Analytical derivation of thermodynamic properties of bolalipid membrane

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Abstract

We consider a model of bilayer lipid membrane with bola-lipids. The bola-lipid is modeled by linking tails of the hydrophobic chains in the opposite monolayers within bilayer as a first approximation. A number of thermodynamical characteristics are calculated analytically and compared with the ones of a regular membrane without chains linkage. Pronounced difference between lateral pressure profiles at the layers interface for linked and regular bilayer models is found. In the linked case, the lateral pressure mid-plane peak disappears, while the free energy per chain increases. We have also calculated distribution of the orientaional order parameter of linked chains across the bilayer, and found it is in contrast with the usual lipids case.

Key words: bilayer lipid membrane, interdigitation, lateral pressure profile, hydrophobic mismatch
I. INTRODUCTION

Studying mechanisms of changes in the structure, elastic and thermodynamic properties of new artificial membranes is of fundamental interest, as well as is important for construction of membranes with higher stability under extreme conditions [1]. Besides, there are also important natural examples of the membranes with such properties, e.g. archaeal lipids with distinctive molecular structure that allows the microorganisms to maintain membrane integrity in harsh environments [2]. We present below first analytical results describing some essential behaviors of bolalipid membrane that are derived using modification of our previous model of lipid bilayer [3].

As a first approximation to the bolalipid bilayer membrane, in which lipid tails from the opposite monolayers interpenetrate, we consider a model with pairwise linked tails of the lipids belonging to the opposite monolayers within a single bilayer, Fig. 1. Our model being rather simplistic nevertheless bears an important property of the bolalipid bilayer in the form of constrained meandering freedom of the chains ends in the vicinity of the monolayers interface. We found important consequences of this constriction: the entropy of the bilayer decreases, the free energy increases, and the lateral pressure $\Pi_t(z)$ and orientational order $S(z)$ profiles change drastically.

The two distinct $\Pi_t(z)$ curves, see Fig. 2, can be understood by comparing orientational fluctuations of the hydrocarbon segments of the semi-flexible lipid chains in the linked- and nonlinked lipid bilayers. These fluctuations can be characterized by an orientational order parameter $S(z)$, see Fig. 4 ($z$ is coordinate measuring depth inside bilayer), calculated using our model. The fluctuations reach their maximum at the monolayers interface inside a nonlinked bilayer, because the chains ends are free there. Hence, the order parameter drops at $z = L$, see the dashed curve in Fig. 4. Simultaneously, a maximum of the entropic lateral pressure occurs at $z = L$, dashed curve in Fig. 2. Distinctly, in the bolalipid "bilayer" fluctuations are significantly suppressed at the "monolayers" interface due to restriction of orientational freedom of the central segments by their peripheral neighbors. Hence, $S(z)$ does not drop at $z = L$, see solid curve in Fig. 4. As a consequence, there is no maximum at $z = L$ in the $\Pi_t(z)$ dependence drawn with solid line in Fig. 2 for linked bilayer case (quotation marks indicate that in purely bolalipid membrane there is actually no strict notion of a bilayer consisting of monolayers sliding upon one another along the interface).
We present our analytical results derived in closed form for thermodynamical properties of a membrane with linked chains in the weak-disorder limit: i.e. thickness of the hydrophobic part of a bilayer is comparable with twice the length of a single monopolar lipid chain. In this limit we use more complete version of the energy functional entering the membrane partition function than developed earlier [3]: besides the bending energy of a chain conformation, we included kinetic energy of the lipid chain. We prove that this makes the path integral representation of the free energy of the chains uniquely normalizable.

Our latteral pressure profile in case of no linkage (see Fig. 2, dashed line) is in good agreement with the molecular dynamics simulations [6, 7] see Fig. 3.

