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Micro Total Analysis Systems. 1. Introduction, Theory, and Technology

Darwin R. Reyes, Dimitri Iossifidis, Pierre-Alain Auroux,† and Andreas Manz*

Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY, U.K.

Review Contents

The area of micro total analysis systems, also called "lab on a chip", or miniaturized analysis systems, is growing rapidly. Since the excellent research documented in many publications easily gets confusing to a newcomer, the aim of this review is to help a novice in the field to find the original papers easier. Sensors, arrays (so-called "biochips"), chemical synthesis on-chip, and many of the more technical (engineering) papers have been omitted, as it is the scope of this paper to cover microfluidic systems for analytical chemistry only.

Excellent information sources about this area are conferences such as Transducers, μTAS, and HPCE, but a lot of authors do not turn up there. Publications are scattered across the literature, with traditional and frequent occurrence in journals such as *Analytical Chemistry*, *Sensors & Actuators*, *Electrophoresis*, and very recently, *Lab on a Chip*. Recommended reviews are as follows: Planar Chips Technology for Miniaturization of Separation Systems: A Developing Perspective in Chemical Monitoring (*1*), Chip Based Microsystems for Genomic and Proteomic Analysis (*2*), and Microfluidic Chips for Clinical and Forensic Analysis (*3*). We will not cite any other review or polemic paper as there are very many out there and they rarely cover the whole area.

Since this is the first of these reviews in this area, we decided to start off with a history section, covering the years from the early beginning to 1997, whereas the following sections cover the period from 1998 to March 2002. The review does not intend to cover 100% of the papers, but rather tries to choose some relevant examples for every distinctive type of method or device.

HISTORY

The Early Days (1975−1989). More than 25 years ago, the first analytical miniaturized device fabricated on silicon, a gas chromatographic analyzer, was presented (*4, 5*). This remarkable gas chromatograph was able to separate a simple mixture of compounds in a matter of seconds. This device included (in a single silicon wafer) an injection valve and a separation column 1.5 m long. A thermal conductivity detector was fabricated on a separate silicon wafer and mechanically clamped on the wafer containing the column. Despite its rapid separation capabilities and minute size, the response of the scientific community to this first silicon chip device was virtually none, presumably because of the lack of technological experience (of the separation scientists) to deal with this kind of device. Instead, the research work related to miniaturization on silicon focused on the fabrication of components such as micropumps (*6−11*), microvalves (*12, 13*), and chemical sensors (e.g., SAW devices and ISFETs). Only few examples demonstrating the use of silicon micromachined devices were reported, basically combining solid-state chemical sensors with other structures in silicon. An example of such devices is a coulometric acid−base titration system, which employed a solid-state pH-sensitive sensor to determine the acid or base concentration in a solution (*14*). Also, the T-injection design was presented early, in 1988, by Verheggen et al. and reproducible pressure-driven injections were demonstrated (*15*).

"The Renaissance" (1990−1993). It was not until 1990 that the reemergence of silicon-based analyzers took place with the presentation of a novel work based on a miniaturized open-tubular liquid chromatograph on a silicon wafer (*16*). This work presented a 5 × 5 mm silicon chip containing an open-tubular column and a conductometric detector, connected to an off-chip conventional LC pump and valves to perform high-pressure liquid chromatography. Simultaneously, the concept of "miniaturized total chemical analysis system" or μTAS was proposed by Manz et al. (*17*), in which silicon chip analyzers incorporating sample pretreatment, separation, and detection played a fundamental role. μTAS was envisioned as a new concept for chemical sensing, needed since sensors at that time were not providing the best results in terms of selectivity and lifetime. Initially, the main reason for miniaturization was therefore to enhance the analytical performance of the device rather than to reduce its size. However, it was also recognized that a small size presented the advantage of a smaller consumption of carrier, reagent, and mobile phase. Moreover, the total chemical analysis system scheme provided an integration of separation techniques that could enable the monitoring of many components within a single device. Such a system was envisioned capable of performing sample handling, analysis (e.g., chroma-

† Current address: Division of Oncology, Functional Genomics Unit, University Children's Hospital, Zurich, Switzerland.

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tography, electrophoresis), and detection and incorporating control of mass transport and measurements.

Early theoretical considerations of the miniaturization concept showed that electroosmotic pumping was an attractive and feasible way to move aqueous media through interconnected channel systems in a miniaturized TAS, particularly when separation was needed (*17*). Conversely, conventional pumps available in the early 1990s showed a major problem with the high pressures necessary for transport in channels in the order of 1−20 -μm i.d. and 1−10-m length. Meanwhile, the efforts to carry on the development of micropump systems (*9, 11*) and sample injectors (*10, 13*) for microflow systems continued.

In an effort to surpass the limitations in the integration of valves, pumps, and detection systems, in miniaturized flow injection analysis (FIA), stacked modular devices in silicon and plexiglass were designed and tested (*18, 19*). This device conformed a three-dimensional structure in which more than 10 chips, having a distinctive access by means of holes, were placed one on top of the other. Two main advantages characterized this device versus a typical microconduit device: first, the viability to rotate each chip independently, so that different accesses could be obtained, and second, the use of flow to control the injection and valve processes without the need of mechanical valves. An even smaller silicon device (less than 1 cm^3) was also designed, and the layouts were presented. In this case, an optical detection cell, connected to a fiber optic, was integrated into the system. Further research work was carried out to test this optical cell (*20*). This work proved the successful use of this cell for UV−visible absorption detection, but due to the loss of light in the multireflection process, the efficiencies were low. The concept is now used commercially in a Hitachi product.

Electroosmotic pumps are characterized by the absence of mechanically moving parts and the lack of a specific localization of the pump in the manifold, producing an even electroosmotic flow in the entire length of the capillary channel. Moreover, the flow in interconnected or branched channels can be controlled by switching voltages, without the need of valves. Experimental efforts to use electroosmotic pumps were, therefore, first directed to optimize injection and separation procedures by the switching of voltages between the carrier, reagents, mobile phase, and waste reservoirs (*21, 22*).

Electrophoresis in planar chips was successfully integrated and its use demonstrated for the first time in 1992 using silicon and glass substrates (*23, 24*). Those papers proved the viability of using electroosmotic pumping for flow control in interconnected channels without the use of valves and the suitability of glass and to some extent silicon substrates for electroosmotic pumping and the electrophoretic separation of samples. In general, the concept of μTAS, integrating injection, separation, and detection within the same device was demonstrated. Subsequent efforts were directed to increase the separation speed in glass (*25−27*) and silicon chips (*28*). Amino acids and dyes were separated in less than 30 s with plate heights of 0.3 μm. It was also demonstrated that an automated repetitive sample injection and separation procedure on a time scale of seconds was achievable. Laser-induced fluorescence was used at this stage to detect mixtures of fluorescein derivatives and fluorescein isothiocyanate-labeled amino acids separated on-chip (*29*). In addition to the separation of biological samples, applications related to the reaction and handling of biomolecules and cells started to emerge. Some examples comprised the use of microfabricated chambers to carry out DNA amplification (PCR) (*30*), the measurement of cellular metabolism in micromachined multichannels (*31*), and the use of microchips to carry out flow cytometry (*32*).

