

Unbinding Transitions of Interacting Membranes

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Molecular membranes in aqueous solutions interact via van der Waals, hydration, and electrostatic forces. In addition, thermal fluctuations of the membranes generate long-range effective repulsion. A systematic theory of the interplay among these interactions reveals a continuous phase transition from a state where the membranes are bound together to a state where they are completely separated. In three dimensions, this unbinding transition is driven by fluctuations. Quantitative correlations with data for lipid bilayers suggest that it can be observed experimentally.

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Flexible membranes, such as lipid bilayers in water, often cohere to form stable aggregates of vesicles or multilayer lamellar phases.¹ The cohesion necessary for the stability of these phases is provided by long-range van der Waals forces.^{1,2} These attractive interactions are balanced, at short membrane separation, by strong repulsions arising from hydration forces¹ for uncharged membranes and, in addition, from electrostatic forces^{1,3} for charged membranes. In some systems, the separation of the membranes does not fully reflect a balance between attractive and repulsive forces because there is insufficient water to fill larger gaps between the membranes; such constrained situations will not be considered here. Instead, we assume that the membranes are allowed to equilibrate in excess water; then, their mean separation should be determined by the intermembrane forces.

For two parallel membrane segments a distance l apart, the total interaction energy per unit area can be written

$$V(l) = V_H(l) + V_E(l) + V_W(l) \quad (1)$$

in which the hydration energy, $V_H(l)$, has the empirical form¹

$$V_H(l) = A_H \exp(-l/\lambda_H) \quad (2)$$

with typical values¹ $A_H \approx 0.2 \text{ J/m}^2$ and $\lambda_H \approx 0.3 \text{ nm}$. The electrostatic energy, V_E , for two charged membranes also decays exponentially,³ i.e.,

$$V_E(l) \approx A_E \exp(-l/\lambda_E) \quad (3)$$

for l greater than the Debye length³ $\lambda_E \propto 1/\sqrt{\chi}$, where χ is the ionic concentration in the aqueous solution. Within the Debye-Hückel approximation, one has $A_E \propto \phi_0^2 \sqrt{\chi} \propto \sigma_0^2 / \sqrt{\chi}$, where ϕ_0 and σ_0 are the electrostatic potential and the surface charge density at the membranes.³ The last term in (1) represents the van der Waals interaction energy resulting from different polarizabilities of the lipid and the water molecules.

This energy can be written, for $l \gtrsim 0.3 \text{ nm}$, as^{1,4}

$$V_W(l) \approx -\frac{W}{12\pi} \left[\frac{1}{l^2} - \frac{2}{(l+\delta)^2} + \frac{1}{(l+2\delta)^2} \right], \quad (4)$$

where^{1,2} the Hamaker constant $W \approx 10^{-22}$ – 10^{-21} J and $\delta \approx 4 \text{ nm}$ denotes the membrane thickness. For large l , this implies⁴

$$V_W(l) \sim -W\delta^2/l^4. \quad (5)$$

Now, the total interaction energy (1) has a minimum at $l = \bar{l} < \infty$ provided that $W > 0$. Thus, one might expect that two membranes always cohere as a result of their van der Waals attractions. However, both uncharged⁵ and charged⁶ bilayers have been found which seem to separate indefinitely far when allowed to equilibrate with excess water. These observations may be explained in terms of an effective steric interaction⁷

$$V_s(l) \sim (k_B T)^2 / \kappa l^2 \quad (6)$$

resulting from thermally excited undulations of the membranes as proposed by Helfrich.⁷ The parameters k_B , T , and κ are the Boltzmann factor, the temperature, and the *rigidity constant* of the membranes. Note that the steric interaction (6) decays more slowly than the van der Waals attraction (5) for large l . A repulsion similar to (6) arises from the fluctuations of domain walls and interfaces.⁸

The steric repulsion (6) was originally derived under the simplifying assumption that the membranes do not interact through any other forces. This is, of course, not the case for real membranes: Here, we report on a systematic study of the interplay between the direct microscopic forces (1)-(4) and the steric interaction (6). We establish the existence of continuous phase transitions from a state where the membranes are bound to a state where they are completely separated. The properties of these transitions *cannot* be obtained by simply superposing (1) and (6). Indeed, such a su-

perposition would indicate a first-order transition while we predict critical behavior with characteristic exponents.

