

Chapter 2

Introduction to Microfluidics

2.1 Introduction

The earliest microfluidic devices demonstrated that fluidic components could be miniaturized and integrated together, leading to the idea that one could fit an entire “lab on a chip”, in much the same way that a microelectronic circuit is an entire computer on a chip. Since then, there has been tremendous interest in harnessing the full potential of this approach and, consequently, the development of countless microfluidic devices and fabrication methods. Elastomeric materials such as poly(dimethylsiloxane) (PDMS) have emerged recently as excellent alternatives to the silicon and glass used in early devices fabricated by MEMS (microelectromechanical systems) processes [205, 218]. Simplified device fabrication and the possibility of incorporating densely integrated microvalves into designs [272, 268] have helped microfluidics to explode into a ubiquitous technology that has found applications in many diverse fields.

This chapter begins with a brief introduction to microfluidics, followed by a description of the PDMS-based microfluidic technology that was developed in our lab. Many factors taken together have contributed to the success of this technology, as discussed in the final section. In Chapter 3, these desirable properties are used as a guide for the development of microfluidic devices from new chemically-resistant materials. Such devices have the potential to serve as powerful tools in novel areas of research and industry that are currently inaccessible due to fundamental incompatibilities of PDMS with many organic solvents [160].

2.2 Microfluidics

As numerous investigators have pointed out, scaling down fluidic processes to the microscale offers many significant advantages [178, 181, 195, 222, 62, 132, 133, 44, 256], some stemming directly from the reduction in size and others a result of the ability to integrate at this scale.

2.2.1 Benefits of size reduction

One obvious advantage is that miniaturized components and processes use smaller volumes of fluid, thus leading to reduced reagent consumption. This decreases costs and permits small quantities of precious samples to be stretched further (for example, divided up into a much larger number of screening assays) [25]. Quantities of waste products are also reduced.

The low thermal mass and large surface to volume ratio of small components facilitates rapid heat transfer, enabling quick temperature changes and precise temperature control. In exothermic reactions, this feature can help to eliminate the buildup of heat or “hot spots” that could otherwise lead to undesired side reactions or even explosions [62]. The large surface to volume ratio is also an advantage in processes involving support-bound catalysts or enzymes, and in solid-phase synthesis.

At the small length scales of microfluidic devices, diffusive mixing is fast, often increasing the speed and accuracy of reactions. Dramatic performance improvements are often seen in microfluidic *assays* as well: reduced measurement times, improved sensitivity, higher selectivity, and greater repeatability, are common. For example, dispersion broadening is reduced in electrophoretic separations by the rapid dissipation of Joule heat. In some separations, sensitivity is improved simply because the reduced measurement time leads to a lower degree of peak broadening [236].

Microfluidic devices sometimes enable tasks to be accomplished in entirely new ways. For example, fluid temperature can be rapidly cycled by moving the fluid among chip regions with different temperatures rather than heating and cooling the fluid in place. A device to screen for protein crystallization conditions harnesses free-interface diffusion—a process that is practical only at the microscale—to explore a continuous range of conditions when protein and salt solutions are gradually

mixed [97]. The laminar nature of fluid flow in microchannels permits new methods for performing solvent exchange, filtering, and two-phase reactions [270].

2.2.2 Benefits of automation and integration

Many microfluidic technologies permit the construction of devices containing multiple components with different functionalities. A single integrated chip could perform significant biological or chemical processing from beginning to end, for example the sampling, pre-processing, and measurement involved in an assay. This is the kind of vision that led to the terms “lab-on-a-chip” and “micro total analysis system (μ TAS)”. Performing all fluid handling operations within a single chip saves time, reduces risk of sample loss or contamination, and can eliminate the need for bulky, expensive laboratory robots. Furthermore, operation of microfluidic devices can be fully automated, thus increasing throughput, improving ease of use, improving repeatability, and reducing the element of human error. Automation is also useful in applications requiring remote operation, such as devices performing continuous monitoring of chemical or environmental processes in inaccessible locations [77].

Another way to increase throughput is to exploit parallelism. Single chips have been demonstrated that perform hundreds or thousands of identical assays or reactions [112, 170, 48]. These chips utilize synchronization and control-sharing so that their operation is not significantly more complex than that of a non-parallel chip. They also feature on-chip distribution of a single input sample to thousands of microreactors—an interesting solution to the micro-to-macro interface problem [82, 170]. This problem refers to the mismatch between sample sizes that can be easily manipulated in the lab (μ L–mL) versus the volume of microreactors (pL–nL). The task of controlling thousands of individual valves with a much smaller number of off-chip control inputs is achieved by implementing multiplexers or other more complex logic *on-chip*, as is done in microelectronic chips.

