

ON REINFORCEMENT AND INTERFERENCE
BETWEEN STIMULI

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It is shown that the current "two-factor" theory of nerve excitation can account for sustained inhibition or enhancement by a sequence of stimulus pulses, and for the decrease in the reinforcement period with each successive pulse of the train.

1. *Excitation equations.* The basic equations in Rashevsky's excitation theory are*

$$\begin{aligned}\frac{d\varepsilon}{dt} &= KI - k\varepsilon, \\ \frac{dj}{dt} &= MI - mj,\end{aligned}\tag{1}$$

which describe the variation of a quantity $\sigma = \varepsilon - j$ under the influence of a stimulating current $I(t)$ reckoned as positive at the cathode and negative at the anode of the stimulating electrodes. The equations are considered to hold so long as σ remains below a positive threshold value h . When σ becomes equal to h , excitation occurs, and the theory makes no claim to hold during the succeeding cycle of membrane activity. It is valid again by the time the nerve has returned to its resting state, and presumably somewhat earlier than this, such as near the beginning of the relative refractory period.

The solution of the equations (1) is given by

$$\begin{aligned}\varepsilon(t) &= e^{-kt} [\varepsilon_0 + K \int_0^t I(x) e^{kx} dx]; \\ j(t) &= e^{-mt} [j_0 + M \int_0^t I(x) e^{mx} dx];\end{aligned}\tag{2}$$

*Here ε and j take the place of $\varepsilon - \varepsilon_0$ and $j - j_0$ in one of Rashevsky's notations (1940, p. 108), and are not restricted to positive values. Our threshold h corresponds to his quantity $j_0 - \varepsilon_0$. The present notation is that used by him in another place. (1940, p. 123).

where the zero subscripts denote values at $t = 0$.†

Equivalent formulations of the theory have been given by Hill and by Monnier, but for our present purposes the Rashevsky form (1) is the most convenient.

For application to actual nerves it is appropriate to restrict attention to the case

$$\begin{aligned} K &> M > 0, \\ k &> m > 0, \end{aligned} \tag{3}$$

and without loss of generality we may set

$$h = 1. \tag{4}$$

2. *No stimulus.* Starting from an initial state of the nerve specified by values ε_0 and j_0 it is seen that in the absence of stimulation, σ varies according to

$$\sigma = \varepsilon_0 e^{-kt} - j_0 e^{-mt}. \tag{5}$$

Depending upon the values ε_0 and j_0 there are various possibilities for the time course of σ . In any case both σ and $d\sigma/dt$ vanish at $t = \infty$; in the various cases they each have 0 or 1 finite positive roots. The zero value of σ comes at the time

$$t_0 = \frac{1}{k - m} \log \frac{\varepsilon_0}{j_0}, \tag{6}$$

provided that this quantity is real and positive; while a maximum or a minimum occurs at

$$t_m = \frac{1}{k - m} \log \frac{k\varepsilon_0}{mj_0}, \tag{7}$$

if this is real and positive. Since $k > m$ it is seen that t_m exists if t_0 does, and that $t_m > t_0$. There are three cases as illustrated in Figure 1, and occurring as follows:

- (a) $\frac{\varepsilon_0}{j_0} > 1$; both t_0 and t_m exist.
- (b) $1 > \frac{\varepsilon_0}{j_0} > \frac{m}{k}$; t_m exists, but not t_0 .
- (c) $\frac{\varepsilon_0}{j_0} < \frac{m}{k}$; neither t_m nor t_0 exist.
- $$\tag{8}$$

Inspection of the diagrams shows that the only cases in which

† Rashevsky's ε_0 and j_0 (1940, p. 108) have a different meaning.

σ rises to a positive value greater than σ_0 are in (a) with σ_0 negative and in (b) with σ_0 positive. Upon reference to (8) it is found that for one or the other of these cases to exist, it is necessary and sufficient that the three inequalities

$$\begin{aligned} \varepsilon &< 0 \\ j &< 0 \\ k\varepsilon - mj &< 0 \end{aligned} \tag{9}$$

shall all be initially satisfied. Hence *excitation cannot occur in the absence of a stimulus unless previous stimulation has brought the nerve to a state in which (9) holds*. Condition (9) is necessary but not sufficient for spontaneous excitation to occur. An example of excitation occurring in the absence of a stimulus is at the anode after a sufficiently strong current has been broken.

If a nerve free of stimulation does not satisfy (9) at one moment, then it never will at any later moment. On the other hand a free nerve can satisfy (9) only up to the time t_m , since the quantity on the left of the last inequality is simply $-d\sigma/dt$ and so changes sign at t_m .

