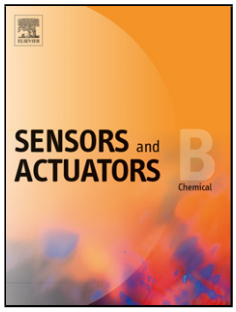

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Review in manufacturing methods of nanochannels of bio-nanofluidic chips

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Abstract

This review reports the progress on the recent development of manufacturing methods of nanochannels of bio-nanofluidic chips. Various manufacturing methods including reactive ion etching, high energy beam processing method, interference lithography, nanoimprinting, thin film deposition processing technology, hot embossing, stress release processing technology, molecular self-assembly processing technology, PDMS deformation processing and biofabrication of nanochannels are illustrated and discussed. The advantages and disadvantages of each manufacturing methods are expatiated. A variety of bio-nanofluidic chips fabricated with different manufacturing methods are also expounded and analyzed. This paper will provide a particularly convenient and valuable reference to those who intend to research the fabrication of bio-nanofluidic chips.

Keywords: Nanochannels; Manufacturing method; Bio-nanofluidic chips; Nanofluidics; Application

1 Introduction

Since the concept of the micro total analysis systems (μTAS) was presented by Manz A, the microfluidic systems have widely been researched because of their significant applications in chemical engineering and bioengineering [1-2]. At present, microfluidic chips have been applied in many biochemical field such as DNA analysis[3], protein research[4], cell separation[5], and play an important role in environmental monitoring[6], food safety[7], information technology[8] and so on.

In recent years, with the rapid development of microfluidic chip technology and nano-processing technology, some nano-structures such as nanochannels and nanofilms can be integrated into microfluidic chips, which makes the nanofluidic chip to be born. With the use of nanofluidic chips, people began to study the transport properties of nanoscale fluid and molecular transport behavior.

Since the smallest channel size of the nanofluidic chip enters the nanoscale from the micrometer scale, the performance of the channel surface changes dramatically, and new fluid phenomena such as overlapping of the electric double layer, increase of the fluid resistance in the channel and the electric constant drops and so on arise. These phenomena attract people to carry on theoretical research including the channel performance, fluid transport and other aspects, and then a new way of thinking is provided for the DNA sequencing[9], macromolecule detection[10], cell culture[11], sample enrichment[12] and so on. The nanofluidic chip can realize the function that the microfluidic chip is difficult to realize by utilizing the new fluid phenomenon in nanochannels. For example, it can greatly improve the sample enrichment efficiency[13], greatly shorten the time of gene sequencing[14], raise the local detection precision[15], realize ultra high-speed transmission of fluid[16], can fabricate supercapacitors[17], create a fast and efficient energy absorption device[18].

Nanochannel is the key structure of nanofluidic chip, and is the important component to determine the performance of nanofluidic device. It is the basis of nanofluidic chip manufacturing, detection and application. How to manufacture low cost and high quality nanochannel becomes the main difficulty in manufacturing nanofluidic chip.

Several good reviews have been already dedicated to the fabrication of nanochannels for bio-nanofluidic analysis[19-21]. In this paper, our review focuses on the main manufacturing methods of nanochannels of bio-nanofluidic chips including reactive ion etching, high energy beam processing method, interference lithography, nanoimprinting, thin film deposition processing technology, hot embossing, stress release processing technology, molecular self-assembly processing technology and PDMS deformation processing and biofabrication of nanochannels. We also discuss the fundamental flow and the material used for each method. The biochemical applications corresponding to these manufacturing methods are also analyzed and discussed. Finally, we summarize and discuss the future challenges and perspectives of bio-nanofluidic chips for the research of biological and chemical engineering.

2 Manufacturing methods of nanochannels of bio-nanofluidic chips

2.1 Conventional photolithography and reactive ion etching

Reactive ion etching utilizes ion bombardment to etch the material surface. This etching process has both physical and chemical effects. The glow discharge is carried out at a low vacuum of 0.1 to several tens of Pa. Since the lateral dimension of the channels is limited by the wavelength of UV light used in photolithography, the channel width can only be fabricated in the micrometer scale. However, the depth of the channel can be controlled precisely by the etching rate of reactive ion etching.

Kelly et al. detailed, for the first time, the construction of dual-scale micro-nanofluidic devices that are relatively large-scale, two-dimensional(2D) network representations of

granular and fractured nanoporous media. The fabrication scheme used in the development of the networks on quartz substrates was facile and replicable: transmission electron microscopy grids with lacey carbon support film were used as shadow masks in thermal evaporation/deposition and reactive ion etch was used for hardmask pattern transfer[22]. Alibakhshi et al. theoretically and experimentally explored a new technique for rectification of ionic current using asymmetric 2D nanochannels. This method of fabrication and control of a nanofluidic diode does not require modification of the surface charge and facilitates the integration with lab-on-a-chip fluidic system. Experimental results obtained from the stepped nanochannels are in good agreement with the one-dimensional theoretical model[23]. Fu et al. fabricated the nanofilter array chip by conventional photolithography and reactive ion etching (RIE) techniques on a silicon wafer. The nanochannels were shaped up on silicon substrate and then were sealed with glass substrate by anode bonding. The nanochannel with the pitch 1μm, depth 60nm and length 1cm was obtained[24]. The layout of the chip is shown in Fig.1.

Mijatovic et al. gave an overview of the most commonly used techniques for nanostructuring and nanochannel fabrication employed in nanofluidics. They were divided into two large categories including top-down and bottom-up methods[25]. Phan et al. fabricated arrays of sealed planar nanochannels in silicon and glass with a depth of 45 nm and low aspect ratios ranging from 0.004 to 0.01. The fabricated device contains both nanochannels and microchannels. The nanochannels were etched with RIE, while the microchannels and the access holes were etched with deep reactive ion etching (DRIE) [26].

Conventional reactive ion etching has some advantages including mature technology and good repeatability. However, the nano-level channels can only be fabricated in the depth direction due to the traditional UV lithography optical system.

2.2 High energy beam processing method

High-energy beam processing method is a maskless technology without the help of molds by writing directly on the material surface using electron beam, proton beam, focused ion beam, femtosecond laser beam and other high energy beam, and making physical and chemical changes of material to obtain nanochannels.