Being planar and on the same scale as semiconductor integrated circuits, microfluidic devices are ideally poised to be integrated with electronic or optical components such as sensors, actuators, and control logic. On the sensing side, significant progress has been made: chemical, electrical, optical absorption, fluorescence, flow, temperature, and pressure sensors are just some examples that

have been reported. Numerous actuators, such as valves, pumps, heating elements, and electrodes for electrophoresis or electrokinetic flow, have also been demonstrated. Beebe *et al.* [16] devised an interesting way to link sensing to actuation—specially tailored hydrogels respond to particular properties of the fluid by swelling and directly actuating a valve. In general, however, the potential of integrated control logic has been largely untapped. In the future, hybrid devices that perform sophisticated *in situ* monitoring and computation may emerge, perhaps to implement feedback control circuits that maintain optimum operating conditions or detect problems.

Small integrated microfluidic devices may also offer the feature of portability, enabling mobile applications in chemical analysis, point-of-care medicine, or forensics. The ability to perform integrated diagnostic tests where they are needed rather than in a centralized lab could reduce costs, improve turn-around time, and reduce the risk of sample mix-up. If manufactured cheaply, devices could be disposable, eliminating cross-contamination between tests. Microfluidic applications in drug delivery are also possible.

2.2.3 Application areas

The literature contains many thousands of reports of reactions and assays that have been carried out in microfluidics devices (see reviews in [8, 133, 111, 188, 69]). Some have shown significant improvements in performance compared with their macroscale counterparts and have successfully competed in the commercial marketplace. In some rare cases, microscale implementations have completely transformed the way that a certain type of experiment is performed or have enabled massively parallel experiments that previously could not even be contemplated.

Among the numerous biological and biochemical processes demonstrated are polymerase chain reaction (PCR) [170], immunoassays [290], drug screening, cell counting and sorting [84], electrophoretic separations, nucleic acid extraction [112], analysis of unpurified blood samples [290], DNA sequencing [142], screens for protein crystallization conditions [97], cell culture studies [9], and single cell manipulation [293].

In chemistry applications, dramatic improvements in synthetic yields and selectivities have been observed [286, 62]. In addition, microfluidic devices may make possible *novel* reactions or processing conditions by unprecedented control over surface chemistry, local heat and mass transfer [186, 132, 133, 44], or reagent concentrations in space and time (using electroosmotic flow) [286, 77]. The greater degree of control may help to design experiments to increase knowledge about many chemical processes [77].

Several investigators have also argued that microreactors could be used in industrial chemical production or waste treatment plants if volumetric processing requirements are low [181, 186, 62, 132]. Scaling up production can be achieved by bringing additional microreactors into service at a relatively low incremental cost rather than constructing a new higher-capacity reactor—an ability that would be especially useful in pilot plants or in industries with production demands that change with time or geographical location [133]. The ability to set up production when and where it is needed could decrease the need for storage and transportation of hazardous or short-lived chemical products. Furthermore, microreactors have the potential to increase the safety of dangerous processes such as the fluorination of aromatic compounds and the synthesis of organic peroxides from acid chlorides by accurate temperature control and prevention of thermal runaway [186, 133]. In case of microreactor failure, the consequences will be relatively minor due to the small mass of material present in the reactor at a given time.

Aside from assays and reactions, microfluidics has played an interesting role in numerous other areas. Examples include microchannels for cooling microelectronic circuits [53], greyscale photomasks consisting of channels filled with different dye concentrations [38], pressurized elastomeric chambers acting as tunable lenses [45], a tunable microfluidic dye laser [22], and fluidic circuits for implementing DNA computing [277].

2.3 PDMS microfluidics

Microfluidic devices have been fabricated from a variety of materials, including silicon, glass, metals, ceramics, hard plastics, and elastomers. Several reviews of microfluidic technologies have been published [244, 133, 25, 278, 69].

