AGAIN ON THE LOCAL RESPONSE AS A SMALL AREA ACTIVITY

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The "local response" (L. R.) of nerve fibre discovered by KATZ\(^1\) was at first interpreted as an all-or-none activity of a small area on the basis of RUSHTON's theory of initiation of impulse\(^2\), but later, after MARMONT\(^3\), as a subthreshold activity of one and the same locality\(^4\). The present author\(^5\) opposed to this, and claimed that MARMONT's observation is rather a support for the active area concept (cf. Discussion).

In recent years, new observations on the L. R. have accumulated, and, on the other hand, a new concept of "active spots" has been developed (cf. Discussion). This paper aims to explain several known facts from the author's theory and, at the same time, to state that the concept of active spots is essentially identical with that of active area.

(1) Quantitative expression of L. R. as a small area activity

In a previous paper\(^6\), the author postulated a "length-to-length" transmission as the basis of conduction. What was meant was that a certain length (not a "point") of fibre must be active for realizing conduction, accordingly, that an activity inside a certain liminal length should necessarily be localized. The theoretical background was as follows:

Assume the fibre diameter uniform, and take "length" for "area" for simplicity. Then, the relation between an active length \(x\) and the resting length \(y\) to be excited by \(x\) is expressed by eq. (1)\(^{5b}\), and its normal graph by Fig. 1A schematically.

\[
y = \ln \frac{P_{y=0}}{S} = \ln \frac{V}{S} \left(1 - e^{-x/k'}\right) = \ln f \left(1 - e^{-x/k'}\right) \quad \cdots \cdots \quad (1)
\]

\(P_{y=0}\), electrotonic potential at \(y=0\); \(k, k'\), length constants of resting and active membranes respectively (cf. N. B. 1 below); \(V\), action potential; \(S\), threshold for excitation in fraction of \(V\); \(f = V/S\), safety factor of excitation.

Now, in case \(x \leq l\) (Fig. 1A), \(y\) is zero, that is, the activity can not spread; and if \(l < x < L\), then \(0 < y < x\), which means that a local decremental

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conduction takes place. These responses may be called the true L.R. (T.L.R.) and apparent L.R. (A.L.R.) respectively. The quantitative expression of the T.L.R., which is important here, can be obtained in the following way.

Suppose a short length \( x \) excited "simultaneously". Be the activity of each excitable unit in \( x \) all-or-none, and its action potential \( V \). An action current will flow between \( x \) and neighboring resting region, producing potential drops along the resistances in the circuit. It is clear that the so-called "action potential measurement" in presence of current flow as in this case, cannot catch \( V \) itself but only the external potential drop which is mainly localized across the resting membrane.

Now, the membrane potential thus produced decays exponentially (FIG. 1B). The observation may catch the mean value (GRUNDFEST\(^9\)) or possibly \( P_{y=0} \), the potential at \( y=0 \), which is expressed by \( P_{y=0}=V(1-e^{-x/k})^{5(b)} \). We may equate, therefore,

\[
\text{Act. pot. (measured)} = P_{y=0} = V(1-e^{-x/k}) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(2)
\]

and

\[
\text{T.L.R. (measured in potential)} = P_{y=0} \quad (\text{for } x \leq l) = V(1-e^{-x/k}), \quad x \leq l \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(3)
\]

The T.L.R. denotes thus a certain fraction of \( V \), that is, a small stimulating potential in conduction due to \( x \leq l \), in view of the present theory. A point of particular importance is that the critical condition \( x=l \) gives \( y=0 \) (FIG. 1A), hence \( P_{y=0} \) (for \( x=l \)) = \( S \) (see eq. (1)). That is to say, the maximal value of the T.L.R. as stimulus is nothing but \( S \) itself, the threshold for excitation expressed in fraction of \( V \). Another point to be remarked is that

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FIG. 1. \( y-x \)-relation (A) and decay of electrotonic potential (B), schematic.

