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Flexibility and roughness of mixed and partially polymerized bilayers in terms of the hat model and local bending frustration

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Abstract. — The flexibility of mixed fluid membranes is examined in terms of the so-called hat model that is based on local curvature fluctuations. For monolayers, the hat model reproduces the increase of the flexibility obtained previously with a continuum model. In bilayers, the bending frustration of the constituent monolayers causes equal molecules to avoid and unequal molecules to seek each other when they are in opposite monolayers. This local interaction across the middle surface of the bilayer leads to an additional increase of bilayer flexibility. The cooperative effect of local bending frustration in partially polymerized bilayers may result in the segregation of polymer chains belonging to opposite monolayers. Possible consequences of the segregation are a nearly divergent flexibility, a pronounced roughness of the bilayer, and budding of bilayer vesicles.

1. Introduction.

There are two entirely different ways of calculating the effective bending rigidity or its inverse, the effective flexibility, of heterogeneous fluid membranes. Continuum theories deal with averages of molecular properties, in particular the spontaneous curvature, over membrane pieces of constant curvature [1-4]. In other words, the membrane is regarded as smooth and uniform. Thermal undulations do not enter these calculations and, if introduced afterwards, are described in terms of nonlocal modes. Specific continuum models underly the work of Safran, Pincus and Andelman [3] and our thermodynamic theory [4] which both express the effective bending rigidities of mixed monolayers and bilayers as functions of molecular parameters.

The other approach, called the hat model [5], starts from local bending fluctuations of the planar membrane. Each molecule in a monolayer (or pair of opposite molecules in a bilayer) is regarded as a spherical cap which in the rest of the membrane is associated with a brim of zero mean curvature. Local curvature fluctuations come about by two mechanisms, the molecular bending fluctuations and the lateral diffusion of conical membrane defects, if such defects exist [5]. In mixed membranes, the subject of the present paper, local curvature fluctuations are produced by fluctuating cap curvatures and the diffusion of surfactant molecules of different

spontaneous curvature. A membrane cannot be smooth, even in the absence of any thermally excited bending, if the component molecules differ in spontaneous curvature.

The bending rigidity of mixed monolayers is in general smaller than the weighted average of the component rigidities. In the continuum model the reduction takes place because the concentrations of surfactants of different spontaneous curvature adjust to a given curvature (if there are appropriate reservoirs). In the hat model, the lateral diffusion of molecules of different spontaneous curvature gives rise to an increase of the total strength of the local curvature fluctuations. This translates, through the equipartition theorem, into an additional contribution to the membrane flexibility.

Based on a microscopic description of membrane curvature, the hat model is more realistic and, therefore, more complex than the continuum model. Its straightforward application is restricted to the almost unstressed membrane near its spontaneously curved state, and a complete description exists only for the case of a planar equilibrium state.

In the following, we will first derive a formula for the flexibility of two-component monolayers, employing local bending fluctuations. The hat model is shown to give the same effective bending rigidity for mixed monolayers as does the continuum model. In the case of mixed bilayers, to be treated next, the hat model predicts qualitatively new results which are missed in the continuum model. This is because the typical frustration of monolayer spontaneous curvature in a bilayer can be alleviated in a mixed bilayer. The local energy of frustration depends on whether equal or unequal molecules face each other across the middle surface of the bilayer. Taking a preference for unequal molecular pairings into account, we obtain a further increase of the flexibility of the two-component bilayer.

Finally, we consider partially polymerized surfactant bilayers, assuming each of the polymers to be embedded in one of the monolayers. For long enough polymer chains the multiple local frustration across the bilayer mid-surface can be so strong as to make polymers in opposite monolayers avoid each other. This is in addition to the well-known segregation of nonintersecting polymer chains sharing the same two-dimensional space, i.e. the same monolayer. We derive a formula for the critical degree of polymerization below which this segregation takes place, assuming semidilute polymer solutions of equal concentration in both monolayers. Possible consequences of the new segregation effect are a near divergence of the flexibility and a considerable roughness of the bilayer. In suitable cases, the latter may result in simultaneous outward and inward budding of bilayer vesicles, as has recently been observed after partial polymerization by Sackmann and coworkers [6].

