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Thermodynamic Behavior of Two-Dimensional Vesicles

Stanislas Leibler,[a] Rajiv R. P. Singh,[b] and Michael E. Fisher[b]
Baker Laboratory, Cornell University, Ithaca, New York 14853
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A Monte Carlo simulation of two-dimensional vesicles, modeled as closed, planar, self-avoiding tethered chains, is presented. The effects of an internal pressure increment, Δp, and a bending rigidity, κ, on the sizes and shapes is studied. For $\kappa=0$ scaling behavior is found, which, in the asymptotic deflated regime, $\Delta p<0$, matches the behavior of branched polymers. For $\kappa>0$ various nontrivial equilibrium shapes or cytotypes appear and dynamical behavior reminiscent of nonlinear flickering in real vesicles is found.

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Polymer physics is a field in which many results from the theory of *random walks* have been applied with marked success.[1] Similarly, recent theoretical studies of *random surfaces,*[2] largely motivated by high-energy physics, may well find their most fruitful applications in describing the behavior of flexible films or *membranes.*[3] Indeed, it is believed that fluidlike random-surface models may apply to amphiphilic films and bilayers,[4] while solidlike models, such as the *tethered-surface model,*[5] should describe cross-linked membranes or polymer sheets.

However, in addition to the issue of fluidity, realistic models of membranes must recognize other features. Foremost among these is the *bending rigidity,* κ, which plays a crucial role in the behavior of "tensionless" membranes.[6] It was recognized by Helfrich and others[7] that the shapes, thermodynamics, and fluctuation behavior of fluid phospholipid vesicles (including red blood cells) could be described by statistical models which include a bending/curvature energy. Recent theoretical work[8] on random surfaces with $\kappa>0$ even suggests that rigidity can lead to new phenomena such as a *crumpling transition*[9] in cross-linked membranes between a rigid, flat phase and a floppy, crumpled phase.

Secondly, membranes often exist as closed *vesicles* containing a volume of space. This naturally entails a finite pressure increment, $\Delta p \equiv p_{\rm int} - p_{\rm ext}$, between the interior and exterior. Experimentally, Δp is easily controlled by, e.g., variation of the osmotic strength of the solvent.

As a step towards applying random-surface models to membranes, we report here on a study of the problem which encompasses *both* pressure *and* rigidity terms in the energy, as well as the physically crucial self-avoiding constraints. Specifically, using Monte Carlo methods we have simulated closed planar random walks or chains and analyzed their dimensions, shapes, and equation of state. The model adopted is the analog of the tethered surfaces of Kantor, Kardar, and Nelson[5]: The centers, $\mathbf{r}_i$, of N impenetrable circular *beads* of diameter a are linked by *tethers* of length $l_0>a$. The bending energy is $E_b=\kappa a^{-1}\sum_{i=1}^{N}(1-\cos\theta_i)$, where θ_i is the angle between $\mathbf{s}_i\equiv\mathbf{r}_i-\mathbf{r}_{i-1}$ and $\mathbf{s}_{i+1}$. Self-crossing of the chain is avoided by our imposing $l_0<2a$ and taking small enough Monte Carlo steps. (Usually $l_0/a=\frac{9}{5}$ is adopted.) Simple, single-bead off-lattice dynamics and a standard Metropolis algorithm have been employed. Although our model omits a spontaneous curvature term,[7a] lacks a crumpling transition,[9] and avoids certain universality questions,[10] its study provides valuable insights into membrane behavior.

As explained below, we find that the size, measured by the mean radius of gyration, $R_G(N,p,T,\kappa)$, and the enclosed area, $A(N,p,T,\kappa)$, are well described for $\kappa=0$

and general $\bar{p}=\Delta p a^2/k_BT$ by the scaling laws

$$R_G^2 \approx N^{2\nu} X(\bar{p}N^{\varphi\nu}), \quad A \approx N^{2\nu_A} Y(\bar{p}N^{\varphi\nu}), \tag{1}$$

in which ν is the standard correlation length or end-to-end exponent for (open) self-avoiding walks; one believes that $\nu \equiv \frac{3}{4}$. We find $\nu = 0.755 \pm 0.018$ and, further, $\nu_A/\nu = 1.007 \pm 0.013$ indicating that $\nu_A = \nu$. Since Δp couples to $A \sim N^{2\nu}$, it is natural to expect[11] that $\varphi = 2$; alternatively one can define[11] an *expansile length*, l_p, via $l_p^2 = k_BT/\Delta p$, and postulate a scaling combination R_G/l_p. We estimate that $\varphi = 2.13 \pm 0.17$.

