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Coupling between line tension and domain contact angle in heterogeneous membranes

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Abstract

The compositional differences between domains in phase-separated membranes are associated with differences in bilayer thickness and moduli. The resulting packing deformation at the phase boundary gives rise to a line tension, the one dimensional equivalent of surface tension. In this paper we calculate the line tension between a large membrane domain and a continuous phase as a function of the thickness mismatch and the contact angle between the phases. We find that the packing-induced line tension is sensitive to the contact angle, reaching a minimum at a specific value. The difference in the line tension between a flat domain (that is within the plane of the continuous phase) and a domain at the optimal contact angle may be of order 40%. This could explain why previous calculations of the thickness mismatch based line tension tend to yield values that are higher than those measured experimentally.

Keywords: Phase separation; Line tension; Vesicle

1. Introduction

Multi-component model membranes have been found to phase separate, resulting in coexistence between domains of different compositions [1–4]. Phase coexistence in these two dimensional systems gives rise to a line tension (the one dimensional equivalent of surface tension), which affects the kinetics of domain growth and equilibrium domain size. An interesting observation found in fluorescence studies is that the domains do not necessarily remain within the plane of the vesicle or continuous phase, but form spherical caps [5–8]. Such shape transitions in phase-separated membranes are thought to be driven by the need to reduce the length of the contact line, while keeping the area of each domain fixed, and arrested by the associated bending penalty [9–11].

Despite extensive studies of phase coexistence in model membranes [1–4], few studies measured the line tension in these systems [5,7,12,13]. Initial measurements obtained values of order 1 pN [5,7], but more recent work suggests that the line tension may be much higher in some cases. Blanchette et al. [12] find the line tension in phase-separated 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC)/galactosylceramide (GalCer) membranes to be 1.7 ± 0.25 pN, but in DOPC/1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) it is found to be 4.3 ± 0.5 pN. They [12] suggest that the difference in the line tension between the two systems may be due to the differences in the hydrophobic mismatch between the domains, which is 1.8 nm in the DSPC case but only 0.9 nm for the GalCer case [14]. Tian et al. [13] investigated the effect of composition on line tension in three component mixtures of DOPC, cholesterol and egg sphingomyeline (ESM), finding that the average line tension increases, with increasing cholesterol content, from 0.5 to 3.3 pN. However, it is interesting to note that several individual samples displayed much higher values of line tension that may reach 5 pN [13].

The line tension in phase-separated membranes is composed of two contributions. The first is a chemical component associated with differences in composition between the phases, and the second is a packing contribution arising from differences in thickness and bilayer moduli. The chemical contribution may be negligible in many systems due to the relatively minor compositional

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differences between the phases [1–4]. Molecular models for lipid packing have found a correlation between lipid packing and line tension [14]. The coupling between a thickness mismatch in phase-separated membranes, which causes a packing perturbation, and the line tension has been previously calculated [15–17]. As may be expected, the line tension is highly sensitive to the thickness mismatch between the phases [15–17]. Examining the effect of domain size and spacing on the line tension [15–17] showed that the line tension should be maximal, for a single domain, when the domain radius is smaller than order 20 nm. This suggests that small domains are unstable and would either coalesce to larger sizes or dissolve. However, domains larger than approximately 30–50 nm are predicted to be meta-stable and may be long-lived due to repulsive interactions between domains at moderate spacing. Substituting typical values for the moduli of the two membrane phases and the thickness mismatch yields values of 0.2 to 3.5 kT/nm, or about 1 to 15 pN, for the line tension [15–17].

The values calculated by the packing models for the thickness mismatch contribution to the line tension [15–17] are generally higher than those measured experimentally, despite the fact that they are expected to be a *lower limit* that may increase when the contribution of the chemical composition difference is included. Is there another mechanism that can reduce the packing line tension?

Models examining the deformation energy imposed by transmembrane proteins (see, for example, [18–20]) suggest that the penalty due to a thickness mismatch is sensitive to the contact angle between the protein and the bilayer. We hypothesize here that the formation of a finite contact angle between the domain and the plane of the continuous phase (see Fig. 1) may reduce the value of the line tension due to the thickness mismatch. Such a contact angle would be on lengthscales of order the bilayer thickness, and thus not observable by current domain imaging techniques [5–8]. However, although the micron-scale contact angle observed in some systems [5–8] is likely dominated by the need to reduce the contact line between the domain and the continuous phase, it does not contradict the possibility of a contact angle on smaller lengthscales that reduces the value of the line tension. Recently, Fournier and Ben Amar [21] examined the effect of a contact angle (or 'a crease' in their terms) between a membrane domain and a continuous phase. They conclude that the stresses at the interface between membrane domains yield a line tension that is contact angle dependent. Fournier and Ben Amar [21] show that the line tension can obtain a sharp minimum at a particular value of the contact angle in some cases.

