

Critical Knowledge Gaps in Mass Transport through Single-Digit Nanopores: A Review and Perspective

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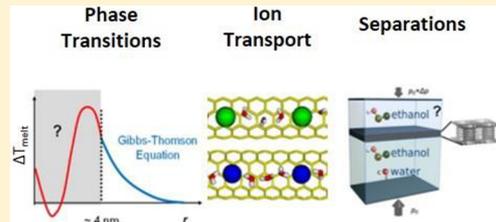
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ABSTRACT: Not all nanopores are created equal. By definition, nanopores have characteristic diameters or conduit widths between ~ 1 and 100 nm. However, the narrowest of such pores, perhaps best called Single Digit Nanopores (SDNs) and defined as those with regular diameters less than 10 nm, have only recently been accessible experimentally for precision transport measurements. This Review summarizes recent experiments on pores in this size range that yield surprising results, pointing toward extraordinary transport efficiencies and selectivities for SDN systems. These studies have identified critical gaps in our understanding of nanoscale hydrodynamics, molecular sieving, fluidic structure, and thermodynamics. These knowledge gaps are, in turn, an opportunity to discover and understand fundamentally new mechanisms of molecular and ionic transport at the nanometer scale that may inspire a host of new technologies, from novel membranes for separations and water purification to new gas-permeable materials and energy storage devices. Here we highlight seven critical knowledge gaps in the study of SDNs and identify the need for new approaches to address these topics.



INTRODUCTION

Nanopores, broadly defined as pores with diameters or conduit widths smaller than 100 nm, underpin a large array of material systems and technological applications. For example, adsorbent technology for chemical and air separations employs activated carbon with pores as small as 0.6 nm in size,^{1–3} while zeolites such as ZSM-5, with a pore diameter of 5.5 Å, have been used for a wide variety of catalysis, adsorption, and pollution abatement applications.^{4,5} Membrane technology for reverse osmosis and nanofiltration typically involves inorganic substrates with pores on the order of 0.5 nm and from 1 to 5 nm, respectively.^{6,7} However, detailed studies of nanopore transport at the single pore level have only become possible recently with the advent of isolated pore systems combined with sophisticated readout mechanisms to probe fluidic motion and mass transport in pores

that are geometrically and compositionally well-defined. Examples of such systems include short⁸ and ultralong carbon nanotubes,^{9,10} boron nitride nanotubes,¹¹ graphene oxide laminates,^{12,13} polymer nanochannels,^{14,15} and silicon nanochannels.^{16,17} These systems have been probed with analytical techniques including fluorescence, Raman, nonlinear,¹⁸ and single-defect spectroscopies,^{19–24} ab initio density functional theory (DFT) simulations,^{25–27} and multiscale models^{28–34} to elucidate solvation phenomena,^{25,27} correlative and dissipative behaviors,³¹ and ionic and molecular selectivity mechanisms³⁵ that arise under extreme confinement.

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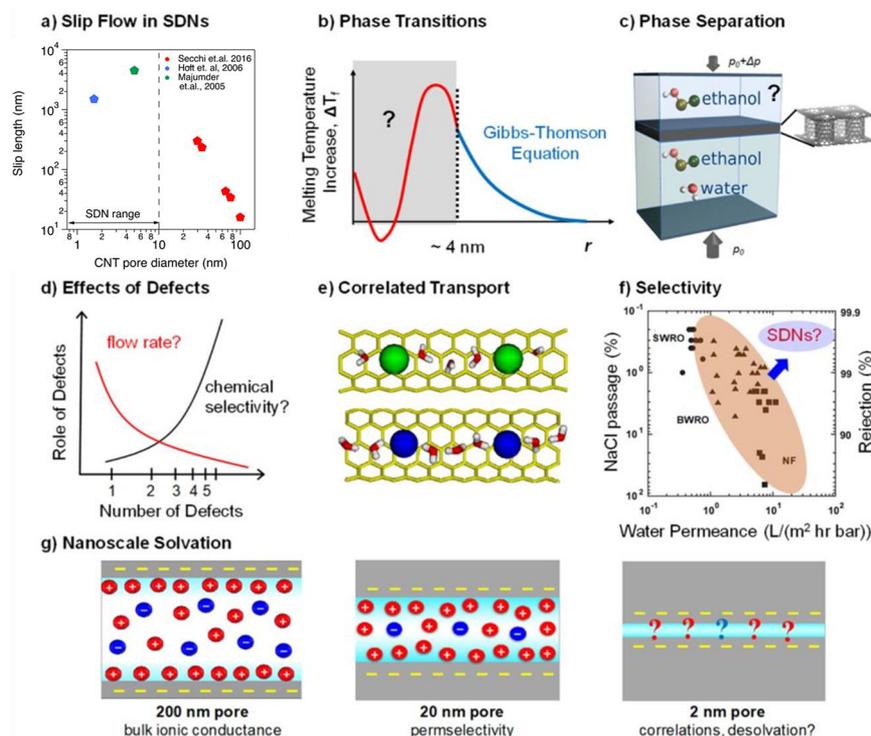


Figure 1. Critical knowledge gaps in SDN nanofluidics. (a) The scaling of slip length with nanopore diameter is unknown and possibly nonmonotonic in the single-digit range. Data taken from refs 36–38. (b) The phase behavior of fluids inside SDNs cannot be predicted by existing theories. (c) Phase separation may be enhanced by nanoconfinement. (d) Defects may have an outsized effect on transport inside SDNs, but the magnitude of these effects is unknown. (e) Transport of ions in SDNs shows novel spatial and temporal correlations. (f) SDNs may form the basis for systems with enhanced molecular and ionic selectivity, surpassing that of membranes currently used for reverse osmosis. (g) Solvation in confinement differs from that in bulk, with profound effects on transport rates and selectivity.

In particular, recent studies of transport in single-digit nanopores (SDNs), that is, pores with a diameter or conduit width smaller than 10 nm, reveal many counterintuitive behaviors that often defy continuum descriptions of fluid flow. These results expose critical knowledge gaps that motivate investigation and challenge existing theories. SDNs also provide exciting opportunities to advance fundamentally new technology, in the form of membranes and fluidic platforms with unprecedented transport rates and selectivities, and a unique opportunity for the seamless integration of wet ionic devices with dry electronics, thus enabling long-sought bioelectronic interfaces.³⁹ Specifically, SDNs can be tailored to (i) sieve ions efficiently from seawater and serve as membranes for seawater desalination,⁴⁰ (ii) differentiate between polar and nonpolar fluids and serve as flow sensors,⁴¹ (iii) enhance proton transport in fuel cell applications,⁴² and (iv) generate electricity from osmotic power harvesting.¹¹ Moreover, a deeper mechanistic understanding of water transport through SDNs may allow us to build robust synthetic analogues of transmembrane proteins, such as aquaporins,⁴³ for water treatment applications. This Review discusses recent work and critical gaps in our understanding of nanoscale hydrodynamics, molecular sieving, fluidic structure, and thermodynamics in SDNs. It also comments on the implications of these new molecular transport mechanisms. We refer the reader to other compelling reviews on other classes of nanopores,^{44,45} nanoporous materials for energy storage,^{46,47} and for water and gas purification.^{48–50}

This brief literature survey identifies knowledge gaps that have recently emerged in the areas of nanofluidics and fluid confinement. Examples of these gaps include: the observation of slip-flow enhancement, in which the narrowest nanopores

demonstrate the highest mass transport rates;^{8,37} non-Gibbs–Thomson phase behavior, in which fluid phase boundaries in SDNs are distorted relative to their bulk fluid counterparts; and nonlinear, correlative effects^{10,51} in ion transport through SDNs that are not observed in larger nanopores (Figure 1). We define these and other observations as critical knowledge gaps, because existing theories—whether continuum, atomistic, or molecular—fail to adequately describe the basis for these exotic effects. In this Review, we identify seven such knowledge gaps, highlight recent progress, and suggest next steps for their exploration.

