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The propagation of nerve pulses

From the Hodgkin-Huxley model to the soliton theory

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ABSTRACT

The present project aims to describe and study the nature and transmission of nerve pulses. First we review a classical model by Hodgkin-Huxley which describes the nerve pulse as a pure electric signal which propagates due to the opening of some time- and voltage-dependent ion channels. Although this model was quite successful when introduced, it fails to provide a satisfactory explanation to other phenomena that occur in the transmission of nerve pulses, therefore a new theory seems to be necessary. The soliton theory is one such theory, which we explain after introducing two topics that are important for its understanding: (i) the lipid melting of membranes, which are found to display nonlinearity and dispersion during the melting transition, and (ii) the discovery and the conditions required for the existence of solitons. In the soliton theory, the pulse is presented as an electromechanical soliton which forces the membrane through the transition while propagating. The action of anesthesia is also explained in the new framework by the melting point depression caused by anesthetics. Finally, we present a comparison between the two models.

CONTENTS

1. INTRODUCTION AND OBJECTIVES

The propagation of information along nerves enables essential processes such as consciousness, movement and sensation. Logically, the human being has tried to address the issue and give a satisfactory explanation of the mechanism underlying the propagation of nerve pulses. Contrary to what someone would expect, nerves have been known for centuries. In the fourth century B.C., the Greek philosopher Aristotle already referred to nerves (from the Greek, meaning tendon) although he confused them with ligaments. Nevertheless, it was only the second century A.C. when the Greek physician and philosopher Galen stated that the source of nerves was the encephalon. He asserted that the brain was the source all sensation and voluntary motion and thus it was the most important organ in the body [1].

Many other physicians and philosophers have tried to understand the nervous system in history. However, it was not until the eighteenth century that physiologists related the theories of nerves with electricity: Galvani discovered a contraction of a frog muscle upon the application of electricity and related this response to something he called “animal electricity”; on the contrary, Volta thought that nerve pulses were purely electrical phenomena. Helmholtz established that the propagation velocity in the frog muscle nerve was 30 m/s [2].

On the other hand, the now accepted concept of the nerves being formed by the union of individual cells called neurons was firstly proposed by the Spanish neuroscientist Santiago Ramon y Cajal (Nobel Laureate 1906) at the end of the XIX century. He developed what is called neuron doctrine which establishes that the nervous system is composed of discrete neurons with an individual body and specialized features (axon and dendrites). Neurons constitute the structural and functional unit of the nervous system. It has been estimated that the human body contains around one hundred thousand million neurons which allow us to feel, think and move due to the electrical and chemical impulses they transmit. It is thus hardly surprising that the neurons’ behaviour has raised so much interest.

One of the biggest steps towards the description of the transmission of electrical impulses by neurons was done by Hodgkin and Huxley. In the paper published in 1952 they proposed a model (HH model) based on the electrical cable theory in which the electric pulse is transmitted thanks to the existence of time- and voltage-dependence ion channels that regulate the permeability of the neurons’ membrane to some ions (mainly Na^+ and K^+) [3]. In 1963 both scientists were awarded the Nobel Prize for this contribution.

Nonetheless further studies have led to findings which suggest that the HH model could be wrong or, at least, not complete. In this context, two biophysicists, Heimburg and Jackson developed a new theory of thermodynamic nature which can account for both the transmission of the pulses through the neurons and other phenomena not explained by the HH model. Solitons play an essential role in this model since it was suggested by Heimburg and Jackson that the adiabatic pulses travelling through the neurons’ membranes could be precisely electromechanical solitons [4].

The present project will be first focused on studying the composition and characteristics of membranes since they comprise the basic medium for the transmission of pulses. In order to

provide a general insight into the transmission of nerves impulses, an analysis of the HH model follows. However, it is beyond the scope of this project to go through the deep details (see [3] for details) but rather present a general vision which enables the reader to understand why the model needs improving. Afterwards, two topics are covered that are important for the soliton theory: (i) the lipid melting of membranes and the behaviour of the thermodynamic variables and (ii) the solitons as mathematical objects. After this, the soliton theory can be readily introduced. Finally, a comparison between the two models is done.

2. NEURONS

2.1 MAIN PARTS OF A NEURON

Nerves are formed by the union of individual cells called neurons. Along the nerves, information is transmitted from the brain to the organs by means of signals. The pulses transmitted were thought to be of electrical nature, but recent studies suggest that they could be of electromechanical nature.

There exists a wide variety of neurons, presenting different shapes and sizes. However, they all have a common structure: the cell body (called soma), the dendrites (where the signal is received), the axon and the terminal branches. We will be studying the transmission of pulses along the axon, which is an extension of the neuron that transmits the signal away from the soma to other neurons, glands or muscles. Most of the axons are only a few millimetres long and measure between $0.1\mu m$ to $20\mu m$ in diameter. However, some neurons have been found whose axon is more than one meter long. Neurons are classified into myelinated and non-myelinated depending on whether the axon is covered by a layer of a dielectric (myelin) or not. The conduction velocity is higher in myelinated nerves, around 100 m/s, while non-myelinated nerves transmit pulses at 1-5 m/s.

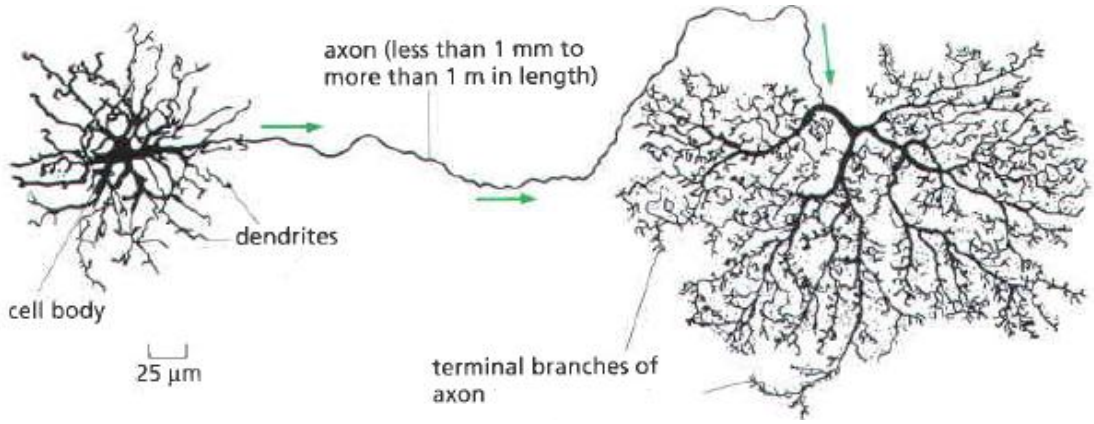

Fig. 1 Neuron from the retina of a monkey. Arrows indicate the direction of transmission. Adapted from [5].

2.2 MEMBRANE

Understanding the nature of membranes is necessary since they constitute the mean for the transmission of pulses. The cell membrane of almost every living organism is formed by a lipid bilayer (plus some proteins embedded). Lipids are arranged into bilayers due to their special properties: all the individual lipids are amphiphilic i.e., they have a polar head group (hydrophilic) and two apolar hydrocarbon chains (hydrophobic) (see Fig. 2a).

Due to their dipole moment, polar substances are miscible in water (they can interact favourably with water molecules) while apolar ones are not. For this reason, it is energetically favourable for the lipids to be assembled with their head group against the aqueous environment (outside and inside the cell) whereas the hydrophobic chains are oriented

towards the inside region of the membrane (see Fig. 2b). In this way, lipid bilayers of about 5 nm width are spontaneously formed.

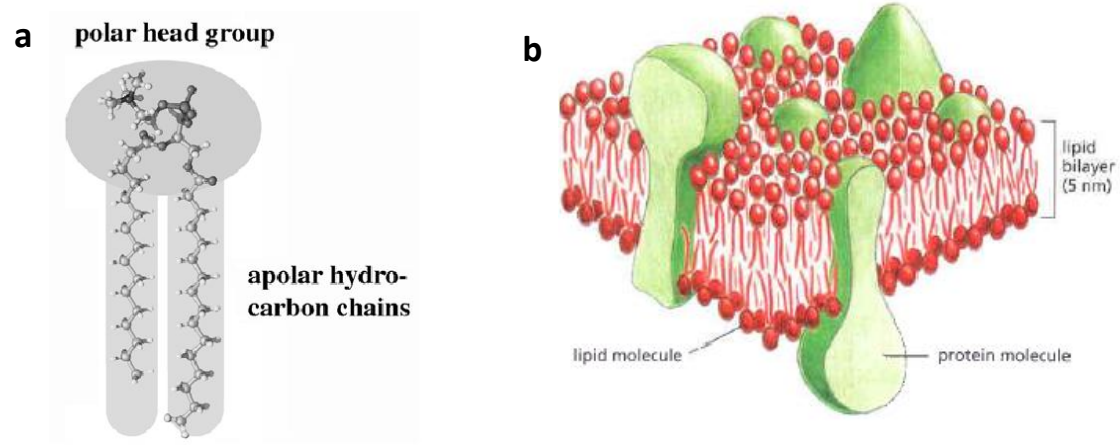

Fig. 2 Lipid bilayer. (**a**) Individual lipid and its main parts. Taken from [6]. (**b**) Three dimensional representation of a membrane. The lipid bilayer and the proteins embedded can be appreciated. Taken from [5].

The composition of cell membranes is very diverse: each membrane can contain from 500 to 1000 different types of lipids and its composition varies from cell to cell and from organism to organism. Furthermore, every membrane presents asymmetry, i.e., the lipid composition is different in each of the two leaflets. In particular, the inner monolayer contains more charged lipids than the outer one. Since all charged lipids are negatively charged (positively charged lipids do not exist naturally), the inside of the membrane is negatively charged with respect to the outside.

Membranes are permeable to some ions, among which Na^+ and $K^+$are especially relevant. The existing negatively charged fixed molecules inside the cell must be counterbalanced by positive K^+ cations, which is why the concentration of K^+ cations is higher inside than outside the cell. However, this high concentration of solutes inside the cell would lead to the continuous movement of water into the cell by osmosis. In order to establish an osmotic balance, the cell maintains a low concentration of Na^+ cations inside the cell. This is why the concentration of K^+ is higher inside than outside the cell whereas the opposite situation is found for Na^+. Actually, the cell posses Na^+-K^+ pumps (a kind of proteins) that maintain this situation at the expense of energy (ATP): Na^+ is pumped out whereas K^+ is pumped in (against their respective gradients).

There also exit leak channels in the membrane that are continuously open and allow the flow of Na^+ and K^+ across the membrane. Nevertheless, due to the high number of K^+ leak channels, the flow of K^+ out of the cell through the leak channels cannot be counteracted by the flow of K^+ pumped into the cell. In this situation, we find a net flow of K^+ cations out of the cell (down its concentration gradient), leaving an excess of negative charges inside the cell. This electric field created then attracts the K^+ cations towards the inside of the cell. The equilibrium is reached when the electric force equals the effect of the concentration gradient.

The existing potential across the membrane at the equilibrium is called resting potential. The resting potential is -70mV, which means that the inside of the cell is negatively charge with respect to the outside.

3. THE HODGKIN-HUXLEY MODEL

The Hodgkin-Huxley model (HH model) was presented for the first time in 1952 by Alan L. Hodgkin and Andrew F. Huxley from the University of Cambridge in their paper "*A quantitative description of membrane current and its application to conduction and excitation in nerve*" [3]. This model treats the transmitted impulses as pure electrical signals and aims to explain the transmission of signals using electrical circuits.

Hodgkin and Huxley (among others) made their experiments with giant squid axons. Giant squid axons were subject to numerous studies due to their convenient size (more than 1mm in diameter) which makes it easy to insert the electrodes used to measure voltage changes across the membrane. In the case of squid axons, K^+ concentrations are 400mM (mol/m^3) inside and only 20mM outside the cell whereas Na^+ concentrations are 50mM inside and 440mM outside it.

As mentioned above, membranes are constituted by a lipid bilayer where some proteins are embedded. The most abundant proteins present in the neuronal membranes are the so-called ion channel proteins. These proteins regulate the flow of ions in and out the cell down to their concentration gradient (contrary to Na^+-K^+ pumps) and therefore, no ATP is consumed. They are characterized by two main features: they are ion selective and they are not continuously open (contrary to the leak channels) but rather their opening is time- and voltage- dependent. In the case of squid axons there exist two main types of ion channels: Na^+ and K^+ channels.

