Proceedings of the Estonian Academy of Sciences,
2019, **68**, 3, 276–283
https://doi.org/10.3176/proc.2019.3.05
Available online at www.eap.ee/proceedings

MATHEMATICAL PHYSICS

Criteria for modelling wave phenomena in complex systems: the case of signals in nerves

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Received 1 March 2019, accepted 18 March 2019, available online 5 June 2019

Abstract. The propagation of signals in nerves is characterized by complexity where the interactions between the electrical signal and accompanying mechanical and thermal effects must be taken into account. That is why in the modelling of wave phenomena the knowledge from physiology, physics, and mathematics must be cast into a whole. In this paper the wave phenomena in nerves are characterized from the viewpoint of complexity and interdisciplinarity, followed by the analysis of principles and criteria in the modelling of biological systems. The central part is the description of the step-by-step approach in building up a coupled mathematical model of signal propagation in axons. Attention is paid to the coupling forces which link the single waves into an ensemble. The mathematical description of the model is presented in the Appendix.

Key words: interdisciplinarity, action potential, mechanical and thermal effects, interactions.

1. INTRODUCTION

Modelling in science means building a description of a system which could help to understand the reality in an abstract way. The conceptual models aim at better understanding of the object or process, the mathematical models use the language of mathematics for the description of reality. The strength of mathematics in modelling is emphasized by Stewart [36] by listing the equations "that changed the world". The growing understanding of the complexity of the world has influenced significantly the ideas of modelling because one should be aware of possible unpredictability, bifurcations, the role of interactions, the emergence of novel structures, etc. [15,30]. The problem of causality needs clear analysis while possible simplifications of a model may also overlook the essential links and the intuition often fails. This means that the modelling in complex systems needs careful analysis of criteria with a clear set of assumptions and hypotheses.

In what follows attention is focused on a special field of systems biology – the propagation of nervous signals. Although traditionally nervous signals are analysed from the viewpoint of physiology, the *in silico* modelling based on mathematics is gaining more and more importance in systems biology and also in studies on nervous signals [31]. So the studies on signal propagation in nerves should be based on many disciplines involving physiology, mathematics, and also physics and chemistry. In other words, these studies are at the interface of the physical and life sciences.

Further we try to systemize the ideas and structures of mathematical models by describing nerve pulse propagation in axons with accompanying mechanical and thermal effects. In general, focus is on wave phenomena in complex media. We shall first describe briefly the interdisciplinarity in the analysis of waves in mechanics [8,9] and then continue with systems biology. Summing up, general principles characterizing the wave phenomena in complex media are formulated. A wave model for the action potential (AP) serves as an example explaining the general principles.

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In Section 2 the problems of modelling are discussed from the viewpoint of interdisciplinarity in complex systems. Section 3 is devoted to the principles and criteria in the modelling of biological systems. In Section 4, the central part of this paper, the modelling of the AP and accompanying effects is analysed. Section 5 provides general conclusions reflecting the specific features of modelling the signals in nerves from the viewpoint of complexity science. The system of coupled equations is presented in the Appendix.

2. COMPLEXITY AND INTERDISCIPLINARITY

Complexity means that the systems are composed of smaller subsystems or constituents which are coupled to each other. The coupling means interactions between the constituents and due to interactions new qualities of the system as a whole may emerge [15,30]. The interactions are, as a rule, nonlinear and that is why the properties of a complex system cannot be summed up by the properties of the constituents. In dynamical processes the interactions are of wave–wave, wave–field or wave–internal structure types [8]. The proper modelling of such interactions is crucial and casts significant insight into understanding the phenomena.

In general terms, models represent phenomena or processes. Leaving aside the fictional models like for example the Bohr model of the atom or the Schrödinger cat, we discuss here the *mathematical models* of real processes. This means describing the process in mathematical terms. The main task is to first determine the variables in the process and then to model how these variables are linked to each other and how they are changing in space and time. Proper models should be able to explain the existing observations and to predict future observations with certain accuracy. Experiments *in silico* with mathematical models are cheaper than natural experiments.

