Principle of Initiation of Impulse Applied to Phenomena of Conduction

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The relation between an active length x and the resting length y to be excited by x is expressed by the following equation^{1,2)}:

$$y = k \ln f(1 - e^{-x/k'}) \dots\dots\dots (1)$$

k, k' , length constants of resting and active membranes respectively;
 f (safety factor of excitation) $= \frac{V}{S} = \frac{V}{r_m i_s}$; V , action potential; S , threshold voltage; r_m, i_s , membrane resistance and threshold current, respectively, for unit length of fibre.

Now, for initiation of impulse, two conditions are required to be satisfied¹⁾:

1) Type I of y - x -curve (Fig. 1), crossing the 45° line at $x=L$ and M , and

2) Simultaneous excitation of "L" (Fig. 1), that is, $\Delta t = t_L - t_0 \leq D$ ($t_{0,L}$, response times at points $x=0$ and $x=L$; D , duration of activity at point $x=0$). Of these two, which together we call here the principle of initiation of impulse, the former is well established in normal fibres³⁾, so usually the latter is the only requirement. This principle was shown to be very useful for explaining a number of facts concerning electric excitation⁴⁾⁻⁶⁾. The present paper describes how well the principle or the original eq. (1) operates in various phenomena of conduction, in more details or more exactly than before¹⁾.

I. Transmission as the Basis of Conduction

The propagation in unmyelinated fibres is certainly continuous. In view of the present principle, however, an active length larger than L exciting another length larger than L (that is, a discontinuous transmission from length to length) must exist throughout as the basis of continuous conduction.¹⁾ A functional significance of the so-called action length, at

Fig. 1. y - x -relation, schematic. x , active length; y , resting length to be excited by x ; $P_{y=0}$, $P_{y=y}$, potentials at $y=0$ and $y=y$ respectively; $l \doteq 0.1$, $L \doteq 0.11$ and $M \doteq 11$ mm in case $k=5$ mm, $k'=1$ mm and $f=10$.¹⁾

least of a portion near the front, is appreciated from this view-point. It is interesting to note that in Lillie's nerve model in particular condition (for example, electrotonus) where the activation wave proceeds decrementally, the wave fails to conduct when the wave length gets down to certain small value.⁷⁾

In myelinated fibres, the so-called action length has almost nothing of this function, because the action current as stimulus is scarcely strengthened by multi-nodal activity^{8), 9)}. But, what is important here is the action length in the nodal membrane itself, where, too, a certain " L " exists highly probably (see App. 1, note 1). Whether the excitation produces a spike or not, depends upon whether L is wholly or partly excited. Details will be stated later.

II. Safety or Initiation of Propagation of Impulse

1) Judgement from y - x -relation

The mathematical condition for establishment of type I of y - x -relation is $f \geq \frac{1}{K}(1+K)^{(1+K)/K}$ ($K=k/k'$)³⁾; hence, the establishment is the safer, the larger f and K or the larger $\frac{V}{S}$ and $\frac{r_m}{r_m'}$ are, if assumed $k = \sqrt{\frac{r_m}{r_i}}$ and $k' = \sqrt{\frac{r_m'}{r_i}}$ (r_m' , active membrane resistance for unit length). The high values of these quantities in normal state, satisfying the condition

with ample reserve, may be appreciated in this view.⁹⁾ Reduction of these values, if occurs, will reduce the safety, modifying type I towards II.

2) *Judgement from the safety factor of propagation, F*

F is a direct measure for the safety under consideration and is known to be so large as about 5⁸⁾ in normal myelinated fibres. Now, in the present theory, conduction is distinguished from excitation, hence the safety factor of conduction, F, from that of excitation, f . How is then F related with f generally, and how does it change in abnormal conditions?

Let us consider the later stage of conduction, where the action length is fully developed, accordingly, $x \gg k'$. Then, for unmyelinated fibres, eq. (1) turns into

$$y = k \ln f = k \ln \frac{V}{S} \left(= \frac{\sqrt{r_m}}{\sqrt{r_i}} \ln \frac{V}{r_{m,i}} \right) = \text{const.} \quad (2)$$

Now, y for $\frac{V}{F}$ should be L , so

$$L = k \ln \frac{V}{FS}; \quad e^{L/k} (=m) = \frac{f}{F}; \quad \text{hence, } F = \frac{f}{m} \quad (3)$$

Normally, m is just slightly larger than unity (see App. 1, note 1), hence $F \doteq f$, that is, f can represent F .