The plan of the article is as follows. In Sec. II we introduce a microscopic model of a bolalipid membrane and calculate the membrane free energy using path-integral summation over the chains conformations. The inter-chain entropic interactions are treated in the mean-field approximation. Several thermodynamic moduli characterizing the bolalipid bilayer are derived as well and compared with nonlinked bilayer case. An increment of the free energy per chain due to linkage is calculated. In Secs. III and IV we calculate analytically the lateral pressure distribution (profile) across the hydrophobic core of the lipid bilayer and make comparison between the cases with- and without linkage. Also calculated is chain order parameter that characterizes correlations between the orientations of the chain segments and clearly demonstrates an increase of the orientation order in the bolalipid case as compared with nonlinked bilayer.

II. MICROSCOPIC MODEL OF BOLALIPID BILAYER

The bolalipid bilayer membrane is modeled by linking pairwise the tails of the chains belonging to the opposite monolayers. Hence, a couple of linked chains is substituted by a single semi-flexible string of length \( \approx 2L \), where \( L \) is the monolayer thickness, see Fig. 5. Correspondingly, conformations of the string as a transmembrane object obey combined boundary conditions at the opposite head group regions of bilayer with coordinates \( z = 0 \) and \( z = 2L \) respectively, as is described below in detail.

By doing so, we take into account the decrease of chain’s freedom in the midplane in case of linkage in comparison with regular membrane. With bending (flexural) rigidity \( K_f \), and with the mean-field approximation accounting for entropic repulsion between neighboring
couples of pairwise linked chains (see Fig. 5), the energy functional of a single string, $E_t$, has the form:

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

Here harmonic potential $U_{eff} = BR^2/2$, with self-consistently defined rigidity $B$, describes entropic repulsion between the strings, $z$ is coordinate along the string axis, and $R(z)$ is vector in the $\{x, y\}$ plane characterizing deviation of the string from the straight line, $R^2 = R_x^2 + R_y^2$ (see 6). The choice of harmonic potential is justified since we assume finite softness of the effective “cage” created by the neighboring lipid chains in the limit of small chain deviations. A harmonic potential was considered in earlier work [11] for a semi-flexible polymer confined along its axis. The elastic energy treatment of the molecular chains, especially well known in the theory of polymers, see e.g. [12, 13, 14]. The first term in Eq. (1) represents kinetic energy of the string, $\rho$ is linear density of mass: $\rho = m(CH_2)N/L$, where $m(CH_2)$ is a hydrocarbon group mass, $N$ is the number of hydrocarbon groups per chain (for numerical estimates we took $N = 18$, see [9]).

The bending energy 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 the chain length $L$:

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

This limit is opposite to the one considered in the long polymer theory [18], where the second derivative in Eq. (1) is substituted by the first derivative in the flexible chain approximation.

Using the functional Eq. (1) the chain partition function is found as a path integral over all string conformations:

$$Z = \int \exp \left( -\frac{E(\dot{R}(z), R(z))}{k_B T} \right) D\dot{R}_x DR_x D\dot{R}_y DR_y =$$

$$\left( \int \exp \left[ -\frac{E(\dot{R}_x(z), R_x(z))}{k_B T} \right] D\dot{R}_x DR_x \right)^2 = Z_x^2.$$  (3)
The second equality in Eq. (3) holds when the membrane is laterally isotropic and \( x \) and \( y \) deviations can be considered independently.

To calculate the path integral Eq. (3) we rewrite the energy functional Eq. (1) using the self-adjoint operator \( \hat{H} \):

\[
E_t = \sum_{i=x,y} \frac{1}{2} \int_0^{2L} \left( \rho \dot{R}_i^2(z) + R_i(z) \hat{H} R_i(z) dz \right),
\]

(4)

\[
\hat{H} = K_f \frac{\partial^4}{\partial z^4} + B.
\]

(5)

The operator \( \hat{H} \) is obtained after integrating by parts the expression Eq. (1) under the following boundary conditions for the string that models two linked chains belonging to the opposite monolayers (the \( z \)-coordinate spans from one head group at \( z = 0 \) to another at \( z = 2L \)). The chain angle is fixed in the head group region:

\[
R'(0) = 0; \ R'(2L) = 0
\]

