

An Exactly Solvable Two-Dimensional Biomembrane Model

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A model for a two-dimensional lipid bilayer, in which both short-range repulsive forces and long-range attractive forces play a role, is solved exactly. First, in the absence of attractive forces, the configurational entropy is calculated by restricting the lipid hydrocarbon tails to a lattice and solving the resulting counting problem exactly. When long-range attractive forces which decrease exponentially with distance are acting between the polar head groups of the lipids, the partition function can still be calculated exactly, using integration over Gaussian random fields. The thermodynamic functions show a singularity which reflects the completion of the process of self-assembly of the lipid bilayer. Finally, the model is used to test an approximation method for lipid bilayers.

KEY WORDS: Biomembrane; functional integration; free-Fermion model.

1. INTRODUCTION

Much of the recent interest in the properties of biological membranes is due to the crucial role which they play in many functions of the living cell. A large variety of membrane structures has been suggested. Most of the proposed structures have a lipid bilayer in common, but they differ in the manner in which the membrane proteins are attached to, or embedded in, the lipid

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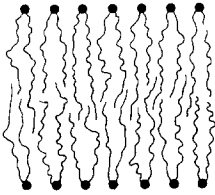


Fig. 1. A simplified representation of a lipid bilayer.

bilayer (see, for example, Johnston and Roots⁽¹⁾ for a recent review). The lipid bilayer, which is about 60–70 Å thick, consists of two layers of lipids, with their (nonpolar) hydrocarbon chains oriented inward to form a hydrophobic phase and their (polar) hydrophilic heads oriented outward toward the solvent. In a specific biomembrane several types of lipids are found; the most abundant ones are lecithin and cephalin. Usually two hydrocarbon tails are attached to one head (see Fig. 1).

Calorimetric studies by Hinz and Sturtevant⁽²⁾ of synthetic bilayers formed from lecithins show that the bilayer undergoes a sharp transition at a temperature of about 40°C and probably another, less pronounced transition at a temperature of about 30°C. Clearly, a phase transition in the membrane thermodynamic functions indicates a change in the physical properties of the bilayer, which can profoundly influence the dynamical behavior of the proteins and thus the biological function of the whole membrane.

A statistical mechanical theory of phase transitions in a lipid bilayer is faced with the task of keeping track of the very large number of available configurations, i.e., the many different ways in which the hydrocarbon chains can be packed inside the bilayer in such a way that the chains do not overlap themselves or each other. This constraint leads to great mathematical difficulties which have only been solved approximately. For example, in a recent paper, Marsh⁽³⁾ has made a simplifying assumption about the way in which the intermolecular steric hindrance between chains restricts their configurations. In Marsh's model every configuration of the hydrocarbon chain in which two successive C–C bonds are in the *gauche* conformation is forbidden; all other configurations are permitted. This assumption simplifies the counting problem for a large number of chains to the counting problem for one hydrocarbon chain without neighboring *gauche* conformations, which can be solved straightforwardly using standard (matrix) methods for free polymer chains. Whereas such an assumption of course eliminates some of the forbidden configurations, others are still counted erroneously as permitted. On the other hand, a configuration of a hydrocarbon chain in which two successive C–C bonds are in the *gauche* conformation need not be forbidden provided the neighboring hydrocarbon chains have moved out of the way in an appropriate fashion. There is clearly a need for: (1) approximation methods in which the effect of steric hindrance on the membrane's thermodynamic functions is

taken into account more accurately; (2) models which, although not entirely realistic, can be analyzed rigorously.

The present paper is devoted to the analysis of a model for a two-dimensional lipid bilayer in which both short-range repulsive forces and long-range attractive forces play a role, and for which several thermodynamic functions can be calculated exactly. The model is related to a class of biomembrane models studied by Nagle,⁽⁴⁾ but differs from Nagle's model in that the effect of long-range attractive forces on the thermodynamic functions can be studied rigorously. In Section 2 the model is discussed and the configurational entropy is calculated in the case that attractive forces are absent.

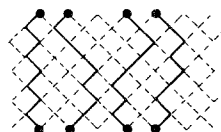
In Section 3 the polar head groups of the lipids are assumed to attract each other with a long-range force which decreases exponentially with increasing separation. For this choice of the attractive force the grand canonical pressure of the lipid bilayer is calculated rigorously, using methods of functional integration. With attractive forces included the model shows some of the characteristics of a self-assembling system.

