Tohoku J. Exp. Med., 2018, **244**, 151-161

Medical Hypothesis

Saltatory Conduction as an Electrostatic Compressional Wave in the Axoplasm

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Saltatory conduction is an essential phenomenon to facilitate the fast conduction in myelinated nerves. The conventional conductive models assumed electric circuits with local current along the axonal membrane to explain the nerve conduction in unmyelinated nerves. However, whether such models with local current can be also applied to the saltatory conduction in myelinated nerves is unknown. In this report, I propose a new model of saltatory conduction by focusing on the behavior of electric charges in the axoplasm, not limited to the membrane. In myelinated nerves, because of the large internodal length and the low ion channel density in the internodal segment, the whole cross-section of the internodal axoplasm would contribute to the signal conduction. Because the conducted signals originate from the sodium ion influx through the voltage-gated sodium (NaV) channel at the Ranvier's nodes, an individual conducted signal can be described as a single electrostatic compressional wave of positive charges in the internodal axoplasm. Based on this model, the total number of NaV channels in one Ranvier's node would regulate the strength of the wave. Also, the internodal length would be important for the faster conduction in larger myelinated axons. Based on the linear relationships between axonal diameter, internodal length, and conduction velocity, the internodal length would be inversely proportional to the ratio of the transmitted overall wave strength at a Ranvier's node to the original strength at the proximal adjacent node. This new mathematical model may have wide applicability and usability for the conduction in myelinated nerves.

Keywords: electrostatic interactions; internodal length; myelinated nerves; saltatory conduction; voltage-gated sodium channel
Tohoku J. Exp. Med., 2018 February, **244** (2), 151-161.

Introduction

In the nervous system, there are two types of nerves by the existence of myelin sheathes on their axons: myelinated nerves and unmyelinated nerves. Myelinated nerves usually have larger axonal diameters and achieve faster conduction velocity than unmyelinated nerves (Fig. 1). In both types of the nerves, influx of positively-charged sodium ions through the voltage-gated sodium (NaV) channels in the axonal membrane is the primary motive force to generate the transmitted signal (Hodgkin and Huxley 1952).

Conduction velocity of unmyelinated nerve (V_U) is known to be proportional to the square root of axonal diameter (D) as shown below.

$$V_U \propto \sqrt{D} \qquad (1)$$

At present, the most popular conductive models in unmyelinated nerves are the equivalent circuit model, proposed by Hodgkin and Huxley in 1940's, and the cable theory (Hodgkin and Huxley 1952; Koch 1984). By using the cable equation of the cable theory shown below, we can quantitatively describe the transition of membrane potential at a specific location and time ($V_m(x, t)$).

$$\lambda^2 \frac{\partial^2 V_m(x,t)}{\partial x^2} - \tau_m \frac{\partial V_m(x,t)}{\partial t} - V_m(x,t) = 0 \qquad (2)$$

(λ, *space constant*; τ_m, *time constant*)

These conventional theories have explained the nerve conduction as a two-dimensional propagation of the membrane potential across the axonal membrane by supposing virtual closed electric circuits stretched across the internal and external surfaces of the membrane, in which the Ohm's law and Kirchhoff's current law hold.

Though these sophisticated conventional theories have been well developed, whether we can really assume such closed electric circuits within the axoplasm has not been

Received December 7, 2017; revised and accepted January 31, 2018. Published online February 22, 2018; doi: 10.1620/tjem.244.151.
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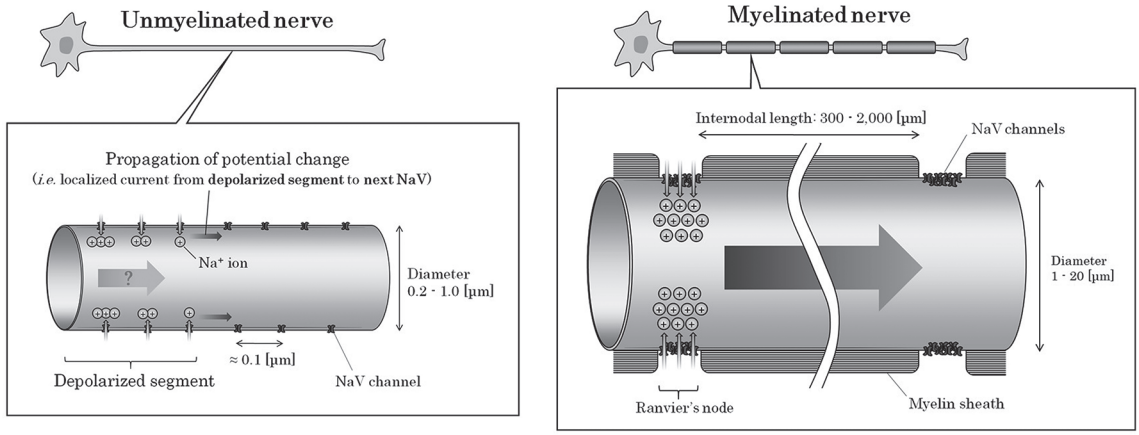


Axonal diameter (D):	0.2 – 1.0	[μm]
Conduction velocity:	0.5 – 2	[m/s]
NaV channel density (C_d):	10 – 100	[$/\mu m^2$]

Axonal diameter (D):	1.0 – 20.0	[μm]
Conduction velocity:	3 – 120	[m/s]
C_d at Ranvier's nodes:	1,000 – 2,000	[$/\mu m^2$]

Fig. 1. Overview of unmyelinated and myelinated nerves.
In unmyelinated nerves, the distance between adjacent NaV channels is much shorter than the axonal diameter. On the other hand, in myelinated nerves, NaV channels are highly concentrated in the segment of Ranvier's nodes and the distance between adjacent Ranvier's nodes is far larger than the axonal diameter. Though the exact mechanism of saltatory conduction is not known yet, we can estimate that the nerve conduction in myelinated nerves take place on the whole cross-section of the internodal axoplasm.
Na^+ ion, sodium ion; NaV channel, voltage-gated sodium channel.