The mathematical cornerstones in the modelling of processes are the classical equations of *mathematical physics*: hyperbolic, parabolic, and elliptic equations. These partial differential equations are able to model the wave-like and diffusion-like dynamical processes and static equilibrium states, respectively. The standard forms of these equations correspond to simple ideal cases and are usually modified for describing the more complicated cases (for wave equations, see [8,24]).

In *mechanics* the conservation laws of mass, momentum, moment of momentum, and energy together with entropy inequality govern all the processes [16]. In solid mechanics one is mostly interested in how the deformation and stress in a structure are changing under the given impact and environment. The scale is important and thermodynamics governs the processes. The basis for modelling is related to Newton's laws which also describe the causality – for every action there is an equal and opposite reaction. The importance of forces in a system follows also from Newton's laws. An excellent example is the wave equation with interaction forces derived by Maugin [24] using the concept of the Eshelby stress. It is not surprising that waves in solids and in fluids are, in principle, described by similar mathematical equations [9], although often written in different forms. When the processes with temperature changes are analysed, then, given the diffusive character of heat production, the problem is how to combine wave-type and diffusion-type equations. In the modelling of waves in microstructured materials the concept of internal variables enables overcoming this difficulty [2]. The overview of the complexity and interaction of waves and fields characteristic of engineering and natural sciences is given by Engelbrecht [8].

The processes are much more complicated in *life sciences*, being related to the functioning of species and to studying the role of their organs and their building blocks over a large scale. In this context systems biology uses a holistic approach involving the interactions within biological systems and, according to Kohl et al. [21], is more an approach to bioresearch. Nevertheless, it takes account of the functional integration of parts into a whole involving physiological, physical, and chemical processes. Mathematical modelling and extensive use of *in silico* analysis helps to understand the complexity and the functions of the biological entities [21]. Integrative biological modelling involves many areas, ranging from organs and organ systems to smaller molecular and atomic scales [27]. The scales are hierarchically coupled and that is why modelling across the different scales is important. It is stressed that the interactions between the components are to be taken into account and the biological processes are forced to obey physicochemical principles (conservation laws). It means a clear need for interdisciplinarity involving physics and mathematics into studies of biological processes. The physiological modelling nowadays is very much following this line because of "the increasing demand in quantitative assessment of element inter-relations in complex biological systems" [17, p. 1099].

One of the characteristic features of complex systems is nonlinearity that has many consequences: nonadditivity, possible unpredictability, multiple equilibrium states, etc. [15,30]. Actually, the methods and principles of "nonlinear science" are clearly interdisciplinary and have opened many possibilities in other fields of research [35]. Indeed, it is not only the chaos theory and nonlinear dynamics, it is also condensed-matter physics, chemical, and biochemical phenomena, fluid dynamics, nonlinear biology including neuroscience, etc. What must be especially stressed is the causality in nonlinear systems. According to Scott [35], the causality must be analysed with care because the relations between the cause and effects in systems with multiple equilibria need special attention.

To sum up, complexity is characteristic of many fields of studies and involves many common fundamental ideas. This is the reason why *interdisciplinarity* plays such a leading role in contemporary research: physical sciences, biological sciences, social sciences, etc. [34].

Further below we use interdisciplinary ideas for building a mathematical model for signals in nerve fibres accounting for electrical, mechanical, and thermal effects.

3. PRINCIPLES AND CRITERIA IN BIOLOGICAL SYSTEMS

In addition to signatures of complexity of physical systems [15,30], in biological systems one should take several conceptual foundations into account [32]. In short, one can list several issues characteristic of biological systems [11]: (i) there is a need for energy exchange with the surrounding environment and between the constituents; (ii) many chemical reactions and transfer mechanisms that are often characterized on the molecular level are involved; (iii) different time scales, adaptivity, and hierarchies should often be taken into account; (iv) nonlinearities, diffusive effects, excitability, spatio-temporal coupling, etc. may have a significant role. All that may give rise to mathematical models where the synchronization of time scales is needed. Criteria for deriving such models are described by Noble [31], starting from the descriptive level collecting the data. The next level is integrative – how all elements or constituents interact. This is the most important question to answer in modelling because in many cases there are still guesses based on experimental results. As a real signature of complexity, interactions lead to a system which works as a whole. The final level of criteria [31] is explanatory and predictive.

