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Strategies to integrate porous layers in microfluidic devices

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Highlights

- An overview of strategies to integrate porous layers in microfluidic chips is given
- Wall coated, membranes, orderly and disorderly coated configurations are discussed
- Hurdles and challenges to integrate porous layers are discussed
- Emerging technologies and applications involving surfaced columns are discussed

1. Abstract

Miniaturization offers formidable opportunities to improve the performance of (bio-)analytical devices and microreactors. A crucial aspect, and for most applications also the largest hurdle, is the necessity to increase the specific surface area of at least part of the device. In the present review paper, some of the most widespread strategies to incorporate porous materials or to increase the surface area of a microfluidic device are discussed.

Keywords

review, porous layer, microreactor, surface enhancement, pillar array column, anodization

2. Introduction

The ‘infection’ of analytical, chemical and biological research fields with micro-precision technologies developed initially for the electronics industry presents unique opportunities in these fields. Most surprisingly, the integration of several chemical steps in a single chip remains to this day more a theoretical exercise. One of the profound reasons for this is the difficulty with process control to properly steer such a large number of simultaneous operations. The benefits regarding enhanced mass and heat transfer have however been indisputably exploited with great success in a number of killer applications. Process intensification has evolved into a mature branch from chemical engineering during the last two decades, aiming at more efficient processes, mostly (but not exclusively, e.g. also relying on novel process control methodologies) achieved through miniaturization of at least one critical component. For most chemical applications relying on some form of interaction with a channel wall (e.g. with a catalyst), the performance (conversion of reagents) scales with the available surface. For one of the

most powerful separation methods, i.e. chromatography, the presence of sufficient surface is crucial to avoid overloading and its concomitant negative impact on separation performance. The implementation of porous zones can however also increase the residence time distribution considerably, a drawback which is of less significance in microreactors but which can be overwhelming in analytical separations. The latter is especially pronounced when the material is deposited in a non-conformal fashion, resulting in unequal velocities at different zones of the channel. The achievement of perfect order is sometimes referred to as the Holy Grail of High Performance Liquid Chromatography (HPLC) [1], indicating the importance of this feature.

In spite of the limited role of the residence time distribution, uniform catalyst coatings nonetheless are critical in microreactors as they could induce hot zones with its accompanying side-effects such as the formation of side products or more dangerously runaways could be induced. Incorporating such a uniform catalyst coating starts with the ordered nature of its support structure, preferably a porous one. Membranes are another important class of surface enhancing materials, as they may lead to the emergence of some specific functions related to the creation of unequal environments at each side of the membrane, like e.g. combined reaction and extraction. In most cases the envisioned function performs best at a maximal pore density and minimal pore size, hence at maximized surface area, as mass fluxes and selectivity will then be maximized as well (see §4).

Similar like catalyst coatings in microreactors, microfluidic immunoassay chips are equipped with porous layers or support structures covered with antibodies to increase the contact surface [2]. Very challenging at the moment is the significantly improvement of the sensitivity [3] of these devices. The principle is based on the enzyme-linked immunosorbent assay (ELISA) protocol for the analysis of proteins. The detection itself is based on the antibody-antigen reaction and as a consequence the detection ability of immunoassay chips is strongly influenced by the surface density of the immobilized antibodies. One way to increase it is therefore the use of porous structures to increase the surface-to-volume ratio [4, 5].

In the field of electroosmotic micropumps a porous section (e.g. packed capillaries [6] or a membrane [7]) is often incorporated, as it allows to overcome higher pressure differences (back pressures). The total flow rate achieved is the sum of the electroosmotic flow rate and the pressure driven flow rate, which flows in the opposite direction as the highest pressure is achieved after the pump. By decreasing the pore radius the electroosmotic flow contribution increases with respect to the pressure driven flow rate. When using multiple parallel flow channels

(e.g. a porous structure) a decrease of the total flow rate can be avoided, hence allowing a higher operational pressure drop. This is because the maximum backpressure only depends on the pore radius and increases with a decreasing pore radius. [8, 9].

When dealing with microfluidics the wetting properties of the channel walls can present a significant problem. For instance, in lab-on-a-chip devices when channel walls are not hydrophilic the introduction of aqueous solutions can be challenging. A similar problem occurs with respect to electro-osmotic flow, which can become unstable. Furthermore analytes can be adsorbed to the channel wall [10-11], which is undesirable. A modification of the wetting properties can be performed by roughening or by introducing porous surfaces.

In the present review, the paramount importance of specific surface area is discussed in view of some of the most relevant applications. Several existing methodologies to increase the specific surface area in channels and structures at the micron-scale (say, below 100 μm) are reviewed, without attempting to provide a complete overview of all available technologies.

3. Different channel configurations

Different approaches exist to increase the surface in a microfluidic device, which should be selected depending on the desired configuration (see Fig. 1).

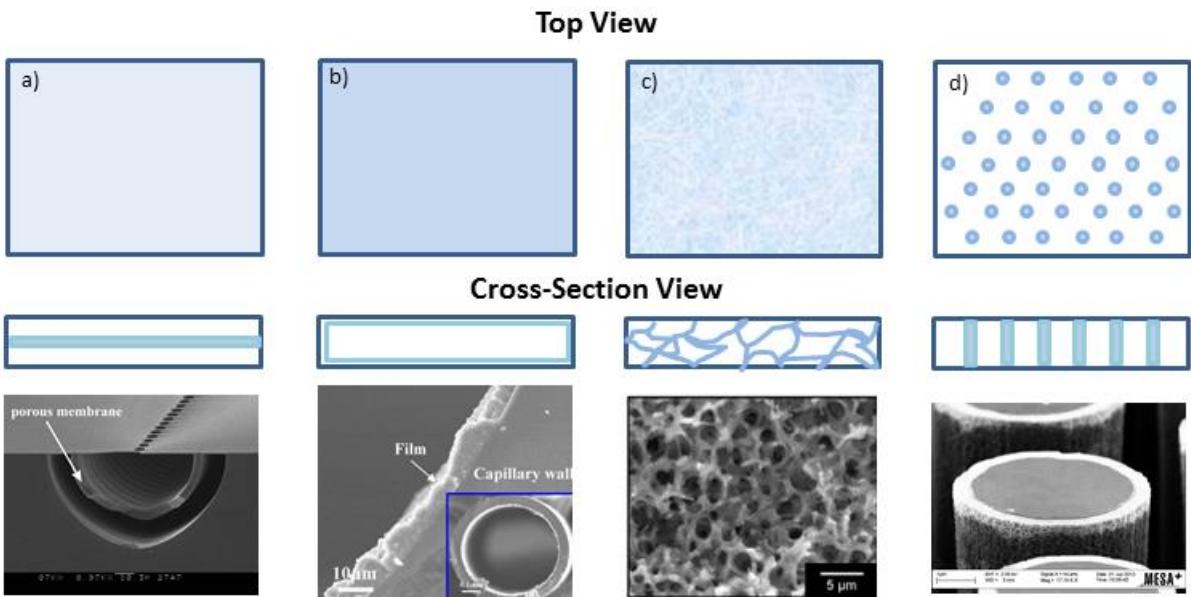


Fig. 1: Different approaches to insert porous layers: a) Membrane, b) Open tubular, c) Disordered support, d) Ordered support.

Membrane operations (Fig 1a) constitute an important branch of applications for microfabrication technologies.

Traditional membranes have been produced commercially since the 1920s and are currently employed in numerous applications, constituting a \$ 9 billion market in 2008 [12]. Most operation modes and applications are aiming at separation (hemodialysis, reverse osmosis, ultrafiltration, microfiltration) and require large amounts of membranes, making the price often the deciding criterion in the selection of membranes. More complex operations have also been described with microreactors in a wide variety of applications [13].

The open tubular approach (Fig 1b) offers the lowest pressure drop, but is limited in achievable surface.

Nonetheless it is applicable for most of the techniques discussed here. For many applications some additional contact surface area is usually required. Packed columns (Fig 1c) have been the preferred format since decades, because of the versatile fabrication protocols that can be applied. After fabrication under optimized conditions, it is quite straightforward to pack them into a closed tube or chip, making packed columns well suited for e.g. for catalyst screening. Pressure drop and preferential flow paths are however important disadvantages for this format. To overcome this, structured packings (Fig 1d) are being studied intensively by several groups, in an attempt to minimize these disadvantages through their high order [14]. Pillar array columns produced for

analytical and reaction purposes have been produced in fused silica and silicon by etching, but also alternative methods such as imprinting (of cyclic olefin copolymer) [15] and UV curing (SU-8) [16] have been applied as well.

