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 millseconds. 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 μmolar 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.

Aboud, S., D. Marreiro, M. Saraniti and R. Eisenberg (2004). "A Poisson P3M Force Field Scheme for Particle-Based Simulations of Ionic Liquids." J. Computational Electronics, in the press.
Aksimentiev, A. and K. Schulten (2005). "Imaging alpha-hemolysin with molecular dynamics: ionic conductance, osmotic permeability, and the electrostatic potential map." Biophys J **88**(6): 3745-61.
Ashcroft, F. M. (1999). Ion Channels and Disease. New York, Academic Press.481.
Barthel, J., H. Krienke and W. Kunz (1998). Physical Chemistry of Electrolyte Solutions: Modern Aspects. New York, Springer
Boda, D., D. Busath, B. Eisenberg, D. Henderson and W. Nonner (2002). "Monte Carlo simulations of ion selectivity in a biological Na+ channel: charge-space competition." Physical Chemistry Chemical Physics (PCCP) **4**: 5154-5160.
Boda, D., D. Gillespie, W. Nonner, D. Henderson and B. Eisenberg (2004). "Computing induced charges in inhomogeneous dielectric media: application in a Monte Carlo simulation of complex ionic systems." Phys Rev E Stat Nonlin Soft Matter Phys **69**(4 Pt 2): 046702.
Cardenas, A. E., R. D. Coalson and M. G. Kurnikova (2000). "Three-Dimensional Poisson-Nernst-Planck Studies. Influence of membrane electrostatics on Gramicidin A Channel Conductance." Biophysical Journal **79**.
Chung, S.-H., M. Hoyles, T. Allen and S. Kuyucak (1998). "Study of ionic currents across a model membrane channel using Brownian dynamics." Biophysical Journal **75**: 793-809.
Chung, S. and S. Kuyucak (2001). "Predicting channel function from channel structure using Brownian dynamics simulations." Clin Exp Pharmacol Physiol. **28**: 89-94.
Corry, B., T. W. Allen, S. Kuyucak and S. H. Chung (2001). "Mechanisms of permeation and selectivity in calcium channels." Biophys J **80**(1): 195-214.
Corry, B. and S.-H. Chung (2005). "Influence of protein flexibility on the electrostatic energy landscape in gramicidin A." European Biophysics Journal **34**: 208-216.
Corry, B., S. Kuyucak and S. H. Chung (2003). "Dielectric self-energy in poisson-boltzmann and poisson-nernst-planck models of ion channels." Biophys J **84**(6): 3594-606.
Damocles (2005). *Damocles Web Site, IBM Research.* http://www.research.ibm.com/DAMOCLES/home.html.
Durand-Vidal, S., J.-P. Simonin and P. Turq (2000). Electrolytes at Interfaces. Boston, Kluwer
Durand-Vidal, S., P. Turq, O. Bernard, C. Treiner and L. Blum (1996). "New Perspectives in Transport Phenomena in electrolytes." Physica A **231**: 123-143.
Edsall, J. and J. Wyman (1958). Biophysical Chemistry. NY, Academic Press
Edwards, S., B. Corry, S. Kuyucak and S. H. Chung (2002). "Continuum electrostatics fails to describe ion permeation in the gramicidin channel." Biophys J **83**(3): 1348-60.
Eisenberg, B. (2003). "Ion Channels as Devices." Journal of Computational Electronics **2**: 245-249.
Eisenberg, B. (2003). "Proteins, Channels, and Crowded Ions." Biophysical Chemistry **100**: 507 - 517.
Eisenberg, R. S. (1996). "Computing the field in proteins and channels." J. Membrane Biol. **150**: 1–25.
Fawcett, W. R. (2004). Liquids, Solutions, and Interfaces: From Classical Macroscopic Descriptions to Modern Microscopic Details. New York, Oxford University Press.621.
Ferry, D. K. (2000). Semiconductor Transport. New York, Taylor and Francis.384.
