FUNDAMENTALS OF

BioMEMS and Medical Microdevices

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WILEY-INTERSCIENCE

SPIE PRESS

Bellingham, Washington USA

Chapter 3

"Soft" Fabrication Techniques

3.1 Introduction

"Soft" fabrication techniques are used for bioMEMS devices that incorporate synthetic polymers, natural polymers such as DNA (deoxyribonucleic acid) and proteins, self-assembled monolayers (SAMs), and biological materials. Many LOC, microfluidic, and microarray devices derive from these fabrication methods, and are at the heart of μTAS.

Polymer devices offer certain advantages for LOC and microfluidic device fabrication. This chapter generally reviews biomaterials: soft lithography techniques, micromolding and embossing, 3D construction with photopolymerization, "smart" polymers and hydrogels (that can be formed *in situ* and respond by changing shape to environmental stimuli), SAMs, and thick-film techniques. Additional fabrication techniques, including microarray fabrication, are introduced in later chapters.

Microfluidic devices may be hybrids of silicon, glass, polymers, and biological materials, and may require both hard and soft fabrication processes. Many of the photolithographic steps discussed previously are used for soft fabrication and include defining regions for etching, plasma treatment, and surface modification.

Glass-based devices may consist of a series of channels or troughs etched into the substrate with techniques already reviewed. These devices take advantage of well-known surface and electro-osmotic properties of glass and quartz. As an alternative, polymers offer the following characteristics:

(1) improved and easier machinability
(2) optical transparency for certain detection strategies
(3) biocompatibility
(4) acceptable thermal and electrical properties
(5) ability to enclose high-aspect-ratio microstructures
(6) ability for surface modification and functionalization

Machinability includes laser ablation, imprinting, embossing, molding, and reactive-ion etching. This also includes interaction with radiation, such as increasing resist solubility with exposure to x rays or ultraviolet light. Optical transparency is necessary for fluorescent, UV-Vis, and Raman detection. The polymer must not absorb at the detection frequency of interest. The sample, solvents, and other reagents in a LOC device must not adversely interact with the material through which they pass. Electrophoretic materials must hold up to electrical fields and be able to dissipate heat (higher dielectric strengths create greater electric fields). Final phases of assembly typically require the device to be enclosed; thus, the substrate and cover plate must be able to withstand bonding temperatures. Finally, walls or surfaces may require modification as required by a specific application [Hupert et al., 2003].

3.2 Biomaterials

Biomaterials for medical diagnostics and therapeutics include natural, synthetic, and biological materials that have contact with humans or human products such as blood, urine, cerebral spinal fluid, organs, and other tissue. These materials include silicon and other ceramics, glass, polymers, and biological materials such as nucleic acids, proteins, cells, antibodies, antigens, and tissue.

There is considerable experience and published data on a number of biomaterials used for existing medical devices, and these should be consulted when developing a bioMEMS device.

Artificial intraocular lenses, hip prosthesis, vascular grafts, extracorporal circulatory devices for dialysis and open-heart surgery, and the ball and cage heart valves were among the ground-breaking attempts to supplant natural systems with artificial ones, and the first to draw awareness to issues of biocompatibility.

Some biomaterials, including synthetic nucleic acid and peptide chains, may be used to *modify* or *pattern* the surface of other materials. These in turn may be used for *immobilization* of sample constituents such as nucleic acid fragments, proteins, and cells. Immobilization permits further processing or detection of the analyte. These concepts are discussed more fully in Chapter 9, *Micro-Total-Analysis Systems*, Chapter 11, *Genomics and DNA Microarrays* and Chapter 12, *Proteomics and Protein Chips.* Biocompatibility of biomaterials is also discussed in Chapter 15, *Biocompatibility, FDA and ISO 10993.*

3.2.1 Classes of biomaterials

It is useful to divide biomaterials into three classes based on their application and function:

(1) Materials that are *implanted* or have other direct contact with humans such as sensors, actuators, pacemakers, lead wires, prosthetic devices, cultured tissues, or biomimetic devices (for example, electroactive polymers).
(2) Materials that have a *transport* and *containment function* for biological samples, such as microfluidic channels, mixers, pumps and other LOC devices used in μTAS.
(3) Materials that have a *process function*, including surface chemical properties (either naturally or through surface modification) that are useful for electrokinetic effects, immobilization, and participation in microreactions. This also includes tissue scaffolding materials, which allows a supply of nutrients and removal of waste products from cultured tissue.

3.2.2 Ionic, covalent, and metallic bonds

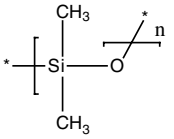
An understanding of bonding mechanisms between atoms will assist in understanding the fabrication and functional characteristics of biomaterials. *Alloys* are metals that are combined to form new materials with different properties than the original components. *Compounds* are chemically combined elements. *Mixtures* are physical blends of two or more materials. Bonding of materials is related to the outermost (valence) shell of the electrons of a material. Combining atoms requires complementary valence shells, such as carbon with four spaces available for four hydrogen bonds. Bonding mechanisms require gaining electrons (*ionic bonding*), sharing electrons (*covalent bonding*), or losing electrons (*metallic bonding*).

Ionic bonding occurs in the ceramic materials, like silicon and glass, which are strong and brittle. Here, one atom loses an electron and becomes positively charged,

while another gains an electron and becomes negatively charge. They are attracted to one another by opposite charges. Covalent bonding is common in polymers and other hydrocarbons. They have good plasticity and strength. Here, negatively charged electrons are shared in the outer rings. Metallic bonding occurs in metals, where valence electrons are easily detached from the atom and move about in the material, leaving the atoms as positive ions. These concepts will take on additional meaning when we review electrokinetic effects and surface modifications later.

3.3 Soft Lithography

Soft lithography is a group of processes including *microcontact printing* (μCP), *microtransfer molding* (μTM), *molding in capillaries* (MIMIC), and *decal-transfer* microlithography (DTM). These methods use a patterned elastomer as a stamp, mold, or mask to generate microstructures.



Poly(dimethyl siloxane) (PDMS)

A PDMS stamp can be made by casting PDMS over a silicon wafer master mold. Using hard fabrication techniques, the silicon wafer is first photolithographically patterned with a resist and is surface treated. The PDMS is applied over the wafer, cured, and peeled away to be used as a stamp in a number of different ways. Figure 3.1 shows fabrication of a PDMS stamp.

In microcontact printing (μCP) the PDMS stamp is coated with the material ("ink") that one desires to pattern. This is like first stamping an ink pad, which puts the material on the raised part of the PDMS stamp. Transfer of materials, including biologically active molecules can be applied to a surface in a well-defined pattern [Ratner and Bryant, 2004].

Figure 3.2 shows application of μCP using the previously described PDMS stamp. The stamp is wetted (coated) with a SAM resist by immersion in an appropriate solution [such as $Y(CH_2)_nX$, where X is a head group and Y is an anchoring group], and pressed on the substrate surface. Once the stamp is removed the

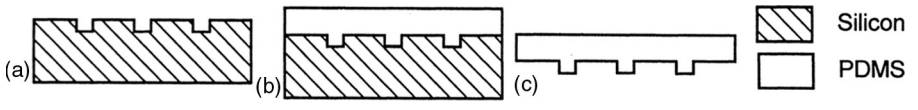


Figure 3.1 Fabrication of a PDMS stamp. (a) DRIE of silicon master, (b) coating, and (c) release. [Reprinted with permission from Man (1997), copyright IEEE.]