(6)

No total force is applied upon chain at the head group:

\[
R''(0) = 0; \ R''(2L) = 0
\]

(7)

These boundary conditions, as well as the energy functional in Eq. (1) differ from the ones used to describe a single monolayer of a nonlinked lipid bilayer (compare [3]):

\[
E_t^m = \int_0^L \left\{ \frac{\rho R^2(z)}{2} + \frac{K_f}{2} \left( \frac{\partial^2 R(z)}{\partial z^2} \right)^2 + \frac{B}{2} R^2(z) \right\} dz
\]

(8)

where \( E_t^m \) is the energy functional of a single monolayer, and the motions of the chains in the opposite monolayers forming a noniterdigitated bilayer are independent. The total energy of a bilayer in this approximation is then twice the energy of a single monolayer: \( 2 \times E_t^m \).

We impose the following boundary conditions for a monolayer: the chain angle is fixed, and no total force is applied to the chain at the head group:

\[
R'(0) = 0; \ R''(0) = 0
\]

(9)

No total force and no torque is applied at the free chain end (i.e. at the monolayers interface inside the bilayer):

\[
R''(L) = 0; \ R''(L) = 0
\]

(10)
Finally, in both cases, the free energy of a bilayer equals \( F = -k_B T \ln(Z) \), where \( Z \) is partition function of a bilayer. Using expressions Eq. (1) or Eq. (8) for linked or nonlinked bilayer respectively, we differentiate the free energy and obtain the self-consistency equation in the form (expressed below for linkage case):

\[
\frac{\partial F}{\partial B} = 2L \langle R^2 \rangle \tag{11}
\]

As in [3], 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. 6). The area occupied by a lipid chain in the bilayer is related to the string mean square deviation \( \langle R^2 \rangle \) by the following formula [3]:

\[
\delta A = \pi \langle R^2 \rangle = \left( \sqrt{A} - \sqrt{A_0} \right)^2, \tag{12}
\]

where \( \delta A \) 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. The self-consistency equation Eq. (11) combined with formuli Eq. (12) permits us to find the \( A \) dependence of the coefficient of entropic repulsion \( B \) and finally derive the membrane equation of state in a form of pressure-area isotherm (see Appendix A for details).

To make numerical estimates based on our model of a lipid bilayer we use the following parameters values: monolayer thickness \( L = 15A \), chain incompressible area \( A_0 = 20A^2 \), \( T_0 = 300K \) as reference temperature. The chain flexural rigidity is defined as [15] \( K_f = EI \), where \( E \approx 0.6GPa \) is the chain Youngs modulus [17] and \( I = A_0^2 / 4\pi \) is the (geometric) moment of inertia. The flexural rigidity can also be evaluated from polymer theory [18] \( K_f = k_B T l_p \), where \( l_p \approx L/3 \) is the chain persistence length [17] and \( k_B \) is the Boltzmann constant. Both estimates give approximately \( K_f \approx k_B T L / 3 \) at chosen \( L \) and at \( T = T_0 \).

III. LINKED-CHAINS BILAYER: THE FREE ENERGY INCREMENT

The eigenvalues and eigenfunctions of the operator \( \hat{H} \) defined in Eq. (5) obey the following equation:

\[
\hat{H} R_n \equiv K_f \frac{\partial^4 R_n}{\partial z^4} + BR_n = E_n R_n \tag{13}
\]
Solving this equation with the boundary conditions Eq. (6)-(7) one obtains:

\[ E_n = B + \frac{k_n^4 K_f}{L^4}, \quad k_n = \pi n/2, \quad n \geq 1; \quad E_0 = B, \quad (14) \]

\[ R_n(z) = c_n \cos(k_n z/L), \quad n \geq 1; \quad R_0(z) = \frac{1}{2L}, \quad (15) \]

where \( c_n = \sqrt{1/L} \) and \( \lambda_n = 2\pi L/k_n \) is the wavelength. Several eigenfunctions are shown in Fig. 7.

