Review

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Components for integrated poly(dimethylsiloxane) microfluidic systems

This review describes the design and fabrication of microfluidic systems in poly(dimethylsiloxane) (PDMS). PDMS is a soft polymer with attractive physical and chemical properties: elasticity, optical transparency, flexible surface chemistry, low permeability to water, and low electrical conductivity. Soft lithography makes fabrication of microfluidic systems in PDMS particularly easy. Integration of components, and interfacing of devices with the user, is also convenient and simpler in PDMS than in systems made in hard materials. Fabrication of both single and multilayer microfluidic systems is straightforward in PDMS. Several components are described in detail: a passive chaotic mixer, pneumatically actuated switches and valves, a magnetic filter, functional membranes, and optical components.

Keywords: Interfacing / Microfluidics / Poly(dimethylsiloxane) / Review EL 5131

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Abbreviations: μAPD, microavalanche photodiode; **CAD**, computer-aided design; **LED**, light emitting diode; **PMMA**, polymethyl methacrylate

1 Introduction

Microfluidic systems have found many applications: in biochemical analysis [1, 2], for chemical reactions [3], and in cell-based assays [4]. Microfluidic devices have many advantages over conventional bench-top systems. The list of these advantages includes – but is not limited to – reduced size of operating systems, flexibility in design, reduced use of reagents, reduced production of wastes, decreased requirements for power, increased speed of analyses, and portability. The design and development of a functional microfluidic device must take into account the type of material used to fabricate the device. The material should be compatible with sensitive methods of detection, enable easy interfacing with the user, and allow integration of functional components. The material should also be inexpensive, and compatible with micrometer-scale features and microfabrication methods, if the devices are aimed for large-scale application.

We have found that soft-polymeric systems, in particular systems made in poly(dimethylsiloxane) (PDMS), have many properties that are desirable for use in microfluidic devices. In this review, we describe a convenient method – soft lithography – for making PDMS-based microfluidic devices. We also discuss the chemical and physical properties of PDMS, and show, using examples, how these properties can be used to interface microfluidic devices

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with the macroscopic world, to fabricate components easily and flexibly, and to integrate components into devices.

2 Materials for microfluidic devices

2.1 Polymers for device fabrication

The earliest microfluidic systems were fabricated in silicon and glass to take advantage of the technology already existing in microelectronics and microelectromechanical systems (MEMs) [5–7]. Although silicon and glass are attractive materials for fabricating microfluidic devices, polymers also have useful characteristics. Polymers are less expensive than silicon and glass, and involve simpler and less expensive manufacturing processes (*e.g.*, replica molding, casting, injection molding, and embossing) [8]. Lower production costs also mean that single-use devices, which eliminate contamination between analyses, are more feasible. Polymers have a range of different physical and chemical properties; this range is attractive since polymers can be tailored to specific applications. Examples of polymers used to fabricate microfluidic systems include: polyurethane [9], polycarbonate [10, 11], polymethyl methacrylate (PMMA) [12], polystyrene [13], polyethyleneterephthalate glycol (PETG) [14], polyvinylchloride [8], and polyethylene [8]. Polymers are also mechanically more rugged than silicon and glass, and can, in principle, be used for some applications where more brittle materials would fail.

Soft polymers (elastomers) have additional advantages for device fabrication. In particular, PDMS is a soft polymer that is being actively developed in both academic and industrial research groups for applications in microfluidics. PDMS devices are fabricated by soft lithography using elastomeric polymer molding, a technique that allows rapid prototyping of microfluidic devices [15]. Using transparencies printed using a high-resolution printer as photomasks, features down to 20 μm – the size range relevant to microfluidics – can be produced with high fidelity. The elastomeric properties of PDMS are useful for certain microfluidic applications. Devices made of PDMS can be easily integrated with outside components because the polymer conforms to most materials. Since PDMS makes conformal contact with smooth plastic or glass substrates, both reversible and irreversible sealing are possible. The polymer is attractive for applications requiring temperature gradients, since it is stable at temperatures necessary for processing biological materials (40–95°C) [16, 17]. PDMS is also compatible with many optical detection methods because it is transparent in the visible/UV region. PDMS channels are appropriate for cellular studies because PDMS is nontoxic to proteins [18] and cells [19, 20], and is gas-permeable [21].

2.2 Microfluidic systems in PDMS

2.2.1 Soft lithography

Soft lithography is a useful methodology for fabricating microfluidic devices. It is particularly useful as a nonphotolithographic technique for pattern replication and enables rapid prototyping of devices. The method involves replication of a structure on a master in a soft elastomer (PDMS). The process can be carried out in ambient laboratory conditions; expensive cleanroom facilities are therefore not required to fabricate features in the size range of 20–100 μm (the size range most relevant to microfluidic systems used in bioanalysis) [22, 23].

2.2.2 Rapid prototyping and replica molding

Rapid prototyping (Fig. 1A) begins by using a computer-aided design (CAD) program to create a design for a channel. The CAD file is then printed onto a transparency

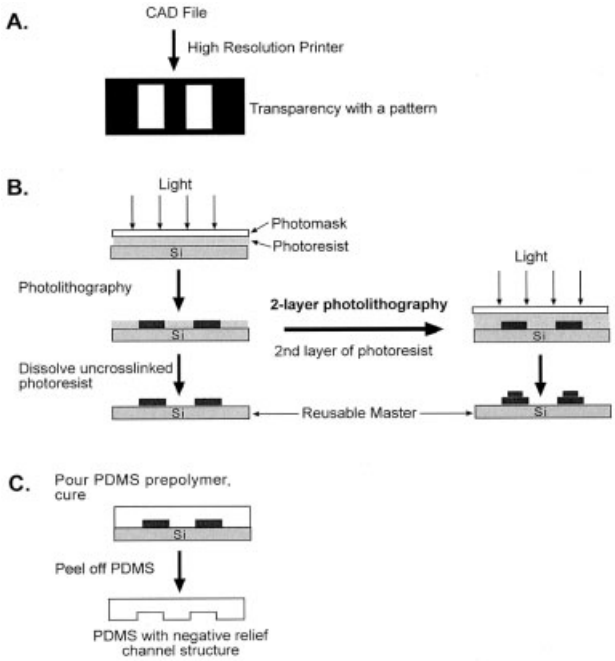

Figure 1. Schemes for (A) rapid prototyping, (B) fabrication of reusable masters, and (C) replica molding of microfluidic systems. (A) Rapid prototyping is the generation of a high-resolution transparency to be used as a photomask. (B) Fabrication of the master involves spin-coating photoresist onto a silicon wafer and developing the photoresist through a photomask. If 3-D structures are desired, an additional step involving spin-coating of the photoresist, mask aligning, and UV exposure can be performed. The uncross-linked photoresist is then dissolved, leaving a master with a positive relief features. (C) Replica molding involves pouring a mixture of PDMS prepolymer and curing agent onto the master, curing at ~70°C for 1 h, and peeling the replica off the master. Unlimited numbers of replicas can be made from the same master.

