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Overview of modification ideas on modelling of signals in nerves

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1 Introduction

We have formulated a mathematical model for describing the ensemble of waves in nerve fibres including electrical (action potential AP and ion current(s) J) and mechanical (longitudinal LW and transverse TW waves in the biomembrane and pressure PW wave in the axoplasm) components together with the temperature change Θ. A detailed analysis of the model is given in a monograph by Engelbrecht et al. [18]. Further on, (i) the role of physics in modelling has been described (Engelbrecht et al., [20]) and (ii) how interdisciplinarity has been used for general modelling ideas (Engelbrecht et al., [19]). This approach explicitly defines the physics involved and links the components of an ensemble through established laws. However, in this model up to now, an ideal unmyelinated fibre [27] is considered but the structure of nerve fibres is complicated and the present model must be modified in order to describe better the reality and possible abnormal electrophysiological functions of nerves, i.e., pathological situations.

In this Research Report, attention is paid to describing the complicated structure of nerve fibres, then recent experimental results are analysed and finally, the ideas for further modification of modelling are presented. Appendices A, B, and C are the working overviews of concrete problems.

2 Present model

The details are given by Engelbrecht et al. [18]. All accompanying effects in fibre are generated due to

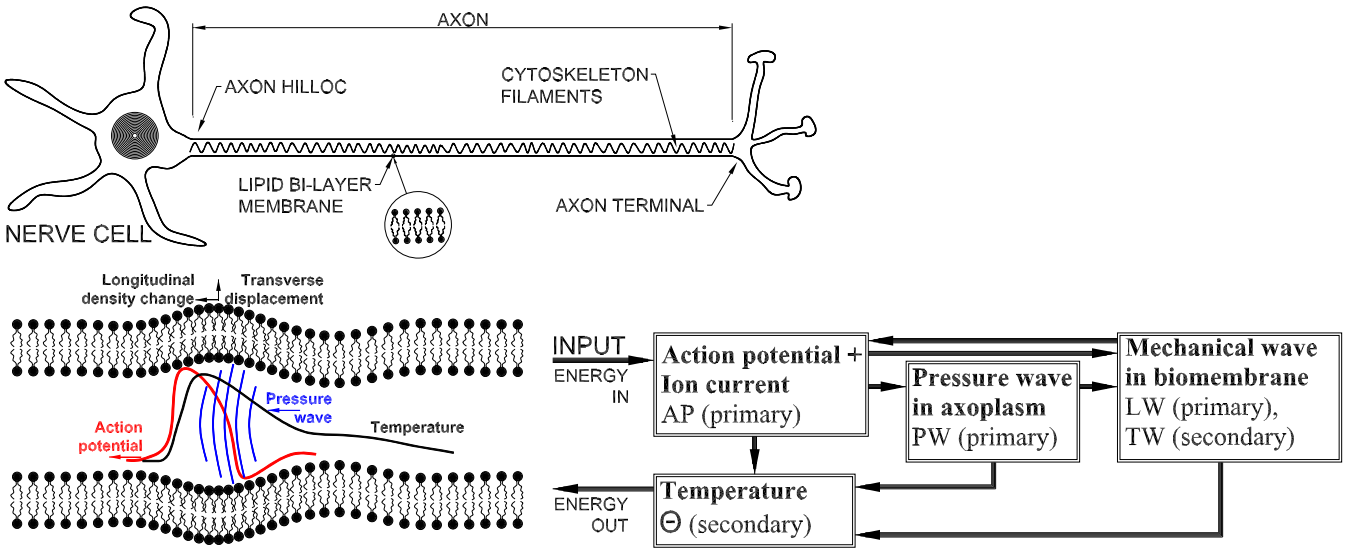


Figure 1: Scheme of the neural cell where the focus is on the axon which is in this context a 1D ideally elastic "tube" with a lipid bi-layer wall (top). Artistic sketch of wave ensemble in the unmyelinated axon (bottom-left). Block diagram of the modelled quantities (bottom-right).

changes in electrical signals (action potential or ion currents) [15]. Emphasis on changes which means the dynamics, not the static value of a given signal is a source of changes within the system.

- the interactions are modelled by the coupling forces between the components of a signal;
- all mechanical waves in the axoplasm and the 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 formalism of internal variables can be used for describing the exo- and endo- thermic processes of heat production;
- not only the influence of an AP on other effects but also possible feedback is considered.

$$Z_T = DZ_{XX} - J + Z\left(Z - [a_1 + b_1] - Z^2 + [a_1 + b_1]\, Z\right);\ J_T = \varepsilon\left([a_2 + b_2]\, Z - J\right),$$

$$P_{TT} = c_f^2 P_{XX} - \mu_1 P_T + F_1(Z, J, U),$$

$$U_{TT} = c_0^2 U_{XX} + NUU_{XX} + MU^2 U_{XX} + NU_X^2 + 2MUU_X^2 - H_1 U_{XXXX} + H_2 U_{XXTT} - \mu_2 U_T + F_2(Z, J, P),$$

$$\Theta_T = \alpha\Theta_{XX} + F_3(Z, J, P, U).$$

$$F_1 = \eta_1 Z_X + \eta_2 J_T + \eta_3 Z_T;\ F_2 = \gamma_1 P_T + \gamma_2 J_T - \gamma_3 Z_T;\ F_3 = \tau_1 Z^2 + \tau_2\left(P_T + \varphi_2(P)\right) + \tau_3\left(U_T + \varphi_3(U)\right) - \tau_4\Omega.$$

Here Z – action potential, J – ion current, ε – the time-scales difference parameter, a_i – "electrical" activation coefficient, b_i – "mechanical" activation coefficient and U – longitudinal density change from lipid bi-layer density model, P – pressure, μ_1 – viscosity coefficient. The F_1 is the coupling term accounting for the possible influence from the AP and TW. Also $U = \Delta\rho$ is the longitudinal density change, c_0 is the sound velocity in the unperturbed state, N, M are nonlinear coefficients, H_i are dispersion coefficients and

μ_2 is the viscous dampening coefficient. Where H_1 accounts for the elastic properties of the bi-layer and H_2 the inertial properties. The F_2 is the coupling term accounting for the possible influence from the AP and pressure wave. Transverse displacement (TW) $W \propto U_X$. Θ – temperature, α – thermal conductivity coefficient. The F_3 is the coupling term accounting for the possible influence from the AP, PW and LW.

In coupling forces for pressure $F_1 = \eta_1 Z_X + \eta_2 J_T + \eta_3 Z_T$ where Z_X presence of charged particles in the presence of potential gradient (along the axon), J_T ionic flows into and out of axon (across the membrane), Z_T possible pressure change as a result of membrane tension changes from electrical field. For improved Heimburg-Jackson $F_2 = \gamma_1 P_T + \gamma_2 J_T - \gamma_3 Z_T$ where P_T possible membrane deformation because of pressure changes (pressure to TW to LW), J_T possible membrane deformation as a result of ionic flows through ion channels, Z_T possible electrically induced membrane tension change. Note the sign, assuming that if tension increases then density decreases. For heat equation $F_3 = \tau_1 Z^2 + \tau_2 (P_T + \varphi_2(P)) + \tau_3 (U_T + \varphi_3(U)) - \tau_4 \Omega$ where $\Omega_T + \epsilon_4 \Omega = \zeta J$ is the evolution of an internal variable [52] and $\varphi_2(P) = \lambda_2 \int P_T dT$, $\varphi_3(U) = \lambda_3 \int U_T dT$. If both endo- and exothermal effects exist in time-scales different from the Z dual internal variables can be used [16]. Heat energy $Q \propto -\Theta_X$, where Q is heat energy and Θ is temperature [44].

• The equations for the AP with an amplitude Z and the ion current J; at this stage this is the FitzHugh–Nagumo (FHN) model;
• the improved Heimburg–Jackson equation with an amplitude U for the LW in the biomembrane involving two dispersive terms, a dissipation term and a coupling force;
• the wave equation for the PW in the axoplasm with an amplitude P involving the dissipation term and a coupling force;
• the diffusion equation for the temperature Θ involving a coupling force with an internal variable Q governed by its own kinetic equation;
• the transverse displacement W is proportional to U_X.

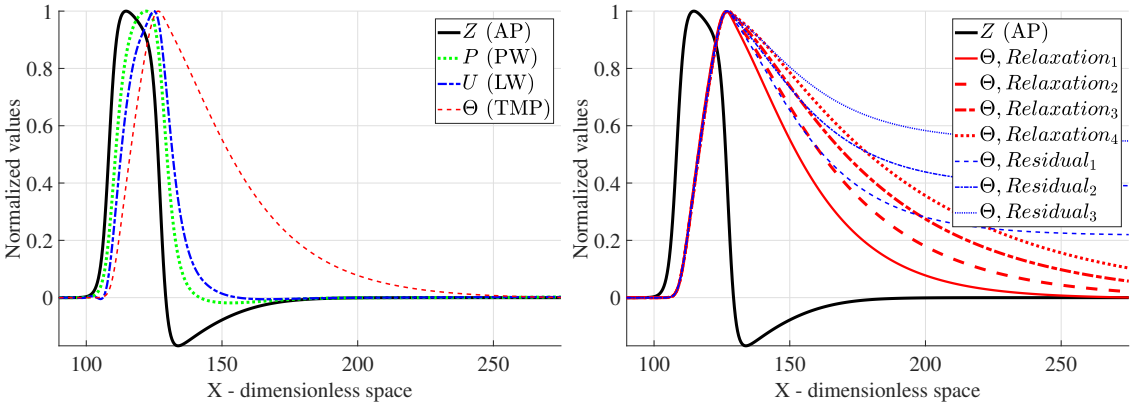


Figure 2: Nerve pulse ensemble (left) and the temperature signal at different relaxation times and different residual heat levels (right). Originally from [16].

2.1 Considering myelination for the mechanical wave

Many axons have myelin sheath (which is composed of several layers of lipids and proteins acting as a glue) and that structure is, apparently, rather important in the context of the nerve pulse propagation. We start, like before, with just the model of the axon wall and longitudinal deformation and then expand from there. While before we could take axon as a tube surrounded by a homogenous thin elastic layer of biomembrane, now we have to take into account some additional structure. What follows is the brief description of the updated structure we are modelling and explanation how this was incorporated into our model.

$$\begin{aligned} U_{TT} =& \gamma_0^2 U_{XX} + NUU_{XX} + MU^2 U_{XX} + NU_X^2 + 2MUU_X^2 - H_1 U_{XXXX} + \\ & H_2 U_{XXTT} - \mu U_T + F(Z, J, P) + A_1 \Phi_X, \\ \Phi_{TT} =& \gamma_2^2 \Phi_{XX} - \eta_0^2 \Phi - A_2 U_X, \end{aligned}$$

where Φ models the influence of the myelination on the macroscopic longitudinal wave propagation; γ_0, γ_2 and η_0 are dimensionless characteristic velocities and frequency, A_i are coupling coefficients. The second microstructure layer (ion channels within nodes of Ranvier) are omitted on assumption that it is small enough to not influence macroscopic longitudinal wave propagation significantly.

