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Lipid vertical motion and related steric effects in bilayer membranes*, **

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Abstract. We present a theoretical model of a lipid bilayer in its gel state which explicitly couples the vertical displacements of the lipid chains to their conformational state. In this model the chains are free to move longitudinally under a potential due to the neighbouring chains. The potential is due to a restoring force with a force constant k and thus acts to keep them in the local plane as defined by their nearest neighbours. It is demonstrated that the force constant k is directly related to the internal bilayer pressure, Π, and that if a value $\Pi = 33$ dynes/cm is assumed then $k = 17.3$ dynes/cm. Steric effects are explicitly included by allowing chains to twist into free volume created by the vertical displacement of neighbouring chains. The Hamiltonian is expressed in terms of the projection operators, P_{ij}, describing the displacement of chain i relative to a neighbour j, and G_{ij} describing the direction of a twist in chain i. The model is solved both analytically and via Monte Carlo simulations for a one-dimensional system. The possibility of phase-transitions in two-dimensions and the relevance to the bilayer pre-transition is discussed.

Key words: Lipid bilayers, statistical mechanics, steric interactions, one dimensional, ripple phase

Introduction

Until recently there has been little experimental or theoretical investigation of out of plane displacements of lipids in planar bilayer membranes.

On the theoretical side there have been models of the ripple phase which invoke the displacement of lipids relative to one another. The first of these models was due to Doniach (1979) who looked at the continuum limit of an interlocking chain model. More recently Pearce and Scott (1982) considered the displacements of "L" shaped molecules on a square lattice. This model was investigated by Scott (1984) using computer simulation techniques. In neither of these models was the possibility of the lipid chains altering their conformational state taken into account. It would appear, however, that the number of gauche bonds per lipid molecule in the gel state close to the main phase transition, though small, is not negligible. This is found from interpretation of Raman spectroscopy and infrared spectra (Pink et al. (1980) and Snyder et al. (1982)). Clearly the chains would preferentially twist into free volume created by the displacement of adjacent lipids vertical to the plane of bilayer. Although experimental evidence for such a picture is sparce a recent spin-label study (Feix et al. 1984) of dimyristoylphosphatidylcholine bilayers in the fluid state has shown that there are pronounced vertical fluctuations of the terminal methyl groups of the acyl chains.

In the present work we shall investigate the steric effects that arise from allowing the lipid acyl chains to twist into the free volume created by the vertical displacement of neighbouring chains. We model the acyl chains as cylinders which occupy the sites of a two-dimensional close-packed (triangular) lattice. The chains are free to move longitudinally under the influence of a potential which acts to keep them in the average local plane of the bilayer as defined by their nearest neighbours. We also allow a chain to twist in any one of the six directions of its nearest neighbours. Obviously it is energetically more favourable to twist into free volume created by the vertical displacement of an adjacent chain. However

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other favourable configurations (such as adjacent chains with parallel twists) are also permitted.

The Hamiltonian describing this model is presented and solved analytically in one-dimension. The model may be studied in two dimensions (representing a lipid bilayer) using Monte Carlo techniques. The results and their possible relevance to the pre-transition and consequent ripple phase are presented in the discussion.

The model

We consider each monolayer of a phospholipid bilayer as an assembly of cylinders, each occupying a site of a triangular lattice in the $x-y$ plane with the cylinder axis in the z direction. Each cylinder has a diameter d and represents an acyl chain. We ascribe to it the following properties:

(i) A cylinder at side i is free to move in the z direction in a potential $V_i(z)$ due to its nearest neighbours. This potential acts to keep it in the average local plane of the bilayer as defined by its nearest neighbours. The physical motivation for assuming such a potential is the following. One can imagine that in a real bilayer work would have to be done to either pull a lipid out of or push a lipid into the bilayer. The effective force against which work is being done is derived from the scalar potential, $V_i(z)$.

(ii) Each cylinder may twist into any one of the six directions of its nearest neighbours and can have at most one twist. Thus a twist is representative of one or two gauche bonds in the chain which is a reasonable representation of a bilayer in its gel state.

(iii) We assume that the short-range attractive forces between the chains are essentially isotropic and enter as an constant additive term in the Hamiltonian. Steric interactions, however, occur whenever a chain twists and must be accounted for explicitly by the model.

The Hamiltonian may thus be written

$$H = H_L(P_{ij}) + H_C(G_{ij}) + H_S(P_{ij}, G_{ij}) , \tag{1}$$

where the Hamiltonian for the longitudinal motion, H_L, is written in terms of an operator P_{ij} describing displacements between neighbouring chains, the Hamiltonian for the chain conformations is written in terms of an operator G_{ij} which describes the twisting of a site i into a site j and H_S is a mixed term describing the steric interactions. We shall consider each part of Eq. (1) in turn.

