

Heat of nervous conduction: A thermodynamic frameworkAymar C. L. de Lichtervelde^{1,*}, J. Pedro de Souza^{2,*} and Martin Z. Bazant^{2,3,†}¹*Department of Physical Chemistry & Soft Matter, Wageningen University, 6708 WG Wageningen, the Netherlands*²*Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA*³*Department of Mathematics, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA*

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Early recordings of nervous conduction revealed a notable thermal signature associated with the electrical signal. The observed production and subsequent absorption of heat arise from physicochemical processes that occur at the cell membrane level during the conduction of the action potential. In particular, the reversible release of electrostatic energy stored as a difference of potential across the cell membrane appears as a simple yet consistent explanation for the heat production, as proposed in the “Condenser Theory.” However, the Condenser Theory has not been analyzed beyond the analogy between the cell membrane and a parallel-plate capacitor, i.e., a condenser, and cannot account for the magnitude of the heat signature. In this work, we use a detailed electrostatic model of the cell membrane to revisit the Condenser Theory. We derive expressions for free energy and entropy changes associated with the depolarization of the membrane by the action potential, which give a direct measure of the heat produced and absorbed by neurons. We show how the density of surface charges on both sides of the membrane impacts the energy changes. Finally, considering a typical action potential, we show that if the membrane holds a bias of surface charges, such that the internal side of the membrane is 0.05 C m^{-2} more negative than the external side, the size of the heat predicted by the model reaches the range of experimental values. Based on our study, we identify the release of electrostatic energy by the membrane as the primary mechanism of heat production and absorption by neurons during nervous conduction.

DOI: [10.1103/PhysRevE.101.022406](https://doi.org/10.1103/PhysRevE.101.022406)**I. INTRODUCTION****A. Thermodynamics of nervous conduction**

Besides the electrical responses classically measured in electrophysiological experiments [1–4], the action potential is accompanied with a production and a subsequent absorption of heat [5], changes in optical properties [6], and mechanical deformations [7,8]. These thermal, optical, and mechanical responses are macroscopic signatures of the physicochemical processes occurring at the cell membrane level during the action potential, such as the transport of ions through ion channels in the membrane [9] or the elastic deformation of the membrane [10]. While such physicochemical signatures are associated with the electrical signal, classical electrical circuit models such as the Hodgkin-Huxley model cannot capture them because they neglect the microscopic physics at the membrane level [11,12].

Here we examine the thermal response of nervous conduction by resolving the microscopic physics of the membrane and its surrounding electrical double layers. We start by reviewing experimental and theoretical backgrounds on the heat signature of nervous conduction. We then apply an equilibrium-thermodynamics framework to calculate the electrostatic energy that is stored by the membrane and the surrounding double layers and released into heat during the

passage of the action potential. Finally, based on typical neurophysiological parameters, we show that the reversible release of electrostatic energy offers a plausible explanation for the heat of nervous conduction.

B. Heat production and absorption by neurons: The experimental context

A substantial record of experiments shows that the propagation of the action potential along neurons is accompanied by the release of a small amount of heat, immediately followed by the absorption of a comparable amount of heat by the neurons [5,7,12–21]. Successfully recorded for the first time by Hill in 1925 [19], the heat of nervous conduction has been most extensively investigated between the 1950s and 1980s by contemporaries and colleagues of Hodgkin and Huxley [5,14,16–20], the pioneers of modern neurophysiology. All neurons possess a similar excitable membrane, and heat production is likely a universal feature of nervous conduction. However, the thermal signals are most easily measured in thin nerve fibers, which have a high surface-to-volume ratio. The magnitude of the thermal signals is indeed extremely small and appears to be proportional to the axon membrane area [5]. The garfish olfactory nerve, for example, is an excellent candidate for recording the heat of nervous conduction: it is made of several millions of fibers of $0.25 \mu\text{m}$ in diameter, totals a membrane area of 6.5 m^2 per g of nerve [22], and releases heat on the order of 1 mJ g^{-1} [5]. When expressed per total membrane area, the size of the heat remains on the

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same order of magnitude from one organism to the other (60–180 $\mu\text{J m}^{-2}$ [5]).

To understand the origin of the thermal signals, scientists attempted to correlate them with the electrical signals [5,14,17,19,20]. Notably, Howarth *et al.* [5] successfully reconstructed the true temperature change that occurs in neurons from recorded heat responses and showed that the time course of the temperature changes closely matches the square of the membrane potential during the action potential. Such finding gave support to the ‘‘Condenser Theory.’’

C. The Condenser Theory

The Condenser Theory offers a simple explanation for the heat production and absorption: it attributes them to the reversible release of electrostatic energy stored across the cell membrane [5,14,17,20]. At rest, the membrane of neurons holds a difference of electric potential, called the ‘‘membrane potential.’’ An ‘‘action potential’’ occurs when the membrane potential at a specific location rapidly rises (depolarization) and falls (repolarization), due to the opening of voltage-gated ion channels [9]. The Condenser Theory states that as the action potential depolarizes the membrane, the electrostatic energy stored across the cell membrane is released into heat. Conversely, upon repolarization of the membrane to its resting potential, the membrane’s electrostatic energy is restored at the expense of some of the thermal energy of the ions in the surrounding solutions, which accounts for the heat absorption phase, in symmetry with the production phase. The membrane is seen as a capacitor (or a ‘‘condenser’’), hence this explanation for the heat of nervous conduction is known as the Condenser Theory. In the first developments of the Condenser Theory, the amount of heat reversibly exchanged between the membrane and its surroundings was calculated as the free energy of a parallel-plate capacitor [5,20]:

$$\Delta F = \frac{1}{2} c_m (V_m^2 - V_{m,0}^2), \quad (1)$$

where ΔF is the free energy change (J m^{-2}), c_m the specific membrane capacitance (F m^{-2}), V_m the membrane potential (inside potential minus outside potential; see Fig. 1), and $V_{m,0}$ the resting potential (≈ -70 mV [23]).

D. Arguments to explain the missing heat

Though in qualitative agreement with the experimental records, Eq. (1) predicts only between a quarter and a half of the heat that is measured. Realizing this, Howarth *et al.* [5] and Ritchie and Keynes [20] suggested that the free energy should be calculated based on the local value of potential falling on each side of the membrane (see ϕ_t in Fig. 1), rather than on the potential values in the internal and external bulk solutions (see V_m in Fig. 1):

$$\Delta F_{\text{Ritchie}} = \frac{1}{2} c_m (\phi_t^2 - \phi_{t,0}^2). \quad (2)$$

In particular, it was pointed out that the presence of an uneven distribution of negative surface charges on the membrane (more charges on the internal side than on the external side) would increase the transmembrane potential difference and lead to more heat being evolved [5,20]. Unfortunately, Howarth *et al.* [5] and Ritchie and Keynes [20] did not provide

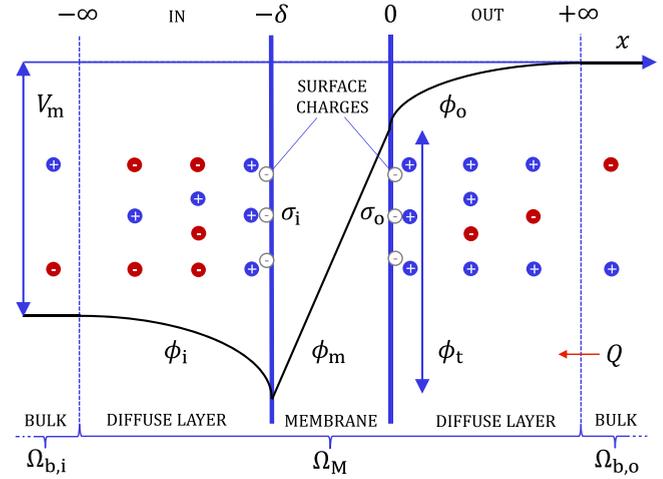


FIG. 1. Profile of the electric potential across the cell membrane and the diffuse layers on each side. The minus signs in white denote surface charges (σ_i inside and σ_o outside), while the charges in solution are drawn in blue and red. The dotted lines delimit thermodynamic domains (see Sec. II B). At rest, the membrane holds a potential difference ($V_m = -70$ mV). Upon excitation, cations cross the membrane through ion channels (not drawn) and V_m jumps to positive values. Simultaneously, electrical energy is dissipated as heat ($Q < 0$).

a careful derivation for Eq. (2), nor did they explore the physics of the cell membrane and its surface charges beyond the analogy with a parallel-plate capacitor.

