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CELL BIOPHYSICS

Models of Nerve Impulse Generation and Conduction

J. L. Hernandez Caceres[a,*], S. S. Dzhimak[b,c], D. A. Semenov[d,e], M. I. Drobotenko[b], and Yu. D. Nechipurenko[f,]**

[a] *Cuban Center for Neurosciences, Havana, Cuba*
[b] *Kuban State University, Krasnodar, 350040 Russia*
[c] *Southern Scientific Center, Russian Academy of Sciences, Rostov-on-Don, 344006 Russia*
[d] *Institute of Biophysics, Siberian Branch, Russian Academy of Sciences, Krasnoyarsk, 660036 Russia*
[e] *Institute of Molecular Medicine and Pathobiochemistry, Voyno-Yasenetsky Krasnoyarsk State Medical University, Krasnoyarsk, 660022 Russia*
[f] *Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, 119991 Russia*
**e-mail: jose.caceres@cneuro.edu.cu*
***e-mail: nech99@mail.ru*

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Abstract—Different models and approaches to studying nerve impulse generation and conduction are discussed. Mechanical, thermodynamic and electrical properties of nerve cells have been addressed in many studies. Although developed 70 years ago, the Hodgkin–Huxley model is still the gold standard in neuroscience. The model theoretically described the electric phenomena known for the action potential at that time and led to the development of novel experimental and theoretical approaches to membrane research in biophysics. A mechanical soliton model was proposed as an alternative explanation of the nerve impulse. According to the mechanical soliton model, the nerve impulse is an undamped mechanical wave associated with a phase transition in the lipid bilayer. Proponents of the mechanical soliton model gave their arguments against some points of the Hodgkin–Huxley model. Most of their statements may find explanation within the Hodgkin–Huxley model, given that changes in membrane potential may lead not only to changes in ion channel permeability, but also to changes in membrane thickness, modifications of protein–lipid interactions, and modulation of cooperativity between ion channels. The appearance of a mechanical soliton might be possible in some cases, but is not the main mechanism of nerve excitability. A universal mathematical model is thus necessary in order to interpret all biophysical changes observed during the nerve impulse. The key to achieving this task is to adapt the Hodgkin–Huxley model. This approach to nerve impulse modelling could lead to new experimental designs and new findings.

Keywords: nerve impulse, Hodgkin–Huxley model, mechanical soliton model, cooperative interactions, phase transition, anesthetics, protein–lipid interactions

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INTRODUCTION

Excitability and nerve impulse conduction are some of the central problems in biophysics. Innovative experimental and theoretical methods and approaches were developed in attempts to solve these problems. In spite of the great progress achieved in the field, there is still no theory that provides a unified explanation to all processes that are experimentally observed to occur upon generation and conduction of a nerve impulse. The Hodgkin–Huxley theory has dominated in the field for the past 70 years and made it possible to describe the majority of electric phenomena accompanying the action potential. The approach proposed by Hodgkin and Huxley led to the development of various methods, such as measurements of gating displacement currents [1], the patch-clamp technique [2], studies of functional activity of nerve tissue [3], optogenetics [4], and bottom-up modeling of cerebral activity [5].

However, there are facts and data that cannot be explained by the Hodgkin–Huxley theory: for example, an adiabatic reversible change in nerve temperature [6, 7], a change in lipid bilayer elasticity with reversible nerve thickening [8], a phase transition in the lipid bilayer [7], and cooperative interactions between ion channels [9].

Findings of this kind elicited a variety of responses in biophysics, from the development of alternative theories, which consider the action potential to be a mechanical soliton [7] and ascribe only a secondary role to ion channels, to the idea to review the molecular mechanisms of ion permeability of the membra-

ne [9]. The development of a functional (universal) model of the nerve impulse depends on the correct understanding of the biophysical processes that accompany the impulse [10]. At the same time, successful construction of such a model will determine success in solving many problems in neuropharmacology and other neurosciences.

Here we discuss the strengths and weaknesses of various theoretical suggestions, outline possible approaches to a universal biophysical model of nerve excitability, and pay attention to Shnoll's ideas considering excitation mechanisms from the viewpoint of biological evolution.

HISTORICAL BACKGROUND

Many scientists have put forward their hypotheses on the mechanisms of nerve excitation. In Russia, Lomonosov believed that propagation of a nerve impulse is a wave-like sequence of coupled cyclic mechanic processes and noted that this occurs within an imperceptible period of time to unite particles in an uninterrupted manner throughout a nerve from its end to the brain [11].

As experimental data became available, more and more details were added to the views of impulse conduction. For example, Galvani's experiments suggested the electric nature for nerve and muscle excitation in the late 18th century [12]. Du Bois-Reymond [13] and Helmholtz [14] reported many experimental findings in the mid-19th century, warranting the development of models that could explain the totality of the available data from a unified standpoint. Models of the second half of the 19th century played a significant role, allowing researchers to develop views of the nerve impulse on the basis of well-known physical mechanisms.