In myelinated fibres, practically just one active node acts as the stimulator as stated above; and y for $\frac{V}{F}$ should be $(d+L) \doteq d$ (d , internodal length). Hence, from eq. (1)

$$d = k_s \ln \frac{\theta f}{F}; \quad F \doteq \theta f e^{-d/k_s} \quad (4)$$

k_s , length const. of sheath membrane; d , internodal length; $\theta = (1 - e^{-b/k'})$; b , nodal breadth, $\doteq 0.5 \mu^{10)}$

Evidently, $F < f$ generally. In frogs, for example, $d \doteq 2$ mm. and $k_s \doteq 5$ mm. (estimated from data in Stämpfli's table¹¹⁾), hence $F \doteq 0.7 f$ even if $\theta = 1$. If adopted $F \doteq 5$ obtained by the air-gap method, then $F \doteq 0.5 f$, because $F \doteq 5$ indicates $f \doteq 10$, if taken (internal axonal resistance) $\doteq$ (nodal membrane resistance). In normal conduction, however, F must be much smaller, because $\theta \doteq 0.3$, as will be stated later.

Thus, the myelination generally changes $F \doteq f$ to $F < f$. But at the same time, the length constant is enlarged practically from that of the nodal membrane ($\doteq 0.05$ mm., estimated from Stämpfli's table¹¹⁾) to that of the sheath ($\doteq 5$ mm.). This will enlarge the conduction velocity, about which see next chapter.

How F changes in abnormal conditions, will be seen from eq. (3) and

(4), respectively.

3) *Judgement from the liminal gradient*

The liminal gradient for initiation of impulse in frog's myelinated fibres is said to be 0.1–1.0 mV/msec.¹²⁾ or 0.8–6 V/sec.¹³⁾ The value required from the present theory⁵⁾ is about the same with Tasaki's.¹²⁾ Now the gradient of the action potential in the rising phase is about 100 mV/0 msec., that is, about 10^{2-3} -times greater than the liminal. The safe of propagation in this view being thus almost complete, some reduction of the slope will not matter at all. Rudolph's interpretation for the observed block¹⁴⁾ becomes then somewhat doubtful. The true cause of the block might have been some other event which took place simultaneously

III. The Conduction Velocity

1) *Unmyelinated fibres*

The eq. (1) represents the resting length y to be excited by x , but does not contain the time factor necessary for it. So, no discussion can be developed therefrom on the conduction velocity, v . However, if we confine our attention to the later stationary stage of conduction where $y = \text{const.}$ (eq. (2)), we may represent the relative velocity by y itself assuming the time factor constant.

a) Relation to stimulation intensity and conduction distance. Eq. (2) indicates directly that as long as observation is made at distant place y is determined by k and f only; that is, that v is independent of stimulation intensity and conduction distance, as is well known since old times.

b) Relation to fibre size. Let the diameter be R . Then, $r_m \propto \frac{1}{R}$; $\propto \frac{1}{R^2}$; $i_s \propto R$; $V = \text{const.}$ Hence $k \propto \sqrt{\frac{r_m}{r_i}} \propto \sqrt{R}$; $f = \frac{V}{r_m i_s} = \text{const.}$; accordingly $y(v) \propto \sqrt{R}$. This conclusion involves the assumption $k \propto \sqrt{\frac{r_m}{r_i + r_e}} \approx \sqrt{\frac{r_m}{r_i}}$ (r_e , external resistance per unit length). Under the same assumption, Hodgkin¹⁵⁾ too obtained $v \propto \sqrt{R}$, which, prior to him, was verified experimentally by Pumphrey—Young¹⁶⁾. Hodes¹⁷⁾ says, however, that this is an experimental mistake, and the correct relation is $v \propto R$. The matter is not yet quite clear.

c) Relation to membrane resistance. As a function of r_m , y in eq. (2) attains maximum at $r_m = \frac{1}{e^2} \frac{V}{i_s}$, that is, at $f (= \frac{V}{r_m i_s}) = e^2 \approx 8.3$, under given V and i_s . It is noteworthy that this is not far from $f \approx 10$, which was estimated for the nodal membrane.

