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A Comment on Models of Ion Transport Across Cell Membranes[1]

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One usually thinks of ionic flow across membranes as controlled by modulation of the energies needed by an ion to get into a membrane. Examination of these energies shows that they are not only large enough to perturb the ionic distribution but also sufficient to deform a thin membrane. The deformability of a cell membrane may then be related to its control of ionic current.

For more than two decades it has been recognized that the nerve signal involves a sequential turning "on" and "off" of pathways for the movement of specific ions across the nerve cell membrane. This process has been elegantly described phenomenologically and mathematically by Hodgkin and Huxley (1964). In addition, Katz (1966) and Cole (1968) give clear summaries by people immediately involved in the original work. [See also the recent reviews by Taylor (1974) and Haydon and Hladky (1972), as well as the treatise by Tasaki (1968)]. A physical understanding of the ion "gating" process still eludes us.

Today there is a confluence between these phenomenological theories and several other approaches. One is an increasingly detailed picture of membrane structure. A second is the construction of model experimental systems made of membrane components that mimic some of the behavior of natural membranes. A third approach is the theoretical analysis, both mathematical and physicochemical, of the processes observed on model systems. My own tastes lie in this third area, and it is this aspect I emphasize most.

In the following, I first describe the formalism one uses to relate the forces on charged ionic particles in solution to the directed flow of those ions across membranes. Charged particles must be driven to surmount a membrane barrier. Modulating that barrier is the apparent means for controlling ionic flow.

I next cite some experimental examples of controlled ion transport. Most of these are from model systems where it has been possible to identify participating chemical species in the membranes and to speculate on the molecular process.

Finally I mention some of the physical interactions between ions and cell membranes. Except for the intervention of special protein components, ions are virtually insoluble in these membranes. Even where this insolubility is overcome, the ions by virtue of their charge encounter repulsive energies. These in-

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teractions can be strong enough for a membrane to be deformed in reaction to a traversing ion. One must then consider the possible consequences of such deformations on the original picture of a membrane acting unilaterally to control ionic flow.

1. FORMALISM

Gibbs in 1892 (1961) pointed out that the effective force on a population of ions was the negative gradient in the local chemical potential of the particular species plus the direct electrical field on each charged particle. (See also Katchalsky and Curran, 1965; Caplan and Mikulecky, 1966; Mikulecky, 1969.) The chemical potential of species i, μ_i, depends on all the thermodynamic variables—concentration, temperature, interactions with other species—that determine the work needed to create a population of that substance at a particular place. This potential μ_i plus the ionic charge $z_i e$ times the local electrical potential Ψ give the electrochemical potential

$$\tilde{\mu}_i = \mu_1 + z_i e \Psi.$$

One speaks of a mobility coefficient m_i and local concentration c_i such that flow of species i is

$$\mathbf{J}_i = m_i c_i \text{ grad } (-\tilde{\mu}_i).$$

The total electric current is a sum over all species

$$\mathbf{I} = \Sigma (z_i e) m_i c_i \text{ grad } (\tilde{\mu}_i).$$

That is, in this language, flow is linear in force. In the formalism of the thermodynamics of irreversible processes one imagines a set of thermodynamic forces $\{X_j\}$ coming from gradients in each system variable related to J_i by a matrix of flow coefficients L_{ij},

$$J_i = \Sigma L_{ij} X_j.$$

There is the "direct flow" $L_{ij}X_j$ and "coupled flow" from cross terms $L_{ij}X_i$ $(j \neq i)$. (The Onsager symmetry relation is $L_{ij} = L_{ji}$.)

The apparent linearity is deceptive. Each of the quantities in the product

$$\text{mobility} \times \text{concentration} \times \text{electrochemical force}$$

can depend on position and will vary with local voltage as well as with all thermodynamic variables. In the vicinity of a structural nonuniformity, such as a membrane, there will be direct interaction of solute particles with that structure.

In addition to outside sources, charged particles will themselves contribute to the electrostatic potential Ψ that occurs in their own electrochemical potential. Coulombic attraction or repulsion will modify local ionic concentrations.

Experimentally, current flow across membranes is not linear in applied voltage. Emergence of this nonlinearity from superficially linear local currents has been derived in analyses of total current flow across model preparations. Alternatively, one speaks of voltage-dependent whole membrane conductances which are introduced as coefficients in linear relations.

2. SOME MODELS AND EXAMPLES

Mathematical facility in setting up flow equations in terms of $\Psi(r)$ and $\mu(r)$ has been extensively exploited to describe flow of ions across lipid membranes. The black lipid membranes (BLM) of Mueller *et al.* (1964) in particular are a useful experimental system (Jain, 1972) for making convenient artificial analogs of excitable nerve cell membranes. Because one has molecular information about many of the participating components, it has begun to be possible to build models for their behavior.

