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Long range electromagnetic field nature of nerve signal propagation in myelinated axons

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The nature of saltatory conduction in myelinated axon described by equivalent circuit and circuit theory is still contentious. Recent experimental observations of action potentials transmitting through disjointed nerve fibers strongly suggest an electromagnetic wave propagation mechanism of the nerve signals. In this paper, we employ the electromagnetic wave model of the myelinated axon to describe action potential signal propagation. We use the experimental frequency-dependent conductivity and permittivity values of the nerve tissues in order to reliably calculate the electromagnetic modes by using electromagnetic mode solvers. We find that the electromagnetic waves above 10 kHz can be well confined in extracellular fluid–myelin sheath–intracellular fluid waveguide and propagate a distance of 7 mm without much attenuation. Our study may serve as one of the fundamental researches for the better understanding of the nervous system.

Keywords: action potential propagation and axons, neuronal wave propagation, neuroscience, electrodynamics in the nervous system

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1. Introduction

Action potential (AP) is an electrical pulse. It is a messenger in the nervous system of the body to send electrical excitation impulses along the nerve fibers. However, the exact mechanism on how it is generated and propagated along different types of nerve fibers is still an open subject under debate. From the mathematical viewpoint, the generation of AP falls in a realm of nonlinear local activity and chaos. Chua,[1] Joglekar and Wolf[2] modeled a neuron system as a memristor which is a resistor plus memory and found that the AP as a direct current (DC) response of memristors occurs at small range of I and V above the edge of chaos. In the conventional Hodgkin–Huxley (HH) model,[3–7] the AP is the potential difference variation across the membrane of the excitable cell. Such a variation is the consequence of ions flowing through the transmembrane protein molecules and charge accumulation. The polarization process and the depolarization process of the insulated phospholipid bilayer are treated as the charging process and the discharging process of the capacitor, respectively, and this local switching activity leads to the action potential. In the present paper, we accept the HH model as the established physical mechanism of AP generation, but do not discuss the model itself further. Instead, we are interested in the contentious physical mechanism behind the AP propagation, especially along myelinated nerve fibers. Various theoretical and experimental studies have been conducted to investigate the exact nature of saltatory conduction, which include solitonic mechanical compression waves,[8–10] double-cable periaxonal conduction,[11] electrostatic fields,[12,13] and electromagnetic waves.[14–18] The recent experimental proofs of the ability of AP signals to transmit across disjointed nerve cells (using a long-range mechanism termed "ephaptic coupling") has provide more credence for electromagnetic wave theory for the AP propagation.[19–22]

In our wave approach, the nerve signal propagation along axons is realized through the wave radiated by ion flow in the ion channel, which depends on the detail of ion transport in the selected protein-based channels, and controlled by ion gates. The ion channels are controlled by ion concentration and electric potential gradient while ion gates by gate reaction. In general, the ion channel is a passive conduit for ion flow according to electro-diffusion gradient. Ion pump is energised by ATP and pushes ions to move against the gradients. In order to excite longitudinal field gradient along the axon, the electromagnetic field must be a dipolar field in nature which is directional. Gadsby proposed a mechanism that a bond ion state can be formed in occluded states to exchange one kind of ion with the other across the membrane.[23] This mechanism drives the dipolar oscillations by alternating the polarity of potential across the membrane. The frequency of radiation depends on the gating reaction and thickness of the membrane.

Recently, high frequency signal generation and transmission through axon[24–27] in high frequency above GHz have received much attention. Those high frequency signals may be

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generated not by current in ion channel but through collective excitation of electromagnetic field and polaritons in cavity or even excitation of unsaturated bond in myelin. In these cases, the frequency of the signal depends on the resonance mode of cavity, bond strength and collective mode. By these recent developments, we are motivated to study the possibility of AP propagation along a myelinated axon as an electromagnetic wave passes through a cladding dielectric waveguide formed by extracellular fluid–myelin sheath–intracellular fluid. The modelling of AP propagation as electromagnetic waves passing through this type of waveguide structure has been established already by Xu J *et al.*,[14] Xu S and Xu J,[15] and Xu S *et al.*[14–16] We take it as the starting template for our study.

