ON THE KINETICS OF POTENTIAL, ELECTROMOTANCE, AND CHEMICAL CHANGE IN THE EXCITABLE SYSTEM OF NERVE*

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ABSTRACT

The kinetics of interaction between potential, chemical equilibrium, and electromotance in the excitable system of nerve are analyzed. The theoretical system has the following properties:

It gives rise to two electromotances each of which depends directly on a chemical equilibrium. The equilibria are determined by the potential across the system.

After a sudden potential shift the equilibria reach their new value with an exponential time course, the time constant of which is determined by the rate constants of the two reactions. The rate constants are different due to different activation energies.

The two electromotances give rise to potentials of opposite sign. The total potential produced by the system is equal to the sum of the two potentials. The two equilibria are thus determined by any externally applied potential as well as by the sum of the internally produced potentials. The dependence of the equilibria on the potential is calculated from first principles.

The equations which describe this system are solved by an analogue computer, which gives instantaneous solutions of the total internal potential as a function of time and any voltage applied from an external source. Comparison between recorded and computed action potentials shows excellent agreement under all experimental conditions.

The electromotances might originate from a Ca++–Na+–K+ exchange at fixed negative sites in the Schwann cell.

INTRODUCTION

The object of this paper is to analyze the events taking place during the action potential in nerve from the viewpoint of the general theory of reaction rates. The analysis has to take into account the special properties of the system and rests in part on experimental results and conclusions presented in two pre-

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ceeding papers (Mueller, 1958 a and b). Since the analysis is restricted to the kinetics, no specific assumptions about the molecular nature of the system are necessary.

The kinetics of normal chemical changes involve only thermal energy and concentration changes of the reactants. In the excitable system of nerve there are in addition changes of potential and electromotance, which result from and interact with the chemical changes.

It should be emphasized that potential and electromotance are not identical phenomena. An electromotance is the result of electrokinetic forces acting on charged particles, tending to separate positive and negative charges and by virtue of this separation creating a potential. Under conditions of no current flow, the potential opposes and exactly balances the electromotance and is under this equilibrium condition a direct measure of the electromotance. The electrokinetic forces can be of very different nature; i.e., magnetic or gravitational forces, diffusion and/or chemical interaction, steric hindrance, etc. (for a detailed discussion, see Langmuir, 1916, and Fowler, 1953). In solutions electromotance usually results from thermal agitation forces together with chemical interaction (covalent or electrovalent bonding, dispersion or induction, etc.), acting on and separating positive and negative ions. The exact nature of the electromotance in nerve is unknown and it cannot be determined from kinetic arguments. On the other hand it is not essential for a kinetic treatment which deals only with changes of quantities in time.

THEORY

Interaction between Electromotance, Potential, and Chemical Equilibrium

The three variables which are to be related are chemical interaction, electromotance, and potential, at constant temperature and pressure. If electromotance and potential are constant there will exist a certain chemical equilibrium in the molecular system which gives rise to the electromotance. In any chemical system deviation from equilibrium can be induced by varying the energy content of the system; e.g., by variation of temperature. In our case the energy content can also be changed by changing the potential (electrical stimulation). Such a potential change causes the deviation from equilibrium which can be registered as action potential.

It can be shown that in fact the potential difference across the system applied from the external source (stimulator) and not the current (transport of charges) initiates the action potential. After the make of a rectangular current, the potential often rises very slowly. The time constant of this rise can be prolonged (e.g. by tetraethylammonium or by CO₂) and values of more than 50 msec are frequently seen. For a current just above threshold the action potential always appears near the maximum of the potential. As a result the latency
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is very long. If the slow rise of the potential is to be explained by a high membrane “capacity,” by polarization phenomena, or by a slowly rising “resistance,” the current would have its maximum immediately after the make, and would then decline at the same rate at which the potential increases. If the action potential were initiated by the current, it should appear at a time when this flow is greatest; that is, immediately after the current is made. This is never observed.

If the node is depolarized by a chemical agent (e.g. KCl or removal of Ca ions), positive charges flow inward through the membrane. The changes of excitability, action potential, duration, and amplitude, however, are the same as if the node were depolarized by an outward current from an external source. Thus with opposite direction of current, but with equal changes of potential, the system behaves according to the potential. The same is true for hyperpolarization by CO₂ and anodal current. Again the current is opposite in both cases while potential change and behavior are equal.

It is now a peculiarity of the excitable system that the chemical change induced by the potential results in a change of the electromotance which then in turn changes the potential.

The interaction between potential, chemical equilibrium, and electromotance can be represented by the following scheme:

U,
Externally applied potential
U₁
Potential generated by the system

Total potential → chemical equilibrium → electromotance

The chemical equilibrium is determined by the total potential which is the sum of any applied potential (e.g. from a stimulator) and the potential generated by the system itself. The quantitative relations are given by the corresponding factors. Since our interest is focussed on the changes rather than the absolute values of U, Q, and E,

\[ \alpha = \frac{dQ}{dU}; \quad \beta = \frac{dE}{dQ}; \quad \gamma = \frac{dU}{dE} \]  

(1)

The value of the electromotance depends upon the value of the potential and since the electromotance in turn produces a potential, a feedback exists between electromotance and potential in which each change of the potential causes a change of the electromotance which again changes the potential.

There is no reason to assume that the potential due to the electromotance of the system has an effect on the chemical equilibrium different from that of the potential established from an external source. In fact if the electromotance is changed by chemical agents causing depolarization or hyperpolariza-
tion, the reaction of the system is the same as if the potential were changed by an external current. For example depolarization by KCl causes the same decrease of the action potential as depolarization by an outward current. Furthermore, the feedback between electromotance and potential is positive because a displacement of the potential to the negative side in turn causes a depolarization (action potential). The total kinetics of the system as function of an external potential change thus depend largely on the way in which the electromotance varies as function of the potential. This coupling between potential and electromotance goes via the chemical equilibrium and thus involves the two factors α and β. The coupling factor γ between electromotance and potential depends only on the resistance of the external circuit; i.e., the pathway of the inside of the nodal membrane through myelin and neighboring nodes to the outside. γ is thus smaller than unity and due to the capacity of those elements not constant in time. For the analysis this is of little importance and for reasons of simplicity γ is set equal to 1.

It can now be shown from simple thermodynamical arguments which are given in the Appendix (C) that the potential changes as they are observed during the action potential in nerve, namely ca. 120 mv. are sufficient to change an equilibrium of a second order reaction almost completely from one side to the other, the equilibrium constant varying over 3 to 4 orders of magnitude. Furthermore this shift of the equilibrium occurs along an S-shaped curve, such as that shown in Fig. 1. The position of this curve with respect to the potential depends on the initial free energy difference of the reaction and on the concentration of the reactants and products while the maximum slope depends on how much of the energy of the potential field is utilized by the reacting molecules. α is thus a function of the potential and as a consequence...
of the S shape of the equilibrium shift, this function can be represented in first approximation by a Gauss curve. However, the relation between potential and electromotance is also modified by the factor $\beta$. For the sake of simplification we assume that the electromotance is directly proportional to the chemical equilibrium. The maximal electromotance given by the system produces a potential of ca. 125 mV. If we assume that at this maximum the equilibrium is way over on one side ($Q$ approaches 0.5) we can assign to $\beta$ a value of 250.

