Chapter 3

Solvent-Resistant Microfluidics

3.1 Introduction

PDMS microfluidic technology has advanced at an astonishing rate over the past several years, far outpacing progress in alternative microfluidic technologies. Where PDMS has not kept pace, however, is in the variety of solvents in which reactions and analyses are performed. Though many impressive devices have been demonstrated, fundamental incompatibilities of PDMS with many solvents [160] have limited this technology primarily to applications involving aqueous media [133]. Solvents can cause swelling, leading to disruption of microscale channel features, or can directly interact with the polymer. Glass, silicon, metal, ceramic, and even some plastic devices have fared far better with regards to solvent variety. However, these technologies suffer from the disadvantages outlined in Chapter 2. Simple manipulation of solvents and reactive species has been demonstrated in devices fabricated from hard materials, but it is difficult to imagine how these devices can be scaled up to the levels of integration seen in recent PDMS devices [268]. In addition, these devices are often designed from scratch for each new application—an indication of the lack of generality of the fabrication and fluid manipulation methods being employed.

It is this limitation that we strive to eliminate. Drawing inspiration from PDMS microfluidic device technology and the many qualities that have led to its success, we have developed several novel device technologies based on fluoroelastomer materials and demonstrated functional crossed-channel microvalves. Due to their elastomeric properties, these devices share many of the same advantages of

PDMS devices with the added advantage that they are resistant to most solvents. These technologies have the potential to expand the field of highly integrated microfluidics to many new applications in chemical synthesis and analysis, currently of great interest for chemical production and drug discovery. In addition, they may be able to expand the range of fluids used in existing applications, including protein crystallization screens [97] and optofluidics. Using similar microvalve architectures, these systems can be used as drop-in replacements for PDMS, leveraging much of the experience that has been accumulated by the community over the years. The fact that the operation of these mechanical valves is completely independent of the solution properties is especially important in chemistry applications where a very wide variety of solvents are in common use. Because the fabrication remains simple, these technologies will allow the kind of tinkering that has led to a near ubiquity of PDMS devices for biochemical and biological microfluidics.

In this chapter, I first briefly describe other work in the field of solvent-resistant microfluidics—where devices are fabricated from glass, silicon, and other inert, hard materials. This first section also serves to highlight the disparity in complexity of such devices compared with state-of-the-art PDMS devices. Next, I describe how the susceptibility of PDMS (or other polymers) to many solvents leads to difficulties in microfluidic device applications. In the last two sections, I discuss our general approach for fabricating resistant devices incorporating elastomers and give a brief account of many specific material systems and device architectures that we considered. Two of the most successful technologies—fluorinated norbornene and perfluoropolyether devices—are discussed in later chapters.

3.2 Prior work

Because the earliest microfluidic devices were fabricated from glass and silicon (both of which are resistant to most solvents and stable at high temperatures), it is not surprising that reactions and separations involving harsh conditions have been possible for many years. Glass and silicon devices are still in use today in such applications, as are microreactors fabricated from other materials such as metals, ceramics, and Teflon. Many impressive devices have been demonstrated over the years,

some containing very sophisticated fluidic components such as micromachined filters and packed bed reactors, integrated electronic heaters and optical sensors, and reactors consisting of thousands of parallel microchannels (see reviews in [278, 133, 227]). The vast range of chemical processes that have been successfully implemented is equally impressive (see reviews in [133, 62, 8, 77, 286]).

In most of this work with microreactors, it has been observed that separations are generally more complete and more rapid, and that synthesis often has improved selectivity and yield, compared to bulk processes. For example, Greenway *et al.* [93] observed sustantial improvements in efficiency over the bulk reaction when performing synthesis of 4-cyanobiphenyl from 4-bromobenzonitrile and phenylboronic acid in a glass microreactor. By immobilizing the $PdSiO_2$ catalyst, the additional benefit of reduced contamination in the product was realized. It is postulated that the catalyst bed also provides an enhancement of electroosmotic flow via a localized concentration effect at the Pd surface and causes partial ionization of water to generate base (the addition of which has been observed to improve the bulk reaction). These secondary results underscore the fact that reactions are very sensitive to flow conditions as well as the channel and catalyst surfaces, and suggest that each new microfluidic reaction could require optimization of these conditions.

The synthesis of peptides in continuous flow[1] borosilicate glass microreactors has been reported by Watts *et al.* [288, 287]. Several input channels branch off from different points along the main reaction channel, allowing reagents to be introduced sequentially. Fluids were driven by pulsed electroosmotic flow with inlet voltages adjusted to optimize the relative flow rates in order to maximize the yield. Dipeptides were synthesized via numerous routes including the following: introducing an (Fmoc)N-protected amino acid in the first channel, an activator in the second channel, and an (Dmab)C-protected amino acid in the third channel to yield a dipeptide (Fmoc- and Dmab-protected) at the output. To synthesize tripeptides, an (Fmoc)N-protected/C-activated amino acid was introduced in the first inlet, a C-protected amino acid in the second, an Fmoc deprotection reagent in the third, and

[1] In a closed reactor, reagents are brought in together and reacted to form the product. Thus, product is created all at once in a "batch". In continuous flow reactors, reagents are introduced continually side by side in a channel or as alternating plugs of reagents. The reagents mix and react as they flow together, allowing products to be collected in a continuous stream at the output. Another method of reaction is solid-phase synthesis, in which the products remain affixed to a substrate and are built-up by sequentially introducing the needed reagents one at a time. Once finished, they can be cleaved from the substrate.

an (Fmoc)N-protected/C-activated amino acid in the fourth. (The final tripeptide was Fmoc- and Dmab-protected.) Multi-step syntheses were observed to occur with much higher yields than bulk reactions, on much shorter time scales, and with much lower reagent concentrations. However, this work also touches on the difficulties of performing multi-step synthesis in continuous flow reactors. If two reagents are not completely converted to product by the time they reach the inlet for the third reagent (which is intended to react with the product), there can be direct cross-reactions of the third reagent with the first two reagents, as there is no means to flush away the excesses. To reduce byproducts in multistep peptide synthesis, one could use orthogonal protecting groups on subsequent amino acids; however, since only a couple of different deprotection conditions are known, this would severely limit the maximum peptide length. A further disadvantage of solution-phase synthesis of peptides is that both ends of the amino acid must be protected during synthesis to avoid unwanted reactions. In solid-phase synthesis, one end is bound to the solid-support and is not free to react so such protection is unnecessary.

Fletcher *et al.* [77] postulate that details of electrokinetic flow may be responsible for the high reaction rates and synthetic yields that are observed in many glass and silicon microdevices. In mechanically driven flow, when two slugs of fluid are brought together, reagents from each slug diffuse into the other across the interface and react. As diffusion proceeds, the concentration locally drops and molecules from one slug encounter lower and lower concentrations in the other upon crossing the interface. Simulations supported by experiments indicate that this is not the case in electrokinetic flow [77]. It is as if one slug passes *through* the other one. Because the "interface" between the slugs is moving, there is no local depletion by diffusion, and concentrations encountered by molecules crossing the interface remain high. For optimal reactions, series of several narrow slugs are injected rather than a single large one. Interestingly, pulsed electrokinetic flow appears to be more effective than introducing two laminar streams side by side in a fluid channel. It should be noted that the concentration effect seen in electrokinetic flow can be "simulated" in mechanical flows as well. For example, one can isolate a slug in a chamber and evaporate the solvent (if the device is

permeable). The second slug can then be brought into this chamber and each reagent will encounter the other at the full original concentration.

Daridon *et al.* [55] report the fabrication of 3-layer glass microfluidic devices for integrated synthesis and analysis. The top and bottom glass plates contain microchannels facing the center plate—a thin glass layer containing holes. These holes (vias) connect channels from one layer to those in the other and can also act as optical cuvettes for analyzing the absorbance (for example) of the fluid inside. The glass device was sandwiched between molded PMMA layers that held the external tubing and ferrules in place and served as guides for optical fibers on either side of the microcuvettes. The authors demonstrated a two-step Wittig reaction in methanol and the Berthelot reaction, a three-step organic reaction involving basic solutions (up to pH 12.5) for the colorimetric detection of ammonium.

Kikutani *et al.* [148] report the fabrication of a three-dimensional glass microchannel network for 2×2 continuous-flow parallel combinatorial synthesis. A set of two different amines in the aqueous phase and a set of two different acid chlorides in the organic phase were reacted in four combinations to produce four different amide products. The reaction is hypothesized to proceed via a phase transfer mechanism, wherein the amine diffuses into the organic phase and reacts, and the product remains in the organic phase. No significant impurities were observed in the organic phase despite there being a competing side reaction (hydrolysis of the acid chlorides). It is believed that the rate of the amide formation reaction is enhanced more than that of acid hydrolysis due to the high specific surface area between the two phases. This observation highlights the importance in microreactor design of carefully considering how the rate of side reactions is affected by the scale-down, in addition to the reaction of interest. More recent enhancements of these devices include integration with an extraction step in a device for heavy metal ion analysis and the fabrication of glass devices with up to 10 layers [270]. Kikutani *et al.* reported difficulties equalizing the flow rates despite careful device design and fluid delivery via accurate syringe pumps, an effect that will likely hamper significant increases in integration density in continuous flow reactors. This problem could be eliminated by using systems with mechanical microvalves, with which fluid volumes can be accurately metered.

Martin *et al.* [181] at Pacific Northwest National Laboratory (PNNL) fabricated continuous flow solvent-exchange devices by stacking several hundred thin stainless steel laminates. The device consists of a very long serpentine pair of microchannels with extremely high aspect ratio separated by a porous membrane. Hexanol was transferred between hexane and an aqueous fluid in this device. The authors also demonstrated a plasma microreactor, fabricated from two milled ceramic blocks sealed together with a Viton gasket. Plasma is a harsh chemical processing environment where UV light, radical species, or photocatalytically active catalysts can facilitate interesting reactions. The reactor was designed to break down methane into ethylene and hydrogen, and convert methane and air to syngas. Ceramic devices have also been fabricated by lamination methods [182]. Janicke *et al.* [130] report the use of laminated stainless steel microreactors to perform the controlled formation of water from explosive mixtures of hydrogen and oxygen gas in fuel cell applications. The heat exchanger in the device was sufficient to remove heat from the exothermic reaction, thus preventing thermal runaway. The reaction takes place on an alumina coating impregnated with platinum on the walls of the reactor.

While significant advancements in solvent-resistant microfluidics have been made in individual device components such as microreactors and separation columns, only modest steps have been taken towards *integrating* multiple functionalities into MEMS fluidic devices [152]. One of only a few exceptions, Burns *et al.* [30] demonstrated a device for performing a multi-stage DNA analysis: sample loading and preparation, heating and reaction, gel electrophoresis and photodetection are all integrated on a single chip. However, the device density and degree of integration do not compare with recent PDMS devices boasting tens of thousands of valves and reaction chambers [48].