2. Model

According to the HH model, when action potential is formed, it can propagate along the axon without attenuation. For unmyelinated axons, the transmembrane protein molecules, which act as ion channels, are distributed throughout the whole fiber. Thus, the local switching activity can spread and propagate along with the nerve fiber as a "wave of activity", and it is described by a nonlinear diffusion equation known as cable equation.[28,29] For unmyelinated axons of invertebrate animals, like the giant squid, this equation yields an impulse velocity of 18.8 m/s, which is consistent with measured speed of 21.2 m/s.[30]

However, some nerve fibers of vertebrate animals are covered by a lipid-rich multilamellar structure named myelin sheath. And different sections of the sheath are separated by gaps called "nodes of Ranvier". There are no ion channels on the myelin sheath, so, the sheath can be considered as insulated cylinder. Since no more ions flow through the internodal region, the action potential will only occur at the nodes of Ranvier[31,32] and completed by ion motion along the interface between extracellular fluid and myelin sheath and also between intracellular fluid and intracellular sheath. This special conduction mode is named saltatory conduction.

The appearance of the myelin sheath greatly accelerates the propagation speed of the neuron signal, some nerve fibers with special structures can support the signal propagating at a speed of 200 m/s.[33] The traditional explanation ascribes the saltatory conduction to the charging of the myelinated section.[34] In the HH model, when the first ion channel is open, the induced currents through the ion channel charge the myelin sheath (Fig. 1) and induce the displacement current, and go back to ion channel and form a closed loop with myelin sheath acting as a capacitor. The potential difference on the myelin sheath surface decreases as it approaches to the next node. The distance between the nodes ensure that the potential difference reaching the neighboring node larger than the threshold voltage, and thus generating the action potential. This is the mechanism for how the action potential transfers from one node to the other according to saltatory conduction. However, for myelinated axon, the existence of ionic charging on the membrane along the axon is not clearly understood. Now, we come to consider the case where the action potential motion is in the form of electromagnetic waves propagating but not charge moving as indicated in Fig. 2. Once an action potential electromagnetic pulse is generated at one node, it will have two possible paths to propagate to the other nearest node, depending on the resistance along the path. The first path is through the extracellular fluid–myelin sheath–intracellular fluid dielectric waveguide, and the other path is along the interface of extracellular/intracellular and myelin sheath surface. The latter path along the interface has been proposed and studied by Cohen *et al.*[11] and Akaishi.[12,13] However, the details of attenuation to wave propagation in the intracellular and extracellular space need to be carefully analyzed.

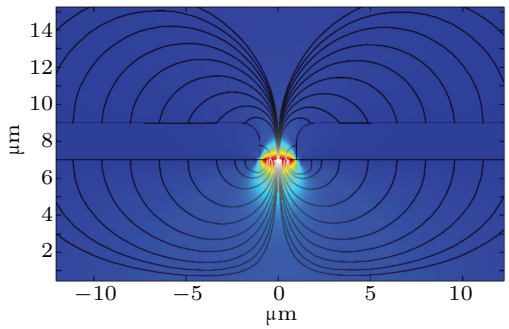


Fig. 1. Longitudinal view of myelinated axon, with active node in the middle, and node-to-node connections established by static electric field diffusion (gray streamlines).

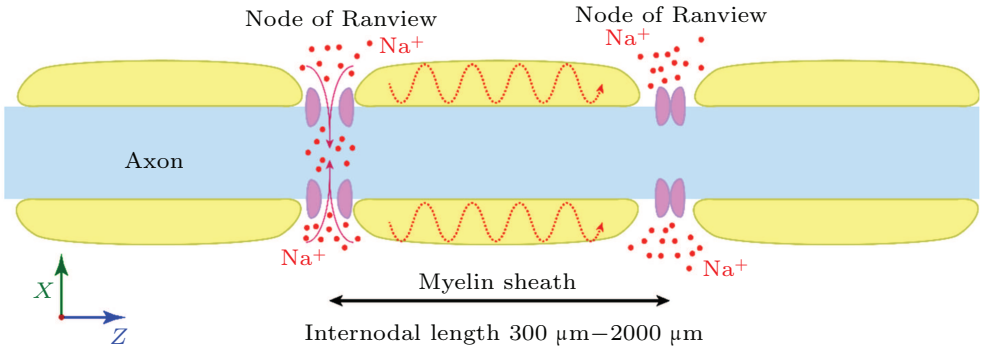


Fig. 2. Cross-sectional view of myelinated axon, and illustration of internode communication through EM wave. Normally, the internodal length of myelinated axon varies from 0.3 mm to 2 mm, and the diameter of myelinated axon varies from 1 μm to 20 μm.

