CHAPTER NINE

A Comparison of the Hodgkin–Huxley Model and the Soliton Theory for the Action Potential in Nerves

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Abstract

We describe the origin and significance of electrical and mechanical observations on nerves. To this end, we compare two models for neural activity, which are the established Hodgkin–Huxley model and the more recent soliton theory, respectively. While the Hodgkin–Huxley model focuses particularly on the electrical aspects of the neural membranes, the soliton model is based on hydrodynamic and thermodynamic properties of the membrane, thus including changes in all thermodynamic variables.

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1. INTRODUCTION

The action potential is a propagating voltage pulse traveling along the nerve axon. Since the first description of its electrical features by Luigi Galvani [1] and Volta [2] in the past decade of the eighteenth century, its nature has been in the focus of intense studies during the recent 200 years. Starting from a famous paper by Bernstein [3] in 1902, it has been assumed that the permeability of the neural membrane for ions is a necessary prerequisite for the propagation of the nervous impulse in excitable membranes. Bernstein based his considerations on the electrochemistry of semipermeable walls, leading to a voltage difference across a membrane upon uneven distribution of positive and negative ions (Nernst potentials). While Bernstein assumed that the permeability for ions breaks down in a nonspecific manner, the later Hodgkin–Huxley (HH) model [4] is based on the assumption that the membrane contains proteins that selectively conduct sodium and potassium ions in a time- and voltage-dependent manner. This model was at the basis of a rapid development in molecular biology, leading to numerous studies on ion channel proteins. Until today, permeation studies on ion channel proteins have been in the center of interest of molecular biology.

The HH model treats the nerve axon as an electrical circuit in which the proteins are resistors and the membrane is a capacitor. Ion currents flow through the membrane and along the nerve axon leading to a propagating pulse. The voltage dependence of the channel proteins results a characteristic spike (Fig. 9.1) described by a partial differential equation that exclusively contains electrical parameters. While the HH model describes various aspects of the action potential in a satisfactory manner (e.g., its velocity and the pulse amplitude), it fails to describe several other aspects of the nerve pulse that are

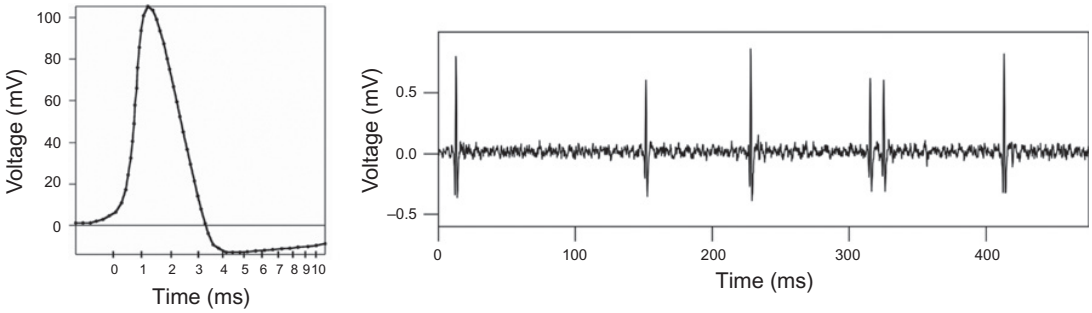

Figure 9.1 The action potential. Left: The action potential in a squid axon, *adapted from Ref. [5]*. Right: Extracellular recording of action potential from grasshopper nerves. Adapted from Ref. [6].

of nonelectrical nature. For instance, it is known that nerves display thickness and length variations under the influence of the action potential [7–13]. Interestingly, the action potential can be excited by a mechanical stimulus, indicating that the nerve pulse possesses a mechanical component. An even more important observation is the heat production of a nerve during the nerve pulse. During the first phase of the nerve pulse, heat is released from the membrane, while it is reabsorbed during the second phase [7,14–18]. The integrated exchange of heat is zero within experimental accuracy, indicating that the action potential is an adiabatic phenomenon. This later observation is in conflict with the HH model that is based on irreversible dissipative processes (currents through resistors) and should lead to dissipation of heat [19]. This, however, is not observed in nerves. In this context, it is interesting to note that a nerve pulse can also be stimulated by local cooling [20], indicating that heat changes take place during the action potential. Summarizing, it seems as if the mechanical and the heat signatures rather indicate that the nerve pulse is an adiabatic and reversible phenomenon such as the propagation of a mechanical wave.

To rationalize the above phenomena, it has been proposed that the propagating nerve pulse is an electromechanical soliton rather than a breakdown of membrane resistance [6,21–23]. The soliton theory is an alternative explanation of the nerve pulse based on the thermodynamics of the membrane and naturally includes all thermodynamic variables including volume, area, and enthalpy changes. In the context of this model, the pulse velocity is close to the velocity of sound in the membrane, and the experimentally observed reversible heat corresponds to the reversible heating of compressible media during the propagation of adiabatic waves.

In the present contribution, we review and compare the HH model and the soliton theory for neuronal signal propagation and discuss the implications of each model. A particular focus is on the collision of pulses.

2. LIPIDS AND PROTEINS IN NEURONAL MEMBRANES

The basic components of the nervous system are cells called neurons. Neurons transmit information by firing and propagating electrical impulses. These pulses (called *action potentials*) display typical amplitudes of 100 mV, velocities between 1 and 100 m/s, and display a characteristic timescale of about 1 ms.

The major units of a neuron are the soma (the cell body) including most organelles, the dendrites (receiving the signals), the axon (propagating

the signal), and synapses (chemical or electrical connections to other cells). Neurons possess a wide variety of shapes, sizes, and electrochemical properties [24]. They are similar to other eukaryotic cells which contain a nucleus and organelles surrounded by membranes [24]. These membranes are mainly composed of two classes of molecules: lipids and proteins.

2.1. The lipid membrane

The plasma membrane acts as the outer boundary of a neuron. It regulates the permeation of substances into and out of the cell. The membrane is composed of a lipid bilayer into which proteins are embedded [25] (Fig. 9.2C). Typical lipid/protein mass ratios of biomembranes are around one [27] (including the peripheral parts of the proteins).

