# Membranes and microfluidics: a review

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The integration of mass transport control by means of membrane functionality into microfluidic devices has shown substantial growth over the last 10 years. Many different examples of mass transport control have been reported, demonstrating the versatile use of membranes. This review provides an overview of the developments in this area of research. Furthermore, it aims to bridge the fields of microfabrication and membrane science from a membrane point-of-view. First the basic terminology of membrane science will be discussed. Then the integration of membrane characteristics on-chip will be categorized based on the used fabrication method. Subsequently, applications in various fields will be reviewed. Considerations for the use of membranes will be discussed and a checklist with selection criteria will be provided that can serve as a starting point for those researchers interested in applying membrane-technology on-chip. Finally, opportunities for microfluidics based on proven membrane technology will be outlined. A special focus in this review is made on the membrane properties of polydimethylsiloxane (PDMS), since this material is frequently used nowadays in master replication.

## 1. Introduction

Since 1990, microfluidics has developed into a versatile technology. While initially focused on flow through simple channel layouts, designs of chips nowadays are much more complicated. Large effort has been put into the integration of unit operations on-chip, *e.g.* sample pre-treatment, mixing with reagents, reaction, and separation/purification of the products.[1,2] Looking at the methods used for integration, people have started out with clever designs of silicon chips, using the toolbox of the semiconductor industry. Lately a shift to new approaches can be recognized, aimed at simple straightforward integration: application of functionalized coatings, adsorption beads and membranes.

The use of membranes in microfluidics has been a topic of growing interest, as is clearly illustrated in Fig. 1. Membrane science and technology is a broad and highly interdisciplinary field, where process engineering, material science and chemistry meet. The interfaces of these fields offer many opportunities, and membranes have already been used for an impressive range of functions. Most known is of course separation of components, but also gas–liquid contacting and emulsification are possible. Using biocompatible or biodegradable polymers, membranes can be used as culturing supports or scaffolds for tissue engineering. Furthermore, membranes provide a large internal surface area that can be used effectively for adsorption or catalysis-based applications. Due to the versatility of membranes, related articles in the area of microfluidics are widespread in the literature. Strikingly, in many of these papers the membrane is not recognized for its function. Illustrative of the articles discussed in this review is the fact that 'membrane' is often not in the keyword list. In many cases an alternative term is used (*e.g.* filter, sieve, porous support, 'film') or the function of the membrane is given (*e.g.* separation, purification, sample pre-treatment, dialysis). Hence, the overall picture of membrane technology in microfluidics is diffuse. In this review we will provide a general overview of the developments at the interface between membrane science and microfluidics. Since our group has its origin in membrane technology and has only recently expanded its research into microfluidics, this review has been written from a membrane point of view.

The aim of this review is fourfold. First, to demonstrate the versatile use of membranes in different microfluidic applications nowadays. Secondly, to bridge the field of microfluidics with membrane technology, by linking these applications to relevant membrane literature. Large steps in scientific progress can be made by using the knowledge already available. Thirdly, to provide guidance in the use of membranes in

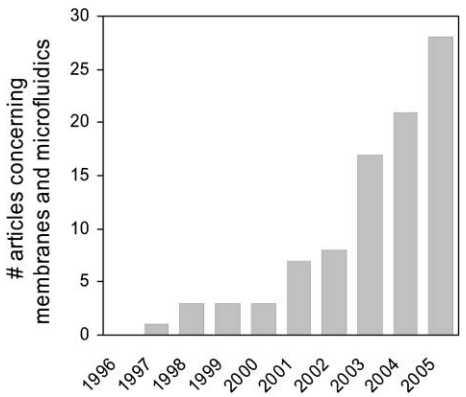


**Fig. 1** Articles concerning membranes and microfluidics discussed in this review, categorized by year of publication. The graph shows substantial growth over the past 10 years.

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microfluidics, and to give a checklist of selection criteria. And finally, to outline future opportunities.

This article is structured in the following way: First the parameters of major importance in membrane technology will be defined and explained. Then the different approaches for integrating membrane functionality in a microfluidic chip will be categorized. An overview of the applications reported in microfluidics literature will be presented. A special focus will be on the use of the highly permeable material polydimethylsiloxane (PDMS). This material has already been applied in membrane technology for a long time and the knowledge created in this field can be very useful for the microfluidic community. Subsequently, practical considerations that can arise when working with membranes will be addressed and general criteria will be provided for the selection of membrane type, material and fabrication method. The final part of this review is dedicated to opportunities not yet investigated and an outlook for the positioning of membrane technology in microfluidics.

## 2. Basics of membrane technology

The word 'membrane' is used in different situations for different functions and thus a clear definition is desired. In this review, we define a membrane as a semi-permeable barrier. Semi-permeable implies that in the considered applications, the membrane is used to control *transport* of some kind of species. When the transport direction is out of a system we speak of separation; when it is into the system we speak of membrane contacting. The cause of transport through a membrane is a difference in chemical potential between both sides. This difference may be due to a gradient in temperature, (partial) pressure, concentration or electrical potential. The mechanisms for transport strongly depend on membrane morphology. Two typical morphologies can be distinguished: porous and dense. Dense membranes are permeable for *single* molecules (transport of ions is also possible, but for reasons of simplicity this transport mechanism will not be described here). Transport in such systems is described by the solution–diffusion model. According to Wijmans and Baker, this model has emerged as the most widely accepted explanation of transport in dialysis, reverse osmosis, gas permeation, and pervaporation.[3] In this model, the permeability $P$ of component i is related to its diffusivity $D$ ($cm^2\ s^{-1}$) and solubility $S$ ($cm^3\ cm^{-3}\ atm^{-1}$) in the membrane material by the following formula:

$$P_i = D_i\ S_i \quad (1)$$

Since both the solubility and diffusivity of component i depend on its interactions with the membrane material, transport is clearly *material* dependent. The permeability of a dense material equals a flow, normalized for the membrane surface area, the difference in partial pressure and the membrane thickness. The value of the permeability is an intrinsic property of the membrane material and gives an indication of the membrane transport capacity.

The second important characteristic of dense membranes is the intrinsic selectivity $\alpha$. For two components i and j, the selectivity $\alpha_{i,j}$ is defined as the ratio of the pure permeabilities of i and j. Its value gives an indication of the separation efficiency of the membrane. The combination of permeability and selectivity indicates the general performance of the membrane material. It is important to stress that *every* material has membrane properties. However, for most materials the permeability and/or selectivity is too low for practical purposes.

For porous membranes, the transport mechanism is completely different. In this case, transport occurs through the empty spaces (pores) in the membrane instead of the material itself. Although interaction with the internal membrane surface can play a crucial role, transport is in the first place governed by membrane morphology. Morphology includes the surface- and volume porosity ($\varepsilon$), pore size distribution, and tortuosity ($\tau$). Tortuosity is a factor used to correct for the deviation of pore shape from perfect cylinders. It is defined by the ratio of the average path length through the pores and the membrane thickness. In porous membranes, again the permeability $P$ is used to indicate the capacity of the membrane. However, since transport is not an intrinsic membrane material property, permeability in porous membranes is *not* normalized for the membrane thickness. Pore sizes range from micrometers down to below 1 nm. Porosities range from more than 80% for micrometer-sized pores to less than 2% for nanometer-sized pores.

For porous membranes an alternative to the term selectivity has been defined: the retention $R$. The retention is measured during actual filtration and is related to the concentration of component i in permeate and feed, respectively, as is given by eqn (2):

$$R_i = 1 - (c_{i,perm}/c_{i,feed}) \quad (2)$$

The retention varies between 0 (no retention of component i) to 1 (component i is completely retained). It depends on the ratio of molecular size to pore size.[4] A second characteristic of a porous membrane that indicates whether separation will occur is the molecular weight cut-off (MWCO). The MWCO is defined as the molecular weight at which 90% is retained by the membrane and gives an indication of the pore size. Combining MWCO and permeability, an estimation of the separation performance of a membrane can be given. Summarizing, the performance of dense membranes is strictly material dependent, while the performance of porous membranes is morphology and material dependent.

