

Micro Total Analysis Systems. 2. Analytical Standard Operations and Applications

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

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

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After having reviewed some aspects of microfluidic system preparation in the first part (1), in this second part of the review we will cover a number of standard operations (namely: sample preparation, sample injection, sample manipulation, reaction, separation, and detection) as well as some biological applications of micro total analysis systems (namely: cell culture, polymerase chain reaction, DNA separation, DNA sequencing, and clinical diagnostics). As previously, we will include papers issued from different scientific journals as well as useful abstracts from three conference proceedings: MEMS, Transducers, and μ TAS. In this second part, we do not include the period covered by the history section (1975–1997) from part 1 but try to cover the relevant examples of the literature published between January 1998 and March 2002. We briefly describe articles that struck us as needing special attention, while more “standard” papers are dutifully reported in groups of interest. An article might be included in more than one section, depending on the ideas developed in it.

ANALYTICAL STANDARD OPERATIONS

Sample Preparation. 1. Sonication. Lysis of anthrax spores was performed by Belgrader and co-workers using a minisonicator system to extract DNA, to amplify it by polymerase chain reaction (PCR), and to detect it in a short period. The device was capable of performing the whole process in less than 15 min (2). A subsequent work performed by Taylor et al. using the same sonicator system studied the conditions to obtain a continuous contact between the sonicator tip and the liquid (3). Meng et al. used an ultrasonic device to concentrate their sample, and they

reported the successful concentration and manipulation of polystyrene spheres using acoustic radiation pressure (4). More literature concerning sonication on chip is available (5).

2. Extraction. Smith's group reported a sample cleanup method using microdialysis as well as an integrated microfabricated device for dual microdialysis: two microdialysis membranes were sandwiched between three polymer layers containing serpentine channels with the fluids running in counterflow one to the other (6, 7). Böhm et al. developed a microdialysis system that allowed them to perform on-line monitoring of clinical substances (8). Jiang et al. performed a dialysis for affinity capture on their plastic microfluidic system by using poly(vinylidene fluoride) membranes (9).

Shaw et al. used a liquid–liquid extraction system to perform multiple parallel extractions of 10 separate organic fluids using a single aqueous feed (10). Hibara et al. developed a liquid–liquid phase separation on chip using 2 glass substrates, one of which had been chemically modified (11). Hisamoto et al. developed a sequential ion-sensing system, which involved the alternating pumping of several organic phases containing a pH indicator dye and an ion-selective neutral ionophore. The organic phase was put in contact with the aqueous phase, forming a stable aqueous–organic layer in the microchannel where the ions were selectively and sequentially extracted (12). The same group also performed an ion pair extraction by a neutral ionophore-based ion (13). Minagawa et al. performed a chelation process of cobalt and a subsequent solvent extraction of the complex in a wet analysis system (14). Tokeshi et al. improved the cobalt complex extraction system (15) and also developed an ion pair microextraction of iron in chloroform by putting two parallel laminar flows of different phases in contact (16).

Yu and co-workers prepared monolithic porous polymers within the microchip channels and used them to perform on-chip solid-phase extraction and preconcentration (17). A microchip with channels modified with C-18 was successfully used for solid-phase extraction. Samples were enriched, and subsequently, an elution of the compound was achieved by changing the acetonitrile concentration in the buffer (18). A microfluidic device with a bead-trapping chamber was fabricated and used with octadecylsilane-coated silica beads for the solid-phase extraction step while elution was performed by means of electroosmotic flow (19). Li et al. performed both a sample stacking and a solid-phase extraction on their device prior to mass spectrometric detection (20). Wolfe et al. fabricated a solid-phase extraction method to isolate nucleic acids. The three-step procedure is as follows: DNA adsorption, contaminants removal, and adsorbed DNA elution (21).

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

Lee et al. presented an electrostatically active filter used for collection of airborne particles (22). Weigl et al. relied on a diffusion-based mixing and extraction device to detect a single analyte (23). Burns and Ramshaw developed an extraction method on-chip using slug flow (24).

3. Preconcentration. Figeys and Aebersold used computer-controlled differential electroosmotic pumping of aqueous and organic phases to generate solvent gradients and solvent flows: they could change in situ and in real time the composition of their solvent/sample by ramping the concentrations of solvents A and B from proportion x and y to proportion y and x (25). The generation of concentration gradients in a microfluidic network was performed by Jeon et al. as well as by Dertinger and co-workers: using three inlets on their device, they could generate parallel streams of solutions of different concentrations in adjacent microchannels and generate a gradient by combining the different streams in one outlet. The gradient obtained could have different shapes depending on the design used (26, 27).

Ikuta and co-workers presented a novel microconcentration chip using an ultrafiltration membrane. The membrane divided the reactor into two compartments and retained the reactive molecules (firefly luciferase and beetle luciferinin) in the bottom part. An optical sensor monitored in real time the biochemical luminescence of the process (28). Jemere et al. presented a microchip structure packed with coated microspheres used for selective sample cleanup and preconcentration (29).

Kutter et al. investigated sample stacking as well as on-chip complexation in order to improve the sensitivity of their capillary electrophoresis microchip (30). Field amplification stacking was developed by Lichtenberg and co-workers as a sample preconcentration method to inject long plugs of samples. Up to 65-fold signal enhancement was obtained, and a minimum electrophoretic discrimination during injection was observed (31). Palmer et al. studied the stacking conditions for neutral analytes in capillary electrokinetic chromatography in order to inject long sample plugs while at the same time narrowing the analyte peak width (32).

Cabrera and Yager employed zone electrophoresis and isoelectric focusing to concentrate bacterial solutions (33). Wen et al. reported a microfabricated isoelectric focusing device and investigated its stability regarding electrospray ionization-mass spectrometry (34). Herr et al. investigated the use of isoelectric focusing as a mean of providing purified and concentrated samples (35).

Pickering et al. performed isotachopheresis on glass chips, integrating a laser system that would allowed them to detect the zone boundaries by measuring the laser beam deflection (36). Fielden et al. developed a miniaturized planar isotachopheresis device that they applied to the separation and detection (via a conductivity method) of transition metal ions (37). Baldock et al. designed a planar poly(dimethyl siloxane) device to perform sample preconcentration using capillary isotachopheresis followed by conductivity detection (38). Grass et al. fabricated, by hot embossing, a PMMA device for isotachopheresis with an integrated conductivity detector. Separations of organic acids were used to demonstrate the principle of the isotachopheresis chips (39). Another approach was suggested by VanderNoot et al. in which the isoelectric focusing was performed by using electrokinetically generated pressure mobilization (40).

Injection. An injection system, which uses a porous membrane to electrically connect a sample reservoir with the separation channel, was used by Khandurina and co-workers to electrokinetically concentrate DNA samples followed by the injection and electrophoretic separation of the samples (41). Deshpande et al. studied novel designs for electrokinetic injections in a micro total analysis system (42). Zhang and Manz studied the influence of cross and tee injectors having narrow sample channels and reported an improvement of resolution, column efficiency, and sensitivity (43). Greenway et al. presented a micro flow injection system optimized for the determination of nitrite by a spectrophotometric detection (44).

