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# Controlling and Expanding the Selectivity of Filtration Membranes†

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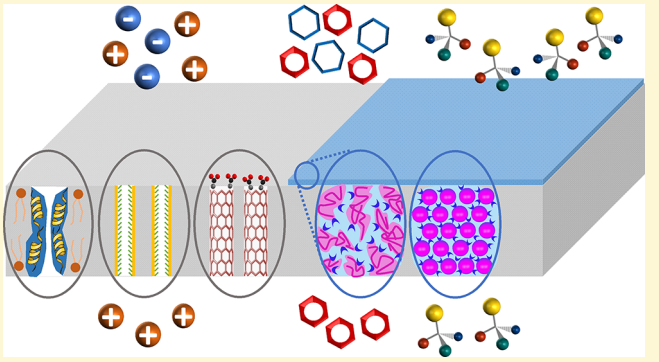
**ABSTRACT:** Chemical separations account for about 50% of costs and energy use associated with chemical and petrochemical manufacturing, corresponding to about 10% of all energy use in the U.S. Membrane separations are highly energy efficient, simple to operate, scalable, and portable. Broader use of membranes is limited by the selectivity of available membranes, mostly confined to the separation of species about an order of magnitude or more different in size in the liquid phase. This perspective focuses on new approaches for creating liquid filtration membranes that can perform more challenging separations. We first discuss the selectivity mechanisms of currently available membranes and compare them with the operation of biological systems that exhibit enhanced selectivity. Then, we review some approaches for creating isoporous membranes with narrow pore size distributions for enhanced size-based selectivity. We discuss biological systems that exhibit selectivity based on factors beyond size and how they can inspire the design of membranes capable of complex separations. After a review of approaches for creating membranes for separating similarly sized solutes, based on their charge, we discuss the development of membranes that can perform even more challenging separations, differentiating between solutes of similar size and charge based on other molecular criteria. This burgeoning area of research promises to transform chemical and pharmaceutical manufacturing if membranes with sufficient selectivity and permeability for realistic separations can be prepared using scalable manufacturing methods.



## 1. INTRODUCTION

Chemical separations account for approximately 50% of costs and energy use associated with chemical and petrochemical manufacturing. On the whole, this corresponds to about 10% of all energy use in the U.S.[1] Separating mixtures is also a critical challenge in pharmaceutical and biopharmaceutical manufacturing, which involves the separation of similar small molecules from each other. Most of these separations are performed by energy intensive unit operations such as distillation, extraction, and absorption. Extraction, absorption, and chromatography also require the use of an auxiliary solvent that can add to the costs and environmental impact of the process.

Membrane separations are extremely energy efficient compared with most other separation technologies.[2,3] For instance, seawater desalination using membranes consumes up to 90% less energy than the thermal methods that previously dominated the field.[4] Membrane systems are very simple to operate. They are modular and easily scalable, capable of addressing both small and large-scale separations. They have small footprints and are portable, exhibit reliable performance that is relatively insensitive to fluctuations in feed composition, and do not require any solvent addition. These advantages have made membrane systems the technology of choice in several separations where sufficiently selective and stable membranes exist. For example, current desalination membranes, designed to retain salt yet pass water, operate at energy efficiencies close to the thermodynamic minimum with lifetimes measured in years in well-designed systems.[4] The use of gas separation membranes in air separation, hydrogen recovery, and natural gas processing is also spreading. Membranes are also widespread in water and wastewater treatment, food and beverage industries, lab and sterile water systems, and biomanufacturing for the concentration of biologic drugs.

Wider use of membrane systems is limited by the availability of membranes that can successfully separate the desired components from each other.[3] Most filtration membranes on the market today are designed to remove all solutes above a given size from a feed stream (e.g., cell debris from a biomolecule solution, hydrated salts from water). Particularly when liquid separations are involved, it is difficult to separate solutes that differ in size by less than an order of magnitude. Nonsize-based separations are rarely attempted using membranes, though many membrane materials exhibit at least some electrostatic contributions to their separation abilities. In other words, the range of separations that can be attempted using membranes is severely limited by membrane selectivity.

If membranes with more controlled selectivity can be designed and manufactured, they can potentially replace more energy-intensive processes such as distillation, extraction, or

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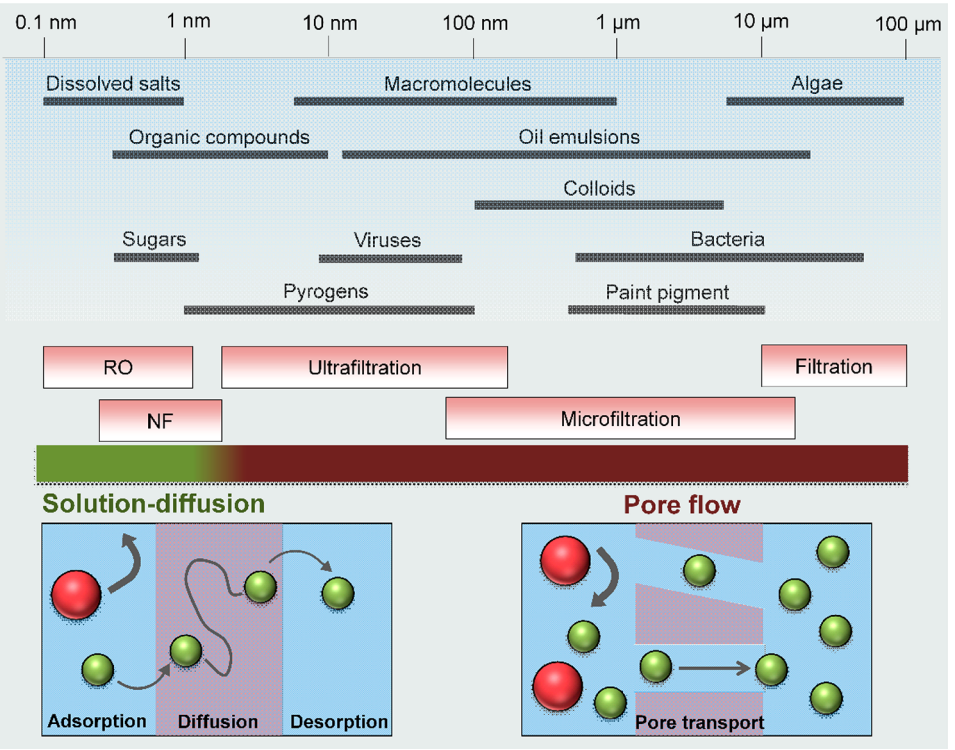


**Figure 1.** Current classification of filtration membranes according to effective pore size and corresponding transport mechanisms in effect. The axis at the top of the figure denotes the typical size scale of filtered materials and thus effective pore sizes of membranes capable of removing them.

chromatography. This would transform the manufacturing processes for many organic chemicals including active ingredients of pharmaceuticals, petroleum products, and bioderived chemicals. Yet, this is a challenging task. Creating isoporous membranes, or membranes with narrow pore size distribution, requires extreme precision in creating a high density of regular features only nanometers in size. This is difficult with scalable processes needed to reliably manufacture membrane rolls several feet in width, thousands of feet in length. Attempting more complex separations, such as the separation of solutes of similar size, requires further manipulating the membrane chemistry to emphasize differences in solute−membrane interactions. These challenges make the search for highly selective membranes manufactured through scalable methods a growing membrane research area with much to explore.

This perspective focuses on novel approaches for designing and manufacturing polymeric membranes with controlled selectivity, with the ultimate objective of developing membranes that can address new separations. The main focus is on liquid separations, as most applications of complex chemical structure- based separations (e.g., pharmaceutical manufacturing, extraction of biomolecules) occur in liquid solutions. We particularly emphasize small molecule separations, though some protein separations are also discussed. We first discuss selectivity mechanisms of membranes on the market today, and briefly discuss efforts to create membranes with improved size-based selectivity by creating narrow pore size distributions. Then, we overview some natural systems that can inspire the design of new membranes with more complex selectivity. The rest of this perspective focuses on approaches for creating membranes that separate solutes based on criteria other than size. A large portion of the literature in this field focuses on charge-based separation of solutes in water. Beyond direct applications, this often serves as an initial proof-of-concept for novel approaches. We then present the relatively few reports of membranes that separate solutes, especially small organic molecules, based on other chemical criteria such as hydrophobicity or chirality. Finally, we discuss our outlook on future directions and on key challenges that still need to be addressed.

## 2. MEMBRANE SELECTIVITY TODAY

Liquid filtration membranes today are typically classified based on the size of solutes or particles they retain (Figure 1),[5,6] though other classifications exist based on operation pressure. Microfiltration (MF) membranes are those with pores 0.1−10 $\mu$m in diameter. They are typically used to remove bacteria and particulates. Membranes with pores 2−100 nm in diameter are classified as ultrafiltration (UF) membranes, though their effective pore size is typically reported in terms of molecular weight cutoff (MWCO), defined as the molecular weight of a probe solute retained by 90%. UF membranes can retain viruses, macromolecules, and emulsified oils. Both MF and UF membranes have porous selective layers, and transport through them follows the pore flow mechanism. This means components that are smaller than the pore size pass through, whereas larger solutes are retained. Separations based on this sieving mechanism are sensitive to the distribution of pore sizes. Commercial porous UF membranes made by traditional fabrication methods usually do not have a narrow pore size distribution or high pore density, especially as membrane pores get smaller.[7] This is why UF and MF are often used to retain all components above a certain size (e.g., sterilization, removal of organic macromolecules for wastewater treatment, concentration of a protein drug), but rarely to separate components of the same class (e.g., separating two proteins, even proteins and viruses) from each other. Industry experts typically suggest it is very challenging to separate liquid mixtures containing


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components whose sizes differ by less than an order of magnitude using membrane filtration processes.

Nanofiltration (NF) and reverse osmosis (RO) membranes are typically included in the same membrane selectivity chart that links removal with solute size. The 1996 IUPAC nomenclature defines RO membranes as those through which only solvent molecules pass through, whereas particles and dissolved molecules smaller than 2 nm are rejected in NF.[5] In practice, NF membranes typically retain doubly charged ions and are designed for water softening, whereas RO membranes retain all salts and can be used for desalination. Yet, their selective layers are not porous. NF and RO membranes typically feature a continuous, thin (~100 nm or less) polymer layer supported by a porous layer that serves as mechanical support. These layers were initially made of the same material, with the asymmetric morphology, termed an integrally skinned membrane, formed though the carefully controlled manufacturing process utilizing nonsolvent induced phase inversion (NIPS). The initial discovery of this process by Loeb and Sourirajan[8] enabled desalination membranes with sufficiently high flux to be used for water treatment. The formation of thin film composite (TFC) membranes, which consist of a porous support coated by a very thin, nonporous layer of another polymer, enabled independent optimization of these two components and achieved better performance. The process of interfacial polymerization (IP) to create cross-linked polyamide selective layers[9] led to the membrane chemistry that most commercial NF and RO membranes utilize today.[10] Transport through RO membranes is best described by the solution-diffusion model, where components that permeate the selective layer get solvated in the polymer, diffuse across, and desorb into the permeate side. Selectivity arises from differences in solubility and diffusivity in this polymer selective layer.[4,6,11] Transport through NF membranes is believed to be in between, or a combination of, pore-flow and solution-diffusion mechanisms, i.e., between UF and RO membranes.[12]

Most membranes on the market today are designed for the filtration of aqueous solutions. However, the polymeric materials used in most of these membranes dissolve, swell, or degrade in many organic solvents. This makes them unusable for the separation of organic mixtures or for the removal or concentration of solutes in nonaqueous solvents. There are extensive and highly demanding applications of such separations including the concentration of products in chemical and pharmaceutical manufacturing, solvent recovery and exchange, catalyst recovery, and the separation and purification of organic compounds such as drugs or consumer chemicals. This has driven extensive research in developing membrane materials that are robust and selective in organic solvents, and membrane processes that utilize such membranes for energy-efficient separations. In general, the goal has been to translate membranes that operate well in aqueous media, particularly NF and RO, to perform in the presence of organic solvents. Organic solvent nanofiltration (OSN), also termed solvent resistant nanofiltration (SRNF), is used to describe membranes that perform NF-type separations in nonaqueous solvents, with typical MWCO values in the 200−1000 Da range.[13] The selectivity of OSN has both size-based and solubility-driven components.[13−16] More recently, organic solvent reverse osmosis (OSRO) membranes with even smaller effective MWCO values have been reported, with the goal of achieving solvent/solvent separations.[14] OSN membranes have been commercially available through several companies. They have been demonstrated to successfully address critical processes in many industries, including lube oil dewaxing, biodiesel production, catalyst recovery, and product concentration and solvent recovery in pharmaceutical and chemical manufacturing.[17] While OSN membranes can successfully address many solvent/solute separations, their ability to separate two solutes from each other is limited unless these solutes exhibit large differences in size.[16] This limits the applications in which they can be used. While improving the selectivity of OSN membranes is a highly active research area, rational control of the selectivity of OSN membranes is, for now, challenging given the complex separation mechanisms involved in their use.

An overall trade-off between selectivity and either permeance (defined as flux normalized by applied pressure) or permeability (defined as permeance normalized by membrane thickness)[5] can be observed for the wide variety of synthetic membranes, used in processes as different as gas separation, desalination, and sterile filtration.[18] Membranes with high selectivity between desired components typically have lower permeances or permeabilities, leading to higher energy use. The permeability−selectivity trade-off is inherent to the solution-diffusion mechanism in effect for gas separation membranes with homogeneous polymer selective layers, linking membrane selectivity to gas diffusivity.[19] A similar inherent trade-off exists for water/salt separation in desalination membranes, which also follow the solution-diffusion model.[4,11,20] Interestingly, similar behaviors are observed for other synthetic membranes that operate on other transport mechanisms, including protein separation in porous UF membranes[7] and ion transport in charged polymers for electrically driven separations.[21] This leads to an effective "upper bound" of performance, describing maximum selectivity achieved for a given permeability, for instance, reported for various membrane processes. This upper bound has been used to describe the state-of-the-art for each membrane process, and as a benchmark for the success of new membrane technologies under development. For instance, isoporous membranes with very narrow pore size distributions, described below, can have high selectivity combined with high permeance, enabling researchers to overcome this upper bound through a radically new approach.[22]

## 3. ISOPOROUS MEMBRANES: BETTER SIZE-BASED SELECTIVITY

Essentially all UF and MF membranes on the market today are manufactured using the nonsolvent induced phase separation (NIPS) process. NIPS involves casting a polymer solution on a solid substrate followed by immersion in a nonsolvent bath.[23] The solvent in the polymer solution mixes with the nonsolvent, causing the polymer to precipitate on the substrate as a solid, porous membrane. NIPS-prepared membranes with a mesoporous skin display a fairly broad pore size distribution in their selective layer. This likely leads to the permeance/selectivity trade-off described above.[7,18] It also limits their use in several applications that require better size-based selectivity or the capability to separate solutes closer in size, including the removal of viruses from protein solutions[24,25] and the separation of two proteins from each other.[26−28] Several approaches that utilize self-assembly of biological pores and/or block copolymers have targeted this gap, offering significant benefits with their narrow pore size distributions, high porosity, and adjustable chemical and physical properties.



