

Technologies for nanofluidic systems: *top-down* vs. *bottom-up*—a review

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This paper gives an overview of the most commonly used techniques for nanostructuring and nanochannel fabrication employed in nanofluidics. They are divided into two large categories: *top-down* and *bottom-up* methods. *Top-down* methods are based on patterning on large scale while reducing the lateral dimensions to the nanoscale. *Bottom-up* methods arrange atoms and molecules in nanostructures. Here, we review the advantages and disadvantages of those methods and give some future perspectives. It is concluded that technology in the region of 1–10 nm is lacking and potentially can be covered by using the pulsed-laser deposition method as a controlled way for thin film deposition (thickness of a few nanometers) and further structuring by the *top-down* method.

Introduction

In the last decade, micromachining technologies have been used to advance the area of microfluidic systems. On the one hand, integrating microchannels with sensors, actuators or other electronics^{1–3} gives new functionalities, but probably even more important is that smart geometries^{4,5} and new fluid manipulation principles^{6–12} have enabled manipulation and detection of nanoliter fluid samples. The behavior of fluidics in such systems has been extensively investigated and exploited in so-called lab-on-a-chip (LOC) systems.^{13,14} Processes such as rapid and well-controlled mixing,^{4,5,15,16} heat transport¹⁷ and manipulation of (sub)nanoliter samples have become state of the art. Recently, expanding interest in scaling down to nanometer dimensions of the channels for fluid transport opened a new window for fundamental and applied studies of nanofluidics. Moreover, in comparison with well-established techniques used in colloid science and membrane fabrication, that only allow the random arrangement of nanopores,

nanostructuring enables the formation and control of individual nanostructures and nanochannels of controllable dimensions, geometry and interconnections.

Nanochannels can be defined as channels with at least one cross section dimension in the nanometer range (1D and 2D nanochannels). The nanometer scale of the channels allows the discovery of a new range of phenomena, because the channel depth or diameter is of the order of the size of the atoms or molecules comprising the fluid or dissolved or dispersed in the fluid. Therefore, fundamental phenomena such as fluid transport and molecular behavior at extremely small dimensions^{18,19} are attractive for investigation.

From the application point of view, evidently nanochannels could represent an important step in developing the lab-on-a-chip (LOC) concept, which is suited to small-scale analyses with high throughput. To make this happen, nanochannel fabrication techniques should be cost-effective and one should be able to precisely control channel dimensions preferably made on large scale wafers.²⁰ The small dimensions of the LOC reduce processing times and the amount of reagents necessary for assay, substantially reducing costs. Additionally, it can be fabricated with many channels, allowing for massively parallel chemical analyses and more sensitive detection.²¹ Sample volumes for a single experiment can be in the nano- to picoliter range enabling the analysis of components from single cells and single molecules. It has been shown that nanofabrication can have advantages in biological sciences, biophysical sciences (e.g. DNA analysis) and chemistry.^{22,23} Moreover, there is an interest in developing the nanostructures employed in electronic components that can be integrated in nanofluidic systems. Furthermore, the nanoelectromechanical systems (NEMS) can be sometimes parts of nanofluidic devices and development of the new class of NEMS can result in advances in sensors, medical diagnostics, displays and data storage.²⁴ NEMS is characterized by small dimensions of the devices in the order of a few hundreds of nanometers down to a few nanometers. Many of the microelectromechanical systems (MEMS), which are in practical use, are made in well-developed silicon-based fabrication technology.²⁴ The fabrication of NEMS devices is, therefore, often done in the same technology.

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However, new physical properties, resulting from the small dimensions, may dominate the device operation as well as the operation of the nanofluidic devices and may require new fabrication approaches.

In this paper, we present an overview of the currently developed techniques for nanofabrication that can be employed in nanochannel production and their future perspectives. We also review some other techniques for nanostructuring that are not used for nanochannel fabrication, but they can be utilized in nanofluidic devices and some of them possibly even later integrated in nanochannel fabrication.

Nanofabrication methods

Nanofabrication methods can be divided roughly into two groups: *top-down* and *bottom-up* methods.²⁵ *Top-down* methods start with patterns made on a large scale and reduce its lateral dimensions before forming nanostructures. On the other hand, *bottom-up* methods begin with atoms or molecules to build up nanostructures, in some cases through smart use of self-organization. At the end of the paper the major properties of the methods will be summarized in Table 1.

Top-down methods

In analogy with micromachining,²⁶ *top-down* methods for nanomachining can be subdivided into 3 categories: (a) bulk-/film-machining; (b) surface-machining; (c) mold-machining.

(a) Bulk-/film-machining

In bulk-/film-machining the channel is created by etching trenches in the substrate wafer or, alternatively, in the film deposited on the substrate. This is done typically by standard photolithography followed by wet or dry etching of the substrate in the case of substrate (bulk) etching and usually chemical etching of the film in the alternative approach, *i.e.*, film etching.^{26,27} The formed structure is closed by bonding another wafer on top of the structured substrate or film (Fig. 1a).

An example of a simplified nanofabrication method used to construct 1D nanochannels for nanofluidics is presented in ref. 28. The processes are significantly simplified by using native oxide as the main mask material and a simple process for wet anisotropic channel etching with a controlled depth up to 500 nm, an accuracy of a few percent and etch roughness less than 0.5 nm.

Later in this paper we will present the standard methods used for patterning, etching and bonding/sealing.

Patterning. Lithographical techniques. Standard lithography, using a mask, is often used for patterning. A beam of light (typically ultraviolet light) passes through the mask and a lens, which focuses an image on photoresist (photosensitive coating of organic polymer) placed on a surface of a silicon wafer or a film (see Fig. 1a). The parts that are exposed to the photoresist can be removed leaving the desired pattern on the silicon wafer or film. The resolution of the photolithographic process determines the width of the channels. In photolithography ultraviolet light is used (typically 250 nm wavelength). The

Table 1 Overview of the techniques described in the text and their most common features

Technique	Capability			Channel materials ^b	Strengths	Weaknesses	Reference
	Nanochannels	Nanostructures	Dimensions ^a				
Top-down							
Bulk-/film-machining	x	x	Down to ~ 10 nm	Si, silicon dioxide, silicon nitride, fused silica.	Well-controlled large area structures; mainly suitable for mass production.	Most lithographic methods are expensive; Most bonding techniques require defect free and flat surfaces, whereas polymer bonding can create deformation.	21,25–48,77
Surface-machining	x	—	Down to 100 nm	Silicon dioxide, silicon nitride, polymers (<i>e.g.</i> polyimide), fused silica. <i>Materials for sacrificial layers:</i> polycrystalline silicon, thermal degradable materials, Al, photoresist, silicon dioxide...	Relatively easy to fabricate; insensitivity to the particles that disrupt the bonding.	Long etching time, special irrigation holes needed, channel tapering, limited channel length.	22,23,26,27, 49,50–54,78
Mold-machining	x	x	Down to ~ 20 nm	Organic molecules, polymers (<i>e.g.</i> parylene, polymethylmethacrylate (PMMA))	Inexpensive and relatively easy replication of the structure in the mold.	Expensive fabrication of the masters. New mold needed when changes in a feature characteristic.	25,55–62
Bottom-up	—	x	2–10 nm	Octapeptides, porin MspA, zeolites, porous carbon, liposomes, carbon nanotubes (CNT).	Mainly used for naturally formed well-defined structures.	Resulting nanostructures are randomly positioned unless combined with top-down methods.	63–71,75,76

^a Height and/or width of the channels. ^b The most common materials used in nanochannel and nanostructure fabrication.

