Analytical derivation of thermodynamic characteristics of lipid bilayer from a flexible string model

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(Received 23 December 2004; published 27 June 2005)

We introduce a flexible string model of the hydrocarbon chain and derive an analytical expression for the lateral pressure profile across the hydrophobic core of the membrane. The pressure profile influences the functioning of the embedded proteins and is difficult to measure experimentally. In our model the hydrocarbon chain is represented as a flexible string of finite thickness with a given bending rigidity. In the mean-field approximation we substitute the entropic repulsion between neighboring chains in a lipid membrane by an effective potential. The effective potential is determined self-consistently. The arbitrary chain conformation is expanded over eigenfunctions of the self-adjoint operator of the chain energy density. The lateral pressure distribution across the bilayer is calculated using the path integral technique. We found that the pressure profile is mainly formed by the sum of the partial contributions of a few discrete lowest-energy "eigenconformations." The dependences on temperature and area per lipid of the lateral pressure produced by the hydrocarbon chains are found. We also calculated the chain contribution to the area compressibility modulus and the temperature coefficient of area expansion.

I. INTRODUCTION

We present analytical results derived in closed form for the lateral pressure distribution in a bilayer lipid membrane. The case of persistence length comparable with the chain full length is considered. In this limit we use a path integral approach different from the one used for description of long polymers [1,2]. In addition to being of fundamental interest for the theory of non-Newtonian fluids, our analytical method, we believe, may also have extensive applications due to the strong dependence of the protein functioning on the lipid environment, i.e., the molecular composition of the membrane and lipid characteristics [3,4]. The lateral pressure profile in the bilayer influences the distribution of the open and closed conformations of mechanosensitive channels [5,6]. The second moment of the lateral pressure profile in the bilayer directly affects the protein channel activity if the cross-sectional area of the channel varies with depth [7,8].

The ensemble of chains is described within the mean-field approximation using a microscopic model of a single hydrocarbon chain in effective potential (see Fig. 1). The effective potential allows for entropic repulsion between neighboring chains in each monolayer. Our model permits analytical derivation of the lateral pressure distributions in a great variety of membrane constituents and lipid characteristics (head group type, chain length, etc.) by appropriate change of the imposed boundary conditions and symmetry of the local self-consistent potential.

A typical example of our calculated lateral pressure profile is shown in Fig. 2. The profile is obtained under the following assumptions. The angle between chain tangent and

chain axis is zero at the head group end and the opposite chain end (in the center of the bilayer) is free. The total tension in the bilayer is zero and, therefore, the integral of the pressure profile produced by the chain, $\Pi_t(z)$, over the chain length equals the balancing effective tension in the bilayer, P_{eff}: $\int_0^L \Pi_t(z)dz = P_{\text{eff}}$.

At the effective tension relevant for a bilayer lipid membrane the main contribution to the pressure profile $\Pi_t(z)$ comes from the first few lowest-energy eigenfunctions of the operator of the chain energy density. The eigenfunctions parametrize the manifold of accessible chain conformations. Hence, a snapshot of a fluid membrane would counterintuitively reveal hydrocarbon chains being involved in a "self-organized dance" with only a few allowed (lowest-energy) standard "pas."

The behavior of the $\Pi_t(z)$ curve can be understood by comparing fluctuations of a lipid chain in bilayer and in empty space. In the bilayer the chain fluctuations are strongly suppressed by the neighboring chains with respect to a free lipid molecule. It will be shown below that the amplitude of chain fluctuations in the bilayer under natural conditions is decreased by one order of magnitude with respect to a free chain. Suppression of chain fluctuation leads
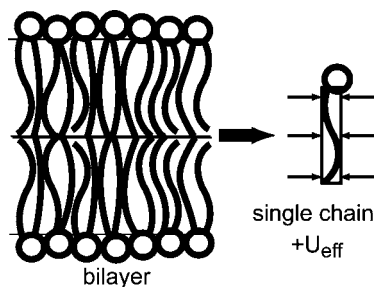

FIG. 1. Model of lipid membrane in mean-field approximation.