The myelinated axon is composed of two parts. One is the very thick phospholipid layer acting as myelin sheath, such an insulating material has high permittivity (ε_2) and low conductivity (σ_2). The other one is aqueous physiological electrolyte solution on both the inside and the outside of the nerve fiber and modelled as the intracellular fluid and the extracellular fluid, respectively. The electrolyte solution contains many free ions; thus, it has low permittivity (ε_1) and high conductivity (σ_1). This conductor–insulator–conductor structure can form a natural bio-waveguide to support the propagation of the EM wave as shown in Fig. 3. In this research, we concentrate only on the EM property of one single myelinated axon, therefore no boundary restriction is imposed on the extracellular space.

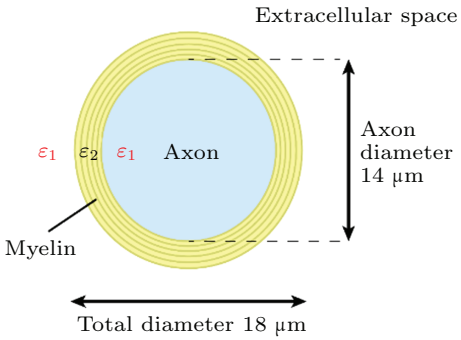


Fig. 3. Cross-sectional view of myelinated axon. The dimension follows the data given by Ref. [35] in which the axon radius is 7 μm, and coating with 2-μm-thick myelin sheath.

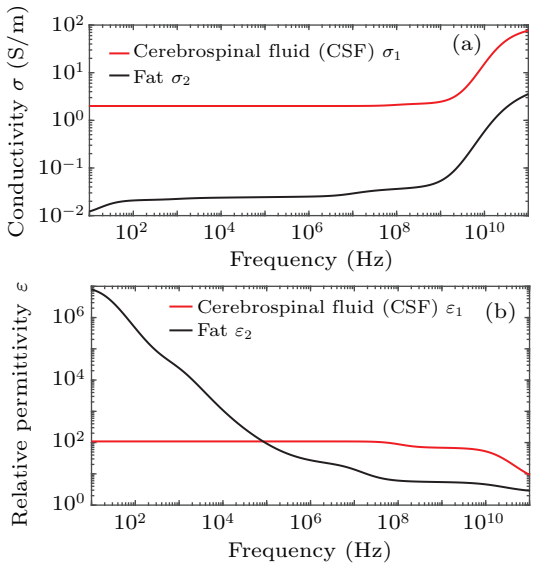


Fig. 4. (a) Plot of experimental frequency-dependent conductivity of fat and CSF,[36–38] and (b) plot of experimental frequency-dependent relative permittivity.[36,37] Cerebrospinal fluid (CFS) parameters (σ_1 and ε_1) belong to the intracellular and extracellular fluid. Lipid (fat) parameters (σ_2 and ε_2) belong to wrapped myelin sheath.

To model the aqueous environment of the nerve fiber, we use the experimental data of cerebrospinal fluid (CSF) solution, σ_1 and ε_1, as extracellular fluid and intracellular fluid, respectively. We assume both extracellular and intracellular space to have approximately the same dielectric properties. And the experimental value of the tissue fat σ_2 and ε_2 used for myelin sheath.[36–38] The relative permittivity and the conductivity are both frequency-dependent, and their values are plotted in Figs. 4(a) and 4(b).

The simulations are conducted by using COMSOL®Multiphysics commercial software, and the frequency range of interest is 10 Hz–100 GHz, and the mode analysis is used to find the field nature of the bio-waveguide. The effective mode index n', which is the ratio of the wavenumber in the waveguide to the wavenumber in the vacuum (k_0) is expressed as

$$n' = \frac{k}{k_0} = n - \kappa \mathrm{i}, \tag{1}$$

where n is the effective refractive index, i is the imaginary unit and $\kappa > 0$ corresponds to the case of loss.

