

## MATHEMATICAL MODELS OF THRESHOLD PHENOMENA IN THE NERVE MEMBRANE

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The types of mathematical model which have been used to represent all-or-none behavior in the nerve membrane may be classified as follows: (1) the *discontinuous threshold phenomenon*, in which differential equations with discontinuous functions provide both a discontinuity of response as a function of stimulus intensity at threshold and a finite maximum latency, (2) the *singular-point threshold phenomenon* which exists in a phase space having analytic functions in its differential equations and having a singular point with one characteristic root positive and the rest with negative real parts, the latency being unbounded, and (3) the *quasi threshold phenomenon*, which has a finite maximum latency and continuous functions, but neither a true discontinuity in response nor an exact threshold. Several models of the nerve membrane in the literature are classified accordingly, and the applicability of the different types of threshold phenomena to the membrane is discussed, including an extension to a stochastic model.

### INTRODUCTION

The presence of a threshold phenomenon in a biological system imposes restrictions on the types of mathematical model suitable to describe that system. This paper is concerned mainly with threshold phenomena in the nerve fiber membrane and was inspired to a great extent by the mathematical models proposed by G. Karreman (1951) and A. L. Hodgkin and A. F. Huxley (1952). A mathematical classification of threshold phenomena will be given and then used to classify several models of the nerve membrane and of the iron wire model of nerve which have been proposed by various authors.

Figure 1a shows a typical picture of the changes of potential ( $V$ ) across the membrane of a single giant nerve fiber of the squid, recorded between an external electrode and an axial internal electrode (Hodgkin, Huxley, and Katz, 1952). Brief current shocks of different intensities ( $z$ ) were applied ending at time  $t = 0$ . During the interval  $t \geq 0$  a uniform zero current flow across the membrane was maintained by the external circuit. The form of each curve depends on the initial state of the membrane at  $t = 0$ . This initial state varies continuously with  $z$ , and the curves of Fig-

ure 1a may therefore be described formally by an equation of the following form:

$$V = F(z; t), \quad (1)$$

in which  $z$  appears as a parameter. As the stimulus  $z$  is increased beyond a threshold value  $z_\theta$ , shape of the curve changes suddenly. As an extrapolation from the experimental data, one assumes that if the curves corresponding to all values of  $z$  (within some finite interval  $Z$ ) were plotted, the shapes of the curves would change discontinuously as  $z$  passed the value  $z_\theta$ . In terms of the all-or-none law of physiology, these curves are divided into two distinct classes, the "all" and the "none" curves. Within

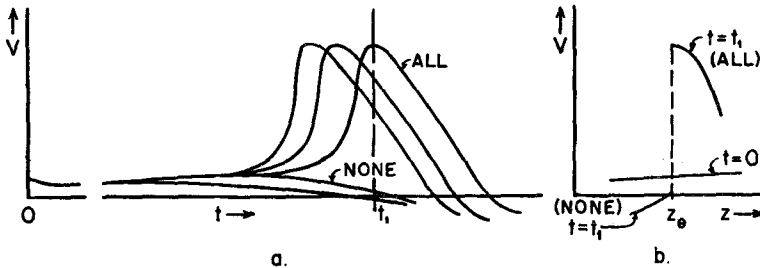


FIGURE 1. *a.* Membrane action potentials from squid giant axon, showing the effect of small differences in stimulus strength  $z$  near its threshold value  $z_\theta$ .  $z > z_\theta$  for the upper three "ALL" curves;  $z < z_\theta$  for the lower two "NONE" curves. Following a brief shock at zero time, a zero membrane current is maintained by the external circuit. (Redrawn from Hodgkin, Huxley, and Katz, 1952). *b.* Curves of potential measured at two fixed times, zero and  $t_1$ , plotted against  $z$ , from the curves in *a.*

each class, the shapes of the curves vary continuously with  $z$ , but there are no intermediates between the members of the two classes. Because of random variations in latency, it is impossible to determine from any finite number of experiments whether the latency of a nerve fiber, as the stimulus intensity approaches threshold from above, is bounded or unbounded. If the maximum latency of the response is assumed finite (Pecher, 1939), there will be some time  $t_1$  such that if the ordinate  $F(t_1; z)$  is plotted against  $z$  (Fig. 1b, curve " $t = t_1$ "), there is a discontinuity at some value  $z_\theta$  of  $z$ . This discontinuous curve may be considered as showing the relation between stimulus (abscissa) and response (ordinate). However, if the initial state  $F(z; 0)$  is plotted against  $z$  (Fig. 1b, broken line), no discontinuity appears. The threshold phenomenon thus involves a "parting of the ways," at some time between zero and  $t_1$ , between the courses of behavior of the membrane for  $z < z_\theta$  and those for  $z > z_\theta$ , at least as reflected in the

potential  $V$ . This property should be present in any mathematical model of the membrane.

The properties sought belong, strictly speaking, not to the membrane by itself, but to the total system consisting of the membrane together with that part of its environment which imposes an external electrical constraint upon it, which here consists of the electronic apparatus connected to the electrodes. The importance of the environment in helping to determine threshold behavior is shown by the fact that such behavior is present when the membrane is stimulated by a short current pulse or a step change in current, but absent when a step change in potential is applied (Cole, 1949; Hodgkin, Huxley, and Katz, 1949). The threshold phenomena to be considered here include only those in which the stimulus is over at time  $t = 0$ , and the external constraint is always the same during the response ( $t > 0$ ). The case of stimulation of nerve by step currents of different strengths will therefore be excluded.

#### DEFINITIONS

Let us assume that the state of the total system at any time may be described by a finite number of variables of state  $x_n$  ( $n = 1, 2, \dots, N$ ), and that the behavior of the system can be defined by a set of differential equations of the form

$$\frac{dx_n}{dt} = f_n(x_1, x_2, \dots, x_n) \quad (2)$$

or, in vector notation,

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}), \quad (3)$$

where the vectors are printed in boldface type. The variables  $x_n$  may be considered as the coordinates of a vector space or phase space of  $N$  dimensions, each point of which corresponds to a single state of the system (Minorsky, 1947; Lefschetz, 1948). The state of the system is represented at any time by a *state point*, which moves along a trajectory in phase space defined by a solution  $\mathbf{x}(x^0; t)$  of equation (3), where  $x^0$  is the initial point for  $t = 0$ . During the stimulus the electrical constraint and therefore the trajectories of the phase space are not the same as for  $t \geq 0$ . The point reached at  $t = 0$  by the state point as a result of the stimulus is  $x^0$  and is some function  $x^0(z)$  of  $z$ . The initial point is thus under the control of the experimenter, who can vary the parameter  $z$  at will, before each stimulus is delivered.