It is interesting to use the exact results obtained in Sections 2 and 3 to test some approximation methods which hopefully will be of use to calculate the thermodynamic functions of the more realistic three-dimensional biomembrane models. In Section 4 an approximation method is developed which enables one to reduce the calculation of the configurational entropy to the determination of the smallest eigenvalue of a partial differential equation of the diffusion type. This "continuum" approach to the counting problem for the hydrocarbon chains considerably simplifies the calculation of the thermodynamic functions. It will turn out that the continuum approach leads to an expression for the configurational entropy which forms a very good approximation to the exact expression provided the density of the lipids is small compared to the close-packing density.

2. THE MODEL AND ITS CONFIGURATIONAL ENTROPY

Let the head groups and the hydrocarbon tails of the lipids be constrained to the vertices and the edges of a square lattice, as indicated in Fig. 2. Since we shall be interested in the combinatorics of the chains the energy difference between a *trans* and a *gauche* conformation of a C-C bond will be neglected. In the next section attractive interactions between the head groups will be incorporated, but in this section the thermodynamic functions will be

Fig. 2. A two-dimensional model for a lipid bilayer. The dashed lines indicate the underlying square lattice, the dots the head groups of the lipids, the heavy lines the hydrocarbon chains of the lipids.



calculated under the assumption that a lattice vertex can be occupied by at most one C atom in a lipid hydrocarbon chain. The chains are not supposed to fold back, i.e., a chain has only one point in common with any line parallel to the surface of the membrane. The structure of the head group of the lipid and the fact that two chains are attached to one head will be disregarded. Finally, the lipids belonging to different halves of the bilayer are merged in pairs by making their tails continuous.

Let $N = nm$ denote the number of different lattice vertices, and R the number of hydrocarbon chains in the membrane. The grand canonical partition function $\Xi_0(z)$ is defined as the generating function

$$\Xi_0(z) = \sum_{R=0}^{\infty} Z_0(R) z^{mR} \quad (1)$$

where $Z_0(R)$ denotes the number of different configurations of R hydrocarbon chains in which no lattice vertex is occupied more than once. If one attaches a weight factor z to every lattice vertex through which a chain passes, and a weight factor 1 to every lattice point through which no chain passes, then only five vertex configurations are permitted, as indicated in Fig. 3. With these weights of the vertex configurations the model reduces to a special case of the "free-fermion model," which has been solved by several authors using a variety of methods.⁽⁵⁻⁷⁾ The grand canonical pressure is found to be

$$\begin{aligned} \beta p_0(z, \beta) &\equiv \lim_{n, m \rightarrow \infty} \frac{\ln \Xi_0(z)}{nm} \\ &= \frac{1}{8\pi^2} \int_0^{2\pi} d\theta \int_0^{2\pi} d\phi \ln [1 + 2z^2 + 2z(\cos \theta + \cos \phi) \\ &\quad + 2z^2 \cos(\theta - \phi)] \end{aligned} \quad (2)$$

Here $\beta = (k_B T)^{-1}$, with k_B denoting Boltzmann's constant and T the absolute temperature. One of the integrations can be performed immediately with the help of the formula

$$\int_0^{2\pi} \ln [A + B \cos \theta + C \sin \theta] d\theta = 2\pi \ln \left[\frac{1}{2} A + \frac{1}{2} (A^2 - B^2 - C^2)^{1/2} \right] \quad (3)$$

which holds provided $B^2 + C^2 < [A + (A^2 - B^2 - C^2)^{1/2}]^2$. This transforms (2) into

$$\beta p_0(z, \beta) = (1/4\pi) \int_0^{2\pi} \ln \left[\frac{1}{2} + z^2 + z \cos \phi + \left| \frac{1}{2} + z \cos \phi \right| \right] d\phi \quad (4)$$



Fig. 3. The five permitted vertices of the lattice of Fig. 2. In the configuration sum (1) these vertices contribute weight factors (from left to right): 1, z , z , z , z .

which holds for all positive z . The density $\rho_0(z)$ is found by differentiating the pressure with respect to $\ln z$:

$$\rho_0(z) = 1 - \frac{a(z)}{\pi} + \frac{z}{2\pi} \int_0^{a(z)} (2z + 2 \cos \phi)(1 + z^2 + 2z \cos \phi)^{-1} d\phi \quad (5)$$

where

$$a(z) \equiv \pi - \arccos(1/2z), \quad \pi/2 < a(z) \leq \pi \quad (6)$$

Note that because the chains cannot fold back on themselves, $\rho_0(z)$ is identical to both the fraction of lattice vertices occupied by hydrocarbon chains and the fraction of lattice points at the outer or inner surface of the membrane occupied by head groups of the lipids, i.e., ρ_0 is both the volume density of chain repeating units and the surface density of lipid heads.

