**Ionic Interactions in Biological and Physical Systems: a Variational Treatment
Bob Eisenberg\***

 Biology depends on interactions of ions. Interactions with trace concentrations of Ca2+ and hormones control proteins. Interactions of Na+, K+, and Cl− with channel proteins produce electrical signals of nerves and coordinate muscle contraction including the heart. Nucleic acids, enzymes, transporters, and channels are all charged molecules that exist in a plasma of interacting Na+, K+, Ca2+ and Cl‑ ions, along with hundreds of types of organic ions, acids and bases, most with specific functions. These biomolecules concentrate ions to number densities greater than 10 M because their active sites have large concentrations of permanent charge, acids and bases. Interactions dominate such concentrated solutions and thus are important for biomolecular function.

 Biomolecules are special structures. They are cathedrals of atoms made visible by the remarkable advances of structural biology. Biomolecules are controlled by ionic interactions and so it is natural that biologists should attribute those interactions to biology’s special structures. But **ions interact strongly wherever they are found**, even without biology’s special structures. An ion attracts opposite charges and creates an atmosphere of interaction in any solution. All molecules participate in an ionic atmosphere because (nearly) all molecules have charge. ‘Everything’ interacts with everything else in concentrated ionic solutions wherever they are found. These interactions are not small even in the solutions outside membranes that provide the power for nerve signals. Interactions are enormous in the highly concentrated solutions in and near nucleic acids, enzyme active sites, transporters, channels, and the membranes that form cellular structures. But biochemical and biophysical theories rarely use excess free energies to describe interactions. Enzymes and transporters are analyzed with the theory of ideal uncharged gases, without physical interactions between reactants. Rate constants of classical theories are constants independent of interactions even in highly concentrated solutions. In classical theories, excess free energies of interaction do not depend on concentrations of multiple species. Physical interactions of ions can be mistaken for interactions with proteins if excess free energies are treated this way. Physical interactions can be mistaken for conformation changes of proteins or complex schemes of chemical reactions.

 Physical interactions have been ignored (in my view) because no one knew how to deal with them. Variational methods that allow interactions to be analyzed in conservative systems have not been available for dissipative systems like ionic solutions. These mathematical problems are now resolved. An Energetic Variational Approach to dissipative systems has been developed by Chun Liu, more than anyone else. Existence and uniqueness have been proven and Navier Stokes equations have been derived. If a component is added to a variational model, the resulting Euler Lagrange differential equations automatically describe new interactions with minimal new parameters. Thus, variational methods are quite specific when confronted with new components of solutions, or additional forms of transport, like convection and heat flow, along with diffusion and electrical migration.

 A variational ‘primitive’ model of finite size ions has been constructed and more atomic detail can be added as needed. The resulting ‘Euler Lagrange’ differential equations have been integrated in and near ion channels. Ionic interactions produce selectivity of ion channels. The variational primitive model is a superset of models already used to predict selectivity of calcium, sodium and ryanodine receptor channels with some success in a wide range of conditions. Variational methods have not yet been applied to bulk solutions to predict the equilibrium and nonequilibrium consequences of finite ion size. Numerical inefficiencies are being removed.

 The energetic variational method is powerful. It treats flow as it treats equilibrium. Flows are driven by spatially nonuniform boundary conditions using the same partial differential equations that describe the zero flow case of classical thermodynamics. Mathematically precise calculations replace problematic assumptions of local equilibrium (that are mathematically inconsistent with global flows) and replace pairwise interactions (that are inconsistent with multiple body interactions, e.g., those that characterize polarization). Variational methods are helpful in dealing with electric fields. Electric fields exist on all scales and couple atomic interactions of ions to boundary conditions far away. Such coupling allows transistors to amplify and ion channels to create action potentials. Methods must deal with coupling of such importance. Of course, variational methods are not magic. If physics is left out of its models, the resulting ‘Euler Lagrange’ differential equations cannot include their effects.

 Chemical interactions like the Hofmeister effect have been studied historically by a diverse set of models that were difficult to compare, because the mathematics analyzing them was not powerful or precise enough to minimize the number of adjustable parameters. Chemical phenomena will be easier to understand (I believe) when a variational approach is used to compare theory with experiment. Adjustable parameters will be reduced in number and easier to specify. Dominant effects will be easier to identify. The interactions that determine biological function will emerge as natural consequences of physical forces, organized by evolution and its structures to make biomolecules into useful devices. Centuries of dreams of physicists/physiologists like Galvani, Volta, and Fick will become biophysical reality, if that happens.