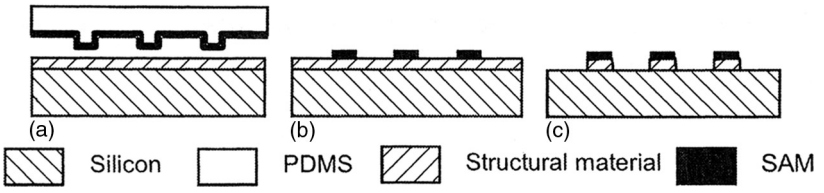


Figure 3.2 Microcontact printing with a PDMS stamp. (a) Immersion, (b) stamping, and (c) etching. [Reprinted with permission from Nguyen and Wereley (2002), copyright Artech House.]

substrate may be patterned by wet etching. Because of the thin nature of the SAM, direct RIE etching is not possible, and wet etching is used to first pattern a sacrificial layer. RIE may then be performed to etch the underlying substrate.

In microtransfer molding (μTM) the PDMS mold is filled with a polymer precursor, such that material is in the relief areas rather than the raised areas as in μCP. The stamp is then pressed against a substrate and cured. Then the mold is removed, a pattern of the substrate remains (see Fig. 3.3).

In *micromolding in capillaries* (MIMIC), the stamp is first applied to the substrate, then a prepolymer liquid is applied at the end of the channels, allowing electro-osmotic forces to carry it into the channels where it is then cured (Fig. 3.4) [Beh et al., 1999; Varadan et al., 2001].

Decal-transfer microlithography (DTL) is a technique based on the transfer of elastomeric detail patterns via the engineered adhesion and release properties of a compliant PDMS patterning tool [Childs and Nuzzo, 2002].

3.4 Micromolding

3.4.1 Injection molding

In *injection molding*, thermoplastics pellets are poured into a hopper, melted, transported by a screw, and then injected into steel or aluminum molds. Plastic enters the mold under high pressure through a machined sprue, and travels to the cavity molds along runners. Figure 3.5 shows a schematic view of a microinjection tool with variotherm heating [Kemmann et al., 1999].

The molds are typically machined and may be rather expensive. Lab-sized injection molders are available for small molds and limited part runs. Molds can be fabricated at lower cost by in-house machining of aluminum blocks.

To reduce mold cost, the author combines machining and casting techniques. PDMS is used as an intermediary mold to cast model impressions with an aluminum-filled resin called Alumacast.* The synthetic mold mates with an aluminum

*Aluma Cast, Appleton, Wisconsin.

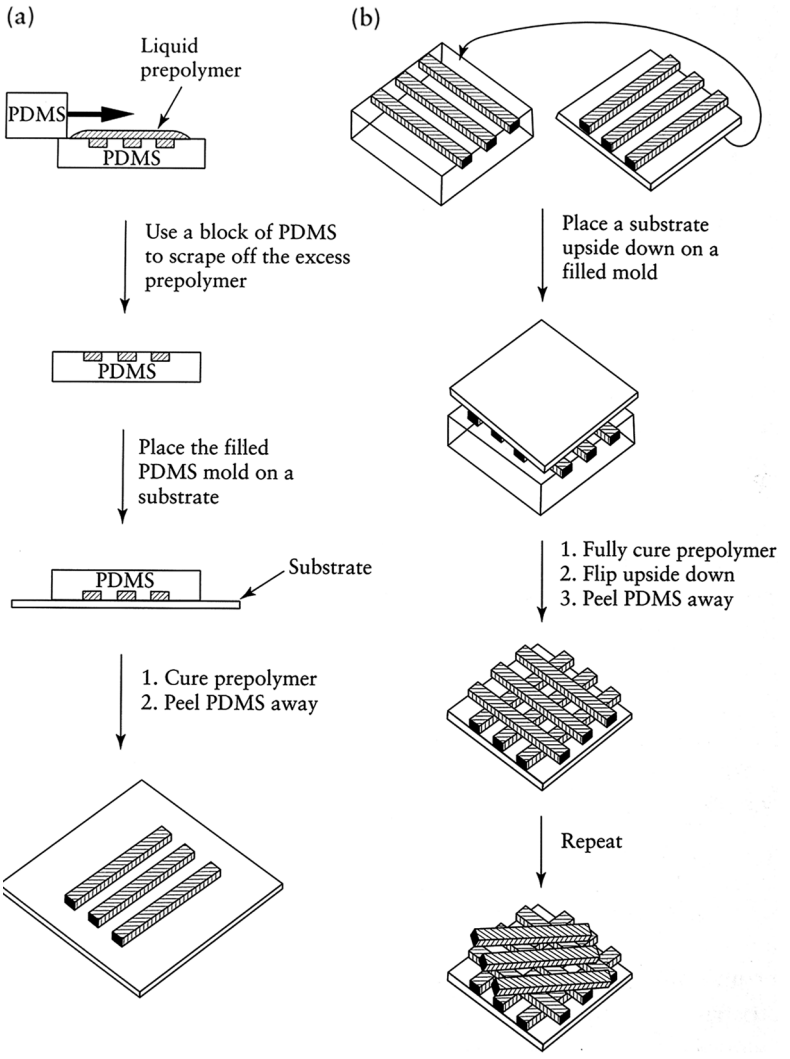


Figure 3.3 Microtransfer molding. (a) Microtransfer molding process flow for a single layer; and (b) multiple layer. [Reprinted with permission from Zhao et al. (1996), copyright Wiley VCH.]

plate by registration pins, and is clamped into the injection molder. This material has high tensile strength and is temperate tolerant. Up to one hundred parts can be made before replacing the mold.

To fabricate microstructures a *variotherm* (temperature control) process is required. In this process the mold is first evacuated and heated above the glass transition temperature of the polymer, and then the molten polymer is injected under pressure (see Fig. 3.6). The mold is cooled prior to demolding the part [Heckele and Schomburg, 2004].

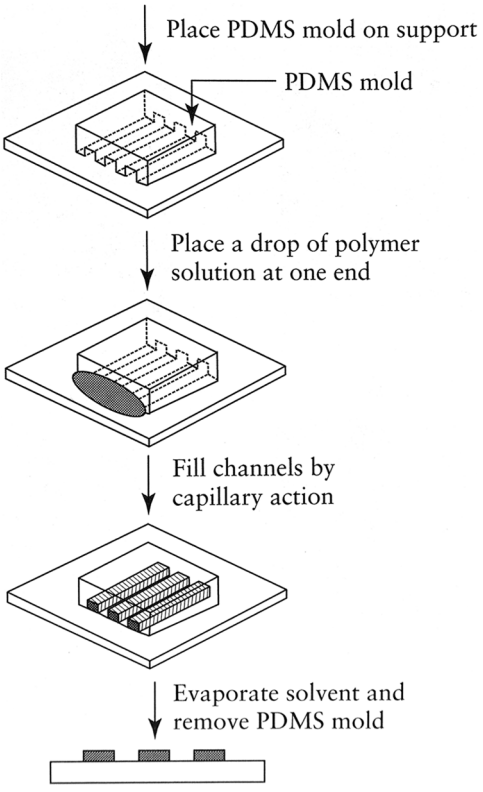


Figure 3.4 Micromolding in capillaries (MIMIC). [Reprinted with permission from Beh et al. (1999), copyright Wiley VCH.]