2. Hat model for the monolayer.

Like nonlocal descriptions of membrane bending fluctuations, the hat model starts from the bending energy per unit area of membrane in its usual form,

$$g = \frac{1}{2} \kappa (J - J_0)^2 + \bar{\kappa} K . \quad (1)$$

Here $J = c_1 + c_2$ is the total curvature, i.e. twice the mean curvature, and $K = c_1 c_2$ is the Gaussian curvature, while g itself is a second-order expansion of the bending energy in the principal curvatures c_1 and c_2 about the flat state. The elastic parameters are the bending rigidity κ , the bending modulus of Gaussian curvature, $\bar{\kappa}$, and the spontaneous curvature J_0 . Unless otherwise stated, we will take $\bar{\kappa}$ to be uniform. The Gaussian curvature term in (1) can then be omitted since its integral is known to depend only on membrane topology which is not affected by fluctuations.

A simple and complete description of the hat model is possible when the membrane is flat in its equilibrium state ($J_0 = 0$). We first consider a flat monolayer consisting of a single species

of molecules of zero spontaneous curvature. Each molecule is viewed as a circular (or hexagonal) disk. Its total curvature, assumed to be uniform, undergoes thermal fluctuations about a mean value which is zero in our example. Let us assume for a moment that there is a single molecule of nonvanishing total curvature in the membrane. It will form a spherical cap which is surrounded by an axisymmetric brim (or foot) whose shape follows from the requirement of zero mean curvature. Cap and brim together make up the hat, as illustrated by figure 1. With z being a coordinate parallel to the axis of rotation, the most general axisymmetric shape of zero mean curvature is the catenoid

$$z - z_0 = \pm r_0 \ln \left(\frac{r}{r_0} + \sqrt{\frac{r^2}{r_0^2} - 1} \right) \quad (2)$$

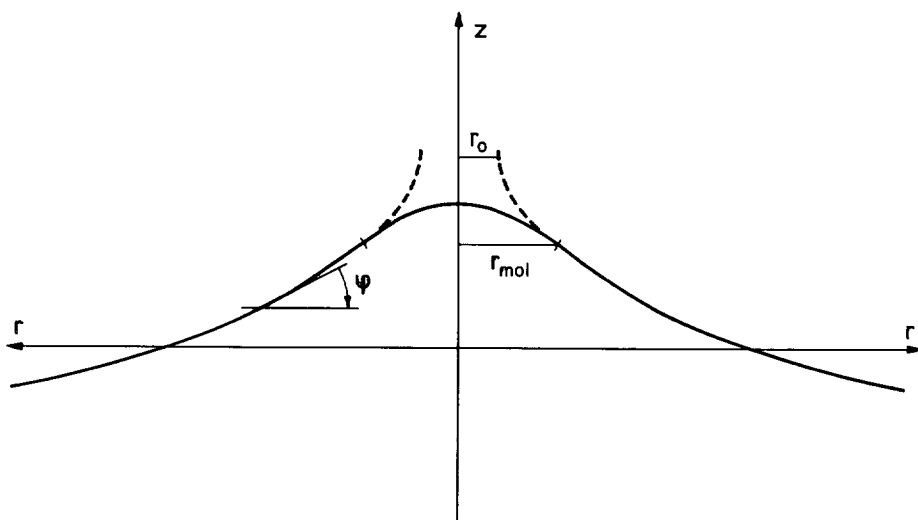


Fig. 1. — Schematic cross section of a single hat through its symmetry axis. The spherical cap in the center extends to $r = r_{\text{mol}}$ and is followed at larger r by the brim of zero mean curvature. The dashed line continues the catenoid representing the brim to its innermost point. The slope (= gradient angle) of the hat is continuous at $r = r_{\text{mol}}$. The equal but opposite principal curvatures of the brim vary as $1/r^2$ at large enough r .

