ACTIVE AND RESTING MEMBRANE RESISTANCES
AND SAFETY FACTOR CO-OPERATING
FOR CONDUCTION

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The nerve membrane resistance is known to be very high in resting and very low in activity. In squid giant axon, for example, they are about 1,000 and 25 ohm cm² respectively (1, 2). As to the functional significance of these facts, however, almost no opinion has been put forward. Certainly, the high resting membrane resistance favours the electrotonic spread of the current, and the low active membrane resistance intensifies the action current as stimulus, so that they act together to enhance the rate of conduction or the “safety of conduction” in generalized sense. But there has been no quantitative analysis of these problems, much less of other implications.

Recently, I have derived a mathematical relation between an excited length, x, and the resting length, y, to be excited by x (3, 4 (correction)), which could explain a number of fundamental facts of conduction and excitation fairly well. Relying on it, I attempt now to approach the problem suggested above.

The equation obtained was

\[ y = k \log f(1 - e^{-\frac{x}{k'}}) \]  

where

\[ k \] (length constant of resting membrane) \( \approx \sqrt{\frac{r_m}{r_i}} \),

\[ r_m, r_i: \text{resting membrane and axonal resistances of unit length of fibre}, \]

\[ k' \] (length constant of active membrane) \( \approx \sqrt{\frac{r'_m}{r_i}} \),

\[ r'_m: \text{active membrane resistance of unit length of fibre}, \]

\[ f \] (safety factor for local excitation) = \( \frac{V}{S} \).

V: action potential (peak value),
S: threshold potential across membrane, in terms of V reduced properly.

y in eq. (1) represents the length to be excited by \( t_m \), the moment of maximal stimulating effect due to x, and can be an approximate measure for the conduction velocity (3); accordingly, successive y-x-relation along conduction can represent successive variation of the velocity.

Now, y-x-relation is modified by the values of k, f and k', and takes one of the three types as illustrated in fig. 1. A particular interest and importance lies in the specific length L (L₁, L₂), than which x must be larger for starting

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an impulse (3). Of course the type I with small $L$ is best of all for the nerve as a signalling system, and in this sense, it is very interesting to note that it seems to be actually the case in the squid giant axon (3). But, further, how $k$, $f$ and $k'$ should be interrelated, of what magnitudes they should be, and how they are in actuality, etc., must be important questions to be asked. The argument will be limited to the squid giant axon.

I. IMPORTANCE OF THE RATIO $k/k'$ OR $r_m/r_m'$

The characteristic of the type I is that the curve crosses the 45°-straight line, which passes the origin. The necessary condition for this is

$$y > x \text{ at } \frac{dy}{dx} = 1$$

1) Put $x/k' = X$ or $x = k'X$ in eq. (1); then

$$\frac{dy}{dx} = \frac{dy}{dX} \frac{dX}{dx} = K \frac{e^{-x}}{1 - e^{-x}}, \text{ where } K = \frac{k}{k'}$$

2) Equate $\frac{dy}{dx} = 1$, then

$$K \frac{e^{-x}}{1 - e^{-x}} = 1; \quad Ke^{-x} = 1 - e^{-x}; \quad e^{-x} = \frac{1}{1 + K};$$

$$X = \log(1 + K) \text{ or } x = k' \log(1 + K)$$

3) From $y > x$ at $\frac{dy}{dx} = 1$, that is, at $X = \log(1 + K)$,

$$k \log f'(1 - e^{-\log(1 + K)}) > k' \log(1 + K)$$

$$\log f \frac{K}{1 + K} > \frac{1}{k'} \log(1 + K)$$

$$\therefore \quad f > \frac{(1 + K)^{k'}}{K}$$

Eq. (2) shows the correlation between $f$ and $K$ necessary for establishing the conduction along the whole length, the so-called all-or-nothing conduction. As seen from fig. 2, $f$ gets smaller with larger $K$, to attain unity at $K = \infty$. The general necessary condition is, therefore, $f > 1$. 