Then an arbitrary string conformation, described with the deviation from the \( z \)-axis, \( R_x(z, t) \), as well as its energy are expanded over eigenfunctions \( R_n \) and eigenvalues \( E_n \) found from Eq. (13):

\[ R_x(z, t) = \sum_{n=0}^\infty C_n(t) R_n(z); \quad \dot{R}_x = \sum_{n=0}^\infty \dot{C}_n R_n; \quad E_t = \frac{1}{2} \sum_{n=0}^\infty (\dot{C}_n^2 + C_n^2 E_n) \quad (16) \]

The bilayer partition function is then found as the integral over the coefficients of expansion \( C_n \) and conjugated momenta \( p_n = \rho \dot{C}_n \) in Eq. (16):

\[ Z_x = \int_{-\infty}^{\infty} \prod_{n=0}^\infty \exp \left( -\frac{p_n^2}{2\rho k_B T} + \frac{C_n^2 E_n}{2k_B T} \right) dp_n dC_n = \prod_{n=0}^\infty \frac{k_B T}{h} \sqrt{\frac{\rho}{E_n}} = \prod_{n=0}^\infty \frac{k_B T}{h\omega_n} \quad (17) \]

where \( \omega_n = \sqrt{E_n/\rho} \). It is important that the latter expression for \( \omega_n \) in the limit of a free string, \( B \equiv 0 \), leads to the well known bending waves spectrum of Euler beam \[15\]:

\[ \omega_n = \sqrt{EI\tilde{k}_n^4/\rho} \quad (with \quad \tilde{k}_n \equiv k_n/L) \]

as it follows from Eq. (14) and expression for the bending rigidity \( K_f = EI \) mentioned above. Hence, by including kinetic energy of the chain into the energy functional \( E_t \) we obtain correct dimensionless expression for partition sum in the Eq. (17).

Using Eq. (17), Eq. (3) and \( F = -k_B T \ln Z \) we find the following expression for the free energy of a bilayer with bolalipids in our model:

\[ F_{\text{int}} = -2k_B T \sum_{n=0}^{n_{\text{max}}} \ln \frac{k_B T}{h\omega_n} \quad (18) \]
Using then relation $S_{\text{int}} = -\partial F_{\text{int}}/\partial T$ we find the following expression for the entropy $S_{\text{int}}$:

$$S_{\text{int}} = -\left(\frac{\partial F}{\partial T}\right)_V = -2k_B \sum_{n=0}^{n_{\text{max}}} \ln \left(\frac{k_B T}{\hbar \omega_n}\right) + T \left\{ \frac{1}{\omega_n} \left(\frac{\partial \omega_n}{\partial T}\right)_V - \frac{1}{T} \right\}$$ \hspace{1cm} (19)

Both expressions are valid provided the motion of the lipid chains at room temperature $T$ is classical (not quantum), i.e.: $\hbar \omega_{n_{\text{max}}}/k_B T << 1$. The upper cutoff $n_{\text{max}}$ in the sums is defined by condition that the shortest half-wavelength $0.5\lambda_{n_{\text{max}}} = \pi L/k_{n_{\text{max}}}$ of the eigenfunction $R_{n_{\text{max}}}$ is not shorter than the $CH_2$-monomer length of the “chain segment”. Hence in case with linkage $n_{\text{max}} = 11$ and $\hbar \omega_{n_{\text{max}}}/k_B T = 0.29$.

The free energy and entropy of the nonlinked bilayer, $F_{\text{non}}$ and $S_{\text{non}}$ respectively, are obtained using the same relations as in Eqs. (18) and (19), but with the corresponding change of the frequencies spectrum $\omega_n$ that results from the noniterdigitated bilayer conditions expressed in Eqs. (9)-(10). Using the above relations we calculated linkage-related free energy and entropy ”cost” as the differences of the respective bilayer free energies and entropies in the linked and nonlinked cases. Our results are represented in Fig. 8 and Fig. 9.

