Ions in Channels, Natural Nanovalves
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Ion channels are the ultimate multiscale device, the ‘nanovalves of life’ controlling most biological functions. Ion channels are built (‘engineered’) by evolution so a handful of atoms control macroscopic flows. Small differences in atomic position turn large flows on and off. Ion channels, like other nanodevices, are a serious challenge to the chemical tradition. Atomic scale chemistry interacts with macroscopic fields, to control biological flows.

Classical statistical mechanics culminated in the magnificent theory of simple fluids of noninteracting particles with minimal boundary conditions. It was not designed with interacting systems in mind, let alone systems in which atoms controlled machines. A different form of mechanics is needed when nanovalves are engineered. In my view, one needs the recently developed variational mechanics of complex fluids, like liquid crystals. Simulation of complex fluids, or ions in channels, is difficult in full atomic detail. Gaps in scales of time, volume, and concentration between atoms and macroscopic functions are each ~1012. All the gaps must be dealt with at once because biology deals with all the scales at once: difficulties multiply. Accurate transferrable calibration is needed because small differences of large forces control large flows.

‘All sphere’ models are surprisingly successful in dealing with ion binding in two very different (and important) channels over a very large range of conditions. Amazingly, the same model with the same two parameters accounts quantitatively for the selectivity of very different calcium Cav and sodium Nav channels. 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.

The effective structure of an ion channel depends on interactions of ions with each other and the channel protein. The theory of complex fluids uses variational methods to deal with such interacting systems. Variational theory allows the engineering of interacting molecules in liquid crystals. Variational methods are just now be applied to ions in channels and solution.

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