\( x \), active length; \( y \), resting length to be excited by \( x \); \( P_{y=0} \), potential at \( y=0 \); \( S \), threshold for excitation in fraction of action potential.
l is normally very small compared to $k'$. In toad's nodal membrane, for example, $l$ is about of the order of $0.1 \mu$ and $k'$ (corrected) is about $1.5 \mu$ though not exact. Hence

\[ \text{T.L.R. (in potential) } \approx V \frac{x}{k'}, \quad x \leq l ............. (4) \]

that is, the T.L.R. (in potential) is approximately proportional to $x$ under constant $V$ and $k'$. The situation is a little different in the current recording of the L.R. of a node of Ranvier under air-gap. The result of calculation on an equivalent circuit (Fig. 5) is as follows:

\[ \text{T.L.R. (in current) } = \frac{V}{R_m'} \frac{x}{p(q-1)x + (p+2)b'}, \quad x \leq l \quad .... (5) \]

where $p = \frac{R_m + R_a}{R_m}$, $q = \frac{R_m}{R_m'}$, and $R_m$, $R_m'$, $R_a$ and $b$ the same as in Fig. 5.

The T.L.R. (in current) -- $x$ -- relation depends thus on the values of $p$ and $q$, but, under $p \approx 2$ and $q \approx 10^3$, it is practically linear for $x$ changing in a small fraction of $b$. We assume here therefore that the T.L.R. in current too is roughly proportional to $x$ in the range of experiment.

Next, the amplitude of the A.L.R. for $l < x < L$ is complicated by the accompanying local conduction which will more or less enlarge the effective active area secondarily or may occasionally cause the "secondary wave" observed by Hodgkin. As a rule, however, the amplitude will get gradually larger than proportional to $x$ and deviate from the straight line the more, the closer $x$ approaches $L$. Occasionally, the A.L.R. may escape from the observation, because the range between $I$ and $L$ is very small normally (cf. 5a). In such a case, the L.R.-x-relation will appear simply linear (cf. 8, 9).

**N.B. 1)** The equation $p_{x=0} = V(1 - e^{-x/k'})$ seems to be satisfactory in form. Quantitatively, however, the value of $k'$ (length constant of active membrane) had to be reduced by an amount to make it accord with facts (for example, from about 8 $\mu$ to about 1.5 $\mu$ in the case of activity of a whole node of Ranvier), perhaps because the resistance of the resting region, on which $p_{x=0}$ stands, was not taken into account in deriving the equation. Such a reduction of $k'$ makes some of the previous arguments inexact but not very much while, on the other hand, it makes the ascent of the $y-x$-curve (Fig. 1A) steeper, and thus makes the appearance of the characteristic length $L$, where $y = x$ and on which most of the important arguments are based, the surer.

**N.B. 2)** The action potential measured in presence of current flow (eq. (2)) gets larger with $x$, but is always smaller than $V$ itself. This is because some potential loss due to the active membrane resistance, which is inversely proportional to $x$, is inevitable. In case $x \geq I$ (strictly $L$), however, an impulse is initiated and a state will soon be attained where $x$ (active length) $> 5k'$ (unmyelinated fibre) or a whole nodal membrane gets excited (myelinated fibre). We have then Act. pot. (measured) $\approx V$, which we call "spike" of all-or-none character usually.
(II) Observed facts and their explanations from the active area concept

1. Linear relation of T.L.R. to stimulus intensity

In Hodgkin's observation on Carcinus fibre and in del Castillo-Stark's on myelinated fibre, the L.R. increased with stronger shocks at first linearly, then at accelerating rate near the threshold. In Uehara's recent observations on myelinated fibre, the curved part was almost missing, but the general tendency appeared to be similar. The author presumes here that the linear part concerns the T.L.R. (x < l) and the curved part the A.L.R. (l < x < L). Then, what requires explanation is the linearity of the former only, because the latter is attributable to the local conduction as stated above.

a. Long pulse stimulation: In view of the present theory, the rheobase for spike (Vr) should be somewhat larger than that for excitation (v), because they are related by Vr = mvr and m = eL/k > 1. In long pulse stimulation, therefore, just the potentials between v and Vr can elicit the L.R.

Let us adopt P = vr / (1 - e-t/\alpha) as a theoretical formula for excitation, and consider the case of sufficiently long t.