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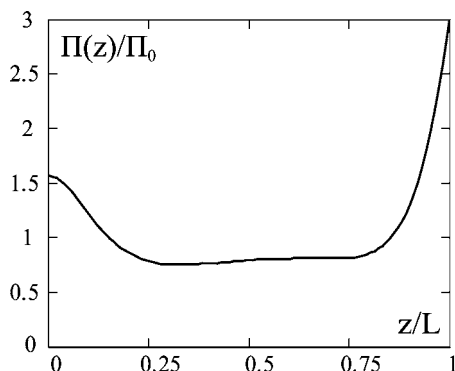†Email address: svt_lana19@yahoo.com

FIG. 2. Lateral pressure distribution in the hydrophobic core of the bilayer. The pressure arises from entropic repulsion between hydrocarbon chains in each monolayer. z is the coordinate along the chain axis normalized by the chain length L and spanning from $z=0$ at the head group to $z=L$ at the free chain end. The parameters for the lipid bilayer are as follows: chain length $L=15$ Å, area per chain in all-trans conformation $A_0=20$ Å^2, chain flexural rigidity $K_f \approx k_B T_0 L/3$, $T_0=300$ K, $P_{eff}=100$ dyn/cm. Pressure is normalized by $\Pi_0 = P_{eff}/3L$.

to a decrease of conformational entropy and, in turn, results in the enhancement of entropic pressure. The most significant relative decrease of fluctuation amplitude takes place at the chain free end ($z \sim L$); at the head group region ($z \sim 0$) the suppression of fluctuations is noticeable too as lipid heads are not fixed; at the midchain region the deviations of a free chain are smaller due to segment connectivity and restriction of the fluctuation freedom of central segments by their peripheral neighbors; hence, the decrease of fluctuations for midchain in the bilayer is less pronounced.

This article is organized as follows. In Sec. II we derive the contribution of hydrocarbon chains to the free energy of the lipid bilayer in the mean-field approximation. We determine the equation of state and find equilibrium characteristics of the bilayer. In Sec. III we calculate analytically the lateral pressure distribution across the hydrophobic core of the lipid bilayer. The results and comparison with previous calculations of lateral pressure are discussed in Sec. IV. Derivation of the analytical solution for the equation of state is given in the Appendix.

II. FREE-ENERGY FUNCTIONAL OF HYDROCARBON CHAIN IN SELF-CONSISTENT APPROXIMATION

The hydrocarbon chain (see Fig. 3) is modeled as a flexible string with bending rigidity K_f. In the mean-field approximation, to account for entropic repulsion between neighboring chains in each monolayer, a harmonic potential $U_{eff}=BR^2/2$ is added to the energy functional of a single hydrocarbon chain, E_t:

$$E_t = \int_0^L \left\{ \frac{K_f}{2} \left(\frac{\partial^2 \mathbf{R}(z)}{\partial z^2} \right)^2 + \frac{B}{2} \mathbf{R}^2(z) \right\} dz. \quad (1)$$

Here L is the chain length, K_f the chain flexural rigidity, B the coefficient of entropic repulsion, z the coordinate along the chain axis, and $\mathbf{R}(z)$ the vector in the $\{x,y\}$ plane char-
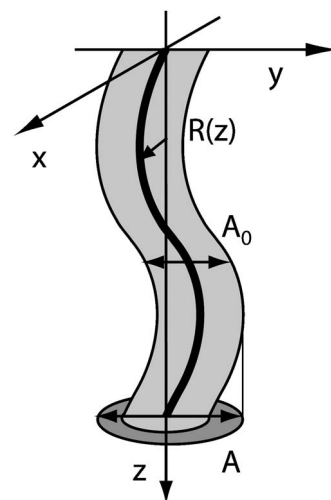

FIG. 3. Hydrocarbon chain as a flexible string of finite thickness. $\mathbf{R}(z)$ is the vector characterizing the deviation of the center of the chain cross section from the z axis, $|\mathbf{R}(z)| = \sqrt{R_x^2(z) + R_y^2(z)}$; A_0 is the "incompressible area" of the chain cross section; $A_1 = \pi < \mathbf{R}^2 >$ is the area swept by the centers of chain cross sections; A is the average area per lipid chain in the bilayer.

acterizing deviation from the z axis, $\mathbf{R}^2 = R_x^2 + R_y^2$, of the string formed by the centers of the chain cross sections.