■ KNOWLEDGE GAP 1: SLIP FLOW ENHANCEMENT

Flow enhancement by slip flow in SDNs is unexpectedly large. Slip flow⁵² occurs when the fluid molecules in contact with the wall have a nonzero velocity, and the no-slip boundary condition in fluid mechanics does not hold. This situation often occurs in nanopores with atomically smooth walls. The slip length is defined mathematically as the distance required beyond the wall for the fluid velocity to decrease linearly to zero. Large values of slip lengths for fluids confined inside SDNs can result in flow rates that greatly exceed the predictions of the Hagen–Poiseuille equation, thereby substantially lowering the pressure drop for narrow conduits.^{8,37,52} Several recent studies^{37,38,53–58} suggest that the narrowest pores demonstrate the largest slip-length enhancements. Mechanistic understanding of this scaling is in its infancy, because theory and simulations^{52,59–65} have failed to match the results of recent measurements on pores that are wider than SDNs.

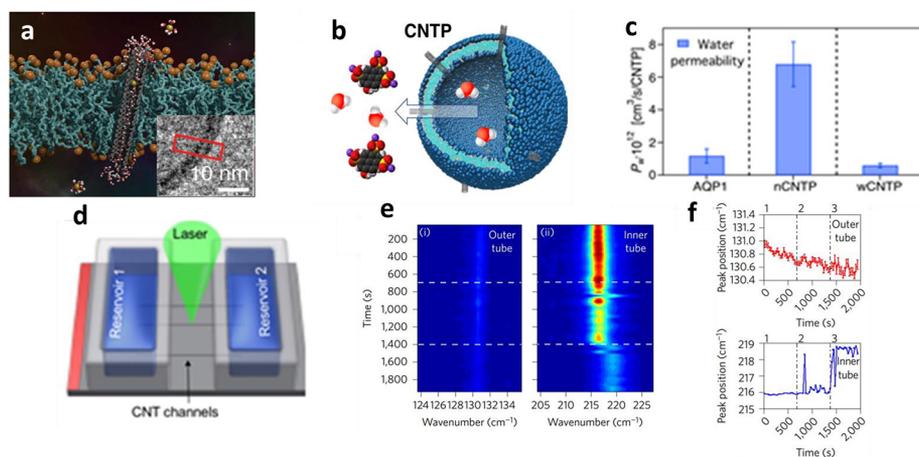


Figure 2. Transport measurements in CNT porins and CNTs. (a) CNT porins (CNTP) in lipid membranes (inset shows a cryo-TEM image of a 0.8 nm diameter CNTP in a lipid membrane). From Tunuguntla, R. H.; Henley, R. Y.; Yao, Y.-C.; Pham, T. A.; Wanunu, M.; Noy, A. Enhanced water permeability and tunable ion selectivity in subnanometer carbon nanotube porins. *Science* **2017**, *357*, 792–796. Reprinted with permission from AAAS. (b) Osmotically driven water transport through CNT porins. From Tunuguntla, R. H.; Henley, R. Y.; Yao, Y.-C.; Pham, T. A.; Wanunu, M.; Noy, A. Enhanced water permeability and tunable ion selectivity in subnanometer carbon nanotube porins. *Science* **2017**, *357*, 792–796. Reprinted with permission from AAAS. (c) Water permeability of aquaporin protein (AQP1) compared with that of 0.8 nm (nCNTP) and 1.5 nm (wCNTP) diameter CNT porins. From Tunuguntla, R. H.; Henley, R. Y.; Yao, Y.-C.; Pham, T. A.; Wanunu, M.; Noy, A. Enhanced water permeability and tunable ion selectivity in subnanometer carbon nanotube porins. *Science* **2017**, *357*, 792–796. Reprinted with permission from AAAS. (d) The CNT experimental platform, which comprises isolated CNTs connected to two reservoirs, enables monitoring by microRaman spectroscopy. Reprinted from ref 10, Springer Nature. (e) Temporal study of the radial breathing mode (RBM) frequency. (i,ii) A time map showing the evolution of the RBM frequency and intensities for a 1.15 nm DWCNT. Dotted lines indicate the time points at which water is added to the reservoirs. Reprinted from ref 10, Springer Nature. (f) Filling is shown for the inner tube of a DWCNT but not the outer tube by an upshift in RBM frequency. Reprinted from ref 10, Springer Nature.

1.1. Carbon Nanotube and 2D Material Assemblies.

Carbon nanotubes (CNTs), with their atomically smooth walls and constant diameters, are an ideal system for probing flow enhancement in SDNs. Following a landmark molecular dynamics (MD) prediction of fast flow in CNT pores,⁶⁶ there has been a long history of experimental investigations of water flow through membranes composed of arrays of vertically aligned CNTs.^{37,38,57,67} For example, Majumdar et al. studied fluid flow through membranes composed of vertically aligned multiwalled CNTs of ~7 nm diameter and reported water slip lengths of 39 to 68 μm , which correspond to water flow rates that are 4 to 5 orders of magnitude faster than the predictions of the Hagen–Poiseuille equation with a no-slip boundary condition.³⁸ Holt et al. studied water and gas flow through membranes composed of double-walled CNTs (DWCNTs) with diameters less than 2 nm and reported water slip lengths from 140 to 1500 nm.³⁷ These studies and others were also motivated by earlier work showing selective ionic and molecular transport through synthetic membranes with nanopores in the single-digit range.^{68–70}

These pioneering CNT studies revealed large slip lengths of water inside CNTs, but they were performed on CNT membranes, and measurement of fluid flow through individual, isolated CNTs remained a technical challenge for many years. In a recent study, Secchi et al.³⁶ devised an experimental platform to measure pressure-driven water flow through isolated CNTs larger than the SDN range and reported a large radius-dependent flow enhancement, with the slip length reaching 300 nm for CNTs with a diameter of 30 nm diameter. Furthermore, by measuring the flow rate of water inside 30–100 nm diameter CNTs, Secchi et al.³⁶ showed that the slip length of water increases monotonically with a decrease in the CNT diameter. This monotonicity, however, may not continue into the SDN range (Figure 1a). When the diameter of the CNT

approaches the van der Waals diameter of water in the range of 0.8–2 nm, for instance, water molecules adopt a layered structure that can result in a nonmonotonic variation of slip length with CNT diameter. Between 2 and 10 nm, experimental results are varied.