Because pure lipids or hydrocarbons present a hostile environment to an ionic charge, thin ($\sim$50 Å) lipid membranes are strong electrical insulators with resistances $\gtrsim 10^9$ ohms cm^2. Addition of specific peptides (usually drugs not found in healthy animals) will increase conductance by several orders of magnitude. Typically one imagines that these peptides form ion "carriers" or "pores" through the membrane. The details of these models have been extensively reviewed (Eisenman *et al.*, 1972; Hladky *et al.*, 1974; Haydon *et al.*, 1972; Eisenman *et al.*, 1973; Szabo *et al.*, 1973; Lauger *et al.*, 1970; Finkelstein, 1974.)

Phenomenologically, proteins labeled as "carriers" are very specific in helping a particular ion species and neglecting others; pores are relatively unselective. Carriers often stop working at low temperatures where the lipid hydrocarbon congeals; pores are relatively insensitive to temperature. To the extent that the stoichiometry is defined, it appears that "carrier" proteins do not increase the conductance as much as pores do. Small amounts of "carrier" will proportionally increase conductance while pore formers create discrete steps in conductance associated with the "opening" of a channel.

Structurally, carrier peptides are cyclic molecules that can wrap around a particular ionic species to replace its water of hydration with dipolar carbonyl groups. This large complex can enter a nonaqueous region more easily than can a bare ion (Parsegian, 1969). The complex then goes across the membrane, in a step usually imagined to be by diffusion (Eisenman *et al.*, 1973). One can predict the current vs. applied voltage for forced diffusion over an energetic barrier.

For example, if movement across a membrane in the x-direction requires surmounting a single barrier $W(x)$, then there will be a nonlinear relation between current and voltage (Neumcke and Lauger, 1969). Conversely, analyses of several current–voltage curves allow one to infer the shape of $W(x)$ (Hall *et al.*, 1973). These are primarily mathematical procedures which do not test a physical picture of the mode of complex movement.

Models of flow through pores are not as structurally well defined as the picture for carriers. Several drugs appear from kinetics and stoichiometry to create channels by forming aggregates that bridge a membrane. Two of these pore formers—EIM (excitability inducing material), a poorly characterized mixture, and the drug alamethicin (Hladky *et al.*, 1974; Mueller and Rudin, 1967, n.d.)—are even able to impart behavior that mimics excitable nerve membrane.

Channels of EIM, alamethicin, and gramicidin-A show "open" (conducting) and "closed" (nonconducting) states (Ehrenstein and Lecar, 1972; Ehrenstein *et al.*, 1974). For the first two compounds the opening and closing rates are voltage

dependent. Resultant current voltage curves are nonlinear. Passage through other kinds of pores involves making a series of small jumps whose height and frequency determine pore conductance (Lauger, 1973).

Before one can be satisfied that ionic flow is in fact controlled by barriers unilaterally set by the membrane, it is necessary to examine the physical basis for these barriers and how they relate to the physical models of "pores" or "carriers."

3. ION–MEMBRANE INTERACTIONS

In Section 1, I said that the force on an ion was the gradient in its electrochemical potential. If one included in this potential the interaction with membrane it would contain a term $W(r)$. This $W(r)$ is the work needed to bring an ion to some position r with respect to the membrane.

As mentioned above, it has been possible to solve some of the current–voltage relations for certain $W(r)$. These solutions assume that the work $W(r)$ is exerted by the membrane to affect the distribution of mobile ion. Now what is the ion–membrane interaction which creates the barrier?

The main reason why an ion has trouble going through a lipid membrane is that its "self-energy" goes up enormously in low dielectric hydrocarbon. By definition, this self-energy represents the mutual electric repulsion between parts of the same charge. Physically it involves the ability of an electric charge to polarize the surrounding medium and to lower its energy by attracting from that medium dipolar charge of opposite sign. Water is easily polarized while hydrocarbon is not. The self-energy of an ion is much less in water than in hydrocarbon.

In terms of the dielectric constant ϵ and ionic radius a, the Born self-energy for charge e is $e^2/2\epsilon a$. Ionic radii are of the order of 1 Å so the transfer energy of an ionic charge ($e = 4.8 \times 10^{-10}$ stat volts) from water ($\epsilon = 80$) to hydrocarbon ($\epsilon = 2$) is of the order of electron volts. This is much more than is available from thermal energy ($\sim 1/40$ eV). Ion entry into a lipid membrane is very improbable.

Association with "carrier" peptides will lower the energy barrier to be of the order ½ eV (~ 15 kcal/mole). (The computations on which these and the following numbers are based have been given in Parsegian, 1969; Parsegian, 1976.) Passage through an aqueous channel requires energies less than one-third of this ($\lesssim 5$ kcal/mole). See Fig. 1.

The coulomb potential $1/r$ that extends from a charge will polarize material at distances far from the ion compared with its physical size a. As an ion in water approaches a hydrocarbon membrane, this polarization is felt as a repulsive image force. (Physically, the hydrocarbon/water interface takes on a positive charge as a positive ion attracts more negative charge from the water side of the interface than it can pull to the interface from the hydrocarbon.) Once within the membrane the charge is attracted toward the water interface. Conversely, by simple action and reaction, the interface is being pulled in toward the ion.

