Excitation and Initiation of Impulse

Part I. Stimulation with Constant Current

By

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(Received for publication, October 28, 1956)

General Introduction and Way of Approach

In investigations hitherto made on the law of excitation, it has always been the excitation at the stimulated locus that was considered in theories, while it has been the propagated impulse that was employed as index of excitation in experiments. This might have been a source of confusion, because excitation and conduction are not always identical.

Rushton\(^1\), later Yamagiwa\(^2\),\(^a\), claimed that a certain minimal length \(L\) of a fibre must be excited for initiation of impulse. According to them, an excitation of a fraction of \(L\) remains localized or conducted just locally, although graded in size of potential or of conducted distance, according to the size of the fraction excited. Whether this genuine "local response" is identical or not with the so-called "subthreshold activity" (see Stampfli\(^3\)), is a problem\(^2\), but it is a different matter here.

Now, if such a length \(L\) really exists, then simple excitation is concerned with a "point", while initiation of impulse with simultaneous excitation of the whole \(L\). From this consideration, theoretical treatments can be developed on various experiments concerning initiation of impulse. In the present argument, eq. (1) (Fig. 1) derived by myself recently\(^2\),\(^a\) was adopted as the quantitative basis of \(L\), when necessary:

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

\(x\) : active (excited) length,
\(y\) : resting length to be activated by \(x\),
\(k, k'\) : length constants of resting and active membranes,
\(f\) : safety factor for local excitation (= \(\frac{V}{S}\), \(V\) peak value of action potential and \(S\) threshold in terms of \(V\) reduced properly).

Assume for simplicity that the stimulating current spreads in one direction only, and pay attention to the point \(L\) (Fig. 1) were \(y = x\). The
length OL (simply L hereafter) represents the minimal length above mentioned. Now, the current $I_L$ at $x=L$ must be weaker than $I_0$ at $x=0$ where the electrode is set, because $I_L = I_0 e^{-L/k} = I_0 e^{-L/m}$ ($m = e^{L/k} > 1$). There must be some time difference $\Delta t$ between the moments of excitation, $t_0$ and $t_L$, of the two points. The necessary condition for propagation is then practically $\Delta t = t_L - t_0 \leq D$, $D$ being the duration of excitation at $x=0$. Our task is to evaluate $t_L$ and $t_0$ and equate $\Delta t \leq D$, to examine the results therefrom.

A rough examination was attempted previously\textsuperscript{2).} The present paper aims at its completion, revising and extending it much farther. Figures and notations were changed in part. Simple repetitions were avoided except of essential points.

Eq. (2) which has appeared repeatedly in the literature\textsuperscript{4)-7}) was chosen as a representative of the law of excitation:

$$I = \frac{i_r}{1 - e^{-t/a}}$$ (2)

$I$: applied current,

$i_r$: rheobase for excitation (for $t=\infty$),

$a$: time constant proper to nerve ($=k_{HB}$, Hill's constant of local potential).

This equation yields $I_r$ ($I$ for $t=\infty$) = $i_r$, which means that the applied current itself becomes identical with $i_r$ in the extreme case. However, the matter appears quite different if viewed from the present theory, as shown below:
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At points $x=0$ and $x=L$ respectively,

$$I = I_0 = \frac{i_r}{1 - e^{-\frac{t_1}{\alpha}}} ; \quad I = I_L = \frac{i_r}{m(1 - e^{-\frac{t_1}{\alpha}})}$$

which give

$$t_1 = \alpha \ln \frac{I_0}{I_0 - i_r} ; \quad t_2 = \alpha \ln \frac{I_0}{I_0 - mi_r} \quad (3)$$

Hence, $\Delta t = t_2 - t_0 = (t_2 + \theta_2) - (t_1 + \theta_1) = \alpha \ln \frac{I_0 - i_r}{I_0 - mi_r} + (\theta_2 - \theta_1)$

$\theta_{1,2}$: latencies at $x=0$ and $x=L$.

$\theta$ must be a function of intensity and duration of the pulse, but $m$ being very near unity as will be stated later, and accordingly $I_0$ and $I_L$ very near each other in normal cases, $(\theta_2 - \theta_1)$ will be small enough to be neglected against $\alpha \ln \frac{I_0 - i_r}{I_0 - mi_r}$, at least when $I_0$ is small. The condition for propagation is then

$$\Delta t = \alpha \ln \frac{I_0 - i_r}{I_0 - mi_r} \leq D \quad (4)$$

$I_r$, the smallest value of $I_0$ which satisfies eq. (4), that is, the rheobase for propagation, is

$$I_r = i_r \frac{me^{\frac{\alpha}{D}} - 1}{e^{\alpha} - 1} = i_r \{1 + \frac{m - 1}{m} \frac{1}{e^{\frac{\alpha}{D}}} - 1\} = m\eta i_r \quad (5)$$

$$\eta = 1 + \frac{m - 1}{m} \frac{1}{e^{\frac{\alpha}{D}}} > 1.$$  

In case $i_r < I_0 < I_r$, a localized excitation will take place in the vicinity of the point $x=0$.

