THEORY OF PROTEIN INFLUENCE ON MEMBRANE THICKNESS

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There is an attraction between membrane proteins inferred from their influence on lipids.[1] Its range is 10–20 nm, the same as the thickness correlation length estimated from studies of membrane elasticity.[2] This suggests that the force arises from the thickness variation around proteins. The influence of proteins on lipid phase transitions can also reveal the range of their effect, again 10–20 nm.[3]

Much theory and spectroscopy has been claimed to show that protein influence on lipid conformation is slight beyond nearest neighbors. If this is true, some other degree of freedom must propagate the thickness perturbation. The thickness elastic modulus is far too small for compression-induced thinning to represent proliferating *gauche* bonds, so tilting is suggested as the mechanism of thinning. This argument would be more convincing if we had a microscopic theory of tilt. Past lipid statistical mechanics have invoked empirical descriptions of the forces between chains. What controls their orientation is unknown.

Some models have attributed chain ordering to anisotropic attraction (Marčelja, 1974; Gruen, 1980). The following suggests that repulsion is more important. In simpler systems, the anisotropy of van der Waals forces is far too small (Wulf, 1976; Warner, 1980). Models with purely repulsive interactions yield qualitatively correct ordering, since it is intimately connected to the geometric constraints of arranging chains in a membrane (Scott, 1977; Dill and Flory, 1980). The different geometry controls the opposite order gradients in membranes and micelles, and the much smaller ordering in liquid hydrocarbons (Vacatello et al., 1980).

Attractive and repulsive anisotropy are not mutually exclusive. Chains can pack most closely when they are parallel, i.e., when they most attract. This will increase the ordering beyond that produced by repulsion alone. Similarly, the closest approach distance of two segments depends on their relative depths in the membrane. This makes the effective chain attraction orientation dependent. I am developing a generalized van der Waals theory (Humphries, et al., 1972; Priest, 1976; Gelbart and Baron, 1977) to study these effects in detail.

RESULTS AND DISCUSSION

Consider a membrane containing N chain segments. The interaction energy of two segments can be taken as

$$U = U(\mathbf{r}, \theta_m; \theta_1, \phi_1; \theta_2, \phi_2) \tag{1}$$

where $\mathbf{r}$ is separation of their centers, θ_m, θ_1, and θ_2 are the angles between a membrane normal and $\mathbf{r}$, segment 1, and segment 2, respectively, and the ϕ's are the azimuthal angles of the segments relative to $\mathbf{r}$. This assumes that both the membrane and the segments are axially symmetric. I divide the energy as $U = U_0 + U_1$, where U_0 will be regarded as the basic energy, and U_1 as a perturbation. Let n_0 denote the doublet distribution function produced by U_0 alone, and n that produced by U. I use the normalization

$$\int d_m\, d_1\, d_2\, n = N$$

where

$$d_m = 2\pi \mathbf{r}^2 \sin\theta_m\, d\theta_m, \text{ and } d_i = \sin\theta_i\, d\theta_i\, d\phi_i \; (i = 1, 2). \tag{2}$$

My analysis is based on a mean field approximation. First assume

$$n = F(\theta_1)\, F(\theta_2) n_0. \tag{3}$$

F represents the influence of U_1 on the orientation distribution. Self-consistency requires

$$F(\theta_1) = \exp(-U_F/KT) / \int d_{\cos}\theta_1 \exp(-U_F/KT) \tag{4}$$

where the effective potential is found by averaging U_1

$$U_F(\theta_1) = \int d\phi_1\, d_m d_2\, F(\theta_2)\, n_0\, U_1. \tag{5}$$

I next introduce multipole expansions. Define

$$F(\theta) = \sum_{K} F_K\, P_K(\cos\theta) \tag{6}$$

and

$$X(m; 1; 2) = \sum_{JJ_1J_2M_1M_2} <X(\mathbf{r}) \,|\, JJ_1M_1J_2M_2> P_J(\cos\theta_{\mathrm{m}}) Y_{J_1M_1}(1)\, Y_{J_2M_2}(2) \tag{7}$$

where P and Y are Legendre polynomials and spherical harmonics, and X is n or U. This yields

$$U_F(\theta_1) = \sum_{LK} d_{LK}\, F_L P_K(\cos\theta_1) \tag{8}$$

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[1] Edelman, J., T. Pearson, and S. I. Chan. Statistical mechanics of lipid membranes: I. Protein aggregation and lipid ordering. Submitted for publication.