In Fig. 8 the free energy increment (per chain) of the order of $5k_B T$ in the bolalipid bilayer with respect to the nonlinked one is caused by the corresponding decrease of the entropy $\sim 5k_B$ (per chain), see Fig. 9. Location of the entropy decrease in the linked bilayer can be found by exploring the chain’s orientational order parameter $S(z)$ defined as:

$$S(z) = \frac{1}{2} \left( 3 \langle \cos^2 \theta(z) \rangle - 1 \right),$$ \hspace{1cm} (20)

where $\theta(z)$ gives distribution of the tangent angle of the chain across the bilayer. Straight (ordered) chain possesses $\theta \equiv 0$ and $S(z) \equiv 1$. In the limit of small deviations from the straight line $\theta \leq 1$ considered in our model the order parameter can be expressed using the following relations:

$$\langle \cos^2 \theta(z) \rangle \approx 1 - \langle \tan^2 \theta(z) \rangle = \langle (R'(z))^2 \rangle = \frac{k_B T}{2} \sum_{n=0} \frac{(R_n'(z))^2}{E_n},$$ \hspace{1cm} (21)

so that finally we obtain:

$$S(z) \approx 1 - \frac{3k_B T}{4} \sum_{n=0} \frac{(R_n'(z))^2}{E_n}. \hspace{1cm} (22)$$

Calculated order parameter distributions across the bilayer, $S(z)$, in our model with and without linkage are represented in Fig. 4. The solid line corresponds to linked chains (modeling bolalipids), and dashed line is calculated for nonlinked case. It is obvious from the
Fig. 4 that main difference occurs at the monolayers interface ($z = L$) inside the bilayer. Free chain ends acquire maximal disorder in this region, while linked tails remain quite ordered. Another manifestation of this mid-bilayer ordering phenomenon will be seen in the next section in the calculated behavior of the lateral pressure profile inside bilayer.

IV. LATERAL PRESSURE PROFILE AND PRESSURE-AREA ISOTHERMS FOR BOLALIPID BILAYER

The equation of state of the lipid chains in the bilayer can be derived as follows:

$$P_t = -\left(\frac{\partial F_t}{\partial A}\right)_T,$$

where $P_t$ is the total lateral pressure (here has dimensionality of a tension), produced by linked hydrocarbon chains. Substituting expression for the free energy from Eq. (18) into Eq. (23) one finds:

$$P_t = -k_B T \sum_{n=0}^{\infty} \left(\frac{\partial E_n}{\partial A}\right)_T \frac{1}{E_n}.$$

(24)

We may consider $P_t$ as an integral of the lateral pressure distribution (profile) function, $\Pi_t(z)$, over the hydrophobic thickness of the bilayer:

$$P_t \equiv \int \Pi_t(z) dz.$$

(25)

In order to find out $\Pi_t(z)$ defined this way, it is possible to use the following formal trick. Namely, the dependence on aria $A$ of $E_n$ arises via dependence of the “potential” $B(A)$, that enters operator $\hat{H}$ in Eq. (13). One may in addition formally consider $B(A)$ as being $z$-dependent function. Then, a well known relation from the perturbation theory leads to the following equation:

$$\left(\frac{\partial E_n}{\partial A}\right)_T = \int \left(\frac{\delta E_n}{\delta B}\right)_T \left(\frac{\partial B}{\partial A}\right)_T dz \equiv \int R_n^2(z) \left(\frac{\partial B}{\partial A}\right)_T dz,$$

(26)

where 1 means unit length. Now, substituting Eq. (26) into Eq. (24) we find analytical expression for the lateral pressure profile from the relation:

$$P_t = -\int k_B T \sum_{n=0}^{\infty} \frac{R_n^2(z)}{E_n} \left(\frac{\partial B}{\partial A}\right)_T dz \equiv \int \Pi_t(z) dz.$$

