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THE PHYSICAL BASIS OF NERVE IMPULSE CONDUCTION

THE IRREVERSIBLE THERMODYNAMIC ANALYSIS OF THE ACTIVE STATE

P. P. SCHMIDT

Department of Chemistry, Oakland University, Rochester, Mich. 48063 (U.S.A.)

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SUMMARY

This communication reports the thermodynamic analysis of the active state in nonmyelinated axons; it is the first step in the development of a theory of the physical basis of nerve impulse transport. The thermodynamic analysis enables one to make proper identification of material and thermal diffusion coefficients and conductivities associated with the impulse transport. Future additions to the details of the theory will involve consideration of molecular models of the axon active state. The complete macroscopic thermodynamic and microscopic statistical mechanical analyses will provide the links between the model representations and the measured quantities, *e.g.* conductivities and action potentials.

This paper is divided into two parts. Part I is an introduction to the representation of the nerve axon used here and a general discussion of the results of the analysis of the active state obtained rigorously in Part II. The analysis contained in Part II involves an examination of the phenomenological transport equations for the coupled material (ionic) and thermal diffusion problems. By means of suitable transformations of the transport equations a correspondence with the theory of thermal explosions results. This correspondence therefore allows a detailed examination of the processes of impulse initiation and propagation.

The thermodynamic analysis is macroscopic and necessarily phenomenological. Nevertheless, in spite of the macroscopic viewpoint it does enable one to make some predictions of a microscopic nature. In particular, these predictions concern the mechanism of synaptic conduction, the nature of impulse initiation at sensory receptors, and very importantly, the nature of allowable microscopic models of the impulse transport in the axon membrane. These points are discussed in the text of the paper.

PART I

INTRODUCTION

A rigorous, physically acceptable explanation of the nerve impulse transport problem has not yet appeared. Past published work has shown that a number of

physical events are associated with the impulse transport (one example is the ion transport across the axon membrane in the active state[1-5]). However, a clear account of the roles played by all the physically observed processes is needed. The purpose of this paper is to report the results of an irreversible thermodynamic analysis of the phenomena associated with the nerve axon in its active state. The goal of this research is the development of the understanding of the physical basis of the phenomenon of impulse transport. The thermodynamic analysis reported here provides a model-independent general description of the process. Future communications will contain reports of detailed nonequilibrium statistical mechanical analyses of model microscopic representations of the axon system. These analyses will provide the transport coefficients identified in this paper. The statistical mechanical analyses are based on the assumption of specific molecular models. The projected statistical mechanical treatment of the phenomenon of impulse transport will provide the ultimate microscopic, molecular basis for a physical interpretation of the process.

Although the irreversible thermodynamic analysis reported here is general and independent of model, it nevertheless does allow one to make a number of molecular scale interpretations of the phenomenon. This thermodynamic analysis places realistic limitations on the types of molecular processes which may be identified as rate-controlling. In particular, a number of previously postulated[6,7], complicated physical steps are ruled out on consideration of the time scales involved. The thermodynamic analysis also immediately suggests the mechanism of synaptic conduction. The mechanism is, in fact, dictated by the necessity of satisfying the general conditions for impulse initiation imposed by the thermodynamic analysis. The details of impulse initiation and synaptic conduction, and also synaptic inhibition, appear later in the text. In considering the general utility of this type of approach one can see that the greatest benefits to be won from both the thermodynamic and statistical mechanical analyses are the predictions about control of the nervous process, both physical and chemical, and the elucidation of the transport process itself. Part of the aim of this research is directed towards predicting means of control. Most of the initial effort in this and subsequent papers, however, is and will continue to be concerned with the theoretical characterization of the process.

In attempting to understand the nerve impulse conduction process it is essential to bear in mind the implications of the existing experimental results. The most significant of these is the observation that Na^+ diffuse into the axon and K^+ out at an accelerated rate during the passage of an impulse (also called the spike potential[8]) along the axon[1-5]. I recently suggested in two published papers[9,10] that the passage of this impulse is aided by the energy released during the ionic diffusions across the membrane. The diffusions themselves do not account for the mechanism of impulse propagation. Changes in the electrochemical potential are experimentally measured. These changes depend on the ionic diffusions through the dependence of the ionic concentrations on the diffusion processes. The diffusion processes occur across the axon membrane. The impulse travels along the membrane. Although the diffusion and impulse transport are inter-dependent, knowledge of the diffusion processes alone is insufficient to explain the molecular nature of the impulse propagation. No completely physically acceptable molecular explanation of all aspects of the impulse conduction has yet been offered. The goal of this research, starting with this report, is to attempt to provide a physically sound theory to explain the phenomenon.

THEORETICAL BACKGROUND

In the last thirty years significant electrophysiological research has advanced the understanding of the physical events associated with the conduction of the nerve impulse, or message. The important work of HODGKIN AND HUXLEY[1,3–5], and HODGKIN, HUXLEY AND KATZ[2] in the early 1950's unequivocally demonstrated the essential role played by ionic conduction across the axon membrane in the course of the passage of an impulse. Employing their accumulated experimental data HODGKIN AND HUXLEY were able to construct circuit analog, phenomenological, *i.e.* experimental, differential equations which when solved gave the time-dependence of the membrane currents and potentials. The agreement between the solutions to these equations and the experimental results is good suggesting that the equations were well chosen. Inherent in these phenomenological equations as they stand, however, is an inability to say much about the molecular processes which govern the observed events. HODGKIN AND HUXLEY[1], and HUXLEY[11] admitted this at the time, and this deficiency remains today. There is, therefore, a real need to examine the axon system for the purpose of understanding the nervous system on the molecular level. Considerations at this level involve model representations which must be founded on and reveal the importance of certain significant governing aspects of the conduction process in the axon. As indicated, the thermodynamic analysis provides some help in constructing molecular model systems to represent the excited, active impulse conducting state. More important, however, is the fact that the thermodynamic analysis provides the proper and rigorous objectives, *i.e.* it provides the correct transport coefficients to be obtained from any statistical mechanical analysis of chosen model systems. No previous work has employed a complete irreversible thermodynamic analysis of the active state*. A complete analysis includes the consideration of energy transport as well as matter transport. Such an analysis is reported in detail in Part II. The remaining sections of this Part are devoted to a discussion of the considerations which necessitate this approach, and to the discussion of the application of the thermodynamic conclusions to a number of problems connected with the impulse transport, namely, to synaptic conduction, synaptic inhibition, and several aspects of the modes of initiation of the impulse at sensory receptors.

PHYSICAL BASIS OF THE THEORY

In order to get a physical perspective for the general discussion of the impulse conduction which follows in the next section, consider the following representative example, the squid giant axon. For this case the impulse velocity is of the order of

* TASAKI[12] and others, most notably KIRKWOOD[13], have made fairly extensive analyses of the material (in particular, ionic) transport equations which apply to the active state. They employed an isothermal constraint to the general transport equations which eliminates the possibility of directly analysing the system to find the instabilities characteristic of the active, explosion-like state. However, they were able to reach conclusions about the nature of the transport process which are the same as those presented here. These conclusions, incidentally, follow automatically from the complete material and heat transport equations; all this is shown in Part II.

One point worth noting at this juncture is the fact that if the membrane system has finite width, the isothermal constraint within the membrane is not valid in nonstationary states. However, an overall isothermal constraint can be applied with respect to the whole system of the axon *plus* its surroundings.