A second argument invoked by several authors to bridge the gap between predicted and measured heats concerns entropy changes presumed to occur inside the lipid bilayer (i.e., the membrane) when the electric field across the membrane relaxes [5,17,19,20]. Specifically, they proposed that the total energy change ΔU associated with the depolarization of the membrane could differ significantly from the free energy change ΔF , by an entropy contribution $T \Delta S$. These changes were calculated proportionally to the free energy term, based on the temperature dependence of the membrane capacitance:

$$T \Delta S = \Delta F \frac{T}{C_m} \frac{\partial C_m}{\partial T}, \quad (3)$$

where ΔS is the entropy change, T the temperature, and C_m the total membrane capacitance (in Farads). Equation (3) predicts an additional heating of the lipid membrane if $T \Delta S$ and ΔF have the same sign, otherwise it predicts a cooling. According to Ritchie and Keynes [20] and Ref. [24], the value of $T/C_m \partial C_m/\partial T$ is positive, between 2 and 4, which would bring a total warming that is 3 to 5 times higher than if the heat was derived only from the release of free energy stored in the membrane capacity. However, no rigorous derivation for Eq. (3) could be found in literature. Furthermore, the prediction of Ritchie and Keynes [20] seems difficult to reconcile with recent measurements of the temperature dependence of the dielectric permittivity ($\partial \epsilon/\partial T$) of fatty acids, the carbon chains that form the cell membrane. Indeed, $\partial \epsilon/\partial T$ appears to be negative [25,26], and if we calculate the membrane capacitance C_m as proportional to its dielectric permittivity

ε_m , we expect $\partial C_m/\partial T$ to be negative rather than positive, which contradicts the argument of Ritchie and Keynes [20].

More than a simple parallel-plate capacitor, the axon membrane consists of a lipid bilayer with surface charges and electrical double layers forming on each side [27]. The analogy with a condenser offers a too limited description of the membrane to verify the correctness of the arguments reviewed above. It does not allow us to judge which of Eqs. (1) or (2) describes correctly the free energy change during the depolarization of the membrane. In addition, as shown above, how entropy changes inside the membrane could contribute to the heat production still needs to be understood.

To assess whether electrostatic energy changes constitute a plausible explanation for the heat production and absorption by neurons, we will now derive the changes in electrostatic free energy and entropy that accompany the action potential, based on a detailed electrostatic model of the membrane, its surface charges, and double layers.

II. THEORY

A. Electrostatic model of the charged lipid bilayer

We use the coupled electrostatic model proposed by Genet *et al.* [27], which applies Poisson-Boltzmann theory on either side of the cell membrane. Figure 1 shows the qualitative electric potential profile inside and surrounding a cell membrane that holds surface charges on the internal and external sides (σ_i and σ_o , respectively). By convention, we use the symbols $-\infty$ and $+\infty$ to denote the (arbitrary) limits between the diffuse layers and bulk regions, in the internal and external solutions, respectively. Note that in physiological conditions, diffuse layers extend over a few nanometers at most (the Debye length is 0.6 nm). The membrane core is located between $x = -\delta$ and $x = 0$, where δ is the thickness of the membrane. The ϕ_i , ϕ_m , and ϕ_o variables represent the potential in the internal solution, membrane core, and external solution, respectively. The *membrane potential* is defined as the difference between the potential in the internal and external bulk solutions, $V_m = \phi(-\infty) - \phi(+\infty)$, whereas the *transmembrane potential* ϕ_t is the potential difference between the internal and external surfaces of the membrane, $\phi_t = \phi_i(-\delta) - \phi_o(0)$. Note that due to the presence of surface charges on each side of the membrane, the local difference of potential ϕ_t can differ significantly from the membrane potential V_m .

We assume that equilibration of diffuse layers with the bulk electrolytes is fast compared to the dynamics of the action potential (this is verified in Appendix A), which allows us to describe the concentration of ions in the diffuse layers close to the membrane with the Boltzmann distribution

$$c_{j,i}(x) = c_{j,i}(b) \exp\left(-\frac{z_j F \phi_i}{RT}\right), \quad (4)$$

$$c_{j,o}(x) = c_{j,o}(b) \exp\left[-\frac{z_j F (\phi_o - V_m)}{RT}\right], \quad (5)$$

where $c_{j,i}$ and $c_{j,o}$ are the concentrations of species j inside and outside, respectively, and RT/F is the thermal voltage ($RT/F = 23.5$ mV at $T = 273$ K). In this subsection, F is used to denote Faraday's constant (whereas in other sections,

F denotes the free energy). Applying Poisson's equation to each compartment gives

$$\frac{d^2 \phi_i}{dx^2} = -\frac{\rho_i}{\varepsilon_w}, \quad (6)$$

$$\frac{d^2 \phi_m}{dx^2} = 0, \quad (7)$$

$$\frac{d^2 \phi_o}{dx^2} = -\frac{\rho_o}{\varepsilon_w}, \quad (8)$$

where ρ is the density of free charges (C m^{-3}), and ε_w the dielectric permittivity in the internal and external solutions (water). Note that we assume that the free charge density is zero inside the membrane ($\rho_m = 0$), with a zero ion concentration inside the membrane. As $\rho_i = \sum z_j F c_{j,i}$ and $\rho_o = \sum z_j F c_{j,o}$, we obtain the following Poisson-Boltzmann equations:

$$\frac{d^2 \phi_i}{dx^2}(x) = -\frac{F}{\varepsilon_w} \sum_j^N z_j c_{j,i}(b) \exp\left[-\frac{z_j F \phi_i(x)}{RT}\right], \quad (9)$$

$$\frac{d^2 \phi_o}{dx^2}(x) = -\frac{F}{\varepsilon_w} \sum_j^N z_j c_{j,o}(b) \exp\left\{-\frac{z_j F [\phi_o(x) - V_m]}{RT}\right\}, \quad (10)$$

which we solve numerically, using boundary conditions given by Maxwell's equations at an interface [Eqs. (15) and (16)]. We now report the electrostatic relations necessary to derive energy changes in following sections. At rest, the membrane acts as a dielectric medium (ion channels are closed), storing a capacitive charge that we define as $-q$ in the internal solution and $+q$ in the external solution. In each compartment, this capacitive charge can be expressed as the sum of the charge that counterbalances the charges that belong to the surface of the membrane (that is, $-\sigma_i$ inside and $-\sigma_o$ outside, both with units C m^{-2}) and the total mobile charge in solution, which we obtain by integrating the free charge density over the diffuse layers:

$$-q = \sigma_i + \int_{-\infty}^{-\delta} \rho_i dx, \quad (11)$$

$$q = \sigma_o + \int_0^{+\infty} \rho_o dx. \quad (12)$$

Applying Poisson's equation to the integrals above, we can relate the slope of the membrane potential at each interface to the total charge density in the internal and external solutions:

$$\frac{d\phi_i}{dx}(-\delta) = \frac{1}{\varepsilon_w}(\sigma_i + q), \quad (13)$$

$$\frac{d\phi_o}{dx}(0) = -\frac{1}{\varepsilon_w}(\sigma_o - q). \quad (14)$$

Boundary conditions for electric potential at the two membrane-solution interfaces are given by

$$\varepsilon \frac{d\phi_i}{dx}(-\delta) - \varepsilon_m \frac{d\phi_m}{dx}(-\delta) = \sigma_i, \quad (15)$$

$$\varepsilon_m \frac{d\phi_m}{dx}(0) - \varepsilon \frac{d\phi_o}{dx}(0) = \sigma_o, \quad (16)$$

where ε_m is the dielectric permittivity of the membrane (F m^{-1}). By substituting Eq. (13) into (15), and Eq. (14) into (16), we can deduce that

$$\frac{q}{\varepsilon_m} = \frac{d\phi_m}{dx}(-\delta) = \frac{d\phi_m}{dx}(0). \quad (17)$$

As the electric field is assumed to be constant inside the membrane, Eq. (17) gives

$$\frac{q}{\varepsilon_m} = \frac{\phi_m(0) - \phi_m(-\delta)}{\delta} \stackrel{\Delta}{=} -\frac{\phi_t}{\delta}. \quad (18)$$

We finally obtain an expression that relates the capacitive charge to the membrane's capacitance (c_m , in F m^{-2}) and the transmembrane potential:

$$q = -\frac{\varepsilon_m}{\delta} \phi_t = -c_m \phi_t, \quad (19)$$

with $c_m \stackrel{\Delta}{=} \varepsilon_m/\delta$, in agreement with Genet *et al.* [27].

