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Review

Integrated microfluidic devices

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Abstract

"With the fundamentals of microscale flow and species transport well developed, the recent trend in microfluidics has been to work towards the development of integrated devices which incorporate multiple fluidic, electronic and mechanical components or chemical processes onto a single chip sized substrate. Along with this has been a major push towards portability and therefore a decreased reliance on external infrastructure (such as detection sensors, heaters or voltage sources)." In this review we provide an in-depth look at the "state-of-the-art" in integrated microfludic devices for a broad range of application areas from on-chip DNA analysis, immunoassays and cytometry to advances in integrated detection technologies for and miniaturized fuel processing devices. In each area a few representative devices are examined with the intent of introducing the operating procedure, construction materials and manufacturing technique, as well as any unique and interesting features.

Keywords: Integrated microfluidic devices; Lab-on-a-chip; Miniaturized total analysis system; Biochips

1. Introduction

Modern microfluidics [1] can be traced back to the development of a silicon chip based gas chromatograph at Stanford University [2] and the ink-jet printer at IBM [3,4]. Though both these devices were quite remarkable, the concept of the integrated microfluidic device (which often fall under the broad categories of labs-on-a-chip or miniaturized total analysis systems) as it is known today was not developed until the early 1990s by Manz et al. [5]. Since that time the field has blossomed and branched off into many different areas, for which a number of excellent general reviews are available (e.g. biological and chemical analysis [6–8], point-of-care testing [9], clinical and forensic analysis [10], molecular diagnostics [11] and medical diagnostics [12]).

An integrated microfluidic device incorporates many of the necessary components and functionality of a typical room-sized laboratory on to a small chip. An example is presented in Fig. 1, which shows a device with on-chip temperature control and gradient generation for use with heterogeneous DNA hybridization assays [13]. Originally it was thought that the most significant benefit of these lab-on-a-chip devices would be the analytical improvements associated with the scaling down of the size [5]. Further development revealed other significant advantages including: minimized consumption of reagents, increased automation, and reduced manufacturing costs [14]. The latter of these has been perhaps the most important advancement as the field drifts from the relatively complex silicon and glass based micromachining originally developed in the electronics industry, to much simpler techniques and other materials [15–18]. As these manufacturing technologies are further and further advanced (both in terms of the potential complexity of an integrated device and the ease with which a simple prototype can be made) in parallel with analytical needs, the development of future integrated devices will inevitably be less expensive and faster than ever before.

In this work we review the "state-of-the-art" in integrated microfluidic technology from the beginning of the year 2000 to present (for earlier microfluidic devices or historical details, readers are referred to the comprehensive set of reviews written by Reyes et al. [19] and Auroux et al. [20]). For the most part we will focus on application-based devices and prototypes (as opposed to works which simply demonstrate an integrated technology or platform) for which significant details on the operation and construction of the device are available in journal publications (as opposed to overviews in conference abstracts). These devices are grouped by specific application areas.

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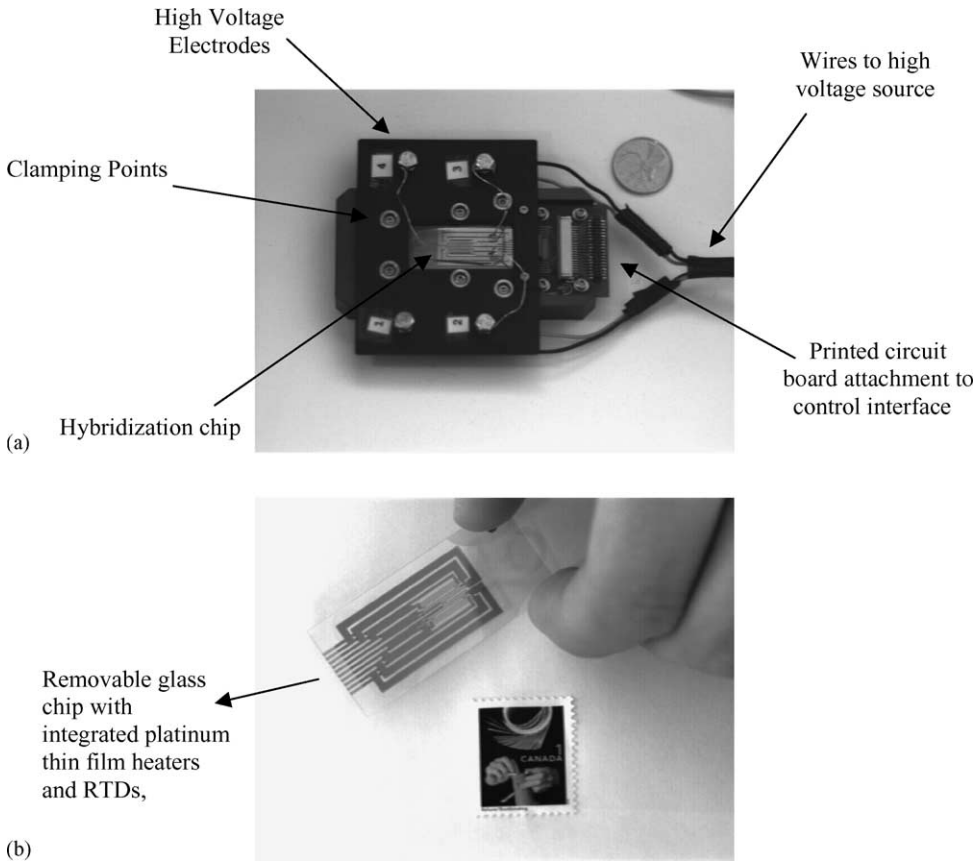


Fig. 1. Integrated microfluidic device with precise on-chip temperature control and gradient generation for use with heterogeneous DNA hybridization assays [13]. The device consists of a thin glass carrier with multiple integrated thin film heaters and resistance temperature devices (b) which is reversibly sealed to a poly(dimethylsiloxane) (PDMS) cover containing the microfluidic channel structure. The chip packaging (a) integrates high voltage electrodes for electrokinetic species transport and a printed circuit board interface for heater control and temperature measurement.

2. Integrated microfluidic devices for DNA analysis

Driven largely by huge potential markets and thanks in no small part to the Human Genome Project, of all the areas into which microfluidics has been introduced, the general field of DNA analysis has produced the most highly integrated procedure chips [21]. Some of the first devices concentrated on rapid and low power polymerase chain reaction (PCR) through either a continuous flow procedure (for example, the three temperature zone flow through device presented by Martin et al. [22]) or batch (such as the silicon microchambers of Daniel et al. [23]). Around the same time others began to look at integrating several stages of the analysis. Examples include Wilding et al. [24] who presented a device that combines the PCR with cell isolation, Burns et al. [25] who introduced a number of microfabricated structures for DNA analysis, and others who began the early work in combining PCR with capillary electrophoresis (CE) [26,27]. In this section we examine many of the recent advancements in on-chip PCR and DNA analysis.