Now, the size of the T.L.R. is proportional to x which is excited "simultaneously" as stated above. Such x may be defined practically by tpx - tp0 ≤ D, where p0 is the applied potential, tpx and tp0 the utilization times at x and under the electrode respectively, and D the duration of activity. A simple calculation based on the above formula gives for the critical case

\[ t_{px} - t_{p0} = \alpha \ln \frac{p_0 - V_r}{p_0 - e^{x/k} v_r} = D, \]

\[ x = k \ln \left( \frac{p_0 - v_r}{v_r} - 1 \right) (1 - e^{-D/\alpha}) + 1 \]

In actuality, p0 is limited by v_r < p0 < V_r (\div mv_r) as stated above, and the normal value of m is estimated to be about 1.02 or smaller. Hence, 1 < p0/v_r < 1.02, accordingly (p0/v_r - 1)(1 - e^{-D/\alpha}) < 1. We have therefore

\[ x = k \left( 1 - e^{-D/\alpha} \right) \left( \frac{p_0}{v_r} - 1 \right), \]

a pure linear relation between x (accordingly, T.L.R.) and the applied potential p0. Unfortunately, experimental data to be compared are missing.

b. Short pulse stimulation: Be the pulse duration shorter than D. Then, tpx < D, accordingly tpx - tpo < D in all cases. That is, the condition for simultaneous excitation is always satisfied, and, therefore, the whole x excitable by p0 can itself be the measure for the T.L.R. Such x can be obtained by solving the equation

\[ p_0 e^{-x/k} = \frac{V_r}{1 - e^{-t_c/\alpha}} (t_c = \text{const.} < D), \]
In this case, \( P_0 \) is limited by \( cV_r < p_0 < cV_r + (\div mcv_r) \), hence \( 1 < \frac{P_0}{cV_r} < m \) as before, so the \( x \)-\( P_0 \)-relation may be said practically linear. In actual experiments, thresholds for the spike and the just appreciable L.R. have been said to be 100 and 50 in relative values in Carcinus fiber and 100 and 60 \( \sim 90 \) in myelinated fibre respectively. This means that \( \frac{P_0}{v_r} = \frac{100}{50 \sim 90} = 2.0 \sim 1.1 \) at largest. Therefore, a practical linearity is expectable all the same.

2. Linear relation of T.L.R. to stimulus duration

According to ICHIOKA-MEVES, the L.R. of a node of Ranvier increases linearly with stimulus duration. In this case, we can equate

\[
x = k \ln \frac{P_0}{cV_r} \implies 1 = 1 - e^{-t/a} \quad \text{(7)}
\]

which gives

\[
x = k \ln \frac{P_0}{v_r} (1 - e^{-t/a}) \quad \text{(8)}
\]

In actuality there are limits in \( t \) available, because, in case \( p_0 > V_r \), \( t \) must be smaller than the utilization time which evokes spike, and in case \( v_r < p_0 < V_r \), the condition \( t - t_0 \) (const.) \( \leq D \) must be satisfied for simultaneous excitation. Under such limitations, \( x \) increases with \( t \) following the above equation. The \( x \)-(L.R.)-\( t \)-relation will then be practically linear in a certain range of \( t \) where \( \frac{P_0}{v_r} (1 - e^{-t/a}) \) is not far from unity. The range is expected, therefore, to get narrower with larger \( p_0 \). An examination is desired.

3. Spike and L.R. in abnormal conditions

a. ICHIOKA found previously some differences between effects of ions upon the nodal spike and L.R. Recently, ICHIOKA et al. found further that the spike gets smaller in narcosis, hypertonicity and NaCl-deficiency, while the maximal L.R. gets larger (in narcosis and hypertonicity) or remains almost unchanged (in NaCl-deficiency) (Fig. 2). It was striking that, in narcosis or hypertonicity of high grades, the decrease of spike and the increase of maximal L.R. were so pronounced that they often gave records with double peaks of nearly equal heights (Fig. 3). (A similar phenomenon had been observed by Hodgkin in Carcinus fibre, refractory or maltreated.) ICHIOKA et al. took these facts as indicating some qualitative differences between the spike and the L.R. ..

