Ions in Channels

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Ion channels are irresistible objects for biological study because they are the 'nanovalves of life' controlling most biological functions, much as transistors control computers. Channels contain an enormous density of crowded charged spheres, fixed and mobile, and induced polarization charge as well. Direct simulation of channel behavior in atomic detail is difficult if not impossible. Gaps in scales of time, volume, and concentration between atoms and biological systems are each ~10^{12}. All the gaps must be dealt with at once, because biology deals with all the scales at once.

Simple models are surprisingly successful in dealing with ion binding in two very different (and important) channels over a large range of conditions, suggesting that mathematical analysis is both possible and useful. Amazingly, the same model **with the same two parameters accounts quantitatively for qualitatively different binding in a wide range conditions for the very different calcium and sodium channels.** The binding free energy is an **output** of the calculation, produced by the crowding of charged spheres in a very small space. The model does not involve any traditional chemical 'quantum' binding energies at all.

How can such a simple model give such specific results when crystallographic wisdom and chemical intuition says that selectivity depends on the precise structural relation of ions and side chains? The answer is that **structure is a computed consequence of forces** in this model and is very important, but as an output of the model, not as an input. **Binding is a consequence of the 'induced fit' of side chains to ions and ions to side chains. Binding sites are self-organized and at their free energy minimum, forming different structures in different conditions.**

Channels function away from equilibrium. A variational approach is obviously needed to replace our equilibrium analysis of binding and one is well under way, treating ionic solutions as complex fluids with simple components, applying the energy variational methods of Chun Liu, used in electrorheology to deal with liquid crystals. Correlations are generated automatically (without arbitrary coefficients) by this variational method from the energy and dissipation of the components of the physical model.