Revisiting the entropic force between fluctuating biological membranes

Yuranan Hanlumyuanga, Liping Liub,c, Pradeep Sharmaa,d,n

a Department of Mechanical Engineering, University of Houston, TX 77204, USA
b Department of Mechanical & Aerospace Engineering, Rutgers University, Piscataway, NJ 08854, USA
c Department of Mathematics, Rutgers University, Piscataway, NJ 08854, USA
d Department of Physics, University of Houston, TX 77204, USA

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Abstract
The complex interplay between the various attractive and repulsive forces that mediate between biological membranes governs an astounding array of biological functions: cell adhesion, membrane fusion, self-assembly, binding-unbinding transition among others. In this work, the entropic repulsive force between membranes—which originates due to thermally excited fluctuations—is critically reexamined both analytically and through systematic Monte Carlo simulations. A recent work by Freund (2013) has questioned the validity of a well-accepted result derived by Helfrich (1978). We find that, in agreement with Freund, for small inter-membrane separations ($d$), the entropic pressure scales as $p \sim d$, in contrast to Helfrich's result: $p \sim 1/d^3$. For intermediate separations, our calculations agree with that of Helfrich and finally, for large inter-membrane separations, we observe an exponentially decaying behavior.

1. Introduction

Biomembranes exert various types of repulsive and attractive forces on each other. The van der Waals forces are weakly attractive—these vary as $1/d^3$ for close separations and transition to $1/d^5$ at larger distances (Helfrich and Servuss, 1984; Ninham and Parsegian, 1970). Here $d$ is the mean distance between the interacting membranes. The notable aspect of the attractive force is that it is long-ranged. A somewhat ambiguous term hydration forces (Rand and Parsegian, 1989), is used to denote the repulsive force that mediates at very small inter-membrane distances. The underlying mechanisms of hydration forces are still under active research (Lipowsky and Sackmann, 1995)—it suffices to simply indicate here that they are quite short ranged and drop off exponentially with distance.

Helfrich, in a pioneering work (Helfrich, 1978), showed that two fluctuating fluid membranes exert a repulsive force on each other. Biomembranes are generally quite flexible and a single membrane fluctuates both freely and appreciably at physiological temperatures. As two membranes approach each other, they hinder or diminish each others out-of-plane fluctuations. This hindrance decreases the entropy and the ensuing overall increase of the free-energy of the membrane system, which depends on the inter-membrane distance, leads to a repulsive force that tends to push the membranes apart. Helfrich (1978), using a variety of physical arguments and approximations, postulated that the entropic force varies as $1/d^3$. In contrast to the other known repulsive forces, this behavior is long-ranged and competes with the van der Waals attraction.
The point-wise hindrance condition that \( |u_x| \leq d \) is enforced throughout this work. This constraint is in fact the key obstacle in the closed-form evaluation of the partition function. Freund (2013) modified the partition function by introducing adjustable integration limits, and then minimized the resultant free energy with respect to these limits to determine the change in free energy with respect to inter membrane separation (and hence the entropic force law). In the Section 4, we discuss Freund’s approach further. Here, we adopt the form of the partition function in Eq. (2) which, notwithstanding the analytical intractability of its integration limits (i.e. pointwise constraint on \( u \)), is exact within the present formulation. We remark here that Helfrich (1978) avoids the point-wise hindrance condition, \( |u(x,y)| \leq d \), and instead imposes a weaker constraint where the mean square membrane displacement is required to be bounded by \( d^2 \), i.e., \( \langle u^2 \rangle \leq d^2 \).

To gain new insights into the partition function, two dimensionless quantities, \( y \) and \( v \), are introduced as
\[
\frac{y}{L} = y \quad \text{and} \quad v = \frac{u(x)}{d}.
\]
By changes of variables we may rewrite the partition function (2) as \( (S_0 = [0,1]^2, A = L^2) \)
\[
Z = (Cd)^N \int_{-1}^{1} \prod_{y \in \mathcal{L}} d v y e^{-\beta d^2/2A \int_0^u d y (d^2 y^2)^2},
\]
where \( y \in \mathcal{L} = \{(l_1/m, l_2/m) : l_1, l_2 = 1, \ldots, m\}. \) Let \( \tau = A/\beta k T d^2 \) be a dimensionless variable. By a change of variable back and forth, \( \sqrt{\tau} \to \sqrt{\tau} \), we obtain

\[
Z = (Cd)^N \left( \frac{A}{\beta k T d^2} \right)^N Z(\tau),
\]

where

\[
Z(\tau) = \tau^{-N/2} \int_{-1}^{1} \prod_{y \in \mathcal{L}} dv_y e^{-1/2 \tau \int_0^\alpha L d^2 x + \tau^2}.
\]

