Modeling of complex signals in nerve fibers

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Abstract

Experiments have demonstrated that signals in nerve fibers are composed by electrical and mechanical components. In this paper a coupled mathematical model is described which unites the governing equations for the action potential, the pressure wave in the axoplasm and the longitudinal and the transverse waves in the surrounding biomembrane into one system of equations. As a solution of this system, an ensemble of waves is generated. The main hypotheses of such a model are related to the nature of coupling forces between the single waves in the ensemble. These coupling forces are assumed to have bi-polar shapes leading to energetically stable solutions. The *in silico* modeling demonstrates the qualitative resemblance of computed wave profiles to experimental ones. The ideas of possible experimental validation of the model are briefly described.

Keywords: nerve signals, ensemble of waves, coupling forces, interdisciplinarity

1. Introduction

The physical background of signal propagation in nerve fibers is complicated combining many phenomena into a whole. Much has been done for studying this process but despite of numerous experiments and theoretical studies not everything is understood. In the analysis one should start from physical properties of nerve fibers in order to formulate the clear backbone for modeling. Bearing in mind axons (not branching nerve networks), a nerve fibre can be modeled as a tube in a certain environment. Inside the tube is the axoplasmatic fluid (shortly axoplasm), called also intracellular fluid. This fluid contains also cytoskeletal filaments, has a certain concentration of ions and in terms of mechanics is usually considered as a viscoelastic medium. The wall of the tube has a bilayered lipid structure which can be considered a microstructured medium. In general terms it is called a biomembrane. Beside lipid molecules, a biomembrane has voltage-gated (also stretch-sensitive) ion channels responsible for changing the ions between the intracellular fluid and the environment (extracellular fluid or interstitial fluid). The intra- and extracellular fluids both are characterized by a certain level of concentration of ions and the exchange of ions (ion currents through the biomembrane leading to changes in ion concentrations) has the main role in generating the nerve signals. The contemporary understanding of axon physiology, excitability, and ionic mechanisms is described by many authors [1, 2, 3, 4]). In what follows, the attention is paid to unmyelinated axons in order to model the basic processes of signal propagation. The ensemble of signals (waves) includes the following components. The action potential (AP) is generated by an electrical impulse with an amplitude above the threshold. The AP propagates in the axoplasm supported by ion cur-

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rents through the biomembrane. The AP generates also a pressure wave (PW) in the axoplasm and a longitudinal wave (LW) in the biomembrane. The LW means a local longitudinal compression which changes the diameter of the biomembrane reflected by a transverse wave (TW). It is under discussion whether and how the PW has a role in generating the deformation of the biomembrane and general signaling [5, 6]. In the ensemble of waves, the AP depends on the properties of the axoplasm and ion currents, the PW depends on the properties of axoplasm. Both the LW and the TW depend on the elastic properties of the biomembrane but experimental studies have paid more attention on the measurable TW, i.e. on the change of the fiber diameter. The crucial elements in emergence of this ensemble of waves are the coupling forces.

Since the pioneering experiments by Hodgkin and Huxley, the ion currents (Na, K, Ca, and others) in the process including the analysis of possible anesthesia have been studied by many authors. There are several ideas about the coupling forces which characterize the electro-mechanical or mechano-electrical transductions but up to now there is no clear agreement on mechanisms of these processes accepted by the whole scientific community. The aim of this paper is to describe a possible mathematical model which generates an ensemble of waves in a nerve fibre, proposed as system of governing equations of motion [7, 8]. In general, mathematical models which describe real physical processes must be built up using the physical principles. For wave processes, these principles are based on conservation laws. In order to account for accompanying essential physical effects, the models need often some modifications but these modifications should also be based on physical considerations avoiding the *ad hoc* terms. In Fig. 1 a block diagram for the possible mathematical model for describing the propagation of wave ensemble in the nerve fiber is visualized.