For $z < \frac{1}{2}$ the integral in (4) can again be evaluated with the help of (3), leading to

$$\beta p_0(z, \beta) = 0, \quad \rho_0(z) = 0, \quad z < \frac{1}{2} \quad (7)$$

It is easy to see that such a result was to be expected because the number of configurations of a chain of m steps will not grow faster than 2^m with increasing m . Therefore, for fixed positions of the lipid heads on the inner and outer membrane surface the grand partition function (1) has an upper bound:

$$\Xi_0(z) \leq \sum_{R=0}^{\infty} (2z)^{mR} = [1 - (2z)^m]^{-1}, \quad z < \frac{1}{2} \quad (8)$$

which implies (7).

For $z > \frac{1}{2}$ the integral in (4) cannot be evaluated in closed form, but (5) is transformed by the substitution $e^{i\phi} = t$ into an integral which can be evaluated explicitly:

$$\rho_0(z) = 1 - \frac{a(z)}{\pi} + \frac{1}{2\pi i} \int_1^{\exp[ia(z)]} (zt^2 + 2z^2t + z)(zt^2 + t + z^2t + z)^{-1} \frac{dt}{t} \quad (9)$$

$$= \frac{1}{\pi} \arcsin\left(1 - \frac{1}{4z^2}\right)^{1/2} + \frac{1}{2\pi} \arcsin \frac{1}{2z^2} (4z^2 - 1)^{1/2} \quad z \geq \frac{1}{2} \quad (10)$$

where in the second term in (10) the arcsin increases continuously from 0 to π if z increases from $\frac{1}{2}$ to ∞ . For values of z near to $\frac{1}{2}$ the last equation gives

$$\rho_0(z) = (4/\pi)(z - \frac{1}{2})^{1/2} + O(z - \frac{1}{2})^{3/2} \quad z \downarrow \frac{1}{2} \quad (11)$$

The pressure is found by integration with respect to $\ln z$:

$$\beta p_0(z, \beta) = \int_{1/2}^z \rho_0(z') \frac{dz'}{z'} = \frac{16}{3\pi} \left(z - \frac{1}{2} \right)^{3/2} + O\left(z - \frac{1}{2} \right)^{5/2}, \quad z \downarrow \frac{1}{2} \quad (12)$$

The residual entropy per lattice point is given by

$$S_0(z)/k_B = \beta p_0(z, \beta) - \rho_0(z) \ln z \quad (13)$$

and behaves in the vicinity of $z = \frac{1}{2}$ as

$$S_0(z)/k_B = (16/3\pi)(z - \frac{1}{2})^{3/2} - \rho_0(z) \ln z + O(z - \frac{1}{2})^{5/2}, \quad z \downarrow \frac{1}{2} \quad (14)$$

Eliminating z between (11), (12), and (13), one obtains the behavior of pressure and entropy for small densities of hydrocarbon chain:

$$\beta p_0(\rho) = (\pi^2/12)\rho^3 + O(\rho^4), \quad \rho \downarrow 0 \quad (15)$$

$$S_0(\rho)/k_B = \rho \ln 2 - (\pi^2/24)\rho^3 + O(\rho^4), \quad \rho \downarrow 0 \quad (16)$$

In a similar way, one obtains the asymptotic behavior of these thermodynamic functions for large values of z :

$$\rho_0(z) = 1 - (1/\pi z) + O(z^{-2}), \quad z \rightarrow \infty \quad (17)$$

$$\beta p_0(z, \beta) = \ln z + (1/\pi z) + O(z^{-2}), \quad z \rightarrow \infty \quad (18)$$

$$S_0(z)/k_B = [1 - \rho_0(z)] \ln z + (1/\pi z) + O(z^{-2}), \quad z \rightarrow \infty \quad (19)$$

from which the high-density behavior follows:

$$\beta p_0(\rho) = (1 - \rho) + \ln \frac{1}{\pi(1 - \rho)} + O(1 - \rho)^2, \quad \rho \uparrow 1 \quad (20)$$

$$\frac{S_0(\rho)}{k_B} = (1 - \rho) + (1 - \rho) \ln \frac{1}{\pi(1 - \rho)} + O(1 - \rho)^2, \quad \rho \uparrow 1 \quad (21)$$

which shows that the pressure diverges and the entropy approaches the value zero with an infinite negative slope when the density approaches the density of close packing. In Figs. 4 and 5, the pressure and the entropy are shown qualitatively as functions of the density.

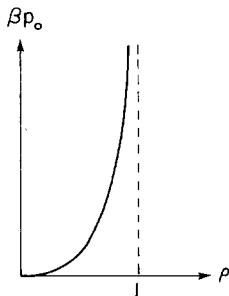


Fig. 4. Qualitative representation of an isotherm for the model of Section 2 in which no attractive forces act between the lipids.

