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**Interactions in Ionic Solutions and Systems  
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Ions come in pairs. Electrical interactions are so strong that only a tiny fraction of all charges are unbalanced. Interactions of point particles are relatively easy to analyze and manipulate. Our semiconductor technology is the direct result of the simple PNP (Poisson Nernst Planck) pic flow driven by macroscopic gradients of concentration (‘power supplies’). Ions are highly concentrated (typically 10 molar) in and near biomolecular devices because of the permanent charge of nucleic acids, enzyme active sites, ion channels, and ion transporters. Biological function is usually controlled by trace concentrations of messengers: Ca2+ ~10‑7Molar; hormones ~10-11 M. Interactions of ionic messengers, ionic power supplies, and ionic flows (e.g., the signals of nerve and muscle fibers) have been a main subject of biology and medicine since Galvani, Volta, and Fick (all as much biologists as physicists) discovered electricity and diffusion.

These realities of biology are difficult to simulate in all atom calculations. The enormous computing power presently available allows qualitative understanding of life’s fabulous atomic structures but quantitative and calibrated calculations are needed. Devices function by balancing large electrostatic and steric forces in tiny spaces. Calibrated analysis is needed because balance depends on numerical values. Structural analysis is the essential beginning, not the end.

The fundamental issues in biology are interactions and so it is natural that biologists should attribute those interactions to biology’s special structures, its proteins, nucleic acids, membranes, cells, tissues and organs. 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 cells that are biological power supplies. The interactions are enormous in the highly concentrated solutions in and near nucleic acids, enzyme active sites, channels, and transporters. But biochemists and biologists use the theory of ideal uncharged gases, with particles that do not interact, to analyze experiments. They ignore nonideal terms that depend on all species present. Physical interactions in and near active sites can easily be mistaken for conformation changes of the biomolecule or complex chemical reactions.

Interactions have been ignored (in my opinion) 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 has been developed by Chun Liu, more than anyone else, that allows systematic treatment of dissipative systems. Existence and uniqueness have been proven and Navier Stokes equations have been derived. Application of the variational method to ionic solutions is just beginning. A variational ‘primitive’ model of finite size ions has been constructed. The resulting ‘Euler Lagrange’ equations are derived by mathematics alone and have been integrated to predict properties of ionic solutions in bulk and near ion channels.

The energetic variational method is remarkably powerful. It treats flow as it treats equilibrium. Both are consequences of the physical model of energy and dissipation, and physical boundary conditions. Flows are driven by spatially nonuniform boundary conditions using the same partial differential equations that describe equilibrium. Assumptions of local equilibrium and pairwise interactions are replaced by mathematically precise calculations of all interactions and flows. Of course, the variational method is not magic. If physics is left out of its models, the resulting ‘Euler Lagrange’ equations cannot include them. But systematic construction of models of ionic interactions like the Hofmeister effect is now possible. All interactions are automatically dealt with in a unique set of partial differential equations, that describe flow and equilibrium, and can be systematically refined as they confront experimental data.

The atomic detail necessary to explain the Hofmeister effect will be revealed (I believe) as numerical inefficiencies are removed and variational models of ionic solutions are refined to deal with the large mass of precise data provided to us by generations of experimental physical chemists.