The integration of such porous layers can either be performed prior to sealing, e.g. by clamping a membrane or anodization (see §5) or the porous layers can be integrated or grown in situ after chip sealing has been performed. Washcoating is a technique that is more suitable to introduce a porous layer in microchannels after closure instead of before, as bonding can become difficult when rough surfaces are present. An example of washcoated material is Al_2O_3 , which can be used as support layer for catalyst particles [17] also monoliths can be introduced after sealing or bonding [18]. Monoliths have been intensively employed as support structure for catalysts as well as for HPLC and can either be ordered or disordered (Fig 1c,d) depending on the fabrication conditions. The most important classes of monoliths are polymeric or silica based. The latter is the most relevant one for analytical applications, and the in-situ sol-gel synthesis process using silicon alkoxides is best known and most frequently applied. The synthesis of this type is achieved by a concurrence of phase separation and sol-gel transition. Silicon alkoxides are first fully hydrolyzed, subsequently followed by a polycondensation reaction, thereby forming siloxane oligomers. During this reaction a spinodal decomposition occurs, which is in fact a phase separation between the solvent phase and the oligomer rich phase due to an unfavorable thermodynamic situation that occurs driven by the polycondensation reaction. One of the main advantages of monoliths is that their permeability can be relatively easily tuned. Unfortunately, the axial dispersion or backmixing follows an opposite trend. However, in the presence of microstructures, this problem can be overcome (see §6). Concerning the problem of axial dispersion, attention should be paid to the necessity to bond the porous polymeric monolith to the channel walls [19]. When no pre-treatment step is performed, the monolith will easily detach from the surface wall due to shrinkage during polymerization and drying, creating large voids increasing dispersion dramatically. Grafting is the preferred choice of pre-treatment as a dramatic improvement in adhesion of the monolith is achieved.

An important driver for miniaturization in flow-devices is the possibility to reduce dispersion. By reducing the dimension of a channel, the time that molecules can travel on flow lines with large differences in velocity is reduced. An equivalent effect is achieved by positioning obstacles inside the channels, which has the additional advantage that a much larger cross section can be maintained, allowing to handle much larger flow rates. The

result is in both approaches that a set of molecules that enters the fluidic channel will substantially move through the channel as a single plug, with a minimal residence time distribution.

For the incorporation of porous layers, either in a membrane, open tubular, disordered or ordered support lay-out, different techniques can be applied, ranging from membrane fabrication, electrochemical anodization, sol-gel, zeolite production and deposition processes to etching techniques and plasma processes. These techniques will be discussed throughout the rest of this review.

4. Membrane fabrication

For the production of polymeric membranes, a number of techniques are being used such as extrusion of melted polymer, formation at the interface of two immiscible liquids containing each a monomer, sintering, stretching, template leaching, casting and phase inversion, which is by far the most popular technique [12]. In this approach, the phase separation of a homogeneous polymer solution is induced by a temperature change, solvent evaporation or immersion in a non-solvent such that a solid porous film is obtained. When membranes with a high chemical resistance are needed, PTFE is often a well suited material. By casting and subsequently evaporating the solvent thin porous films can be formed [20]. Alternatively a coating can be applied as well [21]. Commercially available membranes (e.g., cellulose acetate, glass fiber, and polytetrafluoroethylene (PTFE) filters) made with organic or inorganic materials contain a random network of pores with a wide distribution of pore sizes. When narrow pore size distributions are required for instance to enlarge the selectivity, track-etching is generally preferred. A non-porous polymeric film (e.g. polycarbonate, polyimide and polystyrene) is irradiated with ions and subsequently etched to create pores of 0.02 – 10 µm [22]. A downside of this approach is the low porosity, mostly smaller than 10 %, to keep the probability of pore overlapping low, as it increases with increasing porosity. As the mass flux is inversely proportional to the membrane thickness, asymmetric or composite membranes are often preferred. In asymmetric membranes, a thin layer with narrow pores is deposited onto a support with macropores, still yielding a sufficient mechanical strength and a satisfactory flux. Since the 1990s, micro- and nanomachining techniques have been employed to fabricate membranes. The need for low flow resistances, combined with very uniform pore sizes, led to a number of novel techniques. Considerable efforts have also been devoted to the development of silicon nitride membranes. Various techniques such as block-copolymer-assisted lithography,

nanosphere lithography, electron beam (E-beam) lithography, deep-ultraviolet lithography, focused ion beam (FIB), track-etching and thermal imprint lithography have been employed by different researchers to define sub-micrometer holes (down to 10 nm) in thin nitride films. SiN membranes deposited by low pressure chemical vapor deposition (LPCVD) as thin as [23-27] 1 μm could be fabricated after lithography and etching. With the need for sub-micron structures, laser interference lithography has been frequently applied by the University of Twente and the Dutch company Aquamarijn. Due to the relatively simple periodic structures (orifices and slits) that are needed, with no critical alignment step, the technique is well suited for the production of microsieves, even on non-planar surfaces. Using similar etching techniques to create stamps of regular pillar arrays, also polymeric membranes can be fabricated via hot embossing or other molding processes [23, 28-30]. Defining μm sized pillars in photoresist using lithographic techniques, the emerging voids can be filled with metals such as nickel using electroplating [31]. The substrate with the patterned photoresist is submerged into a solution of the desired metal specie and a current is applied, resulting in the deposition of a smooth metal layer. After removal of the photoresist, a metallic based membrane is obtained.

External fabrication automatically tends to lead to horizontal designs. As a result, manual handling of the membrane becomes inevitable. Growing membranes inside micro-patterned structures allows the formation of thin films without the need for handling supports. It also offers the possibility to align the membranes vertically. Hisamoto et al. [32] demonstrated the formation of a stable $\sim 10 \mu\text{m}$ thick membrane. Gargiuli et al. [33] studied the influence of the geometrical design on the in-situ formation of nylon 6.6 membranes. From the six different investigated designs, the classical Y-channel design came out as superior, as the entrance effect on the parallel flow is minimal. At the interface where the two monomers meet, the membrane is formed and its thickness can be elegantly varied by adjusting the reaction time [34]. To form micrometer-sized pores, Kim et al. [35] added poly(ethylene) glycol (PEG) which is incorporated into the nylon film during formation, by subsequently removing the PEG by dissolving in methanol a porous structure is obtained.

The ability to control single-molecule transport through nanopores offers limitless possibilities for the detection of biomolecules like DNA, RNA and proteins. By placing the nanopore membrane between two electrolytes and applying a voltage across it, individual molecules can be driven through the nanoscale pore while monitoring the change in ionic current [36]. This method can be applied to separate DNA molecules based on their lengths.

5. Electrochemical anodization

A particularly interesting method to introduce porous layers in Si substrates is electrochemical anodization. In this approach, electronic holes are generated and transported near the surface that is contacted with hydrofluoric acid (HF) selectively dissolving the silicon and leaving a porous structure behind. The technique can be employed in the membrane, open tubular and ordered support configuration.

The beauty of the technique is that the pore size is determined by the current density, which is easily varied. Other crucial parameters are the electrolyte type, the HF concentration, the doping type (n or p) and level and for n-type substrates the illumination configuration (back side vs. front side illumination) [37]. The required holes are already present in p-type silicon, whereas in n-type silicon the holes can be generated by illuminating the substrate with photons that have more energy than the band gap (1.1 eV). The holes are continuously forced to the surface throughout the process by applying a potential across the wafer.

By plotting the current versus the applied potential, a characteristic (I-V) curve is obtained for a certain substrate and HF concentration. Three regimes are distinguished: the cathodic range, the porous silicon range and the electropolishing range. The cathodic range is associated with a negative potential and this can only lead to the generation of holes in the case of n-type silicon.

The first zone of the I-V curve, i.e., the zone before the first peak, is associated with the formation of porous silicon (PS). This zone is divided in the microporous zone (pore sizes below 2 nm) and the mesoporous zone (pore sizes between 2 and 50 nm). In the electropolishing range (2nd zone in I-V curve), the current exceeds the critical current density and the surface is smoothed. For a given HF concentration, the porosity increases with increasing current density. For a fixed current density the porosity decreases with increasing HF concentration. The internal surface of PS layers varies from about 200 to 600 m² / cm³ depending on the dopant level of the substrate. Increasing the current density under the same conditions also increases the pore radius size [38]. The separation between the pores is always less than the depletion layer thickness. Because the resistivity of the depleted silicon is several orders of magnitude smaller than that of the bulk material, only the existing pores will be further etched at their porous silicon/silicon surface (at the bottom of the pores) [39]. In general, the created

pores follow the direction of the electrical field lines, but the crystallographic faces can induce (local) deviations of the propagation direction [40].