where $r \geq r_0$ is the radius [7]. There is always a brim obeying (2) that can be matched, with a continuous gradient, to a given spherical cap. We are interested here only in weakly bent molecules, i.e. the case $\varphi^2(r_{\text{mol}}) \ll 1$ where φ is the gradient angle of the membrane and $r_{\text{mol}} \geq r_0$ the molecular radius. This permits, for $r > r_{\text{mol}}$, use of the approximations

$$z - z_0 = \pm r_0 \ln \frac{2r}{r_{\text{mol}}} \quad (3)$$

and, especially,

$$\varphi(r) = \frac{dz}{dr} = \varphi(r_{\text{mol}}) \frac{r_{\text{mol}}}{r} \quad (4)$$

If all the molecules are free to form spherical caps, the curvature of a molecule is determined by its own total curvature and by the saddle curvature (with $J = 0$) produced by the other

molecules. We rely on the superposition principle to describe this situation, which is legitimate as long as the mean square gradient angle is everywhere much less than unity in a membrane of zero (average) spontaneous curvature. The precise shape of a hat in a spontaneously curved membrane is unknown, but we expect the hat model to remain valid for a spherically curved membrane with $J = J_0$. Accordingly, we allow in the following formulas for a nonzero spontaneous curvature.

Since no bending energy resides in the brim associated with a spherical cap (if the Gaussian curvature term in (1) is discarded), the fluctuations of the total curvature of each molecule obey the equipartition theorem which in its usual form reads

$$\frac{1}{2} \kappa \langle (J - J_0)^2 \rangle a = \frac{1}{2} kT. \quad (5)$$

Here $a = \pi r_{\text{mol}}^2$ is the molecular area, k Boltzmann's constant, and T temperature. The ensemble of local bending modes is equivalent to the ensemble of the usual Fourier modes of membrane undulations, with a being related to the upper wave vector cutoff [5].

Solving (5) for $1/\kappa$, we obtain

$$\frac{1}{\kappa} = \langle (J - J_0)^2 \rangle \frac{a}{kT}. \quad (6)$$

This relationship expressing the flexibility as a function of the local bending fluctuations can be generalized to mixed membranes. They are characterized by two kinds of local fluctuations, the thermally excited elastic bending of the molecules and the change of local spontaneous curvature through the lateral diffusion of different surfactant molecules. The two kinds of fluctuations are statistically independent as the bending fluctuations of a particular molecule do not depend on its position on the membrane surface. Therefore, the effective flexibility $1/\kappa_{\text{eff}}$ controlling undulations and other deformations can be written as the sum of two parts

$$\frac{1}{\kappa_{\text{eff}}} + \frac{1}{\kappa_{\text{el}}} + \frac{1}{\kappa_{\text{diff}}} = [\langle (J - J_0)^2 \rangle_{\text{el}} + \langle (J - J_0)^2 \rangle_{\text{diff}}] \frac{a}{kT}, \quad (7)$$

the first resulting from elastic bending fluctuations and the second from lateral diffusion. We have to assume here that every molecular location is independent of all others, especially its neighbors, which implies random mixing for the diffusive part. The effective rigidity given by (7) should apply if the scale of the deformation is larger than the mean distance of the less concentrated monolayer component.

Let us now calculate the effective flexibility of a monolayer consisting of two surfactants 1 and 2 with equal molecular areas $a_1 = a_2 = a$ and equal molecular bending rigidities $\kappa_1 = \kappa_2 = \kappa_{\text{el}}$, but different molecular spontaneous curvatures $J_1 \neq J_2$. The diffusive contribution to the local curvature fluctuations may be expressed by

$$\langle (J - J_0)^2 \rangle_{\text{diff}} = (J_1 - J_0)^2 w_1 + (J_2 - J_0)^2 w_2 \quad (8)$$

with

$$J_0 = J_1 w_1 + J_2 w_2 \quad (9)$$

and

$$w_1 = \frac{N_1}{N_1 + N_2}, \quad w_2 = \frac{N_2}{N_1 + N_2} \quad (10)$$

Here w_1 and w_2 are the probabilities of finding surfactant 1 or 2, respectively, N_1 and N_2 being the numbers of molecules in the monolayer. Equation (8) is easily transformed into

$$\langle (J - J_0)^2 \rangle_{\text{diff}} = (J_1 - J_2)^2 w_1 w_2 \quad (11)$$

so that (7) takes the form

$$\frac{1}{\kappa_{\text{eff}}} = \frac{1}{\kappa_{\text{el}}} + \frac{(J_1 - J_2)^2 a N_1 N_2}{kT(N_1 + N_2)^2} \quad (12)$$

The last equation recovers the result predicted by the continuum theory [4, 8] for the same system in the case of zero spontaneous curvature ($J_0 = 0$).