Chen reviewed a wide range of nanofabrication techniques developed for nanoelectronic devices, nanofluidic chips, nanophotonic metamaterials and other nanostructures, based on electron beam lithography[27]. Xu et al. carried out flexible and in situ fabrication of nanochannels with high aspect ratios and nanopillar arrays in fused silica substrates utilizing focused ion beam. The method involved focused ion beam milling of nanochannel structures through a 100 nm gold layer pre-deposited on the fused silica substrates, under optimized conditions of beam parameters and

processing parameters[28]. Choi et al. presented a simple and useful approach to fabricate self-sealed nanochannel structures using a resistcollapse method during the electron-beam lithography process. This approach facilitates the fabrication of complicated nanofluidic devices and bioanalysis systems. The dense arrays of triangular nanochannels with a spacing of 30 nm and a periodicity of 200 nm before and after covering the channels with another hydrogen silsesquioxane layer can be obtained[29]. Yasui et al. fabricated a nanowall array structure on a quartz chip as a separation matrix of DNA fragments, and a 30s separation was realized for a mixture of DNA fragments by applying the electric voltage. Each fabricated nanowall was 500 nm thick, 5000 nm high, and 215 μm long, and a spacing between the nanowalls in the array structure was 200 nm. A longer DNA fragment migrated faster than a shorter one in a nanowall array chip, and it was completely different from the separation of DNA based on gel electrophoresis, nanopillar chips, and nanoparticle array chips. Although the result was similar to DNA separation by entropic trapping, it could not be fully explained by entropic trapping phenomena. Direct observation of single-DNA molecular dynamics insided a nanowall array structure indicated that both confined elongation and relaxation recoiling of a DNA molecule occur, and an elongated DNA molecule migrates faster than a recoiled DNA molecule. Numerical fitting of DNA molecular dynamics revealed that the balance between times for the transverse of a DNA molecule in the nanowall array chip and the relaxation-recoiling of a DNA molecule governs the separation of DNA[30]. Liu et al. presented the fabrication of micro/nano fluidic devices with the combination of proton beam writing and UV lithography. Proton beam writing was used to generate the fine features with smooth sidewall profiles on ma-N resist, 110 and 600 nm thick. UV lithography was used to fabricate the micron sized feeding channels properly aligned with the nanostructures on ma-P resist[31]. Kan et al. introduced an easy method to allow fast polydimethylsiloxane(PDMS) replication of nanofluidic devices using accurately fabricated molds featuring cross-sections down to 60 nm. The master was obtained through proton beam writing and UV lithography. This method allows to fabricate nanofluidic devices through simple PDMS casting[32]. Fanzio et al. presented the development and the electrical characterization of a polymeric nanochannel device. Standard microfabrication coupled to focused ion beam nanofabrication was used to fabricate a silicon master, which can be then replicated in a polymeric material by soft lithography. The microchannels were connected by a focused ion beam drilled nanochannel, with length 15 μm, height 790 nm and width 290 nm. The fabrication technique allows creation of a low noise device for single molecule analysis[33]. Cheng et al. resolved long-standing difficulties in fabrication of large-scale 3D microfluidics and demonstrated fabrication of nanochannels of a width of 40 nm in glass with femtosecond laser pulses[34]. Dewanda et al. presented the formation of micro/nano-fluidic channels inside fused silica glass using single-beam femtosecond laser. The micro/nano-fluidic channels were fabricated by controlling the irradiation conditions of the femtosecond laser pulses, especially, pulse energy and scanning speed.

They further investigated the influence of various laser parameters on the production of channels. They also evaluated the fluid flowing ability of the fabricated micro/nano-fluidic channels of various diameters, fabricated under different environment and irradiation conditions[35].

The high energy beam processing method can produce high quality nanochannels below 10nm, and can process complex nanostructures. However, this method relies on costly devices and can only be processed in a serial manner, which results in high manufacturing cost and low production efficiency of the nanochannel.

2.3 Interference lithography

Interference lithography is a technique that does not require the use of complex optical systems or photomasks to produce fine structures. The basic principle of interferometric lithography is similar to the principle of interferometry or holography. An interference pattern consisting of two or more coherent light waves is built up and recorded in a recording layer that is photoresist. The interference pattern consists of periodic series of striations, which represent the maximum intensity and the minimum intensity. During the photolithography process after the exposure, a photoresist pattern corresponding to this intensity-periodicity variation pattern appears in this manner.

Xu et al. reported a combined holographic and nanoimprinting lithography technique to produce three-dimensional woodpile photonic crystal templates through only one single exposure. The interference lithography process used an integratable diffractive optical element for large throughout 3D pattern manufacturing[36]. Wei et al. prepared a few kinds of 2-diazo-1-naphthoquinone-4-sulfonates of poly(4-hydroxylstyrene) to form one-component i-line photoresists. In the laser interference lithography experiments of some of the photoresists, nanotunnels were observed to be aligned in the interior of the resist film. The formation of the nanotunnels resulted from the effect of standing waves and the permeation of developer from the surface deep into the resist films[37]. Xia et al. provided a brief review of interference lithography technologies and focused on various applications for nanostructures and functional materials based on interference lithography including directed self-assembly of colloidal nanoparticles, nanophotonics, semiconductor materials growth, and nanofluidic devices[38]. By using interference lithography, O'Brien II et al. fabricated the first enclosed nanochannels, which were an array of solid parallel channels with anodic bonding to seal the channels. interference lithography and anisotropic dry etching were used to produce large areas of nanoscale parallel grooves. Conventional optical lithography was used to create interfacing microchannels. Finally, Pyrex glass was used to seal the grooves to produce nanochannel arrays with anodic bonding[39]. A fluidic field effect transistor based on these nanochannel structures was fabricated to probe the transport of charged molecules and to measure the pH shift in nanochannels in

response to an electrical potential applied to the gate[40]. Fig.2 shows the cross-sectional SEM images of nanochannels.

Lu et al. reviewed the basic principles of interference lithography. The symmetry and shape of the “unit cell” can be conveniently controlled by varying the intensities, geometries, polarizations, and phases of the beams involved. They discussed the wide use of such periodic structures in photonic crystal science, nanofluidic chip, optical telecommunications, data storage, and the integrated circuit industry[41]. Xia et al. reported a simple approach to the formation of three-dimensional colloidal nanoparticle structures incorporating enclosed mesoscopic structures through a simple process of spin-coating-driven directed self-assembly onto lithographically defined polymer templates[42].

Interference lithography eliminates the need of a mask and can produce hundreds of nanometers of uniform, high-quality nanochannels. However, the manufacturing process relies on costly exposure equipment and need difficult processing technology and high manufacturing cost.

2.4 Nanoimprinting

Nanoimprinting is a nanostructure producing technology by copy nanometer pattern of a template coated with a high molecular material into unprocessed substrate. Its processing resolution is only related to the size of the template pattern, without being physically limited by the shortest exposure wavelength of the optical lithography. Nanoimprinting include mainly thermal nanoimprinting and ultraviolet (UV) nanoimprinting.

Sakamoto et al. carried out High aspect ratio fine pattern transfer using a novel mold by nanoimprint lithography. By using edge lithography, a SiO_2 circular line pattern of 35nm width and 3.5μm height was obtained and the aspect ratio was 100[43]. Fig.4 shows the imprint results for PMMA resins with four molecular weights. Liang et al. reported a novel method to fabricate single fluidic-channels of uniform channel width (11-50 nm) and over 1.5 cm in length, which were essential to developing innovative bio/chemical sensors but had not been fabricated previously. The method used unconventional nanofabrication to create an imprint mold of a channel pattern and nanoimprint to duplicate such channel. The centimeter-long channel continuity was verified by flowing fluorescent dye-stained water and stretching and transporting DNAs. The 18 by 20 nm channel cross-section was confirmed by measuring the liquid conductance in the channel[44]. Wu et al. built an inexpensive stand-alone machine based on the wafer bowing nanoimprint process, and demonstrated single-point overlay of two transferred pattern layers with an accuracy of $\leq$60 nm[45]. Fig.3 shows an overlay of two metal layers.