Sophisticated integrated microfluidic devices require a method to deliver fluid in a controlled manner between different on-chip components. While devices based entirely on passive flow mechanisms have been successful in research and in commercial products, only relatively simple assays have been possible to date. Active flow mechanisms are required for more sophisticated applications such as highly parallel arrays of reactors in which inlet and outlet ports must be shared among many chip components. In hard materials, electroosmotic flow has proven to be an effective and flexible low-dispersion means of controlling fluids; however, unlike mechanical valves and pumps, its operation depends sensitively on the physical and chemical properties of the fluids (pH, ionic strength, ionic content), and it is not effective in larger channels [134]. In addition, with electroosmotic flow it is not possible to completely isolate samples within a chip nor is it possible to carry out many simultaneous manipulations due to electrical cross-talk between different parts of the chip. Sophisticated “flow-through” devices have been fabricated, however, including some capable of multi-step synthesis [287].

Other physical phenomena have been successfully harnessed for fluid manipulation, but most suffer from disadvantages such as a dependence on details of fluid and surface properties [54], a lack of reconfigurability [307], or a lack of individual valve control [71]. Mechanical valves and pumps, on the other hand, are completely independent of fluid (liquid or gas) properties and are ideally suited as a generic means to manipulate fluids in nearly any application. Furthermore, they can be actuated individually and can orchestrate fluid manipulations such as closed loop flow that are not possible with other techniques.

Despite much effort, the fabrication of active mechanical components in microfluidic devices consisting of rigid materials remains a difficult, complex, and expensive procedure, hindering the pace of device development. Existing valve technologies include a molten wax piston valve [206], an *in*

situ-polymerized polymer piston valve [102], and a check valve with a parylene membrane [285], as well as numerous diaphragm valves, such as a PDMS membrane actuated pneumatically [94] or thermopneumatically (by heated fluid vapour pressure) [300], a plastic membrane actuated by a piston [305], and a silicon nitride membrane actuated with pyroelectric or piezoelectric transducers [68]. (See Reference [305] for a summary.) Early valves using stiff silicon membranes required large surface areas to achieve reasonable deflections. For some reason, recent valves continue to have large sizes (several millimeters), and thus only a small number of valves can fit into a single device.

In contrast, very small and simple, integrated, mechanical valves can be fabricated in PDMS devices, enabled by the elasticity and sealing properties of this material [272, 218]. Since the invention of these valves in our lab, there has been tremendous progress in the field, and the complexity and capabilities of PDMS devices (measured in valve densities) have improved exponentially [111], with current state-of-the-art devices boasting hundreds of thousands of microvalves.

2.3.1 Elastomeric microvalves

A simple metaphor for the operational mechanism of a PDMS microvalve is someone stepping on a garden hose. The pressure applied by the foot deforms the top surface of the hose until the hose is squeezed completely shut and fluid cannot flow. One could also envision the blockage of fluid flow by a hose clamp. PDMS valves contain a thin elastic membrane that can be deflected to block microchannels by a variety of mechanisms, including direct mechanical force [63, 96, 289], electrostatic force, magnetic force, force of an expanding hydrogel [16], and piezoelectric force, as well as pneumatic and hydraulic force [272]. Typically the latter are controlled by an external pressure supply but have also been demonstrated by electronically controlled on-chip electrolysis of water to generate gas [74]. Pneumatically and hydraulically actuated valves have a very small size (footprint) and have proven particularly practical.

Though many variations are possible, PDMS microvalves typically have one of the two architectures shown in Figure 2.1. Two microchannels are shown: one contains the fluid to be controlled; the other is the controlling channel. They are referred to as the “fluid channel” and the “control

channel”, respectively. When the control channel is pressurized, the thin membrane of PDMS existing between the two channels where they cross (when viewed from above) is deflected into the fluid channel, diminishing the size of the flow path. When sufficient pressure is applied to overcome the PDMS elasticity and the fluid pressure, the valve is fully actuated and closes completely. When the pressure in the control channel is relieved, the elasticity of the PDMS causes the valve membrane to spring back to its original position, opening the valve. A top-view photograph of an open and closed microvalve is shown in Figure 2.2. In this and later chapters, I sometimes refer to this microvalve design as the “crossed-channel” valve architecture. During operation, control channels are typically filled with pressurized water instead of air to prevent the introduction of air bubbles into the fluid stream due to air diffusing through the valve membrane. Since water vapour can also diffuse through the valve membrane, a low viscosity oil such as Krytox Fluorinated Lubricant (DuPont) is used as an alternative when manipulating water-sensitive fluids in the device.