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Many of these "isoporous" membranes can also serve as platforms to implement new routes for creating selective and functional nanopores, as discussed below.

The most established techniques to fabricate isoporous UF and MF membranes today are track etching, anodization of aluminum films, and lithography.[29−31] Figure 2 presents the

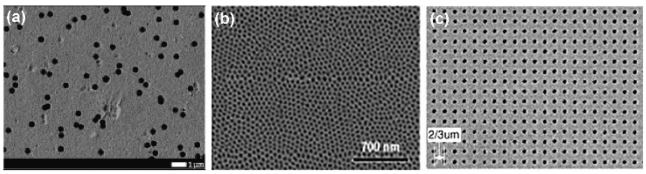


**Figure 2.** Surface SEM of membranes fabricated by track etching, anodic aluminum oxide (AAO), or lithography. (a) Track-etched poly(ethylene terephthalate) (PET) membrane with 423 ± 25 nm pores. Reprinted from ref 35. Copyright 2018, with permission from Elsevier. (b) Anodic aluminum oxide (AAO) film formed by mild anodization. Adapted with permission from ref 30. Copyright 2006, Springer Nature. (c) Polyimide microfiltration membranes with 200 nm pores fabricated by aperture array lithography. Reprinted from ref 33. Copyright 2004, with permission from Elsevier.

pore array and morphology of representative membranes fabricated by track etching, anodic aluminum oxide (AAO), or lithography. In track etching, a latent track of polymer is degraded by ion irradiation, and then chemically etched to transform the damaged area into pores.[32] Membranes manufactured by track etching have a uniform pore size distribution; however, their porosity is limited to <10% due to potential pore superimposition of tracks creating double/triple pores. On the other hand, anodic aluminum oxide (AAO) membranes comprise tightly packed pores of hexagonal geometry in the 10−200 nm diameter range, but their lack of flexibility and brittleness limit their use. Lastly, lithography techniques have emerged as a fairly inexpensive alternative to prepare MF membranes with periodically spaced, uniform cylindrical pores.[33,34] However, lithography is a multistage, laborious process, and it is challenging to attain smaller pores in UF range.

Self-assembly broadly stands for autonomous arrangement of pre-existing components into organized structures or patterns without external guidance.[36] Self-assembly is ever-present in nature, from protein folding to the formation of the cell membrane and other functional biological nanostructures. It is also a convenient avenue for forming membranes with well-controlled nanostructure (e.g., pores) and surface chemistry without the need for complex manufacturing techniques.[37,38] Some of the earliest records of self-assembled membrane selective layers with narrow pore size distribution directly utilized biological materials. The outermost cell envelopes of many eubacteria, and archaebacteria have crystalline surface layers ("S-layers")[39−42] that possess 2−8 nm pores,[43,44] in the UF working range. These S-layers were incorporated into UF membranes as selective layers to leverage these attractive features. In one of the first examples of UF membranes with S-layers, recrystallized S-layer self-assembly products were applied as selective layer on a support membrane.[45] The isolated and purified cell wall protein of bacteria was reconstituted as an ultrathin layer on a porous MF membrane. This layer was then fixed by cross-linking with glutaraldehyde. The resultant UF membranes showed a precisely ordered S-layer protein structure with 5 nm pore size and a sharp molecular weight cutoff (MWCO), with the rejection rising from 0 to 100% within the 30 to 40 kg/mol range. In addition, glutaraldehyde-treated S-layers were shown to have a net negative surface charge owing to free carboxyl groups of the amino acids. In a follow-up study, these carboxyl groups were chemically activated with carbodiimide, and macromolecules with different sizes and structures were immobilized on the membrane surface through the reaction between their amino groups and the carbodiimide.[46] These modified S-layer ultrafiltration membranes showed strong resistance against protein adsorption. Overall, S-layer ultrafiltration membranes had significantly improved size-based selectivity compared to UF membranes manufactured by NIPS. Yet, scale-up of this system was deemed not feasible due to challenges in biopolymer isolation, purification, reconstitution and reproducibility of defect-free films at large-scale.

Block copolymer (BCP) self-assembly has emerged as a promising alternative that can bypass these challenges while achieving narrow pore size distribution and high porosity. BCPs consist of incompatible blocks that microphase-separate into distinct domains with an equilibrium domain size of 3−100 nm. The equilibrium domain size and geometry are determined by the Flory−Huggins interaction parameter between blocks and degree of polymerization. Diblock copolymers may self-assemble into spheres, cylinders, gyroids (a periodic bicontinuous cubic structure), and lamellae.[47−49] Triblock polymers may lead to even more complex geometries. Among these nanostructures, the cylinder and gyroid phases attract great attention from membrane scientists because they can be tailored to form membranes with densely packed nanopores of uniform size.

Porosity can be imparted to self-assembled BCP structures following their formation and stabilization/fixation to create membranes by, for example, selective etching of one of the blocks.[50,51] Another strategy is the addition of a component that interacts with and swells one of the domains during membrane formation, followed by its removal by leaching to leave behind void spaces.[24,52] For instance, thin films were spin-coated from blends of poly(styrene)-*block*-poly(methyl methacrylate) (PS-*b*-PMMA) BCP with PMMA homopolymer.[24] Cylindrical PMMA domains were aligned perpendicular to the surface after high temperature annealing under vacuum. The thin film was removed from the silicon wafer by immersion into HF, and then immersed into acetic acid to extract the PMMA homopolymer. A composite membrane was prepared by carefully transferring the thin film on a porous PS support. The membrane had high flux and could efficiently remove viruses from the feed, and the nanopore size could be adjusted by varying the blend composition.[52] However, scale-up of this approach would be challenging because manufacturing steps used are not readily implemented in industrial systems.

To achieve isoporous membranes using highly scalable approaches, BCP self-assembly has been integrated into the NIPS process to establish a single-step membrane manufacturing method called self-assembly/nonsolvent induced phase separation (SNIPS) (Figure 3).[53−57] SNIPS involves the formation of membranes from BCPs using a carefully controlled NIPS process that utilizes a mixture of two cosolvents with different volatility and polarity. The supramolecular assembly of the block copolymers into micelles, followed by ordering and merging of these micelles as one of the cosolvents evaporates and the system is exposed to water,


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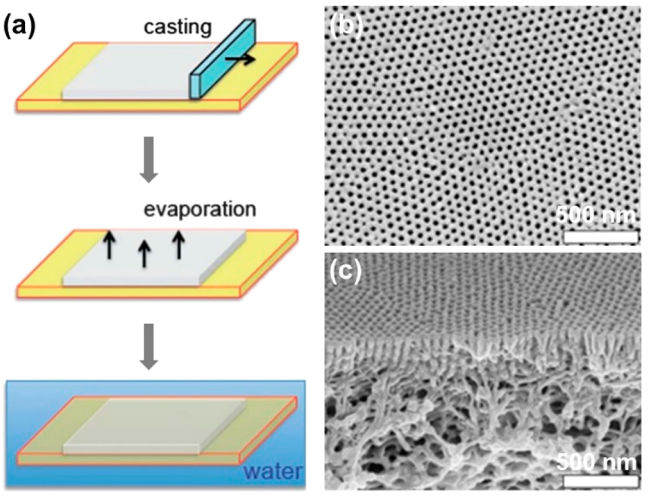


**Figure 3.** (a) Schematic of the SNIPS membrane fabrication technique and resulting membrane morphology. A polymer solution is prepared by dissolving a block polymer in a solvent or mixture of solvents. The solution is then drawn into a thin film through simple casting techniques (e.g., using a doctor blade). Solvent is allowed to evaporate from the thin film in a controlled manner for a predetermined period of time. Then, the thin film is plunged into a nonsolvent bath (e.g., water). The nonsolvent causes the polymer to precipitate, which kinetically traps the nanostructure of the membrane. The result is a nanoporous membrane with an asymmetric structure that comprises a highly selective active layer situated on top of a gutter layer with a high porosity. Republished with permission of Royal Society of Chemistry, from ref 61. (b and c) SEM micrographs of the top layer and cross section of membranes made using the SNIPS process, showing the regular order of membrane pores prepared by SNIPS. Reprinted by permission from ref 62. Copyright 2007, Nature Publishing Group.

has been demonstrated to drive pore formation (Figure 3).[58] This leads to a very narrow pore size distribution and high porosity.[59,60] However, combining the right selective solvents and process conditions is crucial. Cryo-scanning electron microscopy and other advanced imaging technologies have proven useful in tracking the effect of solvent composition and additives on supramolecular assembly in solution, and also on the ultimate membrane morphology.[47]

The first example of an isoporous SNIPS membrane was developed using the diblock copolymer polystyrene-*block*-poly(4-vinylpyridine) (PS-*b*-P4VP) with ∼15 wt % P4VP.[55] The morphology of PS-*b*-P4VP membranes produced by SNIPS showed a fairly thin, ∼100−200 nm layer of isoporous channels on top of a sponge-like macroporous support (Figure 3).[26] Pore size typically ranged between 3 to 20 nm.[26,53−55,59,61] The pore size of SNIPS membranes can be controlled by mixing BCPs with different additives. Additives that preferentially interact with one of the BCP blocks through coordination or hydrogen bonding can alter domain size during self-assembly.[63] For instance, bivalent cations present in the casting dope complex with pyridine and assist the formation of isoporous membranes.[64] In addition, hydrogen-bonding compounds of −OH/−COOH functionalized organic molecules[65] and ionic liquids[66] were proven effective in tuning the morphology of PS-*b*-P4VP asymmetric nanoporous membranes. Addition of carbon nanotubes in small amounts has beem shown to stimulate a stronger network between micelles and result in more stable membranes.[60] Additives used in other BCP membranes span organic materials such as homopolymers,[67] carbohydrates,[68] and small organic molecules,[65] as well as inorganic materials such as metal salts[59,64,69] and $TiO_2$ nanoparticles.[63] Overall, use of additives served as an efficient strategy to achieve membranes with highly uniform pores, improved permeance and selectivity, depending on the system of interest. The narrowest domain size attained with BCP self-assembly is ∼3 nm.[70] Thus, membranes prepared by BCP self-assembly are excellent for separations in the UF size range. However, accessible pore sizes are still substantially larger than required for small molecule separations, RO and NF applications. SNIPS process has been modified to access these small pore sizes by modifying BCP self-assembly. In this vein, using mixtures of different block copolymers were found to yield membranes with an effective pore size of ∼1.5 nm.[71] Custom-designed triblock copolymers can also yield membranes whose pore size can be modified by exposing them to particular reactants after manufacture to reduce the effective pore size down to ∼1 nm.[56,72] These membranes, however, all comprise charged polymer chains lining their pores. Thus, while they perform size-based separation of neutral solutes, their selectivity for charged compounds is heavily influenced by electrostatic interactions. Nonetheless, this approach constitutes a very promising method for creating membranes with charged, functionalizable nanopores for many applications.

To create <3 nm nanopores without charged groups, polymers with random and comb-shaped architectures have been exploited. The microphase separation of amphiphilic comb-shaped copolymers with hydrophobic backbones and hydrophilic poly(ethylene oxide) (PEO) side-chains were studied as membrane selective layers.[73−78] These copolymers microphase separate to form bicontinuous nanodomains of PEO and the hydrophobic backbone, with domain size controlled by side-chain length. PEO domains can absorb water and act as effective nanochannels with an effective size of ∼1 nm in diameter,[74,75] allowing permeation of water and solutes sufficiently small to pass through the channels. These membranes not only displayed size-based separation of dye molecules, but also exceptional fouling resistance. As the pores are partially filled with the PEO chains, the effective pore size of the membrane was responsive to parameters that changed the solvent quality of the feed for PEO, including temperature, pressure, ionic strength, and the presence of an alcohol.[76] While these responsive properties are intriguing for some applications, they can also lead to changes in selectivity during operation due to fluctuations in feed properties. It should also be pointed out that these membrane chemistries have the potential to be further functionalized through the inclusion of a third monomer during synthesis, to create functional pores with different rejection properties.[79,80]

Random copolymers that combine hydrophilic and zwitterionic repeat units have also been shown to self-assemble into similar water-permeable nanochannel networks (Figure 4a,b).[81] When coated onto a porous support, these membranes form isoporous membranes with ∼1 nm effective pore size, exhibiting a sharp rejection curve independent of solute charge (Figure 4c).[81,82] These membranes can be formed of copolymers with a variety of hydrophobic[81] and zwitterionic[82] groups. For a specific subset of zwitterionic repeat units, membranes exhibit unprecedented degrees of fouling resistance, with little to no flux decline even during the filtration of high fouling solutions and no measurable flux decline that cannot be recovered by a simple water rinse (Figure 4d).[81−83] The effective pore size of these membranes is particularly


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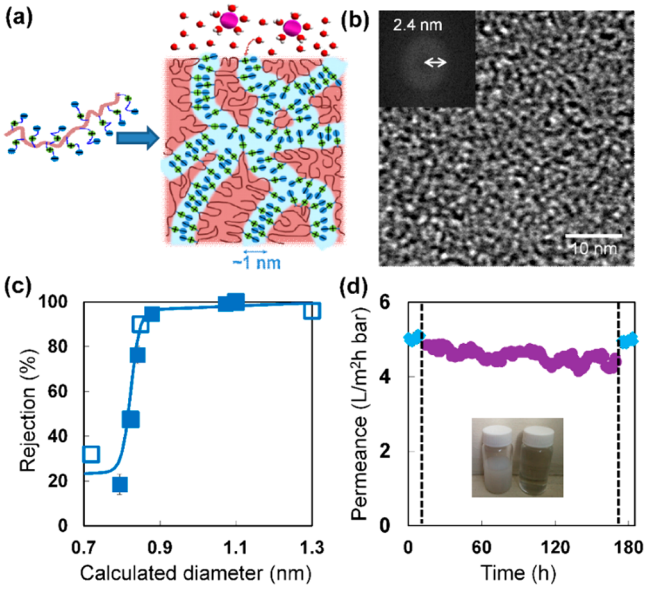


**Figure 4.** Formation of isoporous, highly fouling resistant membranes through the self-assembly of zwitterionic random copolymers. (a) Schematic showing the self-assembly of zwitterionic groups into bicontinuous networks of zwitterionic (indicated by green and blue charged groups) and hydrophobic (pink) domains. The zwitterionic domains act as a network of hydrophilic nanochannels ~1 nm in diameter, held together by the glassy hydrophobic domains. Water molecules and solutes smaller than or equal to the domain size (red) can enter these channels and permeate through the membrane, while larger solutes (fuchsia) are retained. Reproduced from ref 81 with permission from Elsevier. (b) Transmission electron microscopy (TEM) brightfield image of the self-assembled nanostructure of a zwitterionic copolymer, poly(trifluoroethyl methacrylate-*random*-sulfobetaine methacrylate) (PTFEMA-*r*-SBMA), exhibiting bicontinuous networks of zwitterionic (dark) and TFEMA (light) microphases. The inset shows fast Fourier transform (FFT) of the images with the characteristic period of 2.4 nm shown on the arrow, corresponding to a channel size of ~1.2 nm. Reprinted with permission from ref 82. Copyright 2017 American Chemical Society. (c) Rejections of charged (filled symbols) and neutral (empty symbols) dyes by a PTFEMA-*r*-SBMA TFC membrane. Charged and neutral dyes roughly fit onto a single rejection curve, demonstrating the selectivity is size-based, and not charge-based. The sharp rejection curve demonstrates narrow pore size distribution. Reproduced from ref 81 with permission from Elsevier. (d) Dead-end filtration of an oil emulsions through PTFEMA-*r*-SBMA TFC membrane. Plot shows the initial permeance of water (blue), followed by the permeance of a 1500 mg/L oil-in-water emulsion (purple). Then, the membrane is rinsed with water several times, and water permeance is measured again (blue). The membrane exhibits no measurable irreversible flux loss. Inset shows a photo of the feed (left) and permeate (right), showing high oil removal. Adapted from ref 83. Copyright 2017, with permission from Elsevier.

promising for small molecule separations based on size, difficult to achieve by existing membranes. Their manufacture is simple, involving only the coating of a porous support with the copolymer. If the selective layer is thin, membrane permeances much higher than commercial membranes with similar nominal MWCO, but broader pore size distribution. However, to date, it has been difficult to tune the pore size of these membranes.

