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Micro Total Analysis Systems. Recent Developments

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Review Contents

The area of micro total analysis systems (μTAS), also called "lab on a chip" or miniaturized analysis systems, is growing rapidly. This paper represents an update of the earlier reviews (*1, 2*) and covers the period from March 2002 to February 2004. The intention of this review paper is to provide help for a novice in the field to find the original papers. Publications in the area of μTAS are scattered over a larger number of journals, but most frequently articles can be found in *Lab on a Chip*, *Analytical Chemistry*, *Electrophoresis*, *Sensors & Actuators*, and others. Excellent sources of information are also conference proceedings from regular international meetings such as μTAS, Transducers, and HPCE. However, not all active groups participate in these conferences regularly. An on-line keyword search resulted in more than 3000 hits for the years 2002 and 2003. For this survey, we focused on about 1000 of these articles. Many publications about sensors, arrays (so-called "biochips"), chemical synthesis on-chip, and the more technical (engineering) papers have been omitted, as it is the scope of this paper to review microfluidic systems for analytical chemistry. We did not intend to cover 100% of the papers but rather tried to choose relevant examples for every distinct method or device. Interested readers may refer to citations in the original papers for additional references. In contrast to the earlier two reviews, we now focused on papers presented in peer-reviewed journals and dramatically reduced those presented at conferences as they have generally been published elsewhere or will be soon. We also recommend the text books by Madou (*3*) and Geschke et al. (*4*) for an extensive coverage of technological aspects in microengineering and the book by Oosterbroek and van den Berg (*5*) as well as Nguyen and Wereley (*289*) for further information about methods and applications in microfluidics.

TECHNOLOGIES

Microfabrication. Wolfe et al. described the use of a Ti:sapphire laser to create topographical structures in the flat surface of PDMS (*6*). Lee and co-workers investigated solvent compatibility of PDMS microfluidic devices (*7*). Camou et al. fabricated a two-dimensional lens of PDMS by SU-8 molding a channel with an arcuated end for the optical fiber (*8*). Different methods to remove highly cross-linked SU-8 photoresist from high aspect ratio structures after the development process were discussed by Dentinger et al. (*9*). Wu and co-workers reported on a technique called microlens array lithography where the design of a single photomask was projected via an array of microlenses onto a layer of photoresist (*10*). The same technique could also generate three-dimensional structures utilizing gray scale masks (*11*). Chen et al. proposed the use of microfluidic photomasks for certain applications in gray scale photolithography, where the transparency level was determined by different concentrations of dye solutions that filled the channels in the photomask (*12*). Pan et al. reported the fabrication of calcium fluoride microfluidic devices that demonstrated the application of FT-IR spectroscopy for real-time observation of analytes in microchannels (*13*). Gray scale masks were also implemented in an excimer laser micromachining system to produce structures with a continuous profile, for example, in PET (*14*). A process described by Elsner and co-workers, that combines replica molding with UV-curing, can be used to form acrylate-based 3D microstructures (*15*). McDonald et al. presented the use of solid-object printing to manufacture 3D microfluidic devices larger than 250 μm (*16*). Instead of using a spin-coater, a constant-volume injection was used by Lin and co-workers to create a planar SU-8 film of up to 1.5-mm thickness (*17*). A new technique, in which laser printer toner selectively deposited between two laminated polyester films formed channel walls, can be used to produce simple and low-cost microfluidic chips as shown by do Lago et al. (*18*). Hulme et al. fabricated a

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spectrophotometric absorbance flow cell in PMMA using injection molding (*19*). Klank and co-workers investigated the enormous potential of CO_2 laser systems to produce microfluidic systems in PMMA as well as several associated bonding techniques (*20*). Ion track etching was successfully applied to thin polyimide-based microfluidic devices in order to convert channels into nanoporous membranes as reported by Metz and co-workers (*21*). Mayer et al. report on a simple method to fabricate micropores with diameters from 2 to 800 μm in films of amorphous Teflon for ion channel measurements in lipid bilayers (*22*).

Bien and co-workers investigated different masking materials for deep glass etching (*23*). Powder blasting at an oblique angle onto a masked and rotated substrate was used to fabricate high aspect ratio structures in glass (*24*). Rodriguez et al. demonstrated rapid prototyping of microstructures in glass by pumping HF solution through channels in a PDMS slab on the glass substrate and achieved faster etching rates through a higher HF concentration on the glass surface (*25*). The application of sacrificial poly-Si etching to create important components for microfluidic systems, such as V-grooved channels, channel crossings, and injectors, in a single etching step was shown by Berenschot et al. (*26*). Nanochannels in a fused-silica chip were fabricated by Hibara and co-workers, who also showed liquid introduction and carried out time-resolved fluorescent measurements of the introduced aqueous solutions (*27*). Griss and Stemme reported the fabrication of side-opened out-of-plane microneedles for transdermal liquid transfer, which is based on a three-step deep reactive ion etching process (*28*). A high-brightness diode-pumped Nd:YAG laser direct-writing method for fabricating multiple-level microfluidic channels was proposed by Lim et al. (*29*).

The integration of injection-molded carbon-filled polymer electrodes with driving and detecting functions in a miniaturized isotachophoresis chip was demonstrated by Baldock and co-workers (*30*). A combination of a micromolding in capillary technique and electroless metal deposition was used to fabricate an integrated electrode for electrochemical detection as shown by Yan et al. (*31*). Porous polymer monoliths could be attached to channel walls in plastic microchips after UV-initiated grafting with ethylene diacrylate (*32*). Hisamoto and co-workers demonstrated the generation of a polymer membrane within a channel by a polycondensation reaction at the interface between the flows of an aqueous and an organic phase (*33*). Maruo and Ikuta developed a microstereolithography system capable of fabricating true 3D objects and freely movable mechanisms, which is based on internal solidification of a liquid photopolymer at the focal point of a He−Cd laser (*34*). A two-photon-generated photoacid that can fabricate three-dimensional microstructures in a positive-tone resist was synthesized and applied by Zhou and co-workers (*35*). Harrison et al. demonstrated a rapid prototyping method for the fabrication of solvent-resistant channels of up to 1 mm in height utilizing a Thiolene adhesive (*36*). The integration of high-voltage electrodes for electrophoretic separation into a polymer substrate, allowing for the application of similar voltages as in standard interfaces, was achieved by Sanders et al. (*37*).