The voltage pulse that travels along the nerve axons is denoted as action potential (AP). During the AP, the difference in voltage between the inside and outside of the cell changes locally by about 100mV. In the HH model, the transmission of the AP is explained as follows:

- The AP is triggered by a depolarization of the membrane i.e., the shift of the membrane potential towards a less negative value.
- As a result of the depolarization, the Na^+channels open (see Fig. 3a) giving rise to a net flow of Na^+cations into the cell which contributes to depolarize the membrane even more.
- After a while the Na^+channels become inactivated (see Fig. 3b): they would not respond to further stimuli.
- However, the depolarization in that segment of the axon is then large enough to further depolarize the nearby region which then goes through the same process. It serves as stimulus for the opening of the neighbouring Na^+ channels.
- The initial potential is restored by the opening of the K^+ channels, which leads to a net flow of potassium ions leaving the cell. The K^+ channels are also opened due to the depolarization of the membrane but a bit later than Na^+channels. This is why they are called delayed K^+ channels.

The idea of the net current being composed by two different ones, a quicker Na^+ current flowing into the cell and a delayed K^+ flowing out of the cell, was first proposed by Hodgkin and Huxley and it is known as the "ionic hypothesis". All this changes can be reversed by repolarizing the membrane.

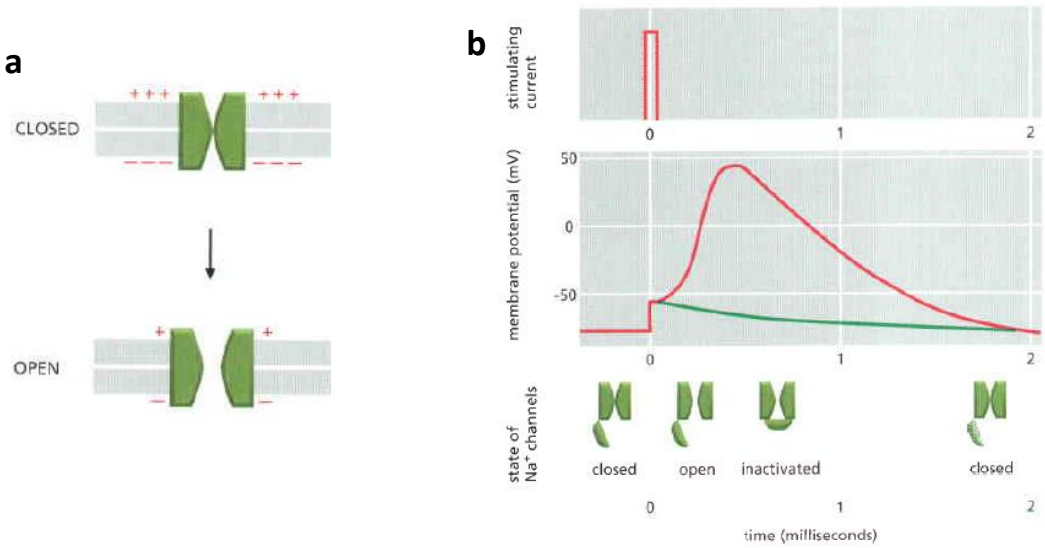

Fig. 3 The AP. (**a**) The depolarization causes the opening of the ion channels. (**b**) AP caused by a stimulating current. The green line represents how the membrane would return to its equilibrium state if the $\boldsymbol{Na^+}$ channels were not opened. From ref. [5].

As mentioned before, the HH model aims to explain the transmission of impulses along the nerves by means of electric circuits. This model describes the membrane as an insulator which acts as a capacitor with constant capacity C_m and the channel proteins as resistors with conductances g_{Na} and g_K. We can see the equivalent circuit in Figure 4. In the presence of a voltage V_m we can see two different currents: a capacitive current charging the capacitor and an ohmic one passing through the resistors.

Capacitive current: $C = \frac{Q}{V} \rightarrow I_c = \frac{dQ}{dt} = \frac{d(C \cdot V)}{dt} = C_m \frac{dV}{dt}$ considering the capacity constant.

Ionic current: $V = IR \rightarrow I_o = \frac{V}{R} = g \cdot V$

Therefore, we can write the total membrane current as

$$I_m(t) = C_m \frac{dV}{dt} + g_{Na}(V_m - E_{Na}) + g_K(V_m - E_K) \qquad (1)$$

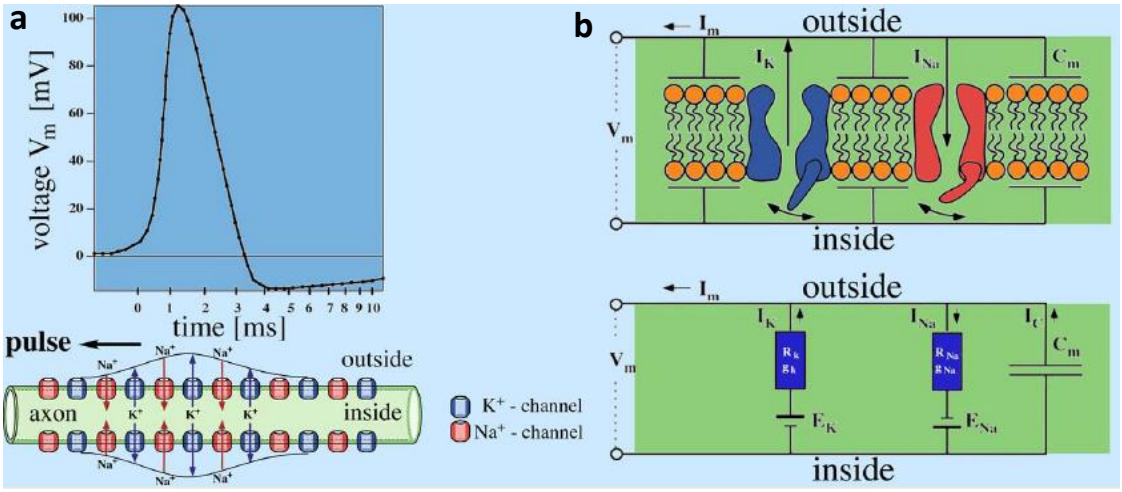

Fig. 4 (**a**) Propagation of the voltage pulse. (**b**) Equivalent circuit of the membrane. The protein channels are described as resistances while the membrane is treated as a capacitor. From ref [2].

In Eq. (1) we encounter the parameters E_{Na} and E_K which are the Nernst potentials i.e. equilibrium potentials for Na^+ and K^+ respectively. They are calculated as follows:

The free energy change due to a mole of ions crossing the membrane is $\Delta G_c = -RTln\frac{C_o}{C_i}$

The free energy change due to the change in voltage is $\Delta G_V = zFV$

Then, $\Delta G_c + \Delta G_V = 0 \rightarrow$ $$V = E = \frac{RT}{zF}\ln\frac{C_o}{C_i} \quad (2)$$

where R is the gas constant, T is the absolute temperature, z is the charge of the corresponding ion, F is the Faraday constant and c_0, c_i are the concentrations from the ion considered outside and inside the cell.

All the data necessary to calculate the Nernst potentials is known. The Nernst potentials are different in each case since the concentration in and out the cell is different for each type of ions.

However, the conductances g_{Na} and g_K are different from the Nernst potentials in the sense that they cannot be calculated using first principles. Hodgkin and Huxley even said that there was "little hope of calculating the time course of the sodium and potassium conductances from first principles" [3]. Instead, they assumed that they were voltage and time dependent, and they parameterized them introducing three functions $m(V_m, t)$, $h(V_m, t)$ and $n(V_m, t)$:

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

The functions m, h and n can adopt values between 0 and 1. They are called gating variables since they are related to the probability of finding the channels open. In this way, if $m^3h = 1$, the Na^+ channel is open and the conductance is the characteristic conductance $g_{Na,0}$. The same holds true for the K^+ channel is $n^4 = 1$. The power and number of the gating variables was fixed such that the theoretical evolution matches with the observed evolution of the conductances.

Furthermore, each gating variable depends on some voltage-dependent rate constants which, in turn, depend on several other parameters that must be found experimentally. In total, more than 20 parameters must be found empirically as they are not derived from any first principle. This is the reason why the concept proposed by Hodgkin and Huxley is denoted as model, and not as a theory.

The following equation is known from cable theory:

$$\frac{\partial^2 V_m}{\partial x^2} = \frac{2R_i}{a}I_m \quad (4)$$

where a is the radius of the axon and R_i is the resistance of the cytosol (intracellular fluid) within the membrane. We can introduce this expression in equation (1) which yields:

$$\frac{\partial^2 V_m}{\partial x^2} = \frac{2R_i}{a}\left(C_m\frac{dV_m}{dt} + g_{Na}(V_m - E_{Na}) + g_K(V_m - E_K)\right) \quad (5)$$

Furthermore, Hodgkin and Huxley found that the shape curve of V_m vs. t was similar to the shape of the curve V_m vs. x and they assumed that the membrane potential satisfies:

$$\frac{\partial^2 \mathrm{V_m}}{\partial \mathrm{t}^2} = \theta^2 \frac{\partial^2 \mathrm{V_m}}{\partial \mathrm{x}^2} \tag{6}$$

where θ is the propagation velocity which is independent of the voltage.

Using the wave equation, we can calculate the following differential equation for the propagation of the AP:

$$\frac{a}{2R_i\theta^2}\frac{\partial^2 V_m}{\partial t^2} = C_m \frac{dV_m}{dt} + g_{Na}(V_m - E_{Na}) + g_K(V_m - E_K) \tag{7}$$

This differential equation can be solved numerically. Nevertheless, a value for the propagation velocity θ must be guessed. Hodgkin and Huxley found that if the value of the assumed θ is too small or too large, the potential goes towards either $+\infty$ or $-\infty$. The right value of θ is that for which the resting potential is restored once the AP is over. In their paper, Hodgkin and Huxley made a change of variables and set the resting potential equal to zero (Fig. 5).

One of the virtues of this model, which made it so accepted among the neuroscience community, was its accurate description of the velocity and amplitude of the pulse (Fig. 5). Measuring the necessary parameters, they predicted a value for the conduction velocity of 18.8 m/s. The velocity measured experimentally was 21.2 m/s [3].

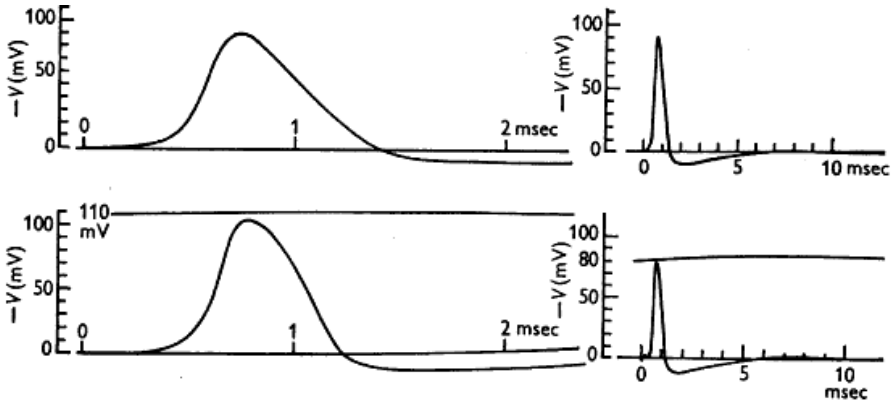

Fig. 5 AP in the HH model. Comparison between the calculated AP (upper image) and the experimental records (lower image) at 18.5°C. Two different time scales are shown. From ref. [3].

It should nevertheless be added that Hodgkin and Huxley did not know how the permeability of ions was regulated at a molecular level. They detected the flow of ions across the membrane, but it was not until years later that the existence of ion channel proteins was discovered. In their own words [3]: “our experiments are therefore unlikely to give any certain information about the nature of the molecular events underlying changes in permeability”.

4. THERMODINAMICS OF THE MEMBRANE

4.1 LIPID MELTING

One important characteristic of lipid bilayers which will be essential for the propagation of solitons is the lipid melting. On the one hand, lipids can change their lateral order: at low temperatures they are arranged in a triangular lattice whereas at higher temperatures they do not present any lateral order. This is called solid-liquid transition. On the other hand, lipid chains also shift from ordered to disordered states, which corresponds to trans-gauche isomerizations. At low temperatures there are only trans configurations corresponding to the lowest energy state. However, at higher temperatures gauche configurations are also found. Gauche conformations, which yield higher energy states, correspond to rotations of the groups attached to the C atoms around the C-C bonds.

In conclusion, lipid bilayers display transitions from solid-ordered to liquid-disordered states (see Fig. 6a). Melting transitions are characterized by a severe increase in the heat capacity of the membrane. Profiles as the ones shown in Fig. 6b have been found in experiments based in differential scanning calorimetry.