All or only some of the  $x_n$  may be measured experimentally. The membrane potential  $V$ , which is usually measured, may in general be assumed

to be some continuous function of the  $x_n$ . Several authors simply take the membrane potential as one of the  $x_n$ . In the following discussion, definitions of three different types of threshold phenomena will be formulated in terms of the properties of trajectories in phase space, and not just in terms of the behavior of  $V$  as a function of time. However, it will always be assumed that  $V$  is so defined as a function of the  $x_n$  that the continuities or discontinuities of shape between neighboring trajectories are not lost when they are converted to curves of  $V$  plotted against  $t$ .

The following definition is an attempt to describe a threshold phenomenon mathematically. Figure 2 illustrates this definition for a phase plane

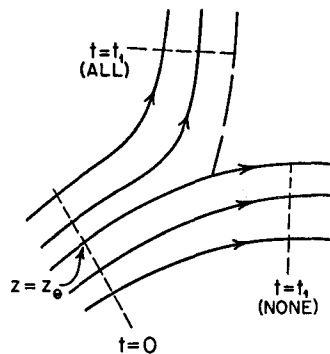


FIGURE 2. Diagram of a discontinuous threshold phenomenon in a phase plane. Broken line labeled " $t = 0$ " in this and subsequent figures is the locus of initial points resulting when the stimulus intensity  $z$  is varied.  $z = z_0$  at the point indicated. The two broken lines labeled " $t = t_1$ " are loci of state points for time  $t_1$  and correspond to "ALL" and "NONE" responses.

( $N = 2$ ). The trajectories in the upper right-hand region of Figure 2 could be filled in, in various ways, or simply left undefined.

#### *Definition I.*

If  $\mathbf{x}^0(z)$  is continuous in  $z$  over some interval  $Z$ , except possibly for a step discontinuity at  $z = z_0$ , and if, for some time  $t_1 \geq 0$ ,  $\mathbf{x}(\mathbf{x}^0(z); t_1)$  is continuous in  $z$  except for a step discontinuity at  $z = z_0$ , then a *discontinuous threshold phenomenon (DTP)* will be said to exist in the phase space.

This definition is designed to describe a threshold phenomenon with a bounded latency ( $t_1$ ). The discontinuity in the state of the system at time  $t_1$ , as a function of  $z$ , is provided either (1) simply by a discontinuity in the initial condition at  $z = z_0$ , with no special conditions on  $f(\mathbf{x})$ , or (2) with the initial condition continuous in  $z$ , in which case limitations must be imposed on  $f(\mathbf{x})$ . One may wish both  $\mathbf{x}^0(z)$  of Definition I and  $f(\mathbf{x})$  of (3) to have as components some of the elementary, differentiable

functions of calculus. The justifications for such a choice seem to be that (1) physical and chemical processes involving many molecules are usually described by such functions, (2) the results of several experiments always differ so much that there is a limit to the preciseness to which the functions should be specified, and therefore the simplest ones should be chosen, and (3) to explain a discontinuous process by using discontinuous functions is to use an *ad hoc* assumption and dodge the issue. But by the Cauchy-Lipschitz theorem for the existence of the solutions of differential equations (Lefschetz, 1948) one can show that if  $f(x)$  is differentiable, with all partial derivatives uniformly bounded in a certain region, the solution  $x(x^0; t)$  is continuous in  $(x^0; t)$  for all  $t$ . Then if  $x^0(z)$  is also continuous in  $z$ , a *DTP* is impossible. Nevertheless, several authors have successfully used *DTP*'s with discontinuous functions, as will be discussed below.

It should be mentioned that in order to have a *DTP* with  $x^0(z)$  continuous it is not necessary that  $f(x)$  be discontinuous, but only that it fail to satisfy a Lipschitz condition at some point. For example, a *DTP* appears in the following system:\*

$$\frac{dx}{dt} = -x^{1/3}$$

$$\frac{dy}{dt} = y^{1/3}.$$

If one wishes to use differentiable functions, it is necessary to set up a new definition of threshold phenomenon. One way to revise Definition I is to sacrifice the existence of a maximum latency, or finite  $t_1$ . A point of a phase space at which all  $dx_n/dt = 0$  is a degenerate trajectory and is called a *singular point*. Figure 3 shows a phase plane with a saddle point (one type of singular point) at the origin of coordinates arising from equations of the following form:

$$\left. \begin{aligned} \frac{dx_1}{dt} &= p_{11}x_1 + p_{12}x_2 + q_1(x_1, x_2), \\ \frac{dx_2}{dt} &= p_{21}x_1 + p_{22}x_2 + q_2(x_1, x_2). \end{aligned} \right\} \quad (4)$$

In this case the  $p$ 's are constants, and the characteristic equation

$$\begin{vmatrix} p_{11} - \lambda & p_{12} \\ p_{21} & p_{22} - \lambda \end{vmatrix} = 0 \quad (5)$$

\* Suggested by Dr. F. H. Clauser.

in  $\lambda$  has one positive and one negative root, and  $q_1$  and  $q_2$  are power series in  $x_1$  and  $x_2$ , beginning with terms of degree two or greater. If  $x^0(z)$  is a continuous function of  $z$  and describes a line segment such as that labelled " $t = 0$ " in Figure 3 as  $z$  is varied over the interval  $Z$ , the trajectory having  $x^0(z)$  as its initial point changes its shape discontinuously at a trajectory called the *separatrix*, for which  $z$  has the value  $z_\theta$ . This discontinuity is of a different kind from that of Definition I. In fact, according to the Cauchy-Lipschitz Theorem,  $x(x^0(z); t_1)$  is continuous in  $z$  for every fixed  $t_1$ , and as  $z$  is varied,  $x(x^0(z); t_1)$  travels continuously along a line such as that labelled " $t = t_1$ " in Figure 3. Let us arbitrarily define the latency as the time required for  $x$  to go from its initial point along an "all" trajectory to some line such as that labelled "criterion of excitation" in Figure 3. For a

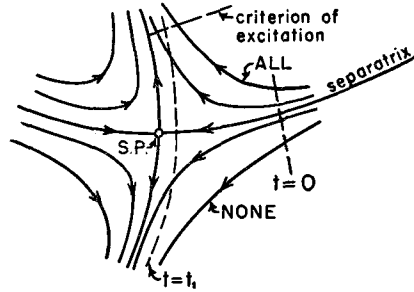


FIGURE 3. Diagram of an *STP* in a phase plane. *S.P.* is a saddle point. Typical trajectories of the "ALL" and "NONE" classes are labeled. See text.

model of the nerve membrane, for example, this line might correspond to the condition that  $V$  be halfway between the resting potential and the peak value of an action potential. There is now no maximum latency. The nearer  $z$  approaches  $z_\theta$ , the longer the state point subsequently remains in the neighborhood of the saddle point, where the phase velocity vector  $dx/dt$  is very small. The latency can in this way be made arbitrarily large. This property of the saddle point may be shown by plotting latency against  $z$ . In Figure 4, typical curves of this kind are diagrammed for a *DTP* and a saddle-point threshold phenomenon (*STP*). If the latter curve were to diverge from the experimental curve (broken line) only for  $z$  very near  $z_\theta$ , such a model could be accepted as a good approximate representation of the nerve membrane. Both the *STP* and the real nerve fiber may then show increases of latency near threshold which are similar except that the latency of the *STP* approaches infinity, as  $z$  approaches  $z_\theta$ , while that of the real fiber remains finite.