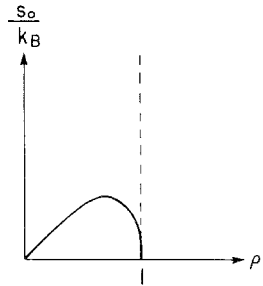


Fig. 5. Qualitative representation of the configurational entropy per lattice point for the model of Section 2.

3. INCLUSION OF LONG-RANGE ATTRACTIVE FORCES

The model which formed the subject of the preceding section is unrealistic especially because of the absence of attractive forces. These forces, which hold the membrane together and which are responsible for the self-assemblage of the membrane out of a solution of lipids, are due to van der Waals interactions, hydrophobic interactions, ionic interactions, etc. Since only the head groups of the lipids carry a dipole moment and interact with the solvent, it is probably a good approximation to assume that the attractive forces act between the head groups only. In this section we shall calculate the thermodynamic functions of a biomembrane model which arises out of the model of Section 2 when a total attractive force with potential

$$V(x - x') \equiv -\frac{1}{2}W_0\gamma \exp(-\gamma|x - x'|) \tag{22}$$

is assumed to act between the end points (situated at x and x') of two chains on the inner or outer surface of the membrane. So γ^{-1} is the range of the attractive force, and W_0 is a positive constant which equals the space integral of the potential. Since the attractive force acts only at the boundaries of the membrane, its presence will not influence the bulk thermodynamic functions in the limit in which the thickness ml of the bilayer goes to infinity. It is only when W_0 increases with m ,

$$W_0 = mw_0 \tag{23}$$

(where w_0 is an m -independent positive constant) that the interactions in the membrane surface have a nonvanishing effect on the bulk thermodynamic functions. However, since membranes are systems of an essentially finite thickness, we shall analyze this model both in the limit $m \rightarrow \infty$ and for finite $m \gg 1$. In biomembranes m is approximately 40.

Let the lattice points be labeled with a row index $i = 1, 2, \dots, m + 1$ and a column index $j = 1, 2, \dots, n$. The surfaces of the membrane are located at $i = 1$ and $i = m + 1$. For convenience, cylindrical boundary conditions will be imposed by identifying the first and $(m + 1)$ th row. The number of different configurations of R chains, each of length ml , with endpoints at

$(1, j_1), (m + 1, j_1'); (1, j_2), (m + 1, j_2'); \dots; (1, j_R), (m + 1, j_R')$ will be denoted by $Q_m(j_1', j_2', \dots, j_R' | j_1, j_2, \dots, j_R)$. This function is related to the canonical partition function by

$$Z_0(R) = \sum'_{(j)} Q_m(j_1, j_2, \dots, j_R | j_1, j_2, \dots, j_R) \tag{24}$$

where the prime on the summation indicates the constraint

$$1 \leq j_1 < j_2 < \dots < j_{R-1} < j_R \leq n \tag{25}$$

With these notations the thermodynamic functions follow from the grand partition function:

$$\Xi(z) = \sum_{R=0}^{\infty} z^{mR} \sum'_{(j)} Q_m(j_1, j_2, \dots, j_R | j_1, j_2, \dots, j_R) \times \exp\left\{-\beta \sum_{1 \leq \alpha < \alpha' \leq R} V(x_\alpha - x_{\alpha'})\right\} \tag{26}$$

in the limit $n \rightarrow \infty, m \rightarrow \infty$. The exponential on the right-hand side favors those configurations in which the lipids are packed as close as possible; the function Q_m , however, favors configurations in which the density of lipids is not too near zero or one, as was shown in Fig. 5. The thermodynamics results from the competition of these two factors.

In order to calculate (26) explicitly, one introduces Gaussian random functions $\Phi(x)$ defined for $0 < x < L = 2ln$, with a vanishing average, and a covariance

$$\langle \Phi(x)\Phi(x') \rangle = -\beta V(x - x') \tag{27}$$

Since the applications of functional integration have been reviewed in detail in a recent report,⁽⁸⁾ we only need to outline the main steps in the calculation.

