

# Chapter 2

## Microfabrication Techniques for Microfluidic Devices

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### 2.1 Introduction

Microfluidic technology usually, but not exclusively, aims at the miniaturization of conventional laboratorial processes to handle fluids (liquids and/or gases) within submillimeter ranges. The manipulation of fluids follows different strategies (e.g., sample/reagent actuation, mixing, separation, filtration, reaction, control, monitoring, detection, etc.) depending on the final objective and available space for operation. Recent efforts focus on integration of e.g., micro-to-nano elements, sensing, electronics or automation for high throughput and low-cost devices [3]. Additionally, microfabrication strategies aim at providing unique and increased functionality for sample-to-answer compact platforms for intelligent systems design towards e.g., biological, medical or chemical applications.

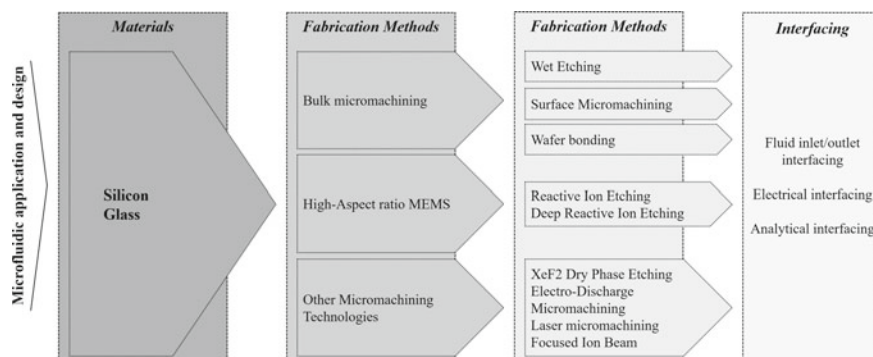
The fabrication methods and their limitations together with the application largely determine the size, shape and material of microchannels and the layout configuration of their arrays [29]. The correct selection of material used in the microfabrication process is necessary for the successful application of advanced and low-cost microfluidic devices. Common viable compatible materials used are silicon, metal, silica, polymeric or paper [28].

Fabrication techniques used for silicon-based microfluidic devices are mostly based in Micro-Electro-Mechanical Systems (MEMS) methods, which have dramatically developed alongside semiconductor technology [38]. MEMS fabrication adopted techniques well established in the integrated circuit (IC) industry. These include oxidation, ion implantation, low pressure chemical vapor deposition

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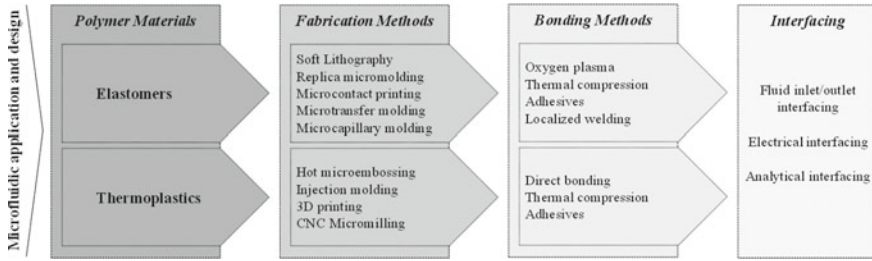
**Fig. 2.1** Fabrication methods for rigid substrates

(LPCVD), diffusion, sputtering, etc. Actuation, control and measurement functions can be simultaneously microfabricated on silicon wafers by combining IC techniques with dedicated micromachining processes e.g., deposition of  $\text{SiO}_2$  as a sacrificial layer and for electrical insulation, polysilicon deposition for conductive or resistive features, metal deposition for conductive elements or  $\text{TiN}$  and  $\text{Si}_3\text{N}_4$  deposition for passivation and electrical insulation (Fig. 2.1).

Depending on the type of microfabricated systems, they can go from 20 nm to 50  $\mu\text{m}$  feature size. Recording heads or MRAM (Magnetoresistive Random-Access Memory) technologies for example, must have features below 100 nm to be competitive [40] whereas dimensions of e.g., RF and power transistors are set from 100 nm to 1  $\mu\text{m}$  [12]. MEMS devices typically have 1–10  $\mu\text{m}$  minimum features and microfluidic devices might have features as small as 5–10  $\mu\text{m}$ , but are usually larger.

On the other hand, using polymer materials to fabricate microfluidic devices (Fig. 2.2) reduces fabrication times while providing simple, cost effective, and disposal advantages when compared to Silicon. Polydimethylsiloxane (PDMS) elastomer and thermoplastics (polyethylene terephthalate—PET, polymethyl methacrylate—PMMA, polycarbonate—PC, or polyimide—PI) are the major polymeric materials used in microfluidics mainly due to their flexibility, optical transparency to visible/UV, easiness of molding with high fidelity, simplicity in the modification of surface properties, biocompatibility or bioactivity, durability, chemical inertness and low-toxicity. Contrarily, low thermal stability and low thermal and electrical conductivity can severely limit the choice of polymeric materials for microfluidic applications.

Rapid prototyping of the microfluidic devices in elastomers is achieved using soft lithography, where the PDMS is poured over a master mold to create the required fluidic passages. The molding master is fabricated by either patterning positive photoresist, e.g., AZ 40XT or negative photoresist, e.g., SU-8, on a silicon substrate for precise microstructures (sizes below 50  $\mu\text{m}$ ) or by direct micromilling of polymeric material (e.g., PMMA) for larger microstructures (sizes above 50  $\mu\text{m}$ ). These process are simple and inexpensive, yet time consuming and unviable for mass production.



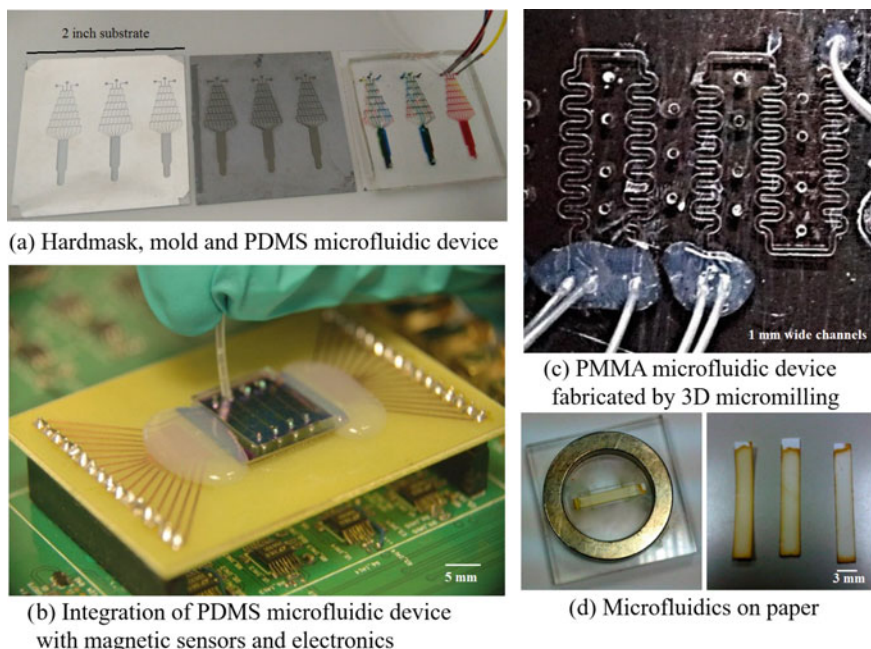
**Fig. 2.2** Microfabrication techniques for polymer based microfluidic devices

Alternatively, thermoplastics are softened or fully melted and reshaped upon heating. Various methods exist for the fabrication of thermoplastic microdevices e.g., hot embossing, injection molding, micromilling or 3D printing. The process is implemented guaranteeing thermoplastics remain chemically and dimensionally stable over the range of operational temperatures and pressures [43]. Depending on the fabrication process and molds, devices up to a few micrometers can be fabricated onto thermoplastics to high impact resistances. From the fabrication processes presented, hot embossing is viewed as the most commercially viable for mass production [16].