![Fig. 1. y-x-relation.](image-url)
Thus, \( K \) and \( f \), in combination, cooperate intimately for realizing the all-or-nothing conduction. Thereby, large \( K \) is advantageous because \( f \) can then be relatively small. A large \( K \) can be achieved by enlarging \( r_m \) or diminishing \( r'_m \). But, large \( r_m \) makes \( f \) smaller, because \( f = \frac{V}{S} = \frac{V}{r_m r_i}, r_i \) being constant. Therefore, if \( r_m \) is very large, the actual \( f \) will become smaller than the theoretical, and the conduction will cease to be all-or-nothing. On the other hand, small \( r'_m \) enlarges \( K \) up to infinity without affecting \( f \), so it is more advantageous than enlargement of \( r_m \), as long as all-or-nothing or “safe” conduction is concerned.

Now, in the squid giant axon, \( r'_m \approx 1/40 \) \( r_m \) as quoted above, hence \( K = k/k' = \sqrt{r_m/r'_m} \approx 6 \). The theoretical value of \( f \) for \( K = 6 \) is about 1.6 (fig. 2). To be compared with this, the actual value of \( f \) is missing. We must await for the right value until it will be worked out on the giant axon itself, because it depends on some characteristic physiological constants. But presumably it must be near or somewhat larger than \( F \), the safety factor for propagation (4), and \( F \) again somewhat larger than that of myelinated fibres, because there is no internode along which the potential drops (4). So, it will not be very unreasonable to take \( f \) of the giant axon as comparable with \( f \), at least with \( F \), of myelinated fibres. Now, in myelinated fibres, \( f/F \approx 1.5 \sim 1.8 \) (4), and \( F \approx 7 \sim 8 \) if averaged from 5 \sim 7 (5), 6 \sim 8 (6) and 10 (7). Hence, we have, for the giant axon, \( f \approx 7 \sim 8 \) at least, or \( f \approx (7 \sim 8) \times (1.5 \sim 1.8) \approx 11 \sim 14 \). It is open to question, to what extent this estimation is valid, but it seems at least certain that \( f \) of the giant axon will be much larger than 1.6. This, together with the mathematical result (3, fig. 14), indicates perhaps that the type I is actually the case in the giant axon with ample reserve. Here we find an important meaning of the high value of the ratio \( k/k' \) or \( r_m/r'_m \) relative to \( f \), or, conversely, of the high value of \( f \) relative to the ratio. As regards other significances, see next section.

II. ABSOLUTE VALUE OF \( r_m \) AND CONDUCTION VELOCITY

As stated above, very large \( r_m \) is not beneficial for “safe conduction”. Here we describe a particular importance of \( r_m \) from the view-point of conduction velocity, \( v \).

Suppose a potential \( P_0 \) applied from outside to a point of membrane. The potential at \( y \) is expressed by

\[
P_y = P_0 - \frac{y}{k}, \quad k \text{ (length constant)} = \sqrt{r_m/r_i}.
\]
Py rises if rm is raised, but, at the same time, the transverse current there decreases because of the raised rm. The same thing can be said about the action potential and current. And, as the stimulating effect is based on the current, the resting length y which can be excited by an active length x, should be a function of rm.

Let us take x and \( y' \) (consequently \( k' \)) as constant, and consider y as a function of rm only in eq. (1).

Introducing \( k' = \sqrt{\frac{\text{rm}}{r_i}} \) and \( f = \frac{V}{S} = \frac{V}{r_m i_s} \) (is, const.), we have

\[
y = \sqrt{\frac{\text{rm}}{r_i}} \log \left( \frac{1 - e^{-\frac{x}{k'}}}{r_m i_s} \right)
\]

\[
\sqrt{r_i} y = \sqrt{\text{rm}} N \log \left( 1 - e^{-\frac{x}{k'}} \right)
\]

\[
\sqrt{r_i} \frac{dy}{dr_m} = \frac{1}{2} \frac{N}{r_m} \log \left( 1 - e^{-\frac{x}{k'}} \right)
\]

Hence, \( \frac{dy}{dr_m} = 0 \) for \( \frac{1}{2} \frac{N}{r_m} = 1 \), that is, for \( \frac{N}{r_m} = e^2 \) or \( rm = \frac{N}{e^2} \).