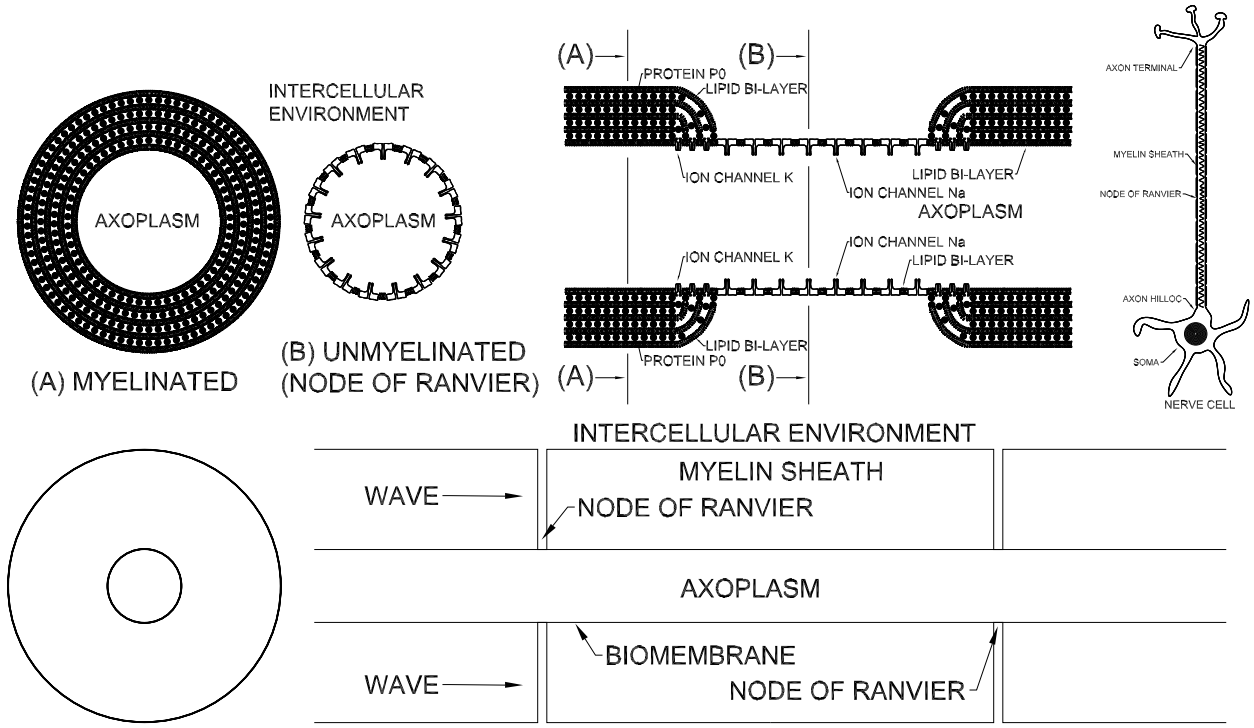


Figure 3: A simplified scheme of the geometry of the myelinated axon. (A) a cross-section of the myelinated axon segment, (B) a cross-section of the unmyelinated section of the axon (node of Ranvier). Bottom panel – simplified geometry for the mechanical wave propagation.

3 Problems

The present model describes processes in an unmyelinated axon. Further research will be related to describing the structural properties of axons in more detail. Attention must be paid to the myelin sheath and axoplasm. The ideas about the structure of a myelinated biomembrane are presented in Appendix A. Note Mueller and Tyler [38] who described the structure of the biomembrane with ion channels of different origin, axoplasm with cytoskeletal proteins (actin filaments, microtubules) that all play role in signal propagation as an ensemble. Concerning the myelinated axon, Arancibia-Carcamo and Atwell [2] have clarified the structure of Ranvier nodes and the character of ion channels at a node and its vicinity. The modelling of the myelin sheath based on ideas of a microstructured continuum [53] describes only the propagation of an LW. This approach may serve as a basis for further research. Several questions arise immediately: Can a single bi-layer be modelled as a homogeneous structure or the ion channels should be taken into account? How the TW is affected by the myelin sheath? How the AP in a myelinated fibre is propagating and what is the role of various ion channels under the sheath and in Ranvier nodes? How the wave ensemble is generated in myelinated nerve fibres? How the cytoskeleton in the axoplasm influences the propagation of the AP and PW? How the temperature change Θ is dependent on the structural elements of a fibre? Should a modified Fourier's law be used for the description of temperature changes? What is the role of thresholds for ion currents and even more important, for the contact forces?

In what follows, a short overview of recent research is presented.

4 Overview of recent results

First, it must be mentioned that experimental techniques are developing all the time. Atomic force microscopy (AFM) has been an excellent tool to examine the processes in cells [31, 49], label-free optical imaging has been developed for imaging of membrane potential [33, 58]. Recent experimental studies, for example, have revealed detailed data about the molecular architecture of myelin sheaths [5]. The general understanding of the multiphysics nature of the complex process in neurons is growing. Engelbrecht et al. [18] have stressed the importance of physics in the modelling of multicomponent signals in nerves involving electrical, mechanical and thermal components. Schneider [46] has formulated three key ideas needed

for understanding the processes in nerves: (i) bridging physical state and biological function directly; (ii) the importance of the momentum conservation for processes in nerves; (iii) accounting for the interaction of pulses and enzymes. Jerusalem et al. [31] have explicitly analysed the role of structural elements of the biomembrane, axoplasm and extracellular matrix in the forming signals in nerves. They also stress the need to define explicitly the physics involved that helps to interpret experimental results.

How all these ideas are reflected in modelling?

It must be stressed that ion channels in the myelinated fibre are different in the node and the neighbouring paranodes and juxtaparanodes [2]. They characterize the interaction between the axon and the sheath: (i) node as an area free of the sheath; (ii) localised voltage-gated Na channels at the node; (iii) localised K channels on either side of a node and (iv) region of attaching the sheath to the axon (paranodes). Based on the model of electrical circuits [23], numerical simulation has revealed many characteristics of the AP propagation [4]. It has been shown that the node of Ranvier length varies considerably (examples are about 4.4-fold and 8.7-fold range) and this alters conduction speed similarly to the changes produced by altering the internode length or the thickness of the sheath. It means that the adjustment of the node of Ranvier length may serve as a mechanism for tuning the arrival time of information. The understanding of the functions of a Ranvier node and its neighbouring paranodes and juxtaparanodes helps to describe the pathological situations of psychiatric diseases [2]. The model of Halter and Clark [23] has also been used for modelling the AP propagation in a myelinated axon bifurcating into two daughter branches [57]. McIntyre et al. [37] have used a double cable model with a different representation of Ranvier nodes, paranodes and internodal sections of the axon. They have explained the changes in the AP shape, strength-duration relationship and recovery cycle can be attributed to kinetic differences in nodal Na conductances. The structure of the myelin sheath can also be modelled as an inhomogeneous structure: the regions of a sheath are interrupted by the Ranvier nodes. Drapaca et al. [13] have proposed to model the AP in such a structure by a space-fractional cable equation. Indeed, such an approach permits the involvement of inhomogeneity but the parameters of the governing equation are not directly related to physiological parameters. Frankenhaeuser and Huxley [22] has proposed to modify the HH model by adding the fourth phenomenological variable p to three variables in a standard HH model (m,h,n), However, they stress that the mechanism of the permeability changes remains unknown. Another idea of how to model the influence of the myelin sheath is proposed by Schmidt and Knösche [45]. They consider the influence of ion currents only in the Ranvier nodes placed periodically on an infinitely long cable. The ion current is initiated after the membrane potential has crossed a certain threshold. Four possible cases for the ion current are analysed: a delta spike, a delayed delta spike, an exponential current and a combination of several exponential currents. The cable equation is linear and it is possible to find the closed analytical solutions for the AP. It is found that the diameter of an axon and the thickness of the sheath (g-ratio) influence the velocity of the AP whereas the lengths of the sheath and the Ranvier nodes have less influence.

Concerning the processes in the axoplasm, Singh et al. [47, 48] have demonstrated that the filaments in the axoplasm can generate vortices that play a significant role in communication. They suggest [48] the coexistence of different waves propagating in different carriers. This suggestion waits for a mathematical description. Summing up, the mainstream research in studying the processes in myelinated nerve fibres is related to explaining the changes in the characteristics of the AP. The main tool is a modified cable equation where the ion conductances and membrane capacitance play an important role. The role of various ion channels is clarified as well as the varying length of Ranvier nodes and myelin sheath. Although it is clear that the energy of a signal in unmyelinated fibres is distributed between the components of a wave ensemble, for myelinated fibres this distribution waits for clarification.

5 Further research

(i) Modelling of the AP in myelinated nerves and coupling effects. How can the differentiation of sodium and potassium ion channels (under the myelin sheath and in Ranvier nodes) be taken into account? Comparative analysis of proposed models.

(ii) What is the influence of the cytoskeleton in the axoplasm on the components of the ensemble? This concerns both the AP and the PW. Can the idea of a microstructured solid be useful?

(iii) How are the coupling forces influenced by the internal structure of the biomembrane and the axoplasm? Are there thresholds for contact forces?

(iv) The transverse distribution of the temperature change Θ should be analysed. What happens in myelinated axons?

(v) The energy changes during the propagation of an AP and the role of dissipation and the recovery of the equilibrium state.

(vi) The role of other ion currents besides K and Na, like for example, Ca2+.

(vii) All data about scales in the process must be collected and analysed.

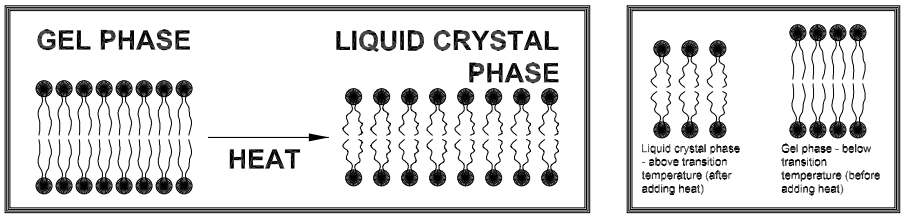
In further research, we should think first about the unmyelinated fibre - whether the modifications of the proposed model [18] could enhance the modelling to involve more structural properties and second, what could be done for casting the special properties and characteristic mechanisms of myelinated fibres into mathematical form.

We are interested in the modelling of processes but certainly, there are many problems to be solved using experiments. For example, Arancibia-Carcamo et al. [4] have listed several questions: (i) what is the mechanism regulating the nodal ion channel density; (ii) what signal regulates the nodal length; (iii) how does the length of nodes and internodes are regulated by local molecular mechanisms.

5.1 Open questions and some ideas to be (maybe) considered

- Phase change of lipide bi-layer vs 'regular' density/pressure wave in the lipid bilayer. What is the difference and is it possible to experimentally determine this difference from something that can be measured? What other processes can give a similar/same signal for the measured/observed characteristic and what more is needed to tell the difference between the phase changes and these 'other processes' that can give off similar signatures?

