

The subtleties of water in small spaces

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The transport of fluids through conduits conjures up notions of pumps, pipes, and valves for students of the engineering sciences. It also represents a basic physical process that can be described by continuum hydrodynamics as long as the diameter of the “pipe” is much larger than any relevant length scale in the fluid, and, for many practical situations, it is. In fact, although the reasons are far from clear, continuum hydrodynamics can make accurate predictions even outside of the range of physical scenarios where it is expected to apply. One notable example is the success of the Stokes–Einstein(–Debye) model that relates the diffusivity of a dilute probe particle to the viscosity of the solvent. Although strictly valid only for Brownian particles that are much larger than the solvent molecules, it also works well for probe particles that are of similar size or even smaller (1). Moreover, experiments have shown that macroscopic hydrodynamics can reliably describe the flow of fluids through channels with cross-sectional dimensions that range from tens to hundreds of micrometers (2). The success of the continuum approach for modeling microfluidics has led some to suggest that the design paradigm for the engineer will soon be to “scale down” rather than “scale up” (3).

However, one cannot simply scale down ad infinitum. For transport through sufficiently narrow channels (tens of nanometers), microscopic fluctuations play an important role, and it no longer makes sense to describe the permeant fluid as a continuum. This is a gray area where our understanding of physicochemical processes is perhaps the fuzziest: between the large and the small, where the continuum begins to give way to the molecular and the statistical (4). Ironically, it is this gray area that is becoming increasingly relevant in technological applications (5–8), a trend that will no doubt persist as economic forces continue to drive the semiconductor industry toward nanoscale features. However, as the analysis of Kalra *et al.* demonstrates in this issue of PNAS (9), life becomes simpler again, albeit different, once we arrive at molecular-sized channels.

Kalra *et al.* have used molecular dynamics simulations to study osmotically driven flow of liquid water through semipermeable membranes of carbon nanotubes (CNTs). Their simulation box

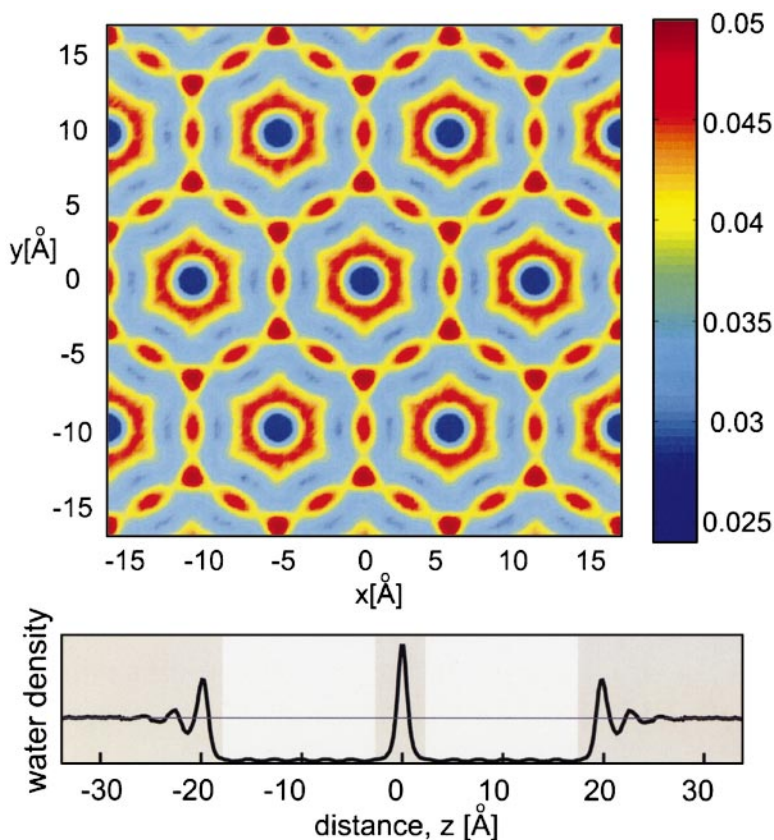


Fig. 1. Molecular structuring of water. (*Upper*) The average in-plane density profile of water molecules in the kinetically stabilized monolayer that separates two CNT membranes at the end of an osmotic transport simulation (9). (*Lower*) The corresponding density profile in the direction normal to the membranes. The light regions represent the location of the membranes, and the horizontal line is the bulk density of water. This figure was adapted from figures 5 and 6 of ref. 9.