Paper microfluidics has been recently proposed as a convenient alternative for a new class of microfluidic devices where the manipulation of fluids is accomplished within paper-like porous materials [8]. Paper is a low-priced, lightweighted and disposable material, ready accessible in a wide spectrum of thicknesses, making it extremely attractive for versatile, low-cost, easy to use and fast sample-to-answer microfluidic devices [31]. However, small and imprecise sample volumes limit precision and sensitivity of paper microfluidic devices. Moreover, their design aims at individual testing, making them unsuitable for high-throughput screening.

Bonding is a critical step in microfabrication processes necessary to provide a tight seal to prevent leakage without deformation of the channels. Bonding can be chemical (e.g.,  $UV/O_3$  or plasma activation), thermal (compression at temperature elevated to the glass transition  $T_{glass}$ ), or adhesive (e.g., resins or curable materials), etc. [42]. A large variety of materials can be joined to form microfluidic passages which may include sensing and actuation. Two distinct materials can be bonded together (e.g., silicon/glass, glass/polymer, etc.) or the channels can be fabricated with several parts of the same material.

The choice of the fabrication method relies on its capability to create the part with the desired features. Other technical capabilities have to do with the compatibility with the material to use and the quality of the finished part. With this in mind, microfabrication techniques for microfluidic devices (examples in Fig. 2.3) are detailed below. The discussion of a set of unique challenges such as the best material and adequate fabrication process to be used for particular applications and the total cost of fabrication is also presented.



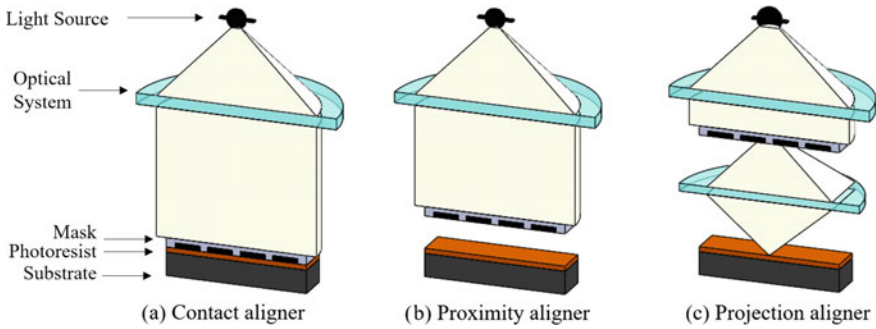
**Fig. 2.3** Examples of microfluidic devices

## 2.2 Fabrication of Microfluidic Devices in Rigid Substrates: Silicon/Glass

Microfabrication of microfluidic devices in rigid substrates makes use of well established techniques of semiconductor industry such as lithography, subtractive and/or additive techniques (e.g., etching and thin-film deposition), to achieve few to hundreds of micrometer devices on top or within the substrate. Microfabrication techniques can be used sole or combined to obtain simple or intricate devices as reported below.

### 2.2.1 *Lithography*

Lithography is the process used to transfer three-dimensional patterns onto a surface [32]. This is seen as the most important step in the microfabrication process as the definition of the shape of elements constituting the devices is performed here.



**Fig. 2.4** Methods to transfer a pattern to a surface

Lithography steps: (1) designing the pattern, (2) making the mask, (3) coating the wafer, (4) exposing the photoresist, (5) developing the photoresist.

Several steps define the lithographic process. The geometric pattern is designed using computer-aided design (CAD). The pattern is then transferred to a light-sensitive polymer, (also called photoresist, PR) previously coated on the substrate, by exposing the PR to light (UV, Laser, beam of electrons). The light can pass through a hardmask or a photomask (photolithography) to expose the PR or the lithography can be maskless, as is the case of Laser lithography. After the development of the PR, the substrate is ready to proceed for the next step of fabrication.

The PR is exposed to light under programmed duration and energy, determined by its energy adsorption. Laser lithography is the lithographic technique using laser light to fabricate large precision patterns. The minimum feature size achieved with this technique ( $\sim 0.8 \mu\text{m}$  or less) depends on the laser light wavelength and optical path. Additionally, modulating the intensity of the laser can result in partially exposed PR (Laser Direct write grayscale photolithography), which can be used to create microscale features with multilevel topography. Photolithography, also called optical or UV lithography, predominantly uses UV light through a photomask or hardmask to expose the PR. The photomask or hardmask is usually defined on a metallic thin film layer (e.g., aluminum, chromium, etc.) opaque to UV light, deposited onto a flat UV-transparent substrate (Table 2.1). The geometric patterns are usually determined by computer-aided design for increased definition and can be defined over large sized substrates (up to  $\sim 30\text{cm}$ ).

The strategy of exposure will define the process resolution, which is diffraction limited. For example, in contact lithography (Fig. 2.4a), the hardmask is in direct contact with the PR. The features to be transferred are so at a 1:1 ratio (no magnification) for minimum feature sizes (m.f.s.) of  $0.5 \mu\text{m}$ . Although this is a very simple to use and inexpensive technique, the direct contact with the mask usually smears and degrades the features, leading to a loss of sharpness and

**Table 2.1** Types of basic materials used to make photolithography masks

Quartz	Soda lime	Plastic mask
Expensive	Good price/quality ratio	Low price
High resolution	High resolution	Low resolution
Very stable	Stable	Weak stability
Can break	Can break	Easy to handle
Wavelength >180 nm	Wavelength >350 nm	Wavelength >350 nm

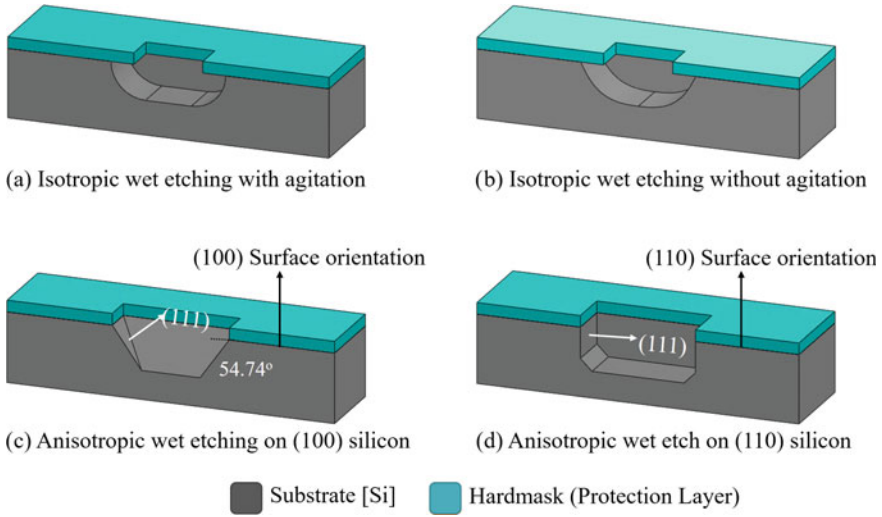
definition. Exposure strategies where the mask is not in direct contact with the PR, are either proximity printing (small gap between mask and PR, magnification 1:1) Fig. 2.4b or projection printing (projection from a distance and demagnification 1:4–1:10 or even lower) Fig. 2.4c. In proximity printing, the diffraction effects limit the accuracy and repeatability of pattern transfer and resolution worsens ( $\sim 1\text{--}2\text{ }\mu\text{m}$ ). The optical path in projection printing defines the resolution of the process, which can achieve m.f.s. of  $\sim 0.065\text{ }\mu\text{m}$  or slightly better, however, it is also the most expensive of the three.

Photoresist is a light-sensitive polymeric solution. Negative PR (the regions exposed to light become insoluble in the developer) originate m.f.s. up to  $2\text{ }\mu\text{m}$  and spin-coated spreading thickness from  $1\text{ to }3\text{ }\mu\text{m}$  (the photoresist film thickness is determined by the spinning speed), while positive PR (the regions exposed to light become soluble in the developer) has m.f.s. of  $\sim 1\text{ }\mu\text{m}$  for spreading thicknesses between  $1.5\text{ to }7\text{ }\mu\text{m}$ .

The m.f.s. on the pattern are also defined by the type of PR used in the process. After exposure, the development of PR is pursued to remove the unwanted regions. The resolution and definition of fabricated patterns is directly dependent of the development time and conditions (e.g., temperature, agitation, concentration, etc.). The PR still remaining on the substrate will define etching regions or deposition regions either remove or add material in a subsequent fabrication step.

