comparison of the different application niches and contributions of flow techniques to past and modern analytical chemistry is given, including (i) the development of sample pretreatment approaches, (ii) the potential applicability for in-situ/on-site monitoring of environmental compartments or technical processes, (iii) the ability of miniaturization of laboratory chemistry, (iv) the unique advantages for implementation of kinetic assays, and finally (v) the beneficial online coupling with scanning or separation analytical techniques. We also give a critical comparison to alternative approaches for automation based on autosamplers and robotic systems. Finally, an outlook on future applications and developments including 3D prototyping and specific needs for further improvements is given.

Keywords Flow techniques · Automation and miniaturization · Lab-On-Valve and Lab-In-Syringe · Sample pretreatment · Monitoring and surveillance · Hyphenation

Introduction to analytical flow techniques

Flow techniques (FT) belong to the lesser-known analytical techniques and are often underestimated by non-users. Therefore at first, an overview on common principles and operation differences of FT shall be given.

FT describe a family of different methodologies used for the automation of analysts' work, generally with a gain in procedural repeatability, system miniaturization, reduction of reagent consumption, increase in sample throughput, and performance reliability for fast kinetic reactions. Eminently for the automation of later task, FT are still unbeaten in terms of simplicity and versatility.

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The common principle is carrying and treating a sample in a carrier flow within a tubing manifold including valves for sample introduction and flow direction and further elements for unit operations (e.g., gas diffusion or analyte conversion) such as membrane separators or enzyme cartridges. In contrast to batch automation using autosampler or robotic systems, FT systems generally integrate a flow-through detection cell. Exemplary manifold configurations including main characteristics of operation, flow patterns, and transient signals for different FT and operation modes are given in Fig. 1.

A common misconception is that flow analyzers resemble liquid chromatographs without a column. Instead, the focus of FT lays rather on the automation of conventional laboratory tasks including sample metering, mixing, and transport to a detector aiming for analyte discrimination without demanding separations. For instance, FT allow for short but reproducible contact times of the sample with immobilized enzymes or an analyte-selective electrode followed by sample flush-out with a regenerating solution, thus prolonging the sensors lifetime and enabling faster analysis by circumventing lasting signal stabilization. Typically, FT feature faster sample processing, simplicity, lower costs of instrument and maintenance, and flexibility in use against high-performance separation techniques.
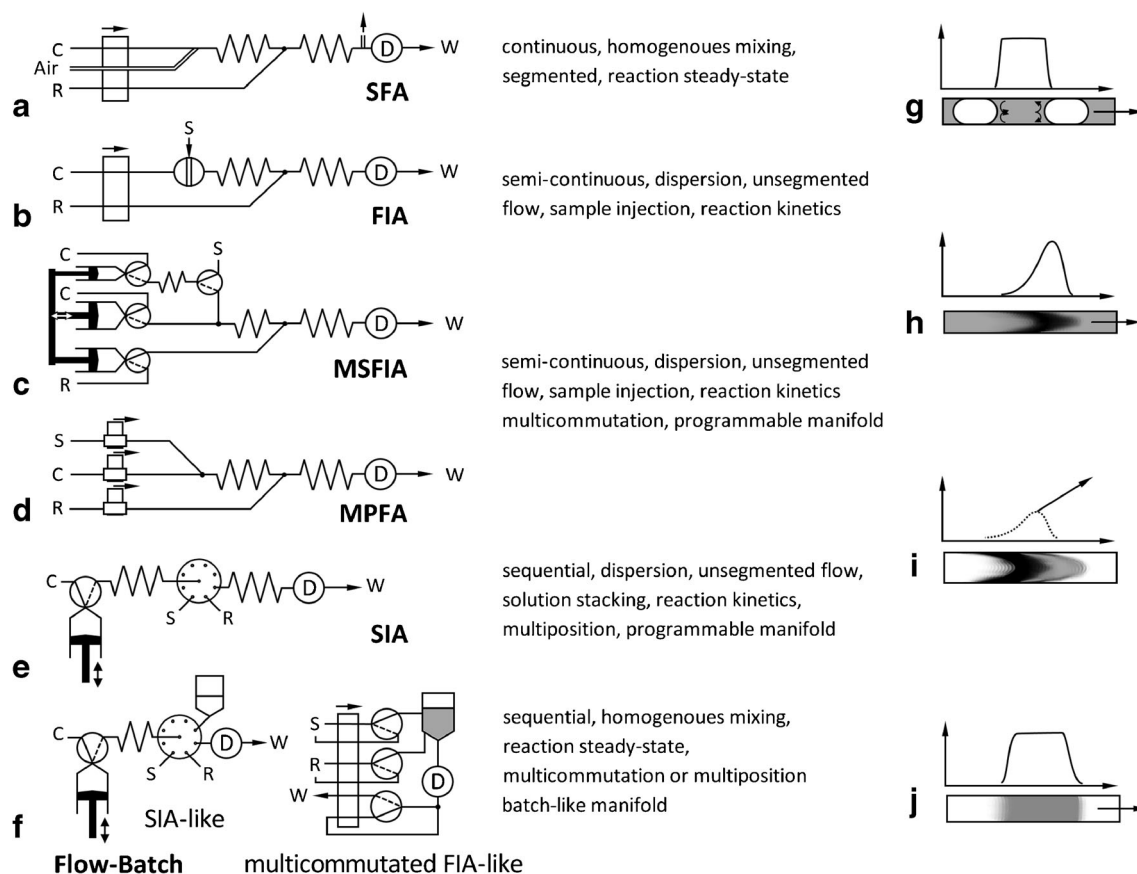
Fig. 1 Overview of manifold configurations, basic operation characteristics, mixing and signal pattern for flow techniques including continuous approaches: **a** segmented flow analysis and **b** flow injection analysis; multicommutation approaches: **c** multisyringe flow injection analysis and **d** multipumping flow analysis; and sequential approaches: **e** sequential injection analysis and **f** flow-batch analysis

