

ACCOUNTS of CHEMICAL RESEARCH®

JULY 2002

Registered in U.S. Patent and Trademark Office; Copyright 2002 by the American Chemical Society

Poly(dimethylsiloxane) as a Material for Fabricating Microfluidic Devices

J. COOPER MCDONALD AND
GEORGE M. WHITESIDES*

*Department of Chemistry and Chemical Biology,
Harvard University, 12 Oxford Street,
Cambridge, Massachusetts 02138*

Received September 19, 2001

ABSTRACT

This Account summarizes techniques for fabrication and applications in biomedicine of microfluidic devices fabricated in poly(dimethylsiloxane) (PDMS). The methods and applications described focus on the exploitation of the physical and chemical properties of PDMS in the fabrication or actuation of the devices. Fabrication of channels in PDMS is simple, and it can be used to incorporate other materials and structures through encapsulation or sealing (both reversible and irreversible).

I. Introduction

Microfluidic Systems. Capillaries are commonly used in chemistry to minimize the quantities of sample or reagents used in analyses, to increase resolution in separations, and to increase the density of arrays.¹ Microfluidic devices based on capillaries that typically have lateral dimensions of 10–1000 μm are now applied in medical analysis, environmental monitoring, biochemical analysis,

and microchemistry.² Simple two-dimensional (2D) channel systems can be used for many applications, but more complex devices may require pumps, valves, detectors, and channel systems that are three-dimensional (3D).

The first microfluidic devices used silicon and glass, since the techniques for fabrication in these materials were well-developed.^{3,4} These techniques are, however, expensive and time-consuming, and they require access to specialized facilities;^{4–6} they are therefore only marginally useful in research requiring rapid evaluation of prototypes.

Polymers and Poly(dimethylsiloxane). Fabrication in polymers is easy, and their use as materials reduces the time, complexity, and cost of prototyping and manufacturing.^{7,8} Poly(dimethylsiloxane) (PDMS) has been one of the most actively developed polymers for microfluidics.⁹ Fabrication of systems of channels in PDMS is particularly straightforward since it can be cast against a suitable mold with sub-0.1- μm fidelity. PDMS is also more than a structural material: its chemical and physical properties make possible fabrication of devices with useful functionality (Table 1).

Scope. This Account details recent developments in microfluidic devices that exploit the physical and chemical properties of PDMS. We organize this Account into three sections. The first discusses techniques for the fabrication of microfluidic channels in PDMS. The second describes functional components of devices such as valves, inlets, and outlets, and the third describes analytical devices.

II. Methods for Fabrication

Soft Lithography. (a) Replica Molding and Rapid Prototyping. Soft lithography starts with the production of a PDMS replica of a master (or mold). The PDMS used in these experiments is supplied in two components, a base and a curing agent. Silicon hydride groups present in the curing agent react with vinyl groups present in the base and form a cross-linked, elastomeric solid. To produce a replica, we mix the two parts together (typically at 10:1

J. Cooper McDonald was born in Athens, AL, in 1974. He received his B.S. Degree from Erskine College in 1996 and his Ph.D. degree with George M. Whitesides from Harvard University in 2001. He is now a Technology Specialist in the intellectual property law firm Clark & Elbing in Boston, MA.

George M. Whitesides was born in Lexington, KY, in 1939. He received his A.B. degree from Harvard University in 1960 and his Ph.D. degree with John D. Roberts from the California Institute of Technology in 1964. He was a member of the faculty of the Massachusetts Institute of Technology from 1963 to 1982. He joined the Department of Chemistry at Harvard University in 1982, where he is now the Mallinckrodt Professor of Chemistry. His research interests include microfabrication, materials science, surface chemistry, self-assembly, rational drug design, and molecular recognition.

*To whom correspondence should be addressed. Telephone: (617) 495-9430. Telefax: (617) 495-9857. E-mail: gwhitesides@gmgroup.harvard.edu.

Table 1. Physical and Chemical Properties of PDMS

property	characteristic	consequence
optical	transparent; UV cutoff, 240 nm	optical detection from 240 to 1100 nm
electrical	insulating; breakdown voltage, 2×10^7 V/m ⁷¹	allows embedded circuits; intentional breakdown to open connections ⁴³
mechanical	elastomeric; tunable Young's modulus, typical value of ~ 750 kPa ²⁴	conforms to surfaces; allows actuation by reversible deformation; ²⁴ facilitates release from molds
thermal	insulating; thermal conductivity, 0.2 W/(m·K); coefficient of thermal expansion, $310 \mu\text{m}/(\text{m}\cdot^\circ\text{C})$ ⁷¹	can be used to insulate heated solutions; ⁶⁴ does not allow dissipation of resistive heating from electrophoretic separation
interfacial	low surface free energy ~ 20 erg/cm ² ²⁰	replicas release easily from molds; can be reversibly sealed to materials
permeability	impermeable to liquid water; permeable to gases and nonpolar organic solvents	contains aqueous solutions in channels; allows gas transport through the bulk material; incompatible with many organic solvents
reactivity	inert; can be oxidized by exposure to a plasma; $\text{Bu}_4\text{N}^+\text{F}^-(\text{TBAF})$	unreactive toward most reagents; surface can be etched; can be modified to be hydrophilic and also reactive toward silanes; ²⁰ etching with (TBA)F can alter topography of surfaces ⁵⁹
toxicity	nontoxic.	can be implanted in vivo; supports mammalian cell growth ^{57,59}

(v/v) base:curing agent), pour the liquid pre-polymer over the master, and cure it. The liquid PDMS pre-polymer conforms to the shape of the master and replicates the features of the master with high (10's of nm) fidelity. The low surface free energy and elasticity of PDMS allow it to release from masters without damaging the master or itself. Obtaining a master is the limiting factor in the production of PDMS replicas. The master can be obtained by a range of methods.^{8,10–17} A common method starts with a high-resolution transparency as a photomask for generation of the master by photolithography (Figure 1).¹⁰ The resolution of the transparency ($>20 \mu\text{m}$) is adequate for most microfluidic applications.

(b) Sealing. One advantage of PDMS is that it can seal to itself, or to other surfaces, reversibly or irreversibly and

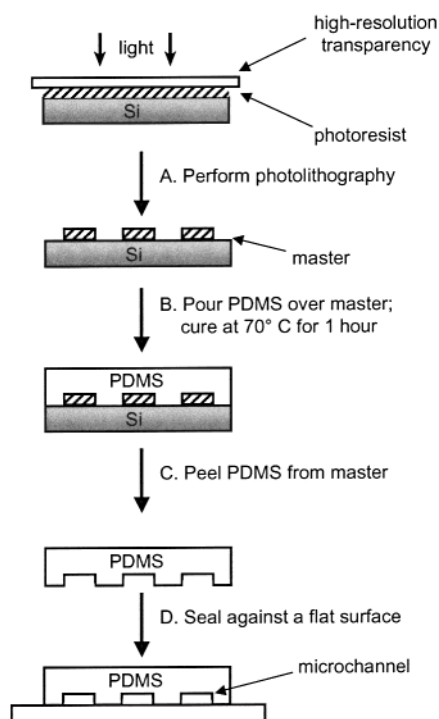


FIGURE 1. Scheme for rapid prototyping. A system of channels is designed in a CAD program. A commercial printer uses the CAD file to produce a high-resolution transparency (~ 5000 dpi). (A) This transparency is used as a photomask in contact photolithography to produce a master. A master consists of a positive relief of photoresist on a silicon wafer and serves as a mold for PDMS. (B) Liquid PDMS pre-polymer is poured over the master and cured for 1 h at 70°C . (C) The PDMS replica is peeled from the master, and (D) the replica is sealed to a flat surface to enclose the channels. The overall process takes ~ 24 h.

without distortion of the channels.^{9,10,18} Sealing of PDMS channels is substantially simpler than sealing channels in glass, silicon, or thermoplastics.^{5–7,19} PDMS that has been molded against a smooth surface can conformally contact other smooth surfaces, even if they are nonplanar, because PDMS is elastomeric. A reversible seal provided by simple van der Waals contact is watertight but cannot withstand pressures greater than ~ 5 psi.⁹ Adhesive tapes—silicone or cellophane—also seal the PDMS channels reversibly.¹³ Cellophane tape provides only a temporary seal; silicone tape makes a much stronger seal, is waterproof, and provides a fourth wall composed of PDMS.

