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Miniaturized Total Chemical Analysis Systems: a Novel Concept for Chemical Sensing

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Abstract

Following the trend towards smaller channel inner diameter for better separation performance and shorter channel length for shorter transport time, a modular construction of a miniaturized 'total chemical analysis system' is proposed. The theoretical performances of such systems based on flow injection analysis, chromatography and electrophoresis, are compared with those of existing chemical sensors and analysis systems.

Introduction

The continuous monitoring of a chemical parameter, usually the concentration of a chemical species, is gaining increasing attention in the chemical production, environmental and medical sciences. The chemical compound of interest is usually accompanied by interfering species. Figure 1 shows the average concentrations of all known compounds in human blood serum. If the compound of interest has a concentration of 10^{-5} moles per liter (several ppm), the analysis system must be sufficiently selective to reject at least 100 compounds of higher concentration. The state-of-the-art strategy for solving analytical problems like these is the introduction of a 'total chemical analysis system' (TAS), which periodically transforms chemical information into electronic information. Sampling, sample transport, any necessary chemical reactions, chromatographic separations as well as detection are automatically carried out (see Fig. 2, for examples see ref. 2). This approach presents a possibility for accommodating the rapidly changing composition of industrial samples (e.g., river water, chemical reaction mixtures, fermentation broths). In this paper we present a general concept for a miniaturized TAS.

Concept

A miniaturized TAS must be defined both in relation to a chemical sensor and to a TAS (Fig. 3).

An ideal sensor is specific, i.e. it transduces the concentration of the chemical compound of interest, to the exclusion of all others, into an electrical signal. In addition, the sensor can be immersed directly into a sample solution or stream. This concept is the goal of many sensor technologists, but so far the results (selectivity, lifetime) have been unconvincing.

Analytical chemistry offers a great number of methods for the analysis of almost every compound in any environment. Most of these methods are time consuming and require a fully-equipped chemical laboratory and a qualified technician. Some of these techniques, such as chromatography, electrophoresis or flow injection analysis can be integrated into a TAS. The detector or sensor in a TAS does not need high selectivity, because the sample pretreatment serves to eliminate most of the interfering chemical compounds. Furthermore, calibration can be incorporated into the system.

If a TAS performs all sample handling steps extremely close to the place of measurement, then we propose that it be called a 'miniaturized total

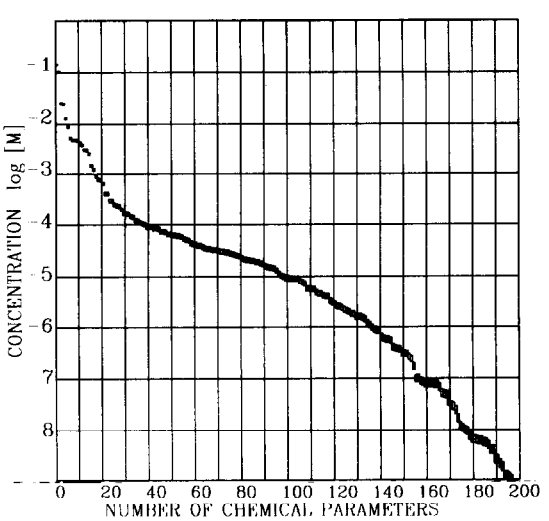

Fig. 1. Typical concentrations (moles per liter) of known chemical components (molecular weight less than 1000) in human blood serum [1].

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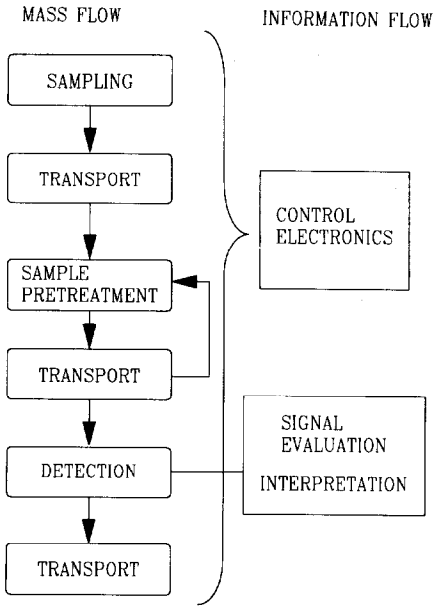

Fig. 2. General flow chart of a quantitative chemical analysis.

