

Ions in Solutions and Proteins

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Nearly all biology occurs in ionic solutions and involves the transport of ionic charge: it is only mild hyperbole to call ionic solutions the ‘liquid of life’ (Edsall and Wyman 1958; Tanford and Reynolds 2001). Nearly all biology is controlled by proteins, because proteins are the only product of genes, and genes are the blueprints of life. Genes contain (almost) all the information needed to make an animal. The transport of ions through proteins with holes down their middle (called ion channels and transporters) is the control mechanism for a vast range of biological function in health (Ashcroft 1999; Hille 2001) and disease (Ashcroft 1999; Lehmann-Horn and Jurkat-Rott 2000; Rose and Griggs 2001). Ion channels are nano—nearly pico—valves that allow atomic scale structures to control macroscopic flow and so are of enormous technological interest. It is hard to exaggerate the importance of studying the transport of charge in channels.

Theories and simulations of charge transport in proteins (and in solution) have had great difficulty, despite their evident importance, because their essential behavior extends over so many scales. Theories must accurately deal with long range electric fields, atomic scale structures, and devices that function only far from equilibrium. Theories and simulations have been unable to calculate or derive the fundamental properties of solutions and ions in channels, or to calculate or derive the approximate ‘device equations’ that are known to describe these systems.

Simulations face particular difficulties. Simulations in atomic detail must deal with atomic motions that are computed with femto to picosecond time steps in systems that move significantly only after micro or milliseconds. Methods to average these atomic motions are not known. Simulations must deal with chemical modulators whose action depends on the precise number density (‘concentration’) of modulator in ranges of μM even though direct simulations of such densities must include some 10^{11} molecules of solvent if they are done in atomic detail, as they nearly always are. Simulations must deal with electric fields that are known experimentally to spread mm in long cells like nerve fibers and to change the transport of ions through individual channel proteins mm from the source of the field (Jack, Noble et al. 1975).

Charge transport in semiconductors occurs by electrodiffusion of quasiparticles and so is surprisingly similar to charge transport in ionic solutions, which occurs by electrodiffusion of real particles. Electrodiffusion in transistors occurs through a background of immobile doping charge, which forms the transistor; electrodiffusion in channels (and transporters) occurs through a background of immobile permanent charge on the channel protein. The similarity is striking (Eisenberg 1996; Eisenberg 2003; Eisenberg 2003).

Charge transport in semiconductors has been simulated with great success in the field of computational physics (Selberherr 1984; Jacoboni and Lugli 1989; Hess 1991; Hess, Leburton et al. 1991; Ferry 2000; Hess 2000; Damocles 2005) where simulations routinely compute macroscopic properties in atomic detail. Our overall goal is to achieve similar success in the theory and simulation of ionic transport in solutions and proteins.

Theory and simulations of semiconductors and transistors start (both historically—Shockley 1950—and logically, references above) with the electric field, in contrast to theory and simulations of ions in solutions and proteins. Theory and simulation of ions in solution customarily start with uncharged particles. Theory and simulations of semiconductors and transistors (nearly) always compute the electric field whenever charge moves: they are said to be ‘self-consistent’.

Self-consistent simulations of ions (which have finite size compared to the point quasiparticles of semiconductors) have been done successfully by semiconductor workers associated with our group (Aboud, Marreiro et al. 2004; Saraniti, Aboud et al. 2004; van der Straaten, Kathawala et al. 2004) and by labs starting from different traditions, chemical tradition (Kurnikova, Coalson et al. 1999; Cardenas, Coalson et al. 2000; Graf, Nitzan et al. 2000; Mamonov, Coalson et al. 2003), physical tradition (Chung, Hoyles et al. 1998; Moy, Corry et al. 2000; Chung and Kuyucak 2001; Corry, Allen et al. 2001; Edwards, Corry et al. 2002; Corry, Kuyucak et al. 2003; Corry and Chung 2005) and biophysical tradition (Im and Roux 2002; Im and Roux 2002; Aksimentiev and Schulten 2005). I only cite the established workers in the field and do not mean to give offence to the many other workers entering the field making contributions of enormous promise.

Despite this growing literature, the main issues in simulations are unsolved. Simulations of current voltage curves controlled by μ molar concentrations of modulators cannot be done in atomic detail.

Theoretical work is in a very different state. Self-consistent theories of ion transport are noticeable by their absence. Theoretical work on ion transport is of course enormous, but it historically has grown from the study of transport of uncharged particles, and rarely computes the electric field from the charges being transported and the boundary conditions that drive that transport. The historical work of Einstein, Langevin, Smoluchowski, and Sutherland described the diffusion of colloids in water, and colloids are highly charged—as are water molecules, even though the net charge of water is zero—but this work did not include explicit treatment of the electric field and did not calculate the electric field from the charges whose motion is described in the stochastic differential equations.