Takei et al. applied fluorinated silicon-based resist materials applied as ultraviolet cross-linkable materials for nano imprint lithography. He reported and demonstrated the step and flash nano imprint lithography process using the newly fluorinated silicon-based resist materials for next generation technologies[46]. Chou et al. demonstrated a nanoimprint process that presses a mold into a thin thermoplastic polymer film on a substrate to create vias and trenches with a minimum size of 25 nm and a depth of 100 nm in the polymer[47]. Haisma et al. described a process for reproducibly and reliably realizing thin-layer patterning having details with dimensions of 100nm or even less. The strengths of this process are its simplicity and low cost while maintaining compatibility with standard semiconductor technology processing[48]. Fernandez-Cuesta et al. presented an innovative approach to the fabrication of a complete micro/nano fluidic system, based on direct nanoimprint lithography. The fabricated device consisted of nanochannels connected to U-shaped microchannels by triangular tapered inlets, and has four large reservoirs for liquid input[49]. Chou et al. reviewed the research development of nanoimprint lithography in terms of feature size, manufacturing accuracy, operational flexibility, durability and application[50]. Schift et al. nanoimprint lithography between two poles: the need to establish standard processes and tools for research and industry, and the issues that make nanoimprint lithography a scientific endeavor[51]. Guo reviewed the basic principles of nanoimprinting, with an emphasis on the requirements on materials for the imprinting mold, surface properties, and resist materials for successful and reliable nanostructure replication[52].

Thermal nanoimprinting is a compatible manufacturing method that can be combined with other micro and nano fabrication processes. This method can be used to emboss out of the nanochannel below 100nm. However, there are many other problems in the nanoimprint process, such as the mold damage by high pressure press, the sticking problem between the mold and the used polymer during the demolding process. And in the process of embossing, because the polymer thickness is smaller, the surface of the mold is easy to direct contact with the hard substrate, resulting in damage to nano-mold, die life reduced.

UV nanoimprinting is also a compatible manufacturing method, and can be combined with other micro-nano manufacturing process. By using UV nanoimprinting, nanochannels of less than 100 nm can be manufactured. However, this method also requires spin-coating the polymer material onto a rigid substrate, which also increas the manufacturing cost and complexity of the process. In addition, UV curing in UV nanoimprinting is achieved by UV irradiation, which need the need to use professional UV light irradiation equipment and high transparency nano-mold (such as quartz nano-mold). This increases the mold making difficulty and the processing cost of the method.

2.5 Thin film deposition processing technology

In a high vacuum environment, the source material is released as particles of atoms, molecules or ions by heating or high-energy particle bombardment, and the escaping particles are deposited on the substrate to form a thin film. According to changing the morphology of the substrate, the nanochannels can be obtained.

Ilic et al. described a method for fabricating narrow, flexible, polymeric fluid conduction tubes with dimensions down to the 100nm regime. Vapor deposited parylene tubes of various dimensions were integrated into silicon substrates forming a microfluidic network with thin film deposition processing method. They demonstrated capillary flow and electrophoretic drive of ions through polymer tubes of up to 5cm in length[53]. Wong et al. realized self-sealing fluidics channels with circular cross-sections having diameters ranging between 30 and 2000 nm on a 200 mm glass wafer through CMOS compatible processes. Lateral voids were narrowed and sealed with non-conformal plasma enhanced chemical vapour deposition of phospho silicate glass along silicon oxide trenches on silicon wafers[54]. Mao et al. developed a novel fabrication strategy for generating massively-parallel, regular vertical nanochannel membranes with a uniform, well-controlled gap size of 50 nm and a depth up to 40 μm, by using only standard semiconductor fabrication techniques. They demonstrated efficient continuous-flow separation of large DNAs and small molecules in a 2D vertical nanochannel array device. These ultra-high-aspect-ratio nanochannels have the advantage of large open volume, enabling high-throughput applications[55]. Jiang et al. presented the development of a laser microwelding method for assembly and packaging of polymer based microfluidic devices. A diode laser was used to weld two PMMA substrates together at the interface using a thin film metal spot based intermediate layer design as a localized absorber. A broad laser beam with a top-hat profile was used to carry out the laser microwelding work. The laser microwelding method has been demonstrated successfully in leak-free encapsulation of a microfluidic channel[56]. Glynn et al. showed how pinholes were formed due to heterogeneous nucleation during hydrolysis as the precursor forms a nanofluid. Using knowledge of instability formation often found in composite nanofluid films and the influence of cluster formation on the stability of these films, They showed how polymer–precursor mixtures provide optimum uniformity and very low surface roughness in amorphous V_2O_5 and also orthorhombic V_2O_5 after crystallization by heating. The method could be extended to improve the consistency in sequential or iterative multilayer deposits of a range of liquid precursors for functional materials and coatings[57]. Nam et al. presented a novel fabrication method of a nanochannel ionic field effect transistor structure with sub-10-nm dimensions. A self-sealing and self-limiting atomic layer deposition facilitated the fabrication of lateral type nanochannels smallerthan the e-beam or optical lithographic limits[58]. The full integration scheme of the nanochannel AAG-IFET based on the SS-ALD process is shown Fig.4 shows the cross-sectional scanning electron microscope.

Zhou et al. spin-coated a 500 nm-thick PMMA film on a silicon substrate and etched the PMMA material with electron beams to develop lines with widths and heights of 200 nm[59]. Eijkel et al. fabricated all-polyimide nanochannels with 100nm height by using spin-deposition and sacrificial layer etching. The nanochannels were characterized using spontaneous capillary filling with water, ethanol and isopropanol, and with electroosmotic flow[60]. Tas et al. developed two new methods to fabricate nanochannels by conventional micromachining. The first method was based on the sacrificial etching of a nano-wire, which was formed on the side wall of a step. The second method was based on the adhesion of the capping layer to the substrate after removal of a sacrificial strip separating the two. The fabricated nanochannels were localized and can be connected to microchannels and reservoirs[61]. Liang et al. developed a simple and inexpensive approach to fabricate a nanochannel device with a glass-epoxy resin-glass structure. The grooves were engraved using a UV laser on an aluminum sacrificial layer on the substrate glass, and epoxy resin was coated on the substrate and stuffed fully into the grooves. Another glass plate with holes for fluidic inlets and outlets was bonded on the top of the resin layer. The nanochannels were formed by etching thin sacrificial layers electrochemically[62]. Fig.5 shows SEM pictures of the nanochannel's cross-section with a depth of 20 nm.