At the integrative level hierarchies characteristic of biological systems must be distinguished [7,9,27]. First, there are structural hierarchies which involve strong dependence across physical scales of biological structures. The fundamental sequence of the structural hierarchy is: atom – molecule – cell – tissue – organ – human. At the tissue level one can again distinguish the structural hierarchy. For example, the structural hierarchy in the heart has many levels and sublevels [27]. One sublevel is related to the contraction: sarcomeres – myofibrils – fibres – myocardium – contraction. Second, one must stress the functional hierarchy which is related to various dynamical processes across the multiple scale. For the same example of heart contraction the functional hierarchy is: oxygen consumption – energy transfer – Ca^{2+} signals – cross-bridge motion – tissue motion.

The existence of many scales in structural hierarchies of biological systems can be compared with the microstructured materials in continuum mechanics [9]. In order to model the behaviour of the macrostructure, the microstructure is described by the concept of internal variables [25]. This concept takes into account that besides observable (measurable) variables there are unobservable internal variables describing the behaviour of the internal structure. These variables compensate our inability to precisely describe the properties of a microstructure. The governing equations of internal variables are derived from thermodynamical considerations [2,25]. As shown in [26] it is possible to use the formalism of internal variables also in the analysis of the Hodgkin–Huxley (HH)and FitzHugh–Nagumo (FHN) equations. Indeed, the "phenomenological" variables in the HH equations [19] or the "recovery" variable in the FHN equation [29] can be treated as internal variables. In addition, the concepts of internal variables and functional hierarchy have been combined for the description of the active stress in myocardium, starting from the Ca^{2+} signal as an internal variable which influences the next-order internal variable – the number of activated cross-bridges, followed by the next-order internal variables – the number of force producing cross-bridges [14]. Combining the ideas of continuum mechanics with the modelling of biological systems is a clear sign of interdisciplinarity.

An important notion in science and philosophy is the notion of paradigm which means a distinct set of thought patterns. The contemporary understanding of paradigms in science goes along the ideas of Kuhn [22]. According to him, the normal evolution of science is based on a widely accepted framework of certain understandings using the well-known experiments and theories. Many paradigms are known in biology, such as the paradigms of evolution (C. Darwin), blood circulation (W. Harvey), etc. From the paradigms in biophysics, Noble [32] stresses the HH paradigm on the electro-physiological nature of nerve signals. This viewpoint is supported by Drukarch et al. [5]. However, Hodgkin [20] himself has noted the need for thinking about the physical basis of the action potential paying attention also to unexplained observations which have been neglected for one reason or another. The criticism of the HH model has brought over the ideas of the mechanical character of the nervous signal by Heimburg and Jackson [18]. Currently there is no consensus about the role of electrical and non-electrical manifestations but the discussion clearly indicates the essence of interdisciplinarity in modelling. In this context there is really a need "to frame a theory that incorporates all observed phenomena in one coherent and predictive theory of nerve signal propagation" [1, p. 112].

To sum up, multilevel analysis, working at the interface of physiology, physics, and mathematics, and mastering *in silico* simulations are all tools for the better understanding of biological processes. The best way is not to exaggerate the role of one or another approach but to combine them into a whole. The mathematical modelling is a powerful tool to understand the reality because "to think is to model" [21, p. 29].

4. MODELLING OF AN ACTION POTENTIAL

Further the ideology for modelling signal propagation in nerve fibres is presented using the interdisciplinary approach. The modelling is performed at the interface of physiology, physics together with thermodynamics, and mathematics.

Here we follow the HH paradigm based on contemporary understandings on axon physiology [3,4] – the

action potential (AP) carries information and is accompanied by other effects. As signal propagation is related to wave motion, the basic models of the electrical pulse are wave-type governing equations. Both the basic HH and simplified FHN equations are derived from the telegraph equations neglecting the inductance. The metabolic pump generates the voltage gradient that is responsible for driving the AP along the axon. The existence of ion currents in the process means that the governing equations are of the diffusion-reaction type which involves the finite velocity of an AP.

