

Conformations and Currents Make the Nerve Signal

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Abstract. Conformation changes control the function of many proteins and thus much of biology. But it is not always clear what conformation means: is it the distribution of mass? Is it the distribution of permanent charge, like that on acid and base side chains? Is it the distribution of dielectric polarization? Here we point out that one of the most important conformation changes in biology can be directly measured and the meaning of conformation is explored in simulations and theory. The conformation change that underlies the main signal of the nervous system produces a displacement current—NOT an ionic current—that has been measured. Macroscopic measurements of atomic scale currents are possible because total current (including displacement current) is everywhere exactly the same in a one dimensional series system like a voltage clamped nerve membrane, as implied by the mathematical properties of the Maxwell Ampere law and the Kirchhoff law it implies. We use multiscale models to show how the change of a single side chain is enough to modulate dielectric polarization and change the speed of opening of voltage dependent channels. The idea of conformation change is thus made concrete by experimental measurements, theory, and simulations.

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1 Introduction

Conformation changes regulate and control an enormous range of functions, as biochemists imagined they would from the beginning of molecular biology [1,2]. Conformation changes are no longer ideas. Conformation changes now have exact coordinates of

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tens of thousands of atoms in multiple conformations, thanks to the remarkable advances of structural biology [3].

Despite these wonderful advances, little is known about the physical or physiological correlates of these conformation changes. How do the atoms move in time? How do the changes in atomic locations control biological function? How do the locations reveal themselves as measurable physical properties of the protein?

One place these questions can be (mostly) answered is in the proteins that form the voltage activated sodium channel of nerve, the ion channel Na_V and the voltage activated potassium channel of nerve K_V [4]. These channels are responsible for signaling in the nervous system. Conformation changes of these channels on the atomic scale produce electrical signals that move meters and carry nearly all long range information in the nervous system. Indeed, the propagating voltage signal of nerve fibers—the action potential[†]—may have been the first binary signal to be studied in electrical detail [5], by an undergraduate, against notable opposition, at the time [6]. The binary property of the action potential is called ‘all or none’ in the biological literature [7, 8]. These Cambridge dons no doubt would be amused at High Table (at Trinity Cambridge) that an all-or-none, base-2 binary signal is handily misnamed as ‘digital’ (base-10) in popular language today.

Voltage activated channels have been studied in great detail. Indeed, their study has formed the substrate for most of our knowledge of channels, if not membranes, as recognized in a sequence of Nobel Prizes, to Hodgkin and Huxley [9-11], who worked in Adrian’s department; Neher and Sakmann [12]; and MacKinnon [13]. The work of Hodgkin and Huxley has formed the keystone of membrane biophysics, as it was inherited [14] and spread [15-17] to the biological community as a whole.

Hodgkin and Huxley, following Cole [9, 18, 19], recognized even before the Second World War that the crucial mechanism generating the action potential waveform was a voltage sensitive ‘conductance’, as they each explained to a nineteen-year-old student many years ago (RSE personal communication). We now know that the voltage sensitivity Cole, Hodgkin, and Huxley observed in whole nerve fibers comes from voltage activated protein channels [20, 21], first proposed as voltage activated pores by Lorin Mullins [22, 23], to the best of our knowledge. Voltage acts on the sodium and potassium channels Na_V and the nerve K_V by changing the fraction of time individual channel proteins conduct current and in that sense are open. Mullins identified three key questions: the origin of selectivity [24-30] the mechanism of voltage dependence [31-37], and the difference in the time course of currents through the sodium and potassium pores, as he called them.

The crucial step in the action potential is the flow of current inwards across the membrane, through open Na_V channels, that use a gradient of concentration to create an electrical current. The open sodium Na_V channels allow Na ions to move down their gradient of electrochemical potential changing the internal potential of the nerve from negative to positive and carrying electrical current into the nerve fiber. Note that the concentration

[†]‘Potential’ is usually a number in physical science. The action potential is a phenomenon, not a number, in biological science. It is best represented as a waveform $V(x,t)$ in physical and mathematical language.