Kanno et al. developed an electrochemical device consisting of electrode arrays, nanocavities, and microwells for multi-electrochemical detection with high sensitivity. A local redox cycling-based electrochemical system was used for multi-electrochemical detection and signal amplification. The local redox cycling-based electrochemical system consists of n^2 sensors with only 2n bonding pads for external connection. The nanocavities were fabricated by etching of sacrificial Cr layers, and Ti/Pt was sputtered onto a glass substrate to fabricate the bottom ring electrodesconnected to the column electrodes. The nanocavities fabricated in the sensor microwells enable significant improvement of the signal amplification[63].

The thin film deposition method can produce nanochannels in tens of nanometers, and the process is simple. However, this method usually uses a high-temperature process, which makes the internal stress of the nanochannels be large, and easily leads to nanochannel deformation.

2.6 Hot embossing

Hot embossing technology can directly copy the pattern of the mold onto the polymer substrate with a certain temperature and pressure. The polymer is not required to be spin-coated during the hot embossing process, so hot embossing process is simpler and less expensive to manufacture than the nanoimprint method.

Wang et al. presented a novel method for the fabrication of high density pattern in PET foils employing hot embossing. The temperature and pressure dependence on the

imprinted pattern were investigated. Well resolved PET nanopatterns with sub-100nm resolution were transferred successfully[64]. Liu et al. developed a novel hot embossing method to fabricate polymer nanochannels. The pattern on the silicon nanomould was transferred to PMMA plates, and then polyethylene terephthalate (PET) nanochannels were embossed by using the PMMA mould. The use of the PMMA intermediate mould can extremely increase the device yield of the expensive silicon nanomould[65]. Fig.6 shows the section views of silicon nanomoulds.

Yin et al. presented a method for obtaining a low cost and high replication precision 2D nanofluidic chip with a PET sheet, which used hot embossing and a thermal bonding technique. The hot embossing process parameters were optimized by both experiments and the finite element method to improve the replication precision of the 2D nanochannels. With the optimized process parameters, 174.67 ± 4.51 nm wide and 179.00 ± 4.00 nm deep nanochannels were successfully replicated into the PET sheet with high replication precision of 98.4%[66]. Liang et al. conducted a novel method of hot embossing lithography for replication of multiple nano bar structure mould. The effects of hot embossing temperature and pressure on fabrication precision were studied. Linewidth of the pattern on the mould was from 71nm to 980nm[67]. Cheng et al. presented a novel method for fabricating 2D polymer nanochannels by combining the sidewall lithography technique with the hot embossing approach. Polymer nanochannel arrays with dimensions of about 100nm in width, 100nm in depth and 4mm in length fabricated uniformly over a large area were obtained. The proposed method provided a low-cost way to produce high-quality and high-throughput 2D polymer nanochannels[68]. They also carried out experimental and numerical study on deformation behavior of polyethylene terephthalate 2D nanochannels during hot embossing process[69]. Dumond et al. carried out high resolution UV roll-to-roll nanoimprinting of resin moulds and subsequent replication via thermal nanoimprint lithography. The nanoscale features were down to 50nm feature diameter[70]. Song et al. developed a prototype of roll-to-flat thermal imprint system for large area micro pattern replication process, which was one the key process in the fabrication of flexible displays. Tests were conducted to evaluate the system feasibility and process parameters effect, such as flat mold temperature, loading pressure and rolling speed. 100 mm × 100 mm stainless steel flat mold and commercially available polycarbonate sheets were used for tests and results showed that the developed roll-to-flat system was suitable for fabrication of various micro devices with micro pattern replication on large area[71]. Ahn et al. presented large-area roll-to-roll and roll-to-plate nanoimprint lithography by a step toward high-throughput application of continuous nanoimprinting. They had demonstrated large-area imprinting of 300 nm line width grating structures on either hard or flexible substrate by developing a new apparatus capable of both processes with greatly enhanced throughput[72].

Hot embossing has been widely used in the microstructure of the molding, but it is currently rarely used to the nano-structure molding because of the material used. After hot embossing, the substrate will shrink due to the large coefficient of thermal expansion of the polymer, resulting in deformation of the nano-pattern. In addition, compared with thermal nanoimprinting, the polymer material used in hot embossing is not bound by the rigid substrate. The internal stress of the polymer material after hot embossing will make the polymer substrate more prone to bending, resulting in serious deformation of the nano-pattern. Therefore, in order to produce high-quality 2D polymer nanochannels, it need to study the process of hot embossing flow behavior of polymers, and precisely optimize the hot embossing process parameters.

2.7 Biofabrication of nanochannels

Utilization of biomolecules for fabrication of nanochannels has been harnessed to construct nanofluidic devices. Although the unconventional approach has no reliable controllability on channel geometry and size, it do provide a alternative solution for the preparation of nanofluidic devices, and are even simpler and cheaper than nanofabrication methods as been introduced above.

Wang et al. presented a simple and cost-effective UV-ablation technique for fabrication of size-tunable nanofluidics devices via photochemical decomposition reaction. Using this device, about 10^3-10^5 fold protein concentration can be achieved within 10 min. The present approach offered a simple and practical solution to fabricate nanofluidics devices at low-cost, and the resulting device could provide ideal platforms for μTAS towards various applications in biology and chemistry[73]. Hu et al. carried out fabrication of fluidic chips with 1-D nanochannels on PMMA substrates by photoresist-free UV-lithography and UV-assisted low-temperature bonding[74]. Kuh et al. described the use of nanoscale fracturing of oxidized poly(dimethylsiloxane) to conveniently fabricate nanofluidic systems with arrays of nanochannels that can actively manipulate nanofluidic transport through dynamic modulation of the channel cross-section. They demonstrated the versatility of the elastomeric nanochannels through tuneable sieving and trapping of nanoparticles, dynamic manipulation of the conformation of single DNA molecules and in situ photofabrication of movable polymeric nanostructures[75]. Mills et al. proposed a direct fabrication method capable of producing fully-reversible, tunable nanochannel arrays, without the use of a molding step. It was based on tunnel cracking of a readily-prepared brittle layer constrained between elastomeric substrates. The ease of fabrication and operation required to open and close the nanochannels was superior to previous approaches[76]. Lo et al. developed a relatively simple, inexpensive and reliable technique to fabricate an array of nanochannels. Moreover, the nanochannels were directly integrated to microchannels as a whole, which facilitated solution loading from the millimeter-scaled loading reservoirs into the nanochannels. It was found that continuous bovine serum albumin line structures with triangle-like cross