As a consequence, the free energy destiny, \( \mathcal{F} = -(K_B T/\alpha) \ln Z \) has the form

\[
\mathcal{F} = -\frac{k_BT}{2 \pi^2} \ln \left( \frac{k_BTAC^2}{\pi^2} \right) - \frac{k_BT}{A} \ln Z (k_BTAC^2/\pi^2).
\]

It should be noted here that our free energy density has a subtle difference from the one in Janke and Kleinert (1986). The first term in the free energy does not depend on \( d \) and vanishes upon differentiation with respect to \( d \). It follows that the steric pressure is

\[
p = -\frac{\partial \mathcal{F}}{\partial \tau} = \left( \frac{k_BT}{\pi^2} \right) g(\tau).
\]

where \( g(\tau) = -\partial \ln Z(\tau)/\partial \tau \). Janke and Kleinert (1986) have performed Monte Carlo calculations and found that \( g(\tau) \) is a constant in the thermodynamic limit (Janke and Kleinert, 1986). The value of this constant was also found by Kleinert using a variational approach (Kleinert, 1999). We remark that in the past works that have performed Monte Carlo calculations of this problem, the veracity of the Helfrich’s pressure law has been implicitly embraced and the focus has not been on examining the dependence of the entropic pressure on inter membrane distance but rather calculation of \( g(\tau) \) assuming that Helfrich’s inverse cube law is correct. This is the reason, we believe, that Freund’s result and (now ours) has not been noted until now.

As evident from the definition in Eq. (8), \( g(\tau) \) is a function of the separation between the rigid walls confining the membrane. It is interesting to consider the energy variation, and consequently the pressure, at some small distances. As Freund has shown, this limit is analytically tractable. Below we reproduce the result using a slightly different procedure. Consider the scaled partition function in Eq. (6), by Fourier transformation we introduce

\[
\hat{v}_k = \frac{1}{m} \sum_{y \in \mathcal{L}} e^{-ik \cdot y} v_y, \quad v_y = \frac{1}{m} \sum_{k \in \mathcal{K}} e^{ik \cdot v_k}.
\]

where \( \mathcal{K} = (2\pi (n_1, n_2) : n_1, n_2 = 1, \ldots, m) \) is the reciprocal lattice of \( \mathcal{L} \). In matrix notations the above equations can be rewritten as

\[
\hat{v}_y = L^\dagger \hat{v}_k, \quad \hat{v}_k = L \hat{v}_y,
\]

where \( \tilde{v}_y \) (resp. \( \hat{v}_k \)) denotes the column vector formed by \( v_y \), \( y \in \mathcal{L} \) (resp. \( v_k \), \( k \in \mathcal{K} \), and \( L^\dagger \) is a unitary matrix satisfying \( L^\dagger L = L L^\dagger = 1 \). Since \( a \in \mathbb{L} \), we may convert an integral over \( S \) as a summation over \( \mathcal{L} \):

\[
\int_{S} d^2 y = \alpha^2 \sum_{k \in \mathcal{K}}.
\]

Applying the Parseval’s theorem, we rewrite

\[
\int_{S} d^2 y (\hat{v}_y^2) = \frac{1}{m^2} \sum_{k \in \mathcal{K}} |\hat{v}_k|^2 = \frac{1}{m^2} \tilde{v}_y : L^\dagger D(k) L \tilde{v}_y,
\]

where \( D(k) \) is the diagonal matrix with entries \( |k|^4, k \in \mathcal{K} \). Defining a dimensionless variable \( p = k/m \), the scaled partition function is

\[
Z(\tau) = \tau^{-N/2} \int_{-1}^{1} \prod_{y \in \mathcal{L}} C d v_y e^{-m^2/2 \tau \tilde{v}_y : L^\dagger D(k) L \tilde{v}_y}
\]