For three-dimensional systems, our results have direct applications. For *uncharged* membranes with $V_E(l) = 0$, one may vary the Hamaker constant W by changing the polarizability of the aqueous medium.¹ We predict that the mean separation of the membranes diverges as

$$\bar{l} \sim (W - W_c)^{-\psi} \quad (7)$$

when W approaches, from above, a critical value $W_c > 0$. We have determined both W_c and the *universal* critical exponent

$$\psi \approx 1.00 \pm 0.03 \quad (8)$$

from a special renormalization-group calculation. The critical value W_c depends on temperature T and on the parameters A_H , λ_H , δ , and κ . For room temperatures and $A_H = 0.2 \text{ J/m}^2$, $\lambda_H = 0.3 \text{ nm}$, and $\delta = 4 \text{ nm}$, we obtain $W_c \approx (6.3-0.61) \times 10^{-21} \text{ J}$ as the rigidity constant κ varies within the range $(1-20) \times 10^{-19} \text{ J}$. For egg lecithin, for instance, one has^{5,9} $\kappa \approx (1-2) \times 10^{-19} \text{ J}$ which leads to $W_c \approx (6.3-4.1) \times 10^{-21} \text{ J}$.

Experimental results on the separation of egg lecithin (PC) bilayers have been somewhat controversial: While one experimental group⁵ claims that these membranes separate completely in excess water, another group² found a finite mean separation. However, these two groups also differ in their estimate of the Hamaker constant: The former⁵ quote $W \approx (2.3-3.8) \times 10^{-21} \text{ J}$, and the latter² $W \approx 8.2 \times 10^{-21} \text{ J}$. It is remarkable that these two values for W bracket the critical value $W_c \approx (6.3-4.1) \times 10^{-21} \text{ J}$ predicted by our analysis. Further experiments could well reveal the transition directly.

For *charged* membranes, the phase diagram is more complex since the ionic concentration χ and the electrostatic membrane potential ϕ_0 play a role. Suppose, for example, that ϕ_0 stays roughly constant as χ is varied. Then, there is a *critical concentration* χ_c such that the mean membrane separation diverges as

$$\bar{l} \sim (\chi - \chi_c)^{-\psi} \quad (9)$$

when $\chi_c \rightarrow \chi_c^+$ where the critical exponent ψ is again given by (8).⁶ As an example, we estimated χ_c for a 2:1 electrolyte at room temperature with $A_H = 0.2 \text{ J/m}^2$, $\lambda_H = 0.3 \text{ nm}$, $\phi_0 = 40 \text{ mV}$, $W = 6 \times 10^{-21} \text{ J}$, and $\delta = 4 \text{ nm}$, obtaining $\chi_c \approx 84-10 \text{ mM}$ for a rigidity constant $\kappa = (2-20) \times 10^{-19} \text{ J}$. These values for χ_c are consistent with the experimental data⁶ on dipalmitoylphosphatidylcholine (DPPC) bilayers in CaCl_2 solutions. However, the rigidity constant of these bilayers which, at room temperature, are in the gel phase is not known and, therefore, we cannot make a definite pre-

diction for χ_c .

