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Thermal–Mechanical Fluctuations of Fluid Membranes in Confined Geometries: The Case of Soft Confinement

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By definition, membrane or macromolecular assembly is an event of molecular confinement against the configurational entropy of a disordered state. Bilayer membranes under progressive confinement experience a continual damping of undulatory fluctuations, first interpreted as a steric force (Helfrich. *Z. Naturforsch.* 1978). This paper uses a new, diffusion-equation formalism based on the Feynman-type variational principle to describe how direct interbilayer forces—of hydration, electrostatic double layers, and van der Waals attraction—confine membrane fluctuations. We recover theoretical results to examine measured forces in multilamellar arrays showing that "soft" collisions, through long-range forces, create a mutual enhancement of both the direct forces and the undulatory steric interactions. Thus, there is yet another way to resolve the old, but false, dilemma to choose between steric and direct forces driving membrane assembly. One may develop a systematic connection between bilayer charge, hydration, and flexibility and the action of configurational entropic forces. The results make clear that one should measure forces between membranes or macromolecules in a way that allows them to express their native mechanical freedom.

Introduction

Traditionally, interactions between macroscopic surfaces immersed in aqueous solution were usually thought of as a competition between electrostatic double-layer repulsion and the electrodynamic or van der Waals–Lifshitz attraction.[1] This statement forms the basis of the widely used DLVO theory of colloid stability. For strongly hydrated surfaces an additional repulsive force is now frequently added to the force balance equation. It is thought to stem from the overlap of the ordered water regions on the interacting surfaces upon their mutual approach and is usually dubbed the hydration force.[2]

If we think of a stack of deformable fluid membranes (as in, e.g., a multilayer phospholipid system) where each of them interacts with its nearest neighbors through the forces enumerated above, these forces clearly act to suppress thermally driven out-of-plane fluctuations in the shape of the membranes and to confine them to their mean positions. It is in this respect and context that we shall use the term *confinement forces* in this work as a synonym for DLVO and hydration forces operating in a multilamellar assembly of fluid membranes.

It was Helfrich[3] who first proposed that the above forces still miss an important facet of the macromolecular interactions. Concentrating on the interactions in the multilamellar bilayer system, he showed that thermally driven elastic fluctuations of the fluid membranes give an important contribution to the total free energy of interaction. The physical mechanism responsible for this interaction is the coupling between confinement forces and undulation disorder of the membrane surfaces. In his original formulation Helfrich considered the interplay between the pure steric hindrance and the undulation disorder in a multilamellar system. He showed that on close approach the steric hindrance acts to decrease the amplitudes of the thermal–mechanical fluctuations and thus to change the entropy of the thermodynamic system. These changes in the entropy are further manifested as the emergence of an additional repulsive force with a long-range power law dependence on the intermembrane separation.

The influence of the enlarged set of confinement forces (i.e., DLVO plus hydration repulsion) on the undulation disorder was investigated first by Sornette and Ostrowski and later by Evans and Parsegian.[4] They showed that thermally driven undulation disorder not only enhances the underlying confinement forces but also displaces the minimum energy position to greater values of intermembrane spacings. The modifications in the DLVO forces due to the undulation disorder have been worked out in detail by the subsequent work of Lipowsky and Leibler.[5] They established that under certain conditions the secondary minimum in the two-membrane system can altogether disappear leading to unbinding of the membrane system.

Here we develop a new approach based on the original ideas of Evans and Parsegian[4] to analyze the interplay between the undulation disorder and confinement forces in multilamellar arrays. We have determined the mean square deviation of the membrane surface from the planar configuration by a self-consistent procedure involving the solutions of a diffusion equation in confined geometry. We were able to formulate our approach for the case where confinement forces are composed of hard (steric) and soft (all the other DLVO-type forces) potentials. We based our approach on a variant of the Feynman-type variational principle[6] for the partition function in an effective Gauss-

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ian model with soft (DLVO-type) and hard (steric) confinement potentials. We derived the free energy of a confined elastic surface as a function of the average intersurface separation in a multilamellar stack. We show that in the presence of purely repulsive soft confinement potential this free energy function exhibits three distinct regimes of behavior: At small intersurface separations, the bare soft confinement forces dominate the overall thermodynamic behavior of the system. At intermediate spacings, the free energy depends on the parameters of the soft potential. If the soft potential is purely repulsive, the free energy has a term that goes as the square root of the mean potential. At very large spacings, the dependence of the free energy on the average intersurface separation reverts to the steric form with a modified value of the interlamellar spacing that depends on the parameters of the soft confinement potential.