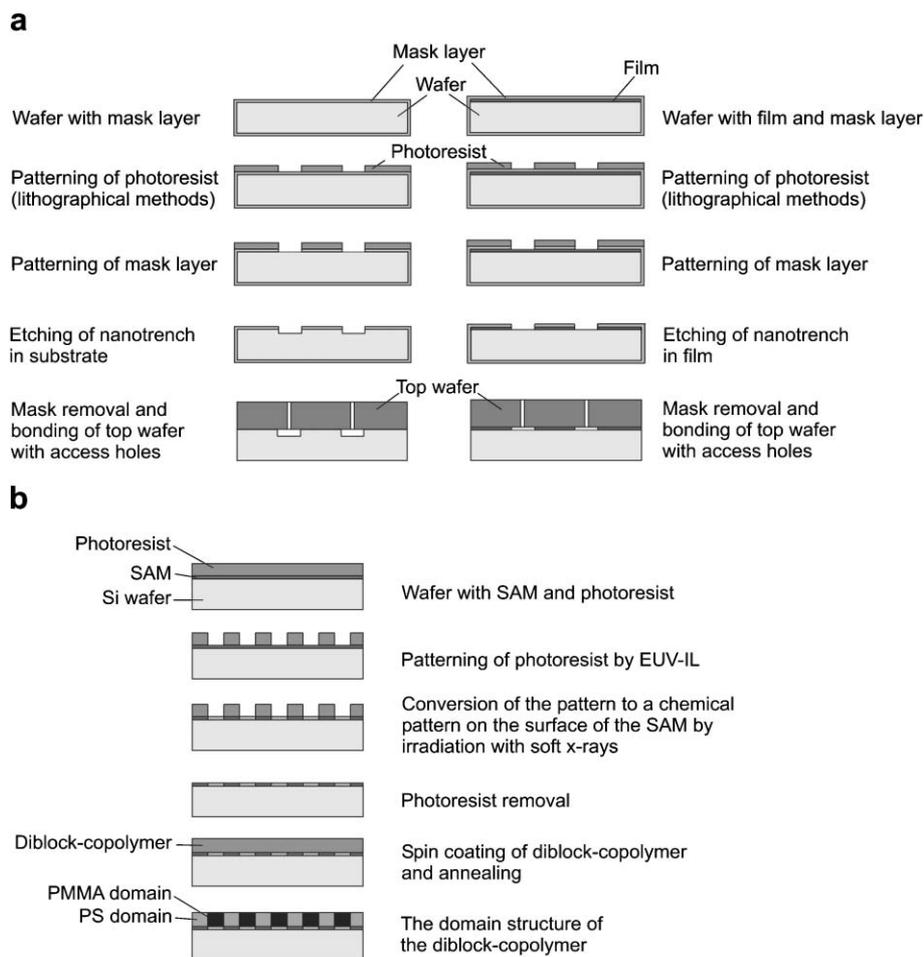


Fig. 1 (a) Bulk-/film-machining;²⁶ (b) hybrid-method for patterning.⁴⁶

fabrication of spacings smaller than half this length causes blurred features, which can melt together. Various technical improvements managed to reach structural resolutions in the order of 70 nm in experimental setups and about 100 nm in mass production.^{25,29} The technical difficulties to make such small structures using light, make this technique rather expensive. Modification of this technique by using X-rays or extreme ultraviolet light^{30,31} reduces the blurring and allows for smaller structures. However, the conventional lenses are not transparent to extreme ultraviolet light, they do not focus X-rays and the energy of these radiations easily damages most of the materials used in masks and lenses.

Therefore, instead of masks, lithography technologies based on focused beams are used as an alternative, such as electron-beam lithography (EBL) and focused-ion beam (FIB) lithography (typically using Ga ions) to create nanochannels, *e.g.*, for DNA separation.³² Features of 10 nm in scale can be achieved by both methods. In the case of EBL, the pattern is written in the photoresist with a beam of electrons,²⁵ whereas FIB directly machines the material, *i.e.*, the film or substrate. However, the use of electron beams is costly and slow and therefore impractical for large-scale manufacturing. Another drawback of EBL is the proximity effect caused by the scattering of the electrons in the resist. This limits the resolution and contrast due to backscattering.^{33,34} The advantage of

using FIB patterning is the possibility of using well-known methods for producing high-quality thin films (including epitaxial films), such as pulsed-laser deposition (PLD), metal organic chemical-vapor deposition, sputter deposition *etc.* A disadvantage of FIB is the appearance of damage that occurs during milling and imaging and especially Ga ion doping of the films.²⁹ Especially promising is the newly developed PLD technique using interval deposition (a certain amount of the material is deposited, which is followed by an interval without deposition that allows the deposited material to rearrange), which allows *layer-by-layer* film growth on a unit cell scale (unit cell of a crystal structure).^{35,36} This method could possibly be used in the fabrication of the nanochannels with height in a unit cell-range.

Interferometric lithography (IL) can be used for patterning as well. It is based on the interference of two and more coherent beams.³⁷ Its advantage is that it is a maskless, inexpensive and quick technique, which allows patterning of nanoscopic features into silicon over large areas with easily varied features dimensions (*e.g.*, pitch size and channel width).

A variety of wafer-bonding techniques (mentioned below) allow the sealing of the trenches made with these techniques and in this way nanochannels are formed.

Furthermore, in ref. 38 laser patterning of nanotrenches in Si has been reported as another maskless approach with a

better resolution as compared to the writing in photoresist (feature sizes of < 40 nm for laser-etched Si structures and line widths of < 200 nm). Laser machining (especially use of pulsed lasers) enables precise fabrication of sub-micron features in materials that are hard to machine, such as ceramics and semiconductors.³⁹ However, from the technological point of view the disadvantage of this method is that it is not a batch process.