A gated valve using a single voltage source and three reservoirs was demonstrated by Jacobson and co-workers. The system utilized a high-voltage relay to interrupt the buffer flow and to allow the injection of a plug of sample (45). Valving characteristics were controlled by the manipulation of the electric field strength during the sample loading and dispensing (46, 47). A system for continuous multisample injection was studied by Lee et al. They first established a theoretical model and then fabricated a matrix of flow switches comprising M inlet ports \times N outlet ports on a quartz substrate (48).

Nilsson et al. presented a microdispenser with which the ejected droplets were covered with a secondary layer of liquid, decreasing the contamination of the nozzle by the primary liquid (49). Attiya et al. studied different parameters in order to provide an optimized interface for sample injection from the external environment to microfluidic electrophoresis chips (50). O'Neill et al. presented an injection system able to deliver picoliter sample plugs for miniaturized liquid chromatography (51). Lin et al. offered a novel approach that enables a microchip to be directly coupled with a flow-through analyzer for uninterrupted sampling: as the sampling channel is kept electrically floating, there is no need for electrical connections, thus allowing the connection with any pressure-driven system without further modification (52). Fang and co-workers designed a world-to-chip interfacing including a flow-through sampling reservoir featuring a guided overflow design (53). The reader can find more literature concerning injection (54–56).

Fluid and Particle Handling. Jacobson et al. used a single voltage source to electrokinetically control their sample. Three sample reservoirs and three buffer reservoirs were present on the device, and the electrokinetic control was used to bring the reactants to different mixing stations (57). Polson and Hayes published a detailed study of electroosmotic flow control of fluids on a capillary electrophoresis microdevice (58). Lin and Wu developed an array electrode design for moving the electric field of capillary electrophoresis chips, thus reducing the required driving voltage (59). Prins et al. used the electrostatic forces on the meniscus originating from the solid/fluid interface to control the fluid position in a multichannel structure (60). Moorthy et al. performed an active control of electroosmotic flow by using light. To do so, they coated the inner walls with a semiconductor (TiO_2) whose surface charge changed when irradiated with UV light, modifying the ζ potential and thus changing the electroosmotic flow (61). Ghosal investigated the effect that analyte adsorption on walls had on electroosmotic flow (62). Jacobson et al. studied electrokinetic transport through nanometer-deep channels and

obtained results in good agreement with theoretical predictions (63). Modulated concentrations of a dye were used by Bühler et al. to study the characteristics of laminar flow in microchannels. The process could be approximately described by simple mathematical expressions (64). A study of gas flow in microchannels was performed by Lee et al. investigating the pressure loss due to friction occurring at channel bends (65). Grant and co-workers described several new approaches regarding magneto-hydrodynamic flow control (66). The manipulation of magnetic beads in an aqueous suspension in a microchannel by using microfabricated circuits was demonstrated by Deng et al. (67, 68). Monahan et al. presented a method based on atmospheric pressure reduction to remove trapped air bubbles in microchannels (69).

Kwok et al. presented a radiative technique used to measure the velocity of electrokinetically driven fluorescent particles, by employing Shah convolution Fourier transform detection (70). An optical approach to measure particulate flow in a microchannel using fluorescently labeled microspheres and a focused laser beam was presented and proved useful to measure flow rates between 50 and 8 $\mu\text{L}/\text{min}$ (71). Singh et al. used fluorescent liposome flow markers to perform microscale particle-image velocimetry (72).

Fluorescently labeled and unlabeled particles were detected and counted by focusing the particle flow electrokinetically and then using laser light scattering and fluorescence coincidence measurements (73). Voldman et al. reported the micromachining of single-particle dielectrophoretic traps whose properties they found in excellent agreement with their model (74). Larsen et al. developed the "Coulter sizing" method on a chip with silicon apertures of different diameters and used their device on dairy farms where somatic cells counts are used for quality control (75). Gawad et al. demonstrated the successful use of a micromachined cell impedance analyzer in which counting, sizing, and population studies of cells, with screening rates of over 100 samples/s, were performed (76). Voldman et al. reported the fabrication of a dielectrophoresis-based array cytometer with integrated cell traps that were proven to capture, hold, and selectively release multiple single bioparticles (77). Cui et al. used a multilayer traveling wave dielectrophoretic electrode array for manipulating particles, fluids, or both. They could detect single molecules by using either light scattering or fluorescence emission (78). For more literature about isoelectric focusing, the reader is referred to Isoelectric Focusing in the section Separations.

Reactors and Mixers. 1. Micromixers. A mixer based on diffusion was designed by Veenstra and co-workers for the mixing of a phenolic solution with water. The mixer dimensions could be easily adapted to match a specific time frame regarding the mixing of the molecules of interest (79). Liu et al. developed a three-dimensional serpentine microchannel as a passive micromixer (80). Bessoth et al. fabricated a continuous-flow mixing device able to reach 95% of mixing completion in ~ 15 ms. This device is commercially available from Upchurch Scientific (81). Floyd et al. used a chip consisting of a laminar flow mixer, a heat exchanger, and a probing region to perform infrared transmission kinetics studies (82). Hong et al. presented a passive micromixer based on the Coanda effect (83). The fabrication of a 100-pL mixer was achieved by He et al. In this design, the channels parallel to the flow were narrow whereas a larger channel ran back and forth

across the set of parallel channels at an angle of 45° . Simulations were also performed to describe the mixing within this system (84). A mixer that used a passive method for mixing streams of steady flows in microchannels at low Reynolds numbers was presented by Stroock et al. The relationship between the channel length and the Peclet number was investigated, and it was found that mixing could be achieved when the channel length grew logarithmically with the Peclet number (85).

Yasuda and Ichiki designed an ultrasonic mixer where the samples were introduced from the side wall (86). Yang and co-workers designed an active micromixer based on ultrasonic vibrations and successfully tested their microfluidic system using water and ethanol (87). The system was then studied further and a solution of water with uranine (sodium fluorescein salt) was used to characterize the mixing effectiveness (88). Woias et al. reported an active silicon micromixer whose key element is a silicon chip with a thin piezoelectrically actuated membrane (89).

Electrokinetically driven parallel and serial mixing was demonstrated by Jacobson et al., using a single voltage source and choosing the dimensions of the channels to obtain the desired splitting of the sample (57). Lee and co-workers developed two mixing devices, one electrokinetically driven and the other one pressure driven. The approach was based on folding and stretching the material lines, leading to chaotic-like mixing (90). Lettieri et al. opposed electrokinetically and pressure-induced flows to form vortices inside microchannels of varying geometries (91, 92). Oddy et al. applied sinusoidally alternating electric fields to induce an electrokinetic instability as the mixing factor (93) and designed and fabricated micromixing devices for the stirring of fluid streams by initiating a flow instability in electroosmotic channel flows (94). Hinsmann et al. designed and tested a micromixing device to study rapid chemical reactions by stopped-flow resolved Fourier transform infrared spectroscopy. Computational simulations were in agreement with the experimental results (95).

Yang et al. reported a micromixer using turbulences produced by valveless micropumps (96). Lu et al. described the fabrication of microstirrers composed of a cap, a hub, and two rotary blades, all micromachined (97). Böhm et al. used a rapid vortex micromixer reactor to study high-speed chemical reactions. The reactor consisted of 16 tangential inlets for injecting the liquid to be mixed into a circular vortex chamber, and the velocities were high enough to induce a swirling flow field (98). Mixing geometries used in large industrial equipment, for chemical and food processing, were incorporated in a micromixer using microstereolithography, a process allowing the fabrication of three-dimensional features in polymers (99). Johnson et al. presented a rapid microfluidic mixing device with slanted wells etched at the bottom of the channels, creating a high degree of lateral transport and rapid mixing (100).