B. Thermodynamic definitions

To relate electrical energy changes at the membrane level to the exchange of heat with the surroundings, we must define the membrane as a thermodynamic system. We divide the space into three domains (see Fig. 1): Ω_M is the ‘‘membrane domain,’’ i.e., the region comprising the membrane and the diffuse layers that form in the internal and external solutions, while $\Omega_{b,i}$ and $\Omega_{b,o}$ denote the internal and external bulk solutions, respectively. The first law of thermodynamics, $\Delta U_{el} = Q + W_{el}$, applies, in which ΔU_{el} is the internal energy change associated with the variation of the membrane potential from $V_{m,0}$ to V_m , Q is the heat added to Ω_M ($Q < 0$ when heat is dissipated), and W_{el} is the electrical work done on Ω_M by the surroundings. Since the capacitive charges $+q$ and $-q$ are confined to the diffuse layers close to the membrane (the bulk solutions are electroneutral), no electrical work is done on Ω_M by the surrounding domains $\Omega_{b,i}$ and $\Omega_{b,o}$. The first law thus becomes

$$\Delta U_{el} = Q. \quad (20)$$

The electrostatic internal energy of the membrane system can be expressed as a sum of free and entropy-related energies:

$$\Delta U_{el} = \Delta F_{el} + T \Delta S_{el}, \quad (21)$$

where ΔF_{el} and ΔS_{el} are, respectively, the electrostatic free energy and entropy change with respect to the resting state ($V_{m,0} = -70$ mV). Thus, based on the aforementioned definitions, as the internal energy of the membrane domain decreases ($\Delta U_{el} < 0$), heat is released ($Q < 0$) from the membrane domain Ω_M to the surroundings. In the following sections, we will derive the free energy and entropy changes in the membrane domain as a function of the membrane potentials V_m and ϕ_t . By Eq. (21), the sum of these energies will give the internal energy change associated with the (de)polarization of the membrane and by Eq. (20) the quantity of heat that is reversibly released from the membrane domain Ω_M .

To be comprehensive, our thermodynamic analysis must also include the energy changes involved in the mixing of ions

across the membrane. Indeed, the depolarization of the membrane is caused by an inward current of *sodium* ions, while it is an outward current of *potassium* ions that is responsible for its repolarization [9]. Both ions are transported down their electrochemical gradient, and the action potential is thus associated with a loss of free energy inherent to the dissipation of such gradient. In fact, Margineanu and Schoffeniels calculated the free energy changes based on application of the Hodgkin-Huxley model [28] and estimated a free energy dissipation of $496 \mu\text{J m}^{-2}$ per impulse from ionic transfer through the membrane. However, the mixing process is also subject to an increase of entropy, and, in the limit of ideal solutions, the free energy of mixing is exactly counterbalanced by the entropy of mixing [29]:

$$\Delta U_{\text{mix}} = \Delta F_{\text{mix}} + T \Delta S_{\text{mix}} = 0. \quad (22)$$

While Margineanu and Schoffeniels considered the free energy dissipation of ionic currents to be equivalent to a heat dissipation, they did not consider how the free energy dissipation relates to their thermodynamic system. The contribution of entropy of mixing to the measured heat has been an open question since Bernstein first considered the thermodynamics of the action potential [30]. Abbott *et al.* [14] clarified the role of ionic currents through the membrane further by explaining that in an ideal solution without any external work, no heat is produced by the exchange of ions across the membrane interface. In agreement with Abbott *et al.* [14], we do not consider the entropy of mixing to contribute to the heat production, even if it contributes to the overall free energy dissipation in the system. One may also ask about the entropy of mixing involved in the dynamic formation of the double layers. Similarly, in ideal solutions, the entropy of mixing related to the reorganization of the double layers as a function of the membrane potential has no contribution to the heat.

In summary, while free energy of mixing is dissipated during the action potential, the mixing of ions across the membrane and in the double layers does not contribute to the heat of nervous conduction in the limit of ideal solutions. Following the action potential, chemical energy in the form of ATP is converted into electrochemical energy by ion pumps in order to maintain the concentration gradient across the cell membrane [23]. The whole action potential including subsequent active transport is thus not a reversible transformation, but we assert that the initial passive phases of depolarization and repolarization that capacitively charge the membrane can be described as a reversible process.

C. Electrostatic free energy

The electrostatic free energy of a linear dielectric medium is equal to its field energy [31–33], that is, in one dimension,

$$F_{el} = \frac{1}{2} \int_{-\infty}^{+\infty} E D dx, \quad (23)$$

where E is the electric field (V m^{-1}) and $D = \varepsilon E$ the displacement field (C m^{-2}). The electric and displacement fields are expressed as scalars corresponding to the x component of the vector due to the planar symmetry in the problem. Interestingly, the field energy can be equated with the amount of heat dissipated by ionic currents in an electric field, using

one of Maxwell's equations (this is shown in Appendix C). The field energy is often regarded as an *internal energy* (U_{el}); however, this is only true in a primitive model that considers the medium as structureless. In a more refined model that takes into the effect of the electric field on the entropy of the dielectric medium (see Sec. IID), the field energy must be regarded as a *free energy* (F_{el}) [31,34]. Applying Eq. (23) to the Ω_M domain, we obtain the electrostatic free energy as a function of the membrane potential V_m . We obtain a free energy contribution from the double layers, which is

$$F_{\text{el}}^{\text{DL}} = \frac{1}{2} \left\{ \int_{-\infty}^{-\delta} \rho_i (\phi_i - V_m) dx + \sigma_i [\phi_i(-\delta) - V_m] + \int_0^{+\infty} \rho_o \phi_o dx + \sigma_o \phi_o(0) \right\}, \quad (24)$$

and one from the membrane capacitance, which is

$$F_{\text{el}}^{\text{m}} = \frac{1}{2} c_m \phi_t V_m, \quad (25)$$

with $F_{\text{el}} = F_{\text{el}}^{\text{DL}} + F_{\text{el}}^{\text{m}}$. The first and third terms in Eq. (24) correspond to the energy of bulk charges in the diffuse layers of internal and external solutions and the second and fourth to the energy of the surface charges fixed onto the membrane. As shown by Eq. (25), the free energy contribution of the membrane capacitance is $1/2 c_m \phi_t V_m$, and not $1/2 c_m \phi_t^2$ as proposed in Refs. [5,20]. The latter overestimates free energy changes, as we will see in the Discussion (see Sec. IV). The full derivation of Eqs. (24) and (25) is presented in Appendix D.

Finally, we calculate the free energy *changes* associated with the depolarization of the membrane as $\Delta F_{\text{el}}^{\text{DL}} = F_{\text{el}}^{\text{DL}} - F_{\text{el},0}^{\text{DL}}$ and $\Delta F_{\text{el}}^{\text{m}} = F_{\text{el}}^{\text{m}} - F_{\text{el},0}^{\text{m}}$, where subscripts "0" mark the free energies calculated at the resting membrane potential, $V_{m,0} = -70$ mV.

D. Entropy associated with the electric field

We consider two entropy terms: entropy changes associated with the polarization of water in the diffuse layers and entropy changes in the membrane.

1. In the diffuse layers

The electric field orders water dipoles in the diffuse layers, which decreases entropy. The change of entropy associated with the alignment of dipoles in a dielectric medium (water in our case) is related to the electrostatic free energy by [34]

$$T \Delta S_{\text{el}}^{\text{DL}} = \frac{T}{\varepsilon_w} \frac{\partial \varepsilon_w}{\partial T} \Delta F_{\text{el}}^{\text{DL}}. \quad (26)$$

The value of $T/\varepsilon_w \partial \varepsilon_w/\partial T$ for water is -1.17 at 0°C and -1.4 at human body temperature (37°C) [35,36].

2. In the membrane

Similarly, entropy changes inside the lipid membrane have been proposed based on the temperature dependence of the membrane capacitance [5,17,20]:

$$T \Delta S_{\text{el}}^{\text{m}} = \frac{T}{C_m} \frac{\partial C_m}{\partial T} \Delta F_{\text{el}}^{\text{m}}. \quad (27)$$

To verify that Eq. (27) holds, we adapted the derivation of Eq. (26), in which entropy is a function of $\partial \varepsilon_w/\partial T$, to the case in which entropy is a function of $\partial C_m/\partial T$, the temperature dependence of the membrane capacitance. As shown in Appendix E, Eq. (27) holds under the assumption that the membrane capacitance is constant with potential but has a linear dependence on temperature. Interestingly, it appears from recent experiments that the temperature dependence of the membrane capacitance arises from the variation of the lipid bilayer's dimensions (thickness, δ , and area, A , per lipid molecule) with temperature, rather than from the variation of its dielectric permittivity ($\partial \varepsilon_m/\partial T \simeq 0$) [25,37–39]:

$$\frac{\partial C_m}{\partial T} = \frac{\partial (\varepsilon_m A/\delta)}{\partial T} \simeq \varepsilon_m \frac{\partial (A/\delta)}{\partial T}. \quad (28)$$

Based on recent measurements of these dimensional changes [37–39], Plaksin *et al.* [25] have pointed out that the temperature dependence of the membrane capacitance remains close to $+0.3\%/^\circ\text{C}$ across several cellular types and artificial lipid membranes, suggesting that the rate of thermal response of the membrane is universal.