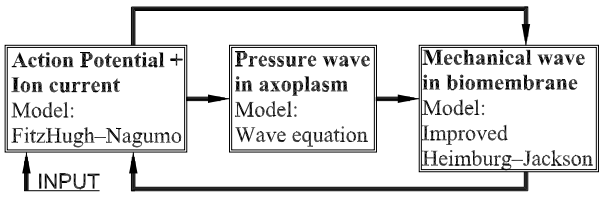

Figure 1: The block diagram of the possible mathematical model for the ensemble of waves in the nerve fiber.

Further on, in Section 2 the main hypotheses are described followed by a detailed description of governing equations and coupling forces in Section 3. The results of numerical simulations are analyzed in Section 4. The general discussion in Section 5 turns attention to pro's and contra's of such modeling. The final remarks are given in Section 6.

2. Hypotheses

In the complicated ensemble of various signals in nerve fibres, the mechanisms of relations between the AP and ionic currents are well understood starting from the pioneering studies of Hodgkin and Huxley [9] see, for example, the review by Clay [2]. The mechanism of electro-mechanical coupling is still under discussion.

Here we propose the following main hypothesis: the mechanical waves in axoplasm and surrounding biomembrane are generated due to changes in electrical signals (the AP or ion currents).

The seconding hypothesis is: the changes in the pressure wave may also influence the waves in biomembrane.

Two essential remarks are the following: (i) the changes of variables mean mathematically either the space or time derivatives; (ii) the pulse-type profiles of electrical signals mean that the derivatives have a bi-polar shape which is energetically balanced. In what follows, mathematical modeling is used which means casting a real world phenomenon into a mathematical representation. This is not just a tool in describing the physical processes but also a possibility to understand the mechanisms from a different viewpoint and perform *in silico* experiments. This enhances our ability to understand and predict the behavior of processes but certainly needs later the validation of theoretical ideas by physical experiments. Such an approach is more and more used in system biology [10, 11] and also called integrative biological

modeling [12]. The preliminary studies following the hypotheses presented above [7, 8, 13] are promising.

3. Coupling forces and governing equations

There are several ideas about the nature of physical mechanisms about electro-mechanical coupling of processes in nerve fibres. Gross et al [14] indicate that either electrostrictive or piezoelectric mechanisms could be the candidates for coupling. They also argue about the importance of molecular gating of ion channels and stress that water swelling as a source for mechanical effects seems highly improbable because of much stronger ion currents needed for that. Terakawa [5] argues that the pressure wave arises either from a change in electrostriction across the axolemma or from a change in charge-dependent tension along the axolemma. Tasaki [15] states that mechanical trace resembles the first derivative of the voltage trace but Gonzalez-Perez et al [16] believe that mechanical changes are proportional to voltage changes. El Hady and Machta [17] assume that the force exerted on the biomembrane is proportional to the voltage square. Further on, based on hypotheses (see above) we assume that mechanical changes are dependent on changes of electrical signals, either of the action potential (AP) or of the ion current(s) [7, 8]. It means that the functional dependence is given by the derivatives with respect to space (gradients) or with respect of time. Given a pulse-type electrical signal (either the AP or ion current(s)), the resulting function has a bi-polar shape which gives an energetically stable solution. As far as the ensemble of waves is described by the corresponding single governing equations coupled into a system by coupling forces, the uni-polar shape of the force means constant energy influx into the system which is energetically not possible. That is why the bi-polarity of coupling forces makes the system mathematically consistent and in physical terms able to model a stable running ensemble of waves. In this respect it seems that the assumption about the functional dependence of the stress in a biomembrane on the voltage square [4, 14] corresponds to a static case. The following assumptions are made [8]:
(i) electrical signals are the carriers of information and trigger all the other processes;
(ii) the axoplasm in a fibre can be modeled as a viscous fluid where a pressure wave is generated due to the electrical signal [5];
(iii) the biomembrane can be deformed in the longitudinal as well as in the transverse direction;
(iv) the channels in biomembranes can be opened and closed under the influence of electrical signals as well as of the mechanical input [4].
Following the hypotheses and assumptions, the governing system proposed by Engelbrecht et al [7, 13] in its dimensionless form is the following:

$$\begin{aligned} &Z_T = DZ_{XX} - J + \\ &+ Z\left(Z - [a_1 + b_1] - Z^2 + [a_1 + b_1]\, Z\right), \\ &J_T = \varepsilon\left([a_2 + b_2]\, Z - J\right), \end{aligned} \tag{1}$$

$$\begin{aligned} &U_{TT} = c^2 U_{XX} + NUU_{XX} + MU^2 U_{XX} + \\ &+ NU_X^2 + 2MUU_X^2 - H_1 U_{XXXX} + \\ &+ H_2 U_{XXTT} + F_1(P, J, Z), \end{aligned} \tag{2}$$

$$P_{TT} = c_f^2 P_{XX} - \mu P_T + F_2(Z, J). \tag{3}$$

Here Eqs (1) represent the FitzHugh Nagumo (FHN) equation [18], Eq. (2) is the improved Heimburg-Jackson (iHJ) model [19, 20] and Eq. (3) is the classical wave equation with the added viscous dampening term. The following notations are used: Z denotes action potential, J is the ion current, a_i, b_i are 'electrical' and 'mechanical' activation coefficients, D, ε are coefficients, U is the longitudinal density change, c is the sound velocity of unperturbed state in the lipid bi-layer, N, M are nonlinear coefficients, H_1, H_2 are dispersion coefficients, P is the pressure, c_f is the sound velocity in axoplasm, and μ is the viscosity coefficient. The indices X, T here and further denote the differentiation with respect to space and time, respectively. In Eqs (1), a_i are constants and $b_1 = -\beta_1 U$ and $b_2 = -\beta_2 U$, where the β_i are the mechanical coupling coefficients.

The block diagram for the combined model is shown in Fig. 1. In Fig. 2 an artistic sketch of an wave ensemble is depicted. It is assumed that the coupling forces are

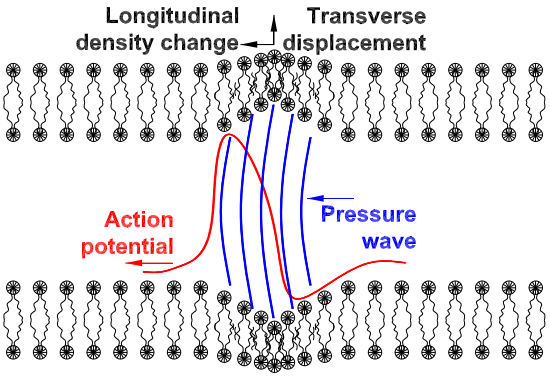

Figure 2: An artistic sketch of an wave ensemble in axon.

$$F_1 = f_1(P_T, J_T), \quad F_2 = f_2(Z_X, J_T). \tag{4}$$

Such a choice of derivatives is motivated by the assumption that time derivatives (P_T, J_T) at a certain point (X, T) characterize changes perpendicular to the biomembrane and gradient Z_X characterizes force along the fiber in the axoplasm. The simplest way to model the forces is using the first order polynomials:

$$F_1 = \gamma_1 P_T + \gamma_2 J_T, \quad F_2 = \eta_1 Z_X + \eta_2 J_T, \tag{5}$$

where $\gamma_i, \eta_i, i = 1, 2$ are coefficients.