theoretically fully considered from the viewpoint of electrostatic ionic interactions. In the actual site of the nervous system, there is almost no free electron; the principal electric carrier is believed to be the positively- or negatively-charged ion particles. Thus, before the activation of the NaV channels, the distribution and the gradient of electric charges around the channels need to be changed with shifted membrane potential (Yarov-Yarovoy et al. 2006; Khalili-Araghi et al. 2010). These facts imply that we need to principally focus on the drift of electric charges around the ion channels, resulting in the change of potential gradient around the channel. In electrolytic solutions like the axoplasm, the distance and the velocity of ionic drift are substantially limited by the surrounding innumerable water molecules and other ion particles. Thus, to explain the fast velocity of nerve conduction, we need to regard the conducted signal as a kind of successive electrostatic compressional wave of the electrically-charged ions (Akaishi 2017). The ion particles not only exert electrostatic force to the surrounding molecules but also work as a medium to transmit the electrostatic compressional wave. As a result, influx of sodium ions through a NaV channel would result in sequential propagation of short ionic drifts around the channel, creating a single electrostatic compressional wave in total that conducts the signal to the next NaV channel (Dani 1986; Cukierman et al. 1988; Miedema 2002; Akaishi 2017).

Though the molecular components and ionic concentrations would be almost similar between the axoplasm in myelinated nerves and that in unmyelinated nerves, the conduction patterns are totally different between them. In myelinated nerves, signals are transmitted from one Ranvier's node to the next without producing active membrane currents in the internodal segment, which is known as the saltatory conduction (Tasaki 1939). Unlike the conduction velocity in unmyelinated nerves, conduction velocity in myelinated nerves (V_M) is known to be proportional to the length of axonal diameter (D [μm]).

$$V_M \propto D \tag{3}$$

Though we know that the contribution of D to the conduction velocity is different between in myelinated nerves and in unmyelinated nerves, the exact physiological mechanism behind such difference is not known. We need fundamentally new theories to distinguish the different conductive patterns between them. However, though there are several mathematical models for the nerve conduction in unmyelinated nerves (Koch 1984; Akaishi 2017), there is no mathematical model for the saltatory conduction in myelinated nerves. If we can develop such a conductive model in myelinated nerves, it would be useful not only for evaluating the validity of the conventional theories but also for understanding the physiological phenomena of the saltatory conduction. Furthermore, with a new mathematical model of saltatory conduction, we would be able to achieve new insights into the mechanisms of many neurological disorders related to the altered function of the ionic channels like amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, and Alzheimer's disease (Kumar et al. 2016). In this report, I introduce a theoretical model of saltatory conduction from the new viewpoint of ionic behavior within the electrolyte solution of axoplasm and estimate the theoretical relations between the axonal size and the con-

ductive parameters.

Material and Methods

List of abbreviated parameters

The parameters used in this report are listed below in alphabetical order.

A_{NaV}: Total amount of NaV channels in each Ranvier's node

D: Axonal diameter [μm]

$F_{(x, t)}$: Strength of the electrostatic force from the proximal axoplasm to the axoplasm at the longitudinal location of "x" and the time of "t"

$L_{internode}$: Length of an internode between two adjacent Ranvier's nodes [μm]

$Q_{(x, t)}$: Amount of electrical charges in the axoplasm at the longitudinal location of "x" from the proximal adjacent node and the time of "t".

V_M: Conduction velocity in myelinated nerves with a specific axonal diameter

$T_{internode}$: Time lapse in one internodal segment

Handling of the internodal length and length of Ranvier's node

First, we need to decide how to treat the size of each component of axon. Axonal diameter can differ among myelinated nerves and will be defined as "D" in this study. Longitudinal length of each myelin sheath is usually around 300-2,000 μm (Simpson et al. 2013; Seidl 2014; Johnson et al. 2015). Previous reports showed that the internodal length could vary in axons with different sizes (Rushton 1951; Arbuthnott et al. 1980; Ibrahim et al. 1995). Based on these previous reports, the internodal length and the axonal diameter are almost linearly correlated each other. In this report, first, we provisionally set the internodal length to be constant at 1,000 [μm]. Then, in later sections, we change the internodal length variously to evaluate the theoretical importance of the internodal length for the conduction velocity.

The length of one Ranvier's node is usually around 0.5-5.0 μm, but the exact relationship between the axonal diameter (D) and the length of Ranvier's node has not been known (Arancibia-Carcamo et al. 2017), and the relationship between the axonal diameter and the density of NaV channel at the Ranvier's nodes has not been known either. Thus, in this study, we avoid to discuss about the theoretical relationship between the channel density in Ranvier's nodes and the axonal diameter; we simply discuss about the amount of NaV channel in each Ranvier's node (A_{NaV}) as a function of the axonal diameter (D).

Reliability of remote electric current jumping internodal segment

At present, the most accepted theory to explain the saltatory conduction is that remote "local current" flowing from one Ranvier's node to the next node. The myelin sheath is believed to provide an insulation that increases the resistance of the membrane. Both of the conventional equivalent circuit model and cable theory have equally contributed to form the basic concept of this theory (Huxley and Stampfli 1949; Arancibia-Carcamo and Attwell 2014; Seidl 2014). On the other hand, it has been of concern whether we can really apply a closed electric circuit to the actual nervous system. Certainly, the actual site of axoplasm is filled with numerous amounts of electrically-charged ion particles and much more amounts of water molecules. Different from the situation in metal circuits, there is almost no free electron that can freely transmit the electric current within the axoplasm; the axoplasm is an electrolyte solution after all.

Here, we consider whether we can really assume remote electric current from a node to the next by skipping the internodal segment. First, we consider about the pattern of electric field in electrolyte solution between two spots with different electric potentials. The electrolytes within a solution create "electrical double layer" on the surface of the spots with an elevated or decreased electric potential (Gebbie et al. 2013). Most of the other bulk solution remains equipotential without potential gradient; thus, we cannot always expect an enough amount of ionic drift within the bulk solution between the two spots with different potentials (Feng et al. 2010). We cannot simply assume metal leads running through the internodal segment inside and outside the membrane without theoretical deliberations. Also, we need to be deliberate in applying the Ohm's law or the Kirchhoff's law to the physiological phenomena in the axoplasm.