The lipid bilayer consists of various small amphiphilic molecules ranging from phospholipids (Fig. 9.2A) and sphingolipids to cholesterol. The hydrophobic tails of these lipids are directed toward the membrane center and away from extra- and intracellular fluid. In contrast, head groups are zwitterionic, polar, or charged. Therefore, the head groups are exposed to the aqueous medium and are in contact with extra- and intracellular fluid. The lipid membrane displays order transitions as a function of temperature,

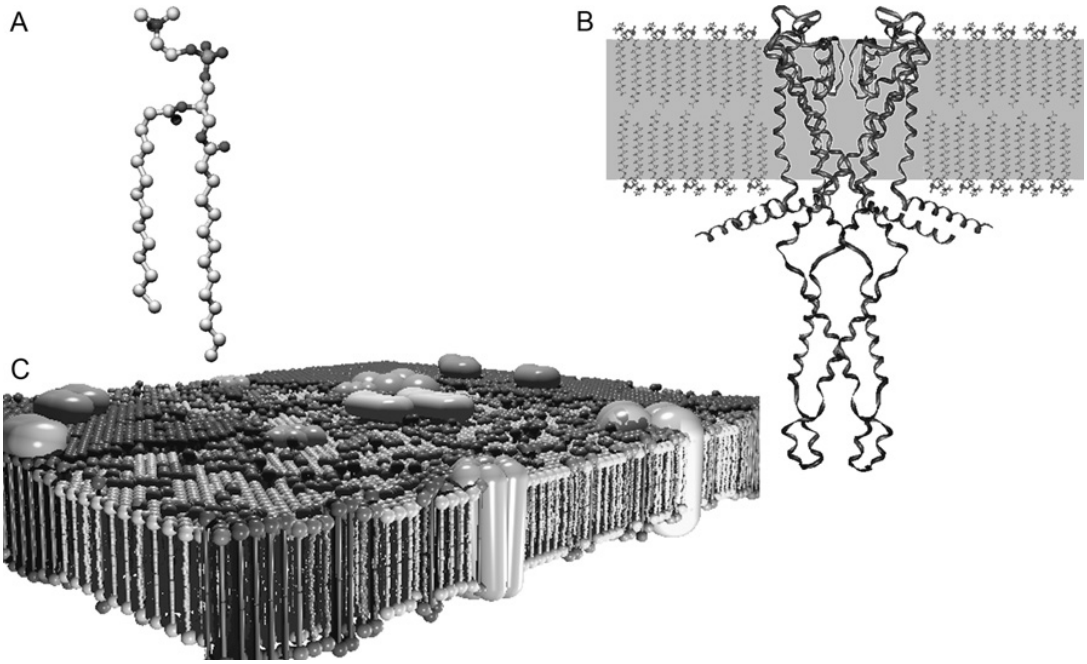

Figure 9.2 Schematic diagrams of a phospholipid (A) of the KscA potassium channel protein embedded in a lipid membrane (B) and the biomembrane in the presence of proteins and compositional separation of lipids into domains (C). *Reproduced with permission from Ref. [26].*

pressure, pH, or voltage. In these transitions, the number of configurations of individual lipid molecules increases dramatically. In the melting regime, one finds coexisting domains of ordered and disordered lipid. Figure 9.2C shows a membrane with coexisting domains of different physical states. Proteins are associated with the membrane.

2.2. Membrane proteins

While the lipid bilayer is often believed to mainly determine the basic structure of the plasma membrane, the embedded proteins are thought to be responsible for its function. They are involved in transport process into and out of the cell. A particular class of proteins abundant in neuronal membranes are the so-called channel proteins that are believed to form pores for particular ions. They contribute to the passive transport of ions. For instance, the Na^+-channel has been reported to display a specific conductance for sodium, while K^+-channel has been reported to show potassium conductance along concentration gradients between the inside and the outside of the cells. Figure 9.2B displays the crystal structure of the KscA potassium channel proteins embedded into a lipid membrane. Such ion channel proteins are considered to be responsible for the ion currents observed in conduction experiments on nerve membranes. The presently accepted model for nerve pulse generation and propagation proposed by Hodgkin and Huxley in 1952 [4] is based on voltage- and time-dependent properties of such ion channels. We will discuss the experimental results that lead to the theory as well as to the model in more detail in the next section.

However, it will be shown below that the lipid membrane itself plays a much more active role in biological processes than hitherto believed.

3. ELECTRICAL CIRCUITS AND THE HH MODEL

The present understanding of the nerve membrane is based on some important experimental works from the 1930s to the 1950s. The association of the action potential in nerves with a large increase in membrane conductance, first proposed by Ludwig Bernstein, was confirmed by Cole and Curtis [5] in 1939. These recordings demonstrated that the action potential is not just a reduction of the membrane potential due to an unspecific breakdown of membrane resistance during the action potential but involves a change in sign (overshoot), implying a more sophisticated mechanism. Hodgkin and Katz [28] explained the overshooting action potential as a result of an increase

in sodium permeability, thus supporting the suggestion of Overton [29]. Finally, Hodgkin, Huxley, and Katz developed the voltage-clamp circuit to facilitate quantitative measurement of ionic currents from squid axon. Hodgkin and Huxley proposed that the membrane can be selectively permeable for either sodium or potassium in a voltage- and time-dependent manner. This mechanism ultimately leads to the famous HH model [4].

Hodgkin and Huxley studied the conductance properties of nerve axons from squid in voltage-clamp experiments [30]. In such experiments, an electrode is inserted into a nerve axon such that the voltage difference between inside and outside is constant along the whole axon. Under such conditions no pulse can propagate. The voltage-clamp experiments by Hodgkin and Huxley showed that a stepwise depolarization (reduction of transmembrane voltage) of the membrane by electrodes first triggered an inward current (against the applied field) followed by an outward current (along the external field). With the aid of ionic substitution, they demonstrated that the net current could be separated into two distinct components: a fast inward current carried by Na^+ ions, and a more slowly activated outward current carried by K^+ ions. They concluded that these two currents result from independent permeation mechanisms for Na^+ and K^+ involving time- and voltage-dependent conductances of particular objects in the membrane. This new concept was named the "ionic hypothesis" [31]. The schematic diagram for the electrical circuit in the voltage-clamp experiment is shown in Fig. 9.3.

In the HH picture, three different ion currents contribute to the voltage signal of the neuron, that is, a sodium current, a potassium current, and a leak current that consists mainly of Cl^- ions. The flow of these ions through the cell membrane is controlled by their respective voltage-dependent ion

