Relating microscopic charge movement to macroscopic currents: the Ramo-Shockley theorem applied to ion channels

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ABSTRACT

Since the discovery of gating current, electrophysiologists have studied the movement of charged groups within channel proteins by changing potential and measuring the resulting capacitive current. The relation of atomic-scale movements of charged groups to the gating current measured in an external circuit, however, is not obvious. We report here that a general solution to this problem exists in the form of the Ramo-Shockley theorem. For systems with different amounts of atomic detail, we use the theorem to calculate the gating charge produced by movements of protein charges. Even without calculation or simulation, the Ramo-Shockley theorem eliminates a class of interpretations of experimental results. The theorem may also be used at each time step of simulations to compute external current.

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INTRODUCTION

Since Schneider and Chandler (1973), the internal movements of channel proteins have been estimated by measuring gating current (reviewed by Armstrong, 1975, 1981; Almers, 1978; Sigworth, 1994; Bezanilla, 2000; Hille, 2001). Gating current is the capacitive current (recorded as electron flow between macroscopic electrodes) produced by the movement of charged atoms in a channel protein, when the voltage between the electrodes is changed. It is distinct from the conduction current produced by the flow of ions through the open channel and can be separated from total measured current in a variety of ways, which give quite consistent results. Experiments using site-directed mutagenesis have since identified charged amino acid residues of channels that contribute to voltage-dependent gating (Stühmer et al., 1989) and gating current (Aggarwal and MacKinnon, 1996; Seoh et al., 1996).

To interpret these measurements quantitatively, one must know the relationship between the atomic-scale charge movements and the externally recorded current. Such a relation has recently been derived using a particular equilibrium model of statistical mechanics (linearized Poisson-Boltzmann theory) to describe the charges in the bathing solutions (Roux, 1997). Here, we present a general solution, one that has been known for some time in computational electronics. An extension of Kirchoff's current law, the Ramo-Shockley theorem, links current flowing in the external circuit to charge movement inside the system (Shockley, 1938; Ramo, 1939). Recent generalizations of the original theorem directly relate microscopic charge movements and macroscopic current in complex systems. We apply the Ramo-Shockley theorem to gating current experiments and show how it can be used to calculate measured charged movements

from atomic models. We use the theorem to rule out certain interpretations of experimental results and to compute external currents in simulated systems with high efficiency. The generalized theorem provides a concise formula and model-independent results that are applicable to many biophysical problems.

THE RAMO-SHOCKLEY THEOREM

In voltage clamp experiments used to study currents through a biological membrane, two electrodes impose a controlled voltage across a domain that contains different dielectrics and charged particles (ions in the baths and channels, and charged groups in the protein) (Hodgkin *et al.,* 1952). The charged particles move because of thermal agitation (heat) and the local electric field. The current measured by the external circuit has two components: the particle current carried by ions entering or leaving the electrodes and the displacement current. The displacement current is the movement of charge (electrons) in the electrodes induced by changes in the electric field caused by the movement of all the charged particles that do *not* reach the electrode (Jackson, 1999; Purcell, 1985, p. 371; Feynman *et al.*, 1964, for example, Ch. 23, p. 2). The Ramo-Shockley theorem equates the total current (particle plus displacement) measured in the external circuit with the microscopic motion of the charged particles in the domain between the electrodes.

Voltage-clamp experiments measure the total current I flowing into an electrode held at voltage E_m with respect to a grounded electrode. The Ramo-Shockley theorem (references given below) states that this current is

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

We use the nomenclature of Yoder *et al*. (1997) where $\mathbf{v}_j$ 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. **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 **W** are the charges needed to impose ground potential and 1 volt at the electrodes and charges induced by the electrode charges on and in the dielectrics of the domain. **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 the bath solutions and the pore of the channel.

The measured current *I* of Eq. 1 is converted to charge 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 externally measured gating charge:

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

where $U\left(\mathbf{r}\right)$ is the potential at location **r** that would be generated by removing *all* particle charges (mobile and fixed) from the domain and setting the clamped voltage to 1

volt. Again, the potential field present while the clamped voltage is held at E_m enters the equation only indirectly; it determines the locations of the charged particles.