Recent experimental advances using CNT porins,⁷¹ that is, 10 nm long nanotube segments inserted into lipid membranes (Figure 2a,b), complement experimental results using isolated CNTs. CNT porins occupy a unique place in the arsenal of nanofluidic tools, because these materials allow researchers to probe ensemble-scale transport in the important sub-1 nm size regime of nanotube pores that are inaccessible for conventional aligned CNT membrane platforms.⁸ The osmotic water permeability of 0.8 nm diameter CNT porins exceeds that of 1.5 nm diameter CNTs by an order of magnitude (Figure 2c),⁸ suggesting that a one-dimensional (1D) arrangement of water molecules,^{72,73} which is only achievable at small diameters, introduces an additional enhancement mechanism besides the wall slip and promotes ultrafast water transport in collective bursts.⁶⁶ The same 1D arrangement of water molecules appears to produce a significant enhancement of Grotthuss proton transport rates in narrow CNT pores.^{42,74} Transport through short CNT porins can be compared with the results from a complementary platform^{9,10} that uses Raman spectroscopy to characterize transport in ultralong CNTs (Figure 2d–f). A recent study with ultralong CNTs reported highly non-monotonic freezing point elevation of confined water as a function of nanotube diameter.¹⁰ Taken together, these results suggest that slip flow may be highly nonmonotonic with diameter, especially for the smallest diameters and channel lengths. These intriguing findings highlight the need to develop structure/function relationships for SDNs that can predict exotic transport given specific confinement conditions.

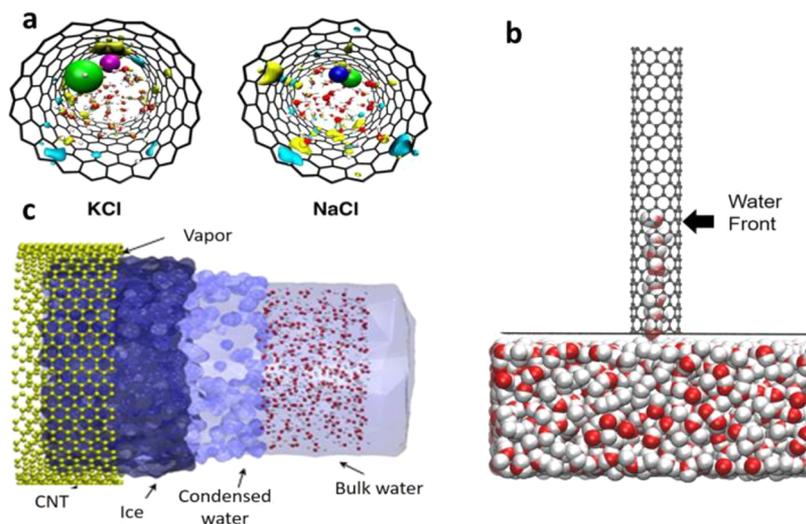


Figure 3. Modeling confinement effects on transport and phase transitions in SDNs. (a) Simulations of NaCl and KCl solutions confined in 1.4 nm diameter CNTs. Reproduced from ref 25. Copyright 2016 American Chemical Society. (b) MD simulation snapshot showing the capillary filling of a (10,0) chirality CNT by a single file of water molecules. (c) Multiphase structure of water near a CNT interface where the vapor phase, ice, condensed water, and the bulk phase of water coexist. Reproduced from ref 28. Copyright 2016 American Chemical Society.

The van der Waals assembly of two-dimensional (2D) materials to form nanoconduits, pioneered by Andre Geim and co-workers, provides another avenue to study fluids under extreme confinement.⁷⁵ In this series of experiments, fluid flow was measured through nanocapillaries formed by sandwiching few-layer 2D materials like graphene, hBN, or MoS₂ between atomically smooth crystals of graphite, hBN, or MoS₂.^{75–80} Gravimetric measurements of water permeation through channels formed by graphene spacers show extreme slip flow and suggest high capillary driving pressures.⁷⁶ The structure and properties of water under 2D confinement are quite different from bulk, with unusually low dielectric constant,⁷⁷ changes in viscosity that arise from finite-size effects,⁸¹ and the appearance of unusual phases like 2D square ice.⁸² These slit pores with 2D material spacers also show remarkable ionic transport properties, including transport of protons with complete rejection of larger ions⁷⁹ and asymmetric transport between similarly sized cations and ions even in the absence of substantial surface charge.⁸⁰ While fluid structure and transport are likely different under 2D confinement than in the 1D systems discussed elsewhere in this Article, the implications of these differences for slip flow and ion transport have not been fully established.

1.2. Slip Flow Simulations. Molecular dynamics simulations show wide disparities in slip flow inside carbon nanotubes. Snapshots and illustrations from several MD simulations are shown below (Figure 3). Slip lengths determined from MD simulation studies differ by ~ 3 orders of magnitude, varying between 1 nm and 1 μm for water flow through CNTs with diameters ranging from 0.81 to 7 nm.⁶⁵ The slip length of water can be estimated using both nonequilibrium and equilibrium MD simulations. In nonequilibrium MD (NEMD) simulations, a pressure-driven water flow is simulated by applying an external force on the water molecules. However, results from NEMD simulations can depend sensitively on: (i) the choice of the thermostat used to maintain the temperature of the water molecules and CNT;⁸³ (ii) the length of the CNT when considering finite-size CNTs due to entrance/exit effects;⁸⁴ and (iii) the type of fitting of the velocity profile used to obtain the slip length due to the nearly pluglike velocity profile of water inside CNTs.⁶⁵ In contrast, equilibrium MD

simulations of water confined inside a periodic CNT can be performed to obtain the slip length reliably based on the Green–Kubo relationship.⁵²

Several factors have contributed to the large variation in the slip lengths of water reported in previous MD simulation studies, including (i) the use of different methods (e.g., NEMD vs equilibrium MD) to calculate the slip length, (ii) the nature and strength of the force field used to model water–carbon interactions, and (iii) the water model used to model water–water interactions inside the CNT.⁸⁵ The concept of slip length itself is ambiguous in the case of 0.8–1.6 nm diameter CNTs. In such small pores, water molecules arrange in separate chains connected through intrachain and interchain hydrogen bonding, and so the water velocity profile is not well-defined. Therefore, it is more reasonable to describe the water flow rate in terms of the CNT permeability, which is expressed as a function of the water friction coefficient.⁵² Additional studies are required to elucidate the dependence of the CNT permeability on water–CNT and water–water interactions.

It is noteworthy that previous MD simulation studies have used a simple pairwise additive Lennard-Jones potential to model the interactions of water molecules with CNTs. However, water, as a polar solvent, can exert strong electric fields that can result in a significant polarization of the carbon atoms in CNTs. Polarizable force fields, which can self-consistently model the polarization and dispersion energy components of the water–CNT binding energy, can be used to obtain a more realistic modeling of the water–CNT interface at a modest increase in computational cost.³² Additionally, hybrid quantum mechanical/molecular mechanics (QM/MM) and full ab initio molecular dynamics (AIMD) simulations can be performed to obtain more accurate estimates of the friction coefficient of water inside some of the small-diameter CNTs, although the computational cost for performing these simulations will be significantly higher than that incurred using classical, force-field-based MD simulations.⁸⁶ Finally, the study of fluid flow through nanotubes made of heteropolar nanomaterials, such as molybdenum disulfide and hexagonal boron nitride, will allow for decoupling the effects of electrostatic and London dispersion forces on nanofluidic phenomena.^{33,87,88}

■ KNOWLEDGE GAP 2: PHASE TRANSITIONS IN SDNS

Fluids confined in nanopores exhibit significant distortions of the temperature–pressure phase boundary. This has been shown experimentally in carbon nanotubes^{10,51} and discussed at length for fluids in nanoporous silica.⁸⁹ These distorted phase transitions can be described by modifying the Gibbs–Thomson equation with the Turnbull coefficient.⁵¹ This coefficient, which was originally proposed in metal nucleation theory, is the ratio of the nanopore–liquid interfacial tension γ_{SL} to the enthalpy of fusion ΔH_{m} of the liquid (which is also proportional to the molar volume to the two-thirds power, $V_{\text{m}}^{2/3}$)⁹⁰ and has been shown to be invariant with pore size for a given liquid. In this model, the change in freezing point is given by

$$\Delta T_{\text{f}} = T_{\text{f,bulk}} - T_{\text{f,pore}} = \frac{2T_{\text{f,bulk}}V_{\text{m}}\gamma_{\text{SL}}}{r_{\text{pore}}\Delta H_{\text{m}}} \quad (1)$$

where T_{f} is the freezing point, and r_{pore} is the radius of the nanopore.