20 m/sec. It is instructive to translate this value to a molecular scale. Arbitrarily divide the axon into 10-Å segments with the understanding that the message transfers from site to site, the sites separated by 10 Å. The characteristic time it takes the message (*i.e.* the propagating disturbance) to pass from one site to the next is easily found to be of the order of $5 \cdot 10^{-11}$ sec. For diffusion in liquids under normal conditions the characteristic diffusion time is $1 \cdot 10^{-9}$ sec (ref. 14). Furthermore, under normal conditions very fast reactions in solution are diffusion controlled and $1 \cdot 10^{9}$ sec^{-1} is about the magnitude of the maximum measured rate constant when measured with the aid of normal experimental techniques. Note, however, that the nerve impulse conduction process involves diffusion of ions through the membrane which, unlike a true liquid, is a semisolid, plastic substance. Ionic diffusion under normal conditions in the membrane material is much slower than in solution. The values for the nerve impulse lifetime cited above therefore indicate an explosion or combustion type process. (Note, even increasing or decreasing the site-to-site separation by an order of magnitude does not materially alter the above conclusion.) These numerical considerations immediately render suspect any multistep chemical process governing the site-to-site rate of ionic diffusion through the membrane in the active state. Chemical reactions possess finite rates, and even fast reactions are diffusion controlled (diffusion is the slow, rate-determining step). In the active state the coupling of ionic diffusion to other reaction and diffusion processes is not the most efficient method for overall ionic diffusion activation. Such coupled reaction processes do not seem likely. (Coupled reactions, of course, dominate the resting state active transport, Na^+ pump process.) In fact, schemes such as described by WILSON AND NACHMANSOHN[6] to transport ions through the membrane in the active state do not agree with the physical model of diffusion. In general any model of the axon which proports to be molecular should at least tacitly account for numbers with the above magnitudes. Certain discussions of the transport process have ignored this (*e.g.* WEI's theory[7]).

MODEL OF THE AXON MEMBRANE AND MECHANISM OF IMPULSE TRANSPORT

In two recent papers[9,10] I proposed a model for the mechanism of message transport in the axon in the active state. The basic feature of the model was the assumption that an externally introduced charge distribution interacts with the energy-rich ionic concentration gradients inducing ionic diffusions in the direction of the equilibrium state. By coupling the energy released during the ionic diffusion with the mechanism of message transport (defined as the propagating depolarization disturbance) the transport is accelerated. Under these special conditions the diffusion coupled to the message charge transport reaches an explosive limit and the message travels near sonic velocity without attenuation. As the actual velocities reached are subsonic, by definition the impulse does not travel as a detonation wave. It travels instead as a combustion wave.

The reported model[9,10] suggested that the externally introduced charge disturbance, or message charge, was either an electron or some other mobile charged species, *e.g.* a proton. It further suggested that within the axoplasm, very near the inner surface of the membrane, there was a charge transfer network. The injected (electronic) charge migrates along the axon by a site hopping, small polaron[15,35], charge transfer mechanism. However, the charge transfer rate is accelerated by coupling to

the energy releasing ionic diffusions which take place across the membrane. The physical reason for using the electron transfer as the message carrier was the intrinsically very fast fundamental transfer time for the electron migration between sites. This meant that the electron transfer mechanics did not necessarily govern the message propagation rate. The case where the electron transfer dynamics enter was reported in the two papers (*cf.* refs. 9, 10). In the explosion limit the message transfer rate is governed by the rates of ionic diffusion through the axon membrane.

In the more general analysis, which I report here, the same general features described above have been used. Specific aspects of the model have been reconstructed by replacing the electronic message charges and charge transfer network with a more reasonable and general propagating charge disturbance. In particular, charge density fluctuations in the dielectric medium (*i.e.* the bulk of the membrane) account for the migrating depolarization which triggers the ionic diffusions. These charge density fluctuations are intimately connected with the process of heat conduction in dielectric substances.

The axon possesses two living states: the resting and the active, excited states, neither of which is an equilibrium state. The resting state is definitely a nonequilibrium steady state (I. TASAKI and co-workers[16, 36]). Across the membrane there is a measurable electrochemical potential associated with an observed ionic concentration difference on either side of the membrane. Within the membrane, although never directly measured, there is a potential gradient. Since a generalized potential (affinity) accompanies the concentration difference, there is a non-zero gradient which leads to a net force on the ions. Thus, there is a flux of Na^+ into and K^+ out of the axon. Yet, the axon preserves the observed steady state by some metabolic means. It accomplishes this with the use of energy rich substances to "pump" the ions against the concentration gradients. The rates of ionic pumping against the gradients equal the rates of diffusion into areas of lower concentration, thus a steady state prevails. Clearly, such a situation constitutes an energy rich state. Any net ionic diffusion induced by an externally applied force temporarily destroys the steady state.

In contrast to the resting state, the active state of the axon is one in which an impulse propagates without attenuation. The impulse propagation uses the accelerated message transfer rate. The most notable characteristic of the active state is its explosion–combustion nature. The energy released locally by the ionic diffusions into the axoplasm acts in the same way as any exothermic chemical reaction in a combustion wave.

In terms of the description of the axon membrane system so far given any condition less than the explosion limit is an aspect of the resting state. The active state, then, exists only in the explosion limit.

In order further to characterize the axon membrane in the active state consider the following experimental situation. By the appropriate means the polarization across the axon membrane is reversed, *e.g.* by electrical means through an externally applied potential difference; experimentally the axoplasm is rendered negative with respect to the external ionic environment. Under these conditions, which initially apply to a very local portion of the axon, Na^+ diffuse into the axon and K^+ ions diffuse out. Because the diffusions take place from the nonequilibrium steady states, the process releases energy as local heating. This acts through the Arrhenius factor $\exp(-E_a/kT)$ (E_a is the diffusion activation energy including the effect of any

applied external potential) to account for the marked increase in the neighboring ionic diffusion rates. These increased rates in turn increase the message propagation rate because more energy is released at a faster rate. The message is the migrating energy wave. As the energy disturbance moves along the axon it triggers the catastrophic ionic diffusions across the membrane in the direction of the remaining concentration gradients. The energy thus released ensures the continued propagation of the originally induced charge disturbance. This, however, is strictly true only under the conditions of an explosion. In any other situation there is insufficient energy released from the ionic nonequilibrium steady state to counter the resistive effects of the intrinsic damping mechanisms and thermal conduction away from the diffusion site.

It might appear that at this point some consideration should be given to the roles played by other ions, especially divalent cations, such as Ca^{2+}, and anions, notably Cl^-. However, important as these species are (in particular Ca^{2+} without which the excited state is not attained) there is no peremptory reason to give them direct attention as their action seems to be associated specifically with salt linkages between charged groups attached to the lipoprotein structures which constitute the membrane. Attainment of the excited state appears (*cf.* especially TASAKI[12], pp. 112–120) to depend at least in part on the dissolution of the divalent cationic salt linkages which is followed by the postulated[12] concomitant rise in univalent cationic permeability. Divalent cations, and the anions, Cl^-, do not contribute significantly to the gross number of ions crossing the membrane in the excited state. The thermodynamic analysis requires only the fluxes and associated forces. The divalent cations and the anions make their existences known and felt through their effects on the univalent ionic diffusion coefficients.

One may see from the above discussion that on the basis of relatively few assumptions about the nature of the nerve axon system, and on the basis of the consideration of only the most important experimental observations (in particular, those connected with the ionic diffusions) a sound, physically acceptable understanding of the general process of impulse transport ensues. Most importantly, the analysis is independent of any restrictive assumptions which would be made on the basis of consideration of molecular models.

IMPULSE INITIATION, SYNAPTIC CONDUCTION, AND SYNAPTIC INHIBITION

The picture of the propagating impulse is that of a migrating energy pulse, or disturbance. Clearly, the initiation of the impulse at the synapse or sensory ending must involve some similar process. The explanation of synaptic conduction that immediately follows, and indeed is required by the analysis of the conduction mechanism, depends on the generation of electrochemical potential disturbances and heat in definite regions in the membrane at a particular synapse. Suppose that an impulse has travelled the length of one complete axon and has reached the region near the synapse. Since the message is an energy wave, it is capable of activating the release of the substance acetylcholine, an ester, from the end-plate of the axon. An important structural feature of acetylcholine is its quaternary amine group which is highly ionized and very strongly attracted to ionic attachment sites on the efferent axon membrane within the synapse. These sites, it is assumed, are sufficiently closely spaced that a definite critical number of acetylcholine molecules accumulate. In the regions

surrounding these sites abundant concentrations of the acetylcholine esterase catalyse the observed rapid, exothermic de-esterification reaction. The energy evolved in this process together with the acetate ions released are sufficient to "ignite" the combustion-like, propagating nerve message impulse. The action of the heat released is obvious, it increases the ionic diffusional activity. The action of the released acetate ion is more interesting. The acetate can diffuse across the membrane, alter the ionic composition on the axoplasm side and, therefore, lead to the imposition of a new potential on the system (G. A. RECHNITZ, personal communication, and ref. 17). In the presence of this new electrochemical potential the response of the axon system is ionic diffusion. Provided the ionic diffusions together with the heat released constitute a substantial disturbance, the axon will then pass from the stationary resting state to the active, excited state. This is the explanation of synaptic conduction. It is a combined diffusion and chemical reaction process. The chemical reaction, the de-esterification reaction, takes place only at definite sites on the membrane.

