THE DIPOLE MODEL AND
PHASE TRANSITIONS
IN BIOLOGICAL MEMBRANES

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ABSTRACT   Assuming the dipole model for a membrane, approximate calculations are made which employ a dipole-dipole interaction energy. The calculations are based upon the assumption of cooperative coupling of membrane polar molecules and make use of the Bragg-Williams approximation. A theoretical estimate is made of the critical temperature at which phase changes might occur in certain biological membranes. Proposals are presented which explain how the dipole transition might relate to the sometimes observed thermal phase transitions in biological membranes.

INTRODUCTION

It is generally conceded that all biological membranes are composed of some complex arrangement of macromolecules, primarily phopholipids and proteins, but the precise structural configuration of such a macromolecular system is the subject of much scientific debate. It is expected that some of the uncertainty associated with membrane structure will be elucidated within the next few years as a consequence of the development of experimental instruments with greater resolving power, in particular, the electron microscope; however, until such time as all ambiguities associated with membrane stereochemistry are resolved, we must be content with approximate model descriptions of both membrane structure and membrane-associated phenomena such as nerve excitation and nerve conduction. While perhaps lacking in sophistication, these models, if consistent with available knowledge, illuminate the possible paths for future work to follow. One such approach is presented in this paper.

We have been particularly intrigued by the so-called dipole model (Goldman, 1964; Wei, 1969) because of its relative simplicity which allows for the application of some fundamental principles of theoretical physics and chemistry. We are certainly aware of the dangers involved in oversimplification; however, until more concrete evidence concerning membrane structure and function is firmly established, we must content ourselves with such model calculations, and hope that, from a theoretical

point of view, we can gain some insight into the various aspects of membrane phenomena.

Wei (1969) has suggested that the nerve impulse is a macroscopic manifestation of quantum transitions of electric dipoles, located at the membrane surface, during the stimulation process, and he has demonstrated that the all-or-none response, the strength-duration relation, refractoriness and refractory period, and frequency modulation can be accounted for on the basis of dipole transitions (Wei, 1971) between two available states. It has also been shown that the characteristic steady-state current-voltage relations, with regions of negative resistance, of squid axonal membranes can be accounted for on the basis of the dipole model (Hamel and Zimmerman, 1970).[1]

Mărgineanu and Moisescu (1970) have demonstrated, upon the basis of the thermodynamics of irreversible processes, that the energy dissipated during the action potential of a giant axon is 6 $\mu w/cm^2$ which is precisely the value measured by Fraser and Frey (1968), and they further suggest that their calculations "harmonize with Wei's recent theory on nerve excitation and conduction and offer quantitative support for these conceptions." Friedenberg (1967), too, has suggested that the role of electric dipoles in biological membranes is significant in respect to the fields that they generate, and that their effects cannot be neglected.

With regard to our own efforts, we have adopted the view that the membrane dipoles or dipolar regions participate in a cooperative structural transition during the electrical excitation process. The resulting configurational rearrangement is suggestive of the extensively larger but nevertheless similar thermal phase changes that have been observed (Steim et al., 1969; Engelman, 1970; Chernitskii et al., 1969).

PHASE TRANSITIONS VIA THE DIPOLE MODEL

As stated in the introduction we have invoked the idea of cooperative behavior in conjunction with the basic ideas of the proponents of the dipole model. There exist several excellent treatments of cooperative membrane phenomena without reference to a specific model such as the dipole model (Hill, 1967; Hill and Chen, 1970; Changeux et al., 1967; Blumenthal et al., 1970). Also, Hamel and Zimmerman (1970), and Wobschall (1968) have developed a mathematical model in which they assume a cooperative dipole realignment of individual layers of a bilayer membrane. Our basic premise is that the membrane dipoles interact via cooperative coupling, and in turn initiate or trigger the over-all conformational change of the membrane macromolecules in a time-dependent way. The membrane prototype that we originally had in mind was the bimolecular phospholipid leaflet of Davson and Danielli (1943) and Robertson (1962); however, the development is readily adaptable to other specific membrane models, for example, the protein crystal model (Vanderkooi

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[1] Arndt, R. A., J. D. Bond, and L. D. Roper. To be published.

and Green, 1970). With respect to the bimolecular phospholipid leaflet one readily makes the correspondence of the polar head groups of the phospholipids with the membrane dipoles; however, it is certainly conceivable, especially in view of the aforementioned uncertainties in membrane structure, that perhaps the membrane exists in a discrete domain structure as suggested by Kilkson (1970), and the electrical coupling mentioned by Kilkson could be the coupling between net dipole moments of various domains. This viewpoint is at least consistent with the protein crystal model and other alternative membrane structural models recently proposed (Deamer, 1970).

