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MATHEMATICAL
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On mechanisms of electromechanophysiological interactions between the components of signals in axons

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Abstract. Recent studies have revealed the complex structure of nerve signals in axons. There is experimental evidence that the propagation of an electrical signal (action potential) is accompanied by mechanical and thermal effects. In this paper, first, an overview is presented on experimental results and possible mechanisms of electromechanophysiological couplings which govern the signal formation in axons. This forms a basis for building up a mathematical model describing an ensemble of waves. Three basic physical mechanisms responsible for coupling are (i) electric-lipid bi-layer interaction resulting in the mechanical wave in biomembrane; (ii) electric-fluid interaction resulting in the mechanical wave in the axoplasm; (iii) electric-fluid interaction resulting in the temperature change in axoplasm. The influence of possible changes in variables which could have a role for interactions are analysed and the concept of internal variables introduced for describing the endothermic processes. The previously proposed mathematical model is modified reflecting the possible physical explanation of these interactions.

Key words: nerve signals, interactions, physical mechanisms, mathematical description.

1. INTRODUCTION

Although the studies into the propagation of signals in nerves have a long history [7,49], the research is going on. It is accepted that besides the electrical signal (action potential), the accompanying non-electrical manifestations like mechanical effects together with local temperature changes should also be taken into account to get a full picture on this fascinating phenomenon. There is strong experimental evidence [36, 37,56,59,61,62,65] on accompanying effects and there are several mathematical models [8,15,18,31,58] proposed for describing a signal with such effects. However, there is no clear consensus about the possible physical mechanisms governing the processes of propagation and coupling. A need for such a consensus is stressed by many researchers, from Hodgkin [33] to recent studies [2,13, etc.]. In this paper, a brief overview of experimental results and proposed physical mechanisms of coupling is given and analysed within the framework of a robust mathematical model for unmyelinated nerves [17,21]. As a result, based on known experimental studies, the coupling forces are specified in more detail to reflect better the physics of the process. It is concluded that there are several mechanisms responsible for emerging an ensemble

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of waves in nerve fibres. Based on experimental results, these mechanisms are cast into the mathematical descriptions.

In Section 2 a brief overview of experimental studies is given. The possible physical mechanisms are analysed in Section 3. Based on this analysis, possible mathematical descriptions and coupling forces are proposed in Section 4. The mathematical model with coupling forces related to physical effects is described in Section 5, which enlarges our previous proposals [17,21,58]. Finally, the conclusions are presented in Section 6.

2. BRIEF OVERVIEW OF EXPERIMENTAL STUDIES

The contemporary understanding of processes in nerve fibres is based on experimental studies in axons. In simplified physical terms, axons are cylindrical tubes embedded in an extracellular fluid. The wall of the tube has a bilayered lipid structure called biomembrane, formed by phospholipids (a head group and a fatty acid tail) and various proteins which altogether is about 3–4 nm thick. Inside the tube is axoplasm (intracellular fluid) with cytoskeleton elements where the action potential (AP) propagates. The squid giant axon which is the classical experimental object, has the diameter up to 1 mm but the usual mammalian axons have the diameter around 20 μm . A more detailed description of axon morphology is given, for example, by Debanne et al. [12] and of biomembranes – by Mueller and Tyler [45]. It must be noted that the structure of biomembranes can be more complicated with asymmetric structure and strong influence of proteins. However, for modelling the signal propagation in axons, the simple lipid bi-layer description seems to be sufficient.

Further, the results of basic experiments are briefly described in order to prepare the background to the analysis. The way to understand the propagation of APs is paved by experiments of Hodgkin and Huxley [34]. They have measured the AP in the unmyelinated squid axon and explained the role of ionic (Na^+ and K^+) currents. The absolute amplitude of the AP was about 100 mV, duration (without the overshoot) about 1 ms and the velocity 18.9 m/s. The contemporary measurements have demonstrated that the velocities of electric signals in nerves vary in a large interval (from ca 1 m/s to ca 100 m/s). The measurements of the AP together with the quantitative measurements of ionic currents [34] form the basis for the corresponding Hodgkin-Huxley (HH) model [33] which is nowadays called also the Hodgkin-Huxley paradigm.

Many experiments have shown that the propagation of an AP in a nerve fibre is accompanied by transverse displacements of the biomembrane which mean changes in the axon diameter [37,59,61]. These local changes also called swelling are small being in the range of 1–2 nm and compared with the diameter of fibres are of several orders smaller. This is confirmed by recent experiments by Yang et al. [65]. In addition to the deformation of the biomembrane, the pressure wave in axoplasm has been measured by Terakawa [62]. In a squid axon the amplitude of a pressure wave, measured simultaneously with the AP, was about 1 to 10 mPa. The temperature change during the passage of an AP is also measured, it is in the range about 20–30 μK for garfish [59] and much less for bullfrog [60]. The earlier findings on mechanical and thermal effects are summarized by Watanabe [64], and more recently by Andersen et al. [2].

The transverse displacement W of the cylindrical biomembrane is associated with the longitudinal displacement U of the biomembrane. This effect – W is proportional to the gradient of U – is well understood in mechanics [53] for the theory of rods. It means that the bipolar W measured by Tasaki [59] corresponds to the unipolar U (and vice versa). The possible deformation of a biomembrane under loading is studied by measuring the transverse displacement [27,51] and interpreted then as an accompanying mechanical wave along the biomembrane [27,31]. This longitudinal wave may have a soliton-type shape [31], i.e., is unipolar. It must be noted that the excitable plant cells (*Chara braunii*) behave similarly: the electrical signal is coupled with a mechanical effect [26].

To sum up, there is strong experimental evidence about several effects accompanying the propagation of APs. We shall analyse next the proposed mechanisms of coupling.

3. POSSIBLE PHYSICAL MECHANISMS OF COUPLING

3.1. Basic elements of an ensemble of waves

Here we present the analysis of qualitative observations needed to build up the mathematical model. This analysis is followed by the overview on proposed mechanisms which will be used further in Section 4.

