Binding and Unbinding of Lipid Membranes: A Monte Carlo Study

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The behavior of interacting fluid membranes is simulated using a vectorized Monte Carlo code. The Monte Carlo data give clear evidence for the existence of continuous unbinding transitions from a bound to an unbound state of the membranes. The location of the phase boundary and, thus, the *macroscopic* membrane state is found to be strongly affected by shape fluctuations on *microscopic* length scales. The observed critical behavior confirms theoretical predictions even though the accessible critical region is severely restricted by the rapid growth of relaxation times.

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Biological membranes form the surfaces of cells and organelles and, thus, give rise to an amazingly complex and diverse architecture.[1] Nevertheless, all biomembranes have the same basic structure: A lipid bilayer which is "decorated" by various macromolecules. The physical properties of such bilayers have been intensively studied during the last decade.[2] One useful concept which has emerged is that the shape of membranes is mainly controlled by *bending elasticity* and, thus, by *curvature.* Likewise, typical shape fluctuations are thermally excited bending modes which can be directly observed in the microscope.[3]

In this paper, we explore the possibility of studying fluctuating membranes by computer simulations. Such simulations should be useful for many membrane phenomena. Here, we study the shape fluctuations of a membrane which interacts with another membrane or surface. This interaction has an attractive part which leads to a bound state of the membrane and, thus, to a confinement of its fluctuations. Such a confinement turns out to be crucial for computer simulations since the relaxation times grow very rapidly when the membranes become unbound.

Interactions of membranes play an essential role for many biological and biophysical phenomena. For example, attractive interactions between cell membranes lead to mutual adhesion or binding of cells. Likewise, many transport processes involve the binding and unbinding of vesicles to and from the membrane surfaces of cells and organelles.[1] This latter process can be used for the delivery of drugs to specific cell types. Another example is the construction of biosensors which is often based on the binding of membranes to solid surfaces.

If one ignores thermally excited fluctuations, the membranes can be regarded as *planar* sheets which interact as a result of various intermolecular forces. This *direct interaction* consists of two contributions: "Nonspecific" interactions such as those arising from van der Waals and electrostatic forces, and "specific" interactions mediated by biologically relevant macromolecules.

Shape fluctuations give rise to an effective repulsion between the membranes.[4] The interplay between this fluctuation-induced repulsion and the direct interaction can lead to continuous *unbinding transitions* at a finite unbinding temperature T_u, as has been found from renormalization-group calculations.[5] For $T < T_u$, the membranes are bound together, while they are unbound for $T > T_u$. The critical behavior at T_u depends on the internal membrane structure which can be fluid or crystalline. Very recently, unbinding transitions have been observed experimentally for fluid digalactosyl diclyceride (DGDG) membranes.[6]

Here, we present the *first* Monte Carlo (MC) simulations for unbinding transitions of fluid membranes. We find clear evidence for the existence and for the continuous nature of such transitions. The unbinding temperature T_u is found to depend *strongly* on the choice of the small-scale cutoff a. Thus, fluctuations on *microscopic* scales have a strong effect on the location of the phase boundary. Furthermore, equilibration near the transition is very slow: The relaxation time t_R scales as $t_R \approx t_{\rm sc}(\xi_\parallel/a)^z$, where $\xi_\parallel$ is the parallel correlation length, with $z=4$ and $t_{\rm sc}$ found to be of order 100 MC steps (per site). In fact, our simulations were only feasible because we used a *fully vectorized* MC code on a Cray XM-P computer.

Our method can, in principle, be applied to any interaction $V(l)$ of two membranes with separation l. Below, we describe results for several model interactions: (i) We briefly discuss the harmonic interaction, $V(l) = \frac{1}{2}G(l-l_0)^2$. The associated critical behavior is trivial and can be obtained analytically which provides a useful test for our MC code. (ii) Next, we consider the interaction defined by

$$V(l) = \begin{cases} \infty & \text{for } l < 0\,, \\ Pl & \text{for } l > 0\,, \end{cases} \tag{1}$$

where P represents an effective external pressure. For $P > 0$, the membranes are bound, but they unbind as P goes to zero. (iii) The simplest interaction which should lead to an unbinding transition with *finite* unbinding temperature T_u is given by the square-well interaction,

$$V(l) = \begin{cases} \infty \text{ for } l < 0 , \\ -W \text{ for } 0 < l < l_0 , \\ 0 \text{ for } l_0 < l . \end{cases} \tag{2}$$

This interaction depends on two parameters, W and l_0. For several values of l_0, we locate the critical point with $W = W_u(l_0)$ at which the membranes unbind in a continuous fashion. Thus, the corresponding phase diagram exhibits a line of critical transitions (shown in Fig. 2). The critical behavior along this line is universal.