Ostwald [15] was the first to hypothesize in 1890 that cell membranes play a role in generating bioelectric phenomena. Experiments with precipitated membranes allowed Ostwald to say that "It is perhaps not too bold to suggest that not only the currents in muscles and nerves, but also the puzzling actions of electric fishes can also be explained by the properties of semipermeable membranes" [15]. Bernstein [16], a student of du Bois-Reymond, further developed Ostwald's ideas.

Limitations and advantages of various models were the matter of intense discussion at the turn of the 20th century, and this discussion gave origin to a theoretical proposal that became the first truly quantitative model of nerve excitation. Bernstein believed that the resting membrane potential results from the thermodynamic equilibrium of potassium ions located on both sides of a semipermeable membrane. The action potential was thought to result from changes that arise in membrane permeability on excitation. Thus, three key ideas were combined in Bernstein's model:

(1) the membrane is a place where excitation processes occur,

(2) a thermodynamic approach is necessary for understanding bioelectric phenomena, and

(3) changes in membrane permeability to different ions underlie the total diversity of the phenomena accompanying nerve and muscle excitation.

In parallel, two other models were put forward in the early 20th century to explain nerve impulse conduction. Wilke and Atzler [17] considered mechanical excitation of a gelatin cylinder, where mechanical and electric waves arose simultaneously. Lillie [18] proposed a model that consisted of an iron wire immersed in a nitric acid solution and showed propagation of an excitation wave along the wire.

Wilke and Atzler [17] studied nerve excitation upon mechanical stimulation and concluded as early as 1913 that a nerve impulse cannot be a purely electrical phenomenon. Its piezoelectric nature was assumed, and mechanical changes were demonstrated in a simple experiment; i.e., a thin glass fiber attached to a nerve end started fluctuating upon stimulation of the nerve.

On the other hand, Bernstein's ideas were further developed in experimental and theoretical studies of the Cambridge school and especially works by Hodgkin, Huxley, and Katz. In 1952, Hodgkin and Huxley [19] reported their well-known system of equations.

In 1956, Del Castillo and Katz [20] predicted quantal release of neurotransmitters for synaptic transmission, proceeding from the results of electrophysiological experiments with intracellular recording of membrane potentials. Electron microscopy confirmed the hypothesis a few years later [21].

The Hodgkin–Huxley equations were based on vast experimental data, which were obtained by the then-new technique of voltage clamp. The intention was to construct an empirical model that would fit the experimental data and, at the same time, would quantitatively describe generation of the action potential and its propagation along an axon.

Although a conceptual model was beyond their claims, Hodgkin and Huxley made every effort to ensure that the mathematical equations in their model are physically plausible (for example, activation of ion conduction is described by first-order chemical reactions, etc.). Mathematical equations had to quantitatively describe the vast body of experimental data and to predict the system behavior in response to changes in various parameters.

Hodgkin and Huxley did not proceed from a particular physical model, but insisted that their experimental data and the respective system of equations agree with certain basic ideas. Following the Hodgkin–Huxley system of equations, it is possible to imagine a physical model where activating and inactivating particles are postulated to exist. Their existence

was confirmed 20 years later, when gating currents were detected experimentally [22].

The model described virtually all electrophysiological phenomena known for the squid axon at that time; simple adaptations made it possible to apply the equations to other excitation systems. The Hodgkin–Huxley approach was used to describe synaptic transmission and to study gating displacement currents.

ALTERNATIVES TO THE HODGKIN–HUXLEY APPROACH

Although the Hodgkin–Huxley model was met with success and the authors were awarded the Nobel Prize in physiology or medicine in 1963, some researchers questioned it in the 1950s–1970s. Two outstanding biophysicists, D.N. Nasonov (1895–1957) and I. Tasaki (1910–2009), were among these.

Nasonov [23] introduced the concept of parabiosis as a state in which the cell protoplasm greatly changes its physical properties as a result of reversible adsorption of potassium ions on protoplasmic proteins. Nasonov's student Troshin [24] and the American biophysicist Ling [25] further developed Nasonov's ideas.

Nasonov's school essentially rejected the role of the cell membrane in excitation processes (protoplasmic proteins were thought to play a crucial role in this phase transition) [26]. However, the main postulates of Nasonov's school disagree with the experimental findings that functional action potentials and ion currents are detectable in perfused giant axons and isolated nerve cell bodies (where the protoplasm is fully replaced with a protein-free ion solution) [27].

Tasaki is one of the most prominent scientists in neurophysiology. The discovery of the role that myelin plays in nerve impulse conduction is associated with him. Tasaki broadly employed the voltage clamp technique in his research, and his experimental data were not questioned even by those who disagreed with his ideas.

