Voltage Sensor of Sodium Channels: Natural Nanotechnology

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Voltage signals in biology are binary 'action potentials' that propagate meters in nerve fibers diameter $= 10^{-6}$m and coordinate contraction in skeletal muscle and the heart. These signals are conducted by ions, not electrons. Ions are massive so movement is dominated by friction. Ionic signals require continual regeneration to travel meters, much as electron signals require regeneration to travel $> 10^{6}$ m through oceans in submarine cables. Regeneration in nerve fibers is provided by ion channel proteins, particularly sodium channels, that convert the gradient of chemical potential of sodium into electric current. Sodium is much more concentrated outside than inside cells, 0.14 vs. ~0.05 Molar. Sodium channels are proteins with a hole down their middle embedded in a thin 2×10^{-9}m lipid membrane that is nearly an ideal dielectric. Sodium channels are closed at rest but respond to small positive going signals by opening, allowing sodium ions to carry current across the otherwise insulating membrane. The response of the sodium channel to voltage is a crucial determinant of the speed of signaling in nerves, and of the regularity of the heart beat. Evolution has created an atomic machine called the voltage sensor to open sodium channels as voltage goes positive. Every atom's location is known in crystals of the channel protein. Channel structures are a triumph of anatomical science but structures do not contain chemical potentials to energize function, nor do they conduct currents or action potentials. A model and a theory are needed for that.

We [1] constructed an electromechanical model showing how the voltage sensor responds to potential as positively charged atoms (of the arginine side chains of the protein) are pulled through a dielectric plug. Arginine movement creates a voltage and time dependent displacement current in a nonlinear capacitor. That displacement current flows into ionic solutions outside the nerve and can be collected with great fidelity by amplifiers in a voltage clamp apparatus. The resulting 'gating currents' have been studied in hundreds of papers [2].

Few atomic scale machines, or changes in shape of proteins, are known in such experimental detail, although conformation changes control a large fraction of biological processes. Our one dimensional model includes essential structural details and accounts for many, but not all of the features of gating currents observed in experiments.

[1] T.-L. Horng, R.S. Eisenberg, C. Liu, and F. Bezanilla, Biophysical Journal, **116**, 270 (2019)

[2] F. Bezanilla, and E. Stefani Methods in Enzymology, **293**, 331(1998); F. Bezanilla, Nat Rev Mol Cell Biol **9** 323 (2008); F. Bezanilla and E. Perozo Adv. Protein Chem., **63,** 211 (2003)

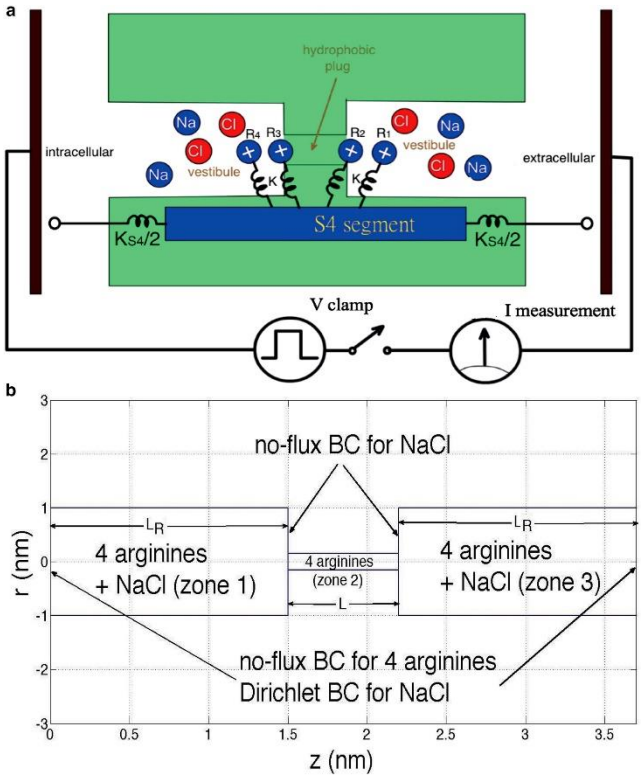

Fig. 1 Setup of Voltage Sensor and Gating Current Estimation from ref. [1]

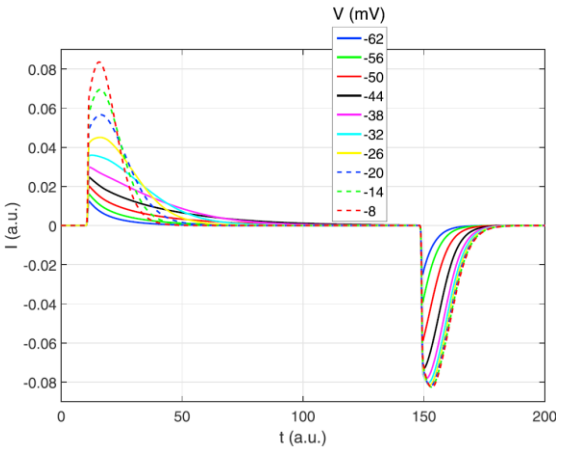

Fig. 2 Gating current response to rectangular voltage V, from ref. [1]

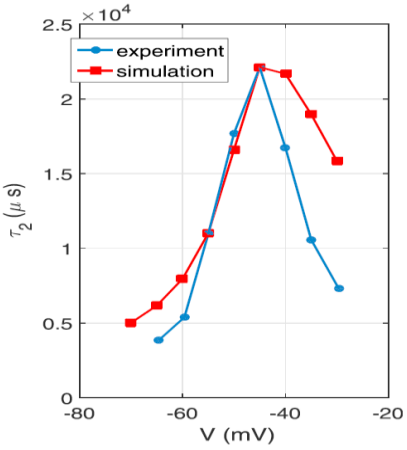

Fig.3: Experiment vs. Simulation. OFF Time constant τ_2 vs. Voltage V, from ref. [1]

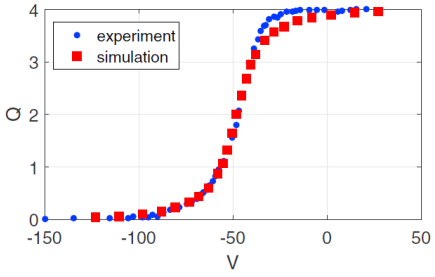

Fig. 4. Charge Q vs. Voltage V, from ref. [1]