In addition to self-assembling polymers, lyotropic liquid crystals (LLCs) have been proposed as a class of materials for designing membranes with very small pores.[84−90] In a selective solvent, amphiphilic LLCs can self-assemble into various ordered structures, including lamellar, cylindrical, hexagonal, and 3D bicontinuous cubic phases with interconnected channels (Figure 5).[91,92] To form stable selective layers for

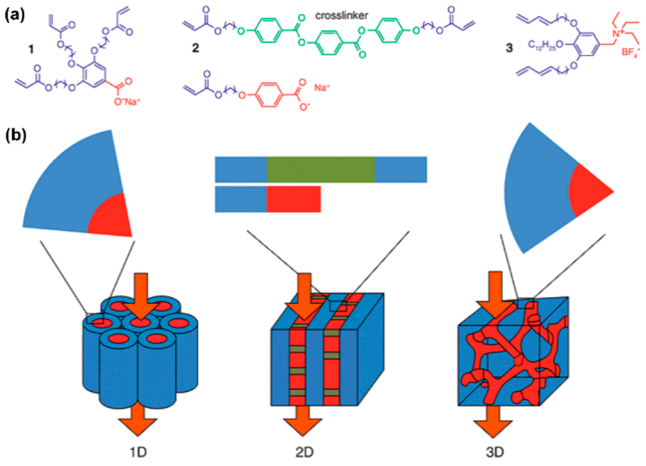


**Figure 5.** Liquid crystal membranes. (a) Examples of chemical structures of the LCs used in the construction of nanoporous membranes. One columnar or hexagonal LC, two smectic or lamellar LCs, and three bicontinuous cubic LCs. (b) The self-assembly of these materials to form nanostructured materials, with respectively one, two, or three-dimensional pores. The red part represents the pore while the blue fraction is the molecular region. Adapted from ref 91. Copyright 2010, John Wiley and Sons. Reprinted from ref 92. Copyright 2016, Springer-Verlag Berlin Heidelberg.

filtration membranes, self-assembly of polymerizable LLCs into one of these geometries is induced by appropriate selection of a solvent system and amphiphilic monomers.[84,86] The self-assembled structure is then fixed by photo-cross-linking. Membranes with effective pore size between ~0.29−1.2 nm have been achieved using polymerizable LLCs.[87−90] To manufacture the early LLC membranes for small molecule separations, a self-assembling inverse hexagonal LLC containing ionizable carboxylic acid groups was coated as a thin film on porous support by solution casting, followed by solvent evaporation and photo-cross-linking.[87] The amphiphilic self-assembly process localizes the ionic headgroups exclusively at the hydrophilic/hydrophobic interface, resulting a membrane with negatively charged pores of ~1.2 nm. The membrane exhibited size-based separation for small organic anionic solutes, but very low flux as many of the cylindrical domains were not aligned vertically to the surface. In a more recent approach, a cubic phase forming LLC was hot-pressed onto a porous fabric and then cross-linked to form a supported membrane with a bicontinuous 3D network of channels.[88,90] The effective pore size of the membranes was estimated between ~0.29−0.75 nm depending on the pore model used, and salt ions as well as organic solutes with diameters above 9 Å were rejected. The bicontinuous cubic structure eliminated the need for vertical alignment of the channels, but the high thickness of the membrane again resulted in low flux.

Thermotropic liquid crystals (TLCs) undergo temperature-driven self-assembly because of phase separation between the ionic and nonionic units of the monomer.[93−99] This leads to bicontinuous cubic structures with a 3D network of narrow channels, which allow passage of smaller molecules. In this vein, TLC membranes were manufactured by coating the


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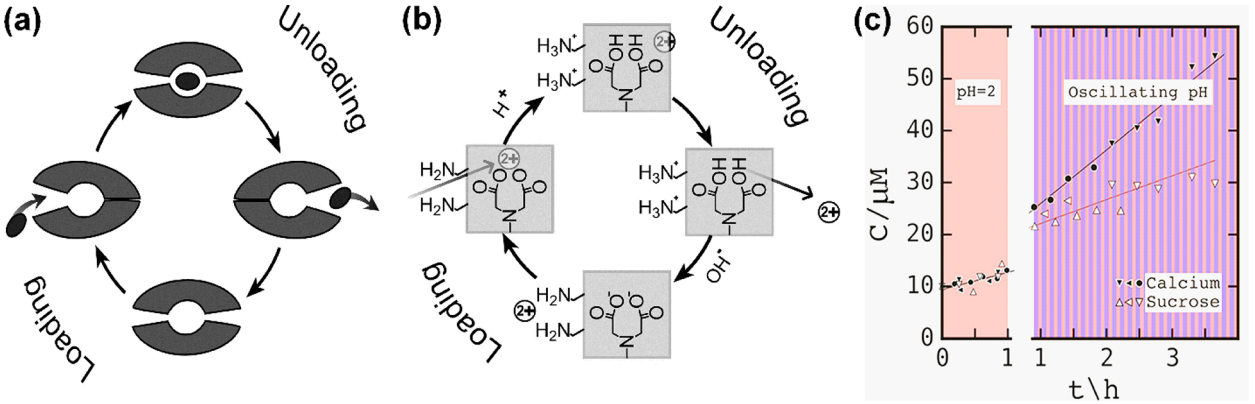


**Figure 6.** Selective transport of $Ca^{2+}$ ions over sucrose through a biomimetic membrane modeled after ion pumps. Reprinted with permission form ref 106. Copyright 2018 American Chemical Society.

bicontinuous cubic TLC phase on a layered base.[99] The membranes showed 0.6 nm pore size, and the flux and salt rejection were found approximately in the nanofiltration range. One drawback in this composite system is the multistage process, which renders scalability challenging. Despite that the bicontinuous organization in TLCs are promising for membrane applications, TLCs have not been widely studied by membrane researchers.

More recently, more scalable methods to create thin film composite (TFC) membranes with a polymerized LLC selective layer have been developed.[84] The use of glycerol instead of more volatile solvents and a specially designed polymerizable surfactant enabled the formation of LLCs that remained stable during a coating process. The resultant membranes exhibit rejection properties between NF and RO membranes.[100] Due to their uniform pore size, charge, and subnanometer pores, cross-linked LLCs are very promising for treatment of complex, highly saline wastewaters.[89,101] The effective pore size of LLC-based membranes can be further modified through postprocessing methods, such as by cross-linking the bicontinuous cubic LLC phase with butyl rubber[102] or conducting alumina atomic layer deposition (ALD) inside the pores.[103] The cross-linking method could yield a pore diameter as small as 0.57 nm, tight enough to reject water-miscible nerve agent stimulant by over 99%. The ALD coating could bring the pore size below 0.55 nm, and these membranes could be utilized for light gas separations. As the technology stands today, the pores of these membranes are likely too small to enable the formation of membranes that separate most small organic molecules, even upon functionalization. Expanding the library of functionalizable amphiphiles that can self-assemble to create different domain sizes can further broaden the use of this family of materials to a wide range of selective membranes.[104] Nonetheless, polymerizable LLCs comprise a promising approach for the rational design of highly selective membranes.

## 4. BIOMIMETIC APPROACHES TO MEMBRANE DESIGN

Unlike the synthetic membranes today, biological transport systems have extremely high selectivity−permeability combinations, enabling the regulation of the transport of a huge array of molecules and ions into and out of cells.[105] The cell membrane is a lipid bilayer. Hydrophobic small molecules can partition into this bilayer and permeate following the solution-diffusion mechanism, but large and/or hydrophilic molecules and ions cannot. Thus, cell walls and membranes feature a variety of transport structures that control permeation of various species. These include transport proteins that perform active transport of solutes against a concentration gradient, compounds that bind and carry specific solutes across the lipid bilayer membrane, and transmembrane proteins that form biological pores that synergistically use size, charge, and intermolecular interactions to only allow a specific solute through. The high selectivity and permeability of these biological systems has inspired many researchers to either incorporate biological materials such as transport proteins into membranes, or mimic these structures using synthetic means. An example of this, the incorporation of S-layer proteins into membranes, was described in the previous section. Many others are described in an excellent recent review.[105] Here, we briefly discuss some of these systems with a focus on controlling selectivity with the goal of accessing novel separations.

Some transport proteins pump specific solutes from one side of the cell membrane to the other, capturing a molecule outside the cell and releasing it inside by changing its conformation. These fascinating features were recently mimicked by a two-layer membrane to selectively transport $Ca^{2+}$ ions over sugar molecules.[106] These membranes feature two pH-responsive layers: an amine-functionalized gating layer that allows permeation of solutes only at high pH, and a matrix rich in imidoacetic acid groups that bind $Ca^{2+}$ ions at high pH but release them in low pH (Figure 6). When an oscillating pH is applied to the feed, the membrane acts as an ion pump. At low pH, $Ca^{2+}$ ions pass through the gate layer and bind the imidoacetic acid groups. At low pH, the gate is closed, and $Ca^{2+}$ ions in the matrix are released. $Ca^{2+}$ and sucrose permeate through the membrane at similar rates at constant pH. When an oscillating pH is used, $Ca^{2+}$ permeation rate is about four times that of sucrose. The oscillating pH process needed for the ion pumping effect by this membrane is challenging to execute in a large-scale membrane system. Nonetheless, this study demonstrates that we can mimic complex biological systems using relatively simple materials through thoughtful design of not only a novel functional membrane but also a novel process to leverage its unique responsive properties.

Another interesting feature of cell membranes is the presence of compounds that act as carriers of specific ions or molecules. These hydrophobic molecules, called ionophores, bind their target ion outside the cell, making it soluble in the


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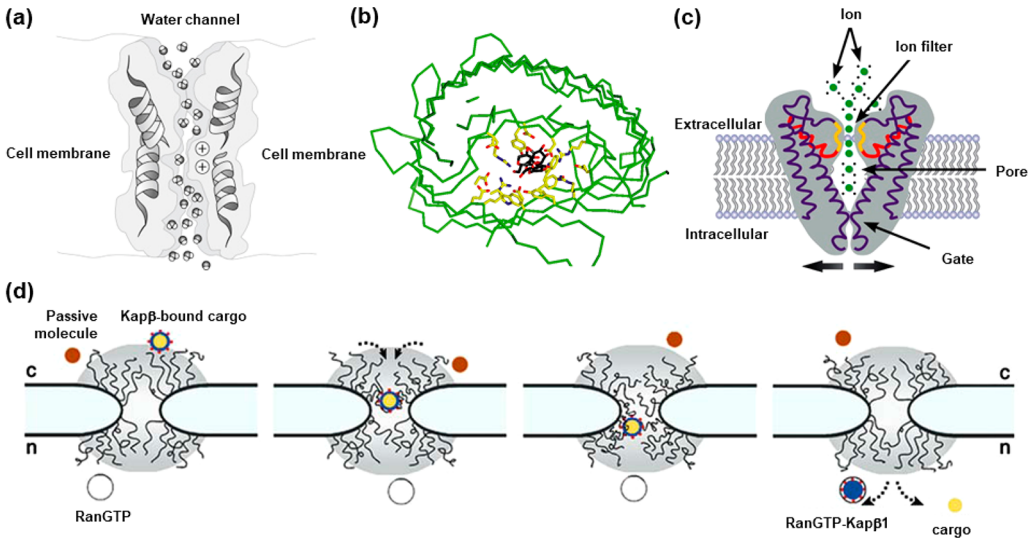


**Figure 7.** Some biological structures that inspired biomimetic approaches for creating membranes with controlled selectivity. (a) Aquaporin, showing single file diffusion of water molecules through its pore. Reproduced from ref 124 with permission from Elsevier. (b) Cross-section through a maltoporin monomer bound to maltotriose (depicted black), showing the interaction between the sugar molecule and the pore walls. Reproduced from ref 114 with permission from Elsevier. (c) Schematic diagram of the basic structural elements of an ion channel including the ion selectivity filter, the water-filled pore, and the channel gate. Ions are depicted as circles moving through the filter in a single-file manner. Reproduced from ref 125 with permission from Elsevier. (d) Schematic of a proposed model of operation for the NPC, regulated by binding and unbinding interactions between phenylalanine−glycine domains and the carrier proteins. From ref 126. Reprinted with permission from AAAS.

cell membrane. They then release it into the cytoplasm, allowing permeation following the concentration gradient. This mechanism, called facilitated or carrier mediated transport,[6,107] exhibits exceptional selectivity, as only the target compound can interact with the carrier. This is often combined with high permeability for the target compound, making facilitated transport an ideal mode of operation for highly selective membranes.[108,109] This has led researchers to incorporate ionophores into membrane selective layers to create ion-selective membranes, particularly for sensors and ion-selective electrodes.[110] However, most membranes that use this mechanism involve a liquid carrier phase, which limits their application in large scale, pressure-driven separations.[6,108]

Finally, cells have several types of biological pores that regulate transport following a concentration gradient. These pores include aquaporin and other water channels, ion channels, porins that selectively pass specific solutes such as sugars, and the nuclear pore complex (NPC), which regulates permeation between the cytoplasm and the cell nucleus (Figure 7).[111] These biological pores frequently feature a constricted pore similar in diameter to the target compound (<1 nm for ion channels and porins[112−114]) and functional groups lining the pore that interact with the target during passage (e.g., anionic or hydrogen bonding groups[112−114]). This is an exquisite example of how nature uses nanostructure and chemical functionality synergistically. The nanostructure constricts flow and confines all components passing through, forcing them to interact with the chemically functional walls. Solutes that interact favorably with the functional groups are shuttled through by carrier-mediated or facilitated transport, whereas those that do not are excluded.[107] They have the highest transport rates among transport proteins, predicting high flux and selectivity in membrane applications. This has led the majority of researchers pursuing biomimetic approaches to model this family of transport systems in their work.