Introducing eq. (5) into (3),

$$t_2 = \alpha \ln \frac{m\eta i_r}{m\eta i_r - mi_r} = \alpha \ln \frac{\eta}{\eta - 1}$$

This $t_2$ represents $t_r$, the so-called "Hauptnutzzeit", because $t_2$ in general is nothing but the utilization time being explored in experiments. Hence,

$$t_r = \alpha \ln \frac{\eta}{\eta - 1} \quad (6)$$

Eq. (5) expresses that the current flowing at $x=0$ in the so-called rheobasic stimulation is $m\eta$-times, and the current at $x=L$ ($= \frac{I_r}{m}$) is $\eta$-times larger than $i_r$. The value of $\eta$ depends upon $m$, $D$, and $\alpha$. In frog's motor nerve, we may put $D=1$ msec, and $\alpha=0.5$ msec in average, so
The normal value of $m$ is estimated to be about 1.02 as will be shown in Part II, hence $\gamma \approx 1.003$ and $\frac{1}{\gamma} \approx 3 \times 10^{-6}$. Then, putting $\gamma \approx 1$ in eq. (5), we have $I_r = m_i = 1.02$ and from eq. (6), $t_e \approx 0.5 \times 2.3 \times 2.5 \approx 2 - 3$ msec. We see thus that 1) $I_r$ is larger than $i$, by a few %, and 2) $t_e$ is as large as a few msec, which is just about the value actually obtained. It is important to remember here that $I_r$ is the rheobase for propagation, and $t_e$ the utilization time of $I_r$ flowing at $x=L$.

In the previous paper, it was shown that Weiss' and Nernst's equations give similar results, too. Other equations will do the same, provided that $I$ as a function of $t$ yields gradually larger $\Delta t$ for gradually smaller $I$.

II. Repetitive responses

Nerve fibres are known to respond repetitively to long-lasting constant current. The characteristics are said to be considerably variable, but the typical ones seem to be the following three: 1) larger frequencies in stronger stimuli, 2) gradual decline of frequency with time, and 3) cessation of the response after a certain time. If assumed that each response does not disturb the local processes, then the cessation of the response is comprehensive from the theory of accommodation as the result of $i_r$-rise up to the level of the local potential evoked (Katz), but the other two are not always so, because, the local potential being assumed to remain fixed after once evoked, the response interval should be determined solely by the refractory period.

If viewed from the present theory, whether the response is repeated or not, depends upon whether eq. (4) is established or not for new $\Delta t$ after the first response. One possible occurrence may be a gradual rise of $i_r$ or $m$ with time, which makes $t_{1,2}$ (eq. (3)) and $\Delta t$ (eq. (4)) gradually larger. Leaving this to be dealt with in Part III, we will consider here another possibility, i.e., the gradual rise of $a$. This is a speculation at present, but seems fairly probable as a result of gradual reduction of the membrane polarizability, probably taking place in repeating the responses. If it occurs, then it, too, enlarges both $t_{1,2}$ and $\Delta t$. Gradually larger $t_e$ will result in gradual prolongation of the response interval, and gradually larger $\Delta t$ in cessation of the response at the moment where $\Delta t = D$ is reached. The higher frequency in stronger $I_o$ is shown in eq. (3) (for $t_e$) itself. The three typical features can thus be well understood, without introducing "accommodation" although just qualitatively.
Important findings have been made by Katz\textsuperscript{9} and Sato\textsuperscript{10} that fibres with small $\beta_r$ (the liminal gradient, see Part II) or large $\lambda$ (Hill’s constant of accommodation) are liable to give rise to repetitive responses.

In the present theory, $\beta_r=\frac{I_r(m-1)}{\eta D m}$ (Part II, eq. (1)) and $\lambda=\frac{I_r}{\beta_r}=\frac{\eta D m}{m-1}$.