The relation between potential, chemical changes, and electromotance expressed in equations (1) would only permit a description of the system in the steady state and only in the event that there was no feedback between the internally produced potential ($u_i$) and the chemical equilibrium. Since we are interested in the kinetics of the system, the rate at which changes of potential, molecular interaction, and electromotance take place must be considered. Actually each of the three variables $Q$, $E$, and $U$ is time-dependent. After a change of $Q$, $E$ will reach its corresponding value almost immediately, the delay being determined only by the relaxation time of the ions and thus of the order of $10^{-10}$ sec. Potential and electromotance will be out of phase because of the distributed capacities of myelin and axoplasm. This time lag is constant and can be neglected for the purpose of the analysis. We must therefore focus on the rate with which the system reaches its new equilibrium after a change of the potential. Suppose that there is no feedback between electromotance and potential, then, after an abrupt stepwise displacement of the potential the molecular system will reach its new equilibrium with a certain time course, which is determined by the reaction rate. For a bimolecular reaction of the type $A \cdot B \rightleftharpoons AB$ this time course is determined by the rate constants $k_1$ and $k_2$ of the forward and backward reaction. The reaction rate depends to a large extent on the energy of activation according to

$$k = P \exp \left( \frac{E}{RT} \right)$$

(2)

in which $P$ is a probability factor and $E$ the energy of activation (see e.g. Laidler 1950; Hinshelwood, 1940). The general time course of the reaction after a potential step is calculated in the Appendix (D), assuming that the potential step changes $k_1$ and $k_2$. For computing purposes the time course can be approximated by an equation of the form

$$Q = Q_0 + \Delta Q \left( 1 - e^{-t/\tau} \right)$$

(3)

in which

$$\Delta Q = \int_{U_0}^{U_1} \alpha \, dU$$

for a potential step from $U_0$ to $U_1$. 

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A system as it has been described so far has only two stable states; the equilibrium would always be at one of the two extreme sides and the electromotive force at its maximum or at its minimum. For any external potential displacement in the direction of the opposite state the system would go into this state, the velocity of the transition depending on the magnitude of $\tau$ and $\alpha$. Obviously the excitable system at the node of Ranvier does not behave in this way.

In a preceding paper (Mueller 1958 b) the conclusion was reached that not only one but two electromotances of opposite signs ($E$ and $S$) undergo changes during the action potential. It was furthermore concluded that both electromotive forces increase for a potential displacement towards the negative side, while they decrease for a displacement to the positive side. For a given potential change they both reach their new value with different rates, the positive electromotive force having the smaller rate. The different rate constants for $E$ and $S$ follow also directly from the different activation energies (see Equation 2) which in first approximation can be estimated from the temperature dependence of rise phase and duration of the action potential. An Arrhenius plot for these quantities gives activation energies of 4 and 10 kcal. for $E$ and $S$ respectively. Let $E$ be the negative, $S$ the positive electromotive force. Under conditions where current could flow, $E$ would cause an inward current, $S$ an outward current of positive charges, through the nodal membrane. The assumptions made above for the relation between potential, chemical equilibrium, and electromotive force will apply equally and separately to $E$ and $S$. Thus

$$\alpha_E = \frac{dQ_E}{dU}, \alpha_S = \frac{dQ_S}{dU} \tag{4,5}$$

Let the potentials produced by the electromotive forces $E$ and $S$ be $U_E$ and $U_S$ respectively; since it was assumed that $\gamma = 1$ (see above), $E = U_E$ and $S = U_S$. Since $E$ and $S$ produce potentials of opposite sign, the total potential difference across the system will be proportional to the sum of the individual potentials. The potential produced by the entire excitable system:

$$U_i = (U_E + U_S) = (E + S) \tag{6}$$

Any change of either electromotive force will induce a change of the other because the feedback goes via the potential which in turn is equal to the difference of both electromotances.

If the system is now considered under the hypothetical condition that there is no internal feedback between electromotive force and potential, the steady state values of both electromotances and chemical equilibria can be plotted as function of the potential across the system ($U$). This is done in Fig. 1, which shows a plot of $E$ and $S$ as function of the external potential $U$ under the assumption that $S$ and $E$ are directly proportional to the chemical equilibrium ($\beta = 250$).
The derivation of the curve is given in the Appendix (C). The opposite signs of $E$ and $S$ are not taken into account. The least complicated situation is assumed, thus $E$ and $S$ reach the same maximal value. $E$ and $S$ both can go to zero but cannot become negative. $E_f(U)$ and $S_f(U)$ are symmetrical. These simplifications are convenient for the analysis but not necessary for the functioning of the system. The $S_f(U)$ curve is displaced to the positive side with respect to $E_f(U)$. There are experimental observations which could be readily explained on the basis of a small displacement. One is the fact that at rest the system always stays at the positive side i.e. produces a positive resting

**Fig. 2.** Schematic diagram of relations between chemical equilibria, electromotances, and potentials (see text).

electromotance which does not belong to the excitable system. Differentiation of $E_f(U)$ and $S_f(U)$ with respect to $U$ gives a maximum of 3.6 for $\frac{dE}{dU}$ and $\frac{dS}{dU}$.

The essential properties of the theoretical system can now be summarized (see Fig. 2).

1. The system gives rise to two electromotances ($E$ and $S$) each of which depends on a chemical equilibrium $Q_E$ and $Q_S$.

2. The values of $Q_E$ and $Q_S$ are determined by the potential ($U$) across the system.

3. If the potential is changed, $E$ and $S$ reach their new value with an exponential time course. The time constants $\tau_E$ and $\tau_S$ are different and depend mostly on the activation energies of the two reactions, $\tau_E < \tau_S$.

4. By varying the potential ($U$) across the system the chemical equilibria can be shifted from one side to the other along an S-shaped curve. As a result $\frac{dE}{dU}$ and $\frac{dS}{dU}$ as function of $U$ have the form of Gaussian distribution. The maxima of $\frac{dE}{dU}$ and $\frac{dS}{dU}$ may differ at $U = 0$ by positive or negative amounts de-
pending on the free energy of the reactants and the concentration of reacting molecules.