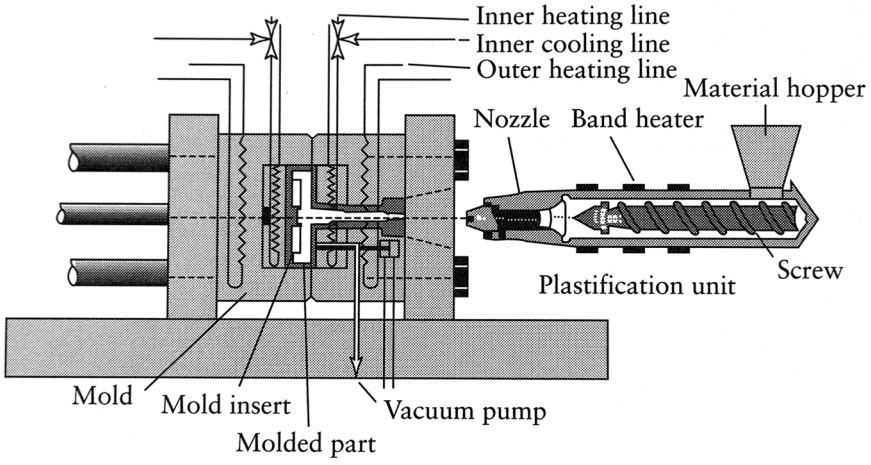


Figure 3.5 Microinjection tool with variotherm heating [Kemmann et al., 1999].

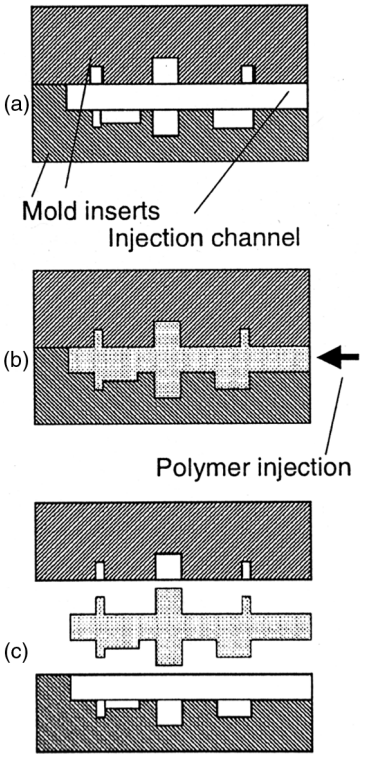


Figure 3.6 Microinjection molding: (a) the molding tool is closed, evacuated, and heated above the glass transition temperature of the polymer; (b) the polymer is injected into the tool; and (c) tool and polymer are cooled down and the polymer is demolded. [Reprinted with permission from Heckele and Schomburg (2004), copyright IOP Publishing Ltd.]

Reactive-injection molding is similar to injection molding, except that two components instead of one are injected into the closed molding tool. This allows fabrication of parts from polymers that are not thermoplastics, such as thermosetting materials and elastomers [Heckele and Schomburg, 2004].

3.4.2 Hot embossing

In *hot embossing*, a thermoplastic material is inserted into a molding machine and formed under pressure. Figure 3.7 shows the process steps. Hot embossing requires heat and compression, and is performed in a press with pressures from 5 to 10 tons required. Structures in the micro and nano ranges may be fabricated, and nickel and silicon molds may be used. [Heckele and Schomburg 2004].

Advantages of hot embossing include low polymer flow, high-molecular-weight polymers that provide better mechanical and thermal properties, the ability for continuous cycle, and it is good for small structures. Disadvantages

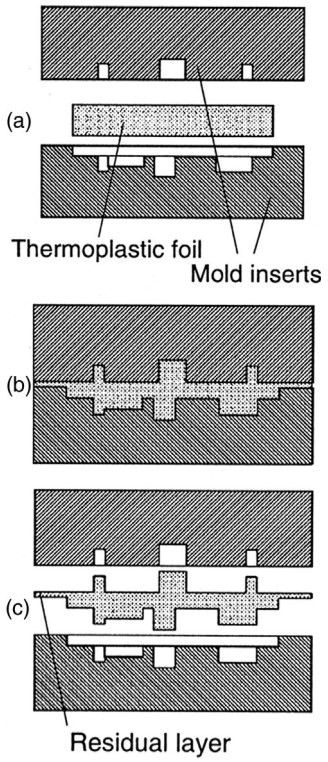


Figure 3.7 Hot embossing. (a) The thermoplastic foil is placed between two mold inserts; (b) the machine tool is evacuated and heats the polymer above its softening temperature; and (c) the polymer is cooled and demolded. [Reprinted with permission from Heckele and Schomburg (2004), copyright IOP Publishing Ltd.]

of hot embossing include more difficulty for structures with high aspect ratios, less dimension control, limited to planar features (to release from the mold), high residual stresses on molded parts, and difficulty making large parts or parts with multiple feature depth [Madou, 2002].

Injection-compression molding is a combination of injection molding and embossing. Polymer is injected into a semiclosed molding tool, which is then closed, compressing the material into the mold cavities. This method is used to produce CDs and DVDs [Heckele and Schomburg, 2004].

In *thermoforming*, a polymer is placed between two mold inserts, softened by heating, and then formed by compression (Fig. 3.8).

AMANDA is an acronym for a German expression (in English): "surf**a**ce micro**ma**chining, micromold**in**g, and **d**iaphragm tr**a**nsfer." A flexible *diaphragm* of a structural material such as polyimide is first deposited and patterned on a silicon substrate. A *housing* structure is then molded to complement the diaphragm structure. The diaphragm is then *transferred* to the housing by an *adhesive*, and additional assemblies are added as necessary. The process steps are shown in

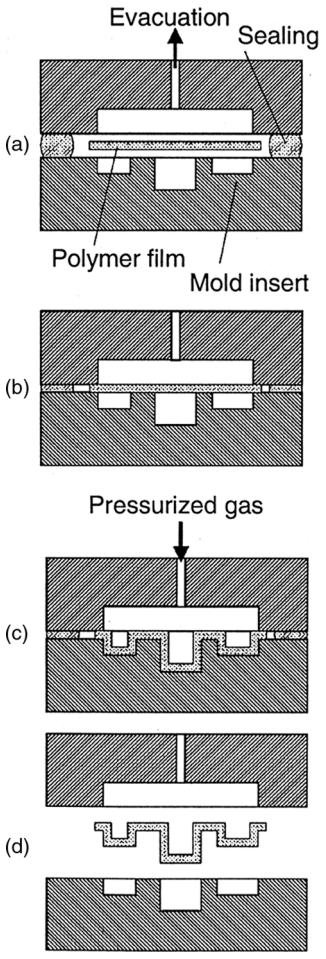


Figure 3.8 Thermoforming. (a) A polymer film is placed into a mold tool that is then evacuated; (b) the film is clamped; (c) the polymer is then heated above its softening temperature, and pressurized gas applied from above presses the film against the mold insert; and (d) the part is demolded. [Reprinted with permission from Heckele and Schomburg (2004), copyright IOP Publishing Ltd.]