2.1. Polymerase chain reaction (PCR)

PCR typically constitutes a key stage in a complete DNA analysis. There are several PCR based microfluidic devices which have been recently introduced. Liu et al. [28] presented a rotary microfluidic chip for rapid PCR cycling, constructed using a multi-layer poly(dimethylsiloxane) (PDMS) elastomer with control channels (to actuate peristaltic pumping and control valves) in the upper layer, fluidic channels in the middle layer and a bottom glass slide layer which carried the integrated heaters (deposited via a sputtering technique). The Temperature control was accomplished by calibrating current load on the heaters with direct measurements of the in-channel solution temperature using thermochromatic liquid crystals. The device could be operated in a time-domain cycling mode (in which the entire chip was heated and cooled), and a spatial-domain mode (in which the solution was pumped in a circulatory fashion between different on-chip temperature zones). The spatial mode was found to be much faster.

West et al. [29] presented an annular continuous flow PCR microreactor which pumped fluid through three temperature

zones using an ac magenetohydrodynamic [30] where a body (Lorenz) force is applied to the fluid continuum through the interaction of the perpendicular electric and magnetic fields. In this device electrodes were embedded in the channel walls (which were machined either through bulk micromachining in silicon or rapid prototyping in thick photoresist) and a magnetic coil was located below the chip. The device was shown to successfully amplify a 142 bp template.

Sun et al. [31] presented a continuous flow PCR device in glass. It consists of a single channel which continuously looped through two regions with integrated indium–tin-oxide heaters to provide the temperature control. Direct measurements of the in-channel temperature profile revealed a very uniform temperature distribution and amplification of a 450 bp segment of *Escherichia coli* HB101 was successfully performed. A novel room temperature bonding technique was also used and is discussed by Sayah et al., [32].

Based on some of their group's previous work [33,34], Yuen et al. [35] developed a microchip device which combined sample preparation, one of the more practically difficult aspects of on-chip DNA analysis, with PCR. Cell isolation was accomplished using a weir type filter, built directly into the silicon base (constructed using standard photolithographic techniques), which served to trap cells between it and the underside of the glass module. The chip was set into another Plexiglas module that contained the heating and cooling elements. In this work the authors also described an interesting microfluidic design process whereby flow patterns and delivery mechanisms are tested in macroscale models.

2.2. Integrated PCR and separation based detection

Lagally et al. [36] presented a highly integrated glass device for performing multiple (eight) PCR and capillary electrophoritic analyses on-chip. The fluidic channels, CE channel and PCR reactor (which comprised the major components of the device) were etched in a glass wafer using a standard HF etching technique. Submicroliter amounts of reactant were pneumatically pumped into the reaction chamber using a unique valve/vent manifold system. Heaters and thermocouples were then taped to the back of the device (except for a specially constructed deep channel version where a thermocouple was inserted directly into the channel through the valve structure). After PCR, the products were injected into the CE separation channel that contained the separation medium (introduced earlier via syringe pump). The device demonstrated very rapid thermal cycling (30 s per three stage cycle) [37] and demonstrated the potential for single template PCR analysis [38].

Khandurina et al. [39] also demonstrated on-chip PCR and CE in a conventional cross microchannel chip by attaching a pair of Peltier type thermoelectric heating/cooling elements over the reactant reservoir, performing cycling at a rate of approximately 1 cycle/min, and separating the products via traditional on-chip CE. A more advanced version incorporated a unique on-chip concentration scheme (fabricated directly into the glass chip) in which a porous glass wall was integrated into the double T injector arrangement which allowed buffer solution to pass, but forced the larger DNA molecules to accumulate in the sample plug.

Rodriquez et al. [40] demonstrated the practical integration of a silicon based μPCR device with a standard glass cross microchannel chip for capillary electrophoresis. The PCR device consisted of a silicon base anodically bonded to a glass top substrate with embedded aluminum heaters and thermocouples. The high thermal conductivity of the silicon allows for very uniform temperature profiles (±0.3 °C) and fast thermal cycling (as low as 16 s/cycle in some cases). More information on the specifics of the reactor design is available in [41]. Pressure driven flow was used to transport the PCR products from the reactor to the coupled (via a PDMS gasket) CE chip. The device was shown to resolve DNA fragments that differed in size by 18 bp, and was used to analyze genomic DNA from chicken and pigeon species.

Also of interest is the PDMS/Glass combined PCR and capillary gel electrophoresis device presented by Hong et al. [42]. Here a reaction well was cycled using a Peltier type heater/cooler (at a rate of about 1 cycle every 2 min) prior to the sample being introduced into the separation channel. Ueda et al. [43] presented a poly(methyl methacrylate) (PMMA) device, manufactured by a LIGA (LIGA being a German acronym for lithography, electroplating and molding, i.e. lithographie, galvanoformung und abformung) process using synchrotron radiation, with an integrated PCR reaction vessel and capillary array electrophoresis system for ultrafast DNA analysis. Several groups, for example McCaman et al. [44] and Sohnia et al. [45], have also made use of the commercially available Agilent 2100 Bioanalyzer chip [46]. The disposable glass chip and associated chip reader allows the automatic separation, quantification and sizing of the DNA fragments. He et al. [47] presented an integrated capillary based device for conducting all steps in a DNA analysis of cheek cells.

2.3. Integrated DNA hybridization

Liu et al. [48] introduced a disposable microfluidic device, fabricated in polycarbonate plastic by CO_2 laser micromachining, which integrated PCR amplification with DNA hybridization onto a "credit card" sized substrate, see Fig. 2. The high temperature required for polycarbonate bonding (139 °C) necessitated that oligonucleotide spotting was done afterwards and thus that section of the device was sealed by an adhesive tape. Species transport in the device was accomplished via an external syringe pump in combination with a series of on-chip Pluronic valves which hardened in place at room temperature and liquefied (such that they could no longer hold pressure) when cooled to 5 °C. Thermal cycling and valve control were accomplished using a series of Peltier thermoelectric devices. The hybridization detection of both

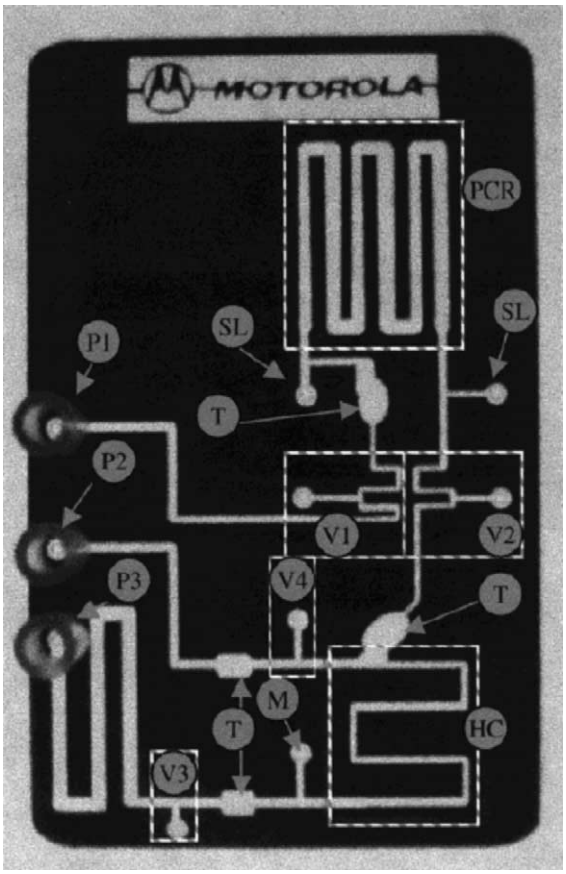


Fig. 2. Monolithic integrated polycarbonate DNA assay device. Serpentine PCR channel (PCR), hybridization channel (HC), Pluronics valves (V1–V4), Pluronic traps (T), hydrophobic air-permeable membrane (M), PCR reagent loading holes (SL), sample driving syringe pump P1, waste-withdrawing syringe pump (P2), and wash syringe pump (P3). Reprinted from [48] with permission.