Hitherto, large r_m has been interpreted simply as a mechanism for

enhancing v by enlarging k . The above consideration suggests that there is a limit in the validity of the interpretation. The point is that only the distribution of potential and not of the current as stimulus has been considered. Unfortunately we cannot test the above conclusion experimentally, because we have no proper method of modifying just r_m , keeping other features unchanged.

2) *Myelinated fibres*

a) Relative v . The length constant k of a nodal membrane is about 0.05 mm. while the breadth about 0.5μ , as stated before; hence, the potential drop along a single membrane is just about 1%. We may neglect this drop and take a fibre as covered uniformly by a sheath membrane, as far as the current distribution is concerned. Taking just one active node as the stimulator as before, and supposing the internodal portion to be excitable too for convenience, we have from eq. (1)

$$y = k_s \ln \frac{\theta V}{S} = k_s \ln \theta f, \quad \theta = \text{const.} \dots \dots \dots (5)$$

Eq. (5) is just the same in form with eq. (2), so that the arguments developed on relative v of unmyelinated fibres are available also for myelinated. Points of notice are that 1) activity takes place only at nodes inside y , 2) f is invariably that of the nodal membrane, so that 3) y , being simply proportional to k_s , gives no maximum for variable sheath-resistance.

Now, if k and f of eq. (2) are taken those of the nodal membrane, the equation represents y of an imaginary unmyelinated fibre which is covered uniformly by the nodal membrane. Introducing $k \doteq 0.05$ mm. and $f \doteq 10$, we have $y \doteq 0.12$ mm. By comparing this with y of eq. (5), representing an actual myelinated fibre, we can clarify the role of myelination as regards v . Unfortunately, the correct value of k' , accordingly of θ is unknown (see App. 1), so that theoretical evaluation of y of eq. (5) is impossible. However, we know the fact that excitation of a node jumps over 1–2 resting nodes^{11, 18}). This shows that $4 \text{ mm.} < y < 8 \text{ mm.}$ or $y \doteq 6 \text{ mm.}$ in average; in other words that y of eq. (5) is about 6 mm in actuality (The length of narcotized regions necessary for block-making is known to be about 6 mm, too). Then we have $\frac{6}{0.12} = 50$, which, expressing that $y(v)$ of an actual myelinated fibre can be, although not exact, about 50-times greater than that of an imaginary unmyelinated, makes us see how effective the myelination is for enhancing v . It may be remembered here that squid's giant axon and frog's myelinated fibre are almost equally quick, inspite of the great difference in diameter (500:10) and the similar values of the action potential.

On the other hand, F is reduced greatly by myelination, as stated

before. The myelination appears thus to be a means for enhancing v at the cost of F .

b) The value of F . Introducing $k_s \doteq 5$ mm. and $y \doteq 6$ mm. into eq. (5), we have $\theta f \doteq e^{1.2}$. This introduced into eq. (4), together with $k_s \doteq 5$ mm. and $d \doteq 2$ mm., gives $F \doteq e^{1.2-0.4} \doteq 2.1$. The evaluation is never exact, but it should be noticed that F thus obtained is very much smaller than $F \doteq 5$ obtained by the air-gap method, which, checking the current leak from the internode, must have given a somewhat larger F than in normal conduction. Experimental examinations are desired.

Note. From $\theta f \doteq e^{1.2} \doteq 3$ and $f \doteq 10$, we have $\theta \doteq 0.3$.

c) Absolute v . Hodler *et al.*¹⁹⁾ and Tasaki²⁰⁾ claimed that the internodal conduction time is nothing but the time for potential spreading along an internode as a physical cable. They think that the reduction of v in low temperature is due to elongation of this time resulting from rise of the resistance. Certainly, some time must be needed for potential spreading, but the point is how much. If no time is spent at the node as they think, then v will be independent of the internodal distance, or rather larger in case of shorter internodal distance. Further, in the transmission via air-gap where about one half of the action potential is impressed upon the resting node, the measured conduction time is about 0.1 msec that is, about the same with the actual one in normal conduction. This fact seems to indicate that the normal conduction time is largely, though not all, spent at the nodes for their excitations. If so, v should depend upon the internodal length. Let us examine it below, neglecting the time for potential spreading on purpose.

