Theory of Nerve Excitation in Reference to Energy Dissipation

—An Example of Far from Equilibrium System—

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Excitation phenomena in living membranes are studied theoretically, taking the dissipative interaction caused by local electric current in the membrane into consideration. The steady state solutions are obtained subject to the variational principle under the assumptions that the statistical ensemble theory and the equal a priori probability distribution are applicable to the dissipative processes in the membrane. It is noted that the transition between two steady states of the membrane is induced cooperatively by the dissipative interaction of the local eddy current. The characteristic N-shaped current vs. voltage relation derived is favorably compared to the experimental data obtained with squid giant axons.

Phenomenological equations basic to the dynamic feature of the process of transition of steady states are derived on the basis of continuity of electric current in conjunction with the non-markovian effect caused by an irreversible ion accumulation at the membrane surface. The time course of an action potential and the abolition threshold potential during excitation obtained theoretically are in accord with experiments obtained from squid giant axons perfused internally. The probable causes for the discrepancies between theory and experiments are discussed briefly.

§ 1. Introduction

Recent physicochemical studies carried out with internally perfused squid giant axons have revealed that the process of excitation is interpreted in terms of conformational change of macromolecules constituting the membrane rather than a transient variation of membrane permeabilities for some specific ion species such as K+ and Na+. It is hazardous, however, to conclude that the excitation of living tissues is accompanied by a phase transition of membrane structure in a classical thermodynamic sense. In fact, as pointed out by Teorell, the excitation phenomena similar to those observed in living membranes are reproduced by a sintered glass filter under appropriate external and boundary conditions. In this case, the characteristic behavior of stimulus-response relation is interpreted in terms of dissipative structure or a transition between multiple steady states. Therefore, a transition of states in a more wide sense may be necessary to account for the process of excitation in living membrane.

It has been proved experimentally that the structure of the membrane is not uniform along the axon surface, and many active patches are coexisting with the
resting parts. The depolarized (excited) and repolarized (resting) portions in the membrane have been found to be fluctuating with time. When the exciting patch coexists with the resting patch on the membrane, the local membrane potential will vary from one position to another along the membrane surface. A depolarized patch has a smaller negative membrane potential than that of a resting state has. This non-uniform distribution of the membrane emf along the membrane surface creates local electric currents even if there is no net electric current across the membrane. The local currents are inwardly directed in excited patches, and outwardly directed in resting patches. The inward current through the excited patch of the membrane tends to induce repolarization, while the outward current through the resting portion tends to bring about depolarization of the portion. As a consequence of this long range interaction between resting and excited portions of the membrane, an excitable axon which is as a whole in its resting state, is considered to possess active (excited) spots which appear and disappear spontaneously and randomly. The dissipative interaction due to the local eddy current may induce the cooperative change of membrane state. The dynamical feature associated with the local electric current mentioned above should be properly taken into consideration for proceeding a theoretical analysis of excitation of an axon membrane. In this respect, the thermostatistical treatment based on a phase transition of membrane explored by Changeux et al.\textsuperscript{5} and by Hill\textsuperscript{6} must be an insufficient theory. Furthermore, a theoretical approach proposed by Blumental et al.\textsuperscript{7} did not include the long range interaction of the local electric current described above. Hence their theory must be improved too.

In the present article, we describe a theoretical approach on the process of excitation by taking account of the long range dissipative interaction of local eddy current. Results obtained are favorably compared to the experimental data carried out with squid giant axons perfused internally.

§ 2. Transition in an open system and dissipative ensemble theory of excitable membrane

Since the membrane system under consideration is not in equilibrium, and is dissipating energy by the ion diffusion and by the local electric current, the transition observed in the nerve system cannot be described in terms of the principle of minimum free energy as in the classical thermodynamics. On the other hand, the steady state near equilibrium characterized by the least dissipation principle is obtained by the Onsager-Machlup method based on a linear Langevin equation.\textsuperscript{8} Since the force-flux relation in the excitable membrane system is not linear, the Onsager-Machlup method is not applicable to the present system as it stands. Therefore, we have to recourse to the other approach. Here, we apply an ensemble concept together with a variational principle to the membrane system by taking both the energy dissipation due to local electric current and
the statistical character of active patches into consideration.