Further, \( \sqrt{r_i} \frac{d^2 y}{dr_m^2} = -\frac{1}{2} \left( \frac{e^{\frac{x}{k'}}}{\sqrt{N}} \right)^2 \) at \( rm = \frac{N}{e^2} \).

Hence, y, accordingly v, attains maximum

at

\[
rm = R_m = \frac{N}{e^2} = \frac{V}{e^2 i_s} \left( 1 - e^{-\frac{x}{k'}} \right) = \frac{V \alpha}{e^2 i_s}
\]

\( R_m \): critical value of rm for \( y_{max} \); \( \alpha = 1 - e^{-\frac{x}{k'}} \)

or at

\[
f = f_{\mu_m} = \frac{V}{R_m i_s} = \frac{e^2}{\alpha}
\]

\( f_{\mu_m} \): critical value of f at \( rm = R_m \)

Introducing eq. (3) and (4) into (1), we have

\[
y_{max} = \sqrt{\frac{V \alpha}{e^2 i_s r_i}} \log \left( \frac{e^2}{\alpha} \right) = 2 \sqrt{\frac{V \alpha}{e^2 i_s r_i}}
\]

or

\[
y_{max} = \sqrt{\frac{R_m}{r_i}} \log \left( \frac{e^2}{\alpha} \right) = 2 \sqrt{\frac{r_m}{r_i}} = 2 \times \text{(length const. at \( rm = R_m \))}
\]

Eq. (3) and (5) show that \( R_m \) and \( y_{max} \) rise with \( V/i_s \) as well as \( x/k' \). Very probably, there is here a reason for the high value of the actual \( rm \), although \( R_m \) cannot be evaluated at present because \( i_s \) is unknown. Eq. (4) gives the value of \( f \) required at \( rm = R_m \), and shows that it decreases exponentially with \( x/k' \) towards \( e^2 \), allowing its evaluation for known \( x/k' \). We see therefrom that 1) the general necessary condition for maximal \( v \) is \( f = e^2 \), and 2) we can enlarge \( v \) by raising \( rm \) until \( f = \frac{V}{r_m i_s} \) is lowered down to a certain critical value corresponding to the given value of \( x/k' \). The interrelation among eq. (3), (4) and (5) is illustrated schematically in fig. 3.
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As clarified above, increase of $r_m$ enlarges $v$ to a certain extent. There appears, however, also a disadvantage, because $x$ for $y = 0$, accordingly $L$, get larger with larger $r_m$, as follows:

Putting eq. (1) = 0, we have

$$\frac{V}{r_m i_s} \left( 1 - e^{-\frac{x}{V}} \right) = 1,$$

from which

$$x = k' \log \frac{V}{V - r_m i_s} \quad (7)$$

Hence, $x$ increases with $r_m$ under other quantities constant, which results in making $L$ larger and, as a consequence, $F$ smaller. Therefore, $r_m$ should not be too large not only because $v$ becomes submaximal, but also because $L$ becomes large. It is interesting to compare this effect with that of $r_m'$, which will be described in the following section.

Now let us apply eq. (4) to the squid giant axon, and examine how large $f$ should be for maximal $v$. To do so, we have to know the value of $\alpha$. As stated elsewhere, the ratio $k/k'$ is about 6, while $k$ is said to be about 6 mm. in average in sea water for fibres 360-500 $\mu$ thick (1). Hence, we have $k' \approx 1$ mm. For the value of $x$, we may take the action length, and if we confine our attention to the steady state of conduction, where the action length is definite, say, $\lambda_m$, then we have $\alpha = 1 - e^{-\lambda_m (mm)}$. Now, $\lambda_m = v$ (velocity) $\times t$ (duration of excitation), of which $t$ can be taken about 0.4 msec. in average, because, according to Grundfest’s new measurement (8), it was 0.35-0.5 msec. $v$ has been said to be about 20 m/sec. for fibres of 500-700 $\mu$ thicknesses (9, 10), but according to recent investigations, about 19 m/sec. for a fibre of 400 $\mu$ diameter (8) or 20-30 m/sec. for fibres 300-500 $\mu$ thick (11). The slower velocity obtained by previous workers was ascribed to technical failure by Hodes. We may then adopt Hodes’ data and put $v = 25$ m/sec. in average; then we have $\lambda_m = vt \approx 10$ mm., and consequently

$$f_{\lambda_m} = \frac{e^2}{1 - e^{-\lambda_m}} = \frac{e^2}{1 - e^{-10}} \approx e^2$$