Possibility of remote electrostatic force jumping internodal segment

First, we consider whether the electrostatic force from the inflowing sodium ions through the NaV channels can directly work on the ions around the next NaV channel and can trigger its opening. The electrostatic force between two electric charges can be calculated as below.

$$Coulomb\ force = \frac{q_1 q_2}{4\pi\varepsilon r^2} \quad (4)$$

In the equation above, r is the distance between the two spots, q_1 and q_2 are the strength of electric charges in two different spots, and ε is the permittivity of substance lying between the two electric charges. Now, we assume a model in which there is no NaV channel in the internodal segment and all the NaV channels are concentrated in the Ranvier's nodes. Also, we assume that the length of one Ranvier's node is constant at 1.0 [μm] and the length of one internode at 1,000 [μm]. Under these assumptions, the distance between the group of NaV channels in one Ranvier's node and that in the next node, which is equivalent to r in the equation (*4*), would be more than 1,000 times larger than the distance between adjacent NaV channels in unmyelinated nerves. Here, we assume an ideal situation that the density of NaV channels at Ranvier's nodes is also 1,000 times higher than that in the axonal membrane of unmyelinated nerves, though it is not achieved in the actual site. Then, in myelinated nerves, r in the equation (*4*) becomes 1,000 times larger, q_1 becomes up to 1,000 times larger, compared to those in unmyelinated nerves. The Coulomb force directly exerted from the inflowing ions at one node to the ions at the next node will become more than 1,000 times smaller than that between the adjacent NaV channels in unmyelinated nerves.

$$Coulomb\ force\ (r = 10^3 \times A,\ q_1 = 10^3 \times B) = \frac{Coulomb\ force\ (r = A,\ q_1 = B)}{10^3} \quad (5)$$

In the equation above, "A" and "B" are the constants, "*Coulomb force* ($r = 10^3 \times A$, $q_1 = 10^3 \times B$)" stands for the Coulomb force between adjacent Ranvier's nodes in myelinated nerves, and "*Coulomb force* ($r = A$, $q_1 = B$)" stands for the Coulomb force between adjacent NaV channels in unmyelinated nerves. As a conclusion here, faster conduction velocity in myelinated nerves than in unmyelinated nerves cannot be explained based on a remote electrostatic force transmitted directly from the inflowing ions at one

Ranvier's node to the ions around the next channel (Fig. 2). The realized conduction velocity would be the same at most with that in unmyelinated nerves with similar size. Because the actual density of NaV channel at Ranvier's nodes is much less than the above-described ideal assumption (*i.e.*, 1,000 times larger than that in unmyelinated nerves), the expected conduction velocity in myelinated nerves would fall to be slower than that in unmyelinated nerves based on the above-described model. In the first place, if we consider the actual scale of each structure in myelinated nerves, we can easily imagine that explaining the saltatory conduction with direct remote Coulomb force from one Ranvier's node to the next node would be unreasonable (Fig. 3); the axonal diameter is only 1-10 μm, but the distance between each adjacent Ranvier's nodes reach up to 1,000 μm. Transmission of sodium ion from extra-cellular fluid to intra-cellular fluid across the thin axon membrane (around 0.01 μm) at one Ranvier's node will never significantly affect the electric field at the next node.

The amount of ions and water molecules in axoplasm

Before we consider about a new theoretical model of saltatory conduction, we consider about the number of ion particles and water molecules in the axoplasm and also those passed through each NaV channel into axoplasm during its activation. The volume of axoplasm between two adjacent Ranvier's nodes can be described as below.

$$\textit{Volume of one internodal segment} = \pi\left(\frac{D}{2}\right)^2 \times 10^3\ [\mu\mathrm{m}^3] = 2.5 \times 10^{-10}\,\pi D^2\ [\mathrm{cm}^3] \quad (6)$$

Here, if we assume the specific gravity of axoplasm to be 1.0 g/cm^3, molecular weight of water to be 18, and the Avogadro constant to be 6×10^{23} mol^{-1}, the total amount of water molecule in the axoplasm of one internodal segment can be described as below.

$$\textit{Number of water molecules in one internodal segment} \approx 2.6 \times 10^{13}\,D^2 \quad (7)$$

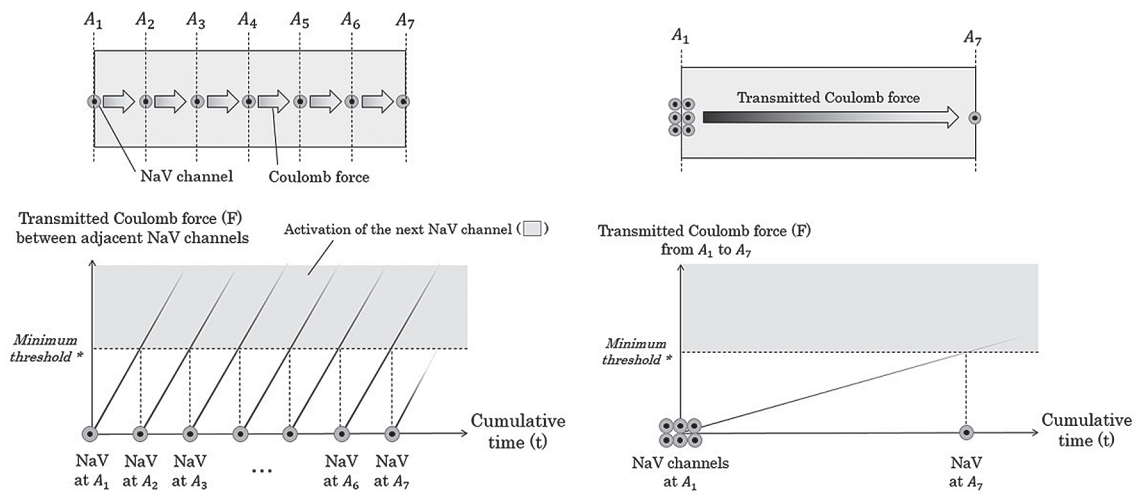
Also, if we assume the cation concentration in the axoplasm to be around 200 mmol/L, the total number of cation particles in the axoplasm of one internodal segment can be described as below.

$$\textit{Number of cation particles in one internodal segment} \approx 10^{11} \times D^2 \quad (8)$$

