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Towards a thermodynamic theory of nerve pulse propagation

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ABSTRACT

Nerve membranes consist of an approximately equal mixture of lipids and proteins. The propagation of nerve pulses is usually described with the ionic hypothesis, also known as the Hodgkin–Huxley model. This model assumes that proteins alone enable nerves to conduct signals due to the ability of various ion channel proteins to transport selectively sodium and potassium ions. While the ionic hypothesis describes electrical aspects of the action potential, it does not provide a theoretical framework for understanding other experimentally observed phenomena associated with nerve pulse propagation. This fact has led to a revised view of the action potential based on the laws of thermodynamics and the assumption that membrane lipids play a fundamental role in the propagation of nerve pulses. In general terms, we describe how pulses propagating in nerve membranes resemble propagating sound waves. We explain how the language of thermodynamics enables us to account for a number of phenomena not addressed by the ionic hypothesis. These include a thermodynamic explanation of the effect of anesthetics, the induction of action potentials by local nerve cooling, the physical expansion of nerves during pulse propagation, reversible heat production and the absence of net heat release during the action potential. We describe how these measurable features of a propagating nerve pulse, as well as the observed voltage change that accompanies an action potential, represent different aspects of a single phenomenon that can be predicted and explained by thermodynamics. We suggest that the proteins and lipids of the nerve membrane naturally constitute a single ensemble with thermodynamic properties appropriate for the description of a broad range of phenomena associated with a propagating nerve pulse.

Contents

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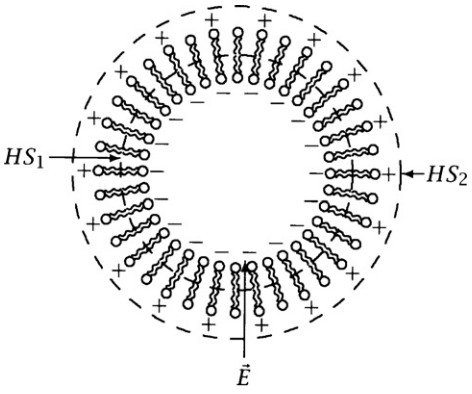
1. Introduction

Consciousness and the ability to move are examples of processes that involve the propagation of information from one neuron to another in the form of nerve signals. How do nerve signals propagate? Why do they have velocities of 100 m/s over the meter-long distance from brain to legs? Clearly such questions are long standing, and many models have been proposed to answer them.

In most modern models, the nerve membrane is thought to play a fundamental role in nerve signal propagation. Biological membranes consist of a lipid bilayer and proteins. The charges on the two surfaces of the membrane are not equal, with the interior of the membrane negatively charged relative to the exterior. Therefore, there is a membrane potential difference, ψ measured in millivolts, which is proportional to the difference in charges between the outside and the inside of the membrane (Box 1A). Given this asymmetry, there are many processes that can change the value of ψ. These include changes in membrane surface area and thickness during the action potential (see Box 1B), currents of ions across the membrane, and changes in the ion concentration in solutes in contact with the membrane.

At the beginning of the 20th century, the nerve signal, or action potential, was thought to involve the propagation of a transient local breakdown of ψ (Box 2Aa; reviewed in Hodgkin and Huxley, 1945). Since the membrane potential difference was assumed to vanish locally during the action potential (Box 2Aa), the resting value of ψ was expected to be larger than the membrane potential during the action potential. When this assumption was tested experimentally, Curtis and Cole reported in 1942 that the opposite is the case. Namely, the membrane potential during the action potential is much larger than the resting potential (Box 2Ab; Curtis and Cole, 1942; Hodgkin and Huxley, 1945). Such experiments led to the Hodgkin and Huxley model, also called the ionic hypothesis

Box 1.



(A) Schematic diagram of a nerve in cross-section.
The two hypothetical spherical surfaces (HS_1 and HS_2, dashed lines) enclose different amounts of electric charge. According to Gauss' law, the electric field E is nonzero in the region between these surfaces. The measured electric potential at the inner surface of a nerve is approximately −70 mV relative to that of the outer surface which is set at 0 mV by convention (Johnston and Wu, 1995; reprinted with permission by the MIT Press).
(B) Changes in the membrane potential during a propagating density pulse (the action potential) are expected. This is because the membrane's charge density is different in the fluid and gel states. Thus, based on the knowledge of structural changes occurring in a pure lipid membrane going from fluid to gel phase, it is known that for a given constant number of lipids, the membrane thickness increases by about 16%, the lipid area decreases by about 24%, and the lipid volume increase by about 4% (Heimburg and Jackson, 2007b). These geometric changes are consistent with experimental observations showing both a shortening and a thickening of the nerve during the nerve pulse (Iwasa et al., 1980; Tasaki et al., 1989). In piezoelectric materials, voltage and density changes are tightly correlated (Cole, 1941), and coupling between lateral density and electrostatic potential is also known as electromechanical coupling (Gross et al., 1983).
The membrane potential, Ψ, during passage of the electromechanical pulse may be estimated using the Gouy-Chapman theory. For physiological conditions (>200 mM salt, 10% charged lipid) Ψ can be calculated approximately as