Synaptic inhibition also is easily explained. Assume basically the same model as for excitation. For the case of inhibition, however, there are some select synapses which possess too few acetylcholine attachment sites. Thus, insufficient acetylcholine is de-esterified by the esterase at one time to yield the requisite quantity of energy and acetate ion to initiate the travelling message. However, there is sufficient activation of ionic diffusion across the membrane to force the axon system to "recover" by a combination of normal diffusion and active transport which together remove the accumulated ions at the axon membrane surfaces both in the axoplasm side and on the outside of the axon.

Very clearly, any physical or chemical disturbance which transfers additional energy to the nonequilibrium axon resting state is capable of initiating the action potential if sufficient ionic diffusions take place. The synapse seems to accomplish its conduction by a combination of physical diffusion of acetylcholine, an exothermic chemical reaction, and diffusion of acetate across the axon membrane which disrupts the potential profiles. Sensory nerve endings can certainly initiate impulses by either physical or chemical means. Pressure and temperature sensors would seem to fit into a catagory of physical initiators. Those connected with taste, smell, and sight are probably more chemical. Visual sensors, however, like the synaptic conductors, probably initiate impulses by a combination of physical and chemical steps: *e.g.* the absorption of light to promote the *cis, trans* inversion in the visual pigment followed by some more obviously chemical interaction.

The utility of this approach to the questions of impulse initiation is evident. Any biological structural subsystem which initiates or inhibits impulse transport in the axon must involve some physical and/or chemical exothermic process or combination of processes. It may also involve the production of charged, diffusable species which alter the potential profiles. With this in mind the search for these specific processes, *e.g.* all the steps connected with synaptic conduction, should be more orderly. It seems, moreover, that many of the answers to questions yet unanswered, as for example, the question concerning the exact nature of the synaptic conduction mechanism, may be more readily found with less conventional techniques. The focus of the experimental work, I believe, should be on exothermic activating possibilities of any potential process. This will involve a certain amount of thermochemical investigation.

PART II

INTRODUCTION

In 1954 KIRKWOOD[13] reported an initial, formal, irreversible thermodynamic analysis of the ion transport phenomenon through biological membranes. Since then there has been considerably more effort applied to understand ion transport processes in general in ion exchange membranes (see for example, refs. 18–20). KIRKWOOD's[13] analysis, however, allowed a number of conclusions about the message transport process in the axon. In particular, he noted that the axon membrane is in a metastable state which can undergo spontaneous phase transitions or chemical reactions in such a manner as to allow for a propagating explosive change in the membrane permeabilities. This is in agreement with the conclusions reached in my analysis of the phenomenon.

The purpose of this Part is to present the irreversible thermodynamics of the membrane process for the membrane only in the active state. The analysis reduces to the form necessary for the study of combustion waves and material diffusion aided by thermal effects. It therefore provides a firm foundation, independent of model, for the suggestions made in Part I.

The formulation of the problem requires a clear statement of the initiation and propagation process. In the resting state the axon is said to be polarized. Message transport begins with the depolarization of the axon membrane by any of a large number of means. This depolarization has a dual nature. First, it presents to the ionic species an additional electric or electrochemical force to induce diffusion into the concentration gradients. Second, it amounts to a local heat source. That is, the depolarization amounts to a disturbance the effect of which tends to dissipate thermally. This disturbance first induces ionic diffusions which take place from the nonequilibrium steady state. The energy released then propagates along the axon. This propagating energy further activates neighbor diffusions and the process is self-sustaining.

Characteristic of the propagation is transverse ionic motion, and transverse and longitudinal heat flux. The longitudinal heat-energy flux is the essence of the message transport. At the end of the axon it initiates chemical processes involved in, for example, synaptic conduction, etc. The transverse heat flux is that normally attendant any thermodynamic system in contact with a reservoir. The ionic motions supply enough energy to the general energy transport process. Uniquely, though, it is only the ionic motions of the system which are experimentally observed in the active state. In particular, only the change in the membrane potential is observed. This is the action potential[1]. Thus, with the axon active state one is confronted with the problem of the distinction between measurables and events. Events specifically correspond to the working processes, the energy transport along the axon. This clearly is the important primary process. Ion transport is ancillary to this for the reasons noted. However, ion transport (diffusion) is the observed process, and therefore, one must infer the different primary event from the changes in the variables followed.

IRREVERSIBLE THERMODYNAMICS

Material flux equations

For reference purposes the membrane has the coordinate system shown in Fig. 1. For these considerations only the Cartesian coordinate system is needed. Cylindrical

symmetry is ignored as the membrane thickness compared to the axon radius is relatively small. This is especially so in the case of the squid giant axon.

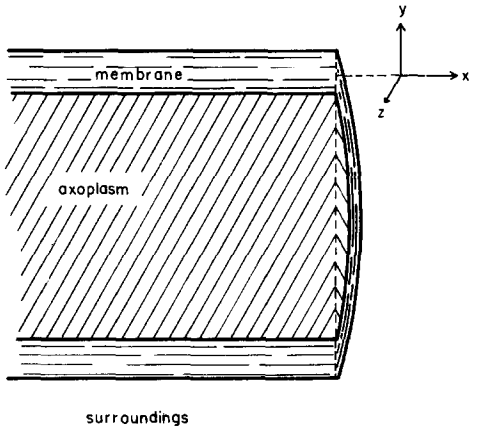

Fig. 1. The reference coordinate system for the axon.

The irreversible thermodynamic transport equations now follow.

Consider the ionic flux j_i for the i-th ionic species and the heat fluxes q_x and q_y in the longitudinal and transverse directions respectively. There is also a q_z which, however, is unimportant compared to the others. It corresponds to the heat conduction around the membrane and does not contribute as much to the message transport as heat conduction along and out of the system. In any case its inclusion, if needed, is easily accomplished. The required equations for the fluxes are

$$\begin{aligned} j_i &= -\sum_k L_{ik} \frac{\partial \bar{\mu}_k}{\partial y} - L_{iT}^{xx} \frac{\partial \ln T}{\partial x} - L_{iT}^{yy} \frac{\partial \ln T}{\partial y} \\ q_x &= -\sum_k L_{Tk}^{xx} \frac{\partial \bar{\mu}_k}{\partial y} - L_{TT}^{xx} \frac{\partial \ln T}{\partial x} - L_{TT}^{xy} \frac{\partial \ln T}{\partial y} \\ q_y &= -\sum_k L_{Tk}^{yy} \frac{\partial \bar{\mu}_k}{\partial y} - L_{TT}^{yx} \frac{\partial \ln T}{\partial x} - L_{TT}^{yy} \frac{\partial \ln T}{\partial y} \end{aligned} \tag{1}$$

$\bar{\mu}_i$ is the total chemical potential of the species i. For charged particles

$$\bar{\mu}_i = \mu_i + z_i F \phi \tag{2}$$

which when used in the first terms in Eqn. 1 leads to the usual Nernst-Planck diffusion equations. μ_i is the purely chemical potential, z_i is the charge on i, F the Faraday constant and ϕ the electric potential. The coefficients L_{ab} satisfy the Onsager reciprocal relations[21]

$$L_{ab} = L_{ba}; \tag{3}$$

specifically,

$$\begin{aligned} &L_{iT}^{xx} = L_{Ti}^{xx}, \; L_{iT}^{yy} = L_{Ti}^{yy}, \\ &L_{TT}^{xy} = L_{TT}^{yx}, \; L_{ik} = L_{ki} \text{ (for } x \text{ or } y) \end{aligned} \tag{4}$$

The validity of the reciprocal relations in describing the system in the excited state is assured by the following observation: the resting state, though not an equilibrium state, is a steady state which behaves as an equilibrium state, *e.g.* the Nernst law applies. When stimulated the system moves from the resting state to the excited state. For a time, during part of this transition, the system is amenable to analysis employing the linear transport laws. The point at which linearity breaks down for heat conduction marks the explosion limit (*cf.* the section on the *Attainment of the active state* post). The analysis of the active state is concerned with the determination of this point, and, thus, for the reasons noted the validity and applicability of the Onsager relations is guaranteed. The validity of the Onsager relations in the analysis also depends on the proviso that the analysis be restricted to the region defined by and contained within the membrane surface boundaries. The complete quantitative analysis of the material (ionic) transport problem requires consideration of material transport in the surroundings and the axoplasm together with the transport through the membrane. Such an analysis using the results reported in this paper will be reported shortly.