However, being automation tools, such comparisons are futile. FT do not exhibit selectivity per se but carry out analytical procedures with increased reliability and feasibility. Selectivity is achieved either by tactical employment of selective reagents, enzymes, detectors, or kinetic differentiation, i.e., precise timing of data acquisition during the reaction progress.

Generally, reagents are added in-line to minute volumes of sample to increase both detection sensitivity and selectivity, thus minimizing solution consumption while avoiding sample consumption and user's exposure to harmful reagents. However, the outstanding feature of FT is the high repeatability of mixing and timing. This allows analyte quantification long before reaching the reaction steady-state and reliable measurements of catalysis, (electro-)chemiluminescence, intermediate products, or analyte quantification within seconds. The impact of this feature is better understood when contemplating that flow injection analysis (FIA), the mother of modern FT, was proposed in 1974, i.e., in precomputer times [1]. Allowing reliable sample processing by sheer setting of tubing dimensions and flow rates surely contributed to the triumphal procession of FIA.

Over time, FT automation of virtually all methodologies for analyte enrichment and matrix elimination has been demonstrated including sample filtration, digestions, gas-diffusion, solid-phase extraction (SPE), co-precipitation, effervescence, and many liquid-phase (micro-)extraction (LPME) approaches. A multitude of flow devices was developed for these purposes including interfaces to couple FT to high performance detection techniques.

Different FT can be defined by instrumental configuration, operation, and flow pattern, whereas IUPAC [2] only distinguishes four basic categories: unsegmented continuous flow, air-segmented flow (Fig. 1a), FIA (Fig. 1b), and sequential injection analysis [3] (SIA, Fig. 1e, see also "Advanced flow techniques" section). Further modalities with improvements in versatility are achieved by replacing the multichannel peristaltic pump by individually actuable units, such as multicommutation valves, stand-alone/multichannel syringe pumps (see Fig. 1c), or solenoid pumps (Fig. 1d), which allow reducing reagent consumption and re-directing solutions in a computer-controlled tubing network. A further differentiation can be made by the way the sample is inserted and handled in the flow system. The controlled introduction of segmentation bubbles to the tubing manifold for instance allows suppressing dispersion and to achieve homogenous mixing of sample and reagents (Fig. 1g). Without bubbles, stacked solutions are

mixed by dispersion, which in turns yields peak-shaped signals (Fig. 1h). Tracing the sole progress of the reaction by stopping the sample/reagent mixture inside the flow-through detection cell is known as "Stopped-Flow" approach, which facilitates subtraction of the sample background and kinetic approaches (Fig. 1i). Finally, combinations of FT with mixing chambers for automatic batch operations, e.g., homogenous mixing of sample and reagents, are known as flow-batch techniques (Fig. 1f, j) [4]. It is by taking advantage of these combinations that yields continuous advances of FT. Therefore, aiming to a strict classification of FT might just be missing the point, yet interested readers are directed to a recent FT classification-related review [5]. For more thorough introduction and comparison of FT, specialized treatises [6–8] and a comprehensive online tutorial and publication database are recommended [9].

Advanced flow techniques

At first, a brief description of the technique SIA is given not only for its increasing acceptance in industry but mainly for elucidating its descendant techniques Lab-On-Valve and Lab-In-Syringe. These are gaining steady attention for their suitability for analyte extraction and sample clean-up approaches, including miniaturized SPE and LPME, two evergreens in FT usage.

