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ORIGINAL ARTICLE

A note on the local current associated with the rising phase of a propagating impulse in nonmyelinated nerve fibers

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Abstract To extend our recent paper dealing with the cable properties and the conduction velocity of nonmyelinated nerve fibers (Bull. Math. Biol. **64**, 1069; 2002), the behavior of the local current associated with the rising phase of a propagating action potential is discussed. It is shown that the process of charging the membrane capacity by means of the local current plays a crucial role in determining the velocity of nerve conduction. The symmetry of the local current with respect to the boundary between the resting and active regions of the nerve fiber is emphasized. It is noted that there are several simple quantitative rules governing the intensities of the capacitive, resistive and total membrane currents observed during the rising phase of an action potential.

Keywords Nerve conduction velocity, Local current

1. Introduction

In 1977, using squid giant axons available at Woods Hole, MA, we closely examined electrophysiological properties of the axon membrane under intracellular perfusion and found that there is a simple quantitative relation between the conduction velocity and the electrical parameters of the axon (Matsumoto and Tasaki, 1977). We derived the following equation relating the conduction velocity v with the membrane capacity per unit area, C, the resistivity of the axon interior, ρ, the unit area membrane resistance at the peak of excitation, R^*, and the axon diameter, d:

$$v = \frac{1}{C}\sqrt{\frac{d}{8\rho R^*}} \tag{1}$$

This equation adequately describes the conduction velocities of nonmyelinated nerve fibers in general.

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Subsequently, it was found that the production of action potentials in squid giant axons and other excitable cells is accompanied by simultaneous swelling of the cortical layer of the cells (Iwasa and Tasaki, 1980; Tasaki, 1999). Furthermore, it became evident that this swelling is a manifestation of an extremely sharp structural transition associated with a Ca–Na ion-exchange process taking place in the superficial gel layer termed "axolemma-ectoplasm complex" of the axon (Metuzals et al., 1981). The conclusion drawn from these findings is that the process of nerve conduction is nothing but a continuous displacement of the boundary between the active (excited) and resting regions of the axon *induced by the local current* (Hermann, 1879) linking these two structurally distinct regions.

The present note supplements our recent article published in this Bulletin (Tasaki and Matsumoto, 2002) dealing with the cable theory of nerve conduction. We first discuss several aspects of the local current in intracellularly perfused squid axons that have not been discussed previously. Then, we treat the linkage between the process of nerve conduction and the distribution of the local current in the vicinity of the boundary between the active and resting regions of the axon.

2. The local current and the membrane capacity

The experimental basis of the following mathematical analysis of the local current is derived from the studies of squid giant axons under intracellular perfusion (Matsumoto and Tasaki, 1977). The schematic diagram at the top of Fig. 1 illustrates the cortical layer of a giant axon (of which the endoplasm had been surgically removed beforehand), separating the internal perfusion solution (400 mM KF, pH 7.3) from the external artificial sea water (containing 423 mM NaCl and 58 mM divalent cations, Mg^{2+} and Ca^{2+}).

Note that, under this continuous intracellular perfusion, the Na-ion concentration inside the axon is kept at zero and the K-ion concentration outside the axon can be maintained also at zero. Under these conditions, the electric resistance of the cortical polyanionic gel layer of the axon is related, in accordance with the well-known Nernst–Einstein equation, directly to the fluxes of Na- and K-ions interdiffusing through the layer (see Tasaki, 1982, p. 219). Since the mobilities of the divalent cations in the layer are far smaller than those of monovalent cations, the intensity of the ohmic (resistive) component of an inwardly directed membrane current—observed during the rising phase of the action potential—is considered to be given approximately by $(J_{Na}–J_K)F$, where J's represent the fluxes of these monovalent cations and F is the Faraday constant.

Suppose that we deliver a brief electrical shock to the axon near one of its ends and evoke a wave of gel swelling in association with the production of a propagating impulse. Now, imagine that we observe the rising phase of this swelling through a microscope that is moving along with the traveling excitation wave. Under these circumstances, the position of the boundary between the active and resting regions of the axon is expected to be seen as remaining stationary. The diagram of an electrical network in Fig. 1, bottom, represents the electrophysiological properties of the superficial polyanionic gel layer (for short designated as "membrane") in the