Small $\beta_r$ means therefore small $I_r$, small $m$ (> 1) and large $D$. Large $\lambda$ also means small $m$ and large $D$. Evidently, large $D$ makes the establishment of the condition $\Delta t \leq D$ easier. Small $i_r$ and $m$ (accordingly $I_r$) do the same by reducing $\Delta t$. Katz’ and Sato’s findings can thus be explained satisfactorily. Sato’s\textsuperscript{11} and Diecke’s\textsuperscript{12} observations that a larger Na-concentration of the bathing fluid makes $I_r$ smaller and at the same time repetitive responses easier, are very interesting in this connexion.

**DISCUSSION**

1) Existence of L. The length $L$ is not yet verified experimentally because of methodical difficulties, but the possibility is suggested also by an ideal experiment, as follows:

Suppose a fibre separated into halves by a wall of zero thickness, and the surrounding medium shunted over the wall with a break-key in the circuit. Excite the fibre at its one end, and break the key shortly after the impulse has reached the wall. If the time is short enough, the impulse would not propagate beyond the wall, because there must be some utilization time as regards the action current as stimulus. Denote the critical time by $\Delta t$ and the conduction velocity measured separately by $v$. The quantity $v \times \Delta t$ represents the length which has been travelled (activated) during $\Delta t$ by the impulse. The actual cause of interruption must have been that $v \times \Delta t$ was not large enough for evoking further propagation.

2) Strength-duration relation in initiation of impulse. 1) Current and time to be related. Eq. (2) may be granted as a law of local excitation. But, as stated above, the time $t$ explored in experiments employing propagated impulses as indices, is nothing but $t_2$ (eq. (3)), the utilization time of $I_{\infty}$ flowing at $x=L$. Therefore the obtained $t$ should be related to $I_0$, but not to $I_0$. 2) The region of $I_0 < I_r$ and $t > t_r$. As long as eq. (2) is correct, $I_0$ weaker than $I_r$ (but stronger than $i_r$) and $t$ larger than $t_r$ must also be effective for eliciting a local excitation. But as far as initiation of impulse is concerned, $I_r$ and $t_r$ represent respectively the weakest current and the longest time available, and, therefore, the point $(I_r, t_r)$ in the strength-duration-curve marks the termination of the curve, theoretically as well as practically. The continuation of the curve might be
drawn horizontal, but it has no significance. 3) Eq. (3) as the proper expression of the relation. From 1) and 2) above, it follows necessarily that the theoretical strength-duration-relation in experiments employing propagated impulses as indices should be expressed by eq. (3), not eq. (2), in combination with a limitation in t, as follows:

\[ t_2 = \alpha \ln \frac{I_0}{I_0 - mI_r}, \quad t_2 \leq t_r. \]

Or, taking the original form \[ \frac{I_0}{m} = \frac{i_r}{1 - e^{-\frac{t}{\alpha}}}, \]

replacing \( t_2 \) by \( t \),

\[ \frac{\eta I_0}{1 - e^{-\frac{t}{\alpha}}} = \frac{I_r}{t}, \quad t \leq t_r \quad (= t_{10} = t_r = \alpha \ln \frac{\eta}{\eta - 1}) \]

This equation is scarecely different from eq. (2), but there are two points to be noticed, i.e., \( I_r \) and \( t \leq t_r \). \( I_r \), the rheobase for propagation, is a certain definite quantity which can be caught experimentally, in contrast to \( i \) which is imaginative. The limitation \( t \leq t_r \), excluding the region of \( t > t_0 \), makes us free from the ambiguities and uncertainties which we have encountered in theoretical considerations of the whole range of \( t \) in connexion with \( i_r \).

3) \( I_r \) and \( t_r \). Hill's interpretation of the so-called rheobase and its utilization time fails when no accommodation occurs. Hashida made distinction between theoretical (for \( t = \infty \)) and experimental rheobases, and took it as the utilization time of the latter. This made the matter simpler and clearer, but still it was strange, as well as suggestive, that a slight reduction of the applied voltage makes the stimulus totally ineffective, or, so to speak, the utilization time jump from \( t_r \) abruptly to \( \infty \).

\( I_r \) in the present theory might appear to correspond to Hashida's experimental rheobase, and \( t_r \) to its utilization time. But in the present argument, the appearance of \( I_r \) and \( t_r \) of certain definite values is a matter of theory, not simply of practice, expected to occur in the extreme case. The abrupt jump of \( t_r \) is in actuality an expression of \( \Delta t > D \), and does never mean a true elongation of \( t_r \). The point is that \( I_r \) refers to the point \( x=0 \) and \( t_r \) to the point \( x=L \).

4) \( I_r \) and \( i_r \). The existence of \( i_r \) seems highly probable, but as long as the present theory is correct, it will never be detected by employing propagated impulses as indices, because what is caught in this way is \( I_r \) and not \( i_r \).