(a) H Longitudinal

Since we assume that there is a restoring force between two neighbouring cylinders which acts to keep them level, the leading term of the scalar potential must be an even power of their relative displacement. For small displacements this leading term will be the dominant term. For the simplest case we may choose a quadratic term, i.e. a harmonic potential. Then the potential on a site i due to a neighbour j is

$$V_i^{(j)} = \frac{k}{2} x^2 , \tag{2}$$

where k is the force constant and x is the displacement from the minimum of the potential. Simple geometrical arguments (see Fig. 1) show that

$$x = [d^2 + (z_i - z_j)^2]^{1/2} - d_0 , \tag{3}$$

where z_i, z_j are the positions of the tops of cylinders i, j respectively and d_0 is the equilibrium distance. We may substitute x into (2) and, for small displacements, expand to first-order to give

$$V_i^{(j)} = \frac{k}{2}(d - d_0)^2 + \frac{k}{2}\left(\frac{d - d_0}{d}\right)(z_i - z_j)^2 \tag{4}$$

and summing over all j nearest neighbours of i $(j\,n\,n\,i)$

$$V_i = q\frac{k}{2}(d - d_0)^2 + \frac{k}{2}\left(\frac{d - d_0}{d}\right)\sum_{(jnni)}(z_i - z_j)^2, \tag{5}$$

where $q = 6$ is the coordination number of the lattice. Equation (5) is a mathematical expression of the statement that a cylinder will tend to sit in the local plane defined by its nearest neighbours. Let us define the quantity P_{ij} by

$$P_{ij} = \frac{(z_i - z_j)}{z_0} , \tag{6}$$

where z_0 is a constant. Before discussing Eq. (6) we note a general lattice property of the P_{ij}'s. It of course follows immediately from (6) that

$$P_{ij} + P_{ji} = 0 . \tag{7}$$

In fact any closed walk on the lattice will have the property that

$$P_{ij} + P_{jk} + \ldots + P_{rs} + P_{si} = 0 . \tag{8}$$

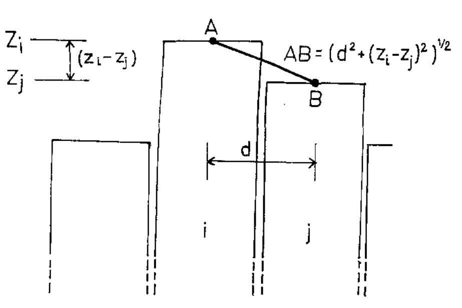

Fig. 1. The displacement of cylindrical molecules relative to each other

It is straightforward to show that a necessary and sufficient condition to ensure (8) is that, for any three neighbouring sites i, j, k forming a triangle in the triangular lattice, we must have

$$P_{ij} + P_{jk} + P_{ki} = 0 . \tag{9}$$

In order to give a physical interpretation of the quantities P_{ij} and z_0 we rewrite (6) as

$$z_j = z_i - z_0 P_{ij} . \tag{10}$$

This recursion says that the cylinder at site j is displaced by an amount $-z_0 P_{ij}$ relative to its neighbour at site i. It is not physically unreasonable to assume that these displacements are discrete, for example the length of a $C-C$ bond. Then the displacements may only be by an amount $+z_0$, 0, $-z_0$ and P_{ij} takes the character of a projection operator with eigenvalues -1, 0, $+1$. For example, from Eq. (7) it can be seen that $P_{ij} = -1$ gives a displacement of cylinder j relative to i of z_0 in the $+z$ direction. We may substitute (6) into (5) and sum over all lattice sites to form

$$H_L = \sum_i V_i = N q \frac{k}{2}(d-d_0)^2 + \frac{k z_0^2}{4}\left(\frac{d-d_0}{d}\right) \sum_{\langle ij \rangle} P_{ij}^2 , \tag{11}$$

where N is the total number of sites and $\langle ij \rangle$ implies that the summation runs over all nearest neighbour pairs, ij. We note that in obtaining (11) we made use of the fact that $P_{ij}^2 = (-P_{ij})^2 = P_{ij}^2$.

Before continuing we make a brief diversion and ask if the force constant k is directly accessible by experiment. We first note that the interchain distance is kept constant in our calculations, since the model in its present form is only applicable to lipid systems in the gel phase and does not describe chain melting. Any extension of the model in this direction requires a detailed description of chain flexibility by the inclusion of higher energy gauche conformers resulting in a variable interchain separation.

We can make a simple attempt at including a variable interchain separation in the following way. We note from Eq. (11) that the "constant" term in the Hamiltonian contains a factor $k\,d^2/2$ where d is the interchain separation. Suppose this separation depended on the states of the nearest neighbour lipids i and j. Then the term would become

$$\sum_{\langle ij \rangle} \frac{k}{2} d_{ij}^2 = \sum_{\langle ij \rangle} \frac{k}{2} (r_i + r_j)^2 , \tag{11 a}$$

where r_i and r_j are the radii of chains i and j respectively. Following Pink et al. (1980) suppose a chain can be in any of n states each of which has an associated radius, r_n. Then by introducing a projection operator $\mathscr{L}_{in}$ (which projects the chain at i into a state n) Eq. (11 a) becomes

$$\frac{k}{2} \sum_{\langle ij \rangle} \sum_n (\mathscr{L}_{in} r_n + \mathscr{L}_{jn} r_n)^2 . \tag{11 b}$$