We assume a statistical ensemble for the non-equilibrium system and define a state of the system, $\xi$, which dissipates the energy $Q_\xi$. Furthermore, we assume that the state having the same energy dissipation appears with the same probability. For the sake of convenience, the system which obeys the principle of equal a priori probability is referred to as the "ideal dissipative system" in this article. This may be valid when the interaction between two dissipative processes is not very strong. We denote the probability of the non-equilibrium system in the $\xi$-state as $\text{Prob}(Q_\xi)$. Since the energy dissipation is an additive quantity, the distribution function is given by the following equation:

$$\text{Prob}(Q_\xi) = \text{const} \exp(-\gamma Q_\xi), \quad (1)$$

where const is the normalization factor. In Eq. (1), $\gamma$ is a positive constant, and $Q_\xi$ is the dissipation of energy in the $\xi$-th state. In the linear region of dissipative processes, the ensemble given by Eq. (1) is related to the Gibbs ensemble as follows: If the energy dissipation stems from the total energy (a phase function) of a system which is contiguous with a heat bath of a given temperature $T$, i.e., $Q = -dE/dt = (E - \langle E \rangle)/\tau$, the probability is represented by

$$\text{Prob}(Q) \propto \exp(-\gamma Q) \propto \exp(-\gamma / \tau \cdot E),$$

where $\langle E \rangle$ is the mean value of energy of the system at equilibrium. Furthermore, Eq. (1) is compared to the Einstein relation between the probability of fluctuation and entropy, $S$, represented by

$$Q = T(dS/dt) = -T(S - S_0)/\tau$$

and

$$\text{Prob}(Q) \propto \exp(-\gamma Q) \propto \exp(-\gamma / \tau \cdot (S_0 - S)).$$

In the above equations, $\tau$ stands for the relaxation time of the dissipative process involved. The positive constant $\gamma$ appeared in Eq. (1) is the product of $\beta (=1/kT)$ and the relaxation time of the process in question. Therefore, the ensemble for the energy dissipation given by Eq. (1) is a plausible representation in a linear dissipative system. In the case where non-linear processes are involved in the system under consideration there is no evidence that Eq. (1) is valid. Thus we may consider that the distribution function for dissipative process given by Eq. (1) is a working hypothesis for the subsequent argument.

Considering the dynamical features of excitable membrane mentioned above, we take a theoretical model as illustrated in Fig. 1, where the shaded parts represent excited patches, and the other parts show resting regions. The membrane potential at the excited patch is different from that in the resting patches, i.e., the electric potential in the inside of the axon is about $-50 \text{mV}$ in comparison with the external solution in the resting state, while the inside becomes about $+50 \text{mV}$ high with the external medium in the excited state. The
total energy dissipation \( Q \) of the system is given as follows:

\[
Q = \sum_{i=1}^{N} [\sigma_i g_a (V - E_a)^2 + (1 - \sigma_i) g_r (V - E_r)^2] \Delta A + 1/2 \sum_{i,j=1}^{N} \sigma_i \sigma_j (E_a - E_r)^2,
\]

where \( \sigma_i \) is the state variable of the \( i \)-th site. In the derivation of Eq. (2), we neglected the energy dissipation caused by ion diffusion in the membrane, because we are mainly interested in the additional effect of the local eddy current of the process of excitation, and because to avoid the complexity of mathematical expressions. The essential part of the subsequent arguments, however, is not altered by this simplification. Without loss of generality, we may assign the values of \( \sigma_i \) as follows:

\[
\sigma_i = \begin{cases} 
1 & \text{for excited state}, \\
0 & \text{for resting state}, 
\end{cases}
\]

where suffix \( i \) indicates the \( i \)-th active patch. In Eq. (2) \( g_a \) and \( g_r \) are the conductances of the excited and the resting states of a site in mho/cm\(^2\), \( E_a \) and \( E_r \) are the emf in a region of the excited and the resting states in Volt, \( g_{ij} \) represents the conductance between \( i \) and \( j \) sites, and \( \Delta A \) and \( N \) are the area of a site and the total number of sites on the membrane surface, respectively. Note that the dissipation of energy represented by Eq. (2) is composed of two parts; one is the dissipation in the membrane, and the other is the dissipation in the bulk solutions of inner and outer solution phases. These two contributions are shown schematically in Fig. 1(b). Under the condition of voltage clump, we may put \( V_i = V = \) constant, i.e., the voltage applied externally.