E. Parameters

Two important parameters in this model are the surface charge density on the interior (σ_i) and exterior (σ_o) sides of the membrane. Here we report ranges of values found in literature and then choose baselines for these two parameters. Hille [9] compiled experimental data on excitable membranes, showing that extracellular and intracellular surface charge densities vary from -0.04 to -0.16 C m^{-2} . Other estimates give a wider range of values, from -0.002 to -0.37 C m^{-2} [40]. Several lines of evidence suggest that neurons have more negative surface charges on the internal side of the membrane than on the external one. In rat cortical neurons for instance, Plaksin *et al.* [25] estimated this surface charge *bias* to be $\sigma_i - \sigma_o = -0.1 \text{ C m}^{-2}$. Further support for this hypothesis arises from the uneven distribution of phospholipids between the two sides of the membrane. In particular, phosphatidylserine, the most abundant negatively charged phospholipid in cell membranes, is found exclusively on the internal side of the cell membrane of neurons, where it has key signaling functions [41]. In this work, the external surface charge density will be fixed to $\sigma_o = -0.05 \text{ C m}^{-2}$, and we will evaluate three cases for the internal surface charge density: $\sigma_i = -0.05$, -0.1 , and -0.15 C m^{-2} . Figure 2 shows the profile of the electrostatic potential across and in the vicinity of the membrane, as calculated by our model in the three cases of surface charge density. Table I reports the other model parameters.

III. RESULTS

A. Free energy changes

The change in electrostatic free energy with membrane potential is depicted in Fig. 3, in the membrane ($\Delta F_{\text{el}}^{\text{m}}$) and in diffuse layers ($\Delta F_{\text{el}}^{\text{DL}}$), with and without surface charges on the membrane. First, when there are no surface charges, the free energy follows a parabola centered around $V_m = 0$ mV. The diffuse layers bring a relatively negligible contribution to the free energy in this case. Interestingly, the presence of an

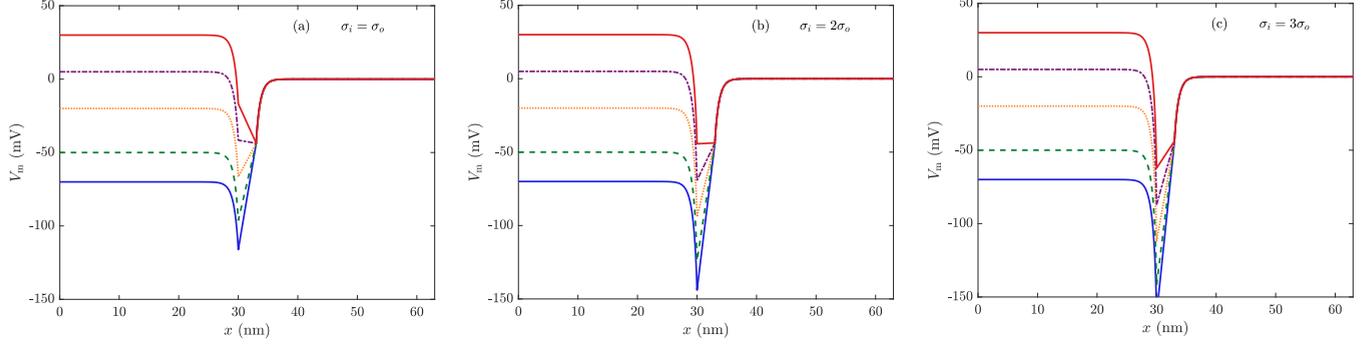


FIG. 2. Profiles of the electric potential across the membrane and the surrounding diffuse layers, for different values of the membrane potential V_i (-70 to $+30$ mV). (a) Surface charge densities are equal on each side ($\sigma_i = \sigma_o = -0.05 \text{ C m}^{-2}$). (b) and (c) A bias of surface charges makes the internal side more negative ($\sigma_i = -0.1$ and 0.15 C m^{-2} and $\sigma_o = -0.05 \text{ C m}^{-2}$), such that the transmembrane potential ϕ_t need not to reverse as soon as the membrane potential becomes positive (purple dash-dotted curves).

equal amount of surface charges on each side of the membrane ($\sigma_i = \sigma_o = -0.05 \text{ C m}^{-2}$) results in almost no alteration of the energy changes as compared to the zero surface charge case. However, as more surface charges are present on the internal side than on the external side of the membrane ($\sigma_i = 2\sigma_o$ and $3\sigma_o$), both $\Delta F_{\text{el}}^{\text{m}}$ and $\Delta F_{\text{el}}^{\text{DL}}$ follow a steeper decrease, such that more free energy is released with increasing V_m .

B. Entropy changes

Entropy changes, depicted in Fig. 4, are proportional to the free energy changes presented above [Eqs. (26) and (27)]. As the membrane depolarizes (increasing V_m), the entropy in the membrane ($T\Delta S_{\text{el}}^{\text{m}}$) decreases, while the one in diffuse layers ($T\Delta S_{\text{el}}^{\text{DL}}$) increases. Both entropy changes follow the same trend with surface charge distribution as the free energy changes in Fig. 3.

C. Internal energy change, heat production, and temperature change

The internal energy change occurring inside the Ω_M domain, i.e., the sum of the free and the entropic energy changes, is depicted in Fig. 5 according to the different scenarios of surface charge distribution used until now. The internal energy change provides a direct measure of the heat produced and

absorbed by the nerve during the course of the action potential [Eq. (20)]: an internal energy decrease ($\Delta U_{\text{el}} < 0$) corresponds to a release of heat by the membrane domain ($Q < 0$), whereas an internal energy increase ($\Delta U_{\text{el}} > 0$) corresponds to an absorption of heat by the membrane domain ($Q > 0$). An idealized action potential (modeled with a normal distribution function, for simplicity) and the corresponding heat profile are depicted in Fig. 6. We find that the presence of negative surface charges on the membrane leads to a more important decrease in internal energy (Fig. 5) and thus heat production (Fig. 6), especially when the membrane holds more fixed charges on its inside than outside. Interestingly, the bottom curve in Fig. 5 shows that when surface charges are distributed unevenly, the internal energy must not rise immediately after that V_m takes positive values. In other words, the membrane can release heat even when the membrane potential overshoots to positive values. This is reflected in Fig. 6 by the progressive disappearance of the “notch” in the energy profiles as σ_i becomes more negative than σ_o . Another way to understand how the internal energy of the membrane can keep on decreasing at positive membrane potentials, is to notice that the transmembrane potential ϕ_t need not to reverse as soon as V_m becomes positive, as shown in Figs. 2(b) and 2(c).

TABLE I. Parameters used in the electrostatic model and energy calculations. Concentrations are given in the format internal solution/external solution.

Parameter	Value	Unit	Source
δ	3	nm	[27]
c_m	9	mF m $^{-2}$	[27]
$V_{m,0}$	-70	mV	[9,23,27]
$1/\varepsilon_m \partial \varepsilon_m / \partial T$	-0.43 at 0°C	%K $^{-1}$	[35,36]
$1/C_m \partial C_m / \partial T$	$+0.3$	%K $^{-1}$	[25]
$c_{\text{Na}^+,i} c_{\text{Na}^+,o}$	5 145	mM	[42]
$c_{\text{K}^+,i} c_{\text{K}^+,o}$	140 5	mM	[42]
$c_{\text{Ca}^{2+},i} c_{\text{Ca}^{2+},o}$	0.0001 2.5	mM	[42]
$c_{\text{Cl}^-,i} c_{\text{Cl}^-,o}$	145 155	mM	[42]
T	273	K	[5]

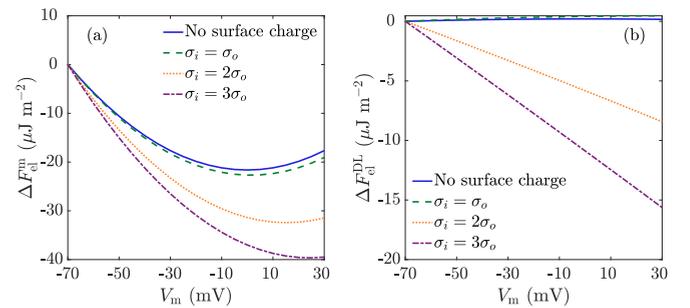


FIG. 3. Change in electrostatic free energy in the membrane $\Delta F_{\text{el}}^{\text{m}}$ (a) and in diffuse layers $\Delta F_{\text{el}}^{\text{DL}}$ (b) as a function of membrane potential, for an equal amount of surface charges ($\sigma_i = \sigma_o = -0.05 \text{ C m}^{-2}$) and with a surface charge bias ($\sigma_i = 2\sigma_o$ and $3\sigma_o$). When a surface charge bias is present, more free energy is released, in both the membrane and diffuse layers.