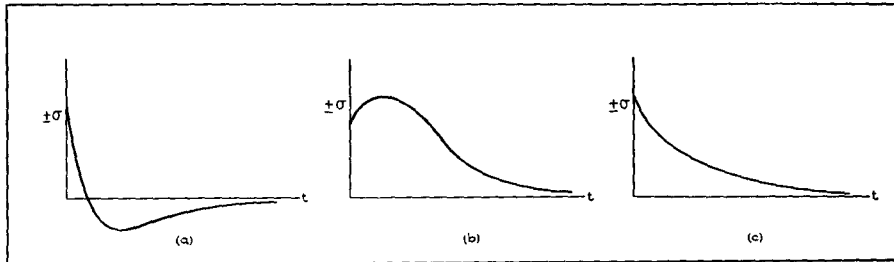


FIGURE 1

From (2) it is seen that a positive stimulus ($I > 0$) applied to a resting nerve ($\varepsilon_0 = j_0 = 0$) can never bring the nerve into a state in which (9) holds, and thus *excitation cannot occur after the cessation of a positive stimulus applied to a resting nerve*.

3. *Instantaneous pulse*. For t very small the exponential factors in (2) are sensibly equal to unity and thus after a very brief or instantaneous pulse we have

$$\begin{aligned} \varepsilon &= \varepsilon_0 + KQ \\ j &= j_0 + MQ ; \end{aligned} \tag{10}$$

where
$$Q = \int_0^t I(x) dx \tag{11}$$

is the total quantity of electricity passed during the pulse. Upon reference to (3) it is seen that a positive or cathodic (i.e. $Q > 0$) pulse increases all three quantities on the left sides of the inequalities (9). Hence a nerve which is about to fire spontaneously can be stopped from so doing by a sufficiently strong positive pulse. A positive pulse cannot leave a nerve in state (9) unless it was already there.

From (10) it follows at once that

$$\sigma = \sigma_0 + (K - M)Q. \quad (12)$$

Let Q_0 denote the positive pulse strength just sufficient to fire the resting nerve. Then upon setting $\sigma = h = 1$, $\sigma_0 = 0$, it is seen that

$$K - M = \frac{1}{Q_0}. \quad (13)$$

If Q is the positive pulse just sufficient to produce *immediate* excitation of the nerve in some other state,* then the value of σ in that state just before the pulse passed was

$$\sigma = 1 - \frac{Q}{Q_0}. \quad (14)$$

Thus the value of σ can be experimentally determined (Hill, 1936; Coppee, 1936; Katz and Schmitt, 1940), providing a test for the theory. Apart from the constant unity, σ is merely the negative of the "relative threshold" and may thus be called the "excitability". Its range is from $-\infty$, corresponding to absolute refractoriness, up to unity, at which excitation occurs.

4. *Sequence of instantaneous pulses.* After a positive pulse of strength Q is applied to a resting nerve, σ is given by (5) with

$$\begin{aligned} \varepsilon_0 &= KQ \\ j_0 &= MQ. \end{aligned} \quad (15)$$

Since $K > M$, we have case (a) in (8) and in Figure 1 (cf. Hill, 1936, Figure 76). A second positive pulse following the first within an interval up to t_0 will be reinforced, while if it comes later than t_0 , it will be opposed by the stimulus trace or residue of the first. For any two sub-liminal pulses such that $Q_1 + Q_2 > Q_0$ there will be a period, greater than zero and less than t_0 , within which they will "sum" to bring about excitation. This interval depends on the nerve and on

* The word *immediate* is needed to handle those cases in which the nerve was about to fire spontaneously. A zero pulse would then be followed by excitation, but not immediately.

the strengths of the stimuli. Furthermore, if the strengths are unequal it depends on the order in which they are presented, being greater if the weaker stimulus is presented first.

At a time Δ after the first pulse, we have

$$\begin{aligned}\varepsilon &= KQe^{-k\Delta} \\ j &= MQe^{-m\Delta} ;\end{aligned}\tag{16}$$

and if another equal pulse be then applied these values jump to

$$\varepsilon = KQ(1 + e^{-k\Delta})\tag{17}$$

$$j = MQ(1 + e^{-m\Delta}).\tag{18}$$

Continuing in this manner with equal and equally spaced stimuli we have just after the n -th pulse

$$\varepsilon = KQ(1 + e^{-k\Delta} + e^{-2k\Delta} + \dots + e^{-(n-1)k\Delta}),\tag{19}$$

with a similar expression for j . Upon summing the geometric progressions we obtain

$$\begin{aligned}\varepsilon &= KQ \frac{1 - e^{-nk\Delta}}{1 - e^{-k\Delta}} \\ j &= MQ \frac{1 - e^{-nm\Delta}}{1 - e^{-m\Delta}},\end{aligned}\tag{20}$$

which, as n becomes large, reduce to

$$\begin{aligned}\varepsilon &= KQ \frac{1}{1 - e^{-k\Delta}} \\ j &= MQ \frac{1}{1 - e^{-m\Delta}}.\end{aligned}\tag{21}$$