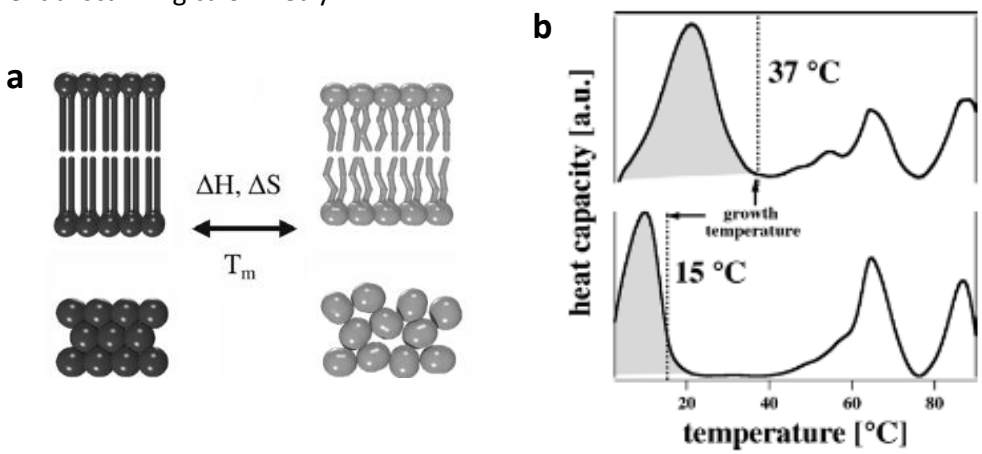

Fig. 6 Lipid melting. (**a**) Lipid bilayers display transitions from solid-ordered (left) to liquid-disordered (right) states. An increase in area and a decrease in thickness can be observed. (**b**) The melting point is slightly below the growth temperature. The shadow area corresponds to the increase in heat capacity during the AP. The peaks above the growth temperature are not relevant for this discussion. From ref. [6].

It has been found that organisms adapt their membranes' lipid composition such that the melting temperature is just below the body or growth temperature (Fig. 6b). This is a crucial fact for the soliton propagation, as we will see later. The melting temperature T_m is affected by the length and the saturation of the lipid chains: shorter and unsaturated chains (i.e. containing double bonds between carbon atoms) yield lower melting points. There are other factors, such as changes in pressure or pH, that influence the melting temperature e.g., an increase in pressure leads to an increase of the melting point. Hence, organisms grown under higher pressure conditions will adapt their lipid composition such that the melting temperature is lower than normal.

On the other hand we know that the heat capacity is related to the enthalpy and entropy of the system:

$$C_P = \left(\frac{dH}{dT}\right)_P \qquad C_p = T\left(\frac{dS}{dT}\right)_P \tag{8}$$

Integrating the expressions in (8) we get the values of the melting entropy and the melting enthalpy:

$$\Delta H = \int_{T_1}^{T_2} C_P dT$$
$$\Delta S = \int_{T_1}^{T_2} \frac{C_P}{T}\, dT = \frac{1}{T_m}\int_{T_1}^{T_2} C_P dT = \frac{\Delta H}{T_m} \tag{9}$$

where T_1 and T_2 are temperatures below and above the melting transition. In the case of entropy, it has been assumed that the peak in the heat capacity is sharp enough to approximate the temperature as constant during the lipid melting. From Eq. (9) we can conclude that the enthalpy and the entropy increase during the transition, and hence heat is absorbed.

In this case and in others that will follow, DPPC lipids (dipalmitoyl phosphatidylcholine) are going to be used as example in order to give an insight into the numerical values obtained. DPPC is the main component of lung surfactant, a substance present in the lung alveoli which enables the respiratory activity. For DPPC one finds one finds $T_m = 314.2K$, $\Delta\mathrm{H} = 35kJ/mol$ and $\Delta S = 114.4$J/mol [6].

4.2 BEHAVIOUR OF THE THERMODYNAMIC VARIABLES IN THE MELTING TRANSITION

4.2.1 Mechanical variations

There are several mechanical changes that take place during the lipid transition [7]. While changing from a solid-ordered state to a liquid-disordered state, the thickness of the membrane decreases about -16% (Fig. 6a), the area of the membrane increases around 25% and there is a general volume increment of 4% (Fig. 7a).

4.2.2 Changes in the elastic constants

The heat capacity and compressibility can also be measured empirically. Before going further, I would like to revise the existing relations between the heat capacity C_P, isothermal volume compressibility κ_T^V and isothermal area compressibility κ_T^A and the fluctuations in enthalpy H, volume V and area A respectively (fluctuation theorem).

$$C_P = \frac{\langle H^2\rangle - \langle H\rangle^2}{RT^2} \qquad \kappa_T^V = \frac{\langle V^2\rangle - \langle V\rangle^2}{\langle V\rangle RT} \qquad \kappa_T^A = \frac{\langle A^2\rangle - \langle A\rangle^2}{\langle A\rangle RT} \tag{10}$$

According to the first expression in (10), we can conclude that the enthalpy fluctuations $(\Delta H)^2 = \langle H^2 \rangle - \langle H \rangle^2$ will be maximal during the lipid melting because the heat capacity is also maximal.

On the other hand, Anthony et al. [8] and Ebel et al. [9] found in a densitometry experiment that the excess heat capacity ΔC_P and the excess volume change ΔV (see Fig. 7b) were proportional during the melting transition:

$$\Delta V(T) = \gamma_V \Delta H(T) \tag{11}$$

where γ_V is the proportionality constant. From Eq. (11) we can deduce that fluctuations in enthalpy are proportional to fluctuations in volume during the lipid melting (Fig. 7b). Furthermore, Ebel et al. reproduced the same result in another experiment based on pressure calorimetry [9]. In this study, the value of the proportionality constant was found to be roughly the same for several lipids and mixtures of lipids: $\gamma_V = 7.8 \times 10^{-4}\ cm^3/J$.

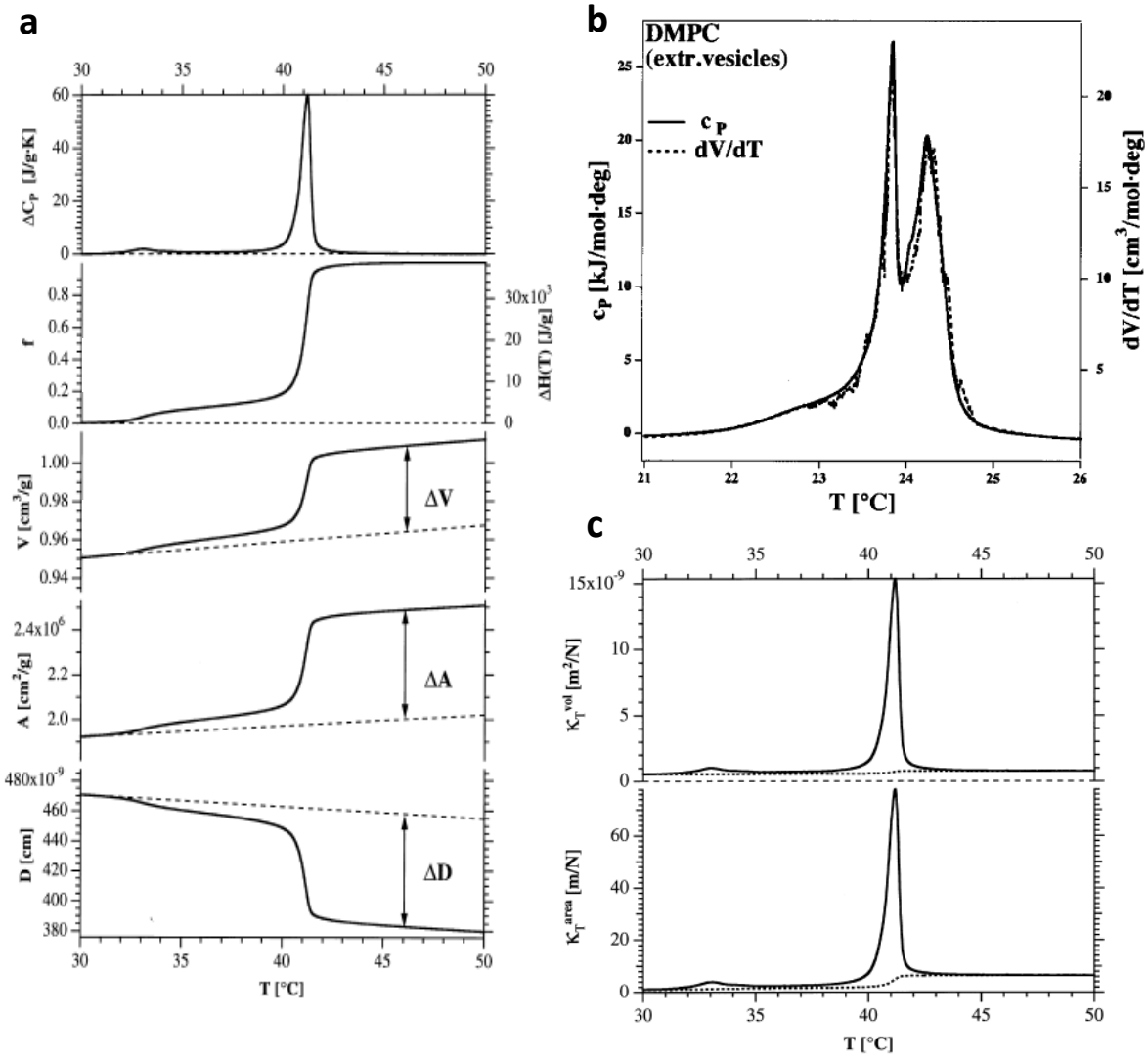

Fig. 7 Thermodynamic changes during the lipid melting transition. (**a**) During the transition several mechanical changes take place: there is an increase in volume and area and a decrease in thickness. Data calculated from the heat capacity profile. (**b**) Proportionality between the excess heat capacity and the volume expansion coefficient during the transition regime. From ref. [9](**c**) During the transition both the volume and area isothermal compressibilities reach a maximum i.e., the membrane becomes softer during the transition. Figures a and b belong to extruded DPPC LUV. From ref. [7].

Although it has not been accurately proved, a similar relation for the excess area change was assumed by Heimburg: $\Delta A(T) = \gamma_A \Delta H(T)$. However, it seems to be a right assumption as it leads to right predictions. The value of the proportionality constant in the case of area fluctuations has been approximated as $\gamma_A = 8.9 \times 10^3 cm^2/J$ [7].

Eq. (11) allows us to express the value of the volume and area compressibilities as functions of the heat capacity. Introducing Eq. (11) in the second expression in (10) we get:

$$\Delta\kappa_T^V = \frac{\gamma_V^2 T}{\langle V \rangle} \Delta C_P \tag{12}$$

Similarly, we can obtain the following expression for the area excess compressibility $\Delta\kappa_T^A = \frac{\gamma_A^2 T}{\langle A \rangle} \Delta C_P$. These relations describe a property of lipid bilayers which is essential for the propagation of solitons. Since the excess heat capacity reaches maxima during the melting transition, the area and volume isothermal compressib...ies will reach a maximum as well, i.e., the membrane becomes softer in the transition regime (Fig. 8a).

It is possible to separate the intrinsic enthalpy H_0 of the membrane lipids from the excess enthalpy ΔH associated to the transition (see (9)). This yields

$$C_P = C_{P,0} + \Delta C_P = \left(\frac{dH_0}{dT}\right)_P + \left(\frac{d(\Delta H)}{dT}\right)_P = \frac{\langle H_0^2 \rangle - \langle H_0 \rangle^2}{RT^2} + \frac{\langle \Delta H^2 \rangle - \langle \Delta H \rangle^2}{RT^2} \tag{13}$$

The value of the intrinsic heat capacity is different in the gel and in the liquid phase. The following assumption is made to approximate the value of the intrinsic capacity during the melting transition:

$$C_{P,0}(T) = (1 - f) \cdot C_{P,0}^{gel} + f \cdot C_{P,0}^{liq} \tag{14}$$

The function f represents the fraction of liquid lipids (Fig. 7a) and is given by

$$f(T) = \frac{\int_{T_1}^{T} C_P \, dT}{\int_{T_1}^{T_2} C_P \, dT} \tag{15}$$

where T_1 and T_2 are temperatures far below and far above the melting transition and satisfy $T_1 < T < T_2$.

Exactly the same can be said about the isothermal compressibilities: the intrinsic compressibility can be separated from the excess compressibility associated with the lipid melting. Taking into account the relations derived above (11), the compressibilities are then given by

$$\begin{aligned} \kappa_T^V(T) &= \kappa_{T,0}^V(T) + \Delta\kappa_T^V = \kappa_{T,0}^V + \frac{\gamma_V^2 T}{\langle V \rangle} \Delta C_P(T) \\ \kappa_T^A(T) &= \kappa_{T,0}^A(T) + \Delta\kappa_T^A = \kappa_{T,0}^A + \frac{\gamma_A^2 T}{\langle A \rangle} \Delta C_P(T) \end{aligned} \tag{16}$$

As in the case of the heat capacity, the intrinsic compressibility differs from the gel to the liquid phase. A similar assumption to that in Eq. (14) is made in order to calculate the intrinsic compressibilities as functions of temperature.