**2.2.2 Subtractive Techniques for Pattern Transfer Microfabrication**

The etching process is a subtractive process in which the pattern is transferred by chemical/physical removal of the material. Generally two approaches are followed depending on the etching strategy. Wet etching uses chemical solutions as dry etching is performed through plasma methods. Additionally, a combination of the two methods (reactive ion etching) if often used.



**Fig. 2.5** Characteristic etched profiles obtained by isotropic or anisotropic etching

### 2.2.2.1 Wet Etching

Wet etching involves using liquid etchant to remove material from a surface. This is achieved isotropically or anisotropically (Fig. 2.5). Anisotropic etching uses crystal-orientation etchants of silicon (e.g., hydroxides of alkali metals: RbOH, KOH, CeOH, NaOH, ethylenediamine-pyrocatechol solution-EDP process). Planes (111)<sup>1</sup> are etched slower than other planes. Moreover, etching at concave corners on Si (100) planes stop at (111) intersections creating walls with 54.74° angle to the surface while convex corners are undercut.

- Isotropic etch : surface material is removed uniformly in all directions of the chemical structure.
- Anisotropic etch: the removal of surface material is dependent on the crystalline structure orientation of the surface.

Although very important in a fluid dynamics point of view, the EDP process is incompatible with MOS (Metal Oxide Semiconductor) or CMOS (Complementary Metal Oxide Semiconductor) processing as it is highly corrosive consequently rusting

<sup>1</sup>The orientation of a crystal plane or a surface are defined considering the plane intersection with the main crystallographic axes of the solid. The lattice directions and planes are mathematically described by the Miller Indices. The Miller Index notation is used as follows: family of directions  $\langle \dots \rangle$ , particular direction  $[\dots]$ , family of planes  $\{\dots\}$ , particular plane  $(\dots)$ .

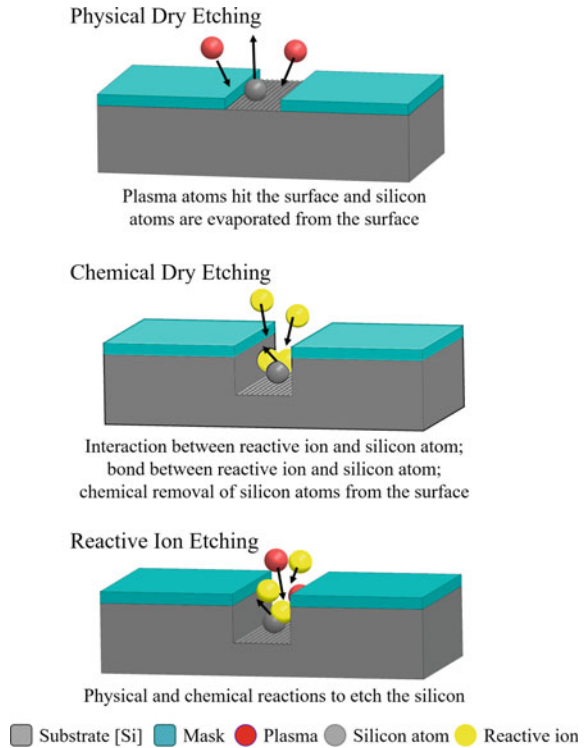


any metal deposited on the wafer and it permanently stains the surface. On the other hand, KOH displays an etch rate selectivity  $400\times$  higher in  $\langle 100 \rangle$  crystal directions than in  $\langle 111 \rangle$  directions making it extremely suitable for selective etching, as opposed to EDP whose selectivity for  $\langle 100 \rangle$  is only  $17\times$  higher than for  $\langle 111 \rangle$ , mobile potassium ions may drift to silicon dioxide or violently attack exposed metal contacts if etch rates higher than  $1\text{ }\mu\text{m}\cdot\text{min}^{-1}$  are used [27].

Wet isotropic etching (orientation independent) makes use of aqueous acidic solutions containing HF (hydrogen fluoride) and HNO (azanone) or HNA (HNA is a mixture of HF,  $\text{CH}_3\text{COOH}$  (acetic acid) and  $\text{HNO}_3$  (nitric acid)) to remove materials from the substrate. Factors such as agitation and temperature can affect the time and homogeneity of the process. The final etched shape is defined by the composition of the surface [35]. Characteristic round corner structures are obtained by isotropic etching of silicon, which is limited by diffusion.

The etch rate in wet etching can be enhanced by tuning agitation and temperature.

**Fig. 2.6** Physical dry etching, chemical dry etching and reactive ion etching mechanisms

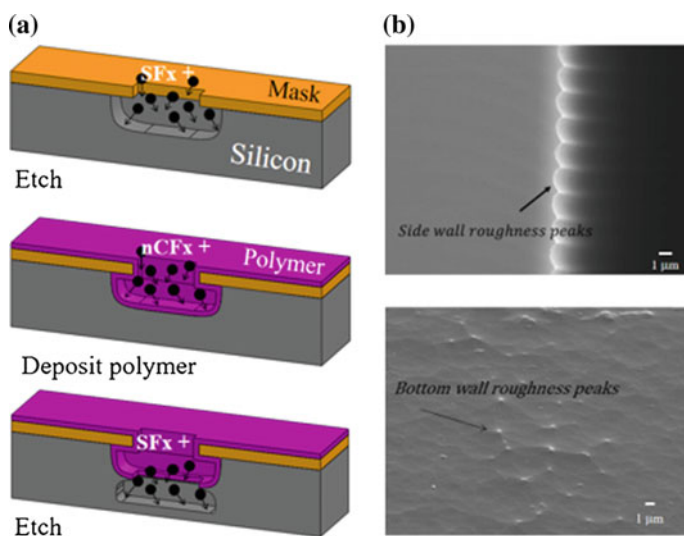




Both anisotropic and isotropic wet etchants can produce only a few specific channel geometries, limited by the wafer type and channel orientation, and lead to largely biased dimensions as well. Nonetheless, wet etching is a fast and simple etching technique suitable for low cost production.

### 2.2.2.2 Dry Etching

Dry etching uses plasma or etchant gases to remove material from the substrate at low pressure (few millitorr) and low temperature (from room temperature to 250 °C). The reactions taking place use high kinetic energy of particle beams (ion, electron or photon) to etch the substrate atoms (physical dry etching), chemical reactions between etchant gases to attack the surface (chemical dry etching) or a combination of both (reactive ion etching—RIE) to achieve high resolution (Fig. 2.6). Chemical dry etching uses reactive gases such as  $\text{CH}_4$ ,  $\text{SF}_6$ ,  $\text{NF}_3$ ,  $\text{Cl}_2$  and  $\text{F}_2$ . RIE is one of the most used in research and industrial processes. Typical RIE gases for silicon substrates are  $\text{CF}_4$ ,  $\text{SF}_6$  and  $\text{BCl}_2 + \text{Cl}_2$ . The reactions proceed almost spontaneously originating nearly isotropic profiles and and, therefore, very precise pattern transfers.



**Fig. 2.7** **a** Schematics of the DRIE process; **b** SEM of microchannel side wall roughness peaks (M 5000 $\times$ ) and SEM of roughness peaks on the microchannel bottom wall (M 3300 $\times$ ), resulting from the Bosh process

### 2.2.2.3 High-aspect-ratio: Deep Reactive Ion Etching

Deep Reactive Ion Etching (DRIE) is a relatively recent fabrication technique which enables high aspect ratio elements to be defined into silicon substrates, as well as into metal or glass.

The DRIE process provides deep features of hundreds to thousands of micrometers into the substrate with nearly vertical walls.

The Bosch etch is one of the most commercially employed DRIE technique [25], which uses alternating etch/passivation/etch chemistries. The technique is known to form these deep vertical walls with a characteristic scalloped sidewall typically with a peak-to-peak roughness of about  $0.3\text{ }\mu\text{m}$  [17]. It requires laser lithography to outline the patterns in the photoresist mask which will define the unprotected areas of the substrate to be etched.