Because the volume of axoplasm at one Ranvier's node would be about 1/1,000 of that in one internodal segment, numbers of water molecules and cations in axoplasm at one Ranvier's node with 1 μm length can be described as below.

$$\textit{Number of water molecules in one nodal segment} \approx 2.6 \times 10^{10}\,D^2$$
$$\textit{Number of cation particles in one nodal segment} \approx 10^8 \times D^2 \quad (9)$$

Next, we will consider about the total number of sodium ions flowing into axoplasm through NaV channels in one Ranvier's node. Now, the density of NaV channel in Ranvier's nodes is known to be no less than 10^4 channels/μm^2. If we can assume the circularity for the cross-section of axon, the surface area of one Ranvier's node is described as πD μm^2. Here, in a myelinated nerve with the conduction velocity of 10 m/s, an allowed time lapse at each Ranvier's node is 10^{-1} milli-



*Minimum threshold *: minimum transmitted Coulomb force to move ions around the next NaV channel and triggers its opening.*

Fig. 2. A hypothetical model of nerve conduction only with remote electrostatic force in unmyelinated nerves (left) and myelinated nerves (right).
When the NaV channels are totally gathered at Ranvier's nodes by the function of myelin sheathes, NaV channel density at each Ranvier's node will dramatically increase. However, because the distance from one Ranvier's node to the next will also increase proportionally to the channel density or with higher proportionality, the transmitted Coulomb force from one node to the next will not be increased. In other words, we cannot explain the saltatory conduction by direct remote electrostatic force from the inflowing sodium ions at one Ranvier's node to the ions at the next.
A_n, longitudinal position of each NaV channel on axonal membrane from proximal to distal; NaV, voltage-gated sodium channel.

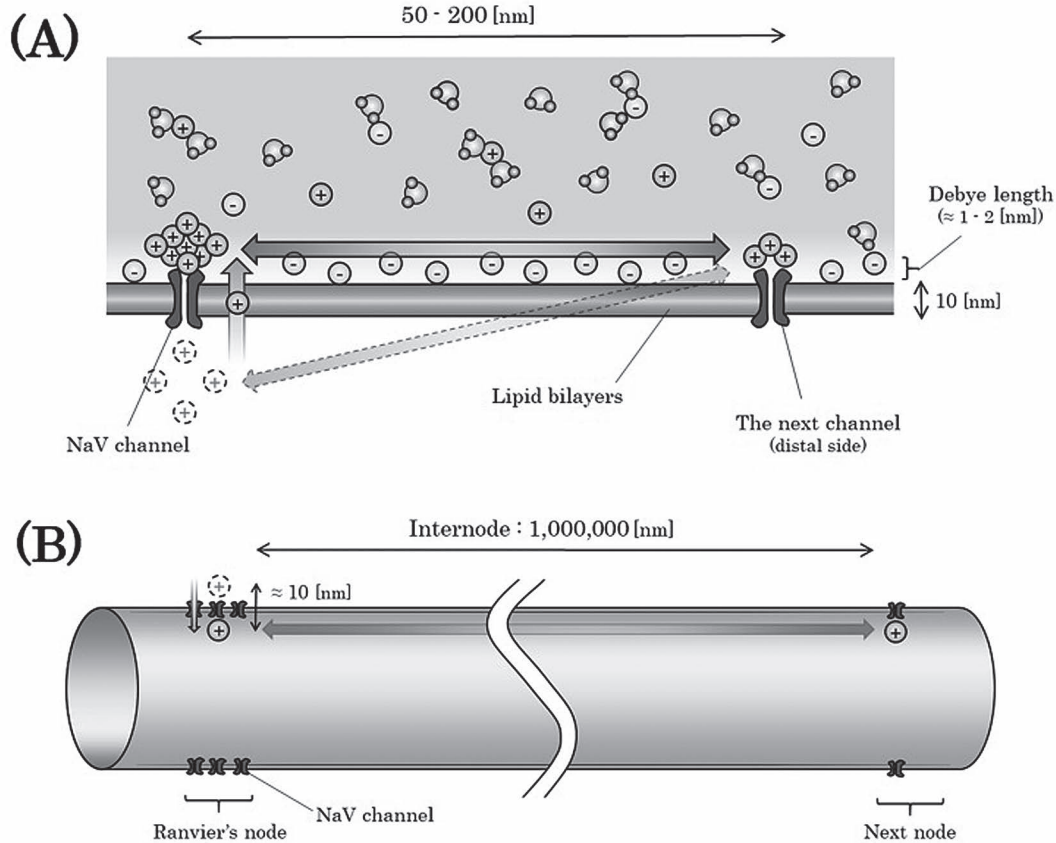


Fig. 3. Schematic illustration of nerve conduction in unmyelinated nerves (upper) and in myelinated nerves (lower) with the actual scale of structures.
(Upper) In unmyelinated nerves, because two adjacent NaV channels are relatively close for the size of axonal diameter, remote electrostatic force from the inflowing ions through the proximal depolarized NaV channels would be transmitted along the internal surface of the membrane and cause a potential change at the distal NaV channel, depending on the amount of inflowing ions at the proximal channel. Thus, channel density of NaV channel on the membrane would be important in unmyelinated nerves. (Lower) In myelinated nerves, because the distance between one Ranvier's node and the next is much larger than the axonal diameter, such direct remote electrostatic force is difficult to suppose. Instead, a compressional wave of electrically-charged ion particles will transmit the potential change to the distal resting node, depending on the total amount of inflowing ions through NaV channels at the proximal adjacent node. Thus, the total number of NaV channel at one Ranvier's node would be important in myelinated nerves.
NaV, voltage-gated sodium channel.

second. One NaV channel is known to pass more than 10^8 particles per second. Considering these facts together, the number of sodium ion particles flowing through NaV channels in one Ranvier's node in one signal transmission can be estimated as below.

$$\textit{Number of inflowing sodium ion particles in one node per signal} \approx 3 \times 10^8 D \quad (10)$$

Because the axonal diameter (D) with the conduction velocity of 10 m/s is about 2 μm, based on (*9*) and (*10*), almost the same amount of cations with that existed in one nodal region would flow into axoplasm through NaV channels in one Ranvier's node per signal. This result suggests that inflowing sodium ions at one Ranvier's node would hold enough amount of energy to produce an electrostatic compressional wave based on their repulsive force with cations and their attractive force with anions.

