New and Notable

Explicit Channel Conductance: Can It Be Computed?

Andriy Anishkin
and Sergei Sukharev
University of Maryland, College Park,
Maryland 20742

In the next article of this issue, readers will find the results of what the authors report is the first explicit computation of the conductance of a large membrane channel based on its crystal structure. Aksimentiev and Schulten, the authors of the article, chose the well-known α-hemolysin as a proving ground for their all-atom molecular dynamics approach.

The problem of relating the conductance of channel pores to their organization predates the first channel structures by at least 60 years, when Cole and Curtis (1939), using a high-frequency impedance bridge, demonstrated that the sites of ion permeation in excitable membranes must be very local. With the advent of patch clamp, the amplitudes of discrete single-channel currents were carefully resolved, and this posed many more questions about the chemical and spatial organization of channel pores. Known ionic permeation properties of the pore constrain the possible pore configurations that can be imagined.

While watching patch-clamp traces on a screen, many of us instinctively take a pencil and estimate physical dimensions of the observed channel with the Hille equation (Hille, 2001), which approximates the channel as a cylinder filled with a bulklike electrolyte and flanked by access resistances of the adjacent buffer. This step always gives us a ''zero approximation'' of what the pore in question may look like. When the need for a more accurate way to estimate the electrostatic contribution was realized, first Monte Carlo, then Poisson-Nernst-Planck (PNP) and Brownian dynamics (BD) computations were introduced and have remained popular and relatively ''inexpensive'' ways of computing fluxes of charged particles across a charged pore in a self-consistent way (Nonner et al., 1999; Roux, 2002). Such computations use implicit solvent inside the pore with some effective density, viscosity, and dielectric properties, in many instances postulated to be constant. The unaccounted problem here is that the water interacts differently with the pore wall (and the ions) in specific channel regions, and thus the implicit and uniform solvent assumptions may not be valid. Computation of the local electric bias imposed by the externally applied voltage has not been straightforward either.

Now, when several high-resolution structures of pores are available, and when refined force-field parameters make molecular dynamics simulations more and more realistic, could accurate prediction of the transport rate and ionic specificity be done explicitly? Until recently, all-atom simulations have not been used for conductance computations simply due to insufficient simulation time given the frequency of permeation events. Indeed, a typical permeation rate for the KscA channel of one ion per 100 ns would require unattainably long simulations.

It is not that hemolysin is the most puzzling channel, as its steady conductance has been studied in great detail experimentally (multiple references in the Aksimentiev and Schulten article), and the PNP and BD approaches provided accurate estimations of ion transport parameters inside the pore (Noskov et al., 2004). Even the simplest estimation procedures, using the Hille equation, correspond well with experimental values, especially when the mean size of the ion's hydration shell reducing the accessible pore cross section is taken into account.

It takes ~15 min with ready-to-use software to create the internal surface of a channel from Protein Data Bank coordinates (Fig. 1, *left panel*), split the internal volume into thin slices, and sum up their macroscopic resistances. The program HOLE (Smart et al., 1997), designed to probe internal volume of pores with squeezable spheres, performs this task with about the same success. Why spend hundreds of CPU hours of computation time to obtain similar conductance estimation?

The estimation is clearly not the same, because the detail provided by the atomic picture of permeation in the completely solvated system presented by Aksimentiev and Schulten is incomparably greater than that available from any of the previously used approaches. Readers will find that equilibration after ''switching on'' the electric field produces excess charges on polarized protein and membrane surfaces, automatically reducing the electric field in the bulk in a self-consistent way. The solvated ions undergo electrodiffusion from the bulk into the channel vestibule along the electric field lines converging in the aqueous pore (Fig. 1, *right panel*) without the ''source'' and ''sink'' assumptions typical of PNP and BD. Fluctuations of the pore wall surrounded by lipids and realistic dynamics of side chains are also taken into account in the all-atom representation. The authors estimate the average density of water in the pore, making sure that it is relatively uniform, lacking the density irregularities or the complete constriction dewetting previously computed for the mechanosensitive channel MscS (Anishkin and Sukharev, 2004; Sotomayor and Schulten, 2004). However, even with dewetting events interrupting the conductive pathway, the current (perhaps extremely low) would still be assessed correctly. Along the entire trajectory, ion movements occur in an electrostatically self-consistent

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Address reprint requests to Sergei Sukharev, E-mail: sukharev@umd.edu.