The Fournier and Ben Amar [21] analysis clearly supports our hypothesis that a molecular scale contact angle can reduce the line tension between membrane domains. However, their analysis, which is limited to domains with strong spontaneous curvature such as biological rafts, cannot explain the low line tension measured in synthetic vesicles [5,7,12,13]. Moreover, their [21] analysis is based on a continuous model where the coupling between the thickness and the shape of the membrane was taken to be (somewhat arbitrarily) linear.

In this paper we examine the effect of the contact angle between a domain phase and a continuous membrane phase on the packing, or thickness mismatch contribution to the line tension. Our analysis focuses on domains that have zero spontaneous curvature, and uses a meso-scale model which has been found to successfully apply to membrane perturbation by proteins [18–20] to couple between the membrane profile and deformation penalties. We find that allowing for a contact angle between the domain and the continuous phase may reduce the line tension by up to 40%, even in systems where both phases have zero spontaneous curvature. Thus, it is possible that the low values of line tension measured experimentally [5,7,12,13], when compared to the predictions of packing models [15–17] may be due to this additional degree of freedom.

2. Model

Previous studies [15–18] have shown that a thickness mismatch at the boundary of a self-assembled membrane leads to a perturbation in the bilayer profile and an energetic penalty that can be correlated to the line tension. Taking the unperturbed monolayer thickness to be h, the degree of perturbation may be defined by the normalized thickness of the monolayer at distance

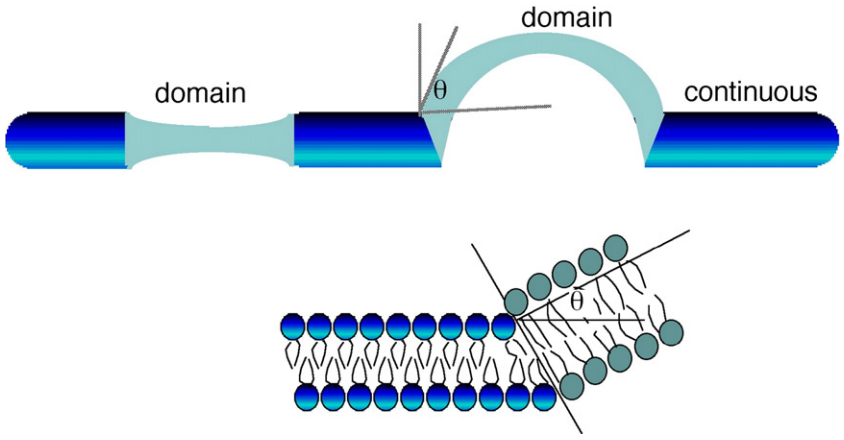

Fig. 1. A sketch of our system. The domain phase and the continuous phase differ in their thickness, and possibly also their bending and area moduli. The energetic penalty due to the formation of a deformed perimeter (for the domain and the continuous phase) is the line tension. The domain may remain in the plane of the continuous phase, or form a contact angle θ with the continuous phase. Note that in our notation, a flat domain is denoted by $\theta=0$.

z from the perturbation boundary, such that $\Delta(z)=h(z)/h-1$. The free energy penalty associated with the perturbation may be written, for a phase with zero spontaneous curvature, as [15–17]:

$$d\gamma_m = B\Delta^2 + 2Kh^2\left[\frac{d^2\Delta}{dr^2}\right]^2 \quad (1)$$

γ denotes the free energy penalty per unit length of the perturbation interface, namely, the line tension of one monolayer. B is the area stretch modulus, and K the bending modulus of the membrane.

The bending term in Eq. (1) requires a brief discussion: Monolayers and bilayers display a bending penalty which scales as $1/C^2$, where C is the curvature. The curvature is composed of two contributions: One is the global membrane curvature (e.g. the radius of curvature in a vesicle, or membrane fluctuations). The second is due to a local curvature on the molecular scale due to the insertion of a perturbation locus, e.g. by a membrane protein. Thus, a flat bilayer may display local bending due to the insertion an interface (see, for example, [16,18]).

The two curvatures are decoupled and additive, for example when considering the overall curvature in a vesicle with embedded proteins.