E. coli and *Enterococcus faecalis* were demonstrated. Details of the sensitivity of the PCR in the polycarbonate microsystem were presented by Yang et al. [49].

Anderson et al. [50] presented a 40 mm × 70 mm highly integrated microfluidic device for automated multi-step genetic analysis. This device was made from polycarbonate using conventional computer machining techniques and was used in the detection of mutations in the HIV genome. The chip was shown capable of extracting and concentrating nucleic acids from aqueous samples, performing chemical amplification, enzymatic reactions, metering and mixing, and hybridization to GeneChip® oligonucleotide microarrays [51]. Species transport was accomplished pneumatically and hydrophobic vents and mylar/silicon valves (also pneumatically actuated) are also integrated into the chip.

Lenigk et al. [52] presented an integrated DNA hybridization biochip consisting of a single polycarbonate channel (etched by CO_2 laser) coupled with a Motorola E-sensor chip [53] which allowed for continuous monitoring of the rate of hybridization at the spotted locations. An oscillation pump was also incorporated into the device to provide some convective mixing of the solution phase targets (which were otherwise stationary) in order to enhance the normally diffusion limited hybridization rate. Also of interest in this work is the detailed numerical modeling of the hybridization reaction on such biochips.

Fan et al. [54] presented a glass microfluidic chip for performing dynamic DNA hybridization (DDH) on paramagnetic beads which were incorporated into the device and held in place via an external magnet. Target samples were introduced into the 8-channel structure pneumatically, and integrated heaters enabled dehybridization to allow for subsequent samples to also be tested. Channels were etched in the device using standard photolithographic procedures and the device was assembled using a modified anodic bonding technique [55].

Lee et al. [56] developed a silicon/glass based microchip which coupled PCR with sequence-specific electrochemical detection. In this device probes were immobilized on electrodes patterned on the glass substrate which was bonded to the 8 μl reaction chamber formed in a silicon substrate. The “on-line”, integrated nature of the device, along with the observed detection limits on the order of a few hundred copies, makes it a promising technology for portable DNA analysis systems. Also of interest from this group is an earlier device that combined PCR with microarrays [57].

2.4. Other devices of interest

Huang et al. [58] presented a unique device which consisted of a series of microchannels with integrated microscale posts, which served as a sieving matrix for continuous flow fractionation of DNA molecules. This was touted as a replacement for pulse-field gel electrophoresis due to orders of magnitude decrease in the running time. Also of interest are other microfabricated devices by this [59] and other groups [60], which further explain this device and describe the entropic trapping method used here for DNA separation.

Bruckner-Lea et al. [61] described the development of an integrated DNA purification and PCR amplification system configured specifically for environmental sample analysis. Tang et al. [62] presented a glass device for demonstrating on-chip cycling probe technology (an isothermal signal amplification technique for specific DNA sequences). Wolfe et al. [63] and Breadmore et al. [64] presented a silica-based solid-phase extraction system suitable for incorporation into a microchip platform that would find utility in a variety of genetic analysis protocols, including DNA sequencing.

3. Devices for separation based detection

As mentioned above, due to the shorter analysis times and potential for more theoretical plates [5], one of the first major applications of modern microfluidics was separation based on electrokinetic processes. An excellent, all encompassing paper covering the fundamentals of capillary

electrophoresis and the progress to that time was written in 1996 by St. Claire [65]. More recently some excellent reviews focusing on microchip based separations have been published [10,66] as well as several papers which take an in-depth view into some areas of particular interest including: sample stacking [67], wall coatings [68], DNA analysis [69], and amperometric detection [70]. In general the mechanisms of on-chip separation and techniques for performing them are reasonably well understood. As such a large amount of current research is directed towards integrating detection mechanisms, or creating chips for highly parallel analysis. Thus the following review will mainly focus on these areas.

3.1. General capillary electrophoresis

Paegel et al. [71,72] presented a microfabricated electrophoretic bioprocessor for DNA sequencing, sample desalting, template removal, preconcentration, and CE analysis. This highly integrated device has been optimized so as to have as many as 384 separate lanes for capillary array electrophoresis on a single chip [73]. The chip incorporated a number of interesting channel features including low dispersion turns [74], and detection was done using a 4 color rotary confocal scanner [75].

Sanders et al. [76] presented a PDMS device with integrated high voltage electrodes for performing on-chip capillary electrophoresis separations. The platinum electrodes were cast directly into the elastomer prior to curing and the sealed chip was formed by reversibly bonding the PDMS to an etched glass plate. The chip was used to separate DNA fragments and performed a molecular diagnostic analysis of a variety of DNA samples for Duschenne Muscular Dystrophy and cytomegalovirus (CMV) infection.

Baldwin et al. [77] developed a glass CE chip, shown in Fig. 3, which fully integrates electrochemical detection and high voltage electrodes and is designed for use with a portable system. The use of microfabrication techniques to integrate permanent electrodes into the chip minimized the number of manual operations required for operation and reduced difficulties associated with variability in electrode placement and geometry. A later article describes a portable power supply for the chip [78].

A number of researchers have recently presented devices that integrate contactless electrodes with a standard CE chip. The non-contact approach allows isolation of the detector from the separation voltages and has several operational advantages including the elimination of bubble formation associated with electrode solution contact. Lichtenberg et al. [79] presented a novel method for integrating electrodes into a glass CE chip. In this device electrodes are separated from the buffer via a 15 μm thick glass wall which provides the necessary isolation. A lumped element circuit model was also developed which accounted for the additional capacitance of the glass walls and double layer. Tanyanyiwa et al. [80] demonstrated contactless conductivity detection through a 1 mm thick substrate. Pumera