SIA operates on a different principle of sample introduction and solution mixing than earlier FIA. For one it is a monochannel technique (see Fig. 1e) while manifolds of FIA and related techniques generally comprise confluences for the addition of reagents (Fig. 1a–c) and secondly, it uses a bidirectional pump. The characteristic injection valve from FIA is replaced by a multiposition selection valve, from which all solutions are subsequently aspirated into a so-denoted holding coil. By flow reversal, the stacked solutions are propelled backwards undergoing further mixing toward the detector (Fig. 2).

An advantage is the possibility to adapt the procedural parameters (volumes, flow rates, delay times) simply by computer control while earlier FT required manifold re-configuration. While FIA was welcome for being simple and economic, making it also a wonderful tool for teaching, SIA offers flexible and precise operation control. This includes stopped-flow operation, easy adaptation of sample volume or dispersion, or reproducible formation of concentration gradients, e.g., to obtain a reaction zone with varying acidity within. Moreover, various procedures can be executed on the same analyzer differing, e.g., in the used reagents, the chosen flow path for different sample treatment, or the detector system to be hyphenated with. However, for such "programmable manifold," a versatile control software is an imperative requirement. This was surely a limitation in 1990 when SIA was proposed [3], but it is also a general bottleneck for lab-made FT automation.

The improved pressure resistance of the typically used syringe pumps for SIA allowed using separation columns of low flow resistance, which led to sequential injection chromatography (SIC) [10], combining the advantages of chromatography with the versatility of FT for automation of sample pretreatment.

Particularly interesting is the possibility to handle SPE sorbent particles (beads) as a suspension by SIA and to trap them in the flow manifold to create a packing of a few microgram sorbent. Bead re-aspiration and discharge allows creating a fresh active surface for each analysis such as for analyte sensing or preconcentration. This "Bead-Injection" concept became universally applicable on a purpose-designed selection valve stator of transparent polymer, featuring straight, smooth flow paths, which facilitates handling the bead suspension and allows visual control for optimization. The related technique is termed Lab-On-Valve (LOV) and was proposed in 2000 [11]. The valve-embedded manifold also integrates a flow-through port allowing sampling from process streams with virtually zero dead volume as well as a multipurpose detection cell for electrochemical or fiber-optic detection. Trapping the beads inside the detection cell enables on-bead sensing (Fig. 2) and is thus amenable to ELISA assays and micro-affinity separations using beads with immobilized antibodies [12, 13]. In summary, LOV can be considered as ideal tool and best-suited FT for the automation of SPE procedures and miniaturization of SIA applications [14], which do not need further manifold accessories.

The main characteristics of SIA are solution stacking and mixing by dispersion. By repeated aspiration, flow reversal or using air-bubbles for segmentation, multiple stacked solutions can be mixed efficiently but with steadily increasing procedural complexity and time. As the contact area of the stacked solutions in the tubing manifold is small, mixing of widely different volumes is tricky. Moreover, presence of bubbles and variable sample viscosity and temperature can have tremendous effects on mixing patterns and peak heights. Expanding the manifold by a mixing chamber (Fig. 1f) can bring clear advantages [4, 15] but requires multiple steps for cleaning and bears the risk of ambient contamination.