The theorem was derived independently by Shockley (1938) and Ramo (1939) and is commonly used in computational electronics as a generalization of Kirchoff's current law that includes displacement current. The original derivations assumed negligible magnetic and radiation effects (that is, they assumed quasi-electrostatics) to describe electron transport in vacuum tubes. The theorem has subsequently been generalized to systems containing inhomogeneous linear dielectrics (Pellegrini, 1986; Kim *et al.,* 1991). An extended version for the full electrodynamic regime has been derived (Yoder *et al.,* 1996, 1997). We use the generalized quasi-electrostatic version of the theorem.

To illustrate the theorem, we give a simple derivation for a capacitive linear circuit that applies to a voltage-clamped system. Imagine that a vanishingly small conductive sphere *j* is placed at location $\mathbf{r}_j$, where it forms capacitors C_{jR} and C_{jG} (Fig. 1). The surfaces of capacitor C_{jR} are the conductive sphere and the recording electrode *R* (the electrode where E_m is applied in a voltage clamp experiment). The surfaces of capacitor C_{jG} are the conductive sphere and the second (grounded) voltage clamp electrode *G* and any other grounded surfaces.

We consider two experiments. In the first experiment, labeled (1), a single, mobile, charged particle with charge q_j is placed in the small conductive sphere located at $\mathbf{r}_j$ and the electrode *R* is set to zero potential. The charge induced on *R* (the charge that the voltage clamp applies to maintain *R* at zero potential) will be

$$q_R^{(1)} = q_j \frac{C_{jR}}{C_{jR} + C_{jG}}. \tag{3}$$

The charge induced on the electrode can be computed by Eq. 3 for any q_j if the calibration factor $C_{jR} \Big/ \left(C_{jR} + C_{jG} \right)$ is known. We determine this factor in a separate, second experiment, labeled (2).

In the second experiment, the charge of all charged particles is removed (that is, $q_j^{(2)} = 0$), and a voltage of 1 volt is imposed on *R*. The capacitors C_{jR} and C_{jG} now form a voltage divider, and the resulting voltage at $\mathbf{r}_j$ is

$$U^{(2)}\left(\mathbf{r}_j\right) = \frac{C_{jR}}{C_{jR} + C_{jG}} \quad \left(1 \text{ volt}\right) \tag{4}$$

Combining the results of the two experiments, we have

$$q_R^{(1)} = \frac{1}{1 \text{ volt}} q_j U^{(2)}\left(\mathbf{r}_j\right). \tag{5}$$

This treatment can be extended to a system of many small spheres *j* that contain charges q_j ; by superposition, we then have

$$q_R^{(1)} = \frac{1}{1 \text{ volt}} \sum_j q_j U^{(2)}\left(\mathbf{r}_j\right) \tag{6}$$

If we move the charges *j* from locations $\mathbf{r}_j$ to locations $\mathbf{r}_j$, the electrode charge will change by

$$Q = \frac{1}{1 \text{ volt}} \sum_j q_j \left[U^{(2)}\left(\mathbf{r}_j\right) - U^{(2)}\left(\mathbf{r}_j\right) \right] \tag{7}$$

which is the Ramo-Shockley theorem in the form of Eq. 2.

APPLICATIONS TO ION CHANNELS

Defining electrical coordinate and electrical travel

For a given dielectric geometry of the baths, membrane, and channel, Eq. 2 relates induced electrode charge with microscopic charge and the function $U(\mathbf{r})$. The geometric coordinate $\mathbf{r}$ is thereby mapped onto the electrical coordinate $U(\mathbf{r})/(1\text{ volt})$ and the geometric travel $\mathbf{r}_j \quad \mathbf{r}_j$ onto the electrical travel, T_{el}, of the charge j:

$$T_{el} \quad \frac{1}{1\text{ volt}} \; U\left(\mathbf{r}_j\right) \quad U\left(\mathbf{r}_j\right) \; . \tag{8}$$

The potential U is found by solving the Poisson equation for the channel geometry with 1 volt of potential on the electrode R and all the linear dielectrics in place, but no charged particles of any kind (neither fixed or mobile structural charges, nor bath ions). The only charges present are the electrode charges that maintain boundary conditions like the potential of 1 volt and polarization charges induced by the electrodes on and in the dielectrics. The dielectrics that we include are linear and isotropic; their polarization settles much faster than the experimentally observable charge movements. The effects of these linear dielectrics are expressed in Eqs. 1 and 2 by the field $\mathbf{W}$ or the potential U. A voltage-gated channel will add what might be described as a nonlinear, time-dependent, and probably location-dependent anisotropic polarizability to the membrane; charge movements underlying such complex behavior reflect the interesting gating movements of the channel protein. They are included as explicit charge movements in the sums of Eqs. 1 and 2.