Estimated physical phenomenon taking place in saltatory conduction

Based on the results described above, the suggested model to explain saltatory conduction would be an electrostatic compressional wave mainly transmitted by the electrically-charged ion particles within the axoplasm, proceeding within the internodal axoplasm from one Ranvier's node to the next. Though the exact mechanism of NaV channel-opening in the membrane is not fully understood yet, a propagation of electric potential change in the axoplasm with the form of an electrostatic compressional wave would collapse the potential gradient on the internal surface of NaV channels at the next node and trigger their openings. Because of the long distance of the internodal length and the low density of NaV channels in the internodal segment, the compressional wave would be transmitted across the whole cross-section of the internodal axoplasm. Because the diffusive flux of ions in an electrolyte solution is very slow, chain reaction of electrostatic interactions would much more contribute to the saltatory conduction than diffusive flux of ion particles, though both forms would take place. The successive electrostatic compressional wave will be instantly transmitted to the distal side, successively changing the electric potential of the distal axoplasm, and will shortly activate the NaV channels at the next Ranvier's node.

Because the water molecules are polar molecule, they may receive a couple of force from the transmitted electrostatic compressional wave. Though such moment of a couple would result in rotations of the water molecules, the position or mechanical energy of water molecules in total would not be affected by the force couple.

The propagation speed of the compressional wave in the axoplasm would be much faster than the conduction velocity of signals (V_M) and the wave will be almost instantly transmitted to the next node; the conduction efficiency or the attenuation ratio of the wave between the adjacent nodes will be regulated by the type of medium between the nodes. Thus, the propagation speed of the compressional wave would be almost constant within a living organism. The theoretical effects from the parameters of nerve structures (*i.e.*, axonal diameter, internodal length) to the strength of the compressional wave will be discussed in the results section.

The instantly transmitted compressional wave at the next node will gradually change the electric field around the NaV channels at the next node. Once the strength of transmitted compressional wave around each NaV channel surpasses the minimum threshold, the horizontal gradient of electric field on the internal surface of the channels will be collapsed and the NaV channels at the next node will be opened.

If we regard each internodal segment of axoplasm as a closed isolated physical system, the sum of energy inside the system will be preserved by the principle of energy conservation. Added energy from the inflowing sodium ions at each Ranvier's node to the ion particles in the axoplasm will be eventually converted not only to kinetic energy of ion particles but also to thermal energy after colliding with water molecules or the internal surface of axonal membrane. Though the exact scale of such energy loss by collision and friction is not known, we can reasonably estimate that energy loss from collision with axonal membrane would be far smaller than that from collision with water molecules. Thus, the attenuation rate of the compressional wave per unit length of axoplasm would be theoretically constant, irrespective of the axonal diameter. Such attenuation is further suppressed by the low capacitance of internodal membrane with low density of ion pumps and channels in the internodal segment, which would realize the high values of safety factor in myelinated nerves ranging from 4 to 5.

For reference, whether such kind of electrostatic compressional waves on the whole cross-section of the axoplasm can be also expected in unmyelinated nerves or not is unknown yet. Based on the normal channel density and axonal diameter in the unmyelinated nerves, though the forefront of the wave may proceed along the internal surface of axonal membrane, electrostatic compressional waves on the whole cross-section of axoplasm could also be assumed in unmyelinated nerves.

Conduction time lapse in nodal and internodal segments

In Ranvier's node, a high density of NaV channels is known to exist (Caldwell et al. 2000; Black et al. 2002). We can estimate that the physiological mechanism of nerve conduction within Ranvier's nodes would be the same with that in unmyelinated nerves, only with the exception that the NaV channel density would be much higher in Ranvier's nodes (Arancibia-Carcamo and Attwell 2014). Thus, the conduction velocity within Ranvier's nodes can be estimated as below.

$$\textit{Conduction velocity in Ranvier's nodes} \propto \sqrt{D} \qquad (11)$$

However, no matter of the NaV channel density in Ranvier's nodes, the sum of longitudinal length of nodal segment is only about one-thousandth of the full length of axon. Furthermore, because the density of NaV channels in Ranvier's nodes is much higher than that in unmyelinated nerves, the estimated time lapse in Ranvier's nodes would be shorter than that in unmyelinated nerves with the same length. Thus, we can ignore the time lapse in the nodal segments when we consider about the conduction velocity in myelinated nerves.

$$\textit{Time lapse in the internodal segments} >> \textit{Time lapse in the Ranvier's nodes} \qquad (12)$$

Theoretical relation between amount of NaV channels in one Ranvier's node and axonal diameter

In this section, we discuss about the theoretical relationship between the axonal diameter (D) and amount of expressed NaV channels in one Ranvier's node (A_{NaV}). In a previous report, the amount of axonal transport is shown to be proportional to the cross-sectional area of the axon (Wujek et al. 1986). Some other reports showed that the number of microtubules was proportional to the cross-sectional area of the axon (Hoffman et al. 1985; Iturriaga 1985). Thus, theoretically, we can estimate that the total amount of the transported NaV channels in an axon per unit time would be proportional to D^2.

$$\textit{Total amount of transported NaV channel in an axon} \propto D^2 \qquad (13)$$

Here, the total number of Ranvier's nodes within a specific length of axon would be inversely proportional to the internodal length ($L_{internode}$).

$$\textit{Number of the Ranvier's nodes} \propto \frac{1}{L_{internode}} \qquad (14)$$

Now, because the amount of expressed NaV channels in one Ranvier's node (A_{NaV}) would be proportional to the transported amount of NaV channels and inversely proportional to the total number of the Ranvier's nodes, the following relationship as to A_{NaV} would hold.

$$A_{NaV} \propto \frac{\textit{Amount of transported NaV channels}}{\textit{Number of the Ranvier's nodes}} \propto D^2 \bullet L_{internode} \qquad (15)$$

Electrical state of NaV channels in Ranvier's node

Each nodal membrane would take one of the following electrical states during the propagation of action potential.