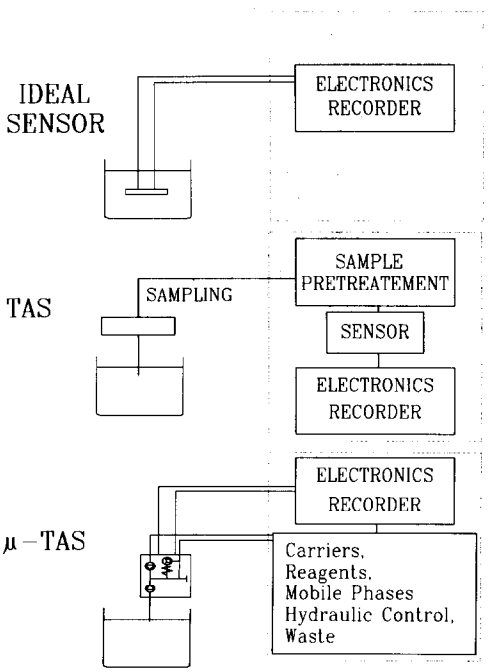

Fig. 3. Schematic diagram of an ideal chemical sensor, a 'total chemical analysis system' (TAS) and a miniaturized TAS (μ-TAS).

chemical analysis system' (μ-TAS). The interface to the control and measurement electronics could include, for instance, tubing for mass flow and optical fibers. If the analysis time of a μ-TAS is comparable to the response time of a selective chemical sensor, both are very similar in appearance and use (Fig. 4). Several research groups have done basic developmental work on micro pumps and valves [3, 4], small flow injection analysis systems [5] and open-tubular column chromatography [6, 7]. Our main reason for the miniaturization of the TAS is related to an enhancement of its analytical performance, rather than a reduction of its size.

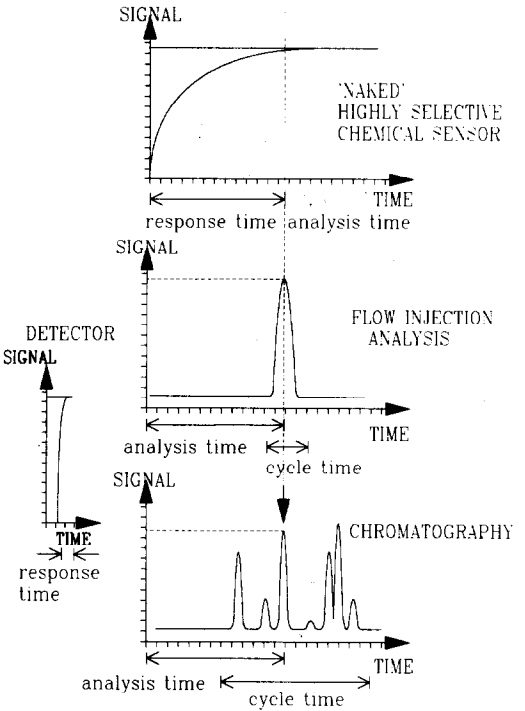

Fig. 4. Comparison of response time, analysis time and cycle time for an ideal chemical sensor, a flow injection analysis-based and a chromatography-based TAS.

Theory and Discussion

General

Let d be a typical length in a given system (for example the diameter of a tube). By multiplying each variable by d^n and the appropriate constants, it can be reduced to a dimensionless parameter which is independent of the spatial scale of the given system (for example the flow rate and the Péclet number). Similar systems of different sizes can easily be compared. If we assume that a miniaturization is a simple three-dimensional downscale, we can easily demonstrate the behaviour of the relevant physical variables. There remains one degree of freedom for mechanical parameters: time.

Time Constant System

In this case, the time scale is the same for the large and for the small system. Consequently, all

relevant time variables (analysis time, transport time, response time) don't change. The consequences are shown in Table 1(a).

The *Diffusion-controlled system* becomes important when molecular diffusion, heat diffusion or flow characteristics control the separation efficiency in the given system. In this system the time scale is treated as a surface, i.e. time is proportional to d^2.

This means that a down-scale to 1/10 of the original size (diameter of a tube) reduces the related time variables (transport time, required response time of a detector) to 1/100. The Reynolds number remains constant, but the pressure requirements increase by a factor of 100.

In the case of some electrical parameters the time scale must be constant in order for the definitions of the electric current, the electrical capacity and Ohm's law to be consistent. Nevertheless, three possibilities are presented in Table 1(b): constant charge density (system a.I), constant electrical field strength (system a.II) and constant voltage (system a.III). Experiments are needed to show which system is best suited to miniaturization.

For any given system, it is possible to start from one point and extrapolate to get the order of magnitude of the variables of a scaled-down system. Changes in geometry only change the estimation by a constant factor. Although these considerations do not contribute to a prediction of the feasibility of a system, they can, in principle, lead to the exclusion of impossible cases and give an idea of the order of magnitude.