In the “push-down” architecture [272], pressure is applied in the upper channels to deflect the membrane downwards. The “push-up” architecture [259] has control channels at the bottom and the membrane deflects upwards. Typically the latter configuration can be actuated at significantly lower pressure due to the membrane shape [259]. It has the additional advantage that there is more space above the fluid channels to implement tall fluid-containing features such as reaction chambers. Such features would not fit in the confined space of the bottom layer in a push-down device. Note that a valve is created simply where a control channel crosses a fluid channel (above or below). To allow crossing without creating a valve, the width of the control channel can be reduced. This restricts the amount of deformation of the valve membrane, preventing it from deflecting completely at the pressure that is sufficient to close (full width) valves.

In order for the valve to close completely, the fluid channel must have a rounded profile, otherwise the corners will leak. A semicircular profile is common, but a bell-shaped profile has been shown by computer modelling to have a lower actuation pressure; it also has the additional advantage that part of its top surface is completely flat and thus is superior for optical detection and imaging [85]. By deliberately using a square channel profile and thus a leaky valve, one can implement a sort of

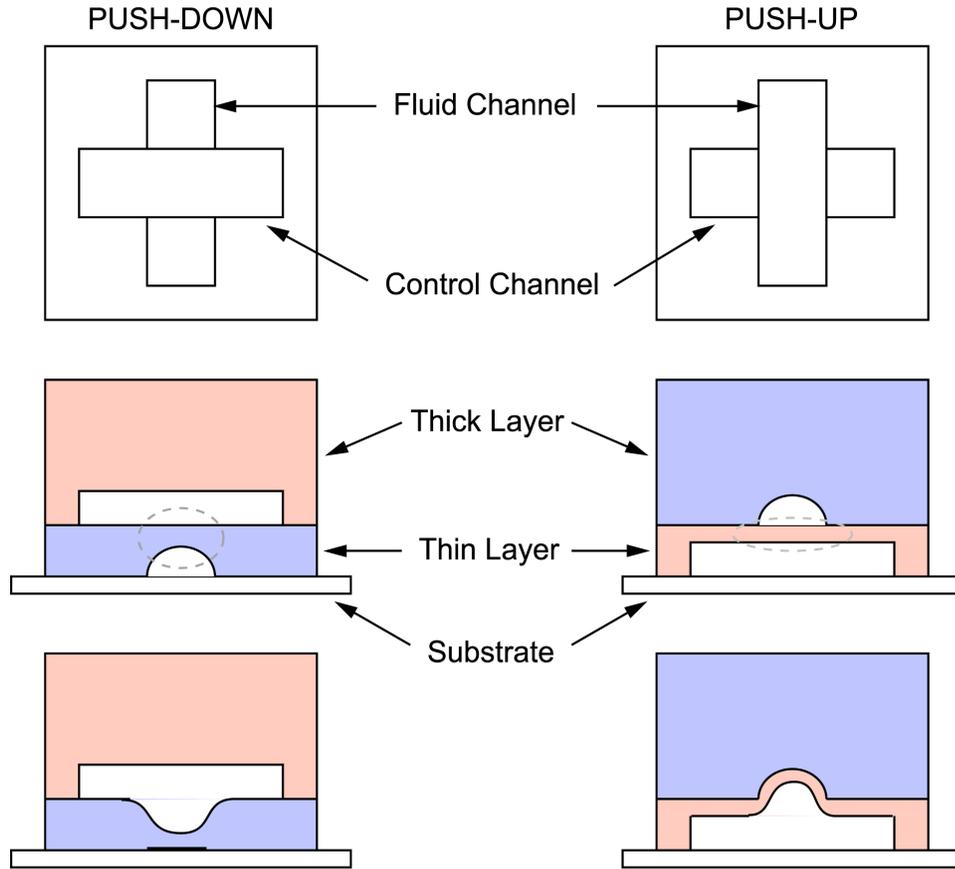


Figure 2.1: **Schematic of two common PDMS microvalve architectures.** (Left) Three diagrams of a *push-down* elastomeric valve. A top-view of the valve is shown in the upper diagram and a side-view is shown below. The fluid channel with rounded profile is in the bottom thin layer and flows beneath the control channel in the thick layer. A dashed circle highlights the thin elastomeric membrane that separates these channels and that is deflected during actuation. The lower diagram shows the valve in the closed state: the control channel is pressurized and deflects the membrane downwards until it completely blocks the fluid channel. A reduced control channel pressure would deflect the membrane only part way, leaving a reduced size opening for the passage of fluid. (Right) Corresponding three diagrams for a *push-up* elastomeric valve. In this case the fluid channel is in the thick layer and flows over the control channel. When actuated, the control channel deflects the intervening elastic membrane upwards, closing off the fluid channel. Typically devices are fabricated from two bonded layers; in both sets of figures, light red indicates the layer with actuation channels and light blue indicates the layer with fluid channels. Note the different shape of the valve membrane in the two cases. The valve membrane in a push-up device is a uniform thickness and is easier to deflect, resulting in lower actuation pressures.

