

Micro Total Analysis Systems. Latest Advancements and Trends

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The area of micro total analysis systems (μ TAS), also called “lab on a chip”, miniaturized or microfluidic analysis systems, is a rapidly developing field. During the last several years, we have witnessed a steady expansion in the number of publications made associated with this research field. Simultaneously, there is an obvious increase in the overall quality of the study performances, as numerous obstacles have been overcome and microfluidic devices are, nowadays, considered as a common aid to various applications in natural and life sciences. For the period from March 2004 to February 2006, we found several thousands of excellent publications related to μ TAS by on-line keyword search. The articles are spread over a large number of journals, but most frequently found in journals with considerably high impact factors, such as *Lab on a Chip*, *Analytical Chemistry*, and *Electrophoresis*. Excellent sources of information are also proceedings of regular international conferences such as μ TAS and MSB (microscale bioseparation), Transducers and IMRET (microreaction technology), recently published text books, and specialized review articles (for instance, refs 1–7).

Our purpose in this review was to select only some relevant examples for every distinct method or device, to give a broad

overview of the novel achievements, and to assist newcomers to the field. In the tradition of the former reviews (8–10), this paper focuses on novel developments of *fluidic* systems for applied analytical purposes. For this reason, publications about sensors, arrays (so-called “biochips”), chemical syntheses on microchips, theory, and simulations as well as review and trend articles have been omitted. Furthermore, we reduced the technology section, as the majority of work is carried out by employing simple planar microchips fabricated in glass or polymers such as silicone elastomer. However, we observed a staggering rise in publications related to cellular applications; therefore, the section was naturally expanded.

TECHNOLOGIES

Microfabrication. *Materials.* Microfluidic systems, fabricated by utilizing biomaterials, have gathered enormous attention in the recent years. Cabodi et al. fabricated the entire system within calcium alginate, a versatile hydrogel (11). Gelatin, cross-linked with the naturally occurring enzyme transglutaminase, was molded by Paguirigan and Beebe to produce channels suitable for adherent cell culture and analysis (12). A 3D device made entirely from prototypical, biodegradable thermoplastic was developed by King et al. (13). Burdick et al. introduced the fabrication of gradient hydrogels using a microfluidics and photopolymerization process (14).

With more artificial materials, Sudarsan et al. utilized thermoplastic elastomer gels for a chemical analysis system (15). Solvent-resistant photocurable “liquid Teflon” was used to fabricate a device (16). Photopatternable silicon elastomer, with adjustable physical toughness, was also developed (17). Thermoset polyester was used for fabrication the system by Fiorini et al. (18). Liu and co-workers evaluated the suitability of a surface-reactive acrylic copolymer. It has the advantage that the surface can be easily modified (19). A dry film resist (Ordyl SY300/500) was demonstrated to be applicable for creating networks by sandwiching the patterned resist between two substrates (20). Shown by Takeuchi et al., parylene flexible neural probes that have an integrated microfluidic channel were fabricated (21).

Techniques. Park and Madou researched the use of 3D electrode designs for a high-throughput dielectrophoretic separation/concentration/filtration system (22). Direct 3D machining of submicrometer diameter via optical breakdown near critical intensity using a femtosecond pulsed laser was demonstrated by Ke et al. (23). An apparatus capable of producing microscale fibers and tubes by employing 3D multiple-stream laminar flow and in situ photopolymerization was introduced by Jeong et al. (24). Kim et al. reported hydrodynamic fabrication of polymeric bar-coded

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strips as components for parallel bioanalysis and programmable microactuation (25). A method for direct microfabrication of a glass substrate utilizing a high-viscosity photoresist was introduced by Fujii et al. (26). Brister and Weston demonstrated that patterned poly(dimethylsiloxane) (PDMS) can be used as a template to control the flow path of an etching solvent through a channel design to be reproduced on the plastic substrate (27). Porous polymer networks were fabricated in situ in channels using radical photopolymerization and salt leaching (28). A method for producing devices with tunable porosity was also presented (29). Polyimide and SU-8 (negative photoresist) devices were manufactured by a heat-depolymerizable sacrificial material technique (30). Acoustic micromachining was used for manufacturing spatial patterns such as grooves into nickel templates, from which polymer molds were obtained (31). Spin deposition and sacrificial layer etching were used to fabricate all-polyimide channels with nanometer dimensions as shown by Eijkel et al. (32). Ionescu et al. used active enzymes (proteases) to fabricate nanochannels. They presented a study of how to precisely control the channel dimensions (33). A technique to create sealed 3D networks was developed by Reano and Pang using sequentially stacked thermal nanoimprint lithography (34).

Bonding Techniques. A room-temperature bonding process was developed by Jia et al. for the fabrication of glass microfluidic chips, which resulted in >95% bonding quality without the requirement of clean room facilities, programmed high-temperature furnaces, pressurized water sources, adhesives, or pressurizing weights (35). Howlader et al. also reported the bonding of glass/glass wafers by using the surface-activated bonding method at room temperature without heating (36). Kelly et al. have shown that polymeric microchips can be created by using a sacrificial material to protect channel integrity during solvent bonding. They can withstand 10-fold higher internal pressures than thermally bonded substrates (37). A method to bond PDMS to PDMS and other materials to form enclosed microfluidic channels, by transferring a thin layer of adhesive to a patterned substrate and sealing the substrate to a flat plate to form a microchip, was demonstrated by Wu et al. (38). Microwave plasma was generated by Hui et al. in a glass bottle containing 2–3 Torr oxygen for plasma treatment of a polymer surface to activate the PDMS surface for irreversible sealing (39). Bhattacharya et al. explored the existence of a common scale, which can be used to gauge bond strength between various surfaces, and obtained a good correlation between contact angle of deionized water on the PDMS and glass surfaces based on various dosages of oxygen plasma treatment (40). The use of microwave energy and a conductive polymer was investigated by Yussuf et al., where the absorbed electromagnetic energy was converted into heat, facilitating the localized microwave bonding of two poly(methyl methacrylate) (PMMA) substrates (41). Different types of surface modifications were examined by Brown et al. to enhance substrate and cover plate adhesion to yield carboxyl- and amine-terminated PMMA surfaces (42). Satyanarayana et al. described an adhesive bonding process that overcomes the disadvantages of the traditional wafer bonding processes, i.e., a room-temperature “stamp and stick” technique for silicon, glass, and nitride surfaces using a UV-curable adhesive (43).

Surface Modification. Homogeneous Surface Modification. The applications can be divided into two main areas: for obtaining hydrophilic channel walls with improved control over electro-osmotic flow and for a better separation of biological samples. Roman et al. used a sol–gel method to fabricate PDMS chips with SiO₂ particles homogeneously distributed within the PDMS polymer matrix (44). A hydrophobic–hydrophilic patterning in channels on a glass chip was prepared for guiding gas and liquid flows along (45). Other modification methods utilize electrostatic self-assembly of polyethyleneimine and poly(acrylic acid) (46), poly(oxyethylene) (47), and poly(vinyl alcohol) (48) on PDMS.

Several publications were made for both PMMA and PDMS surface modifications for effective protein, peptide, and DNA separations (49–52). Allbritton and co-workers developed techniques to tailor the surface properties of PDMS by comixing a neutral and a charged monomer (53) and to coat the surfaces of enclosed PDMS microchannels by UV-mediated graft polymerization (54). Ma et al. have presented a method to rejuvenate glass chips that had been used for capillary electrophoresis (CE) to the extent that their performance was degraded (55).

Patterning. Khademhosseini et al. developed a technique for precise control over the spatial surface properties inside microchannels. The patterned regions were protected from oxygen plasma by controlling the dimensions of the PDMS stamp and by leaving the stamp in place during the plasma treatment process (56). Wang et al. demonstrated the covalent micropatterning of PDMS. Acrylic acid sandwiched between benzophenone-implanted PDMS and a photomask was exposed to UV light to initiate polymerization. The carboxylic groups of the poly(acrylic acid) graft could be derivatized to covalently bond other molecules (57). Balakirev et al. patterned biological molecules onto the inner wall of a fused-silica capillary that was coated with photoactive benzophenone and irradiated with UV light (58). Another basic strategy for the photoimmobilization of multiple, well-defined enzyme patches was developed by Holden et al. using a specific photoattachment chemistry (59). A three-step photomodification protocol using PMMA and polycarbonate to produce functional scaffolds consisting of carboxylic groups, which allow covalent attachment of amine-terminated oligonucleotide probes to these surface groups through carbodiimide coupling, was proposed by Situma et al. (60). Patterning of peptide arrays for multienzyme assays using a microfluidic network was reported by Su et al. (61).

A general method for the fabrication of immobilized gradients of biomolecules on surfaces utilizing the specific interactions of avidin and biotin was presented by Jiang et al. (62). Fabrication of stable, covalently immobilized gradients of different extracellular matrix (ECM) proteins and the spatial variation of cellular responses directed by these engineered ECM patterns in vitro was demonstrated by Gunawan et al. (63). Dusseiller et al. reported a way to position proteins or lipid vesicles using a crossed microfluidic device that relied on combination of specific surface chemistry and the use of crossing microfluidic channels (64). A method to pattern supported lipid bilayer membranes onto a surface inside a microchannel was presented by Kim et al. (65) and by Moran-Mirabal et al. (66).

Alignment and deposition of molecular assemblies were presented. Mahajan and Fang reported that lipid nano- and microtubules can be assembled into 2D parallel arrays with

controlled separations by combining fluidic alignment with dewetting, which occurs within microchannels (67). Hirst et al. reported a technique for the alignment of self-assembled protein systems, such as F-actin bundles and microtubules, in a surface-modified titanium or silicon microfluidic device (68). Park et al. introduced a technique for depositing single-walled carbon nanotubes through the use of controlled flocculation in laminar microfluidic networks (69).

Design. A chip for biochemical reaction and electrophoretic separation that can quantitatively control the volume of samples was developed (70). Urbanski et al. described a PDMS system with programmable and scalable control of discrete fluid samples using multiphase flows (71).

PDMS channels with cross-sectional profiles that are upside down bell-shaped have been fabricated by Futai et al. These profiles are shown to be ideal for use as deformation-based valves (72). Shelby et al. designed a channel to create microvortexes in order to manipulate and observe rotational motion of single optically trapped particles and living cells (73). A device generating patterned laminar flow in open volumes was also characterized (74). A hand-held microanalytical instrument was reported by Renzi et al. for electrophoretic separations of proteins at nanomolar levels (75). Another portable device with a reusable integrated high-voltage power supply was presented (76).