The bending term in Eq. (1) represents the energy of the chain trans or gauche conformations. It contains the second derivative over the z coordinate rather than over the contour length of the chain. This approximation is valid provided that deviations from the z axis are small with respect to chain length. The limit of small chain deviations, $|\mathbf{R}(z)| \ll L$ is controlled by the (small) parameter (this condition is verified below)

$$\frac{\sqrt{\langle \mathbf{R}^2(z) \rangle}}{L} \le \left(\frac{k_B T}{L^2 P_{eff}} \right)^{1/2} \ll 1. \quad (2)$$

This limit is opposite to the one considered in the long polymer theory [2], where the second derivative in Eq. (1) is substituted by the first derivative in the random chain approximation. The presence of the second derivative in the chain energy functional prohibits direct mapping on the problem of a quantum particle moving in an external potential. In the latter case the square of the first derivative ("velocity") should be involved instead of "acceleration," as given in expression (1). We demonstrate below how to circumvent this difficulty.

The choice of harmonic potential in the second term of the energy functional (1) is justified since we assume "softness" of neighboring lipid chains in the limit of small chain deviation. A harmonic potential was considered in earlier work [9] for a semiflexible polymer confined along its axis. In general, B should be z dependent. In this paper we consider the $B=$const case as a first step in calculating the pressure profile produced by hydrocarbon chains.

Next, we take into account that hydrocarbon chains of lipid molecules are bulky objects that possess finite thickness and introduce an "incompressible area" of the chain cross

section A_0 (see Fig. 3). The area occupied by a lipid chain in the bilayer is related to the string mean square deviation $\langle \mathbf{R}^2 \rangle$ by the following formula:

$$\delta A = \pi \langle \mathbf{R}^2 \rangle = (\sqrt{A} - \sqrt{A_0})^2, \tag{3}$$

where δA is the area swept by the string formed with the centers of the chain cross sections. In the text below we imply by chain deviations those of a string described by the $\mathbf{R}$ vector.

To make numerical estimates based on our model of a lipid bilayer we use the parameters chain length $L=15$ Å, chain incompressible area $A_0=20$ Å^2, $T_0=300$ K as reference temperature. The chain flexural rigidity is defined as [10] $K_f=EI$, where $E \approx 0.6$ GPa is the chain Young's modulus [11] and $I=A_0^2/4\pi$ is the (geometric) moment of inertia. The flexural rigidity can also be evaluated from polymer theory [2] $K_f=k_B T l_p$, where $l_p \approx L/3$ is the chain persistence length [11] and k_B is the Boltzmann constant. Both estimates give approximately $K_f \approx k_B TL/3$ at chosen L and at $T=T_0$.

Using the functional (1) the chain partition function is found as a path integral over all chain conformations in the Gaussian approximation:

$$Z = \int \exp[-E(R(z))/kT]DR_x DR_y$$

$$= \left(\int \exp[-E(R_x(z))/kT]DR_x \right)^2$$

$$= Z_x^2. \tag{4}$$

The second equality in Eq. (4) holds as the membrane is laterally isotropic and the x and y deviations can be considered independent.

To calculate the path integral (4) we rewrite the energy functional (1) using the self-adjoint operator H_0:

$$E_t = \sum_{i=x,y} \int R_i(z) H_0 R_i(z) dz, \tag{5}$$

$$H_0 = \frac{1}{2} \left(K_f \frac{\partial^4}{\partial z^4} + B \right). \tag{6}$$

The operator H_0 is obtained after integrating by parts the expression (1) under the following boundary conditions (the z-coordinate spans from the head group at $z=0$ to the chain free end at $z=L$):

(1) $R'(0)=0$, the chain angle is fixed in the head group region;

(2) $R'''(0)=0$, no total force is applied to chain at the head group;

(3) $R''(L)=0$, zero torque at the chain free end; and

(4) $R'''(L)=0$, zero total force at the chain free end. (7)