Suppose the node N_1 excited (Fig. 2). The action potential, spreading as shown in the figure, acts upon the resting node N_2 with the intensity P_d . Taking the action potential constant for simplicity, we may regard the case as one of the direct current stimulation, where the equation $\gamma I =$

Fig. 2. Spreading of action potential along a myelinated fibre, schematic. N_1 , active node; N_2 , resting node; V , action potential; P_0 , P_d , potentials at both ends of internode.

$\frac{I_r}{1-e^{-t/\alpha}}$ ($t \leq t_r$)⁴⁾ holds for initiation of impulse. Replacing I and I_r with P_d and P_r (the smallest value of P_d effective for propagation) respectively, we have

$$\gamma P_d (= \gamma P_o e^{-d/k_s} = \gamma \theta V e^{-d/k_s}) = \frac{P_r}{1-e^{-t/\alpha}}, \quad t \leq t_r$$

which gives $t = \alpha \ln \frac{\gamma P_d}{\gamma P_d - P_r} = -\alpha \ln (1 - \frac{P_r}{\gamma \theta V} e^{d/k_s})$

We may take $P_r \doteq \frac{30}{3} \text{ mV}$, because the rheobasic potential for initiation of impulse in node-to-node stimulation via air-gap is about 30 mV, and the nodal membrane resistance is about equal to the internodal axonal. Then, introducing $\alpha \doteq 0.5 \text{ msec.}$, $V \doteq 100 \text{ mV}$, $k_s \doteq 5 \text{ mm.}$, $\gamma \doteq 1$ and $\theta \doteq 0.3$, we have

$$v = \frac{d+b}{t} \quad (b, \text{ nodal breadth}) \doteq - \frac{d}{\log (1 - 0.3 e^{d/5})}$$

The result of computation is as follows:

$d \text{ (mm)}$	0.5	1	2	3	4	5	5.5	6
$v \text{ (mm/msec)}$	2.9	5.0	7.7	8.8	8.3	6.8	5.5	2.5

It is quite interesting and note-worthy that v has a relatively flat maximum at $d \doteq 3 \text{ mm}$. The obtained maximal velocity is too small compared to the actual, but it is probably because of the inexactness of the values of the physiological data employed, particularly of θ . If θ is taken 0.5 instead of 0.3 (which is not improbable), then we have $v \doteq 20 \text{ mm/msec}$ at $d = 3 \text{ mm}$. Thus, in the light of the present theory, the myelinated fibres appear to be provided with two efficient mechanisms as regards v , namely, 1) $f \doteq 10$ of the nodal membrane, showing that the membrane is made so resistant as to make v in it nearly maximal under given V and i_s , and 2) a proper internodal length, enhancing v greatly, if not most, effectively.

IV. Effect of Temperature

1) Variation of D and its significances

a) In the node-to-node stimulation in low temperature, V_r remains practically constant, while the liminal gradient β_r decreases enormously¹²⁾. As one of the possible causes, some reduction of m was supposed to occur in a previous paper⁶⁾, but there was a confusion arising from mistaking V_r -constancy as I_r -constancy.

From $I_r = m \gamma i_r$ ⁴⁾ and $\beta_r = \frac{I_r(m-1)}{m \gamma D}$ (Amp/sec),⁵⁾ we have

$$V_r = aW I_r \doteq aW m i_r \quad (\gamma \doteq 1, \text{ assumed}) \dots\dots\dots (6)$$

$$\text{and} \quad \beta_r = \frac{aW I_r (m-1)}{m \gamma D} \doteq \frac{V_r (m-1)}{m D} \text{ (Volt/sec)} \quad (\gamma \doteq 1, \text{ assumed}) \dots\dots\dots (7)$$

$W, a I_r$, total resistance and current respectively in stimulating circuit;

a , proportionality factor.