TABLE 1(a). Proportionalities of some mechanical parameters in relation to the characteristic length d. System a: time scale remains constant during miniaturization, system b: time scale compensates for diffusion

	Time constant system a	Diffusion control system b
Time	constant	d^2
Space	d	d
	↓	↓
Linear velocity	d	d^{-1}
Volume flow rate	d^3	d
Linear acceleration	d	d^{-3}
Angular velocity	constant	d^{-2}
Impulse	d^4	d^2
Force	d^4	constant
Energy (work)	d^5	d
Power	d^5	d^{-1}
Reynolds number	d^2	constant
Pressure	d^2	d^{-2}
Pressure drop (laminar flow)	constant	d^{-2}
Pressure drop (turbulent flow)	$d^{1.5}$	d^{-2}

TABLE 1(b). Proportionalities of some electrical parameters in relation to the characteristic length d. (a.I): charge per volume remains constant, (a.II): electrical field strength remains constant and (a.III): voltage remains constant

	Time constant system a		
Time	constant		
Space	d		
Ohmic resistance	d^{-1}		
Electrical capacity	d		
	a.I	a.II	a.III
Electrical charge	d^3	d^2	d
Voltage	d^2	d	constant
Electrical field strength	d	constant	d^{-1}
Electrical current	d^3	d^2	d
Magnetic field strength	d^2	d	constant

Liquid Flow

Figure 5 shows the laminar flow rates required for time constant (flow injection analysis) and diffusion-controlled tubing systems (chromatography, electrophoresis). A pressure gradient yields flow rates proportional to those needed in a time constant system, regardless of the spatial scale. The electroosmotic flow generated by an electrical field remains constant as long as the electrical field is kept constant during miniaturization. In addition, the reduced production of heat might allow higher electrical field strengths with smaller tube diameters. Electroosmotic propulsion can therefore meet the demands of separation systems better than a pressure-driven flow (limited to aqueous electrolyte solutions).

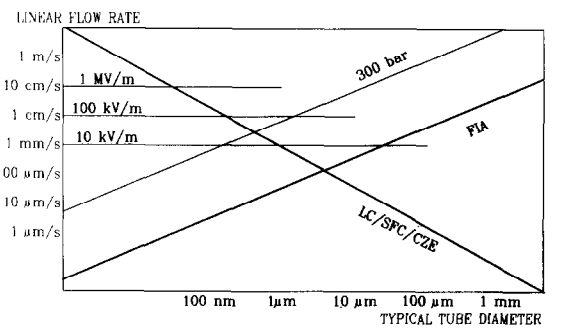

Fig. 5. Linear flow rate as a function of the tube inner diameter. The required flow rates for a time constant flow system (FIA: flow injection analysis) and for diffusion-controlled separation systems (LC/SFC/CZE: liquid chromatography, supercritical fluid chromatography, capillary zone electrophoresis) are compared with flow rates resulting from a pressure drop of 300 bar/m and of an electric field of 10 to 1000 kV/m.

Sample Pretreatment

Almost all methods of standard flow injection analysis [8] can be adopted. In a time constant flow system, the effect of turbulence decreases (Reynolds number changes, Table 1(a)) whereas molecular diffusion increases. A simple 'T' can thus function as a good mixing chamber in a miniaturized system.

Separation techniques can be considered as a special case of a sample pretreatment. In Table 2 the operational conditions needed to attain equal separation performances (number of theoretical plates) with electroosmotic chromatography [9], open-tubular liquid chromatography and supercritical fluid chromatography are compared. With increasing separation performance the open-tubular column inner diameter must decrease. A separation corresponding to 100 000 theoretical plates in 1 min is, by far, better than the experimental state of the art obtained with larger capillary diameters.

Detection

As Table 2 indicates, the detection volume restrictions are drastic in high performance separation systems (in the order of picoliters). The relationship of the signal output to the size of a detection system is critical for the detection limits in small volumes. For example, a fluorescence detector signal is proportional to d^3 and an amperometric to d^2. Refractive index and potentiometric detectors are almost totally insensitive to volume changes, as was experimentally proved with a Ca^{2+}-selective electrode [10, 11]. Despite the excellent detection limits obtained with fluorescence detectors, there must exist a detection volume at which potentiometric detectors are superior (see Fig. 6). In a flow injection analysis system, the detection volume would be comparably greater.

