Phase transitions and membrane stiffness in a class of asymmetric heterogeneous fluid membranes

Niladri Sarkar and Abhik Basu
Condensed Matter Physics Division, Saha Institute of Nuclear Physics, Calcutta 700064, India
E-mail: niladri.sarkar@saha.ac.in and abhik.basu@saha.ac.in

Received 28 October 2014
Accepted for publication 16 July 2015
Published 26 August 2015

Abstract. We propose a minimal model for miscibility phase transitions (MPTs) in a class of asymmetric two-component heterogeneous fluid membranes at equilibrium that generically display both first and second order MPTs, controlled by the interplay of asymmetry and heterogeneity. In the vicinity of the MPTs, the membrane fluctuations are generally enhanced. However, the degree of enhancement is found to depend sensitively on the asymmetry-heterogeneity coupling. We argue that experimental measurements of the membrane fluctuations at the MPTs should provide physical information about the forms of the asymmetry-heterogeneity couplings.

Keywords: classical phase transitions (theory), correlation functions (theory), phase diagrams (theory)
Introduction

Miscibility phase transitions (MPTs) in heterogeneous membranes at equilibrium are a subject of intense research. Symmetric model lipid bilayers (i.e. lipid bilayers with inversion symmetry) undergo an MPT from a high temperature ($T$) homogeneous phase to a low temperature coexistence phase of liquid disordered and liquid ordered domains [1]. Extensive experimental results suggest that the MPTs in symmetric model membranes are generically second order in nature, belonging to the two-dimensional (2D) Ising universality class [2]. In contrast to their symmetric counterparts, model heterogeneous asymmetric membranes are distinguished by the lack of inversion symmetry and their composition dependent local spontaneous curvatures $C_0$, that affect the coarsening dynamics and equilibrium shapes [3]. Nonetheless, a general understanding of how asymmetry affects the nature of the associated MPTs is still lacking.

In this paper we theoretically describe how the interplay of asymmetry and inhomogeneity in a fluid membrane affects the phases and the associated MPTs. To this end, we construct a generic minimal model in the spirit of coarse-grained Ginzburg–Landau approaches in terms of the local composition inhomogeneity and curvature as the relevant thermodynamic variables. In order to focus on the essential physical aspects of the problem, we consider a tension-less single fluid membrane with two-component heterogeneities. For the sake of simplicity and generality, we do not distinguish between bilayer membranes and monolayer amphiphilic films [4, 5]. Apart from its phenomenological significance, our model is a good candidate to theoretically study 2D critical behaviour on a fluctuating membrane.

---

1 See for recent reviews [1].

2 See also Bagatolli and Kumar (2009) for a recent review on this and related topics.
Our model displays a complex phase diagram with a rich variety of phases and MPTs, including both second order transitions through critical (CP) and tricritical (TP) points, and first order transitions. Coupling constants that parametrise $C_0$ in our model appear as control parameters. Associated membrane conformation fluctuations are generically enhanced; however, the degree of enhancement can be controlled by these tuning parameters. Furthermore, the magnitude and sign of $C_0$ in the ordered, phase-separated state in our model can be tuned at a given $T$ by controlling the parameters. Our results demonstrate the importance of measuring the membrane fluctuations in experimental characterisation of MPTs in asymmetric membranes.

Our model is designed to capture the essential physical consequences of nonlinear asymmetry-inhomogeneity interactions and has few biological or microscopic details. Nonetheless, considering the generality of our model, we expect the basic features of our results, e.g. the significance of nonlinear asymmetry-inhomogeneity couplings on the MPT and the nature of the associated membrane fluctuations should be relevant for non-linear curvature-composition interactions in generic experiments on heterogeneous membranes and nonlinear aspects of lipid sorting near phase transitions in bilayer lipid membranes [6].

Construction of our model

We describe inhomogeneity by a single composition field $\phi(x)$. Physical interpretations of $\phi$ depend on specific systems. For instance, for an amphiphilic monolayers separating two distinct solvents (e.g. oil and water), $\phi$ is the local difference between the concentrations of the two types of lipids A and B; where as for lamellae or vesicles made of bilayer membranes, it is the local composition difference between the two layers of the bilayer [4, 5], or, for a diffusing chemical in a membrane, e.g. in echinocytosis of red blood cells, it is the local density fluctuations of the diffusing molecules [5, 7, 8]. Naturally, the underlying microscopic mechanisms behind the inversion asymmetry differ from one system to another, e.g. different intrinsic spontaneous curvatures of the two components in a two-component monolayer, the composition difference between the inner and the outer layers [5], or, the preference of the intercalated molecules for the tilted configurations of their surrounding phospholipids [7] in a bilayer. We adopt the standard Ginzburg–Landau free energy functional for binary mixtures [4, 9, 10], useful near a critical point. We consider $C_0(\phi)$ to be a generic nonlinear function of $\phi$, and for purposes of illustration assume $C_0(\phi) = -C_0(-\phi)$, so that A and B-excess regions have opposite local curvatures (assuming an amphiphilic membrane); see figure 1. Next, assume the standard Helfrich–Canham curvature energy for a tensionless [11],

3 Given our wisdom gathered from extensive studies on critical phenomena, symmetry-allowed nonlinear terms in $C_0$ may become relevant near CPs.