The whole ensemble of waves is the following: (i) action potential AP and the corresponding voltage Z associated with the ion current(s), here denoted by J ; (ii) longitudinal wave LW in the biomembrane with the amplitude U ; (iii) pressure wave PW in the axoplasm with the amplitude P ; (iv) transverse displacement TW with the amplitude W ; (v) temperature change Θ . Note that above just one ion current is listed as a variable. The crucial question is: what are the physical mechanisms which link these signal components into a whole?

The starting point of the analysis is related to causality. The classical understanding in axon physiology is the HH paradigm: the whole process is electricity-centred and starts with generating the AP. However, according to the original HH model, the accompanying effects (see above) are not considered. Recently much attention is also paid to another paradigm: the whole process starts with generating the mechanical disturbance (LW) as proposed by Heimbürg and Jackson [31]. The governing equation of the LW has a soliton-type solution describing the region of higher density in the biomembrane and that is why this approach is called soliton theory. The pros and cons of both approaches are analysed by Appali et al. [3] and Meissner [44].

Later in Section 4 we follow the HH paradigm as the fundamental approach in contemporary axon physiology [10,12] but try to link it to the accompanying effects. This means that one should pay attention to electrical-to-mechanical and mechanical-to-electrical couplings and to possible heat generation.

3.2. Qualitative observations from experiments

The following observations can be noted from the published experiments:

- The measured TW is bi-polar for the squid giant axon and its peak coincides with the peak of the AP [59], both have approximately the same duration.
- The measured TW is close to uni-polar for the garfish olfactory nerve and its peak coincides with the peak of the AP [61].
- The peak of the force developed at the axon surface coincides fairly accurately with the peak of the AP [59].
- The peak of the pressure PW lags behind the peak of the AP for the squid giant axon [62].
- Mechanical and thermal signals are in phase with the voltage changes [27].
- The shape and the width of a TW are similar to those of the measured AP (without the overshoot) for the rat neuron [65].
- The experiments with *Chara braunii* cells have demonstrated that the mechanical pulse (out-of-plane displacement of the cell surface) propagates with the same velocity as the electrical pulse and is (in most cases) of bi-polar nature [26].
- The AP and temperature Θ for the garfish olfactory nerve are almost in phase and the duration of the positive phase of heat production is very close to the duration of the depolarizing phase of the AP [59].
- The AP is narrower than the temperature change and the thermal response cannot be directly proportional to the change of voltage [56].
- A good correlation exists between the initial positive heat and the potassium (K^+) leakage [36].
- The residual heat exists after the passage of the AP and it is absorbed in time [55].

3.3. Possible mechanisms of coupling, experimental and theoretical ideas

The well-studied HH model describes the AP dependence on ion currents [33]. Based on experiments with the squid giant axons, the role of opening and closing of ion channels has been demonstrated resulting in

the asymmetric shape of the AP with an overshoot, the existence of a threshold for generating the pulse and the refractory period. The HH model is analysed in many details as the fundamental model of axon physiology [12]. It has been shown that in addition to Na^+ and K^+ ion currents there may be many more ion currents regulating the AP properties, especially for human atrial APs [5,11]. However, the HH model does not describe accompanying effects, although Hodgkin said [33]: “In thinking about the physical basis of the action potential perhaps the most important thing to do at the present moment is to consider whether there are any unexplained observations which have been neglected in an attempt to make the experiments fit into a tidy pattern”.

The physical mechanism governing the HH model is based on the flow of ions through the biomembrane upon the change of voltage in axoplasm. Contemporary understanding is that the ion channels may be voltage-gated like in the HH model but also mechanically-sensitive [45,54]. This must be taken into account in building up a fully coupled model.

Gross et al. [28] have analysed electromechanical transductions in nerves. For electrical-to-mechanical transductions, the mechanisms of electrostriction and piezoelectricity are analysed and argued that both mechanisms could predict the swelling effects. For mechanical-to-electrical transductions, it is proposed that the stress-induced changes due to surface charges influence the intracellular electric field. It is argued that osmosis has no significant influence on nerve pulse propagation. Terakawa [62] has noted on the same subject that osmotic effects are not significant enough to explain the experimental observations.

A promising mechanism for coupling the electrical and mechanical signals is the flexoelectric effect which is manifested in the deformation of the biomembrane curvature under an imposed electric field [52]. The flexoelectric effect is used by Chen et al. [8] for modelling the coupling of the AP and mechanical wave (TW). The classical HH model combined with cable theory includes density change in the biomembrane induced by the flexoelectricity. The biomembrane is modelled as an elastic (or viscoelastic) tube where the flexoelectric force is included into the governing equation. This force depends on the local change in the membrane potential. The changes in the axon diameter are taken into account and the system is reciprocal – it can be triggered either by an electrical pulse resulting in an AP or by a mechanical stimulus.

A coupled model based on the primary AP which generates all other effects is proposed by El Hady and Machta [15]. A Gaussian profile (a pulse) for an AP is taken as a basic without modelling. The assumption is made that in the fibre the membrane has potential energy, and axoplasmic fluid has kinetic energy. The idea is that a surface wave (meaning the surface of the fibre) is generated in the membrane and the bulk field within the axon; and the linearized Navier-Stokes equations are used for calculating the pressure. The ensemble includes voltage (pulse, not a typical AP), radial membrane displacement TW and the lateral displacement inside the axon (i.e., the PW). The heat is assumed to be produced as an additional release of mechanical energy, summing transverse changes in the diameter and lateral stretch. So the sequence: AP – mechanical waves – heat (temperature) is followed.

Rvachev [57] has proposed that the axoplasmic pressure pulse (PW) triggers all the process. The PW triggers the Na^+ channels and the local HH voltage spike develops, which in its turn opens the Ca^{2+} channels. Free intracellular Ca^{2+} activates then the contraction of filaments in the axoplasm which gives rise to the radial contraction in the lipid bilayer. The similar idea that a PW could cause excitement is proposed by Barz et al. [4].

Based on experimental results, Terakawa [62] has suggested that the pressure PW arises either from a change in electrostriction across the axoplasm or from a change in charge-dependent tension along the axoplasm. He states that pressure response is correlated with membrane potential and not with the membrane current. A slight influence of electro-osmotic water flow to pressure response is detected.