Fig. 3.9. This is a method for low-cost production of microdevices by batch processing.

3.4.3 Implementation

A simple method of fabricating hot embossing tools using PDMS has been reported by Narasimhan and Papautsky (2003). The tools are then used to fabricate microfluidic systems in PMMA of various aspect ratios. A negative photoepoxy

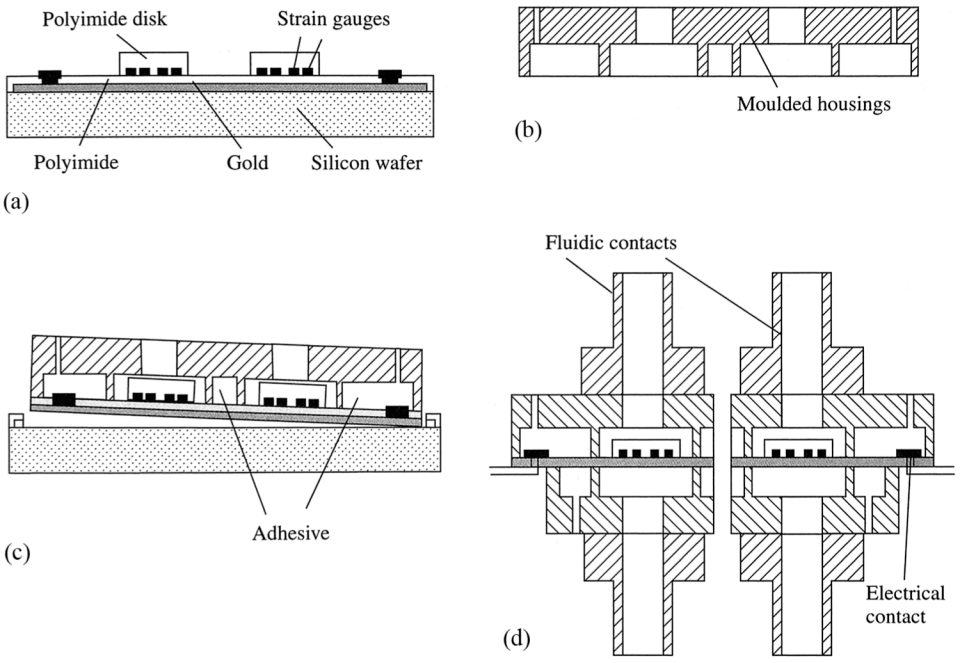
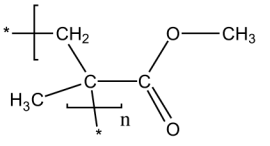


Figure 3.9 Production of pressure sensors with the AMANDA process: (a) diaphragm is surface micromachined; (b) housings are made by molding; (c) diaphragm is transferred to the housings; and (d) the diced chips with fluidic and electrical contacts. [Reprinted with permission from Schomburg et al. (1998), copyright Elsevier.]

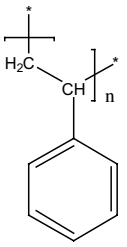
(SU-8) or thick positive photoresist (AZ4620) on silicon is used as a molding template for the casting process to obtain a negative of the desired features in PDMS (allowing high aspect ratios). A technique to fabricate microchannels over a wide range of aspect ratios in PMMA is described. Advantages compared to the conventional methods of fabricating hot embossing tools include rapid processing and a reduction in complexity and cost.



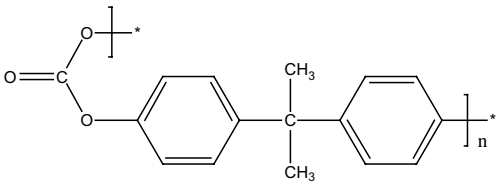
Poly(methyl methacrylate) (PMMA)

A device for separation of blood from plasma using microchannels manufactured with UV-LIGA and hot embossing has been produced [Blattert et al., 2004].

Becker and Dietz (1998) describe hot embossing as a replication method for planar microstructures based on polymer substrates containing microchannels for capillary electrophoresis (CE). An investigation of a hot embossing process including the optimization of operating parameters for polystyrene (PS) and polycarbonate (PC) substrate materials, and the implications for the replication of microchannels with various aspect ratios have been reported [Simdikova et al., 2002].



Polystyrene (PS)



Poly(bisphenol A carbonate)

Use of the AMANDA technique has been shown to produce reliable micropumps using polyimide (Nylon 6) and other polymers (PSU, PA, PC, PVDF, and PEEK). Lifetime of the pumps has been demonstrated for up to 7,600 hours [Schomburg et al., 1999]. Development of a micro-annular-gear pump by micro-powder-injection molding has also been performed [Gietzelt et al., 2004].

Injection molding and other techniques that heat and compress polymers raise questions about the processing effects on the rheological, mechanical, and tribological properties of polymers and composites [Martyn et al., 2003]. *Atmospheric molding* is an alternative molding technique that offers the advantage of not requiring pressure and heat, which might otherwise influence the accuracy of the device to be fabricated. PMMA-separation microchips have been fabricated with UV-initiated polymerization of a monomer solution in an open mold under ambient pressure [Muck Jr. et al., 2004].

3.5 Three-Dimensional Photopolymerization

Three-dimensional fabrication techniques based on layer-by-layer assembly ("additive" processes) have application in bioMEMS design. Rapid production of devices used primarily for modeling and prototyping can be accomplished with high accuracy by a number of processes.

Stereolithography (SL) and microstereolithography (MSL) use light to initiate polymerization, and are reviewed in this section.

3.5.1 Photopolymerization

Photoinitiated polymerization based on UV curing occurs between 225 and 550 nm. Free radical and cationic curing mechanisms may be used.

When the *photoinitiator* is exposed to UV, they break down leaving components with an unpaired electron, or *free radical. Propagation* occurs with the addition of monomers, and transfer of the free radical down the propagating chain to continue the process of adding monomers. *Termination* occurs when the growing chain stops. Acrylates are associated with free radical polymerization.

In contrast, *ionic polymerization* involves an attack on the π electron pair of a monomer. Cationic polymerization occurs when the active site has a positive charge (in contrast to anionic polymerization in which the active site has a negative charge). The addition of monomers moves the charge down the chain until termination occurs. Epoxies are associated with cationic curing [Varadan et al., 2001].

3.5.2 Stereolithography (SL) and microstereolithography (MSL)

In stereolithography (SL) a computer-driven laser scans a photocurable resin causing photopolymerization in a layer-by-layer manner, building the structure in "planes" from the "ground up." A computer-aided design (CAD) program takes a 3D rendering from a drawing program, "slices" the image into 2D images, and operates *x-y* translational stages (positioners) for moving the laser in a precise scan pattern. Software turns the laser on and off as it scans, causing selective polymerization. Parts are fabricated as layers pass through the *z*-axis focal plane. The part is lowered (or focal plane elevated) after each layer is polymerized, bringing the next layer to be polymerized into the focal plane of the laser. The photopolymer solution may consist of monomers, oligomers, and photoinitiators. Ceramic and metallic materials may also be incorporated. The polymerized spot size and thickness may be hundreds of microns.