For ultimate resolution, scanning probe techniques are employed, such as atomic force microscopy (AFM)⁴⁰ and scanning tunneling microscopy (STM)⁴¹ by moving individual nanoparticles or even atoms or molecules and arranging them in patterns. The rings and wires built in this way can be of one atom width. However, these methods are too slow for mass production.²⁵ The latter two methods (laser machining and scanning probe techniques) have not yet been used for nanochannel fabrication and they are listed here as a way of nanostructuring with an interest in use in nanofluidics.

Self-assembly lithography. Self-assembly lithography is an approach that provides a low-cost and efficient way for creating nanostructures with critical dimensions below photolithographic resolution limits (which are in the order of 100 nm)^{42,43} (for a review see ref. 44). The formation of self-assembled structures can be considered as a *bottom-up* approach towards formation of nanostructures and it will be mentioned in that classification as well. Here, we would like to stress its use in the patterning process in bulk-/film-machining. An example of self-assembly lithography is the formation of a mask by self-assembly.⁴³ A diblock copolymer (macromolecules composed of two covalently bonded immiscible polymer blocks A and B; in this example it consists of polystyrene, PS, and poly(methylmethacrylate), PMMA) is placed on top of the silicon wafer that should be structured instead of photoresist. The chemical link between the two blocks prevents phase separation on the macroscopic length scale, but allows microphase separation of the two blocks leading to self-assembled morphologies of the minority polymer block. Such self-assembly patterning occurs when the diblock copolymer is heated above the glass transition temperature of the two polymer blocks, by separation of the two polymers. In the case of PS and PMMA spontaneously microphase separation occurs into a hexagonal lattice of PMMA cylinders in a matrix of PS. The PMMA is then etched away by exposure to ultraviolet light and a development process. This approach allows tailoring in the range of hundreds of nanometers to below 10 nm. The polymer (PS) template pattern can be faithfully transferred into both silicon wafers and oxide films by reactive-ion etching (RIE). This opens opportunities to integrate diblock copolymer films in semiconductor processing, since this method enables patterning of ordered domains with dimensions below photolithographic resolution limits over wafer areas. To form nanochannels, this method needs to be adapted (possibly by a hybrid-method discussed below) for formation of nanotrenches, which also need to be further sealed.

In ref. 45 the authors used self-assembly diblock copolymer thin films as sacrificial layers for transfer of dense nanoscale patterns into more robust material. This was further used as a

hard mask to achieve uniform nanoporous dielectric films, high-aspect-ratio nanotextured silicon, silicon nitride dot arrays, silicon pillar arrays, and silicon tip arrays. In the case of high-aspect-ratio silicon pore formation, the final step was atomic layer deposition of a TaN coating that oxidizes the trench sidewalls. The other structures were not, however, coated which in the case of nanochannel formation will be needed.

Hybrid-method. In this method⁴⁶ nanopatterns are formed by merging the principles of two methods—lithography and self-assembly (Fig. 1b). In this way the costs are lowered and the control of producing materials at the molecular level is increased. A substrate was covered by a self-assembly monolayer (SAM), on top of which photoresist was spin-coated and patterned by lithography (extreme ultraviolet interferometric lithography (EUV-IL)). The pattern was converted to a chemical pattern of the SAM by irradiating the sample with soft X-rays. Then, a film of block copolymers was deposited on the surface and the molecules arranged themselves into the underlying pattern without imperfections. Thin films of diblock-copolymers can self-assemble into ordered periodic structures (~5 to 50 nm). This inexpensive method has the disadvantage that can result in defects. Therefore, the thin films of block copolymers were integrated with lithography to induce epitaxial self-assembly of domains. The final patterns are free of defects, oriented and can be created over arbitrarily large areas. Additionally, this method will need appropriate sealing to create nanochannels.

Etching. During etching moderate and accurate etch rates are needed to ensure a precise etch depth and a smooth surface finish²⁶ important for further bonding. Wet etching is orientation dependent and is, for example, done with alkaline solution in the case of silicon etching. It can be isotropic and anisotropic. The techniques used for dry etching are ion-beam etching, focused-ion beam etching (FIB), reactive ion etching (RIE) and deep reactive ion etching (DRIE).⁴⁷

Bonding/sealing. The bonding/sealing methods depend very much on the bulk material used and they are anodic, fusion, polymer, direct and eutectic bonding.²⁷ Polymer bonding (using, for instance, polydimethylsiloxane, PDMS) is employed in rapid prototyping and used for plastic substrates.²⁷ PDMS is spun onto a cover slip (in the thickness of several micrometers) and cured. The cover slip with PDMS is then brought in contact with the chip, that contains trenches.²¹ The advantage of this sealing is that the channels can be easily opened and cleaned. The disadvantage is that the seal can sag into the channels, since it is made of a soft material. In anodic bonding large electric fields are applied to assist bonding and it is used usually for glass and silicon, whereas in fusion bonding high temperatures are used and it is employed in glass bonding. Eutectic bonding is mainly used for metallic alloys²⁷ or often for Au and Si by heating two materials in a joint such that they diffuse together to form an alloy composition, whose melting point is lower than that of the base materials. Direct bonding can be used for highly polished substrates, such as

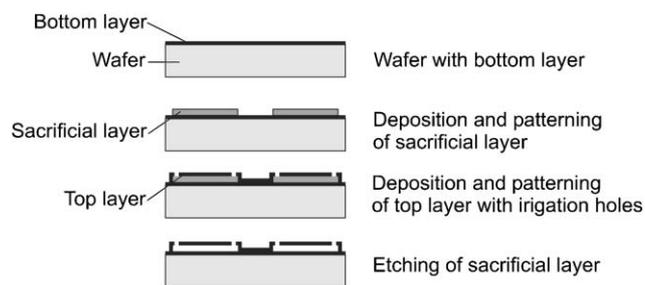


Fig. 2 Surface-machining.²⁷

silicon²⁷ and it relies on the tendency for two smooth and flat surfaces to adhere together.²⁶

Direct sealing to create nanochannels is based on non-uniform deposition of the sealing material during sputter deposition^{21,48} or e-beam evaporation.⁴⁸ These processes result in narrowing and sealing the trenches.

(b) Surface-machining

In surface-machining,^{49,27} first a bottom layer is deposited on the wafer followed by the deposition of the sacrificial layer and its patterning (Fig. 2). Then, the top layer is deposited on top of the sacrificial layer and patterned (often with irrigation holes, which provide the access to the sacrificial layer). The nanochannel is finally formed by removing, *i.e.*, etching the sacrificial layer leaving the bottom and the top layer to form the walls of the nanochannel. The bottom layer is not always required. It is mainly introduced to form the channel of one material (the same material as the top layer).