The trajectories in the neighborhood of the saddle point in Figure 3 fall into three classes according to their behavior: (1) two trajectories are *stable*, approaching the saddle point as time increases; (2) two others are *unstable*, approaching it as time decreases; and (3) all the rest are *hyperbolic*, first approaching and then leaving the saddle point as time increases. Furthermore, the hyperbolic trajectories can be divided into four subclasses according to the directions along which they approach and leave the saddle point. If two trajectories are chosen from any two of these different classes or subclasses, it is impossible to deform one into the other

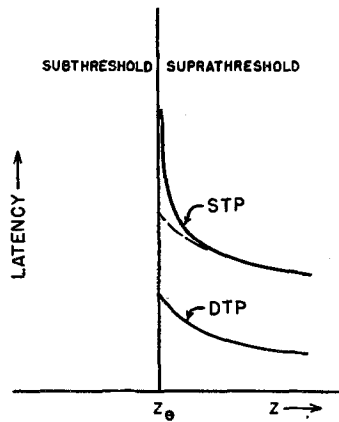


FIGURE 4. Diagram of latency as a function of stimulus intensity for a *DTP* and an *STP*. See text.

by passing through a continuum of intermediate trajectories. It is this topological property which is responsible for the threshold characteristics of the saddle point. As  $z$  is varied through  $Z$  and the initial point  $x^0(z)$  moves along the line " $t = 0$ ," it passes discontinuously from one subclass of hyperbolic trajectories to another subclass which behaves in a qualitatively different manner for increasing  $t$ . Both of these subclasses occupy contiguous 2-dimensional regions of the phase plane and are separated by a single stable trajectory, the separatrix.

The saddle-point threshold phenomenon may be generalized to a phase space of any finite number of dimensions. The following definition is applicable to systems with functions  $f(x)$  which are analytic at a singular point, i.e., can be expanded in a Taylor series about that point. For somewhat more general conditions, see I. Petrowsky (1934).

*Definition II.*

A *singular-point threshold phenomenon* (STP) will be said to exist in an  $N$ -dimensional phase space ( $N \geq 1$ ) if there exists an isolated singular point having one characteristic root positive and all of the others (if any) with negative real parts, and if  $x^0(z)$  is a continuous function which intersects and is not tangent to the  $(N - 1)$ -dimensional surface (the *separatrix*) composed of stable trajectories, for  $z = z_\theta$ .

In two dimensions, the condition on the characteristic roots defines a saddle point. In three dimensions the properties of the singular point can be visualized if we let the trajectories be described by the solutions

$$x_n = a_n e^{\lambda_n t} \quad (n = 1, 2, 3) \quad (6)$$

of the differential equations

$$\frac{dx_n}{dt} = \lambda_n x_n. \quad (7)$$

The  $a_n$ 's are constants of integration and are the coordinates of the initial point. The origin of coordinates is a singular point.

If  $\lambda_1 < \lambda_2 < 0 < \lambda_3$ , then the plane  $x_3 = 0$  (the separatrix) contains the stable solutions and divides the space locally into two regions in both of which the trajectories are hyperbolic, but in which their behavior for increasing  $t$  is qualitatively different. Those trajectories for which  $a_3 < 0$  approach the negative  $x_3$ -axis pointing toward minus infinity on that axis and may be taken to represent the "none" response. Those trajectories for which  $a_3 > 0$  approach the positive  $x_3$ -axis and point toward plus infinity ("all" response). The separatrix separates the "all" from the "none" trajectories. However, if  $\lambda_1 < 0 < \lambda_2 < \lambda_3$ , the hyperbolic trajectories fall into two subclasses which do not differ qualitatively in their behavior for increasing  $t$ , but approach the plane  $x_1 = 0$ , pointing in all possible directions in that plane. In the latter case, therefore, there is no threshold phenomenon.

In general, for an STP to exist in any  $N$ -dimensional phase space, the singular point must have the property that an  $(N - 1)$ -dimensional surface consisting of stable trajectories (the separatrix) forms a local boundary between two  $N$ -dimensional regions both of which consist of hyperbolic trajectories which for large enough  $t$  leave the singular point in two opposite directions. If all the characteristic roots have non-zero real parts, then the above conditions are fulfilled if, and only if, the roots are as specified in Definition II (Petrowsky, 1934; Lefschetz, 1948). Cases in which



some of the roots have zero real parts are more complicated and have to be examined separately.

A second way to revise Definition I is to keep the existence of a maximum latency, but sacrifice the discontinuity between the “all” and the “none” trajectories. Figure 5a shows an example in a phase plane. For all  $t_1$ ,  $\mathbf{x}(\mathbf{x}^0(z); t_1)$  is continuous in  $z$ , but for some values of  $t_1$  it varies very rapidly when  $z$  is near  $z_\theta$ . Figure 5b shows how  $V = F(t_1; z)$  might appear

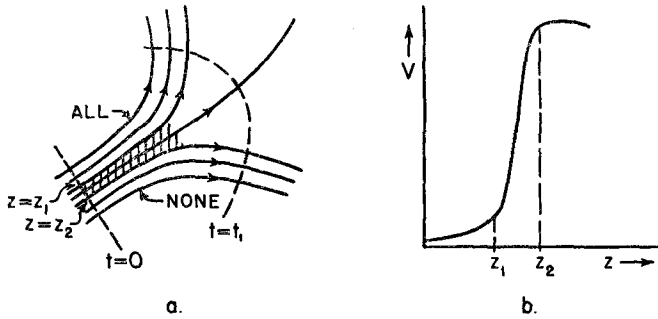


FIGURE 5. *a.* Diagram of a *QTP* in a phase plane. The shape of the trajectory changes continuously as  $z$  is varied. The two-dimensional separatrix is cross-hatched. *b.* Curve analogous to that of Figure 1*b*, but plotted for the case of Figure 5*a*.

as plotted against  $z$ . The discontinuous curve of Figure 1*b* has been replaced by a continuous curve with a very rapid rise near  $z = z_\theta$ . We may describe these properties mathematically as follows:

*Definition III.*

If  $\mathbf{x}^0(z)$  is continuous in  $z$  over some interval  $Z$ , and if there exist a positive time  $t_1$  and two values  $z_1$  and  $z_2$  of  $z$  such that the ratio

$$\frac{|\mathbf{x}[\mathbf{x}^0(z_2); t_1] - \mathbf{x}[\mathbf{x}^0(z_1); t_1]|}{|z_2 - z_1|}$$

is sufficiently large, then a *quasi threshold phenomenon (QTP)* will be said to exist in the phase space.