In SIA, entrance of solutions into the syringe's void is strictly evaded by prolonging the holding coil as required to avoid carry-overs. However, omitting the holding coil, using the syringe as steadily sealed yet size-adaptable chamber, and enabling homogeneous solution mixing by placing a magnetic stirring bar inside it allows new operation modes. This marriage of flow-batch and SIA concepts termed Lab-In-Syringe (LIS) [16, 17] is the most recent FT offspring, proposed in 2014. It allows in-syringe mixing of stepwise aspirated solutions of different volumes, independent from their volumes, viscosity, gas content, or miscibility. Thus, LIS can be considered as ideal FT for downscaling standard analytical procedures and automation of liquid-liquid and headspace extraction approaches yet in its first 6 years, use of magnetic
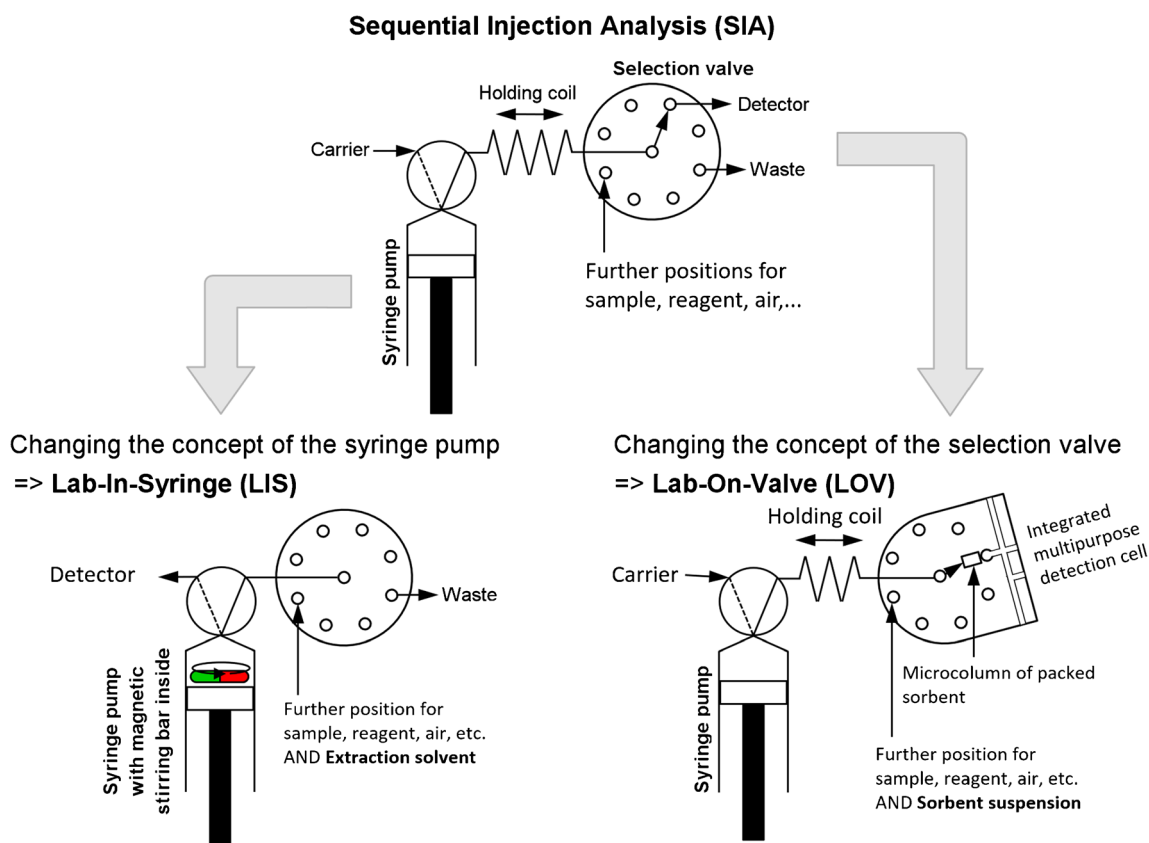
Sequential Injection Analysis (SIA)

Fig. 2 Derivation of Lab-On-Valve and Lab-In-Syringe techniques from sequential injection analysis based on changing the operation and conception of either selection valve or syringe pump

sorbents, cloud point extraction, dispersive SPE, or stirrer-modifications have been reported, too [18].

Descending both from SIA, LOV and LIS can be considered as two unlike siblings. By using directly opposed operation principles, they complement each other in their capabilities, features, and characteristic domains like a "Yin and Yang" as summarized in Table 1. There is an increasing interest in using FT for analyte preconcentration and matrix removal in hyphenation with high performance instrumentation such as HPLC, CE, MS, or ICP-techniques. Thus, automation of μSPE and LPME approaches using LOV and LIS as tools, respectively, has become a focus point in the field of FT.

Flow techniques versus robotic batch automation

Expected benefits from automation of any analytical procedures are (i) high procedural reproducibility, (ii) cost and workflow reduction, and, especially true for FT, (iii) miniaturization and high time efficiency. Another point to cover is the linkage of processes following the idea of "internet of things", i.e., wireless notification of finished tasks and errors, online available results, etc. However, automation also requires time for system setup and initialization as well as user training and instrumentation

purchase, which pays off only for large sample numbers or otherwise impractical tasks, such as measuring chemiluminescence emission with precise timing just after solution mixing.

There are fundamental differences in operation and conception of automation by robotic or autosampler systems (or "discrete analyzers") toward FT [19]. Such batch (vial, beaker, etc.) automation, e.g., of chromogenic reactions on a discrete analyzer, is quite predictable due to homogenous solution mixing. The concept of dispersion and gradient formation in FT, as ingeniously as it can be used, requires deeper insights, experimental optimization, and evaluation. Versatile autosamplers (e.g., PAL systems, www.palsystem.com) and even more, robotic systems (e.g. , Symbiosis stations, Spark Holland, www.sparkholland.com), have made a great progress during the last decade and are likely to progress further considering the potential for higher flexibility using tactile sensors, visual recognition, and artificial intelligence. Before, FT were clearly superior to batch automation in many aspects, in particular, faster processing time, versatility, and practically no consumables. Today, FT face a fierce competition from robotic systems that emulate human-like sample handling or automation in 96-microwell format allowing parallel processing and sample throughputs, which are "virtually independent of the rate of chemical reactions involved" [9]. In contrast, FT automated sample pretreatment is carried out just-in-time and with one sample at a time.