Bonding Techniques. Kelly and Woolley demonstrated thermal bonding of PMMA substrates in boiling water and verified the performance of the chip by an electrophoretic separation of amino acids (*38*). The integration of temperature-sensitive layers in microfluidic chips can be achieved by UV bonding at room temperature utilizing a UV-curable glue as reported by Schlautmann et al. (*39*). A simplified glass bonding technique utilizing a water glass solution was developed by Ito et al. (*40*). A novel heating technique for silicon−silicon bonding using electromagnetic radiation, which has the potential for multiwafer bonds, was presented by Thompson and co-workers (*41*). Different procedures for bonding silicon and 7740 Pyrex wafers were also discussed (*42, 43*).

Surface Modification. Shin and co-workers treated PDMS surfaces of a PCR chip with a parylene film to overcome problems caused by the porosity of PDMS (*44*). A one-step procedure to covalently link polymers to PDMS by ultraviolet graft polymerization was presented by Hu et al. (*45*). PDMS microfluidic devices fabricated with pentafluorophenol ester functionalized surfaces showed excellent adhesion and high reactivity for primary amino groups as reported by Lahann and co-workers (*46*). Aging effects of oxidized PDMS surfaces, which can be overcome by amine modification, were studied by Wang et al. (*47*). PTFE surface passivation of PDMS channels improved the durability for organic solvents and reduced the adsorption of biomolecules as shown by Kanai et al. (*48*). To make polycarbonate surfaces more hydrophilic and manipulate electroosmotic flow, Vaidya et al. used chemical treatment with sulfur trioxide gas (*49*). Zhao and co-workers continued their studies on surface-directed liquid flow (*50*) and also presented pressure-sensitive microfluidic gates based on that technique (*51*). Yoon and Garrell controlled the surface wettability in biofluidic chips by adjusting the bias, magnitude, and duration of the applied voltage (*52*). Malmstadt et al. used temperature-responsive beads, which aggregate and adhere to the channel walls above a certain temperature, to form a smart affinity chromatography matrix in microfluidic channels (*53*). Yi and co-workers coated microfabricated surfaces of biochips with chitosan to facilitate the assembly of labile biological sensing molecules (*54*). Sharma et al. investigated the stability of thin PEG films on silicon-based implantable microdevices under in vivo conditions (*55*). A coating method to attach silica particles to a flat substrate for use as a stationary phase in shear-driven chromatography, where the particles only bond to the glass and not to each other in order to form a monolayer, was developed by Vervoort et al. (*56*).

Design. Gitlin and co-workers used topographical features on one channel wall to achieve electrokinetic pumping by applying the field across the channel (*57*). Chen et al. carried out true 2D-capillary electrophoresis through assembling, disassembling, and reassembling of PDMS chip components with perpendicular separation channels (*58*). Thorsen and co-workers developed microfluidic networks analogous to electronic integrated circuits. The devices, which consist of 1024 flow channels addressed by only 20 control channels and a multiplexed valve system, were fabricated using microfluidic large-scale integration (*59*). A high-density microchannel network with integrated valves and photodiodes, which allows parallel processing of nanoparticles, was also realized (*60*). Chang et al. designed and fabricated a PDMS microchip that generates eight dilutions with serially increasing concentrations of a biological sample by merging different numbers of microchannels from sample and diluting medium (*61*). A similar approach of a microfluidic network for serial dilution

was combined with chaotic advective mixers to fabricate an immunoassay chip for analyzing multiple antigens that were presented in parallel stripes running perpendicularly to the channels on a membrane underneath the microfluidic network (*62*). Handling of detected DNA was achieved through individually addressable microchambers that were separated by UV-cross-linked hydrogel plugs in one direction, which allowed for electrokinetic pumping, and weirs in perpendicular direction, which only permitted pressure-driven flow (*63*). Fiechtner and Cummings introduced a new methodology to design conduction channels for ideal electrokinetic flow in order to minimize band broadening and stretching (*64*). More efficient sample delivery to biosensor surfaces was obtained when the sample flow was merged with a confinement flow in perpendicular direction as shown by Hofmann and co-workers (*65*).

Interfaces and Interconnections. 1. Chip to Mass Spectrometer. Kameoka et al. demonstrated an electrospray ionization device incorporating a triangular thin-film polymer tip that was bonded to a microfluidic channel and aided the formation of a stable Taylor cone at the apex of the tip (*66*). Le Gac and co-workers investigated the performance of a planar nib-shaped microelectrospray emitter (*67*). The microchannel itself was employed as the orifice for ESI-MS in a PDMS device made by Huikko et al. (*68*). The integration of a microfluidic chip for biochemical reactions into a standard MALDI-TOF-MS sample plate and a pumping mechanism utilizing the vacuum inside the ionization chamber of the instrument proved to be simple and effective as shown by Brivio and co-workers (*69*).

2. Chip to Other Detectors. Laugere et al. presented a small electronic interface (106−170 μm) to detect liquid conductivity in microcapillary electrophoresis devices by means of capacitive four-electrode coupling (*70*). A device capable of measuring the light generated by a chemiluminescence reaction with integrated photodiodes, which were placed on the opposite side of the channel network, was developed by Jorgensen and co-workers (*71*). Uchiyama et al. described a connection between a capillary electrophoresis chip and a thermal lens microscope (*72*).

3. Fluidic Connections. Pattekar and Kothare presented microfluidic interconnectors for high-temperature and -pressure applications. Teflon capillaries were briefly melted inside the chip and their pulling-up closed the connection hole, which was then sealed with a high-temperature curing epoxy (*73*). Lee and co-workers fabricated hourglass-shaped and threaded removable fluidic connections by molding plastic in the actual ECD (electrochemical discharge) machined glass holes (*74*). A standard interface with electrical connectors and valves to regulate the input and output of liquids or gases was developed by Yang and Maeda (*75*). Liu and co-workers proposed their solution for the "world-to-chip" interface problem by using a microfluidic matrix and thus reducing the number of pipetting steps for 400 distinct PCR reactions to 41 compared to 1200 required with conventional fluid handling (*76*). A capillary electrophoresis microchip that was connected to a portable, battery-powered high-voltage power supply was tested successfully to separate dopamine and catechol and was run for 15 h without being recharged (*77*). Another versatile three-channel, high-voltage power supply for CE was presented by Garcia and co-workers, who used it successfully for the separation of ethanol and phenol (*78*).