This definition is necessarily inexact, since the phrase “sufficiently large” is subject to arbitrary interpretation. A *QTP* may therefore grade insensibly into what is for all practical purposes not a threshold phenomenon at all. However, *QTP*’s have been used by several authors, and a criterion for judging a *QTP*, based on statistical considerations, is discussed below.

For the sake of comparison, one may say that the  $(N - 1)$ -dimensional separatrix of the *STP* has been replaced in the *QTP* by a “thin”  $N$ -di-

mensional neighborhood of an  $(N - 1)$ -dimensional surface, as indicated by the cross-hatched region in Figure 5a. The thickness of this neighborhood, i.e., the magnitude of its smallest dimension, determines the sharpness of the *QTP*. The single threshold value  $z_0$  of stimulus may be considered as replaced by the closed interval  $[z_1, z_2]$ .

The three types of threshold phenomenon mentioned above do not exhaust the possibilities. One can also set up a threshold phenomenon with some of the properties of the saddle-point type by using a line or surface consisting of singular points instead of an isolated one. Also, a limit cycle (periodic closed trajectory), to which some trajectories are stable and others unstable, can be substituted for the saddle point. In this case again hyperbolic trajectories can be found with any specified latency, no matter how large, most of which may be spent with the state point oscillating in the neighborhood of the limit cycle.

#### EXAMPLES

Some of the models of excitable surfaces which have been proposed by various authors can now be classified according to the type of threshold phenomenon present. First, however, it will be necessary to define more precisely the conditions of environmental constraint to be imposed on the systems under discussion. As mentioned above, an excitable system is not isolated from its environment, but linked to it by one or more variables, which for a nerve fiber membrane are membrane potential difference and membrane current density. Moreover, the potential difference and current density in general are not constant everywhere on the membrane, but vary from point to point. A nerve membrane may be considered as being made up of a large number of elementary areas of molecular dimensions. Over each such area the current density and potential difference may be considered to have single values, but in different areas they may have different values at the same time. If a region in the neighborhood of a stimulating electrode were to be described mathematically, it would be necessary to have a complete set of variables of state for each elementary area, and the corresponding phase space would have too many dimensions for convenient treatment. Fortunately, the presence of threshold behavior in a membrane does not appear to depend necessarily on the interaction of different elementary areas, as does the conduction of a nerve impulse. Both the giant axon of the squid (Cole, 1949; Marmont, 1949; Hodgkin, Huxley, and Katz, 1949) and the iron wire model of nerve (Bonhoeffer, 1941, 1948) have been stimulated to produce an all-or-none response uniform over the surface—named by A. L. Hodgkin and A. F. Huxley (1952) the “mem-

brane action potential"—during which the membrane current is held uniformly at zero, following an initial current pulse as stimulus.

### 1. *Discontinuous Threshold Phenomena*

The models of nerve of N. Rashevsky (1933, 1948) and A. V. Hill (1936) are incomplete in the sense that they describe the behavior of the system only up until the time that a certain variable of state reaches a threshold value. If the subsequent events were to be described by an extended model, of the type considered in this paper, either the differential equations in these models would have to be changed in order to describe the behavior of the system during the response, or new variables of state would have to be introduced for this purpose. In either case, since there is in these models a maximum time  $t_m$  after stimulation at which time the threshold value can be reached, if it is to be reached at all, there is some time  $t_1 (> t_m)$  for which Definition I would apply.

W. A. H. Rushton's (1938) model of nerve contains in the equivalent circuit of the membrane an e.m.f. which disappears when  $V$  reaches a certain value during the stimulating shock. This makes  $x^0(z)$  discontinuous at  $z$ , and there is a *DTP*.

In the model of F. Offner, A. Weinberg, and G. Young (1940), when the membrane potential  $V$  reaches a critical value  $V_c$ , a resistance in the equivalent circuit of the membrane decreases discontinuously from its resting value to its excited value. This is a *DTP* with  $N = 1$ ;  $x$  is  $V$ ,  $x^0(z)$  is continuous, but  $f(x)$  is discontinuous at  $V = V_c$ .

### 2. *Singular-point Threshold Phenomena*

G. Karreman and H. D. Landahl have described several models of an excitable membrane. In the simplest (Karreman, 1951; Karreman and Landahl, 1952),  $N = 1$ , and the phase space is a line on which there are three singular points. The first in succession is stable and corresponds to the resting state. The second is unstable and is the site of an *STP*. The third corresponds to a stable excited state; no provision is made for recovery from excitation in this model. As the stimulus  $z$  (applied negative potential difference) is increased beyond its threshold value,  $x^0(z)$  passes the unstable singular point. Thereafter the state point passes to the excited state.

In a more complicated model,  $N = 2$ , and the system can be represented on a phase plane with coordinates  $x$  and  $y$  (Karreman and Landahl, 1952, 1953). This model shows different mathematical properties according to the value of the parameter  $r$ , which depends on various physi-

cal properties of the membrane. The singular points, at which  $dx/dt = dy/dt = 0$ , are the points of intersection between two curves called *isoclines*: the vertical isocline is the curve on which  $dx/dt = 0$ ; the horizontal isocline, that on which  $dy/dt = 0$ . The isoclines are shown in all figures with short straight arrows crossing them in a direction which is the same as that of the trajectories crossing them. When  $r = 183$ , there are three singular points (Fig. 6). Singular point *A* corresponds to the

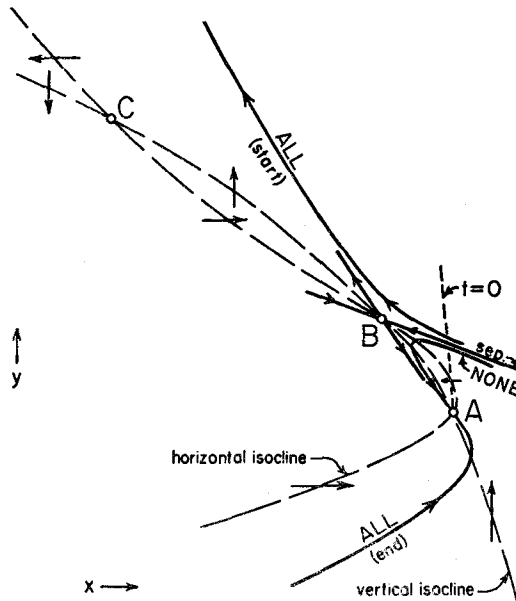


FIGURE 6. *STP* in Karreman and Landahl's membrane model when the parameter  $r = 183$ . (Modified from Karreman and Landahl, 1952, 1953). *A* is the stable resting state, *B* a saddle point, and *C* an unstable singular point. "sep." indicates the separatrix. Typical "ALL" and "NONE" trajectories are shown, the former only at its beginning and end; the omitted central part circles around *C*.

stable resting state. Point *B* is a saddle point at which there is an *STP*, and *C* is unstable. When  $r$  has larger values, the threshold phenomenon changes to a *QTP*, as described below.