Growing to Critical Mass (1994−1997). In 1994, the number of published papers related to μTAS increased abruptly since more research groups joined the efforts to develop the area. The use of chip-based analyses started broadening and varied from integration of reactor chambers for continuous precolumn reactions (*33*) and postcolumn labeling reactions (*34*) to fast and highly efficient separations (in the order of hundreds of milliseconds and up to 18 600 plates/s) (*35*). Branebjerg et al. studied the mixing conditions in two different channels on the same device (*36*) while Mensinger et al. incorporated Möbius-type static mixing stations at the bottom of the device channel (*37*). Also, separation of oligonucleotides (*38*), DNA (*39*), and amino acids (*40*) and cell manipulation by electrical fields (*41*) were successfully introduced. These results later led to a range of commercial products by Caliper, Agilent, Shimadzu, and Hitachi. More specialized separation modes included synchronized cyclic capillary electrophoresis (*42*) and free flow electrophoresis (FFE) (*43*). The modular concept was revisited, but this time using both electrochemical and optical detection (*44*). An on-chip liquid chromatography with an electrochemical detector was characterized by Cowen and Craston using an iron complex in solution (*45*). Flow control studies using the rules for resistive networks (Kirchhoff's law) to predict the currents and fluid flow within interconnected microchannels driven by electroosmotic flow were reported (*46*). Injection modes using a cross-type channel geometry were studied (*47*). Surface chemical modification of the channels, using octadecylsilane as stationary phase for open channel chromatography, was achieved for the first time in planar chips (*48*). Feustel et al. developed a miniaturized mass spectrometer incorporating an integrated plasma chamber for electron generation, an ionization chamber, and an array of electrodes acting as the mass separator (*49*).

In the subsequent years, new approaches in microfabrication, separation modes, detection schemes, analysis of biological species, and bio- and chemical reactors were studied. The following section reviews the work done between the years 1995 and 1997.

1. Microfabrication (1995−1997). Most of the methods used in micro total analysis device manufacturing were developed in the 1970s and 1980s in the silicon microprocessors industry and can be found in textbooks, for example, *Fundamentals of Microfabrication: The Science of Miniaturization* (*50*) and *Handbook of Microlithography, Micromachining, and Microfabrication* (*51, 52*). To cover a broader range of applications for use in chemistry, new materials and microfabrication procedures were tested and added to the existing repertoire. The references given here represent only a small fraction of the actually published work. For more detailed information a study of Transducers, MEMS, and μTAS conference proceedings is recommended.

A molding procedure was used to pattern network channels by placing in contact a substrate and a patterned elastomeric master (*53*). A new technique, known as microcontact printing,

was used to pattern structures of self-assembled monolayers (SAMs) on the submicrometer scale (*54*). Microtransfer molding, another new technique, could be used for the rapid fabrication of structures in the micrometer scale over large areas and could generate microstructures of organic polymers and ceramics in three dimensions using a layer-by-layer structuring (*55*). Poly(methyl methacrylate) (PMMA) substrates were imprinted, using an inverse three-dimensional image of the device micromachined on silicon, and used to fabricate microfluidic devices (*56*). A low-temperature bonding process was created by spinning a sodium silicate layer as an adhesive, on a glass cover plate, and sealing it against the microfluidic channels glass plate either at 90 °C for 1 h or overnight at room temperature (*57*). A technology in which a substrate containing a set of periodic vertical groves can be interlocked with another substrate having the complementary structure (allowing the interconnection of fluids) was proposed by Gonzalez and co-workers (*58*). Microchannels of 80-nm width on carbon-based resist were fabricated by Johnson et al. on Si, SiO_2, and gold substrates by exposing them to a metastable argon atom beam in the presence of dilute vapors of trimethylpentaphenyltrisiloxane (*59*).

The preparation and characterization of optical and mechanical properties of SU-8 negative photoresist for the fabrication of high-aspect-ratio structures were reported by Lorenz and co-workers (*60*). Using alternating spin-coating of SU-8 photoresist and exposure steps followed by a single development step to remove the unpolymerized resist, Guérin et al. have fabricated monolithic SU-8 channels (*61*). Larsson et al. fabricated 3D microstructures by conventional CD injection molding against an electroform mold insert produced by wet and DRI etched silicon master (*62*).

Arquint and co-workers bonded silicon−polysiloxane−silicon by first depositing poly(dimethylsiloxane)-based photosensitive prepolymer onto a silicon substrate, then photopolymerization by UV light followed by development in xylene, and finally bonding to the second silicon wafer by humidity-induced polymerization at ambient air (*63*).

Other micromachining techniques have been presented using deep reactive ion etching (DRIE) and surface fusion bonding (SFB) (*64*) and an electron cyclotron resonance (ECR) source (*65*) to produce high-aspect-ratio narrow-gap silicon devices. Soft lithographic techniques for the fabrication of nanostructures have been reviewed before (*66*).

2. Design (1995−1997). Bousse and co-workers have described a microfabricated electrokinetic device, which consists of a loading channel intersecting a series of parallel separation channels, that is capable of distributing a serial sample into the parallel separation channels, eliminating leaking into the side channels in the loading step, and achieving a identical separation conditions in each separation channel (*67*).

Another serial to parallel converter for CE was developed by Manz and Becker in which 17 parallel channels were intersected by an injection channel while having only 4 electrodes controlling the injection (*68*).

3. Separations (1995−1997). Various electrophoretic separation modes were for the first time applied on microchips. Jacobson et al. used a microchip of fused quartz to separate complexed metal ions in polyacrylamide-modified channels (*69*). Another liquid chromatograph was presented by Ocvirk et al. where a split injector, a packed small-bore column, a frit, and an optical detector cell were all integrated onto a silicon chip (*70*). Micellar electrokinetic capillary chromatography (MECC) of neutral dyes (*71*) and biological samples (*72*) was performed on glass microchips. The same method was applied in a monolithic micromachined device, which allowed the adjustment of the content of organic modifiers in the running buffer (*73*). A FFE silicon microstructure was used to perform a continuous separation of high molecular weight compounds (*74*). Capillary gel electrophoresis of amino acids, using a linear, non-cross-linked polyacrylamide gel matrix, was performed obtaining a highly reproducible separation and submicrometer plate heights (*75*). Capillary array electrophoresis (CAE) devices were designed and fabricated with the capacity to analyze and detect 12 different DNA samples in parallel in less than 160 s, proving to be useful for high-throughput genotyping (*76*).

4. Biochemical Reactors (1995−1997). Reaction chambers on-chip for PCR, DNA sequencing, immunological reactions, and other biological reactions, followed by subsequent analysis of the biomolecules involved, were also developed. Woolley and Mathies carried out ultra-high-speed DNA sequencing and separation, using denaturing polyacrylamide as sieving medium and one- and four-color separations on microfabricated capillary electrophoresis chips (*77*). A miniature thermal cycling device based on silicon chambers was developed by Northrup et al. This battery-operated apparatus was tested using biological DNA samples such as from the human immunodeficiency virus, the gene for the genetic disease cystic fibrosis, and others (*78*). Surface passivation of silicon chip devices, to obtain amplifications comparable with those obtained in conventional PCR amplification systems, was accomplished (*79*, *80*). Microfabricated silicon PCR reactors were successfully coupled to glass capillary electrophoresis chips, filled with hydroxyethylcellulose sieving matrix to form an integrated DNA analysis system (*81*). A postcolumn reactor in fused silica and glass for *o*-phthaldialdehyde labeling of amino acids (*82*) and a preseparation mixing of chemical reagents for reaction, post-separation fluorescent labeling, and immunological assays were presented (*83*). A competitive immunoassay in which free and bound labeled antigens were separated by CE and quantified was presented by Koutny et al. The analysis of a blood serum sample for the determination of cortisol in the range of clinical interest was successfully accomplished (*84*).