To outline the analysis yielding these results, consider two roughly parallel membranes which may represent the contact region of two vesicles or two lamellae within a multilayer phase. For the lamellar systems, we ignore next-to-nearest-neighbor interactions between membranes. Such interactions are expected to affect the values of W_c and χ_c but should not affect the universal properties at the unbinding transition. We will also neglect finite size effects and suppose these membranes to be infinite in extent. Likewise, we will ignore their internal structure and denote their distance from a reference plane by $l_1(\mathbf{x})$ and $l_2(\mathbf{x}) < l_1(\mathbf{x})$, where \mathbf{x} is a $(d-1)$ -dimensional coordinate in this plane. Thus, our model is restricted to membrane configurations without overhangs. The interaction energy per unit area for these configurations is $V(l_1 - l_2)$ with $V(l)$ given in (1). In addition, the undulations of the membranes lead to a total elastic bending energy per unit area¹¹⁻¹⁴

$$\frac{1}{2} \kappa H^2 [l_1] + \frac{1}{2} \kappa H^2 [l_2], \quad (10)$$

where $H[l] = \nabla^2 l + O((\nabla l)^3 \nabla)$ is the mean curvature. If the nonlinear gradient terms are ignored,¹⁵ the effective Hamiltonian or free-energy functional for the membrane configurations can now be written as

$$H\{l\} = \int d^{d-1}x \left\{ \frac{1}{2} \kappa (\nabla^2 l)^2 + V(l) \right\} / k_B T \quad (11)$$

with $l = l_1 - l_2$. This Hamiltonian implicitly contains a high-momentum cutoff $\Lambda \approx 1/\delta$ (δ being the membrane thickness).

The effective Hamiltonian (11) resembles the interface models studied in other contexts such as roughening and wetting transitions. Indeed, these models differ from (11) mainly in the form of the bending energy: For interfaces separating different thermodynamic phases, this energy per unit area is $\propto (\nabla l)^2$ whereas, for membranes, it is $\propto (\nabla^2 l)^2$.

For wetting transitions, three different scaling regimes have been found¹⁶⁻¹⁸: (i) a *mean-field* (MF) regime for $d > d_1$; (ii) a *weak-fluctuation* (WFL) regime for $d_1 > d > d_2$; and (iii) a *strong-fluctuation* (SFL) regime for $d_2 > d$. In the WFL regime, the phase boundaries are as in MF theory but the critical exponents have nonclassical values. In the SFL regime, however, these phase boundaries are *shifted* and the critical exponents acquire nontrivial universal values.

As shown below, the membrane model (11) also exhibits three such scaling regimes, the borderline dimensionalities being $d_1 = 5$ and¹⁹ $d_2 = 3\frac{2}{3}$ for the interactions (1)-(4). Since $d_2 < 3$, unbinding transitions of membranes in three-dimensional systems are nontrivial, belonging to the SFL regime.

Within mean-field theory (MFT), the average separation $\bar{l} = \langle l \rangle$ of the two membranes follows from

$\partial V/\partial l|_{\bar{l}}=0$. This length scale becomes large for small values of W . Thus, within MFT, an unbinding transition occurs only for $W \rightarrow 0^+$, i.e., one finds the critical value $W_c=0$. In addition to l , the configurations of the membranes will be characterized by correlation lengths, ξ_{\parallel} and ξ_{\perp} , which enter into the difference correlation function

$$\Delta C(\mathbf{x}) = \frac{1}{2} \langle [l(\mathbf{x}) - l(0)]^2 \rangle. \quad (12)$$

Within MFT, one has

$$\Delta C(\mathbf{x}) = \frac{k_B T}{\kappa} \int_{p < \Lambda} \frac{d^{d-1} p}{(2\pi)^{d-1}} \frac{1 - e^{i\mathbf{p} \cdot \mathbf{x}}}{p^4 + \xi_{\parallel}^{-4}}, \quad (13)$$

where the longitudinal length is given by¹³

$$\xi_{\parallel} = [\kappa^{-1}(d^2 V/dl^2)_{\bar{l}}]^{-1/4}. \quad (14)$$

The correlation length ξ_{\perp} , on the other hand, is defined via

$$\xi_{\perp}^2 = \langle (l - \bar{l})^2 \rangle = \Delta C(\infty) \quad (15)$$