Microvalves and Flow Control. Stroock et al. quantified how grooved surfaces can influence pressure-driven flow in microchannels and proposed various groove patterns and possible applications (*79*). Harmon and co-workers introduced an actuator, which is based on a thermoresponsive hydrogel, that shrinks or swells with fluid from a separate reservoir and thereby displaces a PDMS membrane to actuate fluid in the microchannel underneath (*80*). Seong et al. employed hydrogel plugs as passive valves to address microchambers separately by pressure driven flow (*63*). Monolithic membrane valves, fabricated by sandwiching an elastomer membrane between etched glass fluidic channels, that are suitable for large-scale integration were presented by Grover and co-workers (*81*). Waibel and co-workers presented the first fountain pen with an electronically controlled fluid dosage system consisting of microsized fluid-handling parts as well as power supply and control electronics (*82*). Hasselbrink et al. were able to create check valves, diverter valves, and micropipets within minutes by employing moving micropistons, which were formed in situ in the microchannel by laser polymerization (*83*). Yu et al. used monolithic plugs, which were prepared within the microchannel by photoinitiated polymerization, as valves to open and close the channel, which was enabled by the volume change associated with the phase transition at a certain temperature (*84*). Aqueous viscoelastic polymer solutions employed as working fluids change their rheological properties when they flow through small orifices in microfluidic systems, which can be utilized to introduce microfluidic memory and control elements as shown by Groisman et al. (*85*). An in-plane compliance structure that dampened the pressure gradients that may arise from a micropump was designed and built by Veenstra and co-workers (*86*). Nieuwenhuis et al. developed two new flow cells for adjustable sheath flow (*87*). Fabrication of paraffin-based on−off valves has also been reported (*88*, *89*).

Micropumps. 1. Nonmechanical. Chen and Santiago developed an analytical model applicable to planar electroosmotic micropumps, which then guided the design of a pump for near-optimal hydraulic performance (*90*). Takamura et al. fabricated a low-voltage electroosmotic pump using a short narrow channel (*91*). The addition of zwitterionic solutes increased the performance of electrokinetic pumps as shown by Reichmuth et al. (*92*). Studer and co-workers fabricated an ac electrokinetic pump on a chip that consisted of an array of interdigitated asymmetric electrodes in a straight channel (*93*). Gitlin et al. pumped fluid electrokinetically with an electric field applied across the channel. Flow occurred due to topographical features such as oblique grooves in one wall of the microchannel (*57*). A circular ac magnetohydrodynamic micropump for chromatographic applications was presented by Eijkel et al. (*94*). Namasivayam and co-workers used a heating system to assist a transpiration-based micropump for continuous low flow rates (*95*). Tsai and Lin developed a thermal-bubble-actuated pump (*96*). The electrochemical formation of hydrogen gas on the working electrode is the actuation principle of the pump shown by Suzuki and Yoneyama (*97*). A combined nanofluidic pumping and injection system based on the surface tension directed injection of a gas into the liquid flow was presented by Tas and co-workers (*98*). Hong et al. used pressure that was generated on chip by a temperature-sensitive solid chemical propellant to pump liquid

through microchannels (*99*). A liquid driving system without moving parts or electrodes that is based on suction and exclusion generated by a stable airflow was presented by Jen et al. (*100*). Chien and Bousse proposed a general equation to calculate the node pressure in a microfluidic network for electrokinetic and hydrodynamic flow (*101*). A theoretical description of the feasibility of electrokinetic ratchet pumps in microfluidics was given by Ajdari (*102*).

2. Mechanical. Schabmueller et al. presented a self-aligning gas/liquid pump using screen-printed PZT as an actuator (*103*). The handling of picoliters in PDMS microchannels using a squeeze pump with linearly actuated ball bearings was reported by Lim and co-workers (*104*). The diaphragm pumps shown by Grover et al. were pneumatically actuated and suitable for large-scale integration (*81*).

ANALYTICAL STANDARD OPERATIONS

Sample Preparation. Effective degassing was achieved using ultrasonic-induced cavitation and the concentration of dissolved oxygen was kept below 6 ppm (*105*). Di Carlo et al. reported on a highly effective, reagentless, mechanical cell lysis system employing an integrated nanoknives-structured filter (*106*). Jandik et al. described a microfluidic device that uses a laminar fluid diffusion interface for blood sample preparation prior to HPLC. This method completely eliminated the need for centrifugation and reduced the preparation time from 30 to 60 min to 5 min per sample (*107*). Kuban et al. presented a miniaturized continuous ion exchanger based on two parallel liquid streams, an organic phase with an immiscible lipophilic ion exchanger and an aqueous suspension of a finely ground ion exchanger (*108*). A membrane-based desalting step, permitting the controlled elution of analytes from the membrane, and the direct mass spectrometric analysis of small drugs, peptides, and proteins by electrospray ionization MS was successfully carried out by Lion et al. (*109*). Gustafsson et al. described the high-throughput microfluidic processing of protein digests integrated with MALDI-MS on a compact disk format. The peptides in the digests were concentrated, desalted, and subsequently eluted from the columns directly into MALDI target areas on the CD using a solvent containing the MALDI matrix (*110*). Timmer an co-workers presented an analyte concentrator that made use of evaporation through a hydrophobic vapor permeable membrane and achieved a 3-fold concentration effect (*111*). Using free-flow isoelectric focusing (IEF), Xu et al. increased the concentration of nano- or microliter sample volumes by a factor of up to 400 within 430 ms (*112*). In IEF, Li et al. achieved a 10−100-fold enhancement of sample loading utilizing electrokinetic injection of proteins/peptides from solution reservoirs (*113*). Grass et al. conducted an isotachophoretic preconcentration step prior to capillary electrophoretic separation and detected separated seleno amino acids in the micromolar concentration range (*114*). The detection limit for SDS−protein complexes was decreased by a factor of 30−40 through the use of an on-line super-charging preconcentration mode as shown by Xu et al. (*115*). A 1000-fold signal increase using field-amplified sample stacking for on-chip electrophoresis was reported by Jung et al. (*116*). Ross and Locascio described a new technique, temperature gradient focusing, for the concentration and separation of ionic species within microchannels or capillaries. Concentrations up to 10 000-fold are achieved by balancing the electrophoretic velocity of analyte against the bulk flow of solution in the presence of a temperature gradient (*117*). The purification of DNA from whole blood in less than 15 min on a microchip was demonstrated by Breadmore et al., who used a solid phase of immobilized silica beads onto which DNA was adsorbed (*118*). Broyles and co-workers reported on a microfabricated device that combined on-chip filtration by an array of thin channels to exclude particulates, sample concentration employing C18 as a stationary phase, and electrochromatographic separation with solvent programming (*119*). A 2000-fold concentration increase through solid-phase extraction in octadecylsilane-packed columns allowed for subpicomolar detection of peptides by CE and was described by Jemere et al. (*120*). Through the application of an electric field across the channel, large molecules were concentrated in front of an integrated nanocapillary array and a concentrated analyte band was ejected from the channel by reversing the polarity of the electric field, which resulted in concentration factors of 300 as reported by Zhang and Timperman (*121*). Holden et al. designed and built a laminar microfluidic diffusion diluter to obtain fixed concentration gradients (*122*). Xu et al. used a photoactivated polycarbonate solid-phase reversible immobilization format for the effective removal of excess dye terminator and other soluble components in DNA sequencing cocktails prior to capillary gel electrophoresis (*123*).