- Phase change. Time scale of this physical process in both directions (melting, 'freezing' transition speeds/time scales)? Can it happen in roughly 1 ms in one direction and roughly 4 ms in the opposite direction? [NOTE: based on discussion with Matthias the answer is 'yes' – phase changes can be very fast and happen in microseconds in lipids]. Is it known how the phase change interacts with ion channels, i.e., does it force the channels to close or open or allow ion channels to move along the membrane more freely somehow? Does the phase change affect the membrane permeability for ions/molecules outside the ion channels or allow something to dissolve in the membrane that could not do so in the opposite phase of the membrane? Is the phase change front speed the same as the sound speed in the membrane? Fig. inspired from [56]



- Temperature measurements at microscopic scale/volume. Accuracy, time-scale, fluctuations measurements? Can techniques used in [40] be used to do high-frequency and small-scale temperature sampling? [Apparently 'no'] Could the techniques used in [40] be adapted to track the motion or pressure in the axoplasm/cytoskeleton? [Answer: 'maybe, not trivial' based on discussion with Anne]

- The total energy of a nerve pulse ensemble. What are the dominant processes (in the sense of energetics)? Could the energetically lower magnitude processes be left aside or could they still be relevant in the grand scheme of things due to the nonlinear nature of the nerve pulse (i.e., small changes could be triggers for large effects)? How much of the chemistry involved can be left aside for the sake of simplicity or how much of the chemistry would be so essential for the nerve pulse propagation that

it would need to be included? For the AP, for the mechanical waves, for the temperature? Can we consider the energetic balance of the nerve pulse without involving chemistry? Maybe for single nerve pulses? See also appendix B.

- Thresholds. For the AP the concept of threshold is well established. Could the same concept be relevant also to the other constituents of the nerve pulse ensemble? Thresholds for contact forces? If we seriously consider thresholds for contact forces we should, quite likely, also consider if the current linear-proportional formulation is good enough and if not how could the non-linear contacts be formulated so that it would preserve energetically important bi-polarity of the contacts (and if such a formulation is physically plausible).

- Contact forces - we have something that more or less includes everything that seems potentially relevant, at a first glance. Maybe we are missing something - suggestions? Maybe we should focus on simplifying these, what could be left aside as a speculative suggestion?

- Heat transfer in biomembranes? Something other than basic Fourier law? Time-scales vs distances. Local chemistry and time scales where it should be taken into account. What about heat transfer *away* from the axon - should it be taken into account and if it seems relevant at what time scale? For single nerve pulses, for hundred repeated pulses, etc?

- Models for action potentials on myelinated axons. Is there any such model that is considered an 'industry standard' so to say? Or is it all just normal Hodgkin–Huxley in the nodes of Ranvier that is 'jumping' between the nodes with some other algorithm. This question was to a significant degree addressed under the overview of recent results.

- Transverse displacement of the axonal membrane. The thing that is usually measured in experiments. What could be the real mechanism and the most significant causal connections? We have used a relatively naive assumption that it is like in (solid) rods taking it as a gradient of longitudinal density change. While it is more like a tube with a very thin and elastic wall filled with axoplasm and involves potentially many interactions with internal structures (like cytoskeleton) as well as surrounding structures (interstellar medium, other cells, myelin, etc). Meaning, phase changes, pressure waves in axoplasm and flexoelectricity could, in theory, be relevant as well. Then there is a question of how would all these effects behave if one would assume a myelinated axon.

- Continuum vs 'discrete' models. Can we combine these models? Should we combine these models? For example, axon as continuum versus modelling individual myelin sheath segments, nodes of Ranvier, ion channels and finer structure within nodes of Ranvier. Question of wave-lengths, spatial and temporal scales and what benefits would be got by spending all these extra computational resources? In essence, the model is a system of PDE or integral equations versus a numerical/algorithmic/grid model.

- The bio-membrane surface potential changes. The classical ion-channel-based mechanism vs the 'flexoelectric' AP - are they combined or mutually exclusive phenomenons. How to differentiate between these two if it is even possible to differentiate?

- First principles and the models in use – (1) AP: what, exactly, needs to happen to get Hodgkin-Huxley (or FHN) model from Maxwell equations? Are these assumptions physically reasonable one has to do to get the HH model from Maxwell equations? What kind of model would we have if we would start from Maxwell equations and do the needed assumptions to apply it in the context of an action potential propagating along the axon? Could we even solve such a model? (2) LW: If we would start from wave equation or first principles for LW (as opposed to the paper by Heimburg and Jackson) what kind of model would we have then? Probably at least nonlinear terms could be somehow different. (3) PW: Navier-Stokes vs wave equation - we should take a minute and consider what simplifications (assumptions) are we really making if we go straight for the wave equation from the Navier-Stokes equations and then consider if all these assumptions actually make sense in the context of the physical system under consideration. Maybe we have gone too simple and cut out some effects that should be included.

5.2 From Maxwell to Hodgkin-Huxley?

If we want to start from the first principles perhaps it would make sense to start from the Maxwell equations, figure out what assumptions/simplifications need to be done to get from there to the cable/telegraph equation and then take another look at what more needs to be assumed to get the HH model. That way maybe it would be possible to get a good overview of what, exactly, has been omitted in the process and maybe assess if something that should be taken into account has been omitted somewhere along that path.

It appears we are not the first ones considering the question of how to get from Maxwell equations to the Telegrapher's equation as there is a book written about this [36]. From [36] the Maxwell equations in conducting dielectric medium can be written as:

(a) $\mathrm{curl}(\mathbf{H}) = \mathbf{D}_t + \mathbf{J}$, where $\mathbf{H}$ is magnetic field, $\mathbf{D}$ is electric displacement and $\mathbf{J}$ is conduction current

(b) $\mathrm{curl}(\mathbf{E}) = -\mathbf{B}_t$, where $\mathbf{E}$ is electric field and $\mathbf{B}$ is magnetic field

(c) $\mathrm{div}(\mathbf{D}) = \rho$, where $\mathbf{D}$ is electric displacement and ρ is free charge density

(d) $\mathrm{div}(\mathbf{B}) = 0$, where $\mathbf{B}$ is magnetic field

(e) $\mathbf{B} = \mu\mathbf{H}$, where $\mathbf{B}$ is magnetic field, μ is magnetic permeability and $\mathbf{H}$ is magnetic field

(f) $\mathbf{D} = \varepsilon\mathbf{E}$, where $\mathbf{D}$ is electric displacement, ε is dielectric constant (el. permeability), $\mathbf{E}$ is electric field

(g) $\mathbf{J} = \sigma\mathbf{E}$, where $\mathbf{J}$ is conduction current, σ is conductivity and $\mathbf{E}$ is electric field (this is Ohm's Law)

(h) $\mathrm{div}(\mathbf{J}) = -\rho_t$, where $\mathbf{J}$ is conduction current and ρ is free charge density (eq. of continuity).

Here the EQs. (a) to (d) are the Maxwell equations and (e) to (h) are accompanying things (assumptions), also subscript t denotes $\partial/\partial t$ i.e., time derivative. It is noted that these are for average fields, i.e., there are at least 1000 (or more) charged particles in considered volume plus the usual assumptions about things being homogeneous and isotropic (meaning σ, μ, ε are constant scalars (not tensors)). There is also an assumption that for considered frequencies of interest, these quantities are constant (i.e., they pass through time derivatives as they are).

If there is a polarization of bound charge in a medium some additional complications emerge. In the context of nerve fibres, this could be important as lipids are clearly asymmetrically charged. See [36] pages 20 to 22. For a pure bi-layer, however, it seems safe to assume that this effect could be left aside on assumption that interaction with nearby water molecules is stronger than any polarization effects during nerve pulse propagation as otherwise, the bio-membrane would just have to disintegrate during nerve pulse propagation if some of the lipid molecules could be flipped around because of the electric field applied across the membrane.

Maxwell equations have also an integral form. For these one needs a couple of fundamental mathematical theorems, which are

1. $\int_{\mathrm{V}} \mathrm{div}(\mathbf{F}) d\mathrm{V} = \int_{\mathrm{S}} \mathbf{F} \cdot d\mathrm{S}$, which is "the divergence theorem"
2. $\int_{\mathrm{S}} \mathrm{curl}(\mathbf{F}) \cdot d\mathrm{S} = \oint_{\mathrm{C}} \mathbf{F} \cdot d\mathrm{s}$, which is the "Stokes theorem".

Here in the first theorem, S is a closed boundary surface enclosing volume V and in the second theorem, C is a closed bounding curve (possibly non-planar) bounding an arbitrary open surface S (also possibly non-planar).

(A) $\mathrm{curl}(\mathbf{H}) = \mathbf{D}_t + \mathbf{J} \quad \rightarrow \quad \oint_{\mathrm{C}} \mathbf{H} \cdot d\mathrm{s} = \int_{\mathrm{S}} [\mathbf{D}_t + \mathbf{J}] \cdot d\mathrm{S}$

(B) $\mathrm{curl}(\mathbf{E}) = -\mathbf{B}_t \quad \rightarrow \quad \oint_{\mathrm{C}} \mathbf{E} \cdot d\mathrm{s} = \left[\int_{\mathrm{S}} \mathbf{B} \cdot d\mathrm{S}\right]_t$

(C) $\mathrm{div}(\mathbf{D}) = \rho \quad \rightarrow \quad \int_{\mathrm{V}} \rho d\mathrm{V} = \int_{\mathrm{S}} \mathbf{D} \cdot d\mathrm{S}$

(D) $\mathrm{div}(\mathbf{B}) = 0 \quad \rightarrow \quad \int_{\mathrm{S}} \mathbf{B} \cdot d\mathrm{S} = 0$

So, these are the Maxwell equations. However, assembling a proper full list of all the assumptions made when one goes from here to Telegrapher's equation seems to require a bit more than just leafing through the [36] as this seems to be a pretty good book, but because its a pretty good book spelling out what is being done and why it is a bit longer process to extract the list of assumptions with thinking involved about what makes sense in the context of the nerve pulse propagation and what does not make sense.

5.3 From Navier-Stokes to wave equation?

The classical wave equation is probably one of the most classical equations in physics. But there is a question of what, exactly, have we omitted to use for the pressure wave in axoplasm. What is the full list of assumptions one needs to do to reduce a full 3D Navier-Stokes into a 1D wave equation and do all of these assumptions make sense in the context of the nerve pulse propagation? For a start, a short list of comments made back in 2018 when we included axoplasm pressure in our model system:

1. Navier-Stokes vs just picking a wave equation out of thin air. Is it possible to derive that wave equation from the full Navier-Stokes by doing the "right" assumptions? Lin and Morgan [34] just basically pick it and after looking into their paper a bit more most of their science is about doing the boundary conditions. It works, solutions we get are correct in shape, however, can we just pick it like that? Using 1D Navier Stokes which can be solved just fine is inconvenient (nasty mixed derivatives emerge) because it is not trivial to get from the flow velocity field (which should be close to zero for us) back to the pressure which we need.