Figs. 2 and 3A,B show calculations of electrical coordinate maps, found by solving the Poisson equation numerically on a domain in which bath solutions, lipid, and

protein are represented as linear, isotropic dielectrics. The dielectric geometries shown are low-resolution representations of an open conduction pore (Fig. 2) and of a "gating pore" that allows an S4 segment to slide back and forth through the membrane (Fig. 3). Note that all protein charges and ions are removed from the system, as is necessary for the determination of electrical coordinates. The domain is cylindrical about the vertical axis and is represented in an axial cross-section. The points **r** of each contour line are each at the same potential U; they are plotted at increments of $\Delta U = 0.05$ volt (*solid lines*), and some at $\Delta U = 0.025$ volt (*dashed lines*). Each electrical coordinate $U(\mathbf{r})/(1\text{ volt})$ is a surface and not a unique location **r**; all points of the surface represented by a contour line are at the same electrical coordinate from the external voltage clamp electrode.

A map of electrical coordinates can help predict the gating charge measured in a thought experiment, for example, if a charge q were moved between two locations. According to Eq. 2, the gating charge would be $Q = q\Delta T_{el}$, where T_{el} can be read from the map. Note that manipulating one or many charges this way does not affect the map; the map changes only when the geometry of the linear dielectrics changes. If many charges are moved simultaneously, their contributions to the gating charge sum algebraically. This additivity itself may appear surprising because it holds in a domain of condensed matter. The invariance of the map and the additivity of individual readings make the "electrical travel" defined via the Ramo-Shockley theorem a useful concept.

Figs. 2 and 3A are computed in a small domain that is typical for a simulation. In actual experiments, electrodes are much farther away from the membrane, making the electrical travel across each bath much larger than the electrical travel across the mem-

brane. This leads to an apparent paradox: in the experimental situation, movement of structural charge in the membrane itself contributes very little to the measured charge Q in Eq. 2, since the structural charge is scaled by a small electrical travel. The paradox is due to the fact that the electrical coordinate is computed with all source charges removed from the interior of the system (including the ions in the bathing solutions), whereas the external charge movement Q is computed from the movements of all mobile charges of the system (including the ions in the bathing solutions). In a system with deep baths, Q is dominated by the contributions of the bath ions that move in response to the movement of charges in the membrane (and thus conduct the gating current towards the electrodes).

In principle, Eqs. 1 and 2 can be applied to any domain in a circuit that is bounded by surfaces where controlled potentials are applied, provided that the movements of *all* charges in the domain (for example, all ions in the bathing solutions) are included in the summation. If the domain is geometrically expanded the electrical travel of all charges is reduced, but charges newly included in the domain are appended to the summation. For a chosen domain (large or small), the Ramo-Shockley theorem *exactly* computes the current that would be measured in an experiment performed in that geometry.

Realistic simulations of an actual biological experiment are frustrating because most of the computational effort concerns ions in the baths, not charges in the pore or channel protein of biological interest. It is more efficient to use a multi-scale approach. At one level of multi-scale approach, one could treat the bathing solutions as ideal conductors. Such idealized baths extend the electrodes to the boundaries of the membrane and protein and reduce the summations in Eqs. 1 and 2 to the movements of only the charges within the channel/membrane. The summations then give an upper bound to the

measured gating charge because each geometrical movement results in the maximal possible electrical travel. Such a map is shown in Fig. 3C; later we show how an upper limit of the gating charge helps explain experimental results.