For \( \tau \to \infty \) i.e. \( d/a \to 0 \), one has

\[
Z(\tau) = \tau^{-N/2} \left[ \frac{m^2}{2 \tau} (L^\dagger D \tau L) \cdot \int_{-1}^{1} \prod_{y \in \mathcal{L}} d v_y \tilde{v}_y \otimes \tilde{v}_y + O\left( \frac{d^4}{\tau^4} \right) \right],
\]

where the identity \( \tilde{v}_y \cdot L^\dagger D \tau L \tilde{v}_y = (L^\dagger D \tau L) \cdot (\tilde{v}_y \otimes \tilde{v}_y) \) was used. Since \( \int_{-1}^{1} \prod_{y \in \mathcal{L}} d v_y \tilde{v}_y \otimes \tilde{v}_y \approx 2^{-N/2} \mathcal{I} = 2^N \pi^N \), and the inner product of \( L^\dagger D \tau L \) with the identity matrix yields its trace, the reduced partition function in the asymptotic limit is

\[
Z(\tau) = \tau^{-N/2} \left[ \frac{m^2}{2 \tau} - \frac{2^N}{3} \sum_{mp} p^4 + O\left( \frac{d^4}{\tau^4} \right) \right].
\]
It is clear from the definition $g(x) = -\partial \ln Z/\partial x$ that the steric pressure has the leading order term of $p \approx k_BT/2a^2$. The next correction term can be obtained using the identity $\sum_{\varphi} e^{ip} = (2\pi)^d (28m^2/45 + 5m/3 + \mathcal{O}(1))$, where $m^2 = N$. The steric pressure in the limit $d \to \infty$ ($d/a \to 0$) is thus
\begin{equation}
\frac{1}{2a^2} \left[ -d^2 \right] + \mathcal{O} \left( \frac{d^4}{a^4} \right). \tag{15}
\end{equation}

This pressure law has a very different $d$-dependence than any known theories or simulations to date (Helfrich, 1978; Janke and Kleinert, 1986; Gompper and Kroll, 1989; David, 1990; Netz and Lipowsky, 1995; Gouliaev and Nagle, 1998; Kleinert, 1999) except of course the work by Freund (2013).

Another interesting point obtained from Eq. (15) is that the first term in the right-hand side has the form of pressure of the ideal gas. Physically, this implies that the membrane fluctuates similar to an ideal gas in the limit $d/a \to 0$, with a correction term which is in the order of $\mathcal{O}(d)$ (the second term in Eq. (15)). This ideal-gas contribution does not depend on the bending modulus $\kappa$, hence every type of membranes should exhibit the $p \sim 1/d$ pressure law at the limit $d/a \to 0$.

In order to elucidate the full $d$-dependence including the limit $d/a \to 0$, a natural step is to take recourse in numerical Monte Carlo simulations which are discussed in the next section.

3. Monte Carlo simulations

In the Monte Carlo simulations, the spatial coordinates are replaced by a square grid $x$ with lattice constant $a$. The membrane displacement along the $z$-direction is specified by $u_x \equiv u(x)$, where it is also discretized to a grid of space $\delta d$. This scheme has been shown to be sufficient in prior Monte Carlo calculations (Janke and Kleinert, 1986; Lipowsky and Zielinska, 1989). The Hamiltonian over these lattice points is
\begin{equation}
H = a^2 \sum_{x \in L} \kappa \frac{1}{2} (\partial u_x)^2,
\end{equation}
where the discretized Laplacian
\begin{equation}
(\partial^2 u)_x = \frac{1}{a^2} \left[ \sum_{\rho \in \text{nbr}} u_{x+\rho} - 4u_x \right],
\end{equation}
and $\rho$ denotes the displacement vectors to the four nearest neighbors to the site $x$.

Our simulation code was fully parallelized using spatial decompositions. The lattice was divided into strips so that each strip can be updated independently using the usual Metropolis algorithm (Nakano, 2010; Heermann and Burkitt, 1991). Since each strip is updated in parallel, some care has been taken in order to account for the lattice sites at the boundary. Fig. 2(a) illustrates a typical geometry in the simulations. Updating the central point requires the knowledge of the values at all points inside the dashed square. It is forbidden to update any other site in this neighborhood until the update of the central site has been completed. This can be accomplished by an appropriate choice of strip lengths along the $x$-axis and performing a row-by-row update. In our simulations, the minimal lattice length along the $x$-axis is 5, so that there is no overlap between dashed square in Fig. 2(a). A message passing routine was employed in updating the top and bottom two rows of the strips, while along the $y$-axis a simple periodic boundary condition was used. In this way, our choice of lattice sizes are 50 by 50, 100 by 100, 600 by 600, and 1000 by 1000. An MC realization is shown in Fig. 2(b), where the parameters used for its generation are listed in the caption.