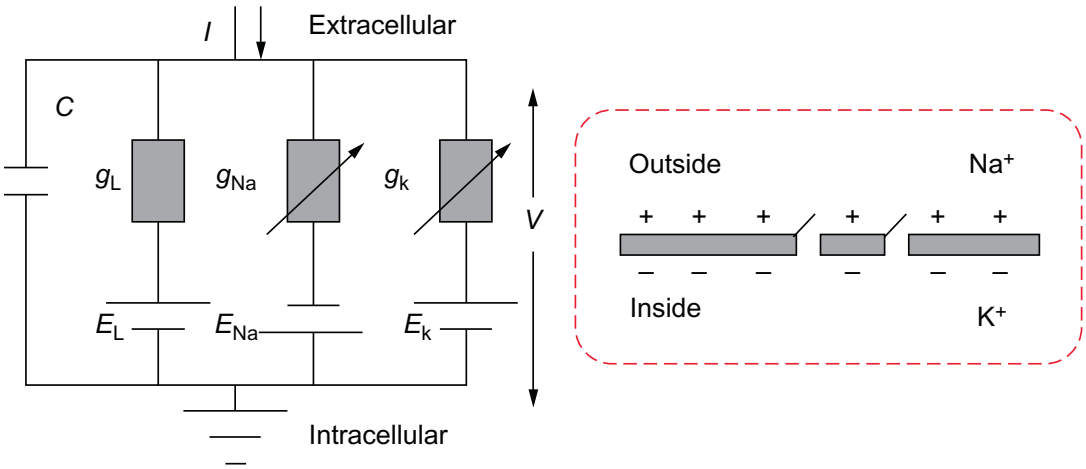

Figure 9.3 Schematic diagram of Hodgkin–Huxley circuit in a voltage-clamp experiment *adapted from Ref. [32].*

channels. The leak current also takes care of other channel types which are not described in particular. The most remarkable achievement of this theory was the self-consistent agreement of the experimental voltage-clamp data (in the absence of a pulse) with a quantitative model for the propagating nerve pulse [4], which made it the very first complete description of the excitability of a single neuron.

The semipermeable cell membrane separates the interior of the cell from the extracellular liquid. The lipid membrane is considered an insulator that acts as a capacitor with constant capacitance, C_m. The proteins are considered being resistors described by conductances g_i (i being the index for a particular channel and ion). Upon change of voltage, V_m, two currents can be observed—a capacitive current charging the capacitor and ohmic currents through the protein. The total current through the membrane, I_m, is the sum of these two currents. The equivalent circuit is shown in Fig. 9.3. The time-dependent membrane current I_m is given by the following equation:

$$I_{\mathrm{m}}(t) = C_{\mathrm{m}}\frac{\mathrm{d}V_{\mathrm{m}}}{\mathrm{d}t} + g_{\mathrm{Na}}(V_{\mathrm{m}} - E_{\mathrm{Na}}) + g_{\mathrm{K}}(V_{\mathrm{m}} - E_{\mathrm{K}}) + g_{\mathrm{L}}(V_{\mathrm{m}} - E_{\mathrm{L}}) \quad (9.1)$$

The last term in this equation accounts for small leak currents and will be omitted in the following. The quantities E_{Na}, E_{K} (and E_{L}) are the Nernst potentials of different ions. The concentrations of ions on the inner and outer side of the cell (c_{in} and c_{out}) are different (K^+ concentrations of the giant squid are 400 mM inside and 20 mM outside. Na^+ concentrations are 50 and 440 mM, respectively [33]). As a consequence, current flows even in the absence of an external voltage due to diffusion along the gradients. This is taken into account by the Nernst potentials in the above equation:

$$E_{\mathrm{i}} = \frac{RT}{zF}\ln\frac{c_{\mathrm{out}}}{c_{\mathrm{in}}} \quad (9.2)$$

If the external voltage is equal to the Nernst potential, no current flows. The Nernst potentials are different for different ions.

The functions g_{Na} and g_{K} are the conductances of the ion channel proteins for the respective ions. They are assumed to be functions of voltage and time. Hodgkin and Huxley parameterized these conductances by using their voltage-clamp data in the following manner:

$$\begin{aligned} g_{\mathrm{Na}} &= g_{\mathrm{Na},0}m^3h, \\ g_{\mathrm{K}} &= g_{\mathrm{K}_0}n^4 \end{aligned} \quad (9.3)$$

introducing the functions $m(V_m, t)$, $h(V_m, t)$, and $n(V_m, t)$ that depend on voltage and time. These functions range between 0 and 1 and are related to the likelihood that the channel is open. If $m^3h = 1$, the sodium channel is open and conducts with the characteristic conductance $g_{Na,0}$. If $n^4 = 1$, the potassium channel is open and conducts with its characteristic conductance $g_{K,0}$. The functions m, h, and n are called *gating variables*. Each of them follows a simple linear differential equation after changing voltage yielding an exponential relaxation in time:

$$\begin{aligned} \frac{dm}{dt} &= \alpha_m(V_m)(1-m) - \beta_m(V_m)m, \\ \frac{dn}{dt} &= \alpha_n(V_m)(1-n) - \beta_n(V_m)n, \\ \frac{dh}{dt} &= \alpha_h(V_m)(1-h) - \beta_h(V_m)h \end{aligned} \tag{9.4}$$

The newly introduced functions $\alpha_m(V_m)$, $\alpha_h(V_m)$, $\alpha_n(V_m)$ and $\beta_m(V_m)$, $\beta_h(V_m)$, $\beta_n(V_m)$ are voltage-dependent rate constants that cannot be derived by any theory. Instead, they are fitted to experimental data. Each of the rate constants requires several parameters to obtain an empirical fit. All together, one has more than 20 empirical fit parameters. This indicates that the HH model is not a theory based on first principles but rather a parameterization of the electrical features of the membrane.

The propagating action potential is now calculated by combining Eq. (9.1) with cable theory (Fig. 9.4). Using Kirchhoff's laws, cable theory describes the spreading of a voltage along a cylindrical membrane as a function of distance x, the specific resistance of the membrane (R_m) and the specific inner resistance of the intracellular medium along the cable (R_i). A central equation originating from cable theory is

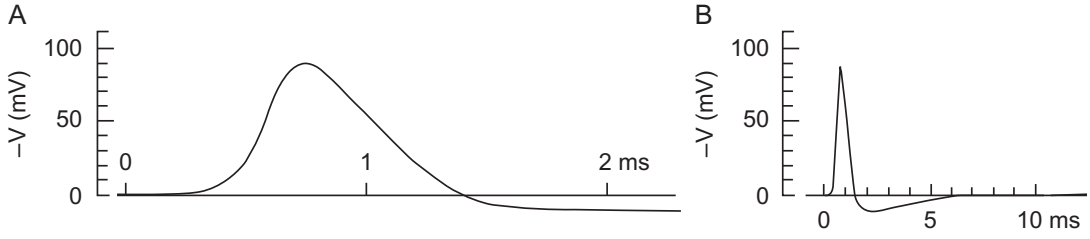

Figure 9.4 Action potential in squid axons simulated by Hodgkin and Huxley in 1952. The pulse is shown in two different time windows. *From Ref. [4].*

$$\frac{\partial^2 V_\mathrm{m}}{\partial x^2} = \frac{2R_i}{a} I_\mathrm{m} \tag{9.5}$$

for a cable with radius a, which together with Eq. (9.1) yields

$$\frac{\partial^2 V_\mathrm{m}}{\partial x^2} = \frac{2R_\mathrm{i}}{a}\left(C_\mathrm{m}\frac{\mathrm{d}V_\mathrm{m}}{\mathrm{d}t} + g_\mathrm{Na}(V_\mathrm{m} - E_\mathrm{Na}) + g_\mathrm{K}(V_\mathrm{m} - E_\mathrm{K})\right) \tag{9.6}$$

Finally, it is assumed that a pulse exists that propagates with constant speed θ independent of voltage. This implies that the wave equation

$$\frac{\partial^2 V_\mathrm{m}}{\partial t^2} = \theta^2 \frac{\partial^2 V_\mathrm{m}}{\partial x^2} \tag{9.7}$$

can be used. Combining Eq. (9.7) with Eq. (9.6) yields the final equation for the propagation of the electrical pulse:

$$\frac{a}{2R_\mathrm{i}\theta^2}\frac{\partial^2 V_\mathrm{m}}{\partial t^2} = C_\mathrm{m}\frac{\mathrm{d}V_\mathrm{m}}{\mathrm{d}t} + g_\mathrm{Na}(V_\mathrm{m} - E_\mathrm{Na}) + g_\mathrm{K}(V_\mathrm{m} - E_\mathrm{K}) \tag{9.8}$$

This partial differential equation has to be solved and yields the HH action potential.