Recently M. J. Polissar (in Johnson, Eyring, and Polissar, 1954) has presented a mathematical model of the nerve or muscle membrane in which  $N = 2$ . The variables of state of the system are in his notation  $E$ , the membrane potential, and the *P.D.M.*, or "potential demand of the membrane." The model is based on a phenomenological picture of the membrane in which "it is assumed that the change in the transmembrane

potential  $E$  is the chief factor determining the change in the structure of the membrane. . . . A given transmembrane potential demands a particular state of the membrane. In turn, each instantaneous state of the membrane demands a particular value for the transmembrane potential." This situation is then described more specifically as the tendency of  $E$  and the  $P.D.M.$  to vary in certain directions which depend on the values of both of them. Polissar represents the state of the system at any moment by the position of two "conjugate points" in a plane having  $E$  and the  $P.D.M.$  as coordinates (but not a phase plane). Each of these points is constrained to move only along a corresponding curve in the plane. The position of one point on its curve is determined by the value of  $E$ ; that of the other by the value of the  $P.D.M.$  But if we replace these two points by a single state point which can range over a phase plane with coordinates  $E$  and  $P.D.M.$ , the resulting representation is mathematically equivalent to Polissar's, and allows one to visualize the over-all behavior of the system more easily than does his. The phase plane representation will therefore be used in the following discussion.

Polissar does not explicitly state differential equations corresponding to (2), but gives qualitative rules for the behavior of  $E$  and the  $P.D.M.$  under the condition of zero membrane current. These rules determine the qualitative properties of the trajectories. In Figure 7, the vertical isocline is defined by the condition  $dE/dt = 0$ , and the horizontal isocline by  $[d(P.D.M.)]/dt = 0$ . These isoclines happen to be the same lines as those along which the two conjugate points move in Polissar's original representation. The two isoclines intersect at three singular points  $A$ ,  $B$ , and  $C$ . In the region above the vertical isocline  $dE/dt$  is positive and is negative below it. Above the horizontal isocline  $[d(P.D.M.)]/dt$  is negative and positive below it. The trajectories which have been sketched in Figure 7 show that  $A$  and  $C$  are stable singular points, and  $B$  is a saddle point, at which there is an  $STP$ . Point  $A$  corresponds to the resting state.

Polissar takes our  $z$  to be the duration of a stimulating current pulse of constant intensity, which we may take as ending at zero time. If  $z < z_\theta$ , the initial point will be at a point such as  $D$  and will return to  $A$  along a trajectory such as that labelled "NONE." If  $z > z_\theta$ , the state point will move along a trajectory such as that marked "ALL," going from  $E$  to  $C$ . Point  $C$  represents a state of excitation which is stable—this model does not describe the process of recovery. However, with the phase plane representation it would be possible to modify this model to show recovery by changing  $C$  to an unstable singular point, as in Karreman and Landahl's two-dimensional model mentioned above.

### 3. Quasi Threshold Phenomena

K. F. Bonhoeffer (1948) described the behavior of the iron wire model of the nerve fiber qualitatively in a phase plane ( $N = 2$ ). The coordinates  $x$  and  $y$  are two quantities of which the physical nature is not completely specified;  $x$  is the "degree of activation" and  $y$  is the "refractoriness" of the wire. Bonhoeffer did not state his differential equations explicitly, but

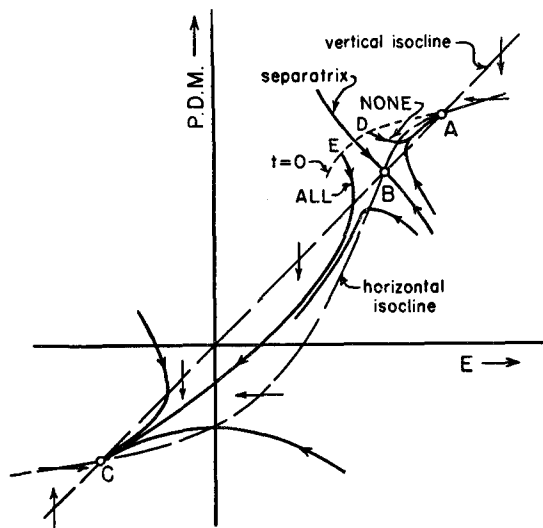


FIGURE 7. STP in Polissar's membrane model. (Modified from Johnson, Eyring, and Polissar, 1954.) See text.

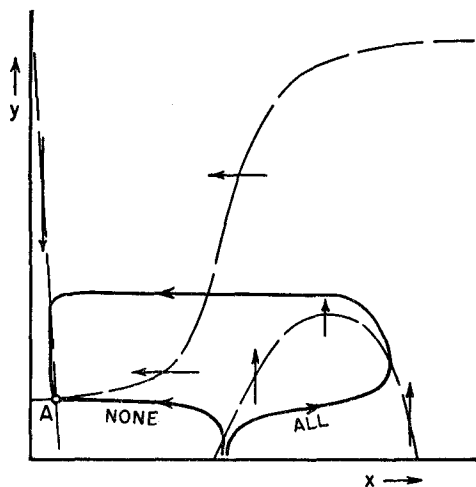


FIGURE 8. QTP in Bonhoeffer's model of the iron wire model of nerve. (Redrawn from Bonhoeffer, 1948.) See text.

represented the isoclines and a few of the trajectories graphically. Figure 8 shows no singular point in the region of divergence of the “all” from the “none” trajectories for this model. Since the trajectories and isoclines are drawn as smooth lines, all functions were presumably intended to be differentiable, and this model may be classified as a *QTP*.