4.2.3 Adiabatic compressibility

For reasons that will become clear later, let me introduce the adiabatic compressibility. Adiabatic conditions imply that no heat is exchanged between the system and its surroundings ($dQ = 0$). Furthermore, since $dQ = TdS$, it is also denoted as isentropic compressibility. The adiabatic compressibility can be written as a function of known variables [10]

$$\kappa_S = \kappa_T - \frac{T}{V \cdot C_P}\left(\frac{\partial V}{\partial T}\right)_P^2 \tag{17}$$

In most of the cases physicists work with lipids dispersions, so let us assume that the system is a lipid dispersion. We can understand the expression (16) as follows: the heat produced by the lipid transition must be absorbed by the aqueous environment; therefore, the higher the heat capacity of the aqueous environment, the larger the adiabatic compressibility (as can be check in expression (16)) [7].

Let us consider the case of a periodic perturbation such a sound wave of frequency ω. In the case of low frequency and large amount of water, the heat has time to be absorbed and thus the heat capacity assumes a large value. In this case, the period of the perturbation is smaller than the relaxation times. In low-frequency limit, the adiabatic compressibility gets closer to the isothermal compressibility

$$\lim_{\omega \to 0} \kappa_S = \kappa_T \tag{18}$$

On the other hand, if the frequency of the perturbation is very high, the heat cannot longer be absorbed and one gets

$$\lim_{\omega \to \infty} \kappa_S = 0 \tag{19}$$

For lipid dispersions in the 5 MHz regime, membranes are considered to be adiabatically decoupled from the aqueous environment [7]. In this case, the adiabatic compressibility of the membrane and the environment can be added

$$\kappa_S^{disp} = f_{H_2O} \cdot \kappa_S^{H_2O} + f_{lipids} \cdot \kappa_S^{lipids} \tag{20}$$

where f_{H_2O} and f_{lipids} are the fractions of water and lipids respectively. Now, we can make use of Eq. (16) to calculate the adiabatic compressibility of lipids since all the parameters required (isothermal compressibility, heat capacity and volume expansion coefficient) can be derived from the heat capacity profile.

It can be concluded from the discussion above that the adiabatic compressibility is frequency dependent (Fig. 8a). This fact will have important implications later.

4.3 SOUND PROPAGATION

The propagation of a sound wave is described by the following equation

$$\frac{\partial^2 D}{\partial t^2} - c_0^2 \frac{\partial^2 D}{\partial x^2} = 0 \tag{21}$$

where c_0 is the sound velocity and it is given by

$$c_0^2 = \frac{1}{\kappa_S \cdot \rho} \tag{22}$$

where κ_S is the adiabatic compressibility and ρ is the density of the medium where the sound propagates. In the case of lipid dispersions, the value of the velocity can be calculated using Eq. (20). Besides, the sound velocity can be determined empirically from an ultrasonic resonator experiment.

The same can be applied to a sound wave propagating along a cylindrical membrane as the membrane of an axon. In this case, we would substitute the adiabatic area compressibility and the lateral density in Eq. (22). As can be seen in Fig. 8b, the sound velocity presents a strong dependence with the medium density. There are two lines in each panel. The solid one corresponds to the low frequency limit, at which the adiabatic compressibility approaches the isothermal compressibility, whereas the dotted line corresponds to the 5 MHz regime. They have been calculated from the heat capacity profile (Fig. 8b).

In the previous section we discussed the frequency dependence of the adiabatic compressibility. Taking into account the expression for the sound velocity (20), we can conclude that the propagation velocity of sound is frequency dependent i.e., the membranes present *dispersion*. This is consistent with behaviour shown in Fig. 8a.

Finally, let me point out that the sound velocity reaches minima during the melting transition. We could have expected it since the adiabatic compressibility presents a maximum.

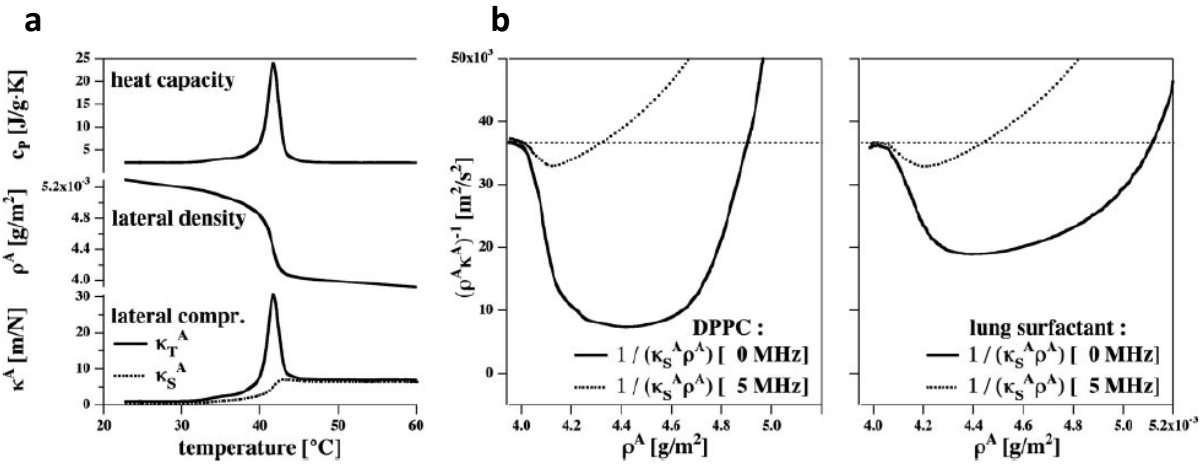

Fig. 8 (**a**) Adiabatic lateral compressibility calculated from the heat capacity profile. It is frequency-dependent: the isothermal compressibility (corresponding to the low-frequency limit) is compared to the adiabatic compressibility (in a 5MHz-ultrasonic experiment). (**b**) The lateral sound velocity depends strongly on the density. Furthermore, the sound velocity reaches minima during the melting transition. Profiles corresponding to DPPC vesicles at 45°C (left) and lung surfactant at 37°C (right). From ref. [4].

5. SOLITONS

5.1 THE DISCOVERY OF SOLITONS

The first documented observation of a soliton was done by John S. Russell in 1834. This naval engineer was riding a horse along the Edinburgh-Glasgow canal when he saw a wave created by a boat incident. He chased it for several kilometres without the wave weakening. He reported his experience to the British Association as follows:

> I believe I shall best introduce the phenomenon by describing the circumstances of my first acquaintance with it. I was observing the motion of a boat which was rapidly drawn along a narrow channel by a pair of horses, when the boat suddenly stopped – not so the mass of water in the channel which it had put in motion; it accumulated round the prow of the vessel in a state of violent agitation, then suddenly leaving it behind, rolled forward with great velocity, assuming the form of a large solitary elevation, a rounded, smooth and well-defined heap of water, which continued its course along the channel apparently without change of form or diminution of speed. I followed it on horseback, and overtook it still rolling on at a rate of some eight or nine miles an hour, preserving its original figure some thirty feet long and a foot to a foot and a half in height. Its height gradually diminished, and after a chase of one or two miles I lost it in the windings of the channel. Such, in the month of August 1834, was my first chance interview with that singular and beautiful phenomenon which I have called the Wave of Translation. [11]

Russell's finding led to a big research in the soliton area field has continued until today. He himself made some theoretical and experimental studies deducing that the volume of water carried by the wave was equal to the volume of water displaced in the perturbation. He even derived experimentally an expression for the velocity of the wave. However, he encountered resistance from some of his contemporaries such as Stokes or Airy, who rejected Russell's formula for being incompatible with their own theory of shallow water waves. It was not until a few years later that Boussinesq (1871) and Lord Rayleigh (1876) succeed in extending the theory of shallow water waves, finding the same expression for the velocity of the soliton as Russell. Furthermore, they were able to provide a profile for the wave:

$$c^2 = g(h + a)$$
$$\xi(x,t) = a\,\mathrm{sech}^2[\beta(x - ct)] \tag{23}$$

where a is the amplitude of the wave, h is the depth of the canal, c is the propagation velocity g is the acceleration of gravity and β is a constant whose value is not relevant to this discussion.

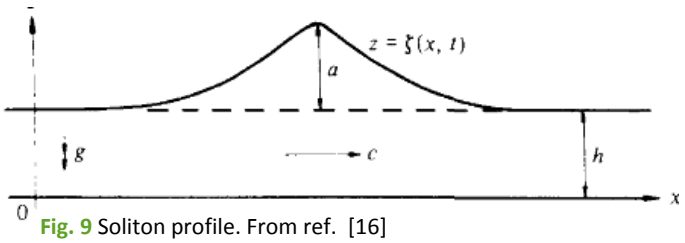

Fig. 9 Soliton profile. From ref. [16]

However, Boussinesq and Rayleigh were not able to write the equation which has Eq. (23) as solution. This was done by Kortewev and de Vries in 1895 who discovered the equation which carries their name (also called KdV equation).

Solitons appeared again in 1953 when Fermi, Pasta and Ulam were investigating the equipartition of energy in a classical non-linear system (FPU problem) [12]. They studied the motion of the particles in a one-dimensional anharmonic lattice. Contrary to what they expected, the system presented an almost periodic behaviour: even if the system followed the equipartition theorem at the beginning, they found that the energy tended to concentrate in the initial mode for times sufficiently long. In 1965 Kruskal and Zabusky showed that the continuum limit of the governing equation in the FPU problem was precisely the KdV equation. After studying the KdV equation with periodic boundary conditions, Zabusky and Kruskal argued that the almost periodic behaviour was due to the solitons' property of being able to pass through each other without changing their shape or velocity. If the energy is large enough, the initial wave steepens and almost produces a shock, but then some balance is reached between nonlinearity and dispersion and several $sech^2$ profile waves are formed (Fig. 10b) which then preserve their shape and velocity until sometime later they concur at the initial position giving rise to the initial situation (first mode) [13].

As Russell did a century before, Zabusky and Kruskal showed that an arbitrary initial profile develops into two or more solitons as $t \to \infty$. Furthermore, the taller waves, therefore quicker waves according to Eq. (23), seem to overtake shorter ones and continue maintaining their shape and velocity afterwards (Fig. 10a). It is important to keep in mind that this process takes place in nonlinear conditions thus the superposition principle is not fulfilled. The only sign of the interaction is just a change in the phase i.e. the solitons suffer a displacement from the position they should occupy if the interaction had not taken place. Zabusky and Kruskal called this kind of waves *solitons* due to their particle-like behaviour (same as phonon, photon...).

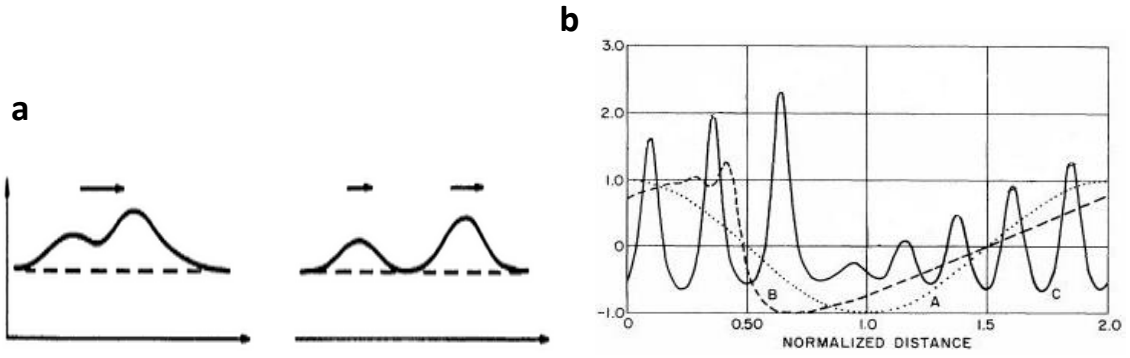

Fig. 10 (**a**) Evolution of an arbitrary-profile wave into two solitons. From ref. [11](**b**) Zabusky and Kruskal solution for the KdV equation. The dotted line corresponds to the initial profile. As time goes by, the wave steepens (broken line). Finally, eight solitons are formed (full line). For longer times, we would get a profile similar to the initial one corresponding to the solitons reaching their initial positions. Adapted from [13].

The discovery of the inverse scattering method by Gardner, Greene, Kruskal and Miura in 1965 was a decisive step. This method is employed to find soliton solutions to the KdV and other nonlinear PDE equations such as the nonlinear Schrödinger equation or the sine-Gordon equation. The inverse scattering method can be described in a simplified way as follows:

1. Knowing an initial condition for the KdV equation $u(x,0)$, it is possible to solve the stationary Schrödinger equation taking as the potential the function $u(x,0)$. This yields the spectrum of the equation which is called scattering data.
2. Then it is possible to know the time evolution of the scattering data for $t > 0$.
3. Finally, one only needs to find the potential $u(x,t)$ which corresponds to the calculated scattering data at $t > 0$. The function $u(x,t)$ obtained is precisely the solution to the KdV equation.