The ideas from continuum mechanics are used for modelling the mechanical effects in the surrounding biomembrane and axoplasm. Longitudinal waves in the biomembrane (lipid bilayer) are modelled by the wave equation (conservation of momentum). Heimburg and Jackson [18] have modified the wave equation with special nonlinearities taking into account that the velocity depends on changes in density which could be treated as longitudinal displacement. These displacement-type nonlinearities are different from gradient-type nonlinearities in conventional solids [7]. Heimburg and Jackson also added a dispersive term which reflects the elasticity of the biomembrane. Based on ideas of wave motion in microstructured solids, the Heimburg–Jackson model has been modified by an additional dispersion term which reflects the inertia of the microstructure, i.e., inertia of lipid molecules [12]. This improved Heimburg–Jackson model follows the general understanding of continuum mechanics – all effects of the same order should be taken into account, and in a "microstructured" bilayer the elasticity and inertia of the internal structure must both be taken into account. In some sense, the biomembrane acts as a wave-guide (cf. [33]). The pressure wave in the axoplasm which can be modelled like a viscous fluid could be governed by Navier–Stokes equations. However, as it has been shown experimentally that the amplitude of a pressure wave is very small [40], the usual wave equation with a viscous term added will be sufficient for simulations. For modelling the measured transverse displacements [38] again the idea from mechanics is used. The theory of rods states that longitudinal and radial transverse displacements have a functional link – the transverse displacement is a space derivative of the longitudinal displacement [33].

Finally, the temperature changes accompanying the propagation of an AP should obey the principles of thermodynamics. Consequently the diffusion-type models should be constructed and Fourier's law must be satisfied.

In such a way an electrical signal and accompanying effects are modelled by equations which can be deduced from the classical equations of mathematical physics (see Section 2) by using the interdisciplinary ideas from physiology, physics, and mathematics. However, the crucial question is now: how are these waves and accompanying effects coupled? In terms of complexity science it means that the interactions must be modelled as precisely as possible in order to get a general picture. According to a recent state-of-art overview by Drukarch et al. [5], there is no general consensus about the possible mechanisms of interactions.

Starting from physical considerations, the balance of momentum involves forces. Apart from the classical wave equation, the additional forces reflect the possible influences from the environment, like the modified wave equation in terms of the Eshelby stress modelling waves in microstructured materials [24]. Following this idea in the analysis of nerve signals, the additional forces should be added in all the single equations modelling the separate waves. This is actually the requirement from the viewpoint of the balance of momentum. Note that the ion currents are added to the HH or FHN equations in order to satisfy the physiological considerations.

The next question is about the functional form of these forces. Here a strong hypothesis was introduced by Engelbrecht et al. [13]: the mechanical waves in the axoplasm and surrounding biomembrane are generated due to changes in electrical signals (the AP or ion currents).

In mathematical terms, the changes mean non-zero space or time derivatives. Note that, in principle, the electrical signals are pulse-type, i.e., uni-polar (leaving aside the refractory part of the AP). It means that their derivatives are bi-polar and in this way energetically balanced. Supposing a uni-polar force leads to the energy pump which is not acceptable.

As a proof of the concept, a general coupled model where the AP and the mechanical waves in the axoplasm and biomembrane are united into one system is formulated, completing the mathematical description of the whole process of signal propagation in axons. The overview of basic and derived equations of such a model is presented in the Appendix. The numerical simulations without [10,11,13] and with [37] temperature changes have demonstrated that this model is able to qualitatively explain the observations obtained experimentally.