We checked that the following natural generalization of the hat model preserves agreement with the continuum theory when the surfactant molecules differ not only in spontaneous curvature but also in molecular area ($a_1 \neq a_2$), and bending rigidity ($\kappa_1 \neq \kappa_2$). Equation (6) is replaced by

$$\frac{1}{\kappa_{\text{eff}}} = \langle (J - J_0)^2 \rangle \frac{\bar{a}}{kT} \quad (13)$$

with

$$\bar{a} = a_1 w_1 + a_2 w_2 \quad (14)$$

and

$$\langle (J - J_0)^2 \rangle \bar{a}^2 = [\langle (J - J_1)^2 \rangle_1 + (J_1 - J_0)^2] a_1^2 w_1 + [\langle (J - J_2)^2 \rangle_2 + (J_2 - J_0)^2] a_2^2 w_2. \quad (15)$$

The subscripts 1 and 2 denote the mean square bending fluctuations of surfactant 1 and 2, respectively. The two terms carrying a subscript contribute to $1/\kappa_{\text{el}}$, the others to $1/\kappa_{\text{diff}}$. The probabilities w_1 and w_2 as given by (10) are retained, although modifications may apply for $a_1 \neq a_2$. The same naive random mixing was adopted in this case in the continuum theory. One of the results obtained from (10) and (13-15) is

$$\frac{1}{\kappa_{\text{el}}} = \frac{(a_1/\kappa_1) N_1 + (a_2/\kappa_2) N_2}{a_1 N_1 + a_2 N_2} \quad (16)$$

a formula used first in the continuum model, but inspired by the hat model [9].

No direct comparison of the two models is possible for $J_0 \neq 0$ as the hat model applies to (small enough) deformations of the spontaneously curved state of the monolayer with spherical curvature $J = J_0$, while the bending rigidity of the thermodynamic theory derives from a second order expansion of the bending energy about the flat state. The continuum model starting from the flat state contains a correction of the bending rigidity which is due to the monolayer bending tension and vanishes for zero monolayer spontaneous curvature [4, 10]. This correction vanishes generally for an expansion about the spontaneously curved state ($J = J_0$). It exists for the bilayer with monolayer bending frustration, to be treated below, but will be omitted in the present article.

Difficult problems arise if $\bar{\kappa}_1 \neq \bar{\kappa}_2$, i.e. if the assumption of a uniform modulus of Gaussian curvature has to be abandoned. They cannot be handled by a continuum theory averaging over molecules. Inspection of the hat model suggests that in a monolayer consisting of two different surfactants the bending fluctuations of the surfactant molecules with the larger $\bar{\kappa}$ should be diminished and those of the other molecules enhanced, as compared to the one-component

monolayers. The situation is complicated by an interaction between surfactant molecules through the Gaussian curvature which the spherical cap produces in its surroundings. The negative Gaussian curvature « attracts » the molecules with the larger $\bar{\kappa}$ and « repels » the others with regard to the spherically curved center. This is a special case of the $1/r^4$ interaction between disklike membrane singularities recently predicted by Goulian, Bruinsma and Pincus [11]. Any selective mutual repulsion or attraction of molecules is in conflict with the assumption of random mixing.

In order to estimate the interaction energy that results from $\Delta\bar{\kappa} = \bar{\kappa}_1 - \bar{\kappa}_2$, we consider two nearest-neighbor molecules of equal area $a = \pi r_{\text{mol}}^2$. One of them (type 1) is a fluctuating spherical cap, the other (type 2) interacts with it through the Gaussian curvature of the brim which, according to (4), is $-\left[\varphi(r_{\text{mol}}) r_{\text{mol}}/r^2\right]^2$. (Here we make use of the fact that for $J = 0$ the equatorial principal curvature is equal but opposite to the meridional principal curvature, $\varphi(r_{\text{mol}}) r_{\text{mol}}/r^2$). Considering a nearest-neighbor molecule, we estimate its average interaction energy from the average Gaussian curvature at $r = 2 r_{\text{mol}}$, as

$$\Delta\bar{\kappa} \langle K(2 r_{\text{mol}}) \rangle a = \Delta\bar{\kappa} \langle \varphi^2(r_{\text{mol}}) \rangle \frac{\pi}{16}. \quad (17)$$