We have also studied more realistic interactions such as the superposition of hydration and van der Waals forces, and determined critical unbinding transitions for several interaction parameters. These simulations, which are still in progress, will be described in a future publication.

To proceed, consider two membranes with coordinates $l_1(\mathbf{x})$ and $l_2(\mathbf{x})$, and separation $l \equiv l_1(\mathbf{x}) - l_2(\mathbf{x})$. Both membranes are assumed to be *fluid* which implies that their bending energies per unit area are given by $\frac{1}{2}\kappa_1(\nabla^2 l_1)^2$ and $\frac{1}{2}\kappa_2(\nabla^2 l_2)^2$, respectively. Here, $\nabla^2 l_1$ and $\nabla^2 l_2$ are the leading terms of the mean curvature,[2] and the bending rigidities κ_1 and κ_2 are of order 10^{-20}-10^{-19} J.[7] The effective Hamiltonian for their separation $l(\mathbf{x})$ is then given by[5]

$$\mathcal{H}\{l\}/T = \int d^2x [\tfrac{1}{2}(\kappa/T)(\nabla^2 l)^2 + V(l)/T] , \tag{3}$$

with $\kappa = \kappa_1\kappa_2/(\kappa_1+\kappa_2)$ and temperature T. This continuum model implicitly contains a microscopic cutoff a which is of the order of the membrane thickness.

In the MC work, the spatial coordinate $\mathbf{x}$ is replaced by a square lattice with lattice sites $\{\mathbf{x}_i\}$ and lattice constant a. The membrane configuration is then specified by $l_i \equiv l(\mathbf{x}_i)$, and the effective Hamiltonian becomes

$$\mathcal{H}\{l_i\}/T = \sum_i [\tfrac{1}{2}(\kappa/Ta^2)(\nabla_d^2 l_i)^2 + a^2 V(l_i)/T] , \tag{4}$$

with the discrete Laplacian

$$\nabla_d^2 l_i \equiv l(\mathbf{x}_i + a\hat{\mathbf{x}}_1) + l(\mathbf{x}_i - a\hat{\mathbf{x}}_1) + l(\mathbf{x}_i + a\hat{\mathbf{x}}_2) + l(\mathbf{x}_i - a\hat{\mathbf{x}}_2) - 4l(\mathbf{x}_i) .$$

It will be convenient to use the dimensionless variables $z_i \equiv (\kappa/T)^{1/2} l_i/a$ and

$$\mathcal{H}\{z_i\}/T = \sum_i [\tfrac{1}{2}(\nabla_d^2 z_i)^2 + U(z_i)] , \tag{5}$$

with

$$U(z_i) \equiv a^2 V((T/\kappa)^{1/2} a z_i)/T . \tag{6}$$

As usual, the statistical weight for $\{l_i\}$ or $\{z_i\}$ is given by the Boltzmann factor $\exp(-\mathcal{H}/T)$.

Note that the discrete variables l_i and z_i must not be regarded as the coordinates for the molecules (or mass points) of the membranes. Instead, these variables give a discrete representation for the smooth *shape* of the membranes. For *fluid* membranes as considered here, a MC simulation of the actual motion of the molecules is difficult since these molecules can diffuse freely within the membranes. In contrast, a simulation of the molecular motion is simple for *crystalline* (or tethered or polymerized) membranes for which the molecules form a two-dimensional network of fixed connectivity.

Our simulations have been performed on a Cray X-MP 22 and on a Cray X-MP 48. A fully vectorized code was used: The lattice was divided into nine sublattices such that each sublattice can be updated independently in a vector loop using the usual Metropolis algorithm. In this way, we have studied $N \times N$ square lattices with periodic boundary conditions for $N = 11$, 20, and 41. We also did some runs with $N = 80$ in order to check for possible finite-size effects. In most runs, we did $\simeq 10^6$ MC steps (per site) which gives a statistical error of a few percent as long as the relaxation time t_R, defined in (8) below, satisfies $t_R \lesssim 5 \times 10^2$. For larger values of t_R, up to $t_R \simeq 10^4$, we did $\simeq 10^7$ MC steps.