It is not unreasonable to approximate the membrane system under consideration by an ideal dissipative system unless the system is at or near the critical point of transition, because the energy dissipation produced by eddy current between two different patches is very small in comparison with total dissipation of energy in the membrane, and because the behavior of a patch is assumed to be random. If we take only the nearest neighbour interaction as a first approximation, and the Weiss approximation is applied to the intersites interaction, the energy dissipation of a site \( Q_i \) is represented by

\[
Q_i = Q/N = [\sigma_i g_a (V - E_a)^2 + (1 - \sigma_i) g_r (V - E_r)^2] \Delta A + 1/2nG(\sigma_i - \langle \sigma \rangle)^2(E_a - E_r)^2,
\]

Fig. 1. Schematic diagrams of active patches and eddy current in the membrane system. (a) The hatched meshes represent the excited domains and the blank meshes show the resting domains. (b) shows directions of local eddy current near an excited domain.
Fig. 2. Diagram for the graphical solution of the steady states. (a) The solid lines show the $\langle \sigma \rangle$ vs. $V$ relations given by Eqs. (5) and (6), and the dotted line represents the relation $I=0$ in Eq. (7). The lines denoted by $a$, $b$, $c$ and $d$ show the case where the values of $\gamma (\times 10^{-18})$ are taken as $2.5 \times 10^{-1}$, $1.25 \times 10^{-1}$, 0.5 and 3.0, respectively. Other parameters used are as follows:

$g_a=10^{-4}$ (mho/cm$^2$), $g_r=5 \times 10^{-4}$ (mho/cm$^2$),
$E_a=70$ (mV), $E_r=-50$ (mV), $nG=2 \times 10^{-9}$ (mho), $\Delta A=10^{-6}$ (cm$^2$).

(b) N-shaped $I$-$V$ relation in the case where $\gamma =1.0 \times 10^{14}$. The system is the same as in Fig. 2(a).

where $n$ is the number of the nearest neighboring sites, and $G$ is the intersites conductance. On the basis of Eq. (4)', we can evaluate the averaged fraction of the excited region $\langle \sigma \rangle$ as a function of $V$. The result is given by the following equation:

$$\langle \sigma \rangle = e^{-\gamma t}/(1 + e^{-\gamma t})$$  \hspace{1cm} (5)

and

$$\Theta = \Delta A [g_a(V-E_a)^2-g_r(V-E_r)^2] + 1/2 \cdot nG(1-2\langle \sigma \rangle)(E_a-E_r)^2.$$  \hspace{1cm} (6)

The mean fraction of the active sites as a function of clamped voltage $V$ in various value of $\gamma$ is shown in Fig. 2(a). When the conductance of the external solution $G$, which is sum of the conductances of the inner and outer solutions, is large enough in comparison with that of $g_a$ and $g_r$, and $\gamma$ is larger than a certain critical value, $\gamma_c$, three values of $\langle \sigma \rangle$ exist for a fixed $V$. As seen in Fig. 2(a), the relation between $\langle \sigma \rangle$ and $V$ is similar to that between the magnetization and the magnetic field in the ferromagnetic spin system. Using Eqs. (5) and (6), together with the continuity equation of electric current $I$ per unit area given by

$$\langle 1/2 \frac{\partial Q}{\partial V} \rangle/(\Delta AN) = I=g_a\langle \sigma \rangle(V-E_a) + g_r(1-\langle \sigma \rangle)(V-E_r),$$  \hspace{1cm} (7)
we obtain the steady state relation between current $I$ and the clamped voltage $V$. By way of an example, Fig. 2(b) shows the calculated $I$-$V$ relationship under the external conditions given in the figure caption. The $I$-$V$ relation thus obtained is well in accord with experimental data obtained with squid giant axons.\(^1\)

Before proceeding further discussion, it may be worthwhile to note the significance of a variational principle for the ensemble theory of an open system described above. We introduce the concept of the generalized free energy dissipation $F^*$ in an open system as follows:

$$F^* = -\frac{1}{\tau} \ln Z$$

$$= -\frac{\partial \ln Z}{\partial \tau} + \frac{1}{\tau} \sum_i [\text{Prob}(Q_i)] \ln [\text{Prob}(Q_i)]. \quad (8)$$