film with a high-resolution image setter; the transparency serves as a photomask in contact photolithography. A layer of resist (in our work, normally a photo-curable epoxy, SU-8) is exposed to UV light through the mask to polymerize regions that are exposed. After dissolving the unpolymerized photoresist, a positive relief of the channel structure is left on the wafer; this structure acts as a master for casting PDMS channels. This process can be repeated for two-level photolithography to make multilayered structures (Fig. 1B). Instead of dissolving the unpolymerized photoresist after the first exposure, a second layer of photoresist is spun on top of the first. A second mask is aligned on top of the photoresist layers, and the second layer is polymerized; dissolving the unpolymerized photoresist leaves a multilayered channel structure. After a master has been fabricated, the surface of the wafer is treated with a silane containing fluorinated functional groups. This monolayer of silane prevents irreversible bonding between the silicon and PDMS. Using the master, a negative relief of the structure on the master is made in PDMS by replica molding (Fig. 1C). Replica molding involves pouring PDMS prepolymer over the master, curing the polymer at 40–80°C for ~1 h, and peeling it off of the master. Channel inlets and outlets are drilled into the PDMS using a borer (a small drill will do), and the channel is sealed (reversibly or irreversibly) against a flat substrate [24].

Rapid prototyping and replica molding are less expensive and require less time for design, fabrication, and testing of new channel configurations than conventional fabrication techniques. These advantages are especially important in the prototype stage of designing devices, since it may take a few iterations before a final design is chosen. The reduced costs associated with this process also imply a low overhead for running a microfluidics research program. This economy means that it is feasible for many types of research groups to participate in this rapidly growing area, including those without routine access to cleanrooms and mask writers. It is no longer necessary to be an expert in microfabrication to make microstructures.

2.2.3 Surface chemistry and sealing

2.2.3.1 Surface chemistry of PDMS

PDMS has repeating units of –O-Si$(CH_3)_2$-groups. This chemical structure leads to a hydrophobic surface. This surface can be made hydrophilic by exposing it to an oxygen or air plasma. Exposure to plasma introduces silanol (Si-OH) groups, and destroys methyl groups (Si-CH_3) [25, 26]. Channels that have been treated with plasma can be kept hydrophilic indefinitely by keeping the surfaces in contact with water or polar organic solvents; otherwise, surface rearrangements may occur that bring new hydrophobic groups to the surface to lower the surface free energy.* Silanol groups allow the surface of PDMS to be made reactive to a wide range of silanes (Si-R) that are terminated with important functional groups (*i.e.*, R=NH_2, COOH, SH). These functional groups make it possible to tailor the surface of PDMS to be hydrophilic or hydrophobic, or to introduce other reactive groups. For example, grafting a poly(ethylene glycol)di-(triethoxy)silane onto an oxidized PDMS surface rendered the surface permanently hydrophilic, and reduced nonspecific adsorption of proteins [28]. Silanizing oxidized PDMS with an amino-terminated silane (aminopropyltriethoxysilate) provided a reactive surface for a bifunctional cross-linker for protein attachment [29]. A similar technique was used to attach amino-terminated polyethylene glycol (PEG) to make the surface stable against surface rearrangements and hydrophilic for days in air [30]. Another method for controlling surface chemistry of PDMS is to use polyelectrolyte multilayers (PEMs). PEMs consist of alternating ionic polymers that coat surfaces through Coloumbic interactions and prevent surface rearrangements [14, 31, 32].

2.2.3.2 Irreversible sealing

Sealing of PDMS channels is much simpler than sealing channels that are made in glass, silicon, or thermoplastics, because high temperatures, pressures, and high voltages are not required. PDMS channels can be sealed irreversibly to PDMS, glass, silicon, polystyrene, polyethylene, or silicon nitride by exposing both the surface of PDMS and the surface of the substrate to an air or oxygen-plasma [23]. Oxidization using a plasma produces silanol groups on PDMS, and –OH-containing functional groups on the other materials; these polar groups form covalent –O-Si-O-bonds with oxidized PDMS when these surfaces are brought into contact [33]. Another way to seal two slabs of PDMS irreversibly involves adding an excess of the monomer to one slab and an excess of the curing agent to the other. When the two slabs are cured together, an irreversible seal, indistinguishable from the bulk properties of PDMS, forms [34]. In contrast to sealing PDMS to itself or glass, sealing glass to glass or silicon to silicon requires high temperatures (~600°C for glass; > 800 oC for silicon) or voltages (500–1500 V for anodic bonding of glass) [35].

* Uncross-linked PDMS chains tend to migrate to the surface within one day after plasma treatment if the surface is exposed to air. Keeping the surface exposed to water prevents this process. Low-molecular-weight residues can also be extracted by swelling PDMS in various organic solvents [27].

2.2.3.3 Reversible sealing

PDMS has an additional advantage over glass, silicon, and hard plastics in that it makes reversible van der Waals contact (conformal contact) to smooth surfaces. PDMS devices can therefore be demountable. Demountable microfluidic devices are useful in patterning surfaces with proteins, cells, or biomolecules using fluid flow [36]. For example, our group [37] and others [1] have demonstrated surface patterning of antibodies on a glass substrate by flowing a solution of antibody through a set of parallel channels. The elastomer was then peeled off of the substrate, washed, and placed perpendicular to the first set of channels. In order to perform a binding assay, solutions containing antigens were then allowed to flow through the channels, and antibody-antigen complexes were detected at the crossings of the channels.

PDMS channels can also be sealed reversibly against silicone (or cellophane) adhesive tapes [24]. Silicone adhesive tapes are convenient because they form a stronger (but still reversible) bond than that between PDMS and other flat surfaces. Tapes are mechanically flexible and allow for the incorporation of nonsealing layers such as filter papers and certain membranes. It is also easy to cut entry ports into these tapes for various purposes.

2.2.4 3-D fabrication

Integration of functional components into a complex microfluidic system requires a method for fabricating 3-D channel geometries. For example, in fluorescent detection schemes, the axis of the excitation light, the collection light, and the sample channel need to be mutually orthogonal; this situation requires a 3-D structure. Methods such as stereolithography [38, 39], laser-chemical 3-D writing [40], and modular assembly [41] are available for fabricating 3-D features in hard materials, but these processes are expensive in both prototyping and manufacturing. Fabrication of 3-D channels in PDMS is inexpensive, easy, and a versatile method of making complex geometries [42]. We have demonstrated three methods of fabricating 3-D microchannel structures: (i) the use of two-level photolithography [43, 44], (ii) the "membrane-sandwich" method [43], and (iii) solid-object printing [37]. The group of Beebe [45] has also described a useful method similar to the membrane sandwich method.