A property of projection operators is that $\mathscr{L}_{in}^2 = \mathscr{L}_{in}$. Thus (11 b) becomes

$$q\,k \sum_i \mathscr{L}_{in} r_n^2 + \text{cross terms} , \tag{11 c}$$

where q is the coordination number of the lattice. Finally we note that the area of the lipid is given by $A_n = \pi r_n^2$, thus we obtain

$$\sum_i \left(\frac{q\,k}{\pi}\right) \mathscr{L}_{in} A_n . \tag{11 d}$$

A comparison with the model of Pink et al. (1980) shows that a term of the form

$$\sum_i \Pi A_n \mathscr{L}_{in} \tag{11 e}$$

occurs in the ten state Hamiltonian, where Π is the internal lateral pressure in the bilayer. Thus we obtain the relation

$$\frac{q\,k}{\pi} = \Pi \tag{11 f}$$

between the lateral pressure Π and the force constant k. Using a value of 33 dynes/cm for the internal pressure of the bilayer we find the $k = 17.3$ dynes/cm.

(b) H Conformations

We stated earlier that a cylinder can twist into any one of the six directions of its neighbours and that a twist represents one or two gauche bonds in the acyl chain. We denote the energy required to produce a twist by ε_T. We introduce an operator G_{ij} such that if the cylinder at site i is twisted into site j then $G_{ij} = 1$, otherwise $G_{ij} = 0$. Of course the chain at i need not be twisted which we will denote $G_{ii} = 1$. Since a cylinder must either be straight or twisted into one of its neighbours we must have

$$G_{ii} + \sum_{(j\,n\,n\,i)} G_{ij} = 1 . \tag{12}$$

Then for a site i the energy is given by

$$H_c^{(i)} = \varepsilon_T \sum_{(j\,n\,n\,i)} G_{ij} = \varepsilon_T (1 - G_{ii}) . \tag{13}$$

So that for the whole lattice

$$H_c = N \varepsilon_T - \varepsilon_T \sum_i G_{ii} . \tag{14}$$

(c) H Steric

This part of the Hamiltonian disfavours sterically undesirable configurations. Let us consider the steric effects introduced when a given site i twists into one

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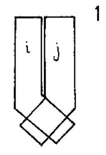
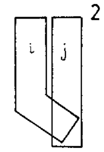
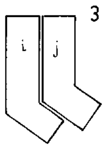
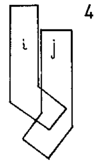
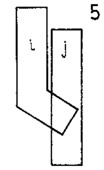
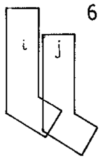
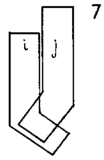
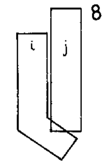
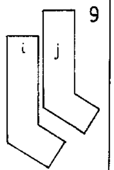
$P_{ij}=0$	 $W=1$	 $W=1$	 $W=0$
$P_{ij}=1$	 $W=1$	 $W=2$	 $W=0$
$P_{ij}=-1$	 $W=1$	 $W=0$	 $W=0$

Table 1. The nine steric interactions possible when site i is twisted into a neighbouring site j and the weight ascribed to each by the weighting function of Eq. (15)

of its neighbours j. There are no steric interactions introduced by site i with site j when it is straight or twisted away from j (i.e. when $G_{ij}=0$). When $G_{ij}=1$ we must consider the nine possible cases illustrated schematically in Table 1.

We introduce the following weighting function

$$W = G_{ij}\, G_{ji} + G_{ij}\, G_{jj}\,(1+P_{ij}) \tag{15}$$

and note the following:

(i) Unless $G_{ij}=1$ (chain i is twisted towards j) then $W=0$.

(ii) If the twists are parallel (Table 1 (3), (6), (9)) then $W=0$.

(iii) If j is elevated relative to i (Table 1 (8)) then $W=0$.

(iv) All other configurations are sterically unfavourable and have a positive value for W.

We associate with W a steric energy ε_s which is positive and large, thus making the weighted configurations energetically unfavourable. For site i

$$H_s^{(i)} = \varepsilon_s \sum_{(jnni)} G_{ij}\,(G_{ij} + G_{jj}\,(1+P_{ij})) \tag{16}$$

and for the entire lattice

$$H_s = \frac{\varepsilon_s}{2} \sum_{\langle ij\rangle} G_{ij}\,(G_{ji} + G_{jj}\,(1+P_{ij}))\,. \tag{17}$$

(d) The complete Hamiltonian

The complete Hamiltonian for the model is given by adding Eqs. (11), (14) and (17), giving

$$H = C + \frac{\varepsilon_0}{4} \sum_{\langle ij\rangle} P_{ij}^2 - \varepsilon_T \sum_i G_{ii} + \frac{\varepsilon_s}{2} \sum_{\langle ij\rangle} G_{ij}\,(G_{ji} + G_{jj}\,(1+P_{ij}))\,, \tag{18}$$

where C is an additive constant (and hence plays no role in determining the thermodynamic properties of the system) given by

$$C = N\,q\,\frac{k}{2}\,(d-d_0)^2 + N\,\varepsilon_T \tag{19}$$

and

$$\varepsilon_0 = k\,z_0^2 \left(\frac{d-d_0}{d}\right). \tag{20}$$

We recall here that the operator P_{ij} can take values 0, ± 1 subject to the constraints (7), (9) and that $G_{ij}=0, 1$ subject to (12).