5. FINAL REMARKS AND CONCLUSIONS

The consecutive steps of modelling the propagation of an AP were presented in Sections 2–4. These steps are based on mathematical and physical considerations applied to the physiological process following the second level of criteria [31] – the integrative level. As a result, a coupled mathematical model was derived where the interactions have the crucial role. Simulations have demonstrated that based on the HH paradigm, widely used in axon physiology, a wave ensemble is generated which has primary (i.e., wave-like) and secondary (i.e., not wave-like) components. The primary components are the AP itself, the pressure wave in the axoplasm, and the longitudinal wave in the surrounding biomembrane. The secondary components are the transverse displacement of the biomembrane and temperature change, which are not governed by wave-type equations. The hypothesis that the interaction forces between the primary components and also in the diffusion equation for temperature change

depend on changes in variables and not on their absolute values is of fundamental importance. This gives also the insight into the causality but surely more experiments are needed in order to establish the quantitative parameters and the physical mechanisms which have a role in these interactions.

The ideas from interdisciplinarity permitted us to improve the accuracy of model equations. For example, when the internal inertia of a biomembrane in the improved Heimburg–Jackson equation is accounted for, the width of a solitary wave may be much narrower and closer to physiological reality [12]. Another mathematical feature is the bi-polarity of coupling forces for ensuring the energetically balanced solution. As the AP is described by the FHN model, the activation and inactivation of sodium and potassium currents must be taken into account in order to improve the predictive power of this model. In the present model, the aim was to get a correct shape of an AP which was then used in interaction forces.

The authors are of the opinion that such an interdisciplinary approach could give a better insight into the interaction of effects accompanying the propagation of an AP and goes in line with challenges in systems biology [32]. In general terms, as pointed out in the Report of the US National Research Council [41], a mathematical model can highlight basic conceptions and identify key factors or components of a biological system. In addition, models enable formalizing the intuitive understandings and "link what is known to what is yet unknown". The modelling of the AP with accompanying effects, described above, serves clearly these ideas at the frontiers of the interface between biology and mathematics. The ensemble of waves includes electrical and mechanical components together with the accompanying temperature change. The ensemble is energetically stable but the energy transfer between the components needs further detailed analysis after the mechanisms of coupling are proved by experiments.

ACKNOWLEDGEMENTS

This research was supported by the European Union through the European Regional Development Fund (Estonian Programme TK 124) and by the Estonian Research Council (project IUT 33-24). The authors would like to thank the reviewers for constructive remarks and interesting questions. The publication costs of this article were covered by the Estonian Academy of Sciences.

APPENDIX

BASIC EQUATIONS

The wave ensemble in an axon has primary and secondary components. The primary components are governed by wave-type equations: the action potential (AP), the longitudinal wave in the biomembrane (LW), and the pressure wave (PW) in the axoplasm. All the primary components possess finite velocities. The secondary components have no independent velocities: the transverse displacement (TW) of the biomembrane is derived from the LW and the temperature (Θ) change is governed by the diffusion process. Below the corresponding governing equations are presented. The starting wave equations are also described for primary components.

Action potential. The AP is an electric signal and the derivation starts from the hyperbolic telegraph equations. Following Lieberstein [23], these equations are the following:

$$\begin{aligned} \pi a^2 C_a \frac{\partial v}{\partial t} + \frac{\partial i_a}{\partial x} + 2\pi a I = 0, \\ \frac{L}{\pi a^2}\frac{\partial i_a}{\partial t} + \frac{\partial v}{\partial x} + \frac{R}{\pi a^2} i_a = 0. \end{aligned} \tag{1}$$

Here v is the potential difference across the biomembrane, i_a is the axon current per unit length, I is ion current density, C_a is the axon self-capacitance per unit area per unit length, L is the axon-specific self-inductance, and R is the axon-specific resistance. As usual, x and t are space coordinate and time, respectively, and a is the radius.

It is possible to rewrite system (1) in the form of one second-order equation:

$$\frac{\partial^2 v}{\partial x^2} - LC_a \frac{\partial^2 v}{\partial t^2} = RC_a \frac{\partial v}{\partial t} + \frac{2}{a} RI + \frac{2}{a} L \frac{\partial I}{\partial t}. \tag{2}$$

In the electrophysiology of axons it is assumed that inductance L is so small that it can be neglected. Then a parabolic equation follows from hyperbolic equation (2):

$$\frac{\partial^2 v}{\partial x^2} = RC_a \frac{\partial v}{\partial t} + \frac{2}{a} RI. \tag{3}$$

Equation (3) is the basis for the HH model as well as for the FHN model. If inductance is not neglected, it is possible to derive from system (1) or equation (2) an evolution equation [6] which is a one-wave equation. The corresponding stationary profile is described then by a Liénaŕd-type equation.