2. Compressibility vs non-compressible. There is a difference between these two - if we pick just a wave equation for the pressure we would have compressible fluid - it is basically just an acoustic problem at that point and no longer really fluid dynamics if we take just the classical wave equation and perhaps some minor additional corrections.

3. Newtonian vs Non-Newtonian fluid. Adding viscous dampening assumes Newtonian fluid. However, many organic fluids are apparently non-Newtonian, blood, for example. Meaning that viscosity depends on the strain and in the case of the blood - the faster it flows (the greater the pressure gradient) the smaller is the viscosity. For us the measured pressures are small (1 mPa with cytoskeleton intact [54]) so this effect could be probably negligible but could think about it some more.

4. Nonlinearity. If there would be nonlinear terms in the pressure equation then for the "correct" behaviour of the system the temptation would be to add the "wrong" kind of nonlinearity. Ideally, some kind of nonlinear dampening term that dampens the harder the greater the pressure gradient. Why is it the "wrong" type at the first glance? Because all the organic fluids listed in Wikipedia under non-Newtonian fluids as examples behave in an opposite way and flow more freely if the pressure gradient is greater. That is the main motivation behind adding a viscous term to the pressure equation. Nonlinear dampening would be a substitute for considering saturation (there is a limit above which you can not easily increase the pressure in the axon as at some point the bio-membrane has to break).

There are a few different ways to go about these questions. Getting to the classical wave equation for pressure from full 3D Navier-Stokes is certainly not a trivial task. An interesting paper I have been planning to read properly for a few years by now is [1] where Ivan Christov (and one co-author) have taken an in-depth poking at a flow in rather small radius elastic tubes coming at it from shell theory. It is not easily adapted to our model or to even properly answer the question about all the assumptions that would be needed to get what they are doing from 3D Navier-Stokes. Finally, from handwritten notes some remarks:

(a) $\rho\left(v_t + vv_x\right) + p_x - \mu v_{xx} = F$ is 1D Navier-Stokes formulation where ρ is density, p is pressure, μ is viscosity, F is body force. That can be written as $\rho v_t + \rho v v_x + p_x - \mu v_{xx} - F = 0$ from where $\rightarrow$ we can get $v_t = (1/\rho)F + (\mu/\rho)v_{xx} - (1/\rho)p_x - vv_x$ which is something we could easily solve, however, this is not very helpful as it is formulated in terms of flow velocity.

(b) From [11] (Modeling Fluid Flows in Distensible Tubes for Applications in Hemodynamics) a relatively simple pair of PDEs has been written down, but, again, it is in terms of flows and moreover is containing some parameters that are specific for their numerical scheme. It feels like not a good rabbit hole to dive into for getting into wonderland.

(c) $$\underbrace{\rho\left(\vec{u}_t + \vec{u}\cdot\nabla\vec{u}\right)}_{\text{inertial forces}} = \underbrace{-\nabla p}_{\text{pressure forces}} \underbrace{+\nabla\cdot\left(\mu\left[\nabla\vec{u} + (\nabla\vec{u})^T\right] - \frac{2}{3}\mu\left[\nabla\vec{u}\right]I\right)}_{\text{viscous forces}} + \underbrace{F}_{\text{external force}} \quad \text{and} \quad \underbrace{\rho_t + \nabla\left(\rho\vec{u}\right) = 0}_{\text{continuity eq.}}$$

It should be noted that Navier-Stokes eq. is itself conservation of momentum (similarly to wave equation) while the continuity eq. that is always solved with Navier-Stokes eq. is conservation of mass.

6 Appendix A – Notes on myelin sheath

The main paper for drawing inspiration for this is [35].

Let us start with a sketch of a problem.

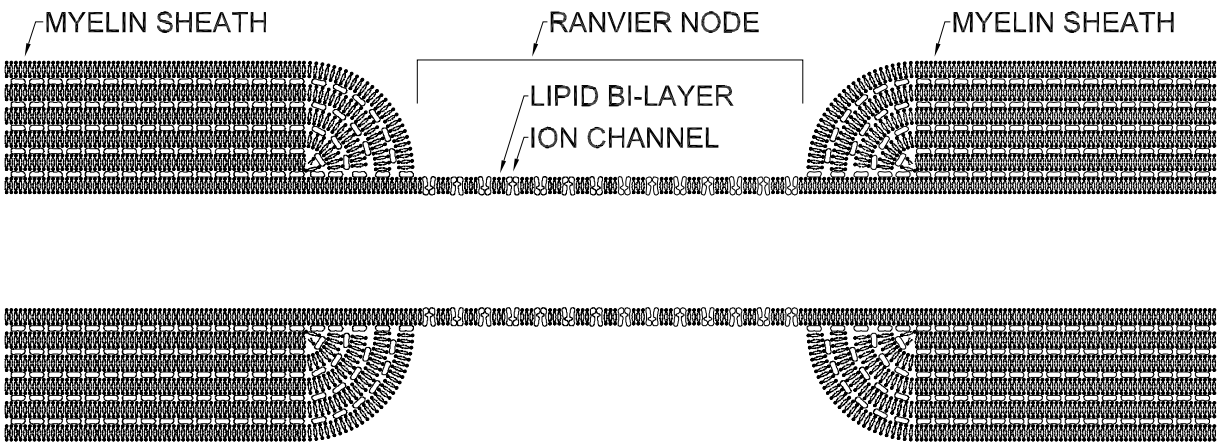


Figure 4: Sketch of myelinated axon and Ranvier node.

The axon is an elastic tube filled with axoplasm with a lipid-bilayer wall. Some axons are unmyelinated which has been the case for the ones we have modelled so far. However, many axons are myelinated. Myelin is several layers of lipid bilayers wrapped around the axon glued together with a special protein. Usually 5 to 10 layers of lipid bilayers. There are special cells which produce myelin but it seems to be safe to do an assumption that these cells are not relevant for adding myelin sheaths into our model and it is sufficient to model only myelin sheath. The Ranvier node is a segment between different myelin sheath segments and has usually a high density of ion channels. Ion channels are not modelled explicitly in our model as well.

Scales and properties of the problem.

- Wavelengths. Duration 2 ms, velocity 2 m/s $\rightarrow$ 4 mm. Duration 2 ms, velocity 100 m/s $\rightarrow$ 20 cm. In both cases, the wavelength is at least a few magnitudes greater than the scale of the structures on which it is propagating so it seems safe to assume it can be modelled as the microstructured environment.
- Axon diameter varies from a micrometre in certain nerves of the human brain to a millimetre in the giant fibre of the squid [35].
- The cycle of membrane depolarization, hyperpolarization, and return to the resting value that constitutes an action potential lasts 1-2 milliseconds and can occur hundreds of times a second in a typical neuron [35].
- Node of Ranvier is typically around 1 μm in length and has a high density of ion channels [35].
- Myelin sheath segment is typically from $\approx 50\mu$m to $\approx 300\mu$m in length.
- Lipid bi-layer is typically 3 to 4 nm in thickness.
- Mechanical transverse displacement during AP propagation is typically $\approx$ 1nm in amplitude.
- Mammals have about 50 different small-molecule pumps [35] (we probably do not want to model any of them specifically).
- Pure phospholipid bilayers are essentially impermeable to water, but most cellular membranes contain water-channel proteins that facilitate the rapid movement of water in and out of cells [35] (osmosis is a thing, but we assume it not relevant for us at this time).
- Special transport processes involving microtubules move proteins and membranes from their sites of synthesis in the cell body down the length of the axon to the terminals [35] (cytoskeleton is relevant is the point of this).

- The electrochemical gradients are essentially independent of the supply of ATP over the short time [35] – meaning that AP can be propagated from a few hundred to up to a thousand times even if the ATP supply is suppressed in an axon from existing gradient across the membrane.
- AP can move down an axon without diminution at speeds **up to** 1 m/s (without myelin sheath) [35]. In non-myelinated neurons, the conduction velocity of an action potential is roughly proportional to the diameter of the axon [35].
- The presence of a myelin sheath around an axon increases the velocity of impulse conduction to 10-100 m/s [35].
- The myelin sheath is a stack of specialized plasma membrane sheets produced by a glial cell that wraps itself around the axon [35].
- Two proteins predominate in the myelin membrane around peripheral axons: P0, which causes adjacent plasma membranes to stack tightly together, and PMP22 [35].
- Tight junctions between the axon and the glial cell plasma membrane in the paranodal junctions immediately adjacent to the nodes may prevent diffusion of Na channels and Na/K pumps away from the nodes [35] (not relevant for us, just a note why ion channels can maintain high density in nodes of Ranvier, supposedly).
- Mainstream explanation – The excess cytosolic positive ions generated at a node during the membrane depolarization associated with an action potential spread passively through the axonal cytosol to the next node with very little loss or attenuation, since they cannot cross the myelinated axonal membrane. This causes a depolarization at one node to spread rapidly to the next node, permitting, in effect, the action potential to "jump" from node to node. This phenomenon explains why the conduction velocity of myelinated neurons are about the same as that of much larger diameter unmyelinated neurons [35]. REMARK - diffusion is slow, I am not entirely convinced by this explanation.
- ALTERNATIVE HYPOTHESIS - Considering mechanical wave velocity is roughly 170 m/s in a lipid bi-layer the alternate mechanism which could facilitate fast signal propagation between nodes of Ranvier is a mechanical wave which is propagating with minimal attenuation in the myelin sheath and is then "focused" into the single lipid bilayer in the node of Ranvier where though flexoelectricity sufficient potential gradient could be induced to open voltage-gated ion channels.
- Typical ion channel diameter is about 9 nm and length about 11 nm (Fig 7-45 in [35]). The cross-section of the channel opening is about 0.65 to 0.8 nm typically internally (might be relevant for channel mechanical sensitivity, meaning that roughly 1 nm displacement might be sufficient to significantly affect the ion channel mechanically).