Membranes can be operated in two modes. In the so-called "dead end mode", a feed stream is completely transported through the membrane. This operation is always a batch process, since the components rejected by the membrane will accumulate at the membrane surface. In continuous mode, the feed flows along the membrane. The stream that passes the membrane is called 'permeate', whereas the remainder is defined as 'retentate'. Depending on the application, either permeate or retentate can be the desired product: *e.g.* preparation of safe and clean drinking water (permeate) or concentration of a protein solution (retentate). Similar to heat exchange, continuous operation can be performed in co-current, counter-current and cross flow.

 

**Table 1** Categorization of different approaches to integrate membrane functionality on-chip

| Method | Approach |
|---|---|
| Direct incorporation of (commercial) membranes | Clamping or gluing of commercial flat membranes[9–33]<br>—Similar, followed by functionalization[34–38]<br>Incorporation of membrane during micro stereo lithography[39]<br>Use of hollow fiber membranes between capillaries[35,40–44] |
| Membrane preparation as part of the chip fabrication process | Production of sieves with well-defined pores by etching[45]<br>Thin metal film deposition[46–49]<br>Growing of zeolite crystals[50,51]<br>Preparation of porous silicon in wafers[52,53]<br>Preparation of porous oxide layers[54–56]<br>Creation of pores by ion track technology[57]<br>Preparation of polymeric membranes by casting[58–60]<br>Photo polymerization of ion-permeable hydrogels[61,62] |
| *In-situ* preparation of membranes | Local photo polymerization of acrylate monomers[63–65]<br>Interfacial polymerization in two-phase flow[66]<br>Liquid membranes by three-phase flow[2,67,68]<br>Formation of lipid bilayers[69,70] |
| Use of membrane properties of bulk chip material | PDMS chips[71–85]<br>Other polymeric chips[86–88]<br>Hydrogel based chip[89]<br>Fabrication of completely porous chips[90] |

More basic information on membrane transport, processes, fabrication and other membrane related topics can be found in the standard works of Mulder[5] and Baker.[6] For details on specific processes we like to refer to the *Journal of Membrane Science*[7] and a very recent review on advanced functional polymer membranes.[8]

## 3. Membranes in microfluidics

### 3.1. How to integrate membrane functionality on-chip?

Many different approaches have been reported to combine membranes and microfluidics. A rough division into four fabrication methods can be made: (1) Direct incorporation of (commercial) membranes. (2) Membrane preparation as part of the chip fabrication process. (3) *In-situ* preparation of membranes. (4) Use of membrane properties of bulk chip material. Table 1 categorizes different approaches within these four classes.

**Direct incorporation of (commercial) membranes.** First, and most straight-forward, is the direct incorporation of a membrane into a microfluidic device, simply by clamping or gluing.[9–33] The membrane can be easily prepared in-house, or directly purchased from a commercial supplier. Modification may be used to functionalize the membrane, *e.g.* by immobilization of trypsin,[34–36] bovine serum albumin (BSA)[37] or impregnation with an extraction fluid.[38] By using multiple membranes in a stack, a certain fraction of a sample can be collected, as is illustrated in Fig. 2A. Instead of flat sheets, also hollow fiber membranes can be considered. These hollow fibers are available with diameters down to 100 μm and can be directly connected to silica capillaries in order to make simple devices.[35,40–44]

A major problem in the direct incorporation of membranes is the sealing step, especially when inorganic substrates such as glass or silicon are combined with polymeric membranes. Due to capillary forces, fluids can easily get sucked in between

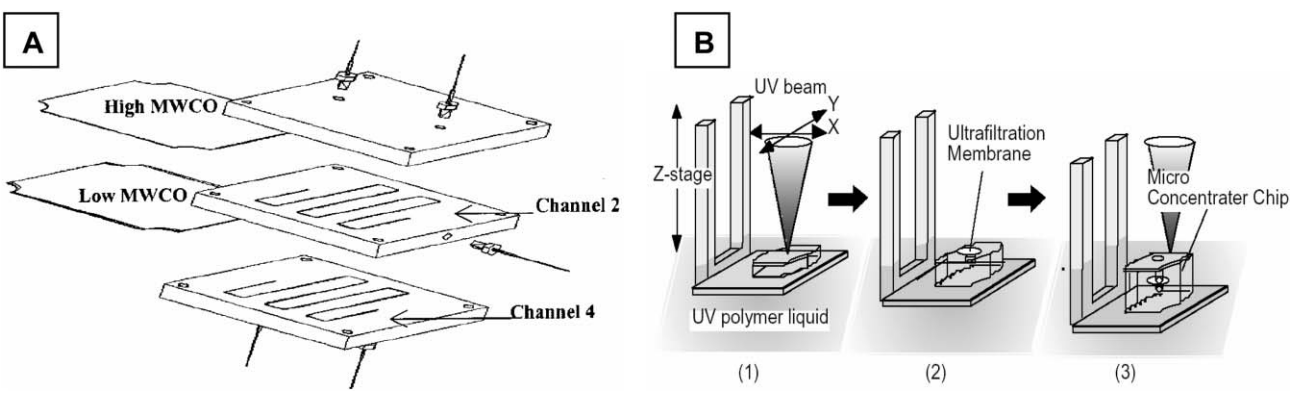


**Fig. 2** Incorporation of commercial membranes in microfluidic devices: (A) clamping of membranes with different MWCO between microfluidic sheets in order to fractionate samples (reprinted with permission from ref. 12, © 1999 American Chemical Society); (B) incorporation of a membrane during micro stereo lithography (reprinted with permission from ref. 39, ©1999 IEEE).

cover plates. Using glue, the same forces can cause complete blocking of the membrane due to filling of the pores. An elegant way to overcome this problem is to make a chip by micro stereo lithography.[39] In this process, a chip is built in 3D from a photo curable liquid polymer using a focused UV beam. The membrane can be put in the precursor solution, thereby eliminating the need for a sealing step. Non-cross linked polymer can be washed away after chip preparation. The fabrication process is illustrated in Fig. 2B.

The largest advantages of directly incorporating membranes are the simplicity of the process and the wide choice of membrane materials and morphologies. Based on a certain application the most suitable membrane can be directly selected. If not commercially available it can be prepared in the lab, or obtained from other research groups. An additional advantage is the flexibility of configuration. With a standardized 'clamp-and-play' chip design, many different applications can be targeted, simply by changing the type of membrane.

**Membrane preparation as part of the chip fabrication process.** A second approach to integrate membrane functionality is to prepare the membrane during the fabrication process of the chip. In this case the toolbox of the semiconductor industry can be used. Examples are presented in Fig. 3. According to a recent review by Eijkel and Van den Berg, nanotechnology is at a level that any structure can be tailor-made, enabling the integration of membranes with very specific properties.[91] Many fabrication methods can be applied, *e.g.* etching for the preparation of microsieves[45] and thin metallic film deposition.[46–49] Also porous layers can be fabricated, from materials such as zeolite,[50,51] silicon,[52,53] silica,[54,56] alumina,[55,56] or titania.[56] These and other methods are discussed in more detail in Van Rijn's book on nano and micro engineered membrane technology.[92] Major advantages of clean room technologies include (a) the immense knowledge already available in this field; (b) good control over feature sizes, down to tens of nanometers; (c) chemical/thermal resistance of used materials and (d) sealing of the membrane. In fact the last issue is in many cases avoided, since the membrane is directly made in or on the wafer. Disadvantages of semiconductor technologies in general are the complexity of the production process and, related to this, the high price. Especially for single-use applications the high price can form an insuperable problem.