In the model ( $N = 2$ ) of Karreman and Landahl (1952, 1953) discussed above, a *QTP* is obtained when the parameter  $r$  has a value of 190 or greater. The horizontal isocline moves to the right as  $r$  is increased, points

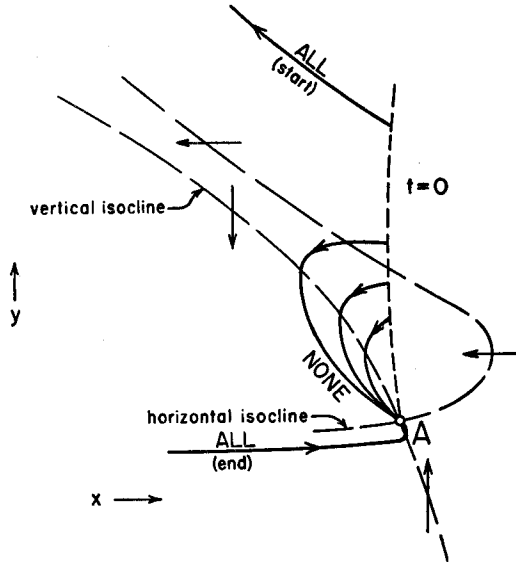


FIGURE 9. *QTP* appearing in Karreman and Landahl’s model when  $r = 200$ . (Redrawn from Karreman and Landahl, 1953.)

$B$  and  $C$  approach each other, coalesce, and disappear leaving  $A$  as the only singular point (Fig. 9).

Hodgkin and Huxley’s (1952) model of the squid giant axon membrane is the most complex yet proposed. It has five variables of state: the membrane current density  $I$ , the membrane potential  $V$ , and three variables  $n$ ,  $m$ , and  $h$ , which determine the potassium and sodium conductances. The equations describing the behavior of these variables are of the following form:

$$I = C_M \frac{dV}{dt} + F_1(n, m, h, V), \tag{8}$$

$$\frac{dn}{dt} = F_2(n, V), \tag{9}$$

$$\frac{dm}{dt} = F_3(m, V), \quad (10)$$

$$\frac{dh}{dt} = F_4(h, V), \quad (11)$$

where  $C_M$  is the membrane capacitance per unit area of membrane and the  $F$ 's are analytic functions. In the case of the membrane action potential, the condition of external electrical constraint during  $t \geq 0$  is  $I = 0$ , the variables of state are reduced to  $V, n, m$ , and  $h$ . Equation (8) then becomes

$$\frac{dV}{dt} = -\frac{1}{C_M} F_1(n, m, h, V). \quad (12)$$

Equations (9) through (12) represent the equations (2) for this model, and  $N = 4$ . The singular points in this four-dimensional phase space can be determined from (9)–(12) by setting

$$\frac{dV}{dt} = \frac{dn}{dt} = \frac{dm}{dt} = \frac{dh}{dt} = 0. \quad (13)$$

There is a line in the five-dimensional space (with coordinates  $I, V, n, m, h$ ) defined by the four equations which result when (13) is substituted into (8)–(11). This line is the locus of all possible singular points that can arise in the five-space as a result of applying any arbitrary external electrical constraint to  $I$  and  $V$ . For the membrane action potential, there will be as many singular points as there are intersections of this locus with the hyperplane  $I = 0$ . These may be found by studying the projections of the locus and of the hyperplane on the  $I$ - $V$  plane. The projection of the hyperplane is simply the line  $I = 0$ . The projection of the locus is described by the following equation,

$$I = F_1(n_\infty, m_\infty, h_\infty, V), \quad (14)$$

which is obtained by substituting (13) into (8). Here  $n_\infty, m_\infty$ , and  $h_\infty$  are the values assumed by  $n, m$ , and  $h$  when (13) is substituted into (9)–(11); they are analytic functions of  $V$  only. The right-hand side of (14) is equal to the sum of the steady-state potassium, sodium, and "leakage" currents ( $I_K, I_{Na}$ , and  $I_l$ ). These currents are plotted as functions of  $V$  in Figure 10. The curve labelled " $I$ " is the projected locus of singular points in the  $I$ - $V$  plane, and intersects the horizontal axis only once, at the origin. This intersection determines the only singular point, which corresponds to the stable resting state. Since there is no saddle point, there is no *STP*. Since all functions are analytic and therefore satisfy the conditions of the Cau-



chy-Lipschitz theorem, there is no *DTP*, and a *QTP* is indicated. If a *QTP* exists here, it should be possible to find a value of stimulus which would produce a response intermediate between "all" and "none" for this model. K. S. Cole (1954; Cole *et al.*, 1955), however, found a value for the threshold stimulus (intensity of a 0.01 msec shock) in this case accurate to one part in sixty thousand, with no intermediate responses. By studying the projections of trajectories in the four-dimensional phase space onto a plane with coordinates  $V$  and  $dV/dt$ , he concluded that there are two non-stable singular points, in addition to the stable singular point mentioned above. Certain of these projected trajectories do behave in such a way as to suggest the presence of a saddle point, but since the method just described indicates the existence of only one singular point (at least as defined in the present paper), the stable one, it would appear that the complete phase velocity vector in the four-dimensional phase space, although it may become very small in a certain region, does not vanish completely. In such a case, it might be possible to interpret a *QTP* as a lower-dimensional "moving saddle point," in a way similar to A. J. Lotka's (1925) interpretation of a quasi-equilibrium state governed by one slowly changing variable as a "moving equilibrium," but this idea will not be pursued further here.

Since the experimentally produced membrane action potential obeys the all-or-none law, it might be thought that a *QTP* would be unsuitable for a model of the membrane. Whether or not this is so will depend considerably on the magnitude of certain statistical variations inherent in the assumed physical nature of the Hodgkin-Huxley model, although they do not appear explicitly in their differential equations. The mathematical formulation of the model could be extended to include these statistical variations in the values of the variables of state by assuming that the state point travels through phase space with a "Brownian motion" superimposed on an average drift velocity given by the phase velocity vector. In most of the phase space, this random motion would be so small compared to that resulting from the phase velocity vector that the former would be negligible in determining the behavior of the system. In the neighborhood of the separatrix of a threshold phenomenon, however, the random motion might be so large as to decide whether a state point tends to follow the "all" or the "none" set of trajectories. In a statistical ensemble of systems originally in the resting state, all of which are given identical stimulus shocks of the same near-threshold intensity, a certain proportion of them may give an action potential and the remainder may not. A similar result has been found experimentally; a nerve fiber may re-

spond to some, but not all of a succession of stimuli, and this is due to variability in the behavior of the fiber rather than in the strength of the stimulus (Blair and Erlanger, 1933).