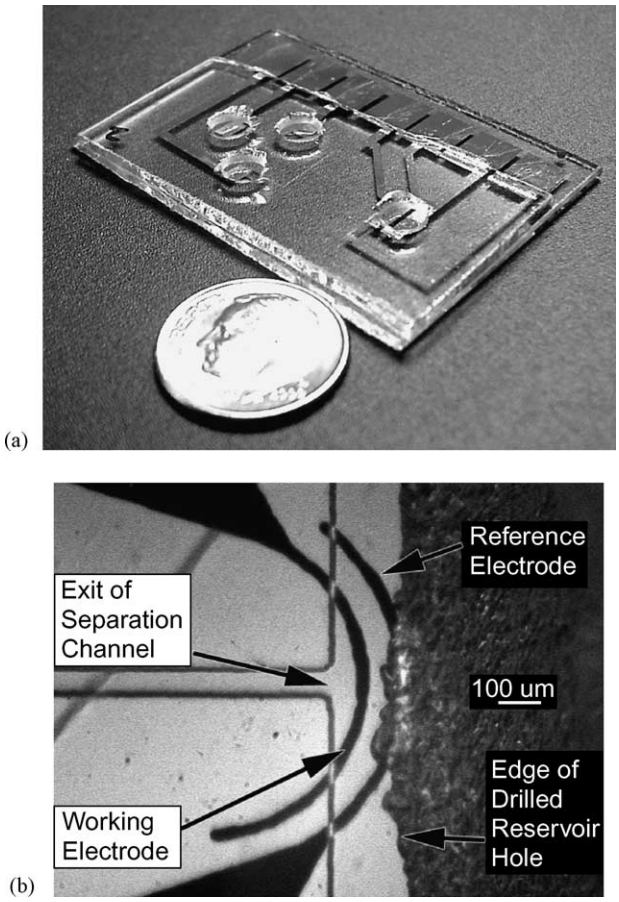


Fig. 3. (a) Photograph of a glass CE/EC microchip with integrated electrochemical detection and high voltage electrodes, designed for use with a portable system. The use of microfabrication techniques to integrate permanent electrodes into the chip minimizes the number of manual operations required for operation and reduces difficulties associated with variability in electrode placement and geometry. (b) Magnified top view of EC detection cell and electrodes. Reprinted from [77] with permission.

et al. [81] also presented a chip with integrated contactless conductivity detection which they used to detect a series of cations and anions at limits as low as 2.8 μM. The PMMA chips were manufactured as per the procedure outlined by Wang et al. [82] and the detection electrodes were constructed from aluminum foil strips embedded in the upper cover plate. Also of interest is an earlier detection system by this group based on thick film technology [83,84] and the amperometric detection of organic peroxides [85].

Guijt et al. [86] presented a glass CE chip with an integrated four electrode contactless detection system. A unique manufacturing technique was developed for this device in that the aluminum electrodes were embedded in a two-stage trench (cut by reactive ion etching) in the Pyrex chip. The first stage of the chip contained an aluminum electrode that was then covered with a silicon nitride layer (or silicon carbide when a dielectric medium was required). The resulting planar surface enabled leak free bonding and eliminated the difficulty associated with bonding glass substrates with electrode interference. Further details on the manufacturing

of this device were presented by Berthold et al. [87]. An earlier version of the chip with an on-chip and on-column galvanic contact conductivity detector was presented by Guijt et al. [88].

Chen et al. [89] introduced a CE device with an integrated palladium film decoupler along with a series of working electrodes for amperometric detection. The decoupler served to prohibit electrolysis of water (which tends to interfere with the electrochemical signal) during CE. A hot wire imprinting technique was used to form the microchannel structure in the plastic substrate. Noise levels on the order of 15 pA were observed when a 570 V/cm electric field was applied.

Martin et al. [90] also presented a PDMS based device with a series of four gold detection electrodes for dual-electrode electrochemical detection. The device consisted of a PDMS substrate reversibly bonded to a bottom glass layer. The chip was shown to be useful for the selective monitoring of species undergoing chemically reversible redox reactions. A carbon based dual-electrode device (also fabricated in PDMS) has also been developed by this group [91]. A similar integrated device [92] was used to monitor mixing reactions in microfluidic devices. Wu et al. [93] developed a PDMS/Glass CE-EC chip with an integrated three electrode electrochemical detector and platinum film decoupler for amperometric detection. Osbourn and Lunte [94] presented a CE chip with an integrated cellulose acetate decoupler. Zeng et al. [95] presented a microchip CE with an integrated electrochemical detection cell.

Also of interest is the CE chip described by Trumbull et al. [96] that is equipped with an integrated planar radio-frequency detector coil for nuclear magnetic resonance spectroscopy. A lift-off process was used to create the 5 mm diameter coil for the glass chip. While separations were accomplished with the device, the NMR detection was only successful for high concentration samples.

3.2. Integrated detectors for laser induced fluorescence

Roulet et al. [97] developed a glass (Pyrex) device with an integrated micro-optical system for laser induced flouresence (LIF) detection. The integrated optical system consisted of arrays of circular or elliptical microlenses (fabricated by a photoresist melting technique [98]) and apertures (which are etched in a 300 nm thick chromium layer on the surface). A unique off-axis illumination scheme, described in detail in ref [99] was used which enables detection performance comparable to that of a standard confocal system.

Webster et al. [100] presented a CE system with integrated optical detection via a series of photodiodes integrated into a silicon substrate. Other unique capabilities were also incorporated into the device including a thin film interference filter, to prevent excitation light from interfering with the fluorescence detection, and an on-chip grounding plate, to prevent the high CE electric field from interfering with the photodiode response. Separation results of DNA fragments revealed femtogram detection limits for the device.

Chabinyc et al. [101] introduced a disposable PDMS based device containing CE channels (fabricated via the rapid prototyping technique developed by this group [102]) and an integrated multimode optical fiber. The channel substrate was then sealed with a thin PDMS layer and separated from the reusable detector device (which consisted of a PDMS embedded avalanche photodiode) by a polymeric filter. Detection levels for fluorescein on the order of 25 nM were observed. Another PDMS based device with integrated hollow wave-guides for adsorption measurements in chip-based electrophoresis was also presented by Splawn and Lytle [103].

Qi et al. [104] presented a PMMA device with two integrated fiber optics (excitation and collection) used for fluorescence detection. A hot embossing fabrication technique using nickel based molding dyes (prepared via a LIGA technique) for obtaining extremely high aspect ratio channels was described along with a method for embedding an optical fiber in a hard plastic. The device was used to perform electrophoretic separations of double stranded DNA ladders using near-IR excitation. Sub-attomole detection limits were observed.

Hubner et al. [105], Petersen et al. [106] and Morgensen et al. [107] also developed devices for fluorescence detection with integrated wave-guides. Here the wave-guides were monolithically integrated into microfluidic system in three layers (buffer, core and cladding) via a plasma enhanced chemical vapor deposition system and permanently connected to the external light source, detection and data processing units. Detection levels on the order of 250 pM to 100 nM were observed for different fluorescent dyes.

3.3. Other detection or separation mechanisms

Galloway et al. [108] developed a PMMA separation device with an integrated conductivity detector used for monitoring separation (via microcapillary electrochromatography) of double stranded DNA fragments. Prior to bonding, the platinum electrodes were manually inserted into the channel matrix and the device was then sealed with a flat sheet of PMMA. The channel walls were fuctionalized to produce a C_{18}-terminated surface to act as the stationary phase in the separation. Ceriotti et al. [109] demonstrated a PDMS microfluidic device with integrated octadecylsilanized silica microspheres with injection elements for performing fritless capillary electrochromatography. The microspheres were introduced via vacuum and the packing was stabilized using a thermal treatment. Oleschuk et al. [110] presented a glass device which integrated two weirs within a sample channel to form a cavity in which octadecylsilane (ODS) coated silica beads (1.5–4 μm diameter) were trapped for electrochromatography. The design allowed for fast exchange of the microspheres. Wang et al. [111] presented a membrane chromatography system which consisted of a capillary molded PDMS slab with embed-