With random functions defined by (27) the partition function can be written as an average over function space:

$$\Xi(z) = \left\langle \exp\left\{m \sum_{j=1}^n \beta p_0(\zeta \exp[(1/m)\Phi_j])\right\} \right\rangle \tag{28}$$

where

$$\zeta = z \exp\{+(\beta/2m)V(0)\} \tag{29}$$

and where Φ_j denotes the value of the random function at lattice point $(1, j)$:

$$\Phi_j = \Phi(2lj) \tag{30}$$

The expression (28) is rigorous only in the limit $\gamma \downarrow 0$, but will be a very good approximation provided $\gamma l \ll 1$. Thus, if the range of the attractive forces is

very large compared to the linear dimension of one repeating unit in the hydrocarbon chain, the discrete sum in the exponential can be replaced by an integral, and one has to evaluate the average over Gaussian random functions:

$$\Xi(z) = \left\langle \exp \left\{ \frac{m}{2l} \int_0^L \beta p_0 \left(\zeta \exp \left[\frac{1}{m} \Phi(x) \right] \right) dx \right\} \right\rangle \quad (31)$$

With the special choice (22) for the potential of interaction between the head groups of the lipids the evaluation of the average over Gaussian random functions is entirely analogous to the solution of the model of Kac, Uhlenbeck, and Hemmer in Ref. 8: The average can be written as the ratio of two Wiener integrals:

$$\Xi(z) = \frac{\int_{-\infty}^{+\infty} G_B(\Phi, L | \Phi, 0) d\Phi}{\int_{-\infty}^{+\infty} G_{B_0}(\Phi, L | \Phi, 0) d\Phi} \quad (32)$$

where periodic boundary conditions were imposed on the random functions $\Phi(x)$, and where

$$G_B(\Phi, L | \Phi, 0) = \int_{(\Phi, 0)}^{(\Phi, L)} \exp \left\{ - (2\beta W_0 \gamma^2)^{-1} \int_0^L \left(\frac{d\Phi}{dx} \right)^2 dx - \int_0^L B(\Phi) dx \right\} d[\Phi(x)] \quad (33)$$

$$B(\Phi) = \frac{\Phi^2}{2\beta W_0} - \frac{m}{2l} \beta p_0 (\zeta e^{(1/m)\Phi}); \quad B_0(\Phi) = \frac{\Phi^2}{2\beta W_0} \quad (34)$$

The Wiener integral (33) is the propagator of a differential equation of the diffusion type and has an expansion

$$G_B(\Phi, L | \Phi, 0) = \sum_n |f_n(\Phi)|^2 e^{-E_n L} \quad (35)$$

in terms of the eigenvalues and eigenfunctions of the corresponding differential operator:

$$\left[-\frac{1}{2} \beta W_0 \gamma^2 (d^2/d\Phi^2) + B(\Phi) \right] f_n(\Phi) = E_n f_n(\Phi) \quad (36)$$

Substitution of (35) and the corresponding expression for the denominator into (32) gives the partition function for a membrane of finite thickness ml and a finite length L :

$$\Xi(z) = \left[\sum_n \exp(-E_n L) \right] / \left[\sum_n \exp(-E_n^{(0)} L) \right] \quad (37)$$

The grand canonical pressure of a membrane which has finite thickness ml

but infinite length is thus found to be

$$\beta p(z, \beta) = \lim_{n \rightarrow \infty} \frac{1}{mn} \ln \Xi = \frac{2l}{m} (E_0^{(0)} - E_0) = \frac{\gamma l}{m} - \frac{2l}{m} E_0 \quad (38)$$

where we used the harmonic oscillator spectrum:

$$E_n^{(0)} = (n + \frac{1}{2})\gamma, \quad n = 0, 1, 2, \dots \quad (39)$$

The pressure is determined by the ground state of the eigenvalue problem (36). The substitutions

$$\Phi(x) = m\phi(x): \quad E_0 = m\epsilon_0 \quad (40)$$

and the introduction of (23) transform this eigenvalue problem into

$$\left[-\frac{1}{2} \beta w_0 \left(\frac{\gamma}{m} \right)^2 \frac{d^2}{d\phi^2} + \frac{\phi^2}{2\beta w_0} - \frac{1}{2l} \beta p_0(\zeta e^\phi) \right] f_0(\phi) = \epsilon_0 f_0(\phi) \quad (41)$$

In the remainder of this section the result (38) will be considered for two specific situations: (a) in the limit $m \rightarrow \infty$; (b) for finite $m \gg 1$.