2.2.4.1 Two-level photolithography

Two-level photolithography is useful for making topographical surface features within microfluidic channels. This technique involves two steps of mask alignment and polymerization of SU-8 photoresist (Fig. 1). We have used this method to make grooved structures inside channels for chaotic mixing [44].

2.2.4.2 "Membrane sandwich" method

Layering is possible with hard materials, but adhesion failure, thermal stress, and mechanical stress and failure can occur when bonding the layers. Layering soft polymers eliminates these problems because the layers can be sealed by chemical processes, and contact between surfaces is easily achieved at low pressure. We have developed the "membrane sandwich" method for fabricating topographically complex 3-D channel structures in PDMS (Fig. 2) [43]. The "membrane sandwich" method involves fabricating up to three levels of features within a single thin (on the order of 100 μm) layer of PDMS. This membrane is then sandwiched between two thicker pieces of PDMS that provide structural support. The features of the membrane are fabricated using two masters – a top master (made in PDMS by replica molding and silanized) that contains one level of features, and a bottom master that is made in silicon and photoresist (by two-level photolithography), and that contains two levels of features (Fig. 2A). The membrane is fabricated by placing PDMS prepolymer between the two masters and applying a small pressure (P = 1000 kPa) until the masters are in physical contact and the prepolymer is excluded from the area of contact. Both masters contain complementary macroscopic alignment tracks that can be slipped into one another; a microscope is therefore unnecessary and registration is straightforward. Once the prepolymer is cured, the silicon master is easily removed since it is not covalently attached to the PDMS; this removal leaves the membrane attached to the silanized PDMS master. The exposed surface of the membrane and a PDMS flat are oxidized by plasma-treatment and brought into conformal contact. The PDMS master is then peeled away and the other side of the membrane is sealed against another PDMS flat. We have used membrane-sandwich method to fabricate a three-level basketweave structure that contains channels crossing over and under each other (Figs. 2C, D).

2.2.4.3 Solid-object printing

An alternative to photolithography for creating masters for molding microfluidic channels is solid-object printing (SOP) [37]. SOP involves the design of a 3-D channel system using a CAD program. The CAD file is read by a commercial solid-object printer to fabricate a master directly in a thermoplastic material, without the use of a mask. This process eliminates the alignment steps that are

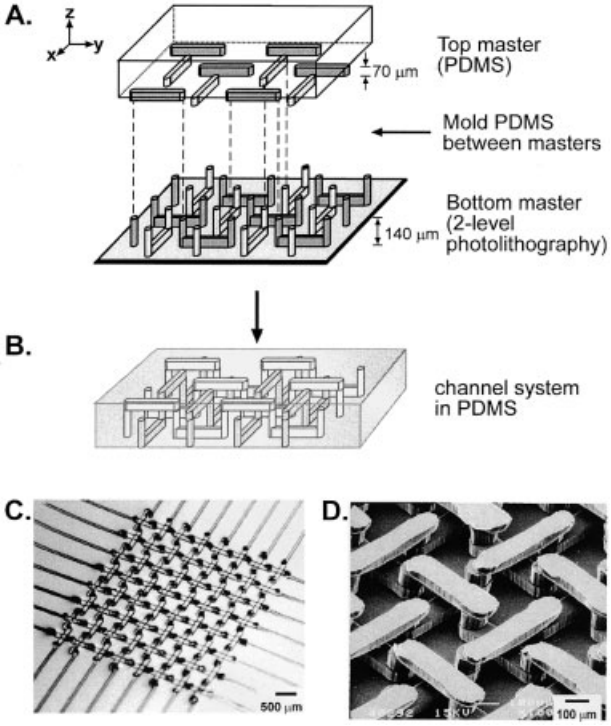

Figure 2. The membrane sandwich method for making a three-level channel system in a single membrane. Diagrams show the fabrication of a basketweave pattern. (A) The top master contains one level of features and is made in PDMS by molding against a master. The bottom master is a positive relief of photoresist containing two levels of features, and is made using two-level photolithography. The channel system is made by placing PDMS prepolymer between the two masters, aligning the masters, and applying pressure until the masters are in contact by excluding the PDMS. For clarity, features on the master oriented in the *y*-direction are depicted with a darker pattern than those in the *x*-direction. (B) Schematic diagram of the three-level channel system in a PDMS membrane. (C) Optical image (looking down the *z*-axis) of the PDMS membrane alone, which contains an 8×8 channel system. The channels are 100 μm wide (*x*- or *y*-direction), and each of the three levels used in the fabrication is 70 μm high (*z*-direction), but is not enclosed. To make the final channel structure, both sides of the membrane are sealed to PDMS flats (not shown). (D) Scanning electron micrograph of the channel system in epoxy polymer. The microstructure was formed by filling the channels with epoxy prepolymer, curing under ultraviolet light for 10 min, and dissolving the PDMS casing in tetrabutylammonium fluoride. Adapted from [43].

necessary when 3-D structures are fabricated using either two-level photolithography or the membrane-sandwich method. Once the master is generated, PDMS prepolymer is poured over the mold, cured, and peeled from the mold. SOP provides a method for creating microfluidic devices over a larger area (up to $250 \times 190 \times 200$ mm, *xyz*) with increased height in features. The resolution of the printer is, however, low ($300 \times 400 \times 600$ dpi, *xyz*); thus resolution limits this method to fabrication of features $\geq$ 250 μm, and generates masters whose surfaces are rough (~8 μm).

2.2.5 Interfacing

It is difficult to interface microfluidic systems made in hard materials to the outside world. For example, making a watertight seal between the device and tubing for sample introduction often requires either inserting a polymer interface [46], or using expensive high precision micromachining, reactive ion etching, or related techniques [47, 48]. If the microfluidic devices are fabricated in PDMS, interfacing with internal components and with the outside world is straightforward. We have shown encapsulation of components such as optical fibers, photodiodes, optical filters, glass capillaries, and silicone tubing in PDMS [24]. Electrodes that are electroplated or evaporated on a substrate can also be easily integrated because PDMS conforms to the electrodes if they are thin ($<$ 200 nm) [49].