Random motion of the state point in phase space could produce this result in any of the three types of threshold phenomenon described earlier. It assumes particular importance for the *QTP*, however, since it provides a criterion for judging whether a *QTP* is sufficiently sharp to portray adequately an all-or-none process. If the random motion during and following the stimulus is of an order of magnitude equal to or greater than the thickness of the "thin"  $N$ -dimensional separatrix (mentioned earlier), the *QTP* may be considered satisfactory, since the state point will then very seldom stay within the separatrix long enough to be carried to a region of phase space corresponding to a response intermediate between "all" and "none." Cole's (unpublished) calculations give the figures  $-6.373043$  and  $-6.372943$  mV for the values of  $V$  immediately following brief stimulating pulses which are slightly "suprathreshold" and "subthreshold" respectively. The difference between these two values is  $0.100 \mu\text{V}$ , which may be taken as the difference in stimulus intensities which appears in the denominator of the fraction appearing in Definition III. Time  $t_1$  can be taken to be 7.9 msec, the time of the peak of the action potential following a just suprathreshold stimulus. Then the difference between the values of  $V$  for the "all" and "none" responses, measured at time  $t_1$ , is 98 mV. Therefore the ratio in Definition III will have  $9.8 \times 10^5$  as a lower limit. If it can be shown that fluctuations in  $V$  of the order of magnitude of  $0.100 \mu\text{V}$  can often be expected by chance, then the *QTP* of the Hodgkin-Huxley model is sufficiently sharp for its purpose.

Fluctuations might be expected in any of the variables  $n$ ,  $m$ ,  $h$ , and  $V$ , but only those in  $V$  resulting from a random e.m.f., similar to that which appears across all electrical conductors (Johnson, 1928), will be considered. These fluctuations are of the same nature as those considered at the end-plate of muscle by P. Fatt and B. Katz (1952). The properties of this "noise e.m.f." are independent of the physical nature of the conductor and depend only on the value of the resistance and the temperature. The mean square noise e.m.f. across any linear, passive impedance in the frequency range  $df$  is given by the formula

$$(E^2)_{df} = 4R_f kT df, \quad (15)$$

where  $R_f$  is the real part of the impedance for frequency  $f$ ,  $k$  is Boltzmann's constant, and  $T$  is the absolute temperature (Nyquist, 1928). Hodgkin and Huxley's equivalent circuit for a unit area of the membrane is a capacitance  $C_M$  in parallel with three branches, each consisting of an e.m.f. and

a resistor in series. If  $g$  denotes the total D.C. conductance of this circuit for the resting state, then

$$R_f = \frac{g}{g^2 + 4\pi^2 f^2 C_M^2}. \quad (16)$$

The total root-mean-square noise e.m.f. over the entire frequency range from zero to infinity of a section of membrane of area  $A$  in  $\text{cm}^2$  at  $6.3^\circ \text{C}$  and for  $C_M = 1.0 \mu\text{F}/\text{cm}^2$  is

$$\left( \int_0^\infty (E^2)_f df \right)^{1/2} = \left( \frac{kT}{C_M A} \right)^{1/2} = \frac{0.062 \mu\text{V}}{\sqrt{A}}. \quad (17)$$

The experiments on which Hodgkin and Huxley based their model were done using an area of approximately  $0.110 \text{ cm}^2$  (Hodgkin, Huxley, and Katz, 1952), which gives a root-mean-square noise e.m.f. of  $0.19 \mu\text{V}$ , when substituted into (17). This value includes noise of all frequencies, but noise of too low and too high frequencies may be ineffective in causing random transitions between "all" and "none" trajectories. Since the latency of the Hodgkin-Huxley model just at threshold is about 6 msec (Cole *et al.*, 1955), the most effective frequency range may be estimated as between 10 and 1000 cycles/sec. Integration of (15) between these limits, assuming  $g = 0.639 \text{ mmho}/\text{cm}^2$ , gives a root-mean-square noise e.m.f. of  $0.17 \mu\text{V}$  in the resting state. Moreover, noise in the physical model resulting from sources other than the conducting ions would increase this figure. Since the figure of  $0.17 \mu\text{V}$  is of the same order of magnitude as the value of  $0.100 \mu\text{V}$  calculated by Cole for the difference in  $V$  between an "all" and a "none" trajectory, the *QTP* of the Hodgkin-Huxley model is sufficiently sharp for its purpose.

This discussion has shown that any intermediates between "all" and "none" behavior in the Hodgkin-Huxley model will appear only when the accuracy of specifying the initial conditions is increased beyond the limits of uncertainty which appear when the physical interpretation of the model is considered. Moreover, the possibility remains that just at the threshold of excitation the assumption that  $I = 0$  at each point of the membrane fails in the experimental situation. If a slight inhomogeneity of the state of the membrane or of the potential distribution could cause an excitation to begin locally and spread elsewhere rapidly as a result of current flow between different areas, the assumptions of the above analysis would be false and its conclusions might no longer be applicable.

The experimentally obtained static or steady-state  $I$ - $V$  curve of a membrane forms at least one branch of the projected locus of singular points mentioned above. The experimental data for this curve for the squid axon (circles in Fig. 10) lie along a curve of similar shape to the theoretical

locus, crossing the horizontal axis only once, at the origin. *S*-shaped curves of the type shown in Figure 10 of Hodgkin, Huxley, and Katz (1952), showing the relation between ionic current density and membrane potential measured at a fixed time after shocks of various strengths, do not imply the presence of three singular points, although they cross the horizontal axis ( $I = 0$ ) in three places, since such a curve is not a projection

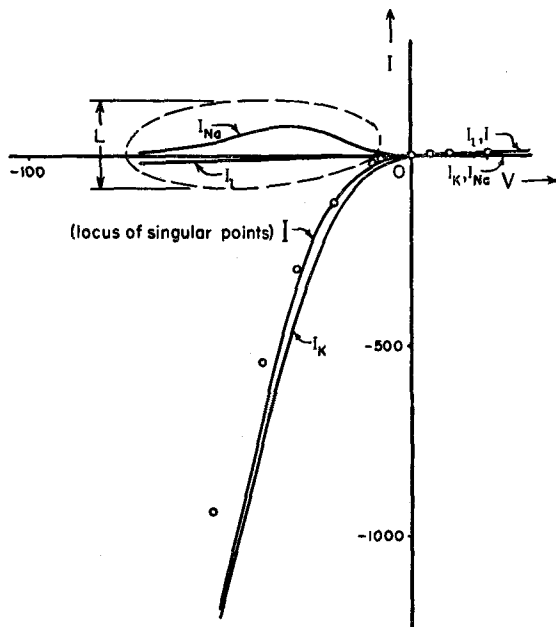


FIGURE 10. Components of membrane current plotted against membrane potential  $V$  in the steady state, for Hodgkin and Huxley's membrane model. Circles are experimental data taken from Figure 13 of Hodgkin, Huxley, and Katz (1952) for the curve " $I$ ," which represents both the steady-state total membrane current as a function of  $V$  and the projection of the locus of singular points onto the  $I$ - $V$  plane. The single intersection of curve " $I$ " with the horizontal axis excludes an *STP*. Curves of the potassium, sodium, and leakage current components of  $I$  are labeled " $I_K$ ," " $I_{Na}$ ," and " $I$ " respectively. For oval, see text.

of a locus of singular points. Therefore when such an *S*-shaped curve is obtained experimentally, it does not mean that the real system can be described by an *STP*, as seems to be implied by Bonhoeffer (1953). It might be possible to modify Hodgkin and Huxley's model to contain an *STP* if an additional branch were added to the locus of singular points, as, for example, the oval sketched as a broken line in Figure 10. In such a model there would be three singular points whenever  $I$  took a constant value within a certain interval  $L$  which includes zero. An *STP* would not be obtained if  $I$  were fixed at any constant value outside of  $L$ .

