Ionic Interactions in Biological Systems: a Variational Treatment

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Biology depends on interactions of ions. Interactions with trace concentrations of Ca^{2+} control most proteins. Interactions of Na^{+}, K^{+}, and Ca^{2+} with channel proteins produce electrical signals of nerves and coordinate the heart. Nucleic acids, enzymes, transporters, and channels are all charged macromolecules in a plasma of interacting Na^{+}, K^{+}, Ca^{2+} and Cl^{-} ions, along with hundreds of types of organic ions, acids and bases, most with specific functions. Bio-macromolecules concentrate small ions to number densities >10 M because their active sites have large densities of permanent charge. Solid $Na^{+}Cl^{-}$ is ~37 M. Interactions of crowded charged spheres dominate solutions >1 M and thus are vital 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 power nerve signals.

Interactions are enormous in the highly concentrated solutions in and near nucleic acids, enzyme active sites, transporters, channels, and other special structures within biomolecules and cells. But classical biochemical and biophysical theories rarely include ion-ion interactions. Enzymes and transporters are analyzed classically with the theory of ideal uncharged gases, without physical interactions between 'ions'. More modern electrostatic theories like Poisson Boltzmann and PNP deal with electrostatic interactions of point ions without steric repulsion. But ions are very crowded in and near nucleic acids and proteins. **Steric repulsion often controls natural function.**

Ion-ion interactions of finite size ions 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. These mathematical problems are now resolved. A general Energetic Variational Approach to dissipative systems has been developed by Chun Liu, more than anyone else. Existence and uniqueness are proven and incompressible Navier Stokes equations have been derived. If a component is added to variational models, the resulting Euler Lagrange equations automatically describe new interactions with minimal new parameters. Thus, variational methods are quite specific when confronting new finite size ions in solution, or additional forms of transport, like convection, along with the usual diffusion and electrical migration.

A variational model of finite ions in solution is available. More atomic and chemical detail can be added as needed. The resulting 'Euler-Lagrange' equations have been integrated in and near ion channels. The variational electrolyte model is a superset of models already used to analyze and predict selectivity of ryanodine receptors, and binding selectivity of Ca and Na channels in many conditions. Numerical inefficiencies are being removed but a great deal remains to be done and many new applications explored.

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 and strictly pairwise interactions (mathematically inconsistent with multiple body interactions and global flows). Variational methods are helpful in dealing with electric fields. Electric fields exist on all scales and create interactions between ions, macromolecules, and boundary conditions far away. Extended interactions are allow transistors to amplify and nerves to propagate signals. Mathematics must deal with extended coupling to understand biological function. Of course, variational methods are not magic. If physics is left out of its models, the resulting Euler-Lagrange equations cannot include their effects.

Biological phenomena will be easier to understand (I believe) when an energetic variational approach is used. 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 special structures so biomolecules are useful devices. Interactions of finite size ions and long range electric field must be extended from atomic to macroscopic scales. Centuries of dreams of physicists/physiologists like Galvani, Volta, and Fick will become biophysical reality, if that happens and nerve signals can be understood by mathematical analysis of physical models.