Sacrificial material is usually polysilicon,⁵⁰ but can also be thermal-degradable materials.^{22,51} The sacrificial layer is removed by wet etching or thermal degradation. However, these techniques are not suitable for fabricating long-scale nanofluidic channels due to the very long time needed for the etching of the sacrificial layer²³ and in the case of wet etching special irrigation holes are often necessary to dissolve the sacrificial layer in a reasonable time span. Tapering of the channels can appear by wet etching due to the limited specificity of the etchant for the sacrificial material over the wall material. Isotropic sacrificial etching is very important in nanotechnology due to the very sensitive nature of the nanostructures. Dry etching is favored since the nanostructures can be damaged during wet etching by the drag forces during wafer handling and the possibility of sticking of nanostructures during drying.²⁶ In addition, the uniformity of the channel height and insensitivity to particles, which would disrupt bonding, present advantages of this method.

Recently two methods were developed for nanochannel fabrication⁵² based on conventional lithography, thin film deposition and sacrificial layer etching. This combination made possible the realization of very long 2D nanochannels (in the order of millimeters). The width of the nanochannels is usually determined by the photolithographic process used (a resolution of typically 1 μm). However, these new methods enable the realization of sub-micrometer channel widths using standard photolithography. The first method is based on the sacrificial etching of a nanowire, deposited on a side wall of a

step. In the second method the sacrificial strip, that separates the substrate and the capping layer, is etched and the nanochannel is formed by the adhesion of the capping layer to the substrate.

A simple method recently presented allows the fabrication of 1D nanochannels in polyimide by sacrificial etching of an aluminum layer.⁵³ The very high etch specificity between polyimide and aluminum leads to a virtual absence of channel tapering, which is sometimes observed in surface-machining. Polyimide is a promising material due to its favorable electrical and mechanical properties and its biocompatibility. However, its autofluorescence⁵⁴ limits the use of fluorescence detection due to the high background signal.

(c) Mold-machining

In principle, in mold-machining first the mold in the inverse shape of the desired structure is formed. This is filled with a structural material and then the mold can be etched or removed leaving the desired structure behind.

The mold machining is mainly performed by soft lithography. In soft lithography (Fig. 3a) the mold is usually made by producing a pattern (master) in a layer of photoresist on the surface of the silicon wafer by photolithography or electron-beam lithography (EBL).²⁵ Then a liquid precursor to polydimethylsiloxane (PDMS) is poured over it and cured into the rubbery solid. The PDMS stamp is then peeled off the master. The fabrication of the master is rather expensive due to use of the electron-beam lithography or other advanced techniques. Copying the pattern on the PDMS stamp as well as the use of the stamp is, however, cheap and easy.

The PDMS stamp is then further used in different ways to make nanostructures: by microcontact printing⁵⁵ (Fig. 3b) or micromolding in capillaries⁵⁶ (Fig. 3c).²⁵ In microcontact printing the stamp is inked in a solution of organic molecules and pressed against a thin golden film on a silicon plate. The organic molecules form a self-assembled monolayer (SAM) on the gold reproducing the stamp's pattern. In the micromolding in capillaries method the PDMS stamp is placed on a hard surface and a liquid polymer, flown into the recesses between the surface and the stamp by capillary forces, solidifies into the given pattern.

The advantage of the soft lithography is that it does not need to be carried out in the clean room (apart from the master fabrication by photolithography). If some dust particles are trapped between the stamp and the surface, the elasticity of the PDMS stamp allows the reproduction of the correct pattern except in the contaminated area.²⁵ The nanostructures made by this method can be produced in a wide range of materials and the patterns can be formed on curved and planar surfaces. However, this technique is not suitable for complex nanoelectronic devices, *i.e.*, for making multilayered structures due to the deformations and distortions of the soft PDMS stamp that can cause small errors in the replicated pattern and/or the misalignment of the pattern with the underlying one.

The latter limitation can be overcome by employing a rigid stamp in step-and-flash imprint lithography^{57,58} and nanoimprint lithography (NIL).^{59,60} In step-and-flash imprint lithography a master is made in a quartz plate by photolithography

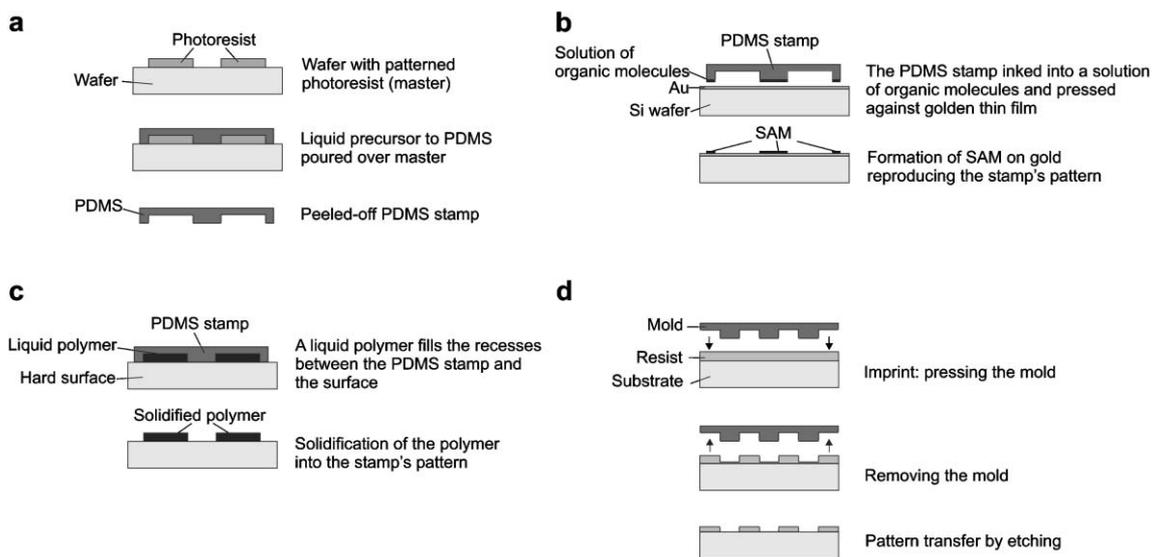


Fig. 3 Mold-machining: (a)–(c) Soft lithography;²⁵ (a) formation of an elastic stamp, (b) microcontact printing, (c) micromolding in capillaries; (d) nanoimprint lithography (NIL).⁶⁰

and directly pressed against a thin film of liquid polymer, which fills the master's recesses. Ultraviolet light, to which the master is exposed, solidifies the polymer creating the desired replica. In NIL,^{59,60} a rigid master (mold) is pressed into a thin resist heated above its glass transition temperature. After the resist is cooled below its glass transition temperature, the mold is removed and an anisotropic etching process, such as RIE, is employed to remove the residual resist in the compressed area (Fig. 3d). NIL is fast and well suited for large-scale fabrication. Standard NIL allows the formation of nanostructures down to 20 nm.²⁹ However, a new mold needs to be created whenever some changes in a feature characteristic are required (*e.g.*, channel size *etc.*). NIL has also certain limitations in replicating large-scale (in micrometers range or larger) and nanoscale patterns simultaneously.