Designs for integration of multiple functions and applications were proposed. For instance, a modular microfluidic architecture for biochemical analysis was introduced by Shaikh et al. (77). A biochip consisting of microfluidic mixers, valves, pumps, channels, chambers, heaters, and DNA microarray sensors was developed to perform DNA analysis by Liu et al. (78). Tesar et al. reported a microfluidic unit for sequencing fluid samples for composition analysis (79). Juncker et al. combined the concept of microfluidics and scanning probes by utilizing a mobile clamping rod comprising fluidic channels. It can be used to process large surfaces and objects, while they are being scanned across (80).

Interfaces and Interconnections. Publications on interfaces, especially to mass spectrometry (MS), are described. An integrated gradient liquid chromatography chip to perform reversed-phase separations of complex peptide mixtures was presented by Xie et al. (81). A microfabricated heated nebulizer chip for atmospheric pressure photoionization-mass spectrometry was presented by Kauppila et al. (82). Several groups designed and fabricated tips to couple microfluidic channels and electrospray ionization-mass spectrometry (ESI-MS) using various materials, such as negative photoresist SU-8 (83, 84), polymers (85, 86), or a glassy carbon device (87). Thorslund et al. presented a device where sample injection, separation, and ESI-emitter structures are integrated in a single platform, fabricated in the same bulk PDMS, enabling one to eliminate problems at module connections (88). Yang et al. described the integration of a cycloolefin polymer-based chip with a sheathless capillary tip for ESI-MS without the use of transfer capillaries or liquid junctions (89). A study on a glass membrane prepared for conducting high voltage for generation of liquid electrospray was carried out by Yue et al. This method avoids direct metal/liquid contact, eliminating bubble formation in the channel due to water hydrolysis on the surface of the metal (90). Two interfaces, namely, a monolithic design (ionization assisted by on-chip gas nebulization) and a modular

approach (use of commercially available tips), enabling on-line coupling to a nanoflow ESI time-of-flight MS, were realized by Brivio et al. (91).

Li et al. reported a study on direct interfacing of microfluidic chip-based CE to a sensitive and selective detector for atomic fluorescence spectrometry for rapid speciation analysis (92). A world-to-chip microfluidic interconnection for sample loading and sealing with no dead volume was designed by Oh et al. (93).

Flow Control. Micropumps and Fluid Transport. An electroosmotic pump based on inline frit with ion exchange membranes was tested by Brask et al. (94). Another multistage electroosmotic pump was characterized by Chen et al. (95). Micropumps driven electrokinetically with a low ac signal (96) and an electrostatically actuated peristaltic pump, where the pumped fluid is isolated from the electric field (97), were also reported. A self-priming, displacement micropump combining soft lithography with bulk machining was fabricated by Sin et al. (98). Circular electroosmotic pumping was achieved by Debesset et al. in a closed-loop channel with an array of large and small electrodes (99). Liquids were transported through microchannels with integrated gold electrodes on the basis of electrowetting as demonstrated by Satoh et al. (100). The control of fluid flow based on the electrocapillary effect was shown by Shiu and Chen for a microchannel network with integrated indium tin oxide (ITO) electrodes (101).

Homsy et al. demonstrated a dc magnetohydrodynamic micropump that can be operated at high dc current densities in 75- μm -deep channels without introducing gas bubbles into the pumping channel (102). A planar bidirectional valveless peristaltic micropump for controlling biological sample fluids was designed by Lee et al. (103). Microgear of known birefringence, which may be readily rotated by purely optical control, was fabricated by Neale et al. (104). Sundararajan et al. created operating channels that were separated from the main microfluidic channel via a deformable membrane, i.e., a thin PDMS wall, and demonstrated pumping, sorting, and mixing within the device (105).

A micropump with its power generated through the chemical production of oxygen gas was described by Choi et al. (106). A pump delivered discrete amounts of liquid in a half-open microchannel based on thermal gas expansion of trapped air (107). Yin and Prosperetti described periodic growth and collapse of a single vapor bubble generated by a vacuum-deposited platinum heater on a quartz chip that is utilized to pump liquids (108). An electrolytically actuated bubble micropump was discussed by Ateya et al. (109).

A power-free pumping method that relies on the gas permeability of PDMS was presented by Hosokawa et al. To realize pumping, the complete PDMS chip has to be degassed. While the outlet reservoir was sealed with a tape, liquids were introduced to the inlet reservoir(s). Dissolution of air into PDMS, which could not be delivered through the reservoirs, reduced the pressure inside the microchannel and caused movement of the liquids into the microchannel (110). Fluids can be moved through a microchannel by controlled evaporation at the output reservoir while the liquid in the input reservoirs was prevented from evaporation by cooling as demonstrated by Zimmerman et al. (111). Likewise, pervaporation of water through the roof of polyimide channels caused liquid flow, shown by Eijkel et al. (112). The model and experimental validation of flow, driven by permeation of a solvent

into a PDMS wall, was presented by Randall and Doyle (113).

By controlling the geometry of two inlets and a junction, and by regulating the hydrophilicity of a substrate, Kim et al. demonstrated a passive scheme to control the merging and volumetric flow rate of two streams (114). Controlling the wetting properties of a surface by photopatterning hydrophilic pathways between two mainly hydrophobic layers, liquid transport along the hydrophilic pathway was shown (115).

Gravity-induced convective flow generated by tilting the whole microchip was studied by Morier et al. (116). Marmottant and Hilgenfeldt proposed a transport method whereby a piezoelectric transducer generated a standing ultrasound field, which directly excited microbubbles adsorbed at the bottom and indirectly lead to streaming flow around solid particles (117). Lammertink et al. studied recirculation of flow in a dead-end channel that resulted from counterbalancing hydrodynamic pressure against electroosmotically generated flow (118). Liu et al. introduced an optofluidic application based on a direct optical-to-hydrodynamic energy conversion using suspended photothermal nanoparticles near the liquid–air interface. The fluid can be guided using light beams with submilliwatt power (119).

Microfabricated Valves. Weibel et al. used small machine screws integrated in a PDMS chip. Turning the screws resulted in collapsing the PDMS layer between the valve and the underlying microchannel (120). Automated and manual actuation of solenoid plungers that deformed PDMS channels was used by Vestad et al. (121), and fingerlike valves actuated by a servomotor were integrated on a chip for controlling liquid flow in a polymerase chain reaction (PCR) chamber by Pilarski et al. (122). A pneumatic valve was fabricated by applying a liquid flow in a control layer that contacted a microchannel with the working fluid via a polysilicone membrane (123). A thermopneumatic valve was realized by integration of an ITO-coated glass that enabled heating of an air chamber and, at the same time, the deformation of a PDMS membrane that formed the valve (124). Control of PDMS membrane deformation with switching times of 10 ms was successfully achieved using a giant electrorheological fluid in a control layer (125).

Nonmechanical Valves. Valves could be formed by plugs that noninvasively close and open the microchannel and, thus, prevented or enabled the liquid flow through the channel. In the following, different strategies to form reversible plugs are listed. Gui and Liu designed an ice valve by use of a thermoelectric cooling and heating device that is in contact with a microtube. The valve opened and closed by phase change of the aqueous solution, i.e., melting and freezing, within several seconds (126). In a similar approach, Chen et al. applied this technique to a polycarbonate microchip comprising a more complicated channel structure and demonstrated PCR inside an ice valve-controlled chamber (127). Furthermore, phase transition of paraffin plugs and their utilization as single-use microvalves was shown (128). Pal et al. developed a meltable piston, inherently latched reusable, and leak proof, to obstruct fluid flow (129). A thermoresponsive polymer was utilized by Hisamoto et al. on a capillary-assembled microchip (130).

A plug of ferrofluid, controlled by a movement of a magnet and its application to form valves and to pump liquid, was presented by Hartshorne et al. (131). Hydrogels were imple-

mented in microfluidic channels that change their volume upon stimulation. Bassetti et al. determined the volume changes of such electrically stimulated hydrogels (132). Stoeber et al. as well as Wang et al. studied gel formation inside microfluidic channels upon heating (133, 134). Eddington and Beebe designed an array of stimulus-responsive hydrogels that provide the actuation pressure for valving and dispensing functions (135). The work of Sershen et al. demonstrated the feasibility of forming hydrogel valves via optical control. The material chosen was a composite of a thermally responsive polymer and particles that have distinct and strong optical absorption profiles. The valves integrated in a 100- μm -wide channel opened upon illumination with laser light of a specific wavelength within 5 s (136). Free-standing microfluidic polymer elements and their use for high-pressure fluid control in glass microsystems were studied by Kirby et al. (137). A valve based on electrowetting is demonstrated by Cheng and Hsiung, using a plasma-modified Teflon surface (138).

A microfluidic rectifier in a microscopic channel of a special shape, whose flow resistance is strongly anisotropic, was presented by Groisman and Quake (139). Brenner et al. realized a fluidic switch on a centrifugal platform by change of rotation frequency (140). Similarly, on a CD-like platform and controllable by rotation speed was the valve designed by Leu and Chang, which relied on the capillary pressure barrier when the channel geometry changed abruptly (141). Hydrophobic and narrow channels acted like a valve in a rotating system reported by Yamada and Seki (142).

ANALYTICAL STANDARD OPERATIONS

Sample Preparation. Several sample preparation methods via electric field application have been reported. Wang et al. developed a preconcentration device based on the electrokinetic trapping mechanism enabled by nanofluidic filters. The trapping and collection can be maintained for several hours, and concentration factors as high as 10^6 – 10^8 were achieved (143). Electrokinetic concentration of charged analytes inside microchannels, containing a hydrogel microplug, showing enrichment factors of 500 within 150 s using low bias voltages was observed by Dhopeswarkar et al. (144). An electrokinetic processor, which combined electrophoretic and dielectrophoretic forces and the electrohydrodynamic flow to concentrate various bioparticles from micrometer to nanometer in size, was demonstrated by Wong et al. (145). It was shown by Lui et al. that sample stacking can occur in isoconductive buffer systems as a result of ion transport mismatches that cause changes in buffer conductivity during electrophoresis (146). A process was described by Leinweber et al. where induced charge electrokinetics in structured electrode arrays enabled electrohydrodynamic demixing and concentration accumulation of any type of electrolyte (147).

With the aid of membranes, sample preparations and preconcentrations were conducted. For instance, Foote et al. concentrated proteins using a porous silica membrane between adjacent microchannels that allowed the passage of buffer ions but excluded larger migrating molecules, showing ~ 600 -fold signal enhancement (148). Miniaturized supported liquid membrane extraction followed by HPLC–UV detection was designed and fabricated by Wang et al. for sample enrichment (149). Song et al. presented a protein preconcentration system using a 50- μm -

thick nanoporous polymer membrane fabricated in the junction of a cross channel of a chip, a pinched electrokinetic injection, and a single buffer (150).