Comparison with a linear equilibrium analysis

An expression for the external charge similar to Eq. 2 has been derived by Roux (1997) and used by Islas and Sigworth (2001). Roux sought to include the effects of the bath ions into the electrical potential that defines the electrical coordinate (the potential $U(\mathbf{r})$ in our nomenclature), much like the polarization charge of linear dielectrics has been included in the potential used in the generalized Ramo-Shockley theorem (Eq. 2). Including the bath ions this way requires that the polarization of the bath electrolyte solutions be linear in the applied voltage. Roux linearizes bath polarization by describing the bath electrolytes in the linearized Poisson-Boltzmann (PB) theory, which assumes that the interaction between charges is significantly smaller than 1 kT. This linearization renders the electrical capacitance of the double layers at the membrane-bath boundaries independent of the applied voltage, and thus yields a well-defined electric coordinate for the protein charges. Application of this linearized theory to scenarios where the protein bears charges (such as a cluster of gating charges that can be exposed to the baths) requires that the screening of these charges by bath ions be adequately described by linearized PB theory. Systems containing charges of high density (like concentrated electrolyte solutions), however, cannot be described by linearized PB theory if the charge interaction is more than a fraction of kT, as it is likely to be. Although one expects that only a small fraction of the applied voltage drops over the boundary layers of the baths (because of the small dielectric constant of the membrane), the actual error of Roux's

approximation needs to be assessed for the specific charge distribution on the protein, which likely requires an explicit simulation of the bath solutions (Boda *et al*., 2004). Upper and lower bounds for the screening effect of bath ions, however, could be estimated, at less computational cost, from computations without bath ions: one where the electrode surface is set directly at the membrane, and another where the electrode surface is set back several Debye lengths (Fig. 3).

In deriving an electric coordinate using an equilibrium theory of screening, Roux assumed that the baths are in thermodynamic equilibrium. Given that ions in solutions can form screening configurations very fast (~1 ns), this approximation appears well justified in studies in which the charge movements of interest are relatively slow (such as gating currents). On the other hand, Roux's *ansatz* cannot be used wherever bath ions can flow from one side of the membrane to the other, such as through an open ion channel (Roux, 1997). By contrast, the Ramo-Shockley theorem applies to all situations, equilibrium or non-equilibrium, up to the time scale where magnetic and radiation effects become significant (Pellegrini,1986).

Interpreting gating charges

When applied to gating charge experiments, the Ramo-Shockley theorem expresses gating charge as the product of the physical charge and the well-defined electrical travel of the physical charge, summed over all mobile charges present in the domain. To apply Ramo-Shockley to a specific example, we consider an experiment by Seoh *et al*. (1996) that produced an unforeseen result. Seoh *et al*. created mutants in which a charged residue of a membrane-spanning segment in a K channel monomer was replaced by a neutral residue. They found that deleting a positive charge of the S4

segment eliminated up to $7e_0$ of measured gating charge. (e_0 is the proton charge.) Because of the tetrameric structure of the protein, one might expect that at most $4e_0$ of gating charge would be eliminated in such mutants. In the Seoh *et al*. experiment, upper bounds for the magnitude of the physical charges in the wild type and mutants are known. The movements of the charges in the protein are not known. It is not clear a priori if the movement of these atomic charges (in the native protein) could contribute a disproportionately large amount to the gating charge recorded by the external electrodes.

Eq. 2 allows one to narrow the interpretation of these results. For instance, one might think that even if the charges move between the same starting and ending points, the measured charge would depend on the local electric field in which the physical charges travel. If this were true, charges traveling across a region of high local field strength might contribute disproportionately to the measured gating charge, or their deletion might reduce gating charge disproportionately. Eq. 2 states, however, that neither structural charges nor their polarization charges can exert such an amplifying effect on the relation between atomic and measured charge movements; if the mobile charges move between the same points $\mathbf{r}_j$ and $\mathbf{r}_j$, the electrical travel

$U\left(\mathbf{r}_j\right) \quad U\left(\mathbf{r}_j\right) \Big/ 1 \text{ volt}$ does not change because neither the particle charges nor polarization charges induced by the particle charges contribute to $U\left(\mathbf{r}\right)$.

The gating process is, of course, not independent of the local electric field present where and when the charges move. In particular, changes in the local electric field can change the electrical travel that the mobile charges actually undergo when perturbed by an applied voltage, although they do not change the map defining electrical coordinates.

For example, deletion of some of the mobile structural charges of an S4 helix that moves as a solid body likely reduces the total electric force acting on the helix. Consequently, the geometric travel of the mutated helix, and of the undeleted S4 charges on it, might be reduced. The positions $\mathbf{r}_j$ and/or $\mathbf{r}_j$ would change, reducing the measured gating charge.