Following Tasaki's ideas, a nerve impulse arises as a result of a phase transition, which appears in the membrane and propagates along the axon [28]. Tasaki thought that the excitable membrane is a macromolecular complex of proteins and lipids. Each subunit of the complex is capable of ion exchange and occurs in one of the two stable conformational states, a resting state or an active state.

MECHANICAL SOLITON THEORY

The so-called mechanical soliton theory was developed on the basis of Tasaki's ideas. The theory suggests that propagation of the action potential is accompanied by a stable soliton of mechanical deformation in the cell membrane; the soliton propagates with a constant velocity and has a nondecreasing amplitude [29].

It is thought that the mechanical wave accompanying the action potential is associated with main excitation mechanisms. In particular, mechanical changes in the lipid bilayer are presumably necessary for the opening of ion channels involved in generating the electric phenomena of nerve excitation. An argument in favor of this assumption is that membrane deformation and reversible axon heating occur during activation of ion channels. The nerve impulse was described as a non-classic soliton (a compacton) in the mechanical soliton model [30].

To provide a theoretical explanation for the observation that the impulse velocity depends on the axon radius, Rvachev [31] developed a model where the nerve impulse is considered as a pressure impulse that spreads through the axoplasm. As discussed above, experiments with perfused axons showed that the axoplasm is not essential for nerve impulse conduction.

Below we consider the main arguments that were advanced by proponents of the mechanical soliton theory and pointed to certain drawbacks of the Hodgkin–Huxley model (see [32]).

(1) Only voltage-dependent aspects of the nerve impulse are described by the Hodgkin–Huxley model. In other words, the Hodgkin–Huxley model is limited to the electric phenomena associated with excitation.

(2) An important feature of the Hodgkin–Huxley model is that the model is based on dissipative processes and is therefore irreversible.

(3) It is still impossible to determine how the conductivity of channel proteins depends on time and voltage and to deal with the problem, this dependence is parametrized. Based on this, proponents of the mechanical soliton theory state that the Hodgkin–Huxley model is not a theory in a strict physical sense of the word. The model does not predict system behavior, but rather describes the measured results in an a posteriori manner.

(4) Changes in other physical parameters, such as heat or work to enlarge or extend the nerve fiber, are disregarded in the Hodgkin–Huxley model. However, thorough measurements have shown that other thermodynamic parameters change as well as the membrane potential during excitation.

(5) Generation of the action potential is possible in a sodium-free medium.

(6) Reversible heat production is a special problem of the Hodgkin–Huxley model. Hill and colleagues [6] were the first to reliably measure heat production in nerves. They showed that heat is released in the early phase of a nerve impulse and is reabsorbed to a substantial extent in the second phase, so that the total heat production is zero within measurement accuracy. In other words, the nerve impulse can be considered as an adiabatic reversible process. This idea disagrees

with the Hodgkin–Huxley model, which is dissipative in nature.

(7) Discrete ion channels form in a bilayer membrane devoid of protein components. Currents detectable in this case are similar to the currents that are usually ascribed to protein ion channels. In particular, these discrete currents are observed in phase transitions. It should be expected that the lipid membrane becomes permeable to ions upon impulse propagation. An agent that suppresses impulse generation in the soliton model will probably inhibit the discrete currents because the two phenomena are inevitably related thermodynamically.

(8) A melting-like phase transition in the biomembrane is an important prerequisite to the generation of localized impulses, but this fact is disregarded in the Hodgkin–Huxley model. The phase transition is responsible not only for reversible heating, but also for impulse localization.

(9) Many substances are known to cause anesthesia, including nitrous oxide, halothane, chloroform, many alcohols, and the noble gas xenon. All of these anesthetics obey the Meyer–Overton rule [33], which states that activity of an anesthetic is directly proportional to its solubility in lipid membranes. This is observed in a broad solubility range, from nitrous oxide to long-chain alcohols. In spite of the differences in chemical nature, the same membrane concentration of an active substance is always found at the effective dose ED_{50} (at which 50% of patients become unconscious). This correlation is difficult to explain in terms of the Hodgkin–Huxley model.

(10) Mutual penetration is known for action potentials moving towards each other. A feature of mechanical solitons is that two colliding impulses pass through each other without dissipation [29], rather than annihilating, while annihilation is expected for Hodgkin–Huxley impulses because of the presence of a refractory period. Penetration of colliding nerve impulses was experimentally demonstrated with earthworm nerves in recent years [34].

Criticism of the ideas of mechanical soliton proponents. Below we describe our views on certain ideas advanced by proponents of the mechanical soliton model.