The lag of silicon and glass devices is likely due to the fact that fabrication is difficult and expensive as discussed in Chapter 2. Mechanical pumps and valves are particularly difficult to fabricate in rigid materials—those that have been demonstrated are typically quite large (millimeters) and do not lend themselves to dense integration in devices. This limits devices to relatively simple flow-through configurations using capillary or electrokinetic flow. Furthermore, not all fluids can be electrokinetically pumped, and some researchers have altered the solvents used in reactions to

fit this pumping technology [62]. Clearly, fixing the microfluidic chip technology by incorporating a more generic pumping method (e.g., mechanical pumping) would be preferable.

Fabrication of devices from polymers has helped to simplify and reduce the cost of device fabrication [272, 25, 244]; however, the materials used are typically not resistant to solvents. (The majority of applications are currently in the area of biotechnology and involve aqueous chemistry.) Photopolymerization has emerged as a simple fabrication technique that can use a variety of polymers [147], and Harrison *et al.* [100] have fabricated devices by this method from a thiolene-based optical adhesive. This material is resistant to many solvents including toluene, tetrahydrofuran, and ethanol, but it is susceptible to others such as methylene chloride and therefore is not suitable as a generalized platform for all applications in solvent-resistant fludics. Furthermore, it is a rigid material and does not solve the valve and pump problem. Rather than the current situation, where the device material must be carefully selected for each new microfluidic application, or, worse, where the chemistry must be altered to be compatibile with the available device technologies [62], the field of microfluidics would benefit tremendously from a generalized microfluidics platform that is suitable for nearly all applications.

We believe solvent-resistant elastomeric microfluidic devices can solve all of these problems. Possessing all of the properties of PDMS that facilitate very high levels of integration and simple fabrication, and additionally providing resistance to solvents, these devices have the potential to serve as powerful new tools in organic chemistry. The generality achieved (by both the device material and the mechanical valve operation being insensitive to the fluid properties) should help to speed the advancement of the field by reducing the effort that is currently spent tailoring devices and chemistries to each application.

Densely integrated, solvent-resistant devices would be ideal for novel applications in combinatorial chemistry, high throughput screening, and parallel multi-sample multi-analysis chips, possibly integrated with sample preparation or purification steps. A highly parallel combinatorial chemistry chip could have dedicated reactors for every possible output product, obviating the need for current

techniques such as mix and split synthesis [148], which add complexity to assays by requiring a probe identification step after performing a screen.

3.3 Organic solvents and elastomers

Many polymers, including elastomers such as PDMS, are susceptible to swelling or to chemical attack upon exposure to at least some organic solvents or acids and bases. Such adverse interactions can have considerable impact on the operation of polymeric microfluidic devices due to the fragility and high surface to volume ratio of microscale features. Interactions with the solvent or with impurities in the solvent can adversely impact not only the device integrity but also the reaction or analysis being performed inside the device.

3.3.1 Adverse interactions

In general, the following four problems can arise: (i) swelling of the polymer; (ii) extraction of impurities; (iii) partitioning between the polymer and solvent; and (iv) chemical reaction with the polymer. Each of these is discussed below.

Swelling can deform microchannels, altering their dimensions or even closing them completely [200]. For example, dichloromethane cannot be flowed through PDMS microchannels for this reason. Dichloromethane swells PDMS by 22% in each linear dimension [160]. In an elastomeric device that is several millimeters thick, this represents a substantial deformation compared with the channel depth—typically tens of microns. Channels can easily be plugged due to non-uniform swelling, arising as a result of the exposure occurring within a microchannel or input port (and gradually diffusing outward). Swelling can also create stresses that disrupt bonding, leading to leaks and cross-contamination in devices that lack covalent bonding at solvent-exposed interfaces. This might be the case, for example, in applications involving *in situ* synthesis on the substrate, which employs *reversible* bonding so the microfluidic device can be removed during or after synthesis. An additional possible effect of swelling is the alteration of elastic properties, impacting microvalve performance (such as a change in actuation pressure).

Extraction of impurities such as unpolymerized monomers or oligomers from the polymer can impact mechanical properties in some materials, but more importantly, it can introduce contaminants into the fluid channels that interfere with reactions or are present as contaminants in the final products. To a certain extent, this problem can be eliminated by pre-extracting the device in the solvent(s) with which it will be used. High swelling solvents enhance extraction.

Partitioning is the effect whereby a solute can be divided between the solution in the fluid channel and the polymer adjacent to the fluid channel. This effect can alter reagent concentrations in the fluid channels. Furthermore, solute trapped in the polymer may be difficult to flush out of channels and may be released during a later stage in a multi-step process, causing unwanted contamination.

Finally, some polymers are susceptible to direct chemical or ionic interactions with solvents or solutes. Such reactions can have a wide variety of adverse effects including significant depletion of reagents in fluid channels, contamination of the desired reaction with byproducts of polymer interaction, or chemical modifications to microchannel surfaces that can affect wetting properties or leave functional groups that interfere in later stages of a microfluidic process. Furthermore, some reactions can uncrosslink the polymer, affecting elasticity and even destroying the device. For example, I observed that PDMS soaked in dichloromethane with 3% trichloroacetic acid for several days became brittle and crumbled apart.

Clearly, these interactions should be avoided in microfluidic devices by appropriate choice of device materials. As a first approximation, the material should exhibit low swelling in the solvent(s) of interest and be chemically inert. Further evaluation requires the fabrication of actual microfluidic devices to accurately determine the extent of other interactions. To avoid having to tailor the device material to each application, it is desirable to find a *universal* material.

3.3.2 The problem with PDMS

PDMS is incompatible with a wide range of solvents, as recently reported in depth by Lee *et al.* [160]. Swelling data from that study is reproduced in Figure 3.1. It should be noted that 20 of the solvents tested caused equal or greater swelling compared to methylene chloride—a solvent that we

found completely blocks flow in channels—and thus would be unlikely to be usable in PDMS devices. The additional incompatible solvents include acyclic and cyclic hydrocarbons (pentanes, hexanes, heptane, cyclohexane), aromatic hydrocarbons (xylenes, toluene, benzene), halogenated compounds (chloroform, trichloroethylene), ethers (diethyl ether, dimethoxyethane, tetrahydrofuran), and amines (diisopropylamine, dipropylamine, triethylamine) [160].

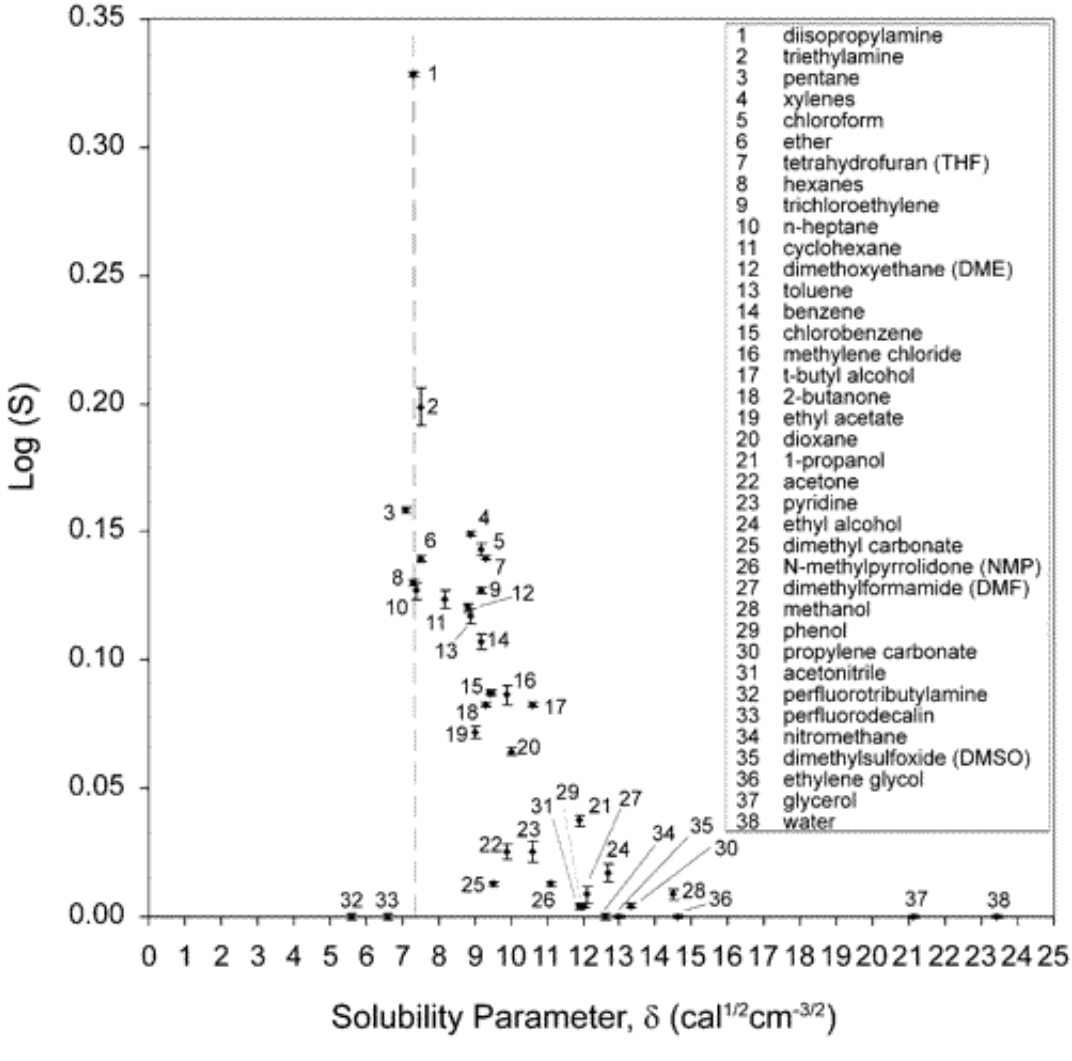

Figure 3.1: **Swelling of PDMS in various solvents**. The logarithm of the linear swelling ratio after 1 day immersion, S, is plotted as a function of the Hildebrand solubility parameter, δ, for a wide variety of solvents. Qualitatively, as predicted by solubility theory, the greatest degree of swelling is observed for solvents having a solubility parameter closest to that of PDMS (dotted vertical line). (Reproduced from [160]. Copyright the American Chemical Society, 2003.)

It may be possible that PDMS devices are suitable in a narrow range of applications in synthetic or analytical chemistry involving non-swelling solvents. The range of solvents may be extended to some high-swelling solvents if the chemical process can tolerate dilution with a non-swelling solvent—such solvent mixtures often cause reduced swelling. However, PDMS devices are not suitable as a *generalized* microfluidics platform for chemistry. Certainly PDMS is not compatible with our original aim of DNA synthesis chemistry (involving dichloromethane and tetrahydrofan among other solvents).

3.3.3 Alternative materials

To help determine which materials are compatible with particular solvents, a variety of sources provide tabulated data such as (i) quantitative swelling measurements, (ii) qualitative compatibility data (sometimes with a letter or number scale), and (iii) solubility parameters. Alternatively, one can perform experiments to determine these data.