From what we did for the double microstructure model - as a source of inspiration, perhaps: For different double microstructure configurations, the free energy W can be extended (for details see [7]). A double concurrent microstructure where micro-structures interact with each other can be considered the most general model

$$\begin{aligned} W = &\frac{Y}{2}u_x^2 + A_1\varphi_1 u_x + \frac{B_1}{2}\varphi_1^2 + \frac{C_1}{2}\varphi_{1x}^2 + A_{12}\varphi_{1x}\varphi_2 + \frac{B_2}{2}\varphi_2^2 + \\ &+ \frac{C_2}{2}\varphi_{2x}^2 + A_2\varphi_2 u_x + \frac{N}{6}u_x^3 + \frac{M_1}{6}\varphi_{1x}^3 + \frac{M_2}{6}\varphi_{2x}^3, \end{aligned} \tag{1}$$

if we take $A_{12} = 0$ then we get a double microstructure model where concurrent microstructures do not interact and taking $A_2 = 0$ results in a hierarchical microstructure model where the second microstructure is contained within the first one. The governing equations for the double microstructure model in the dimensionless form are

$$\begin{aligned} \frac{YU_0}{L^2}U_{TT} &= \frac{YU_0}{L^2}U_{XX} + \frac{A_1 l_1}{L^2}\Phi_{1X} + \frac{A_2 l_2}{L^2}\Phi_{2X} + \frac{NU_0^2}{L^3}U_X U_{XX} \\ \frac{I_1}{\rho}\frac{Yl_1}{L^3}\Phi_{1TT} &= \frac{C_1 l_1}{L^3}\Phi_{1XX} + \frac{A_{12}l_2}{L^2}\Phi_{2X} + \frac{M_1 l_1^2}{L^5}\Phi_{1X}\Phi_{1XX} - \frac{B_1 l_1}{L}\Phi_1 - \frac{A_1 U_0}{L}U_X \\ \frac{I_2}{\rho}\frac{Yl_2}{L^3}\Phi_{2TT} &= \frac{C_2 l_2}{L^3}\Phi_{2XX} - \frac{A_{12}l_1}{L^2}\Phi_{1X} + \frac{M_2 l_2^2}{L^5}\Phi_{2X}\Phi_{2XX} - \frac{B_2 l_2}{L}\Phi_2 - \frac{A_2 U_0}{L}U_X. \end{aligned} \tag{2}$$

In our current model – longitudinal wave in lipid bilayer is modelled by the improved HJ model (homogeneous lipid bi-layer without ion channels) [14, 17, 24]

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

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 contact force accounting for the possible influence from the AP and PW. The transverse displacement (TW) is $W \propto U_X$.

Overall there do not seem to be many studies about wave propagation in the walls of an elastic tube with variable wall thickness. Most studies seem to be focused on blood vessels - a paper on flow in an elastic tube with variable diameter was something we might want to take a look if we want to look into 2D pressure wave modelling [10]. But this is not all that good for doing something significant with a myelin sheath.

What to do:

- Consider adding elements from our double microstructure model (2) into the iHJ model (3).
- Take another in-depth look at fractional derivatives [32] for inspiration - it is quite possible that when the wall thickness is changing in such a significant manner (plus the layered nature of the environment) a fractional derivative might be the most fitting for describing the combined effects of increased dispersion and attenuation.
- The "naive" option - keep the same iHJ model, change M, N, μ_3, H_1 downwards and H_2 upwards in myelin sheath sections (reduced non-linearity, dissipation and elastic dispersion, increased inertial dispersion). However, I'm not sure this is really well-motivated physically.

Feb. 16 from 2021 updates

For a start couple of drafts in the light of our discussions on the 15th Feb. Some numbers:

Figure 5: Sketch of myelinated axon and Ranvier node. Variant where Ca channels are exposed. References [12] for Ca/K channel structure and [50] for Na channel structure (it appears that Na channel exact structure is still open to some investigations, considering the recent paper in Nature from 2017 on this subject) and for the structure of P_0 protein [43].

- P_0 protein is about 45 $\mathring{A}$ central part and similar size insertions into the lipid bilayers which are acting as a glue to hold the lipid bilayer together in the myelin sheath.
- K and Ca channels are about 100 $\mathring{A}$ in length and roughly 40 $\mathring{A}$ in diameter.
- Na channel is about 120 $\mathring{A}$ long and about 100 $\mathring{A}$ in diameter although the bit sticking out inside the axon appears to be relatively narrow (at least in the open configuration).
- Both ion channels appear to be sticking out about 1 nm (10 $\mathring{A}$) outside the axon and have longer ($\approx$ 6 nm or 60 $\mathring{A}$) bit sticking out inside the axon.

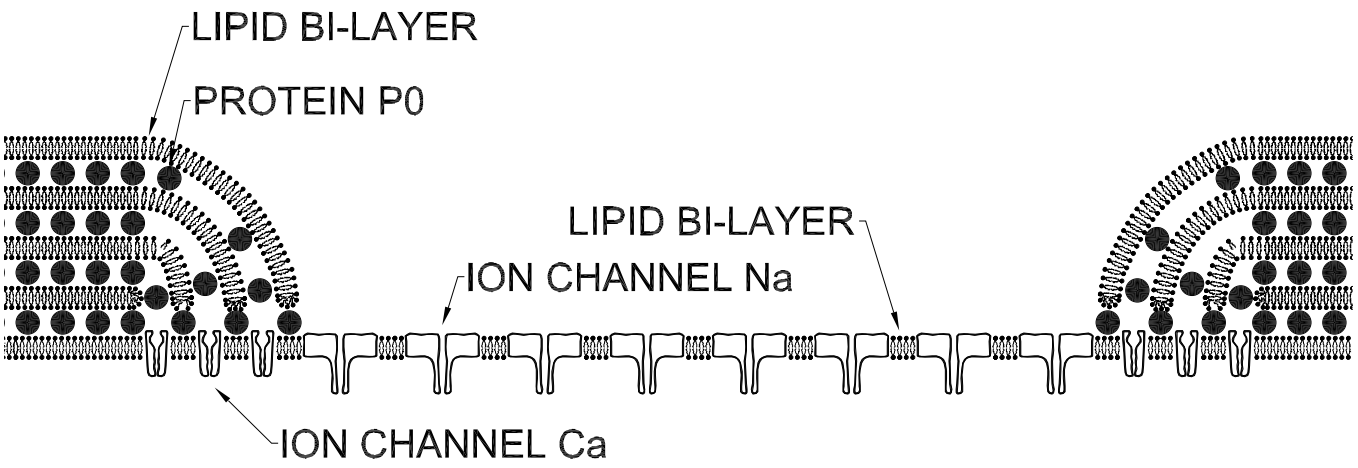


Figure 6: Sketch of myelinated axon and Ranvier node. Variant where Ca channels are covered. References [12] for Ca/K channel structure and [50] for Na channel structure (it appears that Na channel exact structure is still open to some investigations, considering the recent paper in Nature from 2017 on this subject) and for the structure of P_0 protein [43].

Next – a draft of the geometry of the problem we are trying to solve for a mechanical wave in Fig. 7. Many lipids have density **lower than water** in general and some exceed the density of water marginally. This is a problem for us because that would mean that the mechanical wave could escape our lipid bilayer relatively easily. If the density difference with the environment would be larger one option could be to look at this problem as a mechanical wave-guide for sound waves. We might still be able to do so but would, probably, have to assume heavy dissipation (a portion of the mechanical energy escaping into the environment).

The geometry:

- Ranvier node is about 1μm in length.
- Myelin sheath is about 100 to 300μm in length typically per segment.
- Myelin sheath is composed of the same material as biomembrane, i.e., about 3 nm thick layers of lipid-bilayers, glued together with protein P_0 (about 4.5 nm thick plus the bits that stick into bilayers).
- in the literature some sources seem to claim that myelin is about 10 layers thick typically, however, many sources show that myelin is 1 μm or more in thickness which would mean several hundred lipid bilayers glued together with P_0 so there are some conflicting signals in this regard.
- wavelength of the mechanical wave propagating on this structure is from some mm to a few tens of cm meaning it is at minimum several orders of magnitude greater than the internal structure. This might allow us to take this structure as homogeneous, perhaps.

- ... nerve impulses are not transmitted through neuronal axons the way electrons are conducted through a copper wire, and the myelin sheath is far more than an insulator. [21]
- Myelin sheath is made by Schwann cells in PNS and by oligodendrocytes in CNS.
- Nodes of Ranvier act as repeaters [21].
- Recent studies show that in addition to the nodes of Ranvier, there are long stretches (up to 55 μm) along an individual axon of pyramidal neurons in layer II/III where there is no myelin sheath interspersed with segments that are myelinated [21, 55]. Variation in myelination along an axon could adjust transmission speed to optimize the time of arrival of signals from multiple axons at a relay point in a neural circuit. Unusually long nodes of Ranvier (50 μm) may even delay action potential propagation [55], as they increase the electrical capacitance of the axon membrane and consequently increase the time required to charge and discharge it.

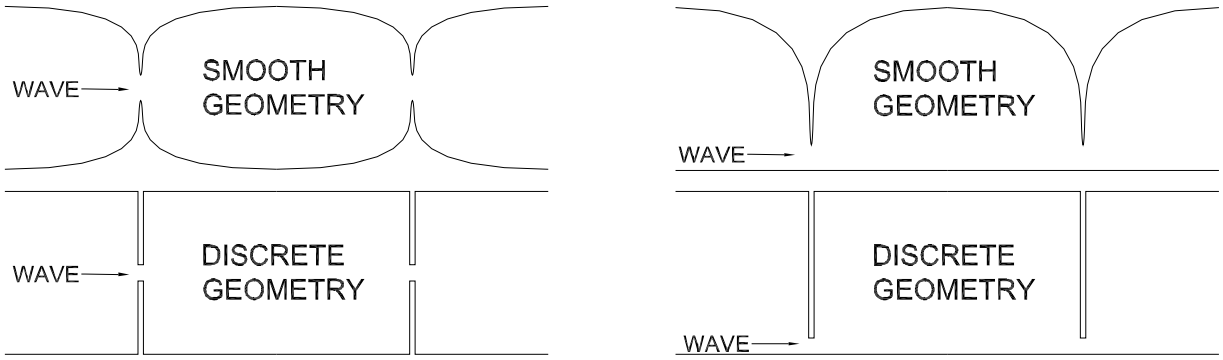


Figure 7: The draft of the geometry of the problem for a mechanical wave. Top, 'smooth' geometry, Bottom, 'discrete' geometry. Here one would need to keep in mind that the wavelength of the excitation is a lot longer than the structures depicted. The left – a simplified scheme which is symmetrical. Right – a more physically correct scheme which is asymmetrical. For the sake of simplicity, it should be OK to assume the simplified symmetrical layout as the wavelengths are much longer than the scale of the structures. The tricky question is the boundary conditions. As lipids and water are close in density we cant probably take the boundary as fully rigid. It should be noted that this is a figure for the lipid bi-layer and myelin sheath, not for the axon geometry!

- Synapses can form on unmyelinated segments of axons, and bare axons can release neurotransmitters, signalling by nonsynaptic communication [21].
- Action potentials also propagate back into the cell body, affecting neural integration and synaptic plasticity [21].
- Oscillations and waves of electrical activity at different frequencies couple neurons into functional assemblies that coordinate and gate information and the frequency of oscillation differs in layers II/III and V [21]
- The most critical segment of the unmyelinated axon is the axon initial segment. The 5 to 80 μm-long unmyelinated section between the cell body and the first myelin segment is the decision point where action potentials are triggered. The morphological features of this segment, and the types of ion channels present in it, regulate the excitability of the neuron. This region also controls the shape of the action potential, which affects the amount of neurotransmitter released from the synapse, the frequency of action potential firing, and other aspects of action potential signalling. Action potentials are initiated at the distal end of the axon initial segment, and the distance to this trigger point has important functional consequences. Tomassy et al. [55] found that this region of the axon was longer in layers III/IV than V/VI [21].
- The length of the myelinated axon between nodes may be determined by neuronal signals, intrinsic properties of the oligodendrocytes, and region-specific factors [21].
- Myelin sheath increases the effective resistance of the axonal membrane, lengthening its electrical space constant and thus promoting signal spread along the axon. More importantly, however, myelin decreases the effective capacitance of the axonal membrane, so less charge (in the form of Na+) needs to enter to depolarize the cell. Both of these effects increase the action potential conduction speed. In addition, the reduction of Na+ entry leads to less ATP being used by the axon on Na+ pumping, thereby allowing the conduction of the action potential to be more energetically efficient for the axon, at the expense of more energy being used to maintain the resting potential of the ensheathing oligodendrocyte [3].
- In order for the nodes of Ranvier to form and function correctly, highly complex interactions are needed between the axon and its ensheathing glial cell. These interactions have four functions. They serve to: (1) define the node as an area free of the glial sheath, (2) localise voltage-gated Na+ (Nav) channels

in the axonal membrane at the node, (3) localise axonal K+ channels on either side of the node, and (4) attach the ends of the myelin sheaths to the axon on either side of the node so that current cannot easily pass under the myelin (which would negate its membrane capacitance-reducing and resistance-increasing effects). A large array of scaffolding and cell adhesion proteins is required to mediate these axon–glial interactions (Fig. 2 in cited paper?), and the complexity of the protein–protein interactions involved makes the structure of the node and surrounding regions prone to disruption in pathological conditions [3].