—The Hodgkin–Huxley model describes only the voltage-dependent aspects of the nerve impulse. Currents and voltages were the only parameters that were technically possible to thoroughly measure over time and space in the mid-20th century. Interestingly, other parameters, such as the membrane thickness, temperature, and aggregation phase, can now be assumed to change as a result of changes in voltage. In this context, viewing other processes as voltage dependent seems reasonable, even though not all of the processes that accompany the nerve impulse were considered in the Hodgkin–Huxley model.

—The Hodgkin–Huxley model is based on dissipative processes and is therefore irreversible in its nature. This is not surprising because life itself is far from a steady-state process. Hodgkin [35] estimated that an axon is capable of generating up to one million action potentials without needing gradient equilibration. Dissipative processes do occur in the brain, as is evident from the fact that the function of sodium pumps accounts for at least 50% of the brain's energy consumption. In other words, nerve impulse conduction can be dissipative because ion gradients are restored by various active transport systems, whose work is ensured by continuous syntheses of ATP and other energy sources in the body.

—It is still poorly understood how the permeability of channel proteins depends on the voltage and time. Current knowledge was achieved mostly with electrophysiological methods (displacement currents and patch-clamp), genetic mapping, and molecular biology. The majority of these methods were inspired by the ideas and problems stemming from the Hodgkin–Huxley model [36].

—As mentioned above, the Hodgkin–Huxley model is not a theory in the strict sense of the word. The authors of the model were self-critical enough. For example, Huxley stated, "Hodgkin and I, consider that these equations must be regarded as a first approximation which in many respects requires further clarification and development during the search for the actual mechanism of the changes in ionic permeability at the molecular level" [37].

Deshcherevskii, who was Shnoll's student, noted in this regard that modeling processes in biology substantially differs from creating a theory of a physical phenomenon. There are only few elementary models in physics, such as material point, rigid body, statistical assembly, electromagnetic field, quantum system, etc. Their behaviors are governed by natural laws, which were formulated once and forever and are not subject to any appeal.

The situation is different when modeling biological processes. Direct application of the elementary models of theoretical physics in the field of biology is generally a losing battle. It is therefore necessary to create a set of true "biological elementary models." An example of such models is provided by the Hodgkin–Huxley equations, which describe the origin and propagation of the nerve impulse. If main vital processes were modeled similarly, it would be possible to speak about a "dynamic model of the cell" (Zhabotinsky's term), tissue, or whole body [38].

Hodgkin and Huxley [19] wrote in their original article that they did not intend to develop a biophysical model. At the same time, they noted, "At present the thickness and composition of the excitable membrane are unknown. Our experiments are therefore unlikely to give any certain information about the nature of the molecular events underlying changes in permeability.

The object of this section is to show that certain types of theory are excluded by our experiments and that others are consistent with them."

Following from Kandel [39], we think that potential of a model to pose new questions and to plan new experiments is more important than its description of a phenomenon. From this viewpoint, the Hodgkin–Huxley model has already posed new questions for 70 years.

—Changes in a number of parameters, such as heat or nerve thickness and length, are not considered in the Hodgkin–Huxley model. These parameters change together with changes in membrane voltage. However, it cannot be excluded that their changes are caused by changes in membrane potential. Given the known membrane thickness (approximately 5 nm), specific capacitance (approximately 1 $\mu F/cm^2$), and a change in membrane potential by 0.1 V, a giant electric field (approximately 10^9 V/m) can be expected to arise in the membrane and induce substantial membrane changes. Based on elementary considerations (Young's modulus, etc.), this pressure is capable of inducing mechanical changes in lipid bilayer dimensions. Estimates indicate that a pressure close to 1.8×10^4 Pa (15 times greater than that created by a metal pressing machine) is applied to the bilayer when the membrane potential changes by 0.07 V (as in axon depolarization). With a typical Young's modulus of real biological membranes (10–100 kPa), the expected relative change in membrane thickness is 10–50%. The expectation is comparable with experimental observations [40]. On the other hand, it was shown theoretically as early as 1974 that adiabatic heating may be caused by membrane depolarization, and this heating can explain the experimental observations of phase transitions and adiabatic processes [41]. In other words, changes in membrane potential that occur during the nerve impulse and are measurable experimentally are sufficient for describing the changes observed in membrane geometry. Phase transitions can also occur in various materials (e.g., carbon nanotubes [42]) on exposure to the above pressure.

—The formation of action potentials in a sodium-free medium was studied in detail, and ion selectivity of sodium channels was characterized as a result (Kostyuk et al. [43] also worked in the field). However, the findings do not necessarily indicate that the Hodgkin–Huxley model is wrong [43].