The magnitude of this force, on the order of 10^{-6} dynes when the charge is 10 to 15 Å from the interface, is small on a macroscopic scale. But exerted on a small patch of interface it is a pressure of 10's of atmospheres. The model

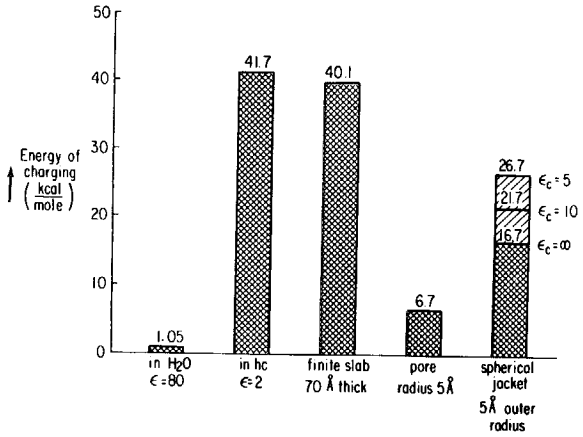

FIG. 1. "Self-energy" of charging a particle of unit ionic charge and of radius 2 Å in different surroundings: bulk water, bulk hydrocarbon, center of a layer of hydrocarbon 70 Å thick bounded by water, at the center of an aqueous pore bounded by lipid, in a spherical jacket or carrier. One kilocalorie per mole ≈ 2 thermal (kT) units per particle ≈ 8×10^{-13} ergs at room temperature.

(BLM) membranes will in general break under pressures of 1 atm or more. During passage across even a membrane 70 Å thick, a single ionic charge will pull on one or both faces with a pressure exceeding this critical value.

By pulling in the membrane walls the charge would lower the very high electrostatic self-energy it would ordinarily have in a lipid medium. Pinching will yield energy reductions of the order of 10 kcal/mole or $\approx 10^{-13}$ ergs per event. This is of the order of energies apparently required for local deformation of lipid membranes.

The ion–lipid interaction has both the force and the energy to effect transient rearrangement in the membrane structure during ion transport.

In the context of the purpose of this symposium, one might make the following distinction. Analyses of ion transport, across natural nerve membranes as well as artificial systems, have aimed for a mathematical description of the process with parameters either derived from physical measurement or defined as hypothetical physical quantities (such as fixed-energy barriers). This differs from a physical model which identifies molecular components and predicts how these components interact to form membranes and change to control transport across them.

If a membrane does change shape while bearing an ionic current the flow process cannot be described in terms of mobilities and gradients as has been the practice for bulk media. One might better speak of controlled instabilities in the overall membrane. What is needed is to develop a new intuition for transport across thin membranes, i.e., those comparable in dimension to the range of interaction of transported species. This is difficult since even the stress–strain moduli needed to describe transient structural changes are not known for local, short-lived perturbations of a membrane.

Controlled instabilities can easily lead to the nonlinear current–voltage structure relationships that typify natural membranes. Our growing understanding of the chemical structure of membrane-active proteins as well as of the phenome-

nology of model preparations now makes possible a critical rethinking of the molecular basis of ion transport across membranes.

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Application of Control Theory to Endocrine Regulation and Control

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This paper considers some aspects of the application of control theory to endocrine regulation and control. Consideration is given to both the structural and functional aspects of various control concepts and ideas in this context. For single-input, single-output feedback control structures, emphasis is placed on loop gain and its importance in establishing the functional capability of such structures. Examples are given of both functional and nonfunctional feedback structures proposed by endocrinologists. For multi-input, multi-output structures, emphasis is placed on the concept of input and output decoupling, and the possible applicability of these concepts to hormonal control system interrelationships is illustrated. Finally, the possible application of optimal control theory to endocrine regulation and control is illustrated by means of a naive and highly simplified example involving control of the thyroid gland by the pituitary gland, and several surprising and interesting implications are shown to be implicit in the resulting control structure.

INTRODUCTION

In a previous paper (Stear, 1973), past applications of systems theory to the study of physiological systems were briefly reviewed and some of the more significant deficiencies (from a control engineer's point of view) in such applications up to that point in time were pointed out. The deficiencies noted ranged across a broad spectrum of topics and included the following:

1. the lack of sufficient emphasis on quantitative measures of the degree of regulation achieved in physiological "feedback" systems,
2. the lack of any substantial or effective use of well-known multivariable and multilevel control concepts to further the understanding of the functioning of coupled physiological control processes,
3. the lack of an adequate and fundamental theory of noise and fluctuations endogenous to physiological systems and to measurements on them,
4. the use of outdated statistical analysis procedures for processing experimental data from physiological systems,
5. the need for a more general theoretical framework to support further study and research on physiological control processes.

This paper can properly be considered to be a sequel to the previous paper in that it deals with some of the same topics (points 1, 2, and 5 above) and directly addresses some of the deficiencies noted. The underlying theme of the paper is

[1] Some of the material in this paper was developed while the author was an MHTP Fellow, Department of Psychiatry and Laboratory of Environmental Neurobiology, UCLA School of Medicine.