5. The potentials resulting from $E$ and $S$ have opposite signs; with $E$ giving rise to a negative, $S$ to a positive potential. The internally produced potential across the system, $U_i$, is equal to the sum of potentials produced by $E$ and $S$ ($U_E$ and $U_S$). The total potential across the system $U = U_i + U_e$ plus any externally applied potential, $(U_e)$. The values of $U_E$ and $U_S$ are determined by $U_i$ and $(U_E + U_S)$ multiplied by $\frac{dE}{dU}$ and $\frac{dS}{dU}$ respectively.

COMPUTATIONS

In order to obtain quantitative information about the behavior of this system solutions of $(U_E + U_S)$, $f (U, i)$ must be obtained for different values of the constants in Equation 27 and different forms of the externally applied potential. On paper the treatment of the mathematical equations involved is difficult; however, feedback problems can be comparatively easily and accurately solved by means of analogue computers. Such a computer was assembled which

Fig. 3. Schematic diagram of the computer.
gave instantaneous solutions of \((E + S), f(U, t)\). The principle of the computer is shown in Fig. 3.

The functions \(Q_E, f(U)\) and \(Q_S, f(U)\) were realized by two function fitters (G. A. Philbrick model FFR.) whose output voltages were made to vary as function of the input in agreement with Equation 27 (see Fig. 4). The output voltages of the function fitter represent \(Q_E\) and \(Q_S\). They were multiplied by \(\beta_E\) and \(\beta_S\) by two amplifiers. The resulting voltages represent \(E\) and \(S\). \(\gamma\) was supposed to be 1, so that \(E = U_E\) and \(S = U_S\). \(U_E, U_S, U,\) and \(U_s\) were added and the sum, \(U\), was fed back into the function fitters via resistance capacitance networks, representing \(\tau_E\) and \(\tau_S\).

\[\begin{align*}
\text{Behavior of the System without Internal Feedback}
\end{align*}\]

The system will first be examined under the condition when there is no feedback between the internally produced potential and the electromotance, but when the electromotance still reacts to an external potential change. Under this condition Fig. 5 shows the theoretical behavior of \(U_E\) and \(U_S\) and the resulting potential \(U_i\) as function of an external steplike potential change.

If initially \(U_S\) is bigger than \(U_E\), \(U_i\) will be positive. At \(t_0\) the potential across the system is suddenly displaced to the negative side by a current from an
Fig. 5. Changes of $U_E$, $U_S$, and $U_i$, as function of a rectangular voltage step from an external source. The feedback between the internal potential ($U_i$) and the equilibria was supposed to be blocked.

Fig. 6 A, computer output as function of negative potential steps of increasing magnitude applied to the input. The records represent $U_g + U_b$. However, the feedback loop between $U$ and the input (the two $R\ C$ networks) (see Fig. 3) was interrupted. The stimulating potential step ($U_s$) was applied to the input.

B, computer output recorded under the same conditions as in Fig. 6 A. In record $a\beta = \beta_s$; in record $b\beta_s < \beta_s$. $U_s$ was equal in both records.
external source. Let this externally applied potential be $U_e$. The potential produced by the system ($U_i$) as function of the potential step $U_e$ and time is then

$$U_i = U_B + U_S = \Delta U_B (1-e^{-t/\tau_B}) + \Delta U_S (1-e^{-t/\tau_S}) + U_{i0}$$

in which

$$\Delta U_B = \beta \int_{V_{th}}^{V_e} \alpha_B dV$$

and

$$\Delta U_S = \beta \int_{V_{th}}^{V_e} \alpha_S dV$$

As can be seen from Fig. 5, $U_i$ shows an initial negative maximum while the steady-state value is more positive than $U_{i0}$. The height of the maximum will increase with the amplitude of the external potential change. However, since $\Delta U_B$ and $\Delta U_S$ change as function of the potential (Fig. 1), the maximum of $U_i$ will not increase indefinitely.

At the node of Ranvier it is difficult to prevent the internal feedback. However, Marmont (1949) and Hodgkin and Huxley (1952, a to d) described a method by which giant axons of squid can be studied under this condition. Under the assumption of a fixed membrane capacity, the time course of the potential produced by the electromotance can be estimated from the records of Hodgkin and Huxley (1952, a to d). Its general form and behavior agree with the theoretical time course of $U_i$ in Fig. 5. With increasing height of the potential step, the maximum of $U_i$ increases towards a maximal value.

Fig. 6 A shows the corresponding records from the computer. The feedback between ($U_n + U_S$) and $Q_r$ and $Q_S$ was interrupted. Only $U_e$ was fed into the two RC networks.

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**Fig. 7.** Computer output under conditions as in Fig. 6. Equal steps of $U_e$ were superimposed on different constant potentials. The white line indicates the output level for zero input.
The situation is actually equivalent to the "voltage clamp" of Hodgkin and Huxley (1952, a to d). In both cases the regenerative action of \( U_i \) is prevented. If \( \beta_g \) is made smaller than \( \beta_s \), the initial hump of \( U_i \) disappears and a curve results which resembles closely voltage clamp records in Na-free media (Fig. 6 B).

For a given potential step the maximal value of \( U_i \) also depends on the potential level from which the step started. If the step starts from a more positive value, \( U_{i_{\text{max}}} \) will be larger. For negative constant polarization it will be smaller (see Fig. 7). Calculations show that for a given potential step, \( U_{i_{\text{max}}} \) as func-

![Image](https://via.placeholder.com/150)

Fig. 8. Computed potential time course for the make of a rectangular voltage step of \( U_e \), just below and above threshold. Two traces were superimposed. The records represent the sum (\( U_e + U_s + U_i \)) (see Fig. 3).

The same behavior of \( U_{i_{\text{max}}} \) can be taken from the records of Hodgkin and Huxley (1952 c, Fig. 5). The S shape of \( U_{i_{\text{max}}} \) as function of \( U \) follows from the shape of the \( E_f (U) \) and \( S_f (U) \) curve (Fig. 1).

**Behavior of the System with Internal Feedback**

There now remains the question of how the system will behave under normal conditions; i.e., when the feedback between the internally produced potential and the chemical equilibrium is operating.

Fig. 8 illustrates the computed reaction of the system to a sudden stepwise displacement of the externally applied potential (\( U_e \)). The values of \( \tau_e \) and
\( \tau_s \) were chosen as they would be expected in the nerve under normal conditions.

\[
\tau_E = 0.05 \text{ m sec}^{-1}; \quad \tau_S = 1 \text{ m sec}^{-1}; \quad \beta_E = \beta_S
\]

If the stimulating current stays below a certain threshold value, the potential produced by the system reaches a new constant value. It stays constant as long as the stimulating current flows. Before the constant value is reached \( U_i \) shows a hump which is comparatively small here, and obviously corresponds to the subthreshold response in nerve. Within certain limits the size of the hump varies with the strength of the stimulating current. If the stimulus strength is further increased by a small amount, \( U_i \) shows a completely different behavior. Shortly after the make of the stimulating current, it reaches a short lasting maximum independent of a further increase of the stimulus, and shows a fast rise phase and a slower falling phase. The system gives a typical action potential.