In ref. 61 a novel lithographic technique that integrates photolithography into the NIL patterning process is reported, successfully overcoming the NIL limitations. This technique employs a hybrid mask-mold that has large metal pads embedded in a transparent NIL mold. This hybrid mold allows the patterning of large-scale and sub-micron feature size structures in one step. Therefore this technique has a future in fabrication of a wide range of nanoscale electronics, photonics and biological devices where patterns of various sizes are needed.

Another type of mold-machining for fabricating nanochannels was reported in ref. 62. The authors used channels etched in a silicon wafer as a mold in which Parylene was deposited to form tubes (Fig. 4). The Parylene polymer is chemically inert and biocompatible. The tubes are self-sealed with submicrometer lateral dimensions. When the tubes are formed, access holes for fluidic interconnects are created by standard lithography and the resulting tube can be removed from the mold or left integrated with the already existing device. With this approach multilevel three-dimensional interconnected fluidic networks can be produced that can be employed in complex microfluidic systems and maybe in the

future in nanofluidic networks. Parylene tubes could be promising as artificial blood vessel and implantable fluidic networks due to the biocompatibility of this polymer.

Bottom-up methods

For the completeness of this paper, we briefly summarize here the *bottom-up* methods for nanostructuring. In such methods, the atoms and molecules are assembled into the smallest nanostructures (dimensions of typically 2 to 10 nm) by carefully controlled chemical reactions, which make this technique cheaper as compared to the lithographical methods.

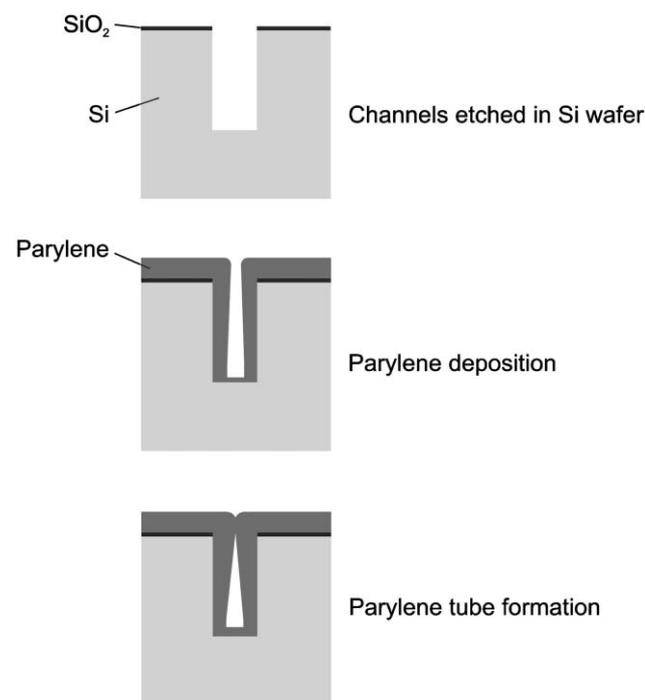


Fig. 4 Fabrication of flexible polymer tubes by mold-machining.⁶²

Self-assembly of atoms and molecules into nanostructures can be classified as a *bottom-up* method. In nature self-assembly is often used to make complex structures. At present, the mastery of self-assembly is limited to relatively simple systems. To achieve complex systems hierarchical self-assembly can assist, where the products of one self-assembly step is a base for the next one. The formation of self-assembled monolayers (SAMs), that are produced when a substance spontaneously forms a molecular monolayer on a surface, could be successfully combined with standard lithographical methods (as described earlier) to achieve large-scale and better controlled structures.

Biologically inspired self-assembly holds great promise in nanostructuring. For instance, it can be used in the formation of peptide nanotubes by self-assembly of cylindrical octapeptides, tubes that function as ion channels (Fig. 5a).⁶³ The structures were shown to have bactericidal properties by making the bacterial cell wall permeable to ions. In ref. 64 the unique stability and self-assembling properties of porin MspA (a channel protein isolated from *Mycrobacterium smegmatis*) was used to form nanopores (nanochannels) due to the ability of the porin to reconstitute within strongly hydrophobic layers on highly ordered pyrolytic graphite. The diameter of the MspA nanopores of about 3.1 nm was confirmed.

There are other nanostructures formed in nature that can be employed in nanofabrication. For instance, regularly and naturally formed nanochannels of zeolites (aluminosilicates) can be used to study dynamical behavior of water adsorbed in bikitaite (a rare lithium containing zeolite)⁶⁵ or for the synthesis of novel materials, such as porous carbon, using well ordered zeolite channels as a template⁶⁶ that can be later removed leaving the porous carbon structure behind.

In ref. 67–69 techniques are presented for creating complex two- and three-dimensional networks of nanotubes and micrometer sized containers from liquid crystalline lipid bilayer materials (Fig. 5b). Three-dimensional compact liposome networks are important for increasing the information density and processing capability of such networks in applications such as nanofluidics and computational devices as well as for nanoscale templating.⁶⁹

Bottom-up methods are also used, for instance, for the fabrication of carbon nanotubes (CNT) and quantum dots. CNT are graphene cylindrical tubes of a few nanometers to some hundred nanometers in diameter. They can be produced

by evaporation of solid carbon in an arc discharge, laser ablation, catalytic decomposition of fullerenes *etc.*⁷⁰ They can serve for studying the physics in one-dimensional solids as well as being used in various nanoscale devices⁷⁰ and can be self-assembled into hierarchical structures with controlled nanotube orientation (*e.g.* ref. 71).