Here $Z$ is the partition function defined by $Z = \sum_i \text{Prob}(Q_i)$. The first term of the r.h.s. of Eq. (8) corresponds to the mean value of the total energy dissipation $Q^*$ and the last term is the entropy $S^*$ of the dissipative open system. If we take the molecular field approximation together with Eq. (1), the entropy can be taken as the entropy of mixing of an ideal dissipative system,

$$S^* = -\langle \ln [\text{Prob}(Q)] \rangle = -N[\langle \sigma \rangle \ln \langle \sigma \rangle + (1 - \langle \sigma \rangle) \ln (1 - \langle \sigma \rangle)] \quad (9)$$

and the mean value of the total energy dissipation $Q^*$ is given by

$$Q^* = -\frac{\partial \ln Z}{\partial \tau}$$

$$= N\{g_a \langle \sigma \rangle (V - E_a) + g_r (1 - \langle \sigma \rangle) (V - E_r) \}$$

$$\times \Delta A + \frac{1}{2} n G (\langle \sigma \rangle - \langle \sigma' \rangle) (E_a - E_r) \}, \quad (10)$$

where we have used the condition $\sigma^4 = \sigma_1$ (see Eq. (3)). Therefore, the variational principle given by

$$F^* = Q^* - \frac{1}{\tau} S^* = \text{min} \quad (11)$$

leads to the relation between $\langle \sigma \rangle$ and $V$ again. In other words, Eqs. (5) and (6) are obtained by using the relation $\langle \partial F^*/\partial \langle \sigma \rangle \rangle = 0$. Equation (11) is an extension of the least dissipation principle against the open system including the statistical processes. If we take $\tau \to \infty$, the above expression agrees with the principle of the least dissipation in deterministic sense.

### § 3. Dynamical aspects of excitation

In the preceding section, we explored the stationary state theory of excitation, in which we explained the $N$-shaped relationship of $I$ vs $V$ in terms of cooperativity in an open system by taking the energy dissipation into accounts. In
this section, the dynamical aspects of the process of excitation are explained as a consequence of the model and assumptions used above. The process of excitation observed in living membrane such as fluctuations of potential and flip-back catastrophe are essentially cooperative non-local and non-markoffian processes. As introduced in the preceding section, we use the state variable \( \langle \sigma \rangle \) and the transmembrane potential \( V \). The total electric current \( I \) across the unit area of the membrane is represented by the equation for a given value of \( \langle \sigma \rangle \).

\[
I = C \frac{\partial V}{\partial t} + \langle \sigma \rangle g_a (V - E_a) + (1 - \langle \sigma \rangle) g_r (V - E_r) - G^* \left( \frac{\partial^2 V}{\partial x_1^2} + \frac{\partial^2 V}{\partial x_2^2} \right),
\]

where \( C \) and \( G^* \) are the electric capacitance per unit area of the membrane and the electric conductance of solution phases, respectively, \( x_1 \) and \( x_2 \) refer to the coordinate along the membrane surface. Equation (12) is the continuity equation of current and can be used in place of Eq. (7). The last term in Eq. (12) describes the effect of the spatial non-uniformity, where the electrical interaction in the \( x_1 \)-direction is assumed to be not coupled with that of the \( x_2 \)-direction.

If we consider the energy dissipation caused by eddy current in the membrane and in the solution phases, \( Q \) is represented by

\[
Q = \int \left[ \langle \sigma \rangle g_a (V - E_a) + (1 - \langle \sigma \rangle) g_r (V - E_r) + G^* \left( \frac{\partial^2 V}{\partial x_1^2} + \frac{\partial^2 V}{\partial x_2^2} \right) \right] dA.
\]

(13)

When the system is in the steady state under the condition of \( I = 0 \), Eq. (12) can be derived from the Euler-Lagrange equation with respect to \( V \), i.e., by the following equation:

\[
\sum_{i=1}^{2} \frac{\partial}{\partial x_i} \left( \frac{\partial Q}{\partial V_{x_i}} \right) - \frac{\partial Q}{\partial V} = 0.
\]

(14)