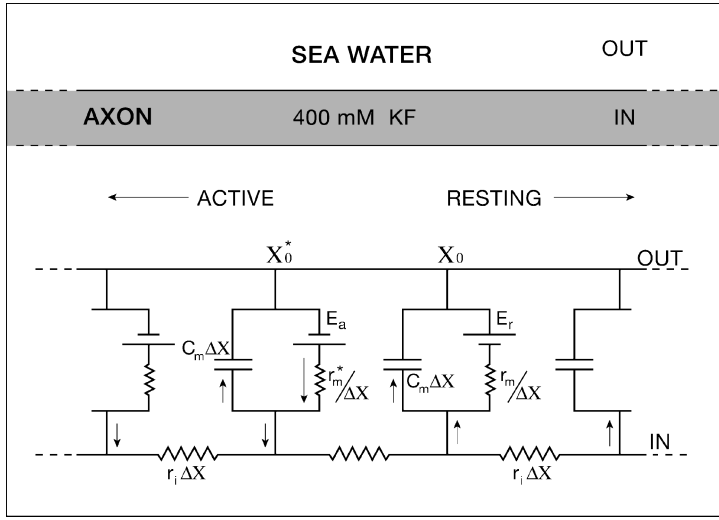

Fig. 1 Electrical network used to describe the physiological behavior of a squid giant axon that is intracellularly perfused with a KF solution and immersed in a large volume of artificial seawater. The network represents the electric property of the superficial gel layer (axolemma–ectoplasm complex) in the vicinity of its boundary between the active (excited) and resting regions. E_a and E_r represent the membrane-emf in the active and resting state, respectively; $r^*_m/\Delta X$ and $r_m/\Delta X$ are the membrane resistances of elements of the axon of ΔX (infinitesimal) in length in the two regions; $c_m \Delta X$ and $r_i \Delta X$ denote the membrane capacity and the longitudinal resistance of a portion of the axon of length ΔX.

vicinity of the boundary between the active and resting regions of the axon under these conditions.

In the following analysis, X denotes the position of a point measured along the axon from the boundary that is moving at a constant velocity v. The portion of the axon between X^*_o and X_o constitutes the *transitional zone* between the active and resting regions. The distribution of the transmembrane electric current, generated as a consequence of a difference between the membrane emf in the active region, E_a, and that in the resting region, E_r, is shown by the small arrows in the diagram.

As in our previous publication (Tasaki and Matsumoto, 2002), the differential equation describing the potential difference across the membrane in the resting state, V, is given by

$$\frac{1}{r_i}\frac{d^2V}{dX^2} + c_m v \frac{dV}{dX} - \frac{1}{r_m}(V - E_r) = 0 \tag{2}$$

where r_i represents the longitudinal resistance ($r_i = 4\rho/\pi d^2$), c_m is the membrane capacitance per unit length ($c_m = C\pi d$), and r_m is the unit length membrane resistance at rest ($r_m = R/\pi d$). The solution of this equation is

$$V = E_r + (V_0 - E_r)e^{-\xi(X - X_0)} \tag{3}$$

where V_0 is the potential at the receding end, $X_{0,}$ of the resting region and ξ, the reciprocal of the space parameter, is given by

$$\xi = \frac{c_{\mathrm{m}} r_{\mathrm{i}} v}{2} + \sqrt{\left(\frac{c_{\mathrm{m}} r_{\mathrm{i}} v}{2}\right)^2 + \frac{r_{\mathrm{i}}}{r_{\mathrm{m}}}} \tag{4}$$

Analogously, the distribution of the potential in the active region is described by

$$\frac{1}{r_{\mathrm{i}}} \frac{\mathrm{d}^2 V}{\mathrm{d}X^2} + c_{\mathrm{m}} v \frac{\mathrm{d}V}{\mathrm{d}X} + \frac{1}{r_{\mathrm{m}}^*} (E_{\mathrm{a}} - V) = 0 \tag{5}$$

and by its solution

$$V = E_{\mathrm{a}} - (E_{\mathrm{a}} - V_0^*)\, \mathrm{e}^{-\eta\left(X_0^* - X\right)} \tag{6}$$

where V_0^* represents the potential at the advancing end of the active region, X_{o}^*, $r_{\mathrm{m}}^*(= R^*/\pi \mathrm{d})$ is the resistance of the membrane in its active state and the reciprocal of the space parameter of the active region is given by

$$\eta = -\frac{c_{\mathrm{m}} v r_{\mathrm{i}}}{2} + \sqrt{\left(\frac{c_{\mathrm{m}} v r_{\mathrm{i}}}{2}\right)^2 + \frac{r_{\mathrm{i}}}{r_{\mathrm{m}}^*}} \tag{7}$$

[Note that the active region extends from $X = X_0^*$ formally to $-\infty$.]