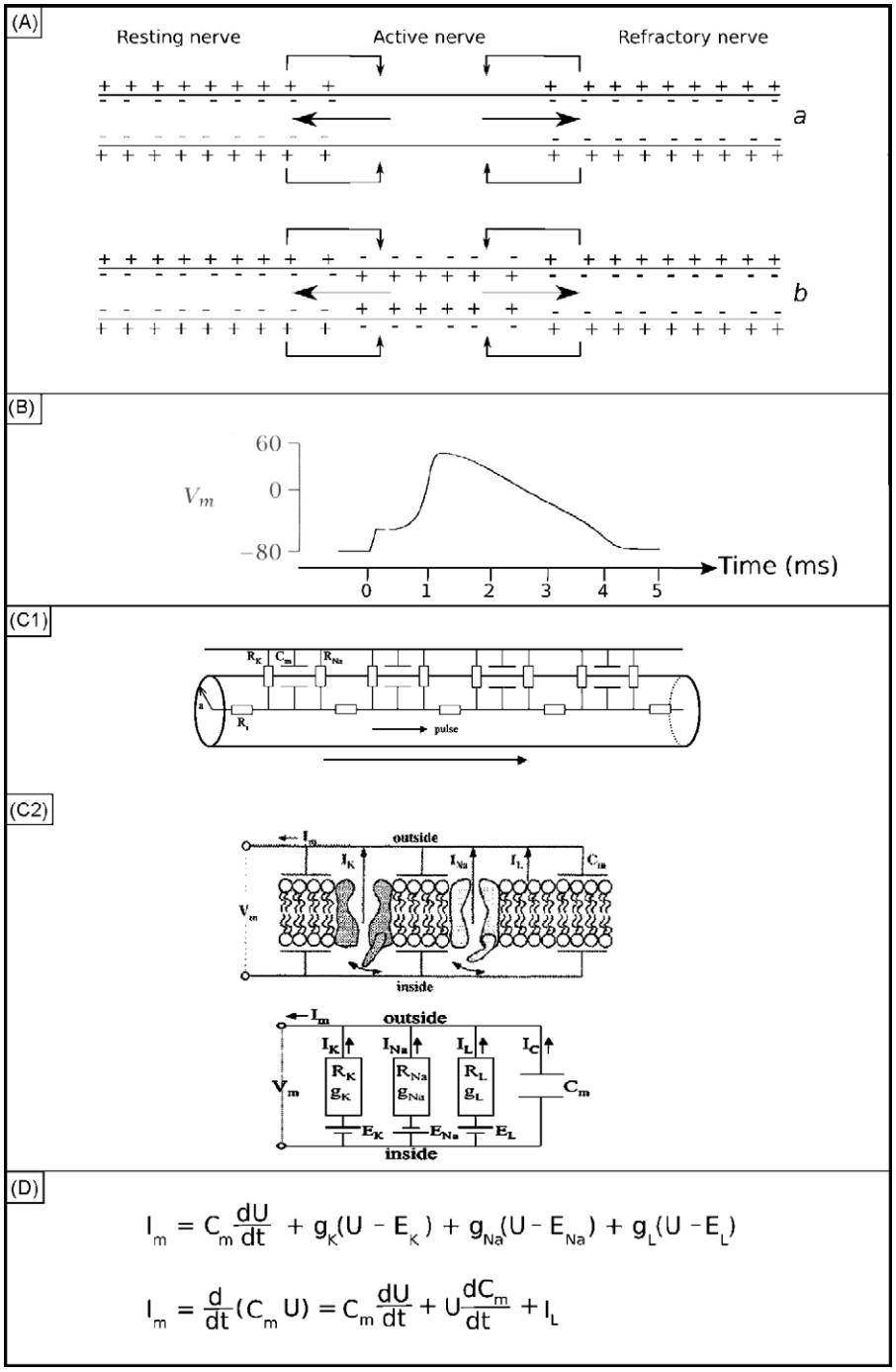
$$\Psi = \left[\frac{1}{\varepsilon_0 \varepsilon \kappa}\right]\sigma$$

where ε_0 is the dielectric constant in vacuum: 8.86×10^{-12} C^2/Jm; ε is the relative permittivity for water: 80 C^2/Jm; κ is the Debye constant that depends on the ionic strength. For a monovalent salt at concentration c, it is given by $\kappa = [2e^2/(\varepsilon_0 \varepsilon \kappa T)c]^{1/2}$; σ is the charge density. Using this equation for Ψ and the relatively crude simplifying assumptions regarding lipid distribution (i.e., 10 mol% charged lipids with all charged lipids located at the inner membrane at physiological ionic strength), the potential of the inner membrane at the lipid surface is calculated to (Heimburg and Jackson, 2007a):

$$\begin{array}{lll} \text{Fluid}: & \Psi^{\text{in}} \sim -100\,\text{mV} & \Psi^{\text{out}} = 0\,\text{mV} \\ \text{Gel}: & \Psi^{\text{in}} \sim -150\,\text{mV} & \Psi^{\text{out}} = 0\,\text{mV} \end{array}$$

This corresponds to a voltage change of $\Delta\Psi \sim 50$ mV at the peak of the soliton. This is of the same order as the voltage change in the action potential, which is about 100 mV. This is a very rough estimate since the exact charge of the lipid membrane on both sides of the membrane is not known and protein charges have not been considered. However, it seems that known changes in membrane area during the action potential are of an order of magnitude sufficient to account for the observed voltage changes during the action potential. Furthermore, the membrane alters thickness during the action potential, thereby changing the membrane capacitance (see Boxes 2–4). Hence, the approximation of constant capacitance, made in the Hodgkin and Huxley model, is unjustified (see Box 2; Heimburg and Jackson, 2007a).