The elasticity of PDMS enables objects such as polyethylene tubing, glass capillaries, and sippers to be tightly but easily fitted into holes made in PDMS by press fitting. These access holes are fabricated to be ~20–50% smaller than the diameter of the object, so that a force is exerted against the walls of the hole when the object is inserted; this force ensures a nonleaky seal. This ease of insertion makes sample introduction and recovery easy in PDMS systems. We commonly use polyethylene tubing for connection to PDMS devices, because this type of tubing can conform to syringe needles (and therefore syringe pumps) for pumping fluids through channels. The access holes also fit micropipette tips for manual injection of samples.

3 Integrated components in PDMS systems

The use of soft polymers such as PDMS for fabrication of microfluidic systems allows easy sealing, coupling to the macroscopic world, and construction of 3-D structures. The development and integration of even simple components – mixers, pumps, valves, and other components, necessary in any functional analytical device – into these structures remains a challenge. Fabrication and integration of components is particularly easy in PDMS-based systems. We have successfully integrated membranes [50], gels [50], metallic posts [51], and optical fibers [52] into microfluidic systems. We have also demonstrated that certain components, such as mixers [44], switches

[53], and lenses ([54]; Wu and Whitesides, submitted) can be fabricated directly in PDMS. In the following section we describe some of the components that we have developed, and the integration of these components into PDMS-based systems. Other groups are also successful in turning simple microfluidic channels in PDMS and other polymers into functional devices. Quake [55] has demonstrated one of the most complex soft-polymeric systems to date – an integrated fluorescence-activated cell sorter that uses a combination of pumps, valves, mixers, and multiplexers.

3.1 Chaotic mixer

Mixing of fluid flowing through microchannels is important for many biological and chemical applications, but mixing in microchannels is difficult since fluid flow is slow and there is no turbulence. The tendency of fluid to develop turbulence is characterized by the Reynolds number, *Re* (*Re* = *Ul*/*v,* where *U* is the average flow speed, *l* is the cross-sectional dimension of the channel, and *v* is the kinematic viscosity) [56]. For microfluidic systems, where the dimensions are small (~100 μm), the values of *Re* are almost always low (*Re* < 1). Mixers are thus indispensable in homogenizing reagents rapidly and reducing dispersion in pressure-driven flows.

We have designed a mixer that is easily fabricated by two-level lithography, that is compatible with rapid prototyping, and that does not require moving parts [44]. This mixer uses asymmetric grooves on the floor of the channel (the "staggered herringbone" design) to generate a transverse component to the flow when an axial pressure gradient is applied (Fig. 3A). Because of this transverse component, the fluid elements are stretched and folded into one another; this process increases the contact area between the flowing streams and facilitates mixing by diffusion (Fig. 3B). Channels with the staggered herringbone design thus have a higher efficiency of mixing laminar streams of fluid than channels with smooth walls. The length of the channel required to achieve full mixing increases only logarithmically with Peclet number (*Pe*, the ratio of convective transport to diffusive transport) instead of linearly (*Pe* = *Ul*/*D*, where *D* is the molecular diffusivity [56]).

Another application of the herringbone mixer is the reduction of axial dispersion in pressure-driven flows. In an unmixed Poiseuille flow, the parabolic flow profile stretches out miscible plugs of analyte along the direction of the flow [57]; the contents of the plug mix rapidly into the carrier fluid. Introducing the staggered herringbone mixer (SHM) in the channel carries the solute back and forth between the fast and slow moving regions of the flow,

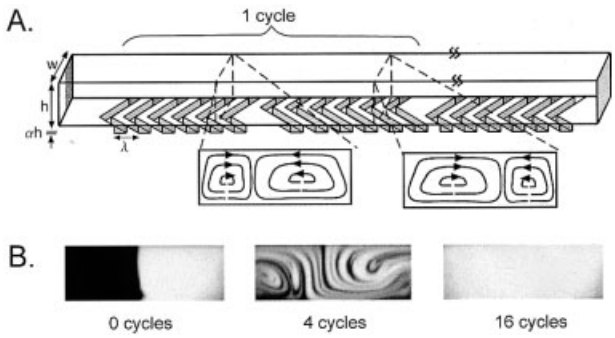

Figure 3. (A) Staggered herringbone mixer showing topography of channel and the streamlines of the flow in the cross-section. Each half cycle, the ridges change their orientation with respect to the center of the channel. One cycle is composed of two sections of ridges; the direction of the asymmetry of the ridges switches from one half cycle to the next. The length of one cycle is 2 mm, and there are six ridges per half-cycle. The dimensions of the channel are: $h = 85$ μm, $w = 200$ μm, $\alpha = 0.18$, $\lambda = 100$ μm. (B) Fluorescent confocal micrographs of the channel cross-section taken 0, 4 and 16 cycles downstream from the junction of a clear stream and a fluorescein-containing stream. Adapted from [44].

and thus reduces the dispersion [44]. In a 100 μm scale channel with the SHM, discrete plugs of a few microliters can be transported for many centimeters without significant dilution into the carrier fluid [44]. We believe that the staggered herringbone mixer will find many applications in pressure-driven microfluidic systems. Other 3-D mixers have been developed [10, 58], such as the serpentine channel by the group of Beebe [59]; this mixer functions by producing eddies at the bends of a channel. This design does not mix efficiently at low *Re* (*Re* < 1) and is difficult to fabricate. The herringbone mixer works in low *Re* regimes and can be fabricated easily in both PDMS and hard materials.

3.2 Elastomeric switch

Switches and valves are important for controlling fluid flow in microfluidic systems. Electrokinetic [60, 61] methods of flow control require integrating electrodes in channels and flow is controlled externally by an applied electric field. Thermally formed microbubbles [62] and responsive hydrogels [63, 64], which expand and contract according to various stimuli (*e.g.*, solution pH), have also been demonstrated. Mechanical means of controlling flow are possible; in particular, the elastomeric properties of PDMS enable easy integration of switches and valves into microfluidic systems. We have developed an elastomeric switch by applying an external pressure across the contact area of two crossing channels in different layers