Injection. Blom and co-workers used a design where three small injection slits are connected perpendicularly to the separation channel to inject a defined sample plug, which was subsequently separated through hydrodynamic chromatography (*124*). Solignac and Gijs described pressure pulse injection as an alternative to electrokinetic injection for electrophoresis systems due to a reduced injection bias (*125*). An electrokinetic focusing injection method employing a double-cross injection design, where the sample stream is focused at one channel crossing and a plug of the focused stream injected at the other crossing, was proposed by Fu and co-workers (*126*). Cannon et al. developed an electrokinetic injection scheme between different layers of the chip using a nanoporous membrane interface (*127*). A zero dead-volume injection procedure for shear-flow-based chromatography has been developed by Desmet et al. (*128*).

Fluid and Particle Handling. Monodispersed emulsions can be generated using a chip consisting of multiple narrow inlet channels which form droplets that are subsequently detached from the fluid stream by falling over a "microterrace" as described by Sugiura et al. (*129*). A different approach to the same problem is proposed and described by Yi and co-workers. Uniform droplets are formed at a T-junction where a water and an oil phase are merged (*130*). Kuo et al. used nanoporous membranes to interface vertically separated channels and controlled the flow direction through pore size and applied bias (*131*, *132*). Microfluidic sorting of differently sized particles in an optical lattice has been reported by MacDonald et al. (*133*). Digital sorting of two-phase droplets was achieved by Go and co-workers (*134*). Qiao and Aluru proposed an algorithm of a new approach for controlling turn-induced dispersion in nanofluidic channels that is based on the idea of locally controlling the ζ-potential at the bends (*135*). Heat-activated thermoexpandable microspheres were used by Griss and co-workers to develop a one-shot micropump and a one-shot valve

(*136*). Harris et al. described a silicone and Pyrex microfabricated device that provided filtration of particles on the microscale by concentrating particles within the flow at the node of ultrasonic standing waves in the megahertz frequency range (*137*). Petersson et al. took advantage of the same principle in order to switch suspended particles from one medium to another (*138*). Deng and co-workers fabricated a miniaturized system to catch and release magnetic beads within a microchannel by means of electrodeposited nickel columns that were placed in an array formation in the middle of the channel (*139*). Microdevices for manipulation and accumulation of particles by dielectrophoresis utilizing electrode arrays that were aligned on both top and bottom of the microchannel under varying angles were described by Durr et al. (*140*). Lee and co-workers investigated the principles of electrowetting and electrowetting-on-dielectric applied to microfluidic devices (*141*). Lettieri et al. developed a device that allows capture, preconcentration, and controlled manipulation of small beads by means of fluid flow only. Opposing electroosmotic and pressure-driven flow lead to the generation of circulating flows at certain channel positions where beads could be captured (*142*).

Reactors and Mixers. Losey et al. presented two microfabricated devices with either integrated filter structures or porous silicon as a catalyst support for conducting heterogeneously catalyzed multiphase reactions (*143*). A reactor for thermally efficient fuel processing, consisting of U-shaped fluidic channels that were thermally interconnected by silicon slabs, was reported by Arana and co-workers (*144*). A silicon cross-flow microreactor for testing catalyst particles, which minimized the pressure drop over the packed bed of particles by dividing the fluidic channel into an array of 256 pressure-drop channels, was developed by Ajmera et al. (*145*). Tice and co-workers characterized experimentally a simple method for rapid formation of plugs of multiple reagents without bringing the reagents into prior contact (*146*). Scale-up of chip-based microreactors was achieved through piling up and bonding identical glass−chip reactors that were connected via drilled-through inlet and outlet holes (*147*). Edel et al. presented a microfluidic route to the production of nanoparticles with a microreactor (*148*). Size-controlled growth of CdSe nanocrystals by means of varying the temperature, flow rate, and concentration of precursors was achieved by Chan et al. (*149*). The selective direct fluorination of aromatics, a highly exothermic process, was carried out by de Mas et al. in a microfabricated multiphase reactor (*150*). Wootton and co-workers demonstrated the use of nanoreactors in continuous-flow syntheses involving unstable, reactive intermediates, considering Azo dye chemistry as example (*151*). Yamamoto and co-workers created a PDMS−glass hybrid microreactor with embedded temperature control devices on the glass part and flow channels and reaction chambers in the PDMS part (*152*).

A magnetic microstirrer, inspired by large-scale magnetic bar stirrers, was presented by Lu et al. (*153*). Stretching and folding of fluid in the main and many side channels results in efficient spatial chaotic mixing as reported by Niu and Lee (*154*). A rapid three-dimensional passive rotation micromixer employing the breakup process to generate mixing at low Reynolds numbers was proposed by Park and co-workers (*155*). Paik et al. applied a "split and merge" and a "rotation around pivot points" scheme to rapidly mix droplets of analytes and reagents *(156)*. Vreeland and Locascio demonstrated the initial segregation and subsequent controlled release of reagents using a system of bioinspired thermally triggered liposomes (*157*). Experiments by Liu and co-workers showed that air bubbles, which were trapped in micromachined air pockets and set into vibration by a piezoelectric disk, generated circulatory flows and subsequent rapid liquid mixing in a 22-μL chamber (*158*). A novel micromixing device where the segments of a meandering flow channel of 50 μm width were interconnected by perforations of 7-μm width, which introduced shortcuts for the liquid, was presented by Melin et al. (*159*). Munson and Yager proposed a new microfluidic mixing method based on the principle of flow lamination (*160*).

Separation. 1. Chromatography. Clicq et al. realized reversed-phase liquid chromatography separations of a coumarin C440−460 mixture in flat rectangular nanochannels as thin as 100 nm coated with a C8 monolayer within subsecond time range (*161*). Bessoth et al. developed a gas chromatograph-on-a-chip that consisted of a cross structure for injection and a capillary dc microplasma and detected chlorine with a limit of 0.8 $g \cdot s^{-1}$ (*162*).

2. Electrophoresis. Backhouse et al. presented a field inversion electrophoresis method with an improved resolution for an extremely short microchannel and relatively low voltage requirements (*163*). Zhang and Manz developed a glass−PDMS hybrid device for continuous separation in a free-flow electrophoresis mode. A mixture of two fluorescent reagents was separated into two component streams in 75 ms using a sample flow rate of 2 $nL \cdot s^{-1}$ (*164*). Monahan et al. described a split-channel microfluidic device that could be used to compensate for changes in electroosmotic flow and that eliminated the need for a separate electroosmotic marker (*165*). Dielectrophoresis in microchips containing arrays of insulating posts was performed by Cummings and Singh (*166*).