Box 2. The ionic hypothesis. (A) Diagram illustrating (a) the classical and (b) the revised ionic hypothesis concept of action potential propagation (redrawn after Hodgkin and Huxley, 1945). (B) At time zero, the nerve is stimulated, and a propagating nerve signal is measurable as a time-dependent change in the membrane potential. (The results shown are for a calculated action potential.) (C) Nerve signal propagation model: depolarization causes voltage-gated ion channels to open locally allowing Na^+ ions to flow in and K^+ ions to flow out through the nerve membrane. In addition, there is a nonspecific leakage current, I_L. By such mechanisms, the depolarization is continuously regenerated and moved along the nerve. The equivalent electrical circuit is shown in C1 where each unit of membrane resistors and capacitor, shown in detail in a voltage clamp situation in C2, corresponds to a local area element of the membrane. The arrow in the middle of the cylinder (C1) indicates the electric current running inside the neuron. The neuron has an associated cytoplasmic resistance (the resistors inside the cylinder), which is assumed to be much larger than the extracellular resistance (considered negligible). Current flowing through the resistors should result in a net heat dissipation that is not observed experimentally. To restore the cellular gradients in sodium and potassium ion concentrations, pumps fueled by ATP work in the background to pump Na^+ out of the cell and simultaneously pump K^+ into the cell (not shown, Morth et al., 2007); this may be facilitated by the cellular cytoplasm having a higher affinity for K^+ ions than the extracellular environment (Ling, 1984). (D) The current across the membrane is described classically by the top equation which assumes the membrane capacitance to be constant. As shown in Box 1, this is incorrect due to physical changes in membrane thickness and area during passage of a nerve pulse. A more complete description of the capacitive current is provided by the bottom equation, which includes the effects of capacitance change, $U\,dC_m/dt$.



(Albright et al., 2000). This model suggests that ψ is reversed locally during the action potential (Boxes 1B and 2Ab, B), changing from −70 mV at rest to +30 mV during the action potential (Hodgkin and Huxley, 1945, 1952; Hodgkin, 1976; Albright et al., 2000; Huxley, 2002).

2. What characterizes a good model for a biological process?

In scientific inquiry, a good model is one with high predictive power. From a theory of a given system it should be possible to explain how the system functions and predict how it will respond to perturbations. While the ionic hypothesis provides a possible explanation for understanding the propagating change in voltage during the action potential, its foundation is based exclusively on a change in charge distribution (Box 2). It is incapable of explaining or predicting many experimentally observed characteristics of nerve signal propagation. We describe here that the nerve membrane has generic physical properties which permit the propagation of localized electromechanical pulses that can be described using the language of thermodynamics. It has been suggested that describing the action potential as a phenomenon that can be described as an electromechanical, piezoelectric, hydrodynamic or pseudo-acoustical pulse provides a more complete description of the propagating action potential than the purely electrical model offered by the ionic hypothesis (Wilke and Atzler, 1913; Cole, 1941; Hodgkin and Huxley, 1945; Kobatake et al., 1971; Kaufmann, 1989; Heimburg and Jackson, 2005; Heimburg and Jackson, 2007a). Since this electromechanical description is based on thermodynamics, it allows for correct predictions of many of the observed properties of nerve signal propagation such as the change in membrane potential, the reversible heat, the induction of axon potentials through local nerve cooling, the physical expansion of nerves during the action potential, and the action of anesthetics.

3. The soliton model for nerve pulse propagation

3.1. Lipids are soft in the melting transition

Biological lipid membranes are predominantly in a fluid phase with only a minor portion in the gel phase. Slightly below body temperature, they display a transition from a fluid to a gel state over an interval of several degrees. This has been demonstrated in native bacterial membrane (Heimburg and Jackson, 2005, and references therein). The occurrence in the membrane of a mosaic of ordered lipid domains surrounded by fluid phase has been observed in living fibroblast cells and is typical in the vicinity of the transition temperature (Gaus et al., 2003).

When a biological membrane is compressed, the fluid membrane approaches the denser, more ordered, gel state. Sufficient compression either in membrane area or volume will induce a transition to the gel state. As in the familiar phase transition from water to ice, the transition from lipid fluid to gel state is associated with the release of heat (Box 3A). In the following, we will typically refer to the area compressibility.

Local compression is required to start a wave in water, air or membrane lipids. This increases the local density of the medium and creates a wave. In the soliton model, when the membrane is subjected to a propagating action potential, a region of the membrane is compressed locally and forced through the transition from fluid to gel state (Box 3B1). This suggests that the creation of a local region of gel state should induce an action potential (Box 1B). In support of this notion, it has been observed that local cooling of a nerve, which should cause a local transition from fluid to gel, does induce an action potential (Inoue et al., 1973). It has further been found in squid axons that the anisotropy of fluorescence markers changes during the pulse in ways that are typical for changes in lipid state. On this basis, the existence of transition phenomena during the action potential has been proposed (Kobatake et al., 1971).

Lipid membranes have the properties required for the generation and propagation of solitons. Pure lipid membranes are maximally compressible in the vicinity of the transition, and this has also been shown for native bacterial membranes. Thereafter, compressibility decreases sharply with increasing density or pressure. This effect is commonly denoted as "non-linearity". It is also known that lipid compressibility is frequency dependent (Box 3A; Heimburg and Jackson, 2005). This effect is known as "dispersion". This is true for both volume and area compressibilities.

The combined effects of non-linearity and dispersion are sufficient to produce a self-sustaining and localized density pulse with a moving segment of the nerve membrane in the gel state (Box 3B1). In mathematical physics, a pulse of this kind is called a "soliton". It is a self-reinforcing solitary wave (i.e., a wave packet or pulse, French, 1971) that maintains its shape while it travels at a constant speed which is somewhat less than the sound velocity in the lipid membrane.

Solitons are robust in the sense that any medium with the qualitative non-linear and dispersive characteristics described above is expected to support them. Solitons can propagate over extended distances without loss of energy (Heimburg and Jackson, 2005). Since no energy is lost to the environment during propagation, the pulse is also called an adiabatic pulse. The propagation of ordinary sound is a familiar example of an adiabatic wave. Solitons were first observed and described by John Scott Russell in the early 19th century as propagating solitary water waves on the Union Canal in Edinburgh. Russell followed these solitons for several miles and found no change in their shape, height or velocity. The soliton mode of pulse propagation is fundamentally different from the action potential picture given by the ionic hypothesis. In the latter, continuous free energy input is required to sustain propagation of the action potential.

