New and Notable

Computational Electrophysiology: The Molecular Dynamics of Ion Channel Permeation and Selectivity in Atomistic Detail

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An electrical potential difference exists across the cell membrane due to the different ion concentrations in the cytoplasm and the extracellular medium. This membrane potential underlies numerous important physiological processes including the propagation of nerve impulses, cell excitability, and signal transduction; thus, the asymmetry in ions concentration across biological membranes is of paramount importance. In electrophysiological experiments, one can measure the ionic current across an ion channel as a function of an applied membrane potential, while being able to independently control the concentration of the ionic solutions on both sides of the membrane. Measurements of the I/V curve under symmetric or asymmetric conditions are often important steps to quantitatively characterize an ion channel experimentally. Theoretical models and computer simulations based on detailed models offer a virtual route to help interpret such experimental I/V curves. In recent years, molecular dynamics studies of detailed atomic models of biomolecular systems of increasing complexity have been carried out. MD simulations of ion channels are, however, confronted with particular difficulties.

All-atom simulations of biomolecular systems are typically carried out on models that are extremely small compared with the real world, and periodic boundary conditions must be imposed on the simulation cell to reduce the artifacts caused by finite-size effects. In the case of soluble proteins, which are surrounded by an isotropic bulk solution, the imposed periodicity does not adversely affect the results as long as the simulation cell is sufficiently large. In the case of a membrane protein, however, the periodicity poses some special challenge because the solutions on the two sides of the membrane actually belong to the same bulk liquid phase. For this reason, there is only one bulk solution with a unique composition surrounding the membrane. Despite this limitation, a membrane potential can be applied realistically by introducing a constant external electric field E acting on all the charges across the entire system in the direction of the membrane normal; the total membrane potential V is equal to $E \cdot L_z$, where L_z is the length of the simulation cell in that direction (1). However, there is no straightforward way to simulate a system with two bulk solutions of different compositions on both sides of a membrane due to the periodicity. Because of this problem, the only simulations of ion channels able to tackle asymmetric conditions were based on grand canonical Monte Carlo Brownian dynamics (GCMC/BD), in which the solvent was represented as a continuum dielectric (2). Until now, no methodology has been available to simulate the I/V curve for an ion channel under asymmetric ionic conditions in MD simulations with explicit membrane and solvent.

In this issue of *Biophysical Journal*, Kutzner et al. (3) present one possible solution to this important problem. The authors build on the ideas of Sachs et al. (4), who considered a dual-membrane system in the simulation cell. The two separated bilayers, while doubling the size of the simulation system, permit two physically distinct bulk phases of different compositions. This allows for the simulation of a realistic membrane potential by carefully managing the small charge imbalance across the two membranes. However, a difficulty with the dual-membrane approach has been that any small charge movement from either the protein or the ions may cause a large shift in the effective membrane potential. Thus, one has to constantly monitor the actual membrane potential, and correct it by inserting or destroying ions on either side in the two bulk solutions. This is particularly demanding when, for example, one is trying to simulate the ionic flow through a channel under steady-state conditions, as it would require resetting the composition of the two bulk phases continuously to properly maintain the desired membrane potential.

Kutzner et al. (3) have designed an elegant strategy inspired by grand canonical Monte Carlo, in which they transfer ions from one bulk phase to the other in a manner that causes minimal perturbations to the rest of the system. The computational method allows one to directly simulate ion flux through membrane channels based on realistic electrochemical gradients. They illustrate this novel approach by successfully reproducing the experimental conductance and selectivity for the bacterial channel PorB from pathogenic *Neisseria meningitidis*.

The innovative contribution by Kutzner et al. (3) is a good opportunity to remind ourselves that the design of effective computational methodologies aimed at realistically simulating the complex conditions present in experiments is a subject of continued importance in theoretical studies of biomolecular systems.

Useful discussions with F. Khalili-Araghi and J. C. Gumbart are gratefully acknowledged. B.R. is supported by National Institutes of Health grant GM062342.

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Submitted June 29, 2011, and accepted for publication July 6, 2011.

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Editor: Gerhard Hummer.

0006-3495/11/08/0755/2 $2.00

doi: 10.1016/j.bpj.2011.07.002

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