To form an irreversible seal, we expose the PDMS (and perhaps the second surface) to an air plasma for 1 min.^{9,20} We, and others, believe this treatment generates silanol groups (Si–OH) on the surface of the PDMS by the oxidation of methyl groups.²¹ Surface-oxidized PDMS can seal to itself, glass, silicon, polystyrene, polyethylene, or silicon nitride, provided that these surfaces have also been exposed to an air plasma.

This sealing process, while simple and reproducible, requires technical agility. The two surfaces must be brought into contact quickly (<1 min) after oxidation, because the surface of the oxidized PDMS reconstructs in air.^{22,23} Contact with water or polar organic solvents maintains the hydrophilic nature of the surface indefinitely.^{10,22} Empirical evidence shows that oxidative sealing works best when the samples and chamber are clean, the samples are dry, the surfaces are smooth on the micron scale, and the oxidized surfaces are not mechanically stressed. Heating a weak seal in an oven at 70°C can sometimes improve the strength of the seal.

Quake et al. have developed an alternative method for irreversibly sealing that involves adding an excess of the base to one slab of PDMS and the curing agent to another slab.²⁴ When these layers were brought into conformal contact and again cured, the seal that formed was indistinguishable in physical properties from bulk PDMS. The method allows for careful alignment of two slabs since sealing is initiated by heat, but the method limits sealing to devices containing only PDMS and generates hydrophobic channels. Treatment with hydrochloric acid makes the channels slightly hydrophilic.²⁵

3D Fabrication by Stacking Multiple Layers. The “membrane sandwich” method¹¹ (Figure 2) allows the fabrication of complex systems of channels by stacking multiple, thin ($\sim 100 \mu\text{m}$) 2D layers. Since PDMS is

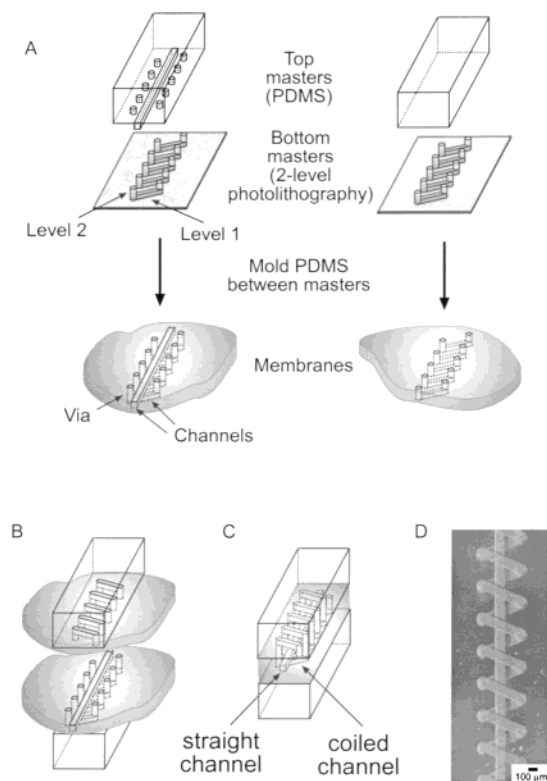


FIGURE 2. Scheme outlining the membrane sandwich method of fabricating a five-level channel system comprising two membranes. (A) The bottom master is a positive relief of photoresist on a silicon wafer and contains two levels of features. We produce the two levels by two-level photolithography that consists of two successive rounds of spin coating to determine the height of the photoresist, alignment of the photomask to the wafer, and exposure to UV light. The first round defines the lower level of features. The second round uses a thicker layer of photoresist than the first round to define the higher level of features. The top master has a single level of features (or is a flat layer) and was fabricated in PDMS by molding against a suitable master. PDMS pre-polymer is placed between the two masters, which are then aligned to one another. Applying pressure to the sandwich causes the higher features on each level to come into contact by excluding the PDMS. (B) The bottom masters were removed from the membranes, which were then oxidatively sealed to flat slabs of PDMS, and the top masters were peeled off. (C) The newly exposed surfaces of the two membranes were aligned using micromanipulators and oxidatively sealed. (D) This panel shows an optical micrograph of a portion of the fluorescein-filled channel system. Adapted from ref 11.

transparent, visual alignment of the layers required to form 3D systems is usually straightforward, when using a stereomicroscope. In contrast to other methods,^{18,24,26–28} the “membrane sandwich” method allows up to three levels of features to be present in a single layer.^{11,29,30} We mold membranes between two masters, a “top” master and a “bottom” master, by placing a small amount of liquid PDMS between the two masters and aligning them relative to one another (Figure 2). When pressure is applied, features on each master that contact one another form vias.

The alignment of two oxidized layers of PDMS containing embedded channels to form multilevel systems of channels can be difficult, since oxidative sealing occurs

on contact. One way we address this problem is with micromanipulators.^{11,29,30} The micromanipulators allow the two layers to be translated, rotated, and tilted relative to one another. We place the two layers in the micromanipulator, bring the two faces into close proximity, and align them under a stereomicroscope. We then separate the two pieces, place the entire assembly (including the micromanipulators) in the plasma cleaner, oxidize the surfaces, remove the assembly from the cleaner, and bring the oxidized layers into contact with the micromanipulators.

Another method for the alignment of multilayer systems uses solvent-assisted sealing.^{1,18,31} In this method, we cover the oxidized surface of the PDMS with a film of polar solvent—methanol, ethanol, or trifluoroethanol—immediately after removing the PDMS from the plasma cleaner (these liquids do not swell PDMS). The solvent acts in three ways: (1) It prevents instantaneous sealing when two layers are brought into contact; (2) it provides lubrication and allows the layers to be moved laterally relative to one another; and (3) it prevents the oxidized surface from reconstructing to a lower free-energy form before sealing is accomplished. To seal the device, we allow the solvent to evaporate from between the layers of PDMS while they are warmed on a hot plate or in an oven. Sealing with this method produces a bond equivalent to sealing immediately upon removal from the plasma cleaner. Since, in this method, we heat the PDMS to form the seal, the surfaces of the channels formed are hydrophobic.