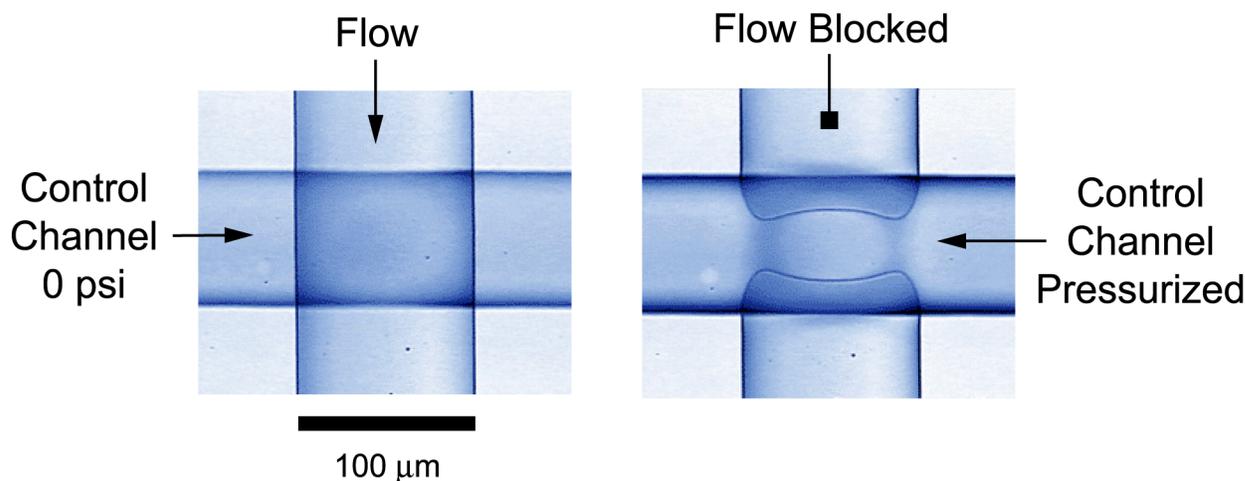


Figure 2.2: **Photograph of an elastomeric microfluidic valve.** (Left) Photograph of an open PDMS valve. (Right) Photograph of same valve closed by pressurizing the control channel. (Reproduced from <http://www.fluidigm.com/nanoflex.htm> with permission. Copyright Fluidigm Corporation.)

filter. The gaps at the incompletely closed corners are large enough to allow fluids to pass through but small enough to trap particles such as microbeads or biological cells [179]. By flowing a solution of beads through such a valve I have created packed columns of $0.7 \mu\text{m}$ microbeads on the upstream side of the valve for solid phase synthesis.

Three or more adjacent valves can be actuated in a cyclical fashion to act as a peristaltic pump [272], drawing or pushing fluids through a flow channel or circulating the fluid around a closed path to perform mixing [43]. Two adjacent valves along a fluid channel can be closed simultaneously to isolate the contents of the intervening length of fluid channel, thus forming a tiny chamber or reactor. Large arrays of isolated chambers can be implemented in this manner [268].

It should be noted that other mechanical valve architectures have been considered in PDMS including check valves such as diaphragm and flap valves [134], and a biologically inspired “lymph” valve [188]. However, such valves tend to be somewhat large, and they are passive, preventing sophisticated fluid handling. Ismagilov *et al.* [126] reported an interesting microfluidic switch based on fluid channels in separate layers *meeting* tangentially. The flow pattern (straight through or turning a corner) is determined by the relative aspect ratios of the channels and the size of the opening between them, as well as the position of the input stream within the channel. Pressure-

actuated control channels were shown to squeeze the tangential channels to alter their relative aspect ratios and dynamically switch the flow pattern. Such switch elements do not offer all of the flexibility of valves, however, but may be useful in flow-through applications.