For the scaling functions we get $X(0)/a^2 = 0.116 \pm 0.008$ and $Y(0)/a^2 = 0.29 \pm 0.02$; this *excludes*, for $\Delta p = 0$, any "area collapse" in which $A/R_G^2 \to 0$ as $N \to \infty$: see Inset (i) in Fig. 1. On the other hand, in the *deflated regime*, $\Delta p < 0$, we find

$$X(x) \approx X_- / x^{\sigma} \text{ and } Y(x) \approx Y_- / x^{\tau}, \tag{2}$$

with $\sigma = 0.13 \pm 0.05$ and $\tau = 0.25 \pm 0.04$. These exponent values are consistent with a *collapse into a form matching branched polymers*[12]; see Inset (ii).

One also expects definite asymptotic laws in the *inflated regime*, $\Delta p > 0$, analogous to an open chain under a large external stretching force, $\mathbf{f}$, applied to its ends. In this regime, first analyzed by Pincus,[11] the random walk should resemble a diffuse cylinder of projected end-to-end length $Z_N \approx N^{\nu} W(fN^{\nu}/k_BT) \sim Nf^{(1/\nu)-1}$ as $f \to \infty$. We have, indeed, confirmed this prediction for *open*, planar tethered chains[13] but were unable to attain the analogous inflated regime for closed chains, where $A \sim N^2 \bar{p}^{(1/\nu)-1}$ is expected, because of computer limitations.

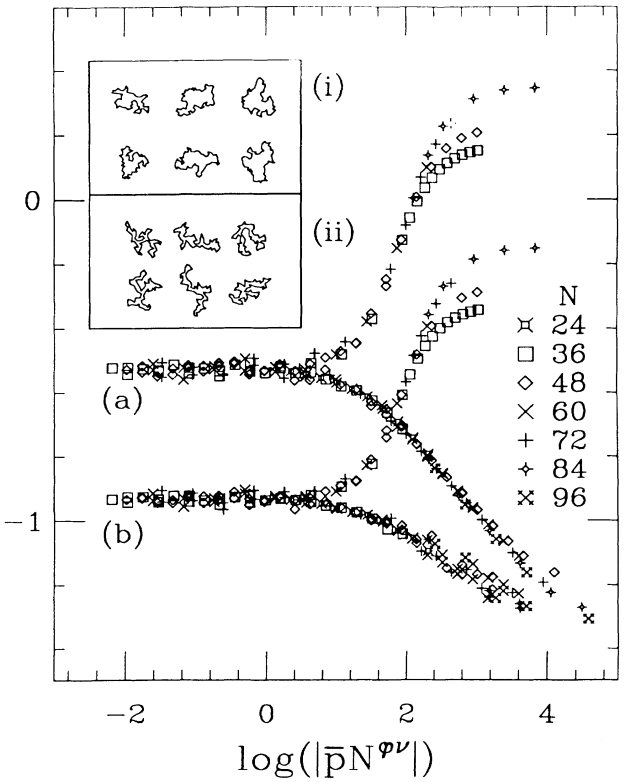

FIG. 1. Scaling plots and vesicle configurations for rigidity $\kappa = 0$: (a) $\log_{10}(A/N^{2\nu})$ and (b) $\log_{10}(R_G^2/N^{2\nu})$ vs $\log_{10}|\bar{p}N^{\varphi\nu}|$ with $2\nu = 1.51$ and $\varphi = 2.13$; samples for $N = 60$ with (i) $\Delta p = 0$, (ii) $\bar{p} \equiv a^2\Delta p/k_BT = -1.25$.