However, the phenomena are well comprehensive also from the present
Fig. 2. Spike, max. L.R., threshold and Q in urethane-Ringer (A, B, C) and NaCl-deficiency (D). From ICHIOKA et al\(^{(15)}\), rearranged.

theory. As stated before, the spike and the max. T.L.R. correspond to \( V \) and \( S \) respectively, so their changes in opposite directions seem to be rather natural. Mathematically, further, the max. T.L.R. is proportional to two factors \( V \) and \( \frac{l}{k'} \) or \( \frac{1}{R_m' p(q-1)l+(p+2)b} \) (eq. (5, 6)). Supposedly, \( \frac{l}{k'} \) or \( \frac{1}{R_m' p(q-1)l+(p+2)b} \) increased more than \( V \) decreased in narcosis and hypertonicity to enlarge the product, while they almost cancelled each other in NaCl-deficiency. In actuality, perhaps \( l \) gets larger when \( V \) gets smaller.

Fig. 3. Spike decreasing and max. L.R. increasing with urethane concentration (from ICHIOKA et al\(^{(15)}\)).

A, Ringer; B, C, D, E, F, 0.5%, 0.75%, 1.0%, 1.25% and 1.5% urethane-Ringer respectively.
until it occupies a whole nodal breadth. The double peak will then become single and simply decrease in height thereafter owing to decrease of $V$. This was actually the case, showing that the size of a L.R. depends on $V$, if the active area is invariable.

Another remark is that $V_r$ (threshold for spike) and the max. L.R. increased together in narcosis and hypertonicity, while just the former increased but the latter remained almost unchanged in NaCl-deficiency (Fig. 2). This is explained as follows:

Change of max. T.L.R. means change of $S$, accordingly, of $v_r$ (rheobase for excitation), because $S$ is equivalent with $v_r$. Now, $V_r \div m v_r$ as stated before, hence $V_r$ can change with $v_r$ under constant $m$, as well as with $m$ under constant $v_r$. In the former case, $V_r$ and the max. T.L.R. will change together as in narcosis and hypertonicity, while in the latter case only $V_r$ will change as in NaCl-deficiency.

Finally, ICHIOKA et al observed that the duration of the L.R. gets remarkably long when elicited by a long pulse, while that of the spike not much. This can be understood in the following way. Be the applied voltage $p_0 (< V_r)$ and its duration $T$, and consider the maximal fibre length $x_m$ which can be excited. Then, the excitation of the whole $x_m$ will be accomplished in $(t_{x_m} - t_{x_0})$, where $t_{x_m}$ is the utilization time at $x_m$ and $t_{x_0}$ the same under the electrode. In actuality, $t_{x_m} = T$ and $t_{x_0} = t_{x_0} = \text{constant}$, hence $(t_{x_m} - t_{x_0})$ gets larger linearly with $T$, even up to $\infty$ in extreme case. We know thus that the whole duration of the L.R. can be lengthened infinitely with $T$ by successive, not simultaneous, addition of active area.

b. According to ROSENBLUETH\(^{16}\), the spike gets larger while the L.R. smaller in anelectrotonus. Just the opposite was observed in catelectrotonus by KITAMURA\(^{18}\) in our laboratory. The reason is probably the same as in abnormal conditions, that is, $V$ and $l/k'$ changing in opposite directions in different grades.

c. SASAKI et al\(^{17}\) pointed out that L.R. is elicitable also in bad conditions, for example, NaCl-deficiency, where the spike is not so. UEHARA\(^{9}\) observed the same fact also in urethane application. In view of the present theory, this is not an essential difference but is only a result from enlargement of $l$. Namely, if $l$ gets as wide as a whole nodal breadth, then the graded L.R. will be still possible as long as the membrane is excitable, but the spike not, because there is no room for expansion of the active area.

4. Effect of high-frequency, just subthreshold repetitive stimulation upon L.R.

Quite recently, KITAMURA\(^{18}\) carried out repetitive stimulations of a single node of RANVIER, varying the frequency and intensity in a wide range. Of the results, those obtained by subthreshold stimuli of relatively high frequencies are of interest here.
a. Gradual development of L.R. before and after spike initiation: First, a certain number of L.R. did appear in advance to the first spike. Then, the same thing was repeated after the spike until the second spike was initiated, and so on (Fig. 4). In both, the size of the L.R. increased gradually towards, perhaps, a critical value required for spike initiation.

The initiation of spike after repeated stimulation might appear to be due to the so-called addition latente. In actuality, however, it is certainly due to growth, not summation, of each L.R. as shown in the figure. And, the growth of the L.R. is easily comprehensive from the present theory as due to growth of active area, because some adjacent resting region will be brought into activity anew at each successive stimulation as a result of addition latente there. In the similar phenomenon after a spike, the effects of recovery of \( V \) and \( v_r \) (see eq. (4) and (7)) must be involved in addition.