(1) Resting state
(2) Rising phase of action potential during which the Na^+ influx is maximal
(3) Peak action potential during which the Na^+ influx is balanced with the K^+ efflux
(4) Refractory period of action potential during which the K^+ efflux overwhelms the Na^+ influx

The state (2) is equivalent to the phase of depolarization and the state (4) is equivalent to the phase of repolarization. Each Ranvier's node repeats the above-mentioned four electric states as the node transmits the signals repeatedly. If we focus on one Ranvier's node

and consider that the NaV channels in that specific node has just been activated, some of the proximal nodes would still remain under the phase of state (2) and state (3), but more former channels could have already shifted to state (4) and state (1). Cations in the axoplasm will soon receive repulsive forces from the nodes under the electrical phase of state (2), but will receive attractive forces from the nodes under the phase of state (4); vice versa for the anions.

If we focus on two adjacent Ranvier's nodes and the internode between them, we can regard the electrical state of the proximal node to remain within the early phase of state (2) when the distal node has just been depolarized. This is because the allocated time lapse in each Ranvier's node under the normal conduction velocity would be < 0.1 ms, which is less than the time required for each NaV channel to shift from depolarization to repolarization.

Though the electrostatic force from more proximal nodes would be weaker and less influential, the strength of the compressional wave would be certainly affected by the electrical states of more proximal nodes than the closest proximal node. This is supported by the fact that the safety factor of myelinated nerves can reach up to 4.0-5.0. There could be an electric push-pull power gradient, depending on the distribution of nodal electric states. Thus, in the last part of the results section, we will consider about the effects from the distribution of nodal electric states and the attenuation ratio of the wave per internode to the results and discussions of this report.

Results

Strength of the electrostatic compressional wave with fixed internodal length

Fig. 4 shows the schema of a myelinated axon, in which the variables used in this study are written. Though the safety factor of myelinated nerves is known to be ≥ 2, as explained in the previous section, we ignore the electrostatic force passed down from ≥ 2 proximal internodes and regard the focused internodal segment as a closed physical system for convenience in this study. Here, we define $F_{(x,\,t)}$ as the sum of electrostatic force [N] at the time of "t" from ions in the proximal axoplasm to ions at the longitudinal location of "x" μm from the proximal adjacent node ($x = 0$).

$F_{(x,\,t)} :=$ *electrostatic force [N] from the proximal axoplasm to the ions in axoplasm on the longitudinal location of* "x" *[μm] at the time of* "t"

Now, we define $Q_{(x,\,t)}$ as the total amount of positive electric charges [C] in the cross-section of axoplasm at the longitudinal location of "x" at the time of "t". Next, we tentatively divide the proximal segment of axoplasm into n-portions with the longitudinal length of x/n μm for each portion. Then, the rate of change in $F_{(x,\,t)}$ is the sum of the rate of changes in electrostatic forces between the axoplasm on the location of "x" and the n-portions of proximal axoplasm. The electrostatic force between the axoplasm on the location of "x" and each of the k-th portion ($1 \le k \le n$) of the proximal axoplasm is proportional to the product of electric charges in the two portions and is inversely proportional to the squared distance of the two locations. Thus, the following equations would hold.

$$\frac{\partial F_{(x,\,t)}}{\partial t} = lim_{n\to\infty} \sum_{k=1}^{n} \left(\frac{1}{4\pi\varepsilon}\right) \left[\left(\frac{\partial Q_{(x,\,t)}}{\partial t} \cdot \frac{\partial Q_{(\frac{k}{n}x,\,t)}}{\partial t}\right) \Big/ \left(\left(1-\frac{k}{n}\right)x \cdot 10^{-6}\right)^2\right]$$

$$F_{(x,\,t)} = lim_{n\to\infty} \sum_{k=1}^{n} \left(\frac{1}{4\pi\varepsilon}\right) \left[\left(Q_{(x,\,t)} \cdot Q_{(\frac{k}{n}x,\,t)}\right) \Big/ \left(\left(1-\frac{k}{n}\right)x \cdot 10^{-6}\right)^2\right] \quad (16)$$

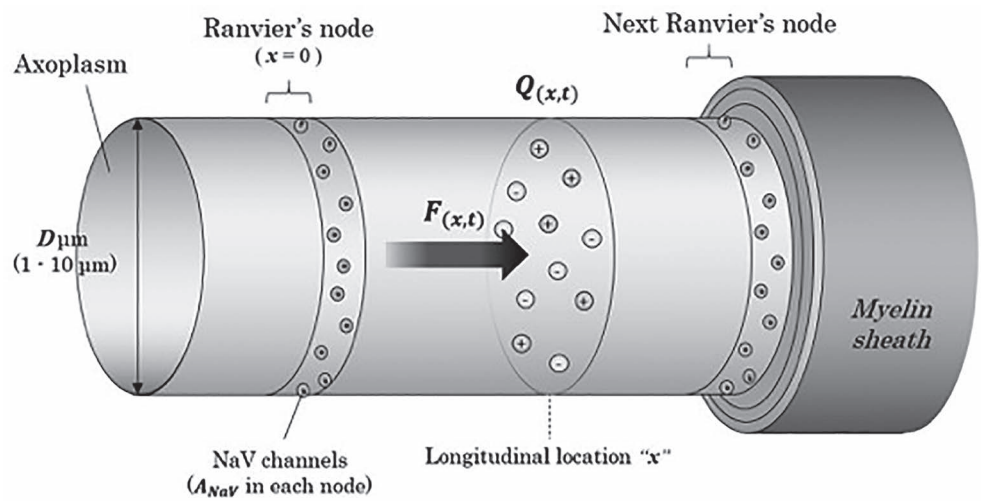


Fig. 4. Schema of a myelinated axon with variables defined in this study.
A_{NaV}, amount of NaV channels in one Ranvier's node; D, axonal diameter; $F_{(x,t)}$, sum of electrostatic force from ions in the proximal part of axoplasm to ions in axoplasm at the location of "x" at the time of "t"; NaV, voltage-gated sodium channel; $Q_{(x,t)}$, sum of electric charges on the cross-section of axoplasm at the location of "x" at the time of "t"; x, longitudinal location on the axon or the distance from the proximal adjacent Ranvier's node ($x = 0$).