However, no theory currently exists for describing phase transitions in the narrowest of pores.¹⁰ Below ~ 4 nm, water structuring effects cause the Gibbs–Thomson equation to fail, with freezing points varying dramatically and changing non-monotonically with pore diameter. For example, recent simulations^{91,92} and experimental data¹⁰ show water freezing above 100 °C in a narrow range of CNTs close to 1 nm in diameter and confirm the nonmonotonic dependence on diameter of confined phase transitions predicted by simulation. Experimentally, phase transitions in CNT pores can be tracked by shifts of the radial breathing mode (RBM) using Raman spectroscopy.¹⁰ MD studies have also shown that the phase transition temperature of polar fluids such as water inside CNTs can be strongly modulated by external electric fields.^{93–96} However, because the results of force-field-based MD simulations can depend sensitively on the force-field parameters used to model water–CNT interactions and on the choice of the water model, it is not yet clear how the complex interplay between water–CNT and water–water interactions determines the phase behavior of water inside CNTs. The thermodynamics and phase behavior of confined water represent a significant knowledge gap that needs to be understood with a new theory and modeling approaches supported by comprehensive experimental data. One promising technique is to incorporate chemically specific emissive defects in CNTs. These defects can then be used as molecular rulers to resolve the state of the fluid at the single defect level.^{19,20,97}

■ KNOWLEDGE GAP 3: PHASE SEPARATION UNDER EXTREME CONFINEMENT

Phase separation, in which a single phase transitions into a two-phase or multiphase coexistence region, is also influenced under the extreme confinement of SDNs.^{98–100} Of particular interest is the use of this phenomenon in new nanopore and membrane separation mechanisms.^{100,101} Gravelle et al. noted from MD simulations that CNT membranes may achieve selective transport by nanoconfinement-induced preferential adsorption of water over ethanol.⁹⁹ MD studies have shown that gases such as CO₂, O₂, and H₂ from gas–water mixtures exhibit selective physisorption into single-digit CNTs. Furthermore, the solubility difference of gases in water combined with phase separation using SDNs can be exploited for the separation of gases.¹⁰² Nanoscale confinement has also been shown to change

the phase diagram and azeotrope location of CCl₄/C₆H₁₂ mixtures in activated carbon fibers, with implications for phase separation.⁸⁰ In water, it could also be important in future work to investigate the role of dissolved ions on phase transformations, such as freezing or evaporation, which would tend to reject and concentrate ions in the liquid phase after nucleation and potentially generate large disjoining pressures.

Even less is known about the behavior of nonaqueous fluids under similar conditions of extreme nanoconfinement inside SDNs. Solvent–solvent and solvent–solute interactions necessarily change as the fluid phase squeezes into molecularly sized channels, but the nature of the change is not understood in detail.^{98,100,103–106} Simulation studies have so far focused on understanding the fluidic structure of liquids, such as methanol¹⁰⁷ and ethanol,⁹⁹ confined inside CNTs. On the experimental front, Ellison et al. studied the transport of methanol, lithium ions, and various amino acid cations in the presence of water through a 2.25 nm CNT and rationalized the different dwell times of the various species based on a simple model that took into account molecular and ionic sizes.^{108,109}

Other relevant questions are whether and how confinement in a small nanopore changes the thermodynamics and kinetics of phase separation of ordinarily miscible fluids.¹¹⁰ For example, demixing induced by confinement⁹⁹ could be used to control fluid transport or to achieve more efficient or selective separations. Examples could include separating alcohols from water, fractionating hydrocarbons, and separating other complex macromolecular mixtures. For example, Mao and Sinnott used classical MD simulations to investigate the use of CNTs for separation of light gases, such as methane, ethane, and butane, from one another.¹¹¹ In another study, Rodriguez et al. studied polar mixtures of water and acetonitrile nanoconfined between silica surfaces and found an almost equal reduction in the diffusion coefficients of confined water and acetonitrile molecules as compared to their respective bulk diffusion coefficients.¹¹² As the nanochannel diameter approaches 1–5 nm, surface tension starts to exert an outsized influence on the fluid inside the channel, potentially creating conditions for spontaneous phase separation via spinodal decomposition.^{113–115}

■ KNOWLEDGE GAP 4: THE OUTSIZED IMPACT OF DEFECTS

Defects are ubiquitous in nanopores, but their effects on nanofluidic transport are poorly understood. Structurally, defects are deviations within an otherwise continuous and regular conduit, manifesting as changes in diameter or CNT chirality, atomic vacancies or substitutions, dangling bonds, and point defects that can be as simple as the addition of a hydrogen atom or as complex as a charged organic functional group.

In large pores a fluid may flow around a defect site. However, the effect of defects can become increasingly pronounced as the size of the pore/channel decreases. The role of defects in molecular transport by SDNs can be as critical as it is in electrical transport, in which defects are known to dominate conductive pathways at the nanometer scale.^{116,117} In a spectacular example of the power of defects to influence molecular transport, a few strategically placed charges in aquaporin proteins block proton flow through the protein channel.¹¹⁸ Comparing aquaporin to other protein channels, the elimination of hydrogen-bonding interactions increases the diffusion coefficient of single-file water by up to 2 orders of magnitude.^{119,120} Similarly, in an AIMD study of synthetic nanopores, Joly et al. found significantly larger

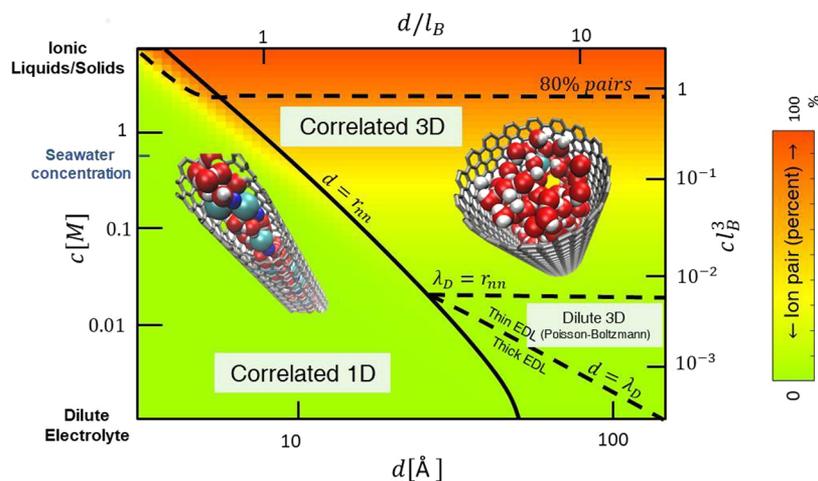


Figure 4. Electrostatics under confinement. Different behavior expected for the electrostatic interactions in a nanopore as a function of ionic concentration (c) and pore radius (d). Classical theories (Poisson–Boltzmann) are only appropriate in the bottom right corner. New approaches are needed under extreme confinement and high concentrations. The Bjerrum length, or the characteristic length for electrostatic interactions, determines the extent of ion pairing relative to r_{nn} . Under extreme confinement, $d < r_{nn}$ or $d < \lambda_D$, 1D correlated transport is expected to dominate. At high concentrations, $\lambda_D < r_{nn}$, 3D correlations and ion pairing can play a bigger role.

friction of the liquid as water flowed past wall defects that caused the molecules to dissociate.¹²⁰ In extreme cases, fluid interactions with defects in SDNs, and the resultant pinning effects, could completely change the nature of transport through the pore.