In giant axons intracellularly perfused with a 400 mM KF solution and immersed in artificial sea water, the electric parameters characterizing the axons (about 0.4 mm in diameter) are known to have the following values: c_{m} is 0.126 μF/cm; r_{i} is 29 kΩ/cm; r_{m}^* is 175 Ω cm; r_{m} is 16 kΩ cm. By introducing these observed values into Eqs. (4) and (7), we now examine the dependence of ξ and η on the velocity v in the equations. In Fig. 2, the reciprocals of ξ and η, computed by use of Eqs. (4) and (7), are plotted against velocity v. Note that, corresponding to every arbitrarily chosen value of v, a pair of space-parameters, $1/\xi$ and $1/\eta$, are determined by this computation. It is seen in the figure that the two curves intersect at one point where $1/\xi = 1/\eta = 1.1$ mm and $v = 24.5$ m/sec.

In normal axons, the term $r_{\mathrm{i}}/r_{\mathrm{m}}$ in Eq. (4) is very small as compared with other terms in the equation. When this term is neglected, Eq. (4) may be rewritten as follows:

$$v = \frac{\xi}{c_{\mathrm{m}} r_{\mathrm{i}}} = \frac{1/\xi}{(c_{\mathrm{m}}/\xi)(r_{\mathrm{i}}/\xi)} \tag{8}$$

The first part of this equation indicates that, in Fig. 2, there is inverse proportionality between the value of $1/\xi$ and velocity v. In this part, we recognize also that, when the numerical value of ξ is given, the velocity v can be obtained by dividing this value by the product $c_{\mathrm{m}} r_{\mathrm{i}}$. Note that this product represents the time-constant of the process of *charging the membrane capacity* of a unit length of the axon via a longitudinal resistance of the axon of the same length.

To illustrate the importance of the process of charging the membrane capacity in nerve conduction, the second part is added to Eq. (8) (simply by dividing both

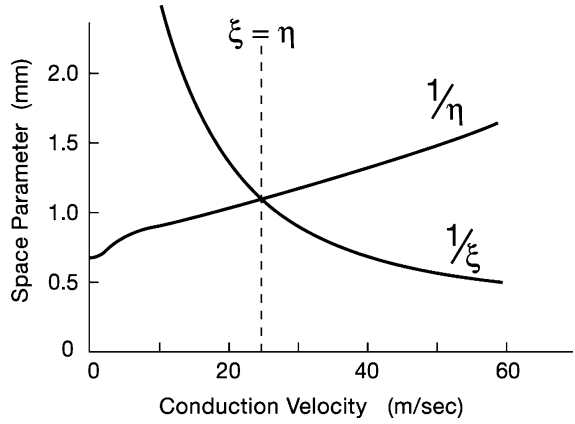

Fig. 2 The space parameters, $1/\eta$ and $1/\xi$, of the squid giant axon computed, by using Eqs. (4) and (7) in the text, as functions of velocity v. The electric parameters of the axon chosen here are: R^*, 22 Ω/cm^2; ρ, 36 Ω cm; C, 1.0 μF/cm^2 and d, 0.04 cm.

the numerator and denominator in the first part by ξ^2). In this part, the numerator $1/\xi$ has a dimension of length, and the denominator represents the capacity of a $1/\xi$ long portion of the axon, c_m/ξ, multiplied by the resistance of the axon interior of the same length, r_i/ξ. We thus find that the velocity v is equal to the length $1/\xi$ divided by the time-constant of the process of charging capacity c_m/ξ via resistance r_i/ξ.

Analogously, by solving Eq. (7) for v, we obtain the following equation:

$$v = \frac{(1/\eta)\left\{(1/r_m^*\eta) - (\eta/r_i)\right\}}{(c_m/\eta)} \tag{9}$$

Now, by replacing ξ in (8) with η and (r_i/ξ) in (8) with the reciprocal of the conductance term inside the braces on the upper right side of (9), we find that (9) has the same form as (8). Thus, we see that the velocity v in Eq. (9) is equal to the distance $(1/\eta)$ divided by the time constant of the process of charging the capacity (c_m/η) by way of conductance $\{(1/r_m^*\eta) - (\eta/r_i)\}$. It will be shown later that, in the axons under study, the first (positive) term in this conductance is approximately twice as large as the second (negative) terms (see Eq. (13)).

Thus far, we have treated the two neighboring regions, active and resting, of the axon almost separately, although the boundaries between the two regions are moving at a common velocity v. In the next section, we closely examine the electrical properties of the transitional zone linking the two regions and investigate the effect of this linkage on the distribution of the local current.