- Four general principles must be obeyed if the node of Ranvier is to function correctly [3]:
  - Firstly, the molecular mechanisms described below must produce a high concentration of Nav channels in the nodal membrane, where they will experience the full transmembrane voltage change of the action potential. This is needed for the rapid activation of the channels. Any channels that are mislocalised to internodal regions, where they are covered with multiple layers of myelin, will experience a smaller voltage change and activate less
  - Secondly, most voltage-gated K+ channels (Kv1 type, see below) are localised to the juxtaparanodal region, although Kv3.1b channels and slowly activating KCNQ (also known as Kv7) channels are present at the node itself. Placing K+ channels in the juxtaparanode under the myelin sheath will reduce the voltage they experience, and hence reduce their activation under normal conditions. However, the exact degree of activation occurring will depend on how much current flow can occur under the myelin to the juxtaparanodal region, to maintain the extra-axonal voltage close to the bulk extracellular value of 0 mv.
  - Thirdly, for the myelin to reduce the effective axonal membrane capacitance well, there needs to be little current flow under the myelin sheath. As described below in the description of the molecular apparatus at the paranode, this current flow is reduced by the formation of adhesive junctions between the ensheathing glial cells and the axon. However, these septate-type junctions still leave a spiral pathway between the extracellular space at the node and the extracellular space at the juxtaparanode, through which some current may flow to allow partial activation of juxtaparanodal K+ channels.
  - Fourthly, the nodal length and diameter need to be controlled. The speed with which nodal Nav channels activate is partly determined by the capacitance of the node, and hence by its membrane area.
- PNS and CNS nodes have the same function, however, they differ slightly in structure and the mechanisms for their assembly are different [3].
- The clustering of Nav channels at nodes of Ranvier is mediated by the scaffolding protein ankyrin G [3].
- Although small changes at the node of Ranvier can have large effects on the speed of action potential propagation, it is only in the last decade that disruption of this site in pathology has been investigated in depth [3].
- The correct function of nodal Nav1.6, Nav1.1 and KCNQ channels is important for saltatory conduction along myelinated axons. Alteration of the electrical excitability, permeability or expression of Nav1.6 or Nav1.1 channels can result in autism, epilepsy syndromes, periodic paralysis, or fibromyalgia [3].
- The paranode plays three important roles [3]:
  - Firstly, it acts as a diffusion barrier that separates the Nav channels in the node of Ranvier from the Kv1 channels in the juxtaparanodes.
  - Secondly, the paranode is required for "glueing" the myelin to the axon and ensuring a tight connection between the myelin and the axolemma. This is not only important for restricting membrane proteins to the node of Ranvier, but also for reducing current flow under the myelin sheath. The strong interaction between myelin and the axolemma is achieved by a complex of three proteins: axonal contactin-1 and contactin-associated protein 1 (Caspr1) and oligodendrocyte NF155.

  - Thirdly, using electron tomography Nans et al. [92] suggested a role for the paranode in directing protein traffic to the nodes. They identified an extensive network of filamentous linkers in the paranodal axoplasm connecting the juxtaparanode, the paranode and the node of Ranvier to each other, and showed that transport vesicles were tethered to the paranode by short filaments [92].

- Juxtaparanodes are enriched in Shaker-type Kv1 channels with Kv1.1 and Kv1.2 being the most predominant forms [3].

- the AIS contains a high density of voltage-gated K+ channels, which regulate intrinsic firing, excitability (Kv7.2 and Kv7.3 channels—"M- channel"), as well as AP firing and waveform (Kv1.1 and Kv1.2). Correspondingly, disruption of ion channel localization at the AIS can alter cell excitability and AP shape in vivo [51].

- In an unmyelinated or pre-myelinated axon, Nav channels are distributed uniformly along the axon. With the formation of myelin sheaths, Navs along with many other ion channels become spatially restricted to the nodes of Ranvier between consecutive myelin sheaths and others at juxtaparanodes, which is the myelinated axon subdomain underneath the myelin sheath at the other side of the paranodal junction [51].

- the node of Ranvier is another potential determinant of action potential conduction speed. Increasing the length of the node will increase the node capacitance and the axial resistance for current flow into the internode, which will both decrease conduction speed [4].

- Using electron microscopy (EM) we found the mean node length was 1.08 ± 0.02 μm (mean ± s.e.m., n = 46 nodes). Node lengths varied 2-fold, from 0.7 to 1.4 μm with a standard deviation of 0.15 μm [4]. Node lengths were not significantly correlated with axon diameter at the node, which had a mean value of 0.80 ± 0.03 μm.

- In the grey matter of the adult cerebral cortex (layer V of motor cortex) an even larger, 8.7-fold, range of node lengths was observed from 0.43 to 3.72 μm (mean value ± s.e.m 1.50 ± 0.05, standard deviation 0.58 μm, n = 158). Again there was no significant dependence on node diameter (Figure 1H, p=0.42), the mean value of which was 0.64 ± 0.01 μm [4].

- variability of node length is a general feature of myelinated axons. The greater variability of node length observed in the cortex than in the optic nerve has parallels with the far greater variability of myelination seen in the adult cortex (Tomassy et al., 2014) and could reflect tuning of individual axon conduction speeds to meet information processing needs [4].

- The deposition of compact myelin in a spiralling pattern around an axon generates two morphological features that can be observed by electron microscopy, (1) the major dense line (MDL), which is the tight apposition of the cytoplasmic leaflets, and (2) the intraperiod line (IPL), which is the apposition of the extracellular leaflets [42].

- One oligodendrocyte forms myelin sheath segments for several neurons, whereas a single Schwann cell myelinates one segment for a single neuron [42].

- most myelination will be completed in the PNS shortly after birth (within two years after birth in humans; within four weeks after birth in rodents), myelination in the CNS is an ongoing process that continues throughout adulthood. During active CNS myelination in rodents, the myelin sheath expands at a rate 5 × 103 – 5 × 104 μm2/cell/day [42].

- The myelin sheath is characterized by a high proportion of lipids (70%–85%) and consequently a low proportion of proteins (15%–30%). In contrast, most biological membranes have an approximatively equivalent ratio of proteins to lipids (50% lipid/50% protein) [42].

- The three major classes of membrane lipids are cholesterol, phospholipids (e.g., plasmalogen, lecithin, sphingomyelin) and glycolipids (e.g., galactosylceramide). The lipid composition of the myelin sheath is distinctive, made of high amounts of cholesterol and enriched in glycolipid, in a ratio of 40%:40%:20% (cholesterol, phospholipid, and glycolipid, respectively) compared to most biological membranes (25%:65%:10%) [42].

- The brain contains about 20% of the body's cholesterol, which makes it the richest cholesterol-containing organ [42].

7 Appendix B – On energy of the wave ensemble in nerve axon

Some thoughts on the energy of the wave ensemble in nerve axon

There are some things established already, as has been outlined by Jüri in the "Heat and Energy" paper draft (published as [41] later in 2021). The general energy E balance:

$$E = E_{\mathrm{AP}} + E_{\mathrm{PW}} + E_{\mathrm{LW}} + E_{\Theta}, \tag{4}$$

where indices denote the corresponding waves and temperature. The energy E_{AP} of an AP is [26, 44]

$$E_{\mathrm{AP}} = \frac{1}{2} C Z^2 \tag{5}$$

where C is the membrane capacitance and Z is the amplitude of the AP. In general, in a dynamic process like a nerve pulse propagation the part of the energy under focus should be related to motion, ie kinetic energy (see also Barz et al, [6]). Heimburg and Jackson [25] have explicitly proposed that for the LW according to their model, the energy is

$$E_{\mathrm{LW}} = \frac{c_0^2}{\rho_0^A} U^2 + \frac{p}{3} \rho_0^A U^3 + \frac{q}{6} \rho_0^A U^4, \tag{6}$$

where c_0 is the velocity, ρ_0^A is the density, U is the amplitude and p, q are the nonlinear parameters (see also Mueller and Tyler, [38]). It seems to me this is a variation of the standard kinetic energy expression of

$$E_{KIN} = \frac{1}{2} m V^2, \tag{7}$$

where m is mass and V is the velocity. Heimburg et al just assumed that their velocity is polynomial and got their higher-order terms from there as far as I can see. It is a bit fuzzy to me, however, how is their density change "amplitude" equivalent to the velocity of a lipid bilayer particle? To me, it seems more akin to a potential-energy-like quantity where the displacement of the particle has the potential to do some work when the membrane elastic properties (spring, if you will) pull it back to its resting position once the wave has passed. Of course, in the HJ model, the sum of potential and kinetic energies must be constant, because the equation in question is conservative. So technically using a potential-like quantity instead of the kinetic energy of such a density change wave might not be totally unreasonable.

Thoughts on how to construct LW energy alternatively

However, if I would have to construct an energy expression for the iHJ equation I would rather focus instead of the rate of change of the density so that

$$E_{\mathrm{LW}} \propto M \cdot (U_T)^2, \tag{8}$$

Where M is a quantity related to the mass of the biomembrane - as not the whole biomembrane is moving in space but only the local density change is modelled by the iHJ equation this could be characterised by U which is the change of density compared to some equilibrium value. A portion of that energy must be lost to the heat because we have added the viscosity. On the other hand, there is also an energy source in there because we have the coupling with the AP. In a nutshell, while the base equations are very classical and conservative the contact forces/couplings we have added act as energy sources/sinks added to the corresponding classical energy expressions for such processes (the classical wave equation, and heat equation, however for the reaction-diffusion equations it seems to be a bit more complicated). It might be possible to express the E_{LW} like this:

$$E_{\mathrm{LW}} = U \cdot (U_T)^2 + E_{\mathrm{U}}(F_3) - E_{\mathrm{U}}(\mu_3 \cdot U_T), \tag{9}$$

where the $U \cdot (U_T)^2$ characterises the *kinetic* energy of the LW, $E_{\mathrm{U}}(F_3)$ is used to emphasize that the LW is getting additional *kinetic* energy as a function of the contact force F_3 and the term $E_{\mathrm{U}}(\mu_3 \cdot U_T)$ emphasises that some *kinetic* energy must be lost (which goes as an energy source into the heat energy expression later). This way of writing this up might not be technically totally correct, because the term $U \cdot (U_T)^2$ is the total *kinetic* energy (leaving out the 1/2 coefficient) at *that particular time moment* and the changes are taken into account if the signal changes in time. It seems safe to assume that $E_{\mathrm{LW}} \propto E_{\mathrm{TW}}$ as in our description these two are not independent - if one needs to track the energy of the TW in a more formal manner we might use the kinetic energy definition for the waves on a string which is $E = \int w(x,t)dx$, where the $w(x,t) = \nu u_x$ and ν is the Poisson coefficient like quantity if u is the longitudinal density change.