The HH model can reproduce a wide range of data from squid axon, for instance the shape and propagation of the action potential (see Fig. 9.2), its sharp threshold, its refractory period, and the hyperpolarization. However, it has to be noted that the model contains a hidden complexity since the conductances are empirical functions of voltage and time that were parameterized from experiment (see above).

There have been various attempts to simplify the complexity of the equation, for instance by FitzHugh and Nagumo [34,35] (called the FitzHugh–Nagumo (FHN) model), Hindmarsh–Rose [36] and Rajagopal [37]. Such models are widely used in simulating the neural networks in order to rationalize experimental data.

4. PULSE PROPAGATION BASED ON THE THERMODYNAMICS OF THE BIOLOGICAL MEMBRANE: THE SOLITON MODEL

The HH model describes the electrical processes during signal generation and propagation in the nerves. However, the model fails to explain several nonelectrical properties observed during experiments. For instance, it has been observed that one finds a reversible release and reuptake of heat during the action potential [7,14–18]. The integral over the heat exchange

during the nerve pulse is zero within the experimental accuracy. While this is in conflict with a dissipative model based on electrical resistors, it is rather consistent with an adiabatic wave (e.g., a sound wave). In fact, mechanical changes during the action potential have been found in various experiments [7–13], indicating that the action potential is accompanied by a mechanical pulse. The thickness of the nerve increases, and a simultaneous shortening of the nerve can be observed. The HH model also fails to explain the effect of anesthetics on nerve pulse conduction.

In 2005, Heimburg and Jackson proposed a thermodynamic theory of nerve pulse propagation in which the action potential is a reversible electro-mechanical soliton [6,19,21,22,38]. It is based on the thermodynamics and in particular the phase behavior of the lipids which are the major components of the membrane. In the following, we will refer to this theory as the "soliton model." A central prerequisite of this theory is the chain-melting transition of the lipid membranes, which in biological cells can be found a few degrees below body temperature (see Fig. 9.5; Refs. [21,27]). At physiological temperatures, the state of the biological membranes is fluid. The melting transition is linked to changes in enthalpy, entropy, but also to changes in volume, area, and thickness. This implies that the state of the membrane can be influenced not only by temperature but also by hydrostatic pressure and lateral pressure in the membrane plane. Due to the fluctuation–dissipation theorem, the fluctuations in enthalpy, volume, and area in the transition are at a maximum. Therefore, the heat capacity and the volume compressibility all reach maxima. Simultaneously, the relaxation timescale reaches a

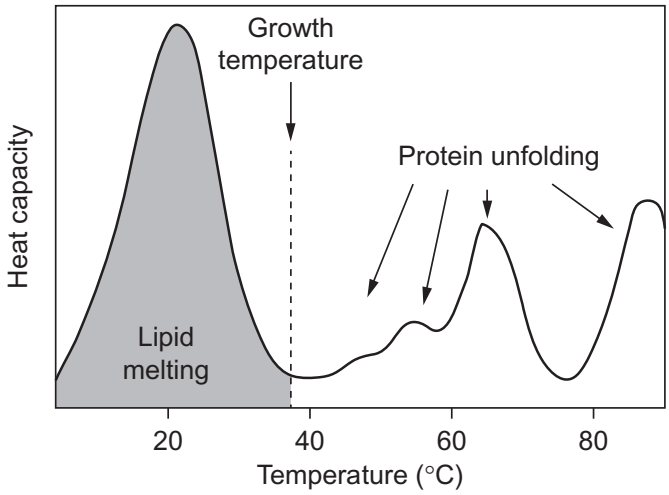

Figure 9.5 Heat capacity profile of native *Escherichia coli* membranes showing a lipid melting peak below physiological temperature. *Adapted from Ref. [26].*

maximum. This implies that the lateral compression of a fluid membrane leads to an increase in compressibility. This effect is known as a *nonlinearity*. From experiment, it is known that the compressibility is also frequency dependent, an effect that is known as *dispersion*. These two phenomena are necessary conditions for the propagation of solitons. It can be shown that the features of lipid membranes slightly above a transition are sufficient to allow the propagation of mechanical solitons along membrane cylinders [21]. The solitons consists of a reversible compression of the membrane that is linked to a reversible release of heat, mechanical changes in the membrane. Furthermore, the soliton model also implies a mechanism for anesthesia that lies in the well-understood influence that anesthetics have on the lipid phase transition [38].

The soliton model starts with the well-known wave equation for area density changes $\Delta\rho^A$

$$\frac{\partial^2}{\partial\tau^2}\Delta\rho^A = \frac{\partial}{\partial z}\left(c^2\frac{\partial}{\partial z}\Delta\rho^A\right) \tag{9.9}$$

that originates from the Euler equations of compressible media (e.g., [39,40]). Here, τ is the time, z is the position along the nerve axon, and c is the sound velocity. If $c = c_0$ is constant, one finds the relation for sound propagation $(\partial^2\rho/\partial\tau^2) = c_0^2(\partial^2\rho/\partial z^2)$.

However, it has been shown that close to melting transitions in membranes, the sound velocity is a sensitive function of density [41,42]. As shown in Fig. 9.5, such transitions are found in biomembranes. This is taken into account by expanding the sound velocity around its value in the fluid phase

$$c^2 = c_0^2 + p\Delta\rho^A + q(\Delta\rho^A)^2 + \cdots \tag{9.10}$$

up to terms of quadratic order. The parameters p and q describe the dependence of the sound velocity on density close to the melting transition and are fitted to experimental data [21].

It is further known that the speed of sound is frequency dependent. This effect is known as *dispersion*. In order to take dispersion into account, a second term is introduced into Eq. (9.9) that assumes the form:

$$-h\frac{\partial^4}{\partial z^4}\Delta\rho^A \tag{9.11}$$

where h is a constant. For low-amplitude sound, this term leads to the most simple dispersion relation $c^2 = c_0^2 + (h/c_0^2)\omega^2 = c_0^2 + \text{const}\cdot\omega^2$. Lacking

good data on the frequency dependence of sound in the kilohertz regime, the term given by Eq. (9.11) is most natural dispersion term.