The time course of variation of the excited fraction \( \langle \sigma \rangle \) is proportional to the strength of the eddy current. The current strength is represented by a product of \( \langle \sigma \rangle \) and \( (1 - \langle \sigma \rangle) \), and the difference in potential. Note that the eddy current is controlled by the threshold potential \( V_\tau \) obtained in the previous section. Thus we obtain the following equation:

\[
\frac{\partial \langle \sigma \rangle}{\partial t} = a (V - V_\tau) \langle \sigma \rangle (1 - \langle \sigma \rangle) - b \langle \sigma \rangle \Gamma (t),
\]

(15)

where \( \Gamma (t) \) stands for the relaxation process of the excited spot, which may stem from the ion accumulation at the membrane surface. The relaxation process \( \Gamma (t) \) due to ion accumulation at the membrane surface can be represented by the following equation:

\[
\Gamma (t) = \int_{-\infty}^{t} (V - E_r) \varphi (t - t') dt',
\]

(16)
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where \( \phi(t) \) may be given by \( \exp(-t/\tau) \) as a first approximation, and \( \tau \) stands for the relaxation time of ion accumulation. Equation (12) together with Eq. (15) give a set of differential equations basic to the process of excitation of nervous activity. The solution to Eqs. (12) and (15) gives the time course of the action potential. Figure 3 shows an example of the graphical solutions of quasi-steady state, which obtained from Eqs. (12) and (15) equating to zero. Here the last term in Eq. (12) was neglected because we limited our discussion to a non-propagating phenomenon in this article. Strictly speaking, a term related to the long range interaction caused by non-uniformity of the membrane must be added to the right-hand side of Eq. (15). This additional term is, however, also dropped out by the same reason described above. Once the membrane is transformed to the excited state, \( \Gamma(t) \) increases with time. As seen in Fig. 3, during the time between \( t_s \) and \( t_n \), the threshold potential increases with time, and the potential in the excited state decreases monotonically. At \( t=t_n \), these two states (excited and the threshold states) degenerate each other, and the membrane potential flips back to the original resting state catastrophically. In the region of \( t>t_n \) the excited state of the membrane disappears, and the membrane potential decreases toward the resting state immediately. At \( t=t_s \), \( \Gamma(t) \) takes a maximum value. For \( t>t_n \), \( \Gamma(t) \) decreases, and further increase of time \( t \geq t_s \), both the exciting and the threshold states appear simultaneously again. During the time between \( t_s \) and \( t_n \) there is no exciting branch for the system. Experimentally, this is observed as the refractory period, in which no excitation of the system can be elicited by any strength of the external stimulus. The relationship between \( \langle \phi \rangle \) and \( V \) given in Fig. 3 is in accord with that obtained from the ensemble theory (see Fig. 2), and with experiments obtained with squid

![Fig. 3. V vs. \( \langle \phi \rangle \) relation at various fixed times, \( t \). The line \( h \) shows the continuity relation of electric current at the steady state with \( I=0 \). The lines \( l_i \)'s show the relations calculated from Eq. (15) at \( t=t_i \) \( (i=0, 1, 2, 3, 4, 5 \text{ and } t_m) \). The intersections of \( h \) and \( l_i \)'s give the quasi-steady state of the membrane system. The resting state is at \( \langle \phi \rangle =0 \) and \( V=E_r \) invariantly. The lower intersection of two curves \( h \) and \( l_i \) represents a threshold level and the upper one shows the excited level.

![Fig. 4. Abolition threshold potential in various stages at the plateau of an action potential obtained experimentally with a squid giant axon perfused with 30 mM CsF internally, and 100 mM CaCl\(_2\) externally.](http://ptp.oxfordjournals.org/)

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giant axons perfused internally. By way of an example, Fig. 4 illustrates the time course of the abolition threshold potential obtained with an axon perfused internally with 30 mM CsF and externally with 100 mM CaCl₂.