The eigensolutions of the operator (6) with boundary conditions (7) have the form
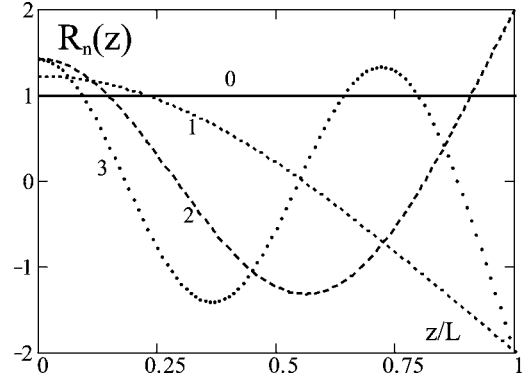

FIG. 4. The eigenfunctions $R_n(z)$ (normalized by $1/\sqrt{L}$) of the self-adjoint operator H_0 for the given boundary conditions. Other parameters are as in Fig. 2.

$$E_n = B + \frac{K_f}{L^4} \left(\frac{\pi}{4} \right)^4 (4n-1)^4, \quad n \geq 1,$$

$$E_0 = B, \tag{8}$$

$$R_n(z) = c_n \left[\cos(\lambda_n z) + \frac{\cos(\lambda_n L)}{\cosh(\lambda_n L)} \cosh(\lambda_n z) \right], \quad R_0(z) = \frac{1}{\sqrt{L}}, \tag{9}$$

where $c_n \cong \sqrt{2/L}$ and $\lambda_{n \geq 1} L = -\pi/4 + \pi n$. Several eigefunctions are shown in Fig. 4.

Then for an arbitrary chain conformation the deviation from the z axis and corresponding energy are expanded over eigenfunctions R_n and eigenvalues E_n of the operator (6):

$$R_x = \sum C_n R_n,$$

$$E_t = \sum C_n^2 E_n. \tag{10}$$

The chain partition function is then found as the integral over the coefficients of expansion (10):

$$Z_x = \int_{-\infty}^{\infty} \prod_n \exp(-C_n^2 E_n/kT) dC_n = \prod_n \sqrt{\frac{\pi kT}{E_n}}. \tag{11}$$

The free energy equals $F=-kT \ln(Z)$. The B-dependent chain contribution to the free energy of the bilayer is defined as follows:

$$\Delta F_t = F_t(B) - F_t(B=0) = kT \sum_n \ln \frac{E_n(B)}{E_n(B=0)}. \tag{12}$$

Using expression (1) we differentiate the free energy and obtain the self-consistency equation in the form

$$\frac{\partial \Delta F_t}{\partial B} = L \langle R^2 \rangle \tag{13}$$

The self-consistency equation (13) combined with formula (3) permits us to find the $B(A)$ dependence and to exclude the coefficient of entropic repulsion B from the equation of state and equilibrium condition.
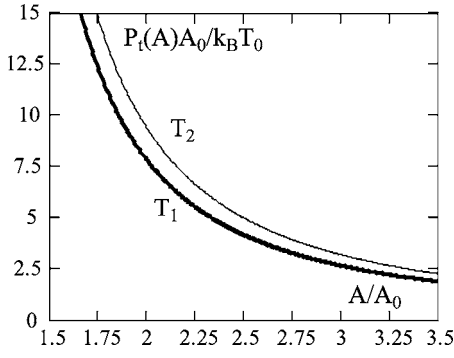
FIG. 5. Calculated lateral pressure P_t produced by hydrocarbon chains as a function of area per chain at two temperatures T_2 (solid line) $>T_1$ (dashed line). Lateral pressure is normalized by $k_B T_0 / A_0$, area is normalized by A_0. Other parameters are as in Fig. 2.