Solid-Object Printing. An alternative, non-photolithographic technique for producing masters is solid-object printing (SOP).¹³ This technique prints a thermoplastic material without the need for masks, alignment, timed exposures, or development, and it requires only an appropriate CAD file to direct the printer (Figure 3). The benefit of SOP is that it can produce masters having multiple levels of features and masters covering a large area (or several smaller masters) in one round of printing. The increased area and height of masters comes at a cost of limited resolution: the masters have significant surface roughness because of the resolution of the printer ($300 \times 400 \times 600$ dpi, xyz), and we cannot fabricate channels having dimensions $<250 \mu\text{m}$ using this method. The equipment for SOP is widely available and can produce devices with an area up to 480 cm^2 and a height up to 20 cm. This method can also make masters for lost wax molding.^{13,32}

III. Components

Components such as valves,^{24,33–35} pumps,^{24,35} mixers,^{36,37} and switches²⁷ are needed to control the flow of fluids in complex devices.³⁸ Molding in PDMS can encapsulate structures—glass capillaries, silicone tubing, optical fibers, and electronic devices—into a microfluidic device.^{10,27,31,34,39–41} The incorporation of organic polymeric membranes (for separation, filtration, or chemical reaction) is also trivial, since they can be sandwiched between

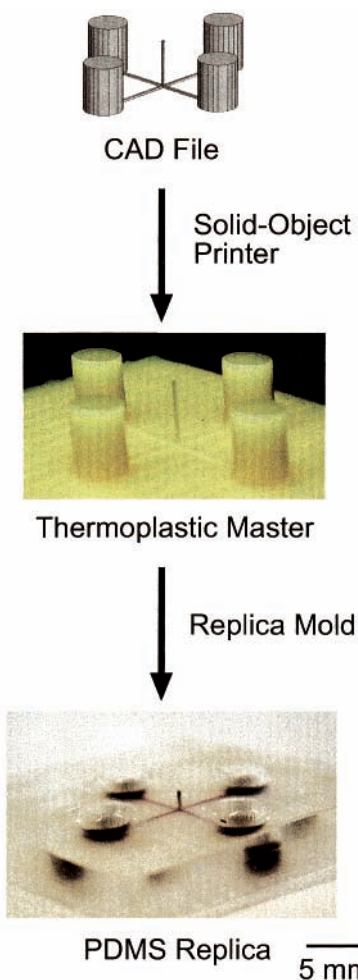


FIGURE 3. Scheme for prototyping devices in PDMS using solid-object printing. First, a CAD file is generated that defines the system in 3D. Next, the solid-object printer printed the object layer by layer. The ink is a melted thermoplastic material that cools and solidifies once it leaves the print head. Once the object is printed, liquid PDMS pre-polymer is poured over the mold and cured at 70 °C for ~1 h. The PDMS replica is then peeled from the thermoplastic mold. The device depicted in this figure is a 3D cross of microfluidic channels conformally sealed to a flat piece of PDMS and filled with ink. Reproduced from ref 13.

two layers of PDMS.^{26,30,42} Including organic membranes in glass or silicon devices is generally impractical, since they do not withstand the processing temperatures required to seal these materials.

Inlets and Outlets. Introducing and recovering fluids (e.g., samples, reagents, or buffers) can be accomplished by using compression fitting of polyethylene tubing.^{26,27,43} Holes slightly smaller than the outer diameter of the tubing are bored in the PDMS; when the tubing is inserted, it exerts pressure on the PDMS and provides a waterproof seal. This method provides a reversible seal, since the tubing can be removed and replaced with minimal effort. The polyethylene tubing also conforms to syringe needles. This ability allows for syringes (and syringe pumps) to be coupled easily to microfluidic channels. It is also straightforward to make fluidic connections by using reservoirs that are accessible by pipet. Figure 4 shows a system

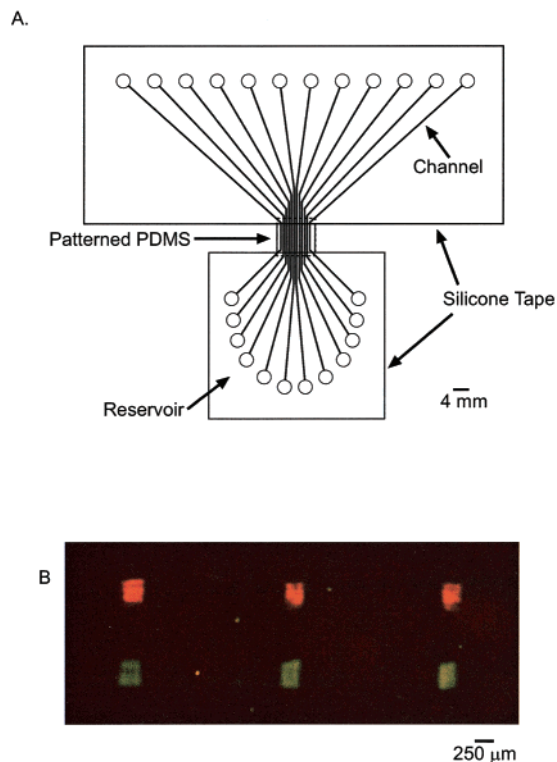


FIGURE 4. Scheme for a device to mate a 12-channel pipettor with microfluidic channels for parallel analyses. (A) Twelve input reservoirs were molded to match the spacing of a standard 12-channel pipettor. Each of these reservoirs was connected to a microfluidic channel. The channels were all the same length so that flow rates were the same in each channel. The PDMS replica was sealed with two pieces of silicone tape, except for a region where the channels are parallel. A small piece of PDMS (dashed box, 1 × 1 cm², ~1 mm thick) was pressure fit to the exposed region of the channel. (B) This panel depicts the results of an immunoassay for mouse IgG performed in the device. The immunoassay occurred in two parts. In the first part, solutions of mouse IgG flowed through every other channel. The result was a pattern of six straight lines of IgG on the small piece of PDMS clamped to the channel system. In the second part, the patterned piece of PDMS was separated from the channel system, rotated 90° and clamped to the surface again. The lines of IgG deposited in the first step were then perpendicular to the direction of flow in the channels. After the newly exposed PDMS was blocked to prevent nonspecific absorption of species, solutions of goat anti-mouse IgG conjugated to phycoerythrin (Ab-phyco) and fluorescein (Ab-FITC), placed in adjacent channels, flowed over the patterned surface. The micrograph shows the pattern of squares formed from Ab-phyco (red) and Ab-FITC (green) binding to the mouse IgG absorbed to the surface. Adapted from ref 13.

designed for sample addition that uses a 12-channel pipettor.¹³

Valves and Pumps. Several groups have used the elasticity of PDMS in the actuation of valves and pumps.^{24,26,33,34,40,43,44} The valves operate by applying a force that pinches a fluidic channel closed at a precise location, and these valves can be incorporated into membrane³⁵ and peristaltic pumps.²⁴ Compression of the channels can occur from air pressure,²⁴ water pressure,³⁵ expansion of a hydrogel,³³ or force from magnetic fields.³⁴ We developed a check valve loosely based on those found in the mammalian lymph system (Figure 5A).³⁵ This valve con-