A significant portion of this research has focused on permeating water while retaining all else with the ultimate goal of water desalination and purification. These studies have heavily focused on aquaporins (Figure 7a), biological water channels that selectively permeate water while preventing the permeation of ions through size exclusion and electrostatic repulsion mechanisms. Their selectivity and flux is enhanced due to the single file transport of water molecules.[115] Researchers have utilized these features either by incorporating biological water channels such as aquaporin into membranes,[116,117] or by mimicking these using artificial water channels embedded in membranes.[115,118,119] This highly active research direction led to the commercialization of aquaporin-containing membranes for water treatment by forward osmosis (FO) and other processes.[115,117] Systems utilizing aquaporin or its mimics can remove salts with extremely high water fluxes, mimicking the selectivity of RO and NF membranes. It also has potential applications in wastewater treatment of reuse,[120] though this is highly dependent on the matrix the water channels are embedded in.[121] Their selectivity is hard to tune, though with the advent of synthetic water channels,[122,123] the potential exists for tuning their separation capabilities.

There are also numerous biological channels that transport other solutes with great selectivity. For instance, porins that bridge bacterial cell walls can selectively allow the passage of specific biomolecules such as sugars (Figure 7b). Ion channels allow the permeation of select ions and often also feature gating/responsive properties (Figure 7c). The nuclear pore complex (NPC) controls the passage of a variety of biomacromolecules through the membrane that separates the cell nucleus from the cytoplasm; only solutes that are bound to carrier molecules are ferried through (Figure 7d). These intriguing nanostructures have inspired the design of nano-structured materials that modulate the transport of solutes with selectivity based on factors other than size, several of which are described below. Similar to aquaporins, these biological


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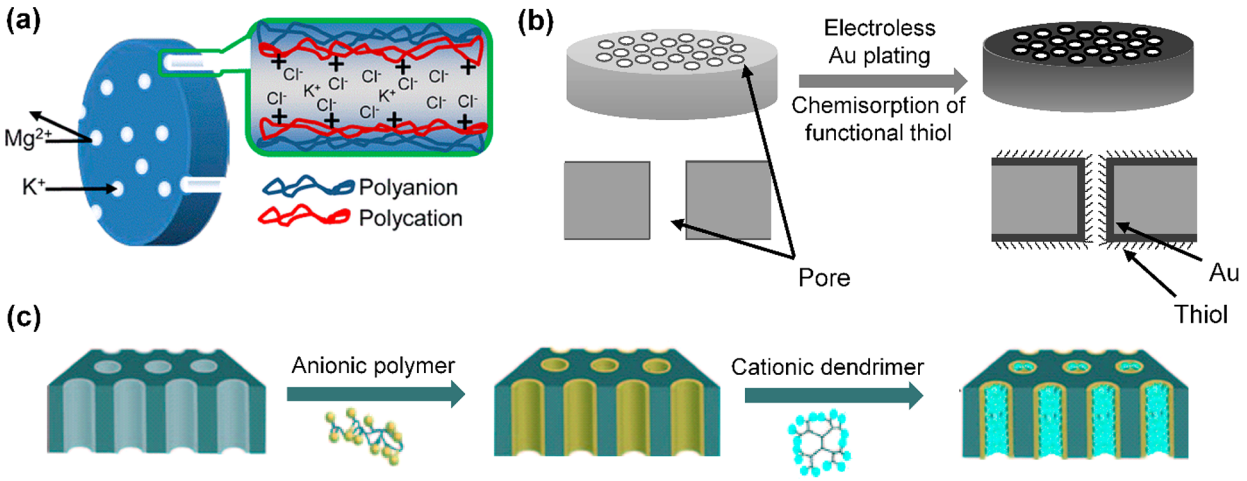


**Figure 8.** Template methods for the fabrication of membranes with charge-based selectivity. (a) LBL assembly within the pores of TE membranes showing transport selectivity between monovalent and multivalent ions. Reprinted with permission from ref 153. Copyright 2013 American Chemical Society. (b) Formation of gold nanotubule membranes by electroless gold plating within the pores of a TE membrane followed by the functionalization of pore walls with self-assembled thiol monolayers. Reprinted from ref 182. Copyright 2008, with permission from Elsevier. (c) Tethering self-assembled anionic polymers within the pores of a TE membrane followed by vacuum filtration of a high generation cationic dendrimer. Reprinted with permission from ref 167. Copyright 2008, John Wiley and Sons.

systems also feature pores only slightly larger than their target, lined with functional groups that interact with their target exclusively and reversibly. A key challenge to mimicking these functional nanochannels, however, is the creating nanoscale, functionalizable pores through scalable manufacturing techniques.

## 5. ELECTROSTATIC INTERACTIONS: CHARGE-BASED SELECTIVITY

A very large portion of the current literature on controlling membrane selectivity focuses on separating solutes based on their charge. Such separations have a range of practical applications including water softening, heavy metal removal, recovery of valuable ions, and desalination.[127] Ion transport also has implications on areas such as energy conversion, nanofluidic transistors, drug delivery, medical analytics, and sensing.[128−130] Membranes that can separate small organic molecules of similar size but differing charges also have several applications, especially in the extraction and purification of small pharmaceutical molecules such as amino acids[131−133] and antibiotics.[134,135] Separation of large biomolecules (e.g., proteins) based on their charge is also of interest in areas such as biotechnology and biopharmaceuticals.[136]

It should be pointed out that essentially all membranes with charged surfaces are capable of exhibiting some charge-based selectivity due to electrostatic interactions between the membrane surface and ionic species that permeate through the membrane.[137−140] Furthermore, most commercial membranes have at least mildly charged surfaces by design, though this is not necessarily aimed at achieving charge-based separations. Membranes are typically made of hydrophobic materials as these remain mechanically stable in water. Hydrophobic surfaces, however, are prone to the adsorption of organic compounds, oil, and microorganisms from the feed. This phenomenon, termed fouling, leads to pore clogging and is a major issue in the operation of membrane systems that causes increased energy use, frequent need for maintenance, and shorter membrane lives.[141−143] To limit fouling, most MF and UF membranes are manufactured using methods that will improve their surface hydrophilicity. Most of these methods result in negatively charged surfaces that electrostatically repel negatively charged solutes that make up a large fraction of common foulants (e.g., bacteria, alginate, natural organic matter, proteins). NF and RO membranes typically have residual negative charges on their surface that arise from the synthesis method. These charges not only prevent fouling, but also enhance salt rejection through Donnan exclusion.[144] Intermolecular interactions (e.g., hydrogen bonding, polarity, hydrophobic interactions), which affect the solubility of solutes in the dense selective layer, also play a role in solute rejection and membrane selectivity.[145−148] As a result, the selectivity of NF and RO membranes for organic molecules is complex, affected by not only solute size but also charge and a combination of other molecular features, while size exclusion is the main separation mechanism.[140,148,149]

Nonetheless, the preparation of membranes that exhibit varying rejections of solutes (salt ions or organic molecules) based on charge through electrostatic and other interactions has attracted extensive attention. Beyond the applications discussed above, many novel membrane materials designed for this purpose result in structures with promise for more complex separations such as nanoscale channels that can be further functionalized to control their selectivity. Thus, beyond their performance as charge selective membranes, these technologies are promising starting points for filtration systems with more complex selectivity.

### 5.1. Charged Nanopores through Template Methods.

Ion channels (Figure 7c) are exquisite examples of charged nanopores that control transport of ions.[150] Highly efficient transport selectivity of these channels is due to their narrow diameter, slightly larger than solute being transferred, and the high density functional groups lining the pores. Their efficient ion transport and high ion selectivity has inspired several researchers to mimic these structures and create ion selective membranes that feature nanopores with charged pore surfaces. However, the preparation of membranes with a high density of well-defined, uniform, and small (1−2 nm) pores with charged surfaces needed to get effective separation of ions and small


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molecules is a major challenge. To create these structures, many researchers have used commercial membranes with evenly sized but larger pores as "templates", narrowing down and functionalizing the pores by various means (Figure 8).

*5.1.1. Layer by Layer Deposition and Polyelectrolyte Adsorption.* One relatively straightforward approach to creating charged nanopores involves the modification of membranes with cylindrical through-pores with a polyelectrolyte multilayer (PEM) built by layer-by-layer (LBL) deposition of oppositely charged polyelectrolytes. These systems use track-etched (TE) or anodized aluminum oxide (AAO) membranes, described earlier, as templates. To deposit the PEM inside the membrane pores as opposed to just the top surface of the membrane, polyelectrolyte solutions are filtered through the template membrane in the desired order.[151] This creates narrower, charged pores that can exclude divalent ions more than monovalent ions, leading to moderate selectivity between monovalent and divalent ions at low ionic strength. For example, the deposition of 1−2 bilayer(s) of polyelectrolytes within TE membranes with 200 nm pores reduces the pore size to 60−100 nm and leads to some selectivity between $Cl^-$ and $SO_4^{2-}$ ions.[152] LBL deposition inside smaller pores (<50 nm) can yield narrower pore size (Figure 8a),[153] but is particularly challenging and difficult to control. Adsorption near the pore entrance can result in a nonuniform layer within the pores, with the majority of pore modification occurring near the pore entrance.[153,154] The addition of more bilayers leads to smaller pores, but also causes a dramatic decrease in surface charge density due to structural reorganization and ion pairing, reducing ion selectivity.[155] LBL deposition into membrane pores is not very scalable, because it requires multiple steps of adsorption for each polyelectrolyte and subsequent rinsing. Furthermore, PEM coatings often have low stability during prolonged use, extreme pH levels, ionic strengths, or temperatures.[156]

The LBL method has also been utilized to build PEM nanotubes with charged cores on a template (AAO or TE) that are then removed and integrated into a new membrane selective layer.[157,158] This approach allows the packing of a higher number of nanotubes within the membrane, leading to higher pore density. Furthermore, it can be used for the fabrication of charge mosaic membranes, which possess discrete oppositely charged domains that traverse through the membrane thickness.[159] This structure allows for higher ionic flux in comparison to similarly sized neutral molecules, resulting in enrichment of ions in the permeate solution. Charge mosaic membranes can be used for the recovery of valued ions and removing dilute ionic contaminants. In addition to LBL deposition to build PEM nanotubes, charged mosaic membranes have been fabricated by several methods including the self-assembly of multiblock polymers,[160] ion exchange resins embedded in permeable matrices,[161] and conjugate electrospinning.[162] All these approaches require the orientation of the ionic domains perpendicular to the membrane surface. Recently, inkjet printing, a rapid and precise technique for the deposition of functional materials,[163] has been used for the fabrication of charge mosaic membranes on both porous membranes formed by functional copolymer self-assembly[164] and on templated TE membranes.[165] These studies combine functional polymers with the ease of manufacturing provided by inkjet printing to prepare membranes with unusual selectivity.

*5.1.2. Adsorption of Self-Assembling Polyelectrolytes.* An alternative method for simultaneously narrowing down and functionalizing the pores of TE membranes is to tether a charged polymer that has already self-assembled into supramolecular structures in solution (vesicles, micelles, etc.) through ionic interactions (Figure 8c). In comparison with the adsorption of a polyelectrolyte, this approach will lead to a more significant decrease in pore size with just one layer unless these structures completely dissemble during the process. In this method, $Sn^{2+}$ ions are adsorbed into the pores of a TE membrane, followed by the vacuum filtration of a solution of a self-assembling anionic polymer. This approach can be continued further by consecutive filtration of oppositely charged polymers, similar to LBL assembly, to further narrow down the pores down to ∼6 nm and to control pore surface charge.[166] This method is simple and fast, though it still suffers from the low porosity of the TE membranes used as templates. The pore size achieved by this technique is suitable for protein separations, but too large for separating small molecules.

To reach smaller pore size and higher functional group density, a positively charged dendrimer can be similarly deposited into the pores following the deposition of an anionic polymer (Figure 8c). Small pores and high functional group density upon tethering high generation dendrimers results in very high separation selectivity between small organic molecules of opposite charge.[167] However, the low resultant porosity and flux of these membranes, the high cost of high generation dendrimers and the limited stability of coatings held together by Coulombic interactions limit the broader use of this approach for industrial separations.

*5.1.3. Gold Nanotube Membranes through Electroless Deposition.* Electroless gold plating is likely the most versatile and well-controlled template-based method for creating membranes with controlled pore size and surface chemistry. This method involves sensitizing a modified-TE membrane with $SnCl_2$, followed by immersing the membrane in an $AgNO_3$ solution and finally a gold plating solution. This leads to the conformal coating of the membrane pores with a layer of gold, creating gold nanotubules (Figure 8b).[168] Pore size can be controlled by varying the plating time, making it possible to reach down to molecular dimensions (<1 nm) suitable for size-based separation of small molecules.[169] The chemical functionality of the pore walls of these membranes can be controlled through the formation of a self-assembled monolayer (SAM) upon exposure to functional thiols.[170] Ion permselectivity can be introduced by two different routes. The first involves imparting excess charge on the membrane by applying an electrical potential in an electrolyte solution. This enables the permselectivity to be switched reversibly. Ideal cation permselectivity similar to Nafion can be obtained when the pore radius is small relative to the thickness of the electrical double layer within the pores.[168] However, obtaining switchable ion transport is only possible in electrolytes containing nonadsorbing anions such as $F^-$. Anions such as $Cl^-$ or $Br^-$ adsorb at positive applied potentials, resulting in a cation permselective membrane independent of applied potential. This can be prevented by the formation of an alkanethiol SAM on the membrane.[171] The second approach for creating membranes with ion transport selectivity utilizes the chemisorption of an ionizable thiol onto gold nanotubules. For example, chemisorption of carboxyl and amino functional thiols yield cation- and anion- permselective membranes, respectively.[172] Switchable ion permselectivity can be obtained


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by the chemisorption of the amino acid cysteine. Varying solution pH affects the ionization of the amine and carboxylic acid groups on cysteine.[173] At small nanotube diameters (1.4 nm) and pH 12, a charged-based selectivity of 15 is reported between two small organic molecules of opposite charge in single-ion diffusion experiments. The selectivity was further enhanced to ~110 in a competitive diffusion experiment.