An online desalting of macromolecule solutions within tens of milliseconds by utilizing a two-layered laminar flow geometry that exploits the differential diffusion of macromolecular analytes and low molecular weight contaminants was studied by Wilson and Konermann (151). A method, where spores were mixed with a laser light absorbing matrix and cocrystallized into 200- μm -wide, 20- μm -deep vials formed in a PDMS target plate, was introduced by Hofmann et al. (152). A first direct coupling of microdialysis sampling to a chip-based CE system was described by Huynh et al. (153). An inline sample purification method for MALDI-MS, which relies on an electrowetting-on-dielectric-based technique, was reported by Wheeler et al. (154). Autonomous coupling of solid-phase extraction (SPE) to micellar electrokinetic chromatography, where completely automated sequences of extraction, elution, injection, separation, and detection were performed in less than 5 min, was described by Ramsey and Collins (155). Coupling SPE of DNA and PCR on a chip was performed by Legendre et al. DNA was purified in a silica bead/sol-gel SPE bed and then directly eluted into a downstream chamber, where conventional thermocycling allowed for PCR amplification of the DNA sequences (156). A polymeric device for SPE-based isolation of nucleic acids was studied by Bhattacharyya and Klapperich (157). Chiesl et al. created water-soluble block copolymers of acrylamide and *N*-alkylacrylamides to selectively remove proteins from DNA (158).

A microchip for liquid-liquid extraction was presented by Chen et al. Organic solvent droplets were trapped in recesses fabricated in the channel walls. By delivering an aqueous solution containing analytes (here, for example, butyl rhodamine B), the analytes were enriched within the organic solvent droplets with high preconcentration factors (159). Lee et al. achieved the synthesis of an ^{18}F -radiolabeled molecular imaging probe in an integrated microfluidic device with high yield and purity and with shorter synthesis time relative to conventional automated synthesis (160).

Injection. Thomas et al. fabricated valves with a cross and two tee intersections in proximity to each other and tested them for repetitive pinched injections (161). The functionality of an integrated diaphragm pump on a hybrid PDMS-glass chip to perform pressure injections for electrophoretic separations was tested by Karlinsey et al. (162). A flow injection analysis system with gravity-driven flows and liquid-core waveguide spectrometric detection was developed by Du et al. (163). A >3-MPa on-chip injector, allowing reproducible injections as small as 180 pL with <250-ms duration was presented by Reichmuth et al. (164). Cho et al. investigated, on a chip with a pneumatic injection scheme, introduction of a solution without sampling bias based upon the hydrophobicity and wettability of channel surfaces (165). A microchip was designed by Chen and Wang, where the sample introduction is carried out directly in the separation channel through a sharp inlet tip placed in the sample vial, i.e., without an injection cross, complex microchannel layouts, or hardware modification (166). A triple-injection method that resulted in a higher intensity of DNA peaks, which included a combination of a sample loading voltage and a separation voltage in each interval

prior to electrophoretic separation, was conducted by Tabuchi and Baba (167). A microchip electrophoresis utilizing the new solution filling technique, where loading of the sieving polymer and formation of the sample plug are carried out by the degassed PDMS microchip, was achieved by Ito et al. (168). Wu et al. presented a sample introduction method based on push/pull pressure flow for microfluidic systems with cross, double T, and multichannel structure (169). A combination of negative pressure and electrokinetic and hydrostatic forces was utilized to inject well-defined nonbiased sample plugs by Zhang et al. (170). PDMS-based pneumatic valves to discretely inject samples from a hydrodynamically pumped flow stream directly into an electrophoresis channel were described by Li et al. (171).

Fluid and Particle Handling. *Temporal and Spatial Control of Reagent Supply.* By varying the ratio of flows of two guiding streams flanking a middle stream, the position of the middle stream can be controlled. Besselink et al. controlled the flow rates of the outer and middle streams by electroosmotic flow (172), while in the approach by Regenberget al., the flow was induced by pumping. In these experiments, the middle stream contained reactive species that were deposited on the chip surface in patterns of 50- μm -wide lanes (173). Olofsson et al. developed algorithms and methods to generate time-dependent variations of one or several chemical species such as formation of sine waves, damped oscillations, and more complex patterns (174).

Lin et al. described a microfluidic device with a gradient generating network. Dynamic linear and nonlinear gradients (here of a buffer solution and FITC-dextran) were produced by changing the flow rates at the fluid inputs (175). Bang et al. used a microfluidic device to prepare serial dilution for delivery to 96-well plates for cytotoxicity testing (176). Linder et al. described the use of cartridges made of commercially available tubings for storing and delivering a sequence of reagents (e.g., for immunoassays) to a microfluidic device (177). Kang and Park developed a microfluidic device for substrate dilution that is compatible to a microplate reader (178).

Generation and Handling of Small Liquid Volumes. Wheeler et al. presented a technique that relies on electrowetting to move droplets on an array of electrodes. Droplets containing proteins, or peptides and matrix, were moved to specific locations and prepared for MALDI-MS analysis (179). The movement of droplets in an immiscible medium on an 32×32 electrode array driven by dielectrophoresis (DEP) was demonstrated by Gascoyne et al. DEP does not require contact with control surfaces, and strategies for minimizing surface contact were presented (180). Controlled droplet dispensing by electrowetting actuation was realized by Ren et al. Furthermore, capacitance feedback was used to meter the droplet volume and control the dispensing process (181). Droplet motion on a nonwetttable surface driven by asymmetric lateral vibration was also studied (182). A method was described by Hsu and Folch that enabled physical trapping of nanoliter-sized volumes using pneumatic doughnut structures (183).

Various groups studied the generation of aqueous droplets in a liquid hydrophobic carrier medium or in gas with homogeneous size distribution (184-190) and demonstrated controlled droplet breakup using T junctions (186), fusing and sorting feasibility (187), mixing performance within the droplets (188, 189), and

generation of cell suspension aliquots (191). The feasibility to concentrate solutes and colloidal entities in microdroplets was reported by He et al. (192). Takeuchi et al. generated nylon-coated water droplets in an axisymmetric flow focusing device. They formed droplets of a diamine/water solution in a hexadecane carrier, which were directed into a solution of acid chloride in hexadecane which initiated a polymerization (193).

Particle Handling. Particle filtration and concentration using dielectrophoretic manipulation was presented by Barrett et al. Due to ridgelike structures that were fabricated in insulating material, a nonuniform electric field was formed near the ridges when a dc field was applied along the channel, which affected particle motion parallel to the ridges (194). Kumar et al. combined negative dielectrophoresis and phase separation to concentrate particles in prespecified regions using microchips with planar electrodes (195). Dielectrophoresis is also used to control the adhesion of microbeads. To prove irreversible adhesion, the beads were coated with biotin, and binding of fluorescently labeled streptavidin was detected that was supplied after turning off the DEP voltage (196). Particle trapping in acoustic standing waves was applied by Petersson et al. to change buffer solutions in which the particles are suspended (197). Biswal and Gast reported the use of linked chains of paramagnetic particles in a rotating magnetic field to perform microscale mixing (198). Ramadan et al. integrated 3D magnetic devices in a microfluidic chamber to trap magnetic particles (199). Vilkner et al. presented two methods to inject and transport minute amounts of dry powder in a microfluidic channel, in which the particles are fluidized in a gas stream (200).

Reactors and Mixers. Several groups worked on the development of a micromixer using splitting and recombining channel geometries, realized in particular by use of multilayer chips (e.g., refs 201–204). Munson and Yager fabricated a lamination mixer and applied a quantitative optical method for monitoring the extent of mixing (205). Chaotic mixing was also shown in a channel that is a chain of repeating segments with a custom-designed profile that generated steady 3D flow with stretching and folding (206). Burghelca et al. added a polymer solution to improve mixing efficiency (207). By applying a magnetic field, mixing was shown for bead-based systems (208, 209) and by utilizing a magnetic stir bar (210). Mixing in batch mode (stopped-flow) on centrifugal platforms with and without utilization of magnetic beads was investigated by Grumann et al. (211).

A 3D microchannel that has slanted microgrooves on top and side walls for chaotic mixing was introduced by Sato et al. (212). The use of compact spiral-shaped flow geometries designed to achieve efficient step mixing was explored by Sudarsan and Ugaz (213). Electroosmotic mixing with periodic electric field variation utilizing a T-form mixer was described (214–218). Mixing 2 orders of magnitude higher than molecular diffusion by creating electroosmotic microvortexes was achieved by Wang et al., when dc and ac electric fields were applied (219). Rapid polarity switching was used by Sanders et al. as a means for inline mixing of two reactant solutions via 1–5 s and sequential switching of the applied potential field (220).

Separation. Separation of Particles. Huang et al. developed a device for size-dependent separation of particles that made use of the asymmetric bifurcation of laminar flow around obstacles.

Particles of 0.8–1.0- μm diameter as well as bacterial artificial chromosomes were separated (221).

A concept of “pinched flow fractionation” for the continuous separation of particles of different sizes was proposed and demonstrated by Yamada et al. In this method, particles were aligned to one sidewall at a narrow segment of the microchannel by another liquid flow without particles. By spreading the flow profile (by widening the microchannel), particles were separated perpendicular to the flow direction (222). In the following work, they modified the technique by utilizing a microchannel with multiple branch points, in which the flow profile controlled the particles that are concentrated in the side channels (223). Kang et al. achieved the separation of particles by direct current electrophoresis. A locally nonuniform electric field is generated by an insulation block fabricated in a PDMS channel (224) or an oil droplet acting as an insulating hurdle as shown by Barbulovic-Nad et al. (225). Choi and Park also succeeded in the separation of beads by (negative) dielectrophoresis using a trapezoidal electrode array (226). Split-flow thin fractionation was reported by Narayanan et al. to separate particles based on their electrophoretic mobility (227). Pamme and Manz realized free-flow magnetophoresis to separate particles with different magnetic susceptibilities. Furthermore, agglomerates of magnetic particles were found to be deflected in a magnetic field to a larger extent than single particles (228).

Electrophoresis and Related Techniques. A free-flow electrophoresis device was fabricated into a glass wafer by Fonslow and Bowser, where the separation of fluorescent standards was achieved within electrical fields ranging from 0 to 283 V/cm (229). Kohlheyer et al. presented a microfabricated free-flow electrophoresis device with integrated ion-permeable membranes. Separation of standard fluorescent markers was demonstrated by applying focused free-flow zone electrophoresis and free-flow isoelectric focusing (230).