In each run, we measured the mean separation $\bar{l} = \langle l \rangle$ of the membranes and various quantities related to their fluctuations. In the continuum limit, the two-point correlation function is defined by

$$C(x,t) = \langle [l(\mathbf{x},t) - \langle l \rangle][l(\mathbf{0},0) - \langle l \rangle] \rangle ,$$

its spatial Fourier transform will be denoted by $\tilde{C}(q,t)$. This function contains two length scales, $\xi_\perp$ and $\xi_\parallel$. The roughness $\xi_\perp \equiv [C(x=0,0)]^{1/2}$ gives the amplitude of typical membrane humps; the longitudinal extension of these humps is set by the parallel correlation length $\xi_\parallel \equiv [(\kappa/T)\tilde{C}(q=0,0)]^{1/4}$. We always measured $\xi_\perp$ and $\langle(\nabla l)^2\rangle$, and estimated $\xi_\parallel$ from $\hat{\xi}_\parallel/a \equiv \exp[2\pi(\kappa/T) \times \langle(\nabla l)^2\rangle]$ since scaling implies $\hat{\xi}_\parallel \approx B_\parallel \xi_\parallel$ for large $\xi_\parallel$. In part of our runs, we also measured the whole function $C(x,t=0)$, and thus determined $\xi_\parallel$ directly. Inspection of $C(x,0)$ for different values of N shows that finite-size effects are negligible as long as $\xi_\parallel \lesssim N/10$. All data reported here belong to this regime.

The time evolution generated by the Metropolis algorithm has the same scaling properties as the Langevin dynamics for a nonconserved order parameter which is defined by

$$\partial l/\partial t = -D[-\kappa\nabla^4 l + \partial V/\partial l] + f , \tag{7}$$

where D is a kinetic coefficient and f is a random white noise. A similar equation has been studied in the context of wetting,[8] and the results have been confirmed by MC simulations for one-dimensional interfaces.[9] The arguments of Ref. 8 can also be applied to (7). One then finds for *general* $V(l)$ that the relaxation time,

$$t_R \equiv \int_0^\infty dt\, t\tilde{C}(q=0,t) \Big/ \int_0^\infty dt\, \tilde{C}(q=0,t) \tag{8}$$

behaves as $t_R \approx t_{\text{sc}}(\xi_\parallel/a)^z$ for large $\xi_\parallel$ with $z = 4$.

Time-dependent quantities such as $\tilde{C}(q=0,t)$ are, in

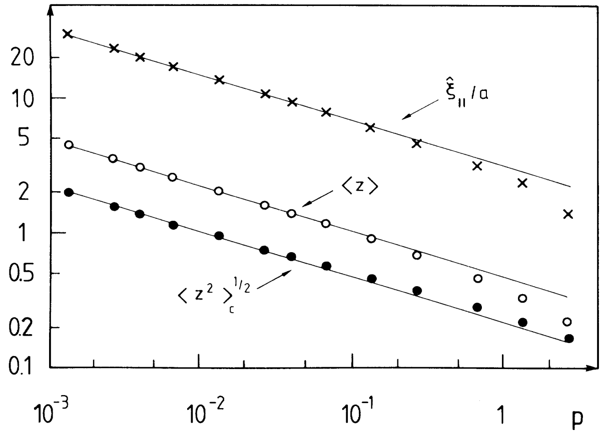

FIG. 1. Critical behavior for the interaction defined by Eqs. (1) and (6). The straight lines have slope $\psi^c = \frac{1}{3}$.

general, more difficult to determine and have a larger statistical error than static quantities. Thus, our measurements of the relaxation time t_R yield only relatively rough estimates for its prefactor t_{sc} (see below). It would also be desirable to study nonequilibrium properties such as the time evolution of membrane shapes or the (un)binding (or adhesion) dynamics in more detail,[10] but this requires even longer MC runs than used here.