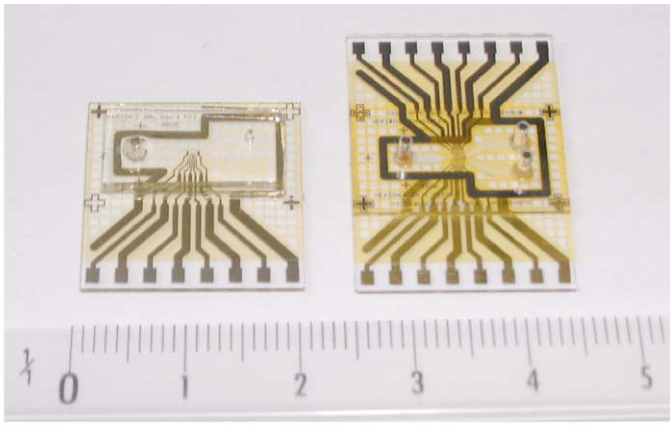
ded PVDF (poly(vinylidene fluoride)) membranes adsorbed with BSA. Prest et al. [112] describes an integrated single working electrode PDMS device for the isotachophoretic separation of metal cations. The electrode was integrated into the chip by placing it between the two polymer layers prior to thermal bonding of the two substrates.

4. Devices for cell handling, sorting and general analysis

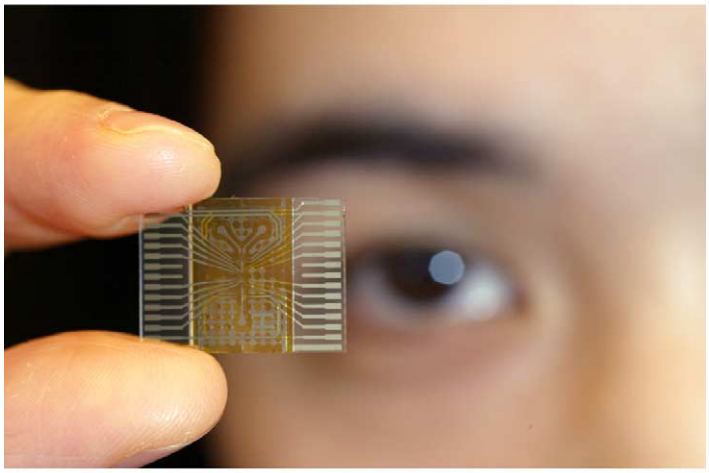
In addition to on-chip DNA analysis and capillary electrophoresis, there has been a large amount of research directed towards the integration of microfluidic technologies with different aspects of cellular analysis [6,20]. Recent reviews have discussed these directions in the context of single cell analysis by capillary electrophoresis [113], drug development [114], tissue engineering [115], sample preparation for molecular diagnostics [11] and biosensors [116]. Here, we review some of the interesting devices with applications in cell handling and microscale flow cytometry, dielectrophoretic sorting, and other general cell analysis techniques.

4.1. Cell handling and cytometry

Gawad et al. [117] presented a microfluidic cytological tool, based on the micro Coulter particle counter principal, for cell counting and separation. The device, shown in Fig. 4, consists of a glass–polymer chip with integrated channels and electrodes and functions by introducing suspended particles into the measurement area, via pressure driven laminar flow, where the spectral impedance of the cell is measured and subsequently used to determine its size. Screening rates on the order of 100 samples/s were reported. An interesting study on the effectiveness of different electrode arrangements, based on FEM simulations, and details of the signal conditioning technique were also presented in this work.



(a)



(b)

Fig. 4. (a) Microfluidic cytological tool, for cell counting and separation, consiting of an integrated microfabricated chip with a PDMS cover and molded fluidic connections. Chip-on-chip configuration designed with two outlets, top and bottom electrodes and an experimental sorting chamber. The two chips are assembled by pressure contact during a final 300 °C cure under N_2. A grid design was used to allow the evacuation of the evaporated solvent. (b) Latest design iteration of chip. (a) Reproduced from [117] by permission of the Royal Society of Chemistry, and (b) courtesy of S. Gawad.

The basics of the microchannel impedance spectroscopy technique was presented by Ayliffe et al. [118].

Fu et al. [119] presented an integrated cell sorter, constructed via soft lithography (using both PDMS and RTV elastomers). The device incorporated a three valve peristaltic pump (with dampers to minimize fluid pulsations) and switching valves. Here an upper control layer that contained a series of channels for introducing pressurized nitrogen and vacuum are used to actuate the valves and pump. Both cell sorting and cell trapping were demonstrated with this device. This pressure driven version replaced an earlier, less integrated, electroosmotic flow-based switching device [120], which was also used for fluorescence-based DNA sorting [121]. Information on the two-layer PDMS valve technique is available from reference [122]. An important extension of this work was outlined by Thorsen et al. [123], who described one of the first very large scale (VLS) integrated microfluidic devices. In that work the valving technique was combined with a multiplexing control scheme to allow access to hundreds of on-chip reaction chambers and for selected retrieval of products of interest.

Wolff et al. [124] presented a highly integrated microfluidic device for high-throughput fluorescent-activated cell sorting. A second generation microfabricated fluorescent activated cell sorting μ (FacS) chip integrated a novel "smoking chimney" pressure driven flow cell sheathing configuration, a chamber for culturing the sorted cells and wave-guides for cell detection.

Kruger et al. [125] demonstrated the feasibility of integrating micro-optical components and used a flip-chip technique to bond a high gain photodiode directly over the sorting microchannel in their flow cytometry device. Using this device, cytometry calibration beads were sorted using off-chip computer controlled valves coupled to the disposable channel device.

Cho et al. [126] demonstrated an integrated device for separating motile from nonmotile sperm that they called a termed MISS (microscale integrated sperm sorter). The device used a unique horizontal capillary driven flow scheme where nonmotile sperm followed the flow streamline to the waste reservoir, while motile sperm, which show much more rapid cross streamline diffusion due to their relatively high swim velocities, were separated from the main flow to a collection reservoir.

Also of interest is the device of Huh et al. [127] who presented a disposable two-phase flow based cytometer made from PDMS. Berger et al. [128] presented a magnetic cell separation chip device that was comprised of an array of magnetized wires embedded in a silicon substrate. The wires were oriented at an angle to the flow stream that was proposed to deflect the cells into a series of collection channels.

4.2. Dielectrophoretic cellular manipulation and sorting

Cui et al. [129] presented a linear traveling wave dielectrophoretic (twDEP) microchip with an array of integrated electrodes. The electrodes were energized with sequentially phase-shifted ac voltages to produce the traveling waves. The device was demonstrated by separating latex beads and rabbit heart cells. Details of the fabrication and design of the device were presented in an earlier paper [130]. Wang et al. [131] presented a similar device with an array of integrated electrodes for dielectrophoretic field-flow-fractionation separation of cells. Also of interest is the integrated device by Schnelle et al. [132] that used ac octode field cages to dielectrophoretically trap latex particles.

4.3. General cellular analysis

Other devices of interest include the muscle cell analysis chip developed by Li et al. [133] which integrated microfluidic channels with a thickness-shear mode (TSM) acoustic wave sensor. The chip itself consisted of an upper glass plate and a bottom quartz crystal sensor plate with patterned electrodes for launching and detecting the acoustic waves. Both cell and bath solutions were introduced into the chip via pressure driven flow. Hediger et al. presented both modular [134] and disposable [135] systems for electrical characterization of epithelial cell layers. The devices were composed of polycarbonate membranes for support of the cell culture, fluidic structures and integrated electrodes.