section at nanoscale can be obtained by evaporation of BSA solution with concentration between 0.5 wt. % and 1 wt. % inside the microchannels. The poly(dimethyl siloxane) nanochannels were replicated from these linestructures, followed by sealing with the glass slide[77]. Guan et al. presented a fabrication technology of large laterally ordered nanochannel arrays from DNA combing and imprinting. They employed patterned surfaces to guide DNA combing in a de-wetting process to form laterally ordered DNA nanostrands. A simple resin imprinting method then converted this structure into nanochannels micro- or nanowell arrays[78]. Abérem et al. proposed the protein detecting arrays based on cationic polythiophene–DNA-aptamer complexes. They depicteds biochips based on responsive nanoaggregates made from stoichiometric complexes between a cationic polythiophene and an appropriate DNA aptamer. These structures underwent a conformational transition from an unfolded to a folded structure in the presence of a specific target protein that resulted in a significant increase of the fluorescence intensity[79]. Wang et al. focused on capillary, hydrodynamics and electrokinetic flow-guided assembly processes that can produce patterned or gradient functional surfaces either on solid surfaces or in deep micro- and nanoscale channels. This concept had the potential to produce low-cost nanostructures, internal surface modifications, and devices in nanomedicine[80]. Jiang et al. presented a highly-efficient gating of solid-state nanochannels by DNA supersandwich structure containing ATP aptamers. The DNA supersandwich and ATP gated nanofluidic device can exhibit high ON-OFF ratios up to 106. The ON-OFF ratio was distinctly higher than existing chemically modified nanofluidic gating systems. The gigaohm seal was comparable with that required in ion channel electrophysiological recording and some lipid bilayer-coated nanopore sensors. The gating function was implemented by self-assembling DNA supersandwich structures into solid-state nanochannels and their disassembly through ATP-DNA binding interactions. On the basis of the reversible and all-or-none electrochemical switching properties, they further achieved the IMPLICATION logic operations within the nanofluidic structures[81]. Yalizay et al. reported nanometer-scale fabrication on metal thin films using ablation by femtosecond laser pulses, with Bessel beam profiles. Choosing the laser fluence around ablation threshold allowed control of the structure size below the diffraction limit. Bessel beams have focal spot sizes insensitive to longitudinal position, which significantly relaxes alignment constraints. By using the proposed method, they generated structures with resolution below 200 nm[82]. Khoutorsky et al. demonstrated for the first time that the ringlike Stable Protein 1 (Sp1) and its derivatives can be used to generate hydrophilic nanochannels in the plasma membrane of living cells. Since SP1-derivatives can be linked to both the plasma membrane, gold or silicon surfaces, they may serve to ohmically link between cells interior and electronic sensing devices[83].

At present, the biological manufacturing methods of nanochannels have been successful in some occasions, however, it has not yet formed a systematic methodology

and more general processing technology. It needs to be further developed and perfected.

2.8 Other processing technology

Stress release is a phenomenon in which the stress at a certain point in the body decreases due to the release of energy. By controlling the rate of the stress decrease, nanochannels can be obtained during the release of energy. Xu et al. reported a new fabrication method of large scale lithography-free nano channel array on polystyrene based on the cracking process on the surface of a polystyrene petri-dish. Under proper conditions, parallel nanochannels with equal interspaces were obtained. Control over the channel depth from 20nm to 200nm was achieved, with the channel length reaching tens of millimetres. The PDMS replication based on polystyrene nanochannel array has been successfully carried out[84]. Xia et al. proposed a simple and low-cost process of imprinting-induced cracks to fabricate controllable nanochannel structures with high depth-to-width ratio, in ultraviolet curable photoresist. The nanochannels were formed by the cracks of UV-curable photoresist due to its volume reduction as a result of solidification, with imprinting induced predesigned crack patterns[85]. Huh et al. described the use of nanoscale fracturing of oxidized poly(dimethylsiloxane) to conveniently fabricate nanofluidic systems with arrays of nanochannels that can actively manipulate nanofluidic transport through dynamic modulation of the channel cross-section. They presented the design parameters for engineering material properties and channel geometry to achieve reversible nanochannel deformation using remarkably small forces[86].

Molecular self-assembly is a component of the system without interference from human forces, the self-assembly, organized into a regular structure. Molecular self-assembly routines usually transform the molecular system from an out-of-order state to an ordered state, which can occur at different scales. Molecular self-assembly is an important means to create ordered molecular aggregates with novel structures and functions. Cheng et al. carried out a lithography-friendly self-assembly process on sparse chemical patterns by rectifying and multiplying lithographic patterns using block copolymers. A polymer film was assembled at a 14 nm half-pitch on a thin resist pattern at twice the period. This directed self-assembly process dramatically heals defects and reduces feature size variation of the ill-defined resist patterns[87]. Faustini et al. proposed a bottom-up, scalable, low-cost, and robust alternative to construct large areas of extremely homogeneous pillared planar nanochannels for nanofluidic applications. The complex hierarchical structure can be achieved when combining diverse bottom-up processing strategies that include self-assembly of block copolymer, nanostructured sol-gel coatings, and highly controlled liquid deposition processing, with powerful top-down techniques such as deep X-ray lithography[88]. Syed et al. described

a novel and simple self-assembly process of colloidal silica beads to create a nanofluidic junction between two microchannels. The nanoporous membrane was used to induce ion concentration polarization inside the microchannel and this electrokinetic preconcentration system allowed rapid concentration of DNA samples by 1700 times and of protein samples by 100 times within 5 minutes[89]. Polydimethylsiloxane (PDMS) is a soft material with high elasticity and its Young's modulus is only a few megapascals. So, when subjected to external force, PDMS easily deformed. Park et al. presented a technique for nanofluidic fabrication based on the controlled collapse of microchannel structures by exploiting the deformability of PDMS. This method converted the easy to control vertical dimension of a PDMS mold to the lateral dimension of a nanochannel. They demonstrated the creation of complex nanochannel structures as small as 60 nm and provided simple design rules for determining the conditions under which nanochannel formation will occur[90]. Viero et al. explored the potential of PDMS-based phase-shift lithography for the fabrication of nanofluidic devices. Their work demonstrated the efficiency and the performances of PDMS-based phase-shift lithography for prototyping nanofluidic systems[91]. Fig.7 shows the principle and results of PDMS-based phase-shift lithography.

Lo et al. developed a relatively simple, inexpensive and reliable technique to fabricate an PDMS array of nanochannels using the deformability of PDMS. Moreover, the nanochannels were directly integrated to microchannels as a whole, which facilitated solution loading from the millimeter-scaled loading reservoirs into the nanochannels[92].

Gu et al. carried out a simple polysilsesquioxane sealing of nanofluidic channels below 10 at room temperature. This method showed precise dimension control below 10nm with easy experimental setup. Smooth transfer of DNA fragments from microchannel to nanochannel through the interface area was observed[93].

The stress release method has the advantages of low manufacturing cost and simple processing method. However, the size of nanochannel is not uniform, and the direction of nano-crack is not easy to control and the yield is low. The molecular self-assembly method has the advantages of low manufacturing cost and the ability to fabricate nano-channels with a few nanometers in diameter. However, the nanochannels produced by this method are not uniform in size and complicated in process, and can only produce nanochannels with a certain porosity. PDMS deformation method can produce nanochannels in hundreds of nanometers, with the simple processing method and low cost. However, the morphology and size of nanochannels are difficult to be controlled, and clogging is likely to occur in the bonding process, resulting in low yield of finished product.