Combining Eqs. (9.9)–(9.11) leads to the final time and position-dependent partial differential equation [21,23]:

$$\frac{\partial^2}{\partial\tau^2}\Delta\rho^A = \frac{\partial}{\partial z}\left[\left(c_0^2 + p\Delta\rho^A + q(\Delta\rho^A)^2 + \cdots\right)\frac{\partial}{\partial z}\Delta\rho^A\right] - h\frac{\partial^4}{\partial z^4}\Delta\rho^A \quad (9.12)$$

which describes the propagation of a longitudinal density pulse in a myelinated nerve. In this equation,

- $\Delta\rho^A$ is the change in lateral density of the membrane $\Delta\rho^A = \rho^A - \rho_0^A$;
- ρ^A is the lateral density of the membrane;
- ρ_0^A is the equilibrium lateral density of the membrane in the fluid phase;
- c_0 is the velocity of small-amplitude sound;
- p and q are the parameters determined from density dependence of the sound velocity. These two constants parameterize the experimental shape of the melting transition of the membrane and are given in Ref. [21];
- h is a parameter describing the frequency dependence of the speed of sound, that is, the dispersion.

All parameters except h are known from experiment. The empirical equilibrium value of ${\rho_0}^A$ is $4.035 \times 10^{-3}\,\mathrm{g/m^2}$, and the low-frequency sound velocity c_0 is 176.6 m/s. The coefficients p and q were fitted to measured values of the sound velocity as a function of density. The parameter h is not known experimentally due to difficulties to measure the velocity of sound in the kilohertz regime. However, Chapter 2 attempts to derive this parameter theoretically from relaxation measurements.

The nonlinearity and dispersive effects of the lipids can produce a self-sustaining and localized density pulse (soliton) in the fluid membrane (see Fig. 9.6). The pulse consists of a segment of the membrane that locally is found in a solid (gel) state. It preserves its amplitude, shape, and velocity while propagating along the nerve axon. Further, the pulse propagates over long distances without loss of energy.

In the following, we work with the dimensionless variables u (dimensionless density change), x, and t defined in Ref. [23] as

$$u = \frac{\Delta\rho^A}{\rho_0^A}, \quad x = \frac{c_0}{h}z, \quad t = \frac{c_0^2}{\sqrt{h}}\tau, \quad B_1 = \frac{\rho_0}{c_0^2}p, \quad B_2 = \frac{\rho_0^2}{c_0^2}q \quad (9.13)$$

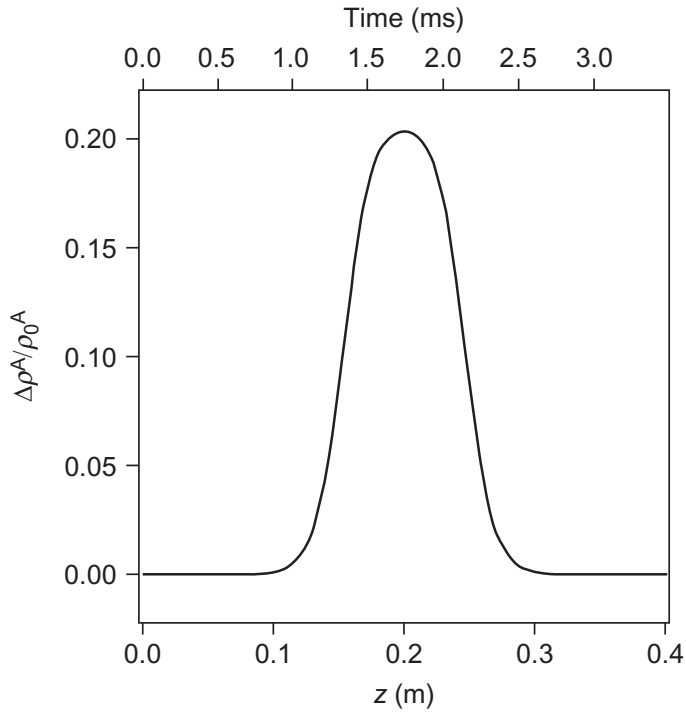

Figure 9.6 Calculated solitary density pulse as a function of lateral position calculated using experimental parameters for a synthetic membrane. The pulse travels with about 100 m/s. *From Ref. [43].*

Equation (9.12) now assumes the following form:

$$\frac{\partial^2 u}{\partial t^2} = \frac{\partial}{\partial x}(B(u))\frac{\partial u}{\partial x} - \frac{\partial^4 u}{\partial x^4} \tag{9.14}$$

with

$$B(u) = 1 + B_1 u + B_2 u^2 \tag{9.15}$$

$B_1 = -16.6$ and $B_2 = 79.5$ were determined experimentally for a synthetic lipid membrane in Ref. [21]. If we consider a density pulse u propagating with constant velocity, we can use the coordinate transformation $\xi = x - \beta t$ (where β is the dimensionless propagation velocity of the density pulse) and we yield the following form:

$$\beta^2 \frac{\partial^2 u}{\partial \xi^2} = \frac{\partial}{\partial \xi}\left(B(u)\frac{\partial u}{\partial \xi}\right) - \frac{\partial^4 u}{\partial \xi^4} \tag{9.16}$$

This is very much in the spirit of Eq. (9.7) used to obtain a propagating solution. Equation (9.15) displays exponentially localized *solitary* solutions which propagate without distortion for a finite range of subsonic velocities [21,23].

The above differential equation possesses analytical solutions given by

$$u(\xi) = \frac{2a_+ a_-}{(a_+ + a_-) + (a_+ - a_-)\cosh(\xi\sqrt{1-\beta^2})} \tag{9.17}$$

where $u = a_\pm$ is given by

$$a_\pm = \frac{-B_1}{B_2}\left(1 \pm \sqrt{\frac{\beta^2 - \beta_0^2}{1-\beta_0^2}}\right) \tag{9.18}$$

for the velocity range $\beta_0 < |\beta| < 1$ (with 1 being the low-amplitude sound velocity). There exists a lower limit for the propagation velocity of the pulse given by $\beta_0 = 0.649851$ for a synthetic membrane. No solitons exist for slower velocities. The density change $u(\xi)$ describes the shape of the propagating soliton, which depends on the velocity β. A typical soliton generated by Eq. (9.16) is shown in Fig. 9.6. The minimum propagation velocity β is about 100 m/s, very similar to the measured propagation velocity of the action potential in myelinated nerves. Since the pulse describes a reversible mechanical pulse, it possesses a reversible heat production, a thickening and a simultaneous shortening of the nerve axon, in agreement with observation. Due to the electrostatic features of biomembranes, the pulse possesses a voltage component. Thus, the traveling soliton can be considered a piezoelectric pulse.