We miss here again the actual value of $f$ for comparison, but it appears to be at least 7~8 ($\approx e^3$) or eventually larger than 10 if the estimation (p. 169) is not very absurd. This might appear to suggest that the actual $r_m$ is not high enough for establishing $f = V/r_m i_s \approx e^3$, the condition for maximal $v$ for the given value of $V/i_s$. However, it is very important to recognize here that in actuality $r_m$ is so high as 1,000 ohm cm$^2$, that is, about 10$^{10}$-times as high as that of Ringer’s fluid, if assumed that the membrane is 100 $\AA$ thick. Very probably, it is not that $r_m$ is too small, but that $V/i_s$ is larger than necessary for simple
establishment of \( f \approx e^3 \). Such a large \( V/i_s \), if prepared, can provide various benefits, viz. 1) \( v \) is enlarged, because \( v \) changes with \( \log V/i_s \) (see eq. (1)); 2) type I of \( y-x \)-relation is ensured (see Section I); 3) small rise of \( r_m \) does not diminish but augment \( v \), because the membrane condition approaches that of maximal \( v \); 4) in abnormal cases where \( V/i_s \) runs down, the condition for maximal \( v \) is not lost until \( V/r_m i_s = e^3 \) is reached. None of these benefits would be gained if the actual \( f \) were not larger than \( e^3 \). It appears thus to be quite significant that a high value of \( r_m \) is combined with a value of \( f \) larger than required for maximal \( v \).

Finally, it may be interesting to compare \( f > 1 \), the condition for all-or-nothing conduction, with the actual \( f \left( = \frac{V}{r_m i_s} \right) \). As stated elsewhere, the actual \( f \) is about \( e^3 \) or somewhat larger at \( K = 6 \), then diminishes hyperbolically towards zero \( (f_m \text{ in fig. 4}) \), while the theoretical \( f \) is 1.6 at \( K = 6 \) and tends to unity at \( K = \infty \) \( (f_K \text{ in fig. 4}) \). Hence, \( f_m \) and \( f_K \)-curves intersect at a certain \( K \) or \( r_m \), say \( r_N \). In the region of \( r_m > r_N \), type I of \( y-x \)-relation can no more be the case, because \( f_K > f_m \) there. \( r_N \) marks thus the limit where the conduction transits from all-or-nothing into decremental type. In the region of small \( r_m \) (or \( K \)), on the contrary, \( f_m \) is always larger than \( f_K \), because, in the range of \( K \ll 1 \), we have \( f_K = \frac{1}{K} \) from eq. (2), and \( f_m = \frac{V}{i_s r_m} = \frac{V}{i_s f_m} \frac{1}{K^2} \) on the other. Exact evaluation of \( V/i_s f_m \) is impossible, but roughly it will be of the order of \( 10^5 \), because \( \frac{V}{i_s} = \frac{V}{i_s f_m r_m} = f_m o \times \frac{r_m o}{r_m} \), where \( r_m o \) and \( f_m o \) represent respectively \( r_m \) and \( f_m \) in normal condition.

We see thus that the conduction in the squid giant axon can always be all-or-nothing, except in the imaginative range of \( r_m > r_N \). The value of \( r_N \) depends upon how \( K \) changes with \( r_m \). In the above treatment, \( r_m \) was assumed to be constant, therefore \( K \) to vary simply with \( \sqrt{r_m} \), but in actuality \( r_m \) might change with change of \( r_m \).

III. SIGNIFICANCES OF THE LOW VALUE OF \( r_m' \)

The fact \( r_m' \approx r_m \) is now a common knowledge, as stated at the start. The significance may be appreciated from two aspects, viz., 1) \( r_m' / r_m' \approx 1 \) or \( k / k' \approx 1 \), and 2) the smallness of the absolute value of \( r_m' \). The former was treated already in Section I, so just the latter will be considered here.

1) \( r_m' \) and \( v \).