An enzyme assay in a microchannel network of nanoliter volume in which the substrate, enzyme, and inhibitor were mixed using electrokinetic flow was presented by Hadd et al (*85*). An enzymatic restriction reaction with DNA and the electrophoretic sizing of the mixture were performed using a monolithic device that executed the biochemical procedure automatically (*86*). Effenhauser et al. collected oligonucleotides by isolation of fraction zones after fast CE size separation (*87*) and in a later work performed the analysis of DNA restriction fragments and DNA single molecules using capillary electrophoresis on a poly(dimethyl siloxane) device (*88*). An ultrafast allelic profiling analysis of short tandem repeats was achieved in a device filled with polyacrylamide. Electrophoretic separation of PCR samples was accomplished in less than 2 min (*89*). Li and Harrison mobilized biological cells through a network of capillary channels using electrokinetic pumping (*90*). Separation and relative quan-

titation of human serum proteins were successfully resolved on-chip (*91*). Delamarche et al. used elastomeric microfluidic devices to pattern immunoglobulins with high resolution on a variety of substrates (gold, glass, polystyrene) (*92*). Products of immunological reactions were separated in a microchip capillary electrophoresis device within 40 s (*93*). A prototype of a miniaturized flow injection analysis system comprising biosensors and microdialysis was developed by Freaney et al. and applied to on-line monitoring of glucose and lactate in blood in vivo (*94, 95*). Gavin and Ewing characterized an electrochemical array detector for the continuous electrophoretic separation and detection in narrow channels (0.6 μm in height) of dopamine samples (*96*). A diffusion-based extraction device was developed by Brody and Yager and tested with a mixture of water, a small fluorescent dye carboxyfluorescein, and some bigger fluorescent beads. The dye and the beads were successfully separated (*97*).

5. Detection (1995−1997). Bousse and McReynolds presented the fabrication of the light-addressable potentiometric sensor (LAPS) and applied their detection system on two types of biological components: enzymes and living cells (*98*). Liang et al. micromachined an absorbance and fluorescence U-shaped glass detection cell for application in capillary electrophoresis and obtained a 10-fold increase in absorbance compared to a path transverse to the flow direction (*99*). Electrochemical cells for the generation and detection of electrochemiluminescence were fabricated in silicon (*100*) and PMMA (*101*) and successfully tested. A silicon flow structure was fabricated and used to detect chemical concentrations optically, in a complex solution, by mixing with a fluorescent indicator whose properties are a function of the concentration of the analytes (*102*). Hodder et al. microfabricated a flow chamber to perform fluorescence-based assays. They also used stopped-flow injection analysis to achieve a better reproducibility when mixing the sample and the reagent streams (*103*). A miniaturized Coulter particle counter was realized by hydrodynamic focusing of the particle containing sample using a multilaminar flow (nonelectrolyte−electrolyte−sample−electrolyte−nonelectrolyte) to a single particle stream, through an orifice in a wide channel where an electrode measures the drop in the resistivity of the flow when a particle goes through (*104*).

First efforts to couple mass spectrometry and microfluidic devices started in 1994 (*49*), and in the subsequent years, the continuous efforts brought about new and important results in this area. Xue et al. successfully interfaced a glass device with an electrospray mass spectrometer and achieved detection limits lower than 6×10^{-8} M for myoglobin (*105*). Ramsey and Ramsey described a method to generate electrospray from small channels etched on glass planar substrates and demonstrated its successful use by connecting to an ion trap mass spectrometer (*106*). A nanoelectrospray mass spectrometry approach, in which a device for the introduction of a sequential mixture of peptides without the need for sample manipulation was used, proved to be suitable for the analysis of small amounts of proteins (*107*). The system was further tested and allowed sample analysis of peptides from on-chip tryptic digestion of melittin (*108*). Desai and co-workers developed an electrospray microdevice with an integrated particle filter which ends on a 1 μm high and 2 μm wide silicon nitride microchannel from which the fluid is sprayed when subjected to a potential drop between 1 and 4 kV (*109*).

THEORY OF MINIATURIZATION

Early Conceptions. At the same time as the concept of μTAS was proposed, theoretical considerations in terms of similarity and proportionality were shaped (*1, 17*). One approach employed dimensionless parameters to consider similarity; the other used the characteristic length of known systems versus scaled-down systems to consider proportionality. Dimensionless parameters can be used to correlate in an easy way experimental results when a great deal of variables are involved and are defined in terms of parameters that are assumed to be constant through the whole system under study. The Reynolds number, for example, used to characterize laminar and turbulent flow regimes, is one of the parameters well known in fluidics. Using these parameters, the extrapolation of results obtained for one system to another is possible. It is less well known, however, that dimensionless parameters can be used for plate number and retention time in separation-based systems by expressing these variables in the constant factors of internal diameter, volume, and diameter (*1*).

On the other hand, the approach that considers proportionality provides helpful information related to the behavior of a simple flow system when miniaturized. If miniaturization is assumed as a downscaling process in three dimensions, represented by atypical length (d), the behavior of the physical variables of interest is predictable. For example, two systems can be distinguished, a time-constant system and a diffusion-controlled system. In the former, the time scale is the same in both large and miniaturized systems and variables such as analysis time and transport time stay unaffected, while others such as linear and volume flow rate decrease. Meanwhile, in the diffusion-controlled system, the time is regarded as a surface and proportional to d^2. Hence, this system is in accordance with the band-broadening theory in chromatography and electrophoresis, which means that diffusion processes such as heat diffusion, hydrodynamic diffusion, and molecular diffusion behave the same in both systems. In other words, if a system is downscaled by 1/10, the time variables decrease by a factor of 1/100, pressure increases by a factor of 100, and voltage requirements remain constant, but the essential chemistry and separation behavior retain the same quality (*1*).

The behavior of FIA, LC, SFC, and CE in terms of linear flow rates versus internal tube diameters was compared to give an extrapolation of the behavior in miniaturized systems (*1, 17*). For open tubular chromatography and supercritical fluid chromatography, the linear flow rate needs to be decreased when the tube diameter is increased; the opposite occurs with FIA where an increasing linear flow rate is needed when the tube diameter is increased. Whereas, in miniaturized systems, the linear flow could be maintained constant throughout diameters of up to ~100 μm. In electrophoretic separations, the linear flow rate will be independent of the tube diameter due to the electroosmotic flow. Also, because of the increase in heat transfer observable in miniaturization, the use of higher voltages is allowed providing faster separations compared to larger systems. Other operational conditions, such as pressure drop, capillary length, peak capacity, and some others, were examined and estimated for specific separation efficiencies (*17*).

Theoretical Descriptions and Simulations. Electroosmotic flow has played a key role in the development of the μTAS concept

and the publications concerning the theory cover aspects of EOF in microfluidic systems, as well as scaling laws, diffusion and dispersion processes, and detection schemes. Initial theoretical work on electroosmotic flow showing, for example, that it decreases when the ratio of the capillary diameter and the double-layer thickness is smaller than 20 was performed as early as the 1960s (*110*− *112*).