It is seen from (20) that ε and j are always positive. Hence (9) is never satisfied and excitation cannot occur between pulses. Also, if σ is less than zero just after a pulse it remains so until the next pulse, as may be seen by noting that case (a) in (8) is not possible with $j_0 > \varepsilon_0 > 0$. Consider in particular the steady state for which (21) holds. σ will be less than zero at the beginning of a cycle (just after a pulse) if and only if the quantity

$$\frac{K}{M} \frac{1 - e^{-m\Delta}}{1 - e^{-k\Delta}}\tag{22}$$

is less than unity. The second factor has its minimum value m/k at $\Delta = 0$ and increases monotonically to unity as Δ becomes large. Hence if

$$\frac{K}{k} < \frac{M}{m} \quad (23)$$

the quantity σ can be maintained less than zero throughout the steady state cycle if Δ is small enough.

Conversely, if σ is greater than zero at the end of a cycle it must have been so throughout. In the steady state the values at the end of a cycle (just before a pulse) are

$$\begin{aligned} \varepsilon &= KQ \frac{e^{-k\Delta}}{1 - e^{-k\Delta}} = KQ \frac{1}{e^{k\Delta} - 1} \\ j &= MQ \frac{e^{-m\Delta}}{1 - e^{-m\Delta}} = MQ \frac{1}{e^{m\Delta} - 1}. \end{aligned} \quad (24)$$

Hence σ will be greater than zero throughout the cycle if and only if the quantity

$$\frac{K e^{m\Delta} - 1}{M e^{k\Delta} - 1} \quad (25)$$

is greater than unity. The second factor has its maximum value m/k at $\Delta = 0$ and decreases monotonically to zero as Δ becomes large. Hence if

$$\frac{K}{k} > \frac{M}{m} \quad (26)$$

the quantity σ can be maintained greater than zero throughout the steady state cycle if Δ is small enough.

In either case, (23) or (26), if Δ is not sufficiently small then $\sigma > 0$ during the first part of the cycle and $\sigma < 0$ during the remainder of the cycle. The mean value of σ over a cycle gives a measure of the average increase in excitability. Defining

$$\Delta \bar{\sigma} = \int_0^{\Delta} \sigma dt, \quad (27)$$

we find from (5) and (21) that in the steady state

$$\bar{\sigma} = \frac{Q}{\Delta} \left(\frac{K}{k} - \frac{M}{m} \right). \quad (28)$$

From (1) it is seen that this state is the steady state value of σ which would be produced by a constant current of strength $I = Q/\Delta$, and is

thus somewhat of the nature of an electrotonus effect. The relation of (28) to (23) and (26) is obvious, and sheds additional light upon the significance of a "normal accommodation" (Hill, 1936; Rashevsky, 1940, p. 111) described by $K/k = M/m$.

From (6) and (20) it is seen that the "reinforcement period" after the n -th pulse is proportional to the logarithm of

$$\frac{K}{M} \frac{1 - e^{-m\Delta}}{1 - e^{-k\Delta}} \frac{1 - e^{-nk\Delta}}{1 - e^{-nm\Delta}}. \quad (29)$$

The last factor decreases monotonically to unity as n increases, and so *the reinforcement period diminishes with each successive pulse*. (Lorentte de No, 1938, p. 240). Since $K > M$ the reinforcement period is always positive after the first pulse ($n=1$), and is in fact equal to the time at which σ reaches its maximum value when a steady current is applied to the resting nerve. If, however, the product of the first two factors in (29) is less than unity, then the reinforcement period becomes negative after a sufficient number of pulses and the nerve is inhibited from then on as long as the stimuli continue, in accordance with the discussion of (22).

Let $\sigma(n)$ be the value of σ immediately after the n -th pulse, and denote

$$\delta(n) = \sigma(n+1) - \sigma(n). \quad (30)$$

If the first n pulses have failed to fire the nerve, then there is a possibility of the next pulse being successful only if $\delta(n) > 0$. From (19) it is seen that

$$\delta(n) = Q(K e^{-nk\Delta} - M e^{-nm\Delta}), \quad (31)$$

so that δ is negative for n sufficiently large. If $\delta(1) < 0$ then so is δ for all larger values of n , and $\sigma(n)$ is a monotonically decreasing function of n . If $\delta(1) > 0$ (which, upon reference to (6) and (29), is the same as saying that Δ is less than the reinforcement period after the first stimulus) then $\sigma(n)$ first rises and then falls as n increases, attaining its maximum value at one (or possibly both) of the two pulses occurring respectively just before and just after the time

$$\frac{1}{k - m} \log \frac{K}{M}. \quad (32)$$

This time is the reinforcement period for a single pulse and also, as mentioned above, the time for the attainment of a maximum σ under the influence of a constant current. The rise and fall of σ under a steady current is thus quite closely related to the rise and fall of its peak values with a steady sequence of pulses.

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