4 Surface tension $\sigma$ of an interface saturated by surfactant molecules is expected to vanish (see, e.g. [9]), and thus $\sigma$ for a fluid membrane fluctuating freely in a solvent is usually assumed to be zero. For a membrane with finite $\sigma$, for length scales $<\sqrt{\kappa/\sigma}$, $\sigma$ is irrelevant. See also [11] for discussions on physical situations, when the notion of a tensionless fluid membrane holds. On the other hand if $\sigma$ dominates over the curvature contribution in the relevant length scales, $\phi$ will undergo a second order MPT belonging to the 2D Ising universality class; with the $b$-fluctuations remaining unchanged at the CP of MPT.
zero thickness [12] membrane, parametrised by the bending modulus $\kappa$ and a single-valued height field $h(x, t)$, of the form $\kappa [\nabla^2 h - C_0(\phi)]^2$ in the Monge gauge [13], for planar fluid membrane configurations. Evidently, the free energy functional $F$ is invariant under $h \rightarrow -h$ together with $\phi \rightarrow -\phi$. We have then, \[
abla \kappa \phi \nabla C (h) \in \text{Monge gauge} [13], \text{for planar fluid membrane configurations.} \]

truncating to the lowest order nonlinear terms. Here $r \sim (T - T_c)$, $T_c$ being the mean-field (MF) critical temperature without any coupling to $h$. Coupling constants $u > 0$ and $v > 0$ determine the strength of the local lipid–lipid interactions. The $v$-term in $F$ is required for thermodynamic stability as we discuss below. The absence of invariance under the inversion of $h$ for a given $\phi$ enforces asymmetry in the model [7, 14]. We have $C_0(\phi) = -(\lambda \phi + \lambda_1 \phi^3)/\kappa$. Notice that the individual signs of $\lambda$ and $\lambda_1$ are arbitrary: signs of both $\lambda$, $\lambda_1$ may be flipped by redefining $h \rightarrow -h$, or, $\phi \rightarrow -\phi$. The sign of the product $\lambda \lambda_1$, however, cannot be transformed away. In fact, the signature of $\lambda \lambda_1$ pertains to important microscopic material properties: $\lambda \lambda_1 > 0$ implies that the contributions of the microscopic interactions between curvature and three or one lipid molecules to $F$ are mutually cooperative; on the other hand for $\lambda \lambda_1 < 0$, these microscopic interactions are mutually competing. In the latter case, for $\lambda \sim -\lambda_0 \phi^2$ the two contributions roughly cancel out. This has strong ramifications on the MPTs, as we find below. On dimensional ground in 2D, following the arguments in [4], $\lambda n_0 \sim \kappa H_0$, $\lambda_1 n_0^3 \sim \kappa H_0$, where $n_0$ is the mean concentration and $H_0$ is a typical microscopic (local) curvature, yielding $\lambda \sim \kappa H_0 \xi_0^2$, $\lambda_1 \sim \kappa H_0 \xi_0^6$ [15], with $\xi_0$ being the microscopic correlation length scale. Taking $\xi_0 \sim 10^{-9} m$ [4], $\kappa \sim 100 k_B T$ ($k_B$ is the Boltzmann constant) and $H_0 \sim 10^6 m^{-1}$, we find $\lambda \sim 10^{-10} k_B T m$, $\lambda_1 \sim 10^{-46} k_B T m^3$.

Mean-field analysis

We now construct a mean-field theory (MFT) [10] by minimizing $F$ with respect to (constant in MFT) twice the negative of the mean curvature $C = \nabla^2 h$ and order parameter $m = \phi$. We find a flat bilayer membrane with (finite) variable local thickness $s(x)$, free energies vary explicitly with $s(x)$, thus two overall flat bilayers may have different free energies, see, e.g. [12]. Our work with $s = 0$ everywhere may be extended to include finite $s(x)$ by allowing all symmetry allowed coupling between $s$ and other variables ($h, \phi$). Additional non-trivial features may emerge due to couplings of $s$ with $h, \phi$.