Recently, also combinations of semiconductor technology with polymer technologies have been reported, and even new methods that do not require clean room facilities anymore. Metz *et al.* used ion beam track etch technology to create pores in polyimide chips.[57] Moore and co-workers prepared a bio anode for a microchip fuel cell based on a membrane with immobilized alcohol dehydrogenase.[60] In their process, an electrode was covered by a PDMS channel that was filled with a Nafion suspension containing the enzyme. The membrane was formed by evaporation of the solvent through the PDMS. Russo *et al.* prepared membranes on pre-etched microsieves by casting a thin layer of cellulose acetate solution that was phase separated afterwards upon contact with water.[58,59] By varying the process conditions they could obtain different values for permeability and MWCO. Since phase separation is a standard procedure in membrane technology, and very well documented, their approach may lead to the implementation of a wide range of membrane materials and morphologies. A key factor for success will then be the adhesion strength between the silicon structure and the membrane, during preparation, drying and operation of the membrane.

Woolley and co-workers prepared ion-permeable membranes by photo polymerization of a hydrogel in a cavity that was created in a polymer sheet.[61,62] They reported two possibilities to interface the membrane with a microfluidic channel. The first option was to thread a thin wire through capillaries that would be used for connections later on. After polymerization, the wire could be withdrawn from the membrane, leaving a round channel.[61] The dimensions of this channel were limited by the minimum diameter of the wire. The second method was to position the cavity above a microfluidic channel filled with a phase-changing sacrificial material.[62] After polymerization, this material was removed by melting. This method allowed for smaller channel dimensions. Furthermore, it enables the use of specific channel geometries.

***In situ* preparation of membranes.** A third integration approach is to start with a microfluidic chip and fabricate a membrane *in situ*, as illustrated in Fig. 4. Moorthy and Beebe prepared porous membranes in microfluidic channels by emulsion photo polymerization.[63] Song *et al.* used a laser to induce phase separation polymerization with acrylate monomers in fused silica chips.[64,65] This principle offers an

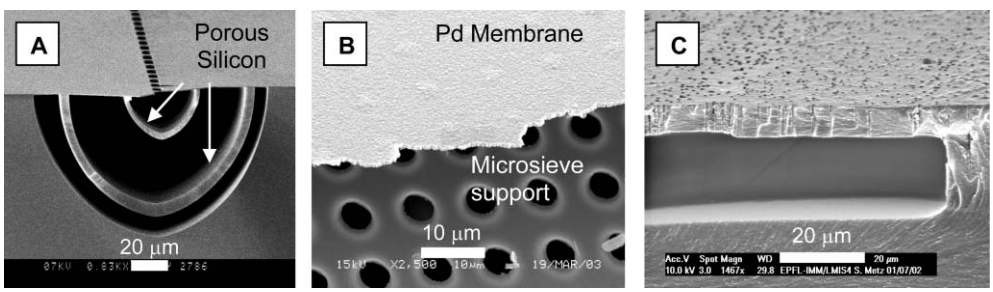


**Fig. 3** Membrane features introduced during chip fabrication using clean room technology: (A) free-standing layers of porous silicon, prepared by electrochemical etching followed by under etching of the bulk silicon beneath (reprinted with permission from ref. 52, © 2000 IEEE); (B) sputtered dense Pd membrane on a microsieve support structure prepared by back etching (reprinted with permission from ref. 48, © 2004 Elsevier ); (C) close-up of a polyimide chip with pores fabricated by ion beam track technology (reprinted with permission from ref. 57, © Institute of Physics Publishing).

 

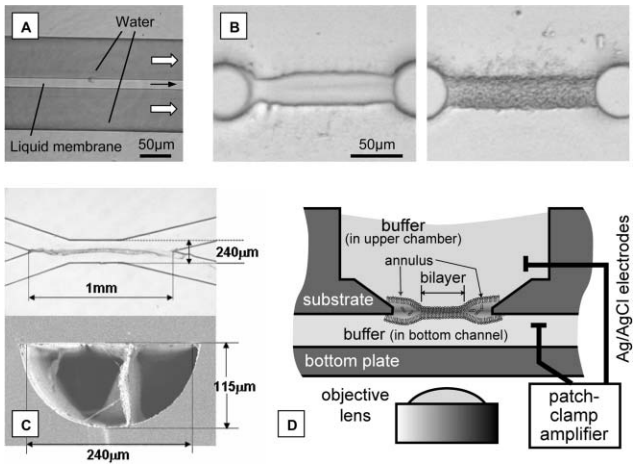


**Fig. 4** Membranes prepared inside microfluidic devices: (A) heptane flow between water flows acting as a liquid membrane (reprinted from ref. 68); (B) membranes formed between pillars by laser induced phase separation of acrylate monomers. The molecular weight cut-off of the membranes can be varied by changing the monomer/crosslinker ratio (left: low, right: high) (reprinted from ref. 65); (C) membranes formed by a polycondensation reaction at the interface of an organic and aqueous flow. Top: optical image of the chip layout, bottom: cross section of the centre channel (reprinted from ref. 66); (D) schematic of a lipid bilayer membrane, formed by self-organization (reprinted from ref. 70). All images are reprinted with permission, © American Chemical Society.

interesting opportunity to control the position and thickness of the membrane, simply by controlling the position of exposure. Non-polymerized monomers can be washed out afterwards. The MWCO of produced membranes can be changed by varying the ratio between monomer and cross linking agent, as is illustrated in Fig. 4B. An additional advantage of this method is its application in existing chip formats (provided that the used chip material is transparent to UV light). Disadvantages include complexity and the limited range of materials that can be applied. Furthermore, tailoring of membranes towards a certain retention or MWCO has to be done by trial and error experiments based on an educated guess.

Kitamori's group has demonstrated the fabrication of membranes by interfacial polymerization.[66] In this case, an organic and aqueous solution are joined, both containing a certain monomer, *e.g.* an acid chloride and an amine. These two monomers can react *via* a poly condensation reaction at the interface and form a thin polyamide membrane. Fig. 4C illustrates membranes produced by this method. By alternating water and oil phases, multiple membranes can be prepared next to each other. However, to obtain defect-free membranes, a well defined interface is required. Although flows in microfluidic devices are laminar, this requirement poses a challenge for oil/water based systems. Preferential wetting of one phase easily results in droplet formation. Either the channel shape has to be modified, or selective coating of channel walls is needed.

All membranes discussed so far are based on solid materials. However, a liquid can also act as a membrane (so-called liquid membranes). In this area the fields of extraction and membrane technology are combined. A stable three-layer flow of immiscible fluids is required, where the middle layer is used for the separation. Examples are systems of water/cyclohexane/water,[67] water/m-xylene/water[2] and water/n-heptane/water.[68] In contrast to the membranes discussed above, the membrane is in this case a *dynamic* layer. Separation of components is based on a difference in solubility in the liquid membrane phase. This solubility can be enhanced dramatically by the addition of carrier molecules, leading to very high selectivities. Another big advantage of liquid membranes is the ability to simultaneously operate in forward and backward extraction mode: in a single step components can be removed while others are added. Disadvantages include the difficulty of obtaining a stable interface (as mentioned above), low extraction efficiencies and the limited knowledge available in this field: stable three layer flow is impossible on the macro-scale and liquid membranes can only be formed by either using porous supports or by making double emulsions followed by an additional separation step.

Finally, a special class of liquid membranes can be prepared in a chip: the so-called artificial lipid bilayers, schematically depicted in Fig. 4D.[69,70] These structures mimic cell walls and can be prepared by contacting lipid solutions with buffers. Artificial lipid bilayers can be used for the study of transport mechanisms of components in and out of cells.

**Use of membrane properties of chip material.** The last method for integration of membrane features on-chip is to choose a chip material that has the required membrane properties *itself*. This method is simple but elegant, since no additional fabrication steps are required. Examples are presented in Fig. 5. A material that has been exploited in microfluidics for its high gas permeability is polydimethylsiloxane (PDMS).[71–85] Although PDMS is relatively new to the microfluidic community, it has been used for over 20 years in membrane technology, and a lot of knowledge is readily available. Therefore we will return to PDMS later and use it as an example to indicate the importance of bridging scientific fields.