Furthermore, we show that the inclusion of attractive potential can severely affect the asymptotic behavior of the interaction free energy at large intersurface separations due to the competition between attractive and repulsive (entropic) terms that have the same functional dependence on the intersurface separation. In our analysis we will be dealing with a constrained system where the mean intersurface separation is set by the application of an external osmotic pressure. This constraint was chosen in view of the osmotic stress method used for the direct measurement of forces between membranes or macromolecules.[2]

Analysis

We start our discussion by considering the energy of a stack composed of N fluid membranes, where each membrane can interact with its nearest neighbors. The total energy of such a system can be written as a sum

$$W = \sum_{n=1}^{N} E_n + \sum_{n=1}^{N} V_{n,n+1} \tag{1}$$

of intrinsic energies due to elastic deformation

$$E_n = {}^1/_2 K_c \int (\nabla_\rho^2 z_n(\rho))^2 \, d^2\rho \tag{2}$$

and the interaction terms $V_{n,n+1}$ acting between nearest neighbors; K_c is the elastic modulus while the local curvature of the membrane surface was taken in its lowest order form $\nabla_\rho^2 z_n(\rho)$, with $\rho = (x,y)$ being a two-dimensional radius vector and ∇_ρ^2 a two-dimensional Laplacian.

In order to reduce eq 1 to a tractable form, we use an equivalent of the Einstein model of the harmonic crystal of the form

$$V_{n,n+1} = w(z_n(\rho)) = {}^1/_2(V(a + z_n(\rho)) + V(a - z_n(\rho))) \tag{3}$$

that leads to the following form for the total energy of a single fluid membrane in the stack:

$$W = {}^1/_2 K_c \int (\nabla_\rho^2 z_n(\rho))^2 \, d^2\rho + w(z_n(\rho)) \tag{4}$$

The total energy of the stack is just N times the above expression. The additivity is purely a consequence of the Einstein ansatz. This ansatz is equivalent to the interaction energy of a single elastic membrane bounded by two rigid surfaces separated by $2a$ and interacting with them through potential $w(z(\rho))$; see Figure 1. The partition function of a single membrane can now be written as

$$f = \langle \exp(-\beta W) \rangle = \int_n \exp(-\beta W) \, dz(\rho_1) \ldots dz(\rho_n) \qquad n \to \infty \tag{5}$$

where the index n now enumerates different points on a single membrane surface and $\beta = (kT)^{-1}$ is the inverse thermal energy. In spite of the Einstein ansatz, the partition function is still difficult to evaluate since in general $w(z)$ is not a quadratic function of z.

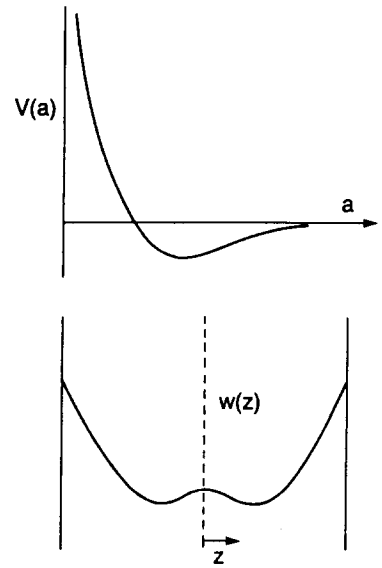

Figure 1. Schematic transition from the two-membrane potential to the Einstein model eq 3. The interaction potential is symmetrized with respect to the first two neighbors. The average separation between the membranes in the stack is a.

It is important to recognize that, correctly speaking, one may not ignore the fact that the direct potential of interaction between layers is not actually zero with a quadratic expansion about the mean position. Particularly in situations where systems spontaneously arrange under the action of dominant attractive forces, there will not be a quadratic minimum, and neglect of this fact will make a difference in estimates of the depth of the energy minimum organizing the layers.