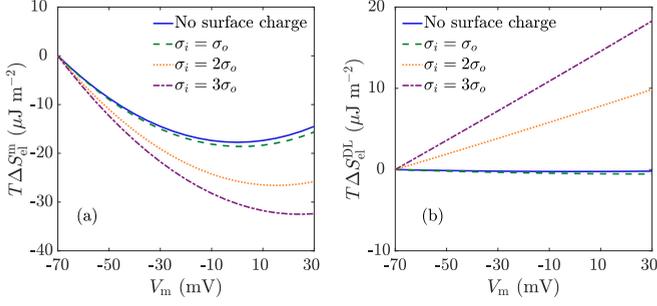


FIG. 4. Entropy changes in the membrane $T\Delta S_m^m$ (a) and diffuse layers $T\Delta S_{el}^{DL}$ (b) with no surface charges, an equal amount of surface charges ($\sigma_i = \sigma_o = -0.05 \text{ C m}^{-2}$), and with a surface charge bias ($\sigma_i = 2\sigma_o$ and $3\sigma_o$). The surface charge bias decreases the entropy in the membrane decrease more upon depolarization, whereas it increases the entropy in diffuse layers.

Based on Fig. 6, we predict that a typical depolarization of the membrane from -70 mV to $+20 \text{ mV}$ [23,43] leads to a heat production of $-Q = 40$ to $70 \mu\text{J m}^{-2}$, depending on the magnitude of the bias of surface charges present on the membrane (0 to -0.1 C m^{-2}). Strikingly, in the scenario of no or equal surface charge density on each side of the membrane ($\sigma_i = \sigma_o$), the overshoot of the membrane potential to positive values results in a notch-like heat profile, that is never observed in experiments [5,14,17,19,20]. Only when a sufficient bias of surface charge is present ($\sigma_i = 2$ and $3\sigma_o$) does the notch disappear, and the predicted heat profile reaches better qualitative agreement with the experimental heat profiles [5,14,17,19,20]. If we consider an action potential that starts from a lower resting potential than in Fig. 6, which can be

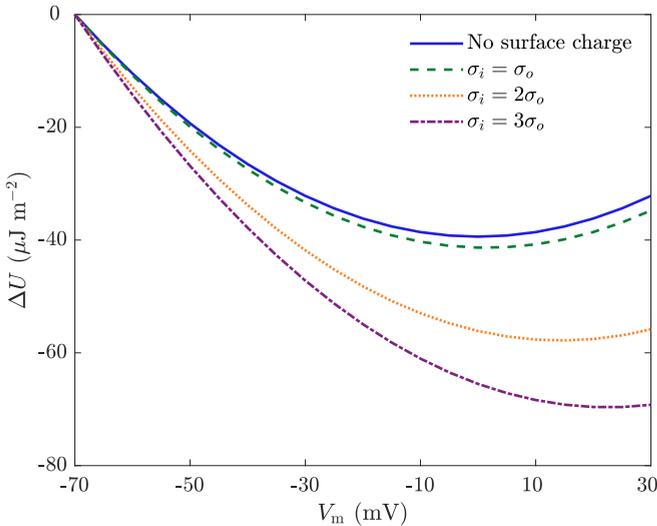


FIG. 5. Internal energy changes of the membrane system, from top to bottom: without surface charge ($\sigma_i = \sigma_o = 0$), with an equal amount of surface charges ($\sigma_i = \sigma_o = -0.05 \text{ C m}^{-2}$), with a moderate surface charge bias ($\sigma_i = 2\sigma_o$), and with a bigger one ($\sigma_i = 3\sigma_o$). The internal energy release increases with the presence of negative surface charges on each side of the membrane, and significantly more as the surface charge difference between the internal and external sides of the membrane rises.

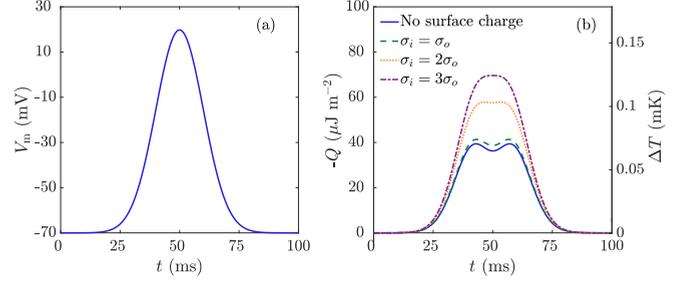


FIG. 6. (a) An action potential depolarizes the membrane, starting from a resting potential of $V_m = -70 \text{ mV}$ at time 0, the membrane depolarizes to $V_m = +20 \text{ mV}$ at the peak of the action potential, before decreasing back to the resting potential. (b) Concomitantly with the action potential, heat ($-Q$) is produced and absorbed, increasing the nerve temperature (ΔT). See Appendix B for the calculation of temperature increase as a function of the heat released.

down to -100 mV [9], up to $150 \mu\text{J m}^{-2}$ of heat is predicted by the model (not shown in Fig. 6). The predicted values fall in the range of experimental values (60 – $180 \mu\text{J m}^{-2}$) [5].

IV. DISCUSSION

The purpose of this work was to provide a theoretical background for heat production and absorption in neurons that goes beyond the simplistic analogy with a capacitor. Based on an equilibrium thermodynamics description of the membrane, its surface charges, and double layers forming on each side, we evaluated the amount of heat released due to electrostatic free energy and entropy changes during the action potential. First, we found that the electrostatic free energy of the cell membrane depends on both the membrane potential and the transmembrane potential, as shown by the expression derived in this work: $F_{cl}^m = \frac{1}{2}c_m \phi_t V_m$. In consequence, the amount of free energy stored and released as heat increases as more surface charges are present on the internal versus the external side of the membrane. Our expression thus predicts a larger free energy change than classical electrical circuit models such as the Hodgkin-Huxley model, which neglect the membrane's surface charges and calculate the free energy as $1/2C_m V_m^2$, i.e., the electrostatic energy stored by a capacitor. However, our expression predicts a smaller energy change than the formula suggested by Howarth *et al.* [5] and Ritchie and Keynes [20], as shown in Fig. 7. Second, free energy changes in the diffuse layers surrounding the membrane also increase significantly when a bias of surface charge is present; however, these changes are offset by the entropy changes associated with the polarization of water by the electric field, which are of comparable magnitude but of opposite sign ($\sim -117\%$ at 0°C). Last, entropy changes upon depolarization and repolarization of the cell membrane bring a contribution to the heat of nervous conduction that is comparable to the free energy contribution ($\sim +82\%$). This result is consistent with the early intuition of Howarth *et al.* [17], who first hypothesized the entropy of the membrane as a possible contribution to the heat of nervous conduction, but could not prove nor quantify such hypothesis. In our work, we showed that the entropy changes can be