Gillespie, D., W. Nonner and R. S. Eisenberg (2002). "Coupling Poisson-Nernst-Planck and

Density Functional Theory to Calculate Ion Flux." Journal of Physics (Condensed Matter) **14**: 12129-12145.
Gillespie, D., W. Nonner and R. S. Eisenberg (2003). "Density functional theory of charged, hard-sphere fluids." Phys Rev E **68**: 0313503 1-10.
Gillespie, D., W. Nonner, D. Henderson and R. S. Eisenberg (2002). "A physical mechanism for large-ion selectivity of ion channels." Physical Chemistry Chemical Physics **4**: 4763-4769.
Graf, P., A. Nitzan, M. G. Kurnikova and R. D. Coalson (2000). "A dynamic lattice Monte Carlo model of ion transport in inhomogeneous dielectric environments: method and implementation." Journal of Physical Chemistry B **104**: 12324-12338.
Hess, K. (1991). Monte Carlo Device Simulation: Full Band and Beyond. Boston, MA USA, Kluwer.310.
Hess, K. (2000). Advanced Theory of Semiconductor Devices. New York, IEEE Press.350.
Hess, K., J. P. Leburton and U. Ravaioli (1991). Computational Electronics: Semiconductor Transport and Device Simulation. Boston, MA USA, Kluwer.268.
Hille, B. (2001). Ionic Channels of Excitable Membranes. Sunderland, Sinauer Associates Inc.1-814.
Im, W. and B. Roux (2002). "Ion permeation and selectivity of OmpF porin: a theoretical study based on molecular dynamics, Brownian dynamics, and continuum electrodiffusion theory." J Mol Biol **322**(4): 851-69.
Im, W. and B. Roux (2002). "Ions and counterions in a biological channel: a molecular dynamics simulation of OmpF porin from Escherichia coli in an explicit membrane with 1 M KCl aqueous salt solution." J Mol Biol **319**(5): 1177-97.
Jack, J. J. B., D. Noble and R. W. Tsien (1975). Electric Current Flow in Excitable Cells. New York, Oxford, Clarendon Press.
Jacoboni, C. and P. Lugli (1989). The Monte Carlo Method for Semiconductor Device Simulation. New York, Springer Verlag.pp. 1-356.
Kurnikova, M. G., R. D. Coalson, P. Graf and A. Nitzan (1999). "A Lattice Relaxation Algorithm for 3D Poisson-Nernst-Planck Theory with Application to Ion Transport Through the Gramicidin A Channel." Biophysical Journal **76**: 642-656.
Lehmann-Horn, F. and K. Jurkat-Rott (2000). Channelopathies. New York, Elsevier Science.384.
Mamonov, A. B., R. D. Coalson, A. Nitzan and M. G. Kurnikova (2003). "The role of the dielectric barrier in narrow biological channels: a novel composite approach to modeling single-channel currents." Biophys J **84**(6): 3646-61.
Miedema, H., A. Meter-Arkema, J. Wierenga, J. Tang, B. Eisenberg, W. Nonner, H. Hektor, D. Gillespie and W. Wim Meijberg (2004). "Permeation properties of an engineered bacterial OmpF porin containing the EEEE-locus of Ca2+ channels." Biophysical Journal **87**: 3137-3147.
Moy, G., B. Corry, S. Kuyucak and S. H. Chung (2000). "Tests of continuum theories as models of ion channels. I. Poisson-Boltzmann theory versus Brownian dynamics." Biophys J **78**(5): 2349-63.
Nadler, B., T. Naeh and Z. Schuss (2001). "The stationary arrival process of independent diffusers from a continuum to an absorbing boundary is Poissonian." SIAM J Appl Math **62**: 443-447.
Nadler, B., Z. Schuss and A. Singer (2005). "Langevin Trajectories between fixed concentrations." Physical Review Letters. **in the press**.