We next proceed with a slight digression. In the particular case of an elastic membrane constrained between two boundary surfaces separated by $2a$, Figure 1, by an effective quadratic potential W_0

$$W_0(z(\rho)) = {}^1/_2 K_c \int (\nabla_\rho^2 z_n(\rho))^2 \, d^2\rho + {}^1/_2 B(a) \int z^2(\rho) \, d^2\rho + w_0(a) \tag{6}$$

where w_0 is a constant added to recognize the difference, noted in the paragraph above, between the mean potential and the effective "zero" of a quadratic form. The interaction free energy per unit surface area of a single membrane F_0/S can be deduced from the partition function f_0 in the form

$$F_0/S = -(kT/S) \ln f_0 = (kT/8)\sqrt{B/K_c} + w_0 \tag{7}$$

where $f_0 = \langle \exp(-\beta W_0) \rangle$. This result can be arrived at in a standard way by introducing the Fourier components of the local displacement, $z(\mathbf{Q})$, and writing $z(\rho) = \sum_{\mathbf{Q} \neq 0} (z(\mathbf{Q}) e^{i\mathbf{Q}\rho} + \text{cc})$. The $z(\mathbf{Q})$ integrations are now in a form of multidimensional Gaussian integrals and can be easily evaluated.

Then using the inequality suggested by Feynman,[6] we can establish an upper bound to the free energy defined for the case of total energy (eq 4) and are led to

$$F/S \leq -(kT/S) \ln f_0 + \langle W - W_0 \rangle_{W_0} \tag{8}$$

where f_0 is again the partition function associated with the mean field quadratic potential W_0. The averaging in the above equation has to be done over W_0. We now proceed with the following observation, viz., that the averaging of a term $e^{ikz(\rho)}$ can be reduced to

$$\langle e^{ikz(\rho)} \rangle_{W_0} = e^{-(1/2)k^2\sigma^2} \tag{9}$$

since W_0 has a Gaussian form, where in deriving the above identity we have used the same Fourier decomposition as before. Furthermore, in the above equation we have introduced σ^2 as the average mean square value of $z(\rho)$; thus

$$\sigma^2 = \langle z^2(\rho)\rangle_{W_0} = \frac{2}{\beta}\sum_{Q\neq 0}\frac{1}{K_c Q^4 + B} = \left(\frac{kT}{8}\right)\frac{1}{\sqrt{BK_c}} \quad (10)$$

This permits us to write $B(a)$ as a function of $\sigma(a)$ in the form

$$B(a) = (kT/8)^2(1/K_c\sigma^4) \quad (11)$$

We can now proceed to the evaluation of the free energy. The Feynman inequality suggests that we could use a variational principle to approximate the free energy with the expression eq 7 if we could establish a minimum for the quantity $\langle W - W_0\rangle_{W_0}$. This average can again be handled by the Fourier decomposition starting from the following expression:

$$\langle W - W_0\rangle_{W_0} = \langle w(z)\rangle_{W_0} - {}^1/_2 B(a)\langle z^2\rangle_{W_0} - w_0(a) \quad (12)$$

Using now the Fourier representation for the interaction potential in the form

$$w(z) = \int_{-\infty}^{+\infty}(dk/2\pi)w(k)e^{ikz}$$

we obtain

$$\langle w(z)\rangle_{W_0} = \int_{-\infty}^{+\infty}(dk/2\pi)w(k)\langle e^{ikz}\rangle_{W_0} = \int_{-\infty}^{+\infty}(dk/2\pi)w(k)e^{-(1/2)k^2\sigma^2} \quad (13)$$

if we use the result derived in eq 9. Thus, we are led to the following compact expression for $\langle W - W_0\rangle_{W_0}$ in the form

$$\langle W - W_0\rangle_{W_0} = w_{\sigma^2}(a) - {}^1/_2 B(a)\sigma^2 - w_0(a) \quad (14)$$

where we introduced

$$w_{\sigma^2}(a) = \int_{-\infty}^{+\infty}(dz/\sqrt{2\pi\sigma^2})w(z)e^{-(1/2)(z^2/\sigma^2)} = \int_{-\infty}^{+\infty}dz\, w(z)\,\rho_\sigma(z) \quad (15)$$

Obviously $\rho_\sigma(z)$ is a transverse displacement distribution function of the fluctuating membrane and is clearly a solution of

$$2(\partial\rho_\sigma(z)/\partial\sigma^2) = \partial^2\rho_\sigma(z)/\partial z^2 \quad (16)$$

Equation 16 is thus in a form of a diffusion equation with a unit diffusion constant where σ^2 plays the role of time. In the limit of a very stiff membrane ($K_c \to \infty$) or of low temperatures, the transverse distribution function is essentially a Dirac distribution centered at $z = 0$.