3.2. A propagating nerve pulse is associated with a transient voltage change

In the soliton model, the nerve pulse forces the membrane through the transition from fluid to gel state (Box 3B1; Heimburg and Jackson, 2005). This transient state change has a profound effect on the membrane potential difference, ψ. Specifically, it changes both the area and thickness of the membrane and, hence, its capacitance. Since the membrane is asymmetrically charged, these changes appear as a voltage pulse (Boxes 1B and 3B) and lead to a capacitive current.

4. Reversible heat

4.1. Reversible heat: energy efficient nerve pulse propagation

Experimental observations by Hill dating back to 1925 showed that nerves heat locally during the initial rising phase of the action potential and cool by an equal amount during the recovery phase (Abbott et al., 1958; Howarth et al., 1968, reviewed in Ritchie and Keynes, 1985). The heat released during the first phase of the action potential is not dissipated by passive thermal conduction but is actively reabsorbed in phase with the change in voltage during the second phase of the action potential. Control experiments revealed that the observed cooling of the nerve is much more rapid than would be expected if this cooling were due to heat conduction (upper trace in Box 4B; Howarth et al., 1968; Tasaki et al., 1989; Tasaki and Byrne, 1992). As no net heat is released to the environment, the heat production is said to be reversible. In

thermodynamics, a process that occurs without heating the environment is said to be an adiabatic process (Atkins and de Paula, 2006). This observation is in marked contrast to the ionic hypothesis, where irreversible heat is produced and released to the environment (Box 2C).

Nerves communicate by transporting packets of energy in the form of action potentials. In the ionic hypothesis this energy is proportional to the electrostatic energy stored in the membrane capacitor, and electrical current is conducted across the membrane by ion channels that function as resistors (see Box 2C). Nerve pulse propagation is then explained as a moving self-regenerating pulse of local capacitive discharges through the resistors followed by capacitor recharging (Boxes 2C and 3B2). The passage of current through a resistor results in irreversible heat production, which should be observable in conjunction with propagation of the action potential (Box 2C). The ionic hypothesis predicts that the energy dissipated as heat should be approximately 600 times greater than the capacitive energy transported by an action potential propagating over one meter. Hence, the purely electrical view of the ionic hypothesis suggests that propagation of a nerve pulse is an energetically inefficient process. Such irreversible heat release is not observed experimentally (Box 4B). The reversible heat that is observed is not consistent with the predictions of the ionic hypothesis.

In contrast, in accord with the experimental observations, solitonic propagation of the action potential involves no dissipative heat production (Heimburg and Jackson, 2007a; Heimburg and Jackson, 2007b).

4.2. Reversible heat: a molecular explanation?

The appearance of reversible heat seems to be correlated with the discharging and recharging of the membrane. The experiments demonstrating reversible heat production required measurements in the μK range and on a millisecond time scale (see Box 4), and they are subject to considerable uncertainty despite the ingenious experimental techniques employed (Tasaki et al., 1989). Indeed, it is likely that the reversible heat production is significantly larger than currently estimated since the millisecond response time of the heat sensors may have been insufficient to measure the heat production profile accurately. Nevertheless, the elegant experiments of Hill and of Tasaki and co-workers (Abbott et al., 1958; Tasaki et al., 1989; Tasaki and Byrne, 1992) unequivocally show the reversible heat phenomenon. Current data indicate that the uncertainties in these measurements are at the level of 10–20% (Ritchie and Keynes, 1985). Hence, the heat may not be exactly reversible and, as in other real processes, some dissipation may occur (Ritchie and Keynes, 1985; Tasaki and Byrne, 1992).

Can reversible heat be explained within the framework of the ionic hypothesis? Ion flow, regarded as flow of current through resistors, is central to the ionic hypothesis (summarized in Boxes 2 and 3B2). It has been suggested that it is more appropriate to view the flow of ions from a high to a low concentration compartment as the expansion of an ideal gas, which cools as work is performed in charging the capacitor (extensively discussed in Abbott et al., 1958; Howarth et al., 1968; Ritchie and Keynes, 1985). The magnitude of this cooling should be related to the energy required to recharge the capacitor (Box 2C). Unfortunately, this energy appears to be several times too small to account for the magnitude of the observed reversible heat (Abbott et al., 1958; Howarth et al., 1968; Ritchie and Keynes, 1985). Instead, it was suggested to stem primarily from the free energy and entropy changes in the membrane dielectric (Howarth et al., 1968; Ritchie and Keynes, 1985). These changes also appear to be too small to account for the reversible heat (Tasaki et al., 1989; Tasaki, 1999). Therefore, at present the analogy of capacitors and resistors, which is central to the ionic hypothesis, cannot explain the reversible heat phenomenon. Indeed, Hodgkin noted that Hill's most puzzling observation was that of reversible heat and, in particular, that its cooling phase could not be explained within the framework of the ionic hypothesis (Hodgkin, 1964, p. 70, quoted in part by Heimburg and Jackson, 2007a, note also Box 4B upper trace). Tasaki has proposed that enthalpy contributions from reversible intracellular ionic exchange may be associated with reversible heat (Tasaki, 1982; Tasaki et al., 1989).