There are two ways to incorporate a pattern of porous silicon. In a first approach, silicon areas that should not become porous can be masked by a material that is not (intensively) attacked by HF, such as e.g. SiN. An alternative approach consists in etching the already formed layers after an additional masking step.

However, during the patterning of these layers using reactive ion etching, the dimensions of the patterned features change during etching and also considerable tapering occurs [41, 42]. This happens because the etching gasses diffuse into the meso-pores. Since the top of the pillars is inevitably longer subjected to the etching plasma, pillars with a smaller top than bottom cross-section can be obtained. This makes the technique not suitable to generate pillars with a high degree of verticality, as is required for e.g. most demanding chromatography applications.

Similar like silicon, aluminum can be anodized as well into porous layers for microfluidic applications. Oxalic acid is then used instead of hydrofluoric acid. For example, Park et al. [43] used photoresist to create such patterned porous aluminum channels. Alternatively, patterned pillars have been constructed by Vorobyova et al. [44] using anodization. Using a SiO_2 mask local selective anodization can be achieved with near vertical anodized interfaces. Optionally, these anodized aluminum layers can be selectively removed in a next step, forming high-aspect-ratio structures [45]. Anodization was already used by several groups for a number of applications. Pioneering work was performed by the group of Thomas Laurell in the context of immobilized enzyme reactors [46]. The conversion of massive silicon to porous silicon increased the surface area, which enabled a larger density of immobilized trypsin, thereby increasing the turnover rate of a peptide by a factor of 350 [47]. The group of Klavs Jنسن designed and fabricated a microfluidic device containing porous pillars upon which a catalyst was deposited. The channel was sealed by anodic bonding of the silicon substrate to a Pyrex substrate. In order to stabilize the porous silicon, a thermal oxidation step was performed prior to bonding [48]. A drawback of this procedure is that the porosity decreases due to a volume expansion of the pore walls during oxidation. Thermal oxidation was also performed by Sukas et al. [49], who produced very thick layers of insulating (partly porous) SiO_2 . Because their device was intended for capillary electrochromatography (CEC), generally requiring

large voltages (voltages up to 20 kV are applied in this analytical technique), an insulating layer had to be applied in the vicinity of the channel walls to avoid electrical shortcuts through the channel substrate.

During the last decade, our group theoretically studied and developed technology for pressure-driven liquid chromatography in pillar array columns [50], mainly aiming at very demanding separations of complex samples. The achievement of a large uniformity of the layers on the wafer scale level [51], as well as locally on an individual pillar level, is vital to produce the high required separation efficiencies. The anodization approach proved to be excellently suited to achieve these high efficiencies.

Dispersion should be as small as possible in chromatography, in order to not wipe out the separation that is achieved by the different degree of retention the different analyte types experience when they get in contact with the stationary phase. Even though a selective retention effect can in theory be achieved using non-porous structures at low analyte concentrations, the surface area of stationary phases that is required for practical applications is much larger (typically a factor of 10-400 larger). A major challenge here is to maintain the order on the one hand, and simultaneously keep the final dimensions of the structures close to the designed dimensions on the other hand. Anodization is a unique technique that can address both requirements, because it induces pores growing towards the inside of the support structures, leaving the position of the original external boundary unaltered, though perforated. This is illustrated in Fig. 2a. In the context of shear-driven chromatography, which is performed by sliding a cover substrate over a nanochannel (forming an open tubular channel when assembled) [52], anodization was used to increase the interaction surface mainly at the bottom at the separation channel [53].

Another great feature of anodization is the additional degree of freedom introduced by the involved electrical current. By varying the current, another anodization regime can be reached, allowing an alternation between either etching the entire surface or solely defining pores. This is exemplified in Fig. 2b, where this alternating method was used to make walled porous channels.

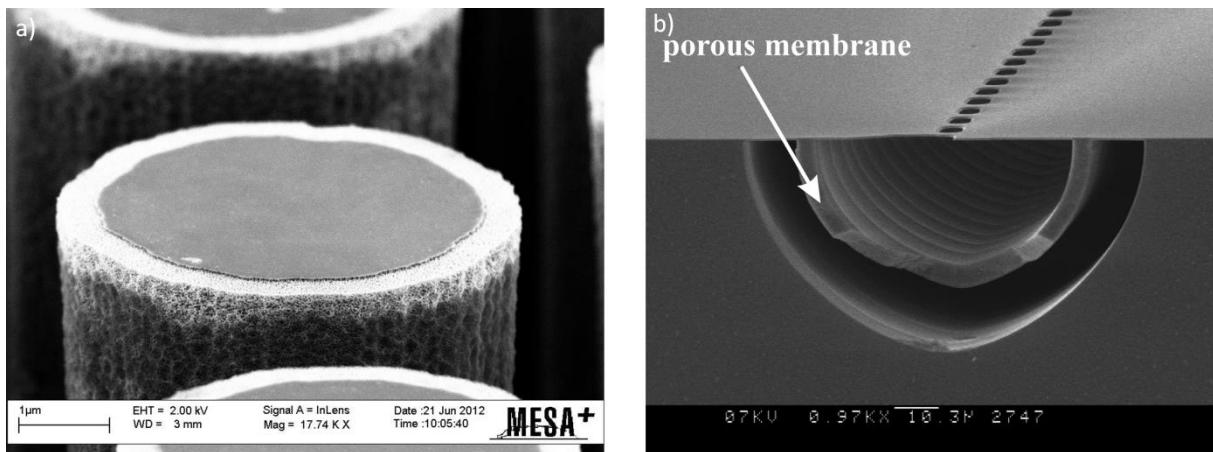


Fig. 2 a) Anodized Si pillar arrays. Reproduced from Analyst 139/3, Callewaert M., Op De Beeck J., Maeno K., Sukas S., Thienpont H., Ottevaere H., Gardeniers H., Desmet G., De Malsche W., Integration of uniform porous shell layers in very long pillar array columns using electrochemical anodization for liquid chromatography, 618-625, 2014, with permission from The Royal Society of Chemistry. **b)** Multi-walled Si membranes with anodized nanopores. © 2014 IEEE. Reprinted, with permission, from Tjerkstra R.W., Gardeniers J.G.E., Kelly J.J., van den Berg A., Multi-Walled Microchannels: Free-Standing Porous Silicon Membranes for Use in μTAS, Journal of Microelectromechanical Systems 9/4, 2000, 495-501.

6. Sol-gel deposition

Sol-gel deposition is a technique that is used to fabricate silica based monoliths, which are porous structures which can be either disordered or ordered in nature (Fig 1c, d). When these packing materials are disordered the efficiency (or the extent by which plug-flow is obtained) is limited in monolithic columns (as well as in packed beds). In an attempt to increase the order of a monolithic packing, Detobel et al. [54] grew silica monolithic material in the presence of (ordered) pillar arrays. Intriguingly they could, depending on the conditions, distinguish 3 regimes: disorder, 2D order and 3D order.

The formed structures were to a large extent nearly exclusively determined by the ratio between the bulk domain size of the monolith on the one hand and the distance between the micro-pillars on the other hand. When this ratio is small, the presence of the pillars nearly has an effect on the morphology of the produced monoliths. However, when the ratio approaches unity and ascends above it, some new types of monolith morphologies are induced, two of which appear to have interesting properties for use as novel chromatographic supports. One of

these structures (obtained when the domain size/inter-pillar distance ratio is around unity) is a 3D network of linear interconnections between the pillars, organized such that all skeleton branches are perpendicular oriented to the micro-pillar surface. A second interesting structure is obtained at even higher values of the domain size/inter-pillar distance ratio. In this case, each individual micro-pillar is uniformly coated with a mesoporous shell (See Fig. 3). The excellent stability and uniformity was also demonstrated by the repeatable and high pressure separation (operated at 350 bar) of a protein digest with a commercial HPLC [55].