Returning to the Feynman inequality, we can now consider both σ^2 and B as functions of a and calculate at each a the minimum of $\langle W - W_0\rangle_{W_0}$. This is exactly the procedure embraced by Feynman and Kleinert[12] in their treatment of the quantum mechanical partition function. The minimization conditions can be expressed simply as

$${}^1/_2 B(a) = (\partial/\partial\sigma^2)w_{\sigma^2}(a) \quad (17)$$

$$w_0(a) = w_{\sigma^2}(a) - {}^1/_2 B(a)\sigma^2 \quad (18)$$

and thus lead to the following simplified form of the free energy:

$$F/S = {}^1/_2 B(a)\sigma^2 + w_{\sigma^2}(a) \quad (19)$$

This completes the formal development connected with the application of the Feynman–Kleinert variational principle. We should add here that the variational result for the free energy is in fact exact to the first order in $w(z)$.[12] Furthermore the interaction potential should be a smooth enough function of z that its Fourier transform, which enters eq 13, exists. We note at this point that the variationally obtained free energy has two terms: The first one corresponds to the elastic energy of undulation modes and the second one to the renormalized interaction potential due to the elastic fluctuations on all scales up to σ. In this respect $w_{\sigma^2}(a)$ is closely related to the renormalized interaction potential used in the linearized renormalization group (LRG) treatment of the elastic membrane interactions[13] where it is also a consequence of integrating out different undulatory modes from the original Hamiltonian of the system.

This is as far as we can proceed by purely formal means. The first problem that we have to clarify at this point is connected with the fact that the interaction potential $w(z)$ has a hard core due to the impenetrability of the boundaries at $z = \pm a$. This part of the interaction potential (the steric interaction) does not have a Fourier transform, and we have to deal with it on separate grounds. The same problem occurs also in the LRG treatment where it is resolved through the use of the full nonlinear recursion relation satisfied by the renormalized interaction potential.[15]

Clearly in the case that the interaction potential has a steric component, the distribution function $\rho_\sigma(z)$ that enters the definition of the renormalized potential cannot be given by a simple Gaussian as in eq 15. The impenetrability of the bounding surfaces at $z = \pm a$ demands that the probability of a mode for crossing this boundary equals zero. Thus, we take a modified distribution function that enters the definition of the renormalized potential eq 15 in the form

$$\rho_\sigma(z) = \frac{\sum_{n=0}^{\infty} e^{-(1/2)(2n+1)^2(\pi/2)^2(\sigma/a)^2}\cos(2n+1)(\pi/2)(z/a)}{2\sum_{n=0}^{\infty}\frac{(-1)n}{(2n+1)(\pi/2a)}e^{-(1/2)(2n+1)^2(\pi/2)^2(\sigma/a)^2}} \quad (20)$$

It is still a solution of the "diffusion equation" eq 16, but it also has the property of going to zero at the hard boundaries. The introduction of this modified form of the distribution function is not really a formal derivation but more likely a heuristic statement that is plausible on completely physical grounds (e.g., by comparison with the related confined polymer or the confined diffusion[9] problem). Since the steric potential is zero in the region between the bounding surfaces, the free energy in this case reduces to

$$F_s/S = {}^1/_2 B_s(a)\sigma^2 \quad (21)$$

The minimization relations eqs 17 and 18 derived for the soft part of the potential do not help in this case to determine σ. However, it is clear that if the heuristic treatment of the hard-core part of the interaction potential should remain self-consistent, one should demand that

$$\int_{-a}^{+a} z^2\rho_\sigma(z)\,dz = \sigma^2 \quad (22)$$

This is the self-consistent condition supplementing eqs 17 and 18 in the case of the steric potential. In extenso the above equation can be written as

$$\sigma^2 = a^2\left(1 - 2\frac{\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)^3(\pi/2)^3}e^{-(1/2)(2n+1)^2(\pi/2)^2(\sigma/a)^2}}{\sum_{n=0}^{\infty}\frac{(-1)n}{(2n+1)(\pi/2)}e^{-(1/2)(2n+1)^2(\pi/2)^2(\sigma/a)^2}}\right) \quad (23)$$