With $\langle \varphi^2(r_{\text{mol}}) \rangle^{1/2} = 3^\circ$, the value computed from the hat model for $\kappa = 1 \times 10^{-19}$ J regardless of molecular area [5], one finds $5.3 \times 10^{-4} \Delta\bar{\kappa}$ for the interaction energy. Assuming $\Delta\bar{\kappa} = 1 \times 10^{-19}$ J, probably a generous guess, and $kT = 4 \times 10^{-21}$ J, one arrives at ca. $10^{-2} kT$. While this energy seems small enough to be neglected, gradient angles of 10° or more of the spherical cap boundary could seriously impair random mixing. In the following treatment of bilayers we return to the simple case $\kappa_1 = \kappa_2$, $\bar{\kappa}_1 = \bar{\kappa}_2$ and $a_1 = a_2$.

3. Hat model for the bilayer.

Deriving the effective bending rigidity of the symmetric bilayer from the hat model is straightforward on one hand since the spontaneous curvature of a bilayer with equal sides is zero for reasons of symmetry. On the other hand, there is a new degree of freedom in mixed bilayers because a given molecule in one of the monolayers can face either an equal molecule or a different one in the other monolayer. For simplicity, we will assume in our calculations that the pairings are precise so that each surfactant molecules faces just one counterpart in the other monolayer.

The bending rigidity of a symmetric bilayer is twice that of the monolayer provided there is free exchange of both types of surfactant molecules and no local molecular coupling between the monolayers. The absence of such a coupling seems to be a common (tacit) assumption of continuum theories. A doubling of the bending rigidity is also predicted by the hat model for the one-component bilayer, the local mean square bending fluctuation of a pair of opposite molecules being half that of a single molecule.

In the one-component symmetric bilayer the spontaneous curvatures of the molecules on the two sides counteract each other so that both monolayers cannot assume their spontaneous curvatures but remain flat. The energy ε of this frustration is for a pair of opposite molecules

$$\varepsilon = \kappa J_m^2 a, \quad (18)$$

where κ still refers to the monolayer and J_m is the molecular spontaneous curvature. Inserting $\kappa = 0.5 \times 10^{-19}$ J, $a = 0.6 \text{ nm}^2$, and $J_m = 2 \times 10^8 \text{ m}^{-1}$, values typical of phosphatidylethanolamine [12], one computes

$$\varepsilon = 1.2 \times 10^{-21} \text{ J}. \quad (19)$$

The result is less than $kT = 4 \times 10^{-21}$ J (at room temperature). The energy of frustration could be increased by using surfactant molecules with larger areas and should in general be smaller than our estimate which is based on a rather large spontaneous curvature.

In mixed symmetric bilayers the local energy of bending frustration depends on which of the molecules are paired. Overall, the surfactant molecules will tend to pair in such a way that the total energy of bending frustration is less than with random pairing. This implies that in a bilayer consisting of two surfactants of different spontaneous curvature unequal pairs will be favored over equal ones. The associated increase of the number of pairs with a net spontaneous curvature leads to an increase of the bilayer flexibility due to molecular diffusion. In mixed bilayers, lateral diffusion includes changes in local pairing.