Besides PDMS other polymers can also be used, such as polyimides. Although the gas permeability of polyimide is much lower than the value for PDMS, this may be compensated by a lower thickness of the layer through which permeation occurs. Eijkel *et al.* made nanochannels in a photo patternable polymide layer with a 2.3 μm thick polyimide 'roof'.[86] Su *et al.* prepared dense cellulose acetate membranes that enabled transport of water into a micro actuator.[87,88] Cabodi and co-workers developed microfluidic chips out of a calcium alginate based hydrogel.[89] They showed that a fluorescent dextran could be both delivered into—and extracted from—the gel matrix. By fitting mass transfer models to their data, they determined values for diffusivity in the gel that are close to those in free solution.

In our group, completely porous chips have been prepared by adapting the phase separation method that is used to fabricate membranes on a large scale. When a polymer solution is phase separated on a microstructured mold, a membrane is formed with an inverse replication of the mold features.[93] Using rigs on a mold, we have been able to produce membranes with channel networks in the lateral direction.[90] The morphology of these 'membrane chips' can be tuned by

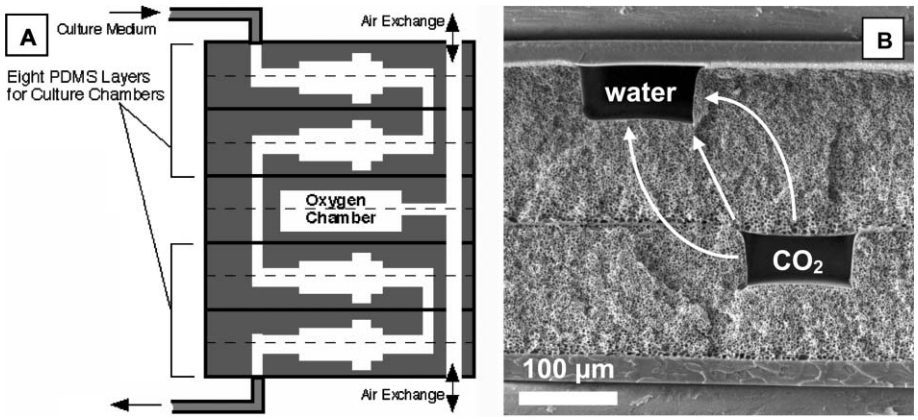


**Fig. 5** Microfluidic chips in which the membrane characteristics of the bulk chip material are exploited: (A) PDMS-based bioreactor with integrated oxygenation chamber, where the permeability of PDMS is used to supply oxygen to cells (reprinted with permission from ref. 74, © 2004 American Chemical Society); (B) cross section of a porous chip produced by phase separation micromolding, where gasses can be supplied from one channel to the other through the porous matrix (reprinted from ref. 90, © The Royal Society of Chemistry)

controlling the parameters of the phase separation process and by changing the composition of the polymer solution. The channel walls can have pores in the range of a few microns down to nanometers, or even have dense skin layers. The phase separation micromolding technique (PSμM) is applicable for many different polymers, since the only requirement is to find a solvent/non-solvent system. Besides polymeric structures, ceramic or metallic structures can also be prepared, by adding powders to the starting solution and performing a pyrolysis/sintering step afterwards.

### 3.2. Which applications exploit integrated membrane functionality?

Although the use of membranes in microfluidics is spreading across many fields, most applications are found in analytical chemistry. Since analytical equipment is often sensitive to sample composition, in most cases samples cannot be directly analyzed and need a pre-treatment. This may include selective removal of large components, impurities and dust on one side and low molecular weight components such as salts on the other. Furthermore, in many cases the concentration of the components of interest is below the detection limit of the analysis equipment. In such cases, removal of solvent is necessary. Membranes are very suitable for these operations. Next to analytical applications, also new fields emerge in which membranes are used, such as cell-based studies, micro reaction technology and fuel cells.

In the following section examples will be given of both traditional and new applications of membranes in microfluidics. The aim is to show the versatility of membranes in microfluidics without discussion in much detail. More in-depth knowledge can be found in the following reviews: The use of membranes in analytical chemistry has been described in a comprehensive review by Moskvin and Nikitina.[94] Wang *et al.* have written a review specifically aimed at polymeric membranes in bioanalytical applications.[95] Lichtenberg and co-workers have discussed membrane-based sample pre-treatment and made a comparison with alternatives such as electrophoresis or extraction.[96] Peterson has discussed solid supports in micro analytical processes, comparing beads, gels and monoliths with membranes.[97] Erickson and Li took an even more general approach in their review about 'integrated microfluidic devices', describing all kinds of unit operations, including membranes.[1]

**Sample concentration.** Eijkel *et al.* prepared a 2.3 μm thick polyimide membrane with 500 nm high nanochannels by spinning and thin film deposition.[86] Water could be removed from the channels in two ways: either by evaporation or by osmosis. In the case of osmosis, a solution with high salt concentration was placed on top of the membrane. Due to osmotic pressure and the impermeability of polyimide for salts, water was transported through the membrane. Next to concentration, the removal of water from a channel was also mentioned as an effective means to obtain passive pumping. By fabricating a reservoir with a high surface to volume ratio at the end of a channel, evaporation will lead to an effective flow from the channel to the reservoir. Timmer and co-workers applied a nitrogen flow over a microchannel covered with a hydrophobic Teflon membrane, to concentrate the solution in the channel by evaporation.[18] A threefold concentration increase was reported. Ikuta *et al.* describe a micro concentrator that is based on an ultrafiltration membrane, operated in dead-end mode.[39] In time, the signal increases due to a concentrating effect, making the device suitable for the detection of trace elements. The same principle is also applicable to detect bacterial cells or spores, eliminating the need for culturing of bacterial colonies and expensive ELISA tests.[29] Jiang *et al.* combined two membranes in a PDMS chip for drug screening and residue analysis.[15] In their tests they examined a mixture of aflatoxins and an antibody that specifically binds to a certain type of aflatoxin. The first membrane was used in dialysis mode for removal of the unbound aflatoxins, while the second was used for evaporation of water. In this way, the concentration could be dramatically increased. In the same article the authors also propose a batch process for barbiturate detection. For this purpose a single ultrafiltration membrane in dead-end operation was sufficient. Using a similar complexation reaction with an antibody, a

 

desired barbiturate could be retained on the membrane. Subsequently, the complex could be dissociated with a buffer and eluted through the membrane. A concentration increase of 50 times was achieved. A different approach to obtain very high concentration factors is by applying electric fields, using the principle of electrophoretic mobility. Molecules can be focused in bands at the location where their electrophoretic migration velocity matches the applied hydrodynamic flow velocity. These highly concentrated bands can be collected afterwards. Also in this application membranes have proven useful. Kirby's group prepared a nanoporous membrane by photo polymerization of acrylates in a channel.[64] Proteins were retained by the membrane, while buffer ions were allowed to pass, leading to concentration factors between 2 and 4. Ramsey's group achieved even higher concentration factors for proteins and DNA in a similar system based on porous silica membranes.[54] Signal enhancements up to two orders in magnitude were reported. In both cases the electric field gradient was over the membrane. Another possibility is to apply an electric field gradient in the separation channel itself, by gradually decreasing the buffer conductivity. This decrease can be achieved by means of dialysis. A dialysis fluid induces a salt concentration gradient, while proteins and other large molecules are retained in the separation channel by the dialysis membrane.[10,44] Related to this application, but using a different working principle, is the work of Woolley and co-workers.[61,62] They applied an ion conducting membrane of increasing width to create the electric field gradient. The permeability of the polymeric material was in this case exploited for the supply of new buffer ions from a reservoir to the separation channel, to avoid depletion in the separation channel. Concentration factors up to 10 000 were demonstrated. An additional advantage of electrophoretic concentration in a field gradient is that the process can be simultaneously used for *separation*, based on differences in electrophoretic mobility of species.