2. Chemical Reactors. A heated chemical microreactor, made of glass and silicon, with a heating rate of $2^\circ\text{C}/\text{s}$ was built by Eijkel and co-workers and its performance investigated by the derivatization of amino acids (101). Greenway et al. used a reactor for the determination of nitrite: it reacts with sulfanilamide to form the diazonium salt, which coupled with *N*-(1-naphthyl)-ethylenediamine produces an azo dye whose absorbance can be measured (44). Protein synthesis reactors have been presented by Ikuta et al. as well as by Yamamoto et al. (102, 103). The use

of quartz substrates to induce a photochemical reaction using UV light and further detection of the products in a microreactor was demonstrated by Lu and co-workers (104). A nanotitrator integrating electroosmotically driven nanopumps, and a sensor measuring the potential difference between the titrant and the titrated sample, were fabricated and presented by Guenat et al. (105). An interesting approach where a microreactor generates compound libraries based on an "AND" logic operator has been presented by Mitchell et al. (106). Mitchell et al. performed a highly exothermic reaction on-chip, namely, the multistep reaction of piperidine hydrochloride with formaldehyde followed by the addition of cyclohexyl isocyanide to give α -dialkylacetamide, and monitored each step of the reaction using a mass spectrometer (107).

3. Enzymatic Reactors. A microreactor using enzymes immobilized on glass beads was used by L'Hostis and co-workers to determine the concentration of glucose by enzymatic reaction (108). Tryptic digestion in a heated channel, electrophoretic separation, and postcolumn labeling of proteins and peptides were all integrated in a microfluidic device and its performance was demonstrated by Gottschlich et al. (109). The production of electroactive products by an enzymatic reaction (catalyzed aerobic oxidation of glucose to gluconic acid and hydrogen peroxide) and subsequent separation and amperometric detection was carried out in a microfluidic device by Wang and co-workers. Reaction and separation took place in the same microchannel (110). The use of an enzymatic reactor whose temperature is photothermally controlled by means of a diode laser was demonstrated by Tanaka et al. (111). They also reported the acceleration of an enzymatic reaction and preliminary kinetic studies compared to a bulk-scale reaction (112).

4. Immunoassay Reactors. Hadd et al. described flow injection analysis, electrophoretic separation, and detection of acetylcholinesterase inhibitors. The inhibition constants obtained proved comparable to those obtained in conventional assays (113). A rapid diffusion competitive immunoassay based on the interdiffusion of two fluid components and further detection downstream was developed by Hatch et al. An analysis time of less than 1 min, direct analysis of blood samples, and detection in the subnanomolar range were demonstrated (114).

Calibration standards were produced by Qiu and Harrison within a microchip device using an immunoassay reaction as the model. The mixing ratios were determined by modeling the fluidic network; the mixing was performed electrokinetically (115). A multichannel microfluidic device for immunoassays was described by Cheng et al. This device integrated six independent mixing, reaction, and separation manifolds that worked simultaneously. A single-point fluorescent detector with a galvanoscanner was used to acquire the data (116).

5. Postcolumn Labeling. Noncovalent postcolumn labeling of proteins, with NanoOrange dye, was achieved by Liu and co-workers by forming a fluorescent complex that was detectable by laser-induced fluorescence (117). Spikmans et al. coupled a high-performance liquid chromatograph to a mass spectrometer in a postcolumn derivatization step inside a micromixer (118).

Separation. 1. Chromatography. Fintschenko et al. reported the first use of a UV-initiated porous polymer monolith in a microfabricated electrochromatographic separation device (119).

Oleschuk et al. prepared a packed bed for capillary electrochromatography (CEC) separation by constructing a cavity in which beads coated with a stationary phase could be trapped (19). Constantin et al. reported the utilization of the sol-gel technique to produce self-containing open-tubular microcapillary electrochromatography columns in a fast and easy way (120). A glass chip with polymer monolith was developed by Throckmorton et al. for reversed-phase electrochromatography (121). Electrochromatographic separations in open channels coated with octadecylsilane were presented by Kutter et al. Solvent programming and different channel dimensions were used to evaluate the performance of this system (122). Gottschlich et al. demonstrated a two-dimensional separation using open-channel electrochromatography and capillary electrophoresis as the first and second dimensions, respectively (123). Rapid separation of peptides and amino acids in glass microchips was performed by Singh et al. using reversed-phase electrochromatography (124). Slentz et al. reported the fabrication of a poly(dimethyl siloxane) column with integrated collocated monolith support structures that gave a reproducible CEC separation over a month with a synthetic peptide mixture (125).

He et al. reported the microfabrication of a column with integrated collocated monolith support structures on a quartz substrate and compared this device with existing macroscale devices for liquid chromatography and CEC (126, 127). Björkman et al. performed capillary chromatography of proteins using diamond chips (128).

Desmet et al. experimentally demonstrated the possibility of performing shear-driven chromatographic separation; subsequent axial sliding of these parts moved the mobile phase in the channel along by viscous drag. The microchannels were made using transparencies, an ink-jet printer, and microscope slides (129). Chmela et al. addressed the issue of analytical separation of (bio)-polymers and particles by introducing a novel on-chip hydrodynamic chromatography device (130). Hydrodynamic chromatography was used by Blom et al. to separate polymer particles based on their geometries. This separation scheme (hydrodynamic chromatography) is based on parabolic flow in which larger molecules are favored to have a higher average velocity because of the impossibility of approaching the wall of the channel (131, 132). Wang et al. developed a high-resolution chiral separation of racemic tryptophan and thiopental mixtures using microfluidics-based membrane chromatography: the chiral stationary phase consisted of a porous membrane with adsorbed bovine serum albumin (133). Seki et al. presented a pressure-driven chromatographic chip for separation of proteins made from poly(dimethyl siloxane) (134). Murrhly et al. presented an on-chip system for ion chromatography and compared it with an open-tubular column separating inorganic ions (135).

A spiral-shaped separation channel of 25-cm length was fabricated and tested for electrophoretic and micellar electrokinetic chromatographic separations. Up to 21 000 plates/s were generated with this high-efficiency separation microfluidic device (136). Micellar electrokinetic chromatography and high-speed open-channel electrophoresis were integrated in a single microfluidic device to perform a two-dimensional separation. The performance of the device was demonstrated by Rocklin and co-workers for the separation of peptides (137).

Hannoe et al. micromachined a separation column for an integrated on-chip gas chromatograph. The stationary phase was made of amino acid films and the system tested with a methane sample (138). Lehmann et al. presented a gas chromatography device on which the stationary phase had been plasma polymerized (139). Frye-Mason et al. fabricated an on-chip gas chromatograph and demonstrated its capability by separating a mixture of gases such as methane, acetylene, ethane, and ethene (140).