Brody et al. explained how flow at small Reynolds numbers, in microscopic sizes, could govern the design of microfluidic devices and gave some examples for biological processes (*113*). For a review on Reynolds numbers in microfluidics devices, the reader should refer to Gravesen et al. (*114*). Electrokinetic migration and diffusion were simulated and compared with experimental data in two key microfluidic elements, a cross and a mixing tee (*115*). A numerical scheme for the injection in a cross-channel geometry was developed, and the electroosmotic characteristics of the injection were studied (*116*). Theoretical and experimental studies were carried out for five microstructures to study the effect of the dispersion of a dye in a microflow system. The flow profile, pressure distribution, and concentration distribution of the species studied were obtained from a theoretical model (*117*).

Culbertson et al. studied the theoretical aspect of the differential transport of anions through an electrically floating channel. This work showed an electrokinetically induced hydraulic pressure difference throughout a field-free channel, using a T-intersection, and presented the mathematical treatment to predict the length of the field-free arm to accept or discard anions of known electrophoretic mobility (*118*). Peles et al. investigated laminar flow in a capillary, induced by liquid evaporation from the interface and assuming an uniform profile of the hydrodynamic and thermal parameters (*119*). Ermakov et al. studied electrokinetic injection modes (pinched and gated) by means of simulations to obtain the operating parameters for optimal valve functioning (*120*).

Using experimental data, an analytical model was developed by Kamholz et al. to quantitatively describe the molecular interactions in the microchannel of a T-sensor (a microfluidic chemical measurement device that takes advantage of the low Reynolds number condition observed in microchannels) (*121*). In a subsequent work, one- and two-dimensional models were used to quantify the analyte time-dependent distribution in the flow of a T-sensor and a depiction of the interdiffusion region and calculation of the diffusive scaling law were obtained (*122*). A theoretical analysis of the scaling laws of the T-sensor, in terms of the diffusion of the analyte, was later presented (*123*).

The diffusion of low molecular weight species across the interface between two pressure-driven laminar flows at high Peclet numbers was experimentally and theoretically quantified by Ismagilov et al. (*124*). The effect of the quarter-circular end geometry of microchannels was investigated by Dutta and Leighton in terms of the magnitude of longitudinal dispersion for pressure-driven flows and modifications of the design to minimize such dispersion (*125*). In another work related to dispersion, but in this case due to microchannel turns, Griffiths and Nilson used numerical methods to optimize the two-dimensional geometry of microchannel turns in order to minimize the turn-induced spreading of a solute (*126*). Molho et al. developed numerical models to minimize dispersions in microchannel turns and experimentally validated (*127*).

Santiago presented an analysis of the effects of fluid inertia and pressure on the inner and outer flow regions of the velocity field in electroosmotic flow in microchannels. The validity of the assumption that the slip velocity condition, which divides the inner and outer regions of the flow, is determined by the Helmholtz−Smoulochowski equation was studied. Also, a theoretical study of the scaling laws that govern analyte diffusion in a pressure-driven flow with nonuniform velocity distribution in microfluidic channels was presented (*128*). A theoretical description of the behavior of partial electroosmotic and hydrodynamic flows in complex capillary systems was presented by Morf et al. (*129*). Dutta and Beskok studied parameters such as the velocity distribution, mass flow rate, and pressure gradient (among others) of mixed electroosmotic/pressure-driven flows using numerical methods (*130*). Gale et al. presented a theoretical analysis of the fundamental scaling laws associated with electrical field flow fractionation channels (*131*). A theoretical explanation for the strong additional band broadening induced by the side walls in flow channels of large rectangular cross section was presented and validated for pressure-driven and shear-driven flow (*132*). The effect of microchannel turns on the spreading of a species in an electrophoretic separation band was physically and numerically modeled by Fu et al. (*133*).

A spiral geometry microchannel with a modified inner wall was designed and investigated to minimized electrokinetic dispersion in systems of large Peclet numbers or small radii (*134*). A use of dynamic correction of altered elution times caused by anomalous flux, due to protein adsorption onto capillary walls in electrophoretic separations, was suggested by Ghosal (*135*). Kuksenok et al. simulated the regulation of the flow of binary fluids in microfluidic channels and observed that the wettability of the substrate surface has a significant effect on the flow patterns (*136*). A theoretical work that described the convective−diffusive transport of solute particles in solvent-filled networks was presented by Dorfman and Brenner (*137*). The temperature patterns of continuous-flow PCR in glass−glass and silicon−glass chips was studied using finite element analysis (*138*).

TECHNOLOGIES

The design and use of microfluidic devices is dictated by the availability of technology to fabricate them, modify their surfaces, and interface them with a variety of detection modes. Since the concept of a micro total analysis system is conceived as an analytical device capable of performing all required processes of a sample analysis, it is crucial to improve the existing technology while researching for new substrate material, fabrication techniques, designs of features, channels, electrodes, etc., and interfaces to the world. This section reports on important research that has been carried out, over the period from 1998 to March 2002, related to microfabrication, bonding techniques, surface modification, design, and interfaces, as well as developments in the fields of micropumps and microvalves, as far as considered relevant to μTAS.

Microfabrication. While silicon and glass dominated the early years, a trend toward polymers as substrate material is observed.

In addition, much of the recent technology research focuses on submicrometer structures.

Laser ablation was used by Grzybowski et al. for rapid fabrication of elastomeric masters (poly(dimethylsiloxane), PDMS) for microcontact printing (μCP) and a technique named controlled sagging microcontact printing (CSμCP) was developed, capable of patterning structures of 1 μm in width without the need of a cleanroom environment or specialized photolithographic tools (*139*). A method to fabricate 3D complex microstructures was presented by Jackman and co-workers, using two different strategies, both starting with a two-dimensional pattern, which is transformed in a free-standing 3D microstructure by connecting patterns on intersecting areas (*140, 141*). Using a rapid prototyping technique, Anderson and co-workers fabricated a multilayer "basket weave" structured channel that can cross over and under itself in any knot configuration (*142*). Juncker et al. showed the use of elastomeric (PDMS) or silicon two-level microfluidic networks (as masters) to pattern surfaces in a single step (*143*). 3D aligned microstructures have been fabricated by Tien and co-workers, by pressing a multilevel PDMS stamp on a substrate and applying a soft lithographic technique every time a new level of the stamp came into contact with the substrate surface, to produce complex patterns of aligned microstructures (*144*). Jo et al. developed 3D microchannel structures by stacking sub-100-nm patterned PDMS films (*145*). Employing oxygen plasma oxidation of PDMS, irreversible bonds with glass, silicon, and other PDMS substrates were achieved while the surface was rendered hydrophilic, capable of supporting electroosmotic flow (EOF) (*146*).