**Sample filtration.** In filtration, porous membranes are applied as barriers and transport occurs by a pressure difference. Fluids can pass the membrane, while fragments larger than the pore size are retained. In most cases a dead-end configuration is applied, because of practical reasons. Membrane filtration on-chip is used for separation of cells from whole blood,[28,63] removal of dust or aggregates[29] and removal of solutes such as proteins.[59] Instead of separation defined by pore size, Lion *et al.* exploited the adsorption capacity of PVDF membranes as a means for desalination.[20] In the first step, a sample solution was filtrated through the membrane. The sample fluid and present salts were not retained, while drugs, proteins and peptides adsorbed on the internal surface. Desorption of these components was achieved by flushing the membrane with an elution buffer.

**Sample preparation by microdialysis and other liquid–liquid contacting applications.** Membranes can be used as selective barriers between fluid flows in extraction applications, the most known example being microdialysis. In this application, a dialysis fluid is used to remove solutes from a sample solution. The driving force is a difference in activity, and separation is determined by the MWCO of the membrane and differences in diffusion coefficients of components. Kurita *et al.* applied a cellulose dialysis membrane between two acrylic plates to directly analyze lactate concentration in dog whole blood.[30] Xu and co-workers used a dialysis membrane between serpentine channels to desalt DNA and protein samples before electrospray ionization mass spectroscopy (ESI-MS).[9] Wu and Pawliszyn used a dialysis hollow fiber membrane to remove salts from protein solutions prior to capillary isoelectric focusing (CIEF).[40] Lamoree *et al.* applied a cellulose ester based device *after* CIEF for the online removal of ampholytes that were added for the CIEF step. In this way, the signal of subsequent ESI-MS could be greatly improved.[11,41] Using dual microdialysis even a double separation step can be integrated.[12] The first dialysis membrane has a high MWCO in order to remove large components from the sample. The second membrane has a low MWCO and is used to desalt the sample. Song *et al.* used dialysis membranes prepared by photo polymerization to separate salts from proteins, and to separate protein fractions based on size.[65] Torto *et al.* have examined the performance of many different hollow fiber membranes for microdialysis sampling of oligosaccharides.[42] Hsieh and Zahn prepared a microdialysis device for fast glucose recovery, which is needed in glucose sensors.[24]

Instead of the aqueous solutions used in dialysis, organic streams can be used as well. Gao *et al.* used a membrane junction based on a polysulfone hollow fiber to acidify a peptide solution and simultaneously increase organic solvent content by adding methanol. Protonation and ionization efficiency of the peptides before ESI-MS could be enhanced significantly.[35] Cai and co-workers directly applied a microporous hydrophobic PTFE membrane between microfluidic glass substrates as a contactor to obtain a stable interface between water and an organic phase (isobutanol).[31] The chip was used for extraction of a model compound, butyl rhodamine B.

Next to size exclusion (based on the MWCO of a membrane), also a difference in affinity can be used to obtain a separation. Wang and co-workers adsorbed BSA on hydrophobic PVDF membranes in order to obtain high resolution in the chiral separation of racemic mixtures.[37]

As discussed in the previous paragraph, liquids themselves can also be used as a membrane. Surmeian *et al.* demonstrated a water/cyclohexane/water system, in which methyl red could be rapidly extracted from the donor to the acceptor phase.[67] The equilibrium time was reported to be in the range of seconds, compared to tens of minutes in conventional equipment. Maruyama *et al.* used a water/heptane/water system to selectively remove yttrium ions from a $Y^{3+}/Zn^{2+}$ solution.[68] An extraction ratio of $\sim$40% could be achieved within seconds. To avoid stability problems in three phase flow systems, Wang and co-workers used a supported liquid membrane.[38] For this purpose, a membrane was soaked in an extraction liquid and clamped between microfluidic channels. The feasibility of the system was demonstrated by showing enrichment factors of halo acetic acids in water up to 65.

Ismagilov and co-workers applied single and double membranes between crossing channels as fluid–fluid diffusional contacts.[14] Due to the resistance of the membrane,

convective transport was avoided. The concept of diffusional contacts was reported to be feasible as a general tool in detection.

**Gateable interconnects with external control.** In the applications discussed so far, transport has been governed by the membrane material and/or morphology. Sweedler and co-workers have demonstrated that the pores of membranes can be used as gateable interconnects that allow for *external* control over separation characteristics.[19] They incorporated flat track-etched membranes with nanosized pores between microfluidic channels. Transport of components in- and out of the channels could be controlled by the applied bias, polarity and density of the immobile surface charge of the membrane. The authors used their device for sample injection and fraction collection of attomolar quantities. Schmuhl *et al.* applied mesoporous and microporous oxide layers as ion-selective electrophoretic gates in microfluidic devices.[56] Fickian diffusion of charged and uncharged species was suppressed by the interconnects, opening the possibility for use as dosing valves or sensors. Selective ion transport occurred when there was an overlap of the electric double layers in the pores of these membranes, which could be achieved by a proper choice of pH and electrolyte concentration.

Astorga-Wells *et al.* applied conductive fiber junctions made of cation exchange membranes between tubing for the desalination of protein samples before MALDI-MS.[43] Proteins and peptides could be retained by means of an electric field, followed by exchange of the original solution for a solvent suitable for mass spectrometry.

**Gas sensors and other gas-related applications.** Many gas sensors are based on the absorption of gas in an analysis liquid. For this purpose, membranes can serve as efficient gas–liquid contactors. PDMS is a very well suited material, due to its high permeability for gasses and vapors. Different groups have used PDMS in oxygen sensors[79,81,82] or $CO_2$ sensors.[84] Toda *et al.* prepared a PDMS membrane of only 7 μm in a micro scrubber for the continuous detection of $H_2S$ traces.[75] The same group also used a porous PTFE membrane in a PDMS device with honeycomb structures for measurement of $H_2S$ and $SO_2$.[26] In an earlier publication, several membranes were compared for use in a hybrid microfabricated device for field measurement of atmospheric $SO_2$.[17]

Next to gas–liquid contacting, membranes can also be used to *remove* gas from a channel. Van den Berg's group has presented a miniaturized gas sampler for ammonia detection, in which sample gas is introduced together with an absorption liquid.[22] Excess gas is in this case easily removed through an incorporated microporous Teflon membrane by pressure generated in the chip. The adsorption liquid stays in the channel because of the hydrophobic nature of Teflon. Liu and co-workers used this principle in PCR chips to avoid problems with filling.[16] Meng *et al.* fabricated a micro degassing plate, based on a hydrophobic polypropylene membrane.[32] They showed that $CO_2$ bubbles that were formed during a reaction in the chip could be effectively removed.

**Membranes microreactors.** The standard procedure of making a product in chemical engineering used to consist of a reaction step followed by separation. These operations might be easily integrated on chip. Reaction yields and selectivity may be pushed to 100% by selectively removing components, thereby shifting the reaction equilibrium in favor of the end-product. Although this concept is relatively new in microfluidics, already quite some examples can be found. Most of them are related to hydrogen and based on thin foils of noble metals. Cui *et al.* describe a membrane reactor for the dehydrogenation of cyclohexane to benzene at 200 °C.[46] Hydrogen produced during the reaction is selectively removed through a 4 μm thick folded Pd film. Karnik and co-workers used a similar membrane to remove hydrogen from a water gas shift reaction.[47] In their microreactor, methanol reacted with water at 200 °C. The palladium membrane was prepared on top of a copper perforated structure, which acted as a catalyst for the reaction.

Yeung's group worked on the incorporation of freestanding zeolite membranes in silicon chips.[50,51] Zeolites have a very well defined pore network and are therefore extremely effective in separation. Furthermore, they can be easily functionalized with metal catalysts. The authors report that the equilibrium state in Knoevenagel condensation reactions can be shifted to higher conversion and better product purity by the selective removal of water.