In Eq. (1) we consider only the contribution of the *local bending*, neglecting that of the overall vesicle radius and the macroscopic bending of the domain. Therefore, interface curvature is defined here by $d^2h/dz^2 \sim d^2\Delta/dz^2$ namely, the second derivative of the thickness as a function of distance from the perturbation center [18–20]. Thus, in our model the curvature term becomes zero when there is no bilayer perturbation.

In a phase-separated membrane, the free energy penalty associated with the interface is composed of two contributions: one for the domain phase (D) and one for the continuous phase (C). Since the moduli (K, B) of the two phases may differ significantly, the line tension is composed of two contributions

$$\gamma = \gamma_D + \gamma_C = 2\int_{-D_D}^{0}\left(B_D\Delta^2 + K_D h_D^2\left[\frac{d^2\Delta}{dz^2}\right]^2\right)dz + 2\int_{0}^{D_C}\left(B_C\Delta^2 + K_C h_C^2\left[\frac{d^2\Delta}{dz^2}\right]^2\right)dz \quad (2)$$

where $z=0$ denotes the interface between the phases, D is the dimension (along the z axis) of a phase, and the subscripts D, C refer to the domain and continuous phase, respectively. Note that here the line tension is composed of the contributions from *both* monolayers. At the interface, the thickness of the two phases must match (see Fig. 1), and the slope of the domain phase is set by the contact angle (see Fig. 1). The remaining boundary conditions are determined by the functional minimization as obtained by calculus of variations (see [17–20]).

3. Results and discussion

Minimization of the line tension with respect to the optimal membrane deformation profile in both the continuous and the domain phase yields the value of γ as a function of the phase moduli and thickness. In the limit where the domains are large (when compared to the bilayer thickness) and widely spaced, the line tension is found to vary with the contact angle as

$$\gamma(\theta) = \frac{B_D^{1/4}K_D^{1/4}\left\{49\sqrt{h_D B_D}B_C^{3/4}K_C^{1/4}(h_C-h_D)^2 + 42\sqrt{2}B_C^{3/4}B_D^{1/4}h_D K_D^{1/4}K_C^{1/4}(h_C-h_D)\sin\theta + \sqrt{K_D}\left(35B_C^{3/4}h_D^{3/2}K_C^{1/4} + 17B_D^{3/4}h_C^{3/2}K_D^{1/4}\right)\sin^2\theta\right\}}{14\sqrt{2h_D}\left(B_C^{3/4}h_D^{3/2}K_C^{1/4} + B_D^{3/4}h_C^{3/2}K_D^{1/4}\right)} \quad (3.a)$$

which reduces, when there is no thickness mismatch ($h_C=h_D$) to

$$\gamma(\theta) = \frac{B_D^{1/4}K_D^{3/4}\left(35B_C^{3/4}K_C^{1/4} + 17B_D^{3/4}K_D^{1/4}\right)\sin^2\theta}{14\sqrt{2h}\left(B_C^{3/4}K_C^{1/4} + B_D^{3/4}K_D^{1/4}\right)} \quad (3.b)$$

If $\theta=0$ so that the domain is flat, Eq. (3.a). reduces to

$$\gamma(0) = \frac{7B_C^{3/4}B_D^{3/4}K_C^{1/4}K_D^{1/4}(h_C-h_D)^2}{2\sqrt{2}\left(B_C^{3/4}h_D^{3/2}K_C^{1/4} + B_D^{3/4}h_C^{3/2}K_D^{1/4}\right)} \quad (4)$$

as previously calculated [16]. Thus, the line tension increases with the degree of thickness mismatch h_C-h_D.

In Fig. 2 we plot the line tension (Eq. (3.a)) as a function of the contact angle. We see that when there is no thickness mismatch between the phases ($h_D=h_C$) the line tension is zero when the contact angle is 0, as expected: There is no penalty for interface formation if the phases have identical thicknesses if the domain remains within the plane of the continuous phase. However, forcing a domain without a thickness mismatch to protrude from the continuous phase ($\theta\neq0$) induces a packing *tilt* penalty which is