5. Devices for protein based applications

In general the development integrated microfluidic devices that are specifically designed for protein analysis, beyond traditional CE chips, is less mature than some of the applications already listed. Such work has however been addressed in some reviews [20,136], and more specifically by Sanders and Manz [137], and Figeys and Pinto [138]. These latter two authors provide a good review of chip based devices for proteomics. As before, we present some examples of the more highly integrated microdevices in this application area general.

5.1. Protein digestion, identification and synthesis

Gao et al. [139] developed a PDMS based device enabling protein digestion, peptide separation, and subsequent protein identification. The device consisted of a capillary tube embedded in a PDMS sandwich which contained a miniaturized PVDF membrane reactor with adsorbed trypsin to catalyze the protein digestion. The peptide products were then concentrated and resolved by electrophoretic separations prior to electrospray ionization mass spectrometric analysis. Pressure driven flow was used to drive the protein solutions through the reactor and regulate the extent of digestion by manipulating the dwell time. Another flow-through protein digestion device was presented by Wang et al. [140] that consisted of integrated beads of immobilized trypsin in a microchannel.

Yamamoto et al. [141] presented a hybrid PDMS/glass microreactor device which was used for protein synthesis. The device consisted of a sealed PDMS reaction chamber that was placed in thermal contact with a glass temperature control chip. Very rapid heating and cooling times (170 ms for heating and 3 s for cooling) were observed due to the low thermal mass of the reaction chamber. An earlier version of the device was presented in [142].

Mizukami et al. [143] presented an integrated acrylic microelectrophoresis chip with a photosensor array, manufactured via a "stereolithography with double controlled surface" method which was outlined in detail. The embedded photosensor array provided real-time access to electrophoretic signal at any location in the channel. The device was used to conduct capillary gel electrophoresis separation of two proteins.

5.2. Coupling of microfluidic devices with protein arrays and mass spectrometry

A significant amount of research in this field has been directed towards the coupling of microfluidic technologies with protein arrays [144] and mass spectrometry [145]. An example of the former is the work of Pawlak et al. [146] who describe the integration of a Zeptosens protein array with a microfluidic delivery system. The device had high sensitivity and signal to noise ratio largely due to the integrated, planar wave guide detection system. As is discussed by Figeys and Pinto [138] widespread integration of microfluidic devices with mass spectrometry required the incorporation of electrospray ionization. Examples of this type of integration include the ESI emitter and sheath gas approach developed by Wen et al. [147], the PDMS devices of Chen et al. [148] and Chiou et al. [149], and the user-friendly device presented by Pinto et al. [150].

5.3. Other devices of interest

Hansen et al. [151] introduced a highly integrated microfluidic device for the rapid screening of protein crystallization conditions, allowing for as many as 144 parallel reactions each using only 10 nl of protein sample. The device was based upon a novel fluid metering and control system, referred to as BIM or Barrier Interface Metering, which used (in this case) 480 active valves. The device (which evolved from earlier control schemes developed by this group [122]) used a multi-layer elastomer construction in which upper control channels were pressurized causing the soft elastomer to expand and pinch off fluid channels in a lower layer. A procedure for priming complex elastomer based microfluidic systems (particularly dead end channels) called pressurized outgas priming was also introduced. In addition to showing highly integrated microfluidic control, the device also demonstrated faster crystal growth than conventional techniques.

Ekström et al. [152] presented a silicon microextraction chip (SMEC) with an integrated weir structure for sample clean-up and trace enrichment of peptides. The structure was used to trap reversed-phase chromatography media (POROS R2 beads), and facilitated sample purification and enzymatic digestion of proteins by trapping beads immobilized with trypsin. Improvements in the weir design were suggested by Bergkvist et al. [153]. Also of interest is the glass microchip developed by Bousse et al. [154] which integrated the required separation, staining, virtual destaining, and detection steps for a protein sizing assay.

6. Integrated microfluidic devices for immunoassay

Generally a large number of repetitive steps are involved in an immunoassay analysis, resulting in high time and labor costs. As such the advantages in automation and reaction rates offered by microfluidics are particularly well suited to this application. Currently, the development of integrated devices for immunoassay is significantly less advanced than that for DNA analysis. A few reviews have focused immunoassays using microfluidics [155,156]. Here we review both surface and solution phase immunoassay devices.

Rossier et al. [157] presented a polymeric disposable microfluidic device with an integrated electrode for enzyme-linked-immunosorbant-assay (ELISA). The integrated electrodes allowed direct in-channel electrochemical detection of the redox active enzyme substrate. Stokes et al. [158] demonstrated a microfluidics chip with an integrated photosensor array and associated amplifiers and control logic for on-chip monitoring of bioassays (specifically *E. coli*). The device used pressure driven flow to introduce detection targets to the reaction chamber where the targets were selectively captured with a series of immobilized bioreceptors. A similar integrated circuit DNA hybridization chip was presented in an earlier work by Vo-Dinh. et al. [159]. Dodge et al. [160] presented an electrokinetically controlled glass microfluidic chip with an integrated reaction chamber for heterogeneous bioassays.

Bead based devices have been presented by Choi et al. [161], whose device consisted of an integrated biofilter (comprising of a planar electromagnet used to capture magnetic beads that carried the target antigen), an electrochemical immunosensor (an interdigitated array of microelectrodes), and a series of custom designed microvalves integrated onto a glass substrate. Further details about the magnetic bead approach that used is available in an earlier work by Choi et al. [162]. Sato et al. [163,164] presented a glass immunoassay microchip that integrated polystyrene beads, precoated with anti-CEA antibody, with a microfluidic system using thermal lens microscopy as the detection method. Using this device, reaction times were reduced to as little as 1% of that required for a conventional ELISA.

Wang et al. [165] presented a microfluidic device for conducting electrochemical enzyme immunoassays which integrated precolumn reactions of alkaline phosphatase-labeled antibody with the antigen, followed by electrophoretic separation of the free antibody and antibody–antigen complex. Cheng et al. [166] presented a channel-based device with integrated mixing, reaction and separation manifolds for performing affinity capillary electrophoresis for immunoassay. The device also incorporated a printed circuit board for routing electroosmotic control voltages to the many reservoirs.

7. Integrated devices for chemical analysis, detection and processing

7.1. Integrated microreactors

Microreactors form an integral component of many microfluidic devices and have been reviewed by a number of authors, most notably by Haswell et al. [167–169]. These authors have written a number of excellent reviews on some of the promising advantages that microreactors have to offer in terms of synthetic chemistry. Here we examine just a few devices to provide an overview of the field.

Losey et al. [170] presented a highly integrated microfluidic device for two-phase mixing, and for conducting heterogeneous, catalyzed reactions. The device consisted of separate gas and liquid entrances which mixed and flowed into one of 10 microchannels. All the microchannels contained an intricate pattern of porous, high aspect ratio posts (50 μm diameter and 300 μm tall, 60% void fraction) which provided support for the catalyst. Titanium/platinum films were also incorporated to provide on-chip heating and temperature measurement. Fabrication of the channels and integrated posts was done using a detailed silicon micromachining technique (of particular note is the technique that was used to increase the porosity of the posts). Some details of two-phase flow in microchannels and some interesting comments on the thermal analysis of the device was also presented, particularly with respect to the performance of the heaters being entirely dependent on the packaging scheme. Further details on a similar device and the chip packaging are available from Losey et al. [171].