Microstereolithography (MSL) differs from SL in that submicron resolution of the *x-y-z* translational stages and a finely focused UV laser spot allow for polymerizations of layers of $1-10\ \mu m$ in thickness. MSL was proposed by Ikuta in 1995. Projection MSL builds an entire layer at a time, using a focused image from a mask for each layer rather than *x-y* scanning. Figure 3.10 shows the concept of real mask projection MSL. Dynamic mask projection MSL uses a dynamic mask created and focused from a computer driven liquid crystal display (LCD), allowing rapid layer-by-layer polymerization (Fig. 3.11). There are a variety of shapes and functional parts that can be achieved with MSL, including pipe structures [shown in Fig. 3.12 (a–d)].

An interesting variation in the method has been shown by Im (2002). An SL system has been developed that imparts multiple colors to a prototype part (rather than the typical monocolor). Whereas typical evaluation of a layer-by-layer part is usually confined to the external features, by combining transparent

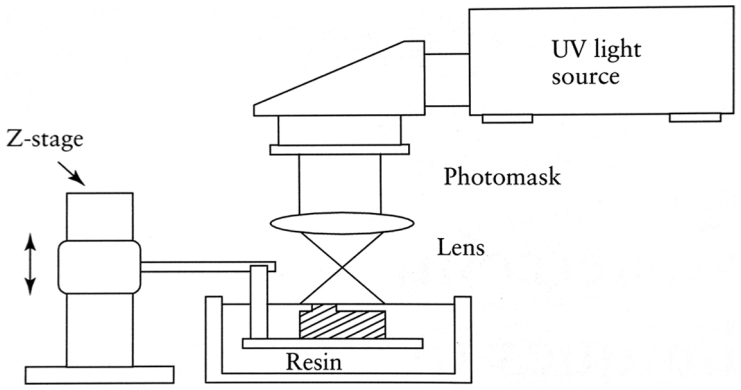


Figure 3.10 Real mask MSL. [Reprinted with permission from Suzumori et al. (1994), copyright IEEE.]

and colored areas within a single fabricated part, visualization of "inner structures" is possible. This may be helpful in modeling a bioMEMS device, including inner components and packaging from a single SL fabrication, or organ systems such as the heart or arteries.

It is not hard to imagine future refinement of these processes as being able to produce commercially suitable medical devices. High resolution imaging data from a patient could be used to design specific characteristics, dimensions, and packaging of a device, and layer-by-layer techniques used to fabricate one-of-a-kind components cost effectively. Moreover, the combined device and host interface could be modeled with color SL techniques to assist in the design and

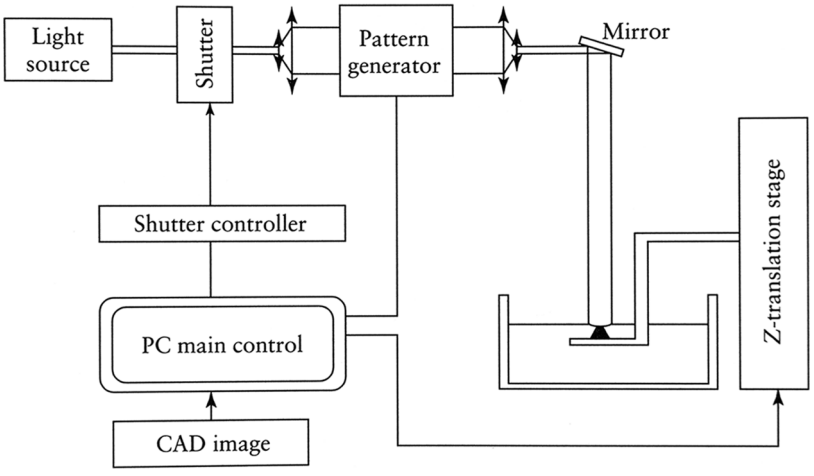


Figure 3.11 Dynamic mask MSL. [Reprinted with permission from Bertsch et al. (1997), copyright Elsevier.]

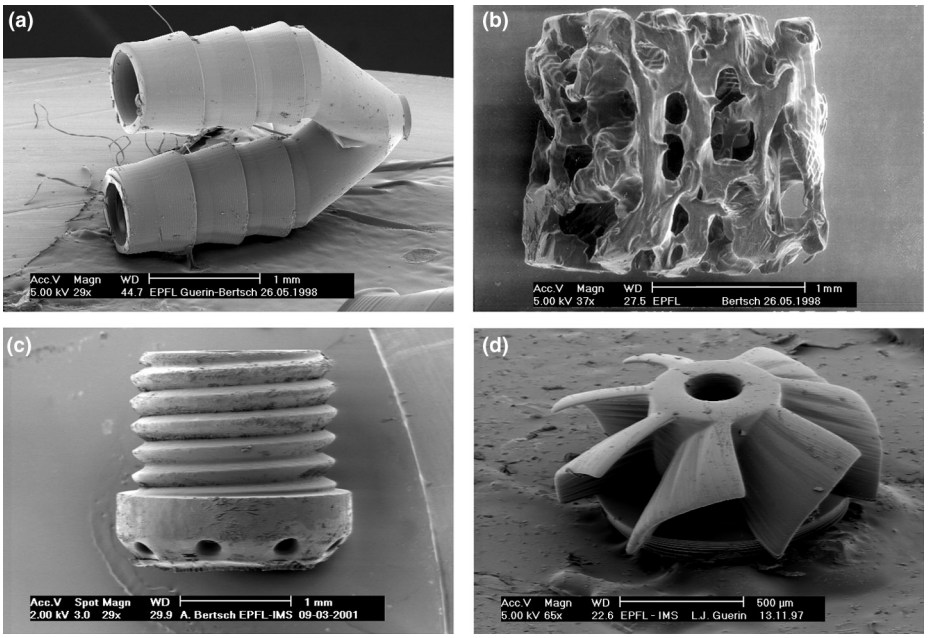


Figure 3.12 Examples of devices that may be fabricated by high resolution stereolithography (a) pipe structure; (b) bone material; (c) nozzle; and (d) turbine. [Reprinted with permission from Bertsch (2005).]

evaluation phase, and to communicate the proposed medical device to the patient and doctors.

3.6 Smart Polymers and Hydrogels

3.6.1 Introduction

"Smart" polymeric materials exhibit significant changes in their characteristics with small changes in their environment. These *external stimuli* include pH, calcium, magnesium, organic solvents, temperature, magnetic field, electrical potential, and IR and UV radiation. Roy and Gupta (2003) published an excellent review of these materials. Some materials respond to *dual stimuli* such as calcium and PEG, calcium and temperature, calcium and acetonitrile, pH and temperature, and light and temperature. Table 3.1 shows a variety of single and dual stimuli and suitable polymer materials. While electroactive polymers (EAPs) are also considered smart polymers, they are discussed in Chapter 7, *Microactuators and Drug Delivery.*

Smart polymers are either reversible soluble-insoluble (SIS) in aqueous media or cross-linked in the form of hydrogels. SIS polymers include synthetic polymers such as poly(N-isopropylacrylamide) (PNIPAAm) and methyl-methacrylate

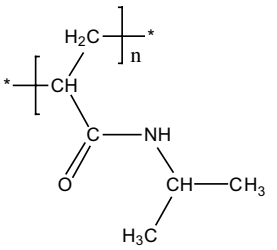
Table 3.1 Smart Materials and their Stimulus. [Adapted with permission from Roy and Gupta (2003), copyright Elsevier.]