This electroless gold plating technique provides exquisite control over pore size and surface chemistry. This has led to some of the most selective membranes reported to date, not only based on charge but also based on other molecular parameters, as discussed below.[174,175] Nonetheless, its complicated and lengthy manufacturing process limits its commercial use. The electroless gold deposition contains multiple steps and involves use of toxic chemicals and heavy/precious metal ions (Sn, Ag, Au). The plating step takes over 20 h to generate small pores. Furthermore, controlling the uniformity of the gold layer within the nanotubes during the gold deposition process is difficult, especially given the curvature of the track-etched pores.[169] Also, chemisorption of self-assembled monolayers within the narrow pores is very slow.

An important drawback of all these template methods is the very low porosities of the resultant membranes, down to <0.1% (compared with 70−90% for a typical filtration membrane[176]). This leads to very low permeability and severely limits the use of these gold nanotubule membranes for large scale separations. Another inherent challenge is the difficulty in obtaining a uniform coating layer along the pores. Uneven coatings create bottleneck shaped pores that limit the nanoconfinement effects and pore−solute interactions to the pore entrance, resulting in lower selectivity.[169,177−179] This approach, however, has led to novel and powerful approaches to create a wide variety of template nanomaterials for other applications, including but not limited to drug delivery, sensors, and electrode arrays.[180,181]

**5.2. Aligned, Functionalized Carbon Nanotubes (CNTs).** Inner cores of carbon nanotubes (CNTs) can act as nanopores for filtration applications. CNTs exhibit extraordinary transport properties arising from their exquisite, highly defined structure. The graphitic pore walls of CNTs are atomically smooth and hydrophobic. This leads to the conduction of water molecules at speeds orders of magnitude higher than that observed in bulk water, leading to high permeability per pore.[183] If CNTs are vertically aligned and processed to form the pores of a membrane selective layer, they can be used to create membranes with uniform pore sizes (6−7 nm for multiwalled carbon nanotubes (MWNTs) or 1.3−2 nm for double-walled nanotubes). These features have led to the exploration of CNT-based membranes for desalination and gas separation.[184−186]

Several researchers have attempted to incorporate prema-nufactured CNTs into membrane selective layers. For CNTs to act as membrane pores, they have to be vertically aligned across the membrane thickness, surrounded by an impermeable matrix. This has been attempted by a wide range of methods that include the use of lyotropic liquid crystals (LLCs),[187] strong magnetic fields,[188,189] gel extrusion,[190] mechanical shear,[191] melt stretching,[192] and anisotropic flow.[193] Many of these methods are limited in their effectiveness for achieving vertical orientation and/or their scalability. They also require a supply of large quantities of high quality CNTs of even length and with open ends. Despite these challenges, a new start-up company, Mattershift, is currently attempting the scale-up of a technology for the manufacture of membranes featuring aligned CNTs. These membranes exhibit charge-based selectivity,[194] but their potential for functionalizability for more complex separations is unknown due to the proprietary nature of the technology.

As opposed to aligning CNTs after manufacture, a template method has been utilized to grow CNTs in situ within the pores of an AAO support.[195,196] The nanotubes were subsequently uncapped by etching. The underlying AAO template can be dissolved away in concentrated HF solution and the gaps between CNTs can be filled with an impermeable matrix. However, the inner diameter of CNTs obtained by this method depends on the membrane pore size, ranging from 20−200 nm. The large pore size limits their application in chemical and biological separation applications. Furthermore, low areal tube density resulting from low porosity of AAO supports further limits their application.

Alternatively, highly dense arrays of CNTs can be can be grown on silicon or quartz substrates using catalytic CVD, followed by conformal encapsulation of nanotubes in an impermeable matrix (polymer,[197] silicon nitride[198,199]) to confine the flow within the CNT lumina. Subsequently, excess matrix is removed from both sides of membrane and CNTs are uncapped by reactive ion etching (Figure 9). Yet, producing

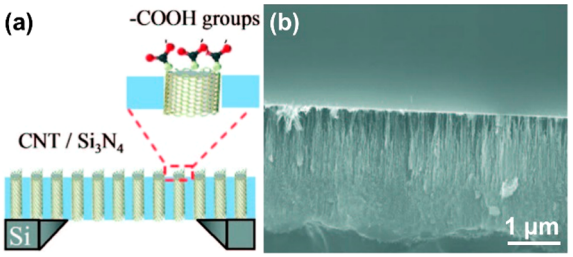


**Figure 9.** Membranes with CNT nanopores formed by growing vertically aligned CNTs, followed by the deposition of silicon nitride to fill gaps between the CNTs and etching to expose lumina. (a) Cross-section schematic of a CNT membrane representing the silicon support chip, aligned CNTs, the filling silicon nitride matrix, and the CNT tip functionalized with carboxylic acid groups. (b) Cross-section SEM image of the CNT/silicon nitride composite membrane showing the gap-free coating of silicon nitride. Reproduced with permission from ref 199. Copyright 2008 National Academy of Sciences.

membranes composed of densely packed, well-aligned CNTs is not simple, because several steps needs to be conducted in a clean room environment. In addition, these very thin membranes are brittle and fragile, which limits the use of these free-standing or silicon chip supported CNT membranes to subcm$^2$ areas. As such, this approach is not amenable for large scale separation applications, though it may be interesting for drug delivery, microfluidic devices, and sensing.[197,200,201]

An important feature of CNTs is the functionalizability of the pore entrance, creating pores reminiscent of ion channels. The oxidation process to uncap CNTs during manufacturing results in charged pore entrances. Thus, resultant membranes exhibit ion exclusion properties and charge-based selectivity of solutes in dilute aqueous electrolyte solutions.[194,199,202] The pore entrances of CNTs can also be further functionalized using carbodiimide mediated chemistry to control selectivity and to narrow down the pore size at the entrance, including tuning and enhancing charge-based selectivity. However,


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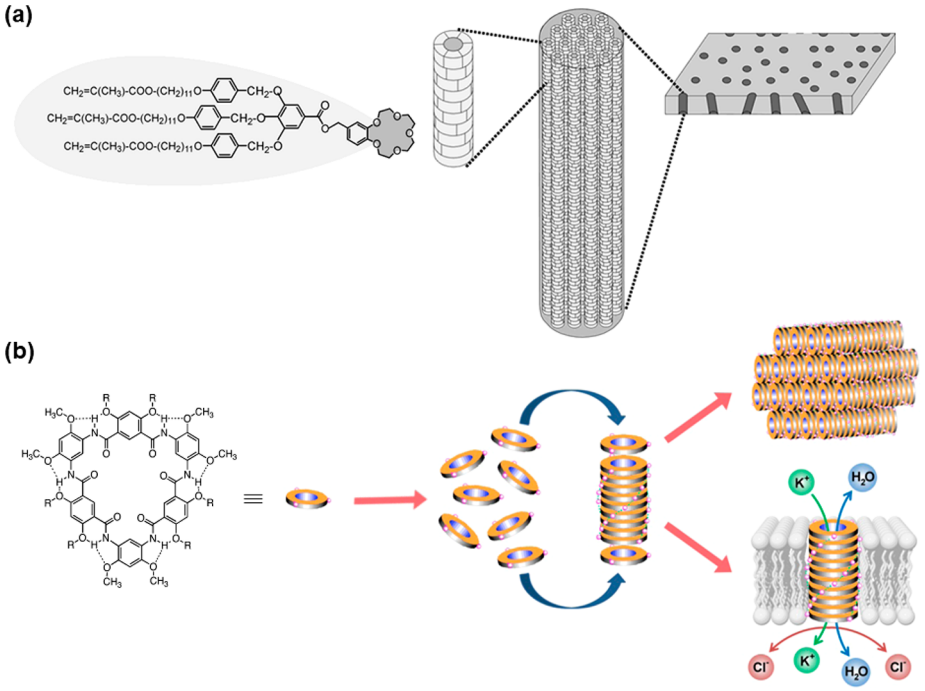


**Figure 10.** Formation of ion-selective nanopores by self-assembly of small molecules. (a) Self-assembly of a wedge-shaped monomer containing crown ether within the pores of TE membrane. Reprinted with permission from ref 223. Copyright 2000, John Wiley and Sons. (b) Self-assembly of macrocyclic peptides inside the hydrophobic core of lipid bilayers. Both show preferential cation transport. Reproduced with permission from ref 234. Copyright 2013 American Chemical Society.

separation efficiencies obtained have been lower than observed in pores that are functionalized throughout their length, because the interactions between solute and pore wall is limited to near tip entrance (only a distance of 7% of the nanotube length). Furthermore, the number of carboxylic acid groups at the CNT tips is relatively low, further contributing to the low selectivity.[203]

To increase the density of carboxyl groups on the pore surfaces and enhance the molecular interactions, the entire core of CNTs have been modified by electrochemical grafting.[204] The pores were further narrowed down using a polypeptide spacer and a tetravalent sulfonated anionic molecule. Although the pores are not covered by grafting, the core-grafted CNT membrane showed a dramatic flux decline and almost no detectable pressure driven flow. This is because grafting the CNTs core compromises the smoothness and inertness nature of CNTs, required criteria for achieving high flux.[205,206] Severe flux decline has also been reported for tip-functionalized MWNTs,[205,206] and predicted for tip-functionalized SWNTs.[207,208] There is ongoing research directed toward effective functionalization of CNTs to impart chemical selectivity while maintaining ultrafast permeation properties. Nevertheless, the current chemical modification techniques would likely adversely affect the permeation properties and raise a challenging question regarding their broader use.

Current fabrication procedures for membranes with aligned CNTs are often prohibitive for the manufacture of filtration membranes at large scale.[209−211] This is particularly true if the manufacturing process involves growing vertically aligned CNTs by CVD followed by the filling of interstices, the most well-studied approach for chemically functionalized CNT membranes.[209−211] The production of these membranes involves many complex steps, often performed in a micro-fabrication facility. It is also difficult to manufacture high purity CNTs without defects over large areas.[212] Filling the interstices between CNTs to force permeation to the CNT lumina without disrupting the alignment or creating defects also remains a challenge.[197,213] After this step, the membrane needs to be selectively etched to open up a high number of CNTs without creating voids in the matrix.[202,203] All these complex manufacturing steps severely limit the applicability of aligned CNT membranes prepared by this method in filtration and separation applications, where hundreds of $m^2$ of membrane are needed. The exceptional properties of these functional CNT membranes have shown great promise in other applications that do not require low cost, large area manufacturing. For instance, functional aligned CNT films have been used for controlled drug delivery and in sensing utilizing their gating properties.[197,200,201]

**5.3. Functional Nanopores through Small Molecule Self-Assembly.** Self-assembly of soft matter is a particularly powerful approach to forming functional nanostructures using scalable processes. Many natural materials form subnanometer organic nanotubes by self-assembly, including small molecule amphiphiles, dendrimers, peptides, peptidomimetics, DNAs, foldamers, and J-type rosettes.[214−219] These self-assembled nanotubes could potentially serve as nanopores of membranes with controlled selectivity (Figure 10). However, forming large-area membranes with aligned nanochannels is, again, a crucial challenge. Below, we describe some studies where self-assembled nanotubes have been incorporated in membranes of sufficient area and integrity to study their transport properties and discuss their potential for scale-up.

*5.3.1. Thermotropic Liquid Crystals with Functional Pores.* Crown ethers are known for their selective binding to alkali metal cations through complexation.[220] They can also stack and form effective nanopores with high cation selectivity


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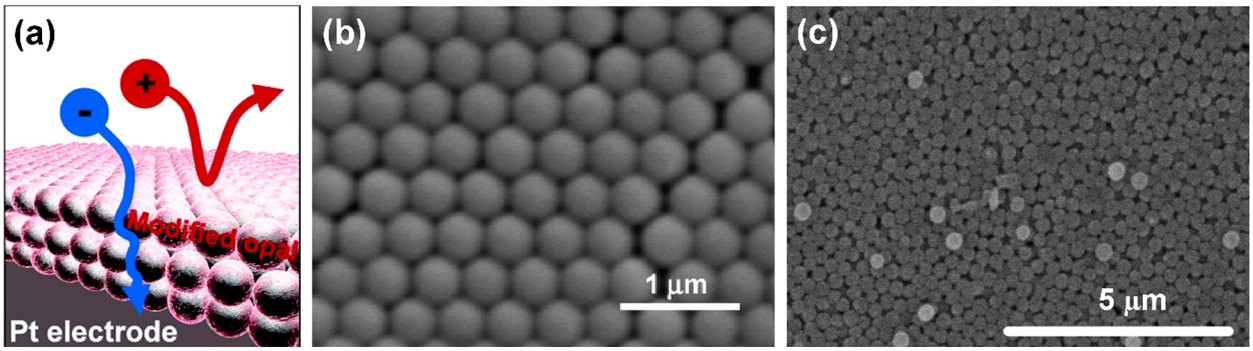


**Figure 11.** Layers and membranes formed by the self-assembly of silica nanoparticles into packed arrays. (a) Schematic of thin opal film comprising three layers of amine-modified silica spheres on a Pt electrode. Reprinted with permission from ref 236. Copyright 2005 American Chemical Society. (b) SEM image of the surface morphology of the opal film showing nanoparticles arranged in a hexagonal close packed array. Reprinted with permission from ref 235. Copyright 2006 American Chemical Society. (c) SEM image of the surface morphology of amine-modified, sintered free-standing membrane showing partial fusion of silica nanoparticles. Reprinted with permission from ref 241. Copyright 2009 American Chemical Society.