These forces can be interpreted as follows. The existence of the P_T in the F_1 expression models the influence of pressure P to the membrane – the growth of P means also outward displacement of the biomembrane but taken into account through the elastic properties of the biomembrane. The second term J_T in F_1 models the influence of the ion current to the mechanical deformation of the biomembrane. Note that the opening of ion channels definitely deforms the biomembrane. The existence of the Z_X in the F_2 expression models the influence of the AP gradient along the axon on the pressure (because there are ions inside the axon which might affect pressure response inside the axon in the presence of the potential gradient along the axon) while the second term J_T regulates pressure dependent on the moving of ions through the membrane including the osmosis, should it to be deemed significant enough effect to be taken into account. Another possible modification of coupling forces is to follow explanations by Terakawa [5]. He stressed that the pressure response might be caused by a potential dependent change in the membrane tension. This means that the sign of the force is to be taken into account, because the increase of the membrane potential leads to the increase of the pressure and also the tension of the membrane and vice versa. Physically it means that the membrane density is decreasing with the increasing membrane tension (adding term $-\gamma_3 Z_T$) and the pressure inside the axon increases with the increasing membrane tension (adding term $+\eta_3 Z_T$). Terakawa estimated the membrane static tension change to be roughly 0.2% in [5]. Consequently, one could also assume that

$$\begin{aligned} F_1 &= \gamma_1 P_T + \gamma_2 J_T - \gamma_3 Z_T, \\ F_2 &= \eta_1 Z_X + \eta_2 J_T + \eta_3 Z_T, \end{aligned} \tag{6}$$

where all the coefficients $\gamma_i, \eta_i, i = 1, 2, 3$ are positive. Whether some additional scaling in the coupling forces like, for example,

$$\begin{aligned} F_1 &= \frac{\gamma_1 P_T}{1 + \mathrm{sign}(P_T)U} + \frac{\gamma_2 J_T}{1 + \mathrm{sign}(J_T)U} - \\ &\quad \frac{\gamma_3 Z_T}{1 + \mathrm{sign}(Z_T)U}, \\ F_2 &= \frac{\eta_1 Z_X}{1 + \mathrm{sign}(Z_X)P} + \frac{\eta_2 J_T}{1 + \mathrm{sign}(J_T)P} + \\ &\quad \frac{\eta_3 Z_T}{1 + \mathrm{sign}(Z_T)P}, \end{aligned} \tag{7}$$

might be needed, is an open question. The idea behind such a scaling can accent the changes in positive (increasing) or negative (decreasing) direction from the equilibrium of variables under consideration. However, it should be noted that Terakawa assumed the 'potential-dependent change in membrane tension' to be quadratic [5] when demonstrating that such a mechanism might be used for interpreting the experimental observations.

4. Ensemble of waves

The waves are characterized by the following values of their physical parameters: (i) the AP has a resting potential in the axoplasm about -60 to -80 mV,

the AP increase (amplitude) is about 100-110 mV, its duration about 1 or less ms, its velocity depends on the diameter and varies from 10 to 110 m/s (estimates by many authors), the AP has an overshoot responsible for the refractory period; (ii) the PW has a value of about 5 mPa [5]; (iii) the TW has a value about 1-2 nm [5, 15]. Based on measurements, the AP has an asymmetric shape with an overshoot with respect of the resting potential, the PW has a uni-polar shape with a possible overshoot, the TW has a bi-polar shape which corresponds to a uni-polar LW. However, the experimental results under various conditions may differ from these estimations.

It must be emphasized, that in the present paper the results are obtained by solving the model equations in the dimensionless form (see [7, 20] for details) and moreover, the graphs are normalized against the maximum positive amplitude of the individual waves for the sake of being able to visually compare waves which can be of different amplitudes. It means that quantitative characteristics are overlooked in favor of focusing on qualitative aspects of the solutions.

For presenting the solutions of the proposed mathematical model the system of equations (Eqs (1), (3), (2)) is solved numerically using pseudospectral method. Here the numerical method is summarized briefly and for more details the reader is referred to [8, 21] and references therein.