5 For a flat bilayer membrane with (finite) variable local thickness $s(x)$, free energies vary explicitly with $s(x)$, thus two overall flat bilayers may have different free energies, see, e.g. [12]. Our work with $s = 0$ everywhere may be extended to include finite $s(x)$ by allowing all symmetry allowed coupling between $s$ and other variables ($h, \phi$). Additional non-trivial features may emerge due to couplings of $s$ with $h, \phi$.

6 This is formally similar to mutually competing or cooperative $\Psi^4$ and $\Psi^6$ terms in a Ginzburg–Landau descriptions for magnetic spin models having a tricritical point with $\Psi$ being the local spin [10].
Phase transitions and membrane stiffness in a class of asymmetric heterogeneous fluid membranes

\[ rm + \lambda C + 3\lambda_k m^2 C + \frac{u}{3!} m^3 + \frac{v}{5!} m^5 = 0, \]  
\( \kappa C + \lambda m + \lambda_0 m^3 = 0. \)

For symmetric membranes \( \lambda = 0 = \lambda_1 \). Hence, \( C = 0 \) for all \( T \) and \( m = 0 \) for all \( T \geq T_c \) and \( \phi = m \neq 0 \) for all \( T < T_c \) with a second order transition at \( T_c \), belonging to the Ising MF universality class. Our results for an asymmetric membrane are far richer in behavior: equation (3) shows that for an asymmetric membrane in the ordered phase with a non-zero \( m \) (a) \( C \neq 0 \), and (b) the signatures of \( C \), being dependent on that of \( m \) not surprisingly, are opposite in the A or B rich domains in the ordered phase. Now eliminate \( C \) in equation (2) by using equation (3) to construct an effective Landau free energy \( F_e \):

\[ F_e = \frac{\hat{r}}{2} m^2 + \hat{u} m^4 + \hat{v} m^6, \]

where \( \hat{r} = r - \frac{\lambda_1}{\kappa}, \hat{u} = \frac{u}{4!} - \frac{\lambda_0}{\kappa} \) and \( \hat{v} = \frac{v}{6!} - \frac{\lambda^2}{2\kappa} \). Parameter \( \hat{r} \) defines effective MF critical temperature \( \hat{T}_c = T_c + \frac{\lambda^2}{\kappa} \). Effective coupling constants \( \hat{u} \) and \( \hat{v} \) can be either positive, negative or zero, separately or together. We assume \( \hat{v} > 0 \) always. Then, \( F_e \) is identical to that for the normal superfluid transition in liquid helium mixtures [16].

Free energy (4) allows for both first and second order transitions in the system, depending upon the relative magnitudes and signatures of \( \hat{r}, \hat{u} [10] \): (i) By construction when \( \hat{r} = 0, \hat{u} > 0, \hat{v} > 0, F_e \) admits a second order phase transition for \( m \) belonging to the MF Ising universality class. This holds for all \( \lambda, \lambda_1 \), such that \( \lambda \lambda_1 < 0 \), and also for \( \lambda \lambda_1 > 0 \) as long as \( \hat{u} > 0 \), (ii) For sufficiently large \( \lambda \lambda_1 > 0, \hat{u} < 0 \) and the \( \hat{v} \)-term is then necessary for thermodynamic stability. For this, the system undergoes a first order phase transition with \( m = \pm \sqrt{\frac{1}{2\hat{v}}} \neq 0 \) at \( \hat{T}_c^* = 4\hat{u} m^2 - 6\hat{v} m^4 = \frac{\hat{u}^2}{2\hat{v}} > 0 \), yielding a transition temperature \( \hat{T}_c^* = \hat{T}_c + \frac{\hat{u}^2}{2\hat{v}} \). This meets the second order transition at \( \hat{r} = 0, \hat{u} = 0, \) which defines a TP. The corresponding MF critical scaling exponents belong to the MF TP universality class [10].

For an asymmetric membrane, \( C = 0 \) in the disordered phase and in general \( C = C(m) = - (\lambda m + \lambda_1 m^3)/\kappa \neq 0 \) in the ordered phase. Hence, with equal and opposite \( C \) in the A and B-rich domains, \( C(m) \) changes sign as \( m \) changes sign in the ordered phase. Variation of \( C(m) \) across the transition temperature, that originates in the corresponding \( T \) dependence of \( m \), may be used to delineate the nature of the transition: below CP or TP, it grows continuously from zero as \( T \) decreases; in contrast, it displays a jump, controlled by the jump in \( m \), across a first order transition. In addition, the magnitude and sign of \( C \) may be tuned in the ordered phase by controlling \( \lambda \) and \( \lambda_1 \).
λ_1 : C = 0 along the zero curvature line given by λ + λ_1 m^2 = 0 in the ordered phase. This requires λ_1 < 0 and hence 〈u〉 > 0.