3. Other Separation Methods. Fast chiral separations of a variety of basic and acidic compounds on microfluidic quartz chips with a separation length of only 12 mm was realized by Ludwig et al. Using sulfated cyclodextrins as chiral selectors, a baseline separation of 19 compounds was achieved in less than 1 min while the fastest separation was obtained in 2.5 s (*167*). Ista et al. described a countercurrent electroseparation method on a microchip based on superposition of electroosmotic, electrophoretic, and hydrodynamic flow for separating and accumulating charged molecules according to differences in electrophoretic mobility (*168*). An alternative approach in microelectric field flow fractionation to increase the effective electric field and to improve separation performance of nanoparticles was demonstrated by Lao et al. (*169*). Prest et al. presented the simultaneous separation of a mixture of three anions and three cations performing bidirectional isotachophoresis on a miniaturized PMMA chip with integrated platinum detection electrodes (*170*). A separation concept, selective ion extraction, based on the combination of hydrodynamic and electrokinetic flow controls in microfluidic devices was proposed by Kerby et al. Using a control system with multiple pressure and voltage sources, they extracted several enzymatic products of varying mobilities from their unmodified substrate pairs, producing a highly efficient separation while adding minimal dispersion (*171*).

4. Coupling of Separation Methods. Herr et al. developed an acrylic microfluidic device that sequentially coupled liquid-

phase isoelectric focusing and free solution capillary electrophoresis. With a peak capacity of ~1300, a comprehensive 2D analysis of a fluid volume spanning 15% of the total IEF channel length was completed in less than 5 min (*172*). An integrated protein concentration/separation system, combining non-native IEF with SDS gel electrophoresis on a polymer microfluidic chip, was reported by Li and co-workers. A 2D protein separation was completed in less than 10 min with an overall peak capacity of ~1700 (*173*). Ramsey et al. achieved highly efficient 2D separations of tryptic digests by coupling micellar electrokinetic chromatography separation and capillary electrophoresis. In less than 15 min, a 2D separation of a bovine serum albumin tryptic digest produced an overall peak capacity of 4200 (*174*). Vreeland et al. presented a technique that combined isotachophoretic and zone electrophoretic (ZE) separation on a single microfluidic chip and achieved a ~50-fold increase in detection sensitivity relative to equivalent separations that are obtained with ZE alone (*175*).

Detection. 1. Electrochemical Detection. García and Henry described the application of pulsed amperometric detection of underivatized carbohydrates, amino acids, and sulfur-containing antibiotics in an electrophoresis PDMS microchip. They obtained detection limits ranging from 5 μM for penicillin and ampicillin to 350 μM for histidine (*176*). Hebert and co-workers utilized pyrolyzed photoresist films (PPF) as planar carbon electrodes in a PDMS−quartz hybrid microchip device. They separated and detected various neurotransmitters using sinusoidal voltammetric detection at the PPF electrodes (*177*). Wu and co-workers presented a three-electrode amperometric detector and an electric platinum film decoupler integrated with a capillary electrophoresis PDMS chip. They measured dopamine in the concentration range of 0.25−50 μM with a detection limit of 0.125 μM (*178*). Klett and Nyholm utilized the induced potential difference between two microband electrodes positioned in the CE electric field for amperometrical detection purposes in the absence of both a decoupler and a potentiostat (*179*). Using a PMMA-based microfluidic device with an integrated contact conductivity detector consisting of a pair of platinum electrodes, Galloway et al. obtained detection limits for various mono- and polyanionic compounds that were comparable to those using indirect laser fluorescence detection (*180*). Wang et al. introduced a movable contactless conductivity detection system for microchip capillary electrophoresis, which relied on positioning the detector at different points along the separation channel via "sliding" the electrode holder. The detector provided insights into the separation process as well as enhanced analytical performance by switching between "total" and "individual" measurements (*181*). Laugere and co-workers presented a capillary electrophoresis microchip with an integrated on-chip contactless conductivity detector in a four-electrode configuration. The detector required no adjustment of the measurement frequency (*182*). Hüller et al. demonstrated an ultrathin ion-selective chip electrode for Cu^{2+} ions (*183*).

2. Chemiluminescence and Electrochemiluminescence. Liu et al. integrated metal ion-catalyzed luminol−peroxide chemiluminescence detection as well as dansyl species-conjugated peroxalate−peroxide reaction with a capillary electrophoresis system on a PDMS microchip. They obtained successful separation of Cr(III), Co(II), and Cu(II) and chiral recognition of dansylphenylalanine enantiomers within 1 min with detection limits down to submicromolar concentrations (*184*). Zhan et al. utilized a three-channel, two-electrode microfluidic system that detected electroactive substances by electrochemical oxidation and reported their presence using electrooxidation of tris(2,2′-bipyridyl)ruthenium(II) and tripropylamine (*185*).

3. Fluorescence. Qin et al. used a tunable dye laser for laser-induced fluorescence and an intensified CCD for the improved, direct detection of the native fluorescence of flavins in microchip capillary electrophoresis (*186*). Namasivayam et al. developed an on-chip fluorescence detector structure that uses a $PINN^{+}$ photodiode with an on-chip interference filter and a robust liquid barrier layer. Using the detector embedded in a DNA analysis device, which included a microreactor, a microseparation column, and fluidic channels, DNA was detected with a limit of 0.9 ng·μL^{-1} (*187*). Roulet an co-workers described an integrated microfluidic/microoptic device with detection elements that were directly deposited on both sides of the microchemical chip (*188*). Mogensen et al. realized a microfabricated capillary electrophoresis device with an integrated waveguide beam splitter for fluorescence excitation at multiple points of the fluidic channel network and measured the velocity of flowing particles by Fourier transformation with a Shah function (*189*). A laser-induced fluorescence detection method that scanned the whole channel and made use of acoustooptical deflection was developed by Sanders et al. and was demonstrated in combination with the isoelectric focusing separation of three naturally fluorescent proteins (*190*). Spatial two-photon fluorescence cross-correlation spectroscopy for controlling molecular transport in microfluidic structures was presented by Dittrich and Schwille (*191*). Using a photoactivated fluorophore, nanosecond-duration photolysis pulses from a nitrogen laser and high-sensitivity single-molecule detection with Ar^{+} laser excitation, Shelby and Chiu measured liquid flow speeds of up to 47 m·s^{-1} in a 33-μm-wide straight channel and obtained a 3D map of flow profiles in a 55-μm-wide microchamber (*192*).