Instead of separating reaction products, membranes can also be used for transport of reagents into a reaction chamber. The advantage of such a system is the ability to supply a reagent in a controllable way at exactly the position where it is required, for example near a catalyst. As a consequence, the premixing step that is normally required can be omitted. Furthermore, reactions can be easily quenched by stopping supply of a reagent, preventing the formation of unwanted by-products elsewhere in the system. Hisamoto *et al.* prepared nylon membranes that were used to provide hydrogen peroxide for an enzymatic conversion.[66] The enzyme itself was immobilized on the membrane. Our group has recently demonstrated the formation of carbonic acid in porous PMMA chips by $CO_2$ absorption.[90] The $CO_2$ was provided through the porous structure of the chip. Mitrovski and co-workers present a $H_2$–$O_2$ fuel cell based on diffusion of both gasses through a PDMS layer to the cathode and anode, respectively.[80] They report minor problems with cross-over of both reagents. Shah *et al.* made a micro fuel cell where hydrogen was supplied through a PDMS array of microchannels, enclosed by a proton conducting Nafion membrane.[23] The other side of the membrane directly faced air for the supply of oxygen. Using this approach, cross-over problems could be largely avoided. Water produced in the reaction was used to keep the membrane humidified. Chan and co-workers reported the fabrication of a similar device out of PMMA.[25]

Besides structures that control mass transport, membranes can also be used for their large internal surface. An example is the impregnation of membranes with a catalyst, in order to obtain high conversion rates. This concept has been proven to work for on-line protein digestion, catalyzed by trypsin adsorbed in a PVDF microfiltration membrane. Both a dead-end capillary configuration[34] and a microfluidic PDMS

 

chip[35,36] have been described. Moore *et al.* fabricated a microchip-based ethanol/oxygen biofuel cell, by coating Nafion membranes with alcohol dehydrogenase on the carbon anode.[60] Kim *et al.* used functionalized membrane pads for the quantitative analysis of cholesterol and high density lipoproteins (HDL) in blood. First, a separation pad was prepared by treating an anion exchange membrane with BSA, dextran sulfate and $MgCl_2$ in order to separate HDL from other lipoproteins, either by precipitation or a difference in charge. The second pad consisted of a glass microfiber membrane that was impregnated with enzymes and detergents. These components could open the lipid particles and react with cholesterol/HDL to give a colored reaction product. Since all membrane pads were used in a dried state, the capillary pressure of the membrane pores could be used for passive pumping, eliminating the need for external pumping equipment.

**Cell related studies.** Microfluidic devices provide a general platform for cell culturing experiments. To study the reaction of cells often membranes are used. These membranes act as porous supports for the cells, enabling the supply of nutrients and removal of waste products. Russo *et al.* prepared porous cellulose acetate membranes on a silicon chip and demonstrated the possibility of culturing lung fibroblasts.[58] Ostrovidov and co-workers reported on perfusion of hepatocyte cultures in two types of micro bioreactors, either based on a PDMS or a commercial polyester membrane.[77] In operation, no large differences were found, but both systems performed better than static cultures in dishes. Tokuyama *et al.* described a PDMS chip where a nitrocellulose membrane is integrated to retain the cells.[27] In their chip, the response of rat mast cells to histamine could be examined. Hediger *et al.* clamped a 0.4 μm polycarbonate membrane in a PDMS device to perform electrical characterization of epithelial cell layers.[13] A big advantage of their system is that the membrane can be easily removed, analyzed and/or replaced. Although the PDMS chip has in these cases been chosen because of its ease of production, it can also be used for its high gas permeability. Several authors have reported on this principle, mostly for the transport of oxygen and carbon dioxide in cell bioreactors. Leclerc *et al.* cultured hepatocyte cells in a PDMS chip.[73,74] Walker and co-workers used a similar device for culturing of ovary cells.[83] Wu *et al.* have presented a PDMS based Clark oxygen cell for the supply and direct study of oxygen consumption by *E. Coli* bacteria.[81] Zanzotto and co-workers prepared a PDMS bioreactor, where a 100 μm thick layer was used for aeration.[72] They provided data for oxygen transport through PDMS and experimentally determined the oxygen uptake.

Biological cells themselves have walls that also show membrane characteristics. These walls consist of lipid bilayers and membrane proteins that can regulate transport of species such as ions, glucose, drugs and amino acids. Different groups have prepared artificial lipid bilayers in PMMA microfluidic chips.[69,70] Membrane proteins are simply built-in by diffusion, and transport can be measured by channel currents.

**Various.** In mass spectroscopy, electrospray ionization tips are used to create a Taylor cone. A problem encountered in these tips is lateral dispersion of the cone, leading to a decreased signal-to-noise ratio. Wang *et al.* applied a 50 μm thick hydrophobic PTFE membrane with pores of 0.22 μm at the end of a polycarbonate (PC) tip.[21] According to the authors, the pores of the membrane can be perceived as a dense array of nanoscale ESI tips. The new hybrid tip resulted in stable and reliable Taylor cones at very low flow rates and a large improvement in signal. Su *et al.* have demonstrated an effective water-powered micro actuator, based on osmosis.[87] A salt solution is enclosed in a compartment with dense walls, impermeable for the ions but permeable for water. Due to the high activity of the solution, water is transported into the compartment. The volume increase is used to deform a flexible actuation diaphragm. In a later article they show that the deformation can be used in a micro drug delivery system.[88]

Another practical application of membranes can be found in the improvement of the stability in applications based on electro-osmotic flow (EOF). The EOF can be directly related to the zeta potential of the immobile phase, which can strongly depend on pH. Since the electric fields applied in EOF surpass the water splitting potentials, reactions at the anode and cathode lead to the formation of acids and bases. Buffers can be used to delay changes in pH, but at a certain point in time the EOF will drop. Brask *et al.* have demonstrated that this time can be extended by placing anion exchange membranes between pumping compartment and the electrodes.[98] Since this type of membrane is not permeable for positively charged ions, H+ ions are rejected and the pump can be operated for hours after the buffer has depleted.

## 4. Bridge between membrane technology and microfluidics: the case of PDMS

Master replication by PDMS crosslinking has revolutionized microfluidic research. The opportunities that PDMS offers have been reviewed by Whitesides' group.[99] The fabrication process is both simple and cheap and can be performed outside a clean room. The resulting films are transparent, flexible and biocompatible. Sealing of chips is very straightforward and in many cases reversible. Furthermore, valves and pumps can be easily integrated.[100] PDMS also has very interesting properties as a *membrane material*, and these properties have been utilized for a long time in membrane technology practice. For example, PDMS coatings are applied on a large scale in solvent resistant nanofiltration to separate low molecular weight components from solvents such as toluene.[101] Another application can be found in pervaporation, for instance in the removal of VOC-components from aqueous streams.[3] Finally, PDMS coatings are applied to plug defects in gas separation membranes.[102] In all these examples, the high permeability of PDMS is exploited. Not surprising, this property has been extensively investigated and much knowledge is readily available. Table 2 summarizes permeability and calculated selectivity data from membrane literature for gasses/vapors that seem directly relevant to microfluidics at this moment. Data in brackets represent data for polyimide, a typical glassy polymer, to illustrate the high permeability of PDMS.

**Table 2** Permeability and selectivity data of different gasses and vapors in PDMS[a] (adapted from ref. 112).

| Gas/vapor | Permeability[b]/barrer[c] | Ideal selectivity over $N_2$ |
|---|---|---|
| $N_2$ | (0.6) 280 | — |
| $O_2$ | (3.0) 600 | ~2 |
| $CO_2$ | (13) 3 200 | ~12 |
| $H_2O$ | 23 000 | ~80 |
| Ethanol | 45 000 | ~160 |
| Chloroform | 283 000 | ~1000 |
| Toluene | 1 460 000 | ~5200 |

[a] PDMS RTV 615, measured at 40 °C. [b] Numbers in brackets represent data for a typical glassy polymer to illustrate the high permeability of PDMS (polyimide, Ube Industry, measured at 60 °C).[6] [c] 1 barrer = $1 \times 10^{-10}$ $cm^3$(STP) cm $cm^{-2}$ $s^{-1}$ $cmHg^{-1}$.