2.3.2 Multilayer device fabrication

Devices containing microvalves are typically fabricated by the two-layer replication molding process depicted in Figure 2.3. Replication molding is the process by which a material is cast on a mold that contains a microfabricated relief pattern. Using standard photolithographic techniques, two relief molds are created, each consisting of a pattern of photoresist on a silicon wafer or glass slide. Ridges on the mold become microchannels in the cast PDMS. One mold represents a pattern of rounded-profile fluid channels and will create the “fluid layer”; the other represents control channels and will create the “control layer”. Typical channel dimensions are 100–200 μm in width by 10–50 μm in depth. Ridges on the fluid-layer mold must have a rounded profile to allow complete valve closing. Molds are prepared by spin-coating photoresist on a wafer, performing a soft-bake to solidify the resist, exposing the resist through a photomask defining the channel pattern, then immersing in a developer solution to remove uncrosslinked resist. In many resists, rounding can be achieved by heating above the resist melting temperature, causing it to reflow into a profile determined by surface tension; in some resists (such as SU-8), rounding can be achieved during the exposure stage [85]. Molds are typically treated with a mold release agent such as trimethylchlorosilane (TMCS) vapour prior to casting. Details of the mold preparation depend on the desired dimensions of fluid and control channels.

Depending on the configuration (push-up or push-down), PDMS prepolymer is spin-coated onto the mold representing the thin layer. The difference between the PDMS thickness and height of photoresist on the molds determines the valve membrane thickness. On the other mold, PDMS prepolymer is poured to a thickness of 3–7 mm. The layers are then cured into solids.

Subsequently, the thick layer is removed from its mold and holes are punched completely through to serve as inlet/outlet ports for channels in the bottom surface. This layer is then aligned and