It is clear that the thermodynamic properties of the model will depend on the values assigned to the energies ε_0, ε_T and ε_s. The choice of these energies is not entirely arbitrary. In the case of ε_T, which is the energy required to produce one to two gauche bonds in a chain, we are restricted to the range $\varepsilon_T \sim (0.45-0.9)\times 10^{-13}$ ergs for a realistic bilayer model (see, for example, Marcelja et al. (1974)). In the case of ε_s a value of 0 would eliminate the difference between sterically hindered states and energetically favourable states whereas an arbitrarily large value would preclude the sterically hindered states entirely. Thus, provided ε_s is large and positive its exact numerical value should have little effect on the properties of the system. This leaves ε_0 as the only truly adjustable parameter. Clearly it must be positive, but its exact value will determine the stiffness of the bilayer. A small value would allow the chains to move freely in the vertical direction whereas a large value would hinder vertical motion.

To produce an analytical solution of Eq. (18) for a two-dimensional triangular lattice is a formidable task and the model is best tackled via computer simulations. We can, however, solve the model in one dimension and from this solution make some general speculations concerning the nature of the two dimensional properties we expect to obtain.

(e) Solution in one dimension

In one dimension the model reduces to a line of cylinders which can twist in the backwards or forwards directions only. The constraint (12) becomes

$$G_{ii} + G_{ii-1} + G_{ii+1} = G_i(\downarrow) + G_i(\swarrow) + G_i(\searrow) = 1. \tag{21}$$

We can replace the G_i's by dummy spin variables $S_i = 0, \pm 1$ by the usual transformation

$$\begin{aligned} G_i(\swarrow) &= \tfrac{1}{2} S_i (S_i - 1) \\ G_i(\downarrow) &= 1 - S_i^2 \\ G_i(\searrow) &= \tfrac{1}{2} S_i (S_i + 1) \end{aligned} \tag{22}$$

so that at a given site i a value $S_i = 1$ corresponds to a twist in the $i+1$ direction, $S_i = -1$ to a twist in the $i-1$ direction and $S_i = 0$ to an untwisted chain. We also note that in one-dimension

$$\begin{aligned} \frac{\varepsilon_0}{4} \sum_{\langle ij \rangle} P_{ij}^2 &= \frac{\varepsilon_0}{4} \sum_i (P_{i-1i}^2 + P_{ii-1}^2 + P_{ii+1}^2 + P_{i+1i}^2) \\ &= \varepsilon_0 \sum_i P_{ii+1}^2 = \varepsilon_0 \sum_i P_i^2 . \end{aligned} \tag{23}$$

We can now write the Hamiltonian for the one-dimensional system by substituting (22) and (23) into (18). After some lengthy but elementary algebraic manipulation we find that (omitting the constant term)

$$\begin{aligned} H_N = \varepsilon_0 \sum_i^N P_i^2 + (\varepsilon_T + \varepsilon_s) \sum_i^N S_i^2 \\ - \frac{\varepsilon_s}{2} \sum_i^N (1 + S_i S_{i+1}) S_i S_{i+1} \qquad (24) \\ + \frac{\varepsilon_s}{2} \sum_i^N (S_i + S_{i+1}) (1 + S_i) (1 - S_{i+1}) P_i \qquad (24) \end{aligned}$$

where we have used the shorthand notation $P_i = P_{ii+1}$. The corresponding partition function is

$$Z_N = \sum_{\{P_i\}} \sum_{\{S_i\}} \exp(-\beta H_N) , \tag{25}$$

where $\beta = (K_B T)^{-1}$, T being the absolute temperature and K_B Boltzmann's Constant.

This partition function may be evaluated analytically using a transfer matrix method. Although the evaluation is straightforward it is somewhat tedious and is best left to an appendix. The result is that

$$\ln Z_N \sim N \ln \lambda , \tag{26}$$

where λ is the largest eigenvalue of a 3×3 transfer matrix, and is given by solving the appropriate secular equation. We find (see appendix) that λ is given by the real root of the cubic

$$\lambda^3 - a\lambda^3 + b\lambda - c = 0 \tag{27}$$

the coefficients being

$$\begin{aligned} a &= A(2y - 1) \\ b &= A^2 y (2y - 1) - A B y z (2 + y z) \\ c &= A^3 y^2 (1 + z^2) - y^2 z A^2 B (2 + z) + y^2 z^2 B^3 , \end{aligned} \tag{28}$$

where

$$\begin{aligned} A &= 2x + 1 \\ B &= 2x \cosh(\varepsilon_0 \beta) + 1 \end{aligned} \tag{29}$$

and

$$\begin{aligned} x &= e^{-\beta\varepsilon_0} \\ y &= e^{-\beta\varepsilon_T} \\ z &= e^{-\beta\varepsilon_s} . \end{aligned} \tag{30}$$