It is significant that we describe the dipolar regions and the forces these regions generate as initiators of membrane reconfiguration. They should not necessarily be viewed as the only changing membrane constituents in a transition nor as the sole energy sources for such change. The sort of triggering mechanism we had in mind has precedents in related phenomena. Just a few of these are:

(a) The helix-coil transition in polypeptides is initiated in some cases by very slight electrostatic balance changes (Poland and Scheraga, 1970).

(b) The equivalence of an ion concentration change–induced and a thermally induced phase transition in biological macromolecules has been established in certain cases (Schleich and Von Hippel 1970).

(c) The transmission of conformational information (allosteric effects) is well-known in enzymes, information traveling from an "initiator" site and through the enzyme structure.

(d) In synthetic semicrystalline polymers the amorphous regions pass through their glass transition point on temperature increase generally before the crystalline melting point is reached. This glass transition temperature can be significantly affected by polar substituents or steric hindrance along the macromolecular chain. The bulk physical properties of the polymeric system are rather drastically altered by passing through the glass transition temperature (Mandelkern, 1964; Nielsen, 1962).

(e) The conversion of a number of different forms of energy into mechanical energy of reconformation of macromolecules in the solid state is well-known (see Miller, 1966, p. 641, for a general listing).

In our calculations we consider the membrane to be composed of a two-dimensional array or lattice. Each individual lattice site is occupied either by a single polar molecule or perhaps a composite group of several or more polar molecules, thus forming discrete dipole domains. Each site is assumed to possess some net dipole moment because of the polar nature of the constituent molecules, and only nearest neighbor interactions are considered. There are only two energy states available to each site, and a transition involves thus a shifting or repopulating of the two available states upon application of some external influence such as an external electric field or a temperature variation. The transition between the two accessible states is a result of either a reorientation of the permanent moments or deformation polarization due to the induced moments or both; however, when considering thermal

effects only the reorientation contribution is important since the induced moment can be regarded as essentially temperature independent. We adopt the Bragg-Williams approximation in our calculations.[2] The work of Hill (1960, 1967) should be consulted for the details of such a calculation. Our basic ideas closely follow those of Hill (1967); however, we explicitly work with the parameters associated with the dipole model, for example, the dipole moments, and, as a first approximation, we use the classical electrostatic dipole-dipole potential in considering nearest neighbor interactions. Although this seems a drastic assumption similar calculations of transition parameters based on the nearest neighbor dipole-dipole interaction have been in reasonable agreement with experiment (Fröhlich, 1946). We are currently extending our considerations to higher order neighbors.

We assume that the membrane dipoles are oriented in a plane parallel to the plane of the membrane, in one of two directions, parallel and antiparallel. This is consistent with the fact that such an orientation yields the minimum energy configuration, and, also, it has been observed that in certain lecithin bilayers the phosphate and trimethylamine groups are in a plane parallel to the leaflet (Hanai et al., 1965). We make this assumption merely for convenience here, and we are presently investigating other orientations. We assume one orientation corresponds to a state A, and the other orientation, antiparallel to the first, corresponds to a state B. Transitions, whether thermally, electrically, or otherwise induced, will occur under conditions that correspond to a shift in the population of the two available states to the one that is thermodynamically favored.

In more physical terms the initiation in the trigger region may occur in response to an imposed electric field, as in membrane excitation where the new configuration could contain channels for ion transport, or in response to the acquisition of enough thermal energy to lead to a liquid crystal type of new configuration in the rest of the membrane. Because of our concentration on the dipolar regions as the key to the transition mechanics and because these regions are held together by a balance of electrostatic against thermal forces then our calculations should show the interrelationship between temperature and electric field in the membrane. The following paragraphs illustrate this calculation.

Let w_{AB} be the electrostatic dipole-dipole interaction potential between two electric dipoles, $\mathbf{p}_A$ and $\mathbf{p}_B$. Then,

$$w_{AB} = \frac{\mathbf{p}_A \cdot \mathbf{p}_B - 3(\mathbf{n} \cdot \mathbf{p}_A)(\mathbf{n} \cdot \mathbf{p}_B)}{4\pi K \epsilon_0 |\mathbf{x}_A - \mathbf{x}_B|^3}, \qquad (1)$$

where $\mathbf{n}$ is a unit vector in the direction $(\mathbf{x}_A - \mathbf{x}_B)$, $\mathbf{x}_A$ is the position vector of dipole A, $\mathbf{x}_B$ the position vector of dipole B, K is the dielectric constant of the medium, and ϵ_0 is the permittivity of free space (Jackson, 1962) (see Fig. 1). Equation 1 is written
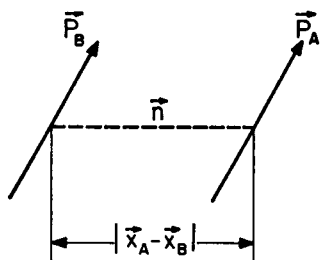
FIGURE 1. The vector geometry corresponding to equation 1.