In low temperature, r_m and r_i rise similarly ($Q_{10} \doteq 2$ for both)² hence, $W \propto r_m$; accordingly, if $W i_r$ increases (or decreases), then $r_m i_r$ increases (or decreases) parallel with it, which in turn increases (or decreases) m (see eq. (9)). As the result, V_r must become larger (or smaller) in contradiction to the observed fact. In actuality, therefore, $W i_r$ ($r_m i_r$ accordingly m , must remain about constant. If thus $V_r \doteq \text{const.}$ and m const., then β_r should vary simply with D in inverse manner (see eq. (7). This is in accord with D -prolongation in low temperature, which is large enough ($Q_{10} \doteq 3.3^{22}$) to explain the actual reduction of β_r satisfactorily.

b) Tasaki²³) observed hysteresis-effect of temperature upon β_r , as Schriever²⁴) some temporal variation of β_r under constant temperature where V_r and τ (chronaxie) were constant. In view of the present theory the observed facts on β_r are comprehensive as resulting from delay-effect of temperature upon D , and the constancy of V_r and τ as due to small effect of D upon these quantities (see eq. (6) above and eq. (7) of the previous paper⁴).

2) Reduction of v in low temperature

As mentioned above, r_m and r_i change nearly proportionally, hence $k \doteq \text{const.}$ In addition, $V \doteq \text{const.}$ and $r_m i_r \doteq \text{const.}$, accordingly $f \doteq \text{const.}$ Therefore, we should expect $y(v) \doteq \text{const.}$ from eq. (2). If Fatt-Katz data ($Q_{10(rm)} = 2.5$; $Q_{10(ri)} = 1.2$) are adopted, y should be even larger in low temperature. In fact, however, v decreases greatly in apparent contradiction to the theory. In low temperature, however, the action current must be very weak, because V is practically unchanged while the local circuit resistance enormously raised. In addition, the stimulatory process of whatever nature it may be, must proceed slowly. Tasaki²³) not only proved this slowness but also discovered that thereby the electrical quantity necessary for excitation increases enormously ($Q_{10} \doteq 1.7$). These together will lengthen the time for completion of stimulation, which should result in reducing v . It is interesting to note in this connexion that $Q_{10} (\doteq 1.7)$ of the necessary electrical quantity above cited is about the same with Q of v ($\doteq 1.8$)²²); further that D is prolonged, perhaps to supply ample time and energy for stimulation.

We may say after all that "y might be unchanged or even larger in low temperature, but the time necessary for exciting it will become large to make v smaller." The electrical nature of conducting stimulus has

been fully evidenced²⁶⁾, but the process which follows the current flow must be of a complicated chemical or physico-chemical nature, which must be influenced by temperature a great deal.

V. Block-making

1) *By electrotonus (E.T.)*

Modification of v under E.T. is well known, but precise discussion on it is impossible, because details are unknown about the changes of V , r_m , r_i , i_s etc. under E.T. of various intensities and durations. The only fact which can be treated with certainty, may be that of block which takes place in strong E.T.

In strong C.E.T., a small rise of V_r and a violent fall of V take place, while in strong A.E.T. a small rise of V and a violent rise of V_r .^{27, 28)} As the result, F gets smaller and smaller until finally block occurs at $F=1$ in both cases. Now, $F=\frac{f}{m}$ (eq. (3)) and $F=\theta f e^{-d/k_s}$ (eq. (4)) in unmyelinated and myelinated fibres, hence block occurs respectively at $f=m$ and $f=\frac{1}{\theta} e^{d/k_s}$. This means that f is still larger than unity by an amount at the moment of block, that is to say, conduction block in general is not always excitation block.

2) *By narcosis*

a) Unmyelinated fibres. First, consider a fibre wholly narcotized. As r_m remains practically constant,^{18, 20)} k and perhaps k' will do so, too. Then, as the result of V -, accordingly of f -decrease, the type of y - x -relation will change from I to II, and the conduction from decrementless to decremental to become finally just local.¹⁾ The matter is the same when an impulse transits from normal to narcotized region, because there is no difference in condition except that the intensity of the stimulus acting upon the narcotized region is invariable. The length, X , of the narcotized part necessary for block-making is estimated from

$$V e^{-(X+L)/k} \leq S; \quad X \geq k \ln \frac{f}{m} \dots\dots\dots 8)$$

For the squid's giant axon, for example, we have $X \geq 14$ mm., if taken $k \doteq 6$ mm., $m \doteq 1$, and $f \doteq 10$ as in the nodal membrane.

b) Myelinated fibres. The type of y - x -relation of the nodal membrane will change from I to II with progress of narcosis, but it is always possible to excite a "whole" node by a proper stimulus. An impulse will be initiated as long as a node thus activated can excite the next "whole" node. The matter is the same in the case of transition from normal to narcotized region. Whether an impulse passes through or not depends

upon whether the activity of a narcotized node can excite the following narcotized node as a whole, or not.