Quantum dots are crystals which contain only a few hundred atoms and on excitation emit different wavelengths of light, depending on their size.²⁵ Therefore, they can be used to tag proteins and nucleic acids and when the sample is illuminated with ultraviolet light, the crystals will fluoresce and the location of the attached protein can be seen. There are several routes developed to synthesize nanoscale materials of numerous simple systems, such as semiconductors (Si, CdS, InAs/GaAs) and metals.²⁹ Up to now, they have been classified in two categories:²⁹ self-patterning *via* physical routes and self-patterning *via* chemical routes. The first one employs well-known physical growth concepts, such as island growth. It is based on the phenomenon that the initial growth of an epitaxial film deposited on the single-crystal substrate with high lattice mismatch, would result in the island (Volmer–Weber) or layer-then-island (Stranski–Krastanov) growth modes. Those two growth modes are suitable to grow crystalline nano-size (quantum) dots. The latter method uses simple chemical routes (for instance, the microemulsion concept) to fabricate nanosize crystals or nanoparticles in colloidal suspensions, which can be later spread onto the substrate. After solvent evaporation, the nanoparticles can be crystallized in two- or even three-dimensional arrays. Quantum dots may find application in devices such as lasers,⁷² quantum computing⁷³ and thermoelectric power generation.⁷⁴ They could also be applied in nanofluidic systems. One idea could be to use quantum dots regularly positioned along a nanofluidic channel to create an array of fluorescing dots, *e.g.*, to determine the position of a passing single cell.

In another approach^{75,76} ion-channel nanopores with an inner diameter of 1.4 to 4.6 nm were created by self-assembly of seven α -hemolysin monomers in a lipid bilayer. These structures are of optimal size for detecting the passage of small molecules (such as DNA and RNA) by changes in the electrical properties of the channel recognition element.

The *bottom-up* approaches mainly use naturally formed and rather well-defined structures. However, in general they are not suitable for the formation of nanofluidic devices at this stage of development, because they can not produce designed, interconnected patterns due to the random positioning of the obtained nanostructures.^{25,29} Therefore, longer, better controlled and interconnected structures are required that could be achieved combining the *bottom-up* with the *top-down* approach.

Conclusions and outlook

In this paper we summarized the most commonly used methods in nanofabrication categorized as *top-down* and *bottom-up* methods, and their the most common features are overviewed in Table 1. Within these groups there are several approaches utilized to achieve nanostructures and nanochannels. Methods

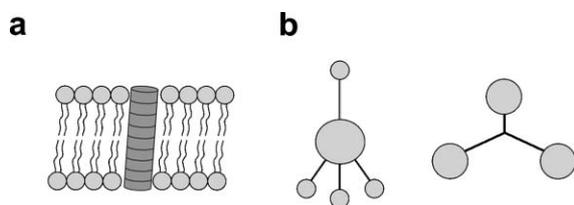


Fig. 5 (a) Simplified schematics of the self-assembly peptide nanotubes (cylinder) in the membrane.⁶³ (b) Schematic representation of nanotube-vesicle networks.⁶⁸ The radius of the nanotubes are between 100 and 200 nm and the diameters of the containers are 4 to 10 μm . The left image shows a five container network consisting of four daughter vesicles, which was formed from the central vesicle. The right image displays a three-way nanotube junction.

are constantly developed further to satisfy the conditions required for nanochannels used in LOC, NEMS *etc.*

There are a number of concepts that might in the future improve the quality of the nanochannels. A promising approach is combining *top-down* and *bottom-up* methods, where the smallest nanostructures achieved by *bottom-up* methods can be controlled and interconnected by previously employed lithographical methods. In ref. 79 and 80 experiments describe CNTs grown by the CVD technique within anodic aluminum oxide nanopore arrays (AAO). In this way excellent uniformity in the size and disposition of nanotubes was achieved as well as naturally perpendicular growth to the rigid substrate without a need for an extra processing step. The CNT arrays show promising properties for several applications, such as nanoelectronics. Additionally, one could think of using CNT as a sacrificial layer in surface-machining.

Also very promising is a variety of self-assembled block copolymers that can serve as a tool for nanomaterial fabrication. This fabrication can be categorized as a *bottom-up* method and has been reviewed in ref. 44. They can be used to construct nanopores, nanotubes, as templates for the synthesis of metallic or semiconducting nanomaterials *etc.* Some of them can be also combined with standard lithographical methods and used in a *top-down* approach as mentioned above.

From the above we can conclude there is still a gap in the range of nanochannel fabrication from 1 to 10 nm. A potential technology covering this gap is the pulsed-laser deposition (PLD) technique combined with reflection high energy electron diffraction (RHEED) that allows the formation of a thin film with very well-controlled thickness (in the order of a (few) unit-cell sizes).^{35,36} This method is based on a periodic sequence (Fig. 6): fast deposition of the amount of material needed to complete one monolayer followed by an interval in which no deposition takes place and the film can reorganize. In this way, the film is grown in a *layer-by-layer* fashion instead of island growth that would dominate otherwise. This rearranging of the deposited atoms can be considered as their

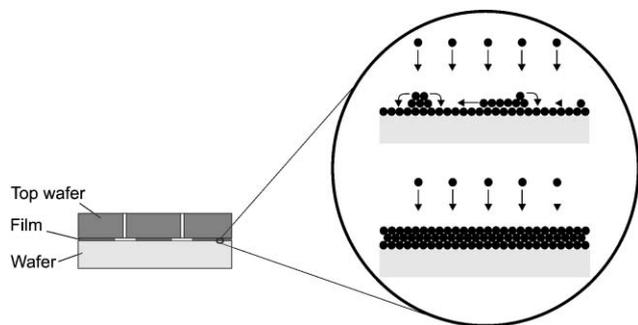


Fig. 6 Combined *top-down* and *bottom-up* approach: Nanochannels are made by film-machining (as described in Fig. 1a). The magnified part shows *layer-by-layer* thin film growth made by pulsed laser deposition. Material, deposited in pulses, rearranges between the pulses forming monolayers. This type of growth is the ideal case that depends on several parameters, such as deposition temperature, pressure and the strain induced by the substrate on the film in the case of heteroepitaxial growth (all these parameters determine the surface mobility of the adatoms, *i.e.*, atoms coming from the target and arriving on the surface).

self-assembly arrangement. These films could be further structured by film-machining or used as sacrificial layers in surface-machining (combining in this way again the *top-down* and *bottom-up* approach) making possible the formation of very thin nanochannels.

Finally, it is expected that the importance of availability of well-defined nanochannels for fundamental and applied research will strongly encourage the further development and optimization of the techniques for nanochannel fabrication.