2. Electrophoresis. An ultrafast capillary electrophoresis was performed by Jacobson et al. in which a two-compound mixture was separated in 0.8 ms in a capillary length of 200 μm and a field strength of 53 kV/cm (141). Capillary electrophoresis in a poly(dimethyl siloxane) microfluidic system was reported by Duffy et al. (142). Chiral separation of extraterrestrial amino acids extracted from the Murchison meteorite was performed in a microfabricated electrophoresis device using laser fluorescence detection (143). Shi et al. performed a nucleic acid analysis using a radial 96-channel capillary electrophoresis device (144). Jeong et al. investigated a cyclic capillary electrophoresis separator on a silicon substrate (145). Morishima et al. combined both capillary electrophoresis and dielectrophoresis on a glass wafer to trap polystyrene beads (146). Harley et al. discussed the use of CAD software to design two-dimensional microchip separation devices (147). Lazar et al. presented an integrated system comprising liquid-phase separation elements, microdigestion units, pumping units, and a separation channel. The device was interfaced with an electrospray mass spectrometer and the over-all performance tested with complex peptide mixtures (148). Electrophoretic separation in a channel loop was carried out using a synchronized cyclic electrophoresis method. Such a system is capable of increasing plate numbers linearly with cycle numbers (149). Capillary gel electrophoresis separation of DNA molecules of 100–1000 bp was performed using PDMS microchips, with partially filled agarose gel channels (150). An analytical system that incorporated electrophoresis and a thick-film amperometric detector for the separation and detection of organophosphate neurotoxic compounds was presented by Wang et al. (151). An integrated system for the detection of inorganic anions in water samples was presented by Bodor et al. It coupled capillary zone electrophoresis with on-line isotachopheresis sample pretreatment and a conductivity detector (152). Schwarz and Hauser used capillary electrophoresis to achieve a chiral separation of the enantiomers of adrenaline, noradrenaline, ephedrine, and pseudoephedrine (153). A fritless separation channel on a PDMS device was packed with octadecylsilanized-silica microspheres, and capillary electrochromatography separation of amino acids and neutral species was performed (154).

Liu et al. optimized the separation matrix and temperature, the channel length and depth, the injector size, and the injection parameters in order to perform high-speed DNA sequencing (155). Ocvirk et al. provided a detailed study of electrokinetic control of fluid flow in native poly(dimethyl siloxane) capillary electrophoresis devices (156). The properties of the electroosmotic flow in PDMS oxidized channels with low ionic strength solutions was studied, and a 4-fold increase in electroosmotic mobility versus native PDMS was observed (157). A study that demonstrated the use of low voltage in capillary electrophoresis was presented by Lin. In this study, an arrangement of electrodes

in the separation channel was placed to create small separation zones and a voltage was applied between pairs creating zones of a high enough electric field to separate the samples (158). Kwok and Manz reported the elimination of sample bias in CE by applying Shah convolution differentiation Fourier transform for rear analysis (159). Ronai et al. studied the effect of operational variables (sieving matrix concentration, migration characteristics, separation temperature) on the separation of DNA fragments (160).

The separation of herbicides using isotachopheresis was performed on a glass chip and monitored using Raman spectroscopy by directly coupling the microchip to a Raman microprobe (161). The determination of metals within a device that integrated sample stacking, electrophoretic separation, derivatization, and detection was accomplished by Kutter et al. (30). Yang and Chien applied a new sample stacking technique based on a static stacking idea in which the microchannels were coated to eliminate the electroosmotic flow, followed by electrophoretic separation on the same device (162). Separation of DNA molecules based on field inversion electrophoresis (periodic reversion of the direction of the electric field) was presented by Ueda et al. In this approach, an optimized frequency produced an electrophoretic separation in a shorter effective length (163). Brahmasandra et al. offered a gel-loading approach to perform gel electrophoresis using photopolymerized polyacrylamide gels (164).

Capillary electrophoresis has been widely applied on-chip over the past few years and more literature is available (31, 55, 109, 165–194).

3. Isoelectric Focusing. A first step in adapting capillary isoelectric focusing to microfluidic devices was performed by Hofmann et al. Using glass chips Cy-5-labeled peptides were focused in less than 30 s (195). Isoelectric focusing was performed on quartz chip channels coated with linear polyacrylamide, and UV absorption images of the zones were produced in real time (196). A new approach for isoelectric focusing based on the formation of natural pH gradients and a model describing the phenomenon were presented by Macounova et al. (197) and later in a more detailed study by Cabrera et al. (198). Transverse isoelectric focusing was performed in a pressure-driven flow, and optimal conditions for the continuous fractionation of protein mixtures were obtained (199).

4. Other Separation Methods. It is to be noted that some isotachopheresis articles can also be found under Preconcentration in the section Sample Preparation.

Chou et al. developed an asymmetric obstacle course rectifying the Brownian motion, causing the molecules to be sorted by their diffusion coefficient (200). Edwards et al. introduced a thermal field-flow fractionation system on-chip and its theory and tested it with an acetone sample (201). Hammond and co-workers developed a device containing periodic arrays of anodes and cathodes, generating an anisotropic electric field, to trap DNA molecules at a potential energy minimum. By switching the voltage off, molecules were allowed to diffuse, only to be trapped in a nearby potential energy minimum when the voltage was reapplied. Continuous repetition of this process resulted in the separation of DNA molecules according to their diffusion coefficients (202). Wang et al. reported a dielectrophoretic field-flow fractionation device tested on several cell separation problems, including the

purging of human breast cancer cell from normal cells (203). Also based on field-flow fractionation is the system presented by Gale et al. for blood and protein separations (204). Shinohara et al. designed a free-flow electrophoresis module with 6 inlets for buffer, 1 inlet for sample, and 30 outlets for collection of separated fractions (205). An entropic trap array was developed by Han and Craighead to separate DNA molecules according to size: the channel comprises narrow constrictions and wider regions that cause size-dependent trapping (206). Holmes et al. developed a dielectrophoretic separation system in order to isolate rare molecules from a complex sample (207). Vykoukal et al. combined dielectrophoresis with field-flow fractionation and applied their device to biomedical separation and analysis (208). Arai et al. presented a high-speed separation system using a laser trap and dielectrophoresis that they applied to arbitrarily selected single microbes (209). Gaudioso et al. reported the micromachining of a diffusion-based separation device. On this chip, numerous wells were incorporated along the separation channel and are more likely to trap the smaller, and thus faster diffusing, molecules, consequently retarding them relative to the slower diffusing proteins (210). Edwards et al. developed a microfabricated thermal field-flow fractionation system with characteristics comparable to macrosystems (211).

Detection. 1. Chemiluminescence and Electrochemiluminescence. A microsystem that combines both the electrode transducer and the photodetector for electrochemiluminescence was fabricated by Fiaccabrino and co-workers. The influence of the pH as well as the distance between the interdigitated array electrodes on the luminiscence was investigated using as model system a ruthenium complex and tripropylamine (212). Electrochemiluminescence detection was used by L'Hostis et al. to determine the concentration of glucose after an enzymatic reaction, and also for the determination of codeine, without pretreatment, in pharmaceutical samples (108). Arora et al. presented a wireless electrochemiluminescence detector that they applied to a micellar electrokinetic chromatographic separation. They used a U-shaped floating electrode (the electrode is not connected to any external electric circuit) for the redox reaction and succeeded in performing indirect ECL flow cell detection of amino acids (213). The same group had previously achieved a detection limit as low as 0.5 pM for tris(2,2'-bipyridyl)ruthenium(II) using a flow cell for ECL detection (214). DNA molecules immobilized to glass microchannels were hybridized and detected via enzyme-catalyzed chemiluminescence reactions, and the sensitivity and dynamic range of the method were determined (215). Xu et al. performed an on-line monitoring of chromium(III) by using chemiluminescence generated in a micromixer (216).

