**All-atom simulations of Signals in Nerves: the impossible dream**

**Bob Eisenberg**

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Finite numbers are sometimes so large that they seem infinite. But they are not. Computation has increased so much in power (since Moore[1](#_ENREF_1) said it could not increase much more), that computers seem to be able to calculate anything. They cannot.[2](#_ENREF_2), [3](#_ENREF_3)

Computers can calculate the motions of all the atoms of proteins and that capability was recognized recently in a Nobel Prize celebrating the importance of the work of Warshel, Levitt, and Karplus. But many important biological functions (produced by proteins) cannot be computed in an all-atom simulation, and that needs to be remembered as we celebrate what can be done so well.

The nerve signal called the action potential. This waveform of electrical potential carries information as a binary electrical signal over long distances (say 0.001 m to 10 m) in nerve cells, mostly nerve axons. The electrical potential is a waveform in time and distance. It is a propagating wave that forms the neuronal signal. 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. The channels provide the currents that generate the nerve signal. The electrical voltage that is the nerve signal help control the channels, both sodium and potassium channels.

(3.14\*20\*0.001\*(0.3\*0.001)^2)/4)\*6\*10^23=8.478e+14

Potassium is abundant inside cells. Sodium is abundant outside cells. One channel type selectively catalyzes[4](#_ENREF_4) the flow of potassium ions. The other channel type selectively catalyzes the flow of sodium 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 potassium drive potassium ions (and their electrical current) outward through the potassium channel when it opens. The different gradients of concentration, electrical and electrochemical potential for sodium drive sodium ions inwards when the sodium channel opens. The inward sodium current provides the energy for propagation. The outward potassium currents helps promptly terminate the nerve signal. They determine the duration of the action potential waveform.

The electric current carried across the membrane by these channels spread down the length of axons the way electric current flows down transmission lines. Both follow Kelvin’s (sub-marine) cable equations,[5](#_ENREF_5), [6](#_ENREF_6) 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, a fact expected in theory and easy to verify in experiments. Some 1015 ions interact this way, in a 0.3 mm diameter squid never fiber, to pick a case in which the wave length of the action potential of 1 msec duration might be 20 mm, when propagating at a velocity of 20 m/sec.

An all-atom computation of the interactions of 1015 interacting ions is not possible, if each ion interacts with all the others, through the electric field even if water is neglected. The electric field induces (voltage dependent) polarization charge in the lipid membrane. That charge couples every ion to every other ion, producing a staggering number of interactions. Everything interacts with everything else, through the induced charge on the lipid membrane and at any other places that polarization varies with location and electrical potential. The number of computations needed to compute the interactions of 1015 interacting ions is beyond astronomical. Indeed, just the pairwise interactions of 1015 ions is a serious computational challenge.

It may not be possible to compute the waveform of the action potential with atomic resolution. But there is no need to do so. The waveform that is the nerve signal—the 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,[7](#_ENREF_7), [8](#_ENREF_8), [9](#_ENREF_9) also recognized in a Nobel Prize (to two of them). The atomic description of nerve propagation is not needed. The atomic scale description of current through single protein molecules—individual sodium and potassium channels—is nearly enough, because the interaction of channels is described accurately[7](#_ENREF_7), [8](#_ENREF_8), [9](#_ENREF_9) by Kelvin’s cable equation, usually called the transmission line equation in the mathematics literature today.

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 as celebrated by the Nobel Prize to Neher and Sakmann. The voltage and time dependence of ensembles of noninteracting channels is simple. An action potential can be reconstructed by summing the currents through single channels themselves and then using the summed current in the intermediate scale equation, the transmission line equation.[7](#_ENREF_7), [8](#_ENREF_8), [9](#_ENREF_9)

A multiscale analysis succeeds in this way. It links atomic scale currents through single channels with the biological reality of the action potential (waveform), the nerve signal. 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 propagating action potential waveform.

Atomic scale simulations are needed then of the ions flowing through single channel proteins. Such simulations may not be impossible, but they are beyond our immediate reach.[10](#_ENREF_10) The reasons are obvious if one thinks of these channels as known from decades of experiments in hundreds of laboratories.[11](#_ENREF_11)

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.[12](#_ENREF_12), [13](#_ENREF_13), [14](#_ENREF_14)

Computations in atomic detail of ionic mixtures containing calcium ions pose certain challenges for all-atom simulations. 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. Calibration against the main physical properties of these mixtures (the free energy per mole, i.e., the electrochemical potential) is needed, and the calibration of the free energy (per mole) of calcium must be accurate.

Most channels change properties dramatically if the concentration of calcium ions is changed, particularly on the inside of the channel. If the concentration of calcium is changed too much, many channels disappear (from experiments measuring current), and are dead to the world, as far as those measurements are concerned. The concentration of calcium inside cells is typically 0.0000001 M. Changes 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 must be simulated accurately in biology, just as changes in the location of the gas pedal must be known in simulations of cars, to understand their speed.[11](#_ENREF_11), [15](#_ENREF_15)

Computations in atomic detail must face the well known problem of time scales. Time scales of action potentials range from milliseconds (for nerve) to nearly seconds (for the 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 accuracy and reproducibility. Reproducibility is difficult in simulations like these of systems with unlimited dependence unlimited dependence of individual trajectories on initial conditions. Sampling errors can arise because of inaccessible regions of phase space in chaotic systems and convergence of simulations to stable results is not guaranteed. These problems limit computations no matter how fast they are done.[2](#_ENREF_2), [3](#_ENREF_3)

The spatial scale of the action potential is millimeters to centimeters or more. All-atom simulations must calculate atoms (some 10-10 m in radius) to millimeters or more if the simulation is to generate the waveform of the action potential from ions moving through channels

All-atom simulations of biological systems have to be done away from equilibrium, in systems in which flows are involved in biological function. Many biological systems are at equilibrium only when they are dead.

Nerve signals do not occur at equilibrium because nerve signals depend on flows of current that link single channels to the waveform of the propagating action potential[7](#_ENREF_7), [8](#_ENREF_8), [9](#_ENREF_9) These flows cannot occur in equilibrium systems (by definition). 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 different concentrations of ions inside and outside cells. We need to calculate ion flows driven by the different electrical, chemical, and electrochemical potentials found inside and outside cells. 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 enough and a lot simpler. The daunting challenges of an all-atom simulation of current through an ion channel may not have to be faced in full, all at once. The multiscale analysis can take advantage of the laws of electricity, and of electrodiffusion, to simplify the simulation.

Certainly, the laws of electrodiffusion and electricity are not enough. 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.[16](#_ENREF_16), [17](#_ENREF_17)

All-atom simulations of ion channels remain an admirable dream, whether impossible or not. They form a productive inspiring goal as long as simulations are calibrated. Otherwise, the admirable dream can turn into a dreadful nightmare, demanding results that cannot be produced. Simulations must actually reproduce the experimental properties of ions in mixtures, in bulk and in channels, as measured in the laboratory, if they are to reach their promise of helping biologists and physicians in their everyday work. .

In my view, multi-scale analysis will be needed to reach that goal, motivated and focused by the challenges of all-atom simulations.

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