**Effect of small fluctuations**

Consider now (small) fluctuations in the disordered phase (r > 0). Retaining terms up to the harmonic order in $F$ and integrating $\phi$ in the partition function $Z = \int D\phi \exp[-F]$ ($k_B T = 1$) yields a wavevector $q$-dependent effective bending modulus

$$κ_e = κ - λ^2/(r + q^2) \approx κ - λ_1^2/r = κ_0 < κ $$

for $q \to 0$ at $r > 0$. Thus, $κ_e(q = 0) = 0$ at $κ = λ^2/r$ or $r = 0$. Similarly in the ordered phase define $ϕ = m + ψ$, $∇^2 h = C + δc$, where $m$ and $C$ are the solutions of equations (2) and (3) in the ordered state and $〈ψ〉 = 0 = 〈δc〉$. Expand $F$ to the bilinear order in $ψ$ and $δc$. The terms linear in $ψ$ and $δc$ vanish, since $m$ and $C$ minimise $F$ in the ordered phase. We obtain

$$F_o = \int d^4x \left[ \frac{r}{2} ψ^2 + \frac{1}{2} (∇ψ)^2 + \frac{6u}{4!} m^2 ψ^2 + 15\frac{v}{6!} m^4 ψ^2 + \frac{κ}{2} (δc)^2 + λψ δc + 3λ_1 m^2 ψ δc \right]$$

then, proceeding as before and integrating out $ψ$, we obtain an effective free energy functional for $h$, and thence extract $κ_e$ from there. Due to the anharmonicity, an exact integration is ruled out; instead perturbative calculations based on renormalisation group (RG) calculations should be employed to systematically handle the large (formally diverging in the thermodynamic limit (TL)) critical point fluctuations [10, 17]. This is a technically challenging task. It is, however,

**Role of the anharmonic fluctuations**

Anharmonic fluctuation contributions to $κ_e$, neglected above, should dominate near CP, due to the large (formally diverging in the thermodynamic limit) critical fluctuations. As above, we need to integrate over $ϕ$ (now retaining the anharmonic terms in $F$) in $Z$ near CP and obtain an effective free energy functional for $h$, and thence extract $κ_e$ from there. Due to the anharmonicity, an exact integration is ruled out; instead perturbative calculations based on renormalisation group (RG) calculations should be employed to systematically handle the large (formally diverging in the thermodynamic limit (TL)) critical point fluctuations [10, 17]. This is a technically challenging task. It is, however,
easier to calculate the height fluctuation correlator $\langle |h_{\mathbf{q}}|^2 \rangle_{\phi}$ for a given configuration of $\phi$. This is given by

$$\langle |h_{\mathbf{q}}|^2 \rangle_{\phi} = \int \mathcal{D}h \exp[\mathcal{F}] \frac{1}{Z_{\phi}},$$

where $Z_{\phi} = \int \mathcal{D}h \exp[-\mathcal{F}]$. Equation (8) yields

$$\langle |h_{\mathbf{q}}|^2 \rangle_{\phi} = \frac{1}{\kappa q^4} + \left( \lambda \phi + \lambda_1 \phi^3 \right) \int \frac{1}{\kappa^2 q^4} > \frac{1}{\kappa q^4}. \quad (9)$$

Thus, $\langle |h_{\mathbf{q}}|^2 \rangle_{\phi}$ is always enhanced in the presence of a given arbitrary configuration of $\phi$. Hence, the height fluctuation correlator $\langle |h_{\mathbf{q}}|^2 \rangle$, averaged over all possible configurations of $\phi$ with respect to the Boltzmann distribution determined by $\mathcal{F}_0$ should be enhanced by $\phi$-fluctuations. Thus, $\kappa_e < \kappa$ necessarily.

Actual enumeration of $\kappa_e$ can only be done perturbatively. This is conveniently done by naively expanding $Z$ in powers of (assumed small) $\lambda, \lambda_1, \mu$. This immediately yields,

$$\kappa_e(\mathbf{q}) = \kappa - \langle \lambda \phi + \lambda_1 \phi^3 \rangle,$$

(10)

to $O(\mu^0)$. The last term in the rhs of (10) involves calculation of higher order correlation functions of $\phi$, a difficult task by itself. In order to get a quantitative sense of the nature of the correction to $\kappa$ in (10), we resort to the Hartree approximation [10] and replace $\phi^2$ in (10) by $3\langle \phi^2 \rangle \phi$ (this amounts to ignoring higher-order connected correlators of $\phi$). This yields

$$\kappa_e(\mathbf{q}) = \kappa - \langle \lambda \phi + \lambda_1 \phi^3 \rangle,$$

(11)

where $\langle \phi^2 \rangle = \int \frac{d^d \phi}{(2\pi)^d} \langle |\phi_{\mathbf{q}}|^2 \rangle$ in $d$-dimensions that should be obtained self-consistently.