—The possibility to detect the ion currents that pass through single channels is something that lead on from the Hodgkin–Huxley approach. Discussion between Tasaki and proponents of the Hodgkin–Huxley model prompted a search for an experimental evidence to demonstrate that discrete channels exist in the membrane. One of the earliest studies to provide such evidence focused on the effect that ionizing radiation exerts on the axon capability of generating action potentials. The results showed that the target theory is suitable for modeling the effect. Theoretical estimates of the target size were comparable with typical dimensions of membrane proteins. For example, Fox and Stámpfli [44] showed that ultraviolet radiation (wavelength 280 nm) irreversibly blocks sodium channels and that inhibition of the sodium current I_{Na} exponentially depends on the radiation dose. In the context of the target theory, a singlefold exponential relationship in the dose–effect curve means that the radiation effect is associated with a single event, which is limited to a discrete target region. The volume of the target region is estimated to be 200 $Å^3$. This estimate was theoretically obtained more than 50 years ago and is comparable with current estimates of the dimensions of sensory subunits in a sodium channel. As for the formation of conductive pores in bilayer membranes, the phenomenon has been known for a long time. Pore formation is usually explained by structural modification of the lipid bilayer (regions with non-bilayer packaging of molecules arise). Channels form at the boundary between bilayer and monolayer regions. These pores were even assumed to be a physical substrate of the leak current in the Hodgkin–Huxley model. We consider it unlikely that the pores provide a physical substrate to the total diversity of finely regulated electrophysiological events that take place upon nerve impulse generation and conduction.

—The finding that colliding action potentials pass through each other is considered to support the mechanical soliton theory and to argue against the Hodgkin–Huxley model [34]. However, the finding, which was made in experiments with earthworm nerves, was not confirmed in experiments by other researchers [45].

—An intricate axonal transport system developed in neurons during evolution to ensure the transfer of ion channels and ion pumps throughout the axon. Potential-dependent ion channels play almost no role in mechanical solitons, and it seems justified to doubt the idea that their conduction is the main biological function of the axon.

To summarize, we think that the mechanical and heat-related changes observed to accompany the action potential are most likely a result of the electrical phenomena described by the Hodgkin–Huxley model, rather than the primary cause of nerve and muscle excitation.

The conclusion does not mean that one should neglect the mechanical changes and phase transitions that take place in the lipid bilayer. These phenomena should be considered from a viewpoint that is more general than the mechanical soliton theory. Because the processes accompanying the nerve impulse are nonlinear in nature, it cannot be excluded that a mechanical soliton may also arise during propagation of excitation.

The possibility of solitons arising in biological structures was discussed over many years [46–48].

In particular, Davydov showed theoretically that mechanical solitons are capable of propagating along a protein α helix with a velocity of approximately 30 m/s [49] (note that ion channels assume the α-helical conformation at their sites of contact with the lipid bilayer). Changes that arise in membrane thickness in the vicinity of an ion channel as a result of rapid membrane depolarization may affect the state of α helices in the channel and, therefore, the soliton conduction along the channel α helices. This may provide a key mechanism to mediate protein–lipid interactions during nerve impulse conduction.

On the other hand, Cosic, who proposed a model of resonance interactions (recognition) of proteins, thinks that soliton propagation plays an important role in resonant recognition [50].

We think that the effects of anesthetics and anticonvulsants on the lipid bilayer indicate that protein–lipid interactions play a role in nerve impulse conduction. Little is currently known as to how substances incorporated in the lipid bilayer act to block conduction of the action potential in some cases [51, 52] or to cause paroxysmal depolarization in other cases [53]. Several hypotheses are possible, including the mechanical soliton theory.

Various bilayer-modifying agents (e.g., alcohols and acetone) can change affinity of Na,K-ATPase for sodium and potassium [54]. Similar effects can be expected for ion-selective channels.

COOPERATIVE EFFECTS IN GENERATION OF THE ACTION POTENTIAL

The concerted work of several subunits is necessary for the function of an ion channel. Lipids must play a key role in the interactions between subunits. Moreover, cooperative coordination of many channels is thought to occur during the development of the action potential. These cooperative interactions may arise via a positive feedback scenario. Changes in membrane potential causes mechanical and phase alterations in the lipid bilayer, and the alterations may facilitate the coordination of subunits within a channel and, on the other hand, the cooperative interactions between different channels. The particular details of these mechanisms are still unknown.

The Hodgkin–Huxley model suggests that both activating and inactivating particles act independently of each other. Moreover, channels also function independently during nerve impulse conduction according to the model. Cooperative interactions between activated subunits in channels are therefore not considered in the Hodgkin–Huxley model.

In principle, cooperative phenomena may occur at various levels:

(1) upon ion binding within the channel [55],

(2) in the form of cooperative interactions between subunits upon their activation [56–59], and

(3) in the form of cooperative interactions between channels [9].

A sharply rising initial phase was observed in action potentials recorded from mammalian cortical neurons [60]. This sharp rise cannot be explained in terms of the Hodgkin–Huxley model [61]. Cooperative interactions between channels were hypothesized in order to explain this discrepancy. The hypothesis suggests that the opening of one channel makes the opening of neighbor channels more likely. The resulting modification of the model better describes the experimental observations and suggests a higher coding potential for cortical neurons. In other words, cooperative interactions between individual sodium channels might be acquired during evolution of mammalian neurons to ensure fast processing of abrupt environmental changes [9].