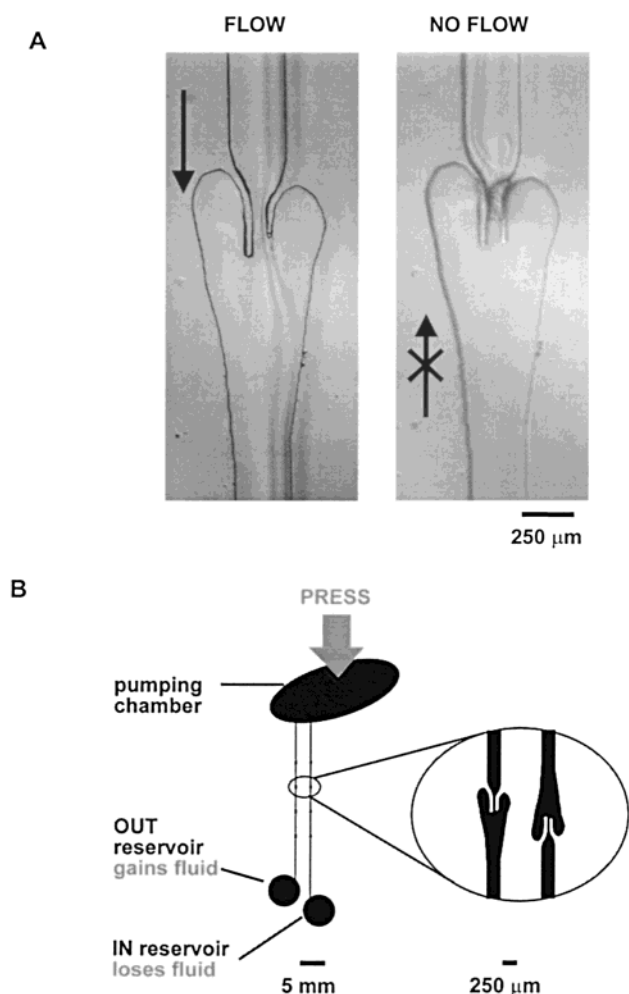


FIGURE 5. (A) Demonstration of a passive "lymph" valve. Two flaps are present in the valve. Flow in one direction pushes the flaps apart, but flow in the opposite direction causes the flaps to collapse together and block the channel. (B) Scheme for the fabrication of a membrane pump. Two reservoirs are connected to a pumping chamber through channels containing lymph valves. When the pumping chamber is manually depressed, the valves in the IN channel are closed while fluid is pushed through the OUT channel. When the pumping chamber expands, fluid is pulled from the IN reservoir, but the valves in the OUT channel prevent backflow. Repeated compression of the membrane pump moves all the liquid from the IN reservoir to the OUT reservoir. Adapted from ref 35.

sists of two parallel flaps in the middle of the channel that are secured to only one wall. Since PDMS is elastomeric, the flaps collapse together or spread apart on the basis of the direction of the flow in the channel. Fabrication is simple since the valve is fabricated in one material and consists of only one level of features. These valves, placed in series, form the basis of a simple membrane pump (Figure 5B).

IV. Devices

Since the initial report¹⁵ of a microfluidic device for CE fabricated in PDMS and the widespread development of soft lithography,^{10,11,13,18,39,43,45} a number of systems have been described (Table 2).

Table 2. Applications of Microfluidic Devices Fabricated in PDMS

application	reference
biochemical assays	17, 43, 47, 50
capillary electrophoresis	10, 15, 28, 39, 51–54
cell counting and sorting	55, 56
cell growth	29, 57–59
chemical reactions	26, 41
computation	30
control of fluid flow	16, 24, 27, 33–35, 40, 60
detection of biological species	12, 61
mixing	36, 37
generating gradients	62, 63
genomics	25, 64
liquid chromatography	65
mass spectrometry	31, 42, 66, 67
optical components	68, 69
patterning surfaces	46, 49, 70

Capillary Electrophoresis. Confocal microscopy is often used for detection in micro-capillary electrophoresis (micro-CE) devices. While this method is useful for validating concepts, it is expensive and cannot be used in portable devices. We (in collaboration with Arieh Karger and Jim Christian at Radiation Monitoring Devices, Inc., <http://www.rmdinc.com>) have developed an inexpensive, compact, and potentially portable detection system for CE in PDMS based on an encapsulated optical fiber and microavalanche photodiode (μ APD) (Figure 6).³⁹ The μ APD is a sensitive photon counter that, because of its size, can be easily incorporated in a layer of PDMS. We embedded an optical fiber in another layer containing channels. The fiber couples light from a blue LED into the separation channel to excite fluorophores. We sandwiched a polymeric, colored filter between the layer with the channels and the layer with the μ APD, using reversible sealing. The filter allows fluorescence from the analytes to reach the detector but blocks scattered excitation light. The incorporation of the fiber and the detector into the PDMS makes the system more compact than those that use external detectors; it also eliminates the need for transfer optics. PDMS is an ideal material for this application since it is transparent to visible light, conforms to the embedded components, and seals reversibly to the polymeric filter.

Immunoassays. Several groups have reported immunoassays in devices that exploit the reversible assembly/disassembly of PDMS channel systems.^{13,17,46,47} We have developed a device that uses the intentional electrical breakdown of PDMS as a way to control the storage and dispensing of the solutions necessary for ELISA.⁴³ We fabricated a microfluidic system in which disconnected channels are separated by a 20- μ m membrane of PDMS (Figure 7). By applying a voltage (typically 1–2 kV) well above the breakdown voltage (420 V) across the 20 μ m of PDMS, catastrophic breakdown occurs and a fluidic connection opens (irreversibly) between the channels. This method of controlling fluid flow is simple since replica molding forms both the channels and the PDMS that separates the channels: electrical connection, provided by platinum wires, is the only other component required. While the voltages used to open connections are high, connections could be opened using an inexpensive, hand-held igniter for a gas grill.⁴³