In (11), contributions to $\kappa_e$ from connected higher order correlations of $\phi$ are ignored. Ignoring self-consistency and noting that under spatial rescaling $x' = b x$, coupling constants $\lambda$ and $\lambda_1$ and field $\phi$ scale as $b \lambda, b^{3-d} \lambda_1$ and $b^{2-d}/2 \phi$, all the contributions to the corrections for $\kappa$ in (11) are equally relevant at 2D in a scaling sense. For a system of linear size $L \sim 1/q_0$,

$$\Delta \kappa_e(q_0) = \kappa_e(q_0) - \kappa \sim - \frac{\lambda + \lambda_1 \langle \phi^3 \rangle}{\mu + q_0^2} \rightarrow - \frac{\lambda + \lambda_1 \langle \phi^3 \rangle}{q_0^2}$$

$$\sim - (\lambda + \lambda_1 \langle \phi^3 \rangle)^2 L^2,$$

(12)

near the critical point of MPT. Evidently, for a large enough $L$, $\kappa_e(L) = 0$. This allows us to define a persistence length $\zeta_h$ for the membrane conformation fluctuations by $\kappa_e(\zeta_h) = 0$, giving

$$\zeta_h \sim \frac{\kappa}{\sqrt{\left[ \lambda + \lambda_1 \langle \phi^3 \rangle \right]^2}}.$$

(13)
Thus, if \( \lambda \) and \( \lambda_1 \) are of the same sign, then \( \Delta \kappa_e \) is increased in magnitude and \( \zeta_h \) is decreased. In contrast, when they are of opposite signs, \( \Delta \kappa_e \) is reduced and \( \zeta_h \) is enhanced; see figure 2 for schematic variation of \( \zeta_h \) with \( \lambda_1 \) for a fixed \( \lambda > 0 \). Accordingly, the membrane fluctuates more for \( \lambda_1 > 0 \) (‘more soft’) than for \( \lambda_1 < 0 \) (‘less soft’). Since \( \lambda \) and \( \lambda_1 \) are free parameters in our model, it is possible to make \( \Delta \kappa_e \) vanishingly small by choosing \( \lambda \sim -\lambda_1 \langle \phi^2 \rangle \). Within our analysis, this makes \( \zeta_h \) diverging. The corresponding anharmonic fluctuation corrections to \( \kappa_e(q) \) in the ordered phase close to CP to the lowest order in \( \lambda \), \( \lambda_1 \)

\[
\kappa_e(q) \approx \kappa - \frac{(\lambda + 3\lambda_1 m^2 + 3\lambda_1 \langle \psi^2 \rangle)^2}{-2r + q^2},
\]

(14)

where \( \langle \psi^2 \rangle = \int \frac{d^2q}{(2\pi)^2} \langle |\psi(q)|^2 \rangle \). Thus, \( \Delta \kappa_e < 0 \) in general; its magnitude may be controlled (can be increased or decreased) by tuning the magnitudes and signs of \( \lambda \), \( \lambda_1 \) as for above CP. In contrast, across a first order transition, fluctuation effects should be negligible. Hence, by using (7)

\[
\Delta \kappa_e(q = q_0) = -\frac{(\lambda + 3\lambda_1 m^2)^2}{r^* + q_0^2},
\]

(15)

\( m^2 = 0, |\bar{u}|/(2\bar{v}) \) in the disordered and ordered phase respectively. Hence, there is a jump in \( \kappa_e \) across a first order transition. For a first order transition, \( \lambda \lambda_1 > 0 \), and hence, both \( \lambda \) and \( \lambda_1 \) are either positive or negative. Thus, \( \Delta \kappa_e(q = q_0) < 0 \) necessarily for a first order transition. Further, (15) reveals a jump in \( \kappa_e \), due to the jump in \( m \). Overall, thus we see that the harmonic composition fluctuation contributions to \( \kappa_e \) always reduces \( \kappa_e \). The corresponding anharmonic contribution may further reduce \( \kappa_e \), or, may partly

---

8 In this case, several symmetric nonlinearities of both geometric and thermodynamic origin which are neglected here, should become relevant. Their interplay will determine \( \zeta_h \); see text for more discussions; see also [22].
suppress reduction of $\kappa_e$ by the composition fluctuations at the harmonic order. This can be argued heuristically from the form of (1). When $\lambda_l = 0$, Gaussian fluctuations of $\phi$ is known to soften the membrane as evident from (5), due to a possible reduction in free energy in a given bent configuration by adjusting $\phi$-fluctuations. Noting that for $\lambda_l < 0$, free energy reduction due to the fluctuations of $\phi$ at the Gaussian order is compensated by a free energy cost due to the $\lambda_l$-term. These two contributions (1) should balance when $\lambda_l \sim -\lambda_0 \phi^2$. This explains the mutually cooperative (competing) nature of the contributions to $\kappa_e$ from the composition fluctuations at the harmonic and anharmonic orders for $\lambda_l > (<) 0$.