Now, in order that a node can excite the next node as a whole, the activity of the former must excite "L" of the latter, and, furthermore, L must be smaller than b , the nodal breadth. For, if $L > b$, the case of single node activity corresponds to that of $x < L$ in eq. (1), so that no impulse can be initiated even if there were no internode. It seems certain that the normal L is smaller than b , as stated before, but it will grow with progress of narcosis and tend to $L \geq b$, to bring forth block at a certain stage.

3) Cold block

There are not sufficient data for discussing the matter quantitatively, so the argument is only speculative.

As stated above, reduction of v in low temperature is comprehensive as the result of elongation of the excitation time, but the fact of block not. For understanding this, we have to consider fall of $f (= \frac{V}{r_m i_s})$ towards unity, because k remains about constant or gets larger in eq. (2), as stated before. Now, fall of f must be due to enlargement of $r_m i_s$, because $V \equiv \text{const.}$; and, enlargement of $r_m i_s$ (that is, of $r_m i_r$), if occurs, enlarges $W i_r$ and m as stated before; as a consequence, we should first expect rise of V_r from eq. (6) in very low temperature. Next, enlargement of $r_m i_r$ must be due to relatively less reduction of i_r in comparison to r_m -increase; and relatively less reduction of i_r may possibly be due to relatively less prolongation of D in very low temperature. Thus, experimental examinations of V_r and D may be clues for clarifying the matter.

SUMMARY

The principle of initiation of impulse derived theoretically by myself was applied to various phenomena of conduction. As the result, many experimental facts could be understood or explained quite reasonably. A few suggestions were obtained, too.

APPENDICES

1) Derivation of $P_{y=0}$ (Fig. 1, A) and the value of k'

For deriving eq. (1), it was first assumed²⁾

$$P_{y=0} = \int_0^x a V e^{-x/k'} dx, \quad \begin{array}{l} P_{y=0}, \text{ potential at } y=0; \\ \alpha, \text{ proportionality factor.} \end{array}$$

Introducing the condition $P_{y=0}$ (for $x=\infty$) = V into it, we obtained $P_{y=0} \equiv V (1 - e^{-x/k'})$. The method may be open to question, but the result seems to be reasonable, at least qualitatively, showing $P_{y=0}$ growing from zero towards a definite value, V . The point is the value of k' . If as-

summed $k' \doteq \sqrt{\frac{r_m'}{r_i}} \doteq k \sqrt{\frac{r_m'^{(1)}}{r_m'}}$ and $\frac{r_m'}{r_m} \doteq \frac{1}{40}$ for both squid's giant axon and frog's nodal membrane, then we have $k' \doteq 1$ mm. for the former where $k \doteq 6$ mm., and $k' \doteq 8 \mu$ for the latter where $k \doteq 50 \mu$. Then, to have $P_{y=0} \doteq V$, x must be larger than about 5 mm. in the case of squid, which seems doubtful. Further, in frog's myelinated fibres where practically just one active node acts as the stimulator, we ought to have $P_{y=0} = V (1 - e^{-0.5/8}) \doteq 0.06 V$. If $\frac{r_m'}{r_m} > \frac{1}{40}$ (Tasaki-Freygang says that $\frac{r_m'}{r_m} < \frac{1}{10}^{29}$), $P_{y=0}$ will be still smaller, which is evidently incompatible with $F(\doteq 5)$ or $f(\doteq 10)$.

Now, as to the nodal membrane, a much smaller k' is obtainable from $\theta \doteq 0.3$ evaluated before. Introducing this and $b \doteq 0.5 \mu$ into $\theta = 1 - e^{-b/k'}$, we have $k' \doteq 1.5 \mu$. We take this much more reliable, because it is based on the facts $y \doteq 6$ mm. and $f \doteq 10$ (see p. 93).