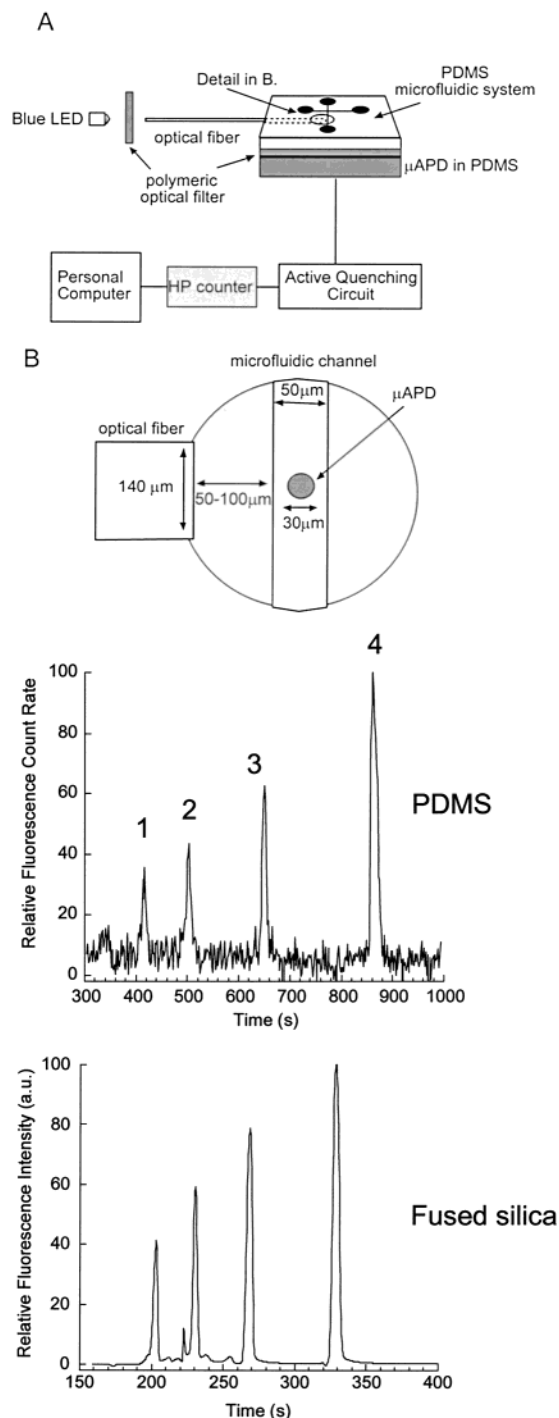


FIGURE 6. Schematic diagrams of the encapsulation of an optical fiber and a μ APD in PDMS for detection of fluorescence in CE. (A) The device consisted of two layers of PDMS with a polymeric filter sandwiched between them. The light from a blue LED was coupled into the optical fiber to excite fluorophores in the channel. The emitted photons were detected by the actively quenched μ APD and counted with a Hewlett-Packard universal counter interfaced with a personal computer. (B) This panel shows the detail of the excitation/detection region showing the relative position of the μ APD, the channel, and the optical fiber. (C) Comparisons are made between electropherograms of a $\sim 5 \mu\text{M}$ mixture of (1) fluorescein-labeled carbonic anhydrase, (2) fluorescein-labeled α -lactalbumin, (3) fluorescein, and (4) 5-carboxyfluorescein separated in a PDMS device and those of a fused-silica capillary in a commercial instrument. Adapted from ref 39.

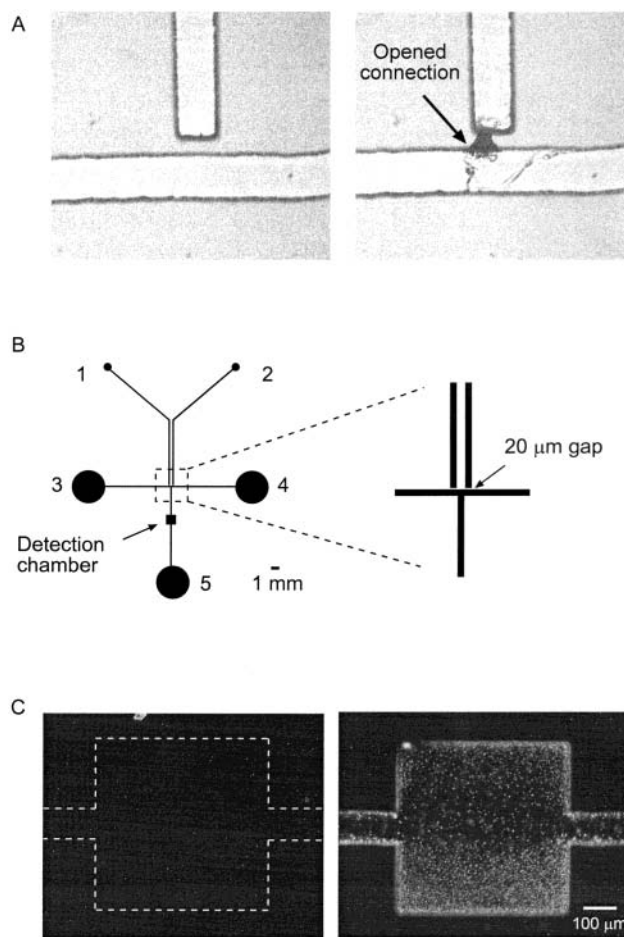


FIGURE 7. Scheme describing the opening of connections between channels by using electrical breakdown. (A) Optical micrographs of closed and open connections. Applying a 2 kV pulse for 1 s opened a fluidic connection. (B) Scheme of a configurable device for ELISA. Two channels were separated from a T channel by $\sim 20 \mu\text{m}$ (see inset). To perform an ELISA experiment, solutions of the capture antibody, blocking agent, and sample flowed in order from reservoirs 3 and 4 to 5 under pressure from gravity. Placing a high-voltage electrode in reservoir 1, grounding reservoir 3, and applying a -1 kV pulse for 1 s opened the first connection. Once the connection opened, a solution of antibody conjugated to alkaline phosphatase was pumped into the T channel by a syringe pump. Applying -1 kV for 1 s between reservoirs 2 and 3 then opened the second connection. The substrate was then pumped into the device. The substrate hydrolyzed and precipitated if hemoglobin was present in the sample. (C) Results of an ELISA experiment. A micrograph of the control experiment (no hemoglobin in the sample) shows no fluorescence. A micrograph of an experiment in which the sample contained hemoglobin shows the fluorescent precipitate. Adapted from ref 43.

Microreactors. Chemical reactions in microfluidic channels allow for the *in situ* production of reagents or modification of samples for analysis and the minimal production or consumption of potentially hazardous, expensive, or rare compounds. McCreedy et al. achieved reactions in PDMS by immobilizing a solid catalyst in a thin film of PDMS.⁴¹ Since membranes can be pressure fit into a device or “glued” in place with pre-polymer, they represent another simple way to incorporate functionality