(a) *The case $m \rightarrow \infty$.* For a membrane of infinite thickness the limit $m \rightarrow \infty$ implies the classical limit of the eigenvalue problem (41), so the pressure is given by

$$\beta p(z, \beta) = -\min \left[\frac{l\phi^2}{\beta w_0} - \beta p_0(\zeta e^{\phi_0}) \right] = \beta p_0(\zeta e^{\phi_0}) - \frac{l\phi_0^2}{\beta w_0} \quad (42)$$

where ϕ_0 is that solution of

$$2l\phi_0/\beta w_0 = \rho_0(\zeta e^{\phi_0}) \quad (43)$$

which minimizes the expression in the square brackets. Since the density is given by

$$\rho(z, \beta) = \rho_0(\zeta e^{\phi_0}) \quad (44)$$

the equation of state is found to be

$$p(\rho, \beta) = p_0(\rho, \beta) - (w_0/4l)\rho^2, \quad \rho > \rho_s(T) \quad (45a)$$

provided the right-hand side is nonnegative. The density $\rho_s(T)$ is the solution of

$$p_0(\rho_s, \beta) = (w_0/4l)\rho_s^2 \quad (46)$$

For densities smaller than ρ_s the pressure vanishes:

$$p(\rho, \beta) = 0, \quad \rho < \rho_s(T) \quad (45b)$$

From (15), (46), and Fig. 4 it is easy to see that $\rho_s(T)$ decreases from 1 to 0 if T increases from 0 to ∞ . For fixed temperature, ρ_s increases from 0 to 1 if w_0

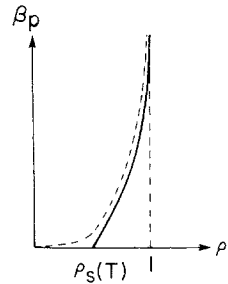


Fig. 6. The solid line is a qualitative representation of an isotherm of the model of Section 3 in the limit of infinite thickness of the bilayer. The isotherm of a bilayer of finite thickness, indicated by the dashed line, approaches the solid line very rapidly with increasing $m(\gamma l)^{-1}$, as indicated by Eq. (47).

increases from 0 to ∞ . The equation of state is sketched in Fig. 6. It is interesting to note that the equation of state of this system always shows two phases regardless of the temperature.

(b) *The case $1 \ll m < \infty$.* For a membrane of finite thickness, Eq. (41) is an eigenvalue problem for a quantum mechanical particle in a potential. Due to the property (7), the potential equals $\phi^2/2\beta w_0$ for $\phi \leq -\ln 2\zeta$. The ground state ϵ_0 will now be slightly larger than the absolute minimum of the potential and an analytic function of ζ . The isotherm is indicated qualitatively in Fig. 6 by the dashed line. The phase transition at $\rho = \rho_s(T)$ develops only in the limit $m \rightarrow \infty$. A calculation of the ground state with the WKB method, indicated in Ref. 8, shows that the pressure in the point $\rho = \rho_s(T)$ is small, of order

$$\beta p(\rho_s, \beta) \sim \exp(-cm/\gamma l) \tag{47}$$

where c does not depend on m or γl . Since the exponential is proportional to the product of the membrane thickness and the range of the attractive forces, it is seen that with more or less realistic values $m \sim 30$ and $\gamma l \sim 1/10$ the thermodynamic functions of the membrane are already very close to those of a membrane of infinite thickness.

The presence or absence of a phase transition in the isotherm is indicated in Table I for the various different cases discussed in Sections 2 and 3. Of course, a phase transition will also develop if the limit $\gamma \downarrow 0$ is taken for

Table I. Presence or Absence of a Singularity in the Isotherm

	No attractive forces	$0 < \gamma l \ll 1$	$\gamma l \downarrow 0$
$1 \ll m < \infty$	No	No	Yes
$m \rightarrow \infty$	No	Yes	Yes

finite m . This case is represented in the third column of Table I. The first column summarizes the results of Section 2 for the system without attractive forces.

4. AN APPROXIMATION METHOD IN THE STATISTICAL MECHANICS OF LIPID BILAYERS

Whereas for the present model the statistical mechanics can in many respects be solved exactly, this is not the case for more realistic biomembrane models. In this section an approximation method for the calculation of the configurational entropy will be developed, the merits of which can subsequently be judged by comparison with the exact results of the preceding sections. The method to be followed is related to a method employed by de Gennes⁽⁹⁾ for the study of fibrous structures; it is hoped that the calculations in this and the preceding section will help to clarify the approximate nature of this continuum approach.

Again consider the model without attractive forces, as in Section 2. As before the number of configurations of R hydrocarbon chains, each of length ml , starting at lattice points $(1, j_1), (1, j_2), \dots, (1, j_R)$ and ending at lattice points $(m+1, j_1'), (m+1, j_2'), \dots, (m+1, j_R')$ will be denoted by $Q_m(j_1', j_2', \dots, j_R' | j_1, j_2, \dots, j_R)$. Comparing the configurations of R chains for chain lengths $m+1$ and m , one finds that Q_{m+1} is related to Q_m by the relation

$$Q_{m+1}(\mathbf{j}' | \mathbf{j}) = \sum_{\mathbf{j}''} Q_m(\mathbf{j}'' | \mathbf{j}) \quad (48)$$