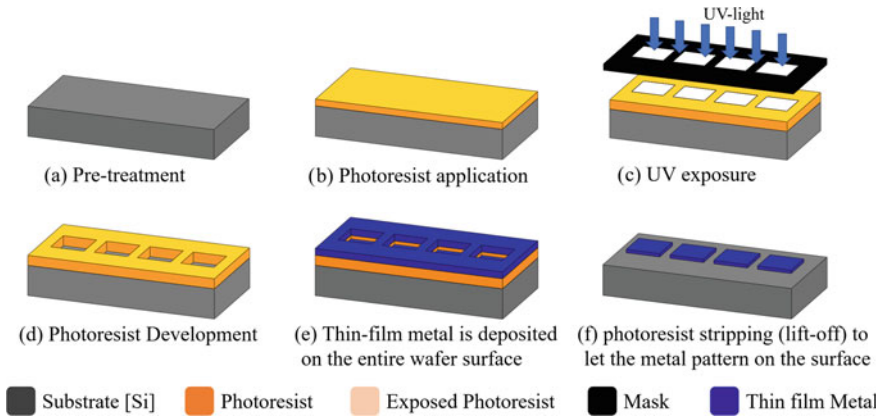
Although time consuming and expensive, the DRIE fabrication technique has very low manufacturing uncertainty. Moreover, this method can potentially manufacture an unlimited number of geometries and achieve feature sizes of the order of a few micrometers, which makes it very attractive for the growing field of integrated sensors and actuators and microfabrication of silicon microchannels.

The DRIE process is as follows: The etch uses high-density dry plasma to alternately etch the silicon and deposit a layer of polymer resistant to etching on the side walls. The process is done as many times as to achieve deep, vertical etch profiles. Silicon etching is conducted using sulphur hexafluoride ( $\text{SF}_6$ ) chemistry to provide the free radical fluorine in high-density plasma for silicon etching Fig. 2.7a. The protection of the side walls and the bottom of the etch pit is accomplished with the deposition of octofluorocyclobutane ( $\text{c-C}_4\text{F}_8$ ). These two steps alternate continuously until the desired depth is attained and depend largely on the size of the silicon area exposed to etching. Large unprotected areas of the substrate etch at much larger etch rates when compared to smaller areas. Moreover, the etch rate at the bottom pit is higher than that at the walls and a characteristic washboard or scalloping pattern is seen in the side walls due to the anisotropic nature of the process Fig. 2.7b. The etch rates on most commercial DRIE systems varies from  $1$  to  $4\text{ }\mu\text{m}\cdot\text{min}^{-1}$ .

### 2.2.3 Additive Techniques for Pattern Transfer

Additive microfabrication techniques are based on the addition of materials, usually selectively, to a substrate (Fig. 2.8). The addition can be mechanical, chemical or thermal depending on the energy used for adhesion.

Physical vapor deposition, PVD, is one of the methods used in the fabrication of microfluidic devices. It consists in depositing thin films onto the substrate by condensable vapor of the material to deposit through low-pressure or vacuum gaseous



**Fig. 2.8** Common fabrication steps for patterning metal onto a silicon wafer

environment. The vapor is shifted from the target source to the rigid substrate by various techniques (e.g., sputtering, thermal evaporation, ion plating and cluster deposition, laser ablation or laser sputter deposition, aerosol deposition, etc.).

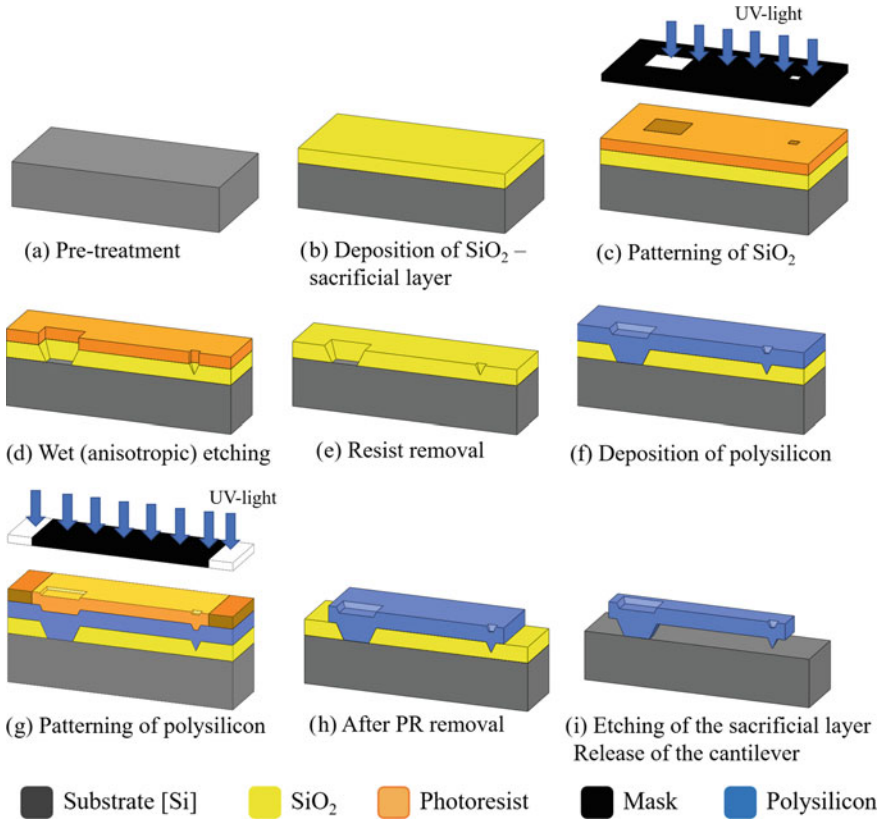
Additive microfabrication steps: (1) synthesize the vapor coating from the source (target) material, (2) transport the vapor to the substrate, (3) condense the vapor coating onto the surface of the substrate.

Sputtering deposition consists in bombarding a sputtering target by accelerated inert ions (e.g.,  $\text{Ar}^+$ ) in plasma atmosphere. The ions impinging on the target erode (sputter etch) the target surface by momentum transfer. The plasma can be obtained by DC (direct current), reactive sputtering, radio frequency (RF), magnetron, etc. The material ejected from the target becomes condensable vapor for deposition.

Thermal evaporation is used to deposit mainly metals (e.g., Au, Al, Ti, Cr) or compounds with low fusion temperature (e.g.,  $\text{SiO}_2$ ,  $\text{Si}_3\text{N}_4$ ) by means of resistive or electron beam heating. Unlike sputtering, evaporation deposits directionally from the source and sidewall coating is poor when compared to surface coating. Additionally, this technique provides lower deposition rates at higher substrate temperature than sputtering, generating thin films with higher tensile stresses.

Surface micromachining is characterized by the fabrication of micromechanical structures from thin films deposited above the surface of the silicon substrate [2]. Thin-film deposition is an additive process where layers of thin films (e.g., silicon dioxide, polysilicon, silicon nitride, and metal) are added to the substrate surface.

An example of the combination of surface micromachining and wet etching for the fabrication of a cantilever is shown in Fig. 2.9. The process starts with the deposition



**Fig. 2.9** Surface micromachining as a fabrication process for a cantilever

of a thin film material to act as a temporary mechanical layer also called sacrificial layer, onto which the subsequent device layers are built (Fig. 2.9b); next, patterning and etching of this sacrificial layer the deposition and patterning of the structural layer of thin film material (Fig. 2.9f, g). Etching of the sacrificial layer and release of the cantilever finalize the process (Fig. 2.9i), allowing the polysilicon structural mechanical layer to move.

## 2.3 Microfabrication Techniques for Polymer Based Microfluidic Devices

Along with silicon and glass microfabrication, cheaper and easier solutions are being followed, particularly in biological detection applications. Polymeric materials are gaining considerable attention as raw materials for microfabrication of fluidic

passages. They are easily replicable, transparent, biocompatible and have thermal and electrical properties suitable for e.g., biological detection applications. Two main types of polymeric materials (elastomers and thermoplastics) and their microfabrication techniques are addressed below.

### 2.3.1 *Elastomers: PDMS*

PDMS has become the most commonly used elastomer in rapid prototyping of microfluidic devices because of its simple fabrication procedure through casting and curing onto a microscale mold and strong sealing to a wide variety of materials.