It comes as no surprise that this self-consistency relation can now be solved with the Helfrich ansatz[3] $\sigma^2 = \mu_s a^2$, with the numeric value $\mu_s \approx 0.183$, giving for the free energy of the fluctuating membrane in the confined region

$$F_s/S = {}^1/_2(kT/8)^2(1/K_c\mu_s a^2) \quad (24)$$

The repulsive pressure corresponding to this confinement free energy is obtained in the form

$$p_s = -\frac{\partial}{\partial a}\frac{F_s}{S} = \left(\frac{kT}{8}\right)^2\frac{1}{K_c\mu_s a^3} \quad (25)$$

At a specified value of a this expression is within 10% of the estimate given by Helfrich[3] who takes $\mu_s \approx {}^1/_6$. It is also not very far off from the more accurate value for μ_s derived by Janke and

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Kleinert.[14] The path to the interaction pressure stemming from the hard, steric interactions alone and leading through the solution of the diffusion equation eq 16 in confined geometry is thus essentially equivalent to other (also basically heuristic) treatments of the same problem. It will however provide us with a simple treatment of other potentials if we connect it with the variational principle derived before.

Results and Certain Limiting Forms

In the previous section we have derived separately the interaction free energies for the case of a fluctuating elastic membrane in soft and hard (steric) confinement potentials. Since the DLVO confinement potential is composed of both terms, we now proceed to give a unified treatment for a general confinement potential. First of all, we note that in the absence of the soft part in the confinement potential the minimization condition should reduce to $B(a) = B_s(a)$. Thus, we can assume an additive form of the minimization condition eq 17 for the combined confinement potential in the form

$$B(a) = B_s(a) + 2(\partial/\partial\sigma^2)w_{\sigma^2}(a) \tag{26}$$

In order to extract $\sigma^2(a)$ from this relation, we use the connection between $B(a)$ and $\sigma^2(a)$, eq 11, while for $B_s(a)$ the same relation holds but with $\sigma^2 = \mu_s a^2$. The free energy, however, retains the form

$$F/S = {}^1/_2 B(a)\sigma^2 + w_{\sigma^2}(a) \tag{27}$$

First of all, we investigate the following form of the soft part of the confinement potential:

$$w(z) = (A/\kappa)e^{-\kappa z} \tag{28}$$

This choice is in accord with the form of the electrostatic interaction in standard DLVO theory[1] or equivalently with the form of repulsion given by the phenomenological theory of the hydration force.[7,8] The renormalized form of the soft part of the confinement potential of the above form can now be derived as

$$w_{\sigma^2}(a) = \int_{-a}^{+a} dz\, w(z)\, \rho_\sigma(z) = (A/\kappa)e^{-\kappa a}F(\kappa a,(\sigma/a)^2) \tag{29}$$

with $\rho_\sigma(z)$ given by eq 20 while the function $F(x,y)$ has been obtained as

$$F(\kappa a,(\sigma/a)^2) = ch(\kappa a)\sum_{n=0}^{\infty}\frac{(-1)^n(2n+1)(\pi/2)}{(\kappa a)^2 + (2n+1)^2(\pi/2)^2}\exp(-(2n+1)^2(\pi/2)^2(\sigma/a)^2)$$

$$\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)(\pi/2a)}\exp(-(2n+1)^2(\pi/2)^2(\sigma/a)^2) \tag{30}$$

In view of later developments we introduce here a function $f(y) = (\partial^2/\partial x^2)F(x,y)_{x=0}$ and its derivative $f'(y)$ that enter the minimization condition eq 26 in the limit of small κa. Also this condition can be considerably simplified if one again resorts to the Helfrich ansatz $\sigma^2 = \mu a^2$.