In addition to the ensemble average of the energy $\mathcal{E}$, the second physical quantity needed for this problem is the pressure. The pressure can be derived by differentiating the change in free energy with respect to the inter membrane separation. Alternatively and more conveniently, the pressure can be related to the ensemble average of the Hamiltonian density $\mathcal{H} = H/Na^2$. Rewriting Eq. (4) as
\begin{equation}
Z = (Cd)^N \int_{-1}^{1} \prod_{y \in L} d\mathcal{V}_y e^{-1/\mathcal{H}(\mathcal{V}_y)} \tag{18}
\end{equation}
where $\mathcal{H} = (1/2) \int_{-1}^{1} d\mathcal{V}_y (\partial \mathcal{V}_y)^2 \equiv \tau \mathcal{H}$ is a scaled Hamiltonian. The membrane configuration $u_x$ is parameterized by the set of variable $\mathcal{V}_y = u_y/d$. Differentiation of the free energy can be carried out straightforwardly by using these rescaled parameters $\mathcal{V}_y$; the concept which also appears in the derivation for the Hellmann–Feynman forces in quantum mechanics (Feynman, 1939). It follows that
\begin{equation}
\frac{\partial F}{\partial \mathcal{V}_y} = -\frac{k_BT}{Z} \left[ (Cd)^N \int_{-1}^{1} \prod_{y \in L} d\mathcal{V}_y \left( -\frac{2\mathcal{H}(\mathcal{V}_y)}{d}\right) e^{-1/\mathcal{H}(\mathcal{V}_y)} + \frac{N}{d} (Cd)^N \int_{-1}^{1} \prod_{y \in L} d\mathcal{V}_y e^{-1/\mathcal{H}(\mathcal{V}_y)} \right] \tag{19}
\end{equation}

Using the concept of ensemble average and Eq. (18), the derivative of the free energy is
\begin{equation}
\frac{\partial F}{\partial \mathcal{V}_y} = -\frac{d}{d} \langle H \rangle - \frac{Nk_BT}{d} \tag{20}
\end{equation}
In terms of the energy density $\mathcal{F} = \mathcal{F}/A$ and $\mathcal{H} = \mathcal{H}/A$ for a continuous membrane, or $\mathcal{F} = \mathcal{F}/N\alpha^2$ and $\mathcal{H} = \mathcal{H}/N\alpha^2$ for a discretized membrane, where $N$ is the number of molecules and $\alpha^2$ is a square encompassing each of them

$$\frac{d\mathcal{F}}{d^2} = \frac{2}{d} \langle \mathcal{H} \rangle - \frac{Nk_BT}{L^2d} = \frac{2}{d} \langle \mathcal{H} \rangle - \frac{k_BT}{\alpha^2d}. \quad (21)$$

Consequently for a membrane situated between two rigid plates of separation $2d$, the steric pressure

$$p = -\frac{d\mathcal{F}}{d(2d)} = \frac{k_BT}{2\alpha^2d} - \frac{1}{d} \langle \mathcal{H} \rangle = \frac{k_BT}{2\alpha^2d} - \frac{1}{d} \mathcal{E}, \quad (22)$$

where $\mathcal{E} = \langle \mathcal{H} \rangle$. The above pressure is exact, and makes the computation of its value straightforward. Furthermore, the errors on the pressure $p$ stems from only the errors on $\langle \mathcal{H} \rangle$, which for sufficiently long Monte Carlo time steps become small compared to the value of $\langle \mathcal{H} \rangle$.

The validity of Eq. (22) for both the asymptotic and general form of the pressure can be easily checked. In the asymptotic limit $\tau \to \infty$ or $d/\alpha \to 0$, Eq. (14) gives the free energy density $\mathcal{F} = -k_BT \ln Z/N\alpha^2$ of the form

$$\mathcal{F} = -\frac{k_BT}{\alpha^2} \left[ \ln(2d) - (2\pi)^4 \frac{56}{540} \frac{m^2}{\tau} + O \left( \frac{d^4}{\alpha^4} \right) \right]. \quad (23)$$

It then follows that

$$\mathcal{E} = \frac{\partial}{\partial \tau} \beta \mathcal{F} \approx (2\pi)^4 \frac{28}{270} \frac{kd^2}{\alpha^2}. \quad (24)$$

and

$$p \approx \frac{k_BT}{2\alpha^2d} - (2\pi)^4 \frac{28}{270} \frac{kd}{\alpha^4}, \quad (25)$$

in agreement with Eq. (15). In the general case, it can be deduced from Eq. (7) that

$$\mathcal{E} = \frac{k_BT}{2\alpha^2} - \frac{(k_BT)^2}{kd^2} g^{(4)}(\tau). \quad (26)$$
As a result, the pressure obtained from Eq. (22) is
\[
p = \frac{(k_BT)^2}{\kappa d^2} g(r),
\]
which is again in agreement with Eq. (7).

