# Ion Channels – From Structure to Electrophysiology and Back

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A reliable way to establish whether our understanding of a channel is satisfactory is to reproduce its measured ionic conductance over a broad range of applied voltages in computer simulations. In molecular dynamics (MD), this can be done by way of applying an external electric field to the system and counting the number of ions that traverse the channel per unit time. Since this approach is computationally very expensive, we have developed a markedly more efficient alternative in which MD is combined with the electrodiffusion (ED) equation. In this approach, the assumptions of the ED equation can be rigorously tested, and the precision and consistency of the calculated conductance can be determined. We have demonstrated that the full current/voltage dependence and the underlying free energy profile for a simple channel can be reliably calculated from equilibrium or non-equilibrium MD simulations at a single voltage. Free energy profiles can be obtained from non-equilibrium simulations without a loss of accuracy even without the knowledge of diffusion coefficient.

To carry out MD simulations, a structural model of a channel has to be assumed, which is an important constraint, considering that high-resolution structures are available for only very few simple channels. If the comparison of calculated ionic conductance with electrophysiological data is satisfactory, it greatly increases our confidence that the structure and the function are described sufficiently accurately. We examined the validity of the ED for several channels embedded in phospholipid membranes - four naturally occurring channels: trichotoxin, alamethicin, p7 from hepatitis C virus (HCV) and Vpu from the HIV-1 virus, a synthetic, hexameric channel, formed by a 21-residue peptide that contains only leucine and serine and a bacterial pentameric ligand-gated ion channel, GLIC. All these channels mediate transport of potassium and chloride ions. It was found that the ED equation is satisfactory for these systems. In some of them, experimental and calculated electrophysiological properties are in good agreement, whereas in others there are strong indications that the structural models are incorrect.