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References

- 1 A. Rasmussen, M. Gaitan, L. E. Locascio and M. E. Zaghoul, *J. Microelectromech. Syst.*, 2001, **10**, 286.
- 2 F. Laugere, R. M. Guijt, J. Bastemeijer, G. van der Steen, A. Berthold, E. Baltussen, P. Sarro, G. W. K. van Dedem, M. Vellekoop and A. Bossche, *Anal. Chem.*, 2003, **75**, 306.
- 3 G. Pandraud, T. M. Koster, C. Gui, M. Dijkstra, A. van den Berg and P. V. Lambeck, *Sens. Actuators, A—Physical*, 2000, **85**, 158.
- 4 M. S. Munson, C. R. Cabrera and P. Yager, *Electrophoresis*, 2002, **23**, 2642.
- 5 A. E. Kamholz, B. H. Weigl, B. A. Finlayson and P. Yager, *Anal. Chem.*, 1999, **71**, 5340.
- 6 S. C. Jacobson, T. E. McKnight and J. M. Ramsey, *Anal. Chem.*, 1999, **71**, 4455.
- 7 R. G. H. Lammertink, S. Schlautmann, G. A. J. Besselink and R. B. M. Schasfoort, *Anal. Chem.*, 2004, **76**, 3018.
- 8 S. Fiedler, S. G. Shirley, T. Schnelle and G. Fuhr, *Anal. Chem.*, 1998, **70**, 1909.
- 9 B. H. Lapizco-Encinas, B. A. Simmons, E. B. Cummings and Y. Fintschenko, *Anal. Chem.*, 2004, **76**, 1571.
- 10 J. Lee, H. Moon, J. Fowler, T. Schoellhammer and C. J. Kim, *Sens. Actuators, A—Physical*, 2002, **95**, 259.
- 11 R. B. M. Schasfoort, S. Schlautmann, L. Hendrikse and A. van den Berg, *Science*, 1999, **286**, 942.
- 12 T. Thorsen, S. J. Maerkl and S. R. Quake, *Science*, 2002, **298**, 580.
- 13 D. R. Reyes, D. Iossifidis, P. A. Auroux and A. Manz, *Anal. Chem.*, 2002, **74**, 2623.
- 14 P. A. Auroux, D. Iossifidis, D. R. Reyes and A. Manz, *Anal. Chem.*, 2002, **74**, 2637.
- 15 T. T. Veenstra, T. S. J. Lammerink, M. C. Elwenspoek and A. van den Berg, *J. Micromech. Microeng.*, 1999, **9**, 199.
- 16 B. H. Weigl, J. Kriebel, K. J. Mayes, T. Bui and P. Yager, *Microchim. Acta*, 1999, **131**, 75.
- 17 S. Hardt, W. Ehrfeld, V. Hessel and K. M. Van den Bussche, *Chem. Eng. Commun.*, 2003, **190**, 540.
- 18 S. W. P. Turner, M. Cabodi and H. G. Craighead, *Phys. Rev. Lett.*, 2002, **88**, 128103.
- 19 O. B. Bakajin, T. A. J. Duke, C. F. Chou, S. S. Chan, R. H. Austin and E. C. Cox, *Phys. Rev. Lett.*, 1998, **80**, 2737.
- 20 C. Lee, E. H. Yang, N. V. Myung and T. George, *Nano Lett.*, 2003, **3**, 1339.
- 21 J. O. Tegenfeldt, C. Prinz, H. Cao, R. L. Huang, R. H. Austin, S. Y. Chao, E. C. Cox and J. C. Sturm, *Anal. Bioanal. Chem.*, 2004, **378**, 1678.