A critical note has to be placed in interpreting the presented permeability data. First, as mentioned earlier, permeability is a strongly material dependant property. For PDMS, this means that the value may vary for different types of prepolymer solution and crosslinking agent, and the chosen ratio. Secondly, data is also strongly temperature dependent, as was demonstrated by Hagg.[103] Finally, when using mixed gasses such as air, competition between species can lead to strong deviations from the pure gas permeabilities. Merkel *et al.* have extensively determined permeability, solubility and diffusion data for a wide range of gasses in PDMS, including fluorinated gasses.[104] In their article also theory, fundamental mechanisms and trends are reported, making it a suitable starting point for any researcher using PDMS for gas or vapor transport.

Since the flux of gasses and vapors is inversely proportional to the membrane thickness, researchers have strived for minimization, only limited by the low mechanical strength of very thin PDMS films. At this moment, the smallest reported value for free-standing PDMS membranes is 7 μm.[75] In common membrane technology practice, the mechanical stability issue is avoided by using porous supports. PDMS prepolymer solutions are diluted with a solvent, typically hexane, and coated on the support. This approach enables PDMS layers in the sub-micron range. However, as Zanzotto *et al.* concluded, it is important to know which step in the system presents the major resistance to mass transfer.[72] For PDMS bioreactors, they found that the uptake of oxygen was limited by absorption in the *culture medium* rather than diffusion through the membrane. In such a case, a reduction in membrane thickness, which complicates the production process, is not necessary.

In microfluidic literature, the high permeability of PDMS is mostly exploited for supply of oxygen or removal of carbon dioxide, especially in cell related experiments. However, as is visible in Table 2, permeability for water vapor is even 1–2 orders in magnitude higher. Several authors have pointed out that evaporation of water can therefore form a serious issue that should be taken into account. Verneuil *et al.* demonstrated that the permeation of water through PDMS films can lead to flow velocities in the channels up to 20 μm $s^{-1}$, depending on channel geometry.[76] Especially in PCR reactions, where samples are heated for long times, the evaporation may lead to deviations. Randall and Doyle performed experiments using latex beads, and obtained even higher flow velocities in microfluidic channels, up to 100 μm $s^{-1}$.[71] They report their method to be suitable for passive pumping, concentration of chemical species or controlled stacking of microbeads. Zheng and co-workers used the permeability of PDMS for the study of protein crystallization.[78] They prepared water-in-oil emulsions in microfluidic channels and induced crystallization by water removal by evaporation through the PDMS matrix. Leng *et al.* proposed this 'crystallization by evaporation' principle for kinetic exploration of phase diagrams.[85]

Several solutions are available for cases where permeation of water is unwanted. First, the complete chips can be submerged in water, thereby eliminating the driving force for permeation.[71] This solution is also applied in other groups.[78,83] Another possibility is to work in a closed chamber with high humidity.[72] However, one should be careful when working with concentrated solutions in the chip, since osmotic pressure effects can lead to transport of water *into* the chip. Finally, since the evaporation is directly related to the diffusion distance, one could make very thick chips.

Another difficulty with PDMS is the swelling behavior in organic solvents, and related to this, high permeability for organic vapors. The values for some typical solvents have been included in Table 2. Data for the compatibility of PDMS with a wide range of solvents can be found elsewhere.[105] The combination of swelling and high permeability makes PDMS chips less suitable for *e.g.* organic synthesis, unless the material is chemically or physically modified. Bennett *et al.* have published a thorough study on modification of PDMS with a wide range of functionalized groups and its consequences for permeability.[106] Although the incentive for their research was to *increase* solvent permeability, the presented data can also be used to find the functional groups that reduce swelling and permeability. In their article they also review physical modifications, such as the addition of fluorinated copolymers or zeolite powders. The last mentioned material causes a decrease in water sorption and an increase in effective path length, leading to much lower water evaporation rates. Instead of modifying PDMS, another option is to search for new crosslinkable polymers with lower swelling degree. Rolland and co-workers developed a photo curable "liquid teflon" material that can be used to fabricate chips suitable for organic synthesis.[107] Such material development within the field of microfluidics may also have its impact on macro scale membrane technology, where swelling issues lead to decreased membrane selectivity.

## 5. Implementing membrane technology on-chip yourself

In the previous paragraphs all kinds of membrane applications and their use in microfluidics have been discussed. Furthermore, the methods to incorporate membrane features on chip have been categorized and explained. Now the question may arise, how do you choose the right membrane material, type and fabrication method for a certain application? And what challenges may be encountered when operating a membrane-based system? These questions will be addressed below.

### Membrane selection

Fig. 6 represents a scheme with criteria that can be used as a starting point in the selection process. In our opinion, the initial approach should be based on choosing the best membrane *material and type* for the targeted application. Subsequently, fabrication methods and practical considerations can be taken into account. Specific information on membranes can be found in membrane literature mentioned earlier and in datasheets of membrane suppliers on the internet. In case the desired membrane properties are not met by any commercial membrane, it is worthwhile considering an in-house preparation of membranes. The preparation route is fairly simple and enables the use of more exotic materials. Also, functionalization of existing membranes may be a good option. The following authors have compared different membrane types and materials, and their reasoning could be of interest in the selection process. Ohira *et al.* have evaluated different types of Teflon and polypropylene membranes for use in gas sensors, having pore size and thickness as variables.[17] Cai *et al.* tested Teflon membranes with pore size of 0.2, 0.45 and 1.0 μm as supports to obtain a stable oil/water interface.[31] They found an improved extraction efficiency with larger pore size, but the effect was not very strong. Torto *et al.* have evaluated different membranes for microdialysis sampling of oligosaccharides.[42] Influence of membrane material and morphology was evaluated for extraction factors, permeability, temperature stability and protein interaction. Finally, Thorslund and co-workers have recently tested different membrane materials for whole blood filtration.[33] These materials, including polypropylene, polycarbonate, polyethersulfone, polyvinyldifluoride and cellulose acetate, were evaluated on the bases of non-specific adsorption of free and protein-bound testosterone.

Since the application of membranes in microfluidic devices is relatively new, the necessary information for choosing the best membrane type and operating conditions may not be directly available. In those cases, modeling and simulation of mass transport can be a very useful tool. Already several publications can be found in the literature on membrane related transport in microfluidic devices. Examples include (a) oxygen transport in PDMS based chips for micro bioreactors[72] or oxygen sensors;[82] (b) oxygen transport through dense perovskite membranes in solid oxide fuel cells;[108] (c) hydrogen

