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Shockley-Ramo theorem measures conformation changes of ion channels and proteins

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Abstract Theorems are rarely used in biology because they rarely help the descriptive experimentation to which biologists are devoted. A generalization of Kirchoff's current law—the Shockley-Ramo (SR) theorem [1–6]—seems an exception. SR allows interpretation of macroscopic scale 'gating' currents associated with atomic scale charge movements within proteins.

Keywords Ion channels · Shockley-Ramo · Gating current

1 Introduction

Nonlinear displacement currents have been measured in biology [7] and used to estimate changes in shape ('conformation') of proteins in hundreds of publications [8–19] since Hodgkin and Huxley [20] postulated their existence and Schneider and Chandler and Bezanilla and Armstrong observed them [9, 21], using an ingenious signal averager [13] and clever algorithm that apparently had not been used in electrical engineering.

Despite this extensive experimentation, the relation of the currents recorded and underlying atomic motions within the protein was not understood. Energetic arguments have been used to link atomic motions to charge movements measured in an external circuit. Unfortunately, energetic considerations are best suited to isolated closed systems of classical thermodynamics where total energy (e.g., of the protein) is constant. Energetic considerations are difficult to use in open complex systems like a protein in a membrane, from which gating currents are measured. In open systems, heat, matter, energy, and charge flow in unknown amounts in and out of proteins—and are stored in the protein on long time scales of inactivation [22–24] and desensitization. In open systems, electrical energy supplied to the electrodes for milliseconds and reoirted as 'gating current' or 'gating charge' is not easily related to the energy of the channel protein.

The Shockley-Ramo theorem replaces these energetic arguments and allows a new view of the conformation currents and internal dynamics of proteins in general. Fortunately, general conclusions of previous work are justified by the theorem, although specific molecular interpretations are not.

2 Conformations and currents in proteins

Proteins are the central objects of molecular biology—even of biology in general—because they perform most of the functions of life. Proteins are complex nearly macroscopic molecular machines. Many of their functions involve motions of charges within the protein, just as many functions of semiconductor devices involve motions of charges within them. Atomic movements inside proteins are rarely measured convincingly, particularly those directly relevant to biological function. Here, we show that SR allows convincing interpretation of charge movements within proteins.

3 Shockley-Ramo and voltage clamp

Almost all our knowledge of electrical signals in nerve and muscle fibers [25, 26] comes from measurements of currents

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using the voltage clamp protocol introduced by Cole [27, 28] and brilliantly exploited and extended by Hodgkin and Huxley [26, 29]. The voltage/patch clamp technique can measure currents through single channels [30–32] but gating currents have not been measured in patch clamp or in single channels reconstituted into artificial lipid bilayers [33, 34], as far as we know, because the signal is too small and fast and noise too large [35].

Voltage clamp uses macroscopic reversible Ag ‖ AgCl 'current' electrodes to apply ionic current in series with channels and membranes. Another pair of ('voltage') electrodes is used to estimate potential across the membrane and channel. Feedback supplies current needed to control the potential between voltage electrodes to the desired waveform, typically a step function or series of steps, because the system is far too nonlinear to allow easy analysis of triangular, sinusoidal, or stochastic inputs. Because the electrodes are in series with channel and membrane, the measured current (flowing through the external circuit between current electrodes) equals the current flowing through the membrane and channel protein, and through parallel parasitic admittances.

The SR theorem relates the measured current to the atomic motion of charge

$$I = \frac{1}{1 \text{ volt}} \sum_j q_j \mathbf{W}(\mathbf{r}_j) \cdot \mathbf{v}_j \tag{1}$$

We follow Yoder et al. (1997): $\mathbf{v}_j$ and $\mathbf{r}_j$ are the instantaneous velocity and position vectors, respectively, of the particle j with charge q_j when the clamped voltage E_m is applied. $\mathbf{W}$ is the electric field that would be generated by removing *all* particle charges (mobile and fixed) from the domain and setting the clamped voltage to 1 volt. The only charges contributing to $\mathbf{W}$ are (1) the charges needed to impose ground potential and 1 volt at the voltage electrodes and (2) the charges induced by the electrode charges on and in the dielectrics of the domain. $\mathbf{W}$ is *not* the field that is present when the clamped voltage E_m is applied and the current is observed. The field resulting from the clamped voltage E_m enters the equation indirectly, through the positions $\mathbf{r}_j$ and velocities $\mathbf{v}_j$ that it imparts to mobile charged particles. The sum in Eq. (1) is over all mobile particle charges q_j in the domain; that is, it is the sum of all charges q_j moving with velocity $\mathbf{v}_j$ at the time the sum is taken, including both those that belong to the channel protein and all ions in bath solutions and in the pore of the channel.

The measured current I of Eq. (1) is converted to the charge (e.g., the gating charge reported extensively in the biological literature) by integrating over arbitrary trajectories that connect known starting locations $\mathbf{r'}_j$ of the particles to known ending locations $\mathbf{r}''_j$. This integration yields the gating charge measured in an external circuit connected to the current electrodes:

$$Q = -\frac{1}{1 \text{ volt}} \sum_j q_j \left[U\left(\mathbf{r}''_j\right) - U\left(\mathbf{r}'_j\right) \right] \tag{2}$$

$\boldsymbol{U}(\mathbf{r})$ is the potential of field $\mathbf{W}$, cf. Eq. (1).

An expression for external charge has been derived by Roux [36] using a linearized Poisson-Boltzmann equation to describe equilibrium systems without current flow. Channel systems, however, function with large current flows and are usually nonlinear. Often, $U > kT/e$.

Equations (1) and (2) can estimate charge movements in proteins from charge motions in any part of the system in series with the channel protein, provided that the movements of all charges (for example, all ions in the bathing solutions) are included in the summation. If the domain is geometrically enlarged, the electrical travel [37] of all charges is reduced, but charges newly included in the domain are now in the summation. For a chosen domain (large or small), the SR theorem exactly computes the current measured in that geometry.

The optimal choice of domains for SR has not been determined. Optimizing the domain could be of considerable help. Simulations of channels are frustrating because most of the computational effort concerns uninteresting ions in the baths, not the biologically and chemically important charges in the pore or channel protein [14].

4 Discussion

We include extensive literature references here because biological applications of SR [7, 37] are not well known to the electronics community.

The biological significance of 'gating' current perceived long ago is reinforced by our derivation using the SR theorem. Specific atomic interpretations are strongly affected, however, as discussed in detail in one case by [37].

Simulations of ionic current containing larger numbers of charged particles can be dramatically improved by use of Eq. (1) to estimate current through a channel, instead of counting particles that cross boundaries [14, 37–41].

5 Conclusion

The Shockley-Ramo theorem allows unambiguous computation of the macroscopic gating current produced by atomic movements within channel proteins. SR justifies the experimental method of measuring gating (i.e., conformation) currents. It thereby supports their biological significance. Analysis based on SR will constrain and most likely change the specific molecular and atomic interpretation of this vast experimental literature.

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