We have also explored the interplay between rigidity ($\kappa > 0$) and the external forces, Δp or $\mathbf{f}$, for both open and closed chains. For small κ and large N this amounts to no more than a renormalization of the effective bead size $\tilde{a}(\kappa)$ defined, say, via $R_G \approx \tilde{a}N^{\nu}$. However, for large κ with $\Delta p, |\mathbf{f}| \geq 0$ one enters a *stiff regime*: It appears that this occurs in nonuniversal fashion when $\rho_\kappa/R_G^0 \equiv (l_\kappa/L)^{1/2} \gtrsim 1$, where $R_G^0 = aN^{1/2}$ describes a free or Gaussian chain while $\rho_\kappa = (\kappa a/k_BT)^{1/2}$ is a characteristic radius of curvature imposed by $\kappa > 0$; alternatively, $l_\kappa = \kappa/k_BT$ is the *rigidity length* while $L = Na$ is the *contour* or *chemical length*. The effects are more spectacular for closed chains with $\kappa > 0$ and $\Delta p < 0$, i.e., *deflated vesicles*. The many sharp hairpin bends characteristic of the branched-polymer regime, $\bar{p}N^{\nu} \ll -1$ [see Inset (ii) in Fig. 1], become too energetic and are progressively suppressed; thus the vesicles completely modify their typical shapes. When $\rho^* \equiv (l_\kappa l_p^2)^{1/3} \lesssim L$ one finds well-defined equilibrium shapes or *cytotypes* strongly reminiscent of membrane vesicles and red blood cells[7a]: See Fig. 2. Moreover, in the process of the simulation one discovers a striking dynamic phenomenon reminiscent of strong, nonlinear "flickering"[7b]: explicitly for fixed $\Delta p < 0$ and some interval of κ or T several distinct cytotypes have comparable free energies with energy barriers of order k_BT between them. The vesicle spends a mean time τ_α, of order of the rotational diffusion time τ_{rot} in our simulations, fluctuating about cytotype α; this represents harmonic flickering.[7b] Then in a time $\tau_0 \ll \tau_{\text{rot}}$ the barrier is crossed and the vesicle fluctuates around cytotype β. Figure 2(c) illustrates this process.

We now address various issues underlying these results.[14] A significant feature in studying walks and surfaces of *finite size* is the *non*equivalence of stress and strain ensembles.[15] As indicated, we use a stress ensemble, keeping Δp fixed and letting A fluctuate subject to a Boltzmann factor $\exp(-\Delta pA/k_BT)$. This is appropriate for experiments on vesicles in which the permeation time for the solution is short compared to other time scales, such as $\tau_{\text{rot}}, \tau_0, \tau_\alpha$, etc.

As a first step we checked Pincus scaling[11] for open chains[13]: The scaling function, $W(y)$, switches from a pseudo Hooke's-law regime,[16] where $W(y) \approx W_0 y^{\omega_0}$ with $\omega_0 = 1.00 \pm 0.010$, for $y \equiv fN^{\nu}/k_BT \lesssim 0.25$ to the stretched regime, where $W(y) \approx W_+ y^{\omega_+}$ and $\omega_+ = 0.33 \pm 0.03 \simeq \nu^{-1} - 1$, for $y \gtrsim 0.45$. Evidently, the crossover is quite sharp.[17] These simulations allowed us to gauge

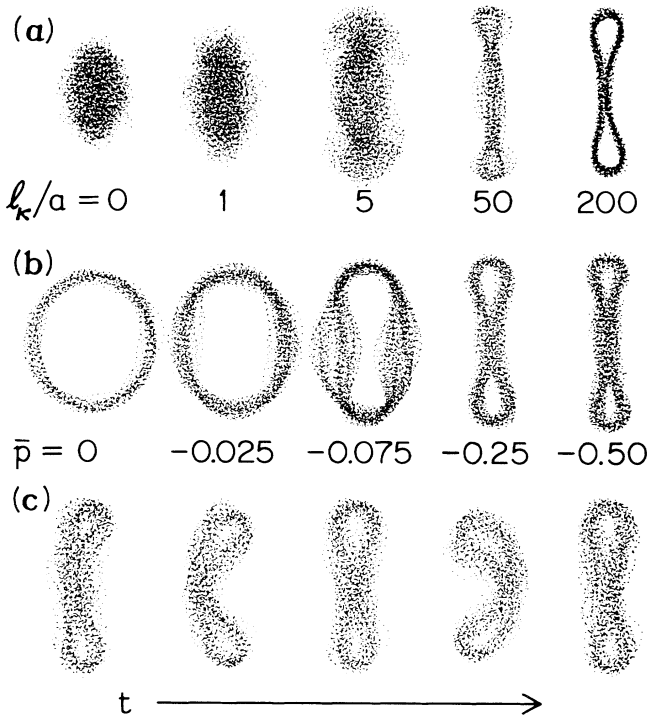

FIG. 2. Vesicle cytotypes: (a) for $\bar{p} = -1.25$ as $l_\kappa/a \equiv \kappa/ak_BT$ increases; (b) for $l_\kappa/a = 50$; and (c) as a function of time, t, for $\bar{p} = -0.075$ and $l_\kappa/a = 10$.