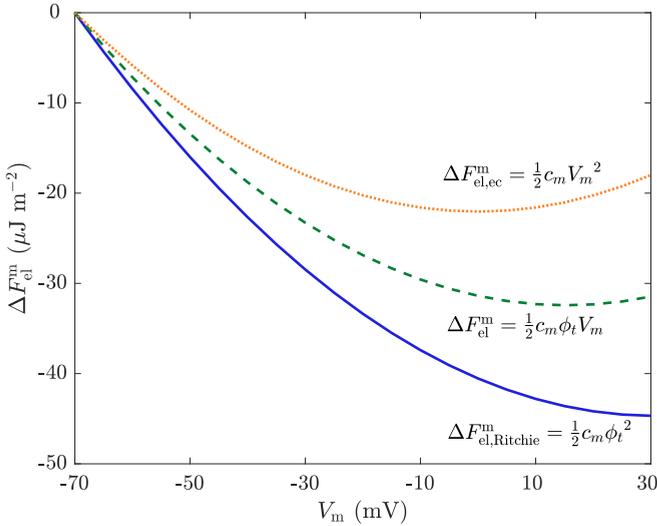


FIG. 7. Free energy changes in the membrane, according to the classical electrical circuit expression, ($\Delta F_{el,ec}^m$, orange dotted curve), the expression suggested by Howarth *et al.* [5] and Ritchie and Keynes [20] ($\Delta F_{el,Ritchie}^m$, blue solid curve), and the revised Condenser Theory (this work, ΔF_{el}^m , green dashed curve). Our expression predicts a larger energy change than the electrical-circuit-based expression, which neglects the presence of surface charges, but a smaller change than the expression of Ritchie and coworkers. Assumed surface charge densities are $\sigma_i = -0.1 \text{ C m}^{-2}$ and $\sigma_o = -0.05 \text{ C m}^{-2}$.

calculated as $T \Delta S_{el}^m / \Delta F_{el}^m = T / C_m \partial C_m / \partial T$ provided that the membrane capacitance is constant with potential but has a linear dependence on temperature ($\partial C_m / \partial T$). Furthermore, new experimental data allowed us to reinterpret and quantify these entropy changes: while previous researchers sought to calculate $\partial C_m / \partial T$ based on the variation of the membrane's dielectric permittivity with temperature ($\partial \epsilon_m / \partial T$) [17,18], we propose to calculate the entropy changes based on the variation of the cell membrane's thickness and area with temperature ($\partial \delta / \partial T$ and $\partial A / \partial T$), in agreement with Plaksin *et al.* [25] and recent experimental [37–39] and molecular dynamic studies [44] that have quantified these changes.

The comparison of the model predictions with the best-available measurements of the heat production and absorption in neurons supports the idea that the heat of nervous conduction has an electrostatic origin: assuming a typical action potential that depolarizes the membrane from -70 mV to $+20 \text{ mV}$ and a surface charge bias of -0.05 C m^{-2} between the two sides of the membrane, we predict a production and absorption of heat of $\sim 60 \mu\text{J m}^{-2}$, which is sufficient to reach the range of experimental values measured in the neurons of different organisms ($60\text{--}180 \mu\text{J m}^{-2}$) [5]. Should the size of the action potential be larger (starting from a more negative resting potential) or the surface charge bias be more pronounced, more heat would be evolved.

Clearly, our predictions have a critical dependency on the action potential size and the surface charge distribution between the internal and external sides of the membrane. Surface charge distribution can vary from one type of neuron to the other; however, the values used for our calculations do not seem extravagant, considering the range of values reported in the literature [9,40]. Regarding the size of the action potential,

while we assumed a typical depolarization from -70 mV to $+20 \text{ mV}$ [23,43], a thorough experimental validation of our predictions would require us to compare the heat production with the true time course of the action potential in the neurons from which the heat is measured, which can be obtained only by measuring the membrane potential intracellularly. It is in practice extremely challenging to insert an electrode inside the minuscule neuronal fibers from which the thermal signals are most easily measured. In consequence, most of the data that compare electrical and thermal signals [5,14,17,20] are based on extracellular recordings of the membrane potential, which give signals of a necessarily much smaller magnitude than the intracellular changes in membrane potential [45,46]. With the recent development of nano-electrodes [47–49], there is hope that it is becoming possible to record true membrane potentials in the small neurons in which temperature changes can effectively be measured.

For simplicity, we have assumed that the heat of nervous conduction is evolved in a reversible process: during the depolarization phase, all internal energy is converted into heat, while during the subsequent repolarization phase, all this heat is converted back to internal energy. In consequence, a symmetric action potential input into our model results in a symmetric heat profile, as shown in Fig. 6. The shape of heat profiles reported in the literature [5,18] supports the assumption of a reversible process, since the amount of heat produced closely matches the amount of heat reabsorbed ($937 \mu\text{J g}^{-1}$ vs $962 \mu\text{J g}^{-1}$ for the negative heat in Ref. [5]). However, produced and absorbed heat rarely coincides exactly, and the heat profiles are generally slightly asymmetric: in some experimental records, the positive heat is larger than the negative heat [17,19,20], whereas in others, the positive heat is smaller than the negative heat [5,18]. Temperature could be a determining factor in the relative size of the positive and negative heats [18]. Taken together, the experimental observations suggest that the heat of nervous conduction could have an irreversible component, although it is minimal as compared to the reversible component.

While in our model we have considered ideal solutions, for which the enthalpy of mixing is zero [29], deviations from ideal behavior could lead to a nonzero heat of mixing. Abbott *et al.* [14] considered the fact that the physiological solutions are not actually ideal solutions and should have some enthalpy of mixing. It was challenging to measure the enthalpy of mixing expected from the small exchanges of ions during the action potential. Even so, in 1968 Howarth *et al.* [17] showed that the contribution from the mixing of a solution of 0.15 M NaCl and a 0.15 M KCl solution gives an expected heat of 3.7 cal/mol . Based on this figure and our model parameters (Table I), we estimate this contribution as $0.26 \mu\text{J m}^{-2}$ per impulse. This represents merely 0.5% of the lowest experimental value for the heat production [5], which supports the present treatment. Evidently, the salt solutions used in the experiment of Howarth *et al.* [17] are only simple models of the more complex physiological solutions. The real physiological solutions might further deviate from the ideal behavior, which could help to explain the asymmetry observed in the heat records.

In our analysis, we have made strong assumptions of complete reversibility, ideal solutions, constant bulk

concentrations, and equilibrium conditions in order to isolate the energy stored in the dielectric membrane and double layers as a function of voltage and surface charge asymmetry. There are numerous articles on the heat released with the action potential; however, there has been no thorough attempt to analyze the electrostatic part of the heat production including thermodynamics and dielectric theory, beyond the simplistic analogy with a condenser. Several works have suggested that the experimentally observed heat cannot be accounted for from the condenser model, and thus mechanical effects were explored in more detail. While other models attempt to capture nonequilibrium dissipation [28] or mechanical effects [8,10–12,50], they do not account for the entropy changes due to the temperature dependence of the membrane capacitance or the solution's permittivity, nor do they model the surface charge at the membrane interfaces. We have shown that the surface charge effects can bring the predicted heat within the range of experimentally measured values without considering these additional contributions. We cannot rule out the importance of the mechanical surface waves [10] or density pulses [8,11,12,50] that accompany the electrical signal in determining the heat signature, but we can point to another important contribution to the heat. The asymmetry of surface charge, the presence of which is supported by the experimental heat signatures, strongly affects the local potential drop across the cell membrane and the local concentrations of ions in the vicinity of the membrane [27].

Models of ionic conduction through protein channels embedded in the cell membrane may need to account for the fixed charge on both sides of the membrane to properly describe the voltage-dependent conductance of the channel. Gating kinetics of channels are typically expressed in terms of the global membrane potential, rather than in terms of the local membrane potential drop experienced by the ion channel. Furthermore, emerging neurotechnologies that rely upon the conversion of heat to electrical responses, such as infrared neural stimulation [25,51–56], could benefit from our thermodynamic framework. Besides neurosciences, the physics our work explores could be relevant for engineering electrical double-layer capacitors [57] or designing capacitive deionization processes, which performance can be influenced by the presence of surface charges, either immobile [58] or modulated electrochemically [59]. Moreover, thermodynamic analyses in capacitive systems typically do not include the entropy of dipoles in dielectric media [60]. Here we showed that the entropy of dipoles brings a significant contribution to the internal energy stored by the double layers and the associated heat production and absorption.

Since early measurements of nervous activity, the observed thermal response has been a mystery, yet it contains information that could deepen our understanding of nervous conduction, and serves as additional evidence of the microscopic physics of the action potential. Although we cannot discard the possibility of other sources of heat, such as heat arising from mechanical displacements of the membrane [10,61,62], our analysis suggests that the reversible release of electrostatic energy by the membrane represents the most prominent mechanism of heat production and absorption by neurons during the propagation of the action potential.