There are two significant challenges to understanding the effects of defects on nanopore transport. First, most defects occur randomly, and it is difficult to locate and resolve them in a pore.^{116,121} Second, there is a lack of tools to resolve defects and quantify their impact on fluidic transport in situ. Although techniques such as transmission electron microscopy (TEM) can resolve defects at atomic resolution, such methods typically require ultrahigh vacuum and can cause significant beam damage to nanomaterials, prohibiting a direct correlation between defects and fluid transport.

SDN platforms provide a unique opportunity to quantify the effects of defects on molecular transport. With the development of new tools and synthetic methods to control and probe defects, the effect of defects on fluid transport may be observed unambiguously. Defects can be intentionally implanted to control various material properties, such as electrical conductivity and photoluminescence, and can thereby be used as experimental markers to understand better the system and the effects of molecular transport.^{116,122} When we control and intentionally add defects in a limited manner, their properties can be spatially localized, acting as perturbations rather than completely changing the structure of the host. In combination with advanced imaging techniques, controlled defects can therefore be used to understand behaviors like molecular transport in SDNs. In fact, recent theoretical work has enabled the prediction of the exact shapes of extended vacancy defects or nanopores in graphitic surfaces, thereby allowing for direct linkages with experimental data through the simulation of realistic defect morphologies in nanofluidic systems.¹²³

Single-defect spectroscopy may enable the understanding of how defects affect, and can be used to control, fluid transport.²³ Recent advances in super-resolved hyperspectral imaging^{22,23,124} and our knowledge of defects in 1D and 2D systems^{19,20,24,122,125} are rapidly making this prospect a reality. For instance, to quantify the effect of molecular defects on

nanofluidic transport, single defects can be used as quantum light emitters.^{97,126–128} Such defects can be installed synthetically along single-walled CNTs by covalently attaching organic functional groups to the sidewall and pore mouth of the nanotube.^{20,21} A particularly exciting property is that these emissive defects create potential wells that trap excitons that can recombine to produce bright photoluminescence that is sensitive to the chemical environment.^{19,20,97,126,128,129} At the single-molecule level, ion pairs can cause much more substantial perturbation to the local environment of the trapped excitons than do individual ions. Thus, it also should be possible to perform spectral differentiation to count ion pairs. With advances in precision spectroscopic techniques, a more detailed understanding of defects in SDN transport is forthcoming.

■ KNOWLEDGE GAP 5: CORRELATED TRANSPORT OF IONS

Strong nanopore confinement, which is often accompanied by partial or complete desolvation of solutes, gives rise to interesting physical phenomena in which ions and molecules exhibit unusual spatial and temporal correlations.^{130,131} A good theoretical description is currently available only for wide nanopores in dilute solutions (Figure 4). In these larger nanopores under dilute conditions, when the Debye screening (λ_D) length is larger than the average ionic distance, and the average ionic distance (r_{nn}) is smaller than the pore diameter (d), mean field theories can correctly predict the transport behavior of ionic channels, including interesting physical phenomena such as channel gating and a nonlinear diode-like behavior.^{17,30,67,132,133} In concentrated electrolytes, ion–ion correlations lead to ordering of ions in nanopores, and even to charge inversion in highly charged pores. Ion–ion correlations require a departure from classical mean-field electrostatics models to describe charge inversion, leading to attractive pressures or bridging between like-charged pore walls.^{134,135} Charge inversion can also result in electro-osmotic flow reversals and electrophoretic mobility reversals.^{30,136}

The effect of confinement is most pronounced in small nanopores, in which the average ionic separation is larger than the pore diameter and ions effectively form a 1D chain, for which

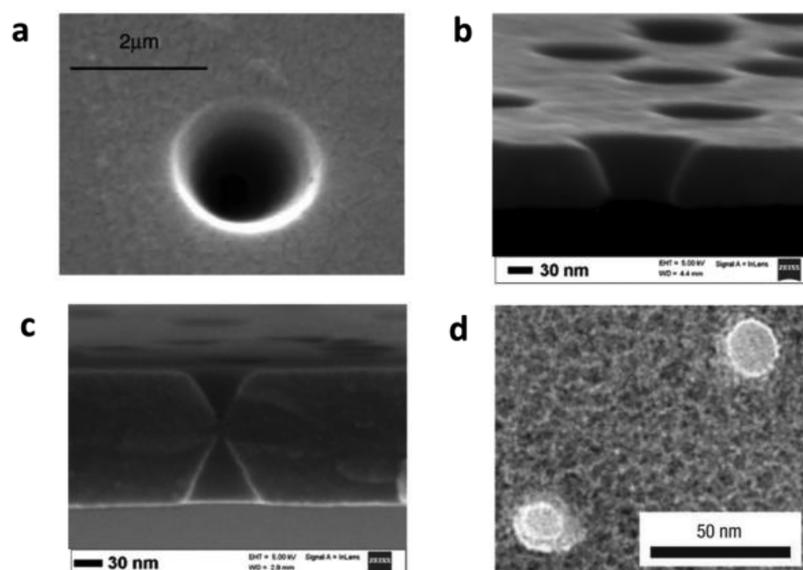


Figure 5. Single-nanopore system construction. (a) Track-etched nanopores in polyimide. From Siwy, Z.; Dobrev, D.; Neumann, R.; Trautmann, C.; Voss, K. J. A. P. A. Electro-responsive asymmetric nanopores in polyimide with stable ion-current signal, 2003. Reprinted by permission from Springer Nature. (b, c) Track-etched nanopores in silicon nitride. Reproduced from ref 155. Copyright 2009 National Academy of Sciences. (d) A nanopore drilled by TEM. From Storm, A.; Chen, J.; Ling, X.; Zandbergen, H.; Dekker, C. Fabrication of solid-state nanopores with single-nanometre precision, 2003. Reprinted by permission from Springer Nature.