The binary, diagonal diffusion coefficients D_{ii} are related to the L_{ii} by[13]

$$D_{ii} = \frac{RT}{c_i} L_{ii} \left[1 + \left[\frac{\partial \ln f_i}{\partial \ln c_i} \right]_{T,p} \right] \tag{5}$$

where f_i is the activity coefficient of the i-th particle and c_i is the concentration. The L_{ik}, on the other hand, are the co-diffusion coefficients which arise through interionic and intermolecular interactions which couple ionic motions. Thus, the diffusion of one ionic species influences the motions of others. If the average interspecies intermolecular forces are attractive, the L_{ik} are positive and coupled species diffuse in the same direction. In particular, in connection with the Na^+ diffusion into and the K^+ diffusion out of the axon in the active state the $L_{Na^+K^+} = L_{K^+Na^+}$ are reasonably assumed negative. HODGKIN AND HUXLEY[1] assumed in their analysis of the active state that the ionic species diffusions were uncoupled. In the thermodynamic analysis this is equivalent to $L_{Na^+K^+} = L_{K^+Na^+} = 0$. Lack of coupling, however, is not necessarily observed in the excited state. HODGKIN[22] proposed that at peak excitation the Na^+ concentrations are approximately given by the Nernst law distribution. On the assumption of the independence of the K^+ and Na^+ currents, the K^+ distribution does not obey such a distribution. TASAKI[23], however, has already noted that this assumption is not consistent with the observed increased interdiffusion in the active state. There is no sound physicochemical reason to suspect that in the excited state any particular ionic concentration should obey a Nernstian equilibrium (and steady state) ionic distribution law. In any case, account of any coupling which exists is easily taken in the general irreversible thermodynamic analysis. Assume, therefore, that the $L_{Na^+K^+} \neq 0$. The ensuing equations are completely general and the case for which the $L_{Na^+K^+}$ vanish automatically is included.

The coefficients $L^{xx}_{TNa^+}$, *etc.*, are connected with thermal diffusion effects[21]. The coefficients L^{xy}_{TT} indicate a coupling of the pure thermal (energy) transport processes in the various directions. These coefficients are important for the active message transport process as they effectively constitute attenuation factors. The message is the disturbance propagating in the x-direction. Any heat diffusion in the positive (outward) y-direction is energy lost to the surroundings.

KIRKWOOD's[13] analysis of the set of Eqns. 1 was simplified by the assumption that the system is and remains isothermal, *viz.*

$$\frac{\partial \ln T}{\partial x} = \frac{\partial \ln T}{\partial y} = \frac{\partial \ln T}{\partial z} = 0$$

In making this assumption KIRKWOOD, when confronted with the necessity of explaining the dramatic change in ionic membrane permittivities in the active state, relied on qualitative statements; in particular, these statements are contained in ref. 13. The problem of the ionic diffusions in the active state is made quantitative and resolved in a later section by retaining the temperature-dependent terms.

For simplicity consider only the diffusion of two ionic species, namely, Na^+ and K^+. Others pass through the membrane in the active state, but their fluxes are minimal and their influences are not so great (their presences, like the presence of Ca^{2+}, generally influence the magnitudes of the diffusing ion diffusion coefficients). The Eqns. 1 are now

$$\begin{aligned}
j_{Na^+} &= -L_{Na^+Na^+}\frac{\partial \bar{\mu}_{Na^+}}{\partial y} - L_{Na^+K^+}\frac{\partial \bar{\mu}_{K^+}}{\partial y} - L^{xx}_{Na^+T}\frac{\partial \ln T}{\partial x} - L^{yy}_{Na^+T}\frac{\partial \ln T}{\partial y} \\
j_{K^+} &= -L_{K^+Na^+}\frac{\partial \bar{\mu}_{Na^+}}{\partial y} - L_{K^+K^+}\frac{\partial \bar{\mu}_{K^+}}{\partial y} - L^{xx}_{K^+T}\frac{\partial \ln T}{\partial x} - L^{yy}_{K^+T}\frac{\partial \ln T}{\partial y} \\
q_x &= -L^{xx}_{TNa^+}\frac{\partial \bar{\mu}_{Na^+}}{\partial y} - L^{xx}_{TK^+}\frac{\partial \bar{\mu}_{K^+}}{\partial y} - L^{xx}_{TT}\frac{\partial \ln T}{\partial x} - L^{xy}_{TT}\frac{\partial \ln T}{\partial y} \\
q_y &= -L^{yy}_{TNa^+}\frac{\partial \bar{\mu}_{Na^+}}{\partial y} - L^{yy}_{TK^+}\frac{\partial \bar{\mu}_{K^+}}{\partial y} - L^{yx}_{TT}\frac{\partial \ln T}{\partial x} - L^{yy}_{TT}\frac{\partial \ln T}{\partial y}
\end{aligned} \tag{6}$$

A number of transformations apply to the above set of equations. The fluxes, for example, can be brought into a diagonal form[21]

$$j' = \beta j$$

under the influence of a transformation matrix β such that

$$j' = L'X', \; L' = \beta L \beta^{\dagger}$$

with

$$L'_{ik} = 0 \text{ for } i \neq k.$$

Alternately, the matrix equation (equivalent to Eqns. 6)

$$j = LX$$

may be inverted to get a set of equations for the generalized forces X in terms of the fluxes:

$$X = L^{-1}j; \; L^{-1}L = 1 \tag{7}$$

There are two important problems which require thermodynamic analysis. The first is the nature of the change in the membrane potential which attends the impulse transport, and the second is the analysis of the instabilities associated with the transport. These two problems, although correlated, are best studied separately. These separate analyses are carried out under a partial transformation of the Eqns. 6. Specifically, for the study of the ionic diffusions one needs the two ion fluxes related to their respective affinities (through the algebraic relations involving the derivatives

of the affinities) and the thermal diffusion fluxes. On the other hand, for the study of the combustion-like nature of the travelling instability one requires the heat fluxes and their respective affinities together with any coupled material-heat flux contributions.

The required equations are

$$\begin{aligned} j_{Na^+} &= -\lambda_{Na^+Na^+}\frac{\partial\bar{\mu}_{Na^+}}{\partial y} - \lambda_{Na^+K^+}\frac{\partial\bar{\mu}_{K^+}}{\partial y} - A^{x}_{Na^+T}q_x - A^{y}_{Na^+T}q_y \\ j_{K^+} &= -\lambda_{K^+Na^+}\frac{\partial\bar{\mu}_{Na^+}}{\partial y} - \lambda_{K^+K^+}\frac{\partial\bar{\mu}_{K^+}}{\partial y} - A^{x}_{K^+T}q_x - A^{y}_{K^+T}q_y \end{aligned} \tag{8}$$

where the coefficients take the values

$$\lambda_{Na^+Na^+} = L_{Na^+Na^+} - \Omega^{-1}_{TT}[(L^{xx}_{Na^+T})^2L^{yy}_{TT} + (L^{yy}_{Na^+T})^2L^{xx}_{TT} - 2L^{xx}_{Na^+T}L^{yy}_{Na^+T}L^{xy}_{TT}]$$

$\lambda_{K^+K^+}$ is the same as $\lambda_{Na^+Na^+}$ with K^+ replacing Na^+.

$$\begin{aligned} \lambda_{Na^+K^+} = \lambda_{K^+Na^+} &= L_{Na^+K^+} - \Omega^{-1}_{TT}[L^{xx}_{Na^+T}L^{xx}_{K^+T}L^{yy}_{TT} + L^{xx}_{Na^+}L^{yy}_{K^+T}L^{xy}_{TT} \\ &\quad + L^{yy}_{Na^+T}L^{xx}_{K^+T}L^{xy}_{TT} + L^{yy}_{Na^+T}L^{yy}_{K^+T}L^{xx}_{TT}] \end{aligned} \tag{9}$$

$$A^{x}_{Na^+(K^+)T} = -\Omega^{-1}_{TT}(L^{xx}_{Na^+T}L^{yy}_{TT} - L^{yy}_{Na^+T}L^{xy}_{TT})$$

$$A^{y}_{Na^+(K^+)T} = -\Omega^{-1}_{TT}(L^{xx}_{Na^+T}L^{xy}_{TT} - L^{yy}_{Na^+T}L^{xx}_{TT})$$

$$\Omega_{TT} = L^{xx}_{TT}L^{yy}_{TT} - (L^{xy}_{TT})^2.$$

These latter A-coefficients, together with the q_x and q_y, yield the contributions to the ion currents from thermal effects. This can be significant in the active state of the axon.