Generally, a definite limit is provided by the concentration at which exactly one molecule exists in the closed detection volume (Table 3(a)). This only holds for non-buffered molecules of interest. With pH measurements, for example, the total

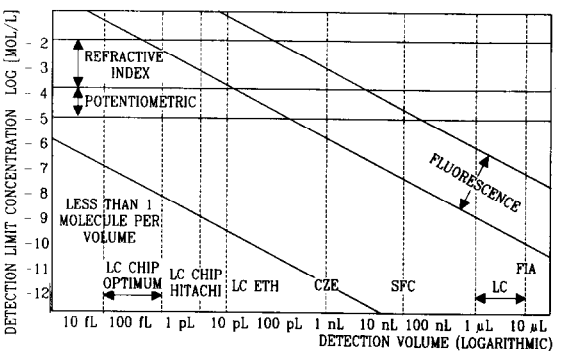

Fig. 6. Detection limits as a function of the detection volume for refractive index, potentiometric and fluorescence detectors. FIA: flow injection analysis, LC: conventional liquid chromatography, SFC: capillary supercritical fluid chromatography, CZE: capillary zone electrophoresis, LC ETH: capillary LC [12], LC CHIP HITACHI: see ref. 7.

TABLE 2. Calculated parameter sets for a given separation performance obtained with capillary electroosmotic (EC), liquid (LC) and supercritical fluid chromatography (SFC). Assumed constants are: diffusion coefficients 1.6×10^{-9} m²/s (LC, EC) and 10^{-8} m²/s (SFC), viscosities of the mobile phase 10^{-3} Ns/m² (LC, EC) and 5×10^{-5} Ns/m² (SFC), electrical conductivity of the mobile phase 0.3 Siemens/m (EC), electrical permittivity × zeta potential 5.6×10^{-11} N/V (EC), heating power 1.1 W/m (EC)

Parameter		Electroosmotic chromatography			Liquid chromatography		Supercritical fluid chromatography	
No. theoretical plates	N	100k	1M	10M	100k	1M	100k	1M
Analysis time	t ($k' = 5$) (min)	1	1	1	1	1	1	1
Heating power	P/L (W/m)	1.1	1.1	1.1				
Capillary i.d.	d (µm)	24	7.6	2.4	2.8	0.9	6.9	2.2
Capillary length	L (cm)	6.5	21	65	8.1	26	20	64
Pressure drop	p (atm)				26	2600	1.4	140
Voltage	U (kV)	5.8	58	580				
Peak capacity	n	180	570	>2000	220	700	220	700
Signal bandwidth	σ (mm)	0.21	0.21	0.21	0.56	0.56	1.4	1.4
	σ (ms)	42	13	4.2	70	22	70	22
	σ (pl)	94	9.4	0.94	3.3	0.33	52	5.2
Detection volume	V (pl)	47	4.7	0.47	0.8	0.08	1.2	12
Response time	t (ms)	21	6.5	2.1	16	5	16	5
Injection pulse	p^*t (s*atm)				1.5	49	0.075	2.4
	U^*t (s*kV)	0.41	1.3	4.1				
Stop time	t (s)	3.3	3.3	3.3	5.1	5.1	5.1	5.1

TABLE 3. Theoretical limitations of detection for non-buffered solutions of small molecules: (a) concentration and corresponding volume, which contains exactly one molecule, (b) response time of a detector and corresponding uncertainty in length or volume caused by molecular diffusion. Diffusion coefficient 10^{-9} m^2/s

(a) Closed volumes: less than 1 molecule per volume

Concentration log (mol/l)	Detection volume	Corresponding length
−3	0.002 al	12 nm
−4	0.02 al	26 nm
−5	0.2 al	55 nm
−6	2 al	120 nm
−7	20 al	260 nm
−8	200 al	550 nm
−9	2 fl	1.2 μm
−10	20 fl	2.6 μm
−11	200 fl	5.5 μm
−12	2 pl	12 μm

(b) Infinite volumes: uncertainty relation (space and time)

Response time	Detection volume	Corresponding length
10 μs	1 al	0.1 μm
100 μs	32 al	0.32 μm
1 ms	1 fl	1 μm
10 ms	32 fl	3.2 μm
100 ms	1 pl	10 μm
1 s	32 pl	32 μm
10 s	1 nl	100 μm
1.5 min	32 nl	320 μm
15 min	1 μl	1 mm

concentration of protons is, by far, larger than the concentration of free H^+. An uncertainty relation caused by the diffusion of molecules exists even in large detection volumes. A given response time of the detector dictates the spatial resolution of a measurement (Table 3(b)).

Conclusions

A basic theory of hydrodynamics and diffusion indicates faster and more efficient chromatographic separations, faster electrophoretic separations and shorter transport times for a miniaturized TAS. The consumption of carrier, reagent or mobile phase is dramatically smaller. A multi-channel device would allow the simultaneous performance of a large number of measurements (under the same conditions).

A μ-TAS will cause less problems than a chemical sensor in terms of selectivity, because well-known techniques of analytical chemistry can be applied as sample pretreatment. The integration of separation techniques enables multi-component monitoring with a single device.

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