(Figure 10a). Unlike previously described approaches that rely on electrostatic interactions to exclude ions, crown ether nanochannel membranes would retain their selectivity independent of feed ionic strength. One approach to incorporate stacked crown ethers into membranes involves vertical stacking of cylindrical thermotropic liquid crystals (TLCs) from amphiphiles containing crown ether moieties and polymerizable, hydrophobic methacrylate end groups, held together by a cross-linked methacrylate resin.[221] This was obtained by casting a solution containing the wedge-shaped amphiphilic monomer containing the crown ether groups, a methacrylate, a cross-linker and a photoinitiator onto a support. Subsequent cooling to −50 °C results in the formation of cylindrical aggregates containing stacked crown ether units and causes thermo-reversible gelation. The layer is then polymerized, fixing the supramolecular stacks into the membrane selective layer. These membranes exhibit preferential transport of $Li^+ > Na^+ > K^+$ with $Li^+/K^+$ selectivity of about 3. They also show very low water permeation rate due to poorly aligned channels within a highly cross-linked, nonpolar matrix polymer, which limits the probability of ions to transfer and enter the next channel and permeate through.[222]

To improve permeability, a TE membrane was used as a template to grow vertically aligned crown ether stacks within the through-pores.[223] For this purpose, the TE membrane was soaked in a hot methacrylate solution containing polymerizable crown ether amphiphiles and a photoinitiator and then cooled to grow supramolecular aggregates and cross-linked to arrest the supramolecular structure. While this led to the formation of some supramolecular channels perpendicular to the membrane surface and subsequently some enhancement in ion transport rate, a significant fraction of assemblies was still not aligned, leading to low flux. Nonetheless, this directed assembly of nanopores in a template demonstrates another promising approach for creating narrow, functionalizable nanochannels that can be utilized in future studies.

*5.3.2. Macrocyclic Peptides.* Cyclic peptides with flat, rigid conformation and the correct number and placement of the amino acids can stack atop one another through intermolecular hydrogen bonding and form tubular assemblies called cyclic peptide nanotubes (CPNs) (Figure 10b). The diameter of these nanotubes can be tailored by controlling the cyclic peptide chemistry, from a few angstroms to a few nanometers.[224] It is also possible to place specific functional groups within the interior of nanotubes by varying the amino acids forming the ring. These properties make CPNs highly promising for the creation of biomimetic membranes with controlled selectivity. When embedded across the lipid bilayer, these nanotubes can serve as efficient cation-selective channels with high conductance and water flux.[225,226] Functional groups in the peptides can also be altered to potentially control ion selectivity,[227] though results remain hard to predict, as demonstrated by a study showing similar cation transport selectivity for channels of varying peptide length, polarity, charge, and ring size.[228] Such changes also require complex synthesis procedures and may disrupt self-assembly.[229,230]

As with other functional nanotubes, the true challenge lies in integrating these nanotubes into membrane selective layers. Difficulty in aligning these highly aggregate-prone nanotubes vertical to the surface of a thin membrane selective layer makes their use in filtration applications hard to realize. Directed coassembly of polymer-conjugated macrocyclic peptides and a BCP was used to circumvent the need for the fabrication and alignment of nanotubes of uniform length and size.[231] CPN growth was confined to one BCP domain, aligned vertical to the surface of a thin film by annealing. When this membrane was used as the cover of a PDMS mold separating acidic and basic solutions containing a pH-indicator dye, a change in solution pH indicating cation transport selectivity was observed. This method results in some alignment of CPNs within the very thin, ∼30 nm film. Nonetheless, ensuring a high density of CPNs that span the membrane thickness remains difficult, as does creating films that are mechanically stable enough to perform as a filtration membrane.[232]

**5.4. Charged Nanopores through Self-Assembly of Inorganic Nanoparticles.** While most of this perspective focuses on polymeric membranes, inorganic membranes are particularly attractive for specific applications that include high temperature gas separation, water treatment, and membrane reactors due to their high mechanical, chemical, and thermal stability. Inorganic nanoporous membranes are most commonly prepared by anodization of aluminum, sol−gel methods, lithography, dip-coating, and chemical vapor deposition.[233] More recently, highly porous membranes have been formed by the self-assembly of inorganic nanoparticles (NPs), the interstices between which form permeation pathways. This approach is attractive due to the ability to control pore size and functionality through straightforward methods. In this section,


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we describe the nanoporous membranes formed by self-assembly of inorganic and hybrid NPs.

*5.4.1. Close-Packed Arrays of Colloidal Silica Nanoparticles.* Colloidal silica NPs can self-assemble into well-ordered, close-packed arrays, or opals, of nanospheres that act as porous membranes (Figure 11). The interstitial space between the spheres serves as the pores whose size can be controlled in the 10−100 nm range by changing the size of silica nanospheres. The NP surfaces can then be functionalized using well-established silanol chemistry, creating a bicontinuous network of functionalizable nanopores.

Initial studies on this approach focused on thin opal films (~three layers) coated onto a Pt microelectrode and characterized the selectivity of these layers by measuring the permeation of redox-active molecules by voltammetry (Figure 11a). These opal films were formed simply by dipping an electrode vertically in a colloidal alcohol solution followed by solvent evaporation (Figure 11b). The resultant silica opal film is negatively charged at high pH due to deprotonated hydroxyl groups on the surface, but minimal charge-based selectivity was observed.[235] When the silica surfaces were functionalized with cationic amine moieties, a significant decrease was observed in the permeation of the cationic molecule $Ru(NH_3)_6^{3+}$ while the flux of neutral and negatively charged molecules of similar size remained unchanged.[235,236] To narrow down the pores, the NP surface can be modified by attaching macrocycles such as calix[*n*]arenes or thiacalix[*n*]arenes that can selectively bind ions, resulting in charged nanopores[237] that exhibit transport selectivity between neutral and positively charged solutes of similar size.[238] Pores can be further narrowed down to about 10 nm by grafting polyelectrolyte brushes inside the pores using surface-initiated ATRP.[239] Grafting a weak cationic polyelectrolyte brush, poly(2-(dimethylamino)ethyl methacrylate), results in a 30−40% decrease in the limiting current for the cationic molecule $Ru(NH_3)_6^{3+}$ in voltammetry experiments, whereas the limiting current for the neutral molecule $Fc(CH_2OH)_2$ decreases by only 10%. Polymer brush length can also be altered to tune the final pore size without perturbing the colloidal crystal lattice.[240]

These initial electrochemical experiments suggest that these mesoporous silica colloidal materials can also be promising for membrane filtration applications. To test this premise, free-standing membranes with larger surface area were prepared by calcinating the silica nanospheres, forming a layer of nanospheres on a glass slide by solvent evaporation, and then sintering the colloidal film at temperatures above 1000 °C. This causes the silica spheres to partially fuse with one another (Figure 11c), forming a more mechanically robust membrane. Further functionalization of these so-called nanofrit membranes has proven difficult due to the loss of silanol groups at high temperatures.[241,242] To achieve more effective functionalization, free-standing sintered membranes were prepared using gold coated nanospheres. The surface was then modified with a SAM of thiol-containing molecules (e.g., cysteine), though this did not lead to significant pH response due to low surface coverage. When the pores were modified by grafting a brush of poly(methacrylic acid) (PMAA), a weak polyelectrolyte, the permeation rate of a neutral molecule, ferrocenecarboxaldehyde, was 13 times higher in acidic solutions where the PMMA chains were protonated and collapsed onto the pore walls.[243]

Opals formed by colloidal silica NPs exemplify a relatively simple approach to creating membranes with highly functionalizable nanopores. This is reflected in the studies described in the next section, where the silica surfaces are modified to achieve more complex separations. Due to the size of colloidal NPs and the packing geometry, the membrane pores formed by Si NPs are an order of magnitude larger than small molecule solutes. Yet, significant selectivity is achieved, likely due to the tortuous permeation pathway and high surface area that enforces a large number of solute−pore wall contacts.[244] This phenomenon demonstrates the need for more detailed studies, both theoretical and experimental, to understand the effect of solute−wall interactions in complex geometries.

*5.4.2. Co-Assembly of Gold Nanoparticles and Dendrimers.* An alternative approach to building functional membranes that leverage inorganic nanoparticles to confine flow involves the coassembly of gold nanoparticles (AuNP) and dendrimers. These membranes are prepared by immersing an amine-functionalized glass substrate in a solution of AuNPs functionalized with ammonium-terminated ligands, polydopamine dendrimers, and carbon disulfide. As the dendrimers are cross-linked by carbon disulfide, the mixture precipitates onto the substrate and forms a selective coating layer (Figure 12).

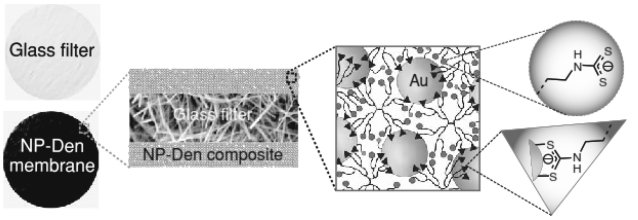


**Figure 12.** Schematic illustration of the fabrication and postfunctionalization of NP-Den composite membrane formed by dithiocarbamate cross-linking on a glass filter. Reproduced with permission from ref 246. Copyright 2012, John Wiley and Sons.

The spaces between the AuNPs act as effective pores whose size can be altered by the dendrimer generation in the 7−12 nm range, with lower generation dendrimers yielding smaller pores. Unreacted amine groups of the dendrimers can be further utilized for the functionalization of the membrane to create quaternary amine or carboxylate groups. These membranes exhibit modest charge-based selectivity between small organic molecules, likely because even the smallest pore size is quite large in comparison with small molecules.[245]

**5.5. Polymer Self-Assembly To Create Charged Nanopores.** Polymer self-assembly is a promising approach for addressing some of the key manufacturing challenges described above for template methods and often simpler than the multistep manufacturing schemes required for small molecule and nanoparticle self-assembly. Polymer self-assembly has already been shown to enable the fabrication of highly porous membranes with narrow pore-size distributions, mostly investigated as size-selective membranes for aqueous filtration.[56−58,74,75,81,83,247−249] Many of these self-assembled structures can be modified to address chemical structure-based separations by the incorporation of additional functionalities into their nanopores. By careful design of polymer chemistry and architecture, the final structure and functionality of membranes can be engineered to achieve separation selectivity that goes beyond size-screening.[250,251]

*5.5.1. BCP Self-Assembly and SNIPS.* SNIPS, a highly scalable approach for creating isoporous UF membranes


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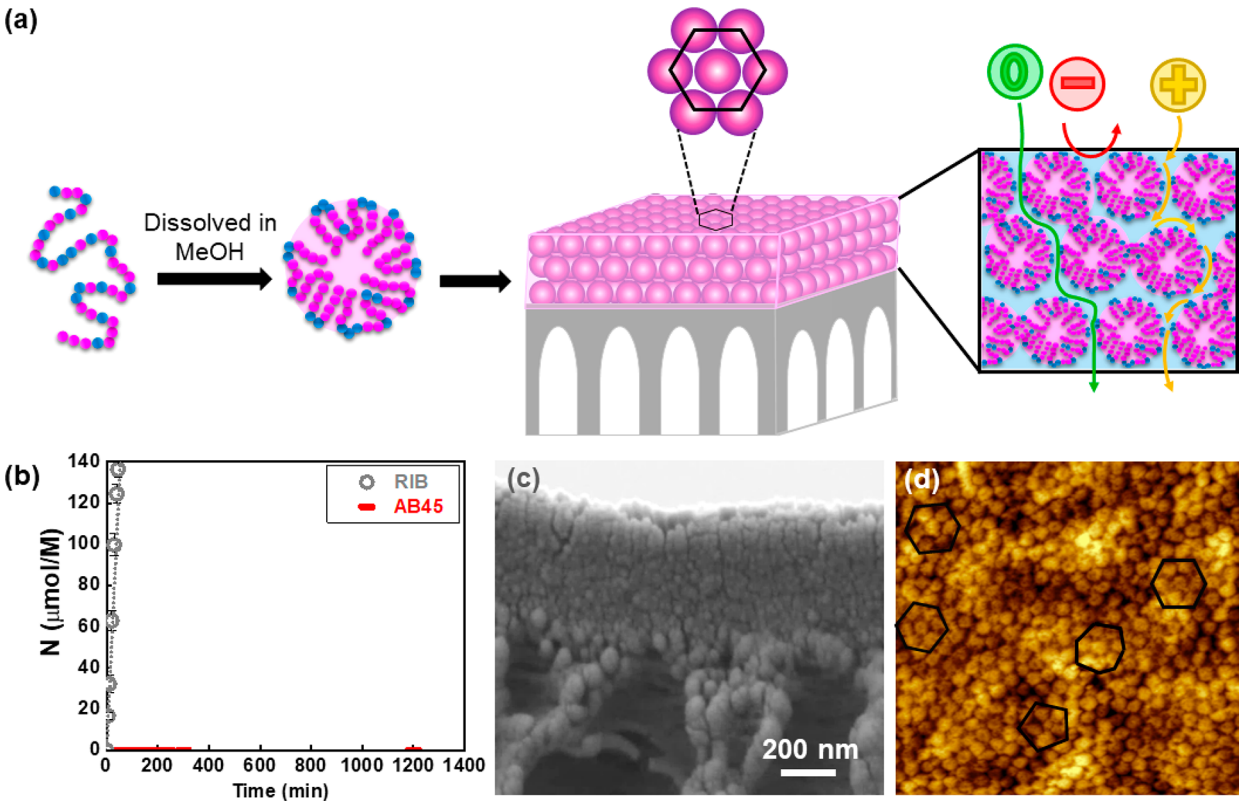


**Figure 13.** (a) Schematic illustration of the self-assembly of random copolymer micelles to create a packed array of polymer nanospheres, the interstices between which act as charged nanochannels 1−4 nm in diameter. (b) Permeation of neutral, riboflavin (RIB, gray) and anionic, acid blue 45 (AB45, red) through the membrane in competitive diffusion experiment, showing the complete blockage of anionic solute (N: moles of solute transferred normalized by feed concentration). (c) SEM cross-section and (d) AFM surface topography of the membrane, showing the packed micelle array. Reprinted with permission from ref 251. Copyright 2017 American Chemical Society.

through BCP self-assembly, was described earlier (Figures 3). This approach leads to membranes with evenly sized pores typically in the 3−30 nm range, though some approaches can further reduce this pore size. These membranes can be further modified by tailoring the pore wall chemistry to impart separation selectivity based on additional factors such as charge. For example, isoporous membranes formed by SNIPS using PS-*b*-P4VP have been further modified by the quaternization of the P4VP block. This has led to the formation of positively charged membranes that can effectively separate proteins of similar size (bovine serum albumin and globulin-$\gamma$) based on their charge with a selectivity of 87.[26] To access a wider variety of pore wall chemistries, a triblock terpolymer, polyisoprene-*b*-polystyrene-*b*-poly(*N*,*N*-dimethylacrylamide) (PI−PS−PDMA), has been synthesized and formed into membranes by SNIPS. The PDMA domains lining the pore walls can be further converted to poly(acrylic acid) by hydrolysis, yielding negatively charged pore walls[56] that can potentially be conjugated with a variety of moieties using carbodiimide mediated coupling chemistry. Alternatively, the addition of a very short functional (4 wt %), third block of polypropylene sulfide to PS-*b*-P4VP can create covalent binding sites for the functionalization of pore walls.[252] Although these systems seem to have the potential to create functional membranes with targeted selectivity, this has not yet been studied in depth.