The general solution of eq 26 leads to some interesting limiting cases. First of all, let us limit ourselves to the case of small a, or more specifically $\kappa a \ll \pi/2$. In this case the effects of the elastic fluctuations are small and we are led to the following limiting form

$$\lim_{\kappa a\to 0} F(\kappa a,(\sigma/a)^2) \approx 1 + {}^1/_2(\kappa a)^2 f(\sigma^2/a^2) \tag{31}$$

This approximation leads furthermore to the following form of the minimization condition that can be derived from eq 26 by the application of the Helfrich ansatz:

$$1/\mu^2 = 1/\mu_s^2 + \chi_A(\kappa a)^4 e^{-\kappa a} f'(\mu) \tag{32}$$

Its solution leads to the free energy of the form

$$F/S \approx {}^1/_2(kT/8)^2(1/K_c)\sqrt{1/\mu_s^2 a^4 + \chi_A \kappa^4 e^{-\kappa a} f'(\mu)} + (A/\kappa)e^{-\kappa a}(1 + {}^1/_2(\kappa a)^2 f(\mu)) \tag{33}$$

where μ is the solution of the minimization condition eq 32. In the strict limit of $a \to 0$, the free energy now assumes a somewhat more simplified form:

$$F/S \approx {}^1/_2(kT/8)^2(1/K_c\mu_s a^2) + (A/\kappa)e^{-\kappa a} \tag{34}$$

In this limit steric interactions make an appreciable contribution to the free energy only if $(\kappa a)^2 \ll 1/\chi_A\mu_s$, where we introduce a dimensionless constant $\chi_A = AK_c(8/kT)^2/\kappa^3$ that measures the relative strength of the soft (exponential) versus the hard wall confinement potential. Inserting experimental values for A, K_c, and κ, one obtains χ_A in the range of 10–10^3. For the hydration force parameters and lecithin bending elastic modulus, we thus obtain an appreciable contribution of the steric part of the free energy to the total interaction free energy only if $a \ll 0.3$ Å, a value of the interlamellar separation that is experimentally meaningless.

For small but finite κa the free energy assumes a different form. In this case the potential $w(z)$ becomes steep enough to have a well-defined minimum and the thermal wanderings of $z(\rho)$ are confined only to the region of this minimum. Thus, we obtain from eq 33

$$F/S \approx (A/\kappa)(e^{-\kappa a} + {}^1/_2\sqrt{(f'(\mu)/K_c\chi_A)}e^{-\kappa a/2}) \tag{35}$$

This form of the free energy has already been obtained by Evans and Parsegian[4] in their more simplified analysis of the same problem. The elastic fluctuations, in this limit, therefore become important only for those interlamellar separations where $\kappa a \gg \ln K_c\chi_A$. Fluctuation-enhanced interaction therefore comes into play when, in general, interlamellar spacing becomes larger than several decay lengths of the soft potential and has a general form going as the square root of the bare interaction potential.

We now examine the limit of large spacings, $\kappa a \to \infty$. The soft confinement potential is almost zero everywhere in the interval $[-a, +a]$ except for the exponential tails of length $\cong \kappa^{-1}$ at the edges of the interval. We therefore expect that the free energy should again retain a form similar to the pure steric confinement case, eq 24. This can be seen as follows. We have

$$F((\kappa a \to \infty),(\sigma/a)^2) \cong (e^{\kappa a}/2(\kappa a)^2)F(\mu) \tag{36}$$

where $F(\mu)$ does not depend on κa any more as can be checked by a direct evaluation of the limit. The solution of the extremum condition eq 26 can again be obtained with the Helfrich ansatz $\sigma^2 = \mu_\infty a^2$, where $\mu_\infty = \mu(\kappa a \to \infty)$ and $\mu_\infty \neq \mu_s$. Furthermore we observe that μ_∞ is no more a function of a; however, it still depends on χ_A since it satisfies the minimization condition in the form

$$1/\mu_\infty^2 = 1/\mu_s^2 + \chi_A F'(\mu_\infty) \tag{37}$$

The free energy can in this case be obtained as

$$\frac{F}{S} = \frac{1}{2}\left(\frac{kT}{8}\right)^2\frac{1}{K_c\mu_\infty a^2} + \frac{1}{2}\frac{AF(\mu_\infty)}{\kappa^3 a^2} = \frac{1}{2}\left(\frac{kT}{8}\right)^2\frac{1}{K_c\mu_{\text{eff}}a^2} \tag{38}$$

The free energy thus has a form identical to eq 24, except that the intersurface separation a is now changed to an

effective separation, $a_{eff} = \sqrt{\mu_{eff}/\mu_s}a$. This result can be interpreted in the sense that in the limit of large a the soft potential acts to diminish (since $\mu_{eff} < \mu_s$) the effective separation between the interacting surfaces, while the form of the a dependence remains the same as in the pure steric case.