Abbott et al. [1] discuss the heat generation in Maia nerves. They give three possible reasons for heat production: (i) the positive heat is derived from the energy released during the rising phase of the AP and the negative heat due to the absorption of energy during the falling phase of the AP; (ii) the positive heat is due to the interchange of Na^+ and K^+ ions, and the negative heat represents the partial reversal of this interchange; (iii) the heat production is related to exothermic and endothermic chemical reactions. Richie and Keynes [56] have supported similar experimental data like Abbott et al. [1]. They also stated that the

energy of the membrane capacitor is proportional to the voltage square and that the thermal response cannot be directly proportional to the change of voltage.

Tasaki and Byrne [60] have analysed the heat production in bullfrog myelinated nerve fibres. They estimated theoretically the relation of voltage V to temperature Θ in dependence of time constant RC (capacity \times resistance in operational amplifier). For RC longer, they used V related to Θ and for RC shorter V related to $d\Theta/dt$.

3.4. Summing up the overview

To sum up, there is no consensus about the coupling and transduction of energy. Some studies concentrate on the electromechanical transductions, some upon the coupling of an electrical signal and temperature. This way or another, the qualitative experimental observations serve as guides in modelling. According to the HH paradigm, the process is triggered by an electrical stimulus which generates the AP but it is also proposed that the stimulus could be mechanical. This could be the LW [31] or the PW [57]. The model by Chen et al. [8] based on using the flexoelectric effect involves reciprocity of electrical and mechanical components of the process. The generation of the temperature during the process is associated either with the electrical signal [1,60] or with mechanical effects [15]. However, the role of chemical reactions in producing temperature changes is also under discussion [1].

This way or another, in most of the studies (both experimental and theoretical), the coupling is associated with local changes of fields which cause changes in the whole system.

4. MODELLING OF COUPLED SIGNALS AND COUPLING FORCES

To overcome (or to unite) the possible differences in proposing the various mechanisms of interactions described in Section 3, the best way is to return to basics. This means starting from physical considerations. Indeed, the signal propagation in nerves is a dynamical process which in terms of continuum theories is far from the molecular range (although some molecular mechanisms may be of influence) and the amplitudes of the components (AP, PW, TW, Θ) are in micro- or meso-scale. The question is then: what is the role of wave equations or diffusion equations, which usually govern the physical dynamical processes, in the nerve pulse propagation. The celebrated HH model is based on the telegraph equation where the inductivity is neglected but ion currents added resulting in a reaction-diffusion equation which predicts a finite velocity of the AP. The longitudinal wave in the biomembrane and the pressure wave in the axoplasm are waves by definition. There is no consensus about the heat generation mechanisms(s) in axons but here we propose to start with the basic Fourier law and the corresponding heat equation. So the conservation laws, well-known in continuum theories could be used. In general formulation, they all include the possible forces which correspond to given physical situations (see for example [25]) and may also include more variables for which some thermodynamical constraints must be satisfied [16]. The next step is to describe the forces in correspondence with governing mechanisms. Although for the modelling of signals in nerves, several mechanisms (see Section 3) have been proposed, it is a challenge to find the proper physical description of possible coupling. Here certain flexibility is desirable because it has been mentioned in several studies (for example, in [1]) that there might be several mechanisms involved simultaneously in the signal propagation.

Consequently, the crucial issue is how to model the coupling. It is proposed that the main hypothesis for constructing the coupling forces could be [21]: all mechanical waves in axoplasm and surrounding biomembrane together with the heat production are generated due to changes in electrical signals (AP or ion currents) that dictate the functional shape of coupling forces. The seconding hypotheses are: the changes in the pressure wave may also influence the waves in biomembrane and mechanical waves may influence the AP and ion currents. This means reciprocity between the signal components. In many studies referred to in Section 3, the changes are mentioned [8,28,60,62] as reasons for interactions. And back to the history: the German physiologist Emil Du Bois-Reymond has noticed in the 19th century that “the variation of current

density, and not the absolute value of the current density at any given time, acts as a stimulus to a muscle or motor nerve” [29]. This statement is called the Du Bois-Reymond law.

What is the change? In mathematical terms changes mean either space (X) or time (T) derivatives of variables. This gives the clue for proposing the functional shapes of forces which at the first approximation could be described in the form of first-order polynomials of gradients or time derivatives of variables (Z_X , J_X , U_X , P_X , and Z_T , J_T , U_T , P_T). Here and further subscripts X and T denote partial derivatives with respect to space and time, respectively. Such an approach involves also certain flexibility in choosing the model.

Further on, a possible approach in modelling is envisaged based on ideas described above [17,21,58]. The processes which compose the leading effects in signal propagation can each be described by single model equations. In the coupled model these single equations are united into a system by coupling forces. For a proof of concept, the coupling could be modelled by a simpler approach: from the AP and ion currents to all the other effects. It has been proposed that the process could be divided into primary and secondary components [22]. The primary components are characterized by corresponding velocities and their mathematical models are derived from wave equation(s). These components are the AP, LW and PW. The secondary components are either derived from the primary components like TW or their models are derived from basic equations which do not possess velocities like temperature Θ . In the latter case, the diffusion-type equation could serve as a basic mathematical model.

Based on experimental studies (Section 3) it seems plausible that there are several physical mechanisms of coupling. This concerns electrical-mechanical (AP to PW and AP to LW) and electrical-thermal (AP to Θ) transduction. In essence, the mechanisms should also include feedback and coupling between all the components of the ensemble. However, these effects could be of more importance in pathological situations (axon dysfunction) or for a detailed understanding of neural communication and neural activity in general.

As stated above, the coupling forces could be described by changes in variables. Note that gradients (space derivatives) act along the axon and time derivatives across the membrane. Based on thermodynamics (see Richie and Keynes [56], Tamm et al. [58]), for temperature changes one should consider also the possible effects of Z or Z^2 (alternatively J or J^2). In general terms, the basic mechanisms might be the following:

- (i) electric-biomembrane interaction resulting in a mechanical response (LW, variable U);
- (ii) electric-fluid (axoplasm) interaction resulting in a mechanical response (PW, variable P);
- (iii) electric-fluid (axoplasm) interaction resulting in a thermal response (Θ).

