# All-atom Simulations of Biological Function: the impossible dream

Bob Eisenberg

Dept. of Molecular Biophysics and Physiology
Rush University Medical Center
Chicago IL
60612

April 23, 2014

**Abstract:**

A few atoms can control biological function, so simulations in atomic detail are a goal of many scientists today, recognized by a recent Nobel Prize. But many biological functions like the propagating nerve signal (the action potential) involve atomic motions (well described by simulations) and macroscopic properties of enormous numbers ($\sim 10^{15}$) of atoms in surrounding solutions. All atom simulations of such systems are not possible. Coarse grained, multiscale analysis links simulation of atomic details to macroscopic biological function, computing atomic detail where it is important. The action potential is useful template for a general multiscale approach: the classical cable equations of Hodgkin and Huxley (also recognized by a Nobel Prize) provide the link between atomic details that need to be simulated, and biological function.

Finite numbers are sometimes so large that they seem infinite. But they are not. Computers are so powerful nowadays[§](1), that their power seems infinite too. It is not.(2,3)

Computers can calculate motions of all the atoms of proteins, a capability celebrated recently in a Nobel Prize to 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—so we focus our efforts on the coarse grain multi-scale analysis needed to understand and compute biological function.

We need to compute the motions of some atoms and their macroscopic effects. We do not need to do the impossible. We do not need to compute the motions of all atoms.

**Nerve Signal.** The nerve signal, for example, is an important biological function called the action potential that involves both the motions of some atoms of a protein and the averaged properties of enormous numbers of atoms millimeters away. The action potential carries information as an all-or-none 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 action potential. The electric currents are carried by two types of ions—sodium and potassium ions—as they move 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. The channels generate the voltage; the voltage helps control the channels. Macroscopic electric fields interact with atomic structures to make the nerve signal.

Sodium is abundant outside cells. Potassium is abundant inside cells. One channel type selectively catalyzes (4) the flow of sodium ions across the otherwise insulating lipid membrane. The other channel type selectively catalyzes the flow of potassium ions. These channels open in response to changes in the electrical potential across the voltage sensors of the channels, one after the other, loosely speaking. 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 of the action potential waveform. 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 proper termination of the action potential is an important determinant of the total energy consumption of a human being.(5,6)

The electric current carried across the insulating 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 (7,8), 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 interact this way, in a 0.3 mm diameter giant nerve fiber (from the

[§] Computer power is some $10^9$ greater than in 1965, when Moore *(1)* feared it could not continue to increase exponentially very much longer.

squid), with action potential wave length of 20 mm, if the action potential duration is 1 msec with velocity 20 m/sec.

**All-atom simulation.** 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 charge of one ion induces (voltage-dependent) polarization charge in the lipid membrane. That charge produces forces that act on every ion. The interactions are not just one pair at a time. Every ion is coupled to 'every' other ion over macroscopic distances, producing a staggering number of interactions, far beyond the number of pairwise interactions. Everything interacts with everything else, through the induced charge on the lipid membrane and induced charge at any other place 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.

**Multi-scale analysis of the action potential.** 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 coarse grain multiscale description of the action potential is known, thanks to the work of Hodgkin, Huxley, and Cole, (9-11) 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 (9-11) by Kelvin's cable equation, usually called the transmission line equation in the mathematics literature today.

Current through single protein 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 Neher (12) and Sakmann.(13) The voltage and time dependence of ensembles of noninteracting channels is simple to compute. An action potential can be reconstructed by summing the currents through single channels themselves (13) and then using the summed current in an intermediate scale equation (9-11), the transmission line equation.

A coarse grain 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, as it propagates in both space and time.

Ions moving through just one channel protein are an obvious candidate for all-atoms simulations if induced polarization charges (at dielectric boundaries inside and near channel proteins) are not too important. Such simulations may be possible, but are beyond our immediate reach (14) if we wish to compute single channel currents as they actually have been studied in hundreds or thousands of laboratories.(15)

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.(16-18)

**Calcium and Calibration.** Atomic detail computations of ionic mixtures containing calcium ions pose certain challenges for all-atom simulations. All-atom calculation of a trace concentration of intracellular calcium ion 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 a necessary part of the calculation.(2,3)

The calibration of the free energy (per mole) of calcium must be accurate because changes in this free energy (and in the concentration) serve as control signals in many biological systems. The resting concentration of calcium inside cells is typically 0.0000001 M. Four to ten-fold increases in calcium concentration control many biological systems. The calcium concentration determines the speed of many chemical reactions in cells the way a gas pedal controls the speed of a car. 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.(15,19) In addition, many channels become 'sick' (i.e., change properties pathologically sometimes irreversibly) if the concentration of calcium ions is changed too much, particularly on the inside of the channel. If the concentration of calcium is changed too much, many channels disappear from experiments that measure current, and are dead to the world, as far as those measurements are concerned, and cannot be studied. Realistic calibrated simulations reproduce all the properties of the systems they simulate. So channels will 'disappear' in accurate simulations in just those conditions in which they disappear in experiments. Uncalibrated simulations are likely to study 'invisible' (nonfunctional) channels or sick channels because simulations are likely to reproduce calcium concentrations incorrectly. Incorrect calcium concentrations would make the simulated channel nonfunctional, or sick, as they would in experiment. Uncalibrated simulations are likely to have different (effective) calcium concentrations each time the simulation is programmed or run in different conditions. Uncalibrated simulations are likely to be irreproducible, and give different results in different laboratories. Much confusion would result from these different results and progress would be slow.