Quantitative swelling data are available from several sources [167, 166]. Such sources indicate that most polymers are susceptible to at least some solvents. According to data in the Plastics Design Library (PDL) Chemical Resistance handbooks, several plastics and elastomers exhibit excellent resistance to a *wide variety* of solvents and may be suitable as materials for generalized solvent-resistant microfluidics. These plastics include PVDF (polyvinylidene fluoride), polyolefins (including polypropylene), PEEK (polyetheretherketone), Tefzel (ETFE, ethylene-tetrafluoroethylene), Teflon (PTFE, poly-tetrafluoroethylene; TFE, tetrafluorethylene; FEP, fluoro ethylene propylene; PFA, perfluoroalkoxy), and others [167], while the elastomers include tetrafluoroethylene propylene copolymer and terpolymer, FKM fluoroelastomers, and FFKM fluoroelastomers, among others.

Qualitative compatibility data are generally available from the manufacturers or suppliers of polymers. However, such data are of limited usefulness due to inconsistencies arising from the different rating systems common in different industries and from the different solvents commonly used in those industries. For example, when a manufacturer claims “high chemical resistance”, this is often true only for a few classes of solvents. Inconsistencies may also arise due to different ways in which

various factors (such as weight change, length change, and visible change such as colour) are combined into a single rating or due to the presence of differing quantities of additives (e.g., colourants, plasticizers, etc.) from one manufacturer to another. Furthermore, because most studies pertain to macroscopic sizes of polymers and quantities of solvents, the data are not immediately applicable to the conditions under which microfluidic device channels are exposed to solvents.

Solubility parameters are a third type of data to guide materials selection. In order to explain their relevance, it is necessary to briefly introduce the principles of solubility theory. Based on Flory-Huggins theory and the lattice model of mixing, one can calculate a free energy change that occurs when a solvent is "mixed" with a polymer and causes swelling. This energy contains terms for mixing (subscript "mix") and deformation due to swelling (subscript "def"):

$$\Delta G = \Delta G_{mix} + \Delta G_{def} = \Delta H_{mix} - T\Delta S_{mix} - T\Delta S_{def} \tag{3.1}$$

where

$$\Delta H_{mix} = kT\chi n_s \Phi_p \tag{3.2}$$

$$\Delta S_{mix} = -k[n_s \ln \Phi_p + n_p \ln \Phi_p] \tag{3.3}$$

$$\Delta S_{def} = -k(3/2)n_p(\alpha^2 - 1) \tag{3.4}$$

where k is the Boltzmann factor, T is the temperature, n_p is the number of polymer segments, n_s is the number of solvent molecules, Φ_p is the volume fraction of polymer, Φ_s is the volume fraction of solvent, and α is the fractional length change due to swelling. The solvent can dissolve (and thus swell) the polymer if $\Delta G < 0$.

In practice, one makes predictions of *relative* solubilities based solely on the enthalpy term, ΔH_{mix}. This term depends on the Flory-Huggins parameter $\chi \sim (\delta_p - \delta_s)^2$ where δ_p and δ_s are the Hildebrand solubility parameters for the polymer and solvent, respectively. This factor is the average cohesive energy density difference. When the solvent and polymer have similar cohesive

energies, this factor is small and swelling is more likely to occur. This is related to the well-known principle of "like dissolves like". When two species have similar cohesive energy densities, it is more likely that one can be mixed into the other with little energy penalty.

Other sets of solubility parameters distinguish among the proportions of different *types* of cohesive interactions such as dispersion forces (d), polar forces (p), and hydrogen-bonding forces (h) that make up the total cohesive energy density. For example, Hansen parameters are defined as

$$\delta^2 = \delta_{\mathrm{d}}^2 + \delta_{\mathrm{p}}^2 + \delta_{\mathrm{h}}^2, \tag{3.5}$$

and fractional parameters are defined as

$$\mathrm{f_d} = \frac{\delta_{\mathrm{d}}}{\delta_{\mathrm{d}} + \delta_{\mathrm{p}} + \delta_{\mathrm{h}}}. \tag{3.6}$$

These types parameters are often more accurate as they are only similar if both the solvent and polymer have similar contributions of each type of bonding to their cohesive energy density. This further emphasizes the need for solvent and polymer to be chemically similar for swelling to occur.

Hildebrand parameters are tabulated for many solvents and polymers. However, as shown in Figure 3.1, the parameters are only a very rough guide. In PDMS, two perfluorinated solvents have very similar solubility parameters to PDMS but cause no swelling; compare this to, say, dioxane, which causes significant swelling but has a solubility parameter further from that of PDMS. Other types of parameters would clearly be more predictive in this case, but these more informative parameters are not available for many polymers. For novel polymers, such as the perfluoropolyether (Chapter 5) and fluorinated norbornene (Chapter 4) polymers developed by our collaborators, pre-existing solubility data are not available at all.

Fluorcarbon polymers are widely known to have exceptional solvent-resistance, particularly the *per*fluorinated (fully fluorinated) ones. These polymers are particularly stable due to the strength of the carbon-fluorine bond and due to steric hindrance arising from the strong forces between hydrogen and fluorine atoms in the macromolecules [175]. Using the colloquial principle of "like dissolves like",

one can argue that fluoropolymers exhibit low swelling because they are chemically dissimilar to most solvents (other than fluorinated solvents) encountered in chemistry. Fluor*oelastomer* history and chemistry are reviewed in References [175] and [106]. Good elastic properties are exhibited primarily by those materials consisting of long, linear chain molecules, exhibiting functional groups such that strong intermolecular forces that lead to crystallinity and hardness are avoided. Crosslinking of the network ensures complete recovery after deformation. Elastomers are often made by first polymerizing long chains of monomers, then crosslinking or "curing" these chains into a three-dimensional network. Cure sites are often the most vulnerable point in solvent-resistant elastomers [106] and account for many of the differences in solvent-resistance exhibited by different fluoropolymers.

With our original goal of performing DNA synthesis in chips, our solvent-resistance requirements were quite stringent due to the broad range of different solvents involved. In effect, this drove us to find a material that was resistant to nearly everything and that could serve as a material in *generalized* solvent-resistant microfluidics (i.e., suitable for any application). Instead of attempting to make predictions of the single best material, our approach was to select materials such as fluoropolymers that looked promising according to the available solvent-resistance data and then perform relevant *in situ* evaluations by attempting to fabricate simple microfluidic devices. When no solvent-resistance data was available, we performed our own experiments to assess compatibility. Typically, in such cases, a polymer sample was first evaluated by a surface exposure test. Drops of several solvents (dichloromethane, tetrahydrofuran, acetonitrile, and others) were deposited on the surface and monitored for signs of swelling or chemical attack. Highly swelling solvents were immediately visible due to a raised bump at the droplet location. Chemical attack was inferred if the surface exhibited pitting, discoloration, or other effects after evaporation of the solvents. While not quantitative, such experiments more closely resemble the conditions within a microfluidic device than do bulk solvent immersion tests.

3.4 Solvent-resistant device principles

When considering the fabrication of microfluidic devices from solvent-resistant materials, it is instructive to carefully examine which parts of devices (in addition to the elastic valve membrane) are actually exposed to solvents.

3.4.1 Two-layer architectures

As illustrated in Figure 3.2, in a push-up device, the fluid channel in the thick layer is sealed by the thin layer. Thus, solvents in the fluid channel are in direct contact with both layers of the device, and solvent-resistant materials must be used throughout. In contrast, solvents contact only the thin layer and the substrate in a push-down device. In principle, one could fabricate devices that are resistant only in their bottom layer. This is useful when the resistant material is very expensive or scarce. To avoid flowing solvents through holes punched in an incompatible material in the upper layer of the device, holes can be drilled through the substrate for solvent delivery directly into fluid channels. In Chapter 4, I describe two methods for connecting tubing to a drilled glass substrate for delivering solvents in this manner—a custom-built fluid delivery jig and commercial fluidic connectors. Note that solvent-resistant tubing is required for solvent delivery.

3.4.2 Coated devices

As an alternative to making the whole device or a device layer out of a resistant material, solvent-resistance may be conferred by a protective coating. In a push-down device, it is sufficient to apply the coating to the bottom surface. In such cases, solvents must typically be delivered through the glass as we found hole punching to severely damage most coatings in a large area around the hole. Furthermore, it is difficult to apply a complete coating in the interior of the punched inlet holes. Bottom coating protects the device while also permitting solvent in the fluid channel to contact the substrate if desired for *in situ* solid-phase synthesis on the substrate, for example. This procedure can complicate device fabrication, however, as it is necessary to find a method for bonding the coated device to the desired substrate. Another way to apply coatings is to flow a coating solution through

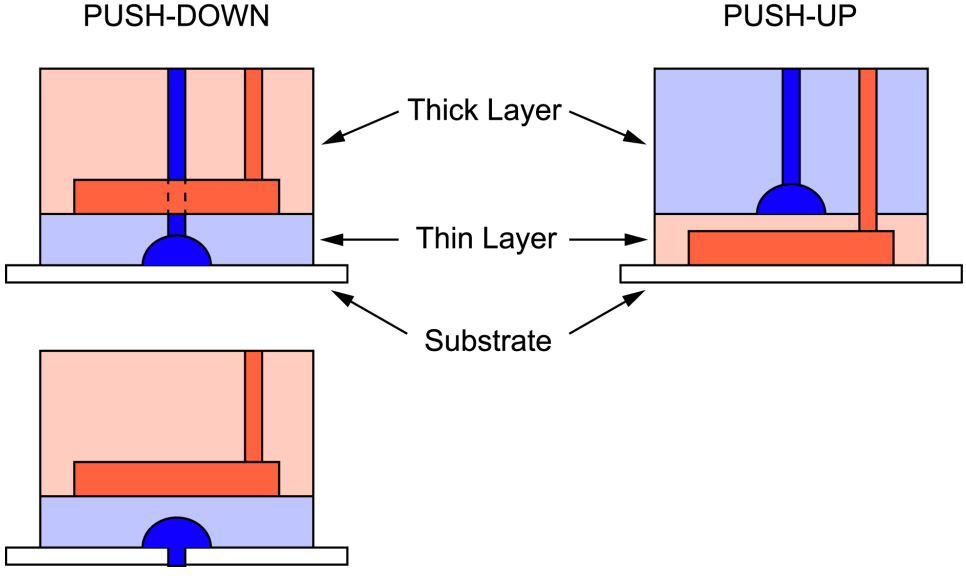

Figure 3.2: **Exposure of device layers to solvents in different valve architectures**. (Left) In the push-down valve architecture, solvents are carried by the fluid channels in the thin layer. Solvents (dark blue) contact the channel walls, consisting of the material in the lower layer (light blue) as well as the substrate. To deliver solvents to the fluid channels, holes can be punched through the whole device (top diagram) or holes can be drilled through the substrate (bottom). The latter is preferred for devices in which only the bottom layer is solvent-resistant or if solvent resistance is conferred by a protective coating. (Right) In the push-up architecture, solvents (dark blue) come into contact with both layers of the device. Thus, the device must be constructed entirely from materials that are compatible with the solvent or the fluid channel must be coated on all surfaces. In all diagrams, dark red represents the contents of the control channels, which may be air or a hydraulic fluid such as water or oil.

microchannels after the device is fully assembled. However, this can often lead to non-uniform coatings or to clogging of channels. To avoid the bonding problem, it may be possible to coat only part of the surface (i.e., the inside of fluid channels, but not the bottom of walls between them), perhaps using a masking technique.