4.1. Possible interactions

However, as said above, the feedback from mechanical waves to other components of the whole ensemble might also influence the process. In more detail, these interactions can be characterized in the following ways:

(a) influence from the AP with amplitude Z :

- (1) Pressure change in axoplasm – Z_X , i.e., AP gradient along the axon axis can influence the pressure as a result of charged particles present in axoplasm reacting to the potential gradient along the axon;
- (2) Pressure change in axoplasm – Z_T , i.e., potential changes across the biomembrane can lead to a pressure change proportional to the potential change through electrically motivated membrane tension changes (also taken into account for LW, and this is accounting for the influence from the mechanical displacement which is taken proportional to Z_T);
- (3) Pressure change in axoplasm – J_T , i.e., the axoplasm volume change from ion currents in and out of axon through the biomembrane plus the effect of possible osmosis which is assumed to be proportional to the ionic flows;
- (4) Density change in biomembrane – Z_T , i.e., electrically induced membrane tension change or flexoelectricity;
- (5) Density change in biomembrane – J_T , i.e., membrane deformation as a result of ionic flow through the membrane (ion channels deforming surrounding biomembrane when opening/closing); note that ion

channels are not modelled in the FitzHugh-Nagumo (FHN) model explicitly;

- (6) Temperature change – Z^2 or J^2 , i.e., temperature increase from current flowing through the environment (power); this effect is related to Joule heating;
 - (7) Temperature change – the endothermic term is dependent on the integral of J which is taken to be proportional to the concentration of reactants which decays exponentially in time after the signal passage; needs a new kinetic equation to be added.
- (b) influence from the pressure the PW with amplitude P :
- (1) Density change in biomembrane – P_T , i.e., membrane deformation (displacement) from the local pressure changes inside the axon;
 - (2) Temperature change – P_T , i.e., reversible local temperature change: when pressure increases then temperature increases proportionally and when pressure decreases then temperature decreases proportionally, this happens at the same timescale as pressure changes;
 - (3) Temperature – the irreversible local temperature increase from energy consumed by viscosity (friction) – this is actually time integral of P_T .
- (c) influence from the mechanical wave LW with amplitude U in biomembrane:
- (1) Action potential change – U_T , i.e., ion currents are suppressed when membrane density is increased and amplified when membrane density is decreased;
 - (2) Temperature change – U_T , i.e., the reversible local temperature change, when density increases the local temperature is increased proportionally and when density decreases the local temperature decreases proportionally, this happens at the same timescale as the density changes in biomembrane;
 - (3) Temperature change – the irreversible local temperature increase from energy consumed by the added friction/viscosity term in longitudinal density change model – this is actually time integral of U_T which is proportional to U .

These are the plausible processes which can influence the dynamics of nerve pulse propagation. However, not all of the listed effects might be energetically at the same scale as far as the dynamics of the nerve pulses are concerned. At this stage, the possible influence of temperature changes on properties of fibres is disregarded as experimental observations are showing temperature changes low enough (up to about 50 μK) to be probably negligible for these processes [56,60]. In addition, the possible changes in the fibre diameter which could change the physical properties are also disregarded being of many scales lower compared with leading effects (about 1–2 nm displacement vs axon diameter of about 20 μm or more). In general, the significance of the listed effects must be determined by experimental and theoretical studies in the future.

5. A MATHEMATICAL MODEL WITH SPECIFIED COUPLING FORCES

We have proposed a mathematical model of nerve pulse propagation including the accompanying effects [17,21]. This model served as a proof of concept and was based on using the basic equations of mathematical physics which were modified to reflect the physiological effects. The following single models have been used: the reaction-diffusion model for describing the AP (the FitzHugh-Nagumo (FHN) model) and accompanying ion current; the modified wave equation for describing the LW in the biomembrane (the improved Heimburg-Jackson (iHJ) model); the wave equation with dissipation for the PW; the diffusion equation for the Θ . The coupling forces [21] have been proposed to model the interaction between the components of the whole ensemble.

The criticism on this model [35] is based on the seeming inconsistency of the coupling of the AP and LW described by indicated models. The main point of the criticism is that in the HH model the capacitance of the neural membrane is taken constant [35]. However, it must be noted that in the coupled model one has used the modelling of an AP only for obtaining a correct (measured by numerous experiments) asymmetric shape of an AP with an overshoot and a corresponding ion current. Note that the overshoot has a definite role in signal propagation [2,12]. Certainly, other models could also be used for this purpose. For example, El Hady and Machta have used just a symmetrical Gaussian pulse without an overshoot for the AP [15]. The

present understanding of electrophysiology gives strong evidence of the importance of electrical signals [10,12] in axons with an asymmetric shape.

In mathematical terms, such “simple conceptual models can be used to gain insight, develop intuition, and understand “how something works”” [48]. In physical terms, much must be understood before one could realize a complete unifying model. Following the HH paradigm [50], the causality relies on the propagation of an electrical signal in the axon. It must be noted that, alternatively, following Heimburg and Jackson [30] or Mussel and Schneider [46], the mechanical wave in a biomembrane can generate voltage changes. The manifestations of physical processes described briefly in Section 3 are suggesting the causality related to the AP but indicate the need to modify both the model equations as well as coupling forces for describing the accompanying effects.

The main reason for the modification is the possible plurality of dynamical processes and coupling effects. Changes compared with the previous model [17,21,58] are following: dissipation is added to the iHJ equation; the coupling force for the temperature equation is specified accounting for multiple mechanisms which also include endothermic processes. The latter means proposing an additional kinetic equation involving the ion current. It means that the whole system involves the dissipative effects and the endothermic processes involve internal variables [24]. Internal variables are not observable and characterize the internal structure or processes [43]. It has been used for describing some microscopic effect leading to local structural rearrangements [43] which have no inertial influence. Such a concept is widely used in contemporary continuum mechanics [6] and relies on the thermodynamical description of dissipative effects. The first attempt to use internal variables in nerve pulse dynamics is described by Maugin and Engelbrecht [42] for describing the role of ion currents. Here such a formalism [63] is used for describing the possible chemical processes [1] which influence the temperature changes. The mechanism of such changes is proposed to be similar to the behaviour of phenomenological variables in the HH model – the change from one level to another.