All studies revealed that solitons are exceptionally stable: we do not need to have particularly special initial conditions in order to get soliton solutions; moreover, solitons are stable under variations of the differential equation describing them, e.g. if a dissipative term is added. This stability may be the reason why solitons have been related with so many different phenomena as mentioned below.

5.2 EVIDENCE OF THE EXISTANCE OF SOLITONS

From the first observation of a soliton in 1845 by Russell, many other solitons have been recognized. Solitons have been identified in different phenomena such as tidal waves, rogue waves, proteins, DNA denaturalization, conformational change of the DNA α-helix (Davydov soliton), atmospheric solitons (Morning glory cloud), Jupiter's Great Red Spot, Bose-Einstein condensates, nonlinear optics (light bullets, fiber optic), plasmas, superconductors (long Josephson junctions), surface waves, solid waveguides, screw dislocations… Furthermore, topological solitons are present in cosmology as well (string theory or supergravity). It is thought that some topological solitons were formed at early stages of the universe such as magnetic monopoles, cosmic strings, domain walls, skyrmions, instantons… Finally, some studies have suggested that electric impulses travelling through the nerves could precisely be electromechanical solitons.

As can be noted from the discussion above, solitons constitute a phenomenon present in a wide variety of fields and consequently a big effort has been made both by physicist and mathematicians in order to understand and describe them. A lot has been written about solitons, with different approaches depending on the area of study. It is not my intention to deepen in the study of solitons beyond the necessary knowledge to understand the soliton theory in neuroscience.

5.3 SOLITARY WAVES AND SOLITONS: A DEFINITION

I have used the word soliton indifferently, but there are actually some differences between solitary waves and solitons that I would like to point out.

The well-known wave equation

$$\partial_{tt}u - c^2\partial_{xx}u = 0 \tag{24}$$

accepts a solution of the form $u(x,t) = f(x-ct) + g(x+ct)$ representing waves travelling to the left and to the right respectively with velocity c (d'Alambert's solution). These waves present two important characteristics.

- It can be constructed by the superposition of plane waves such that a wave packet is formed. Therefore it will travel at constant velocity c and it will preserve its shape since all the components will travel at the same speed (there is no dispersion).
- Since (22) is a linear equation, the solution will satisfy the superposition principle. As described by Rajaraman [14], this implies that for $t \to -\infty$, $u(x,t)$ consists of two packets approaching each other but still infinitely separated. At a finite t they will collide and they will continue their way recovering their initial shape and velocity as $t \to \infty$.

These two features are not surprising because we are treating with a linear system. However, in the case of nonlinear equations, they would constitute two remarkable characteristics. Solutions satisfying the first condition i.e. preserving their shape and velocity are called *solitary waves.* We have briefly mentioned before that solitons (and solitary waves as well) arises due to the balance reached between the non-linearity and the dispersion present in the field equation. We can intuitively see that.

Let us consider the linear equation $u_t + u_x = 0$, whose solution is any function $u = f(x+t)$ which presents the two features mentioned before (note that we have made $c = 1$). Now, let see what happen if we introduce a dispersion term.

$$u_t + u_x + u_{xxx} = 0 \tag{25}$$

We can construct the solution as a superposition of plane waves.

$$u(x,t) = \int A(k)e^{i(kx-wt)}dk \tag{26}$$

For each wave the following dispersion relation must be satisfied:

$$\omega = k - k^3 \tag{27}$$

$$c = \frac{\omega}{k} = 1 - k^2 \tag{28}$$

Eq. (28) describes the propagation velocity which depends on the value of the wave number k. This implies that each component of the wave packet will travel at different speed, and consequently, the wave packet profile will change. In fact, it will spread out (Fig. 11a).

On the other hand, we can analyze the behaviour of solutions to non-linear partial differential equations. One of the simplest non-linear equation is

$$u_t + (1+u)u_x = 0 \tag{29}$$

We can solve this equation using the method of characteristics. We find that u is constant along the direction of the vector $(1,1+u)$ i.e. u is constant along the lines $\frac{dx}{dt} = 1+u$ in the xt space. Therefore the characteristics lines are $x = (1+u)t + constant$. Hence, the solution is an arbitrary function of the form

$$u(x,t) = f(x-(1+u)t) \tag{30}$$

However, a wave of this form will steepen and produce a shock. Thus it will be single-valued only for a limited time (Fig. 11b).

Combining Eq. (25) and (29) we get the famous KdV equation

$$u_t + (1+u)u_x + u_{xxx} = 0 \tag{31}$$

The changes in the profile of the wave caused by dispersion and non-linearity will counteract each other giving rise to a wave profile which retains its shape despite the mentioned effects.

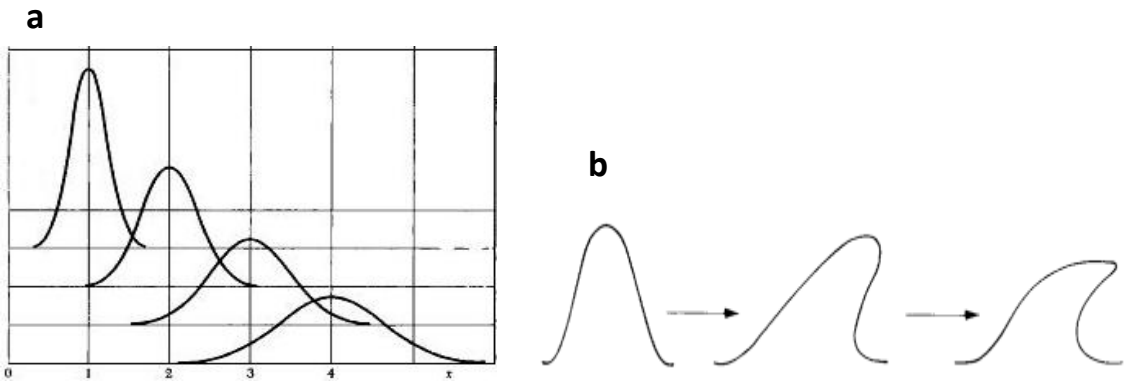

Fig. 11 Effects of dispersion (**a**) and non-linearity (**b**) in the wave profile. In the first case the wave spreads out whereas in the second case the wave steepens and finally breaks becoming non-unique. Adapted from ref. [15] and [16] respectively.

There exist several definitions for solitary wave in the literature, but I will adopt that of Rajaraman [14] for a more formal description. A solitary wave is a "localized non-singular solution of any non-linear field equation whose energy density, as well as being localized, has a space-time dependence of the form

$$\varepsilon(x,t) = \varepsilon(x - \boldsymbol{u}t) \tag{32}$$

where $\boldsymbol{u}$ is the velocity vector."

On the other hand, *solitons* are solutions that not only display the first characteristic but the second as well. Roughly speaking, solitons are solitary waves that preserve their shape and velocity after a collision with another soliton. According to Rajaraman, solitons must satisfy what follows: consider a solution to a nonlinear equation that in the past consists on N solitary waves. Its energy density will be given by the following

$$\varepsilon(x,t) \xrightarrow[t\to-\infty]{} \sum_{i=1}^{N} \varepsilon(x - a_i - \boldsymbol{u_i}t) \tag{33}$$

If it meets the following requirement as it evolves in time

$$\varepsilon(x,t) \underset{t\to\infty}{\longrightarrow} \sum_{i=1}^{N} \varepsilon(x - a_i - \boldsymbol{u_i}t + \boldsymbol{\delta_i}) \tag{34}$$

where $\boldsymbol{\delta_i}$ are some constant vectors, then we can conclude that such solitary waves are, in fact, solitons. Therefore solitons are defined as "solitary waves whose energy density profiles are asymptotically restored (as $t \to \infty$) to their original shapes and velocities". The solitons may suffer a phase-shift, meaning that they could be displaced from the position they would occupy in the absence of the interactions. It can be said then that all solitons are solitary waves, but the opposite is not true. Therefore, there exit multiple non-linear equations whose solutions are solitary waves. Nonetheless, not so many display soliton solutions.

For the sake of completeness I would like to mention that solitons can also arise from a balance between the nonlinearity and the dissipation effect. An example of a nonlinear equation which displays soliton solutions and furthermore has a dissipative term is the Burgers equation.

$$u_t + (1+u)u_x - u_{xx} = 0 \tag{35}$$

6. SOLITON THEORY FOR NERVES

6.1 THE NECESSITY OF A NEW THEORY

During the last half of the twentieth century there were a series of discoveries which made scientists believe that the current HH model was not correct or at least, was not complete. Perhaps the most important finding was that there is no net heat release during the AP [16,17].

Thermal responses in the nerves have been subject of extensive studies and multiple papers can be found in the literature about this topic. Many authors (Abbott, Hill, Howard, Keynes, Richie and Tasaki among others) agree that during the first phase of the AP there is actually some heat release accompanied by a temperature increase whereas during the second phase of the AP there is a temperature decrease and the heat is again reabsorbed such that the integrated heat is zero within experimental error (see Fig. 12a). Uncertainties of 9-22% have been found (see ref. [18]) which can be justified by the difficulty entailed by the experiments, which required a resolution in the range of μK and ms. In any case, the fact that there is no net heat release suggests that the propagation of pulses along the nerves is an adiabatic and isentropic ($dQ = tdS = 0$) phenomenon and therefore it is logic to think that it should be based in adiabatic and reversible processes.

This is in conflict with the HH model. On the one hand, the HH model explains the propagation of the AP by means of ion-channel proteins that regulate the flow of certain ions in and out of the cell. Hodgkin and Huxley interpreted these flows of ions as currents going through resistors. According to Joule effect this yields some heat dissipation

$$\frac{dQ}{dt} = U \cdot I_m = gU^2 > 0 \tag{36}$$

where Q is the heat produced, U is the voltage across the channels, I_m is the transmembrane current and g is the conductance of the channel. As can be seen, the heat variation will be positive in any case, no matter the direction of flow of the ions. Moreover, the cooling of the nerve in the second phase of the AP is too quick to be caused by normal heat conduction (see Fig. 12b). On the other hand, reversible processes are required to justify that the whole phenomenon is reversible. However, as I have explained in the third section of the present writing, the flow of ions is caused by the different ion concentrations inside and outside the cell and the concentration equilibration is not a reversible process. Finally, it was noted by Andersen et al. [19] that the propagation of pulses would not be a very efficient process according to the HH model since the heat dissipated in the channel proteins is about 600 times larger than the capacitive energy transported by the AP over one meter.

It has been suggested that the observed heat changes could correspond to the discharge and recharge of a capacitor: the energy stored would be released during the depolarization by means of Joule dissipation whereas the energy restored during the repolarization would come from the thermal energy of the ions in the aqueous environment [18]. Nevertheless, another discrepancy arises when comparing quantitatively the reversible heat change found empirically with the capacitive energy of the membrane. Although it has been found they are proportional

to each other i.e. $\Delta Q(t) \propto \frac{1}{2} C_m U(t)^2$ (see Fig. 12c), the energy required to recharge the capacitor is much smaller than the reversible heat measured thus it seems that the observation of reversible heat cannot be explained in the HH model frame.

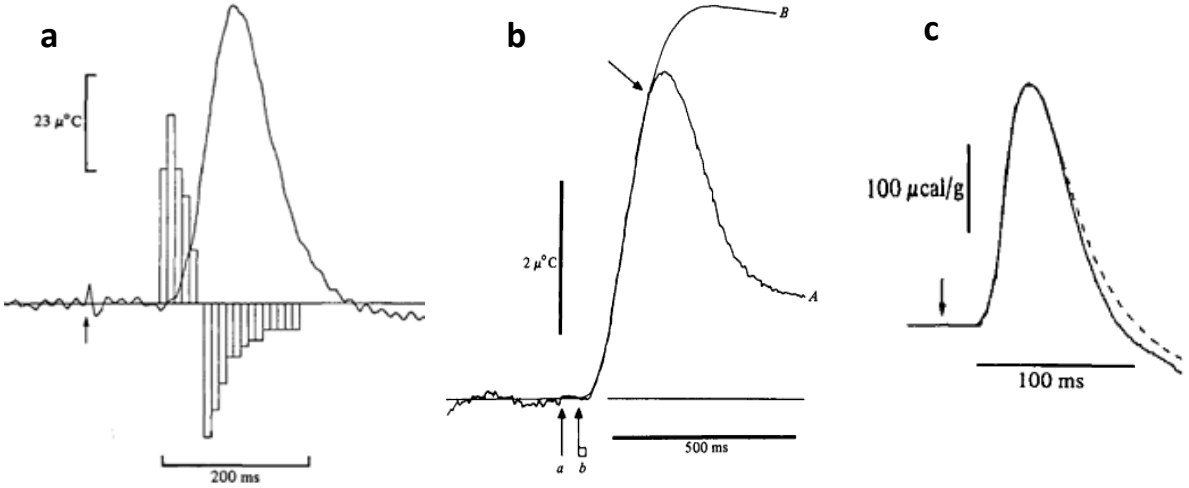

Fig. 12 Reversible heat associated to the AP. (**a**) The solid line corresponds to the temperature changes in non-myelinated pike olfactory nerves at 0°C after a single stimulus applied at the arrow. Heat changes calculated by heat block analysis are superimposed. The two phases in the heat production can be distinguished. (**b**) Line 1 corresponds to the temperature variation in rabbit vagus nerve at 4°C in response to a single stimulus applied at point a. Line 2 shows a slower cooling due to dissipation or passive heat conduction. (**c**) Proportional relation found between the reversible heat (broken line) and the thermal response expected from the capacitor theory (solid line). From ref. [18].