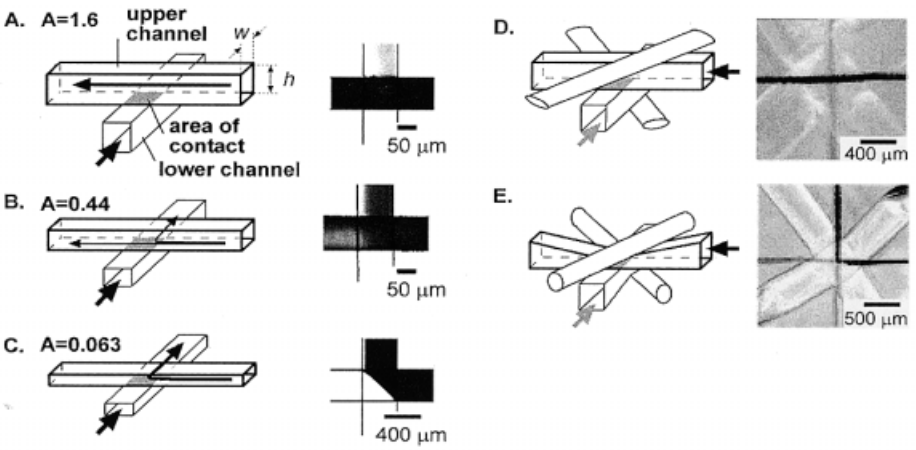

Figure 4. Schematic drawings (left column) and top view microphotographs (right column) of laminar flow at *Re* = 10 through channels of different aspect ratios. (A) When the aspect ratio *A* (defined as the ratio of height of the channel to the width) is 1.6, fluid continues straight through channel. (B) When *A* = 0.44, fluid continues straight through channel and turns. (C) When *A* = 0.063, fluid turns. (D–E) Schematic diagrams and photographs of the elastomeric switch. The channels were actuated by applying pneumatic pressure through elastomeric tubing molded above and below the crossing. (D) When pressure is not applied at the point of crossing, the channels have high aspect ratio and fluid continues straight through channel. (E) When pressure is applied, the aspect ratio of the channels is reduced and the fluid turns its path by 90°. The photographs in (D and (E) were converted from color to grayscale for this publication, and the contrast was enhanced for clearer viewing. Adapted from [53].

[53] (Fig. 4). At the crossing, fluid either flows straight through the channel with cross sectional area $h \times w$, or turns into the other channel, through area $w \times w$. A change in the aspect ratio of the channel – the ratio of the height to width of the channel – determines the flow profile. When the aspect ratio is high ($h \gg w$), fluids flow straight through the crossing without significant exchange of fluid between the channels because there is less resistance to flow through the crossing with area $h \times w$ than the area $w \times w$ (Fig. 4A). When the aspect ratio is low ($h \ll w$), the fluid turns from one channel into the other since the crossing with area $w \times w$ has lower resistance than the area $h \times w$ (Fig. 4C). The channels in the elastomeric switch are actuated pneumatically by pressurizing elastic tubing above and below the crossing of the channels to change the aspect ratio at the crossing (Figs. 4D, E).

Quake *et al.* [34] also exploit the elastomeric properties of PDMS and showed that microfluidic channels can be actuated pneumatically. They have fabricated a device in which a top layer of channels, made in a thin (~40 μm) PDMS membrane, is crossed with a bottom layer of channels in thicker (~4 mm) PDMS. Air flows through the top layer and fluid through the bottom layer. When pneumatic pressure is applied to the top channels, the membrane deflects and closes off the bottom channel [34]. Advantages of pneumatic actuation for switching over other methods include easy fabrication compared to micromachining methods, rapid actuation, avoidance of air bubbles in solution, and switching independent of the fluid (unlike hydrogels).

3.3 Embedded membranes and gels

Organic membranes are often not compatible with the fabrication of glass or silicon devices because the high temperatures required to seal the devices will destroy the membranes. Organic membranes can, however, be easily integrated into PDMS systems. These membranes make conformal contact with PDMS and are not deformed by the forces involved in plasma-mediated sealing. If they are thin (~10 μm), leakage around the edges of the membrane is minimal if sealed against another piece of PDMS. To completely prevent leakage, PDMS prepolymer can be applied to the edges of the membrane before sealing against PDMS [50].

Organic membranes integrated into microfluidic systems enhance the functionality of devices. They are commonly used for separating species in the microchannel, *e.g.*, by molecular weight, size, charge, partition coefficient, or bioaffinity. Membranes are porous structures that have a high surface-to-volume ratio, and enable adsorption and immobilization of protein. The group of Lee showed chiral separation of a DL-tryptophan solution in microchannels by sandwiching two layers of PVDF membrane – coated with bovine serum albumin (BSA) – between two PDMS substrates. BSA had a higher affinity for L-tryptophan than for D-tryptophan; the affinity was modified by changing pH of the solution [65].

We have used polycarbonate membranes to make arrays of microwells between PDMS channels; these microwells serve as microreactors [50]. In this system, two sets of microfluidic channels crossed at right angles, and