and measures the thermally induced roughness of membranes. In the limit $\bar{l} \rightarrow \infty$, the MFT expression (13) for $\Delta C(\mathbf{x})$ yields $\xi_{\perp} \sim \text{const}$ for $d > 5$, $\xi_{\perp} \sim \ln(\xi_{\parallel} \Lambda)$ for $d = 5$, and

$$\xi_{\perp} \sim (k_B T/\kappa)^{1/2} \xi_{\parallel}^{(5-d)/2} \text{ for } d < 5. \quad (16)$$

Then, one can show by a systematic perturbation expansion around $l = \bar{l}$ that MFT is valid but only for $d \geq 5$. However, the relation (16) remains valid beyond MFT. To see this, consider the limiting case $W = 0$. The repulsive forces then dominate and the membranes will be completely separated. Therefore, the fluctuations will be controlled solely by the bending energies (10).¹⁵ In this case, the difference correlation function (12) behaves like $\Delta C(\mathbf{x}) \sim (k_B T/\kappa) x^{5-d}$ for $d < 5$. On the other hand, when ξ_{\parallel} is finite, scaling implies $\Delta C(\mathbf{x}) \xi_{\parallel}^{(5-d)} \Omega(x/\xi_{\parallel})$, which leads, via (15), back to the relation (16).

Let us now estimate the bending free energy for typical configurations of the membranes. These configurations consist of humps of longitudinal and transverse dimensions ξ_{\parallel} and $\xi_{\perp} \sim \xi_{\parallel}^{(5-d)/2}$ (compare Refs. 17 and 18), and lead, via the Laplacian term in (11), to a bending free energy per unit area

$$f_s \simeq \kappa (\xi_{\perp}/\xi_{\parallel}^2)^2 \simeq k_B T (k_B T/\kappa)^{\tau/2} \xi_{\perp}^{-\tau}, \quad (17)$$

where the last term holds for $d < d_1 = 5$ with

$$\tau = 2(d-1)/(5-d). \quad (18)$$

This term in the free energy represents an effective repulsion between the membranes as a result of their fluctuations.

Now let us assume that the effective free energy f is given simply by the sum $f = f_s + V$ with f_s from (17)

and V from (1). In this way, one recovers the results of MFT for $d > d_1 = 5$. In the MF regime, $\bar{l} \gg \xi_{\perp}$ near the transition. Now, suppose that one has $\bar{l} \approx \xi_{\perp}$. Then, for $d < d_1 = 5$, the repulsive terms in $V(l)$, see (2) and (3), can be neglected relative to f_s as given by (17), and one finds a WFL regime where

$$\bar{l} \sim \xi_{\perp} \sim W^{-\psi}, \quad \psi = \frac{1}{6}(5-d)/(d-d_2) \quad (19)$$

for $W \rightarrow 0$ with $d_2 \equiv 3\frac{2}{3}$.¹⁹ The same results follow from a self-consistent perturbation expansion of (11) along the lines of Ref. 16 which fully confirms the simple minimization procedure for $d > d_2 = 3\frac{2}{3}$.²⁰

The relation $\bar{l} \sim \xi_{\perp}$ implies that the separation of the membranes is driven by their fluctuations. Since these fluctuations become more pronounced for lower d , this relation should also hold for $d < d_2 = 3\frac{2}{3}$. Using $\bar{l} \sim \xi_{\perp}$ in (17) precisely reproduces the steric interaction (6) when $d = 3$. However, it is apparent from (19) that $d = d_2 = 3\frac{2}{3} > 3$ is another boundary dimension since $\psi \rightarrow \infty$ when $d \rightarrow 3\frac{2}{3} +$. By analogy with wetting transitions,¹⁶⁻¹⁸ we take this to imply a SFL regime for $d \leq d_2$ where the unbinding transition now occurs at a nonzero Hamaker constant $W = W_c > 0$ rather than at $W = 0$ as in the MF and the WFL regimes. For $W > W_c$, the van der Waals attractions are sufficient to bind the membranes together while, for $W < W_c$, the membrane fluctuations overcome the attractive forces so that the membranes separate completely.