In a push-up device, one must coat all surfaces of the fluid channel. Options are to flow a coating solution through channels, or to coat both device layers (i.e., the top of the thin layer and the bottom of the thick layer) prior to device assembly. In the latter case, a method for producing a strong coating-coating bond is needed. A subtle difference between push-up and push-down devices is that a coating on the valve membrane will be stretched in the former but compressed in the latter. This is an important consideration for plastic coatings (which do not stretch) or weak coatings (which can break if stretched).

It is important that the coating adhere well to the elastomeric device material and that the coating provide a barrier to diffusion of the solvents of interest. Coatings with high permeability or pin-hole defects are not sufficient as they allow solvents and reagents to rapidly reach the non-resistant material underneath.

3.4.3 Membrane architecture

We devised an additional novel architecture for crossed-channel microvalves, shown in Figure 3.3. It consists of a fluid- and control-channel layer separated by a thin uniform elastic membrane. Valve operation is identical to push-down or push-up valves. The main difference is that the elastic valve membrane is no longer part of the bottom molded device layer, but is contained in a separate non-patterned layer. This architecture was invented after learning that several promising fluoroelastomers could not be easily molded at the micron scale but were commercially available as flat sheets. Coated membranes are also an option and may enable superior coating quality compared to coated 2-layer devices in which the negative relief pattern of the microchannels interferes with the coating process. Because the fluid layer must be resistant to solvents, we frequently fabricated it from glass, which can be chemically etched to give rounded microchannels. However, the use of glass

eliminates permeability and complicates connections for solvent delivery. The control layer need not be resistant to solvents.

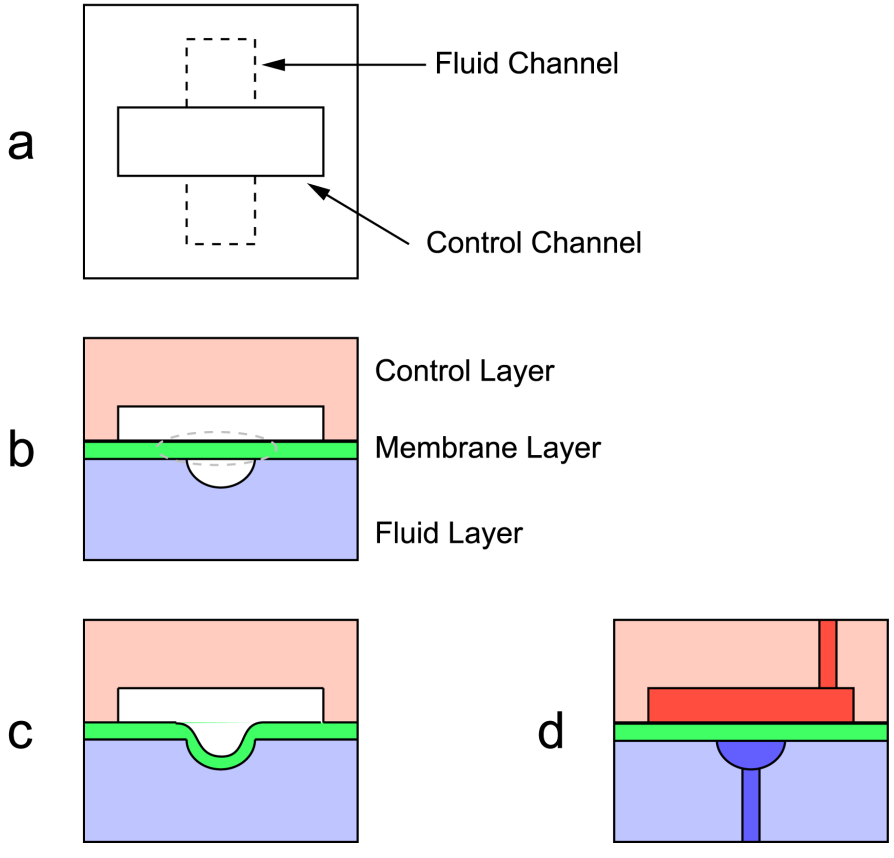

Figure 3.3: **Novel membrane architecture for crossed-channel microvalves**. (a) Top-down schematic of a membrane device illustrating orientation of fluid and control channels. (b) Side view schematic of the device. The fluid and control channel layers are not in contact but are separated by a thin elastic membrane. The materials from which the fluid and control layers are made need not be elastic. Note that the deflecting membrane is simply a flat featureless layer, useful in cases where resistant materials are available as flat sheets but cannot be molded with micron scale channel features. (c) Schematic of the device with the valve closed. As usual in crossed-channel valves, pressurizing the control channel deflects the membrane further and further into the fluid channel until it completely blocks the flow as shown here. (d) Schematic showing the device filled with fluids. Solvent (dark blue) contacts the fluid layer material as well as the membrane. Fluids are delivered to each layer by drilled or punched holes as shown.

A membrane device constructed with fluid and control layers made from glass contains only a very small amount of elastomer. We believe the effects of swelling are therefore reduced and that this might allow even high-swelling solvents to be used in such devices. As a demonstration, we

fabricated a device with a PDMS membrane and successfully flowed dichloromethane through the channels. Unlike in bulk PDMS, the channels did not swell shut and block the flow.

Membrane devices, like conventional 2-layer devices, require strong adhesion between all layers for proper operation. At first glance, it appears that chemical bonding is not necessary and that one could simply hold the device together by applying force. However, after fabricating several devices it became clear that this is not the case. When actuating a valve, the membrane intially deflects as expected; however, the membrane continues to peel free of the control layer surface along the fluid channel in both directions, greatly expanding the region of deflection. Eventually, the entire fluid channel is "closed" due to the actuation of a single valve. This also leads to cross-talk between any valves connected to that channel.

3.4.4 Summary

To summarize, solvent-resistance can be conferred by choosing resistant materials or by applying protective coatings or surface treatments. Push-down devices allow construction from two materials in which only the thin layer need be fabricated from a resistant material, an important feature when using expensive or scarce materials. The membrane valve architecture is an alternative to push-up and push-down valves with the primary difference that the elastic membrane is not part of any patterned device layer but rather is a flat uniform sheet. This has implications for certain elastomers that are not easily patterned.

One other approach to solvent resistance may be the use of a "sheath flow", whereby a sheath of one solvent surrounds the flow of the desired reagents. They do not mix (except slowly by diffusion) if in the laminar flow regime. Obviously, the sheath solvent must be compatible with the reagents, and the polymer must be compatible with the sheath solvent. The difficulty is to arrange for the reagents to flow as desired—to truly protect the fluid channel, the sheath must surround the reagent in all three dimensions. Furthermore, the flow distance is severely limited unless flow rates are extremely high; therefore, pursuit of other methods had priority.

3.5 Research results

Our research into solvent-resistant microfluidic devices proceeded in many different directions: (i) investigation of new materials; (ii) investigation of coatings and surface treatments; (iii) design and demonstration of the membrane device architecture; and (iv) development of a three-dimensional molding procedure.

To fabricate devices from new materials, many factors must be considered. Of course the polymer must be elastic and must be compatible with the desired applications. We initially considered room temperature DNA synthesis, which turned out to impose stringent conditions on compatibility due to the wide range of solvents involved. It must also be possible to pattern the polymer surface at the 10–100 μm scale by methods such as replication molding or etching, and it must be possible to bond polymer layers. Though not essential, it is convenient if it is possible to punch holes in the material for making simple off-chip connections and if the material is transparent or translucent such that fluid flow can be observed directly.

One of the most important issues is bonding—both between layers and between the device and the substrate. Strong, covalent bonding is needed in order to withstand the large local pressures generated inside control channels and the deformation stresses that arise when polymers swell (even slightly) in solvents. Weak bonding leads to delamination of layers, which can result in cross-contamination of fluids in different channels or in device failure. A lack of covalent bonding has been observed to permit proteins to migrate up to 5 μm laterally in between layers despite no signs of delamination [57]. One other problem I have observed is that very weak bonding of the device to the substrate allows the device to lift from the surface when push-down valves are actuated, causing valve membranes to continue to extend downwards, eventually rupturing. This problem could be solved by gently clamping the device to the substrate. One must be aware of the relative strengths of layer-layer and substrate-device bonding when choosing whether to use the push-down or push-up valve architecture. The latter has the highest pressure requirements at the device-substrate interface, for example.

Bonding of cured layers can be achieved in many ways: gluing, modification of the polymer to allow covalent attachment of layers, preparing layers with different fractions of constituents [272], and surfaces treatments [67], among others. When working with off-the-shelf polymers or polymers with proprietary structures, we found it challenging to find reliable bonding procedures, especially with fluoropolymers that often exhibit non-stick surfaces. Even in collaborations where polymers were being specifically designed with microfluidics applications in mind (Chapters 4 and 5), determining and optimizing a bonding protocol took considerable time (sometimes more than a year). It was important to find a *reliable* method of adhesion, to avoid wasting rare material samples while trying to fabricate full devices and to enable the investigation of more complex fluidic networks. This search for a bonding process hinders the evaluation of new materials in microfluidic devices and was often our most significant bottleneck. One way to avoid this problem is to eliminate bonding steps altogether. For example we recently developed three-dimensional molding techniques (discussed in Chapter 6) to cure both layers simultaneously into a monolithic device. Another way to eliminate the need for bonding is to use a different valve actuation scheme such as mechanical pins [96] so that a second device layer is unnecessary; however many of the desirable properties of 2-layer PDMS microfluidics would then be lost.

For coatings, it is necessary to find a method for reliably covering the solvent-exposed surfaces without clogging microchannel features. In addition, it must be shown that the coating provides an effective barrier to the solvents of interest and that it does not interfere with valve actuation. The coating must also adhere strongly to the polymer.

In the remainder of this section, I describe our specific achievements with respect to the first three research directions. The work has been organized into three sections: modified PDMS devices, fabrication from other materials, and fabrication of membrane devices. For completeness, I have included materials and processes that looked promising initially but that ultimately did not lead to practical devices. Particularly successful and extensive work done with two novel polymer materials—fluorinated norbornene and perfluoropolyether polymers—is discussed separately in Chapters 4 and 5.

3.5.1 Modified PDMS devices

The simplest approach to fabricating solvent-resistant elastomeric devices is the modification of PDMS devices to confer solvent resistance, thus leveraging the existing device design and fabrication expertise. In this section, I describe several experiments to confer solvent-resistance by applying coatings and by performing surface treatments and chemical modifications.

Flexible fluoropolymer coatings such as Viton, CYTOP, and Chemraz seem to be the most promising approaches, but are likely suitable only in applications having moderate solvent-resistance requirements. Most coatings (up to several microns thick) do not seem to provide a complete barrier to solvents; rather, they just slow down adverse effects such as swelling or chemical attack. Perhaps the coating is too thin and the diffusion time of the solvent through the coating is very fast, even for low diffusivities. Another possibility is that the coatings are highly porous due to the fact that they are deposited from solutions with very low solids content and therefore shrink considerably upon drying. Lack of barrier protection was observed both in CYTOP, an uncrosslinked (but annealed) coating, and Viton, a crosslinked coating. Coatings may prove most useful in applications where the problem is chemical attack rather than swelling. For example, PDMS valves stick shut if exposed to heated hydrochloric acid [159]; a coating may not prevent the underlying attack of the PDMS but could provide a barrier to at least prevent the sticking.