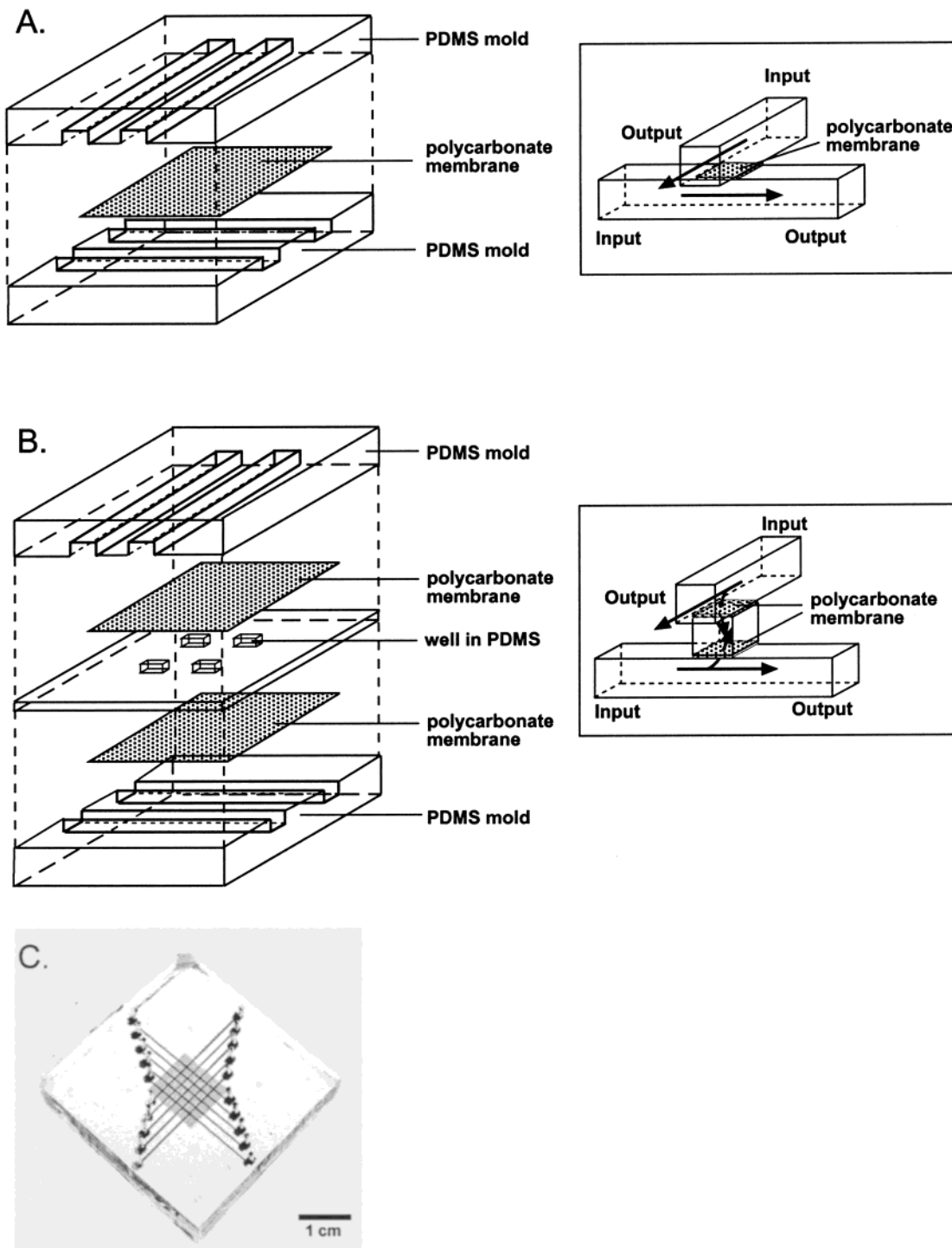


FIGURE 8. Schematic drawings illustrating the fabrication of an array of crossed microfluidic channels. (A) In the membrane system, crossing channels are separated by a single polycarbonate membrane ($10\ \mu\text{m}$ thick with $0.1\ \mu\text{m}$ diameter pores). The pores of the membrane provide a volume for species to diffuse into from the two channels. (B) In the microwell system, crossing channels are separated by two of the polycarbonate membranes and a microwell. In this case, the membranes allow diffusion of species into the microwell while providing high resistance to convective flow through the intersection. (C) This panel exhibits a photograph of a typical device. Reproduced with permission from ref 26. Copyright 2001 American Chemical Society.

into PDMS devices. Lee et al. fabricated a reactor by placing a membrane coated with trypsin between two layers of PDMS.⁴² As proteins pass through the membrane, they are digested by the trypsin. We fabricated a microfluidic array consisting of two layers of channels that cross at 90° and that are separated by a membrane or a

microwell (Figure 8).²⁶ Chemical reactions can take place in the pores of the membrane or the microwell as reagents diffuse from both layers of channels into the region of intersection. Using these microfluidic arrays, we have demonstrated assays for inorganic ions, bacteria, and enzymatic activity.²⁶

Conclusions

In the still-developing field of microfluidics, the characteristics of PDMS are particularly useful in prototyping new systems^{10,11,13,18,43} and in studies of fundamental fluid mechanics.^{16,36,48,49} Since the fabrication of systems in PDMS is simple, chemists and biologists working at a benchtop can make devices quickly and easily. As the focus of microfluidics shifts from demonstration of components and devices to development of fully functional devices, the ease of production of multifunctional systems will become more important.

Probably no single device will be able to take full advantage of the properties of PDMS, and as with all materials, some properties of PDMS may be advantageous or detrimental depending on the application. PDMS has been applied primarily to aqueous solutions, since non-polar organic solvents swell it. The high solubility of nonpolar compounds (including organic solvents) can also be an advantage, for example, in removing small amounts of organic contaminants from an aqueous sample prior to analysis.

While PDMS is a useful material for prototyping microfluidic devices, its application to commercial systems remains to be established. For example, the fabrication of devices in thermoplastic polymers by hot embossing and injection molding for applications that do not require replication of features with nanometer precision would be faster than fabrication in PDMS (minutes versus hours). PDMS, however, has the ability to seal reversibly and irreversibly to many materials and to encapsulate micro-electronic and optical components. This ability to integrate systems easily is crucial to the development of complex, multifunctional microfluidic systems.

Research in our laboratory was supported by DARPA and NSF Grants ECS-9729405 and ECS-0004030 and used MRSEC supported facilities Grant DMR 9809363. We wish to thank our colleagues who participated in this research and Steve Metallo and Michael Chabinyk for helpful comments on the manuscript.