First, consider the effective Hamiltonian (4) with the harmonic interaction $V(l) = \frac{1}{2} G(l - l_0)^2$. Then, the reduced interaction (6) is $U(z) = \frac{1}{2} g(z - z_0)^2$ with $g \equiv Ga^4/\kappa$. For this model, $\tilde{C}(q,0) \approx T/(\kappa q^4 + G)$ for small q. It then follows that $\xi_{\parallel} \approx a g^{-1/4}$, and that $C(x,0)$ is nonmonotonic as a function of x since $[\nabla_q^2 C(q,0)]_{q=0} = 0$. For a *finite* lattice size N, $C(x,0)$ can be easily calculated by performing a sum over the first Brillouin zone. In this way, we found that $C(0,0)$ is also nonmonotonic as a function of N. These properties have all been confirmed in our simulations. In addition, the relaxation time t_R in (8) was found to scale as $t_R \approx t_{\text{sc}}(\xi_{\parallel}/a)^4$ with $t_{\text{sc}} = 40 \pm 4$ MC steps.

For the interaction $V(l) = Pl$ as given by (1), or the corresponding reduced interaction $U(z) = pz$ with $p \equiv a^3 P/(T\kappa)^{1/2}$, the membranes unbind at $P \sim p = 0$, i.e., at $T_u = \infty$. In Fig. 1, we display the behavior of the mean separation $\bar{l} \sim \langle z \rangle$, the roughness $\xi_{\perp} \sim \langle z^2 \rangle_c^{1/2}$, and the length scale $\hat{\xi}_{\parallel}/a = \exp[2\pi(\kappa/T)\langle(\nabla l)^2\rangle]$. The parallel correlation length satisfies $\xi_{\parallel} \approx \hat{\xi}_{\parallel}/B_{\parallel}$ with $B_{\parallel} = 5 \pm 0.3$. As shown in Fig. 1, all three length scales have the critical behavior $\bar{l} \sim \xi_{\perp} \sim \xi_{\parallel} \sim 1/P^{\psi^c}$, with $\psi^c = \frac{1}{3}$ as predicted theoretically.[5] The growth of the time scale t_R was found to scale as $t_R \approx t_{\text{sc}}(\xi_{\parallel}/a)^4 \sim 1/P^{4/3}$, and $t_{\text{sc}} = 50 \pm 10$ MC steps.

Now, let us discuss the square-well interaction as defined in (2), which leads to the reduced interaction $U(z) = -w \equiv -a^2 W/T$ for $0 < z < z_0$ with $z_0 \equiv (\kappa/T)^{1/2} l_0/a$. This model has a line of continuous unbinding transitions, $w = w_u(z_0^{-2})$, as shown in Fig. 2.

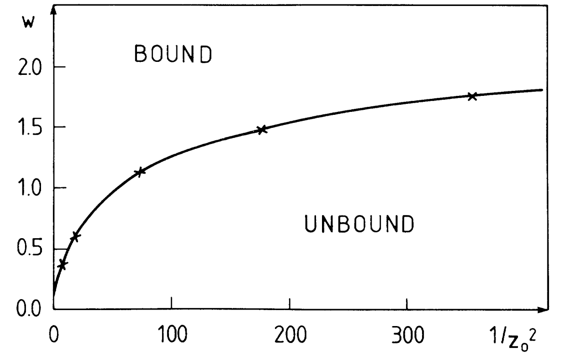

FIG. 2. Phase diagram for the interaction defined by Eqs. (2) and (6) with $w = a^2 W/T$ and $z_0 = (\kappa/T)^{1/2} l_0/a$.

The membranes are bound and unbound for $w > w_u$ and $w < w_u$, respectively. Each critical point was obtained by varying w for fixed z_0 and by estimating the intersection of the graph of $1/[\langle z \rangle - z_0/2]$ with the w axis.

The parameters w and z_0^{-2} *strongly* depend on the small-scale cutoff: $w \sim a^2$ and $z_0^{-2} \sim a^2$. For $a \to 0$, dimensional analysis implies that the phase boundary is given by $W/T_u = c_* T_u/\kappa l_0^2$. Thus, the critical locus $w = w_u(z_0^{-2})$ as displayed in Fig. 2 has the *finite* slope $\partial w/\partial z_0^{-2} = c_*$ at $z_0^{-2} = 0$. Extrapolation of our data indicates $c_* = 0.2 \pm 0.1$. Since $w_u \le c_* z_0^{-2}$, the unbinding temperature $T_u(a)$ satisfies $c_* T_u^2(a) \ge \kappa l_0^2 W$, where the equality holds for $a = 0$.