Furthermore, I have also mentioned in section 4.2.1. that some mechanical changes take placed during the AP namely an increase in volume and area and a decrease in thickness. It is believed by some authors (Heimburg and Jackson) that a pure electrical model cannot account for the phenomena accompanying the AP and a thermodynamic theory would better explain all the changes in the thermodynamic variables during the AP. In the third section I briefly introduced the HH model and we saw that Hodgkin and Huxley assumed that the capacitance was not a function of time i.e. they assumed a constant value for the capacitance. However, we know from electromagnetism that the capacitance of a capacitor is given by $C_m = \varepsilon_r \varepsilon_0 \frac{A}{D}$ and hence changes in the area (A) and the thickness (D) of the membrane suggest that $\frac{dC_m}{dt} = 0$ is not a correct assumption.

6.2 EVIDENDE OF PHASE TRANSITION DURING THE ACTION POTENTIAL

There is strong evidence that a lipid phase transition occurs during the propagation of an AP. As mentioned above, some mechanical changes have been measured during the AP (see Fig. 13) that correspond to changes found during the lipid transition (see section 4.2.1). Tasaki and his collaborators have measured mechanical changes and heat changes during the propagation

of nerve pulses ([17] and [20] among others). With the help of a mechanical detector in contact with the membrane, they were able to measure the force developed in response to the electrical stimulus (see ref. [17] and [20]). In fact it was found that both the AP and the mechanical response reached their peak almost simultaneously (see Fig. 13a). This result suggests that the membrane thickness has a peak during the AP. On the other hand, Tasaki et al. also encountered a shortening of the nerve associated to the electrical stimulus (see Fig. 13b) [17]. This result is consistent with a decrease in the area of the membrane during the melting transition.

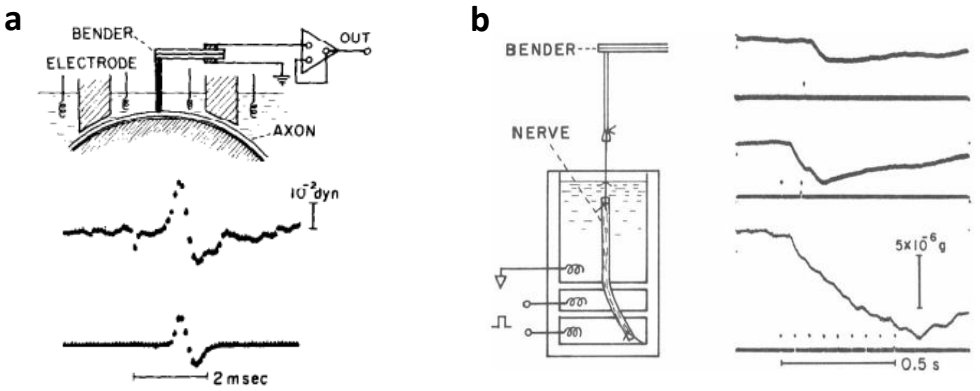

Fig. 13 Mechanical changes associated to the AP (**a**) Setup used to measure changes in the pressure of the axon (up) and the corresponding records: force changes (middle) and the AP (bottom). Adapted from [20]. (**b**) A shortening of the nerve has been associated to the AP. Left: Setup used to measure the force developed along the longitudinal axis. Right: corresponding records. A force downwards indicates a shortening of the nerve. From [17].

On the other hand, the

6.3 SOLITON PROPAGATION

6.3.1 Conditions for soliton propagation

One can wonder how it is possible that we get lipid melting transitions during the propagation of pulses. As it was mentioned in section 4.1, living organism adapt their membranes lipid composition such that the melting point is a few degrees below body temperature. Therefore, the membranes can be easily forced through the transition in various ways namely by cooling, changing the pH or applying pressure. As mentioned in section 4.1, pressure application leads to a shift of the melting point toward higher temperatures. Furthermore, we have concluded in section 6.1 that pulse propagation through the axons is an adiabatic (isentropic) process, precisely as a sound wave is. A similar process would be possible in membranes if there was no energy dissipation into the aqueous environment (or the dissipation was small, at least). On the basis of these two features, Thomas Heimburg and Andrew D. Jackson, from the Niels Bohr Institute (Copenhagen), proposed in 2005 a new soliton neural theory. In the well-know article *"On soliton propagation in biomembranes and nerves"* [4], they suggested that propagated pulses could be "localized density excitations which propagate without distortion" i.e. solitons. Actually, we will see that they are not solitons but rather solitary waves, although they are loosely called solitons in the literature as I will do.

We already know that very particular conditions are required for having soliton propagation namely non-linearity and dispersion. Regarding the first one, the non-linear behaviour of the elastic constants upon density changes was analyzed in section 4.2.2. Upon compression, membranes can be brought through the melting transition where the volume and area compressibilities are maximum i.e. membranes become softer; however, they become rigid again once they reach the gel state. On the other hand, the dispersive property of membranes was also studied. In particular, we saw (see section 4.3) that the velocity of sound is given by $c_0 = (\kappa_S \rho)^{-1/2}$ where κ_S is the adiabatic compressibility, which is frequency dependent (see Fig. 8a). We have checked then that both requirements are fulfilled close to the melting transition. Hence, if a density (pressure) wave were able to force the membrane partially through the melting transition, the conditions for soliton propagation would be met. This density wave described is precisely a soliton. The soliton causes a segment of the membrane to be locally in a gel state (see Fig. 14) [4].

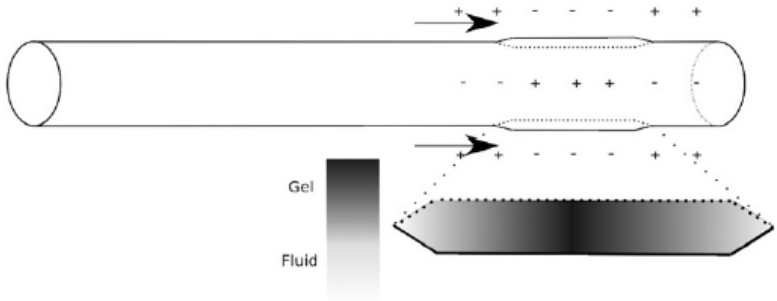

Fig. 14 Soliton propagation. While propagating, the soliton forces the membrane through the transition. From ref. [19]

6.3.2 Analytical description

Heimburg and Jackson [4] considered one-dimensional sound propagation along the longitudinal axis of an axon i.e. along a cylindrical membrane with coordinate x. In the absence of dispersion the area density changes $\Delta\rho^A$ are governed by the following equation

$$\frac{\partial^2}{\partial t^2}\Delta\rho^A = \frac{\partial}{\partial x}\left(\frac{1}{\kappa_S^A \cdot \rho^A}\left(\frac{\partial}{\partial x}\Delta\rho^A\right)\right) \tag{37}$$

where $\Delta\rho^A(x,t)$ is given by $\rho^A - \rho_0^A$.

If $\kappa_S^A \approx$ constant and $\Delta\rho^A \ll \rho_0^A$, this reduces to the equation for sound propagation $\partial^2\Delta\rho^A/\partial t^2 - c_0^2(\partial^2\Delta\rho^A/\partial t^2) = 0$ where $c_0 = \left(\kappa_S^A \cdot \rho_0^A\right)^{-1/2}$ is the sound velocity for small sound amplitude. Nonetheless, we saw in section 4.3 that the lateral sound velocity depends strongly in the density variations (see Fig. 8b), in particular close to the melting transition. For this reason, Heimburg and Jackson expand the velocity in terms of density change

$$c^2 = \frac{1}{\kappa_S^A \cdot \rho^A} = c_0^2 + p\Delta\rho^A + q\,(\Delta\rho^A)^2 + \vartheta((\Delta\rho^A)^3) \tag{38}$$

where p and q are fitted experimentally. As an example, consider the case of DPPC vesicles in Fig. 8b. For the low frequency case ($\omega \to 0$) at 45°C, the following values are found: $c_0 = 176.6\ \mathrm{m/s}$, $\rho_0^A = 4.035 \times 10^{-3}\ \mathrm{g/m^2}$, $p = -16.6 c_0^2/\rho_0^A$ and $q = 79.5 c_0^2/\left(\rho_0^A\right)^2$.

Furthermore a dispersive term must be introduced such that higher frequencies yield higher propagation velocities. Heimburg and Jackson thus propose the following equation for soliton propagation in nerves

$$\frac{\partial^2}{\partial t^2}\Delta\rho^A = \frac{\partial}{\partial x}\left[\left(c_0^2 + p\Delta\rho^A + q\,(\Delta\rho^A)^2\right)\left(\frac{\partial}{\partial x}\Delta\rho^A\right)\right] - h\frac{\partial^4}{\partial x^4}\Delta\rho^A \tag{39}$$

where the last term is the dispersive term and $h > 0$.

It must be mentioned that the exact form of the dispersive term in the millisecond range (time scale of the pulses) is not known yet and the assumption made is ad hoc and was not determined empirically. However, Heimburg and Jackson found that different dispersive terms lead to extremely similar soliton profiles. In any case, for low amplitude solutions with $\Delta\rho^A = \rho_0^A \sin(\omega t - kx)$ the following dispersion relation is found

$$c^2 = \frac{\omega^2}{k^2} = c_0^2 + hk^2 \approx c_0^2 + \frac{h\omega^2}{c_0^2} \tag{40}$$

This relation fulfils the requirement of getting higher velocities for higher frequencies which justifies that Heimburg and Jackson introduced a dispersive term of that form.

For the sake of simplicity I will adopt a similar notation to that employed by Lautrup, Jackson and Heimburg [21]. If we introduce the following dimensionless variables

$$u = \frac{\Delta\rho^A}{\rho_0^A} \qquad z = \frac{c_0}{\sqrt{h}}x \qquad \tau = \frac{c_0^2}{\sqrt{h}}t \tag{41}$$

we can rewrite Eq. (39) as follows

$$\frac{\partial^2 u}{\partial \tau^2} = \frac{\partial}{\partial z}\left(B(u)\frac{\partial u}{\partial z}\right) - \frac{\partial^4 u}{\partial z^4} \tag{42}$$

where $B(u) = 1 + B_1 u + B_2 u^2$ and $B_1 = \frac{p\rho_0^A}{c_0^2}$ and $B_2 = \frac{q\left(\rho_0^A\right)^2}{c_0^2}$. Again, we take as example the values measured for unilamellar DPPC vesicles, $B_1 = -16.6$ and $B_2 = 79.5$.

We are interested in soliton solutions which propagate without change in shape and velocity i.e. $u = u(z - \beta\tau) = u(\xi)$. Therefore it is convenient to rewrite Eq. (42) introducing the new variable ξ:

$$\beta^2\frac{\partial^2 u}{\partial \xi^2} = \frac{\partial}{\partial \xi}\left(B(u)\frac{\partial u}{\partial \xi}\right) - \frac{\partial^4 u}{\partial \xi^4} \tag{43}$$

Since we are looking for soliton solutions it seems logic to ask for localized solutions such that u vanishes at $|\xi| \to \infty$. We then integrate twice the previous equation and we find the following

$$\frac{\partial^2 u}{\partial \xi^2} = (1-\beta^2)u + \frac{B_1}{2}u^2 + \frac{B_2}{3}u^3 \tag{44}$$

We make use of the integrating factor $\partial u/\partial \xi$ and integrate once more to obtain

$$\left(\frac{\partial u}{\partial \xi}\right)^2 = (1-\beta^2)u^2 + \frac{B_1}{3}u^3 + \frac{B_2}{6}u^4 \tag{45}$$

This final equation (with a different notation) was first derived by Heimburg and Jackson [4] although we have followed the derivation made by Lautrup et al. [21].

What we know now about the function u is that it has a zero value at $\xi \to -\infty$ from which it grows until it reaches a maximum at the point ξ_0 satisfying $\partial u/\partial \xi = 0$. Then it decreases until it reaches again zero at $\xi \to \infty$. Furthermore, we can deduce from Eq. (45) that the function u will be symmetric about ξ_0.