For the sake of completeness, the modified general model is presented here in the dimensionless form. The FHN equations describing the AP are [47]:

$$\begin{aligned} Z_T &= DZ_{XX} - J + Z(Z - C_1 - Z^2 + C_1Z), \\ J_T &= \varepsilon_1 (C_2Z - J), \end{aligned} \quad (1)$$

where $C_i = a_i + b_i$ and $b_i = -\beta_i U$. Here Z is the voltage, J is ion current, ε_1 is the parameter governing the difference of time scales, a_i is the ‘electrical’ activation coefficient, b_i is the ‘mechanical’ activation coefficient and U is a longitudinal density change from lipid bi-layer density model.

For the PW a modified wave equation with viscosity effect included is used

$$P_{TT} = c_2^2 P_{XX} - \mu_2 P_T + F_2(Z, J), \quad (2)$$

where P is pressure, μ_2 is a viscosity coefficient, F_2 is the coupling term accounting for the possible influence from the AP and TW.

Longitudinal wave in lipid bilayer is modelled by the improved HJ model [19,30]

$$U_{TT} = c_3^2 U_{XX} + NUU_{XX} + MU^2 U_{XX} + NU_X^2 + 2MUU_X^2 - H_1 U_{XXX} + H_2 U_{XTT} - \mu_3 U_T + F_3(Z, J, P), \quad (3)$$

where $U = \Delta\rho$ is the longitudinal density change, c_3 is the sound velocity in the unperturbed state, N , M are nonlinear coefficients, H_i are dispersion coefficients and μ_3 is the dissipation coefficient. Note that H_1 accounts for the elastic properties of the bi-layer and H_2 – for the inertial properties. The F_3 is the coupling force accounting for the possible influence from the AP and PW. The transverse displacement (TW) is $W \propto U_X$.

In Eq. (3) a viscous term U_T is included as the simplest dissipative term. This follows the idea by Kaufmann [39] who stressed the need to account for the dissipative processes in the biomembrane (see also [38,40]). In soliton physics the dissipative solitons are well known [9] because the real systems are not

conservative like the classical soliton theory describes. Here including such a term means a step closer to reality.

The local temperature Θ is governed by

$$\Theta_T = \alpha \Theta_{XX} + F_4(Z, J, U, P), \quad (4)$$

where Θ is the temperature, α is a thermal conductivity coefficient and F_4 is the coupling force accounting for the possible influence from the AP, LW and PW.

As said before (Section 4), the coupling forces model the possible mechanisms of interaction between the effects. Coupling force F_2 is taken as

$$F_2 = \eta_1 Z_X + \eta_2 J_T + \eta_3 Z_T, \quad (5)$$

where Z_X accounts for the presence of charged particles under the influence of the potential gradient (along the axon), J_T accounts for the ionic flows into and out of an axon (across the membrane) and Z_T accounts for the possible pressure change as a result of membrane tension changes from the electrical field and $\eta_i = \text{const}$. The coupling force F_3 is

$$F_3 = \gamma_1 P_T + \gamma_2 J_T - \gamma_3 Z_T, \quad (6)$$

where P_T accounts for possible membrane deformation because of pressure changes (pressure to TW to LW), J_T accounts for possible membrane deformation as a result of ionic flows through ion channels and Z_T accounts for possible electrically induced membrane tension change and $\gamma_i = \text{const}$. Note the sign, assuming that density decreases with the increasing tension.

In case of the temperature changes several functional forms were used for F_4 [58] in order to find the best match with experimental results. The terms in [58] were considered from the viewpoint of possible mathematical description. However, it is possible that Eq. (4) needs to be improved to match better experimental observations when the time-scale for the temperature changes is larger than the time-scale for AP changes. Note that Abbott et al. [1] have argued about the possible combination of many reasons for heat production. Consequently, for modelling the temperature changes one could use Eq. (4) with either

$$F_4 = \tau_{11} Z^2 + \tau_2 (P_T + \varphi_2(P)) + \tau_3 (U_T + \varphi_3(U)) - \tau_4 \Omega \quad (7)$$

or

$$F_4 = \tau_{12} J^2 + \tau_2 (P_T + \varphi_2(P)) + \tau_3 (U_T + \varphi_3(U)) - \tau_4 \Omega. \quad (8)$$

Here Ω is an internal variable, modelling all endothermic processes and $\tau_i = \text{const}$. In principle, it describes the change from one level to another like the phenomenological variables describing ion currents in the HH model [34]. The corresponding evolution equation for Ω in Eqs (8) and (7) is [6,42]

$$\Omega_T + \varepsilon_4 \Omega = \zeta J, \quad (9)$$

where ε_4 and ζ are constants. An alternative way of representing the evolution of Ω could be

$$\Omega_T = \varphi_4(J) - \frac{\Omega - \Omega_0}{\tau_\Omega}, \quad \text{where } \Omega_0 = 0, \quad \tau_\Omega = \frac{1}{\varepsilon_4}, \quad (10)$$

where Ω_0 is the equilibrium level (in our setting equilibrium has been taken as zero level) and τ_Ω is the relaxation time. Clearly, Ω as an internal variable has a certain relaxation time before reaching its equilibrium value. Following the discussion of Abbott et al. [1], the thermal influence of chemical reactions might initially be endothermic and in the later stages of the recovery – exothermic. In principle, this internal variable can describe both endo- and exothermic chemical influence, which means that the value of Ω has to change the sign (overshooting equilibrium value). However, this might need several ion currents to be taken into account.

The usage of the complicated formulation of coupling force F_4 is motivated by many possible mechanisms mentioned in experimental studies [1,56]. The physical explanation of terms in Expressions (7) and (8) stems from results listed in Section 4.

We propose in (7) and (8)

$$\varphi_2(P) = \lambda_2 \int P_T dT \quad \text{and} \quad \varphi_3(U) = \lambda_3 \int U_T dT, \quad (11)$$

where integrals in (11) characterize the thermal influence from mechanical waves into the temperature (4) as a result of friction–type terms in Eqs (2) and (3); and λ_i are coefficients. In dimensionless case $\lambda_i = \mu_i$.