2. Electrochemical Detection. Woolley et al. fabricated an amperometric detector system on glass substrates and tested it for the determination of neurotransmitters. The device also performed indirect detection of DNA restriction fragments and PCR products after an electrophoretic separation (217). A screen-printed carbon electrode perpendicular to the flow direction of an electrophoretic separation channel was fabricated, and the factors that affected the efficiency of separation and the amperometric signal were appraised (218). Gold electrodes were sputtered directly into the separation microchannel of a microfluidic device to operate as a working electrode of an amperometric

detection system (219). Systems that combined precolumn reactions, electrophoretic separation, and amperometric detection were shown by Wang et al. to be suitable for both amino acid and enzymatic analysis. Oxidase and dehydrogenase reactions were carried out, and the products of both reactions were simultaneously detected showing the feasibility of a multienzyme assay on-chip (191, 220). Gawron et al. presented the first carbon-based dual-electrode detector for microchip capillary electrophoresis: the amperometric detection was performed in either a three-electrode (single-electrode detection) or a four-electrode (dual-electrode detection) format (221). Chen et al. presented a palladium film decoupler that allows the separation of the electrical system of the electrochemical detection from that of the electrophoretic separation when using amperometric detection in electrophoresis chips (222). Wang et al. described a novel approach generating two electrophoretic peaks for a single analyte using amperometric detection (223).

Laugere et al. studied the characteristics of a conventional conductivity detector and then considered the downscaling aspects to perform conductivity detection on a capillary electrophoresis chip (224). Darling et al. compared conductivity and anodic stripping voltametry, using three different device types with varying electrode distances (225). Weber et al. performed capillary electrophoresis with direct and contactless conductivity detection on a PMMA device (226), and Lichtenberg et al. optimized the operating parameters for a glass-based microchip for CE with an integrated conductivity detector (227, 228). Guijt et al. tested the performance of powder-blasted devices by performing the separation of lithium, sodium, and potassium ions, followed by conductivity detection (190). Using carbon microband electrodes, Rossier et al. fabricated an electrochemical detector on which they successfully performed cyclic voltammetry (229).

An integrated potentiometric detector based on a solvent polymeric membrane has been described by Tantra and Manz (230). Wang et al. presented a glass device that integrated chemical derivatization reactions of amino acids with electroactive species with separation and electrochemical detection (191). Electrochemical detection in a PDMS chip using a dual-electrode array was presented by Martin and co-workers. The arrangement of two electrodes in series allowed the detection of chemically reversible redox species and the identification of unresolved peaks (174). Martin et al. also developed a new electrode configuration applied to capillary electrophoresis and electrochemical detection: by using an electrically isolated potentiostat, they could place the working electrode in the separation channel and compare its performance to the more traditional end-channel approach (231).

3. Fluorescence. Roulet et al. presented an array of micro-lenses to perform on-chip fluorescence detection (232). Weigl et al. used a reference solution directly present in the device's channel to quantitatively detect clinical substances (23). Multi-channel laser-induced fluorescence detection was carried out by using an acoustooptical deflector to move the laser between the parallel channels. Important features of this approach are the absence of moving parts and fast-scan frequencies (233). Cross-correlation electrophoresis was employed, along with fluorescence detection, to resolve and detect a mixture of dyes that could not be detected in conventional ways (234). Liu et al. used a fluorogenic dye that binds reversibly with hydrophobic protein

regions in order to form highly fluorescent complexes; detection limits as low as 0.5 pg of injected sample were achieved (117). Zügel et al. demonstrated the successful use of two-photon-excitation fluorescence detection by measuring the product of a clinically significant tissue enzyme in an electrophoretically mediated microanalysis. The microanalysis is based on the mixing of the reactants due to their differences in mobility. When the slower reactant is injected first the faster reactant will overtake it, mixing with it at the same time (235). The use of a microavalanche photodiode detector embedded in a PDMS microfluidic device, along with an optical fiber for the excitation of fluorescent species, was demonstrated by Chabynec and co-workers. The need of collection optics was eliminated as the size of the detector was comparable with the width of the channel (236). Using a lamp and a photomultiplier tube on a moving stage, scanning fluorescent detection used for isoelectric focusing analysis in plastic microchips was developed (237).

Indirect fluorescence detection of a set of amino acids was performed by using fluorescein as the background and avoiding the need for derivatization of samples (238). Simpson et al. reported the fabrication of a DNA analysis system allowing simultaneous detection of various samples (239). By using indirect fluorescence detection, Sirichai and de Mello were able to achieve quality control of a film-processing solution (240). Schilling et al. characterized a fluorogenic enzyme assay for the detection of cell lysis products and proteins (241). Flow cytometry of *Escherichia coli*, in poly(dimethylacrylamide)-coated channels, was performed by transporting and focusing the cells electrophoretically and detecting them using coincident light scattering and fluorescence (242). Jin et al. used a dynamic labeling method for the detection of protein–SDS complexes. They incorporated a fluorescent dye in the buffer, which interacted hydrophobically with complexes, allowing detection by laser-induced fluorescence (192). Berti et al. reported that the use of energy-transfer dye-labeled primers significantly improved DNA fluorescent detection (243). Maims et al. used a grating waveguide for optical analysis enabling fluorescence and absorption measurements to be undertaken on-line in microchips (244).

Wang and Morris applied analyte velocity modulation to reject fluorescence background in plastic devices. To do so, they used a driving voltage modulated at low frequency (~20 Hz). The consequence was that migration velocities were modulated at the same frequency whereas the inherent microchip fluorescence was not, thus allowing the two signals to be separated by a synchronous demodulation (245). The diffusion coefficient of proteins and small molecules was studied in the T-sensor, using conventional epifluorescence microscopy (246). Ocvirk et al. showed the use of confocal epifluorescence detection to obtain detection limits between 0.3 and 1 pM. A focused laser spot of ~12 μm in diameter was obtained and allowed the detection of an average of 570 molecules (247).

4. Nonfluorescence Optical Measurements. A detection based on holographic refractive index was used, along with a cyclic square separation channel, to follow the separation of carbohydrates, demonstrating the potential of this approach as a universal detection system for microfluidic systems (248). Kameoka and Craighead developed a nanorefractive index sensor using photon tunneling (249). Hosokawa presented a novel optical

method to determine local pressure using a deformable diffraction grating (250). A module that coupled a fiber-optic reflection probe and a small-volume silicon flow cell was used for reflection–absorption measurements. The fiber optic included one emitting fiber and six receiving fibers and was used for optical monitoring of biological fluids (251). Mao and Pawlizyn developed an isoelectric focusing method on a quartz chip coupled to UV absorption imaging detection (196). Nishimoto et al. incorporated an optical slit for UV absorption detection on a microfabricated CE chip (252). Jackman et al. reported two different devices to perform in situ UV–visible detection and IR spectroscopy (253). On-line UV detection in microfabricated reactors allowed Lu et al. to study the pinacol formation reaction of benzophenone in 2-propanol (104). Mogensen et al. used monolithically integrated optical waveguides to perform UV absorbance detection (254). A CE microfluidic device in which enhanced absorbance detection was achieved by means of a multireflection cell was fabricated and tested. The effective optical path length in this device ranged from 50 to 272 μm corresponding to 5–10-fold enhancement when compared to single-pass devices (255). The integration of an evanescent wave optical sensor for visible absorption measurements in optical cells of small cross-sectional dimensions was demonstrated by Pandraud and co-workers (256).