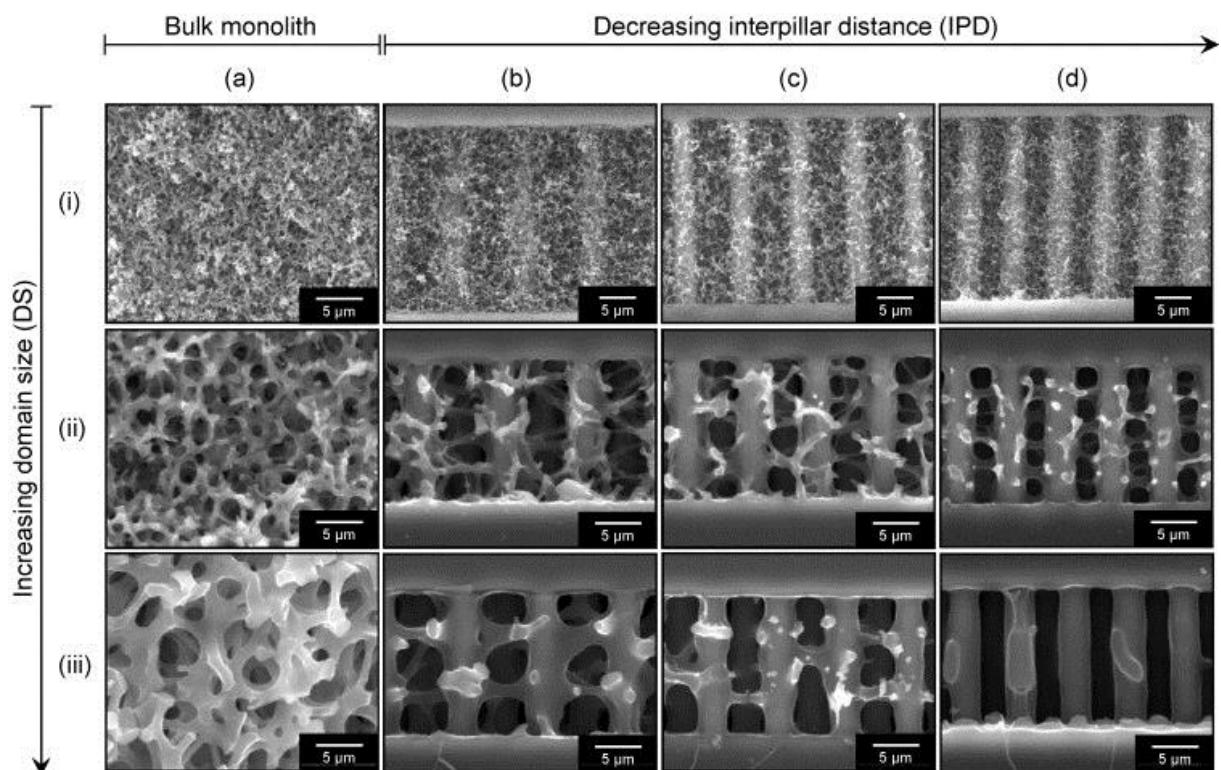


Fig. 3: SEM-images of methyltrimethoxysilane(MTMS)-based gel structures, derived from three different compositions, molar ratio (MTMS:MeOH:H₂O): (i) 1:1:2, (ii) 1:1.15:2 and (iii) 1:1.2:2. These silica gels were synthesized (a) under bulk conditions (yielding domain sizes of respectively 0.8, 3.2 and 7.0 μm) and inside micro-pillar array columns with an inter-pillar distance of (b) 7.6, (c) 5.6 and (d) 3.6 μm. Reprinted from Journal of Chromatography A, 1026/44, Detobel F., Eghbali H., De Bruyne S., Terryn H., Gardeniers H., Desmet G., Effect of the presence of an ordered micro-pillar array on the formation of silica monoliths, 7360-7367, Copyright (2014), with permission from Elsevier.

Besides during the fabrication of silica monoliths sol-gel deposition processes are also used for fabricating polymeric or ceramic monoliths. Younes-Metzler et al. [56] demonstrated the growth of an Al₂O₃ porous bed in a

microchannel using sol-gel deposition as a catalyst support. By impregnation of palladium(II)-acetylacetone and subsequently heating to 400°C in air metal oxide particles can be deposited on the Al₂O₃ porous bed for the partial oxidation of methane to CO and H₂.

A very straightforward way to incorporate monolithic material consists of first depositing a meso-porous material in a channel using one of the well-known sol-gel techniques [57, 58], subsequently followed by a patterning step using reactive ion etching. A drawback however is that the dimensions of the patterned features change significantly during etching and that also considerable tapering occurs [42, 59]. This happens because the etching gasses diffuse into the meso-pores. Since the top of the structures that are formed is inevitably longer subjected to the etching plasma, the cross-section of the created through-pores is at the bottom inevitably smaller than at the top. This is highly undesirable when high efficiency separations are envisioned, requiring a minimal degree of dispersion.

7. Zeolites and metal organic frameworks (MOFs)

Zeolites are mesoporous aluminosilicate molecular sieves. They are widely used in diverse applications such as adsorption, ion exchange beds, water purification and softening. Zeolites have recently been incorporated in microfluidic devices in numerous fields: separation, catalysis, sensors and anti-corrosion coatings. Inside the cages, metal ions can be trapped, yielding active catalysts. Due to their high thermal stability, elevated temperatures do not pose a problem and with the gained experience over the years, zeolites can be grown in a very controlled manner on a range of different substrates and in all the configurations distinguished in Fig. 1.

Rebrov et al. [60] e.g. deposited a single layer zeolite ZSM-5 crystals with a layer thickness as thin as 1 µm in semi-circular stainless steel channels with a diameter of 500 µm and subsequently studied the influence of different coating parameters. The reduction of NO to N₂ was demonstrated reaching reaction rates of 0.194 $\frac{\mu\text{mol}_{\text{NO}}}{\text{s} * \text{g}_{\text{catalyst}}}$. Zhang et al. [61] coated a quartz capillary tube of 500 µm inner diameter and 200 mm long with a NaX zeolite (see Fig. 4). Depending on the synthesis time, different uniform layer thicknesses are formed, i.e. 7 µm after 6 h and 15 µm after 10 h. By ion exchange, catalytically active CsNaX was obtained for the Knoevengel condensation reaction between benzaldehyde and ethyl cyanoacetate. Near complete benzaldehyde conversion

was reached after 30 min of residence time. The use of an ionic liquid to absorb water and prevent catalyst poisoning resulted in a stable conversion for over 50 h.

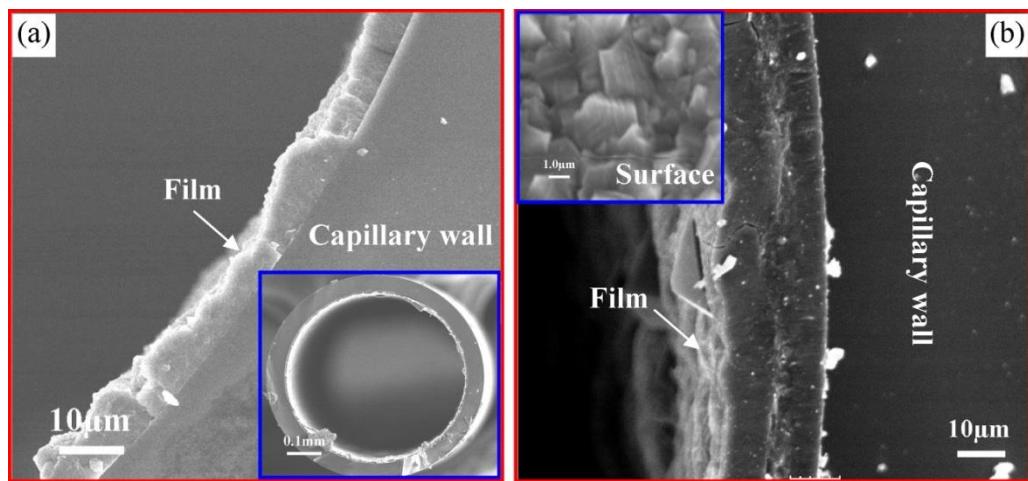


Fig. 4: SEM images of the cross-sections of zeolite capillary microreactor prepared by flow synthesis method after (a) 6 and (b) 10h of zeolite regrowth. Reprinted from *Catalysis Today* 193/1, Zhang G.C., Zhang X.F., Lv, J., Liu H.O., Qiu J.S., Yeung K.L., Zeolite capillary microreactor by flow synthesis method, 221-225, Copyright (2014), with permission from Elsevier.

Using a stack of micro-corrugated foils forming a microreactor as support Pérez et al. [62] deposited a mordenite zeolite film of 1 μm to 12 μm with synthesis times of respectively 3 and 24 h. By ion exchange and impregnation Cu and Ce was deposited onto the film making it catalytically active for the oxidation of CO.