The equation of state reads as

$$-\partial \Delta F_t(A)/\partial A = P_t, \qquad (14)$$

where P_t is the total lateral pressure (or tension), produced by hydrocarbon chains, integrated over the hydrophobic thickness of the monolayer. In Fig. 5 the calculated lateral pressure produced by hydrocarbon chains is shown as a function of the area per chain. Differentiation of $P_t(A)$ gives the area compressibility modulus

$$K_a = -A \frac{dP_t(A,T)}{dA} \qquad (15)$$

as a function of the area per chain and temperature. The equilibrium condition is found by equating the pressure produced by chains to the effective lateral pressure in the bilayer:

$$P_t(A(T)) = P_{\text{eff}} = \gamma + P_{\text{HG}} + P_{\text{vdW}}, \qquad (16)$$

where γ is the surface tension at the hydrophobic-hydrophilic interface; P_{HG} is the head group repulsion of electrostatic origin; P_{vdW} is the pressure arising from the van der Waals interactions between chains, etc. We choose $P_{\text{eff}} > \gamma \sim 50$ dyn/cm because attractive dispersion interactions between hydrocarbon chains are included in the effective surface tension [12]. At room temperature for a typical lipid bilayer with effective surface tension $50 \le P_{\text{eff}} \le 150$ dyn/cm [4,12] the analytic solution for the equation of state reads (the detailed derivation is given in Appendix)

$$P_t(a,T) = \frac{kT}{A_0} \frac{2^{1/3}}{v^{1/3}} \frac{1}{\sqrt{a}(\sqrt{a}-1)^{5/3}}, \qquad (17)$$

where $a = A/A_0$, $v = K_f A_0 / 2\pi k_B T L^3 \cong 0.005$ is a dimensionless parameter. For the estimates at T_0 we adopt $P_{\text{eff}} = 100$ dyn/cm.

We derive the area per chain in the thermodynamic equilibrium at a given temperature T, $A(T)$, from the equilibrium condition (16). Differentiating it we find the temperature coefficient of area expansion

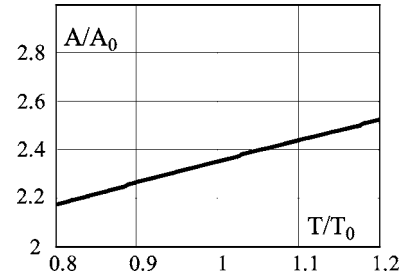$$K_T = \frac{1}{A} \frac{dA}{dT}. \qquad (18)$$

FIG. 6. Temperature dependence of equilibrium area per chain, A. Temperature is normalized by T_0, area is normalized by A_0.

In Fig. 6 the temperature dependence of the area per chain in the bilayer is shown. Solutions of Eq. (14) yielding analytical dependence $P_t(A)$ displayed in Fig. 5 is given in the Appendix.

III. ANALYTICAL CALCULATION OF LATERAL PRESSURE PROFILE

So far, the equation of state derived above permits one to find the lateral pressure integrated over the chain length, i.e., over the hydrophobic thickness of a monolayer. To find the distribution of lateral pressure across the bilayer, i.e., along the z axis normal to the bilayer plane, we apply the following procedure. We perform differentiation of the free energy over the chain area A under the constancy of the chain specific volume: $V = LA$. The energy functional of the hydrocarbon chains (1) can be rewritten in equivalent form allowing for orthonormality of the eigenfunctions $R_n(z)$:

$$E_t = \sum_n E_n C_n^2 \int_0^L R_n^2(z) dz. \qquad (19)$$

Then, differentiating the chain partition function we obtain

$$\frac{\partial \Delta F_t}{\partial A} = -2k_B T \left(\frac{1}{Z_x(B)} \frac{\partial Z_x(B)}{\partial A} - \frac{1}{Z_x(B=0)} \frac{\partial Z_x(B=0)}{\partial A} \right)$$

$$= k_B T \sum_n \frac{\partial}{\partial A} \ln \left(\frac{E_n(B)}{E_n(B=0)} \right) \int_0^L R_n^2(z) dz. \qquad (20)$$

Then comparing the relation thus obtained with the normalization condition for the lateral pressure distribution,

$$\int_0^L \Pi_t(z) dz = P_t, \qquad (21)$$

we finally find

$$\Pi_t(z) = -k_B T \sum_{n \ge 1} R_n^2(z) \frac{\partial}{\partial A} \ln \left[b(A) + \left(\frac{\pi}{4} \right)^4 (4n-1)^4 \right]$$

$$- \frac{k_B T}{L} \frac{\partial \ln[b(A)]}{\partial A}, \qquad (22)$$

where the dimensionless parameter $b = BL^4 / K_f$ is introduced in the Appendix. The $b(A)$ dependence follows from the self-consistency equation (13) [see Eq. (A5) in the Appendix].