On the other hand, in order to know the points at which $\partial u/\partial \xi$ vanishes, we need to find the roots of the right-hand side of Eq. (45). If we reject the trivial solution $u = 0$, we are left with a quadratic equation which has two roots

$$a_\pm = \frac{-\frac{B_1}{3} \pm \sqrt{\frac{B_1^2}{9} - \frac{2}{3}B_2(1-\beta^2)}}{\frac{B_2}{3}} \tag{46}$$

However, in order for the roots to be real, the radicand must be equal or greater than zero. This requirement provide us with a minimum value for the propagation velocity, namely

$$1 > |\beta| > \beta_0 = \sqrt{1 - \frac{B_1^2}{6B_2}} \tag{47}$$

Substituting the value of β_0 in Eq. (46), we can rewrite the roots (points at which $\partial u/\partial \xi$ vanishes) as follows

$$a_\pm = -\frac{B_1}{B_2}\left(1 \pm \sqrt{\frac{\beta^2 - \beta_0^2}{1-\beta_0^2}}\right) \tag{48}$$

It has been shown by Lautrup, Jackson and Heimburg [21] that Eq. (45) has a localized analytic solution for each value of the velocity β

$$u(\xi) = \frac{2a_+a_-}{(a_+ + a_-) + (a_+ - a_-)\cosh\left(\xi\sqrt{1-\beta^2}\right)} \tag{49}$$

It easily shown that solitons propagating at the lowest possible velocity present maximum amplitude:

$$u_{max} = \frac{|B_1|}{B_2} \tag{50}$$

Actually, the higher the propagation velocity the smaller the soliton amplitude (see Fig. 15). Furthermore, the solution diverges in the lower ($\beta \to \beta_0$) and in the higher ($\beta \to 1$) limit.

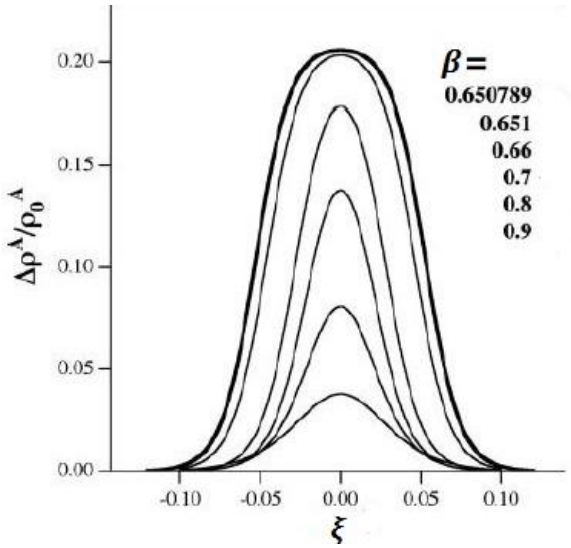

Fig. 15 Soliton profile for unilamellar DPPC vesicles at 45°C. Larger profiles correspond to smaller velocities (up to the maximum amplitude). Adapted from ref. [4].

Continuing with the previous example (DPPC vesicles), the following empirical values were found [4]: $\beta_0 = 0.650$ which corresponds to a velocity $c \approx 115\text{m/s}$ and $u_{max} = 0.209$.

It should be added that the dispersion parameter h does not modify the shape of the solution. However, it alters the length scale of the pulse i.e. its width: it can be shown that the dimensionless variable ξ can be rewritten as $\xi = z - \beta\tau = \frac{c_0}{\sqrt{h}}(x - vt)$ (see Eq. (41)) and hence the parameter h is only present in the hyperbolic cosine of the solution (see Eq. (49)), thereby modifying the width of the soliton. For this reason, Heimburg and Jackson chose the value of h such that the solitons are a few centimetres width as has been measured. They set $h = 2\ \text{m}^4/\text{s}^2$ [4].

6.3.3 Achievements of the theory

The biggest achievement of this theory is to give a successful explanation of several phenomena that did not fit in the HH model. First of all, we can explain the reversible heat in terms of the latent heat associated with the lipid melting: during the first phase, heat is produced in the change from fluid to gel state and the same amount of heat is later absorbed when the transition from gel to fluid takes place.

Furthermore, we have seen that several mechanical variations occur in phase with the AP. These changes get automatically explained if we assume that there is a lipid transition during the AP. Actually, Heimburg and Jackson [4] found that the maximum area change for unilamellar DPPC vesicles (corresponding to maximum amplitude solitons) is 21% which means that the soliton moves the membrane 85% through the lipid transition (see section 4.2.1). If 85% of transition takes place, we get a thickness change of about $+6.4\text{Å}$ and hence a change in

the membrane thickness of $+12.8\text{Å}$. This value is close to that measured by Iwasa and Tasaki, who found a change in the diameter of the axon of about $\approx 10\text{Å}$ in phase with the AP [20].

These changes in area allow us to explain the voltage pulses (the AP itself) [22]. The potential at the membrane surface is given by the Gouy-Chapman theory for planar surfaces in electrolyte solutions. At high ionic strength (low potential limit) we get the following surface potential (see ref. [6]for a complete derivation):

$$\Psi_0 = \frac{\sigma}{\varepsilon\varepsilon_0\kappa} \tag{51}$$

where σ is the surface density charge, ε_0 and ε are the permittivity of vacuum and the dielectric constant for water respectively and κ is the Debye constant. Besides, we know that there are fixed charges in the surface of the membrane (negatively charged lipids) and therefore it seems logic to expect that a change in area during the AP yields a change in the charge density of the membrane, which in turn yields a change in the electrostatic potential. Nevertheless, quantitative calculations get complicated by the fact that the exact composition of membranes changes from one membrane to another and it even changes locally within a membrane. Moreover, around 50% of the membrane weight is constituted by proteins although it is thought that only lipids are subject of area changes. Heimburg and Jackson [22] made a rough estimation: they assumed that the inner leaflet contains 40% charged lipids whereas the outer leaflet does not contain almost any charged lipid. In this situation they determined that the voltage change at the peak of the soliton was about $\Delta\Psi_0 \approx 40\,mV$. Despite the rough calculation, we see that the estimated voltage change is of the same order as that measured during the AP (around $100mV$). Therefore it could be possible that mechanical changes would cause the voltage changes observed during the AP. This coupling between density changes and voltage changes is known as electromechanical coupling and this is the reason why the term electromechanical soliton is sometimes used in the literature.

The soliton theory can also explain why APs have also been triggered by mechanical stimulus or local cooling. According to the soliton theory, it would be possible to force the membrane through the transition by lowering the temperature or applying pressure and therefore giving rise to soliton propagation.

Finally, the propagation velocity predicted by the soliton theory [4] is about 115 m/s which is of the order of that found in myelinated nerves ($100\ \text{m/s}$). The reason why non-myelinated nerves display lower propagation velocities is still an unanswered question.

6.3.4 The stability of solitons in nerves

Some studies have been done in order to check the stability of solitons in the presence of noise and dissipation [21] and the behaviour of solitons upon collisions [22, 23].

Soliton stability upon collisions is a conflictive point since the HH model and the soliton theory predict different behaviours. According to the HH model, we learned that ion-channel proteins

become inactivate after a passing pulse. This leads to the existence of a period of time after the passage of a pulse, called refractory period, during which no pulse can propagate (the membrane is unexcitable). Due to the refractory period, it is not possible that two pulses pass through each other. This argument has been supported by numerical simulations [25].

Nonetheless, soliton-like regimes have also been found in the HH model [23]. Aslanidi and Mornev found out that under particular conditions the reflection of colliding nerve pulses occurs. They performed numerical simulations based in the HH equations and studied the behaviour of solutions for different values of the parameter E_K (Nernst potential or equilibrium potential for the K^+ ions). The value of E_K can be altered by changing the K^+concentration outside the cell (see Eq. (2)). Aslanidi and Mornev determined that for $E_K < -2.5\ \mathrm{mV}$ only the annihilation regime is found and the solutions decay after colliding. However, for $-2.5\ \mathrm{mV} < E_K < -2.46\ \mathrm{mV}$ the soliton-like regime emerges and the two colliding pulses are reflected and move apart in opposite directions [23]. They even found one more complex case, $-2.46\ \mathrm{mV} < E_K < -2.40\ \mathrm{mV}$, for which some low amplitude waves accompanying the main pulse can generate two more pulses moving apart in opposite directions.

On the other hand, simulations have also been run in the case of soliton theory [24]. Appali et al. studied the collision of two solitons travelling with the same velocity and in the absence of friction (because the soliton theory is based on adiabatic, reversible processes). They found that post-collision solitons were almost undisturbed but for a small amplitude noise travelling ahead of them. However, the noise produced roughly represents $\ll$ 1% of the energy. Furthermore, some studies were done in the limit case of maximum amplitude (lowest velocity) solitons. In this case, Appali et al. found that the colliding solitons decayed into a sequence of smaller amplitude solitons travelling with different velocities and some noise (see Fig. 16a). Furthermore, Appali et al. found that the closer to the amplitude limit, the more pronounced this effect is. It should be added, however that, even in the worst case, the smaller amplitude solitons and the low amplitude noise constitute less than 4% of the energy of the system. Hence, most of the energy is conserved by the main solitons (see Fig. 16b).

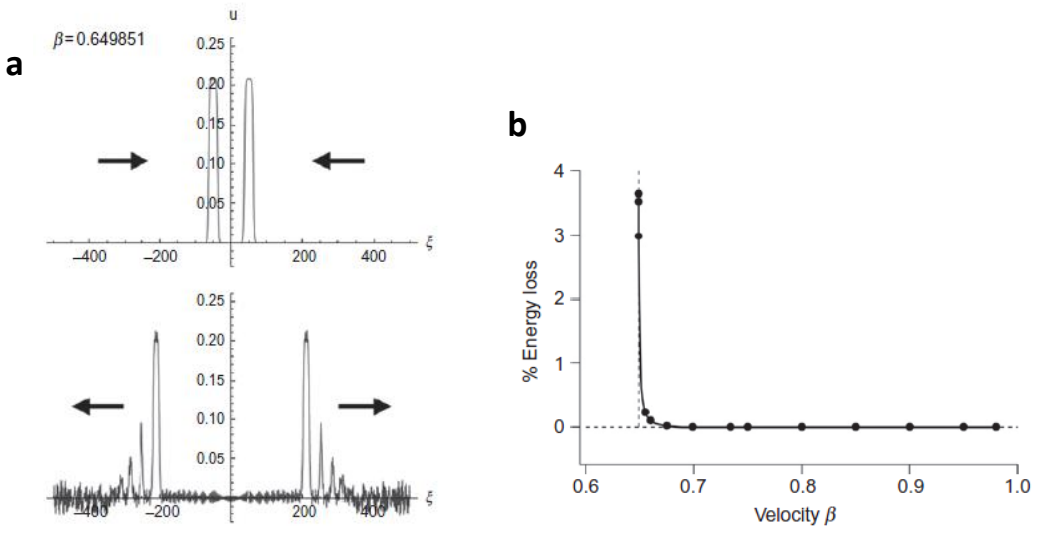

Fig. 16 Stability of solitons upon collision. (**a**) Collision of solitons close to the amplitude limit. The interacting solitons decay in a sequence of smaller amplitude solitons and some low amplitude noise. (**b**) Percentage of energy

loss after the collision. The energy loss only becomes significant in the limit of minimum velocity and maximum amplitude. From ref. [24].

Lautrup et al. [21] also performed some studies on soliton stability in the presence of noise and dissipation. They claimed, and subsequently checked, that the analytical solitons are not identical to solitons on a discrete lattice, which is the source of noise in the system. If solitons were not stable, we would expect an exponential growth of the noise with time in the proximity of the soliton. However, no sign of instability was found and the noise level remained the same far and close to the position of the soliton. Furthermore, Lautrup et al. also analyzed the stability of solitons in the presence of strong dissipation and to this end, they introduced a viscosity term in Eq. (43). They found that solitons accelerate and lose amplitude as the energy is dissipated. However, their profile is roughly consistent with the analytical Eq. (49) during the entire period. Finally, one additional test was performed: they chose localized but non-solitonic initial conditions and checked what happened. In particular they took $\boldsymbol{u}(\boldsymbol{x},\boldsymbol{0})$ according to Eq. (49) but they altered the second condition $\boldsymbol{v}(\boldsymbol{x},\boldsymbol{0})$ and chose the velocity to be half of what corresponded to the initial profile $\boldsymbol{u}(\boldsymbol{x},\boldsymbol{0})$. It turned out that the initial pulse decayed into two solitons of different sizes moving in opposite directions and some low amplitude waves travelling ahead of them. However, these waves represented less than 0.3% of the energy of the system.