(27)
Hence, finally:

\[ \Pi_l(z) = -k_B T \left( \frac{dB(A)}{dA} \right)_T \sum_{n=0}^{\infty} \frac{R_n^2(z)}{E_n}. \]  

(28)

Calculated in our model lateral pressure profiles for the bilayer with and without linkage are presented in Fig. (2). It is remarkable, that lateral pressure peak at the nonlinked monolayers interface, as seen in the dashed curve, disappears in the linked chains case. Hence, entropic repulsion between the lipid chains is indeed weaker in the region where the entropy related with the chain orientation order is smaller (compare with Fig. 4).

Next, it is straightforward to check that due to orthonormality of the eigenfunctions \( R_n(z) \) the integral of \( \Pi_l(z) \) over \( dz \) across the bilayer thickness leads again to the expression in Eq. (24) for the total lateral tension \( P_l \):

\[ P_l = -k_B T \left( \frac{dB(A)}{dA} \right)_T \sum_{n=0}^{\infty} \frac{1}{E_n} \equiv -k_B T \sum_{n=0}^{\infty} \left( \frac{\partial E_n}{\partial A} \right)_T \frac{1}{E_n}, \]  

(29)

where we used relation that follows from Eq. (14):

\[ \left( \frac{dB(A)}{dA} \right)_T = \left( \frac{\partial E_n}{\partial A} \right)_T, \quad \forall n. \]  

(30)

In Figure (10) the calculated pressure-area isotherms for bolalipid (linked chains, solid line) and nonlinked (dashed line) bilayer are presented. It is obvious from the figure that lateral entropic repulsion responsible for the lateral pressure in the hydrophobic part of the bilayer is weaker in the bolalipid bilayer comparatively with nonlinked bilayer at the one and the same area per lipid chain and other parameters fixed.

Differentiation of \( P_l(A) \) gives the area compressibility modulus

\[ K_a = -A \left( \frac{\partial P_l}{\partial A} \right)_T \]  

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

\[ P_l(A(T)) = P_{\text{eff}} = \gamma + P_{HG} + P_{vdW}, \]  

(32)
where $\gamma$ 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 vander Waals interactions between chains, etc. We choose $P_{\text{eff}} > \gamma \sim 70 \text{ dyn/cm}$ because attractive dispersion interactions between hydrocarbon chains are included in the effective surface tension $\gamma$. At room temperature for a typical lipid bilayer with effective surface tension one has: $50 \leq P_{\text{eff}} \leq 150 \text{ dyn/cm}$ [6, 19]. Analytical solution for the total pressure in case of linked chains (bolalipids):

$$P_{t_{\text{linked}}} = \frac{2k_BT}{3A_0\nu^{1/3}\sqrt{\bar{a}}(\sqrt{\bar{a}} - 1)^{5/3}} \cdot (2\nu^{2/3}(\sqrt{\bar{a}} - 1)^{2/3} + 1) \quad (33)$$

Analytical solution for the total pressure in case of nonlinked chains:

$$P_{t_{\text{nonlinked}}} = \frac{2k_BT}{3A_0\nu^{1/3}\sqrt{\bar{a}}(\sqrt{\bar{a}} - 1)^{5/3}} \cdot (4\nu^{2/3}(\sqrt{\bar{a}} - 1)^{2/3} + 1) \quad (34)$$

It follows from the analysis of these expressions that the linkage effect on the total lateral pressure at a given area is more pronounced at larger areas per lipid (lower pressures) region, that corresponds to higher orientational disorder of the chains.

Coefficient of area expansion Eq. (31) calculated using Eq. (33) for bolalipid membrane is smaller than obtained from Eq. (34) for membrane without tails linkage, the latter is in close agreement with the measured ones [20].

In Fig. 11 the temperature dependence of the area per chain in the bilayer is shown. This curve is increasing with temperature due to a more frequent collisions of chains. Fig. 12 displays $P_{t}(A)$ dependence. This curve is decreasing with the area per chain due to the following reason: when the chains occupy more space they collide less frequently and produce less entropic pressure.