In these equations, ε is the relative permittivity of water, which can be regarded as a constant of proportionality. Here, we define "Δt" as an infinitesimally short time. Because the rate of change in $Q_{(x,\,t)}$ at a specific longitudinal location of "X" is regulated by the rate of change in the total amount of ions at the longitudinal location of $(X-\frac{1}{\mathrm{n}}X)$ at the time of "$t-\Delta t$", the following relations hold.

$$\frac{\partial Q_{(X,\ t)}}{\partial t} \propto \frac{\partial Q_{(X-\frac{1}{n}X,\ t-\Delta t)}}{\partial t}$$
$$\frac{\partial Q_{(\frac{k}{n}X,\ t)}}{\partial t} \propto \frac{\partial Q_{(\frac{k-1}{n}X,\ t-\Delta t)}}{\partial t} \quad (17)$$

Based on (*16*) and (*17*), the following relations would hold.

$$\frac{\partial F_{(X,\ t)}}{\partial t} \propto \lim_{n\to\infty}\sum_{k=1}^{n} \left[\left(\frac{\partial Q_{(X,\ t)}}{\partial t} \cdot \frac{\partial Q_{\left(\frac{k}{n}X,\ t\right)}}{\partial t}\right) \Big/ \left(\left(1-\frac{k}{n}\right)X \cdot 10^{-6}\right)^2\right]$$
$$\propto \lim_{n\to\infty}\sum_{k=1}^{n} \left[\left(\frac{\partial Q_{\left(X-\frac{1}{n}X,\ t-\Delta t\right)}}{\partial t} \cdot \frac{\partial Q_{\left(\frac{k-1}{n}X,\ t-\Delta t\right)}}{\partial t}\right) \Big/ \left(\left(1-\frac{k}{n}\right)X \cdot 10^{-6}\right)^2\right]$$
$$\propto \frac{\partial F_{(X-\frac{1}{n}X,\ t-\Delta t)}}{\partial t} \quad (18)$$

Thus, the following relationships as to the strength of the transmitted compressional wave at the specific location of *"X"* hold, based on mathematical induction.

$$F_{(X,\ T)} = \int_0^T \frac{\partial F_{(X,\ t)}}{\partial t}\,dt$$
$$\propto \int_0^T \frac{\partial F_{\left(X-\frac{1}{n}X,\ t-\Delta t\right)}}{\partial t}\,dt = F_{(X-\frac{1}{n}X,\ T-\Delta t)}$$
$$\therefore F_{(X,\ t)} \propto F_{(X-\frac{1}{n}X,\ t-\Delta t)} \propto F_{(X-\frac{2}{n}X,\ t-2\Delta t)} \propto \cdots$$
$$\cdots \propto F_{(x=0,\ t-n\Delta t)} \propto Q_{(x=previous\ node,\ t-n\Delta t)} \quad (19)$$

In these relations, because "Δt" is a minute constant value specific to the longitudinal location of "x", if the location of "x" is fixed, $Q_{(x=previous\ node,\ t-n\Delta t)}$ is proportional to the total number of NaV channels in the proximal adjacent Ranvier's node. Considering these results together, if the internodal length ($L_{internode}$) is constant at 1,000 μm, the transmitted strength of the wave from a Ranvier's node in the electrical state (2) to the next node in the state (1) would hold the following relationship.

$$F_{(x=1{,}000\ \mu m,\ t)} \propto Total\ number\ of\ NaV\ channels\ in\ the\ proximal\ adjacent\ node \quad (20)$$

Now, combined with (*15*), if we regard $L_{internode}$ to be constant at 1,000 μm, transmitted electrostatic force from a depolarized Ranvier's node to the overall ions on the whole axoplasmic cross section at the next node at an arbitrary time ($\forall_t$) would be proportional to D^2, if $L_{internode}$ is fixed at 1,000 μm.

$$F_{(x=next\ node,\ \forall_t)} = F_{(x=1{,}000\ \mu m,\ \forall_t)} \propto D^2 \quad (21)$$

Conduction velocity in myelinated nerves with fixed internodal length

As discussed in material and methods section, NaV channels on the next Ranvier's node should be activated depending on the transmitted electrostatic force to the unit cross-sectional area (ΔS) of the space around the channels. Thus, combined with (*21*), the following relations hold.

$$Transmitted\ force\ to\ each\ NaV\ channel\ at\ the\ next\ node\ (if\ L_{internode}\ is\ fixed\ at\ 1{,}000\ \mu m)$$
$$= \frac{\Delta F_{(x=1{,}000\ \mu m,\ t)}}{\Delta S} \propto \frac{D^2}{D^2}$$
$$= constant\ (irrelevant\ of\ axonal\ diameter) \quad (22)$$

These relations suggest that, if we regard the internodal length as constant, we cannot achieve the established knowledge of "$V_M \propto D$", and the conduction velocity will be misled to be always constant no matter of the axonal diameter. This result shows that we cannot explain the relation between axonal diameter and conduction velocity with fixed internodal length and we need to apply the empirically known linear relationship between axonal diameter and internodal length to explain the established relation of "$V_M \propto D$".

Actual relation between internodal length and time lapse in one internode

As described in the material and methods section, the following two equations have been experimentally known to hold in the myelinated nerves.

1. $Conduction\ velocity\ (V_M) = \alpha \bullet Axonal\ diameter\ (D)$ (*23*)
2. $Internodal\ length\ (L_{internode}) = \beta \bullet Axonal\ diameter\ (D)$ (*24*)

In these equations, "α" and "β" are constants of proportion-

ality. If these equations hold, the following equations as to the conduction time lapse in one internode ($T_{internode}$) would also hold.

$$T_{internode} = \frac{L_{internode}}{V_M} = \frac{\beta}{\alpha} \ (i.e., \ constant) \qquad (25)$$

Therefore, the conduction time lapse between two adjacent nodes would be always constant. This fact means that, when one of the Ranvier's node has just been turned to the depolarization state, the other before and behind nodes can be assigned each of the four electrical states automatically, irrespective of the axonal diameter (D) or internodal length ($L_{internode}$).