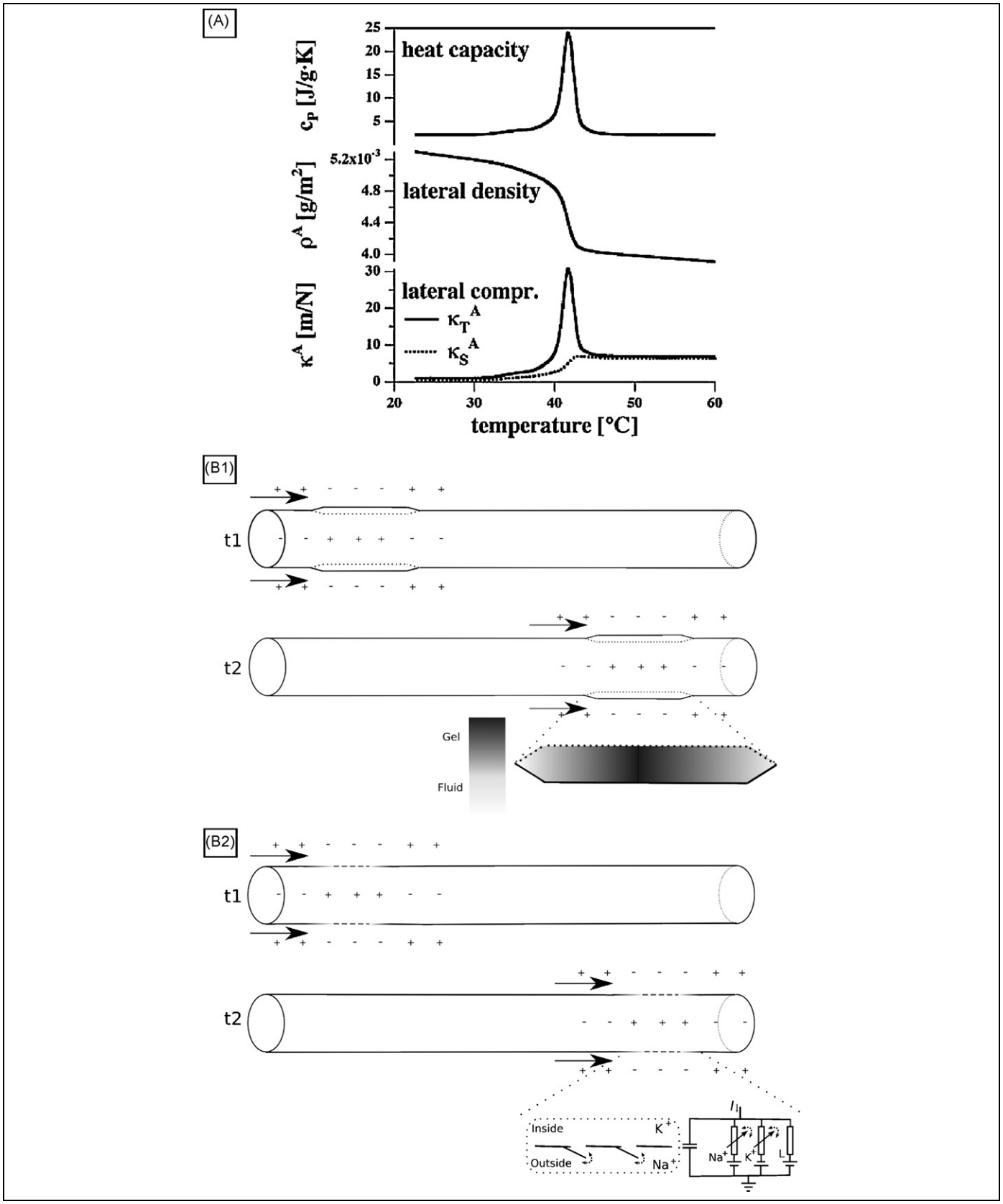
In comparison, the soliton model does not involve any ions or flow of ions. In its current form, the soliton model suggests that the action potential causes a transient transition of the membrane from fluid to gel state with the associated production of latent heat (Box 3A and B1) and the reabsorption of an identical quantity of heat as the system returns to the fluid state. Evidently, this flow of heat is precisely correlated with changes in membrane density and potential. Given a melting enthalpy of 38.1 kJ/mol (Heimburg, 2007a) for the lipid DiPalmitoylPhosphatidylCholine (Box 3A), this corresponds to about 2×10^{-5} J/cm^2, which is of the right order of magnitude (Abbott et al., 1958). We suggest lipid melting enthalpy may be the primary source for the reversible heat.

The intriguing phenomenon of reversible heat may serve to discriminate between various models of the action potential. Given the importance and delicacy of these experiments, this phenomenon merits further investigation.