equilibrium and correlation times: We endeavored to satisfy various criteria: (i) relaxation of the observed variable, R_G, A, etc., (ii) rotation by 180° of the principal axes of inertia; (iii) diffuse translation of the center of mass by $\gtrsim R_G$. The requisite simulation times were $(1-50)\times 10^5$ Monte Carlo steps per bead, which enforced the limit $N \lesssim 100$.[14]

To test the scaling (1) and determine ν, ν_A, and φ we first set $\Delta p = 0$ and study the variation of A *and* its *fluctuations*. Indeed, the linear response theorem and scaling yield

$$(\Delta A)^2 \equiv \langle A^2 \rangle - \langle A \rangle^2 = \partial A/\partial \bar{p} \sim N^{2\nu_A + \varphi\nu}, \quad (3)$$

and similarly for ΔR_G. This leads to the exponent estimates quoted above.[14] Using these we construct scaling plots; as seen in Fig. 1 the data collapse is good and the well-defined power laws (2) emerge for $-\bar{p}N^{\varphi\nu} \gtrsim -10^2$. In this deflated regime one thus has $R_G \sim N^{\nu^-}$ and $A \sim N^{2\nu_A^-}$ with $\nu^- = 0.65 \pm 0.04$ and $2\nu_A^- = 1.11 \pm 0.09$. This compares well with the estimates $\nu^- \simeq 0.65$, 0.61 for branched polymers,[12] and the expectation $A \simeq Na^2$ for deflated or collapsed branches. To confirm the identification fully, our simulations should be extended to larger N, and self-avoiding hinged rods in place of tethered beads might prove advantageous.

Figure 2 shows various vesicle cytotypes for $N = 60$, $\kappa > 0$, and $\Delta p \leq 0$. Each picture consists of the superposition, with common center of mass and principal axes of inertia, of about 50 consecutive but statistically independent vesicle configurations; only the centers of each bead are plotted. The finite thickness of each cytotype, for $\kappa/ak_BT \gtrsim 5$, reflects the harmonic flickering, i.e., thermal fluctuations. As mentioned, the relevant length scales in this cytotype regime are

$$l_p = |k_BT/\Delta p|^{1/2}, \quad l_\kappa = \kappa/k_BT, \text{ and } L = Na.$$

The characteristic radius of curvature of the lobes in the well-developed cytotypes is of order $\rho^* = (l_p^2 l_\kappa)^{1/3} \gtrsim L$. Figure 2(a) shows how increasing l_κ at fixed p moves one from diffuse, fractal branched polymers at $\kappa = 0$ towards the dumbell cytotype which can be regarded as the analog of real discocytes.[7,18] It must be stressed that if one increases N (or L) while keeping Δp and κ fixed, one will recover the random-chain or flaccid-vesicle ($\kappa \simeq 0$) forms illustrated in the Fig. 1 insets. Thus the study of the cytotypes can be regarded as an aspect of *finite-size effects*.

Figure 2(b) shows an evolution at fixed rigidity, $l_\kappa/a = 50$, as the deflation, $|\Delta p|$, is progressively increased: Well-defined "ellipsocytes" are seen on this route. Near $\bar{p} = -0.075$ the plot appears to be the superposition of two distinct cytotypes; indeed, inspection of the time sequences shows that the vesicle evolves back and forth between an ellipsocyte and a "bilobocyte," passing over a free-energy barrier of some few k_BT in height. We call this "nonlinear flickering" to distinguish it from the normal, close-to-harmonic flickering seen around real stable cytotypes.[7b] Figure 2(c) shows the time evolution of another example for $\bar{p} = -0.075$ and $l_\kappa/a = 10$: One symmetric and two conjugate asymmetric cytotypes are involved. What distinguishes this nonlinear flickering is the large separation between the dwell times $\tau_\alpha, \tau_\beta, \ldots$, and the crossing time, τ_0. Of course, the barriers may increase with N and, in real experiments, the dynamics is more complex than ours, entailing hydrodynamic modes of both solvent and fluid membrane as well, for example, as specific biochemical factors in red blood cells.[7b]

In summary, the simulation of the shapes and sizes of two-dimensional vesicles with pressure and rigidity has revealed a variety of very different regimes, some with simple scaling behavior, others more complex.[14] Although the corresponding three-dimensional simulations will be harder and must face the extra complications mentioned initially,[7,9,10] they may be feasible and should prove even more instructive.

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[a]On leave from Service de Physique Théorique, CEN Saclay, 91191 Gif-sur-Yvette, France.

[b]Now at Institute for Physical Science and Technology, University of Maryland, College Park, MD 20742.

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