3. Results and discussion

Simulation results of the cladding waveguide mode for 1 MHz are shown in Fig. 5(a). The mode has two peaks and the wave is well confined when it propagates in the myelin sheath. Some of the $\boldsymbol{E}$ fields enter into the interface region between myelin sheath and extracellular and between myelin sheath and intracellular. Some weak $\boldsymbol{E}$ fields are scattered in the extracellular region. The detailed distribution of electric vectors is also shown in Fig. 5(b).

To determine the longitudinal spatial profile of the EM wave and the attenuation during propagation, we need to find the attenuation constant α. Since the effective mode index $n' = (k/k_0) = n - \kappa \mathrm{i}$, thus, $k = k_0 n' = (2\pi/\lambda_0)n'$, we have

$$\begin{aligned} \alpha + \beta \mathrm{i} &= k\mathrm{i} = \frac{2\pi}{\lambda_0} n' \mathrm{i} = \frac{2\pi}{\lambda_0} (n - \kappa \mathrm{i})\, \mathrm{i} \\ &= \frac{2\pi\kappa}{\lambda_0} + \frac{2\pi n}{\lambda_0} \mathrm{i}, \end{aligned} \tag{2}$$

where α is the attenuation constant, β is the phase constant, λ_0 is the wavelength in the vacuum, k is the wavenumber in the waveguide, n and κ are real and imaginary parts of the effective mode index.

The electric field propagating alone the longitudinal $+z$ direction is expressed as

$$E(z,t) = \mathrm{Re}\left[E_0 \mathrm{e}^{\mathrm{i}(\omega t - kz)}\right] = \mathrm{Re}\left[E_0 \mathrm{e}^{-k\mathrm{i}z} \mathrm{e}^{\mathrm{i}\omega t}\right]. \tag{3}$$

Substitution of $\alpha + \beta \mathrm{i} = k\mathrm{i}$ into Eq. (3) yields

$$E(z,t) = \mathrm{e}^{-\alpha z}\left[E_0 \mathrm{e}^{-\mathrm{i}\beta z} \mathrm{e}^{\mathrm{i}\omega t}\right], \tag{4}$$

indicating that as z increases, the amplitude of electric field will lower by a factor $\mathrm{e}^{-\alpha z}$. The simulation results of corresponding n and κ at different frequencies are shown in Fig. 5(c).

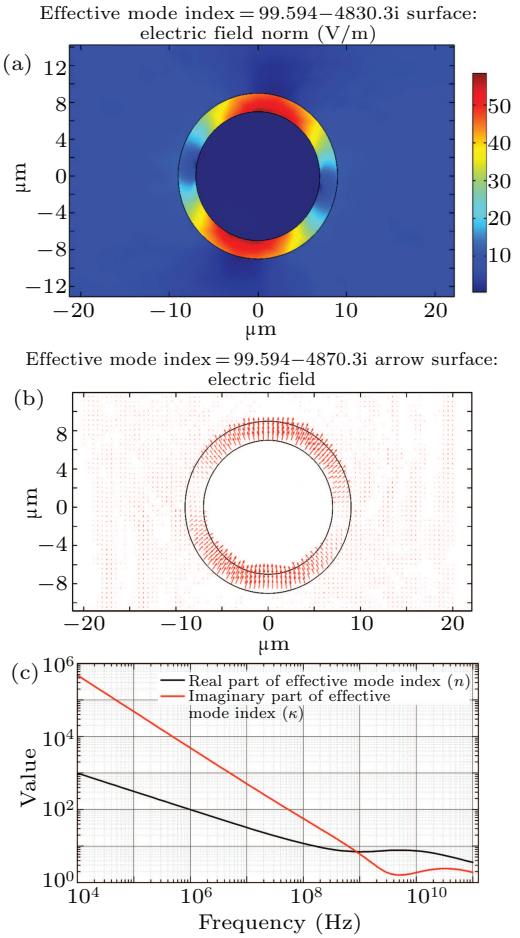


Fig. 5. (a) Normalized electric field intensity, (b) electric field vector distribution of myelinated axon at 1 MHz, and (c) real part of effective mode index (n) and imaginary part of effective mode index (κ).