MATHEMATICAL MODEL

In the Hodgkin–Huxley approach, the behaviors of electric parameters are described as follows:

$$C_{\mathrm{m}} \frac{dV_{\mathrm{m}}}{dt} + I_{\mathrm{ion}} = I_{\mathrm{ext}}, \qquad (1)$$

where I_{ext} is the external current, C_{m} is the capacitance of the lipid bilayer of the cell membrane, V_{m} is the membrane potential, and I_{ion} is the total ion current.

The total ion current I_{ion} consists of the contributions from all channel types:

$$I_{\mathrm{ion}} = \sum_k I_k = \sum_k G_k(V_{\mathrm{m}} - E_k), \qquad (2)$$

where G_k is the conductance of the kth channel, I_k is the current generated by a particular ion type, and E_k is the equilibrium potential of the kth ion channel.

Equations of the Hodgkin–Huxley model describe the dynamic relationships between the individual conductances G_k and the membrane potential. The complete system of equations of the Hodgkin–Huxley model was described in the original article [19].

A system of equations of the mechanical soliton model is based on the Euler equation for lateral membrane density:

$$\frac{\partial^2}{\partial \tau^2} \Delta\rho^A = \frac{\partial}{\partial z}\left(c^2 \frac{\partial}{\partial z} \Delta\rho^A \right), \qquad (3)$$

where $\Delta\rho^A$ is the change in lateral membrane density: $\Delta\rho^A = \rho^A - \rho_0^A$, ρ^A is the lateral membrane density, c is the sound velocity, and ρ_0^A is the steady-state lateral membrane density in the liquid phase.

It is assumed in the soliton theory that the sound velocity is not constant in the vicinity of the phase transition point and can be expanded in a Taylor series:

$$c^2 = c_0^2 + p\Delta\rho^A + q(\Delta\rho^A)^2 + \ldots.$$

Based on the experimental frequency dependence of the sound velocity in two-dimensional artificial membranes, a new term, $-h\frac{\partial^4}{\partial z^4}\Delta\rho^A$ ($h > 0$), was added to describe the dispersion processes [29]. This yields the following nonlinear equation:

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

where c_0 is the low-amplitude sound velocity and h is the dispersion constant.

As is seen from Eq. (4), the basic equation of the soliton model allows for both changes in lateral membrane density and the nonlinear relationships that are established between sound velocity and membrane density because phase transitions arise in the membrane as a result of its mechanical deformations.

It is beyond doubt now that both electrical and mechanical processes take place during the action potential. Heat-related changes may lead to phase transitions. The question as to whether a phase transition in the membrane bilayer is essential for conduction of nerve excitation is still open. A phase transition is essential according to the mechanical soliton theory. The fact that nerve impulses are generated in the temperature range of 0–40°C in certain cold-blooded animals is rather surprising in the context of the soliton theory.

According to the mechanical soliton theory, mechanical deformation of the membrane is a cause of electric and heat-related phenomena. We think that both mechanical and heat-related changes result primarily from changes in membrane potential. In turn, the mechanical and heat-related changes may affect the membrane conductivity, capacitance, and, eventually, the membrane potential.

Further development of universal mathematical models of the nerve impulse depends on what part of the hypotheses is true.

Attempts were made to find a common scenario that combines both approaches. For example, a coupled model was advanced to explain both electric and mechanical phenomena that accompany the action potential, assuming that the action potential is associated with mechanical deformation of the membrane and changes in axoplasm pressure [10].

Numerous experiments demonstrated that nerve impulses can propagate in a perfused axon, where the axoplasm is completely replaced with an aqueous electrolyte solution [62]. It is difficult to expect in these conditions that longitudinal pressure impulses in the axoplasm play an important role in nerve impulse conduction.

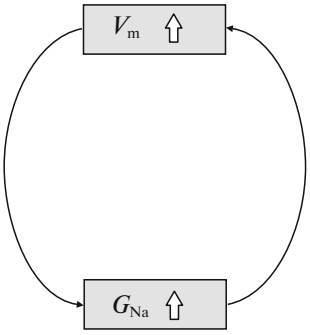

Fig. 1. Schematic relationship between voltage and conductance in the membrane. G_{Na} is the sodium conductance; V_m is the membrane potential.

We think that a mathematical model should be based on the Hodgkin–Huxley equations and allow for both electric and mechanical changes, that is, not only for ion conductances, but also for membrane thickness, heat production, and other voltage-dependent parameters. In turn, these changes affect other physical parameters and directly or indirectly influence the membrane conductance with respect to various ions.