One feature of the soliton model not discussed here in detail is that it provides a mechanism for general anesthesia. It has been shown that general anesthetics lower the melting points of lipid membranes. At critical dose (where 50% of the individuals are anesthetized), the magnitude of this shift is independent of the chemical nature of the anesthetic drugs [38,44]. From this, one can deduce quantitatively how much free energy is required to trigger a soliton. In the presence of anesthetics, this free energy requirement is higher. As a result, nerve pulse stimulation is inhibited. In this respect, it is interesting to note that hydrostatic pressure reverses anesthesia. For instance, tadpoles anesthetized by ethanol wake up at pressures around 50 bars [45]. It is also known that hydrostatic pressure increases melting temperatures of lipid membranes due to the positive excess volume of the transition [46]. The effects of anesthetics and hydrostatic pressure are known quantitatively. Therefore, one can also quantitatively calculate at what pressure the effect of anesthetics is reversed. The resulting pressures are of the order of 25 bars at critical anesthetic dose, which is of same order than the observed pressure reversal of anesthesia [19,38].

Another important aspect discussed elsewhere is that melting of membranes results in quantized conduction events in lipid membranes due to thermal fluctuations. The conduction events are indistinguishable from protein ion channel traces [47–50]. Any change in a thermodynamics variable that is able to trigger a soliton in a nerve membrane is also able to generate lipid ion channel opening.

5. COMPARISON OF HH AND SOLITON MODELS

The HH model of nerve pulse propagation is a remarkable achievement in the field of physiology. It has shaped the thinking of a complete discipline for decades and is in line with the emergence of ion channel proteins and the influence of many drugs on the excitability of a nerve membrane. However, as already mentioned above, the HH model cannot explain several nonelectrical phenomena such as the finding of reversible heat changes [7,14–18], changes in nerve thickness, and nerve contraction described in mechanical and optical experiments [8,10,51–53]. The soliton model is an alternative model that can convincingly describe some of the unexplained observations found in the experiments. It also generates ion channel-like events and provides a mechanism for general anesthesia [38].

In the following, we list some of the major features of the two neural models:

HH model:

- The action potential is based on the electrical cable theory in which the pulse is the consequence of voltage- and time-dependent changes of the conductance for sodium and potassium.
- The nerve pulse consists of a segment of charged membrane capacitor that propagates driven by dissipative flows of ions.
- The model is consistent with quantized ion currents attributed to opening and closing of specific channel proteins.
- It is consistent with the channel-blocking effects of several poisons, such as tetrodotoxin.
- The underlying hypothesis is exclusively of electrical nature and does not refer to changes of any other thermodynamics variables other than charge and electrical potential.
- The HH model is based on ion currents through resistors (channel proteins) and is therefore of dissipative nature.

- Reversible changes in heat and mechanical changes are not explicitly addressed, but heat generation would be expected.
- The propagating pulse dissipates a significant amount of free energy [43].
- The HH model generates a refractory period (minimum distance between pulses) and hyperpolarization as a consequence of the complex time dependence of channel conduction.
- The theory does not provide an explanation of anesthesia.

Soliton model

- The nerve pulse is a solitary electromechanical soliton coupled to the lipid transition in the membrane.
- The solitary character is a consequence of the nonlinearity of the elastic constants close to the melting transition of the lipid membrane and of dispersion.
- The theory is based on macroscopic thermodynamics and implies a role for all thermodynamics variables.
- It does not contain an explicit role of poisons and protein ion channels.
- However, the theory is consistent with channel-like pore formation in lipid membranes that is indistinguishable from protein conductance traces [47–49].
- Additional to changes in the electrical potential and the charge of the membrane, the propagating pulse is associated with changes in all variables including temperature, lateral pressure, area, and length. As found in experiments, the nerve pulse is coupled to changes in thickness and length.
- In agreement with the experiment, the propagating pulse does not dissipate heat because it is based on adiabatic processes.
- The model generates a refractory period and a hyperpolarization that is a consequence of mass conservation [6].
- The soliton model implies a mechanism for general anesthesia [19,38].

Both the theories describe the existence of voltage pulse in nerve pulse propagation. In the HH model, the propagating potential change itself is the signal, while in the soliton model, it is only one inseparable aspect of a more generic adiabatic pulse that implies changes in all variables.

5.1. Numerical simulations of pulse collisions

One important difference between the two models is seemingly what they predict about colliding nerve pulses. Tasaki reported in 1949 that nerve pulses when colliding in an axon eliminate each other [54]. In the following, we discuss what the two models predict about pulse collisions. In particular, we present results of colliding nerve pulses with both models using numerical simulations.

5.1.1 Why performing a collision study?

It has been known since the 1940s that the nerve pulses are blocked upon collision [54]. In the HH model, the cause of the decay in signal amplitude upon collision is the refractory period. This is the minimum distance between two pulses that travel in the same direction. It is caused by the finite relaxation times of the protein conductances of the stimulation of a pulse. In the so-called refractory zone, a nerve fiber is unexcitable, and the existence of these zones prevents two colliding pulses from passing through each other. Simulations based on the HH equations support this view [55,56]. Our own simulations using the FHN model lead to the same results. Figure 9.7 shows that the pulses eliminate each other upon collision.

In contrast, the soliton model does not exhibit a complete annihilation. The pulses pass through each other almost undisturbed with the generation of some small-amplitude noise. Thus, soliton model contradicts the description of the cancelation of pulses suggested in the biology literature. The details of these findings are described in Ref. [23].

Figure 9.8 (left) shows two identical small-amplitude solitons traveling in opposite directions at a velocity of $\beta = 0.8$ (80% of the lateral speed of sound in fluid membranes) before and after a collision. Small-amplitude noise travels ahead of the postcollision pulses, indicating a small dissipation of energy of the order of $\ll 1\%$ compared to the soliton energy. The same was found for solitary pulses with different velocities and amplitudes. Surprisingly, upon the collision of solitons approaching the minimum velocity (maximum amplitude), the solitons fall apart in a sequence of lower amplitude solitons and some high-frequency noise (Fig. 9.8, right). This effect is more pronounced the closer the velocity is to the minimum velocity [23]. Only for the case of solitons approaching minimum velocity and maximum amplitude, the fraction of energy lost into smaller amplitude solitons and small-amplitude noise is significant (Fig. 9.9). Thus, we observed that most of the energy of the major soliton was conserved in collisions even if a maximum density was enforced.