In most simulation runs, at least \(8 \times 10^4\) MC time steps were performed. A Monte Carlo time step is defined as the number of Monte Carlo updates divided by the number of grid points of the membrane. The first 3000 time steps were omitted for thermalization. The calculated statistical errors of a few percent of the energy estimators are obtained. A typical number of Monte Carlo updates divided by the number of grid points of the membrane. The first 3000 time steps were

The pressure–distance relation for the separation ranging from 0.1–7.0 is shown in Fig. 4. The simulation parameters are \(k_BT = 10.0\), \(\alpha d = 0.1\), and \(a = 1.0\), while the bending moduli are \(\kappa = 0.1k_BT, 5k_BT, 20k_BT\). The size of the membrane shown is \(L \times L = 50 \times 50, 600 \times 600,\) and \(1000 \times 1000\). From these log–log plots, it is clear that the relation \(p \sim 1/d\) is applicable within a small range \(d\), while there is a transition to \(p \sim 1/d^3\) as the separation distance increases. The transition from \(1/d^3\) to \(1/d\)-dependence can be estimated from Eq. (12) as
\[
d < d_{\text{tran}} = \sqrt{\frac{2k_BTa^2}{\kappa}}.
\]
which for the choice of parameters \(k_BT = 10, \kappa = 1.0, a = 1.0\) the corresponding transition length is \(d_{\text{tran}} \approx 4.5\) or about five times the spacing between molecule \((a = 1.0)\). For more realistic values of \(\kappa \approx 20k_BT\) and \(a \approx 8\ \text{Å}\) (Goetz and Lipowsky, 1998), the transition length is \(d_{\text{tran}} \approx 2.5\ \text{Å}\).

Is the transition from \(1/d\) to \(1/d^3\)-pressure law a result of finite size effects? Our MC results in Fig. 4 for the membrane as large as \(1000 \times 1000\) indicate otherwise. As evident, the smaller membrane of size \(L \times L = 50 \times 50\) exhibits the same transition length \(d_{\text{tran}}\) to those of much larger ones. Since in real biological membranes the number of possible excitation modes is perhaps much larger than in our model, the transition from the ideal gas \(1/d\) to \(1/d^3\) pressure law could possibly represent some new physics—the exploration of this is deferred to future work. Our results are easily interpreted within the context of the free energy of a tightly confined membrane. At small \(d/a\), the bending energy contribution to the free energy is negligible compared to the entropic contribution. The suppression of the elastic effects hence leads to the limiting pressure law of the ideal gas.

Nevertheless, it should be noted that the transition length \(d_{\text{tran}}\) depends on the bending modulus, temperature, and intermolecular spacing as indicated in Eq. (28). The pressure law transition from \(1/d\) to \(1/d^3\) dependence may have some important implication in the interactions among living cells, potentially opening a new avenue in reevaluating the conventional understandings about how biological cells mechanically interact.

A larger range of the \(p – d\) dependence is shown in Fig. 5. The sizes of the membrane, which are \(L\) by \(L\), are shown in the subfigures. At large \(d\) the pressure follows an exponential decay relation of type \(p \sim Ae^{x} \exp(-ld)\) resulting in the log–log plots of the form \(y = D - \lambda \exp(x)\) where \(x = \ln d, y = \ln p,\) and \(D = \ln A\). This exponential decaying regime has not yet been confirmed by any simulations or theory thus far, despite a speculation in Janke and Kleinert (1986). An interesting conclusion of this result is that the Helfrich entropic force is not really as long-ranged as previously believed. As a future
exploration, it will be intriguing to establish mathematical asymptotic behaviors to this large-separation regime beyond our simulation results.

4. Conclusions

In summary, we conclude that Freund’s (2013) conclusions are correct for short inter-membrane distances and in that regime, his result is a modification of the well-accepted entropic force law due to Helfrich (1978). However, Helfrich is

Fig. 4. Simulation results (symbols) of the pressure $p$ and the distance $d$ between two rigid walls in log–log formats. The lines are drawn to guide the eye. In subfigures (a), (b), and (c) the bending modulus of $\kappa = 0.1k_B T$, $5k_B T$ and $20k_B T$ is used respectively, whereas in all subfigures $\delta d = 0.1$, $a = 1.0$, and $k_B T = 10.0$. For each bending modulus $\kappa$, the sizes of the membranes $L \times L$ are shown in the insets. The scaling pressure is $p_n = k_B T/a^3$. 
correct for intermediate distances and finally, for large separations, the entropic force decays exponentially. At the time of writing this paper, we became aware of a pre-print by T. Auth and G. Gompper, who (at least for short and intermediate membrane separations) have reached similar conclusions as us.

The physical consequences of the modification of the entropic force law between membranes remain an open problem and are expected to be an interesting avenue for future research.

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