Cui et al. improved the resolving power of isoelectric focusing (IEF) by first focusing proteins in a straight channel using broad-range ampholytes followed by refocusing segments of the first channel into secondary channels that branch from the first one at T-junctions (231). Furthermore, they reported the use of methylcellulose to reduce electroosmosis and peak drift (232). IEF combined with SDS gel electrophoresis was reported by Li et al. for protein separations. Proteins focused by IEF were electrokinetically transferred into an array of orthogonal microchannels and further resolved by gel electrophoresis (233). 2D separation of proteins applying IEF and CE was achieved by Wang et al. using integrated microvalves to control the fluid flow at the intersection of the IEF and CE channel (234). Griebel et al. designed a microchip to combine IEF and gel electrophoresis (235).

Zone electrophoresis (ZE) on a microchip was performed by Kaniansky et al. The resolution was enhanced by switching between two separation columns (236). ZE of amino acids in a PDMS–glass device with different methods of surface pretreatment was investigated by Mourzina et al. (237). Ölvecka et al. combined ZE with isotachopheresis (ITP) on a microchip (238). ITP preconcentration before gel electrophoresis (GE) resulted in an increase of ~ 40 -fold of the detectable concentration of SDS–proteins compared to GE in a simple cross channel as shown by

Huang et al. (239). Tsai et al. performed electrophoresis of both native and SDS proteins in an array of microchannels (240). Electrophoretic amino acid and protein separation using electroosmotic flow induced by dynamic SDS coating (241) and applying micellar electrokinetic chromatography in addition to dynamic SDS coating (242) was also presented.

A microdevice for the collection of fractions after electrophoretic separation was presented by Tulock et al. They fabricated a microchip with two channel layers that are connected via a membrane with interconnecting nanometer-sized pores. The signal of an analyte band in one of the channels, sensed by laser-induced fluorescence, was also used to trigger transfer of the analytes into the second channel (243). Lin et al. developed a technique to generate addressable electric fields for selective extraction of target bands during electrophoresis (244).

Chiral Separation. Bals et al. presented the simultaneous concentration and high-resolution separation of chiral compounds by combination of a temperature gradient, an applied electrical field, and a buffer with a temperature-dependent ionic strength. Chiral separation is accomplished by the addition of a chiral selector, which causes the different enantiomers of an analyte to focus at different positions along a microchannel or capillary (245). Chiral separation of dansyl amino acids (246, 247) and FITC-labeled chiral drugs such as baclofen and norfenefrine (248) were also performed on planar microchips.

Chromatography. Electrochromatography was performed in a chromatography column that was fabricated by immobilizing reversed-phase stationary-phase particles using sol-gel technology. Three tryptophan-containing peptides were separated and detected by UV absorbance (249). A centrifugal chromatograph for reversed-phase separation was fabricated and characterized by Penrose et al. (250). Vankrunkelsven et al. reported the separation of a mixture of fluorescein isothiocyanate-labeled angiotensin I and II peptides using shear-driven chromatography (251). Yang et al. developed a circular, shear-driven pumping system that was combined with Fourier transform detection for cyclic chromatography (252).

Other Separation Techniques. A separation strategy was proposed by Astorga-Wells et al. that included first, the electroimmobilization of peptides. Second, the reduction of the electric field in a stepwise manner caused sequential release of captured peptides according to their electrophoretic mobility. Tryptic enzymes were separated by this method and afterward analyzed by MALDI-MS (253). A study of electrokinetic transport in nanochannels using quantitative epifluorescence imaging was presented by Pennathur and Santiago. They demonstrated a technique termed electrokinetic separation by ion valence, whereby both ion valence and mobility may be determined independently (254). Electrokinetic molecular separation in nanoscale channels was furthermore described by Garcia et al. (255). A nanofilter array chip was fabricated by Fu et al. and used for size fractionation of SDS-protein complexes and small DNA molecules. It is based on the Ogston sieving mechanism, in which the size of the molecule is smaller than the size of the nanopore (256).

Detection. Fluorescence Spectroscopy. Beard et al. presented the derivatization of biogenic amines with dichlorotriazine fluorescein that has a faster reaction time compared to former

derivatization agents (257).

Schulze et al. succeeded in the detection of unlabeled drugs and proteins (such as serotonin, propranolol, and tryptophan) in microchip electrophoresis by using deep-UV fluorescence detection at 266-nm excitation wavelength (258), and Hellmich et al. separated and detected in a similar approach the unlabeled proteins lysozyme C and avidin (259). By applying multicolor detection, Stavis et al. demonstrated the characterization of single-molecule binding (quantum dots conjugated to an organic fluorophore) (260). An effective observation volume that is ~100 times smaller than the observation volume, using conventional confocal optics, was realized by Foquet et al. To achieve this, microfluidic channels with submicrometer size were fabricated. Single fluorescent analytes were detected, and the flow velocity was characterized by fluorescence correlation spectroscopy (261). Detection of single DNA molecules transported through a lipid nanotube was realized by Tokarz et al. (262).

Magennis et al. applied fluorescence lifetime imaging microscopy (FLIM) to study mixing of a fluorescent dye and methanol in a T-shaped channel (263). Applying high-speed FLIM, Benninger et al. studied solvent interactions and mixing by using a fluorophore (DASPI) whose fluorescence lifetime is directly dependent on the local solvent viscosity (264). The simultaneous determination of flow velocities (of λ DNA) in the middle and near the wall of a microchannel was presented by Gai et al., by switching from a wide-field excitation mode to an evanescent wave excitation mode within the same optical setup (265).

Integration of Optical Components, Light Sources, and Detectors. Chronis and Lee fabricated a microchip for total internal reflection microscopy. They implemented a micromirror at the sidewall of a silicon chip that facilitates precise alignment of the excitation beam into the microchannel system (266). By integration of an array of microlenses and a diffraction grating, Damean et al. obtained continuous absorbance spectra of samples at multiple locations in microwells and microchannels (267). Seo and Lee described work on a disposable integrated device with self-aligned planar microlenses for bioanalytical systems that had LEDs as excitation sources and photodiodes as detectors (268). Bowden et al. used a fiber-optic microarray consisting of 49 777 individually addressable light pathways that was implemented on a microfluidic platform to study DNA hybridization (269). An absorbance detection cell with an extended optical path length in a Z-shaped channel was fabricated by Ro et al. They integrated optical fibers, a microlens to collimate the light, and two rectangular apertures to block stray light on the PDMS microchip (270).

Mayers et al. described the fabrication and operation of fluidic broadband light sources that consist of cascades and arrays of liquid core, liquid cladding microchannel waveguides. The liquid cores contained fluorescent dyes that were excited by incident light from an external halogen bulb (271). Mitra et al. used discharge-based optical sources for the fluorescence detection of biochemicals. A barium chloride solution is used to emit light at 454 and 493 nm to detect DNA labeled with SYBR green dye, and a lead nitrate solution provides a 280-nm emission for the excitation of L-tryptophan (272).

Edel et al. presented a thin-film polymer (polyfluorene-based) light-emitting diode as integrated excitation sources with the wavelength of 488 nm (273), and the same group used thin-film

organic photodiodes as integrated detectors (274). An integrated detector, in particular for genetic analyses, was also developed by Kamei et al. It consisted of a hydrogenated amorphous silicon (a-Si:H) detector, a ZnS/YF₃ multilayer optical interference filter with a pinhole, and a half-ball lens (275). Namasivayam et al. presented a photodetector that uses a PINN⁺ photodiode with an on-chip interference filter and a liquid barrier layer (276).

Other Optical Techniques. Kang et al. observed native DNA in Nomarski differential interference contrast microscopy and found differences in migration time and dynamics of the native DNA and DNA that is labeled with the (fluorescent) intercalator YOYO-1 (277). Kim et al. combined electrochemical and spectroscopic techniques. A microelectrode was integrated into a glass microchip for electrolysis of *o*-tolidine, and afterward, thermal lens microscopy was applied, which is a photothermal spectroscopy technique that can be applied to nonfluorescent analytes (278). Mawatari et al. developed a portable thermal lens spectrometer that has a novel autofocusing system (279).

Fourier transform infrared (FT-IR) spectroscopy in a multiple internal reflection geometry on a silicon–glass microchip was applied by Herzig-Marx et al., and the applicability was tested for kinetic measurements of acid-catalyzed ethyl acetate hydrolysis and amidization of surface-tethered amine groups (280). Atomic emission detection of metallic species in aqueous solution has been performed by Jenkins et al. A parallel liquid–gas flow was set up in a microchannel, and a glow discharge was ignited between the flowing liquid sample surface and a metal wire anode (281). Surface-enhanced resonance Raman scattering (SERRS) was applied for simultaneous detection of three dye-labeled oligonucleotides by Docherty et al. (282). Using confocal SERRS, Park et al. studied pure solutions and mixtures of DNA, labeled with the fluorescent dyes TAMRA and Cy3, adsorbed on silver colloids (283).

Optical coherence tomography was used for characterizing the mixing efficiency and flow velocities within three different microfluidic mixers. The technique provided 3D images with a resolution of a few micrometers (284).

Electrochemical Detection. Several electrochemical detection techniques were applied and optimized for the use in microchip electrophoresis. Contactless conductivity measurements on an electrophoresis microchip were performed to detect inorganic ions in alcoholic and nonalcoholic beverages by Kubán and Hauser (285), as well as by Abad-Villar et al. to detect amino acids, peptides, and proteins (286). Bai et al. proposed a passive conductivity detection concept validated by numerical simulations and experiments. They placed detection electrodes along the flow, such that the separation electrical field is used to generate the detection signal (287). The fabrication and optimization of an integrated palladium decoupler for amperometric detection in an electrophoresis chip was described by Lacher et al. (288) and by Lai et al. (289). The decoupler allowed the working electrode to be placed directly in the separation channel. A two-chip concept with one chip for electrophoretic separation and integrated conductivity detection and the second chip for fluid handling and electrical connections was proposed by Vogt et al. (290).

Pulsed amperometric detection with an integrated decoupler (a Pd microwire) was also shown by Vickers and Henry with determination of the detection limits for dopamine (5 nM),

glutathione (74 nM), and glucose (100 nM) (291). An indirect amperometric detection method via mounting a single carbon fiber disk working electrode in the end part of a microchannel was established by Xu et al. (292). Sheath flow supported electrochemical detection was reported by Ertl et al. and applied for the analysis of DNA restriction fragments and PCR product sizing (293). Jiang et al. developed a USB-based minielectrochemical detector whose size is compatible with microchip format. It was tested for determination of epinephrine using a PDMS–glass chip with a detection limit of 2.1 μ M (294).