Considering that $\kappa$ has no significant $T$-dependences, measurements of $\kappa_e$ as a function of $T$ yield information about $\lambda_l$ and $\lambda_1$. For instance, for a second order MPT, measuring $\kappa_e$ versus $T$ above CP and using (5) yields $\lambda_l$. Similar procedure below CP, now with the knowledge of $m^2$ (use MFT results or measure experimentally) yields $\lambda_1$.

Similarly, across a first order transition measuring $\Delta \kappa_e$ as a function of $T > T_c^*$ yields $\lambda^2$; see equation (15). Measuring the same quantity for $T < T_c^*$ with the knowledge of $\lambda$ obtained as above then yields $\lambda_1 m^2$. Use then $m^2 = |\bar{u}|/(2 \delta)$ (or measure it separately) below the MPT to obtain $\lambda_l$. For a first order transition, $\lambda_l > 0$, and hence, both $\lambda$ and $\lambda_l$ are either positive or negative. We classify the membrane fluctuations near the associated MPTs according to the nature of the corresponding MPTs—first order ($\lambda_l > 0, \bar{u} < 0$), second order with cooperative asymmetry-heterogeneity interactions ($\lambda_l > 0, \bar{u} > 0$, ‘membrane more soft’) and second order with competing asymmetry-heterogeneity interactions ($\lambda_l < 0, \bar{u} > 0$, ‘membrane less soft’). In the second and third cases, $\Delta \kappa = \kappa_e(\lambda_l) - \kappa_e(\lambda_l = 0)$ is negative and positive, respectively. Thus, measurements of $\Delta \kappa$ yield information about the sign of $\lambda_l$. Notice that at the level of our analysis based on the Hartree approximation, the last two cases differ only in the quantitative degree of membrane fluctuation enhancement. Variations of $\kappa_e$ with $\bar{r}$ are schematically shown in figure 3 across second order and first order transitions.

Phase diagrams

Our results are summarised in schematic phase diagrams figures 4 and 5 below. In figure 4 different types of transitions displayed by our model (within our MF analysis) and the corresponding changes in $\kappa_e$ across the transitions are marked in the $\bar{r} - \lambda_l$ plane ($\lambda_l > 0$). The locations of TP given by the condition $\bar{u} = 0$, and the line of zero spontaneous curvature, given by $C(m) = 0$ for particular choices of $\lambda, \lambda_l$ (in the ordered phase), are shown. Figure 5 shows what type of MPTs are expected for a given set of ($\lambda, \lambda_l$) as temperature is lowered. The two (curved) lines of TP are given by $\bar{u} = 0$, or, $\lambda \lambda_l / \kappa = u/4!$. For $\lambda \lambda_l > u/4!$ (regions marked A), $\bar{u} < 0$, and hence corresponds to first order transitions. In regions marked B, on the other hand, $\bar{u} > 0$ with $\lambda \lambda_l > 0$ and hence they correspond to second order transitions with a very soft membrane across the transition. In contrast, $\bar{u} > 0$ with $\lambda \lambda_l < 0$ in regions marked C; these describe second order transitions with ‘less soft’ membranes across the transitions.
Summary and outlook

Thus, we show how the interplay between composition and asymmetry determine the ensuing phases and phase transitions, and generic suppression of membrane fluctuations.
in asymmetric membranes, which are markedly more complex than symmetric membranes. Furthermore, the degree of enhancement can be controlled by the coupling constants that define the coupling between the local asymmetry and heterogeneity. Since $\lambda$, $\lambda_1$ have very different dependences on $\xi$, performing experiments on model asymmetric heterogeneous membranes with different sizes of the constituent lipid molecules should be a promising route to test our results experimentally. For instance, if $\xi$ changes by 10%, $\lambda$, $\lambda_1$ change by about 20% and 60%, respectively. Thus shows that by varying $\xi$, the effective stiffness of an asymmetric membrane can vary significantly. Our model demonstrates the significance of the sign of the product $\lambda\lambda_1$. Complementary to our analysis above, phases and phase transitions in (1) may also be tested in numerical simulations of suitably constructed equivalent lattice-gas based 2D lattice Hamiltonian with an Ising spin degree of freedom $S_{ij}$, a discrete analogue of $\phi(x)$ here $(i, j)$ is the coordinate of a point on the 2D lattice), and a discretised local curvature of the lattice $h_{ij}$ (see, e.g. [18]). Discrete analogues of the $\lambda$- and $\lambda_1$-terms may be constructed by coupling $S_{ij}$ with $h_{ij}$ appropriately. Additionally, atomistic models for asymmetric lipid bilayers that may correspond to the coarse-grained free energy (1) may be constructed by introducing local many-body interactions involving three atoms (or interaction sites) and the curvature and controlling its sign. In turn, knowledge about $\lambda\lambda_1$ should yield useful information about the underlying microscopic interactions. We look forward to synthesis of model asymmetric lipid membranes which may be used in experiments by standard, e.g. fluorescence, methods (see, e.g. [2]) to study the properties elucidated above. Membrane fluctuations and their dependences on $\lambda$, $\lambda_1$ may be investigated by standard experimental methods, e.g. optical interferometric methods [19]. The number of tunable parameters in our model is similar in number in analogous models for symmetric inhomogeneous membranes (see, e.g. [20]. Nevertheless, the MPTs in our asymmetric inhomogeneous model membranes are starkly different from those for symmetric ones. This highlights the crucial role of asymmetry.