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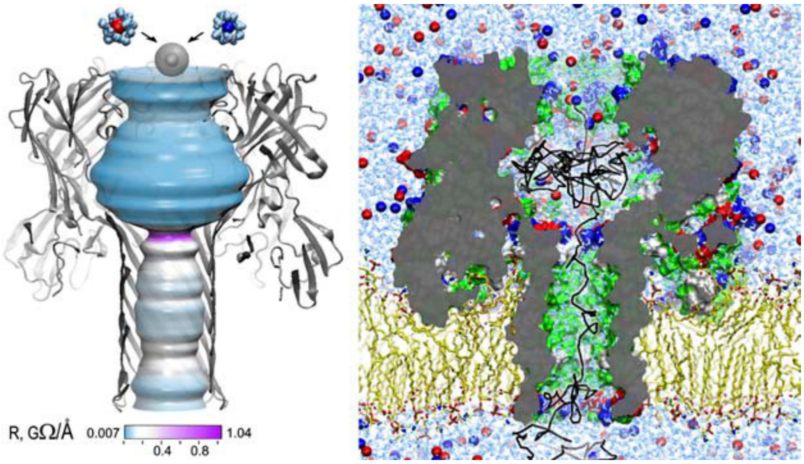

FIGURE 1 α-Hemolysin channel representations in a simplistic way, as a pipe of variable diameter uniformly conducting ions of some ''effective'' size, which includes hydration shells (*left panel*) and in all-atom lipid-embedded and fully hydrated dynamic form (*right panel*). See the article by Aksimentiev and Schulten on explicit computation of hemolysin channel permeation in this issue.

manner, and even interactions with buried charged histidines produce the expected nonlinearity of the current-to-voltage curve. Relying on the accuracy of the force field used, the study predicts the conduction rates for both anions and cations, leading to a total current of correct magnitude, as well as the rates of free diffusion and electro-osmotic fluxes of water. The thoughtful choice of a ''simple'' and well-studied channel with bulklike properties of the solution inside now calls for detailed comparison with other computational approaches and experiments.

If readers do the computations themselves, they will find that the latest version of VMD 1.8.3 used in the Aksimentiev and Schulten article allows for convenient visualization of the electrostatic potential at any point of the simulation box, precomputed with the electrostatic particle-mesh Ewald protocol of NAMD. Indeed, explicit computing of channel currents becomes not only possible, but also easier.

REFERENCES

Anishkin, A., and S. Sukharev. 2004. Water dynamics and dewetting transitions in the small mechanosensitive channel MscS. *Biophys. J.* 86:2883–2895.

Cole, K. S., and H. J. Curtis. 1939. Electrical impedance of the squid giant axon during activity. *J. Gen. Physiol.* 22:37–64.

Hille, B. 2001. Ion channels of excitable membranes. Sinauer Associates, Sunderland, MA.

Nonner W., D. P. Chen, and B. Eisenberg. 1999. Progress and prospects in permeation. *J. Gen. Physiol.* 113:773–782.

Noskov, S. Y., W. Im, and B. Roux. 2004. Ion permeation through the α-hemolysin channel: theoretical studies based on Brownian dynamics and Poisson-Nernst-Plank electrodiffusion theory. *Biophys. J.* 87:2299–2309.

Roux, B. 2002. Theoretical and computational models of ion channels. *Curr. Opin. Struct. Biol.* 12:182–189.

Smart, O. S., J. Breed, G. R. Smith, and M. S. Sansom. 1997. A novel method for structure-based prediction of ion channel conductance properties. *Biophys. J.* 72:1109–1126.

Sotomayor, M., and K. Schulten. 2004. Molecular dynamics study of gating in the mechanosensitive channel of small conductance MscS. *Biophys. J.* 87:3050–3065.