To detect catecholamines electrochemically, Hayashi et al. fabricated a microchip with an interdigitated array electrode. To remove effects of the electroactive interference, L-ascorbic acid, an integrated prereactor with micropillars, immobilized with ascorbate oxidase, was integrated on the chip. Detection limits of dopamine and adrenaline were found to be 108 and 440 pM, respectively (295). Impedance measurements were performed by Costanzo et al. to study nanoparticle aggregation. Aggregates formed by biotinylated nanoparticles and avidin were captured by dielectrophoresis between thin-film electrodes and detected by both fluorescence microscopy and a change in interelectrode impedance (296).

Fast-scan cyclic voltammetry was applied to probe electrical fields inside a microfluidic channel by Forry et al. Carbon-fiber microelectrodes were inserted at various distances into channels, and cyclic voltammograms of the test solute (Ru(bpy)₃²⁺) were recorded (297).

Zhu et al. studied the detection of heavy metal ions (Pb²⁺ and Cd²⁺) using an on-chip generated mercury microelectrode. A mercury droplet of \sim 150- μ m diameter has been generated under the control of thermopneumatic actuation and surface tension (298). Potentiometric titration of Fe(II) with Cr(VI) solution was shown by Ferrigno et al. A titration curve was generated by performing on-chip serial dilution of analyte and detecting the analyte in parallel using integrated Pt electrodes (299). The transport of a reversible redox species at paired microband electrodes was used for monitoring flow rates by Amatore et al. (300).

Other Detection Methods. An integrated planar microcoil was fabricated for nuclear magnetic resonance (NMR) spectroscopy by Wensink et al. Volumes of less than 1 μ L were sufficient for real-time monitoring of imine formation from benzaldehyde and aniline (301). McDonnell et al. presented another approach for NMR imaging by physically separating signal detection from encoding of information with remote detection (302). Pulsed-field gradient NMR was applied to measure the velocity of liquids in a micromixer (303).

The possibility of performing chemical analysis with the techniques of X-ray fluorescence and diffraction on a microfluidic chip was explored by Greaves and Manz, using externally generated radiation, radioisotope irradiation, or on-chip generated X-rays (304). Using synchrotron sources, Reich et al. performed X-ray reflectivity studies at solid–liquid interfaces (lipid bilayer adsorbed on SiO₂) in a microfluidic chamber flooded with water (305).

Hwang et al. reported resonant frequency shift measurements based on a nanomechanical cantilever with a lead zirconate titanate actuating layer that is embedded into a PDMS microfluidic chip.

With this device, specific binding characteristics of the PSA (prostate-specific) antigen to its antibody, which was immobilized on a gold surface deposited on the cantilever, were detected (306). Anderson presented the use of an atomic force microscopy (AFM) cantilever functioning as a microfluidic shear plate for pumping, sampling, and imaging liquid surfaces in microchannels. Additionally, surface-enhanced Raman spectroscopy localized near the AFM tip provided chemical information of the sampled fluids (307).

Gear et al. described a wafer-scale, batch fabrication process for constructing quadrupole mass spectrometers. Mass filtering was demonstrated, with a mass range of ~ 400 amu and a mass resolution of 1 amu at 219 amu, using quadrupoles with rods of 500- μm diameter and 30-mm length, operating at 6-MHz rf frequency (308). Cooks and co-workers developed a miniaturized mass analyzer based on a rectilinear geometry ion trap (309). In another study, they built an instrument based on an array of cylindrical ion traps with four independent channels. A multichannel electrospray ionization source was assembled and used to introduce samples including solutions of organic compounds, peptides, and proteins simultaneously into the instrument in a high-throughput fashion (310).

The viscosity and intrinsic viscosity of polymer solutions were determined by Lee and Tripathi. Polymer samples were diluted with solvent, and the concentration of the polymer sample was calculated from the fluorescent signals, from which the viscosities can be evaluated (311). Blom et al. designed a fluidic system for viscosity detection. It consisted of a Wheatstone bridge and a low hydraulic capacitance pressure sensor that sensed the pressure based on optical detection of a membrane deflection (312). Mela et al. described a device capable of sensing pH. The surface was coated with a self-assembled monolayer and a fluorescent molecule that switched between fluorescent and nonfluorescent state depending on the acidity of the surrounding solution (313).

APPLICATIONS

Cell Handling and Analysis. *Cytometry.* Wang et al. introduced a fluorescence-activated cell sorter, based on optical force switching and evaluated its performance on live, transfected HeLa cells expressing a fused histone–green fluorescent protein (314). Flow control by electrical field switching in order to sort particles and living cells was applied by several groups for various channel geometries (315–317). Yao et al. developed a sorting device, where cells flowed under their own gravity in an upright channel, passed the fluorescence detection region, and were sorted into different output channels by an electrical field (317). Hu et al. used a dielectrophoresis activated cell sorter with a throughput rate of 10 000 cells/s. They showed 200-fold enrichment of rare target cells that were labeled with particles that differ in polarization response (318). A mechanical switch actuated via bubbles that were generated electrochemically was fabricated and successfully demonstrated by Ho et al. (319). Shirasaki et al. implemented a valve made of a thermoreversible gelatin polymer into a Y-shaped channel system that had a response time of 3 ms. They achieved switching times of 120 ms (320).

Various methods were developed to detect and differentiate cells in a microcytometer device. Size-selective counting of beads and blood cells was performed by Cheung et al. using impedance

analysis (321) on a microchip with integrated metal electrodes and by Chun et al. on a microchip with integrated polyelectrolytic salt bridge-based electrodes (322). Ateya et al. measured the volume of small numbers of cells in a microfluidic device with integrated impedance measuring electrodes and determined the volume changes of astrocytes responding to anisotonic stimuli (323).

The implementation of an optical stretcher to measure optical deformability of normal and cancerous cell types was presented by Lincoln et al. (324). The interaction of living cells with optical gradient fields (optophoresis) was studied by Zhang et al. They detected differences between normal skin and melanoma cell lines by applying this method (325). Guck et al. determined the optical deformability for suspended cells in a two-laser trap and demonstrated that it can serve as a sensitive indicator of the state of cellular development, during normal differentiation and disease (326).

Two-color, multiangle fluorescence detection was enabled by insertion of an optical fiber arrangement into the microchip (327). Wang et al. integrated optical fibers and a lens on a microchip to measure scattering and extinction of a passing sample. They demonstrated the applicability using beads with different diameters between 2.8 and 9.1 μm (328). To count particles with high speed, Wood et al. presented an approach that employed a tuned radio frequency probe, which formed the radio frequency analogue of a Coulter counter (329).

A cytotoxicity assay (i.e., the toxicity of Triton X-100 on Jurkat cells) was conducted on a microchip with a long, spiral channel. The cell viability was determined as a function of Triton X-100 concentration and LD_{50} values using the ratio of fluorescence signals from membrane permeant (calcein) and membrane impermeant (propidium iodide) stains (330). Emmelkamp et al. demonstrated the potential of autofluorescence detection to discriminate different cell types (331).

Cell Separation. Applying shear-driven flow in a stepwise tapered microchannel, separation of beads and cells of different sizes was demonstrated by Vankrunkelsven et al. (332). Insulator-based dielectrophoresis was utilized to separate mixtures of two different bacteria species. In a glass microchannel with insulating posts, the bacterial cells exhibited different dielectrophoretic mobilities, under the influence of a nonuniform electrical field, and were trapped into spatially distinct bands (333). Nam et al. fractionated live from dead (CHO-K1) cells using an immiscible aqueous two-phase extraction technique (334). Continuous separation of cell organelles by isoelectric focusing using a field flow fractionation device was reported by Lu et al. The basis of the separation was the presence of membrane proteins that gave rise to the effective isoelectric points of the organelles (335).

Cell Lysis and Whole Cell Analysis. A device for automated nucleic acid purification from small numbers of bacterial or mammalian cells integrating mechanical microvalves was studied by Hong et al. (336). Di Carlo et al. achieved lysis of different cell types by hydroxide ions that were locally generated at an integrated cathode (337). Lu et al. presented a microelectroporation device consisting of electrodes with a sawtooth design, which allowed continuous lysis of the plasma membrane while leaving organelle membrane undamaged (338). Single-cell capture and chemical lysis was performed by Irimia et al. using a

microchamber of 25 pL and four on-chip thermopneumatic actuators (339).

El-Ali et al. combined stimulation and chemical lysis of cells using segmented gas–liquid flow (340). He et al. captured individual (mouse mast) cells within a segmented water–oil flow and performed (laser-induced) photolysis, to study the activity of an intracellular enzyme (β -galactosidase) (341). Mechanical lysis of cells was achieved in a rotating microfluidic CD that was filled with spherical particles (342). To analyze the content of single cells, Wu et al. developed a new kind of three-state valve that allows for liquid metering and flow control. A reaction volume of \sim 70 pL was achieved for chemical lysis and derivatization of the contents of single Jurkat T cells. Separation by electrophoresis and detection by laser-induced fluorescence was additionally performed on the same chip (343). Parallel single-cell capillary electrophoresis was presented by Munce et al. Cells were captured in a tapered channel and lysed by application of an electric field (344). Lagally et al. enriched cells (*Escherichia coli* MC1061) by dielectrophoresis and performed chemical lysis subsequently. Optical detection of the bacterial cells was accomplished via the sequence-specific hybridization of an rRNA-directed optical molecular beacon (345).

Ling et al. described the simultaneous determination of reactive oxygen species and reduced glutathione in individual erythrocyte cells, by conducting all necessary steps (single-cell loading, electrical lysis, and capillary electrophoresis) on a microchip (346). Lee et al. extracted DNA after cell lysis in a microreactor. Afterward, they injected primers and reagents into the microchip and performed PCR in a temperature-controlled microchamber (347).

Cell Traps. Local encapsulation of living cells on a chip was demonstrated in different kinds of hydrogels. Arai et al. used thermosensitive hydrogel (poly(*N*-isopropylacrylamide)) (348). Albrecht et al. formed a 3D cell trapping network in poly(ethylene glycol) (PEG)-based hydrogels that are cross-linked by UV exposure (349). PEG was also used by Khademhosseini et al. to form molded PEG lanes and microwells (350). Furthermore, a method for cell trapping was shown by Braschler et al. that was based on the controlled formation of an alginate hydrogel by bringing two laminar flows of alginate and calcium ions into contact (351).