From the previous discussion, we can draw some conclusions. These stability tests have been performed in order to evaluate the existence of solitons in non ideal environments where they are subject to friction and dissipation. Logically, membranes are not homogeneous and are more complex than what has been suggested. They display local variations in thickness or/and composition. However, the positive results obtained suggest that *"*a model of nerve pulses as stable solitons is viable even in a realistic physiological environment*"* [21]. Finally, I would like to add that the term soliton is not an accurate way of describing the "solitonic" pulses given by Eq. (49). We have seen that some low amplitude waves are produced upon collision which is not expected from real soliton solutions. For this reason, these "solitonic" solutions would be better called solitary waves. In any case, soliton is term adopted in the literature.

6.4 ANESTHESIA IN THE FRAME OF THE SOLITON THEORY

Anesthesia is a very relevant subject which has no satisfactory explanation in the HH model; however the soliton theory may have an impact in our understanding of anesthetics. This is why I decided to give a glimpse of the reasoning behind it. References [5,21,25] may be consulted for further reading.

In 1846 anesthesia was publicly used during an operation for the first time by William Morton from the Massachusetts General Hospital (Boston) who applied diethyl ether as inhibitor of pain. Since then, many other substances, both liquid and gaseous, have been identified for

their anesthetic properties. It was known that anesthetics affect the cells in very different manners, although the most notable effect is probably the loss of consciousness. This is the reason why so many efforts have been made to understand the role of anesthesia in nerves. Since the accepted model for describing the propagation of pulses along the nerves was the HH model, most of the efforts were focused on describing the action of anesthetics on the ion-channels. It was suggested that anesthetic substances would block the ion channel proteins, thus making infeasible the flow of ions. Nevertheless, even though some anesthetics were found to affect the ion channels, others did not. This result suggested that the ion channel-blocking hypothesis was not right.

Furthermore, it was found that almost every anesthetic follows the Meyer-Overton rule: "the anesthetic potency is exactly proportional to their solubility in membranes" [2]. This means that the concentration of an anesthetic in membranes at which 50% of the organisms lose conscience (critical anesthetic dose) is the same for every substance, no matter its chemical composition. This experimental finding has never been explained and we can only deduce that anesthesia must be somehow based on a lipid process.

On the other hand, it was found that anesthetics have the property of lowering the melting temperature T_m. This is known as melting point depression. Heimburg and Jackson [26] showed that the melting point depression is proportional to the molar fraction of anesthetics in the fluid lipid membrane (this effect is similar to that of salt on the melting temperature of ice). If particular they found that there is a drop in the melting temperature of $\Delta T_m = -0.6K$ at the critical anesthetic dose which again is independent of the anesthetic substance or its chemical nature. This is consistent with the Meyer-Overton rule. Actually, Heimburg and Jackson [22] reformulated it and stated that "the potency of anesthetics is proportional to their ability to lower the melting point of lipid membranes". This feature of anesthesia clearly influences the transmission of the electromechanical solitons. The free energy necessary to force the membrane through the lipid melting transition can be calculated using Eq. (9):

$$\Delta G = \Delta H - T\Delta S \approx \Delta H \cdot \left(\frac{T_m - T}{T_m}\right) \tag{52}$$

Therefore the required free energy is proportional to the difference between the physiological temperature T and the melting temperature T_m [22]. If the melting point is lower by the effect of anesthetics, the energy required for a soliton to force the membrane through the melting transition will be higher. For a sufficient dose of anesthetics, the shift of the melting point will be pronounced enough to inhibit the propagation of solitons.

In section 4.1 we saw that the lipid melting point can be altered by other means such as changes in the pressure or the pH. In particular, it was mentioned that an increase in pressure yields a shift of the melting point toward higher temperatures. According to this, the effect of anesthesia could be counteracted by application of pressure. Andersen et al. [19] calculated that the effect of the critical anesthetics dose in DPPC membranes should be reversed at 25 atmospheres of pressure. Actually, this effect of pressure has been found experimentally by Johnson and Flagler among others [27]. Heimburg and Jackson [26] argued that in principle, changes in any other thermodynamic variable could reverse the effect of anesthesia e.g. reduction of pH.

7. COMPARISON BETWEEN THE HH MODEL AND THE SOLITON THEORY

There exist previous papers which compare both theories such as those by Appali et al. [25,28]. In this section I will try to combine previous papers with other conclusions drawn from the present work. The following are the main differences between both approaches.

- The HH model was developed by A. L. Hodgkin and A. F. Huxley in 1952 [3].
- The soliton theory was proposed by T. Heimburg and A. D. Jackson in 2005 [4].

- The HH model is a model. This implies that it is not based in first principles but it is rather a picture which aims to describe the propagation of pulses along nerves. In the HH model, more than 20 parameters must be fixed empirically.
- The soliton theory is a theory. It is derived from first principles

- The HH model is based on pure electrical concepts: cable theory and Kirchhoff's laws.
- The soliton theory relies on macroscopic thermodynamics. It evolves from measurements of thermodynamic variables.

- The HH model describes the voltage pulse as an electric signal.
- In the soliton theory the voltage pulse is accompanied by several mechanical changes. The AP is described as an adiabatic electromechanical soliton.

- The HH model does not explain other phenomena which take place in phase with the AP, namely reversible heat changes, mechanical variations (increase in thickness and decrease in area)...
- The soliton theory gives account for all the phenomena mentioned above.

- The propagation of pulses in the HH model is due to existence of time- and voltage-dependence ion channels that regulate the membrane's permeability to some ions.
- In the soliton theory, the pulse partially forces the membrane through the lipid transition, at which the membrane displays the features required for the propagation of solitons (nonlinearity and dispersion).

- The HH model is based in non-reversible dissipative processes.
- In the soliton theory, the signal transmitted is a density wave which is adiabatic and isentropic.

- In the HH model, the AP is triggered by a depolarization of the membrane.
- In the soliton theory, the AP can also be triggered by mechanical stimulus or local cooling.

- The HH model accounts for the action of several poisons and neurotoxins that block the ion channels and cause damage to the nervous tissue.
- The soliton theory gives no explanation about the effects of poisons.

- In the HH model, the existence of quantized currents across the membrane is explained based on the opening and closing of ion-channel proteins.
- In the soliton theory, quantized currents have been related to the especial features of the membrane at the transition regime. Actually, quantized currents have been found even in synthetic membranes that do not contain proteins.

- In the HH model, the collision of two pulses in not permitted and the signal is predicted to decay after the collision. Alternatively, soliton-like regimes have been found depending on the parameters.
- In the soliton theory, the stability of solitons upon collision has been proved numerically.

- The HH model gives no explanation for the action of anesthetics. The hypothesis of anesthetics blocking the ion channels have been proofed to be false for some substances that do have anesthetic effects.
- In the soliton theory the effect of anesthetics has been explained: anesthetics cause a melting point depression, and thus inhibit the propagation of solitons.

- The length scale is a source of differences between both theories (see below).

7.1 LENGTH SCALE

I consider it is worth explaining a bit more extensively the difference in length scale between the two theories. As Heimburg explains in his article "*The physics of nerves*" [2], the current trend in biology is to think that "one can understand life if one understands all single molecules". In other words, in order to explain the biological activity of cells, one needs to analyze the functioning of individual molecules. This is the idea supporting the HH model. We have seen that a typical voltage has a duration of several milliseconds and it propagates at around $0.1 - 100$ m/s. This implies that the pulse is from several millimetres to a few centimetres long. Nevertheless, ion-channel proteins measure about 5 nanometres in diameter, which is more than 6 orders of magnitude smaller. This is as explaining a process that happens on the length scale of Europe on the basis of objects of the size of a saucer.

Nevertheless, it is frequent in physics to develop theories employing a similar length scale to that of the system analysed instead of focusing in single molecules. In particular, thermodynamics becomes more useful when considering ensembles rather than individual molecules. Andersen et al. [19] and Heimburg [2] used a very similar example: we can describe the propagation of sound by a very simple equation which only depends on the velocity of propagation. And although this parameter changes from one medium to other, the phenomenon behind the propagation of sound it the same. Furthermore, even if molecules are essential for the propagation of a pressure wave (sound), one does not need to make a microscopic analysis of sound in other to describe its propagation. As said by Andersen et al., "too much microscopic detail can obscure those subtle effects which are often of primary interest" [19]. This idea can be seen as an argument against the HH model.

8. CONCLUSION

This project constitutes an introduction into the very interesting topic of propagation of impulses through nerves. As an introduction, I have assumed that the reader was not familiar with the topic and I have tried to explain all the important points for the reader to understand the soliton theory proposed by Heimburg and Jackson. This is why I have devoted the first sections of the project to introducing neurons, lipid bilayers and lipid melting transitions. We learned that nerves were constituted by neurons, which have a long extension called axon along which the pulse is transmitted away from the soma to other neurons, glands or muscles. We then focused of the propagation of pulses along the axon, in particular, along the membrane of the axon. We also learned that the membrane is formed by a lipid bilayer in which some proteins are embedded. Although these proteins have an important role in the transmission of pulses in the HH model, they are not relevant in the soliton theory. Instead, the propagation of electromechanical solitons in the soliton theory is explained due to the especial features (dispersion and nonlinearity) that the membrane displays during the lipid melting, i.e., the transition from liquid-disordered (liquid) phase to solid-ordered (gel) phase.

Besides, I also devoted another section to introducing the theoretical basis required to describe the soliton theory. Although solitons constitute a vast area of study, I decided to focus on the necessary knowledge. For this reason, I would not say that this is a project about solitons but rather a project about the role of solitons in neuroscience: solitons are not the subject of the project, the propagation of pulses through the nerves is. We saw that solitons arise due to the balance reach between the effects of nonlinearity and dispersion. Moreover, we also analyzed the difference between solitons and solitary waves. This distinction allowed us to conclude that the pulses transmitted along the nerves are solitary waves rather than solitons (although we kept calling them solitons for the sake of consistency with the literature).

Nevertheless, one cannot address the subject of pulse propagation in neurons and not mention the HH model. Not only does it accurately describe the shape and velocity of the AP, but for more than fifty years no one else has been able to give a better description of the propagation of pulses. This is why I thought it would be interesting to compare the previous model with the new soliton theory and gain a general insight. We saw that the HH model explains the transmitted pulse as a pure electrical signal that propagates due to the opening of some ion channel proteins which lead to the charge of the membrane capacitor.

For reasons of length and time it has not been possible to deepen more into the topic and I could not include everything I would have liked to. I chose to cover points that I considered interesting and relevant, such as the analysis of soliton stability and the action of anesthetics, instead of getting into details in other sections. In the soliton theory, we studied how the pulse is described as a density wave which forces the membrane through the melting transition as it propagates. This density wave is precisely an electromechanical soliton. We saw that several phenomena, such as the reversible heat or the mechanical variations, get explained in this framework. Furthermore, it has been suggested that the change in area can account for the voltage pulse observed. On the other hand, the action of anesthetics is satisfactorily explained in the soliton theory: anesthetics shift the melting point towards lower temperatures and

therefore inhibit the propagation of solitons (the energy required for the solitons to propagate is higher). The effect of anesthesia could then be reversed by the application of pressure as some research suggest. Finally, we studied the stability of solitons and concluded that they are stable enough to guarantee their existence in more realistic physiologic environments.

To summarize, the soliton theory seems to give a satisfactory explanation to the problem of pulse propagation. Nevertheless, this does not mean that everything is already explained in the soliton framework. On the contrary, there are still remaining questions which should be addressed in order to provide a satisfactory and complete description of the propagation of AP.

As observed by Andersen et al. [19], in a typical membrane roughly half of the weigh corresponds to proteins. These proteins influence the melting point and, together with lipids, determine the thermodynamic behaviour of the membrane. Nevertheless, proteins do not have a clear role in the soliton theory. Furthermore, as we saw in the section 6.3.3, it is plausible that the voltage pulse arises from the change in area (and the corresponding change in charge density) that occurs during the melting transition. However, this is a very general approximation since the exact composition of membranes is not known and the exact value of the potential pulse cannot be calculated. On the other hand, no explanation has been given to the differences observed between myelinated and non myelinated nerves. The range of velocities predicted by the soliton theory is similar to those of myelinated nerves, but the reason why the propagation velocity in non myelinated nerves is lower is still not clarified. Moreover, despite the HH model not being complete, the flow of ions across the membrane is actually a measured phenomenon. However, at no point is the flow of ions is not incorporated in the HH model. Actually, quantized currents have been measured in synthetic protein-free membranes.

In conclusion, I would like to say that, even if there are still some remaining questions, the soliton theory can account for phenomena that do not fit in the HH model. In this sense, the soliton theory is a more complete one. And, as said by Andersen et al., “it is precisely the ability to explain these ‘unexplained’ observations that will ultimately discriminate between alternative models of nerve signal propagation” [19].

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