The very large imaginary part κ indicates that this waveguide is quite lossy, and the EM wave will attenuate very fast within few millimeters as shown in Fig. 6(a). The attenuations of electromagnetic waves at different frequencies are shown in Fig. 6(b).

From the simulation results it follows that the nerve signals can propagate about 6 mm to 7 mm before their intensity is attenuated by half, for the electromagnetic waves with frequencies between 10 kHz and 1 GHz. The propagation length is quite consistent with the typical distance between myelinated internodes. The cutoff frequency of the bio-waveguide is found to be 10 kHz, and any wave with a frequency lower than this value does not have a certain mode to propagate along the bio-waveguide (see Fig. S1 in supplementary information). The energy is no longer confined in the myelin sheath but distributes around the near axon space, and the electric field leaks out of the waveguide and travels along the interface. For frequencies above the cut-off, certain propagation mode exists (see Figs. S2–S4 in supplementary information). The possibility of AP conducted along interface has been studied by Cohen *et al.*[11] and in the form of electrostatic wave by Akaishi.[12,13]

For very high frequencies, say, above 100 GHz, the simulation shows drastic attenuation, and the electric field will lose half of its amplitude within a few hundred micrometers. Simulation results from Liu *et al.*[35] indicated that at THz regime the wave can propagate 500 μm on the myelin sheath without dramatic attenuation, which matches well with our simulation trend. Normally, the internode length varies from 300 μm to 2 mm. Thus high-frequency EM waves like infrared wave are not suitable for long-distance signal transmission.

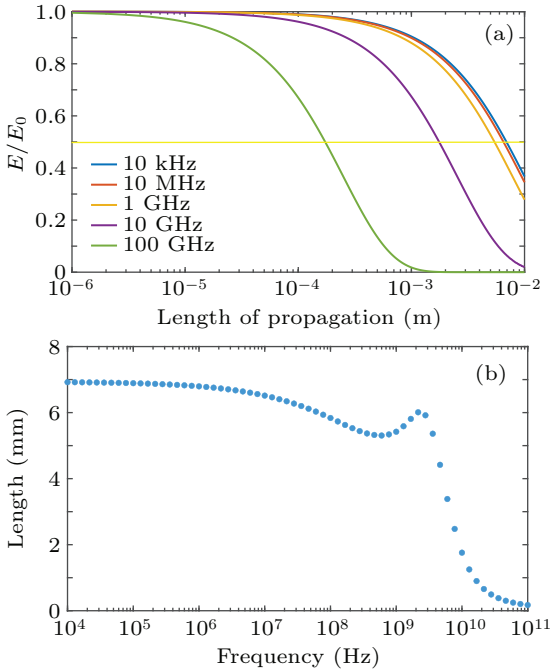


Fig. 6. (a) Attenuations of waves with different frequencies, with yellow line indicating half value and (b) lengths of the waves that propagate after having been attenuated to half of their original values ($E/E_0 = 0.5$).

Whether it is high or low-frequency waves, due to the small n value, the propagation speed $v = c/n$ is very fast, so the transfer time of the EM wave is negligible. Although the EM connection between two nodes is established, the node will not be activated immediately. The node of Ranvier will be active only when a certain energy level is reached. So, there is time needed to accumulate enough electric strength (energy). After the electric strength exceeds the threshold, the action potential will be regenerated at the next node. The macroscopic conduction speed depends on the relay time, which is time-needed for energy accumulation between nodes.[39,40]

4. Conclusions

We have investigated the possibility of AP signals propagating via dynamic electric fields in the myelinated axon. For electromagnetic waves with frequency higher than 10 kHz the extracellular fluid–myelin sheath–intracellular fluid biological waveguide can confine the wave well and propagate a distance of 7 mm without much attenuation. For the lower frequency waves, the signal can propagate along the interface of extracellular fluid and myelin sheath as an interface wave.[11] The driving force for low frequency waves propagating along the

interface may come from Coulomb force generated by the ions accumulated at node of Ranvier channels (see Fig. 1).[12,13] It is hoped that our results may shed light on the long-range nature of nerve signal transmission that has been recently observed in ephaptic coupling phenomenon, and ultimately serve as one of the fundamental researches to better understand the nervous system.

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