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Design principles for selective ion transport across membranes

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Abstract: Development of many next-generation technologies and nano devices, including those for desalination and power generation, require design rules to selectively transport ions across membranes. These sought-after design rules can be furnished by biomolecules that excel at tightly regulating ion concentration gradients across membranes. However, this task has proved more challenging than originally envisioned — experiments yield limited details and molecular simulations, which are capable of providing details, struggle to strike the requisite balance between accuracy and efficiency. In particular, mechanistic insight into biological ion transport requires a precise knowledge of how the energetics, structures, dynamics of ions differ between their hydrated and biomolecule-bound states. While first principles quantum mechanical models can yield reliable estimates for relative binding energies, estimates for thermodynamics and ion-binding response are subject to limitations from conformational sampling and system size. In contrast, molecular mechanics models that do not describe electronic polarization explicitly can technically get past sampling/system-size issues, but suffer severely from accuracy. How do we address this dilemma? Polarizable molecular mechanics models are being developed as a compromise between accuracy and efficiency, but are they sufficiently reliable to derive cause-effect relationships? In general, where do we stand in terms of being able to use molecular simulation techniques to understand the design principles underlying the ability of biomolecules to bind ions selectively, and the response of ion binding to biomolecular structure, dynamics and function? In this talk, I'll present these issues, discuss potential solutions, and provide our perspective on how molecular simulations, despite their shortcomings, have advanced our understanding of the specific chemical and structural design elements of biological molecules that enable selective ion transport. I'll present this in the context of a fundamental problem that we continue to resolve: how do K+-selective biomolecules transport K+ ions across cell membranes, and at the same time discriminate against Na+ ions, which are as similar as they could be to K+ while not being the same.