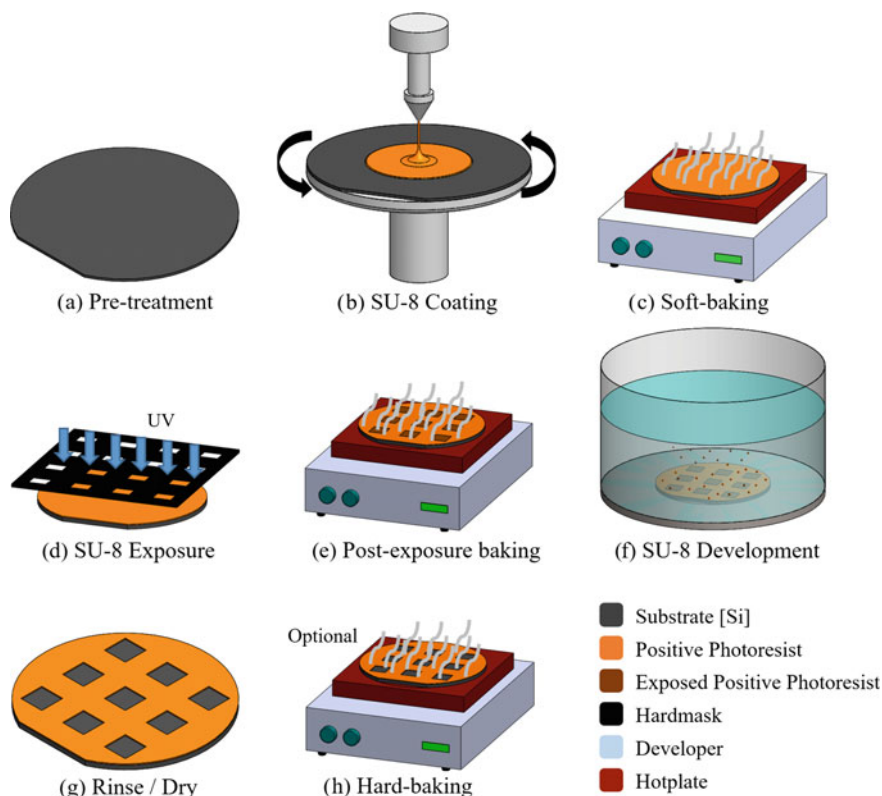
The PDMS is composed of a two-part heat-curable mixture. The pre-polymer is cross-linked with the curing agent usually in a 10:1 ratio in weight, but varying this ratio one can obtain different mechanical and chemical properties of the resulting mixture.

PDMS microfluidic fabrication gains from PDMS low cost, biocompatibility, chemical inertness, low toxicity, versatility on surface chemistry insulating, as well as mechanical flexibility, ease of manipulation and durability. The low stiffness of PDMS ( $\sim 1$  MPa) has additionally been explored for the integration of valves and pumps and to produce 3D multilayered devices [1, 7, 39]. But difficulties in process repeatability and handling such a soft material frustrates fabrication scale-up. PDMS is very sensitive to minute changes in applied pressures. As a result, compression of PDMS structures may lead to cracks and deformation of the feature dimensions. Furthermore, PDMS is more suitable for low aspect-ratio channels as high aspect-ratio channels are difficult to obtain and are prone to collapse.

Gas and water permeability of PDMS and its hydrophobic nature work for and against its usage. For example, non-specific protein/hydrophobic analyte can be absorbed by the PDMS due to strong hydrophobic-hydrophobic interactions [48]. Cell or bacteria can adhere to the PDMS walls, [11]. While in some applications this is the desirable goal [14], if ill designed, such bioanalytes can obstruct the flow and ultimately lead to device fouling.

Soft lithography is the technique used to rapidly and easily fabricate and replicate a wide range of elastomeric devices, i.e., mechanically soft materials (e.g., polymers, gels or organic monolayers) without costly capital equipment.

Soft lithography can be viewed as a prolongation of photolithography. After the definition of the mask (Sect. 4.2.1), the master mold to be used for the definition



**Fig. 2.10** Fabrication of the master mold by photolithography

of elastomeric structures needs to be fabricated. The molding template is fabricated by either patterning photoresist on a flat rigid substrate (e.g., silicon wafer) for precise microstructures (e.g.,  $<50\ \mu\text{m}$ ) or by micromilling thermoplastic polymer substrates for larger microstructures (e.g.,  $>50\ \mu\text{m}$ ). A brief description of photoresist patterning is given below. Thermoplastic microfabrication will be referred in detail in Sect. 4.3.2.

The master mold fabricated by photolithography onto PR roughly follows the steps presented in Fig. 2.10. The photoresist manufacturer's datasheet presents the exact steps and specification/tolerances to be used in the photolithographic process. The process starts with a thorough cleaning of the substrate (Fig. 2.10a). Harsh cleaning methods include piranha clean SOP, reactive ion etching or plasma ashing, but softer cleaning with an anionic detergent e.g.,alconox, followed by solvents such as isopropyl alcohol is usually effective. De-ionized water rinse is then followed by drying with a nitrogen or compressed air stream.

To prevent any entrapped humidity at the surface, the substrate needs to be dehydrated through a thermal treatment (e.g.,  $200\ ^\circ\text{C}$  for 5 min). The PR (e.g., SU-8 neg-

ative PR, AZ 40XT positive PR, etc.) is then dispensed onto the substrate and spread evenly using spinning (Fig. 2.10b). The speed, acceleration and time of spinning are conditioned by PR properties (temperature dependent) and will be defined according to the intended mold thickness. The maximum aspect ratio (width-to-height ratio) of the elements to be fabricated in the mold are dependent on the PR characteristics. Nevertheless, the aspect ratios in the final molded structure e.g., in PDMS, need to be designed guaranteeing the usability and robustness of the microfluidic device.

After coating, a soft-bake step is performed to evaporate PR solvents and prevent shrinkage and cracking of the PR in subsequent steps (Fig. 2.10c). The soft-bake process temperature and time are dependent on the PR formulation and mold thickness. Exposure to UV light through the mask defines the shape of the elements in the mold (Fig. 2.10d). The correct exposure energy and duration are strongly dependent on PR formulation, PR thickness and substrate material.

The definition of PR elements derives from its change in chemical composition due to exposure to UV light. Negative PR exposed regions become insoluble in the developer solution while the unexposed regions remain soluble. The opposite occurs for positive PR.

A post-exposure bake step is conducted to further harden the insoluble regions of PR making it resistant to the action of the developer solution (Fig. 2.10e). Again, the baking procedure is dependent on the PR formulation and mold thickness. The substrate is slowly cooled to prevent the formation of cracks due to thermal stresses. The substrate is now ready for the development step (Fig. 2.10f). The developer solution is PR specific.

The development conditions are dependent on the PR formulation and mold thickness. The development times used not only depend on the PR dissolution rates but also on the agitation conducted to promote dissolution. The completeness of development step is confirmed after washing the substrate with isopropyl alcohol and blow drying. The presence of white precipitates on the structures confirm underdevelopment, so more development time may be required for process completion. The mold is ready for the next step of fabrication after rinse with de-ionized water and blow drying (Fig. 2.10g). An extra step for hard-baking may be required for applications where the imaged resist is to be left as part of the final device.

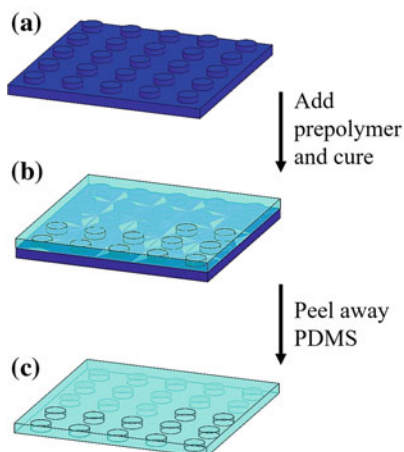
The PDMS is casted onto the mold and cured to increase bond strength. The curing time and temperature define the structure mechanical properties. After curing, the elastomer is peeled from the mold and is now ready to be bonded to a rigid or flexible component to form the microfluidic device or to be used as a microstructured master.

