Gate Control of Ion Flux in Axons

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This discussion deals with certain aspects of axon excitability in terms of the relation between molecular structure and function in the membrane, emphasizing the role of certain explicit assumptions in working out quantitative relations. The problem is formally to calculate the behavior of the axon membrane when exposed to electrical stimuli directly from the molecular structure of the membrane. Calculation of voltage clamp curves under a variety of conditions will suffice.

The concept of the axon membrane as a simple diffusion medium is now known to be inadequate and among the ideas put forward for improving the interpretation of axon behavior are those involving carrier molecules, charged channels through the membrane, and surface layer control. It is, of course, possible that any or all of these are present in the membrane. However, current notions of the composition and arrangement of the bimolecular lipid layer encourage the exploration of the surface layer approach for excitation problems.

Chemical, electron microscopical, and other data suggest the presence of an oriented bimolecular lipid layer roughly 100 A thick, coated with protein or other material on both sides, and protected by Schwann cells and connective tissue on the outside and by axoplasm on the inside. Attention is here directed to the bimolecular layer which contains phospholipids among other elements. These phospholipids have large moment, flexible dipoles at one end of long hydrocarbon chains, and the negative element of these dipoles is provided by partially substituted phosphate groups. Such dipoles are orientable in an electric field and the phosphate groups act as ion exchange sites whose specificity can be affected by their configuration. Thus, there are present in the membrane, molecular elements capable of providing control of ion flow by acting as gates operated by changes in the electric field. Explicit analysis of such a system permits calculation of current–voltage–time curves under voltage clamp conditions for relevant ions, provided of course that the details of the system are appropriately specified. In the absence of exact knowledge of the molecular structure and steric behavior, such specifications require assumptions to be made, explicit and simple, in order for the analysis to be carried through.
The specific phospholipids involved are not known; some of the dipoles may be prevented from moving freely either by bonding with the protein layer or by being packed into a dense molecular medium.

It is assumed that: (1) The mechanisms responsible for excitability are passive and not directly related to maintenance, pumping, or other relatively slow processes. (2) The mechanisms of control of potassium and sodium flow during activity are closely related although they may not involve the same geometrical pathways. (3) The rotation of the dipoles induced by changes in the electric field produces changes in binding specificity of the phosphate primarily with respect to sodium, potassium, and calcium ions. (4) The phosphate groups constitute a double barrier with a potential well in between, through which cations can pass by appropriate collision transfer. (5) The primary gate control is to be found in the external layer. This assumption is a matter of expediency. There is evidence that the effects of the internal layer should be considered although, because of the opposite dipole orientation with respect to the electric fields and the possibility that different phospholipids may be involved, the behavior of the internal layer is unlikely to be the same as that of the external layer. (6) The ions traverse the non-polar lipid region of the membrane in accordance with the usual electrodiffusion relations. Again this assumption is an expedient to permit simple treatment. The possibility that the ions traverse special channels cannot be ruled out. (7) The ions traverse the membrane in partially hydrated form, rather than as bare ions or in combination with carrier molecules.

One then postulates a "reaction network" in which the interaction of the polar group configurations and the binding properties of the phosphates play leading roles. The simplest possible mechanism is represented by the following diagram in which there are three configurations; one of them with the positive ends tucked into the membrane, which exposes the phosphates to the binding action of calcium ion; one with the dipoles oriented outward, which permits sodium to pass readily through the sites; and a third, also oriented outward, which is more stable under the same field conditions than the second and which favors the passage (or binding) of potassium.

\[
\begin{align*}
I_0 & \rightleftharpoons Ca^{++} + I \\
II + Na^+ & \rightleftharpoons II_N \\
III + K^+ & \rightleftharpoons III_K
\end{align*}
\]

The adsorption of sodium on II is indicated in parentheses since it seems likely that the binding is very weak.

It is now convenient to assume tentatively that the interaction of each con-
figuration with its favored ion is relatively rapid so that the exchange between the configurations provides the rate-limiting steps. The field dependence of \( k_1, k_2, k_3, \) and \( k_4 \) can be estimated from considerations of dipole structure and dielectric constant using both equilibrium and simplified absolute reaction rate theory, and involves explicitly the potential drop across the dipole region. Given a fixed number of total sites per unit area of membrane surface, one can then calculate the number in each configuration. It is implied that the significant phospholipid elements occur at intervals on the membrane surface either singly or in small clusters. Configurations I, II, and III in the diagram are the dipole forms and it is evident that the rotating action of the electric field is exerted on the free dipoles and not on the "bound forms."

It is now possible to combine three sets of relations: first, that for the kinetics of configurational interchange; second, that for the passage of ions through the ion exchange region; and third, that for their diffusion through the lipid portion of the membrane. The subsequent computations are tedious and require the use of machine methods but the result is a complete set of curves giving the ionic current elements directly in terms of membrane potential, time, and ion concentrations. The formulation has the advantage of being explicit and of having physically identifiable, if not directly measurable, parameters. It is then possible, by comparison with experimental data, to estimate the parameters and so to complete the calculation. One can also predict the behavior of the axon under "non-standard" conditions and use the new data, including particularly the effects of unusual ions, narcotics, and poisons to challenge the postulated system. Calculations and experiments along these lines are now being carried out.

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