It is obvious that the terms in the sum in (22) decrease as $1/n^4$. Due to the fast convergence of the sum only the first

few terms contribute to the pressure profile. The normalized lateral pressure profile (22) is plotted in Fig. 2.

Now we can verify the exploited approximation of the small chain deviations in the bilayer (2). We calculate the thermodynamic average of the chain fluctuation amplitude $\langle \mathbf{R}^2(z) \rangle$ using the relation $\langle R_{x,y}^2(z) \rangle = \Sigma_n \langle C_n^2 \rangle R_n^2(z)$ and averaging over C_n:

$$\langle \mathbf{R}^2(z) \rangle = 2\langle R_{x,y}^2(z) \rangle = k_B T \sum_n \frac{R_n^2(z)}{E_n}. \tag{23}$$

It is worth mentioning that integration of both sides of Eq. (23) over z from 0 to L provides the self-consistency equation (13). Since $E_n \propto n^4$, the sum in Eq. (23) converges fast and allowing for the relation $R_n^2(z) \sim 1/L$, we estimate it as $\Sigma_n 1/E_n \propto 1/B$. According to Eq. (1), the increase of potential energy associated with the increase of area swept by the string from 0 to δA is of order $BL\delta A$ (the string is formed with the centers of the chain cross sections). On the other hand it is equal to the work against the pressure P_{eff} needed to increase the area per chain in the bilayer from A_0 to A: $BL\delta A \approx P_{eff}(A - A_0)$. From the last equality and relation (3) it follows that $B > P_{eff}/L$. Then we can evaluate

$$\sum_n \frac{R_n^2(z)}{E_n} \leq \frac{1}{P_{eff}}, \tag{24}$$

and find a rough estimate for the upper limit of the small parameter:

$$\sqrt{\langle R^2(z) \rangle}/L \leq (k_B T/L^2 P_{eff})^{1/2} = 0.14. \tag{25}$$

Finally, we compare the amplitudes of chain fluctuations in the bilayer (23) and in empty space. For a free chain with flexural rigidity K_f the characteristic deviation R^0 can be evaluated by equating the chain bending energy to $k_B T$. This yields

$$R^{0^2} \propto \frac{k_B T}{K_f} L^3 \sim L^2 \tag{26}$$

Allowing for Eqs. (23) and (26), we find $\sqrt{\langle R^2 \rangle}/R_0 \sim 0.1$.

IV. DISCUSSION

We derived an analytical expression for the lateral pressure profile across the hydrophobic core of a lipid bilayer. Though difficult to measure experimentally, the profile is an important characteristic of the lipid bilayer that determines the activation barrier of membrane protein channels [7]. The calculated profile qualitatively agrees with the results of molecular dynamics simulations [8,12]. The pressure profile as a function of the depth in the bilayer shows a decrease in the midchain region and noticeably increases farther at the chain end in the center of bilayer. This behavior differs from the earlier mean field and Monte Carlo calculations [2,13,14] that exploited lattice models of the bilayer. In the referenced works the lateral pressure decreases toward the bilayer center, simultaneously with a decrease of the chain order parameter. The latter signifies high conformational entropy of the segments at the chain end. This behavior indicates that the

mean square deviation of the chain in the bilayer model is comparable with that of a single free chain. The authors did not present information on this important characteristic. In our work we calculated the mean square deviation of a chain in the bilayer directly in analytical form. For a single free chain the deviation increases as the square root of the contour length, and thus the fluctuation amplitude is maximal at the chain free end. We demonstrate that the chain deviation in the bilayer is one order of magnitude smaller than that of a free chain. Therefore, this relative reduction of the chain accessible volume leads to a decrease of the conformational entropy and to an increase of lateral pressure toward the bilayer center (chain free end).