Nadler, B., Z. Schuss, A. Singer and B. Eisenberg (2003). "Diffusion through protein channels:

from molecular description to continuum equations." Nanotechnology **3**: 439.
Nadler, B., Z. Schuss, A. Singer and R. Eisenberg (2004). "Ionic diffusion through confined geometries: from Langevin equations to partial differential equations." J. Physics: Condensed Matter **16**: S2153-S2165.
Nonner, W., L. Catacuzzeno and B. Eisenberg (2000). "Binding and Selectivity in L-type Ca Channels: a Mean Spherical Approximation." Biophysical Journal **79**: 1976-1992.
Nonner, W., D. P. Chen and B. Eisenberg (1998). "Anomalous Mole Fraction Effect, Electrostatics, and Binding in Ionic Channels." Biophysical Journal **74**: 2327-2334.
Nonner, W. and B. Eisenberg (1998). "Ion Permeation and Glutamate Residues Linked by Poisson-Nernst-Planck Theory in L-type Calcium Channels." Biophys. J. **75**: 1287-1305.
Nonner, W., D. Gillespie, D. Henderson and B. Eisenberg (2001). "Ion accumulation in a biological calcium channel: effects of solvent and confining pressure." J Physical Chemistry B **105**: 6427-6436.
Nonner, W., L., Catacuzzeno and B. Eisenberg (2000). "Ionic selectivity in K channels." Biophysical Journal **78**: A96.
Nonner, W., A. Peyser, D. Gillespie and B. Eisenberg (2004). "Relating microscopic charge movement to macroscopic currents: the Ramo-Shockley theorem applied to ion channels." Biophys J **87**(6): 3716-22.
Rose, M. R. and R. C. Griggs (2001). Channelopathies of the Nervous System. New York, Butterworth-Heinemann.347.
Saraniti, M., S. Aboud and R. Eisenberg (2004). "The Simulation of Ionic Charge Transport in Biological Ion Channels: an Introduction to Numerical Methods." Reviews in Computational Chemistry (in the press).
Schuss, Z., B. Nadler and R. S. Eisenberg (2001). "Derivation of PNP Equations in Bath and Channel from a Molecular Model." Physical Review E **64**: 036116 1-14.
Schuss, Z., B. Nadler, A. Singer and R. Eisenberg (2002). A PDE formulation of non-equilibrium statistical mechanics for ionic permeation. AIP Conference Proceedings, 3-6 September 2002: Unsolved Problems Of Noise And Fluctuations, UPoN 2002, 3rd International Conference on Unsolved Problems of Noise and Fluctuations in Physics, Biology, and High Technology, Washington, DC, AIP.
Schuss, Z., B. Nadler, A. Singer and R. S. Eisenberg (2004). Models of boundary behavior of particles diffusing between two concentrations. Fluctuations and Noise in Biological, Biophysical, and Biomedical Systems II, Maspalomas, Gran Canaria, Spain.
Selberherr, S. (1984). Analysis and Simulation of Semiconductor Devices. New York, Springer-Verlag. pp. 1-293.
Simonin, J.-P., L. Blum and P. Turq (1996). "Real Ionic Solutions in the Mean Spherical Approximation. 1. Simple Salts in the Primitive Model." Journal of Physical Chemistry **100**: 7704-7709.
Singer, A., Z. Schuss, B. Nadler and R. S. Eisenberg (2004). Models of boundary behavior of particles diffusing between two concentrations. Fluctuations and Noise in Biological, Biophysical, and Biomedical Systems II: series Vol. 5467. D. Abbot, S. M. Bezrukov, A. Der and A. Sanchez. New York, SPIE Proc. **5467:** 345-358.
Tanford, C. and J. Reynolds (2001). Nature's Robots: A History of Proteins. New York, Oxford.304 pages.
van der Straaten, T. A., G. Kathawala, R. S. Eisenberg and U. Ravaioli (2004). "BioMOCA - a Boltzmann transport Monte Carlo model for ion channel simulation." Molecular Simulation **31**:

151–171.