The following considerations will give a picture of the behavior of \( Q_S \) and \( Q_S \) at rest and during the normal action potential.

**Resting Potential**

Initially (i.e. before the stimulating current was applied) \( U_i \) is not zero. The system always produced a certain resting potential, the sign of which depends on the horizontal displacement of \( E_f(U) \) and \( S_f(U) \) with respect to each other (Fig. 1). In the assumed case \( S > E \) for any value of \( U \). Thus in the steady state and for \( U_e = 0 \) the system always produces a positive potential. Suppose the systems were fixed at the negative side by an applied external potential \( (U_e) \). If this external potential is suddenly removed, the positive potential produced by the system will then cause \( Q_S \) to decrease at a faster rate than \( Q_S \), because \( \tau_S > \tau_E \). This in turn will increase the positivity and the system will go to the positive side until it reaches a point at which \( Q_S \) and \( Q_S \) are both small and any change of \( Q_S \) is counteracted by an equal change of \( Q_S \) (i.e. a point at which \( \frac{dQ_S}{dt} \). Now \( \frac{dQ_S}{dt} \) and \( \frac{dQ_S}{dt} \) are functions of \( \frac{dQ_S}{dt} \), \( \frac{dQ_S}{dt} \), \( \tau_E \) and \( \tau_S \) respectively.

Since with no feedback \( Q_S \) and \( Q_S \) will rise exponentially after a potential displacement

\[
Q_S = \frac{\Delta Q_S}{\Delta U} \Delta U (1 - e^{-t/\tau})
\]

and

\[
\frac{dQ_S}{dt} = \frac{\Delta Q_S}{\Delta U} \Delta U \frac{1}{\tau} e^{-t/\tau}
\]

Under feedback conditions only values of \( \frac{dQ_S}{dt} \) at short times are of interest.
Also \( \frac{dQ_s}{dU} \) must be considered instead of \( \frac{\Delta Q_s}{\Delta U} \). Therefore

\[
\frac{dQ_s}{dt} = \frac{dQ_s}{dU} \frac{1}{\tau_S} \quad \text{and} \quad \frac{dQ_s}{dU} \frac{1}{\tau_R}
\]

(12, 13)

The potential value of the equilibrium point will thus be determined by \( \frac{dQ_s}{dU} \) as well as by \( \tau_S \) and \( \tau_R \). If \( \tau_S \) and \( \tau_R \) were equal, this value would be the point at which \( \frac{dQ_s}{dU} = \frac{dQ_s}{dU} \). Since \( \tau_S > \tau_R \), the resting value of \( Q_S \) and \( Q_s \) will be displaced further to the negative side to a point at which

\[
\frac{dQ_s}{dU} \frac{1}{\tau_S} = \frac{dQ_s}{dU} \frac{1}{\tau_R}
\]

(14)

The resting potential itself equals \( U_S - U_R \) at the point of the equilibrium. The theoretical system is thus able to produce a stable positive resting potential.

Of course the system could also be brought to one side by an external potential. For the nerve that would mean that the resting electromotance would be independent and different from the electromotance of the action generator. A decision between both possibilities cannot be made. For the production of an action potential it is only necessary that the system be kept far enough on one side.

**Action Potential**

Suppose now that the potential across the system is suddenly displaced towards the negative side by a current from an external source. Since \( \tau_S \) is bigger than \( \tau_R \), \( Q_S \) will react faster to this potential displacement than \( Q_R \). Therefore the internal potential \( (U_i) \) will change in the negative direction. This in turn will have the same effect as the stimulating current and again make \( U_i \) more negative. Thus \( U_i \) will shift to the negative side at a faster and faster rate until \( Q_S \) approaches its maximum and \( \frac{dQ_S}{dU} \) approaches 0. At that time \( U_i \) has reached its negative maximum, producing the peak of the action potential.

Because of its larger time constant \( S \) could not follow the fast increase of \( Q_S \), but now, when \( Q_S \) cannot increase any further, the increase of \( Q_S \) has marked effect upon \( U_i \). Since \( Q_S \) gives rise to a positive electromotance, \( U_i \) will go in the positive direction. As a result \( Q_S \) will decrease, at first slowly, since \( \frac{dQ_S}{dU} \) is small near \( Q_{\text{max}} \), later, however, with increasing speed. The resulting shift of \( U_i \) to the positive side in turn decreases \( Q_S \). This decrease of \( Q_S \) in turn slows down the positive change of \( U_i \). Thus, the falling phase of the action potential is determined by a complicated interaction of \( Q_S \) and \( Q_R \). It will have two phases,
one of which is to a large extent dependent on the increase of $Q_S$ at a time when $Q_S$ is still near its maximum and $\frac{dQ_S}{dU}$ is small. During the second phase the decrease of $Q_S$ is the dominating factor. This phase will begin at a potential at which $\frac{dQ_S}{dU}$ again increases. During the first phase the potential will fall slowly; during the second phase it will fall faster. The larger $\tau_s$, the more pronounced will be the distinction between the two phases. For the rising phase of the action potential changes of $Q_S$ are of little significance. Its gradient is mostly determined by $\frac{dQ_S}{dt}$. Separate records of $U_S$ and $U_R$ illustrate the behavior of $Q_S$ and $Q_R$ outlined above (see Fig. 9).

**Comparison of Recorded and Computed Action Potentials**

If the general kinetic properties of the theoretical system agreed with those of the excitable system in nerve, one should be able to predict from this system the entire behavior of the action potential including more complicated
phenomena like prolonged action potential, rhythmic firing, etc. The following comparison of recorded and computed action potentials permits a test of this proposition and at the same time provides an analysis of some of the more complicated kinetic phenomena which occur under abnormal conditions in nerve. Action potentials were recorded from single nodes of Ranvier by a previously described method (Mueller, 1958 a).

Most of the computing was done at an earlier date using a simpler analogue system shown in Fig. 10. In this computer the functions $\alpha_\theta$ and $\alpha_\phi$ were incorporated into the differential amplifier, $Q_\theta, f(U)$ and $Q_\phi, f(U)$ being represented by the grid voltage plate current characteristics of the two triodes. Two attenuators accounted for $\beta_\theta$ and $\beta_\phi$.

In this form the computer realizes the simplest properties of the system. There are certain differences between the layout of the computer and the theoretical system. For example $\alpha_\theta$ cannot be varied independently from $\alpha_\phi$ and a change of $\beta_\theta$ and $\beta_\phi$ also changes the grid potential of either tube thus changing the relative position of $Q_\theta, f(U)$ and $Q_\phi, f(U)$. However, later checks made with the more accurate system shown in Fig. 3 confirmed the results obtained.

