Ionic Channels as Biodevices

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ABSTRACT

Ion channels are proteins with a hole down their middle of great biological and medical importance studied in thousand of laboratories. Ions move through channels of known structure obeying the relatively simple laws of electrodiffusion. Ion channels seem ideal objects for interdisciplinary multi-resolution study, using existing methods of computational physics, electronics, and chemistry to predict and control biological function.

Keywords: Ion Channels; Electrostatics; Self-consistent

Protein channels conduct ions (mostly Na^+, K^+, Ca^{++}, and Cl^-) through a narrow tunnel of fixed charge ('doping'), acting as gatekeepers for cells and cell compartments, allowing molecules and electric current to flow across otherwise impermeable membranes [1][2]. Channels thereby control a wide range of biological function; some 20% of all the proteins in a human are thought to be membrane proteins, closely related to channels. Hundreds of types of channels are studied everyday, one molecule at a time, in thousands of laboratories, with the powerful techniques of molecular biology [3]: a substantial fraction of all drugs used by physicians act directly or indirectly on channels and membrane proteins. The amino acids, and sometimes atoms of channels can be manipulated one at a time with the powerful techniques of molecular genetics and the location of every atom can be determined within 0.1 Å in favorable cases, more to come. Channels are appealing objects for biological experimentation because their functions can be manipulated by so many techniques. The resulting knowledge of channel behavior is remarkable, albeit mostly descriptive.

Ionic channels are 'holes in the wall' with irregular but known structure that use the simple physics of electrodiffusion to perform their tasks [4]. Analyzing and computing the movement of charged spheres through a 'hole in the wall' should be easier than computing most other biological functions and the wealth of experimental data makes checking the analysis easy. Channels thus seem nearly ideal objects for joint mathematical, computational, and biological investigation. Each discipline can focus its own tools—mathematical, computational, and experimental —on the same problem. Each discipline is needed; it seems unwise for biologists to perform numerical simulations and theoretical analysis when they are untrained for those tasks; it seems unwise for mathematicians and physicists to imagine the structure and properties of nanotubes when the structure and properties of ion channels—natural nanotubes—are already known.

Multi-resolution analysis of ionic channels has already started. Open channels can be described as biological devices at low but useful resolution if the electric field and current flow are computed by the Poisson-Drift-Diffusion equations (called PNP, for Poisson-Nernst-Planck, in biophysics) 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 has often been done in the chemical and biological tradition. The Poisson-Drift-Diffusion equations describe the flux of individual ions (each moving randomly in the Langevin trajectories of Brownian motion) in the mean electric field. They are nearly identical to the drift diffusion equations of semiconductor physics used there to describe the diffusion and migration of quasi-particles, holes and electrons. They are closely related to the Vlasov equations of plasma physics.

PNP fits a wide range of current voltage (I-V) relations—whether sublinear, linear or superlinear—from 7 types of channels, over ±180 mV of membrane potential, in symmetrical and asymmetrical solutions of 20 mM to 2 M salt. The I-V relation of the gramicidin channel and the porin channel can be predicted directly from their structure, known from NMR and crystallography, respectively, using a single diffusion constant and no important adjustable parameters. Parameter estimates (e.g., of fixed charge) have been made in porin and mutations of porin, both with known structure; the results are close to those predicted (i.e., within 7%).

Complex selectivity properties of channels are easily explained: the anomalous mole fraction effect in K^+ and L-type Ca^{++} channels arise naturally as a consequence of binding [5]. Indeed, the selectivity of the L-type calcium channel can be predicted quantitatively if permeating ions are treated as finite objects with the entropy and electrostatic energy of crowded charged spheres. L-type Ca channels are of particular clinical importance because they control the heart beat and are the target of calcium channel blockers, drugs taken by a substantial fraction of the population. Selectivity in another calcium channel—the calcium release channel—can also be explained: I-V relations in Li^+, K^+, Na^+, Rb^+, and Cs^+ and their mixtures

can be predicted with a few invariant parameters (of reasonable value) over the full range of concentrations and potentials [6].

Taken together, these results suggest that open ionic channels are natural nanotubes, dominated by the enormous fixed charge lining their walls (~5 M, arising from 1 charge in a 7×10Å circular cylinder). Physical chemists [7] have shown that highly charged systems can be dominated by their mean electric field and changes in its shape. Atomic detail is unexpectedly unimportant because correlation effects are small. Biologists and biochemists have traditionally focussed on correlation effects rather than the electric field, even ignoring the electric field in some cases.

The role of the electric field has received more attention in computational physics and electronics than in biology and chemistry. Statistical chemistry of ionic solutions rarely treats the electric field and its boundary conditions explicitly. Simulations of ionic solutions, or proteins, rarely re-compute the electric field every time charges move, i.e., they rarely treat the electric field self-consistently. Simulations of drugs binding to proteins/nucleic acids are central problems in biological research and computational biology, with economic implications hard to exaggerate, given that medical care is some 17% of the GNP of the United States. Simulations of protein and DNA/RNA structure and folding are nearly as important. Yet self-consistent simulation methods (e.g., the Gummel iteration) have apparently not been tried on those problems even though they are widely used in the fields of computational physics and computational electronics to simulate swarms of charged particles, e.g., in plasmas.

An opportunity exists to apply the well established methods of computational physics and electronics to the central problems of computational biology. Of course, the biological and physical problems are not the same, but the essential physical and mathematical properties are similar and, more to the point, the techniques and traditions of computational physics and electronics will be a productive starting point for new investigations in computational biology. In my view, ***the plasmas of biology need to be analyzed in the same tradition as the plasmas of physics.*** Self-consistent simulations may prove as necessary (and productive) for computations of proteins and nucleic acids as for computations of plasmas of gases and semiconductors.

Application of some fundamental ideas of computational physics will help even before these central biological problems are attacked. Research will proceed differently once we agree that direct simulations of macroscopic systems need to be able to reproduce macroscopic properties of simple devices, like Ohm's law, Fick's law, or the energy of (macroscopic) capacitors. The difficulties faced by simulating such macroscopic quantities (particularly macroscopic flows) will highlight the need for multiresolution analysis. Direct simulations of atomic resolution will continue to be the foundation of the hierarchy of models. But direct simulations will be used as inputs and constraints for lower resolution models. They will show what physics must be included in such models. They will be used more to determine the parameters of the models than to directly calculate characteristics of biodevices.

Multi-resolution analysis of ion channels is already under way. Ion channels can serve, in this way, as a test bed for multi-resolution analysis of biodevices in general.

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