Nickel electroforms were produced from a silicon master, for the injection molding of acrylic polymer resins (*147*). Zhao et al. demonstrated the use of shrinkable polystyrene films to reduce the size (width) of microstructures and to increase the height perspective of planar and curved surfaces, from which molds and replicas can be obtained (*148*). Hot embossing was used to fabricate microchannels on PMMA, polycarbonate, and Zoenor 1020, a polymer capable of supporting EOF on its native surface (*149*−*151*). Shen and Lin investigated the theoretical and practical aspects of hot embossing for the fabrication of curved polycarbonate microlenses (*152*). Sub-one-hundred-micrometer PMMA structures have been obtained by dry etching (*153*), imprinting of a surface-treated silicon master (*154*), and hot embossing techniques (*155*). Microchannels on stretched poly(ethylene terephthalate) (PET) films using laser ablation were reported by Wagner et al. (*156*). Webster et al. fabricated parylene-C channels on polycarbonate substrates using vapor deposition to produce plastic CE chips (*157*). Photopolymerization of a prepolymer mixture of monomers and a photoinitiator through a mask was used by Beebe and co-workers, to manufacture microfluidic systems (*158*). Armani and co-workers developed a process that involves the molding, surface metallization, and bonding of polycaprolactone, a biodegradable polymer (*159*). Marangolis et al. fabricated flexible polyimide microchannels using standard photolithographic techniques (*160*). Metz et al. presented a polyimide-based microfluidic device combined with metallization layers to incorporate electrodes in and outside the channels (*161*). The fabrication of borosilicon carbonitride (SiBNC) ceramic microstructures was described by Yang et al. (*162*). Colburn et al. reported the used of a molding process (step and flash imprinting lithography, SFIL) in which structures with sub-100-nm features were patterned (*163*). Lee et al. fabricated high-aspect-ratio Teflon devices using ion beam etching (IBE) (*164*). A direct writing method for the three-dimensional fabrication of Teflon (poly(trifluoroethylene), PTFE) was developed by Katoh and co-workers (*165*). Van Kan et al. used proton beam micromachining (PBM), a technique that focuses megaelectronvolt protons to produce 3D high-aspect-ratio microstructures on SU-8 and PMMA, which were then electroplated to be used for micromolding and imprinting (*166*). Renaud and co-workers reported the fabrication of microchannels in SU-8 using filling, masking, and lamination techniques (*167*). Methods for the fabrication of embedded channels in positive and negative photoresists have been reported by Alderman et al. (*168, 169*).

The micromachining of quartz substrates for liquid chromatography columns was presented by He et al., as an alternative to the conventional packed column approach (*170*). Ceriotti and co-workers fabricated high-aspect-ratio quartz microchannels using inductively coupled plasma reactive ion etching (ICPRIE) through an electrodeposited nickel mask (*171*). Tjerkstra et al. fabricated concentric hemispherical microchannels using electrochemical silicon etching (*172*). Brugger and co-workers developed a method for single-side wet etching of Si and SiO_2 substrates by confining the etching solution to the desired surface using a PDMS O-ring seal (*173*). A widely applicable method of fabrication in PDMS, glass, and silicon using laminar flow was demonstrated by Kenis et al., where lines were patterned by the transport of reactive species throughout a channel (*174*). By depositing a thin layer of silicon nitride on a silicon wafer, anodically bonding it to a glass substrate, and subsequently removing the silicon, a transparent 390-nm free-standing silicon nitride microchannel was fabricated by Schasfoort et al. (*175*). A fabrication method called buried channel technology, in which channels, cavities, and connection holes in the bulk of a silicon wafer were constructed by several steps of trench etching and sidewall coating, was presented (*176, 177*). Deposition of silica, with a variety of diffractive indices for low-loss planar waveguides purposes, and glasses, to incorporate the microfluidic network in the same device, was presented by Ruano et al. and successfully tested with a microtitration system (*178*). Plasma etching was used either to fabricate plastic microfluidic devices directly or to etch a silicon master for hot embossing (*179*). A nozzle 50−100 nm in diameter using neutral radicals from a plasma discharge to fabricate features in the range of hundreds of nanometers was presented by Rangelow and co-workers (*180*). Shroff et al. designed and fabricated a mirror array for extreme UV maskless lithography (*181*). Spin on glass (SOG) was used by Matsui to fabricate line widths of 200 nm as an alternative to PMMA (*182*).

A prototyping method was proposed by Duffy and co-workers, in which a transparency was used as a photomask to create a master in a positive photoresist (*146, 183*). Microscope projection photolithography (MPP), a technique developed by Love and co-workers, also employs a transparency mask which is placed in the microscope light path and is then projected onto a photoresist-coated substrate through the microscope objective (*184*). Paul et al. demonstrated that features embossed on the surface of a photoresist layer could act as optical elements by directing UV light to produce features of 50−250 nm (*185*). Deep reactive ion

etching of Pyrex using SF_6 plasma was reported by Li et al. (*186*). Deng et al. developed a method to fabricate photomasks, masters, and stamps starting with printed structures on paper, followed by its reduction by transferring to a 35-mm film or microfiche and final master and stamp production by using these photographic films as photomasks (*187*). Love and co-workers obtained nanometer-scale channels on silicon substrates by underetching beneath the photoresist, depositing metal over the entire chip, and then by lifting off of the photoresist exposing the gaps, which were used as mask for anisotropic etching or as optical filters (*188*).

The use of powder-blasting, a micromachining method that does not need a cleanroom environment, to create microstructures down to 100 (*189*) and 50 μm (*190, 191*) was presented, and different masking materials for this technique have been investigated (*192*). Diamond microchips for chromatographic separation of proteins were developed by Björkman et al. by hot filament chemical vapor deposition (HFCVD) of diamond films on a sacrificial layer of silicon followed by silicon etching, a second diamond film deposition, and subsequent removal of the remaining silicon (*193*). Wego and co-workers fabricated microfluidic system printed circuit board (PCB)-based substrates (*194*). Microstereolithography, a method based on polymerization of photosensitive polymers by a focused UV beam, was used for the fabrication of 3D structures (*195*) and encapsulating material in microfluidic structures (*196*). Beebe and co-workers used photopolymerization of liquid-phase material contained between two substrates to produce networks of microchannels (*197*). Other microfabrication techniques for polymers (*198*−*202*), glass (*203*), quartz (*204*), and silicon (*205, 206*) have been reported.

Bonding Techniques. Stjernström and Roeraade employed posts to bond thin soda lime glass and minimize cracking of substrates during thermal bonding due to mismatch of thermal expansion coefficients (*207*). A low-temperature and low-external load technique for Si−Si bonding using water glass was presented by Satoh (*208*). Berthold and co-workers achieved glass−glass anodic bonding by the deposition of silicon nitride, polysilicon, or amorphous silicon on the glass surfaces (*209*). Chien et al. used rigorous cleaning to achieve the bonding of glass to glass, of identical or different types of commercially available glass substrates, without thermal treatment (*210*). Huang et al. presented a novel approach for bonding glass chips using a UV-curable glue at room temperature and verified its performance by a capillary zone electrophoretic separation (*211*). Localized anodic bonding of Kovar alloy and Pyrex was performed by Blom and co-workers, using a structure to release the thermal stress caused by the difference in thermal expansion of the two materials (*212*). Wienert and co-workers investigated the room-temperature bonding of silicon, silicon dioxide, and quartz wafers by treating the surfaces with oxygen and argon plasma (*213*). Locally selective bonding (LSB), a technique that uses laser radiation to bond silicon and glass wafers, was developed by Wild et al. (*214*). Ito and co-workers achieved glass-to-glass binding, irrespective of the surface roughness, using a water glass solution (*215*).