The external (stimulating) voltages were applied to the nerve and computer in the same manner, and had in those cases in which comparison was made, equal form and equal relative amplitude and duration.
Excitation Phenomena

Above all the theoretical system displays all those well known phenomena which are connected with the initiation of the action potential by electrical stimulation. The most important ones will be mentioned:

1. The existence of a threshold and a subthreshold response. The potential value of the threshold depends on how much $Q_\alpha$ had to increase until $\frac{d^2(U_{\alpha} + U_s)}{dt^2}$ became positive. This in turn depends on the shape and rela-
tive position of the $Q_r$, $f(U)$ and $Q_s$, $f(U)$ curves, the relation of $\tau_r/\tau_s$, and the time course of the externally applied potential (stimulus).

2. Anodal polarization increases the threshold because it decreases $Q_E$ and thus, removes it further from the threshold value.

3. Increasing stimulus strength decreased the latency (typical strength-latency curve). This follows from the exponential time course of the equilibrium displacement.

4. A potential displacement to the positive side has no stimulating effect, because the system is already at the positive side. If the system were fixed at the negative side a positive stimulating potential could initiate a positive action potential. This can be seen in nerve under certain conditions (high KCl) and can also be computed.

5. Anodal opening excitation occurs especially when the system is already slightly depolarized.

6. Slowly rising stimulating potentials are less effective (accommodation) because they equalize the increase of $Q_E$ and $Q_s$.

7. After the end of the action potential the system shows a refractory period which is due to a decrease of $Q_E$ below its resting value. The following supernormal phase results from the delayed decrease of $Q_s$. The duration of the refractory period is a function of $\tau_s$. A decrease of $\tau_s$ increases the duration of the refractory period. Since the duration of the action potential also increases with decreasing $\tau_s$ prolonged action potentials should be followed by a prolonged refractory period which is experimentally observed.

**Prolonged Action Potentials**

The theoretical system can give an action potential only if $\tau_s > \tau_E$. Shortly after the peak of the action potential its time course is entirely determined by the rise of $Q_s$. If now $\tau_s$ is considerably smaller than $\tau_E$ repolarization will take place at a correspondingly slow speed, until the potential has fallen sufficiently so that the decrease of $Q_E$ will also contribute to the repolarization (see Fig. 11). Since $\tau_E < \tau_s$ this last phase of repolarization will be steep. The duration of the action potential is thus mainly determined by the time which the potential takes to fall to the critical point at which $Q_E$ contributes sufficiently to the potentials so that $\frac{d^2}{dU^2}(U_s + U_E)$ becomes negative. It can be shown that this "turn-off" potential coincides with the second maximum of $\frac{d^2Q_E}{dU^2}$ and a shift of this maximum with respect to the potential, e.g. by a change of the total concentration of reacting molecules, will cause a characteristic change of the turn-off potential and the shape of the action potential which is often observed and which also can be calculated (see Fig. 11).
Effect of External Potential Changes on Duration, Shape, and Amplitude of the Action Potential

The observations made in this respect on nerve were described in a preceding paper (Mueller, 1958b). It would be expected that the computed action potentials would behave in the same way as do the ones from nerve. Figs. 12 to 15 give some representative examples. In the theoretical system the chemical equilibrium shifts between two sides with the transition from one side to the other controlled by the potential. In general the system could operate in four different fashions: (1) Only the positive side is stable (the normal action potential). (2) Only the negative side is stable (not yet seen in nerve
but which can be computed). (3) Both sides are stable (action potential in KCl). (4) Both sides are unstable (rhythmic responses, see below).

In which of the four ways the system operates depends on the form of $Q_e$, $f(U)$ and $Q_s$, $f(U)$ curves, and their relative position with respect to $U$ (see Fig. 1). In case 1 in which the negative side is unstable the repolarization can still be delayed (Fig. 12 B) or enhanced (Fig. 12 A) by externally applied potentials of the appropriate signs. Also the steady potential level can be

![Graphs showing action potentials](image)

**Fig. 13 A**, increase of the amplitude of recorded and computed action potentials as function of increasing stimulus strength. In both cases the resting potential was slightly displaced towards the negative side.

**B**, effect of displacing the resting potential to the negative side on the amplitude of computed and recorded action potentials. The stimulus strength was constant for each sweep (stimulation by cathodal make).

preset and has considerable influence on duration, amplitude, and form of the action potential (Figs. 13 to 15). However, not only the kinetics of the transition of the system from one side to the other are of interest. The system can also be in equilibrium with any external potential and thus stay in an intermediate state in which neither $Q_e$ nor $Q_s$ is fully on one side. It has already been seen in Fig. 8 that for a sudden external potential step the system
produces a potential \( U_i \) which not only consists of a transient potential change (action potential) but also of a steady-state change which lasts as long as the external potential displacement. In correct terminology, both transient and steady-state changes should be called action potentials, in so far as they both are part of the reaction of the system to the external potential change and a clear separation is not possible. The total change of \( U_i \), seen

![Diagram](image.png)

**Fig. 14.** Effect of displacing the resting potential to the negative side on the duration of computed and recorded prolonged action potentials. Node in 2 M glycerin-Ringer's, computer with increased \( \tau_n \). Between each sweep the resting potential was displaced by an external constant current while the strength of the stimulus (cathodal make) was kept constant. In the computed record 4 sweeps were superimposed.

e.g. in Fig. 8, is the function of the step \( U_e \). However, in nerve physiology it is customary to apply the term “action potential” only to the transient change, while for steady-state potential changes the term “electrotonic potential” is used.

Generally in the steady-state the system reacts to any external potential displacement with a change of the internally produced potential. Sign and value of this potential depend on the value of \( \frac{dQ_e}{dQ_i} \) in the region in which the
external potential displacement was made. The sign can be the same or opposite to the one of the external potential displacement.

Obviously the value of \( \frac{dQ_s}{dQ_e} \) depends on several factors. In the simplified case (Fig. 1) it is only determined by the parallel displacement of the two curves. However, if \( Q_{s_{\text{max}}} = Q_{e_{\text{max}}} \), the factor \( \beta_e \) or \( \beta_s \) will play a role. Furthermore it might be possible that \( Q_s\ f(U) \) and \( Q_e\ f(U) \) are not symmetrical, in which case there could appear two or more cross-points of

\[ \text{FIG. 15. Behavior of positive overshoot in recorded and computed action potentials.} \]

In records a, c, 1, 3, the stimulating voltage was turned off during the action potential while in records b, d, 2, 4, the stimulus lasted longer than the action potential.

\( \frac{dQ_s}{dQ_e} \) would then change at each crossing with the result that each time the sign of the internally produced potential change would also vary.