3.5.1.1 Viton coating

Viton is a black liquid-castable FKM fluorelastomer. FKM elastomers provide good chemical resistance, though, due to some hydrogen content, are more susceptible to swelling and chemical attack than perfluoroelastomers. Samples of Viton coating material (PLV 2000 and Accelerator #4) were generously provided by PelSeal Technologies LLC (Newtown, PA). Coating resin was prepared by mixing 44:1 PLV 2000:accelerator.

The coating solvent is methyl ethyl ketone, which swells PDMS significantly. Attempts to coat by flowing through channels failed due to the rapid evaporation of solvent (or diffusion into the PDMS). Instead we coated device surfaces. The best results were obtained by first coating the

mold, then curing 10:1 RTV 615 PDMS prepolymer onto the coated mold. Since Viton sticks to silicon wafers after curing, it was necessary to prepare a mold made from PDMS. Viton was coated onto this mold by spin-coating at 2000 RPM and allowed to dry, then fresh PDMS was poured on top, degassed, and cured by baking for 4 h at 80°C. (This bake simultaneously crosslinked the Viton coating.) Treatment of the Viton-coated mold with oxygen plasma for 1 min prior to casting resulted in greatly improved adhesion of the coating to the newly cast device. Once peeled from the mold, the coated device sealed to glass nearly as well as uncoated PDMS does. Though the coating was not transparent, it was possible to see through it sufficiently well to observe fluid flow within the channels. A typical device is shown in Figure 3.4.

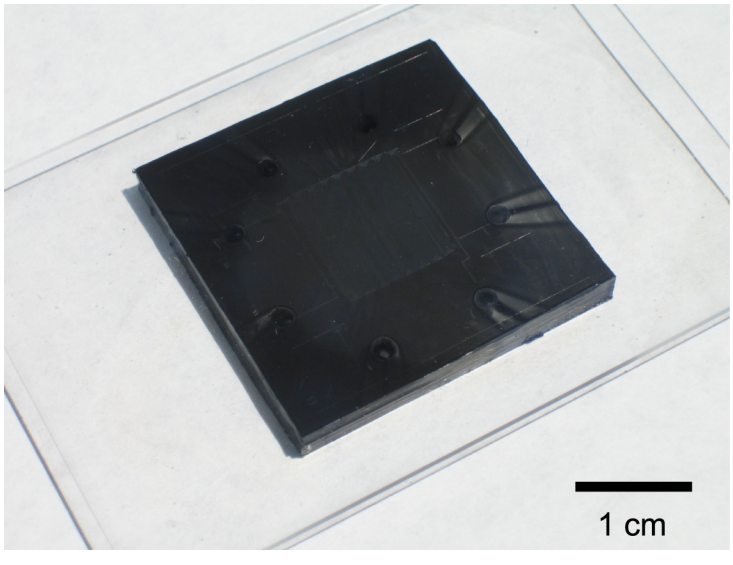

Figure 3.4: **Viton-coated PDMS microfluidic device**. This photograph was taken through the 2×3 inch glass slide to which the device was sealed. In this particular device, inlet holes were made with a hole punch prior to spin-coating the device with Viton.

Coated devices were also fabricated from Ebecryl 3708 Acrylated Epoxy resin (courtesy of UCB Chemicals). The resin was mixed with 5 wt% Irgacure 500 (Ciba Specialty Chemicals), poured on the Viton-coated mold and cured by UV exposure (ELC-500 UV Curing Chamber, Electro-Lite Corporation) for 20 min under a nitrogen purge. The resulting device sealed very strongly to glass (even with the coating), but the coating was not well-adhered to the device.

Since hole-punching was found to destroy the Viton coating, fluids were delivered to the device through holes in the glass substrate. A special jig (see Figure 4.4) was created for this purpose. The jig also helps to hold the device onto the glass substrate, but only a small force can be applied before causing collapse of microchannels. Dichloromethane could be flowed only a few centimeters along a channel before it stopped, suggesting that perhaps the Viton was not preventing swelling of the PDMS by this solvent. Furthermore, the Viton coating itself is not resistant to certain solvents such as acetone: exposure initially caused cracking and then dissolved holes completely through it.

3.5.1.2 CYTOP coating

PDMS devices were also coated with CYTOP 809A (Sigma Aldrich), a solvent-resistant perfluoropolymer coating material consisting of a 9 wt% solution of poly(1,1,2,4,4,5,5,6,7,7-decafluoro-3-oxa-1,6-heptadiene) ($M_n \approx 100000$) in perfluorotributylamine (Figure 3.5). Curing the CYTOP coating is achieved by baking at a moderate temperature (80°C) to evaporate the solvent then baking at a high temperature (above the glass transition temperature, $T_g = 108$°C) to anneal the coating. No crosslinking occurs. However, the CYTOP contains additives to improve adhesion to substrates.

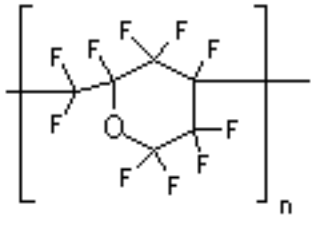

Figure 3.5: **Structure of CYTOP perfluoropolymer coating**.

Kanai *et al.* [140] reported the passivation of PDMS microfluidic channels with a CYTOP coating of 0.2–5 μm thickness. Passivation successfully protected PDMS features from attack by the PDMS solvent tetrabutyl ammonium fluoride (TBAF) and prevented fluorescently labeled λDNA and bovine serum albumin (BSA) from sticking to the surface. Devices were fabricated from two PDMS layers that were first treated with oxygen plasma then CYTOP coated by dip- or spin-

coating. Each layer was prebaked at 75°C, then the layers were bonded (with CYTOP coatings in contact) by baking at 115°C under a pressure of 40 kPa (6 psi). Actuation (complete closure) of a coated millimeter-sized diaphragm valve was also demonstrated. This bonding and annealing process solves an important problem we encountered earlier—CYTOP forms a very corrugated texture when coated and annealed on an isolated PDMS surface.

Mike Toepke (of Paul Kenis' lab at the University of Illinois at Urbana-Champaign) and I sought to duplicate this work and apply this principle to the fabrication of crossed-channel valves in PDMS microfluidic devices with the goal of demonstrating more sophisticated solvent handling applications. Initially, we bonded unpatterned slabs (2–3 mm thick) of Sylgard 184 PDMS after CYTOP coating. Holes were punched prior to coating in each slab to allow testing of the pressure that could be withstood by the layer bond. Slabs of PDMS were prepared from PDMS mixed in ratios of 20:1, 10:1, and 5:1, and were cured for times ranging from 30–90 min at 80°C. CYTOP was diluted 1:10 (w:w) in Fluorinert FC-43 (courtesy of 3M Corporation) and spin-coated onto the PDMS slabs after treating them for 1.5 min with oxygen plasma. PDMS slabs were spin coated by first sealing to a glass slide. Dirty glass slides were used so that the slabs could easily be removed without distortion (and possible damage) of the CYTOP coating. Samples were prebaked for 30 min at 75°C, then placed into contact with CYTOP coated surfaces, and baked for 45 min at 115°C. Among several methods considered for applying pressure during baking, sandwiching the layers between glass slides and clamping them together with standard office binder clips (3/4 inch size) resulted in the strongest and most uniform bond. Furthermore, bonding to a CYTOP-coated PDMS substrate rather than a CYTOP-coated glass substrate resulted in a stronger bond (15–20 psi *vs.* 4–7 psi). Note that when adhesion failed, usually the two CYTOP layers were stuck together, indicating a superior CYTOP-CYTOP than CYTOP-PDMS bond.

The CYTOP thickness was measured to be 0.05–0.1 μm thick by profilometry. Swelling of the PDMS surface was not observed when exposed to dichloromethane droplets, provided the CYTOP had been annealed at 115°C.

Sylgard push-down devices containing a simple valve test pattern (100–500 μm wide fluid channels at 90° to 100–500 μm wide control channels) were fabricated, coated with CYTOP, and bonded to CYTOP-coated PDMS slabs. Since the push-down devices had more mass than the slabs originally used for testing, we found the binder clips to be unnecessary. Note that holes for the fluid channel were punched after the CYTOP coating was applied. Solvents (dyed dichloromethane) could be flowed through the channels at low pressure, and valves could be actuated at 25–30 psi (Figure 3.6). When operated with empty fluid channels, the surface of the fluid channel appeared wrinkled during and after valve actuation. Perhaps this is due to the high stiffness of CYTOP (1–2 GPa): the coating may buckle rather than deform uniformly.

In a later effort, we examined the effect of bake temperature on the CYTOP adhesion. We fabricated PDMS slabs with punched holes, coated them with CYTOP, and bonded them to PDMS-coated glass with a CYTOP coating on top. Devices bonded at 115°C with a 40 g weight for 24 h delaminated within about 30 min when injected with solvent (acetonitrile, dichloromethane, and methanol) at 5 psi. Devices baked at 165°C for 24 h with a 40 g weight withstood these conditions for at least 48 h.

We also tried to apply CYTOP coatings to push-up devices by flowing dilute CYTOP (1:10 in Fluorinert FC-75) through microchannels. Devices were fabricated and adhered to RCA-cleaned glass (Appendix A.2.1) by baking overnight at 80°C with a droplet of 3.7% HCl. CYTOP solution was then flowed at 10–12 psi for approximately 30 min and appeared to apply a uniform coating. With tubing left in place at chip inlets, the coated device was baked at 80°C for 20 min and then at 160°C for 60 min. Solvent flowed several centimeters through the device before stopping, in contrast to uncoated PDMS, where solvent stops flowing after only a few millimeters. Unfortunately every exit channel was clogged, presumably by CYTOP. By carefully watching the coating solution during the baking process, we observed that this problem arises as the solvent evaporates: the CYTOP coalesces—perhaps due to poor wetting of the PDMS—into larger and larger droplets that become solidified. In attempts to fix this problem, we tried: (i) turning devices upside-down during drying to encourage CYTOP to flow out along edges of punched holes rather than pooling in the