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

$$\langle R^2(z) \rangle = k_BT \sum_n \frac{R^2_n(z)}{E_n}. \quad (35)$$

It is worth mentioning that integration of both sides of Eq. (35) over $z$ from 0 to $2L$ provides the self-consistency equation Eq. (11). Since $E_n \propto n^4$, the sum in Eq. (35) converges fast and allowing for the relation $R^2_n(z) \sim 1/L$, we can estimate it as $\sum_n 1/E_n \propto 1/B$. 

11
According to Eq. (1), the increase of potential energy associated with the increase of area swept by the string from 0 to $\delta A$ is of order $B2L\delta A$ (the string is formed by the centers of the chain cross-sections). On the other hand, it is equal to the work against the pressure $P_{\text{eff}}$ needed to increase the area per couple of linked chains in the bilayer from $A_0$ to $A$: $B2L\delta A \approx P_{\text{eff}}(A - A_0)$. From the last equality and relation Eq. (12) it follows that $B > P_{\text{eff}}/L$. Then we evaluate:

$$\sum_n \frac{R_n^2(z)}{E_n} \approx \frac{1}{P_{\text{eff}}},$$

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

$$\sqrt{\langle R_n^2(z) \rangle}/2L \leq (k_BT/L^2 P_{\text{eff}})^{1/2} = 0.16.$$  (37)

Finally, we compare the amplitudes of linked chains fluctuations in the bilayer Eq. (35) and in empty space. For a free couple of chains with flexural rigidity $K_f$ the characteristic deviation $R^0$ can be evaluated by equating the chain bending energy to $k_BT$. This yields

$$R^0 \propto \frac{k_BT}{K_f} L^3 \sim L^2$$  (38)

Allowing for Eq. (35) and Eq. (38), we find $\sqrt{\langle R^2 \rangle}/R_0 \sim 0.1$.

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APPENDIX A: SOLUTION OF SELF-CONSISTENCY EQUATION

Here we present the solution of the self-consistency Eq. (11) and find the analytical temperature and area per couple of chains dependence of the lateral pressure produced by the linked chains using the equation of state Eq. (23). It is convenient to perform the derivations in dimensionless parameters,

\[ a = A/A_0, \quad b = \frac{L^4}{K_f} \]

and to introduce the auxiliary parameters

\[ k_n = \left(\frac{\pi n}{2}\right)^4, \quad n \geq 1; \quad v = \frac{K_f A_0}{\pi k_B T L^3}, \]  

where \( L \sim 15A \) is the chain length, \( A_0 \sim A^2 \) is the ”incompressible area” of the chain cross section, and the chain flexural rigidity \( K_f \approx k_B T L^3 \) at \( T \approx T_0 = 300K \). Using these estimates we obtain \( v \approx 0.009 \).

In the introduced notations Eq. (A1) and Eq. (A2) with \( E_n \) defined in Eq. (14) the self-consistency equation Eq. (11) acquires the form

\[ \frac{1}{b} + \sum_{n=1}^{\infty} \frac{1}{b + k_n^4} = 2v(\sqrt{a} - 1)^2. \]

The terms in the sum on the left hand side of Eq. (A3) decrease fast with growing \( n \) and we can use integration instead of summation over \( n \). For example, for the effective tension \( P_{\text{eff}} = 70 \text{ dyn/cm} \), we have \( b \approx 10^3 \), while \( k_1^4 \approx 6 \). In this regime we can solve Eq. (A3) analytically by substituting summation over \( n \) with integration, which yields

\[ \sum_{n=1}^{\infty} \frac{1}{b + k_n^4} \approx \frac{1}{2} \int_{-\infty}^{\infty} \frac{dn}{b + k_{n+1}^4} = \frac{1}{\sqrt{2}b^{3/4}} \]

where we took integral using complex functions theory, and \( k_n \) is defined in Eq. (A2).