![Fig. 4. Responses to repetitive subthreshold stimulation. Stim. freq. 1630/sec. (from KITAMURA).](image)

b. Gradual development of the max. T.L.R.: We may take the L.R. appearing just before each spike (Fig. 4) as approximate representations of the max. T.L.R. Then, the max. T.L.R. gets clearly larger with time in this case, too, in contrast to the spike which gets smaller. It can be explained in the same way as in section 3, above.

5. Summation of L.R.

It is known that the L.R. can be summated\(^{16,17,18}\), while the spike not. ROSENBLUETH\(^{16}\) took this as a criterion for distinguishing them from each other. However, additional activation of some new area by successive stimulation seems highly probable as stated above. Then, a “summation” due to enlargement of active area, although not of activity itself, becomes a matter of course, provided that two successive stimuli are spaced properly short.

6. Transition from L.R. to spike (inflection and separation).

It has been familiar to the investigators in this field that a spike is elicited suddenly at a certain level of the L.R. Thereby, two cases were encountered. In one, the transition took place on the rising phase or at the
peak, leaving an "inflexion" behind. In the other, the spike started from the falling phase, separated from the L.R. The latter happening has been observed repeatedly, particularly clearly recently by Takahashi and Koyano in normal conditions and by Ichioka et al in abnormal conditions. This fact casts some doubt as to the validity of the concept of "a certain fixed firing level".

In view of the present theory, however, the sudden transition, either with inflexion or separation, is a simple result of explosive expansion of the active length from a small initial value towards the large final value "M" (Fig. 1A) or to the full breadth of a nodal membrane. The separation is nothing more than a representation of a case where the initial active length is so small that its action as stimulus is accomplished first on the falling phase. Such a happening is not strange at all, if the L.R. represents a stimulus as stated before.

7. Threshold of L.R.
The weakest short pulse stimulus, which elicits a barely appreciable L.R., has been said to be 50% (Carcinus) or 60~90% (node of Ranvier) of the threshold for the spike, as stated above. These may be taken as thresholds for the L.R. practically, but whether they are true thresholds or not is not decidedly clear, because the L.R. does not follow the all-or-none. Rosenbluth even said that there is no threshold.

Meanwhile, Spyropoulos reported recently that the "miniature response", discovered by him and regarded as identical with the L.R., has a true threshold. Uehara's recent observations are noteworthy, too, indicating not only the existence of the threshold but also its elevation in abnormal conditions.

In the present theory, the L.R. is regarded as an all-or-none activity of a small area. If this is correct and if there is a threshold for the all-or-none activity in general, there must be a threshold also for the L.R. The observations above quoted are in agreement with this expectation.

8. Graded duration of L.R.
The duration of the L.R. of Carcinus fibre gets clearly longer with stronger shocks. The same was observed recently on the node of Ranvier, particularly in the so-called potential recording. On the other hand, it is known that an applied inward current as well as an inward action current shorten the duration of activity. So, it may be worth while to examine the action current density in the L.R. in general from the active area theory.

The matter is simple in the case of a non-myelinated fibre, i.e.,

\[ \sigma = \frac{V}{r_a/x + W \cdot \frac{1}{x}} = \frac{V}{r_a + Wx} \]
\( \sigma \), current density (per unit length of fibre); \( V \), act. pot.; 
\( r_a \), active membrane resistance (per unit length of fibre); 
\( x \), active length; \( W \), resistance of resting region \( (\approx \text{constant as long as } x \text{ is small compared to fibre length}) \)

Hence, \( \sigma \) increases with smaller \( x \), that is, with smaller L.R. In the case of a myelinated fibre, we may employ an equivalent circuit and neglect the nodal axonal resistance for simplicity, as follows:

Suppose \( b/n \) (\( b \), nodal breadth; \( n > 1 \)) of the middle node in Fig. 5 excited. The currents will flow in the directions as shown by the arrows.