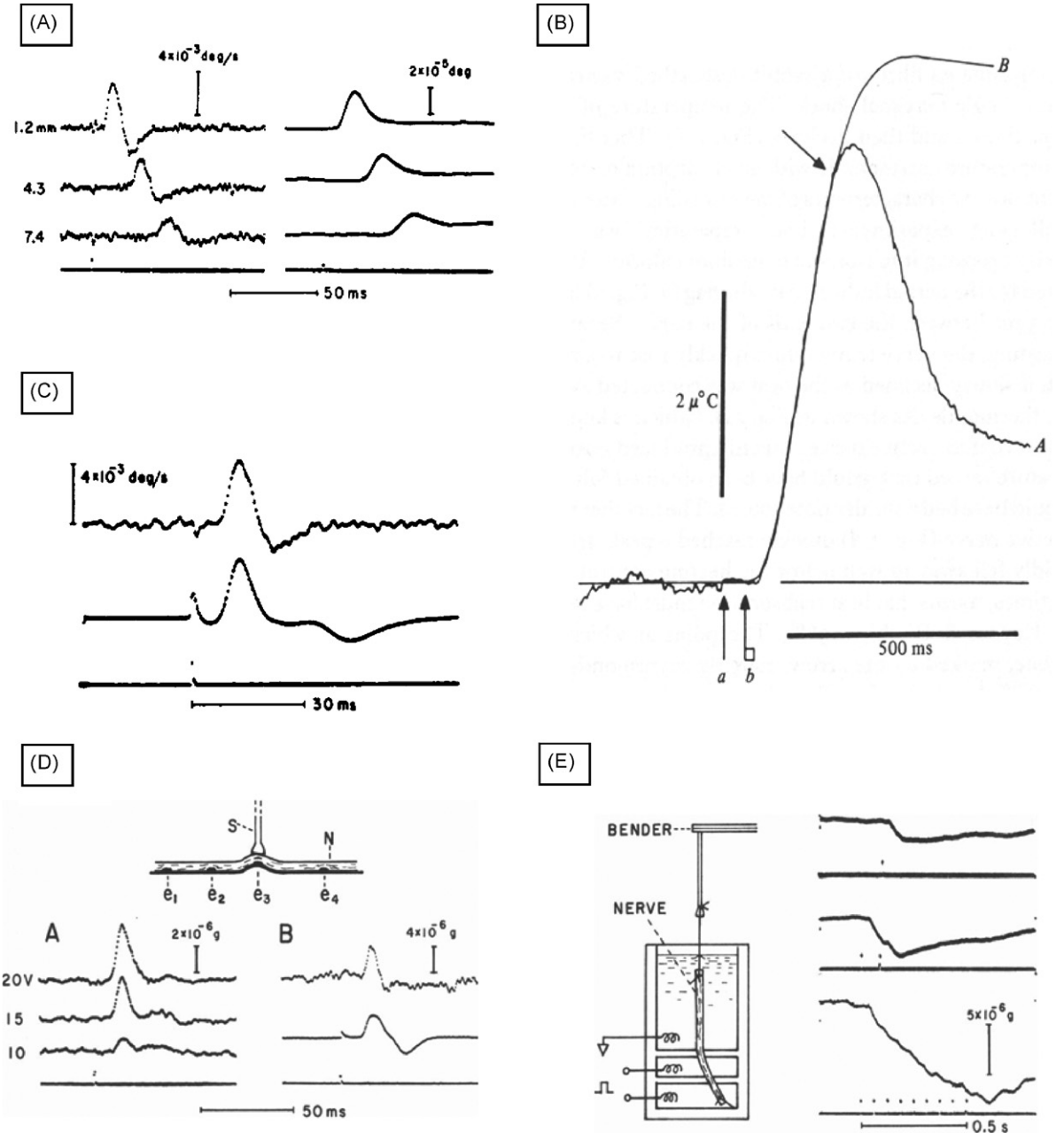
Box 3. (A) Phase transition data for the pure lipid DiPalmitoylPhosphatidylCholine (DPPC) (Heimburg and Jackson, 2005). Top: heat capacity (top vertical axis) as a function of temperature. The heat capacity shows a dramatic peak at the 41 °C phase transition temperature. A plot of heat capacity versus pressure or lateral density would show a similar peak. Middle: when the lipid passes from the high-temperature fluid to the low-temperature gel phase, the lateral density increases abruptly. This is because the membrane is 24% more tightly packed in the gel state. A transient membrane density change of this magnitude can explain the observed change in the membrane potential during the action potential (see Box 1). Bottom: in the region of the phase transition, the membrane becomes dramatically more compressible at low frequencies (solid line); a much smaller softening is observed at ultrasonic (5 MHz) frequencies (dotted line). Nerve transmission is a low frequency phenomenon (e.g., about 1 kHz), for which the area compressibility is expected to be similar to the low frequency results shown. The temperature dependence of the compressibility has not been measured in the 1 kHz region. (Heimburg and Jackson, 2005 and references therein).
(B) Schematic model comparison of the characteristics of the membrane lipid thermodynamic theory (B1) and the ionic hypothesis (B2) for nerve signal propagation.
(B1) An action potential (shown at times *t*1 and *t*2) flows along the neuron as an electromechanical pulse and can be measured, for example, as a local thickening of the membrane (see Box 4D from Tasaki et al., 1989; Iwasa et al., 1980). As shown, the membrane is in a transient gel state in the vicinity of the propagating pulse; the remainder of the system remains in the fluid state.
(B2) An action potential (shown at times *t*1 and *t*2) flows along the neuron as a propagating change in ψ caused by the opening of specific voltage-gated K^+ and Na^+ ion channels which results in an ion-specific increase of membrane permeability (dashed lines indicate increased membrane permeability).
The membrane potential difference, ψ, is denoted with plus and minus signs, and the measured change in ψ during the action potential can be accounted for with either model (see also Boxes 1 and 2).

5. From microscopic to macroscopic: the length scale of models

What is the size of an action potential? Depending on the nerve, an action potential propagates at approximately 0.1–100 m/s and has a duration of 1–20 ms. This corresponds to action potential lengths ranging from a few millimeters to a few centimeters. In the ionic hypothesis, the action potential is described as due to the coordinated opening and closing of specific voltage-gated sodium and potassium ion channels that are roughly 5 nm in diameter (Bean, 2007). These ion channels are uniformly distributed along



Box 4. Physical changes measured in a nerve during nerve signal propagation. (A) Thermal response: during the passage of a nerve pulse, the nerve is heated locally and then cools again. The heat response observed depends on the distance (indicated in mm) between the stimulating electrode and the heat sensor. Records on the right were obtained from the records on the left by integration. (B) The heat is reversible: if the nerve is heated locally to the same extent as during the passage of an action potential, its subsequent cooling by dissipation/passive heat conduction (the horizontal line, B trace) is much slower than that of the reversible heat's cooling phase (A trace). Since no heat is dissipated to the environment, propagation of the pulse is an adiabatic process. (C) The thermal response (top) and the action potential (bottom) coincide temporally. (D) Mechanical response of a nerve to 0.5 ms voltage pulses: (left) the stylus (S) measures an expansion of the nerve which is dependent on stimulus voltage. (Right) temporal relationship between the mechanical response (top) and the action potential (bottom). Here, e1–e4 indicate electrode positions, S is the stylus, and N is the nerve. (E) The nerve shortens during nerve signal propagation: (left) experimental arrangement employed for recording changes in the mechanical force developed in the longitudinal direction of the nerve. (Right) Three experiments, each represented by two pairs of traces. The top traces show the isometric recording of shortening of the nerve associated with the generation of a propagating pulse. The downward movements of the traces represent the development of a force tending to pull the tip of the piezoelectric bender downwards. The lower traces show the electrical pulses delivered (marked by dots) to the end of the nerve, at the opposite end of the piezoelectric bender, at the lower part of the experimental set up (shown on the left) (figure B is from Ritchie and Keynes, 1985 with permission by Cambridge University Press. The remaining figures are from Tasaki et al., 1989 with permission by the Biophysical Society).



the membrane in non-myelinated nerves and localized at the nodes of Ranvier in myelinated nerves. Hence, the current standard description of the action potential is realized on the nanometer scale in terms of ion channels (Bean, 2007) whose density ranges from a few hundred per square μm membrane in non-myelinated nerves to a few thousand per square μm at the nodes of Ranvier (Hille, 2001). By comparison, each square μm membrane contains several million lipid molecules.