Zhang et al. [63] deposited a 100 nm thin layer of ZIF-8 onto magnetic Fe₃O₄ microspheres. Coiling a stainless steel capillary with an internal diameter of 580 μm around a magnet fixates the coated microspheres against the wall of the capillary, preventing them from bleeding out holding the catalyst inside the microreactor. Using this microreactor set-up, a Knoevenagel reaction between benzaldehyde and ethyl cyanoacetate was conducted, resulting in a conversion of 99.1 %, which however dropped to 65.9 % after 24 h. Similar to the zeolite film deposition, Van Assche et al. [64] deposited electrochemically a Cu-BTC single crystal thick metal organic framework (MOF) layer with an average thickness ranging from 5 to 15 μm onto a milled microchannel in copper (see Fig. 5). By means of breakthrough experiments methanol could be separated from n-hexane.

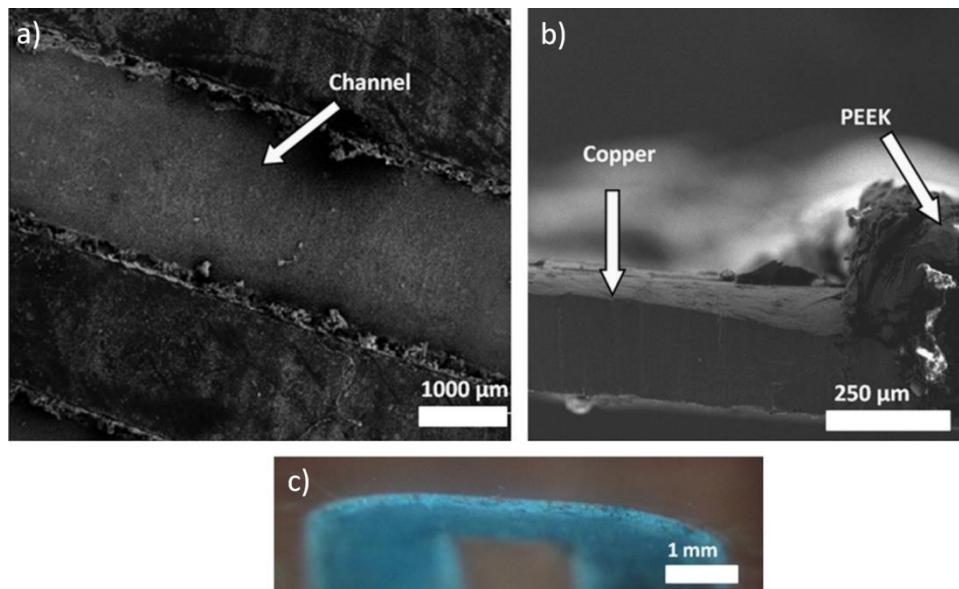


Fig. 5: Top and side views of MOF coated microchannels. The microchannels are formed by a copper base plate and an adhesive PEEK layer (height 180-240 μm) forming the channels and ensuring sealing upon clamping with a top substrate. During electrochemical synthesis the exposed copper surface is coated with MOFs a) Top view channel. b) Side view channel. c) Coated channel. Reprinted from Chemical Engineering Science, 95/24, Van Assche T.R.C., Denayer J.F.M., Fabrication and separation performance evaluation of a metal-organic framework based microseparator device, 65-72, Copyright (2014), with permission from Elsevier.

Having an extremely narrow pore size range, zeolites have a high permeability selectivity, making them very appealing to construct membranes from [65]. However, to maintain their selectivity, defect free membranes are required, rendering this approach very challenging as often very large surfaces are needed. Also the thickness is often a bottleneck, given the intimate relation between flux and membrane thickness. By miniaturizing and foreseeing supports, cracks and other defects can however be reduced to a minimum. Lai et al. [66] studied the influence of selective water removal on the Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate by growing a hydrophilic ZSM-5 zeolite membrane on the back of a porous stainless steel microreactor. The channels of 300 μm x 600 μm on the front were coated with CsNaX zeolite as catalyst. Compared with a packed bed membrane reactor where the zeolite is grown on a porous α -alumina tube, the microreactor reached a product yield of 85 % whereas the packed bed microreactor reached only 45 %. Zhang et al. [67] used a similar design but used a NaA zeolite membrane instead and increased the conversion with 25 %

when water, a catalyst poison, was removed. Wan et al. [68] studied different deposition methods of zeolites including the formation of a free standing Silicate-1 membrane. A 16 μm thick film of $0.7 \times 4.8 \text{ mm}^2$ was formed.

Pérez et al. [69] increased the contact surface by growing 10 μm thick CuO-CeO₂ zeolite films onto brass microgrids (see Fig. 6). The microreactor was assembled by rolling the coated microgrid around a brass cylinder and inserting it in a glass tube and used for the oxidation of CO. The microgrid with 100 μm thick wires and 140 μm spaces in between ensured a proper flow regime. Complete conversion was reached at 175 °C instead of 300 °C without catalyst. Using ceramic foams as support, Zampieri et al. [70] achieved the same effect of increasing the contact surface without substantially increasing the pressure drop. They managed to deposit a silicalite-1 and ZSM-5 coating on a ceramic foam with an average cell size of 8 μm .

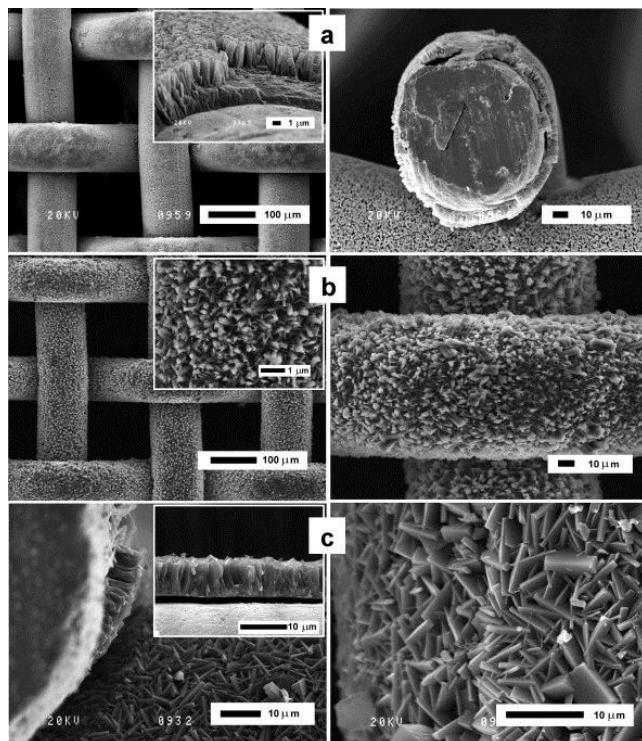


Fig 6: SEM of zeolite films synthesized onto brass microgrids for different gel dilution ratios ($\text{H}_2\text{O:SiO}_2$): (a) 70:1.15 with a planar microgrid; (b) 110:1.15 with a planar microgrid; (c) 70:1.15 with a U-shaped microgrid. Reprinted from Applied Catalysis B: Environmental, 129/17, Pérez N.C., Miro E.E., Zamaro J.M., Microreactors based on CuO-CeO₂/zeolite films synthesized onto brass microgrids for the oxidation of CO, 416-425, Copyright (2014), with permission from Elsevier.

8. Gas phase deposition processes

8.1. CNTs and CNFs

Carbon nanotubes (CNTs) are interesting support structures for the immobilization of catalysts due to their exceptional and unique physical properties such as large specific surface, chemical, mechanical and thermal stability. They typically come into the picture when metal oxide supports fail. Besides their role of bonding stabilizer, the support structure also influences the activity of the catalysts [71]. Yin et al. [72] demonstrated that CNTs are e.g. superior to Ru as catalyst for the generation of CO_x-free H₂ from ammonia over traditional support materials such as Al₂O₃, activated carbon, MgO, TiO₂, ZrO₂, ZrO₂-BD.