In our model we found analytically the temperature and area per lipid dependence of the lateral pressure produced by hydrocarbon chains. The chain contributions to the area compressibility modulus and the temperature coefficient of area expansion are calculated. The obtained temperature coefficient of area expansion ($\sim 2 \times 10^{-3}$ K^{-1}) lies in the interval of experimentally measured values. We conclude that the chain contribution to area expansion with temperature is dominant. At the same time the calculated chain contribution to the area compressibility modulus (~ 100 erg/cm^2) proves to be smaller than the intrinsic area compressibility of the bilayer (~ 300 erg/cm^2) [12]. This suggests that the head group region is more rigid than the hydrophobic core.

To summarize, we proposed a method of analytical self-consistent calculation of the lateral pressure profile from a microscopic model of a lipid bilayer. An analytical expression for the equation of state of the membrane is also derived. It shows reduction of the chain fluctuation amplitude in the bilayer by one order of magnitude with respect to that of a free chain. The calculated lateral pressure profile is in qualitative accord with recent numerical results obtained by molecular dynamics simulations.

APPENDIX

Here we present the solution of the self-consistency equation (13) and find the analytical temperature and area per chain dependence of the lateral pressure produced by the chains using the equation of state (14). It is convenient to perform the derivations in dimensionless parameters,

$$a = A/A_0, \quad b = \frac{L^4}{K_f} B, \tag{A1}$$

and to introduce the auxiliary parameters

$$c_n = \left(\frac{\pi}{4}\right)^4 (4n-1)^4, \quad n \geq 1; \quad v = \frac{K_f A_0}{2\pi k_B T L^3}, \quad \text{(A2)}$$

where $L \sim 15$ Å is the chain length, $A_0 \sim 20$ Å^2 is the "incompressible area" of the chain cross section, and the chain flexural rigidity $K_f \cong k_B T L / 3$ at $T \approx T_0 = 300$ K. Using these estimates we obtain $v \cong 0.005$.

In the introduced notations (A1) and (A2) with E_n defined in Eq. (8) the self-consistency equation (13) acquires the form

$$\frac{1}{b} + \sum_{n=1}^{\infty} \frac{1}{b + c_n} = v(\sqrt{a} - 1)^2. \quad \text{(A3)}$$

The terms in the sum on the left hand side of Eq. (A3) decrease fast with growing n, e.g., $c_1 = 31$, $c_2 = 914$, $c_3 = 5571$, etc. The number of terms contributing significantly to the left hand side of Eq. (A3) depends on the order of magnitude of the parameter b, which is in turn determined by the value of the effective surface tension in the bilayer, P_{eff}, according to the equilibrium condition (16). At room temperature we estimate that the effective surface tension in the real bilayer belongs to the range $50 \leq P_{\text{eff}} \leq 150$ dyn/cm [4,11], which bounds the interval for parameter b: $10^3 \leq b \leq 10^5$. In this regime we can solve Eq. (A3) analytically by substituting summation over n with integration, which yields

$$\sum_{n=1}^{\infty} \frac{1}{b + c_n} \approx \frac{1}{2} \int_{-\infty}^{\infty} \frac{dn}{b + (\pi/4)^4 (4n+3)^4} = \frac{1}{2\sqrt{2}b^{3/4}}. \quad \text{(A4)}$$

It is interesting to mention that integrating the right hand side of expression (A4) over b gives $\Delta F \sim b^{1/4}$, which is in accord with the result [9], obtained using a different method.

This permits us to find the $b(a)$ dependence:

$$b = \frac{1}{4v^{4/3}(\sqrt{a} - 1)^{8/3}}, \quad \text{(A5)}$$

which is then used in the equation of state (14). As a result we find the expression for the lateral pressure produced by the hydrocarbon chains:

$$P_t(a,T) = \frac{kT}{A_0} \frac{2^{1/3}}{v^{1/3}} \frac{1}{\sqrt{a}(\sqrt{a} - 1)^{5/3}}. \quad \text{(A6)}$$

Here the additional multiplier $2^{1/3}$ is introduced to compensate for the substitution of the asymmetric sum in (A4) by a symmetric integral. This multiplier is found by fitting the analytical $P(a)$ curve to the numerically calculated dependence. Plots of the pressure vs area dependence (A6) at different temperatures are displayed in Fig. 5.

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