Positioning of cells and subsequent reagent delivery via microchannels was also achieved using PDMS microwells (352) or microwells fabricated on a Si chip (353). Toriello et al. labeled the cell surface with thiol functional groups and achieved adhesion of the cells to gold pads by applying a driving electric potential (354). Seger et al. constructed a semiopen dielectrophoresis trap to hold cells in a microfluidic channel and to deliver different solutions (here dye and buffer) (355). Peng and Li trapped yeast cells in a niche of a microfluidic channel system (356). They determined the kinetics of intracellular metabolism and calcium mobilization stimulated by glucose and pH changes (357). Using a microfluidic device with mechanical cell traps, Valero et al. studied electrically or chemically induced apoptotic cell death. By exposure to appropriate fluorescent dyes, viable, necrotic, and apoptotic cells could be discriminated (358). The extracellular potential of a single cardiac myocyte was recorded by Werdich et al. The myocyte was trapped in a tapered channel on planar

titanium/platinum electrodes (359).

Cell–cell communication between individual cell pairs was studied in an array of trapping channels by Lee et al. (360). Ionescu-Zanetti et al. achieved trapping of mammalian cells at the entrances of a microfluidic channel array. They developed a simple alternative patch-clamp technique and recorded the activation of the voltage-sensitive potassium channel Kv2.1 (361). Using nanowires fabricated by electrodeposition in nanoporous templates, Tanase et al. achieved magnetic trapping of cells bound to Ni nanowires (362). Zhang et al. fabricated a silicon–glass microchip with an integrated filter, which they used for trapping microbial cells. Labeling by fluorescent in situ hybridization, and a quantum dot-labeled immunofluorescent assay, were used to detect viable and nonviable cells (363).

Cell Culture. Gu et al. developed a microfluidic PDMS chip with a refreshable Braille display that can power integrated pumps and valves through localized deformations. They cultured C2C12 mouse myoblasts for up to 3 weeks under precisely controllable conditions (364).

The growth of central nervous system axons into a fluidically isolated environment, without the use of targeting neutrophins, was observed on a microfluidic culture platform by Tayler et al. (365). A cell culture 10×10 array for cultivation of HeLa cells consisted of circular microchambers, multiple narrow perfusions channels surrounding the main chambers, and fluidic access ports (366). Tourovskaja et al. studied cell differentiation of myoblasts to myotubes over several days on a microfluidic platform (367).

Long-term cultivation of *E. coli* cells in a microchemostat was presented by Balagaddé et al. The device was used to observe the dynamics of *E. coli* carrying a synthetic “population control” circuit that regulated cell density through a feedback mechanism (368). The persistence of single bacterial cells (*E. coli*) to stress such as antibiotic treatment, was investigated by Balaban et al. Quantitative measurements of bacteria growth in narrow grooves led to a mathematic description of the persistence switch (369).

Other Cell Assays and Research Tools. Mangenot et al. presented a fluorescence microscopy study to investigate the dynamics of DNA ejection from single T5 phages adsorbed onto a microfluidic cell (370). The mobility of six species of marine protozoa through narrow channels was investigated by Wang et al. (371). Cell adhesion and cell mechanics for varying shear forces was studied by Lu et al. (372). The motion of *E. coli* cells and their preference to swim on the right-hand side of a microfluidic channel was observed by DiLuzio et al. (373).

PC12 cells positioned on 5- μ m apertures were stimulated in an “artificial synapse chip” by Peterman et al. In these experiments, minute quantities of a bradykinin solution were delivered to the cells via the apertures and the cell response was observed using a Ca^{2+} -sensitive dye (374). Substrates with apertures of subcellular size were fabricated and tested by Matthews and Judy for patch-clamp experiments (375).

The release of nitric oxide from macrophage-like cells stimulated by lipopolysaccharide was monitored in a glass microchip by Goto et al. using thermal lens microscopy (376). Nitric oxide released from bovine pulmonary artery endothelial cells (pPAEC), upon stimulation with adenosine triphosphate, was determined by amperometric detection by Spence et al. (377). Secretion of insulin from single islets of Langerhans was determined by

Shackman et al., while perfusing with different concentration of glucose (378). To detect allergic response, Matsubara et al. cultured rat basophilic leukaemia cells (RBL-2H3) on a microfluidic chip and introduced a stimulating antigen (379). A microbiology assay for antiallergic drug screening by detection of histamine released from mast cells was developed by Tokuyama et al. (380).

Khine et al. presented a polymeric chip to selectively immobilize and electroporate single cells, which was proven by recording the escape of a cytoplasmic dye and by the entrance of Trypan blue, respectively (381). On-chip transformation of bacteria was accomplished by Nagamine et al. Plasmid DNA was first immobilized in microcompartments and then introduced into bacterial cells. Gene expression was monitored in the phenotypes of bacteria using fluorescence spectroscopy and scanning electrochemical microscopy (382). Mammalian cells were transfected in a simple PDMS chip with plasmid DNA encoding enhanced green fluorescent protein by Shin et al. (383). The electroporation of vesicles was also presented (384).

Abkarian et al. proposed a technique to measure dynamical pressure drop variations along a micrometer-sized channels, which they used to determine the mechanical properties of cell membranes (here white and red blood cells) (385). A genotoxic bioassay based on a bioluminescence reporter system was presented by Maehana et al. They fabricated a 3D channel network, where cells were supplied through a channel and immobilized in silicon microwells, while genotoxic substances were fed into another channel (386).

Several studies included the exposure of concentration gradients to biological cells. Jeon and co-workers studied chemotaxis in dependence of chemotactic factors (interleukin 8, IL-8), by generating a stable IL-8 gradient in a microfluidic mixing device that was exposed to neutrophils (387). The same group applied the device further to breast cancer cell chemotaxis, effected by a gradient of epidermal growth factor (388), and to study neural stem cell growth and differentiation in dependence of growth factor concentration (389). Chemotaxis of HL60 promyelocytic leukemia cells, in various gradients of chemokine CXCL8, was studied in a similar device by Walker et al. (390).

Pihl et al. described a gradient-generating device that produced a concentration gradient spanning nearly 5 orders of magnitude starting from a single concentration. It was applied for pharmacological profiling of voltage-gated K⁺ channels and ligand-gated GABA_A effectors (391). Dynamic gene expression profiling was demonstrated in a similar gradient-producing device by Thompson et al. In these experiments, reporter cells (HeLa S3 cells) were stimulated, each containing a green fluorescence reporter plasmid for the gene of interest (here NF- κ B) (392). The cells were exposed to varying doses of the inflammatory cytokine TNF- α and cellular response (i.e., fluorescence intensity) was continuously monitored. Such devices were also used to study cell behavior dependent on the mechanical compliance of the substrates. Zaari et al. demonstrated this by photopolymerization of a hydrogel precursor solution with a defined gradient in the cross-linker concentration (393).

Lucchetta et al. exposed a *Drosophila* embryo to a temperature step created by separately heating one laminar stream of flow and cooling the other. They found a normal development of embryos due to compensation reactions that can counteract the effects of

the unnatural conditions of the temperature step (394).

Biomimetic and Biopowered Systems. Biomimetic Systems.

Runyon et al. developed a system that mimicked hemostasis, i.e., the process to repair damaged blood vessels and, thus, prevent excessive bleeding. They chose an inorganic reaction mixture that formed localized clots when the microchannel was punctured (395). A cell culture analogue system, which provided an in vitro supplement to animal studies, was designed and fabricated by Sin et al. It consisted of three chambers mimicking lung, liver, and other cells (396) and was later expanded to a four-chamber system ("lung, liver, fat, other cells") (397). Tan and Desai combined surface engineering with layer-by-layer microfluidics technology to create 3D tissue-like structures, e.g., blood vessels (398, 399). Ma et al. utilized an ultrathin nanofabricated silicon nitride membrane, where endothelial and astrocyte cells were cocultured on opposite sides of the membrane. This approach could potentially be useful as a model for the blood–brain barrier (400).

Inspired by the behavior of swimming animals and flying insects, Atencia and Beebe designed a micropump that used vortexes shed by an oscillating ferromagnetic bar (401). Chang et al. developed a method for separating cells by mimicking the physiological process of leukocyte recruitment to blood vessel walls, i.e., adhesive cell rolling and transient tethering. These interactions of cells were reproduced on surfaces in microfluidic channels, and two cell types (HL-60 and U-937) were partially fractionated (402).

Cell-like compartments were prepared and utilized. Karlsson et al. presented the controlled initiation of an enzymatic reaction, which yields a fluorescent product in biomimetic compartments, i.e., in nanotube-connected lipid vesicles (403). The use of lipid vesicles as artificial cells was also proposed by Wagler et al. (404), and the formation on a microfluidic chip was realized in the shear flow of a crossed channel (405) and by extrusion through microsized holes (406).

Dittrich et al. realized cell-free protein expression in water-in-oil droplets. The concentration of the expressed protein—the green fluorescent protein—was determined by fluorescence spectroscopy (407).

Biopowered Systems. The implementation of molecular motors or biological systems to power microfluidic devices was demonstrated for various examples. Clemmens et al. described the use of complex track networks, utilizing kinesin motor proteins, to actively transport microtubule shuttles along micropatterned surfaces (408). A similar demonstration was given later by Lin et al. (409). Roos et al. achieved motor-driven microtubule gliding on top of microfabricated pillar arrays with limited and controllable surface interactions. Kinesins immobilized on pillar heads pushed microtubules from the top of one micropillar to the next bridging up to 20- μ m-deep gaps filled with buffer solution (410).

The capability of microorganisms (here algal cells) to move microparticles of a few micrometers was demonstrated by Weibel et al. (411). Xi et al. proposed the use of muscle cells to assemble muscle-powered microdevices (412). Cultured cardiomyocytes to drive polymer micropillars (413) and pumps (414) were presented by Tanaka et al. The intrinsic pulsatile mechanical functions of neonatal rat cardiomyocytes cultured on a microchip were utilized to convert chemical into mechanical energy.

Clinical Diagnosis. Blood Cell Separation and Blood Analysis.