4. Nonfluorescence Optical Measurements. Fletcher et al. used an inverted Raman microscope spectrometer to profile the spatial and temporal evolution of reactant and product concentrations for chemical reactions within a microreactor operating under hydrodynamic flow control (*193*). Palumbo et al. developed a single-chip, multichannel surface plasmon resonance imaging system and demonstrated the simultaneous interrogation of different polyelectrolyte thin films formed by the electrostatic layer-by-layer deposition method (*194*). Duggan et al. reported a liquid-core waveguide, which enabled the extension of the sampling path length for absorbance measurements while maintaining a detection volume of less than 1 μL and also facilitated the effective coupling of the light source with the waveguide (*195*). Hibara et al. reported a novel microscopic quasi-elastic laser scattering method for quantitative analysis of interfacial phenomena in multiphase microflows, such as the transport of chelates through the aqueous/organic interface and the mixing process of two miscible solvents (*196*). Pamme et al. demonstrated a microfluidic device employing hydrodynamic focusing and laser light scattering detection for counting and sizing microspheres and for analyzing particle agglomerates formed in particle enhanced immunoassays. They achieved size discrimination of particles with a diameter ratio of 1:2 and could detect 100 ng·mL^{-1}

C-reactive protein using a particle-enhanced immunoassay (*197*). Costin and Synovec reported a detection scheme that allowed for measuring the refractive index gradient between two adjacent laminar flows in a microfluidic device (*198*). Adams et al. described an approach for miniaturizing spectrometers by combining replica molded elastomeric microchannels with filtered silicon detector arrays. With these miniaturized multichannel spectrometers absorption spectra could be obtained even for dilute dye solutions (*199*). Tamaki et al. combined a scanning thermal lens microscope with a cell culture microchip to monitor the release of cytochrome *c* from mitochondria during the apoptosis process (*200*). Mizukami and co-workers fabricated an integrated microelectrophoretic chip by implementing an acrylic microfluidic channel directly on top of a photosensor array. Capillary gel electrophoresis was performed for a mixture of two proteins (*201*). Firebaugh et al. described a micromachined photoacoustic detector fabricated in silicon. A He−Ne laser was employed to detect propane with concentrations as low as 10 ppm in ambient nitrogen (*202*). dc glow discharge atomic emission spectroscopy of aqueous analytes in a planar glass microstructure at close to atmospheric pressure using argon as carrier gas was carried out by Jenkins and Manz. They detected copper in solution with the observation of five atomic emission lines (*203*). Nakagama et al. reported an atomic emission detector using a helium plasma to measure the flow rate of water in the range from 4 $nL \cdot min^{-1}$ to 1 $\mu L \cdot min^{-1}$ by quantitatively detecting the emission from hydrogen in the water molecules (*204*). Infrared thermal velocimetry was developed by Chung and co-workers, enabling velocity measurements in transparent MEMS-based fluidic devices ranging from centimeters to meters per second (*205*).

5. Mass Spectrometry. Benetton et al. coupled electrospray ionization-mass spectrometry detection to a chip-based in vitro metabolism assay to yield the Michaelis constant of the P450 biotransformation and to determine the IC_{50} value of a chemical inhibitor for this reaction (*206*). Sillon and Baptist realized with silicon microtechnologies a low-cost miniature mass spectrometer working at high pressure. The micromachined device contained ionization chamber, filter, and detector on one chip (*207*). Diaz et al. developed a miniature double-focusing mass spectrometer, with an 8-mm radius, that successfully provided gas composition information on a vacuum test chamber and several different plasma formulations with an operational mass range of 1−50 Da (*208*).

6. Other Detection Methods. Mourlas et al. demonstrated an in-line osmometer for the evaluation of the osmolarity of a sample that is to be used in a system with living cells as primary sensor elements (*209*). Melvås et al. presented a temperature-compensated leverage beam pressure sensor. The device consisted of two beams located inside a reference vacuum cavity beneath a square 2-μm-thick polysilicon diaphragm with a side length of only 100 μm. The sensitivity of the sensor was 0.8 $\mu V \cdot (V \cdot mmHg)^{-1}$ (*210*). A low-hydraulic-capacitance pressure sensor for integration with a microviscosity detector was presented by van der Heyden and co-workers (*211*). Ernst et al. introduced a microsensor for measuring the thermal flow rate in liquids (*212*). Microfabricated small-volume NMR probes consisting of an electroplated planar microcoil integrated onto a glass substrate with etched microfluidic channels were fabricated and tested by Massin et al. They acquired an ^1H spectrum of 160 μg of sucrose in D_2O with a detection volume of 470 nL (*213*). Fortt and co-workers demonstrated precise control of the Reimer−Tiemann reaction using thermochromic liquid crystals (*214*). Sze et al. presented a simple and accurate novel experimental technique to measure the ξ-potentials of flat surfaces by combining the Smoluchowski equation with the measured slope of the current−time relationship in electroosmotic flow (*215*).

APPLICATIONS

Cell Culture and Cell Handling. Cell cultivation was performed in a highly parallelized manner in fluid segments that were formed as droplets at a channel junction where organic and cell containing aqueous phase were merged (*216*). Taylor and co-workers described a microfabricated device for the directed growth of neurites and their isolation from cell bodies. The PDMS device consisted of two compartments that were separated by a physical barrier in which a number of micrometer-size grooves are embedded to allow growth of neurites across the compartments while fluidic isolation is maintained (*217*). Thiébaud et al. realized a microfluidic device for localized drug application to cell cultures based on the low diffusion properties of laminar flows in microchannels (*218*). Matsubara et al. developed a microfluidic cell chip for monitoring the allergic response upon application of antigen stimulus (*219*). Yoshida and co-workers reported a system for fine manipulation and navigation of selected living cells to a desired location on a flat patterned substrate that is applicable to rapid and precise cell pattern formation (*220*). Flynn et al. demonstrated the use of individually addressable vertical cavity surface emitting lasers for optical trapping and active manipulation of living cells and microspheres (*221*). Dittrich and Schwille demonstrated the precise sorting of fluorescent cells and particles in the fluid phase with respect to their spectroscopic properties after their ultrasensitive confocal detection. The sorting process into two different output channels was realized by the application of a perpendicular deflection stream that could be switched electrokinetically (*222*). Wolff and co-workers developed a microfabricated fluorescence-activated cell sorter with novel integrated functions. They designed a "smoking chimney" structure for hydrodynamic focusing of sample flow and incorporated a holding and culturing chamber as well as waveguides for optical detection of the cells (*223*). Cho et al. described a self-containing integrated microfluidic system that could isolate motile sperm from nonmotile sperm and other cellular debris based on the ability of motile sperm to cross streamlines in a laminar fluid flow (*224*). Li and Bashir were able to separate living from heat-treated *Listeria innocua* cells on microfabricated devices by making use of differences in dielectric properties (*225*). Voldman and co-workers developed a microfabricated device for use in parallel luminescence single-cell assays that can sort populations based on dynamic functional responses to stimuli. The device was composed of a physically regular, electrically addressable array of noncontact single-cell traps with a novel asymmetric extruded-quadrupole geometry and used dielectrophoresis to confine cells and hold them against disrupting fluid flows (*226*). Huang and Rubinsky presented a microchip for the controlled electroporation of single cells in a flow-through fashion. Loaded cells were transported precisely to the electroporation site by a microfluidic