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APPENDIX A: FAST EQUILIBRATION OF DOUBLE LAYERS

In this work, we describe ions and the electric potential in the diffuse layers at equilibrium, with the Boltzmann distribution [Eqs. (9) and (10)]. This equilibrium assumption decouples the problem from time dependence for relaxation of the double layers and simplifies it to a single dependence on the membrane potential V_m . However, in reality, V_m is time-dependent. We must thus verify that the double layers reach their equilibrium conformation (ion concentration versus position) significantly faster than the variation of V_m during the course of the action potential. Two timescales can characterize the relaxation of diffuse layers: diffusion $\tau_D = L^2/D$ and charge density relaxation $\tau_L = \lambda_D^2/D$, where L is the characteristic length, D the characteristic diffusivity, and λ_D the Debye length. At low voltages, Bazant *et al.* [63] have shown that the primary timescale for diffuse charges dynamics in a non-Faradaic electrochemical cell is the harmonic mean between these time constants, that is, $\tau_C = \lambda_D L/D$. Interestingly, a recent study by Janssen [64] has shown that the easily obtainable τ_C decently describes double-layer relaxation also in cylindrical geometry, the relevant geometry for neurons. By analogy with the electrochemical cell, the membrane can be seen as sandwiched between two electrodes separated by a distance L and on which a difference of potential is applied [61,65].

In physiological conditions (ionic strength = 150 mM) and at 0 °C, the Debye length is less than 1 nm:

$$\lambda_D = \sqrt{\frac{RT \varepsilon_w}{F^2 \sum z_j^2 c_j}} = 0.6 \text{ nm.} \quad (\text{A1})$$

In the garfish olfactory nerve, one of the smallest axons studied, the characteristic length is given by the radius of the cell, $L/2 = 0.25 \mu\text{m}$. Taking $D = 10^{-9} \text{ m}^2 \text{ s}^{-1}$ we find $\tau_C = 0.3 \mu\text{s}$. In the giant squid axon, one of the largest axons ever studied, we have $L/2 = 200 \mu\text{m}$, and thus $\tau_C = 240 \mu\text{s}$. These characteristic times for relaxation are small compared to the timescale of compound action potentials, which is 10 to 100 ms [5]. While in the nonlinear regime (where the double-layer potential across each side is much larger than the thermal voltage $\sim 24 \text{ mV}$) the timescale for bulk salt diffusion $\tau_D = L^2/D$ can be important, the leading order dynamics occur at the τ_C scale. Therefore, we neglect any double-layer relaxation effect and treat them at equilibrium.

APPENDIX B: FAST EQUILIBRATION OF TEMPERATURE INSIDE THE NERVE

Another important assumption we make is the fast heat equilibration between the cell membrane and the rest of the

nerve. The validity of this assumption can be verified based on scaling analysis on the heat equation, which yields a characteristic time for heat diffusion:

$$\tau_h = \frac{\rho c_p L^2}{K}, \quad (\text{B1})$$

where ρ is the mass density, c_p the specific heat capacity, L the characteristic length, and K the thermal conductivity. With $L = 0.125 \mu\text{m}$, $\rho = 5.8 \text{ g cm}^{-3}$, $c_p = 3.6 \text{ J (g.K)}^{-1}$ [5], and using the thermal conductivity of water at 0°C , $K = 0.0056 \text{ J (K cm s)}^{-1}$ [36], we find $\tau_h \sim 0.6 \mu\text{s}$. Thus, the heat equilibration in the interior of the small nerve fibers in which the heat experiments were conducted [5] is on the order of microseconds, which is much quicker than the timescale of the action potential in these nerves (10 to 100 ms) [5]. The nerve is solely composed of densely packed fibers, such that the mean distance between fibers is smaller than the size of a single fiber [22]. Thus, we assume that the whole nerve volume is at thermal equilibrium during the action potential, and we calculate the rise of the nerve's temperature as proportional to the amount of heat dissipated:

$$\Delta T = -\frac{Q}{c_p} A_m, \quad (\text{B2})$$

where $A_m = 65\,000 \text{ cm}^2 \text{ g}^{-1}$ is the total membrane area per mass of nerve [5].

APPENDIX C: THE CONDENSER THEORY FROM MAXWELL'S EQUATION FOR AMPÈRE'S LAW

Heat production and field energy can be unified using Maxwell's equation for Ampère's law [66],

$$\mathbf{E}(\nabla \times \mathbf{H}) = \mathbf{E} \cdot \mathbf{J} + \mathbf{E} \cdot \frac{\partial \mathbf{D}}{\partial t}, \quad (\text{C1})$$

where \mathbf{J} is the current density (A m^{-2}), \mathbf{H} is the magnetic field, and \mathbf{D} the displacement field. $-\mathbf{E} \cdot \mathbf{J}$ is the energy dissipated by an ionic current \mathbf{J} in an electric field \mathbf{E} as heat per unit of volume and time [66–69], noted $\dot{Q}_{\text{EJ},\text{V}}$ (negative when heat is dissipated). Based on the planar symmetry of the problem, we will reduce all vectorial quantities \mathbf{v} into only their component varying normal to the membrane ($\mathbf{v} = v\hat{x}$). Neglecting magnetic contributions, and in one dimension, we find

$$\dot{Q}_{\text{EJ},\text{V}} = -E J = E \frac{\partial D}{\partial t}. \quad (\text{C2})$$

This relationship offers another way to understand the Condenser Theory: during the action potential, positive charges (Na^+ and K^+ ions) move through ion channels of the membrane [9], first in the same direction as the electric field ($-E J < 0$, in one dimension), then against the electric field ($-E J > 0$), which results in heat production ($\dot{Q}_{\text{EJ},\text{V}} < 0$) and then heat absorption ($\dot{Q}_{\text{EJ},\text{V}} > 0$). Let us consider the situation where the field is 0 at time zero and E at time t . If the dielectric medium is linear ($D = \varepsilon E$), the heat absorbed between time 0 and t is equal to the field energy at time t :

$$Q_{\text{EJ},\text{V}} = \int_0^t E \frac{\partial D}{\partial t} dt = \frac{1}{2} \int_0^t \left(E \frac{\partial D}{\partial t} + \frac{\partial E}{\partial t} D \right) dt = \frac{1}{2} E D. \quad (\text{C3})$$

The second equality holds for any linear dielectric medium, whereas the third is given by the fundamental theorem of calculus. Finally, integrating $Q_{\text{EJ},\text{V}}$ over the membrane domain Ω_M gives the heat dissipated per unit of membrane surface area (J m^{-2}):

$$Q_{\text{EJ}} = \int_{-\infty}^{+\infty} \int_0^t E \frac{\partial D}{\partial t} dt dx = \int_{-\infty}^{+\infty} \frac{1}{2} E D dx. \quad (\text{C4})$$

This last expression shows that upon release of the free energy of the dielectric cell membrane, a quantity of heat equal to the field energy is liberated.

APPENDIX D: DERIVATION OF THE ELECTROSTATIC FREE ENERGY OF THE MEMBRANE CAPACITANCE AND OF DOUBLE LAYERS

In this section we split the free energy of the Ω_M domain [given by Eqs. (23) or (C4)] into a contribution from the membrane capacitance and one from the double layers. This separation is necessary to entropy calculations (Sec. IID). We start by expanding the field energy expression over the internal diffuse layer, the membrane, and the external diffuse layer:

$$F_{\text{el}} = \frac{1}{2} \left[\varepsilon_w \int_{-\infty}^{-\delta} \left[\frac{d\phi_i(x)}{dx} \right]^2 dx + \varepsilon_m \int_{-\delta}^0 \left[\frac{d\phi_m(x)}{dx} \right]^2 dx + \varepsilon_w \int_0^{+\infty} \left[\frac{d\phi_o(x)}{dx} \right]^2 dx \right]. \quad (\text{D1})$$

Assuming the density of free charges to be zero at any point $]-\delta; 0[$ inside the membrane, Poisson's equation requires the field to be constant across the membrane, such that $\frac{d\phi_m(x)}{dx} = \frac{d\phi_m(0)}{dx}$. The second term in the RHS of Eq. (D1) then simplifies to

$$\begin{aligned} \varepsilon_m \int_{-\delta}^0 \left[\frac{d\phi_m(x)}{dx} \right]^2 dx &= \varepsilon_m \int_{-\delta}^0 \left[\frac{d\phi_m(0)}{dx} \right]^2 dx \\ &= \varepsilon_m \left(\frac{q}{\varepsilon_m} \right)^2 \int_{-\delta}^0 dx \\ &= \frac{q^2}{c_m}. \end{aligned} \quad (\text{D2})$$

The second equality is given by boundary conditions for the electric field, Eq. (17). Next, integration by parts of the first and third terms in Eq. (D1) gives

$$F_{\text{el}} = \frac{1}{2} \left[\varepsilon_w \left(\frac{d\phi_i}{dx} \phi_i \right)_{-\infty}^{-\delta} - \varepsilon_w \int_{-\infty}^{-\delta} \phi_i \frac{d^2\phi_i}{dx^2} dx + \frac{q^2}{c_m} + \varepsilon_w \left(\frac{d\phi_o}{dx} \phi_o \right)_0^{+\infty} - \varepsilon_w \int_0^{+\infty} \phi_o \frac{d^2\phi_o}{dx^2} dx \right]. \quad (\text{D3})$$