This solution allows us to calculate all the thermodynamic quantities of interest. In particular we want the average values $\langle P \rangle$, $\langle P^2 \rangle$, $\langle S \rangle$ and $\langle S^2 \rangle$. It is shown in the appendix that in one dimension

$$\begin{aligned} \langle P \rangle &= 0 \\ \langle S \rangle &= 0 . \end{aligned} \tag{31}$$

The physical implications of (31) are obvious. $\langle P \rangle = 0$ implies that no matter how much thermal energy we put into the system the chains remain in a line on the average. (Had the system been two-dimensional the equivalent statement would be that the chains remain planar on the average.) This, of course, does not preclude local (possibly periodic) deviations from the average plane. A measure of such deviations is given by $\langle P^2 \rangle$ which will be discussed shortly. $\langle S \rangle = 0$ simply states that there is no preferred direction of chain twists (i.e. there are as many backwards as there are forwards) on the average. The fraction of chains with twists (in any direction) is given by $\langle S^2 \rangle$.

By definition the average of any quantity Y is given by

$$\langle Y \rangle = \frac{1}{Z} \sum_{\{P_i\}} \sum_{\{S_i\}} Y \exp(-\beta H) . \tag{32}$$

It can be seen from (24) and (26) that this leads to

$$\langle P^2 \rangle = -\frac{1}{N Z_N} \frac{\partial Z_N}{\partial \beta\, \varepsilon_0} = -\frac{1}{\beta} \frac{\partial}{\partial \varepsilon_0} (\ln \lambda) \tag{33}$$

and similarly

$$\langle S^2 \rangle = -\frac{1}{\beta} \frac{\partial}{\partial \varepsilon_T} (\ln \lambda) \tag{34}$$

both of which may be obtained from (27)–(30). Results from $\langle P^2 \rangle$ as a function of temperature for various values of ε_s are shown in Fig. 2 for a relatively elastic membrane ($\varepsilon_0 = 0.6 \times 10^{-13}$ ergs) and for a stiff membrane ($\varepsilon_0 = 2 \times 10^{-13}$ ergs). We stress here that due to the one dimensional nature of the system the exact numerical value of the temperature has no physical relevance. It may be seen that for an elastic membrane $\langle P^2 \rangle$ rises sharply and then approaches asymptotically its theoretical maximum of 2/3. As expected the rise is retarded in the stiffer

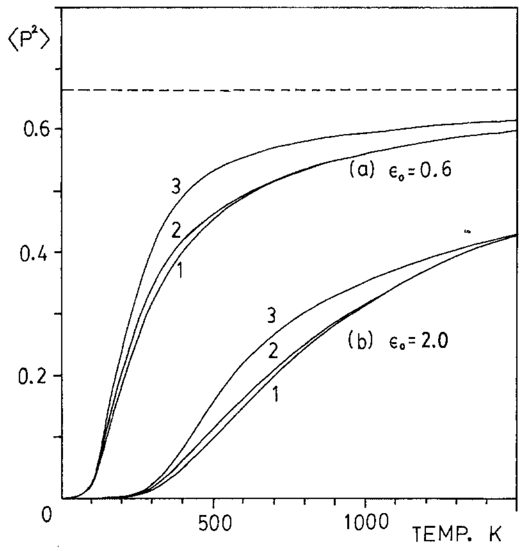


Fig. 2. Mean square relative displacement $\langle P^2 \rangle$ of neighbouring chains as a function of temperature in the one dimensional system. $\langle P^2 \rangle$ is shown for (**a**) a flexible membrane $\varepsilon_0 = 0.6 \times 10^{-13}$ ergs, (**b**) a stiff membrane $\varepsilon_0 = 2 \times 10^{-13}$ ergs for various values of ε_s: (a1) $\varepsilon_s = 0$, (a2) $\varepsilon_s = 0.45$, (a3) $\varepsilon_s = 1.4$, (b1) $\varepsilon_s = 0$, (b2) $\varepsilon_s = 1$, (b3) $\varepsilon_s = 1.9$, where ε_s is in units of 10^{-13} ergs. In all cases the energy of a chain twist is taken to be $\varepsilon_T = 0.45 \times 10^{-13}$ ergs

membrane. It is also seen in the figure that $\langle P^2 \rangle$ is considerably more sensitive to ε_0 than to ε_s. In all cases ε_T was taken to be the energy for the introduction of one gauche rotomer, 0.45×10^{-13} ergs. As may be expected for a one dimensional system with only short range interaction there are no phase transitions.

Though $\langle P^2 \rangle$ gives some measure of the local deviations from the plain it is the correlation functions of the form $\langle P_i P_{i+r} \rangle$ and $\langle S_i S_{i+r} \rangle$ as functions of r that would indicate their nature. Some idea of these local deviations is given by performing a computer simulation which can also be used as an independent check on the results obtained analytically. Such a comparison is shown in Fig. 3. A Metropolis Monte Carlo simulation of the Hamiltonian (24) was done on a lattice of 100 sites. In all cases 500 initialization steps were first performed then one to two thousand passes, depending on temperature (the one dimensional nature of the system ensures fast equilibration). Figure 3 shows that there is excellent agreement between the averages obtained analytically and via simulation. Figure 4 shows four typical configurations for three temperatures using $\varepsilon_0 = 0.6$, $\varepsilon_T = 0.45$, $\varepsilon_s = 1.4$ (in units of 10^{-13} ergs). These pictures suggest that some short-range correlations exist for the one dimensional system, these correlation being enforced through the constraint (9). The implications for two dimensional systems are discussed below.