A simple calculation gives

\[
\sigma = \frac{V}{b} \left\{ \frac{R_m + \frac{R_m(R_m + R_A)}{2nR_m + (n-1)(R_m + R_A)}}{R_m'} \right\} \\
\text{(in current recording)}
\]

\[
\sigma = \frac{V}{b} \left\{ \frac{R_m'(R_m + R_A)}{nR_m' + (n-1)(R_m + R_A)} \right\} \\
\text{(in so-called potential recording)}
\]

\( \sigma \), current density per unit length of nodal membrane; 
\( V \), action potential; \( R_m, R_m' \), membrane resistance of resting and active node respectively; \( R_A \), internodal axonal resistance.

Hence, \( \sigma \) gets larger with larger \( n \), that is, with smaller L.R. The values in extreme cases are

\[
\sigma_n \approx 1 \text{ (the case of spike)} = \frac{V}{b} \left\{ R_m' + \frac{1}{2}(R_m + R_A) \right\} \\
\text{(in current recording)}
\]

or

\[
\sigma = \frac{V}{b} \left\{ R_m' + R_m + R_A \right\} \\
\text{(in potential recording)}
\]
Putting $R_m' = 1$, and $R_m \div R_A = q$ for approximation, and introducing $q > 10^{25}$, we have

$$\frac{\sigma_{n=\infty}}{\sigma_{n=1}} = q \text{ (or } 2q) + 1 \geq 11 \text{ (or } 21)$$

We see thus that $\sigma$ in the minimal L.R. should be at least more than ten times larger compared to that in the spike. Such a large difference in $\sigma$, particularly in the so-called potential recording, may possibly cause the graded duration of the L.R.

**DISCUSSION**

(I) *Classical concepts as regards the nature of L.R.*

Besides the small area concept, there have been presented the following three:

First, HODGKIN's idea\(^4\) of "subthreshold activity" based on MARMONT's observation\(^3\) and the sodium-theory of his own. The explanation, particularly for the sudden transition from L.R. to spike by introducing the idea of "regenerative action", is splendid indeed. However, the very experimental basis is now weakened (see below), and moreover a number of facts require explanations, among others the spike initiation on the falling phase of a L.R., or the increase of the max. L.R. in abnormal conditions. For, according to HODGKIN's theory, the transition is to take place at a certain "firing level" where the Na-permeability (represented by the L.R.) just balances the K-permeability; hence the transition should be on the rising phase or at the peak of the L.R., if examined at the stimulated locus. Similarly, the increase of the max. L.R. in abnormal conditions should indicate the elevation of the Na-permeability required for balancing the K-permeability, hence the K-permeability must be increased in all these abnormal conditions examined, which seems questionable.

ROSENBLUETH\(^16\) regarded the L.R. as a particular kind of activity which differs from the spike in nature and properties, pointing out the following five reasons: 1) L.R. does not follow the all-or-none, 2) summation occurs, 3) L.R. is separable from the spike, 4) spike appears larger while L.R. smaller in A.E.T., and 5) there is no threshold for the L.R. However, it was shown above that 1)–4) can be explained from the present theory, and 5) is perhaps wrong. Further, if the L.R. is an activity which neither follows the all-or-none nor has any threshold, then a L.R. and its decremental conduction should always take place however weak the stimulus is. Any strict
L.R. would then be impossible.

Sakamoto\textsuperscript{56} takes the L.R. as an electrical sign of a certain pre-excitatory process which he calls the “stimulation process”. It seems quite reasonable to distinguish “stimulation process” from “excitation process” which follows. Unfortunately, the properties of the stimulation process are not yet explored concretely, so that observed facts cannot be “explained”, but only “interpreted” from the view at present.

(II) The active spots theory

In a previous paper\textsuperscript{5a}), the present author criticized Marmont’s observation\textsuperscript{3)}, pointing out that 1) the stimulated area is too large (>6 mm\textsuperscript{2} actually) to be uniform in physical as well as physiological senses; 2) therefore, uniform excitation will be impossible even if stimulated by a uniform voltage, and 3) possibly some active islets will appear in weak stimulation, which, increasing in number and area, will be led to conduction and fusion and thus the whole membrane under stimulation will get excited at a critical stimulus. It was thus stressed that Marmont’s observation cannot always be an evidence for subthreshold activity, but is rather an evidence for the active area concept.