4. Comparison with experiments

Fig. 5. Time-course of action potential and abolition threshold potential with various values of \( \tau \) with \( a=10^6 \), and \( b=6\times10^6 \). (a) Time-course of \( V \) in the case where \( \tau=0.8\times10^{-2} \) (sec). (b) Time-course of \( V \) in the case where \( \tau=10^{-4} \) (sec). Note that the abolition potential level \( V_0^* \) and the quasi-steady excited level \( E_a^* \) degenerate at \( t=A \), and that \( E_a^* \) and \( V_0^* \) appear again at \( t=B \) and these bifurcate for \( t>B \). (c) Time-course of \( V \) in the case where \( \tau \) is taken as \( 0.975\times10^{-4} \) (sec). The revived exciting level \( E_a^* \) and the threshold level \( V_0^* \) form closed loops.
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The basic equations (12), (15) and (16) can be solved numerically by the use of the Runge-Kutta-Gill method under a given set of initial and boundary conditions. The solutions are well compared to the experimental data. In the case where an action potential is produced, the total electric current is taken as zero. The characteristic constant of the membrane system were taken as follows:

\[ E_r = -50 \text{ mV}, \quad E_a = 70 \text{ mV}, \quad V_c = -30 \text{ mV}, \]

\[ g_a = 10^{-3} \text{ mho/cm}^2, \quad g_c = 10^{-4} \text{ mho/cm}^2, \quad \text{and} \quad C = 10^{-6} \text{ F/cm}^2. \]

Other coefficients \( a, b, \) and \( \tau \) in the basic equations are adjustable parameters. The duration of an action potential depends on the magnitudes of \( b \) and \( \tau \). If either \( b \) or \( \tau \) is small, the excited state is sustained indefinitely and a catastrophic flip-back at the end of an action potential does not occur (see Fig. 5(a)). When \( \tau \) increases with fixed values of \( a \) and \( b \), the time-course of \( V \) becomes as shown in Fig. 5(b). If \( \tau \) is close to the critical value, an oscillatory feature occurs during the plateau of an action potential (cf., Fig. 5(c)). The oscillation appears just before the flip-back transition, and which is in line with that observed in a prolonged action potential. If we select an appropriate set of parameters, we can reproduce all features of the prolonged action potential observed with internally perfused squid giant axons.

§ 5. Discussion

As shown in the present article, the process of excitation can be reproduced by assuming the non-uniform distribution of active patches coupled with eddy current across the membrane. The interpatch interaction due to the eddy current acts as a long range interaction, and induces a cooperative change of membrane state in the nervous system. It is important to note that the cooperative change in nerve membrane is not equal to the thermodynamic transition in an equilibrium system. In fact, the transition between multiple steady states can occur even when \( \langle \sigma \rangle \) given by Eqs. (5) and (6) increases in a single valued sigmoid shape manner with \( V \) as seen in Fig. 2, which is compared with a spin system where the magnetization, \( M \), must give a multivalued function at the transition point when \( M \) is plotted against the external field. In the problem of excitation, the non-markoffian process plays an indispensable role. We consider that the non-markoffian process in present problem mainly stems from the irreversible accumulation of ions at the membrane surface. The other relaxation process, e.g., relaxation of conformational change of membrane structure, may also play a role in the process of excitation. This will be discussed later.

We would not argue that the mechanism discussed above is the sole cause of the excitation of a living membrane system. It must be one of many others which may account equally well for experimental facts. However, it is our belief that the dissipation of energy due to local eddy current must play an unmistakable
role in various processes in an excitable membrane system. Supports to this belief will be presented in our forthcoming article dealing with propagation of the action potential along the membrane surface.

Even if we confine ourselves to our framework of theory for the process of excitation, the theory developed above may be criticized in many respects. The ensemble theory is, as already noted, merely a working hypothesis in the non-equilibrium system, especially when the system involves non-linear transport processes. The approximation of "ideal dissipative system" for the membrane in problem is far from being realistic to a complex excitable living membrane and may be over simplification of our present problem. This kind of approximation is, however, rather unavoidable for a quantitative theory to be developed. One should not overlook, however, that it enables us to carry through an analytical treatment of the problem. Without recourse to this approximation, we would not have been led to the recognition that the energy dissipation caused by eddy current is responsible for a cooperative transition between multiple steady states.

Considering all these factors among many others, it is not surprising that the theoretically obtained curves of time courses of an action potential and conductance are not consistent with observed results in some points. For example, the theory predicts that the membrane conductance increases with time more rapidly than the membrane potential when an action potential is elicited. This prediction is not obeyed by the data of perfused squid giant axons. The disagreement between theory and experiment, however, easily be dissolved if the conformational change of the membrane structure is assumed to follow the ion accumulation at the membrane surface with a time lapse.

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