In case of membrane with no linkage (see Fig. 5) Eq. (A3) takes the form:

\[ \frac{1}{b} + \sum_{n=1}^{\infty} \frac{1}{b + k_n^4} = v(\sqrt{a} - 1)^2. \]

Since \( b \approx 10^3 \) (\( P_{\text{eff}} = 70 \text{ dyn/cm} \)), we (approximately) integrate over \( n \), so that in case of membrane with no linkage Eq. (A4) takes the form:
\[
\sum_{n=1}^{\infty} \frac{1}{b + k_n^4} \approx \frac{1}{2} \int_{-\infty}^{\infty} \frac{dn}{b + k_{n+1}^4} = \frac{1}{2 \sqrt{2} b^{3/4}}.
\] (A6)

where \( k_n \) is defined as in [3]: \( k_n = \pi n - \pi/4 \).

In both, Eq. (A4) and Eq. (A6), we omit \( 1/b \) as \( b \approx 10^3 \), which leads to the same \( b(a) \) dependences in both cases:

\[
b = \frac{1}{4v^{4/3}(\sqrt{a} - 1)^{8/3}},
\] (A7)

which is then used in the equation of state Eq. (23). As a result we find the expression for the lateral pressure produced by the linked hydrocarbon chains Eq. (23).
FIGURES

FIG. 1: a - Membrane with bolalipids. b - Our model of membrane with bolalipids.

FIG. 2: Lateral pressure distribution in the hydrophobic core of the bilayer with (solid line) and without linkage. $z$ is coordinate along the chain axis normalized by the monolayer thickness $L$ and spanning from one head group ($z = 0$) to another ($z = 2L$). The parameters for the lipid bilayer are as follows: monolayer thickness $L = 15\, \text{A}$, area per chain $A_0 = 20\, \text{A}$, chain flexural rigidity $K = k_B T L/3$, temperature $T = 300\, \text{K}$, pressure normalized by total bilayer pressure $P_t^0 = 140\, \text{dyn/cm}$.
FIG. 3: Figures a) and b) demonstrate molecular dynamics results from [6] and [7] correspondingly. In both figures the pressure profile related to the hydrophobic region of membrane is bounded with dashed rectangular. It is in a good qualitative correspondence with our results (see Fig. 2 dashed line).
FIG. 4: Order parameter in cases with bolalipids (see Fig. 1) and no linkage (see Fig. 5).

FIG. 5: Model of lipid membrane in the mean-field approximation: we substitute interaction between neighboring chains by an effective quadratic potential.
FIG. 6: 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; $A = \pi \langle \mathbf{R}^2 \rangle$ is the area swept by the centers of chain cross sections; $A$ is the average area per lipid chain in the bilayer.

FIG. 7: The eigenfunctions $R_n(z)$ of the self-adjoint operator $\hat{H}$ for the boundary conditions Eq. [6] and Eq. [7]. Other parameters are as in Fig. [2].
FIG. 8: Not normalized free energy (per chain) difference of membranes with linkage and with no linkage between the opposite chains ends. Membrane with linkage “costs” more free energy at fixed area per chain.

FIG. 9: Entropy (per chain) difference between membranes with linkage and without linkage. Entropy of membrane with linkage is lower than that of a membrane without linkage.
FIG. 10: Total lateral pressure comparison. With the same area per chain, membrane with linked chains produce less pressure than nonlinked membrane. Area and pressure normalized by constants described in Fig. 2 caption.

FIG. 11: Temperature dependence of equilibrium area per bolalipid chain, $A$. Temperature is normalized by $T_0 = 300K$, area is normalized by $A_0 = 20A^2$. 
FIG. 12: Calculated total lateral pressure $P_t$ produced by linked hydrocarbon chains as a function of area per chain at two temperatures $T_1$ (solid line) $< T_2$ (dashed line). Area and pressure normalized by constants described in Fig. 2 caption.