It is a common strategy in physics to construct models of physical systems on a length (or time) scale similar to that of the phenomenon to be described rather than on atomic or molecular scales. Indeed, critical phenomena do not even possess a characteristic length scale, and such phenomena cannot be understood on the molecular scale. Too much microscopic detail can obscure those subtle collective effects which are often of primary interest. The propagation of sound provides a useful elementary illustration. An appropriate description of sound starts from the equation of state for air (i.e., the relatively simple relation between the pressure, temperature and volume of a given quantity of air). Application of the laws of thermodynamics quickly reveals that sound corresponds to small collective variations in the density of air on the macroscopic scale of its wavelength (roughly one meter for speech). Since air is composed of molecules, we might be tempted to consider an alternative microscopic description of sound based on molecular dynamics simulations. Our first unpleasant discovery would be that the motion of individual molecules is classically chaotic (i.e., exponentially sensitive to initial conditions) and hence beyond practical calculation. Greater effort would reveal that microscopic chaos leads to the simple regularities of an equation of state and the validity of thermodynamics at length scales relevant for sound. The proof that this is the case is surprisingly recent, and the demonstration that microscopic chaos can lead to macroscopic order and simplicity is little more than a decade old (Sinai, 1994). Although individual air molecules are obviously involved in sound propagation, it is possible to make meaningful models of sound propagation only at length scales corresponding to the wavelength of sound, which is much larger than the size of individual air molecules. In short, the many "trees" of detail in excessively microscopic models can obstruct our view of the "forest" of collective phenomena.

Nevertheless, similar differences in scale form the basis for the description of the action potential in the ionic hypothesis, which is based on nanometer-sized ion channels that are one to ten million times smaller than the action potential. We find this million-fold scale difference to be significant and to provide an additional indication that ion-channel models of nerve pulse propagation are inappropriate. Molecular ensemble properties at the centimeter scale have been demonstrated for lipids (Heimburg and Jackson, 2005), whereas ensemble or cooperative properties of proteins at the centimeter length have not been described, although studies indicate that such properties may exist (Changeux et al., 1967; Naundorf et al., 2006). As with sound propagation in air, the most useful description of nerve pulse propagation is likely to come from models which incorporate the properties of ensembles of molecules on a length scale similar to that of the nerve pulse itself.

6. Anesthetics interfere with nerve pulse generation

Many current models of anesthetic action are based on specific binding to and inhibition of the function of specific neuronal proteins, e.g., ion channel proteins (Miller, 2002). This has led to the experimental study of model systems such as that based on the binding of anesthetics to luciferase, a protein which is not involved in nerve transmission (Franks and Lieb, 1994; Campagna et al., 2003).

These protein-based models of anesthetic action were preceded by the early and remarkably successful century-old Meyer-Overton rule that established a linear relation, valid over six orders of magnitude, between the potency of an anesthetic and its partition coefficient in lipid. This finding led to the hypothesis that a lipid mechanism underlies anesthetic action, and to date no other rule based on physiochemical or structural parameters has been as useful as the Meyer-Overton rule in predicting anesthetic potency (reviewed in: Miller et al., 1973; Smith et al., 1984; Heimburg and Jackson, 2007c; Urban, 2008). However, as Miller pointed out: "Though the regularities observed are consistent with the view that anesthesia is induced at a specified molar concentration in a particular phase, it must be recognized that correlations of this type cannot prove such a hypothesis. Nevertheless, the range over which the generalization appears to hold is a remarkable one and, indeed, unique in biology" (Miller et al., 1965). At the time that the Meyer-Overton correlation was established, it was assumed that anesthesia was a unique state achieved by any anesthetic. Today, anesthesia is often viewed as a collection of a variety of different neurophysiological states acting on a plethora of subcellular structures (Schüttler and Schwilden, 2008; Urban, 2008). It has been argued that anesthetics generate a lateral pressure within the membrane that can affect protein conformations (e.g., open and closed states of an ion channel). This view seems attractive because it combines lipid and protein mechanisms, but it lacks experimental verification (Miller et al., 1973; Cantor, 1997).

Here, we will not consider the precise cause of anesthesia. We will, however, outline some consequences of the presence of anesthetics in membranes and their effect on melting transitions. It has been shown that anesthetics lower the fluid-gel transition temperature, a phenomenon known as "freezing point depression" (Kharakoz, 2001; Heimburg and Jackson, 2007a,c; mentioned in Kinnunen and Virtanen, 1986). By definition, freezing point depression presumes a compound to be ideally miscible in the fluid phase and completely immiscible in the gel phase, and it renders the membrane more fluid at the same temperature. In contrast, such assumptions cannot be made on the basis of the Meyer-Overton correlation which only addresses the compound's partition coefficient into lipid regardless of the phase state. An anesthetic is more potent if it produces the same freezing point depression at a lower concentration. Said in a different way, the potency of an anesthetic is assumed to depend on how well it partitions into the fluid phase of the membrane. Indeed, it seems that the concentration-dependent ability of a given molecule to lower the liquid-gel transition temperature is a better and more selective predictor of the anesthetic potency of a given molecule than its lipid solubility (discussed in Heimburg and Jackson, 2007a). At critical anesthetic dose, i.e., the dose for which 50% of the subjects are anesthetized, the shift in transition temperature is −0.6 degrees for all anesthetics, independent of their chemical nature (Kharakoz, 2001; Heimburg and Jackson, 2007a).