It should be noted here that the conformational changes that arise in proteins (e.g., when channels open or close) exert a reverse effect on the membrane properties. In other words, proteins may affect lipids and lipids may affect proteins during nerve impulse generation and conduction.

To illustrate, Fig. 1 shows the changes that take place in the early rising phase of the action potential according to the classic Hodgkin–Huxley model.

As is seen from Fig. 1, membrane depolarization increases the sodium conductance in this model, and, in turn, the change induces membrane depolarization.

Hodgkin and Huxley proceeded from this hypothesis and further developed the idea to derive their system of equations.

For comparison, Fig. 2 shows the changes that may arise in the membrane as a result of its depolarization and outlines the relationships between the changes.

We think that many of these relationships can be described in a model. Modeling the changes in capacitance during the action potential will be a good start.

Based on the above computations and published experimental data, Eq. (1) is possible to convert as follows:

$$C_m\frac{dV_m}{dt} = \frac{(I_{ext} - I_{ion})}{1 + \alpha(V_m - V_0)^2}. \quad (5)$$

The denominator of the right part of Eq. (5) corresponds to the empirical dependence of the membrane capacitance on the membrane potential. It was proposed recently that changes in membrane capacitance

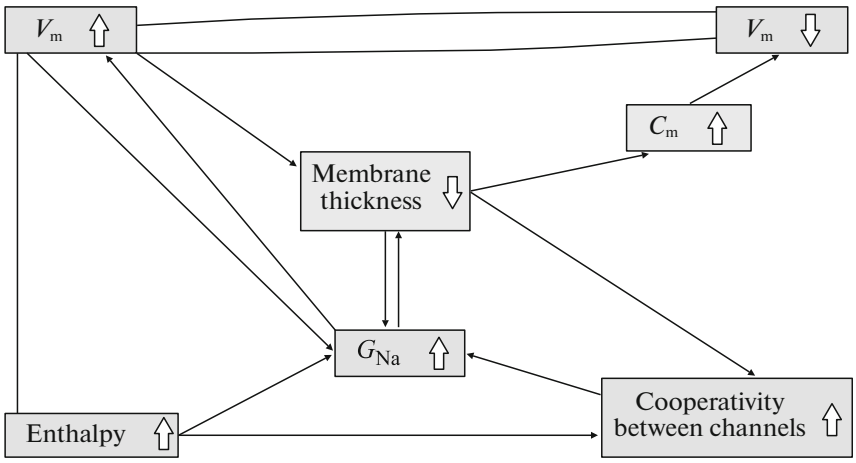

Fig. 2. System of relationships between nerve impulse parameters. C_m is the capacitance of the lipid bilayer of the cell membrane, V_m is the membrane potential, and G_{Na} is the sodium conductance.

during the nerve impulse be modeled from the viewpoint of the mechanical soliton model [63].

The Hodgkin–Huxley equations can yield a great diversity of solutions, and many of the solutions correspond to unexpected experimental results, such as a chaotic series of action potentials or unusually long action potentials. We expect that these additions to the model will lead to the discovery of new phenomena that have not yet been observed in real axons.

MULTIPLICITY OF MECHANISMS RESPONSIBLE FOR NERVE IMPULSE CONDUCTION IS A POSSIBLE EVOLUTIONARY ATAVISM

As mentioned above, in certain cases experimental data on nerve impulse conduction substantially deviate from predictions based on the Hodgkin–Huxley model. These discrepancies may be attributed to the evolutionary nature of the origin of nerve impulse conduction. It is possible to assume that it took some time for ion channels to arise and that primary excitability of a nerve cell prototype was possible long before neurotransmitters and synapses developed.

Shnoll [64] observed that warm bloodedness must be associated with optimal conditions for nerve impulse conduction. What are the features of the range 35–40°C, which warm-blooded animals utilize? One of the versions suggests that specific heat capacity of water is minimal in the range. More accurately, the minimal heat capacity is observed at 34.5°C [65]. Changes in heat capacity within certain limits can be neglected near the minimum. In a first approximation, warm bloodedness is maintained in the given temperature range because a constant temperature is easier to maintain within this range. In other words, minimal changes in energy costs are required to maintain temperature in this range.

Experimental findings demonstrate that the mammalian brain is highly sensitive to cooling and nearly fails to conduct nerve impulses when cooled to 26°C [66]. However, nerve impulses as a phenomenon are evolutionarily older than warm bloodedness. Successful conduction of nerve impulses is characteristic not only of reptiles, worms, and insects, but also of polar fish with a body temperature lower than 0°C. Why are nerve impulses more efficiently conducted in warm-blooded animals?

A possible answer is that the origin of the nerve impulse is initially associated with phenomena that locally change the "temperature" in the vicinity of the membrane; that is, they change the mobility of molecules and ions.