in the rationalized mks system of units. In performing calculations associated with the dipole model, we have found it convenient to use a system of natural units in which length is expressed in angstroms (A), the dipole moment in electron-angstroms, energy in millielectron volts, and the universal physical constants are appropriately modified. In the approximation we are using the critical temperature T_c (Hill, 1967) at which a phase transition is observed is governed by the condition

$$\frac{cw}{kT_c} = -4, \tag{2}$$

where c is the number of nearest neighbor dipoles, k is the universal Boltzmann constant, and w is defined by

$$w = w_{AA} + w_{BB} - 2w_{AB}, \tag{3}$$

with w_{AA}, w_{BB}, and w_{AB} given by equation 1. Actually, in our two-dimensional system, care must be taken in computing the w_{AA}, w_{BB}, and w_{AB} factors, as can be readily seen from equation 1, since interactions between nearest neighbors (assuming for simplicity a cubic lattice) are different between nearest neighbors in a single row and between nearest neighbors in adjacent rows (see Fig. 2). For our particular choice of orientations equation 3 becomes

$$w = \frac{w_{A_xA_x}}{2} + \frac{w_{A_yA_y}}{2} + \frac{w_{B_xB_x}}{2} + \frac{w_{B_yB_y}}{2} - w_{A_xB_x} - w_{A_yB_y}. \tag{4}$$

Using equations 1 and 4 and assuming for simplicity (we are interested in only order of magnitude estimates here) $|\mathbf{p}_A| = |\mathbf{p}_B|$, we find

$$w = \frac{-2|\mathbf{p}_A|^2}{|\mathbf{x}_A - \mathbf{x}_B|^3}. \tag{5}$$

Substituting equation 5 into equation 2, we can immediately solve for the critical temperature T_c. There is considerable uncertainty, however, about the magnitudes of the various parameters involved; for example, the dipole moment has been
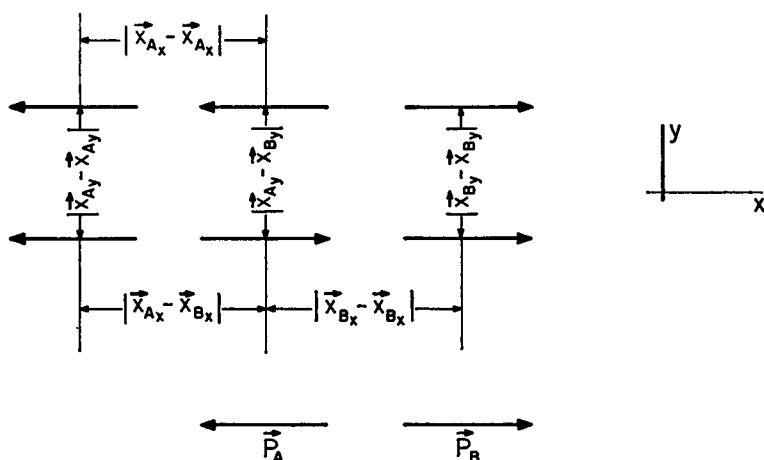
FIGURE 2 The two-dimensional dipole membrane geometry. Note that the dipoles are considered to lie in the plane of the membrane.

estimated to vary from 25 D to 1000 D (Wei, 1969). Measurements of thermally induced phase transitions (Steim et al., 1969) indicate that the critical temperature is somewhere in the neighborhood of $T_c = 300°K$. It should definitely be mentioned that the interpretation of these experiments has been to consider the observed phenomena to correspond to a melting of the hydrocarbon chains in a bilayer membrane. In view of our calculations, as stated previously, we simply suggest that the primary interaction between membrane subunits is the dipole-dipole interaction as given by equation 1, and the cooperative coupling of the dipolar sites precipitate, in this case, the hydrocarbon reconfiguration.

For $\mid p_A \mid = 200$ D, $\mid x_A - x_B \mid = 5A$ (Ohki, 1968), $K = 80$, we find $T_c = 298°K$. The values of the parameters used to obtain agreement with Steim's experiments are certainly reasonable.

By the very nature in which equation 2 was obtained (Hill, 1960) it is not clear what the true thermodynamic significance of these results is. It is certainly most interesting, however, that such good agreement is obtained, especially since using only a slight modification of the above procedure we were able to obtain excitation threshold potentials in good agreement with the well-known experimental values (Ward and Bond, 1971).

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