Note 1. Taking $L \doteq l$ for approximation (see Fig. 1 and legend), we have $L \doteq k'/f \doteq 0.15 \mu$ from eq. (1), and $m = e^{L/k} \doteq e^{0.15/50} \doteq 1.003$ for $e^{0.8/50} \doteq 1.02$ obtained before⁴⁾.

Note 2. The theoretical values of t_r , β_r , τ etc. were still in approximate agreement with the experimental, when corrected by adopting $m \doteq 1.003$.

Note 3. The value of θ ($\doteq 0.3$), is backed up by facts, but $P_0 (= \theta V)$ appears to be too small if judged from the resistance of the sheath membrane which is enormous compared to that of an active nodal membrane. The actual state of affairs is not clear, but possibly some juxta-nodal portion of the sheath may be much less resistant than the central portion.

2) The value of $m = e^{L/k}$ in general

The factor m which plays an essential role in initiation and propagation of impulse, may be termed the "constant of propagation". Its value is determined by $\frac{L}{k}$, which varies according to conditions. It is very small normally, so we may put $m \doteq 1 + \frac{L}{k}$. If taken $L \doteq \frac{k'}{f}$ as above, then $\frac{L}{k} \doteq \frac{k'}{k} \frac{1}{f}$, that is

$$\frac{L}{k} (\doteq m - 1) \propto \frac{1}{f} \text{ (or } \frac{r_{m1s}}{V}, \text{ or } \frac{r_{m1r}}{V}), \dots\dots\dots 9)$$

if assumed $\frac{k'}{k} = \text{constant}$.

This conclusion is not exact but very interesting and important, showing that $(m-1)$, accordingly β_r (eq. (7)), is inversely proportional to f approximately. It also enables us to judge the gross tendency of m -variation in various conditions.

3) Local response (L.R.)

The so-called L.R. of nerve fibres discovered by Katz³⁰⁾ was first taken

as an all-or-none response of a minute area in connexion with Rushton's theory³¹⁾, and then, after Marmont³²⁾, as a subthreshold activity of any area. The present theory has nothing to do directly with this problem, because it takes just the all-or-none activity of various areas into consideration. However, as stated and discussed previously¹⁾, the graded L.R. is well comprehensive as a spatial event inside L from the present theory, and, on the other hand, Marmont's observation does not always prove the subthreshold activity. For, in stimulation of a large area as in Marmont, some "islands" of excitation will appear in weak stimulation as a result of physical and physiological ununiformities of the membrane, which, growing in number and area and thus giving graded L.R. as a whole, will suddenly be led to propagation and fusion at a certain stimulus intensity.

Just recently, some very similar ideas have appeared, namely, the ideas of active "spot" or "unit" or "patch" presented by Grundfest,³³⁾ Tasaki-Hagiwara³⁴⁾ and perhaps also del Castillo-Suckling³⁵⁾. Grundfest argues that observed action potential should increase with number of active units, that is, with stimulus intensity. Perhaps the same thing is considered in del Castillo-Suckling who say that the gradation of the L.R. of a single node is "quantal". Tasaki-Hagiwara claim that, in the so-called threshold excitation, the total area of the active spots should attain a certain fraction of the stimulated area. In all of them, the activity of a spot is considered to be all-or-none. Evidently, they all think, after all, of an area of full-sized activity growing with stimulus, and to this they appear to relate the graded nature of L.R. Another point to be noticed is that each active spot is supposed to stand isolated. This is nothing but an expression of the idea that a too small active area cannot initiate an impulse. In these points, their ideas are just the same with mine. The only but not essential difference is that I took the current distribution ununiform (exponential) and the membrane condition uniform, for simplicity, in usual method of stimulation. In other words, I considered of "an" active area growing with stimulus, while they active spots growing in number.

Nothing has been said about the dimension of the "spot", but presumably it must be of an ultramicroscopic or a still smaller order. Besides such a fine structural unit, I imagine another, so to speak, "functional" unit, a certain assembly of the former, to exist¹⁾. Its dimension is supposed to vary according to conditions. The liminal length "L", for example, may be one, and the node of Ranvier another, of the latter kind of units, in respective senses.

