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Ionic Channels in Biological Membranes: Natural Nanotubes Described by the Drift-Diffusion Equations

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Ionic channels are proteins with a hole down their middle, natural nanotubes of great biological importance because they regulate many activities of cells in health and disease. Ionic channels have simple structure and obey the familiar drift-diffusion equations of semiconductor physics. It seems likely that higher resolution theories of computational electronics (e.g., Monte Carlo simulations) will reveal even more about how channels, and perhaps other proteins, function. Thus, the study of channels is a promising area for interdisciplinary investigation.

Protein channels conduct ions (Na^+, K^+, Ca^{++}, and Cl^-) through a narrow tunnel of fixed charge ('doping'), thereby acting as gatekeepers for cells and cell compartments [1]. Hundreds of types of channels are studied everyday in thousands of laboratories because of their biological and medical importance: a substantial fraction of all drugs used by physicians act directly or indirectly on channels [2]. Ionic channels are studied with the powerful techniques of molecular biology. Atoms can be modified one at a time and the location of every atom can be determined within 0.01 nm.

The function of open channels can be described if the electric field and current flow are computed by the Poisson-Drift-Diffusion (that we call PNP for Poisson-Nernst-Planck) equations [3] and the channel protein is described as an invariant arrangement of fixed charges-not as an invariant potential of mean force or set of rate constants, as is done in the chemical and biological tradition. The PNP equations describe the flux of individual ions (each moving randomly in the Langevin trajectories of Brownian motion) in the mean electric field specified in traditional theories of electrolyte solutions and proteins, that are identified in the textbooks by the names Gouy-Chapman, Debye-Huckel, or Poisson-Boltzmann. The PNP equations are nearly identical to the drift diffusion equations of semiconductor physics.

PNP fits a wide range of current voltage (IV)relations—whether sublinearlinear or superlinear—from 6 types of channels, over a wide range of membrane potential, in symmetrical and asymmetrical solutions of 20 mM to 2 M salt. Porins with known structure have been studied, and parameter estimates (in mutations of known structure) are surprisingly close to those predicted (i.e., within 7%). Selectivity has been studied extensively in the calcium release channel: IV relations in Li^+, K^+, Na^+, Rb^+, and Cs^+ and their mixtures can be explained with a few invariant parameters (of reasonable value) over the full range of concentrations and potentials. Complex selectivity properties of channels are easily explained: the anomalous mole fraction effect in K^+ and L-type calcium channels arise naturally as a consequence of binding.

Taken together, these results suggest that open ionic channels are natural nanotubes, dominated by the enormous fixed charge lining their walls (some 5 M, arising from 1 charge in a volume 1 nm by 1 nm). Physical chemists [4] have shown that highly charged systems are dominated by their mean electric field and the changes in its shape. Atomic detail is unexpectedly unimportant because correlation effects are small.

Ionic channels form a biological system of great biological significance and potential technological importance that can be immediately studied by the techniques of computational electronics. Many of those techniques have not yet been used to analyze proteins, or ionic solutions. Perhaps they should be: the application of the even the lowest resolution techniques involving the drift diffusion equation has revolutionized the study of channels and it is likely that application of higher resolution methods, like self-consistent Monte Carlo analysis, would have an even larger effect on physical chemistry and computational biology. The enormous efforts in those fields (symbolized by the billions of dollars spent on computing

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protein dynamics) can only benefit from the insights of computational electronics.

References

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