In order to more easily understand and study these manufacturing methods, the comparison of typical fabrication methods to form nanochannels is shown at Table 1.

3 Conclusions and Outlook

Bio-nanofluidic chips have been widely applied in many situations due to its validity to solve thorny problems for biochemical application. The fabrication of nanochannels is a critical step for obtaining effective bio-nanofluidic chips. This work reviews manufacturing methods of nanochannels of bio-nanofluidic chips. Reactive ion etching, high energy beam processing method, interference lithography, nanoimprinting, thin film deposition processing technology, hot embossing, stress release processing technology, molecular self-assembly processing technology and PDMS deformation processing and biofabrication of nanochannels are analyzed, and the advantages and disadvantages of each method are discussed.

In summary, although the conventional reactive ion etching process is mature, the cost is high and it only can enforce the manufacture of one-dimensional nanochannels. The self-assembly processing method, stress release processing technology, sacrificial layer technique and PDMS deformation processing method can produce low-cost 2D nanochannels, and the fabrication methods are also relatively simple, but the morphology and size of the nanochannels are difficult to control, and the nanochannels are easily clogged, resulting in a decrease in yield. The processing quality of high energy beam processing methods and interference lithography are high. These methods can create uniform nanochannels, but rely on expensive equipment, not suitable for mass production. Nanoimprinting is a low-cost processing method and can achieve mass production of nanochannels. Nanoimprinting can fabricate the polymer nanochannel below 100nm, can be compatible with other micro-nano manufacturing technology, and is suitable for manufacturing complex nanofluidic chip. However, nanoimprinting requires spin-coating the polymer onto the hard substrate surface, followed by nanoimprint replication. This not only increases the cost but also increases the complexity of the process. Hot embossing is a low-cost and batch-based process method for nanochannels. However, in the hot embossing process, if the polymer can not completely fill the nano-mold cavity, the manufacturing quality of the nanochannel will be affected. The process method is in its infancy and needs further study. In addition, the sealing methods of nanofluidic channels need be studied further, and it is urgent to give a generalized sealing method that is inexpensive and practical for mass production of bio-nanofluidic chips.

With the increasing maturity of MEMS processing technology and continuous development of nano-processing technology, the advanced manufacturing methods of nanochannels will be developed further and a variety of applications will be successfully achieved. This review can provide a helpful reference to the ones who want to study in this direction.

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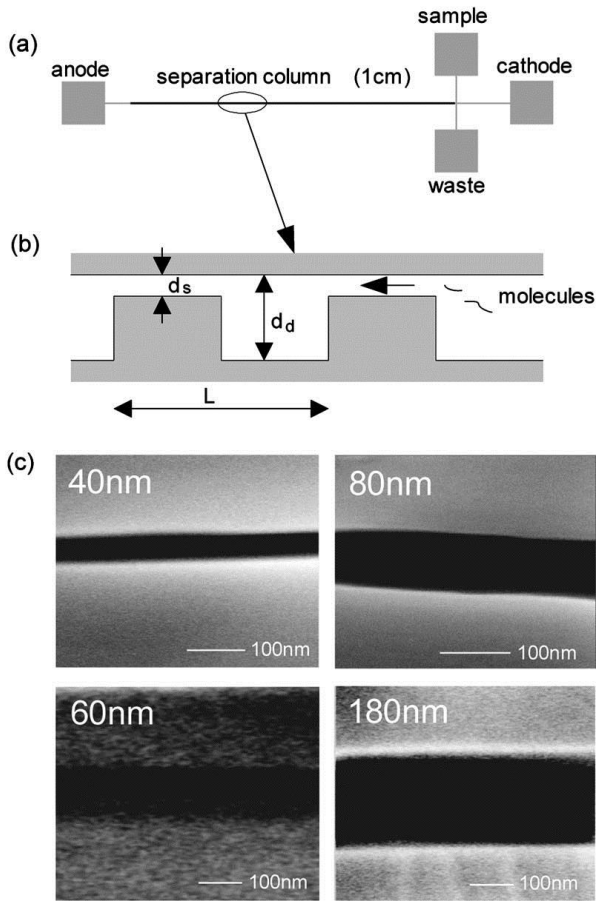

Fig.1 (a) Layout of the nanofilter array chip. The device includes four buffer access holes anode, cathode, sample and waste), a 1 cm separation column (a periodic array of nanofilters) and a T-shaped injector. (b) Cross sectional schematic diagram of the nanofilter array along the separation channel. The nanofilter consists of a thin region(d_s) and a thick region (d_d) of equal lengths. The period of one nanofilter is L. (c) Scanning electron microscopy images of the cross section of thin regions with different depths (40, 60, 80, and 180 nm). [24]

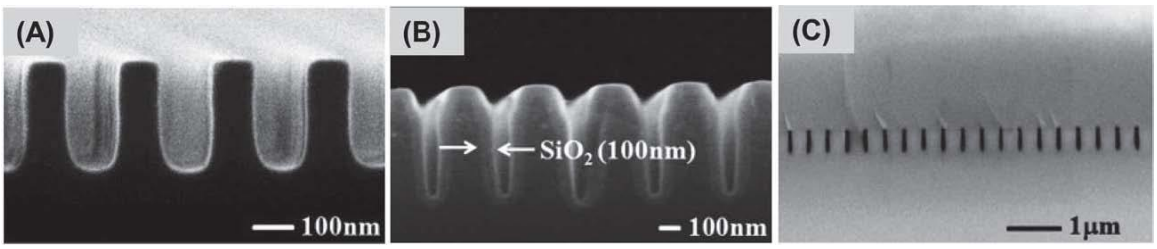

Fig.2 Cross-sectional SEM images of nanochannels: (A) nanochannels after plasma etching; (B) SiO2-covered nanochannels after thermal oxidation; and (C) nanochannels sealed with a Pyrex cover after anodic bonding. [40]