The formation of sub-millimeter channels for the subsequent incorporation of a ‘packing’ material such as CNTs, often requires expensive high-tech technologies such as lithography. Liu et al. [73] constructed a hybrid system in which 2 plates with respectively an inlet and an outlet are pressed respectively on each side against a densely grown layer of CNTs. In this way a nanoscopic porous bed is formed, demonstrating the most effective liquid-liquid mixing over a foam (strut diameter: 100 µm) or felt-like (microfilament diameter: 10 µm) structure. The high external surface area combined with the high tortuosity of the CNT packed structure leads to a high mixing degree, demonstrated by mixing water and toluene yielding droplet sizes of 35 µm. One could imagine that such a structure is well suited as catalyst support for liquid-liquid reactions. With a CNT surface, high surface-to-volume ratios are yielded, which makes the material well suited as catalyst carrier. By impregnation followed by a calcination step they can easily be deposited. The catalysts can furthermore also easily be recovered by simply burning the carbon skeleton. Besides catalyst support, CNTs can also be used as stationary phase for separations. Based on the fabrication, two distinct processes can be defined. The CNTs can be either formed externally and be incorporated as powder or they can alternatively be formed directly inside the microfluidic device. Powder CNTs were e.g. directly embedded into an organic polymer monolith by Li et al. [74], allowing the separation of small organic molecules with micro-HPLC, or packed in a glass column (ID: 0.3 cm) for gas chromatography [75]. To use CNTs into micro-patterned devices, in-situ growth is necessary. This is typically done by a deposition process, established by decomposing methane, ethane or acetylene at the surface at elevated temperatures in the presence of hydrogen. To improve the growth and the anchoring effectiveness, first

a layer of nickel particles is deposited. In this step, it is critical that the particles are uniformly deposited [76, 77]. By first etching a meandering 50 cm long, 100 µm wide and 90-100 µm deep channel and depositing metal particles, Stadermann et al. [78] grew CNTs by chemical vapor deposition onto the channel walls for gas chromatographic purposes. To increase the surface area and concomitantly the mass loadability and retention capacity, Fonverne et al. [79,80] (see Fig. 7) grew CNT layers onto etched micropillars for liquid chromatographic purposes, characterized by the separation of test mixtures. Wu et al. [81] grew CNTs in an etched silicon channel, with the CNTs vertically aligned to perform capillary electrochromatography. The device was used for the separation of dsDNA fragments.

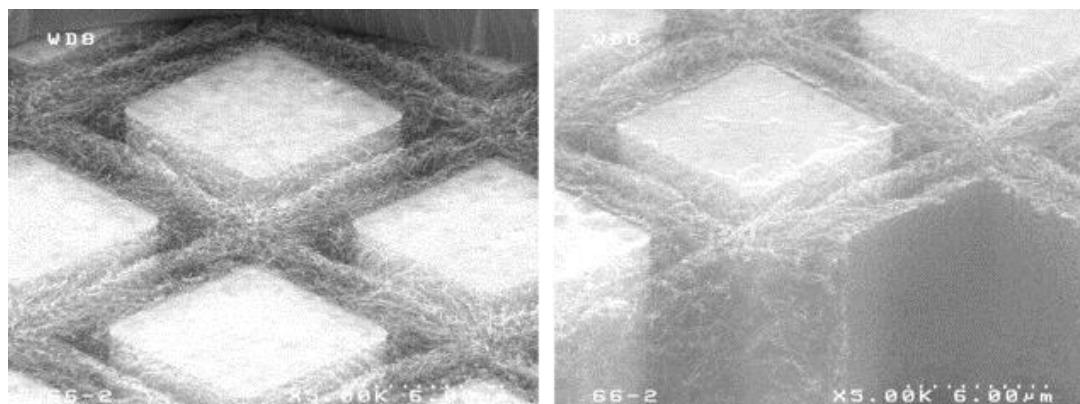


Fig. 7: SEM images of the micropillar array after the CNTs growth in a closed microsystem (700 °C, atmospheric pressure, 30 min, 50 nm of nickel on the plane surface). Reprinted from Sensors and Actuators A: Physical, 167/2, Fonverne A., Demesmay C., Ricoul F., Rouviere E., Dijon J., Vinet F., New carbon nanotubes growth process in a closed microfabricated channel for liquid chromatography application, 517-523, Copyright (2014), with permission from Elsevier.

The deposition of catalyst particles inside the pores of porous materials makes them only accessible by means of diffusion, resulting in poor mass transfer rates. Using carbon nanofibers (CNFs), the mass transfer can be increased, by enforcing flow around the fibers [82]. As CNFs are typically only a few µm long, depositing them only onto the channel wall would result in a low surface-to-volume ratio. Thakur et al. [82] (see Fig. 8) have grown them onto regularly ordered elongated hexagonal pillars, thereby enhancing the surface-to-volume ratio with a factor of 3 to 4.

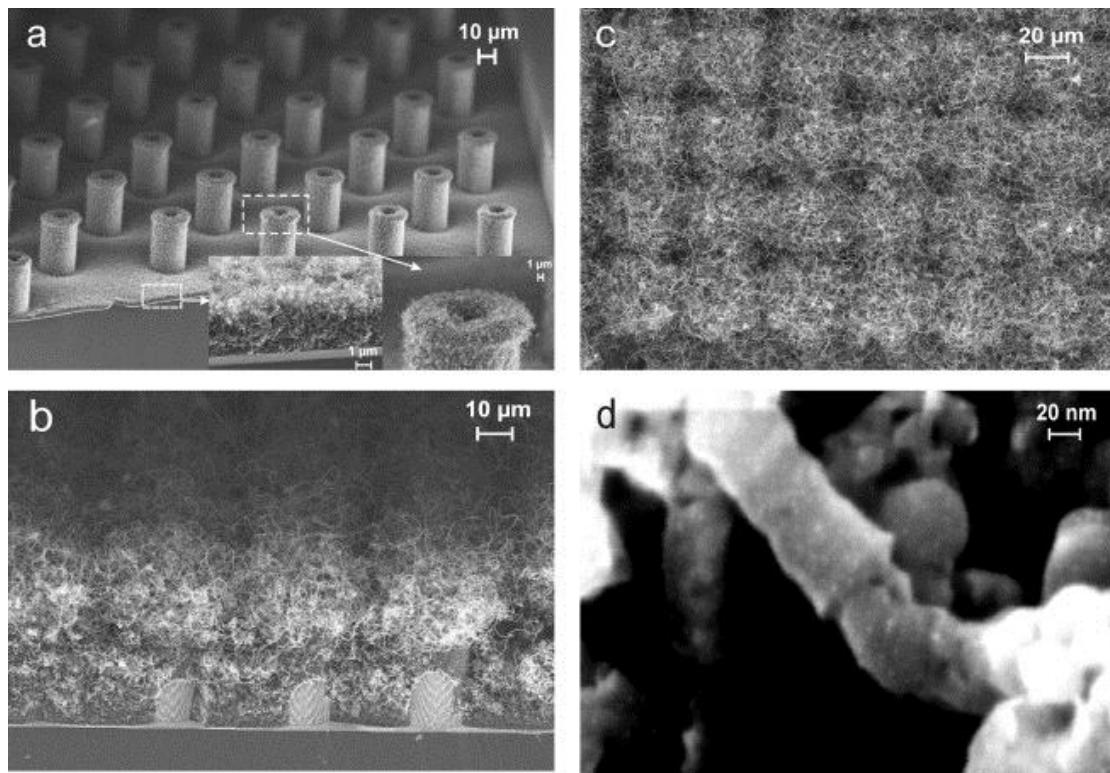


Fig. 8: SEM images of oxidized CNF layer in microchannel with array of cylinders: (a) 50 μm spacing between cylinders and 1h catalytic thermal chemical vapor deposition (C-TCVD) at 635 $^{\circ}\text{C}$ with C_2H_4 , (b) 20 μm spacing between cylinders and 10 min C-TCVD at 635 $^{\circ}\text{C}$ with $\text{H}_2/\text{C}_2\text{H}_4$, (c) top-view of CNF layers uniformly covering the microchannel, (d) HR-SEM image of well distributed homogeneous deposited Ru nanoparticles on CNFs in microchannel (after reduction). Reprinted from Applied Catalysis B: Environmental 102/1-2, Thakur D.B., Tiggelaar R.M., Hoang T.M.C., Gardeniers J.G.E., Lefferts L., Seshan K., Ruthenium catalyst on carbon nanofiber support layers for use in silicon-based structured microreactors, Part1: Preparation and characterization, 232-242, Copyright (2014), with permission from Elsevier.

8.2. Glancing angle deposition (GLAD)

Similar to CNFs, GLAD allows the formation of fibrous-like tentacles by vapor deposition onto a target substrate. A unique feature of GLAD is that the substrate is rotated during deposition, allowing for the formation of dedicated 3D-structures (see Fig. 9). Structures like helical columns or squared helixes can be formed with a resolution of less than 10 nm and this in a variety of materials (e.g. SiO_2 , Mn, Cu, Al, Cr, CaF_2). By decreasing the angle at which the vapor hits the substrate surface as a function of the time, a planar dense cap emerges at the top of the structures. These caps allow them to be used as a support for the deposition of additional thin layers. A reverse

approach, by forming a film first, was shown to enhance the adhesion to the substrate. As the pitches between the structures are comparable to the wavelength of visible light, optical activity is observed [83]. Using the GLAD technique, Zhou et al. [84] constructed organic photovoltaic cells which had a 3 fold larger power conversion efficiency compared to a reference cell. With GLAD, copper iodide nanocrystals were grown onto an indium-tin oxide coated glass substrate, which was subsequently coated with a layer of zinc phthalocyanine, forming the photovoltaic cell. In the reference cell, planar copper iodide instead of nanocrystal shaped was used. Due to the presence of the porous nanocrystal structure, light is converted more efficiently to electricity.