The term J^2 in Eq. (8) (or Z^2 in Eq. (7)) is either related to $\mathcal{P} = J^2 r$ or $\mathcal{P} = Z^2/r$ where r is resistance and \mathcal{P} is power which accounts for the Joule heating from the (electrical) current flowing through the environment. The term P_T accounts for the local temperature increase if the pressure increases and decrease when pressure decreases (reversible), term $\int P_T dT$ accounts for the temperature increase from the energy lost to viscosity in Eq. (2), term U_T accounts for the local temperature increase when the local density is increased and decrease if the local density decreases (reversible), term $\int U_T dT$ accounts for the temperature increase from the energy lost to viscosity in Eq. (3); and finally, as noted, the Ω takes into account the temperature decrease from endothermic processes. In Eq. (9), term J is used on the assumption that endothermic process intensity is proportional to

$$\varphi_4(J) = \zeta \int J dT, \quad (12)$$

which is taken as the time integral of ion currents at the location (ζ is coefficient). This concentration-like quantity is decaying exponentially in time which is accounted by the term $-\varepsilon_4 \Omega$ in Eq. (9). In other words, we are considering some kind of an endothermic chemical reaction. Some other processes are outlined in the literature [32,46] but not considered here as possibly relevant, like, the phase change of the lipid bilayer. In the present framework, the phase change, if relevant, could be accounted by the term U_T when using an alternate physical interpretation where the change in the membrane density is a result of the phase change. However, unless noted otherwise the interpretation used in the present framework for the U is that this is the ‘normal’ density change as a result of the mechanical wave propagating in an elastic environment.

A block diagram of the presented model is shown in Fig. 1, where the main components of the model framework and interactions between previously established individual component models are highlighted. The input is an electrical signal above the threshold which triggers all the processes. The proposed framework is highly flexible and any of the components can be replaced with an improved model with the desired descriptive detail, like, for example, one could use an HH model instead of the FHN model without having to change the framework significantly.

In what follows, the attention is paid to the influence of various sources of heat generation to the temperature changes. The analysis of mechanical components of a wave ensemble is presented earlier [19,21]. An example for the cases where only a single source of thermal energy is present is shown in Fig. 2. The profiles for the Z, P, U are the same but which is different is the thermal response Θ curves. Qualitatively what is relevant here is the location of the thermal response peak compared to the wave ensemble and the shape of the initial thermal response curve.

Two distinct thermal response cases are shown in Fig. 3. It must be noted that the PW and LW profiles are also significantly different. A case with full F_4 in the form of $\tau_1 J^2 + \tau_2 (P_T + \varphi_2(P)) + \tau_3 (U_T + \varphi_3(U)) - \tau_4 \Omega$ and the viscosity in P (2) and U (3) is shown on the left panel in Fig. 3. On the right panel in Fig. 3, the irreversible thermal processes have been significantly suppressed by setting coefficient τ_1 to zero (related to the Joule heating) and reducing the viscosity by two orders of magnitude compared to the case on the left panel. This means that the thermal response in Fig. 3 right panel is dominated by the reversible processes (temperature increase when density increases in axoplasm and membrane and temperature decrease if the density decreases with friction related terms suppressed). It can also be noted that viscosity or lack of it has a significant effect on the shape of the PW and LW profiles within the range of the used parameters. The governing equations for the PW and LW are conservative before adding the coupling forces F_1, F_2 and the

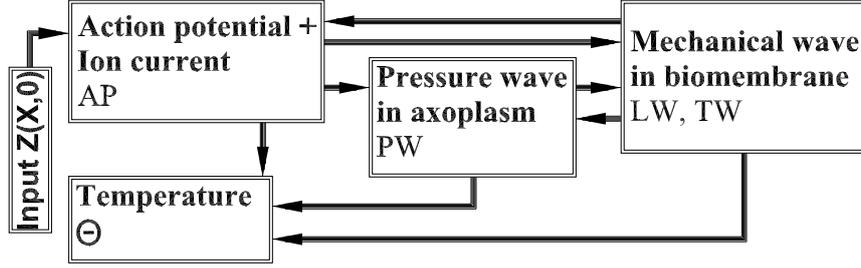


Fig. 1. Block diagram of the model system.

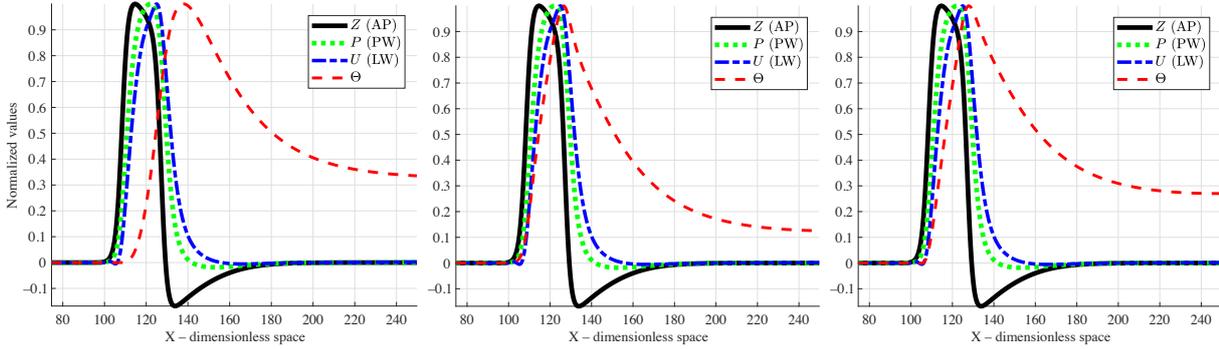


Fig. 2. Wave ensemble Z, P, U, Θ with different temperature models. Left panel ($\Theta \propto J^2$) where $\tau_1 = 0.05, \tau_2 = 0, \tau_3 = 0$; middle panel ($\Theta \propto \varphi_2(P)$) where $\tau_1 = 0, \tau_2 = 0.1, \tau_3 = 0$; right panel ($\Theta \propto \varphi_3(U)$) where $\tau_1 = 0, \tau_2 = 0, \tau_3 = 0.5$.

dissipative terms. Without accounting for some kind of friction-like term in PW and LW the different sound velocities in the corresponding environments have an opportunity to spread the wave-profiles out as the driving force from the AP is taken with a different velocity than the sound speed in axoplasm and biomembrane. While not demonstrated in the figures, it should be noted that the thermal signal drop off rate is dependent on the relaxation time τ_Ω . If relaxation is taken fast enough it is possible to model thermal response curves which are almost perfectly in-phase with the propagating wave ensemble. Some endothermic chemical processes in the context of the nerve pulse propagation have been discussed by Abbott et al. [1]. Alternatively, thermal response in-phase with the propagating wave ensemble can emerge if the reversible thermal changes are dominating (Fig. 3 right panel).