Within the constraints set by the Ramo-Shockley theorem, the experiment of Seoh *et al*. can be interpreted in two ways: (1) that deletion of charges q_k restricts in some way the electrical travel of the other mobile charges q_j (changing $\mathbf{r}_j$ and/or $\mathbf{r}_j$) or (2) that the mutant channels have a different dielectric geometry from the native channel, changing $U(\mathbf{r})$. Of course, the experiment might both restrict electric travel and change the dielectric geometry.

Ramo-Shockley and energy

Electrophysiologists have long used effective parameters to assign energy contributions to physical processes inferred from experiments. For example, Hodgkin and Huxley (1952) hypothesized that charged particles moving in the membrane electric field do the work $W = ze_0E_m$ on the membrane component that creates the voltage dependence of the Na^+ and K^+ conductances. Here, E_m is the membrane potential, z the effective valency of the particle, and e_0 the proton charge. Similarly, Woodhull (1973) described the voltage-dependent block of Na^+ current by protons assuming that the "potential energy" of the blocking proton included a contribution $W = e_0 \ E_m$, where is the "fraction of membrane potential acting at the site." Whereas the relationship between the moving microscopic charges and the externally recorded charge is given by the Maxwell Equations (which lead to the Ramo-Shockley theorem), the definition of effective charges

is based on energetics.

Energetics, however, are difficult to assess in an open system (such as an ion channel), which exchanges heat, charge, matter, and energy with the environment. *Heat* flows between the channel and baths because (1) the motion of ions in the pore and the motions of gating particles of the protein involve atomic collisions, and (2) the ions typically flow down a concentration gradient. *Charge* flows between the channel protein and baths because ions flow through the pore and capacitive charge flows between gating machinery and baths. *Matter* flows between the channel and baths because ions enter and leave the channel. Some of the ions may cross the channel, but most do not. Ions may also enter and leave other places in the channel protein besides the conduction pore. Obviously, the energy supplied by an external circuit and the heat exchanged with the baths must equal the energy of all these processes, only one part of which is the energy of particular interest, namely the energy that modulates the ion flow. This energy and its associated effective charge are difficult to define. Specific physical models of the gating or blocking process are needed to evaluate these energy terms.

Calculating current in simulations of ion channels

Eq. 1 allows calculation of currents in a simulation when charged particles move between positions, for instance in simulations of gating current, or of ionic current flowing through the pore of an ion channel. Eq. 1 estimates current much more efficiently than counting ions crossing a surface (Chung *et al.*, 1998), because it provides a sample of the instantaneous current at each time step of the simulation, whereas counting of crossings produces relatively few current pulses and does not capture displacement current nor its essential contribution to the noise. Similarly, Eq. 2 allows one to track

charge efficiently.

The sampling of current is an important application of the Ramo-Shockley theorem in electronic device simulations at the particle level (Gruzinskis *et al.,* 1991; Babiker *et al.,* 1998). This method is just now finding its way into simulations of ion channels (U. Ravaioli (University of Illinois, Urbana-Champaign), personal communication; M. Saraniti (Illinois Institute of Technology), personal communication).

CONCLUSION

The Ramo-Shockley theorem allows one to relate, in a general way, microscopic movements of physical charges in ion channels to macroscopic currents recorded in a voltage clamp.

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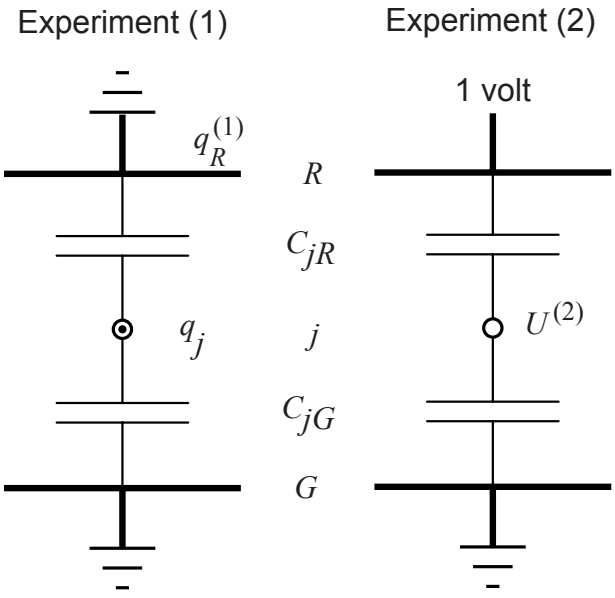
Figure Captions

Figure 1. Equivalent circuits for the two thought experiments used to derive the Ramo-Shockley theorem (see text).