Core techniques to fabricate patterns and structures based on the use of a patterned layer of elastomer are e.g., replica micromolding, microcontact printing ( $\mu$ CP), microtransfer molding ( $\mu$ TM), and microcapillary molding (MIMIC) (Fig. 2.11).

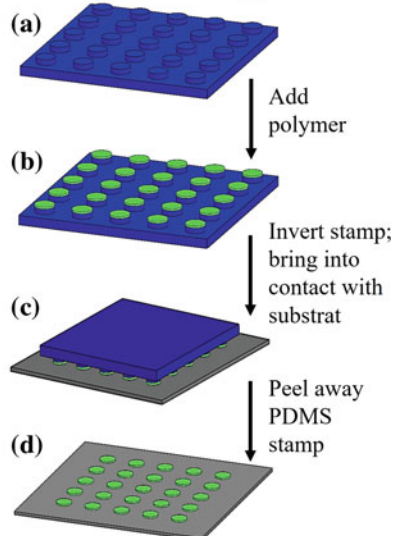
Replica micromolding is used to replicate soft microstructured masters on polymers. The polymer (e.g., agar, agarose, other biocompatible polymers) is poured on the soft mold and cured, after which is separated. Similarly to a rigid master used in photolithography (e.g., photoresist), the 3D elements defined onto the soft mold are imprinted onto the surface of the polymer. The soft mold can be reused several times before starting to collapse.



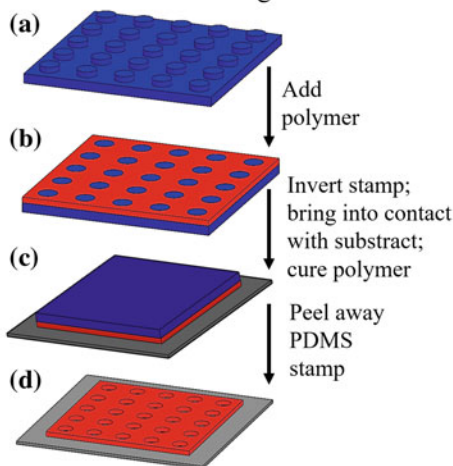
### Replica Molding



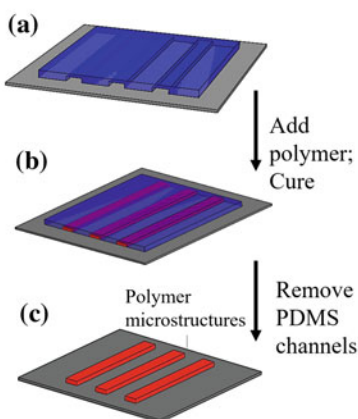
### Microcontact Printing



### Microtransfer Molding



### Microcapillary Molding



■ PDMS molding template 
 ■ PDMS 
 ■ Ink 
 ■ Substrate 
 ■ Prepolymer

**Fig. 2.11** Schematics of fabrication steps adopted in replica molding, microcontact printing, micro-transfer molding and microcapillary molding

Microcontact printing ( $\mu\text{Cp}$ ) is a well-established soft-lithography technique consisting in transferring material (usually biomolecules or organic molecules) to the substrate in selectively-defined areas. The fabrication process, consists in four

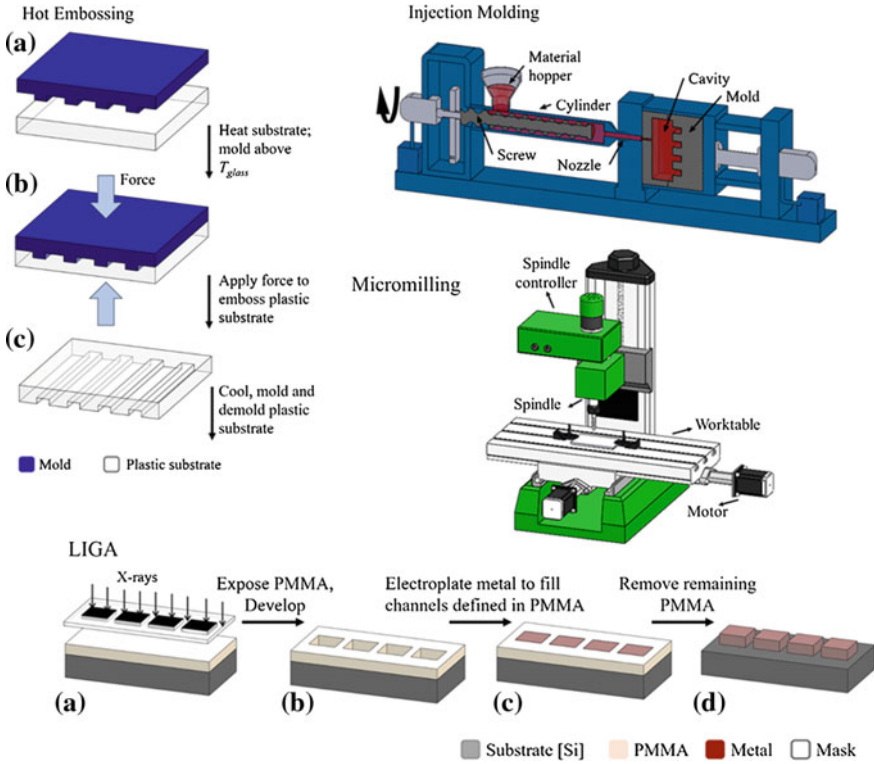
main steps. Firstly it is necessary to fabricate the PDMS stamp with the desired convex pattern using the soft-lithography steps described above. The PDMS stamp is then placed in contact with the material to be selectively transferred and subsequently pressed against the substrate surface to contain the material transfer. The stamp is then removed and the transferring material is retained at the substrate surface.  $\mu$ Cp fabrication is relatively easy and cheap, and allows high-resolution patterns to be transferred into a wide variety of substrates e.g., glass [34], gold [6] or polymers [13] resulting in a diverseness of applications (e.g., microelectronics, cell biology or surface chemistry). The high compressibility of PDMS can be a major disadvantage [18], which may lead to ill-defined features and ultimately to the collapse of the stamp.

The micropatterned PDMS soft mold may be transferred to liquid polymer by microtransfer molding ( $\mu$ TM). The mold is filled with the liquid polymer which is turned, put in contact with the substrate and cured. The PDMS is then gently peeled from the polymer, leaving solid microstructures on top of the substrate. The PDMS soft mold can be reused similarly to replica molding. The PDMS soft mold can also define microcapillary molded (MIMIC) polymers. Here, the PDMS is brought in contact with the rigid substrate and the available volume between the two is filled with the liquid polymer by capillarity. Alternatively, the mold can be filled by suction. Curing, peeling and reusability steps are followed as defined previously.

### 2.3.2 *Thermoplastic Polymers*

Thermoplastic-based microfluidic devices are gaining attention mainly for their easiness towards large-scale production. Additionally from being cheaper in large-scale, thermoplastic fabrication allows faster processing with almost unlimited tailoring while not requiring clean-room environment. Thermoplastic properties such as high glass transition temperature, negligible impact resistance, low chemical absorption, biocompatibility, low intrinsic fluorescence and broad visible transmittance make them easy and appealing to use [24]. Of course, their chemical and physical properties can too be a drawback depending on the application. Some organic solvents may dissolve thermoplastics reducing their mechanical stiffness. Moreover, thermoplastics absorb UV-light inhibiting their use in a wide range of applications.

The possibility of rapid implementation of thermoplastic-based microfluidics allied to the necessity of reducing minimum feature sizes, increase bonding strengths, and fabricate intricate 3D solutions has been pushing investigation further. Techniques to fabricate microfluidic channels from thermoplastics include hot microembossing, injection micromolding, 3D printing, micromilling, LIGA and more recently, direct-write laser micromachining, among others [26]. Despite some of the polymeric-based techniques are still expensive and not readily available for microfluidic fabrication, they are slowly becoming more accessible as a result of intensified research efforts and growing interest in the field.



**Fig. 2.12** Fabrication processes used to mold thermoplastic polymers

Micromolding the thermoplastics by hot microembossing consists in pressing the thermoplastic against the mold under controlled temperature and pressure (Fig. 2.12a). Operation temperatures are usually set above the glass transition temperature,  $T_{glass}$  of the thermoplastic [5], but never to a point where the thermoplastic is molten. Henceforth, high molecular weight polymers are well-suited for the process, provided their mechanical and thermal properties. The master mold can be PDMS [9], SU-8 [36] or other material, e.g., metals [22], which withstand molding operational conditions without deformation. After cooling, the thermoplastic polymer hardens.