Soughayer et al. developed and characterized cellular optoporation (a method that consists of rendering a cell membrane temporarily permeable so that some molecules can be incorporated or extracted into/from the cells) with visible wavelengths using standard glass cover slips as adsorptive media (257). Reichert et al. used a nanobead-labeling method in order to detect DNA hybridization (258). Reshni et al. proposed an on-line detection by Raman spectroscopy of an electrophoretic separation on-chip (259). Time-resolved resonance Raman spectroscopy, in microfluidic device flow, was used by Pan and Mathies to elucidate the structure of a chromophore and changes in protein–chromophore interactions (260). After having separated seven transition metal ions, Lu and Collins demonstrated the detection of the 4-(2-pyridylazo)resorcinol metal chelates by using a diode and a miniaturized photomultiplier tube (261). Mizukami and co-workers used a novel microfabrication technique, “stereolithography with double controlled surface”, to make a chip with a photosensor array. The device was tested with a Blue Dextran sample measuring the absorbance with distilled water as the reference (262). Furuki et al. presented a surface plasmon resonance detector utilizing microfabricated channels that they applied to the study of protein adsorption onto chemically modified gold surfaces (263). A theoretical understanding of surface plasmon resonance sensors has been presented by Kurihara and Suzuki (264). Miclea et al. presented a microchip capable of being a source for analytical spectrometry. The device could dissociate molecular species due to the presence of a dielectric barrier discharge plasma. It was used in plasma modulation diode laser absorption spectrometry (265).

5. Mass Spectrometry. Different microfabricated devices have been reported by Li and co-workers as well as by Zhang et al. for coupling capillary electrophoresis to an electrospray mass spectrometer; they were applied to the analysis of proteolytic digests as well as peptides (266, 267). Ayliffe et al. reported the use of microelectric impedance spectroscopy for the electrophysi-

ological characterization of cells (268). Two mass spectrometer analyzers, a triple quadrupole and time of flight, were connected separately to microfluidic devices through nanoelectrospray emitters to perform trace analysis of membrane proteins (269) and carnitines in human urine (270). A device that integrated the synthesis of compound libraries via an "AND" logic operator and a detection mode that relied on time-of-flight mass spectrometry was presented (106). This system also allowed the parallel processing, in real time, of multicomponent reaction subreactions. A modular microsystem including an autosampler, microfluidic separation device, and interface for nanoelectrospray mass spectrometry was presented (271). Such a system was able to perform sequential injections and separations of up to 30 samples/h. Deng et al. used a chip-based CE/MS system to make quantitative determinations of drugs in human plasma (272). Wang and co-workers achieved a 15-amol sample detection limit by coupling a chip and a mass spectrometer (273).

6. Other Detection Methods. A miniaturized time-scanning Fourier transform spectrometer based on silicon technology has been presented by Manzano et al. showing a resolution of 6 nm at a wavelength of 633 nm after optimization (274). Fuller et al. developed a multifrequency particle impedance characterization system allowing impedance measurements at three or more frequencies simultaneously (275). Gawad et al. introduced an impedance spectrometer for cell analysis in microchannels (276, 277).

A molecular emission detector employing a direct current microplasma has been reported by Eijkel et al. The device employs direct current helium plasma for molecular fragmentation and excitation (278). Eijkel et al. also reported an atmospheric pressure dc glow discharge and its use as a molecular emission detector. Methane was detected with a detection limit of 2×10^{-14} g/s and a linear dynamic range of two decades (279). Atomic emission spectrometry using a microwave-induced plasma (280), a capacitively coupled microplasma (281), and a pulsed plasma source was also reported (282); absorption spectrometry using a dielectric barrier discharge and a diode laser was also reported (283). Jenkins and Manz used a micromachined dc glow-discharge device at atmospheric pressure for the optical detection of metal ions in water (284).

Zimmermann et al. manufactured micromachined flame analyzers for atomic emission flame spectrometry and flame ionization detection (285–287). A microfluidic device that used oligonucleotide-tagged liposomes as hybridization markers in a sandwich-hybridization assay for RNA sensing was presented by Esch et al. (288). Veenstra et al. compared two different systems for the μ -FIA ammonium detection (289). Jackman et al. reported the integration of multiple internal reflection (MIR) infrared spectroscopy with microreactors. These devices incorporated crystals suitable for MIR IR spectroscopy and were used for kinetic studies of the hydrolysis of ethyl acetate (290). Massin et al. performed on-chip NMR spectroscopy and detected concentrations of a few percent ethanol in water by ^1H NMR in a 30-nL volume with only three scans (291, 292).

7. Single-Molecule Detection. Analysis of single molecules was performed by Fister and co-workers by focusing a laser beam in an area of a few micrometers and counting the fluorescent burst from each molecule. Detection limits in the picomolar range were

obtained (170). Also utilizing a fluorescence burst counting technique, single DNA molecules were detected by Haab and Mathies. They used a cross-shape intersection to create a sheath flow, narrow the sample flow, and subsequently lead the sample through the focused laser beam. The device sensitivity was improved by such an arrangement (293). A single nonfluorescent molecule detection method based on the thermal lens effect was successfully demonstrated. Using photothermal spectroscopy, the heat produced by the relaxation process after light absorption was measured (294). Using the same principle, Sato et al. reported detection in the subzeptomole range in glass devices (295) and Tokeshi et al. measured the photothermal signal at a subsingle molecule level expressed as expected molecule number (296). Chou et al. compared different devices for biomolecules sorting such as a single-molecule mapping device using near-field optics (297). Turner et al. developed optical waveguides to confine the excitation volume in single-molecule fluorescence detection (298). Kurosawa and co-workers established a novel method for single-molecule DNA analysis based on physical molecular analysis. The device consisted of a glass substrate with a sacrificial layer and a pair of electrodes on which the DNA solution is fed. Applying high-frequency voltage stretches and aligns the DNA molecule. A portion of the DNA molecule can then be cut off with an AFM tip as a knife, and the sacrificial layer is dissolved. The DNA fragments are recovered by filtration and amplified by polymerase chain reaction (299). Cui et al. presented an optical particle detection integrated in a dielectrophoretic device (78). More literature concerning chemiluminescence (54, 300), optical detection (44, 246, 301–306), electrochemical detection (51, 55, 152, 153, 307, 308), mass spectrometer coupling (7, 107, 271), or more exotic methods of detection (159, 309) can be found.

APPLICATIONS

The vast majority of research work on microfluidic devices has been directed toward the biological and life sciences. This section covers papers dealing with analytical methodology for the handling, separation, and detection of biological moieties on-chip. A recent review on applications for microfluidic devices, covering the analysis of drugs, explosives residues, enzymes, antibodies, peptides, DNA, and other biological samples, is referred to for more examples on this topic (310).