References

- Ramsey, J. M.; Jacobsen, S. C.; Knapp, M. R. Microfabricated Chemical Measurement Systems. *Nature Med.* **1995**, *1*, 1093–1096.
- Bruin, G. J. M. Recent Developments in Electrokinetically Driven Analysis on Microfabricated Devices. *Electrophoresis* **2000**, *21*, 3931–3951.
- Microsystem Technology: A Powerful Tool for Biomolecular Studies*; Kohler, J. M., Mejevaia, T., Saluz, H. P., Eds.; Birkhauser Verlag: Boston, 1999; Vol. 10.
- Kovacs, G. T. A. *Micromachined Transducers Sourcebook*; McGraw-Hill: New York, 1998.
- Madou, M. *Fundamentals of Microfabrication*; CRC: New York, 1997.
- Maluf, N. *An Introduction to Microelectromechanical Systems Engineering*; Artech: Boston, 2000.
- Soper, S. A.; Ford, S. M.; Qi, S.; McCarley, R. L.; Kelly, K.; Murphy, M. C. Polymeric Microelectromechanical Systems. *Anal. Chem.* **2000**, *72*, 642A–651A.
- Becker, H.; Gartner, C. Polymer Microfabrication Methods for Microfluidic Analytical Applications. *Electrophoresis* **2000**, *21*, 12–26.
- McDonald, J. C.; Duffy, D. C.; Anderson, J. R.; Chiu, D. T.; Wu, H.; Schueller, O. J. A.; Whitesides, G. M. Fabrication of Microfluidic Systems in Poly(dimethylsiloxane). *Electrophoresis* **2000**, *21*, 27–40.
- Duffy, D. C.; McDonald, J. C.; Schueller, O. J. A.; Whitesides, G. M. Rapid Prototyping of Microfluidic Systems in Poly(dimethylsiloxane). *Anal. Chem.* **1998**, *70*, 4974–4984.
- Anderson, J. R.; Chiu, D. T.; Jackman, R. J.; Chemiavskaya, O.; McDonald, J. C.; Wu, H.; Whitesides, S. H.; Whitesides, G. M. Fabrication of Topologically Complex Three-Dimensional Microfluidic Systems in PDMS by Rapid Prototyping. *Anal. Chem.* **2000**, *72*, 3158–3164.
- DeBusschere, B. D.; Kovacs, G. T. A. Portable Cell-Based Biosensor System Using Integrated CMOS Cell-Cartridges. *Biosens. Bioelectron.* **2001**, *16*, 543–556.
- McDonald, J. C.; Chabinyk, M. L.; Metallo, S. J.; Anderson, J. R.; Stroock, A. D.; Whitesides, G. M. Prototyping of Microfluidic Devices Using Solid-Object Printing. *Anal. Chem.* **2002**, *74*, 1537–1545.
- Love, J. C.; Wolfe, D. B.; Jacobs, H. O.; Whitesides, G. M. Microscope Projection Photolithography for Rapid Prototyping of Masters with Micron-Scale Features for Use in Soft Lithography. *Langmuir* **2001**, *17*, 6005–6012.
- Effenhauser, C. S.; Bruin, G. J. M.; Paulus, A.; Ehrat, M. Integrated Capillary Electrophoresis on Flexible Silicone Microdevices: Analysis of DNA Restriction Fragments and Detection of Single DNA Molecules on Microchips. *Anal. Chem.* **1997**, *69*, 3451–3457.
- McKnight, T. E.; Culbertson, C. T.; Jacobson, S. C.; Ramsey, J. M. Electroosmotically Induced Hydraulic Pumping with Integrated Electrodes on Microfluidic Devices. *Anal. Chem.* **2001**, *73*, 4045–4049.
- Bernard, A.; Michel, B.; Delamarque, E. Micromosaic Immunoassays. *Anal. Chem.* **2001**, *73*, 8–12.
- Jo, B.-H.; Van Lerberghe, L. M.; Motsegood, K. M.; Beebe, D. J. Three-Dimensional Micro-Channel Fabrication in Polydimethylsiloxane (PDMS) elastomer. *J. Microelectromech. Syst.* **2000**, *9*, 76–81.
- Martynova, L.; Locascio, L. E.; Gaitan, M.; Kramer, G. W.; Christensen, R. G.; MacCrehan, W. A. Fabrication of Plastic Microfluidic Channels by Imprinting Methods. *Anal. Chem.* **1997**, *69*, 4783–4789.
- Chaudhury, M. K.; Whitesides, G. M. Direct Measurement of Interfacial Interactions between Semispherical Lenses and Flat Sheets of Poly(dimethylsiloxane) and Their Chemical Derivatives. *Langmuir* **1991**, *7*, 1013–1025.
- Owen, M. J.; Smith, P. J. Plasma Treatment of Polydimethylsiloxane. *J. Adhes. Sci. Technol.* **1994**, *8*, 1063–1075.
- Morra, M.; Occhiello, E.; Marola, R.; Garbassi, F.; Humphrey, P.; Johnson, D. On the Aging of Oxygen Plasma-Treated Polydimethylsiloxane Surfaces. *J. Colloid Interface Sci.* **1990**, *137*, 11–24.
- Kim, J.; Chaudhury, M. K.; Owen, M. J. Hydrophobic Recovery of Polydimethylsiloxane Elastomer Exposed to Partial Electrical Discharge. *J. Colloid Interface Sci.* **2000**, *226*, 231–236.
- Unger, M. A.; Chou, H.-P.; Thorsen, T.; Scherer, A.; Quake, S. R. Monolithic Microfabricated Valves and Pumps by Multilayer Soft Lithography. *Science* **2000**, *288*, 113–116.
- Chou, H.-P.; Spence, C.; Scherer, A.; Quake, S. A. Microfabricated Device for Sizing and Sorting DNA Molecules. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 11–13.
- Ismagilov, R.; Ng, J. M. K.; Kenis, P. J. A.; Whitesides, G. M. Microfluidic Arrays of Fluid-Fluid Diffusional Contacts as Detection Elements and Combinatorial Tools. *Anal. Chem.* **2001**, *73*, 5207–5213.
- Ismagilov, R. F.; Rosmarin, D.; Kenis, P. J. A.; Chiu, D. T.; Zhang, W.; Stone, H. A.; Whitesides, G. M. Pressure-Driven Laminar Flow in Tangential Microchannels: An Elastomeric Microfluidic Switch. *Anal. Chem.* **2001**, *73*, 4682–4687.
- Ocvirk, G.; Munroe, M.; Tang, T.; Oleschuk, R.; Westra, K.; Harrison, D. J. Electrokinetic Control of Fluid Flow in Native Poly(dimethylsiloxane) Capillary Electrophoresis Devices. *Electrophoresis* **2000**, *21*, 107–115.
- Chiu, D. T.; Jeon, N. L.; Huang, S.; Kane, R. S.; Wargo, C. J.; Choi, I. S.; Ingber, D. E.; Whitesides, G. M. Patterned Deposition of Cells and Proteins onto Surfaces by Using Three-Dimensional Microfluidic Systems. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 2408–2413.
- Chiu, D. T.; Pezzoli, E.; Wu, H.; Stroock, A. D.; Whitesides, G. M. Using Three-Dimensional Microfluidic Networks for Solving Computationally Hard Problems. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 2961–2966.
- Kim, J.-S.; Knapp, D. R. Microfabricated PDMS Multichannel Emitter for Electrospray Ionization Mass Spectrometry. *J. Am. Soc. Mass. Spectrom.* **2001**, *12*, 463–469.
- Dharmatilleke, S.; Henderson, H. T. Three-Dimensional Silicone Device Fabrication and Interconnection Scheme for Microfluidic Applications Using Sacrificial Wax Layers. *Micro-Electro-Mech. Syst.* **2000**, *2*, 413–418.