Remembering that the potential is constant at $-\infty$ and $+\infty$, using Eqs. (13) and (14) and Poisson's equation, Eq. (D3) can be rearranged into

$$F_{\text{el}} = \frac{1}{2} \left[\int_{-\infty}^{-\delta} \rho_i \phi_i dx + (\sigma_i + q) \phi_i(-\delta) + \int_0^{+\infty} \rho_o \phi_o dx + (\sigma_o - q) \phi_o(0) + \frac{q^2}{c_m} \right]. \quad (\text{D4})$$

As $q = -c_m(\phi_i(-\delta) - \phi_o(0))$ by Eq. (19), this last expression simplifies to

$$F_{el} = \frac{1}{2} \left[\int_{-\infty}^{-\delta} \rho_i \phi_i dx + \sigma_i \phi_i(-\delta) + \int_0^{+\infty} \rho_o \phi_o dx + \sigma_o \phi_o(0) \right]. \quad (D5)$$

By applying the substitution $\phi_i = (\phi_i - V_m) + V_m$ and using Eqs. (11) and (19), we separate the free energy in the diffuse layers (F_{el}^{DL}) from the one in the membrane (F_{el}^m):

$$F_{el}^{DL} = \frac{1}{2} \left[\int_{-\infty}^{-\delta} \rho_i (\phi_i - V_m) dx + \sigma_i (\phi_i(-\delta) - V_m) + \int_0^{+\infty} \rho_o \phi_o dx + \sigma_o \phi_o(0) \right] \quad (D6)$$

and

$$F_{el}^m = \frac{1}{2} c_m \phi_i V_m, \quad (D7)$$

with $F_{el} = F_{el}^{DL} + F_{el}^m$.

APPENDIX E: DERIVATION OF ENTROPY CHANGES IN THE MEMBRANE

In Appendix C we showed that the electrostatic free energy the cell membrane can be released as heat. In this Appendix, we will show that if the membrane capacitance has a dependence on temperature, an additional quantity of heat will be liberated, due to entropy changes. This idea was brought up in earlier works on the Condenser Theory, in which Refs. [5,19] argued that entropy changes in the lipid bilayer could account for up to 4 times the free energy changes. They calculated the ratio between the entropy-related energy and the free energy as

$$\frac{T \Delta S}{\Delta F} = \frac{T}{C_m} \frac{\partial C_m}{\partial T}, \quad (E1)$$

where C_m is the membrane capacitance expressed in F ($C_m = c_m A_m$). However, no full derivation of this equation is reported in the literature. Here we will derive Eq. (E1) and show under which conditions it holds. Our demonstration will be based to a great extent on a derivation by Fröhlich [34] of the entropy of a dielectric in an electric field. Let us consider a membrane that holds a potential difference V between its two sides and that does not hold any fixed surface charges, for simplicity. This simplification will ease notations without modifying the relation between the membrane's entropy and electrostatic free energy. We start by evaluating the change of internal energy dU (in J) following an increment of charge dq (here q is the capacitive charge in C). The first law of thermodynamics reads

$$dU = dQ + dW = dQ + V dq,$$

where dQ is the influx of heat and dW is the electrical work done on the membrane. Note that the electrical work did not appear explicitly in the thermodynamic system defined in Sec. II B, since no electrical work is done on Ω_M by the surroundings [the latter is, however, implicitly accounted for as ΔF_{el} in Eq. (21)]. For the purpose of this demonstration,

the thermodynamic system we consider here consists of the membrane only ($x \in]-\delta; 0[$), which allows us to express the electrical work associated with the depolarization and repolarization of the membrane explicitly. Assuming that the capacitance C_m remains constant with V but depends on the temperature T , we obtain

$$dq = d(C_m \cdot V) = dC_m V + C_m dV = \frac{\partial C_m}{\partial T} dT V + C_m d(V). \quad (E2)$$

Thus, a variation of q may be due to a variation of temperature or of potential, the capacitance being assumed to remain constant for the range of physiological potentials (*ca.* -100 mV to $+20$ mV). By taking T and V^2 as independent variables, the first law now becomes

$$dQ + V^2 \frac{\partial C_m}{\partial T} dT + \frac{1}{2} C_m d(V^2) = dU = \frac{\partial U}{\partial T} dT + \frac{\partial U}{\partial (V^2)} d(V^2). \quad (E3)$$

Note that dQ is not a *total differential*; however, $dS = dQ/T$ is one, for a reversible process [34]. This property means that a unique function $S(T, V^2)$ must exist, such that

$$dS = \frac{\partial S}{\partial T} dT + \frac{\partial S}{\partial (V^2)} d(V^2). \quad (E4)$$

Thus if there is a relation $dS = f(T, V^2) dT + g(T, V^2) dV^2$, where f and g are two unknown functions, the condition that dS is a *total differential* requires that

$$\frac{\partial f}{\partial (V^2)} = \frac{\partial g}{\partial T}, \quad (E5)$$

as both sides of Eq. (E5) are equal to $\partial^2 S / [\partial T \partial (V^2)]$, by Eq. (E4). Next, by substituting for $dS = dQ/T$ in Eq. (E3), we find

$$dS = \frac{1}{T} \left(\frac{\partial U}{\partial T} - V^2 \frac{\partial C}{\partial T} \right) dT + \frac{1}{T} \left[\frac{\partial U}{\partial (V^2)} - \frac{C_m}{2} \right] d(V^2). \quad (E6)$$

This equation is analogous to Eq. (E4) and therefore, Eq. (E5) becomes

$$\frac{\partial}{\partial (V^2)} \left[\frac{1}{T} \left(\frac{\partial U}{\partial T} - V^2 \frac{\partial C_m}{\partial T} \right) \right] = \frac{\partial}{\partial T} \left\{ \frac{1}{T} \left[\frac{\partial U}{\partial (V^2)} - \frac{C_m}{2} \right] \right\}. \quad (E7)$$

By carrying out differentiations we find (take $\partial C_m / \partial T$ as a constant):

$$\frac{\partial U}{\partial (V^2)} = \frac{C_m}{2} + \frac{1}{2} \frac{\partial C_m}{\partial T} T. \quad (E8)$$

Finally, upon integration, we obtain

$$\begin{aligned} \Delta U &= \frac{1}{2} \int_0^{V^2} \left(C_m + \frac{\partial C_m}{\partial T} T \right) d(V^2) \\ &= \frac{1}{2} C_m V^2 + \frac{1}{2} \frac{\partial C_m}{\partial T} T V^2. \end{aligned} \quad (E9)$$

The first term is the free energy change ΔF of the capacitor, whereas the second is the energy associated with a change of

entropy $T \Delta S$. Thus we have

$$T \Delta S = \Delta U - \Delta F = \frac{1}{2} \frac{\partial C_m}{\partial T} T V^2 = \frac{T}{C_m} \frac{\partial C_m}{\partial T} \Delta F, \quad (\text{E10})$$

and Eq. (27) holds, under the condition that the membrane capacitance has a linear dependence on temperature but is constant with potential. A number of recent studies indicate that there exists such a linear dependence and that the value of $\partial C_m / \partial T$ is $\sim 0.3\% / ^\circ\text{C}$ for a wide range of cell membranes [25,54,70–72]. Why does the membrane capacitance change with temperature? Using the classical model for the membrane capacitance, $C_m = \epsilon_m A_m / \delta$, where δ is the membrane thickness, the temperature dependence could be attributed

to a variation of the dielectric permittivity $\partial \epsilon_m / \partial T$ or to a variation of the membrane dimensions ($\partial A_m / \partial T$ and $\partial \delta / \partial T$). Dimensional changes have been measured in artificial lipid bilayers [37–39], and in neurons, these changes correspond to a $0.11 + -0.03\% / \text{K}$ reduction in the lipid membrane thickness and a $0.22 + -0.03\% / ^\circ\text{C}$ increase in the area per lipid, resulting in a linear increase of the capacitance with temperature of $0.3\% / \text{K}$ [25]. Little is known on how the membrane's dielectric permittivity varies with temperature; however, $\partial \epsilon_m / \partial T$ has been measured for unsaturated fatty acids (the molecules composing the core of the membrane), yielding values more than one order of magnitude smaller than the combined dimensional changes [25,26].

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