Table 1 Contrasting juxtaposition of typical instrumentation, concepts, operation characteristics, and potentials of modern flow techniques Lab-On-Valve and Lab-In-Syringe techniques

	Lab-On-Valve	Lab-In-Syringe
Manifold/processing in	Valve manifold	Syringe void
Configuration	Channel/tube-based	Chamber-based
Automation approach	SIA-like	Flow batch-like
Sample mixing	Laminar, dispersion, gradual	Turbulent, stirring, homogenous
Reagent application	Stacking (aspiration into holding coil)	Addition (aspiration into syringe)
Detection	In-Valve, optionally on sorbent	At-Syringe or In-Syringe
Most commonly automated task	Solid-phase extraction	Liquid-phase extraction Gas-phase extraction
Advantages for	Fast kinetics Gradient-based techniques Multiplex analysis Micro-volume analysis Miniaturization of SIA	Multistep procedures Large volume operations Handling of distinct liquid and gaseous phases Downscaling manual procedures
Matrix compensation by	e.g., stop-flow analysis	e.g., standard addition

The main task automated in-batch is matrix elimination and analyte preconcentration by headspace techniques, LPME, and SPE procedures prior to extract injection to GC, LC, or CE. In FT, pretreatment procedures are mostly performed to achieve analyte selectivity for on-system detection mostly by optical methods yet the benefits of online coupling of FT-automated sample preparation to analyte separation is more and more explored [20].

Preparative operations of increasing complexity for automation are dilution, heating, derivatization, extractions, digestion, evaporation, precipitation, and distillation. In contrast, centrifugation, sieving, and sample weighting require manual exchange of consumables and are limited to robotic automation and versatile autosampler systems [18, 19]. What is more, batch automation of manual procedures is coherent and easy to comprehend while FT automation demands familiarizing of the user with a new operation concept. Thus, autosamplers and discrete analyzers are more readily accepted by commercial laboratories and for routine analysis than FT analyzers but on account of higher implementation costs. The consequently larger market and competition pressure result in autosampler systems of universal applicability with perfected software. For FT, fit-for-purpose system development and method adaptation is typical.

On the other hand, coupling of FT-automated analyte enrichment to posterior separation bears the potential of improved performance as the sample quantity is not limited to the volume of an autosampler vial and higher analyte transfer is often feasible by online coupling of FT with high-performance instrumentation. Moreover, FT will always be at an advantage for monitoring purposes (e.g., from continuous sample stream), for coupling with detection techniques allowing continuous feed (e.g., ICP OES), field work (portability), miniaturization of classical analytical assays, automation of fast kinetic reactions and catalytic determinations, and