Initial and boundary conditions. A sech^2–type localized initial condition is used. As the pseudospectral method is used for numerical solving, the boundary conditions must be periodic. The initial and boundary conditions are the following:

$$
\begin{aligned}
&Z(X,0) = Z_0 \mathrm{sech}^2 B_o X, \quad Z_T(X,0) = 0,\\
&Z(X,T) = Z(X + 2Lm\pi, T), \quad m = 1, 2, \ldots,\\
&J(X,0) = J_0 \mathrm{sech}^2 B_o X, \quad J_T(X,0) = 0,\\
&J(X,T) = J(X + 2Lm\pi, T), \quad m = 1, 2, \ldots,\\
&U(X,0) = 0, \quad U_T(X,0) = 0,\\
&U(X,T) = U(X + 2Lm\pi, T), \quad m = 1, 2, \ldots,\\
&P(X,0) = 0, \quad P_T(X,0) = 0,\\
&P(X,T) = P(X + 2Lm\pi, T), \quad m = 1, 2, \ldots,
\end{aligned}
$$

where Z_0 and J_0 are the initial amplitude for the AP and ion current respectively, B_o is the initial pulse width and L is the number of 2π sections in the space domain.

Numerical scheme. The discrete Fourier transform (DFT) based pseudospectral method (PSM) [see 8, 21, 22] is used for numerical solving of the system of governing equations. Normally the PSM algorithm is intended for $u_t = \Phi(u, u_x, u_{2x}, \ldots, u_{mx})$ type equations where all time derivatives are on the left hand side and all spatial derivatives on the right hand side. However, there is a mixed partial derivative term $H_2 U_{XXTT}$ in Eq. (2) and as a result some modifications are in order. In a nutshell one has to introduce a new variable $\Phi = U - H_2 U_{XX}$ and after that, making use of properties of the DFT, it is possible to express the variable U and its spatial derivatives in terms of the new variable Φ. For the details on the numerical scheme as used here, see [21] (appendix and references therein).

Coefficients. The parameters for the governing equations and numerical scheme are taken as follows. First, in the FHN-type Eq. (1): $D = 1$, $\varepsilon = 0.01$, $a_1 = 0.2$, $a_2 = 0.2$, $b_1 = -\beta_1 U$ and $b_2 = -\beta_2 U$ where U is the solution of Eq. (2) and $\beta_1 = \beta_2 = 0.05$. For the initial conditions $Z_0 = 2$, $J_0 = 0.005$ and $B_0 = 1$, where Z_0 and J_0 were the initial amplitudes and B_0 was the sech^2–type pulse width. Second, in the iHJ model Eq. (2): $N = -0.05$, $M = 0.02$, $H_1 = 0.2$, $H_2 = 0.8$ and $c^2 = 0.144$ unless noted otherwise. For the pressure wave Eq. (3) we have $c_f^2 = 0.09$ and $\mu = 0.01$. The coefficients for the coupling forces are taken as $\gamma_1 = 0.001$, $\gamma_2 = 0.001$, $\gamma_3 = 0.0001$, $\eta_1 = 0.001$, $\eta_2 = 0.01$, $\eta_3 = 0.02$ unless noted otherwise. For the numerical scheme the number of spatial grid points is taken as $n = 2^{12}$, $L = 256$ and the solution is integrated up to the final dimensionless time of $T_{final} = 1600$.

Numerical solutions. An example of an ensemble of the solutions of the model Eqs (1) – (3) can be seen in Fig. 3 where in the top panel a solution corresponding to the coupling forces with two terms (5) and in the bottom panel a solution corresponding to