In order to calculate the diffusive contribution to the flexibility of a two-component bilayer, we imagine two types of surfactant molecules, 1 and 2, with equal areas but different spontaneous curvatures. The numbers of the two types of molecules are N_1 and N_2 , respectively, now in each monolayer. In the relaxed state the different spontaneous curvatures manifest themselves by different cone shapes. Examples are sketched in figure 2 which also defines the probabilities w_{ij} of the four possible pairings. The two unequal pairs should have the same probability for symmetry reasons, i.e.

$$w_{12} = w_{21} = w'. \quad (20)$$

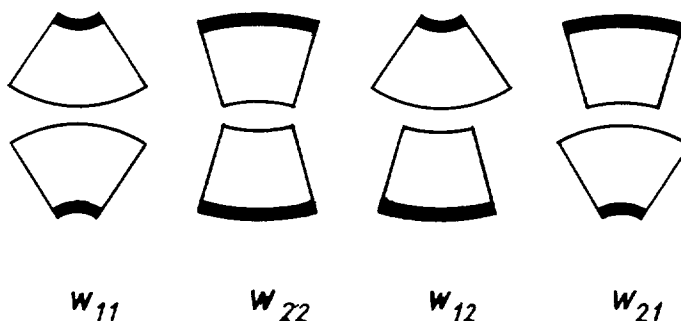


Fig. 2. — The four possible one-to-one molecular pairings between the monolayers of a two-component bilayer. The two surfactants differ only in spontaneous curvature. Cross sections of the spontaneously curved molecules are shown. The figure defines the probabilities w of the pairings.

The probabilities of finding in a monolayer molecules of type 1 or 2 obey

$$w + w_{11} = \frac{N_1}{N_1 + N_2} \quad (21)$$

$$w + w_{22} = \frac{N_2}{N_1 + N_2} \quad (22)$$

since w_{11} and w_{22} are the probabilities of finding equal pairs. Two unequal pairs may transform into two equal pairs and *vice versa*. The probabilities of all four pairings are related through the detailed balance condition

$$w_{11} w_{22} = w'^2 e^{-E/kT} \quad (23)$$

where $E > 0$ is the energy difference between the two equal and the two unequal pairs. Equations (21) to (23) lead to

$$w = \frac{1}{2(1 - e^{-E/kT})} \left[1 - \sqrt{1 - \frac{4 N_1 N_2}{(N_1 + N_2)^2} (1 - e^{-E/kT})} \right]. \quad (24)$$

The diffusive part of the mean square local curvature fluctuations of the bilayer is obtained by inserting this into the formula

$$\langle J^2 \rangle_{\text{diff}} = \left(\frac{J_1 - J_2}{2} \right)^2 2 w \quad (25)$$

which takes the local bilayer spontaneous curvature to be $(J_1 - J_2)/2$ or zero for unequal or equal pairings, respectively, J_1 and J_2 being the spontaneous curvatures of the two types of molecules in a free monolayer. Here we have used the assumption of equal bending rigidities, $\kappa_1 = \kappa_2$.

It is interesting to inspect the two limiting cases of w and the associated bilayer flexibilities following from (24) and (25). For $E = 0$ one finds

$$w = \frac{N_1 N_2}{(N_1 + N_2)^2} \quad (26)$$

while for $E = \infty$ one has

$$w = \frac{1}{2} \left[1 - \sqrt{1 - \frac{4 N_1 N_2}{(N_1 + N_2)^2}} \right] \quad (27)$$

which is always larger than (26). Inserting first (26) in (25) gives diffusive curvature fluctuations just half as strong as those of the monolayers. Because of (7), the diffusive contribution to the membrane flexibility, $(1/\kappa)_{\text{diff}}$, is also halved, in agreement with the continuum theory. If (27) applies instead of (26), w and thus $(1/\kappa)_{\text{diff}}$ are increased. The effect has its maximum for $N_1 = N_2$ where the two quantities are doubled. Accordingly, $1/\kappa_{\text{diff}}$ comes out equal for bilayer and monolayer in this particular case. For the typical lipid molecules with two hydrocarbon chains the energy E will not exceed 2ε as given by (19). However, the polymers in a partially polymerized bilayer may display very pronounced mutual avoidance even for $E \ll kT$ since there is the cooperative effect of many pairings of their monomers when two long polymer chains in opposite monolayers overlap. The case of polymers will be considered next.

4. Partially polymerized bilayers.

It is well-known that certain surfactants containing unsaturated bonds in their hydrocarbon chains can be polymerized *in situ*, i.e. in monolayers and bilayers [13]. At least in certain materials the photochemically triggered polymerization produces long linear chains in a kind of domino effect [6]. In bilayers these chains seem restricted to one of the monolayers where they probably do not intersect. The following calculations refer to polymers which are fully flexible nonintersecting chains confined to one of the monolayers.