Matters get complicated, however, as soon as we include attractive contributions in the confinement potential $V(z)$. Following the DLVO arguments,[1] we could write down the following plausible form of the intermembrane confinement potential at not too large separations

$$V(z) = (A/\kappa)e^{-\kappa z} - H/12\pi z^2 \qquad (39)$$

provided that as $z \to 0$ the attractive contribution remains bounded as can be argued on grounds of detailed calculations.[10] This boundedness can be obtained by different interpolation formulas that need not concern us here since the details of the attractive part of the confinement potential are irrelevant at small intersurface separations where the total interaction is overwhelmed by the repulsive (hydration) contribution. We can thus in principle proceed in the same way as in the case of a purely repulsive confinement potential.

It is most interesting to investigate the form of the interaction free energy in the limit of large spacings. In this case the renormalized interaction potential can be obtained in the form

$$w_{\sigma 2}(a \to \infty) = (A/\kappa)e^{-\kappa a}F(\mu) - (H/12\pi a^2)G(\mu) \qquad (40)$$

where the function $F(\mu)$ has already been defined above, eq 36, while $G(\mu)$ can be obtained in the following form:

$$G(\mu) = \frac{\sum_{n=0}^{\infty}(-1)^n(2n+1)(\pi/2)ci(2n+1)\pi \exp(-(2n+1)^2(\pi/2)^2\mu)}{2\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)(\pi/2)}\exp(-(2n+1)^2(\pi/2)^2\mu)} \qquad (41)$$

where $ci(x)$ is the standard integral cosine function. The minimization condition eq 26 can again be handled by the Helfrich ansatz $\sigma^2 = \mu a^2$ and now leads to the following equation for μ:

$$1/\mu^2 = 1/\mu_s^2 + \chi_A F'(\mu)(1 - 2\chi_H(G'(\mu)/F'(\mu))) \qquad (42)$$

where $F'(\mu)$ and $G'(\mu)$ stand for the derivatives of the respective functions and the dimensionless quantity $\chi_H = H\kappa^3/12\pi A$ measures the relative strength of the repulsive and attractive contributions of the soft confinement potential. Inserting the experimental values for H, κ, and A, one obtains χ_H in the range $1\text{–}10^{-2}$. The interaction free energy in this limit can be obtained as

$$\frac{F}{S}(a \to \infty) \approx \frac{1}{2}\left(\frac{kT}{8}\right)^2\frac{1}{K_c\mu a^2} + \frac{1}{2}\frac{AF(\mu)}{\kappa^3 a^2}\left(1 - \chi_H\frac{G(\mu)}{F(\mu)}\right) \qquad (43)$$

Thus, it follows that the asymptotic form of the free energy again has the a^{-2} limiting form while its magnitude and sign depend only on the dimensionless quantities χ_A and χ_H. We note that this form has been conjectured but not directly proved by Sornette.[15] Whether the solution of the minimization condition eq 42 leads to attractive or repulsive interactions depends clearly only on the respective values of χ_A and χ_H. Thus, the unbinding of the membrane (i.e., the vanishing of a stable secondary minimum) effected by the thermally driven undulations can be reached by changes in either χ_A or χ_H as is represented in Figures 2 and 3. In each of the two cases, there exists a critical value of χ_A or χ_H where a transition sets in between a state with a well-defined secondary minimum at a finite separation and a state without a secondary minimum, where the force is repulsive for all values of the intersurface separation. The details of this (unbinding) transition have been elaborated in the work of Lipowsky and Leibler.[5]