the coupling forces with three terms (6) are depicted. The velocities are chosen so that the AP (Z) is the fastest signal, followed by the pressure response PW (P), followed by the LW (U). It should be mentioned that technically the system is robust enough to allow using arbitrary velocities, including scenarios where PW, LW or both can propagate faster than the AP. However, based on the experimental observations such a scenario might not be characteristic for the nerve pulse propagation in axons as the AP is assumed to be the main source of the 'driving forces' for other components. As a matter of fact, any signal in the environment will propagate with a velocity which is determined by the properties of the environment (for example, elasticity and density). Equation (2) for LW is conservative in principle if we do not consider the added forces for the coupling allowing the signal to separate from the driving force as far as the velocities are sufficiently different and one is integrating for long enough time. Equation (3) contains a dampening term which brings the separated signal down to zero eventually if the observation time is long enough. In reality, however, the axons have a finite length. Meaning that considering the signal behavior for very long times or after traveling for very long distances is more of a mathematical possibility than something that can be reliably physically interpreted. A minor detail in Fig. 3 which need some explanation is that some small amplitude oscillations can actually propagate faster than the bulk of the LW profile although the velocity of the unperturbed state c is lower than the propagation velocity of the AP. The reason for that is the dispersion in Eq. (2) – velocity c determines the velocity of very low frequency disturbances, however, the limiting velocity of the high frequency disturbances is actually proportional to the ratio H_1/H_2 and in the case of anomalous dispersion type this is higher than velocity c (see [23] for details).

Qualitatively some differences can be noted between the solutions depicted in Fig. 3. The main qualitative difference between using the coupling force with two terms (top panel) and with three terms (bottom panel) is the overshoot for the PW (P) – in the case of only two coupling force terms this is practically absent while for the three component coupling force there is a clear overshoot. The solution with three coupling force terms is qualitatively closer to the experimental observations [5]. The second qualitative difference is a more prominent sign of emergence of the soliton-train like structure for the LW (Fig. 3 bottom panel) which can be seen even clearer after integrating for longer time and picking the lower velocity for the unperturbed state (see Fig. 4 top panel). The rest of the differences in Fig. 3 are more quantitative than qualitative like the width of the AP (the two-component AP is narrower than the three-component AP), the AP overshoot (the three-component has slightly larger overshoot than the two-component coupling force), the shape of the pressure profile (the two-component is sharper and narrower (Fig. 3 top panel) than the pressure profile

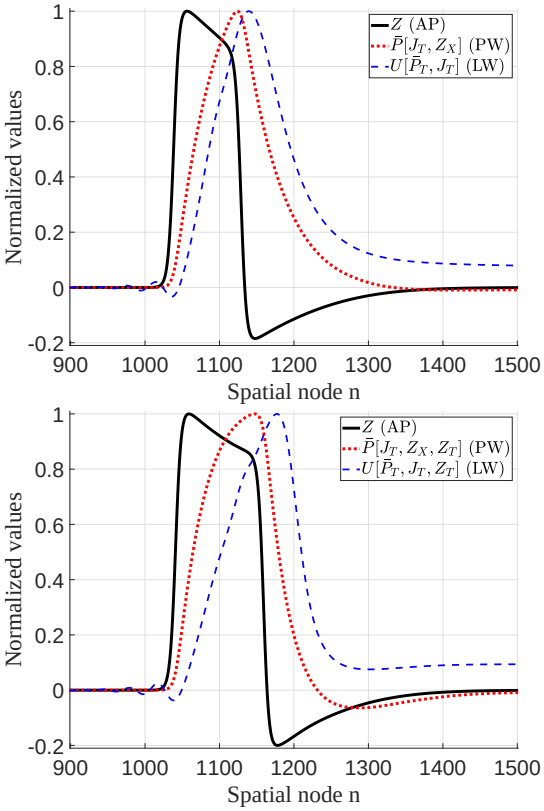

Figure 3: Example solutions of the model system at $T = 1000$. Top panel: $\gamma_3 = \eta_3 = 0$, bottom panel: $\gamma_3 = 0.0001; \eta_3 = 0.02$. All the solutions are propagating from the right to the left.