Finally, the possible dependence of the graded L.R. upon "area" is most simply understood in the following way: the measurement of the action potential is usually carried out under the flow of the local current

covering active and resting regions. Even if an intracellular electrode is employed, the measured potential cannot exceed the so-called terminal voltage, which gets smaller with larger internal resistance of the source battery. It is then natural that the measured potential gets smaller with smaller active area, which possesses larger resistance.

Besides such a L.R. of spatial nature, there might exist the so-called subthreshold activity, too. But in order to distinguish it from the former, it must be verified as an event in a final structural unit above stated, or at least a proper method must be invented for stimulating an area, minute enough to be uniform, under strict limitation. The final decision of the matter seems to be extremely difficult.

References

- 1) Yamagiwa, K., Jap. J. Physiol., 1955, **5**, 131.
- 2) Yamagiwa, K., *ibid.*, 1955, **5**, 317.
- 3) Yamagiwa, K., *ibid.*, 1956, **6**, 167.
- 4) Yamagiwa, K., Tohoku J. exp. Med. 1957, **66**, 153.
- 5) Yamagiwa, K., *ibid.*, 1957, **66**, 163.
- 6) Yamagiwa, K., *ibid.*, 1957, **66**, 175.
- 7) Yamagiwa, K., Jap. Med. J., 1948, **1**, 439.
- 8) Tasaki, I., Nervous Transmission. Charles C. Thomas, Springfield, 1953.
- 9) Yamagiwa, K., Bulletin Tokyo Med. & Dental Univ., 1954, **1**, 133.
- 10) Stämpfli, R., Physiol. Rev., 1954, **34**, 101.
- 11) Stämpfli, R., Ergeb. Physiol., 1953, **47**, 70.
- 12) Tasaki, I., Cytologia, 1950, **15**, 219.
- 13) Diecke, F., Z. Naturf. 1954, **9b**, 713.
- 14) Rudolph, G., Ann. universitatis Saraviensis, 1956, **IV**, I, 1.
- 15) Hodgkin, A. L., J. Physiol., 1954, **125**, 211.
- 16) Pumphrey, R.J. & Young, J.S., J. exp. Biol., 1938, **15**, 453.
- 17) Hodes, R., J. Neurophysiol., 1953, **16**, 145.
- 18) Tasaki, I., Shinkei Sen-i no Seirigaku (Jap.), Tokyo, Kawai, Co., 1944.
- 19) Hodler, J., Stämpfli, R. & Tasaki, I., Pflüg. Arch., 1951., **253**, 380.
- 20) Tasaki, I., Amer. J. Physiol., 1955, **181**, 639.
- 21) Tamashige, M., Ann. Zool. Jap., 1950, **23**, 125.
- 22) Tasaki, I. & Fujita, M., J. Neurophysiol., 1948, **11**, 311.
- 23) Tasaki, I., Biochimica et biophysica Acta, 1949, **3**, 498.
- 24) Schriever, H., Z. Biol., 1932, **93**, 123.
- 25) Fatt, P. & Katz, B., J. Physiol., 1953, **120**, 179.
- 26) Hodgkin, A. L., J. Physiol., 1937, **90**, 183, 211.
- 27) Tasaki, I. & Takeuchi, T., Pflüg. Arch., 1944, **246**, 32.
- 28) Tasaki, I., Mizuguchi, K. & Tasaki, K., J. Neurophysiol., 1948, **11**, 305.
- 29) Tasaki, I. & Freygang, W.H. Jr., J. Gen. Physiol., 1955, **39**, 211.
- 30) Katz, B., Proc. Roy. Soc. B., 1937, **124**, 244.
- 31) Rushton, W.A.H., Proc. Roy. Soc. B., 1937, **124**, 210.
- 32) Marmont, G., J. Cell. Comp. Physiol., 1949, **34**, 351.
- 33) Grundfest, H., Physiol. Rev., 1957, **37**, 337.
- 34) Tasaki, I. & Hagiwara, S., J. Gen. Physiol., 1957, **40**, 859.
- 35) del Castillo, J. & Suckling, E. E., Fed. Proc. 1957, **16**, 29.