## DISCUSSION

In the foregoing classification of threshold phenomena, detailed local mathematical properties ("in the small") such as differentiability and the nature of the characteristic roots of a singular point, play a role which may seem exaggerated, in view of the fact that the precision with which a mathematical model of a biological process can be made to agree with experiment is limited by the variability of the data. This objection can be answered by saying that as long as exact mathematical expressions are used in models of biological systems, the properties and limitations of these expressions are worth understanding. But this answer only poses the further question whether the differential equation, a type of description of nature which has been borrowed from physics and chemistry, really is appropriate to describe a biological system whose properties have not yet been traced to physical and chemical mechanisms.

The types of threshold phenomena discussed here differ not only in the detailed properties of their differential equations, but more generally in the disposition of their trajectories in phase space, in particular (1) the division of trajectories into distinct classes such that those in each class can be obtained one from another by a continuous deformation through other members of that class, while the members of two different classes are not so connected; and (2) the existence of boundary regions in phase space where trajectories of different classes meet. These properties ("in the large") are invariant under continuous, one-to-one transformations of the coordinates of phase space and fall within the domain of topology, a branch of mathematics which may be intrinsically better fitted for the preliminary description and classification of biological systems than analysis, which includes differential equations (cf. Minorsky, 1947, Introduction; Rashevsky, 1954). This suggestion is of little practical value at present, since too little is known of the topology of vector fields in many-dimensional spaces, at least to those interested in theoretical biology. Nevertheless, the most logical procedure in the description of a complex biological system might be to characterize the topology of its phase space, then to establish a set of physically identifiable coordinates in the space, and finally to fit differential equations to the trajectories, instead of trying to reach this final goal at one leap.

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## LITERATURE

- Blair, E. and J. Erlanger. 1933. "A Comparison of the Characteristics of Axons through their Individual Electrical Responses." *Am. Jour. Physiol.*, **106**, 524-64.
- Bonhoeffer, K. F. 1941. "Über die Aktivierung von Passiven Eisen in Salpetersäure." *Ztschr. für Elektrochemie*, **47**, 147-50.
- . 1948. "Activation of Passive Iron as a Model for the Excitation of Nerve." *Jour. Gen. Physiol.*, **32**, 69-91.
- . 1953. "Modelle der Nervenregung." *Die Naturwissenschaften*, **40**, 301-11.
- Cole, K. S. 1949. "Dynamic Electrical Characteristics of the Squid Axon Membrane." *Arch. Sci. Physiol.*, **3**, 253-58.
- . 1954. "Membrane Excitation of the Hodgkin-Huxley Axon." *Fed. Proc.*, **13**, 28.
- Cole, K. S., H. A. Antosiewicz, and P. Rabinowitz. 1955. "Automatic Computation of Nerve Excitation." *Jour. Indust. Appl. Math.* In press.
- Fatt, P. and B. Katz. 1952. "Spontaneous Subthreshold Activity at Motor Nerve Endings." *Jour. Physiol.*, **117**, 109-28.
- Hill, A. V. 1936. "Excitation and Accommodation in Nerve." *Proc. Roy. Soc. Lond., B.*, **119**, 305-55.
- Hodgkin, A. L. 1952. "Measurement of Current-Voltage Relations in the Membrane of the Giant Axon of *Loligo*." *Jour. Physiol.*, **116**, 424-48.
- and A. F. Huxley. 1952. "A Quantitative Description of Membrane Current and Its Application to Conduction and Excitation in Nerve." *Jour. Physiol.*, **117**, 500-544.
- , ———, and B. Katz. 1949. "Ionic Currents Underlying Activity in the Giant Axon of the Squid." *Arch. Sci. Physiol.*, **3**, 129-50.
- Johnson, F. H., H. Eyring, and M. J. Polissar. 1954. *The Kinetic Basis of Molecular Biology*. New York: J. Wiley and Sons, Inc.
- Johnson, J. B. 1928. "Thermal Agitation of Electricity in Conductors." *Phys. Rev.*, **32**, 97-109.
- Karreman, G. 1951. "Contributions to the Mathematical Biology of Excitation with Particular Emphasis on Changes in Membrane Permeability and on Threshold Phenomena." *Bull. Math. Biophysics*, **13**, 189-243.
- and H. D. Landahl. 1952. "On the Mathematical Biology of Excitation Phenomena." *Cold Spring Harbor Symp. Quant. Biol.*, **17**, 293-97.
- and ———. 1953. "On Spontaneous Discharges Obtained from a Physicochemical Model of Excitation." *Bull. Math. Biophysics*, **15**, 83-91.
- Lefschetz, S. 1948. *Lectures on Differential Equations*. Princeton: Princeton University Press.
- Lotka, A. J. 1925. *Elements of Physical Biology*. Baltimore: Williams and Wilkins Co.
- Marmont, G. 1949. "Studies on the Axon Membrane. I. A New Method." *Jour. Cell. Comp. Physiol.*, **34**, 351-82.
- Minorsky, N. 1947. *Introduction to Non-linear Mechanics*. Ann Arbor: J. W. Edwards.
- Nyquist, H. 1928. "Thermal Agitation of Electrical Charge in Conductors." *Phys. Rev.*, **32**, 110-13.
- Offner, F., A. Weinberg, and G. Young. 1940. "Nerve Conduction Theory: Some Mathematical Consequences of Bernstein's Model." *Bull. Math. Biophysics*, **2**, 89-103.
- Pecher, C. 1939. "La Fluctuation d'Excitabilité de la Fibre Nerveuse." *Arch. Internat. Physiol.*, **49**, 129-52.
- Petrowsky, I. 1934. "Über das Verhalten der Integralkurven eines Systems gewöhnlicher Differentialgleichungen in der Nähe eines singulären Punktes." *Recueil Math.*, **41**, 107-56.
- Rashevsky, N. 1933. "Outline of a Physico-mathematical Theory of Excitation and Inhibition." *Protoplasma*, **20**, 42-56.
- . 1948. *Mathematical Biophysics*. Rev. Ed. Chicago: University of Chicago Press.
- . 1954. "Topology and Life: In Search of General Mathematical Principles in Biology and Sociology." *Bull. Math. Biophysics*, **16**, 317-48.
- Rushton, W. A. H. 1938. "Initiation of the Propagated Disturbance." *Proc. Roy. Soc. Lond., B.*, **124**, 210-43.