Stimulus	Polymer Material
pH	Dendrimers*
	Poly(L-lysine) ester
	Poly(hydroxy-proline)
	Lactose-PEG grafted poly(L-lysine) nanoparticle
	Poly(L-lysine)-g-poly (histidine)
	Poly(n-propyl acrylate)
	Poly(ethacrylic acid) (PEA)
	Polysilamine (a heterotelechelic oligomer)
	Eudragit S-100**
	Eudragit L-100**
	Chitosan
	PMAA-PEG copolymer
Calcium	Alginate
Magnesium	Chitosan
Organic solvent	Eudragit S-100
Temperature	Poly(N-isopropylacrylamide) (PNIPAAm)
Magnetic field	PNIPAAm hydrogels with ferromagnetic material
Sol-gel transition	Poloxamers (block copolymers of polyethylene glycol (PEG) and polypropylene glycol (PPG))
	Chitosan-glycerol phosphate-water
Electric potential	Polythiophen gel
IR radiation	Poly(N-vinylcarbazole) composite
UV radiation	Polyacrylamide crosslinked with 4-(methyacryloyamino)azobenzene
	Polyacrylamide-triphenylmethane leuco derivatives
Ultrasound	Dodecyl isocyanate-modified PEG-grafted poly(hydroxyethyl-methacrylate) Poly(HEME)
Dual-stimuli stimulus	
Calcium and PEG	Carboxymethyl cellulose
Calcium and temperature	Eudragit S-100
Calcium and acetonitrile	Eudragit S-100
32°C and 36°C	Hydrogels of oligoNIPAAm and oligo(N-vinylcaprolactum)
pH and temperature	Poly(N-acryloyl-N′-propyl piperazine)
Light and temperature	Poly(vinyl alcohol)-graft-poly-acrylamide-triphenylmethane leucocyanide derivative

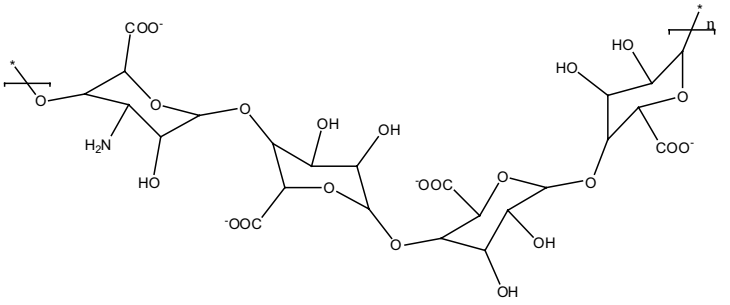
*Dendrimers are large and complex molecules of consistent size and form. They have a regular and highly branched 3D architecture consisting of three components: core, branches, and end groups.

**Eudragit L-100 and Eudragit S-100 (Röhm GmbH & Co., Germany) are ionic copolymers based on methacrylic acid and methyl methacrylate, in ratios of 1:1 and 1:2, respectively.

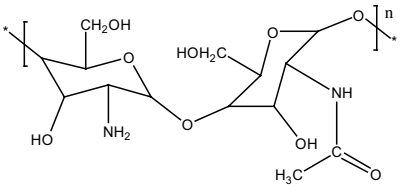
polymers, and natural polymers such as alginate and chitosan (polysaccharides) [Roy and Gupta, 2003].



Poly(N-isopropylacrylamide) (PNIPAAm)



Alginate



Chitosan

Hydrogels are 3D networks of polymers that are capable of retaining solvents. They range from mechanically soft to hard, with varying degrees of porosity. The precursor material is a liquid mixture, and photopolymerization may be used to solidify the hydrogel (below). Photolithographic techniques may be used to polymerize the gel within a LOC device through optically transparent surfaces (e.g., anodically bonded glass on silicon).

Physical hydrogels are held together with noncovalent forces and have hydrophilic and hydrophobic domains; and *chemical hydrogels* are held together by crosslinking, and have regions of high and low cross-linking. Areas of low crosslinking allow higher swelling.

When a stimulus is applied at a critical level, both SIS and hydrogels increase or decrease their overall hydrophilicity and either swell or shrink, respectively. Figure 3.13 shows diagrammatically the volume-to-stimulus relationship and polymer swelling.

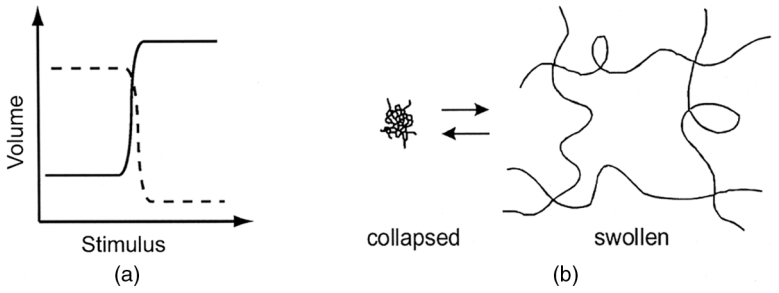
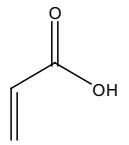


Figure 3.13 Behavior of stimuli-responsive hydrogels: (a) graph of the volume of the hydrogel versus stimulus; (b) contracted and swollen state of the polymer network. [Reprinted with permission from Oosterbroek and van den Berg (2003), copyright Elsevier.]

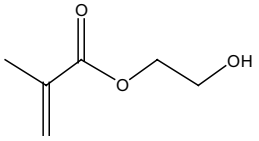
3.6.2 Synthesis

Hydrogels may be selectively polymerized by using UV light (365 nm), a collimating microscope, and photolithography masks. An energy level of 40 mW/cm^2 can induce polymerization.

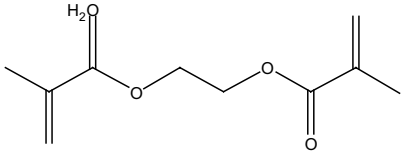
An example of a pH sensitive hydrogel mixture is acrylic acid (AA) and 2-hydroxyethyl methacrylate (HEMA) in a 1:4 molar ratio, ethylene glycol dimethacrylate (EGDMA) at 1 wt %, and a photoinitiator DMPA at 3 wt% and Irgacure 651. This mixture, after polymerization produces a hydrogel that swells in a basic solution and contracts in an acidic solution.



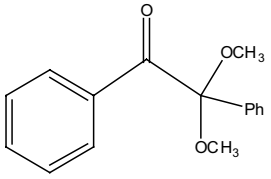
Acrylic Acid (AA)



2-hydroxyethyl methacrylate (HEMA)



Ethyleneglyco dimethacrylate (EGDMA)

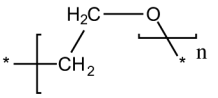


2,2'-dimethoxy-2-phenyl acetophenone (DMPA)

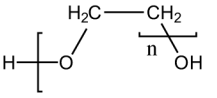
An example of a rigid structural material is isobornyl acrylate (IBA), 2,2-bis (p-2′-hydroxy-3′-methacryloxypropoxy) phenylene] propane or tetraethyleneglycol dimethacrylate (TeEGDMA), and Irgacure 651 photo-initiator. Typical polymerization times are less than a minute [Oosterbroek and van den Berg, 2003].