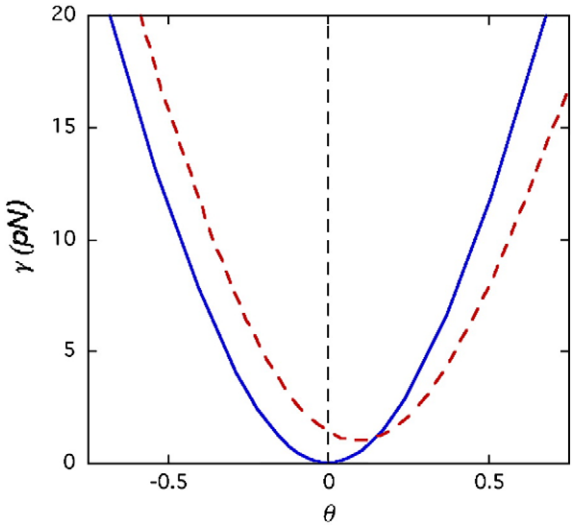

Fig. 2. The packing line tension, θ (in pN) as a function of the contact angle θ. For clarity we plot the angle relative to $\pi/2$ (when the domain is in the plane of the continuous phase). Solid line: No thickness mismatch between the domain and the continuous phase. Dashed line: A 20% thickness mismatch. Membrane parameters used are typical for such systems [18,19]: $K_C=1.2\cdot10^{-19}$, $K_D=0.56\cdot10^{-19}$ J, $B_C=260$ mN/m, $B_D=240$ mN/m, and $h_C=4.4$ nm (i.e. K is of order 50 kT, and B of order 50 kT/nm). We see that, as may be expected, when there is no thickness mismatch the packing line tension is zero when there is no contact angle between the phases, and the domain lies within the plane of the continuous phase 2, since in this case both phases are not deformed at the interface. In this case, forcing the domain to adopt another contact angle introduces a deformation, manifested by an increase in the line tension. However, when there is a thickness mismatch, the line tension is minimal at a specific contact angle that is not $\pi/2$ but is a function of the thickness mismatch (see Eq. (5)); yet, even in this optimal contact angle, there is some deformation of the phases so that the line tension is not zero.

manifested in a non-zero value of the line tension. May et al. [22] defined a membrane 'tilt modulus' k_t as $dF/A=(1/2)\,k_t t^2$, where F is the membrane free energy and t defines the degree of tilt. In our notation, t can be represented by $\sin\theta$, and F/A by γ/h. As a result, the effective tilt modulus for a system without thickness mismatch is, in our model, given by

$$k_t=\frac{B_D^{1/4}K_D^{3/4}\left(35B_C^{3/4}K_C^{1/4}+17B_D^{3/4}K_D^{1/4}\right)}{14h^{3/2}\sqrt{2}\left(B_C^{3/4}K_C^{1/4}+B_D^{3/4}K_D^{1/4}\right)} \tag{5}$$

substituting typical numbers for the moduli [23,24] yields values for k_t which are of order 0.3 kT/Å, quite similar to the 0.2 kT/Å calculated by May et al. [22].

In systems with a finite thickness mismatch ($h_C\neq h_D$) the minimum in the line tension shifts away from $\theta=0$. Also, unlike the thickness-matched case, even at the optimal contact angle the line tension is finite, due to the perturbation induced by the thickness mismatch. Minimization of the line tension with respect to the contact angle yields

$$\sin\theta^*=\frac{21\sqrt{2}B_C^{3/4}B_D^{1/4}h_DK_C^{1/4}(h_D-h_C)}{\left(35B_C^{3/4}h_D^{3/2}K_C^{1/4}K_D^{1/4}+17B_D^{3/4}h_C^{3/2}K_D^{1/2}\right)} \tag{6}$$

and the optimal (minimal) line tension is then

$$\gamma(\theta^*)=\frac{119B_C^{3/4}B_D^{3/4}K_C^{1/4}K_D^{1/4}(h_C-h_D)^2}{2\sqrt{2}\left(35B_C^{3/4}h_D^{3/2}K_C^{1/4}+17B_D^{3/4}h_C^{3/2}K_D^{1/4}\right)} \tag{7.a}$$

The ratio between the optimal line tension at the preferred contact angle θ and the flat-lying domain where $\theta=0$ is given by

$$\frac{\gamma(\theta^*)}{\gamma(0)}=\frac{17\left(B_C^{3/4}h_D^{3/2}K_C^{1/4}+B_D^{3/4}h_C^{3/2}K_D^{1/4}\right)}{\left(35B_C^{3/4}h_D^{3/2}K_C^{1/4}+17B_D^{3/4}h_C^{3/2}K_D^{1/2}\right)}\equiv\frac{17(1+\alpha)}{(35+17\alpha)} \tag{7.b}$$

where $\alpha=\left(B_D^{3/4}h_D^{3/2}K_D^{1/4}\right)/\left(B_C^{3/4}h_D^{3/2}K_C^{1/4}\right)$. Note that Eq. (7.b) does not strictly apply to thickness-matched phases where both $\gamma(\theta^*)$ and $\gamma(\theta)$ are zero. Applying typical numbers for the moduli and thickness [23,24] yields that the line tension at the optimal contact angle for a membrane with a 20% thickness mismatch between phases may be lower than the line tension of the flat domain by ~40%.

