**All Atom Simulation of the Nerve Signal: the Impossible Dream**

Excellent widely available software has made all atom calculations an everyday tool in many laboratories studying biological function as recognized by the recent Nobel Prizes to Warshel, Levitt, and Karplus. All atom simulations of some biological functions are an impossible goal, however, in some important cases. Impossible goals have their psychological role, but it is important to recognize that is what their role is, so inordinate resources are not used to do what cannot be done. In many cases multiscale analysis is necessary and inevitable, in my view.

The nerve signal called the action potential carries information as a binary signal over long distances (say 0.001 m to 10 m) in nerve cells, mostly nerve axons. Currents drive the all-or-none action potential. The electric currents are carried by two types of ions sodium and potassium through two types of channel proteins that sit in nerve membranes. Sodium is abundant outside cells; potassium is abundant inside cells. One channel type selectively catalyzes[1](#_ENREF_1) the flow of sodium ions. The other channel type selectively catalyzes the flow of potassium ions across the otherwise insulating membrane. These channels open in response to changes in the electrical potential across the voltage sensors of the channels. The gradients of concentration, electrical, and electrochemical potential for sodium drive sodium ions (and electrical current) inward through the sodium channel when it opens. The different gradients of concentration, electrical and electrochemical potential for potassium drive potassium ions outwards when the potassium channel opens.

The electric current carried across the membrane by these channels spread down the length of axons as current flows down transmission lines according to Kelvin’s equations[2](#_ENREF_2), [3](#_ENREF_3) worked out to describe current flow in telegraph cables under the ocean. These equations show that the potential at one location depends on the current flow from other locations millimeters to centimeters away. The potential at one location depends on the potential at other locations. Some 1015 ions interact this way, in a 0.3 mm diameter axon, to pick an extreme case in which the wave length of the (squid) action potential of 1 msec duration is 20 mm, when propagating at a velocity of 20 m/sec. (3.14\*20\*0.001\*(0.3\*0.001)^2)/4)\*6\*10^23=8.478e+14

A computation of the interactions of 1015 interacting ions is not possible, even if water is neglected. The memory of computers are not big enough; the time to access the locations of so many particles is much too long; and the number of computations needed to directly compute the (not just pairwise) interactions of 1015 ions is beyond astronomical. The action potential cannot be computed with atomic resolution.

But there is no need to compute an action potential with atomic resolution. The nerve action potential is a macroscopic phenomenon and the multiscale description of the action potential is known, thanks to the work of Hodgkin, Huxley, and Cole[4](#_ENREF_4), [5](#_ENREF_5), [6](#_ENREF_6) also recognized in a Nobel Prize. The atomic description of nerve propagation is not needed. The atomic scale description of individual channels is nearly enough, because the interaction of channels is described accurately by an intermediate scale equation, the transmission line equation.

The voltage clamp technique of Cole and Hodgkin measures the properties of ensembles of noninteracting channels. That is why the technique was invented. Single channel recording allows measurement of current through one channel protein at a time using the patch clamp method (among others) in the Nobel Prize work of Neher and Sakmann. The voltage and time dependence of ensembles of noninteracting channels is simple enough that the action potential can be reconstructed from measurements of channels in the voltage clamp and (nearly) from measurements of single channels themselves.

Calculations of current through single channels then replace calculations of the action potential itself. The multiscale equation of transmission lines is all that is needed to go from ions moving through single protein molecules to the macroscopic biological function of the action potential.

Atomic scale simulations are needed then of the ions flowing through single channel proteins, not of the multitude of ions involved in the propagation of the nerve signal. Calculating ions through single channel proteins is itself a multi-scale problem. Atomic resolution will be difficult to achieve. The reasons are obvious if one starts from the properties of these channels known from decades of experimentation.[7](#_ENREF_7)

The properties of individual sodium and potassium channels depend sensitively on the solutions around them. These solutions are invariably ionic mixtures (made mostly of Na, K, Ca, and Cl ions) derived from roughly half molar seawater. Seawater is highly concentrated compared to the dilute solutions in which  solutions of either NaCl or KCl  have ideal properties.[8](#_ENREF_8), [9](#_ENREF_9), [10](#_ENREF_10) Most channels change properties dramatically if the concentration of calcium ions is changed, particularly on the inside of the channel. The concentration of calcium inside cells is typically 0.0000001 M. Variations in this concentration serve as biological control signals in many systems, much as the position of a gas pedal controls the speed of a car, so the trace concentration of calcium is an important variable to simulate accurately in biology.[7](#_ENREF_7), [11](#_ENREF_11)

Computations in atomic detail of ionic mixtures containing calcium ions pose certain challenges for all-atom simulations. Calibration against the main physical properties of these mixtures (the free energy per mole, i.e., the electrochemical potential) is needed, and the calibration must be accurate given the sensitivity found experimentally to details of composition. All-atom calculation of trace concentrations of intracellular calcium ions is a particular challenge since ~55 moles of water must be calculated for each 10-7 moles of calcium ion in a 10-7 molar calcium solution.

Time scales of action potentials are milliseconds (nerve) to nearly seconds (heart) and so all atom simulations must be computed for milliseconds to seconds. The time step of all-atom simulations is typically 10-15 sec. Differential equations must be integrated for something like 1013 steps, producing certain difficulties of reproducibility (e.g., convergence; unlimited dependence of individual trajectories on initial conditions; sampling errors because of inaccessible regions of phase space in chaotic systems) and accuracy in numerical procedures, that limit computations no matter how fast they are done.

Nerve signals do not occur at equilibrium because flows do not occur in equilibrium systems. Nerves are dead at equilibrium. Flows of current link single channels to the action potential.[4](#_ENREF_4), [5](#_ENREF_5), [6](#_ENREF_6) Calculations of flow from one ionic mixture to another (at different electrical, chemical, and electrochemical potentials) are needed in an all atom simulation, for that reason. Equilibrium analysis (with a single solution on both sides of a channel) can only reproduce a dead system without a nerve signal at all. We need simulations of live systems with ion flow through solutions and channels. Simulations of ‘live’ diodes and ‘triodes’(bipolar and field effect transistors) are done every day in hundreds or thousands of laboratories. It would be productive to show that all atom simulations of ions flowing through channels can actually reproduce the nonequilibrium nonlinear behavior of diodes and transistors, in my opinion.

All-atom simulations of flows through ion channels may not be impossible. They may not be necessary, either. A multiscale analysis of ion flows through channels may be possible, just as a multiscale analysis of current flow down a nerve can be done. The daunting challenges of an all-atom simulation listed above may not have to be faced in full, all at once, if a multiscale analysis is possible. The multiscale analysis can take advantage of the laws of electricity, and of electrodiffusion, to simplify the simulation. Certainly, atomic detail will be crucial in some parts of the system, and atomic scale simulation of those parts of the system will be needed. Changes in a handful of atoms are enough to dramatically change  the properties of single channels. The magnificent cathedrals of channel structure recognized in the Nobel Prize to Mackinnon have architectural detail that controls biological function. But full atomic detail is not needed everywhere, in all likelihood.[12](#_ENREF_12), [13](#_ENREF_13)

All-atom simulations of ion channels remain an admirable dream, whether impossible or not. They form a productive inspiring dream as long as simulations are calibrated. Simulations must actually reproduce the experimental properties of ions in mixtures, in bulk and in channels, as measured in the laboratory. Otherwise, the dream can be a nightmare. The shortcuts of multiscale analysis are well focused (and motivated) by the challenges of all atom simulations, in my view.

**References**

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