Computations in atomic detail must also 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 chaotic systems. Individual trajectories are extremely sensitive to initial conditions in chaotic systems. Chaotic systems have different types of behavior depending on where the system starts. Simulations starting with one set of conditions miss some of the behaviors. Convergence of simulations to stable results is not guaranteed. These problems limit simulations no matter how quickly they can be done.(2,3)

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.

**Simulations Alive.** All-atom simulations of biological systems almost always have to be done away from equilibrium, in systems in which flows are involved, as they are in real 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.(9-11) 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.(20)

All-atom simulations of flows through ion channels may be impossible if induced polarization charges (at dielectric boundaries) are important. They may not be necessary, either. A coarse grain 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 and handle induced polarization charge at dielectric boundaries. (21)

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.(22,23)

**Impossible Dream.** 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, because most of biological function depends on ions in a quite sensitive way. Uncalibrated, simulations can turn into dreadful nightmares, producing results irrelevant to biological function, wasting lifetimes of scientists trying to compute the uncomputable.

I believe coarse grain multi-scale analysis (21-23) of simplified models will be needed, motivated and focused by what all-atom simulations cannot do but biology does so very well.

## References


1. Moore, G. E. 1965. Cramming more components onto integrated circuits. Electronics Magazine. 38:114–117.

2. Maginn, E. J. 2009. From discovery to data: What must happen for molecular simulation to become a mainstream chemical engineering tool. AIChE Journal 55:1304-1310.

3. Post, D. E. and L. G. Votta. 2005. Computational Science Demands a New Paradigm. Physics Today 58:35-41.

4. Eisenberg, R. S. 1990. Channels as enzymes: Oxymoron and Tautology. Journal of Membrane Biology 115:1–12. Available on arXiv as http://arxiv.org/abs/1112.2363.

5. Magistretti, P. J. 2009. Low-Cost Travel in Neurons. Science 325:1349-1351.

6. Alle, H., A. Roth, and J. R. P. Geiger. 2009. Energy-Efficient Action Potentials in Hippocampal Mossy Fibers. Science 325:1405-1408.

7. Jack, J. J. B., D. Noble, and R. W. Tsien. 1975. Electric Current Flow in Excitable Cells. New York: Oxford, Clarendon Press.

8. Gabbiani, F. and S. J. Cox. 2010. Mathematics for Neuroscientists. New York: Academic Press.

9. Huxley, A. 2000. Sir Alan Lloyd Hodgkin, O. M., K. B. E. 5 February 1914-20 December 1998. Biographical Memoirs of Fellows of the Royal Society 46:221-241.

10. Huxley, A. F. 1992. Kenneth Stewart Cole. Biographical Memoirs of Fellows of the Royal Society 38:98-110 , see http://books.nap.edu/html/biomems/kcole.pdf

11. Huxley, A. F. 2002. From overshoot to voltage clamp. Trends in neurosciences 25 553-558.

12. Neher, E. 1997. Ion channels for communication between and within cells Nobel Lecture, December 9, 1991. In Nobel Lectures, Physiology or Medicine 1991-1995. N. Ringertz, editor. World Scientific Publishing Co. Singapore. 10-25.

13. Sakmann, B. and E. Neher. 1995. Single Channel Recording. New York: Plenum. 700 p.

14. Eisenberg, B. 2010. Multiple Scales in the Simulation of Ion Channels and Proteins. The Journal of Physical Chemistry C 114:20719-20733.

15. Hille, B. 2001. Ion Channels of Excitable Membranes. Sunderland: Sinauer Associates Inc. 1-814. p.

16. Fawcett, W. R. 2004. Liquids, Solutions, and Interfaces: From Classical Macroscopic Descriptions to Modern Microscopic Details. New York: Oxford University Press. 621 p.

17. Laidler, K. J., J. H. Meiser, and B. C. Sanctuary. 2003. Physical Chemistry: BrooksCole, Belmont CA. 1060 p.

18. Eisenberg, B. 2013. Interacting ions in Biophysics: Real is not ideal. . Biophysical Journal 104:1849-1866.

19. Alberts, B., D. Bray, J. Lewis, M. Raff, K. Roberts, and J. D. Watson. 1994. Molecular Biology of the Cell. New York: Garland. 1294 p.

20. Vasileska, D., S. M. Goodnick, and G. Klimeck. 2010. Computational Electronics: Semiclassical and Quantum Device Modeling and Simulation. New York: CRC Press. 764 p.

21. Eisenberg, B., Y. Hyon, and C. Liu. 2010. Energy Variational Analysis EnVarA of Ions in Water and Channels: Field Theory for Primitive Models of Complex Ionic Fluids. Journal of Chemical Physics 133:104104

22. Gillespie, D. 2008. Energetics of divalent selectivity in a calcium channel: the ryanodine receptor case study. Biophys J 94:1169-1184.

23. Roux, B. 2012. Ion binding sites and their representations by reduced models. The journal of physical chemistry. B 116:6966-6979.

**Acknowledgement**

This work was supported by the Bard Endowed Chair of Rush Medical College.