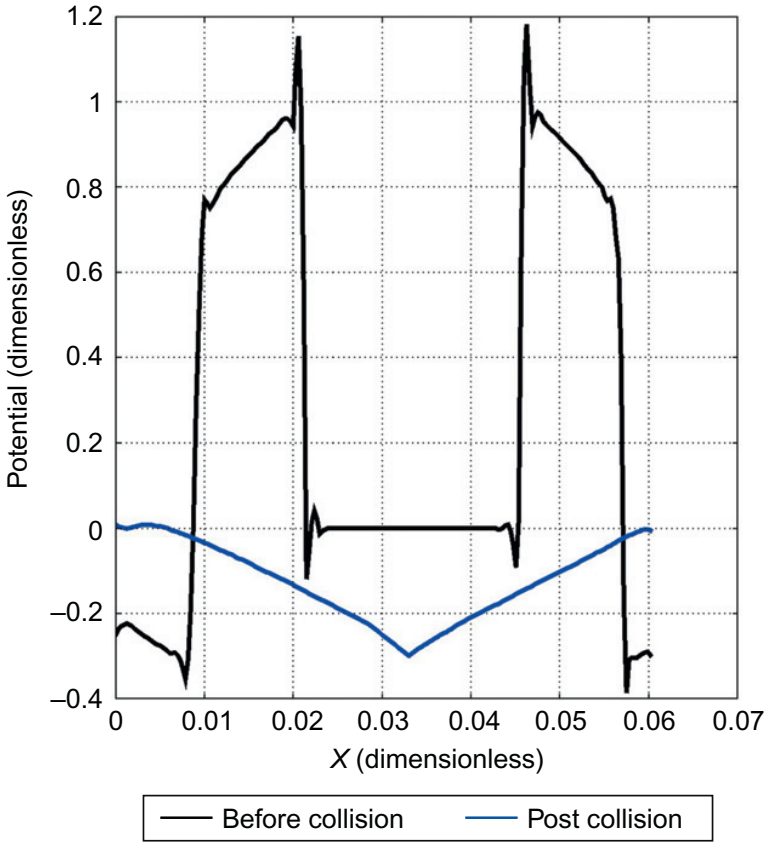

Figure 9.7 Collision of nerve pulses calculated with the FitzHugh–Nagumo equations. Two pulses traveling in opposite directions are shown before (black) and after the collision (blue). The pulses are annihilated after the collision.

Interestingly, soliton-like regimes can be also found in the HH model [55]. The term soliton is used here in a more mathematical sense meaning that one can generate pulses that reflect or penetrate each other when using certain parameters. Since the HH and the FHN models are based on dissipative processes, these are not solitons in a physical sense as in the soliton model.

Aslanidi and Mornev demonstrated that in excitable media under certain conditions, one can expect the emergence of a soliton-like regimes that corresponds to reflection (or loss-free penetration) of colliding waves. Figure 9.10 shows that $E_K = -12\,\text{mV}$ that colliding pulses annihilate. In contrast, a soliton-like regime was found for $-2.50\,\text{mV} < E_K < 2.46\,\text{mV}$ (Fig. 9.10). Furthermore, the pulses can also collide with the fiber boundaries and be reflected [55]. The authors of this study concluded that the soliton-like regime is described by spatially nonuniform time-periodic solutions of the HH equations. The mechanism of pulse reflection is explained as

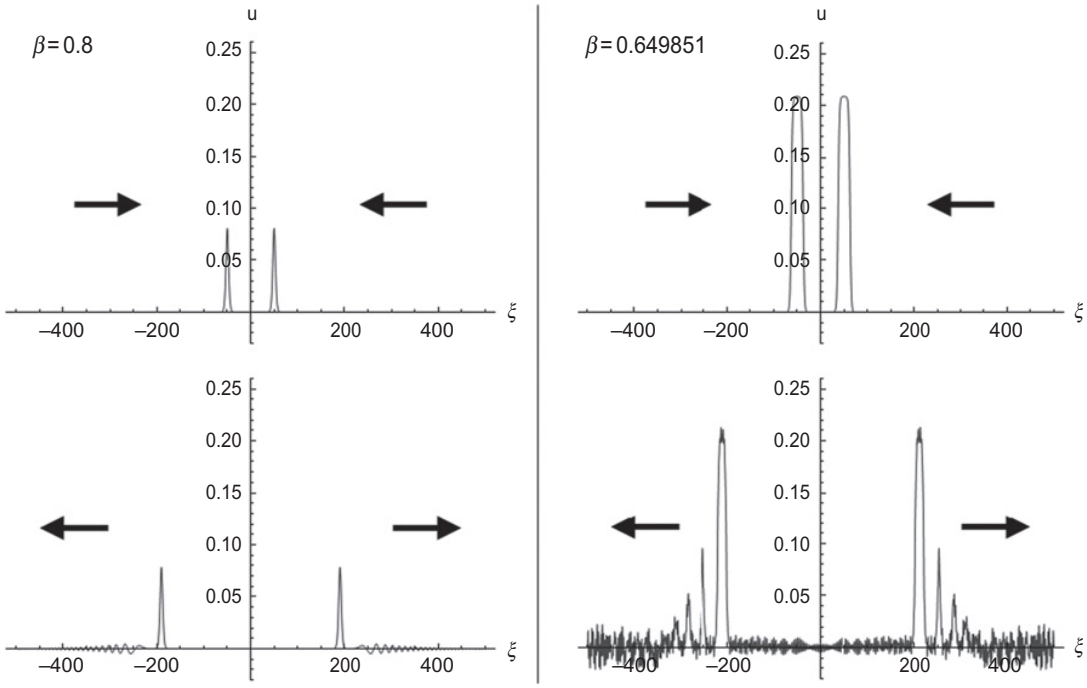

Figure 9.8 Collision of two solitons before (top panels) and after collision (bottom panels) for two different velocities (left and right panels). Left: soliton velocity of $\beta = 0.8$. Small-amplitude noise is traveling ahead of the postcollision pulses. This indicates some dissipation during the collision. Right: soliton velocity $\beta = 0.649850822$ (close to maximum amplitude). *Adapted from Ref. [23].*

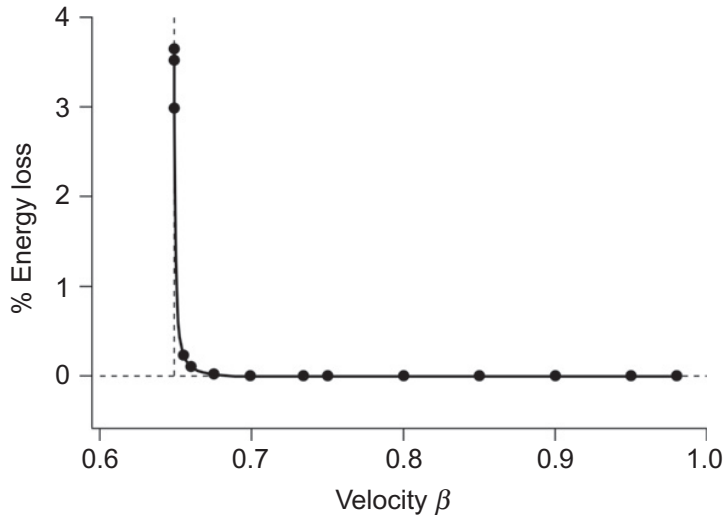

Figure 9.9 Energy loss of soliton after collision in %. The dissipation is significant only when the pulses reach their minimum velocity. *From Ref. [23].*

follows [55]: "In the soliton-like regime the traveling pulse presents a doublet consisting of a high-amplitude pulse-leader and a low-amplitude wave following this pulse. When doublets interact, the leaders are annihilated, and the collision of the low-amplitude waves after a short delay leads to their