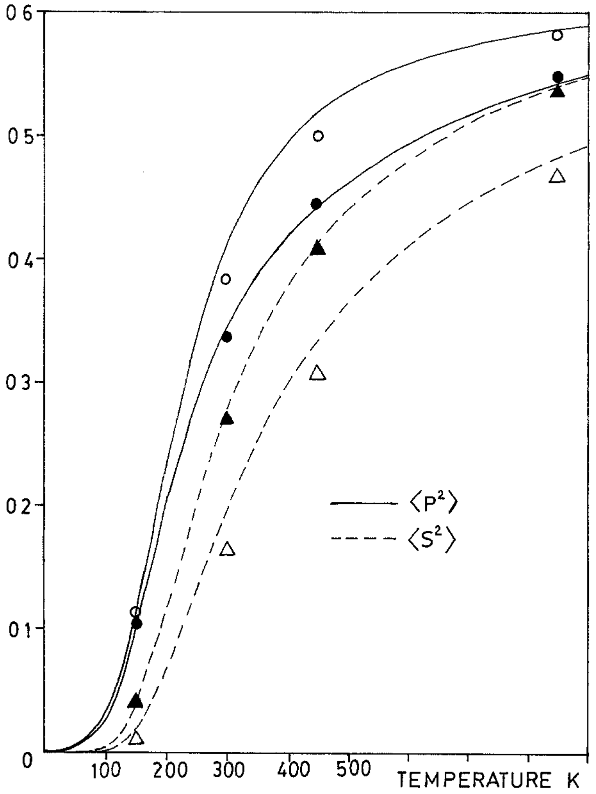


Fig. 3. Monte Carlo averages, $\langle P^2 \rangle$, $\langle S^2 \rangle$ compared to the exact results. The results are for a flexible membrane with $\varepsilon_0 = 0.6$ and $\varepsilon_T = 0.45$. The open circles are for $\langle P^2 \rangle$ with $\varepsilon_s = 1.4$ and the filled circles $\varepsilon_s = 0.45$. The exact results are shown by the continuous lines. $\langle S^2 \rangle$ is shown for $\varepsilon_s = 1.4$ and $\varepsilon_s = 0.45$ by open and filled triangles respectively. The exact results are shown by the broken curves. In all cases the energies are expressed in units of 10^{-13} ergs

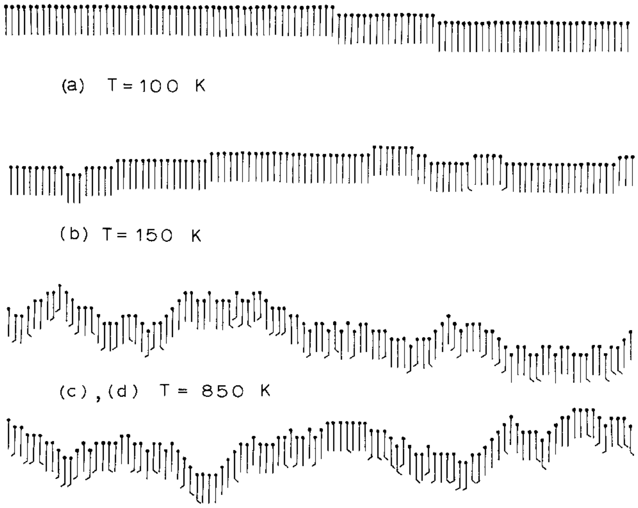


Fig. 4. Typical configurations obtained by a simulation on a lattice of 100 sites for $\varepsilon_0 = 0.6$, $\varepsilon_T = 0.45$, $\varepsilon_s = 1.4$ (in units of 10^{-13} ergs). Each configuration is the result of 500 initializations steps and between one and two thousand passes (depending on temperature). We stress that the exact numerical value of T has little physical meaning in a one-dimensional model

Discussion

We have presented a model which couples the vertical displacements of lipid chains to changes in their conformational state. We now present some observations on what we may expect from a two dimensional solution and simple modifications which would allow the inclusion of unsaturated chains and cholesterol.

A point worthy of discussion is the form of the potential used to model the restoring force between lipids. We chose a harmonic potential expressed in Eq. (2). We believe this term to be sufficient to answer the question: "What is the overall effect of a restoring force acting on the lipid chains in a bilayer?" A more realistic potential would involve higher powers of x, i.e. anharmonic terms. A simple thought experiment shows this to be the case. One can imagine pulling a lipid out of the plane of the bilayer and releasing it. For a small displacement the lipid would stay in the bilayer plane (the harmonic term). For a sufficiently large displacement (e.g. larger than the length of the chain) the lipid would leave the bilayer altogether (the anharmonic terms). However this model concerns itself with small displacements only as expressed in Eq. (4). Further work may include larger displacements and hence anharmonic terms in the Hamiltonian.