Surface Modification. Kutter et al. achieved the coating of channel walls with octadecylsilanes to create stationary phases for the electrochromatographic separation of neutral dyes in open channels (*216*). Mourlas et al. presented a method for coating and sealing silicon-etched channels with silicon carbide, using plasma-enhanced chemical vapor deposition (PECVD) (*217*). By the dynamic coating of a PDMS CE separation channel surface with a cationic Polybrene (PB) and an anionic dextran sulfate (DS) bilayer, Liu and co-workers achieved pH-independent EOF in the range between pH 5 and 10, due to chemical control of the effective ζ-potential (*218*). An octadecyltrichlorosilane (OTS) self-assembled monolayer was deposited on part of a glass channel, by Zhao et al., allowing the patterning of hydrophobic pathways within the channel (*219*). Ziong et al. employed EOF for channel-specific coating of proteins on silanized glass surfaces (*220*). A three-layer sandwich coating (biotinylated IgG, neutravidin, and biotinylated dextran) was used by Linder et al. to decrease the adsorption of low and high molecular weight substances and to carry out electrokinetically driven affinity binding assays (*221*). Silanization of O_2 plasma-treated silicon surfaces and the deposition of proteins on polystyrene and polystyrene-coated surfaces were investigated by Junker et al. (*143*). Enzymes were immobilized on the surface of PDMS−glass and Pyrex microchips by linking the enzyme to surface-bound biotinylated phospholipid bilayers (*222*) and protein A (*223, 224*), respectively. Other methods of depositing proteins on poly(ethylene glycol)-derivatized PDMS, Si/SiO_2, and gold surfaces (*225*) as well as on oxidized silicon substrates (*226*) were reported. Passivation of surfaces such as glass and silicon, for further use in DNA amplification by PCR, was reported by Giordano and co-workers, using polymer dynamic coating and silanization (*227*).

Barker et al. improved EOF in polystyrene (PS) and poly(ethylene terephthalate glycol) (PETG) microchannels by applying alternating coats of poly(allylamine hydrochloride) and poly(styrenesulfonate) (*228*). Laser ablation and chemical modification with NaOH (base hydrolysis) of PETG were used by Henry and co-workers to improve EOF (*229*). To increase the electroosmotic mobility of PMMA surfaces, methods involving reaction with α,ω-diaminoalkane monoanions (aminolysis) to produce an amine terminus on the surface (*230*) and UV laser-pulsed irradiation below the ablation level (*231*) were used.

Munro et al. have investigated a number of silica coatings to improve DNA analysis in chip-based CE (*232*). By coating a CE channel with poly(diallyldimethylammonium chloride) (PDADMAC) and immobilizing on it citrate-stabilized gold particles, Pumera et al. improved the separation efficiency (*233*). Murrihy et al. coated the surface of a silicon microchannel, treated with NaOH, with quaternary ammonium latex particles, to realize an ion-exchange chromatography chip (*234*). Hydrophobic microstrips were produced by Gau et al., using thermal vapor deposition of MgF_2 on silicone rubbers and thiolated gold substrates (*235*). Stable photodefinable hydrophobic and hydrophilic regions were fabricated by Man et al. in polymer channels by the deposition of parylene and silicon oxide layers, respectively (*236*). The properties of plasma polymerization to grow fluorocarbon films on surfaces in terms of CH_4/C_4F_8 ratio and substrate temperature have been systematically studied by Matsumoto and Ishida (*237*). Wet and dry oxidation methods were performed by Björkman et al., to render hydrophilic the natively hydrophobic surfaces of diamond chips (*193*).

Design. The design, i.e., the architecture, is perhaps the single most important feature of a microchip as it defines its function

and the sequence of actions taking place in the device. Here we highlight some remarkable design approaches to microfluidic problems.

Waters et al. individually connected four PCR microchambers to a CE separation channel, allowing simultaneous or sequential analysis of nucleic acid amplification products (*238*). Arrays of biomolecules were designed and tested by Delamarche et al. by attaching immunoglobulins on various solid surfaces for further bioassays (*239*). A capillary array electrophoresis device was designed by Simpson and co-workers, incorporating 96 sample wells and 48 separation channels and having the capacity to analyze two DNA samples in series in the same separation channel (*240*). A high degree of integration was reported by Burns and co-workers in a microfluidic device that incorporates fluid handling and volume measurements, a PCR chamber with integrated heaters and temperature sensors, a gel electrophoresis channel with built-in electrodes, and a photodetector for fluorescence measurements (*241*). PCR was performed in a serpentine-type channel that repeatedly transports the sample through three spatially defined temperature zones (*138, 242, 243*).

A fused-quartz device, designed by Becker and co-workers, for 2D capillary electrophoresis was fabricated with a single channel and an array of 500 channels 900 nm wide perpendicular to the former (*244*). The amount of dispersion introduced by turns in microchannels was predicted from a one-dimensional model, and a number of methods to overcome the geometrical dispersion were examined by Culbertson and co-workers (*245*). Exploiting the negative capillary action of aqueous liquids on hydrophobic surfaces, a channel with four perpendicular microcapillary hydrophobic vents was used by Hosokawa et al. for accurate measurement and mixing of 600-pL droplets (*246*). Schasfoort et al. presented a microdevice that controlled the magnitude and direction of the electroosmotic flow by an axial electric field of 1.5 MV cm^{-1} generated by the application of a 50-V potential across the 400-nm channel walls (*175*). High-resolution DNA sequencing in 50-cm-long independent channels fabricated on a monolithic substrate was reported by Backhouse and co-workers (*247*). Converging CE channels were fabricated by Huang et al. to produce a dense array at the detection window for fast scanning (*248*). Paegel et al. designed and tested microchannels to minimize the turn-induced band broadening by tapering the curves and varying the angle and length of curvature (*249*). A hydrophobic pattern to stop the filling of a hydrophilic channel in conjunction with air pressure pumping was used to accurately measure nanoliter-sized volumes by Handique et al. (*250*).

In a trident system of three converging channels, Hibara et al. created a parallel three-layer flow (aqueous, organic, aqueous) for liquid−liquid extractions (*251*). Bernard and co-workers performed a chip-based immunoassay, using a sealed substrate containing straight channels with a cover lid, and immobilizing lines of antigens on the flat surface, followed by the removal and replacement of the structured component at right angles to the lines and subsequent filling of the channels with the analyte and pattern reading (*226*). The use of laminar streams of etching solutions to create topographical features in sizes ranging from 10 to 100 μm in PDMS was presented by Takayama et al. (*252*). In a complex microfluidic network presented by Dertinger et al., three streams are split by a series of horizontal channels and recombined with their neighboring ones via a series of vertical delay channels to produce linear, periodic, and parabolic concentration gradients in a wide outlet channel (*253*). Based upon this principle and on the fact that the etching rate of solution is proportional to its concentration, flows of etching solutions with concentration gradients across a channel were used by Jeon et al. to generate surface height gradients on substrates (*254*).