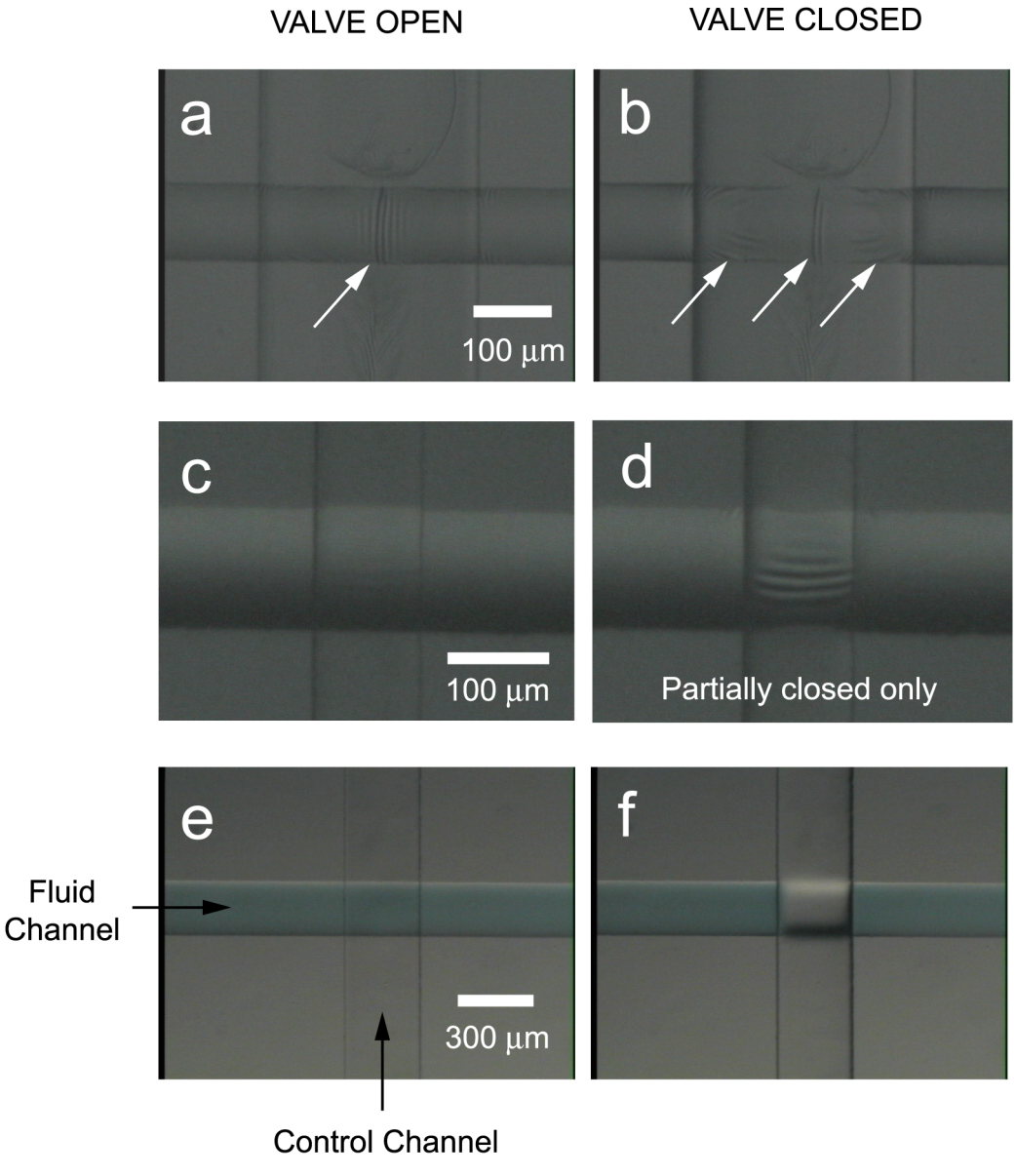

Figure 3.6: **Microvalve actuation in solvent-resistant CYTOP-coated PDMS devices**. (a,b) Micrographs of a CYTOP-coated PDMS device in (a) open and (b) closed states. The 100 μm wide fluid channel is oriented left to right and the 300 μm wide control channel is oriented top to bottom. The CYTOP coating is approximately 50–100 nm thick. Note that because CYTOP is not an elastomer, wrinkling and other effects were observed during actuation (white arrows). The persistent wrinkles in the middle of the channel in the open state appeared after the valve was actuated for the first time. (c,d) Micrographs of another valve in the same device (100 μm wide fluid channel, 100 μm wide control channel). In this case, the valve only partially closed. (e,f) Microvalve (200 μm fluid, 300 μm control) in open and closed states when solvent (dichloromethane with acetonitrile and methanol to dissolve the blue dye xylene cyanol FF) is flowing in the fluid channel. Wrinkles are not apparent, perhaps due to optical effects. The valve was successfully actuated repeatedly over a period of several hours with no apparent degradation in performance.

bottom; (ii) reducing the CYTOP concentration to 1:50 and 1:100; (iii) flowing a continuous stream of air or liquid through the channel after coating, attempting to maintain an open passage during drying; and (iv) fabricating push-up devices with fluid layer holes punched all the way through both layers, thus creating a small cylindrical volume at the bottom of the inlet holes where excess CYTOP could theoretically collect without interfering with the fluid path. The last was partly successful. In devices having a few open channels, we were able to properly test dichloromethane flow. We still observed the flow to stop after several centimeters.

We performed swelling tests (by immersion), to determine if CYTOP coated PDMS was providing a sufficient barrier to solvents. These tests revealed that CYTOP indeed provides a temporary barrier, but eventually the solvent swells the PDMS. Petri dishes were filled with 5:1, 10:1, and 20:1 Sylgard 184 and cured at 80°C overnight. Small PDMS samples (5 mm × 5 mm× 4 cm) were cut out. A batch of uncoated samples was evaluated as well as a batch coated in the following manner. Samples were dip coated three times in CYTOP diluted 1:10 in Fluorinert FC-75. Between coats, the samples were baked for 10 min at 80°C to evaporate solvent. To prevent holes in the coating, samples were supported on two parallel wooden sticks during baking and repositioned after each coat. Samples were then weighed, placed in glass vials, baked for 30 min at 80°C, baked for 60 min at 160 °C, and then slowly cooled down to room temperature. Dichloromethane was added to each vial. To determine the progress of swelling, samples were re-weighed after different lengths of exposure. (Due to the rapid evaporation of dichloromethane, each sample was weighed immediately after removing it from the vial and patting it dry with a Kimwipe.) As shown in Figure 3.7, the CYTOP coating leads to a small reduction (or delay) in swelling; however, the magnitude of swelling in dichloromethane is still quite large in all cases. This experiment was repeated with a 9-day 160°C annealing bake with very similar results.

While not suitable for applications requiring long-term solvent resistance, CYTOP-coated devices may be useful in applications requiring passivated channels [140] or in applications involving only intermittent exposures to solvents.

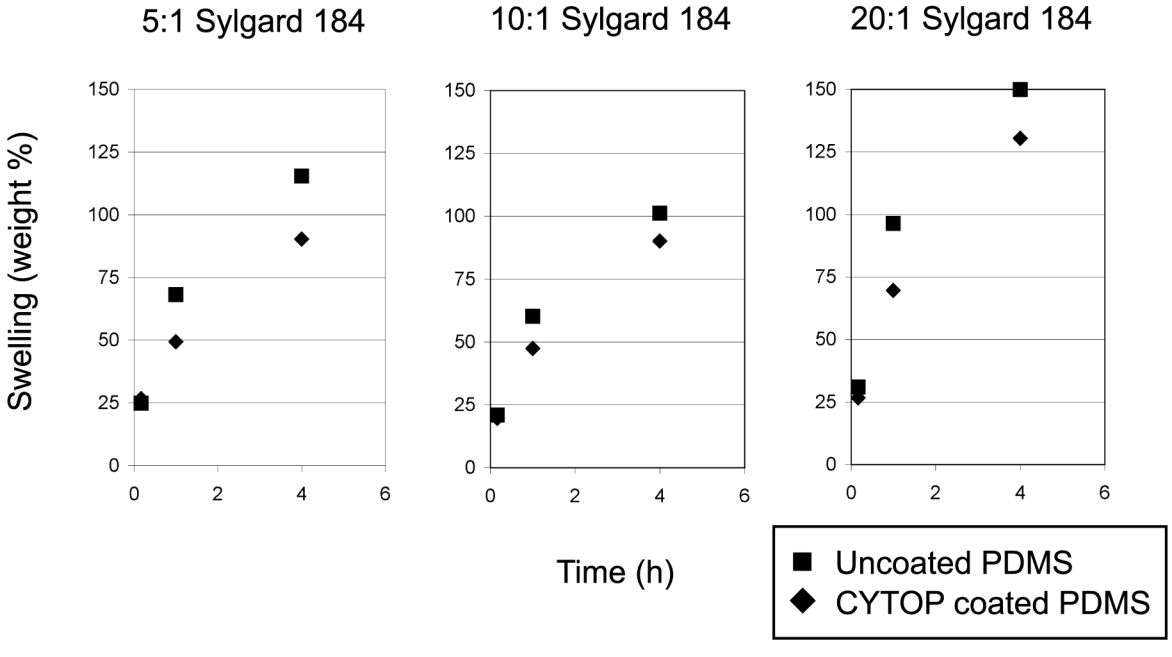

Figure 3.7: **Effect of CYTOP coating on the swelling of PDMS in dichloromethane**. Swelling (weight %) of uncoated and coated Sylgard 184 PDMS was determined after immersion in dichloromethane for different periods of time. Data is shown for several PDMS mixing ratios (5:1, 10:1, and 20:1). In all cases, there is still significant swelling with CYTOP present, though the magnitude is reduced or delayed.

3.5.1.3 Chemraz coating

Chemraz is a perfluorinated elastomer well known for its elasticity and solvent resistance. PDMS push-down microfluidic devices were sent to Jiang Huang at Fluidigm Corporation to be coated with Chemraz by a proprietary process and bonded to glass substrates. Initial devices were not usable as the introduction of solvents (mixture of dichloromethane, methanol, and acetonitrile) caused the fluid channels to delaminate from the substrate at pressures less than 1 psi. However, valves appeared to function normally in these devices, suggesting that the coating does not impede valve membrane deflection.

Recently, Fluidigm has developed a new coating process that solves the bonding issue. The ability of this Chemraz coating to act as a solvent barrier to protect the PDMS needs to be carefully evaluated.

3.5.1.4 Teflon AF coating

Teflon AF is a form of Teflon in solution in a perfluorinated solvent that can be spin-coated then dried and annealed to form thin transparent coatings with extremely high solvent resistance. After testing that the perfluorinated solvent Fluorinert FC-75 (courtesy of 3M Corporation) acceptably wets the surface of PDMS, I attempted spin-coating Teflon AF (DuPont) at 1000 RPM onto 10:1 RTV 615 devices. The coated devices were left at room temperature for 20 min for solvent evaporation, heated for 15 min to 120°C and then for 15 min to 170°C, and finally ramped back down to room temperature.

Upon cooling, the Teflon AF coating was visibly cracked. In fact, under the microscope, it appeared as flakes of Teflon surrounded by uncoated PDMS. Furthermore, the coating can be easily peeled from the PDMS. The coating is very rigid, exhibiting no adhesion at all to substrates such as glass, and undergoes audible cracking when the PDMS device is flexed slightly. For elastomeric microfluidics this does not seem to be a promising solution.

3.5.1.5 Parylene coating

Parylene is a non-fluorinated molecule that can be polymerized from the vapour phase onto a surface, resulting in very uniform conformal coatings. It is frequently used in the microelectronics industry as a surface passivation layer but has also been used in a wide variety of additional applications, including fabrication of microvalves in silicon microfluidic devices [285]. PDMS samples were coated with a 1–2 μm parylene film by Matthieu Liger in Yu-Chong Tai's lab at Caltech. The result was a transparent and flexible coating, strongly bonded to the PDMS. Surface tests revealed that parylene does not provide a barrier to dichloromethane, which swells the underlying PDMS almost instantly upon exposure. Clouding of the parylene was observed after several minutes of exposure.