Relation between attenuation rate per each internode and axonal size

As shown in the equation (*25*), time lapse in one internode ($T_{internode}$) is always constant regardless of the axonal size-related parameters. Here, considered together with (*20*), the following theory holds by using the attenuation ratio of the wave strength per internode at an arbitrary time (*i.e.*, ratio of the received wave strength at a node to the original strength at the proximal adjacent node).

$$T_{internode} = constant$$
$$\therefore \ Transmitted \ force \ per \ unit \ cross\text{-}sectional \ area \ at \ L_{internode} \ at \ T_{internode} = constant$$
$$\therefore \ \frac{(Attenuation \ ratio \ per \ internode) \bullet (Number \ of \ NaV \ channel \ in \ each \ node)}{D^2} = constant \qquad (26)$$

Here, if we apply the known linear relationship between D and $L_{internode}$, based on the relation (*15*), total amount of NaV channel in one Ranvier's node (A_{NaV}) would fulfill the following relation.

$$A_{NaV} \propto D^2 \bullet L_{internode} \propto D^3 \qquad (27)$$

Based on (*26*) and (*27*), the following relations as to the attenuation ratio per internode would hold.

Attenuation ratio of the transmitted force per internode

$$\propto \frac{1}{D} \propto \frac{1}{L_{internode}} \qquad (28)$$

This result implies that the attenuation ratio of the electrostatic compressional wave per each internode (*i.e.*, $F_{(x = next\ node,\ t)}/F_{(x = previous\ node,\ t)}$) would be inversely proportional to D or $L_{internode}$.

Discussion

In this report, a new theoretical model to mathematically explain saltatory conduction in myelinated nerves has been described. Certainly, the conventional equivalent circuit model and cable theory are sophisticated models and can theoretically explain many parts of the nerve conduction in unmyelinated nerves. However, as discussed in this report, we need to be deliberate in applying closed electric circuits, Ohm's law, or Kirchhoff's law to the actual phenomena taking place in the electrolyte solution of axoplasm. More than that, only with the conventional theories, we cannot explain the different properties of nerve conduction in unmyelinated nerves (*i.e.*, $V_U \propto \sqrt{D}$) and in myelinated nerves (*i.e.*, $V_M \propto D$). At present, there is no mathematical model to explain the saltatory conduction. Certainly, we required a new additional model of nerve conduction to separately explain the different conductive patterns in unmyelinated nerves and in myelinated nerves.

At present, any kinds of physical phenomena, except for some phenomena in quantum physics, is believed to be composed of the following four fundamental interactions: gravitational, electromagnetic, strong, and weak interactions. Among these forces, gravitational, strong, and weak interactions can be ignored when we consider about the physiological phenomena in the body. Thus, when we consider about the nerve conduction in human body, we need to think about the electromagnetic interaction working between the electric charges in axoplasm and the voltage-gated ion channels.

In myelinated nerves, the distance between two adjacent Ranvier's nodes are several thousand times as far away as the distance of adjacent NaV channels in unmyelinated nerves. In this situation, the potential change as an electrostatic compressional wave would proceed not only along the internal surface of axonal membrane but on the whole cross section of the internodal axoplasm. Such compressional wave of ion particles is originally resulted from the inflowing sodium ions at the proximal adjacent Ranvier's node. And as discussed in the results sections, all of the axonal diameter (D), total number of NaV channels in each Ranvier's node (A_{NaV}), and the internodal length ($L_{internode}$) would be equally important for determining the strength of the compressional wave.

One thing we need to discuss here is the possible effect of ionic diffusion based on ionic concentration gradient within the axoplasm. Based on the Fick's first law of diffusion, which is shown below, the diffusive flux of ions (J) under steady state is proportional to the concentration gradient of the ion.

$$J = -D \frac{dc}{dx}$$

In this equation, D is a diffusion coefficient, c is the concentration of the ion, and x is the position. With this equation, we can see that the ionic diffusion based on ionic concentration gradient at a specific time and location would be also proportional to the rate of sodium ion influx at the proximal adjacent Ranvier's node. Thus, the relationships of (*17*) and the resulting (*18*) would still hold even when we take ionic diffusion into consideration.

This new model theoretically implied several new theoretical findings. One of them is that the distributional pattern of the electrical state in the proceeding proximal Ranvier's nodes for the conducted signal would be always constant irrespective of the axonal size, if we apply the established fact of "$D \propto L_{internode}$". This new finding ensures that the equations and relationships in this report still hold even when we take the electrostatic effects from more proximal Ranvier's nodes than the closest proximal node into consideration.

Lastly, to be emphasized, the result of this study does not deny or surpass the conventional equivalent circuit model and cable theory. Those established conventional theories have been continuously improved to well explain the actual phenomena taking place in the nervous system. This new model also showed a supportive conclusion for assuming electrical circuits within the axoplasm. Based on the result of relations (*28*), the attenuation ratio of the transmitted wave strength per internode was suggested to be inversely proportional to the internodal length. In other words, the transmitted electrostatic force between NaV channels in adjacent two Ranvier's nodes would be inversely proportional to the internodal length. This finding is supportive for assuming electrical circuits within the axoplasm and regarding the nerve signal as a kind of electric current, as the conventional theories did. At present, this new theoretical model is only a brand-new theory and its applicability is still unknown.

As a limitation of this study, the proposed compressional wave of electrically-charged ion particles within the axoplasm has not yet been experimentally confirmed, though it seems to be the most reasonable physical mechanism to explain the saltatory conduction. Also, the theoretical relationship of (*27*) has not been experimentally confirmed. We will be able to evaluate the theoretical relation of (*27*) by utilizing the immunofluorescence staining against the NaV channels and measuring the luminescence at each Ranvier's node in axons with different sizes.

In conclusion, a new theoretical model of saltatory conduction in myelinated nerves from the viewpoint of ionic behavior based on electrostatic interactions within the axoplasm has been proposed. With this new model, we can explain why the relational forms between axonal diameter and conduction velocity are fundamentally different in unmyelinated nerves and in myelinated nerves. Together with the conventional conductive theories, this new conductive model would give us deeper insights into the actual conductive phenomena and may offer us clues to elucidate the pathomechanisms in the ion channel-related neurological disorders.

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