A disposable PDMS dispensing device was fabricated by McDonald et al., with a series of unconnected side channels at right angles to a separation channel and separated from the latter by means of a narrow wall. A voltage high enough to rupture the separating wall was applied between any side channel and the separation channel, causing them to connect (*255*). Fluid switching in 3D microfluidic systems was investigated by Ismagilov and co-workers, using tangential flow of fluids in a device consisting of channels fabricated in multiple PDMS layers that contact another face to face at a 90° angle (*256*). A similar design with a 0.1−1.0-μm polycarbonate membrane separating the two PDMS layers with channels was proposed by Ismagilov et al. for arrays and combinatorial chemistry reactions (*257*). A modular approach to 3D structures was developed by Hofmann et al., based on the vertical assembly of PDMS components (*258*). Synchronized cyclic capillary electrophoresis (SCCE) was performed by Manz et al. in a triangular channel with narrow corners to reduce the losses and dispersion in the turns (*259*). In a glass microfluidic network with a "double-cross" configuration, Zhao et al. defined hydrophilic and hydrophobic pathways by bringing together aqueous and silanization solutions in a multistream laminar flow (*219*). Bertsch and co-workers developed a Y-shaped 3D micromixer incorporating either a series of stationary rigid elements to split, rearrange, and recombine component flows or a series of alternating left- and right-handed helices (*195*). In a stop-flow micromixer for time-resolved IR spectroscopy presented by Hinsmann et al., reagents are brought together one on top of the other by means of high-aspect-ratio microchannels (*260*). In a microfluidic system incorporating stacked flow and pH-sensitive hydrogel valves, Eddington et al. realized a system with the ability to self-regulate the pH of the out-going solution (*261*). Using the principle of wetting behavior and capillarity, Lam et al. guided liquids along 2D paths without the need of sidewalls by application of a hydrophilic pattern on a hydrophobic substrate and vice versa (*262*). A 96-lane capillary array electrophoresis device with a 159-mm effective separation length was fabricated by Paegel et al. on a 150-mm wafer in a radial configuration for high-throughput DNA sequencing (*263*). Ceriotti and co-workers fabricated in PDMS a fritless capillary electrochromatography (CEC) microchip consisting of a 70-μm-wide packed channel which gradually tapers to form a 10-μm particle-free slanted "double-T" injector (*264*).

Interfaces and Interconnections. Interfaces and interconnections is an important area that is still neglected by many research groups. Here we report some recent developments in "world-to-chip" interfaces.

1. Chip to Mass Spectrometry (MS). Luginbuhl and co-workers fabricated a mass spectrometry injector consisting of a micronozzle coupled to a piezoactuator, which relies upon the minimal and symmetrical wetting surface of the nozzle to reduce unwanted deflections of the ejected droplet (*265*). Figeys et al. demonstrated the successful coupling of a microfluidic device to

electrospray (ESI) time-of-flight mass spectrometry (TOF-MS) (*266*) as well as coupling of a solid-phase extraction cartridge to an electrospray MS/MS, using electroosmotic pumping for sample delivery (*267*). Coupling of a CE microchip to a mass spectrometer was achieved by Li and co-workers, directly via disposable nanoelectrospray emitters and by means of a fused-silica capillary (*268*). Wang and co-workers developed a parylene-based electrospray chip with integrated particle filters and successfully coupled it to a mass spectrometer (*269*). Lazar et al. described an ESI scheme using a nanospray tip microfluidic device coupled to a TOF-MS for the detection of peptides and proteins (*270*). In a microfluidic glass device, an electrically permeable glass membrane was fabricated by Lazar et al. to provide the potential for both ESI and electroosmotic pumping, allowing the successful coupling of a microchip and a TOF-MS (*271*). Fused-silica capillaries have also been used to couple a silicon-based micromixer to an ESI TOF-MS (*272*), and a PMMA microfluidic chip to a Fourier transform cyclotron resonance mass spectrometer via an ESI unit has been reported (*273*). Other research groups have also demonstrated chip−MS coupling (*274*−*277*).

2. Chip to Nuclear Magnetic Resonance (NMR). Massin and co-workers presented a miniaturized high-*Q* factor radio frequency (rf) planar coil fabricated on glass, on which a 500-μm capillary containing the sample is placed. To acquire the ^{1}H NMR spectrum of the sample the coil−chip system was placed in a 7-T superconducting magnet (*278*).

3. Fluidic Interconnections. Low dead volumes were obtained by Bings et al. in a study that used a flat drilling tip to produce flat-bottomed holes to connect the microfluidic device to external detectors through capillaries (*279*). Mourlas et al. have used a method involving two DRIE etch steps and an anodic bonding step to couple standard capillary tubing to microfluidic chips (*217*). Vertical interlocking silicon structures were developed by Gray and co-workers, for high-density reversible fluidic connections (*280*). Puntambenkar and Ahn have developed a method using thermoplastic PEEK tubing to align channels and interfacing tubing (*281*). Meng and co-workers presented self-aligning silicon micromachined fluidic couplers for external connections via fused-silica capillaries (*282*). Using a PEEK interface, adhesive-free, high-pressure connections of microfluidic devices to capillaries and reservoirs have been reported by Nittis and co-workers (*283*).

Microvalves and Flow Control. Wang and co-workers presented a micro check valve incorporating a valve seat with an orifice and a tethered parylene membrane that allows large membrane displacement while minimizing the flow resistance induced by the membrane (*284*). Evans and Liepmann fabricated a silicon mechanical check valve that is based on the directional control of flow by two flaps, each attached to a coiled spring (*285*). A valve that autonomously controls the outlet orifice, and hence the flow rate, by means of micromachined levers activated by the current flow, was reported by Williams et al. (*286*). Oosterbroek et al. developed a microvalve with a duckbill-type muzzle causing the hydraulic resistance to be direction sensitive (*287*). Two hydrogel bistrips reversibly activated and deactivated, i.e., changing volume and shape, based on local pH and with different pH sensitivities, have been employed by Yu et al. to act as valves in microfluidic systems (*288*). Schasfoort and co-workers employed a perpendicular electric field to control the magnitude and direction of EOF in microchannels (*175*). In centrifugal pumping systems, hydrophobic regions were used as valves, allowing the sample solution to pass only when the rotational pressure becomes higher than the capillary pressure (*289, 290*). Jo and co-workers fabricated a microvalve consisting of a PDMS membrane diaphragm resting on an in-channel barrier that opens when sufficient pressure is present in the fluid, while the hold-off pressure can be controlled by adjusting the external pressure (*291*). Papavasiliou and co-workers developed a high-speed, bistable gate valve, actuated by an electrolytically generated gas bubble (*292*). Schultz et al. developed a device for flow switching in a Y-shaped channel by thermally controlling the viscosity of two carrier streams flowing parallel on each side of the sample stream (*293*). Tashiro and co-workers used an IR laser to direct the flow in a Y-shaped microchannel by incorporating 1% cross-linked methyl cellulose (MC) in the carrier flow and thermally controlling the gelation, hence, selectively blocking and unblocking the channel (*294*). A thermopneumatically actuated microvalve was presented by Namasivayam et al. which relies upon the formation of a tight seal between the orifice and a PDMS membrane, actuated by a low boiling point hydrofluorocarbon heated by a Peltier element (*295*). Microcapillary hydrophobic vents have been used by Hosokawa et al. as passive vent valves for the accurate positioning of aqueous solutions without the need for sensors (*296*). The use of nuclear track-etched polycarbonate membranes as nanofluidic diodes between microchannels controlling the transport of material by the application of an appropriate bias was reported by Kuo et al. (*297*). Ismagilov and co-workers developed a flow-switching device by controlling the lateral position of a stream in multiphase laminar flow and the channel aspect ratio in tangentially connected microfluidic systems (*256*). A number of other valves have also been reported (*197, 298*−*300*).