in terms of purchase and operation costs. Differently, FT are versatile and valuable tools above all in chemical research such as for the study of new materials.
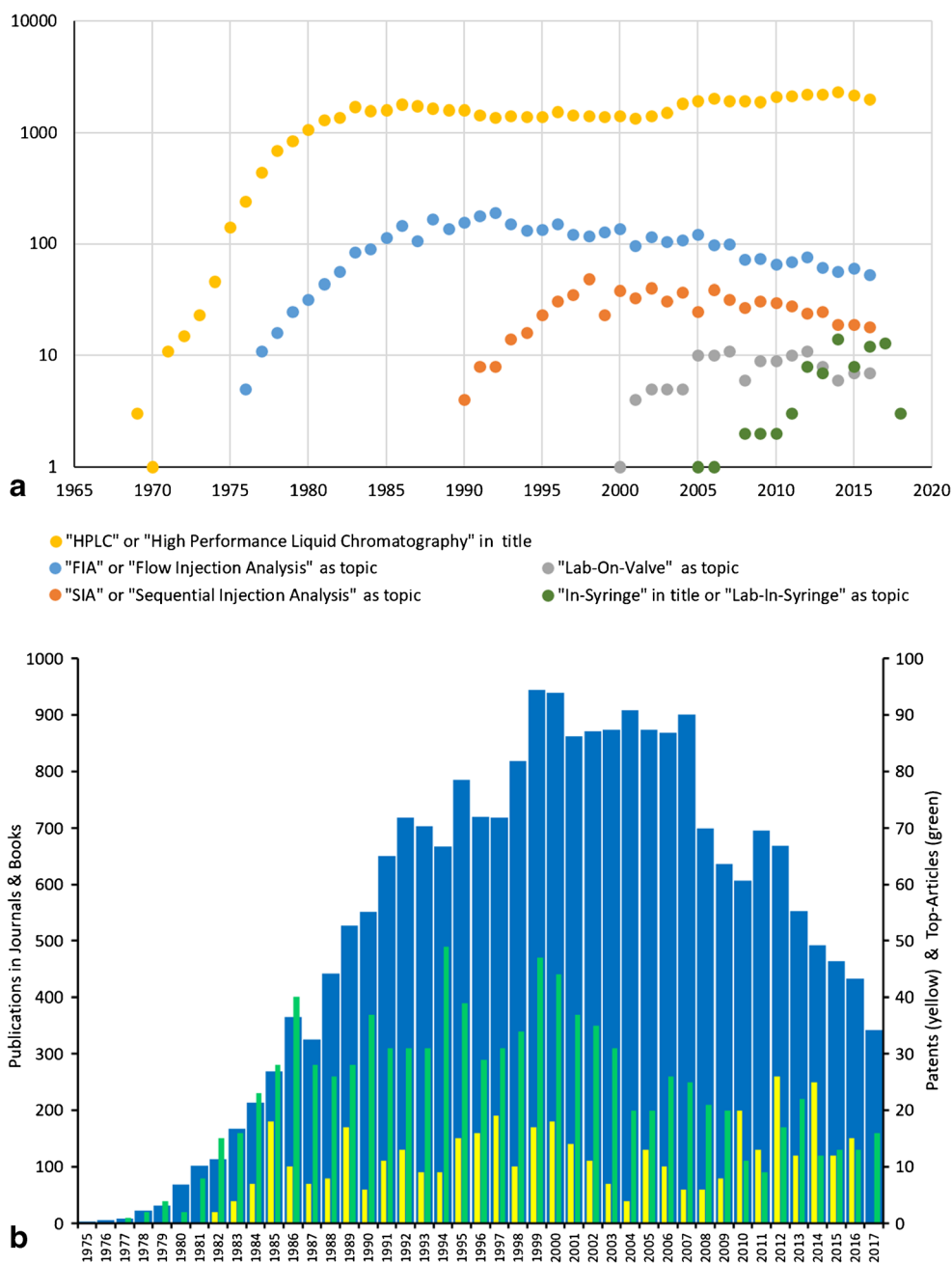
We believe that there is a high potential and observable trend in combining FT and batch automation principles, reflected by the interest in exploiting flow-batch and LIS techniques. Moreover, there are other approaches, based on the use of a syringe as size-adaptable reaction or extraction chamber, termed equally "Lab-In-Syringe" [21], generally performed in a manual way. Based on the mentioned features of autosampler systems and batch-flow technique LIS, exploring the potential of their combination seems to be the nearest future step.

Application of flow techniques, before and today

Assessing the past and present applications of FT, a fading enthusiasm in studying the fundaments of FT, adding modalities, or comparing their operational features can be observed, leaving alone maybe the most recent LOV and LIS techniques. FT are increasingly used as versatile analytical tools for monitoring, study of novel sorbent materials, and automation of sample preparation coupled to advanced detection techniques. This is due to a shift of the most pressing analytical questions driven by the demands of society and consequently grant agencies on applicability or relevance to, e.g., bioanalysis, nanomaterials, or emerging and priority organic pollutants (POPs) as well as by novelty requests by scientific editorials.

The number of publications related to classical HPLC has remained in approximation stable over the last 30 years (Fig. 3a) ignoring recent trends such as supercritical mobile phase, ultrahigh performance, green chromatography, or high temperature chromatography. On the other hand,

Fig. 3 **a** Number of publications taken from Web-of-Knowledge database (March 2018) for the indicated search terms. **b** Number of publications and books as well as patents and articles in the two best ranked journals in the field of general analytical chemistry (Anal. Chem. & TrAC) taken from flow injection tutorial database [9]

- ● "HPLC" or "High Performance Liquid Chromatography" in title
- ● "FIA" or "Flow Injection Analysis" as topic   ● "Lab-On-Valve" as topic
- ● "SIA" or "Sequential Injection Analysis" as topic   ● "In-Syringe" in title or "Lab-In-Syringe" as topic

contributions acknowledging FIA are decreasing but to the benefit of more recent FT such as SIA, LOV, or LIS. A similar picture, focusing rather on FT applications, has been recently drawn by Rocha (2018) [22]. Consulting the FT-dedicated database [9], the number of patents and the ratio of publications accepted in the top-rated analytical journals remain in approximation constant (see Fig. 3b). This indicates the unbrokenly high scientific quality of the field of FT. Two reasons are that FT are much used as tools for analytical research and the need for innovative and unconventional methodologies to compensate for the generally limited selectivity by FT. The question yet to answer is whether FT are currently surpassing the *through-*