5) \( \tau \) (chronaxie)-\( \alpha \)- and \( \tau \)-\( t \)-relation. If \( \alpha \) is replaced by \( k(H) \) (Hill's constant of local potential), eq. (2) turns out Hill's equation itself. There-
fore, \(\tau-z\)-relation is nothing but \(\tau-k_H\)-relation in Hill.

Now, \(\tau-z\)-relation, if derived directly from eq. (2), is

\[
\tau (t \text{ for } I=2 i_r) = ax \ln 2, \tag{7}
\]

which is claimed in Hill as a general relation between \(\tau\) and \(k_(H)\). But if derived from the present theory (eq. (3)),

\[
\tau (t_r \text{ for } I_0=2 I_r) = ax \ln \left(\frac{2m\gamma \eta r}{2m\gamma r - m_r}\right) = ax \ln \left(\frac{2\gamma}{2\gamma - 1}\right) \tag{7}
\]

In case \(\gamma \approx 1\) as in normal frog's motor nerve, \(\tau\) can be equal to \(ax \ln 2\), but not always so in other cases, because \(\gamma\) depends upon \(m\), \(D\) and \(x\).

Further, a general theoretical relation between \(\tau\) and \(t_r\) can be derived from eq. (6) and (7):

\[
\frac{t_r}{\tau} = \ln \frac{2\eta}{\gamma - 1} / \ln \frac{2\gamma}{2\gamma - 1} \tag{8}
\]

If applied to the normal frog's motor nerve, employing the approximate value of \(\gamma\) above estimated, we obtain

\[
\frac{t_r}{\tau} = \ln 300 \quad \ln 2 \approx 8,
\]

which agrees well with Sakamoto's data in average, where \(t_r\) was 1.03–1.24 msec and \(\tau\) 0.04–0.246 msec.

6) Repetitive responses. Katz's interpretation was criticized above. Tasaki also treated the problem from his own theory. He assumed that, after the first response, the rheobase returns back from \(\infty\) to a new steady level \(\beta_0\) following the equation \(\beta(t) = \beta_0 e^{\frac{t}{\tau}}\), \(\kappa\) being a constant; further that the next response takes place after a time \(T\) where \(\beta_0 e^{\frac{1}{\tau T}} = v\) (applied voltage). The equation obtained was \(\frac{1}{T} (c=F, \text{ frequency}) = \kappa \ln \frac{v}{\beta_0}\). He predicts further that one of the necessary conditions for excitation, \(\frac{dE_s(t)}{dt} \approx \frac{1}{\lambda} (E_s(t), \text{ the "excitatory state"})\), will become unfulfilled sooner or later because of \(\lambda\) being reduced. Thus, the rise of \(F\) with \(v\), and the cessation of response after a certain time could be well explained. The gradual fall of \(F\) is comprehensive, too, if introduced the gradual rise of \(\beta_0\). The difference is that repetition of excitation is considered in Tasaki, while repetition of impulse initiation in the present theory. Another point is that Tasaki's equation as it points to infinite rise of \(F\) with \(v\), which is evidently unreasonable because there exists a certain absolutely refractory period. Just the first response, which he did not treat, is free from this, so that, if viewed from the present theory, the response time can be expressed prac-
tically by \( t_2 \) of eq. (3). In this case, we have \( I_0 \left( e^{\alpha} - 1 \right) = m_i e^{\alpha} \), from which \( \frac{I_0}{m_i} (\frac{\eta I_0}{I_r}) = -\frac{1}{e^{\alpha F}-1} \) \((F = \frac{1}{t_2})\). Putting \( \frac{1}{e^{\alpha F}-1} = 1 + \frac{1}{\alpha F} \), excepting the range of small \( \alpha F \), we have

\[
\eta I_0 \frac{I_0}{I_r} = \alpha F \left( \frac{1}{\alpha F} + 1 \right) = 1 + \alpha F, \quad F = \frac{1}{\alpha} \left( \frac{\eta I_0}{I_r} - 1 \right) \quad (\text{Fig. 2, I}) \quad (9)
\]

![Fig. 2. F-I_0-I_r-relation. F: Frequency. t_R: Abs. ref. period. I, II, III: See text.](image)

For the 2nd response, however, \( F \) should be determined by \( \frac{1}{t_2 + t_R} \), where \( t_2 \) represents a new response time and \( t_R \) the refractory period. The effect of \( t_R \) is relatively little in the range of large \( t_2 \) (that is, small \( I_0 \)), but predominant in the range of small \( t_2 \) (that is, large \( I_0 \)). Therefore, \( F \) will depend largely upon \( t_2 \) in weak \( I_0 \) and largely upon \( t_R \) in strong \( I_0 \), so that the \( \frac{I_0}{I_r} \)-curve will run practically linear in some initial stage, almost in coincidence with the curve I, but later bend downwards to attain \( F = \frac{1}{t_R} \) in the end (Fig. 2, II). The same thing can be said about the 3rd and following responses, but every curve is expected to run somewhat below that of the preceding response (curve III), because \( \alpha \) and also \( I_r \) (see Part III) may increase gradually. This was found really the case in Sato10)-11).

