PHYSICAL MATHEMATICS SEMINAR

ION CHANNELS: MOLECULAR DEVICES

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ABSTRACT:

Protein channels conduct ions through a narrow tunnel of fixed charge and act as gatekeepers for cells and cell compartments. Hundreds of types of channels are studied every day 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.

The function of open channels can be described if the protein is described as an arrangement of charges—***not*** as an invariant potential of mean force or set of rate constants—and the electric field and current flow are computed by the Poisson-Nernst-Planck (*PNP*) equations. The *PNP* equations can be derived from a nonequilibrium analysis of Langevin trajectories of charged particles moving in a an electric and concentration field created by the particles themselves (and boundary conditions). *PNP* describes the flux of ions in the mean electric field specified in traditional (nonlinear) Gouy-Chapman/Debye-Hückel/Poisson-Boltzmann theories of electrolyte solutions and proteins. *PNP* is nearly the drift diffusion equation of semiconductor physics used there to describe the diffusion and migration of quasi-particles, holes and electrons. *PNP* is closely related to the Vlasov equations of plasma physics.

The dramatic selectivity of the cardiac Ca channel of clinical fame arises naturally if correlations are introduced into *PNP* in the chemical tradition used to describe concentrated salt solutions. The fixed charge of the selectivity channel forces the channel to hold four positive mobile charges, making a concentration of some 17 molar univalent charge! Four (monovalent) Na^{+} ions occupy twice the volume of two (divalent) Ca^{++}; the resulting difference in excluded volume produces calcium selectivity. This ***crowded charge model of selectivity*** predicts many selectivity properties in a wide range of ions and conditions (e.g., concentrations ranging over 5 orders of magnitude) after two adjustable parameters are set to optimal (unchanging) values.

Taken together, these results suggest that open ionic channels are natural nanotubes with properties dominated by the enormous fixed charge lining their walls and the consequent crowding of ions in their tiny volume. Other atomic detail is unexpectedly ***un***important. Highly charged nonequilibrium systems of this sort are hard to describe by direct simulations of molecular dynamics because those simulations are usually too brief to compute flux or current. Traditional simulations also have difficulty with the electric field since they use periodic boundary conditions and equilibrium boundary conditions, at best. Biomolecules are usually controlled by the number density of modulators present in trace amounts, often $10^{-6}\times$ number density of water. Simulations have inherent difficulty in estimating such densities.

An opportunity exists to apply the well established methods of computational physics to the central problems of computational biology. In my opinion, the plasmas of biology need to be analyzed like the plasmas of physics. The mathematics of semiconductors and ionized gases should be the starting point for the mathematics of ions and proteins as well. It seems likely that the energetics of the ***compressible plasma of ions near active sites of proteins*** is an important determinant of their function. Of course, the plasma of ions and proteins differs significantly from those of physics. The definite structure of proteins, the small size of protein active sites, the spherical shape of metallic ions, and the pervasive presence of water are novel features of biological plasmas. So challenges abound, but I believe they can be addressed by existing tools and traditions of applied mathematics and physics.

TUESDAY, APRIL 11, 2006
2:30 PM
Building 3, Room 270

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