Let us consider a semidilute solution of such polymers in a partially polymerized monolayer. In the semidilute state the polymers form blobs, thus filling the available two-dimensional space rather uniformly [14]. A collection of equally long polymers in two dimensions has been predicted to display a segregation effect [14]. It has recently been confirmed by computer simulation [15] and approximately quantified in terms of a line tension [16].

In a partially polymerized bilayer there will be polymers in both monolayers. If there is no polymer interaction between the monolayers the polymer concentration should be uniform in both of them. However, if the monomer spontaneous curvature changes with polymerization, the polymers will avoid each other to relieve frustration so that an additional segregation effect may act between polymers in opposite monolayers. A different spontaneous curvature could arise, e.g., from a change of the monomer conical shape upon polymerization. If the polymers are long enough, this kind of segregation is possible even in the presence of a certain overlap of the polymers which is unavoidable with $E < kT$.

For a prediction of whether or not polymers in opposite monolayers will segregate we imagine two polymer chains, one in either monolayer, of equal length and packed densely enough to form semidilute solutions. In the absence of polymer interaction between the monolayers each chain will spread over the whole available area A . Its free energy F_{bl} of blob formation should approximately equal kT times the number of blobs. We express it by

$$F_{bl} = kT \frac{A}{R_F^2} \quad (28)$$

where

$$R_F = sN_{bl}^\nu \quad (29)$$

is the Flory radius of the blobs, N_{bl} being the number of polymerized monomers which on average belong to a blob. The polymer chain is assumed to be fully flexible so that s equals the monomer distance in a lattice model [17]. The Flory value of the critical exponent is $\nu = 3/4$ in two dimensions [14]. The number of polymerized monomers in a blob is related to the total number N of polymerized monomers through

$$\frac{AN_{bl}}{(sN_{bl}^\nu)^2} = N \quad (30)$$

Computing F_{bl} as a function of N from (28) to (30) and substituting the fractional concentration of polymerized monomers

$$\Phi = \frac{Ns^2}{A} \quad (31)$$

for N , one obtains, with $\nu = 3/4$,

$$F_{bl} = kT \frac{A}{s^2} \Phi^3 \quad (32)$$

This energy has to be compared to the interaction energy F_{int} of polymers belonging to opposite monolayers. Distinguishing by subscripts between inner and outer monolayer, we may write in a mean field approximation

$$F_{int} = E \frac{A}{s^2} \Phi_{in} \Phi_{out} \quad (33)$$

The total energy of the two interacting monolayers is then

$$F = F_{int} + F_{bl, in} + F_{bl, out} = \alpha A \Phi_{in} \Phi_{out} + \beta A (\Phi_{in}^3 + \Phi_{out}^3) \quad (34)$$

where α and β are the coefficients defined by (32) and (33), respectively. In order to check the stability of a uniform density Φ_0 , equal in both monolayers, we now raise the concentration to $\Phi_0 + \Delta\Phi$ in one half of either monolayer and lower it to $\Phi_0 - \Delta\Phi$ in the other half. The opposite changes are made in the other monolayer so that the total concentration of polymerized monomers remains uniform in the bilayer. The total energy in this case obeys

$$F/A = \alpha (\Phi_0 + \Delta\Phi)(\Phi_0 - \Delta\Phi) + \beta [(\Phi_0 + \Delta\Phi)^3 + (\Phi_0 - \Delta\Phi)^3] \quad (35)$$

which is easily transformed into

$$F/A = \alpha \Phi_0^2 + 2\beta \Phi_0^3 - (\alpha - 6\beta \Phi_0)(\Delta\Phi)^2. \quad (36)$$

The result suggests that the two polymers are spread all over the respective monolayers for $\Phi_0 > \Phi_{0,c} = \alpha/6\beta$ while they are segregated and confined to different halves of the bilayer area for $\Phi_0 < \Phi_{0,c}$. The critical concentration $\Phi_{0,c}$ of polymerized monomers is readily seen to be

$$\Phi_{0,c} = \frac{\alpha}{6\beta} = \frac{1}{6} \frac{E}{kT} \quad (37)$$

Inserting $E/kT = 2 \varepsilon/kT = 1/2$ (from the above estimate), one finds $\Phi_{0,c} = 0.08$. According to this crude estimate, segregation should be possible at the early stages of membrane polymerization. Since segregation implies the creation of bilayer spontaneous curvature, the bending rigidity of the bilayer for large-scale deformations should be zero at the threshold of segregation. Stable deformations of the bilayer from the flat state may be expected at lower polymer concentrations.