Lipid particles were separated from erythrocytes in whole blood with an efficiency close to 100% by applying acoustic standing wave forces (415). In a simple network of rectangular microchannels, Shevkoplyas et al. demonstrated the separation of leukocytes from whole blood. A single pass through the device produced a 34-fold increase of the leukocyte-to-erythrocyte ratio (416). Leukocyte separation from whole blood, in a microfluidic device with an array of magnetic stripes, can also be achieved by selectively tagging the leukocytes with magnetic particles (417). The diamagnetic capture of red and white blood cells in a magnetophoretic microseparator was presented by Han and Frazier (418), and the dielectrophoretic separation was shown by Borgatti et al. (419). Sethu et al. isolated leukocytes by lysis of erythrocytes, using $\text{NH}_4\text{-Cl}$ buffer, to which the whole blood was exposed for a short time (40 s), while $\sim 100\%$ of the leukocytes were recovered (420). They also developed a continuous-flow diffusive filter for depletion of leukocytes (421). Panaro et al. presented a microfluidic platform with micropillars to separate white blood cells from whole blood and to perform subsequent PCR of a genomic target (422). Crowley and Pizziconi isolated plasma from whole blood using planar microfilters (423). Lancaster et al. designed a plastic microfluidic chip in credit card size for antibody labeling and counting of white blood cells (424). Furdulj and Harrison presented an immunomagnetic separation technique for the isolation of specific cells from blood samples (425).

Kamada et al. characterized the relationship between coagulation activation and capillary occlusion using a microchannel flow analyzer, which can evaluate microthrombus formation in whole blood as a function of blood flow rate (426). The determination of lithium directly from whole blood was described by Vrouwe et al. (427). Srivastava et al. developed a self-calibrating nanoliter viscosimeter and tested blood plasma samples collected from patients with the symptoms of hyperviscosity syndrome to an accuracy of 3% (428). Quantitative analyses of high-density lipoprotein cholesterol (HDL-C) and total cholesterol (total-C), in a submicroliter plasma sample, were performed by Kim et al. using enzymatic reactions to produce a colorimetric signal (429). Callewaert et al. profiled the major N-glycans in human serum by microchip electrophoresis (430). Kurita et al. measured the lactate concentration in blood samples (of a dog) in a microchip consisting of gold film electrodes for detection in a microchannel that is separated from the injection channel by a microdialysis membrane (431).

Detection of Pathogens. Zaytseva et al. developed a microfluidic biosensor for detection of Dengue virus RNA. The biosensor employs a magnetic bead-based sandwich hybridization system in conjugation with liposome amplification for the specific detection of nucleic acids (432). The determination of severe acute respiratory syndrome coronavirus (SARS-CoV) was presented by Zhou et al. They performed reverse transcription-PCR (RT-PCR) and electrophoresis on a microchip, which was found to be faster and with a higher positive rate than conventional RT-PCR and agarose gel electrophoresis (433). Wang and Lee designed a diagnostic chip with micropneumatic valves and peristaltic micropneumatic pumps and tested the performance by detecting two diseases, hepatitis C virus and syphilis, using an ELISA-like assay (434). Pal et al. integrated fluidic and thermal components on a

compact microchip for the identification of influenza viral strains and further genetic analyses (435). Real-time nucleic acid sequence-based amplification (NASBA) for detection of artificial human papilloma virus 16 sequences, i.e., a prerequisite for the development of cervical cancer, was performed with a sensitivity limit of $10^{-6} \mu\text{M}$ by Gulliksen et al. (436).

Others. Multilayer soft lithography was used by Cellar et al. to fabricate a chip that allowed for in vivo sampling of amino acid neurotransmitters by low-flow push-pull perfusion. For in vivo measurements, push-pull probes were implanted in the striatum of anesthetized rats and amino acid concentrations were monitored (437, 438).

A simple linear microchannel was used by Horsman et al. to separate sperm and epithelial cells, which is potentially useful for forensic analysis of sexual assault evidence. On the microchip, epithelial cells settled and subsequently adhered to the bottom of the inlet reservoir, while sperm cells flowed through the microchannel toward the outlet reservoir (439). A prototype microsystem for detecting botulinum neurotoxin from whole blood was designed by Moorthy et al. For detection of the toxoid, biotinylated antibodies were immobilized on streptavidin-functionalized agarose gel beads that are introduced into the device (440). The determination of urinary human serum albumin was reported by Hofmann et al. As a step toward a fully disposable stand-alone diagnostic chip, they used an integrated thin-film organic light-emitting diode as an excitation source (441).

Immunoassays. Sia et al. described an immunoassay to distinguish HIV-1 infected from noninfected patients with the emphasis on developing a portable, cost-effective, and easy-to-use diagnosis microchip (442). Herr et al. performed electrophoresis-based immunoassays for detection of tetanus antibodies in buffer and diluted serum samples. In these experiments, photopolymerized cross-linked polyacrylamide gels were integrated within a microfluidic channel (443). By performing a bead-based immunoreaction, electrophoresis, and a chemoluminescence reaction, Tsukagoshi et al. determined human serum albumin or immunorepressive acidic protein as a cancer marker in human serum (444).

Gao et al. accomplished multiantigen immobilization (different dilutions of *E. coli* lysate antigen) by using a microfluidic network. In the second step, an H-shaped microchannel system was put onto the immobilized antigens and the electrokinetically controlled immunoassay was performed (445). The detection of C-reactive protein and other cardiac markers by a micromosaic immunoassay in microfluidic networks was presented by Wolf et al. (446). Sato et al. used a dam-structured microchannel for a bead-based immunoassay. The immunoreaction to determine interferon- γ was monitored applying thermal lens detection (447). A miniaturized immunoassay system based on real-time detection of soluble molecules binding to receptor-bearing microspheres, sequestered in affinity column format, was described by Piyasena et al. (448). A capture method of polystyrene beads coated with mouse anti-FK506 was used by Murakami et al. for detection of tacrolimus, which is an immunosuppressant for preventing allograft rejection (449). For the detection of cytokine tumor necrosis factor α with picomolar sensitivity, Cesaro-Tadic et al. designed a microfluidic platform comprising a number of independent capillary systems, each of which is composed of a filling port, an appended

microchannel, and a capillary pump. Flow control was established by collective control of the evaporation in all capillaries by heating and cooling using Peltier elements (450). Kim and Park described an immunoassay utilizing binding of superparamagnetic nanoparticles to beads that was applied for the detection of rabbit IgG and mouse IgG (451). Millen et al. microfabricated giant magnetoresistors and quantified the immunological interaction between surface-bound mouse IgG and α -mouse IgG coated on superparamagnetic properties (452). Liu et al. designed a microfluidic device with integrated filters for the bead-based detection of viruses (453). The detection of human G-CSF and GM-CSF antigens on a single chip with a resistive-pulse sensor was demonstrated by Carbonaro and Sohn. They measured the decrease in current when functionalized colloids passed a pore with a diameter comparable to that of the colloid (454). ELISA on a rotating disk was demonstrated by Lai et al. for the analysis of rat IgG from hybridoma culture (455). Cho et al. implemented a conventional immunostrip into a plastic chip to detect cardiac troponin I, a specific marker of acute myocardial infarction (456).

The rapid determination of antibody–antigen binding parameters was achieved by total internal reflectance microscopy in a microchip with 20 parallel channels containing planar supported cholesterol/lipid bilayers (457). Surface plasmon resonance imaging was applied to observe the interactions of unlabeled antibodies with antigens that were adsorbed on surfaces patterned with gold (458).

DNA. DNA Analysis. Austin and co-workers developed several techniques for DNA analysis in nanochannels: Riehn et al. were able to measure the positions of restriction sites with a precision of 1.5 kbp within 1 min using single DNA molecules (459). Single-molecule studies of repressor proteins bound to bacteriophage λ DNA containing a 256 tandem *lac* operator insertion confined in nanochannels was conducted by Wang et al. They developed an integrated photon molecular counting method to determine the number of proteins bound to DNA (460). Tegenfeldt et al. determined the contour length of single DNA molecules confined in 100-nm channel arrays (461).

Nanocapillaries, with cross section down to 150×180 nm, were used to study the electrophoretic behavior of single, fluorescently labeled molecules of DNA as a function of capillary size, controlled with voltage manipulation by Campbell et al. (462). Electromigration of biopolymers through a crystalline array of 300-nm silica colloids was demonstrated by Zhang and Wirth (463).

DNA hybridization assays in sequence based on recording the kinetics of hybridization on a microfluidic device with a size of only 10×5 mm was reported by Heule and Manz (464). A microarray, in which the sample/reagent volume was reduced to $1 \mu\text{L}$ and the hybridization time to 500 s compared to a conventional system, called shuttle hybridization, was described by Wei et al. (465). Dodge et al. presented a thin-film heater integrated in a device for studies of DNA hybridization kinetics and double-stranded DNA melting temperature measurements (466). The functionalization of a microchannel with two types of magnetic beads using hydrodynamic focusing combined with a passive magnetic separator with arrays of soft magnetic elements was described by Smistrup et al. It was shown that two sets of beads carrying different probes selectively recognized a single base pair mismatch in target DNA (467). Erickson et al. described

and implemented an electrokinetic approach for single-nucleotide polymorphism discrimination using a PDMS/glass-based microfluidic chip (468). An integrated method of enzymatic digestion, heteroduplex analysis, and electrophoretic sizing on a microfluidic chip was described by Footz et al. to determine the presence or absence of the most important mutations associated with hemochromatosis (469). A method that was capable of quantitative detection of low-abundance DNA/RNA molecules by incorporating confocal fluorescence spectroscopy, molecular beacons, and a molecular-confinement microfluidic reactor was presented by Wang et al. (470). Direct linear analysis, a rapid molecular mapping technology, based on the analysis of individual DNA molecules bound with sequence-specific fluorescent tags was developed by Chan et al. (471).

A study to extract, prepare, and compare human mitochondrial DNA sequences and to assess the degree of heteroplasmy in a sample in ~ 45 min was conducted by Taylor et al. (472). Fluorescence detection of an unlabeled target sequence was shown by Zangmeister and Tarlov, achieved through the development of a DNA displacement assay using two plugs of a hydrogel/DNA copolymer formed in a single-channel device (473). Zheng et al. demonstrated the manipulation of single DNA molecules by lateral focusing to detect target DNA molecules using evanescent field excitation (474).

Hashimoto et al. fabricated a PC chip for performing an allele-specific ligation detection reaction (LDR), and another chip made of PMMA was designed for the detection of the LDR products (475). Guan and Lee developed a method to produce highly ordered arrays of DNA nanostrands with well-defined length, orientation, and precise position over a millimeter-scale area (476).

Sequencing. A heterogeneous assay, combining active plumbing, specific surface chemistry, and parallelism, namely, a system for DNA sequencing-by-synthesis to reliably sequence up to four consecutive base pairs was developed by Kartalov and Quake (477). Russom et al. explored DNA pyrosequencing by trapping the DNA on microbeads in an on-chip filter chamber and monitoring flow-through of the reagents concurrently (478). Doherty et al. developed sparsely cross-linked “nanogels”, sub-colloidal polymer structures composed of covalently linked, linear polyacrylamide chains, as replaceable DNA sequencing matrixes for capillary and microchip electrophoresis (479).

