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Water Chains in Lipid Bilayers

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Several reports have appeared recently that present molecular dynamics simulations of water in channels. (Sagnella and Voth, 1996; Pomes and Roux, 1996; Breed et al., 1996) In this issue of the *Biophysical Journal*, Marrink et al. extend such simulations to the stability of hydrogen-bonded water chains in pure lipid bilayers. The properties of water molecules in lipid bilayers might seem to be so fundamental that the basic facts would have been established decades ago. And yet, nearly 30 years after Cass and Finkelstein (1967) proposed that water partitions into bilayers and diffuses as individual molecules, it is still possible to open a recent journal and find evidence that water can move through porelike discontinuities (Jansen and Blume, 1995). The truth is probably somewhere in between, with most of the water present as individual molecules and a small fraction involved in collective behavior within transient defects in the bilayer.

Marrink et al. use molecular dynamics simulations to estimate the stability of hydrogen-bonded water strands in the bilayer. Such structures are of interest because of earlier proposals that water strands in rare transient defects could account for the high permeability of bilayers to protons (see Marrink et al. (1996)for pertinent references). It is generally considered that the low permeability of bilayers to ions like potassium is attributable to a very high electrostatic energy barrier, in which Born energy is the major component. However, protons do not depend on diffusion alone to move through aqueous media. Instead a proton can hop along chains of hydrogen-bonded water molecules. If such chains are present in lipid bilayers, protons could bypass the electrostatic energy barriers by a wirelike conductance.

This brings us to the question addressed by Marrink: Do such chains have sufficiently long lifetimes to provide a permeation pathway? Because the proposed transient hydrogen-bonded water chains are much too rare to observe as spontaneous events, the simulation was necessarily performed by establishing a water chain within the bilayer and then observing its stability over time. Chains typically last for 2–5 ps, just long enough to permit a single-proton transfer event. By extrapolating from the lifetimes and energy required to produce water chains, it was estimated that ~100 chains form per second in a 0.2-mm diameter liposome. This might seem sufficient to account for the proton permeation anomaly, but there is a problem. If one uses reasonable assumptions for the rate at which protons might be delivered to a given chain at 10^{-7} M H+ (pH 7), the estimated flux falls short by eight orders of magnitude. A similar problem was encountered by Benz and McLaughlin (1983) when attempting to account for the rate at which protonophores carried protons across bilayers. In both cases, it is possible that buffers play a role. Instead of assuming that the rate of proton delivery is a direct function of the pH, it may be that much higher numbers of protons can be delivered as buffer ions interact with the site.

The molecular dynamics simulations of water in channels and in bilayers are intrinsically interesting, allowing us to "see" rare events that are not readily detected by direct measurements. Such simulations will likely spur a new round of experimentation that will advance our understanding of how water and ions interact with bilayers and channels.

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