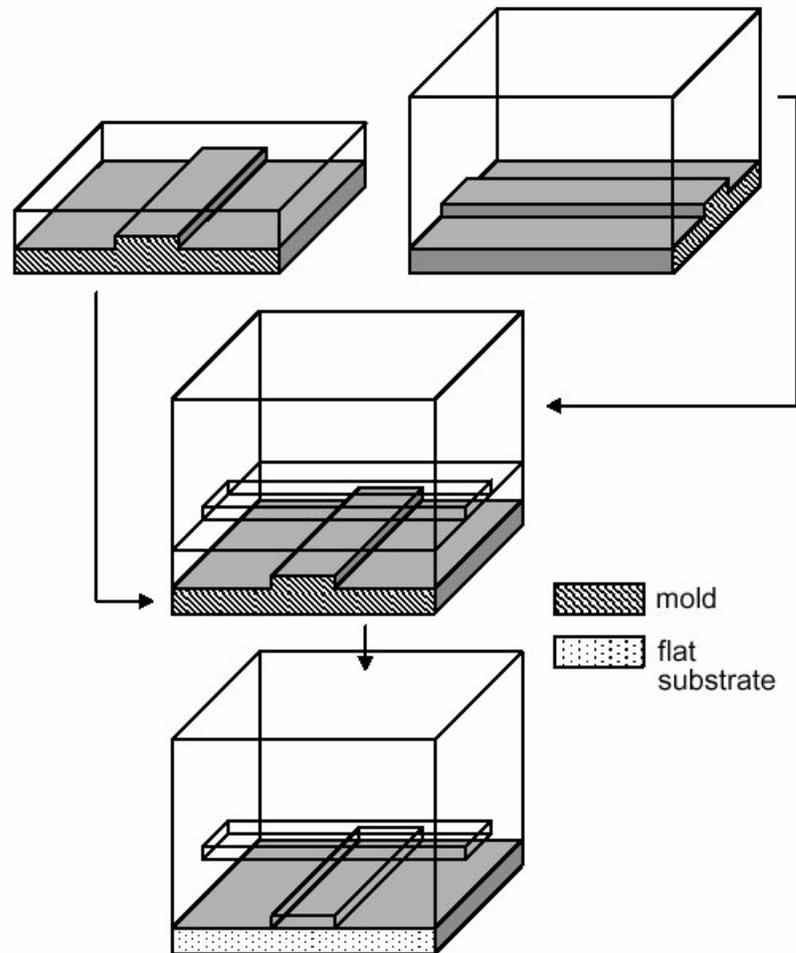


Figure 2.3: **Fabrication of 2-layer microfluidic devices by replication molding.** Molds are created for the lower- and upper-layer channel patterns. Typically these are silicon wafers patterned by photolithography with photoresist traces representing microchannels. In a push-down device, the lower layer contains the fluid channels; in a push-up device, the lower layer contains the control channels. A thin layer of elastomer is cured on the lower-channel-layer mold, while a thick layer is cured on the upper-channel-layer mold. Since the thin layer is generally too thin to be handled without experiencing wrinkling or other damage, the thick layer is first removed from its mold, aligned, and bonded to the thin layer. Once bonded, the 2-layer device can be removed from the mold and is adhered to a substrate to seal the bottom layer of channels. Not shown are inlet and outlet holes. These are typically punched through the thick layer before the first bonding step as a means to access upper-layer channels. In addition, holes are punched through the whole device prior to substrate-bonding to provide access to the lower-layer channels. (Reproduced from [272]. Copyright the American Association for the Advancement of Science, 2000.)

bonded (patterned side down) to the thin layer, still affixed to its mold. Note that the channels in the bottom surface of the thick layer become embedded entirely within polymer, and the valve membrane is made from material in the bottom layer. There are two common techniques for bonding PDMS layers, described below. When bonding is complete, the two-layer device is removed from the mold, and holes are punched completely through to access the microchannels in the thin layer. Holes are typically punched by hand using Luer stubs or by a hole-punching machine (Technical Innovations, Brazoria, TX). The device is then bonded to a substrate such as glass, a slab of PDMS, or PDMS-coated glass to seal the floor of the channels in the thin layer. Tubing is inserted into the punched holes for fluid delivery and pressurization of control channels.

Note that when the thick layer is released from the mold, it instantly shrinks by about 1.5% in each dimension—an empirically determined factor for PDMS. Because the thin layer initially is left on its mold, it does not shrink. Thus, the mold pattern for the thick layer must be enlarged by this factor to arrive at the correct final size to ensure that proper registration is possible during the alignment step.

Devices in our lab are typically made from one of two commercially-available silicone elastomers: RTV 615 (GE Silicones) or Sylgard 184 (Dow Corning). Each is supplied as two components—an oligomer mixture and a cross-linking agent—which are normally mixed in a 10:1 ratio. We achieve bonding by off-ratio mixing, wherein one layer is endowed with an excess of one type of functional group and the second layer with an excess of another [272]. Generally, the thin layer is mixed in a 20:1 ratio while the thick layer is mixed in a 5:1 ratio. The materials are mixed in an automatic mixer (HM-501 hybrid mixer, Keyence Corporation) and degassed in a vacuum desiccator prior to molding. The first casting step involves a partial cure of both layers by baking at 80°C. The bake time is typically 60 min for RTV 615 or 30 min for Sylgard 184. After alignment and stacking of the thick layer, the device is further baked at 80°C to complete the curing process (4 h for RTV; 2 h for Sylgard). During this time, excess functional groups in the two layers interact to form covalent bonds across the interface. Alignment and hole-punching time after the initial cure is limited to about 30 minutes—otherwise layer bonding can fail.

An alternative method for bonding layers employs oxygen plasma treatment [67]. Each layer of the device is made from 10:1 PDMS and fully cured. Layers to be bonded are treated with oxygen plasma and then placed in contact with a drop of methanol between. This fluid provides lubrication for alignment and prevents the treated surfaces from reconstructing to a lower-energy state, thus lengthening the available working time. Once properly aligned, the device is heated to drive out the methanol and surface groups react to covalently bond the layers together.

Strong bonding is crucial to device fabrication. Otherwise the large localized forces generated when channels are pressurized can peel the layers apart, leading to device failure—a process called “delamination”.

2.3.3 Advantages of PDMS devices

More than in other device technologies, interest and research in PDMS microfluidics has exploded in recent years, probably due in large part to two important factors. One is the ability to tinker. The low cost of PDMS and the simplicity of PDMS device fabrication allow nearly any research laboratory to explore ideas without prior microfabrication experience: once molds are prepared, no specialized equipment or facilities are needed. Ideas can be matured quickly, as rapid prototyping enables device improvements and optimizations to be made on very short times scales with minimal expense. Device fabrication from materials such as glass and silicon requires numerous processes such as chemical etching, reactive ion etching (RIE), and thermal bonding; each iteration takes considerable time and effort. Tinkering is limited to those with access to the needed equipment and expertise. For these reasons, PDMS is likely superior from a commercial manufacturing perspective as well.