- 22 W. Li, J. O. Tegenfeldt, L. Chen, R. H. Austin, S. Y. Chou, P. A. Kohl, J. Krotine and J. C. Sturm, *Nanotechnology*, 2003, **14**, 578.
- 23 L. J. Guo, X. Cheng and C.-F. Chou, *Nano Lett.*, 2004, **4**, 69.
- 24 H. G. Craighead, *Science*, 2000, **290**, 1532.
- 25 G. M. Whitesides and J. C. Love, *Sci. Am.*, 2001, 39** This paper gives a very readable overview of some top-down and bottom-up approaches for micro- and nano-machining., September.
- 26 H. V. Jansen, N. R. Tas and J. W. Berenschot, *Encyclopedia of Nanoscience and Nanotechnology*, ed. H. S. Nalwa, 2004, vol. 5, p. 163** This paper is an excellent and detailed overview of all micromachining techniques available up to now.
- 27 P. Mela, N. R. Tas, A. van den Berg and J. E. ten Elshof, *Encyclopedia of Nanoscience and Nanotechnology*, 2004, ed. H. S. Nalwa, vol. 6, 739** The paper summarizes some technologies used in nanofluidics.
- 28 J. Haneveld, H. Jansen, E. Berenschot, N. Tar and M. Elwenspoek, *J. Micromech. Microeng.*, 2003, **13**, S62.
- 29 M. Alexe, C. Harnagea and D. Hesse, *J. Electroceram.*, 2004, **12**, 69.
- 30 H. N. Chapman *et al.*, *J. Vac. Sci. Technol. B*, 2001, **19**, 2389.
- 31 P. Nauellau *et al.*, *J. Vac. Sci. Technol. B*, 2002, **20**, 2829.
- 32 L. C. Campbell, M. J. Wilkinson, A. Manz, P. Camilleri and C. J. Humphreys, *Lab Chip*, 2004, **4**, 225.
- 33 G. Urban, *Sens. Actuators*, 1999, **74**, 219.
- 34 H. Chang, *J. Vac. Sci. Technol.*, 1975, **12**, 1271.
- 35 G. Rijnders, G. Koster, V. Leca, D. H. A. Blank and H. Rogalla, *Appl. Surf. Sci.*, 2000, **168**, 223.
- 36 G. Koster, G. Rijnders, D. H. A. Blank and H. Rogalla, *Appl. Phys. Lett.*, 1999, **74**, 3729* The paper introduces the layer-by-layer growth method by interval pulsed-laser deposition as a controlled way for thin film growth, with a thickness in the order of a (few) unit cell(s).
- 37 M. J. O'Brien II, P. Bisong, L. K. Ista, E. M. Rabinovich, A. L. Garcia, S. S. Sibett, G. P. Lopez and R. Brueck, *J. Vac. Sci. Technol. B*, 2003, **21**, 2941.
- 38 M. Müllenborn, H. Dirac and J. W. Petersen, *Appl. Surf. Sci.*, 1995, **86**, 568.
- 39 M. S. Amer, L. Dosser, S. LeClair and J. F. Maguire, *Appl. Surf. Sci.*, 2002, **187**, 291.
- 40 T. Junno, K. Deppert, L. Montelius and L. Samuelson, *Appl. Phys. Lett.*, 1995, **66**, 3627.
- 41 D. M. Eigler and E. K. Schweizer, *Nature*, 1990, **344**, 524.
- 42 M. Park, C. Harrison, P. M. Chaikin, R. A. Register and D. H. Adamson, *Science*, 1997, **276**, 1401.
- 43 K. W. Guarini, C. T. Black, K. R. Milkove and R. L. Sandstrom, *J. Vac. Sci. Technol. B*, 2001, **19**, 2748.
- 44 M. Lazzari and M. A. Lopez-Quintela, *Adv. Mater.*, 2003, **15**, 1583.
- 45 K. W. Guarini, C. T. Black, Y. Zhang, H. Kim, E. M. Sikorski and I. V. Babich, *J. Vac. Sci. Technol. B*, 2002, **20**, 2788.
- 46 S. O. Kim, H. H. Solak, M. P. Stoykovich, N. J. Ferrier, J. J. de Pablo and P. F. Nealy, *Nature*, 2003, **424**, 411.
- 47 M. J. Madou, *Fundamentals of Microfabrication*, 1997, CRC Press LLC.
- 48 H. Cao, Z. Yu, J. Wang, J. O. Tegenfeldt, R. H. Austin, E. Chen, W. Wu and S. Y. Chou, *Appl. Phys. Lett.*, 2002, **81**, 174.
- 49 S. A. Gajar and M. W. Geis, *J. Electrochem. Soc.*, 1992, **139**, 2883.
- 50 S. W. P. Turner, A. M. Perez, A. Lopez and H. G. Craighead, *J. Vac. Sci. Technol. B*, 1998, **16**, 3835.
- 51 C. K. Harnett, G. W. Coates and H. G. Craighead, *J. Vac. Sci. Technol. B*, 2001, **19**, 2842.
- 52 N. R. Tas, J. W. Berenschot, P. Mela, H. V. Jansen, M. Elwenspoek and A. van den Berg, *Nano Lett.*, 2002, **2**, 1031.
- 53 J. C. T. Eijkel, J. Bomer, N. R. Tas and A. van den Berg, *Lab Chip*, 2004, **4**, 161.
- 54 M. Hasegawa and K. Horie, *Progr. Polym. Sci.*, 2001, **26**, 259.
- 55 J. L. Wilbur, A. Kumar, E. Kim and G. M. Whitesides, *Adv. Mater.*, 1994, **6**, 600.
- 56 E. Kim, Y. N. Xia and G. M. Whitesides, *J. Am. Chem. Soc.*, 1996, **118**, 5722.
- 57 S. Johnson *et al.*, *J. Photopolymer Sci. Technol.*, 2004, **17**, 417.
- 58 M. Colburn, A. Grot, B. J. Choi, M. Amistoso, T. Bailey, S. V. Sreenivasan, J. G. Ekerdt and C. Grant Willson, *J. Vac. Sci. Technol. B*, 2001, **19**, 2162.
- 59 S. Y. Chou, P. R. Krauss and P. J. Renstrom, *Science*, 1996, **272**, 85.
- 60 S. Y. Chou, P. R. Krauss, W. Zhang, L. Guo and L. Zhuang, *J. Vac. Sci. Technol. B*, 1997, **15**, 2897.
- 61 C. X. Cheng and L. J. Guo, *Microelectron. Eng.*, 2004, **71**, 288.
- 62 B. Ilic, D. Czapslewski, M. Zalalutidinov, B. Schmidt and H. G. Craighead, *J. Vac. Sci. Technol. B*, 2002, **20**, 2459.
- 63 S. Fernandez-Lopez *et al.*, *Nature*, 2001, **412**, 452.
- 64 S. H. Bossmann, K. Janik, M. R. Pokhrel, C. Heinz and M. Niederweis, *Surf. Interface Anal.*, 2004, **36**, 127.
- 65 P. Demontis, G. Stara and G. B. Suffritti, *J. Chem. Phys.*, 2004, **120**, 9233.
- 66 T. Kyotani, T. Nagai, S. Inoue and A. Tomita, *Chem. Mater.*, 1997, **9**, 609.
- 67 R. Karlsson, M. Karlsson, A. Karlsson, A.-S. Cans, J. Bergenholtz, B. Åkerman, A. G. Ewing, M. Voinova and O. Orwar, *Langmuir*, 2002, **18**, 4186.
- 68 M. Karlsson, K. Scott, A.-S. Cans, A. Karlsson, R. Karlsson and O. Orwar, *Langmuir*, 2001, **17**, 6754; A. Karlsson, M. Karlsson, R. Karlsson, K. Scott, A. Lundquist, M. Tokarz and O. Orwar, *Anal. Chem.*, 2003, **75**, 2529; www.orwarlab.mc2.chalmers.se.
- 69 J. Hurtig, M. Karlsson and O. Orwar, *Langmuir*, 2004, **20**, 5637.
- 70 H. Dai, *Surf. Sci.*, 2002, **500**, 218.
- 71 H. Shimoda, S. J. Oh, H. Z. Geng, R. J. Walker, X. B. Zhang, L. E. McNeil and O. Zhou, *Adv. Mater.*, 2002, **14**, 899.
- 72 A. E. Zhukov, A. R. Kovsh, V. M. Ustinov, D. A. Livshits, P. S. Kop'ev, Z. I. Alferov, N. N. Ledentsov and D. Bimberg, *Mater. Sci. Eng. B*, 2000, **74**, 70.
- 73 P. Zanardi and F. Rossi, *Phys. Rev. Lett.*, 1998, **81**, 4752.
- 74 A. Khitun, A. Balandin, J. L. Liu and K. L. Wang, *Superlattices Microstruct.*, 2001, **30**, 1.
- 75 E. L. Chandler, A. L. Smith, L. M. Burden, J. J. Kasianowicz and D. L. Burden, *Langmuir*, 2003, **20**, 898.
- 76 M. Akeson, D. Branton, J. J. Kasianowicz, E. Brandin and D. W. Deamer, *Biophys. J.*, 1999, **77**, 3227.
- 77 M. Foquet, J. Korlach, W. Zipfel, W. W. Webb and H. G. Craighead, *Anal. Chem.*, 2002, **74**, 1415.
- 78 A. Hibara, T. Saito, H.-B. Kim, M. Tokeshi, T. Ooi, M. Nakao and T. Kitamori, *Anal. Chem.*, 2002, **74**, 6170.
- 79 C. Papadopoulos, B. H. Chang, A. J. Yin and J. M. Xu, *Int. J. Nanoscience*, 2002, **1**, 205.
- 80 E. J. Bae, W. B. Choi, K. S. Jeong, J. U. Chu, G. S. Park, S. Song and K. Yoo, *Adv. Mater.*, 2002, **14**, 277.