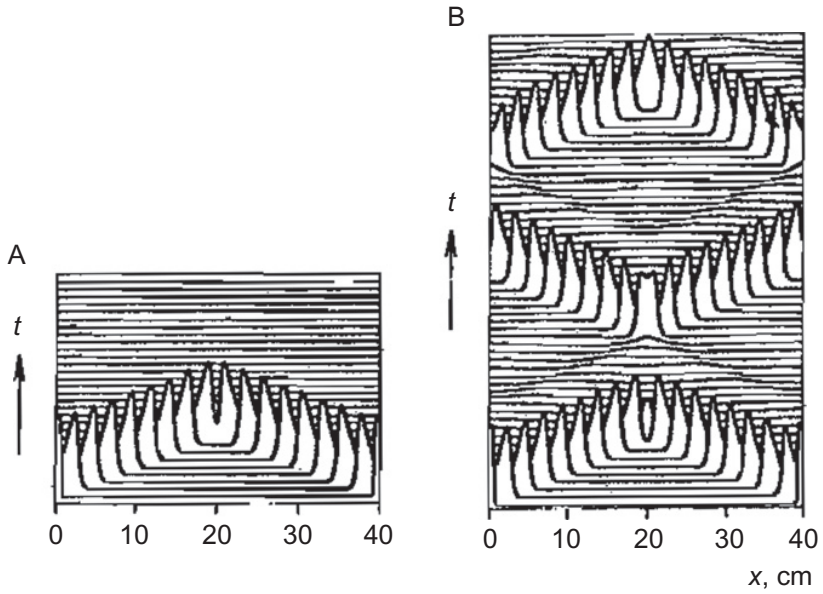

Figure 9.10 Collision of pulses in the HH model. Left: Annihilation of colliding nerve pulses at the standard value $E_K = -12.0$ mV. Right: Reflection (or penetration) of pulses at $E_K = -2.5$ mV. *From Ref. [55] with permission.*

summation. As a result of the summation, the potential V at the site of the collisions reaches a super-threshold value, causing regeneration of the doublets, which thereafter move apart in opposite directions. The process of reflection of excitation pulses from impermeable fiber ends evolves according to the same scenario."

It was also noticed that low-amplitude waves can give rise to new extra pulses which also take part in interactions. When a doublet was initiated at the left end of a fiber, the amplitude of the following pulse rapidly increases while traveling. It reaches threshold value and initiates two "extra pulses." These pulses travel apart to the opposite ends of the axon and are reflected from them. This complex regime was observed for $-2.46\,\text{mV} < E_K < 2.40\,\text{mV}$.

Summarizing, the soliton model does not lead to annihilation of pulses, while the HH model allows for both annihilation and penetration depending on parameters.

5.2. Can the two models be combined?

It seems tempting to combine the two approaches such that the respective strengths of each model can be taken advantage of. Both models account for the occurrence of channel-like conduction events through membranes and the voltage pulse. The behavior upon collision of pulses is somewhat unclear in both models. But there are clear differences.

The protein-based picture of Hodgkin and Huxley provides a discrete target for poisons such as tetrodotoxin that eliminate the nerve pulse. Toxic substances are thought to block the ion channel proteins that are the primary players in this model. In contrast, the soliton model requires a more indirect role of poisons on the physics of membranes that has yet to be demonstrated experimentally. In the case of anesthetics, such an effect has been found in experiments and the effect is understood theoretically—but this is not the case for strong poisons. On the other hand, the soliton model provides a beautifully self-consistent explanation for mechanical and heat changes that occur under the influence of the nerve pulse. One would be inclined to keep this feature in a complete theory for the nerve pulse.

The main argument that lets it seem difficult to combine the models is the measured reversible heat production of the nerve pulse. The HH model is based on dissipative processes that should be related to heat dissipation at the site of the membrane. The soliton model, in contrast, is based on reversible processes and therefore consistent with the reversible heat production. The combination of a dissipative and a reversible model would still be of dissipative nature. The reversible heat observed during the nervous impulse is significantly larger than the capacitive energy of the membrane. This means that one has to assume that there exist relevant processes during the nerve pulse beyond the charging of a capacitor, which is the only process in the HH model associated with work and heat. The least one would have to conclude is that the mechanical (adiabatic) propagation phenomena are by far the dominating processes such that dissipative features are not readily visible in an experiment. Taking the reversible heat of the nerve pulse serious, one is inclined to state that the HH model in itself cannot be correct. The same argument would hold for a combination of both models. Thus, it seems necessary that any protein-based picture would still operate on the basis of reversible processes, for instance, by employing capacitive currents rather than ohmic currents, that is, by transporting charges forth and back in a reversible process. This implies that the HH picture cannot easily be combined with reversible physics and the soliton model without seriously changing its mechanism.

6. CONCLUSIONS

We have reviewed the well-known HH model and the emerging soliton theory of nerve pulse propagation and compared them in some detail. The two models are based on completely different assumptions. While the

HH model is based on microscopic consideration about the behavior of single proteins, the soliton model is a macroscopic thermodynamics theory. The HH model mostly considers the electrical aspects of nerve pulse and rationalizes them within the context of ion channel proteins that can be influenced by drugs. It is of dissipative nature due to fluxes of ions along gradients. The soliton theory is based on the assumption of an adiabatic density pulse in the nerve membrane. As typical for adiabatic phenomena, it goes along with variations in all thermodynamic quantities as thickness, length, lateral pressure, and temperature.

For both models, we show studies of colliding pulses that may help to discriminate between aspects of the models. The HH model can exhibit two regimes of annihilation and reflection (or penetration) depending on the parameters, whereas the soliton theory exhibits a single regime of reflection (or penetration). Mini solitons postcollision are observed in both models. It remains to be tested in experiments what precisely happens under different experimental conditions when two pulses collide.

Both models have advantages and disadvantages. Summarizing, however, it has to be concluded that the ionic hypothesis for explaining nerve pulse propagation (which is at the basis of the HH model) is in conflict with the experimental finding that the nerve pulse is an adiabatic phenomenon. In general, the soliton model has more predictive power due to the strict coupling of different thermodynamic variables. This also implies that it is easier to falsify.

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