3.5.1.6 Plastic coating

Samples of powders of several solvent-resistant plastics—polyvinylchloride (PVC), isotactic polypropylene (PP), and poly(vinylidene fluoride) (PVDF)—were purchased from Scientific Polymer Products Inc. (Ontario, NY). We intended to apply plastic coatings to PDMS, but could not find appropriate solvents for these powders that do not cause extreme swelling of PDMS, nor could we heat the PDMS to a sufficiently high temperature to apply a molten plastic layer.

3.5.1.7 Metal coating

Scraps of PDMS with a gold coating prepared by Scott Driggs via evaporation were evaluated for solvent-resistance. Under the microscope, the gold appeared to have many fine cracks and creases, perhaps from flexing or bending of the PDMS. Exposure to droplets of dichloromethane caused local swelling. When swelled, spaces between the cracks in the coating were clearly visible. It is possible that valve actuation would be sufficient to cause such cracking.

Coating with silver from a silver nitrate solution was also attempted. Coating for 25 min resulted in a visible silver coating. Drops of dichloromethane immediately lifted the silver from the surface and swelled the device. The coating could be rubbed off quite easily suggesting it is not very robust and likely not bonded to the PDMS.

3.5.1.8 Teflon lubricant spray coating

Teflon lubricant was sprayed onto a silicon wafer and PDMS prepolymer cured on top of it. After baking for 4 h at 80°C, the sample was removed. No Teflon remained on the wafer, indicating that it had been incorporated into the PDMS surface. However, solvent exposure tests revealed swelling upon exposure to dichloromethane. Since Teflon sprays consist of suspensions of Teflon particles it is not likely that this method could achieve the needed complete surface coverage.

3.5.1.9 CF_4 plasma-treatment

Anecdotal evidence indicated that exposure of PDMS to a tetrafluoromethane (CF_4) plasma generated Teflon-like compounds on the surface. We sought to test whether this residue could serve as a solvent-resistant coating on PDMS. A sample of cured 10:1 Sylgard 184 in a petri dish was partly covered with a glass cover slip. The sample was exposed to a CF_4 plasma (100 W power, 100 cm^3/min gas flow rate) for 15 min. Profilometry revealed that the exposed surface had been etched down approximately 0.5 μm with a roughness of 50–100 nm. Unexpectedly, qualitative contact angle measurements showed the surface to be more hydrophilic (lower contact angle) after treatment, in contrast with the high contact angle that is common of flurocarbon materials, an effect that may be related to the roughness. Surface testing with droplets of solvents showed no difference in local surface swelling between treated and untreated areas upon exposure to dichloromethane and diisopropylethylamine.

3.5.1.10 Fluorosilanization of PDMS surface

Genzer and Efimenko [91] reported a technique for assembling extremely dense monolayers of fluorinated trichlorosilanes ($F(CF_2)_y(CH_2)_xSiCl_3$) on cured PDMS. They accomplished this by stretching the PDMS by 60–70% during silanization to increase the hydroxyl sites available for attachment. When the stretching was released, the surface molecules packed extremely tightly together.

I treated samples of Sylgard 184 PDMS with (Tridecafluoro-1,1,2,2-tetrahydrooctyl)-1-trichlorosilane while in the stretched state. Upon release, the PDMS exhibited extremely high contact angles with

water ($> 110^{o}$). However, the treatment appears not to provide a barrier to solvents such as dichloromethane, as the samples exhibited significant surface swelling upon contact with solvent droplets.

3.5.1.11 Incorporation of fluorinated additives during polymerization

We attempted to prepare surface-fluorinated PDMS by the method of Thanawala and Chaudhury [267]. Krytox oil (courtesy of DuPont) was added to RTV 615 or Sylgard 184 PDMS during mixing. Device samples prepared by Markus Enzelberger exhibited immediate surface swelling upon exposure to dichloromethane.

3.5.2 Alternative elastomeric device materials

In addition to PDMS modifications, significant effort was expended in developing protocols to fabricate devices from alternative elastomeric materials after preliminary evaluations indicated acceptable elastic properties and solvent-resistance.

Development of a fabrication protocol is a significant undertaking, requiring the following issues to be addressed:

- Ensuring release from silicon wafer molds after curing.
- Developing a technique for fabricating a thin layer (spin coating for viscous prepolymers; other methods for low viscosity materials).
- Devising a method to bond the material to itself sufficiently strongly to withstand pressure inside microchannels. Self-bonding is needed between layers or between the device and a coated-substrate.
- (Optionally) Devising a method to bond material to glass, in cases of fabricating membrane devices or when it is desired that the fluid channel be open to the substrate (e.g., for *in situ* solid-phase synthesis).

- Determining the polymer shrink factor to allow mold designs to be properly scaled for correct layer alignment.

The most successful materials were fluoronorbornene (FNB) and perfluoropolyether (PFPE) polymers developed by our collaborators. These materials were designed specifically with microfluidic applications in mind, and properties were tailored to address the above issues. Details of experiments and results are discussed in Chapters 4 and 5, respectively. Limited success was achieved with other materials as well. In particular, the commercial product SIFEL seems a promising candidate. Work with these other materials is described below.

3.5.2.1 SIFEL

SIFEL [279] is a perfluorinated elastomer (type FFKM) consisting of a perfluoropolyether backbone with terminal silicone crosslinking groups (Figure 3.8). Samples of several SIFEL formulations were generously provided by Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan).

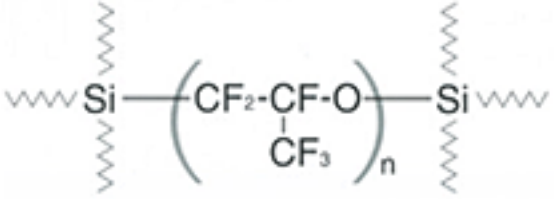

Figure 3.8: **Chemical structure of SIFEL perfluoroelastomer**. SIFEL has a perfluoropolyether backbone with terminal silicone crosslinking groups.

Two samples of adhesives, SIFEL610 and X-71-0603, cured to milky white and milky brown elastomeric materials, respectively. Both had qualitatively good flexibility, and holes could be easily punched with our hole-punching machine (Technical Innovations, Brazoria, TX). Immersion of samples in dichloromethane for 3 days indicated swelling of 13.6 wt% and 10.5 wt% for SIFEL610 and X-71-0603, respectively.

Both materials adhered very strongly to silicon or glass surfaces upon curing. Coating silicon wafers with annealed CYTOP or treating them with fluorosilane permitted samples to be easily released, however. Preliminary bonding tests with these materials were not successful. Cured mate-

rials were stacked on one another and baked at 150°C overnight in all four possible combinations of the two materials. None exhibited any adhesion. The prepolymers were too viscous to attempt spinning a thin "glue" layer between layers. However, curing freshly poured material onto another fully cured sample resulted in significant adhesion, suggesting that a partial curing technique might work. Preliminary attempts indicated that undercuring (by shortening the bake time and/or reducing the bake temperature) left a liquid center inside the thick layer samples. Unfortunately, if baked just long enough for the liquid to disappear, the samples no longer adhered to thin layers. Partial curing may be impossible or may simply be very sensitive to timing. Being one of the few liquid castable perfluoroelastomers available, further investigation may prove fruitful. Our tests ended after initial successes with other materials: perfluoropolyether (PFPE) (Chapter 5) and fluorinated norbornene (FNB) (Chapter 4).

It should be noted that another, non-adhesive SIFEL product, SIFEL8070 ("potting gel"), was also obtained and evaluated. Parts A and B were mixed in a 1:1 ratio and baked for 1 h at 150°C, as per the manufacturer's protocol. The result was a sticky non-solidified gel that was strongly adhered to the fluorosilaned silicon wafer. Other ratios resulted in a similar lack of solidification.

3.5.2.2 New materials for CLiPP synthesis

Hutchison *et al.* [116] report the fabrication of microfluidic devices by a photopolymerization technique called contact liquid photolithographic photopolymerization (CLiPP). Microfluidic devices and other structures are fabricated in layers—each new layer is applied in liquid form then selectively polymerized by UV exposure through a mask. A sacrificial material is filled into the recesses of the previous layer when synthesizing a new layer on top. A unique aspect of this work is the inclusion of "iniferters" in the monomer solutions. These molecules are covalently attached to the layer during polymerization and serve as initiators for the polymerization of subsequent layers. This leads to covalent bonding between adjacent crosslinked layers.

We collaborated with Brian Hutchison and colleagues in Christopher Bowman's lab at the University of Colorado to develop solvent-resistant elastomeric devices by their approach [115]. To

fabricate fluid channels with a rounded profile to allow complete closure by elastomeric microvalves, it was necessary to fabricate the first layer on a silicon mold patterned with rounded channel features. It is not possible to include rounded features at any other stage in the CLiPP fabrication process (except, perhaps, by underexposure techniques [85]). First the material for the (bottom) fluid layer is poured and photopolymerized by flood exposure. Next, a second monomer layer is poured on top of the first and exposed through a mask to define the pattern of control channels, which is then backfilled with sacrificial material. Finally a thick layer is poured on top and polymerized.

Hutchison *et al.* evaluated numerous existing monomers and newly synthesized fluorinated monomers in terms of elastic modulus and swelling in DNA synthesis solvents, among other properties. One of the new formulations, a mixture of PFPE2000-A and F-C10-A, exhibited a modulus of 8 MPa and mass swelling of 10% or less in all solvents [114]. Several stages of the CLiPP process were successfully demonstrated. In order to produce a functional microfluidic device, a couple of issues remain to be resolved: (i) adhesion between layers, and (ii) adhesion to glass [114]. To address the first, Hutchison *et al.* synthesized several fluorinated iniferters but found them to be insoluble in the fluornated monomer formulation. Adhesion to glass is also suspected to be difficult.

With further development, this may be a viable route to solvent-resistant elastomeric device fabrication. The method has the advantage of simple fabrication. Because the second device layer is fabricated in place, there is no need to account for shrinkage differences between layers, and alignment is performed by aligning photomasks rather than soft polymer layers. The problem of adhering layers becomes simply a problem of iniferter design.

3.5.2.3 Fluorosilicones

Fluorosilicones (type FVQM fluoroelastomers), in general, possess most of the physical properties of regular silicone (PDMS) but with enhanced resistance to solvents.

A sample of Q4-2817 fluorosilicone sealant was provided by Dow Corning (Midland, MI) for evaluation. This product is a thick red paste that cures at room temperature in about 24 h, releasing acetic acid in the process. Primitive devices were molded on a patterned silicon wafer, and holes

were punched for fluid channel inlets and outlets. It should be noted that the curing time was about 2 weeks since the paste was sandwiched between the wafer and a petri dish (to form a flat top surface) and presumably acetic acid could not escape rapidly. Though ethanol and acetonitrile could be flowed through the channels, dichloromethane could not. Additional tests showed the fluorosilicone to exhibit surface swelling in the presence of droplets of this solvent.