\( y \) of eq. (1) is considered here as a function of \( r_m' \), regarding \( k, f \) and \( x \) to
be constant. Differentiating $y$ by $r_m'$, we have

$$\frac{dy}{dr_m'} = -\frac{1}{2} k' \frac{e^{-\frac{x}{k'}}}{1 - e^{-\frac{x}{k'}}}$$

which indicates that $y$ (consequently, $v$) simply increases with decrease of $r_m'$. We find here a reason for the low value of $r_m'$, although it can be foreseen very easily from the consideration that the smaller $r_m'$ is, the stronger becomes the action current as stimulus. We see further from eq. (1) that, in extreme case where $r_m' = k' = 0$, $y$ becomes $k \log f$ (constant), without regard to the value of $x$. Physically, this is analogous to the case where source batteries of zero internal resistance are connected in parallel. The actual nerve, where $r_m' \ll r_m$, appears to be designed similarly, and this makes us expect practical independence of $y$ upon $x$, that is, the practical uniformity (10), in spite of the theoretical increment (3), of $v$ along the fibre.

2) $r_m'$ and the shape and position of $y$-$x$-curve

Smaller value of $r_m'$ means smaller value of $k'$, which means, in turn, steeper rise of the curve $\left(1 - e^{-\frac{x}{k'}}\right)$, accordingly, of the whole $y$-$x$-curve. This results not only in making $y$ larger, but also in protecting type I strongly from changing into type II or III.

Furthermore, small $r_m'$ makes the $y$-$x$-curve shift towards $y$-axis as a whole, as the result of steeper rise of $\left(1 - e^{-\frac{x}{k'}}\right)$. This is shown in eq. (7), which expresses that $x$ for $y = 0$ varies linearly with $k'$ or $\sqrt{r_m'}$, provided that $r_m$ is constant. Smaller $x$ for $y = 0$, combined with steeper rise of the curve, makes necessarily $L$ smaller, which makes $F$ larger, as has been stated repeatedly. A particular significance of the small magnitude of $r_m'$ may be found here.

IV. CONSIDERATION

It was described above that $r_m$ and $r_m'$ co-operate intimately with $f$ to realize the all-or-nothing conduction as well as a large or maximal $v$. The whole argument was based on a mathematical equation derived by myself, and on experimental data presented by a number of authors. Experimental confirmations are desired among others for $L$, $f$ (not $F$) and $v$ in relation to $r_m$, but not realizable unless, as stated before (4), some method of strictly uniform stimulation for strictly limited minute area, and also a procedure which modifies $r_m$ but nothing else, are invented. This paper dealt only with a “theoretical appreciation” of the functional significances of $L$, $r_m$, $r_m'$ and $f$ for conduction.

V. SUMMARY

1. Based on the equation derived recently by myself on the relation between an active length $x$, and the resting length, $y$, which can be activated by $x$, the roles of membrane resistance and safety factor being played for conduction, were examined.
2. The ratio of resting to active membrane resistance, \( r_m/r_m' \), or the ratio of length constant of resting to active membranes, \( k/k' \), was found to play an important role, together with the safety factor, \( f \), for local excitation, for realizing the all-or-nothing conduction. Generally, \( f \) decreases with increase of the ratio. The value of \( f \) for infinitely large ratio is unity. It seems very likely that the necessary condition is satisfied with ample reserve in the squid giant axon.

3. Conduction velocity increases with \( r_m \) until it attains maximum at a certain \( r_m \). The safety factor, \( f \), decreases with \( r_m \) and attains a certain definite value at the critical \( r_m \). This value decreases in inverse proportion to \( \left( 1 - e^{-x/k'} \right) \), and attains \( e^2 \) at \( x/k' = \infty \). The theoretical value for the squid giant axon is just about \( e^2 \), while a rough estimate of the actual value is 7~8 or eventually larger than 10. The significances were discussed.

4. The smaller the resistance \( r_m' \), the larger is the conduction velocity and the smaller the minimal active length, \( L \), required for starting an impulse.

5. It was concluded that large \( r_m \) and small \( r_m' \) co-operate intimately with \( f \) for enhancing the "safety of conduction" in generalized sense.

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