Thoughts on how to construct PW energy

Pressure is a trickier proposal. We do not allow actually any *flow* along the axon so it is not entirely technically correct to propose the kinetic energy of a pressure wave as is done normally when using the classical wave equation. However, as a first approximation, this could give us a good enough idea perhaps. Or the energy expression should be treated in a more abstract manner. In which case one might perhaps write something like this:

$$E_{\mathrm{PW}} = P \cdot (P_T)^2 + E_{\mathrm{P}}(F_2) - E_{\mathrm{P}}(\mu_2 \cdot P_T), \tag{10}$$

where P is a pressure change compared to some equilibrium level (which might be interpreted as an increase in the mass density of a given volume, if temperature and volume of the fluid are constant) and P_T is the velocity at which such a pressure wave is propagating in the axoplasm. Like before $E_{\mathrm{P}}(F_2)$ is used to emphasize that the LW is getting additional *kinetic* energy as a function of the contact force F_2 and the term $E_{\mathrm{P}}(\mu_2 \cdot P_T)$ emphasises that some *kinetic* energy must be lost (which goes as an energy source into the heat energy expression later).

Thoughts on how to construct heat energy

The heat should be pretty straightforward. All energy "lost" in the mechanical waves must go into the heat eventually. The AP contribution is a bit trickier, but it is probably safe to assume that from the electrical signal the main contribution is the Joule heating (electrical current passing through an environment with non-zero resistance). It must be noted that in principle (as far as I remember, if the argument is used we would need to find a couple of references to back that claim up), changes in the electrical field strength can affect the local temperature of that environment (both positively and negatively) if the environment contains charged particles. The field strength within the lipid bi-layers is very high, in the order of roughly $10^7[V/m]$. To avoid making too many strong statements in this regard it would be probably safest to stick to a more abstract notation so:

$$E_{\Theta} = E_{\mathrm{AP}}(Z,J) + E_{\mathrm{PW}}(\mu_2 P_T) + E_{\mathrm{LW}}(\mu_3 U_T) - E_{\Omega}(J,T) \tag{11}$$

where $E_{\mathrm{AP}}(Z,J)$ is the Joule heating and (if any) electrostatic temperature-related effects in the bi-layer, E_{PW} is energy added from PW (not accounting for the reversible effects in this notation), E_{LW} is energy added from LW (not accounting the reversible effects in this notation) and $E_{\Omega}(J,T)$ is accounting the net temperature change from the "chemical" influences, currently listed as a function of ion current(s) on assumption that any chemical activity is proportional the concentration difference of the reactants compared to some equilibrium value and time to emphasise, that these processes can last noticeably longer than the duration of the nerve pulse wave ensemble. In the case of heat, the energy density and temperature are kind-of equivalents in most settings. So basically writing an energy expression for the heat is just writing the governing equation and corresponding coupling force in a different notation.

Some thoughts on other things

One thing which we are not directly considering at the moment is membrane tension and its changes. I think it would be more relevant if the focus would be more on potential energy than on kinetic energy. Nevertheless Terakawa [54] assesses this as

$$\mathrm{d}\gamma = \frac{1}{2} C_m \mathrm{d}V^2, \tag{12}$$

where $\mathrm{d}\gamma$ is membrane tension change, C_m is the specific capacitance of the membrane ($\approx 1\mu F/cm^2$) and $\mathrm{d}V$ is the change of voltage across the membrane. Assuming 100 mV yields 0.05 mN/m which is 0.2% of the static tension of a phospholipid membrane and then further estimates that for an axon with 250 μm radius this would be enough to explain the pressure response measured, however, he also notes that in such a case it is "very hard" to explain simultaneous transverse displacement outward and pressure increase internally.

The reason why I am pointing this out is that this expression is, basically, the same capacitor energy expression noted by Jüri earlier in eq (5) and is also basically the standard kinetic energy expression eq (7).

Ritchie and Keynes [44] were also poking at this membrane capacitor idea so that (from [52])

$$E_c = \frac{1}{2}C_m Z^2 \quad \rightarrow \quad Q = -k\Theta_x \quad \rightarrow \quad \Theta \propto \frac{C_m}{2k}\int Z^2 dX, \tag{13}$$

while Joule heating (in terms of "power") is

$$P_J \propto J^2 R, \quad \text{or} \quad P_Z \propto Z^2/R \tag{14}$$

where R is resistance, P_i is power and Z, J are AP and ion current, respectively. From these two I personally prefer the version using the ion current(s), as I am not convinced that the R across the membrane for the Z is constant because ion channels are voltage sensitive so the membrane R would need to change as the AP is propagating along the axon when the ion channels open and close. While for the version using the J one could assume that when J exists the ion channels are open and one could use a value for the ion channel resistance which might be a more consistent value hopefully.

There are some arguments (Bini et al, for example, [8]) who have argued that the effect of Joule heating is "small" - more precisely he claims that "As expected, Joule heating effects generated by the passage of the action potential are extremely small. However, if a strong external electric stimulus is applied to the fibre, such a Joule effect term could produce greater effects." On the opposite side of the argument, Nogueira [9] splits Joule heating into two components, longitudinal (along the axoplasm, using the axoplasm resistance) and across the membrane component (using some kind of average membrane resistance). Nogueira also is using Joule heating in terms of voltage (as seems to be common in literature) and ends up with an expression

$$Q_L = \frac{C_m}{K}\int_{tr}^{t}\left(\frac{\mathrm{d}V}{\mathrm{d}t}\right)^2 \mathrm{d}t, \tag{15}$$

after making a number of assumptions, like that the wave is propagating at constant velocity (so that they can replace the spatial gradient with time derivative) but what is clever in their approach is that they integrate only across the signal itself (tr is the time when the signal is still at its rest state) and using that trick they can avoid the problem of membrane resistance with ion channels open and ion channels closed. What is interesting in [9] is that he estimates heat energy contributions from individual ion channels (Table 1). Nogueira [9] notes that "However, the initial heat production, theoretically expected by the capacitor theory, can account for less than half of the measured positive initial heat in the garfish nerve." while referencing few papers by Howarth [28, 29] and one more which we have not referenced so far ourselves [30].

What this splitting of arguments means for us is, that we should be probably careful with the term "Joule heating" (although I personally prefer that as physically "easier" to interpret) and should be probably using a more general description while, perhaps, noting that this heating could be a result of some kind of combination of the membrane capacitor based process and a Joule heating (which for the sake of consistency needs to be written in terms of Z^2 it seems because everyone else seems to be doing so) and the exact mechanism and individual contribution of these mechanisms should be clarified in some future studies.

As far as specific energy components notations go (AP, LW, TW, PW, Θ) I am a bit in-between between the simplicity of the classical notation of mV^2 and a more general/abstract write-up of using integrals. The latter would probably make more sense if we would attempt to present some kind of more general expression applicable to all our processes but might lead to remarks from mildly confused reviewers who start poking at mathematical details, like integration coefficients.

Another note to make is that what has been written above is most of the time *local* energy, in other words, energy components at the specific point (spatial node, in the numerical scheme), while if we would start using an integral description of the energy it would imply total energy of a signal or an ensemble, so integral and "classical" presentations do not need to be mutually exclusive.

8 Appendix C – On dimensions

For reference, the system of equations in the dimensionless form

$$\begin{aligned} Z_T &= DZ_{XX} + Z\left(Z - [a_1 + b_1] - Z^2 + [a_1 + b_1]\, Z\right) - J \\ J_T &= \varepsilon\left([a_2 + b_2]\, Z - J\right), \end{aligned} \tag{16}$$

$$U_{TT} = c^2 U_{XX} + NUU_{XX} + MU^2 U_{XX} + NU_X^2 + 2MUU_X^2 - H_1 U_{XXXX} + H_2 U_{XXTT} + F_1(P, J, Z), \tag{17}$$

$$P_{TT} = c_f^2 P_{XX} - \mu P_T + F_2(Z, J), \tag{18}$$

where Z is potential, J is the abstracted ion current, a_i, b_i are "electrical" and "mechanical" activation coefficients, D, ε are coefficients, U is longitudinal density change, c^2 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 pressure, c_f^2 is the sound velocity in axoplasm μ is dampening coefficient. Coupling forces

$$F_1 = \gamma_1 P_T + \gamma_2 J_T\left(-\gamma_3 Z_T\right); \quad F_2 = \eta_1 Z_X + \eta_2 J_T\left(+\eta_3 Z_T\right), \tag{19}$$

where γ_i are coupling coefficients for mechanical wave and η_i are coupling coefficients for the pressure wave. Time derivatives act across the membrane and spatial derivatives act along the axon.

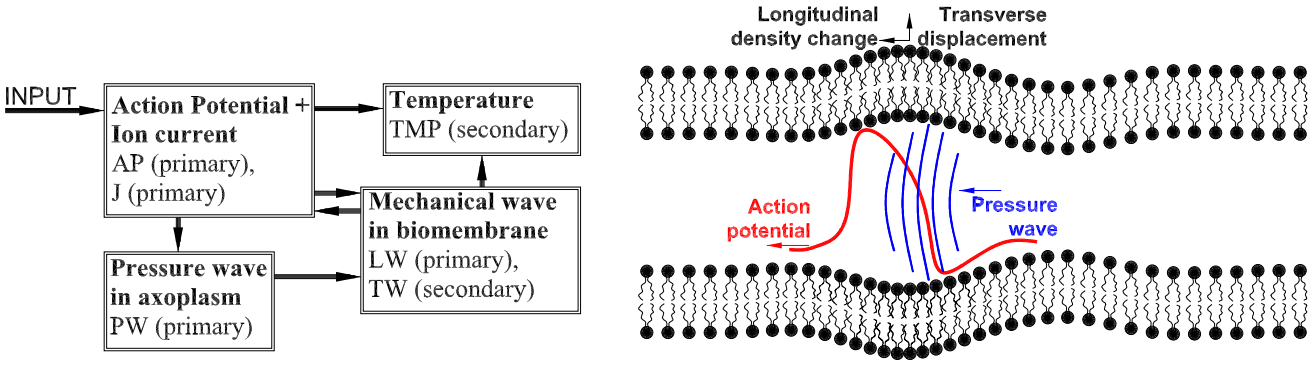


Figure 8: The block diagram of the possible mathematical model for the ensemble of waves in the nerve fibre (left), an artistic sketch of the wave ensemble (right).