In the HH model [19] the ion currents involve three phenomenological variables: m,h,n denoting sodium activation, sodium inactivation, and potassium activation. These variables are governed by reaction equations where the relaxation time and equilibrium values are determined by expressions obtained to match experiments. Further in our model we follow the FHN model [29] where only one general ion current is taken into account.

Leaving aside the details of derivation, the FHN equation in our model in dimensionless variables is the following:

$$\begin{aligned} Z_T = DZ_{XX} + Z(Z - A_1 - Z^2 + A_1 Z) - J, \\ J_T = \varepsilon(A_2 Z - J). \end{aligned} \tag{4}$$

Here Z is potential, J is the abstracted ion current, A_1, A_2 are activation coefficients, D and ε are coefficients. As ion channels can in principle be activated electrically and mechanically [28], it is possible to use $A_1 = a_1 + b_1$ and $A_2 = a_2 + b_2$, where a_i, b_i are "electrical" and "mechanical" activation coefficients. In the present model the "mechanical" activation coefficient $b_i = -\beta_i U$, where β_i are coefficients and U is membrane density change introduced below. It can be noted that b_i could include also influence form the pressure inside the axon which could also be considered as "mechanical" influence. Here and further, indices X and T denote the differentiation with respect to space and time, respectively.

Longitudinal wave in the biomembrane. The starting point for deriving the governing equation for the LW is the wave equation in terms of the density change $\Delta\rho = u$ [18]:

$$\frac{\partial^2 u}{\partial t^2} = \frac{\partial}{\partial x}\left(c_b^2 \frac{\partial u}{\partial x}\right), \tag{5}$$

where the velocity c_b depends on variable u:

$$c_b^2 = c_0^2 + pu + qu^2. \tag{6}$$

Here p, q are coefficients satisfying $p < 0$, $q > 0$ [18]. In order to obtain a soliton-type solution, a dispersion term reflecting the elasticity of the biomembrane is added. Engelbrecht et al. [12] showed that for such a "microstructured" bi-layer the inertia of the microstructure must also be added.

The final form of the governing equation for the LW in dimensionless variables is

$$U_{TT} = c^2 U_{XX} + NUU_{XX} + MU^2 U_{XX} + N\left(U_X\right)^2 + 2MU\left(U_X\right)^2 - H_1 U_{XXXX} + H_2 U_{XXTT} + F_1\left(Z,J,P\right). \tag{7}$$

Here U is the longitudinal density change, P is the pressure in the axoplasm, c is the dimensionless sound velocity of the unperturbed state in the lipid bi-layer, M and N are nonlinear coefficients, H_1 and H_2 are dispersion coefficients (note that the term with H_1 describes elasticity and the term with H_2 describes inertia of the microstructure). The force $F_1(Z,J,P)$ describes the influence on the LW from the AP and PW. According to the hypothesis (see Section 4), we use

$$F_1 = \gamma_1 P_T + \gamma_2 J_T - \gamma_3 Z_T, \tag{8}$$

where γ_i are the coupling coefficients.

Pressure wave in the axoplasm. Pressure wave PW is derived by the usual dimensionless wave equation with additional force and viscosity terms

$$P_{TT} = c_f^2 P_{XX} - \mu P_T + F_2\left(Z,J,T\right). \tag{9}$$

Here P is pressure, c_f is sound velocity in the axoplasm, and μ is the dampening coefficient. Force F_2 is determined by

$$F_2 = \eta_1 Z_X + \eta_2 J_T + \eta_3 Z_T, \tag{10}$$

where η_i are coupling coefficients.