Our results are strongly related to the symmetry properties of (1), i.e. $C_0(\phi) = -C_0(-\phi)$, or, equivalently, symmetry under the joint inversion $(h, \phi) \rightarrow (-h, -\phi)$. If the molecular
curvatures of lipid molecules A and B are different, then this symmetry property will not hold good. Insisting on modeling asymmetric membranes with no particular symmetry under inversion of \( \phi \), we can write down a generalised \( C(\phi) = \lambda_1 \phi + \lambda_2 \phi^3 \) (truncating up to \( \phi^3 \)). The new \( \lambda_2 \)-term evidently breaks the symmetry under the inversion \( (h, \phi) \rightarrow (-h, -\phi) \). Model asymmetric membranes with a non-zero \( \lambda_2 \) but with \( \lambda = 0 = \lambda_1 \) have been studied theoretically in [21], which illustrates the possibility of both first and second order transitions and generic enhancement of membrane fluctuations near the second order transitions. In the more general case with non-zero \( \lambda \), \( \lambda_1 \) and \( \lambda_2 \), we expect a combination of the results from this work and [21] to emerge, including possibly a more complex phase diagram. While a full analysis is beyond the scope of the present work, nonetheless, the results of [21] together with those here strongly highlights the generic nature of enhancement of membrane fluctuations and the possibilities of both first and second order MPTs.

Some technical comments are in order now. In writing \( \mathcal{F} \) (equation (1)) we have neglected the geometric nonlinearities which arise from expanding \( h(x) \) about the perfectly flat base plane in the Monge gauge, e.g. area element \( dS = d^2x \sqrt{1 + (\nabla h)^2} \simeq d^2x [1 + (\nabla h)^2]/2 \), and the mean curvature \( \kappa_{\text{mean}} = -\nabla^2 h + \frac{1}{2} \nabla^2 h(\nabla h)^2 + \partial_i h \partial_j h \partial_i h \partial_j h \) for small fluctuations in \( h, \phi \). Inclusion of the above in (1), generate additional nonlinear terms. Again straightforward scaling analysis near CP directly yields that these geometric nonlinearities are all irrelevant (in a scaling sense) in the presence of the couplings \( u \) and \( \lambda_1 \). Hence, to the leading order, the geometric nonlinearities should be subleading to the existing nonlinearities in (1). This justifies omission of the geometric nonlinearities in our analysis above. Furthermore, there are additional symmetric (invariant under \( h \rightarrow -h \) and \( \phi \rightarrow -\phi \)) nonlinear terms coupling \( h \) and \( \phi \), e.g. \( \varphi^2(\nabla^2 h)^2 \) (ignored here), which are of thermodynamic origin and generically present for both symmetric and asymmetric heterogeneous membranes. This is, however, irrelevant (in a scaling sense), similar to the geometric nonlinearities. Thus, this term leaves the critical properties of MPT and the associated membrane fluctuations in our model asymmetric membrane unaffected. Within our Hartree approximation, there are little qualitative differences between \( \lambda \lambda_1 > 0 \) and \( \lambda \lambda_1 < 0 \) (keeping \( u > 0 \) for both), except for the degree of enhancement of the membrane fluctuations near the associated MPT. Whether this is indeed the case or whether there are indeed significant qualitative differences between the two cases that are missed by our low-order perturbation theory should be investigated by more elaborate calculations. Our results suggest that in the special case with \( \lambda \lambda_1 < 0 \) in (1), when the harmonic and anharmonic composition fluctuation contributions to \( \kappa_e \) nearly mutually cancel to the leading order, the geometric and other symmetric nonlinearities mentioned above should become relevant, and the long wavelength properties of an asymmetric heterogeneous membrane described by (1) should be identical to a symmetric heterogeneous membrane, as described in [22]. Whether or not this actually happens can be determined by more detailed calculations that are beyond the scope of this work. Nonetheless, we can conclude with reasonable confidence that near the MPTs, an asymmetric heterogeneous membrane is likely to be generally softer than the corresponding symmetric heterogeneous membrane with the same bare bending modulus. In addition, in symmetric membranes \( (\lambda = 0) \) the critical behaviour of \( \phi \) will be controlled by the \( u \)-term, and hence, Ising-like. This establishes the 2D Ising
universality for the MPTs in symmetric heterogeneous membranes, consistent with the known experimental results [2].