The model was solved analytically for a one dimensional system and no phase transition or other anomalous thermodynamic behaviour was found. We believe however that this is solely due to the one dimensional nature of the solution. We may speculate as to what effects we expect to occur in a two dimensional membrane modelled by the Hamiltonian of Eq. (18).

In the first place the interaction terms ($G_{ij} G_{ji} + G_{ij} G_{jj}$) alone (giving rise to $S_i S_{i+1} (1 + S_i S_{i+1})$ in the one dimensional case) should lead to an abrupt transition between a membrane with most chains straight to most twisted. However this is not a complete picture because of the mixed term $G_{ij} G_{jj} P_{ij}$. This term describes the trade-off between the energy gained by allowing a chain to twist against the cost in energy of the neighbouring chain moving out of the local plain to accommodate the twist. The picture is further complicated by the constraint (8), (9) (which is very weak in the one dimensional case) which determines how neighbouring groups of chains are allowed to move. Whether these combined factors still allow the first-order phase transition to take place or whether they would smear it out (or abolish it altogether) is still under investigation via simulation techniques. Should such a transition be found (smeared out or first-order) then we may have a physical explanation for the pre-transition in terms of these competitive steric effects. This explanation would be strengthened if short range correlations evident in the one dimensional simulations turn out to be periodic in the two dimensional membrane.

A word here on the possibility (validity) of a mean field solution for the two dimensional model would be in order. It is clear from the Hamiltonian (18) that the coupling between the vertical displacements and the chain conformation is given by the term $G_{ij} G_{jj} P_{ij}$ in Eq. (18). This term gives rise to very strong short range correlations from which any long range correlations (periodic or otherwise) must arise. In any mean field treatment this mixed term involving two operators would have to be decoupled. This being the case it is not clear that the topology of the phase diagram produced by a mean field treatment would be as trustworthy as it is for systems described by a single operator. The authors feel that the only viable solution for the model in two dimensions is through computer simulations.

The model also lends itself particularly well to modifications which include the addition of both cholesterol and unsaturated lipids into the bilayer. In the latter case for cis-double bonded lipids there would be a subset of lipids which are permanently twisted. Mathematically this would be expressed by a subset of the operators G_{ij}, G^{α}_{ij} say, for which $G^{\alpha}_{ii} = 0$ always (the chain can never be straight). For cholesterol it is simple to ensure free volume at the bottom of the molecule (i.e. near the terminal methyl groups of the adjacent chains) by having $G^{c}_{ij} = G^{c}_{ii} = 0$ always. Both of the above cases lend themselves well to computer simulations.

There are fundamental differences in philosophy between our model and that proposed by Pierce and Scott (1982). The most striking differences are the following. The model of Pierce and Scott does not allow for conformational transitions in the lipid chain, which is assumed rigid below the melting transition. This is not in accord with Raman and infrared data as discussed in the introduction. Secondly their basic molecular unit is a "bimolecule" spanning the bilayer with the headgroups in opposite directions. This infinitely strong correlation has no experimental basis and has since been contradicted by recent investigations of transbilayer coupling (Georgallas et al. 1984). Thirdly, their bilayer is built up in linear rows of bimolecules with headgroups only oriented in the direction of the row, thereby giving the bilayer an intrinsic directional anisotropy. In our model none of these restrictive conditions are present, the lipid chains being able to change conformation and twist in any direction (i.e. no directional anisotropy). However the inclusion of the freedom of vertical motion is parallel in both models.

Finally we note that we have explicitly modelled one monolayer of the bilayer. It is clear that for two back-to-back monolayers representing a bilayer each monolayer would experience the identical steric forces but their motion would be subject to the constraint that the average density of the bilayer remains constant.

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Appendix

The partition function for the one dimensional model is obtained directly from Eqs. (24) and (25), i.e.

$$Z = \sum_{\{S_i\}} \exp\Big[- \beta\,(\varepsilon_T + \varepsilon_s) \sum_i^N S_i^2 + \frac{\beta\,\varepsilon_s}{2} \sum_i^N (1 + S_i S_{i+1})\, S_i S_{i+1} \Big]$$

$$\times \sum_{\{P_i\}} \prod_i \exp\Big[- \varepsilon_0\,\beta\,P_i^2 - \frac{\varepsilon_s\,\beta}{2}\,(S_i + S_{i+1})\,(1 + S_i) \times (1 - S_{i+1})\,P_i \Big]\,. \tag{A1}$$

We may immediately perform the sum over $\{P_i\}$ in (A1) to form

$$\begin{aligned} Z_N = \sum_{\{S_i\}} \exp\Big[& - \beta\,(\varepsilon_T + \varepsilon_s) \sum_i^N S_i^2 \\ & + \frac{\beta\,\varepsilon_s}{2} \sum_i^N (1 + S_i S_{i+1})\, S_i S_{i+1} \Big] \\ \times \prod_i \Big[& 2\,\mathrm{e}^{-\varepsilon_0\beta} \cosh \Big\{ (S_i + S_{i+1})\,(1 + S_i) \\ & \times (1 - S_{i+1})\,\frac{\varepsilon_s\,\beta}{2} \Big\} + 1 \Big]\,. \end{aligned} \tag{A2}$$