As an example, consider two lipid bilayers with bending rigidities $\kappa_1 = \kappa_2 = 2\kappa = 10^{-19}$ J as appropriate for DGDG membranes,[6] and assume that they interact via a square-well interaction as in (2) with strength $W = (10^{-21}\ \text{J})/l_M^2$ and range $l_0 = l_M/10$, where l_M is the membrane thickness. For each choice of a, the variation of T leads to a hyperbolic trajectory, $w = (a^4 W/\kappa l_0^2)/z_0^{-2}$, in the (w, z_0^{-2}) phase diagram. From the intersec-

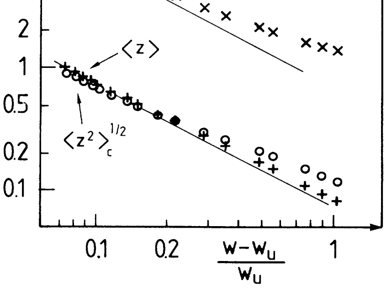

FIG. 3. Critical behavior at the unbinding transition for $z_0 = 0.075$ and $w_u(z_0^{-2}) \simeq 1.48$. The straight lines have slope $\psi = 1$.

tion of three such trajectories with the critical locus, we find $T_u \simeq 0.7T_{\text{room}}$, T_{room}, and $1.5T_{\text{room}}$ for $a = l_M$, $1.6l_M$, and $2l_M$, respectively, with $T_{\text{room}} \equiv 4.114 \times 10^{-21}$ J. Thus, T_u is found to depend strongly on the choice of a.

The critical behavior of the length scales $\bar{l}$, $\xi_\perp$, and $\xi_\parallel$ at the unbinding transition is shown in Fig. 3 for $z_0 = 0.075$ and $w_u(z_0^{-2}) \simeq 1.48$. Furthermore, we find $\xi_\parallel \approx \hat{\xi}_\parallel / B_\parallel$ with $B_\parallel = 3 \pm 0.3$. The accessible range for $(w - w_u)/w_u$ is rather limited due to the strong divergence of the relaxation time t_R, but the available data are clearly consistent with $\bar{l} \sim \xi_\perp \sim \xi_\parallel \sim 1/(w - w_u)^\psi$ and $\psi = 1$ as predicted theoretically.[5] The same exponent applies to all other values of z_0. The growth of t_R is consistent with $t_R \approx t_{\text{sc}}(\xi_\parallel / a)^4$ and $t_{\text{sc}} = 150 \pm 50$ MC steps.

In summary, our MC simulations provide clear evidence for the existence of continuous unbinding transitions of fluid membranes. The observed critical behavior confirms the results of renormalization-group calculations. Furthermore, we find (i) that the unbinding temperature T_u depends strongly on the small-scale excitations, and (ii) that relaxation times become very large near the transition as follows from the form of the curvature energy.

Property (i) implies that T_u will be strongly affected by the molecular structure of the membranes and, in particular, by the presence of *impurities* or *defects* within the bilayers. These will change the character of the small-scale excitations and, thus, the effective size of the cutoff a. Therefore, *biological membranes* which operate at roughly constant temperature *could employ a small change in their microstructure in order to go from a bound to an unbound state.* Property (ii) implies that the unbinding dynamics is very slow for *real* membranes. Indeed, the correlation time t_R as obtained here should represent a *lower* bound for the real correlation time since the transport of water into the intermembrane space can provide an additional bottleneck for the dynamics.[10]

Similar conclusions can be drawn from the recent experiments of Helfrich and Mutz.[6] The binding and unbinding was found to proceed very slowly but without apparent hysteresis. Furthermore, T_u was found to be reproducible for each sample but to vary strongly from sample to sample. In fact, Helfrich and Mutz postulate an additional microroughness of the membranes which could arise from the formation of local saddles. If such a microroughness is indeed present, it will strongly affect the value of T_u but should not alter the critical exponents.

Computer simulations could, in general, be very useful for the study of other membrane phenomena such as, e.g., the flickering and the shape transformations of closed vesicles.[11] However, in these latter problems, the radius L of the vesicle plays the role of $\xi_\parallel$. Thus, the relaxation time will grow as $t_R \approx t_{\text{sc}}(L/a)^4$, and equilibration can hardly be achieved by the usual MC procedure as soon as $L/a \gtrsim 5$. Therefore, new simulation codes are required which greatly reduce the relaxation time.

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