*5.5.2. Microphase Separation of Comb-Shaped Copolymers To Create Permeable Domains.* Copolymers with graft/comb or random architectures can achieve smaller domain sizes than BCPs, potentially better enabling the separation of small molecules. Often, these copolymers are initially designed for size-based separation of organic compounds, as discussed in an earlier section. An example of introducing new functionality to such membranes utilizes self-assembling amphiphilic comb-shaped copolymers with a polyacrylonitrile (PAN) backbone and poly(ethylene glycol) (PEG) side-chains.[74] This copolymer was synthesized by preparing a random copolymer of acrylonitrile and PEG methacrylate, a macromonomer, and was found to microphase separate to create ∼1 nm bicontinuous domains. The PEG-rich domains acted as effective nanochannels for water permeation and enabled size-based separation of organic dyes. To create charged nanochannels using this system, a random terpolymer of acrylonitrile, PEG methacrylate and glycidyl methacrylate (GMA), was synthesized.[79] The terpolymer also microphase separates to form PAN- and PEG-rich domains. The latter acts as effective pores for water permeation. The reaction of GMA with a diamine leads to the introduction of positively charged groups on the pore walls. These functional groups can be further modified to form negatively charge sulfonic acid groups. These membranes exhibit salt rejection following Donnan exclusion theory.[79] Coarse-grain simulations of membrane performance under low to moderate pressures and salt concentrations, showed that the rejection of ions is largely governed by ion/pore wall interactions. Ion selectivity can be further altered by parameters such as charge density and spacer length of moieties used to functionalize the membrane pore walls.[253] Similar approaches to create functional nanochannels can likely


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be used with other copolymers that self-assemble to form interconnected pore networks.

*5.5.3. Self-Assembly of Polymer Micelles.* Recently, we reported a simple and scalable method for manufacturing membranes with a thin selective layer consisting of a packed array of polymer nanospheres, creating a network of ∼1−3 nm nanopores with carboxylate functional walls (Figure 13).[251] This approach relies on the self-assembly of a random copolymer, poly(trifluoroethyl methacrylate-random-methacrylic acid) (PTFEMA-*r*-PMAA), containing highly incompatible segments to spontaneously form ∼20 nm micelles upon dissolving in methanol (Figure 13a).[254] This solution is then coated onto a porous support, and after a brief evaporation time to direct the micelle self-assembly into a packed layer, immersed into water. The copolymer is insoluble in water, so this results in the quick precipitation of the micelles. Layer morphology is preserved due to the hydrophobicity and high glass transition temperature of the PTFEMA cores. The resultant membrane features a selective layer with a packed array of micelles (Figure 13c), arranged in a quasi-hexagonal close-packed array (Figure 13d). The interstices between the micelles serve as permeation pathways ∼1−4 nm in diameter depending on micelle size, lined with carboxylate functional groups. In single solute permeation experiments, these membranes show a very high permeation selectivity of ∼260 between neutral and negatively charged molecules of similar size. In competitive diffusion experiments where both solutes are fed to the membrane simultaneously, the selectivity is enhanced further as the transport of the anionic molecules was completely blocked (Figure 13b). Similar trends were also observed in filtration experiments, where anionic solutes were rejected to a much higher degree than neutral ones of similar size. Unlike membranes prepared by template methods, these membranes also exhibited permeances comparable to commercial NF and tight UF membranes. This high degree of charge-based selectivity is likely the result of confining the flow into narrow channels, the high density of functional groups, and the tortuosity of the permeation pathway. Additionally, the carboxylic acid groups lining the pore walls can be used for functionalization through well-established conjugation chemistries for targeted separations. As such, this approach satisfies many key criteria for promising technologies for chemically selective membranes, including high flux, high selectivity, scalable manufacture, and functionalizability.

## 6. CHEMO-SELECTIVE MEMBRANES: SEPARATION OF ORGANIC MOLECULES BASED ON OTHER MOLECULAR CRITERIA

Performing separations based on criteria other than solute size and charge is the true challenge for broadening the use of membranes to new applications. Only a relatively small number of studies have attempted to demonstrate selectivity between small organic molecules of similar size and charge; none have shown effective separation in a pressure-driven filtration system. Studies to date are all proof-of-concept demonstrations that focus on one molecular feature rather than separating solutes of commercial interest. Nonetheless, they demonstrate creative approaches that pave the way to the realization of such membranes by proposing new manufacturing schemes and exploring design features that yield the most promising results.

**6.1. Hydrophobicity-Based Separations.** Hydrophobic interactions drive many important biological and colloidal self-assembly processes in water.[255−257] For example, hydrophobicity, quantified by total polar surface area (tPSA) of the molecule, has a strong influence on oral drug adsorption and its permeation through the small intestine and the blood-brain barrier.[258] Many chemical reactions involve the introduction or removal of polar groups, differentiating reactants and products in terms of hydrophobicity. As such, developing membranes that can separate molecules based on their hydrophobicity is of interest. Some of the methods described above for preparing membranes with functional nanopores for charge-based separations have been modified to create membranes that can separate solutes of similar size and charge based on their hydrophobicity. All methods reported to date are template methods that result in membranes with 2−6 nm cylindrical nanopores with a hydrophobic surface. Hydrophilic solutes are excluded from the pores, while hydrophobic molecules interact more strongly with the membrane, partition into the pores and permeate through faster.

For example, electroless deposition of gold into the pores of TE or AAO membranes yield gold nanotubule membranes with nanopores down to ∼1 nm in diameter that can be further functionalized through the formation of SAMs using functional thiols. This approach has been adapted to create membranes for separating small molecules based on their hydrophobicity by functionalizing the nanopores by the chemisorption of alkanethiols[259] or perfluorinated thiols.[182] Alkanethiol-modified membranes showed 400 times faster permeation of toluene in comparison to pyridine in single solute diffusion experiments. The selectivity was decreased to 100 in a competitive diffusion experiment, still a very high selectivity and an excellent demonstration of the ability of this approach to create membranes with complex, customizable selectivity. The versatility of thiol chemistry allows the control of chemical interactions between solute and pore walls, so this method can also be expanded to other complex separations, as described below. Nonetheless, manufacturing issues and low porosity still limit the use of this approach for large scale separations.

An alternative approach for narrowing down AAO membrane pores involves atomic layer deposition (ALD) to create a thin, conformal coating layer within the pores. ALD involves sequential exposure of the AAO substrate to two precursors that react with each other, followed by purging to remove excess molecules. Membranes with hydrophobic pores have been fabricated by ALD of a thin silica ($SiO_2$) layer onto AAO membranes, followed by surface modification with a hydrophobic perfluorinated silane.[182] This leads to membranes with a relatively low diffusion selectivity of 5.5 based on hydrophobicity. The brittleness of inorganic AAO substrates and the complex, high temperature coating process further limit the use of this approach for large scale manufacture of filtration membranes,[178] though ALD remains a promising approach for preparing gas separation and catalytic membranes.[260−262]

Initiated chemical vapor deposition (iCVD) is an alternative method for narrowing down the pores of a TE membrane and controlling its surface chemistry. In this method, the TE membrane is placed on a chilled stage, in a reactor held at low vacuum. The monomer(s) and a thermally labile initiator are fed into the reactor as vapors. The initiator is decomposed by interaction with a hot filament and reacts with the monomer adsorbed on the surface. Pores can be narrowed down to about 5 nm and coated with an additional polymer layer to control


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pore functionality. Upon coating the pore walls with a fluorinated polymer, a diffusion selectivity of over 200 was achieved for two small, similarly sized organic molecules based on their hydrophobicity.[179] iCVD has better scale-up potential than ALD and electroless deposition, as it is a relatively shorter procedure and does not involve heating the template membrane to high temperatures. However, it still requires the use of a vacuum system and relatively long deposition times, particularly for achieving conformal coatings. These factors limit its use for large scale processing. Furthermore, functionalization is limited to only volatile monomers.

Although these top-down approaches result in high separation selectivity, their large-scale application is limited due to the low porosity of resultant membranes and the difficulty of manufacturing procedures. Nonetheless, the high selectivities reported demonstrate the value of creating functional nanopores for separations based on hydrophobicity and other complex molecular features.

**6.2. Enantioselective Membranes for Chiral Resolution.** Many biochemicals are chiral, with each stereoisomer having different biological activity and toxicity. This makes the ability to separate stereoisomers of a chiral compound crucial in the production of pharmaceuticals, nutraceuticals, and agricultural chemicals.[263] Conventional methods to obtain chiral resolution are crystallization, kinetic resolution (chemical/enzymatic catalysis) and chromatography.[264,265] Enantioselective membranes, which offer continuous and energy-efficient separation, can be fabricated either by intrinsically chiral polymers (e.g., peptides[266] and polysaccharides including chitosan and sodium alginate[267]) or by immobilizing chiral selectors (e.g., cyclodextrins,[268] proteins,[269] DNA[270]) into the membrane. In this perspective, we focus on diffusion-enantioselective membranes, which preferentially transfer chiral isomer with higher affinity, as opposed to membranes that act as adsorbers to remove one enantiomer from the passing solution.[263]

*6.2.1. Membranes Formed of Chiral Polymers.* One approach for preparing membranes with chiral selectivity involves forming a dense membrane selective layer from a chiral polymer. For example, hydrogel selective layers can be formed from water-soluble chiral polymers such as sodium alginate (SA) or chitosan (CS). These natural polymers can be solution cast onto a polyester film, dried and peeled off, and then immersed into an acetone solution containing glutaraldehyde for cross-linking. A CS membrane prepared this way showed preferential transport of D- isomers of $\alpha$-amino acids with an enantiomeric excess (ee; difference between the accumulated amount of D- and L- isomers in permeate) of up to 95% in pressure driven filtration experiments.[267] These results imply that hydrogels with chiral groups may serve as effective membranes for enantioseparation even in the absence of complex nanostructures. However, most hydrogel membranes are relatively thick films with low flux. A major challenge is the scalable manufacture of TFC membranes with ultrathin hydrogel selective layers that would combine this selectivity with higher operating fluxes necessary for broader use. A recent method, Interfacially Initiated Free Radical Polymerization (IIFRP),[271] can potentially enable the formation of such membranes with high scalability and consistency. It can also potentially be adapted to integrate additional functionalities within the hydrogel selective layer, including but not limited to chiral selector moieties.

*6.2.2. Membranes with Mobile Chiral Selector Moieties.* Rather than forming a continuous selective layer, chiral selectors can be trapped within membrane pores and serve as carriers for facilitated transport. For example, apoenzyme, a protein serving as a chiral selector, has been incorporated in the nanopores of a TE membrane "plugged" by electropolymerized porous polypyrrole layers. The integration of apoenzyme results in high enantioselectivity of up to 4.9 for a chiral amino acid, phenylalanine, without causing irreversible binding or unwanted chemical conversion of the solute.[269] While this approach still suffers from the low porosity inherent to TE membranes and requires many manufacturing steps, it also demonstrates the promise of creating a membrane with mobile carriers for difficult separations.

*6.2.3. Nanopores Functionalized with Chiral Groups.* Following the biomimetic approach inspired by porins and other functional nanochannels, chiral moieties can be integrated into nanopores to impart enantioselectivity to membranes. Pores of UF membranes can be functionalized with chiral groups using relatively simple methods, but the short pore length and the large and polydisperse pore size inherent to these membranes lead to low selectivity.[272−274] Instead, creating uniform, very small nanopores lined with chiral functional groups is expected to yield higher selectivity. This can be achieved utilizing methods described in earlier sections, coupled with well-designed functionalization procedures. For example, antibodies have been immobilized using silane chemistry within the pores of AAO membranes to serve as chiral selectors lining cylindrical nanopores.[275] Antibodies are known as the most specific molecular recognition proteins due to their high binding constant. To chemically tune the strength and reversibility of their interaction, dimethyl sulfoxide was added to the racemic mixture of a chiral drug fed to this membrane. A diffusion selectivity of 4.5 was achieved in separating this mixture.[276] In addition to other limitations of templated approaches discussed earlier, these membranes may not function well with complex feeds due to the potential for nonspecific binding or protein degradation. Nonetheless, this is one of the highest selectivities reported for chiral resolution by a membrane.

In addition to templated nanotubes, colloidal silica NP opal layers can also be functionalized to incorporate chiral selectors by silane chemistry or to graft chiral polymer brushes that partially fill the pores by surface-initiated ATRP (Figure 14). f14 Similar to the studies on charge-based selectivity, most of this work focused on opal layers covering electrodes as opposed to free-standing membranes. By attaching chiral selectors such as enantiopure molecules[277] or thiacalixarene moieties[278] and controlling solvent polarity, permeation selectivities that range between 2 and 4.5 can be achieved between optical isomers.[279] While grafting polymer brushes with chiral selector moieties (e.g., polypeptides) onto the silica spheres can increase the density of chiral binding sites within the pores, it would also narrow them down. Films with grafted chiral polymers exhibited comparable selectivities to those modified with a chiral selector molecule, possibly because most of the chiral sites on the grafted polymers were not accessible due to pore narrowing.[280] When thicker opal films were sintered to create free-standing membranes, lower enantioselectivity was observed due to the loss of functionalizable groups lining the pores.[278] Although films fabricated by self-assembled of silica offer high chiral selectivity, making them into membranes


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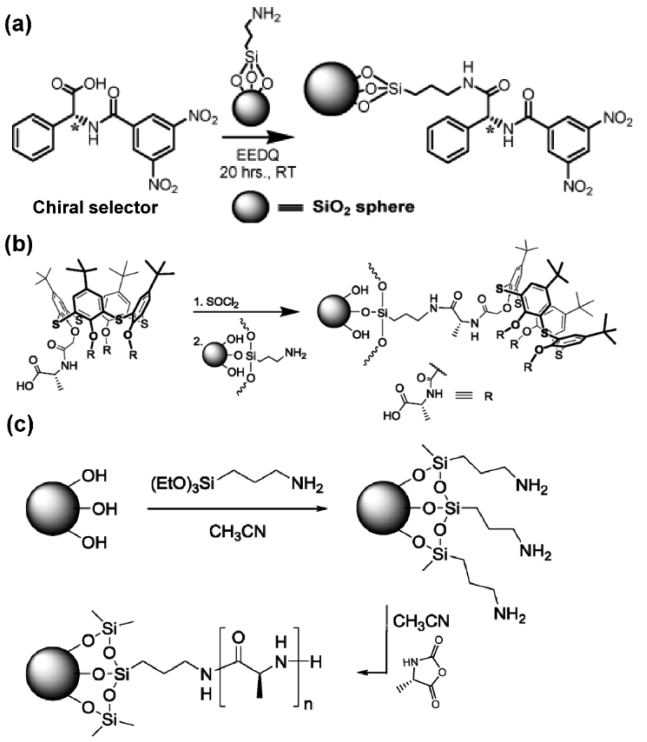


**Figure 14.** Modification of silica spheres by (a) immobilization of chiral selector moieties on the surface of spheres, (b) immobilization of chiral thiacalixarene, and (c) grafting poly(L-alanine) on the surface of silica spheres by surface-initiated ring-opening polymerization. Reprinted with permission from ref 278. Copyright 2014, John Wiley and Sons.

without damaging a high fraction of functional groups is still a challenge.