Brivio et al. [172] presented a continuous flow, glass/silicon, channel based device for performing bio-chemical reactions. This device integrated the chip with a matrix assisted laser desorption ionization time of flight mass spectrometer. Flow through the system was accomplished by using the instrument vacuum. The device was manufactured using a relatively new micromachining technique referred to as powder blasting [173]. Also of interest was the reactor for chemical synthesis developed by Kikutani et al. [174,175]. This device consisted of a series of three dimensional channel-based glass microreactors, manufactured via conventional photolithography and etching techniques.

7.2. Chemical detection and monitoring devices

A number of authors have developed integrated microfluidic devices intended for online monitoring or detection of various chemical compounds. Kurita et al. [176] presented a microfluidic device integrated with pre-reactor and dual enzyme-modified microelectrodes for monitoring in vivo glucose and lactate. The device itself consisted of two glass plates bonded together using a UV curable resin, and used carbon film electrodes. Moser et al. [177] developed a microfluidic flow through chip for simultaneous measurement of glucose, lactate, glutamine, and glutamate. The glass chip integrated a series of thin film platinum working electrodes and an Ag/AgCl reference electrode which were coupled to a data acquisition system using a printed circuit board. Minimization of cross-talk and excellent long-term stability were achieved by modifying the electrochemical transducers and utilizing photo-patternable enzyme membranes. Cai et al. [178] introduced a microdevice with integrated dispensing and microelectrodes that was used for the dynamic amperometric detection of lactate from single heart cells. Wu et al. [179] presented a glucose sensor for integration into a microfluidic system which featured a separate working electrode and enzyme membrane that allowed for easier fabrication. Also of interest is the integrated sequential injection manifold (termed a lab-on-valve) device for automated sample processing for monitoring of small-scale fermentations developed Wu et al. [180]. The lab-on-valve concept is based on that presented in an earlier work [181].

Hisamoto et al. [182] developed an integrated sequential ion-sensing system that involved intermittent pumping of plural organic phases into a microchannel, followed by contact with a single aqueous solution (10^{-2} M KCl) to form an organic two-layer flow in the microchannel. The organic phases contained the same lipophilic pH indicator dye but different ion-selective neutral ionophores. The different ions were extracted into the different organic phases, and determined by thermal lens microscopy (TLM).

Badr et al. [183] and Johnson et al. [184] introduced a centrifugal microfluidic device with integrated fluorescent ion-selective optode membranes. This unique device consisted of a channel/reservoir architecture etched into a hard polymer disk where fluid control was accomplished by centrifugal force and capillary force burst valves. The detection mechanism was based on observing changes in the fluorescence properties of the membranes associated with the varying concentration of the analyte ions. The more recent of these papers discusses the effectiveness of using laser diodes as an excitation source, as the development of the device is geared towards a CD type platform. The centrifugal fluidic transport system used here is based on that developed by Duffy et al. [185], who developed a hard plastic CD type device for multiple enzymatic assays.

Ueno et al. presented a integrated an air-cooled cold trap channel [186] and thin film heaters [187] in a microfluidic device for monitoring airborne benzene, toluene,

ethylbenzene, and xylene (BTEX) gases. The Pyrex device consisted of a series of concentration cells onto which gases were adsorbed and then released using the thin film heater. The cold trap channel prevented dilution of the gases prior to reaching the detection sensor.

Timchalk et al. [188] presented an integrated microanalytical system for the analysis of lead in saliva based on square wave anodic stripping voltammetry. The device consisted of plug-in micropumps and an integrated microelectrochemical flow cell with three electrodes.

7.3. Fuel processing devices and microfuel-cells

Though most of what has been outlined above has been biological or biochemical in nature, there are several applications for integrated microfluidic devices beyond these categories. One example is the development of miniaturized fuel processing devices and microfuel-cells. These devices are typically designed for sub-watt applications such as hand held electronic devices [189] and will likely in the future be integrated themselves into some of the lab-on-chip devices discussed above.

Microfuel-cell designs and devices have been recently published by Lee et al. [190] and Min et al. [191]. Tonkovich et al. [192] presented some experimental results for a water gas shift reactor designed for fuel processing applications. The device consisted of a series of stacked sheets containing an appropriate number of parallel microchannels for rapid heat and mass exchange (few details on the manufacturing of the device were presented in this work and the readers are referred to reference [193] for more details). Millisecond reaction kinetics for the water gas shift reaction was observed using the device.

Holladay et al. [194] present a impressive miniaturized fuel reformer, shown in Fig. 5. This was intended for use with a microfuel-cell with a capability of providing power to remote electronic devices. The assembly consisted of two vaporizer/preheaters, a heat exchanger, a combustor, and a steam reformer, and used methanol as the fuel and a proprietary catalyst. Thermal efficiencies on the order of 9% were reported for the device. It was proposed that combining the reformer with a fuel cell would provide efficiencies on the same order of current Li-ion batteries. Further information on the technologies used in this device is available in some earlier references to this work [195,196]. Readers are also referred to [197] for a description of a portable device intended for military field use based on this technology.

8. Other devices of interest

8.1. Integrated optical sensing elements

The integration of high resolution optical sensing elements into microfluidic devices is one of the inevitable requirements of constructing truly portable lab on-chip devices. Adams et al. [198] developed a technique for integrating replica molded microchannels systems with a complementary metal oxide semiconductor (CMOS) imaging chip to develop an on-chip adsorption or fluorescence microspectrometer. They were able to obtain absorption signatures for dilute ($<100\,\mu M$) dye solutions. Camou et al.

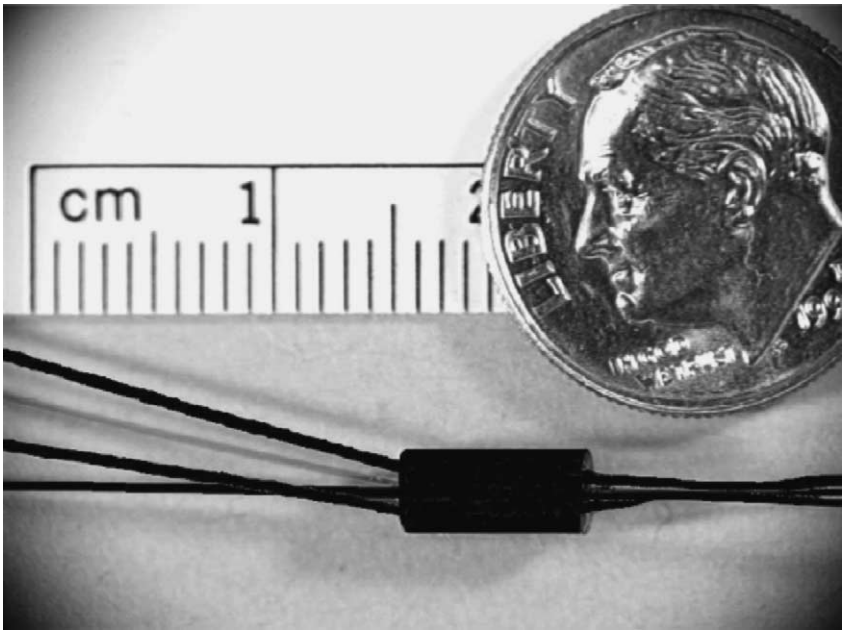


Fig. 5. Integrated fuel processor system, intended for use with a micro-fuel cell with an eye on providing power to remote electronic devices. The assembly consists of two vaporizer/preheaters, a heat exchanger, a combustor, and a steam reformer. Reprinted from [194] with permission. The work for this device was done by the Battelle Memorial Institute, Pacific Northwest Division.