Separation. Tabuchi et al. reported improved separation of DNA via electrophoresis using polymer solution doped with PEGylated-latex nanoparticles with sizes of 80, 110, and 193 nm (480). Buch et al. reported an integrated 2D DNA separation platform, combining standard gel electrophoresis with temperature gradient gel electrophoresis (481). Yamashita et al. confirmed that separation of biomolecule complexes, formed at the interface of a microchannel, occurred as a result of specific molecular localization in the curving part of the microchannel. The method was used for sequence-selective DNA sensing (482). A nanofabrication technique for constructing a nanopillar structure as a DNA sieving matrix on a quartz plate was reported by Kaji et al. (483). A high-density 384-lane capillary array electrophoresis device was evaluated by Tian et al. for high-throughput single-strand conformation polymorphism analysis (484). Kim and Kang presented a strategy for high-sensitivity DNA fragment analysis allowing for a DNA on-channel concentration subjected to base stacking (485).

Lao and Hsing used a electrical field flow fractionation device with a segmented electrode operated under a pulsed voltage for DNA separation (486).

Polymerase Chain Reaction. Lagally et al. presented a portable genetic analysis system where PCR amplification with capillary electrophoresis separation and detection were fully integrated. The reactor volume was as small as 200 nL, and the thermal cycling times of 30 cycles in 20 min was demonstrated in a contact PCR–CE device (487). An electrokinetically driven synchronized continuous-flow PCR that utilized sample volume of 0.5 μ L within a single-loop channel was developed by Chen et al. (488). A pneumatically driven, disposable, inexpensive microfluidic cassette for nucleic acid amplification and integrated detection was introduced by Wang et al. It has hydrogel valves, which were electrically controlled by thermoelectric units (489). A submicroliter-volume PCR chip with a fast thermal response and very low power consumption was developed by Lee et al. for amplifying a human cancer tumor-suppressing DNA sequence (490). A method for the electrochemical detection of the PCR products, based on the catalytic oxidation of dsDNA in a solution phase using a poly-TTCA modified screen-printed carbon electrode was described by Shiddiky et al. (491). Wang et al. studied a droplet-based microoscillating-flow PCR chip, whereby a single-droplet PCR mixture was injected and flowed through the three temperature zones in the main microchannel, in an oscillating manner, to achieve the temperature maintenance and transitions (492).

There were a couple of works carried out where the emphasis was laid on real-time PCR detection. For instance, a system for the rapid detection of bacterial pathogens was developed by Cady et al. The structures allowed for nucleic acids to be selectively bound, washed, and eluted for subsequent real-time PCR (493). An isothermal method with an optical detection called the real-time NASBA was designed for amplification of RNA. Successful identification was performed utilizing oligonucleotides at a concentration of 1.0 and 0.1 μ M, in 10- and 50-nL reaction chambers, respectively, by Gulliksen et al. (494).

A RT-PCR chip was presented by Liao et al. whose system contained the heating and sensing elements made of platinum, located within the reaction chambers, to generate a rapid and uniform thermal cycling (495). Marcus et al. also developed a chip to perform 72 parallel 450-pL RT-PCRs (496). A novel circular heating arrangement and rotary fluid channel layout with integrated Pt thin-film heaters and thermometers, with the chip size 17 \times 40 mm that can achieve 25 cycles in 35 min with flow rate 3 μ L/min, was successfully developed by Jia et al. (497). A circular chip with a circular ITO heater of an equivalent diameter was clamped in contact to demonstrate the temperature cycling capabilities by Cheng et al. (498). Another device that utilized ITO was presented by Fukuba et al. where six heaters were made from ITO and placed on a glass substrate to define three uniform temperature zones for flow-through PCR (499). Hashimoto et al. designed a continuous-flow PCR device to evaluate the thermal and biochemical effects of high flow velocities in a spiral, 20-cycle device using finite element analysis (500).

Proteins. Skelley et al. developed and evaluated a microfabricated capillary electrophoresis instrument for sensitive amino acid biomarker analysis on Mars that consisted of a four-wafer sandwich combining glass CE separation channels, microfabri-

cated pneumatic membrane valves, pumps, and a nanoliter fluidic network (501). The use of microfabricated fluidics technology under reduced gravity and hypergravity conditions for analytical processes in space and planetary environments, in particular electrophoretic separation of amino acids, was also tested by Culbertson et al. (502).

Mao et al. miniaturized lectin affinity chromatography into a microfluidic format that resulted in improvement of performance in separation of all the glycoproteins into several fractions, with different affinities toward the immobilized *Pisum sativum* agglutinin (503). A device that separated and focused charged proteins, a binary mixture of bovine serum albumin, and phycoerythrin, based on electric field gradient focusing was devised by Petsev et al. Separation was achieved by setting a constant electroosmotic flow velocity against step changes in electrophoretic velocity (504). SDS gel electrophoresis was utilized on-chip by Herr and Singh for its sieving gel composition to quantify the migration properties of fluorescently labeled protein standards (505). Migration of fluorescence-labeled amino acids and proteins with a wide range of pI values and molecular weights using the dynamic coating of the PMMA microchip was reported by Kato et al. (506). A biosensor based on an array of hydrogel-entrapped enzymes that can be used to simultaneously detect different concentrations of the same analyte (glucose) or multiple analytes (glucose and galactose) in real time was described by Heo and Crooks (507).

A demonstration of a device for rapidly generating complex mixtures of 32 stock reagents in a 5-nL reactor on a so-called “formulation chip” was given by Hansen et al. The device was fully automated and allowed thousands of experiments to be performed in a single day with minimal reagent consumption (508). A planar lipid bilayer was reconstituted by utilizing a microfluidic system, in a manner that was suitable for automated processing by Suzuki et al. (509). A centrifugal microfluidic platform that was useful in the performance of homogeneous, protein-based assays using fluorescence detection and multiple parallel analyses was established by Puckett et al., showing the ability to dry biological reagents and later reconstitute them on the platform without inhibiting the performance of the assay (510). Miao et al. demonstrated single-step fusion-based affinity purification of proteins with pH-controllable linkers, using a rotating CD format fluidic chip, where scale-down factors of 185 resulted in separations in a 27- μ L bed volume (511). The use of grafted trypsin magnetic beads that acted as a low-hydrodynamic resistance plug in a microchip for performing protein digestion was reported by Slovakova et al., which showed a 100-fold increase in digestion speed (512). Chen et al. analyzed the effect of mixing on nucleation of protein crystals, where the system was capable of setting up hundreds of crystallization experiments in a short period of time, requiring little labor and \sim 1- μ L samples of protein solutions (513). Zheng et al. reported a system for performing protein crystallization trials in nanoliter aqueous droplets inside capillaries, suitable for X-ray diffraction and the evaluation of the quality of the crystals directly by on-chip X-ray diffraction (514).

Other Bioassays. Kinetic studies of biochemical reactions were conducted. Gleason and Carbeck presented a technique for microscale steady-state kinetic analysis by immobilization of enzymes on the surface of the microfluidic channel (515). Dittrich

et al. studied the enzymatic cleavage of stained double-stranded DNA by analyzing the reduction of fluorescence resonance energy transfer (FRET) during the reaction. Simultaneously, the flow velocity was determined by cross-correlation analysis (516). Hertzog et al. studied fast protein folding kinetics using FRET with acyl-CoA binding protein. They found a mixing time of 8 μ s for the used micromixer (517). A micromixer for investigation of protein folding reactions was further described by Bilsel et al. (518). The kinetic of an irreversible conversion of a fluorescent protein (KAEDE) was determined by Dittrich et al. The photo-induced reaction that resulted in a color shift of the protein's fluorescence from green to red was observed on a single-molecule level (519).

A continuous-flow microfluidic assay for the screening of mixtures was described by de Boer et al. The chip featured two microreactors, in which an enzyme inhibition and a substrate conversion reaction were performed, and was coupled with capillary liquid chromatography and mass spectrometry (520). To perform peptide mapping, Wu et al. characterized a microfluidic enzymatic reactor coupled to MALDI-TOF and ESI-MS (521). Zheng and Ismagilov demonstrated screening of submicroliter volumes with a substrate (e.g., fluorescein diphosphate) against multiple enzymes using preformed arrays of nanoliter plugs in a three-phase (liquid-liquid-gas) plug flow (522).

Environmental Concerns and Gas Analysis. *Environmental Concerns.* Wang et al. described a protocol for the CE separation and electrochemical detection of thiol-containing degradation products that offered <4-min simultaneous detection of micromolar concentrations of several V-type nerve agents (523). The concentration of levoglucosan in smoke particles was analyzed, and separation from other carbohydrates (glucose and galactosan) was achieved by Garcia et al. The measurements were clearly faster than utilizing GC/MS (1 vs 54 min) (524). A lead sensor within a two-layer microchip was developed by Chang et al. It was based on the cleavage of fluorescently labeled DNA by a lead-specific enzyme (525).

Fujii et al. conducted a study on the simultaneous determination of sulfite and nitrite in environmental water samples using a fluorescence detection unit (526). The chemiluminescent detection of copper in water samples, based on the measurement of light emitted from the Cu(II)-catalyzed oxidation of 1,10-phenanthroline by hydrogen peroxide, was reported by Tyrrell et al. (527). A field-portable water chemistry testing device by discharge spectroscopy that integrated electrical and optical features was presented by Que et al. (528). A system for the luminol chemiluminescence reaction was described by Marle and Greenway, which was used to determine hydrogen peroxide in rainwater (529).

Gas Analysis. Lu et al. studied quantitative analysis of a mixture of organic vapors by a gas chromatograph employing preconcentration, separation, and sensor array detection components (530). A micro gas analysis system, where a gas-permeable membrane fabricated on a shallow channel to allow for the efficient accumulation of the analyte into the absorbing solution, was proposed by Toda et al. for the continuous and highly sensitive on-site measurement of atmospheric trace gases (531). Wootton and de Mello reported a procedure for the continuous purification of volatile liquids (532). NMR was used to obtain spatially and

temporally resolved profiles of gas flow in devices (533). Naji and Manz introduced the use of simple on-chip and capillary-based dc plasmas as gas sample injectors (534). The gas selectivities of highly ordered mesoporous silicates and commercially obtained porous silicates were studied by Ueno et al. (535). A honeycomb structure scrubber was developed to achieve efficient and stable gas collection (536). The mixing of two gases directly by measuring the concentration of the gases at the outlet of the mixer, only 300–800 μ m long, was investigated by Haas-Santo et al. (537). A gas sampler for a miniaturized ambient ammonia detector was described by Timmer et al. (538).

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