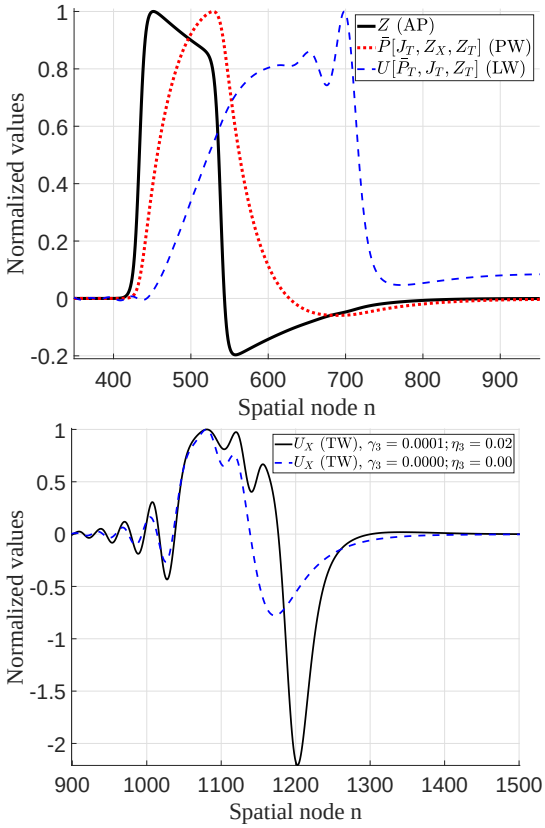

Figure 4: Top panel – solitonic behavior of the solution of Eq. (2) at $T = 1600$ with parameters $c^2 = 0.130; \gamma_3 = 0.0001; \eta_3 = 0.02$. Bottom panel – transverse displacements TW corresponding to the LW profiles shown in Fig. 3 at $T = 1000$. All the solutions are propagating from the right to the left.

for the three-component coupling force (Fig. 3 bottom panel). In addition, it should be stressed that what is usually measured in the experiments is not the LW shown in Fig. 3 but actually the TW (proportional to the U_X). In the presented case the TW what is calculated from the LW is qualitatively similar to what can be observed experimentally (see Fig. 4 bottom panel against measured results [15, 24, 25]).

Returning briefly to the formation of the soliton train the following must be noted. It is known [26] that the pulse–type solution of Eq. (2) describing the LW may lead to the emergence of soliton trains. In the simulations of the wave ensemble over a long time period, such a tendency can be seen while the LW generated by the corresponding contact forces shows the initial stage of changes in the pulse type LW before the emergence of a soliton train (see Fig. 4 top panel). This process is probably not significant for regular signaling in nerves.

5. Discussion

The calculations described above demonstrated that the proposed hypotheses work. Although the model is robust, it serves as a proof of concept in mathematical terms. It is clear that the single processes of signal components (AP, PW, LW, TW) are pretty well studied starting from the pioneering works of Hill [27], Hodgkin [28] and Tasaki [15] until recent ideas how the biomembranes respond to mechanical disturbances [19]. Here an attempt is made to unite all the single mathematical models into a coupled system. Leaving aside the discussions on biophysical nature of coupling (see [4, 5, 14], etc) but relying on qualitative effects, we proposed here the coupling forces to depend on changes of AP, PW or ion current J (see Eqs (5) and (6)). These coupling forces must be bi-polar in order to keep the energetical balance of the whole ensemble and this is realized through the gradients or time derivatives of pulse-like signals. The measurements of TW and PW(experimental studies of Terakawa [5]; Tasaki [15], etc) have demonstrated also a bi-polar shape. From mechanics it is known that the transverse displacements of a rod are related to the longitudinal displacements [29]. This means that a derivative of a pulse-like longitudinal displacement will cause a bi-polar transverse displacement or vice versa, an integral of a bi-polar transverse displacement gives a pulse-like longitudinal displacement. It has been demonstrated (Fig. 3) that the generated LW modeled by the iHJ equation indeed has a pulse-like structure. Calculating the TW from the LW means actually that the elasticity of the biomembrane has been taken into account together with the dispersive properties of a cylindrical wave-guide. Note that Eq. (2) takes also the inertia of lipid molecules into account. As a result, in such a way an ensemble of signals is generated by generating an AP with an input above

