

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

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Finite numbers are sometimes so large that they seem infinite. But they are not. Computation has increased so much ($>10^9$) in power since 1965[§] that computers seem to be able to calculate anything. They cannot.^{1,2}

Computers can calculate 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. We need to remember that even as we celebrate what can be done so well.

The nerve signal is an important biological function called the action potential. The action 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 helps control channels, including sodium and potassium channels.

Potassium is abundant inside cells. Sodium is abundant outside cells. One channel type selectively catalyzes³ the flow of potassium ions across the otherwise insulating lipid membrane. The other channel type selectively catalyzes the flow of sodium ions. 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 their electrical current) inward through the sodium channel, when it opens. The inward sodium current provides the energy for propagation. The different gradients of concentration, electrical and electrochemical potential for potassium drive potassium ions outwards, when the potassium channel opens. The outward potassium currents help promptly terminate the nerve signal so another signal can soon follow.

The electric current carried across the membrane by these channels spreads down the length of axons the way electric current flows down transmission lines. Both follow Kelvin's sub-marine cable equations,^{4,5} 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 10^{15} ions

[§] When Moore¹ feared that computer power could not continue to increase very much longer.

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

interact this way, in a 0.3 mm diameter squid nerve fiber, with action potential wave length of 20 mm, if the action potential duration is 1 msec with velocity 20 m/sec.

An all-atom computation of 10^{15} ions is not possible, if each ion interacts with all the others through the electric field, even if the induced polarization charge of water is neglected. The electric field induces (voltage-dependent) polarization charge in the lipid membrane. That charge produces forces that act on every ion. In that way, every ion is coupled to every other ion, producing a staggering number of interactions. Everything interacts with everything else, through the induced charge on the lipid membrane and induced charge at any other place that where polarization charge varies with location and electrical potential. The number of computations needed to compute all the interactions—not just pairwise—of 10^{15} interacting ions is beyond astronomical. Indeed, computing just the pairwise interactions of 10^{15} ions every 10^{-15} seconds is daunting.

An all-atom simulation of a nerve signal is not needed, which is just as well, since it seems impossible. A multiscale analysis will do all we need. The multiscale description of the action potential is known, thanks to the work of Hodgkin, Huxley, and Cole,^{6, 7, 8} 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^{6, 7, 8} by Kelvin's cable equation, usually called the transmission line equation in the mathematics literature today.

Current through channels is measured every day in hundreds or thousands of laboratories. 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 Neher⁹ and Sakmann.¹⁰ 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 themselves¹⁰ and then using the summed current in an intermediate scale equation,^{6, 7, 8} the transmission line equation.

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 action potential waveform in space and time.

Atomic scale simulations are needed only of the ions flowing through single channel proteins. Such simulations may be possible, but they are beyond our immediate reach.¹¹ The reasons are obvious if one thinks of the properties of these channels as measured in thousands of laboratories.¹²

Experiments show that 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 (599 mM) compared to the dilute solutions (50 mM or much less depending on the criteria) in which either NaCl or KCl have the ideal properties of an infinitely dilute perfect gas.^{13, 14, 15}

Atomic detail computations 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 of course part of the calculation.

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 control signals in many biological systems. The calcium control signal determines the speed of chemical reactions in cells the way 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.^{12, 16}

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 10^{13} steps, producing certain difficulties of accuracy and reproducibility. Reproducibility is difficult in simulations like these of systems with unlimited dependence of individual trajectories on initial conditions. Sampling errors can arise because of inaccessible regions of phase space in chaotic systems. Convergence of simulations to stable results is not guaranteed. These problems limit computations no matter how quickly they can be done.^{1, 2}

The spatial scale of the action potential is millimeters to centimeters or more. All-atom simulations must calculate atoms from 10^{-10} m to action potentials that spread millimeters—and propagate meters—if the simulation is to generate the nerve signal from an all atom simulation of 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. Nerve signals do not occur at equilibrium because nerve signals use flows of current through single channels to generate the propagating action potential.^{6, 7, 8} 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. Many biological systems are at equilibrium only when they are dead.

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’ (both bipolar and field effect transistors) are done every day in hundreds or thousands of laboratories. Techniques used in these simulations of computational electronics may be useful in all-atom simulations of biological systems.

All-atom simulations of flows through ion channels may be impossible. They may not be necessary, either. A multiscale analysis of ion flows through channels may be enough and much simpler. Multiscale analysis can use the laws of electricity, and of electrodiffusion, to simplify the simulation.

Certainly, the laws of electrodiffusion and electricity are not enough by themselves. 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 to calculate biological function, in all likelihood.^{17, 18}

All-atom simulations of ion channels remain an admirable dream, whether impossible or not. They form a productive, inspiring goal, **so long as the simulations are calibrated**. 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 help biologists and physicians in their everyday work. Uncalibrated, simulations can turn into a dreadful nightmare, producing results irrelevant to biological function, wasting lifetimes of scientists trying to compute the uncomputable.

Multi-scale analysis^{17, 18, 19} of simplified models will be needed to reach that goal, in my view, motivated and focused by what all-atom simulations cannot do.

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