The above expectation agrees well with Hodgkin’s statements16 about the response of Carcinus axons (Class 1) that 1) “response time rather than
refractory period is the primary factor in determining the frequency of repetition when the current is weak”, and 2) “the refractory period became important when the current strength was large and the repetition frequency was high. Strong currents reduced the response time towards zero but the repetition interval never became less than 6.5 msec.”

The significance of the length of the response time was interpreted in terms of the duration of the “local response”, the electric sign associated with it, but it is a different matter.

Hodgkin made many other interesting observations, of which some of particular importance will be quoted and discussed below: 1) In axons belonging to Class 1, which could respond over a wide range of frequencies (5–150/sec), “the local subthreshold potentials were small compared to the propagated action potentials”, and further “the response time was extremely long when the strength of current was weak.” The former points to small $m$, because in the present view, the so-called subthreshold potential just necessary for evoking propagation represents the potential due to excitation of just $L$; the smallness of the value can therefore mean small $L$, that is, small $m$. The latter, too, does the same, because it means practically a very long $t_r$, which means in turn that $\gamma (>1)$, accordingly $m (>1)$, is very near unity (see eq. (6)). Such a small $m$ makes $t_2$ and $\Delta t$ small, by which the repetitive response will be maintained long, with frequencies declining with time owing to gradual rise of $\alpha$ or also of $m$, as will be stated in Part III. 2) Axons with pronounced supernormal phase (Class 2) gave trains of impulses of “fairly high” frequencies, which “might last for several seconds but which ended abruptly without giving frequencies lower than 50/sec.” In view of the present theory, supernormality means small $I_r (=m\gamma i_r)$, which can mean again small $m$. Roughly, therefore, the repetitive response may be considered as taking place in a state of reduced $m$. This makes the high frequency and the long duration of the responses comprehensive. However, the abrupt termination without passing the stage of lower frequencies cannot be explained by such a simple assumption. The matter must be much more complicated in actuality. 3) Axons diminish the ability to repeat if left in oil or sea-water for a long period (Class 3). Under these circumstances, “the response time at rheobase is greatly reduced”, and “the rheobase itself had increased considerably.” The latter facts indicate an enlargement of $m$, which, contrary to the case 1) above, makes the repetitive response difficult or impossible. 4) Subthreshold oscillations were observed in just subthreshold stimulations (Text—Fig. 6, 1–J), which “appeared to differ in several respects from the oscillations seen in decalcified nerves or in nerves stimulated with strong currents.” They seemed to occur “over a very narrow range of currents” and “when the axon just fails to propagate.” Such oscillations are of a
particular significance in view of the present theory, because currents lying between $I_r$ and $i_r$ are to elicit repetitive local excitations of relatively low frequencies.

Sato$^{10}$ developed recently a new mathematical treatment of the repetitive response, based on Tasaki’s$^{16}$ theory of excitation and on the idea of accommodation, and was led to the same equation as Katz’s$^{9}$. Katz’s equation, however, represents just a special case of $i_r$-rise if viewed from the present theory as will be stated in Part III. One of Sato’s$^{11}$ observations worthy of special note is that a node of Ranvier responds repetitively only rarely if stimulated directly, even when immersed in a 5% NaCl solution. It is not quite clear at present what this fact signifies, but it might be a clue for clarifying a part of the mechanism of the repetitive initiation of impulse.

**SUMMARY**

1. Standing on a theoretical ground, excitation was distinguished from initiation of impulse.
2. Regarding the initiation of impulse as due to simultaneous excitation of a certain length L in less than D (duration of excitation), a theoretical treatment was developed on various phenomena of excitation. Chief phenomena explained were, a) appearance of $I_r$ (rheobase for initiation of impulse) combined with a proper duration, $t_r$, and b) repetitive responses without rise of threshold.
3. Discussions were made on a) existence of L, b) strength-duration-relation in initiation of impulse, c) $I_r$, $i_r$, $t_r$ and $\tau$ (chronaxie), and 4) repetitive responses.

**References**

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