[2] Edelman, J., and S. I. Chan. Submitted for publication.

[3] Edelman, J. Manuscript in preparation.

where:

$$d_{\mathrm{LK}} = \sum_{JJ_1J_2J_1'J_2'M_1M_2} C^*(LJ_2J_2'; 0M_2)C^*(J_1J_1'K; M_1 - M_2)$$
$$\times \left(\frac{(2J_2 + 1)(2J_1 + 1)(2J_1' + 1)}{2J_2' + 1}\right)^{1/2}$$
$$\times \frac{(-1)^{M_2}}{2J + 1} 2\pi \int \mathbf{r}^2 \, d_{\mathbf{r}}$$
$$\times <n_0(\mathbf{r})\,|\,JJ_1M_1J_2M_2><U_1(\mathbf{r})\,|\,JJ_1'$$
$$-M_1J_2' - M_2> \qquad (9)$$

and

$$C^*(IJK;LM) = C(IJK;LM)\ C(IJK;00). \qquad (10)$$

The C's are Clebsch-Gordon coefficients.

These results can be developed in two ways. One is to take the d's as empirical. Then Eq. 8 can be substituted into Eq. 4, and solved to yield the ordering. Alternatively, Eq. 9 can be used to study the molecular basis of the ordering. The latter is considered here.

Eq. 9 reveals a lack of any simple relation between the tensor characters of the ordering and the forces producing it. To understand d, consider some simpler cases. When U_1 is isotropic,

$$d_{LK} = \frac{(2L + 1)(2K + 1)^2}{(2L - 1 + \delta_{L0})(2K - 1 + \delta_{K0})} \frac{\pi}{2}$$
$$\int \mathbf{r}^2 d\mathbf{r} U_1(\mathbf{r})\rho(\mathbf{r}) <P_K P_L> \mathbf{r} \qquad (11)$$

where δ is a Kronecker δ; $\rho = <n_0|00000>/4$ is the isotropic part of the distribution function; and $<P_K P_L>$ **r** is the mean value of $P_K(\cos\theta_1)$ P_L $(\cos\theta_2)$ for two segments whose separation is **r**. Eq. 11 shows that even isotropic interactions can shift the ordering. At the opposite extreme, take n_0 isotropic. Then

$$d_{LK} = \frac{(2K + 1)^3(2L + 1))^{1/2}}{(2L - 1 + \delta_{L0})(2K - 1 + \delta_{K0})}$$
$$8\pi \int \mathbf{r}^2 \, d\mathbf{r} \, \rho(\mathbf{r}) <U_1(\mathbf{r})\,|\,0K0L0> \qquad (12)$$

When U_1 does not depend on orientation in the membrane, this takes a simpler form which decouples the F's:

$$d_{LK} = \delta_{LK} \left(\frac{2K + 1}{2K - 1 + \delta_{K0}}\right)^2$$
$$8\pi \int \mathbf{r}^2 \, d\mathbf{r} \, \rho(\mathbf{r}) <U_1(\mathbf{r})\,|\,0K0K0>. \qquad (13)$$

Detailed numerical analysis of these results remains to be done. Even without it, though, there are several important lessons. First, the different F_J's are intrinsically coupled. The ready experimental accessibility of F_0 and F_2 is no justification for modeling them alone. Theoretical studies of simple systems do show that the higher order F's are small there (Gelbart and Gelbart, 1977; Workman and Fixman, 1973). However, membrane organization is an important difference. Here, the interaction can depend on orientation. There is thus no $L = K$ selection rule in Eqs. 11 and 12. Second, the separation of U_0 and U_1 is arbitrary. It is thus meaningless to argue whether repulsion or attraction produces the ordering. Further developments of this theory will use molecular models to calculate U and n, which in turn can reveal the correlations and elastic coefficients of the order parameters.

Received for publication 2 May 1981.

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