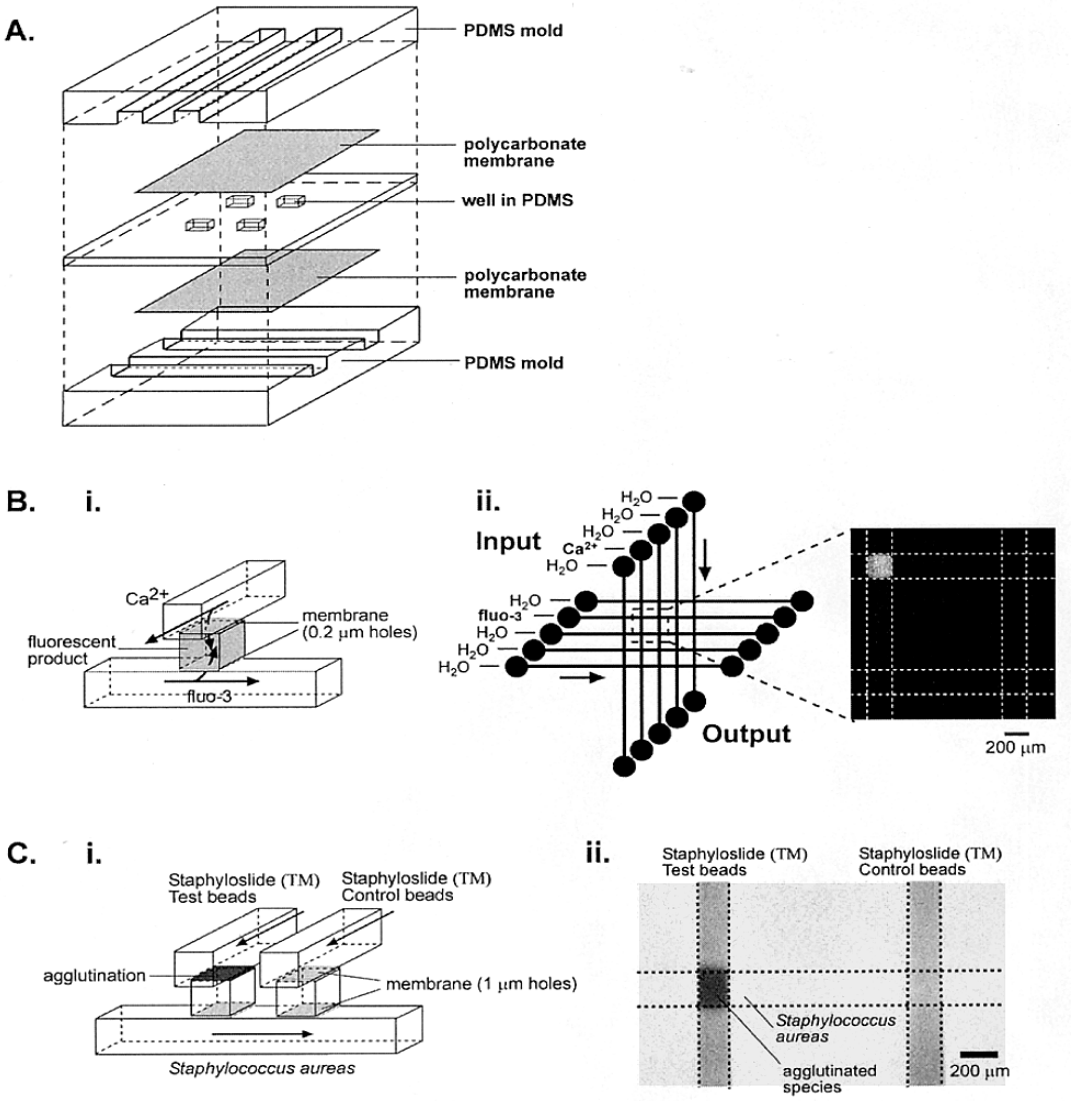

Figure 5. Schematic diagrams and a fluorescent micrograph of the membrane microwell device. (A) The diagram outlines the fabrication of the microwell system. The crossing channels are separated by two polycarbonate membranes and a thin PDMS membrane containing the microwells. (B) i. The solution of Ca^{2+} flows through a top channel and diffuses past a 0.2 μm polycarbonate membrane into a microwell. Fluo-3 flows in the bottom channel and also diffuses past a membrane and into the microwell. A fluorescent precipitate is formed inside the microwell. ii. Fluorescent micrograph illustrates addressibility of individual microwells in a 5×5 array. Fluorescence is localized at the intersection of Ca^{2+} and fluo-3 containing channels; the rest of the intersections are signal-free. (C) Detection of S. *aureus* by agglutination of Staphyloslide™ Test Latex beads with IgG immobilized on their surfaces. i. Schematic diagram of agglutination assay in microfluidic channels. ii. A micrograph of the results of the experiment shown in (C)i. Agglutination occurs only at the crossing of S. *aureus* with the test beads. Adapted from [50].

are separated by a membrane, a PDMS microwell, and another membrane (Fig. 5A). Chemical or biochemical reactions take place at each crossing of channels. In these systems, the membranes reduce convective transport of one fluid stream into the other, and control the distance over which species must diffuse in the area of contact. We demonstrated addressibility of individual microwells (using membranes with 0.2 μm vertical pores) in a 5×5 array by flowing solutions of $CaCl_2$, fluo-3, and H_2O in the channels (Fig. 5B). Fluorescence was localized only at the intersection of the $CaCl_2$ and fluo-3 solutions. We have also shown that these devices can be used to

assay bacteria in suspension by agglutination of latex beads (Fig. 5C). In the upper channels, we flowed a suspension of Staphyloslide™ test beads coated with human fibrinogen and immunoglobulin G (IgG) on the surface of the beads, and a suspension of Staphyloslide™ control beads without fibrinogen or IgG. In the bottom channel we flowed a suspension of *Staphylococcus aureus*. The membranes used for agglutination experiments had 1 μm vertical pores and were permeable to both beads (~0.3 μm in diameter) and bacteria (~1 μm spheres). The pressure was made slightly higher in the channel with bacteria than in the channels containing beads. When bacteria came into contact with the test beads, protein A on the surface of the bacteria wall bound to IgG on multiple beads. This interaction caused the beads to agglutinate on the surface of the membrane. The membranes described in these systems are optically transparent and compatible with many detection methods (fluorescence, colorimetric).

Soft gels such as agarose and alginate are useful for separating and immobilizing species in microchannels. Gels also offer hydrodynamic resistance, eliminating cross-flow and pressure balancing between channels. We have demonstrated a colorimetric and fluorometric assay in a 5×5 channel array that incorporated a functional gel in PDMS [50]. Substrates were immobilized in agarose gel and then molded in one layer of channels. The channels were separated from another layer of channels by a polycarbonate membrane. The assay was performed by injecting solutions of enzymes in the second set of channels. The enzymes diffuse from their respective channels, through the membranes, and into the channels that contain gels with the substrates. The products of the reactions precipitate from aqueous solution and are entrapped in the gel; a signal is therefore localized at the crossing of the channels.

3.4 Magnetic filtration

Filtration is an important step in sample processing. Current methods of filtration in microfluidic devices include the use of membranes, gels, electrophoresis, and dielectrophoresis. Magnetic filtration is another method that is compatible with microfluidics. It has a number of advantages: high filtration rates, low pressure drop across the filter, negligible alteration in fluid flow, ability to filter small (< 1 μm) and soft particulates, and easy release of captured material. Magnetic filtration has been extensively used in large-scale applications in biotechnology [66], and is beginning to be implemented in microfluidic systems [67–69]. Fan *et al.* [70] performed dynamic DNA hybridization in glass microchannels using paramagnetic beads as a transportable solid support. The DNA targets were immobilized on the surfaces of the beads, and the beads were localized for detection by applying an external magnet to the top of the channel. Hayes *et al.* [71] immobilized antibodies on the surfaces of magnetic beads for performing immunoassays and also applied an external magnet to localize the beads. Both of these examples demonstrate the simple use of magnets for filtering paramagnetic beads by placing a permanent magnet next to a microfluidic channel. A more sophisticated method of magnetic filtration is possible by incorporating magnetizable elements that concentrate magnetic fields within microfluidic systems.

Fabrication of magnetizable elements for generating high magnetic field gradients is straightforward using rapid prototyping and PDMS. We have developed a magnetic filtration system by integrating 10 μm scale nickel posts into microfluidic channels [51] (Fig. 6A). When an external magnetic field was applied to the system, the posts generated high magnetic field gradients and captured 4.5 μm superparamagnetic beads, suspended in water, and flowing past the posts. This system was able to separate a flowing mixture of superparamagnetic and diamagnetic beads with 95% efficiency. Nonmagnetic beads continued to flow through the channel and were collected at the outlet. The magnetic beads were then released from the posts and collected. Because PDMS is transparent, capture of magnetic beads was easily detected and visualized. We have also demonstrated the fabrication of current-carrying microcircuits that generate strong magnetic field gradients. These gradients can be used to separate, transport, store, and position 1 to 100 μm sized magnetic microbeads in aqueous suspension [72].