Evaluation of a sample of Dow Corning 730 Solvent Resistant sealant (courtesy of Dow Corning) exhibited releatively little swelling in dichloromethane. However, the material did not cure to a useable consistency—it remained somewhat sticky and plastically deformable.

3.5.2.4 Other materials

Though plenty of highly solvent-resistant materials such as perfluoroelastomers (FFKM fluoroelastomers) are commercially available, most are unsuitable for microfluidic device fabrication by replication molding. Such materials include Kalrez (DuPont Dow Elastomers), Chemraz (Greene Tweed & Co.), Chemtex/PFR (UTEX Industries, Inc.), Parofluor (Parker Hannifin Corp.), Simriz (Simrit), among others. These materials require melt processing, and due to the extremely high viscosity of the melt, it is not possible to mold features on the scale of microfluidic device features, according to engineers in industry.

It is conceivable that chemical or dry etching methods might be suitable for fabrication of micron scale features in the surfaces of such materials. However, samples we received had high surface roughness (several microns), and it is not clear whether starting materials with a sufficiently smooth surface can be obtained. In addition, it is likely that bonding of layers would prove difficult. We focussed on the development of microfluidic devices from liquid castable materials.

3.5.3 Membrane devices

An early search of commercially available elastomers showed that the most solvent-resistant ones (perfluoroelastomers such as Chemraz, Kalrez, Parofluor, etc.) were not easily patternable by molding or other means. These materials can only be melt processed, requiring temperatures of 300–

400°C, very high pressures, and specialized equipment. According to several seal manufacturers, these molding processes cannot produce void-free casts of molds with features below 1 mil (about 25 μm) due to the extremely high viscosity of the melt. Since microfluidic device features are typically comparable to this size, it is unlikely that devices could be reliably molded.

Thin, flat sheets of perfluoroelastomer materials, however, are commercially available. Because the membrane architecture that we devised requires only an *unpatterned* thin sheet of elastomer as the deflecting layer between two channel-containing layers (Section 3.4.3), it seemed ideally suited for such materials. For proper operation, the membrane must be covalently bonded to the two layers; however, to quickly evaluate whether a membrane could be deflected, we often just clamped membranes between two glass or PDMS layers.

The architecture was first validated using PDMS membranes. We also attempted to incorporate solvent-resistant elastomer membranes; however, useful devices were not fabricated since elastomer sheets were not available in sufficiently thin layers or were not bondable.

3.5.3.1 Architecture validation with PDMS membrane

As an initial proof of principle, we fabricated membrane devices with PDMS membranes. PDMS was an ideal material for testing because there is a known method (oxygen plasma treatment, Appendix A.2.4) for covalently bonding the membrane to two glass channel layers. A 5 μm PDMS (10:1 Sylgard 184) membrane was spun (4000 RPM, 60 sec, 15 sec ramp) on a flat unpatterned silicon wafer treated with fluorosilane (see Appendix A.1.5) and cured by baking at 80°C for 2 h. Two glass layers were etched (see Appendix A.2.2) with a simple pattern of parallel channels (100–1000 μm wide by 35 μm deep). One slide served as the control layer and the other (with pattern rotated by 90°) as the fluid layer. First, the PDMS membrane and control layer were treated with oxygen plasma and bonded together with dilute HCl as a lubrication layer. The glass and membrane were then peeled from the wafer and plasma bonded to the glass flow layer. The channels in both glass layers faced the membrane. To provide a means of pressurizing the microchannels, inlet/outlet holes were drilled in each glass layer (see Appendix A.2.3) prior to device assembly, and NanoPort

connectors (see Figure 4.7) were adhered to the back sides at these positions. For simplicity, the channels in the fluid layer are linked together so only a single inlet and outlet are needed. Similarly, in the control layer, only a single inlet is needed to pressurize all channels.

In one device, nearly all 100 valves closed by actuating the control channels to 10 psi. When dichloromethane was introduced into the channels it could be flowed easily, indicating that this architecture solved the swelling problem that leads to plugging of channels in thick elastomer devices. However, dichloromethane very rapidly diffused through the membrane—droplets of solvent condensation were visible at the other side of the membranes (i.e., in control channels) after a few minutes of flow. Allowing the solvent to flow overnight caused the valve membranes to rupture, perhaps due to local weakening of PDMS. In a macroscopic piece of PDMS, maximal swelling with dichloromethane is reached in just a few hours and embrittlement within days; in a thin membrane, these time scales are likely dramatically reduced.

3.5.3.2 CYTOP-coated PDMS membrane

I also attempted fabricating membrane devices with CYTOP-coated PDMS as the membrane. 5 μm PDMS layers were fabricated as above. First the glass control layer was plasma bonded channel-side down onto the membrane, and the bonded structure peeled from the wafer. The membrane was then spin-coated with CYTOP (1:10 dilution in Fluorinert FC-75) at 1000 RPM and baked for 30 min at 80°C and for 2 h at 160°C. The glass flow layer was also CYTOP-coated, then aligned and clamped to the other layers with standard office binder clips, and baked at 160°C for several hours to promote bonding. When tested, fluid leaks were observed at very low pressures (1 psi) due to the poor adhesion of CYTOP-coated PDMS to the rigid glass layer. Successful device fabrication would require finding a solvent-resistant fluid layer material that can be strongly bonded to CYTOP.

3.5.3.3 PFPE membrane

PFPE is a photocurable solvent-resistant perfluoropolymer developed in a collaboration with Joseph DeSimone's group at the University of North Carolina. Details of this material and curing methods are discussed in Chapter 5. Membrane device fabrication was attempted with 20–30 μm films of PFPE cured on silicon wafers after spin-coating. However, due to poor adhesion of PFPE to glass, there was insufficient bonding to the glass control layer to allow the membrane to be peeled from the mold. I also attempted membrane transfer by adhering the membrane to pressure-sensitive tape as reported by the Whitesides group for handling of PDMS membranes [134]. However, the adhesion of PFPE to glass was insufficient to allow transfer of the PFPE from the tape to the glass control layer.

3.5.3.4 Kalrez sheet

Kalrez is a commerically available perfluorinated elastomer that is resistant to a tremendous variety of solvents. We obtained the thinnest available sample of Kalrez compound 6375 (Standard Sheet K#5011) from DuPont Dow Elastomers. The sheet was opaque black in colour. Qualitative tests of solvent resistance upon exposure to acetonitrile, dichloromethane, and tetrahydrofuran did not cause swelling and left no trace of exposure once evaporated. Unfortunately the sample sheet was several hundred microns thick—far too large to serve as a deflectable valve membrane in a *micro*fluidic device. Qualitatively, it had a very high elastic modulus, which would further reduce its ability to be deflected. The sample also had a very high surface roughness, and it was not possible to seal it to a substrate for even preliminary membrane valve testing.

3.5.3.5 Chemraz sheet

Chemraz is a perfluoroelastomer similar to Kalrez in terms of chemical resistance and mechanical properties. We purchased custom fabricated Chemraz sheets (0.005 ± 0.001 inch thick) from Greene, Tweed, & Co. (Kulpsville, PA). Chemraz has a modulus of 2–4 MPa, comparable to PDMS. The thickness of the sheet was measured to be 135 μm by profilometry (see Appendix A.3.1) with a

roughness of several microns. The roughness is presumably due to the fact that the sheet was molded between two metal plates with visible polishing marks in the surfaces. Chemraz sheets were opaque white in colour. We fabricated etched glass slides with attached NanoPort connectors as used in other membrane device testing. The Chemraz membrane was sandwiched between the two etched glass slides using standard office binder clips (3/4 inch wide). Without bonding we didn't expect proper functioning—we simply attempted to achieve membrane deflection. However, the device could not accept more than 2 psi of pressure without leaking, likely due to the surface roughness. If Chemraz membranes of higher surface smoothness and lower thickness should become available, such a device might be feasible, provided that one can determine a reliable bonding method.

3.5.3.6 Teflon PFA film

I obtained some samples of a thin (12.5 μm) Teflon PFA Film (courtesy of DuPont) for attempted construction of membrane devices. While Teflon PFA is a rigid plastic, the film is quite flexible because it is so thin. Due to lack of adhesion, the film could not be sealed between glass plates. Instead, I used two 1-layer PDMS devices as the flow and control layers and clamped the PFA film between them. The Sylgard 184 PDMS layers sealed (reversibly) to the film such that about 5–10 psi could be introduced into the control channel to attempt membrane deflection. No deflection was observed. Because the membrane must lengthen in order to deflect completely into the fluid channel, it is likely that only elastomeric materials are suitable for membrane devices.

3.5.3.7 Teflon tape

Though also not elastomeric, we considered using Teflon tape as a deflectable membrane. This thin white tape is used for sealing gas fittings and can be thinned further by stretching. We evaluated Threadmaster PTFE Sealant Tape (Merco Company, Hackensack, NJ). Droplets of dichloromethane on a piece of tape covering a sample of PDMS rapidly discoloured the tape and soon led to surface swelling of the PDMS below. This indicates that the tape is highly permeable (due to its composition or the presence of pinholes) or that the plasticizers present in the tape reduce its solvent resistance.

Attempts to fabricate membrane devices by sandwiching tape between PDMS layers failed due to the tendency of the tape to plastically deform and due to the difficulty in maintaining its flatness.

3.6 Summary

Solvent-resistant chips with mechanical valves have the potential to provide a *generalized* platform for highly integrated microfluidic chips in applications involving non-aqueous media, such as many areas of synthetic and analytical chemistry and other domains yet to be explored. Such chips could directly benefit those areas by enabling more accurate, rapid, and safe syntheses, and more sensitive and rapid analyses, or by allowing detailed studies of kinetics or reaction pathways [133]. The ability to perform on-chip solvent exchange very simply via evaporation may be particularly useful. As an example application, in Chapter 7, I describe microfluidic device designs suitable for performing combinatorial solid-phase synthesis and report some preliminary successes in the fabrication of DNA and peptide arrays. Solvent-resistant chips may also find use in the exploration of microfluidic phenemona in organic solvents, in expanding the variety of fluids used in existing applications, and perhaps in combining chemistry with biology or biochemistry in integrated synthesis and screening chips. It will be exciting to watch this field unfold.

Over several years, we expended considerable effort in evaluating elastomeric materials, coatings, and PDMS surface treatments as starting points for the fabrication of solvent-resistant elastomeric devices. Based on initial screening for solvent resistance and suitable elasticity, we attempted to devise procedures for fabricating working devices with candidate material systems.

Several promising results were reported in this chapter, such as coating PDMS devices with CYTOP to confer solvent resistance, fabricating devices entirely from fluorinated materials such as SIFEL, and fabricating devices from fluorinated monomers by the CLiPP method. The next two chapters describe additional work with materials developed in collaboration with polymer chemists specifically for microfluidics applications. Like the collaboration with Hutchison *et al.*, these collaborations helped to solve problems related to bonding and molding that hindered progress with commercially available perfluoroelastomers. Fully functional solvent-resistant devices containing

microvalves were demonstrated with these two material systems. Constructed from permeable elastomers, they provide many of the advantages of PDMS devices (see Chapter 2) with the added advantage of chemical resistance, and can leverage the design expertise and experience garnered by the PDMS microfluidics community.

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