Heating and cooling ramps define the mechanical properties of the molded part.

Hot microembossing of polymers which are transparent can increase the material autofluorescence, which can be important in fluorescence detection and microscopy [45]. More often than not, molded thermoplastics are too stiff to enable the integration

of multilayers, valves and membranes. Additionally, high aspect ratio elements are difficult to fabricate and have large size dependent residual stresses. Nevertheless, large-scale production using this technique is straightforward for simple microfluidic structures [30].

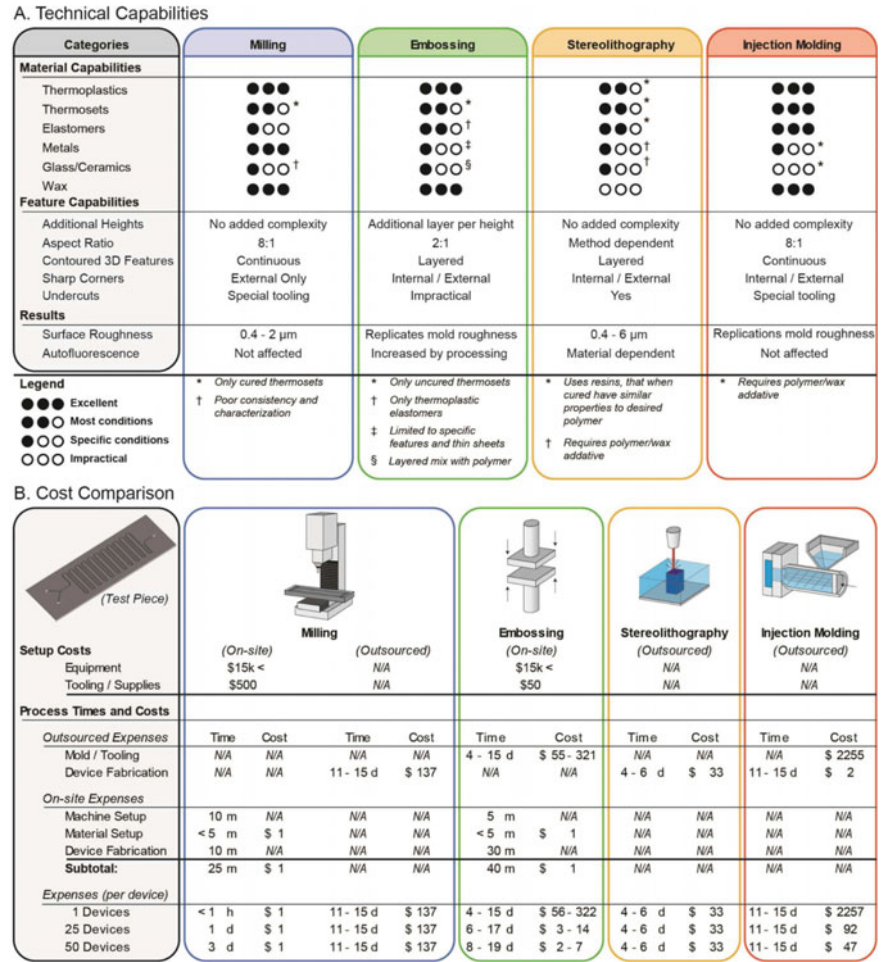
Alternatively, injection molding includes steps for plastication, injection, packing, cooling and mold resetting. The polymer, usually pellets or granules, is plasticized melt and injected into the mold cavity containing the template for the features to be molded. As the polymer melt cools inside the mold, contraction occurs and is dependent on the polymer properties and application. A packing step is necessary to fill empty spaces caused by polymer shrinkage. The cooling step is defined by the cooling rate, which largely determines the success of fabrication. After this step, the molded polymeric piece is removed from the mold and the process is reset to step one.

This is a rather inexpensive microfabrication technique for large-scale production, capable of achieving high quality in a minimum amount of time. However, it is unsuitable for short production, as costs and time needed for the development and fabrication of custom molds can be excessive. Just as hot embossing, the aspect ratios, surface finishing, surface roughness and feature resolutions are not only dependent on the properties of materials used but also on the mold quality.

3D printing is an additive fabrication technique in which the polymer is heated while passing through the head of the printer. The piece is supported in a movable table enabling XYZ positioning. The passage of the printer head prints the polymer one layer at a time without requiring a mold.

While 3D printing is an additive process, micromilling is a subtractive fabrication process. It relies on the use of rotating cutting tools to remove bulk material from the workpiece. The system basically consists in a worktable for XY positioning of the workpiece, the cutting tool (usually endmill or drill) and a spindle for securing, Z positioning and rotating the cutting tool. For micron sized dimensions, the milling control is usually CNC (computer numerical control) for automation, repeatability and precision. This control enables direct conversion of CAD, reducing human error and leading to the fabrication of more intricate parts. Micromilling can be used to directly mill fluidic passages and features into the final device, but also to fabricate molds to be used in other fabrication techniques. At these scales, polymeric materials are the most used, contrarily to steel or copper used at larger scales. Elastomers can also be used, but due to their high elasticity, they are generally difficult to fabricate with this technique.

The LIGA process consists in having a mold, usually from PMMA (up to and exceeding 1 mm thick), which by previous exposure to X-ray (synchrotron) is developed to well defined, extremely smooth and nearly perfect vertical sidewalls. This technique can create structures 100× deeper than wide, with submicron tolerances. For example, SU-8 can also be used as a mold for lower aspect ratio features. The mold is then placed in an electroplating bath and the filling metal (e.g., nickel, gold, copper, etc.) is electroplated from the conductive seed substrate into the open areas of the PMMA. The current density is set by controlling DC electroplating current or pulsed electroplating current. Advantages arise from a pulsed approach. The reactant



**Fig. 2.13** Comparison of material, features, quality and cost of microfabrication processes used for plastics. Reprinted with permission from [10]. © 2015 Royal Society of Chemistry

species from the bulk electroplating solution are given time to reoccupy the region close to the cathode, where reactants are consumed in each electroplating pulse. This decreases plating stress and leads to more homogeneous and finer grain plating. The PMMA is stripped from the substrate to obtain the final structure which can be the final product or the replication mold used in the fabrication techniques previously described. The special mask and synchrotron radiation source make this process relatively expensive, henceforth, not widely used.

A comparison of the main material and feature capabilities is shown in Fig. 2.13.

## 2.4 Microfabrication Techniques for Paper Based Microfluidics

Paper-based microfluidics is gaining attention since its introduction in 2007 [44]. They are based on the fabrication of hydrophobic physical barriers on hydrophilic paper to define microfluidic passages where aqueous solutions will be passively transported. Fabrication methods reported are:

- photolithography—areas covered with negative PR (e.g., SU-8) become hydrophobic, while areas without photoresist continue hydrophilic [46]
- wax printing in a solid ink printer the heated wax melts and spreads vertically and laterally into the paper [4]
- PDMS dispensing—PDMS barriers are printed on filter paper after dissolved with hexanes [37]
- plasma treatment—the plasma treated areas are strongly hydrophilic [21]. Tests on paper-based microfluidics are based on colorimetry, electrophoresis, electrochemistry or magnetic fields.

## 2.5 Bonding

Hybridization represents an important process to assemble the different parts of the device into a final product. Most microfluidic devices require bonding of several parts to produce confined volumes for fluid manipulation. A wide range of bonding strengths can be achieved depending on the materials and bonding technique [33].

In general, the bonding techniques require flat, smooth and clean substrates to prevent voids between the bonded parts and achieve flawless bonding, even though they increase the costs of the overall fabrication and the material.

In addition, bonding may require a high temperature and high electrical field, which may damage the electronic elements on the device.