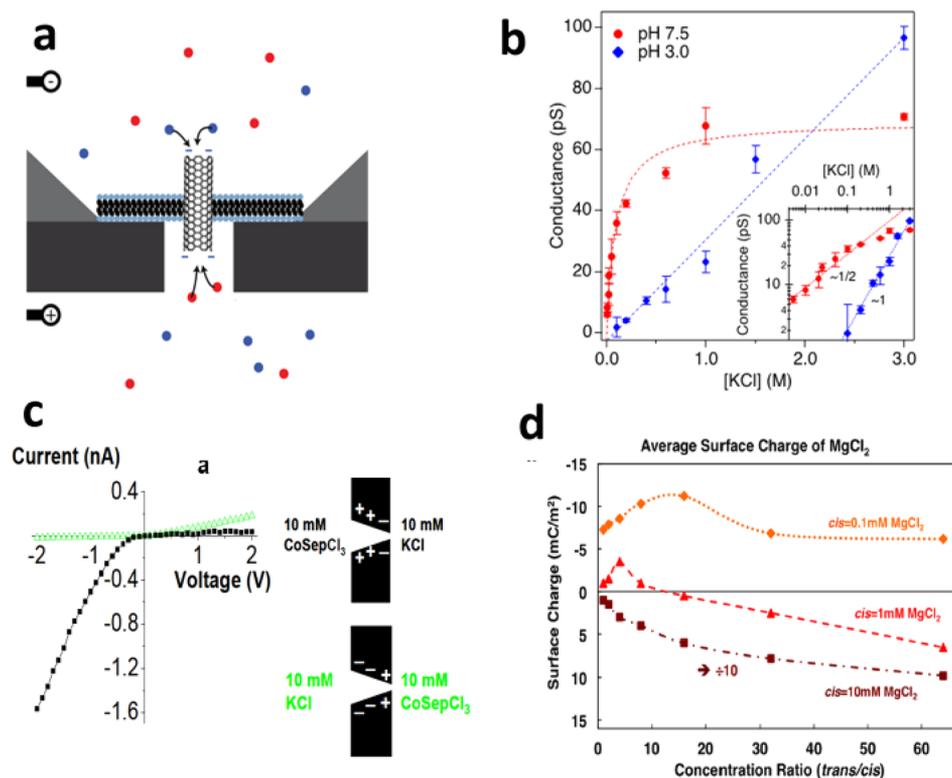


Figure 6. Probing ion transport through SDNs. (a) A platform for single CNT porin ionic conductance measurements. (b) Ionic conductance of individual, 0.8 nm diameter CNT porins. From Tunuguntla, R. H.; Henley, R. Y.; Yao, Y.-C.; Pham, T. A.; Wanunu, M.; Noy, A. Enhanced water permeability and tunable ion selectivity in subnanometer carbon nanotube porins. *Science* 2017, 357, 792–796. Reprinted with permission from AAAS. (c) Local charge inversion induced by trivalent cobalt ions (CoSep) causes the formation of positive surface charges and the appearance of diode-like behavior in individual conical nanopores. Reproduced from ref 157. Copyright 2009 American Chemical Society. (d) Measuring the reversal potential allows the surface charge to be calculated. Data shown are from silica nanochannels, and charge inversion was obtained with Mg^{2+} . Reproduced from ref 161. Copyright 2015 American Chemical Society.

three-dimensional (3D) continuum models are therefore not relevant.¹³⁷ This configuration gives rise to exotic behavior.

Extremely small channels can be modeled as discrete Ising chains of charges, giving rise to anomalous capacitance

curves.^{138,139} Sub-2 nm pores also display ionic and protonic current fluctuations,^{9,140} as well as the formation of ion pairs and even larger aggregates.^{67,141,142} Partial removal of ion solvation shells, which prevents those ions from forming long-term pairs in the bulk, leads to ion pairs with unusually long lifetimes in confinement, along with potentially enhanced reaction dynamics.^{67,141,142} Spontaneous, long-scale ordering in nanopores can also create conditions for efficient and selective transport of particular molecular or ionic species; formation of the hydrogen-bonded single-file water chain in narrow CNTs, for example, gives rise to fast proton conduction via the Grotthuss mechanism.^{8,66} Confinement-induced effects lead to unusually strong correlative transport modes, dramatically enhancing mechanisms such as electro-osmotic transport and ion concentration polarization.^{143,144} As hydrated ions become squeezed into narrow gaps with slippery wall surfaces, the distinction between ion solvation shells and the rest of the solution becomes increasingly blurred, increasing the probability of strong electro-osmotic and diffusio-osmotic coupling effects, which can become dominant in the narrowest of channels.^{144,145} Recent experimental and theoretical work also highlights the importance of considering charge-regulation effects on nanofluidic transport, where the surface charge density in SDNs depends sensitively on the pH of the solution.¹⁴⁶ Even though these effects are not surprising on an intuitive level, their rigorous treatment has occurred only recently,¹⁴⁵ and experimental efforts are still sparse. The incorporation of these effects to enhance scaling of ionic flux and selectivity for SDNs points to operational realms for nanopore membranes that may circumvent flux-selectivity tradeoffs. Finally, future research also must address the behavior of ionic mixtures confined within nanopores. In one of the few examples, the anomalous mole fraction effect, in which permeation of ion mixtures is slower than permeation of either ion individually, was demonstrated inside synthetic nanopores.^{147–149}

Modeling the coupling between driving forces under confinement, such as gradients in pressure and electric potential, is essential for our understanding of these unique transport phenomena. Pressure-driven flow through a nanopore will advect ions in the electric double layer, resulting in a streaming current, whereas electric fields conducting ions through a pore will also drive electro-osmotic flow in the double layer.^{30,150} The interplay between Coulombic ordering and steric repulsion can influence the thermodynamic driving forces for ion transport.^{135,151,152} A more general coupled flux model is necessary, especially at high concentrations within a nanopore, as pioneered by Stefan-Maxwell for dilute gases and Onsager for generalized linear irreversible thermodynamics.¹⁵³

Experimentally, the study of correlated nanopore ion transport could benefit from new approaches to electrical manipulation, spectroscopic probing, and precise pore construction and modification (Figure 5).^{154,156} When pore geometrical and chemical properties are known and controlled, the presence of spatial and temporal correlations of ions will be made evident by examining the ion current. Ion current through a nanopore is extremely sensitive to the properties of the pore walls and distributions of ions in the pore. As an example, the effect of charge inversion at a surface can be probed by recording current–voltage curves of asymmetric nanopores.¹⁵⁷ Structurally asymmetric and charged nanopores behave as rectifiers, transporting ions in one direction and hindering ionic transport in the opposite direction; the direction of preferential ion flow depends on the surface potential.^{158–160} A nanopore that

undergoes charge inversion can be therefore immediately identified by its flipped current–voltage curve (Figure 6).¹⁵⁷ The magnitude and polarity of effective surface potential can also be measured precisely in nanopores via the so-called reversal potential, that is, an electrical potential difference established across a membrane in contact with a salt concentration gradient.¹⁶¹ It is expected that nanoconfinement-induced ion correlation effects, such as the breakdown of electroneutrality,^{130,162} could be probed electrochemically with a nanopore whose geometry and surface chemistry were tuned to make it especially sensitive to the balance of positive and negative charges.

Ion correlations may influence the ion selectivity of nanopores.¹⁶³ Experiments with single nanopores could provide experimental guidance to such modeling and help to design systems with new mechanisms of ionic and molecular selectivity. Probing ion correlation systematically in nanopores of controlled chemical properties, using solvents that vary in dielectric constant and ions that differ in size and valence, would help build a universal description of how correlation of ions influences transport at the nanoscale.¹⁶⁴

Another important direction of inquiry is the identification of current and electrokinetic fingerprints of ion pairs and aggregates. Extreme confinement can lead to the formation of pairs of ions of the same charge¹³¹ and that these pairs can be broken with an electric field. Formation of ion pairs of different charge (i.e., pairs containing both cations and anions) has also been reported,^{130,142,165} but it is not known how their presence influences electrokinetic transport. The possibility of tuning the formation of ion pairs by the properties of the pore wall has also been suggested.¹⁴² Nanopores with tunable electrochemical properties could enable an understanding of the role of ion pairs in ionic transport, as well as how to incorporate ion pairs and aggregates into existing models.