3.5 Integrated fluorescence detection system

A truly portable lab-on-a-chip device will have an integrated on-chip detection system. There are, however, relatively few examples of integrated optical components for the detection of analyte in microfluidic devices. We (in collaboration with Arieh Karger and Jim Christian at Radiation Monitoring Devices, Inc., http://www.rmdinc.com) have taken a step toward a portable microfluidic device by integrating an optical fiber, optical filters, and a microavalanche photodiode (μAPD) as detection elements [52]. This device consists of two parts – the first is a disposable fluidic system containing channels and an embedded optical fiber. The optical fiber is coupled to a blue light-emitting diode used for fluorescence excitation. The second part is a reusable μAPD photocounter embedded in PDMS. A thin (80 μm) colored polymeric optical filter is sandwiched between the two layers and is

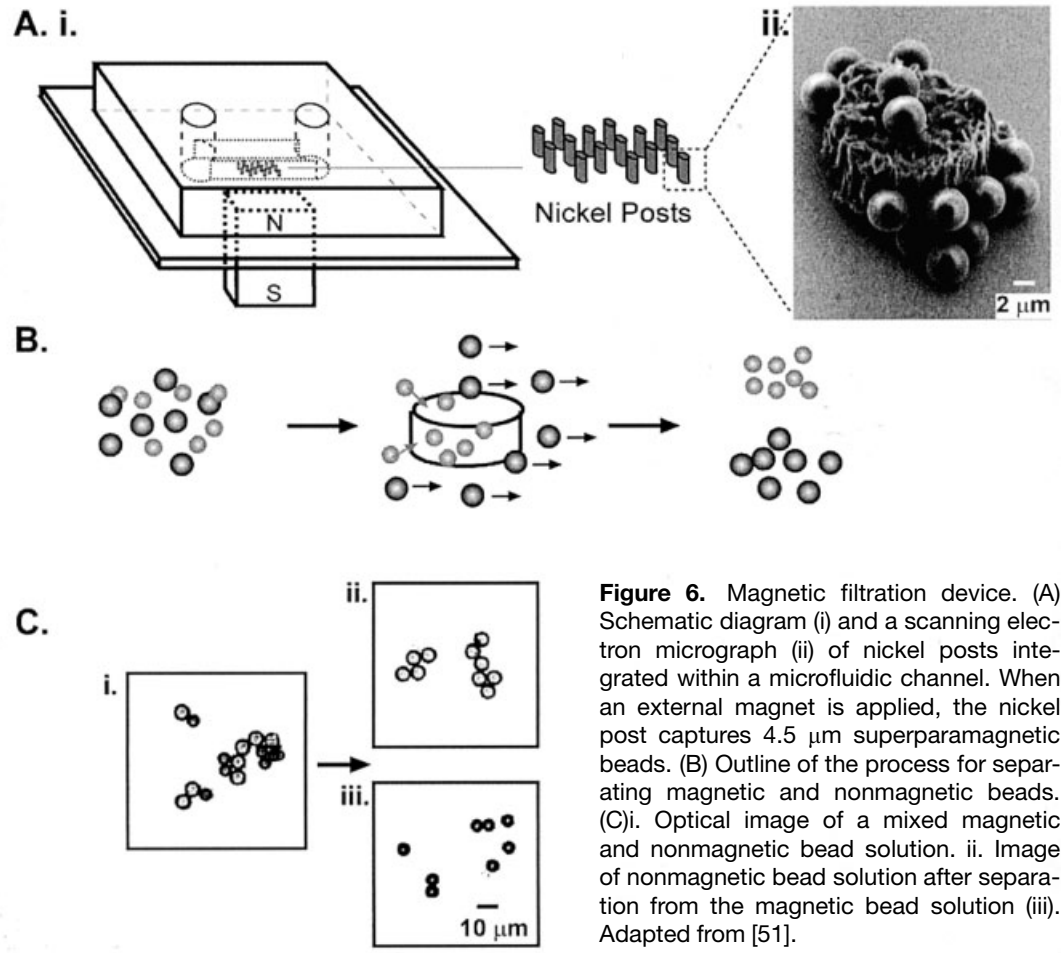

Figure 6. Magnetic filtration device. (A) Schematic diagram (i) and a scanning electron micrograph (ii) of nickel posts integrated within a microfluidic channel. When an external magnet is applied, the nickel post captures 4.5 μm superparamagnetic beads. (B) Outline of the process for separating magnetic and nonmagnetic beads. (C)i. Optical image of a mixed magnetic and nonmagnetic bead solution. ii. Image of nonmagnetic bead solution after separation from the magnetic bead solution (iii). Adapted from [51].

used to filter scattered excitation light before it reaches the detector (Fig. 7A). All of these layers are sealed reversibly by conformal contact.

Optical components can be easily incorporated into PDMS microfluidic systems. We demonstrate this compatibility by describing two simple methods for integrating optical fibers in PDMS systems; both are compatible with rapid prototyping. The first involves embedding an optical fiber in PDMS by clamping it near a channel on a master, pouring PDMS prepolymer over the master, and curing the PDMS. Since the PDMS conforms to the surface of the fiber, an index matching fluid is not needed. Fig. 7B shows a fluorescence micrograph of a 1 mM fluorescein solution detected by an embedded optical fiber in PDMS. Integrating optical fibers in glass, on the other hand, is a complicated process. Liang *et al.* [73] demonstrated a procedure involving etching a channel for the fiber, thermally bonding the channel with a top plate, expanding the channel by pumping HF solution through the channel, and carefully inserting the fiber into the channel. Since the fiber did not completely fill the volume of the channel, the channel had to be filled with an index matching fluid to reduce light scattering.

The second method we developed for integrating optical fibers uses solid-object printing to fabricate tall features for channel insertion [37]. We generated a 3-D microfluidic cross containing two horizontal channels at 90° from one another and a vertical channel that was 5 mm tall (Fig. 7C). Inserting an optical fiber into the vertical channel enables precise positioning of the fiber at the detection site. We have used this integrated fluorescence detection device (with fiber optic integration described in Fig. 7B) for the separation of a mixture of proteins and small molecules by capillary electrophoresis. Resolution obtained using this device is comparable to the resolution obtained using a Beckman P/ACE (Fig. 7D). In this demonstration, the data were collected off-chip, and the light-emitting diode (LED) was not incorporated onto the device. The next step toward a fully integrated system would require on-chip circuitry and a data output device.