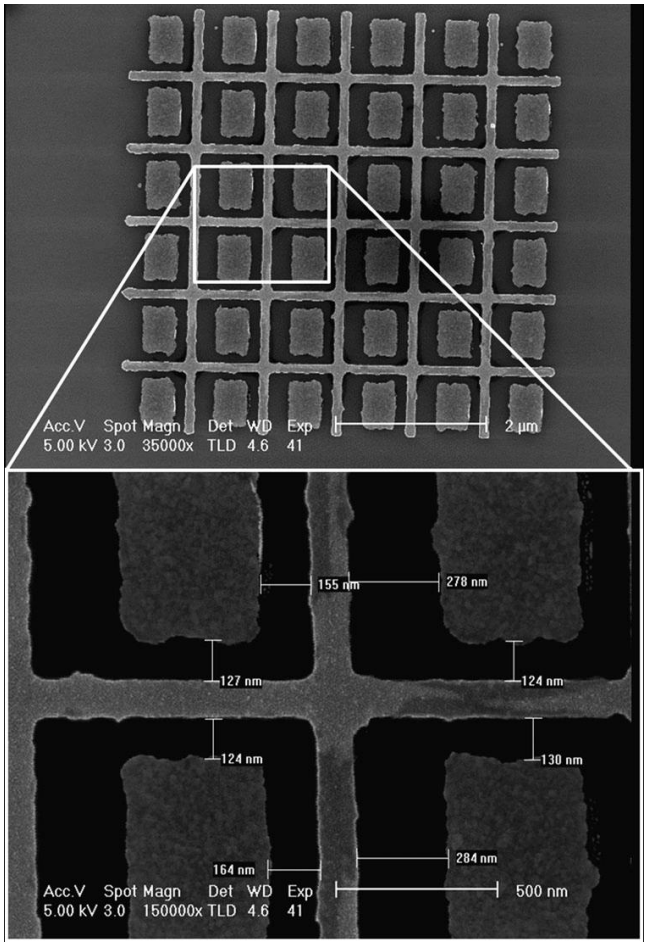

Fig.3 SEM images of two metal layers fabricated by NIL and metal lift-off. The box array was patterned first and the mesh second. The box was made of Au and the mesh was made of Pt. The bottom image shows an overlay accuracy of about 60 nm. [45]

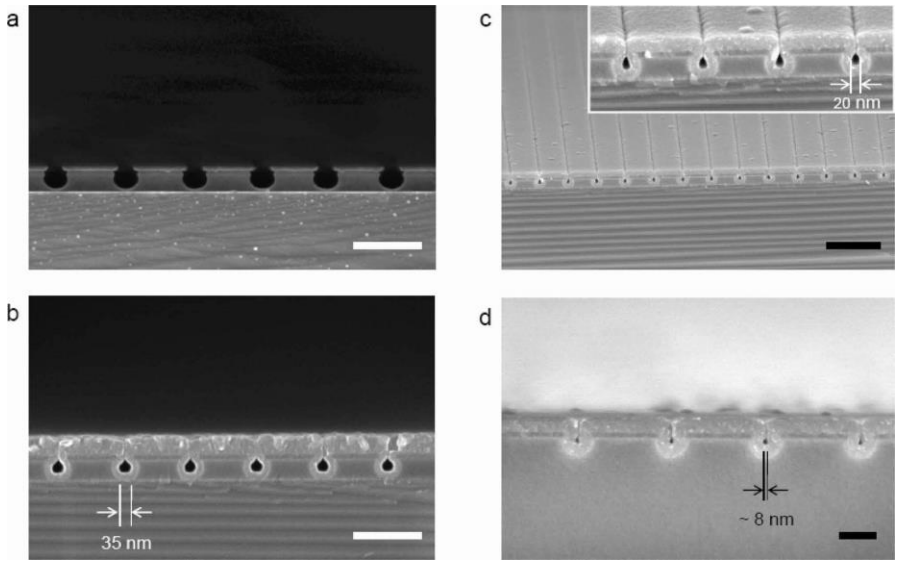

Fig.4 Cross-sectional scanning electron microscope (SEM) images of (a) pipe structures, (b) 35 nm void structures (10 nm wet etching) (c) 20 nm void structures (5 min wet etching), and (d) 8 nm void structures (3 min wet etching). To generate void structures, they deposited SS-ALD TiO2 film on pipe structures in a-Si (20 nm)/ SiO2 (100 nm) on Si substrate. (Scale bars are (a, b) 250 nm, (c) 500 nm, and (d) 100 nm.). [58]

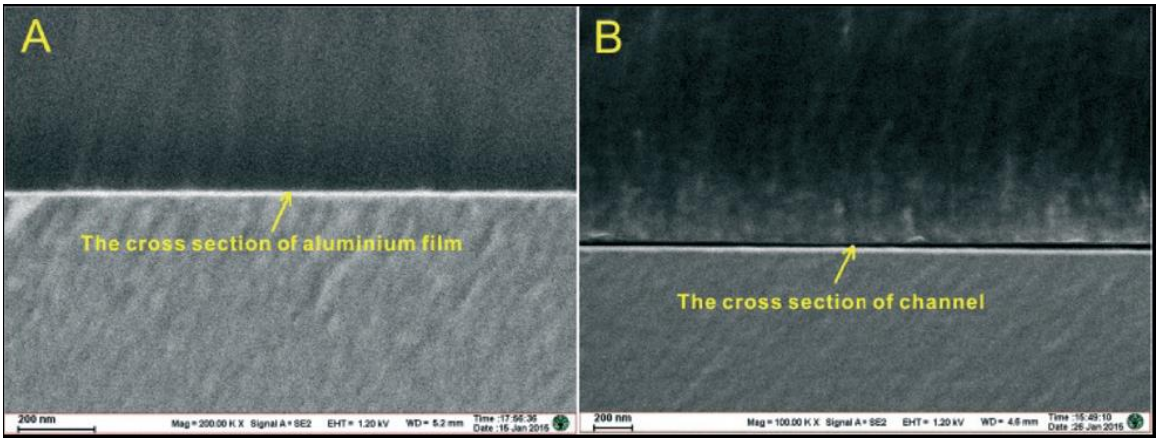

Fig.5 SEM pictures of the nanochannel's cross-section with a depth of 20 nm. The middle structures are the sacrificial layer before etching in (A) and the nanochannel after etching in (B). The bottom structures were the substrate glass and the top structures were the epoxy resin layers in both pictures. [62]

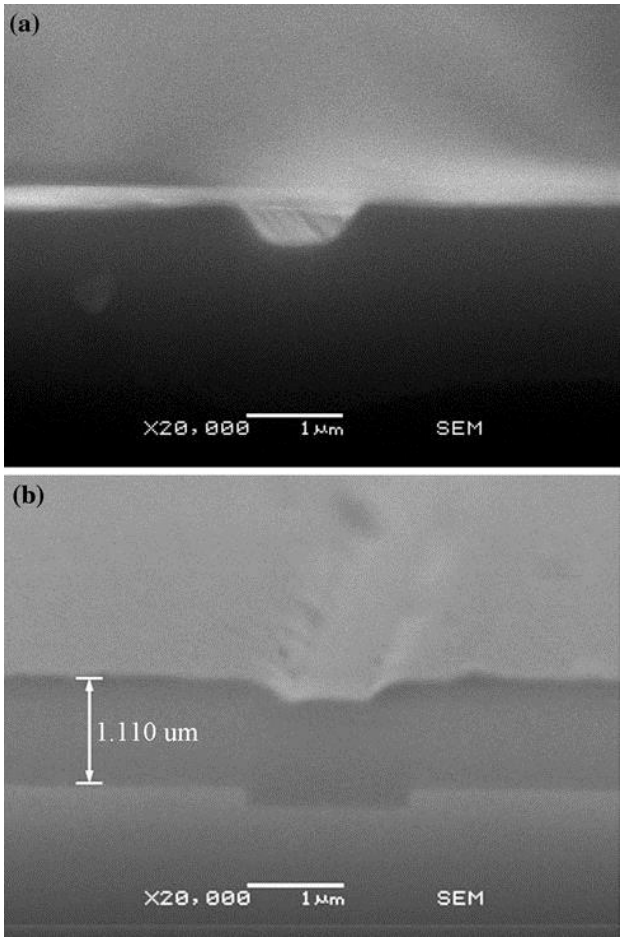

Fig.6 Section views of silicon nanomoulds. (a) Made by thermal oxidation; (b) made by plasma enhanced chemical vapor deposition. [65]