3.6.3 Synthetic hydrogels

While chemically synonymous, PEO generally refers to polymers with molecular weight above 20,000 g/mol, and PEG to polymers of lower molecular weight. Poly(ethylene oxide) (PEO) and poly(ethylene glycol) (PEG) are synthetic hydrogel polymers used for tissue engineering. Both are hydrophilic polymers, and can be photo-cross-linked with acrylates or methacrylates.



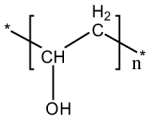
Poly(ethylene oxide) (PEO)



Poly(ethylene glycol) (PEG)

PEO is derived from ethylene oxide and is biocompatible in several ways. It does not promote cell adhesion or protein adsorption, and does not induce thrombosis or activation of the complement system in the body.

Poly(vinyl alcohol) (PVA) is also a synthetic hydrophilic hydrogel polymer and can be cross-linked by repeated freeze-thawing cycles of an aqueous polymer solution, or by chemically cross-linking to form hydrogels [Drury and Mooney, 2003].



Poly(vinyl alcohol)

3.6.4 Implementation

Kamijo et al. (1996) describe production of hydrogel microspheres by precipitation polymerization from acrylamide (AAm), methylenebisacrylamide (MBAAm), and methacrylic acid (MAc) in isopropanol. MAc was found to be essential for the preparation of fine spherical particles. The particle size was depended on various polymerization conditions, including the monomer composition, the amount of initiator and the total monomer concentration. The internal structure of microgels was observed by small-angle x-ray scattering (SAXS).

Hydrogels have been studied as a means for controlled drug delivery by Brahim et al. (2002 and 2003), Soppimath et al. (2002), and Ziaie et al. (2004). A thermo-responsive microfluidic actuator was produced by Harmon et al. (2003), an ultrasensitive microcantilever sensor was produced by Hilt et al. (2003), and components for LOC devices were produced by Oosterbroek and van den Berg (2003).

Optically active nanoparticles have been incorporated into hydrogel structures for the purpose of initiating a temperature increase via targeted absorption of near infrared and green light. Sershen et al. (2002) describes a means for optically addressing hydrogels containing one or the other of these nanoparticles, by

initiating shrinkage depending on which light is shined on them. This form of optical to thermal to chemical energy translation could prove useful for bioMEMS devices that operate as remote drug delivery systems triggered via fiber optics from a distant or integrated electronic controller.

Alexandre et al. (2004) studied star-shaped macromolecules of PEO cross-linked to each other via electron beam irradiation (high-energy exposure induces quasi-spontaneous gelation) This material was grafted onto porous expanded poly (tetrafluoro ethylene) (EXPTFE) to take advantage of the support structure's mechanical properties. The PEO-coated structure was implanted in test animals, and found not to induce the foreign body reaction typically seen with EXPTFE alone. Diffusion of glucose through the hybrid structure was studied.

3.7 Nanomedicine

BioMEMS is the platform for most conceived nanomedicine applications. This is especially true for new sensor and diagnostic technologies, drug-delivery systems, genetic manipulations, and other therapeutic modalities. Patterning techniques for DNA and protein microarrays are discussed in later chapters.

Reducing feature sizes below 100 nm has required new nanofabrication methods including extreme ultraviolet (EUV) and x-ray lithography. Micro-contact printing, soft molding, and molding in capillaries (MIMIC) may also be used for nanoscale applications.

Additional techniques that have been investigated include nanoimprint lithography (NIL), laser-assisted direct imprint (LADI) [Chou et al., 2002], nanotransfer printing (nTP) [Loo et al., 2002; Matsui et al., 2003; Menard et al., 2004; Wang et al., 2004(b)], molecular transfer lithography (MxL) [Schaper, 2003], atomic force microscopy (AFM) material placement, and self-assembled monolayers (SAMs).

3.7.1 Nanoimprint lithography (NIL)

There are basically two types of nanoimprint lithography (NIL): thermal and ultraviolet. Thermal NIL is similar to other molding techniques in that a low-viscosity polymer is heated above its glass transition temperature and mechanically pressed in a stamp containing nano-sized features.

UV-NIL is performed at low pressure and room temperature. A transparent stamp with nano/micro scale patterns is pressed on to a thin resin layer or resin droplets, and then UV light is exposed from above the stamp to cure the resin.

3.7.2 Self-assembled monolayers (SAMs)

Molecular self-assembly of materials is an important tool for bioMEMS device fabrication, and offers a new class of nanoscale materials for nanodevices.

Self-assembly is the spontaneous organization of molecules through the formations of numerous noncovalent weak chemical bonds. These include hydrogen bonds, ionic bonds, and van der Waals' bonds to assemble the molecules into some well-defined and stable hierarchical macroscopic structure. The collective interaction of the structure results in a stable material. Chemical complementarity and structural compatibility are the key elements for the process [Zhang, 2002].

Certain materials can be made to undergo self-assembly onto surfaces rather than among themselves, creating *self-assembled monolayers* (SAMs). These molecular architectures are formed spontaneously upon the interaction of a surface—an active head group with an appropriate substrate (see Fig. 3.14). These "surface anchors" form a covalent bond. Thiols and disulfides are the commonly used reactive molecules on noble metal substrates like gold and silver. Silanes are generally used on nonmetallic oxide surfaces like SiO_2, Ta_2O_5, and TiO_2. The surface-active head is connected to an alkyl or derivatized alkyl chain compound that serves for dense packing and "linking" with some degree of flexibility to a reactive tail group. The tail group or terminal end of the alkyl group is functionalized to yield a number of active groups like $-OH$, $-NH_3$, $-COOH$, and COOR, imparting varied functionality. These ligands recognize specific molecules, and impart different wetting and interfacial properties. Thicknesses in the vertical dimension are typically in the nanometer range, while the horizontal surface may be macroscopic in size. Stabilization between molecules occurs by van der Waals' forces [Schaeferling et al., 2002].