In the soliton model, the lowering of the transition temperature renders it more difficult to force the membrane through the fluid-gel transition. Generation of the action potential is thereby suppressed. Moreover, calculations indicate that at critical anesthetic dose the nerve pulse propagation velocity is not affected. This is consistent with clinical observations showing that anesthetics do not have a significant effect on nerve pulse propagation velocity at critical anesthetic dose.

It is to be emphasized that freezing point depression, like the related phenomenon of boiling point elevation, is a general physical (thermodynamic) phenomenon and not chemical in nature. Given the assumptions of perfect miscibility in the fluid phase and perfect immiscibility in the gel phase of the membrane, the ability of any solute to lower the freezing point of a given

solvent is strictly proportional to its molar concentration. The molar concentration in the fluid membrane at critical anesthetic dose is 2.6 mol% whereas the concentration in the blood stream is much lower (Wlodarczyk et al., 2006; Heimburg and Jackson, 2007a; Heimburg, 2007b).

Generally, deviations from the linear relation are due to deviations from the assumptions of perfect miscibility/immiscibility or from basic thermodynamic assumptions of "large" system size. Thus, long chain alcohols can show deviations from the Meyer-Overton rule when their length exceeds the about 5 nm thickness of the membrane. Another example is fluorinated alkanols (Eger et al., 1999). It is unknown why such molecules deviate and it is beyond the scope of this paper to enter such a discussion. Though, we think long chain alcohols may be too large to enter the membrane or they may have a phase behavior of their own, and fluorinated alkanols could be partly miscible in the gel phase. Other examples are cholesterol, which may dissolve in the gel phase of the membrane (Drew Bennet et al., 2009), and the membrane lipids themselves that simply have the same phase behavior as the membrane they are dissolving in.

If hydrostatic pressure is applied to a membrane, it will cause a membrane in a fluid state to approach the denser gel state. Therefore, freezing point depression can be reversed by an increase in hydrostatic pressure (Trudell et al., 1975; Heimburg and Jackson, 2007a). Since the pressure required to reverse the effect of anesthetics on the lipid transition can be determined directly from known thermodynamic (i.e., elastic) properties of the lipids, calculation of this pressure requires no additional assumptions. We find that 25 atmospheres of pressure is sufficient to reverse the 0.6° depression of the freezing point associated with critical anesthetic dosage. Interestingly, tadpoles anesthetized with a three-fold critical dose are revived at 75–150 atmospheres of pressure (reviewed in Wlodarczyk et al., 2006). Pressure reversal of anesthesia in mice is reversible and seems to occur around 100 atmospheres (Miller et al., 1973; Miller and Wilson, 1978). Pressure is a thermodynamic variable. Changes in other thermodynamic variables such as body temperature, pH and calcium concentration can also reverse the effect of anesthetics on melting transitions and thus on soliton generation (Heimburg and Jackson, 2007a,c).

7. How does a nerve signal propagate?

In this paper, we have seen that a description of the nerve pulse as a propagating adiabatic electromechanical pulse in the membrane lipid leads to the correct prediction of the effect of anesthetics and of various physical changes, including reversible heat production and changes in area and thickness, observed in the nerve during an action potential (Boxes 3B1 and 4). These phenomena cannot readily be explained by the ionic hypothesis, which focuses exclusively on neural-specific ion channel proteins.

In summary, the biggest differences as compared to the ionic hypothesis are:

- Nerve pulse propagation does not continuously dissipate energy in the form of heat to the environment.
- The nerve changes dimensions and gets thicker during the nerve pulse.
- The voltage pulse that accompanies a propagating action potential may be explained as the result of the transient geometric changes of the membrane.

As described, these hallmarks are supported by experimental facts.

All biological membranes contain an approximately equal mixture of lipids and proteins. In this paper, we have concentrated on the lipids and seemingly ignored the many membrane proteins. However, thermodynamic properties of the membrane are determined by the complete ensemble of proteins and lipids. The presence of proteins thus has important quantitative effects which determine the location of the fluid-gel transition and affect the ability of liquid membranes to conduct nerve signals (Box 3B1).

In summary, first-principle thermodynamics arguments can provide an explanation of some of the phenomena associated with nerve signal propagation that cannot be explained within the framework of the ionic hypothesis (Albright et al., 2000). Whether action potentials in living organisms propagate as the adiabatic electromechanical pulses described here remains to be demonstrated. There are evidently formidable challenges inherent in any attempt to frame a theory that incorporates all observed phenomena in one coherent and predictive theory of nerve signal propagation. Many important questions remain. We have, for example, not addressed the question of whether and how some form of ion flow is involved in nerve signal propagation. In this regard, it should be noted that the ion permeability of the membrane increases by several orders of magnitude in the vicinity of the fluid-gel transition (Antonov et al., 1980; Tasaki et al., 1989; Blicher et al., in press). Other outstanding issues of interest include why nerve signals propagate faster in myelinated than in non-myelinated nerves (Cole, 1941; Huxley and Stampeli, 1949; Kaufmann, 1985) and a clarification of the role and nature of dissipation of the action potential along its path (Tasaki et al., 1989; Tasaki and Byrne, 1992; Lautrup et al., 2005). It is imperative to proceed with an open mind. As Hodgkin stated in his 1964 Sherrington Lectures: "In thinking about the physical basis of the action potential perhaps the most important thing to do at the present moment is to consider whether there are any unexplained observations which have been neglected in an attempt to make the experiments fit into a tidy pattern" (Hodgkin, 1964). It is precisely the ability to explain these "unexplained" observations that will ultimately discriminate between alternative models of nerve signal propagation. We are convinced that the language and techniques of thermodynamics are well-suited to this task, and we offer the soliton model as a first step towards a more complete description of the action potential.

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