To understand the initial significance of this mobility, consider the book "Svyazannaya voda. Fakty i gipotezy" (Bound Water: Facts and Hypotheses) by Gabuda [67]. Starting from the phenomenon of anesthesia due to dissolved gases, including inert gases, Gabuda proceeds to the idea that a stratification phase transition with an upper critical point is characteristic of biogenic amines. That is, an amine solution will be converted to an emulsion when heated, which is at variance with intuition. A feature of system behavior in the vicinity of a critical point is that diffusion may stop in these conditions, and the correlation radius of a molecular system extends spontaneously. This may create surprising opportunities for controlling nervous signal transmission in synapses. There is an even greater opportunity, that is, the opportunity to explain the origin of early neurotransmitters in early synapses. The problem of what arose first, a neurotransmitter or its receptor, resolves if a neurotransmitter is capable of working without a receptor. A phase transition might act as a primary regulator, while receptors arose more recently to render far lower transmitter concentrations sufficient. A more stable regulation was achieved with receptors. We can say that receptors tamed phase tran-

sitions, but phase transitions still provide a physicochemical basis to the process.

Similar reasoning can be applied to nerve impulse conduction. Protein ion channels are what the Hodgkin–Huxley equations were obtained for, and proteins occur now in their evolutionarily perfect forms according to Shnoll. Did ion channels have precursors? Certain fatty acids are known to create pores permeable to particular ions when integrated in the mitochondrial membrane [68]. The process is based on a phase transition occurring in the lipid membrane. On the other hand, the specific integral membrane protein thermogenin is utilized by the same fatty acids to induce a proton flow across the mitochondrial membrane in brown adipose tissue [67]. Mitochondrial uncoupling is a component of non-shivering thermogenesis; i.e., proton leakage helps the body to warm [68, 69]. Heat production should also accompany the ion flows associated with nerve impulse conduction. Heat elimination is known to be an important problem at the whole-brain level. Moreover, there is an original hypothesis that brain hypertrophy in whales is due to the need to warm the nervous system [70]. Local heating is potentially capable of provoking a stratification phase transition in amine solutions; i.e., the prototype of nerve impulse conduction might be coupled with the prototype of synaptic transmission.

Pore formation in the lipid bilayer can potentially occur as a propagating wave. As Zakhvataev and Khlebopros [71] showed, a wave that propagates directly in the cell lipid membrane may modulate the formation of such pores.

This physical mechanism might be a precursor of the nerve impulse conduction mechanism. Evolution might ride this wave when creating potential-dependent ion channels. This new system might render the process more efficient and reliable. In this case, channels act like repeaters in a communication network or booster stations in an oil pipeline to prevent the flow from weakening. The ancient processes might principally be incapable of ensuring nerve impulse propagation through long axons. In modern nerve impulse transmission, substantial changes might arise not only in the distance over which a nerve impulse is transmitted stably, but also in the mechanism of transmission. It is possible that the contribution of the previous evolutionary mechanism is disregarded in the Hodgkin–Huxley model.

This mechanism might arise as a potential evolutionary precursor based on the phase transitions in the lipid membrane, therefore the mechanism must be sensitive to the temperature and membrane composition. A constant temperature might be necessary for minimizing the contribution of the archaic mechanism to the modern neural conduction process. The temperature range was chosen so that the solvent properties remain virtually the same when the temperature changes. The remaining dependence of the phase transition on the membrane composition underlies anesthesia induced by certain fat-soluble agents, suggesting significance for the outdated, but not completely abolished mechanism. It seems possible to make the evolutionarily ancient mechanism dominate by selecting proper conditions for an in vitro experiment.

CONCLUSIONS

The Hodgkin–Huxley system of equations was proposed 70 years ago, when little was known on the structure of the cell membrane and only electric aspects of the nerve impulse could be measured. The Hodgkin–Huxley model stimulated the development of new experimental and theoretical approaches in membrane biophysics. Several modifications of the original model were proposed as new data became available. The mechanical soliton model was developed at the same time, assuming that the nerve impulse is a nondecreasing mechanical wave that is associated with a phase transition in the lipid bilayer. We think that many arguments advanced by proponents of the mechanical soliton theory can be explained in terms of the Hodgkin–Huxley approach. We do not reject the possibility of soliton generation during nerve impulse conduction, but think that electric phenomena still play the main role in the nerve impulse.

It seems likely that a unified model that explains nerve impulse generation and conduction and allows for all known experimental findings can be obtained by further developing the Hodgkin–Huxley model. The following issues are important to consider:

(1) the membrane capacitance depends on the membrane potential,

(2) cooperative interactions arise both between activating/inactivating particles within a channel and between different channels, and

(3) membrane constriction/extension arising upon changes in membrane potential affects various aspects of protein–lipid interactions and phase transitions in the bilayer.

This approach to modeling may inspire new experimental ideas and yield new findings.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare that they have no conflicts of interest.

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