■ KNOWLEDGE GAP 6: NANOSCALE SOLVATION BEHAVIOR

Protein ion channels routinely exploit minute differences in solvation behavior to act as exquisitely selective molecular gates (e.g., K⁺ ion channels).^{166,167} As confinement approaches the levels seen in SDNs, solvation effects start to diverge from their bulk behavior, with profound effects on transport efficiency and selectivity.^{168–173} The energetics of solvation under strong confinement affect nanopore entry and lead to ion-specific modulations of the double-layer structure inside the pore.^{25,26} As an example, in extreme confinement and under double-layer overlap, counterions with strong hydration shells, such as sodium ions, were found to create a layered structure close to the charged surfaces.^{173–175} This effect was discovered experimentally with a surface-force apparatus (SFA), in which two mica surfaces were brought into close contact with distance controlled with sub-nanometer precision. Introducing the effects of solvent to solute–solute interactions leads to the prediction of an oscillatory force between two surfaces, an effect that has also been measured with the SFA.¹⁷⁶ These phenomena are only beginning to be probed.

Understanding and exploiting solvation phenomena in synthetic SDNs could lead to a new generation of membranes that are capable of manipulating hydration effects to achieve single-species selectivity in a manner that is virtually impossible with current technologies.¹⁷⁷ Recently, Zwolak and colleagues proposed that dehydration-based selectivity could be indeed the basis for a universal mechanism to achieve selectivity between

ions of the same charge, for example, Na^+ and K^+ .¹⁷⁸ Interestingly, it was shown that, to optimize ion selectivity, both pore diameter and pore length need to be tuned.¹⁶⁸ These concepts could potentially be extended to design systems that could effectively filter out pharmaceutical compounds that plague water supplies in industrialized nations,^{179,180} harvest Li^+ ions for batteries,¹⁸¹ or provide efficient and thin exclusive proton-conducting membranes for fuel-cell technologies.^{182,183}

Probing chemistry and organization in SDNs requires a technique that can offer high spatial resolution, such as infrared spectroscopy, Raman spectroscopy,^{10,184,185} UV/visible (electronic) spectroscopy, fluorescence spectroscopy, X-ray scattering,¹⁸⁶ X-ray photoelectron spectroscopy,¹⁸⁷ optical Kerr effect (OKE) spectroscopy,^{18,188,189} or neutron diffraction.¹⁹⁰ These techniques can have sufficiently high depth resolution to study solid–liquid interfaces, but their lateral resolution is typically limited by diffraction or spot size to something on the order of 1 μm . In SDNs, the width of a pore may provide the desired resolution in one lateral direction but not along the pore axis. A lateral resolution on the nanometer scale would be ideal for understanding, for instance, the chemical bonding in the neighborhood of individual ions. An understanding of the complex interplay among steric, electrostatic, and van der Waals interactions, as well as solvent entropy, becomes possible only at this length scale. Although tip-enhanced Raman spectroscopy (TERS) and other scanning-probe techniques have found success in probing interfaces on this scale,^{191–195} chemical mapping with ~ 1 nm resolution is not yet routine. Furthermore, the dielectric constants of polar solvents, like water, confined inside SDNs can be dramatically lower than those in the bulk. For example, in a recent experimental study of water confined between hexagonal boron nitride (h-BN) and graphite, Fumagalli et al. reported that the out-of-plane dielectric constant of water drops from 78.5 in the bulk to just 2 inside nanocapillaries.⁷⁷ Moreover, the dielectric constants of solvents can also vary with ion concentration.¹⁹⁶ In this regard, the classical Born equation of ion solvation predicts a higher free energy of solvation of an ion in a bulk medium with a higher dielectric constant.¹⁹⁷ However, the manner in which changes in the dielectric constants of solvents confined inside SDNs impacts the solvation of ions remains an open question.

Another issue with many of these techniques is that they are not compatible with every SDN material. Optical spectroscopies are useful for studying behavior in pores in transparent materials. There is a large literature, for instance, in the use of OKE, Raman, and NMR spectroscopies to probe liquid dynamics in silica pores that has led to important insights regarding the behavior of pure solvents. For instance, in OKE spectroscopy,^{18,188,189} a linearly polarized pump induces a small net alignment, and thereby a transient birefringence, in a transparent liquid composed of molecules with an anisotropic polarizability. The return to an isotropic orientational distribution is monitored via depolarization of a probe pulse as a function of time delay. This technique has provided a detailed picture of the spatial dependence of orientational relaxation in liquids confined in silica nanopores¹⁹⁸ and could readily be applied to confined solutions. It is important to note that such studies probe behaviors that are averaged over large numbers of pores, rather than behavior in a single, well-characterized pore. Furthermore, other SDN materials with strong optical signatures, like carbon nanotubes, may present challenges for the use of optical spectroscopies to study confined fluid alone.

Spectroscopic techniques that have never been applied to SDNs may enhance our understanding of solvation behavior under nanoconfinement. Vibrational sum-frequency generation (VSFG) spectroscopy^{199–204} is a surface-selective technique that can reveal chemically specific information at solid/liquid interfaces. For instance, VSFG has been used to show that acetonitrile next to a silica surface forms an unexpected bilayer structure that has a profound influence on the properties of the interface.^{198,205} VSFG probes vibrational modes that are simultaneously IR and Raman active, and by collecting spectra under different polarization conditions, it is possible to obtain information on the structure of interfacial molecules.²⁰¹ VSFG has not been applied to fluids confined within SDNs to our knowledge, but it has great potential for studying nanopores that are transparent to the relevant colors of light. SDN liquid–solid interfaces and ion–solvent interactions might also be probed with the addition of an electron beam in the form of ultrafast electron crystallography²⁰⁶ or in situ TEM with applied electric fields²⁰⁷ or magnetic fields,²⁰⁸ or electron holography.²⁰⁹

■ KNOWLEDGE GAP 7: ENHANCED IONIC SELECTIVITY

The translation of SDN physics to multipore membrane systems with precise ionic selectivity remains elusive. Membrane-based technologies have played an important role in separations, including water purification and seawater desalination, for many years.^{49,177,210,211} Most state-of-the-art solute-rejecting (e.g., reverse osmosis and nanofiltration) and ion-exchange membranes are polymer films with nonuniform pore characteristics, which hinder precise ion–ion selectivity. In these membranes, size- and charge-based separations are the main mechanisms that govern selectivity, rendering the membranes poorly selective when species with similar size or charge are present.^{212–214} On top of the inherent challenge of separating similar species, engineering ultrasensitive pores for separation of small ions (e.g., chloride, fluoride, and lithium) is technologically difficult due to the sub-nanometer precision required.^{49,215} Graphene oxide membranes, for instance, demonstrate remarkable molecular selectivity²¹⁶ but allow fast transport of small ions.²¹⁷ While ion selectivity can be achieved, framework defects and swelling of graphene oxide laminates in water remain issues.^{12,218} For CNT membranes, it is possible to achieve moderate charge- or size-selective transport,^{219–221} but scaling is difficult, and high selectivity between ions of similar size and charge has not been achieved. The major obstacles for aligned CNT membrane development are the difficulty of growing arrays of CNTs with uniform diameters, the difficulty of controlling the arrangement and quality of the nanotubes in those arrays,^{222,223} the low yield of the fabrication process,^{224,225} and the crude nature of the procedures used to remove the nanotube end-caps. An added difficulty is that CNTs would likely need to have diameters less than 1 nm to effect truly selective ion transport. But despite these challenges, the exploration of enhanced ion–ion selectivity in SDNs is a promising area of research. It may assist the development of materials strategies for separating a target ion from multi-ion solutions more generally; example applications include separating Li^+ ions from Na^+ and K^+ ions in seawater and designing an exclusively proton-conducting membrane for fuel cells.²²⁶