Cell Culture and Cell Handling. Red blood cells, various populations of white blood cells, and platelets were differentiated and counted using a microfluidic structure that incorporated hydrodynamic focusing (311). Cytomechanical studies of red cell membrane viscoelastic behavior during flow were performed in a microfluidic device that matched the limitations of cell fragility, sedimentation, and separation effects (312). The interaction of leukocytes with their physical environment was demonstrated using physiological flow conditions and an array of microchannels with length in the range of human capillaries (313). Sorting of paramagnetic particles from nonmagnetic and fluorescent particles from nonfluorescent ones was achieved by Tellemann et al. as a preliminary work to cell sorting (314).

The growth of *E. coli* expressing green fluorescent protein was achieved in gas-permeable PDMS microfluidic devices, and the incubation process was optically monitored by fluorescence for up to a 5-h period (315). Cellular optoporation was characterized

using visible laser light and tested in microfluidic systems by loading cells, attached to microchannel surfaces, with a fluorophore (257). Cellular calcium flux was used to screen for agonists and antagonists for G-protein in cultured cells (316).

Inoue et al. presented an on-chip cell culture system that consisted of an array of chambers in which a single cell or group of cells was isolated from the external environment by means of a permeable membrane. The medium was easily exchanged, and the size of the chamber was flexible (317). A disposable micro fluorescence-activated cell sorter (μ FACS) was developed and used to separate *E. coli* cells expressing green fluorescent proteins from nonfluorescent *E. coli* cells (318). A single microbe was arbitrarily separated, among a large number of microbes in solution, by means of a laser-trapping force and a dielectrophoretic force. The separation procedure took less than 20 s and could be useful for pure cultivation of cells (209). Cabrera and Yager presented a method to concentrate bacterial solutions using zone electrophoresis and isoelectric focusing in carrier-free solutions (33). An electroporation microchip that enclosed two thin film gold electrodes in PMMA was fabricated and tested for continuous gene transfection using Huh-7 cell lines (319). Mammalian cells were cultured in microchambers created by using patterned flows of etching solutions in PDMS microfluidic devices (320). A PDMS microfluidic device consisting of an array of microinjectors and a base-flow channel was tested for cell culture using neuronal cells patterned in a linear fashion (321). A commercial product for cell-based assays is available from Caliper and Agilent.

Clinical Diagnostics. Common mutations in breast cancer-susceptible genes were screened by a single-strand conformation polymorphism analysis, using polymer-coated capillary electrophoresis and microchip electrophoresis (177). The analysis of urine samples with high levels of amino acids as indicative of amino acid metabolism disorders and kidney malfunction was performed using electrophoretic separation with indirect fluorescence detection in a microfluidic device (238). A microfluidic device for clinical diagnostics based on a sandwich immunoassay system that used three antibodies and a thermal lens microscope for detection was presented by Sato et al. (322). A biocompatible polymer was used to coat a microchannel in a quartz chip in order to suppress the adsorption of proteins from blood serum samples. An electroosmotic pump was arranged downstream of the microcapillary to allow the injection of the serum (323). Carnitines and acylcarnitines from standard solutions and human urine were determined on-chip by using capillary electrophoresis and mass spectrometry (272). The concentration of oxalate, from a urine sample, was determined using a PMMA microchip coupled to a pair of conductivity detectors. Detection of concentrations of 80 nM was achieved (324). The determination of homocysteine and reduced glutathione (in human plasma) was achieved, by Padas et al., using capillary electrophoresis on-chip and electrochemical detection (325). Fanguy and Henry determined uric acid in urine by means of capillary electrophoresis and electrochemical detection. Separation of the sample in less than 30 s and a limit of detection of 1 μ M were obtained (326).

Immunoassays. A competitive assay that allowed the measurement of small molecules down to nanomolar concentrations was presented and compared with a fluorescence polarization immunoassay (114). Immunoreagents were immobilized directly

onto the channel walls of a microchip, and the system was tested using protein A for rabbit immunoglobulin G (rIgG) as the immobilized species and rIgG as sample (327). Yang et al. presented an immunoassay based on solid supported lipid bilayers, in which bilayers coating the surface of PDMS microchannels contained dinitrophenyl (DNP)-conjugated lipids for binding with bivalent anti-DNP antibodies (328). A biopassivation procedure enabled the immobilization of antibody and subsequent immunoreaction, using biotinylated IgG, neutravidin, and a biotinylated reagent, to perform affinity binding assays (329). Sato et al. presented a multiple-sample bead-bed immunoassay system. The multichannel system was capable of processing four samples at the same time with one pump unit and completed the assay in 50 min (330). A heterogeneous competitive immunoassay of human IgG, utilizing Cy5-human IgG as tracer and Cy3-mouse IgG as internal standard, was developed by Linder et al. in PDMS/glass devices (331). Locascio et al. presented a bioassay based on an antibody conjugate affinity approach that used liposomes encapsulating carboxyfluorescein molecules to amplify the fluorescent output signal. Competitive assays were carried out within short incubation times due to the high fluorescent output associated with the liposomes (332). The reader is referred to Enzymatic Reactors under the Reactors and Mixers section for more literature regarding immunoassays.

Proteins. The chiral separation of amino acids extracted from the Murchison meteorite was performed on capillary microchannels to investigate the possibility of the use of microfluidic devices to analyze signs of extinct or extant extraterrestrial life (143). A protein-sizing method that incorporated SDS-PAGE gels with the high speed of microchip separations was presented by Bousse (333). Continuous fractionation and separation of proteins was carried out by a combination of transverse isoelectric focusing and pressure-driven flow (199). Protein separation of lysozyme, cytochrome *c*, RNase, and fluorescein-labeled goat anti-human IgG Fab fragment was achieved using fused-silica capillaries and glass microchips coated with thermally pyrolyzed PDMS (334).

Model proteins (α -lactalbumin, β -lactoglobulin A, β -lactoglobulin B) were separated electrophoretically and detected by noncovalent postcolumn labeling (117). A dynamic labeling process during electrophoretic separation was used for the detection of proteins in capillary and microchip devices (192).

Rapid on-chip protein digestion analysis using a microchip coupled to a nanoelectrospray-mass spectrometer was demonstrated by the analysis of human hemoglobin (335). An oxidized insulin B chain was tryptic digested under stopped-flow conditions in a microchip, and the products were separated within the same microchip device (109). Trace analysis of digested proteins was performed by coupling a quadrupole time-of-flight mass spectrometer to microfabricated devices (169). Analysis and identification of proteins using electrospray and mass spectrometry, tandem mass spectrometry, and triple quadrupole mass spectrometry was widely and successfully used (269, 336–338). There is one commercial product by Caliper/Agilent for protein separations (SDS-PAGE).

DNA Separation and Analysis. A parallel design for DNA separation based on a 96-capillary electrophoresis array was fabricated and tested by Shi et al. The analysis of 96 alleles in

parallel was achieved, demonstrating the feasibility of performing high-throughput genotyping separation with this device (144). A system utilizing a capillary electrophoresis array, using PMMA substrate, was developed for ultrafast DNA separation and analysis by imaging of the bands (173).