To generalize Eqn. 5 define the diffusion coefficient:

$$\delta_{ij} = \lambda_{ij}\frac{\partial\mu_i}{\partial c_j} \neq \delta_{ji},\ c_j \text{ is the concentration of } j \tag{5'}$$

With Eqn. 2 the transport equations can be written as

$$\begin{aligned} j_{Na^+} &= -\delta_{Na^+Na^+}\frac{\partial c_{Na}}{\partial y} - \delta_{Na^+K^+}\frac{\partial c_K}{\partial y} - F(\lambda_{Na^+Na^+} + \lambda_{Na^+K^+})\frac{\partial\phi}{\partial y} \\ &\quad + A^{x}_{Na^+T}q_x + A^{y}_{Na^+T}q_y \\ j_{K^+} &= -\delta_{K^+Na^+}\frac{\partial c_{Na^+}}{\partial y} - \delta_{K^+K^+}\frac{\partial c_{K^+}}{\partial y} - F(\lambda_{K^+Na^+} + \lambda_{K^+K^+})\frac{\partial\phi}{\partial y} \\ &\quad + A^{x}_{K^+T}q_x + A^{y}_{K^+T}q_y \end{aligned} \tag{10}$$

The membrane system of the axon preserves electroneutrality. Assume the membrane to be a system of fixed anions. (The participating anions, in particular Cl^-, may not be bound in the sense that $-SO_3^-$ is bound in, for example, polystyrenesulfonic acid. TASAKI (ref. 12, Section (6, 2)), specifically notes that both anions and cations (Ca^{2+}) in the axon membrane may form salt bridges which act as cross-linking agents. In the active state Na^+ and K^+ exchange sites in the process of migration, but there is no measured associated movement of Cl^-. In this sense the anions may

be considered bound. Again, it should be noted here that although there seems to be experimental and theoretical evidence that in the resting state a separate ionic attachment hypothesis works, *i.e.* separate attachment sites for Na^+ and K^+, there is no guarantee that that hypothesis applies at all to the excited state. In fact, TASAKI's[12] experimental evidence and accompanying thesis testifies to this. Diffusion through the membrane occurs by ion exchange involving the interactions between mobile cations and fixed anions. Thus,

$$c_{Na^+} + c_{K^+} = c_X = \text{constant} \tag{11}$$

where c_X is the fixed, effective anion concentration. Note, that even if the separate ionic attachment hypothesis should be valid in the excited state, it makes no difference to the analysis as c_X is then the indiscriminate sum of all the fixed anionic sites. Therefore,

$$\frac{\partial c_{Na^+}}{\partial y} = -\frac{\partial c_{K^+}}{\partial y} \tag{12}$$

Furthermore, the material and charge balance conditions require that

$$j_{Na^+} = -j_{K^+} \tag{13}$$

Hence, with the use of Eqns. 10–13 one finds the potential-dependent terms disappear:

$$j_{Na^+} = -\Delta_{Na^+K^+}\frac{\partial c_{Na^+}}{\partial y} + \theta^x_{Na^+}q_x + \theta^y_{Na^+}q_y \tag{14}$$

and

$$j_{K^+} = \Delta_{K^+Na^+}\frac{\partial c_{K^+}}{\partial y} + \theta^x_{K^+}q_x + \theta^y_{K^+}q_y \tag{15}$$

where the interdiffusion coefficient $\Delta_{Na^+K^+} = -\Delta_{K^+Na^+}$ is defined as

$$\Delta_{Na^+K^+} = \frac{A_1B_2 - A_2B_1}{B_1 + B_2} \tag{16}$$

$$\begin{aligned} &A_1 = \delta_{Na^+Na^+} - \delta_{Na^+K^+};\ A_2 = \delta_{K^+K^+} - \delta_{K^+Na^+};\\ &B_1 = \lambda_{K^+K^+} + \lambda_{Na^+K^+};\ B_2 = \lambda_{Na^+Na^+} + \lambda_{Na^+K^+}\\ &\theta^x_{Na^+T} = \frac{A^x_{K^+T}B_2 - A^x_{Na^+T}B_1}{B_1 + B_2} = -\theta^x_{K^+T}\\ &\theta^y_{Na^+T} = \frac{A^y_{K^+T}B_2 - A^y_{Na^+T}B_1}{B_1 + B_2} = -\theta^y_{K^+T}. \end{aligned} \tag{17}$$

The above equations are generalizations of the expressions obtained for bi-ionic diffusion in membranes by HELFFERICH[25]. Eqns. 14 and 15 with the coefficients defined by Eqns. 16 and 17 are the basic equations needed for the consideration of bi-ionic diffusion in the axon membrane in the active state. The specific problem of ionic diffusion is not covered here. An analysis of the active state diffusion problem will be reported shortly. It differs from the usual membrane problem in that in the active state the membrane diffusion coefficients are time-dependent which, of course, complicates the analysis.

Equations for the heat flux

The equations needed to consider energy transport, which accompanies the travelling disturbance, follow from the same type of analysis as that used to get the ion transport equations in the last section. A partial transformation of the Eqns. 6 yields the energy transport fluxes in terms of the associated affinities and ion fluxes. In particular,

$$q_x = -\mathrm{K}_{xx}\frac{\partial \ln T}{\partial x} - \mathrm{K}_{xy}\frac{\partial \ln T}{\partial y} - G^{x}_{\mathrm{Na}^+T}j_{\mathrm{Na}^+} - G^{x}_{\mathrm{K}^+T}j_{\mathrm{K}^+} \tag{18}$$

$$q_y = -\mathrm{K}_{yx}\frac{\partial \ln T}{\partial x} - \mathrm{K}_{yy}\frac{\partial \ln T}{\partial y} - G^{y}_{\mathrm{Na}^+T}j_{\mathrm{Na}^+} - G^{y}_{\mathrm{K}^+T}j_{\mathrm{K}^+} \tag{19}$$

with

$$\mathrm{K}_{xx} = \mathrm{L}^{xx}_{TT} - \Xi^{-1}_{\mathrm{K}^+\mathrm{Na}^+}(\mathrm{L}^{xx}_{T\mathrm{Na}^+}\mathrm{L}^{xx}_{\mathrm{K}^+\mathrm{K}^+}\mathrm{L}^{xx}_{\mathrm{Na}^+T} - \mathrm{L}^{xx}_{T\mathrm{K}^+}\mathrm{L}_{\mathrm{Na}^+\mathrm{Na}^+}\mathrm{L}^{xx}_{\mathrm{K}^+T}) \tag{20}$$

and K_{yy} is the same as K_{xx} with x replaced by y. Further,

$$\mathrm{K}_{xy} = \mathrm{K}_{yx} = \mathrm{L}^{xy}_{TT} - \Xi^{-1}_{\mathrm{Na}^+\mathrm{K}^+}(\mathrm{L}^{xx}_{T\mathrm{Na}^+}\mathrm{L}_{\mathrm{K}^+\mathrm{K}^+}\mathrm{L}^{yy}_{\mathrm{Na}^+T} - \mathrm{L}^{xx}_{T\mathrm{Na}^+}\mathrm{K}_{\mathrm{Na}^+\mathrm{K}^+}\mathrm{L}^{yy}_{\mathrm{K}^+T} + \mathrm{L}^{xx}_{T\mathrm{K}^+}\mathrm{L}_{\mathrm{K}^+\mathrm{Na}^+}\mathrm{L}^{yy}_{\mathrm{Na}^+T}) \tag{21}$$