Figure 2. Mapping geometric coordinates to electrical coordinates. A conductive pore provides an aqueous bridge through the membrane (qualitatively similar to the open pore of a K channel (Jiang et al., 2003)). The domain (*panel A*, drawn to scale) is a generalized cylinder (maximal radius 5 nm, length 13 nm) and is shown in an axial cross-section; the highlighted part in A is shown at larger scale in *panel B*. Electrodes bound the two hemispherical baths. The top (external) electrode is grounded, whereas the bottom (internal) electrode is maintained at 1 volt. Isopotential lines are shown at 50 mV intervals (*solid lines*); some intermediate isopotentials corresponding to 25 mV intervals are also included (*dashed lines*). The isopotential lines also mark surfaces of constant "electrical coordinate" (with respect to the grounded electrode), corresponding to intervals of 0.05 (or 0.025). The dielectrics are described by dielectric coefficients of 80 (bath solutions and pore, *unshaded*) and 2 (lipid and channel, *shaded in gray*). At the lateral boundary of the membrane (*dark gray lines)*, a linearly varying potential is imposed

Figure 3. Mapping geometric coordinates to electrical coordinates. An S4 helix segment spans the membrane through a "gating pore" (as envisioned by Bezanilla (2002)). Two

different electrode arrangements are used. One arrangement includes bath solutions between the membrane and electrodes (*panel A*, c.f. Fig. 2); *panel B* shows an enlargement of the region bounded by the *dashed line* in A. In the other arrangement, the electrodes cover membrane and protein like a thin metal foil (*panel C*). Isopotential lines are shown at 50 mV intervals (*solid lines*); some intermediate isopotentials corresponding to 25 mV intervals are also included (*dashed lines*). The dielectrics are described by dielectric coefficients of 80 (bath solutions, *unshaded*) and 2 (lipid and channel, *shaded in gray*).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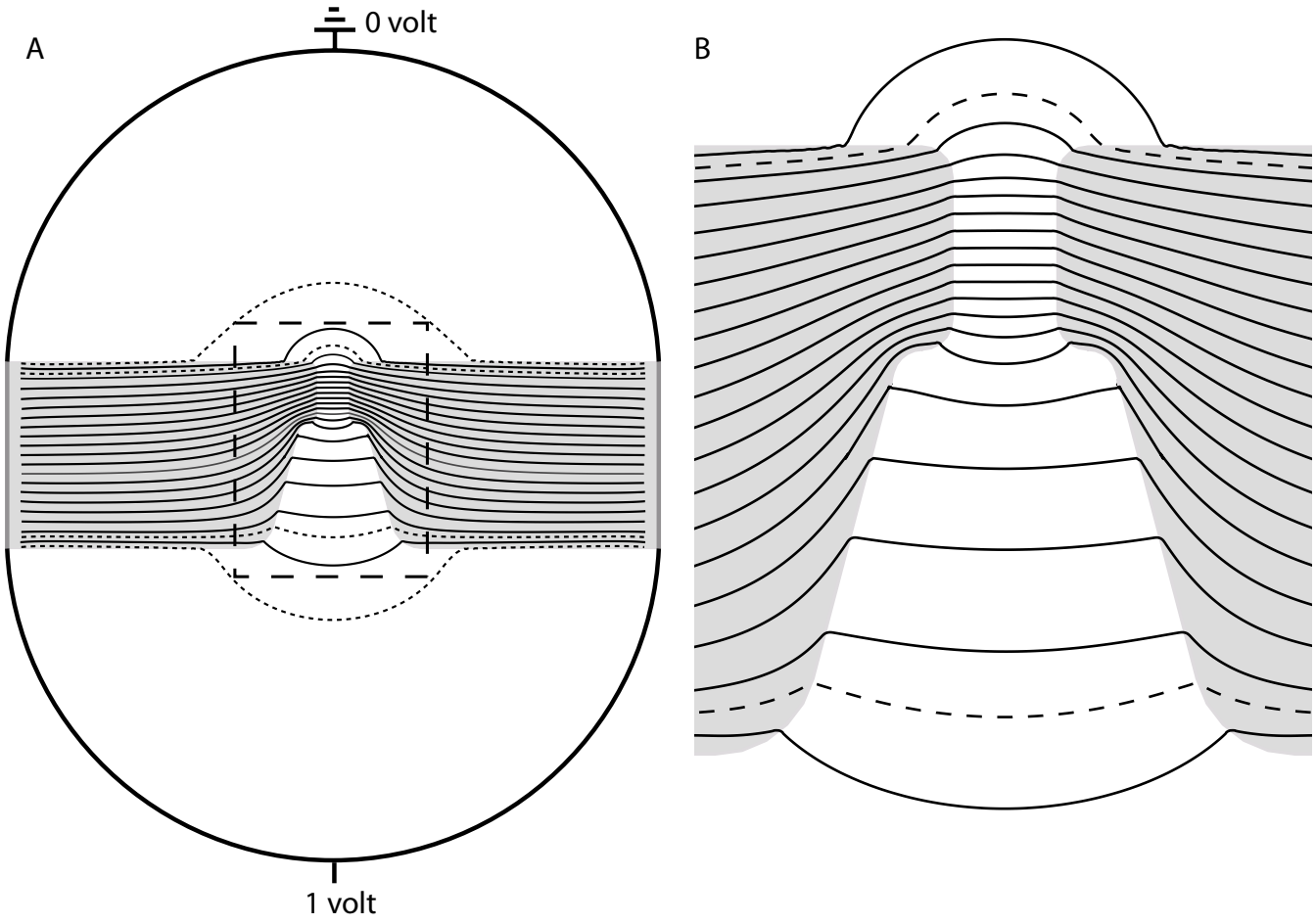
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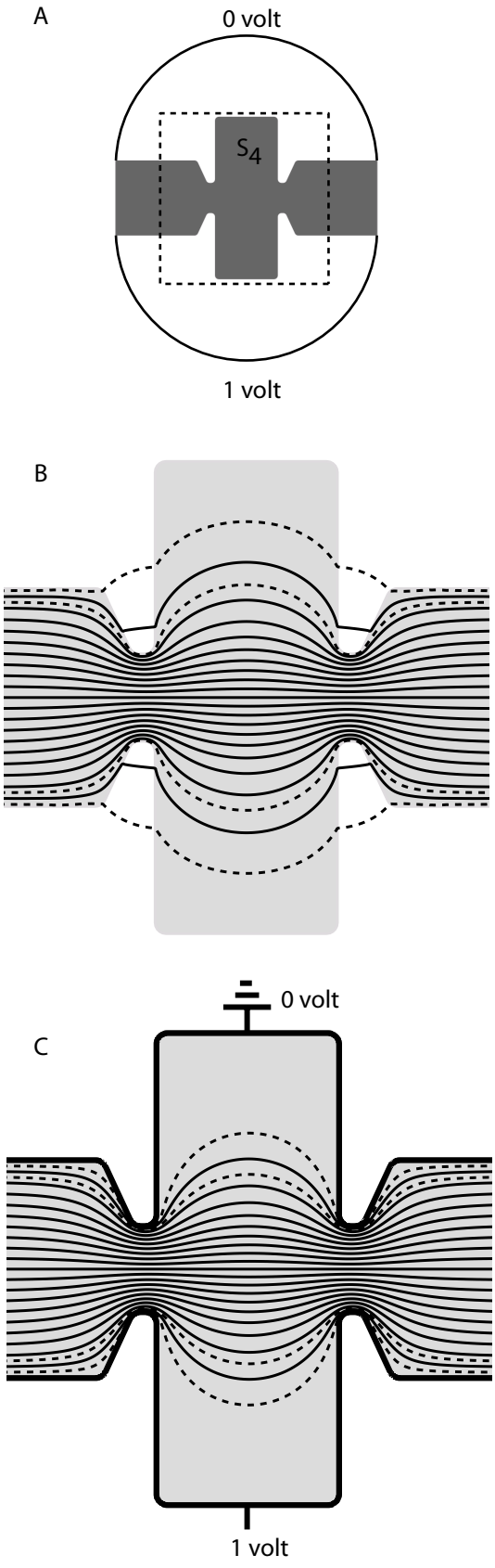
1 volt
B


A
0 volt
S_4
1 volt
B
C
0 volt
1 volt