Figure 4 demonstrates the effect of the Joule heating as a function of Z^2 . On the left panel, the thermal source and thermal sink have been balanced $\tau_1 Z^2 \approx \Omega$ so that the thermal response settles eventually back to its starting value. On the middle panel, the balance between thermal source and thermal sink terms is varied, demonstrating that depending on the balance between these terms there is a different residual level of heat increase after the nerve pulse wave ensemble has passed. In the right panel, the thermal source and thermal sink are balanced and the relaxation time is varied. It demonstrates that depending on the relaxation time related parameters, the equilibrium or residual level can be reached at different rates. In terms of qualitative thermal response curve characteristics, there is no practical difference between formulating the Joule heating in terms of Z^2 or J^2 .

The numerical scheme used (with minor changes) for the example solutions is described in [17,58] and references therein. The parameters used in the present numerical examples are the following. The FHN equation (1): $D = 1, a_i = 0.2, \beta_i = 0.025, \varepsilon_1 = 0.018$. The pressure equation (2): $c_2^2 = 0.09, \mu_2 = 0.05$; and coupling force F_2 (5): $\eta_1 = 10^{-3}, \eta_2 = 10^{-2}, \eta_3 = 10^{-3}$. The iHJ equation (3): $N = -0.05, M = 0.02, H_1 = 0.2, H_2 = 0.99, c_3^2 = 0.1$; and coupling force F_3 (6): $\gamma_1 = 10^{-2}, \gamma_2 = 10^{-3}, \gamma_3 = 10^{-5}$. Parameter μ_3 in (3) is taken as $\mu_3 = 0.05$ unless noted otherwise. The improved heat equation (4): $\alpha = 0.05$ and thermal source/sink function F_4 (8) (or (7)): $\tau_4 = \varepsilon_4/2 = 0.005$ and $\tau_{1,2,3}$ is variable parameter. In addition,

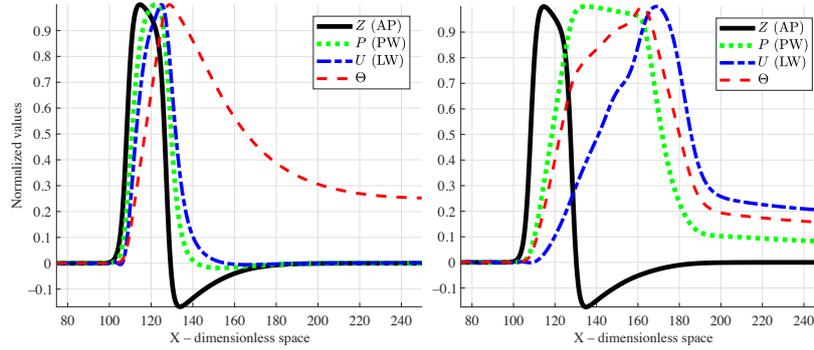


Fig. 3. Wave ensemble Z, P, U, Θ with different thermal sources. Left panel (with small, but noticeable viscous damping in P and U , thermal sources in F_4 are $J^2, \varphi_2(P), \varphi_3(U)$) where $\tau_1 = 0.0167, \tau_2 = 0.0333, \tau_3 = 0.1667$; right panel (thermal sources in F_4 only from P_T and U_T with negligible viscosity) where $\tau_1 = 0, \tau_2 = 0.1, \tau_3 = 0.025, \mu_1 = 0.0001, \mu_2 = 0.0001$.

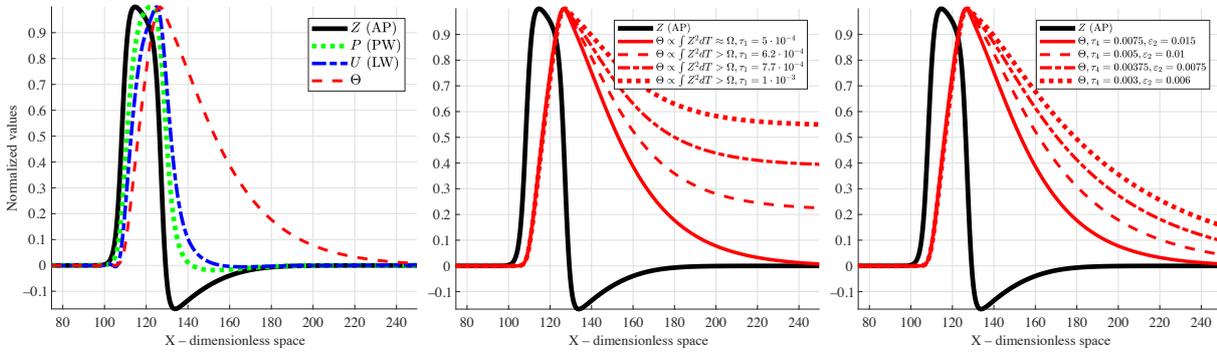


Fig. 4. Waveprofiles Z, P, U, Θ and the effect of the Joule heating. Left panel (thermal source in $F_4 \propto Z^2$) for $\tau_1 Z^2 \approx \Omega$ the parameters are $\tau_1 = 0.0005, \tau_2 = 0, \tau_3 = 0$; middle panel (thermal source in $F_4 \propto Z^2$) for $\tau_1 Z^2 > \Omega$ the parameters are $\tau_1 = 0.001, \tau_2 = 0, \tau_3 = 0$; right panel (thermal source in $F_4 \propto Z^2$): the effect relaxation times on the temperature profiles; the parameters are chosen so that $\tau_1 Z^2 \approx \Omega$.

in (11): $\lambda_2 = \mu_2 = 0.05$ and $\lambda_3 = \mu_3 = 0.05$ unless noted otherwise. In (9): $\zeta = 0.005$ and $\varepsilon_4 = 0.01$ unless noted otherwise. The parameters for the numerical scheme and initial conditions: $n = 2^{11}$ (number of spatial grid points), $L = 128$ (the length of spatial period is $L \cdot 2\pi$), $\Delta T = 1$ and $T_f = 800$ (integration time in dimensionless units). For the initial condition $A_z = 1.2$ (amplitude of the initial excitation for Z) and $B_z = 1$ (width of initial sech^2 -type excitation for Z) while all other initial conditions are taken zero (P, U, Θ at rest). The parameters are chosen in order to fit qualitatively experimental results (see [17,19,21]).