Parameters such as DNA length, buffer additives and pH, sample salt effect, and temperature of separation were used to explore the potential use of microfluidic devices for the detection of deletion, insertion, and substitution mutations by heteroduplex analysis (339). A separation microchannel of 6-mm length and a laser-induced fluorescence detection system were used to separate and detect a triplet repeat DNA fragment and DNA molecular marker. Microchip separation proved to be at least 18 times faster when compared with a conventional capillary electrophoresis system (178). A disposable glass microchip was developed and tested for the analysis of PCR products, sizing of plasmid digests, and detection point mutation using restriction fragment length polymorphism mapping (340). Other works comprising DNA electrophoretic sizing as part of the DNA analysis were presented (239, 341).

A work in which, after PCR, allele-specific products were generated, separated, and typed was presented by Medintz et al. The potential of this device using a capillary electrophoresis array coupled with a laser-excited rotary scanning confocal detection for high-throughput single-nucleotide polymorphism was demonstrated (166). Other allele-specific amplifications (AS-PCR) with heteroduplex analysis (176) using microchip electrophoresis and AS-PCR for high-throughput single-nucleotide polymorphism using a capillary electrophoresis array (342) were described. A filter chamber array in a microfluidic device was used for the analysis of single-nucleotide polymorphism by using pyrosequencing, a sequencing-by-synthesis technique that relies on the detection of pyrophosphate, which is released once a nucleotide is incorporated (343). Fast- and high-resolution DNA separations were carried out by concentrating the DNA samples at the entrance of microfabricated hexagonal arrays and further separation by pulsed field electrophoresis (344). Polycarbonate was used as substrate for the microfabrication of a device designed for PCR and DNA separation using capillary electrophoresis (171).

High-throughput DNA separation utilizing capillary array electrophoresis was carried out for genetic analysis (345–347). The use of a microfluidic electrophoretic device for rapid analysis in genotyping was presented by Barta et al. (348). Separations of DNA introducing new types of electrophoretic separations, detection modes, sample pretreatment, autosampling, and genetic analysis were presented by several research groups (2, 41, 150, 158, 163, 217, 293, 349–351). Using a system capable of repetitive operation, multiplexed short tandem repeats were analyzed by the simultaneous detection of three- and four-color multiplexed polymerase chain reaction samples (352). There are several commercial products available for DNA and RNA separations by Caliper, Agilent, Shimadzu, and Hitachi.

Polymerase Chain Reaction. A PCR device that incorporated cell lysis, PCR amplification, and electrophoretic separation of the PCR products was presented by Waters et al. By thermally cycling the whole device to lyse the cells and to amplify the DNA, genomic and plasmid DNA were amplified and separated (341). In a

subsequent work, multiple PCRs were carried out on a microchip device and the separation of the products was achieved individually or together in the same microchip (353). In a two-step PCR, degenerate oligonucleotide primed-polymerase chain reaction was first carried out in a silicon–glass chip followed by another PCR for specific gene exons to detect deletions causing a type of muscular dystrophy (354). A battery-powered miniature thermal cycling apparatus for real-time PCR assay was presented and later improved for fast distinguishing of single-base polymorphisms (355, 356). Nucleotide differences in viral and human genomic DNA were identified using this apparatus.

A rapid PCR system that integrated a compact thermal cycling element that allowed fast cycles of 1 min and efficient DNA amplification with electrophoretic sizing and detection was presented by Khandurina et al. Analysis times of no more than 20 min were obtained (357). Thermal cycles as fast as 30 s were obtained with a monolithic device that integrated loading, PCR amplification, and separation of a few hundred nanoliters of DNA (358). Two microdevices for PCR reaction, one incorporating fiber optics for excitation and collection of the emitted light, and a second using a photodiode for collection of the emitted light, were designed and tested (302). PCR coupled with capillary electrophoresis was used to demonstrate the potential of a microfluidic device for analyzing polymorphic alleles (359).

Belgrader et al. developed a portable real-time PCR device, consisting of two independent reaction modules that allowed different temperature profiles and integrated optics for four-color fluorescence detection (360). Amplification of single DNA molecule templates was performed by Lagaly et al., demonstrating the most sensitive PCR yet obtained in a microchip device (349). Infrared was used for PCR amplification in polyimide microfabricated devices allowing the production of sufficient amounts of PCR products in only 15 cycles and a total amplification time of 240 s (361). A flow-through thermocycler for PCR in a silicon and glass chip was presented and its capability for high throughput of samples demonstrated (362). Human genomic DNA was amplified directly from cheek cells using a fully integrated and automated microchip capillary-based system (363). The use of additives for dynamic coating or adsorption onto glass surfaces was studied and tested for PCR amplification of DNA (364).

Sequencing. A theoretical model and its experimental evaluation were demonstrated for the sequencing of DNA in microfabricated devices that used sieving matrixes for the separation of single-stranded DNA (365). An optimization study for the use of microchannels to perform DNA sequencing separations of up to 500 bp with 99% of accuracy in less than 20 min was performed by Liu et al. Features such as separation matrix, temperature, channel dimensions, and injection were the scope of this study (155). An independent work also reported the optimization of capillary electrophoresis parameters for the sequencing of DNA, separating 565 bases with 99% accuracy in less than 25 min (366). Longer capillary channels were incorporated in a microfluidic device and read lengths of up to 640 bases were obtained in 150 min (367). A 16-channel electrophoresis array was presented by Liu et al., in which parallel DNA sequencing separation of 450 bases in 15 min was performed with an accuracy of 99% (368).

A polymeric reactor device, which utilized volumes in the order of nano- and subnanoliters, was employed to carry out sequencing reactions and polymerase chain reactions. The system reduced the volume by a 300-fold when compared with typical Sanger chain-termination protocols (187). An optimization study of high-performance DNA sequencing on short microchannels that used replaceable linear poly(acrylamide) was performed by Salas-Solano et al (369). DNA sequencing was accomplished with a system that used a sieving matrix and an imaging detection mode (239). High speed, high-resolution separations of double- and single-stranded DNA in plastic microfluidic systems for sequencing of up to 700 single-stranded DNA fragments in 40 min were reported by Boone and Hooper (370).

A significant achievement in sequencing was demonstrated by Koutny et al. when using microchannels of 40 μm long; a read length of 800 bases with a 98% accuracy was obtained in 80 min (371). Paegel et al. presented a high-throughput sequencing microfabricated capillary array electrophoresis (μCAE) device, which consisted of 96 channels grouped in a radial conformation. The μCAE demonstrated a sequencing rate of 1.7 kbp/min which is a 5-fold increase over the commercial apparatus (372).

This concludes our review of micro total analysis systems. We hope this selection of publications is useful to the student of this interesting area. It should be clear however, that a more in-depth review of a narrower field will always be necessary to precede any new and original research publication. We did not intend to replace that task, but hoped to provide a useful starting point.

“ΤΑ ΒΩ ΚΑΙ ΚΙΝΩ ΤΑΝ ΓΑΝ” “Give me a place to stand, and I will move the earth” (Archimedes 287–212 B.C.).

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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 master's project, he spent fourteen months at Orion Research, Inc. (Beverly, MA), where he helped developing 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.

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.

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.

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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