$$G^{x}_{\mathrm{Na}^+(\mathrm{K}^+)T} = -\Xi^{-1}_{\mathrm{Na}^+\mathrm{K}^+}(\mathrm{L}^{xx}_{T\mathrm{Na}^+}\mathrm{L}_{\mathrm{K}^+\mathrm{K}^+} - \mathrm{L}^{xx}_{T\mathrm{K}^+}\mathrm{L}_{\mathrm{K}^+\mathrm{Na}^+}) \tag{22}$$

$$G^{y}_{\mathrm{Na}^+(\mathrm{K}^+)T} = -\Xi^{-1}_{\mathrm{Na}^+\mathrm{K}^+}(\mathrm{L}^{yy}_{T\mathrm{Na}^+}\mathrm{L}_{\mathrm{K}^+\mathrm{K}^+} - \mathrm{L}^{yy}_{T\mathrm{K}^+}\mathrm{L}_{\mathrm{K}^+\mathrm{Na}^+}) \tag{23}$$

and, finally,

$$\Xi_{\mathrm{Na}^+\mathrm{K}^+} = \mathrm{L}_{\mathrm{Na}^+\mathrm{Na}^+}\mathrm{L}_{\mathrm{K}^+\mathrm{K}^+} - (\mathrm{L}_{\mathrm{Na}^+\mathrm{K}^+})^2. \tag{24}$$

Terms such as $G^{x}_{\mathrm{Na}^+T}j_{Na^+}$ amount to a contribution to the heat flux in the x-direction arising from the ionic diffusions in the y-directions. These terms are equivalent to the rates of heat production used in the usual theory of thermal explosions[26–28]. They are responsible for the all-or-none character of the active state message transport[9,10].

The most important heat transport equation for the membrane in the active state is that for transport in the x-direction, it is the one associated with the message transport. Therefore, from Eqns. 18 and 19 elimination of $\partial \ln T/\partial y$ yields

$$q_x = -(\mathrm{K}_{xx} + \mathrm{K}_{xy}^2/\mathrm{K}_{yy})\frac{\partial \ln T}{\partial x} + (\mathrm{K}_{xy}/\mathrm{K}_{yy})q_y - (G^{x}_{\mathrm{Na}^+T} - G^{x}_{\mathrm{K}^+T} + [G^{y}_{\mathrm{Na}^+T} - G^{y}_{\mathrm{K}^+T}](\mathrm{K}_{xy}/\mathrm{K}_{yy}))j_{\mathrm{Na}^+} \tag{25}$$

using Eqn. 13. Depending on the sign of the term $(\mathrm{K}_{xy}/\mathrm{K}_{yy})q_y$, it acts either as an attenuation factor or as an additional source of energy. In general, in the active state, the membrane system will have a higher temperature than the surroundings. Such terms most likely take on the role of attenuation factors.

The dependence of the action potential on ionic diffusions

Rapid, dramatic changes in the measured membrane potential characterize the axon in the active state. On the one hand, in the stationary resting state the membrane potential dissected reveals dependencies on Donnan and diffusion potentials (*cf.*

ref. 18). The Donnan potentials are tied to the heterogeneity of the membrane-surroundings interfaces; they depend on the ionic concentrations inside and outside the membrane at the interfacial discontinuities. Diffusion potentials are associated with the tendency for ionic transport in the membrane. On the other hand, in the non-stationary active state all the ionic concentrations, except those bound to the membrane, the anions, change. The membrane potential responds to these time-dependent ionic concentrations and fluxes. In this section the dependence of the action potential on the diffusion parameters is demonstrated through the functional relations uniting them.

By virtue of Eqns. 12 and 13 the set of Eqns. 10 may be solved for the y-component of the diffusion potential gradient:

$$F\frac{\partial\phi}{\partial y} = -\frac{\Sigma(\delta)}{B_1 + B_2}\frac{\partial c_{Na^+}}{\partial y} - Q_x q_x - Q_y q_y \tag{26}$$

where

$$\Sigma(\delta) = \delta_{Na^+Na^+} + \delta_{K^+K^+} + \delta_{Na^+K^+} + \delta_{K^+Na^+} \tag{27}$$

$$Q_x = \frac{A^x_{Na^+T} + A^x_{K^+T}}{B_1 + B_2} \tag{28}$$

$$Q_y = \frac{A^y_{Na^+T} + A^y_{K^+T}}{B_1 + B_2} \tag{29}$$

Eqn. 26 is easily integrated to yield the diffusion potential

$$F(\phi(l) - \phi(0)) = \int_{c_{Na^+}(0)}^{c_{Na^+}(l)} \frac{\Sigma(\delta)}{B_1 + B_2} dc_{Na^+} - \int_0^l Q_x q_x dy - \int_0^l Q_y q_y dy \tag{30}$$

where l is the membrane width. From now on terms due to the thermal contributions to the ionic diffusions, *i.e.* terms depending on q_x and q_y, are ignored. (Of course, the contribution of the ionic fluxes to the thermal currents will not be ignored.) Eqn. 30 is general, holding for any manner of time-dependence of the various parameters. In particular, Eqn. 30 reveals the diffusion potential to be most sensitive to changes in the ionic concentration at the two membrane interfaces, *viz.*

$$F(\phi(l) - \phi(0)) \cong \frac{\Sigma(\delta)}{B_1 + B_2}[c_{Na^+}(l) - c_{Na^+}(0)]. \tag{30'}$$

The Donnan potentials, as well as the diffusion potential, depend on the interfacial ionic concentrations. The changes in these concentrations with time are reflected in the Donnan potential through the relation

$$E_D(t) = RT \ln[a_i(t)/a_i'(t)] \tag{31}$$

where a_i is the activity of the i-th ion in the surroundings outside the membrane, and $a_{i'}$ is the activity of the i-th ion on the membrane side of the interfacial discontinuity.

The membrane potential is the sum of the diffusion potential and the two Donnan potentials, one for either side of the membrane:

$$E_{mem} = F\phi + E_D(l) - E_D(0) \tag{32}$$

In view of Eqns. 30 and 31 the membrane potential, under the influence of the changing character of the active state, becomes the action potential. The time-dependence of the action potential clearly depends on the time-dependent ionic concentrations at the membrane interfaces.

Explosion theory, application to message transport

The effort in these following sections is not concerned with the derivation of the equations describing explosions, rather it is concerned with the demonstration that the thermal transport equations of the previous sections admit analyses which (1) show instabilities indicative of an explosion, and (2) yield expressions for the velocity of the propagation of the instability-explosion.

The equation of thermal continuity is

$$\frac{\partial \tau}{\partial t} = -\operatorname{div}(q),\ \tau = RT \tag{33}$$

Ignore the contribution q_z to the thermal flux. Then,

$$q = q_x\hat{i} + q_y\hat{j} \tag{34}$$

and from Eqns. 18 and 19

$$\frac{\partial \tau}{\partial t} = K_{xx}\frac{\partial^2 \ln T}{\partial x^2} + 2K_{xy}\frac{\partial^2 \ln T}{\partial x \partial y} + K_{yy}\frac{\partial^2 \ln T}{\partial y^2} + (G^x_{Na^+T} + G^y_{Na^+T})\operatorname{div}(j_{Na^+}) + (G^x_{K^+T} + G^y_{K^+T})\operatorname{div}(j_{K^+}). \tag{35}$$

From the material continuity equations it follows that

$$-\operatorname{div}(j_{Na^+}) = \frac{\partial c_{Na^+}}{\partial t} \tag{36}$$

etc. These then are the rates of ion transfer. These rates multiplied by the coefficients $G^x_{Na^+T}$, *etc.* are the rates of energy generation in the membrane system at the space-point under investigation. In Eqn. 35 it has been assumed that the thermal coefficients K_{xx} *etc.* are independent of the coordinates. This is, of course, in line with the usual phenomenological approach to irreversible phenomena[29]. The assumption is not so drastic; for a homogeneous system one expects the thermal conductivity to be essentially independent of coordinate, *i.e.* uniform. The only conceivable problem is connected with the temperature dependence of K_{xx}, *etc.* through which the coefficients would derive their spatial dependence. It is probably true that in "hotter" regions, regions within the zone of the axon membrane in the excited state, the K_{xx} differs somewhat from its value in the homogeneous regions in the resting state. However, a similar assumption is made in connection with the theory of thermal explosions, and, judging from the success of these treatments, one expects similar assumptions to be valid for the axon membrane. In order to further simplify the problem, but still retain the features which account for the active state, we ignore the mixed differential $\partial^2 \ln T/\partial x \partial y$. Eqn. 35 forms the basis of the analysis of the conditions for the existence of the explosive state.