Quite recently a new idea similar to that of active area has appeared under the name of active “spots” or “units” with respect to ganglion cell\textsuperscript{27)}, giant fibre\textsuperscript{28,29)}, medullated fibre\textsuperscript{30,31)} and excitable tissue in general\textsuperscript{6}). Finally, a spotwise excitation was proved experimentally, and named the “miniature response” by Spyropoulos\textsuperscript{19}).

Tasaki-Hagiwara\textsuperscript{28)} considers that the number of active spots increases with stimulus strength, and, when the total area of the spots attains a certain definite fraction of the area under stimulation, the whole area gets excited at a time. A similar idea was presented by Matsumoto\textsuperscript{32)} recently with respect to a modified Lillie’s nerve model. These authors deal with “whole area activation of a certain limited area under stimulation”, which is not always identical with initiation of “impulse” travelling beyond the limited area. But at any rate we may say now that the L.R. as a small area activity has acquired a firm experimental basis.

Now, there is another important thing to be considered, that is, the non-uniformity of the stimulating current. When a large area under clamp is stimulated by means of longitudinal electrodes as in Marmont or Spyropoulos, the stimulating potential is uniform, so that chiefly the membrane non-uniformity is questioned. But in stimulation with a stigmatic electrode or in stimulation of a node of Ranvier via air-gap, the stimulating potential decays exponentially, with larger gradients near the electrode or the edge of the node. What is questioned in such a case is the non-uniformity of the stimulus
rather than that of the membrane. The situation is similar in physiological conduction where the action current acts as stimulus. For these reasons, the author took up the latter case of stimulation, and considered "an" active area varying in size near the electrode, instead of the active spots which are scattered. This is a difference but not essential. The active spots concept may thus be regarded as a modification of the active area concept, as Tatsuuki-Bak29) themselves say so.

(III) The ratio spike/max.L.R.

Hodgkin33) defined this ratio as the safety factor for propagation. Ichiooka-Meves33) and Ichioka et al15) accepted the definition from experimental standpoint of view (cf. Fig. 2, "Q"). However, the meaning of "safety" is obscure, because the max. L. R. is only a threshold "response" but not a threshold "stimulus" in Hodgkin.

In view of the present theory, the spike represents V and the max. L. R. S, as stated before. Hence, spike/max. L. R. = V/S = f (see eq. (1)), that is, the ratio expresses f (the safety factor for excitation) itself. This offers a theoretical basis for Hodgkin's definition.

(IV) The all-or-none law

As long as a L.R. is a "response", it makes the all-or-none law untenable as a matter of fact. The conducted "spike" has been said to be all-or-none; theoretically, it can be almost so in view of the present theory (see N.B. 2), p. 453). However, strict all-or-none of the spike seems to be questionable at present not only theoretically but also experimentally9). On the other hand, the activity of a final unit of area or structure is assumed to be all-or-none in the present theory and the active spots theory. The assumption is highly probable and also very useful, but it is an assumption after all, and the possibility of a "subthreshold activity within a unit" cannot be denied.

Thus, the law has no firm basis, either experimentally or theoretically, at present. Originally, however, the law was a simple expression of the fact that a heart responds to suprathreshold stimuli with a constant magnitude of contraction. The situation is similar in a nerve fibre, which always responds to suprathreshold stimuli with a whole-length conduction. It seems adequate at present, therefore, to reserve the term "all-or-none" for this kind of activity only.
LOCAL RESPONSE AND ACTIVE AREA

SUMMARY

1. Old and new facts observed on the L.R. were explained from the author’s active area theory.
2. The maximal L.R. denotes the “threshold stimulus for excitation” expressed in fraction of the action potential. Accordingly, the ratio act. pot./max. L.R. represents the safety factor for excitation in the process of conduction.
3. Classical concepts on the L.R. were criticized.
4. It was stated that the modern active spots theory is essentially identical with the active area theory.
5. The limit of the all-or-none law was discussed.

REFERENCES

26) Sakamoto, S. Electric excitation of the excitable tissue (Jap.), in “The studies of the automaticity”. Bunkodo, Tokyo, 1959.
34) TAKAHASHI, I. In preparation.

Addendum. Quite recently, A. F. Huxley reported that a subthreshold disturbance can be conducted with a slow but uniform velocity (J. Physiol. 148: 80 P, 1959). It is interesting to note that such a conduction is possible in a special case of the present theory, where just $x=L$ (FIG. 1).