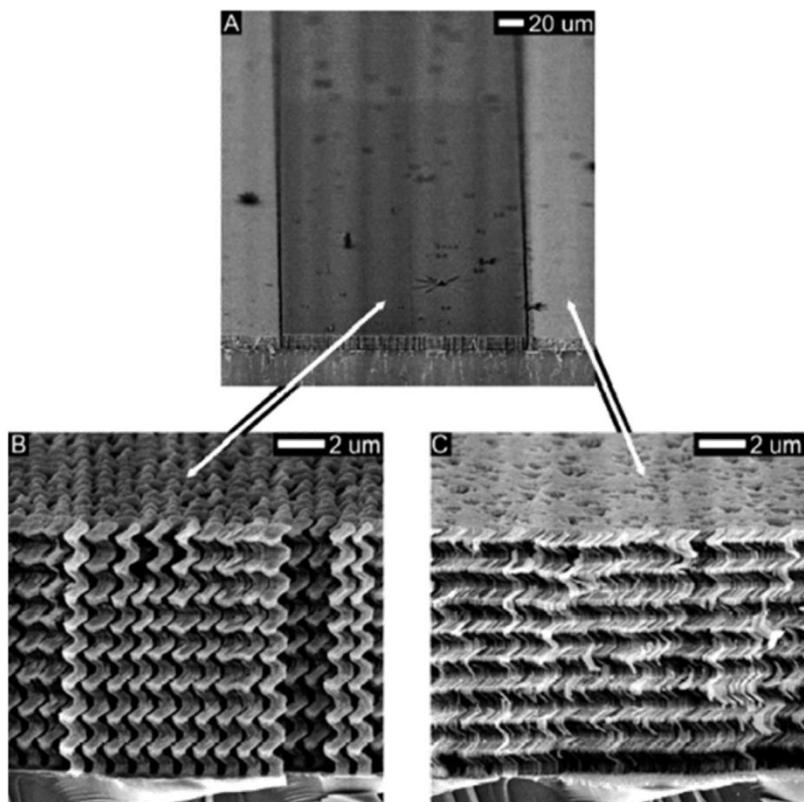


Fig. 9: (a) Scanning electron microscopy image of a GLAD microfluidic channel, 200 μm wide. A higher magnification showing (b) inside the channel with large gaps between the microcolumns and (c) outside the channel with a fairly compact film morphology. Reprinted with permission from Chemistry of Materials 17/16, Kiema G.K., Jensen M.O., Bret M.J., Glancing angle deposition thin films microstructures for microfluidic applications, 4046-4048. Copyright 2005 American Chemical Society.

Integrating GLAD structures into microchannels is very appealing, as precisely controlled morphologies can be formed for a range of materials. Kiema et al. [85] demonstrated the formation of a GLAD-based porous structure into a microchannel and the potential to use it for size exclusion chromatography. Different films of periodically

arranged microcolumns were formed with gaps ranging from 10 nm to 2 μm . By deposition into a channel of 200 μm wide and 3 cm long, a film was formed with a height of 10.5 μm and sealing was performed by bonding with a polydimethyl siloxane (PDMS) cover plate. Using similar techniques, Bezuidenhout et al. [86] successfully embedded GLAD grown nanostructures into PDMS microchannels, presenting a working device capable of separating DNA mixtures. The GLAD nanostructures were deposited onto a clean flat substrate. Subsequently, the porous film was filled with photoresist. Pattering the film photo-lithographically, microchannels could be defined. By casting and curing PDMS over the substrate and removing the photoresist, the microdevice was eventually formed. An inter-column spacing of 115 nm was used to separate a mixture of 10 kbp from 48 kbp DNA into two individual collection streams as well as mixtures of 6, 10 and 20 kbp DNA by applying an electric field.

9. Etching

When there are no objections regarding material incompatibility, there are a number of good reasons to use silicon as a substrate. The definition quality of combined lithography and silicon-optimized deep reactive ion etching (DRIE) processes is unsurpassed, allowing to make virtually any 2.5D structure. These structures are then mostly used as ordered support (e.g. pillar, Fig 1d) on which or from which porous layers are formed. Besides creating ordered support structures the DRIE process is also used for fabricating so-called black silicon, a porous layer which completely inhibits light reflection and which is furthermore well suited as catalyst support [17].

Besides the already discussed processes in the above sections, there are other methods to generate more specific surface, with the most prominent ones based on plasma etching processes.

If no fabrication limits would exist, the ideal chromatographic column format would be entirely made up of pores of typically 10-50 nm (i.e., of the same size as the meso-pores in the particles used in packed beds) but formed by an ordered bed of pillars. The analogue of the particle would then be a cluster of pillars and the flow in the channel would occur between these clusters.

A step in this direction was taken by our group using a Bosch-type DRIE process after step-and-flash imprint lithography [87, 88]. Looking at Fig. 10, an interesting limitation arises in this idea due to the so-called RIE-lag. This loading-dependent etching effect occurs when the areas to be etched vary strongly, giving rise to serious differences in etch-rates. This effect is detrimental for a separation to occur in the channel, as the top area of the clusters represents a larger surface and will withhold the analytes more strongly than the bottom area.

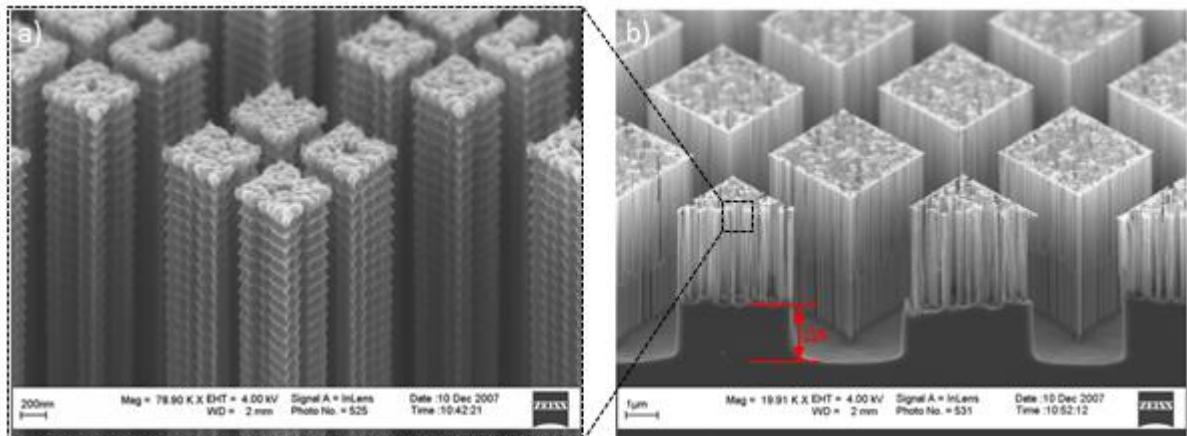


Fig. 10: (a) Detail of clustered pillars and (b) overview of clusters and flow-through channels. Δx is the difference in etching depth due to etch-rates differences because of the RIE-lag effect between the pillars and pillar clusters.

Reproduced from PhD Thesis, De Malsche W., Solving advanced micromachining problems for ultra-rapid and ultra-high resolution on-chip liquid chromatography, Vrije Universiteit Brussel and University of Twente, 2008, Enschede.

The group of Baba [89] performed pioneering work on the definition of nanopillars in quartz for DNA separations. By combining electron beam lithography, Ni electroplating and neutral loop discharge etching, they managed to uniformly fabricate pillars with high aspect ratios (100-500 nm diameter and 500-5000 nm tall), considering that the substrate is quartz. A chip with nanopillar channel and simple cross injector was developed based on the optimal design and used for the separation of DNA fragments (1-38 kbp) and large DNA fragments (48.5 kbp and 165.6 kbp), which are difficult to separate on conventional gel electrophoresis and capillary electrophoresis without using a pulsed-field technique. DNA fragments ranging from 1 to 38 kbp were separated as clear bands, and furthermore, the large size DNA mixture was successfully separated by a 380 μm long nanopillar channel within only 10 s even under a direct current (dc) electric field. The downside of the technique is that it is very slow

and expensive and that it is limited to very low volume productions. An elegant way around this drawback was proposed by the group of Kutter by making use of nanograss. This can be achieved with the so-called black silicon process [87], which relies on a composition between passivation and anisotropic etching in a plasma process. The needles were subsequently thermally oxidized in order to make them compatible with the envisioned electrokinetic application. To apply a cover on the irregular needles, posing a huge challenge to the regular bonding techniques, a plasma enhanced chemical vapor deposition (CVD) process was applied to generate a SiO₂ roof [90].