The velocity of the propagation of the disturbance, which is merely an energy

wave passing along the axon membrane, can be analysed best in terms of the heat flux along the membrane, q_x. The equation of continuity in this case is merely

$$\frac{\partial \tau}{\partial t} = -\frac{\partial q_x}{\partial x} \tag{37}$$

Eqn. 25 gives an expression for q_x which displays q_y as a dissipative term. As in the more general equations, the material (ionic) fluxes together with their multiplicative coefficients give the rates of energy generation. The pertinent expression needed to find the propagation velocity is

$$\frac{\partial \tau}{\partial t} = (\mathrm{K}_{xx} + \mathrm{K}_{xy}^2/\mathrm{K}_{yy})\frac{\partial^2 \ln T}{\partial x^2} - (\mathrm{K}_{xy}/\mathrm{K}_{yy})\frac{\partial q_y}{\partial_x}$$

$$- \nabla \cdot [G^x_{\mathrm{Na}^+T} - G^x_{\mathrm{K}^+T} + (G^y_{\mathrm{Na}^+T} - G^y_{\mathrm{K}^+T})\mathrm{K}_{xy}/\mathrm{K}_{yy}]j_{\mathrm{Na}^+} \tag{38}$$

The term $(\mathrm{K}_{xy}/\mathrm{K}_{yy})\partial q_y/\partial y$ is a thermal dissipation term. In terms of the net rate of temperature change in the x-direction, Eqn. 38 is

$$\frac{\partial \tau_x}{\partial t} = (\mathrm{K}_{xx} + \mathrm{K}_{xy}^2/\mathrm{K}_{yy})\frac{\partial^2 \ln T}{\partial x^2}$$

$$- \nabla \cdot [G^x_{\mathrm{Na}^+T} - G^x_{\mathrm{K}^+T} + (G^y_{\mathrm{Na}^+T} - G^y_{\mathrm{K}^+T})\mathrm{K}_{xy}/\mathrm{K}_{yy}]j_{\mathrm{Na}^+} = \frac{\partial \tau}{\partial t} - \frac{\partial \tau_y}{\partial t} \tag{39}$$

and

$$\frac{\partial \tau_y}{\partial t} = (\mathrm{K}_{xy}/\mathrm{K}_{yy})\frac{\partial q_y}{\partial x} \tag{40}$$

Attainment of the active state

In the resting, stationary state of the axon membrane the rates of energy production (due to diffusions from the nonequilibrium steady state ionic concentrations) and energy dissipation (*i.e.* thermal diffusion) cancel. This combined effect yields in Eqn. 35 $\partial T/\partial t = 0$. The balance of the rates leads to the differential equation

$$\mathrm{K}_{xx}\frac{\partial^2 \ln T}{\partial x^2} + \mathrm{K}_{yy}\frac{\partial^2 \ln T}{\partial y^2} + (G^x_{\mathrm{Na}^+T} - G^x_{\mathrm{K}^+T} + G^y_{\mathrm{Na}^+T} - G^y_{\mathrm{K}^+T})\Delta_{\mathrm{Na}^+\mathrm{K}^+}\frac{\partial^2 c_{\mathrm{Na}^+}}{\partial x^2} = 0 \tag{41}$$

Assuming the thermal conduction part of the problem to be isotropic, one finds

$$\nabla^2\phi_t = \nabla^2[(\mathrm{K}_{xx} + \mathrm{K}_{yy})\ln T + (G^x_{\mathrm{Na}^+T} - G^x_{\mathrm{K}^+T} + G^y_{\mathrm{Na}^+T} - G^y_{\mathrm{K}^+T})\Delta_{\mathrm{Na}^+\mathrm{K}}c_{\mathrm{Na}^+})] = 0 \tag{42}$$

and ϕ_t is defined by this equation. The expression for ϕ_t is altered slightly by the change to the usual form for the thermal diffusion:

$$\nabla^2\Phi = \nabla^2\{\kappa T + \Sigma G^{x,y}_{\mathrm{Na}^+,\mathrm{K}^+,T}\Delta_{\mathrm{Na}^+\mathrm{K}^+}c_{\mathrm{Na}^+}\} = 0 \tag{43}$$

There are several ways the problem can be treated further depending on what is done with either Eqn. 41 or 43. The specification of the membrane boundary conditions allows the determination of the function Φ. Maximization of

$$\Phi = \kappa T - \Sigma G^{x,y}_{\mathrm{Na}^+,\mathrm{K},T}\Delta_{\mathrm{Na}^+\mathrm{K}}c_{\mathrm{Na}^+} \tag{44}$$

yields the critical temperature. For simplicity ignore the detailed temperature depen-

dence in the factors $\Sigma G^{x,y}_{Na^+,K^+,T}$, and combine this term with $\Delta_{Na^+K^+}$. Denote the combination as $\tilde{\Delta}_{Na^+K^+}$. Further, let

$$\tilde{\Delta}_{Na^+K^+} = \tilde{\Delta}_0 \exp(-E_a/RT) \tag{45}$$

which, while departing from the precision of the irreversible thermodynamic treatment, is probably very close to the dependence that should be observed experimentally, if that becomes possible. Maximization of the new equation

$$\Phi' = \kappa(T - T_0) - \tilde{\Delta}_0 \exp(-E_a/RT) c_{Na^+}, \tag{46}$$

where T_0 is the initial temperature, a constant, and clearly Φ' still satisfies the Laplace equation, yields

$$T_c - T_0 = \frac{RT_c^2}{E_a}(1 + \Phi'/\tilde{\Delta} c_{Na^+}), \tag{47}$$

where E_a is the effective activation energy for the normal diffusion. The solution of this equation for T_c is complicated unless an essential simplification is made, namely, ignore the contribution to T_c from the temperature dependence in $\tilde{\Delta}$ in Eqn. 47. The value of T_c, in line with the usual simple treatment of thermal explosions, *cf.* SEMENOFF[27], FRANK-KAMENETSKII[28], or BENSON[26] is

$$T_c \simeq T_0 + \frac{RT_0^2}{E_a}(1 + \Phi'/\tilde{\Delta}(T_c) c_{Na^+}) \simeq T_0 + \frac{RT_0^2}{E_a} \tag{48}$$

The second approximation follows because as T increases $\Phi'/\tilde{\Delta}(T) c_{Na^+}$ contributes less. With the approximations made Eqn. 48 is the same explosion condition for the temperature as found in the simple SEMENOFF[27] theory. Following arguments similar to those encountered in the SEMENOFF theory, the critical ion concentration is found to be

$$\ln(c_{Na^+}) = \frac{E_a}{RT} + \ln\left[\frac{\Phi' + \kappa RT_0^2/E_a}{\tilde{\Delta}_0}\right] \tag{49}$$

which, aside from the factor Φ', is identical to the usual result. The spatially dependent term Φ' is unique to this theory for the reason that, since energy production in the membrane is due to diffusion, the explosion condition is reached only in those areas where there is sufficient activity in the form of diffusions. Certainly, when the active state is reached, the entire membrane diffusion processes will contribute. Thus, it seems reasonable to take the active state critical sodium ion concentration as the value obtained by integrating Eqn. 49 over the y-coordinate, *i.e.* over the width of the membrane:

$$\ln(c_{Na^+})_{active} = \int_0^l dy \ln[c_{Na^+}(y)] \tag{50}$$

The suspicion that in the active state all regions of the membrane in a particular cross section contribute to that state suggests an alternate treatment of the explosion problem. Returning to Eqn. 41 write

$$\frac{\partial^2 c_{Na^+}}{\partial y^2} \simeq c_{Na^+}/l^2$$

The ensuing differential equation (in terms of the phenomenological thermal conductivity coefficients) is

$$\kappa\nabla^2 T = \tilde{A}_0 c_{Na^+} l^{-2} \exp[-E_a/RT] \tag{51}$$

In this form Eqn. 51 is the same (aside from numerical factors) as the equation studied by CHAMBRÉ[30]. Equations of the form of Eqn. 51 have also been examined by RICE[31] and FRANK-KAMENETSKII[28]. Since it has been shown in this section in two instances, one of which was examined in detail, how this heat generation and transport problem reduces to the usual forms, the further study of Eqn. 51 is not warranted.