More recently, graphene oxide (GO) has been used to create functionalizable membrane pores for enantioselective membranes. GO membranes can be effective molecular sieves with ultrafast water permeation.[281,282] GO sheets can be cheaply produced in large scale by oxidation and exfoliation of graphite and deposited onto a support by methods such as filtration, LBL deposition, and drop-casting.[283] GO sheets contain oxygen containing functional groups (e.g., hydroxyl, epoxy, carbonyl, carboxyl) that offer potential for further functionalization.[284] To create enantioselective membranes, GO sheets were modified with chiral glutamic acid by carbodiimide chemistry. Membranes were then fabricated by the deposition of modified GO sheets onto a cellulose acetate (CA) or AAO support membrane by filtration, followed by the removal of water by storing in vacuum. These membranes exhibited lower rejection of dihydroxy-D-phenylalanine (D-DOPA) compared with the L-isomer in filtration experiments.[285] To date, GO-based membranes have mostly been studied in size sieving, desalination, and gas-separation applications.[284] GO-based membranes are at a relatively early stage of development and currently suffer from limited stability. Cross-linking the layer may help in improving stability but results in loss of functional groups. Nonetheless, the presence of very narrow permeation pathways and functionalizable pore entrances may enable the development of more selective membranes.

**6.3. Other Interactions.** Although electrostatic-, hydrophobic-, or stereospecific interactions have been utilized as the main separation mechanisms to date, other noncovalent interactions such as hydrogen bonding and $\pi-\pi$ interactions also affect membrane permeation selectivity.[145,238,250,279,286,287] The same is also true for biological pores. For example, computational studies show that cation$-\pi$ interactions play a key role in ion selectivity in potassium channels,[287] along with electrostatic interactions.[150] Indeed, while researchers seek to focus on a particular, easily predicted interaction mechanism for designing separation membranes, solute−membrane interactions are complex, a sum of various forces affected not only by the pore and solute chemistry but also by the environment (e.g., solvent polarity) and nanoconfinement. As such, a better, more predictive understanding of these noncovalent interactions is needed to enable the rational design of new membranes with controlled selectivity.[279]

Nonetheless, many studies including those listed above show that combining nanoscale confinement with specific solute−pore wall interactions is the biomimetic key to developing membranes featuring chemical-based selectivity. This phenom-

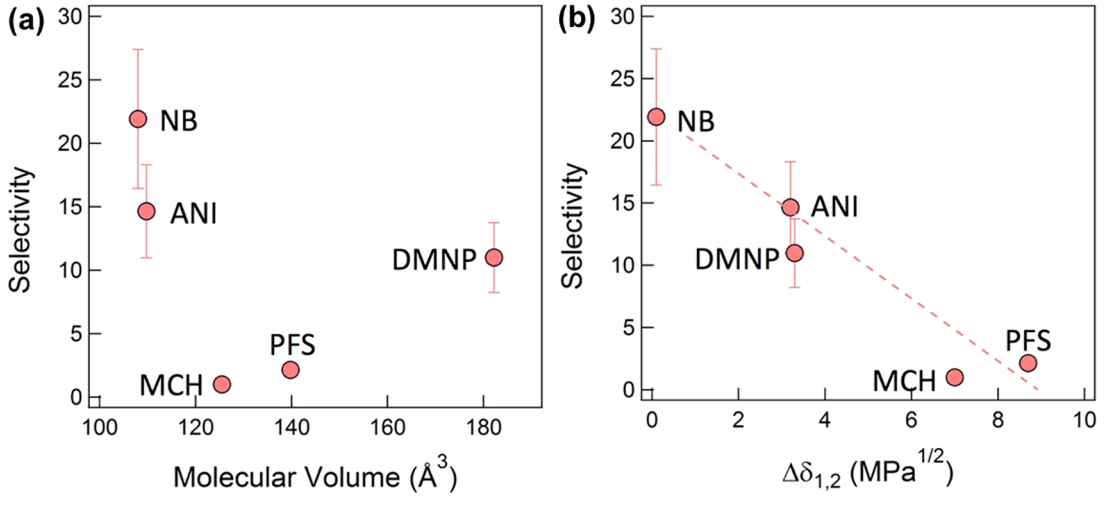


**Figure 15.** Permeation selectivity for small organic molecules, nitrobenzene (NB), methylcyclohexane (MCH), 4-methylphenol (MP), anisole (ANI), pentafluorostyrene (PFS), and dimethoxy naphthalene (DMNP), vs (a) molecular volume and (b) solubility parameter difference between solutes and PEGPEA, $\Delta\delta_{1,2}$, showing strong correlation between the membrane selectivity and solubility parameter difference. Reprinted with permission from ref 250. Copyright 2015 American Chemical Society.



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enon is demonstrated in a recent study comparing permeation in a homogeneous polymer membrane with permeation in confined, polymer-filled ∼1 nm nanochannels, formed by the self-assembly of a comb-shaped copolymer (Figure 15). Permeation rates of organic molecules in isopropanol through a homogeneous, cross-linked film of poly(ethylene glycol phenyl ether acrylate) (PEGPEA) were directly correlated with solute size, indicating diffusivity-based selectivity (Figure 15a). The comb copolymer had a polyvinylidene fluoride (PVDF) backbone and PEGPEA side chains that microphase separated to form bicontinuous 1−3 nm nanodomains.[250] Only PEGPEA was swollen in the solvent, isopropanol, thus confining permeation to only these domains. Interestingly, the permeation rates of different solutes were poorly correlated with size or polarity. Instead, they exhibited a strong correlation with the affinity of solutes to PEGPEA, quantified by solubility parameter differences (Figure 15b). The membrane showed a permeation selectivity of ∼20 for small molecules of similar size. This study highlights the ability of nanoconfinement to emphasize solute−membrane interactions over size differences, significantly altering the basis of selectivity. It also shows that selectivity is driven by global measures of solute/membrane affinity as opposed to a single type of interaction (e.g., polarity, hydrogen bonding).

## 7. FUTURE OUTLOOK

This perspective describes several approaches to creating membranes with improved, often more complex, selectivity. Many of these approaches are inspired, implicitly or explicitly, by biological systems that achieve extremely high selectivities while maintaining high permeability. This weaves a common thread among most of these successful approaches: creating nanoscale structures with controlled pore chemistry. The synthetic systems described here are not exact mimics of the highly complex biological pores with exquisite spatial control of chemical functionalities, so they do not have the same degree of selectivity and permeability of biological pores. Nonetheless, these studies are at the forefront of advanced materials that synergistically control nanoscale morphology and chemical features for an application with great potential impact in chemical, petrochemical, and pharmaceutical manufacturing. They represent innovative approaches to membrane manufacture that can overcome the limitations of existing membrane materials by utilizing modern techniques in chemistry, materials science, self-assembly, surface engineering, and biochemistry.

A major challenge in the realization of these novel membrane materials for large scale use is the development of simple, scalable, and reproducible manufacturing methods that lead to highly controlled nanostructures and surface chemistries. Many of the approaches described involve very complex, multistep manufacturing schemes. Several of them involve techniques that are well-established in lab settings yet hard to apply in the large-scale, continuous, roll-to-roll manufacturing lines used in membrane manufacture. Some of the most promising approaches also use raw materials that are, at least currently, difficult to acquire affordably in large enough quantities for scale-up. An important research and development need is the adaptation of successful approaches that show promise to improve scalability. These developments will be driven by innovations in large-scale, reliable manufacturing of nanoscale structures. We believe that soft matter self-assembly in particular will be a crucial tool in creating the functional nanostructures featured in this review. This is demonstrated by the ongoing commercialization efforts, focused heavily on technologies that feature self-assembly as part of the manufacturing scheme. For example, the manufacture of isoporous membranes prepared by SNIPS, which explicitly utilizes BCP self-assembly to create membranes with tightly controlled pore size and functionalizable pore chemistry, has been demonstrated in roll-to-roll and hollow fiber pilot systems.[57,288,289] The scalability of the SNIPS process has led to ongoing commercialization efforts, including two start-up companies, Anfiro and Terapore, who are seeking to address challenges in water treatment and bioseparations, respectively. Self-assembly has been used to create aligned CNT membranes in both small and large scale. Mattershift, another start-up, is seeking to commercialize this approach. Isoporous, fouling resistant membranes formed by the self-assembly of zwitterionic random copolymers are currently being developed by another start-up, ZwitterCo. Each of these companies focuses on membranes that utilize advanced materials and soft matter self-assembly to overcome challenges yet rely on manufacturing methods that are well-established for roll-to-roll membrane manufacture such as coating or NIPS.

While a large portion of this perspective focuses on size- and charge-based separations, likely the biggest challenge remains the development of membranes that can separate organic molecules of similar size and charge but different chemical structure. To date, the studies in the literature are generally proof-of-concept demonstrations that show the ability to separate probe molecules based on a specific chemical feature (e.g., hydrophobicity). These are not true separation challenges faced by the chemical or pharmaceutical manufacturing industries. Most pharmaceutical manufacturing processes are proprietary, and many are designed during the scale-up stage based on the capabilities of existing separation processes. Industry/academia partnerships can direct separations research toward true industry challenges and lead to more impactful research.

Furthermore, it is rare to find realistic separation challenges that involve mixtures differentiated by only one prominent chemical feature. As membranes are developed with the goal of controlling chemical structure-based selectivity, solute−pore interactions need to be considered holistically. The membrane needs to be designed to control solute−pore wall interactions as a whole so as to impart selectivity. This requires fundamental studies that can enable the prediction and measurement of solute−surface interactions. Simulations and theoretical studies can provide key insights to the interaction of solutes with functional surfaces. Characterization techniques such as quartz crystal microbalance with dissipation, QCM-D, can provide important information on solute adsorption and desorption that can inform membrane design as well as our understanding of selectivity and transport mechanisms.

A significant need is the development of membrane models, both physical and theoretical, to understand the effect of nanoconfinement on transport. While many systems have been developed to create membranes with functional nanopores, fundamental studies of the effect of key parameters (pore size, interaction strength, reversibility of binding) on transport rate and selectivity are limited. This in part arises from challenges in measuring these key quantities. For example, it is very difficult to accurately determine pore sizes that are small enough to control small molecule separations, particularly in the wet state. The same is true for the measurement of


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functional group densities within pores. Another challenge is the lack of detailed theoretical models that account for nanoconfinement, pore/solute interactions, tortuosity and interconnectedness of pores, and other features of real membranes designed for chemical separations. The solution-diffusion and pore-flow models do not explicitly account for these parameters. A handful of simple models have recently shone light on some of these effects and shown some significant features of biological and biomimetic pores.[244,253] Such models will not only enhance our fundamental understanding of ion channels but also enable the rational design and engineering of functional membranes.

In short, a key to the broader use of membranes in chemical, pharmaceutical, and petrochemical manufacturing is the development of membranes with controlled selectivity. This requires the design of membranes with highly controlled nanostructures and surface chemistries. Isoporous membranes with homogeneous pore size can not only serve as better size-selective filters but also serve as scaffolds for creating functional nanopores that enable complex separations. Membranes designed for charge-based separations are useful not only for purifying biochemicals but also for the creation of structures that mimic ion channels that can be further modified to adapt their selectivity. Membranes that separate based on criteria other than size and charge must operate on the basis of novel transport mechanisms that leverage membrane−solute interactions to differentiate between solutes. This requires the development of membranes that utilize state-of-the-art materials science. This burgeoning research area promises to transform chemical and pharmaceutical manufacturing if membranes with sufficient selectivity and flux can be manufactured through scalable methods, and highly customizable membrane systems enable the design of membranes targeted at each challenging separation. Insights gained from these membranes impact not only filters but also sensors, drug delivery, electrochemical systems, and other technologies where solute transport is crucial to performance.

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### Notes

The authors declare no competing financial interest.

### Biographies

Dr. Ilin Sadeghi received her Bachelor's and Master's degrees in Chemical Engineering from Tehran Polytechnic (Amirkabir University), Iran, in 2010 and 2012, respectively. During her Master's studies, she developed a new membrane surface modification technique, corona air plasma, to improve membrane fouling resistance for oil/water separation. She earned her Ph.D. in the Chemical and Biological Engineering Department at Tufts University in Prof. Asatekin's lab. During her PhD, she worked on novel approaches for manufacturing membranes with controlled selectivity. She developed chemoselective membranes for separation of small organic molecules by self-assembly of random copolymer micelles. Furthermore, she developed a new method for manufacturing ultrathin, multifunctional hydrogel selective layers. She also worked on superoleophilic electrospun membranes for oil/water separation by designing a surface-segregating copolymer.

Dr. Papatya Kaner has received her Ph.D. in Chemical Engineering from Tufts University. She obtained her B.Sc. in Chemical Engineering from Istanbul Technical University (ITU), Turkey, in 2009 and her M.Sc. in Chemical Engineering from Florida State University in 2012. Her M.Sc. studies focused on fundamental structure−property relationships that correlate polymer chemistry and architecture with polymer crystallization. She conducted her Ph.D. studies under the supervision of Prof. Ayşe Asatekin. During her Ph.D., she developed stimuli-responsive and fouling resistant water filtration membranes by using custom-designed zwitterionic copolymers. In addition, she implemented comb-shaped, self-assembling zwitterionic copolymers to develop porous thin films with nanoscale, hierarchical morphology, and tunable pore size.

Ayse Asatekin received B.S. degrees in Chemical Engineering and Chemistry from the Middle East Technical University (METU) in Turkey. She completed her Ph.D. in Chemical Engineering at Massachusetts Institute of Technology through the Program in Polymer Science and Technology, working on developing new fouling resistant membrane materials under Anne M. Mayes and Michael F. Rubner. She is a cofounder of Clean Membranes, Inc., a start-up initiated to commercialize this work. She completed her postdoctoral training with Karen K. Gleason at MIT and worked at Clean Membranes between 2011-2012. She is currently an assistant professor at Tufts University's Department of Chemical and Biological Engineering, where she leads a research group focused on utilizing polymer self-assembly for novel membrane materials for highly selective separations as well as water treatment. Her research interests also include surface engineering, multifunctional and responsive materials, polymer science, and energy storage.

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