With these results in mind, the interpretation of electrotonic potentials in nerve becomes extremely difficult. Unless \( \frac{dQ_e}{dQ_s} \) is equal over the entire potential range, any electrotonic potential will consist of a potential drop of the applied current at a fixed or variable membrane resistance and of a potential produced by the electromotance of the excitable system. Both components may be equal or opposite in sign but their individual contribution to the total
potential cannot be separated by an internal or external electrode, which, in any case can only measure the total potential difference or current across the

FIG. 16 A, recorded and computed electrotonic potentials for subthreshold rectangular cathodal currents applied at different levels of resting potential. The middle trace of the computed and the upper trace of the recorded potentials correspond to the normal resting potential which in the other records was displaced by external current. Note the different amplitudes and rise phases at the different levels of constant polarization.

B, recorded and computed potentials resulting from superimposition of a short anodal current on a constant cathodal current. The cathodal current was either subthreshold (lower trace) or above threshold (upper trace in each record). Node in 2 M glycerin-Ringer's, computer with increased \( r_g \).

membrane. This holds true no matter what the nature of the resistance is or how resistance and electromotance are coupled.

This point is also of importance with respect to measurements of membrane resistance or capacity. For these measurements an external current has to be
passed through the membrane. Since the potential set up by this current will change the electromotance, the total (measured) potential will not depend on the resistance alone and all measurements will be inaccurate by an amount proportional to the potential produced by the electromotance. As a matter of fact, in the theoretical system, changes of the electromotance alone can produce all those phenomena which in nerve usually are attributed to changes of the membrane resistance, e.g. the change in time course and amplitude of the electrotonic potential as function of the steady potential level (Fig. 16 A); or the decrease of the amplitude of a square pulse applied during the action potential as compared to the amplitude of the same pulse applied when the system is at rest; i.e., the positive side (Fig. 16 B).

**Action Potential in KCl and after Depolarization**

Case 3, in which both sides are stable, is in nerve represented by the action potentials in KCl and after depolarization. In these action potentials no spon-
taneous repolarization occurs if the externally applied potential exceeds a certain negative value. In the theoretical system repolarization is initiated by an increase of $Q_a$, and a decrease of $\frac{dQ_s}{dU}$ or $Q_{S_{\text{max}}}$ should make the system bistable. Fig. 17 illustrates that this is in fact so. Under these conditions even minor details of the kinetics of the recorded potentials agree with those of the theoretical system. Thus e.g., in Fig. 17 A the height of the initial spike increases continuously with the stimulus strength. In Fig. 18 A the first potential step of the stimulating current is much smaller for the break than for the make. For the computer this cannot be interpreted by resistance changes since these do not enter the calculation (see above discussion of mem-

Fig. 18 A, recorded and computed potentials for cathodal current shown in c. Node in 0.1 M KCl, computer with increased $r_S$ and $Q_{S_{\text{max}}}$.

B, recorded and computed potentials for make of anodal current during “active state.” In the upper sweep of each record the current is below turn-off threshold. When current strength is slightly increased, the system goes to the resting state (positive side). After the end of the anodal current, the system returns to the active state (negative side). Node in 0.1 M KCl, computer with increased $r_S$ and $Q_{S_{\text{max}}}$.
brane resistance). For the bistable case the kinetics for the transition from the positive to the negative side are identical with those for a transition in the opposite direction (see Fig. 18 B).

Fig. 19 A, computed and recorded potentials for the make of constant cathodal currents of increasing strength. Oscillations occur only at medium current strength. Several sweeps superimposed. Node in 2 m glycerin-Ringer's, computer with increased \( r_a \) and slightly increased \( Q_{smax} \).

B, recorded and computed potential changes for a rectangular cathodal current. Damped oscillations. Computer with slightly increased \( Q_{smax} \).

Oscillations and Rhythmic Firing

If in the theoretical system \( \frac{dQ_{smax}}{dU} \) is increased or \( Q_{smax} \) is bigger than \( Q_{shmax} \) the system begins to oscillate between the negative and the positive side as soon as the external potential is displaced somewhat towards the negative side. These oscillations can be either more or less damped (see Fig. 19)
FIG. 20. Recorded and computed rhythmic action potentials, initiated by make of constant cathodal currents. With increasing strength of the current the latency shortens and the discharge frequency increases.

FIG. 21. Recorded and computed rhythmic action potentials for the make of a constant cathodal current. Note the similar form of the positive overshoots and the subthreshold oscillations between spikes in both records.
Fig. 22. Computed rhythmic action potentials for rectangular cathodal currents of increasing strength. In record 1 the stimulating voltage was just above threshold; the system gives only one action potential after a considerable latency. Further increase of the stimulus strength leads to irregular discharges (records 2 to 4) and finally to continuous firing (record 5).
or undamped (see Fig. 20). Form, amplitude, and frequency of the oscillations vary according to the time and potential functions of $Q_s$ and $Q_g$. These functions can be set so that the amplitude and form of the individual oscillations resemble the normal action potential (repetitive discharge or rhythmic firing). The kinetics of initiation as well as the potential time course of the individual spikes are identical in nerve and in the theoretical system. Even finer details such as (1) Form and amplitude of positive overshoots (Fig. 21); (2) subthreshold oscillations (Figs. 20 and 21); (3) variation of discharge latency and frequency as function of stimulus strength (Fig. 20); (4) decline of spike amplitude during a train of discharges (Fig. 22); and (5) groupwise discharge and unequal or alternating spike amplitude (Fig. 22) can be predicted from computation.

**DISCUSSION**

It has been shown that the theoretical system in its present form is sufficient to account for the entire potential kinetics in nerve, including even more complicated phenomena such as prolonged action potentials, rhythmic firing, etc. The unspecific nature of the assumptions leaves a great number of possibilities for actual realizations of the system. However, as long as the basic principles are observed, the kinetic behavior of the generated potentials will be the same. Thus for instance, $Q_s$ need not generate a separate electromotance, it might well be a reaction which counteracts $Q_g$. However, $Q_s$ must in any case be independent of $Q_g$ in so far as a change of $Q_g$ does not simultaneously change $Q_s$ by an equal amount. It might also be that the value of $Q_s$ is determined by $Q_g$, i.e., by chemical interaction with the reaction product of $Q_g$, rather than by the potential field.

The system as it has been described here is the simplest one necessary and sufficient to account for the observed phenomena. But the fact that it gave such good agreement does not exclude the possibility in nerve of a more complicated mechanism or a combination of several such systems. That the latter possibility has to be considered becomes obvious if one tries to identify the assumed electromotances with physicochemical events such as conductances for different ions.