[199] introduced a PDMS device with embedded input and output optical fibers and 2D lenses for integrated fluorescence spectroscopy. The integration of PDMS lenses was shown to increase the sensitivity of the on-chip detection method three-fold over the lensless device. In their work, Ruano et al. [200] described the microfabrication processes required for the successful manufacture, integration and packaging of a microarray of integrated optical sensing elements. Both optics and fluidics were integrated into the device. A pumping system for delivering small amounts of fluid across the array was also described. Baechi et al. [201] presented a highly integrated microchannel system with integrated valves (up to 330 valves/cm^2), heaters and photodiodes that was used for parallel processing and detection of nanoparticles. The valves on this device were actuated by a unique themopneumatic technique that involves the heating of a confined air cavity. An interesting discussion of thermal cross talk on such a device and a cooling method are provided by Haefliger et al. [202].

8.2. Electronics cooling

One of the roadblocks in developing faster electronic chips is the ability to reject the resistive heat released during operation to prevent over heating and eventual failure of the device. The high surface area-to-volume ratio of the microchannel, and the wide variety of silicon based materials into which channels can be etched [203] provide the integrated heat sink with excellent potential for providing some relief of this bottleneck. Recently Jiang et al. [204] presented a closed-loop two-phase cooling system for electronic circuits using a unique integrated electroosmotic pumping technique. Essentially electroosmotic flow was induced locally through the application of an electric field across a porous glass filter that in turn induced a pressure force to drive the two-phase flow through the heat exchanger. The device is able to reject 38 W of heat using 2 W of pumping power. Schütze et al. [205] developed an integrated cooling system which consisted of independently operated cooling microchannels that were etched into a thick copper layer. The device was capable of heat dissipation on the order 20 W per channel. Also of interest is the MEMS enabled droplet impingement system developed by Amon et al. [206] and the Pyrex/silicon device of Hesteroni et al. [207].

8.3. Integrated devices for fundamental analysis

Before closing it is worth while to briefly mention a few of the integrated microfluidic devices which have been developed for the purpose of studying or developing unique mechanisms of microscale fluid flow. Park et al. [208] preformed fundamental microfluidic flow studies on a silicon microfluidic device (fabricated via an RIE process) with 10 integrated platinum RTDs (fabricated using a lift off process), for temperature measurement. Pressure drop and micro-PIV measurements that were taken revealed that the variation in fluid properties along the length of the channel had a significant effect on the flow resistance, but not on the velocity profile. Selvaganapathy et al. [209] presented a unique “bubble free” electroosmotic pumping scheme in which a periodic zero net current, non-zero average potential was applied to a series of integrated electrodes along the length of the channel. The non-zero average potential induced an electroomotic flow while the zero net current minimized electrolytic bubble formation allowing the integration of the electrodes directly into the channel. Pollack et al. [210] described an integrated device for micromanipulation of electrolyte droplets via electrowetting. The device consisted of two sets of opposing planar electrodes fabricated on glass substrates. The advantage of this technique is that there are no permanent channels or structures, making the device highly reconfigurable. Lee et al. [211] introduced an integrated microsystem for studying gas flows in complex microfluidic systems. The device consisted of a microchannel system with distributed and integrated pressure sensors. The same group presented another system [212] consisting of integrated heaters and a distributed temperature sensor array. Lee et al. [213] presented a microfluidic heat sink with integrated components to study the effects of channel size and shape on the developing flow field, and on the thermal performance of the microsystem. The device consisted of a hybrid glass/silicon microchannel system with an integrated heater to simulate the heat source, and a 10×10 array of temperature sensors. The device was used to examine the fundamental aspects of two-phase flow and nucleation in different channel sizes. Lao et al. [214] developed a silicon device with integrated heaters for precise gas and liquid phase temperature control.

9. Conclusions and outlook

In this work we have reviewed a sampling of recently reported (between 2000 and mid 2003) integrated microfluidic devices, otherwise known as lab-on-a-chip. The objective was to present devices from a broad spectrum of application areas, in order to provide a glimpse into the current state-of-the-art in each of these fields. As we have stated, the majority of microfluidics research has been concentrated in those areas that have the highest potential for short-term commercial success. In addition to these important applications, we have also examined a few emerging areas that are not commonly covered in reviews of this sort in order to provide a perspective beyond immediate commercial interests.

The next 5 years are likely to be a critical stage in the future development of highly integrated microfluidic devices. As more and more devices based on microfluidic technology reach commercialization within this time frame, it is likely the market’s response to these early products that will dictate the amount of both private and public funding that will be allocated to the field in the future. Some of

the major developments we foresee within this time period include:

Decreased reliance on external equipment. The majority of the chips described in this review are microscale devices coupled to a macroscale infrastructure. While this has allowed researchers to benefit from some of the aforementioned advantages associated with the scaling down of the size, it is highly desirable to decrease the reliance on the external equipment, in order to achieve a higher degree of portability and hence fully realize the advantages of lab-on-a-chip technology. This requires further development of on-chip raw sample pretreatment capability, miniaturized optical sensors and detectors (e.g., lasers, waveguides, fluorescent microscopes), and low consumption power source.

A further increase in the use of rapid prototyping techniques and polymeric construction materials. One of the significant developments in the field during the period covered by this review is the increased use of polymeric materials (as opposed to glass and silicon) and rapid prototyping techniques. These novel techniques and materials have allowed researchers to significantly reduce the time and cost associated with going from idea to chip, and thus are likely to become more and more prevalent in the near future. In addition, rapid prototyping microfabrication techniques require a minimum of expensive, specialized equipment thereby enabling more researchers, with a diverse array of backgrounds and potential applications, to enter the field with minimal investment.

Increased use of "numerical prototyping" techniques in the design of microfluidic devices. Simulation allows researchers to rapidly determine how design changes will affect chip performance, thereby reducing the number of prototyping iterations. Perhaps even more importantly numerical prototyping applied at the conceptual design stage can provide (at worst) order of magnitude estimates of potential chip performance enabling the researcher to take a fruitful path from the beginning. An existing roadblock that limits the use of numerical prototyping techniques is the relatively specialized nature of the low-level numerical tools currently available. These tools typically require sophisticated computational fluid dynamics skills that are not prevalent amongst the chemists and biologists who currently dominate the field. As a result numerical prototyping tends to be an afterthought, rather than an initial step where the greatest gains could be made. To alleviate this, high-level computational design tools, which can be run on a desktop computer, must be developed with the skills of the end users in mind.

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