channel and were electropermeabilized individiually, resulting in a manipulation rate of virtually 100% (*227*). The high-throughput chemical analysis of single cells was demonstrated by McClain et al., who achieved rapid cell lysis and separation of the cell content. The average analysis rate was 7−12 cells·min^{-1}, which is 100−1000-times faster than standard benchtop analysis of single cells (*228*). Brischwein and co-workers reported a chip device with potentiometric, amperometric and impedimetric sensors to enable investigations of cellular microphysiological patterns (*229*). Wheeler et al. demonstrated cell viability assays, ionophore-mediated intracellular Ca^{2+} flux measurements, and multistep receptor-mediated Ca^{2+} measurements using a PDMS microfluidic device (*230*). For studying the actual changes occurring in isolated cells, Wakamoto et al. investigated a nondestructive, noncontact single-cell-based differential screening method using on-chip microcultivation (*231*). Yasukawa et al. developed a picoliter-volume chamber for detecting the metabolic flux resulting from the stress responses of a single plant cell electrochemically through the determination of peroxides concentrations, thus enabling the investigation of cellular protection mechanism activity *(232)*. Prinz and co-workers utilized an integrated chip for the lysis of *Escherichia coli* cells and the trapping of the released chromosome by means of dielectrophoresis (*233*).

Clinical Diagnostics. Li et al. described an approach for screening cardiovascular drugs by integrating a microfluidic chip with a thickness-shear mode acoustic wave sensor for muscle cell contraction analysis upon chemical stimuli (*234*). Christodoulides and co-workers presented an immunological application for the simultaneous detection of two serum cardiac risk factors, C-reactive protein and interleucin-6, based on microbeads positioned within micromachined cavities on a versatile silicon wafer platform (*235*). A chip-based CE detection system for simultaneous measurements of the renal markers creatine, creatinine, *p*-aminohippuric acid, and uric acid in urine samples was demonstrated by Wang and Chatrathi (*236*). Takai and co-workers fabricated a disposable healthcare chip that allowed the detection of multiple diagnostic markers directly from a trace of blood (*237*). Puntambekar et al. developed another disposable biochip with an integrated microneedle that can be used for point-of-care testing (*238*). Kurita et al. showed a microfluidic device with an integrated microprereactor and glucose- and lactate-sensing microelectrodes in dual channels. This was successfully utilized for in vivo monitoring of glucose and lactate concentrations in veratridine-stimulated rat brain (*239*). Greenwood et al. reported on the electrochemiluminometrical detection of atropine and pethidine using chemically oxidized tris(2,2′-bipyridine)ruthenium(II). They achieved detection limits of 3.8 and 77 nM for atropine and pethidine, respectively (*240*).

Environmental Concerns. Ohira et al. integrated a miniaturized planar membrane-based gas collector of 800-nL internal liquid volume with a microfabricated conductivity detector to measure atmospheric SO_2 and achieved a detection limit of 0.7−1.0 ppb for a sampling period of 90 s (*241*). Ueno et al. reported the separate detection of the individual components of an organic gas mixture (BTX) at ppm levels using mesoporous silica absorbent incorporated in a microfluidic device (*242*). The analysis of inorganic arsenic and selenium species using isotachophoresis on a PMMA chip with integrated conductivity electrodes was reported by Prest and co-workers (*243*, *244*). Wang et al. described the fast measurements of low-explosive ionic components and chemical warfare agent degradation products in less than 1 min using electrophoresis microchips with a contactless conductivity detector (*245*, *246*). The detection of trinitroaromatic explosives was performed by Bromberg and Mathies through employing a homogeneous immunoassay followed by the rapid electrophoretic separation of its equilibrium mixture (*247*). Lu et al.'s approach to the same problem was to use capillary electrophoresis in a nonaqueous electrolyte, following solid-phase extraction (*248*).

Immunoassays. Sato et al. assayed interferon γ by a three-step sandwich immunoassay based on a bead−bed microchip system coupled to a thermal lens microscope as the detector. The branched microchannel layout allows for only one pump to be employed, and thus, the system may be used for simultaneous assays of several kinds of analytes in one sample (*249*). Jiang and co-workers described a microfluidic version of a parallel, serial-dilution fluorescent immunoassay and with this determined the concentration of antibodies in human serum containing HIV (*62*). Silicon microchips with immobilized antibodies were used by Yakovleva et al. to develop microfluidic immunoassays with horseradish peroxidase-labeled enzymes and chemiluminescence detection (*250*). Roos and Skinner described a two-bead multiplex immunoassay using a flat laser intensity profile for illumination where the color combination and the intensities can be used to determine the presence of an antigen. Detection limits of TNF-α and IL-6 were comparable with standard ELISA immunoassays while reducing the time from hours to only minutes (*251*). Saleh and Sohn demonstrated a rapid and highly sensitive technique to perform immunoassays in both inhibition and sandwich configurations. This technique is based on the resistive pulse method of particle sizing with a pore to detect the binding of unlabeled antibodies to the surface of latex colloids (*252*). An integrated microdevice with mixer, valve, filter, and readout that can be used for bioassay development was presented by Mensing and co-workers (*253*).