where the series of indices (j_1, j_2, \dots, j_R) is abbreviated by \mathbf{j} , and where the prime on the summation indicates the constraints

$$j_1'' = j_1' \pm 1, \quad j_2'' = j_2' \pm 1, \dots, \quad j_R'' = j_R' \pm 1 \quad (49a)$$

and

$$1 \leq j_1'' < j_2'' < \dots < j_R'' \leq n \quad (49b)$$

If the density of hydrocarbon chains is not too near unity, $Q_m(\mathbf{j}'' | \mathbf{j})$ will, for fixed m and fixed initial positions \mathbf{j} , be a smoothly varying function of the components of \mathbf{j}'' ; when the value of one of the $j_1'', j_2'', \dots, j_R''$ is increased by ± 1 the relative variation of Q_m will be small compared to unity. It should, therefore, be a good approximation to replace Q_m by a continuous function $Q_m(x_1'', x_2'', \dots, x_R'')$ which equals $Q_m(\mathbf{j}'' | \mathbf{j})$ when $x_1'' = 2lj_1'', x_2'' = 2lj_2'', \dots, x_R'' = 2lj_R''$, and which varies smoothly in between.

In terms of this function, $Q_m(\mathbf{j}''|\mathbf{j})$ can be expanded in a Taylor series in powers of the components of $(\mathbf{j}'' - \mathbf{j}')$:

$$Q_m(\mathbf{j}''|\mathbf{j}) = Q_m(\mathbf{x}') + l \sum_{\alpha=1}^R (j''_{\alpha} - j'_{\alpha}) \frac{\partial Q_m}{\partial x'_{\alpha}} + \frac{l^2}{2!} \sum_{\alpha, \alpha'=1}^R (j''_{\alpha} - j'_{\alpha})(j''_{\alpha'} - j'_{\alpha'}) \frac{\partial^2 Q_m}{\partial x'_{\alpha} \partial x'_{\alpha'}} + \dots \quad (50)$$

Upon summation of both sides of the equality over all \mathbf{j}'' that obey the constraint (49a), all odd terms on the right-hand side vanish, whereas a typical even term is easily shown to be in leading order in R

$$\frac{l^{2k}}{(2k)!} \sum_{\{\alpha\}} \sum_{\{\mathbf{j}'\}} (j''_{\alpha_1} - j'_{\alpha_1})(j''_{\alpha_2} - j'_{\alpha_2}) \dots (j''_{\alpha_{2k}} - j'_{\alpha_{2k}}) \partial^{2k} Q_m | \partial x'_{\alpha_1} \partial x'_{\alpha_2} \dots \partial x'_{\alpha_{2k}} = 2^R \left[\frac{l^{2k}}{2^k k!} \left\{ \sum_{\alpha=1}^R \frac{\partial^2}{\partial x'^2_{\alpha}} \right\}^k + O(R^{k-1}) \right] Q_m(\mathbf{x}') \quad (51)$$

Substitution of (50) and (51) into (48), and picking in the summation over k the contribution of largest order in R , one finds the recurrent relation

$$Q_{m+1}(\mathbf{x}) = 2^R \exp \left\{ \frac{l^2}{2} \sum_{\alpha=1}^R \frac{\partial^2}{\partial x_{\alpha}^2} \right\} Q_m(\mathbf{x}) \quad (52)$$

Thus, if eigenvalues and eigenfunctions of the differential operator in the exponential are denoted by $\lambda_k, \phi_k(\mathbf{x})$,

$$-\frac{l^2}{2} \sum_{\alpha=1}^R \frac{\partial^2}{\partial x_{\alpha}^2} \left] \phi_k(\mathbf{x}) = \lambda_k \phi_k(\mathbf{x}) \quad (53)$$

and if

$$Q_1(\mathbf{x}) = \sum_k c_k \phi_k(\mathbf{x}) \quad (54)$$

then

$$Q_{m+1}(\mathbf{x}) = 2^{mR} \sum_k e^{-m\lambda_k} c_k \phi_k(\mathbf{x}) \quad (55)$$

In the limit $m \rightarrow \infty$ only the term corresponding to the smallest eigenvalue λ_0 will survive, and the configurational entropy per lattice point is found to be

$$S_0(\rho)/k_B = \rho \ln 2 - \lim_{n \rightarrow \infty} (\lambda_0/n) \quad (56)$$

This relation thus expresses the configurational entropy per lattice point in terms of the ground state of the diffusion equation (53).