4. Conclusions

Thickness mismatch between membrane phases gives rise to a packing-induced line tension, arising from the deformation of the lipid organization near the interface. Previous studies [15–17] have calculated this line tension for domains embedded in a continuous phase, assuming that the domain remains within the plane of the vesicle, finding values for the line tension that are between 50% and 100% higher than those measured experimentally [5,7,12,13].

Several studies [5–8] find that phase-separated vesicles undergo shape transitions resulting in a finite contact angle between domains. In this paper we calculate the effect of a finite contact angle between a domain phase and a continuous phase on the packing line tension. As may be expected (Fig. 2), we find that the packing line tension is zero when there is no thickness mismatch and the domain contact angle is zero. 'Forcing' the domain to protrude and form a non-zero contact angle with the continuous phase leads, in this case, to an energetic penalty that is due to lipid tilt. However, unlike previous analysis where tilt was assigned its own modulus [may tilt], our model accounts for the tilt penalty through a combination of the area and bending moduli.

In systems where there is a thickness mismatch between the domain and continuous phases, we find that the line tension is quite sensitive to the contact angle (Fig. 2), achieving a minimum at a finite value of the contact angle that is set by the phase properties and the thickness mismatch (Eq. (6)). The reduction in the line tension due to the adoption of the optimal contact angle, when compared to the flat domain case, is significant and may be of order 40–50%. Moreover, such reductions in the line tension may be obtained at relatively low values of the contact angle. For example, a reduction of order 40% in the line tension, when compared to the flat domain, may be obtained for a thickness mismatch of order 20% if the domain angle is of order 0.23 rad, or 14°. These values are within the same order of magnitude as those calculated by Fournier and Ben Amar [21], although their analysis applies to small domains with high spontaneous curvature (while our domains are large and have zero spontaneous curvature).

It should be noted that in our calculations we did not account for saddle-splay deformation [25–27], so that our calculation strictly applies only to 'stripe' like domains. However, in systems with spherical symmetry such as circular domains, the bending and Gaussian moduli can be combined into an effective bending modulus whose magnitude is similar to the bending modulus K [28]. As a result, including the Gaussian modulus would lead to only a minor change in the value of α in Eq. (7.b), but would not affect our qualitative findings regarding the dependence of the line tension of the contact angle.

Our results suggest an explanation for the high values of previous estimates of the packing line tension, calculated for flat domains [15–18], when compared to the experimentally determined ones [5,7,12,13]. It should be emphasized, though, that the calculation presented here focuses on the line tension only. As previously shown [9,10], the formation of a contact angle between the domain and the continuous phase is associated with an increase in the overall bending energy of the domain (see Fig. 1). The associated bending penalty is likely to be negligible for large domains where the ensuing radius of curvature is low, but for small domains where the radius of curvature is of order the bilayer thickness this penalty may dominate over the reduction in line tension, thereby enforcing a zero contact angle.

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[28] The Helfrich free energy for a monolayer is classically written as [see, for example, [21–23]]. $d\gamma_m = df_0 + \frac{1}{2}Kh^2(c_1 + c_2 - c_0)^2 + \bar{K}h^2c_1c_2$, where df_0 is the energy of a flat membrane (a function of B, the area modulus), c_0 the spontaneous curvature, c_1 and c_2 are the principal curvatures, and $\bar{K}$ is the Gaussian splay modulus. r defines the radial distance. In our notation, if the deformation is spherically symmetrical so that $c_1 = c_2$ and the spontaneous curvature is zero (which applies, as a rule to lipids). $d\gamma_m = B\Delta^2 + 2Kh^2\left[\frac{d^2\Delta}{dr^2}\right]^2 + \bar{K}h^2\left[\frac{d^2\Delta}{dr^2}\right]^2 = B\Delta^2 + \hat{K}h^2\left[\frac{d^2\Delta}{dr^2}\right]^2$, where $\hat{K} = 2K + \bar{K}$. Thus, accounting for the Gaussian splay deformation would change the numerical value of the effective bending modulus, but not the dependence of the line tension on the contact angle. Moreover, it has been shown that in many cases [21–23] $\bar{K} \sim -(2/3)K$, so that $\hat{K} \approx (4/3)K \approx K$.