10. Plasma processes of polymers

Among polymers, PDMS is by far the most dominant material utilized for microfluidics. However, some of its properties can be considered as drawbacks. Due to its hydrophobicity, introducing water in the channels is rather difficult, making electro-osmotic flow unstable and furthermore adsorption of analytes poses a significant problem. A popular technique to solve these problems and increase the hydrophilicity is by oxygen plasma treatment. An ionized oxygen gas is directed towards the PDMS surface, forming a porous layer and hydrophilic silanol groups at the surface. A disadvantage is the “hydrophobic recovery” of PDMS caused by migration of the oligomer chains from the bulk towards the surface and vice versa for the silanol groups [91].

In the field of oxygen plasma treatments, the group of Gogolides is performing pioneering work. Using oxygen plasma, organic and inorganic materials could be micromachined, for surface modification as well as for patterning, resulting in both cases in roughened/porous surfaces. Due to the increase of surface area, the substrates can be rendered super-hydrophobic [92] and can be used in a wide variety of applications such as chromatography. By first patterning parallel lanes and subsequently coating them with TiO₂-ZrO₂, a large surface area is available for retention [93]. By patterning the surface of poly(methyl metacrylate) (PMMA) with oxygen plasma followed by depositing a teflon layer of only nanometers thick they succeeded in rendering PMMA superhydrophobic without affecting its optical transparency [94]. Fabrication of microdevices often required this as valuable information during research can otherwise go lost. Playing with the surface properties “smart” microfluidics can be fabricated, e.g. allowing spontaneous capillary pumping and passive valving [95].

Li et al. [10] constructed a PDMS microchannel for capillary electrophoresis. Treating the surface with an oxygen plasma prior to bonding allowed the separation of a mixture of three vitamins in a short time span below 90 s.

Sunanda et al. [11] studied the argon, oxygen and nitrogen plasma treatment of cyclic olefin copolymer microfluidic chips to make the surface more suited to biological environments and to decrease adsorption of biological components.

11. Emerging technologies, opportunities and challenges

Given the pace of the technological evolutions, the wealth of opportunities to create meso-porous support layers in microdevices described in the previous sections will in the future certainly be further expanded. 3D printing of micro- or meso-porous particles can for example be expected to emerge and become increasingly popular as the printing technology will become available for more and more materials. This technology will most probably also gradually open the road to multi-layered devices, which in turn will allow to solve one of the other main problems of microdevices, i.e, their volumetric scalability.

A second way to tackle this volumetric problem is by scaling the microfluidic device without losing its advantages from the μm -scaled dimensions. This can for instance be achieved by distributing the feed from the inlet hole, typically the internal tubing diameter, to a wide thin channel [96, 97]. Our group has gained quite some experience over the years in flow distribution, which is extremely critical in the field of liquid chromatography, as non-plug like entrance profiles jeopardizes the separation performance. Several distribution geometries were studied in which it was clearly demonstrated that a radially interconnected design was superior over bifurcating designs [98, 99] when taking unavoidable production errors into account. Employing microdevices for water purification is currently a hot topic where limited throughput is presenting a problem. Typical throughputs are in the range of 1 ml/h but a threshold of 1000 l/h is stated to be practically viable. Wang et al. [100] already increased the throughput to 1 l/h by building a microdevice with a footprint the size of an A5 sheet and these researchers are even moving towards the 1000 l/h goal by a continued increase of the channel dimensions. Another possible way to increase the volumetric size is by stacking together a bundle of capillaries. To avoid irregular distribution a 3D H-distributor [101, 102] could be employed, but just as the 2D bifurcating design it is sensitive to fabrication errors.

Now that the use of ordered porous columns is beyond the proof-of-principle stage, researchers and companies are looking at a wide range of applications. In order to ensure a robust operation for the envisioned applications, among which many challenging ones requiring high temperatures and extreme pH values, alternative substrates and coatings will emerge soon along with the protocols that allow maintaining order and structure. A crucial feature of stationary phases for high temperature liquid chromatography (HT-LC), one such emerging application, is that they should have a long lifetime at these high temperatures (up to 200 °C), preferably over a wide pH range (1-14). The most suitable materials in this respect are porous graphitic carbon (PGC) and carbon-clad zirconia (CCZ). Integrating these materials in pillar arrays is extremely challenging and requires (low temperature) approaches that are different from those used for the production of high temperature in particles. The most suitable process appears to be PE (plasma enhanced) CVD. A means to directly incorporate structures that are carbon based is by pyrolysis of photolithographically defined SU-8 structures, a technique which has been studied intensively by the Madou group [103]. Shrinking of the structures is typically unavoidable (see Fig. 11 a, b) but can be reduced to some 20 % using an optimized temperature ramp process. By using carbon pillars as support structures for substrate to apply PECVD deposition of graphene sheets (see Fig. 11 c), the need to pack these generally fragile structures might be omitted in the near future. A similar approach has been described on a flat surface Si surface, creating highly accessible and porous graphene sheets [104]. This would result in well accessible pores anchored on a highly (thermally) conductive and stable particle format.

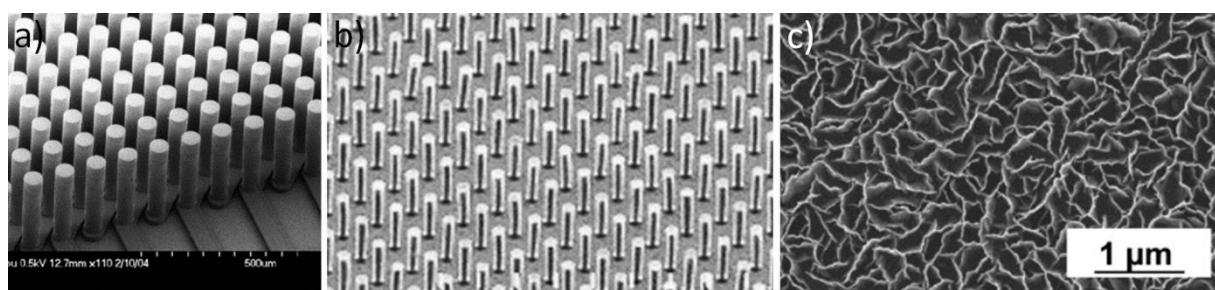


Fig.11 a) SEM image of high aspect ratio SU-8 carbon posts **b)** after pyrolysis. Reprinted from Biosensors and Bioelectronics, 20/10, Wang C., Madou M., From MEMS to NEMS with carbon, 2181-2187, Copyright (2014), with permission from Elsevier. **c)** SEM image of catalyst-free vertically stacked graphene nanosheets deposited directly on a Si substrate. Reprinted from Carbon, 49/13, Seo D.H., Kumar S., Ostrikov K., Control of morphology and electrical properties of self-organized graphenes in a plasma, 4331-4339, Copyright (2014), with permission from Elsevier.

Utilizing porous layers new “green” energy production technologies are being developed and improved with fuel cells probably considered one of the most relevant techniques. Improving the membrane regarding the ohmic drop is one of the largest challenges that are being researched, just the possibility for co-generation in which the fuel cell does not only deliver electricity but also valuable chemical products. Another emerging technology is ‘blue energy’, in which the mixing of river and seawater in the vicinity of ion exchange membranes results in the production of electricity. The group of Nijmeijer is leading in this field and is currently testing the first pilot plant for the production on large scale [105, 106].

The microreactor and process intensification community is currently highly focused on the development of more energy efficient reactors with a higher selectivity. The ability to couple chemical operations like liquid-liquid extraction or filtration with a reaction sequence is considered a text book advantage of microreactors [107], but surprisingly this has not lead to a convincing breakthrough yet. This can be attributed to the fact that the implementation of porous layers in close contact with reactor channels, while maintaining short characteristic dimensions to achieve sufficiently small transport times, appears to be far from trivial. In multiphase systems, the membrane also functions as a stabilizing (capillarity based) element. Ideally, such a membrane has uniform and small pore sizes, a high porosity and a small thickness (max. a few tens of μm). The emergence of membranes that comply with these characteristics would be highly desirable. It is highly probable that the enabling technology to achieve more energy efficient and more selective reactors will be nanofabrication-based.

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