Although major efforts have focused on studying size-based selectivity,^{8,12,217,227} emerging research suggests that enhanced ion–ion selectivity in SDNs may be based on differences in ion hydration, charge, or shape properties (Figure 7). The limited

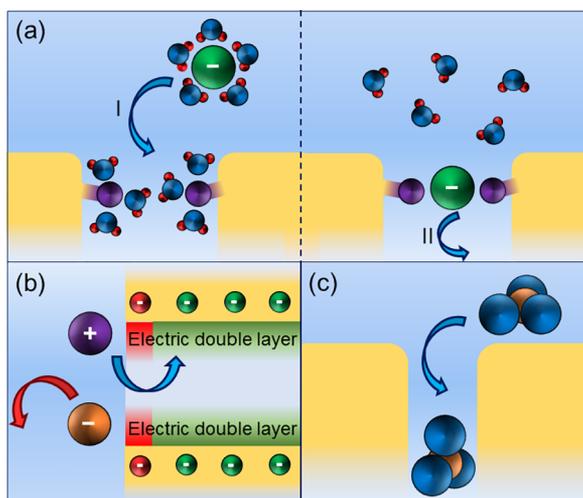


Figure 7. Potential mechanisms for increasing ionic selectivity. These mechanisms include selectivity by (a) ion dehydration; (b) surface charge, in-pore charge, and electric double-layer effects; and (c) shape-related steric exclusion. With a combination of these selectivity mechanisms, it may be possible to design SDN systems with unprecedented ionic selectivity.

difference in selectivity observed for small ions in membranes with sub-nanometer pores, for instance, is often attributed to hydration and dehydration effects. Specifically, an ion with a smaller radius (e.g., F^- or Na^+) acquires a larger and stronger hydration shell and undergoes lower dehydration at the pore mouth compared to an ion with a larger ionic radius (e.g., Cl^- or K^+).^{8,171} Ion dehydration also underlies the precise selectivity observed in selective-ion biological channels.^{228,229} Here, specific sites within the channel create a cavity with a perfect match for a specific bare ion, compensating energetically for its loss of hydration shell and excluding the permeation of other ions (Figure 7a).

Knock-on mechanisms have recently been proposed²³⁰ to explain how biological nanopores discriminate similarly sized ions (i.e., Na^+ vs K^+). Here, fully dehydrated K^+ can pass through a potassium channel all without intervening water molecules, whereas Na^+ does not enter the channel without water. Long-time (i.e., multi- μs) MD simulation has played an essential role in elucidating this mechanism.²³¹ At the same time, computational predictions are known to be sensitive not only to the sampling times, which are getting more and more straightforward, but also to the nature of the physics included in the force field. For instance, beyond scaling charges in nonpolarizable force fields,²³² polarizable force fields²³³ have been suggested²³⁴ to capture essential features of divalent cations (e.g., Ca^{2+} vs Mg^{2+}). Furthermore, effects not captured in any conventional force field, such as charge transfer, have proven essential to describe ion-specific effects in some cases.²³⁵ Thus, predictive modeling in this area requires both development of multiscale approaches as well as careful consideration of the physics involved.

Experimentally, ion dehydration was recently proposed to explain the Arrhenius-type behavior observed for ion permeation through nanopores and membranes:^{8,12,236–238}

$$J = A \exp\left(-\frac{E_a}{RT}\right) \quad (2)$$

where J is the ion flux through the membrane, A is the pre-exponential factor, E_a is the activation energy, R is the gas constant, and T is the temperature in Kelvin. Differences in dehydration-based energy barriers have been shown to boost selectivity between ions permeating through nanopores.^{12,237–240} Experiments that quantify energy barriers as a function of pore diameter, or location-specific functionalization of the pore mouths or bodies of SDNs, may shed light on the physical and chemical effects that induce dehydration and lead to selective transport.

Another aspect of SDNs that can be used for enhanced ionic selectivity is their electric interaction with ions (Figure 7b). In general, charged pores repel co-ions, and the extent of repulsion is correlated with the extent of ion charge. However, recent results show that even ions with the same charge (e.g., Cl^- and NO_3^-) are affected differently by a charged membrane,³⁵ a phenomenon that calls for fundamental investigation of charge-exclusion mechanisms. These results cannot be predicted by traditional models for transport and exclusion of ions in nanofiltration membranes, based on the extended Nernst–Planck equation,^{241,242} even when this equation is modified to include contributions from ion-specific effects in the electric double layer. Experimentally, state-of-the-art membranes are either neutral or contain charged groups on their surfaces and within their pores. As a result, surface and in-pore charge effects on ion selectivity cannot be distinguished. SDNs that have charges localized either in the pore mouth or pore body (e.g., CNTs with a functionalized and negatively charged pore mouth)⁸ may provide an opportunity to highlight surface and/or in-pore charge effects. MD simulation studies have shown that the free-energy barrier for ion transport through CNTs can be changed significantly by chemical functionalization of the pore mouth, raising the possibility of practical applications of SDNs that are chemically functionalized at particular sites.^{243,244}

Finally, pore shape influences selectivity (Figure 7c). This effect can occur, for example, between nonspherical polyatomic ions (e.g., NO_3^- , ClO_4^- , and AsO_4^{3-}) and spherical monatomic ions (e.g., Cl^- and F^-), as evidenced by discrepancies between experimental energy barriers and theoretical hydration free energies.^{35,238,245,246} Structural characterization and modeling techniques such as MD simulations can assess the effect of pore mouth and pore-body shape on permeant selectivity for monatomic and polyatomic ions.²⁴⁶ Overall, fundamental questions about the effect of pore geometry, charge-based selectivity, and dehydration on selective ionic transport will need to be addressed in future research, with the goal of creating rules for the rational design of selective SDN membranes.

CONCLUSIONS

In this Review we have highlighted seven knowledge gaps that are central to the study of molecular and ionic transport in single-digit nanopores. These gaps include the presence and magnitude of slip flow, phase behavior under nanoconfinement, nanoconfined phase separation, the impact of defects on transport, correlated ion transport inside SDNs, nanoscale solvation behavior, and the engineering of enhanced ionic selectivity. Although nanoporous materials with characteristic dimensions smaller than 10 nm have been studied for some time, the confluence within the past decade of precise model systems with well-characterized pores, new spectroscopic techniques, and improved simulations has subjected these knowledge gaps to studies at unprecedented new levels of detail. Although some knowledge gaps, such as the scaling of slip length with SDN

diameter, have been posed but not resolved, other knowledge gaps, like the impact of a single defect on molecular transport inside an SDN, are only now coming into focus. We expect that the study of molecular and ionic transport under extreme confinement will test the limits of bulk-scale fluid mechanics, provide opportunities for the exploration of new synthetic and spectroscopic techniques, and inform our understanding of transport at molecular interfaces. We also anticipate the development of fundamentally new technologies, as the dramatic effects of nanoconfinement give rise to adsorbents, membranes, and fluidic platforms with extraordinary transport efficiencies and selectivities.

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