Studies on the possibility of budding transitions (see, e.g. [23]) in our model and its relation to the divergence or suppression of membrane fluctuations at CPs should be interesting. Time-dependent phenomena in our model, e.g. dynamic scaling and growth of order after a temperature quench through CPs, TPs or first order transitions should be of interest from experimental point of views. Our work should be useful in the context of static and dynamic properties of phase transitions in Langmuir monolayers of polar molecules [24]. We hope our results will stimulate further theoretical and experimental works along these directions.

Acknowledgments

We thank the anonymous Referee for his/her comments and suggestions. One of the authors (AB) wishes to thank the Max–Planck-Society (Germany) and the Department of Science and Technology/Indo-German Science and Technology Centre (India) for partial financial support through the Partner Group programme (2009).

References

[1] Heberle F A and Feigenson G W 2011 Cold Spring Harbor Perspect. Biol. 3 004630

Simons K and Sampaio J L 2011 Cold Spring Harbor Perspect. Biol. 3 4697

Elson E L et al 2010 Annu. Rev. Biophys. 39 207

[2] Veatch S L et al 2007 Proc. Natl Acad. Sci. USA 104 17650

Veatch S L et al 2008 ACS Chem. Biol. 3 287

Honerkamp-Smith A R et al 2008 Biophys. J. 95 238

Honerkamp-Smith A R, Machta B B and Keller S L 2012 Phys. Rev. Lett. 108 265702

[3] Harden J L et al 2005 Phys. Rev. E 72 011903

Laradji M and Kumar P B S 2006 Phys. Rev. E 73 040901

Bagatolli L and Kumar P B S 2009 Soft Matter 5 3234

[4] Leibler S and Andelman D 1987 J. Phys. France 48 2013

Andelman D et al 1992 Europhys. Lett. 19 57

[5] Sorre D et al 2009 Proc. Natl Acad. Sci. 106 5622

Zhu C, Das S L and Baumgart T 2012 Biophys. J. 102 1837

[6] Leibler S 1986 J. Phys. France 47 507

[7] Leibler S et al 1976 J. Cell Biol. 70 193

[8] Safran S A 2003 Statistical Thermodynamics of Surfaces, Interfaces, and Membranes (Boulder, CO: Westview Press)

[9] Chaikin P M and Lubensky T C 2000 Principles of Condensed Matter Physics (Cambridge: Cambridge University Press)

[10] David F and Leibler S 1991 J. Phys. II (France) 1 959

[11] Dan N et al 1993 Langmuir 9 2768

Ursell T et al 2007 PLoS Comput. Biol. 3 e81

[12] Nelson D, Piran T and Weinberg S 1989 Statistical Mechanics of Membranes and Surfaces (Singapore: World Scientific)

[13] Helfrich W 1973 Z. Naturforsch. 28 703

[14] Brocca P, Cantu L, Corti M, Favero E D and Motta S 2004 Langmuir 20 2141

[15] Graf E H et al 1967 Phys. Rev. Lett. 19 417

[16] Zinn-Justin J 1973 Z. Naturforsch. 28 703

[17] Zinn-Justin J 2010 Quantum Field Theory and Critical Phenomena (Oxford: Oxford Science Publication)

[18] Zinn-Justin J 1996 Phase Transitions and Critical Phenomena vol 6 (New York: Academic)
Phase transitions and membrane stiffness in a class of asymmetric heterogeneous fluid membranes

[19] Betz T and Sykes C 2012 Soft Matter 8 5317
   Park Y et al 2010 Proc. Natl Acad. Sci. USA 107 6731
[20] Ayton G S, McWhirter J L, McMurtry P and Voth G A 2005 Biophys. J. 88 3855
[21] Sarkar N and Basu A 2013 Phys. Rev. E 88 042106
[22] Banerjee T and Basu A 2015 Phys. Rev. E 91 012119
[23] Kumar P B S et al 2001 Phys. Rev. Lett. 86 3911
[24] Andelman D, Brochard F and Joanny J-F 1987 J. Chem. Phys. 86 3673
   Brochard F, Joanny J-F and Andelman D 1987 Physics Amphiphilic Layers: Proc. of the Workshop
   (Les Houches, France) (Berlin: Springer) p 13