6. DISCUSSION AND CONCLUSIONS

What has been described above, is the modelling of a complex process of propagation of signals in nerve fibres at the interface of physics, mathematics and physiology [23]. The physical background of wave motion is taken as a basic phenomenon, then processes formulated in the mathematical language and finally based on physiological understandings on the single effects coupled into a whole. In some sense, we have followed A. Einstein [14] who said: "... mathematical construction enables us to discover the concepts and laws connecting them which give us the key to the understanding of the phenomena of Nature".

An overview of experimental physical effects permits to describe the possible mechanisms of interaction between electrical and mechanical signals accompanied by temperature changes. Based on our hypothesis on the role of changes in electrical signals as sources for accompanying effects [21], the full list of possible factors are described and the coupling forces formulated. Compared with our previous studies, the number of possible coupling effects is enlarged and a new internal variable is introduced to account for possible

endothemic reactions which according to experiments [1] could influence the temperature changes. Like the phenomenological variables in the HH model, the change of this internal variable involves a certain equilibrium level and the corresponding relaxation time. In order to justify the energy transduction, the dissipative term is included into the governing equation of the LW. Although we have followed the HH paradigm by starting the process by an electrical signal, the possible feedback is taken into account by coupling forces. As the temperature changes generated by the AP are small then the feedback from these changes to the AP are negligible.

So in the full coupled model, the primary governing equations which are related to wave motion have a physical basis derived from basic principles of continuum theory. The non-wave-like phenomena are governed either by diffusion equation (temperature change) or derived from the primary variables (this concerns the TW). The numerical results described in Section 5, are quantitatively similar to experimental profiles of changes (see references in Section 5). It seems that the Joule heating is the best candidate for generating accompanying temperature while endo- and exothermic reactions [1] are best described by introducing an internal variable [24]. Such a model, originated from continuum mechanics includes also the relaxation time demonstrated by experiments [1,36,56].

The presented model is certainly robust and could be improved or modified in many aspects. As explained in Section 5, the FHN model has been used just for obtaining a qualitatively correct shape of an AP with an overshoot and the corresponding ion current. If the HH model with many physical constants would be used then there would be a possibility to specify the role of various ion currents. This could modify the generation of accompanying effects and may explain the retardation of refraction and also the influence of anesthetics. In the proposed model the mechanical activation of ion channels in the FHN model is described phenomenologically utilizing various coefficients. Such a proposal might also need refinements by specifying activation forces from lipids (influence from the biomembrane) or filaments (influence from the axoplasm) [41]. The LW is governed by iHJ equation which is an excellent description of a mechanical wave in a biomembrane [31]. However, one should note that although this equation has a soliton-type solution, its generation from an input needs time [20] and the time-scale might not be large enough for a real soliton to emerge during the AP propagation. In addition, the existence of ion channels in biomembranes is a clear sign for inhomogeneities in the lipid bi-layer which could also influence the mechanical wave. This is again a challenge for further improvement of the model. The molecular effects related to ion movement, the influence of membrane proteins [44] and the existence of filaments in the axoplasm may have a considerable effect to coupling forces. At this stage, the possible role of chemical reactions accompanying the whole process is taken into account by an internal variable related to possible temperature changes.

Every theoretical model should be validated by experiments. The mathematical modelling described above may be used to uncover new mechanisms that experimental science has not yet encountered [48]. Such an approach is justified from the viewpoint of physical considerations which must be correlated with physiological phenomena. The possible influence of various coupling forces depending on changes of variables demonstrated above (Section 5) indicates the possibilities for interpretation of experiments.

The explanations on coupling forces given above actually represent a rather full theoretical framework of possible interactions. Although there is a doubt whether it is possible to build up “general unifying models” [35], one cannot overlook the mathematical description of the physical background because the signal propagation in nerves is a complex electro-mechano-thermo-physiological process spiced with molecular effects resulting in an ensemble of waves. Surely the different models used so far for the description of single effects may have different levels of idealization but this is not a fundamental obstacle. Every attempt to understand this complexity is welcome and needs close collaboration between theoreticians and experimentalists. In other words, it is a challenge to put the pieces back to the whole. The proposed model is still far from being ideal but forms a backbone in modelling based on physical considerations of wave motion expressed in the mathematical language.

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Elektro-mehhano-füsioloogiliste interaktsioonide mehhanismid aksoni signaalikomponentide vahel

Jüri Engelbrecht, Kert Tamm ja Tanel Peets

Eksperimentaalsed uuringud on tuvastanud, et närvikus (aksonis) leviva elektrilise signaaliga (aktsioonipotentsiaaliga) kaasnevad ka mehaanikalised ja termilised signaalid. Ülevaade eksperimentidest lubab määrata elektro-mehhano-füsioloogiliste interaktsioonide füüsikalised tingimused, mille järgi on interaktsioonide mehhanismide põhjal võimalik koostada leviva laineansambli matemaatiline mudel. Olulised on järgmised interaktsioonid: elektrilise signaali interaktsioon lipiididest koosneva biomembraani, aksoplasma (vedeliku) ja soojusvahetusega. On analüüsitud selliste interaktsioonide mõju laineansambli tekkimisele. Soojusvahetuse juures tekkivate endotermiliste protsesside modelleerimisel on kontiinumi mehaanika eeskujul kasutatud sisemuutujate kontseptsiooni. Esitatud matemaatiline mudel seob elektrilise signaali ja olulised kaasnevad efektid tervikuks, kus on jäävusseadusest lähtudes tagatud põhjuslikkus ning füüsikaliste protsesside sidusus.