Hodgkin and Huxley (1952 d) calculated the action potential of the squid axon on the basis of a system with three components: a variable Na conductance, an inactivation process which opposes changes of the Na conductance, and a variable conductance for K ions. The properties of the system of Na conductance and inactivation are essentially the same as the ones assumed for $Q_g$ and $Q_s$, and a system which consisted only of Na conductance and inactivation would also be able to account for the observed potential changes. On the other hand a system consisting only of a variable Na conductance and K conductance would also give the same potential forms.
The results presented in a previous paper (Mueller, 1958 a) showed that the node is able to give action potentials in KCl alone. If in this case the electromotances are assumed to be due to changes of the K conductance, one has to postulate an additional K inactivation process which would correspond to $Q_s$. Without it the system would not be able to repolarize.

The system could thus consist not only of two equilibria ($Q_e$ and $Q_s$) but also of three or four. Computations with these multiple systems have not been made, but provided that appropriate parameters are chosen, it can be expected that such a multiple system would generate potentials similar to the one described here.

Another question of importance is the mechanism by which the energy of the potential field is utilized by the molecular system. In principle three possibilities exist.

1. The field could act on preexisting or induced molecular dipoles (orientation polarization). This is unlikely for two reasons. First, as is shown in the appendix (A), the energy utilized by dipoles for the field strength occurring in nerve is exceedingly small and not sufficient to change a chemical equilibrium far enough to comply with the postulates of the theory. Second, increasing temperature should counteract the orientation induced by the field, while it is actually observed that an increase of temperature increases the rate of the reactions connected with the action potential.

2. The field could act by displacing the outer electron shell with respect to the atomic nucleus (electron polarization). An objection to this possibility is that because of the relatively weak field the induced dipole moment is too small to account for the postulated change of the interaction energy (see Appendix B).

3. This leaves the third possibility, namely that the field acts on a charged atom, displacing it in the direction of the field and thereby adding additional kinetic energy in that direction. The calculations in the appendix (C) show that this energy would be sufficient to account quantitatively for the equilibrium shift postulated by the theory.

The calculations also suggest that the field acts on a divalent ion and in agreement with experimental observations it is not unlikely that the ion in question is identical with Ca$^{++}$.

Nothing definite can be said about the nature of the electromotances. It is reasonable to assume that the interaction of Na and K ions with molecules of the excitable system is involved. In principle, a number of possibilities exist.

1. If the system were in a true equilibrium, the electromotance would be directly determined by the differences of free energy of interaction between Na and K and the fixed negative charges in the system. While some systems, e.g. glass electrodes, almost fullfill this condition, there are some doubts
whether biological systems are at any time in a thermodynamic equilibrium. The current through the membrane of the node of Ranvier reaches during the action potential values between 10 and 20 ma. cm.\(^{-2}\), which indicates a large deviation from the equilibrium state.

2. The system could vary its conductance for either ion. This conductance change, which is the consequence of changes of the ion mobility due to changes of the activation energy for lattice jumps from one fixed negative charge to the next. The activation energy itself could be determined by the free energy of binding between the ion and the fixed site in which case changes of \(\Delta F\) between ion and site would determine the electromotance changes. However, there is no \(a\ priori\) relation between activation energy and \(\Delta F\) so that conductance changes could be independent of changes of \(\Delta F\) (e.g., if steric hindrance were of importance).

3. On the other hand changes of \(\Delta F\) alone could change the relative conductance of two ions, by changing the relative concentration of the two ions associated with the fixed sites. This conductance change would not involve activation energies and the electromotance would be entirely determined by the free energy of binding between ions and fixed counterions.

4. It is not necessary to assume that the excitable system is located within a thin membrane, which controls diffusion rates between an inside and outside solution phase. The node of Ranvier is surrounded by Schwann cell cytoplasm which could act as ion exchanger, shifting its adsorption equilibrium for Na, K, and Ca ions.

In a more specific way this idea could be outlined as follows: Suppose that the Schwann cell cytoplasm or part of it contains a large number of fixed negative sites (perhaps carboxyl groups) which in the resting state are almost completely associated with Ca ions. A stimulating potential across the system would dissociate this complex as outlined in Appendix C and D. The free sites now begin to associate with Na ions, which are present at high concentrations in the outer medium. This will cause an inward movement of Na ions.

If the rate of inward movement of Na ions is greater than the rate of outward movement of Ca, this Ca-Na exchange will cause a further depolarization resulting in a further dissociation of Ca and exchange for Na. There is, in fact, evidence that due to their higher binding and activation energies, divalent ions diffuse much more slowly in organic and inorganic exchange systems. It is now known that in almost all ion exchange systems, the apparent equilibrium constant changes as function of the relative amounts of the two exchanging ions in the system, with the result that the higher the concentration of any adsorbed ion becomes, the less this particular ion is preferred. (In equations describing ion exchange, this effect is usually taken into account by assuming that the activity of the adsorbed ion is proportional.
to an $n$th power of the adsorbed amount. See e.g. Eisenman, Rudin, and Casby, 1957; Högfeldt, 1955.)

The increased amount of adsorbed Na would thus result in a decreased preference for Na, and an increased preference for K and divalent ions. The shift of the adsorption specificity from Na to K and divalent ions can be predicted from the relation of adsorption isotherms for the alkali metal and earth alkali ions on glass electrodes and permutites studied recently by Rudin, Eisenman, and Casby (personal communication).

The adsorption of K and Ca to the sites will now cause the potential again to rise and the rising potential will further favor the exchange of Na and Ca and finally restore the initial conditions.

In terms of the analytical picture, the initial exchange of Ca for Na would correspond to $Q_e$ while the decrease of the preference of the sites for Na and the resulting adsorption of K and Ca would correspond to $Q_s$. Such a system could also function in either potassium or sodium alone, which seems to be true for nerve.

**APPENDIX**

A. The Energy Gained by Dipole Orientation

If the reacting molecules have a permanent dipole moment, they can be rotated in the direction of the field (orientation polarization). For a small field the average dipole moment in the direction of the field,

$$\bar{\mu} = \frac{E \mu^3}{3 kT}$$

(Debye, 1929; Böttcher, 1952, Syrkin and Diatkina, 1950). in which $E$ is the field strength, $\mu$ the dipole moment, $k$, Boltzmann's constant, and $T$ the absolute temperature. The average energy change of the dipole in the field is then

$$\Delta F = \frac{E_\mu^3}{3 kT}$$

For $\mu = 2 \times 10^{-18}$ e.s.u. and $E = 30,000$ volts cm$^{-1}$ at $290^\circ T$, this amounts to only $4.8 \cdot 10^{-6}$ kcal./mol. This energy is far too small to cause any considerable change of a chemical equilibrium.