- (33) Beebe, D. J.; Moore, J. S.; Yu, Q.; Liu, R. H.; Kraft, M. L.; Jo, B.-H.; Devadoss, C. Microfluidic Tectonics: A Comprehensive Construction Platform for Microfluidic Systems. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 13488–13493.
- (34) Jackson, W. C.; Tran, H. D.; O'Brien, M. J.; Rabinovich, E.; Lopez, G. P. Rapid Prototyping of Active Microfluidic Components Based on Magnetically Modified Elastomeric Materials. *J. Vac. Sci. Technol. B* **2001**, *19*, 596–599.
- (35) Anderson, J. R.; McDonald, J. C.; Stone, H. A.; Whitesides, G. M. Integrated Components in Microfluidic Devices in PDMS: A Biomimetic Check Valve, Pressure Sensor, and Reciprocating Pump. *Anal. Chem.*, submitted for publication.
- (36) Stroock, A. D.; Dertinger, S. K. W.; Adjari, A.; Mezic, I.; Stone, H. A.; Whitesides, G. M. Chaotic Mixer for Microchannels. *Science* **2002**, *295*, 647–651.
- (37) Odom, T. W.; Whitesides, G. M. Unpublished results.
- (38) Polson, N. A.; Hayes, M. A. Microfluidics Controlling Fluids in Small Places. *Anal. Chem.* **2001**, *73*, 312A–319A.
- (39) Chabinyc, M. L.; Chiu, D. T.; McDonald, J. C.; Stroock, A. D.; Christian, J. F.; Karger, A. M.; Whitesides, G. M. An Integrated Fluorescence Detection System in Poly(dimethylsiloxane) for Microfluidic Applications. *Anal. Chem.* **2001**, *73*, 4491–4498.
- (40) Khoo, M.; Chang, L. Micro Magnetic Silicone Elastomer Membrane Actuator. *Sens. Actuators A* **2001**, *89*, 259–266.
- (41) McCreedy, T.; Wilson, N. G. Microfabricated Reactors for On-Chip Heterogeneous Catalysis. *Analyst (Cambridge, U.K.)* **2001**, *126*, 21–23.
- (42) Gao, J.; Xu, J.; Locascio, L. E.; Lee, C. S. Integrated Microfluidic System Enabling Protein Digestion, Peptide Separation, and Protein Identification. *Anal. Chem.* **2001**, *73*, 2648–2655.
- (43) McDonald, J. C.; Metallo, S. J.; Whitesides, G. M. Fabrication of a Configurable, Single-Use Microfluidic Device. *Anal. Chem.* **2001**, *73*, 5645–5650.
- (44) Quake, S. R.; Scherer, A. From Micro- to Nanofabrication with Soft Materials. *Science* **2000**, *290*, 1536–1540.
- (45) Martin, R. S.; Gawron, A. J.; Lunte, S. M.; Henry, C. S. Dual-Electrode Electrochemical Detection for Poly(dimethylsiloxane)-Fabricated Capillary Electrophoresis Microchips. *Anal. Chem.* **2000**, *72*, 3196–3202.
- (46) Delamarche, E.; Bernard, A.; Schmid, H.; Michel, B.; Biebuyck, H. Patterned Delivery of Immunoglobulins to Surfaces Using Microfluidic Networks. *Science* **1997**, *276*, 779–781.
- (47) Eteshola, E.; Leckband, D. Development and Characterization of an ELISA Assay in PDMS Microfluidic Channels. *Sens. Actuators B* **2001**, *72*, 129–133.
- (48) Ismagilov, R. F.; Stroock, A. D.; Kenis, P. J. A.; Stone, H. A.; Whitesides, G. M. Experimental and Theoretical Scaling Laws for Transverse Diffusive Broadening in Two-Phase Laminar Flows in Microchannels. *Appl. Phys. Lett.* **2000**, *76*, 2376–2378.
- (49) Kenis, P. J. A.; Ismagilov, R. F.; Whitesides, G. M. Microfabrication Inside Capillaries Using Multiphase Laminar Flow Patterning. *Science* **1999**, *285*, 83–85.
- (50) Yang, T.; Jung, S.; Mao, H.; Cremer, P. S. Fabrication of Phospholipid Bilayer-Coated Microchannels for On-Chip Immunoassays. *Anal. Chem.* **2001**, *73*, 165–169.
- (51) Gawron, A. J.; Martin, R. S.; Lunte, S. M. Fabrication and Evaluation of a Carbon-Based Dual-Electrode Detector for Poly(dimethylsiloxane) Electrophoresis Chips. *Electrophoresis* **2001**, *22*, 242–248.
- (52) Liu, Y.; Fanguy, J. C.; Bledsoe, J. M.; Henry, C. S. Dynamic Coating Using Polyelectrolyte Multilayers for Chemical Control of Electroosmotic Flow in Capillary Electrophoresis Microchips. *Anal. Chem.* **2000**, *72*, 5939–5944.
- (53) Ross, D.; Johnson, T. J.; Locascio, L. E. Imaging of Electroosmotic Flow in Plastic Microchannels. *Anal. Chem.* **2001**, *73*, 2509–2515.
- (54) Zhang, C.-X.; Manz, A. Narrow Sample Channel Injectors for Capillary Electrophoresis on Microchips. *Anal. Chem.* **2001**, *73*, 2656–2662.
- (55) Fu, A. Y.; Spence, C.; Scherer, A.; Arnold, F. H.; Quake, S. R. A Microfabricated Fluorescence-Activated Cell Sorter. *Nat. Biotechnol.* **1999**, *17*, 1109–1111.
- (56) Sohn, L. L.; Saleh, O. A.; Facer, G. R.; Beavis, A. J.; Allan, R. S.; Notterman, D. A. Capacitance Cytometry: Measuring Biological Cells One by One. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 10687–10690.
- (57) Folch, A.; Ayon, A.; Hurtado, O.; Schmidt, M. A.; Toner, M. Molding of Deep Poly(dimethylsiloxane) Microstructures for Microfluidics and Biological Applications. *J. Biomech. Eng.* **1999**, *121*, 28–34.
- (58) Takayama, S.; McDonald, J. C.; Ostuni, E.; Liang, M. N.; Kenis, P. J. A.; Ismagilov, R. F.; Whitesides, G. M. Patterning Cells and Their Environment using Multiple Laminar Fluid Flows in Capillary Networks. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 5545–5548.
- (59) Takayama, S.; Ostuni, E.; Qian, X.; McDonald, J. C.; Jiang, X.; LeDuc, P.; Wu, M.-H.; Ingber, D. E.; Whitesides, G. M. Topographical Micropatterning of Poly(dimethylsiloxane) Using Laminar Flows of Liquids in Capillaries. *Adv. Mater.* **2001**, *13*, 570–574.
- (60) Hosokawa, K.; Fujii, T.; Endo, I. Handling of Picoliter Liquid Samples in a Poly(dimethylsiloxane)-Based Microfluidic Device. *Anal. Chem.* **1999**, *71*, 4781–4785.
- (61) Facer, G. R.; Notterman, D. A.; Sohn, L. L. Dielectric Spectroscopy for Bioanalysis: From 40 Hz to 26.5 GHz in a Microfabricated Wave Guide. *Appl. Phys. Lett.* **2001**, *78*, 996–998.
- (62) Jeon, N. L.; Dertinger, S. K. W.; Chiu, D. T.; Choi, I. S.; Stroock, A. D.; Whitesides, G. M. Generation of Solution and Surface Gradients Using Microfluidic Systems. *Langmuir* **2000**, *16*, 8311–8316.
- (63) Dertinger, S. K. W.; Chiu, D. T.; Jeon, N. L.; Whitesides, G. M. Generation of Gradients having Complex Shapes Using Microfluidic Networks. *Anal. Chem.* **2001**, *73*, 1240–1246.
- (64) Hong, J. W.; Fujii, T.; Seki, M.; Yamamoto, T.; Endo, I. Integration of Gene Amplification and Capillary Gel Electrophoresis on a Poly(dimethylsiloxane)-Glass Hybrid Microchip. *Electrophoresis* **2001**, *22*, 328–333.
- (65) Vahey, P. G.; Park, S. H.; Marquardt, B. J.; Xia, Y.; Burgess, L. W.; Synovec, R. E. Development of a Positive Pressure Driven Microfabricated Liquid Chromatographic Analyzer Through Rapid-Prototyping with Poly(dimethylsiloxane). *Talanta* **2000**, *51*, 1205–1212.
- (66) Chan, J. H.; Timperman, A. T.; Qin, D.; Aebbersold, R. Microfabricated Polymer Devices for Automated Sample Delivery of Peptides for Analysis by Electrospray Ionization Tandem Mass Spectrometry. *Anal. Chem.* **1999**, *71*, 4437–4444.
- (67) Jiang, Y.; Wang, P.-C.; Locascio, L. E.; Lee, L. P. Integrated Plastic Microfluidic Devices with ESI-MS for Drug Screening and Residue Analysis. *Anal. Chem.* **2001**, *73*, 2048–2053.
- (68) Schueller, O. J. A.; Zhao, X.-M.; Whitesides, G. M.; Smith, S. P.; Prentiss, M. Fabrication of Liquid-Core Waveguides by Soft Lithography. *Adv. Mater.* **1999**, *11*, 37–41.
- (69) Schueller, O. J. A.; Duffy, D. C.; Rogers, J. A.; Brittain, S. T.; Whitesides, G. M. Reconfigurable Diffraction Gratings Based on Elastomeric Microfluidic Devices. *Sens. Actuators A* **1999**, *78*, 149–159.
- (70) Delamarche, E.; Bernard, A.; Schmid, H.; Bietsch, A.; Michel, B.; Biebuyck, H. Microfluidic Networks for Chemical Patterning of Substrates: Design and Application to Bioassays. *J. Am. Chem. Soc.* **1998**, *120*, 500–508.
- (71) Sylgard 184, Dow Corning Corp., Midland, MI, <http://www.dowcorning.com>.

AR010110Q