Up till now the second constraint (49b) has not been taken into account. Since the hydrocarbon chains are impenetrable, $Q_m(x_1, x_2, \dots, x_R)$ has to vanish whenever any two coordinates approach each other within a distance smaller than $2l$. This is most easily taken into account by imposing the boundary condition

$$\lim_{x_{\alpha+1} \downarrow x_{\alpha}} \phi_k(\mathbf{x}) = 0, \quad \alpha = 1, 2, \dots, R-1 \quad (57)$$

on the solutions of (53). Note that the eigenfunctions $\phi_k(\mathbf{x})$ are only defined for $0 \leq x_1 \leq x_2 \leq \dots \leq x_R \leq L$.

It is well known that (53) with the boundary condition (57) represents the eigenvalue problem of: (1) a one-dimensional gas of free fermions; (2) a one-dimensional gas of hard, rodlike bosons, in the limit in which the length of the rods (but not the boundary condition on the wave function!) vanishes. The (unnormalized) ground state was found by Girardeau⁽¹⁰⁾ to have the form:

$$\phi_0(\mathbf{x}) = \prod_{1 \leq \alpha < \alpha' \leq R} \sin \frac{\pi}{L} (x_{\alpha} - x_{\alpha'}) \quad (58)$$

where for convenience R has been assumed to be odd. The ground-state energy was found to be

$$\lambda_0 = \frac{l^2}{2} \left(\frac{2\pi}{L} \right)^2 \sum_{k = -(R-1)/2}^{+(R-1)/2} k^2 \quad (59)$$

The limiting ground-state energy per lattice point on the membrane surface equals

$$\lim_{n \rightarrow \infty} \frac{\lambda_0}{n} = \frac{\pi^2}{2} \int_{-\rho/2}^{+\rho/2} \xi^2 d\xi = \frac{\pi^2}{24} \rho^3 \quad (60)$$

Substituting this result into (56), we find the configurational entropy to be

$$S_0(\rho)/k_B = \rho \ln 2 - (\pi^2/24)\rho^3 \quad (61)$$

Comparison with the exact results (16) and (21) shows that this approximation technique leads to results which are in good agreement with the rigorous ones provided the density of lipids is not too close to unity.

5. CONCLUDING REMARKS

Table I summarizes the main properties of the model for the various cases discussed: finite or infinite thickness, presence or absence of attractive forces, finite or infinite range of the attractive forces. Although further calculations would be needed to unambiguously identify the nature of the

two phases, we would like to suggest the following picture. In the limit $m \rightarrow \infty$ the attractive forces between the head groups of the lipids had to be taken of a strength which diverges with m in order to have the membrane surface exert an influence over the thermodynamic functions even in this limit of an infinitely thick membrane. Thus, if only two lipids are inside the system, their head groups will condense upon each other under the influence of these very strong attractions. If more lipids are added, they will condense onto the previous ones and form a growing semicrystalline lipid bilayer of density $\rho_s(T)$ which has too few degrees of freedom to exert a pressure. It is only when the density reaches the value $\rho_s(T)$ that the bilayer fills the entire system; further addition of lipids is only possible under a pressure exerted on the walls of the container. The equation of state (45) thus directly reflects the process of self-assembly of the lipid bilayer and $\rho_s(T)$ would be the density of such a membrane when spontaneously formed out of a solution of lipids.

Thus from the point of view of physical interpretation the interesting feature of this model is that the solution in the case of attractive forces shows a singularity which reflects the completion of the process of self-assembly of the lipid bilayer. This singularity is found in the isotherm for any temperature.

For densities larger than $\rho_s(T)$ the membrane is probably in a smectic mesophase.

It might be of interest to compare the properties of this model with those of the Zwanzig-Lauritzen model of polymer chain folding.⁽¹¹⁻¹³⁾ The latter model can be considered as describing the self-assembly of a two-dimensional macromolecular crystal by the regular folding of a single polymer chain. Depending on the parameters, the Zwanzig-Lauritzen model has a crystalline phase in a certain regime of the temperature, whereas the model of Section 3 has such a phase for any temperature.

It is finally of interest to remark that the interactions between the polar head groups of the lipids (in the model of Section 3 represented by a decaying exponential) should be identified with the total effective interaction of the lipids in an aqueous medium and not with the interaction of the lipids in vacuum. Actually the bare lipid-lipid interaction will be "renormalized" to a considerable extent by the ionic composition of the aqueous medium. It is even conceivable that the effective lipid-lipid interaction is attractive whereas the bare interaction is repulsive, or that a change in the metabolism of the cell will lead to such a change in the ionic composition of the medium and the effective lipid-lipid interaction that the membrane will make a transition to another phase. This would provide a tentative mechanism for some of the regulatory functions of biomembranes. Since the present model is in many respects accessible to explicit calculation, it is hoped that it will enable a more quantitative study of some of these questions in the near future.

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