was initially arranged, with the help of periodic boundary conditions, such that two CNT membranes partition the system into pure water and aqueous salt solution compartments. The CNTs were sized to exclude the entry of hydrated salt ions but permit the single-file passage of water molecules. Thus, during the course of a typical simulation, the pure water compartment would drain under the osmotic driving force; the salt solution compartment would consequently expand; and the two CNT membranes would self-associate. This setup allowed the authors to simultaneously study (*i*) the single-file transport of water through molecular-sized pores and (*ii*) the behavior of the thin water sheets sandwiched between the two hydrophobic CNT membranes. Their results on both fronts provide insights into the behavior of water in nanoconfined spaces and are worthy of a closer look.

It has been appreciated for some time that single-file molecular transport in narrow channels is a highly collective phenomenon (10), with the motion of one molecule requiring the simultaneous motion of the others. However, water molecules that are “protected” inside a CNT, or similarly inside a biological water channel (11), represent a special case. They can link, forming a tight hydrogen-bonded chain that is rarely ruptured because, unlike in the bulk, there is no additional competition inside the nonpolar channel for the water’s hydrogen-bonding interactions. As a result, the entire chain of water molecules essentially slips back and forth along the channel under thermal agitation, similar to the translocation of a polymer in a

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pore (12), occasionally donating or receiving a new water molecule from the solutions at either end. The kinetic ratio of “donates” to “receives” is ultimately governed by the microscopic fluctuations, and hence the chemical potentials, of the two solutions that the pore bridges.

Kalra *et al.* (9) convincingly show that this stochastic transport process can be quantitatively described by a kinetic random walk model (13), which is simple yet fundamentally different from macroscopic hydrodynamics. Under the conditions that they have simulated, the net osmotic flow rate through each nanotube was approximately six water molecules per nanosecond. This rate of transfer is strikingly similar to those measured in aquaporin-1 (14), a protein that serves as a channel for rapid water transport across cell membranes. Importantly, the simulated flow rates were essentially independent of channel length up to several nanometers, indicating that the chain of water molecules can actually “slip” along the hydrophobic pore walls of the CNTs (15–17). There is little doubt that similarly weak fluid–wall interactions will be essential for reproducing this slip-flow behavior in other systems, an aspect that may

prove vital for generating the high-throughput rates that future nanofluidic devices will demand (18).

Perhaps the most perplexing part of the osmotic simulations of Kalra *et al.*

Water molecules undergo rearrangements within the sheet and exchange with water molecules in the brine solution.

is the end: it never comes. That is to say, the final sheet of molecules sandwiched between the CNT membranes refuses to exit the pure water compartment despite the potential thermodynamic gain. Fig. 1 shows that this kinetically stabilized monolayer is highly ordered, forming large 6- and 12-member rings in which most of the molecules participate in three in-plane hydrogen bonds. Despite maintaining this well structured time-averaged pattern, the

water molecules are actually undergoing dynamic rearrangements within the sheet and exchanging with water molecules in the brine solution. Kalra *et al.* (9) report that the in-plane diffusion coefficient is roughly half the value of bulk water, which leads to some obvious questions. Given the slippery nature of the CNT surfaces and the molecular mobility of the molecules in the sheet, why can't the system find its way to the minimum free-energy state where all the molecules have exited the pure water compartment? What sort of fluctuations would be required to nucleate the emptying process (19–21)? How would this picture change if the CNT membranes were aligned out of registry? Finally, does the structuring of this confined metastable water bear any relevance for solvation-mediated interactions between proteins or biomolecular surfaces (22–25)?

Although the analysis of Kalra *et al.* (9) has illuminated some subtle and important aspects of water's behavior in nanoconfined environments, it does not provide us with all the answers to the “slippery” questions that it poses. Nonetheless, the high level of activity in this area suggests that we will have a firmer grip on the subject soon.

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