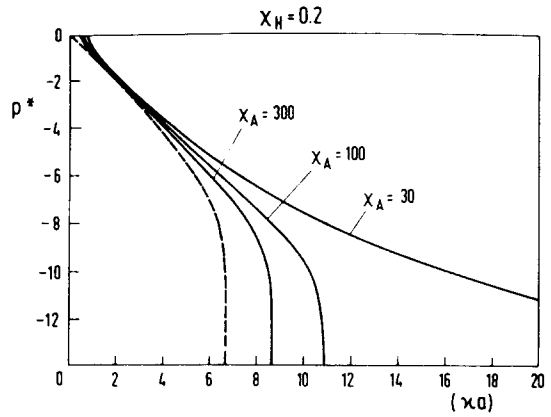

Figure 2. Dimensionless interlamellar pressure $p^* = p/A$, where furthermore $p = -(\partial/\partial a)(F/S)$. The free energy is obtained by solving the minimization condition eq 26 and then using the free energy expression eq 27. The dashed line corresponds to the bare interaction potential eq 39 with $\chi_H = 0.2$. The full lines correspond to the fluctuation-enhanced cases with $\chi_A = 300$, 100, and 30. One clearly distinguishes the transition from the fluctuation-enhanced potential that still has (though displaced) a secondary minimum from the case of the unbinding of the lamellae.

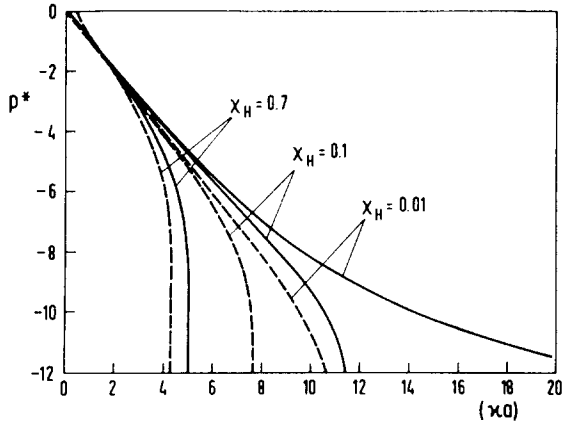

Figure 3. Same as Figure 2 except that here we vary χ_H while keeping $\chi_A = 300$ constant. Dashed lines correspond to bare interaction potentials of the form eq 39 while full lines correspond to fluctuation-enhanced potentials. Again the displacement and the final vanishing of the secondary minimum are clearly seen as one goes from $\chi_H = 0.7$ to $\chi_H = 0.01$.

The variational method of treating the effects of thermal undulations on the interactions between flexible membranes, which is related to the linearized renormalization group studies,[13] has the advantage of giving the complete effective interaction potential (not just its scaling form) for the whole range of experimentally accessible intermembrane separations. It should thus prove valuable to assess intrinsic membrane parameters (e.g., K_c) by comparing measured force curves (not necessarily close to the unbinding transition) with the expectations given by the variational approach developed here. A short formal summary of the results presented in this work is given in the Summary.

Summary

The main results for the interaction free energy are

1. pure steric repulsion, eq 24

$$F_s/S = {}^1/_2(kT/8)^2 1/K_c\mu_s a^2 \qquad \mu_s = 0.183$$

2. fluctuation-enhanced strong exponential repulsion, eq 35

$$F/S = (A/\kappa)\left(e^{-\kappa a} + \frac{1}{2}\sqrt{(f'(\mu)/K_c\chi_A)}e^{-\kappa a/2}\right)$$

where μ is obtained from the minimization condition in the form

$$1/\mu^2 = 1/\mu_s^2 + \chi_A(\kappa a)^4 e^{-\kappa a} f'(\mu)$$

3. exponential repulsion and van der Waals attraction (for $a \to \infty$), eq 43

$$\frac{F}{S}(a \to \infty) = \frac{1}{2}\left(\frac{kT}{8}\right)^2 \frac{1}{K_c\mu a^2} + \frac{1}{2}\frac{AF(\mu)}{\kappa^3 a^2}\left(1 - \chi_H\frac{G(\mu)}{F(\mu)}\right)$$

where μ can be obtained numerically from the solution of the minimization condition

$$1/\mu^2 = 1/\mu_s^2 + \chi_A F'(\mu)(1 - 2\chi_H(G'(\mu)/F'(\mu)))$$

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