SAMs may act as biocompatible interfaces for chemical coupling of proteins to a microarray substrate. Protein microarrays offer the ability to study post-translational modifications (PTM) of proteins such as from phosphorylation, glycosylation, and acylation as well as other protein activity. They may be used

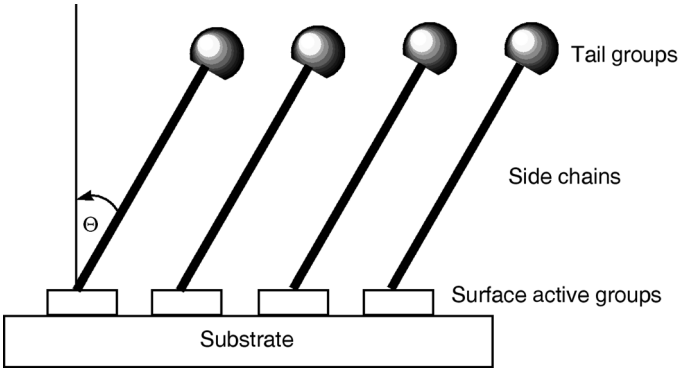


Figure 3.14 SAM assembly. The monolayer is formed by the exothermic interaction of a surface group with the substrate, followed by lateral reordering of the side chains and the tail group. The angular tilt is a result of reordering to maximize van der Waals interactions between the various molecules. [Adapted with permission from Schaeferling et al. (2002), copyright Wiley VCH.]

to identify proteins in disease state and other gene expression less suitable to DNA microarrays. Traditionally, epoxy-, aldehyde-, or polylysine-coated glass slides have been used to immobilize antigens or antibodies. Disadvantages have been the "smearing" of material across individual probes, electrostatic charges on glass that may cause denaturing of proteins, and varying fluorescence signal intensity if the surface chemistry within the spots is not homogeneous. SAMs have been shown to overcome these limitations and offer other advantages. Schaeferling et al. (2002) review the various methods of coupling proteins to the SAM microarray surface and fabrication of 2D and 3D protein microarrays. For example, a well-packed streptavidin surface may be generated by using a surface reaction between a hydrophobic interface comprised of carboxyl groups and their interaction with biotin-terminated linker units attached to amino groups.

DNA microarrays may be fabricated by SAMs as well as by photochemistry and lithographic techniques (discussed below). Oligonucleotide SAMs have been created by exposing gold substrates to a solution containing an inert thiol terminated with DNA. To reduce nonspecific binding the DNA-functionalized thiols are mixed with triethylene glycol-terminated thiol and adsorbed onto gold to form a DNA monolayer [Bamdad, 1998].

Another technique for forming thin films is the *Langmuir-Blodgett* process (see Fig. 3.15). This process allows controlled deposition of a monolayer of molecules on a substrate. The material of interest is floated on an aqueous surface. Then, by dipping the substrate into the aqueous solution through the surface film, a monolayer of the material is deposited onto the substrate surface. The dipping process may be repeated to add layers [Madou, 2002].

3.7.3 Other patterning techniques

Atomic force microscopy (AFM) is a technique for measuring topography of surfaces, and is discussed further in Chapter 10, *Detection and Measurement Methods.* The same instrument is useful for manipulating biomolecules [Takeda et al., 2003]. The AFM tip is 5 to 50 nm in size and by dipping it in organic and inorganic material it may be used for nanolithography. Another approach is to immobilize an enzyme on the AFM tip, and by way of scanning, modify a surface based on enzymatic activity.

Helt et al. (2004) review techniques available for patterning nanostructures on polymers, and introduce a bench-top method for synthesis and transfer of materials to and from polymers (STOMP). This technique may find application in constructing sensors, electronic devices, optical materials, photolithography masks, and layered photonic band gap structures. In STOMP, nanostructures are formed by the compression of a malleable metal film, such as Au, deposited on a rigid support, such as mica, by a polymer stamp, followed by chemical etching while the material is under compression by the stamp.

Banerjee et al. (2004) review the use of "dip-pen nanolithography" for microfluidic "ink" delivery for array fabrication.

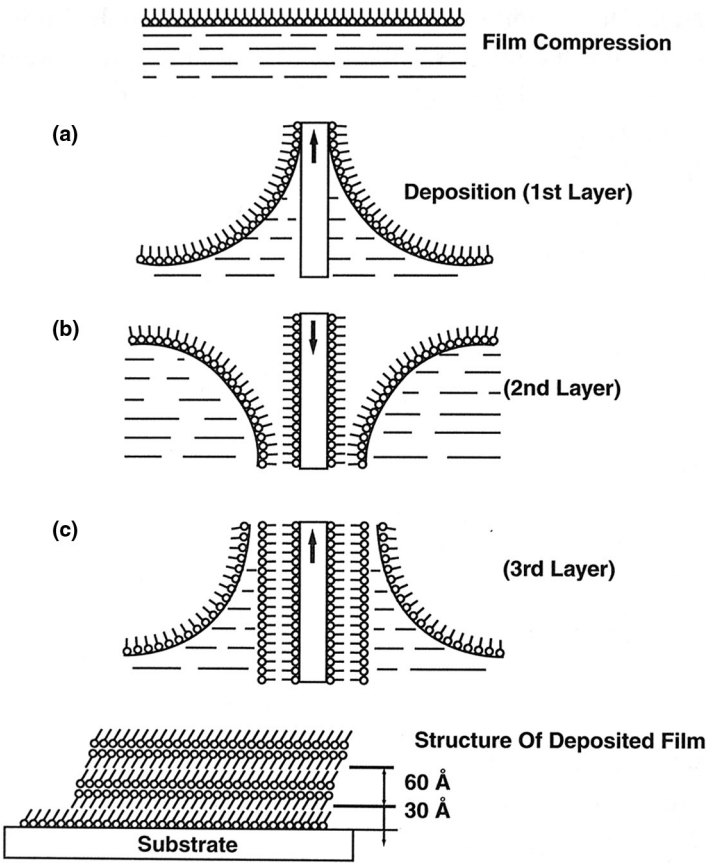


Figure 3.15 Langmuir-Blodgett process. [Reprinted with permission from Madou (2002), copyright Taylor and Francis Group.]

3.8 Thick-Film Technologies

Thick-film technologies incorporate paste and colloidal compounds that may be applied as "inks" by screen-printing (and other techniques) and curing, achieving layer thicknesses of 10 to 50 μm [Harsányi, 2000]. This is in contrast to *thin-film* technology that incorporates high-purity metals, alloys, and compounds that are deposited by physical and chemical deposition methods (PVD, CVD, electrochemical, thermal oxidation, etc.) in layers of 10 to 200 nm. Sensors are commonly fabricated with thick-film techniques and may be useful in LOC devices [Madou, 2002; Wang et al., 2001].

In *sol-gel* techniques a solid particle and other chemical precursors may be suspended in a colloidal solution ("sol"), and brought by dehydration or chemical reaction to the point at which a gelatinous phase transition occurs ("gel"). In the gel state the materials may be applied as a thick film to an appropriate surface, and

then dried and/or sintered into a film coating, powder, or even dense ceramic [Madou and Florkey, 2000].

3.9 Review Questions

1. Define "biomaterials" and their application classes.
2. List advantages and disadvantages of polymer materials over glass for bioMEMS applications.
3. Describe ionic, covalent and metallic bonding, and how they apply to biomaterials.
4. Describe soft lithography and the various methods available for producing microstructures.
5. Explain injection molding and the special requirements of this process for microfabrication.
6. Describe hot embossing, the materials commonly used and its role in fabricating bioMEMS devices.
7. What is atmospheric molding?
8. Define AMANDA.
9. Describe methods for producing three-dimensional parts using photopolymerization, and how this process works.
10. Describe what is meant by "smart" polymers, and list several examples of polymers and their stimulus.
11. What are reversible SIS polymers, and name both synthetic and naturally occurring polymer examples?
12. Outline the steps to produce a hydrogel.
13. Describe what is meant by "nanomedicine," and describe some of the fabrication methodologies available.
14. Describe self-assembled monolayers and techniques to fabricate them.
15. Describe various thick-film preparation techniques.

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