We can evaluate (A2) iteratively, i.e. by forming Z_2, Z_3 and so on. Forming Z_2 from (A2)

$$\begin{aligned} Z_2 = \sum_{\{S_1\}} \sum_{\{S_2\}} \exp\Big[& - \beta\,(\varepsilon_T + \varepsilon_s)\,(S_1^2 + S_2^2) \\ & + \frac{\beta\,\varepsilon_s}{2}\,(1 + S_1 S_2)\, S_1 S_2 \Big] \\ \times \Big[& 2 \exp(- \beta\,\varepsilon_0 \cosh \Big\{ (S_1 + S_2)\,(1 + S_1) \\ & \times (1 - S_2)\,\frac{\varepsilon_s\,\beta}{2} \Big\} + 1 \Big]\,. \end{aligned} \tag{A3}$$

We can perform the sums of S_1, $S_2 = 0, \pm 1$ which, using Eqs. (28)–(30), leads to

$$\begin{aligned} Z_2 = {} & y\,z\,(yA + A + y\,z\,A) + (y\,z\,B + A + y\,z\,A) \\ & + y\,z\,(y\,z\,A + B + y\,a)\,. \end{aligned} \tag{A4}$$

Similarly

$$\begin{aligned} Z_3 = {} & y\,z\,\{y\,a\,(yA + A = y\,z\,A) + A\,(y\,z\,B + A + y\,z\,A) \\ & \quad + y\,z\,A\,(y\,z\,A + B + y\,a)\} \\ & + \{y\,z\,B\,(yA + A + y\,z\,A) + A\,(y\,z\,B + A + yz\,A) \\ & \quad + y\,z\,A\,(y\,z\,A + B + y\,a)\} \\ & + y\,z\,\{y\,z\,A\,(yA + A + y\,z\,A) \\ & \quad + B\,(y\,z\,B + A + y\,z\,A) \\ & \quad + yA\,(y\,z\,A + B + yA)\} \end{aligned} \tag{A5}$$

and so on. If we set up the recursions

$$\begin{aligned} \alpha_N &= yA\,\alpha_{N-1} + A\,\beta_{N-1} + y\,z\,A\,\gamma_{N-1} \\ B_N &= y\,z\,B\,\alpha_{N-1} + A\,\beta_{N-1} + y\,z\,A\,\gamma_{N-1} \\ \gamma_N &= y\,z\,A\,\alpha_{N-1} + B\,\beta_{N-1} + yA\,\gamma_{N-1} \end{aligned} \tag{A6}$$

with $\alpha_1 = \beta_1 = \gamma_1 = 1$. Then we can express (A4) and (A5) as

$$\begin{aligned} Z_2 &= y\,z\,\alpha_2 + \beta_2 + y\,z\,\gamma_2 \\ Z_3 &= y\,z\,\alpha_3 + \beta_3 + y\,z\,\gamma_3 \end{aligned} \tag{A7}$$

and in general

$$Z_N = y\,z\,\alpha_N + \beta_N + y\,z\,\gamma_N\,. \tag{A8}$$

We can write (A6) and (A8) in terms of the matrices

$$\hat{\Gamma} = \begin{pmatrix} yA & A & yzA \\ yB & A & yzA \\ yzA & B & yA \end{pmatrix} \tag{A9}$$

$$\hat{\alpha}_N = \begin{pmatrix} \alpha_N \\ \beta_N \\ \gamma_N \end{pmatrix}, \quad \hat{\alpha}_1 = \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix}. \tag{A10}$$

In matrix form the recursions (A6) become

$$\hat{\alpha}_N = \hat{\Gamma}\,\hat{\alpha}_{N-1} \tag{A11}$$

and

$$\hat{\alpha}_N = \hat{\Gamma}^{N-1}\,\hat{\alpha}_1\,. \tag{A12}$$

Finally if we define the row matrix $\hat{y}$ by

$$\hat{y} = (y\,z \quad 1 \quad y\,a) \tag{A13}$$

we obtain for (A8)

$$Z_N = \mathrm{Tr}\,(\hat{y}\,\hat{\Gamma}^{N-1}\,\hat{\alpha}_1) \tag{A14}$$

from which (26) follows. The eigenvalues, λ, of the matrix $\hat{\Gamma}$ are given by the determinant

$$\begin{vmatrix} yA-\lambda & A & yzB \\ yzB & A-\lambda & yzA \\ yzA & B & yz^2A-\lambda \end{vmatrix} = 0 \tag{A15}$$

from which (27) follows. We may obtain the average $\langle P \rangle$ from the definition

$$\langle P_k \rangle_N = \frac{1}{N Z_N} \sum_{\{P_i\}} \sum_{\{S_i\}} P_k \exp\,(-\beta H_N) \tag{A16}$$

and using the same iterative technique used for determining Z_N we find $\langle P \rangle_2 = 0$, $\langle P \rangle_3 = 0$ and so on. $\langle S \rangle$ is determined in the same way leading to Eq. (31).