of-disillusionment phase of the *Hype cycle* or, as we believe, in a renovation process toward modern FT as indicated in Fig. 3a). In addition, the former focus on FT has partly been adsorbed by "hotter" analytical techniques, which have emerged in the last two decades, partly derived from FT even if not counted as such. Indeed, μTAS on chip format (Lab-on-Chip, LOC) [14], microdroplets (digital microfluidics) [23], and one-use-only approaches such as paper devices [24] are based on similar operation principles and partly derived from FT developments. Still, FT are the most appropriate tools to couple LOC devices to the real world or to interface high-performance analytical techniques to monitoring applications. Ultimately, FT concepts

are applied in many analytical instruments including autosampler systems, yet they are not reflected in the publication record. There are still only a few companies that provide analyzers based on SIA or even more recent FT while there are numerous offering discrete analyzers or those based mainly on segmented flow or, to a lower degree, on FIA. Thus, the *slope-of-enlightenment* for modern FT is most-likely still to come.

Publications of the past decades were focused significantly on the development of FT modalities and new principles of detection and sample pretreatment. In focus were tasks, which are hardly feasible without being automated *in-flow*, such as gas diffusion, turbidimetry, kinetic discrimination [25], or chemiluminescence [26], all benefiting from the key features of FT: reproducible injection and mixing and highly precise timing of detection. Moreover, the miniaturization and automation of enzymatic reactions [13], high-throughput analysis (process monitoring, feed to atomic spectrometers, etc.), and approaches taking advantage of chemical gradients (titrations, kinetic analysis, etc.) were main topics.

Today, mass spectrometry has become the preferentially used detection technique and the common analytical interest has shifted to biological matrices and trace levels of organic species. So, what can FT offer to solve the analytical problems of today?

FT are most successful for analytes of environmental, oceanographic, biotechnological, clinical, and pharmaceutical interest, where specific derivatization reactions are at hand or for which selectivity enhancement by matrix elimination or kinetic discrimination is possible. These are in particular inorganic analytes (international norms based on FT exist for some of them) or organic compounds with characteristic reactivity (e.g., formaldehyde), within sample matrices with predictable or minimal interferences (e.g., pharmaceutical formulations [26, 27]) or assays based on enzymes, molecular-imprinted sorbents, or selective, e.g. electrochemical, detectors. A long running relationship is further the use of FT for the determination of total indices such as the phenol index, methylene blue active substances, or organically bound halogens [28, 29]. An exception to this are applications based on the SIC concept, and—increasingly frequent—hyphenations with high-performance separation techniques where FT take over the part of automated sample processing [20, 30].

Part of the success of FT is surely for proving to be versatile tools of chemical research and for the possibility to do quality analytical work with low instrumentation effort and without the need for implementing sophisticated technologies such as microfabrication. On the other hand, the impact of FT as platforms for the demonstration of proof-of-concepts should not be underestimated. An outstanding exemplary approach developed by means of FT is the first study on using a liquid drop for analyte extraction [31]. Today, immersed and headspace single-drop microextraction have become standard

preconcentration methodologies and automated mainly on autosampler systems. FT will certainly inspire also future developments in analytical chemistry, and their unique features will surely be the key to many applications to come.

Current trends in FT include the study and characterization of novel micro- and nanomaterials for sensing and analyte preconcentration including quantum dots, metal organic frameworks, nanoparticles, nanofibers, molecular-imprinted polymers, and magnetic and carbonized sorbents [32, 33]. The same goes for studying new approaches to sample preparation with focus to SPE (e.g., fluidized particle SPE [34]) and LPME approaches, automated more and more by LOV and LIS, respectively.

Giving the number of applications, a recent comprehensive review comprising a list of > 100 specific treatises on FT aspects and fields of application [8] and a free online FT database [9] are recommended to the interested reader. Detection and separation techniques prone to matrix effects such as ICP-OES/MS or limited in sensitivity such as capillary electrophoresis can significantly benefit from hyphenation to FT automated matrix removal/analyte enrichment. Here, FT applications must level with modern batch automation considering the demands of today's separation science such as adaptation to biological matrices and ultrahigh preconcentration factors for environmental surveillance including, e.g., POPs. For this, the toolbox of FT is immense but to fulfill modern demand on performance and applicability, the interest of coupling study of coupling FT-procedures to MS detection will surely increase in the years to come [30].

Nutrients, classical FT analytes, are nowadays analyzed with high sensitivity and simultaneously by ion chromatography. So, FT are likely to be employed rather for process monitoring and in-situ analysis, where portability, robustness, high sample throughput, compactness of the respective analyzer, and the ability to in-line sampling from a continuous stream are essential features. This includes processes at research scale, e.g., study of membrane permeability of drugs [35] or soil leaching to evaluate toxins' bioaccessibility [36], (bio-)technological process monitoring [37, 38], up to surveillance of environmental systems, e.g., or concentration mapping of seawater by shipboard or submersible FT or µTAS analyzers [39]. Because FT generally feature high sampling rates, they allow valuable insights and improved understanding of the monitored systems. FT surely will retain this niche application, especially in view of the request for on-site or in-situ analyzers, e.g., for oceanographic research [40].