the threshold. The simulations demonstrate that the AP has a typical form with an overshoot [9], the pressure wave PW is a pulse-like but has also an overshoot [5], the transverse wave TW has a typical bi-polar shape [5] which is caused by a pulse-like longitudinal wave LW [19]. The model described above uses the modified FHN model (1) for calculating the AP. Certainly, a more sophisticated Hodgin–Huxley (HH) model can be used but it will need many physical coefficients to be fixed. The main conditions in modeling, however, are (i) the correct shape of the AP and (ii) the coupling does not depend significantly on the nature of the mathematical model. The FHN model serves well this idea. However, as far as the FHN model includes only one ion current, then using a more sophisticated model with several ion currents may give a possibility to account for the changes in ion currents responsible, for example, for anesthesia. In addition, changing the coefficients of forces may model the pathological situations (damage, for example) and the simplest way to take the temperature effects into account is to let the coefficients depend on the temperature. The further experiments should give more information about the coupling forces from a biophysical viewpoint. Another important question is the synchronization of velocities of single components in the ensemble. In our calculations, the leading velocity is the velocity of the AP. We suppose that other components have velocities equal or less of that but again, this assumption needs experimental proof. It is known that in excitable plant cells (*Chara braunii*), the velocities of electrical and mechanical components of a signal are more or less equal [30]. It should be noted that the proposed mathematical model (Eqs (1),(2),(3)) is robust enough to allow modeling situations where pressure and mechanical wave can have propagation velocities greater than the velocity of the AP.

Possibility of experimental verification and calibration. Like all mathematical models describing the natural phenomena there is a number of parameters that require calibration from observations and experiments for the model to be useful in practice. The described model contains three wave components and coupling forces between the components. First, the FHN model describes the AP and a single abstracted ion current which are, in theory, directly measurable from the experiments. If preferred and experimentally more convinient, the FHN model can be substituted by the HH model or the HH model can be used to calibrate the FHN model. The iHJ model (2) is based on experimental observations by Heimburg and Jackson [19]. The added dispersive term H_2U_{XXTT} takes into account the inertia of lipids and can be found by measuring the propagation speed of different frequency signals in the lipid bi-layer [31]. The limiting velocity for high frequencies is determined by the ratio of H_1/H_2 while the slope of the dispersion curve as the frequency increases is a function of H_2. It must be stressed that Eq. (2) is in terms of longitudinal density change while in experiments normally a transverse displacement is measured. Drawing inspiration from the continuum mechanics the longitudinal density change in a point can be found as a time integral of the transverse displacement in that point. For the pressure a simple wave equation with an added viscous dampening term is used meaning that all that is needed is the sound velocity and viscosity coefficient in the axoplasm. The real problem is determining the exact nature of the coupling forces. Measuring the individual force components is difficult, at best, and most likely only the collective influence of all the relevant forces on a given process can be measured. One should keep in mind that the coupling forces in the proposed model are, in essence, the time integrals of a driving process at a fixed spatial point. As the signal is generated at a given point the driving signal itself moves along the axon. For determining the influence and even existence/relevance of the individual driving forces several experiments would be needed where different driving factors are suppressed.

6. Final Remarks

Since Galileo Galilei we know that the Book of Nature is written in the language of mathematics. Contemporary system biology has followed this idea and is using not only mathematical language but also *in silico* simulations of biological processes [10, 11].

Theoretical considerations must certainly be validated by experiments but theory could give hints how the system as a whole works. Here we have been working on the integrative level [12] trying to unite the single elements into a working model. In this paper, the hypotheses made in modeling are clearly formulated and the nature of coupling forces analyzed. The *in silico* simulation has shown that mathematically the coupled system can demonstrate main qualitative features of measured signals (AP, PW, TW) in nerve fibers. Contrary to the rigid statements in favor of one model or another, our viewpoint is flexible trying to connect the phenomena which characterize the processes in nerve fibers using the language of mathematics.

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