Proteins. Jin et al. described the use of a microchip-based proteolytic digestion system driven by electroosmotic pumping. The proteins were electroeluted into the microfluidic system directly from the acrylamide gel, and tryptic digestion was performed simultaneously to the elution step. The digestion of β-casein, cytochrome *c*, and bovine serum albumin was completed in 12 min (*254*). Slentz et al. reported on a microfluidic system that combined tryptic digestion, isolation of histidine-containing peptides by copper(II)-immobilized metal affinity chromatography, and reversed-phase capillary electrochromatography of the isolated peptides. Tryptic digestion and affinity chromatography were achieved in particle-based columns with a microfabricated frit whereas reversed-phase separations were carried out on a column containing monolithic support structures (*255*). Li et al. described an integrated and modular microsystem for proteomics research. It consisted of an autosampler, a relatively large channel packed with beads for reverse-phase or affinity chromatography, and an array of separation channels that could be interfaced to nanoelectrospray mass spectrometry. Sequential injection, preconcentration, and separation of peptide standards and tryptic digests were achieved with a throughput of up to 12 samples/h and a detection

limit of 5 nM (*256*). A microfluidic device, which consisted of both a solid-phase extractor and an enzyme microreactor and was fabricated directly in a nanoelectrospray needle by in situ photolithographic grafting, was presented by Peterson and co-workers. Depending on the flow mode, the digestion step was followed by the extraction or vice versa (*257*). Schilling et al. demonstrated a microfluidic system that integrated the lysis of bacterial cells and the extraction of a large intracellular enzyme, β-galactosidase, which was then detected and quantified using a fluorogenic enzyme assay (*258*). The kinetics of chemically induced conformational changes of proteins, for example, ubiquitin, were studied by Kakuta and co-workers using micromixer-based time-resolved NMR and FT-IR spectroscopy, respectively (*259*, *260*). Hansen et al. fabricated and tested a microfluidic chip for rapid screening of protein crystallization conditions using a robust and scalable microfluidic metering scheme called barrier interface metering. The chip had 480 active valves and performed 144 parallel reactions, each of which used only 10 nL of protein sample (*261*). Zheng et al. described a microfluidic device for screening hundreds of protein crystallization conditions using less than 4 nL of protein solution for each crystallization trial. These trials were set up inside 7.5-nL aqueous droplets that were formed in the flow of immiscible fluids. Each droplet contained a solution of protein, precipitants, and additives in variable ratios (*262*).

DNA Separation and Analysis. Landers' group used hydroxyethyl cellulose and hydroxypropyl cellulose as adsorptive coating sieving matrixes for DNA separation, fragment analysis, and mutation detection via heteroduplex analysis (*263*, *264*). Doyle et al. employed self-assembling (upon the application of a homogeneous magnetic field) suspensions of paramagnetic particles as a matrix in DNA separation chips (*265*). Duong et al. achieved length-dependent DNA migration and separation of λ- and T2-DNA molecules in a gel-free system using topographically structured microfluidic PDMS channels with periodical cavities in the range of the radius of gyration of the tested DNA molecules (*266*). Inatomi et al. separated DNA electrophoretically in an array of 15-μm pillars fabricated in poly(dimethylsiloxane) (*267*). By employing a nanopillar structure on a quartz chip as a sieving matrix, Kaji et al. fractionated long DNA molecules under a dc electric field (*268*). Lin et al. demonstrated the feasibility of on-chip electroelution to selectively extract single or multiple DNA fragments during electrophoresis using a cross-linked polyacrylamide matrix (*269*). Footz et al. combined on-chip enzymatic digestion, the RFLP method with heteroduplex analysis, and electrophoretic sizing in order to screen for the most significant mutations associated with hereditary heamochromatosis in approximately 10 min (*270*). Trau et al. developed a micro-DNA amplification and analysis device consisting of multiple PCR microreactors with integrated DNA microarrays printed onto the bottom of the PCR chambers (*271*). A paramagnetic bead-based sandwich hybridization using enzyme-labeled detection probes coupled to a silicon chip-based potentiometric detector was presented by Gabig-Ciminska and co-workers (*272*). Wang et al. demonstrated the ability to detect a one-point mutation among 10 000 normal DNA sequences in certain gene fragments. The array was configured with zip code sequences that were complementary to sequences present on the target (*273*). Wainright et al. developed a plastic 32-channel LabCard device to analyze dsDNA in 3 min/sample by combining zone electrophoresis separation with a prior ITP sample preconcentration step, which increased the sensitivity by 40-fold compared to standard chip zone electrophoresis (*274*). Paegel et al. presented a microfabricated electrophoretic bioprocessor for integrated DNA sequencing, sample desalting, template removal, preconcentration, and capillary electrophoresis analysis. They decreased the purification time 10-fold and the process volume 100-fold (*275*). A microfabricated 384-lane capillary array electrophoresis device was utilized by Emrich et al. for simultaneous genotyping for the common hemochromatosis-linked H63D mutation in the human *HFE* gene in 325 s (*276*). Ahmadian et al. demonstrated the possibility of analyzing SNPs by allele-specific extensions in a micromachined flow-through filter chamber using pyrosequencing chemistry (*277*).

Polymerase Chain Reaction. Sun et al. developed a heater-integrated transparent microchannel chip for continuous-flow PCR by using quartz glass as the channel substrate and indium−tin oxide films as thermal sources (*278*). Yoon et al. fabricated Si-based micromachined PCR chips with an integrated platinum thin-film microheater and a temperature sensor allowing for heating and cooling rates of 36 and 22 $°C \cdot s^{-1}$, respectively (*279*). El-Ali and co-workers presented an SU-8-based PCR chamber that exhibited a homogeneous temperature distribution and was capable of fast thermal transition (*280*). Rapid cycling times of 16 s/cycle were demonstrated by Rodriguez et al. using a silicon microfabricated PCR chamber with aluminum heaters and temperature sensors that were integrated onto the glass cover (*281*). Liu et al. developed a disposable PDMS rotary microfluidic device with integrated pneumatically controlled on-chip valves and pumps to run PCR in both spatially and temporally cycled formats that required only 12 nL of sample (*282*). Chou an co-workers designed and fabricated the first miniaturized cyclic PCR device in low-temperature ceramics (*283*). Obeid et al. developed a microfabricated, reusable glass chip for the functional integration of reverse transcription and PCR in a continuous-flow mode that allowed for the selection of the number of amplification cycles (*284*). Jabasini and co-workers carried out multiplex PCR on a 12-channel microchip electrophoresis system and were able to detect 72 markers simultaneously in approximately 100 s (*285*).

Sequencing. Liu created a hybrid device of a microfabricated round-channel twin-T injector incorporated with a separation capillary for high-speed and long-read length DNA sequencing. With a 200-μm twin-T injector coupled to a 20-cm-long separation capillary, four-color DNA sequencing was performed. Read lengths of more than 800 bases were obtained in 56 min at an accuracy of 98.5% (*286*). Shi and Anderson demonstrated a disposable plastic electrophoresis system with a separation length of only 4.5 cm for fast and high-resolution DNA analysis. Four-color sequencing of a 320-base standard was achieved in 13 min with an accuracy of 99.1% (*287*). Blazej et al. used a microfabricated capillary array electrophoresis device to screen for sequence variations in two human mitochondrial genomes (*288*).

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