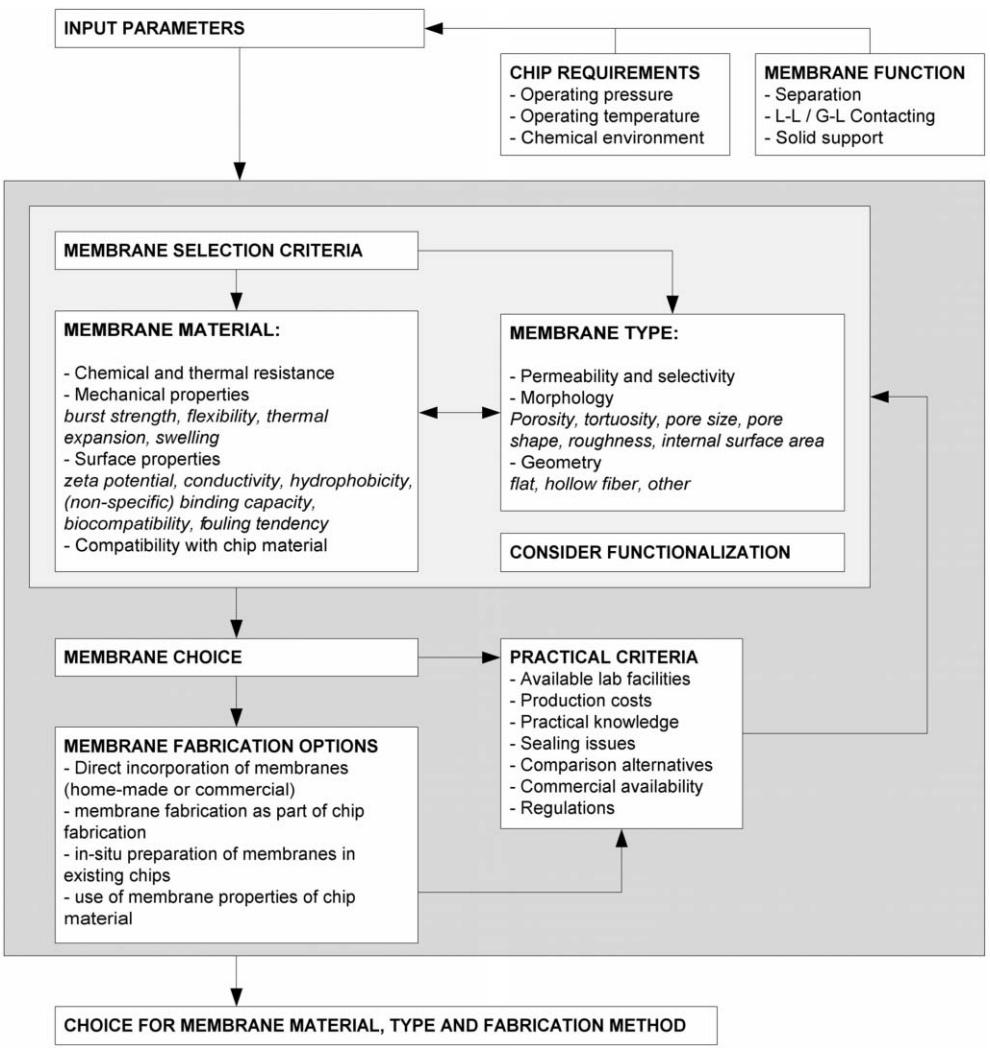


**Fig. 6** Selection scheme for choice of membrane material, type and fabrication method.

transport through noble metal membranes in water gas shift reactions[108] or dehydrogenation reactions;[109] (d) fluor transport through porous membranes in direct fluorination reactions;[110] and (e) transport of water through zeolite membranes in condensation reactions.[51] Based on these models the influence of parameters such as permeability, pressure, flow profiles and concentration on the performance of a microfluidic device with incorporated membrane can be estimated.

### Challenges

Although membranes are very versatile in use, there may be challenges besides the traditional sealing issues that have been mentioned before. Our goal here is not to discourage the integration of membranes, but to present an honest view, keeping the threats of macro-scale membrane technology in mind. The following challenges might be encountered.

First, there is the issue of concentration polarization. In concentration polarization, the removal rate of a solvent from a solution through a membrane is faster than the transport of new solvent from the bulk to the membrane surface. The result, an increased local concentration of solute, leads to a decrease in effective driving force over the membrane and therefore a loss in performance. The macroscale solution to this problem is to induce vigorous mixing at the membrane surface, in order to reduce the thickness of the concentration polarization layer. However, in the laminar regime of microfluidics, this degree of mixing is not achievable. Therefore, concentration polarization is a serious effect to be evaluated.

Second, and related to concentration polarization, fouling and/or scaling of the membrane may occur. Fouling tendency strongly depends on impurities and on interactions between components in the feed and the membrane material. Although the ratio of surface to volume is very high in microfluidics, there will still be a point in time where most membrane area has been covered by a fouling layer that limits transport. At this moment, it is not clear whether standard cleaning procedures are as effective on the micro scale as on the macro scale. Therefore, it may be necessary to prefilter all solutions before entering a chip. Another approach, if permitted by manufacturing costs, would be to use membranes in disposable devices.

Third, in many membrane processes the driving force for transport is a difference in pressure. In most macro-scale applications the pressure difference is assumed constant along the membrane, meaning that pressure drops in the axial direction are neglected. For microfluidic chips this assumption may not be valid, since the channel dimensions approach the pore dimensions of the membrane. Therefore, the driving force may vary in the channel directions, leading to a difference in local performance. Although this principle is not disadvantageous by definition, it is a factor to be considered.

## 6. Summary and outlook

In this review, an overview of the integration of membrane technology in microfluidics has been provided. The main conclusion that can be drawn is that the bond between both fields is vivid and getting stronger every day. The field has shown substantial growth over the last 10 years. The general use of membranes can be found in separation and phase contacting applications. Also the internal surface can be exploited for catalysis or adsorption purposes. Furthermore, membranes can act as a support for cell culturing experiments, where the membrane features can be used to supply nutrients and remove waste products. Clear benefits of membranes include the ease of integration, especially when using a 'clamp-and-play' type of device. Combined with the enormous variety of materials, morphologies and fabrication methods to choose from, devices can be readily tailored to very specific applications. Numerical models are being developed that can provide the necessary information for optimal membrane chip configurations.

Already a lot of the traditional applications of membranes on the macro scale have been tested on-chip, with a bias towards sensors and sample preparation. So what can be expected from the future? Besides further development in the described areas, a second boost of membrane technology can be foreseen in the field of micro reactor technology, where integration of reaction and separation is currently an issue. But also many additional applications and principles can be thought of, and here we will discuss three examples to outline the opportunities.

First, the selectivity of dense membranes has not been exploited yet. In membrane technology, selectivity plays a key role in gas separation applications and pervaporation. Examples for the microfluidic world might be the selective removal of components from a sample gas stream in gas sensors, in order to increase signal to noise ratio. Another option may be found in on-chip pervaporation, where liquids can be separated selectively. This principle may be used in VOC removal from aqueous streams, or in the break-up of emulsions by selectively removing one of the phases. Looking at the high selectivities achievable with PDMS, as presented in Table 2, this material may already be an interesting candidate for future research in this direction.

Second, a sub-field emerging in membrane technology that may be interesting to microfluidics is the implementation of *bipolar* membranes.[111] A bipolar membrane consists of a positively and a negatively charged membrane, with a catalyst in between. By applying a current, water splitting occurs at the interface of the membrane. Since the membranes are either permeable to cations or anions, the protons and hydroxyl ions can be transported to different compartments, one becoming more acidic while the other becomes basic. To keep electro neutrality, charges are compensated by electrode reactions. Since the electrodes can be placed outside the chip, development of gas is not a problem. Therefore, bipolar membranes may be very suitable to create pH gradients on-chip.

A final example of membrane technology that may be downscaled to chip dimensions is membrane emulsification. In this process, one phase is flowing through the channel, while the other phase is supplied through the porosity of the membrane. By switching both phases, both water-in-oil and oil-in-water emulsions can be prepared. The membrane can be used simultaneously for filtration purposes, enlarging the range of possible applications. The droplets produced may be used for the synthesis of monodisperse particles or the study of crystallization.

The bridge between microfluidics and membrane technology works in both directions, meaning that the microworld can also add some advantages of its own to membrane technology. The high surface to volume ratio achievable in microfluidics is expected to push membranes to maximum performance. Furthermore, the laminar flows achievable in microchips may lead to new opportunities. The use of three layer liquid flow as unsupported liquid membranes[2,67,68] is a clear example of a process not feasible on the macro-scale. In conclusion, with so many opportunities in as numerous areas, the general feeling cannot be other than optimistic. The future for membranes and microfluidics looks bright.

## Appendix

| | |
|---|---|
| $\alpha$ | Selectivity |
| $\varepsilon$ | Porosity |
| $\tau$ | Tortuosity |
| $c$ | Concentration |
| BSA | Bovine serum albumin |
| CIEF | Capillary iso electric focusing |
| $D$ | Diffusivity |
| ELISA | Enzyme-linked immuno sorbent assay |
| EOF | Electro osmotic flow |
| ESI | Electro spray ionization |
| HDL | High density lipids |
| MALDI | Matrix assisted laser desorption ionization |
| MS | Mass spectrometry |
| MWCO | Molecular weight cut-off |
| $P$ | Permeability |
| PCR | Polymerase chain reaction |
| PDMS | Poly (dimethylsiloxane) |
| PMMA | Poly (methylmethacrylate) |
| PTFE | Poly (tetrafluorethylene) |
| PVDF | Poly (vinyldifluoride) |
| $R$ | Retention |
| $S$ | Solubility |
| VOC | Volatile organic compounds |

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