

# Shockley-Ramo Theorem Measures Conformation Changes of Ion Channels and Proteins

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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 'gating' currents associated with atomic scale charge movements within proteins.

Conformation currents have been measured in biology [7] and used to estimate atomic motions within proteins in hundreds of publications [8-14] since Hodgkin & Huxley [15] postulated their existence, and Schneider & Chandler observed them [16] with a clever algorithm that apparently has 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 such an open system, heat, matter, energy, and charge flow in unknown amounts in and out of proteins—and is stored in the protein on long time scales of inactivation, and desensitization. In open systems, electrical energy supplied to the electrodes for a few milliseconds 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.

## SHOCKLEY-RAMO AND VOLTAGE CLAMP

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

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

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 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:

$$Q = -\frac{1}{1\text{volt}} \sum_j q_j U(\mathbf{r}_j) - U(\mathbf{r}_j) \quad (2)$$

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

An expression for external charge has been derived by Roux [17] for equilibriums systems without current flow with  $U = kT/e$ . Channel systems, however, function with large current flows and are usually nonlinear, often with  $U > kT/e$ .

Eq (1) & (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. 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 computational effort concerns uninteresting ions in the baths, not the biologically and chemically important charges in the pore or channel protein. [10]

#### DISCUSSION

We include extensive literature references here because biological applications of SR [7, 18] 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 [18]

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. [10, 18-22]

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