So far, we have considered only two polymers, one in either monolayer. Let us now turn to the more realistic situation of many polymers forming semidilute solutions in both monolayers. The segregation of long enough polymers belonging to different monolayers, in addition to the familiar segregation within each monolayer, is likely to break up the bilayer into patches of opposite spontaneous curvature. Patches seem more favorable than the separation into two continuous phases for reasons of entropy and because they permit some overlap between polymers in opposite monolayers. Each polymer should form a roughly circular patch, its size being inversely proportional to the total number of polymer chains (if they are equally long). Since the patches are like molecules with a very large area they may be expected, in view of (12), to result in a near divergence of the effective flexibility, even though their average spontaneous curvature is weak as compared to monomer spontaneous curvatures. In addition, the patches may produce a pronounced roughness of the bilayer. When the area A_p of a patch and its spontaneous curvature are large enough to form a sphere with $J = J_0$, i.e. for

$$A_p J_0^2 \geq 16 \pi, \quad (38)$$

the curved patch can form an outward or inward bud, depending on the sign of its spontaneous curvature. Lateral tension of the membrane may cause an energy barrier to the budding transition [18].

Simultaneous outward and inward budding following partial polymerization has recently been observed on lipid bilayer vesicles by Sackmann and coworkers [6]. It will be interesting to analyze these observations in detail in order to check the concentration of polymerized monomers. In a dilute solution of polymers, budding could be caused by a single polymer chain. However, such buds should deviate strongly from the spherical shape as the density of polymerized monomers is much less uniform in an unfolded polymer (i.e. a single blob) than in an assembly of blobs.

5. Conclusion.

The present article is a first attempt to deal with the problem of local interaction between molecules in opposite monolayers of a mixed bilayer. We considered only the interactions due to molecular bending frustration, adopting here a word that has long been used by Charvolin *et al.* [19] in connection with cubic phases formed by one-component bilayers. While this interaction favors pairings of unequal surfactant molecules, the van der Waals interaction between the monolayers could have the opposite effect. Some other simplifications made remain to be justified. In particular, we assumed one-to-one pairing of the molecules across the bilayer mid-surface which is not the correct description but seems defensible within limits, giving reasonable results for $E < kT$.

Very interesting problems, which we hope to tackle elsewhere, are connected with the embedding of a polymer chain in the otherwise monomeric membrane. We have regarded the polymer chain as a series of loosely linked monomers with a conical shape different from that of free monomers. In other words, the persistence length of the polymer in the plane of the membrane has been assumed to coincide with the molecular distance. The actual polymer chain may have a backbone with its own preferred shape and bending elasticity and this could give rise to additional effects. For instance, an augmented persistence length in the plane of the membrane increases the number of blobs, thus lowering $\Phi_{0,c}$ as calculated from (37). A stiff backbone may, in addition, warp the membrane if it possesses a spontaneous curvature normal to the membrane. The probable result would be an enhanced bending frustration when polymers in opposite monolayers cross each other, and thus a rise of $\Phi_{0,c}$. Finally, a mean field theory will exaggerate the interaction of polymers in different monolayers. Correcting this would result in a smaller theoretical value of $\Phi_{0,c}$.

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- [9] Two remarks may be helpful in checking that the agreement of the two theories is complete. The formula for the effective bending rigidity of our continuum model (with $J_1 \neq J_2$, $\kappa_1 \neq \kappa_2$, $a_1 \neq a_2$) simplifies greatly after some manipulations in the special case $J_0 = 0$. The bending rigidities κ_{eff} and κ_{el} of the hat model respectively correspond to κ and κ_0 of the continuum model for the same system.
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