Dimensions

The dimensions of the primary quantities. The FHN equation is in terms of z [V] (volt), j [A] (ampere), and the iHJ equation is in terms of u $[\frac{g}{m^2}]$ (grams per square meter) area density [24] and the pressure is in terms of p [Pa] (Pascal). The governing equations dimensions and additional coefficients (directly from dimensionless equations by just slapping the required dimensions on them for the primary quantities and making the dimensions fit). First, action potential z $[V]$

$$\begin{aligned} z_t\left[\frac{V}{s}\right] &= d\left[\frac{m^2}{s}\right] \cdot z_{xx}\left[\frac{V}{m^2}\right] - \zeta_1[Hz] \cdot (a_1 + b_1) \cdot z[V] + \\ &\zeta_2\left[\frac{1}{Wb}\right] \cdot (1 + (a_1 + b_1)) \cdot z^2[V^2] - \zeta_3\left[\frac{F \cdot s}{kg \cdot m^2}\right] \cdot z^3[V^3] - \iota_1\left[\frac{1}{F}\right] \cdot j[A], \end{aligned}$$

where $[V]$ - volt, $[s]$ - second, $[m]$ - meter, $[Wb]$ - weber (magnetic flux, $\left[\frac{kg \cdot m^2}{s^2 \cdot A}\right]$), $[Hz]$ - hertz, $[F]$ - farad (capacitance). Ion current j $[A]$

$$j_t\left[\frac{A}{s}\right] = \varepsilon \cdot \zeta_4\left[\frac{1}{H}\right] \cdot (a_2 + b_2)\, z\,[V] - \varepsilon \cdot \iota_2\,[Hz] \cdot j\,[A]\,,$$

where $[V]$ - volt, $[s]$ - second, $[Hz]$ - hertz, $[A]$ - ampere, $[H]$ - henry (inductance). Density change $u\left[\frac{kg}{m^2}\right]$

$$
\begin{aligned}
&u_{tt}\left[\frac{Pa}{m}\right] = \upsilon_1\left[\frac{m^2}{s^2}\right]\cdot c^2\cdot u_{xx}\left[\frac{g}{m^4}\right] + \upsilon_2\left[\frac{m^4}{kg\cdot s^2}\right]\cdot N\cdot u\left[\frac{kg}{m^2}\right]\cdot u_{xx}\left[\frac{kg}{m^4}\right] + \\
&\upsilon_3\left[\frac{m^6}{kg^2\cdot s^2}\right]\cdot M\cdot u^2\left[\frac{kg^2}{m^4}\right]\cdot u_{xx}\left[\frac{kg}{m^4}\right] + \upsilon_4\left[\frac{m^4}{kg\cdot s^2}\right]\cdot N\cdot U_X^2\left[\frac{kg^2}{m^6}\right] + \\
&2\cdot\upsilon_5\left[\frac{m^6}{kg^2\cdot s^2}\right]\cdot M\cdot u\left[\frac{kg}{m^2}\right]\cdot u_x^2\left[\frac{kg^2}{m^6}\right] - \upsilon_6\left[\frac{m^4}{s^2}\right]\cdot H_1\cdot u_{xxxx}\left[\frac{kg}{m^6}\right] + \\
&\upsilon_7\left[m^2\right]\cdot H_2\cdot u_{xxtt}\left[\frac{Pa}{m^3}\right] + f_1(p,j,z)\left[\frac{Pa}{m}\right],
\end{aligned}
$$

where $[Pa]$ - pascal (pressure), $[m]$ - meter, $[kg]$ - kilogram, $[s]$ - second. Pressure p $[Pa]$

$$
p_{tt}\left[\frac{Pa}{s^2}\right] = \pi_1\left[\frac{m^2}{s^2}\right]\cdot c_f^2\cdot p_{xx}\left[\frac{Pa}{m^2}\right] - \pi_2\left[Hz\right]\cdot\mu\cdot p_t\left[\frac{Pa}{s}\right] + f_2(z,j)\left[\frac{Pa}{s^2}\right],
$$

where $[Pa]$ - pascal (pressure), $[m]$ - meter, $[s]$ - second, $[Hz]$ - hertz (frequency). Coupling forces

$$
\begin{aligned}
f_1\left[\frac{Pa}{m}\right] &= \gamma_1\left[\frac{s}{m}\right]\cdot p_t\left[\frac{Pa}{s}\right] + \gamma_2\left[\frac{kg}{C\cdot m^2}\right]\cdot j_t\left[\frac{A}{s}\right] - \gamma_3\left[\frac{C\cdot s}{m^4}\right]\cdot z_t\left[\frac{V}{s}\right]; \\
f_2\left[\frac{Pa}{s^2}\right] &= \eta_1\left[\frac{A}{m^2\cdot s}\right]\cdot z_x\left[\frac{V}{m}\right] + \eta_2\left[\frac{Pa}{C}\right]\cdot j_t\left[\frac{A}{s}\right] + \eta_3\left[\frac{A}{m^3}\right]\cdot z_t\left[\frac{V}{s}\right]
\end{aligned}
\tag{20}
$$

where $[m]$ - meter, $[s]$ - second, $[Pa]$ - pascal (pressure), $[A]$ - ampere (current), $[V]$ - volt (potential), $[C]$ - coulomb (charge).

Magnitudes of the known quantities

For a start, let us list what do we known about the strengths (magnitudes) of the effects normally associated with nerve pulse propagation. After that based on what is known from experimental studies perhaps we can estimate something more about the terms we have added to our governing equations, i.e., are the required order of magnitude of these effects realistic, can anything be neglected as negligibly small compared to other effects and so on?

Pressure in giant squid axon by Terakawa [54]. In the paper [54] the squid *Dorytheusis bleekeri* was used, the extracted giant axon section was about 40 to 50 $[mm]$ long and the diameter of the used axons varied from 500 to 650 $[\mu m]$ with experiments performed roughly at the room temperature (about 16–20 Celsius). Intracellular pressure p response amplitude about 10 $[mPa]$ (note that the cytoskeleton was removed from inside the axon and a special ionic solution was used for achieving that kind of pressure response). Membrane potential z response about 109 $[mV]$. With the cytoskeleton present, the observed pressure response was roughly one magnitude smaller at around 1 $[mPa]$ and the observed action potential change was a bit smaller as well. In the Terakawa experiment, "The pressure maximum always lagged behind the peak of the action potential by about 0 to 5 ms, and the low-pressure phase was delayed even more." [54]. It is also noted in that paper that "... the pressure response depends on the membrane potential in a simple manner no matter how the kinetics of the ionic channel are modified." [54]. While the focus of the Terakawa paper was on the pressure component a transverse displacement was also observed with the increase of the axon diameter noted to be approximately 1 nm (first 1 nm expansion over approximately 3 ms time followed by roughly 1 nm contraction over approximately 5 ms time giving the effect a total magnitude of roughly 2 nm). In the Terakava paper, the signal velocities were roughly 1 to 4 $[m/s]$ and it was noted in [54] that "The pressure wave was conducted more slowly than the electronic potential...". In [54] "... the pressure wave propagated at a velocity of about 2 m/s.".

FitzHugh–Nagumo model [39]And its connection to HH model. In general, the paper [39] is not particularly useful for extracting used values for the parameters or their dimensions as the paper goes through several stages of "... this is similar to ..." which makes the actual dimensions of the solved equations hard to follow. Regardless there is a number of noteworthy sentences printed which deserve highlighting. In the introduction of [39] it is stated "... whereas an electric pulse signal which is transmitted along an animal

nerve axon suffers neither attenuation nor distortion, regardless of the distance covered." This appears to be an assumption made by the authors before deriving their simplified model and not something stated as an observation from the performed experiments with the actual nerve fibres. When deriving the celebrated FHN equation in [39] the authors start with the HH model followed by the FitzHugh derived Bonhoeffer-van der Pol type simplified system from the HH model (eq. 2 in [39])

$$\begin{aligned} J &= \frac{1}{c}u_t - w - \left(u - \frac{u^3}{3}\right) \\ cw_t &+ bw = a - u, \end{aligned} \tag{21}$$

where a, b and c are "constants" satisfying certain relations. The new parameters in the eq. (21) are related to the HH parameters so that HH parameters $V, m \to u$ the parameters $h, n \to w$ and $I \to J$ where In HH model V was the membrane voltage $[mV]$, m was the sodium activation (from 0 to 1, dimensionless), h was sodium inactivation (from 0 to 1, dimensionless), n was potassium activation (from 0 to 1, dimensionless) and I was the membrane current density $\left[\frac{\mu a}{cm^2}\right]$. Taking a moment to digest these relationships noted and the structure of the eq. (21) it is clear that the dimensions on the different sides of the "=" sign do not match without adding some coefficients not written in there to make the dimensions match. After investigating the phase trajectories of the HH system and eq. (21) and noting certain similarities with model electrical circuits the authors establish a certain "equivalence" between the systems so that

$$I = \frac{R_0}{2r_0}V_{SS} \to j = \frac{1}{r}v_{ss}, \tag{22}$$

where I was the membrane current density $\left[\frac{\mu a}{cm^2}\right]$ in the HH model, S $[cm]$ was the distance along the nerve axon in the HH model, R_0 $[cm]$ was the radius of the nerve axon in HH model and r_0 $[K\Omega cm]$ was the specific resistance of the axoplasm in the HH model while in the "equivalent" relationship for the eq. (21) r is the "interstage coupling resistance per unit length of the line". Plugging relationship (22) into eq. (21) allows the authors to write system (21) as

$$\begin{aligned} \frac{h}{r}u_{ss} &= \frac{1}{c}u_t - w - \left(u - \frac{u^3}{3}\right), \\ cw_t &+ bw = a - u, \end{aligned} \tag{23}$$

where $h = \frac{\rho}{r}$ and ρ was some kind of coefficient which appears to not be the density. The authors consider the system (23) as a simplified HH model, eliminating w and obtaining a single partial differential equation in terms of u. The equation normally called the FHN equation in literature is obtained when assuming that $R = 0$ $(b = 0)$ (radius of the axon is zero) leading to an equation in the form

$$z_{txx} = z_{tt} + \mu\left(1 - z - \varepsilon z^2\right)z_t + z, \quad \mu > 0, \quad \frac{3}{16} > \varepsilon > 0. \tag{24}$$

Authors in [39] note that "It seems likely that the partial differential equation (24) is one of the simplest mathematical models of the nerve axon." Overall it seems that FHN equation is somewhat ill-suited for estimating its parameters directly from the physical experiments or for proposing an actual physical experiment. An open question is if the initial interpretation of recovery current as an actual current (measured in amperes) is correct or if should we use instead a current density (amperes per unit area or unit length). The current plan is to keep our initially found dimensions, calibrate the AP so that it has a correct range in millivolts and then decide how to interpret the recovery current based on what are the actual estimated values for individual ion currents in the literature.

Overview by Mueller and Tyler [38].

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