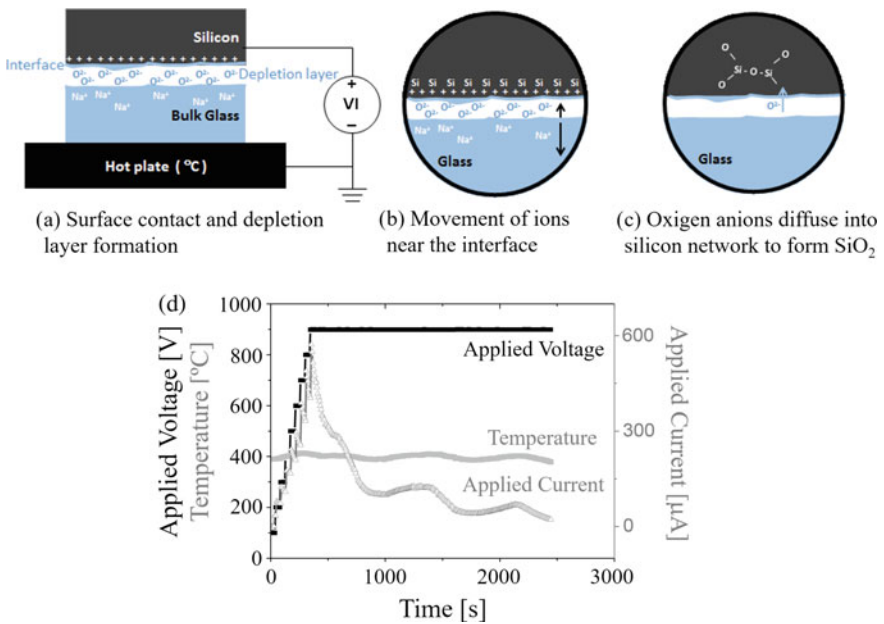
Silicon-to-silicon bonding can be employed by direct or fusion bonding techniques while anodic bonding is usually used to bond silicon-to-glass. Direct or fusion bonding (high-temperature annealing from 300 to 800 °C in oxygen or nitrogen atmosphere) is commonly used to bond two silicon substrates or a silicon substrate to a silicon oxide substrate, but other combinations can be pursued. For example, fusion bonding of bare silicon to a silicon substrate with a  $\text{Si}_3\text{N}_4$  thin film deposit on the surface, or SOI-SOI (silicon on insulator) substrates.

Field assisted, anodic bonding or electrostatic sealing is a currently well-established industrial bonding technique that is reported to account for the majority of packaging applications for MEMS [23]. Its popularity is owed to high bonding



yields, excellent capability in alignment and large process windows. It consists in a wafer bonding process to seal glass, containing a high concentration of alkali ions to either silicon or metal using an electric field and elevated temperature without introducing an intermediate layer. The conditions for bond surface quality are less restrictive than for direct or fusion bonding, substantially decreasing the process complexity.

The bonding process (Fig. 2.14a–c), of high bonding strength, consists in applying a DC voltage to the electrodes ensuring a positive electrode potential on the silicon side (Fig. 2.14a). The two substrates are placed in contact and compressed at 350–400° C (Fig. 2.14d). Thermal stresses are minimized if the thermal expansion coefficients of the two substrates are similar. Then, 900–1000 V direct current is constantly applied across the stack (glass substrate acts as the cathode). The sudden drop occurring in the applied current is due in part to the flow of  $\text{Na}^+$  ions flowing to the cathode [19] (Fig. 2.14b). At 350–400° C, the alkali-metal ions in the glass migrate from the interface creating a depletion layer with high electric field strength and subsequent current flow of the oxygen anions from the glass to the silicon substrate results in an interface anodic reaction (Fig. 2.14c). As the migration of  $\text{Na}^+$  continues, the concentration of positive charges repel incoming  $\text{Na}^+$  ions inducing a



**Fig. 2.14** Illustration of anodic bonding procedure. **a–c** Anodic bonding process. Pressure is applied to guarantee complete surface contact during ion diffusion and temperature is regulated to achieve the bonding layer formation, **d** experimental data of temperature, applied voltage and applied current during anodic bonding process



plateau in current which indicates bond completeness. The bonding seal between the two surfaces assures leakage contention without introducing dimensional errors to the microchannels.

Both fusion and anodic bonding are material specific bonding techniques providing great bonding strength. Generic hetero-bonding techniques such as adhesive techniques are the widely applicable and substrate independent. However, bonding using an intermediate layer produces large thermo-mechanical stresses or presents microvoids between the bonded surfaces, which may degrade the bonding performance of the microfluidic device [47]. Nonetheless, high temperature bonding processes such as anodic bonding and fusion bonding are not applicable for polymeric materials. Oxygen plasma is widely used to permanently bond PDMS-PDMS, PDMS-Si or PDMS-glass layers and the bond is sufficiently strong to impede the two layers to be peeled. Thermal compression at  $T_{glass}$  and adhesives (e.g., resins, UV-curable materials, etc.) are used for polymer-to-polymer bonding. Although simple and low demanding, they may lead to localized deformation of the device and induced inhomogeneities in the interfacial layer thickness. Uniformity of the interfacial layer is achieved by other bonding techniques such as localized welding by ultrasounds [41], microwaves [20] or infrared laser [15] but bonding complexity is increased.

## 2.6 Summary

The demand for small, portable, and simple to use diagnostic devices to obtain fast or even instant diagnostic results is key driver for the development of a wide variety of microfluidic devices. Materials such as silicon, glass, polymers or even paper-based materials are being pursued. The current state-of-the-art of microfabrication techniques are significantly mature and have proven effective in detection applications in controlled environments. Nevertheless, there are a few challenges to overcome before these may become commercially established e.g., pre-treatment steps, concentration steps, reduction/elimination of dead volumes, elimination of external bulky and expensive detection systems, etc.

The present lack of a mass market for the relatively recent diagnostic devices using microfluidic technology makes it expensive to manufacture and therefore less competitive. This becomes more evident when these are compared with solutions already established in the market, with proven results and familiar to the handling personnel, which are the result of decades of continuous improvement and have already gone through all the regulatory approval procedures in different countries.

Apart from all the challenges, currently one of the main areas of application where microfluidic devices have been tested with observable success is in biomedical

diagnostics. As a result, and as microfluidic devices become more common in the market, it is expectable to witness new areas of research and development of such devices for commercial use to become common.

In this chapter, the following 10 key remarks/tips have been provided:

- #1 **Lithography steps:** (1) designing the pattern, (2) making the mask, (3) coating the wafer, (4) exposing the photoresist, (5) developing the photoresist.
- #2 **Photoresist** is a light-sensitive polymeric solution. Negative PR (the regions exposed to light become insoluble in the developer) originate m.f.s. up to 2  $\mu\text{m}$  and spin-coated spreading thickness from 1  $\mu\text{m}$  to 3  $\mu\text{m}$  (the photoresist film thickness is determined by the spinning speed), while positive PR (the regions exposed to light become soluble in the developer) has m.f.s. of  $\sim 1 \mu\text{m}$  for spreading thicknesses between 1.5 to 7  $\mu\text{m}$ .
- #3 **Isotropic etch:** surface material is removed uniformly in all directions of the chemical structure. **Anisotropic etch:** the removal of surface material is dependent on the crystalline structure orientation of the surface.
- #4 The etch rate in **wet etching** can be enhanced by tuning agitation and temperature.
- #5 The **DRIE process** provides deep features of hundreds to thousands of micrometers into the substrate with nearly vertical walls.
- #6 **Additive microfabrication steps:** (1) synthesize the vapor coating from the source (target) material, (2) transport the vapor to the substrate, (3) condense the vapor coating onto the surface of the substrate.
- #7 The **PDMS** is composed of a two-part heat-curable mixture. The pre-polymer is cross-linked with the curing agent usually in a 10:1 ratio in weight, but varying this ratio one can obtain different mechanical and chemical properties of the resulting mixture.
- #8 **Soft lithography** is the technique used to rapidly and easily fabricate and replicate a wide range of elastomeric devices, i.e., mechanically soft materials (e.g., polymers, gels or organic monolayers) without costly capital equipment.
- #9 **Heating and cooling ramps** define the mechanical properties of the molded part.
- #10 In general, the **bonding techniques** require flat, smooth and clean substrates to prevent voids between the bonded parts and achieve flawless bonding, even though they increase the costs of the overall fabrication and the material.

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