3. Symmetry of the local current

In squid giant axons that are about 0.4 mm in diameter, intracellularly perfused with a 400 mM KF solution and immersed in artificial sea water, the conduction

velocity is known to be about 24 m/sec. When this observed value of velocity is introduced into the diagram in Fig. 2 by marking it with a straight vertical line, it is found that the line falls precisely (i.e. within measurement variability) on the point where the two curves in the diagram intersect. In other words, the velocity v which gives a pair of $1/\xi$ and $1/\eta$ that are significantly different from each other in the diagram are not encountered in real axons. That is, only under the condition that the distribution of the local currents on the two sides of the boundary satisfies the relation

$$\xi = \eta, \tag{10}$$

we can observe displacement of the boundary between the active and resting regions at a common, constant velocity v.

Previously, we have argued that this relation $\xi = \eta$ derives its origin from the continuity of the potential gradient, $\mathrm{d}V/\mathrm{d}X$, at the boundary between the active and resting regions (Tasaki and Matsumoto, 2002). In the present note, we supplement our previous treatment of the local current by taking the following properties of the transitional zone into consideration.

In our recent studies of synthetic polyanionic gel strands (Tasaki, 2002), we have seen that the length of the transitional zone between the swollen (Na^+-rich) and compact (Ca^{2+}-rich) regions is close to the diameter of the strand. From this finding, we now infer that the length of the transitional zone in the axon is of the order of the thickness of the axolemma–ectoplasm complex which is definitely shorter than a few micrometers (see Metuzals et al., 1981). We have seen already that the longitudinal resistance r_i of the axons under study is 29 kΩ/cm, and the membrane resistance in the active state r_m^* is 175 Ω cm. From these data, we immediately see that the longitudinal resistance of a 10 μm ($= 10^{-3}$ cm) long portion of the axon is only 29 Ω, while the membrane resistance of this portion is as high as 175 kΩ. Hence, the potential drop across the longitudinal resistance of this length is negligibly small as compared with that across the resistance of the membrane of about the same length, provided that these two resistances are connected to the emf in series. We thus find it quite reasonable to assume that the membrane potential at the advancing end of the active region (at X_o^* in Fig. 1) is practically equal to that at the receding end (at X_o) of the resting region. Hence, we now accept the validity of this approximate relation $V_\mathrm{o}^* = V_\mathrm{o}$ in these highly excitable axons.

When we introduce these two relations, $\xi = \eta$ and $V_\mathrm{o}^* = V_\mathrm{o}$, into Eqs. (3) and (6), we find that the local current associated with the rising phase of a propagating impulse displays the following remarkably simple characteristics.

1. The membrane potential at the boundary between the resting and active regions corresponds to the level of the half-maximum of the action potential, namely,

$$V_o = V_o^* = \frac{1}{2}(E_\mathrm{a} - E_\mathrm{r}) \tag{11}$$

2. The intensity of the longitudinal current, $(1/r_\mathrm{i})\mathrm{d}V/\mathrm{d}X$, is symmetric with respect to the position of the boundary between the active and resting regions.

Furthermore, the absolute value of the membrane current, $|(1/r_i)d^2V/dX^2|$, is also symmetric with respect to the boundary. The rising phase of a propagating action potential is symmetric with respect to the half-maximum point (cf. Cole and Curtis 1939, p. 664).

3. In the electrical network shown in Fig. 1, we see that the outwardly directly current through the capacitive pathway in the membrane element located at X_o^* is equal to that of the outward current traversing the capacitive pathway at X_o. The total current passing through the membrane element at X_o^* is equal in intensity and opposite in direction to that of the outwardly directed capacitive current through the element at X_o. Therefore, the resistive component of the membrane current (inwardly directed) is twice as intense as the capacitive current (outwardly directed) passing through the same membrane element. This 2:1 ratio between the resistive and capacitive component is maintained all along the entire active region of the axon.
4. As stated previously, the conduction velocity formula, Eq. (1) or its alternative form,

$$v = \frac{1}{c_m\sqrt{2r_m^* r_i}} \tag{12}$$

can be derived from the relation $\xi = \eta$. In these axons, the space parameter are given by

$$\frac{1}{\xi} = \frac{1}{\eta} = \sqrt{\frac{2r_m^*}{r_i}} \tag{13}$$

4. Conclusion

1. The process of nerve conduction is treated as a consequence of the coexistence of two structurally distinct regions, active and resting.
2. The process of charging the membrane capacity by the local current determines the velocity of nerve conduction.
3. The local current spreads symmetrically with respect to the boundary between the active and resting regions.
4. There are simple quantitative rules governing the intensity ratio between the capacitive and resistive components of the local current.

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