Another long-distance runner in FT and still with potential to be uncovered is the use of chemometric tools. While in FT, selectivity is often achieved by inventive utilization of chemical reactions or matrix separation (gas diffusion, extractions, etc.), mathematic tools bear the potential of an enormous performance boost to virtually zero-cost just by taking into account another dimension, e.g., reaction kinetics [25] or

spectral information [41], or reaction yield at different pH values [42]. While calibration strategies aim essentially at matrix compensation [43], kinetic approaches focus on the elimination of spectral background, differentiation between analytes, or, if the analyte acts as a catalyst, determinations of nanomolar concentrations. Following the reaction kinetics further allows estimation of an analyte's reactivity and behavior, e.g., as antioxidant, an approach of highest interest in pharmaceutical research [44].

A hot topic is further the accomplishment of analysis in flow on paper devices [24]. Based on similar concepts as FT, these systems are for one-use-only and provide cheap "take-away" laboratories, e.g., for environmental control [45]. Recently, FIA in paper format has been demonstrated for the first time [46].

Similarly, flow analysis in chip format adopts FT principles and likely yields higher acceptance in clinical analysis [47] as the component in contact with the sample is disposable. Layout of an FIA manifold as a laminated chip is dating back to the 1980s [48], formerly termed "integrated microconduits," nowadays "μFIA," and is just another example of the impact of FT on modern analytical chemistry. The interest in microfluidics as well as miniaturization of FT analyzers or parts of them, in particular by microfabrication, is unbroken and has come even more into focus by the possibility of prototyping components by 3D printing. This has already led to a commercial available advancement of the LOV concept (Flo-Pro ChemStack, GlobalFIA Inc., www.globalfia.com).

Finally, the capacity of FT for in-line chemical synthesis should be highlighted, that is the use of generally continuous flow for the parameter control (mixing, temperature, etc.) for high-performance chemical production, known as flow chemistry [49]. Flow chemistry presents some kind of parallel universe to analytical FT but each side can surely learn and benefit from the other.

Concluding, the potential of analysis performed in flow format is far from being exhaustingly explored but a trend toward modern automation FT as well as studying the potentials of microanalysis on chip or in paper format is evident.

Outlook

While many scientists may refer to analytical flow techniques as "toys," we rather concern them as *Tools Of Inventive Science* or "TOIS." We believe that developments in FT will continue to inspire other fields of analytical chemistry in the same way as novel materials, new fabrication techniques, and miniaturized components are being progressively used in FT manifolds, either to be studied or to enhance the analytical performance of the respective analyzers.

FT practitioners will have to deal with modern needs in analytical chemistry, such as the combination with other micro-analytical techniques, which will be of benefit for in-situ monitoring applications and improved understanding of our environment, as to help facing global climate change.

As for laboratory analysis, the development of generalized solutions for the hyphenation of FT to modern separation and advanced detection techniques as well as the adaptation to biological sample matrices and development of sample preparation for medical and bioanalysis are pressing needs. While the interest in versatile automation of these tasks is high, manuals of FT system setup and design, reviews to FT application in bioanalytical and clinical areas, and technical tutorials, e.g., on how to employ chemometric tools for FT are scarce, and adoption of FT automation for preparative procedures into commercial analytical instrumentations are few.

An exception in the future could be the recent Lab-In-Syringe, showing considerable similarity with autosampler systems with respect to instrumentation and operation. Therefore, the combination of both approaches for laboratory automation might bring an interesting advance, which—from the point of view of FT practitioners—could be understood as a "back-to-the-beaker."

On the other hand, considering the importance of sample pretreatment by SPE and the ideally matched suitability of the LOV technique for sorbent handling, i.e., the bead injection approach, we believe that this technique will be more and more employed in other areas of instrumental analysis. In fact, the LOV approach will become even more versatile and task-adaptable by exploring the possibilities of 3D printing. 3D prototyping of flow devices and related usability studies is already becoming a major topic in FT development and will build bridges to chip-based analysis and flow chemistry research and enable smaller, portable analyzers. Such impulses of technical developments reflected in FT development can be observed all the way back to the beginning: While the first SI-analyzer was based on a sinusoidal flow, the technique became launched with commercial availability of linear syringe pumps. So, the question is not only what FT are heading to, but also which stimulus and technical innovations will push FT development further and where flow analysis approaches will show irreplaceable or new niche methodologies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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