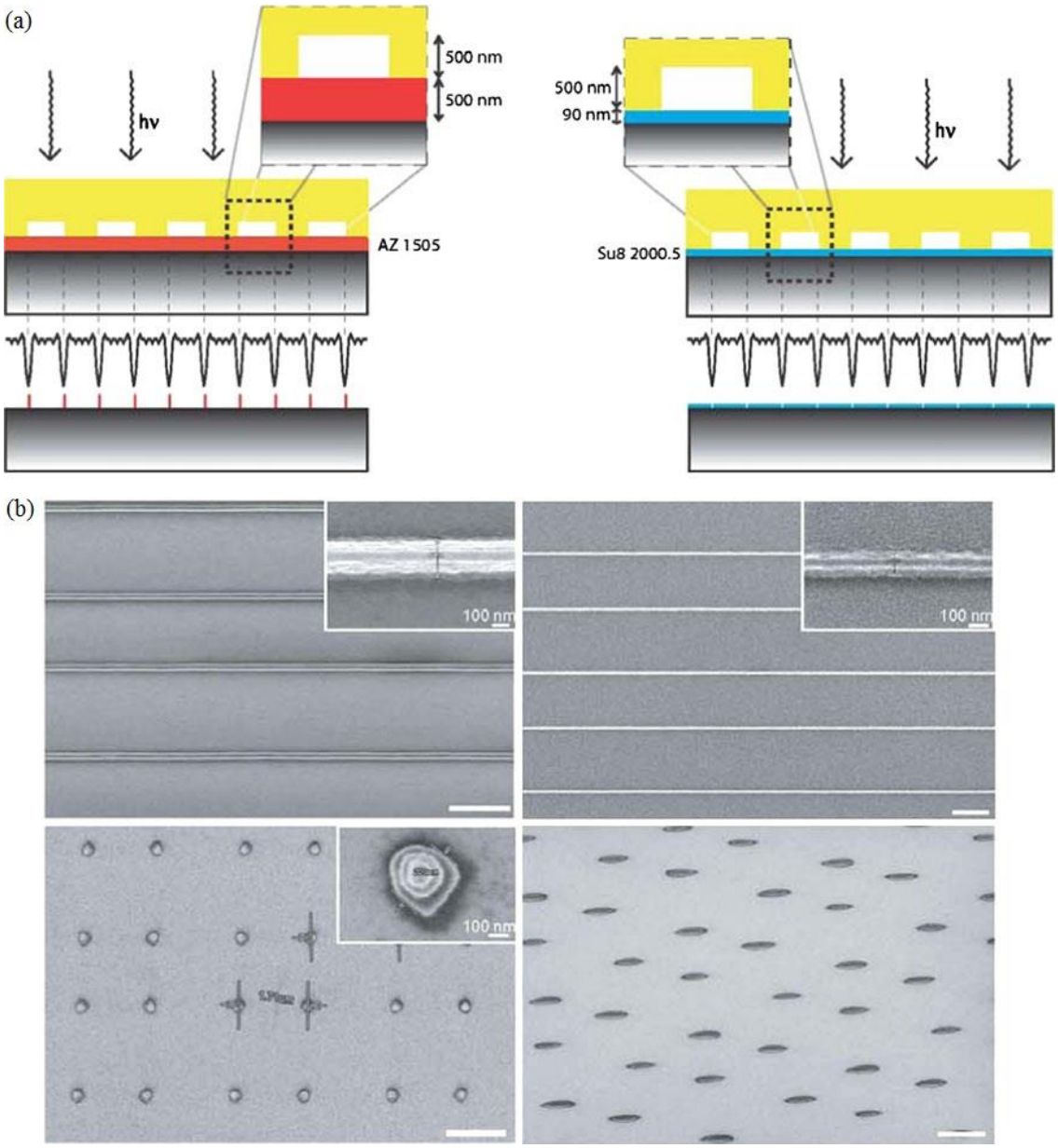

Fig.7 Principle and results of PDMS-based phase-shift lithography. (a) This figure sketches the principle of PPSL, highlighting the dimensions of the PDMS phase mask as well as the photoresist thickness. (b) The upper panels show scanning electron micrographs of 200 and 100 nm PPSL AZ 1505 linear features on silicon wafers. The lower panels represent scanning electron micrographs of 200 nm punctual patterns of AZ1505 with cylindrical and ovoid geometries, which are obtained by two consecutive exposures with two different angular shifts (90^{o} and 30^{o}, respectively). Scale bars = 2 µm, unless mentioned. [91]

Table.1 Comparison of typical fabrication methods to form nanochannels

Fabrication method	Minimum channel size (nm)	Materials	Characteristics	Applications
Reactive ion etching	40-100	Glass, Silicon, Photoresist	(A) Easy, accessible (D) Hard to obtain nanopattern in lateral direction	1D channel large scale array
High energy beam processing	1-100	Glass, Silicon, Photoresist, Chromium, PMMA, et al	(A) Freedom of patterns, small feature size (D) Slow process	1D nanoslit, 2D channel, Rectangular cross-section, controllable pore
Interference lithography	100	Glass, Silicon, Photoresist, Gel, et al	(A) large area patterning, uniform patterning, fast, maskless (D) Common compatibility	1D nanoslit, 2D channel, Large scale channel, large scale pore, large scale array, deep nanochannels
Nanoimprinting	<100	Glass, Silicon, Photoresist, PMMA, et al	(A) High throughput (D) Mold and releasing issue, hard to form deep channels	1D nanoslit, 2D channel, Large scale channel array
Thin film deposition	30-200	Polymer, Silicon nitride, Silicon dioxide, polysilicon	(A) Fast, low cost, simple process (D) Hard to form uniform channels	1D nanoslit, 2D channel, large scale array
Hot embossing	>50	PMMA, PS, PET, PC, et al	(A) Low cost, simple process (D) Easy to deformation	1D nanoslit, 2D channel, large scale array
PDMS deformation	100-800	PDMS	(A) Low cost, simple process (D) Low yield	2D channel, V-shaped channel, large scale array
Stress release	20-800	Photoresist, PDMS, PS	(A) Simple process Maskless, low cost (D) Low yield, Low resolution	1D nanoslit, V-shaped channel, large scale array
Molecular self-assembly	20-800	Polymer, Silicon,	(A) Low cost (D) Low yield,	1D nanoslit, 2D channel