The problem I pose is to derive a theory of ion transport in which the transport equations and electric field equations are solved together. In bulk that is enough. But in devices like transistors and ion channels boundary conditions are different in different places, as they are in (nearly) all devices, worthy of that name. The equations must then be solved with the (spatially nonuniform) boundary conditions needed to describe the supply and removal of ions (and thus charge) from the ends of the channel. These spatially nonuniform boundary conditions (nearly always) drive macroscopic flow—often large flows—and so the problem is nonequilibrium as well as coupled and multiscale in its essence.

Such a problem might seem beyond the reach of mathematics but I think not, if approximations are chosen judiciously so attention is focused on systems where we know (from experiments) that simple behavior occurs. For example, current flow through bulk solutions is usually described very well by a resistor in parallel with a capacitor—that is to say, by Ohm's law and an electrostatic field—at least in the 100 mM NaCl solutions for the voltages and time scales typical of life. For example, current voltage relations of ion channels are simple, reproducible, and follow definite laws, which seem to be device equations much like those used by engineers to characterize transistors.

The challenge is to derive the 'laws' and device equations that characterize these simple behaviors using only mathematics, starting from an atomic description of the trajectories of ions in water and proteins.

I propose to simplify the problem dramatically to focus on its mathematical essence, using simplifications already widely applied in physical chemistry and biophysics with some success, even though the simplifications have not yet been derived in a way that most mathematicians would call satisfactory. Specifically, physical chemistry has shown that equilibrium properties of ionic solutions can be described over an enormous range of concentrations without detailed consideration of the properties of water or the chemical interactions of water and ions

(specifically, without delocalization of the orbitals of electrons of water and ions is not involved) (Durand-Vidal, Turq et al. 1996; Simonin, Blum et al. 1996; Barthel, Krienke et al. 1998; Durand-Vidal, Simonin et al. 2000; Fawcett 2004) and I propose to use such implicit solvent (so-called 'primitive') models of ionic solutions and extend them to include the dynamics of ion transport in bulk and channels. Water will be treated as a uniform dielectric with the dielectric coefficient of the bulk solution (not the dielectric coefficient of bulk water). This approach has been used to calculate ion selectivity in channels with some success (Nonner, Chen et al. 1998; Nonner and Eisenberg 1998; Nonner, Catacuzzeno et al. 2000; Nonner, Catacuzzeno et al. 2000; Nonner, Gillespie et al. 2001; Boda, Busath et al. 2002; Gillespie, Nonner et al. 2002; Gillespie, Nonner et al. 2002; Eisenberg 2003; Gillespie, Nonner et al. 2003; Boda, Gillespie et al. 2004; Nonner, Peyser et al. 2004) and actually to build a calcium selective channel designed by theory (Miedema, Meter-Arkema et al. 2004)

Trajectories of ions could be treated in two traditions (that I know of), namely that of Boltzmann transport theory and that of the Langevin equation. I am hardly familiar with the first, and am concerned about its mathematical foundations, compared to the solid foundations of the theory of stochastic differential equations, and so I propose that we work on trajectories defined by the full Langevin equation, in which forces are computed self-consistently, i.e., by solving Poisson's equation involving the location of the charges transported by the Langevin equation. Such problems have already been formulated and put in the context of the traditional theory of ions in solutions and channels (Nadler, Naeh et al. 2001; Schuss, Nadler et al. 2001; Schuss, Nadler et al. 2002; Nadler, Schuss et al. 2003; Nadler, Schuss et al. 2004; Singer, Schuss et al. 2004; Schuss, Nadler et al. 2004; Nadler, Schuss et al. 2005).

Analysis of these systems is now needed and that is what I propose. I think if we learn to 'count' Langevin trajectories, we will be able to count trajectories with more general properties. Or to put it more formally, I propose we construct probability measures that estimate the number density and flux in a coupled Langevin-Poisson system and then generalize those measures to more general trajectories and (most importantly) to trajectories determined by the simulations of molecular dynamics.

Our first goal will be to write the coupled Langevin and Poisson equations neatly, in dimensional and dimensionless form, showing the different scales of the system. Care should be taken to investigate many different possible scales and combinations of scales since each combination is likely to describe a different 'simplified' system already known to experimentalists, in some area or other.

Our second goal will be to seek systematic approximations taking advantage of the enormous difference in scales between the electrostatic force and the diffusion 'force' and the fluxes they drive.

Our third goal will be to solve these equations in the presence of spatially nonuniform boundary conditions for the electric field and for the average density of ions. These boundary conditions describe the classical concentration cell used by electrochemists for some 150 years, since Faraday, and by biophysicists to study ion channels since Hodgkin and Huxley, working in Cambridge and Plymouth (UK) some 60 years ago.

Our fourth goal will be to solve these equations in the presence of a background of immobile charge and thus to describe (simultaneously) ion channels. We aim for a simple nearly analytical treatment of ion channels, and that may also prove to be a useful, if primitive description of transistors, as well.

Our final goal will be to include an additional equation that describes motion of parts of the

protein, thus developing a theory of conformation change in proteins and enzymes, as well as channels. Channels perform many of their functions without changing conformation. Most proteins, however, change conformation dramatically as they do their work. Neither simulations nor theory have been successful in describing conformation changes.

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