Transverse displacement. Transverse displacement TW belongs to the secondary components of an ensemble. As explained in Section 4, TW is related to the longitudinal deformation

$$W = kU_X, \tag{11}$$

where W is TW and k is the coefficient. Note that in the theory of rods [33] it is related to the Poisson ratio.

Temperature change. We propose to use the diffusion (parabolic) equation for calculating temperature Θ. In dimensionless form this equation is

$$\Theta_T = \alpha\Theta_{XX} + F_3\left(Z,J,U\right), \tag{12}$$

where α is the combined coefficient determining the diffusion speed for thermal energy in the environment. While presently there is no consensus for the mechanism of heat production, we propose the equation

$$F_3 = \tau_3 Z_T + \tau_4 J_T, \tag{13}$$

where τ_i are the coupling coefficients. Expression (13) is able to produce temperature change [37] qualitatively similar to the Tasaki and Byrne [39] experiment. As temperature change is not governed by a wave-like equation, it can be considered as a secondary component in the wave ensemble like the transverse displacement of the biomembrane.

The system of model equations is solved numerically using the initial condition for governing the AP:

$$Z(X,0) = Z_0 \mathrm{sech}^2 B_0 X, \tag{14}$$

where Z_0, B_0 are constants and Z_0 is above the threshold needed for generating the AP. Other variables have initially zero values (the system is at rest). The results of numerical simulation based on using the pseudo-spectral method are presented in our earlier publications [10,11,13]. The block diagram of the coupled model and numerically calculated profiles of some of the modelled quantities are shown in Fig. 1.

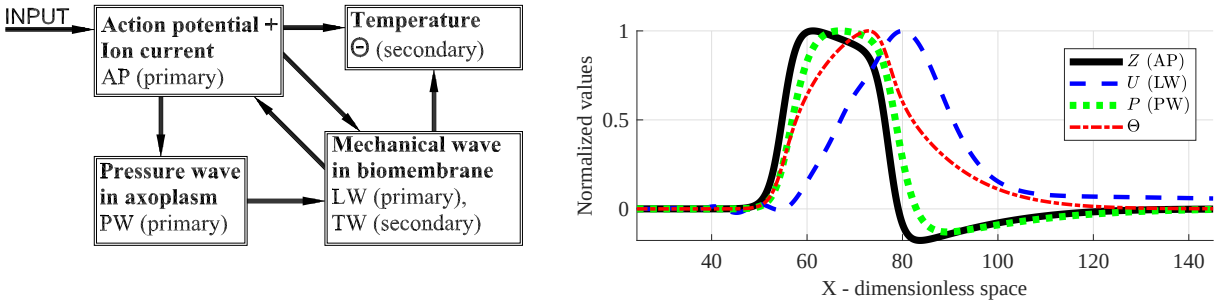

Fig. 1. Left panel – the wave ensemble block diagram. Right panel – action potential Z, pressure P, longitudinal density change U, and temperature Θ left-propagating profiles: an example from [37]. Temperature profile corresponding to the case $F_3 = \tau_3 Z_T + \tau_4 J_T$.

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Lainelevi modelleerimise kriteeriumid komplekssüsteemides: signaalid närvikiududes

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Lainelevi modelleerimisel närvikiududes tuleb arvestada komplekssüsteemide iseärasustega, sest elektriline signaal on interaktsioonide kaudu seotud mehaanikaliste efektide ja temperatuuri muutustega. Seetõttu tuleb ühendada füsioloogia, füüsika ja matemaatika ideed ühtseks tervikuks. Käesolevas artiklis ongi lainelevi analüüsil närvikiudude näitel kirjeldatud kõigepealt vajalikud komplekssüsteemide ja interdistsiplinaarsuse põhimõtted ning siis esitatud bioloogiliste süsteemide modelleerimise printsiibid ja kriteeriumid. Kesksel kohal on närvikius leviva signaali matemaatilise mudeli koostamine samm-sammult, alates üksikute efektide mudelitest kuni nende seostamiseni tervikuks. Suur osa sellises mudelis on kontaktjõududel, mis seovad üksikud lained ansambliks. Mudeli matemaatiline kirjeldus on esitatud lisas.