Micropumps. 1. Nonmechanical. Lemoff and Lee presented an ac magnetohydrodynamic pumping system that used Lorentz forces to drive a solution along a circular silicon channel *(301*). Weigl and co-workers demonstrated flow in a microchannel originating from the hydraulic pressure induced by the height difference between the inlet reservoir and the channel outlet (*302*). Song and Zhao developed a nonmechanical microdevice for pumping by growing and collapsing of vapor bubbles in the working liquid, using a series of suitably phased heating elements embedded in a microchannel (*303*). Gallardo et al. demonstrated pumping of aqueous and organic liquids in millimeter- and micrometer-sized channels by controlling both spatially and temporally the concentration of redox-active surfactants using an electrode array (*304*). Hatch and co-workers used magnetically actuated ferrofluid plugs in a microchannel for both pumping and valving (*305*). Handique et al. developed a microchip-based pumping system that generates pressure by controlling the volume of an air plug trapped in microchannel using resistive heating (*306*). Centrifugal pumping of fluids placed in reservoirs close to the center of a spinning disk-shaped microfluidic chip was reported (*289, 307, 308*). Prins at al. have demonstrated controlled fluid motion in 3D structures with thousands of channels using the electrocapillary pressure by electrostatically controlling the channel−fluid interfacial tension (*309*). A sample containment technique to prevent the separation of analyte mixtures during electrokinetic pumping using a plug of high-conductivity salt to

reduce the local electrophoretic transport was demonstrated by Deshpande et al. (*310*). Seidel et al. presented a self-filling (by capillary forces) mixing device eliminating the need for external pumping (*311*). Continuous liquid transport in microchannels was achieved by Goedecke and Manz by a combination of capillary forces and liquid evaporation at the branched channel termini (*312*). Alarie and co-workers, developed a device that electroosmotically induces hydraulic pumping in a channel by applying a voltage across a second closely spaced microchannel (*313*). Deshmukh et al. achieved accurate volume control mixing using the out-of-phase thermal expansion and contraction of two gas bubbles by resistive heating and a series of mechanical check valves (*314*). Paul et al. reported pressures in excess of 8000 psi using electrokinetic pumping in fused-silica capillaries packed with micrometer-sized silica beads (*315*). Culbertson et al. generated electroosmosis-induced hydraulic flow in the two outlets of a tee microfluidic device (one grounded and the other floating or not connected), by reducing electroosmotic flow in the grounded outlet channel relative the other by applying a viscous polymer coating (*118*). McKnight et al. used multiple thin metal electrodes inside a microchannel to allow electroosmotic pumping of the fluid between separate pairs of electrodes, inducing hydraulic pumping between unconnected sections (*316*). A linear pneumatic pressure source was realized by Takamura and co-workers, using low-voltage electroosmotic pumps that employed a combination of narrow and wide gaps (*317*). By opposing hydraulic and electroosmotic flow, Lettieri and co-workers have generated vortices of controlled shape and amplitude (*318*). The combined influence of electroosmotic pressure and hydraulic pressure on fluid transport in complex systems of parallel capillaries was theoretically investigated. Pumps generating pressure-driven flow from EOF have been fabricated and used to pump a variety of solutions (*129*, *319*). Further nonmechanical micropumps have been reported (*320*−*324*).

2. Mechanical. A silicon−Pyrex piezoelectric bidirectional micropump was realized by Matsumoto et al., using a valving mechanism that relies upon the difference in flow resistance in narrow channels caused by the temperature dependence of the viscosity of liquids (*325*). Shinohara and co-workers developed a piezoactuated micropump incorporating two active and normally closed valves using a silicon rubber post that acts as a gate for shutting the flow off (*326*). Mixing was achieved by Kaajakari and co-workers by actuating polysilicon center-anchored circular plates and sidewall cantilevers at ultrasonic frequencies by means of a piezoelectric plate (*327*). A 3D array of electrostatically actuated bidirectional gas pumping devices consisting of at least three peristaltically working chambers was presented by Cabuz and co-workers (*328*). Bidirectional pumping using a valveless piezoelectrically actuated micropump was demonstrated by Anderson et al. (*329*). Desmet et al. developed a method for generating fluid flow by means of a shear force field generated by the division of a channel into two movable parts that axially slide one past the other (*330*). Lim and co-workers created a peristaltic micropump by using a roller or a gear-shaped rotor to locally collapse in the channel of an elastomeric chip (*331*). Further mechanical micropumps have been reported (*332*−*341*).

This paper is continued in part 2 (*342*), in which we report standard analytical operations performed in miniaturized total analysis systems, as well as a number of their applications.

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Darwin R. Reyes *is a National Science Foundation Postdoctoral Fellow at Imperial College, London, U.K. He received his B.S. in chemistry from the University of Puerto Rico, and after working for two years in SmithKline Beecham Pharmaceutical (Cidra, P.R.), he undertook his Ph.D. studies with Professor Osvaldo Rosario at the University of Puerto Rico. His thesis involved the chemical characterization of airborne particulate matter directed by cell-based toxicological bioassays. He has been working with Professor Manz since 2000 developing isoelectric focusing and other separation modes in microfluidic devices in order to develop two-dimensional separation systems on chip.*

Dimitri Iossifidis *received his B.Sc. in chemistry from Reading University in 1999 and his M.Sc. from Imperial College in 2000. He is currently pursuing a Ph.D. at Imperial College under the supervision of Professor Andreas Manz. His research interests lie in the field of miniaturized biochemical analysis systems and the application of such systems to clinical diagnostics.*

Pierre-Alain Auroux *studied in Strasbourg, France, at the European School of Chemistry, Polymers and Functional Materials (ECPM), where he got his M.Sc. in 2000. As part of his degree work, he spent fourteen months at Orion Research, Inc. (Beverly, MA), where he helped develop electrochemical devices for Mars soil analysis. He also went to Los Alamos National Laboratory (Los Alamos, NM) for four months and elaborated a protocol for capillary electrophoresis analysis of dyes, interfaced with Raman spectroscopy. After graduating, he spent a year and a half in Professor Manz's group familiarizing himself-with microscale-fabrication techniques. He is currently at the Children's Hospital of Zurich (Zurich, Switzerland) working on his Ph.D.*

Andreas Manz *obtained his Ph.D. from the Swiss Federal Institute of Technology (ETH) Zurich, Switzerland, with Professor W. Simon. His thesis dealt with the use of microelectrodes as detectors for picoliter-size volumes. He spent one year at Hitachi Central Research Lab in Tokyo, Japan, as a postdoctoral fellow and produced a liquid chromatography column on a chip. At Ciba-Geigy, Basel, Switzerland, he developed the concept of Miniaturized Total Analysis Systems (μTAS) and built up a research team on chip-based analytical instrumentation during 1988*−*1995. Since joining Imperial College, he has become the SmithKline Beecham Professor for Analytical Chemistry. His research interests include fluid handling and detection principles for chemical analysis, bioassays, and synthesis using microfabricated devices.*

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