B. Energy Gain by Electron Polarization

The field could displace the electron cloud of the outer orbit of a charged atom thereby inducing a dipole. This would result in a change of free energy between the polarized ion and the counterion. If $\alpha$ is the polarizability of the atom and $E$ the field strength, the induced dipole moment

$$\mu = \alpha E$$
If the counterion has the charge $e$, the change in free energy due to an applied field

$$\Delta F = \frac{e\mu}{r^2}$$  \hspace{1cm} (18)

For $E = 30,000$ volts/cm., $r = 2\AA$, $\alpha = 3 \times 10^{-34}$ cm.$^4$, and $e = 4.8 \times 10^{-19}$ e.s.u., $\Delta F$ amounts to only $5.2 \times 10^{-8}$ kcal. This energy would also be too small to cause the required equilibrium shift.

C. Equilibrium Shift of a Second Order Reaction by an Applied Electric Potential

Assume a simple second order reaction of the form $A + B \rightleftharpoons AB$. Let the total number of reacting molecules be constant so that $2[AB] + [A] + [B] = C$ and the equilibrium

$$Q = \frac{[AB]}{C}$$  \hspace{1cm} (19)

Furthermore let the number of molecules $A$ be equal to the number of $B$. Therefore

$$[AB] = \frac{C - 2A}{2}$$  \hspace{1cm} (20)

If the equilibrium constant

$$K = \frac{[AB]}{[A] \cdot [B]}$$  \hspace{1cm} (21)

$$[AB] = \frac{C - 2A}{2} = A^2K$$  \hspace{1cm} (22)

From this follows

$$A^2K + A - \frac{C}{2} = 0$$

so that

$$[AB] = \frac{C - \sqrt{1 + 2CK - 1}}{2K}$$  \hspace{1cm} (23)

and

$$Q = \frac{1}{2C} \left[ C - \sqrt{1 + 2CK - 1} \right]$$  \hspace{1cm} (25)

If now $A$ and $B$ both carry a net charge, $(ze)$, and $B$ is fixed in space with respect to $A$ in such a way that the application of an electric potential can move $A$ in the direction of $B$, the potential energy of the field will increase the average kinetic energy of $A$ in the direction of $B$. The result is a change
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of $\Delta F$ in such a way that the reaction $A + B \rightarrow AB$ is favored. The equilibrium constant can thus be expressed by

$$K = Pe^{\Delta F' + 2z\Delta F'}/RT$$

(26)

in which $\Delta F$ is the initial free energy of the reaction, $\Delta F'$ the change of the free energy due to the applied field and equal to 23 cal./mv., $z$ the valence of $A$, and $P$ a constant. The combination of Equations 25 and 26 allows $Q$ to be calculated as function of the potential.

$$Q = \frac{1}{2C} \cdot \left[ C - \left( \frac{\sqrt{1 + 2CPe^{\Delta F' + 2z\Delta F'}/RT}}{Pe^{\Delta F' + 2z\Delta F'}/RT} - 1 \right) \right]$$

(27)

The calculation shows that potential changes as they occur during the action potential (120 mv.) are sufficient to change $Q$ almost over its entire range that is, from 0 to 0.5 (see Fig. 1). The position with respect to $(U)$ and the slope of the $Q, f(U)$ curves (Fig. 1) are of importance for the threshold, the shape, and the rise phase of the action potential. The position with respect to the potential depends largely on $\Delta F$ at zero potential and on the total concentration of $A$ and $B$. The behavior of the action potential indicated that $\Delta F$ is essentially zero membrane potential for both $Q_{g}$ and $Q_{s}$ is small (<0.5 kcal.).

The slope of $Q, f(U)$ determines to a large extent the velocity of the rise phase of the action potential.

Differentiation of Equation 27 with respect to $\Delta F'$ gives

$$\frac{dQ}{d\Delta F'} = \frac{2z}{RT} \left( \frac{-Ck}{\sqrt{1 + 2ck}} - 1 \sqrt{1 + 2ck} \frac{1}{2ck} \right)$$

(28)

from which $\frac{dU_i}{dU}$ (i.e. the variation of the internally produced potential as function of any potential change) can be obtained by multiplying $\frac{dQ}{d\Delta F'}$ with the appropriate factors (250 and 23). Computations show that the maximal values of $\frac{dU_i}{dU}$ must be >3 in order to give an all or none action potential. Such values are only possible if the valence of the mobile ion, $z$, is greater than one. Fig. 1 was calculated under the assumption that $z = 2$ in which case $\frac{dU_i}{dU} = 3.6$. It is thus suggested that the field acts on a bivalent ion, possibly $Ca^{++}$.

D. Kinetics of a Second Order Reaction As Function of a Rate Constant Change

The effect of the potential on the equilibrium constant as outlined above (Appendix C) is actually due to a change of the two rate constants $k_1$ and $k_2$.
of the reaction

\[ A^- + B^+ \rightleftharpoons AB \]

A stepwise change of the potential causes a sudden change of \( k_1 \) and \( k_2 \), and the reaction approaches its new equilibrium with a certain time course. The two rate constants \( k_1 \) and \( k_2 \) as functions of the potential can be represented by:

\[
\begin{align*}
    k_1 &= \rho \frac{E_0 + E}{R T} \\
    k_2 &= \rho \frac{E_0 - E}{R T}
\end{align*}
\]

in which \( E_0 \) is the activation energy of the corresponding reaction at zero potential, \( E \) the energy change due to the applied potential (equal to \( z \cdot 23 \) cal./mv.; \( z = \) valence), and \( \rho \) a constant.

Assuming that the initial concentrations of \( A \) and \( B \) are equal, so that

\[ [A^-] = [B^+] = a \]

and

\[ [AB] = c \]

the rate of formation of the product, \( c \), can be expressed by:

\[
\frac{dc}{dt} = k_1 (a - c)^2 - k_2 c
\]

After integration:

\[
c = a + \frac{k_3}{2k_1} - D \coth^{-1} (Dk_2 - DC)
\]

in which

\[
D^2 = \frac{k_2^2}{4k_1^2} + \frac{k_2}{k_1} a
\]

and

\[
DC = \coth^{-1} \left[ \frac{c_0 - \left( a + \frac{k_3}{2k_1} \right)}{D} + (Dk_2c_0) \right]
\]

As is seen in Fig. 23, the time course of \( c \) is approximately exponential. The apparent time constants, however, decrease with increasing voltage steps. It was assumed that the positive ion is the mobile one, and that a negative potential increases the reaction rate of \( AB \rightarrow A^-B^+ \). In nerve this could mean, for example, that an increased outside negativity causes a dissociation
of Ca from its fixed counterion. Under these circumstances Fig. 23 shows that the time constant of the reaction is faster for a negative potential step than for a positive step of equal magnitude.

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![Figure 23](image_url)

**Fig. 23.** Kinetics of the reaction $A + B \rightarrow AB$. At $t = 0$ potential steps induced a sudden change of the rate constants $k_1$ and $k_2$. $C$ indicates the concentration of $AB$ and was calculated from Equations 29, 30, 32, assuming $a = 1$, and $E_0 = 0.1$ kcal.

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