In order to determine W_c , the critical value of the Hamaker constant, or any other critical parameter, one may appeal to renormalization-group (RG) techniques. We have used a modified version of Wilson's approximate recursion relation.²¹ This RG method has already been used²² for the SFL regime of wetting transitions: A comparison with exact results available for $d = 2$ shows²² that it gives critical exponents accurate to within a few percent. When this RG approach is applied in the present context, both the real-space coordinate \mathbf{x} and the fluctuating field l are rescaled with a factor $b > 1$: $\mathbf{x} \rightarrow \mathbf{x}/b$ and $l \rightarrow l/b^{\zeta}$ with $\zeta = (5-d)/2$. Then, a partial trace over the short-wavelength fluctuations leads to a map of the function space of interaction energies $V(l)$ into itself. This map is given by the approximate nonlinear recursion relation²³

$$V^{(n)}(l) = -b^{d-1} \ln \left\{ (2/\sqrt{\pi}) \int_0^2 dx e^{-x^2 - E(z, x)} \right\} \quad (20)$$

with $z = b^{\zeta} l$ and

$$E(z, x) = \frac{1}{2} V^{(n-1)}(z-x) + \frac{1}{2} V^{(n-1)}(z+x). \quad (21)$$

We have studied successive iterations of this RG by numerical methods starting with initial interactions $V(l)$ as given by (1). In this way, we have determined the critical parameters W_c and χ_c for $d = 3$ as

described above; see (7) and (9). The universality of ψ in (7) and (9) follows from the fact that, in $d = 3 < d_2$, all transition points are mapped under the RG onto the same nontrivial fixed point.²⁴

In summary, we have analyzed theoretically the effect of fluctuations on the interactions between membranes and, hence, predicted a continuous unbinding transition which seems to correlate well with current observations, although further experiments should be performed.

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⁴This expression is valid for nonretarded van der Waals forces. For $l \geq 50$ nm, retardation effects should become important leading to $V_w(l) \propto 1/l^5$, but this would not change the critical behavior for $d = 3$ predicted by (7)-(9).

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¹⁹The boundary value $d_2 = 3\frac{2}{3}$ applies to the asymptotic behavior (5) for the attractive part of (1). For general $V_{\text{atr}}(l) \sim -1/l^{\sigma+1}$, one finds $d^2 = (5\sigma + 7)/(\sigma + 3)$

²⁰In this way, one may also confirm that the minimization procedure is applicable for the dependence of l on the external pressure P which leads to an extra term Pl in (1). Thus, $l \propto P^{-1/(\tau+1)}$ with τ given by (18) as $P \rightarrow 0^+$ for complete separation and $d < 5$

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²³Our approximate RG procedure preserves the form of the effective Hamiltonian (11). Details will be presented elsewhere.

²⁴In view of the numerical result (8), one might speculate that $\psi = 1$ in $d = 3$. In this case, hyperscaling would imply the specific-heat exponent $\alpha = 0$

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The quoted values for the phase boundaries of the critical unbinding transition as determined by a renormalization-group calculation contain an error. All quoted rigidity constants, κ , are too large by a factor $\frac{1}{9} \pi^4 \approx 10.8$. Thus, the values for κ which are given as $(1-20) \times 10^{-19}$ J and $(2-20) \times 10^{-19}$ J in the Letter should be replaced by $(0.09-1.85) \times 10^{-19}$ J and $(0.19-1.85) \times 10^{-19}$ J, respectively. This correction applies both to neutral and to charged membranes.