The second important factor was the invention of the integrated microvalve [272]. Building two-layer devices does not introduce much additional complexity but provides tremendous power in the ability to manipulate fluids in controlled ways through the use of valves and pumps. Being mechanical, these valves are completely independent of fluid properties, unlike other mechanisms that have been used for flow control in other types of devices. This is a tremendous advantage

in that the same fabrication technology and design parameters can be used for devices in a wide variety of applications. Indeed, current devices are often designed by plugging together standardized components [49].

PDMS crossed-channel valves are exceptionally small, having a square or rectangular footprint comparable in size to the channel width, typically $100\ \mu\text{m}$. They also have a very small dead volume (100 pL for a typical $100\ \mu\text{m} \times 10\ \mu\text{m}$ cross-section), resulting in low carryover and quick response time. Furthermore, PDMS valves are durable: studies have shown no signs of wear or fatigue after millions of actuation cycles [272]. These characteristics enable the fabrication of reliable, high density, integrated fluidic circuits.

Aside from elasticity (which enables microvalve fabrication), many other properties of PDMS have proven well suited for microfluidic devices, including transparency, gas permeability, and ease of surface modification. Optical transparency allows for visual inspection of chip operations for troubleshooting or for performing bright field and fluorescent detection and imaging. High gas permeability enables several unique design features. For example, a microreservoir does not require separate inlet and outlet channels. In a process called “blind filling”, (or “dead end filling”), fluid entering the chamber through a single channel forces trapped air to escape directly through the bulk PDMS. This feature can be used to several advantages: (i) device designs are simplified by reducing the number of fluid channels and valves; (ii) the risk of sample loss (due to incorrect valve timings) is eliminated if a chamber has no outlet; and (iii) fluid volumes can be accurately metered by filling chambers having precisely known volumes. Gas permeability also enables a convenient method for solvent exchange. A closed chamber containing the original solution can be heated to cause evaporation and escape of the vapour through the PDMS, eliminating the original solvent. The desired new solvent can then be introduced via an inlet whereupon the dry solute is redissolved. Including empty, open-ended channels nearby can accelerate evaporation by shortening the thickness of PDMS that must be crossed by the vapour. The permeability of PDMS also allows sufficient gas exchange for biological cells to be cultured in microchannels for extended periods. (Cell survival also depends on the native biocompatibility of PDMS; other device materials often require special treatments or

coatings to avoid adverse interactions with biological materials.) However, gas permeability is not always desirable—unwanted escape of water vapour can lead to concentration increases or sample drying, and unwanted influx can lead to contamination of water-sensitive reagents. Engineering solutions do exist, however.

Another advantage of PDMS devices in comparison with rigid material devices is the simplicity of connections to the external world. In PDMS, holes are punched through the device and metal or plastic microbore tubing is inserted; tubing is held in place simply by friction since the punched hole is slightly smaller than the tubing outer diameter. Depending on various parameters, such connections are sufficient for pressures up to several atmospheres. With other chip technologies, interfaces are often quite elaborate, involving many fabrication steps or several separate components [82]. One advantage of MEMS fabrication with glass or silicon is that electronics and optics can more naturally be incorporated into devices. However, it has also been possible to integrate PDMS devices with such components due to the ability to seal PDMS reversibly or irreversibly with many substrates including silicon [1].

PDMS is suitable in a vast range of applications, but there are circumstances that dictate the use of alternative device materials. For example, very high temperatures preclude the use of polymers, instead requiring devices fabricated from inorganic materials such as glass, silicon, ceramic, or metal. High pressures would likely interfere with the operation of elastomeric valves and may lead to significant loss of fluids by diffusion or evaporation through the permeable channel walls. Hard inorganic materials or plastics should be used in devices operating under such conditions. Most importantly, PDMS is incompatible with many organic solvents [160] and cannot be used in most chemical synthesis and analysis applications. Solvent-resistant fluoroelastomers are preferable under such conditions, as are glass, inert metals such as stainless steel and titanium, and inelastic fluoropolymers such as Teflon. The advantage of *fluoroelastomers*, of course, is that device designs can incorporate the same microvalves and other features that have enabled highly integrated PDMS devices.

In the next several chapters, I describe our efforts to develop devices based on such materials that can be used as drop-in replacements for PDMS devices when solvents or harsh chemicals are required. These devices have the potential to expand the use of microfluidics to new areas, serving as a more generalized platform for rapid-prototypable highly-integrated solvent-resistant microfluidics.