Impulse propagation velocity

It remains only to show how the explosion theory accounts for the velocity of impulse propagation. The analysis utilizes Eqn. 39. In this case interest centers around the study of the nonstationary problem, the active state, which it is assumed has been reached by the membrane system.

In the interest of presenting the most transparent demonstration of the impulse propagation velocity I again opt to sacrifice the rigor and complexity of the irreversible thermodynamic treatment in favor of the simpler and direct phenomenological approach. The connection between these two approaches does not pass without comment; I indicate how one transforms into the other.

The x-coordinate is the propagation axis. Interest therefore centers on the velocity of energy transfer in this direction. The vectorial ionic fluxes have components in the x- and y-directions. The y-direction flux is associated with the ionic diffusion into the negative concentration gradient, and this problem is currently under investigation. The x-direction ionic flux is connected with the velocity with which the migrating impulse encounters ionic species along the axon membrane. It is, therefore, not necessarily connected with any material diffusion problem. It is, however, a consequence of the energy flux.

As the impulse travels $\partial T_x/\partial t = 0$ in the impulse front. Further, the G-factors in Eqn. 39 are temperature-dependent. Let $j_{Na^+}(x) = u$, the velocity with which the advancing front encounters the unspent regions in front of it. With this in mind one finds that

$$(K_{xx} + K_{xy}^2/K_{yy}) \frac{\partial^2 \ln T}{\partial x^2} = \frac{\partial}{\partial x}[G^x_{Na^+T} - G^x_{K^+T} + (G^y_{Na^+T} - G^y_{K^+T})K_{xy}/K_{yy}]u$$
$$- \Delta_{Na^+K^+}[G^x_{Na^+T} - G^x_{K^+T} + (G^y_{Na^+T} - G^y_{K^+T})K_{xy}/K_{yy}] \frac{\partial^2 c_{Na^+}}{\partial x^2}, \tag{52}$$

This equation suggests the phenomenological replacement

$$\kappa \frac{\partial^2 T}{\partial x^2} = \frac{\partial}{\partial x}(c_p T)u - \Delta H \frac{\partial c_{Na^+}}{\partial t} \tag{53}$$

where the G-factors have been replaced by the enthalpy, ΔH, and $\Delta H = c_p T$ where c_p is the constant pressure heat capacity. Eqn. 53 has the same form as the usual starting expression used in the simplified discussion of flame propagation[26]. Therefore, noting that the density of the membrane is ρ, the expression for the impulse propagation velocity follows the result obtained from the flame theory[26]:

$$U_i^2 = \frac{\kappa(\partial c_{Na^+}/\partial t)(T_F - T_c)}{c_p \rho n (T_c - T_0)} \tag{54}$$

where T_0 is the temperature of the resting axon membrane, T_c is the critical initiation temperature, T_F is the final temperature in the spent region just outside the volume occupied by the impulse front, and n is the number (concentration) of ionic diffusion sites available for the release of energy in the resting portion of the membrane ahead of the front. Also, from the flame theory[26] the width of the active zone in the membrane in the active state is

$$\delta_a = \frac{\kappa}{c_p \rho U_i} \left[\frac{T_F - T_c}{T_c - T_0}\right]. \tag{55}$$

The connection between the nerve impulse transport problem and that of flame propagation gives substance to the suggestion that the ionic diffusion coefficients are time-dependent. This time-dependent change results in the following way. Assume the Arrhenius form for the general diffusion coefficient,

$$\Delta = \Delta_0 \exp(-E_a/RT) \tag{56}$$

where E_a is the activation energy. As the impulse moves along the axon in the x-direction with a velocity U_i, the temperature changes at any arbitrary point accordingly. The specific dependence will be of the form

$$T = T(t - U_i x) \tag{57}$$

The time-dependence of the temperature in the impulse front has been examined and is found to be roughly exponential (*cf.* BENSON[26]). A number of other forms are also likely. A reasonable choice for the time-dependence in the diffusion coefficient itself is

$$\Delta = \Delta_0 \exp[-\alpha(t - \tfrac{1}{2}U_i x)^2] \tag{58}$$

where α and Δ_0 are constants. Other forms are of course possible.

The result for the propagation velocity, Eqn. 54, and a modification to be shown, provide an interesting check on the order of magnitude, rough calculation of the impulse transfer time presented earlier in the first part of the paper. By plausibility arguments it has been known for some time that the flame propagation velocity is roughly equal to[26]

$$U_i^2 = (\kappa/\rho c_p) t_f^{-1} \tag{59}$$

where t_f is the half-time of the reaction at the mean flame temperature, T_F. The factor $(\kappa/c_p\rho)$ is the thermal diffusivity. Even for a 20 % KCl solution the thermal conductivity, κ, is $1.34 \cdot 10^{-3}$ (ref. 32). If one assumes that the membrane substance has a heat capacity and density nearly that of water, then the diffusivity is the same order of magnitude as the conductivity. Assume that $t_f \simeq 10^{-10}$ sec which, apart from any earlier arguments, is a reasonable number to choose considering the system involves accelerated diffusion. One easily finds that $U_i = 36$ m/sec. The closeness of this result, even noting how crude it is, with the 20 m/sec observed for the squid axon suggests the merits of the irreversible thermodynamic analysis together with the explosion theory in explaining the phenomenon, *i.e.* the origin and nature of the impulse conduction.

Clearly, the results obtained and presented so far indicate that while ionic transport processes in the active state are important to the impulse propagation,

grossly overlooked to date have been the other thermal transport properties of the system. The material and heat transport problems are obviously closely tied together, as has been demonstrated. Further resolution, by experimental means, of mechanisms of impulse transport must involve close analyses of the thermal properties of the membrane systems.

CONCLUSION

The focus of this paper has been on the macroscopic irreversible thermodynamic description of the axon active state. The active state is characterized by the propagating, unattenuated, depolarization action potential which migrates along the length of the axon fiber; it is the nerve impulse. A complete analysis rests on two experimental observations: one, that there are ionic diffusions associated with the impulse passage, and two, that the resting state of the axon membrane system is a nonequilibrium, energy rich steady state. The ionic diffusions are energy releasing. The energy released migrates along the axon membrane as heat flux activating further ionic diffusions in the flux front. By means of this the impulse is constantly reenforced along the axon length. The analysis presented is successful in describing the phenomenon of impulse transport utilizing only the minimum amount of consistent experimental data. It is seen without much difficulty that most of the remaining experimental data concerning the active state can usually be accounted for with the use of the thermodynamic analysis. The description does not depend on a large quantity of often contradictory experimental data.

The thermodynamic analysis is general and free of representation. It suggests that the active state phenomenon should appear in any system constituted as is the axon. Indeed, TEORELL's[33] sintered glass membrane model shows this to be the case. Even though TEORELL's glass system is physically unlike any living axon, the existence of an active state in it and in the axon indicates that both are members of the same class of phenomena. The implication of this observation is the suggestion that there are relatively few important structures and events associated with the axon which contribute to the active state. It suggests that aside from preparing the resting nonequilibrium steady state, the active transport sodium pump process is unrelated to the active state phenomenon. Many of the complicated biological structures and processes observed in a resting axon system are supportive, or ancillary, to the active state process, the impulse transport. This observation, it seems to me, may be taken as a *modus operandi* in further examination of the active state phenomenon. Specifically, considerable effort should be directed to the resolution of structures and processes into resting and active state catagories. Much of this should be possible by experimentally studying model systems such as TEORELL's.

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