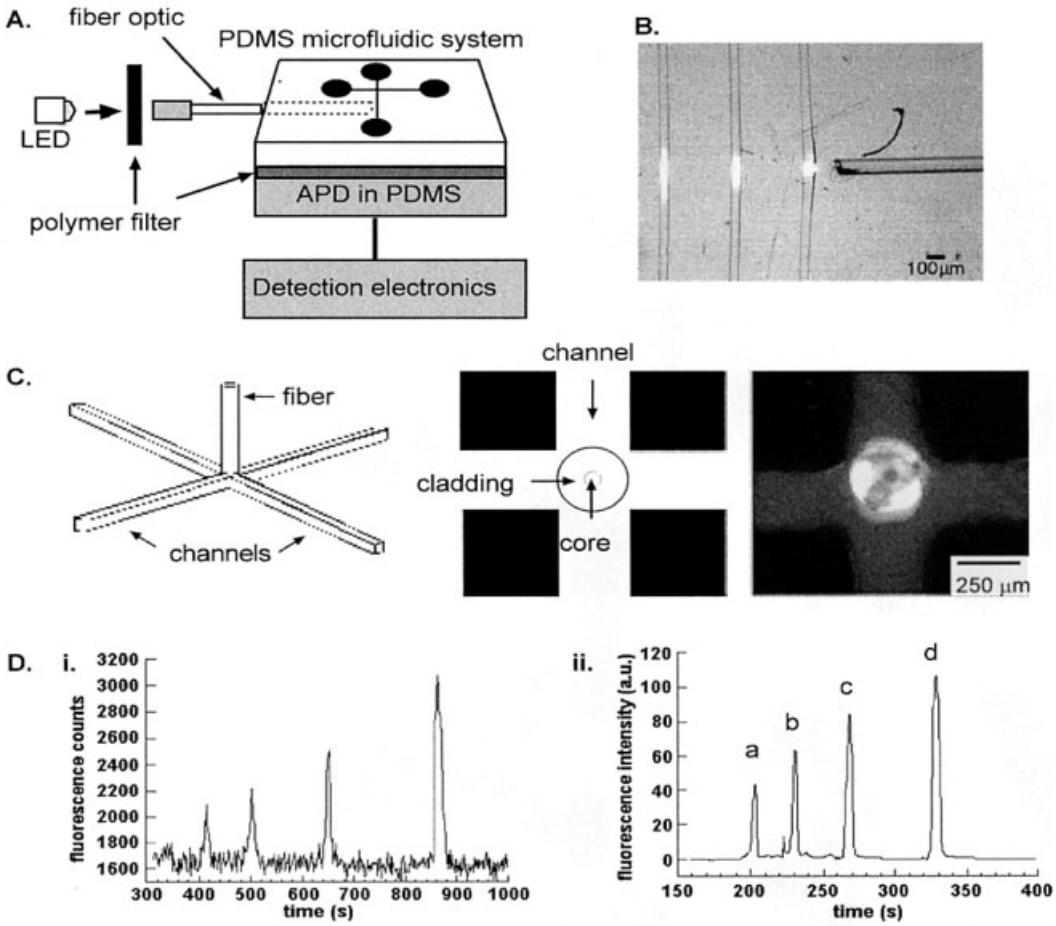

Figure 7. Integrated fluorescence detection system. (A) Schematic diagram of an optical fiber and a μAPD embedded in PDMS. A blue LED, used as an excitation source, was aligned with the optical fiber using an optical positioner. A polymeric filter was then placed between the LED and the fiber to filter the excitation light. The μAPD was wired to off-chip detection electronics. (B) Fluorescence micrograph showing the integrated optical fiber exciting a 1 μM fluorescein solution. Due to the good optical seal between the PDMS and the fiber, the beam of excitation light diverges slowly with the distance from the fiber. (C) Coupling of an optical fiber into a microfluidic device using solid-object printing. The schematic of the master, generated by the solid-object printer, is shown on the left. When the PDMS mold is made from the master, a vertical opening is present for fiber. The fiber is inserted into the vertical channel and aligned in the middle of the intersection of the horizontal channels. PDMS conforms to the cladding of the fiber. The figure on the right shows illumination of the fluorescein-filled horizontal channels by a blue LED coupled into the fiber. (D) Electropherograms of a ~5 μM mixture of proteins by CE. i. Separation in the device shown in (A) using the method for fiber integration from (B). ii. The separation in a commercial Beckman P/ACE system using LIF detection. The peaks are fluorescently-labeled carbonic anhydrase (a), α-lactalbumin (b), fluorescein (c), and 5-carboxyfluorescein (d). Adapted from [37] and [52].

4 Conclusions

The field of microfluidics is developing rapidly. It is clear that polymeric systems will displace glass- and silicon-based systems for most biological analyses involving aqueous solutions, because they are less expensive. Whether the polymers ultimately used will be PDMS or less expensive rigid polymers (polyurethane, polystyrene, polycarbonate, PMMA) remains to be seen. For organic analyses, glass may be the material of choice, since it is compatible with organic solvents.

We find that PDMS-based systems offer many advantages over hard materials. Those advantages include low costs and times required to fabricate small numbers of devices, the ability to modify and fabricate designs

rapidly, feasibility of making devices using soft lithography and replica molding, and the ability to carry out certain types of manipulations (contact sealing, interfacing with optical fibers, inclusion of organic membranes) where nonplanarity is required. PDMS is also compatible with other components that are necessary to build functional devices. The elastomeric properties of PDMS can be exploited in sealing and in designing pneumatically driven actuators. PDMS is transparent in the UV-visible region (its UV cutoff ~240 nm) [24]; its transparency facilitates on- and off-chip detection. The polymer is nontoxic to cells and proteins; it is thus well-suited for biological assays.

Some of the properties of PDMS may be disadvantageous in certain situations. For example, the elastomeric nature of PDMS may cause features to shrink or sag. When working with features $\geq$ 20 mm, shrinking or sagging is not problematic. If features down to 0.1–1 μm prove to be necessary in microfluidic devices, these issues may be overcome with PDMS having a high density of cross-link [74]. PDMS is also limited by being incompatible with many organic solvents [75, 76]. When working with biological samples, nonspecific adsorption may occur. Methods to control the surface chemistry of PDMS are being actively developed to overcome this problem and to expand the range of surface properties of PDMS-based microfluidic systems.

Technology using soft lithography is currently moving towards commercialization. Two start-ups, Surface Logix, Inc. (http://www.surfacelogix.com) and Fluidigm, Inc. (http://www.fluidigm.com) are using PDMS microfluidic chips to develop DNA, protein, and cell-based assays. A related plastics technology – lamination of polymer foils – is being used by Micronics, Inc. (http://www.micronics.net) to fabricate microfluidic analytical systems. Commercialization of these techniques is an indication that polymeric microfluidic systems are indeed a growing area of interest.

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